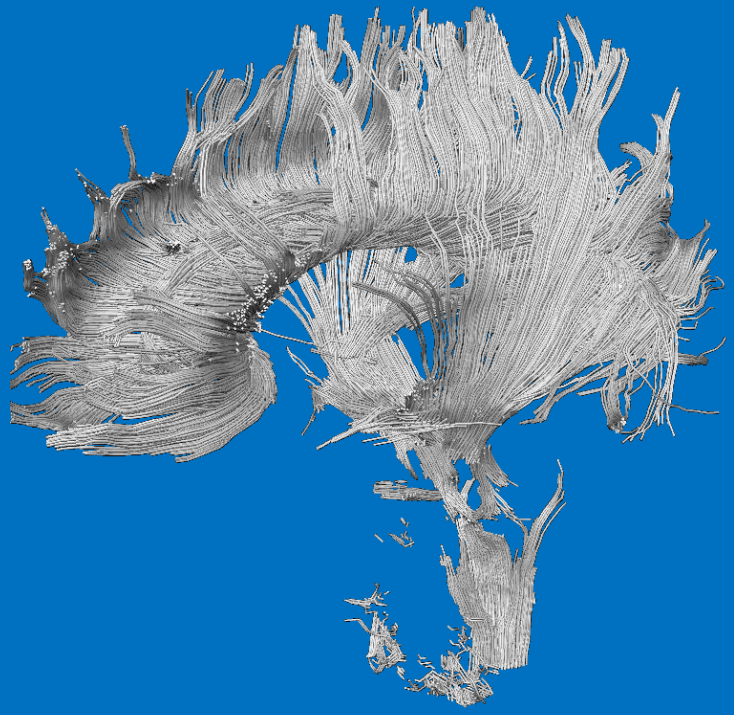
Magnetic resonance imaging of structural and functional connectivity of the brain



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WIAS Workshop on Statistics and Neuroimaging 2011

- Introduction
- The MRI experiment
- Diffusion tensor imaging, fiber orientation mapping, and neuronal fiber tracking
- Functional connectivity: Resting state and optogenetic fMRI

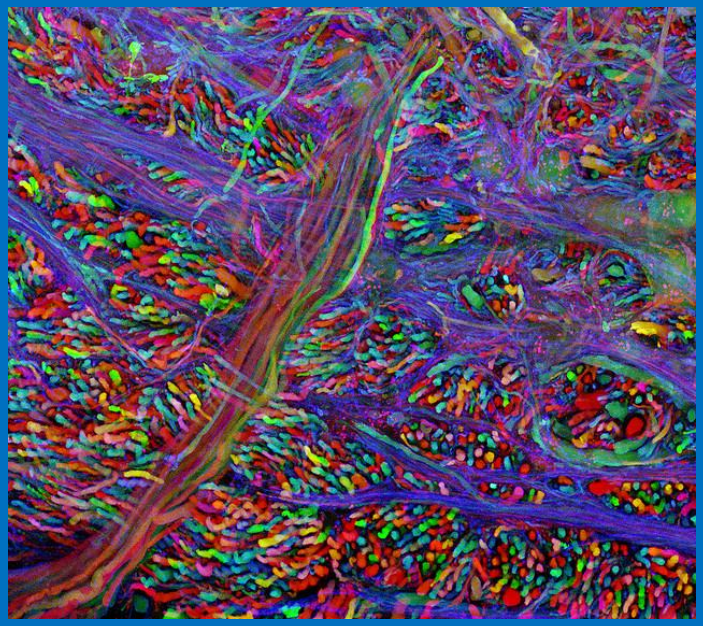
Neuronal networks - from c. elegans to the human brain

- C. elegans, exactly 302 neurons (959 cells total), 6393 synapses total

- Small brains – Mouse ~16 × 10^6 neurons, ~ 8,000 synapses each.

- Human brains – ~10^{11} neurons, ~ 10,000 synapses each

Connectivity



- **C. elegans et al.:** Optical imaging,
  electrical recordings, etc.

- **Small brains:**
  In addition, tracers, brainbow, optogenetic fMRI.
  Example: mouseconnectome.org: 400 antero/retrograde tracer injections

- **Human brains:** Limited in-vivo possibilities. Ex-vivo of limited use. Use DTI!

The MRI experiment

Physics: “Spin echo”

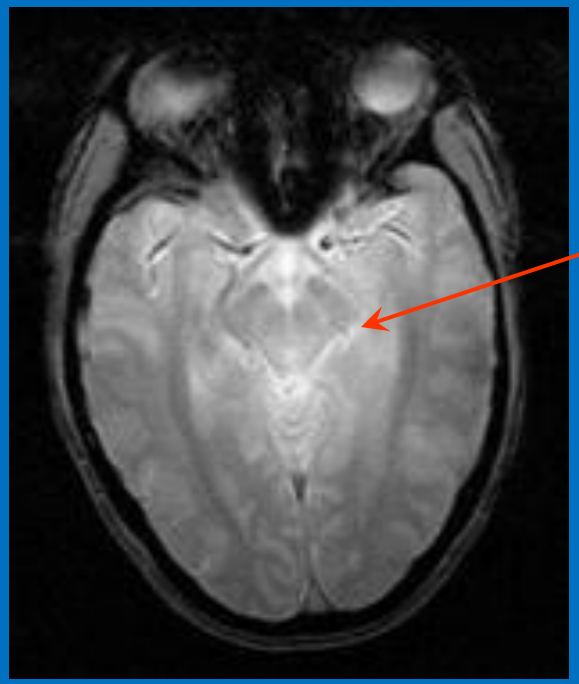
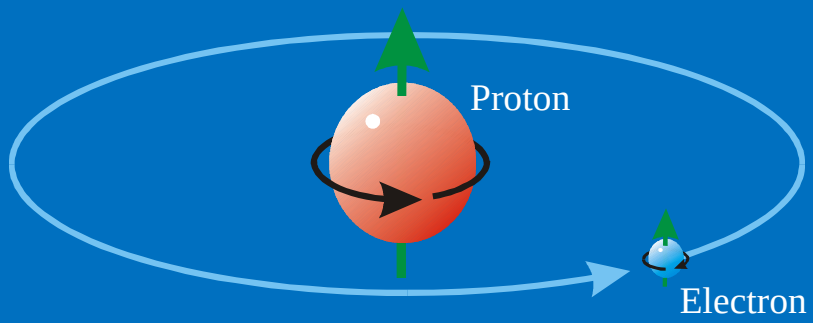


Image: Signal localization and contrast mechanisms

Proton spins

- For MRI, we are using the **spin** of atomic **nuclei**, mainly hydrogen nuclei
- MRI does not affect chemical processes and is **noninvasive**



- For protons and neutrons, spin = +/- 1/2
- For MRI, the atomic nuclei need to have a net spin and a charge to generate a magnetic moment
- Good MR nuclei are $^{\mathbf{1}}\mathbf{H}$, ^{13}C, ^{19}F, ^{23}Na, ^{31}P

Net magnetization

- In a magnetic field $\boldsymbol{B_0}$ the population ratio of spins parallel to $\boldsymbol{B_0}$ versus spins anti-parallel to $\boldsymbol{B_0}$ is roughly 100,006 to 100,000 (at room temperature)

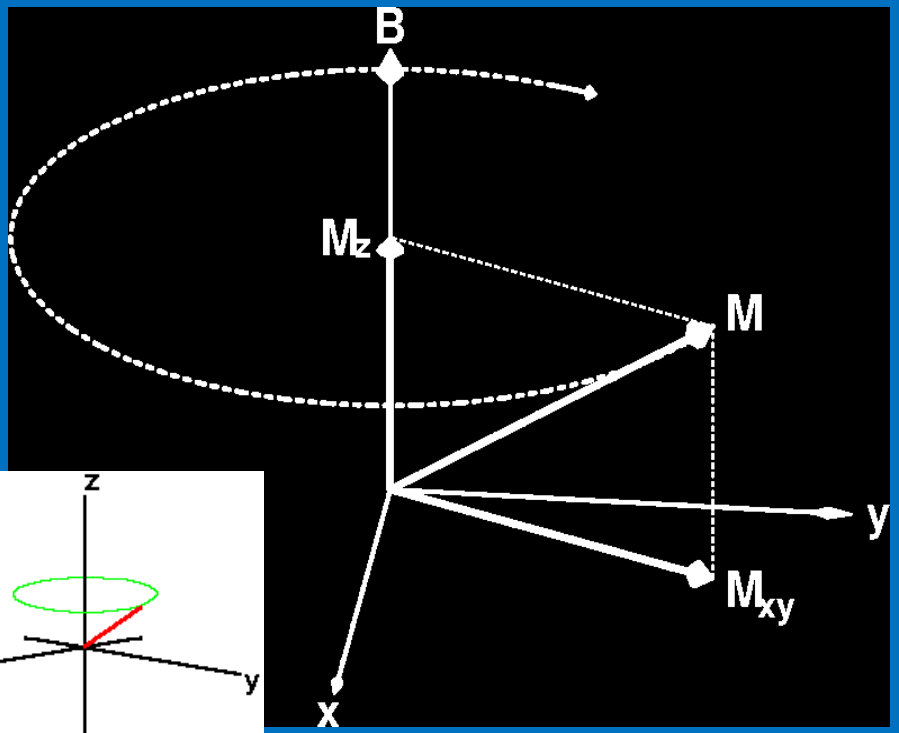
- Due to the surplus of aligned spins to non-aligned spins in an ensemble of spins, there is a small net magnetization (Bloch vector) $\mathbf{M}=(M_x,M_y,M_z)$

Precession

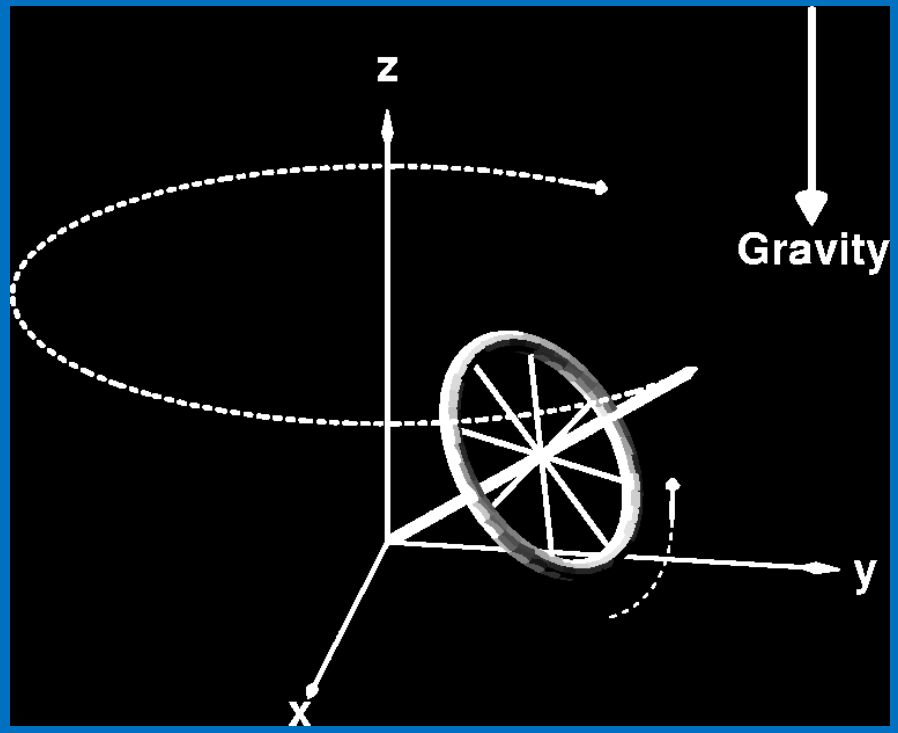
If **M** is not parallel to **B**, then it precesses clockwise around the direction of **B.**

Maxwell-Bloch equations: $$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B} - \frac{1}{T_1}\left(M_z - M_0\right)\hat{\mathbf{z}} - \frac{1}{T_2}\mathbf{M}_{xy}$$

Bloch vector



Analogy: gyroscope



$$\frac{d\mathbf{M}}{dt} = \gamma\,\mathbf{M}\times\mathbf{B} - \frac{1}{T_1}\left(M_z - M_0\right)\hat{\mathbf{z}} - \frac{1}{T_2}\mathbf{M}_{xy}$$

With $\mathbf{B} = (0,0,B_0)$ follows

$$\mathbf{M}_{xy}(t)=M_{xy}(0)\ \exp(-i\gamma B_0 t)\ \exp(-t/T_2)$$

$$M_z(t)=(1-\exp(-t/T_1))\ M_0$$

$\gamma/2\pi$ = gyromagnetic ratio = 42.57 MHz/T

B_0 = main magnetic field [T]

Larmor equation:

$$\omega_0 = \gamma B_0$$

Constant gradients in object:

$$\omega (x,y,z) = \gamma (B_0 + \text{grad } B * (x,y,z))$$

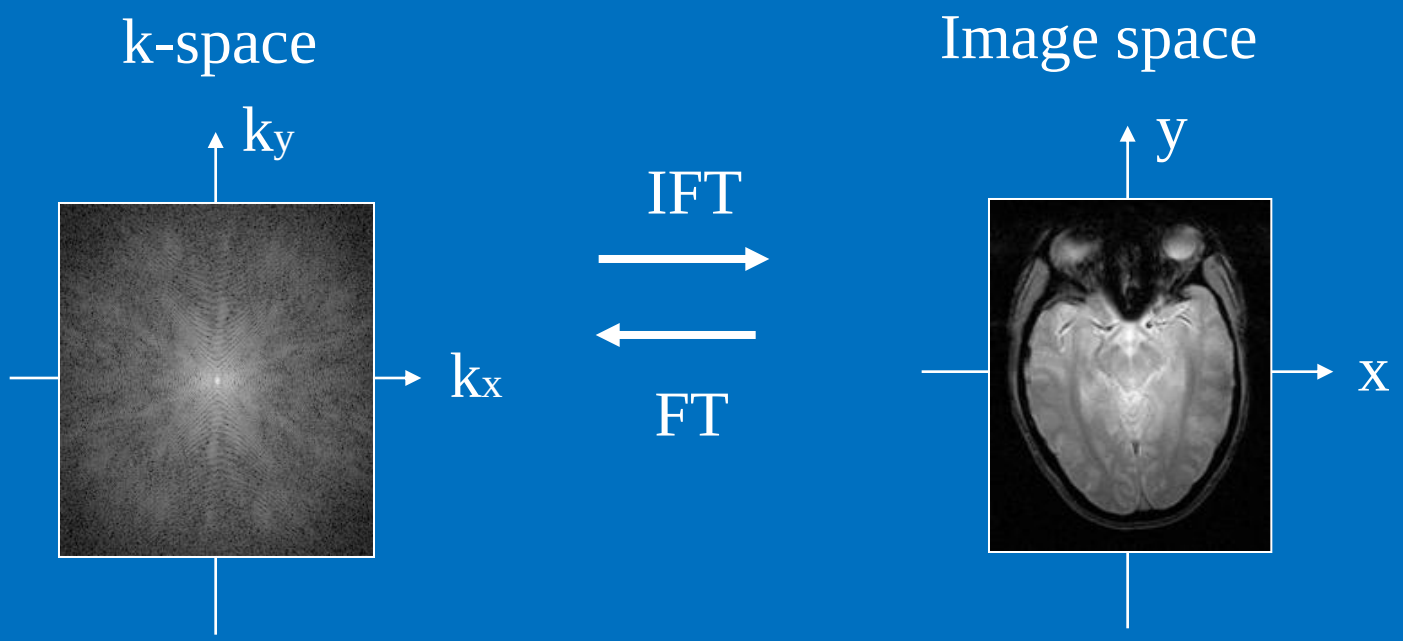
Generalize $\mathbf{B} = \mathbf{B_0} + G_x\,(x,0,0)$:

$$\mathbf{M}_{xy}(t) = M_{xy}(0)\ \exp(\ -i\ (\gamma B_0 t + \gamma\ G_x\ x\ t))\ \ \exp(-t/T_2)$$

$$=: M_{xy}(0)\ \exp(\ -i\ (\omega_0 t + k_x\ x))\ \ \exp(-t/T_2)$$

With magnetic field gradients the transverse magnetization looks like a spatial Fourier basis function

Fourier Transform



The MR signal is the 2D spatial Fourier transform of the imaged object.
The image is the 2D inverse spatial Fourier transform of the k-space data

Diffusion weighted imaging (DWI)

“There is nothing that nuclear spins will not do for you, as long as you treat them as human beings"

(Erwin L. Hahn 1949)

Theory

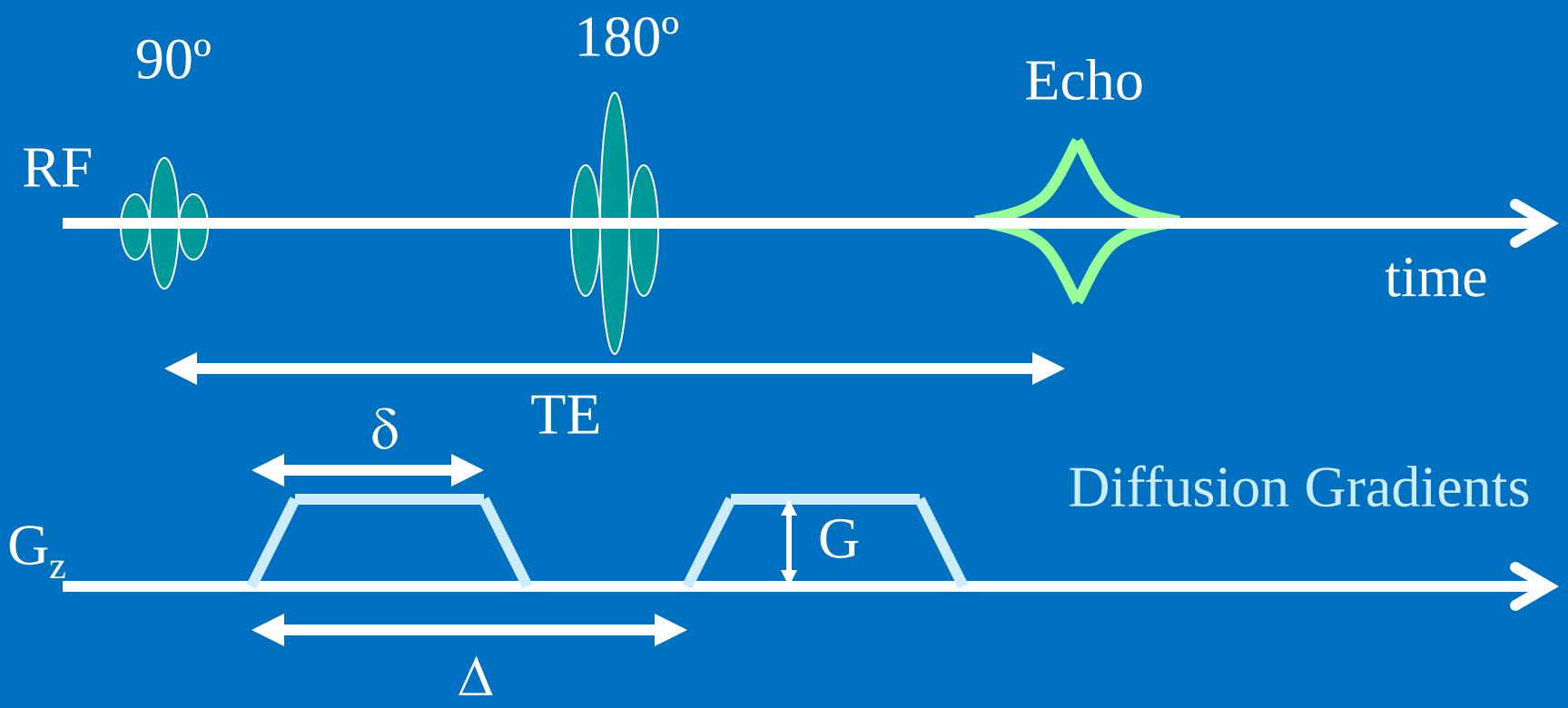
- Rigorous approach:

Add diffusion term to Bloch equations: Bloch-Torrey equation

- More convenient approach:

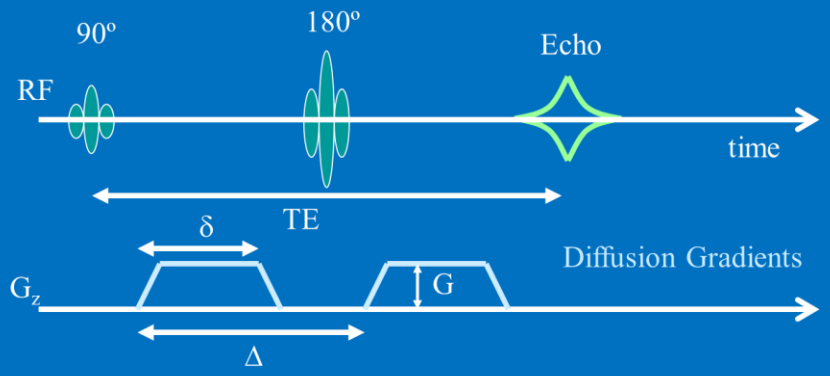
Start with probability distribution of spins and use diffusion equation

Bipolar pulsed gradient spin echo sequence (PGSE)



R. Watts 2004

In one dimension:



δ = length of diffusion gradients

Δ = spacing between diffusion gradients

$P(z)$ = probability distribution

$P(z_2,z_1,\Delta)$ = propagator: conditional probability that after a time Δ the spins are at z_2 when they were at z_1 before

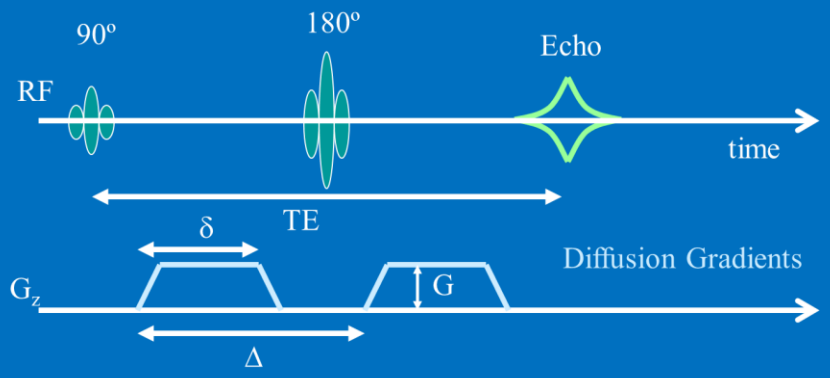
Assume $\delta << \Delta$, then

First gradient: dephasing $\Phi_1 = \gamma \int_0^{\delta} Gz_1 dt = \gamma G z_1 \delta$

2nd gradient: dephasing $\Phi_2 = \gamma \int_{\Delta}^{\Delta+\delta} Gz_2 dt = \gamma G z_2 \delta$

Net dephasing $\Phi_2 - \Phi_1 = \gamma G \delta (z_2 - z_1)$

$$S = S_0 \int dz_1 P(z_1) \int \exp(i\gamma \delta G(z_2 - z_1)) P(z_2, z_1, \Delta) dz_2 \qquad (*)$$



Isotropic diffusion process:

$$\partial P(z_2, z_1, t) / \partial t = D \Delta P(z_2, z_1, t) \qquad (**)$$

P is Gaussian at $t = \Delta$:

$$P(z_2, z_1, \Delta) = (4\pi\Delta D)^{-1/2} \exp(-(z_2 - z_1)^2 / 4\Delta D)$$

Combining this with (*), and using Einstein's law $<z^2>=2Dt$, we obtain (by integration in the complex domain)

$$S \propto \exp(-(\gamma\delta G)^2 \Delta D) = \exp(-(\gamma\delta G)^2 < z^2 > / 2)$$

Note that it is actually the diffusion path, not the diffusion constant, that is measured.

- We only consider lumped parameter model

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

  where b is the b-value, fixed in experiment by Stejskal-Tanner equation: $b = (G\gamma\delta)^2(\Delta - \delta/3)$
- Example:

  D = 0.0007 mm^2/s in in-vivo brain parenchyma

  b = 1/D = 1571 s/mm^2 as rule of thumb.

  Due to relaxation effects for finite diffusion gradient amplitudes (and therefore increased duration)

  smaller b = 800-1000 more appropriate for measuring ADC.

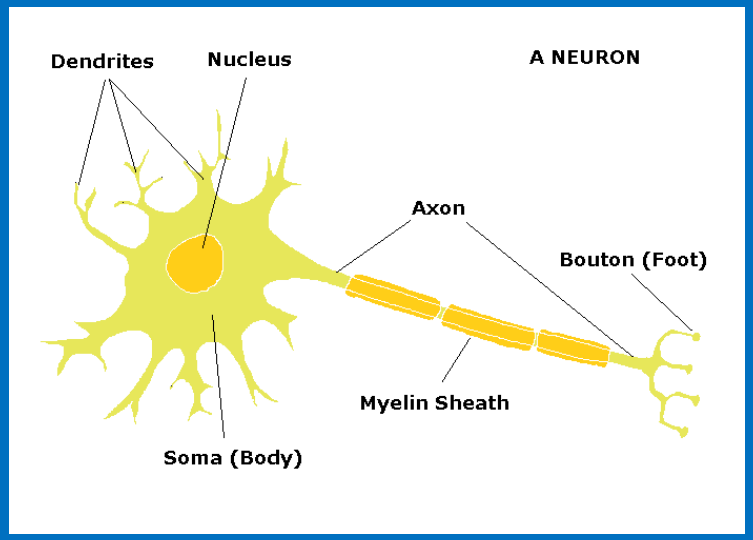
BUT:

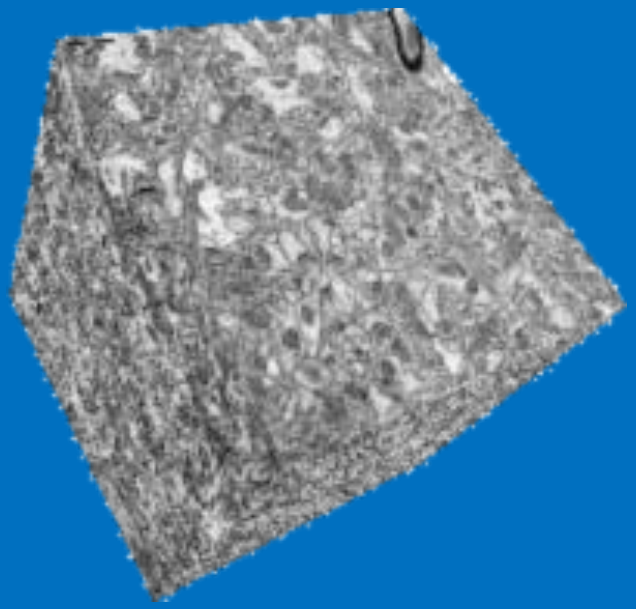
- Our assumptions of free, unlimited, isotropic Gaussian diffusion are not valid in the brain
- One speaks of an apparent diffusion constant or ADC

This is good!

Diffusion tensor imaging

Anisotropic attenuation





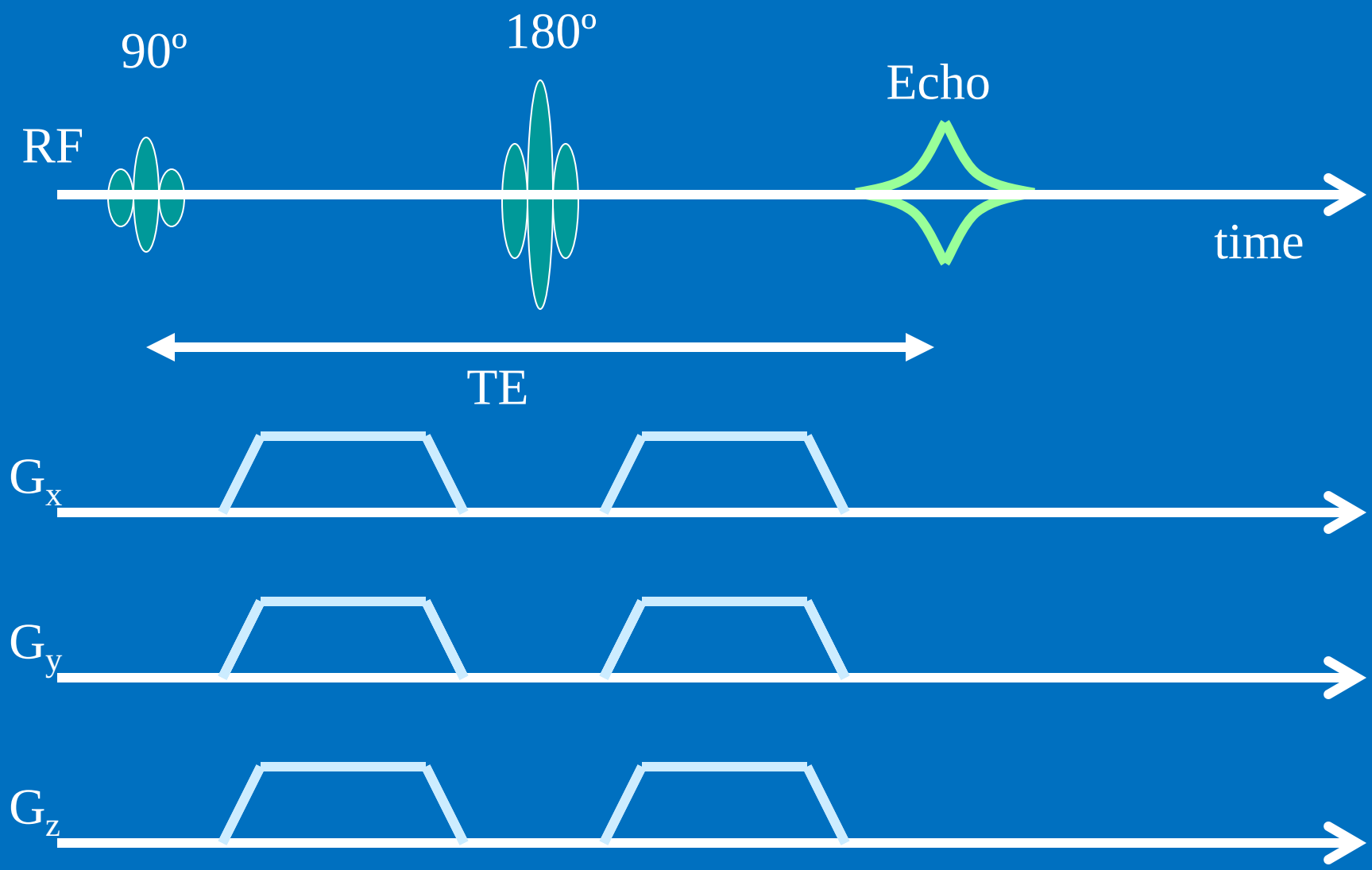
- Remember: One dimensional lumped parameter model:

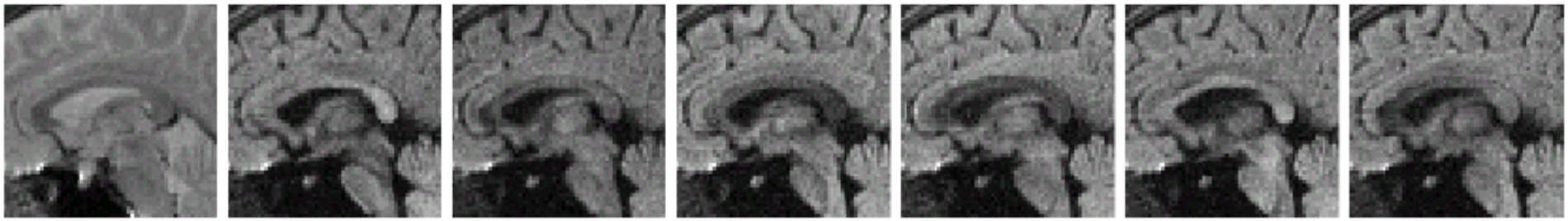
$$S = S_0 \, exp \, (-bD)$$

- Now: Directionality dependence

$$S = S_0 \, exp \, (- \, b \, \mathbf{g}^t \, D \, \mathbf{g}),$$

where **g** is a vector containing the diffusion gradient direction, and D is the diffusion ***tensor***

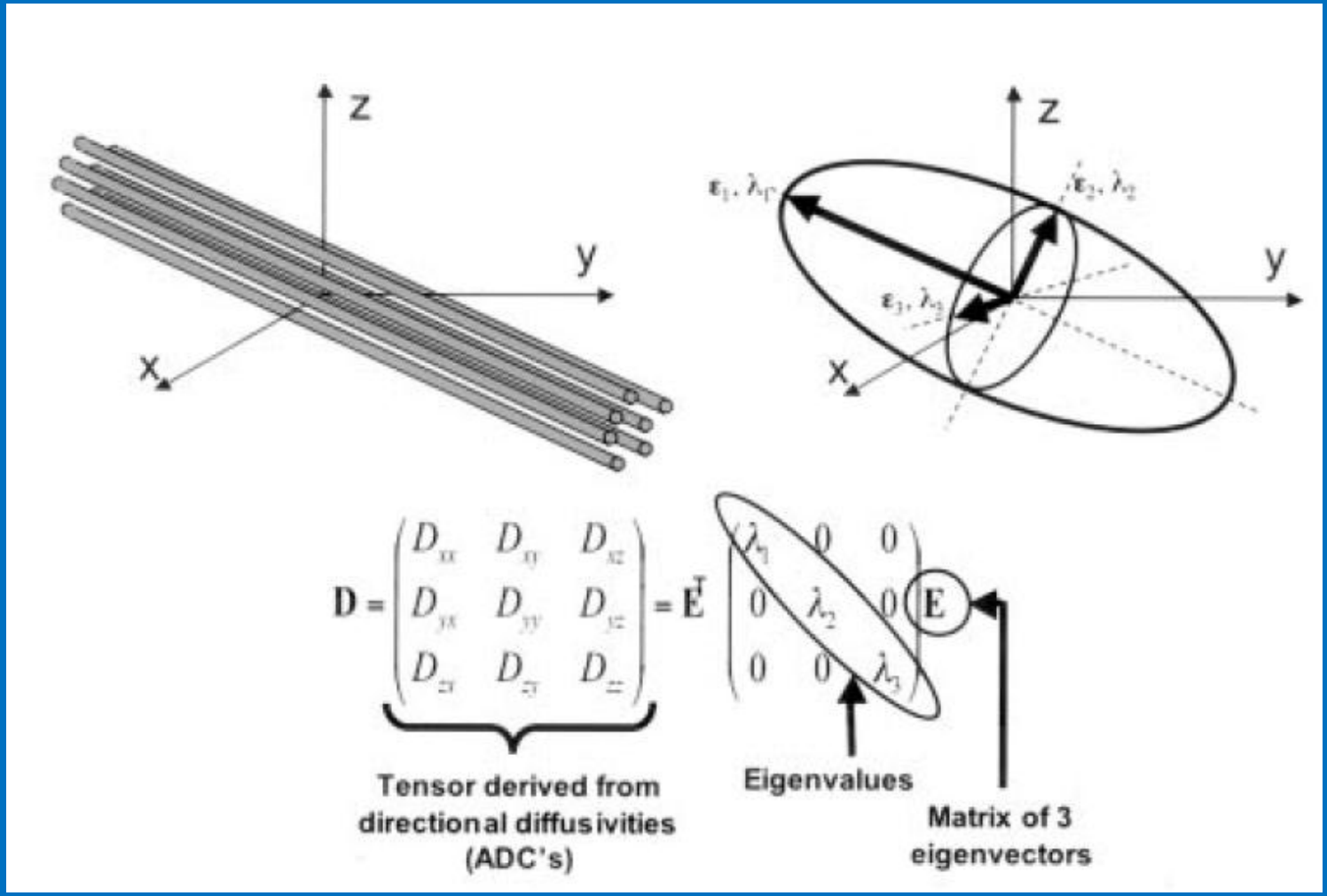




$$\mathbf{g}_0 = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \quad \mathbf{g}_1 = \begin{pmatrix} 1 \\ 1 \\ 0 \end{pmatrix} \quad \mathbf{g}_2 = \begin{pmatrix} 0 \\ 1 \\ 1 \end{pmatrix} \quad \mathbf{g}_3 = \begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix} \quad \mathbf{g}_4 = \begin{pmatrix} 0 \\ 1 \\ -1 \end{pmatrix} \quad \mathbf{g}_5 = \begin{pmatrix} 1 \\ -1 \\ 0 \end{pmatrix} \quad \mathbf{g}_6 = \begin{pmatrix} -1 \\ 0 \\ 1 \end{pmatrix}$$

Westin et al. 2002

The diffusion tensor



Jellison 2004

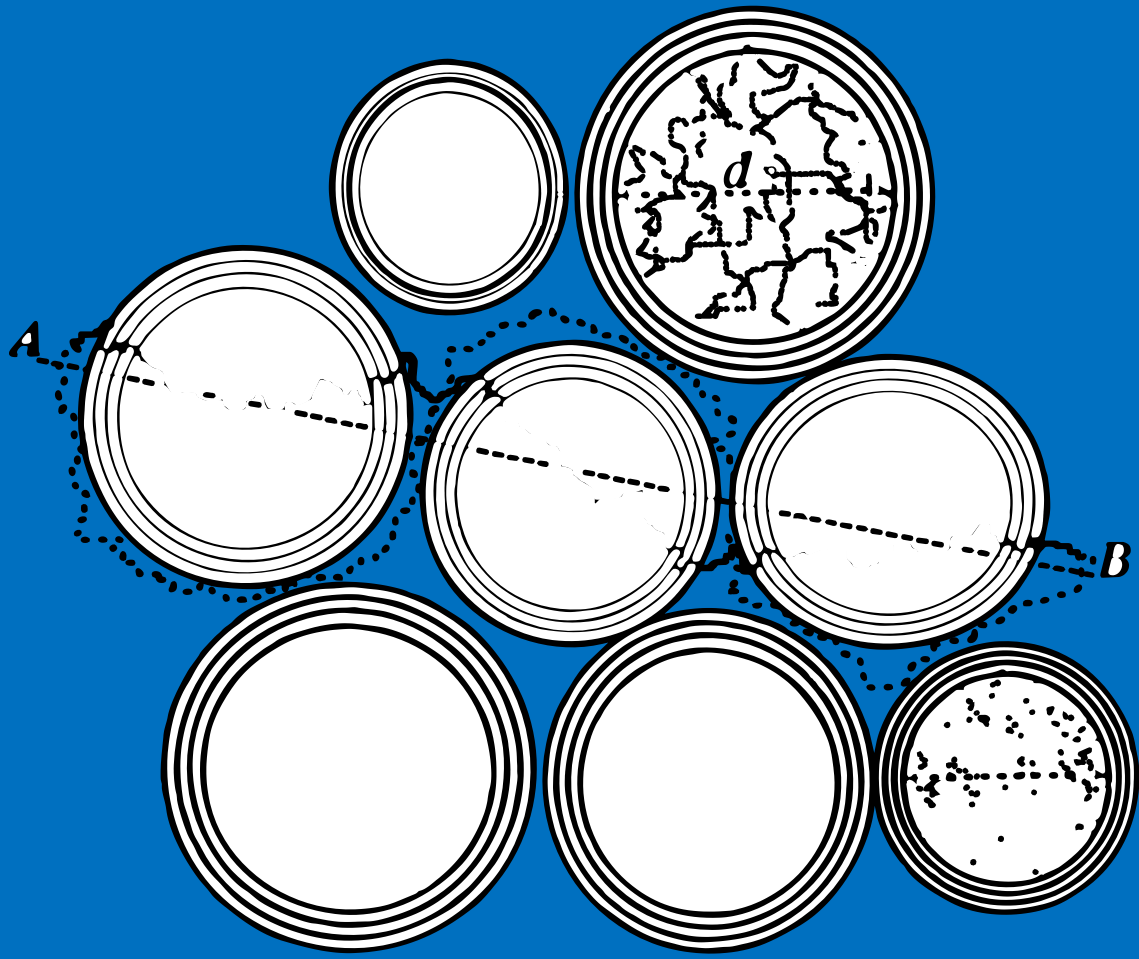
Some invariants
(not depending on angle of coordinate system):

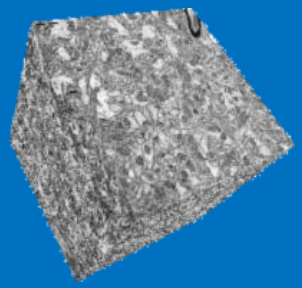
Mean diffusivity (ADC) = $tr(D)/3 = (D_{xx}+D_{yy}+D_{zz})/3$

Fractional anisotropy (FA) = $\sqrt{\frac{3[(\lambda_1-\bar{\lambda})^2+(\lambda_2-\bar{\lambda})^2+(\lambda_3-\bar{\lambda})^2]}{2(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$

What is measured?

Restricted, permeable barrier, hindered diffusion?



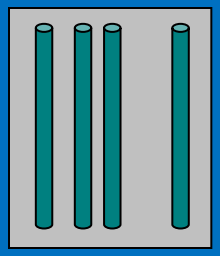


Le Bihan 1995

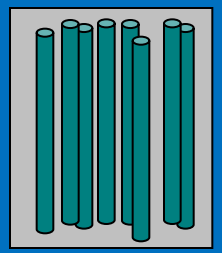
Interpreting ADC and FA

Diffusivity and FA are related to the **density**, **size, type,** and **myelination** of fibers.

Number of fibers

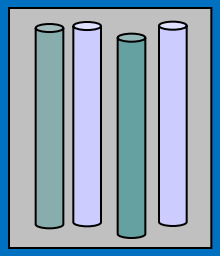


High Diffusivity
Low FA

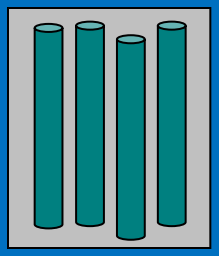


High FA
Low Diffusivity

Myelination of fibers

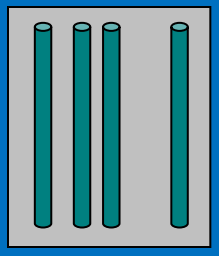


High Diffusivity
Low FA

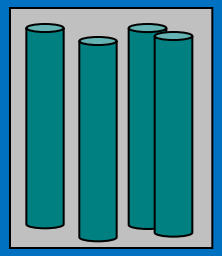


High FA
Low Diffusivity

Size of fibers

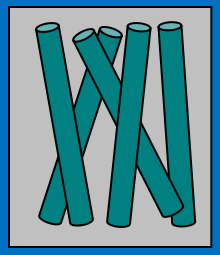


High Diffusivity
Low FA

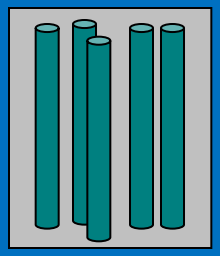


High FA
Low Diffusivity

Directionality of Fibers



Low FA
Same Diffusivity



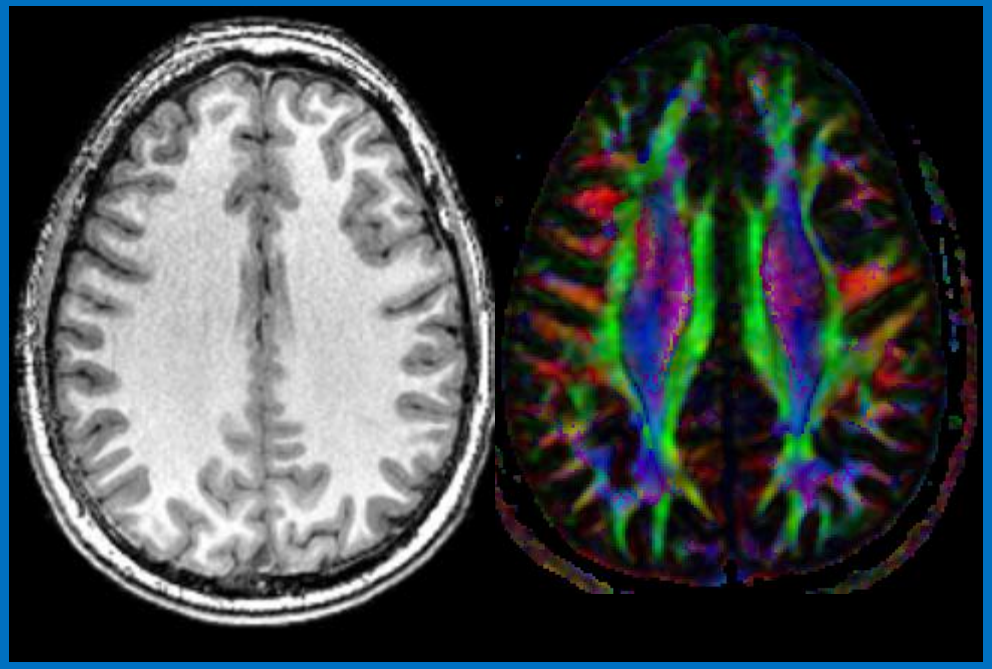
High FA
Same Diffusivity

S. Maier and M. Kubicki
http://www.na-mic.org/

How many measurements?

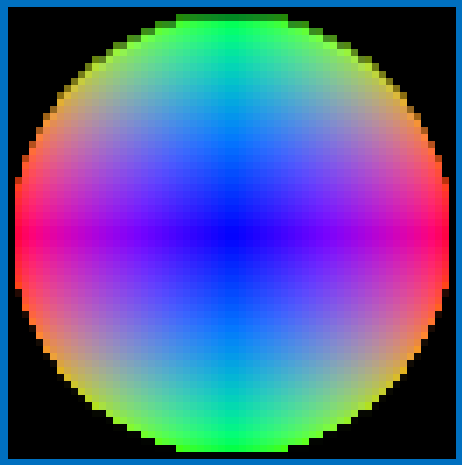
- One needs to measure the symmetric diffusion tensor and a *b=0* weighted image
- 6+1=7 measurements
- It has been shown that more = better:
- 6 icosahedral directions are not rotationally invariant (precision matrix contains 15 independent parameters and depends on tensor itself)

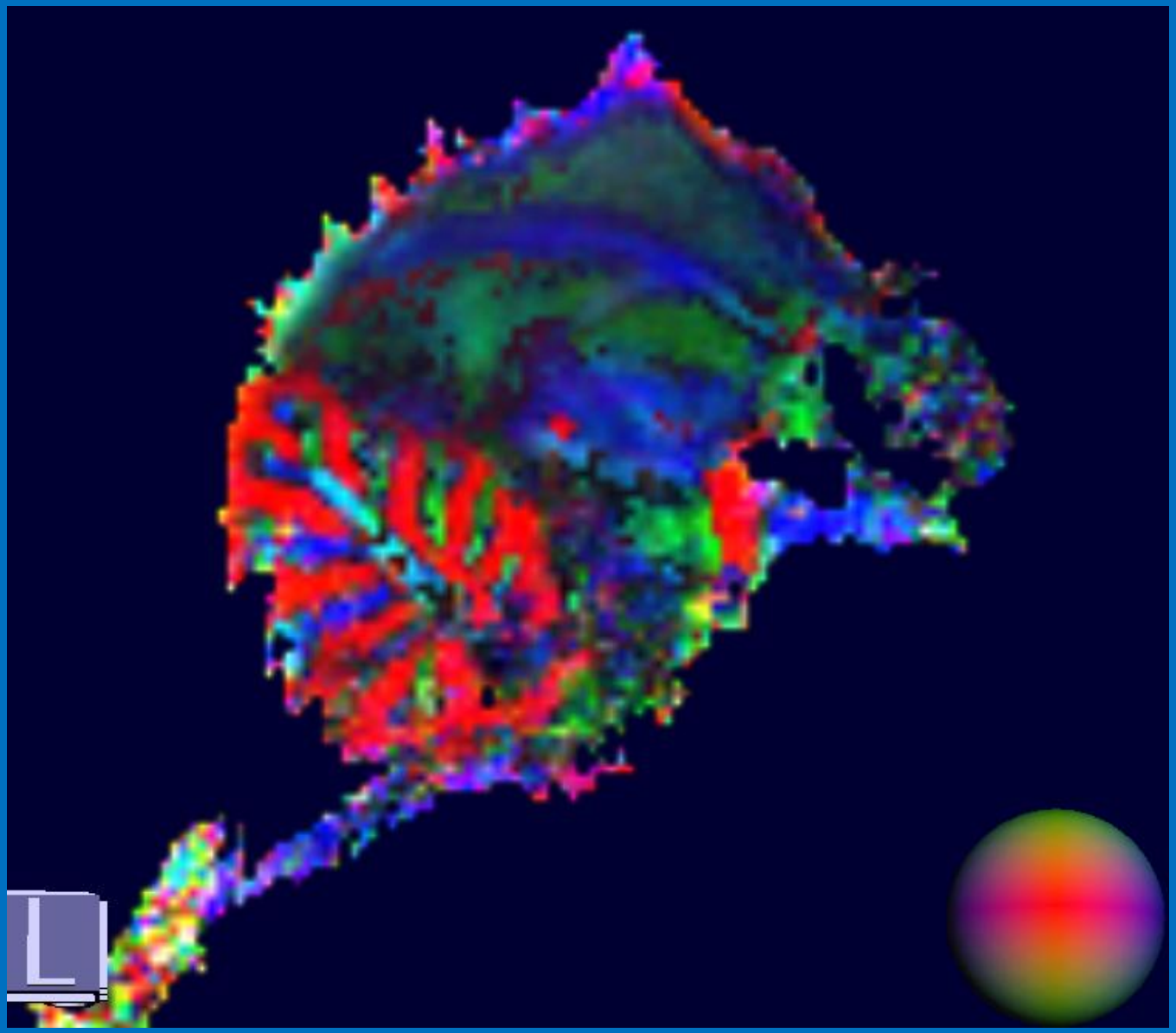
Fiber orientation mapping



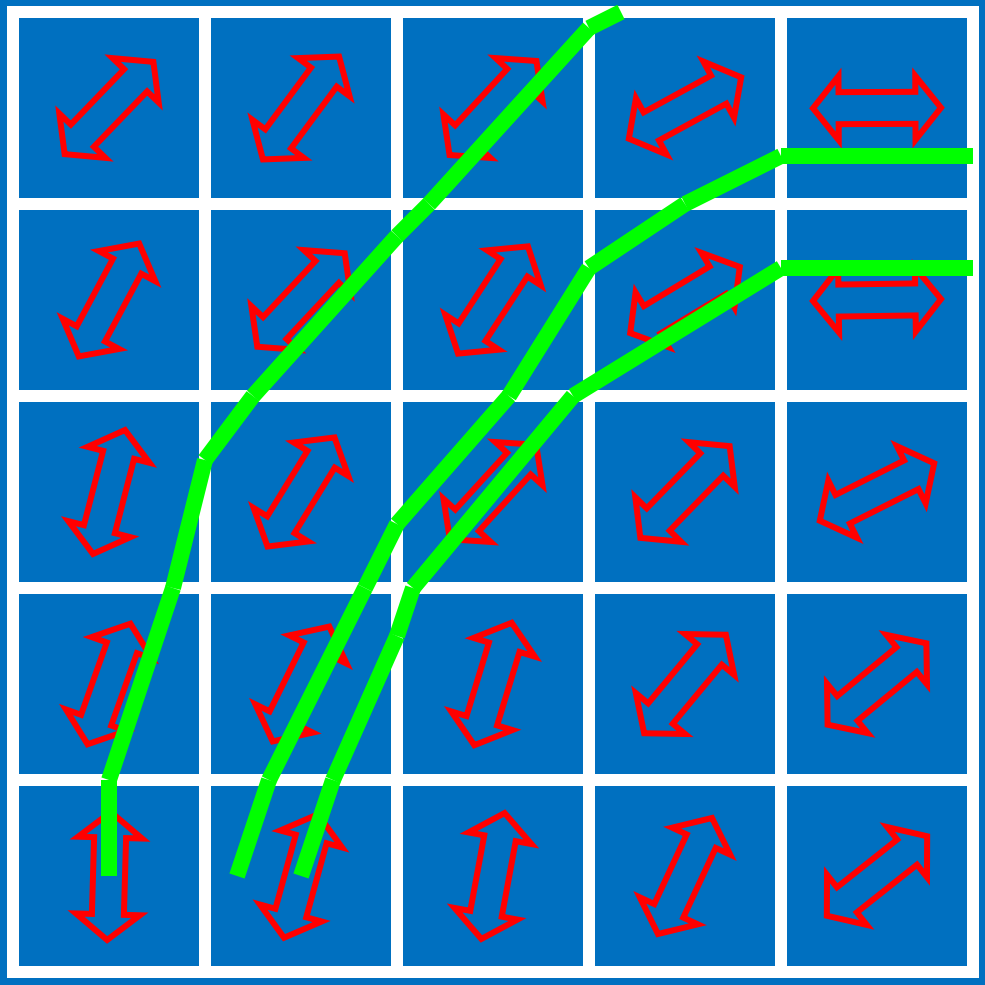
Intensity = Fractional anisotropy

Color = main fiber direction:



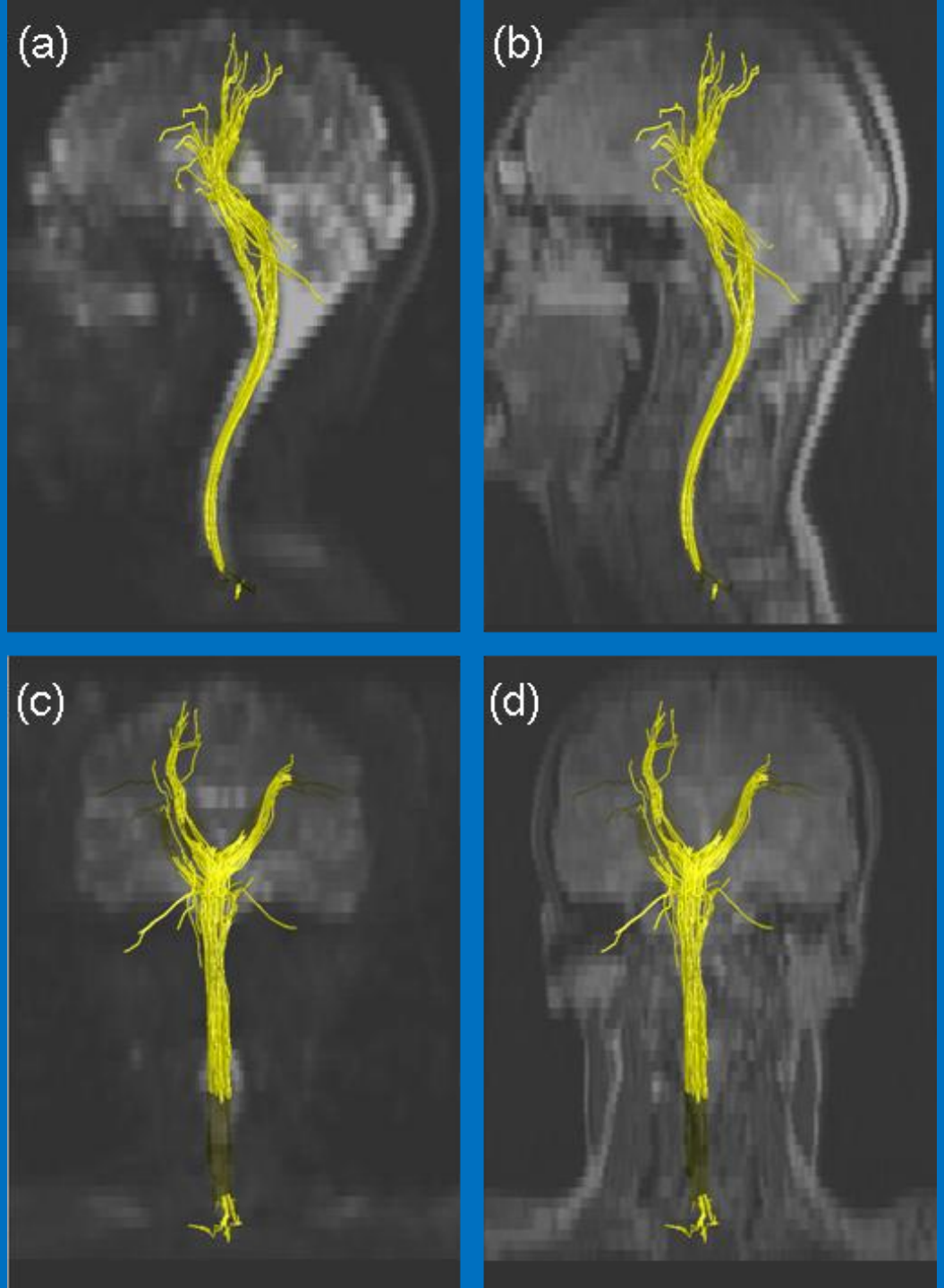

L

White matter fiber tractography

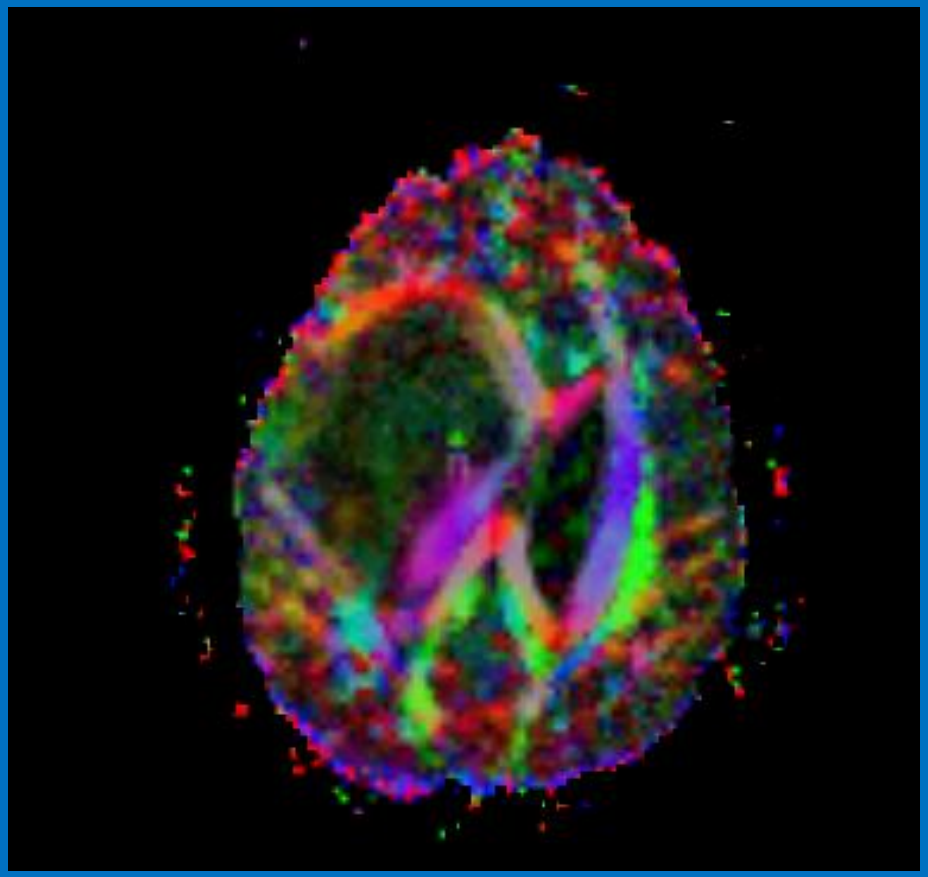


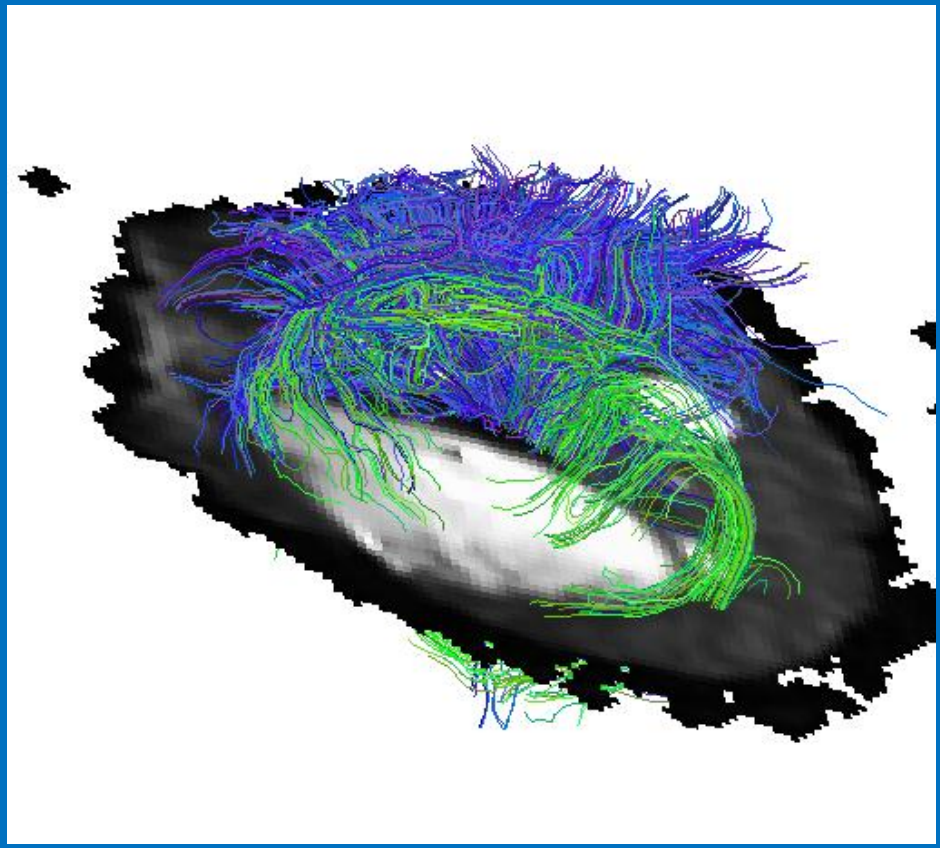
Direction of greatest diffusion

R. Watts 2004,
Mori et al, 1999

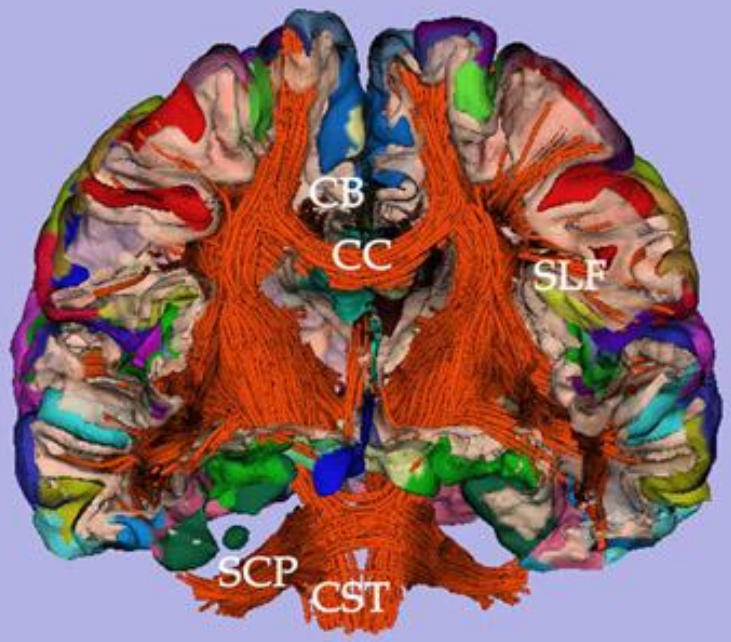

(a)
(b)
(c)
(d)

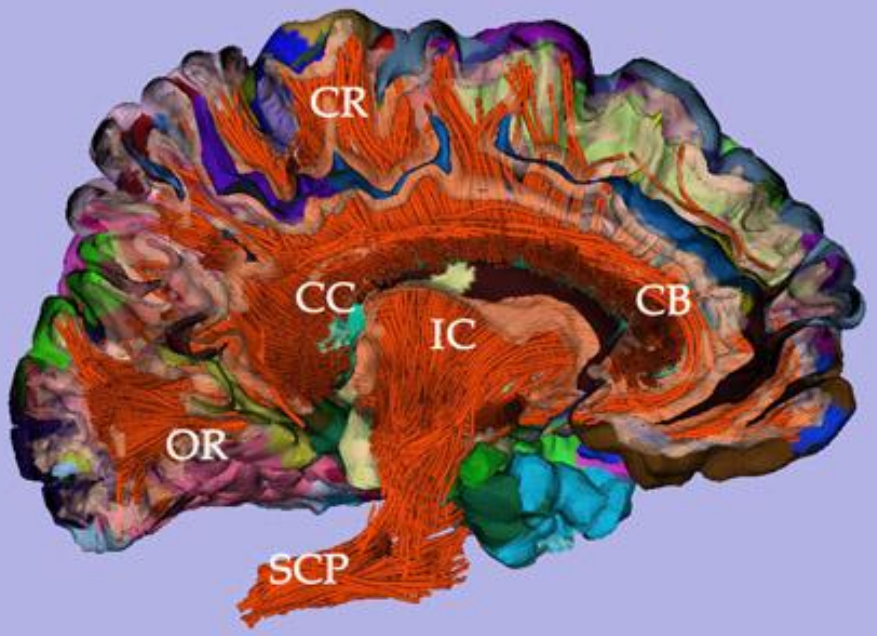
Application: Presurgical planning

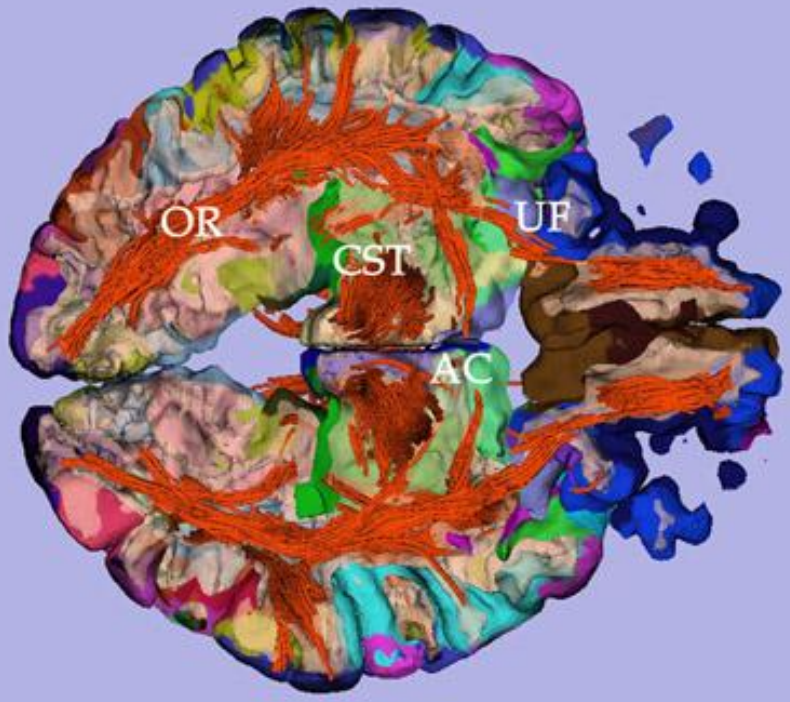


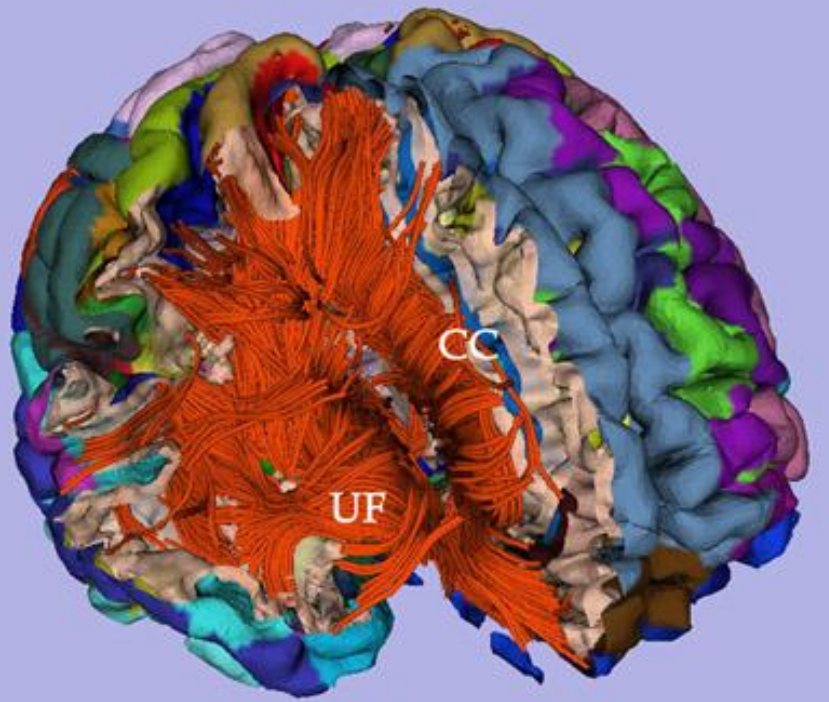


Neurosurgery/Radiology at NYPH (tumor & epileptic surgery) and CBIC









Hae-Jeong Park, Ph.D., 2003

Non-Gaussian diffusion

q-space imaging

Resolves intravoxel orientational heterogeneity
(partial voluming of different fiber tracts and crossing / branching / kissing fibers)

- Remember:

$$S = S_0 \int dz_1 P(z_1) \int \exp(i\gamma\delta G(z_2 - z_1)) P(z_2, z_1, \Delta) dz_2$$

- Define $q = \gamma\delta G$ and $z = z_2 - z_1$ to get

$$S(q, \Delta) = S_0 \int \exp(iqz) P(z, \Delta) dz$$

- Therefore, the signal S is again the Fourier-transform of a density P
- By inversion, one can measure P.
- This requires lots of q-values, i.e., one needs to vary timing δ or gradient strength G.

Q-ball imaging

- Drastically reduced scan time
- HARDI-sequence (High angular resolution diffusion imaging)
- Spherically sampled data
- Postprocessing (Funk Radon transform)

The orientation distribution function (ODF)

$$P(\mathrm{r}) = F[S(\mathrm{q})]$$ (**r** and **q** are reciprocal vectors)

ODF: $$\psi(\mathrm{u}) = \frac{1}{Z} \int_0^\infty P(r\mathrm{u})dr$$

Q-Ball imaging

Sample only on a sphere, not on 3D volume:

Funk-Radon transform
= extension of planar Radon transform to the sphere
= transform from sphere to sphere
= line integral along equator of sphere, for each vector on sphere

w = unit direction vector
f(**w**) = scalar function on sphere
u = direction of interest

$$G[f(\mathrm{w})](\mathrm{u}) = \int f(\mathrm{w})\delta(\mathrm{w}'\mathrm{u})d\mathrm{w}$$

Extended FRT: Maps from 3D Cartesian space to sphere

x = unit direction vector
r = particular radius at which FRT is evaluated
f(**x**) = scalar function in 3D Cartesian space

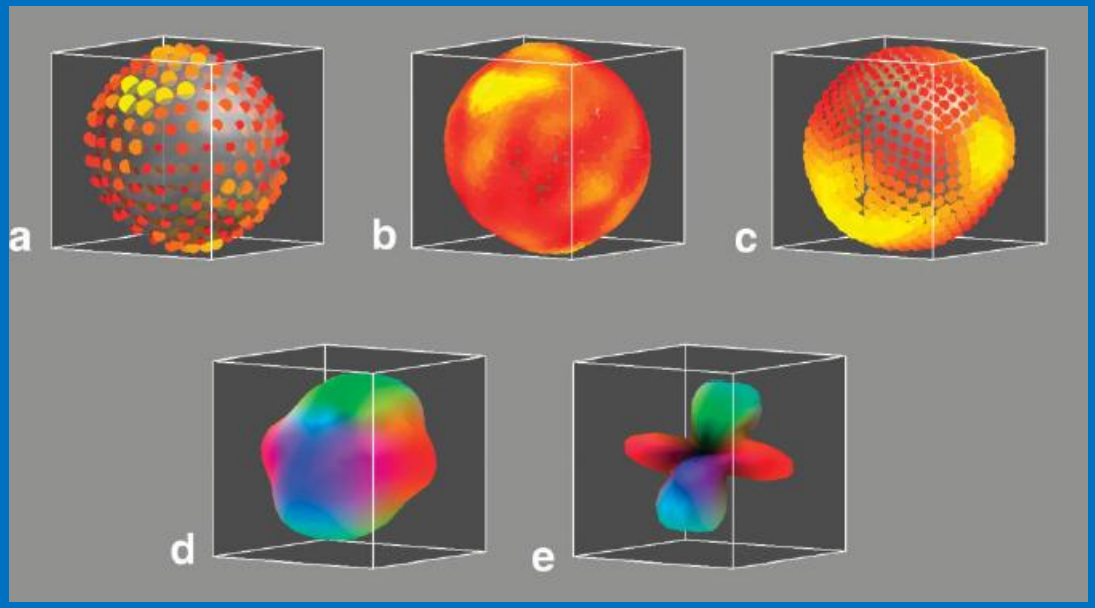
$$G_r = G[f(\mathrm{w})](\mathrm{u}, r) = \int f(\mathrm{x})\delta(\mathrm{x}'\mathrm{u})\delta(|\,\mathrm{x}\,| - r)d\mathrm{x}$$

Theorem (D. S. Tuch):
The extended FRT of the diffusion signal gives a strong approximation to the ODF, i.e.,

$$\psi(\mathrm{u}) \approx \frac{1}{Z}\, G_r[S(\mathrm{q})]$$ (**u** and **q** are reciprocal vectors)

The sum of the diffusion signal over an equator approximately gives the diffusion probability in the direction normal to the plane of the equator.

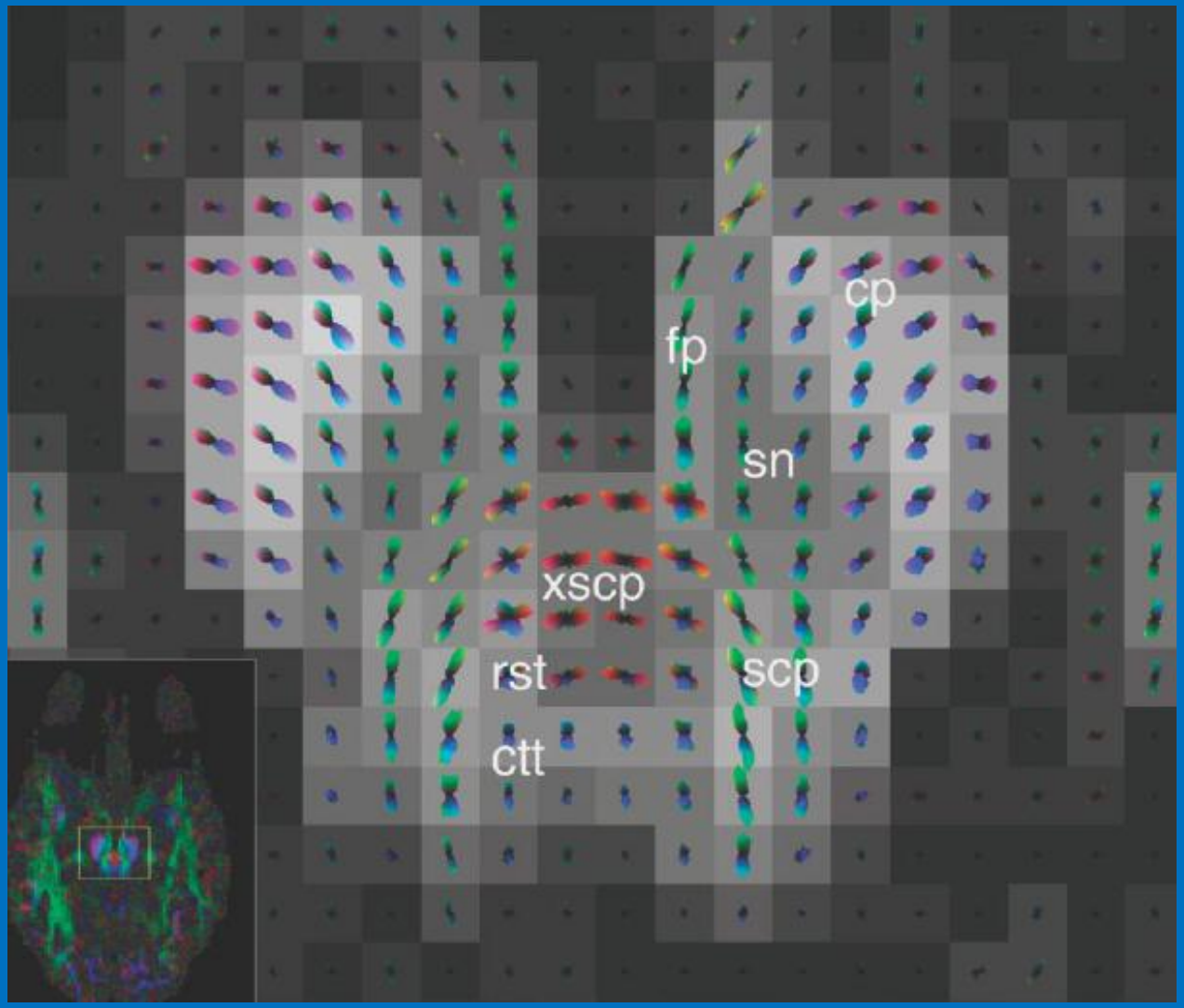
Central element:
The diffusion orientation distribution function (ODF)



(a) Diffusion signal sampled on fivefold tessellated icosahedron (*m* 252).
The signal intensity is indicated by the size and color (white yellow red) of the dots on the sphere.
(**b**) Regridding of diffusion signal onto set of equators around vertices of fivefold tessellated dodecahedron.
(**c**) Diffusion ODF calculated using FRT.
(**d**) Color-coded spherical polar plot rendering of ODF.
(**e**) Min–max normalized ODF.

(Tuch 2004)

ODF map of caudal midbrain



cp, cerebral peduncle;
ctt, central tegmental tract;
fp, frontopontine tract;
rst, reticulospinal tract;
scp, superior cerebellar peduncle;
sn, substantia nigra;
xscp, crossing of the superior cerebellar peduncle.

The multiple wave vector experiment

- Recall $q = \gamma \delta G$ and $z = z_2 - z_1$ to get

$$S(q,\Delta) = S_0 \int \exp(iqz) P(z,\Delta) dz$$

- As $\Delta \rightarrow \infty$, for spins trapped in pore with homogeneous spin density,

$$S_\infty(q) = |S_0(q)|^2$$

- Just as optical diffraction by single slit.
- Introducing more diffusion gradients into the PGSE sequence, in three dimensions $S(\boldsymbol{q_1}, \boldsymbol{q_2}, \boldsymbol{q_3}, ..., \Delta)$ depends on the angle between the $\boldsymbol{q}$-vectors *in case of restricted diffusion*.
- This allows for estimating pore shapes etc., using modified methods of scattering analysis.

Callaghan et al., 1994; Mitra 1995

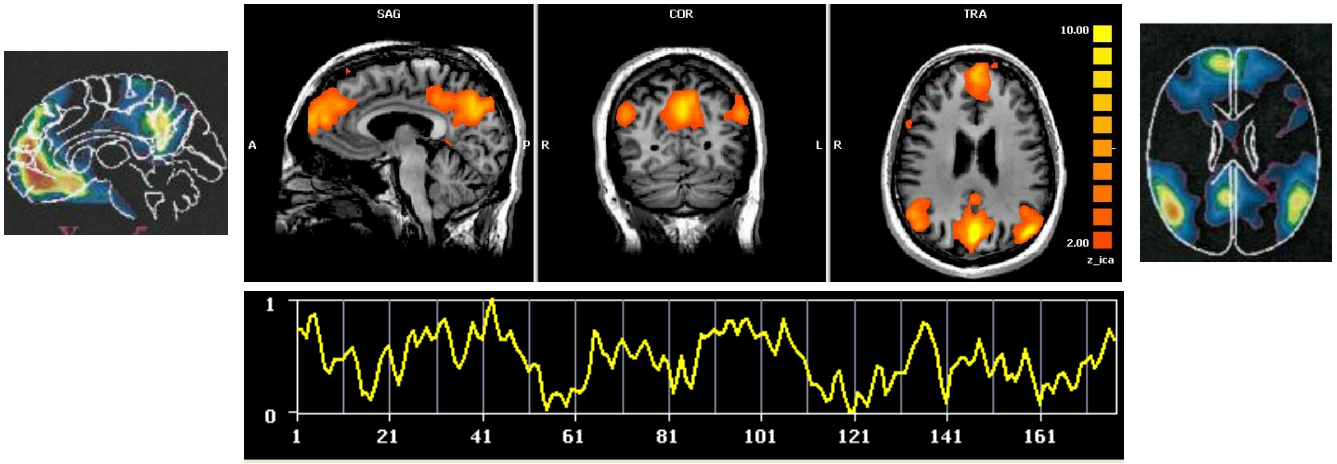
Functional/effective connectivity

Resting state brain networks

The default mode network and fMRI

Default mode network shows up in resting fMRI as areas with temporally correlated baseline activity, 0.01 Hz < frequency < 0.08 Hz

Two approaches: PCA/ICA and ROI

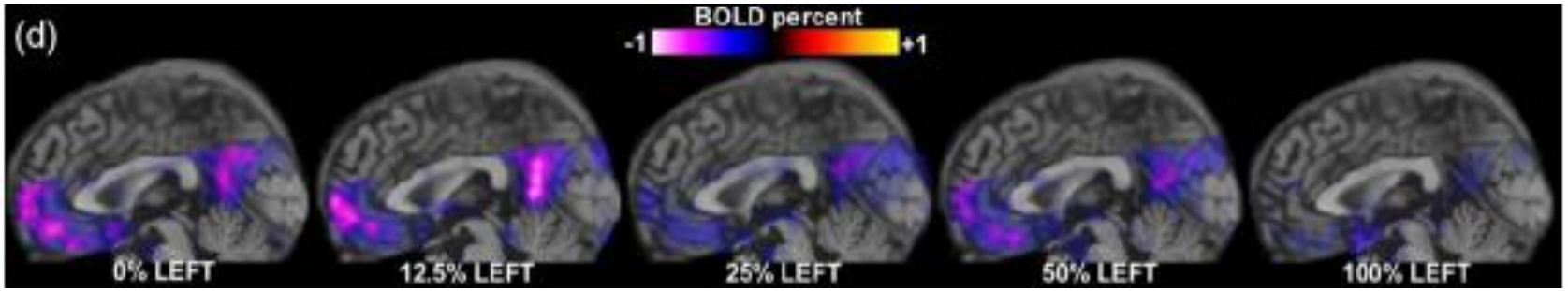


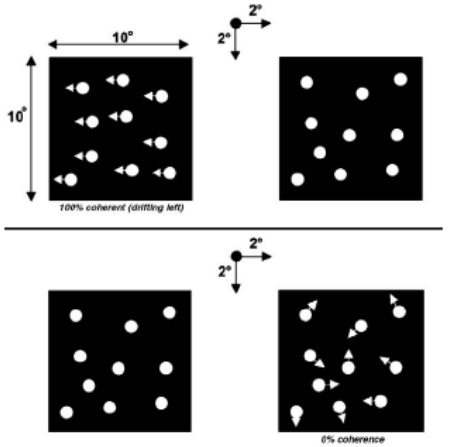
Greicius et al. 2003: First fMRI resting-state connectivity analysis of the default mode

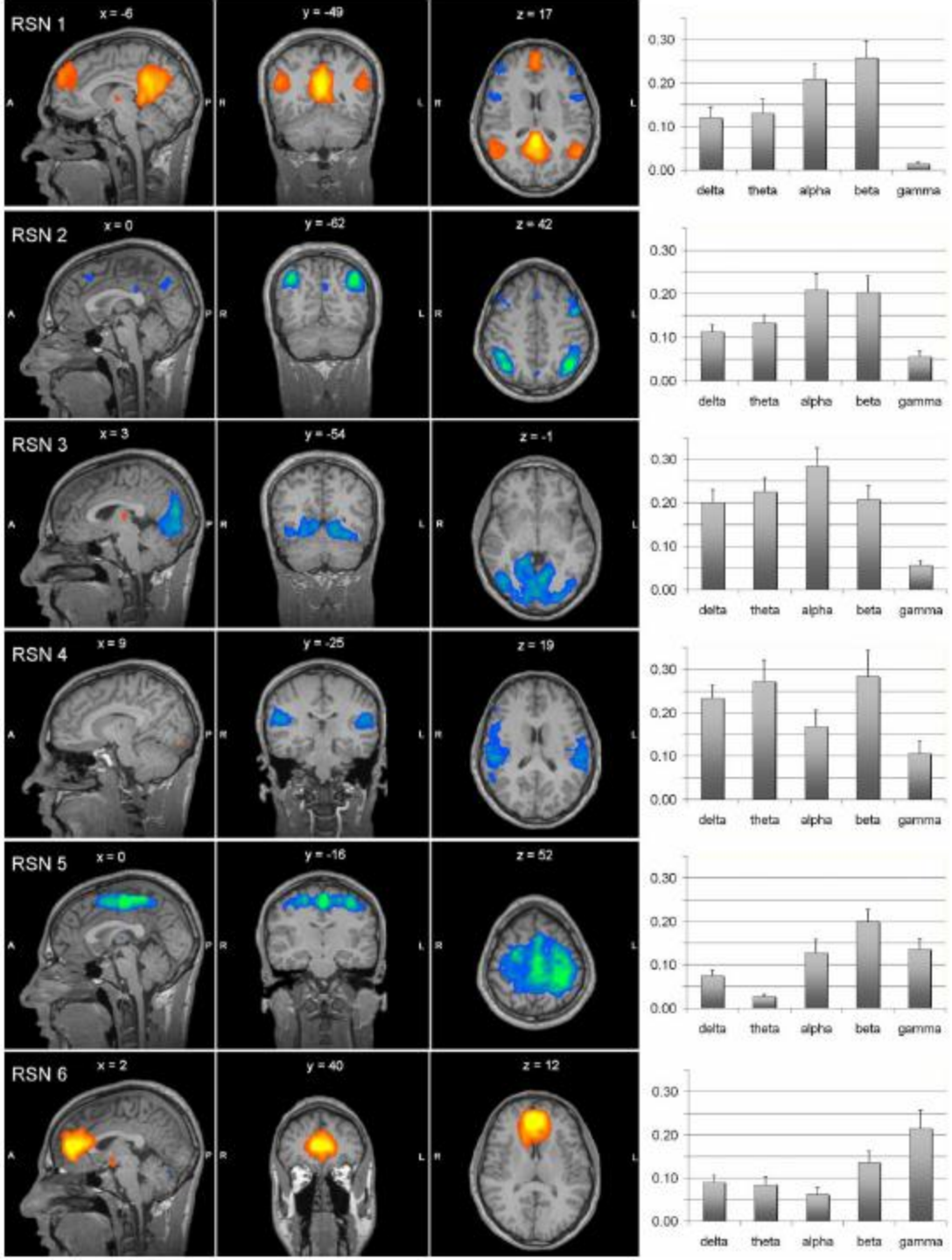
Recent review: Fox & Raichle 2007

Example for the appearance of the default mode network as negative activation in fMRI with a visual stimulation paradigm (Singh et al., 2008):

*"… we demonstrate that this network is **transiently suppressed** in an event-related fashion, reflecting a **true negative activation** compared to baseline… Deactivation across the network varied in an inverse linear relationship with motion coherency, demonstrating that the **strongest suppression occurs for the most error-prone tasks**. .. We also show that the magnitude of task related activation of the individual sub-components of the default-mode network are strongly correlated, indicating a **highly integrated system**."*







Mantini et al. (2007):

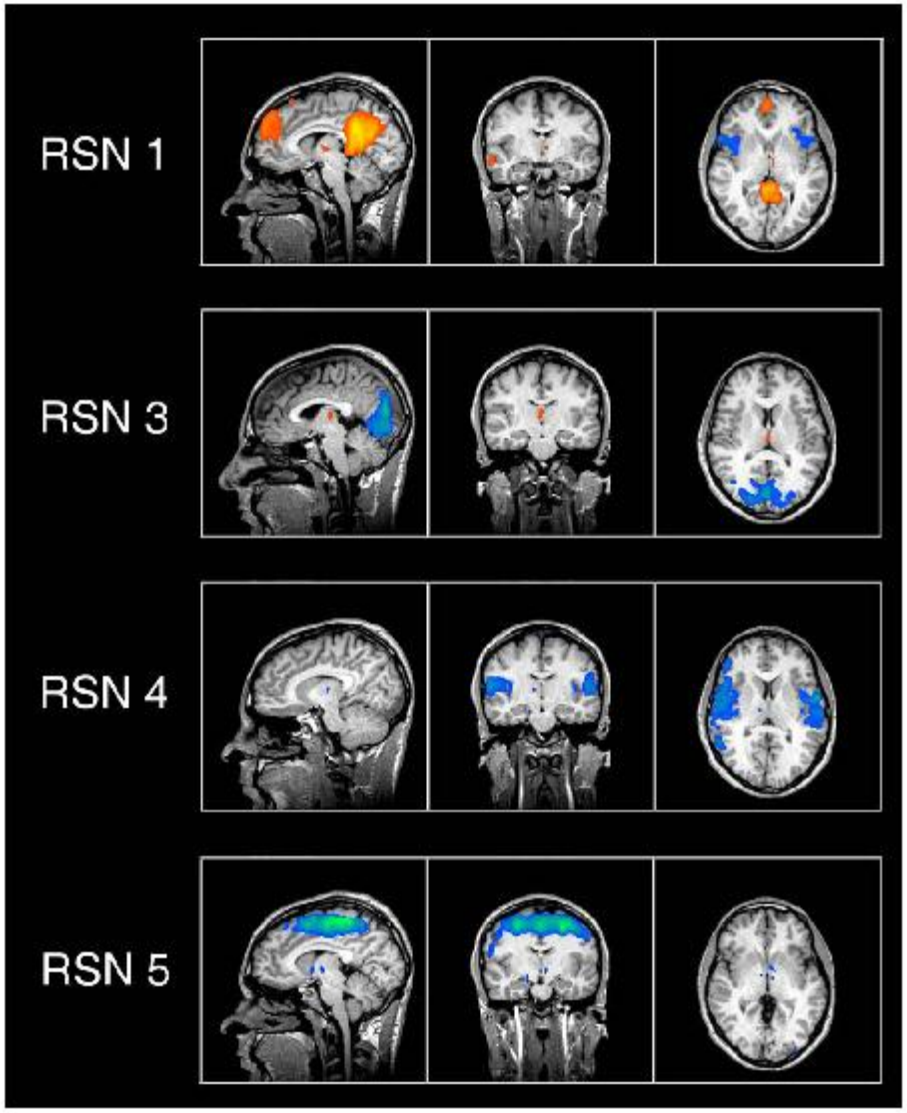
Bar plots of the average correlations between the brain oscillatory activity in the delta, theta, alpha, beta, and gamma bands, and the RSN time courses, selcted from 15 subjects

RSN 1: default mode network, including the posterior cingulate and precuneus, medial prefrontal cortex, dorsal lateral prefrontal cortex and inferior parietal cortex.
RSN 2: dorsal attention network, including the intraparietal sulci, areas at the intersection of precentral and superior frontal sulcus, ventral precentral, and middle frontal gyrus.
RSN 3: visual processing network, including the retinotopic occipital cortex and the temporal-occipital regions.
RSN 4: auditory-phonological network, the superior temporal cortices.
RSN 5: sensory-motor network, including the precentral, postcentral, and medial frontal gyri, the primary sensory-motor cortices, and the supplementary motor area.
RSN 6: self-referential network, including the medial-ventral prefrontal cortex, the pregenual anterior cingulate, the hypothalamus, and the cerebellum.

Damoiseaux et al. 2006 found 10 distinct patterns,
De Luca et al. 2006 found 5 patterns,
Esposito et al. 2005 found 6 patterns,

I found 6 patterns

Thalamo-cortical connectivity for RSNs 1, 3, 4, and 5, showing the participation of the thalamus in the modulation of resting cerebral fluctuations.

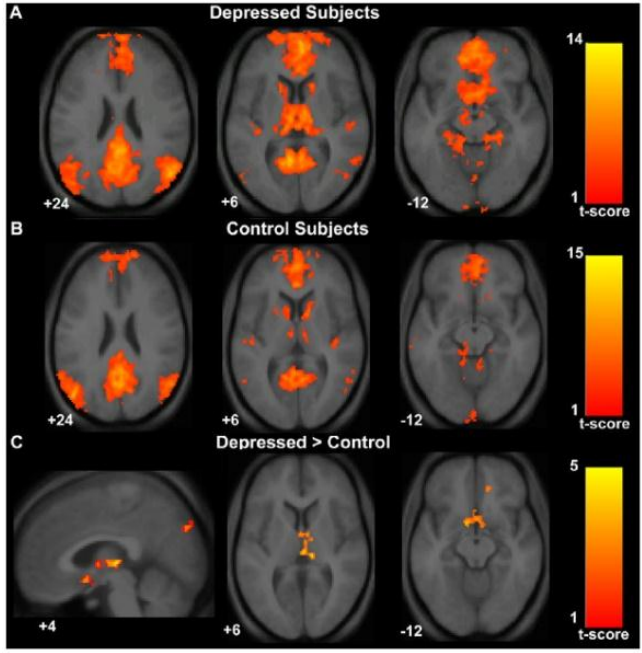


Zhang et al., J Neurophysiol 100:1740-1748, 2008

Clinical applications

AD (Greicius et al. 2004): Decrease
AD (Rombouts et al. 2007): Decrease
AD (Sorg et al. 2007): Decrease
AD (Wang et al. 2007): Decrease + increase

Depression (Greicius et al. 2007): Increase

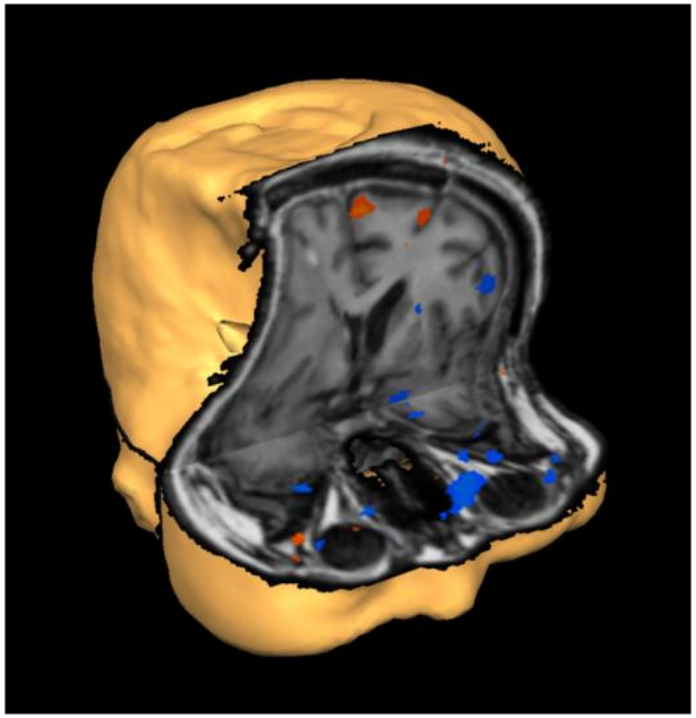


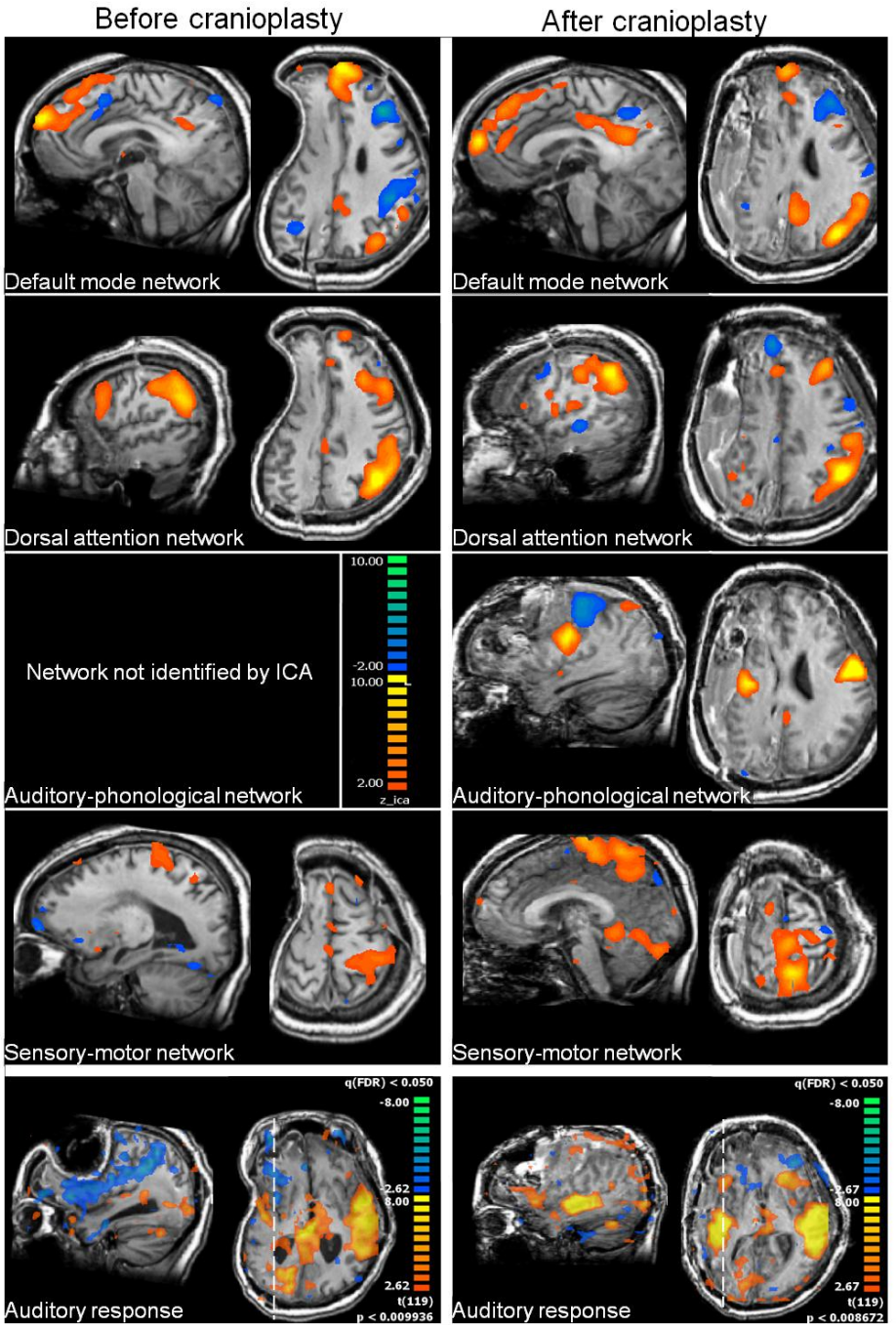
Schizophrenia (Liu et al. 2008): Network disruptions

ADHD (Wang et al., 2007): Altered “small world network” structure
ADHD (Zhu et al. 2008): Thalamus involvement

The aging brain (Andrews-Hanna et al., 2007): Disruption of large-scale brain systems
The aging brain (Wu et al., 2007): Disruption of (motor) network

Epilepsy (Waites et al., 2006): Disruption
Epilepsy (Laufs et al., 2007): Decrease + increase

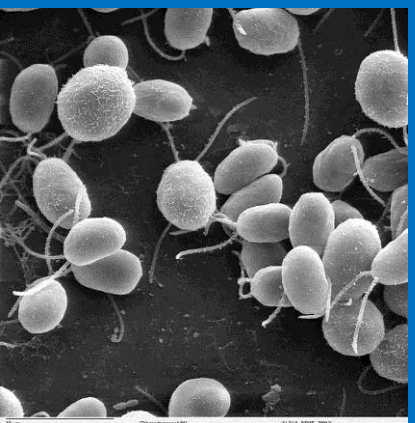



Before cranioplasty
After cranioplasty
Default mode network
Default mode network
Dorsal attention network
Dorsal attention network
Network not identified by ICA
10.00
-2.00
10.00
2.00
z_ica
Auditory-phonological network
Auditory-phonological network
Sensory-motor network
Sensory-motor network
q(FDR) < 0.050
-8.00
2.62
8.00
2.62
t(119)
p < 0.009936
Auditory response
q(FDR) < 0.050
-8.00
2.67
8.00
2.67
t(119)
p < 0.008672
Auditory response

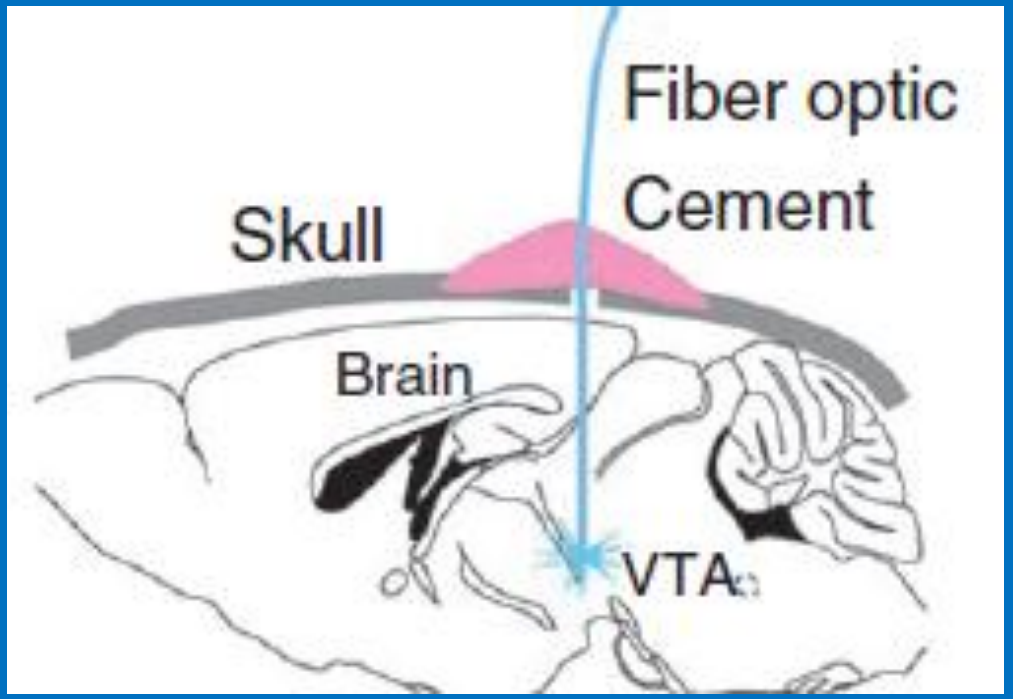
Optogenetic functional MRI

Optogenetics: The combination of genetic and optical methods to control specific events in targeted cells of living tissue, even within freely moving animals, with the temporal needed to keep pace with functioning intact biological systems. Method of the Year 2010 across all fields of science and engineering by Nature Methods.

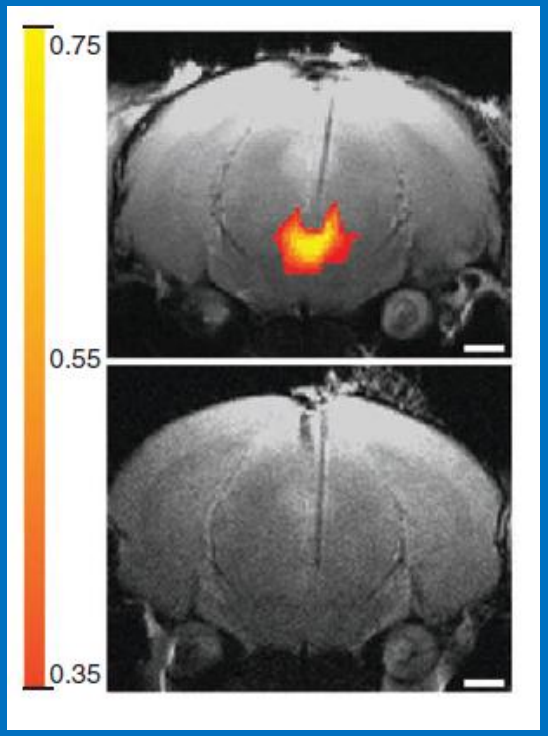
Channelrhodopsins are a subfamily of opsin proteins that function as light-gated ion channels.

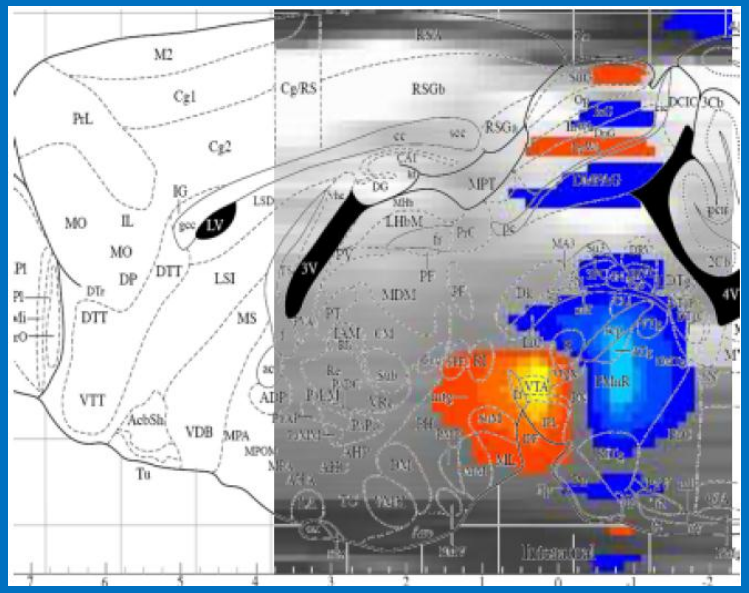


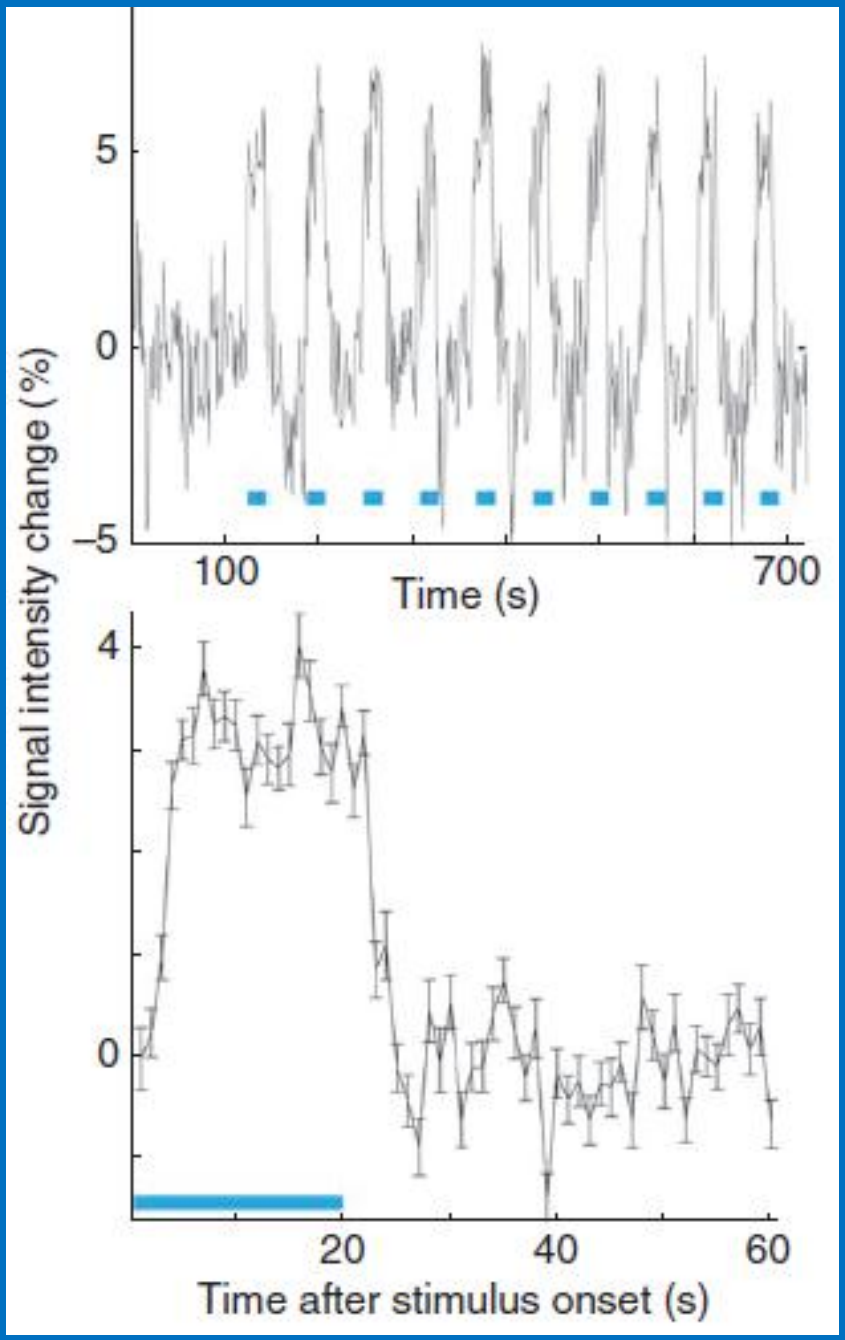
Chlamydomonas reinhardtii

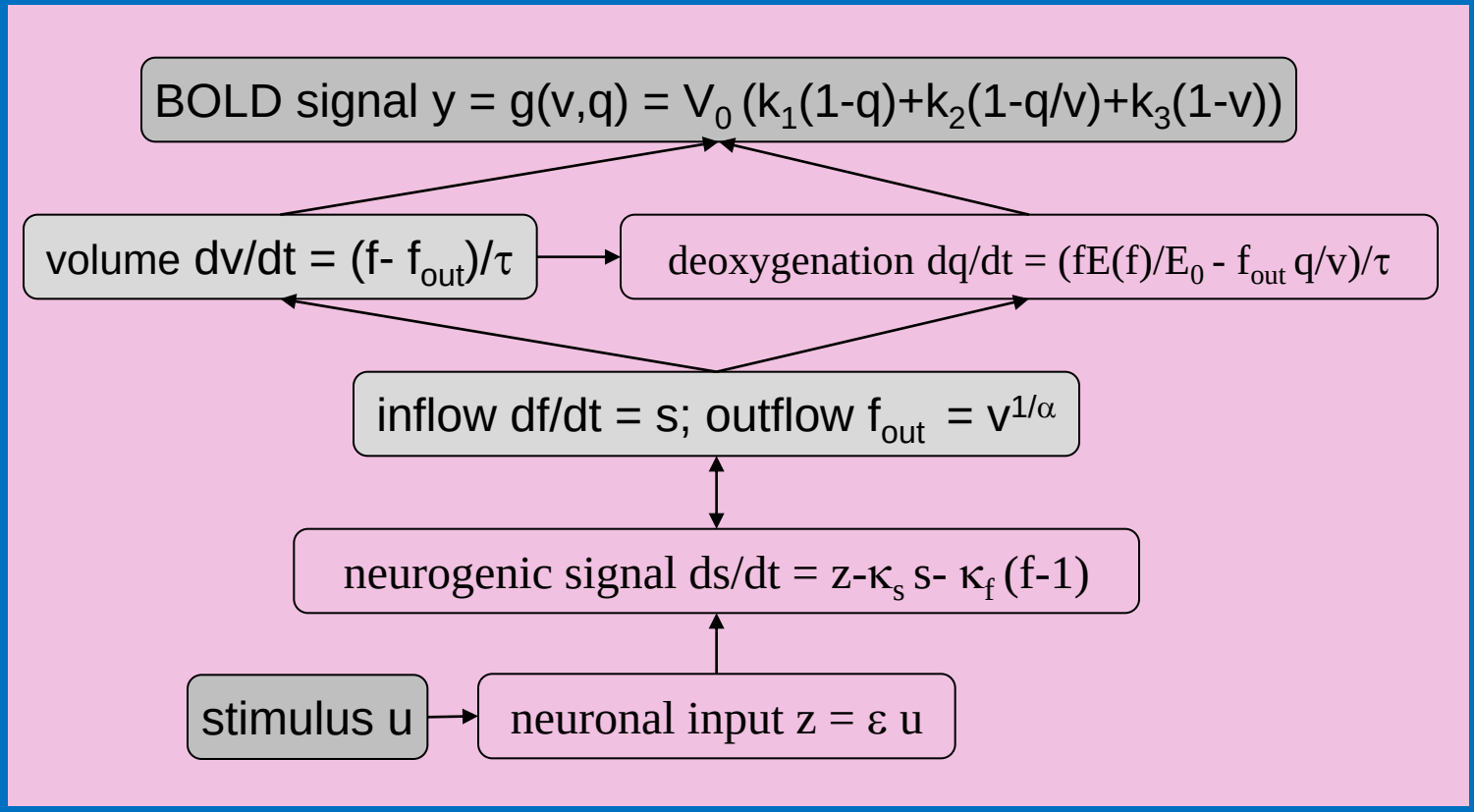


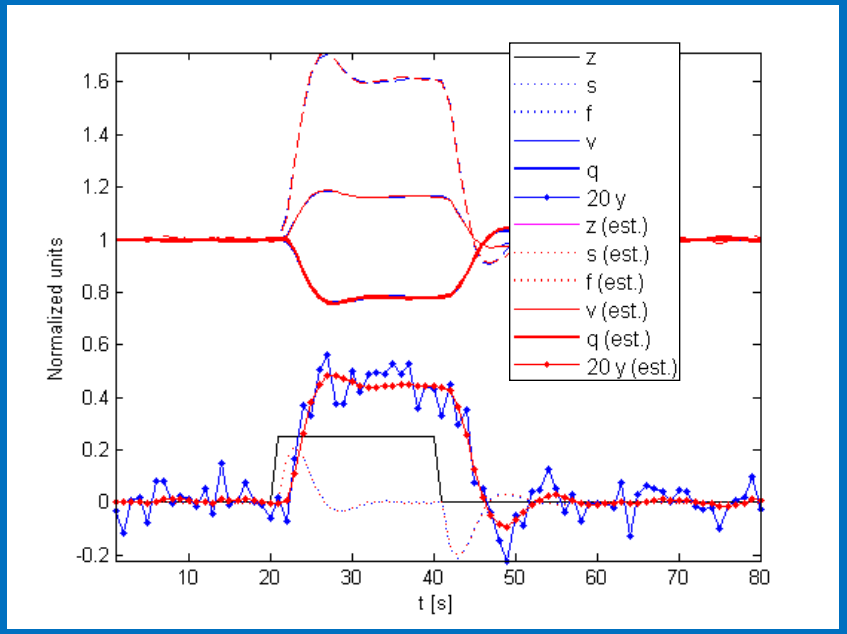
Domingos et al., Nature Neuroscience, in press.

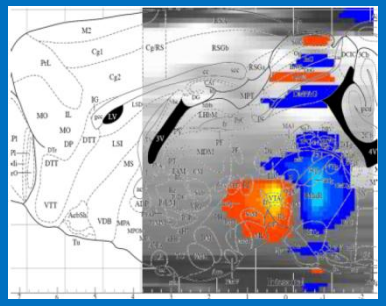

0.75
0.55
0.35

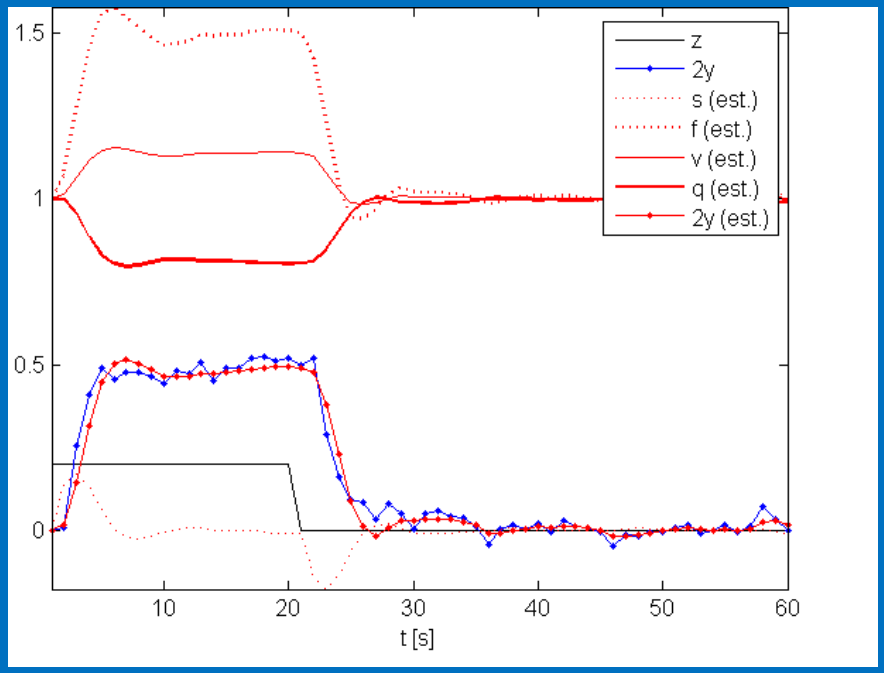

M2
Cg1
PrL
Cg2
IG
LSD
LV
MO
IL
MO
DP
DTT
LSI
DTT
MS
VTT
AcbSh
VDB
MPA
Tu
Cg/RS
RSGb
RSGa
MPT
LHbM
3V
MDM
PF
VTA
PMnR
4V

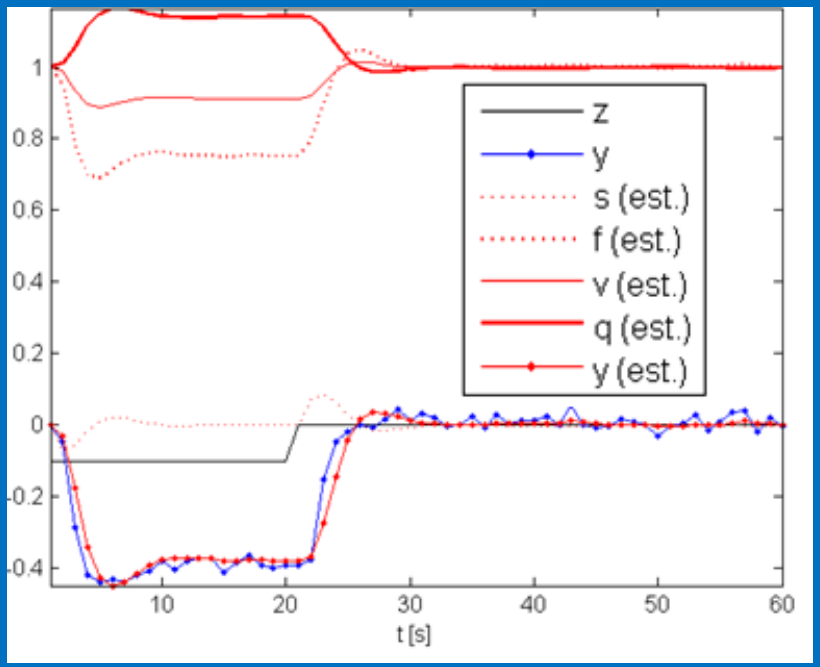

Signal intensity change (%)
5
0
−5
100
Time (s)
700
4
0
20
40
60
Time after stimulus onset (s)


BOLD signal y = g(v,q) = V0 (k1(1-q)+k2(1-q/v)+k3(1-v))
volume dv/dt = (f- fout)/τ
deoxygenation dq/dt = (fE(f)/E0 - fout q/v)/τ
inflow df/dt = s; outflow fout = v1/α
neurogenic signal ds/dt = z-κs s- κf (f-1)
stimulus u
neuronal input z = ε u


z
s
f
v
q
20 y
z (est.)
s (est.)
f (est.)
v (est.)
q (est.)
20 y (est.)
Normalized units
t [s]




z
2y
s (est.)
f (est.)
v (est.)
q (est.)
2y (est.)
t [s]


z
y
s (est.)
f (est.)
v (est.)
q (est.)
y (est.)
t [s]

Mathematical/statistical problems

- How to reduce # of measurements?
- Modeling partial voluming
- How to disentangle fiber density, diameter, myelination, etc?
- Can one learn more about microscopic tissue properties from ODF?