Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

BIOMEDICAL IMAGING

(Orvosbiológiai képalkotás)

Recent Advances in Magnetic Resonance Imaging

(Legújabb trendek a mágneses rezonancia képalkotásban)

LAJOS R. KOZÁK, VIKTOR GÁL

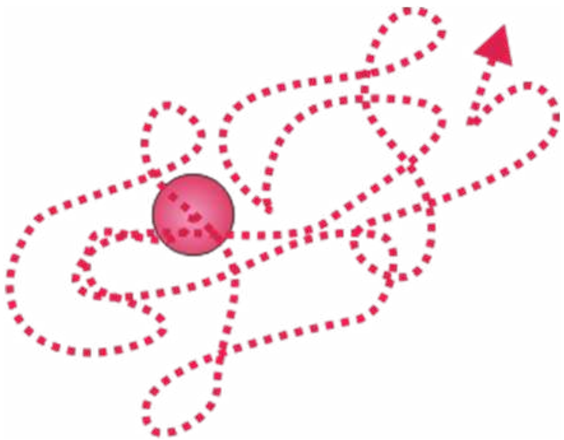
Diffusion Tensor Imaging (DTI)

Diffusion Weighted Imaging (DWI)

Diffusion

The water molecules are in constant motion

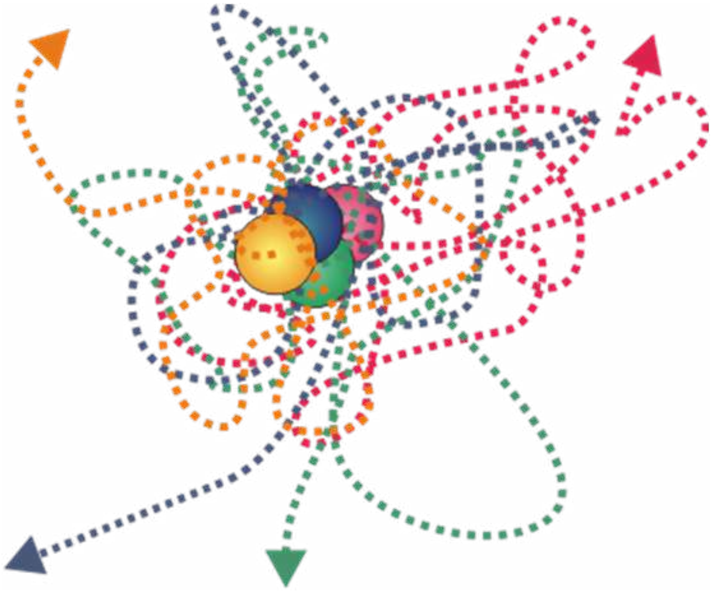
- Random rotations by thermal motions
  - Leading to local magnetic field variations and thus
  - T2 effects
- Random displacements or diffusion
  - Random walk or Brownian motion
  - In a sufficiently big compartment the probability of moving in a given direction is equal across directions (isotropy)



Diffusion

Due to the complete randomness of motion, a group of molecules starting from roughly the same location spread out over time

- The variance of the spread over time along a given spatial axis $\sigma^2 = 2DT$ is where D is the diffusion coefficient
- As they are equally likely to move in any direction, the mean displacement of the molecules is 0
- Diffusion is a local effect, the displacement is present over short distances

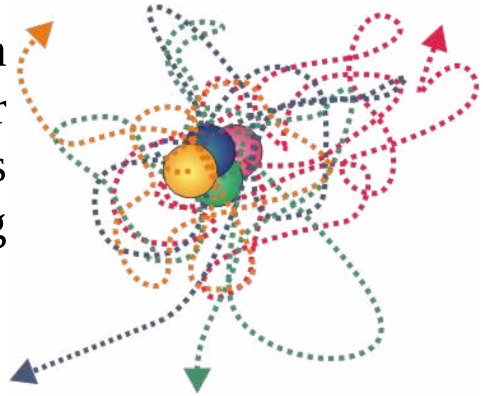


Diffusion anisotropy

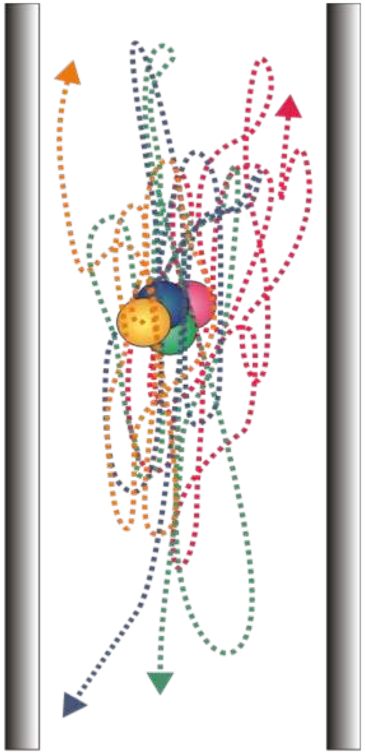
If molecular motion is limited by non-permeable walls, the pattern of diffusion becomes anisotropic, i.e. there is a higher probability of diffusion along directions parallel with the boundaries than along directions perpendicular to them.

Diffusion in the cerebral **gray matter** is **isotropic**.

Diffusion in the cerebral **white matter** is **anisotropic**.



Isotropic diffusion

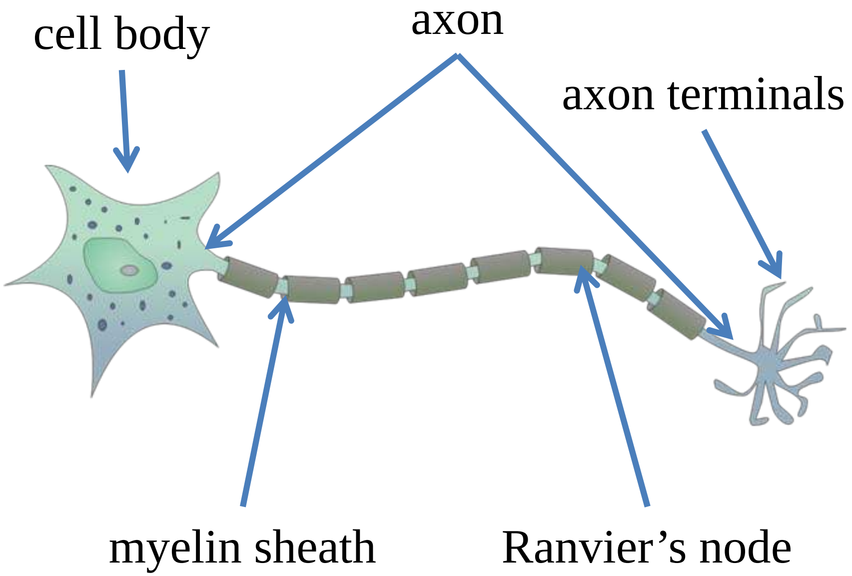


Anisotropic diffusion

Diffusion anisotropy in the human brain

The axons of neurons are surrounded by a myelin sheath

- extended and modified plasma membrane of Schwann cells wrapped around the axon in a spiral fashion
- protects the axons
- facilitates signal transduction
- impermeable to water

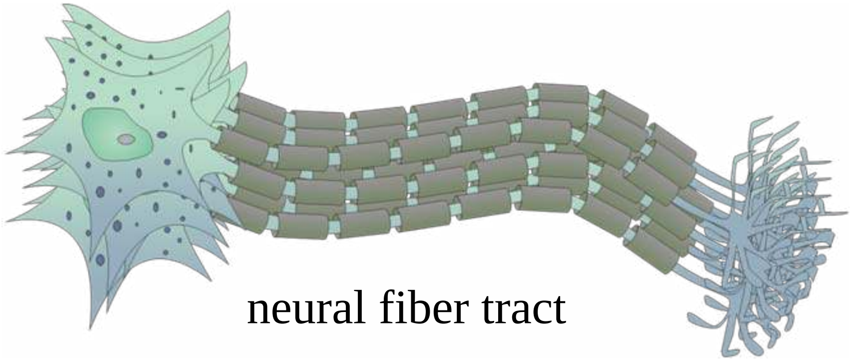


Diffusion anisotropy in the human brain

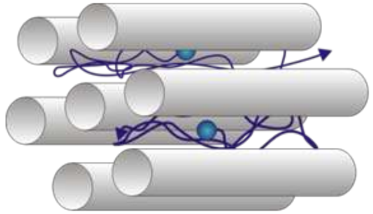
Bundled axons limit the diffusion of water along the axonal axis.

There are 3 main types of axonal bundles found in the white matter of the human brain

- **Commissural bundles** provide connection between the hemispheres
- **Association bundles** provide longitudinal connections within hemispheres
- **Projection bundles** provide connections to the peripheral nervous system

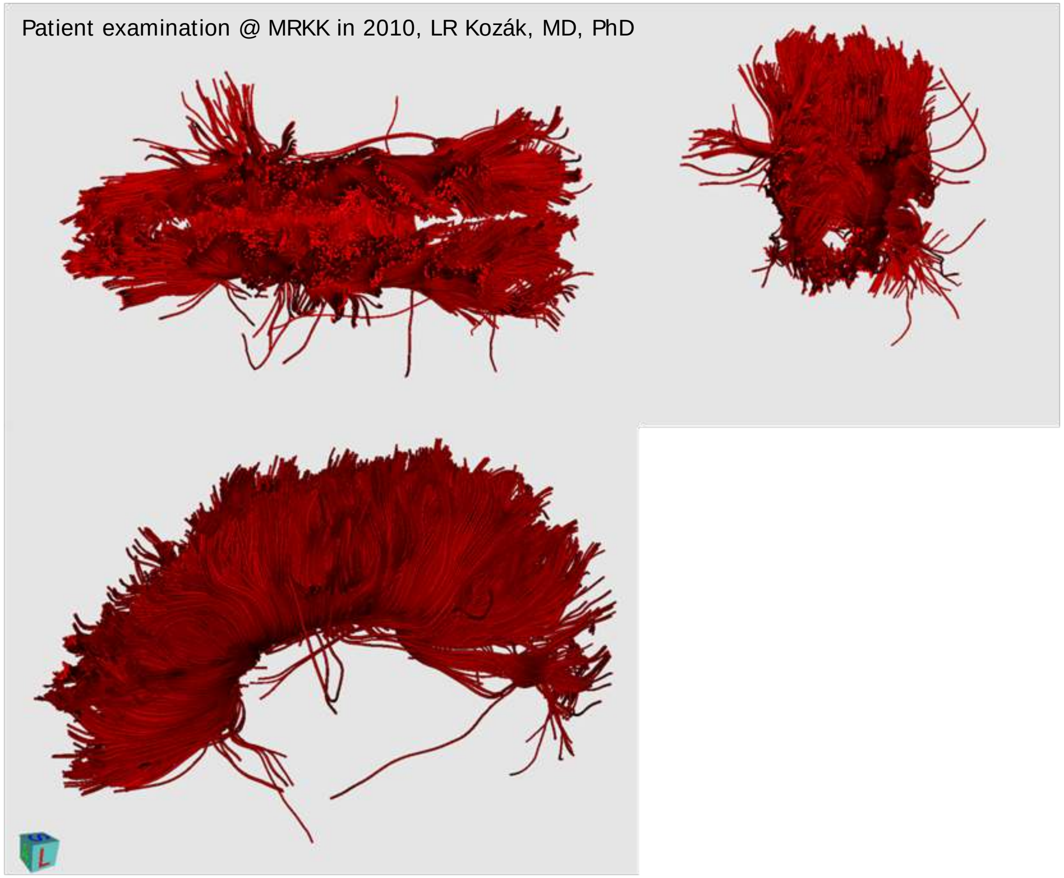


neural fiber tract



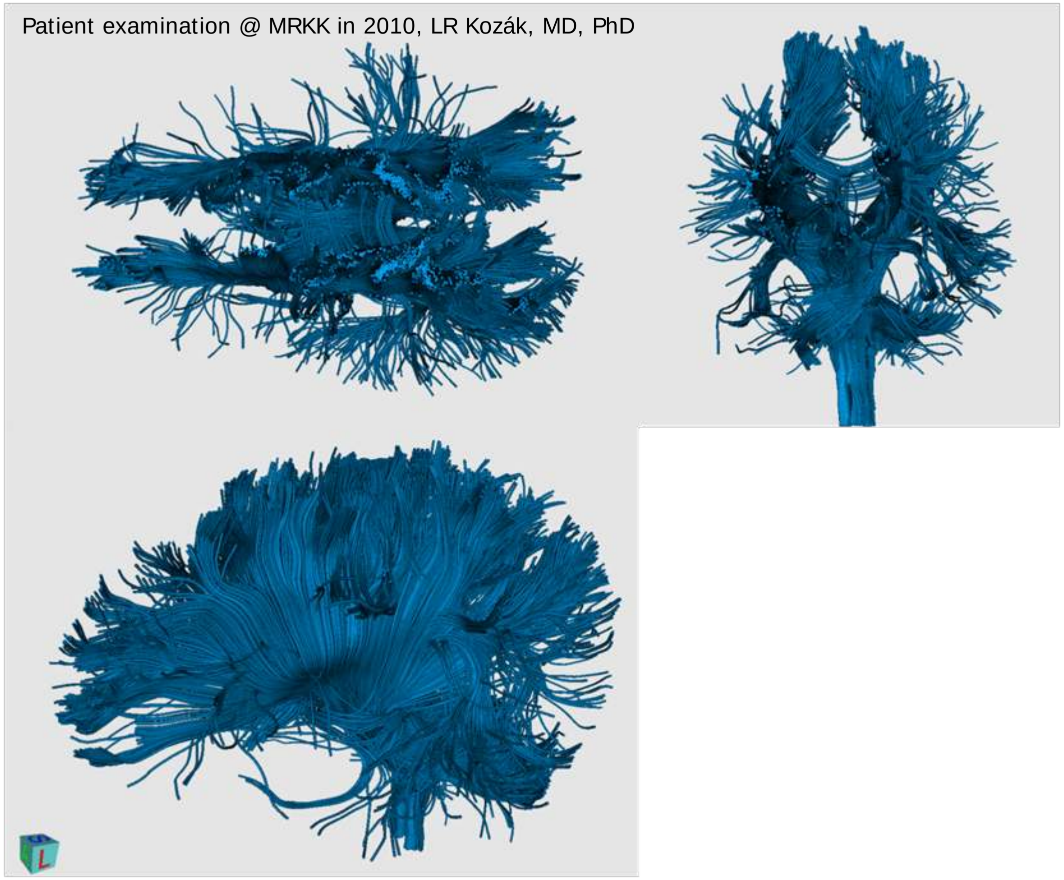
diffusion along axons in a neural fiber tract

Diffusion anisotropy in the human brain



Commissural bundles

Diffusion anisotropy in the human brain

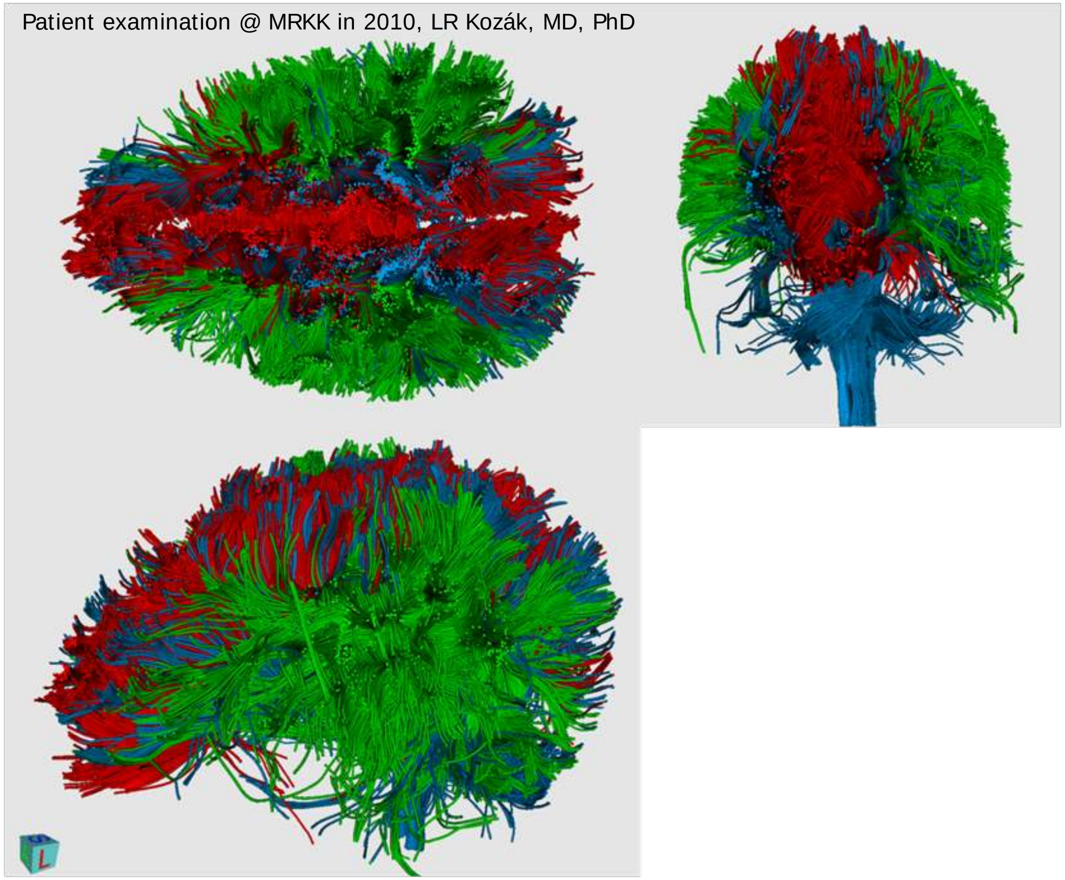


Projection bundles

Diffusion anisotropy in the human brain

Association bundles

Diffusion anisotropy in the human brain



Commissural bundles

Projection bundles

Association bundles

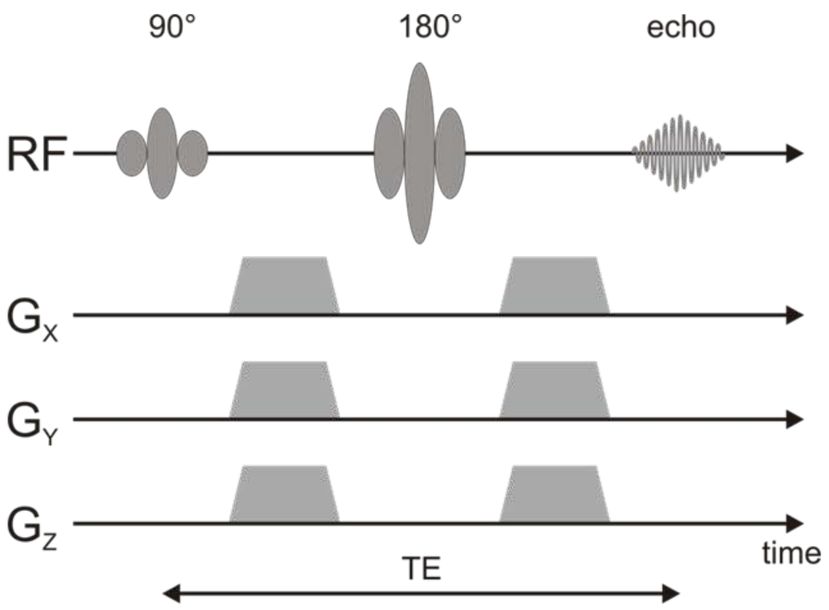
Diffusion weighted MRI (DWI)

Uses a spin-echo pulse sequence with two additional gradients applied during the sequence

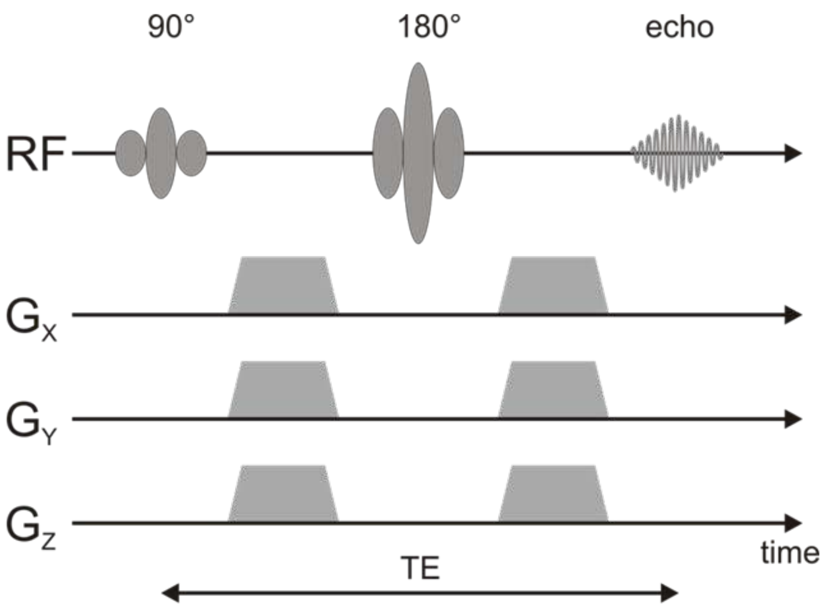
Pulsed-Gradient Spin Echo (PGSE)

EO Stejskal, JE Tanner: *Spin Diffusion Measurements: Spin Echoes in the Presence of a Time-dependent Field Gradient*, J Chem Phys, 42:288-292, 1965

- First gradient disrupts the magnetic phases of all protons
- Second gradient restores the phases of **stationary** protons



Diffusion weighted MRI (DWI) cont'd



- But the second gradient does not completely re-phase the spins
- The restoration of signal is incomplete for protons that have moved (diffused) during the elapsed time

This sequence is very sensitive to bulk head movement, as well

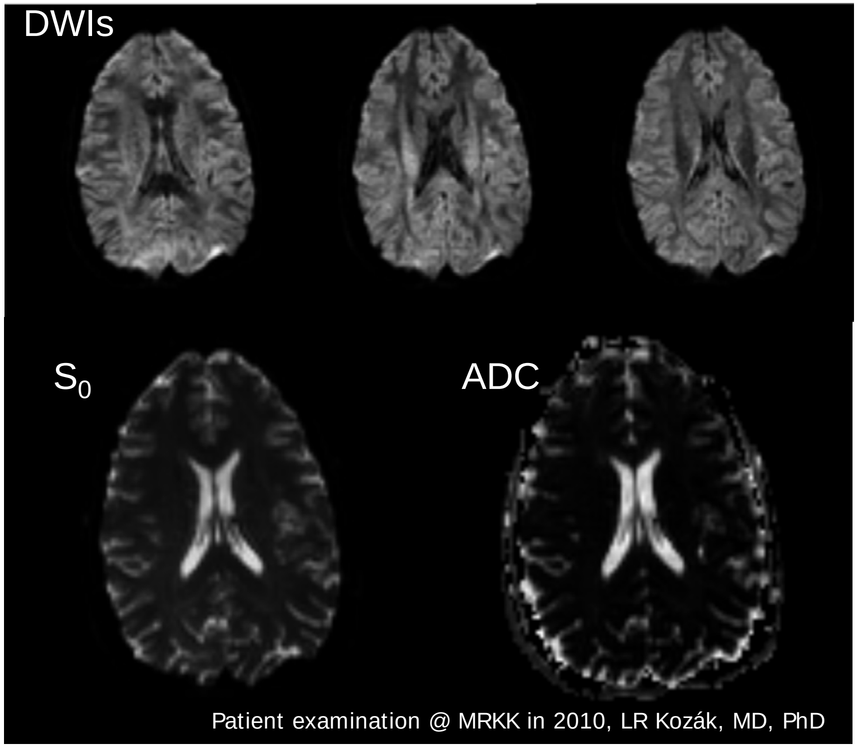
- Diffusion in each voxel can be calculated from the signal decay knowing the acquisition parameter **b**

$$D = \frac{1}{b}\ln\left(S_o / S \right)$$

Diffusion weighted MRI (DWI) cont'd

- On the example DWIs (diffusion sensitive gradients applied in three directions all with the same b-value) dark areas represent areas with high degree of diffusion

- Using a single b=0 reference image, i.e. an image without diffusion weighting (S_0)
- D can be calculated voxelwise, and presented as an apparent diffusion coefficient (ADC) image

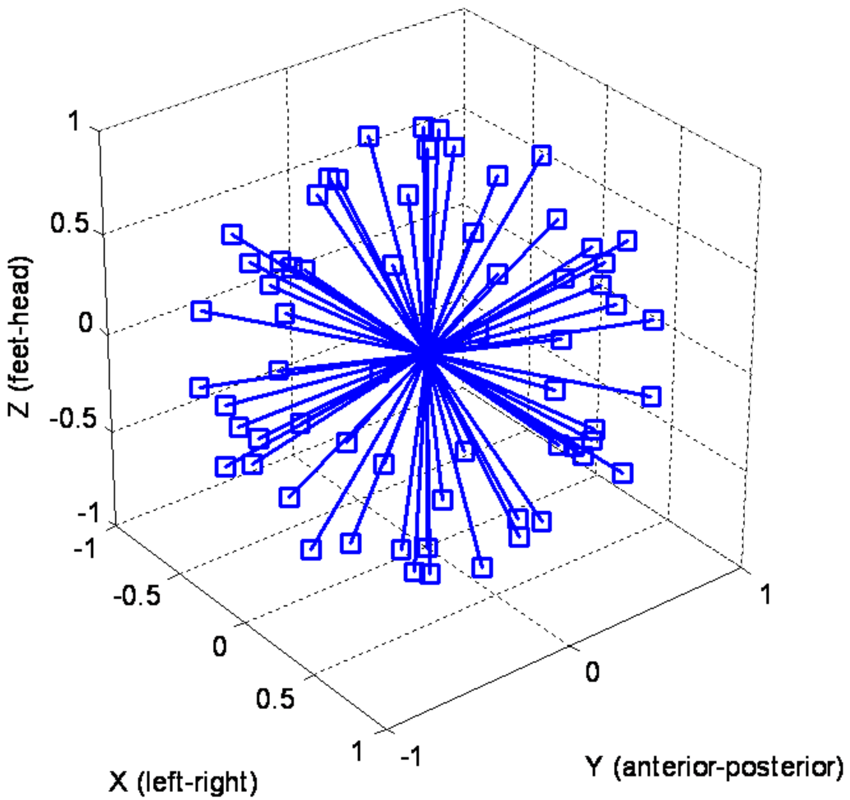


Diffusion weighted MRI (DWI) cont’d

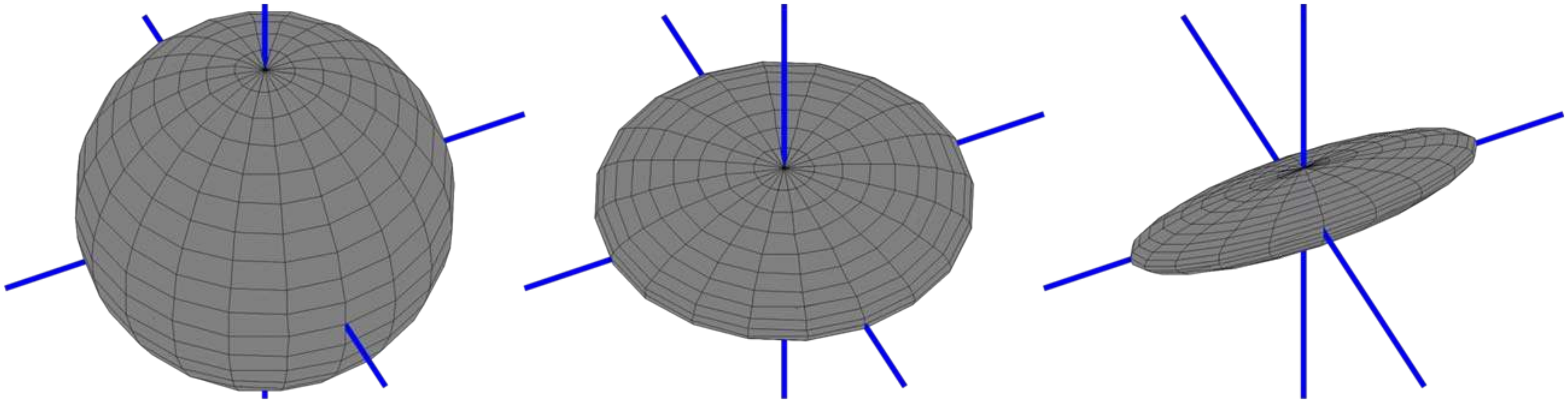
As gradients encode directions in the magnet, diffusion can be measured in arbitrary directions.

This flexibility provides a means for describing neural tract orientations by measuring diffusion anisotropy.

The 32 diffusion direction vectors of the standard high resolution DTI sequence used at the Semmelweis University MR Research Center (MRKK) is visible on the right.



Types of diffusion anisotropy

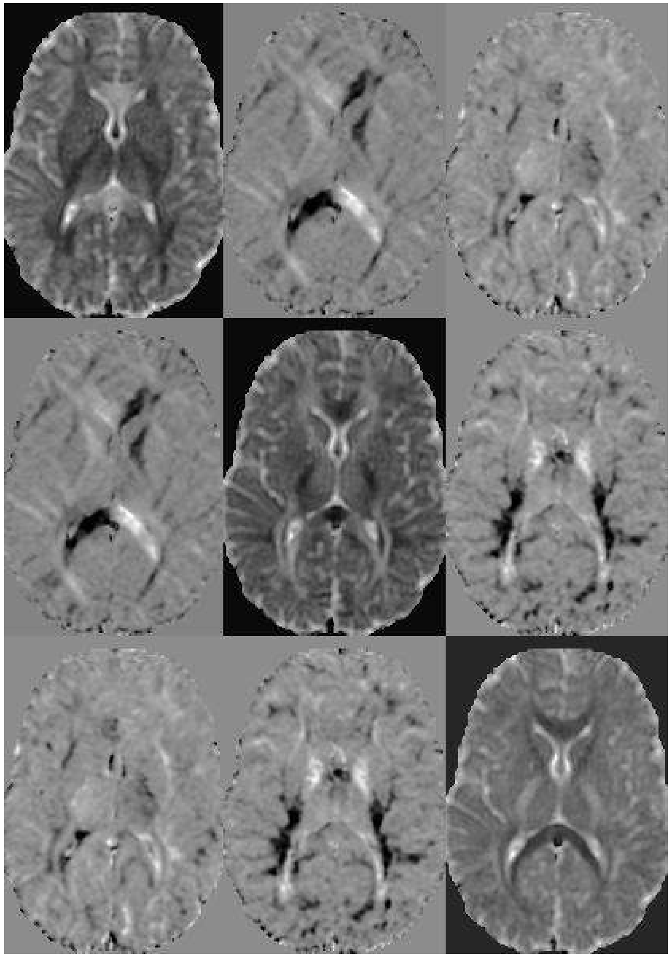


isotropic planar linear

The diffusion tensor

- Diffusive properties can be described with a 3 X 3 symmetric tensor matrix

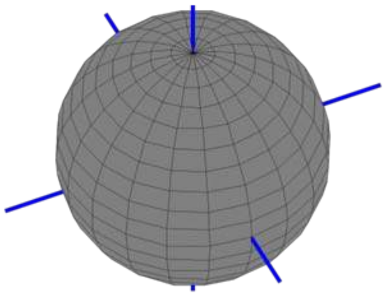
$$D = \begin{bmatrix} D_{XX} & D_{XY} & D_{XZ} \\ D_{YX} & D_{YY} & D_{YZ} \\ D_{ZX} & D_{ZY} & D_{ZZ} \end{bmatrix}$$



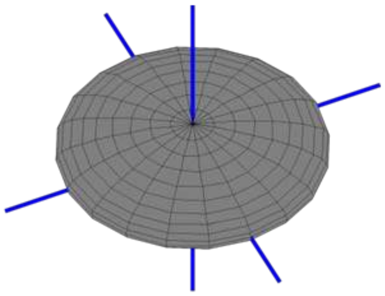
Fractional anisotropy (FA)

$$FA = \sqrt{\frac{(\lambda_X - \lambda_Y)^2 + (\lambda_X - \lambda_Z)^2 + (\lambda_Y - \lambda_Z)^2}{2\left(\lambda_X{}^2 + \lambda_Y{}^2 + \lambda_Z{}^2\right)}}$$

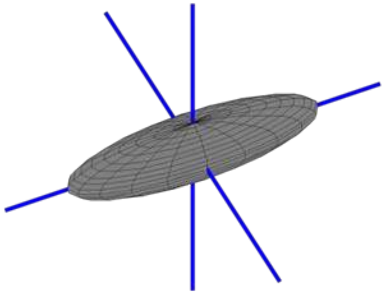
- Direction independent measure of anisotropy
- FA maps can be color coded according to the direction of highest diffusion:
  - **LEFT-RIGHT**
  - **ANTERIOR-POSTERIOR**
  - **FEET-HEAD**



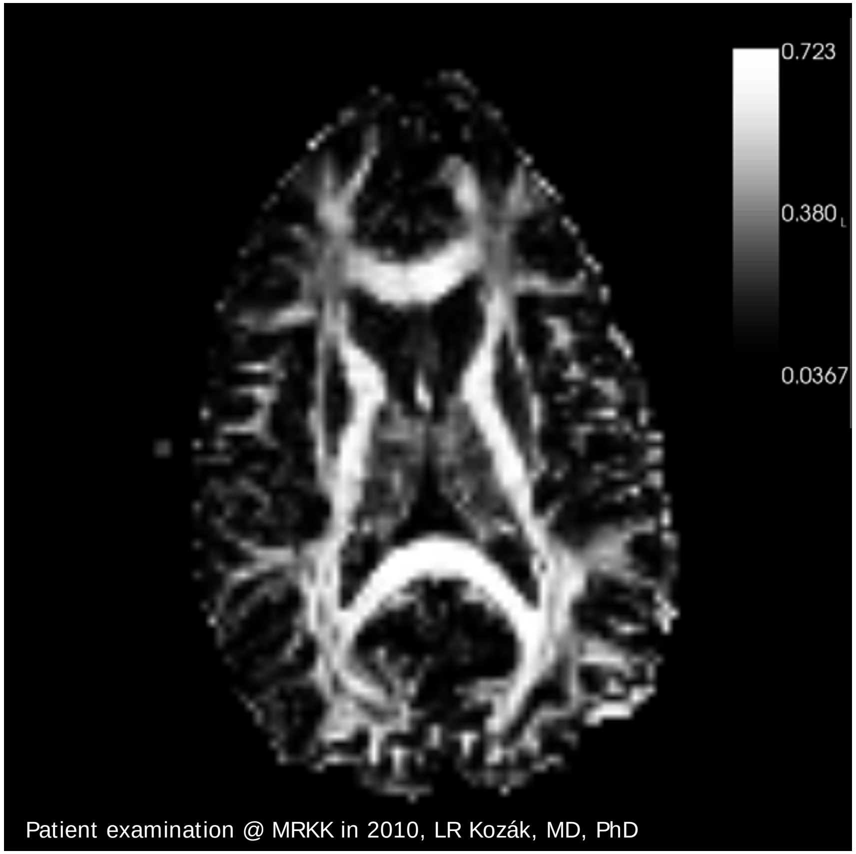
FA=0



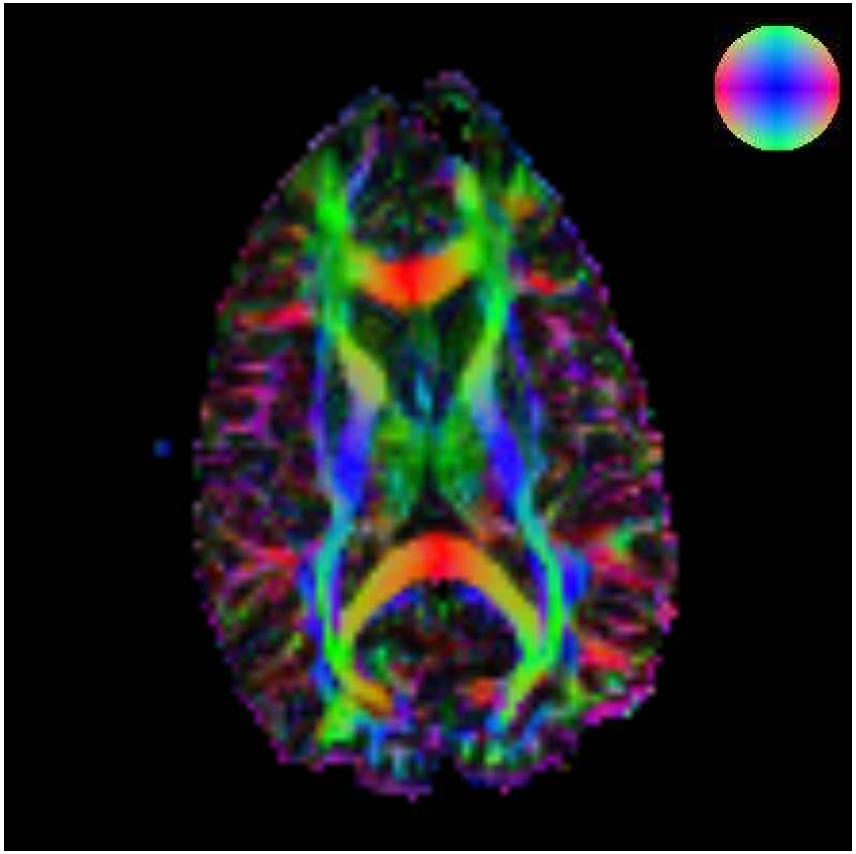
FA=0.52



FA=0.7



FA map

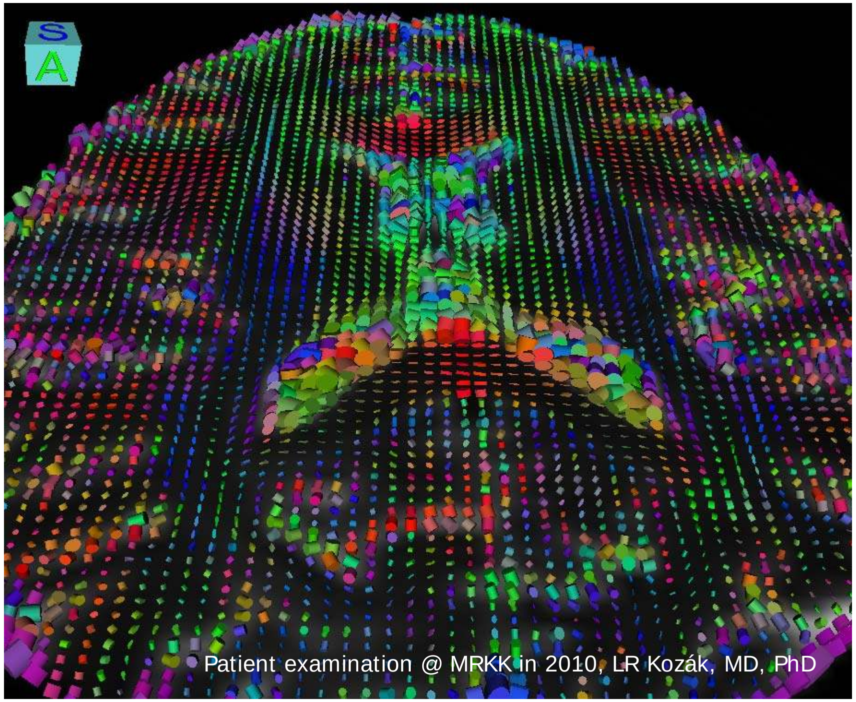


FA map color coded according to the direction of highest diffusion

Diffusion tensor imaging (DTI)

- Diffusion tensors can be calculated and visualized voxelwise

- The primary direction calculated from the tensor can be used as input for tractography



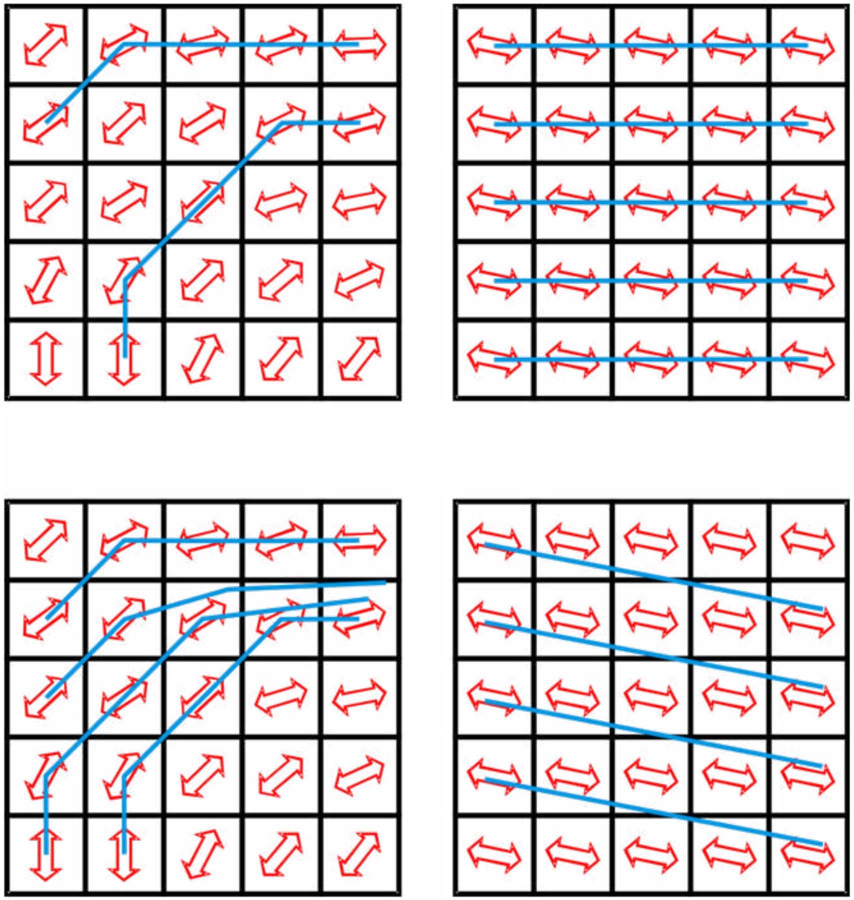
Tractography

Tracts are built from a collection of connected voxels during tractography. During **streamline tractography** neighboring voxels are connected if the tensor in one points towards the other.

DTI voxels are on the scale of 2x2x2 mm, while neuronal fibers are on the scale of microns, therefore tensors provide aggregated information.

Thus connectivity must be modeled

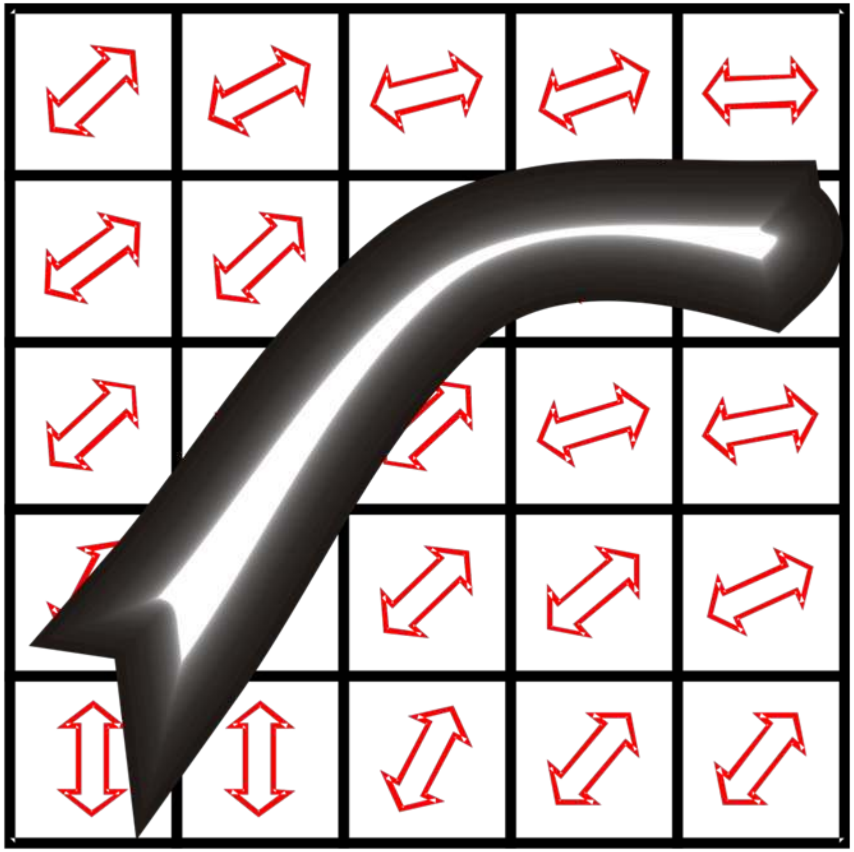
- With a discrete model of tensors (top row) connections or directions can be missed or misinterpreted
- With a continuous model of tensors (bottom row) the results are more realistic.



Tractography

Probabilistic tractography uses a Bayesian approach to estimate the most probable connections

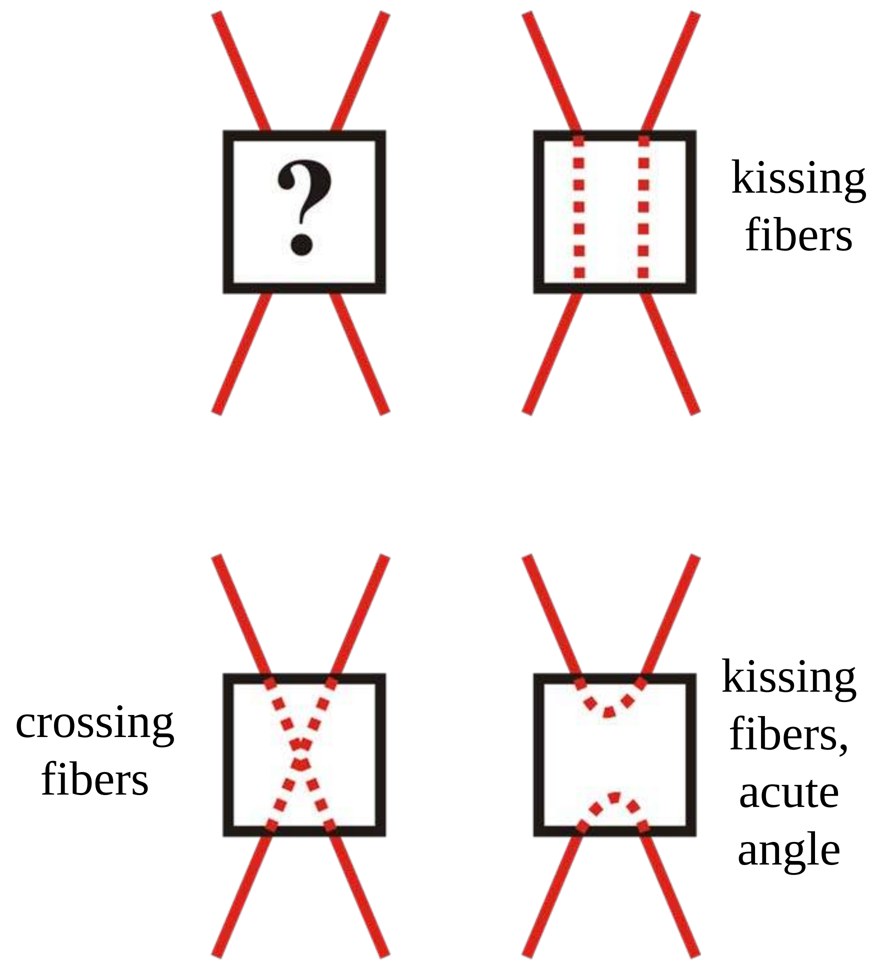
- Time demanding
- Hardware demanding
- Cannot fully solve **crossing fiber** and **kissing fiber** uncertainties
  - Although a priori information helps in some cases



Tractography pitfalls

Due to the low resolution of DTI, especially compared to the size of neural axons, uncertainties arise when:

- fibers cross within a voxel
- fibers come to close vicinity within a voxel (kissing fibers)
- fiber direction changes in an acute angle



Ways to improve DTI

DTI uncertainties can be decreased using special sequences and special post processing methods:

- increasing the number of diffusion directions (HARDI)
  - very time consuming, not appropriate in a clinical setting
  - increased probability of head movement artifacts

Tuch et al., 2002
Descoteaux et al., 2006

- modeling higher order tensors
  - needs HARDI data
  - time consuming
  - computationally intensive
- modeling two (or more) tensors simultaneously
  - Needs HARDI data
  - computationally intensive

Ways to improve DWI/DTI

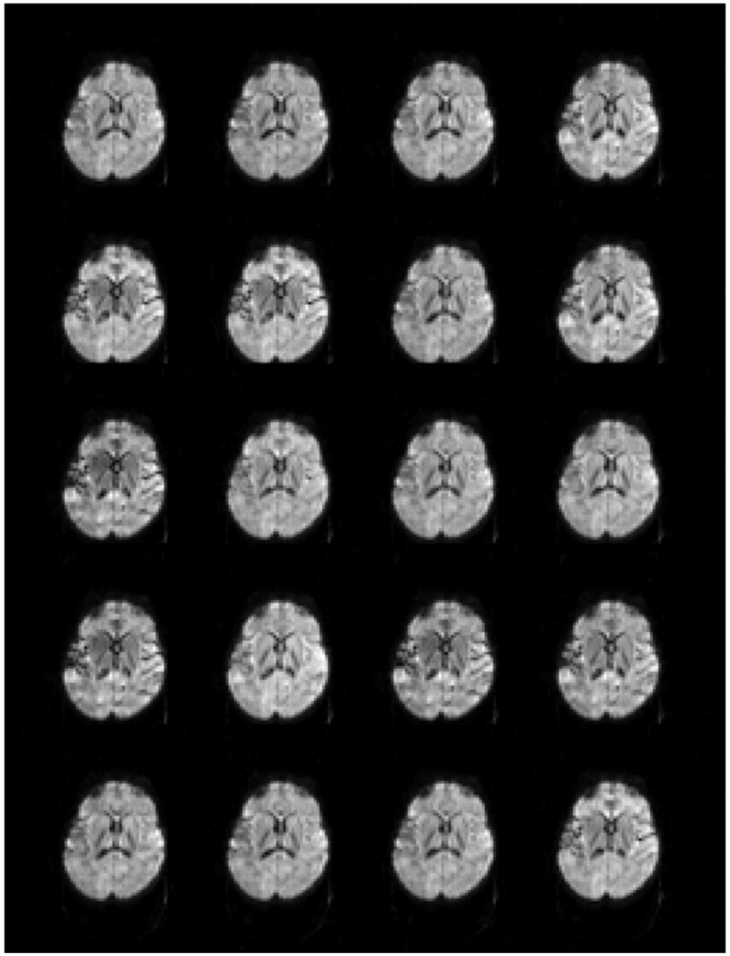
Pulse-triggering improves DWI/DTI image quality

The DWI sequence is very sensitive to tissue motion, but tissue motion is not limited to bulk head movements.

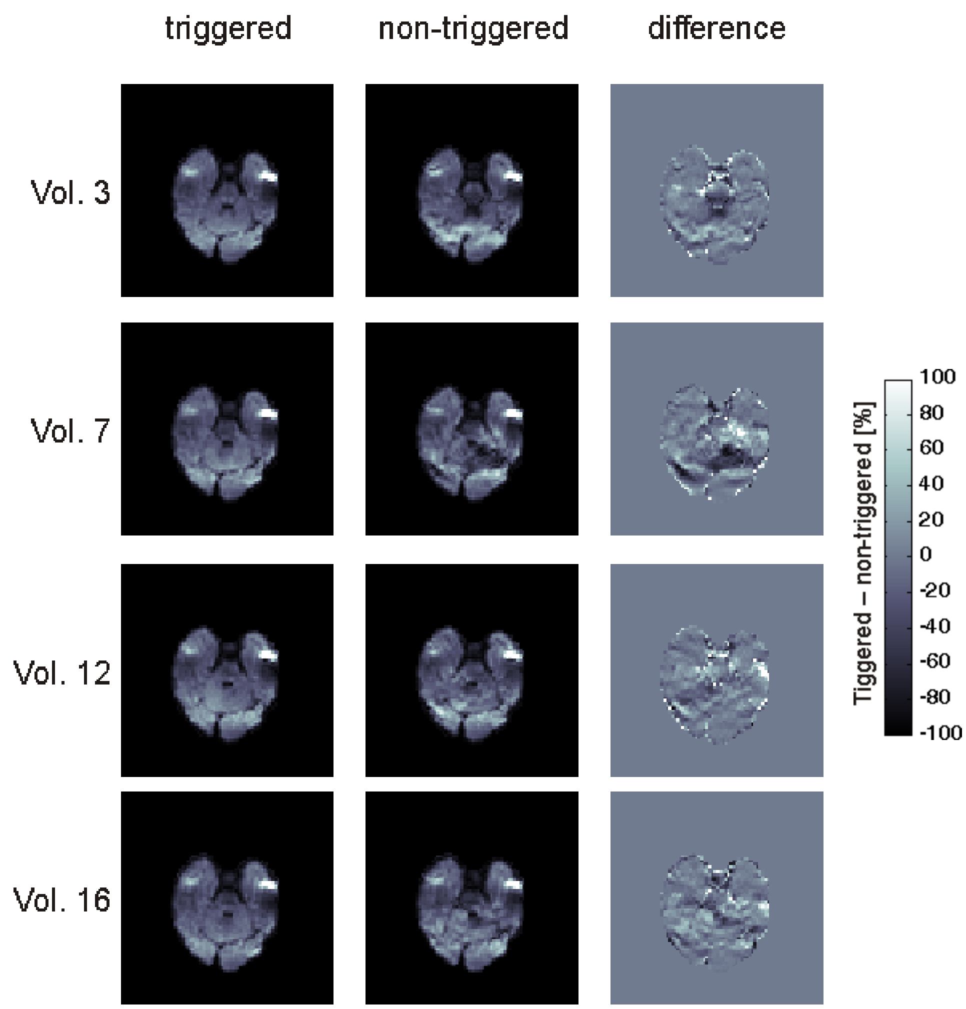
CSF pulsation can also cause movement artifacts, which can be more prominent in the pediatric population.

20 images recorded in the feet-head diffusion direction is shown on the right; the variability in the images is clearly visible.

Kozak et al., ESNR 2010



Ways to improve DWI/DTI



Pulse-triggering improves DWI/DTI image quality

Pulsatile artifacts are often visually identifiable when pulse triggering is not used.

Contrary to what has been shown in adults, the pulsation artifacts can be observed throughout the brain in the pediatric population.

Kozak et al., ESNR 2010

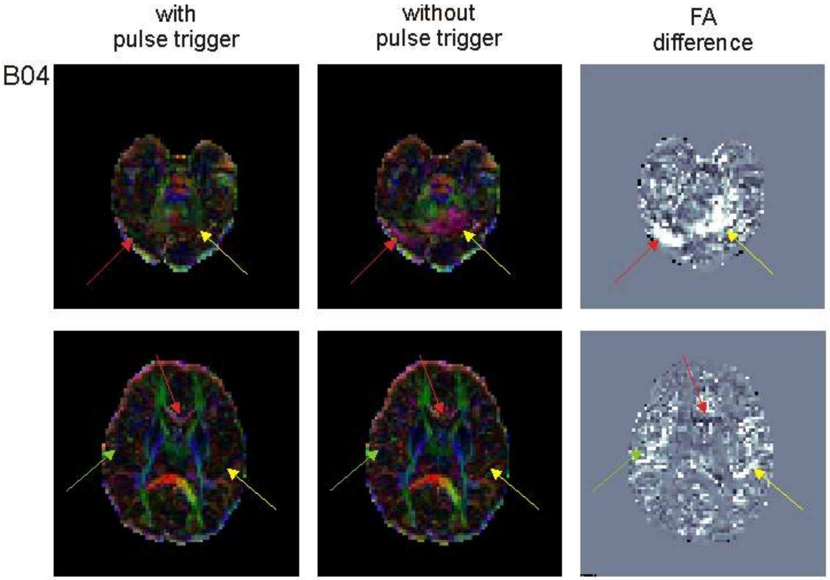
Ways to improve DWI/DTI

Pulse-triggering improves DWI/DTI image quality

These artifacts can strongly influence calculated tensor parameters, such as fractional anisotropy and/or eigenvectors.

Using pulse triggered acquisitions can eliminate pulsatile artifacts.

Pulse triggering is feasible for DWI in infants because it does not increase the acquisition time substantially given the infants' relatively higher heart rate and smaller brain size.



Kozak et al., ESNR 2010

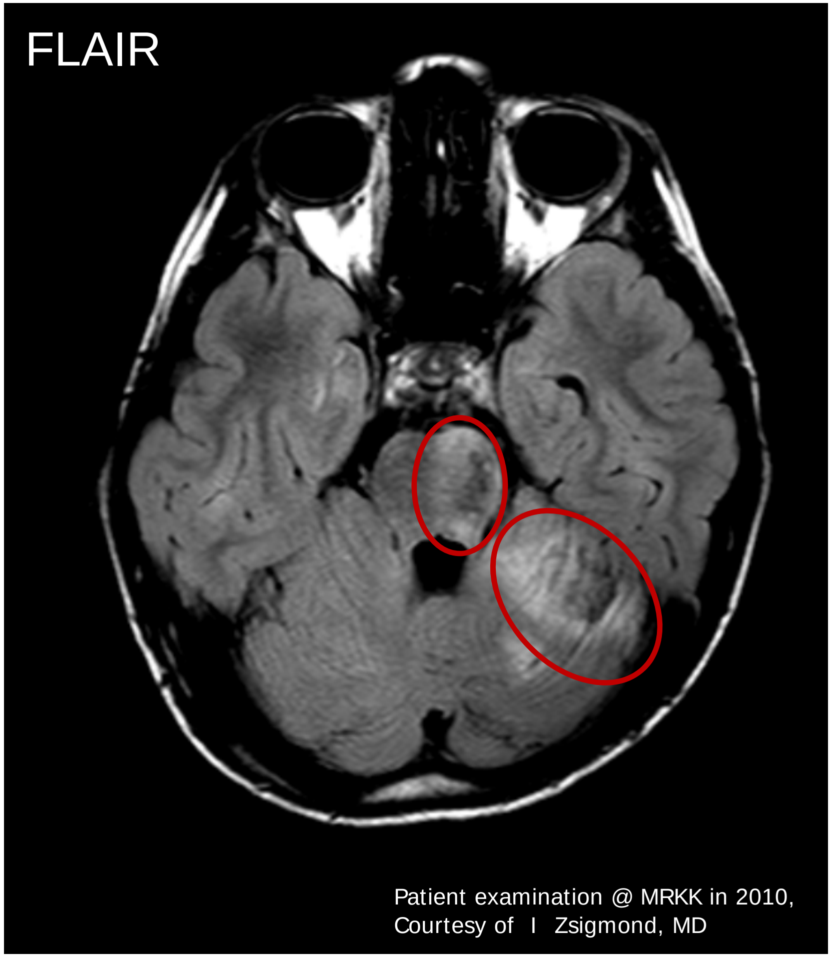
Clinical applications of DWI/DTI

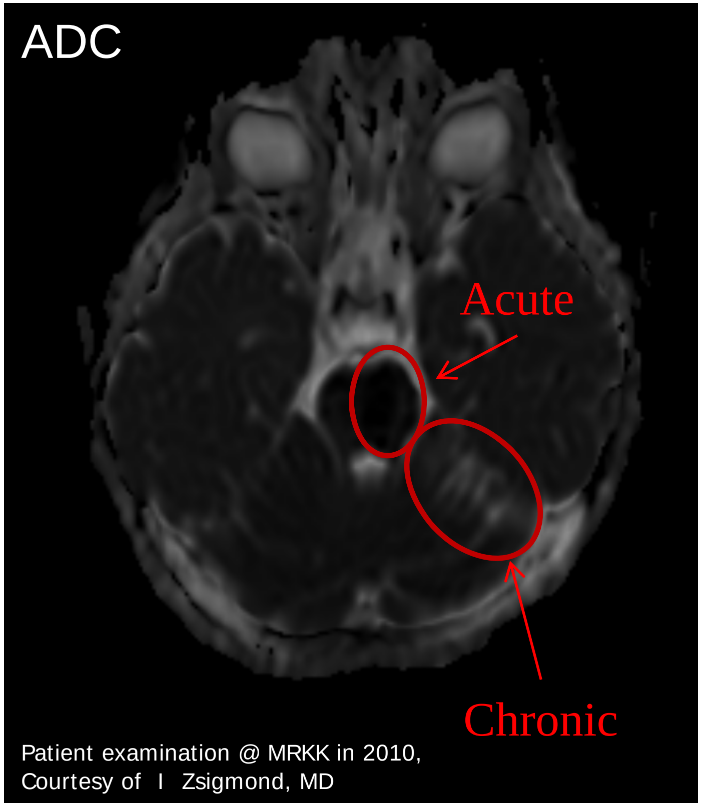
Stroke

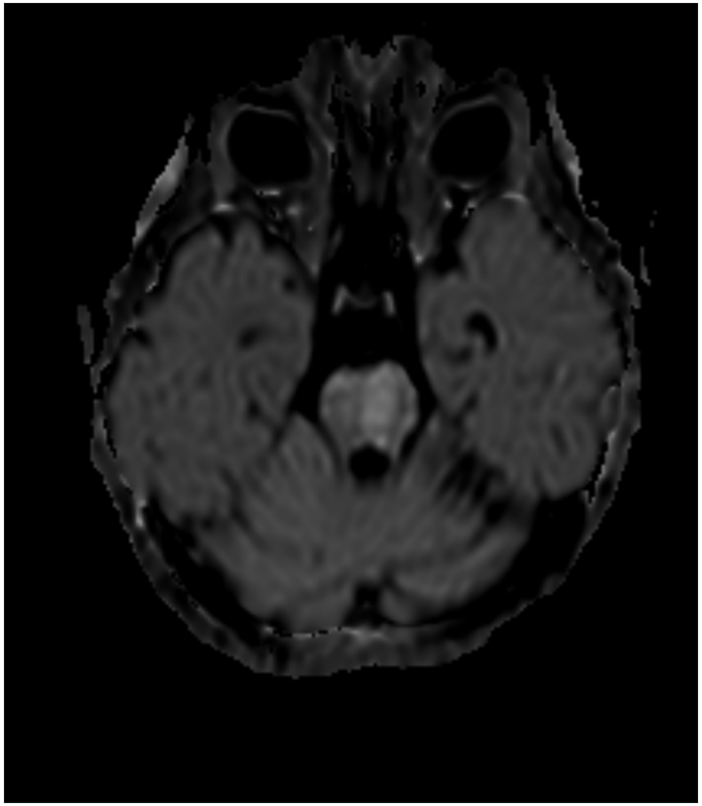
Primary cause is interruption of blood flow to brain region ➔ ischemic injury, infarction.

It is difficult to differentiate between acute and chronic ischemia using standard MR sequences.

As “time means life” in case of stroke, DWI is a very important clinical tool.







Acute and chronic stroke can be differentiated using diffusion MRI.

Acute stroke is seen as reduction in ADC (decreased signal intesity on the ADC image, and increased signal intensity on the DWI), while chronic ischemia has increased ADC (increased signal intensity on ADC, and decreased intensity on DWI).

The reduction in diffusivity is due to cell swelling and increased tortuosity of extracellular fluid spaces.

Clinical applications of DWI/DTI

Brain tumors

DWI can help in **tumor grading**

- high cellular density (lymphomas, dysembryoplastic neuroepithelial tumors)
  ➔ low ADC
- cellular density increases with degree of malignancy in gliomas

DTI is useful for **pre-surgical evaluation** and treatment planning in brain tumor patients.

Fiber tractography can estimate the relationship between the tumor and nerve fiber bundles especially important for the quality of life (corticospinal tract, arcuate fasciculus, callosal fibers, etc.).

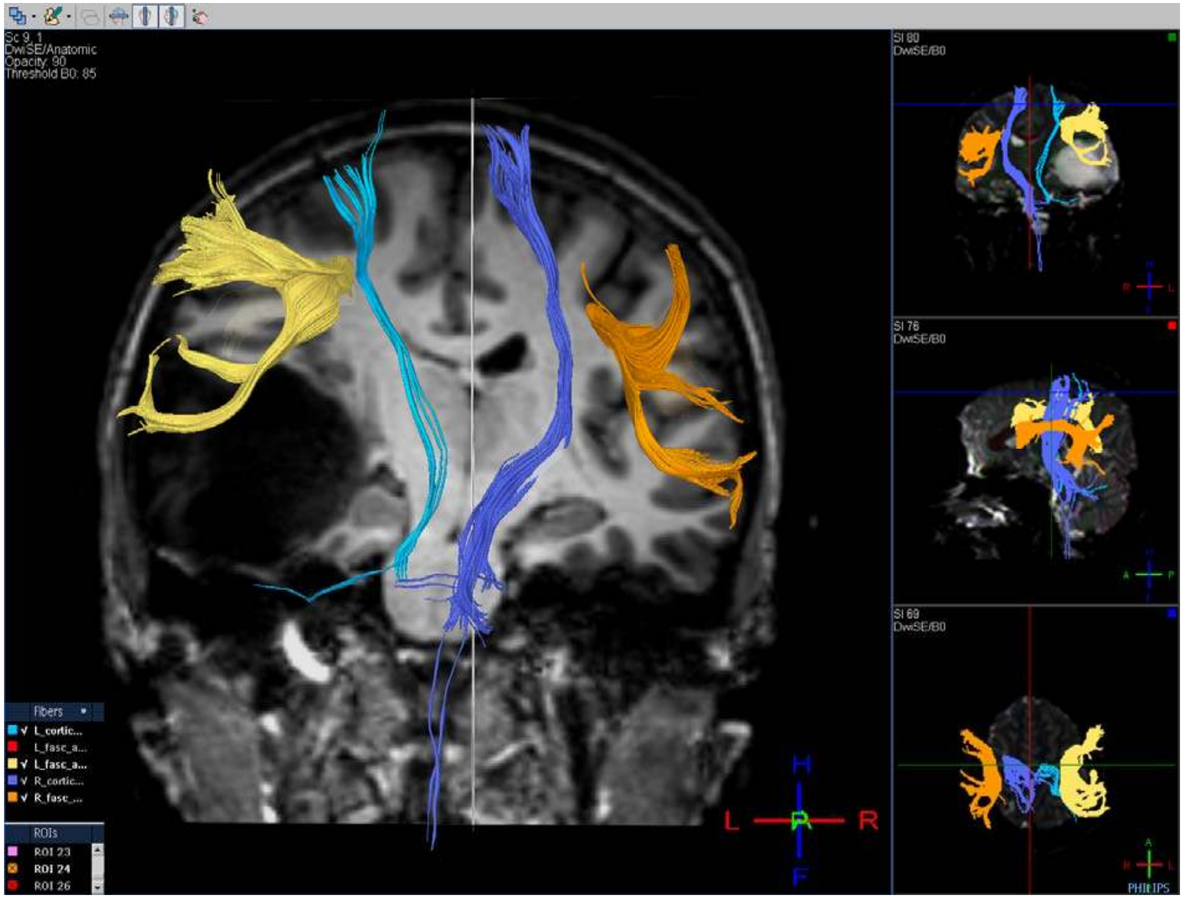
Epilepsies

DTI can be useful for describing epileptogenic neural circuits in epilepsy patients.

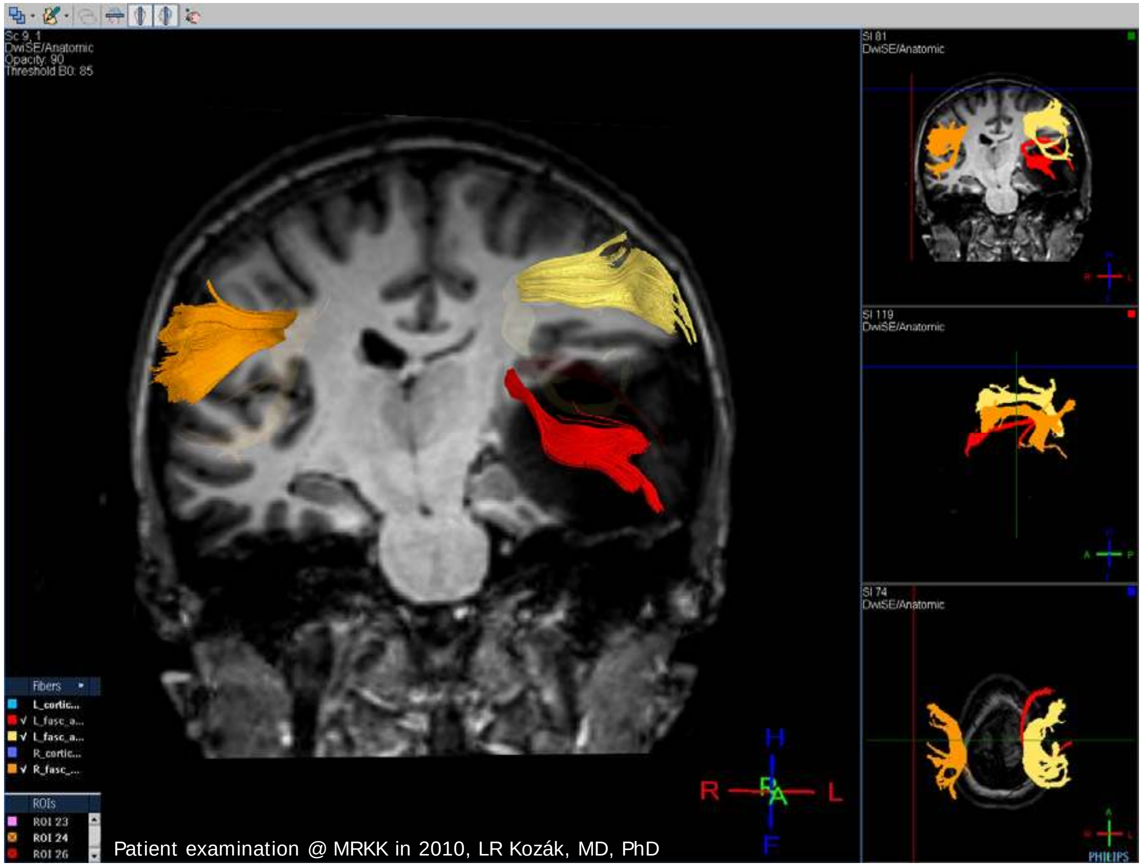
Lymphomas & extracranial tumors

DWIBS (Diffusion Weighted whole body Imaging with Background Suppression) are useful for tumor viability assessment, its predictive value matches that of PET-CT's.

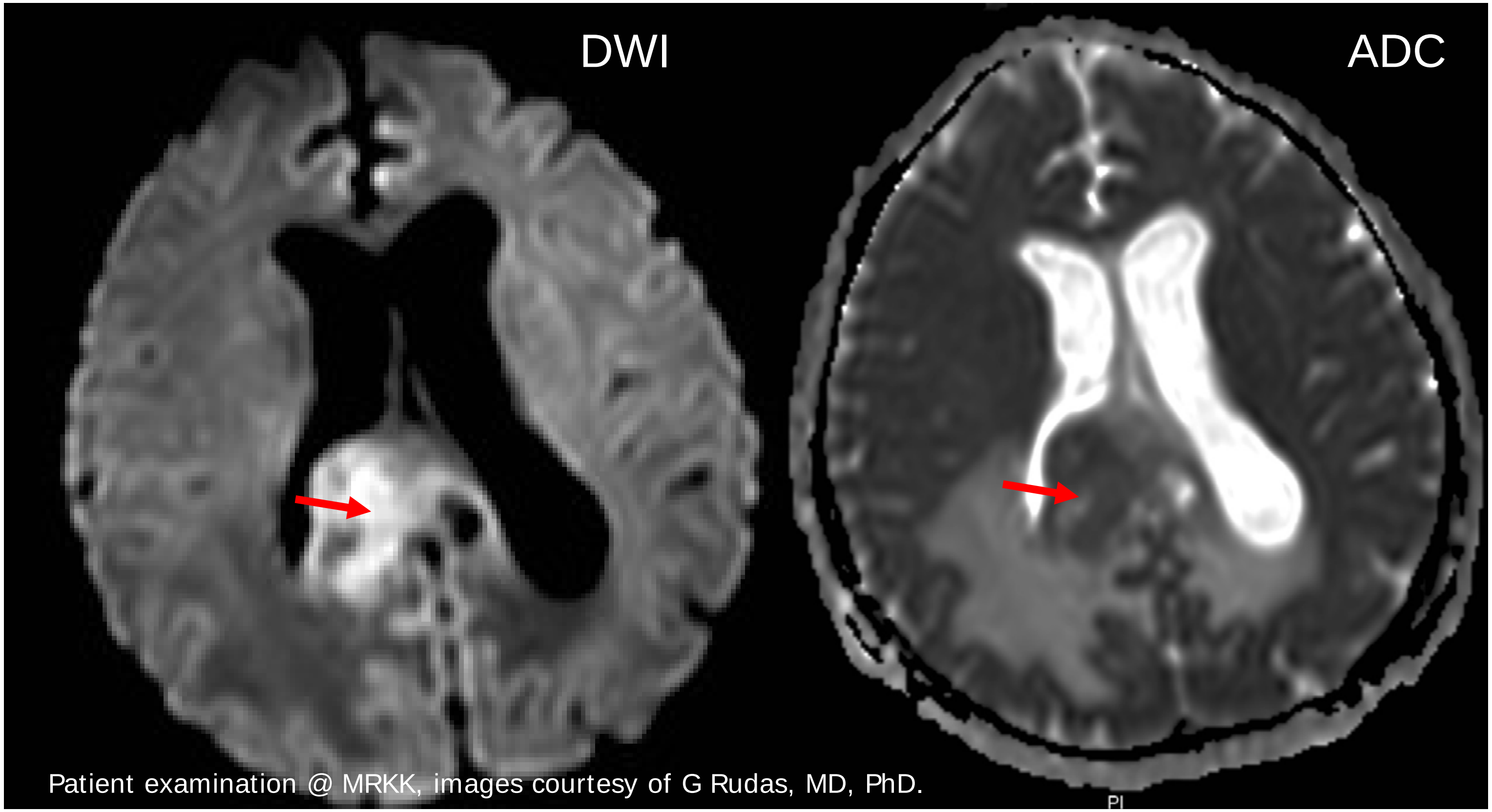
e.g Kwee et al., Eur Radiol, 2008



Both the left corticospinal tract and the arcuate fasciculus are displaced by the large temporal tumor visible as a decreased signal intensity region on the T1W coronal image.

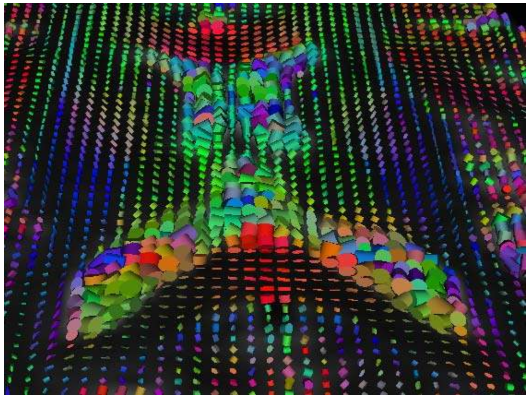


The tumor not only displaces the arcuate fasciculus, but also separates it into an upper and lower bundle.



Diffusion restriction in case of a brain metastasis of pulmonary origin.

Future clinical applications



DTI-based temperature measurements

The cerebrospinal fluid can freely move within the lateral ventricles.

- In case of non-limited diffusivity the diffusion constant of water depends only on the temperature.
- CSF is almost pure water, containing only some ions in normal conditions
- Using artificial CSF containing phantoms, the relationship between temperature and CSF diffusivity can be calculated

$$T = \frac{2256.74K}{\ln\left[\frac{4392.21\times10^{-3}\frac{mm^2}{s}}{D\frac{mm^2}{s}}\right]} - 273.15^{o}K$$

Kozak et al., Acta Paed, 2010

Future clinical applications

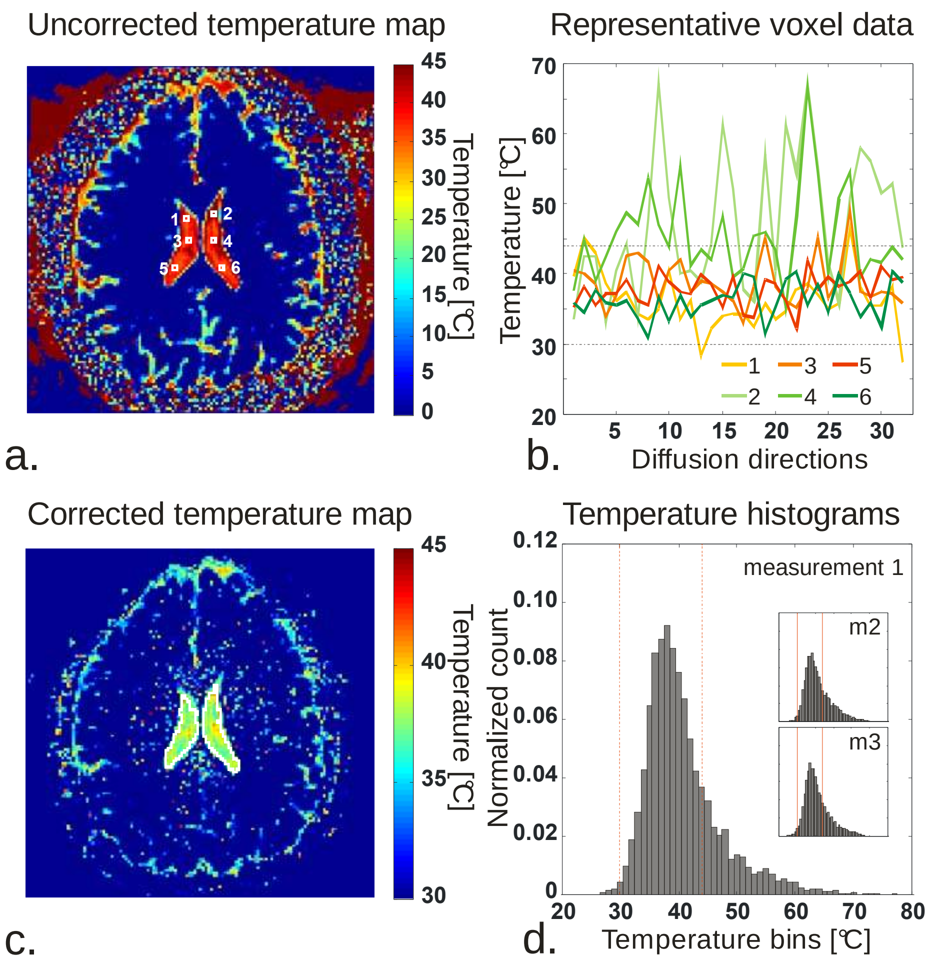
DTI-based temperature measurements

Upon calibration and CSF-pulsation correction, ventricular temperatures can be estimated in vivo.

This can be especially useful in cases of hypothermic treatment following:

- perinatal brain ischemia
- traumatic brain injury

Kozak et al., Acta Paed, 2010



Yamada et al., showed increased temperature in Moyamoya patients using this method (NeuroReport, 2010).

DWI/DTI summary

Diffusion weighted imaging is capable to measure water diffusivity in vivo. These measurements can give information both on structure and function.

Structural aspects

As the main diffusion direction of water is strictly restricted along the axons in the cerebral white matter, DTI can depict neural connections in healthy subjects and patients.

Functional aspects

As water diffusivity depends on the balance of extracellular and intracellular factors, any pathology affecting these compartments (e.g. stroke, lymphoma, etc.) can cause changes in diffusivity, thus DWI can be used for diagnostic and prognostic purposes.

Arterial Spin Labeling (ASL)

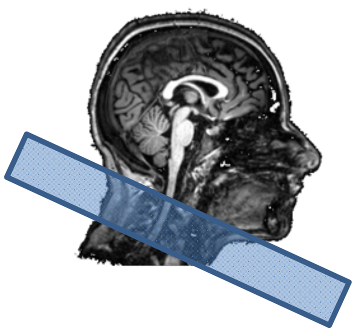
Measuring (local) cerebral perfusion/cerebral blood flow (CBF)

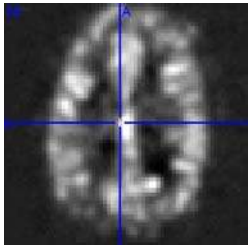
Invasive:

contrast perfusion MRI with contrast materials (Dynamic-susceptibility Contrast perfusion, **DSC**)

Noninvasive:

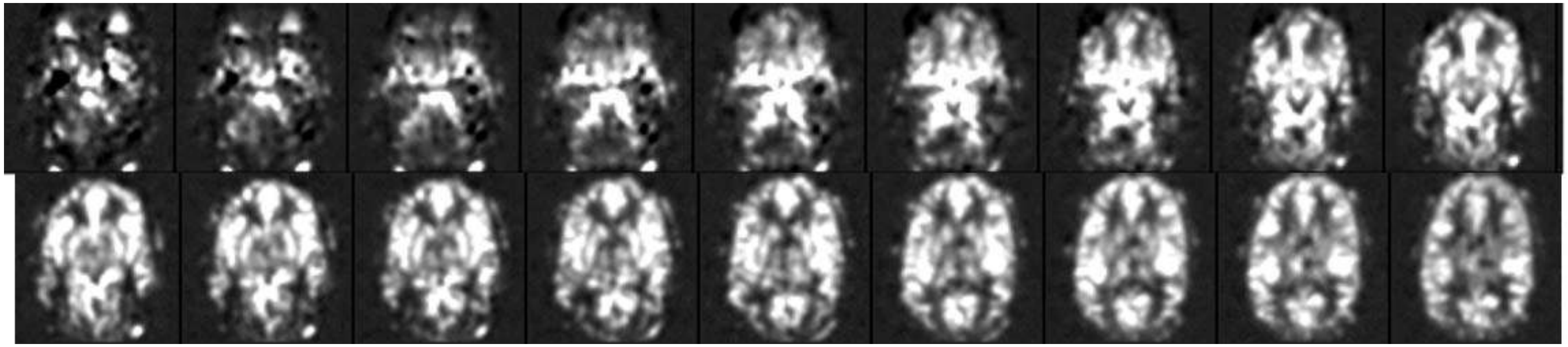
Arterial Spin Labelling (**ASL**)





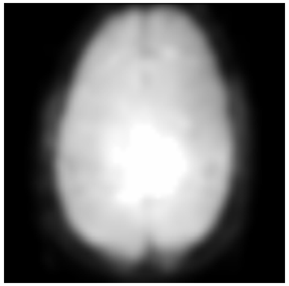
Principles of ASL

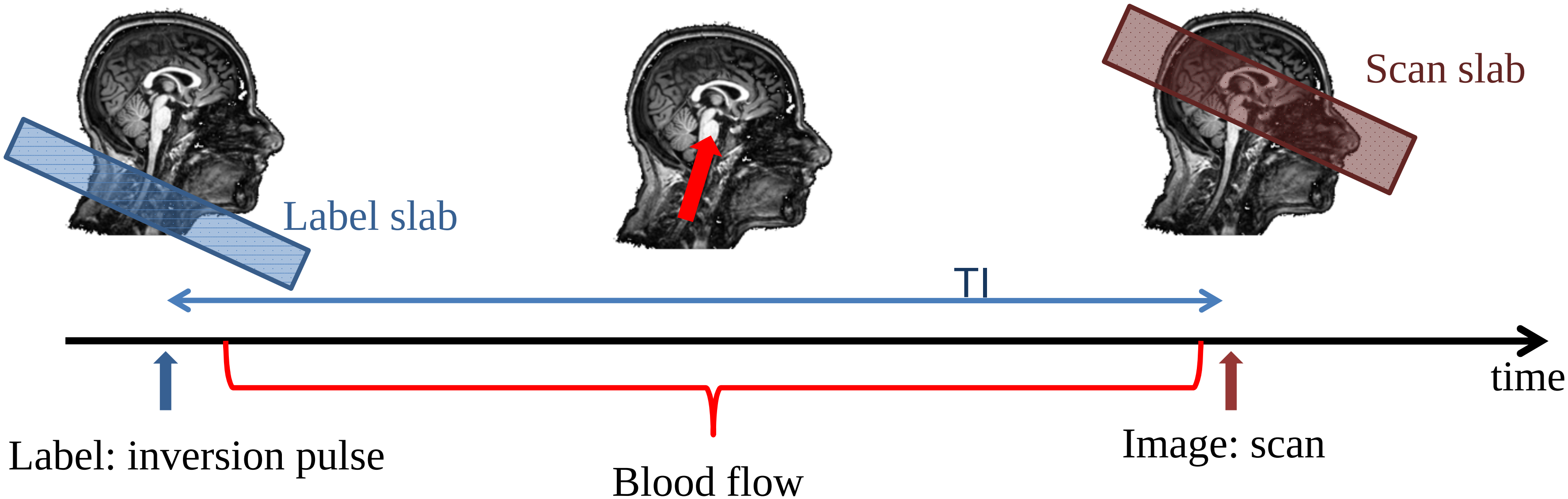
- PET-like for direct CBF measurement (but not CBV as with vascular contrast agents)
- Measurement of slow neural changes
- Absolute quantification of blood flow



Principles of ASL: acquiring tagged image

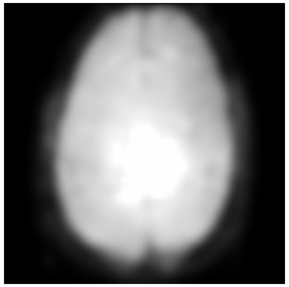
- Tag/label (with inversion) water in the blood proximal of imaging plane
- Wait predefined period of time for blood to arrive
- Acquire tagged image

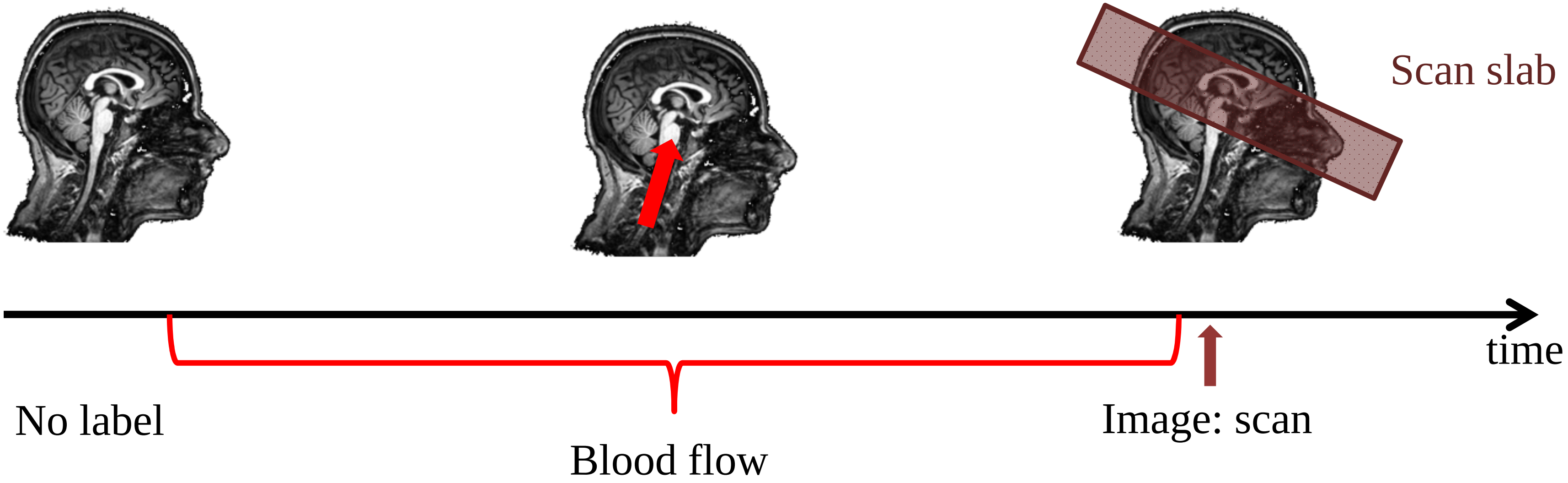




Principles of ASL: acquiring control image

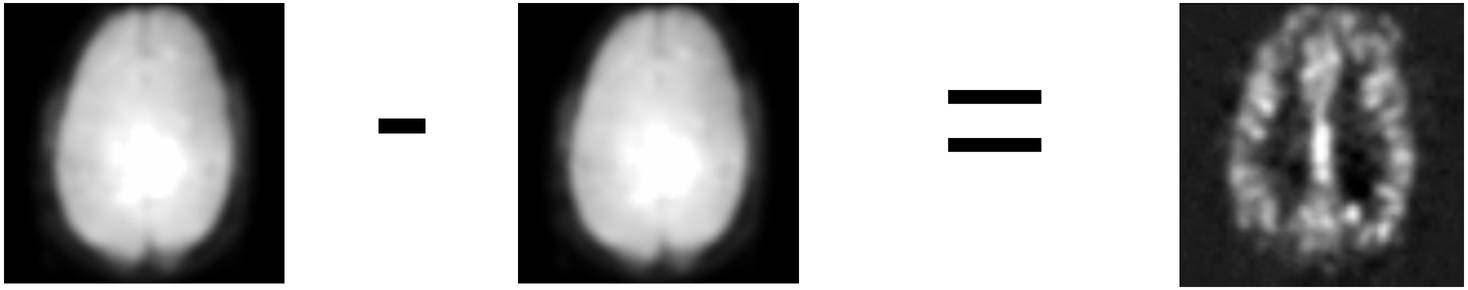
- Do not tag (or use altered, ineffective tag) water in the blood proximal of imaging plane
- Wait predefined period of time for blood to arrive
- Acquire control image



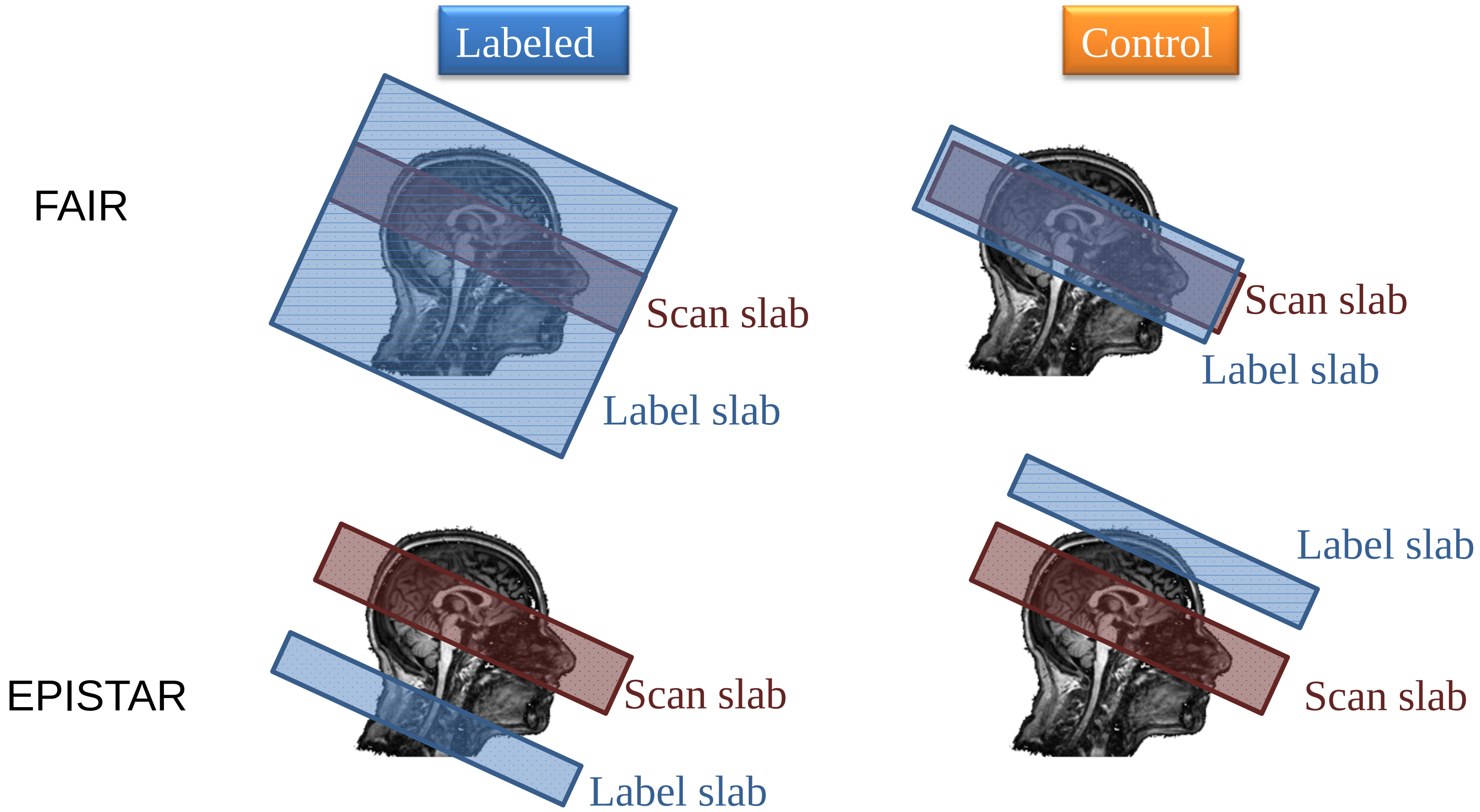


Principles of ASL

- Subtract labeled and unlabeled images gives a blood flow (perfusion) weighted image

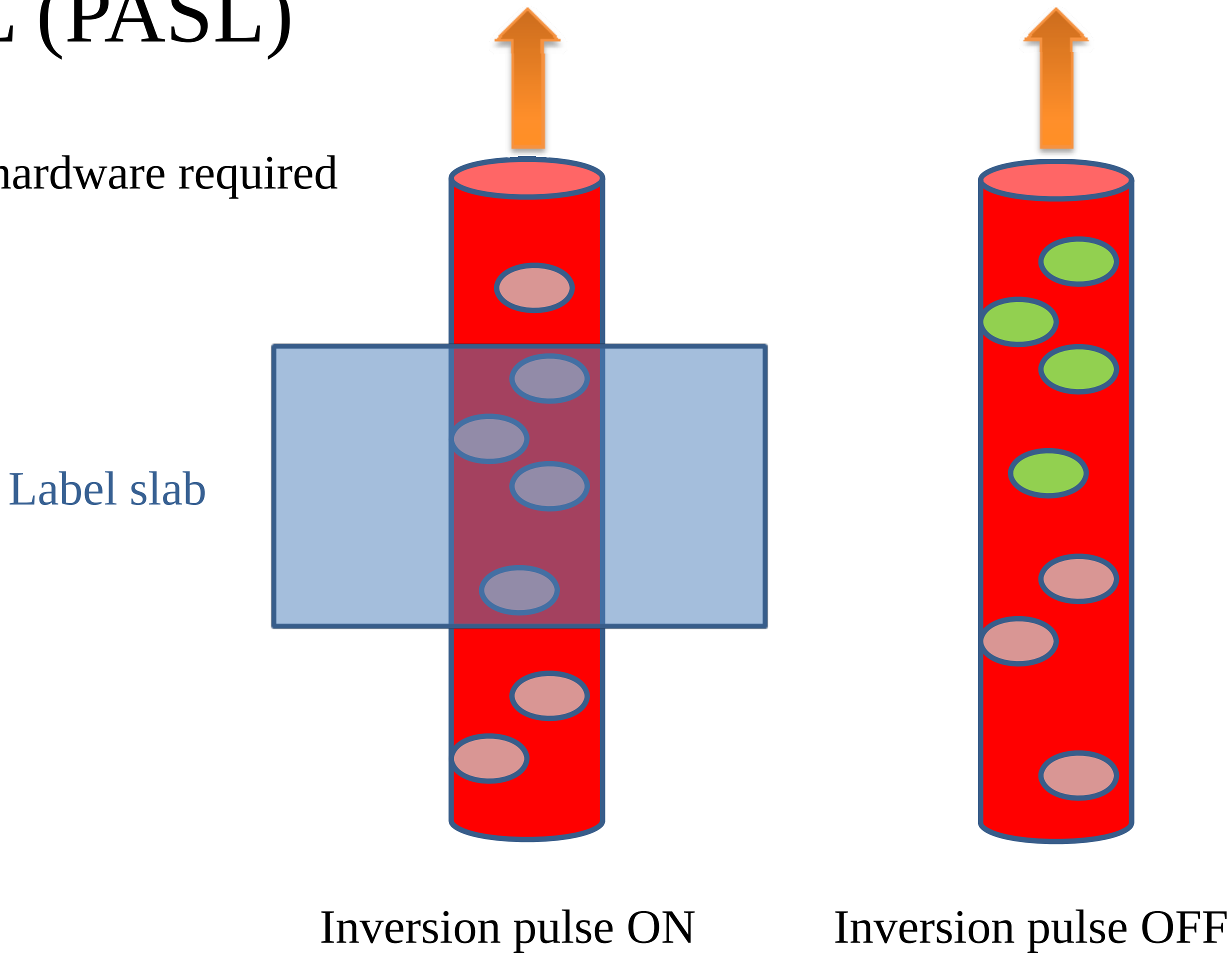


Pulsed ASL (PASL) variants



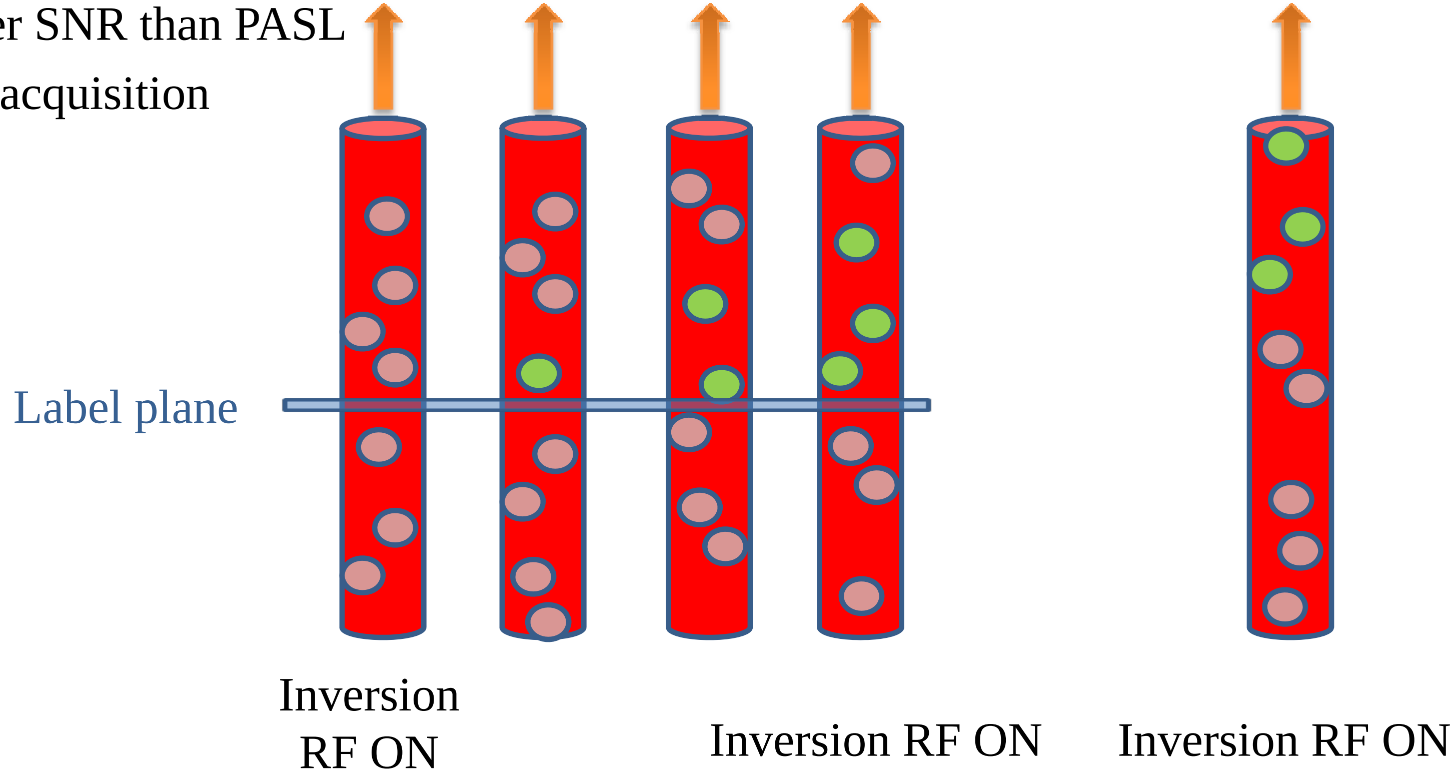
Pulsed ASL (PASL)

- Simple
- No special MR hardware required
- Low signal
- Fast acquisition

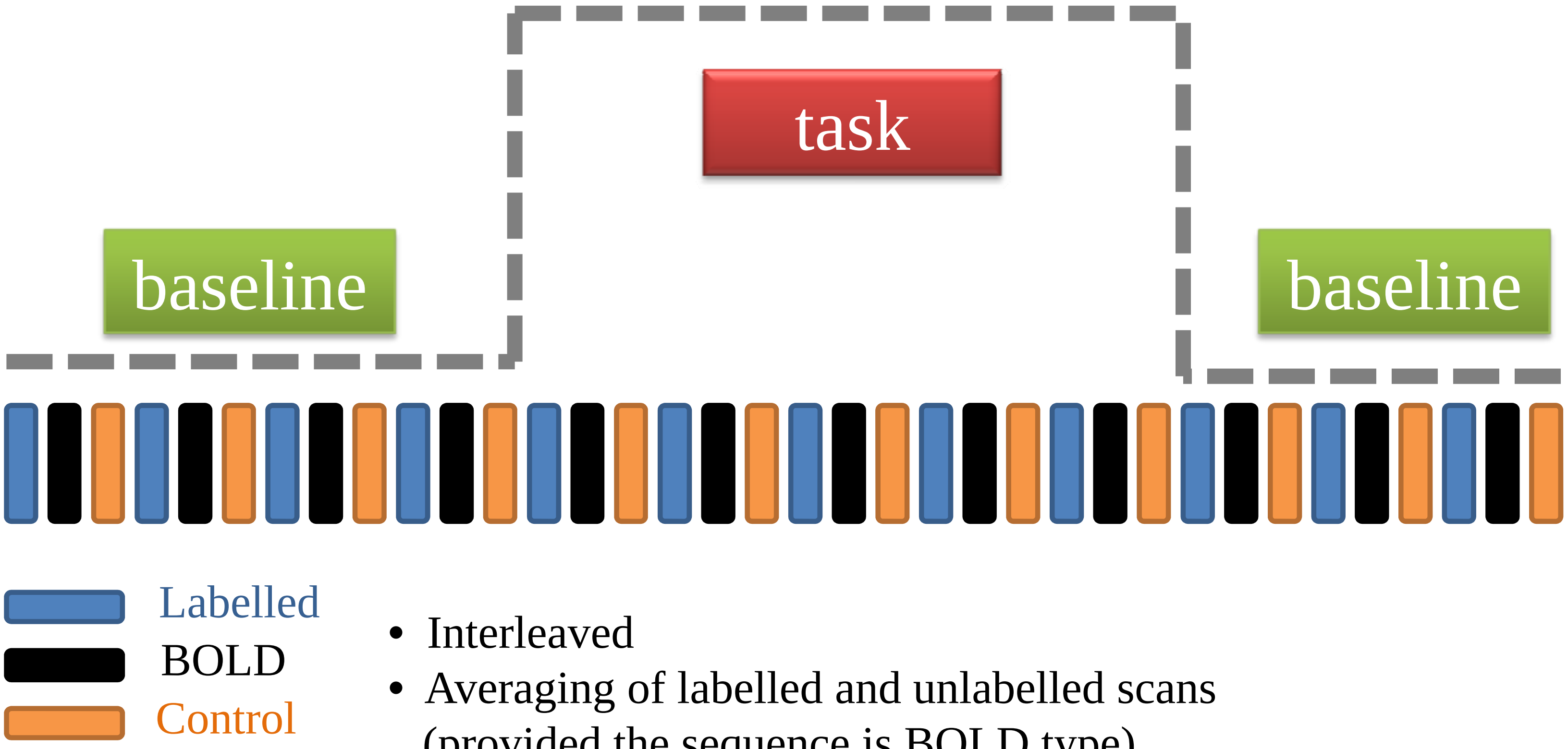


Continuous ASL (CASL)

- Special sequence-programming requirements
- Special (advanced) MR hardware for continues RF generation
- Higher SNR than PASL
- Slow acquisition



Parallel acquisition of ASL and BOLD data



- Interleaved
- Averaging of labelled and unlabelled scans (provided the sequence is BOLD type)

ASL is better than BOLD

Quantitative, independent measurements, white noise, less drifts

↓

- Reduced between-subject variability
- Reduced within-subject, inter-session variability
    - Longitudinal studies
    - Low frequency neural activity (drug response)

- Better functional spatial localization (capillaries)

ASL has problems

Low SNR compared to BOLD (in traditional experiments)

Partial brain coverage
&
Thick slices (>4mm)

Reduced temporal resolution (>4sec/volume sample)

Complex preprocessing
Dozens of possible combinations

Violation of single TI (time-to-inversion) assumptions
Standardization is not solved

Preprocessing and analysis: main issues

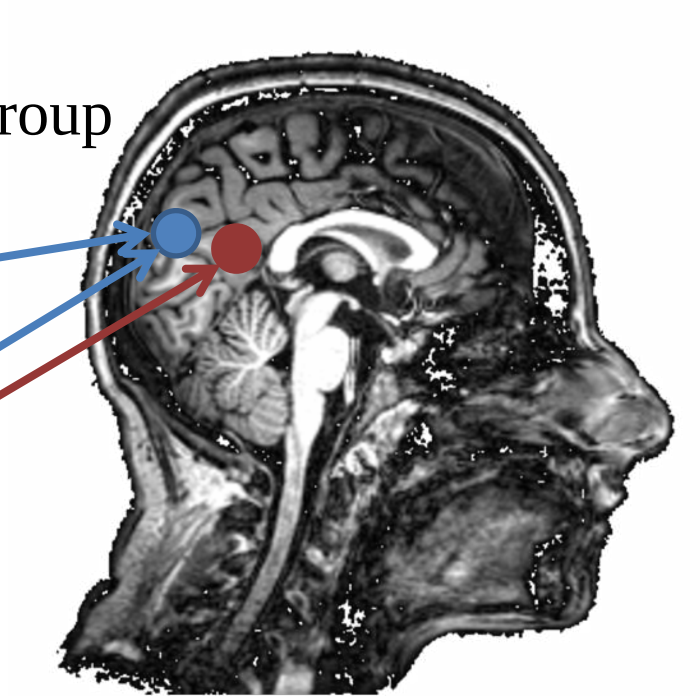
- Motion correction
  - separate (labelled-unlabelled)
  - combined
- Spatial smoothing & normalization
  - before or after subtraction
- Global spike elimination
- Normalization by CBF (calculation based on intesity difference)
  - global signal as covariate
- Spike (jump in average intensity) detection and clean-up based on
  - motion parameters
  - global CBF

Clinical example: amnestic mild cognitive impairment (aMCI).

Direct comparison of patient and healthy group

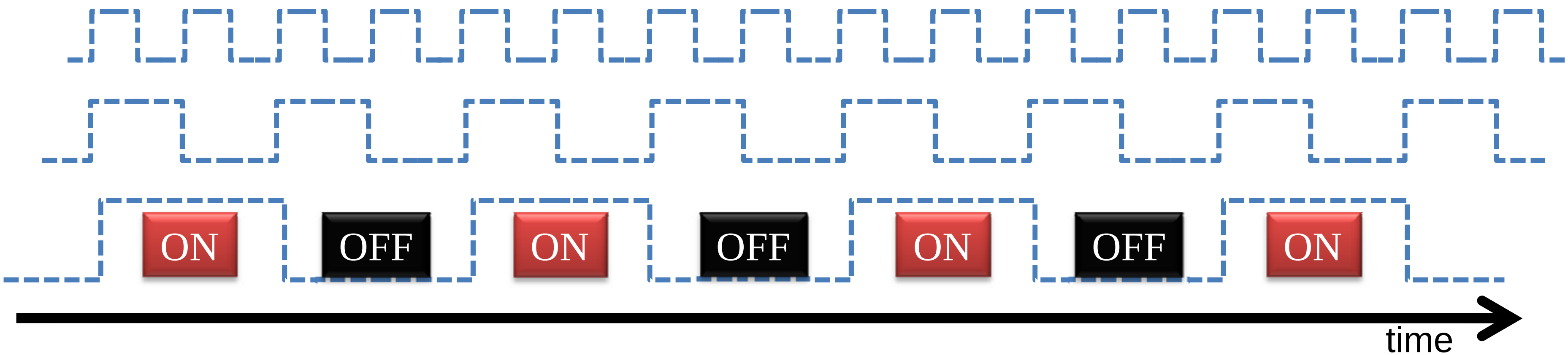
Hypo-perfusion (aMCIs<Controls) in control condition

Hypo-perfusion (aMCIs<Controls) in a memory-encoding task extends to posterior cingulate



(Xu et al, Neurology. 2007 Oct 23;69(17):1645-6.)

ASL fMRI with very low task frequency



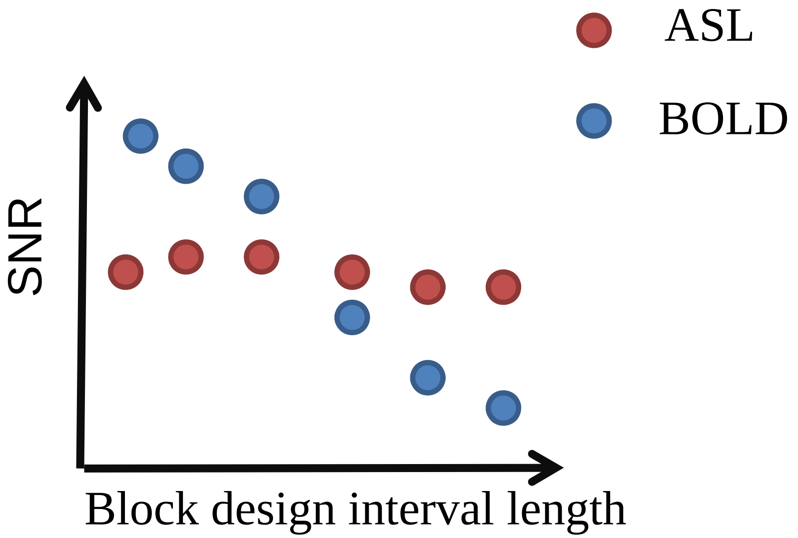
Block type motor task with different alternating time periods (0.5min, 1min .. 20min)

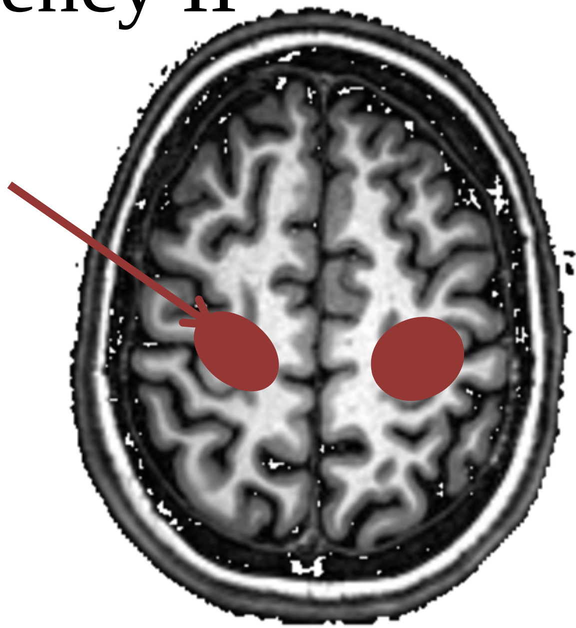
In some cases even 1 hour or a whole day separated the active and rest periods!!!

(Wang et al, Magn Reson Med 49(5), pp 796–802)

ASL fMRI with very low task frequency II

Motor cortex activation analysis showed that ASL overperforms (in terms of SNR) the BOLD technique at low frequency stimulations





ASL fMRI with very low task frequency

Conclusion

Group level analysis indicated that ASL clearly overperforms BOLD except at high frequency (>4min) single subject studies

	High frequency stimulation (<4min)	Low frequency stimulation (>4min)
ASL	+	+
BOLD	++	+/-
Group level ASL	++	++
Group level BOLD	+	+/-