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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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

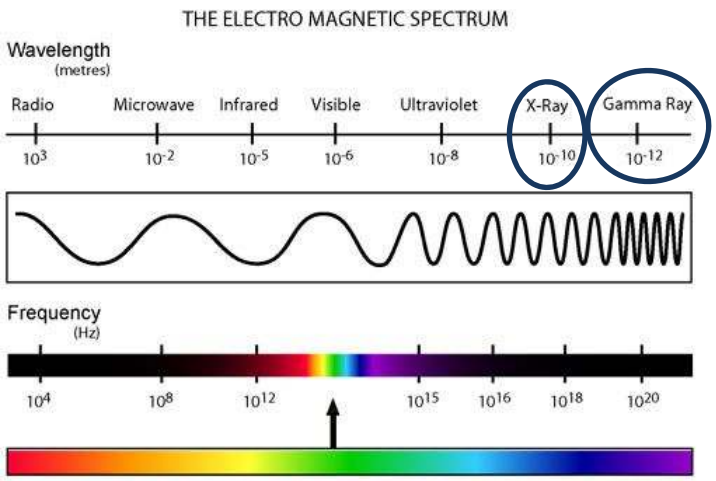
(Orvosbiológiai képalkotás)

INTRODUCTION AND X-RAY

(Bevezetés és röntgenismereti alapok)

GYÖRGY ERŐSS, ZOLTÁN VIDNYÁNSZKY

The electromagnetic spectrum:



- a continuum of all electromagnetic waves arranged according to frequency and wavelength
- electromagnetic energy passes through space at the speed of light in the form of sinusoidal waves

Important waves in the medical imaging technics:

X-rays are very energetic, and are used in X-ray machines to take pictures of bones etc.

Gamma rays are the most energetic light waves found on the electromagnetic spectrum. Gamma rays are used in radiation cancer therapy and some kinds of diagnostic imaging such as PET scans.

Main interactions with matter:

- X-ray: Excitation and ejection of core atomic electrons, Compton scattering (for low atomic numbers)
- Gamma rays: Energetic ejection of core electrons in heavy elements, Compton scattering (for all atomic numbers), excitation of atomic nuclei, including dissociation of nuclei

Biological Imaging vs. The Eye

	Eye	Biological Imaging
Spatial resolution	~0.1 mm	~1 nm
Temporal resolution	~100 ms	~20 ms
Sensitivity	~100 photons	~1 photon
Wavelength range	400 – 700 nm	10^{-13} – 1 m

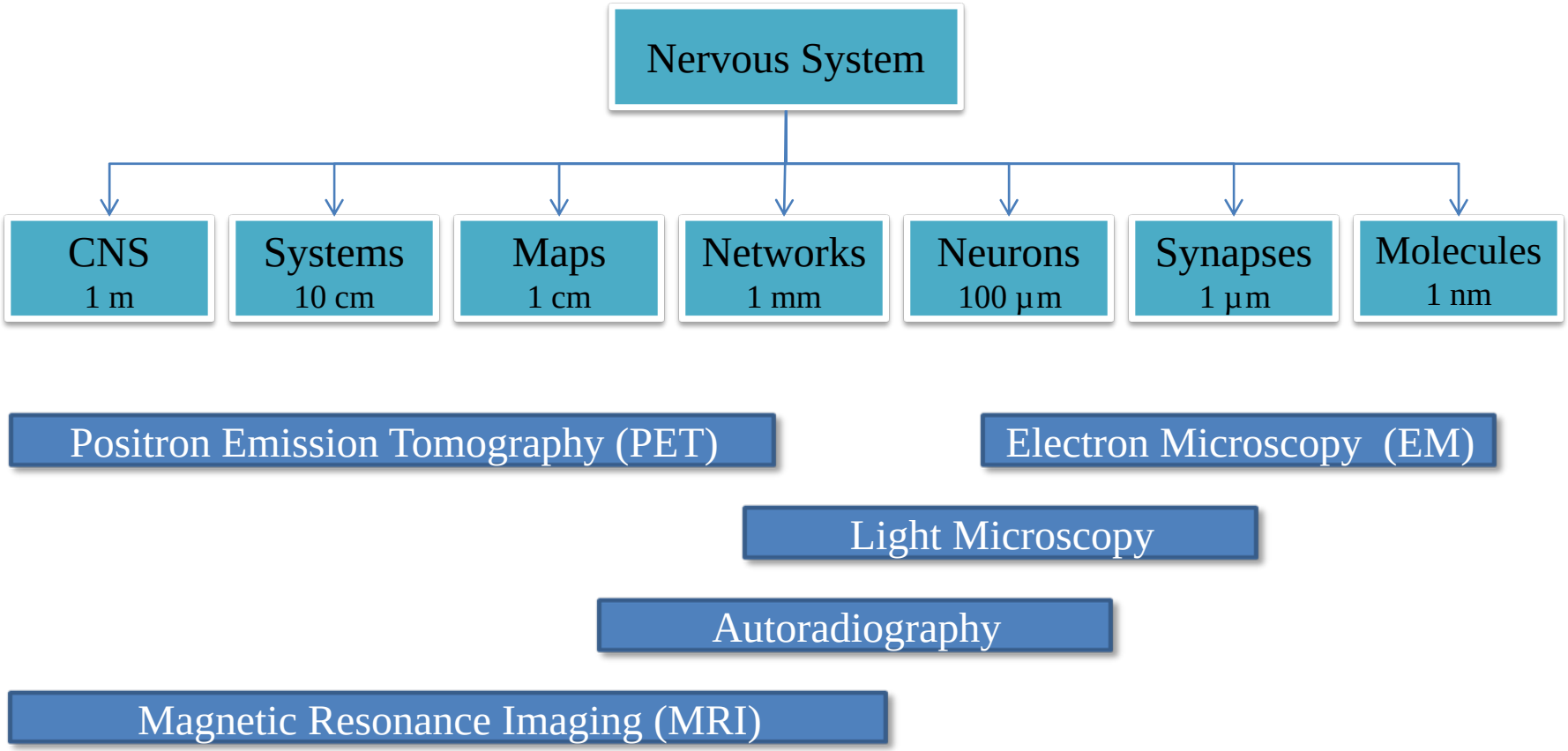
Biological imaging can:

- watch processes too rapid to be perceived
- see objects too small for the eyes to see
- see radiations too faint for the eye or that the eye is not sensitive to
- see inside living objects

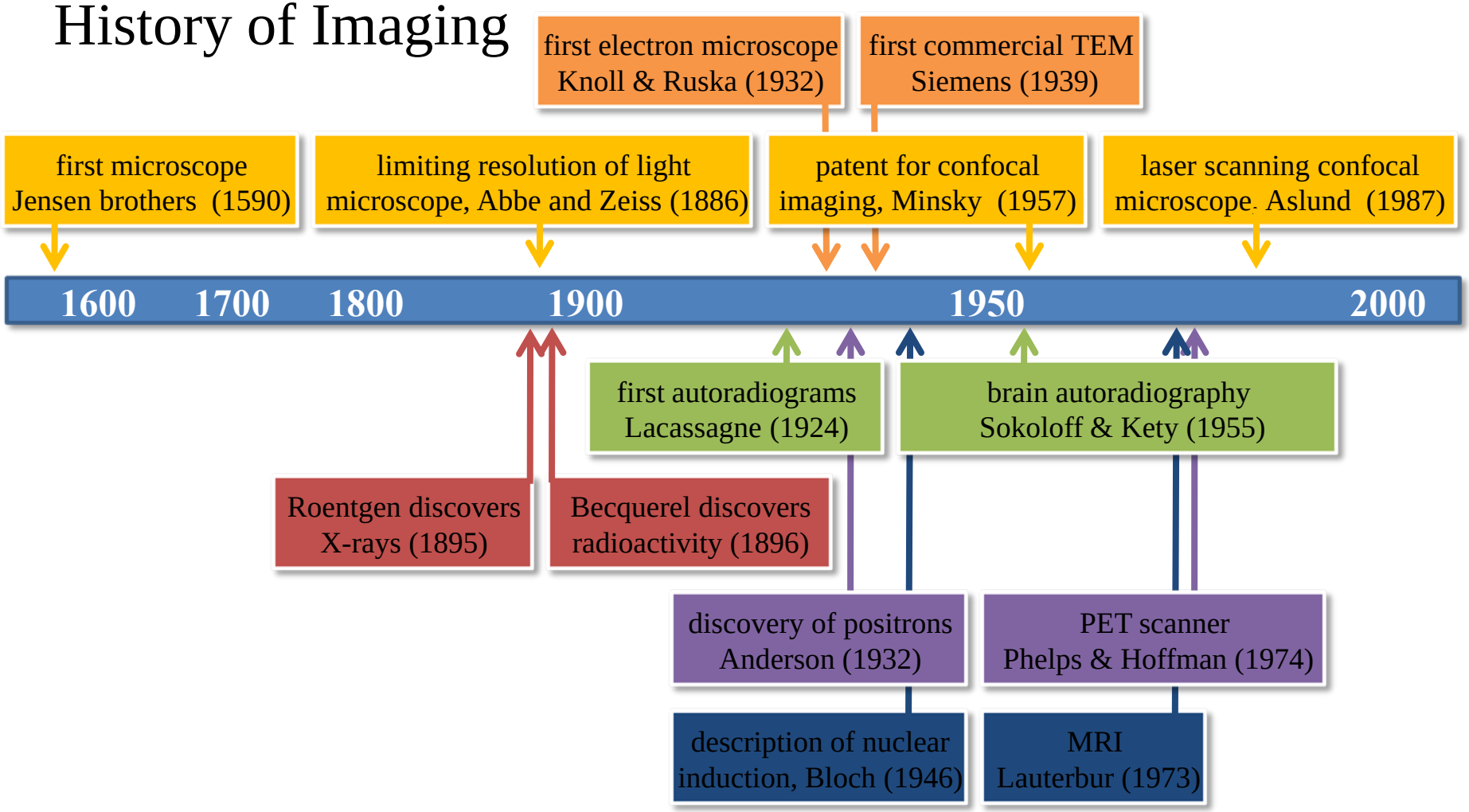
Ideal Biological Imaging Technique

- 1 nm spatial resolution
- 1 ms temporal resolution
- no ionizing radiation
- endogenous source of contrast
- in vivo – no restraint or anesthesia
- shows structure and function
- see everywhere inside the body
- low cost
- ease of use

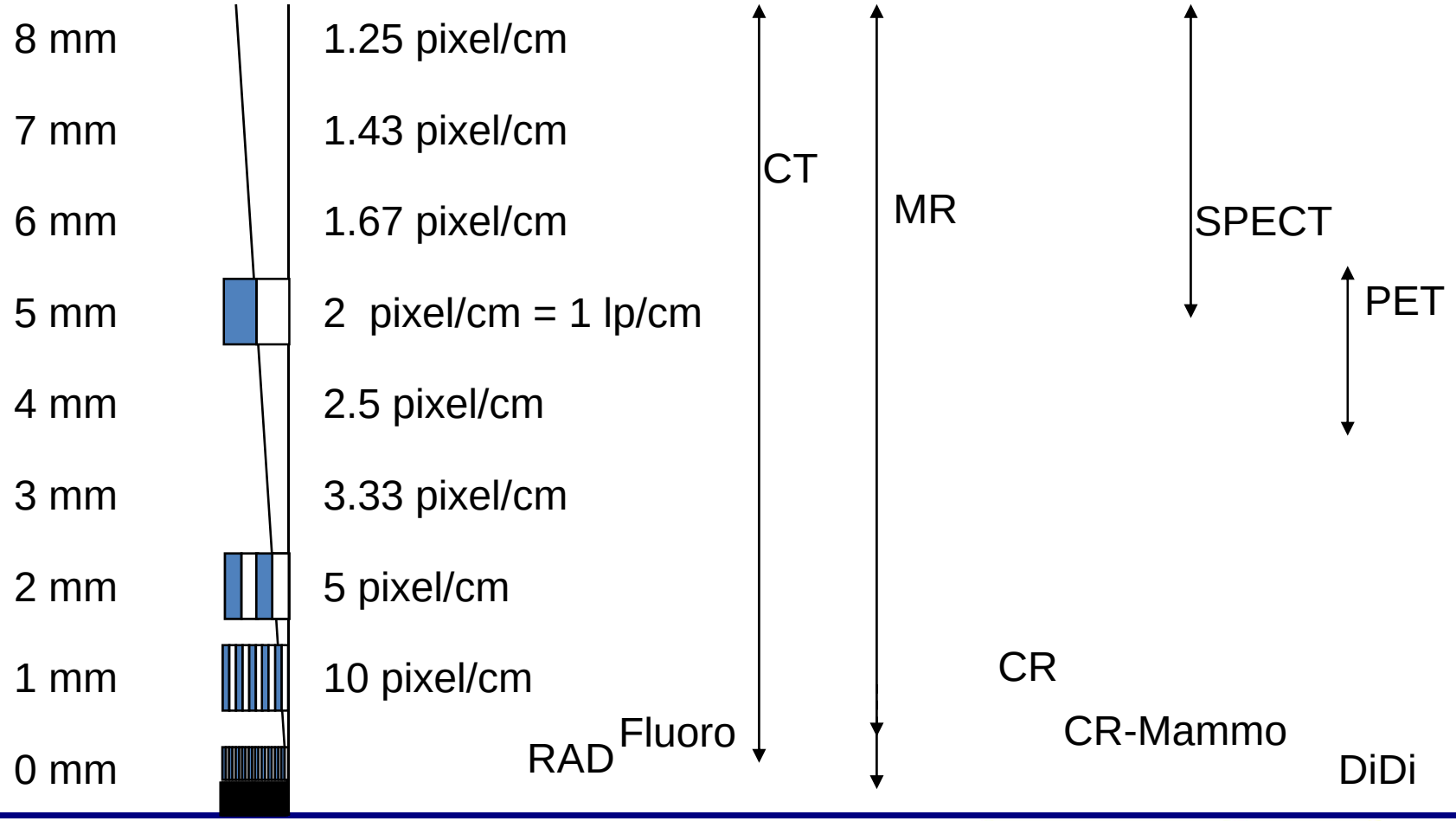
Spatial Scales in the Central Nervous System



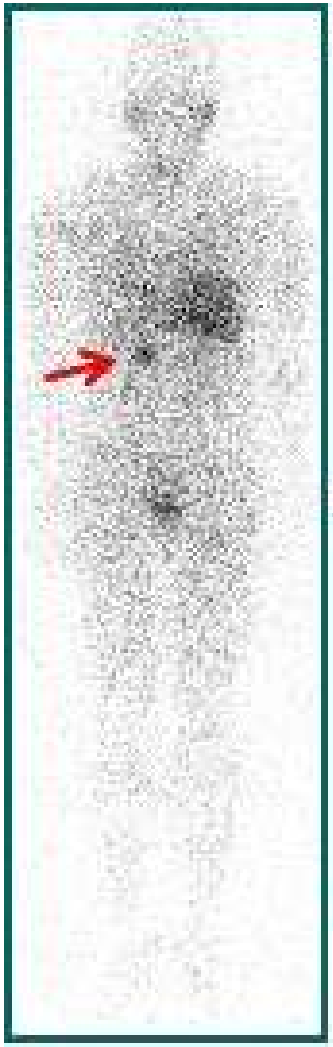
History of Imaging



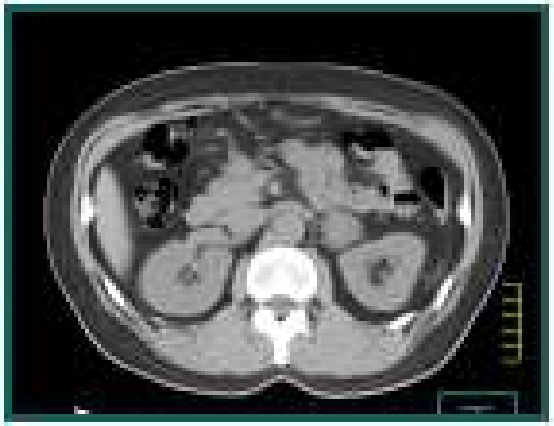
Resolution of different imaging modalities

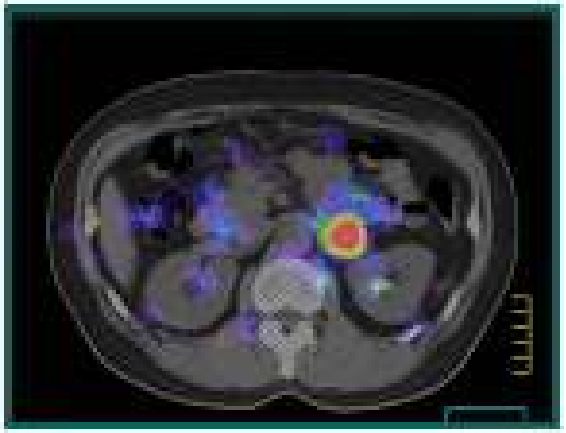


Biomedical Imaging: Introduction and X-ray

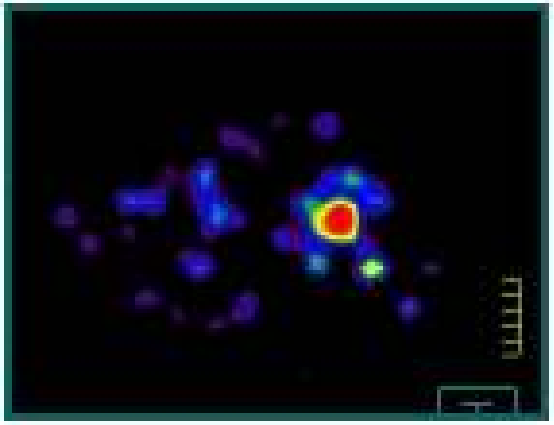


CT





SPECT-CT



SPECT

SPECT- low resolution functional image
CT – high resolution anatomical image

Classification of Different Imaging Methods

External signal:

- Ultrasound
- Conventional X-ray:
  - Radiography
  - Fluoroscopy
- Digital X-ray:
  - Computed Radiography
  - Direct Digital systems
  - CT: Computed Tomography
- MR(I): Magnetic Resonance Imaging

Internal signal:

- Thermography (-), etc.
- Nuclear Medicine
  - SPECT: Single Photon Emission Computed Tomography
  - PET: Positron Emission Tomography

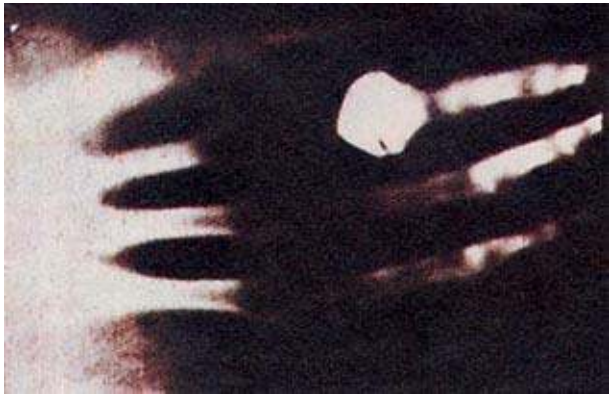
Wilhelm Conrad Röntgen

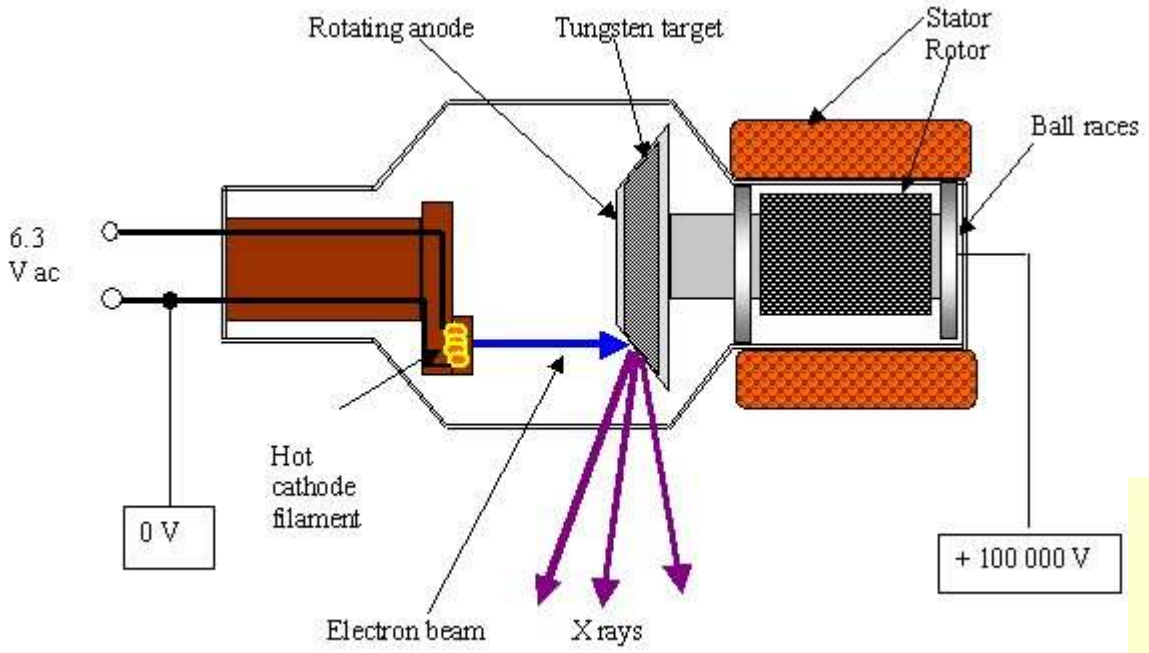
German physicist

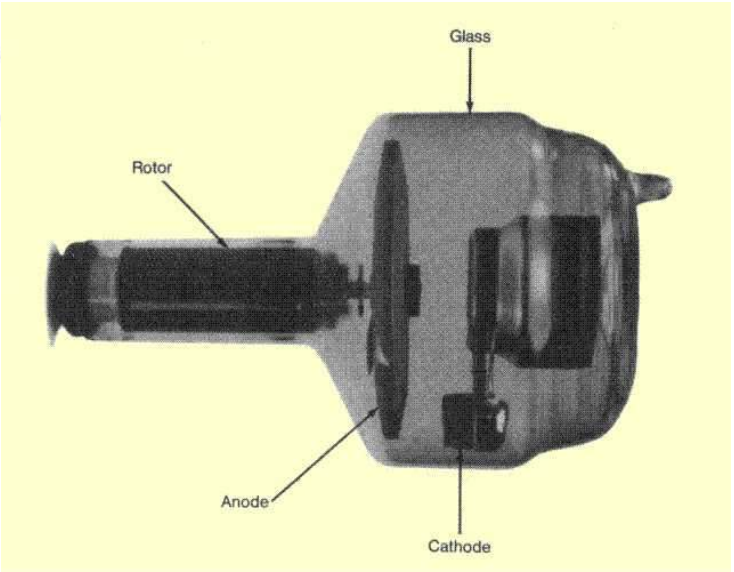
March 27, 1845 - February 10, 1923

Accidentally discovered X rays while experimenting with cathode rays emitted from a Crookes tube,

winning the 1901 Nobel Prize in physics for this accomplishment

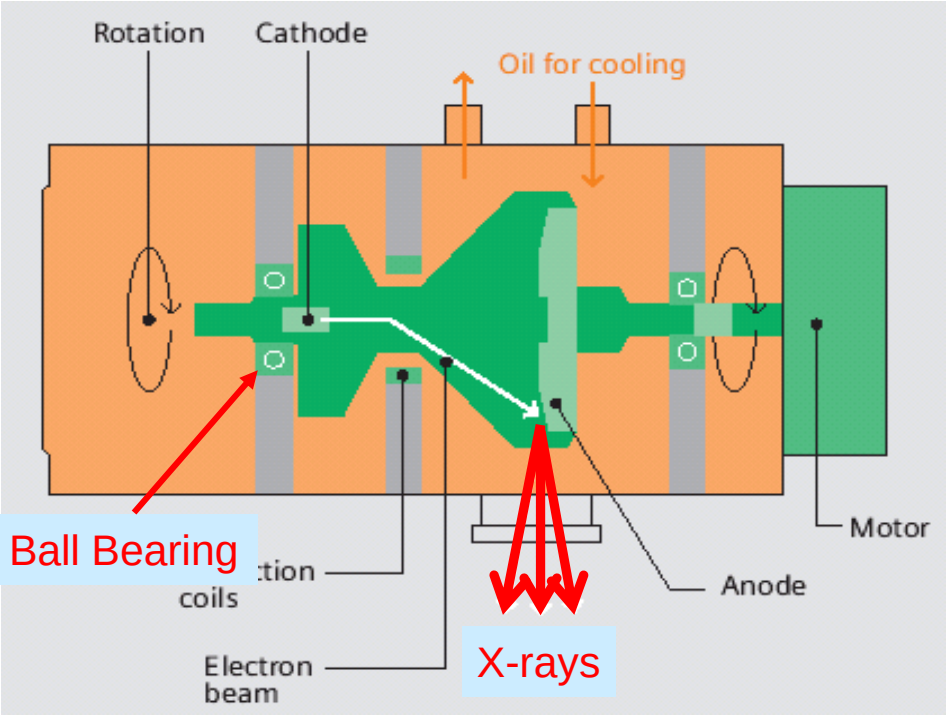


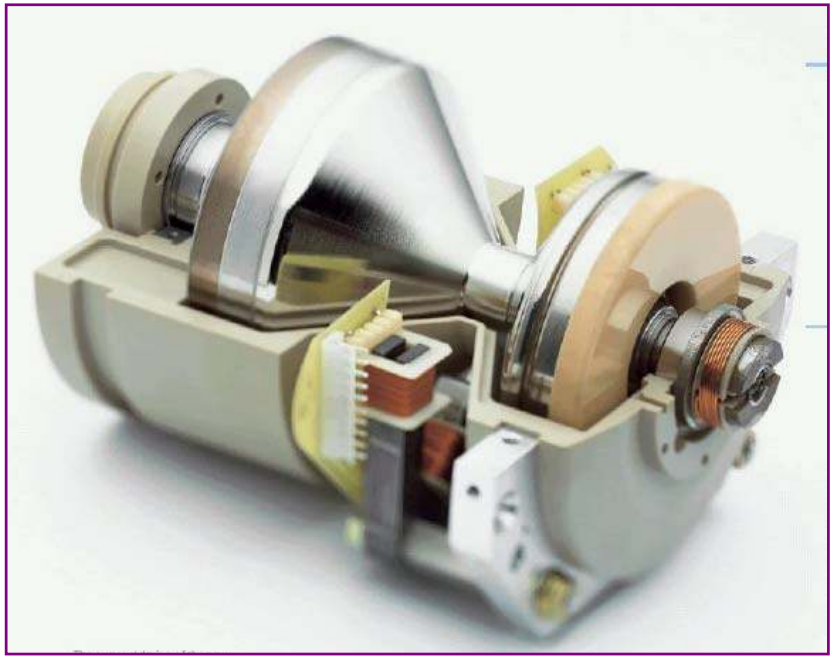




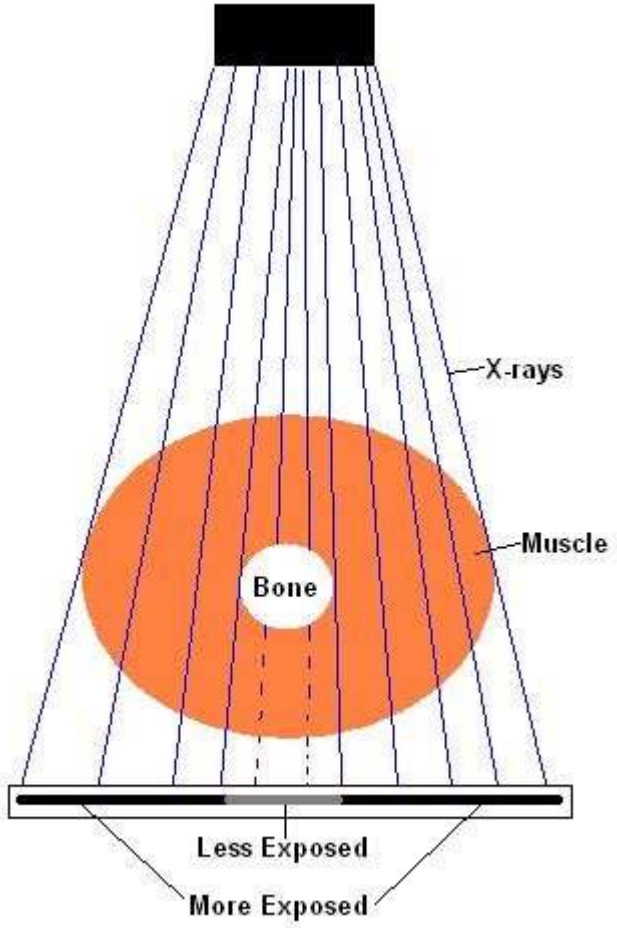
Structure of an x-ray tube with rotating anode

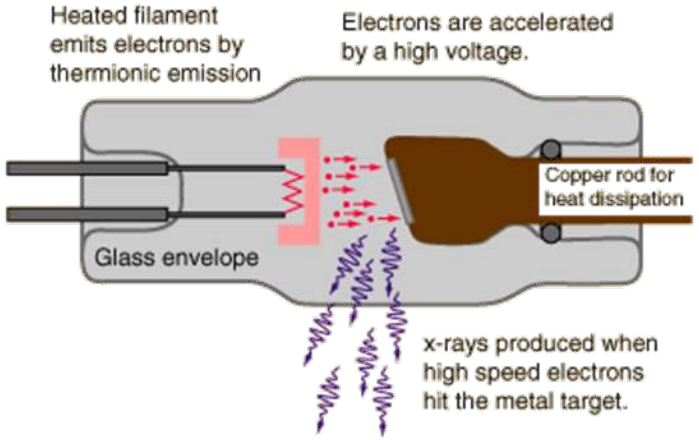
Special structure of high performance x-ray tube for CTs

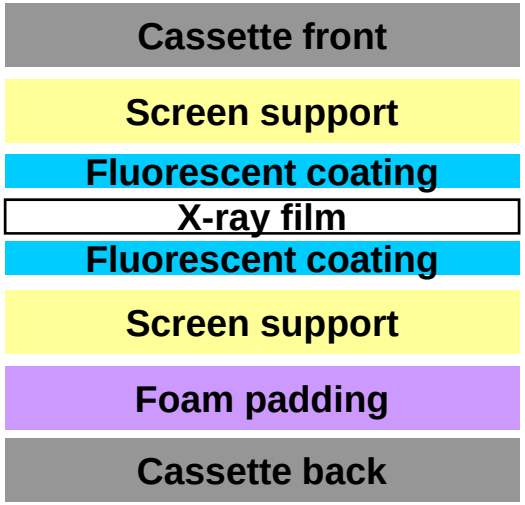




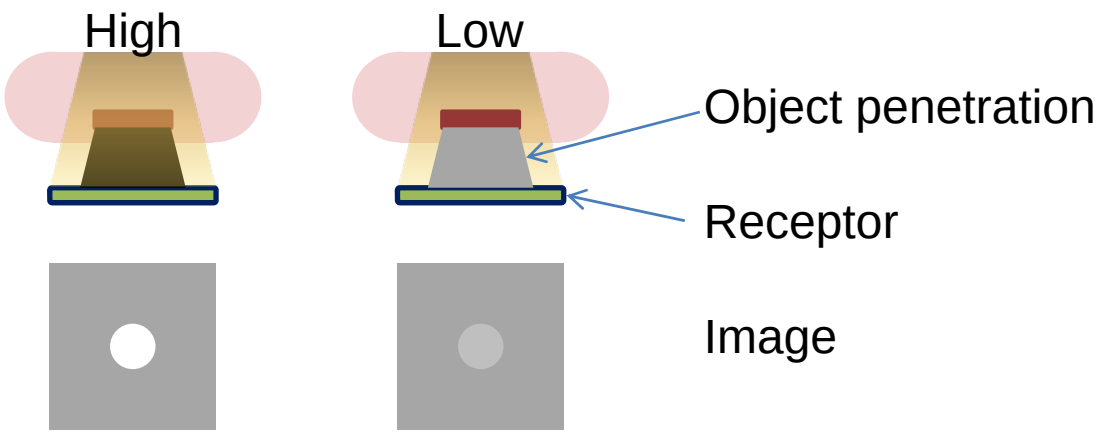
Radiography





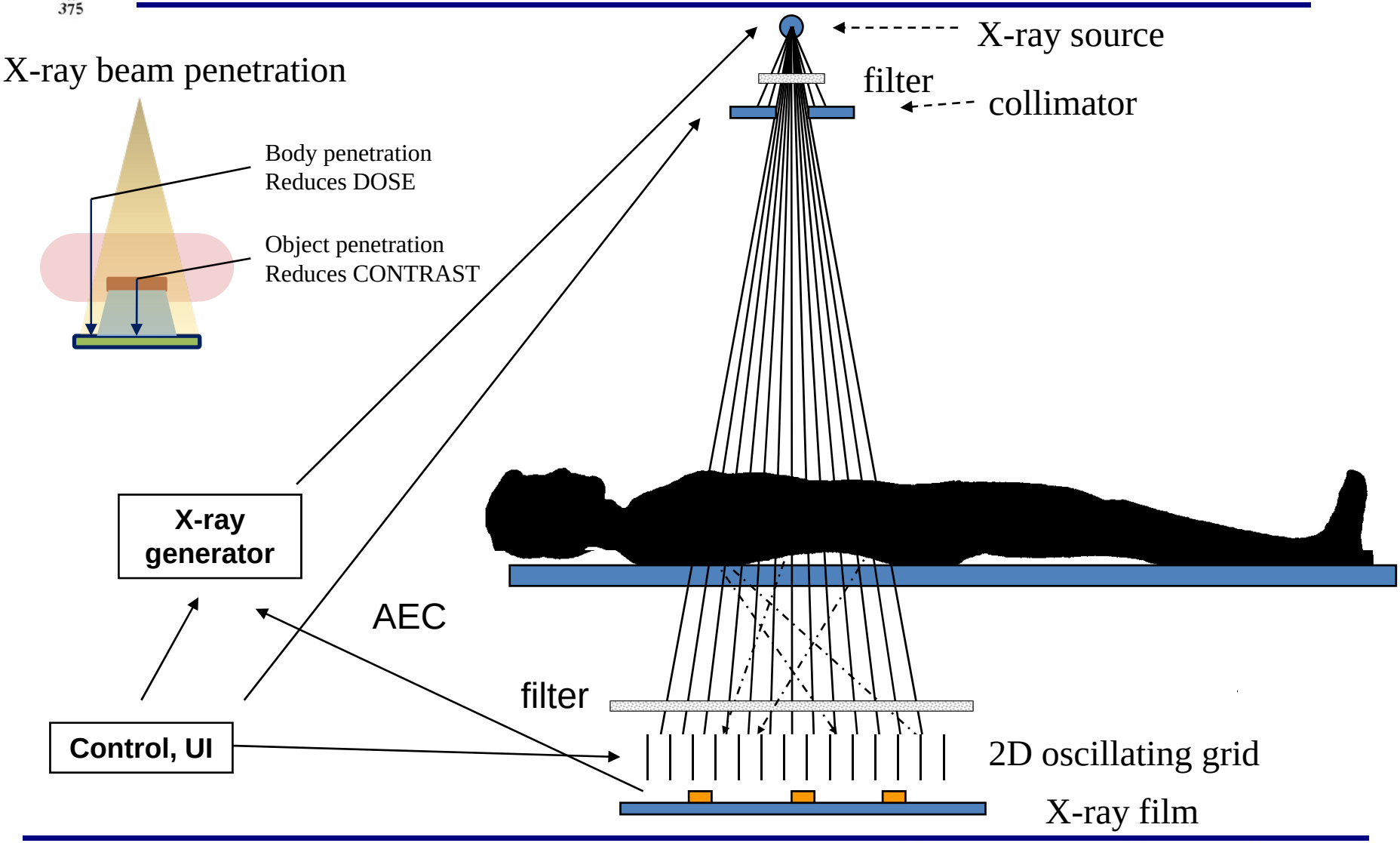


X-ray image contrast

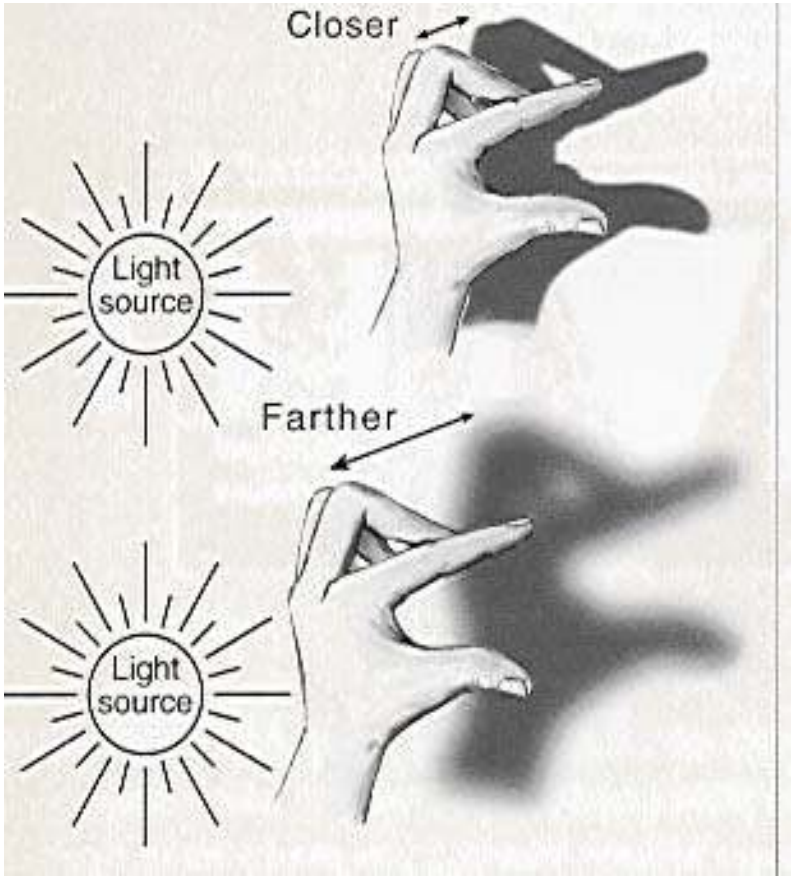


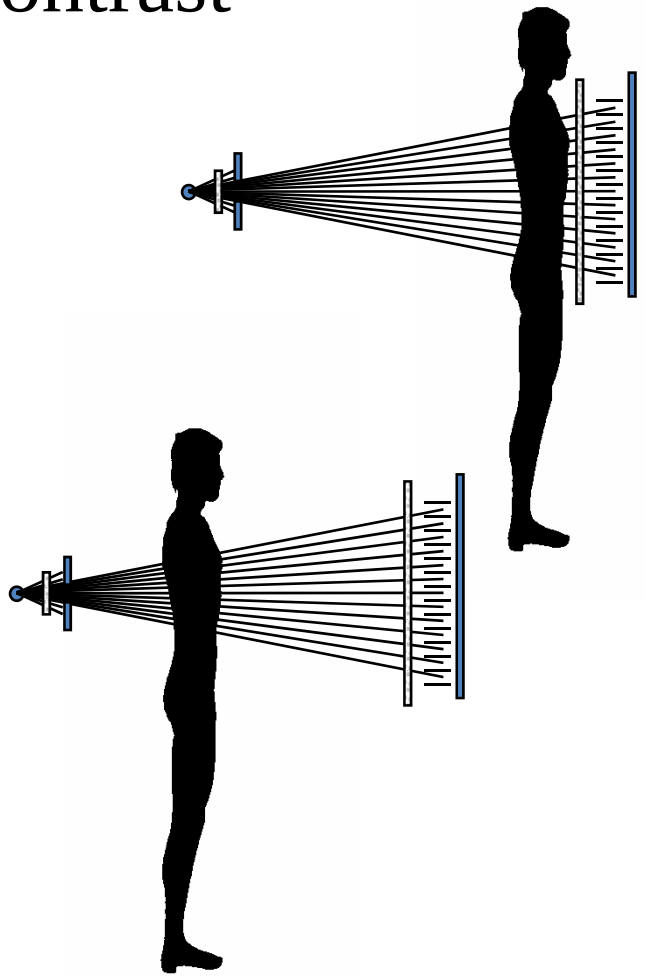
Material	Effective Atomic Number	Density (g/cm3)
Water	7.42	1.0
Muscle	7.46	1.0
Fat	5.92	0.91
Air	7.64	0.00129
Calcium	20.0	1.55
Iodine	53.0	4.94
Barium	56.0	3.5

Biomedical Imaging: Introduction and X-ray

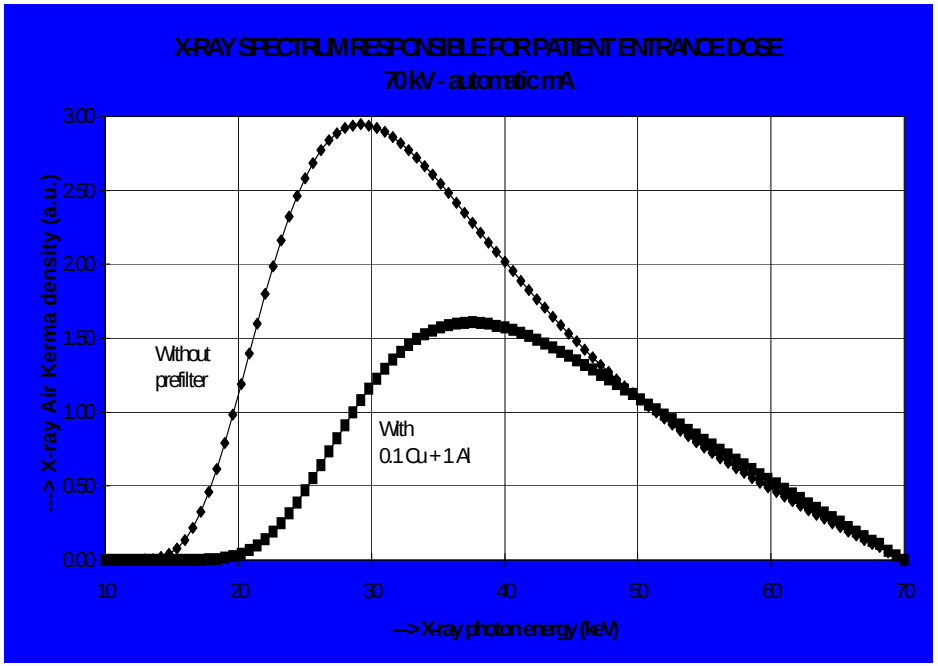


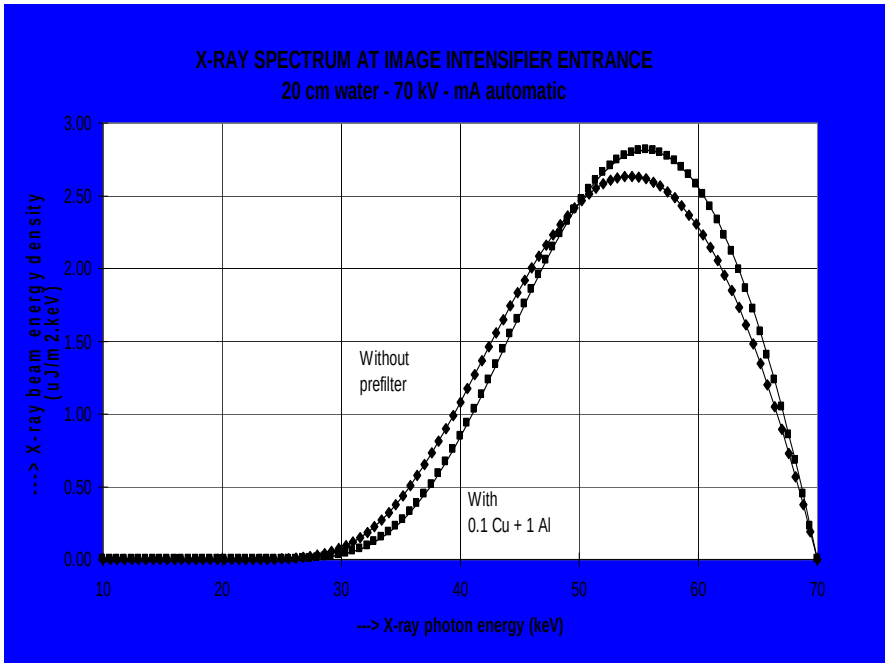
Magnification and edge-contrast





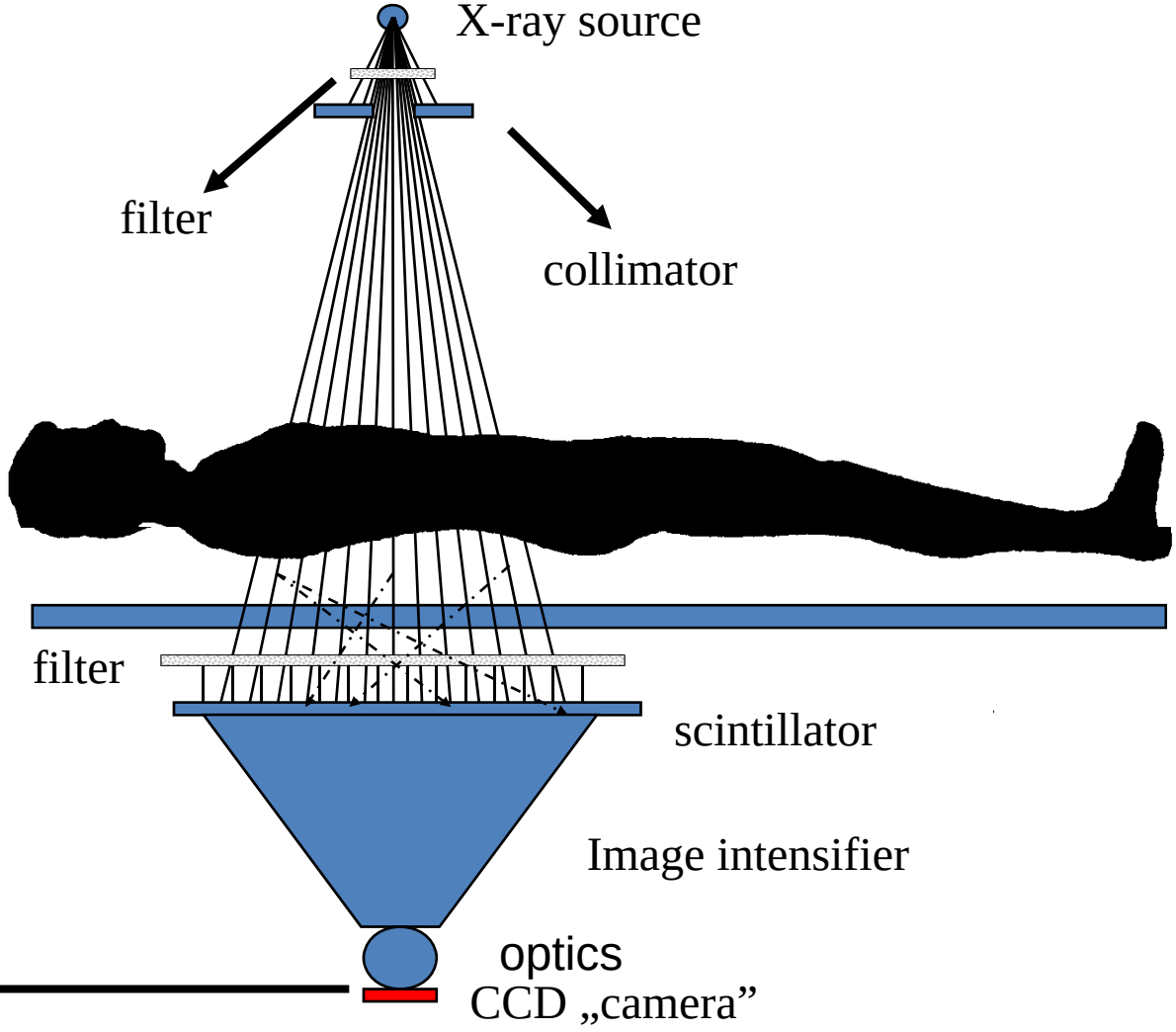
Filtering of x-ray





Typical multipurpose radiography equipment

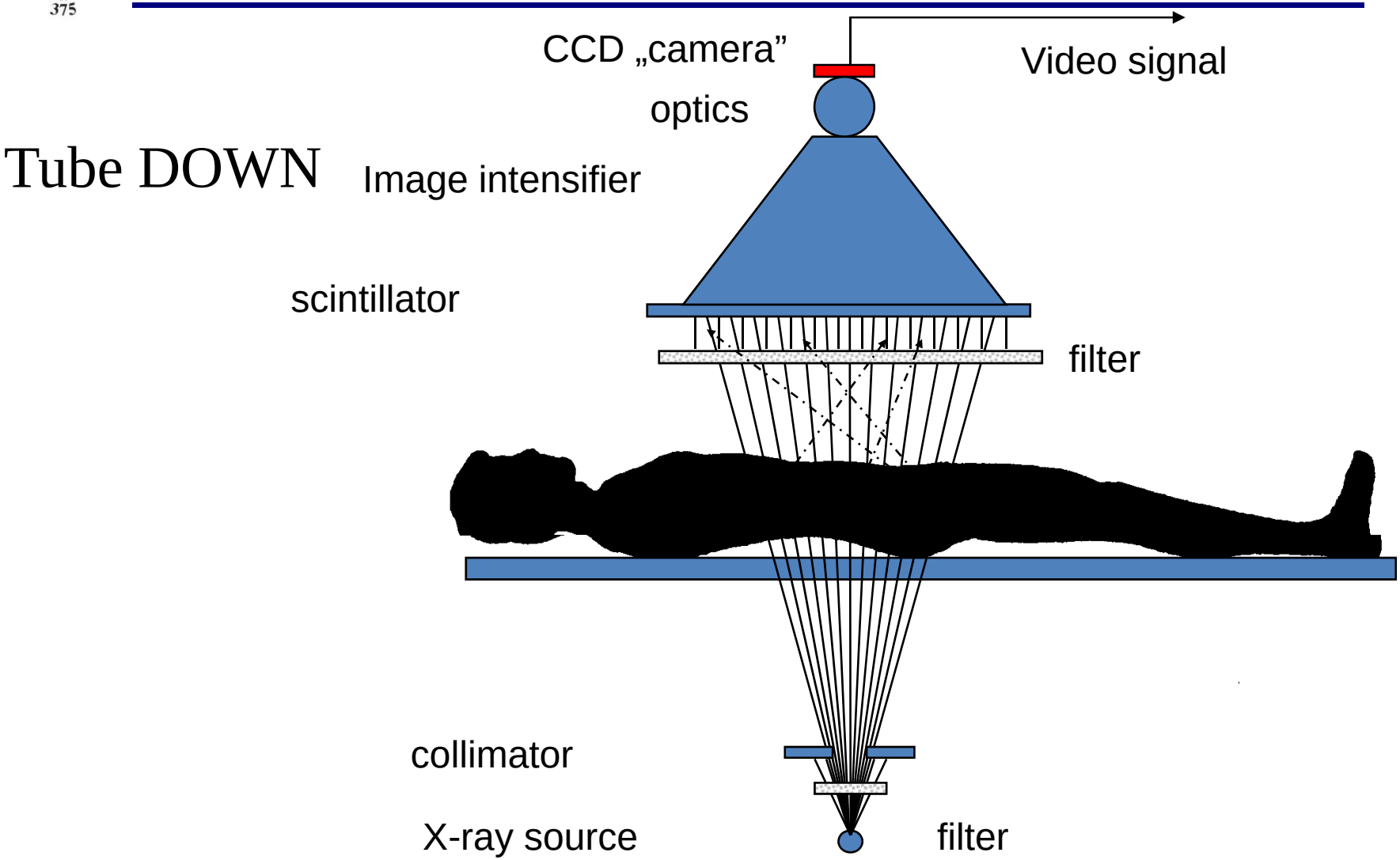
Fluoroscopy



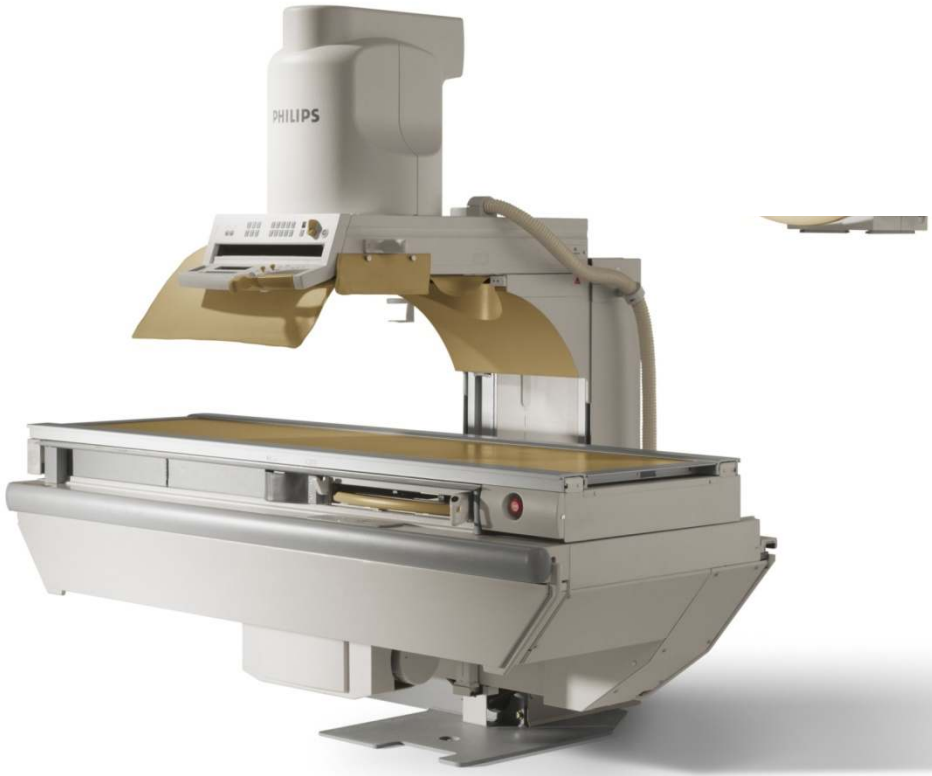
Typical fluoroscopy equipment

Tube in TOP position

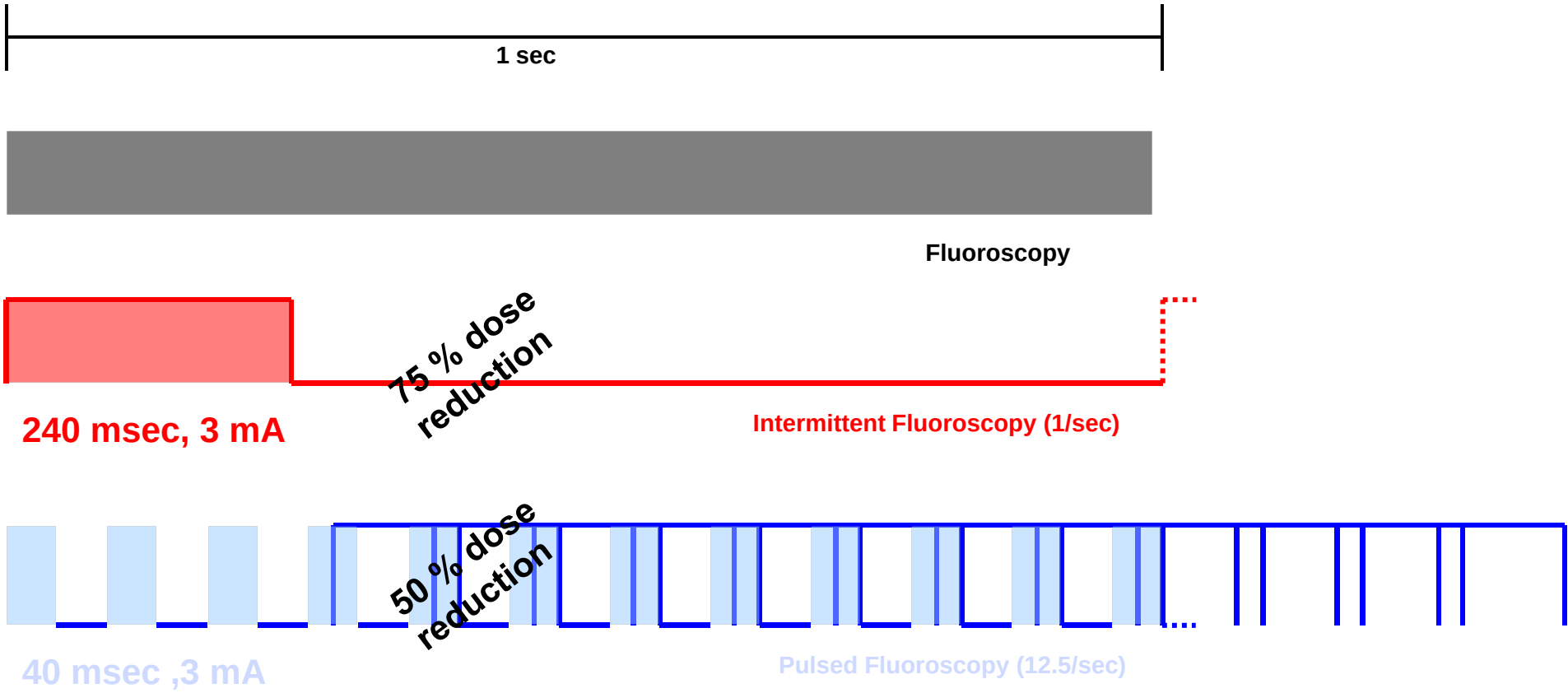
Biomedical Imaging: Introduction and X-ray



Tube in BOTTOM position

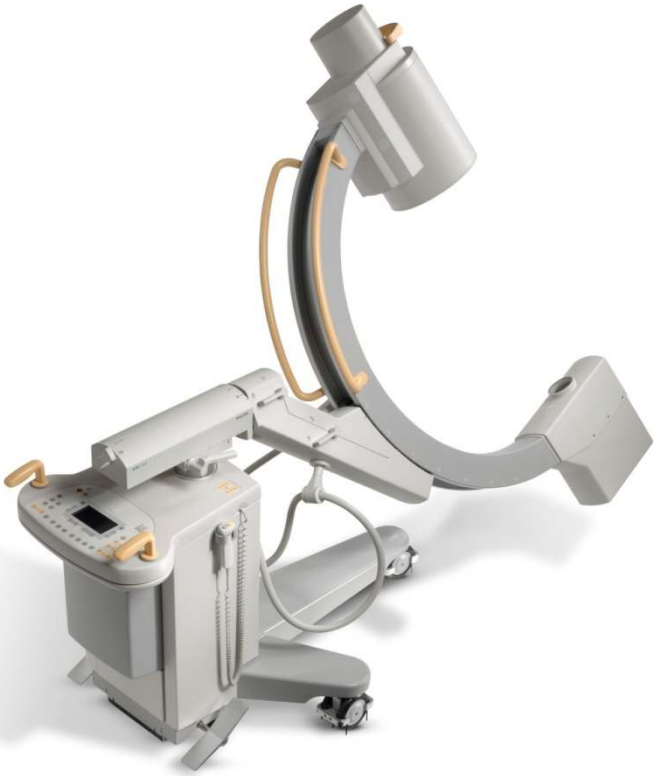


A „dose reduction” technique



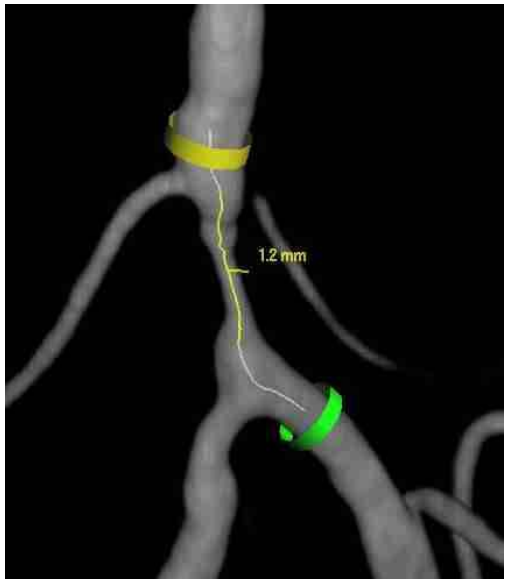
Surgery

Special mobile
fluoroscopy equipment



Digital Subtractive Angiography (DSA)

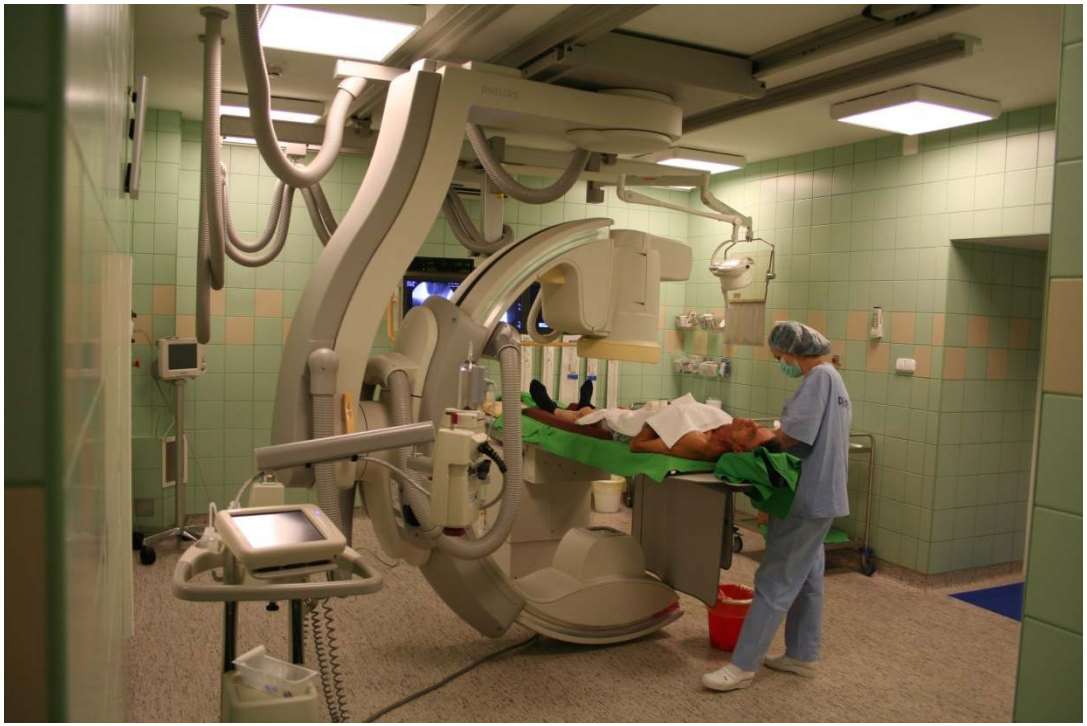
Rotational Angiography



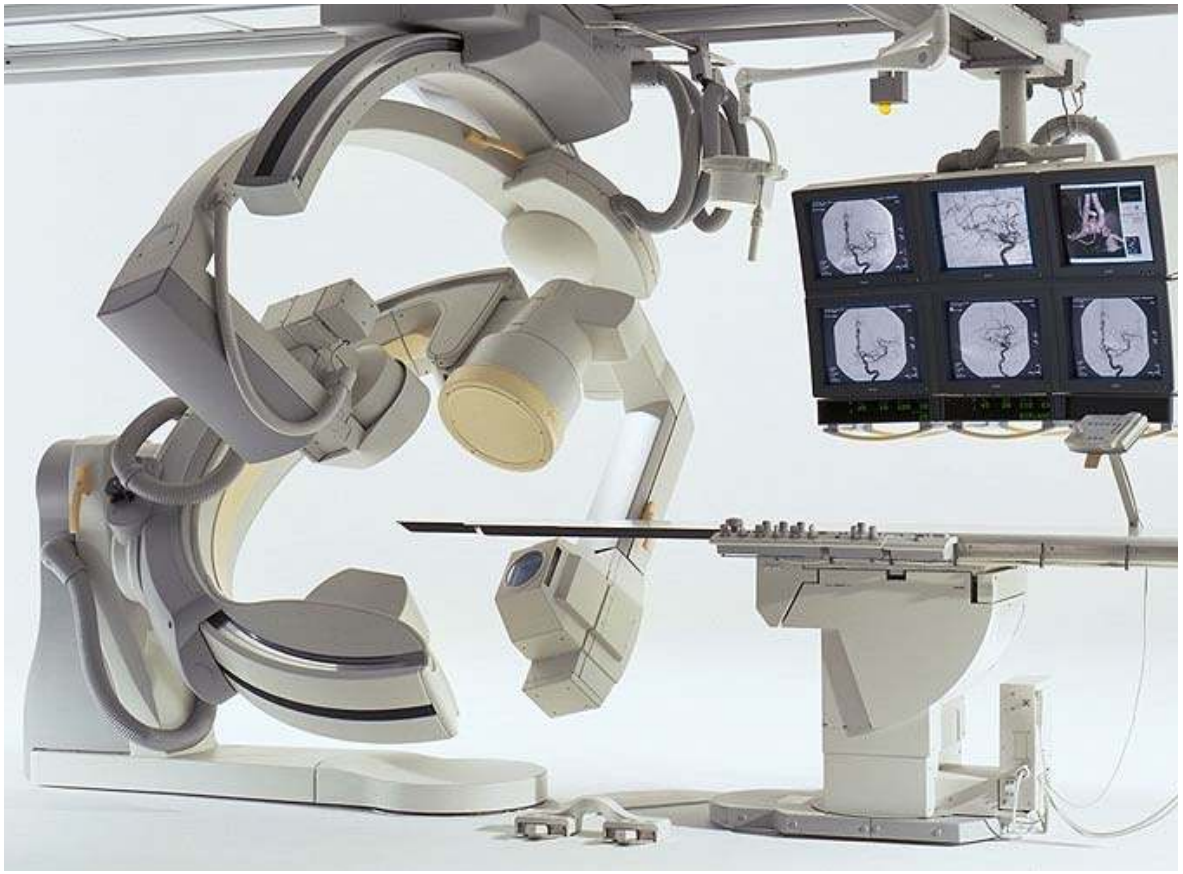
3 D imaging

Simple measurement

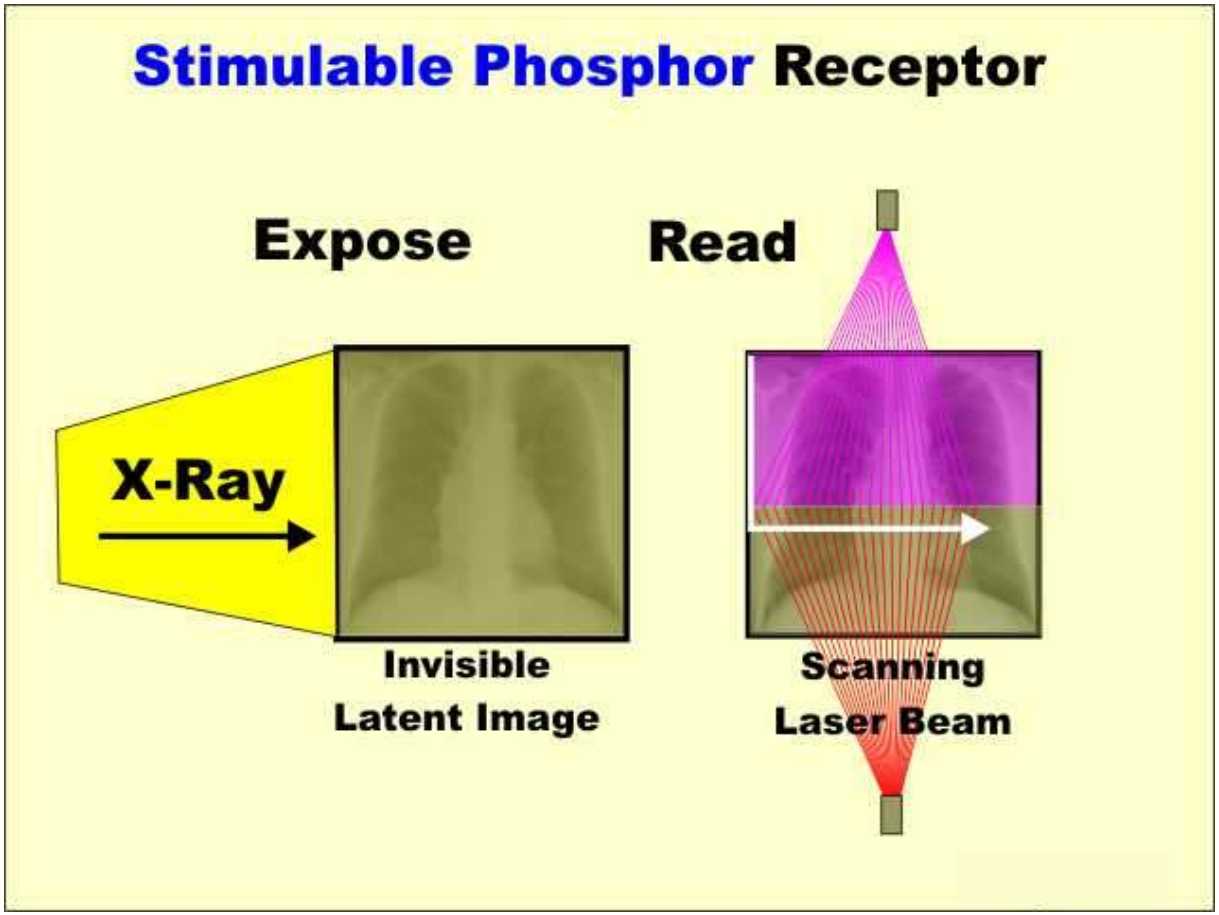
High performance fluoroscopy equipment for angiography (Monoplane)



High performance fluoroscopy equipment for angiography (Bi-plane)

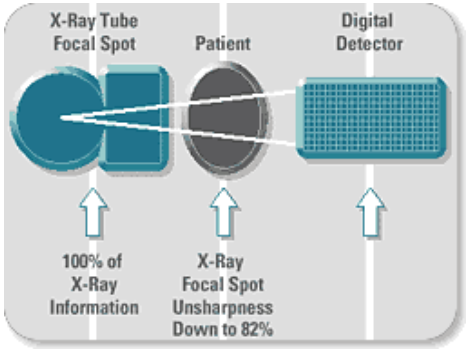


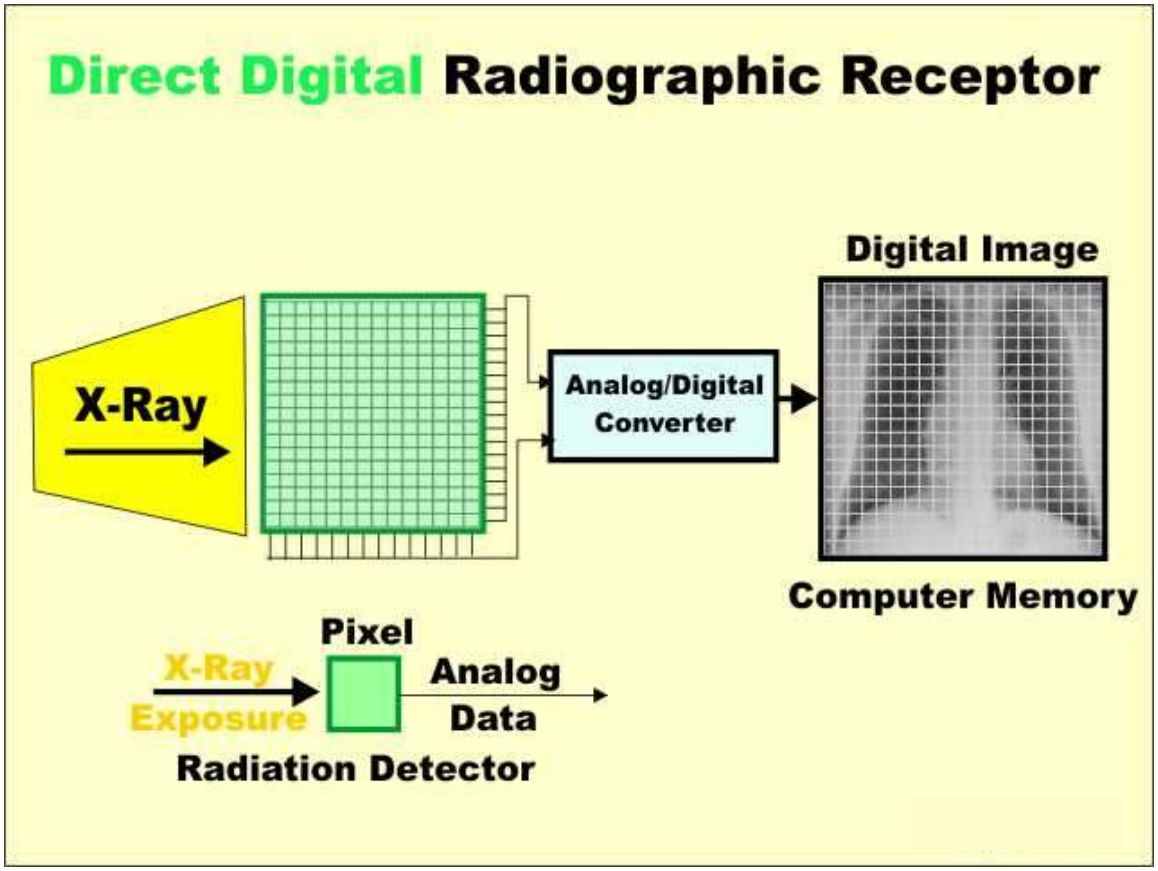
Computed Radiography



Typical phosphor-plate reader and cassettes

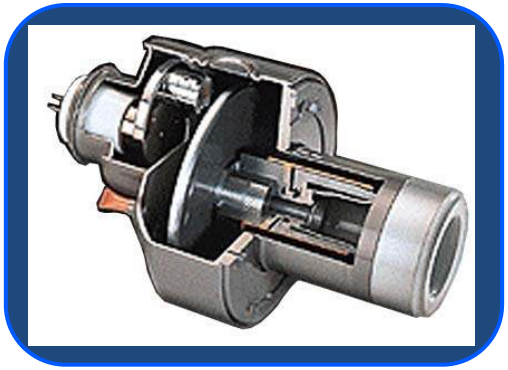
Direct Digital Radiography





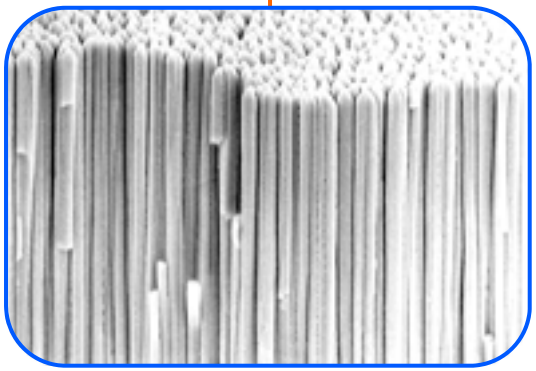
General purpose direct digital radiography system

Direct Digital DSA with Flat-detector

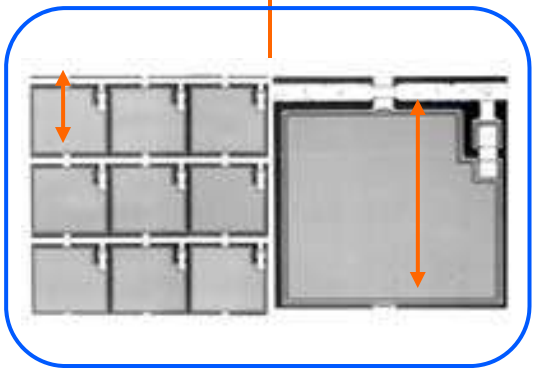


Flat detector

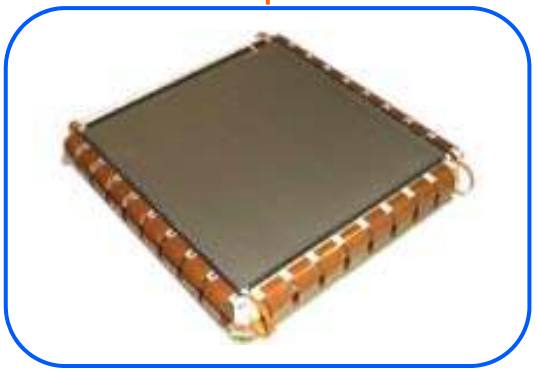
Direct digital x-ray detector for high performance and high speed fluoroscopy, angiography



Detection Layer

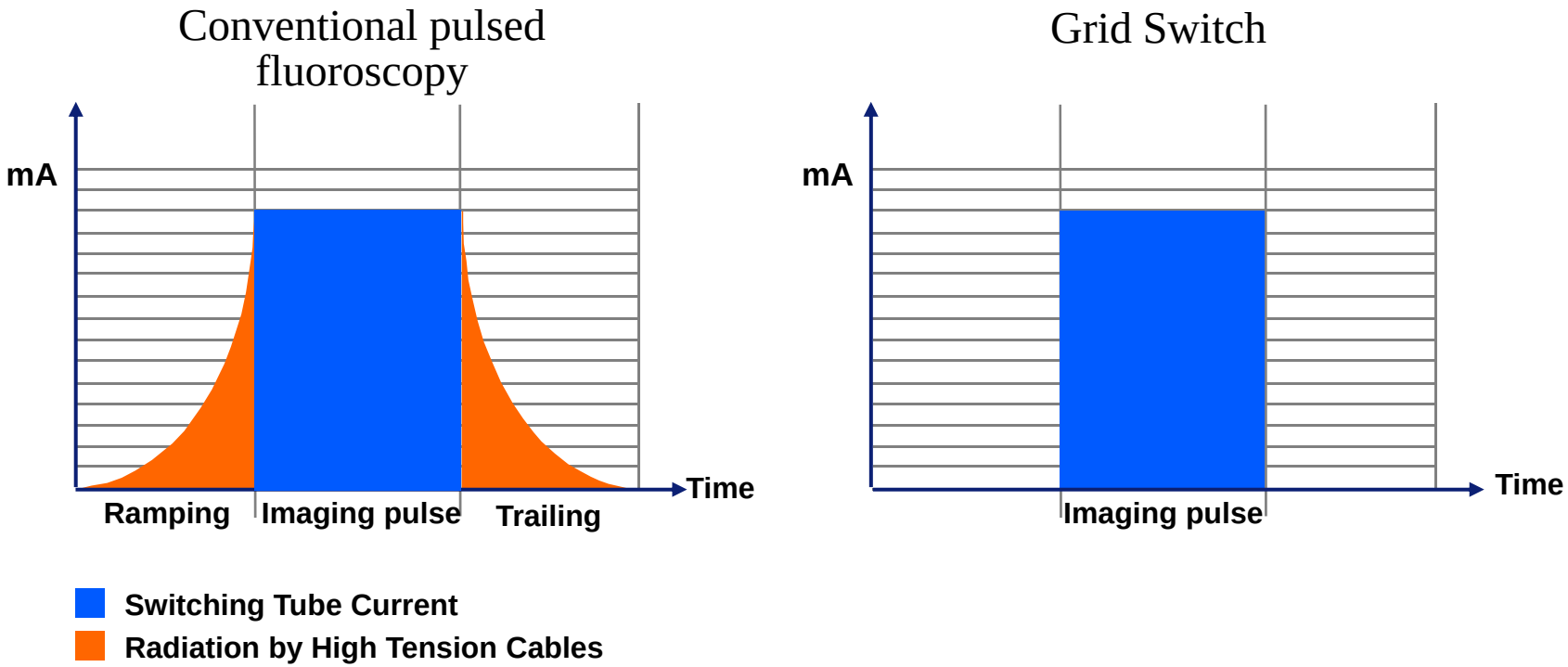


Photodiode Array



Refresh light

Grid Switch principle



SpectraBeam filtration

Filters out low-energy non-contributing X-rays, reducing patient dose:

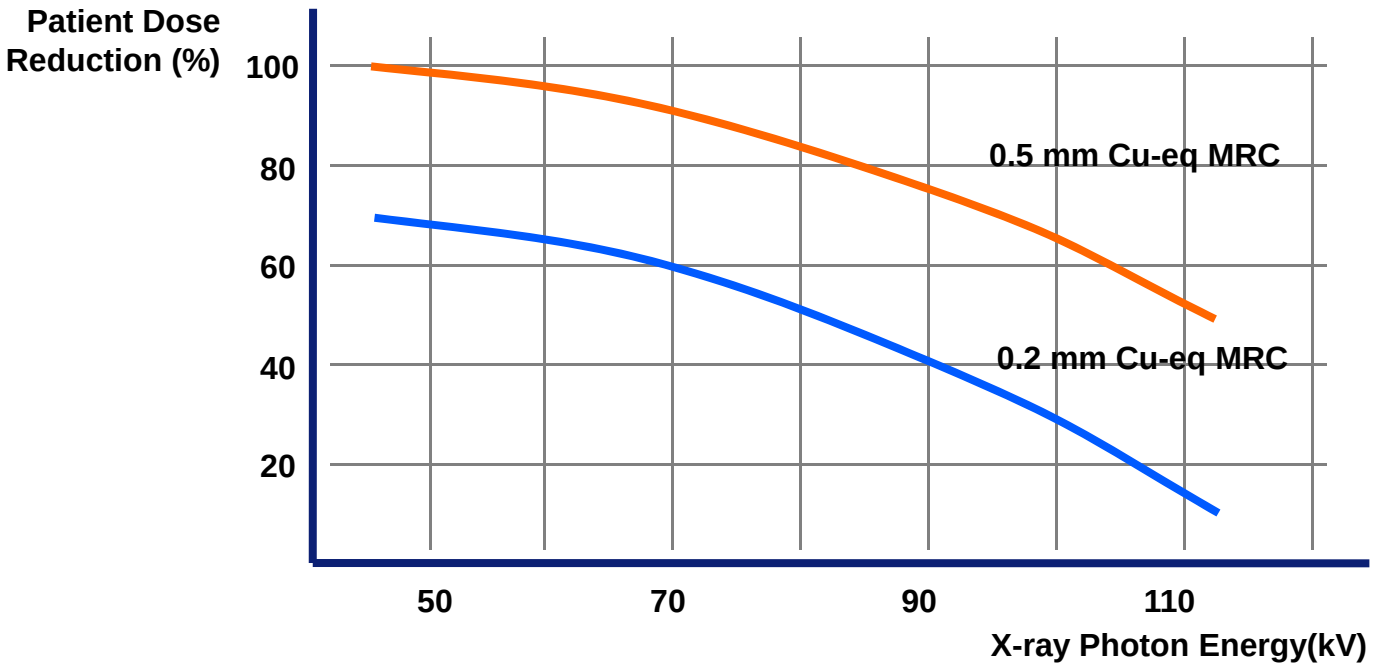


Image quality and dose management

Conventional X-ray tube
MRC X-ray tube – 0.2mm Cu
MRC X-ray tube – 0.5mm Cu

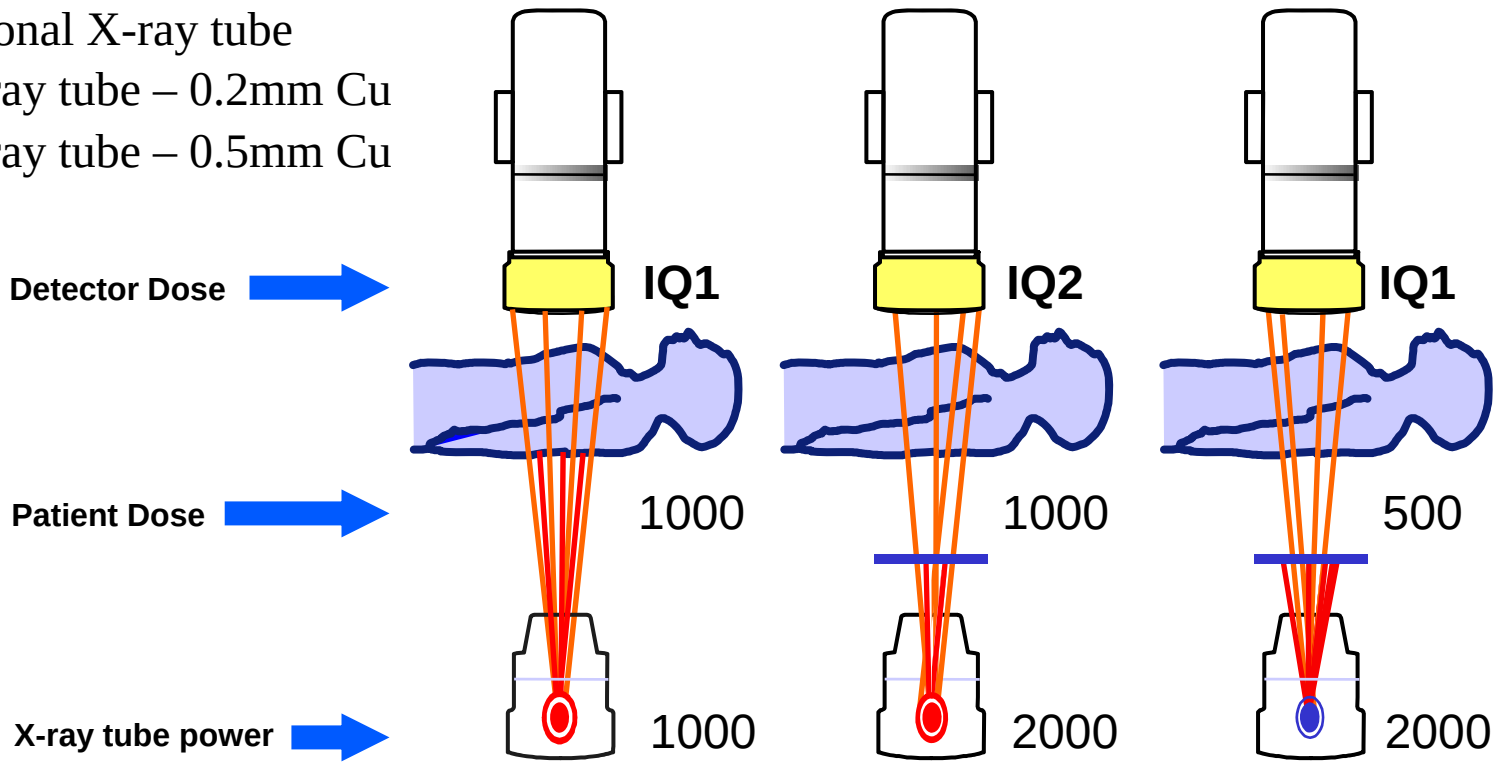
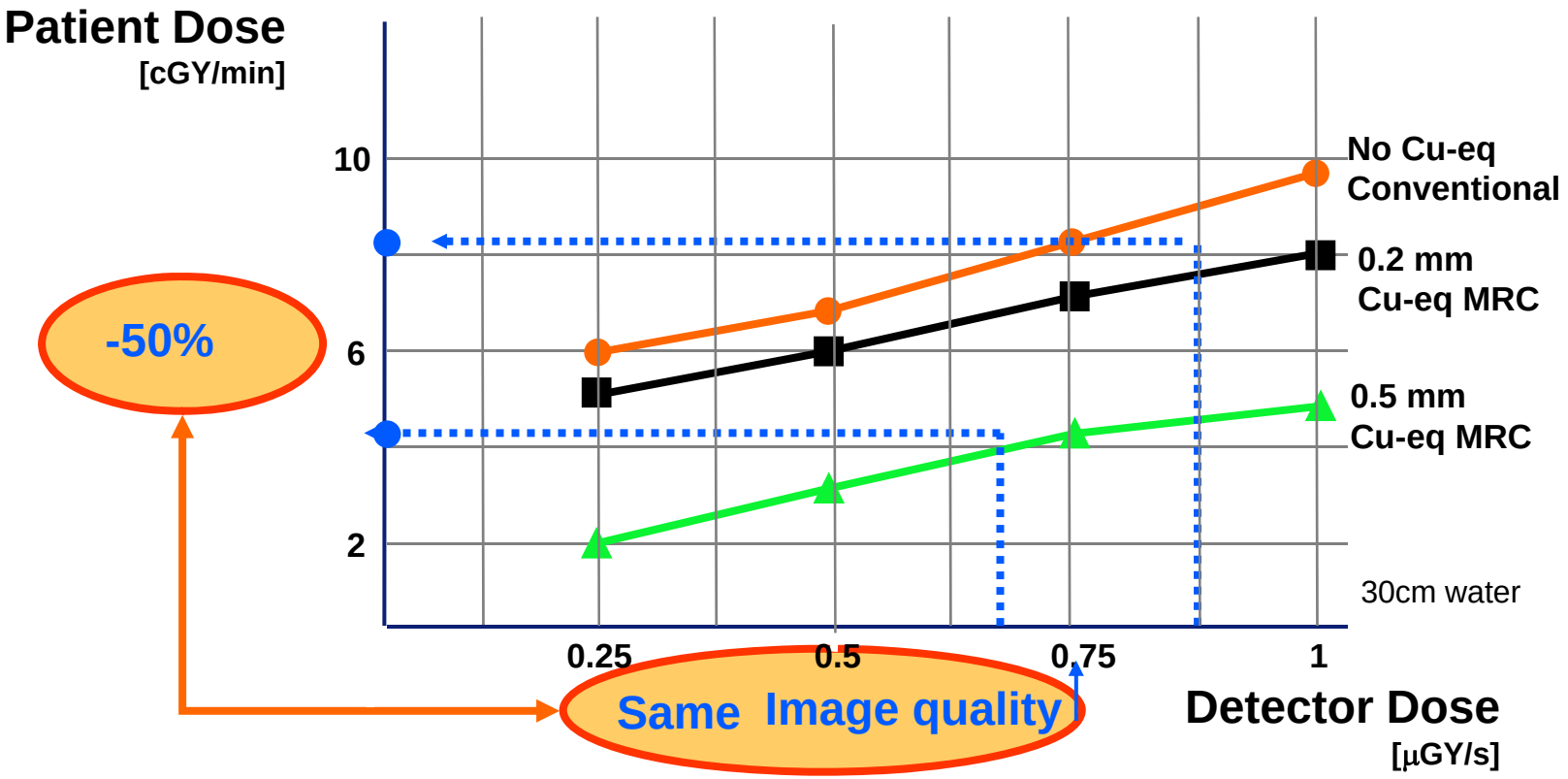


Image quality and dose management



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

BIOMEDICAL IMAGING

(Orvosbiológiai képalkotás)

COMPUTED TOMOGRAPHY (CT)

(Számítógépes tomográfia)

GYÖRGY ERŐSS

Tomography

Tomography is imaging by sections or sectioning. A device used in tomography is called a **tomograph**, while the image produced is a **tomogram**. The method is used in medicine, archaeology, biology, geology, materials science and other sciences. In most cases it is based on the mathematical procedure called **tomographic reconstruction**. There are many different types of tomography, as listed: (Note that the Greek word *tomos* conveys the meaning of "a section" or "a cutting"). A tomography of several sections of the body is known as a polytomography.

Conventional medical X-ray tomography:

- a sectional image through a body by moving an X-ray source and the film in opposite directions during the exposure

- structures in the focal plane appear sharper, while structures in other planes appear blurred

- by modifying the direction and extent of the movement, operators can select different focal planes which contain the structures of interest

Computed tomography (CT)

Conventional X-Rays

Single projection image
⇒ superimposed tissues

Computerized Tomography

Axial image obtained from hundreds of projections

Std. Resolution: 500 - 1200 projections
High Resolution: 900 - 2400 projections

Tissue superposition only within one slice thickness

Measured physical entity: tissue density
Information provided: organ structure

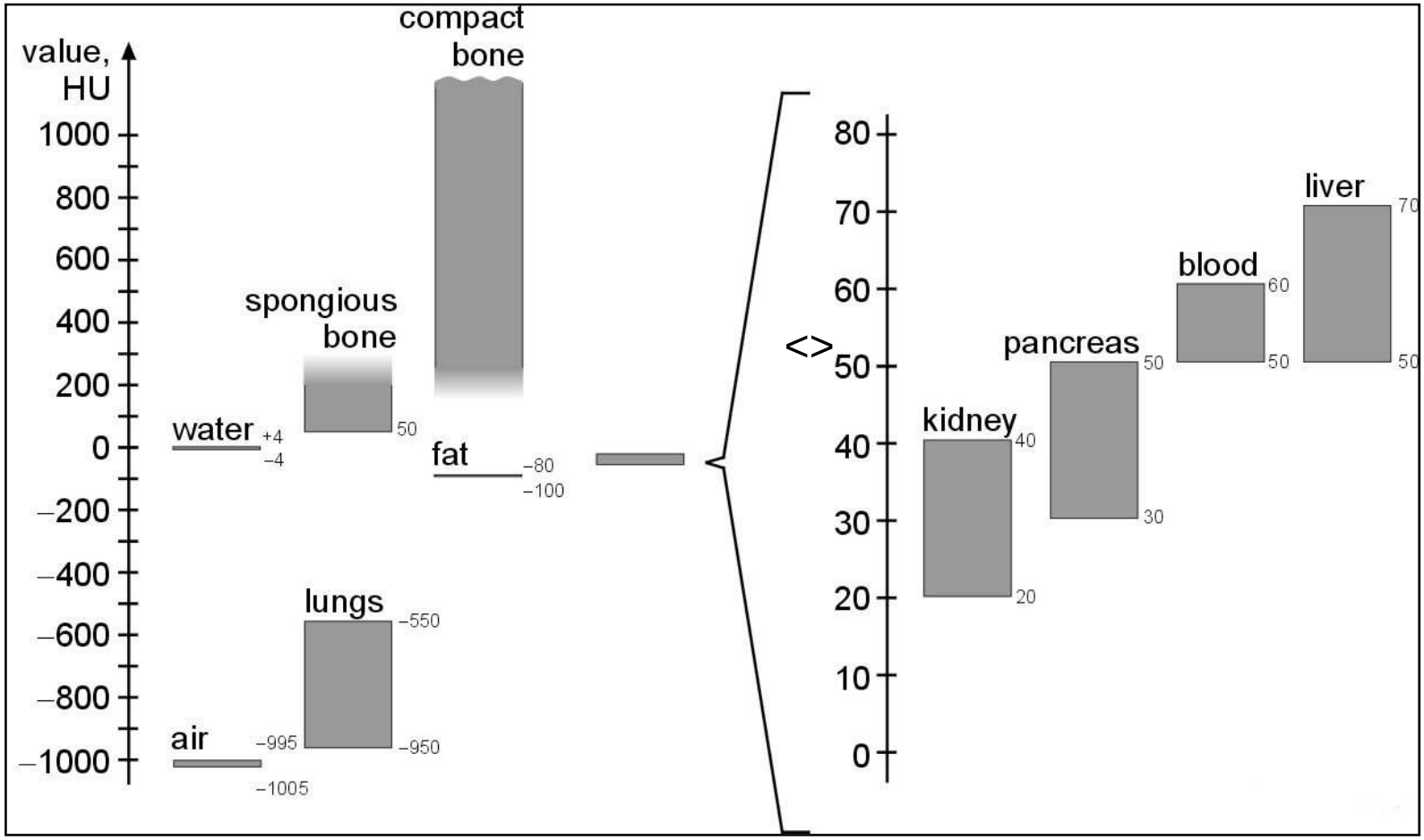
CT density unit: 1 Hounsfield Unit (HU) = 0.1% density of water
Air (zero density) = -1000 HU; Water = 0 HU

Precision & validity of CT densities:

- Relative only; CT uses a polychromatic X-ray beam
- CT densities are voltage, object size & real density dependent
- Precise density measurements in CT require dedicated calibrations

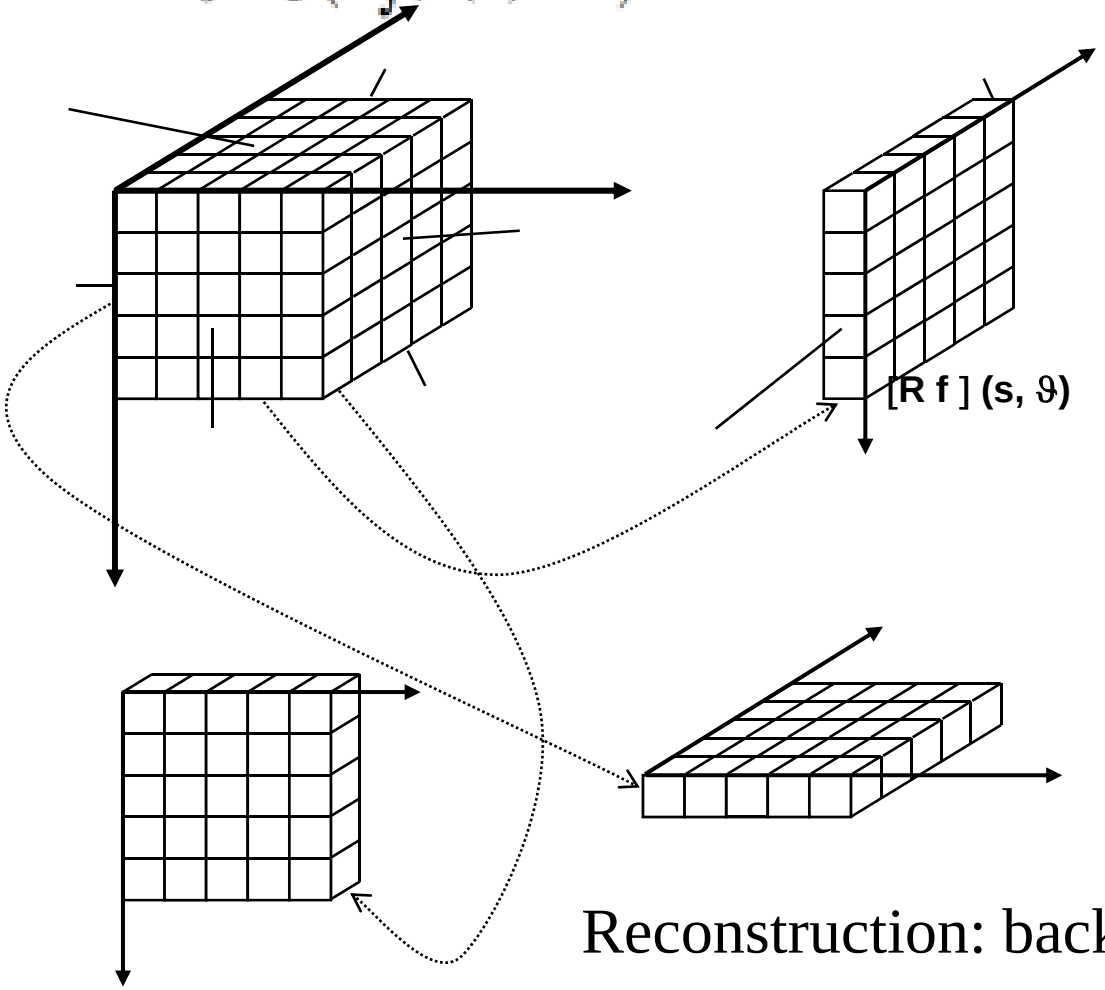
CT Spectrum of densities

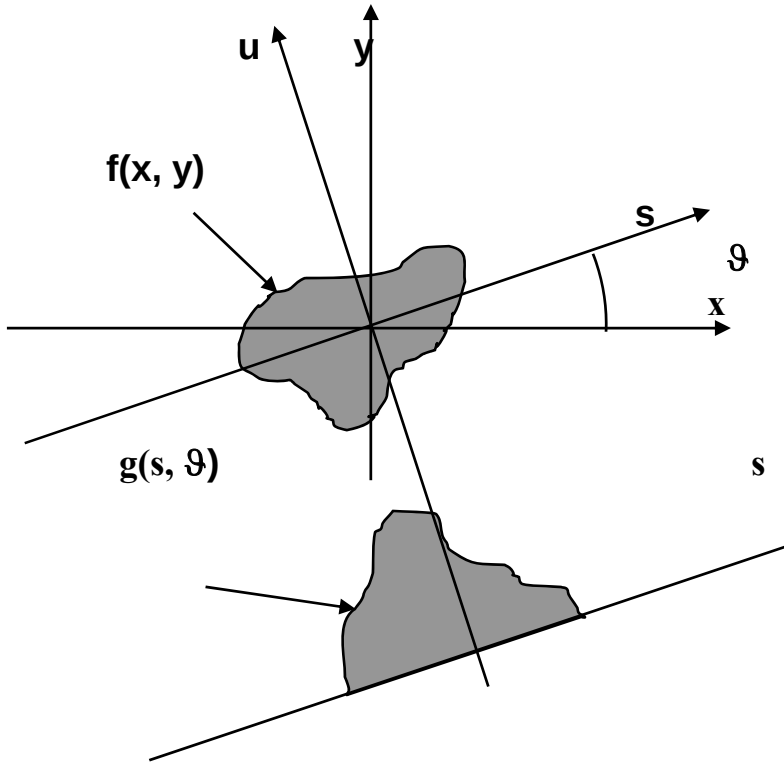
$$HU_{patient} = 1000 \cdot \frac{\mu_{patient} - \mu_{water}}{\mu_{water}}$$



Biomedical Imaging: Computed Tomography (CT)

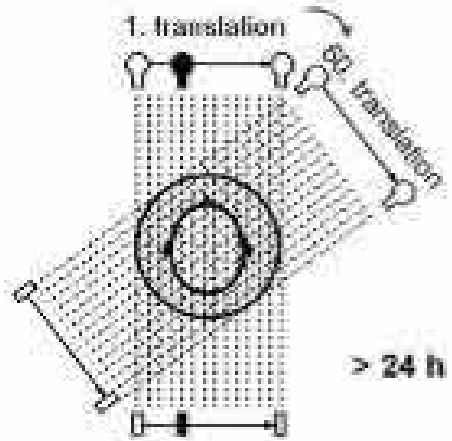
$$I = I_0 \exp\left(-\int \mu(x) \cdot dx\right)$$



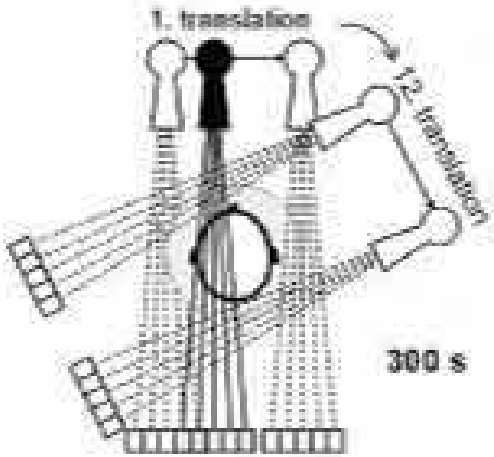


Reconstruction: backprojection => see article

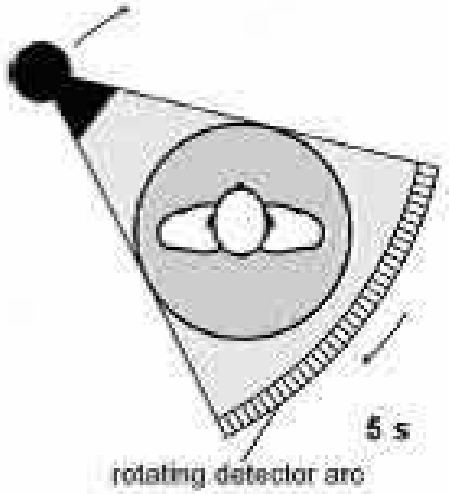
CT generations



1967 => 1972



1975



1976

4th generation:
continuous detector ring

3rd generation CT scanners:

- Axial scan only: „back&force”

  continuous

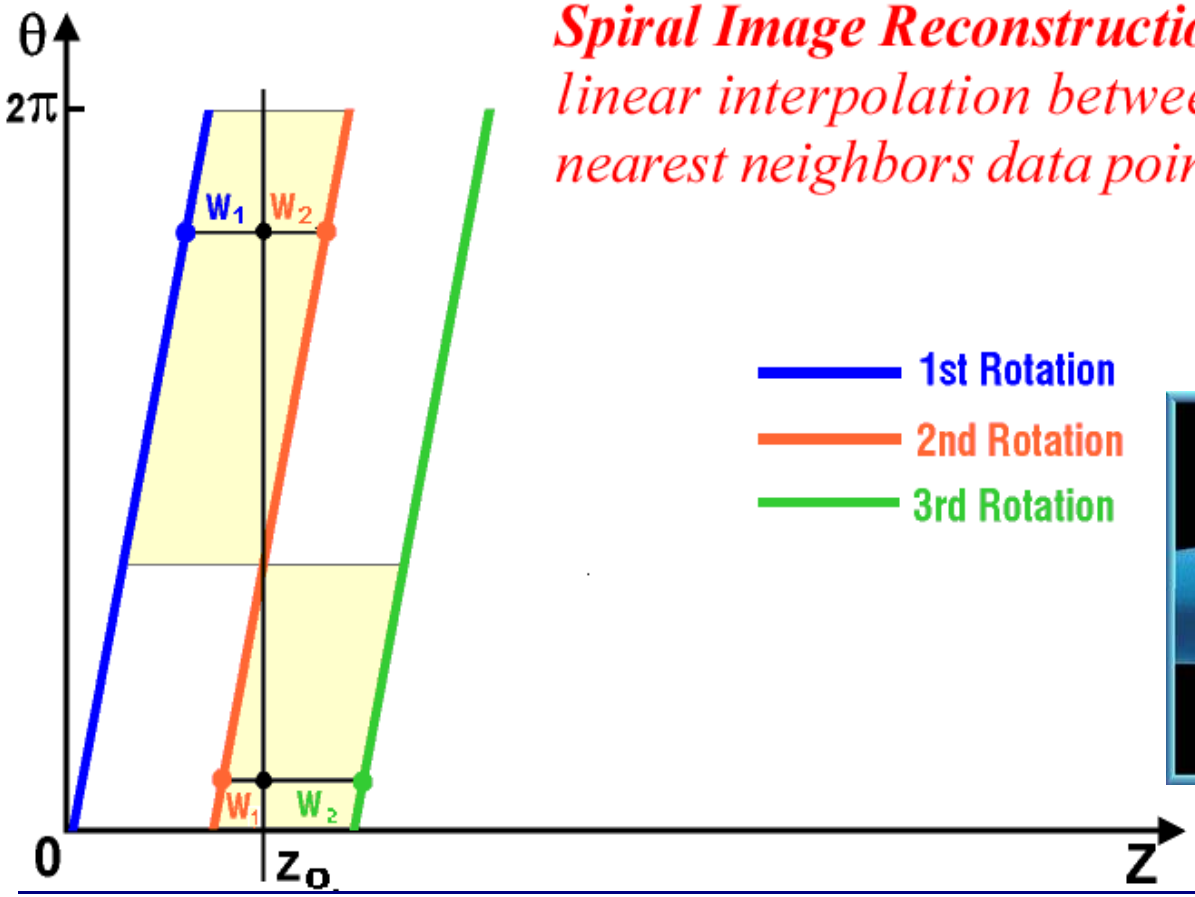
- Helical scan: single slice

  dual slice (1992)

  multi-slice: up to 16 slices — # of detector rows

  >16 slices — # of independent data

Spiral scanner



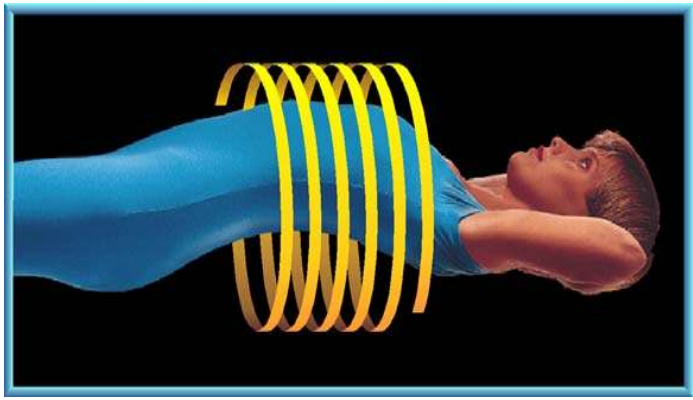
Spiral Image Reconstruction

linear interpolation between nearest neighbors data points

1st Rotation

2nd Rotation

3rd Rotation



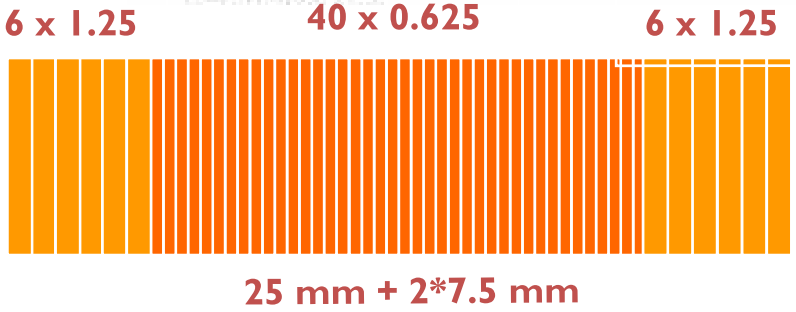
Factors Determining Low Contrast Resolution

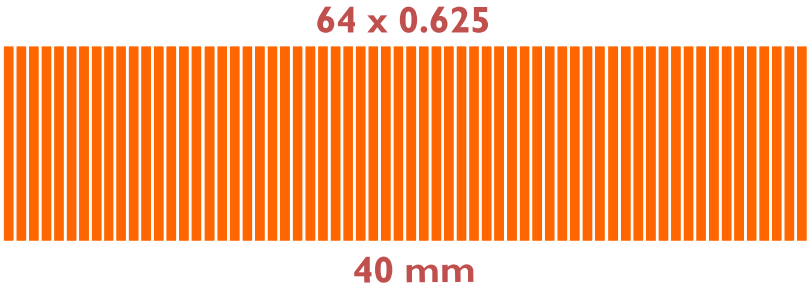
- Detection System: type, design & efficiency
  - » (Xenon or Solid-state)
- X-ray beam filtration: optimal design for beam hardness
- Scan Voltage: lower voltage provides improved low contrast resolution
- Signal-to-Noise Ratio:
  - Proportional to Dose (mAs)
  - Improved when post-collimation is available, protecting the detectors from scattered radiation

Factors Determining Spatial Resolution

- Design Parameters:
  - Detector aperture width (A_{eff}) at isocenter
  - Focal spot size (s)
  - Sampling density ($\leq A_{eff}/2$)
- Reconstruction Algorithm:
  - Filter Modulation Transfer Function
- Display Parameters:
  - Pixel size: p = FOV/(Matrix * Zoom)
  - Good Imaging Practice: p < image spatial resolution

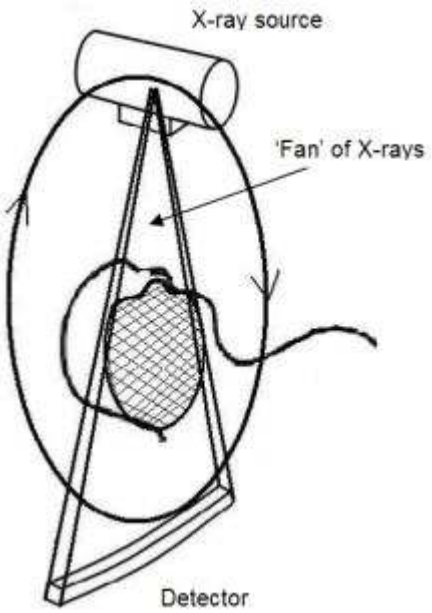
Biomedical Imaging: Computed Tomography (CT)

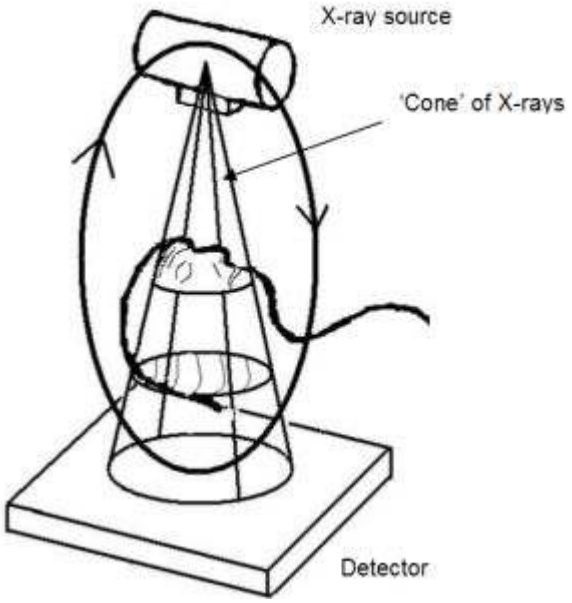




Philips Brilliance 40

Pencil beam => Fan beam => Cone beam





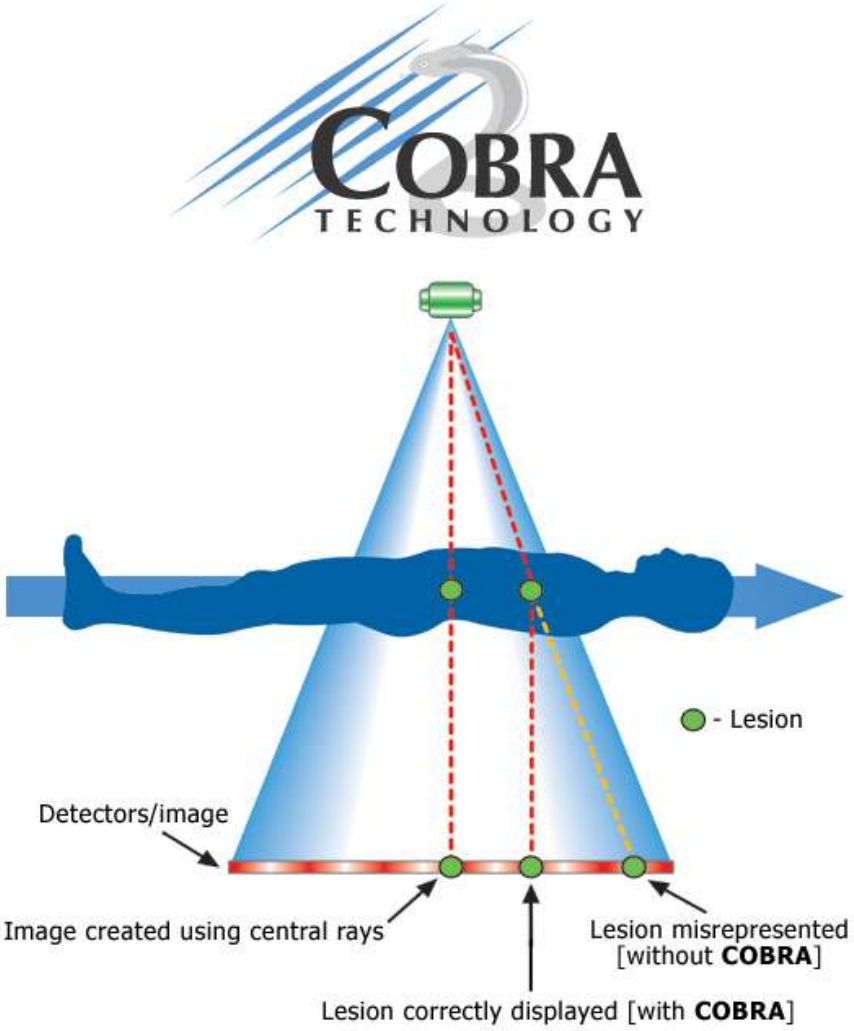
2D Fan Beam Image Reconstruction (1970 – 2001)

Filtered back-projection into a 2D matrix (Pixels) assuming parallel X-ray beams & ignoring the Cone Angle

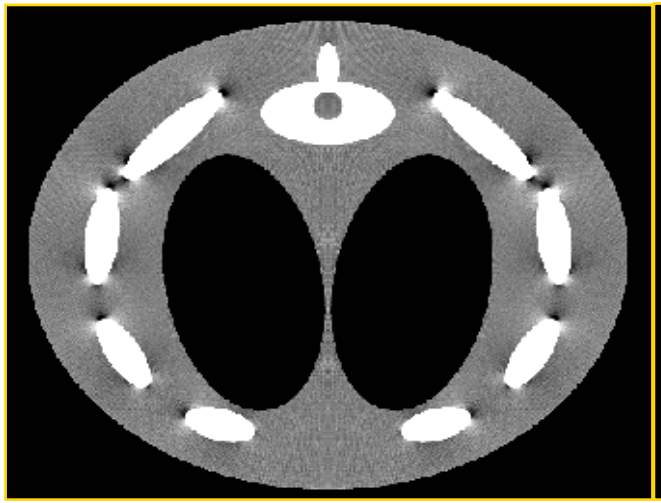
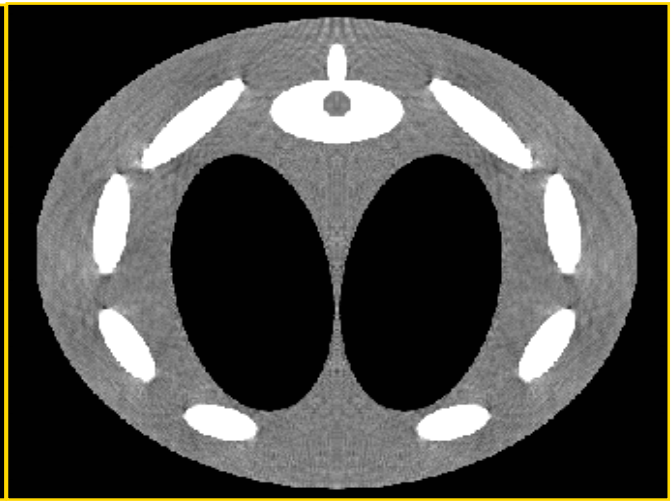
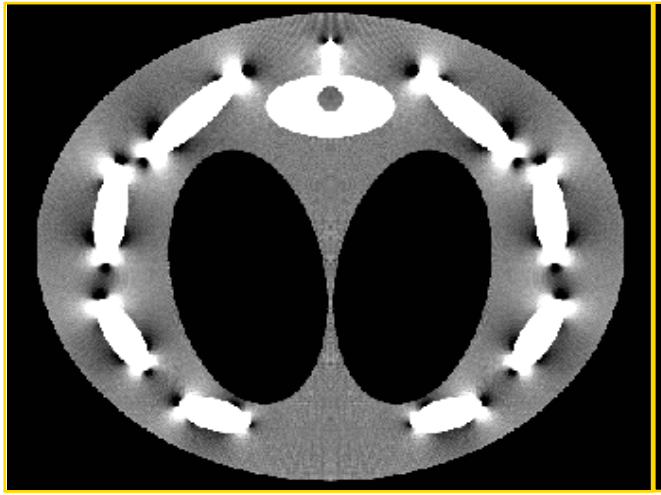
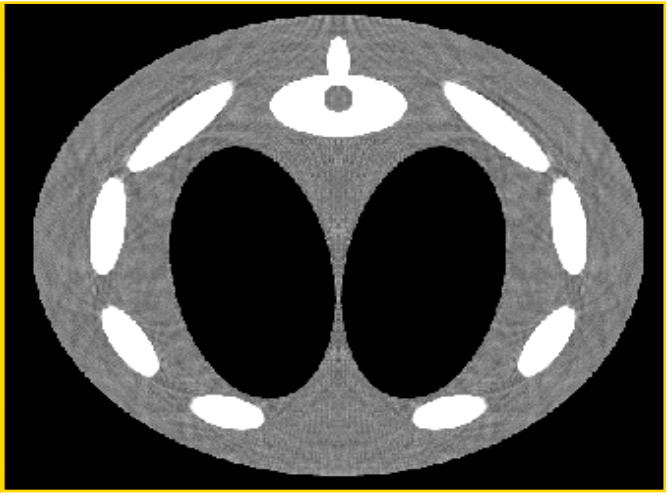
Cone Beam Reconstruction Algorithm (>2001)

Filtered back-projection into a 3D matrix (Voxels)
Each Voxel reconstructed individually.
Only views passing through each individual voxel during the acquisition process are back-projected into it

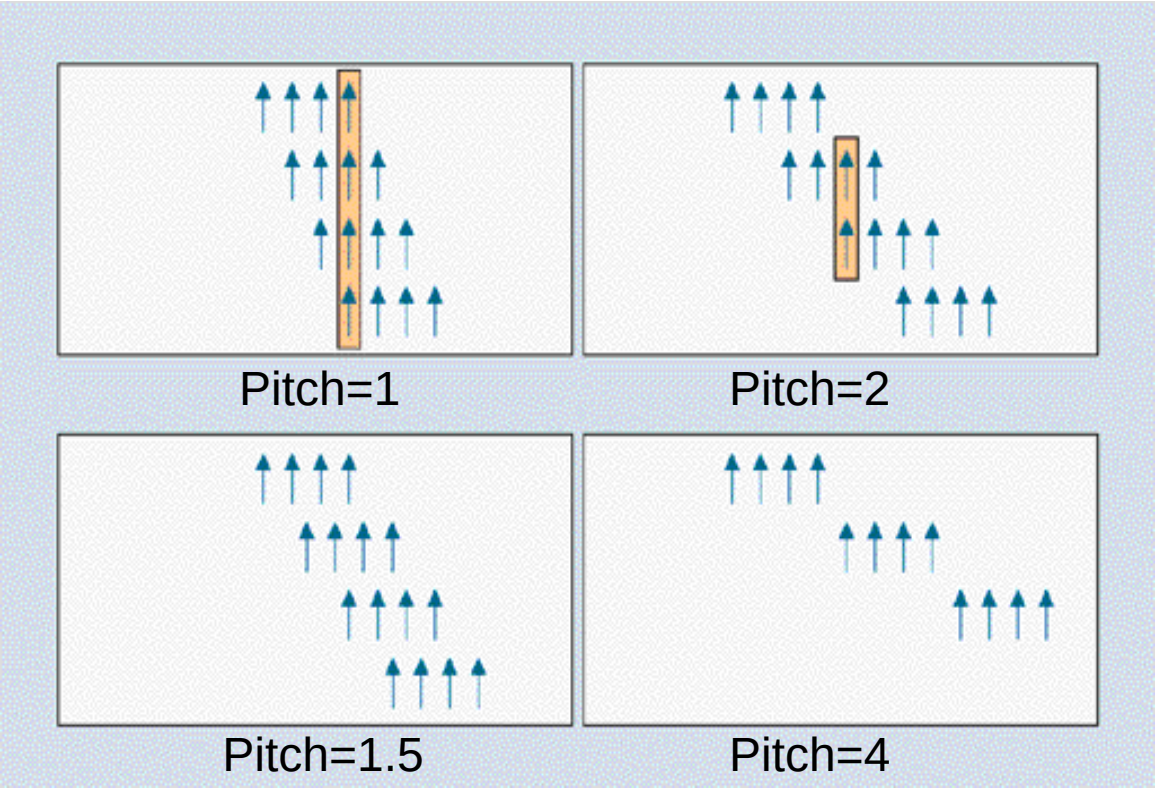
Biomedical Imaging: Computed Tomography (CT)



Biomedical Imaging: Computed Tomography (CT)

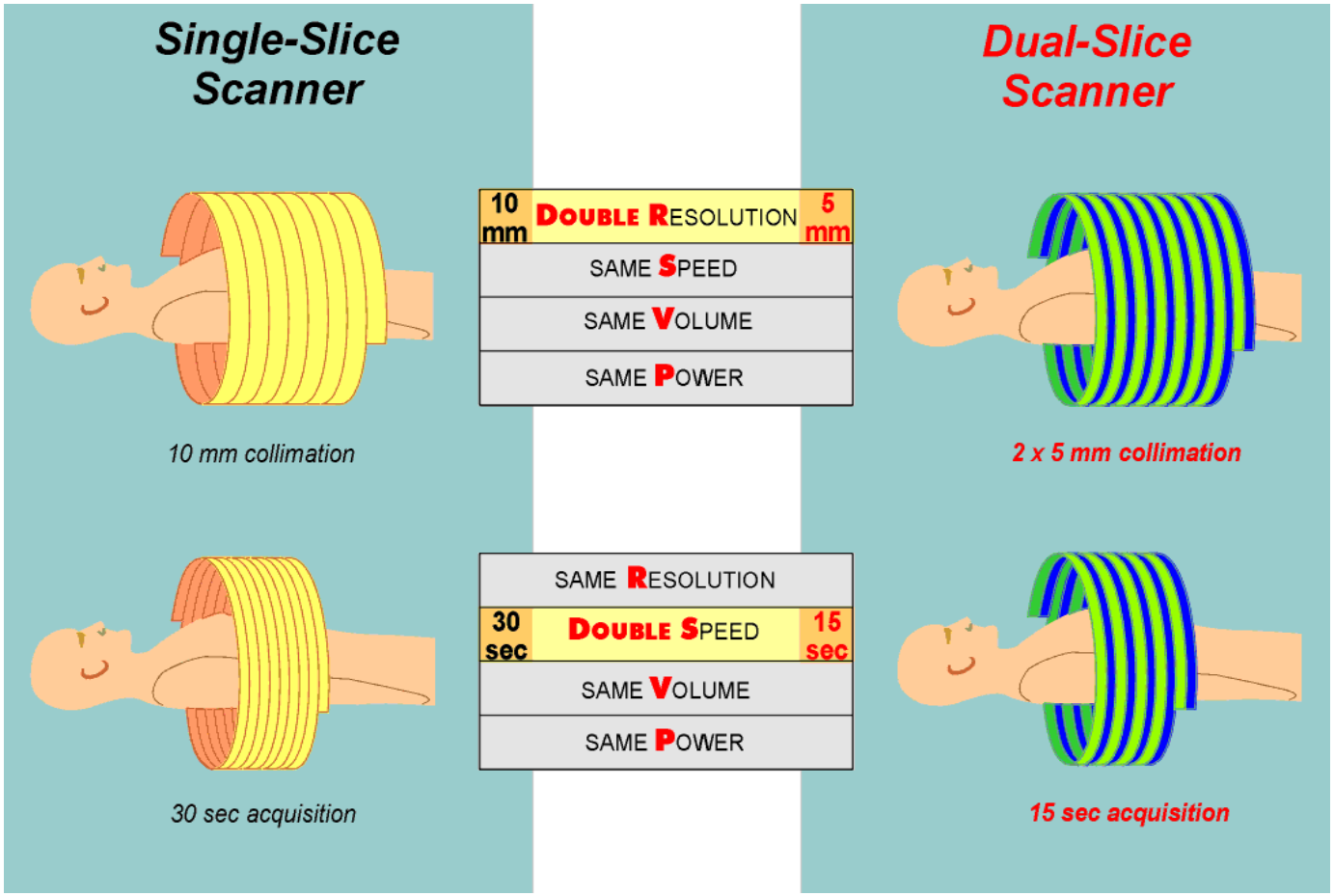
	Fan Beam Recon	Cone Beam Recon
4 mm from mid -plane		
8 mm from mid -plane		

Speed vs. information => Pitch

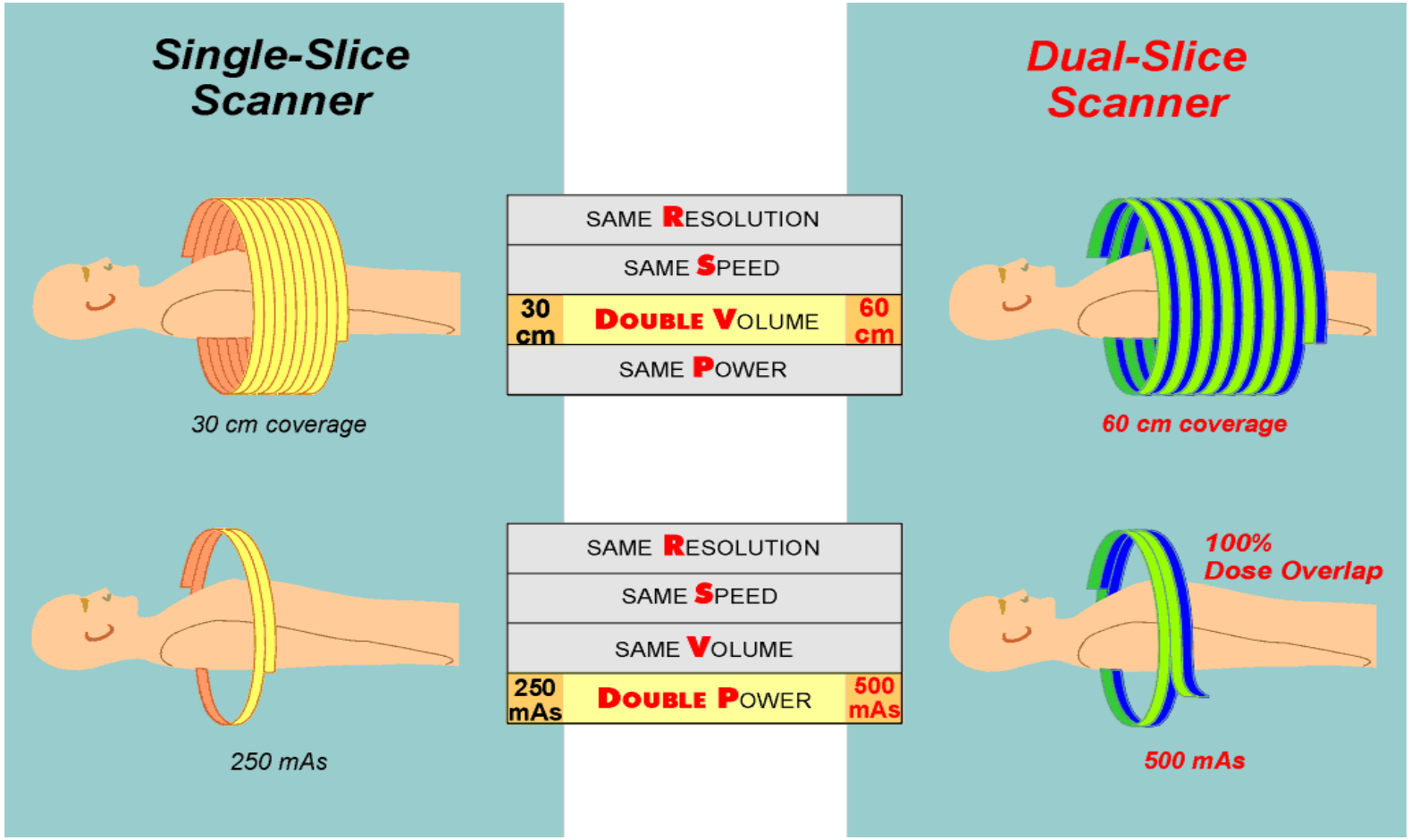


The pitch is the ratio of the patient table increment to the total nominal beam width for the CT scan. The pitch factor relates the volume coverage speed to the thinnest sections that can be reconstructed. In spiral CT, dose is always inversely proportional to pitch.

Multi-Slice RSVP Advantages

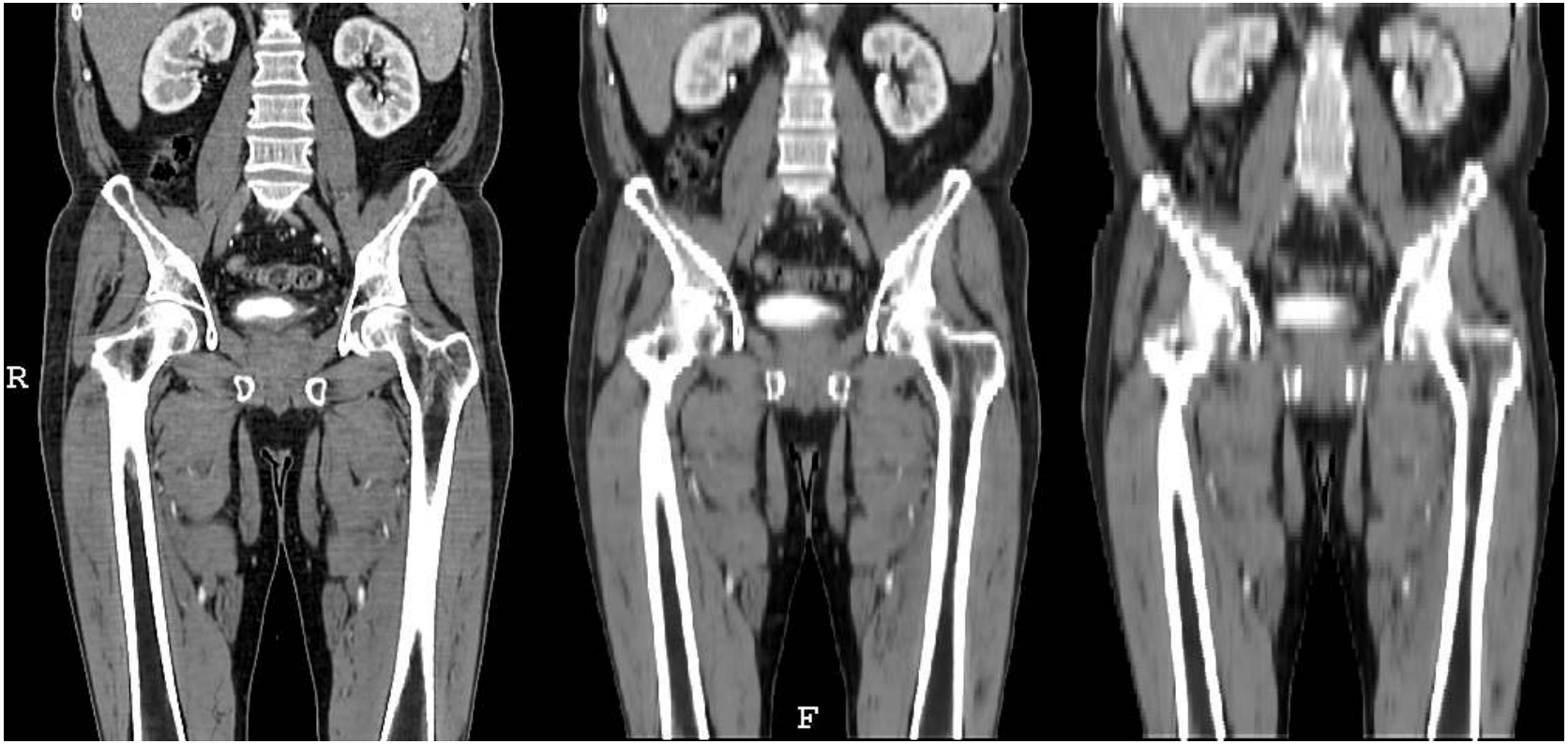


Multi-Slice RSVP Advantages



Multi-Slice Resolution Advantage

Quad-Slice | Dual-Slice | Single-Slice

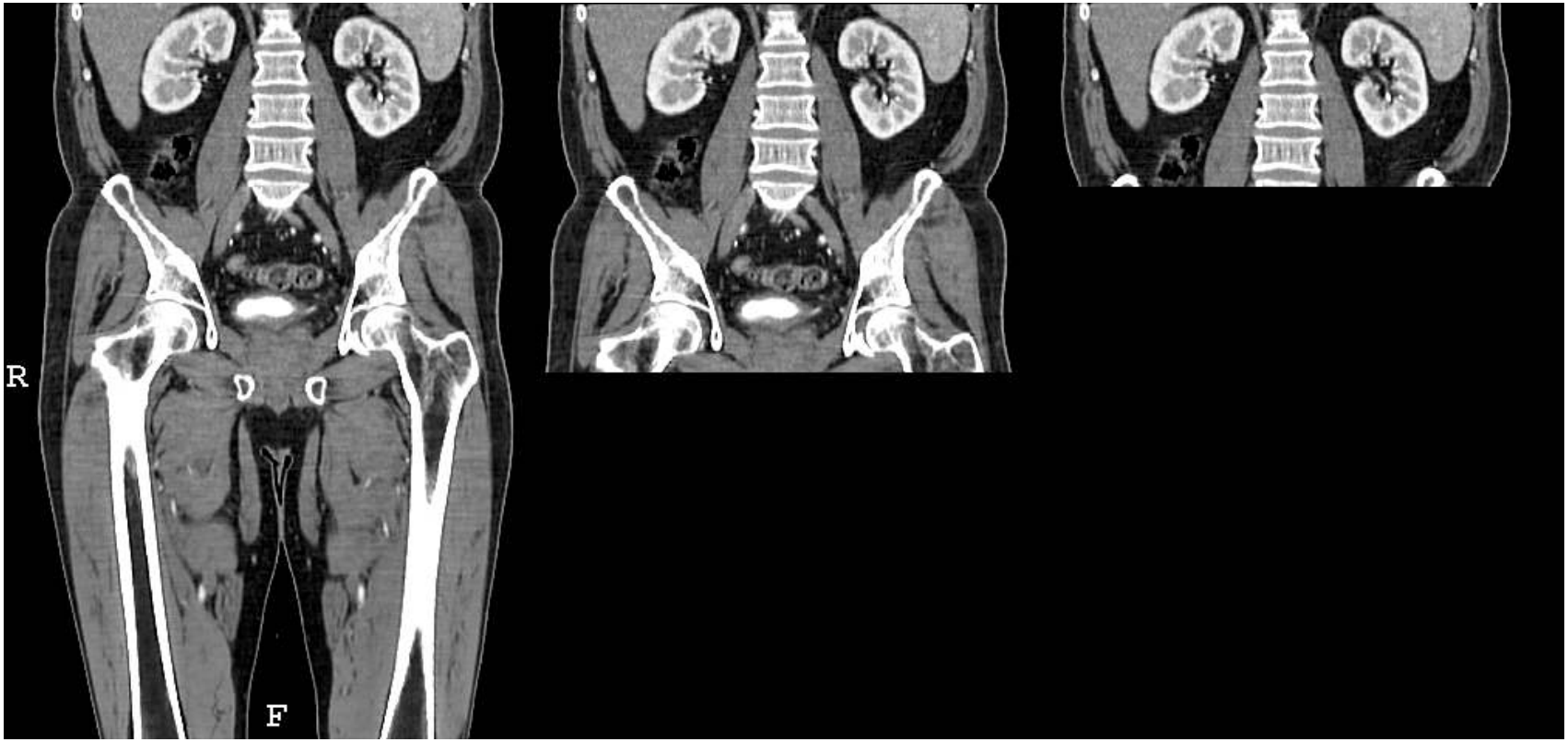


4x2.5mm; 2.5cm/sec | 2x5.0mm; 2.5cm/sec | 10mm; 2.5cm/sec

72 cm coverage; 28 sec; 120kV / 130 mAs

Multi-Slice Volume Advantage

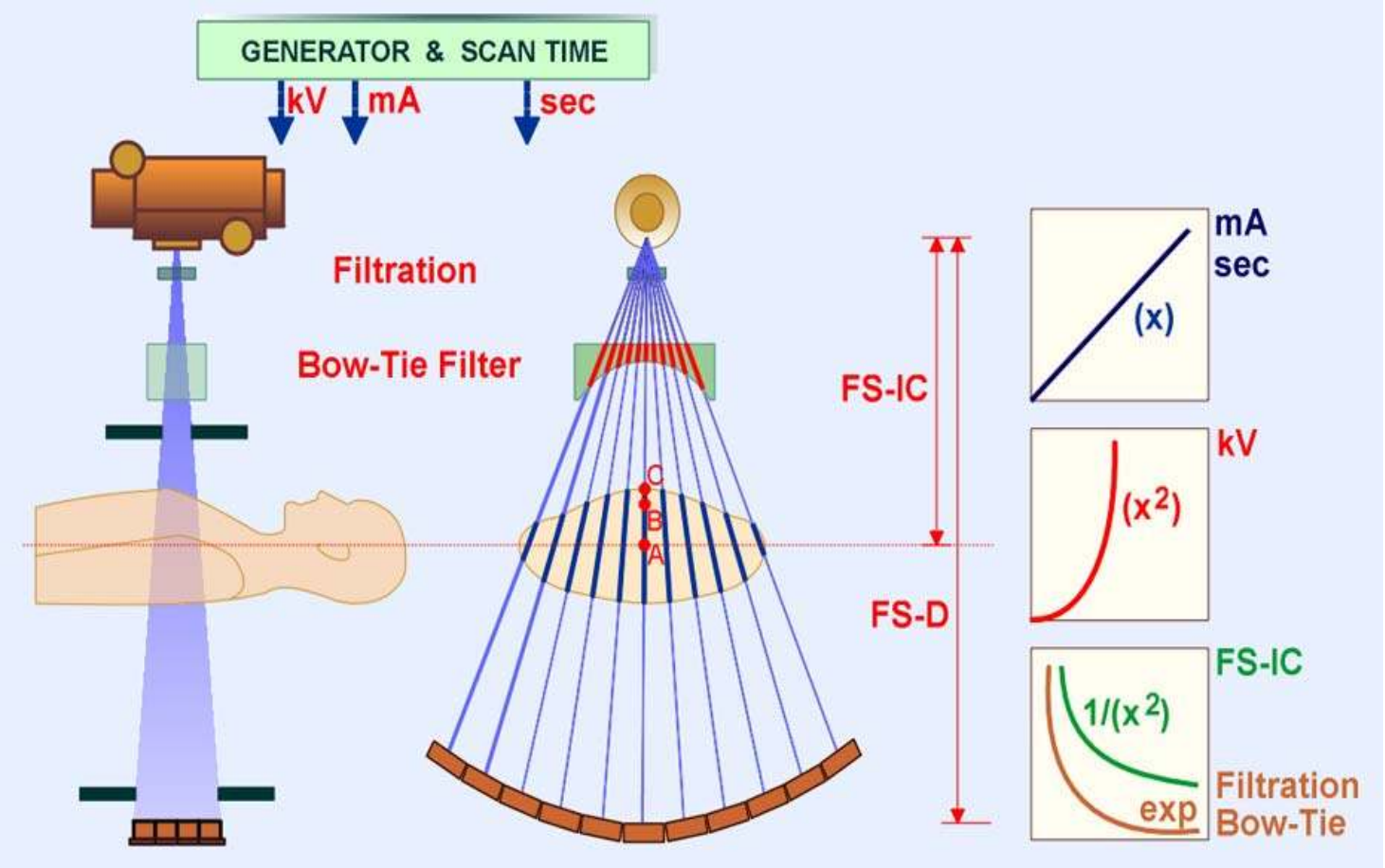
Quad-Slice Dual-Slice Single-Slice



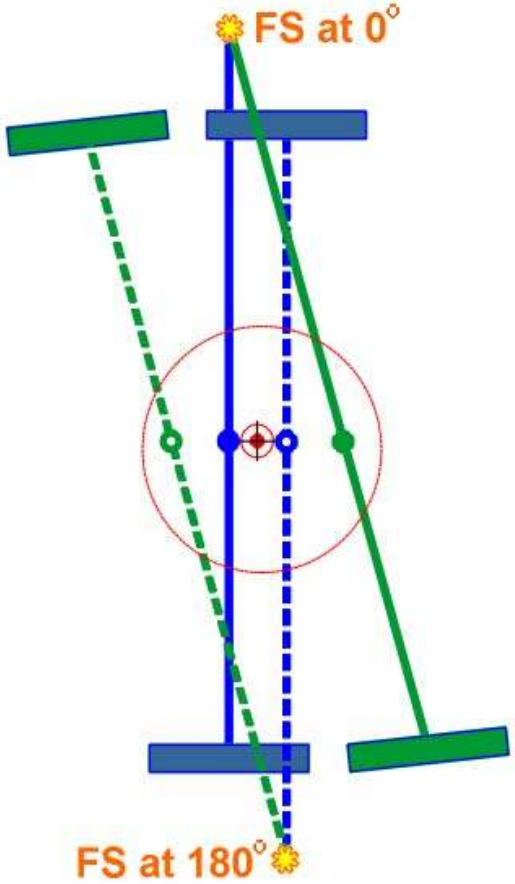
72 cm coverage 36 cm coverage 18 cm coverage

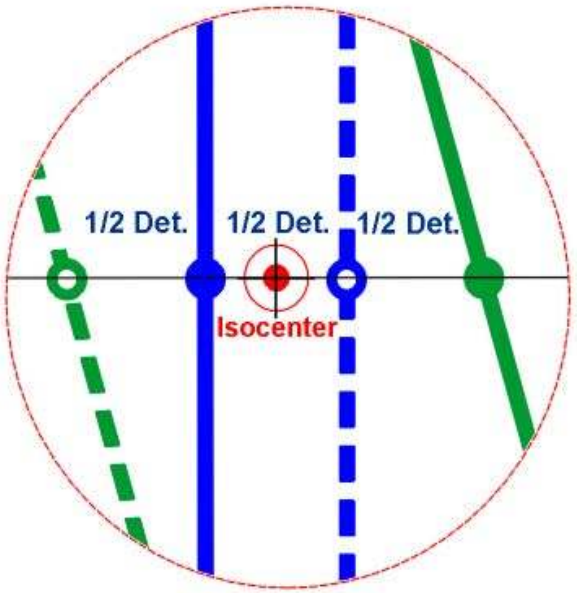
3.2 mm Eff. ST; 28 sec; 120kV / 130mAs

Patient Dose Path

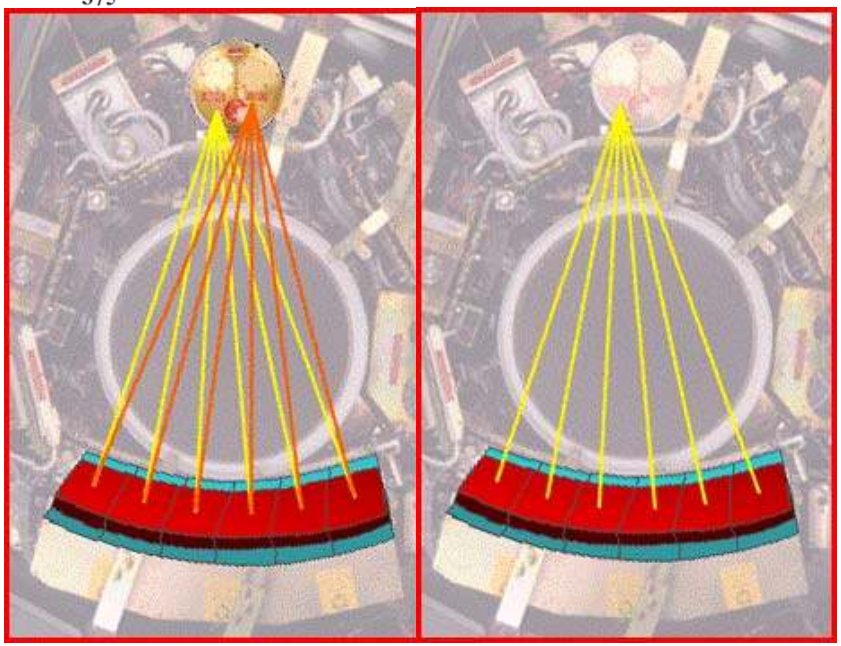


Quarter detector shift

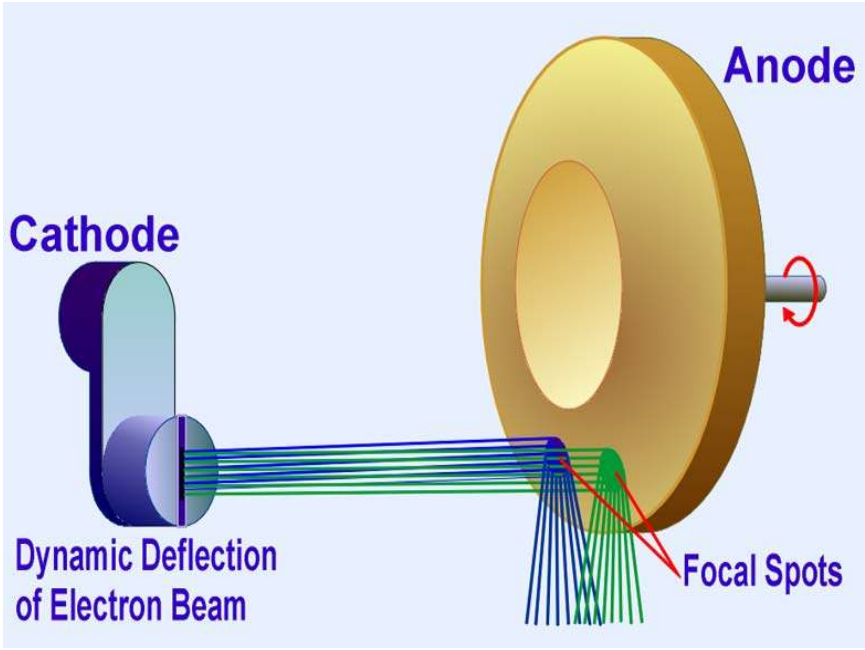




Biomedical Imaging: Computed Tomography (CT)



Dynamic
Focal
Spot



Doubles Ray Density
and thus
Doubles Spatial Resolution
with the same number of detectors

Towards „dual energy” solution

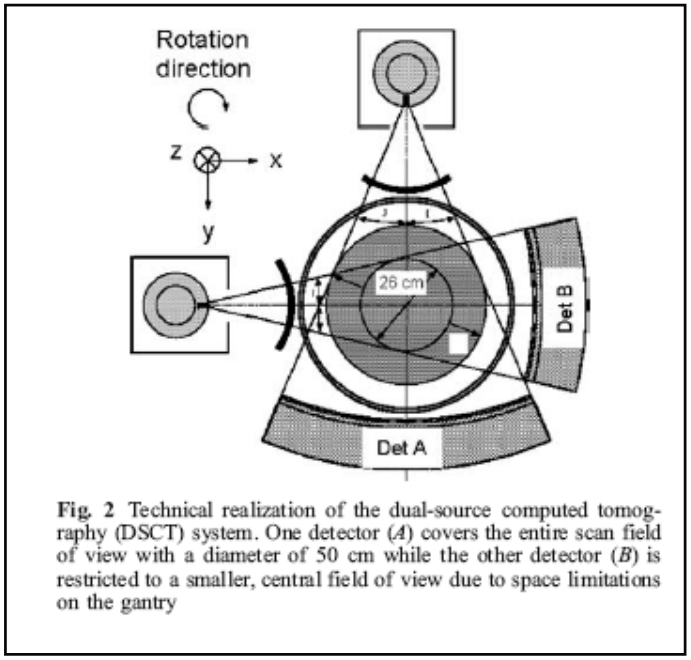
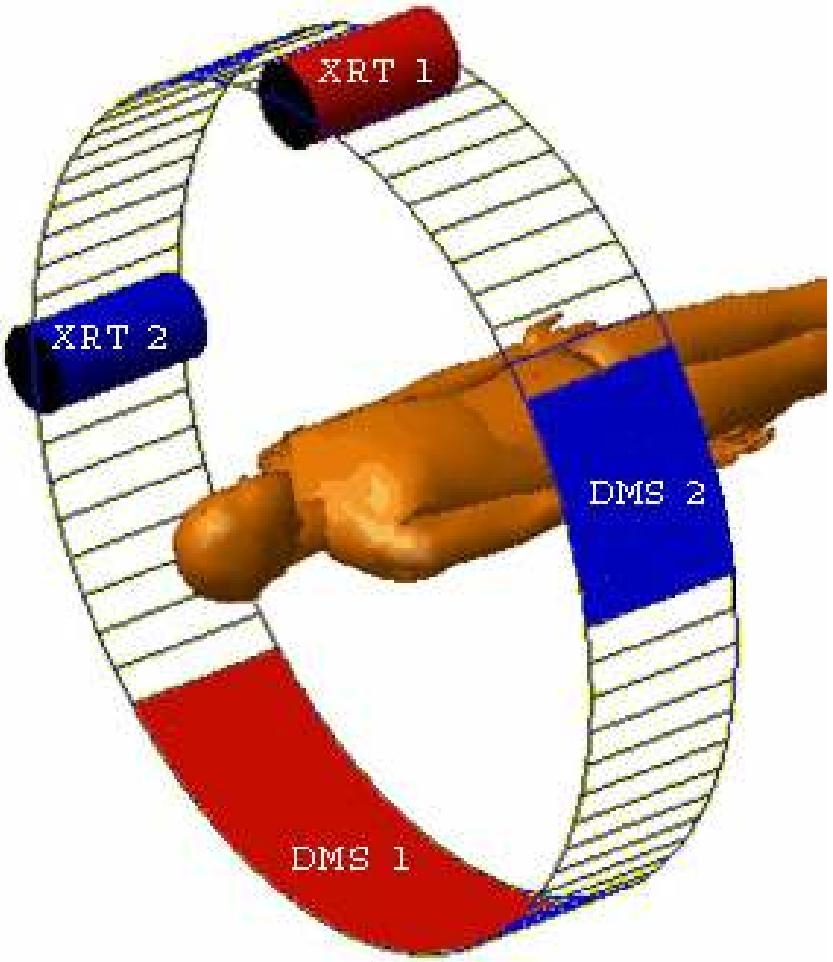
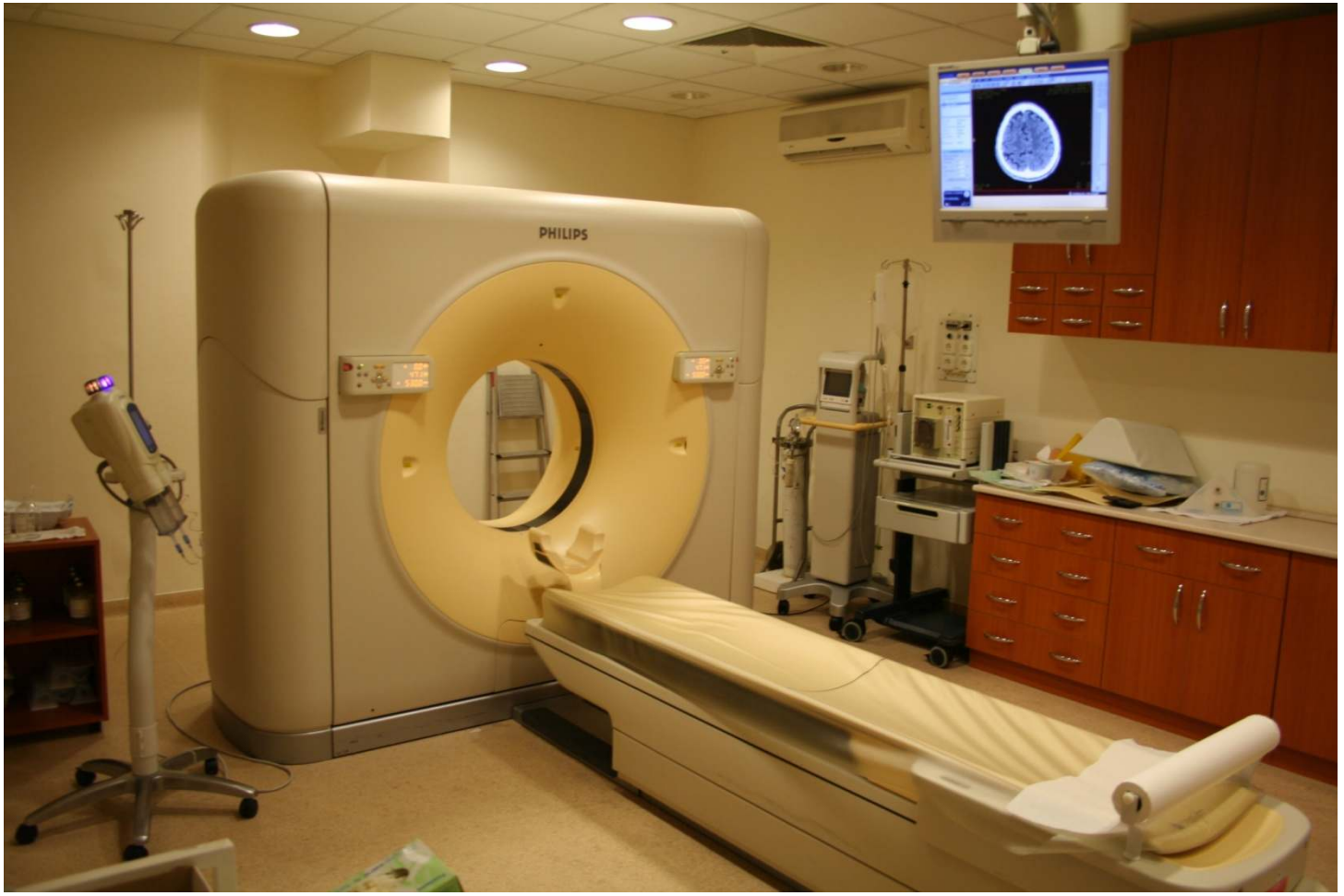


Fig. 2 Technical realization of the dual-source computed tomography (DSCT) system. One detector (*A*) covers the entire scan field of view with a diameter of 50 cm while the other detector (*B*) is restricted to a smaller, central field of view due to space limitations on the gantry



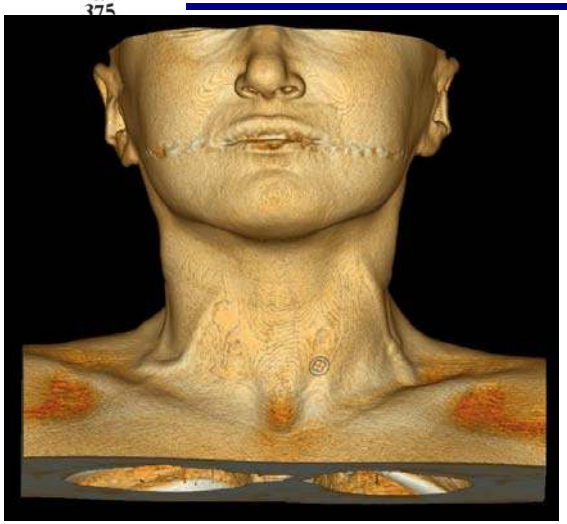
CT examination room with a 16 slice system

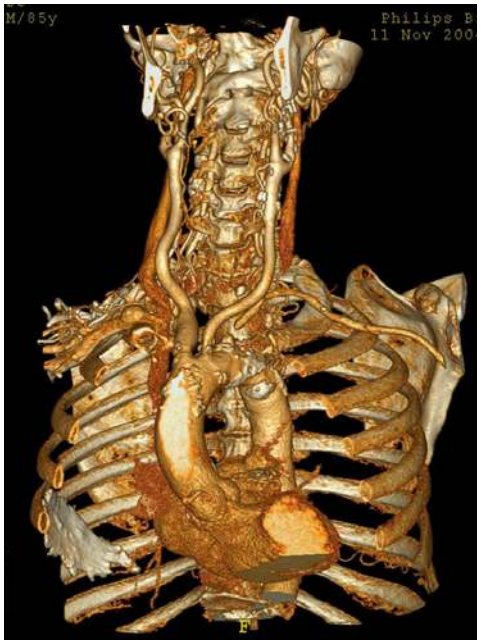


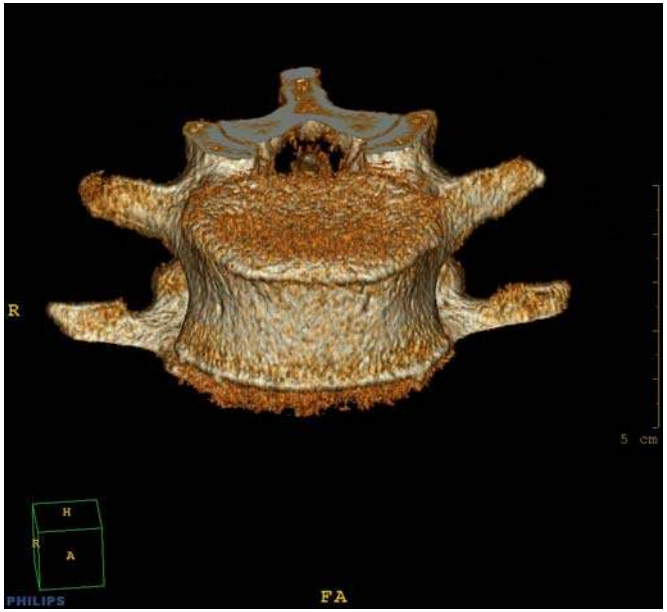
Biomedical Imaging: Computed Tomography (CT)

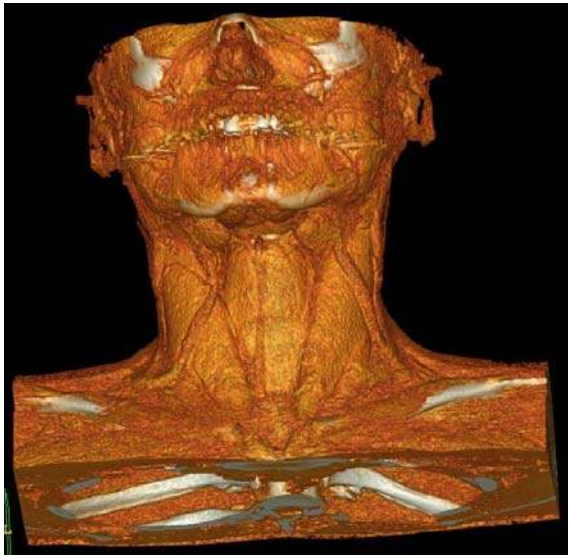
„Anatomy”
of a CT

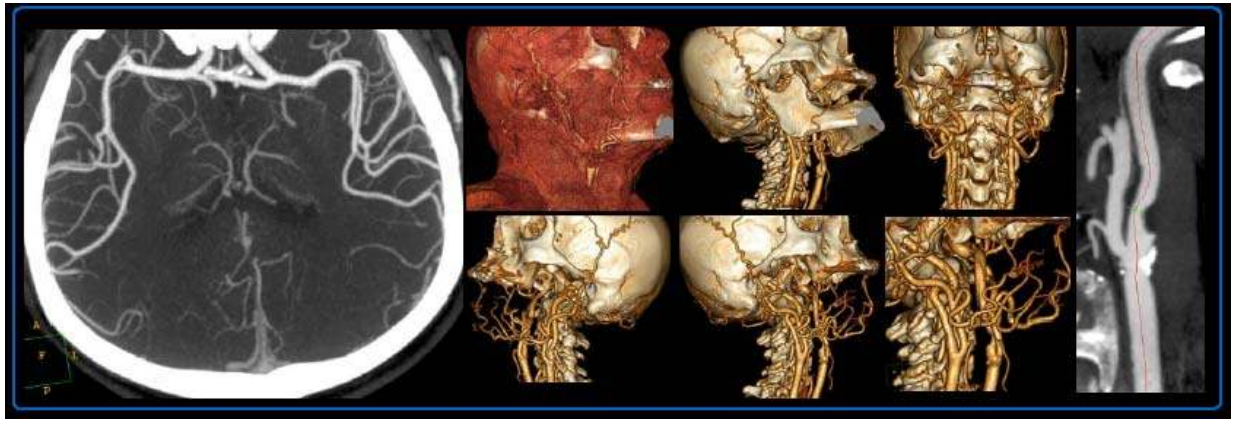
Biomedical Imaging: Computed Tomography (CT)



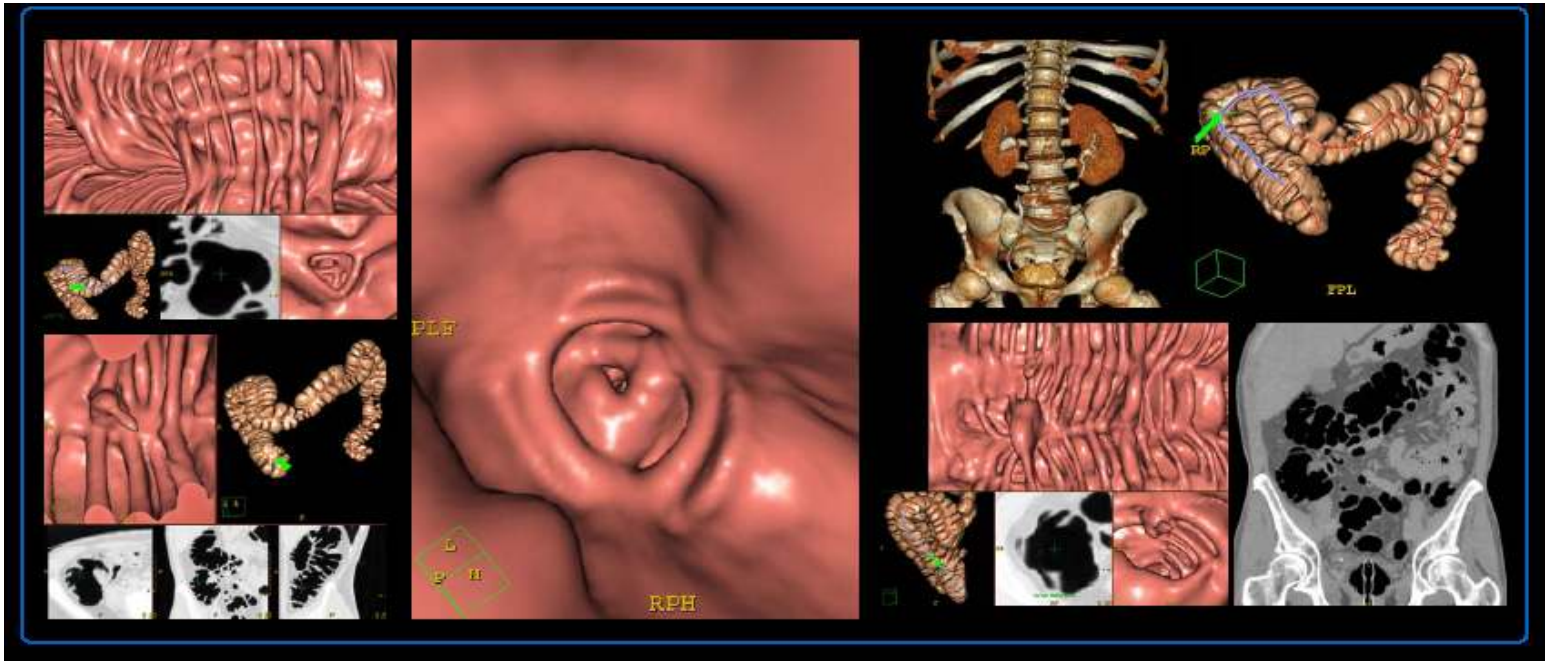




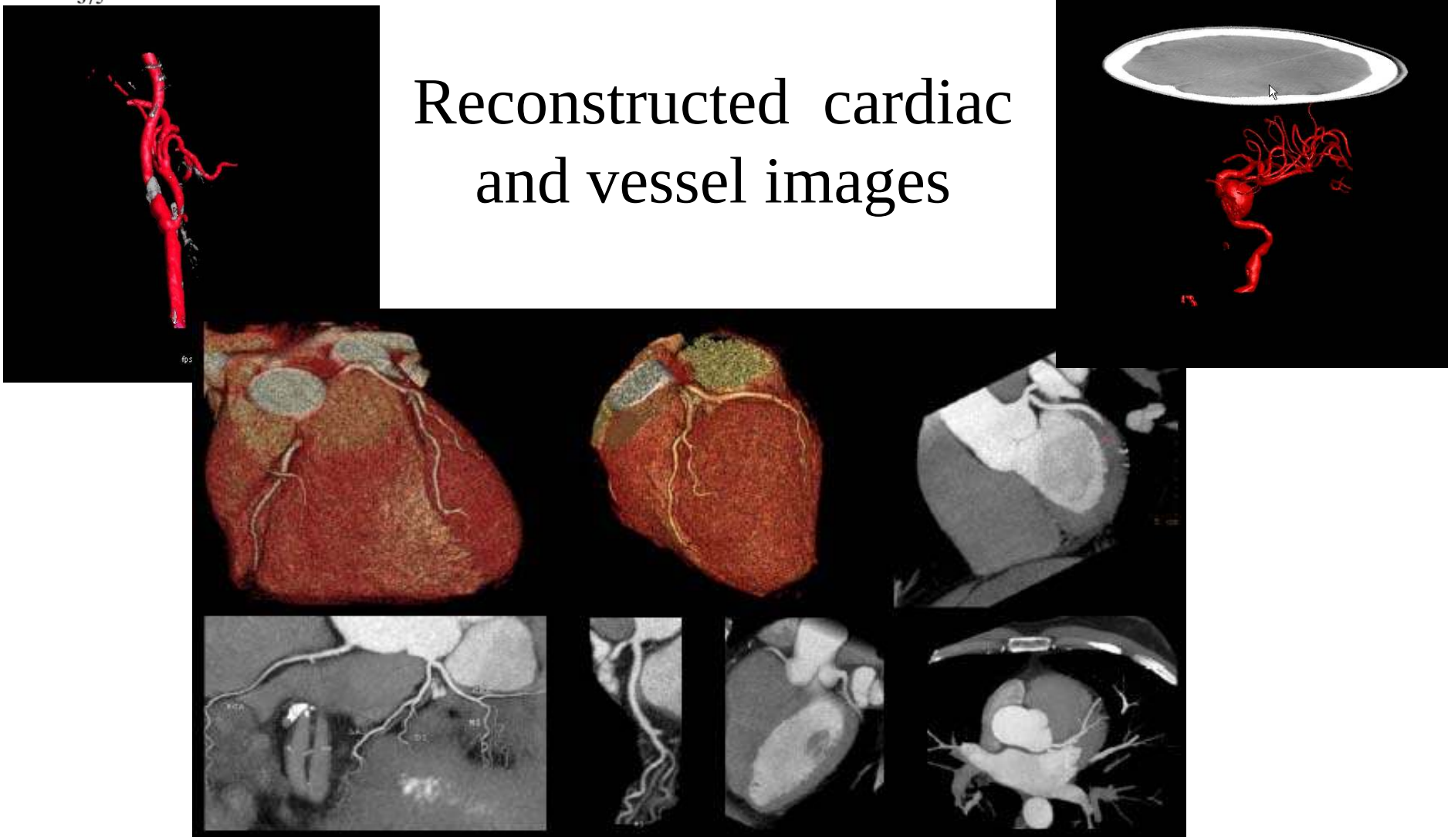




Reconstructed 3D images: virtual colonoscopy



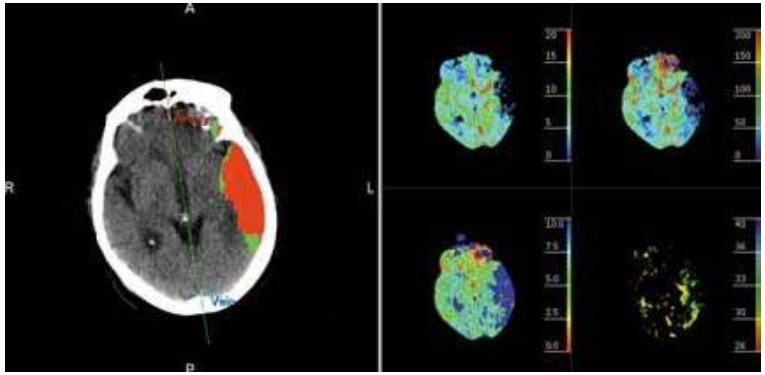
Biomedical Imaging: Computed Tomography (CT)

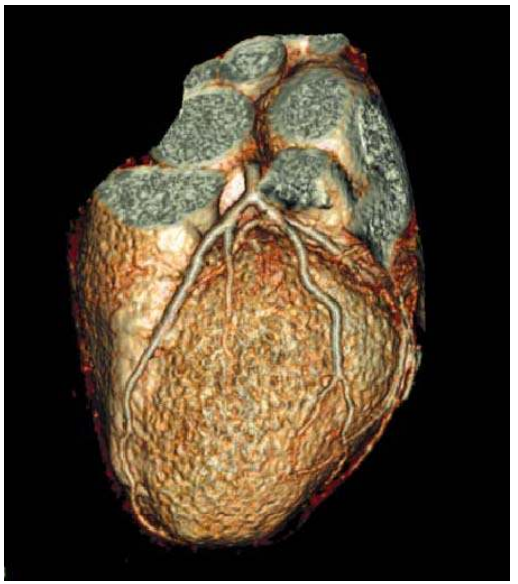


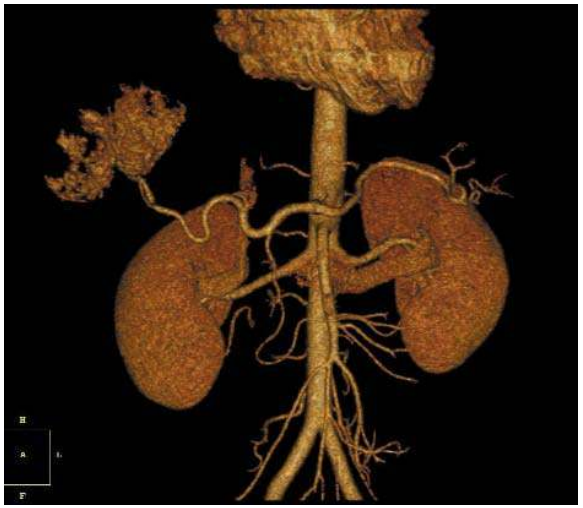
Reconstructed cardiac and vessel images

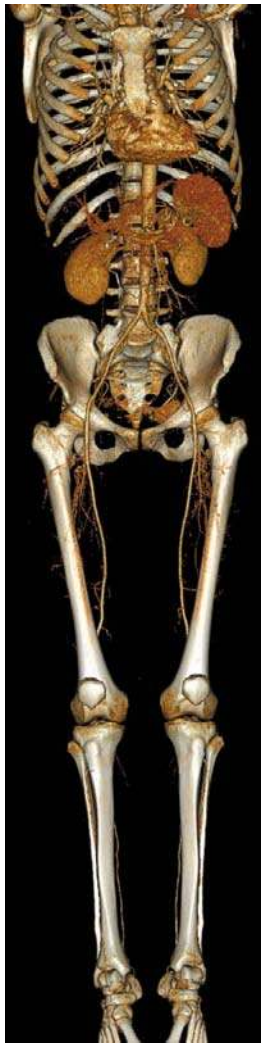
Functional CT images

Functional CT is a imaging method, made possible by fast CT scanners and improved data analysis techniques, to investigate the physiological basis of function and disease in the human body.









Future of CTs:

- more detector row (128/256/340) / higher coverage
  => volume CT
  => specialized CT-s
- detector efficiency / lower dose
- multi-energy detectors

Biomedical Imaging: Computed Tomography (CT)

Target Tissue	Regulatory Limit
Whole Body	12.5 mSv/quarter
Extremities18,750 mrem/quarter	18.75 mSv/quarter
Skin/Other Organs	75 mSv/quarter
Fetus	5 mSv/gestational period

Common Radiation Exposures

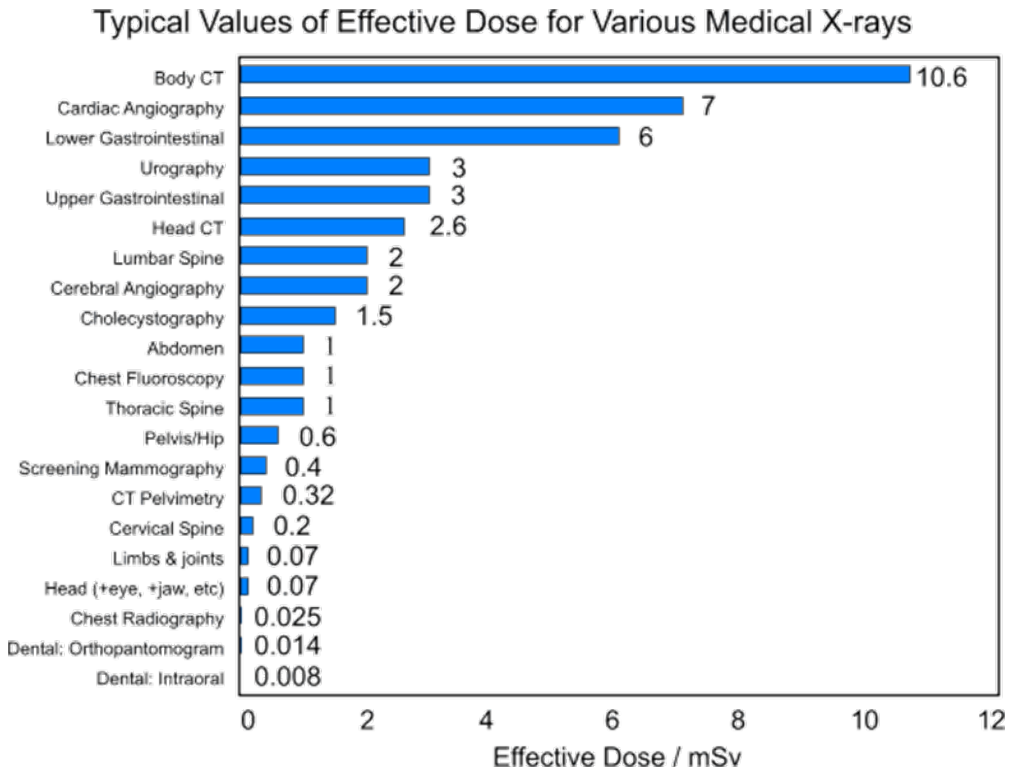
One Coast to Coast Flight	0.03 mSv
Chest Radiograph, Anterior/Posterior view	0.15 - 0.25 mSv/view
Chest Radiograph, Lateral view	0.5 – 0.65 mSv/view
Screening Mammography (Film/Screen Combination)	0.6 – 1.35 mSv/view

Significant Radiation Exposures (Acute Doses)

Temporary Blood Count Change (Whole Body or Torso)	250 mSv
Permanent Sterilization in Men (Gonads)	1000 mSv
Permanent Sterilization in Women (Gonads)	2500 mSv
Skin Erythema (Burn)	3000 mSv
Cataract Formation	6000 mSv

Common units and Conversions:

- 1 rad = 0.01 Gy *or* 100 rads = 1 Gy
- 1 rem = 0.01 Sv *or* 1 Sv = 100 rem
- 1 rem = 1000 mrem *or* 1 mrem = 0.001 rem
- For x-rays: 1 rad = 1 rem (QF = 1)



- Prospective Gating

Prospective Gating automatically triggers axial multislice scan acquisitions using patient information from the ECG monitor.

- Retrospective Tagging

Spiral Retrospective Tagging allows the CT system to acquire a volume of data while the patient's ECG is recorded.
The acquired data is "tagged" and reconstructed retrospectively at any desired phase of the cardiac cycle.

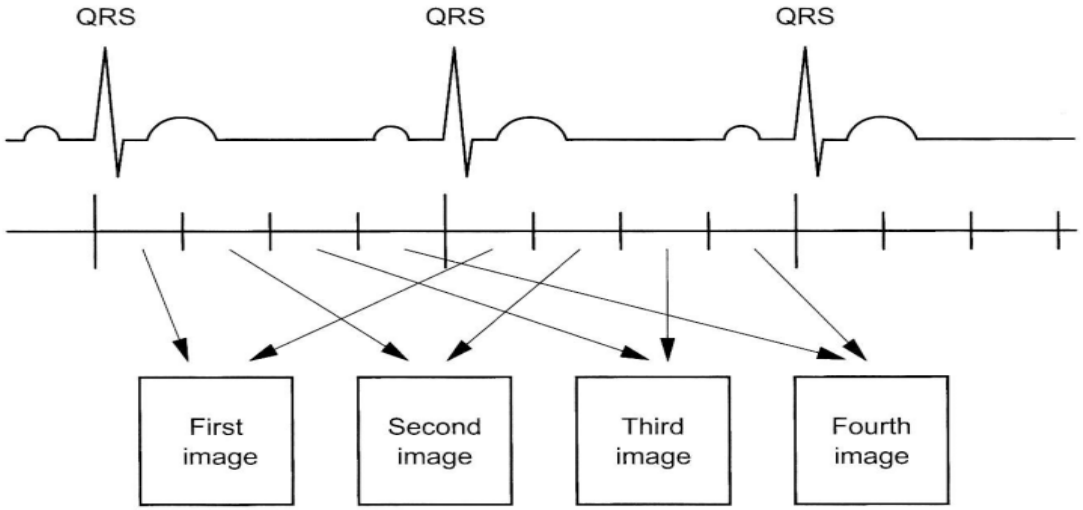


FIGURE 21-22. Acquisition of a gated cardiac image sequence. Only four images are shown here. Sixteen to 24 images are typically acquired.

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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

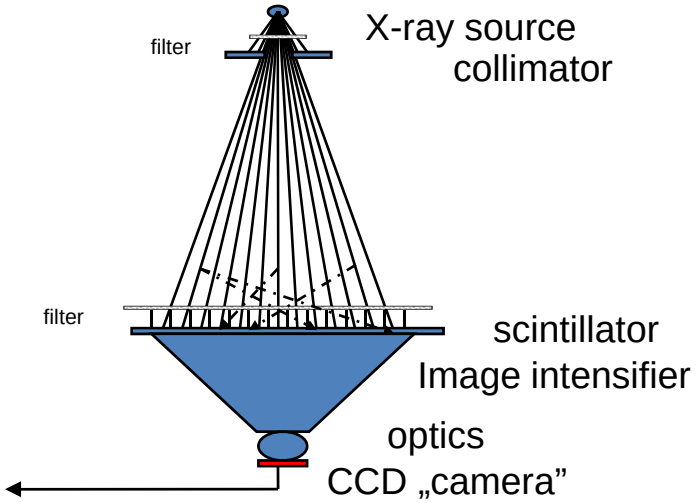
(Orvosbiológiai képalkotás)

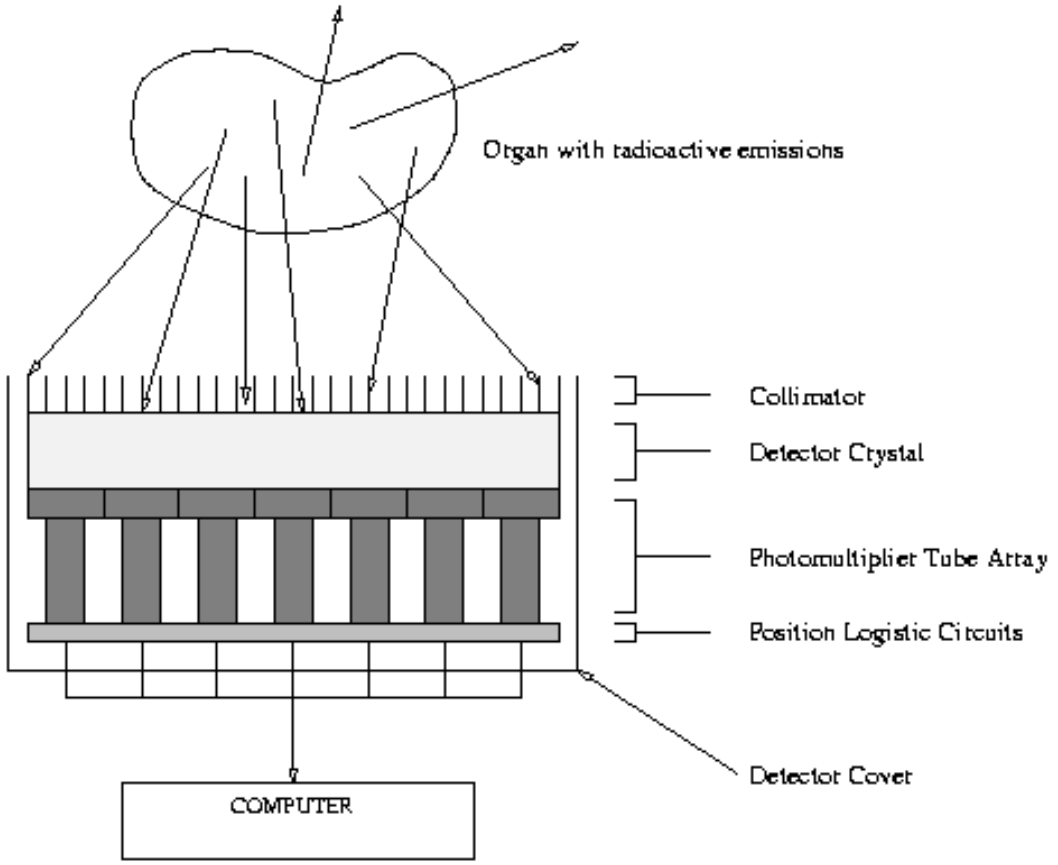
GAMMA CAMERA AND POSITRON EMISSION TOMOGRAPHY (PET)

(Gamma kamera és Pozitron emissziós tomográfia (PET))

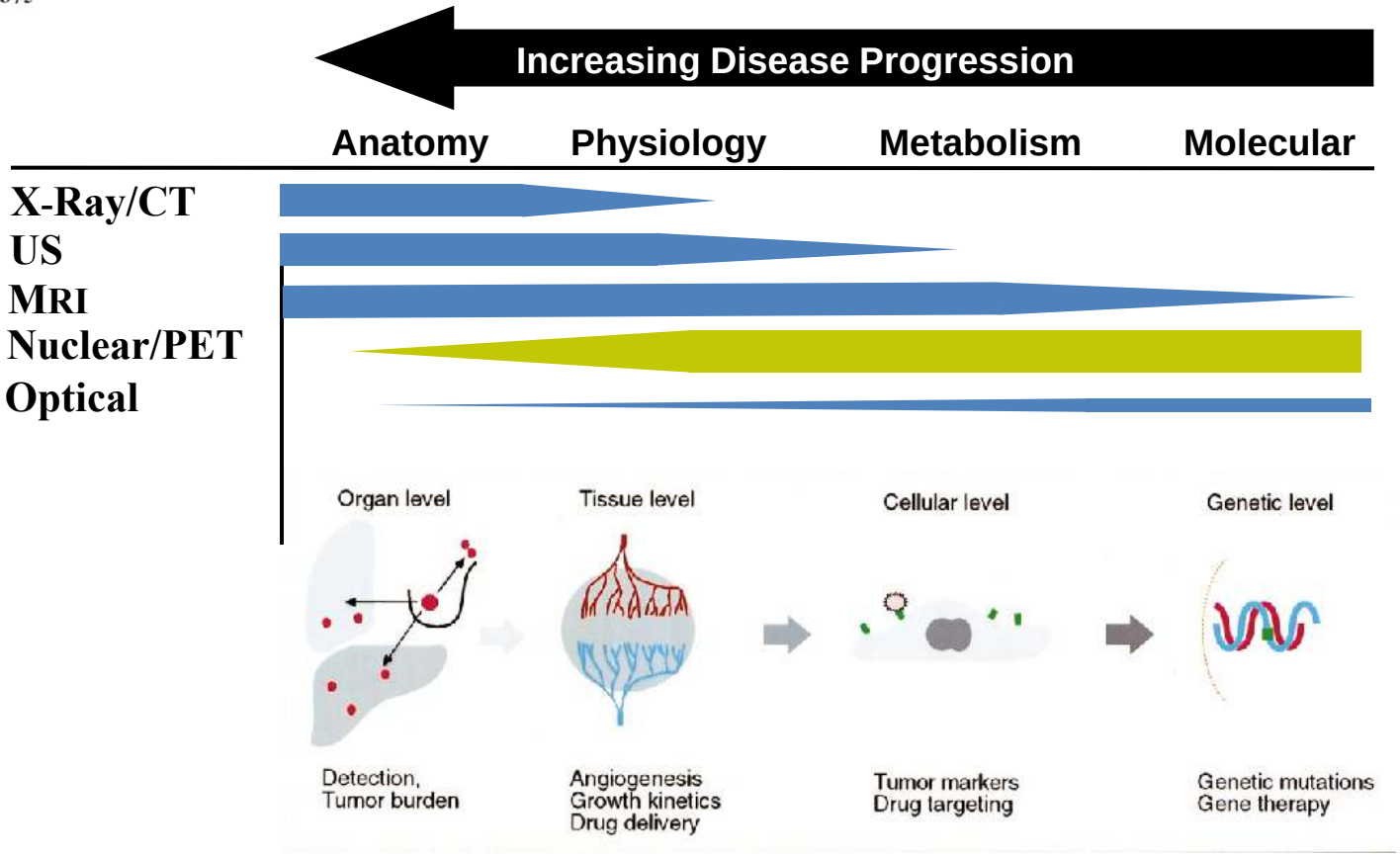
GYÖRGY ERŐSS

Technical Background





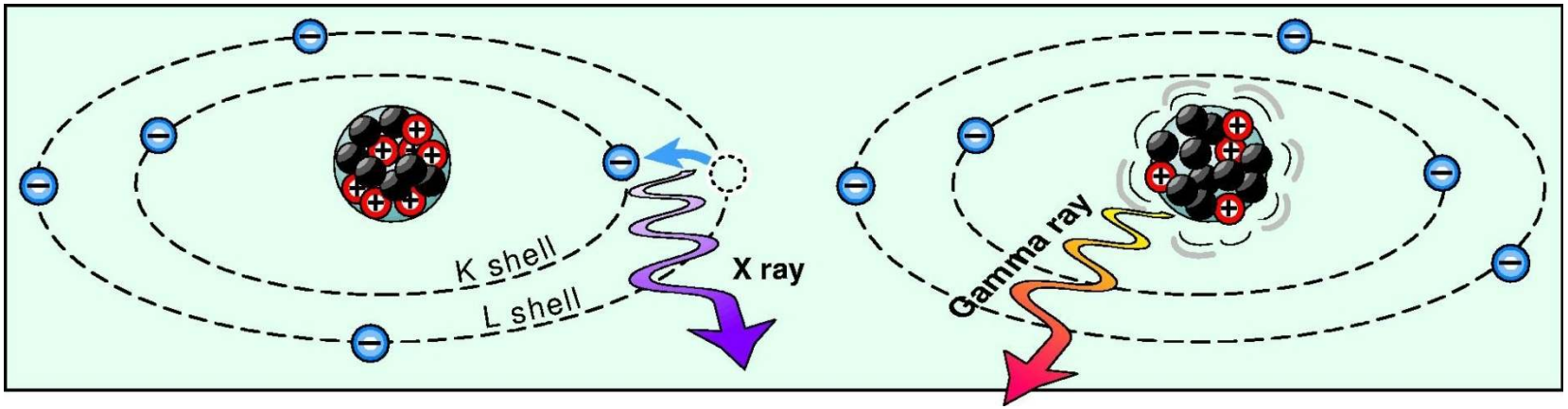
Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)



PET provides metabolic or functional information and may lead to detection of early onset of disease

Nuclear Medicine

γ-ray & X-ray Production – what we image



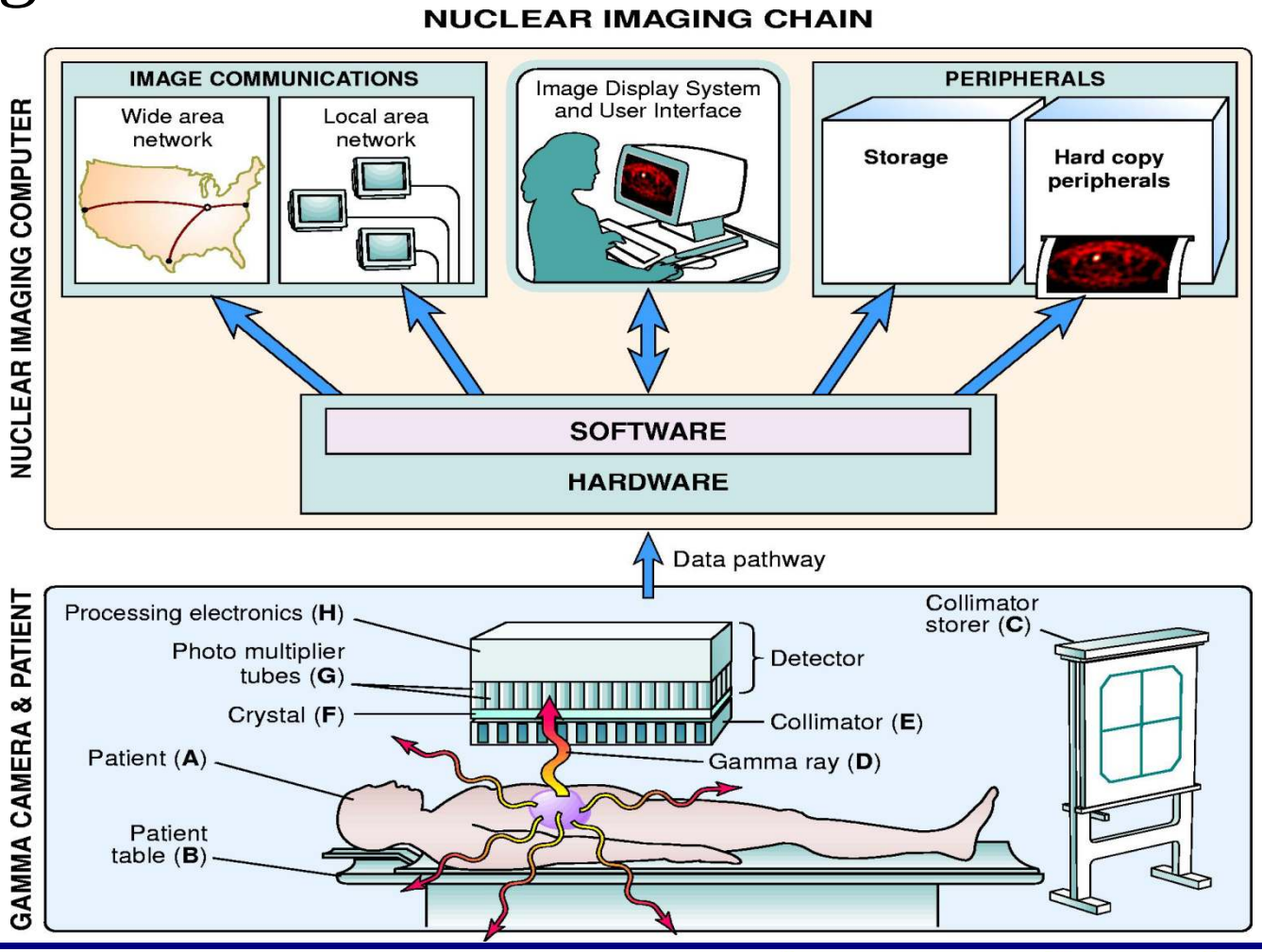
X-ray – high energy photon emitted by electron transition

Gamma ray – high energy photon emitted from nucleus

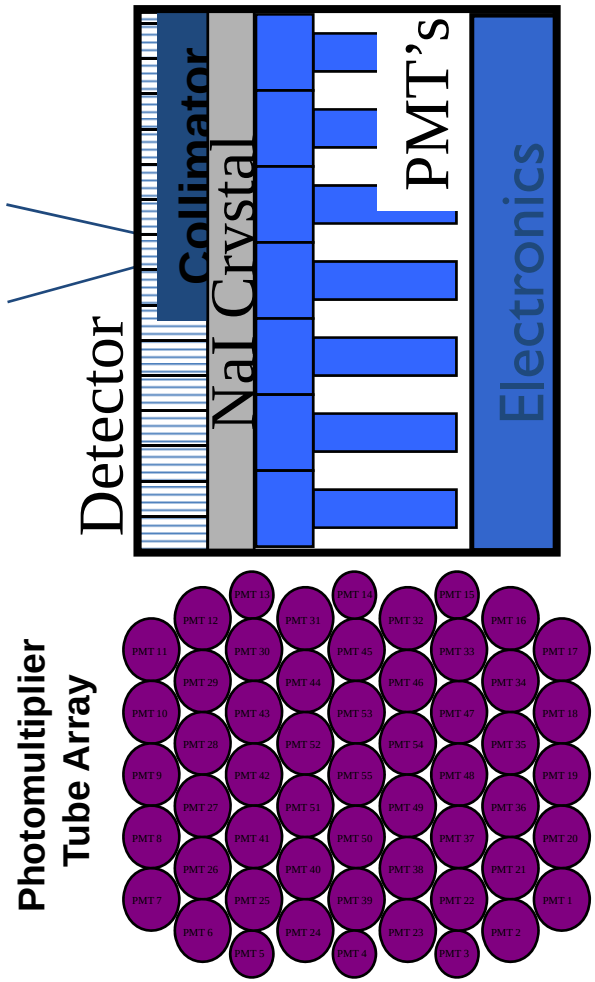
Nuclear Medicine Radionuclides

• Tc99m	140.5 keV	6.03 hours
• I-131	364,637 keV	8.06 days
• I-123	159 keV	13.0 hours
• I-125	35 keV	60.2 days
• In-111	172, 247 keV	2.81 days
• Th-201	~70, 167 keV	3.044 days
• Ga-67	93, 185, 300 keV	3.25 days

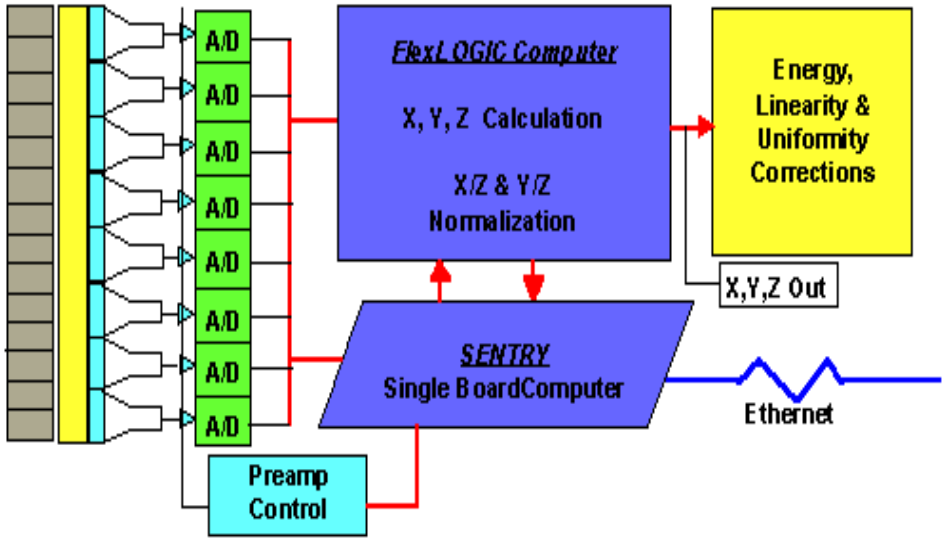
Planar gamma camera



Gamma Camera - Image Formation



- Lead collimator focuses photons (lens)
- NaI crystal scintillates
- PMTs detect scintillation
- Position calculation



Collimators

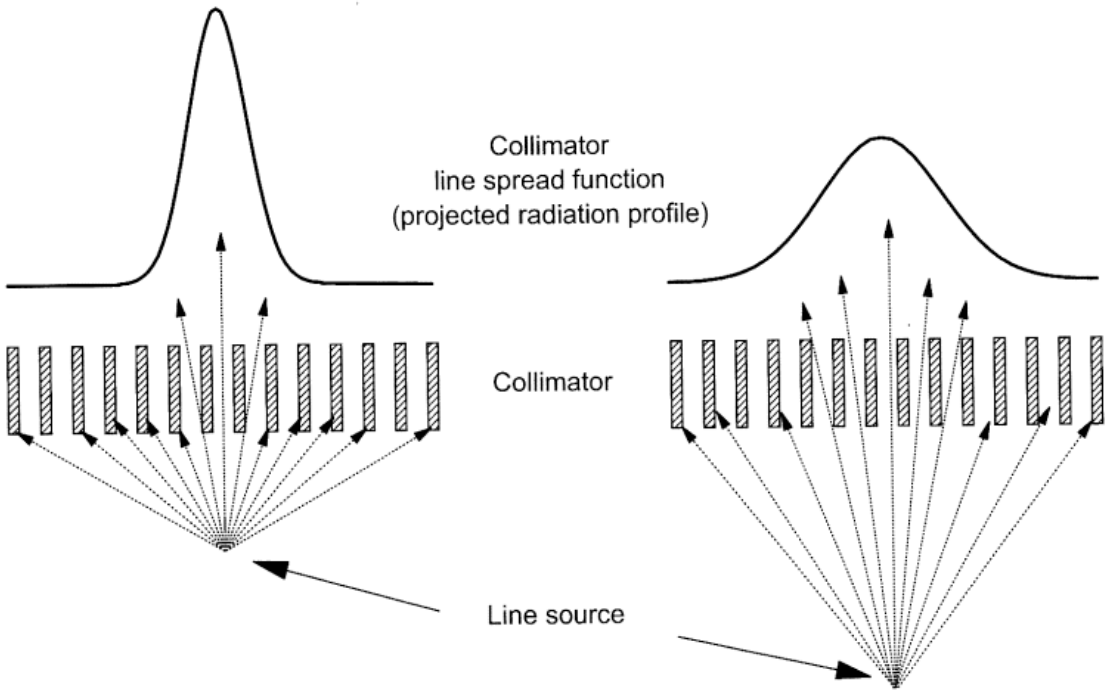


FIGURE 21-12. Line spread function (LSF) of a parallel-hole collimator as a function of source-to-collimator distance. The full-width-at-half-maximum (FWHM) of the LSF increases linearly with distance from the source to the collimator; however, the total area under the LSF (photon fluence through the collimator) decreases very little with source to collimator distance. (In both figures, the line source is seen "end-on.")

Type of collimators

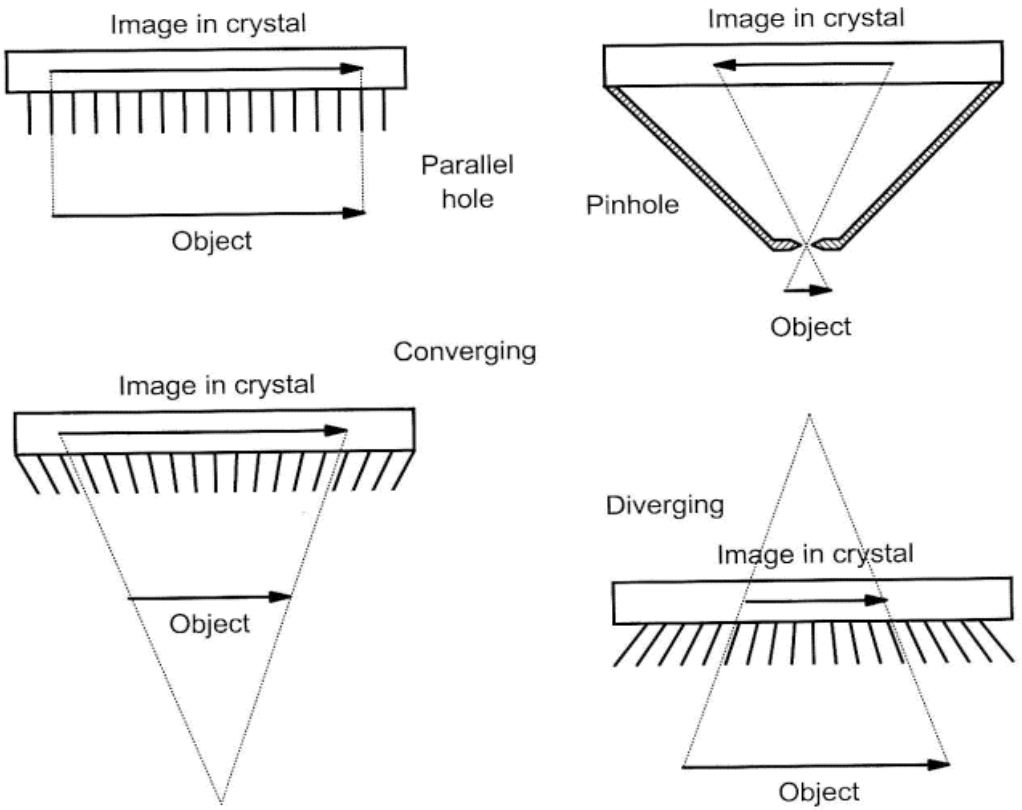


FIGURE 21-6. Collimators.

Collimator: Resolution and Sensitivity

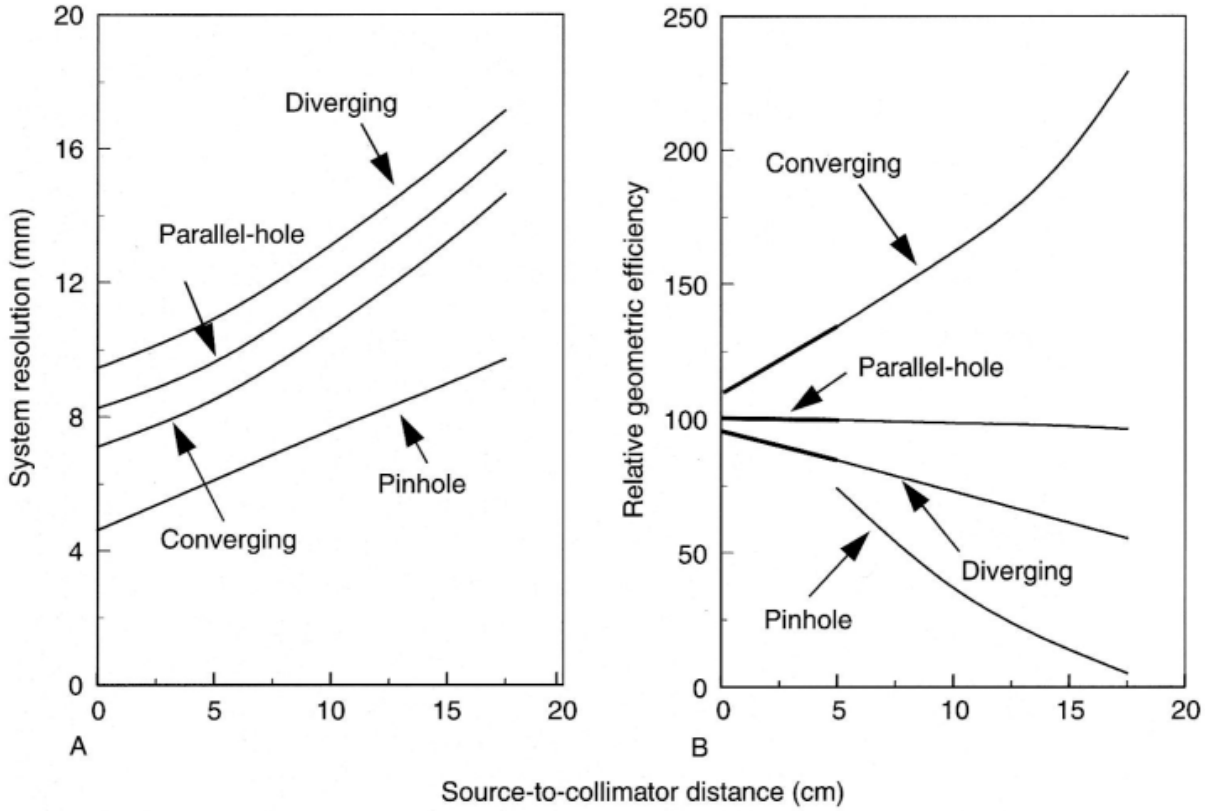
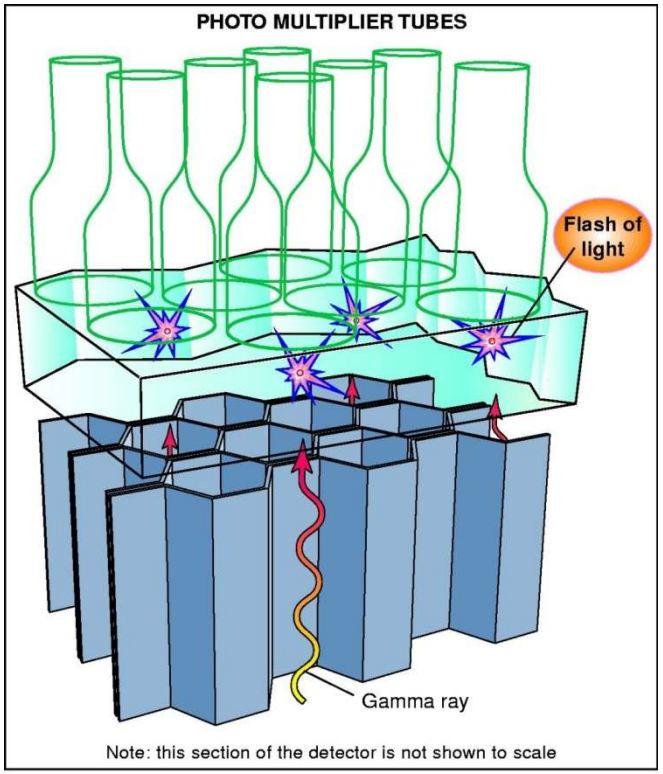


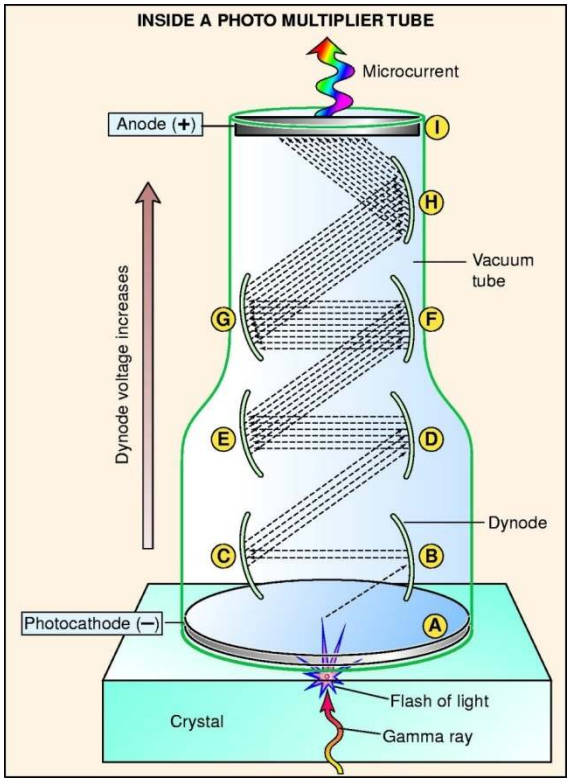
Figure 14–21. Performance characteristics (*A*, system resolution; *B*, point-source geometric efficiency in air) versus source-to-collimator distance for four different types of gamma camera collimators. (Reprinted by permission of the Society of Nuclear Medicine from Moyer RA: A low-energy multihole converging collimator compared with a pinhole collimator. J Nucl Med 15:59–64, 1974.)

Scintillator material

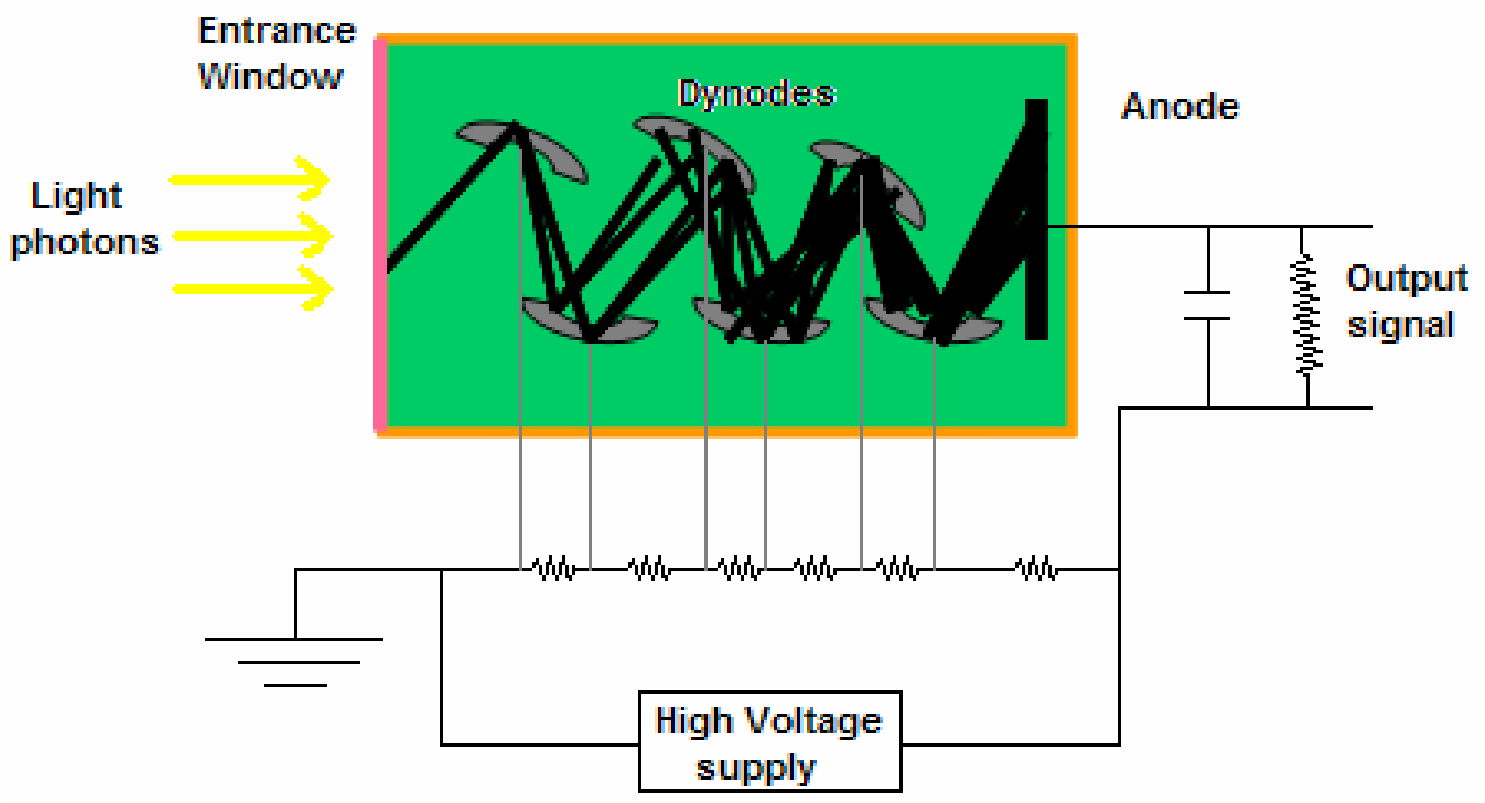
	NaJ	GSO	LSO	LYSO	BGO	LaBr3	
	NaJ:Ti	Gd2SiO5:Ce	Lu2SiO5:Ce		Bi4Ge3O		
Density	3.67	6.7	7.4	7	7.1	5.3	
Effective Z	51	57/59	65/66	64	73/75	47	
Attenuation length		1.4	1.15	1.2	1.04	2.1	sensitivity / dose
Light Yield		<0.5	1	1.2	<0.2	2	image quality / detection accuracy
Decay Time	230 ns	60 ns	40 ns	40 ns	300 ns	35 ns	coincedence window (sc&rnd)
Energy Resolution		8.50%	11%	10%	>13%	3%	scatter & random reduction
Timing Resolution	N/A	N/A	N/A	<450 ps	N/A	<400 ps	
photon/MeV	41000	8000	26000		9000		

Detector system





Photon Multiplier Tube (PMT)



Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)

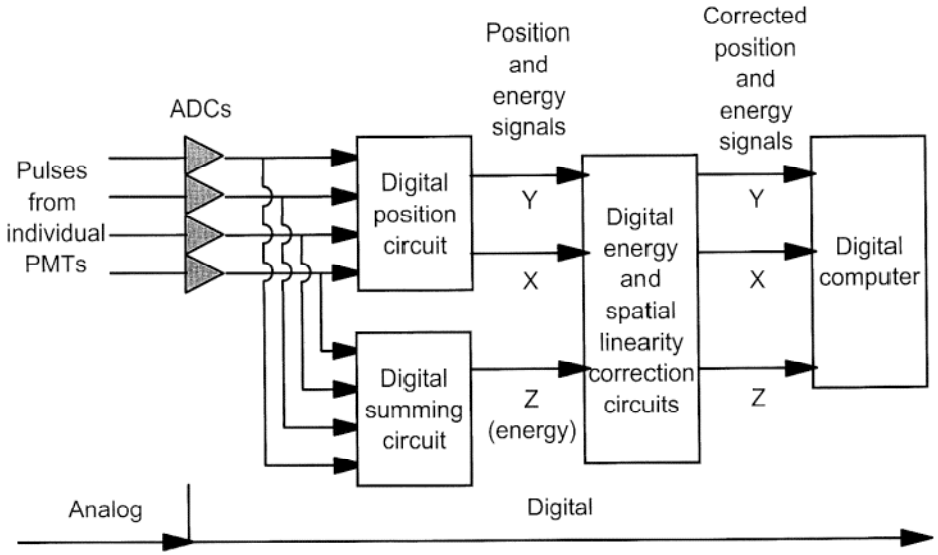
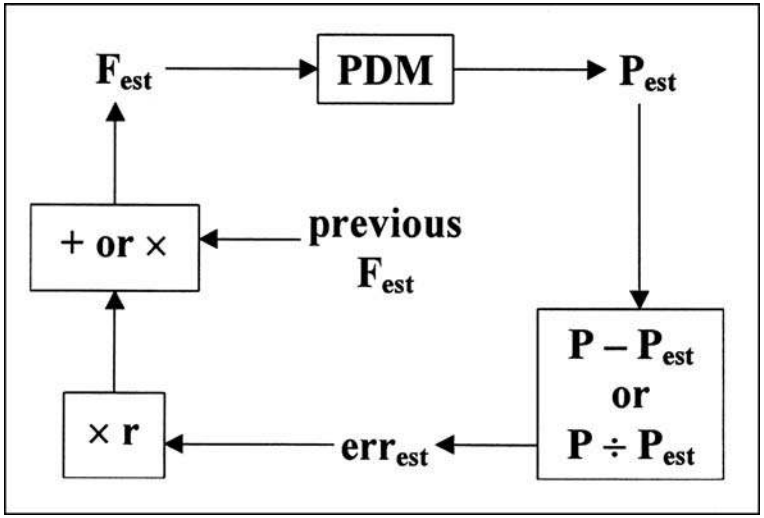


FIGURE 21-5. Electronic circuits of a modern digital scintillation camera.

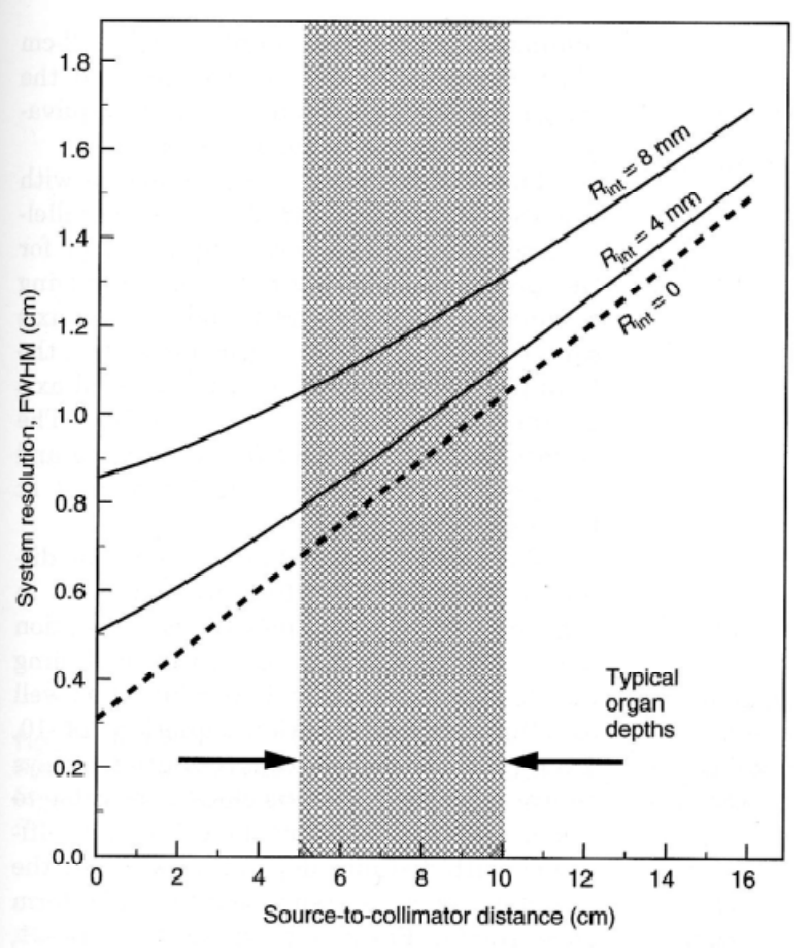
Image reconstruction:

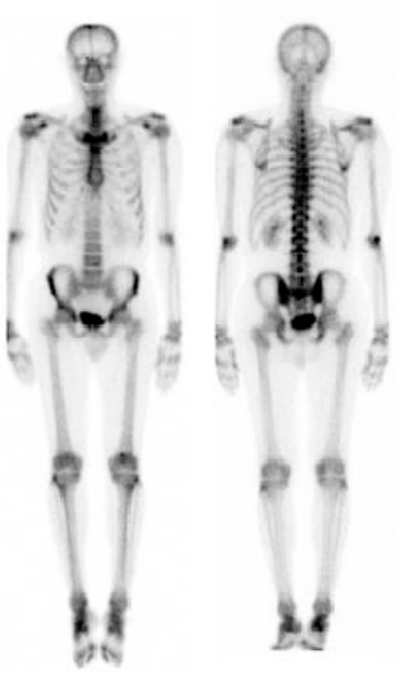
backprojection with iteration




Gamma Camera

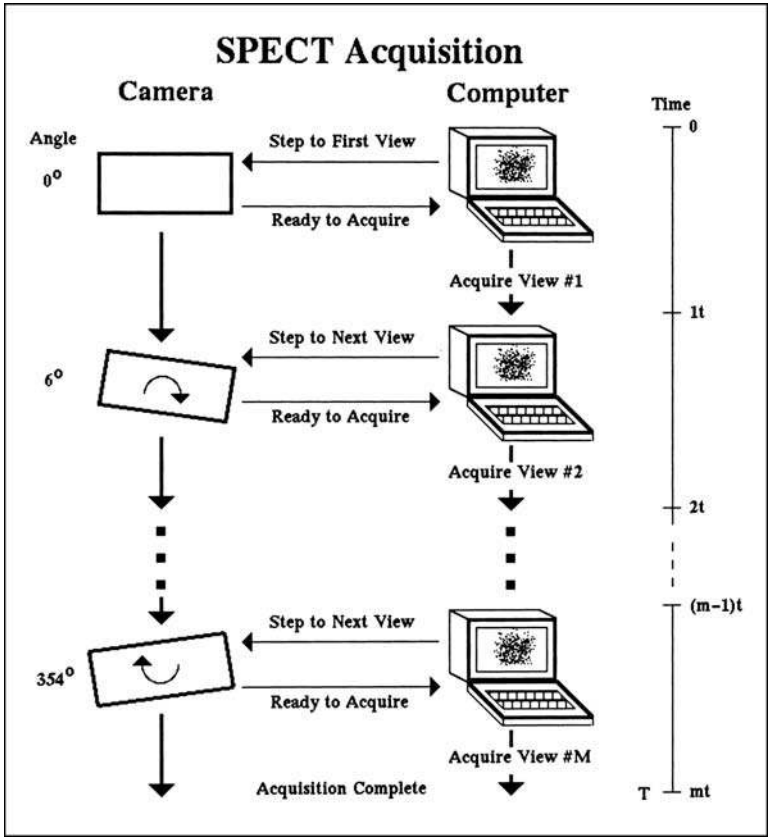
Gamma Camera - spatial resolution



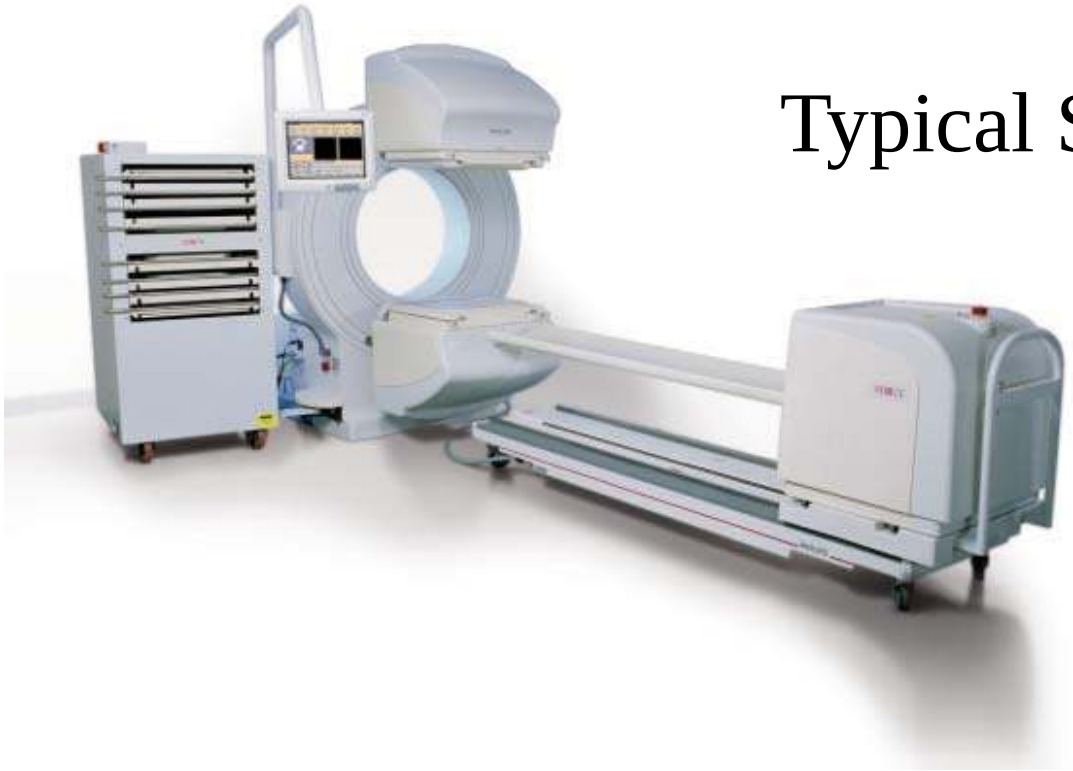


Single Photon Emission Computed Tomography

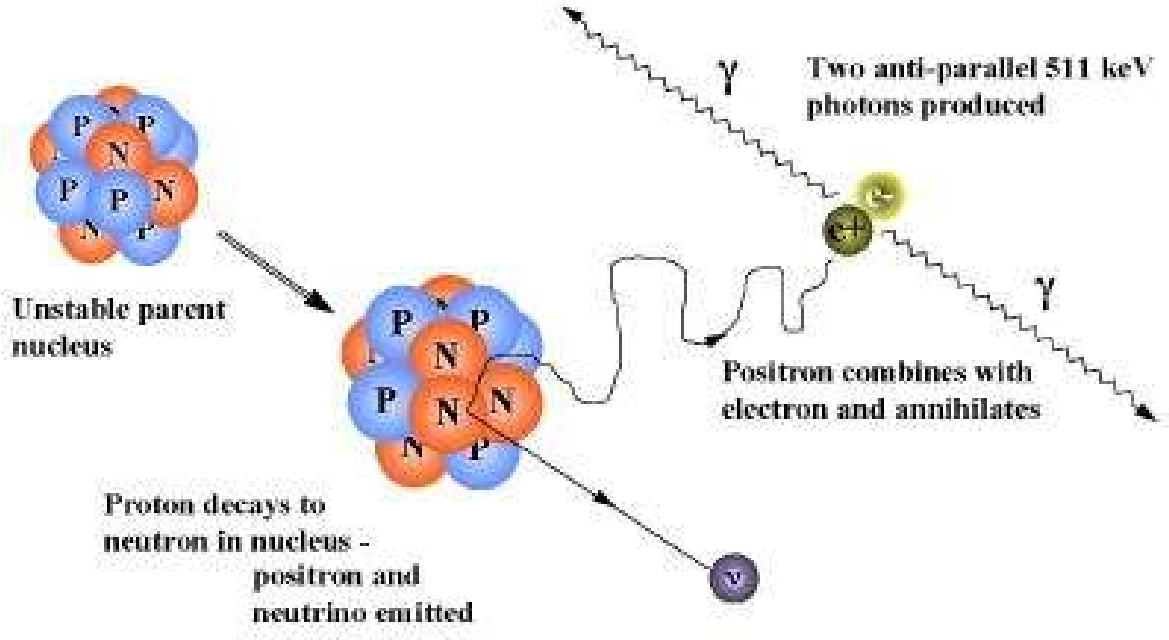
SPECT imaging is performed by using a gamma camera to acquire multiple 2-D images (also called projections), from multiple angles. A computer is then used to apply a tomographic reconstruction algorithm to the multiple projections, yielding a 3-D dataset.



Typical SPECT cameras



Positron Emission Tomograph



Positron emission and annihilation

PET isotopes

Isotope	half-life (min)	Maximum positron energy (MeV)	Positron range in water (FWHM in mm)	Production method
^{11}C	20.3	0.96	1.1	cyclotron
^{13}N	9.97	1.19	1.4	cyclotron
^{15}O	2.03	1.70	1.5	cyclotron
^{18}F	109.8	0.64	1.0	cyclotron
^{68}Ga	67.8	1.89	1.7	generator
^{82}Rb	1.26	3.15	1.7	generator

http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html

Radionuclide Imaging Radiochemistry

- Radioactivity is the means by which we measure the concentration of something
- metabolic *in vivo*.
- What would we want to measure?

Location of drugs, receptors, proteins, genes…

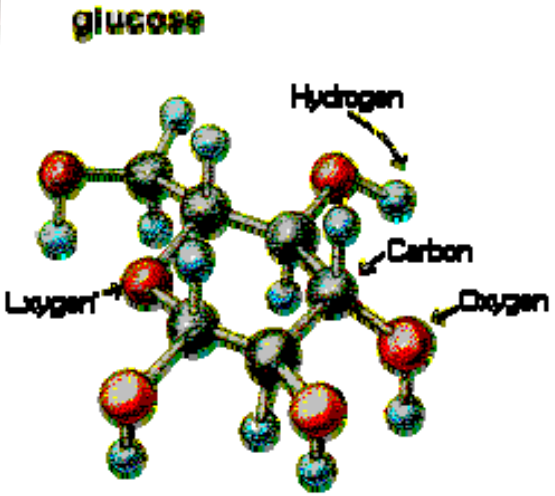
Oxygen	O_2 metabolism	**Fluorodeoxyglucose**	**Glucose metabolism**
Water	Perfusion	FESP	D2 receptor
Ammonia	Perfusion	FMISO	Hypoxia
Carbon monoxide	Blood volume	FCZ	Beta-AR

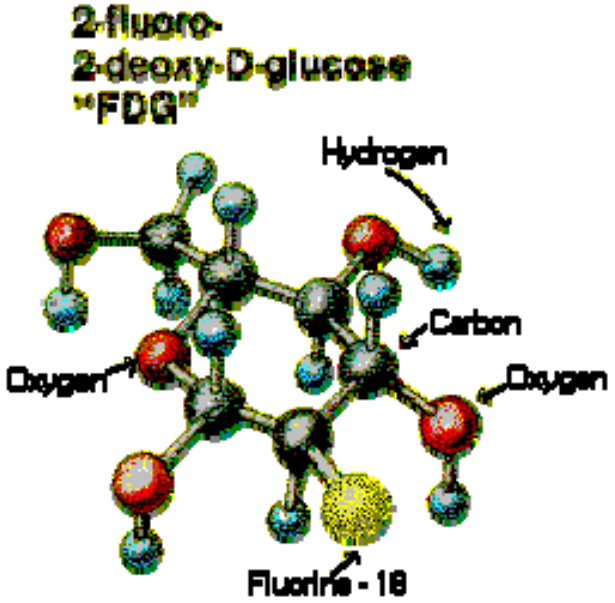
Common PET tracers

Different Radio-pharmaceuticals provide information on different *metabolic* processes

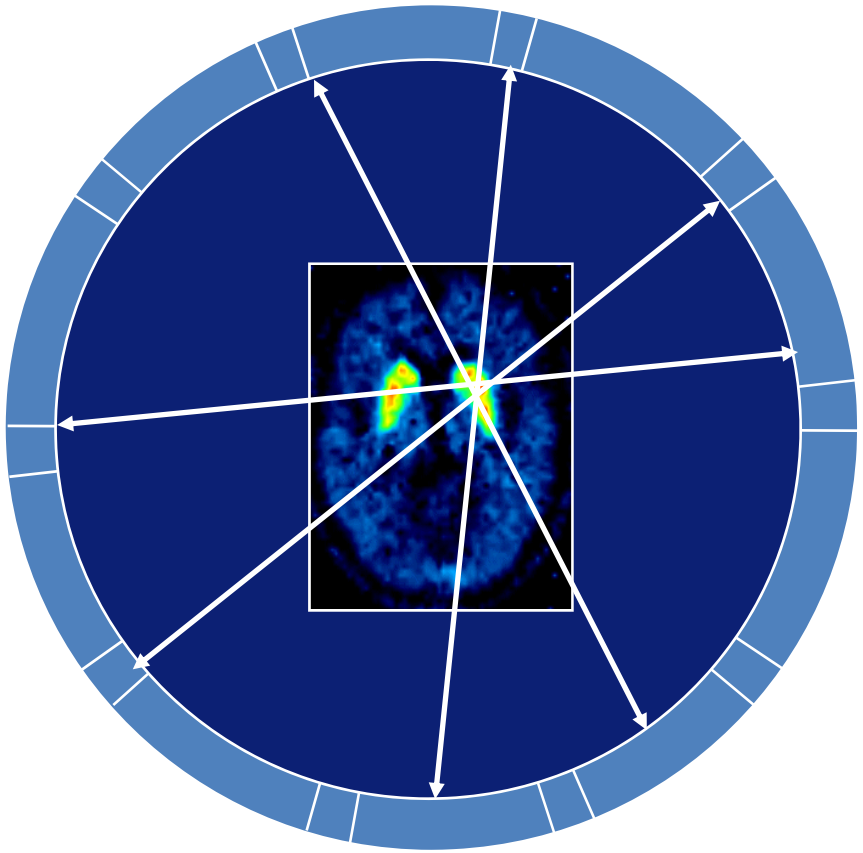
How is a PET image formed?

1. Patient is injected with radio-pharmaceutical (usually FDG)
2. Wait for uptake (usually ~60 minutes)
   - FDG taken up by cells that metabolize glucose





How is a PET image formed?



3. Radioactive isotope emits positrons
   - Collide with and “Annihilate” an electron
   - Two 511 keV photons emitted 180 degrees apart
4. Millions of Coincidence pairs recorded to form image

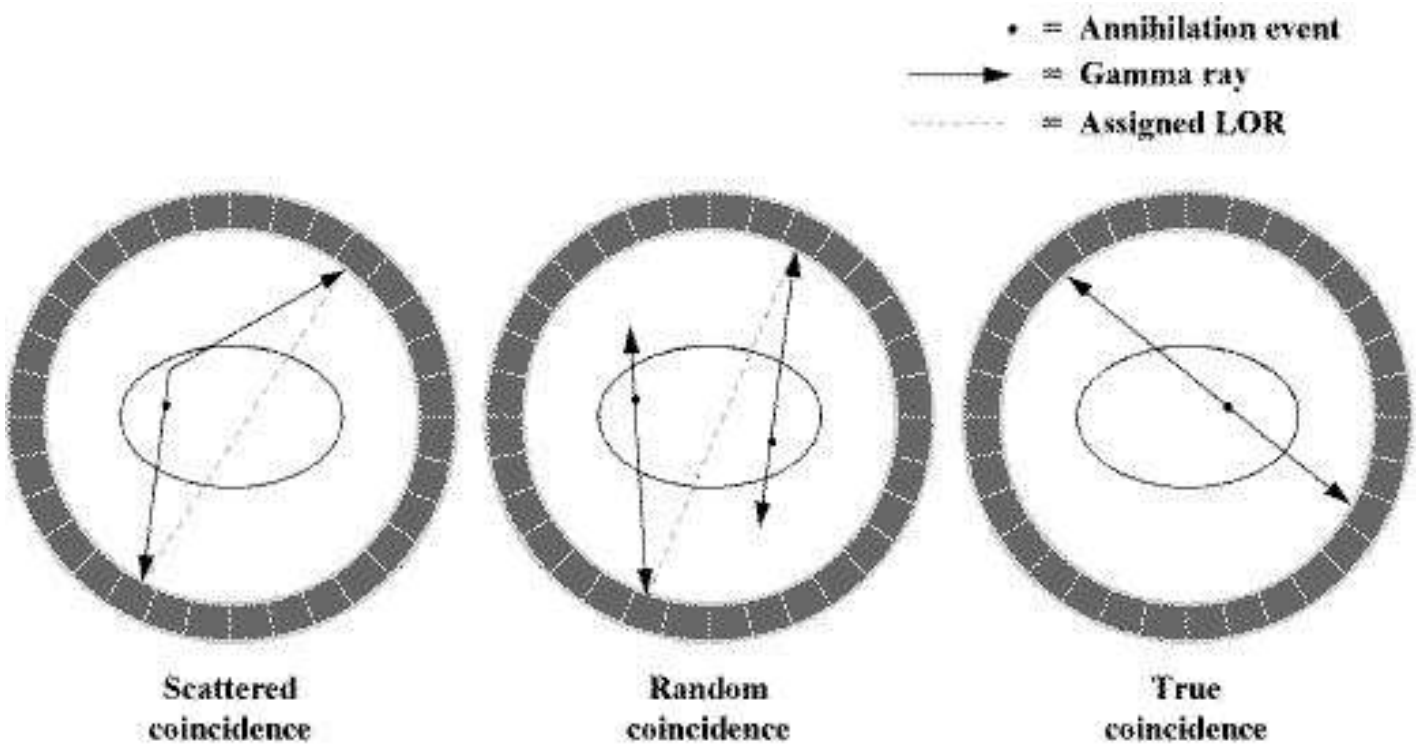
More annihilation (coincidences) – more intensive image

511 keV

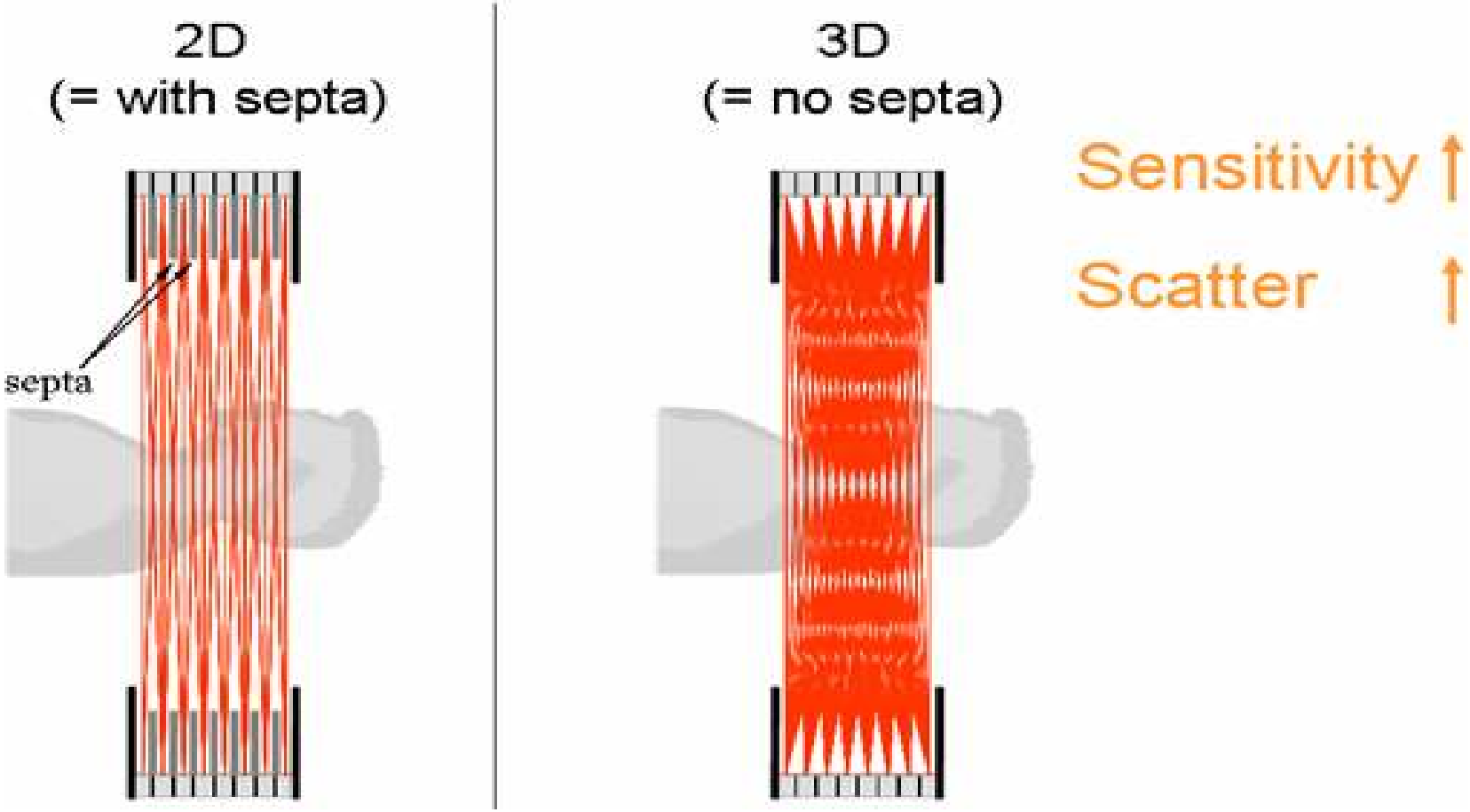
Positron Emission Tomography

511 keV

Coincidence events in PET

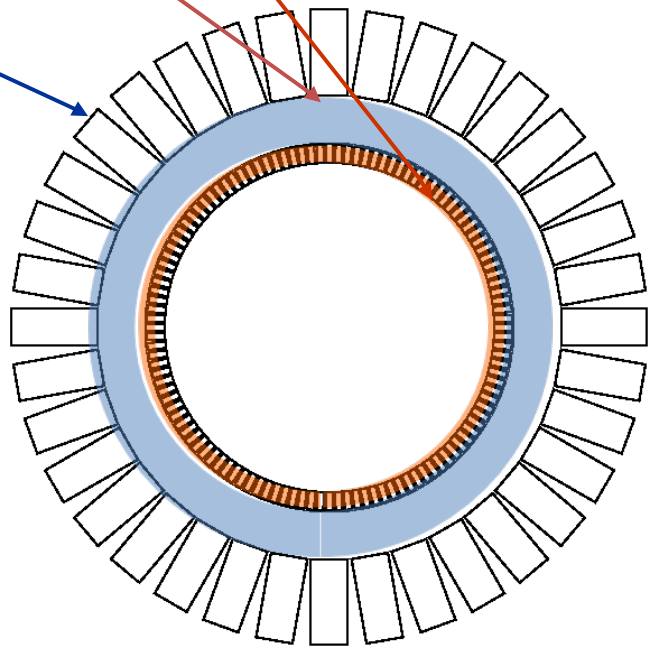


PET 2D and 3D Acquisition Modes

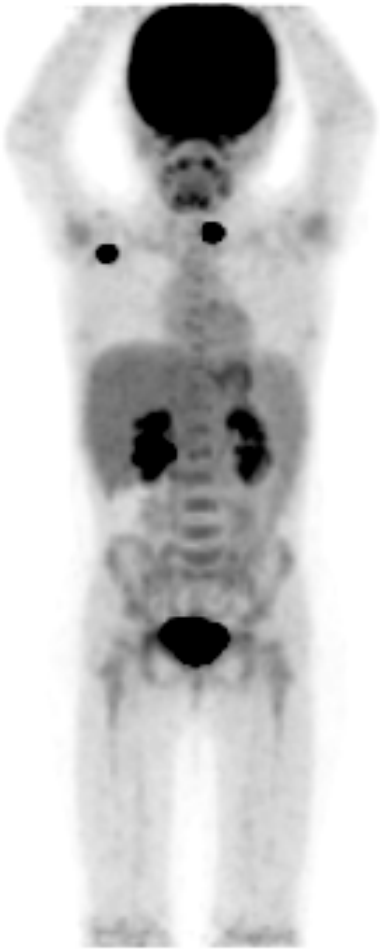


Pixelated-continuous PIXELAR technology:

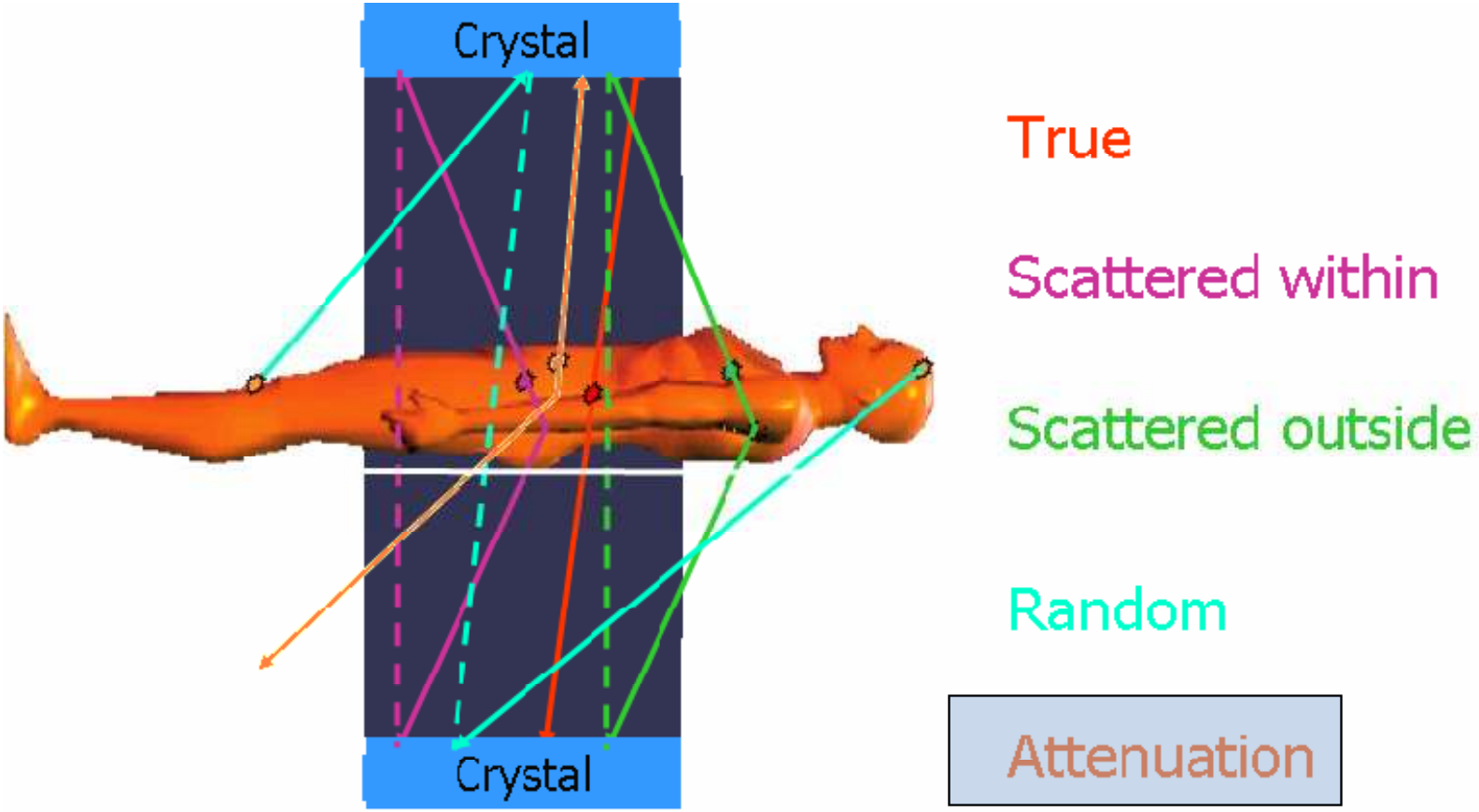
- individual scintillating crystals
- optically continuous lightguide
- closely packed PMTs



Typical PET image



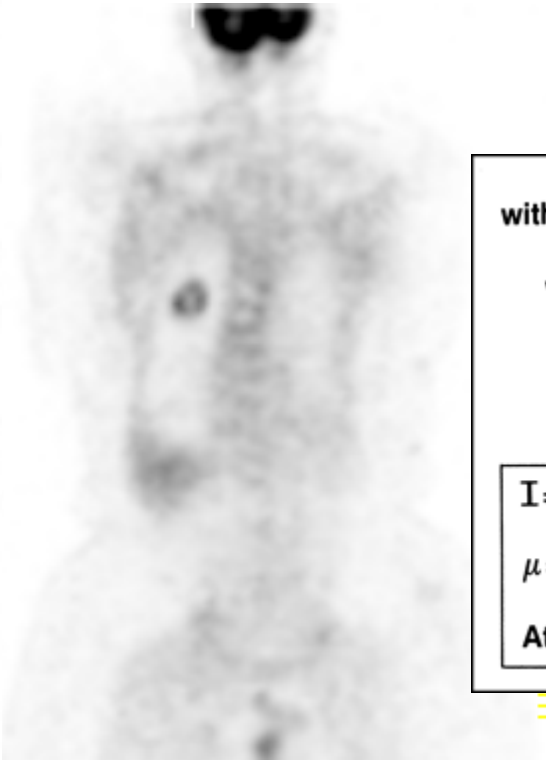
Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)

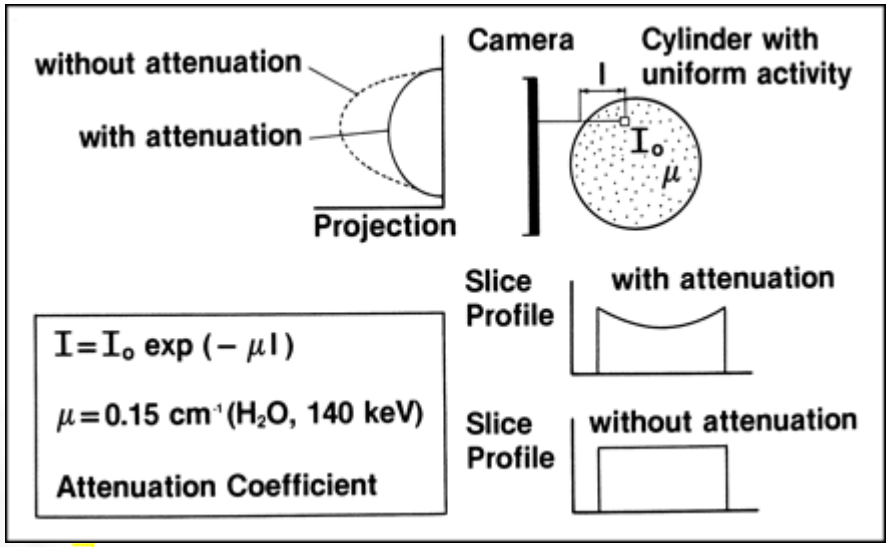


Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)

Small Patient

Large Patient

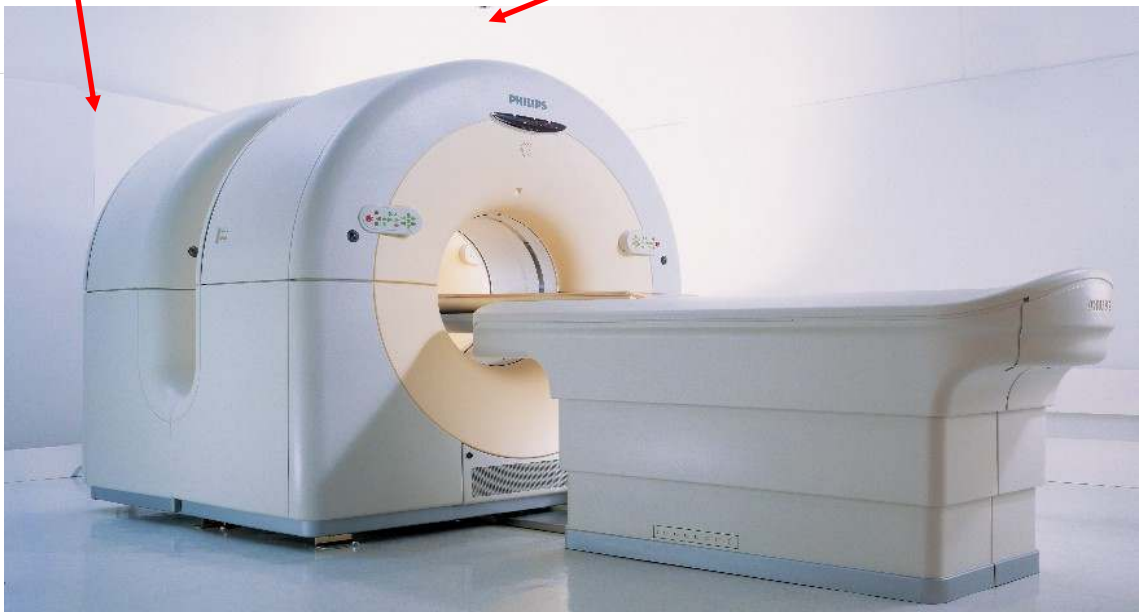




Attenuation correction => density from external source

=> CT scan

Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)



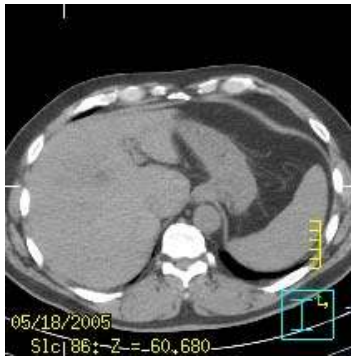
Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)

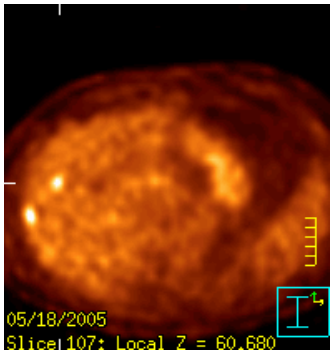
CT by itself provides excellent anatomical detail, but limited functional / metabolic information

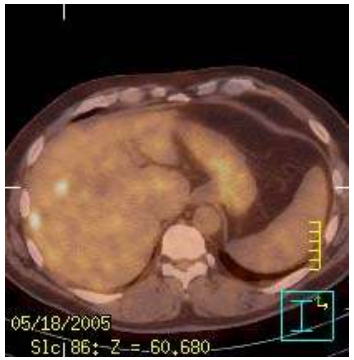
PET by itself provides useful information on functional / metabolic activity, but limited detail on anatomic structures and location

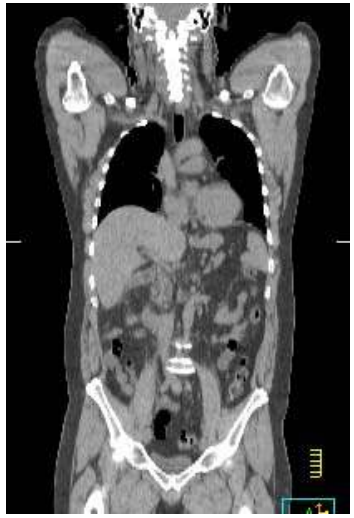
PET/CT combines metabolic and anatomic information in one dataset, in one episode of care

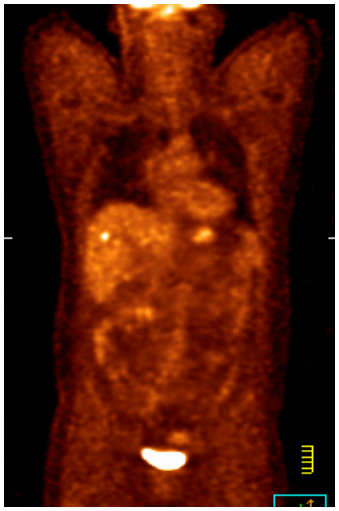
Clinical Need

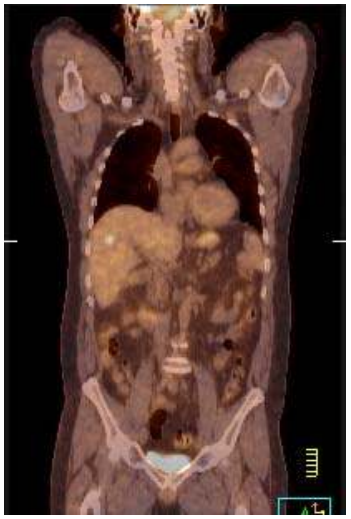












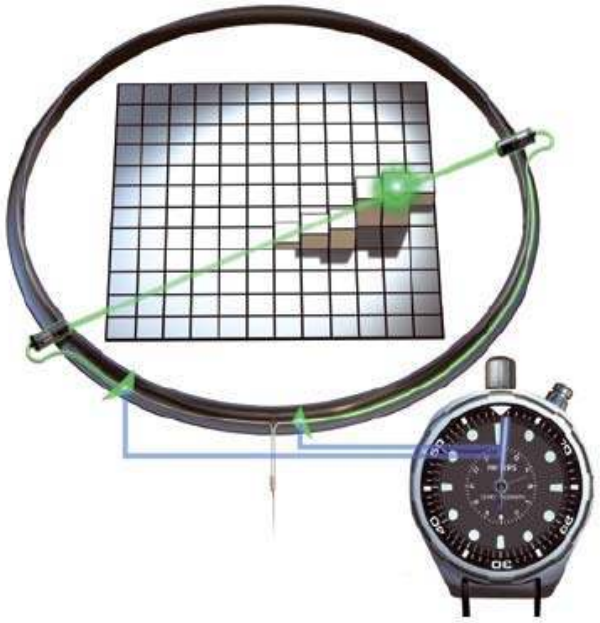
- Assessment of metabolic activity
- Structural detail
- Localization

Resulting in increased diagnostic confidence

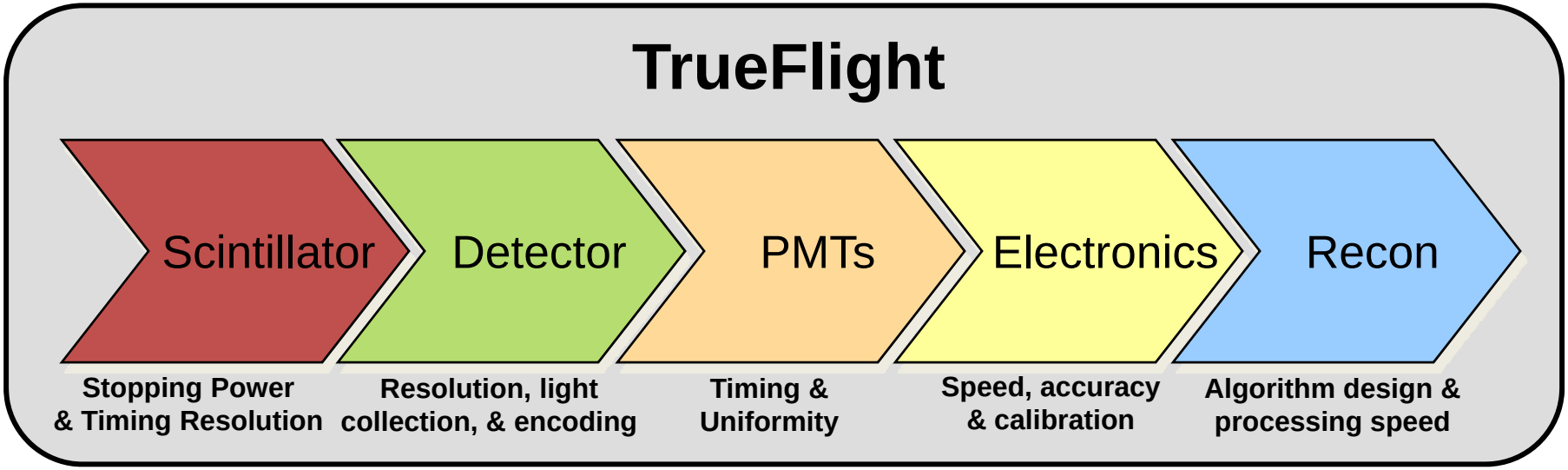
SPECT-CT

Latest Generation PET – Time of Flight (TOF)

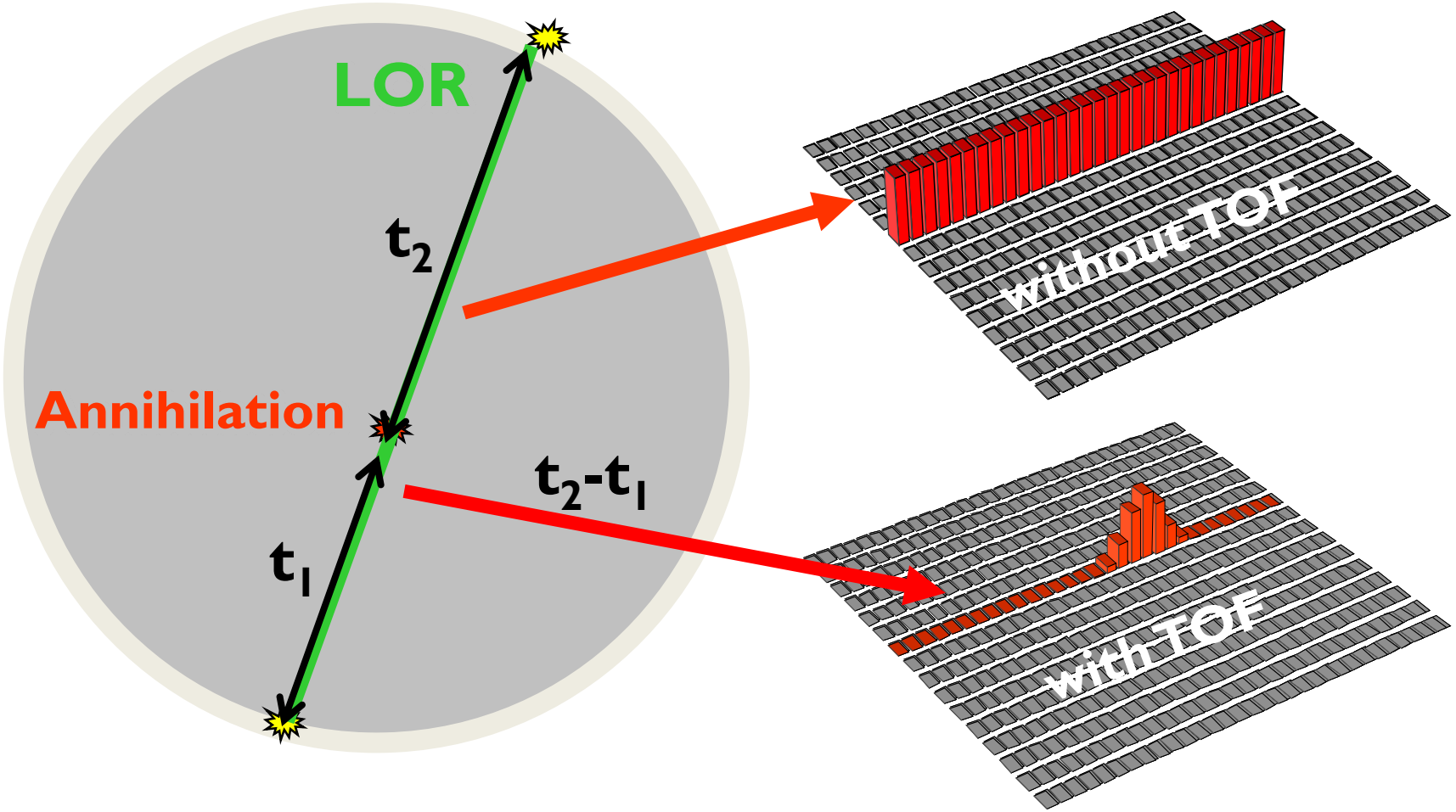
A coincidence event is assigned to a line of response



Time-of-Flight information is used in the data reconstruction to more accurately localize the origin of the annihilation


TrueFlight
Scintillator
Detector
PMTs
Electronics
Recon
Stopping Power & Timing Resolution
Resolution, light collection, & encoding
Timing & Uniformity
Speed, accuracy & calibration
Algorithm design & processing speed

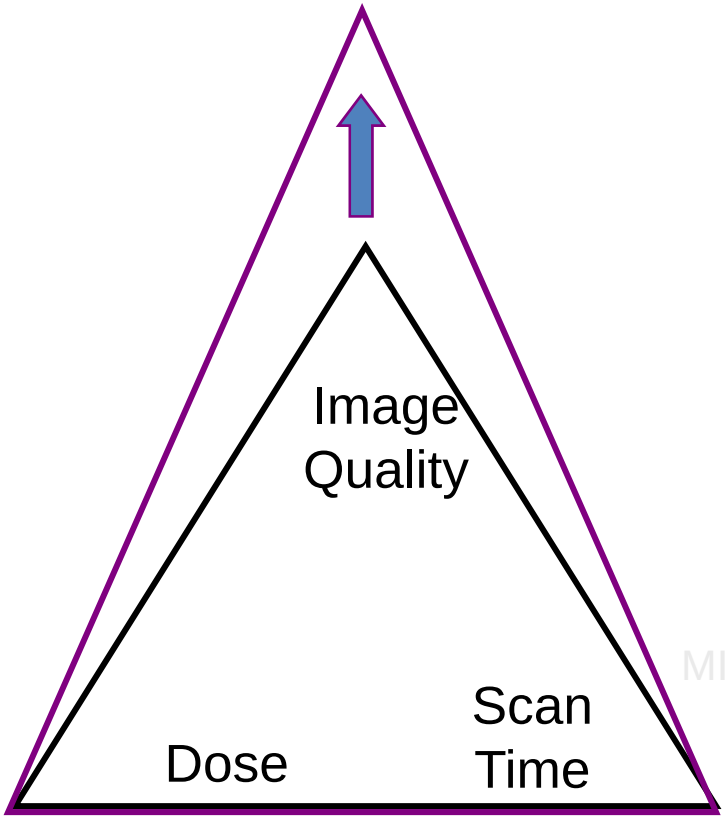
Concept of Time of Flight PET



Clinical Benefits I

How can your observers benefit from reduced noise and higher sensitivity?

Exceptional Image Quality



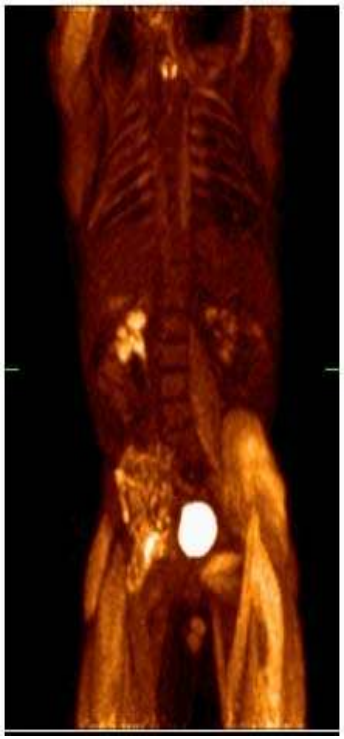


Image courtesy of J Karp, University of Pennsylvania

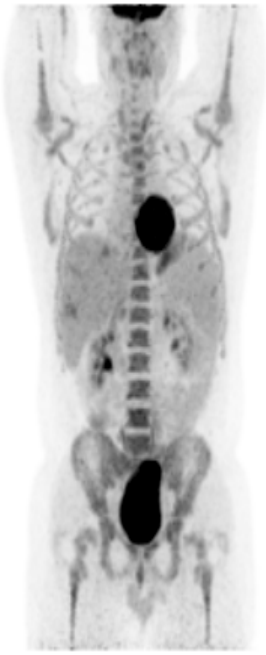
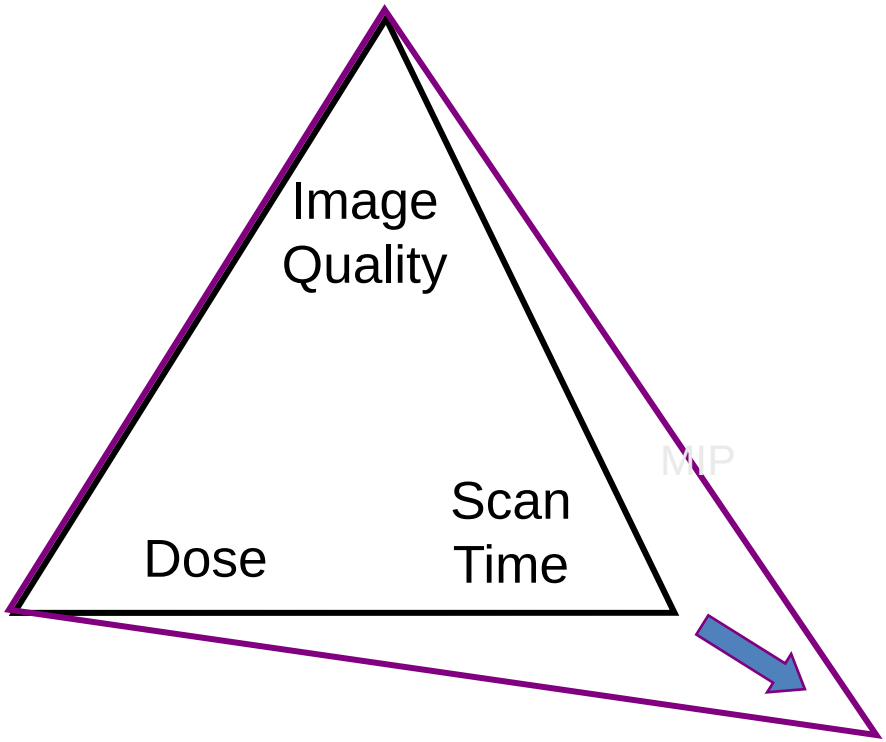


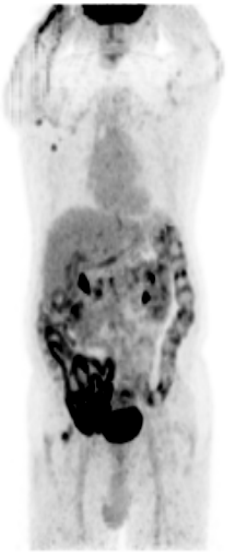
Image courtesy of University Hospitals, Cleveland

Clinical Benefits II

How can your observers benefit from reduced noise and higher sensitivity?



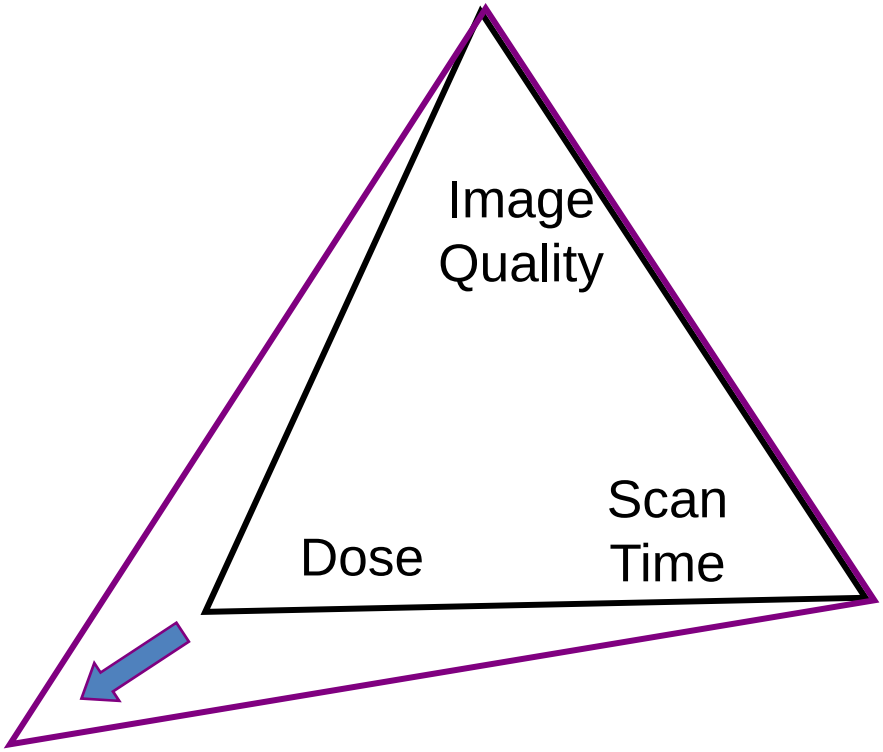
Faster Scan Times



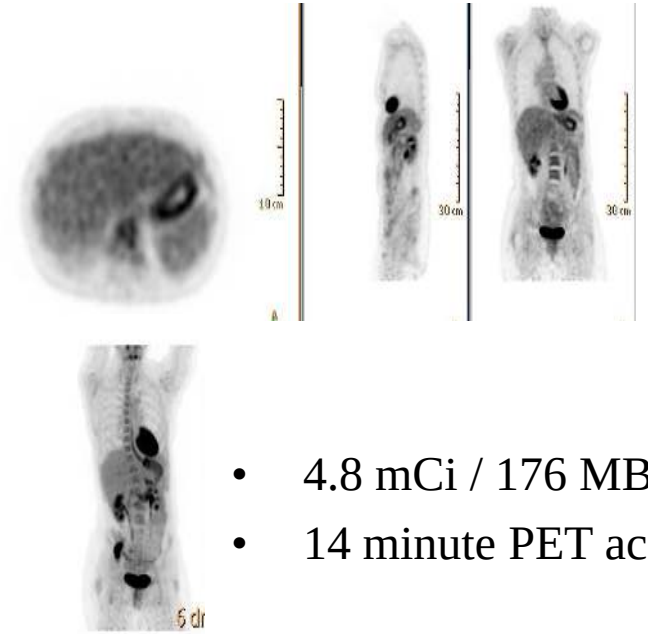
- 11.3 mCi / 418 MBq FDG
- 9 minute PET acquisition
- 76 kg / 168 lb Patient

Clinical Benefits III

How can your customers benefit from reduced noise and higher sensitivity?

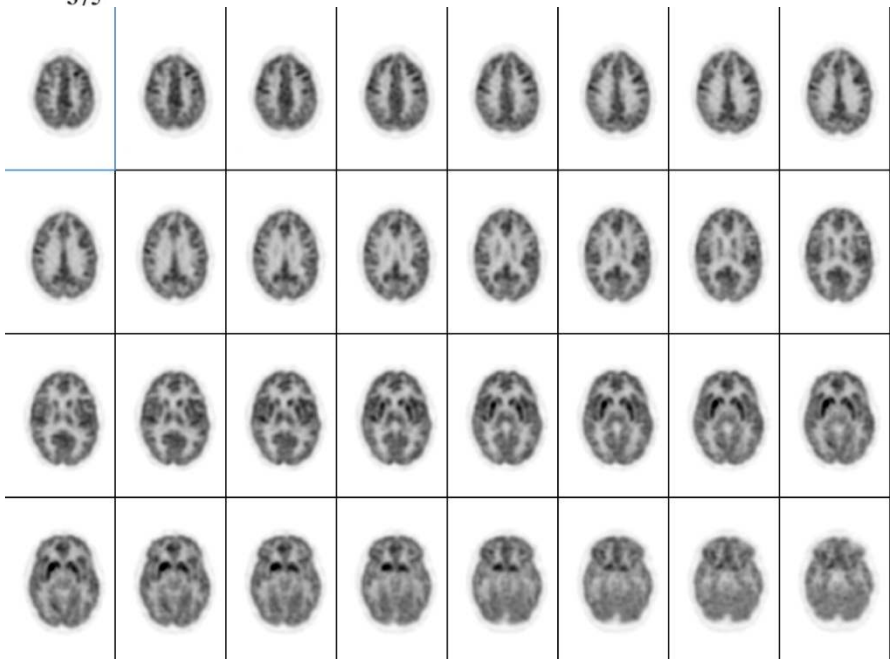


Lower Doses



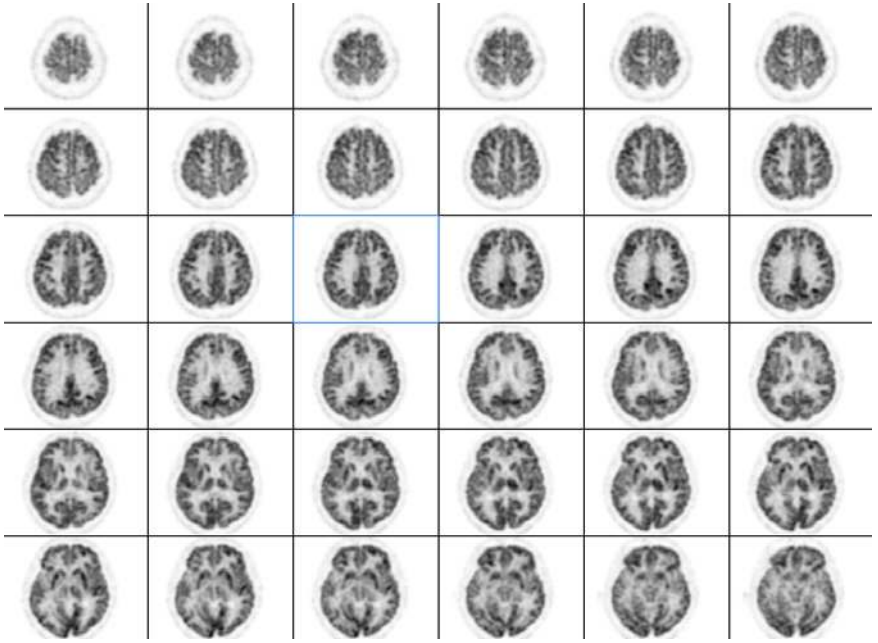
- 4.8 mCi / 176 MBq FDG
- 14 minute PET acquisition

Biomedical Imaging: Gamma camera and Positron Emission Tomography (PET)



Non-TF

TrueFlight



PET in the neuroimaging:

Before fMRI technology PET scanning was the preferred method of functional brain imaging (basic motor, sensory processes and complex cognitive processes).

The images generated by PET represent physiological parameters, such as the rate of glucose uptake or the rate of blood flow, which are inferred from the distribution of positron-emitting radiopharmaceuticals.

Radiotracers:

-ligands for specific neuroreceptor subtypes such as [11C] raclopride and [18F] fallypride for dopamine D2/D3 receptors, [11C] McN 5652 and [11C] DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme).

-These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses.

PET in the neuroimaging:

Activation experiment: increases in local synaptic activity generate increases in local glucose uptake and blood flow.

H215O autoradiographic technique: the short half-life of 15O permitting both successive measurements of cerebral blood flow in a single session and the acquisition of experimental and control images with the same subject .

Tracer kinetics limitation: temporal resolution of PET is several orders of magnitude slower than the neuronal events of interest.

Temporal resolution improvement: experimental designs

-Task repetition

- repetitive performance within the period of time in which a single measurement is taken
- repeated blocks of tasks.

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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

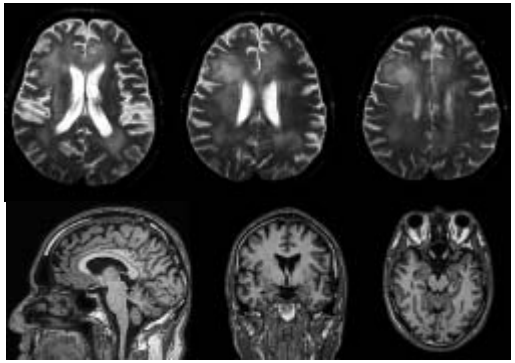
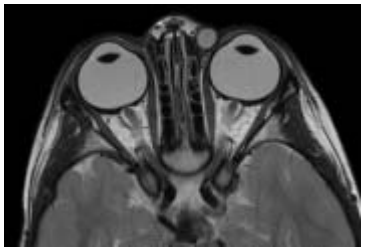
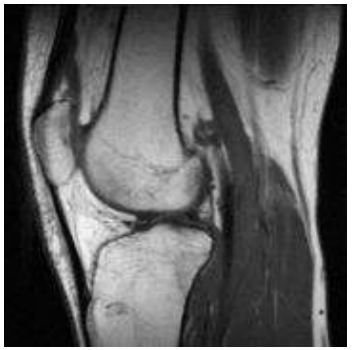
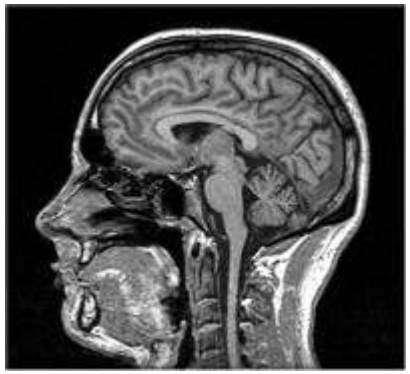
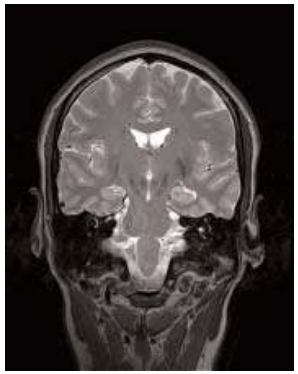
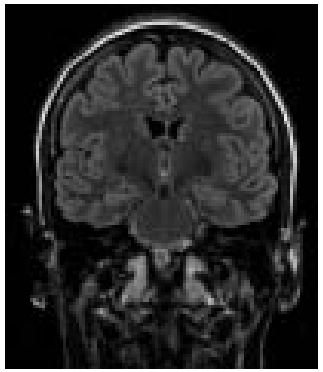
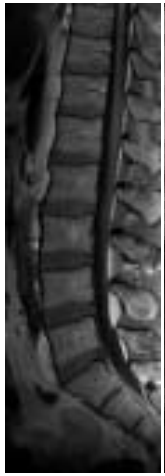
(Orvosbiológiai képalkotás)

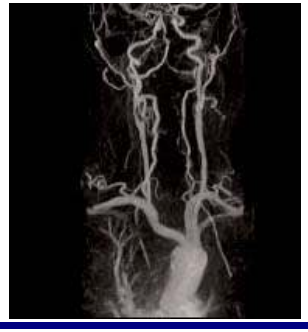
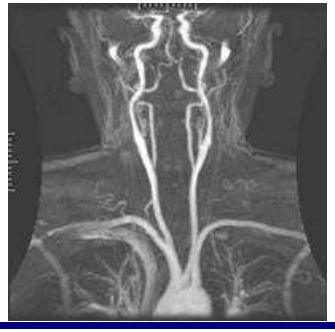
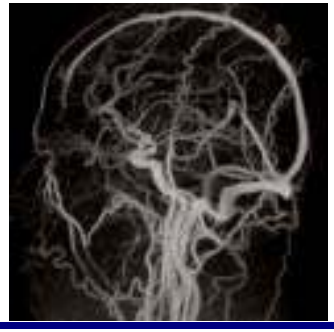
MAGNETIC RESONANCE IMAGING (MRI) - BASICS

(Mágneses Rezonancia Képalkotás (MRI) - Bevezetés)

ISTVÁN KÓBOR, GYÖRGY ERŐSS

MR Images

Tesla and Gauss are measures of magnetic field strength

- Earth's magnetic field ~0.5 Gauss.
- 1Tesla = 10,000 Gauss.
- Our fMRI system is 3T.

  ~x60,000 earth's field strength

Signal and Field Strength

- Outside magnetic field:
  - Spins randomly oriented

- In magnetic field:
  - Spins tend to align parallel or anti-parallel to magnetic field
  - At room temperature, ~4 parts per million more protons per Tesla align with versus against field
  - As field strength increases, there is a bigger energy difference between parallel and anti-parallel alignment (faster rotation = more energy)
  - A larger proportion will align parallel to field
  - More energy will be released as nuclei align
  - Therefore, MR signal increases with square of field strength

Signal and Field Strength

- Most clinical MRI: 1.5T
- fMRI systems: 3.0T
- Maximum for NbTi MRI ~11.7T
- Field strength influences:
  - Faster Larmor frequency
  - Bigger energy difference between parallel and anti-parallel alignment
    - Larger ratio of nuclei aligned = more signal
    - More signal as nuclei realign
  - Reduced TR and TE: less time to take images

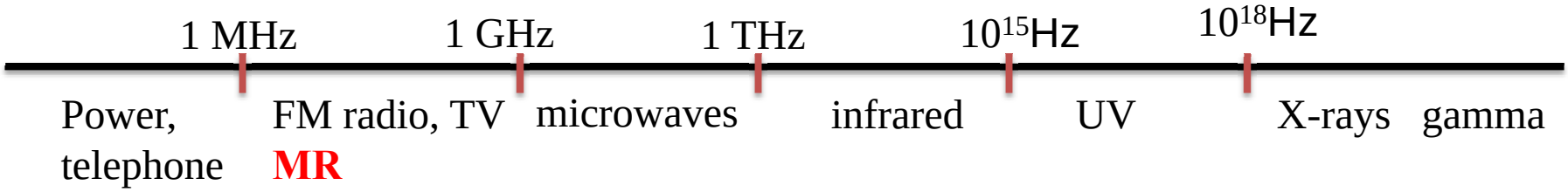
Signal and Field Strength

- In theory:
  - Signal increases with square of field strength
  - Noise increases linearly with field strength
  - A 3T scanner should have twice SNR of 1.5T scanner; 7T should have ~4.7 times SNR of 1.5T

- Unfortunately, physiological artifacts also increase, so advantage is less in practice
- Benefits: speed, resolution
- Costs: artifacts, money, wavelength effects, auditory noise

Electromagnetic Spectrum

- MRI signals are in the same range as FM radio and TV (30-300MHz)
- MRI frequency is non-ionizing radiation, unlike X-rays
- Absorbed RF will cause heating
- Specific absorption rate (SAR): measure of the energy absorbed by tissue
  - Increases ~ with square of field strength
  - Higher SAR = more energy = more signal = more heating
  - FDA limits SAR, and is a limiting factor for some protocols (3 W/kg averaged over 10 minutes)



MRI terminology

- Orientation: typically coronal, sagittal or axial, can be in-between these (oblique)
- Matrix Size:
  - Voxels in each dimension
- Field of view:
  - Spatial extent of each dimension
- Resolution:
  - FOV/Matrix size

Philips Achieva 3T Scanner

•**MRI** magnetic resonance imaging → images of biological tissues, structural studies

- static magnetic field + a series of changing magnetic fields and oscillating electromagnetic fields (pulse sequence)
- depending on frequency of electromagnetic fields, energy is absorbed by hydrogen nuclei (excitation)
- later the energy is emitted by the nuclei
- the amount of energy depends on numbers and types of nuclei present

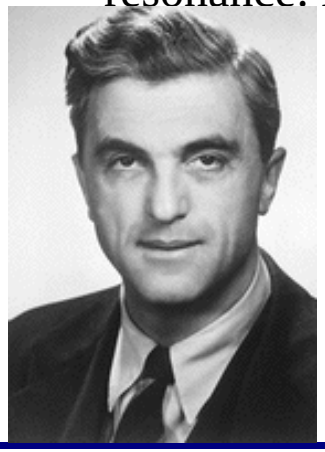
- Advantages of MRI
  - No ionizing radiation exposure
  - Better spatial resolution than CT
- Disadvantages
  - No ferrous metal!

History of MR/ MRI/ fMRI:

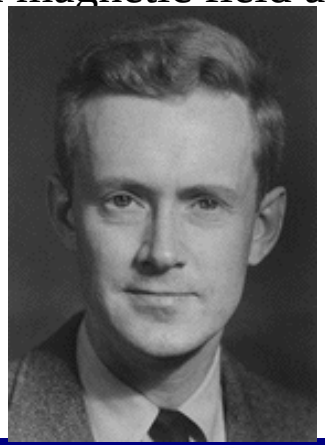
NMR = nuclear magnetic resonance

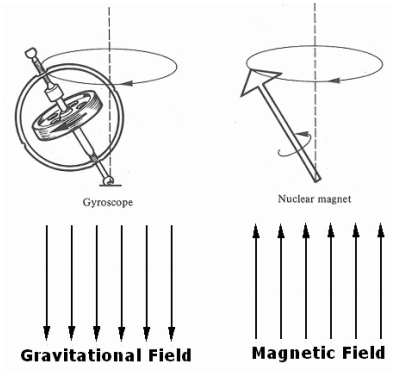
- Felix Block and Edward Purcell
  - 1946: atomic nuclei absorb and re-emit radio frequency energy
  - 1952: Nobel prize in physics
    - nuclear: properties of nuclei of atoms
    - magnetic: magnetic field required
    - resonance: interaction between magnetic field and radio frequency

Felix Bloch



Edward Purcell





History of MR/ MRI/ fMRI:

-1971: MRI Tumor detection (Damadian)

-1973: Lauterbur suggests NMR could be used to form images

-1977: clinical MRI scanner patented

-1977: Mansfield proposes echo-planar imaging (EPI) to acquire images faster

-2003: Nobel prize was awarded to Paul Lauterbur and Sir Peter Mansfield (excluding Damadian – huge controversy)

fMRI

-1990: Ogawa observes BOLD effect with T2*

blood vessels became more visible as blood oxygen decreased

-1991: Belliveau observes first functional images using a contrast agent

-1992: Ogawa et al. and Kwong et al. publish first functional images using BOLD signal

The First ZMR NMR Image

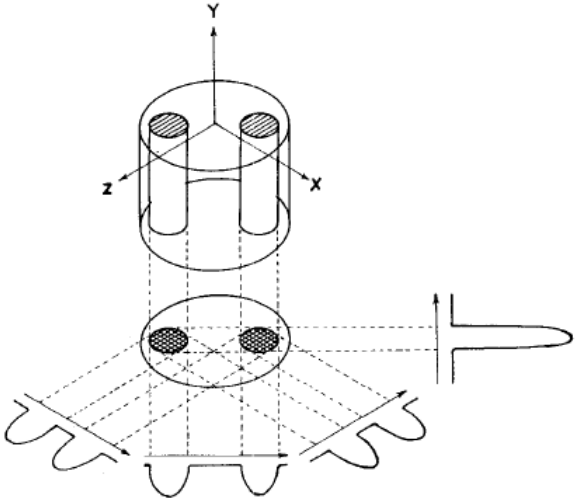
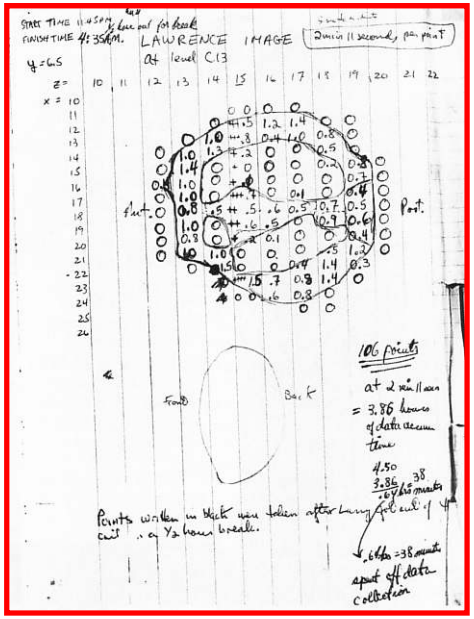


Fig. 1 Relationship between a three-dimensional object, its two-dimensional projection along the Y-axis, and four one-dimensional projections at 45° intervals in the XZ-plane. The arrows indicate the gradient directions.

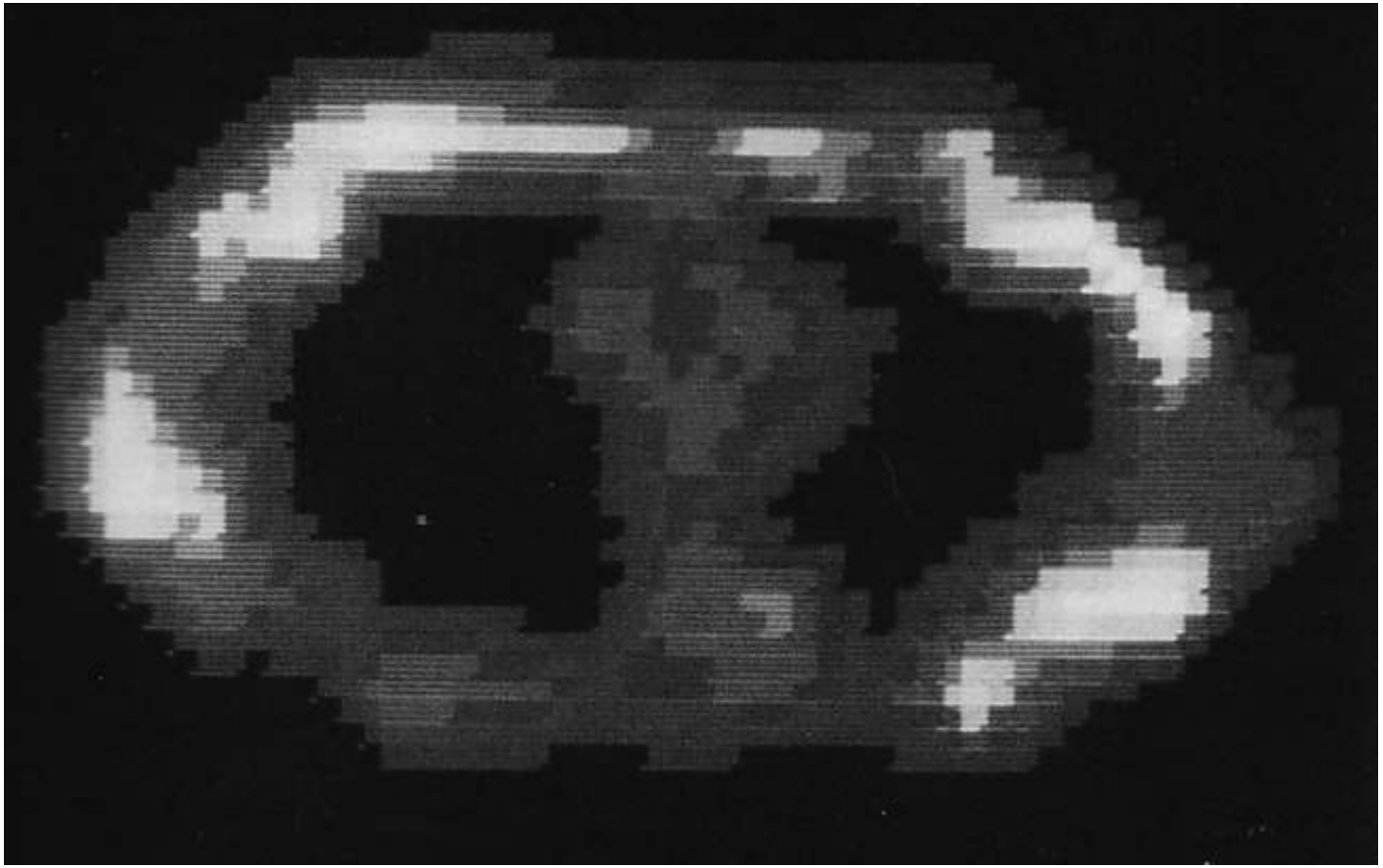
Fig. 2 Proton nuclear magnetic resonance zeugmatogram of the object described in the text, using four relative orientations of object and gradients as diagrammed in Fig. 1.

Lauterbur, P.C. (1973). Image formation by induced local interaction: Examples employing nuclear magnetic resonance. *Nature*, 242, 190-191.

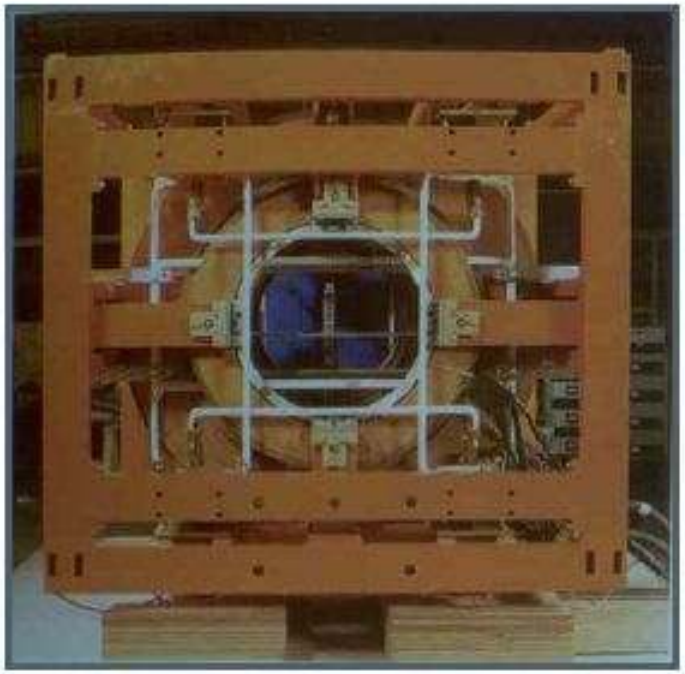
Early Human MR Images (Damadian)

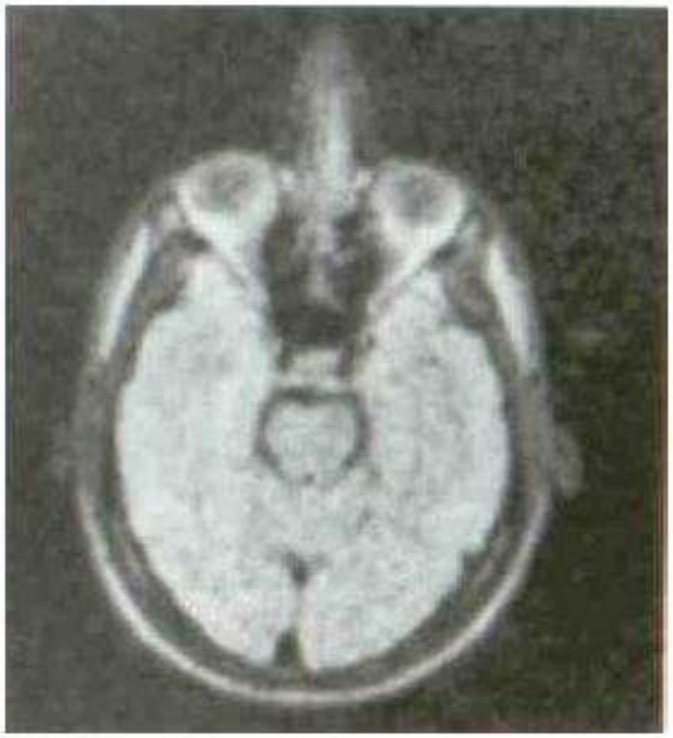


Biomedical Imaging: Magnetic Resonance Imaging - Basics

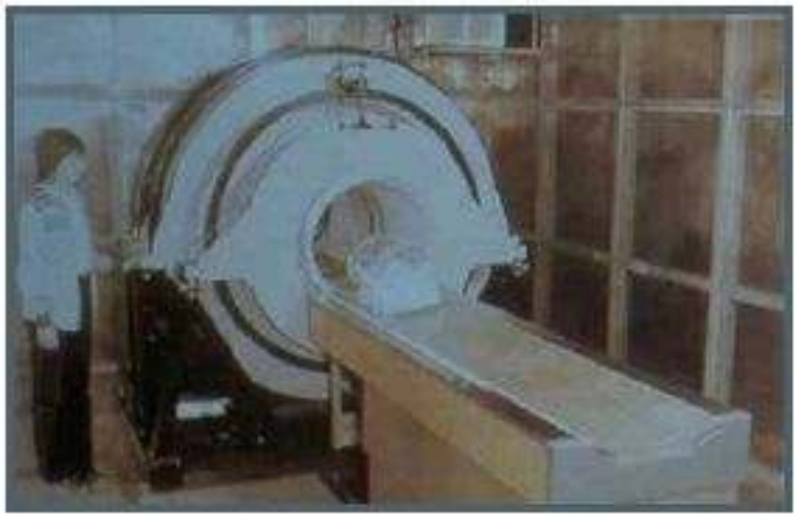


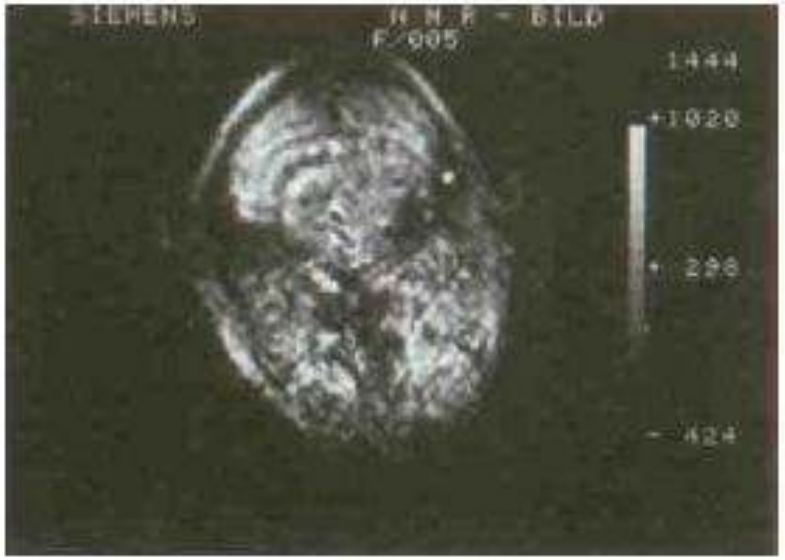
Mink5 Image – Damadian (1977)





The first Philips MR, 1978 (0,15T)





The first Siemens MR, 1980 (0,2T)

Biomedical Imaging: Magnetic Resonance Imaging - Basics

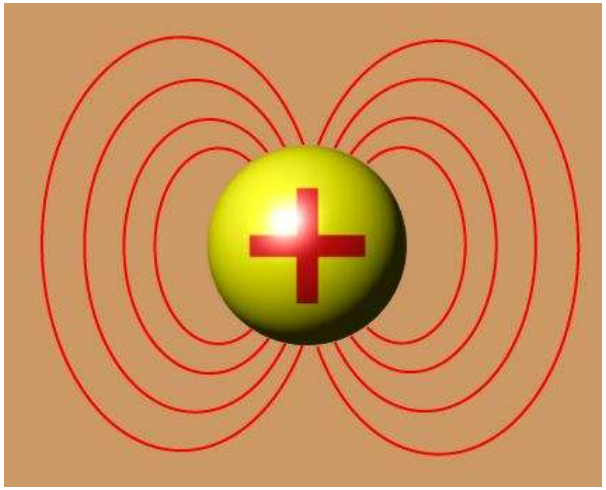
Typical 1.5/3.0T MR system

Special Open-MR system

Nuclear spins

A nucleus of hydrogen

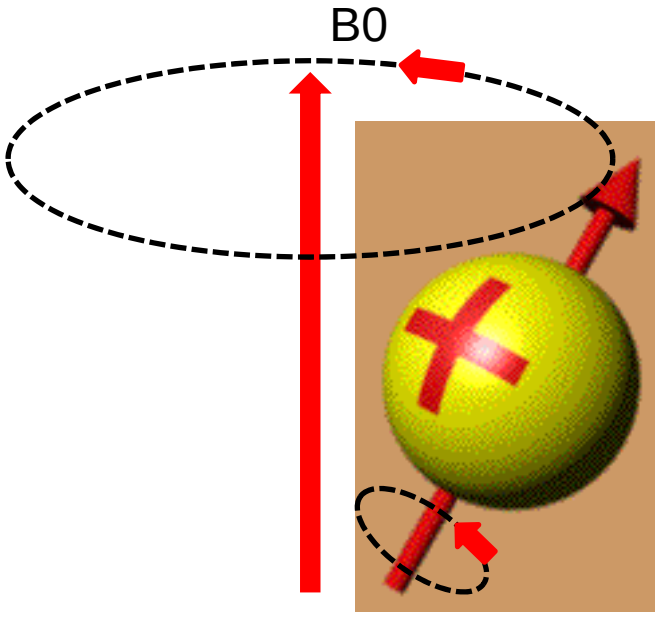
- consists of one proton
- carries a positive charge



- rotates around its axis because of thermal energy

→ electrical current and magnetic source → spin

- Nuclei line up with magnetic moments either in a parallel (low level) or anti-parallel configuration (higher energy level).
- In body tissues more line up in parallel creating a small additional magnetization **M** in the direction of $\mathbf{B}_0$.



Nuclei spin axis not parallel to B_0 field direction.

Nuclear magnetic moments precess about B_0.

Absorption and Relaxation

- Our RF transmission is absorbed by atoms at Larmor frequency
- After the RF pulse, atoms will begin to realign with the magnetic field: relaxation
- During this period, an RF signal is emitted
- This signal will be at the Larmor frequency
- An antenna can measure this signal

- Frequency of precession of magnetic moments given by **Larmor** relationship

$$f = \gamma \times B_0$$

f = Larmor frequency (mHz)
g = Gyromagnetic ratio (mHz/Tesla)
B_0 = Magnetic field strength (Tesla)

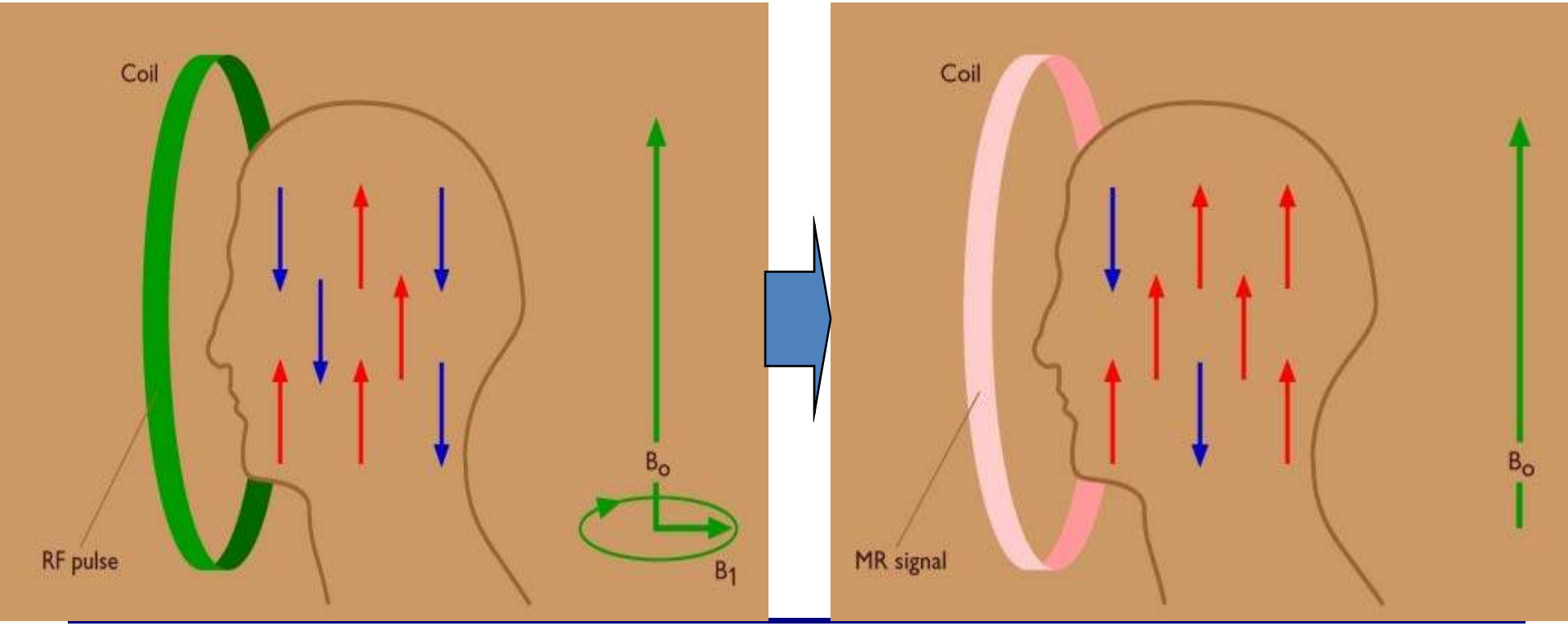
g ~ 43 mHz/Tesla

Larmor frequencies of RICs MRIs

3T ~ 130 mHZ
7T ~ 300 mHz
11.7T ~ 500 mHz

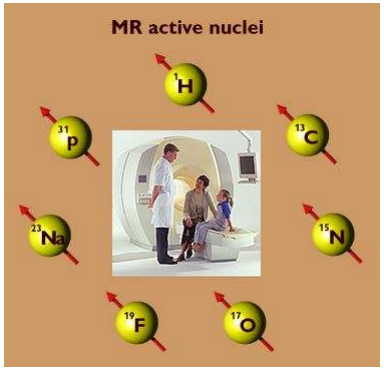
Radiofrequency Pulses

- A radiofrequency (RF) pulse at the Larmor frequency will be absorbed
- This higher energy state tips the spin, so it is no longer aligned to the field
- An RF pulse at any other frequency will not influence the nuclei, only resonance frequency

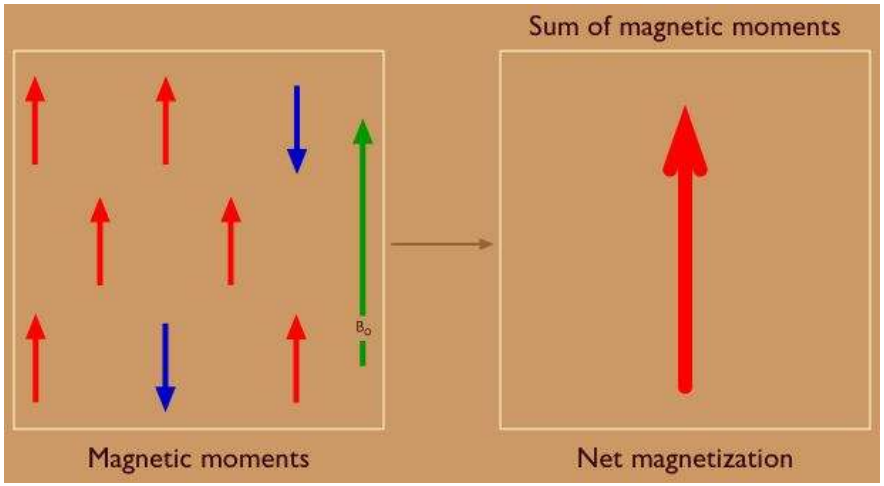


Hydrogen is the mainstay for MRI

- We will focus on Hydrogen
  - Hydrogen abundant in body (63% of atoms)
  - Elements with even numbers of neutrons and protons have no spin, so we can not image them (^{4}He, ^{12}C)
  - ^{23}Na and ^{31}P are relatively abundant, so can be imaged
- Larmor frequency varies for elements:
  - ^{1}H = 42.58 Mhz/T
  - ^{13}C = 10.7 Mhz/T
  - ^{19}F = 40.1 Mhz/T
  - ^{31}P = 17.7 Mhz/T
- Therefore, by sending in a RF pulse at a specific frequency we can selectively energize hydrogen

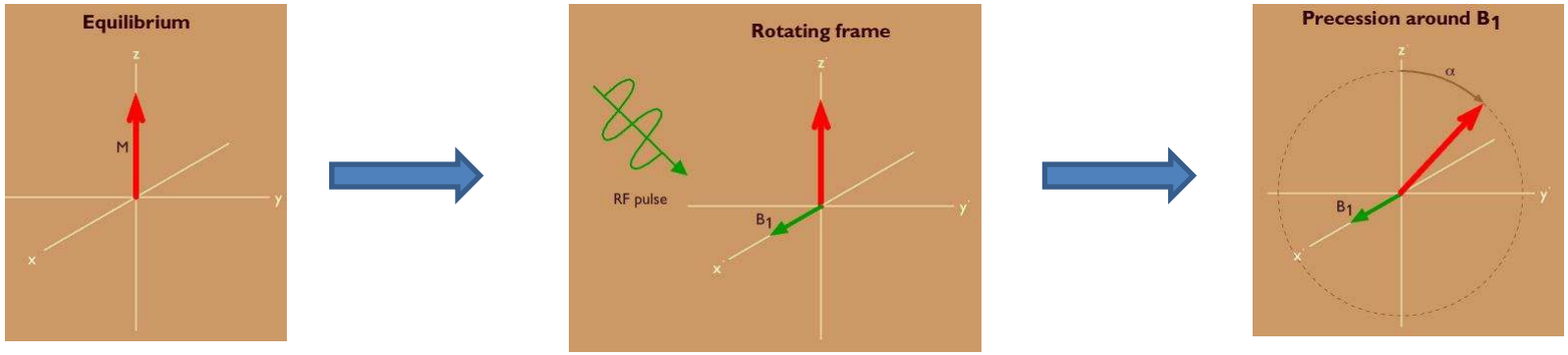


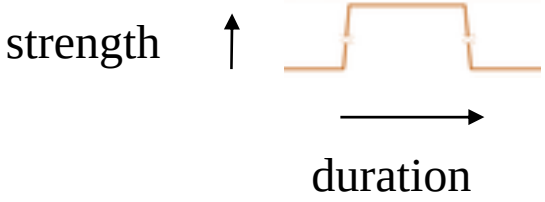
- **M** is parallel to $\mathbf{B}_0$ since transverse components of magnetic moments are randomly oriented
- The difference between the numbers of protons in the parallel and anti-parallel states leads to the ***net magnetization*** (**M**)
- Proton density relates to the number of parallel states per unit volume
- Signal producing capability depends on proton density

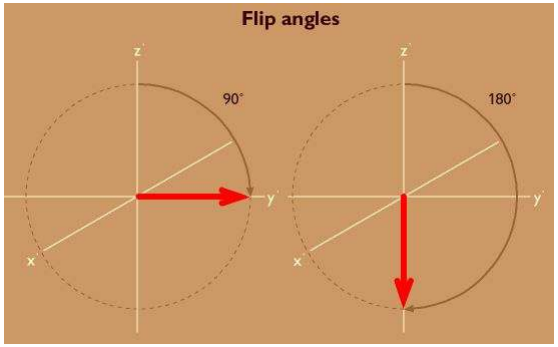


RF Pulse

Frequency of rotation of **M** about B_1 determined by the magnitude (strength) of $\mathbf{B}_1$



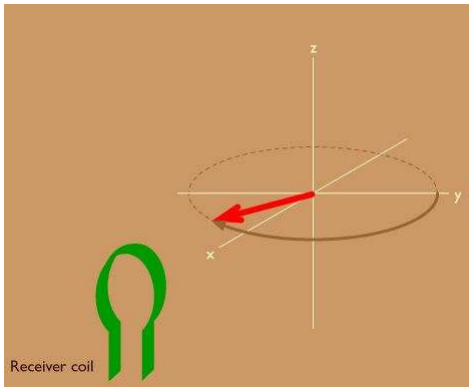




RF pulse duration and strength determine flip angle

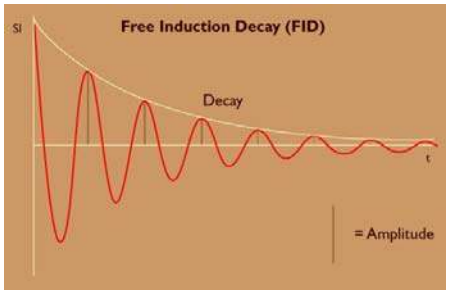
Biomedical Imaging: Magnetic Resonance Imaging - Basics

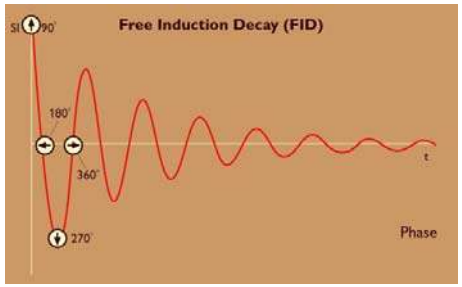
- 90° RF pulse rotates M into transverse (x-y) plane
- Rotation of M within transverse plane induces **signal** in receiver coil at Larmor frequency
- Magnitude **signal** dependent on proton density and $\mathbf{M}_{xy}$

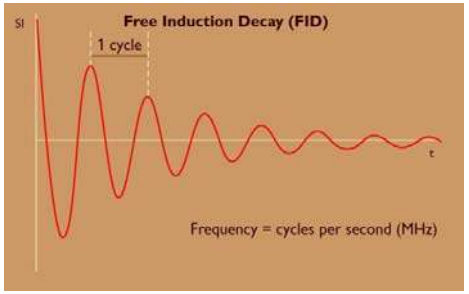


FID = Free Induction Decay

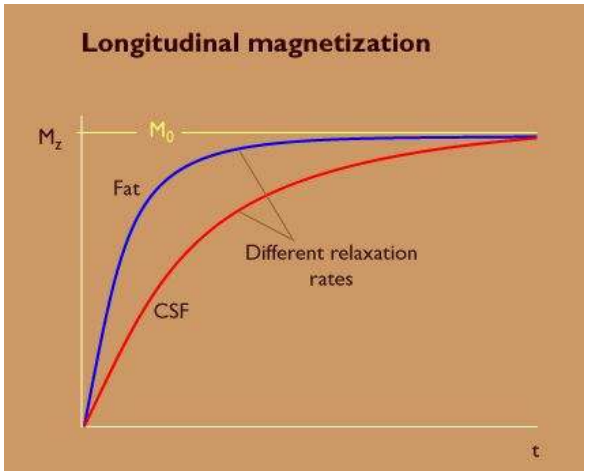
- FID magnitude decays in an exponential manner with a time constant T2. Decay due to spin-spin relaxation



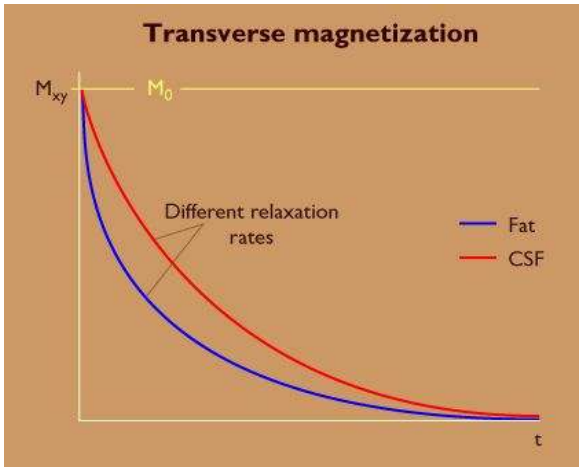




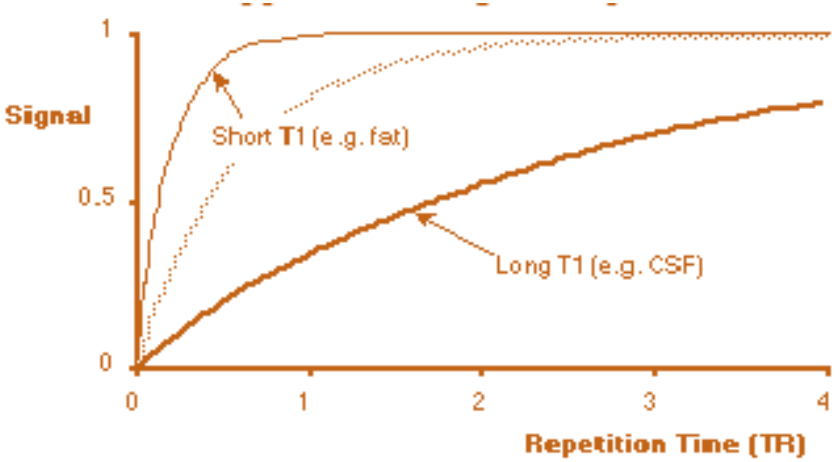
- T1-Relaxation: Recovery
  - Recovery of longitudinal orientation of **M** along z-axis
  - 'T1 time' refers to time interval for 63% recovery of longitudinal magnetization
  - **Spin-Lattice interactions**



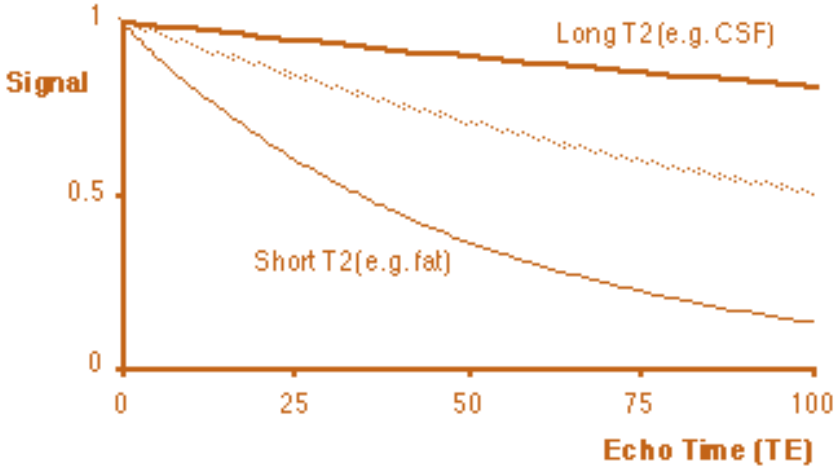
- T2-Relaxation: Dephasing
  - Loss of transverse magnetization $\mathbf{M}_{xy}$
  - 'T2 time' refers to time interval for 37% loss of original transverse magnetization
  - **Spin-spin interactions, and more**



- T1 is shorter in fat (large molecules) and longer in cerebrospinal fluid (CSF) (small molecules). T1 contrast is higher for lower TRs



- T2 is shorter in fat and longer in CSF. Signal contrast increased with TE



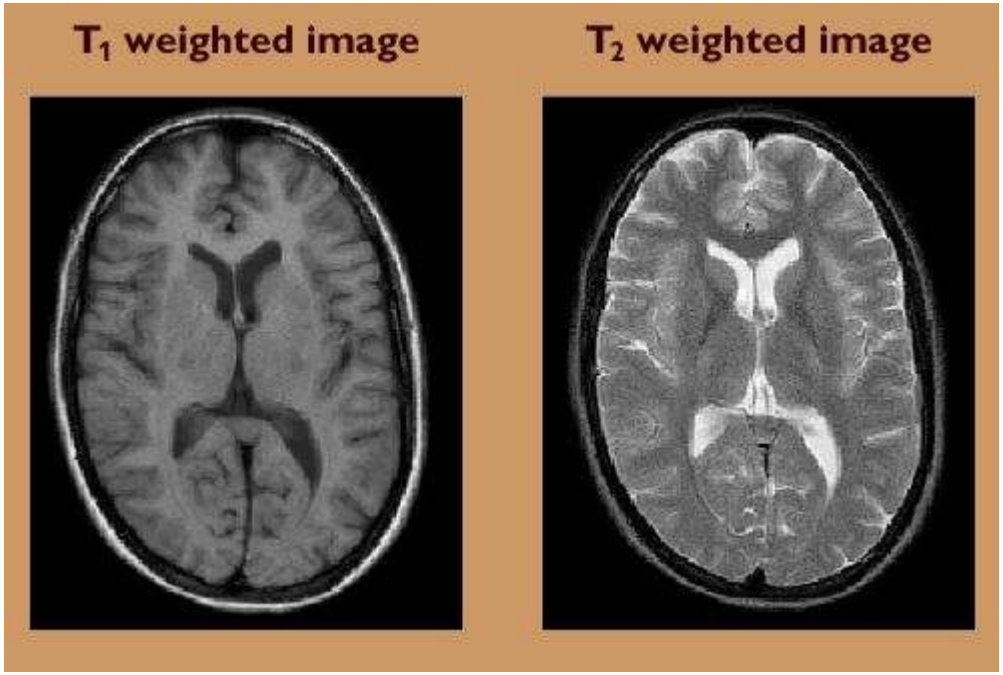
- **TR determines T1 contrast**
- **TE determines T2 contrast**

Properties of Body Tissues

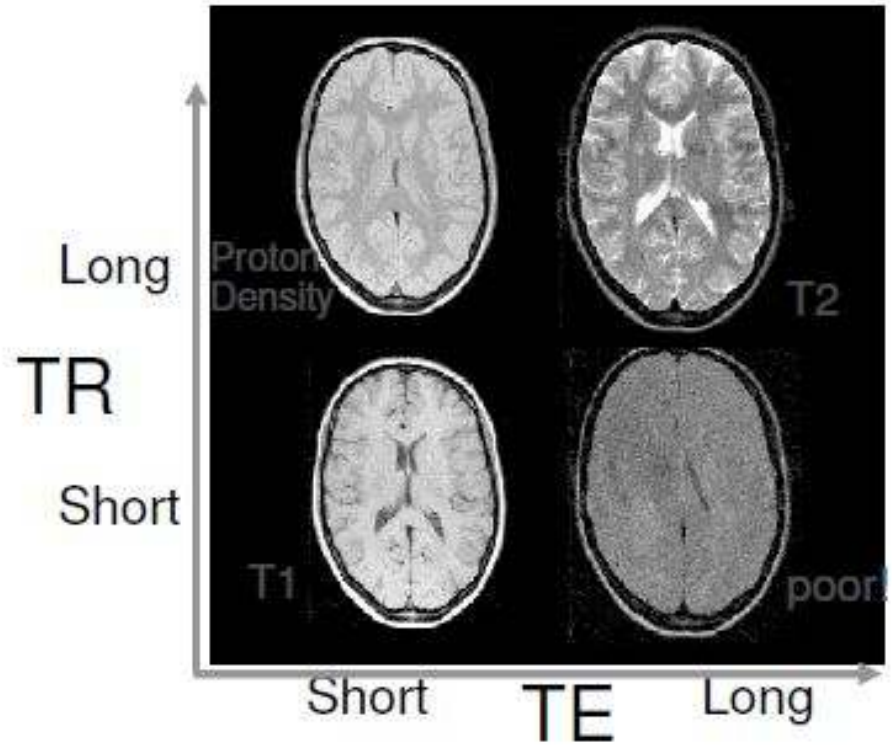
	T1 (msec)	T2 (msec)
Grey Matter	**950**	**100**
White Matter	600	80
Fat	250	60
Blood	1200	100-200
Cerebrospinal Fluid	4500	2200
Muscle	900	50

T1 values for B_0 ~ 1Tesla.
T2 ~ $1/10^{th}$ T1 for soft tissues

T1/T2 weighted images:



Contrast, Imaging Parameters:



- Short TEs reduce T2W
- Long TRs reduce T1W

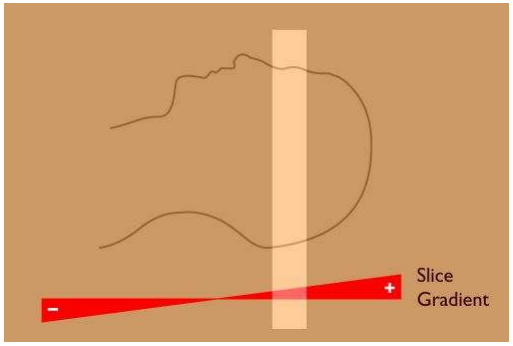
Making a spatial image

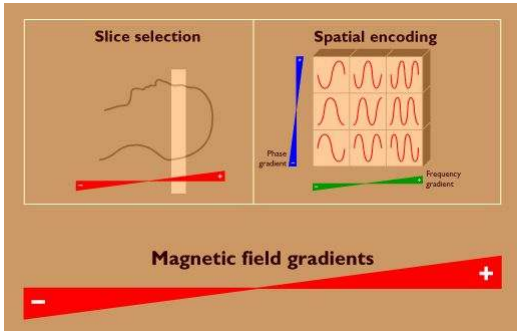
Lauterbur

- To create spatial images, we need a way to cause different locations in the scanner to generate different signals
- To do this, we apply gradients
- Gradients make the magnetic field slightly stronger at one location compared to another
- Lauterbur: first MRI: 2003 Nobel Prize

Slice Selection Gradient

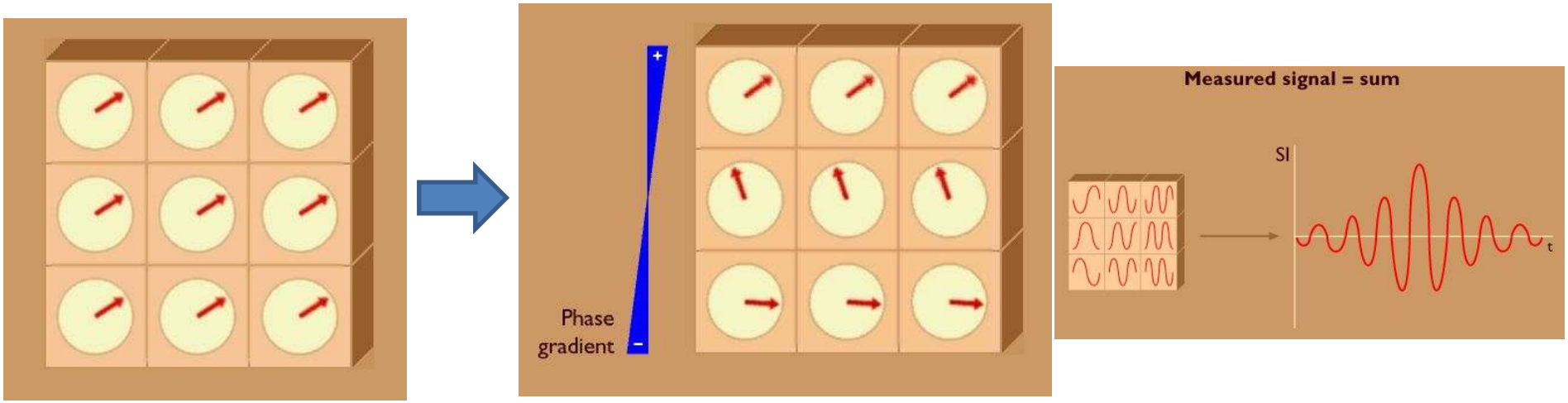
- Gradients make field stronger at one location compared to another
- Larmor frequency different along this dimension
- RF pulse only energizes slice where field strength matches Larmor frequency
- Gradual slice selection gradients will select thick slices, while steep gradients select thinner slices
  - The strength of your scanner's gradients can limit minimum slice thickness
  - FDA limits speed of gradient shift (dB/dt) and some of our protocols can elicit slight tingling sensation or brief muscle twitches
- Position of gradient determines which 2D slice is selected





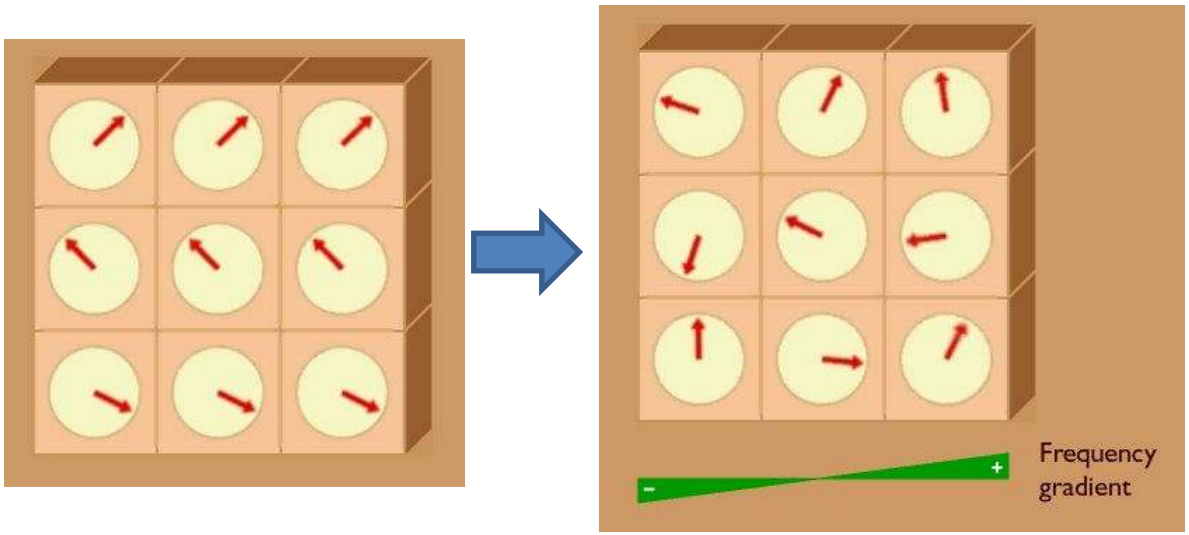
Phase Encoding

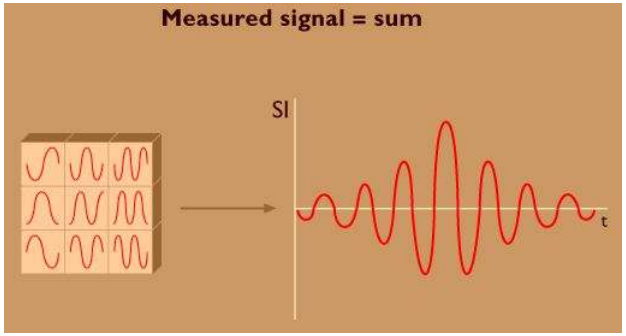
- Phase encoding gradient:
  - Orthogonal gradient applied between RF pulse and readout
  - This adjusts the phase along this dimension
  - Analogy: Phase encoding is like time zones. Clocks in different zones will have different phases



Frequency Encoding

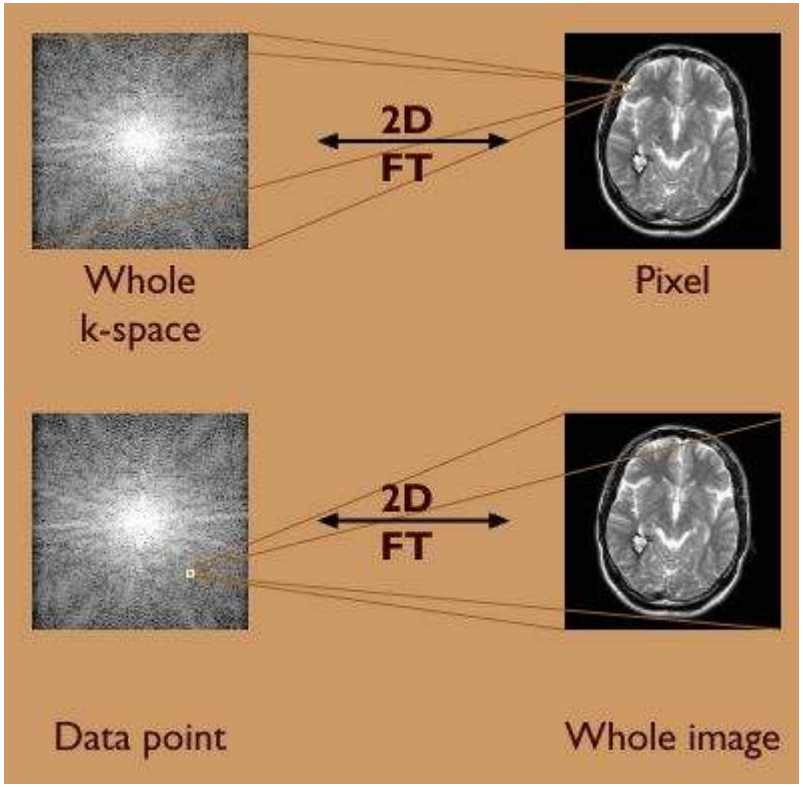
- Frequency encoding gradient:
  - Apply final orthogonal gradient when we wish to acquire image
  - Slice will emit signal at Lamour frequency, e.g. lines at higher fields will have higher frequency signals
  - Aka ‘Readout gradient’





Raw MRI image: k-space (frequency domain)

a k-space domain image is formed using frequency and phase encoding

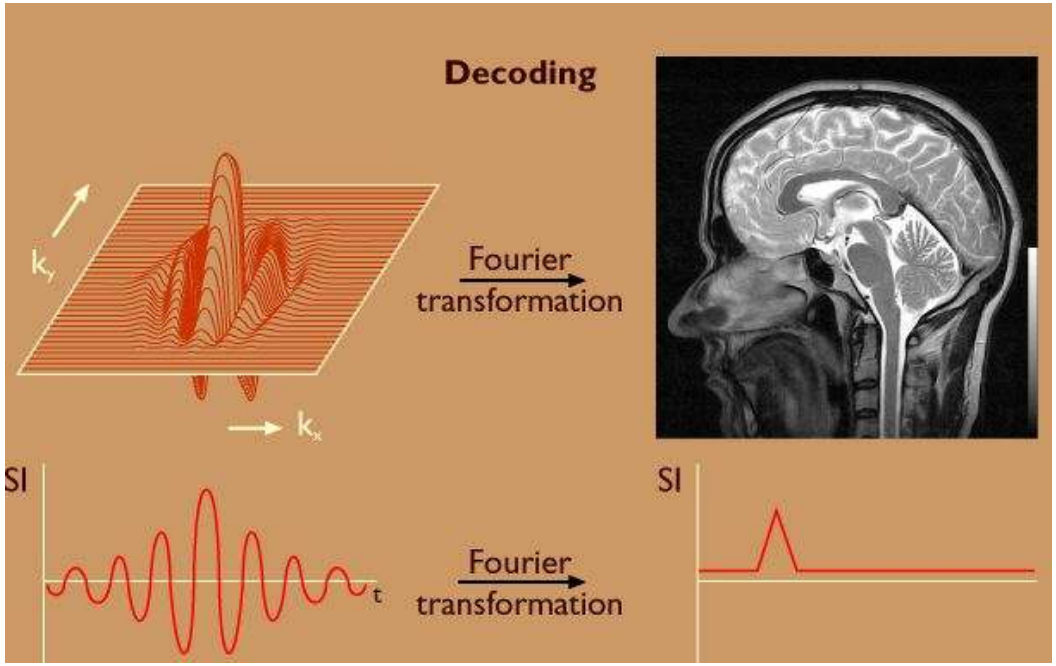


Reconstruction

- Medical scanners automatically reconstruct your data
- You can manually reconstruct data
- Fourier Transforms are slow: 1021-sample data requires >2 million multiplications ($2*N^2$)
- Fast Fourier Transform: 1024-sample data requires 20,000 multiplications (2(N log N))
  - Optimal when data is power of two (64,128,256, 512), reverts to traditional Fourier for prime numbers
  - This is why most image matrices are a power of 2

MRI task is to acquire k-space image then transform to a spatial-domain image. k_x is sampled (read out) in real time to give N samples. k_y is adjusted before each readout

MR image is the magnitude of the Fourier transform of the k-space image



The k-space Trajectory

- Equations that govern 2D k-space trajectory

$$k_x = \int_0^t G_x(t)dt$$

if G_x is constant $\qquad k_x = gG_xt$

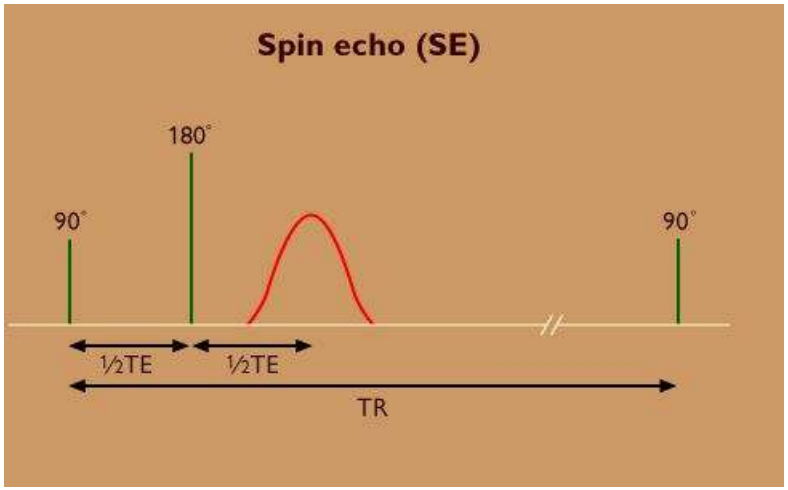
$$k_y = \int_0^{t'} G_y(t)dt$$

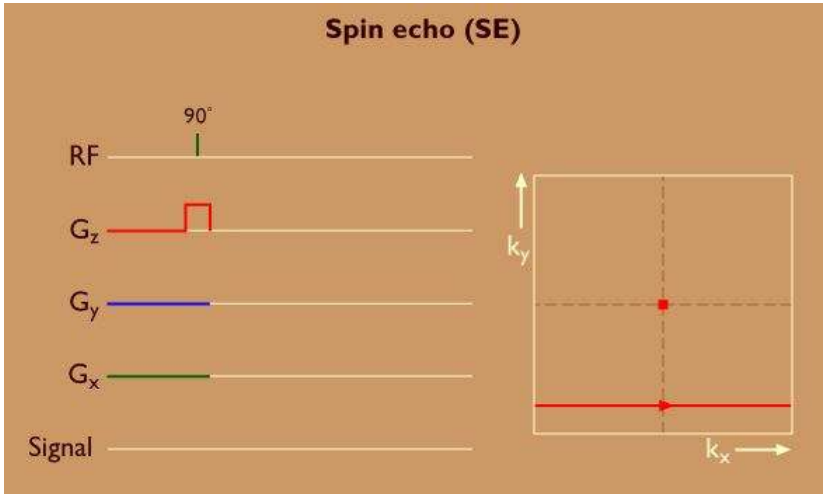
The k_x, k_y frequency coordinates are established by durations (t) and strength of gradients (G)

Primary types of Pulse sequences

- Spin Echo (SE):

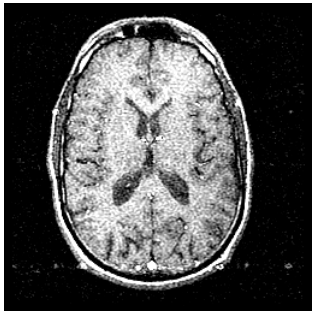
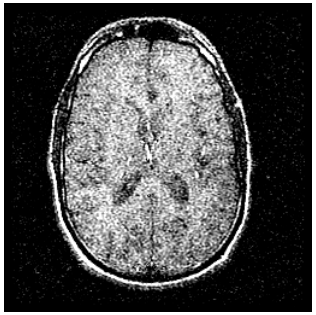
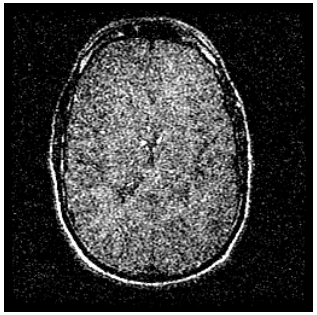
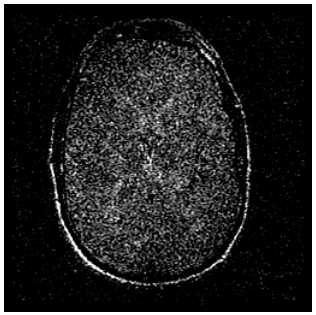
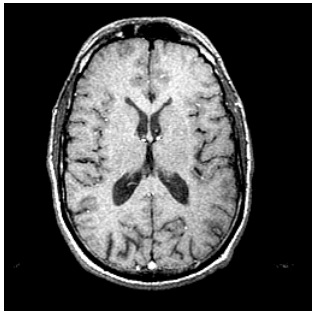
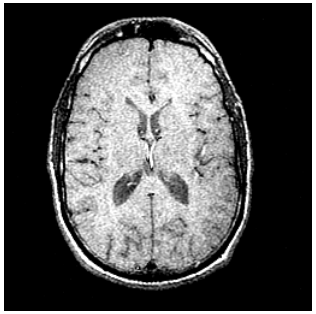
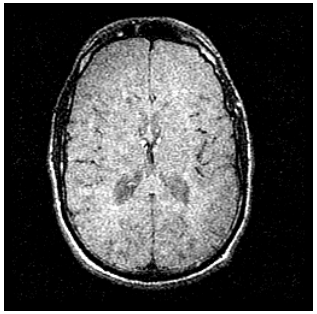
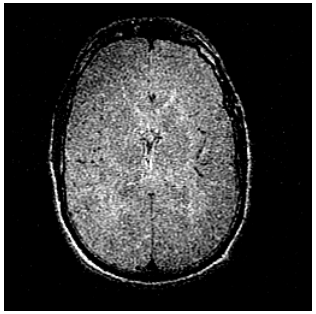
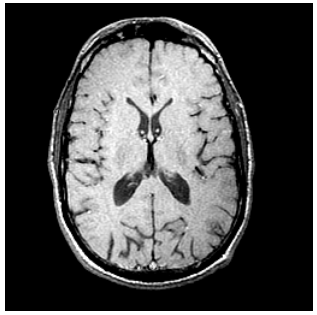
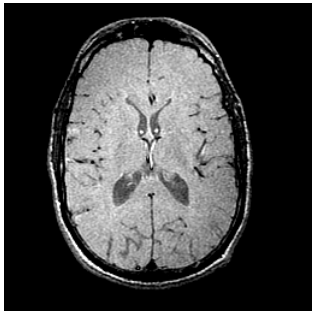
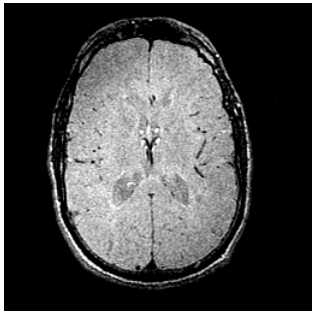
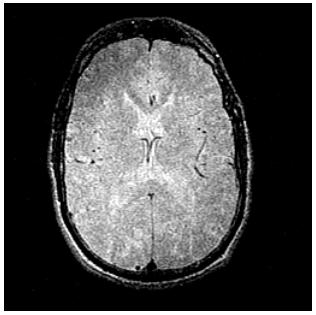
  - The most commonly used pulse sequence
  - Uses 90° radio frequency pulses to excite the magnetization and one or more 180° pulses to refocus the spins to generate signal echoes: SE
  - The two variables of interest in spin echo sequences is TR and TE





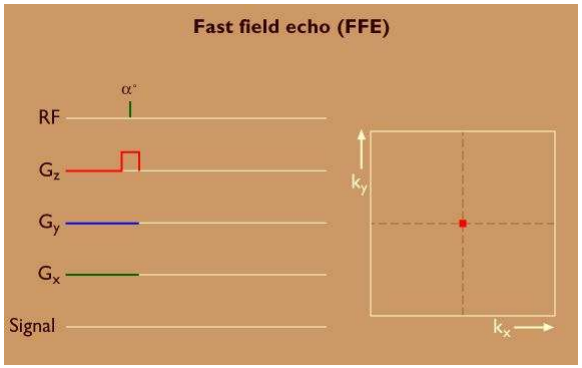
Biomedical Imaging: Magnetic Resonance Imaging - Basics

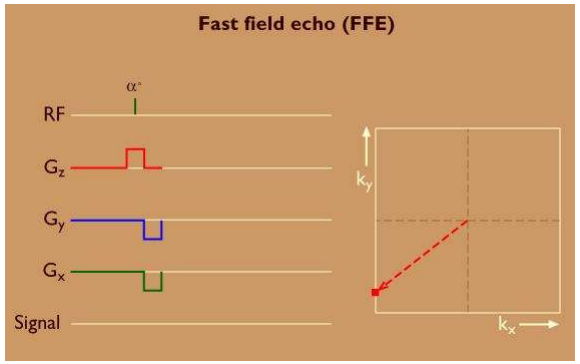
Spin-Echo Image

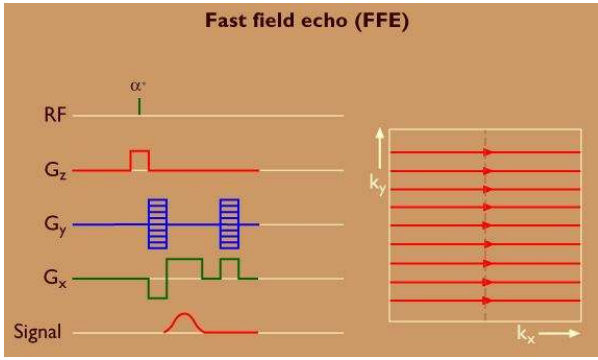
	TE = 20 ms	TE = 50 ms	TE = 75 ms	TE = 100 ms
TR = 250 ms				
TR = 500 ms				
TR = 1000 ms				

- Fast Spin Echo (FSE):

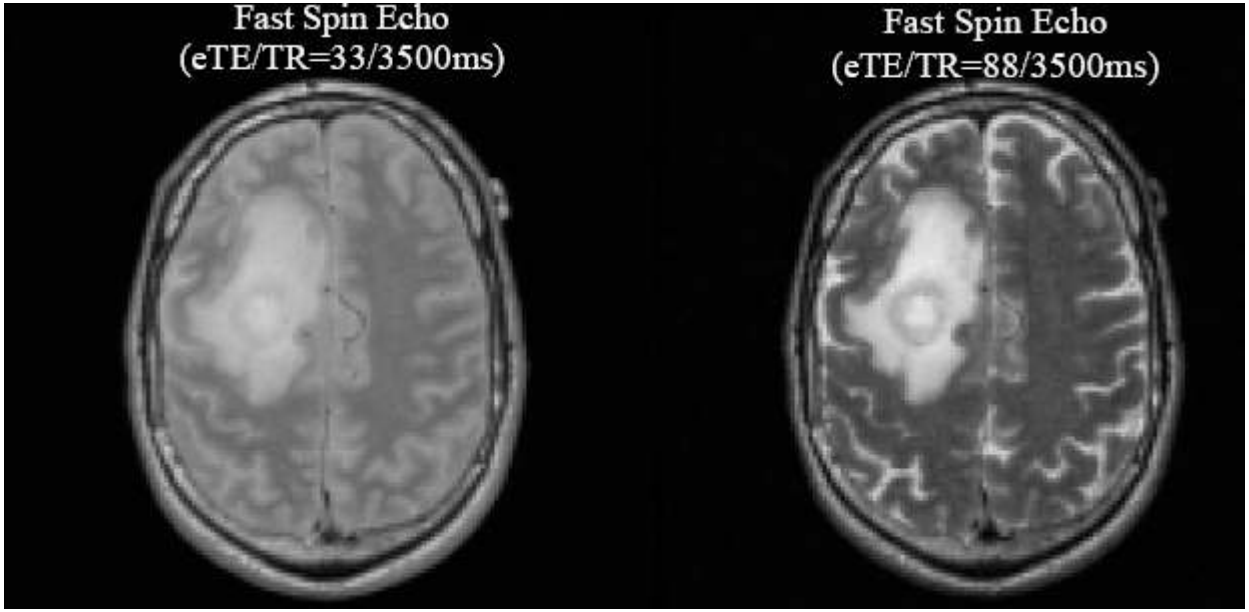
  - Characterized by a series of rapidly applied 180° rephasing pulses and multiple echoes, changing the phase encoding gradient for each echo
  - TE may vary from echo to echo in the echo train
  - T2 weighted imaging profits most from this technique
  - T2 weighted FSE images, both water and fat are hyperintense





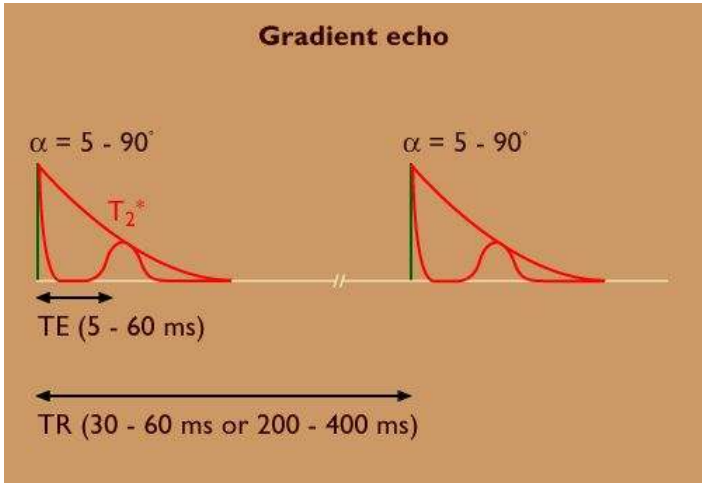


Fast Spin Echo (FSE)



- Gradient Echo (GRE):

  - generated by using a pair of bipolar gradient pulses
  - no refocusing 180° pulse and the data are sampled during a gradient echo, which is achieved by dephasing the spins with a negatively pulsed gradient before they are rephased by an opposite gradient with opposite polarity to generate the echo
  - short repetition time

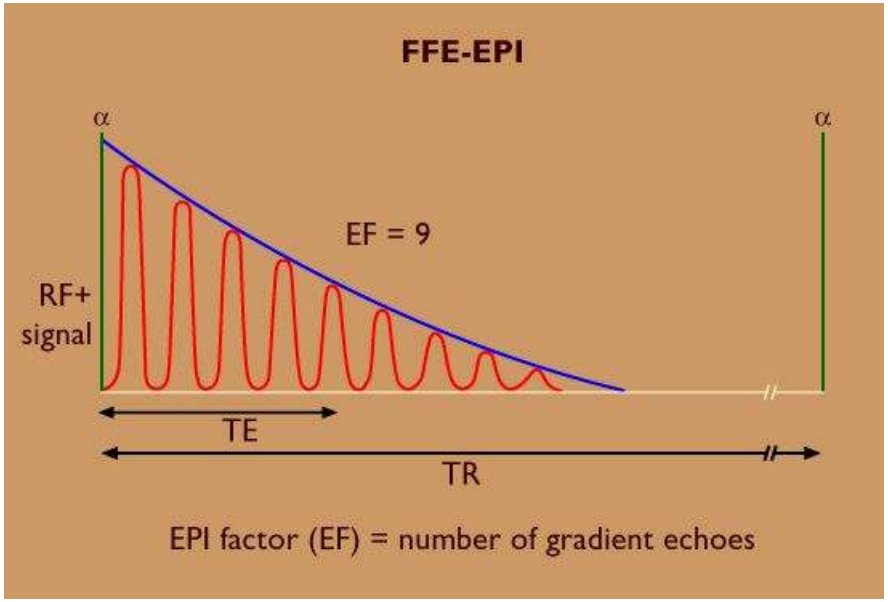


- Fast Low Angle Shot (FLASH):

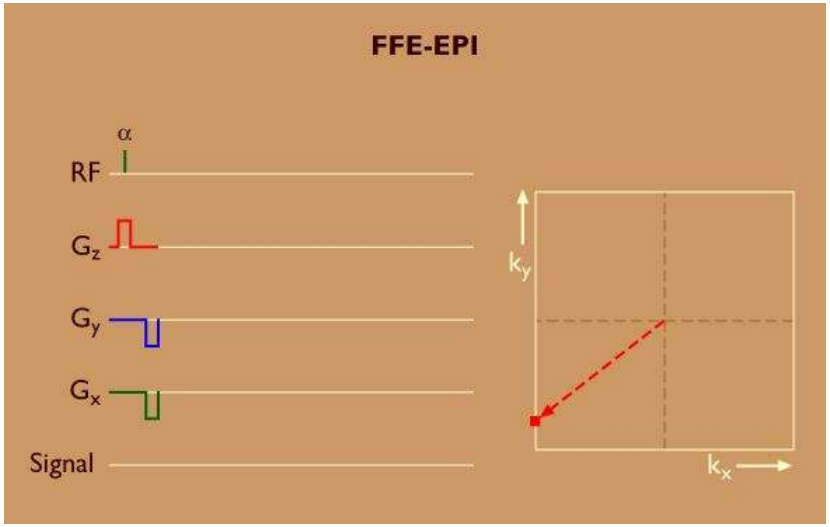
  - a fast sequence producing signals called gradient echo with low flip angles
  - uses a semi-random spoiler gradient after each echo to spoil the steady state by causing a spatially dependent phase shift
  - extremely short TR times are possible, as a result the sequence provides a mechanism for gaining extremely high T1 contrast

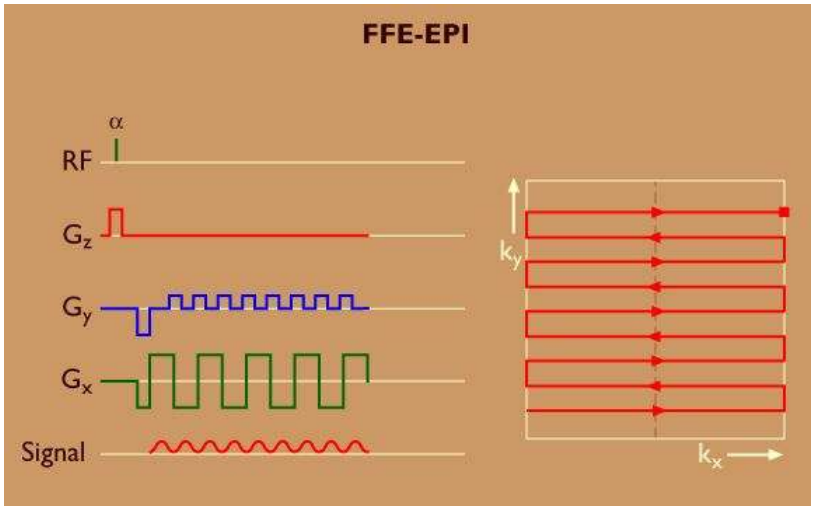
- Echo Planar Imaging (EPI):

  - used in applications like diffusion, perfusion, and functional magnetic resonance imaging
  - complete image is formed from a single data sample (all k-space lines are measured in one repetition time) of a gradient echo or spin echo sequence with an acquisition time of about 20 to 100 ms



EPI


FFE-EPI
α
RF
G_z
G_y
G_x
Signal
k_y
k_x


FFE-EPI
α
RF
G_z
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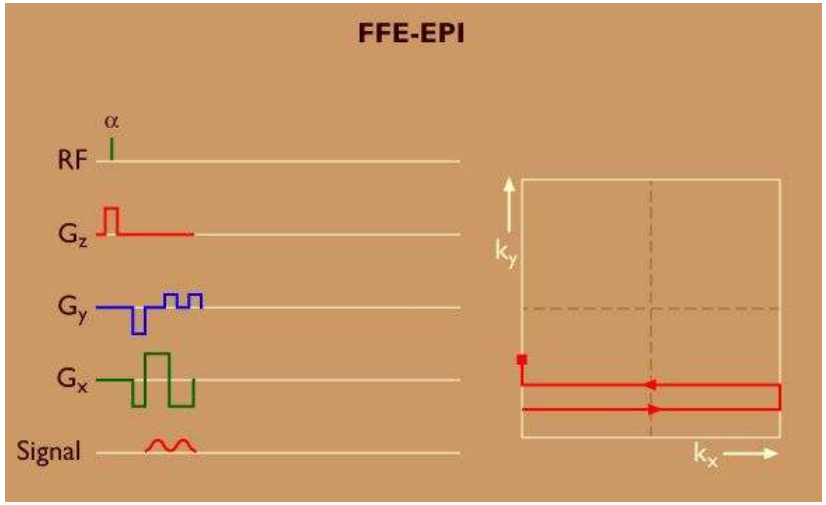
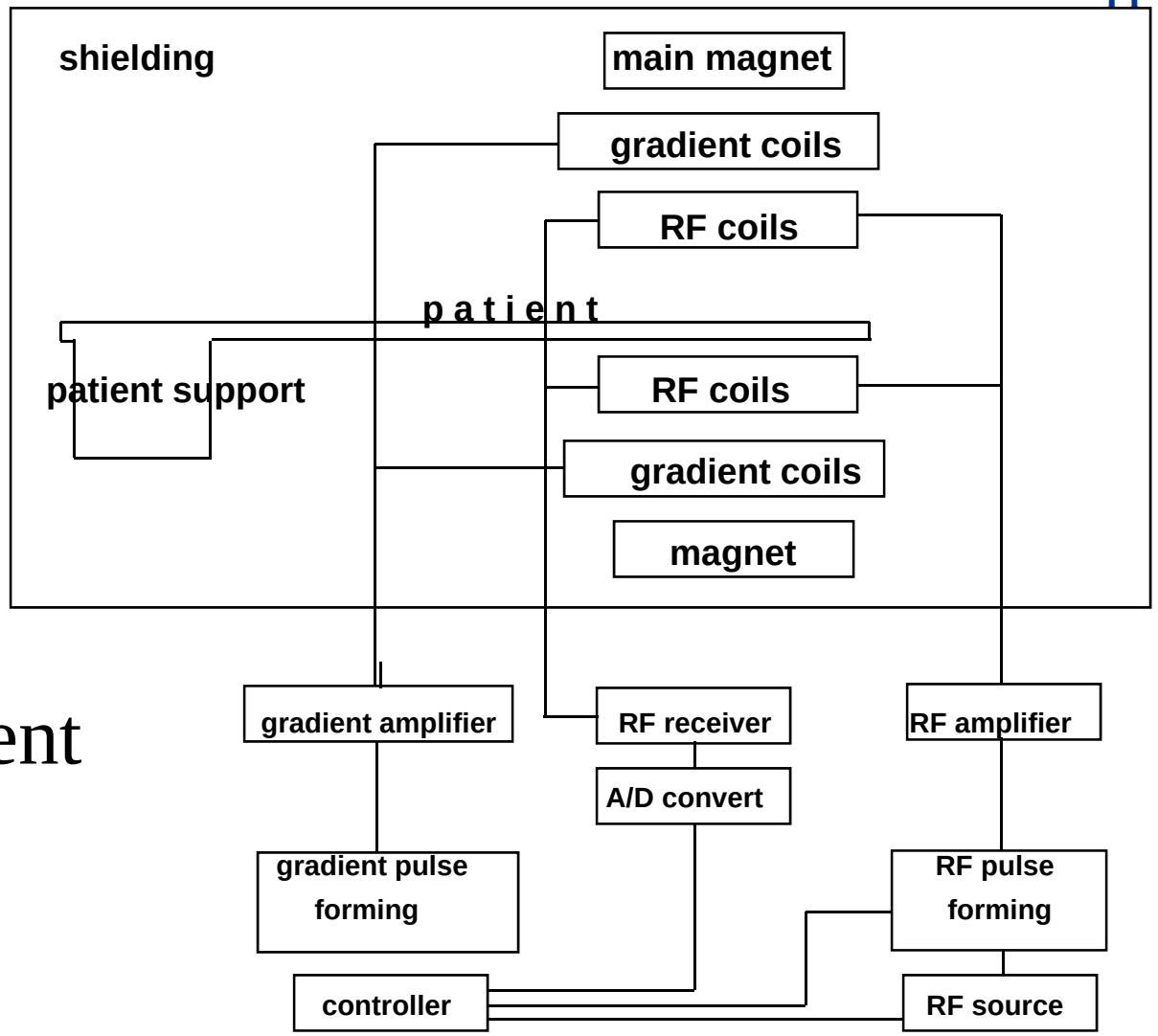
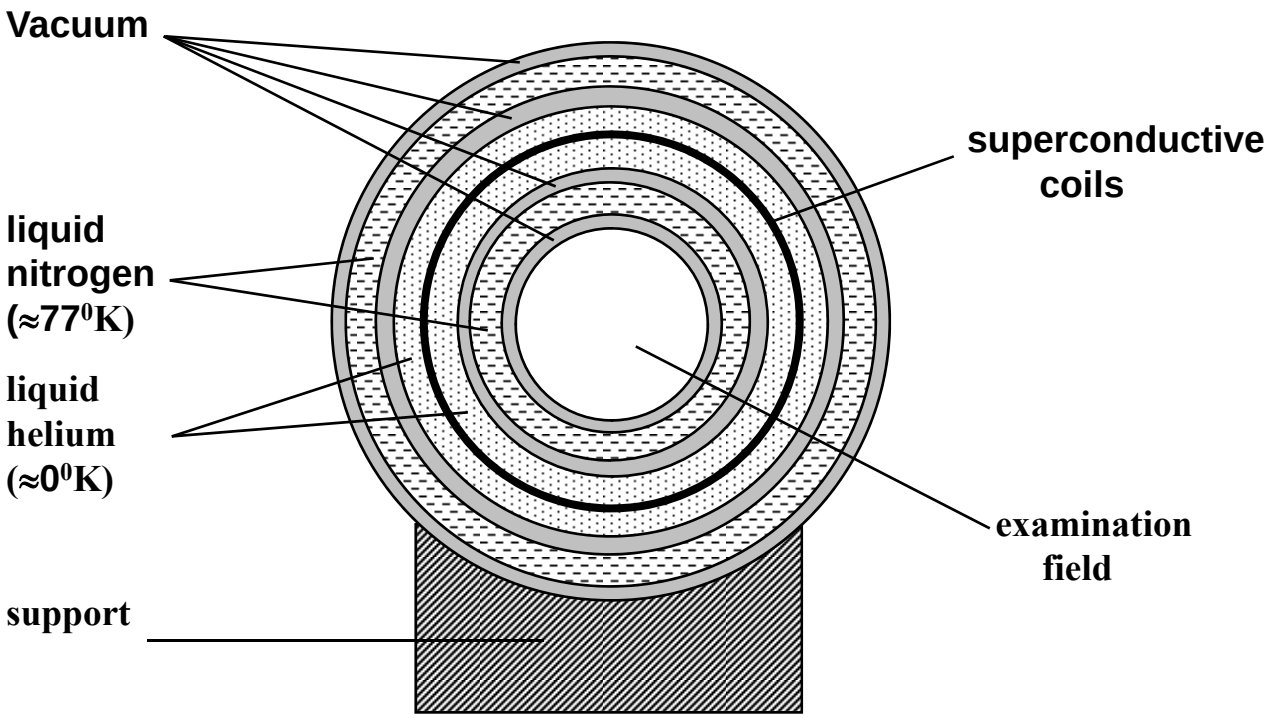
k_y
k_x

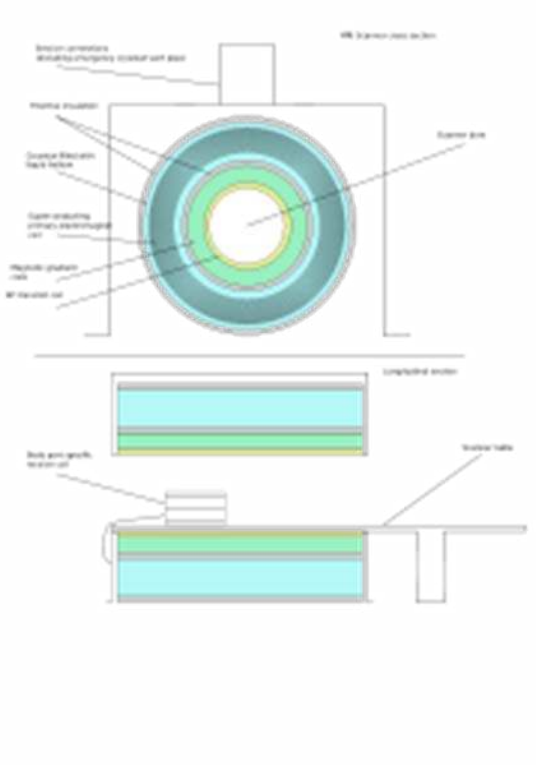

FFE-EPI
α
RF
G_z
G_y
G_x
Signal
k_y
k_x

MRI equipment schematics

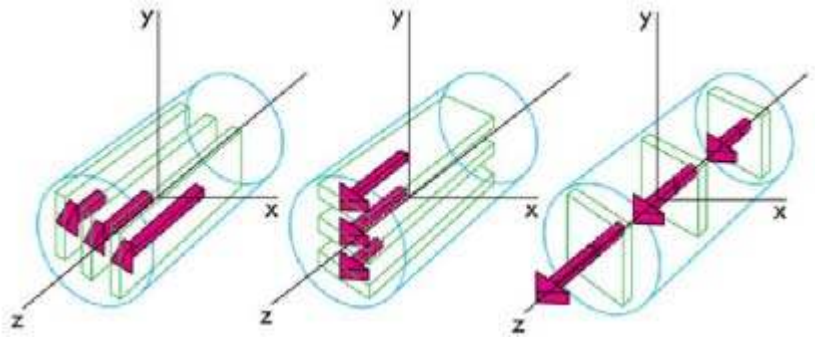


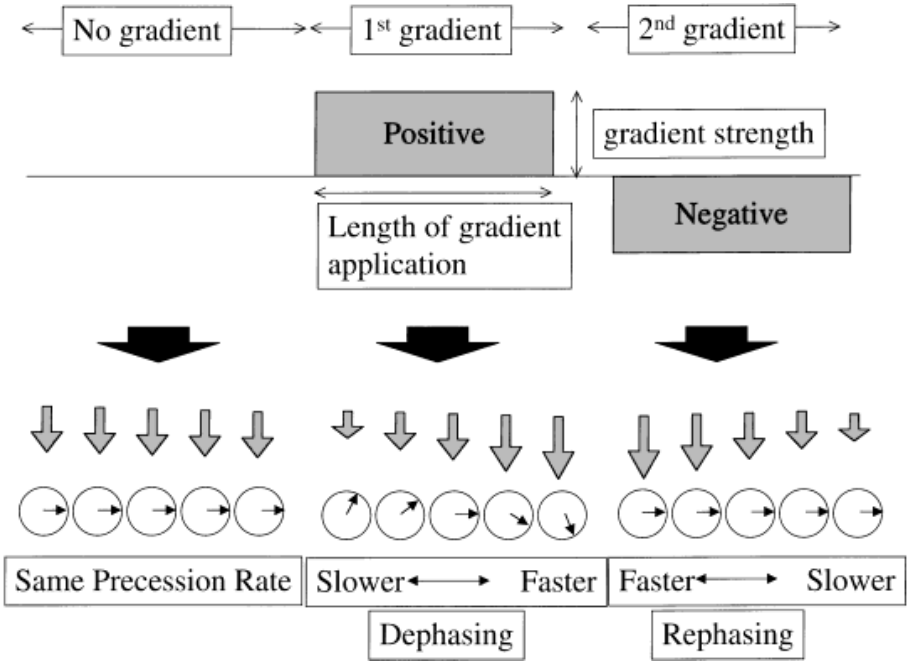
Typical structure of an MR superconductive magnet bore

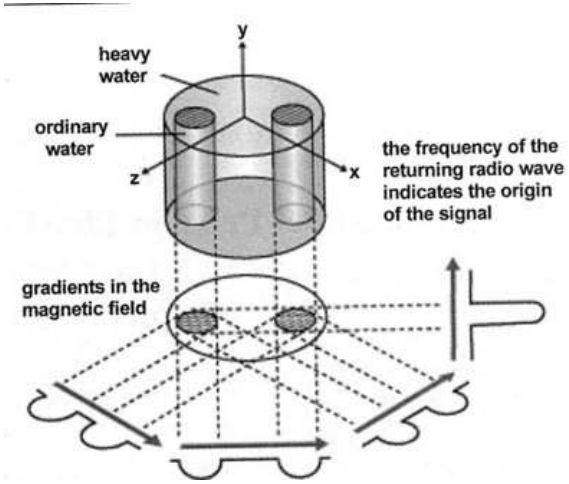




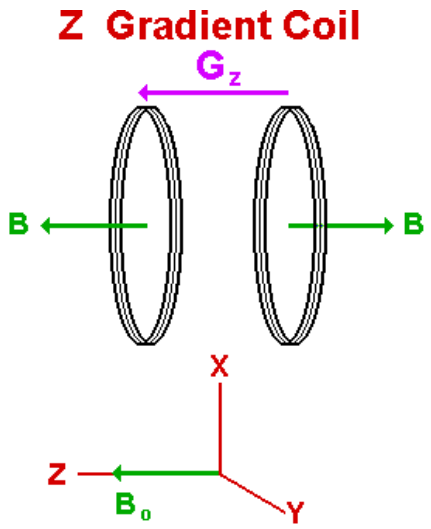
Gradient coils

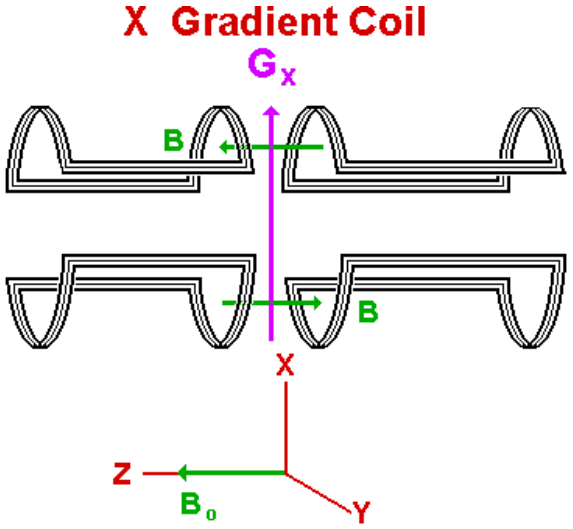


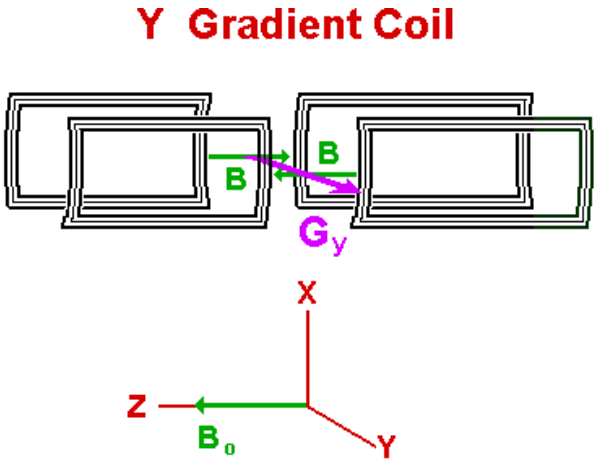


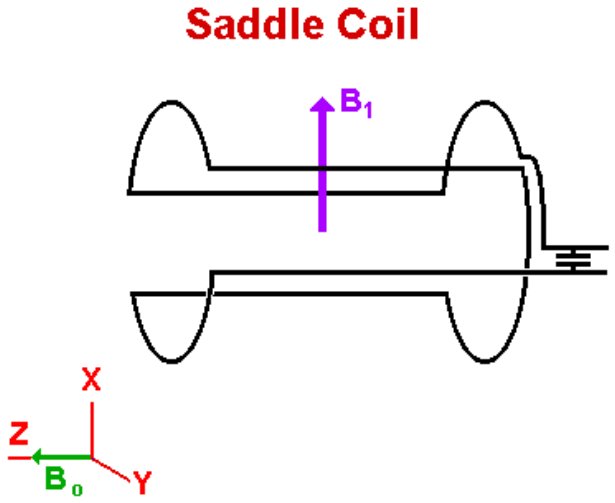


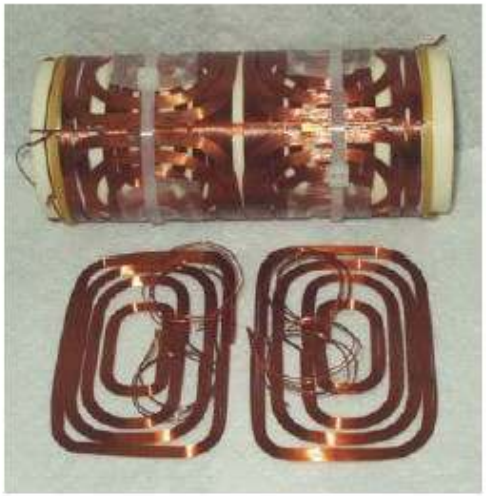
Biomedical Imaging: Magnetic Resonance Imaging - Basics











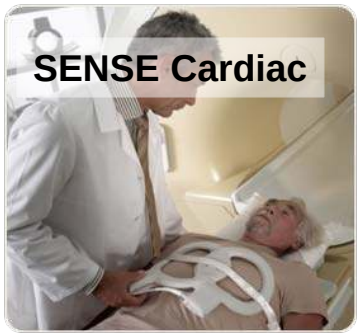
Gradient coil system

„naked” receiver coils
without cover

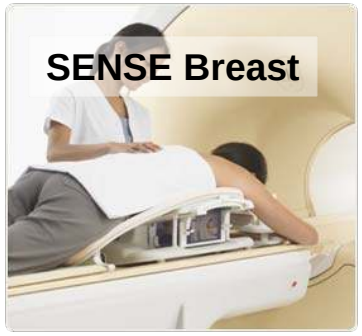

SENSE Head


SENSE NV


SENSE Spine

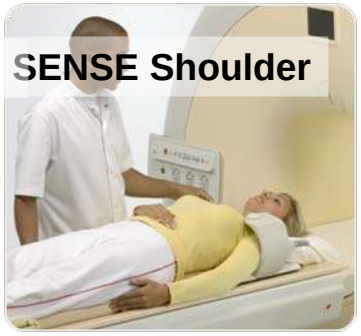

SENSE Cardiac

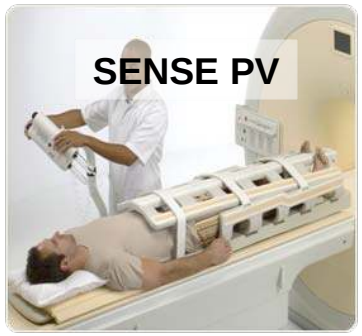

SENSE XL Torso


SENSE Breast


SENSE Knee


SENSE FootAnkle


SENSE Shoulder


SENSE PV


SENSE Wrist

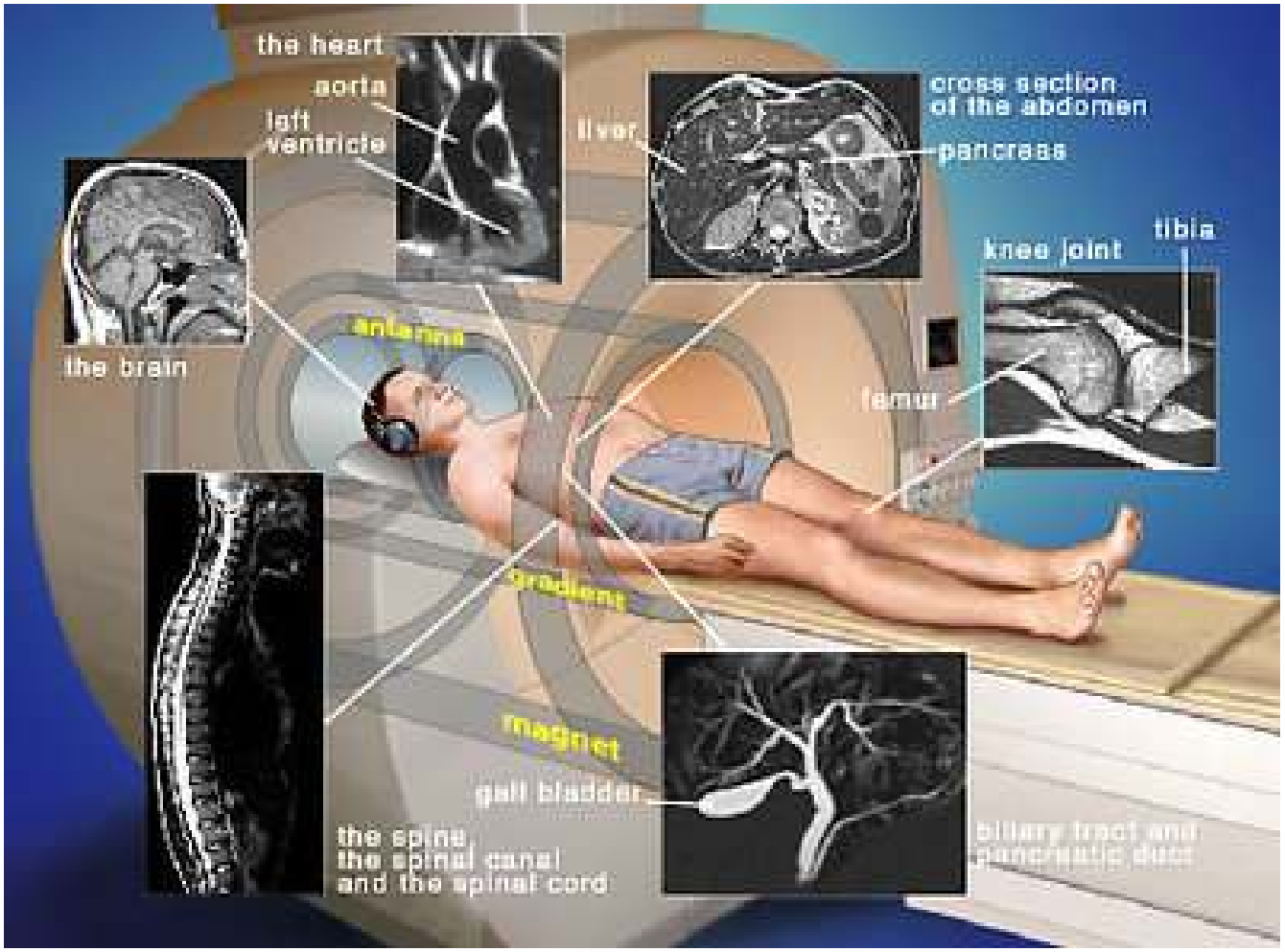

SENSE Flex L


SENSE Flex M


SENSE Flex S


Syn Pediatric

Biomedical Imaging: Magnetic Resonance Imaging - Basics



MR safety:

- Projectile Effects: External
- Projectile Effects: Internal
- Acoustic Noise
- Radiofrequency Energy
- Gradient field changes
- Claustrophobia

Scanner visit

- Anyone with implanted metal should see a doctor before going to the scanner
  - Pacemaker, cochlear implant, shunt, clip, etc.
  - Dental work and piercings are fine

Projectile Effects: Internal

- Motion of implanted medical devices
  - Clips, shunts, valves, etc.
- Motion or rotation of debris, shrapnel, filings
  - Primary risk: Metal fragments in eyes
- Swelling/irritation of skin due to motion of iron oxides in tattoo and makeup pigments

Acoustic noise:

- Potential problem with all scans
  - Short-term and long-term effects
- Sound level

- OSHA maximum exposure guidelines
  - 2-4 hours per day
- Earplugs reduce these values by 14-29 dB, depending upon fit

Radiofrequency Energy

Tissue Heating

- Specific Absorption Rate (SAR; W/kg)
  - Pulse sequences are limited to cause less than a one-degree rise in core body temperature
  - Scanners can be operated at up to 4 W/kg (with large safety margin) for normal subjects, 1.5 W/kg for compromised patients (infants, fetuses, cardiac)
- Weight of subject critical for SAR calculations

Burns

- Looped wires can act as RF antennas and focus energy in a small area
  - Most common problem: ECG leads
  - Necklaces, earrings, piercings, pulse oximeters, any other cabling

Gradient field changes:

Peripheral nerve stimulation

- May range from distracting to painful
- Risk greatly increased by conductive loops
  - Arms clasped
  - Legs crossed

Theoretical risk of cardiac stimulation

- No evidence for effects at gradient strengths used in MRI

Claustrofobia:

Most common subject problem

- About 10% of patients

Ameliorated with comfort measures

- Talking with subject
- Air flow through scanner
- Panic button
- Slow entry into scanner

FDA MRI Guidelines		
B_o	Adults, Children, and Infants age > 1 month	8 T
	neonates (infants age < 1 month)	4 T
dB/dt	No discomfort, pain, or nerve stimulation	
SAR Specific Absorption Rate	whole body, average, over $\geq$15 min	4 W/Kg
	head, average, over $\geq$10 min	3 W/Kg
	head or torso, per g of tissue, in $\geq$5 min	8 W/Kg
	extremities, per g of tissue, in $\geq$5 min	12 W/Kg
Acoustic Level	Peak unweighted	140 dB
	A-weighted rms with hearing protection	99 dBA

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

CLINICAL MRI METHODS

(MRI a diagnosztikában)

LAJOS R. KOZÁK

Basics of MR Spectroscopy (MRS)

MRS or nuclear magnetic resonance (NMR) spectroscopy is one of the earliest MR-based method.

$$\nu = \frac{\gamma}{2\pi} B$$

It operates on the magnetic resonance principle:

- Nuclei in the tissues of the body can become radio transmitters and receivers if they are in an external magnetic field.
- The resonance frequency depends on the strength of the magnetic field B and a constant called gyromagnetic ratio (γ)
- The γ is unique for each specific isotope. The values of γ are sufficiently different that isotopes can be separated easily with tuning the frequency of excitation.
- Variations of the magnetic field strength result in variations of resonance frequency ν

Basics of MR Spectroscopy (MRS)

The gyromagnetic ratio (γ) is the constant term of the equation; it depends only on the isotope to be measured:

- stable isotopes that contain an odd numer of protons and/or neutrons have an intrinsic magnetic moment and thus susceptible to RF excitation

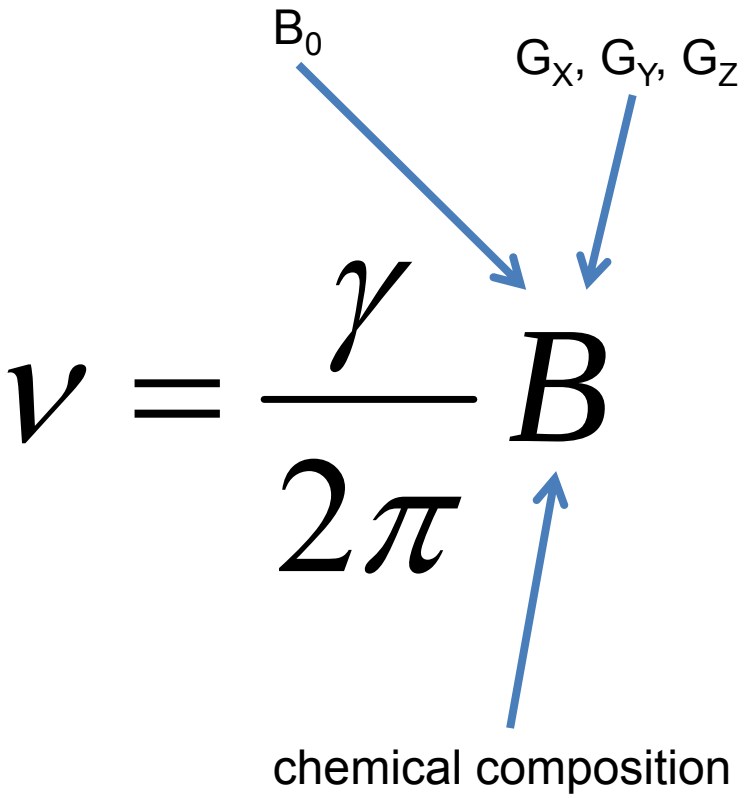
Nuclei	Unpaired p^+	Unpaired n^0	Net spin	γ [MHz/T]
^{1}H	1	0	1/2	42.58
^{13}C	0	1	1/2	10.71
^{19}F	0	1	1/2	40.08
^{23}Na	2	1	3/2	11.27
^{31}P	0	1	1/2	17.25

$$\nu = \frac{\gamma}{2\pi} B$$

Basics of MR Spectroscopy (MRS)

The magnetic field (B) is the technical term of the equation:

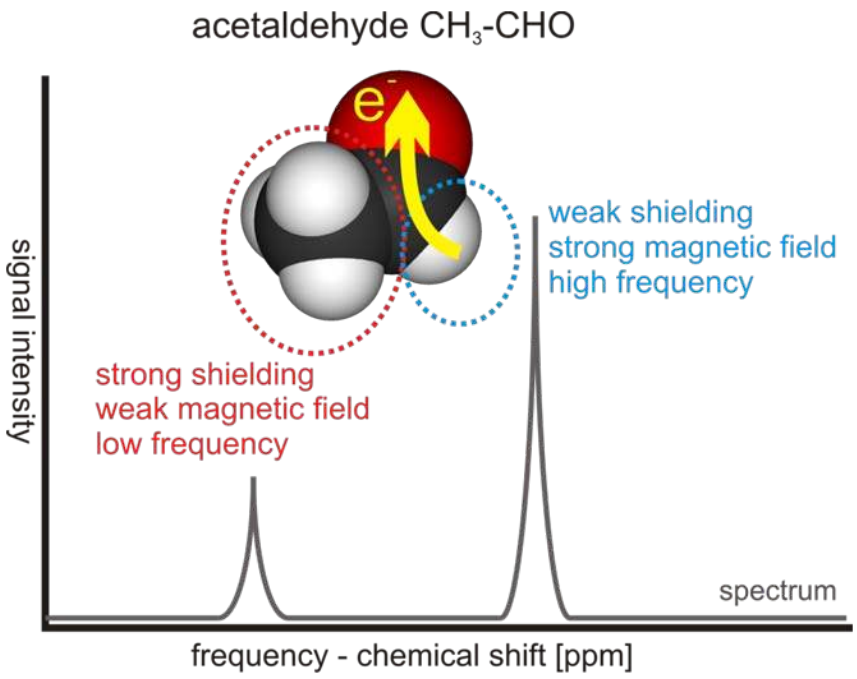
- the main field (B_0) is used to introduce the basic alignment
- gradients (G_X, G_Y, G_Z) are used for spatial encoding (MRI, localized MR spectroscopy)
- **B is affected by the chemical environment:**
  - the distribution of electrons in the chemical bonds introduce local field inhomogeneities, and thus **local differences in resonance frequency**



Basics of MR Spectroscopy (MRS)

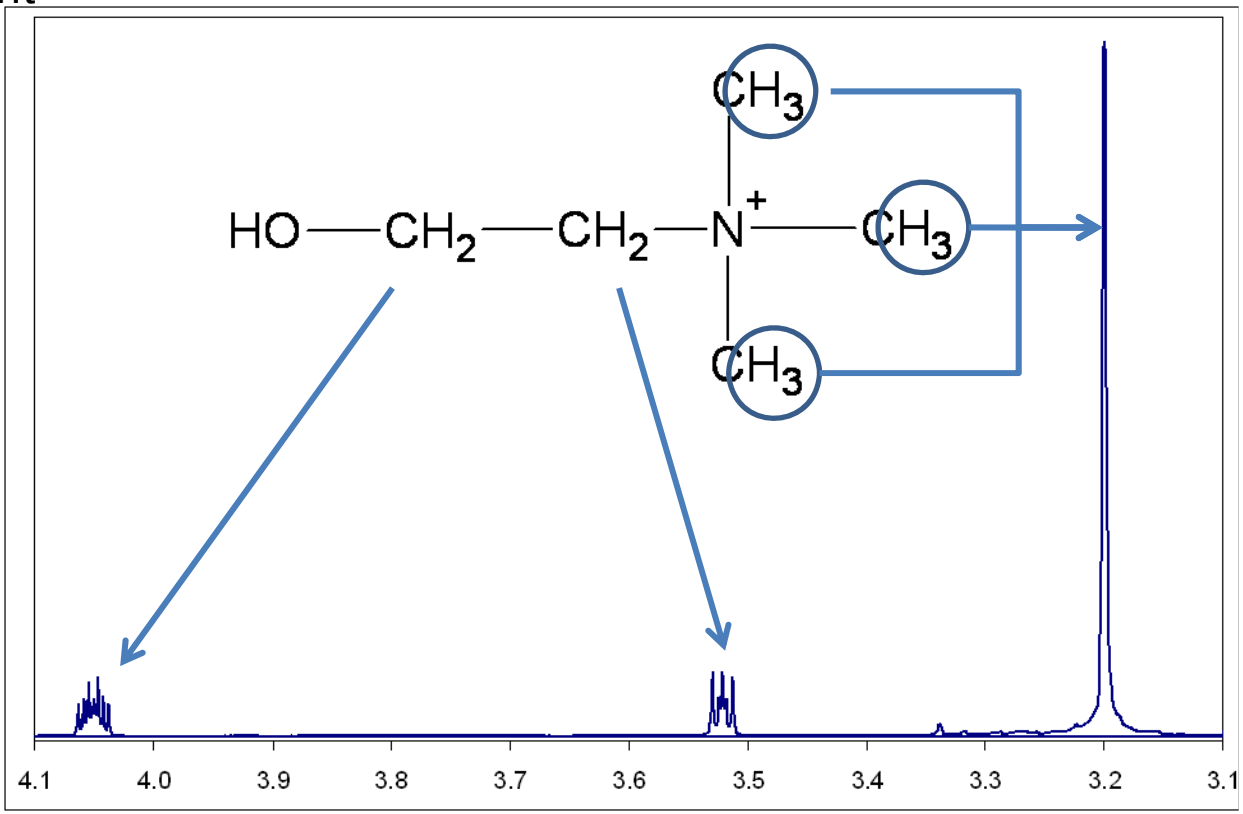
The distribution of electrons in the chemical bonds lead to various shielding effects

- Weak shielding is present when a nucleus draws the e^- from the proton:
  - Strong magnetic field
  - Higher resonance frequency
- Where the shielding remains stronger:
  - Weak magnetic field
  - Lower resonance frequency



^{1}H MR Spectrum of cholin

The peaks corresponding to protons are shifted according to the chemical environment



MRS acquisition

MRS sequences are spin echo sequences, TE strongly influences the resulting spectrum.

Single voxel techniques:

- PRESS (Point RESolved Spectroscopy)
  - Higher SNR
  - Less precisely defined voxels
- STEAM (Stimulated Echo Acquisition Mode)
  - About half the SNR of PRESS
  - More precise voxels
  - Less demanding technologically

Multi voxel technique:

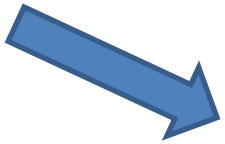
- CSI (Chemical Shift Imaging)

The spectrum depends on:

- Magnetic field
- TE : echo time
- TR : repetition time
- the region of the brain
- the patient's age, etc.

MRS quality criteria

- Volume
  - as big as possible, at least: 1 cm^3
- Max 20% partial volume
- No contact with
  - CSF
  - bone marrow fat
  - air in sinuses
- No patient movement
- Magnetic field inhomogeneities < 10 Hz FWHM
- MRS measurement before contrast material (CM) administration
  - about 10% choline decrease after CM administration



The concentration of H_2O is about 10000 times higher than that of metabolites, this is reflected in the MRS signal.

To have equal SNR for the metabolites 10000 times bigger voxels are needed.

Moreover, water signal has to be suppressed.

Normal compounds

with ^{1}H MRS

Large signals at long TE

- N-acetyl aspartate (NAA)
- Creatine (Cr) and phosphocreatine (PCr)
- Cholines (Cho)
- Glycerophosphocholine (GPC)
- Phosphocholine (PC), free choline (Cho)

Large signals at short TE

- Glutamate (Glu)
- Glutamine (Gln)
- Myo-inositol (mI)

Small signals (short or long TE)

- N-Acetyl aspartylglutamate (NAAG), aspartate
- Taurine, betaine, scyllo-inositol, ethanolamine
- Threonine
- Glucose, glycogen, purine nucleotides
- Histidine

Pathological compounds

with ^{1}H MRS

Long TE

- Lactate (Lac)
- Hydroxy-butyrate, acetone
- Succinate, pyruvate
- Alanine
- Glycine

Short TE

- Galactitol, Lipids
- Macromolecules
- Phenylalanine

Exogenous compounds (short or long TE)

- Propan-1,2-diol
- Mannitol
- Ethanol
- Methyl sulfonylmethane (MSM)

Clinical significance of specific compounds

N-acetyl aspartate (NAA)
~ 2.00 pmm

- neuron specific amino acid derivative
- reflects the health of neurons (**neuronal marker**)
- decreased in neurodegenerative processes
- decreased in large necrotic tumors
- elevated in Canavan disease

Creatine/ Phosphocreatine (Cr, PCr)
~ 3.00 ppm

- a reservoir for high energy phosphate for generation of adenosine triphosphate [ATP] ➔ **energy metabolite**
- the most stable metabolite in the brain usually used as a reference peak to generate NAA/Cr and Cho/Cr ratios for quantification

Choline (Cho)
~ 3.25 ppm

- membrane phospholipid metabolite
- associated with glial cell membrane integrity (**cell membrane marker**)
- elevated in malignant tumors
- elevated in ischemia
- elevated in inflammations
  - can be used to monitor multiple sclerosis

Clinical significance of specific compounds

Lactate (Lac)
~ 1.33 ppm

- indicates **hypoxia** and/ or **glycolysis**
- elevated in infarcts
- elevated in abscesses
- elevated in mitochondrial disorders
- elevated in malignant tumors
- elevated in multiple sclerosis plaques

Lipids
~ 0.9-1.4 ppm

- indicate **tissue necrosis**
- elevated in e.g. metabolic disturbances

Glutamate/ Glutamine (Glu/ Gln)
~ 2.1-2.5 ppm

- **excitatory neurotransmitter**
- elevated in stroke
- elevated in lymphoma
- elevated in hypoxia

Myo-inositol (mI)
~ 3.56 ppm

- cell membrane marker (**shows cell destruction**) / intracellular transmitter
- elevated in Alzheimer's
- elevated in diabetes
- elevated in recovered hypoxia

Specific metabolites

- metabolic diseases
- can be very specific, e.g. in nonketotic hyperglycinemia

Clinical indications of MRS

Oncology

- Neuro-oncology
- Haemato-oncology

Inflammations

- Meningo-encephalitis
- ADEM
- MS
- Abscess
- Differential diagnosis: stroke

Metabolic diseases

Neonatology

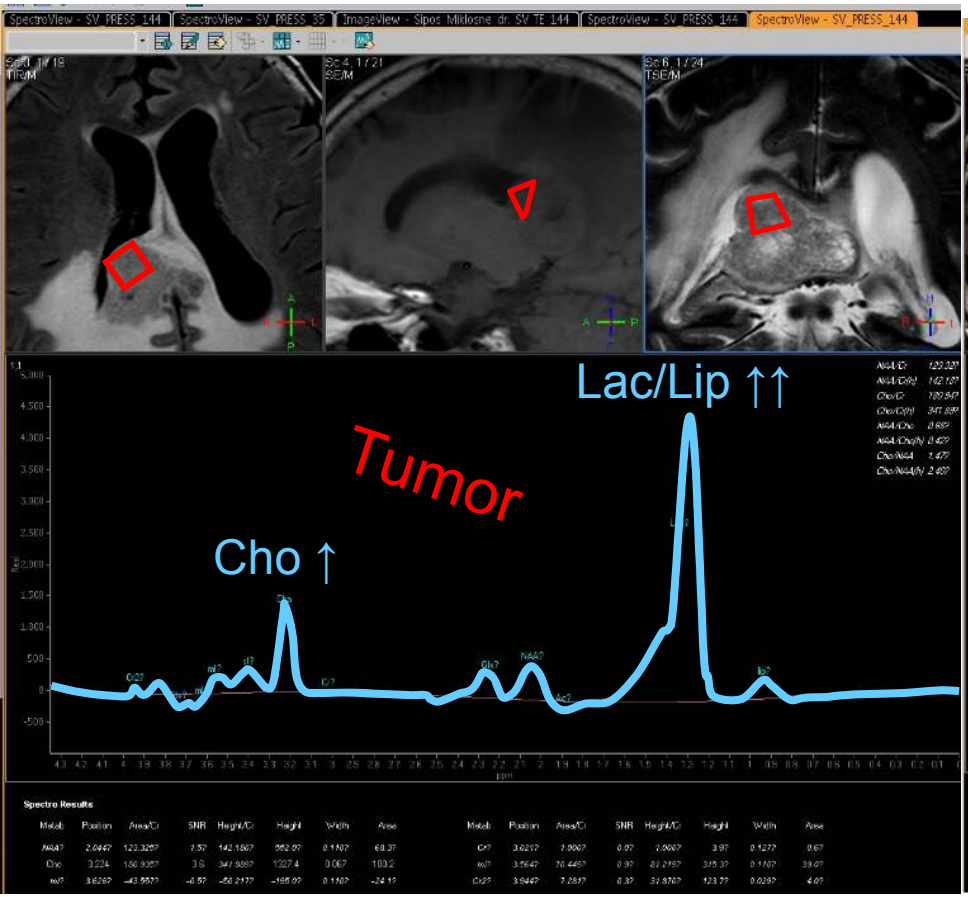
Oncology is the main indication for MRS

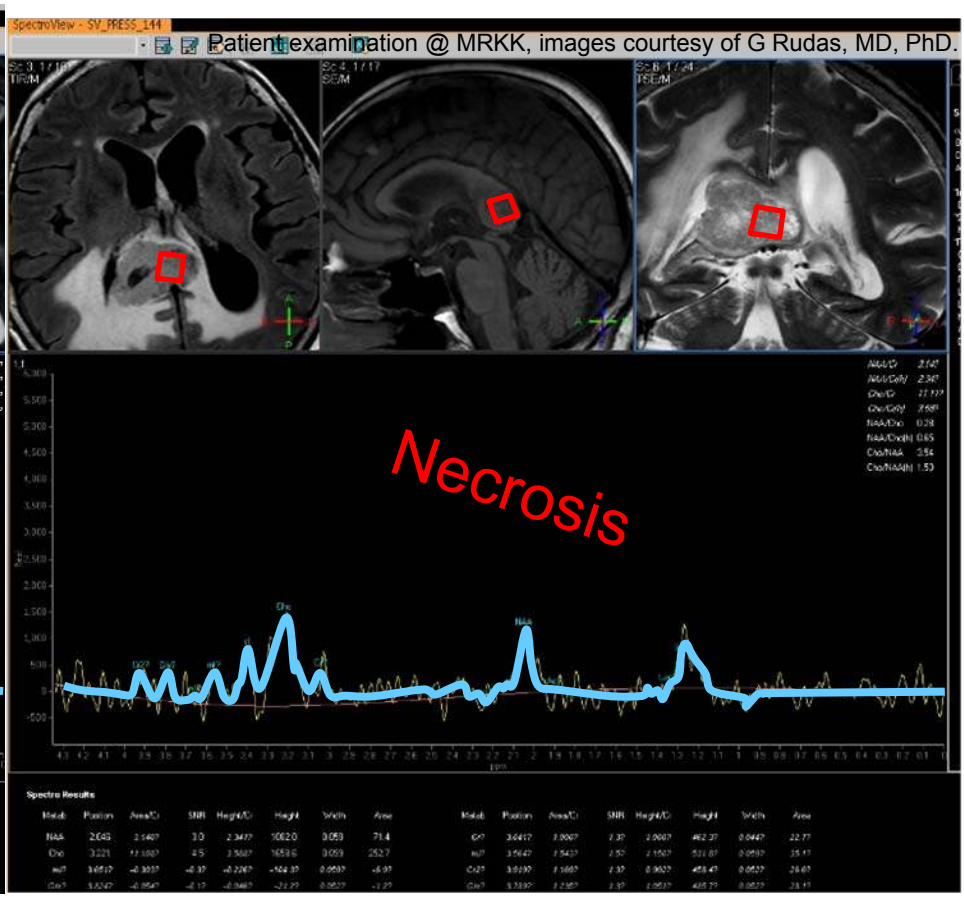
- differential diagnosis: tumor vs. inflammation
- tumor dignity assessment
- tumor inhomogeneity assessment
- assessing residual / recidive tumors
  - choline at least 40-60% higher than in the norm. side
- Post radiation masses
  - all of the typical metabolites strongly decreased, but still present
- Postoperative gliosis
  - all of the typical metabolites are absent

MRS is a non invasive in vivo „biopsy”

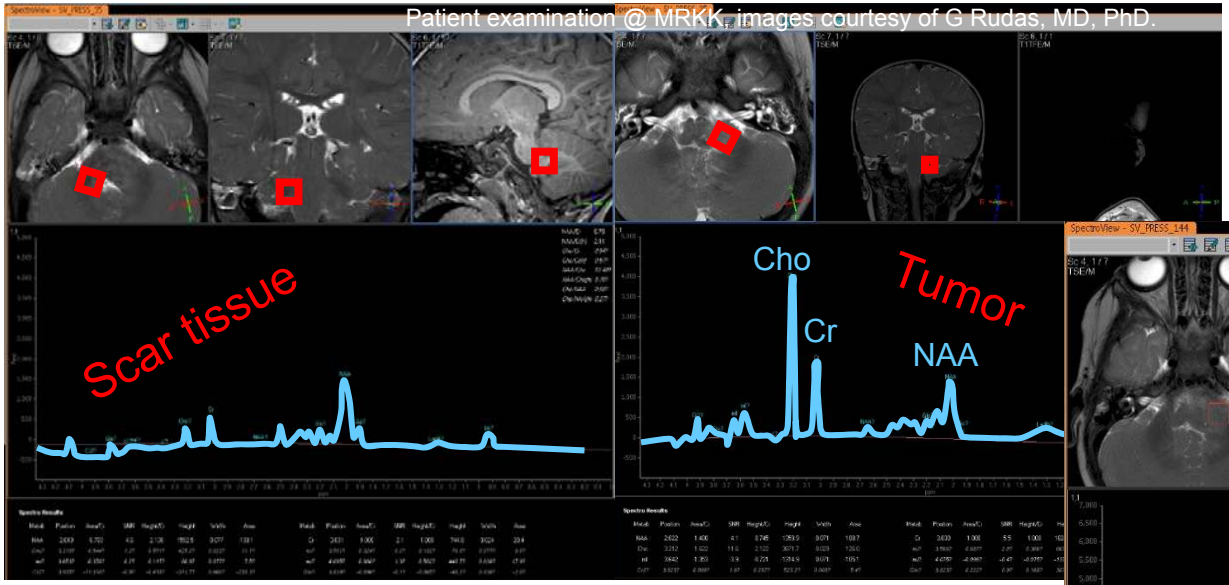
Differentiating viable and necrotic parts of tumor metastasis

Metastasis of pulmonary origin

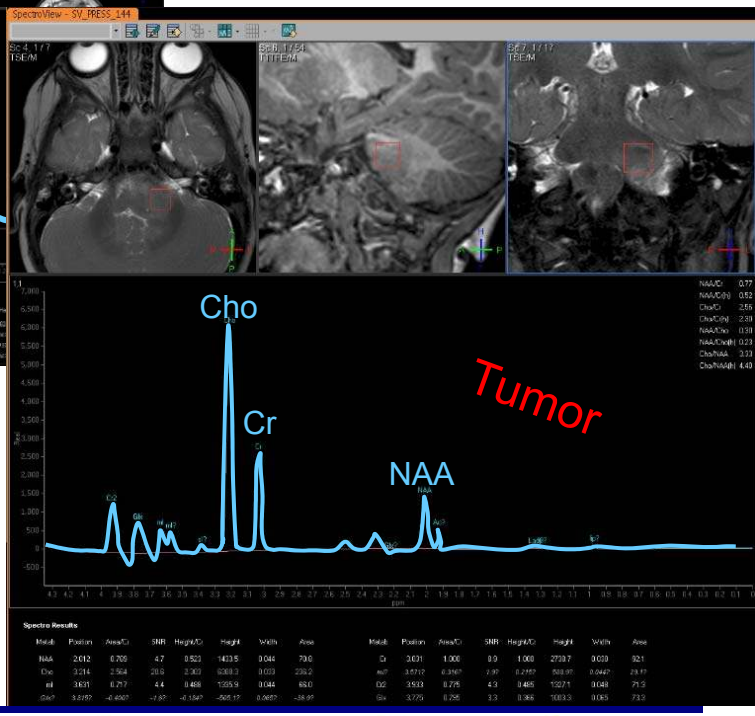




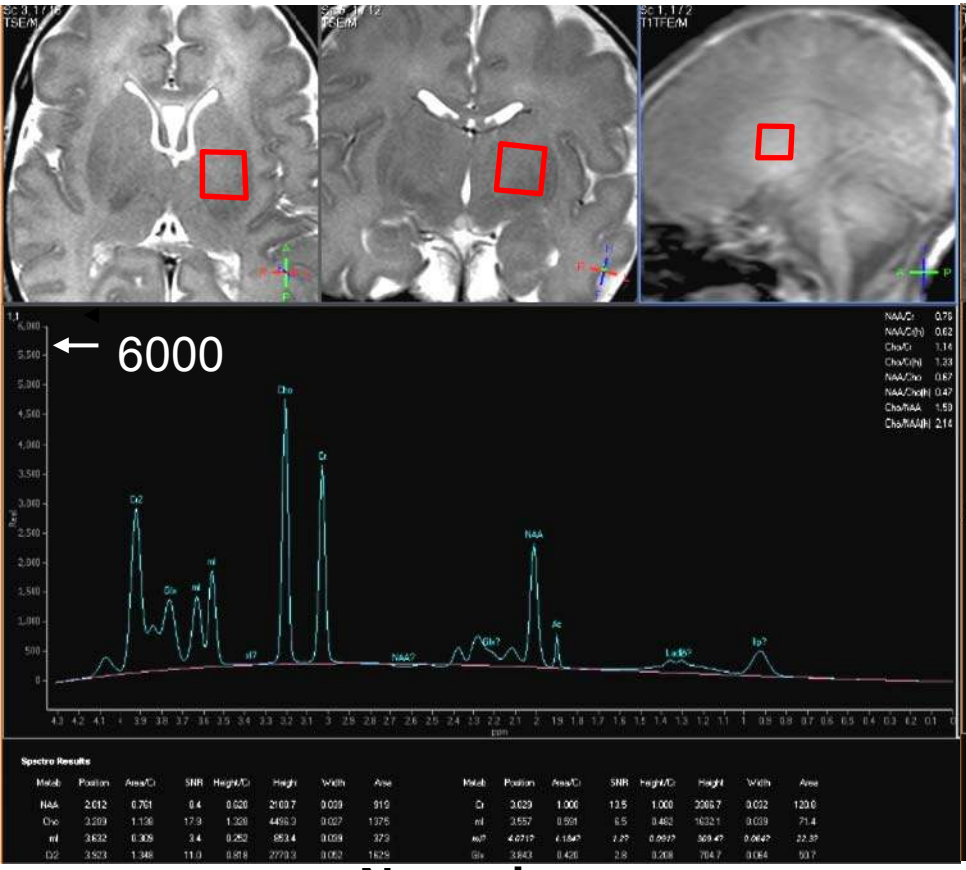
Glioma in the brainstem

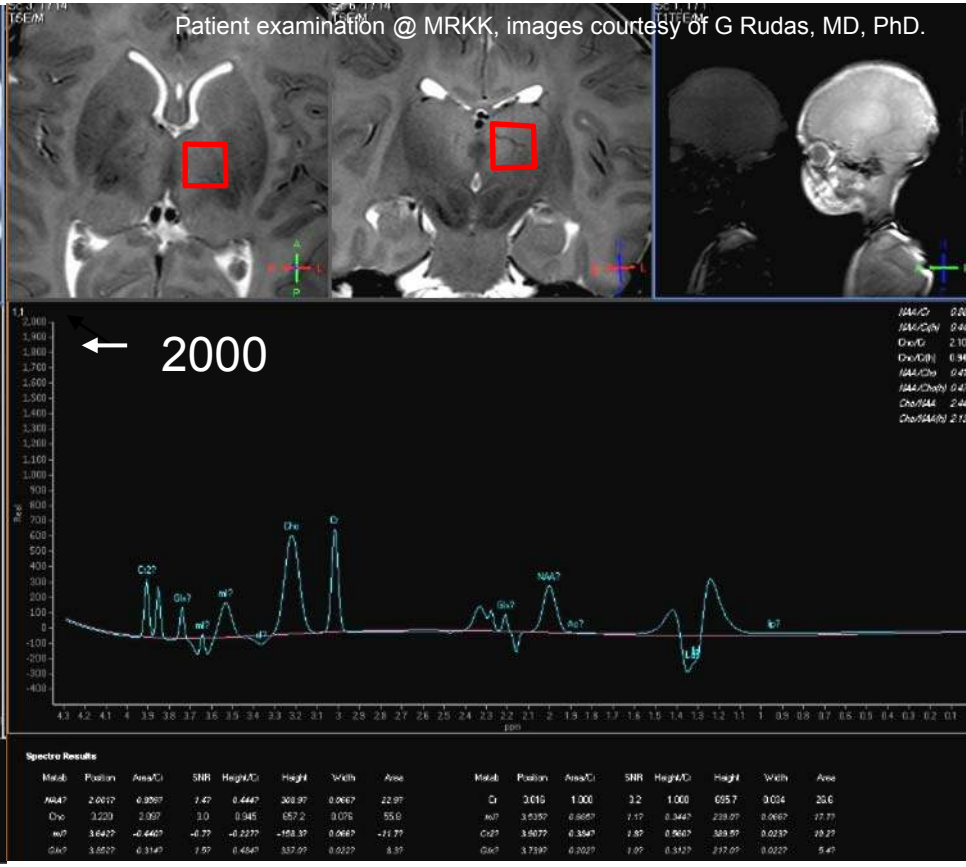


3 mo follow-up



Neonatology example: diagnosis of hypoxic ischemic encephalopa





Normal **HIE**

SENSE Spectro CSI provides spectra in multiple voxels. The lacta is indicative of metastasis in this case.

Future of MRS / research applications

Quantitative MRS *e.g. Marliani et al., AJNR, 2010*

MR spectroscopy is done after calibration with either

- internal endogenous marker
- external reference
- LC-model software

Multinuclear MRS e.g. Lyoo et al., Psychiatry Res, 2003

Specific hardware for simultaneous ^{1}H, ^{13}C, ^{19}F, ^{31}P, MRS spectroscopy measurements

- ^{31}P: measuring ATP, i.e. energy accessibility and consumption
- ^{19}F: not present in the human body, but numerous drugs contain F
  - information on drug distribution / kinetics
  - monitoring cytostatic therapy

MRS thermometry *e.g. Zhu et al., MRM, 2008*

Linear relationship between the ^{1}H MR resonance frequency of tissue water and the tissue's temperature.

MRI contrast agents

MRI contrast agents alter T1, T2, or T2* of various tissues, resulting in changes of image contrast.

Contrast agents are useful for the detection of tumors, infection, inflammation, infarction and lesions.

MRI contrast materials are called contrast "agents" since it is the effect that the magnetic properties of the contrast agent has on the relaxation of tissues that is imaged, and not the contrast material itself.

X-ray contrast media

Barium and iodine compounds are used to enhance contrast in x-ray procedures.

These compounds are referred to as contrast "media" since their presence appears directly on the images.

MRI contrast agents

Endogenous

- e.g. hemoglobin
  - BOLD contrast, see fMRI chapter
    - dexyhemoglobin is diamagnetic
    - deoxyhemoglobin is paramagnetic

Exogenous

- **Paramagnetic agents**
  have positive magnetic susceptibility due to the presence of one or more unpaired electrons
  - Gd^{3+}
  - Dy^{3+}
  - Fe^{2+}
  - Mn^{3+}

Exogenous cont'd

- **Ferromagnetic agents**
  are solids with crystalline structures that develop small magnetic domains. When placed in an external magnetic field (B0), the multitude of magnetic domains will align with the field and retain magnetism when removed from B0
  - Fe
  - Ni
  - Co

- **Superparamagnetic agents**
  are smaller solid particles each of which develop a "single domain". The domains align with B0; but do not retain the alignment after being removed from B0
  - Magnetite (Fe_3O_4)

MRI contrast agents

Positive contrast agents

(relaxation agents)

- cause hyperintensity on T1 weighted images
- the presence of a positive agent stimulates an increase in spin flip transitions resulting in reduced T1 values and increased brightness on T1 weighted images
- cause hypointensity on T2 weighted images because of susceptibility effects

The most common positive contrast agent is the paramagnetic gadolinium (Gd).

Negative contrast agents

(shift agents, chemical shift agents or frequency agents)

- cause hypointensity on T2 weighted images
- produce substantial magnetic inhomogeneity due to magnetic susceptibility
- magnetic inhomogeneity perturbs the Larmor frequency of protons, resulting in a loss of phase coherence and reduced T2 values

Dysprosium (Dy) is also paramagnetic but acts to reduce T2 or T2* without affecting T1.

MRI contrast agents

Safety considerations

Most of the agents appropriate for contrast enhanced MRI are toxic metals, therefore they are usually used in a chelated form.

Gadolinium

- in its pure form can bind to membranes, transport proteins, enzymes, etc. in the lungs, liver, bones and spleen.
- small amount of pure metallic Gd can cause liver necrosis
- chelation shields the toxic metal ion from direct interaction with the tissues
- chelation may also change susceptibility effects

Chelates are cleared from the body via glomerular filtration.

If the glomerular filtration rate is decreased, e.g. due to kidney disease, toxic metals can slowly be released from the chelates and cause toxicity.

Nephrogenic systemic fibrosis is a possible complication which is highly correlated with the use of Gd contrast agents in patients with kidney disease.

MRI contrast agents

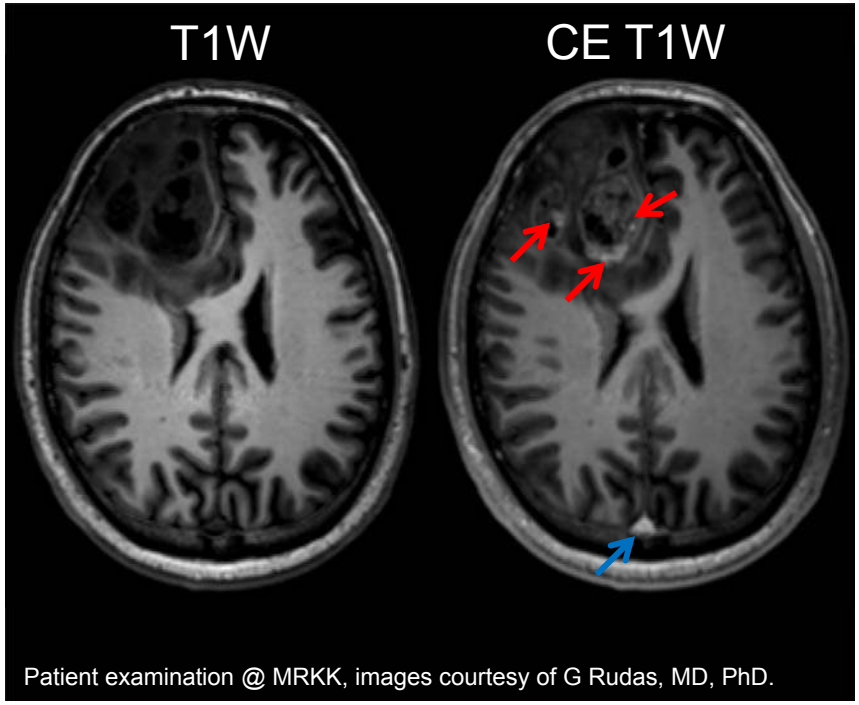
Clinical applications

Mostly Gd-chelates are used, chelation differs between pharmaceuticals.

Some brands are: Magnevist (Bayer-Schering), Ultravist (Bayer-Schering), Optimark (Covidien), ProHance (Bracco), etc.

Contrast enhanced MRI

- Central nervous system tumors (diagnosis, differential diagnosis)
  - Gd-chelates do not pass the blood-brain barrier ➔ if the barrier is distrupted the contrast agent accumulates in the tissue
- Angiography
- MR perfusion (see later)
- etc.



Contrast enhancement in case of a malignant brain tumor (glioblastoma multiforme). Red arrows represent CA enhancement in the lesion, while the blue arrow represent a physiological enhancement in the venous sinus.

MR Perfusion

(Perfusion Weighted Imaging, PWI)

Perfusion

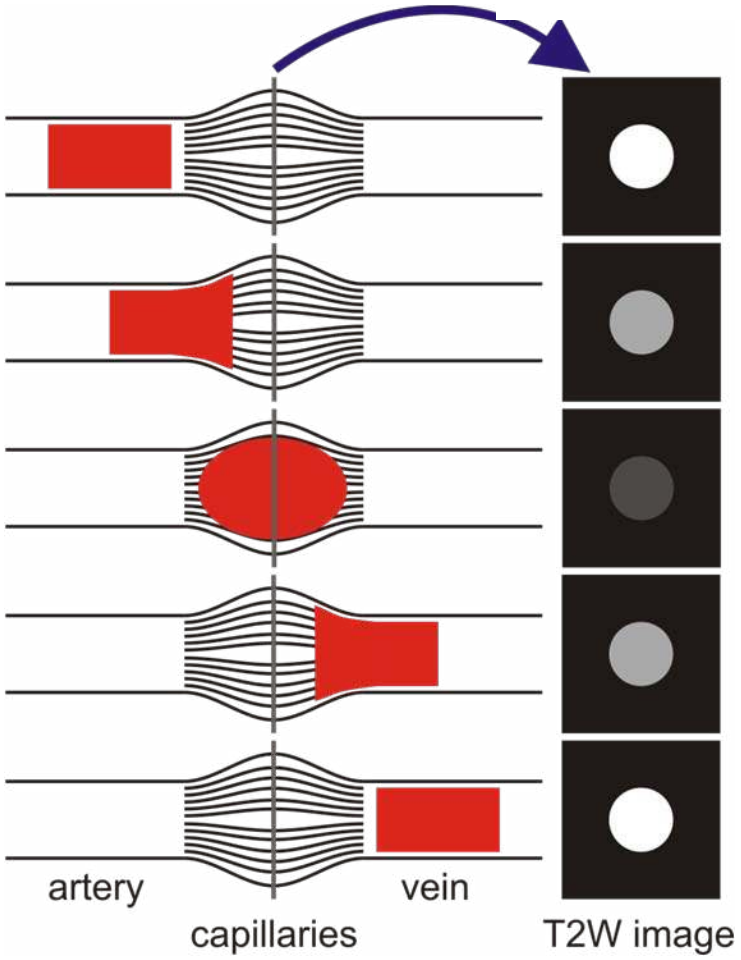
- the delivery of oxygen and nutrients to the cells via capillaries
- Identified with blood flow
- measured in milliliters per minute per 100 g of tissue

Measuring perfusion

- Dynamic susceptibility contrast (DSC) imaging in the brain
  - GD-chelate contrast agent
- Arterial spin labeling
  - See ASL chapter

DSC imaging in the brain

- injection of a bolus of Gd-chelate contrast agent
  - Gd-chelates do not cross the healthy blood-brain barrier
- the paramagnetic Gd causes signal drop at in the vicinity of the bolus on T2W images
- the labeled bolus spreads trough the circulation
- the intensity change during the first pass represents perfusion

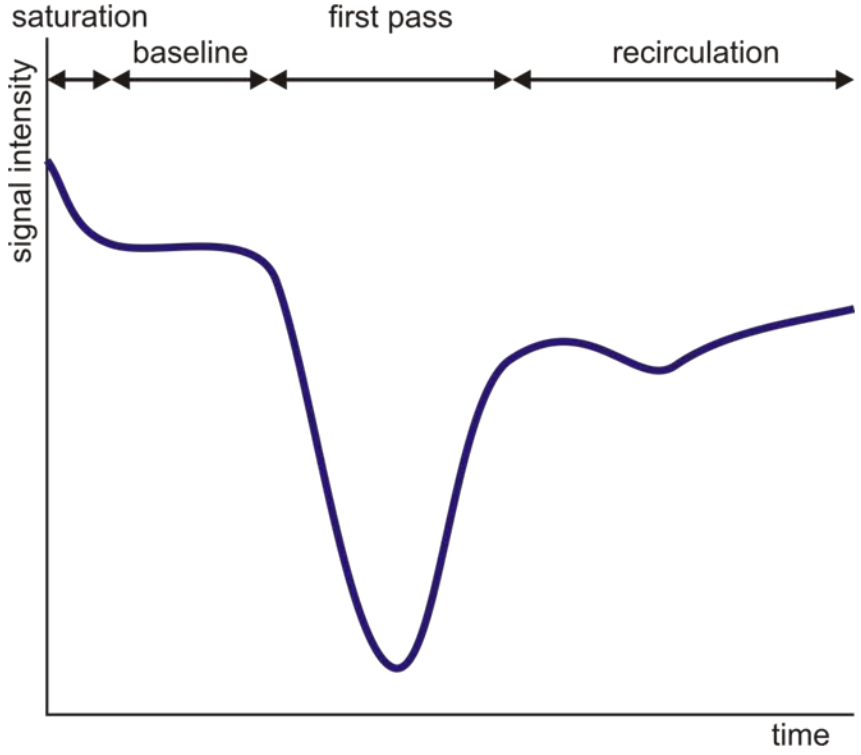


Based on a figure from P Barsi, MD, PhD

DSC imaging

Sequences

- Gradient-Echo EPI (GRE-EPI)
  - High signal drop
  - Sensitive to capillaries & larger vessels
- Spin-Echo EPI (SE-EPI)
  - Signal drop only 25% of GRE-EPI
  - Sensitive mainly to capillaries



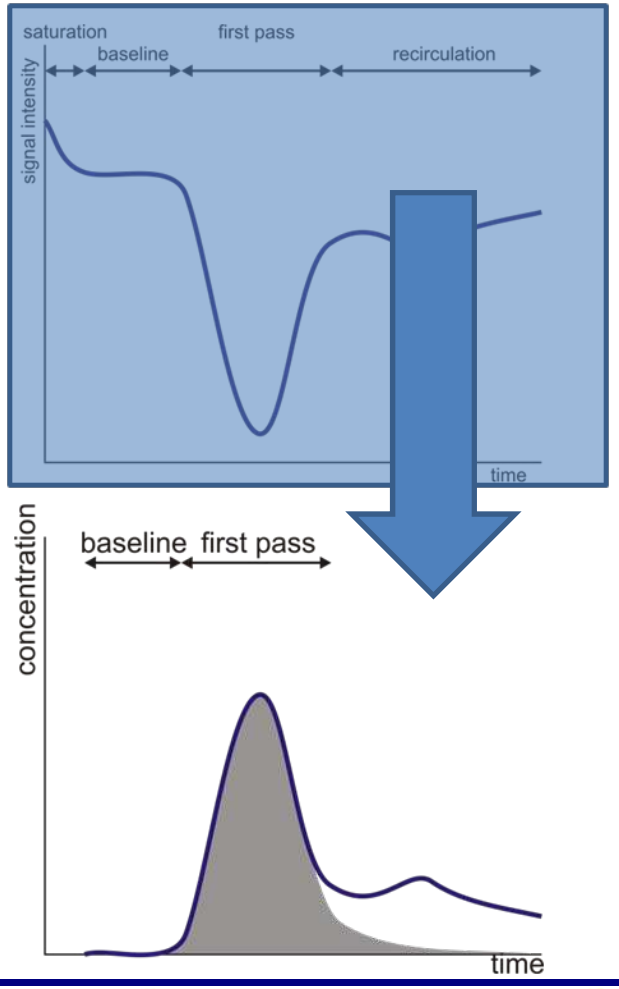
For a detailed account on technical aspects, see Wu et al., Neuroimag Clin N Am, 2005

Perfusion calulation

- Baseline determination
  - starting point
  - endpoint
- Concentration-time curve calculation

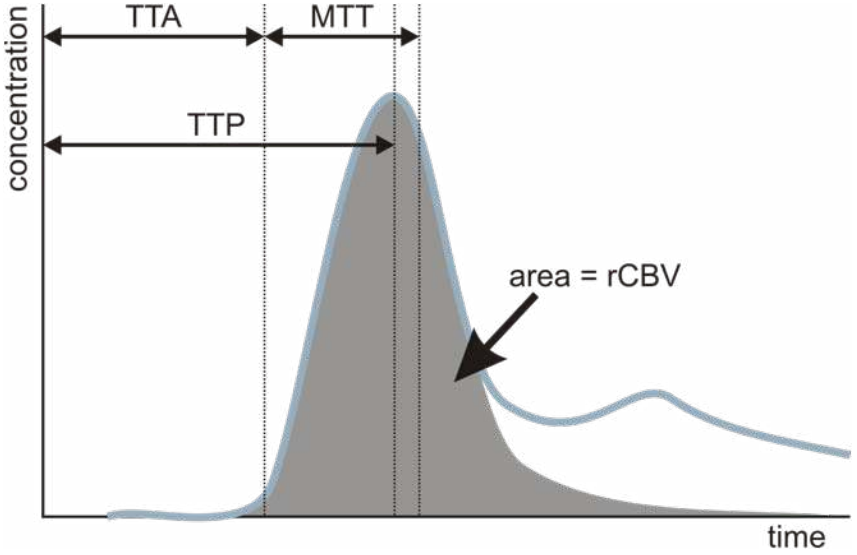
$$c(t) = -\frac{k}{TE} \ln \frac{S(t)}{S_0}$$

- Curve fitting



Perfusion parameters

- Time to arrival (**TTA**, [s])
  - time when the contrast agent reaches the tissue
- Time to peak (**TTP**, [s])
  - time of peak concentration
- Mean transit time (**MTT**, [s])
  - the average time required for any given particle to pass through the tissue, following an idealised input function
- Relative cerebral blood volume (**rCBV**, [ml/100g, %/100g])
  - the volume of distribution of the Gd-chelate during its first passage through the brain



Clinical applications of MR Perfusion

Cerebrocascular diseases

- acute stroke
- stenosis (decrease in vessel diameter)

Tumors

- differential diagnosis
- grading

Other indications

- Trauma
- Dementia
- Epilepsy, etc

PWI in stroke

- Changes seen almost immediately after the ischemic event
  - more sensitive than conventional MRI
- Perfusion findings often more extensive than those on DWI in **early stroke**
  - PWI more accurately reflects the amount of tissue under ischemic conditions in the hyperacute period than DWI
  - abnormal PWI results correlate with an increased risk of stroke
- PWI - DWI = **tissue at risk**

PWI and tumors

- many tumors have high rCBV
- regions of increased rCBV correlate with areas of active tumor
- heterogeneous patterns of perfusion suggest high grade
- radiation necrosis typically demonstrates low rCBV

- Lesion characterization may be possible
  - meningeomas have very high CBV in contrast to Schwannomas

PWI in other diseases

Dementias

- Perfusion parameters correlate well with PET and SPECT findings in Alzheimer's disease

Traumatic brain injury

- focal rCBV deficits correlate with cognitive impairment

Schizophrenia

- decreased frontal lobe rCBV

PWI future applications

Perfusion weighted MRI using the dynamic susceptibility imaging principle poses a risk due to the contrast agents used.

Arterial spin labeling (see the ASL chapter) can eliminate this risk and opens the possibility to serial perfusion measurements for the

- follow-up of therapy, e.g. in stroke, traumatic brain injury, etc.
- follow-up of disease-related perfusion changes, e.g. in dementias

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

Functional Magnetic Resonance Imaging (fMRI) - the BOLD method

(Funkcionális Mágneses Rezonancia- a BOLD módszer)

ISTVÁN KÓBOR, VIKTOR GÁL

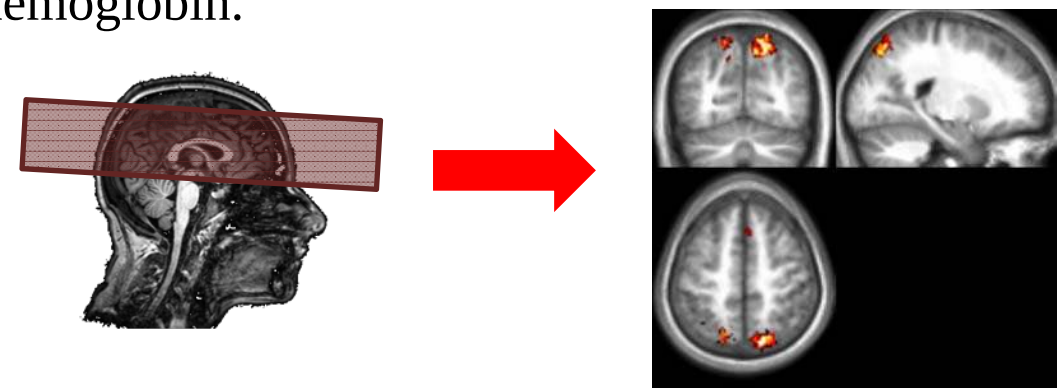
Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (**fMRI**) refers to different types of specialized MRI scans with a common goal:

➢to measure the dynamics of **local neural activity** in the brain or spinal cord of humans or other animals.

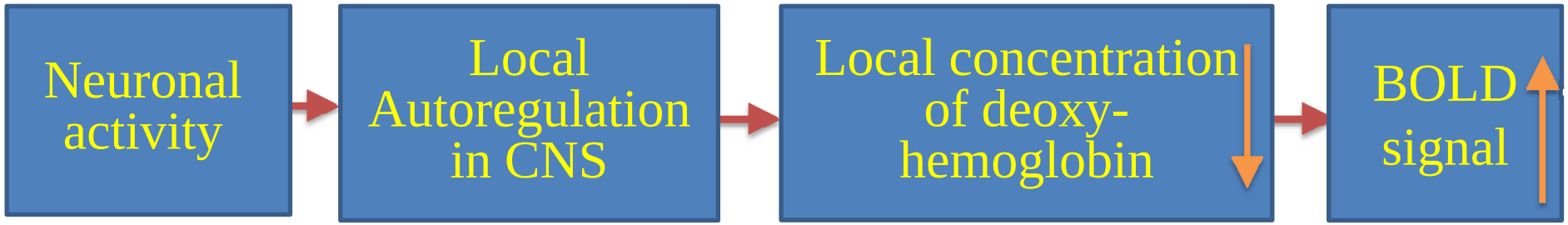
➢**methods:** endogenous or exogenous contrast agents can be used to directly or indirectly detect neural action.

- Blood-oxygen-level dependent imaging (**BOLD**) is the most frequently used technique, where the contrast agent is the blood deoxyhemoglobin.



Sources of the BOLD signal

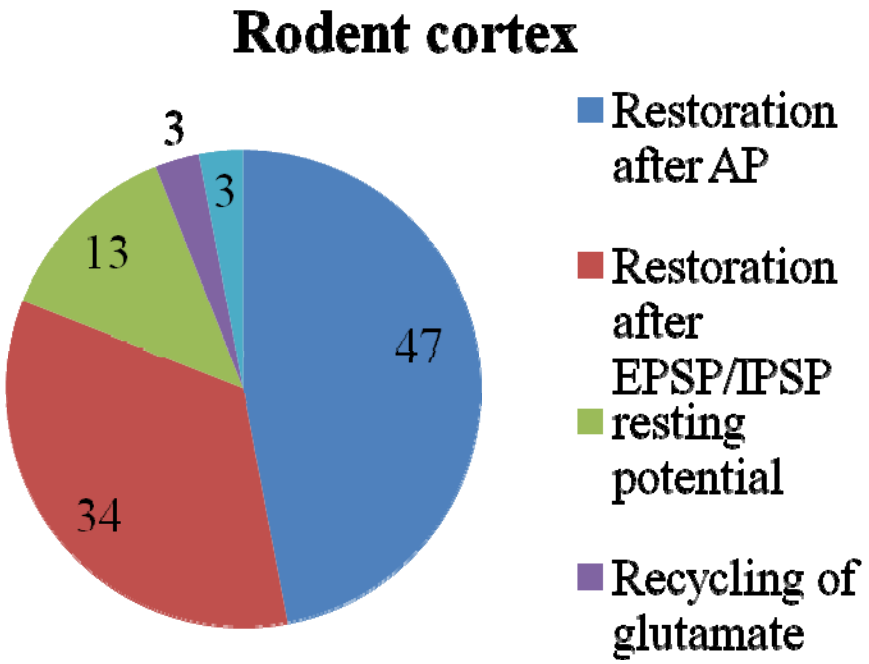
- Auto(vaso)regulation in CNS controls the local oxygen supply according to the local activity.
- Changes in the hemoglobin (oxygen carrier molecule) concentration can be detected by MRI.

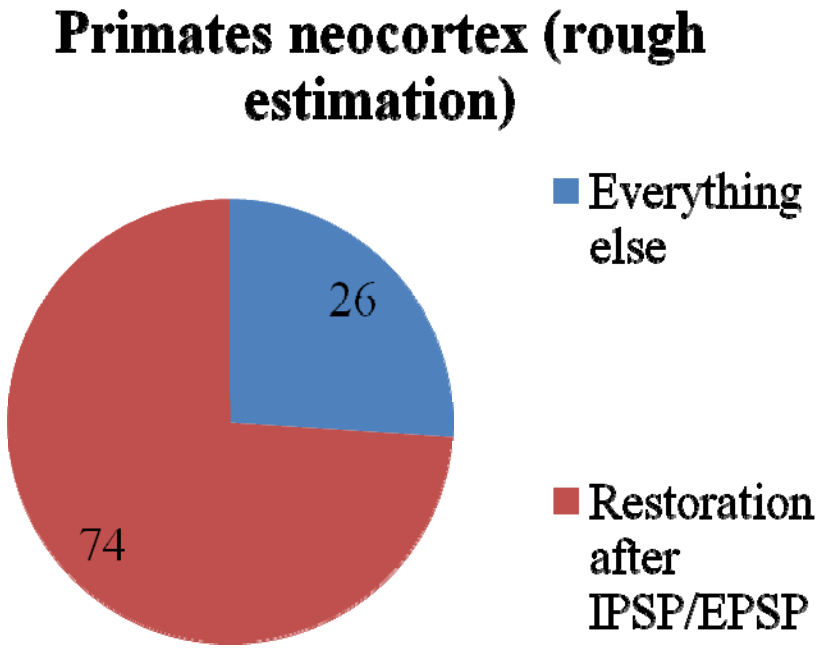


Metabolic requirements of neural activity

- Neural mechanisms require external sources of energy (glucose) and oxygen to support metabolic processes (e.g. restoration of the concentration gradients following changes in membrane potential).
- Direct source of energy at the cell level are the ATP molecules (adenosin-triphosphate). ATP is produced via oxidation of glucose (glycolysis) in the cell
  - When oxygen supply is appropriate: aerobic glycolysis (90%)
  - When oxygen supply is inadequate: anaerobic glycolysis (very fast, 10%)
- Iron-containing Hemoglobin (Hb) in the blood is what transports oxygen from the lungs to the rest of the body (i.e. the tissues), where it releases the oxygen for cell use. 2 forms depending on O_2 binding:
  - oxyhemoglobin (oxyHb) is saturated with O_2
  - deoxyhemoglobin (deoxyHb) binds no O_2
- For imaging purposes, the main vasculature concerned are the capillaries networks – where glucose and oxygen exchanges happen

Metabolic rates of the different components of neuronal activity





Attwell and Laughlin *J of Cerebral Blood Flow & Metabolism* (2001)

How does the brain cope with the increased metabolic demands?

- Activity dependent changes in CBF & CMRO2: autoregulation
- Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate of Oxygen ($CMRO_2$) are coupled under baseline conditions
  - PET measures CBF well, $CMRO_2$ poorly
  - fMRI measures $CMRO_2$ well, CBF poorly

- CBF about .5 ml/g/min under baseline conditions
  - Increases to max of about .7-.8 ml/g/min under activation conditions

- $CMRO_2$ only increases slightly with activation
  - Note: A large CBF change may be needed to support a small change in $CMRO_2$

Energy Consumption and blood supply

- O_2 consumption: 20% of the total body (Brain tissue is 2-3% of body weight)
- Most of the energy is spent maintaining action potentials and in post-synaptic signaling: post-synaptic activity probably dominates in human
- Inhibitory synapses use less energy than excitatory ones
- Neural activity use locally available glucose and Hb bound O_2
  - Glucose, oxyHb
  - deoxyHb, pH, CO_2

Autoregulation: Energy Consumption Theory

- Increased CBF provides higher concentration of glucose and Hb bound O_2:
  - Glucose, oxyHb ↑
  - deoxyHb, pH, CO_2 ↓
- CBF Increases to max of about .7-.8 ml/g/min under activation conditions
- Initial thoughts were that increase of **blood flow is directly linked to** the elevated metabolic rate (and thus increase in energy and **O_2 requirements)** of the active tissue. Candidate signal substrates:
  - Lactate, pH, CO_2, O_2,

But this is not true!

Autoregulation of the blood flow

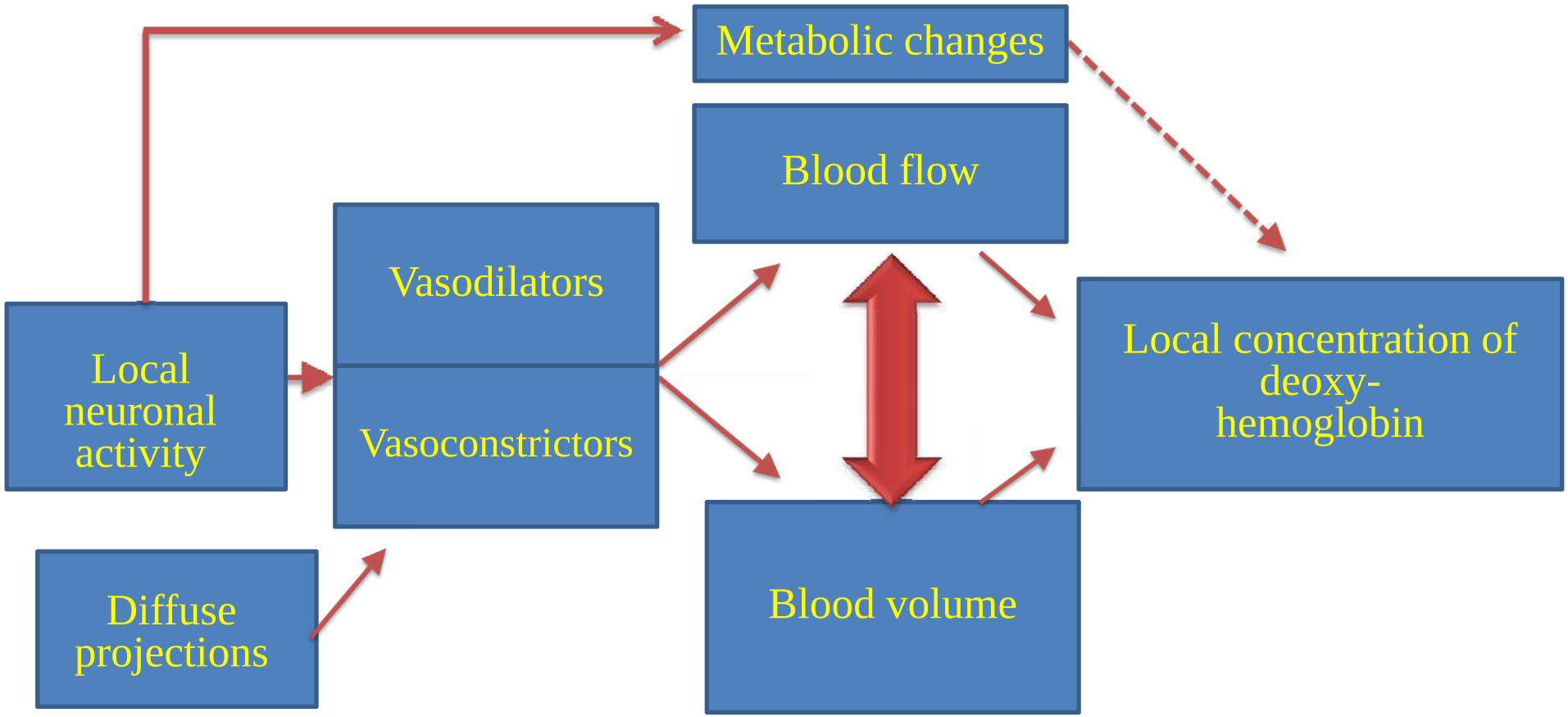
Then how does the brain cope with the increase in glucose and O_2 demands?

- ***Glutamate***-generated Calcium influx at post-synaptic level releases potent vasodilators:
  - Nitric Oxide
  - Adenosine
  - Arachidonic Acid metabolites
- Blood flow is increased over an area larger than the one with elevated neural activity
- Global blood flow changes also associated with dopamine, noradrenaline and serotonin
  - Not related with regional energy utilisation at all!!

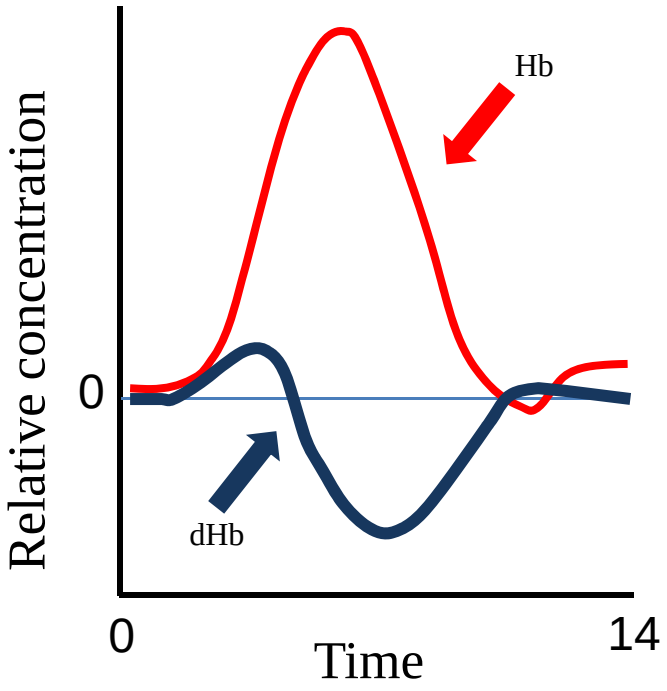
Energy utilisation and increase in blood flow are processes that occur in parallel and are not causally related

Attwell, D. , Iadecola, C. 2002. "The neural basis of functional brain imaging signals". *Trends in Neuroscience*. 25 (12) 621-625

Factors defining local deoxyhemoglobin-concentration



Activity dependent changes in deoxy- and oxyhemoglobin levels



- Quite distinct changes in oxygenated(Hb) and deoxygenated hemoglobin(dHb) following neuronal activation.
- Unlike weak deoxygenated hemoglobin signal spatial pattern of oxygenated hemoglobin does not reflect the pattern of neuronal activity

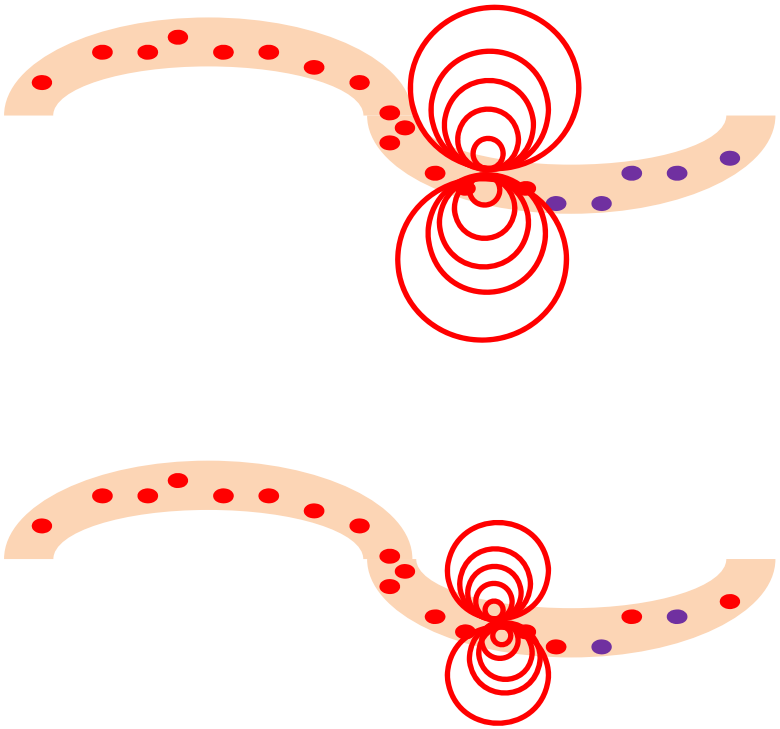
Oxygen and Field homogeneity

Depending on blood oxygen level:

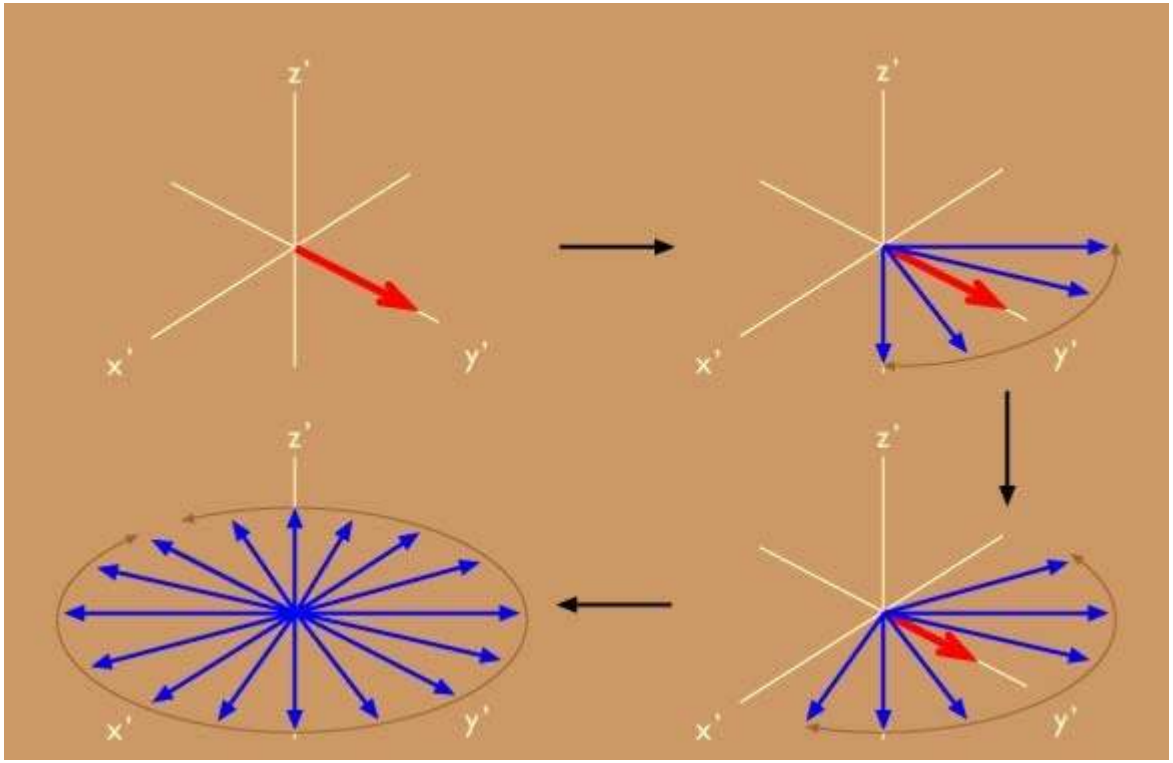
deoxyHb is paramagnetic, increases local inhomogeneity of magnetic field

oxyHb diamagnetic

- local homogeneity of magnetic field increased

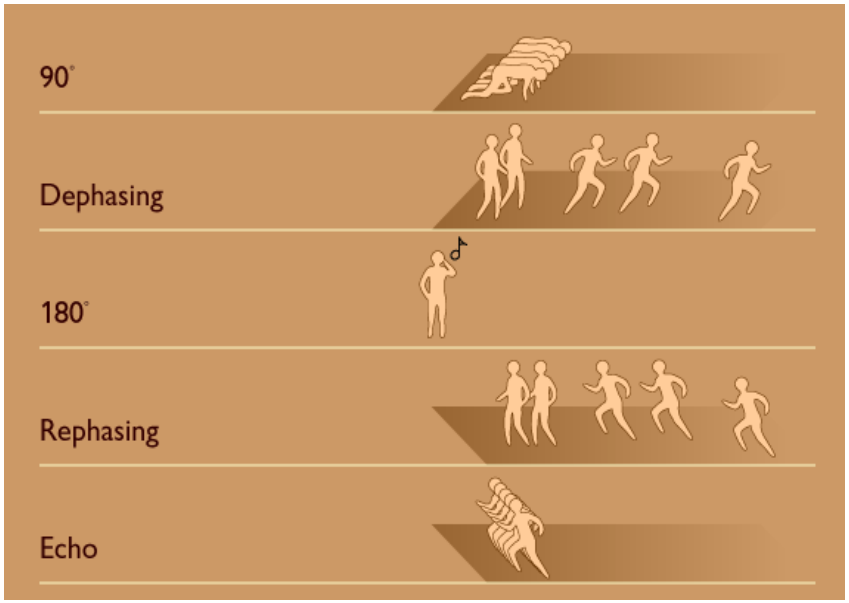


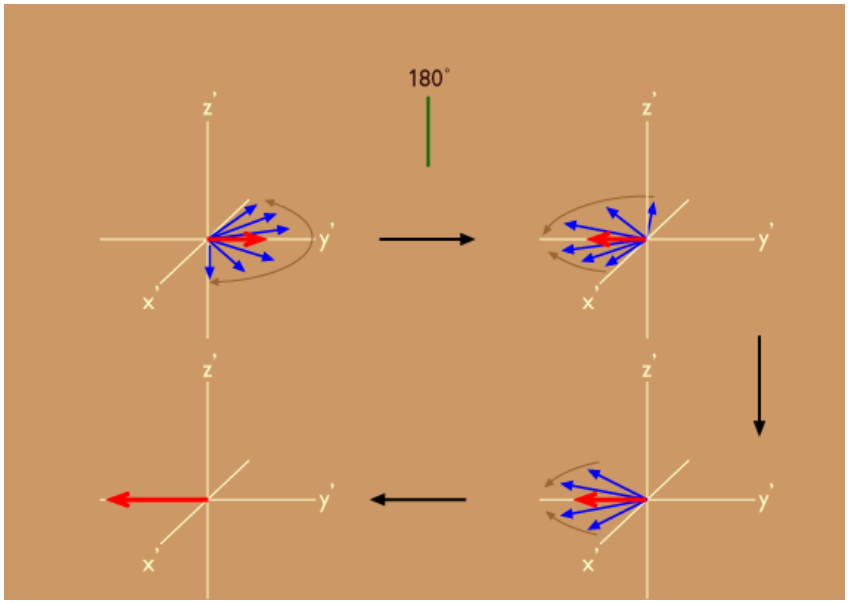
Impact of local inhomogeneity: attenuation of MR signal



Reversible+irreversible, origin: spin-spin (molecular) interaction and **within-voxel inhomogeneities of the magnetic field**

Biomedical Imaging: fMRI - the BOLD method

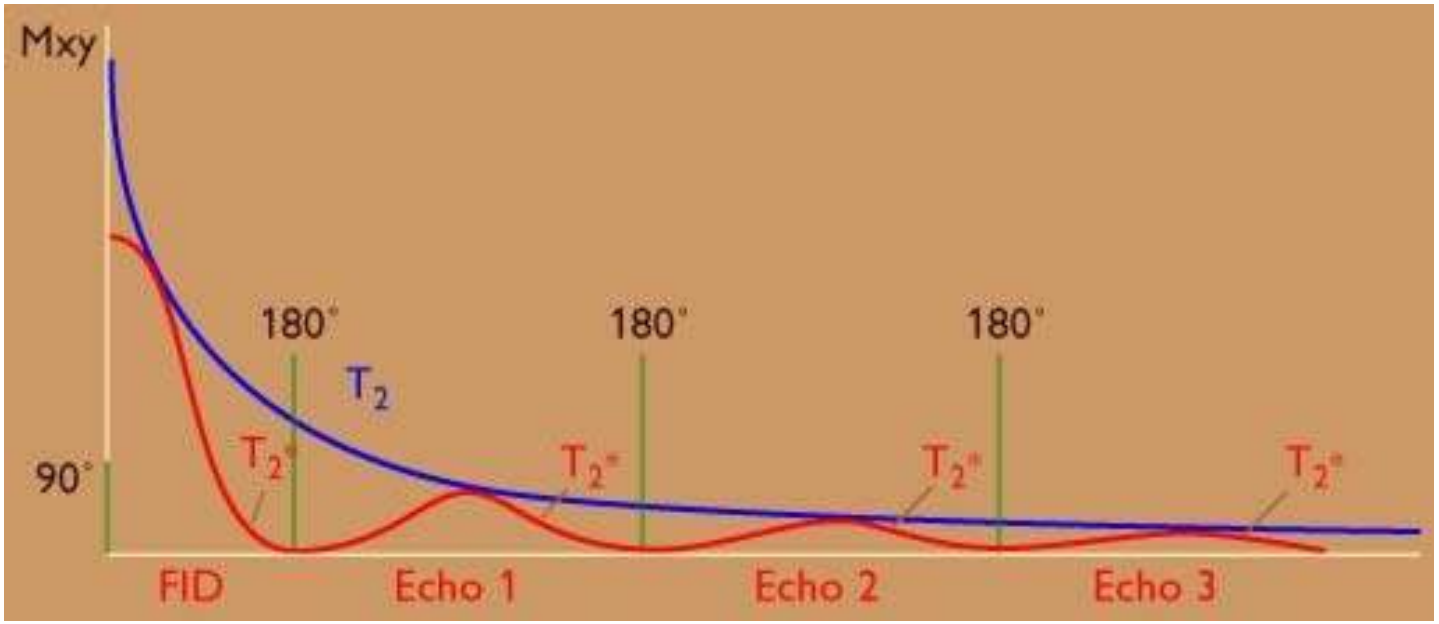




Irreversible: dynamically changing difference in frequency/dephasing of the spin precessions –dephasing is not constant. Source: molecular motion and spin-spin interaction.

Reversible: constant difference in frequency (within one slice acquisition), dephasing speed is not changing, refocusing RF pulse can recover phase coherence. Origin: local magnetic field non-uniformities.

Impact of local inhomogeneity on T_2*



T2 relaxation time: irreversible dephasing, molecular interaction

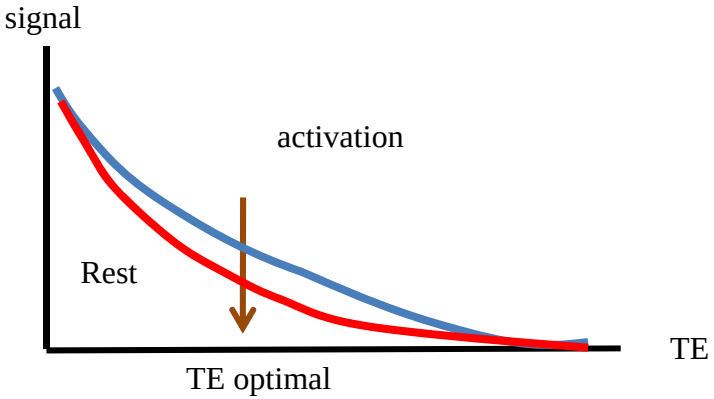
T2* relaxation time: MR signal attenuation due to irreversible+reversible dephasing. Local magnetic field non-uniformity is a major component of the effect: it correlates with local deoxyHb concentration.

How to detect BOLD contrast

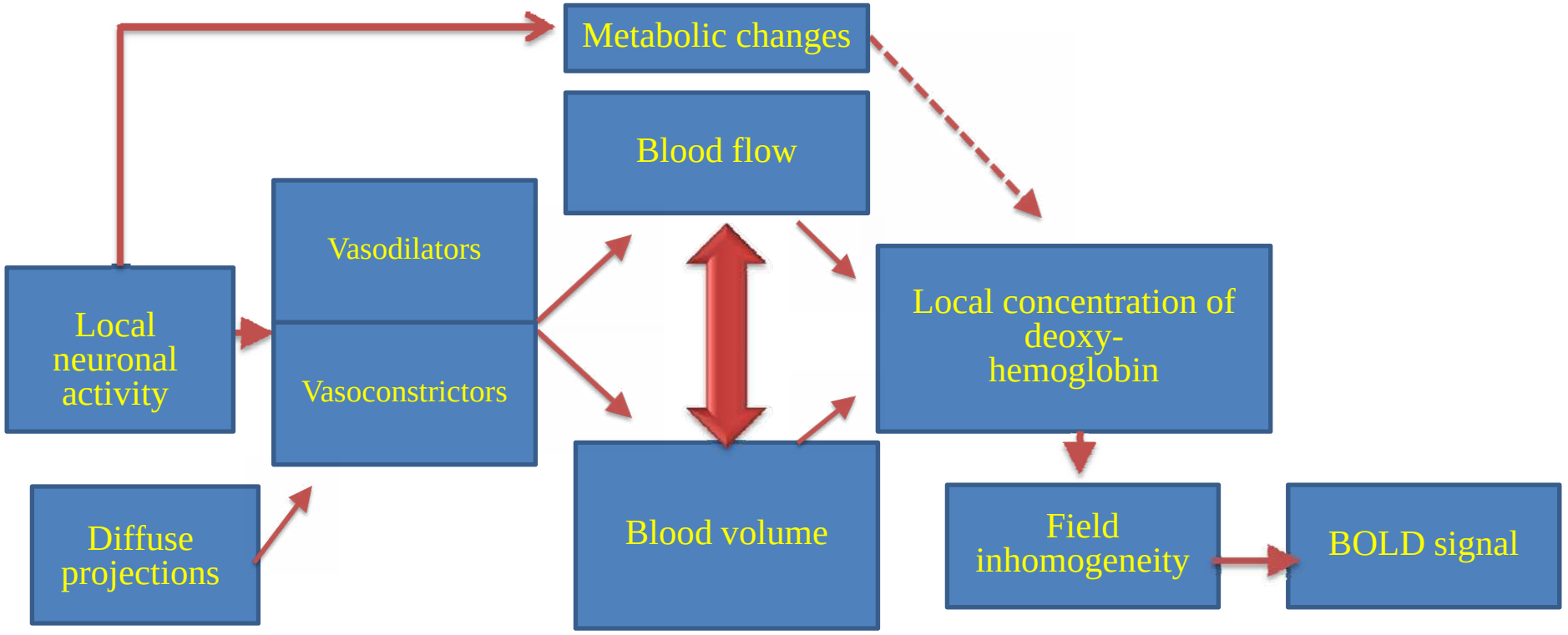
- Signal decay is sensitive to magnetic field inhomogeneities =>
  - Sensitive to signal difference based on deoxyHB concentration

Optimal read-out time:

- When signal difference is highest between different deoxyHB levels
  - TE=25-35ms at 3Tesla (depends on anatomical region as well)



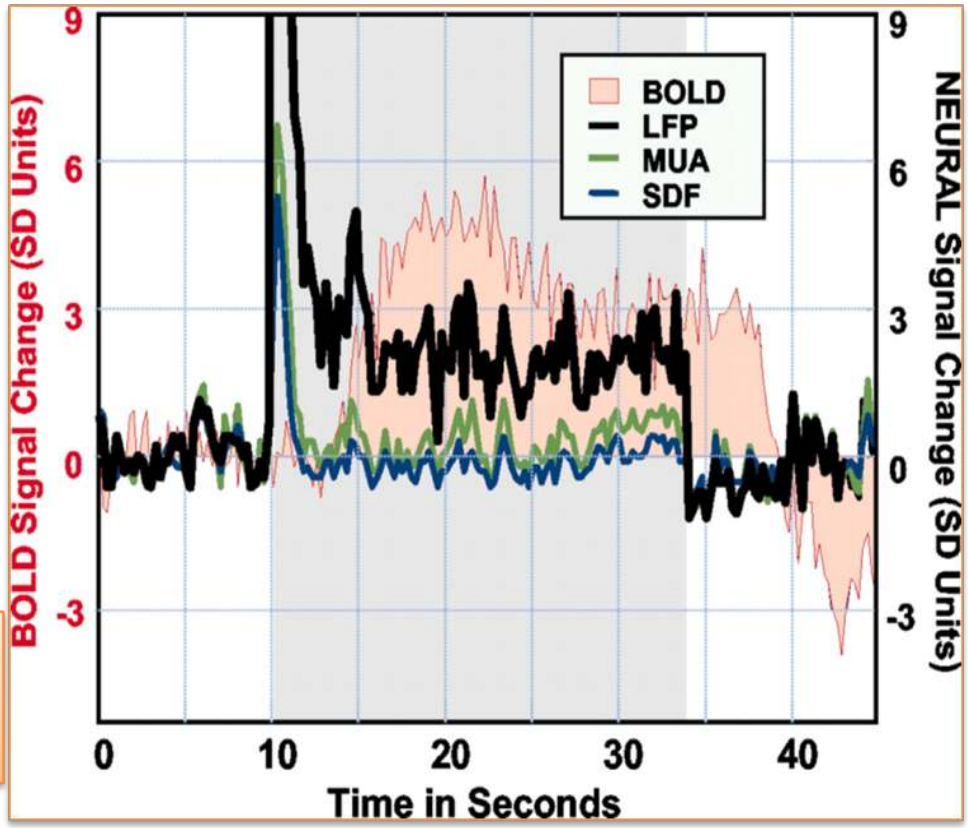
Link between BOLD and neural activity: Neurovascular coupling



Neuronal Origins of BOLD: proof of concept

•BOLD response correlates primarily with Local Field Potential that reflects activity in the neuropil(dendritic activity)

•Increased neuronal activity results in increased MR (T2*) signal



LFP: Local Field Potential
MUA: Multi-Unit Activity
SDF: Spike-Density Function

Logothetis Journal of Neuroscience, 2003,

Gradient EPI: benefits

- Most frequently used sequence in fMRI:
  - Gradient Echo Planar Imaging (gradient EPI)

Why Gradient?

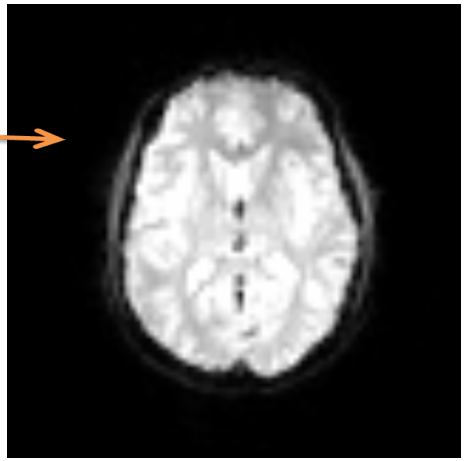
- Requires relatively long read-out time =>
  - Very sensitive to magnetic field inhomogeneities =>
    - Sensitive to signal difference based on deoxyHB concentration
- Signal decay is characterized by T2* relaxation

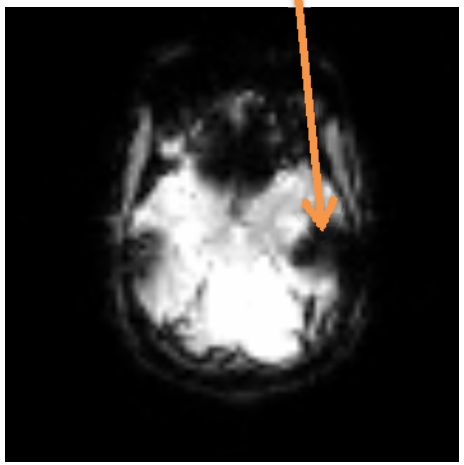
Why EPI?

- Relatively high temporal resolution: required time for a whole brain acquisition typically 2-3sec
- At higher magnetic fields (4.5T, 7T, 9.4T) can be combined with spin-echo sequence

Gradient EPI: disadvantages

- Low contrast and spatial resolution
- Serious distortions near to air/tissue borders (e.g. amygdala/inner ear)
- High water-fat shift
- Signal instability over time





Spatial Resolution and specificity of BOLD response

- In general: high spatial resolution because changes in BOLD response rely on changes in perfusion of *capillaries* (ø 5-10µm)
- Influencing factors:
- Voxel size (depending on region to scan 1-5mm)

  - attention! reduced voxel size → reduced signal compared with noise and increased acquisition time, but less diversity in tissue content
- Concordance of neural activity and vascular response
  - Arteries are fully oxygenated
  - Venous blood has increased proportion of dHb
  - Difference between Hb and dHb states is greater for veins
  - Therefore BOLD is the result of venous blood changes

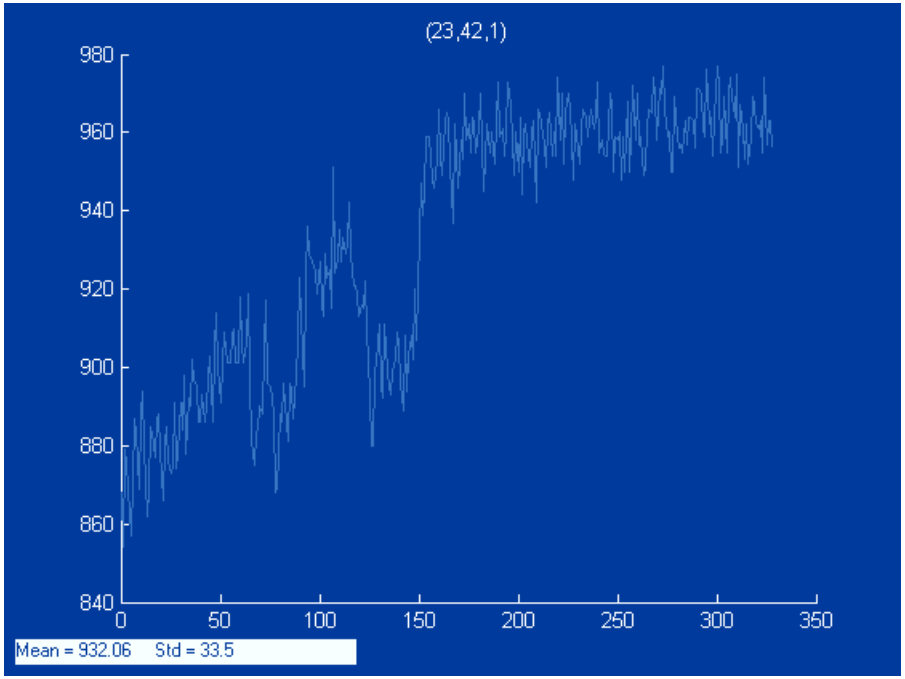
Signal can arise from larger and more distant blood vessels!!!

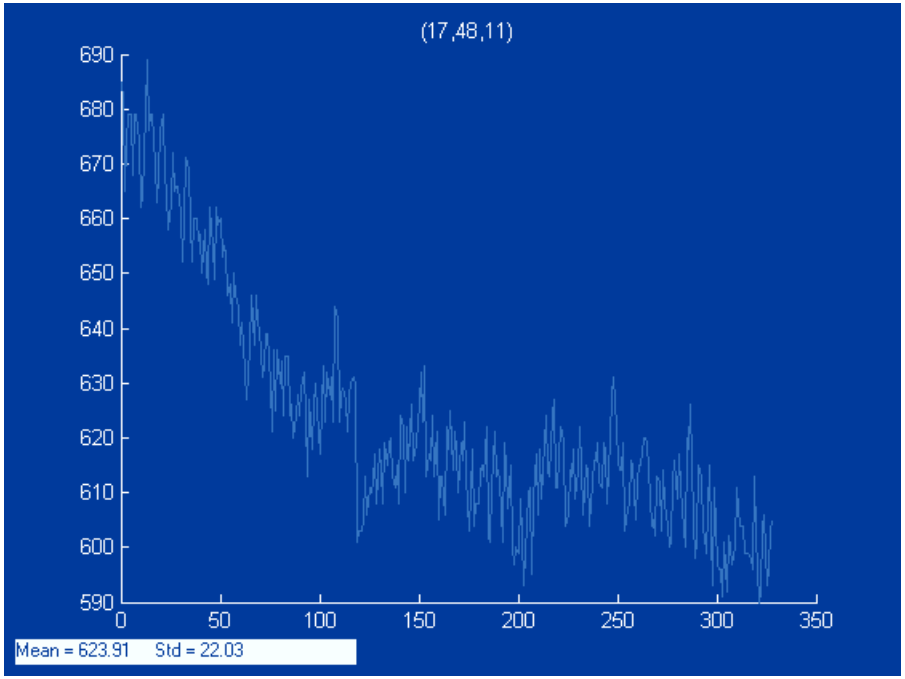
Temporal resolution of fMRI

- Typical sampling time of a volume: 2-3sec
- Temporal resolution is inversely related to
  - Spatial resolution
  - Imaging volume size
  - TE (sensitivity to BOLD)
- Stimuli can be detected:
  - Minimum duration : < 16 ms
  - Minimum onset diff: 100 ms to 2 sec
    - Above 2 sec, linear summation of responses
    - Below 2 sec: nonlinear interactions

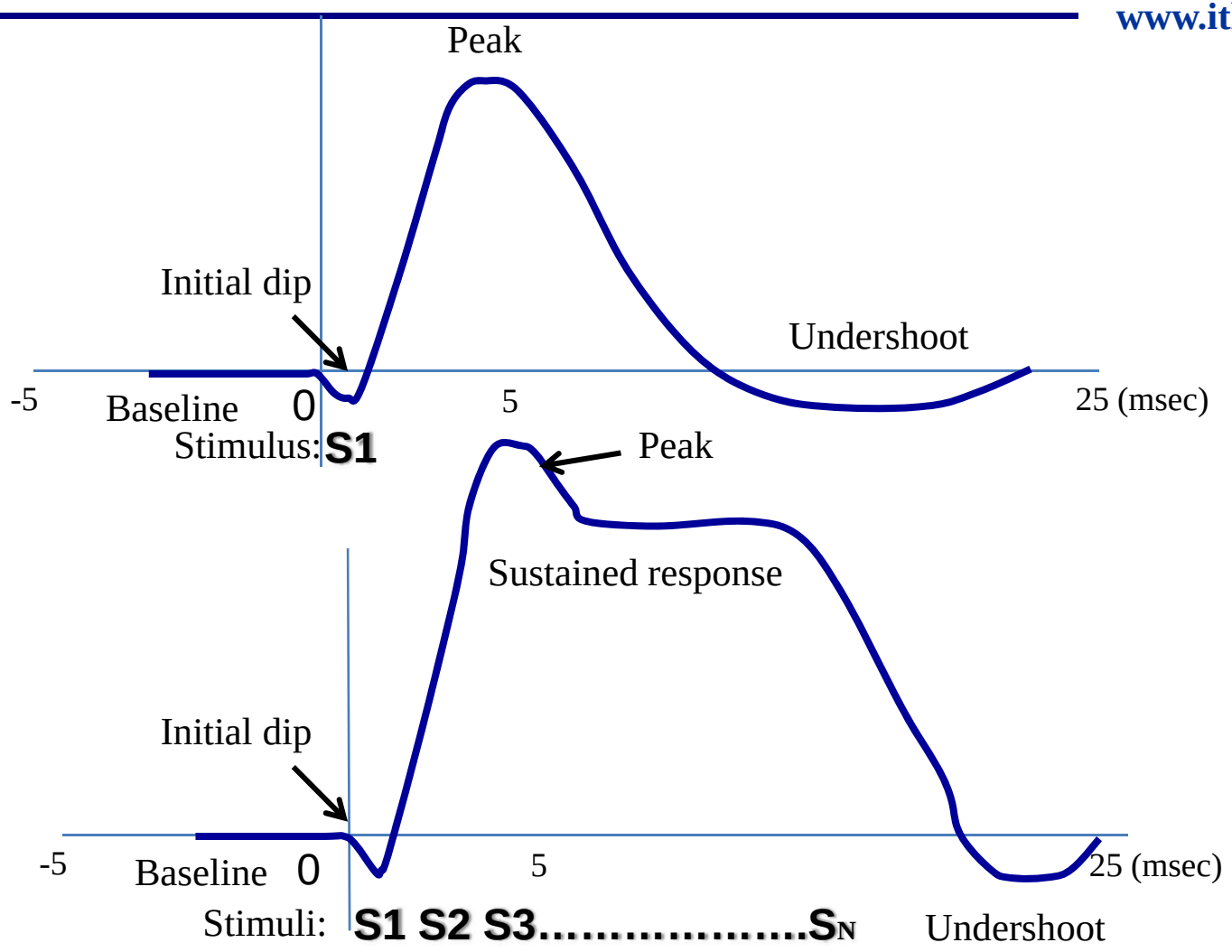
Stability of the BOLD signal

- Low frequency drifts and temporal autocorrelation is an inherent characteristic





Biomedical Imaging: fMRI - the BOLD method



Initial Dip (Hypo-oxic Phase)

- Initial Dip (1-2sec) may result from initial oxygen extraction before later over compensatory response
- Transient increase in oxygen consumption, before change in blood flow
  - Menon et al., 1995; Hu, et al., 1997
- Shown by optical imaging studies
  - Malonek & Grinvald, 1996
- Smaller amplitude than main BOLD signal
  - 10% of peak amplitude (e.g., 0.1% signal change)
- Potentially more spatially specific
  - Oxygen utilization may be more closely associated with neuronal activity than perfusion response

Rise (Hyperoxic Phase)

- Results from vasodilation of arterioles, resulting in a large increase in cerebral blood flow
- Inflection point can be used to index onset of processing

Peak – Overshoot

- Over-compensatory response
  - More pronounced in BOLD signal measures than flow measures
- Overshoot found in blocked designs with extended intervals
  - Signal saturates after ~10s of stimulation

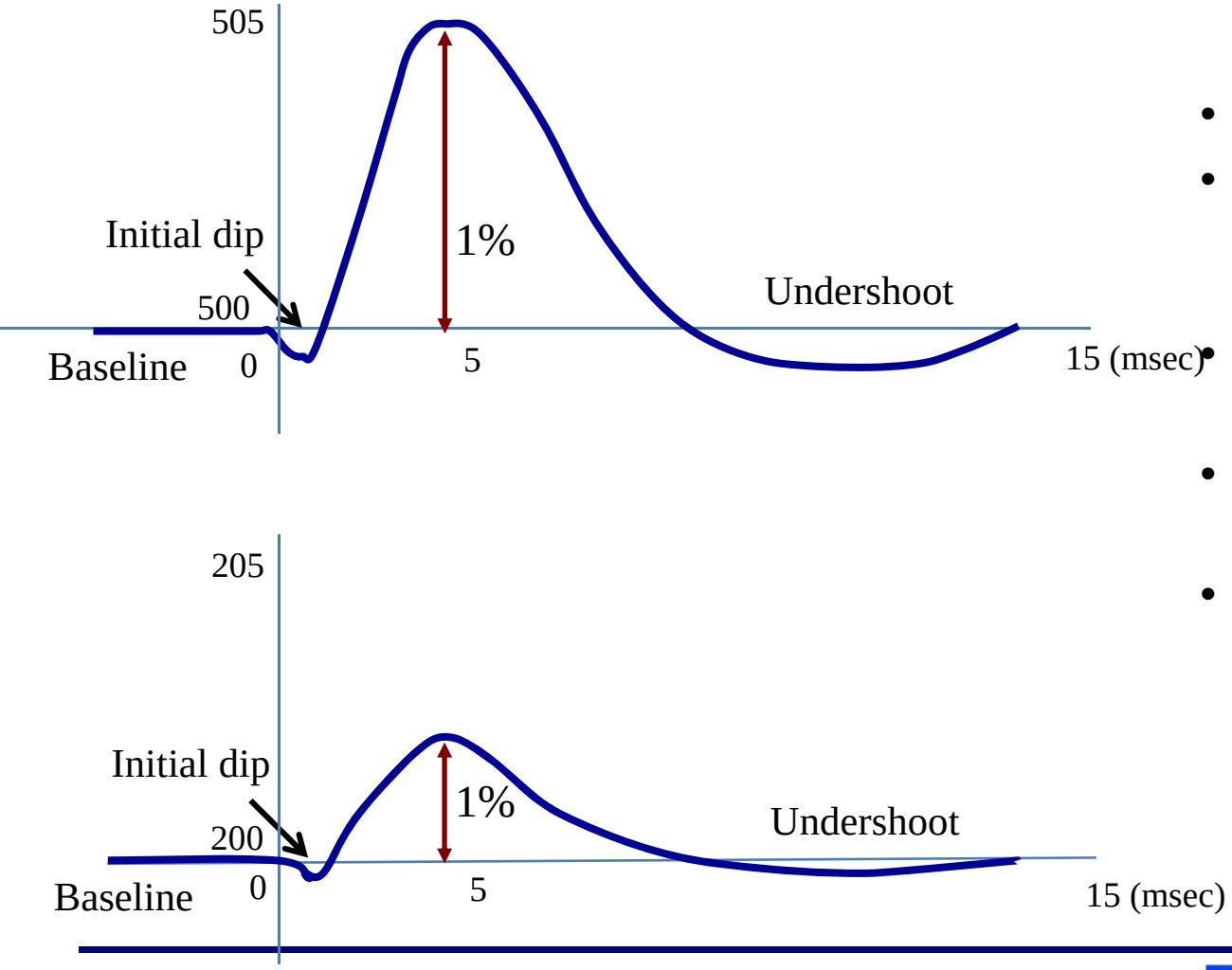
Sustained Response

- Blocked design analyses rest upon presence of sustained response
  - Comparison of sustained activity vs. baseline
  - Statistically simple, powerful
- Problems
  - Difficulty in identifying magnitude of activation
  - Little ability to describe form of hemodynamic response
  - May require detrending of raw time course

Undershoot

- Cerebral blood flow more locked to stimuli than cerebral blood volume
  - Increased blood volume with baseline flow leads to decrease in MR signal
- More frequently observed for longer-duration stimuli (>10s)
  - Short duration stimuli may not evidence
  - May remain for 10s of seconds

Normalization of responses: Percent Signal Change



- Peak / mean(baseline)
- Basic assumption: signal is proportional to mean baseline.
- Question: mean baseline depends on what?
- Amplitude variable across subjects, age groups, etc.
- Peak signal change dependent on:
  - Brain region
  - activation parameters
  - Voxel size
  - Field Strength

Issues: what are we actually measuring?

- Inputs or Outputs?
  - BOLD responses correspond to intra-cortical processing and inputs, not outputs
  - Aligned with previous findings related to high activity and energy expenditure in processing and modulation
- Excitation or inhibition circuits?
  - Excitation increases blood flow, but inhibition might too – ambiguous data
  - Neuronal deactivation is associated with vasoconstriction and reduction in blood flow (hence reduction in BOLD signal)
- And what about the awake, but resting brain?
  - Challenges in interpreting BOLD signal
  - Presence of the signal without neuronal spiking

Issues: what are we actually measuring?

90.000 to 100.000 neurons per $1mm^3$ of brain tissue

10^9 synapses, depending on cortical thickness

What is in a Voxel?

Volume of $55mm^3$

- Using a 9-16 mm^2 plane resolution and slice thickness of 5-7 mm

Only 3% of vessels and the rest are….(be prepared!!)

- 5.5 million neurons
- 2.2-5.5 x 10^{10} synapses
- 22km of dendrites
- 220km of axons

Relative vs. Absolute Measures

- BOLD fMRI provides relative change over time
  - Signal measured in “arbitrary MR units”
  - Percent signal change over baseline
  - Direct longitudinal or intersubject comparisons are impossible
  - within subject interregional (different cortical areas)

  comparisons : only qualitative or indirect
- Arterial spin labeling (another type of fMRI method discussed later) or PET provides absolute signal
  - Measures biological quantity in real units
    - CBF: cerebral blood flow
    - CMRGlc: Cerebral Metabolic Rate of Glucose
    - $CMRO_2$: Cerebral Metabolic Rate of Oxygen
    - CBV: Cerebral Blood Volume

Why the Growth of fMRI?

- Powerful
  - Improved ability to understand cognition
  - Better spatial resolution than PET
  - Allows new forms of analysis
- High benefit/risk ratio
  - Non-invasive (no contrast agents)
  - Repeated studies (multisession, longitudinal)
- Accessible
  - Uses clinically prevalent equipment
  - No isotopes required
  - Little special training for personnel

What fMRI Can Do

Help in understanding healthy brain organization

- map networks involved with specific behavior, stimulus, or performance
- characterize changes over time (seconds to years)
- determine correlates of behavior (response accuracy, etc…)

Current Clinical Applications

- presurgical mapping
- better understanding mechanism of pathology for focused therapy
- drug effect assessment
- assessment of therapy progress, biofeedback
- epileptic foci mapping
- neurovascular physiology assessment

Current Clinical Research

- assessment of recovery and plasticity
- clinical population characterization with probe task or resting state

What fMRI Can't Do

- Too low SNR for routine clinical use (takes too long)
- Requires patient cooperation (too sensitive to motion)
- Too low spatial resolution (each voxel has several million neurons)
- Too low temporal resolution (hemodynamics are variable and sluggish)
- Too indirectly related to neuronal activity
- Too many physiologic variables influence signal
- Requires a task (BOLD cannot look at baseline maps)
- Too confined space and high acoustic noise.

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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

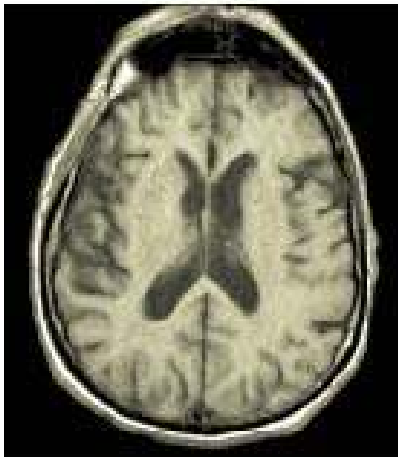
(Orvosbiológiai képalkotás)

fMRI – Data Processing and Basic Analysis

(fMRI – Adatfeldolgozás és elemzés)

ÉVA BANKÓ, VIKTOR GÁL

Acquired Data

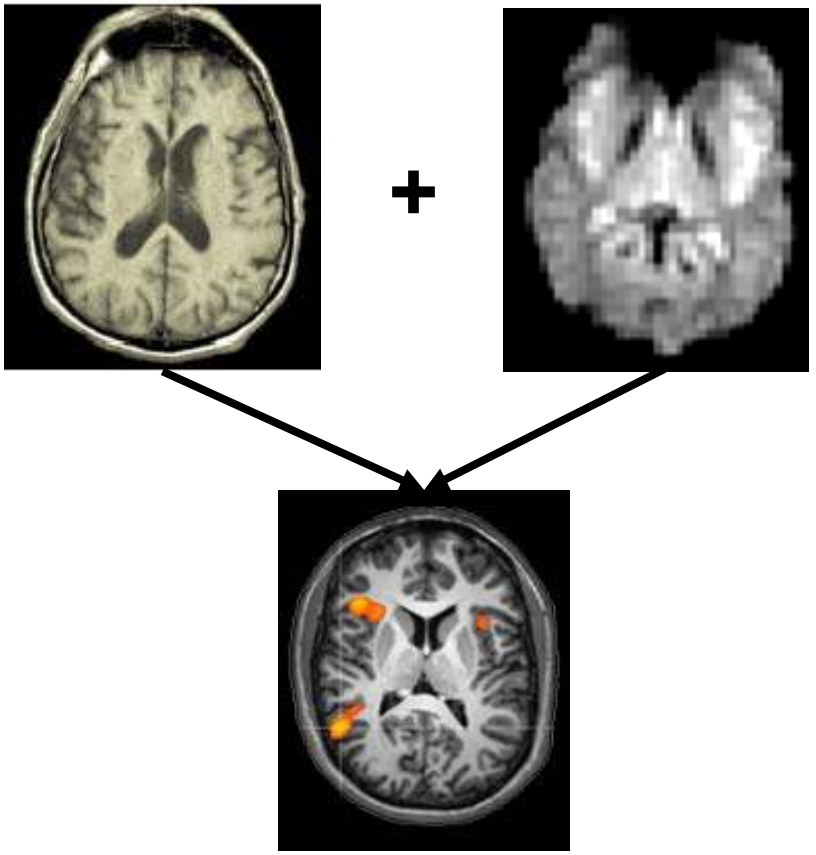


- 3D T1 anatomy
  - 1×1×1 mm resolution

- 4D T2* EPI images
  - 3D timeseries collected at each TR (1-2 s)
  - ~4×3.5×3.5 mm resolution

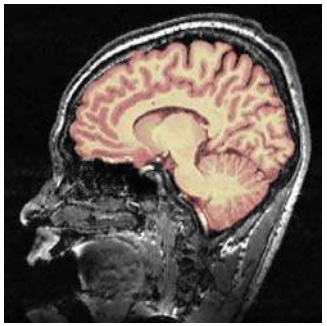
Preprocessing and Processing Steps

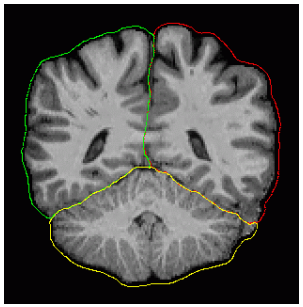
- Anatomical images
  - Intensity normalization
  - Skull-stripping
  - 3D reconstruction
  - Normalization (MNI or Talairach)
- Functional images
  - Coregistration
  - 3D motion correction
  - Slice-time correction
  - Smoothing
  - Defining ROIs
  - Regression analysis

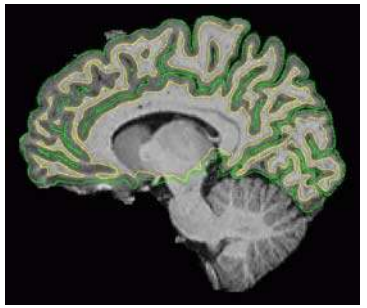


Anatomical Preprocessing I.

- Intensity normalization
  - make white matter (WM) homogenous to aid segmentation
- Skull-stripping
  - remove all non-brain tissues
  - caveat: shouldn't accidentally remove grey matter (GM)
- Segmentation
  - separate hemispheres, then separate GM from WM, so analysis can be restricted to GM

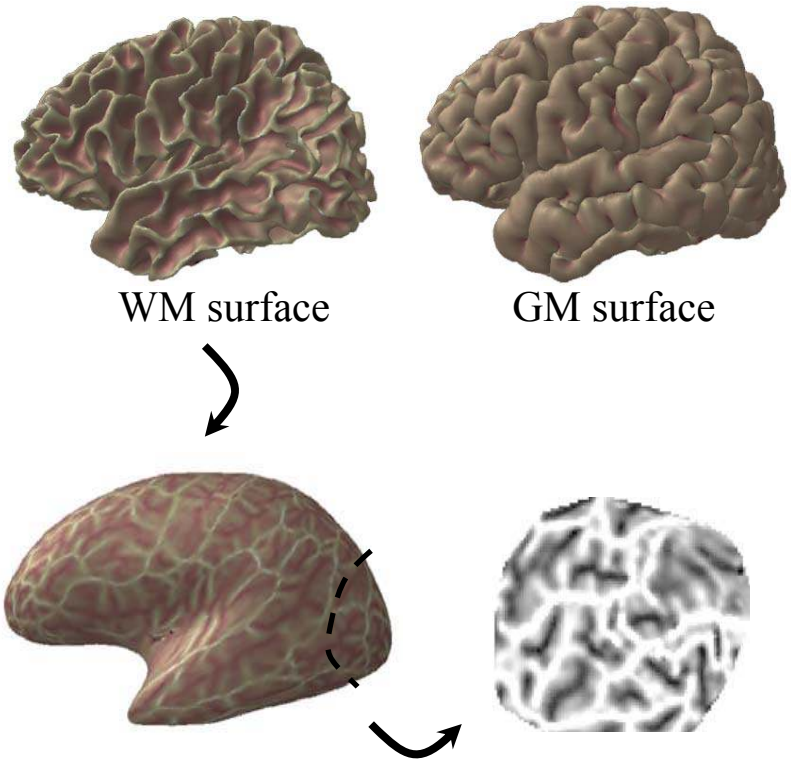






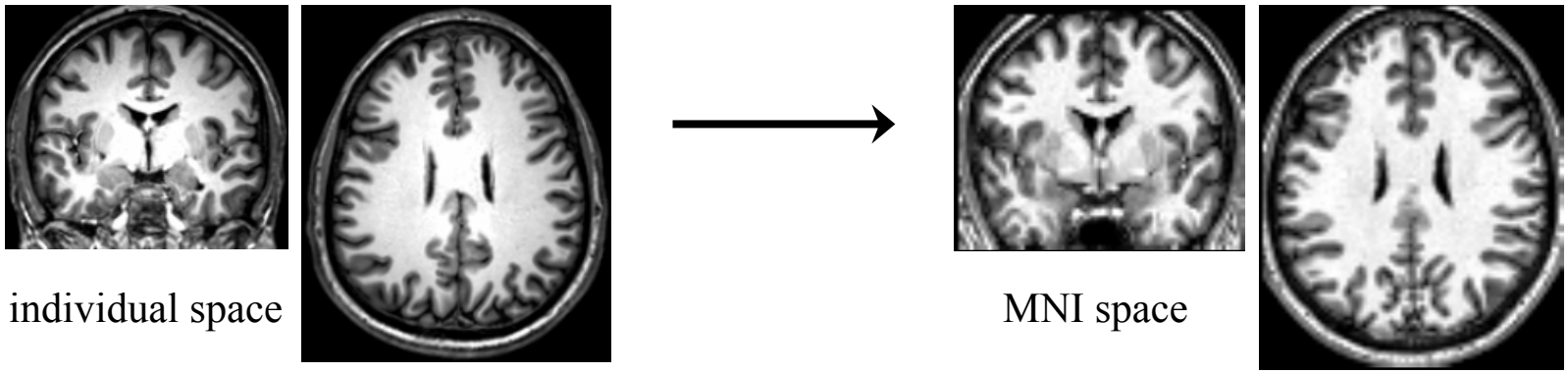
Anatomical Preprocessing II.

- Surface creation
  - make surfaces out of the segmented GM and WM
- Inflation
  - inflate WM surface to better visualize activations in sulci
- Flattening
  - cut a patch and flatten or cut at predefined sulci to flatten the whole brain



Anatomical Preprocessing III.

- Normalization
  - transform each individual brain into a standard space by predefined algorithms so 2nd-level (group-level) analysis can be performed
  - standard spaces:
    - Talairach space based on one post-mortem brain
    - Montreal Neurological Institute (MNI) space based on a large series of MRI scans on normal controls

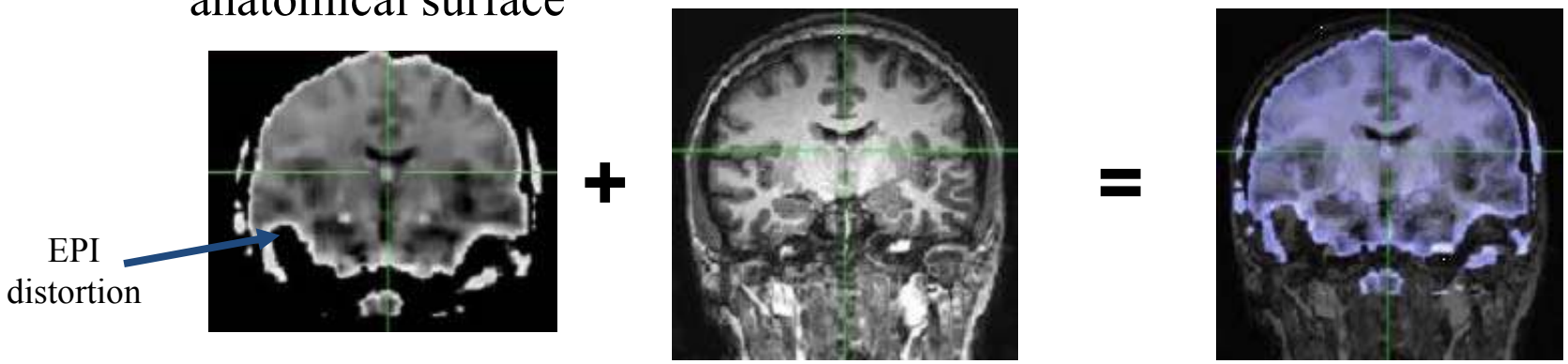


individual space

MNI space

Functional Preprocessing I.

- Coregistration
  - 3D anatomy and the functional images are acquired in a different space; moreover the EPI sequence distorts the brain in the neighborhood of cavities
  - a linear (or non-linear) warping algorithm is required to register both in the same space so statistical activations can be projected to the anatomical surface



Functional Preprocessing II.

- 3D Motion correction
  - align all functional images to a reference image (usually the first image or the image in the middle of the scan) since their location could have slightly changed due to subject motion and all statistical analyses assume that the location of a given voxel within the brain does not change over time
- Slice-timing correction
  - with a continuous descending EPI sequence, the bottom slice is acquired a TR later than the slice on the top, so there is a shift in the onset of the haemodynamic function. One solution to this problem is to interpolate the data during preprocessing as if the slices were acquired simultaneously
- Smoothing
  - spatially smoothing each of the images improves the signal-to-noise ratio (SNR), but will reduce the resolution in each image

Statistical Analysis of Functional Images I.

- Aims:
  - find and describe the effect of stimulation if there is any
- Based on the spatial complexity of the signal, there are:
  - one-dimensional methods
    - doing the statistics separately on a voxel-by-voxel basis (classic GLM regression method)
    - averaging the time course of predefined voxels in a certain area (region-of-interest: ROI) and doing the statistics on that (increases signal-to-noise ratio (SNR)
  - multi-dimensional (multi-variate) methods
    - finding patterns in time *and* space

Statistical Analysis of Functional Images II.

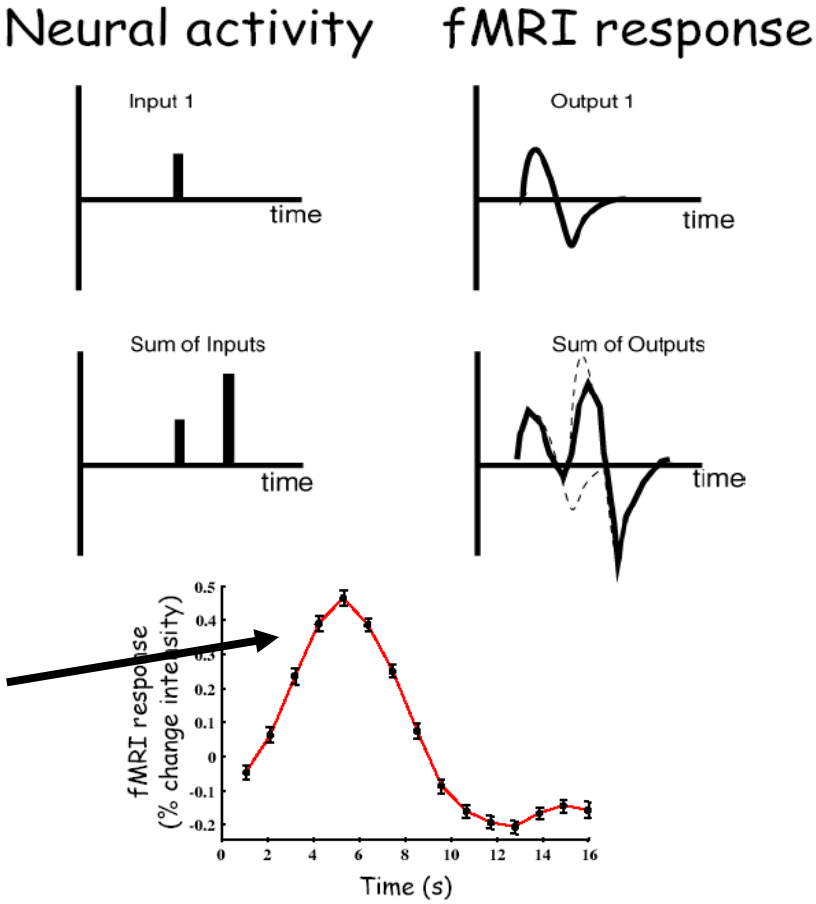
- Fitting models to the data:
  - find models that describe the signal and the noise and evaluate the fit
- Parametric models:
  - linear correlation
  - t-tests
  - event-related averaging
  - general linear models (GLM)
- Non-parametric models
  - bootstrap
  - Monte-Carlo simulations
  - multi-variate models

Statistical Analysis of Functional Images III.

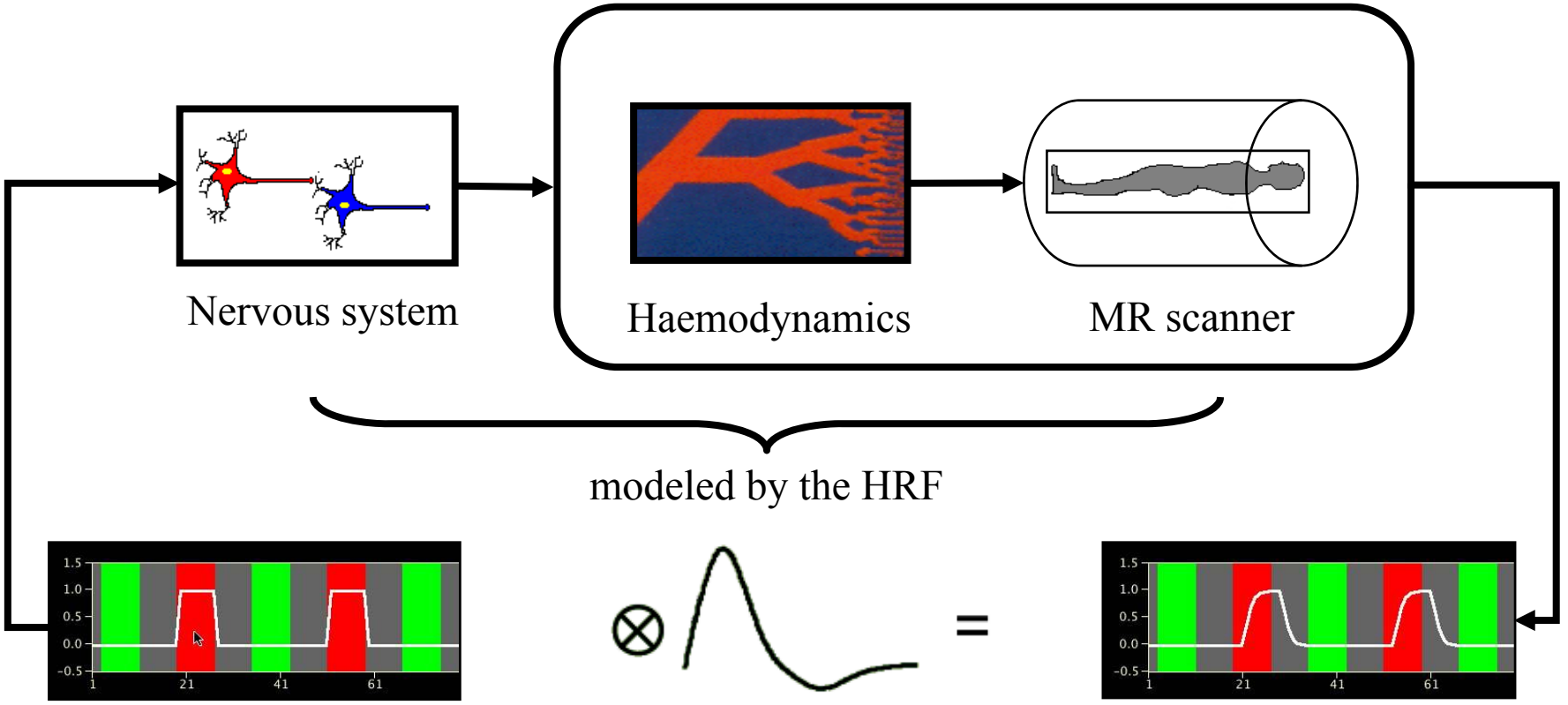
- Noise integration into models
  - models should take noise into account either as a separate term
  - there are models devoted to noise estimation (nuisance variability models) such as time autocorrelation or drift
- Univariate models treating each voxel separately need to be statistically corrected for
  - correction for the multiple comparison problem
- Group-level statistics model the population not particular individuals
  - Random effects models

Linear Transform Hypothesis

- It is assumed that the processes from neuronal firing to BOLD response constitute a time-invariant linear system, so the fMRI signal is approximately proportion to a measure of local neural activity, averaged over a spatial extent of several millimeters and over a time of several seconds.
- *Haemodynamic impulse response function*: (HIRF or HRF) the measurable fMRI signal for a brief stimulus presentation

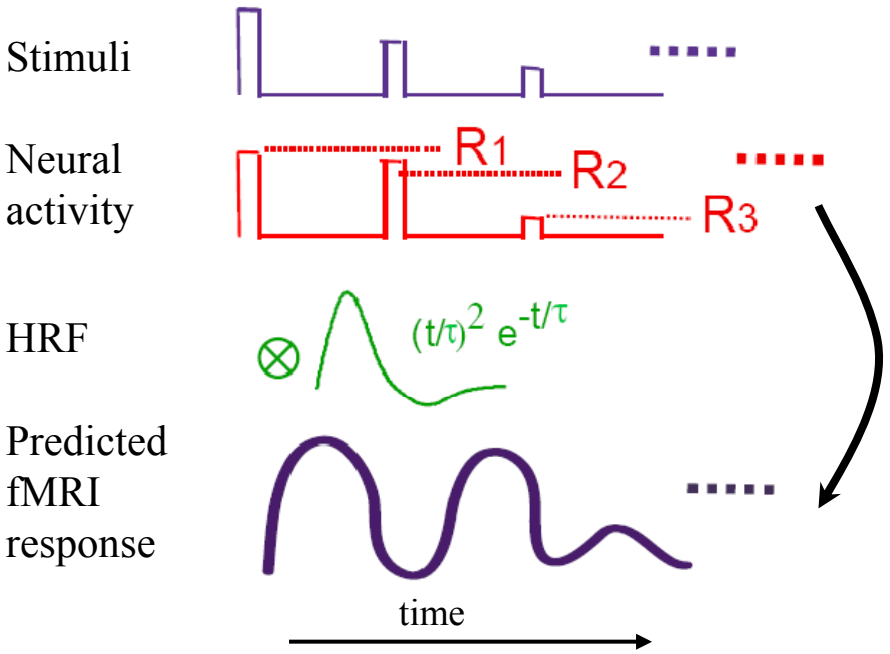


Haemodynamic Response Function

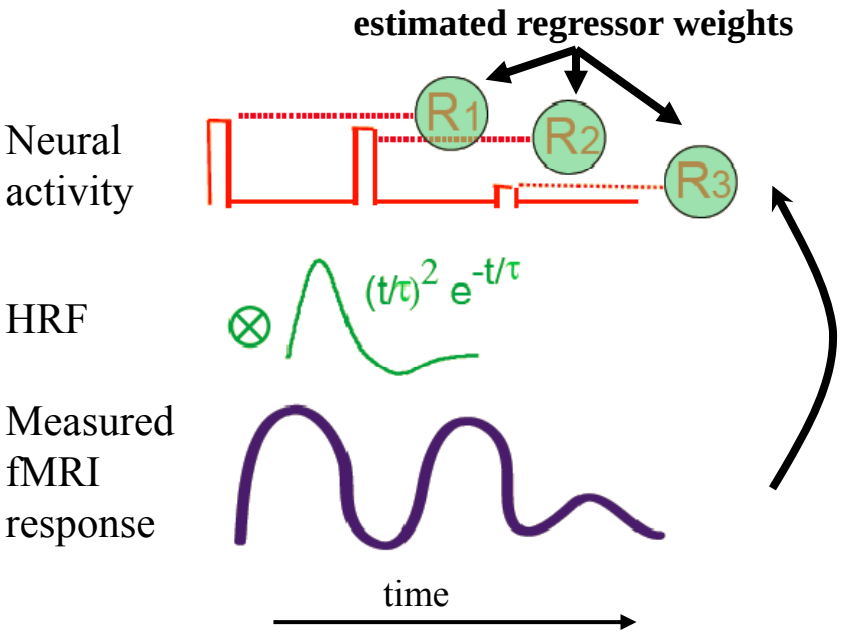


Model of Cortical Activity and Haemodynamic Impulse

fMRI responses from cortical activity



Estimating cortical activity from fMRI responses



General Linear Model Approach

- in the case of continuous signal:

$$y(t) = x_1(t) * h_1(t) + \cdots + x_N(t) * h_N(t) + n(t)$$

y(t): measured fMRI response
x(t): input signal (i.e. the sum of time-shifted Dirac delta functions)
h(t): HRF
n(t): noise
N: number of event types in the experiment

- in the case of discrete signal:

$$y = X_1 h_1 + \cdots + X_N h_N + n$$

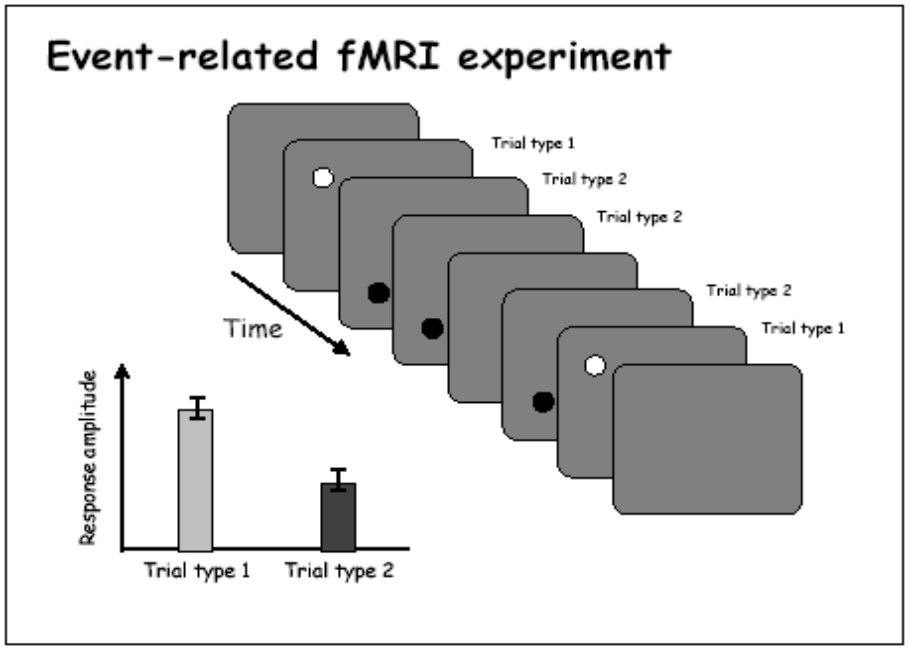
$$y = Xh + n$$

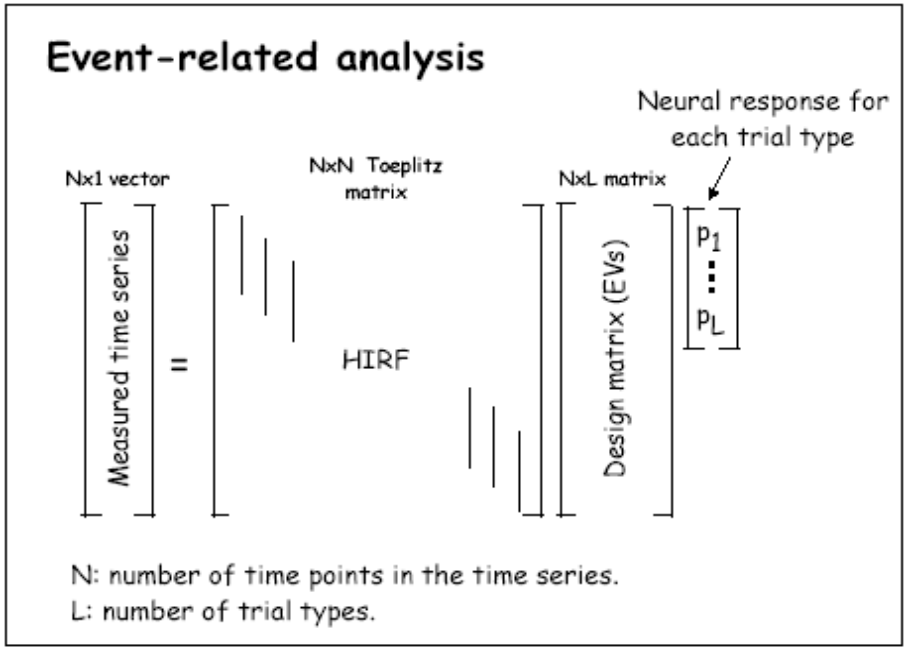
y: measured fMRI response
X: convolution (design) matrix
h: HRF vector

if X = [X1 X2 .. Xn]
h = [h1
:
hN]

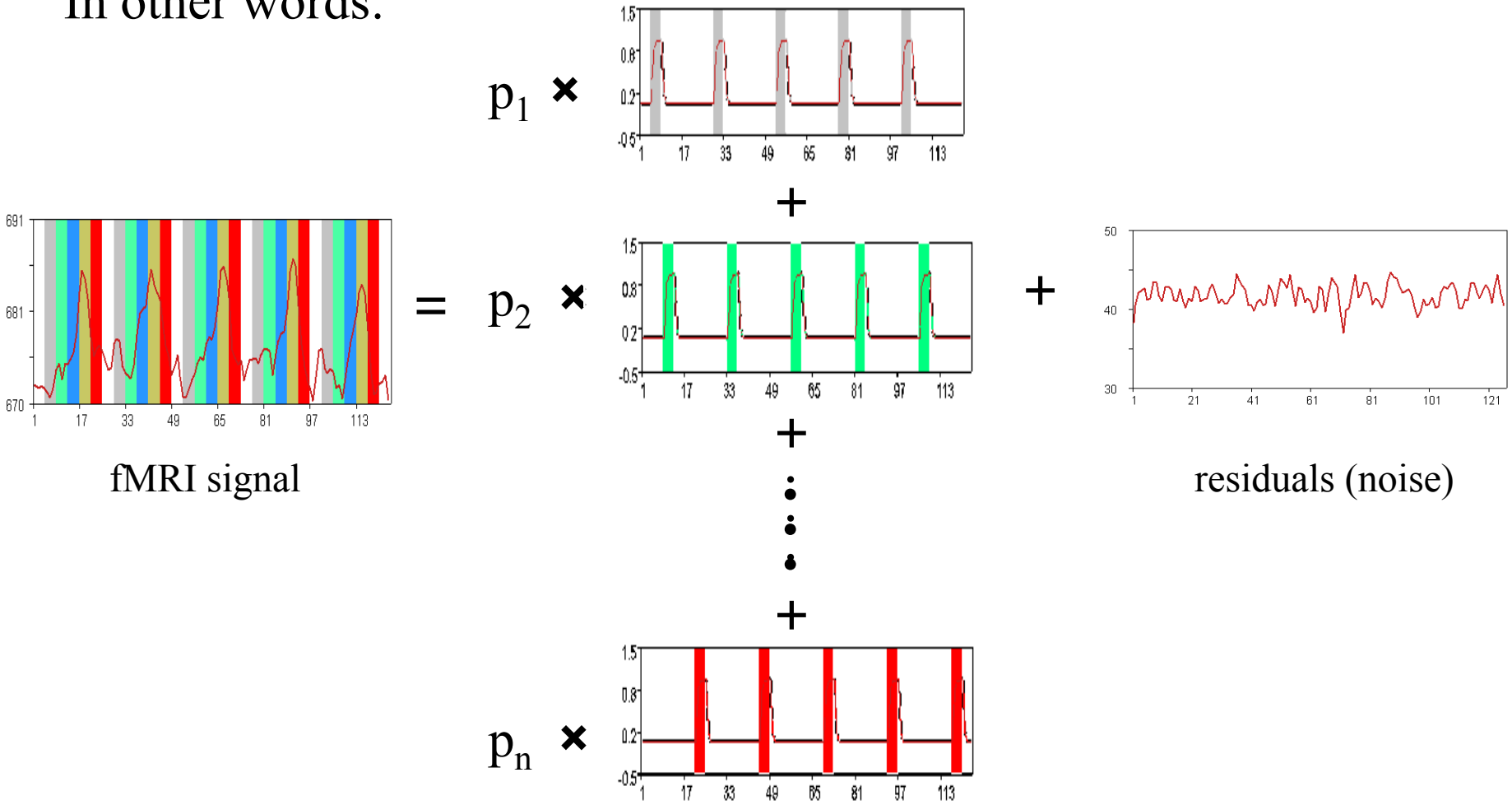
y = Xhp or y = **X**p where ***X*** is the convolution of the known design matrix with the assumed HRF

p: the amplitude of the neural response / weight of the regressor / beta parameter



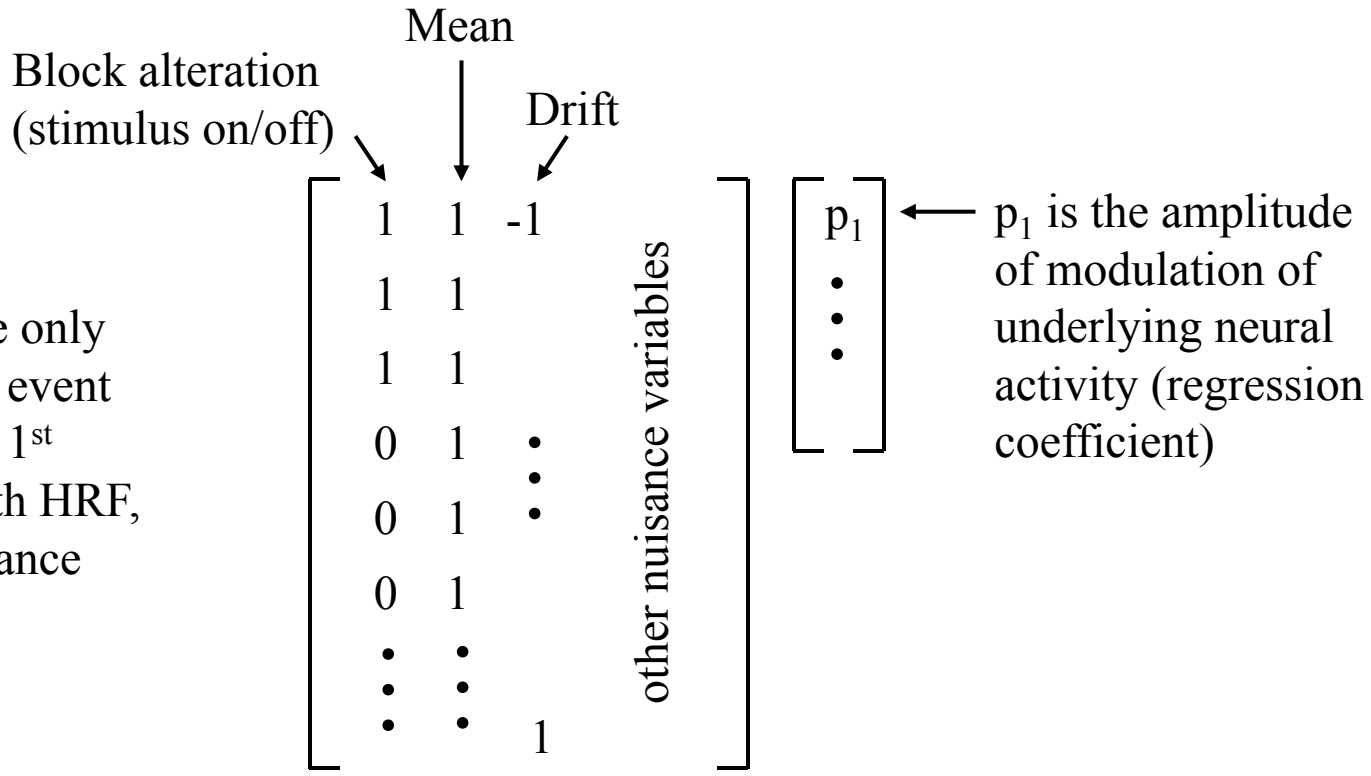


In other words:



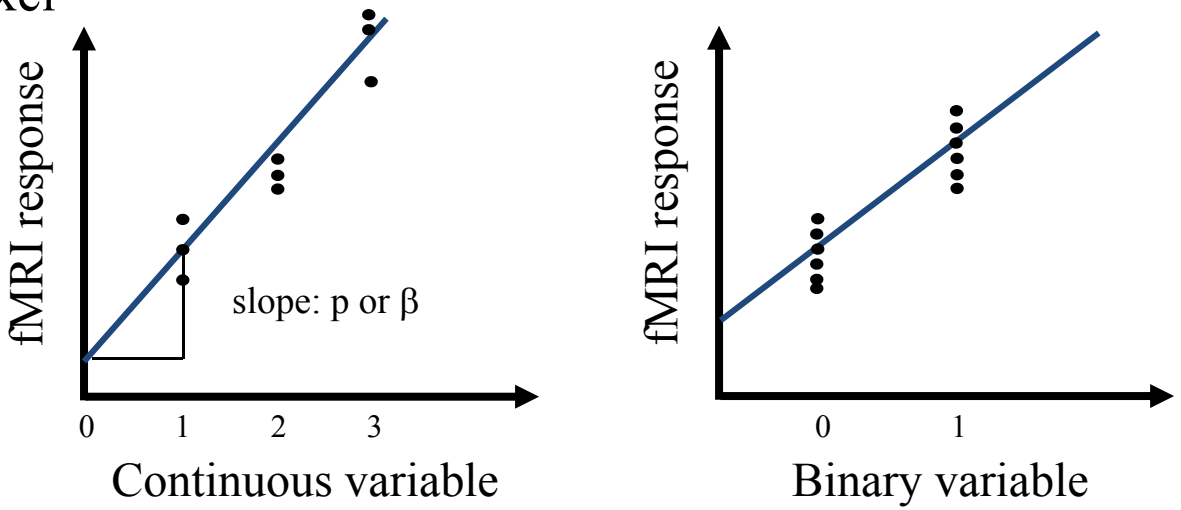
Design Matrix

- in a simple case (block design, one type of event only)



What is *p* (regression coefficient)?

- p or beta (β) is the slope of the regression line that relates the values of the experimental variable to the measured fMRI response to the variable in a given voxel



- Continuous regressor –also called a covariate – contain quantifying exp. variable (e.g. stimulus contrast), while a binary regressor contain distinguishable exp. conditions (e.g. on/off)

To solve, find p to satisfy

$$\vec{y} = X\,\vec{p}$$

p is the product of the measured signal *y* with the pseudoinverse of ***X*** ($\mathbf{X}^{\#}$)

$$\vec{p}_{opt} = X^{\#}\,\vec{y}$$

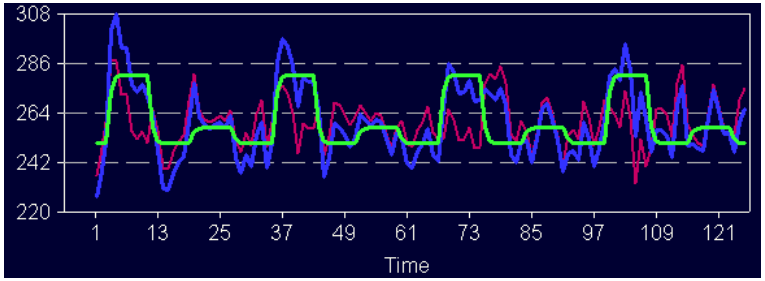
$$X^{\#} = (X^{T}X)^{-1}X^{T}$$

- Advantages:
  - estimation can be done even with superposing fMRI responses
  - noise is accommodated in the model
- Limitations:
  - each event type is estimated with a single *p* parameter
  - GLM approach assumes that the shape of the HRF is identical (canonical HRF) to each event type and at every area in the cortex

Steps in a GLM Analysis

- Defining the regressors (i.e. the design matrix) to model:
  - presentation time, or properties of the stimuli
  - noise parameters (drift, head motion)
  - behavior (performance) of the subjects
- Model fitting
  - determine the regressor coefficients (e.g. by least-squares estimation)
  - estimate the goodness of fit by determining the residuals (the difference between the actual measured signal and the predicted signal)
- Visualization
  - residual variance maps to visualize goodness of fit
  - t-maps to visualize the contrast between two regressors
  - bar diagrams of regressor coefficients (beta values) extracted from a cortical area (ROI analysis)

GLM Summary



Model

$$y = X * p + \varepsilon$$

Observed data:	Design matrix:	Parameters:	Error:
y is the fMRI (BOLD) signal at various time points at a single voxel (GLM treats each voxel as a separate column vector of data).	Several components which explain the observed data, i.e. the BOLD time series for the voxel convolved with the shape of the expected BOLD response over time (HRF). Includes timing info: onset and duration vectors, other regressors, e.g. realignment parameters.	Define the contribution of each component of the design matrix to the value of ***y***. Estimated so as to minimize the error ***ε***, i.e. least sums of squares.	Difference between the observed data, ***y*** and that predicted by the model, ***Xp***. Not assumed to be spherical in fMRI.

Goodness of fit

- it can be quantified how much the model accounts for the variance in the measured data:

$$r^2 = 1 - \frac{\mathrm{var}[data - model]}{\mathrm{var}[data]}$$

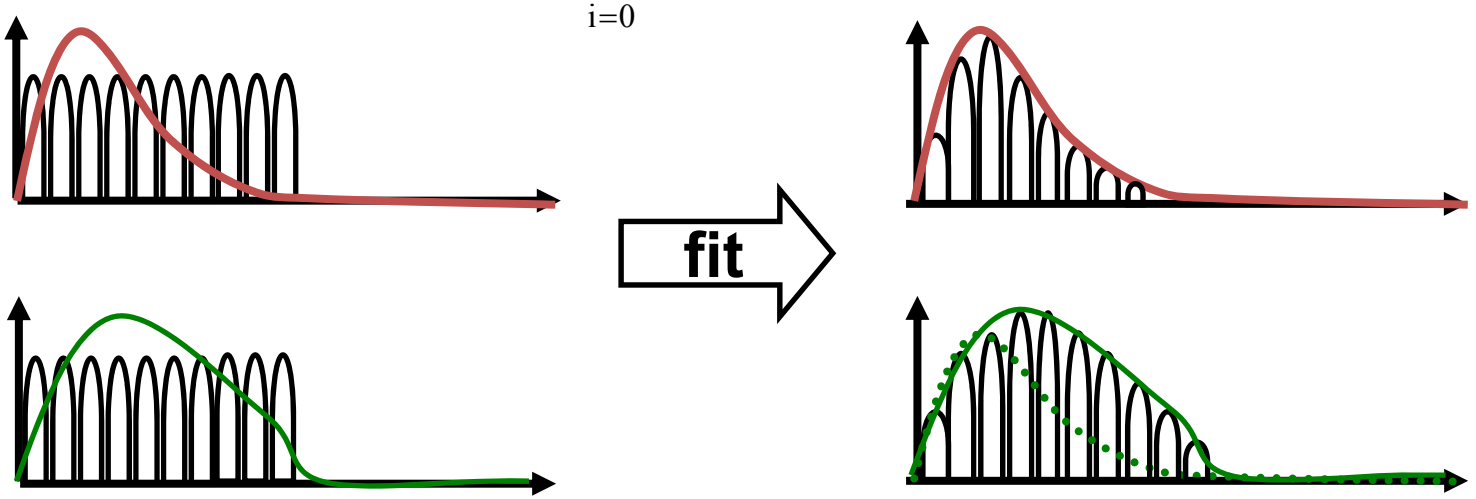
- crucial to determine how well the given parameter estimate describes the fMRI response in that specific condition (or it is just a result of a noisy data)
- a statistical test is needed that does not depend on the perfect fit of the model → *randomization test* (similar to bootstrapping the data)

Finite Impulse Response (FIR) Filter

… an alternate way to estimate the underlying HRF

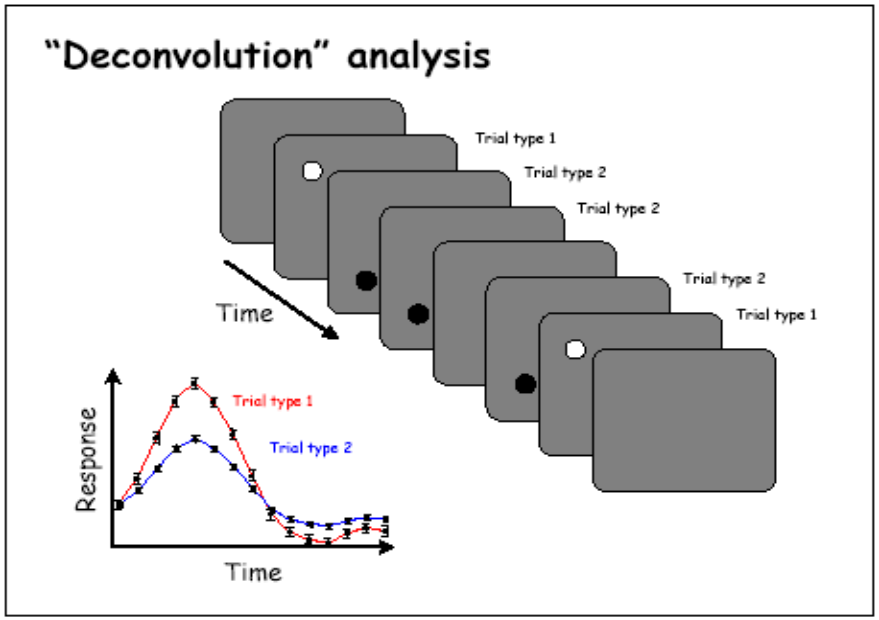
- fits data with many finite impluse responses
- however, it is sensitive to overfitting: to fit to the noise in that particular dataset/condition

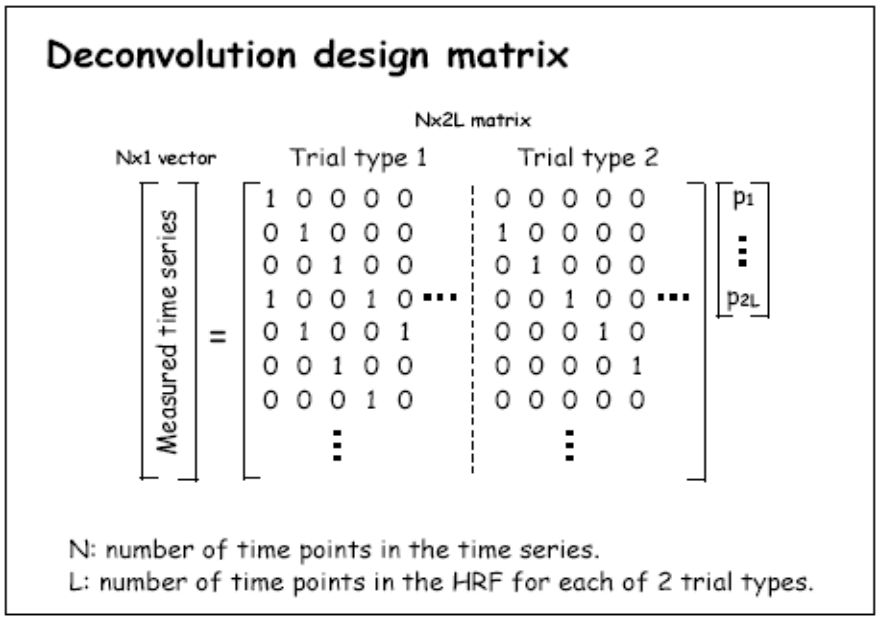
$$y(n) = \sum_{i=0}^{N} b_i \delta(n-i) + \varepsilon$$



Deconvolution Analysis based on FIR model

$$y = Xh$$





- instead of estimating one parameter per condition, the aim is to estimate the whole HRF seperately for each condition
- therefore, it can only done reliably when the number of conditions is low

HRF optimization

To solve, find vector *h* to satisfy

$$y = Xh$$

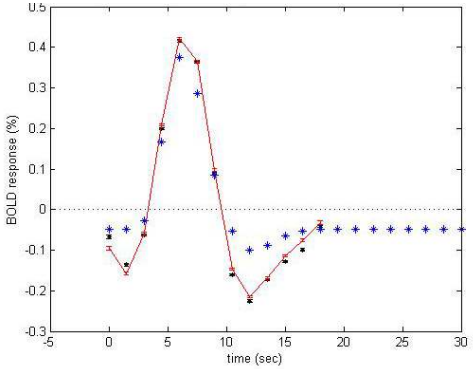
- h can be obtained via „deconvolution” analysis using a non-linear regression method:
  - start out with a canonical HRF, convolve it with the design matrix to get an estimated signal (model)
  - compare measured signal to model and calculate the least-squares error

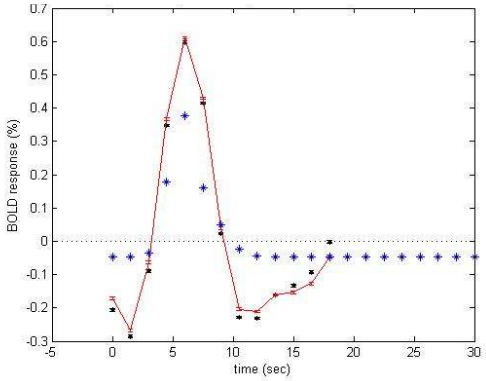
$$R^2 = \sum_{i=1}^{n} [y_i - f(x_i, \alpha_1, \alpha_2, \ldots, \alpha_n)]$$

  - change the parameters of the HRF to minimize the error

HRF can slightly differ between subjects and areas

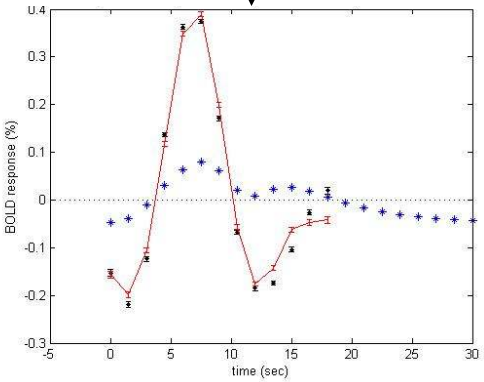
Subj 1 – V1





Subj 1 – V4

- measured signal
- fitted HRF

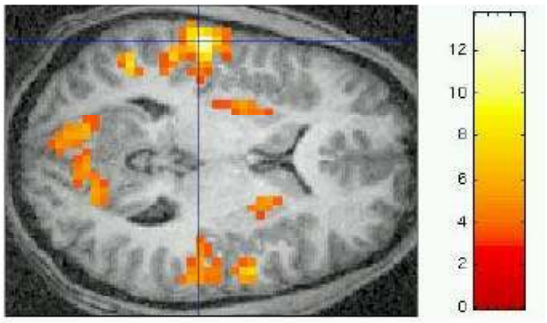


Subj 2 – V4

Why bother to estimate HRF anyway?

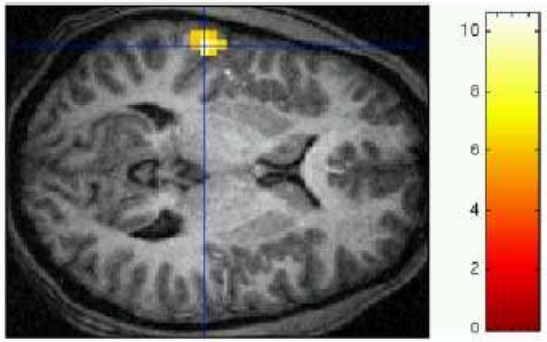
- better sensitivity → improved detection

GLM built using HRF estimate →



more sensible:
bilateral activation
in Heschel gyrus for
(sound-silence)

GLM built upon canonical HRF →

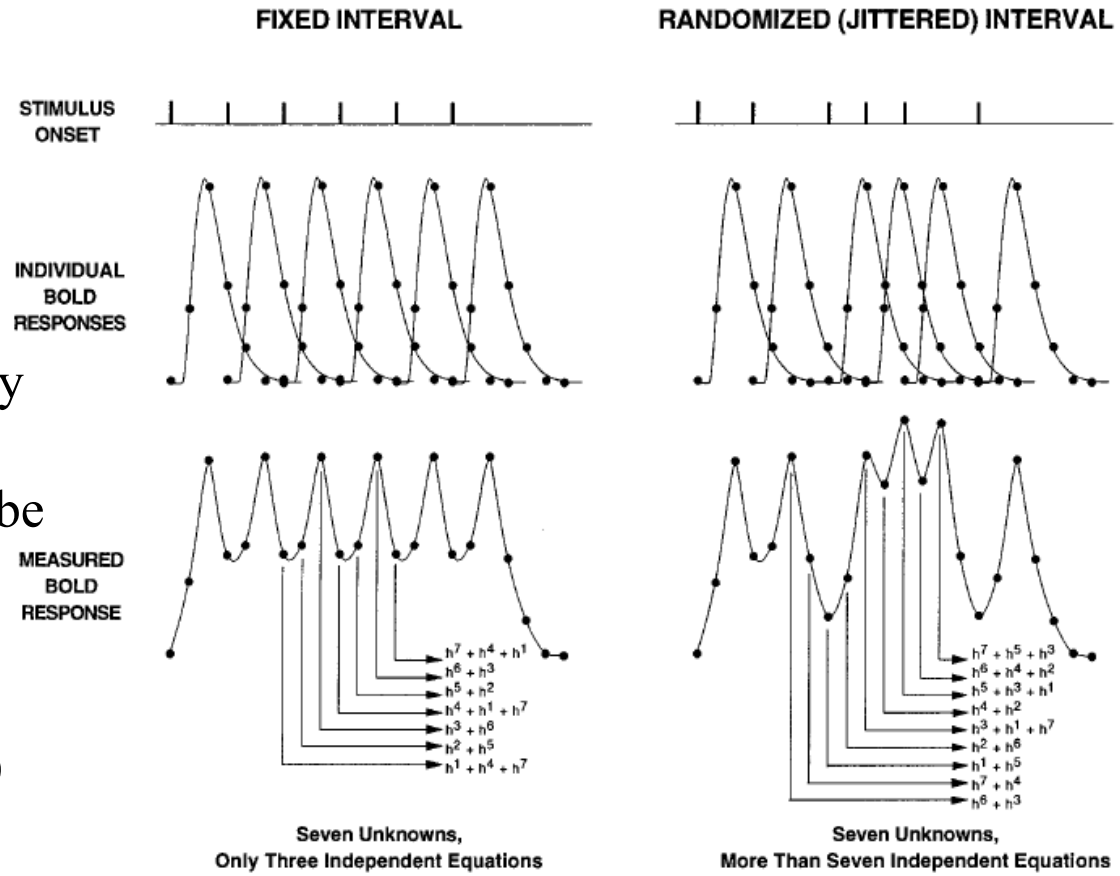


(Ciuciu et al., 2002, 1st Int. Symp. on Biological Imaging)

BUT in order to do so…

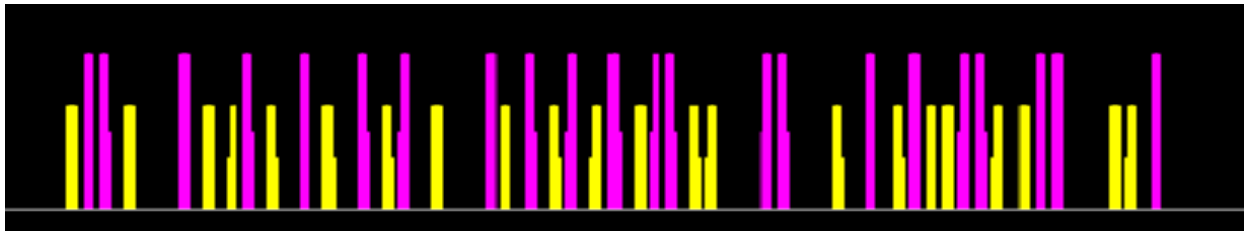
- reasonable SNR is needed
- the design needs to be efficient and random (i.e. jittered intervals and randomized event order) so that the event are linearly independent
- the design matrix needs to be invertible to solve for the parameters

(applies to all experiments)

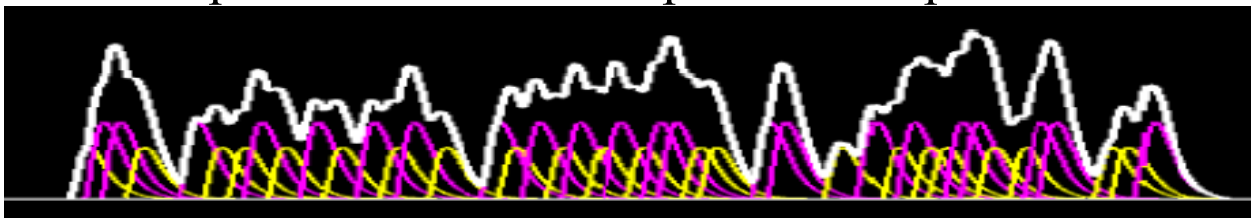


An example…

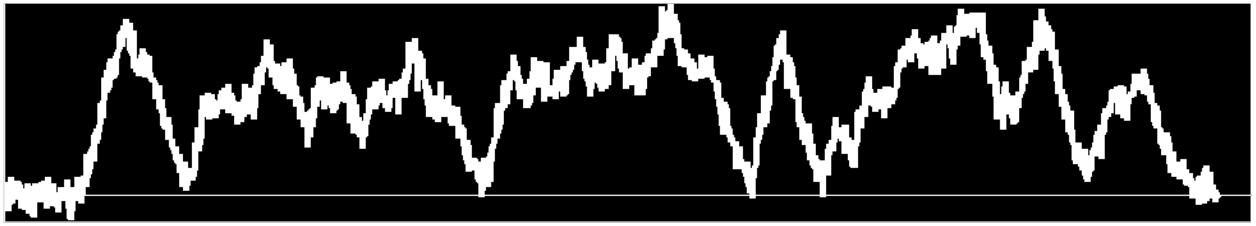
Event (stimulus) sequence



Model: separate and summed up BOLD responses



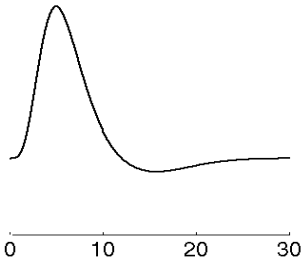
Measured BOLD signal

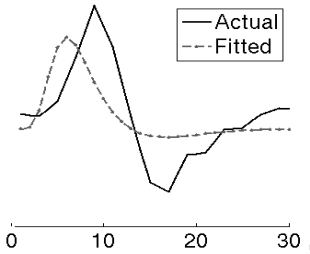


The ultimate goal is to model the data the best possible way

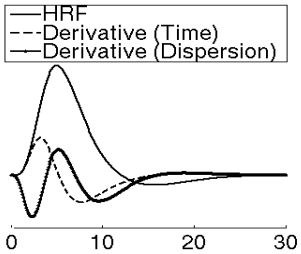
Basis Functions

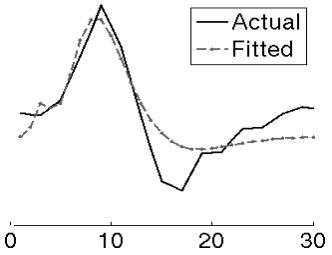
Single HRF



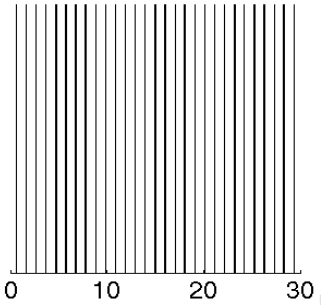


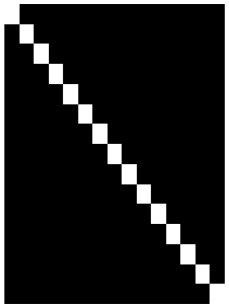
HRF + derivatives

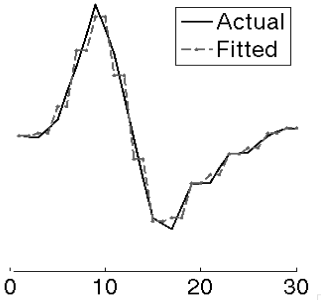




Finite Impulse Response (FIR)





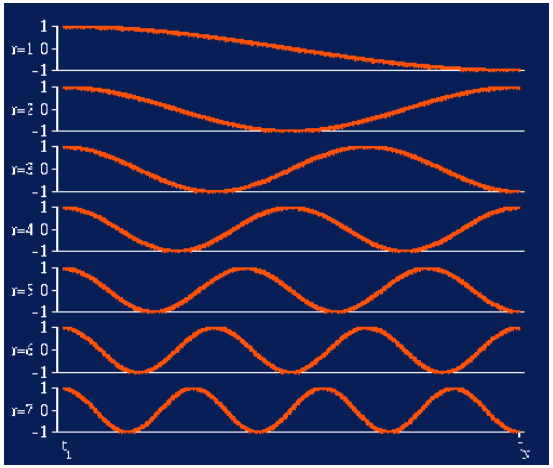


Time (s)

Modeling Noise - "Nuisance Variability"

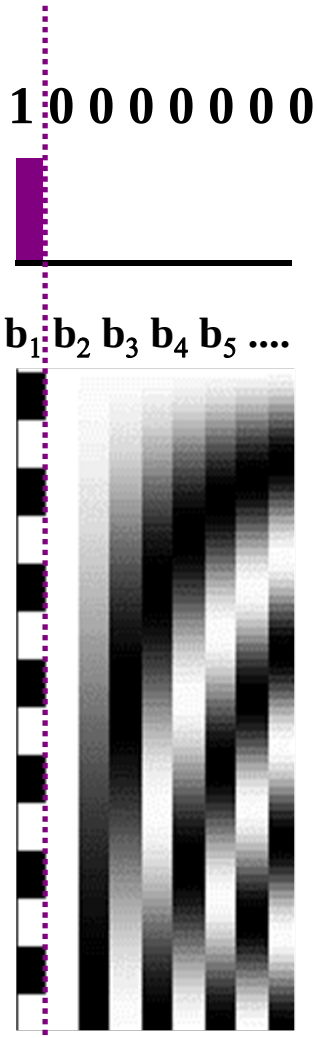
- if not modeled:
  - specificity decreases (due to underestimating variance and increasing the number of false positives)
- types:
  - drift (slow change):
    - can be linear or quadratic
    - denoising: discrete cosine transform (DCT)
  - autocorrelation:
    - fast, periodic autoregressive signals
    - elimination: AR(1): old + new noise

ARMA(1,1): AR + a series of independent white noise



DCT base functions

Parametric maps



F-test

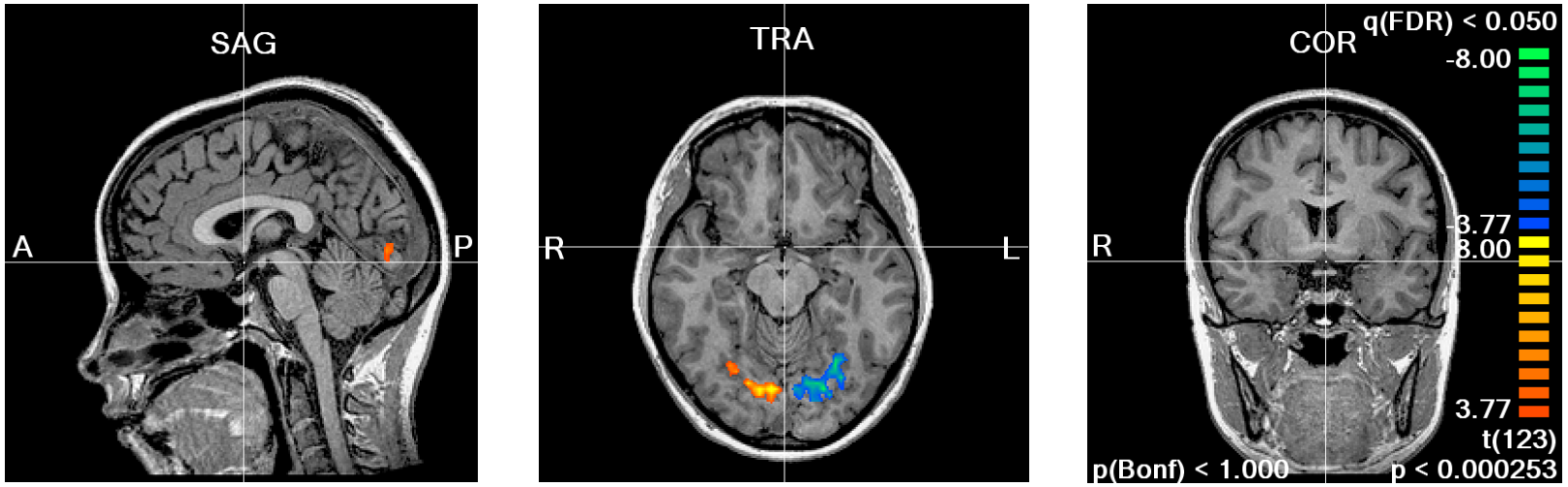
- compare the residuals with and without including one of the explanatory variables to see if it accounts for a statistically significant portion of the variance of the data. The ratio of the variance estimates follows the F distribution.

T-test

- define contrast (c) as a linear combination of parameter estimates and divide by their variance
  (e.g. c=1*b_1 + 0*b_2 + 0*b_3 +…)

T-test example

$c=1*b_1+ -1*b_2$



Experimental Design

- Block design
  - a sequence of longer periods of a fixed type of stimulation and rest intervals
  - simple, robust, high SNR
  - unnatural, rigid frame for doing experiments
- Event-related design (fast or slow)
  - similar to EEG experiments
  - requires more complex statistics
  - yields smaller SNR therefore requires more repetition
  - more flexible, natural experimental frame
  - event spacing needs to be jittered and event sequence randomized

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

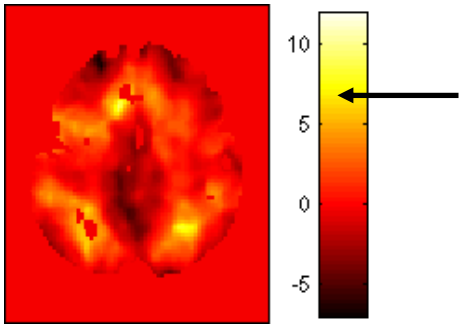
fMRI – Advanced Statistical Analysis

(fMRI – Haladó statisztikai elemzési módszerek)

VIKTOR GÁL, ÉVA BANKÓ

The Multiple Comparison Problem

- doing t-test for every voxel (~100.000) separately will hugely inflate the error-rate (i.e. the number of false positives)
- if α=0.05 $\Rightarrow$ 5,000 false positive!



Where is the significance threshold?

- therefore one needs to correct for this problem of multiple comparison:
  - Bonferroni correction
  - False Discovery Rate (FDR)
  - Familywise Error Rate (FWE)

Bonferroni correction

- if all voxels were independent of each other, than simply:

$$p_{\text{Bonf}} = p_{\text{uncorr}} / \text{N} \qquad \text{where N is the number of voxels}$$

- however, voxels are *not* independent (e.g. neighboring voxels show different pattern, drift affects all of them equally)
- thus, a very conservative correction
- we need to account for the dependency structure between the test statistics

Familywise Error-rate (FWE)

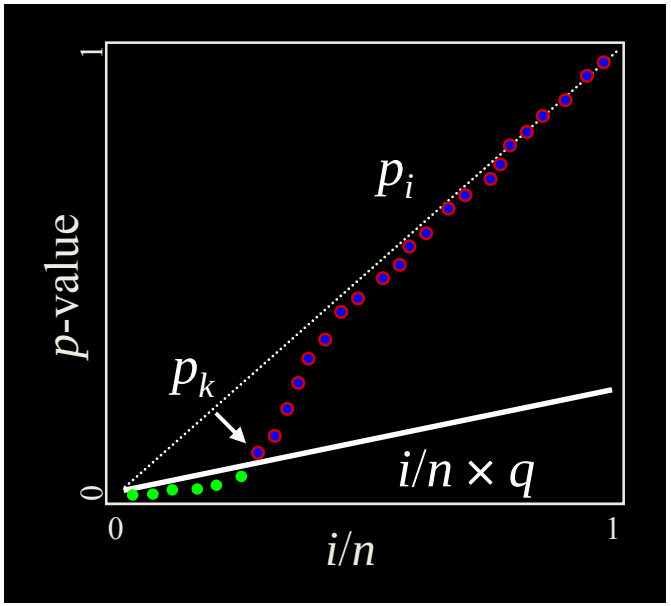
- controls the probability of making even one error (or more)

False Discovery Rate (FDR)

- FDR is the proportion of false discoveries among the discoveries (rejected hypothesis)
- to calculate: order the *p*-values $p_1 \le p_2 \le \ldots \le p_n$
- for a desired FDR level *q*:

  let $$k = \max\{i : p_i \le (i/n)q\}$$

  reject: $$H^0_{(1)}, H^0_{(2)}, \ldots, H^0_{(k)}$$



- If no such *k* exists reject none (i.e. nothing is significant)

Region-of-Interest (ROI) Analysis

… another way out without statistical tweaks

- limit the analysis to a set of voxels comprising an area (i.e. region of interest) and then average across them to get a parameter estimate
- dimension reduction: the number of predefined ROIs are usually <10
- voxels need to be selected individually, based on an independent contrast (e.g. localizer) to insure there is no manipulation of chosen voxels showing the desired effect
- desirable if the location of the ROI has high individual variance
- how to select voxels (for more details see Tracey et al., 2008, NeuroImage):
  - select all active voxels in a given independent contrast individually (what is active? → ~$p_{uncorrected}<10^{-4}$)
  - select the peak activity (i.e. most active voxel) in the cluster and include all voxels in a volume (sphere, cube) around it

Caveats of classical parametric statistics in fMRI

- fMRI voxels ~ dense 3D matrix of low quality EEG electrodes
- Distribution of error, parameters?
- Time and spatial interdependence -> degrees of freedom (DOF)?
- Correction for multiple univariate stats

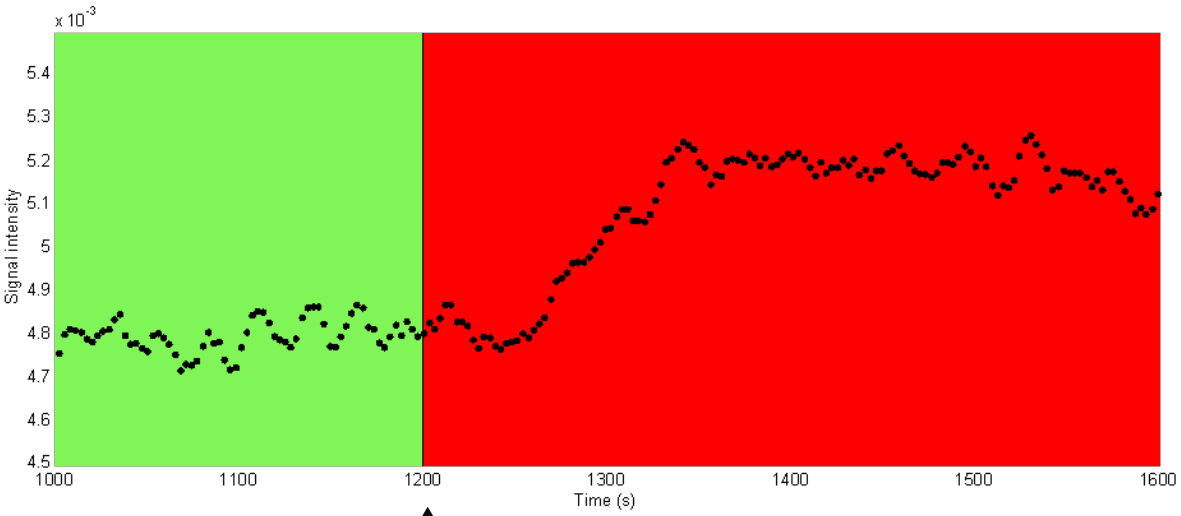
Solution:

- Nonparametric (resampling, bootstrap) methods
- MVPA approach; MVPA & nonparametric analysis

Validation?

Statistical assumptions (fixed-effect analysis):

Acquired datapoints are independent in time



Stimulation

What is our degree of freedom?

- Theoretically: ~ Number of datapoints – Number of predictors
- Can be adjusted by analyzing/modelling of nonsphericity
  - autocorrelation structure
  - AR(1) , ARMA(1,1): AR + white noise
  - drift correction, high pass filtering
  - limited validity

Still it is a question:

- whether an experiment consisting of 1 trial (stimulus) and 1000 data points (very long baseline) is equivalent to an experiment consisting of 500 trials with 2 data points?

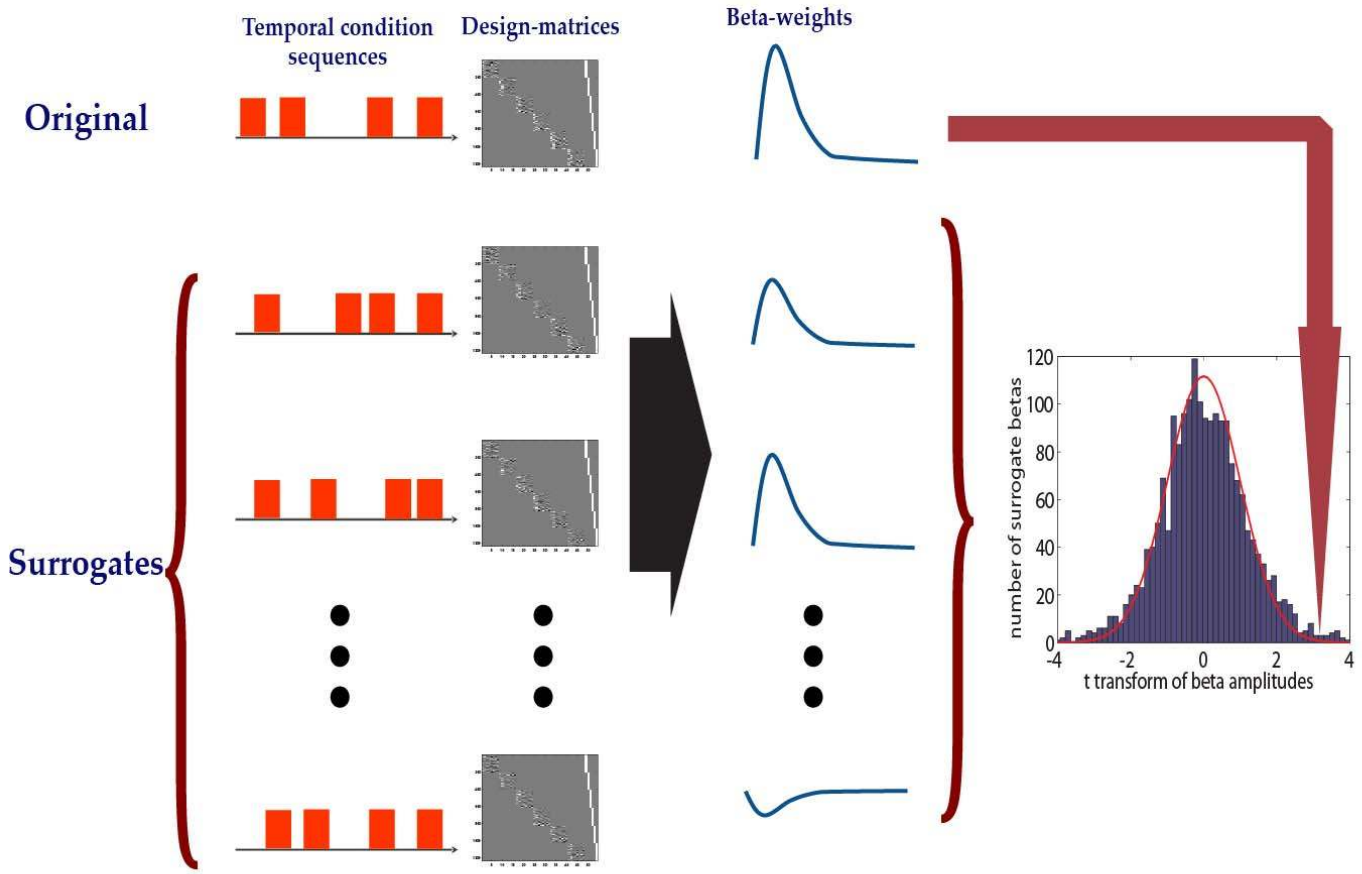
Acquired images of a response to a stimulus are not independent!

Nonparametric methods: sampling statistics

- Generation of surrogate data
  - Surrogates are to be „similar” to the original in any relevant aspect
  - Surrogate stats can be computed via
    - Experiments without stimulation
    - Reshuffling (or decomposing and reshuffling) data points
    - Random predictor time-courses in the design matrix
- Sampling statistics
  - Statistical characterization of the original data and the surrogates
- Decision making
  - Based on rank order of the original

Examples: randomization test, bootstrapping

Biomedical Imaging: fMRI – Advanced Statistical Analysis



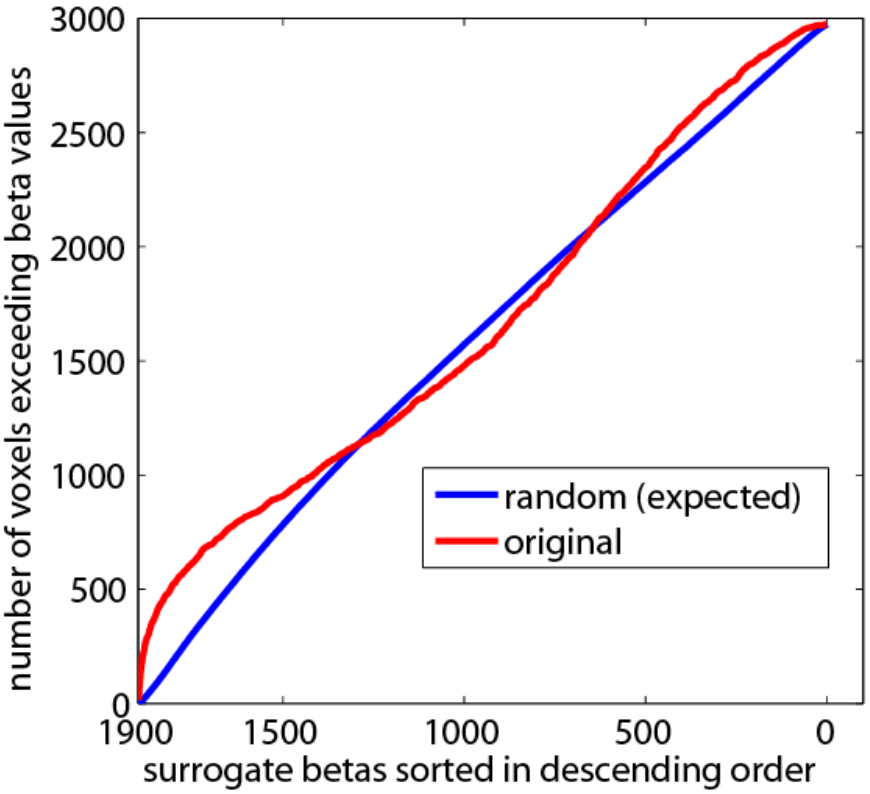
Recipe

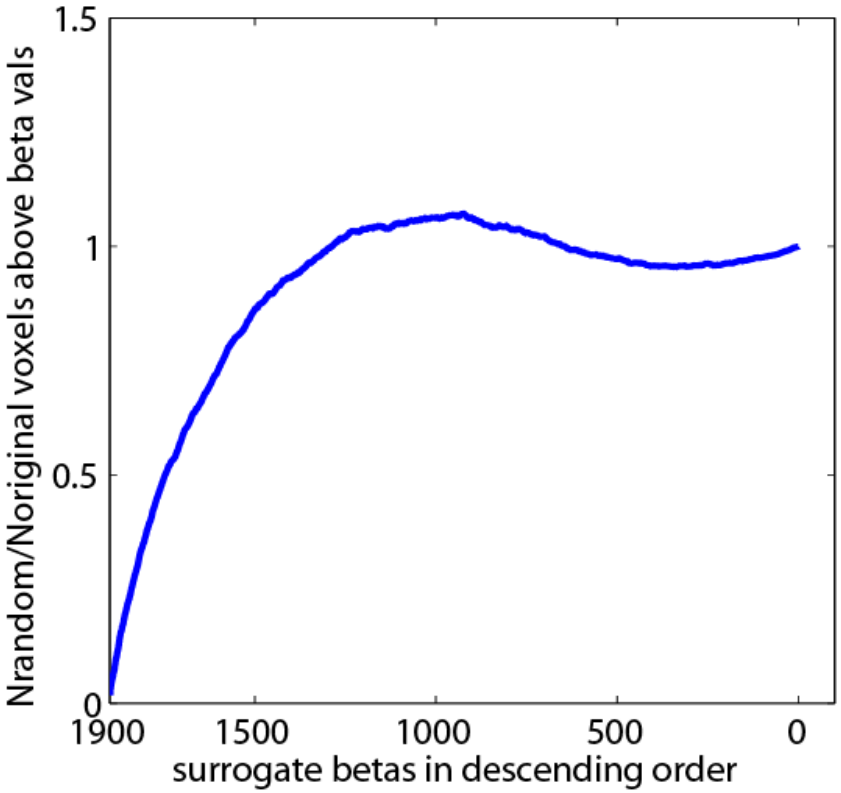
- pseudo-randomize the design matrix (DM)
- estimate parameters from false DM
- repeating these steps we can obtain a parameter distribution centered around 0, which reflect random effects
- compare p estimated from the actual DM to this distribution
- a similar procedure can be used to statistically evaluate the difference between the parameter estimates of two condition
- The same distributions enable an effective correction for multiple comparisons
  - Count the average number of voxels above different threshold with false DM and compare it to the values based on the original DM

„Bootstrap” FDR

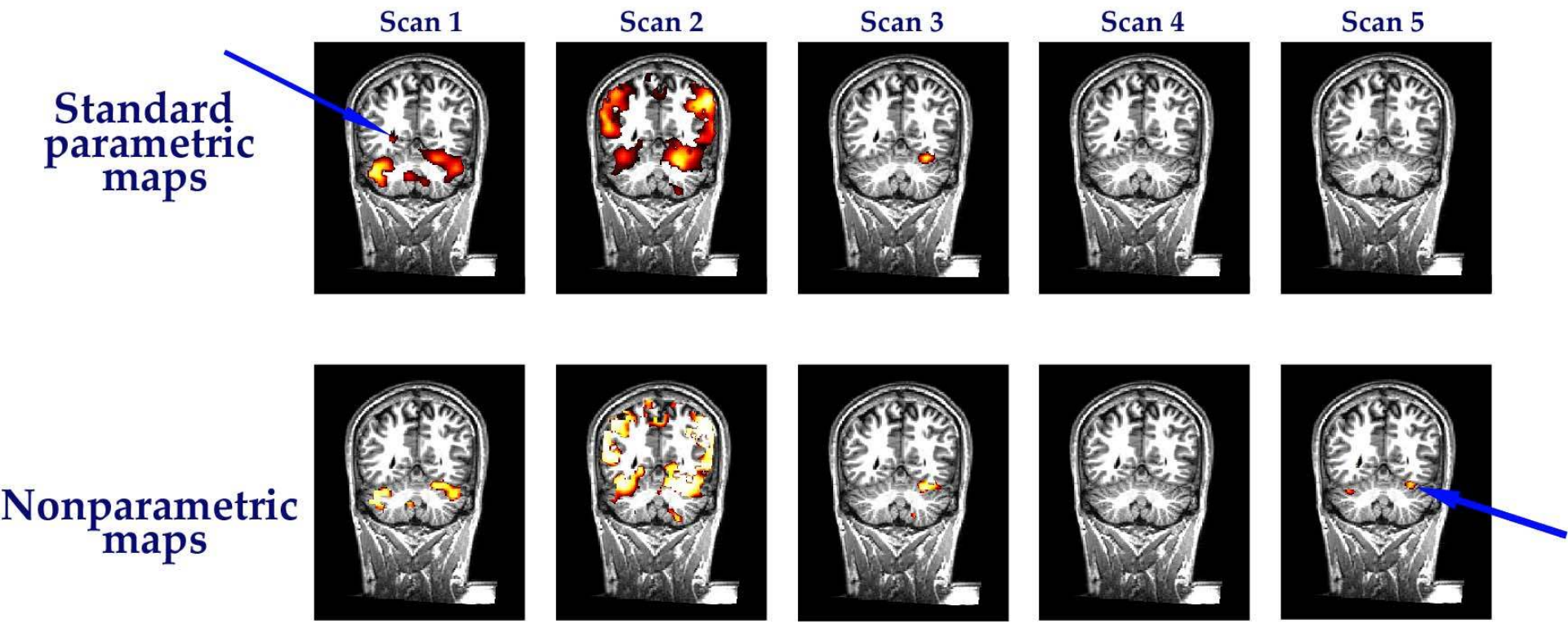
p_voxel	N. active voxels: original	Average n. active voxels: random	FDR:orig/rand ratio
0.0005	241	1.01	0.004190871
0.001	341	2.55	0.007478006
0.0015	408	4.17	0.010220588
0.002	470	6.3	0.013404255
0.0025	527	8.31	0.015768501
0.003	569	10.32	0.018137083
0.0035	610	12.23	0.02004918
0.004	642	14.19	0.022102804
0.0045	660	15.74	0.023848485
0.005	680	17.27	0.025397059
0.0055	712	18.97	0.026643258

„Bootstrap” FDR



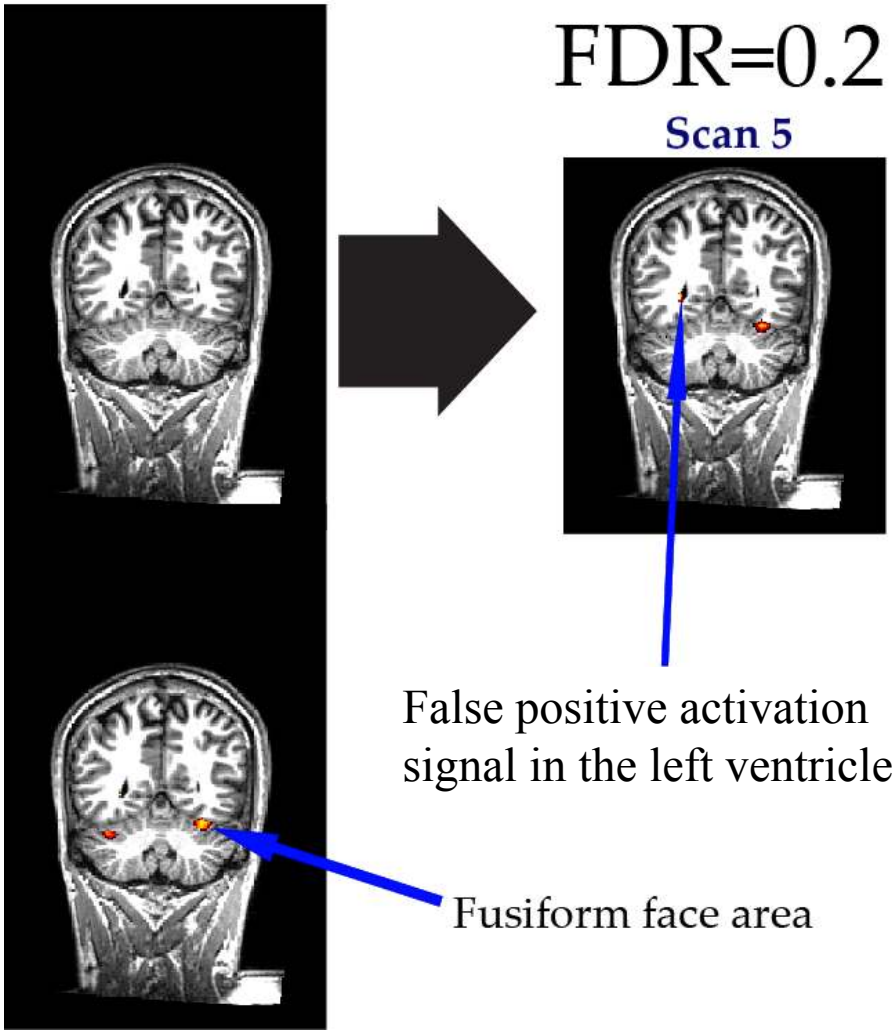


Validation example: activation of the fusiform area (event related design)



Validation example

Standard parametric map



Nonparametric map

Univariant-multivariant analysis in fMRI

Goal

- Is there any effect? Hypothesis testing
- What kind of effect?
- Localization of effect

Complexity of the multi-dimensional signal-processing:

- Separately, one dimension at a time:
  - Traditional: voxelwise, independent
  - Selecting of areas, groups of voxels (ROI: POI, VOI) and averaging
    - S/N may increase
    - correction for multiple univariate comparisons is less important
- Parallel multidimensional:
  - Spatial or spatial-temporal patterns:
    - **Multi-voxel pattern analysis (MVPA)**
    - Multivariate Decomposition: ICA, PICA etc.

Multi-voxel Pattern Analysis (MVPA)
… potentials and requirements

General Purpose:

- ROI based analysis: hypothesis testing
- Search-light: localization

Block design, sparse event-related design

- Training & test based classifiers
  - single event based prediction

Fast event related (& block + sparse ER) design

- Parametric or non-parametric significance estimation of multi-dimensional **distance (**based on standard GLM results)

MVPA details

- Multivariant analysis: decoding („mind reading”)
- Classification of activity patterns:
  - Feature selection
  - Normalization
  - Choosing classification algorithm
  - Optimization-training

•Test, performance estimation

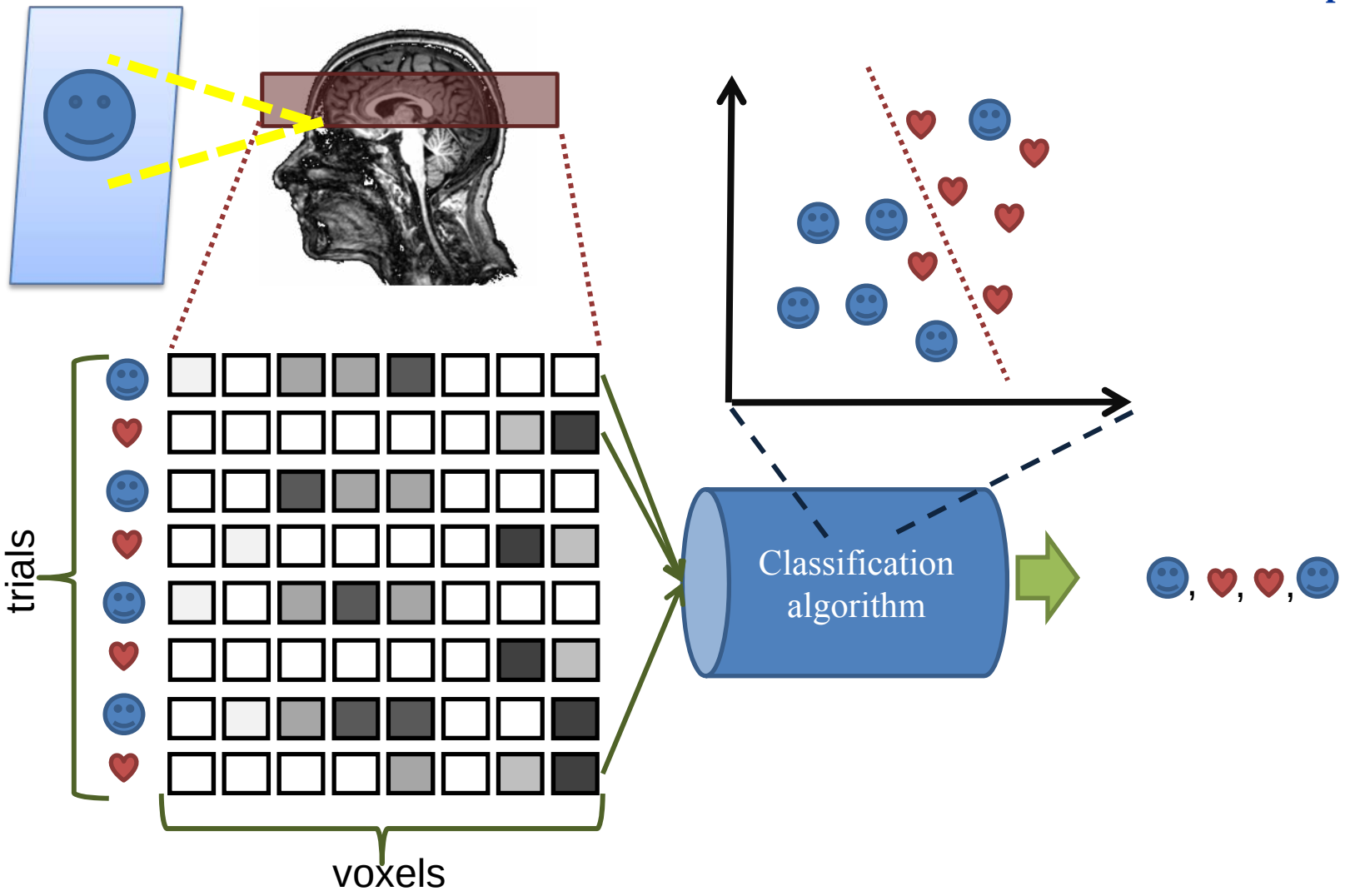
•Validation of efficiency

  •Parametric model

  •Bootstrap, resampling

•Interpretation of results

Biomedical Imaging: fMRI – Advanced Statistical Analysis



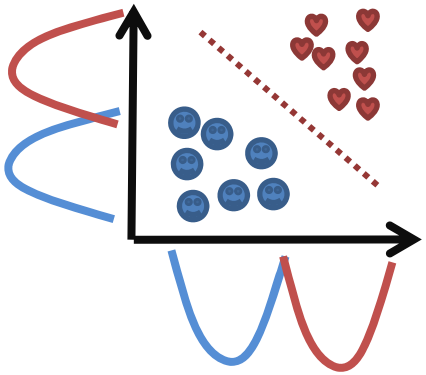
Feature selection

- Dimension (number of voxels) should be reduced
  - To exclude irrelevant and noisy voxels
  - High dimension and small sample size undermines the classification algorithm's
    - Performance
    - Generalization capacity
- Methods:
  - VOI
  - Exlusion of noisy voxels (e.g. (based on variance)
  - Voxelwise univariate statistics (ANOVA, t-test): ordering voxels
- Combinatorial test of MVPA on groups of voxel
  - Full combinatorial, Genetic algorithm etc.

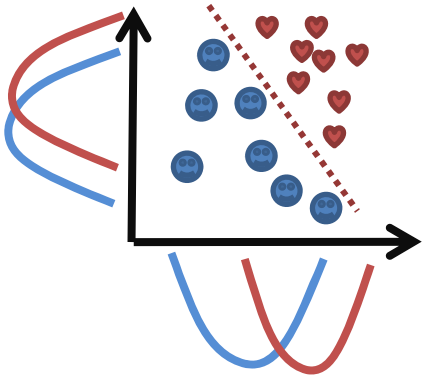
Classifiers (supervised learning)

- Linear
  - Generative models (modeling conditional density functions): fast, non-iterative algorithms
    - Naive Bayes
    - Linear discriminant
    - Mahalanobis distance
  - Discriminative models (slow, iterative optimization)
    - Logistic regression
    - Linear SVM
- Non-linear (interpretation difficulties)
  - SVM
  - Multi-layer neural networks

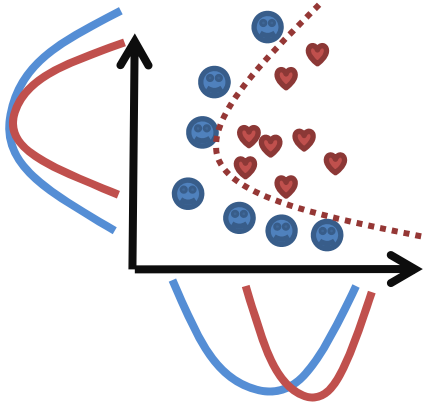
Separability of the activity vectors



Univariate separable

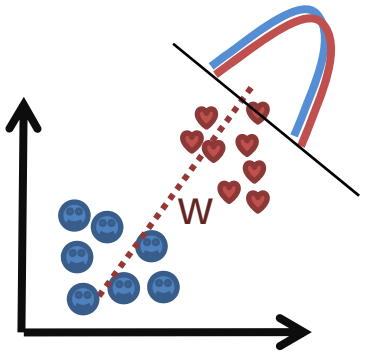


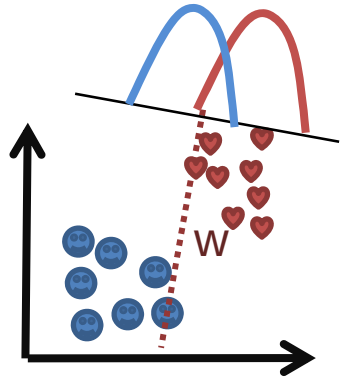
Linearly separable



Linearly not separable

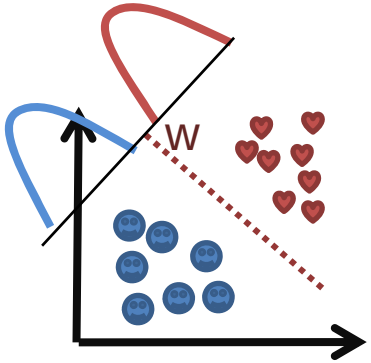
Fisher linear discriminant analysis





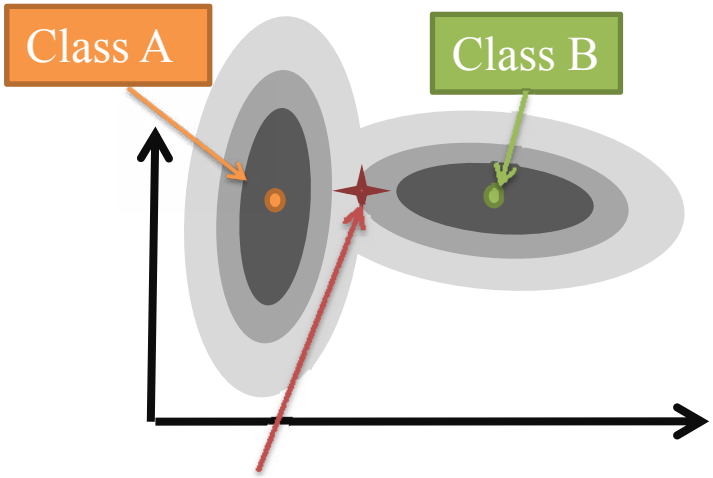
maximize

$$J_{Fisher}(w) = \frac{\text{Between class variance}}{\text{Within class variance}}$$



Mahalanobis distance

- Classify according to distance from class mean
- Takes non-sphericity into account

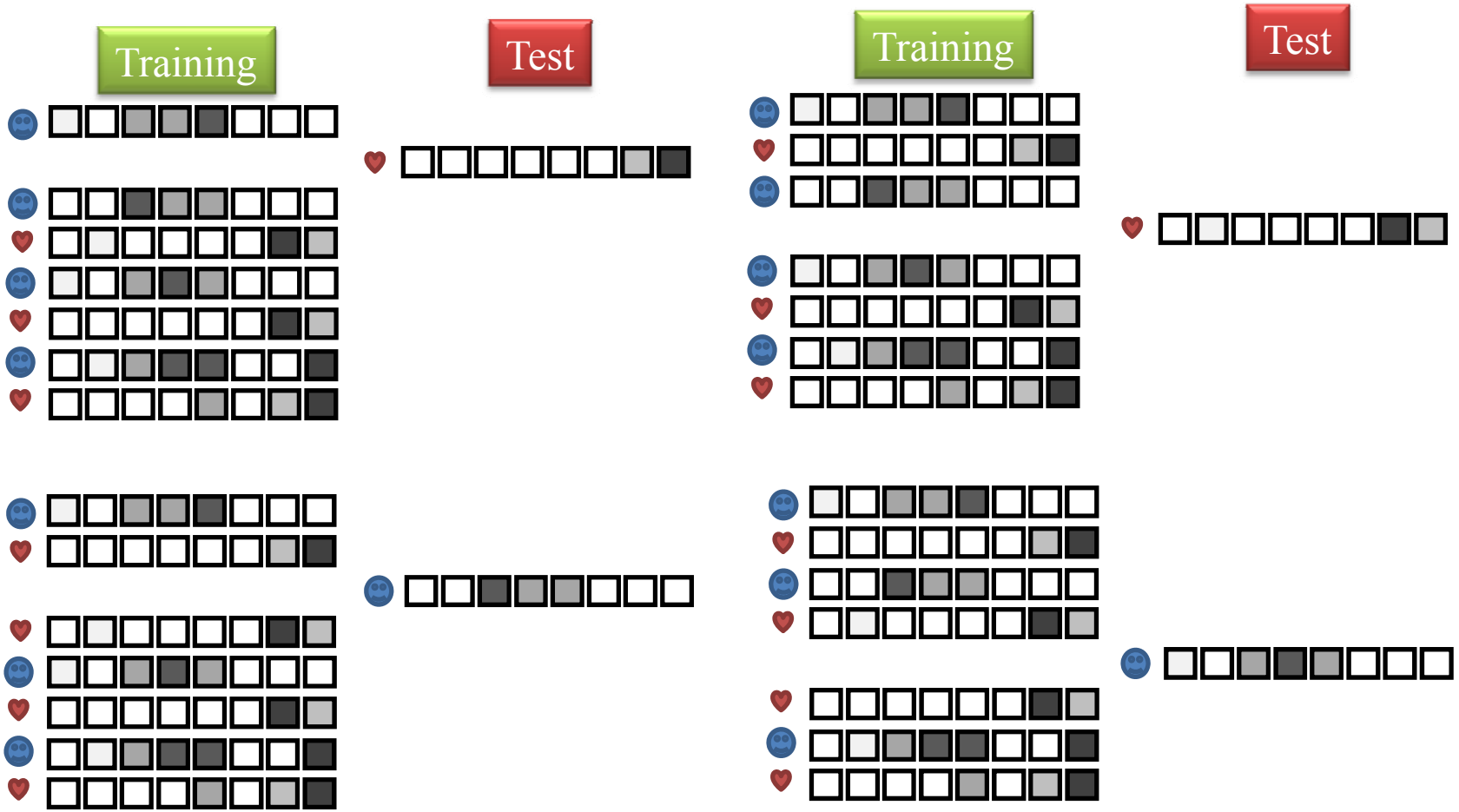


Test vector belongs to
•Class A according to euclidean distance
•Class B according to Mahalanobis distance

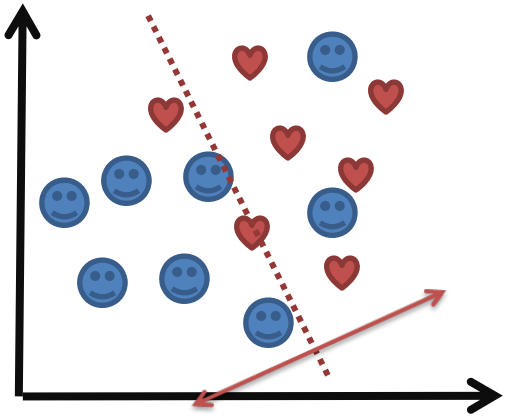
Interpretation of the results

- Linear
  - In scale invariant case, weights of the discriminator can inform about the importance of the voxels separately
  - Patterns can be interpreted and visualized
- Non-linear
  - Difficulties with decoding
  - Different combination of dimensions (voxel subgroups) can be evaluated
- Interpretation of performance
  - Leave-one-out
  - Leave-some out: training-test set
    - Average- variance
  - ROC curve
  - Resampling statistics

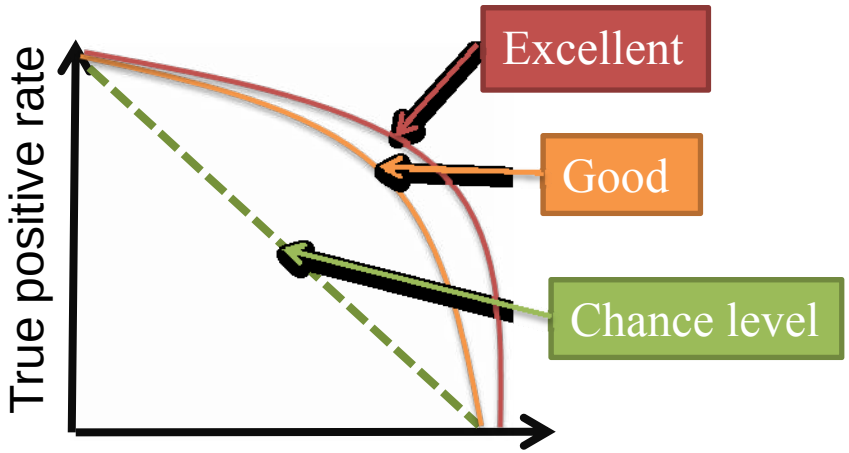
Leave-one-out



ROC curve

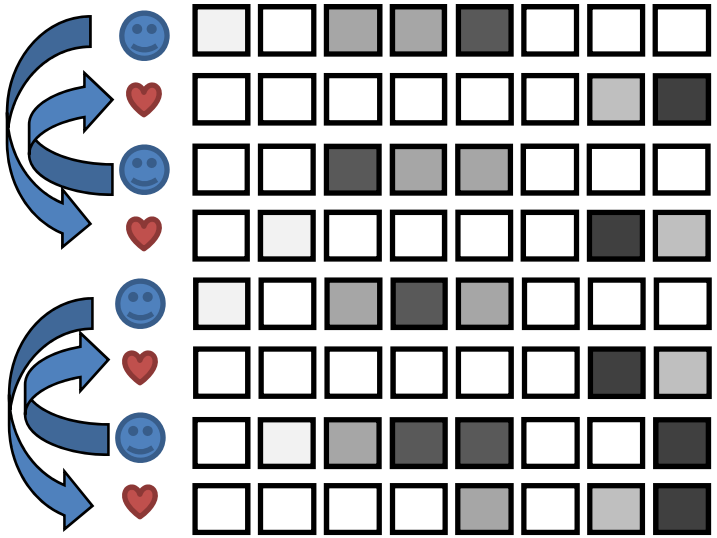


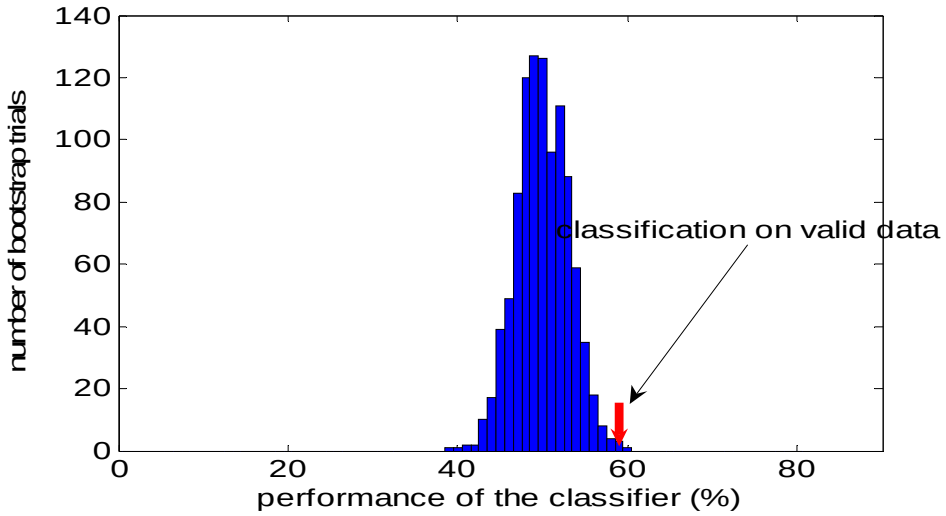
Hyperplane *w* is defined,
Move threshold bias
from min to max



Validation: resampling

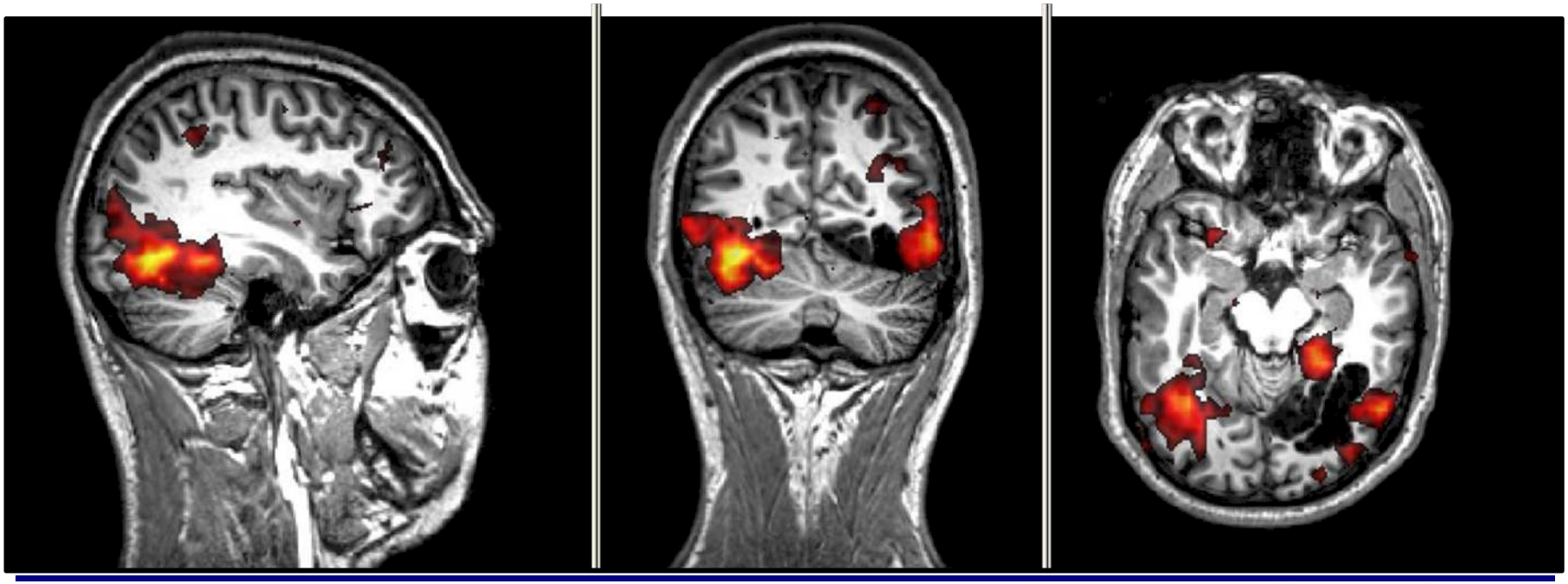
- Shuffling labels on training set
- Measuring performance
- Repetition (~1000) times



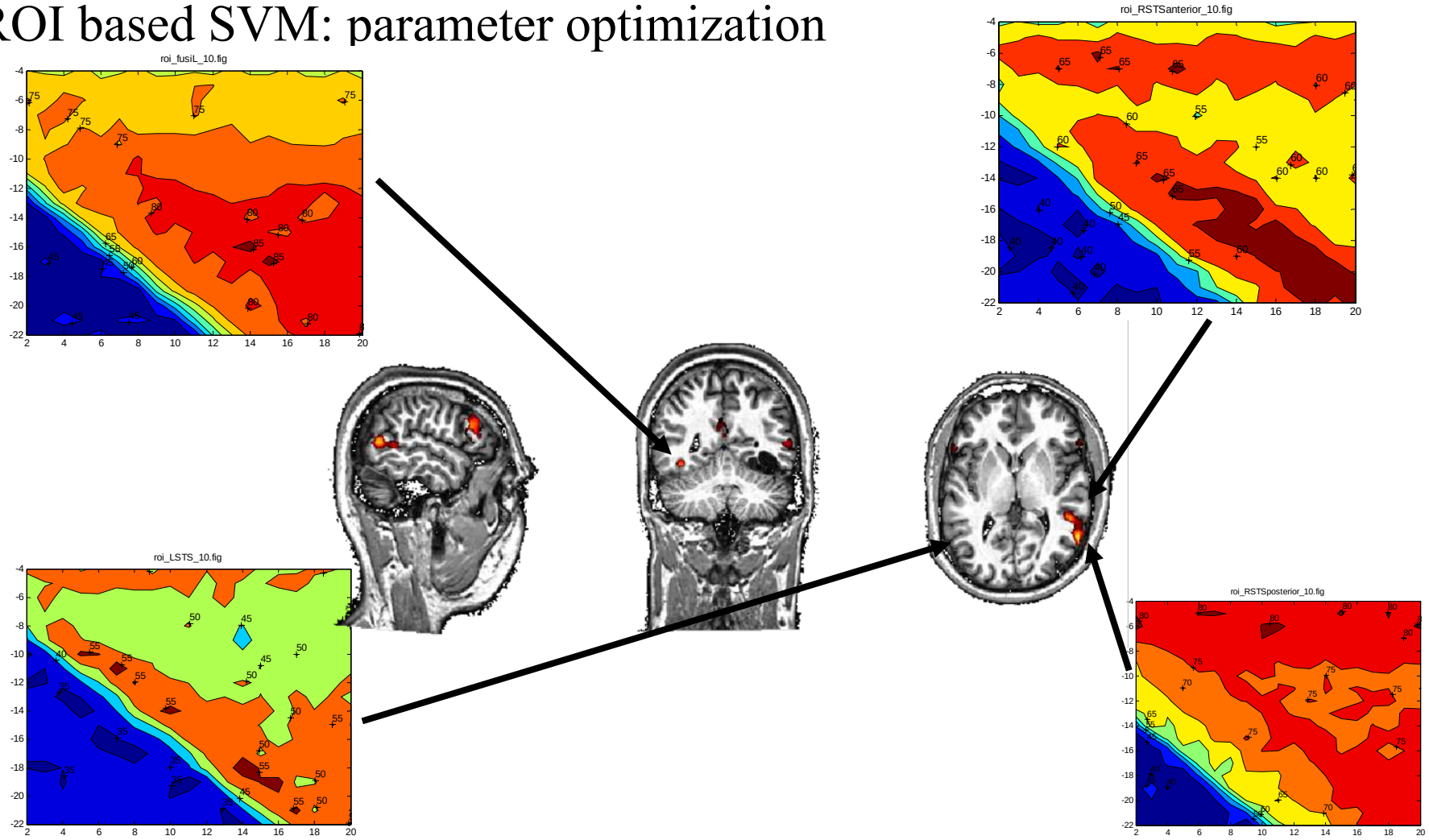


Search-light classification, linear discriminant analysis

- At each voxel 3X3 neighbourhood
- Leave-some trials out 10X
- Average performance: 90% at maxima



ROI based SVM: parameter optimization



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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

fMRI – Neuroscience Applications

(fMRI alkalmazása a kutatásban)

ÉVA BANKÓ, ISTVÁN KÓBOR,
ZOLTÁN VIDNYÁNSZKY

Important Tool to Investigate Brain Function

- Sensory Processing
  - early level
  - higher-order
- Neural Plasticity
  - short-term plasticity
  - long-term cortical reorganization
  - developmental plasticity
- Cognitive Function
  - attentional network
  - decision making
  - memory

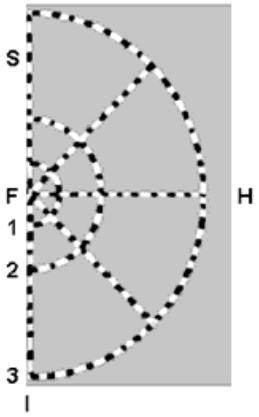
Sensory Processing

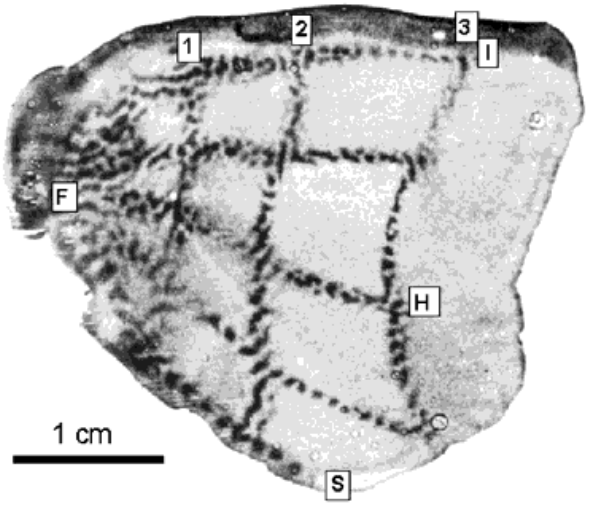
Retinotopical Mapping

Aim is to separate early and mid-level visual areas

Visual areas in the brain are defined by

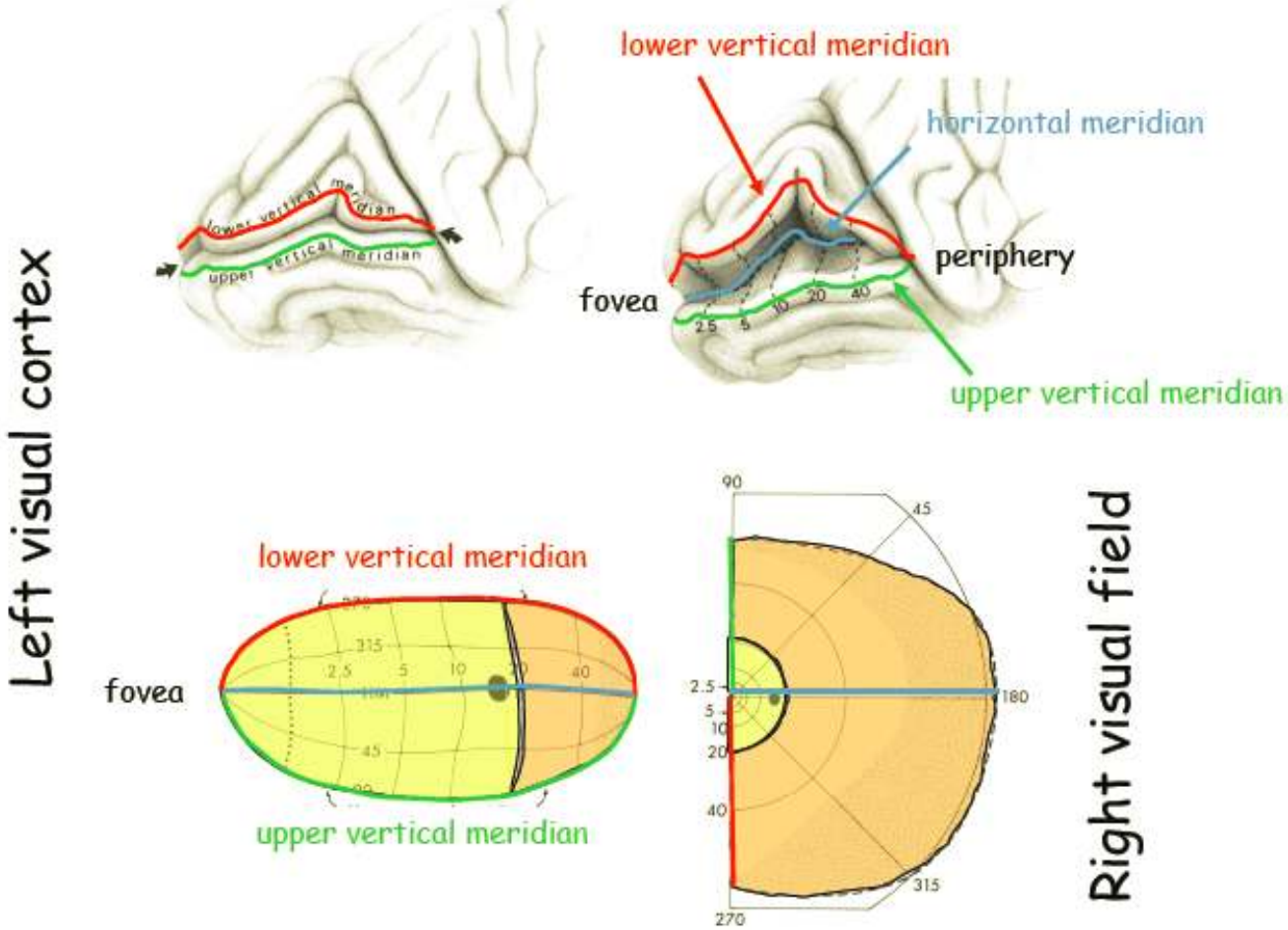
- Physiology
- Cellular architecture
- Connections to other areas
- **Topographical representation of the world**





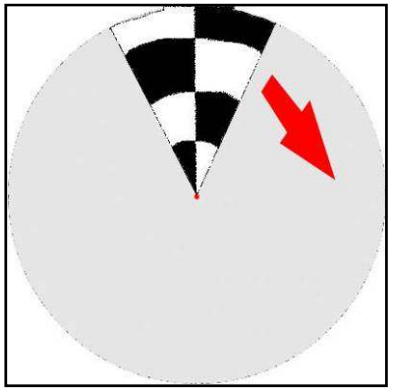
Neural representation of the stimulus in the primary visual cortex of a macaque monkey (Tootell et al. 1988, J Neurosci).

Visual field representation in human primary visual cortex (V1)

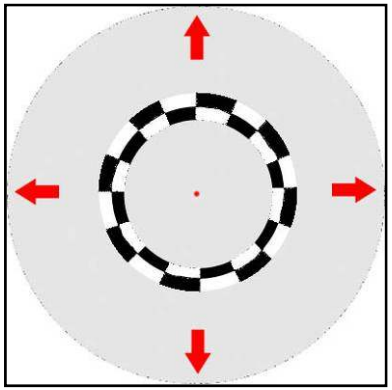


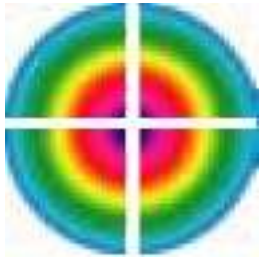
Protocol for Retinotopy

- Phase reversing checkerboard stimulus for strong excitation
- Aim is to probe the entire visual field:
  - Rotating wedge to get information about visual field quadrants
  - Contracting-expanding ring to get information about eccentricity



CW/CCW rotating wedge



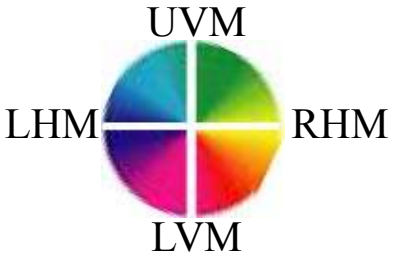


Contracting/expanding ring

Defining visual areas on flattened cortex

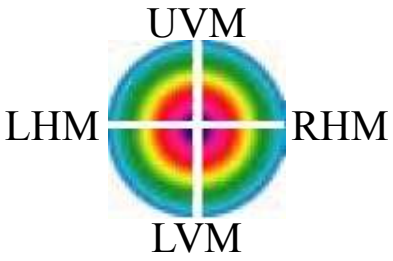
Phase map

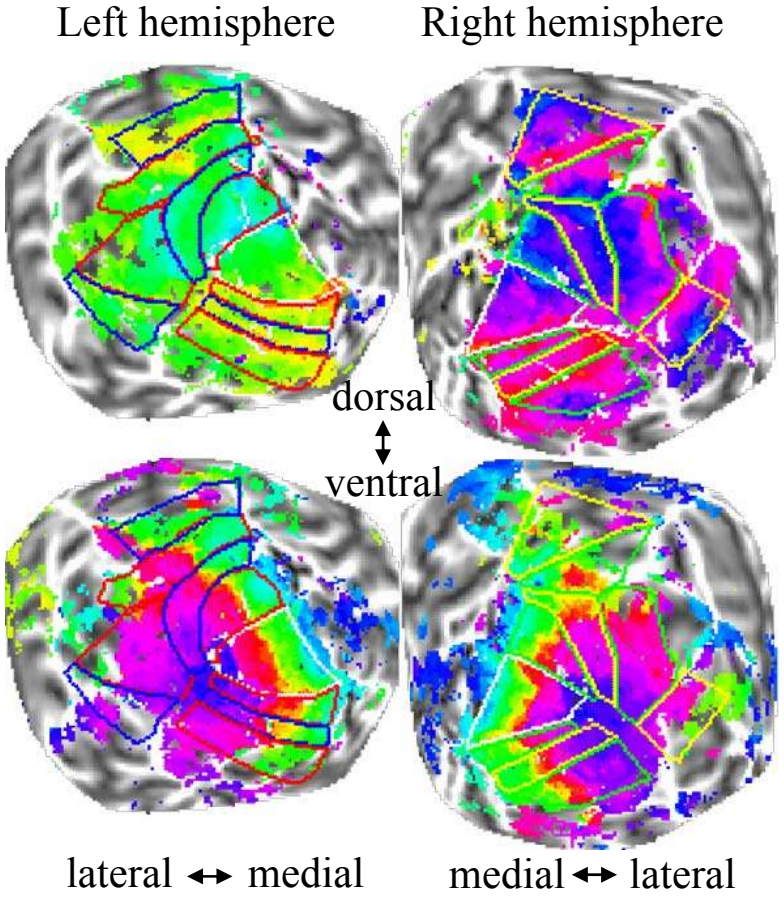
- Phase reversal delineates areas



Eccentricity map

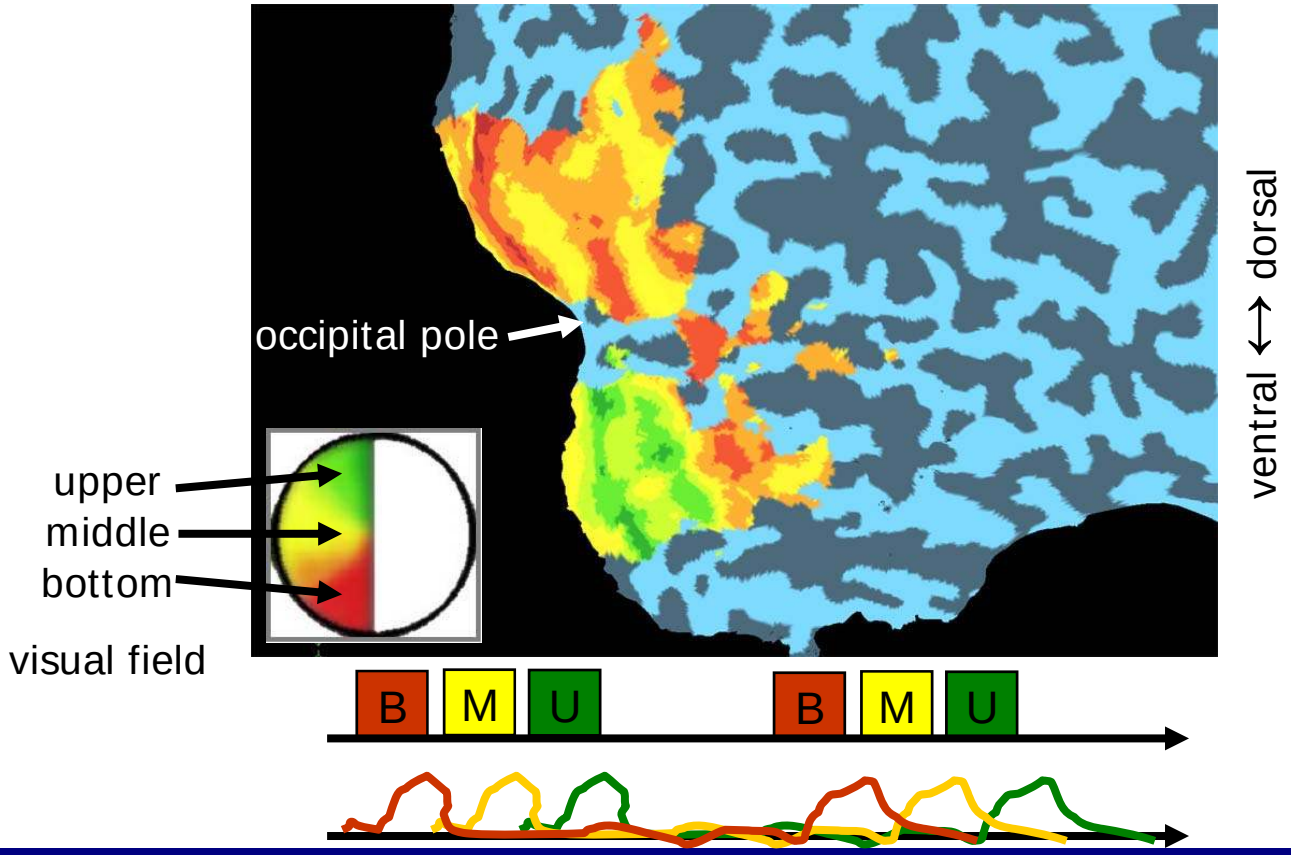
- Tells about foveal and peripheral representation of each area



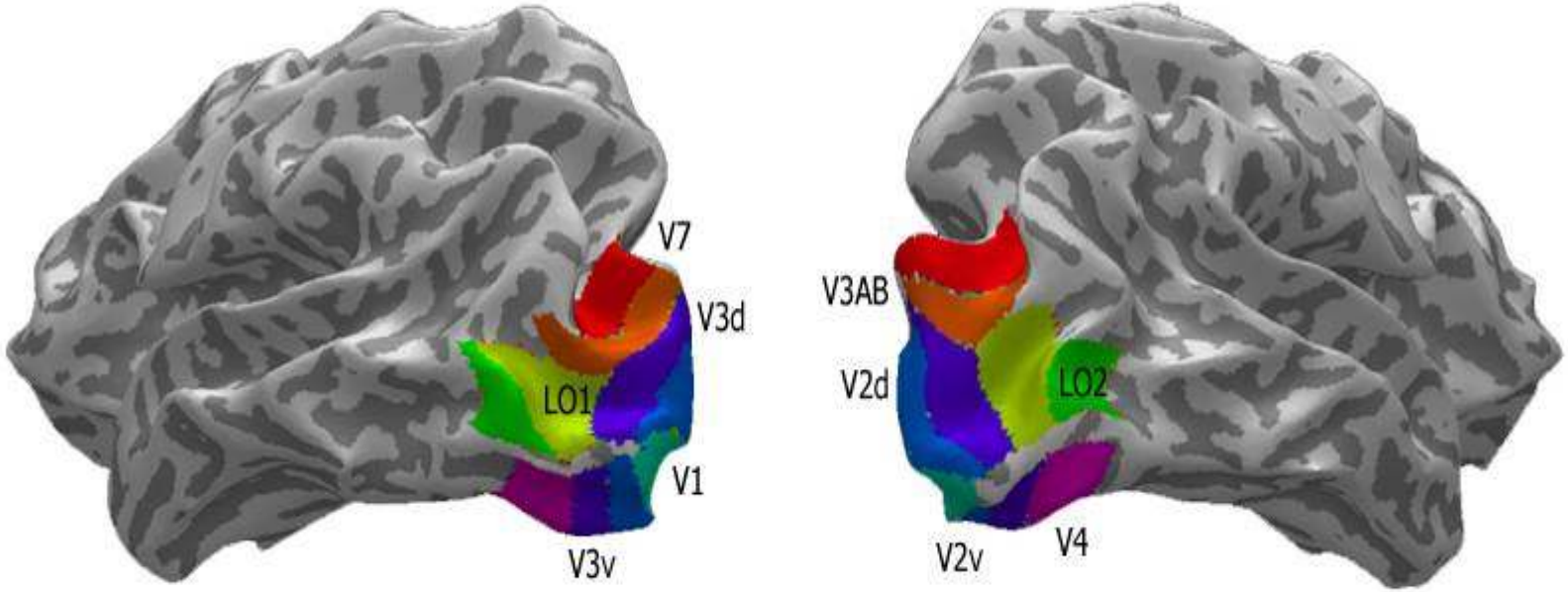


Retinotopy Demo

Flattened right hemisphere, cut through the calcarine sulcus



- As a result the voxels are assigned to areas, so the activation pattern of each area in a specific experimental design can be studied separately.

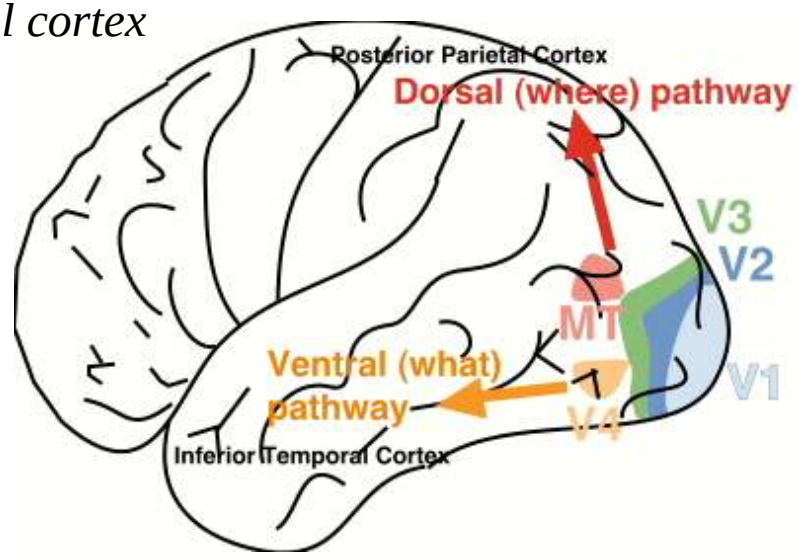


- Topographic mapping can also be done in somatosensory and auditory cortices.

Category-specific higher-order cortical areas

There are two visual processing streams existing in the cortex for processing different visual percepts:

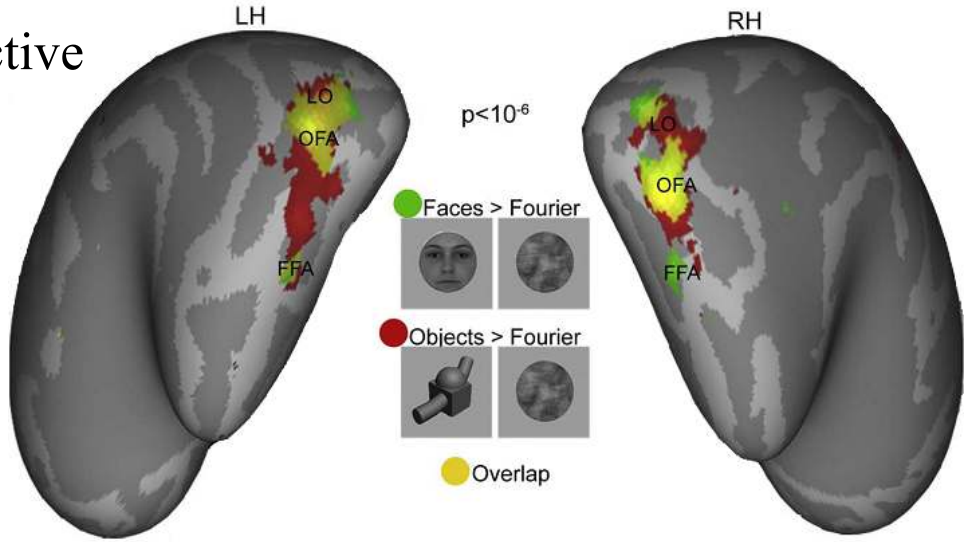
- **Ventral ("what") pathway** – enables the visual identification of objects
  - main input from "slow and detailed" parvo system of LGN
  - ends in *object-selective inferior temporal cortex*
- **Dorsal ("where") pathway** – spatial perception, visual location of objects
  - main input from "quick and dirty" magno system of LGN
  - ends in *posterior parietal cortex, comprises motion selective area MT+*



(Mischkin & Ungerleider 1983, Trends Neurosci)

Functional Localizers

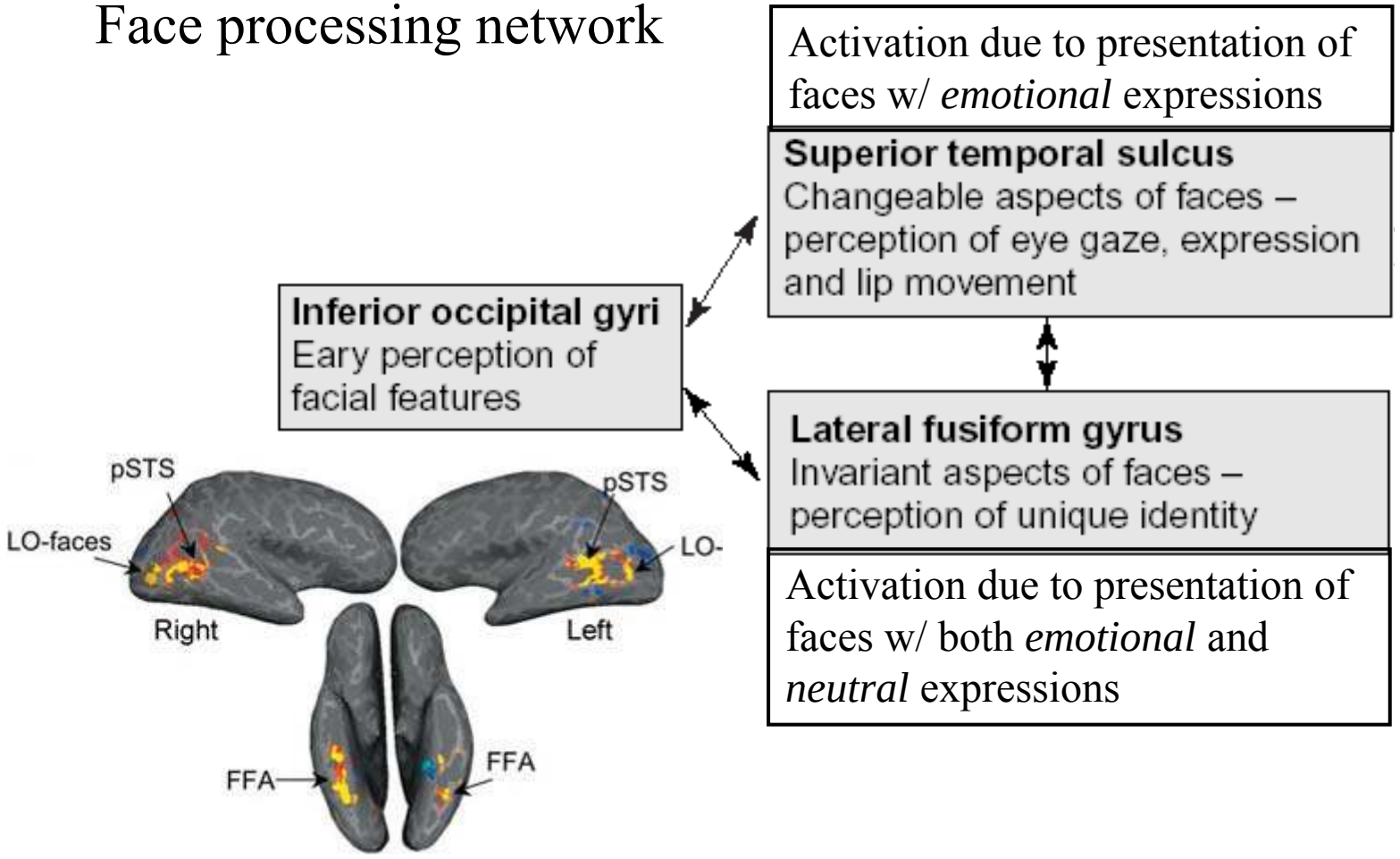
- Higher-order cortical areas lacking topographical organization but being category-specific can still be determined based on functional contrasts
  - E.g. ***Face-localizer***: probing the selectivity of object-selective inferotemporal cortex using the contrast of non-sense objects and faces



LO: Lateral Occipital Complex
OFA: Occipital Face Area
FFA: Fusiform Face Area

(Kovács et al. 2008, Neuroimage)

Face processing network



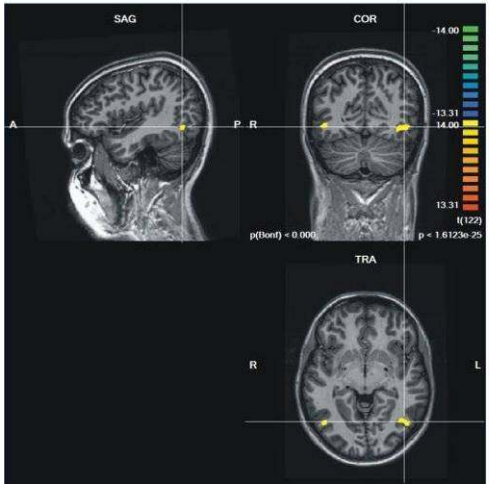
Mainly the posterior part of STS (pSTS)

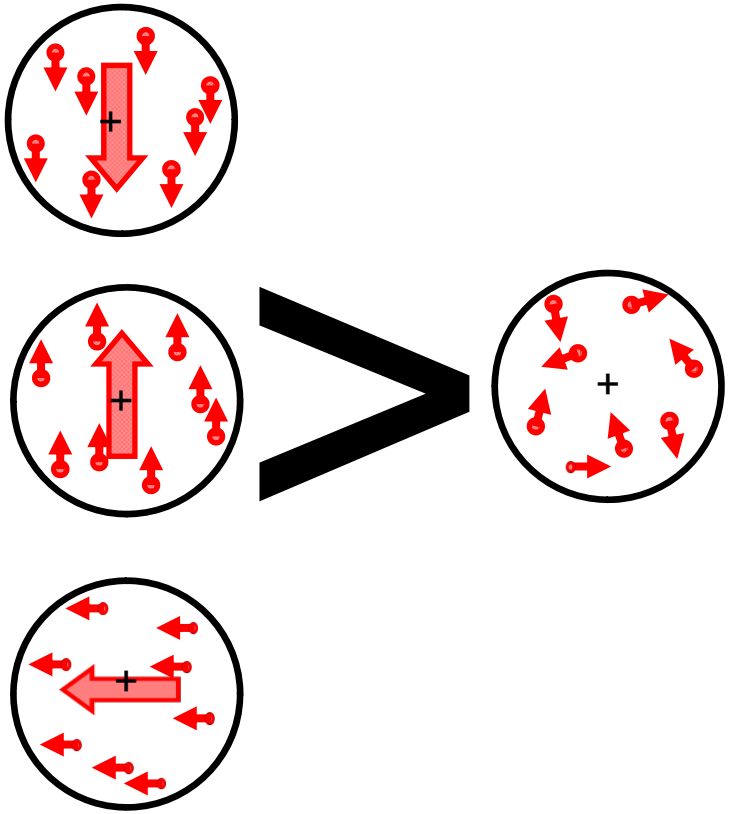
i.e. Fusiform Face Area, strongly right lateralized

(Grill-Spector et al, 2004, Nature Neurosci) (Haxby et al, 2000, Trends Cog Sci)

– ***hMT+ (V5) localizer***: probing the motion-selectivity of the dorsal visual pathway

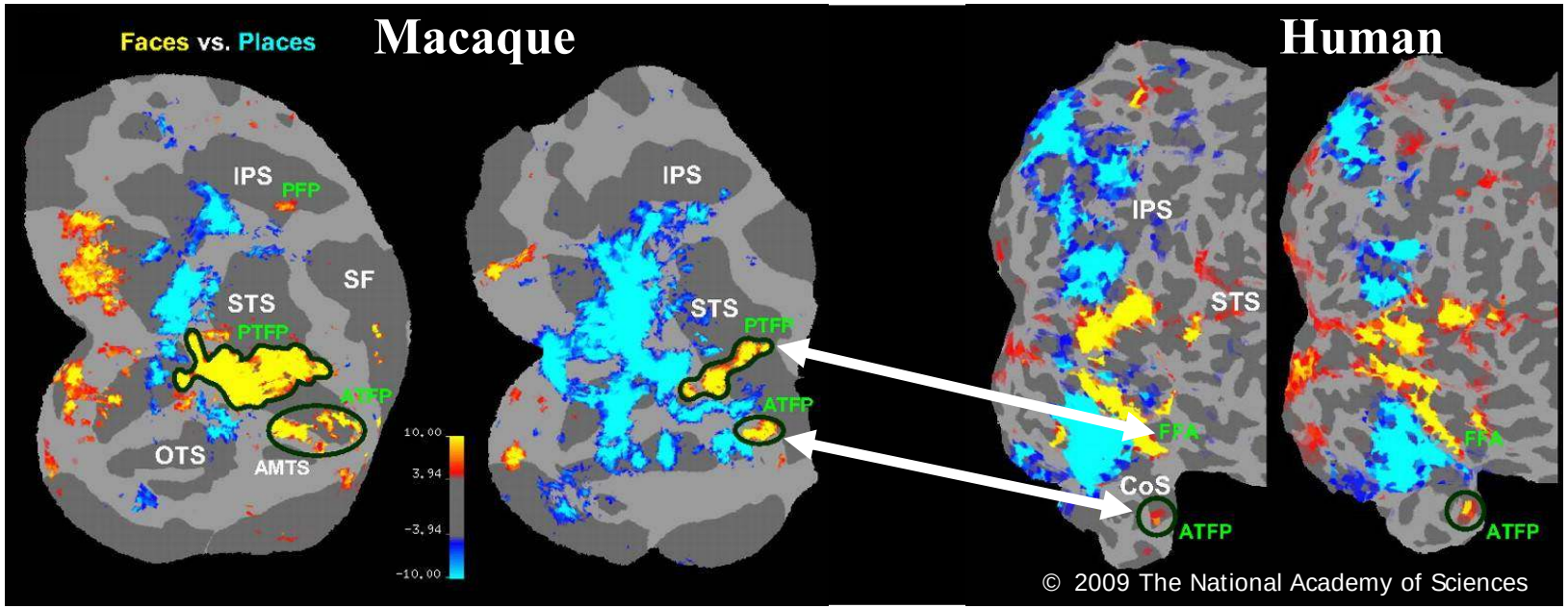
- specialized in the processing of visual motion information: its response to coherent motion is higher than to incoherent motion
- block design: coherently and incoherently moving dots are presented in interleaved order





Localizers as means of studying homology between species

It was shown that both face-selective patches in macaque cortex (Tsao et al. 2003, Nat Neurosci; Pinsk et al. 2005, PNAS) correspond to existing structures in humans.



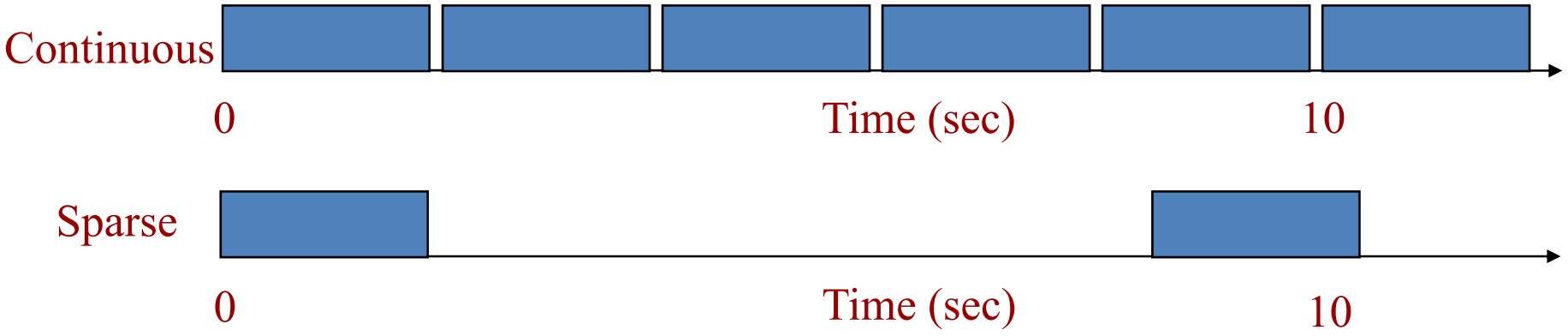
PTFP: Post. Temp. Face Patch FFA: Fusiform Face Area

ATFP: Ant. Temp. Face Patch

(Rajimehr et al., 2009, PNAS)

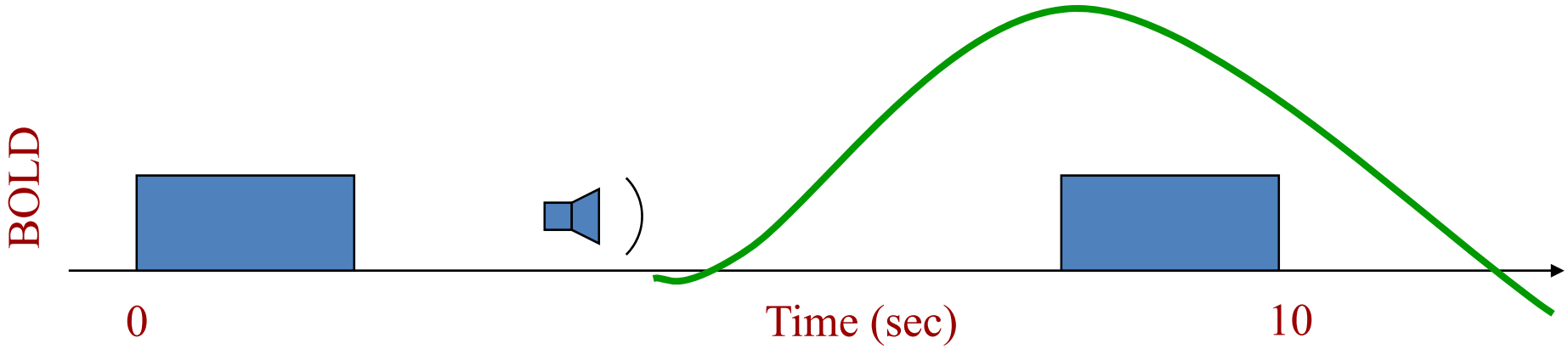
Studying the Auditory System

- Sparse fMRI:
  - To explore central auditory function may be compromised by the intense bursts of stray acoustic noise produced by the scanner whenever the magnetic resonance signal is read out
  - Sparse imaging includes a delay between each fMRI volume, so stimuli can be presented while scanner is silent.



Sparse fMRI:

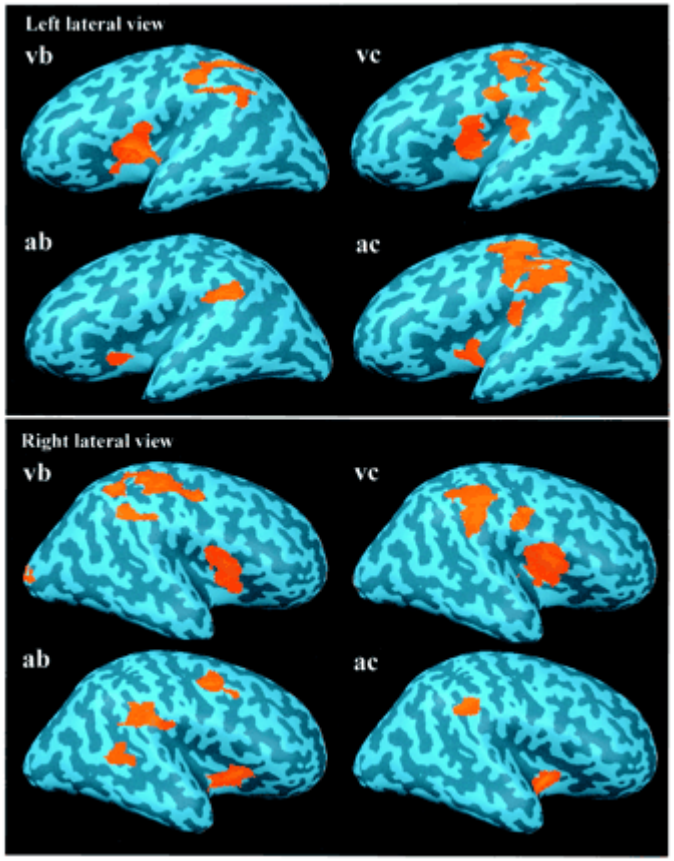
- Typically, sparse design like a block design – each acquisition measures effect of single stimuli.
- Stimuli must be presented ~5sec prior to acquisition.
- Sparse designs have less power than continuous designs, and it is difficult to estimate latency of BOLD response.
- Due to T1 effects, Sparse designs can still have good power.



Continuous fMRI: The functional neuroanatomy of target detection

- When performing both auditory and visual oddball task significant increases in fMRI signal for target versus non-target conditions were observed in the supramarginal gyrus, frontal operculum and insular cortex bilaterally, and in further circumscribed parietal and frontal regions corresponding to the P300 component.

- The effects were consistent over various stimulation and response modalities and can be regarded as specific for target detection in both the auditory and the visual modality. These results therefore contribute to the understanding of the target detection network in human cerebral cortex and impose constraints on attempts at localizing the neuronal P300 generator



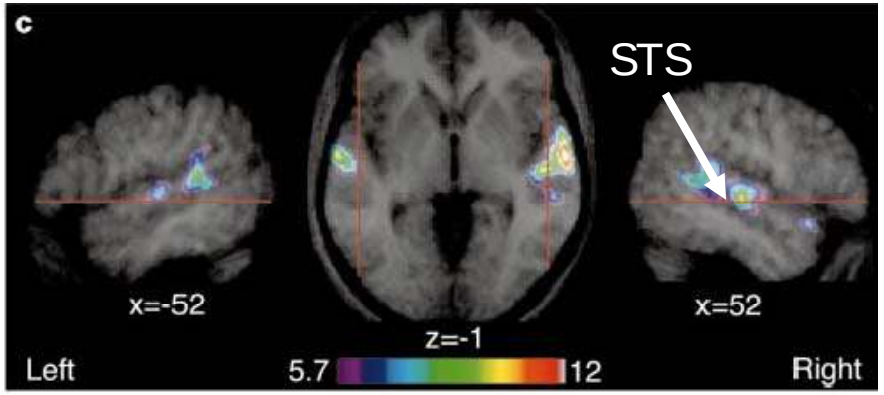
(Linden et al. 1999, Cereb Cortex)

Sparse fMRI: Voice-selective areas in human auditory cortex

• Voice-selective regions can be found bilaterally along the upper bank of the superior temporal sulcus (STS):

  • greater neuronal activity when subjects listened passively to vocal sounds, than to non-vocal environmental sounds

  • high degree of selectivity (central STS) – responding significantly more to vocal sounds than to matched control stimuli, including scrambled voices and amplitude-modulated noise

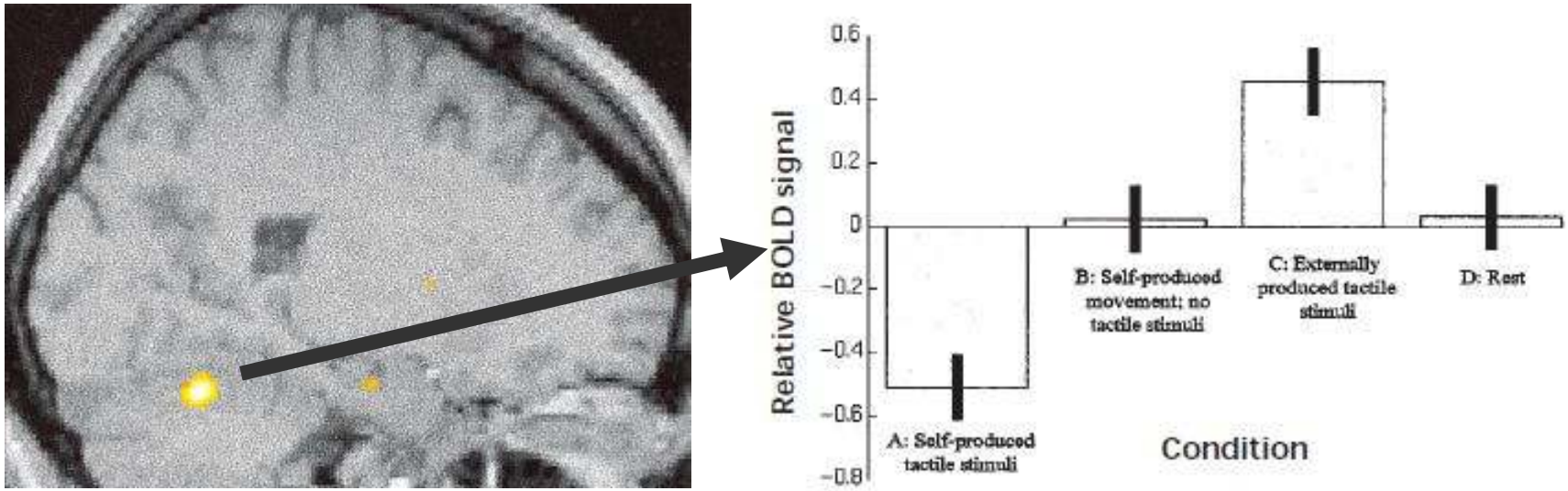


• The voice-selective areas in the STS may represent the counterpart of the face-selective areas in human visual cortex.

(Belin et al. 2000, Nature)

Somatosensory stimulation: self-produced or external?

- Somatosensory cortex: increased BOLD signal to baseline in the case of externally-produced tactile stimulation, while reduced BOLD signal compared to baseline in the case of self-produced tactile stimulation → mediated by the cerebellum



- Significantly decreased activity in right anterior cerebellar cortex associated with the interaction between the effects of self-generated movement and tactile stimulation (external input)

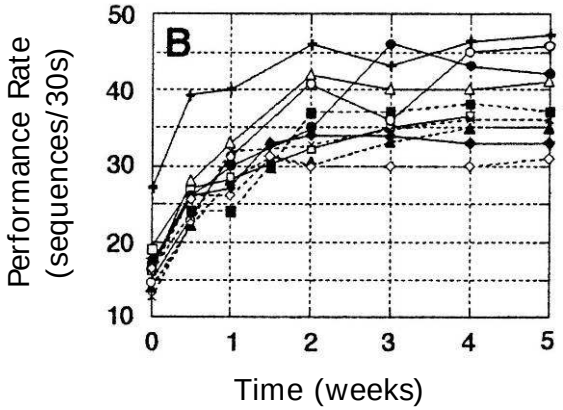
(Blakemore et al., 1998, Nature Neurosci)

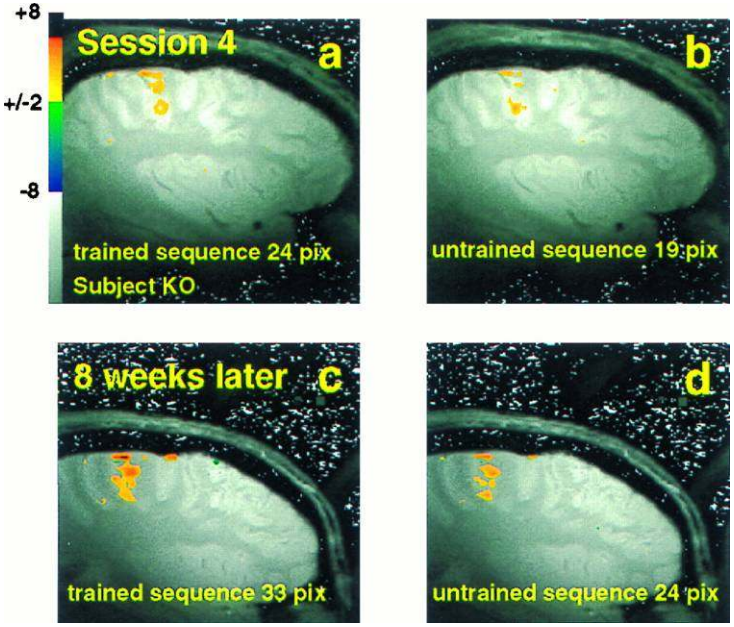
Neuronal Plasticity

Plasticity Underlying Long-term Learning

Long-term practice on sequence performance (motor skill learning)

• In a complex finger moving paradigm after training improved rates of performance induced *increased activation of the primary sensorimotor cortex*, which did not generalize to the contralateral hand.





(Karni et al. 1998, PNAS)

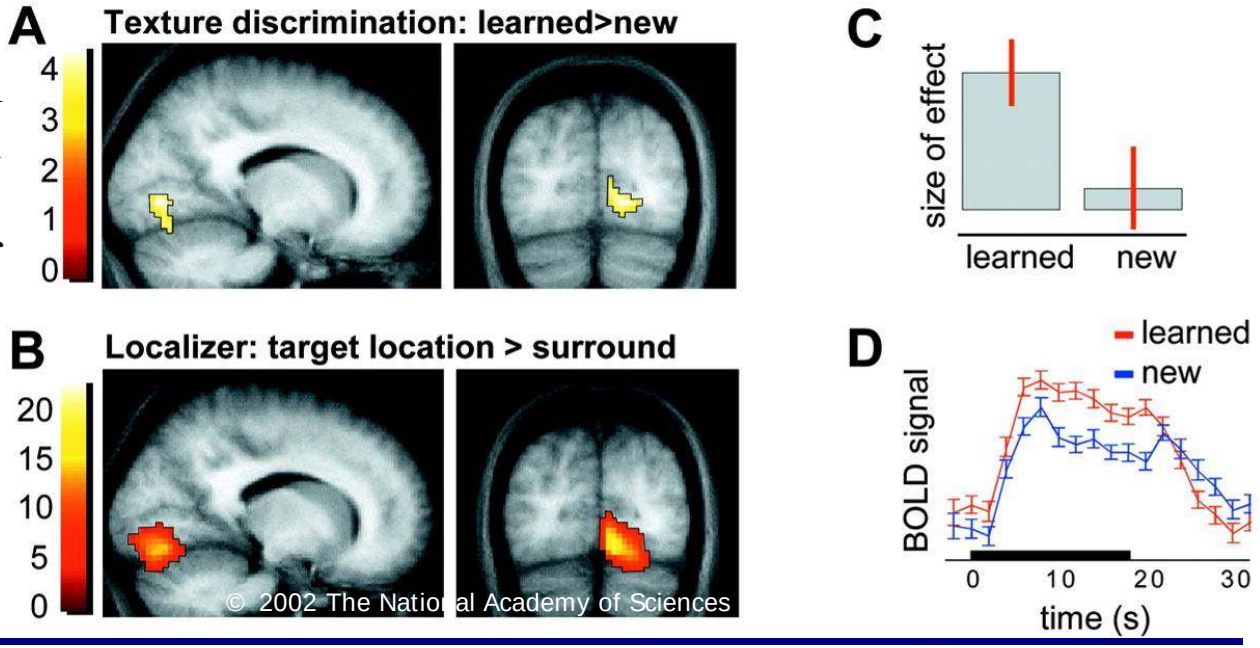
Enhancement of relevant information during perceptual learning

• *Perceptual learning* is defined as performance or sensitivity increase in a sensory feature as a result of repetitive training or exposure to the feature and is regarded as manifestation of sensory plasticity.

• Visual texture discrimination induces long-lasting behavioral improvement restricted to the trained eye and trained location in visual field. Within-subject comparisons between trained and untrained eye for targets presented within the same quadrant revealed higher activity in a corresponding retinotopic area of visual cortex.

⟶ learning leads to *enhanced perceptual and neural responses for the learned relevant stimulus*

(Schwarz et al., 2002, PNAS)

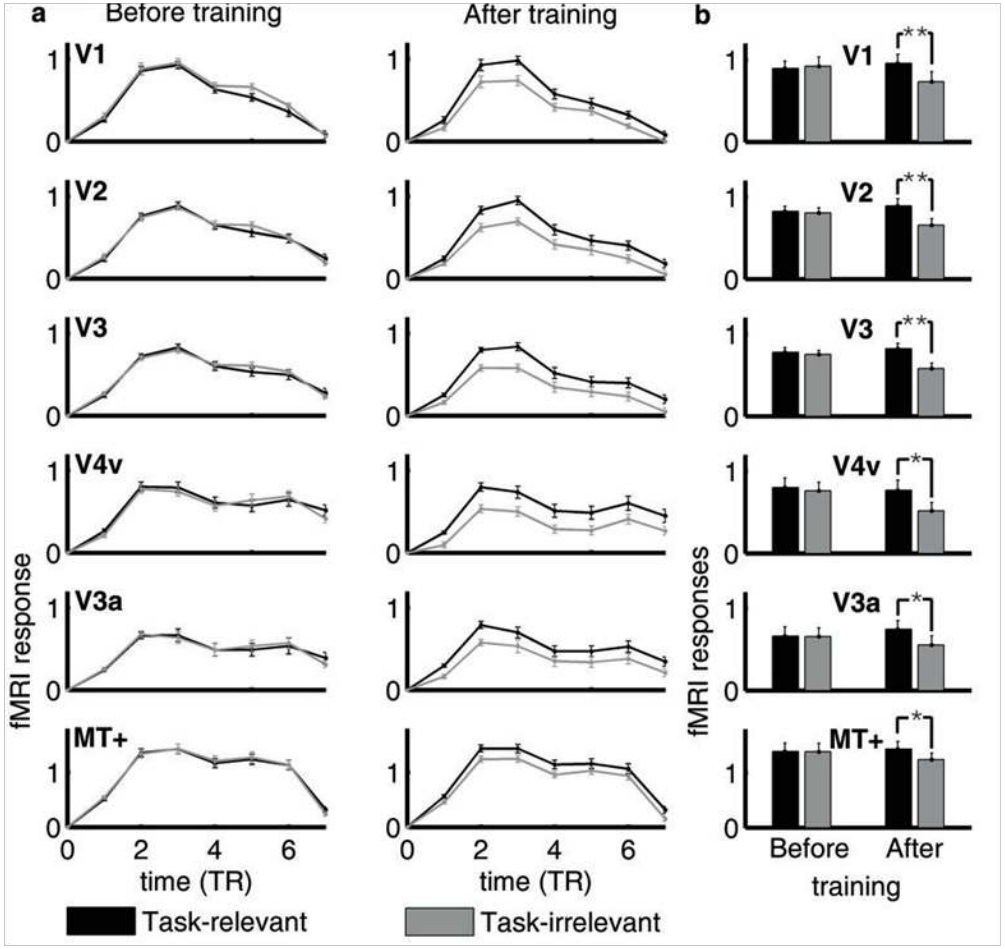


Learning to suppress irrelevant stimuli

- Before training: no difference between the fMRI responses evoked by the task-relevant and task-irrelevant motion directions
- After training: task-irrelevant direction (i.e. distractor stimulus) evoked significantly smaller fMRI responses than task-relevant direction

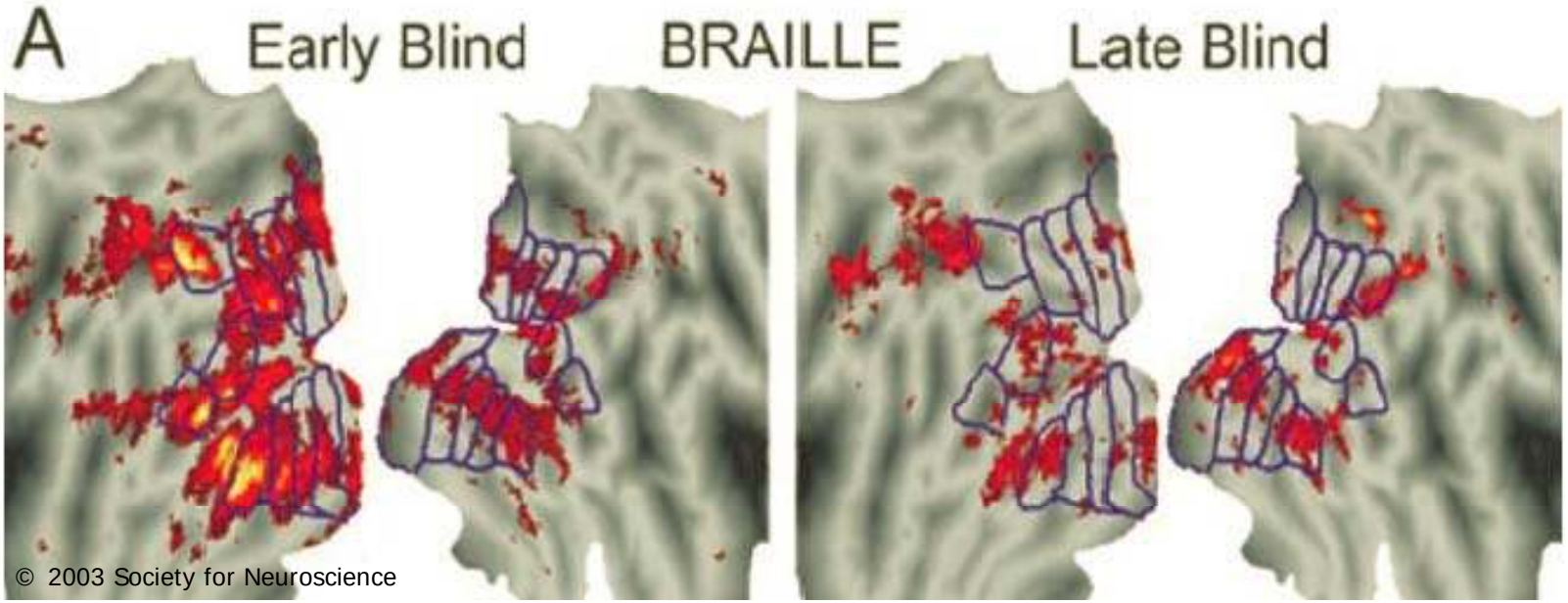
⟶ learning leads to *suppressed perceptual and neural responses for task-irrelevant information*, which competes with the processing of the task-relevant information during training

(Gál et al., 2009, E J Neurosci)



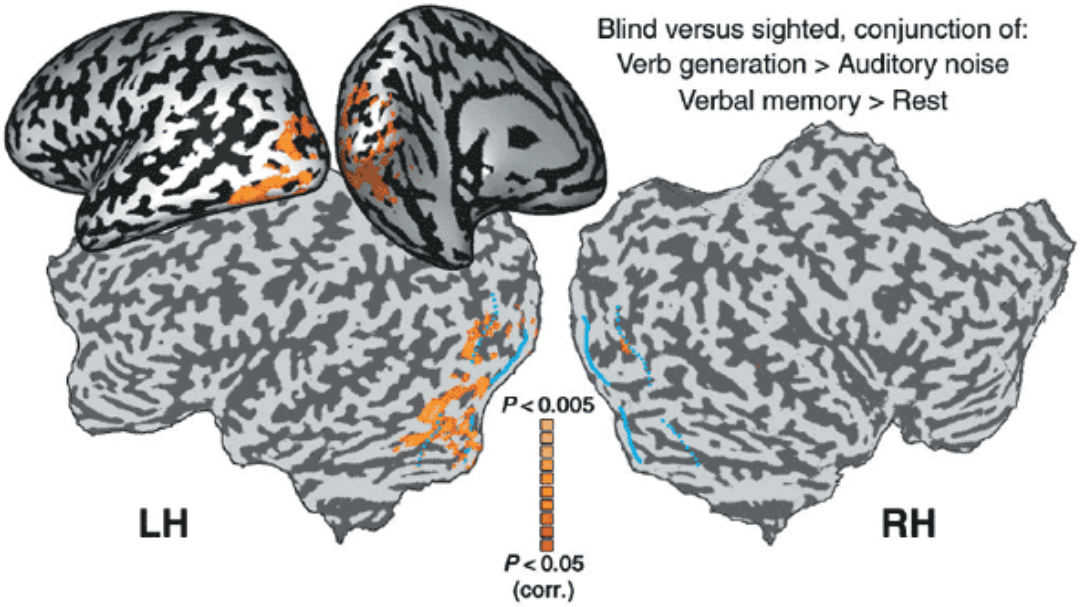
Studying Long-Term Cortical Reorganization

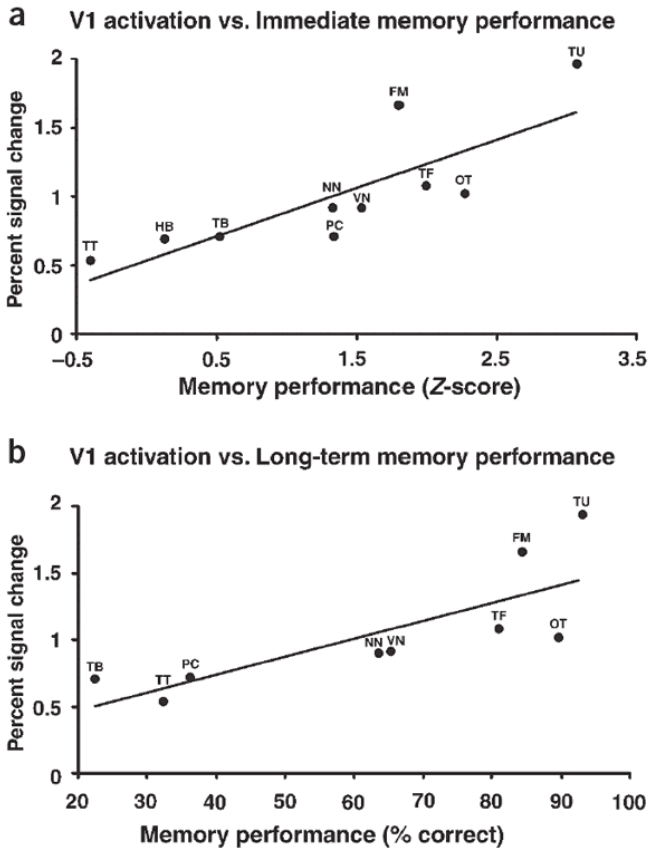
- in congenitally and early blind people retinotopic visual cortex is activated when reading Braille, as opposed to late blind people who show much less activation



(Burton 2003, J Neurosci)

- Visual cortex activation in verbal tasks in blind people also correlates with verbal memory performance

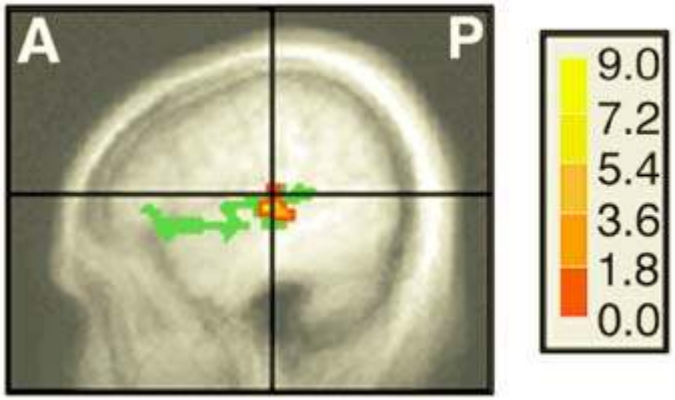


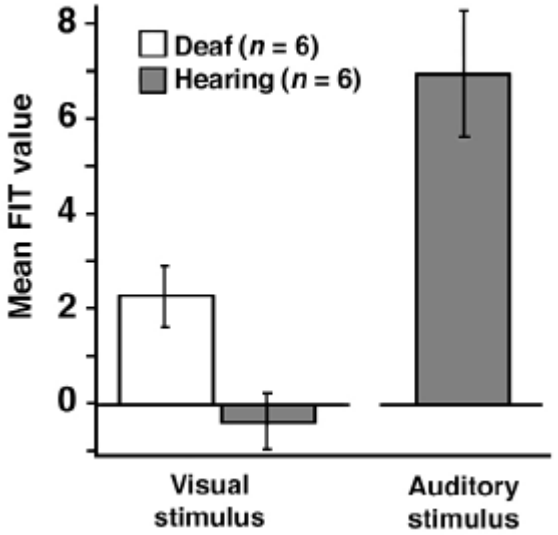


(Amedi et al, 2003, Nature Neurosci)

Cross-modal plasticity in congenitally deaf:

- Auditory cortex activates for simple visual stimuli (moving dot pattern) in early deaf subjects, demonstrating that early deafness results in the processing of visual stimuli in primary auditory cortex.

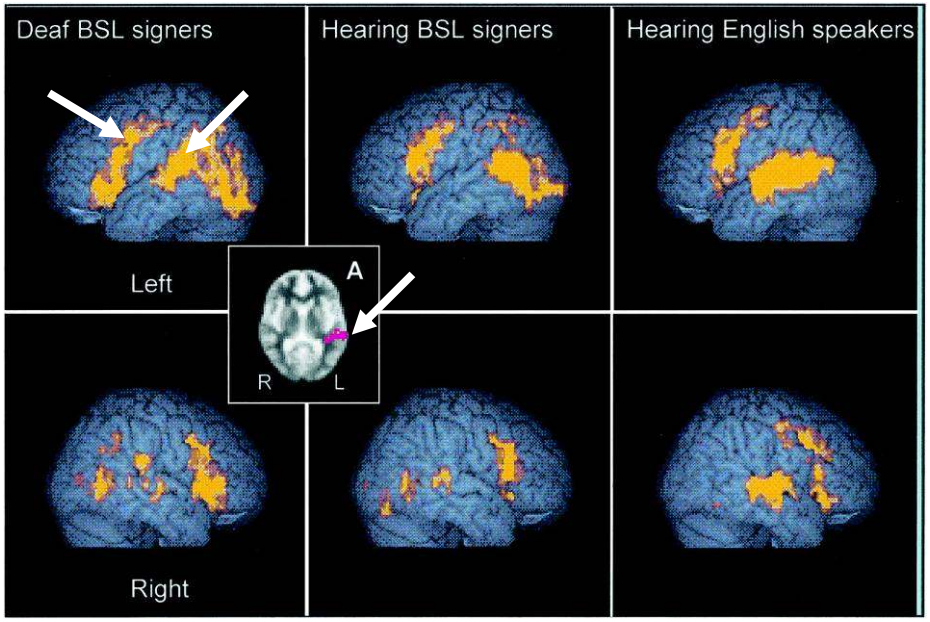




(Finney et al. 2001, Nature Neurosci)

Biomedical Imaging: fMRI – Neuroscience Applications

- Both bilateral inferior prefrontal regions (including Broca's area) and bilateral superior temporal regions (including Wernicke's area) were activated by viewing sign language (BSL) in congenitally deaf signers. Deaf native signers also demonstrated greater activation in the left superior temporal gyrus in response to BSL than hearing native signers (A), which suggests that left temporal auditory regions may be privileged for processing heard speech even in hearing native signers. However, in the absence of auditory input this region can be recruited for visual processing.



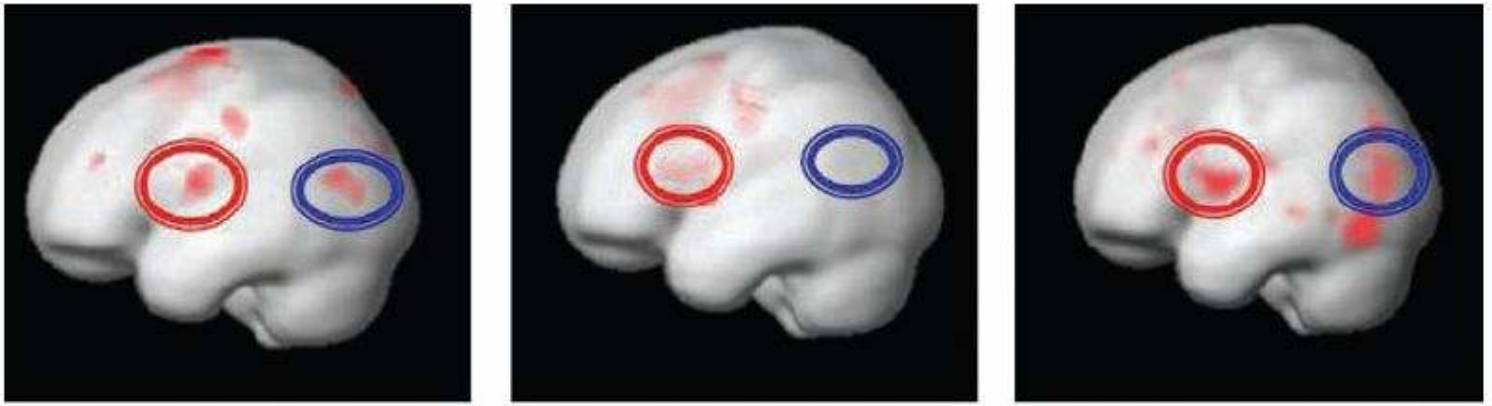
(MacSweeney et al. 2002, Brain)

Studying Developmental Plasticity

Dyslexia, a developmental disorder

- Functional neuroimaging studies have revealed differences in brain function and connectivity that are characteristic of dyslexia, e.g.
  - children and adults with dyslexia exhibit reduced or absent activation in the left temporo-parietal cortex
  - left temporo-parietal region supports the cross-modal relation of auditory and visual processes during reading
  - atypical activations in left middle and superior temporal gyri associated with receptive language, and left occipito-temporal regions associated with visual analysis of letters and words

Brain Plasticity Associated with Treatment



During phonological processing there is a marked frontal (red circles) and temporo-parietal (blue circles) hypoactivation in dyslexic readers compared to typically developing readers, which became more active after remediation.

(Temple et al., 2003, PNAS)

Cognitive Functions

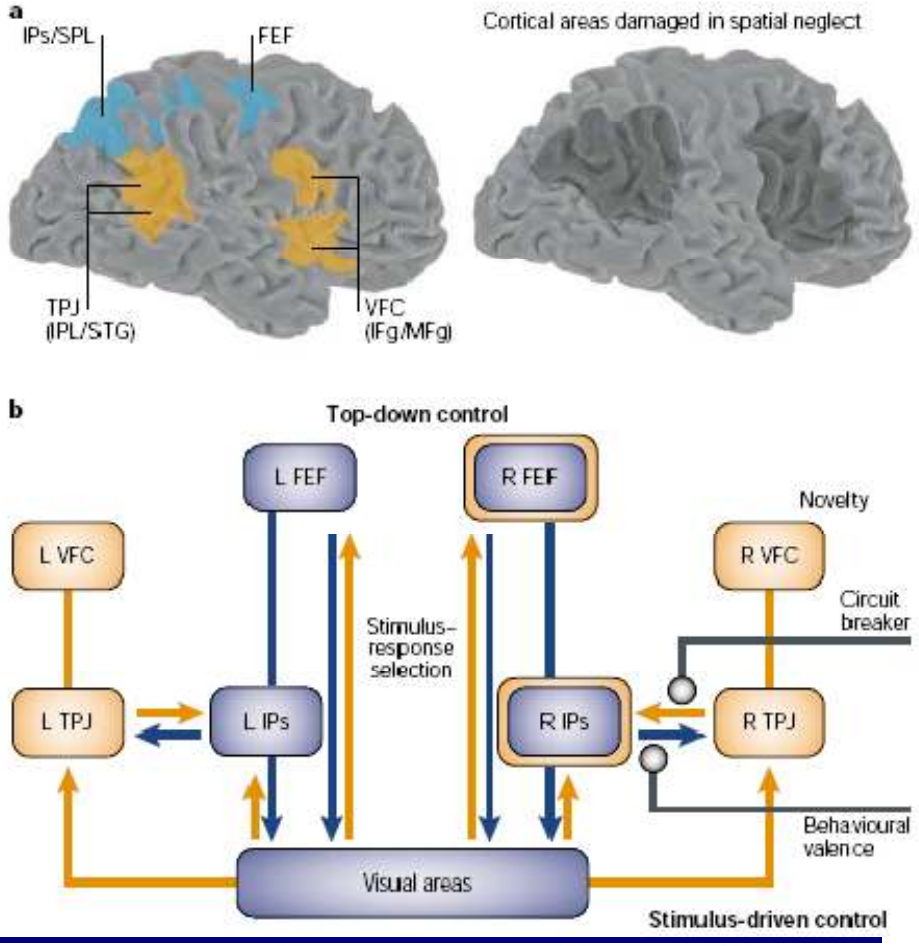
Studying the Organization of Attention System

Attention systems:

• **Dorsal goal-directed attentional network** (blue) is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses. (rightward bias)

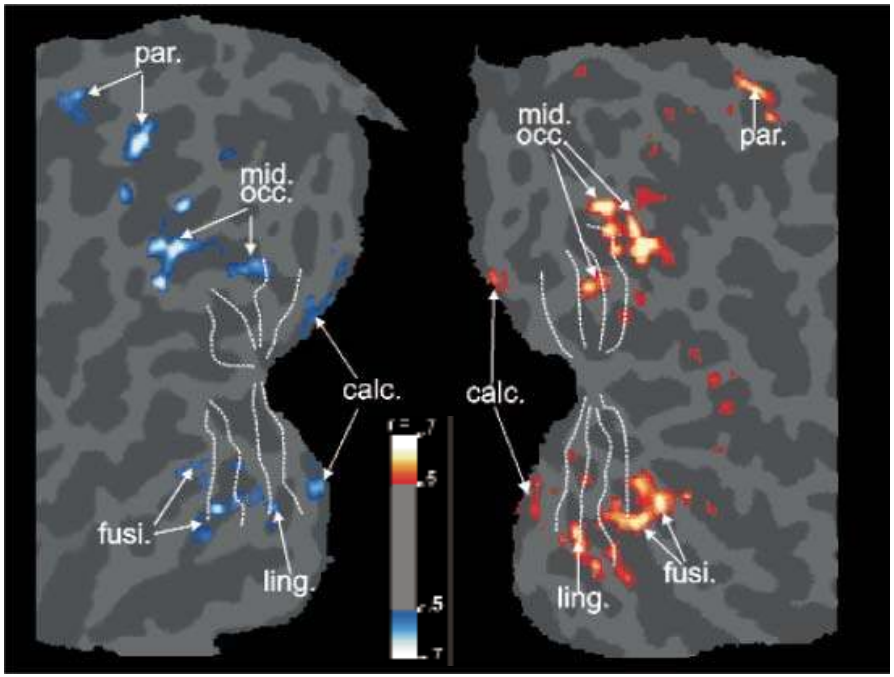
• **Ventral stimulus-driven attentional network** (orange) is not involved in top-down selection. Instead, this system is specialized for the detection of behaviourally relevant stimuli, particularly when they are salient or unexpected. (reorienting deficit)

(Corbetta and Shulman, 2002, Nature Rev Neurosci)



Basis of Attentional Selection: *Location*

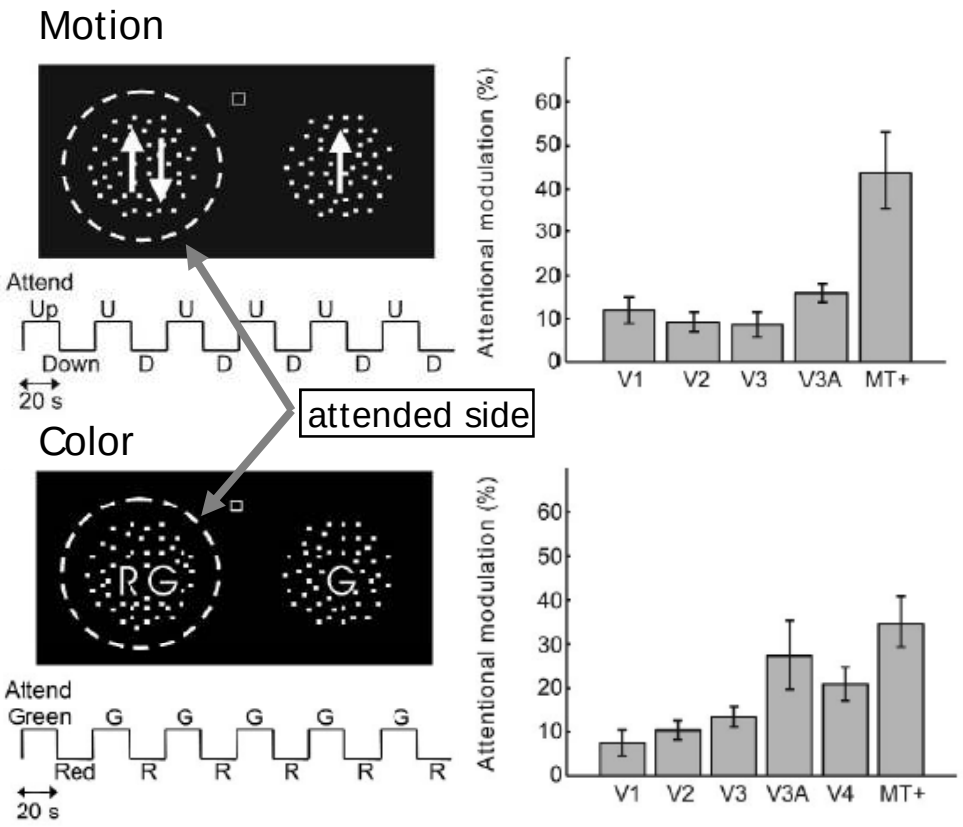
Spatial attentional selection: When subjects are cued to shift their attention between two locations of the visual field, striate and extrastriate cortex responses modulate with the alternation of the attentional cue: responses are greater when the subjects attend to the stimuli in the contralateral hemifield.



(Matrínez et al., 1999, Nature Neurosci)

Basis of Attentional Selection: *Features*

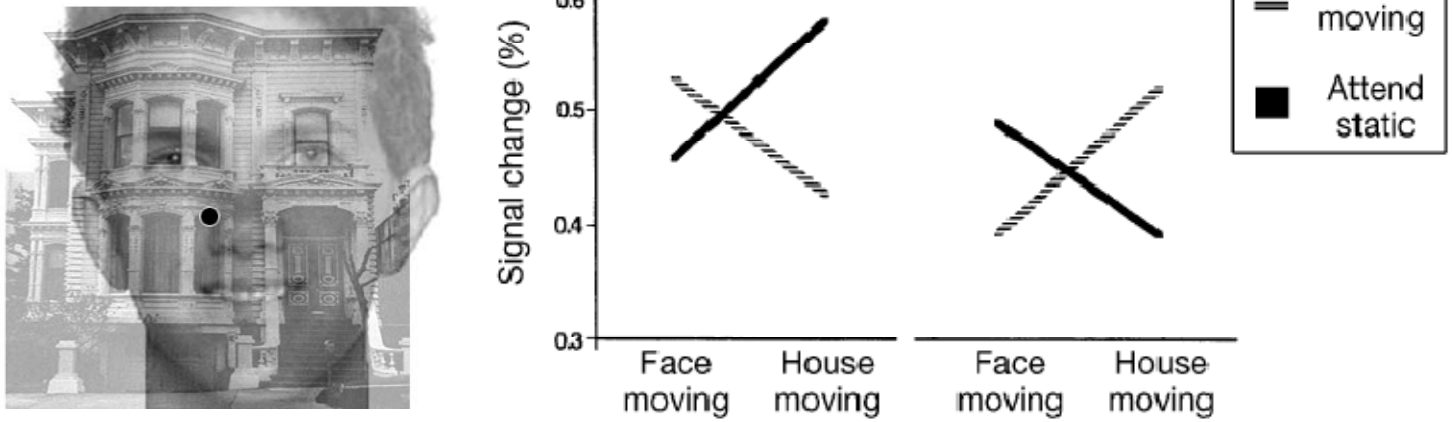
Global attentional selection: attention to a stimulus feature (color or direction of motion) increased the response of cortical visual areas not only to the stimuli at the attended location but also to a spatially distant, ignored stimulus that shared the same feature.



(Saenz et al., 2002, Nature Neurosci)

Basis of Attentional Selection: *Objects*

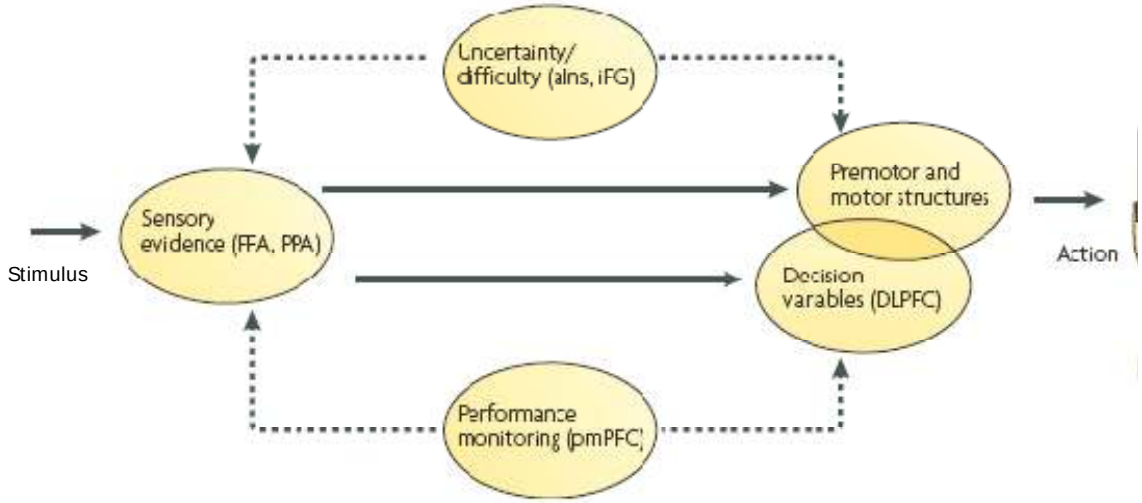
With stimuli consisting of a face transparently superimposed on a house, with one moving and the other stationary or vice versa, attending to the moving object resulted in higher activation not only in motion processing area MT but also in the cortical area selective for the moving object. This provides physiological evidence that whole objects are selected even when only one visual attribute is relevant, instead of locations or feature being the units of attentional selection.



(O'Craven et al., 1999, Nature)

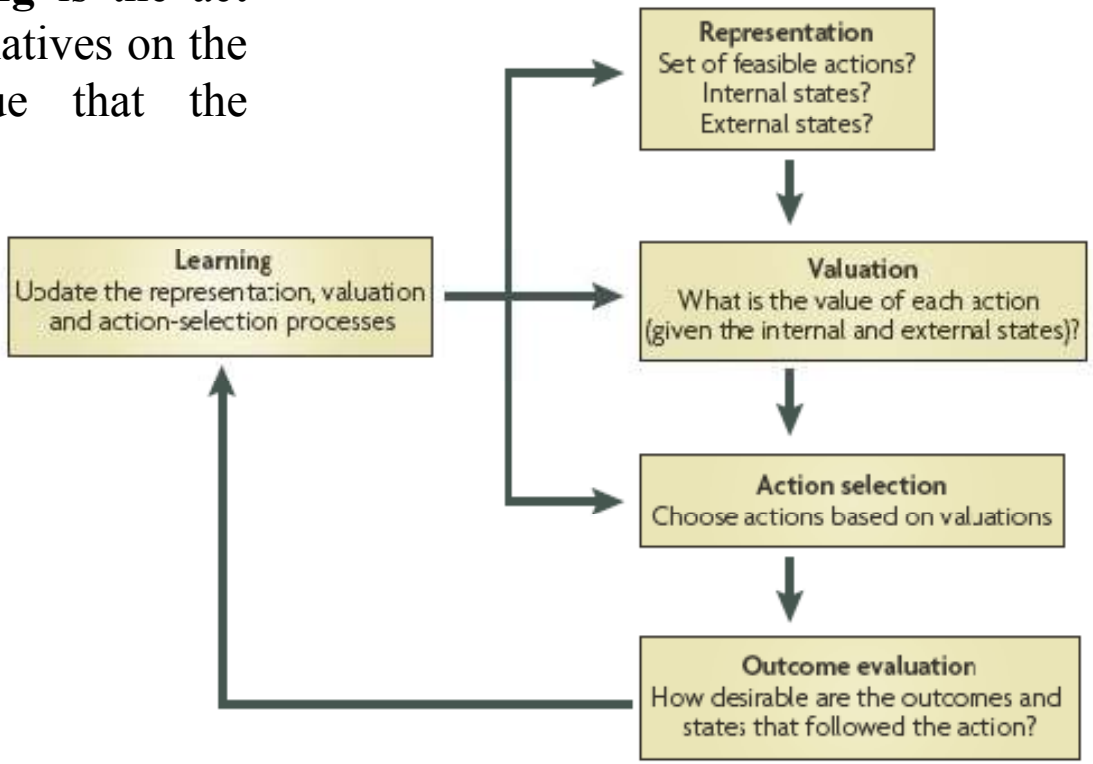
Studying Areas Involved in Decision Making

• **Perceptual decision making** is the act of choosing one option or course of action from a set of alternatives on the basis of available sensory evidence. The cortical areas involved i) represent sensory evidence ii) accumulate and compare sensory evidence to compute a decision variable iii) monitor performance detecting errors to signal for adjustment of decision strategies.



(Heekeren et al. 2008, Nature Rev Neurosci)

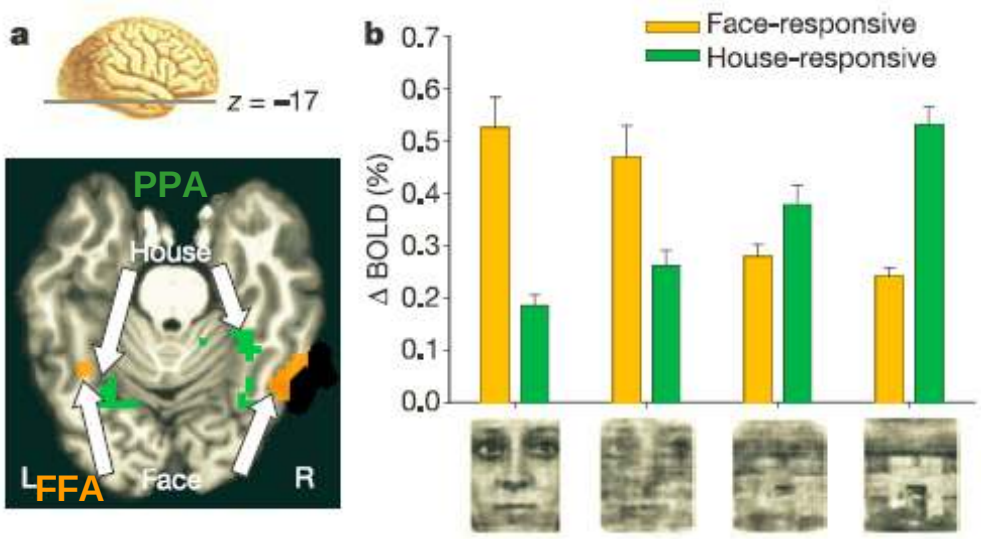
• **Value-based decision making** is the act of choosing from several alternatives on the basis of a subjective value that the individual places on them.



(Rangel et al. 2008, Nature Rev Neurosci)

Sensory evidence representation in perceptual decision making

- For the preferred category, both face- (FFA) and house-selective regions (PPA) responded more to suprathreshold than to peri-threshold images whereas the opposite was true for the non-preferred category, indicating that face- and house-selective regions in inferotemporal cortex represented the sensory evidence for the two respective categories.

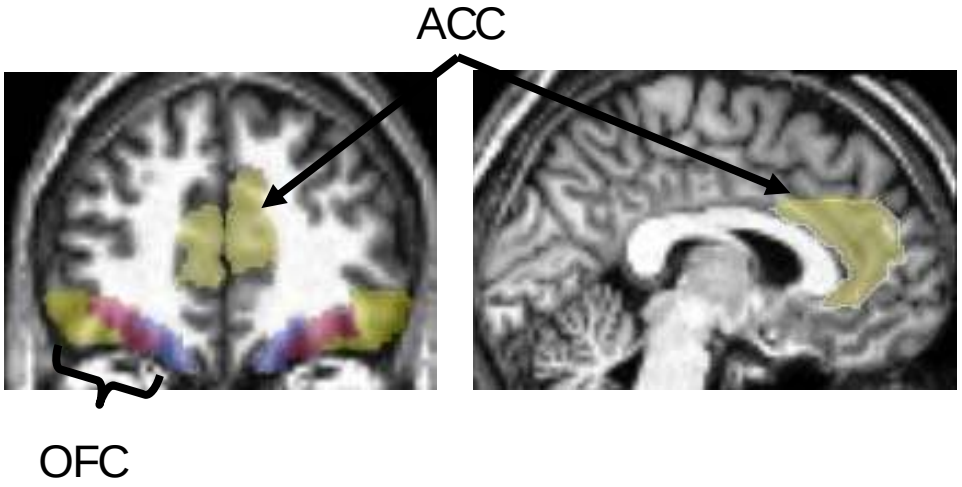


(Heekeren et al., 2004, Nature)

Facets of value-based desision making uncovered by fMRI:

Value representation

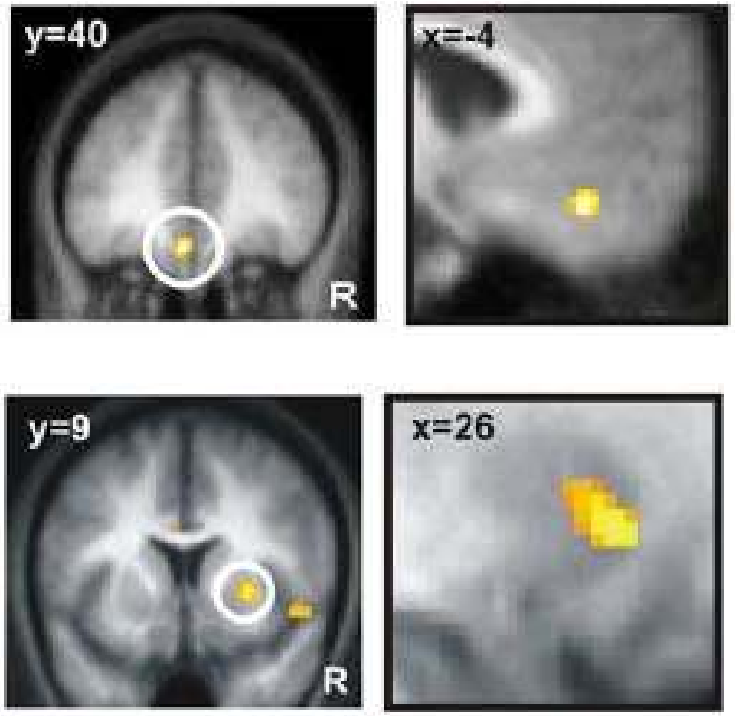
- *Orbitofrontal cortex* (OFC) – primary involved in representing the reinforcement value of objects and value expectations
- *Anterior Cingulate cortex* (ACC) – primary involved in representing the reinforcement value of actions



(Rushworth et al., 2007, Trends Cog Sci)

Reference-dependent value computation

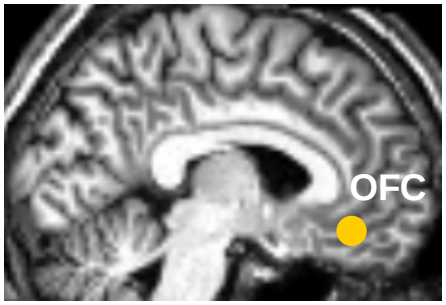
- *Orbitofrontal cortex* (OFC) and *Dorsal Striatum* – track parameters such as expected value indicating the computation of reference-independent value.
- *Ventral Striatum* – indexes the degree to which stated prices are distorted with respect to a reference point (framing effect).



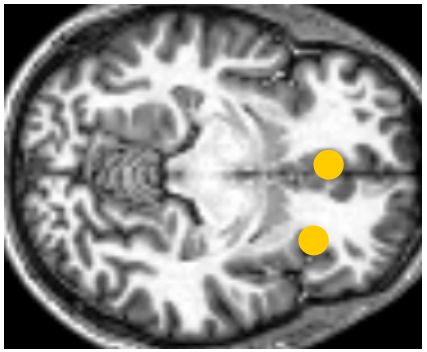
(De Martino et al. 2009, J Neurosci)

Role of emotions in decision making

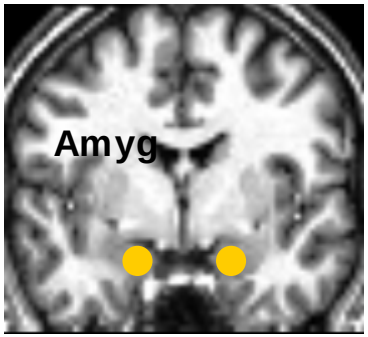
- *Orbitofrontal cortex* (OFC) – has higher activation in the case of rational decisions.
- *Amygdala* – has higher activation in the case of irrational decisions (loss-aversion).



x= -4



z= -10 R



y= -2 R

(De Martino et al. 2006, Science)

Studying the Structures Associated with Memory

Long-term memory systems:

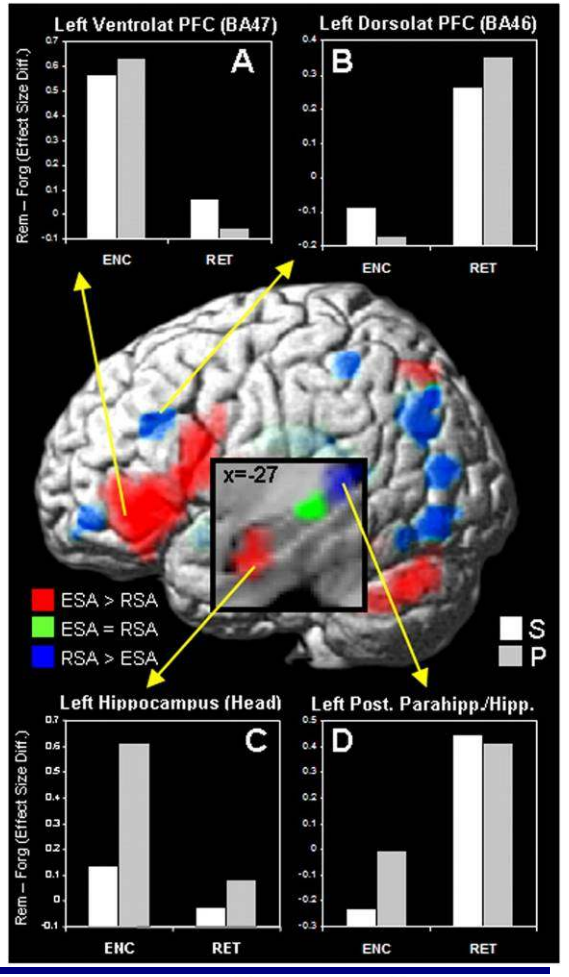
- Declarative (explicit) memory affords the capacity for conscious recollections about facts and events
  - subtypes: semantic memory; episodic memory
  - structures involved are medial-temporal lobe, prefrontal cortex, diencephalon and basal forebrain
- Non-declarative (implicit) memory, a heterogeneous collection of nonconscious abilities that includes the learning of skills and habits, priming and some forms of classical conditioning.

Short-term memory:

- Working memory

Encoding and retrieval of semantic and perceptual associations

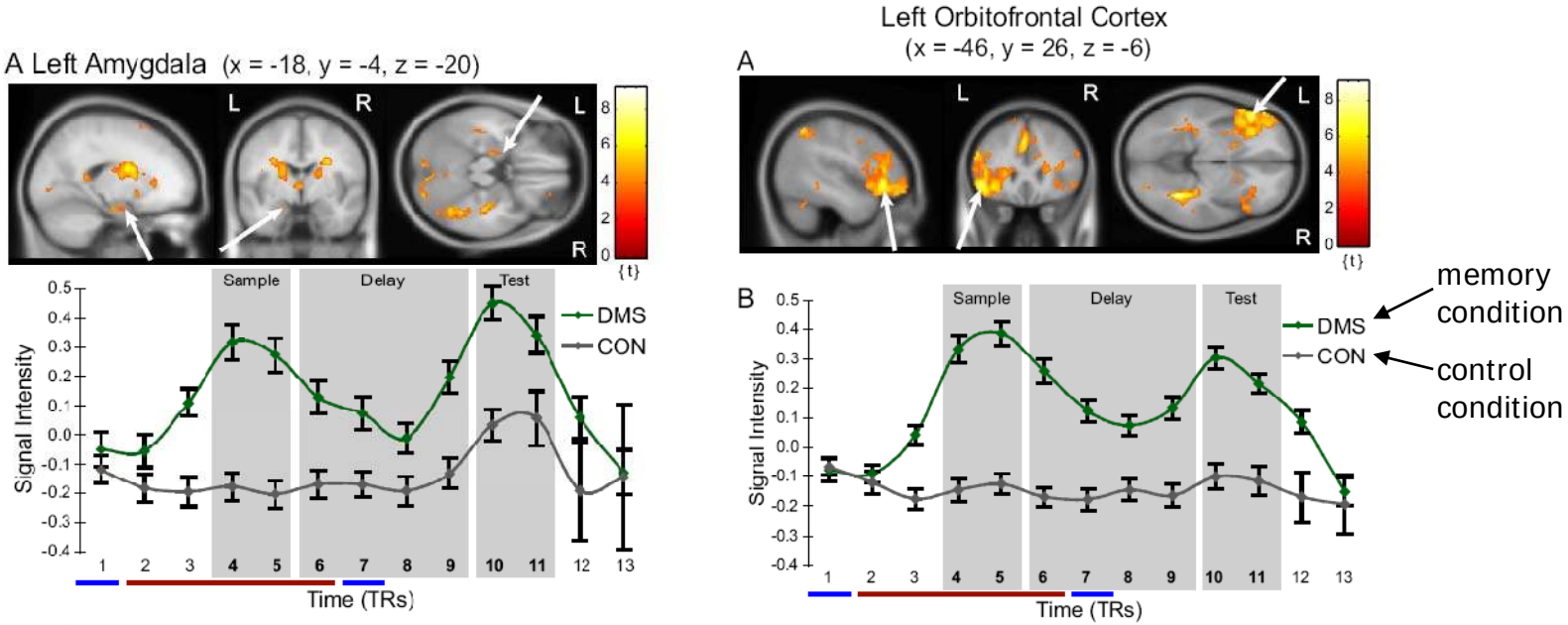
- Encoding and retrieval differences were found within the:
  - medial temporal lobes (MTLs): encoding (ESA) induced greater activity in the anterior hippocampus, while retrieval (RSA) was associated with greater activity in the posterior parahippocampal cortex/hippocampus (encoding-retrieval gradient along the longitudinal MTL axis).
  - prefrontal cortex (PFC): encoding induced greater activity in ventrolateral PFC, while retrieval was associated with greater activity in dorsolateral and anterior PFC.
- Only the left hippocampus was associated with relational memory in general (i.e., for both semantic and perceptual encoding and retrieval)



(Prince et al., 2005, J Neurosci)

Working memory for emotional expressions

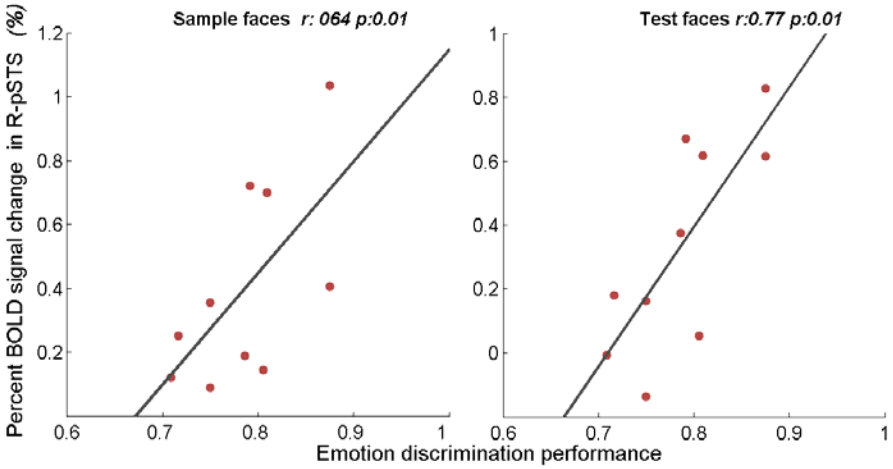
- Although initial processing of emotion and identity is accomplished in anatomically segregated temporal and occipital regions, active maintenance of both facial emotions and identity is associated with a sustained delay-period activity in orbitofrontal cortex (OFC), amygdala and hippocampus.



(LoPresti et al., 2008, J Neurosci)

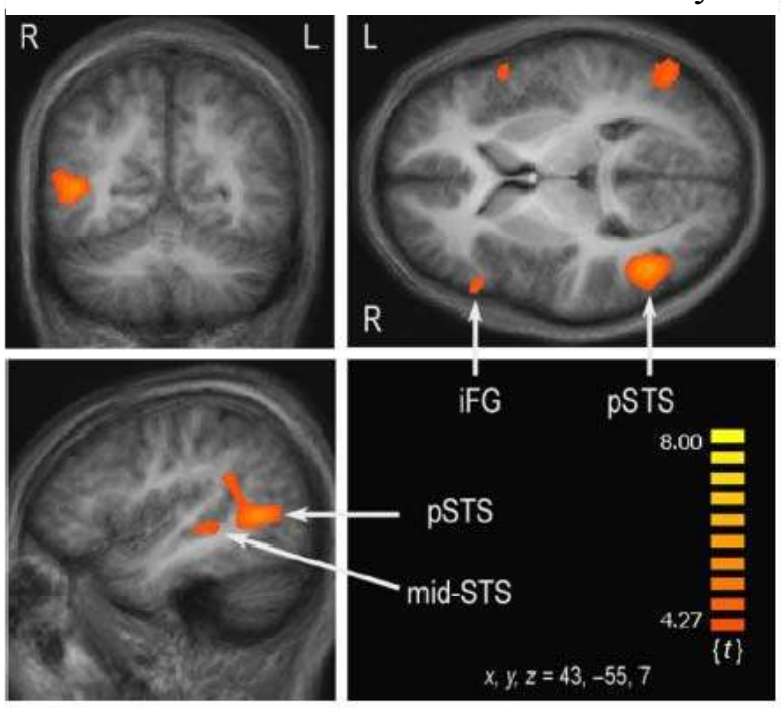
Working memory for emotional expressions II

- Short-term encoding and retrieval of facial expressions depend on the activation level of right pSTS, which predominantly processes changeable facial features such as facial expressions
- Correlation only existed if expression was attended and disappeared when identity was relevant



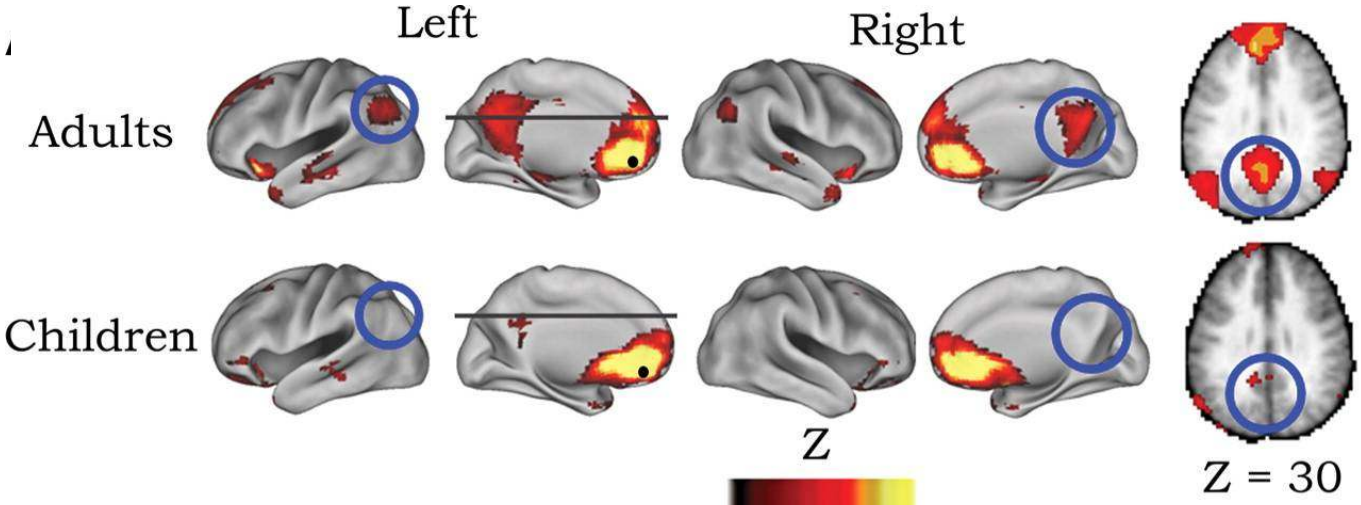
(Bankó et al., 2009, J Vision)

Attend to emotion > attend to identity



Resting State fMRI – Default Network

- Default network: areas that consistently exhibit decreases from baseline activity, during a wide variety of goal-directed behaviors. These decreases suggest the existence of an organized, baseline default mode of brain function that is suspended during specific goal-directed behaviors. However, its specific function is debated.
- Imaging can be difficult, since there is no standard way of measuring the brain in its resting state (i.e. what is resting state?).



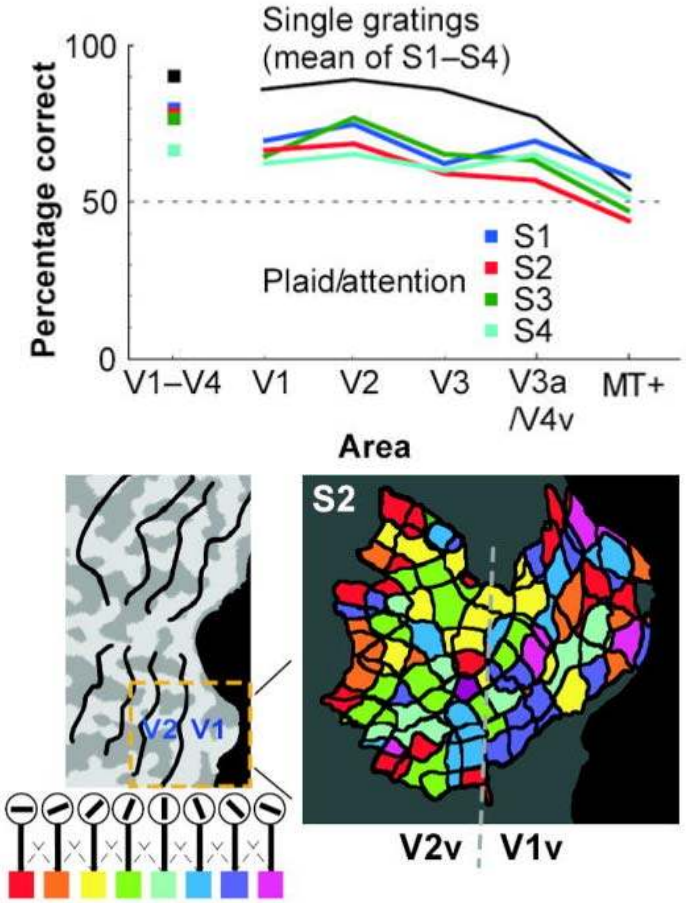
(Fair et al. 2008, PNAS)

Other Applications

"Mindreading" – Decoding Cortical Activity

- Ensemble fMRI signals in early visual areas can reliably predict on individual trials which of eight stimulus orientations the subject was seeing.
- Feature-based attention strongly biased ensemble activity towards the attended orientation

→ fMRI activity patterns in early visual areas, including primary visual cortex (V1), contain detailed orientation information that can reliably predict subjective perception.

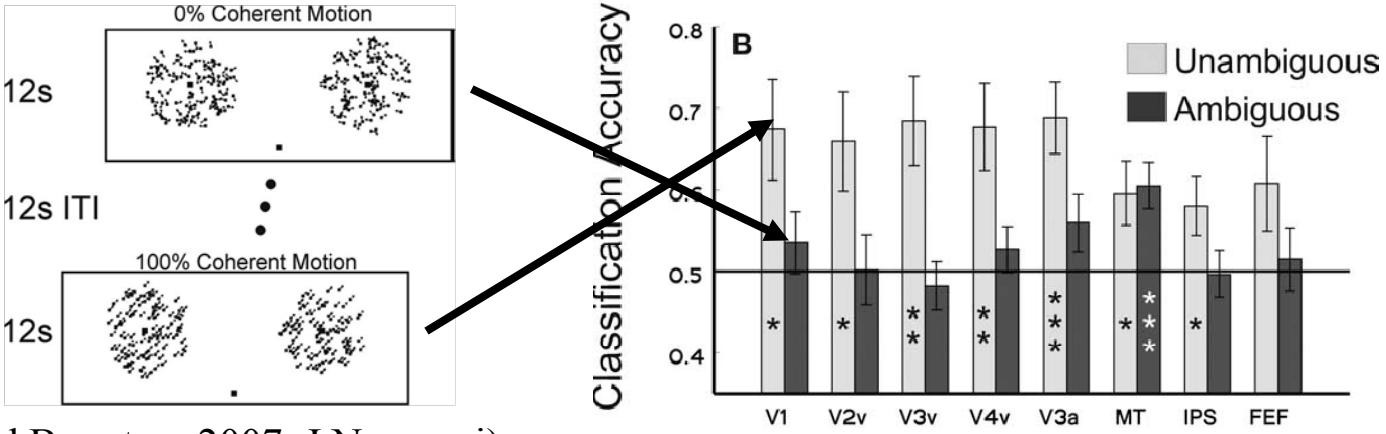


(Kamitani and Tong, 2005, Nature Neurosci)

"Mindreading" – Decoding Cortical Activity II

Representation of Behavioral Choice for Motion in Human Visual Cortex

• Multivoxel pattern analysis (MVPA) enables to discriminate with 60-70% accuracy between leftward and rightward motion in the case of 100% motion coherence in all areas regardless of its motion selectivity. However only motion sensitive area hMT+ was able to discriminate between perceived direction of motion (ambiguos stimulus) making this area the candidate which the conscious experience is based on.



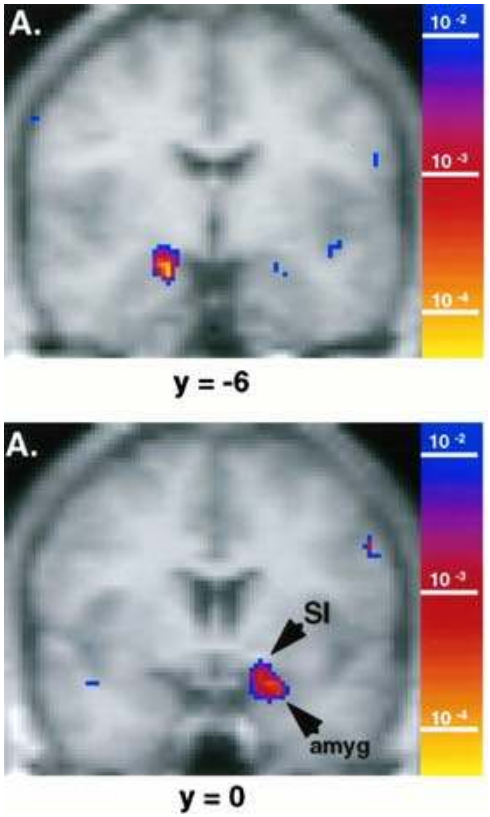
(Serences and Boynton, 2007, J Neurosci)

"Mindreading" – Perception w/o awareness

fMRI is a useful too to investigate perception without awareness, because the neural locus of any activation that occur outside of awareness provides some information about the nature of the information represented:

• The presentation of fearful faces masked with neutral faces elicits a stronger amygdala response than when happy faces are presented before neutral faces, even though subjects failed to see any expressive faces.

→ amygdala responds to nonconscious stimuli



(Whalen et al. 1998, J Neurosci)

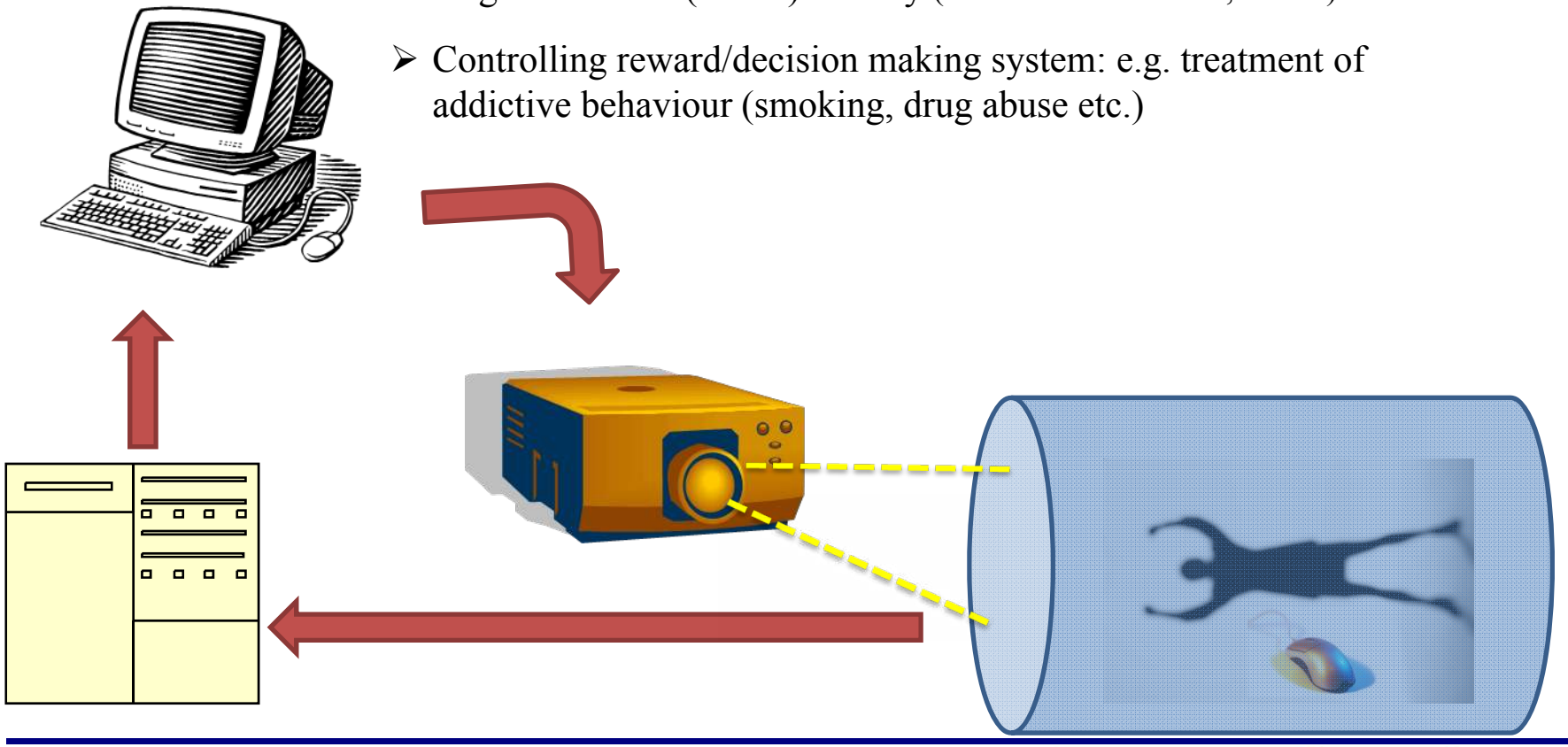
Voluntary Regulation of Brain Activity

Real-time fMRI (rtfMRI): evidence show that voluntary regulation of brain activity can be achieved by training led by on-line (direct or indirect) feedback of BOLD signal

- Delayed:
  - Adjusting motor behavior in order to expand activation in the motor and somatosensory cortex (Yoo and Jolesz 2002 Neuroreport)
  - Effects related to the visual presentation of facial expressions could not be separated from the effects of the feedback from amygdala–hippocampal area (Posse et al 2003 NeuroImage)
- Quasi-realtime
  - Regulation of anterior cingulate and anterior insular cortex (Weiskopf et al 2003 Neuroimage, Caria et al. 2007, NeuroImage)

Prospective clinical/industrial consequences of rtfMRI:

- Pain perception reduced via rtfMRI training based on rostral anterior cingulate cortex (rACC) activity (deCharms et al. 2005, PNAS)
- Controlling reward/decision making system: e.g. treatment of addictive behaviour (smoking, drug abuse etc.)



Combined Methodologies

Pros and Cons of Imaging (fMRI/PET)

- high spatial resolution
- sluggish and temporally blurred: temporal scale is on the order of seconds

Pros and Cons of Electrophysiology (EEG/MEG)

- limited spatial resolution
- excellent millisecond order temporal resolution, which enables studying sequential processing steps as they take place in the brain

Combining the two methodologies can be used to address questions for which neither method would be appropriate alone!

Theoretical considerations

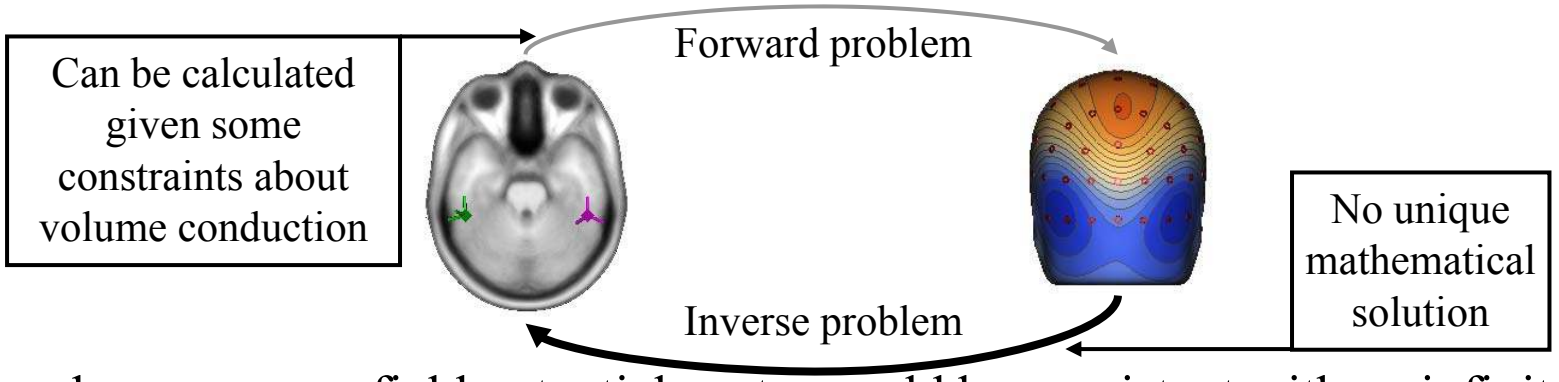
To confidentially correlate haemodynamic and electrophysiologically based measurements of neural activity one must have:

- common sensory frame (identical stimuli)
- common biological reference (identical subjects)
- common experimental frame (identical paradigms)
- appropriate spatial frame (individual dipole modeling of ERP scalp topography i.e *source localization*)

  → to establish an approximate location of the ERP-generating dipole of interest, which has strong correspondence with the foci of haemodynamic activity

Source localization

- aim is to infer the underlying source location from the obtained scalp potential maps

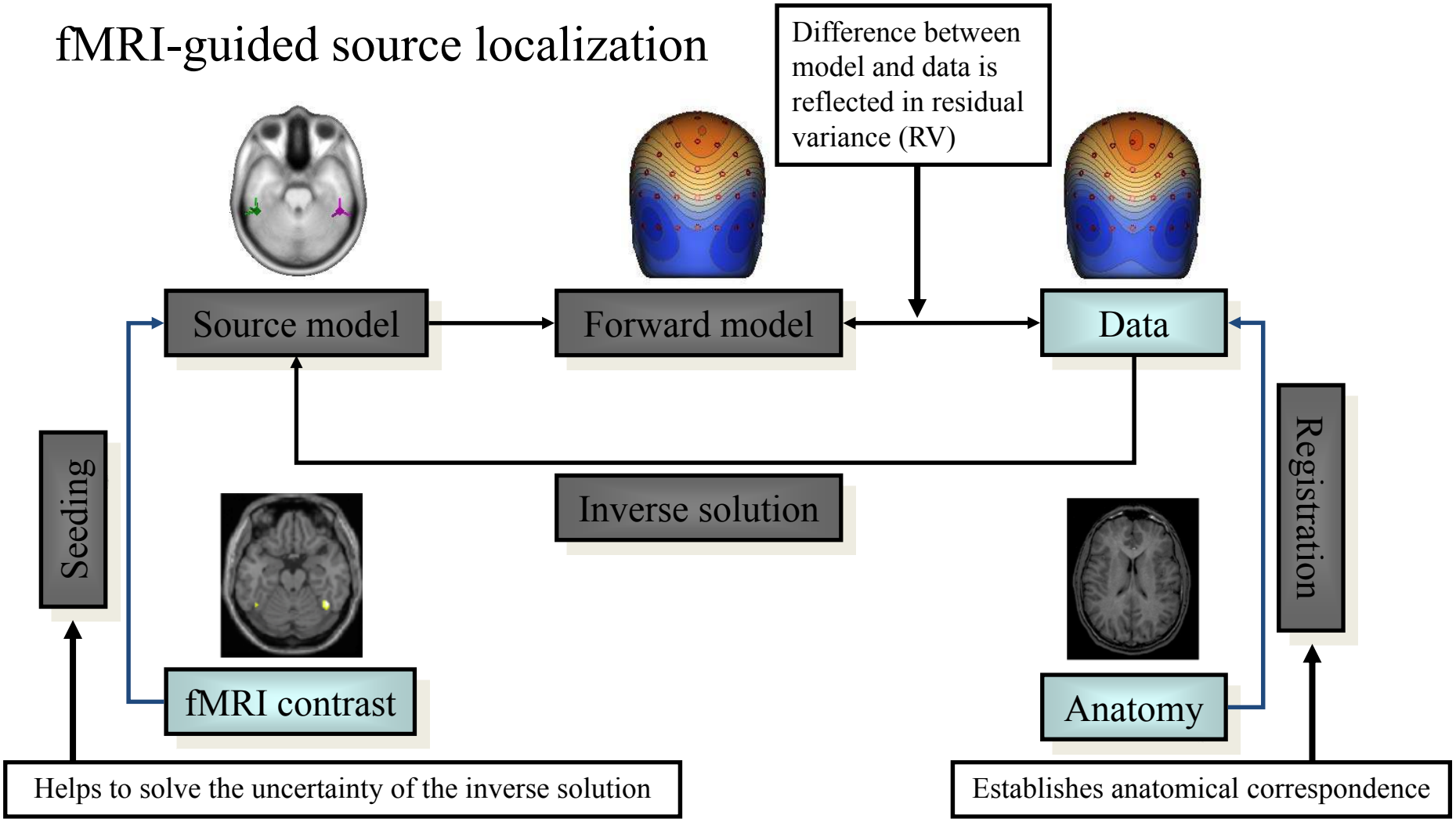


… however, any field potential vector could be consistent with an infinite number of possible dipoles

- there is *no* way to know which one is correct… we can only guess which is better then the other one, but only out of those solutions considered

→ source localization is an ill-defined problem and requires imaging

fMRI-guided source localization



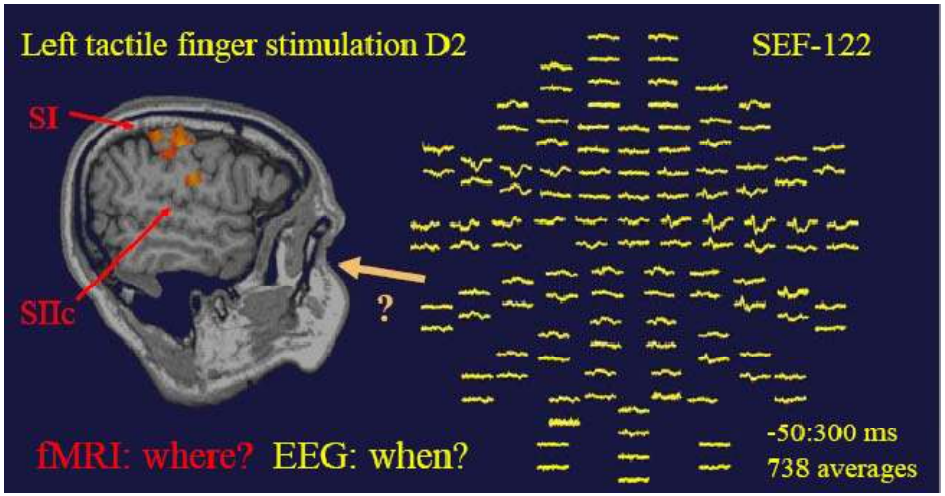
Procedure

- a model-fitting procedure for estimating intracranial sources underlying ERPs (not for ongoing EEG – too many sources)
- Estimation:

  define a source model → calculate the corresponding potential map (forward model) → compare the fit of the forward model to the actual data: if model fits (the residual variance between model and data is low), then data is consistent with these sources; yet there is no unique solution
- Imaging helps:
  - to confine sources to anatomically plausible places after registration with 3D anatomy
    - helps to know the exact locations of electrodes relative to the individuals' brain
    - how to: define fiducial positions in MRI slices to match up EEG/MEG and MRI coordinate systems
    - result is an individual head model

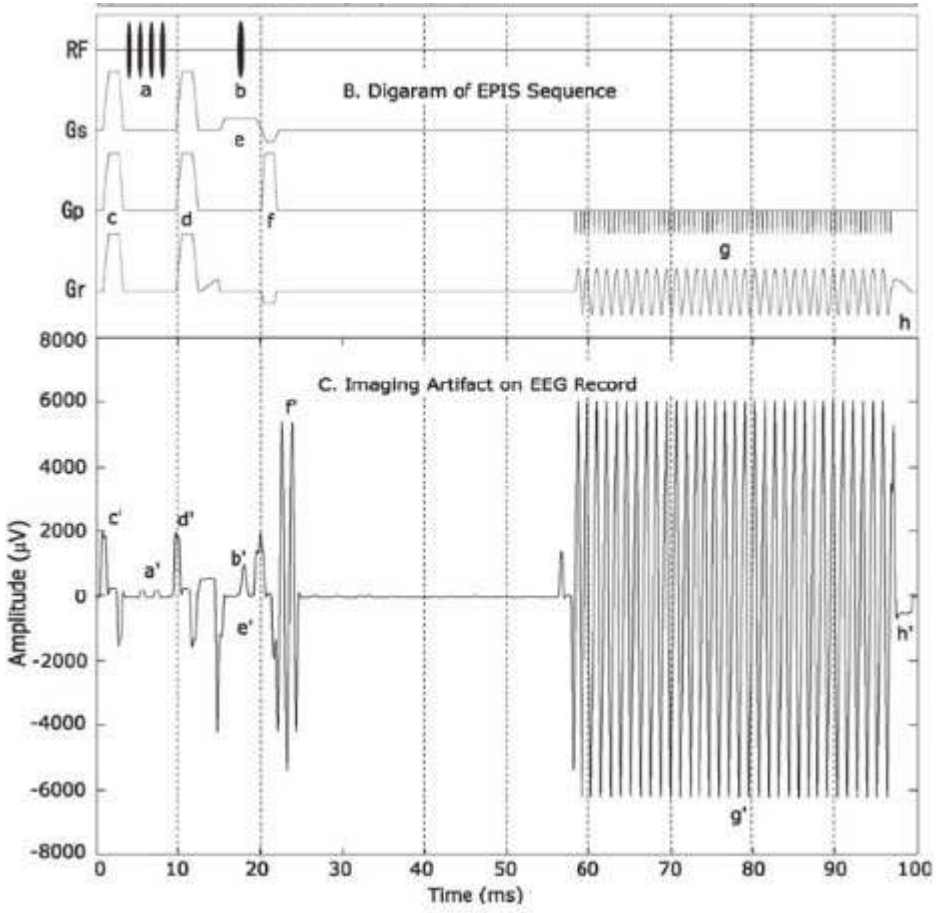
Biomedical Imaging: fMRI – Neuroscience Applications

- Imaging helps:
  - to seed from fMRI activations
    - Orientation and temporal evolution computed from EEG/MEG
    - Inaccuracy of localization not critical for regional source

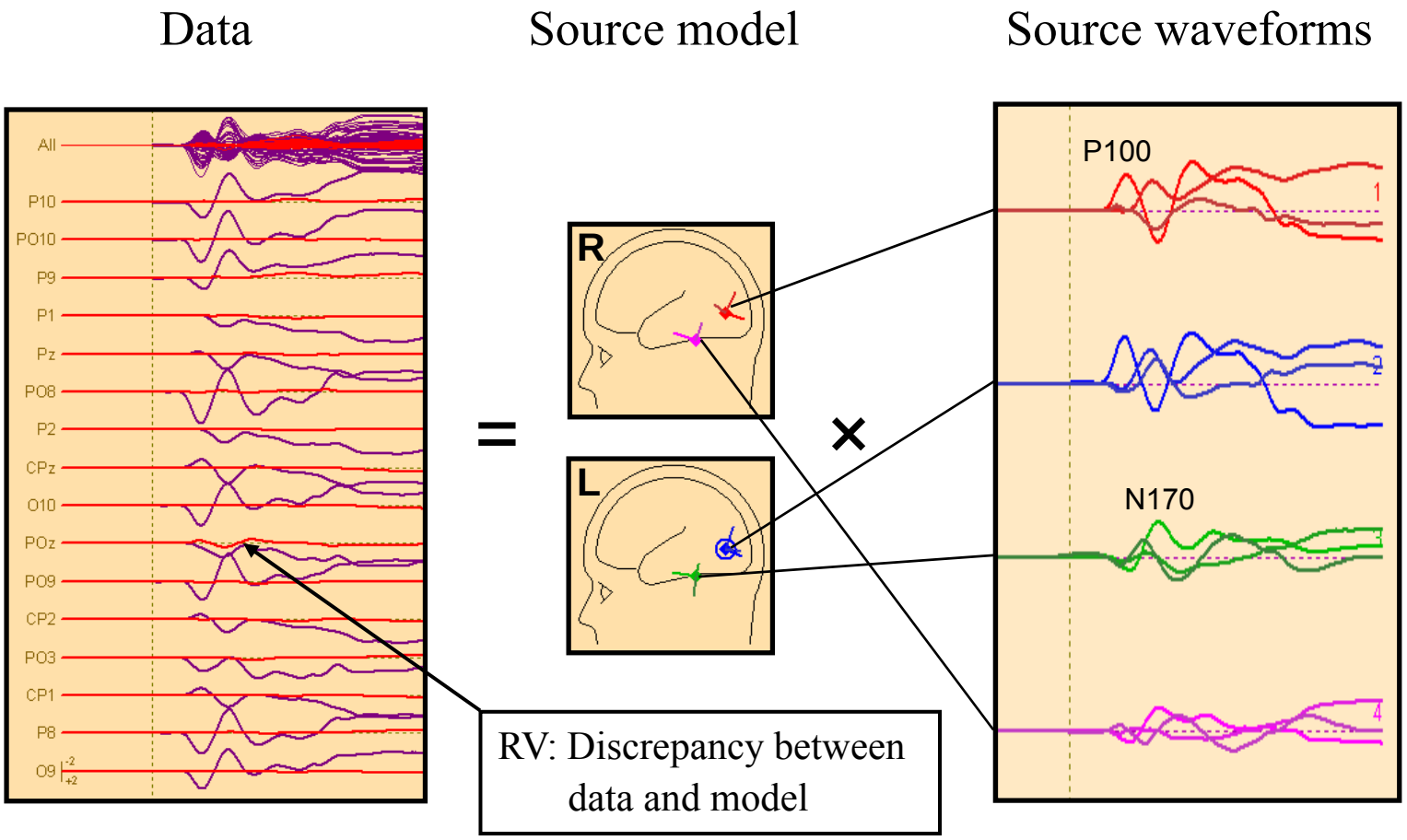


Biomedical Imaging: fMRI – Neuroscience Applications

- Imaging helps:
  - Best results are obtained if measuring EEG/fMRI concurrently
    - However, simultaneous EEG/fMRI registration introduces fMRI acquisition artefacts, which need to be eliminated (big challenge: the artefact can be more than two orders of magnitude higher than the physiological EEG signal)
    - Possible solution is using interleaved EEG-fMRI protocols or doing sequential EEG and fMRI sessions



Linear superposition of source activities at scalp



Mathematically speaking…

- Decompose the reference-free data of ERPs $U_{E\times n}$ into a a set of sources $S_{S\times n}$ and a set of attenuation coefficients $c_{S\times E}$, so that

$$U_{E\times n} = c_{S\times E} \times S_{S\times n}$$

E: number of channels + reference channel

n: number of timepoints

S: number of sources

- Decomposition results in:
  - an electroanatomical time-independent matrix *c* that reflects that anatomical substrates do not move around in the head
  - a time-variant dipole source potential matrix *S* that represents the change in activity of each source over time

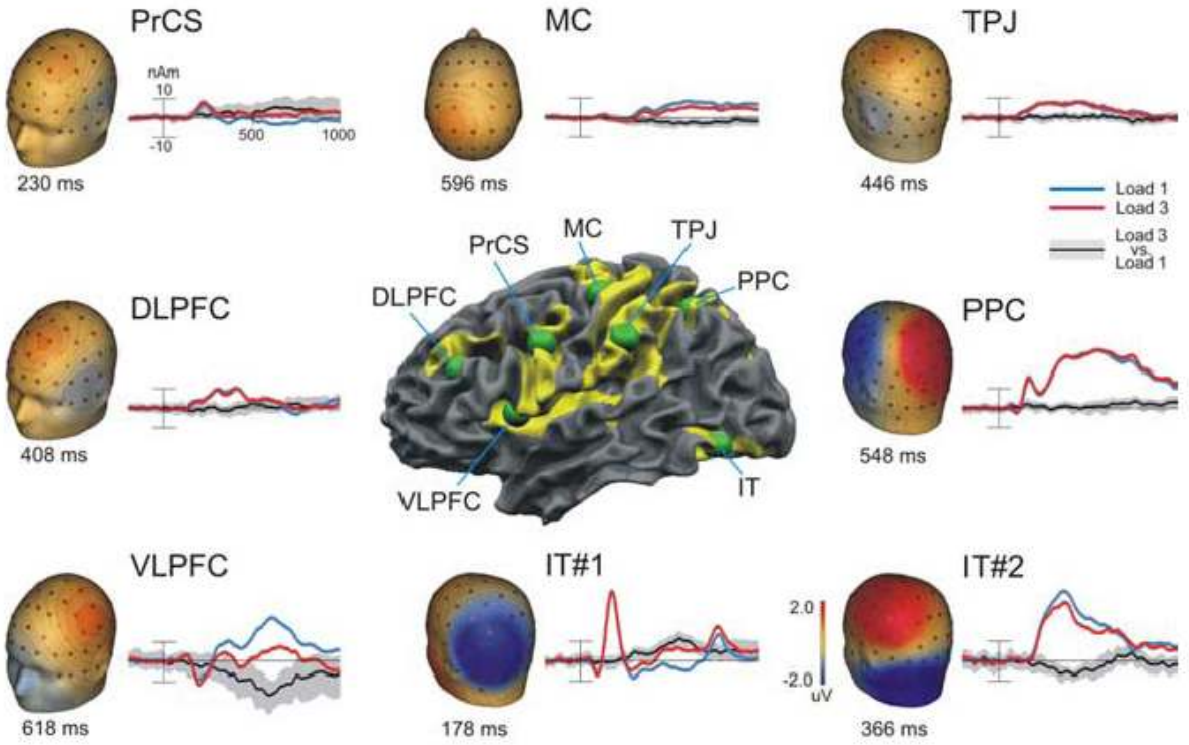
The attenuation matrix *c* is determined by:

- the geometry between the source and the electrodes (the head model)
- the nature of the conductance of the three-layer head model (Brain, Skull, Scalp);
  - the skull is less conductive than the layers on either side this results in a spatial smearing of potentials as they cross the skull

Solutions are constrained by:

- the geometry of the head
- the volume conduction of the dipoles
- the anatomical constraints dictated by the user (e.g., inside the head, symmetrical, not in the ventricles, etc...)

Application – MR guided localization



By using MR guided source localization the authors were able to decompose the processing stages of working memory retrieval

(Bledowski et al., 2006, J Neurosci)

Possible problems of combined methodologies

- Coregistration of EEG electrodes with MRI ~ 5 mm
- Inaccuracy of head model (even for realistic model!) ~ 10 mm
- Coregistration of MRI and fMRI (distortions) ~ 5 mm
- Location of center of gravity of neuronal activity versus BOLD effect, e. g. influence of venous signal ~ 10 mm

⟶ fMRI clusters provide only rough localization of neuronal activation.

Systematic differences (~ 15 mm) between EEG and fMRI are likely. However, source waveform topography is rather *insensitive to small variations* in source location.

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

fMRI – Clinical Applications

(fMRI – Klinikai alkalmazások)

Lajos R. Kozák

Outline

- General introduction to clinical fMRI
  - Goals, approaches, patient groups, paradigm selection
- Introduction to clinical fMRI paradigms used in the MR Research Center (MRKK) at Semmelweis University, with example cases
  - Picture naming, synonym task, speech comprehension, auditory decision, memory encoding, home-town walking, sensory-motor task, retinotopic mapping
- Specific issues in clinical fMRI
  - Single subject analysis, subject specific differences, pathology specific differences, lack of standardization
- Validation specific issues
  - Effect of paradigm length, effect of smoothing, effect of thresholding, threshold-independent lateralization indices
- Educational cases
  - Cortical reorganization, post-surgical follow-up
- Future applications
  - Connectivity mapping, pharmaceutical fMRI, BOLD and ASL mapping
- Summary

Introduction

The main use of fMRI in the clinical practice is the identificantion of the so-called eloquent areas, i.e. areas that are necessary for preserving quality of life.

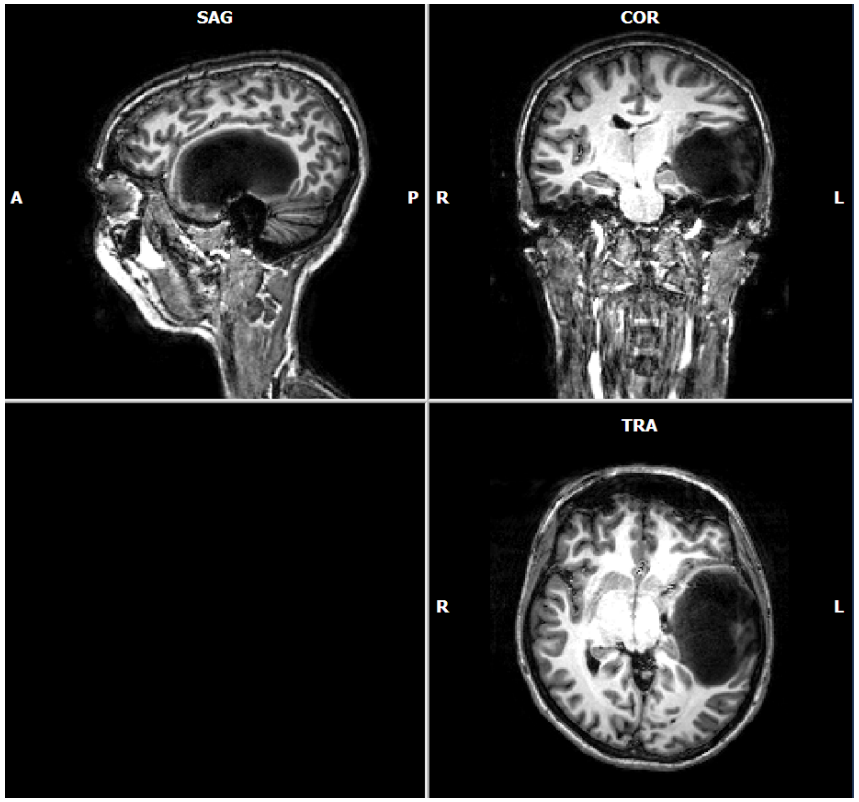
- Sensory-motor cortex
- Language-related areas
  - Broca
  - Wernicke
- Visual cortex, etc.

This goal is, in general, achieved by using the principles of brain mapping.

The goal of pre-surgical fMRI

To help guiding the scalpel of the neurosurgeon during neurosurgery, or the focus of radiation beams during radioablative therapy, while keeping as much function as possible.

Clinical fMRI helps in decision making and treatment plannig to find the right trade-off between the maximal invasiveness of the intervention and the minimal loss of function.



21 yrs female pt.
left temporal astrocytoma (Gr.II)
5 x 7.5 x 4 cm

Patients

The main candidates of pre-surgical fMRI are:

- Patients with brain tumors
- Patients with arterio-venous malformations
- Patients with drug-resistant epilepsies
- Patients with malformations of cortical development
- Patients with drug-resistant pain syndromes

Clinical fMRI is not always a stand-alone method

It is often used in conjunction with other functional mapping approaches, like EEG/MEG and PET, depending on the clinical question.

Compared to EEG/ MEG

Advantage:

- Precise spatial localization

Disadvantage:

- Worse temporal resolution
- Much less flexible, there's no bedside MRI (at the moment)

Compared to PET

Advantage:

- Non-invasive, no ionizing radiation
- More flexible paradigms can be used

Disadvantage:

- Deals with oxygenation only

Paradigm selection depends on the clinical question

- In brain tumor patients the location of the lesion defines the focus and paradigm of mapping
  - Tumors near the central sulcus: sensory-motor cortex mapping
  - Tumors in the frontal of temporal regions: language mapping
  - Tumors in the occipital cortex: visual mapping

- In drug-resistant epilepsy patients the clinical picture defines the paradigm and the approach
  - In case of a clearly defined epileptic focus the same is true as in brain tumors
  - In generalized epilepsies the identification of hemispherial language dominance is crucial
  - In epilepsies related to cortical malformations of development the identification of possible functional re-organizations can be helpful for treatment planning

Paradigms used in clinical fMRI

- Are usually block-design paradigms
  - They provide the highest power in the shortest time
  - Relatively easy to explain to the patients
  - Tasks can be flexibly timed within blocks

- The goal is to maximize functional contrast in the areas of interest while minimizing functional contrast in other areas
  - Well designed "passive" blocks contain no task related to the mapped functions, but contain tasks activating unmapped areas:
    - picture naming task contains pictures in the "active" condition and the phase scrambled version of the same images during the "passive" conditions to minimize functional contrast in low level visual areas by providing the same luminance and spatial frequency components for both conditions
    - passive comprehension contains recorded speech in the "active" condition and the same recording reversed during the "passive" conditions to minimize functional contrast in low level auditory areas by providing the same frequency content for both conditions

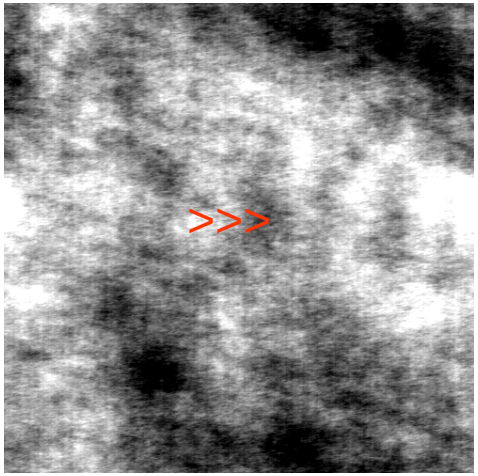
Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Picture naming**

During the **active part** of the task the patient has to covertly name the object presented on the image and has to make a living/object decision

ACTIVE:
Name it!
Living/Object?

…

CONTROL:
Relax!
Direction of arrows?



…

ClinicalMapping v6.6 © LR Kozák 2007-2010 , MRKK

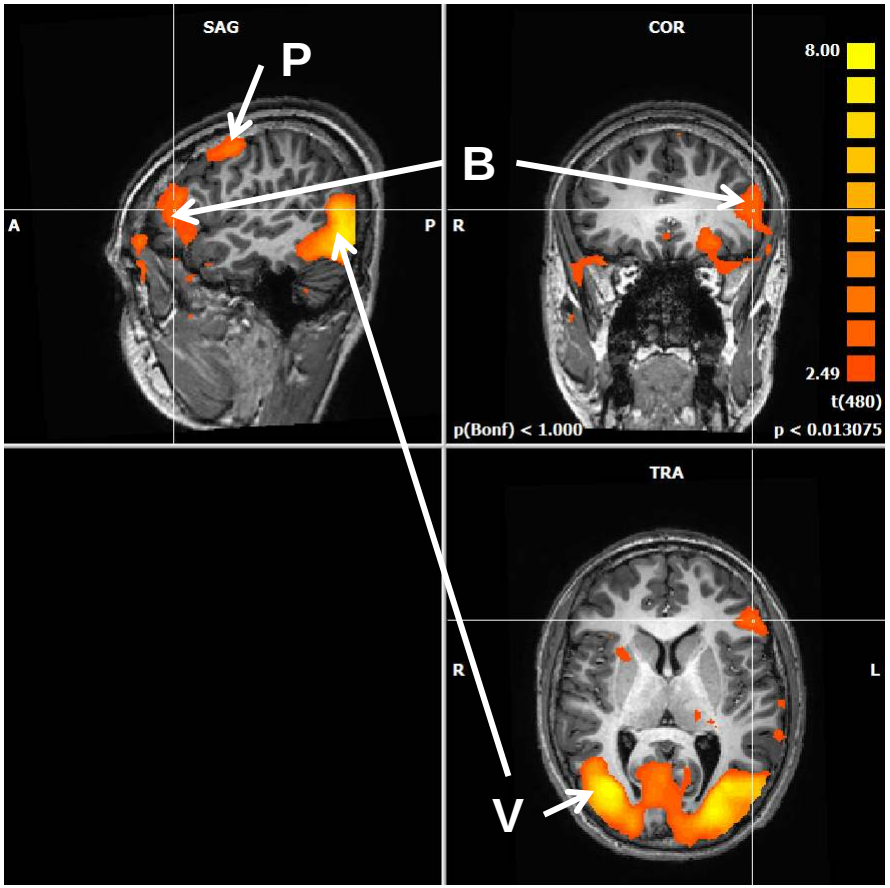
During the **passive part** the patient is instructed to relax without imagining anything into the cloudy image, and press a button indicating the direction of red arrows.

Stimuli are presented in every 3s within 24s blocks.

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Picture naming**

Patient 1 Right temporal lobe epilepsy

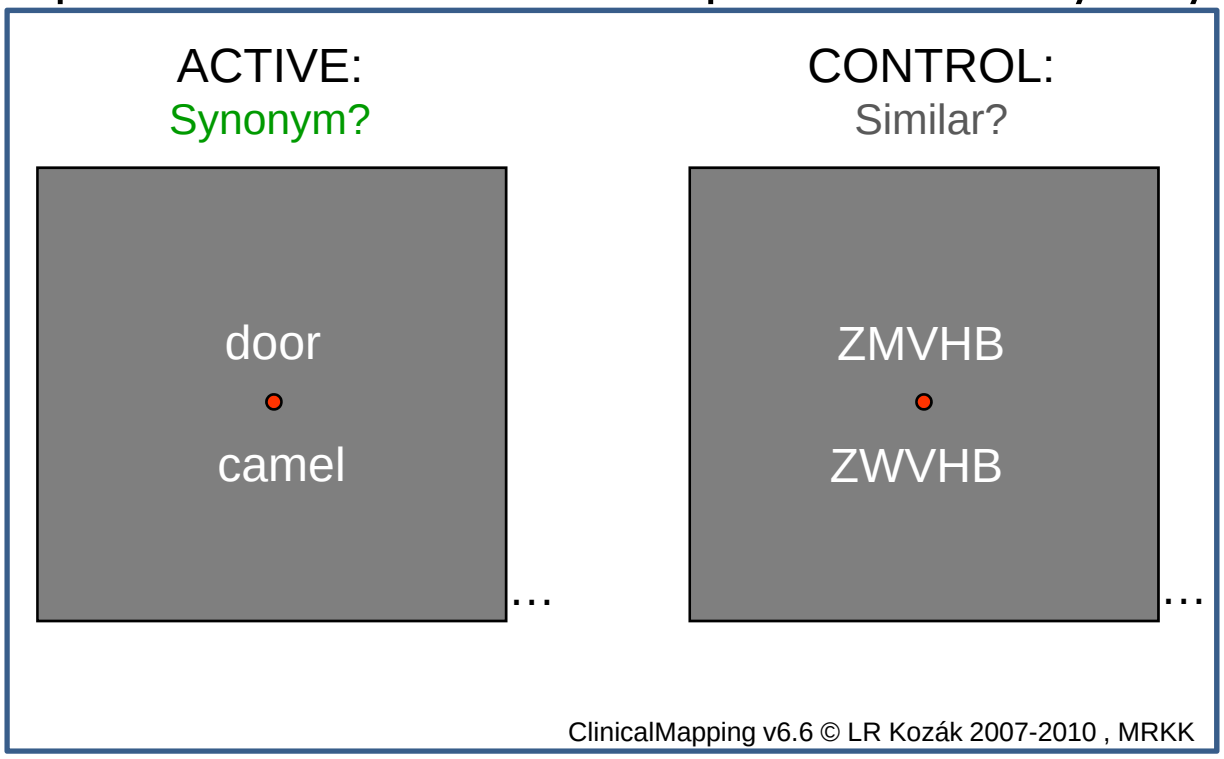
The picture naming task activates the higher order visual areas (V), the Broca area (B) and the left premotor region (P, because of the required motor response)



Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Synonym task**

During the **active part** of the task the patient has to indicate by button presses whether the words presented are synonyms or not.



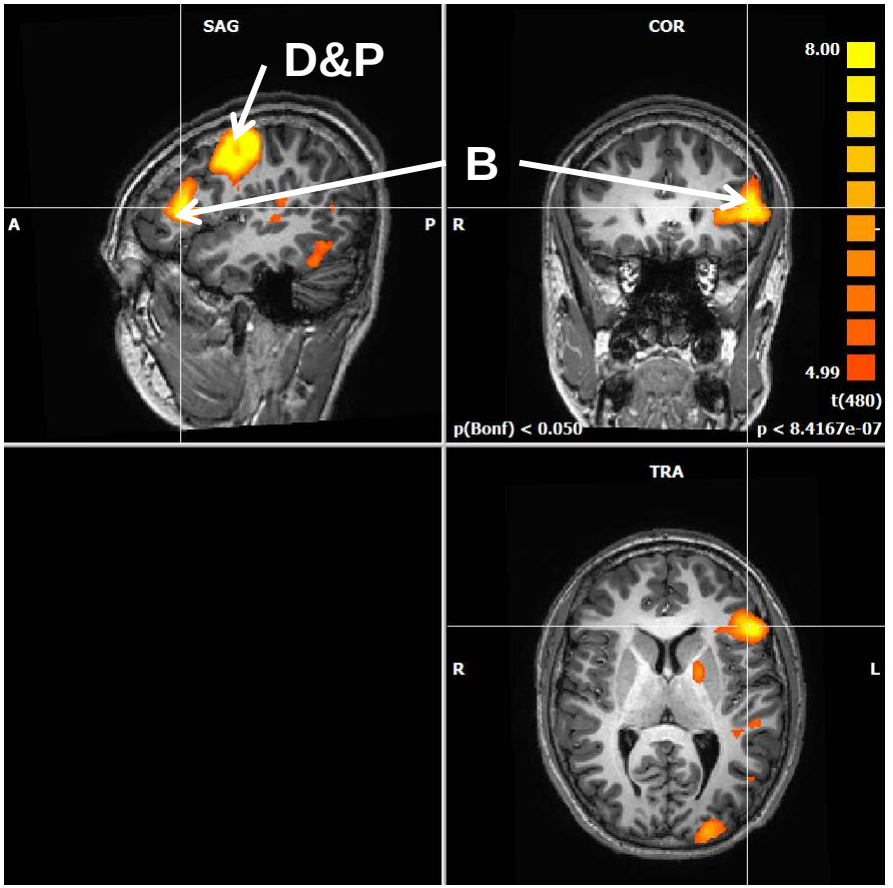
During the **passive part** the patient has to decide whether the two consonant strings are similary, but is instructed not to read the letters.

Stimuli are presented in every 3s within 24s blocks.

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Synonym task**

Patient 1 Right temporal lobe epilepsy

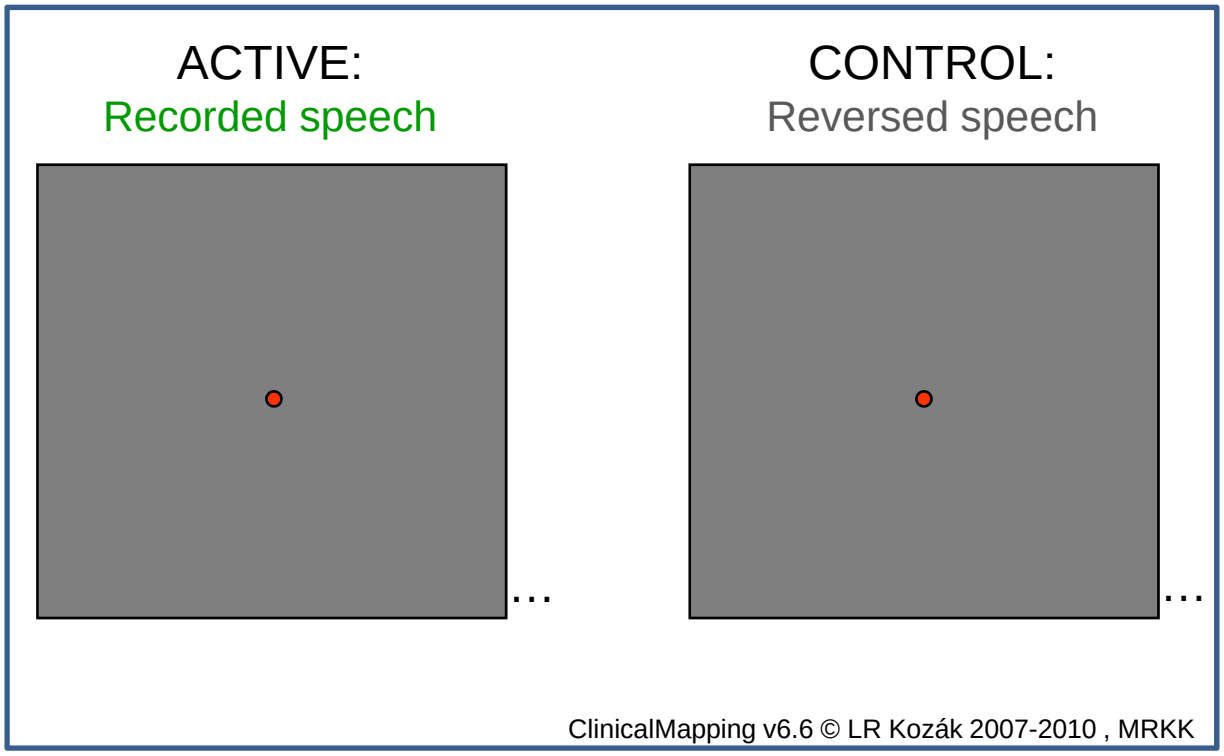
The synonym task activates the Broca area (B) and the left dorsolateral prefrontal cortex (D) and the left premotor region (P)



Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Speech comprehension**

During the **active part** of the task the patient is instructed to listen to a pre-recorded speech about a neutral topic (panda bears).



During the **passive part** the patient listens to the same recording made incomprehensible by reversing it.

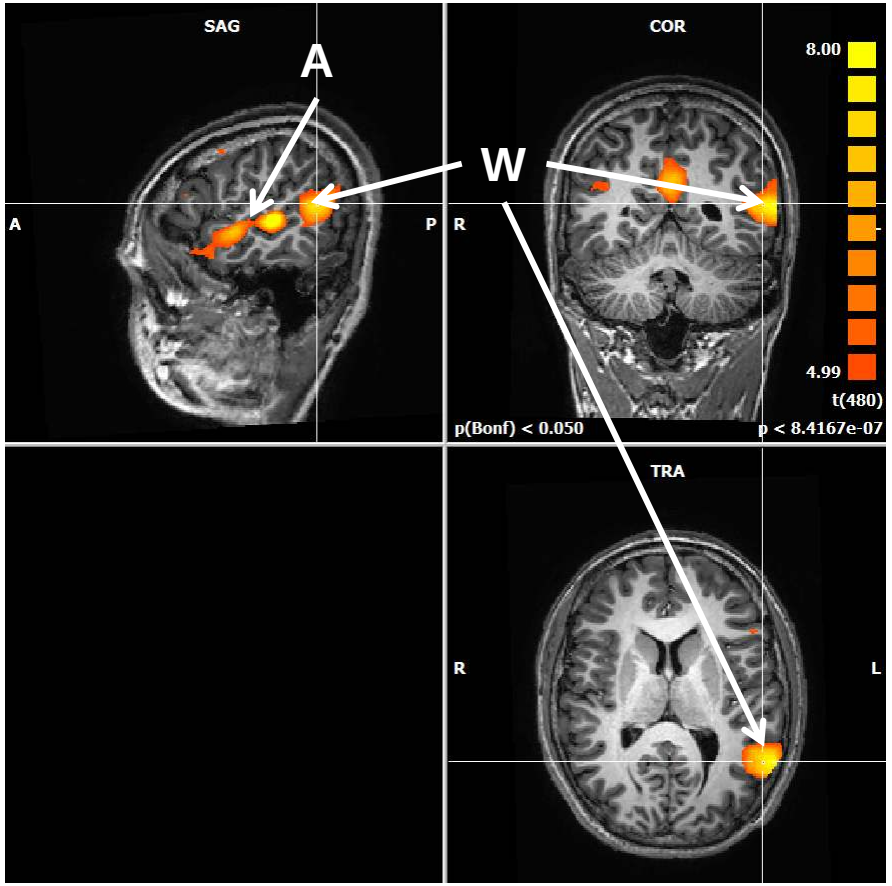
Stimuli are presented in 24s blocks.

After the scanning session the patient is asked some questions about the speech as a check for attention.

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Speech comprehension**

Patient 1 Right temporal lobe epilepsy

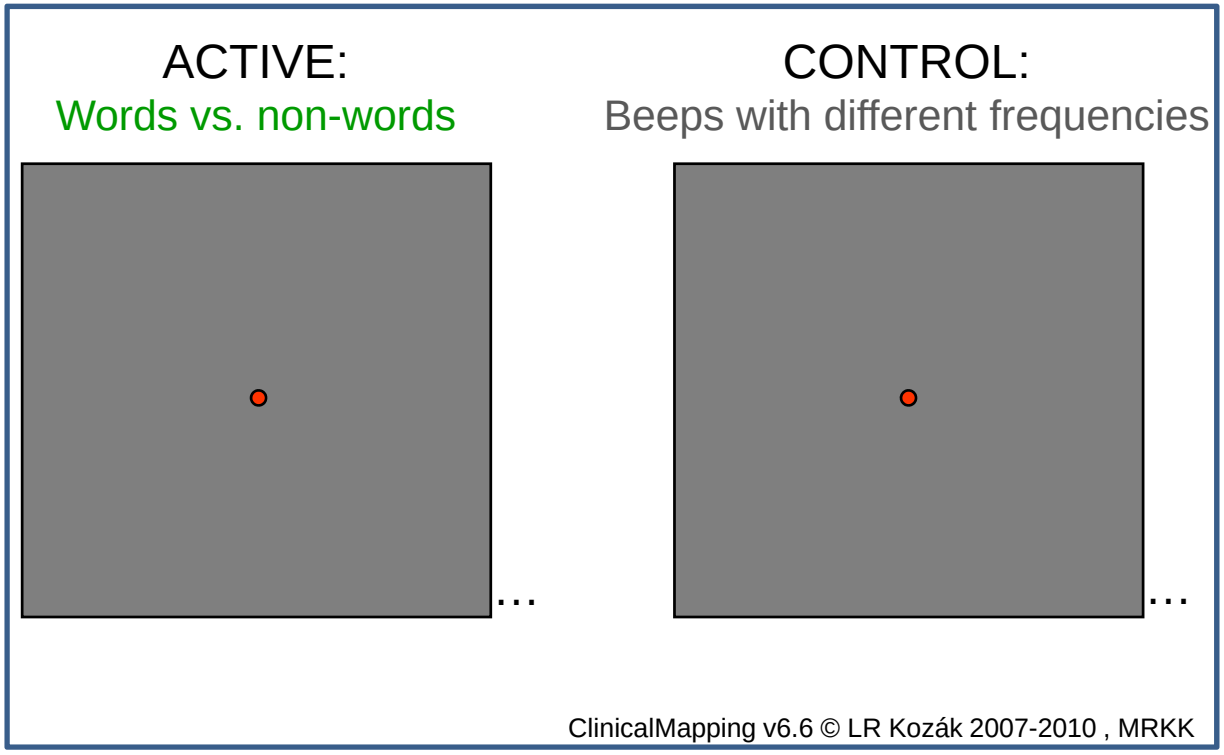
The speech comprehension task activates Wernicke's area (W) and the higher order auditory cortices (A).



Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Word-pseudoword task**

During the **active part** of the task the patient is instructed to make word-pseudoword decision on the presented Hungarian words/pseudowords.



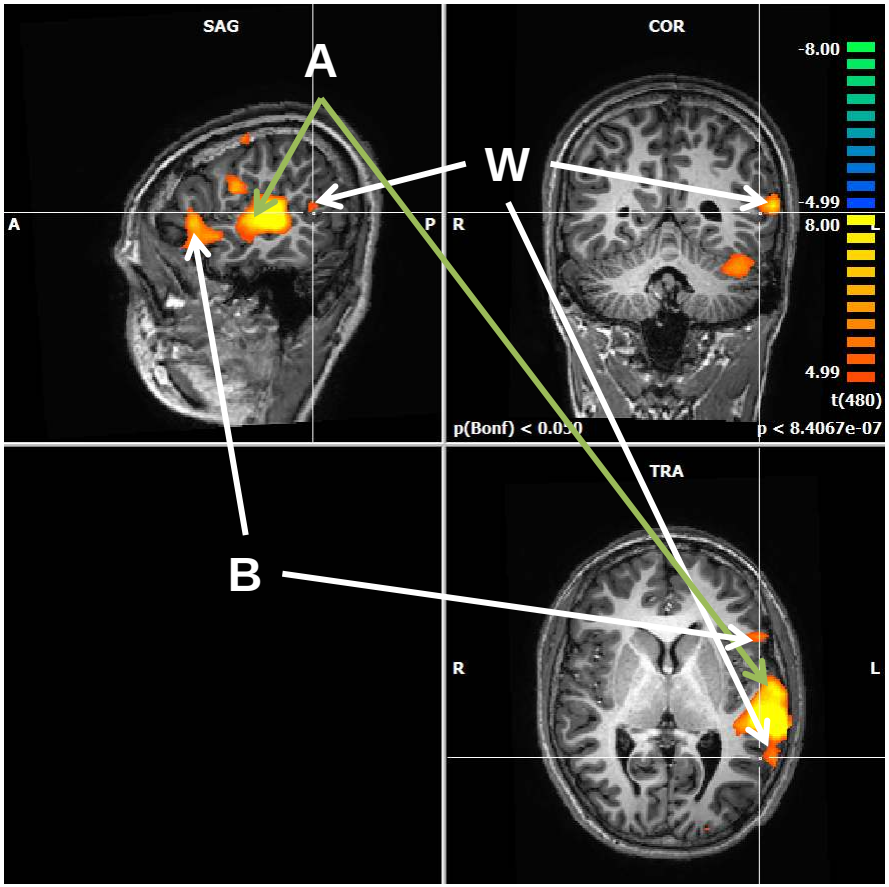
During the **passive part** the patient is instructed to make decision on the pitch of beeps presented.

Stimuli are presented in every 3s within 24s blocks.

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Word-pseudoword task**

Patient 1 Right temporal lobe epilepsy

The word-pseudoword task activates Wernicke's area (W), the higher order auditory cortices (A), and Broca's area (B).

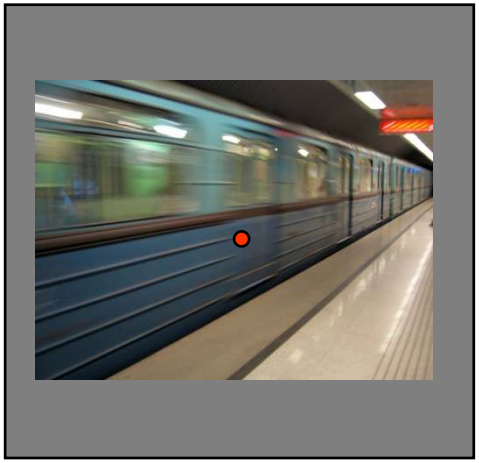


Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Memory encoding**

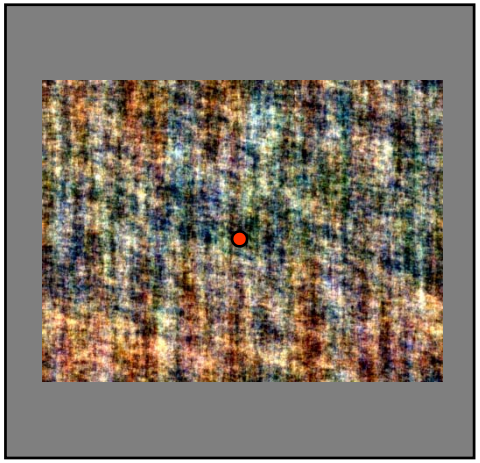
During the **active part** of the task the patient is instructed to look at the images and try to memorize them. The whole set is presented twice.

ACTIVE:
Try to remember



…

CONTROL:
Relax



…

ClinicalMapping v6.6 © LR Kozák 2007-2010 , MRKK

During the **passive part** the patient is instructed to relax.

The image pool contains 60 images. Stimuli are presented in every 3s within 30s blocks.

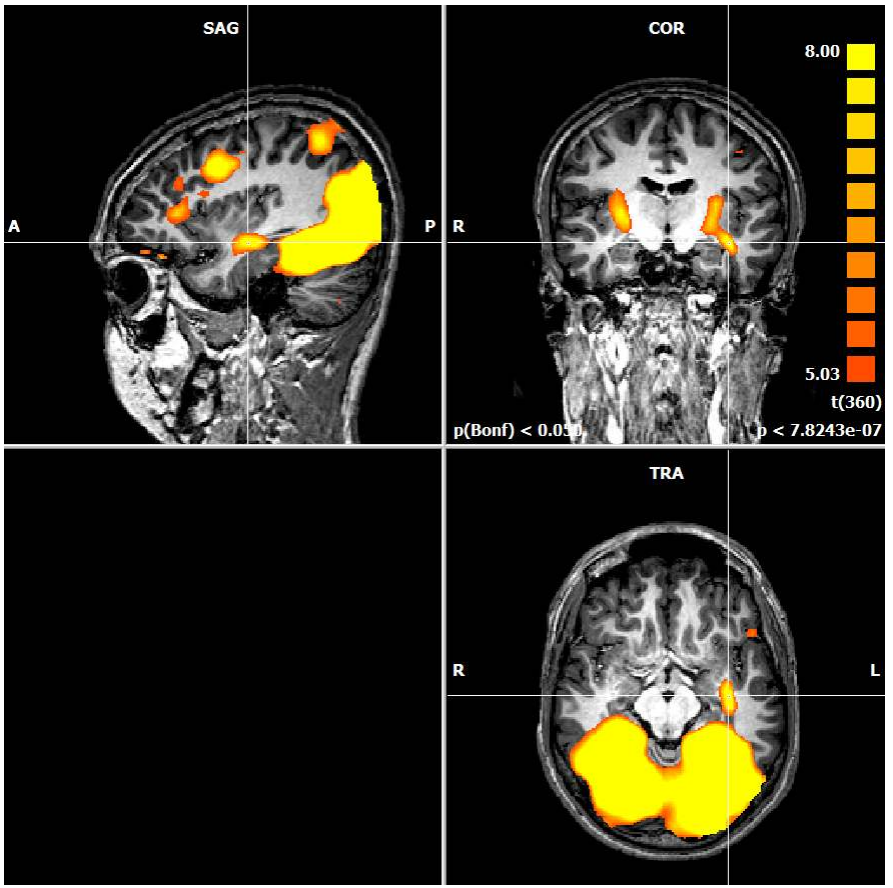
After the scanning session 32 images is shown to the patient who has to indicate which of them were presented previously.

Ávila et al. Am J Neurorad, 2006

Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Memory encoding**

Patient 1 Right temporal lobe epilepsy

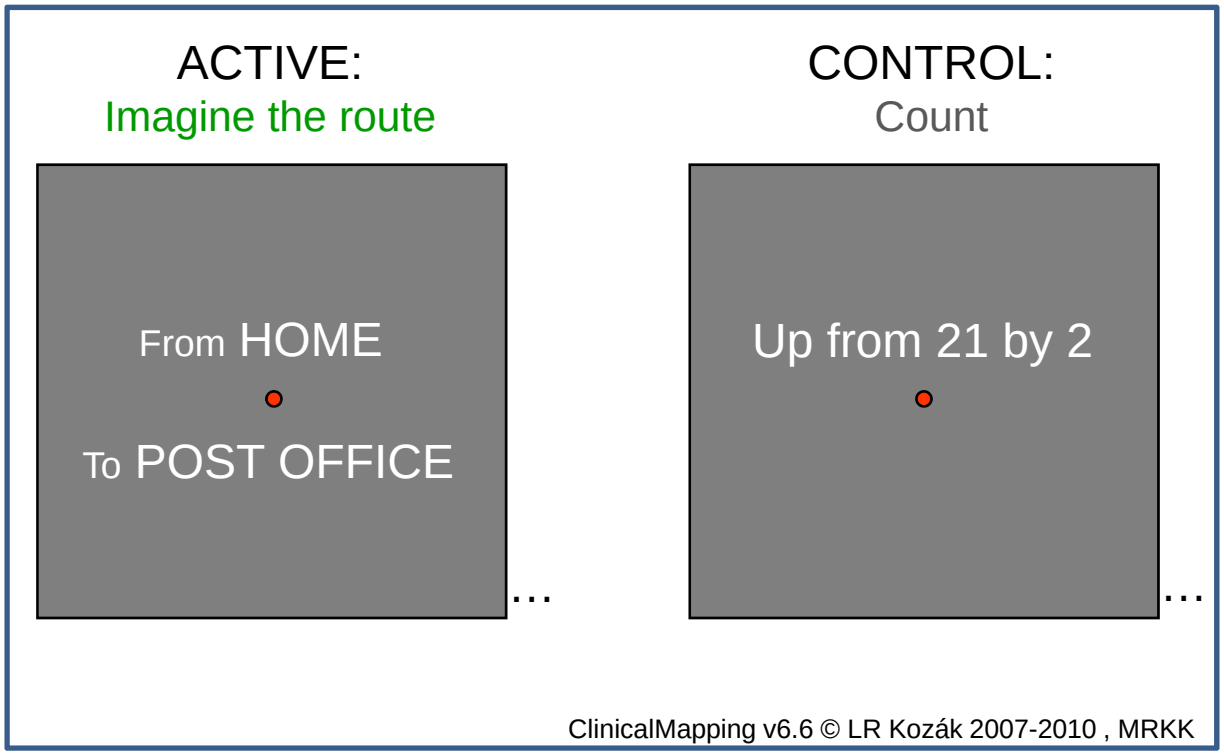
The task activates various areas including the visual cortex, areas involved in visual attention, even the Broca area. The cross shows a left lateralized activation focus in the temporal white matter.



Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Hometown walking**

During the **active part** of the task the patient is instructed to imagine walking along a familiar route, and to visualize the surroundings .



During the **passive part** the patient is instructed to count according to the given instruction.

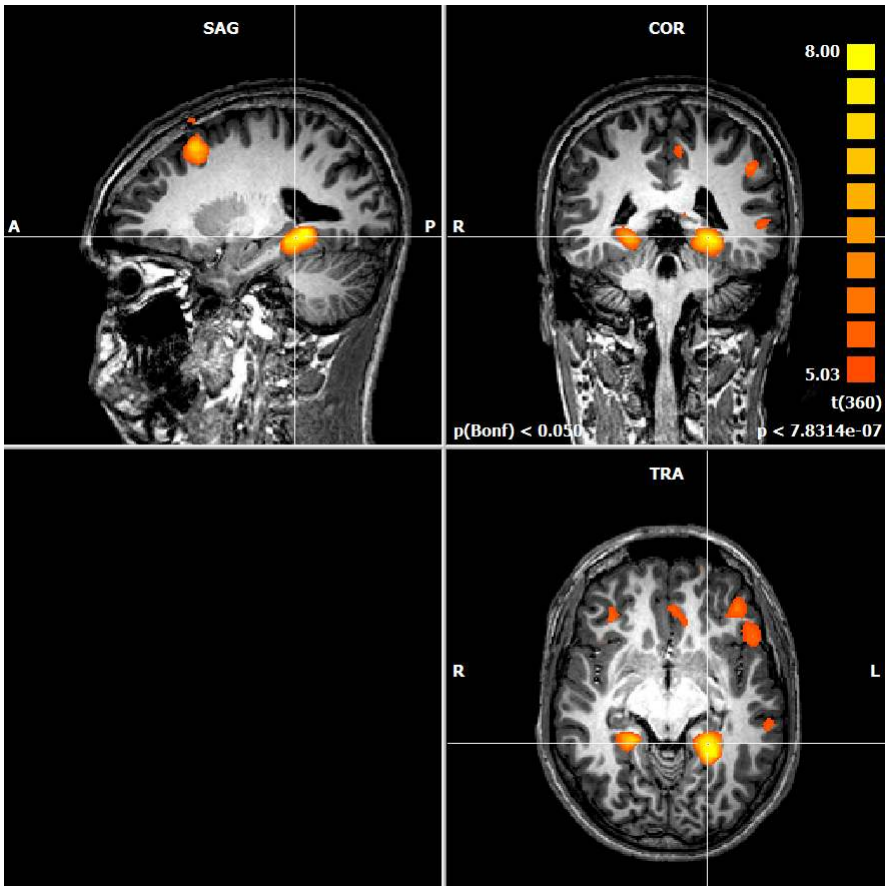
Stimulation is done in 30s blocks.

Ávila et al. Am J Neurorad, 2006

Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Hometown walking**

Patient 1 Right temporal lobe epilepsy

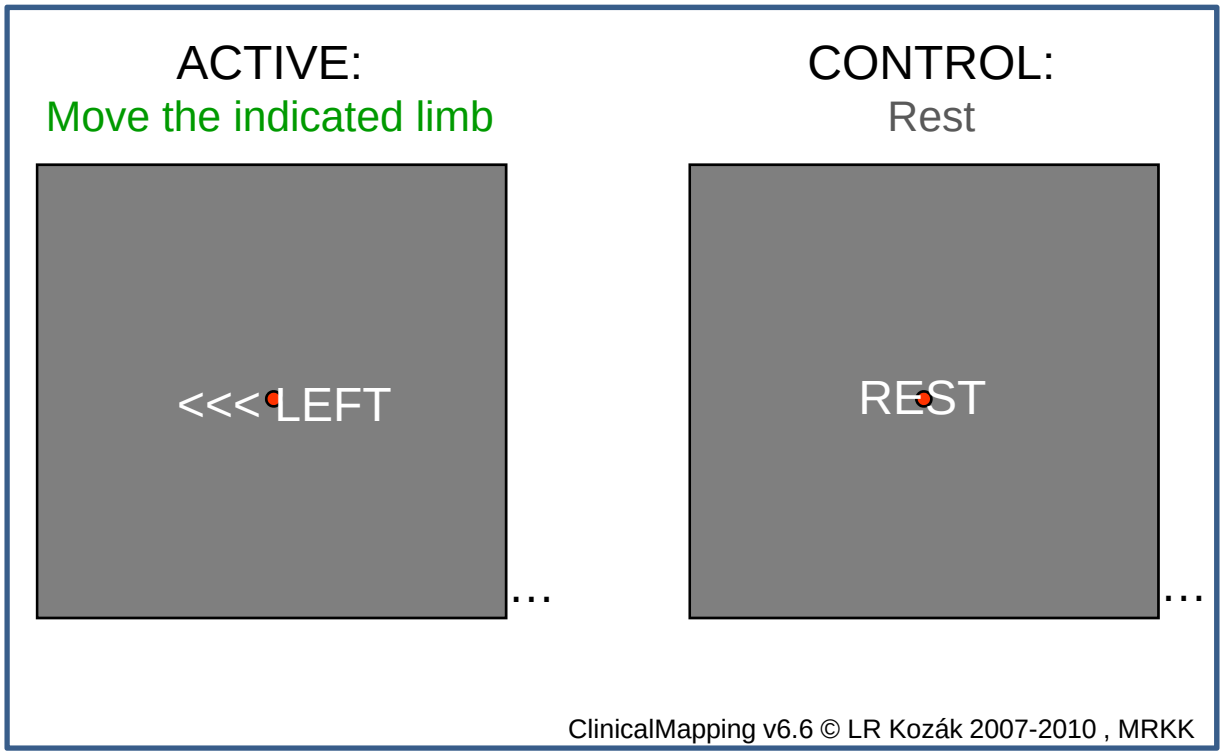
The task activates various areas. The cross shows an activation focus in the left mesial temporal lobe that is more extensive than that of the right mesial temporal lobe, suggestive of left lateralization of memory retrieval.



Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University - **Sensory-motor mapping**

During the **active part** of the task the patient is instructed to move the indicated limb. Hand areas are mapped by thumb opposition tasks;



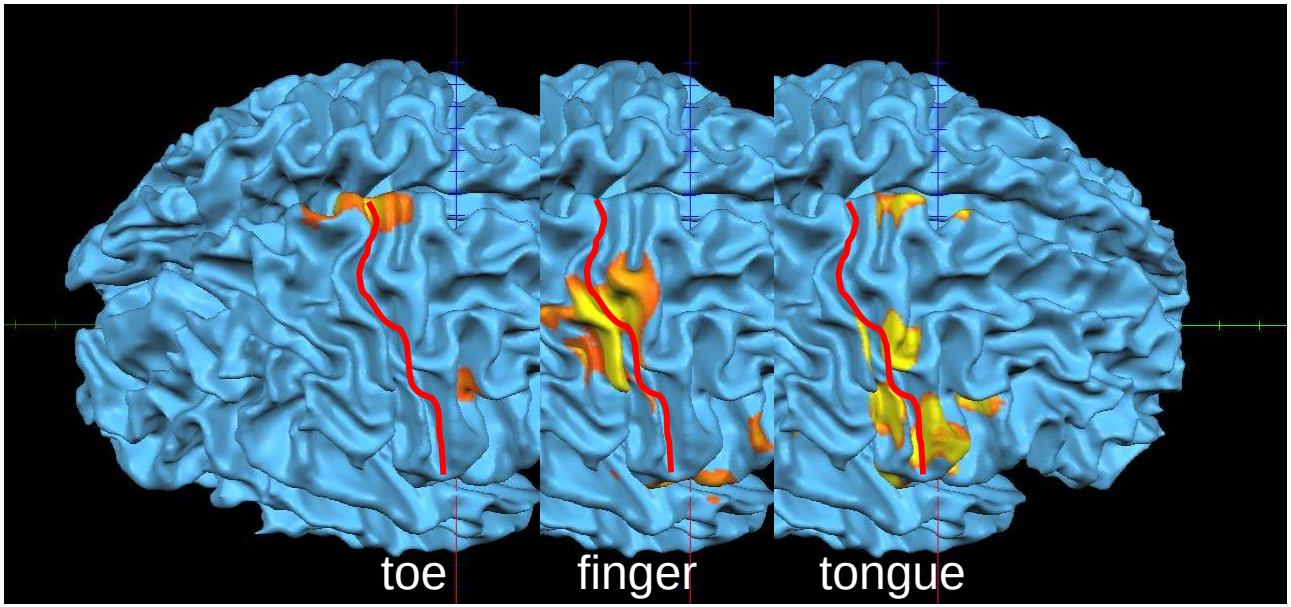
feet areas are mapped by a toe movement tasks; face areas are mapped by tongue movement task.

During the **passive part** the patient is instructed to rest passively.

Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Sensory-motor mapping**

Patient 2 Motor cortex mapping in drug resistant pain syndrome

The three tasks map the sensory-motor region along the central sulcus (marked with red line).



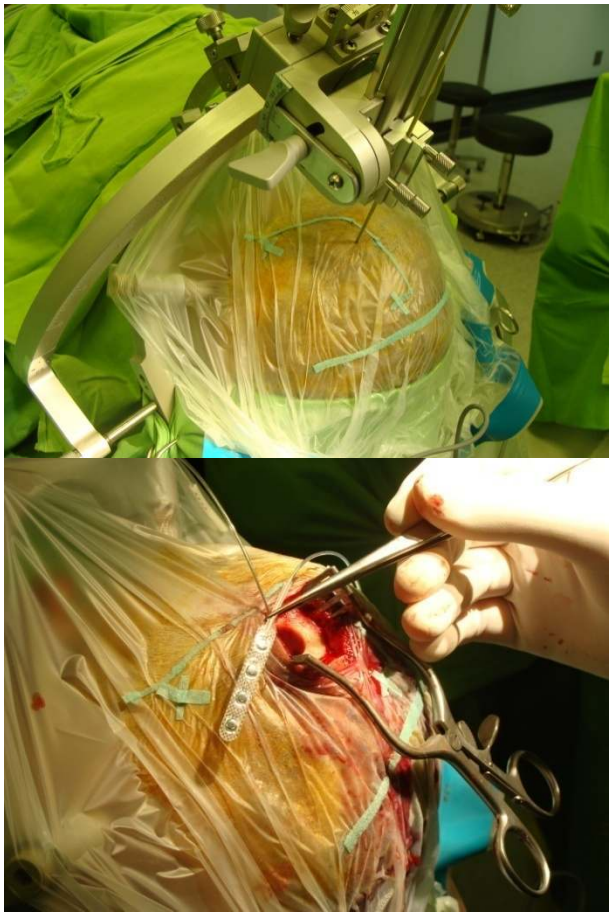
Patient examination @ MRKK in 2009,
LR Kozák, MD, PhD

Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Sensory-motor mapping**

Patient 2 Motor cortex mapping in drug resistant pain syndrome

The three tasks mapped the sensory-motor region along the central sulcus.

The mapping opened the possibility for minimally invasive electrode implantation in a stereotactic setting, that resulted in 60% decrease in perceived pain intensity.



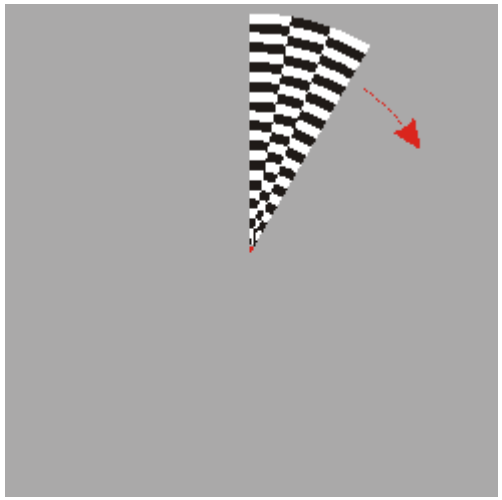
Patient examination @ MRKK in 2009,
LR Kozák, MD, PhD

Intraoperative images courtesy of I Valálik MD
Department of Neurosurgery, Szt János Kórház, Budapest, Hungary

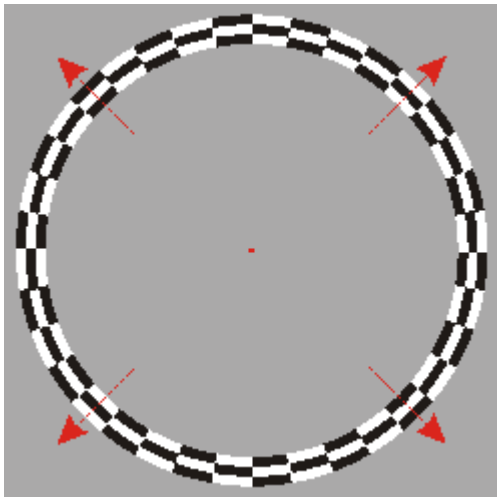
Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Retinotopic mapping**

During retinotopic mapping a polar coordinate system representation of the visual field is fitted to the retinotopic visual areas. The mapping consists of two steps: **polar angle mapping** by a rotating wedge stimulus, and **eccentricity mapping** by an extending ring stimulus.

Polar angle mapping:



Eccentricity mapping:



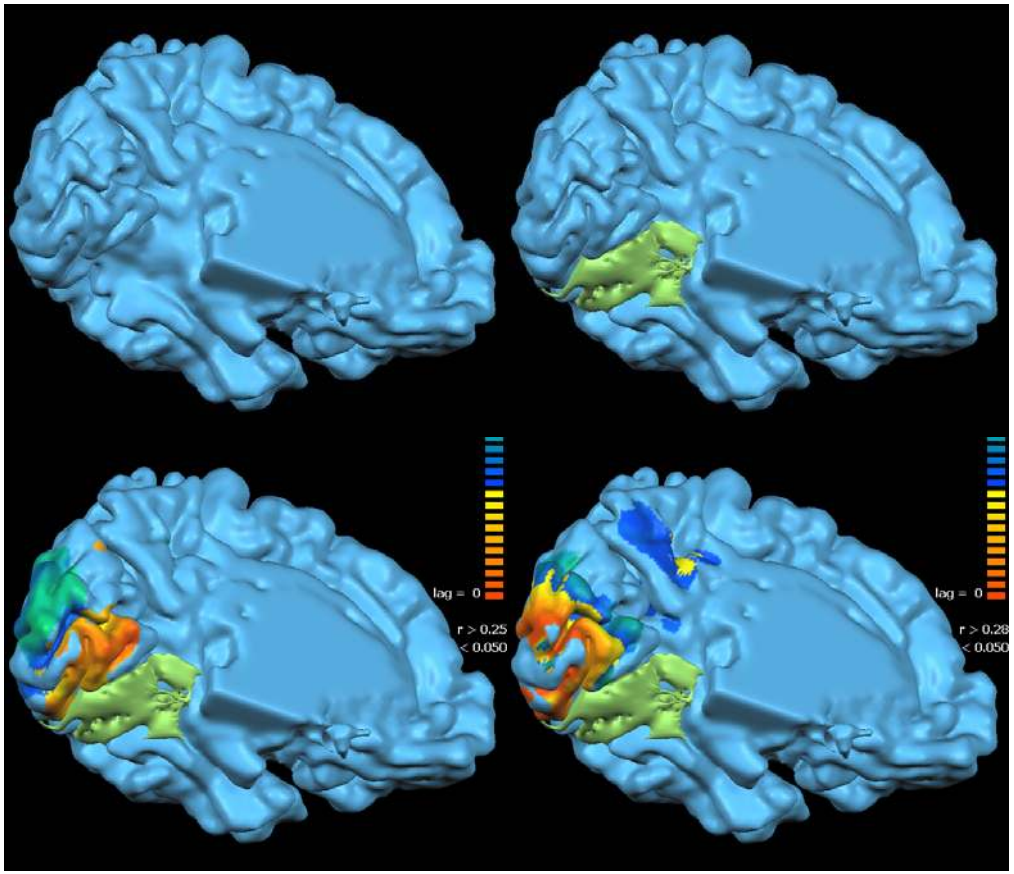
ClinicalMapping v6.6 © LR Kozák 2007-2010 , MRKK

Both stimuli have a superimposed counterphasing (8Hz) checkerboard pattern.

Paradigms used in the MR Research Center (MRKK), Semmelweis University – **Retinotopic mapping**

Patient 3 Retinotopic mapping in a case of occipital cortical dysgenesis

The dysgenesis (marked in green on the top right image) does not interfere with visual processing in the retinotopic visual areas (bottom images).



Patient examination @ MRKK in 2008,
LR Kozák, MD, PhD

Paradigm selection depends on the patient, as well

Patients can't always perform the tasks as intended

- The task is too complicated for the age, IQ, education, etc
  - The solution is simplification:
    - Leaving out attentional task
    - Leaving out task on passive condition
    - Using words to generate sentences
    - Using letters to generate words
- The patient can't see or hear
  - Change stimulus modality
- The patient can't move
  - Ask to imagine movement
  - Do passive movement, even in sedation

Souweidane et al., 1999 Pediatr Neurosurg; Liu et al., 2005 Br J Anaesth, Kozak et. al Symp. Neurorad, 2010

Specific issues in clinical fMRI analysis

While research oriented fMRI studies (including clinical research, as well) are usually group studies with groups level inferences, clinical fMRI studies are usually analyzed on the single subject level.

- While research oriented fMRI analyses deals with the multiple comparison problem by limiting the number of false positives
  - Bonferroni correction
  - False discovery rate
  - Familywise error
- In a single subject analysis limiting false negative voxels might equally be important
  - Using a more liberal statistical threshold with cluster size thresholding
    - But this raises further questions

Specific issues in clinical fMRI analysis cont'd

Everyone "works" in a different way

Although the shape of the hemodynamic response is roughly similar among functional areas,

Boynton et al., J Neurosci, 1996; Josephs et al., HBM, 1997, Zarahn et al., NeuroImage, 1997

response dynamics are different across brain regions

Schacter et al., NeuroImage, 1997

and individuals.

Aguirre et al., NeuroImage, 1998

Specific issues in clinical fMRI analysis cont'd

The pattern of activations depends heavily on the state of the patient (alertness, attention, anxiety, medications taken, etc.)

In the experiment of McGonigle et al. the same subject performed the same task 33 times in a two-months period. The activation maps differed substantially betweens sessions.

Proper pre-processing can limit the inter-session variability.

Smith et al. HBM, 2005

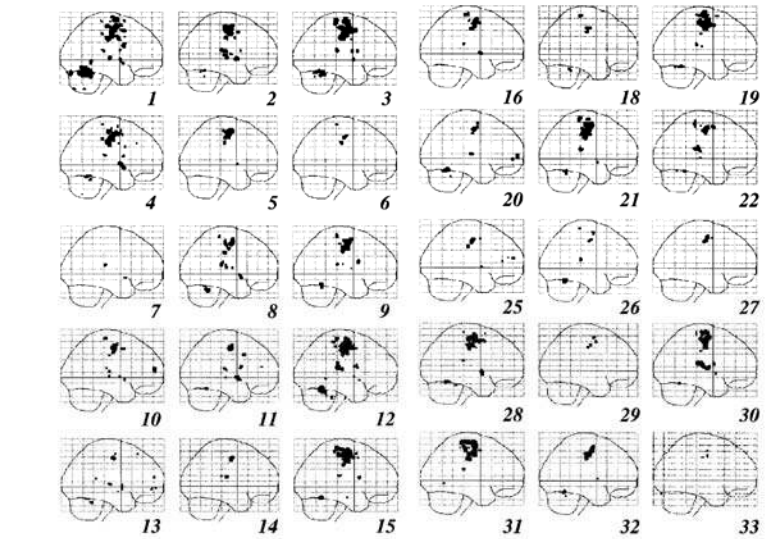


FIG. 2. Single-session sagittal MIPs for the motor paradigm. The number of each session is displayed below it. Although 33 sessions were collected, only 30 are shown here (sessions 17, 23, and 24 were rejected due to movement artifacts). All results are thresholded at $P < 0.05$ corrected for multiple comparisons unless otherwise stated.

McGonigle et al., NeuroImage, 2000

Specific issues in clinical fMRI analysis cont'd

Patients' state and BOLD signal:

- Everything vasodilatator: **signal ↓**
  - hyperventillation (e.g. stress related)
  - administration of insulin in diabetics
  - Anaemia
- Everything vasoconstrictor: **signal ↑**
  - hypercapnia
  - theophyllin / caffeine
  - high hematocrit
- There are cycle-specific effects in females **signal ↓↑**

Specific issues in clinical fMRI analysis cont'd

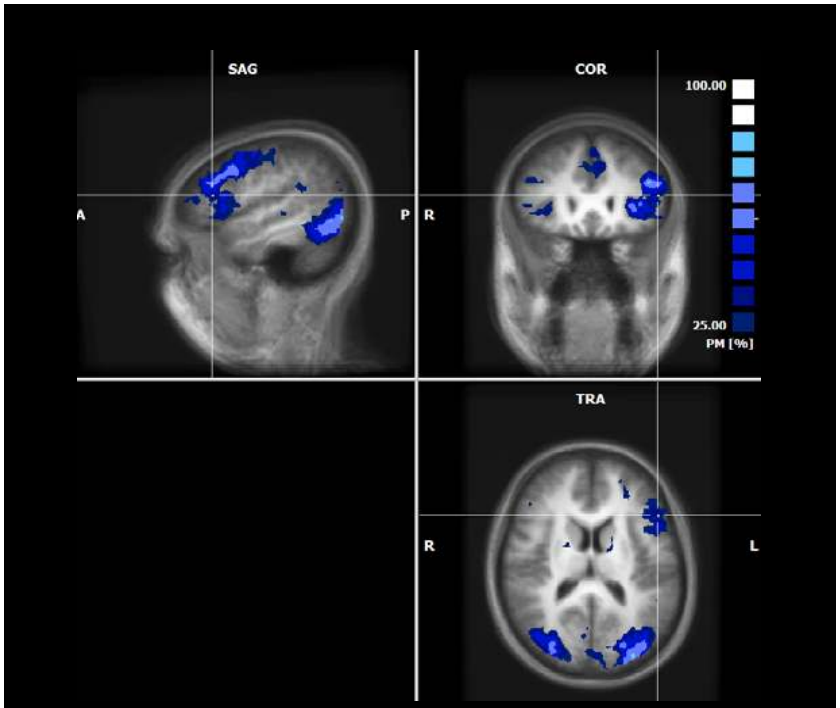
The activation maps differ across individuals

The localization of language areas are very variable across individuals

Binder et al., J Neurosci 1997;
Stippich et al., Neurosci Lett, 2003

Cognitive functions (thus brain responses) are age-dependent

Rotte et al., Age and Ageing, 2005



Probabilistic map of a picture naming task
The more patients activate a given voxel in Talairach normalized space the brighter the color representation is. (Normative data from MRKK, LR Kozak et al., ESNR 2008)

Specific issues in clinical fMRI analysis cont'd

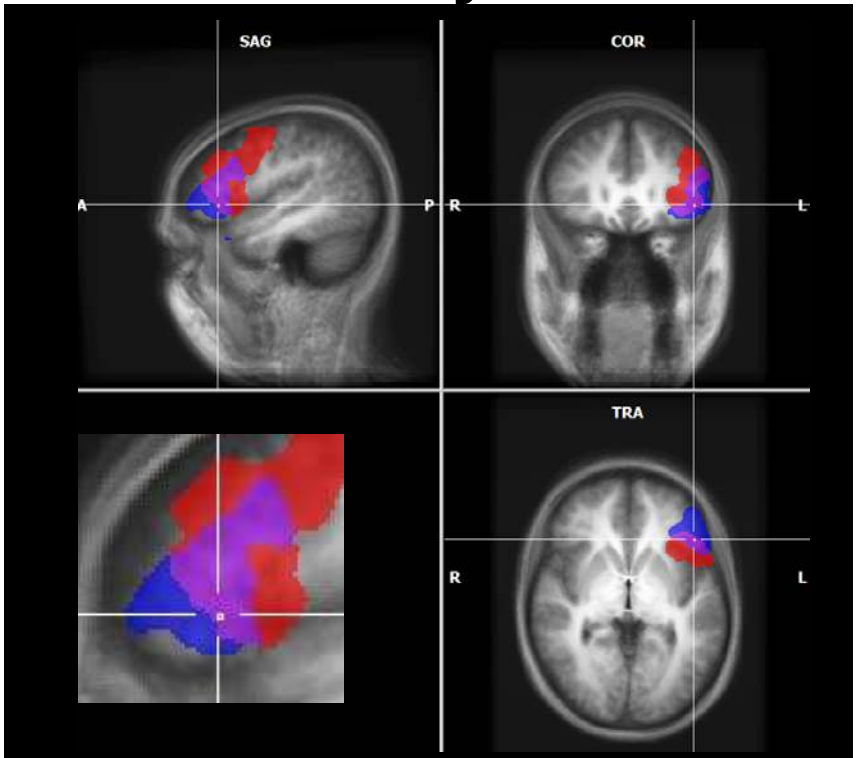
The activation maps differ between paradigms

Language lateralization depends on the paradigms used

Carpentier et al., Epilepsia, 2001;
Baciu et al., Neuroradiol 2005

Language maps depend on the paradigms used

Kozak et al., ESNR, 2008



Language activations in the Broca area depend on the paradigm used
Picture naming; Synonym task; Intersection
(Normative data from MRKK, LR Kozak et al., ESNR 2008)

Specific issues in clinical fMRI analysis cont'd

The BOLD response depends on brain pathology

e.g. in the vicinity of large gliomas, the BOLD amplitude decreases at least in about half of the cases

Grummich et al., NeuroImage, 2006

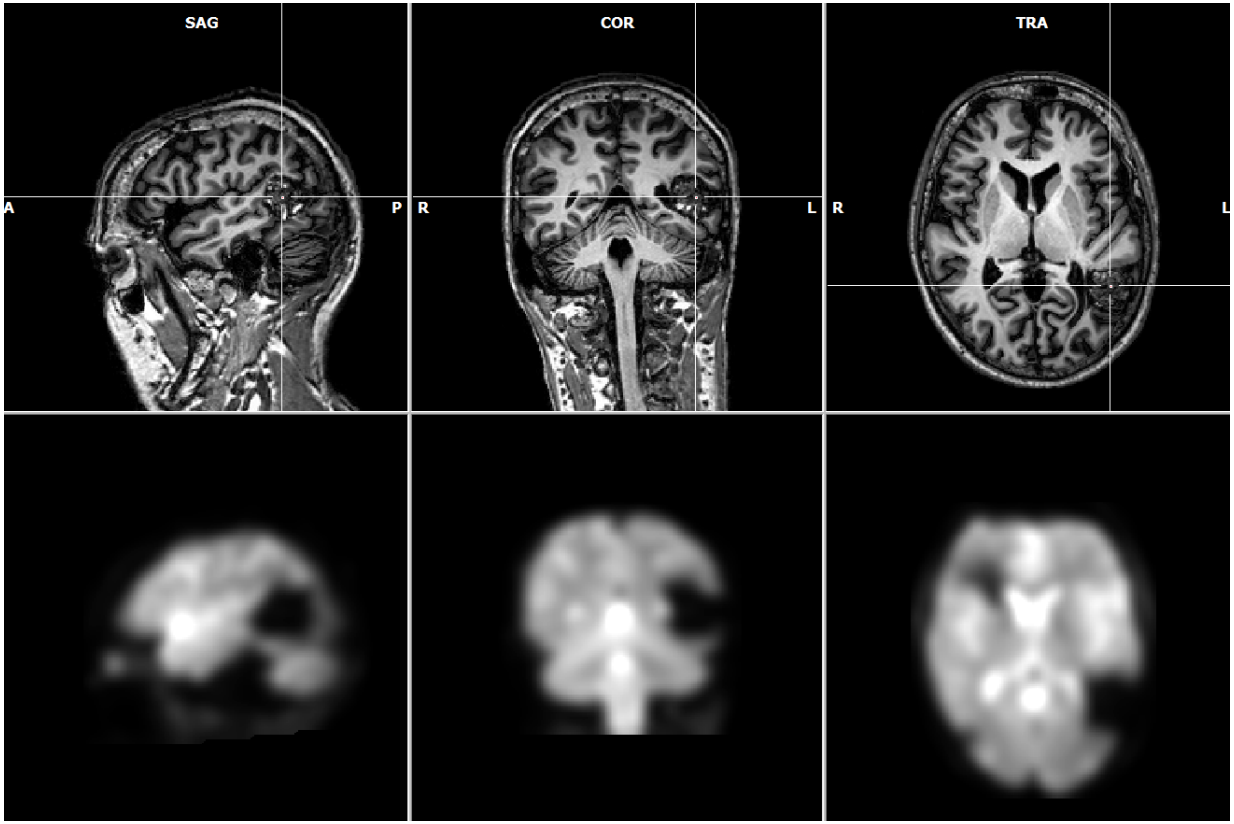
Lesion-related changes might stem from:

- Compression **signal ↓**
- Neovascularization **signal ↑**
- Metabolic changes **signal ↓↑**
- Therapy (drugs, surgery) **signal ↓↑**
- Cavernous angioma (susceptibility) **signal ↓**
- Epileptic activity **signal ↓↑**

Specific issues in clinical fMRI analysis cont'd

Patient 4 Cavernous angioma

The cavernous angioma in the temporo-parieto-occipital junction causes an extensive signal dropout in the BOLD-EPI images near the expected location of the Wernicke area.



Patient examination @ MRKK in 2010,
LR Kozák, MD, PhD

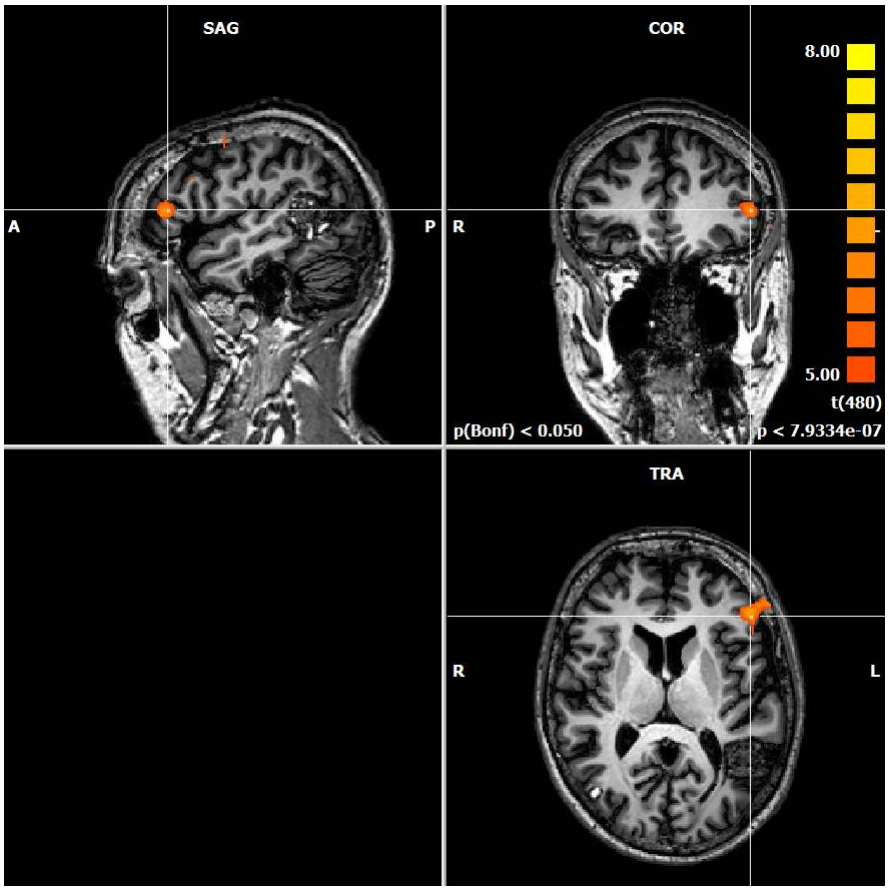
Specific issues in clinical fMRI analysis cont'd

Patient 4 Cavernous angioma

The cavernous angioma in the temporo-parieto-occipital junction causes an extensive signal dropout in the BOLD-EPI images.

The Wernicke area can't be mapped in this patient despite the lack of apparent language deficit.

The cross shows the Broca area which is not affected by the susceptibility artifact caused by cavernous angioma.

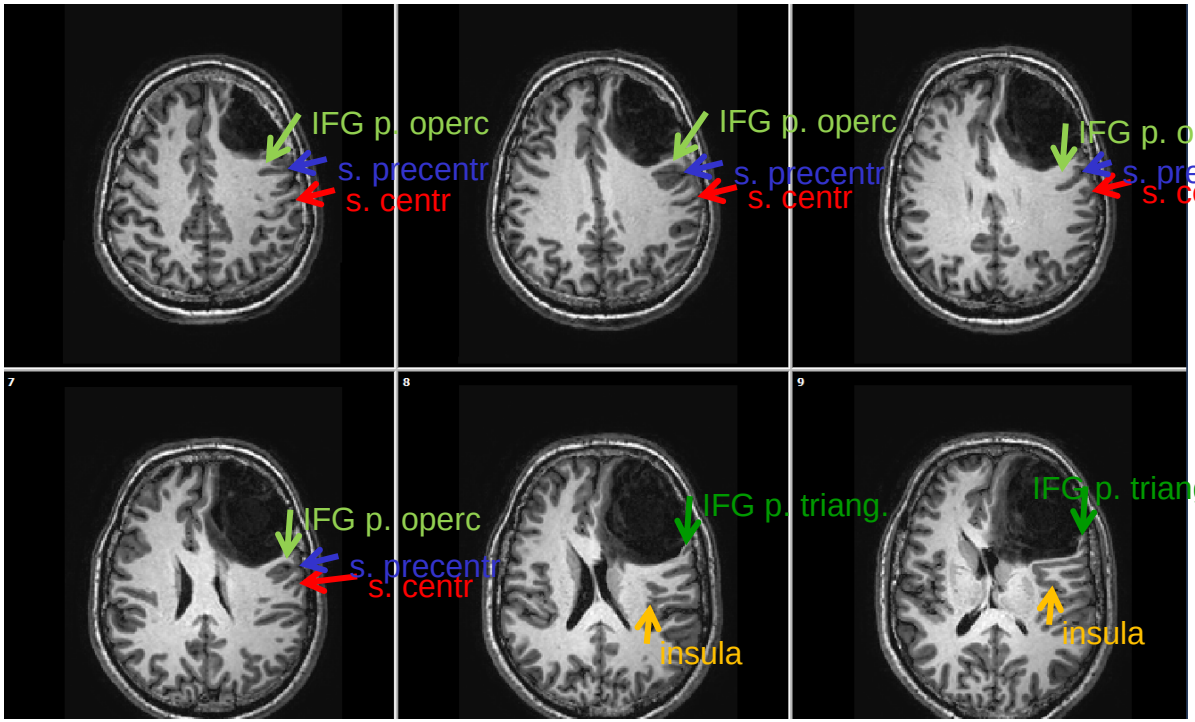


Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

Specific issues in clinical fMRI analysis cont'd

Patient 5 Frontal tumor

The big frontal tumor compresses the inferior frontal gyrus (IFG), the anatomical region where Broca area is expected.



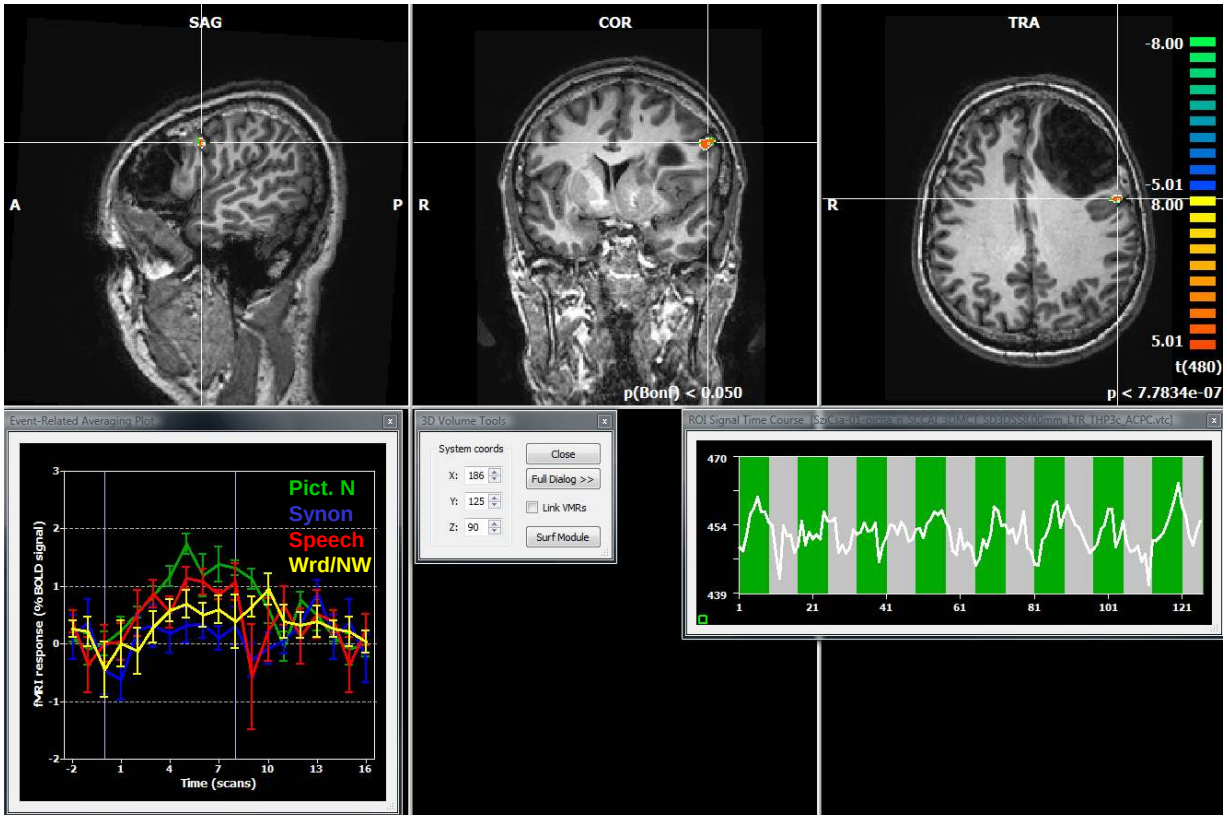
Patient examination @ MRKK in 2010,
LR Kozák, MD, PhD

Specific issues in clinical fMRI analysis cont'd

Patient 5 Frontal tumor

The big frontal tumor compresses the inferior frontal gyrus (IFG), the anatomical region where Broca area is expected.

The activation at the Broca area is less extensive than in normal controls.



Patient examination @ MRKK in 2010,
LR Kozák, MD, PhD

Specific issues in clinical fMRI analysis cont'd

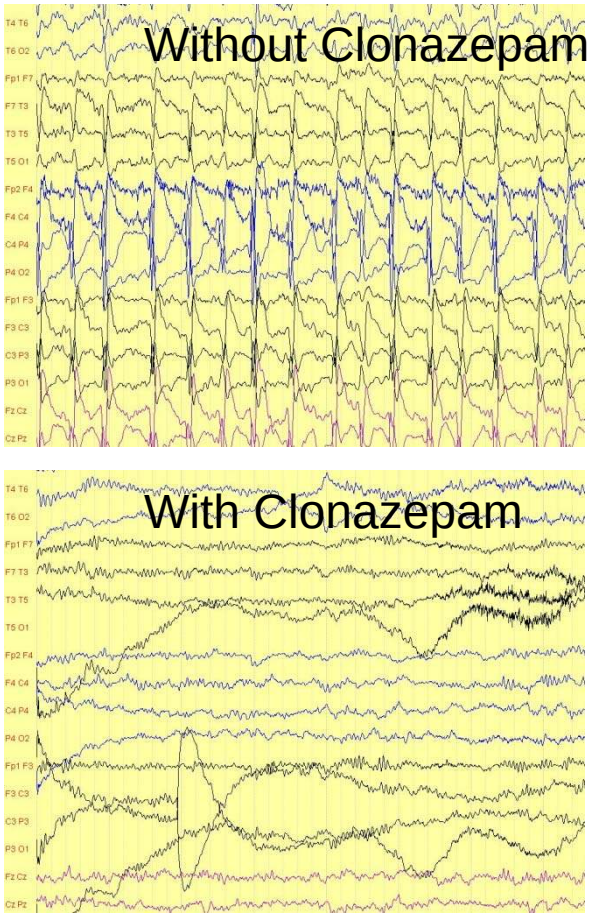
Patient 6 Polymicrogyria with drug resistant epilepsy

Epileptic activity can seriuosly affect fMRI

In a case of cortical dysgenesis in a pediatric patient we encountered a condition of electric status epilepticus during sleep (ESES) upon propofol anesthesia.

As the amplitude of epileptic activity (700μV) was more than 10 times higher than the expected 5μV amplitude of the somatosensory evoked potentials with propofol anesthesia (Liu et al. Br J Anaesth, 2005) ESES masked the effect of passive limb movement.

Patient examination @ MRKK in 2008
Kozak et al., Ideggyogy Sz, 2009
Kozak et al., Symposium Neuroradiologicum, 2010



Specific issues in clinical fMRI analysis cont'd

The lack of standardization

There is still a lack of standardization regarding paradigms, processing steps, statistical methods

- This is partly due to differences in equipment
- Differences in clinical practice

Currently the only solution is to create in-house normative databases

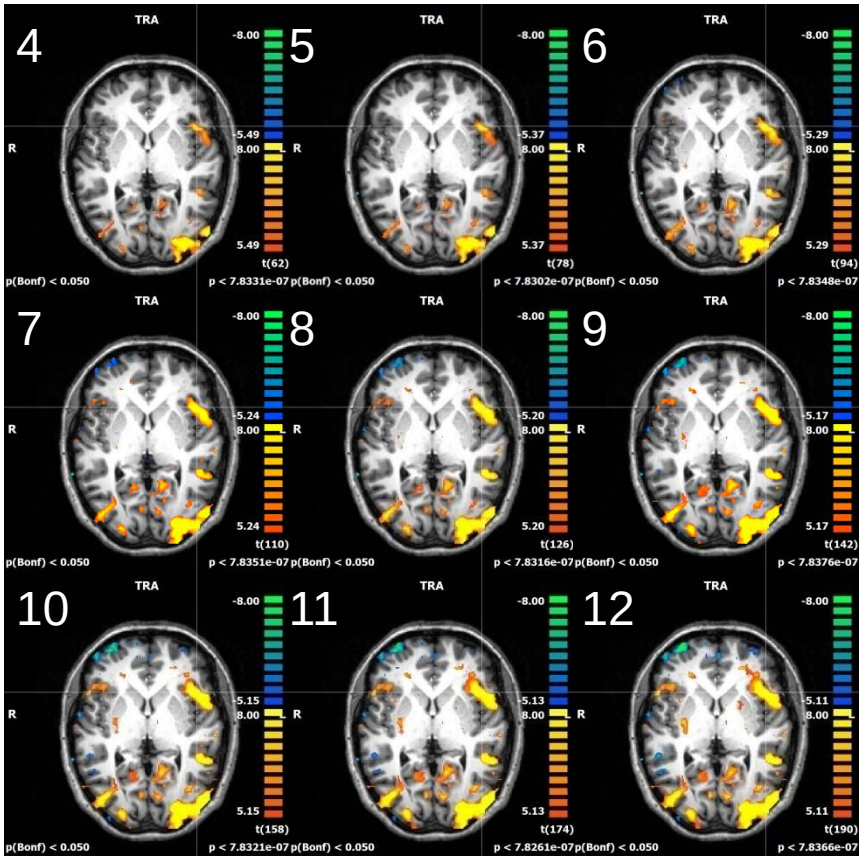
- Evaluate the paradigms on healthy subjects prior to patients
- Re-evaluate the paradigms based on patient studies
- Re-evaluate the paradigms based on input from neurologists and neurosurgeons

Specific issues in in-house validation

The activation maps depend on the number of blocks

As the number of stimulation blocks increases the signal to noise ratio also increases.

The statistical maps become more and more detailed as more voxels survive the multiple comparison correction at a given statistical significance level.



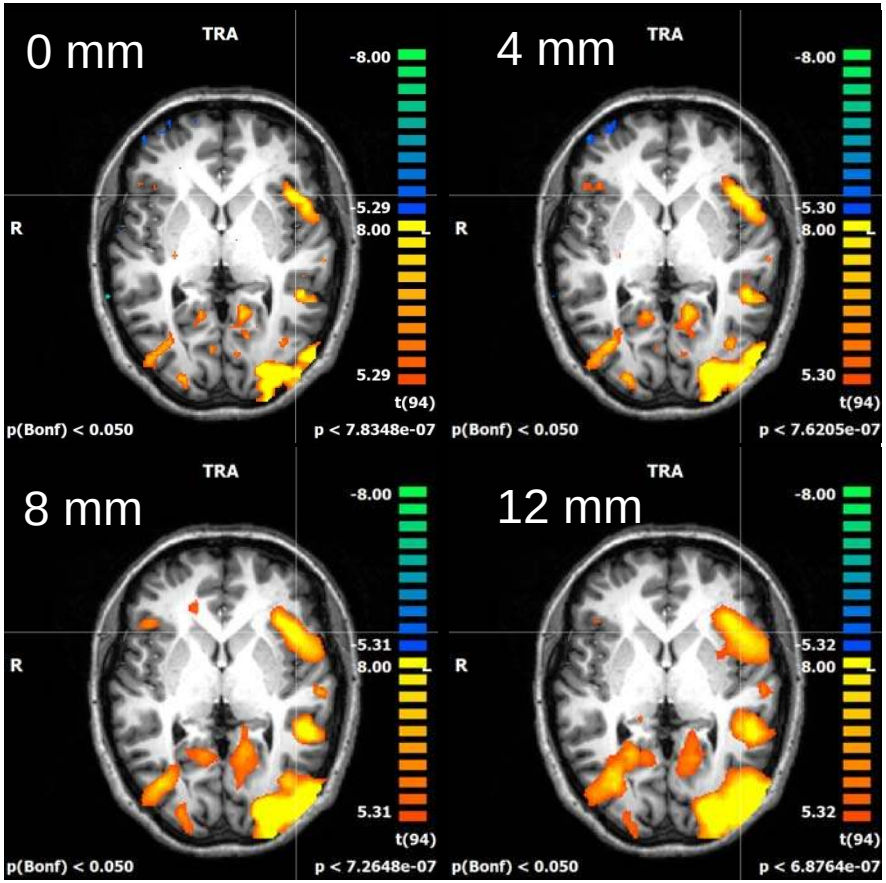
Kozak et al., ESNR, 2008
Kozak et al., Symposium Neuroradiologicum, 2010

Specific issues in in-house validation cont'd

The activation maps depend on preprocessing parameters

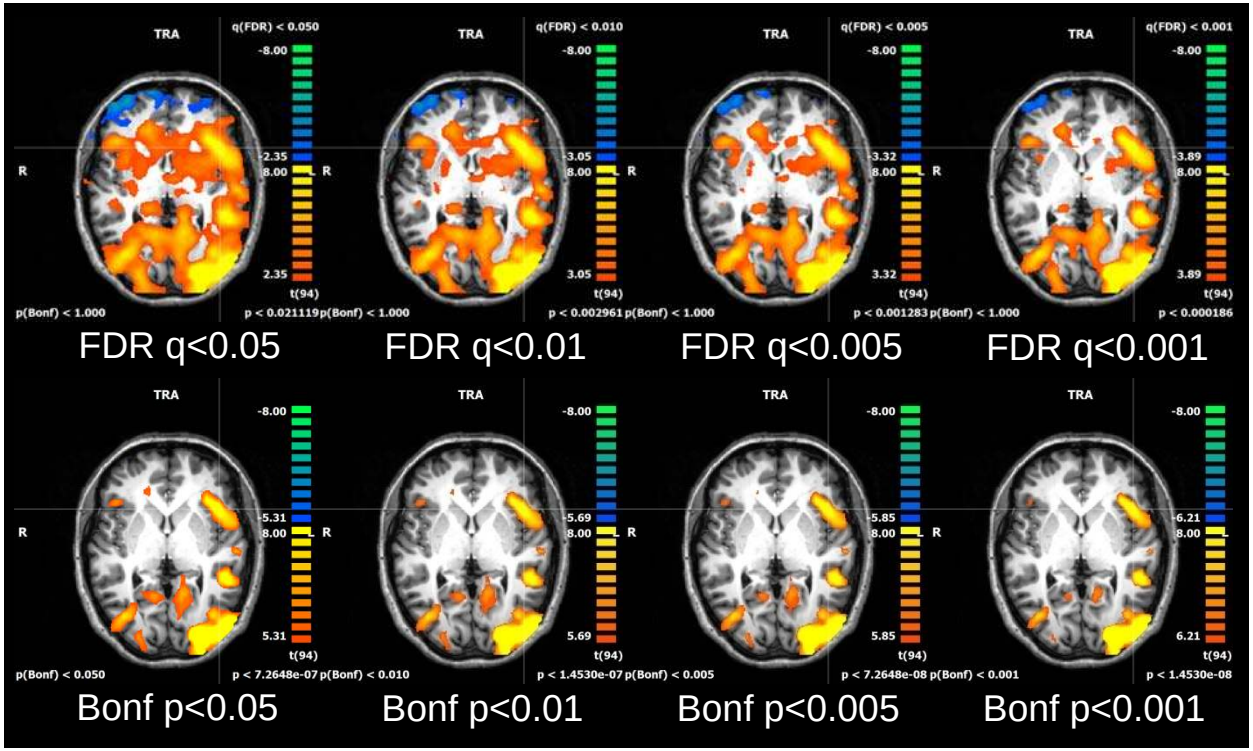
Spatial smoothing increases the signal to noise ratio.

The statistical maps become more widespread with smoothing as more voxels survive the multiple comparison correction at a given statistical significance level. (However, spatial resolution is decreasing with increasing smoothing kernel)



Kozak et al., ESNR, 2008
Kozak et al., Symposium Neuroradiologicum, 2010

Specific issues in in-house validation cont'd



Statistical thresholding determines the activation map. With stricter thresholds the number of false positives decrease, thus the extent of activations also decrease.

Kozak et al., ESNR, 2008; Kozak et al., Symposium Neuroradiologicum, 2010

Specific issues in clinical fMRI analysis cont'd

Lateralization index calculation

Important in generalized epilepsies to asses language lateralization.

$$LI=(Left_{ActiveVoxels}-Right_{ActiveVoxels})/(Left_{ActiveVoxels}+Right_{ActiveVoxels})$$

As the statistical maps heavily depend on thresholding a novel threshold independent method for language lateralization estimation was suggested by Suarez et al. (Epilepsy Behav, 2009). They approach is based on the weighted distribution of t-scores found in the ROIs.

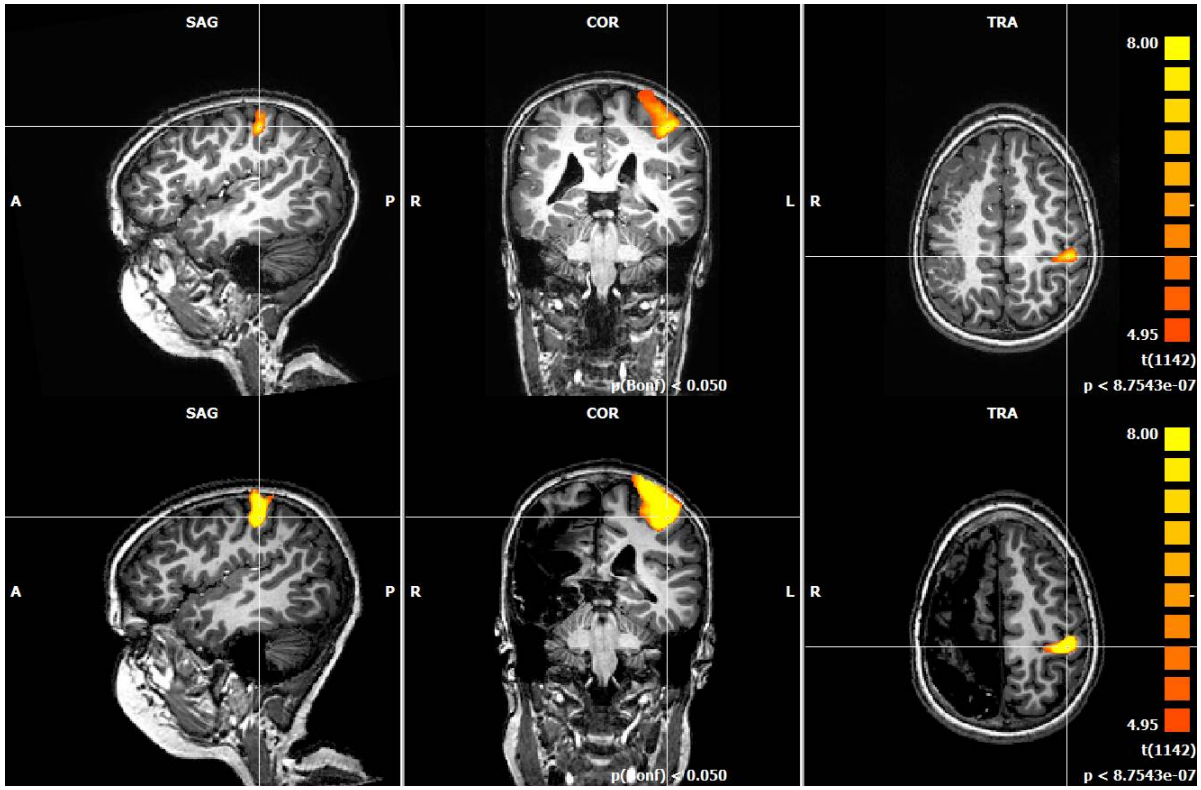
The threshold independ LI calculation leads to the same results as FDR $q<0.05$ thresholding.

Tóth et al. & Kozak et al. Symp. Neurorad., 2010

fMRI can prove functional reorganization

Patient 6 Polymicrogyria with drug resistant epilepsy

Activation upon passive right hand movement (healthy limb) in propofol sedation shows up in the expected location in the contralateral (healthy) hemisphere, both preoperatively and postoperatively

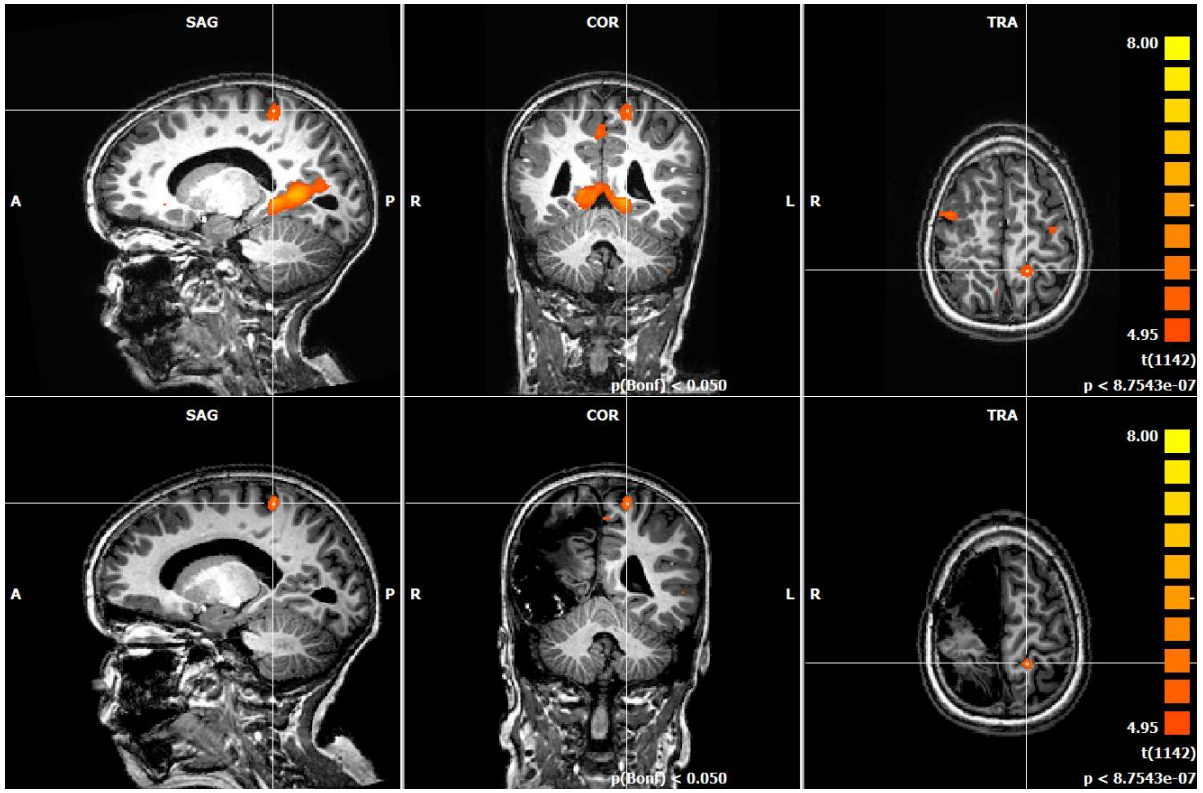


Patient examination @ MRKK in 2008
Kozak et al., Ideggyogy Sz, 2009
Kozak et al., Symp. Neuroradiologicum, 2010

fMRI can prove functional reorganization

Patient 6 Polymicrogyria with drug resistant epilepsy

Activation upon passive left hand movement (affected limb) in propofol sedation shows up in the ipsilateral (healthy) hemisphere, both preoperatively and postoperatively, suggestive of functional reorganization to the healthy hemisphere



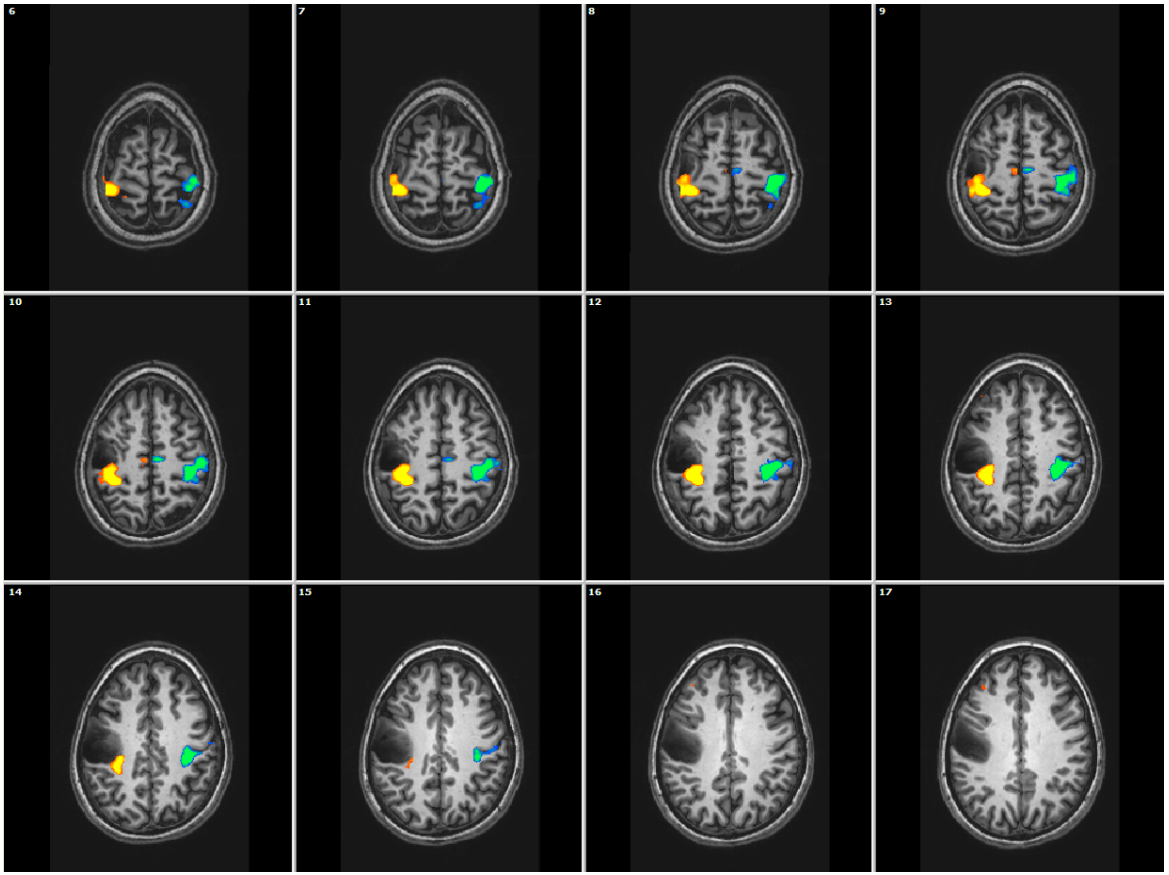
Patient examination @ MRKK in 2008
Kozak et al., Ideggyogy Sz, 2009
Kozak et al., Symp. Neuroradiologicum, 2010

fMRI can be used pre- and postoperatively

Patient 7 Precentral tumor

Right finger tapping activations (shown in greenish blue) and left finger tapping activations (shown in yellow) in a case of precentral tumor.

The left hand activations were present on the posterior edge of the lesion, so fMRI alone was not safe enough to delineate functionally active areas, therefore intraoperative electrocortical stimulation was also applied for motor cortex mapping.



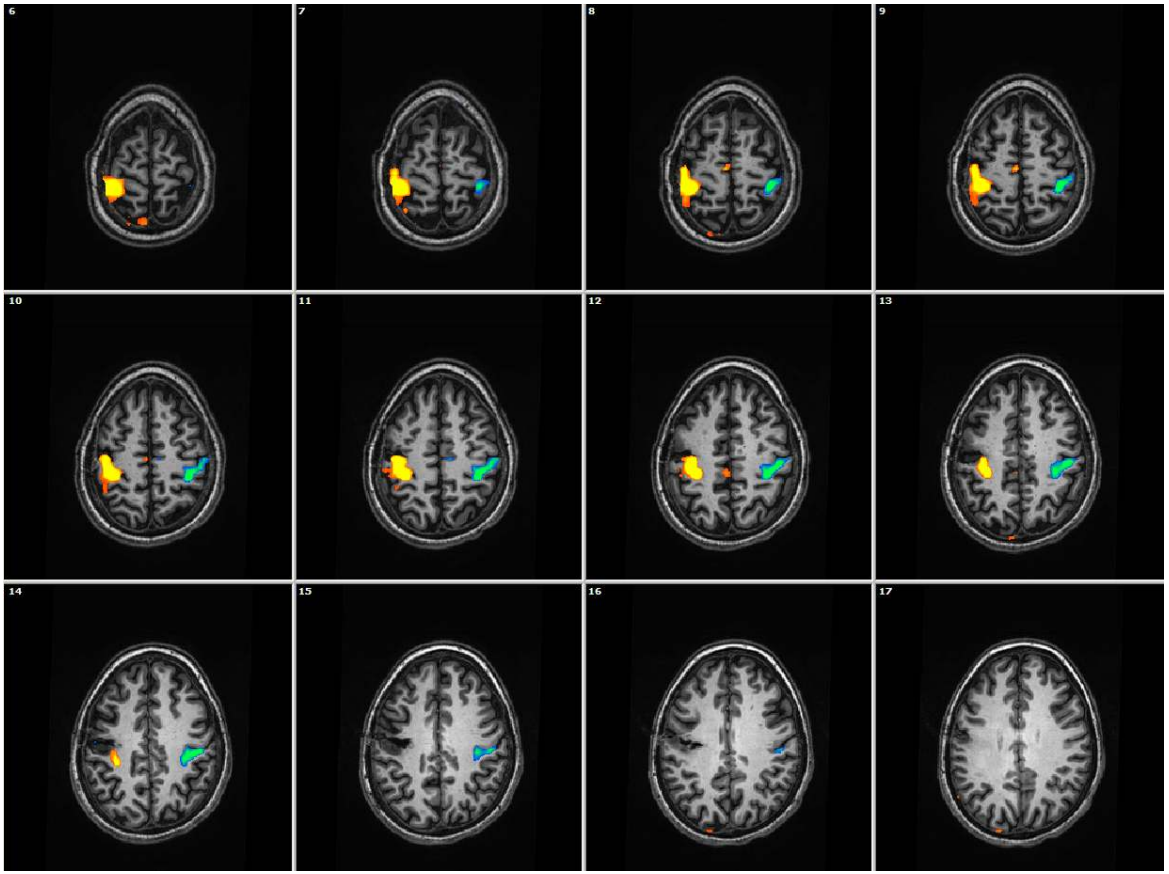
Patient examination @ MRKK in 2009
LR Kozak, MD, PhD

fMRI can be used pre- and postoperatively

Patient 7 Precentral tumor

Right finger tapping activations (shown in greenish blue) and left finger tapping activations (shown in yellow) in the half year follow-up examination of precentral tumor.

Left hand activations shown posterior to the scar, seem to be normal. The fMRI finding is supported by the fact that the patient had intact hand movement capabilities post-op.



Patient examination @ MRKK in 2009
LR Kozak, MD, PhD

Future applications

There is widespread research going on for extending the possibilities of clinical applications of fMRI, these investigations include, but are not limited to, the following:

- Functional connectivity analysis in cases of epilepsy, dementias, etc.

  e.g. Bettus et al., JNNP, 2010
- Calibrated fMRI

  e.g. Mark et al., NeuroImage, 2010
- Cross validation of ASL perfusion imaging, BOLD fMRI and other methods

  e.g. Diekhoff et al., HBM, 2010
- Estimation of drug effects with BOLD fMRI

  e.g. Lui et al., Arch Gen Psychiatry, 2010
- fMRI-based complex biomarker research

  e.g. Paulsen et al., AJNR, 2004

Summary

The introduced paradigms and instructive cases provide a comprehensive overview of the current clinical applications, but clinical fMRI is not limited to pre-surgical workup.

Moreover, research related to clinical fMRI are not limited to methodological investigations, as clinically oriented research may use fMRI as a tool for assessing cognitive or other functional changes in patient groups compared to healthy individuals.

Such research applications may lead to clinically important cut-off values, or complex fMRI-based biomarkers that can later be integral to routine diagnostic or prognostic procedures.

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

PHARMACOLOGICAL FMRI

(fMRI alkalmazása a gyógyszerkutatásban)

VIKTOR GÁL, ZOLTÁN VIDNYÁNSZKY

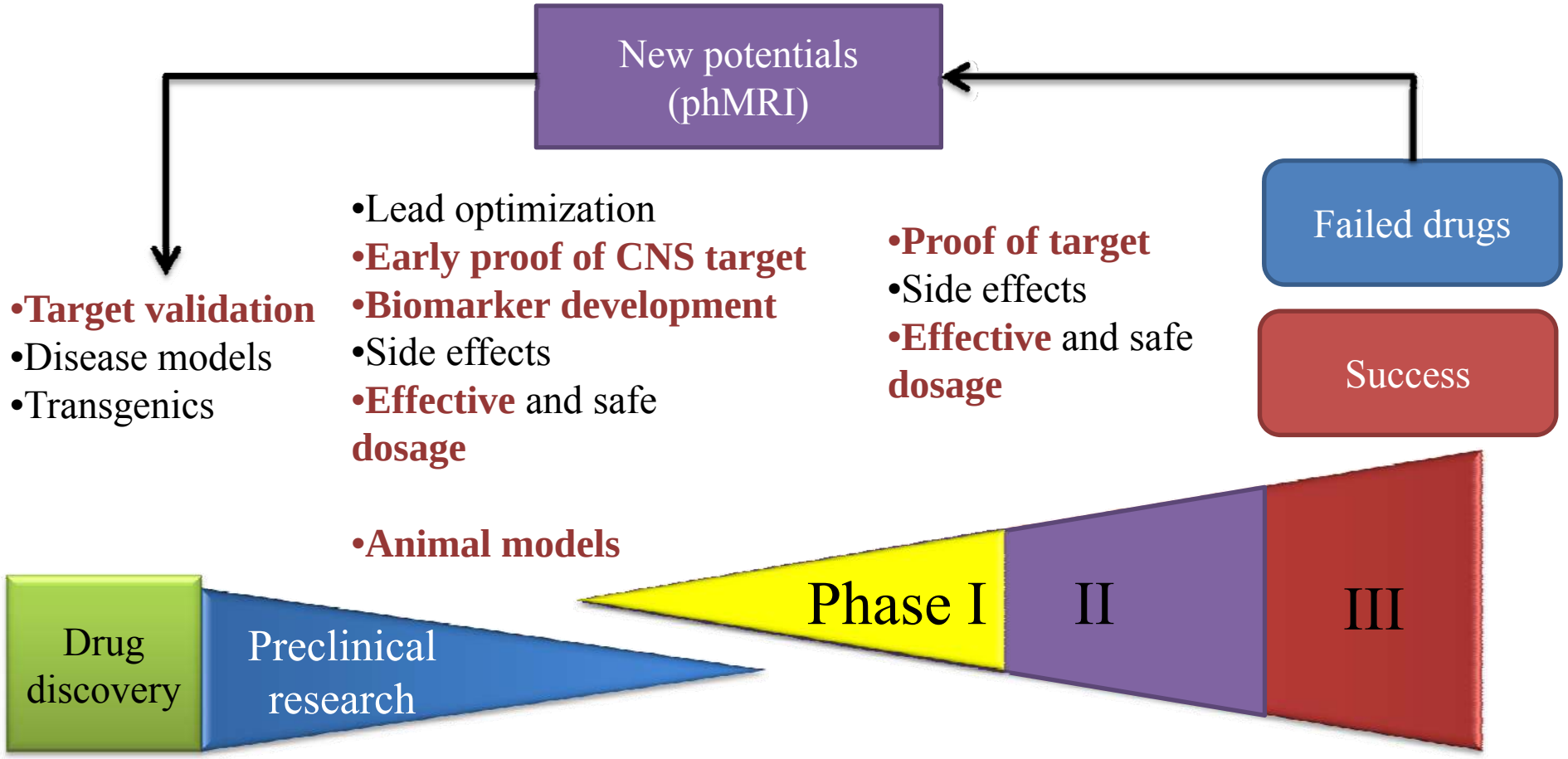
The clinical challenges in drug discovery

- Chronic diseases are increasing: Alzheimer's disease, psychiatric diseases, diabetes, atherosclerosis, arthritis, ...
  - Early onset
  - Slow progression
  - Poor prognosis
- Clinical trials extremely difficult and costly:
  - Long duration (> 3 years)
  - Many co-morbidities, huge group sizes (> 1'000 patients / arm)
  - Low chance of success (8% entering phase 1 will reach market)

Solution

- Search for early indicators (biomarkers)
  - stratify patient population
  - monitor therapy efficacy
- Imaging

Stages of CNS drug discovery, candidate role of phMRI



Role of Neuroimaging in drug discovery and development

Four interrelated categories:

- Neuroreceptor mapping
  - PET tracers
  - SPECT tracers
- Structural imaging to examine morphological changes and their consequences.
- Metabolic mapping
  - 18FDG
  - magnetic resonance spectroscopy
- Functional mapping (fMRI and FDG PET) to examine disease-drug interactions

Role of human and animal fMRI in drug discovery

fMRI is of most value at two distinct stages in the process of drug discovery:

- neuroscientific investigation of mechanisms of drug action
- providing quantitative markers of drug action, or endpoints, in candidate compounds for the clinic

fMRI also provides a means of comparing the potential mechanisms of drug action, at the systems level, between the animal models and humans, as the compound is transferred from animals to humans. This approach offers two benefits:

- the potential for verification of the similarity between the animal model and the human and hence the value of the animal model in future testing.
- the potential for reduction of animal use for investigating mechanisms of drug action and their replacement with comparatively small cohorts of human volunteers.

Applications of phMRI

- Measuring
  - Pharmaco-dynamic response
  - Pharmaco-kinetic characteristics
- Patient categorization
  - Stratification, subgroup definition
- Target identification:
  - proof of mechanism
- Early phase outcome study
- Alternative/surrogate marker of outcome

Advantages of phMRI

- **High information content**
  - novel information
  - faster than conventional analyses
- **Multi-modal**
  - from anatomy to function and molecular information
- **Non-invasive**
  - minimal interference with physiology
  - repeated assessments, intrinsic controls, chronic treatment studies
  - increased statistical power
  - reduced group sizes
- **Bridging the gap: translational research**
  - mouse to man
  - identical readouts in pre-clinical and clinical studies

Biomarkers

Definition: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention

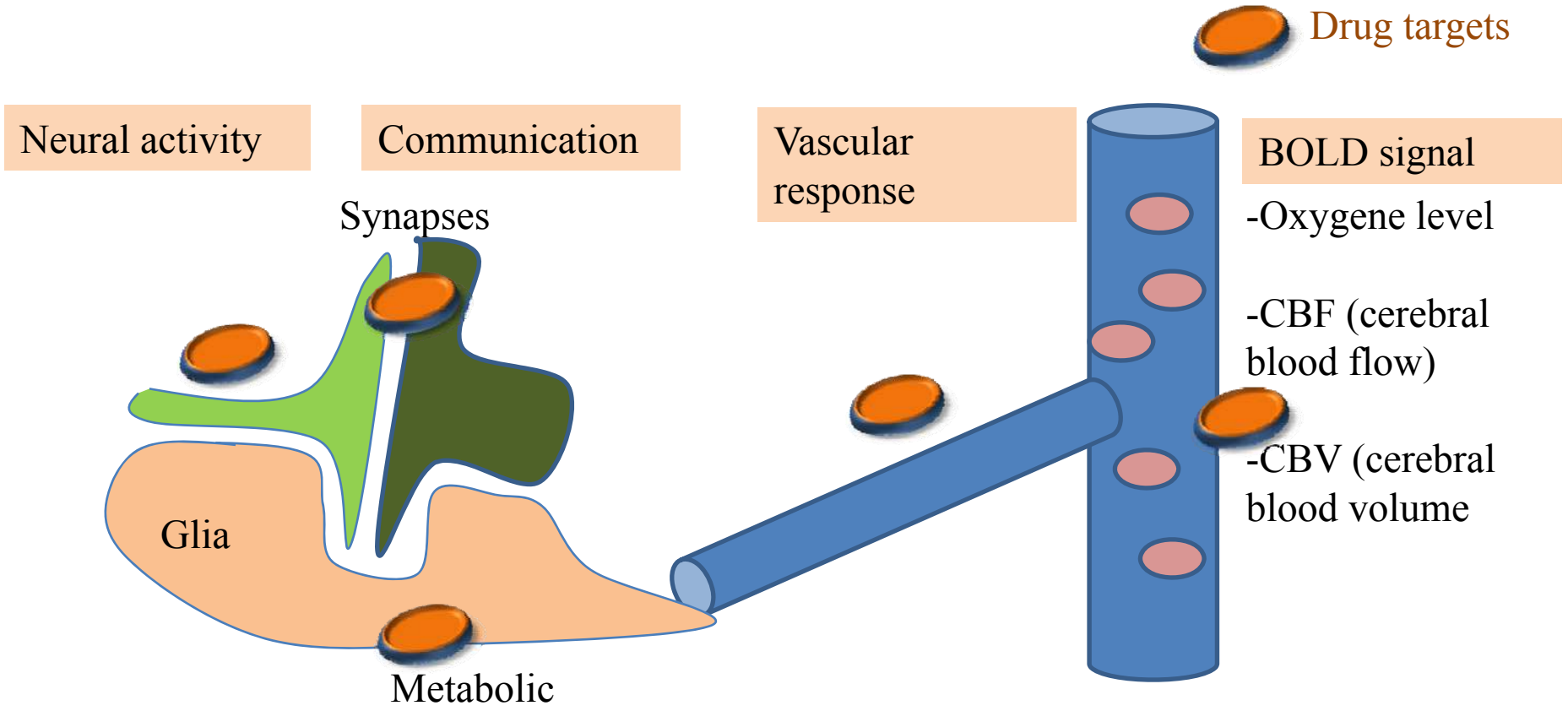
(Lesko & Atkinson, Annu Rev Pharmacol Toxicol 2001)

Biomarkers and the Pharmaceutical Industry

Imaging biomarkers enable:

- characterization of patient populations
- quantification of the extent to which new drugs reach intended targets,
- alter proposed pathophysiological mechanisms,
- achieve clinical outcomes as well as predict drug response.

- Is the drug affecting neuronal activity or just the haemodynamic response?
- FMRI for investigating regional neurovascular coupling mechanisms through pharmacological challenges



Modelling drug-induced responses

➢**BOLD/CBF changes in baseline activity**

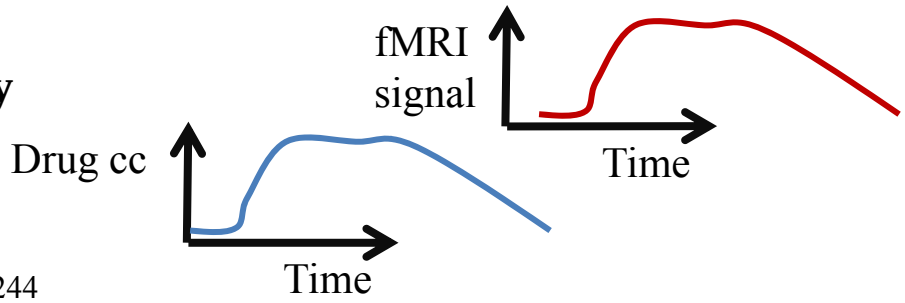
No repetitive specific sensory stimulus(Single evoked activity)

Cocaine: Breiter HC, et al, Neuron, 1997; 19:591-611

Nicotine: Bloom AS, et al, Human Brain Mapping, 1999; 8:235-244

Methamphetamine Völlm et al. *Neuropsychopharmacology* 2004, **29,** 1715–1722

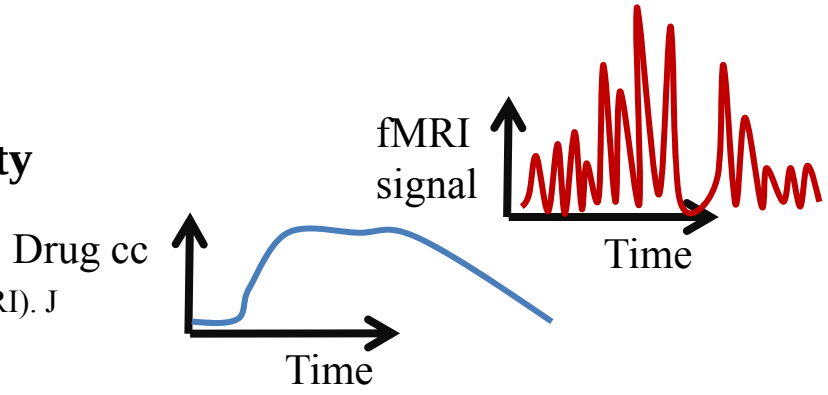
MDMA: Brevard et al. / Magnetic Resonance Imaging **24** (2006) 707– 714



➢**Modulation of stimulus induced activity**

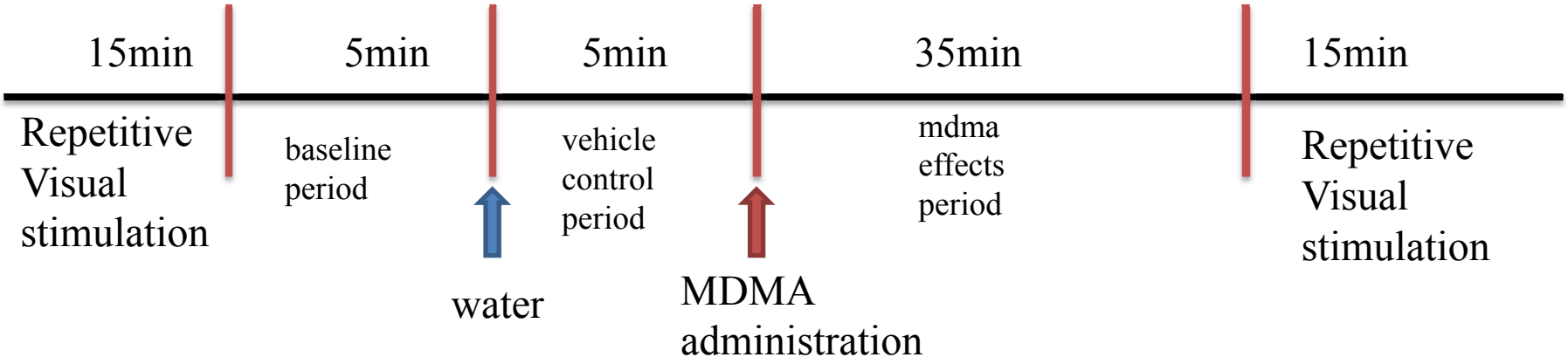
More treatment/disease specific

Remifentanil: Tracey I (2001). Prospects for human pharmacological functional magnetic resonance imaging (phMRI). J Clin Pharmacol 41: 21S–28S.



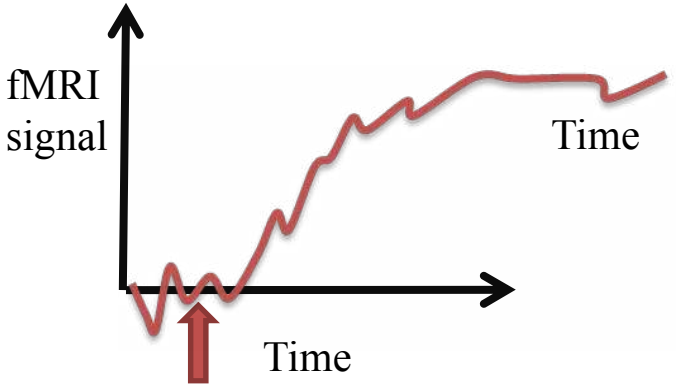
Drug-induced responses: example

Effects of MDMA (3,4-methylenedioxymethamphetamine) on monkey brain Brevard et al. / Magnetic Resonance Imaging 24 (2006) 707– 714



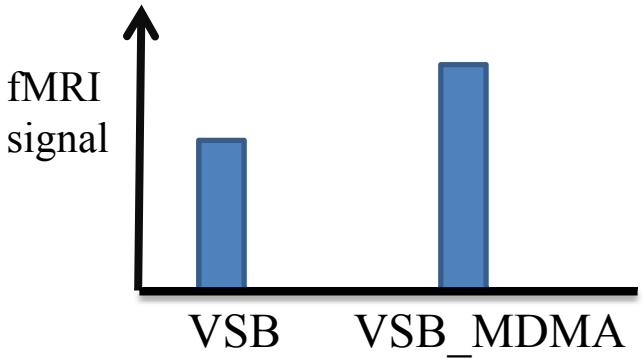
Drug-induced responses: example

BOLD changes in baseline activity
Raphe nucleus, hypothalamus, hippocampus, amygdala, striatal and visual areas followed the same tonic activation pattern



Modulation of stimulus induced activity
VSB: average amplitude of BOLD response to visual stimulation, before MDMA

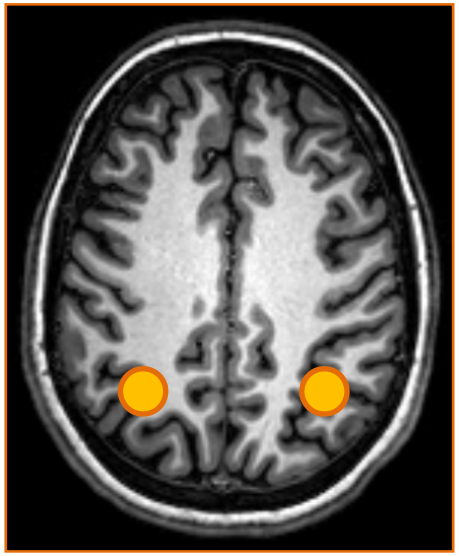
VSB_MDMA: average amplitude of BOLD response to visual stimulation (after MDMA administration)



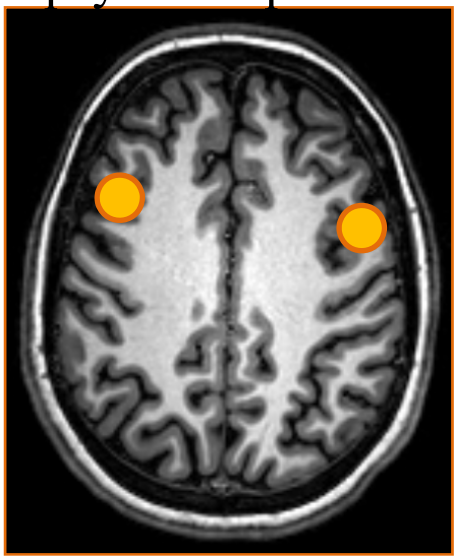
Classification of patients: defining subgroups in range disorders

- Intermediate phenotype of schizophrenia : (Mac Donald et al am J Psychiatry, 2005)
- Expectancy AX Context Processing Task

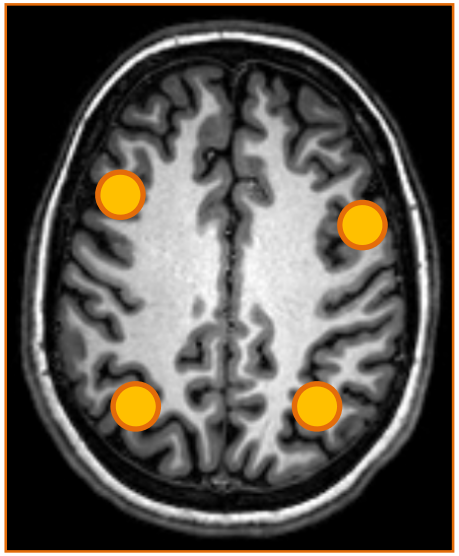
Schizophrenia patients



Nonschizophrenia psychosis patients

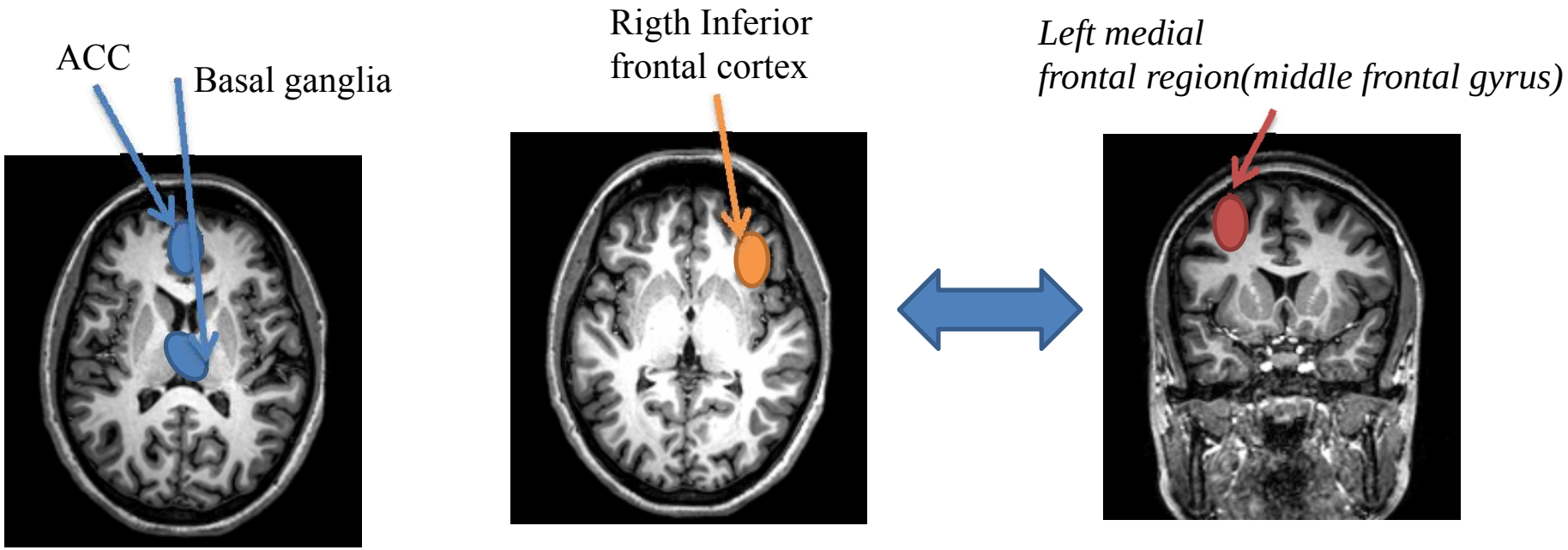


Healthy subjects



Early phase outcome measure: proof of concept (target)

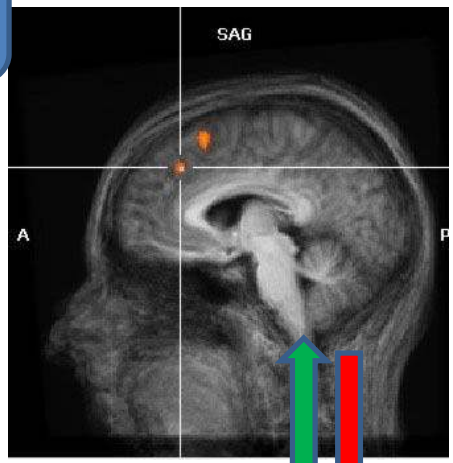
- Stroop task brain activation: basal ganglia, ACC, inferior frontal cortex (with right hemisphere dominance)
- Abnormal brain activation (left dominance over right hemisphere in the frontal cortex) in MS patients transiently normalizes after *rivastigmine* administration



Factors influencing pain experience

COGNITIVE STATE

CONTEXT



MOOD

Molecular and anatomic STRUCTURE

SPINAL CORD

NOCICEPTIVE modulation

Aδ, C fibers harmful input

Perceived pain intensity depends on:

Pain is highly subjective experience as illustrated by the definition given from the International Association for the Study of Pain (Merksey and Bogduk, 1994)

"*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*"

Neuropathic Pain: *caused by damage to or malfunction of the nervous system (no impending tissue damage in the background)*

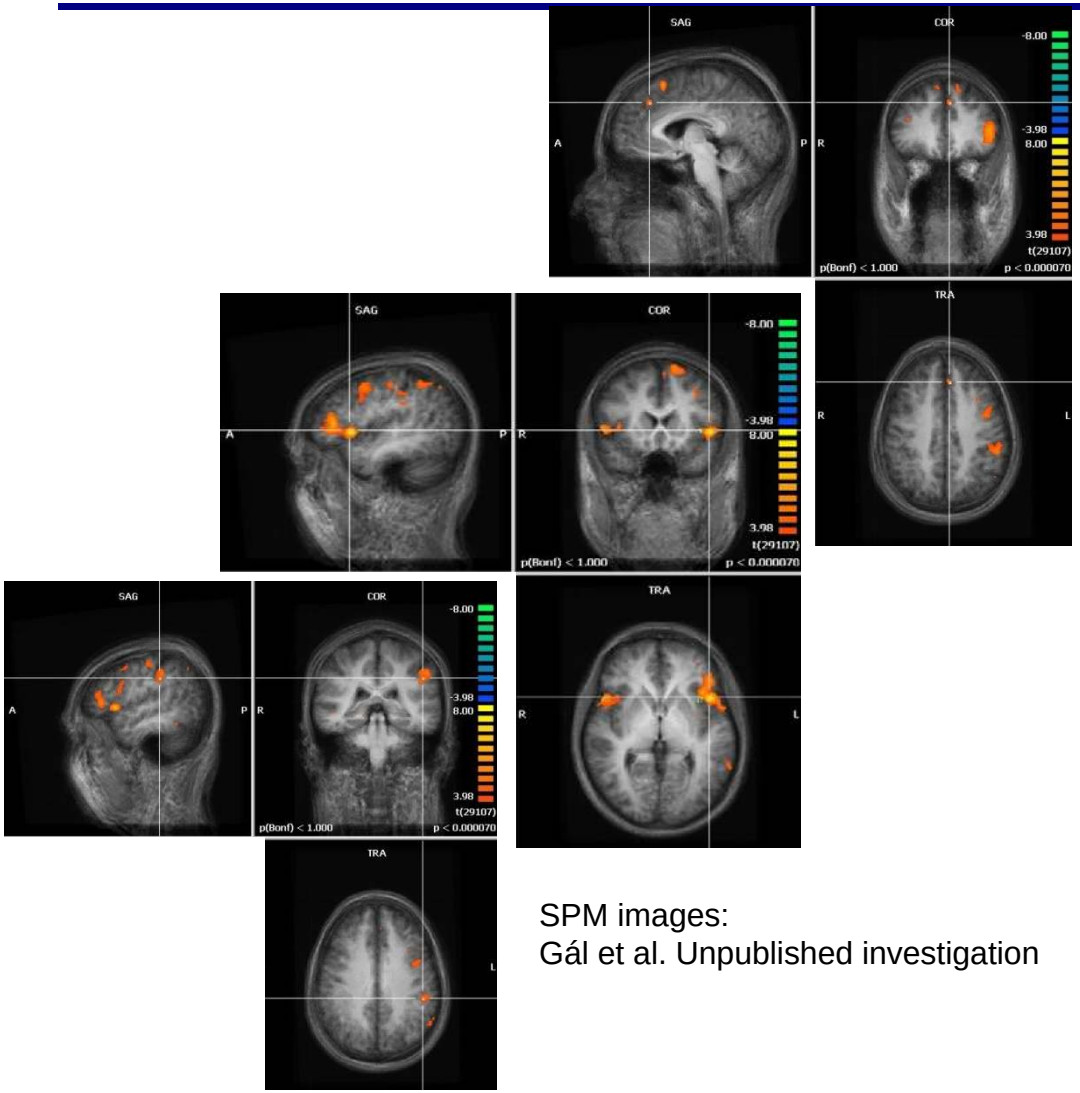
Chronic Pain: *pain that persists for more than three months*

- one of largest medical health problems in the developed world, affecting ~ 20% of the adult population, particularly women and the elderly *(Breivik et al., 2006).*
- to improve the ability to diagnose chronic pain and develop new treatments we need robust and objective ''readouts'' of the pain experience.

fMRI biomarker for chronic pain

should provide an opportunity to:

- assess and correlate pain signals at varying times in either pre-intervention or post-intervention settings.
- generate a unique brain processing "fingerprint" in response to a specific task or stimulus
- correlate behavioral pain scores with most important and relevant brain regions
- generate more specific and relevant definition of pain in early clinical studies (Phase I and II); smaller studies could assess most promising endpoints



SPM images:
Gál et al. Unpublished investigation

Pain matrix

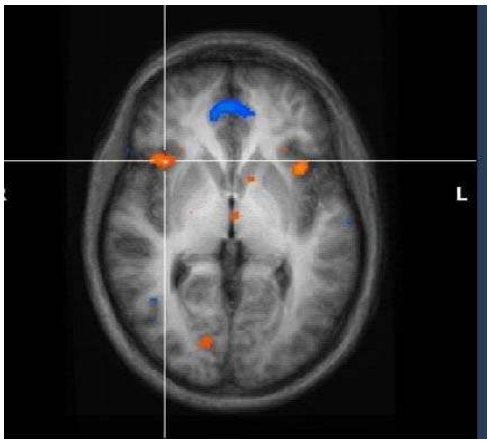
main components:

- Thalamus
- S1/S2
- Insula (several divisions)
- ACC (several divisions)
- Prefrontal

Modulation of the pain system via Remifentanil

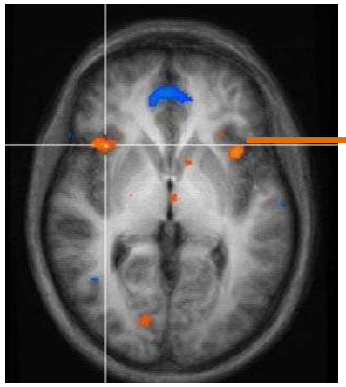
- Modulation of the pain system
- Subjective pain experience controlled by „objective” FMRI vs.
- Identifying regions associated with analgesia
- Novel therapeutic strategies
- FMRI dose-response relationship
  - Finding effective dosage
- Phasic thermal pain
- Remifentanil (peripheral and CNS pain killer) 0, 0.5, 1.0, 2.0 ng/ml
- computer controlled infusion

Tracey I (2001). Prospects for human pharmacological functional magnetic resonance imaging (phMRI). J Clin Pharmacol 41: 21S–28S.

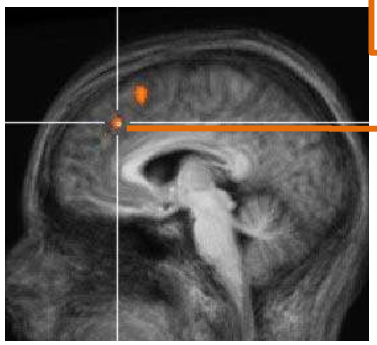


Remifentanil

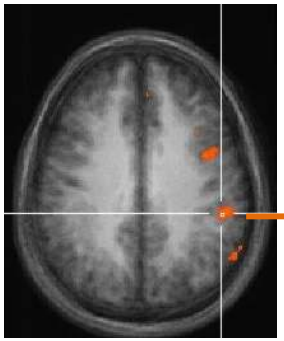
Dose dependent suppression of pain related activity within the pain matrix



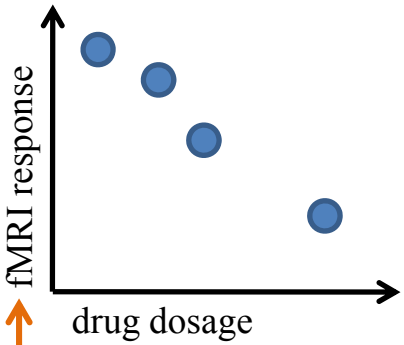
Insula

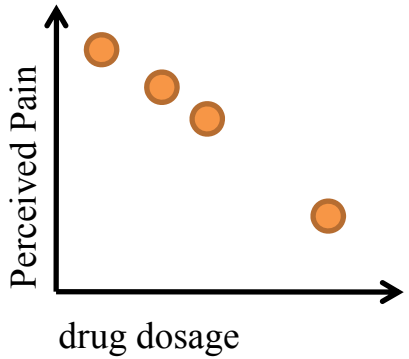


Anterior cingulate cortex



SII

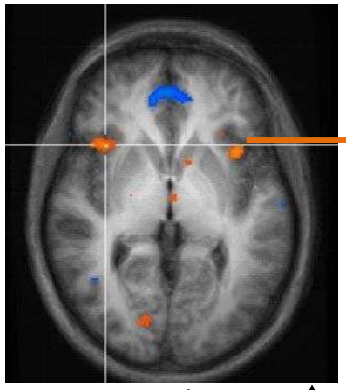




SPM images:
Gál et al. Unpublished investigation

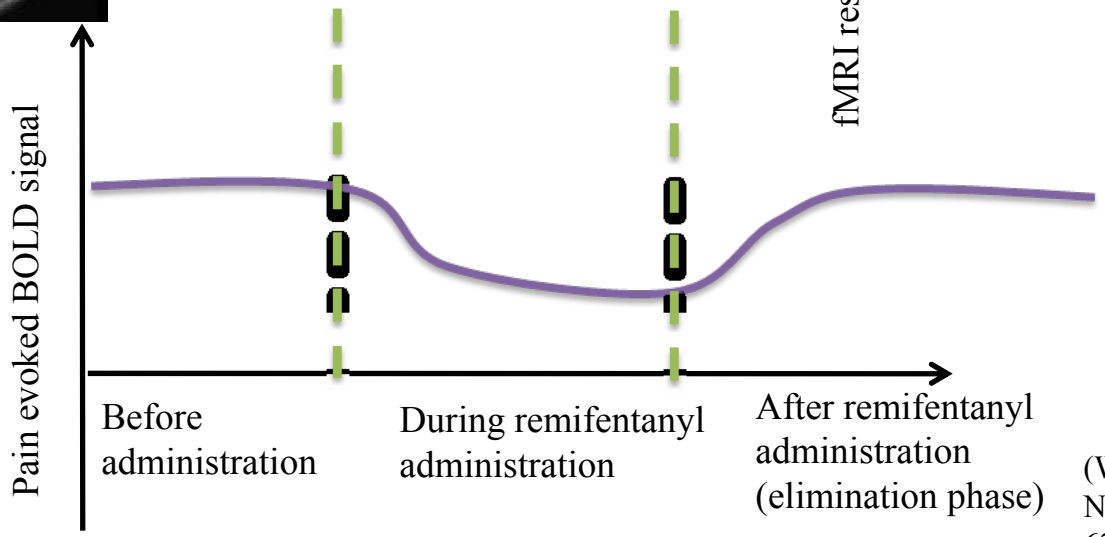
Dynamic modulation of pain matrix activity

SPM images: Gál et al. Unpublished investigation:



Right insula

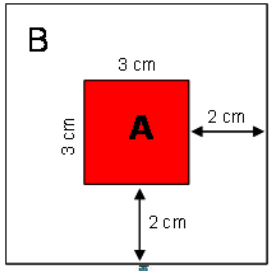
Insula



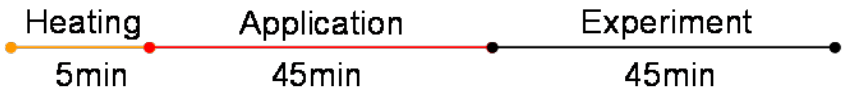
(Wise et al., 2003 Neuropsychopharmacology ***29***, 626-635.)

Chronic pain model: Central sensitisation by topical capsaicin treatment (Petersen and Rowbotham, 1999, Zambreanu et al. Pain 2005)

-Topical application of capsaicin, a vanilloid receptor agonist, which elicits ongoing discharge in C-nociceptors and induces an area of hyperalgesia.

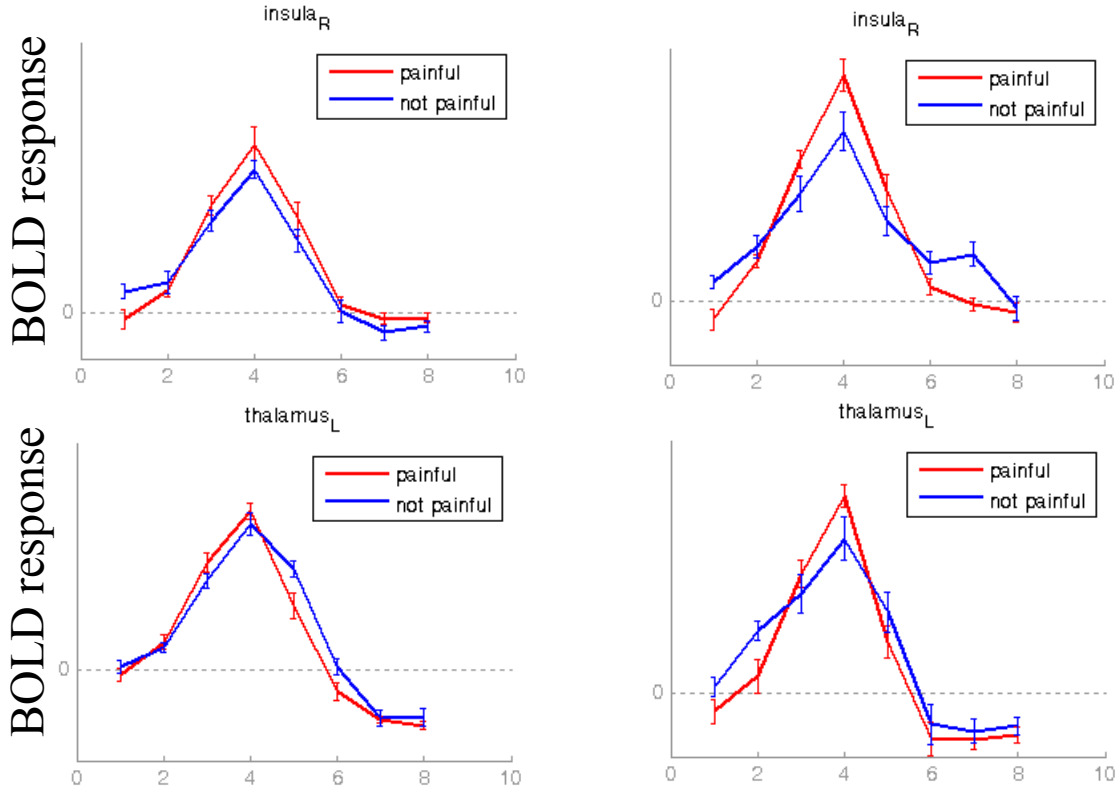


Computer controlled MR-compatible mechanical stimulus presentation equipment



Conditions	Capsaicin treatment	Treated area	Stimulation	Model of sensitization
1	Yes/ Hyperalgesia	A	A	Peripheral sensitization
2	No/ Control	-	A	Control
3	Yes/ Hyperalgesia	A	B	Central sensitization
4	No/ Control	-	B	Control

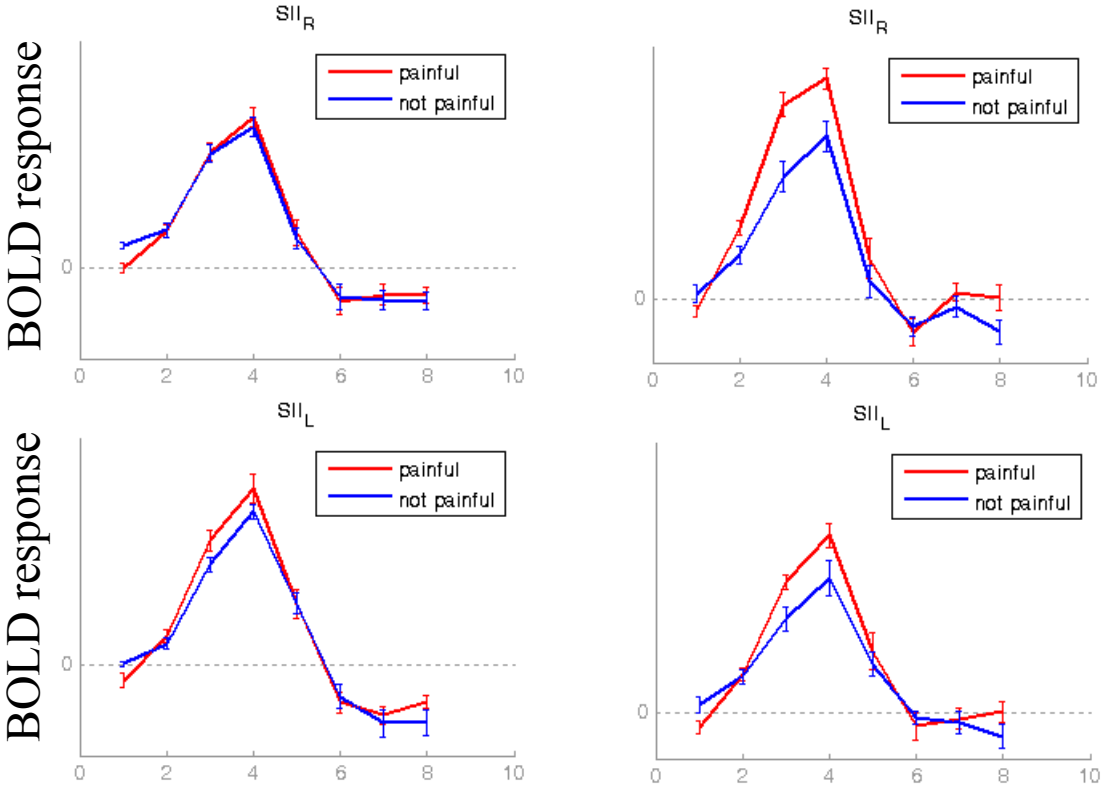
Central sensitisation by topical capsaicin treatment



Gál et al.
Unpublished
investigation

Effects of central sensitiszation: talamus, insula anterior, – BOLD responses in the different brain areas in the conditions of untreated (left column) and central sensitization (right column) when subjects categorized painful and non-painful stimuli

Central sensitisation by topical capsaicin treatment



Gál et al.
Unpublished
investigation

Effects of central sensitiszation: S2 cortex (left, right) – BOLD responses in the different brain areas in the conditions of untreated (left column) and central sensitization (right column) when subjects categorized painful and non-painful stimuli

Animal fMRI

Comparing to human fMRI:

- Larger number of samples
- Testing of potentially noxius/lethal/less known
  - Intervention
  - stimulation (e.g. intracranial microstimulation)
  - chemical agents
  - genetic manipulations
- Translation of small animal models to human models)
  - May validate other drug development methods

Bridging the gap: fMRI in translational studies

Biomarkers

Animal models

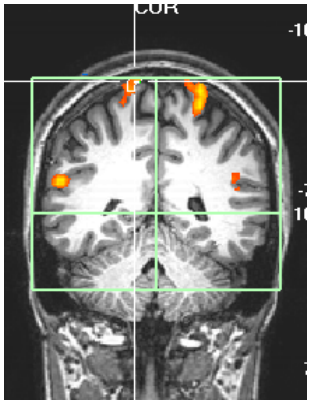
Preclinical imaging

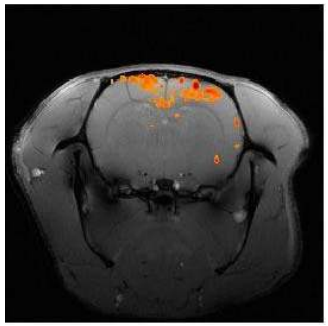
Drug discovery

Basic neuroscience

Clinical trials

Transgenic approach





Better match than behaviour?

Animal pharmacological MRI: issues

- **Is it predictive:**

Do we learn anything about drugs in the human situation?

- Major differences in receptors, circuits and function
- Experiments normally carried out on anesthetized animals

- **Is it cost and time efficient:**

How does it compare to conventional methods?

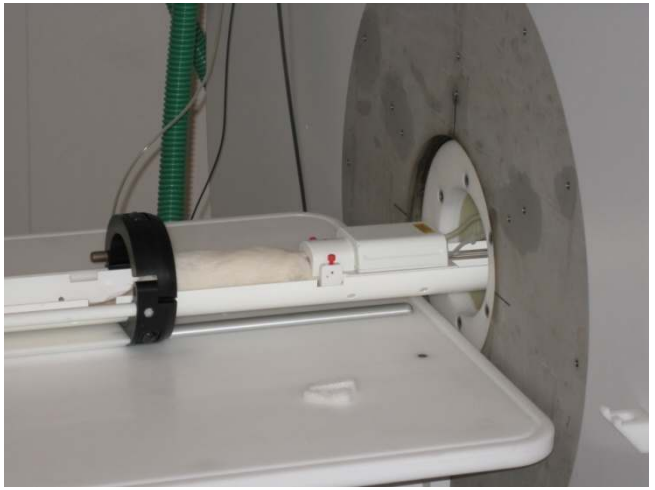
- **Is it relevant:**

What can we learn about new compounds?

- Difficulties at detecting tonic activation via BOLD methods
- Limited stimulus delivery and behavioral response

- **Is it ethical:**

May animals be "used" for research?



Ultra High field MRI

Typical strengths: 4.5T, 7T, 9.4 T

Bruker, Varian

- Pros:
  - high SNR
  - Higher chemical shift (also disadvantage)
  - 100µm or lower spatial resolution
  - T1 higher
  - Shorter imaging sessions (due to high SNR)
    - High susceptibility effects (even 15% signal change in BOLD), lower stimuli repetition required
    - Spin echo also gives BOLD contrast!
- Cons
  - High susceptibility effects
  - Poor field homogeneity
  - Variable signal loss
  - Higher TR for T1

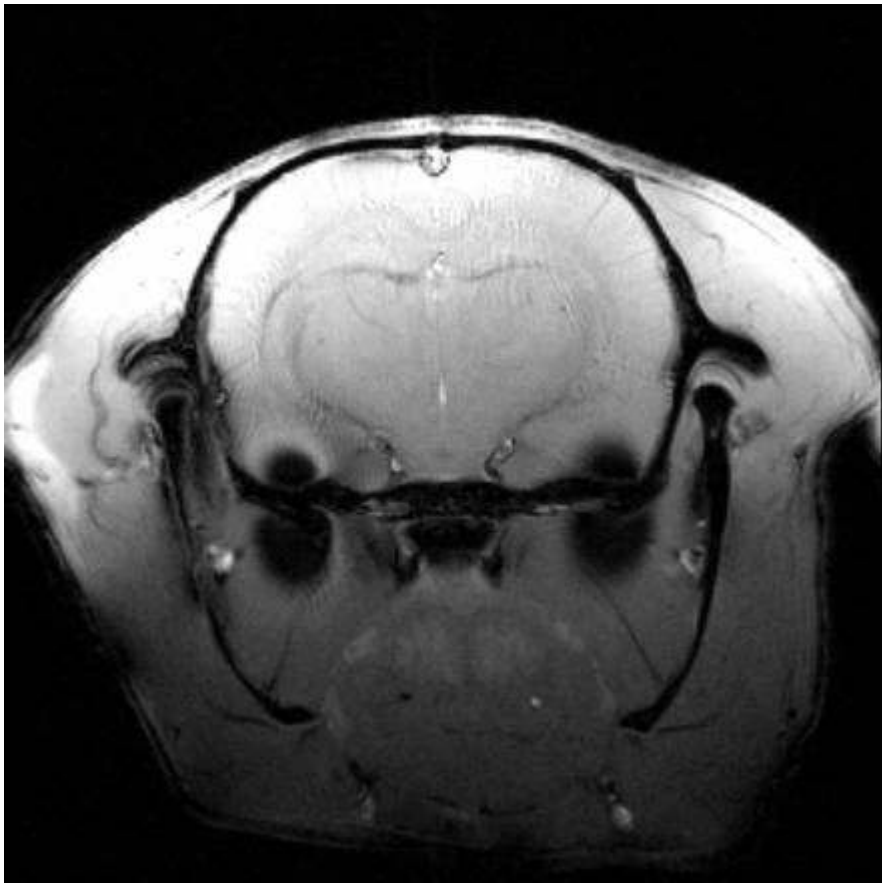
Resolution

- Spatial

Typical

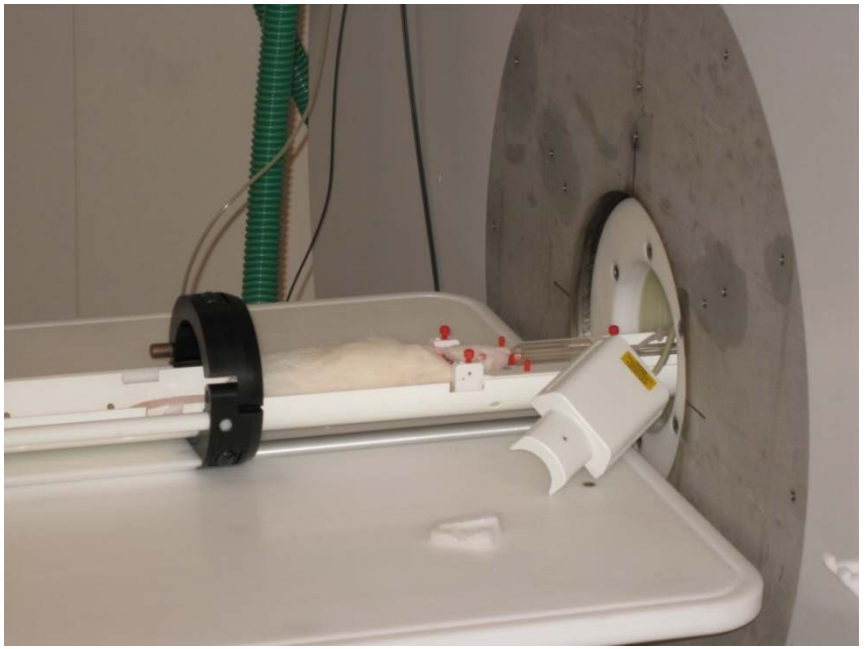
  - 0.1x0.1x0.3mm , 4-6 slices, 5min
  - 0.015x0.015x0.3mm , 20 slices, 1 day
  - Cytoarchitecture can be visualized

- Time
  - Normally acquisition of a volume is not faster than at lower fields, but:
  - even single events (stimulus) can be detected by gradient or spin echo EPI
  - percent signal change can be 10 times higher than at 3T
  - Spectroscopy is accelerated substantially



Preparation

- Intubation
- Catheterization (through the tail vein)
- Placement of the monitors:
  - ECG heart rate
  - Respiration (piezo-electric transducer)
  - Rectal temperature probe
- Mechanical stabilization
  - acrylic stereotactic head holder (incisor bar and blunt earplugs,)
- Insertion of heating tube



Immobilization

Training

Mechanical restraining

Anesthesia:

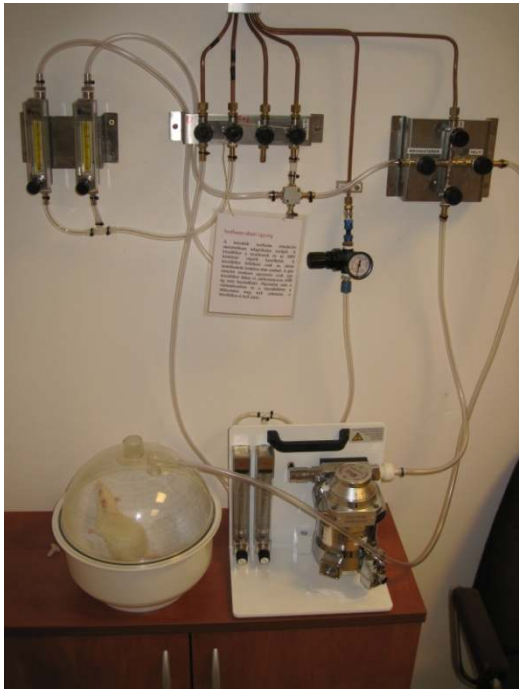
- α-chloralose
- Propofol
- Medetomidine
- Isoflurane

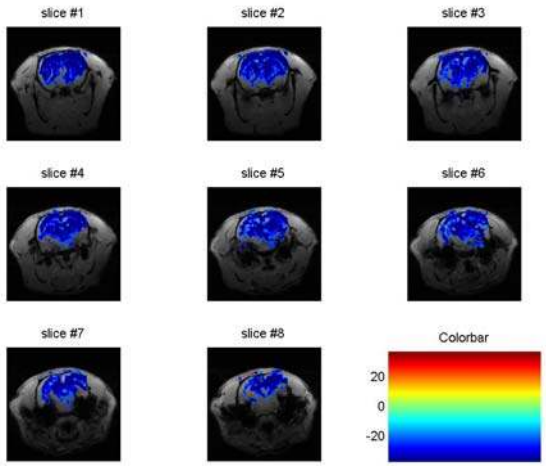
Paralysis

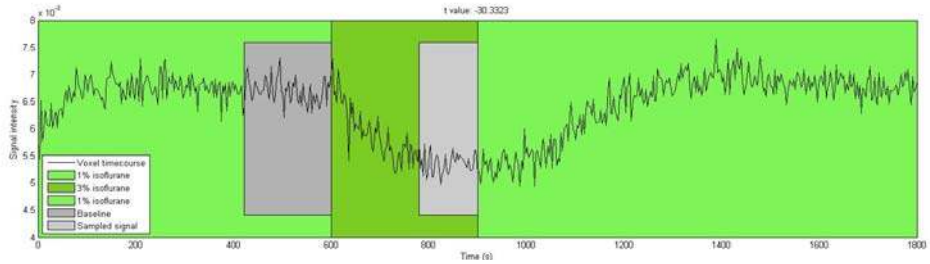
- mivacurium (curarization)
  - Enable awake, conscious experiments
  - Serious ethical issues

Direct effect of anesthesia on BOLD signal

Elevating isofluran concentration decreases baseline level

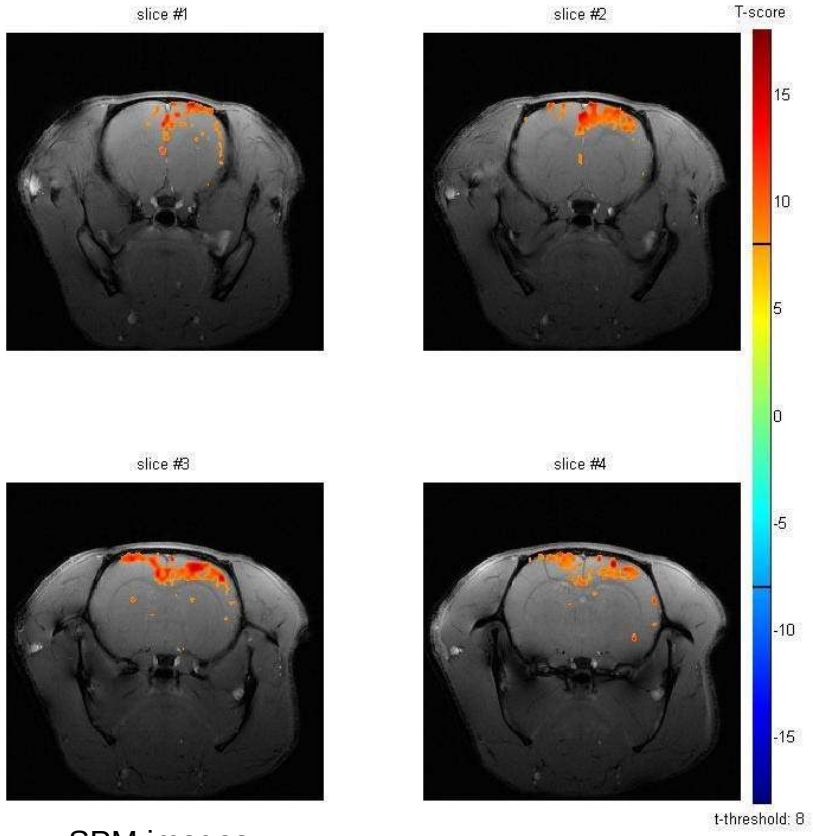






Paw stimulation (electrical)

- One of the most frequently used sensory stimulation in small animal fMRI
- Needle electrodes are inserted under the skin/fixed around fingers
- Basic research in somatosensory system
- Indirect effect of drugs, anesthesia on the sensory system (deprivation)
- Scanning parameter optimization



SPM images:
Gál et al. Unpublished investigation

Normalization of small animal brains

Why normalize?

- Multiple subject experiments
- To report anatomical localization of fMRI effects
- Coregister with other modalities (MRI, autoradiography)

How normalize/coregister?

- 3D digital atlases (Schweinhardt et al., 2003 Schwarz et al., Neuroimage 2006) derived from
  - •Rat: Paxinos and Watson, 2005
  - •Mouse Paxinos and Franklin, 2001;
- Automation of coregistration
  - •Tissue probability maps, brain templates coregistered with known atlases
  - •In-house brain templates
  - •Via finding anatomical landmarks

MRI Contrast agents

Animal MRI has the advantage to use potentially noxious contrast agents more freely than in human studies. Types of contrast materials used in clinical practice:

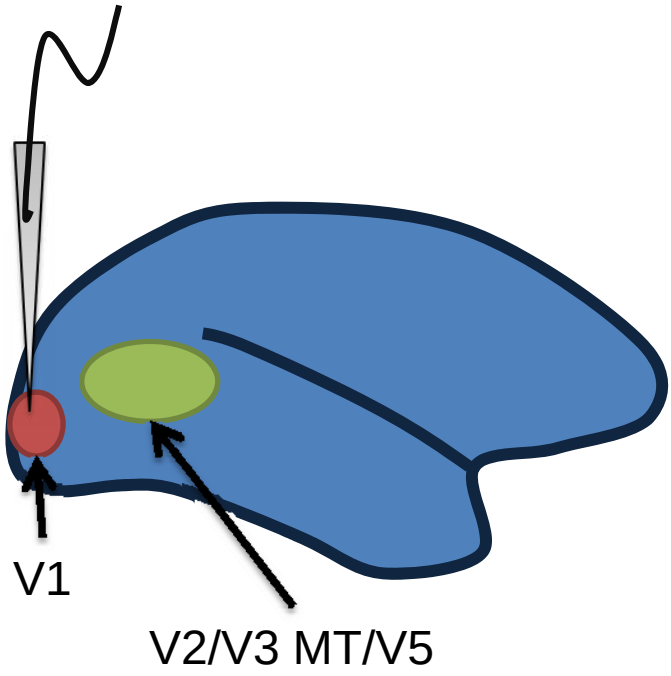
- Oral
- Intravascular
  - Gadolinium (and complexes): Paramagnetic
  - Manganese (and complexes): Paramagnetic
  - Iron oxide: Superparamagnetic
    - SPIO : Superparamagnetic Iron Oxide (SPIO) and UltraSPIO
    - Reduces T2 and T2*
    - Intravascular time: depending on particles size and coating
      - With long iv time they can be used as fMRI contrast agent (next slide)

Potential Functional MRI Contrast agents

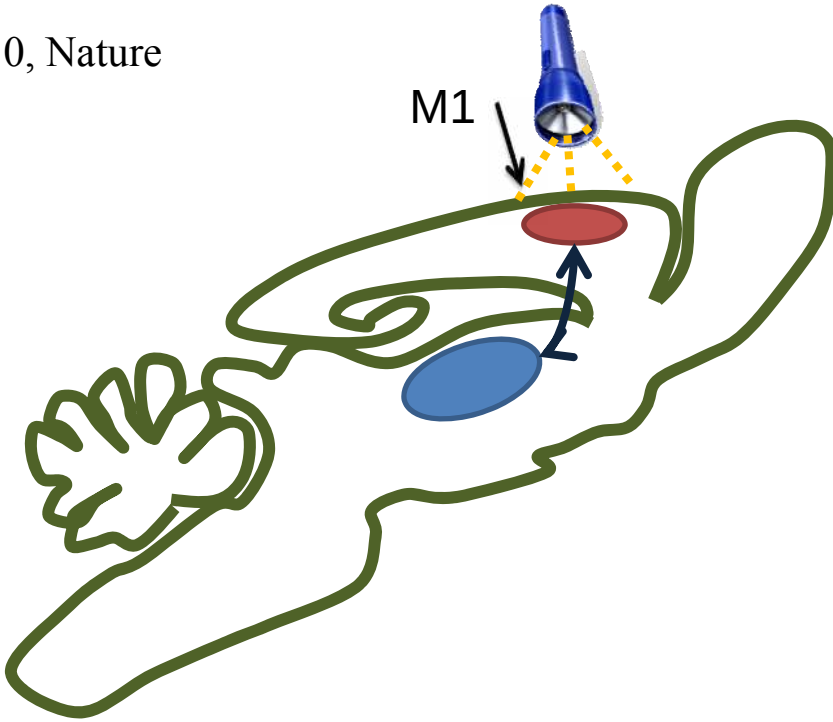
- Indicators of change in local blood flow
  - MION-47, USPIO with long blood half-life
- Indicators for Ca2+ and other metal ions
  - BAPTA-based Gd3+ complex
  - Mn2+ as Ca2+ mimetic
- pH indicators
  - Phosphonated Gd3+ complex, Endogenous amide protons
- Probes for metabolic activity
  - Exogenous hemoglobin
- Genetically controlled contrast agents
  - Ferritin
  - Transferrin (Tf)- conjugated SPIOs
  - Artificial lysine-rich protein

Electrical microstimulation and fMRI

- Local and remote connections of a specific (stimulated) site can be mapped
- Method can detect selective modulatory effects of pharmacological agents on specific connections
- Methodological challenge: MR compatible electrode, MR signal is contaminated by electrical stimulation
- Pioneering work of Logothetis Lab: monkey V1 microstimulation (Tolias et al 2005, Neuron)
  - Significant BOLD signal change in V1, and extrastriate visual areas



Optogenetic fMRI Lee et al 2010, Nature



- Electrical stimulation is not selective:
  - Afferents and efferents, passing axons
  - Inhibitory and excitatory neurons are also activated
- Injection of viral vector (AAV5-CaMKIIa::ChR2(H134R)-EYFP)
  - into primary motor cortex
  - expression of channelrhodopsin (ChR2)
  - only in Ca^{2+}/calmodulin-dependent protein kinase II (CaMKIIa)-expressing **principal cortical neurons**, (not in GABAergic or glial cells)
  - Activation/measurement 10 days after viral injection

➢Optical (laser diode) stimulation of motor cortex resulted in BOLD response shown in the site of stimulation and in relevant thalamic nuclei

Summary

Examples demonstrate promising capabilities of phMRI in:

- Measuring Pharmaco-dynamic response and pharmaco-kinetic characteristics
- Patient categorization, target identification:
- Early phase outcome or surrogate biomarker of outcome

via BOLD/CBF changes in baseline activity or modulation of stimulus induced activity

Animal fMRI broaden the potential of phMRI enabling:

- Larger number of samples
- Testing of potentially noxius/lethal/less known chemical agents (drugs), intervention, stimulation (e.g. intracranial microstimulation) and genetic manipulations
- Translation of small animal models to human models (bridging the gap)
  - May validate other drug development methods

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

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**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)

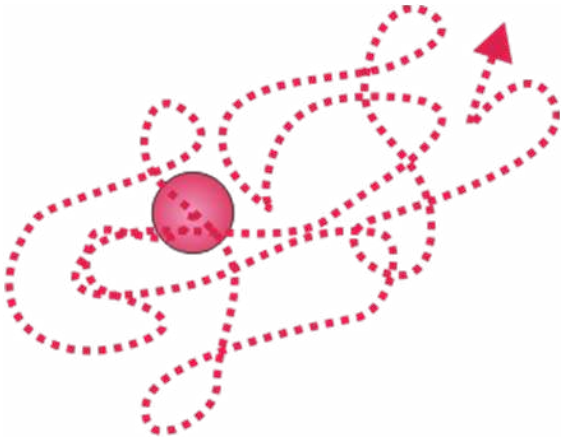
Diffusion Weighted Imaging (DWI)

Diffusion

The water molecules are in constant motion

- Random rotations by thermal motions
  - Leading to local magnetic field variations and thus
  - T2 effects

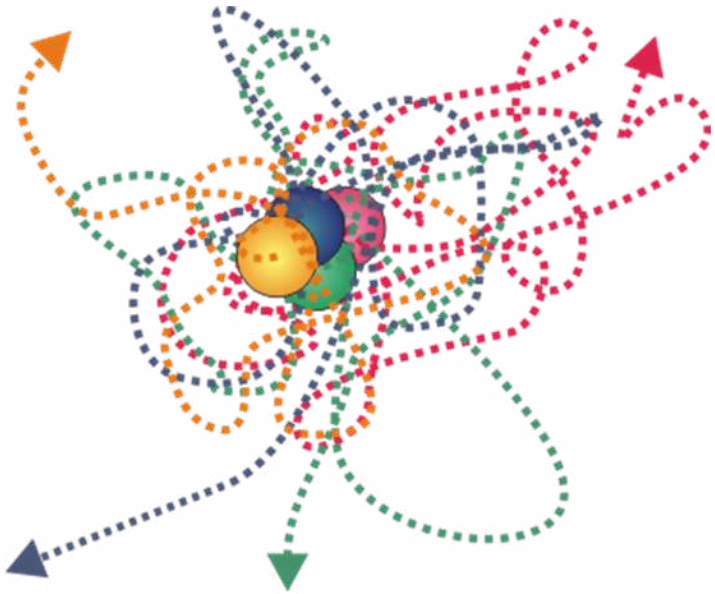
- Random displacements or diffusion
  - Random walk or Brownian motion
  - In a sufficiently big compartment the probability of moving in a given direction is equal across directions (isotropy)



Diffusion

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

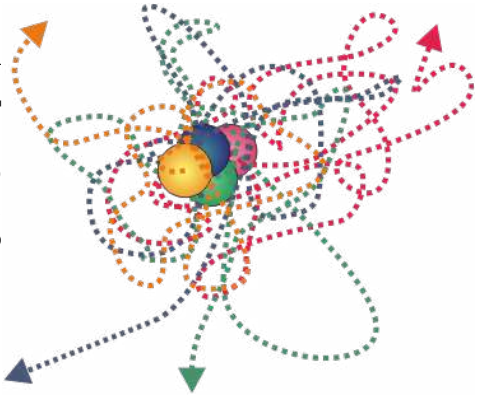
- The variance of the spread over time along a given spatial axis $\sigma^2 = 2DT$ is where D is the diffusion coefficient
- As they are equally likely to move in any direction, the mean displacement of the molecules is 0
- Diffusion is a local effect, the displacement is present over short distances



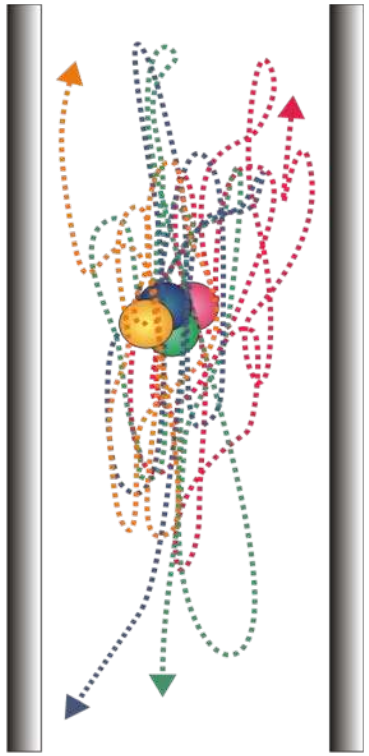
Diffusion anisotropy

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

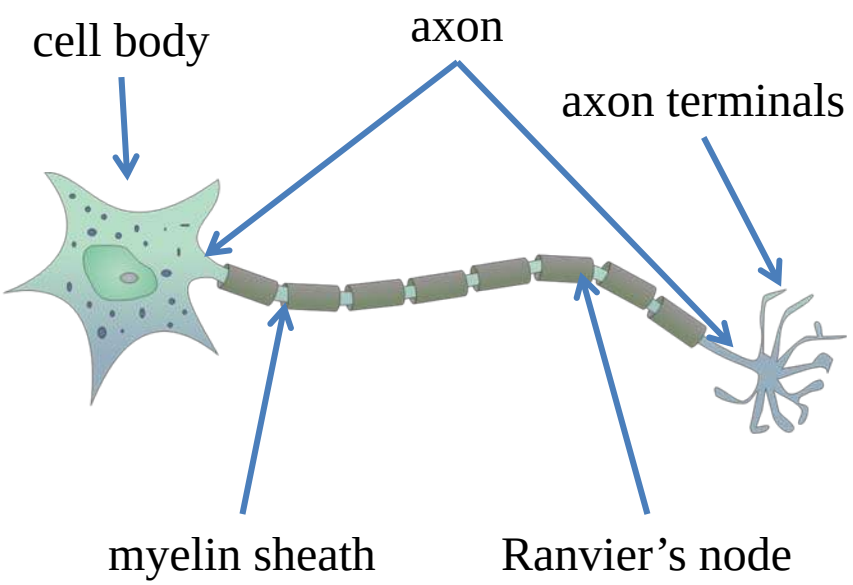


Anisotropic diffusion

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

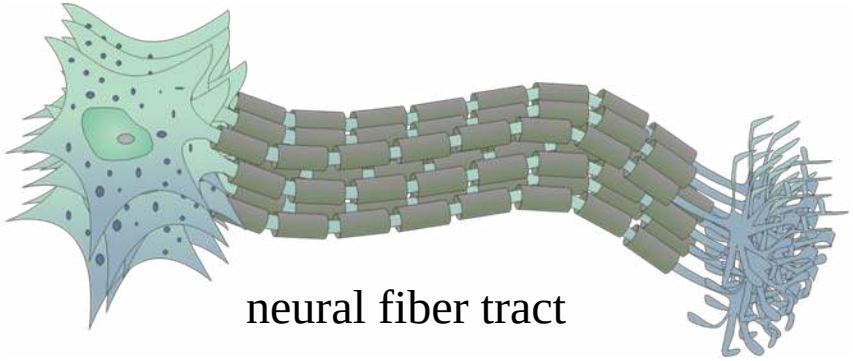


Diffusion anisotropy in the human brain

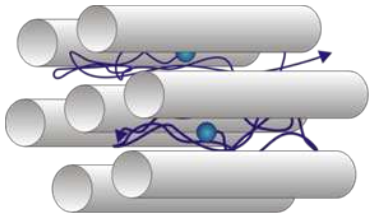
Bundled axons limit the diffusion of water along the axonal axis.

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

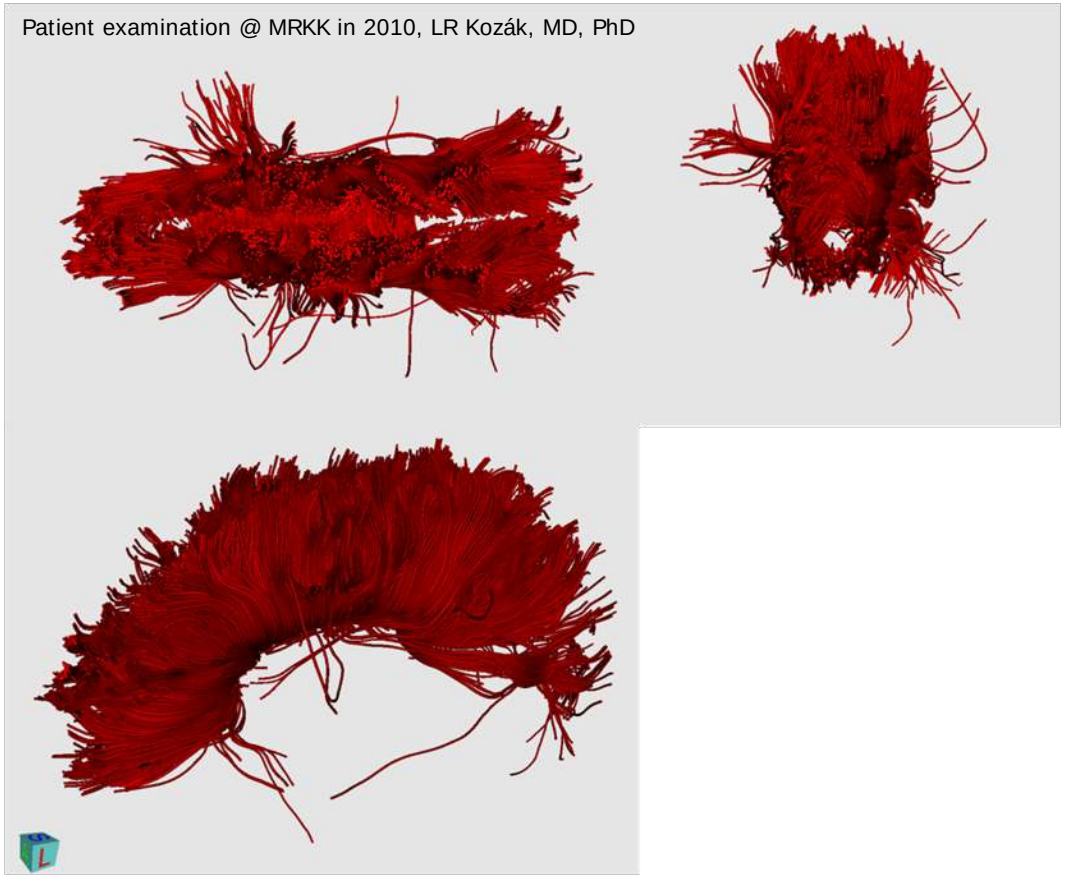


neural fiber tract



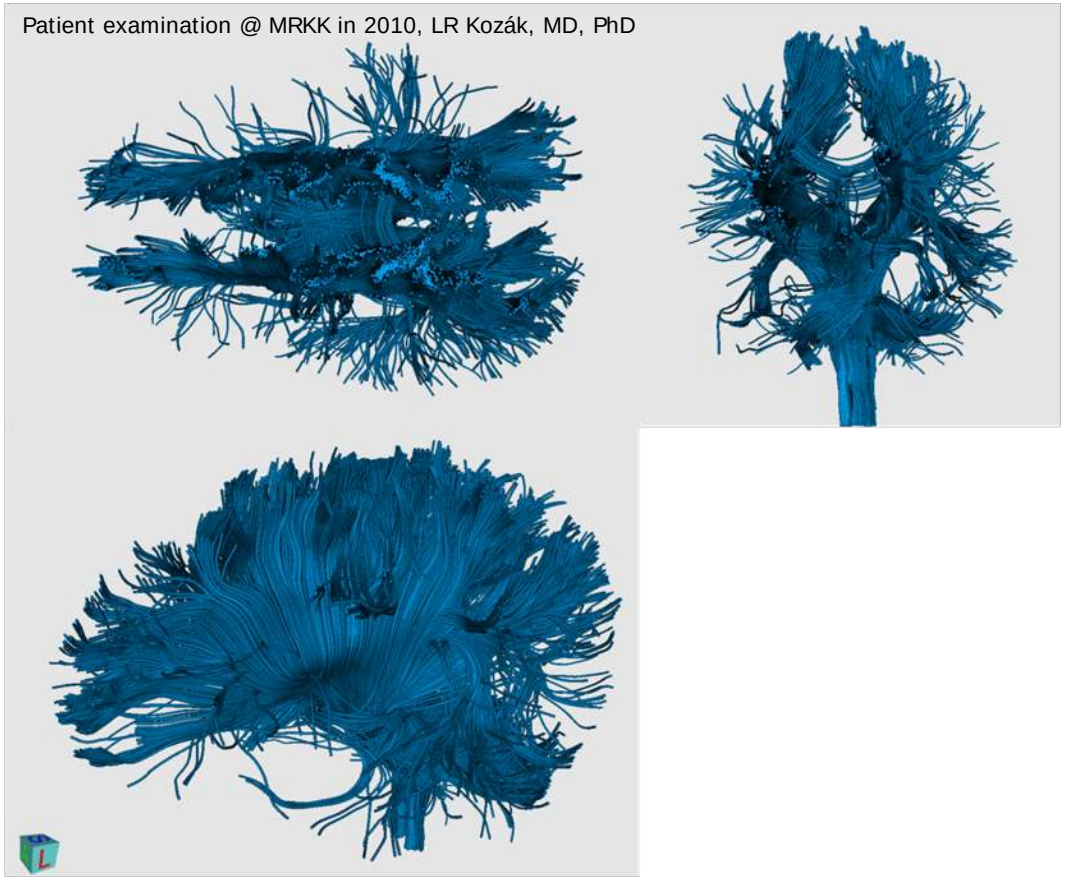
diffusion along axons in a neural fiber tract

Diffusion anisotropy in the human brain



Commissural bundles

Diffusion anisotropy in the human brain

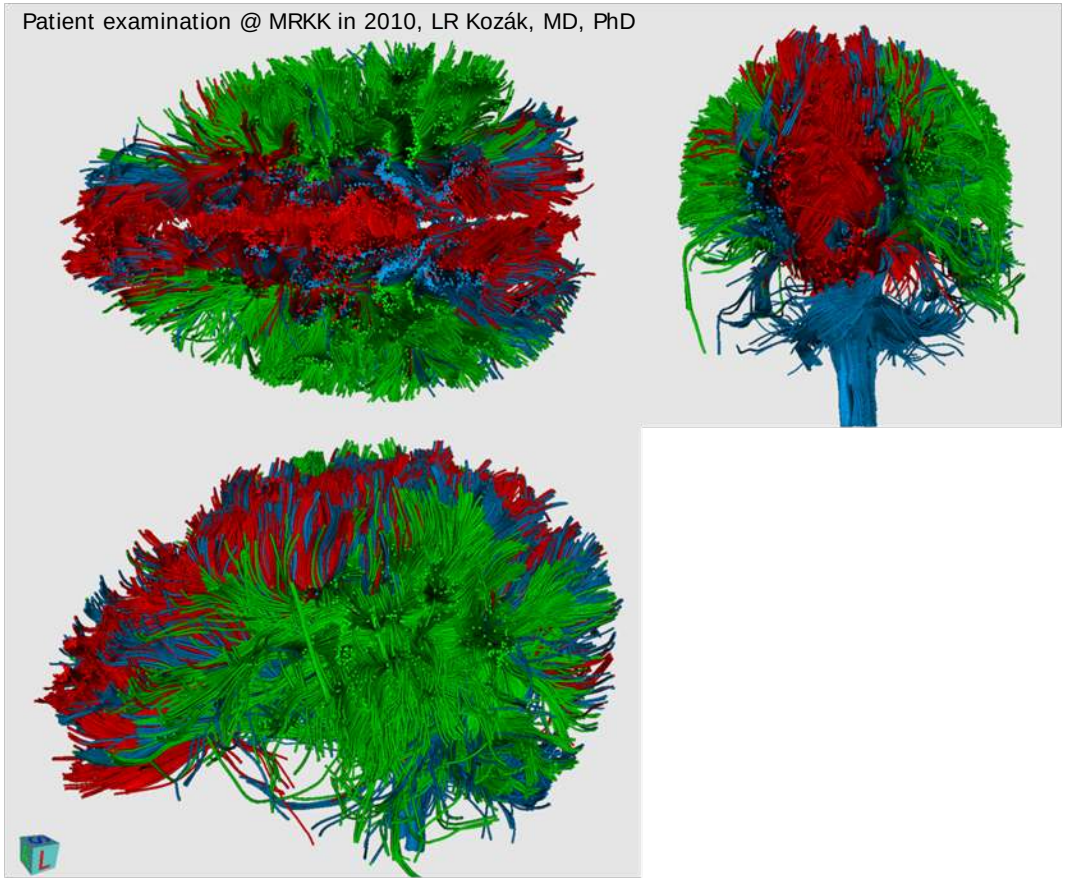


Projection bundles

Diffusion anisotropy in the human brain

Association bundles

Diffusion anisotropy in the human brain



Commissural bundles

Projection bundles

Association bundles

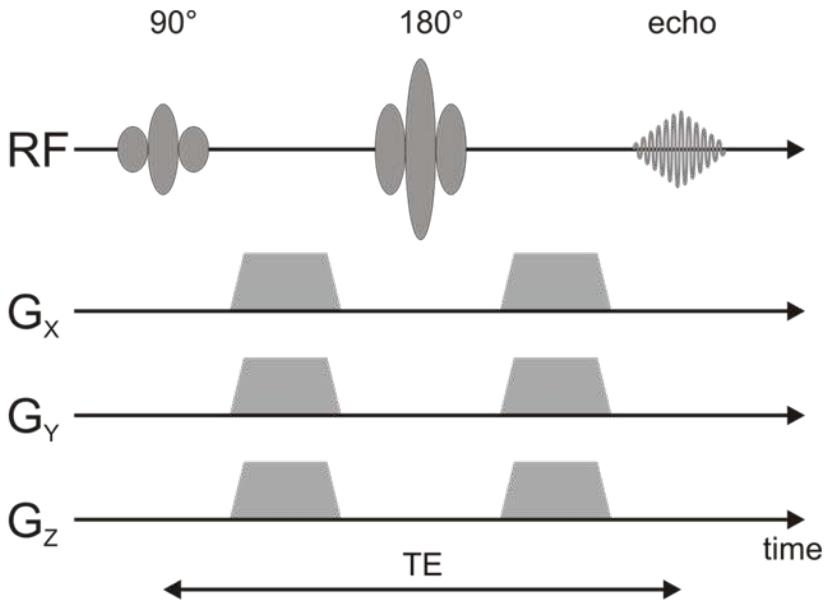
Diffusion weighted MRI (DWI)

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

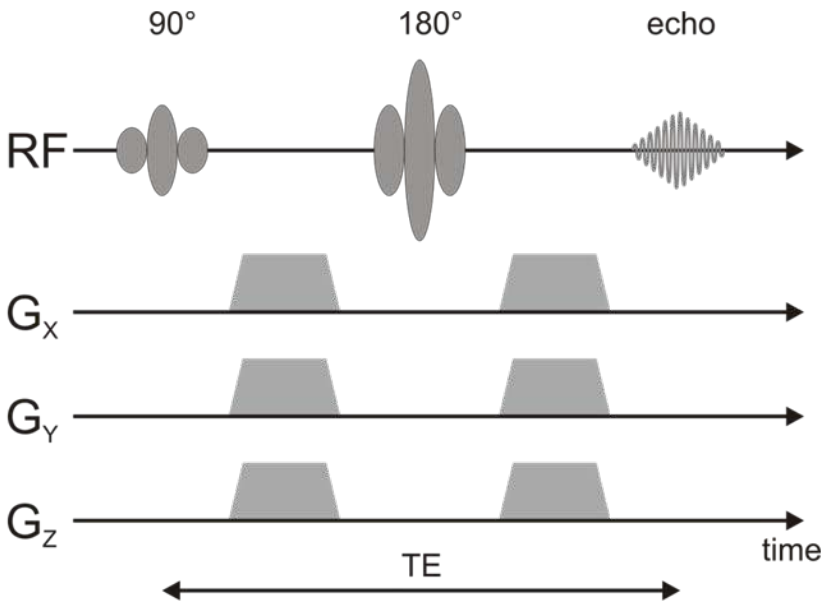
Pulsed-Gradient Spin Echo (PGSE)

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

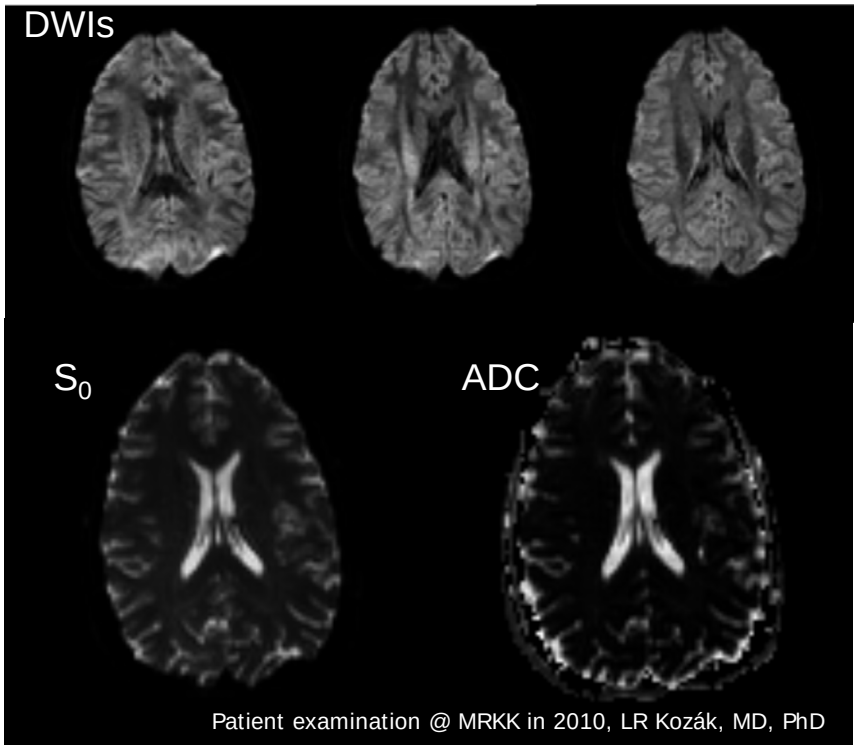
- Diffusion in each voxel can be calculated from the signal decay knowing the acquisition parameter **b**

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

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

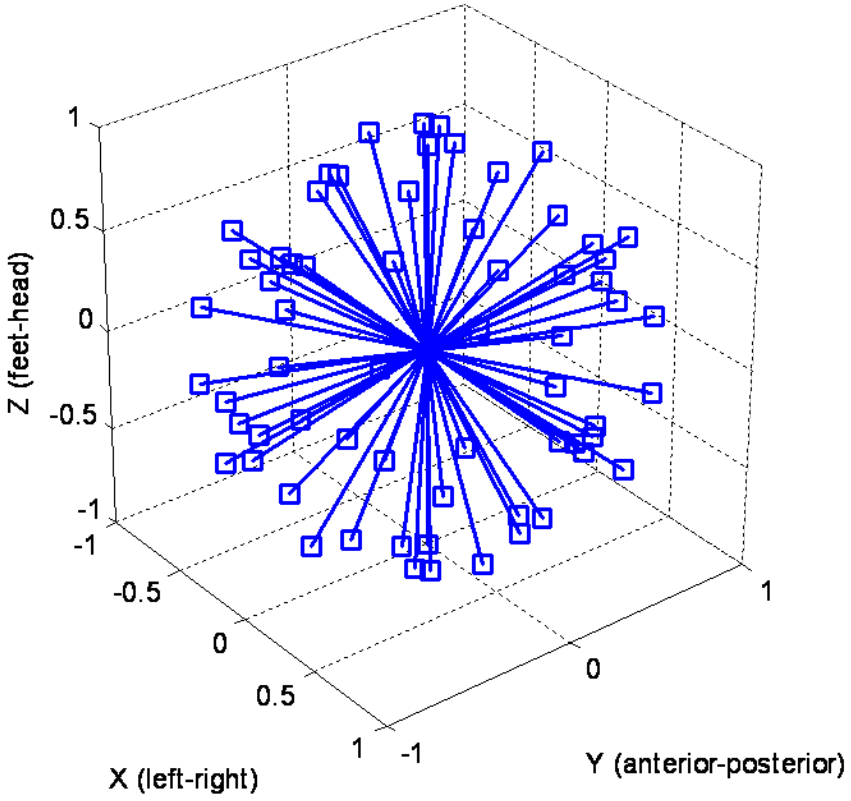
- Using a single b=0 reference image, i.e. an image without diffusion weighting (S_0)
- D can be calculated voxelwise, and presented as an apparent diffusion coefficient (ADC) image



Diffusion weighted MRI (DWI) cont'd

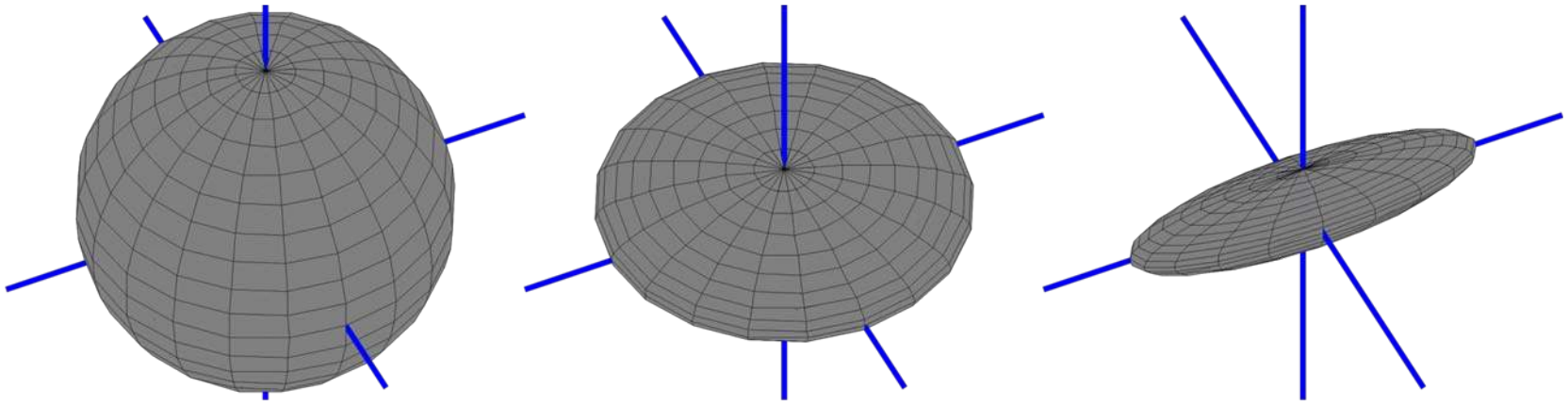
As gradients encode directions in the magnet, diffusion can be measured in arbitrary directions.

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

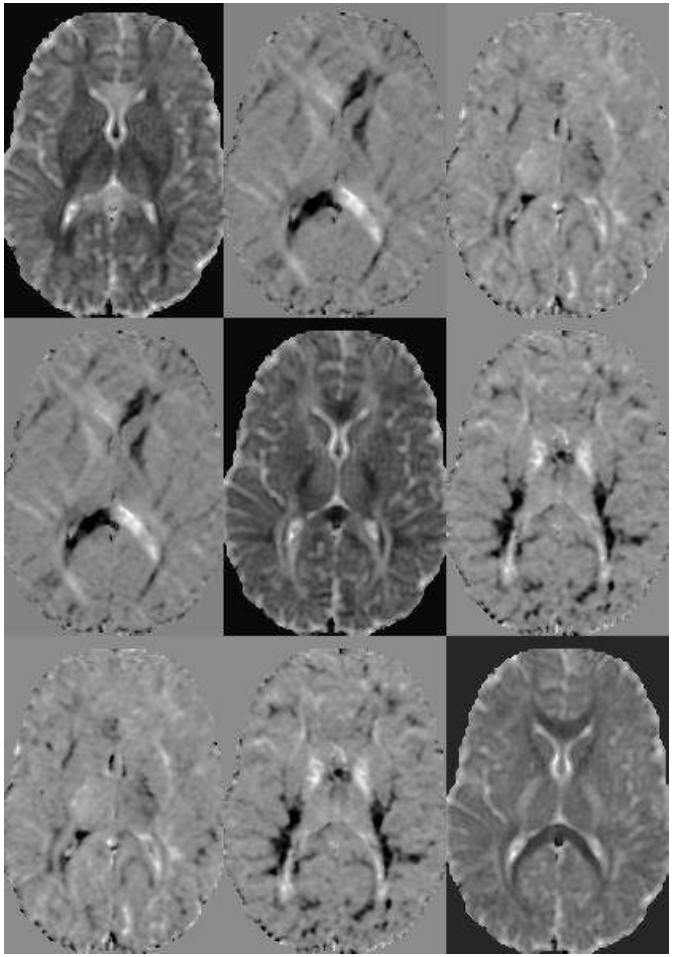


isotropic planar linear

The diffusion tensor

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

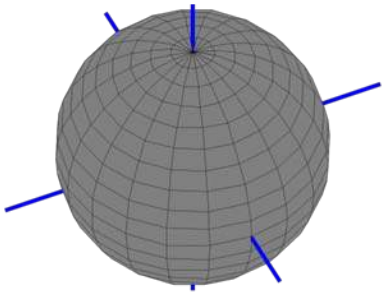
$$D = \begin{bmatrix} D_{XX} & D_{XY} & D_{XZ} \\ D_{YX} & D_{YY} & D_{YZ} \\ D_{ZX} & D_{ZY} & D_{ZZ} \end{bmatrix}$$



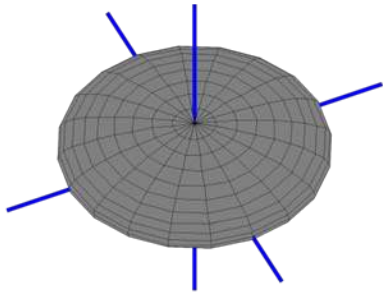
Fractional anisotropy (FA)

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

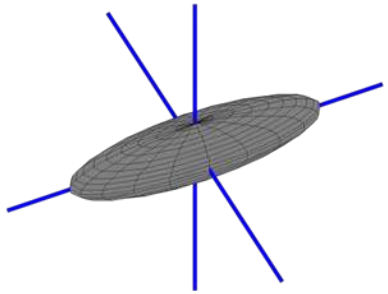
- Direction independent measure of anisotropy
- FA maps can be color coded according to the direction of highest diffusion:
  - **LEFT-RIGHT**
  - **ANTERIOR-POSTERIOR**
  - **FEET-HEAD**



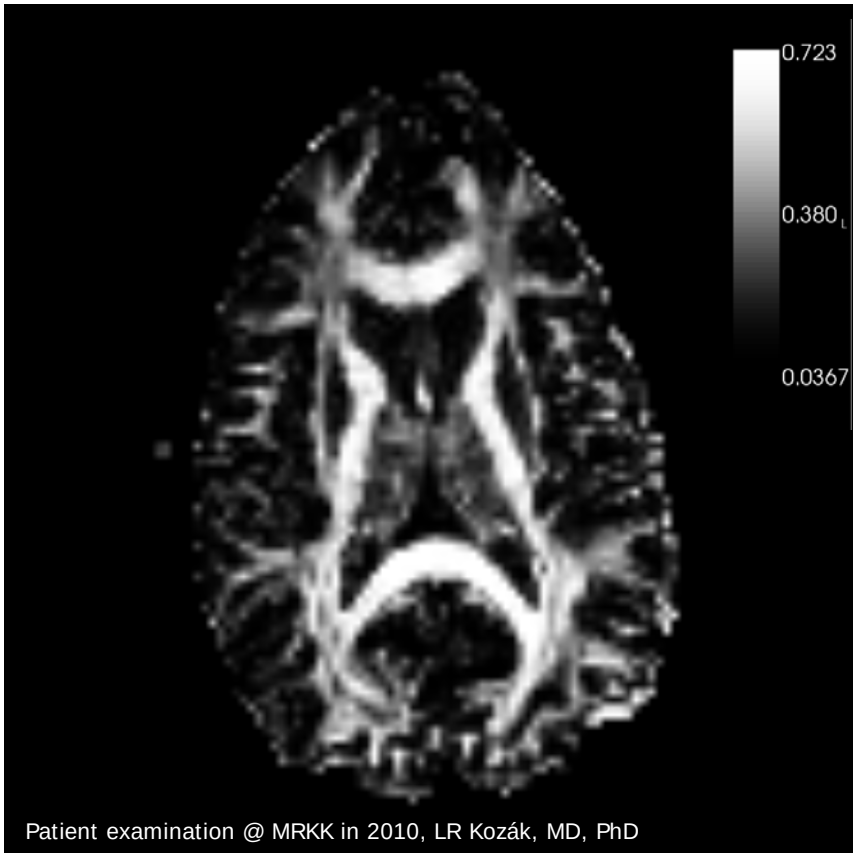
FA=0



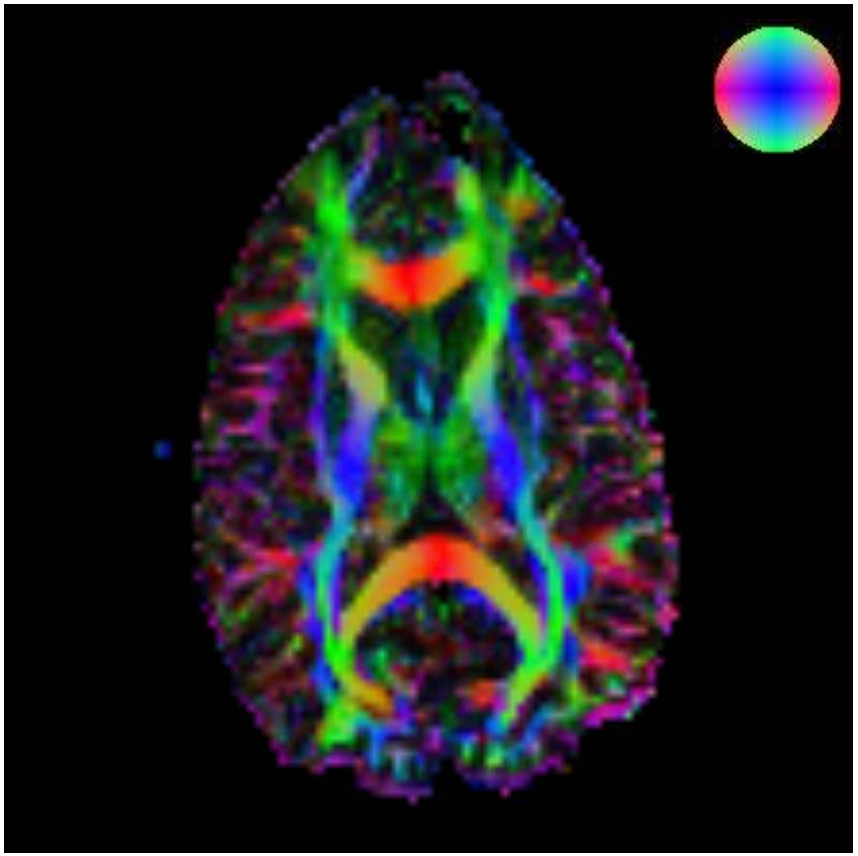
FA=0.52



FA=0.7



FA map

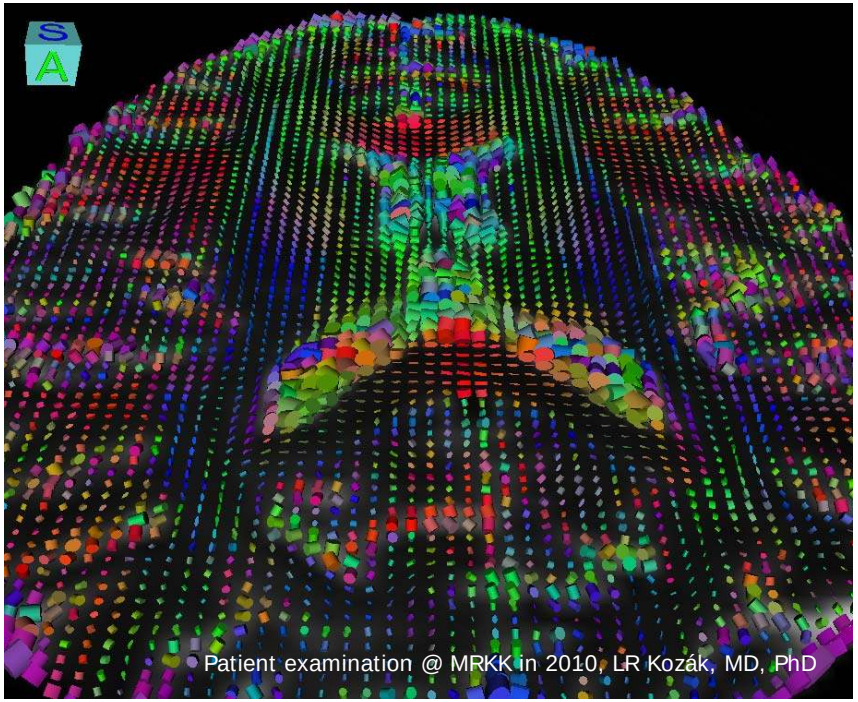


FA map color coded according to the direction of highest diffusion

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



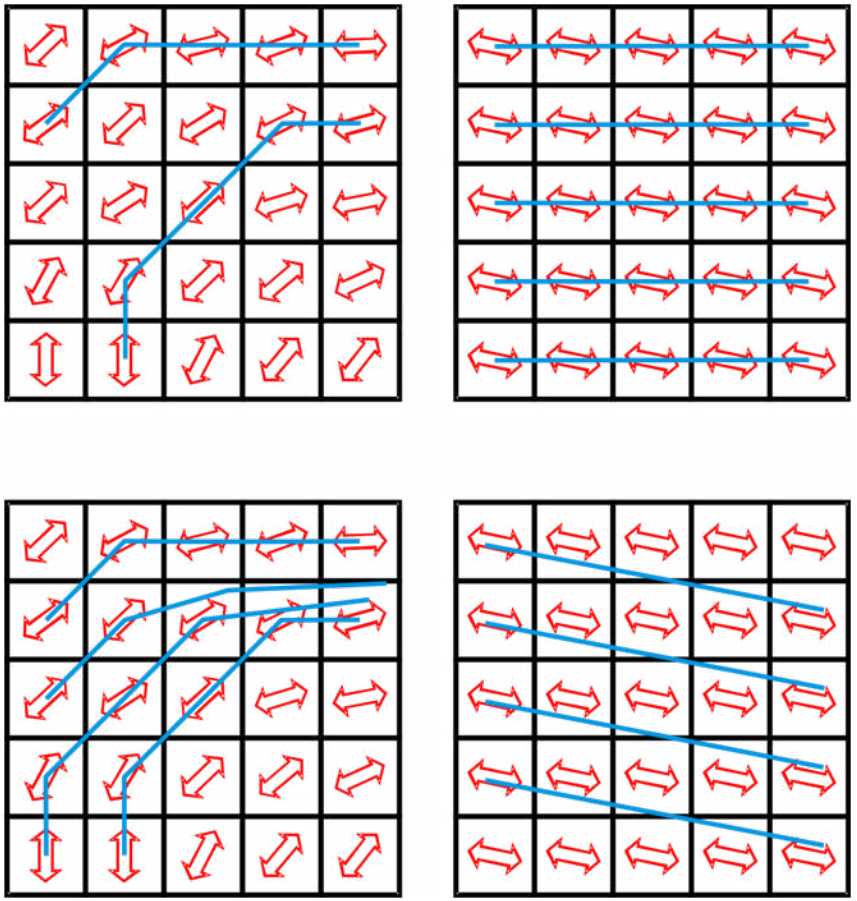
Tractography

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

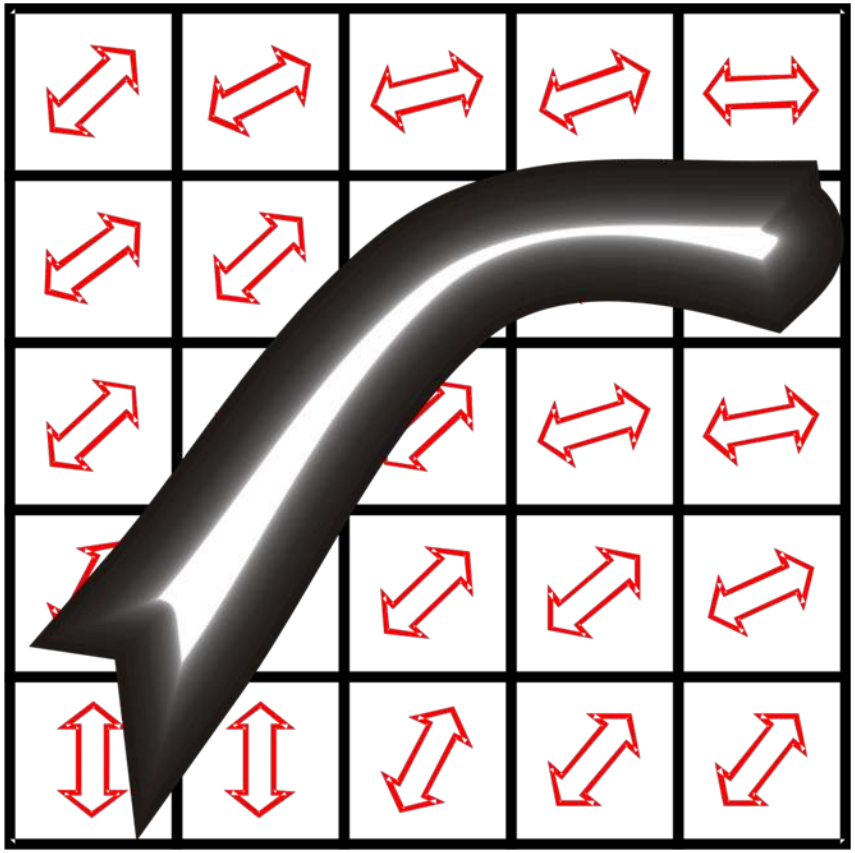
- With a discrete model of tensors (top row) connections or directions can be missed or misinterpreted
- With a continuous model of tensors (bottom row) the results are more realistic.



Tractography

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

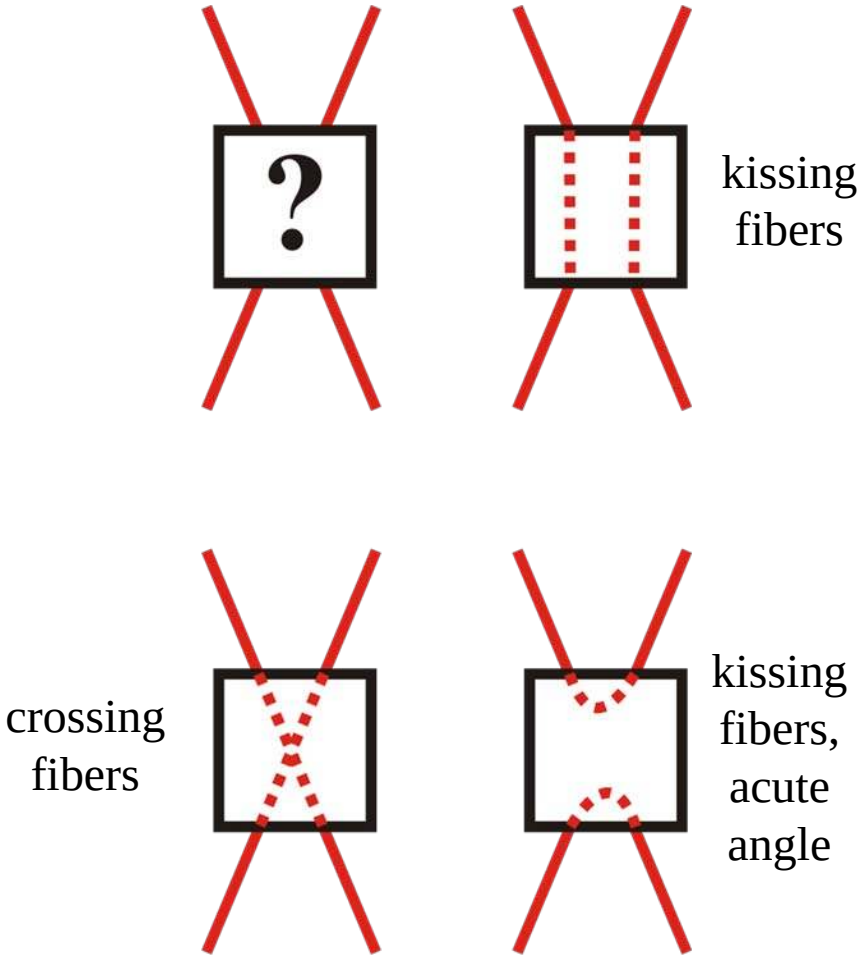
- Time demanding
- Hardware demanding
- Cannot fully solve **crossing fiber** and **kissing fiber** uncertainties
  - Although a priori information helps in some cases



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

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

Ways to improve DWI/DTI

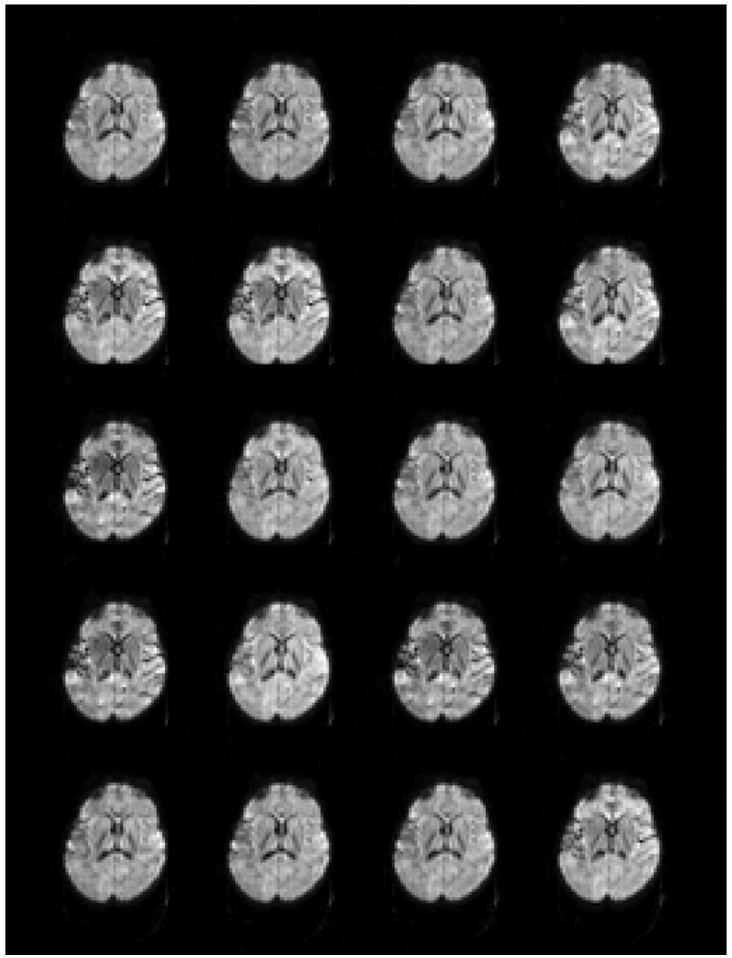
Pulse-triggering improves DWI/DTI image quality

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



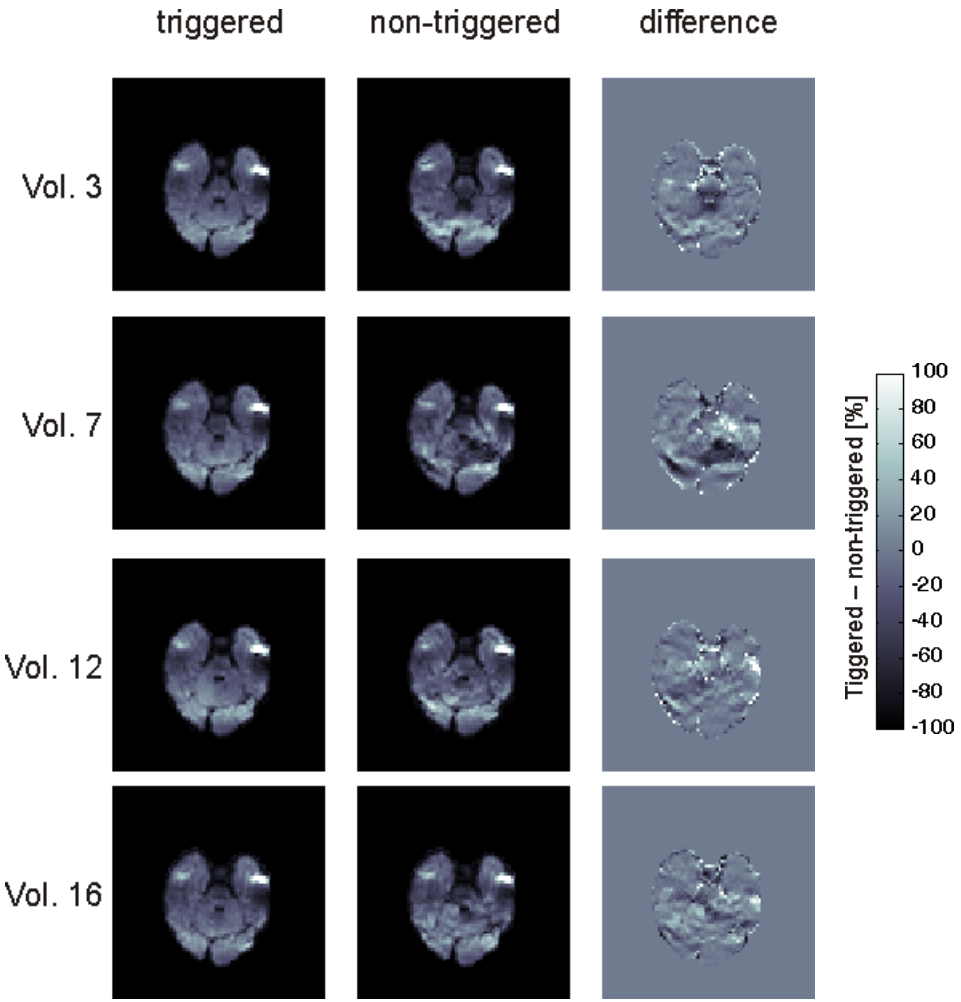
Ways to improve DWI/DTI

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



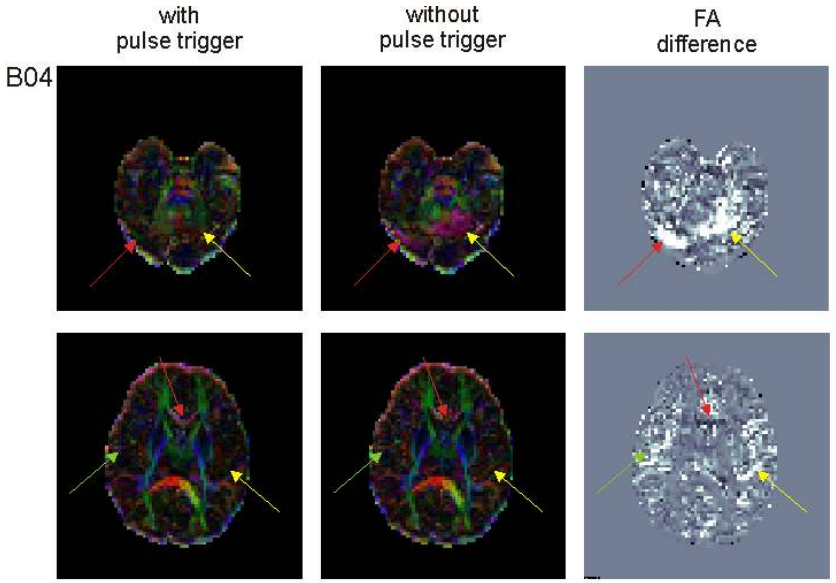
Ways to improve DWI/DTI

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

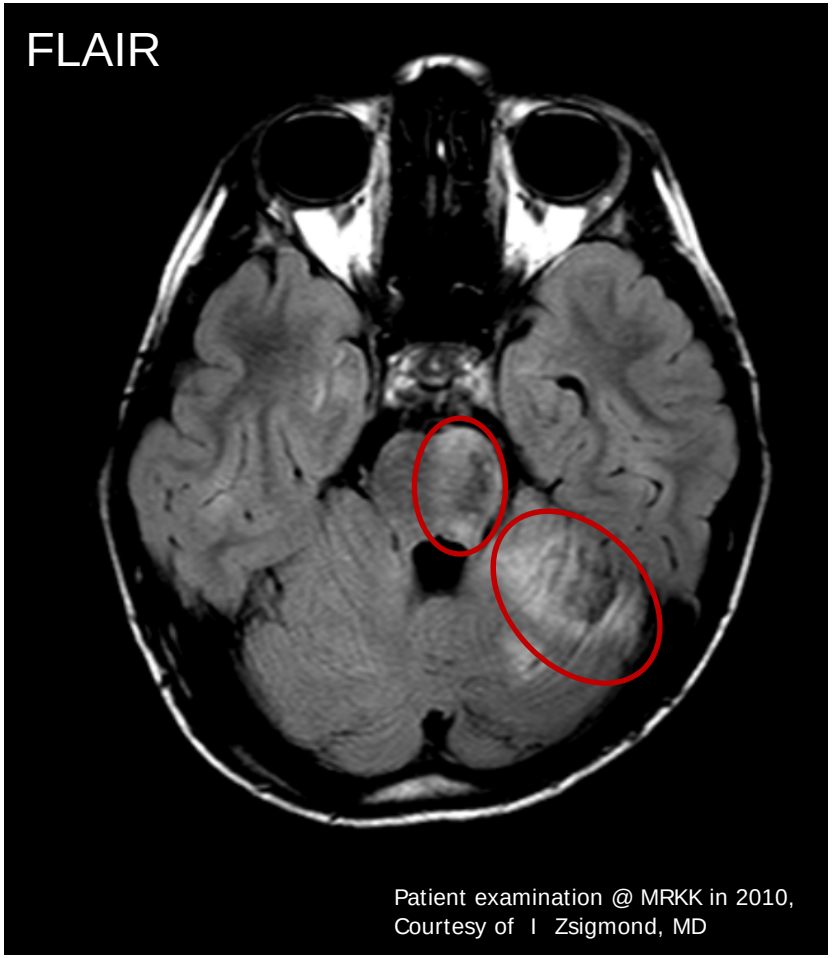
Clinical applications of DWI/DTI

Stroke

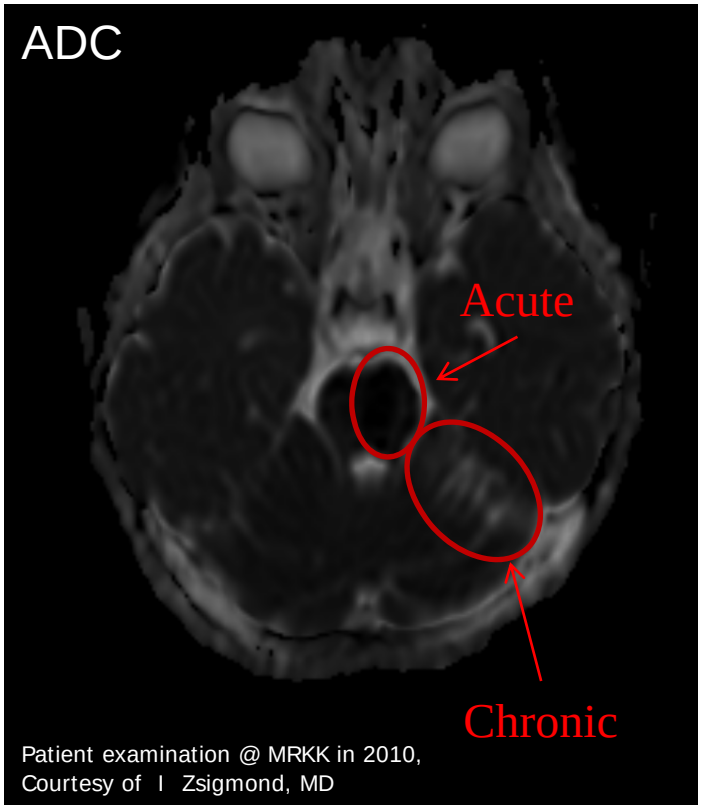
Primary cause is interruption of blood flow to brain region ➔ ischemic injury, infarction.

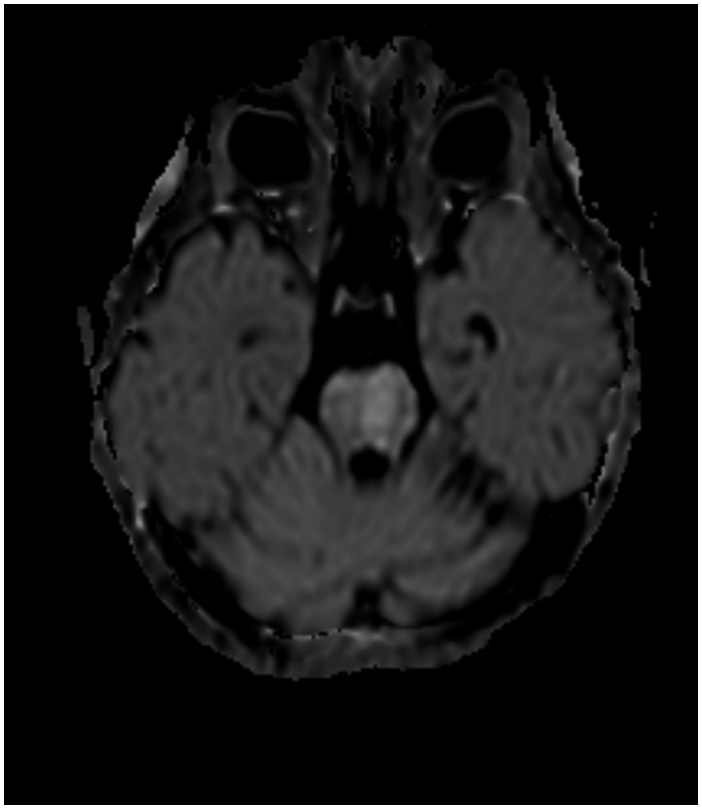
It is difficult to differentiate between acute and chronic ischemia using standard MR sequences.

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



Biomedical Imaging: Recent Advances in MRI





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.).

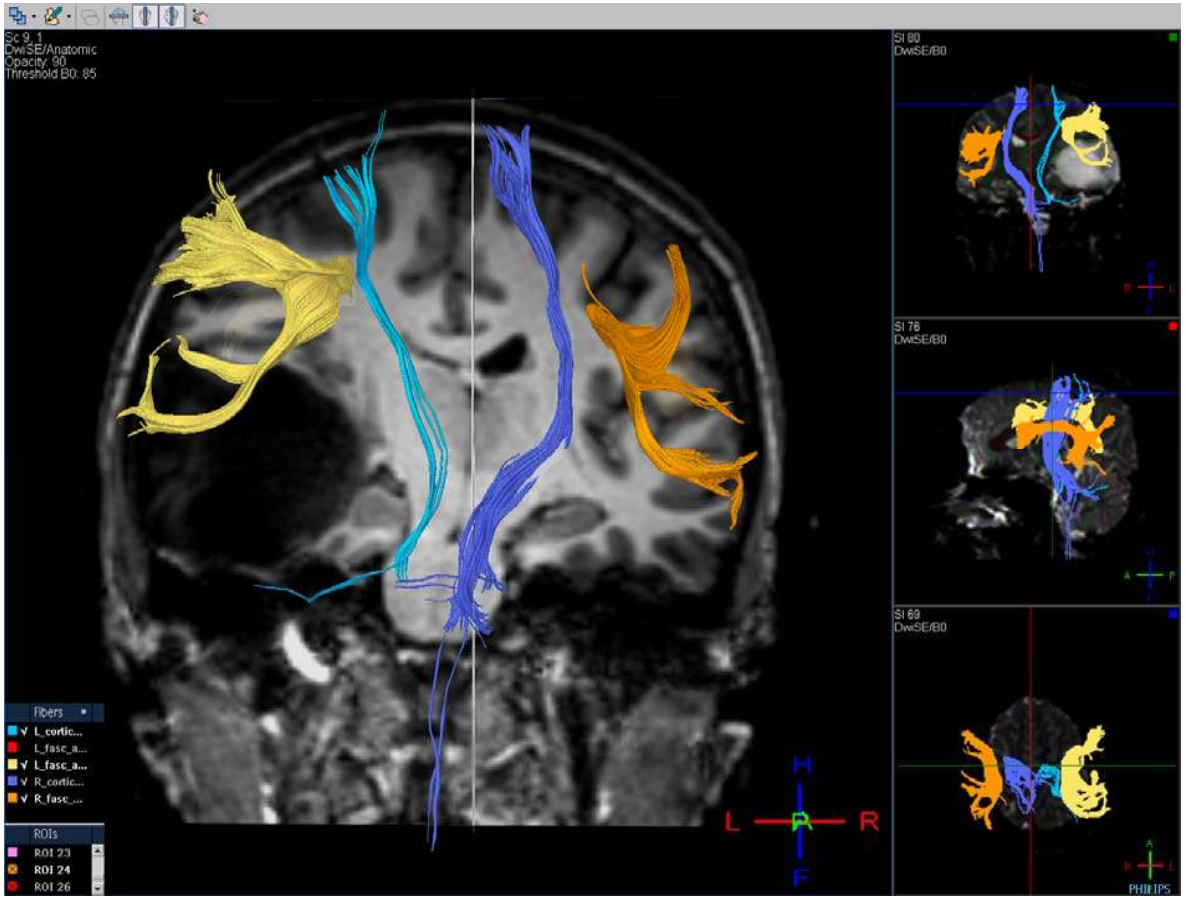
Epilepsies

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

Lymphomas & extracranial tumors

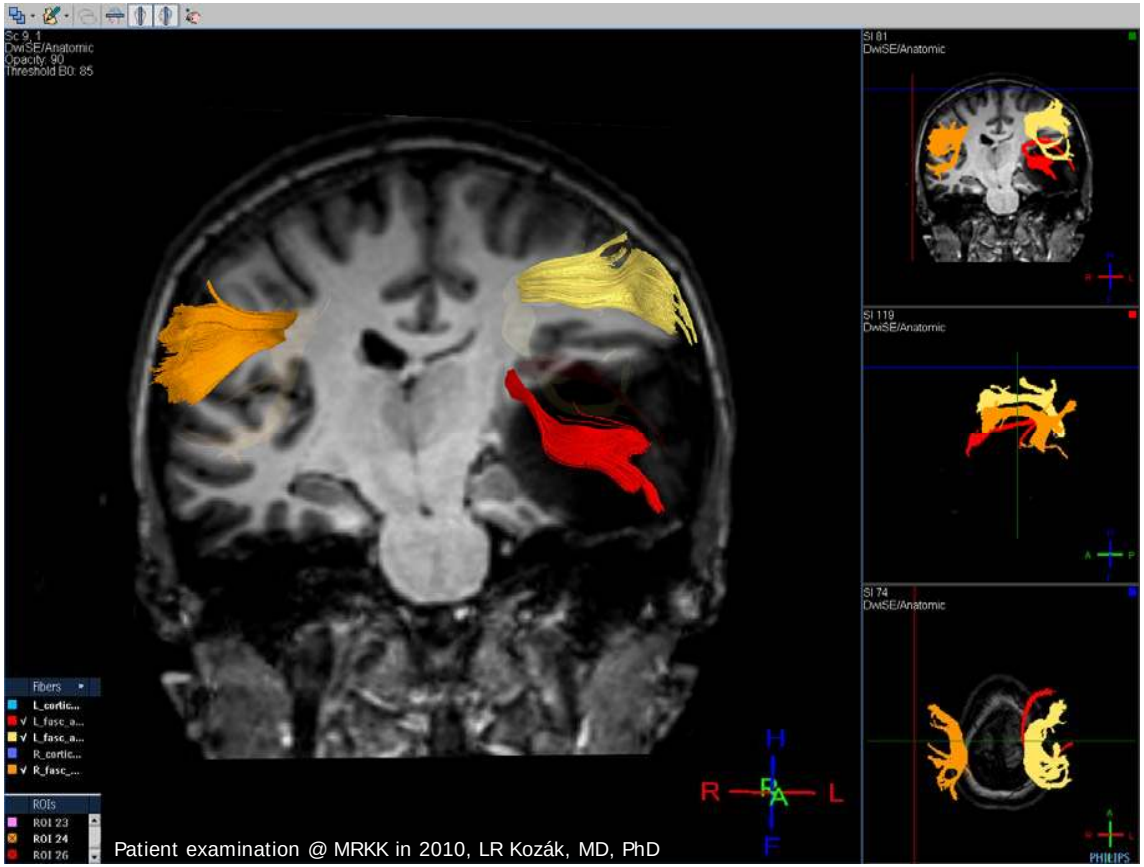
DWIBS (Diffusion Weighted whole body Imaging with Background Suppression) are useful for tumor viability assessment, its predictive value matches that of PET-CT's.

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



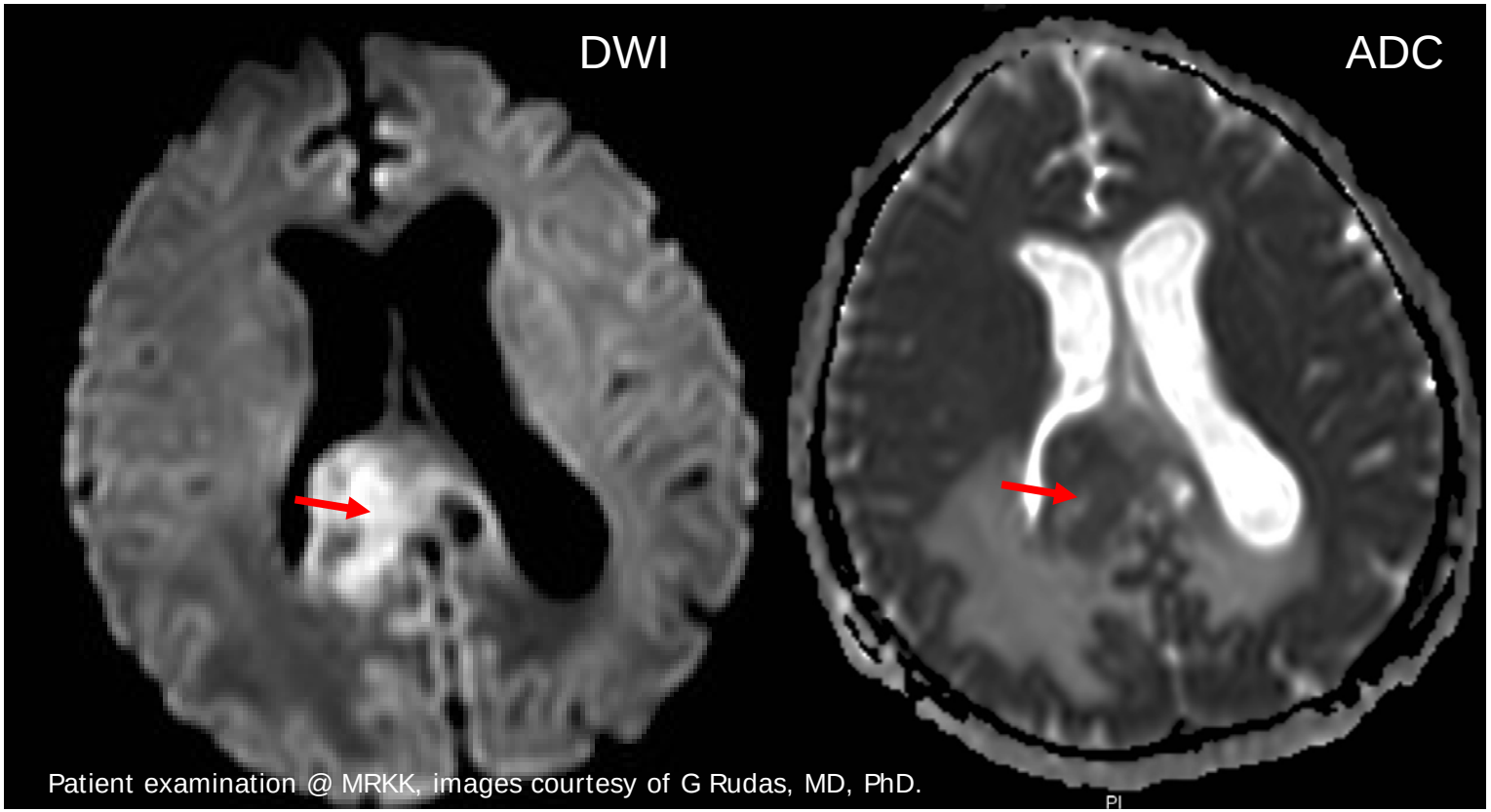
Both the left corticospinal tract and the arcuate fasciculus are displaced by the large temporal tumor visible as a decreased signal intensity region on the T1W coronal image.

Biomedical Imaging: Recent Advances in MRI



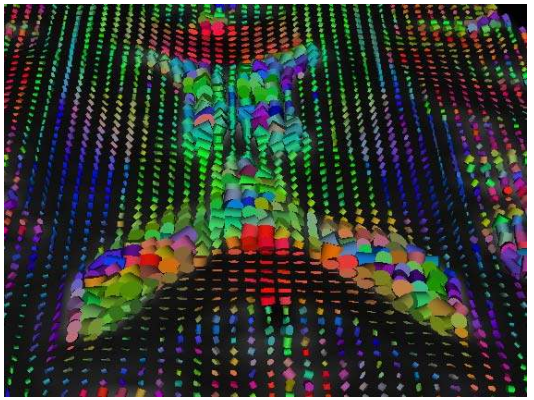
Patient examination @ MRKK in 2010, LR Kozák, MD, PhD

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

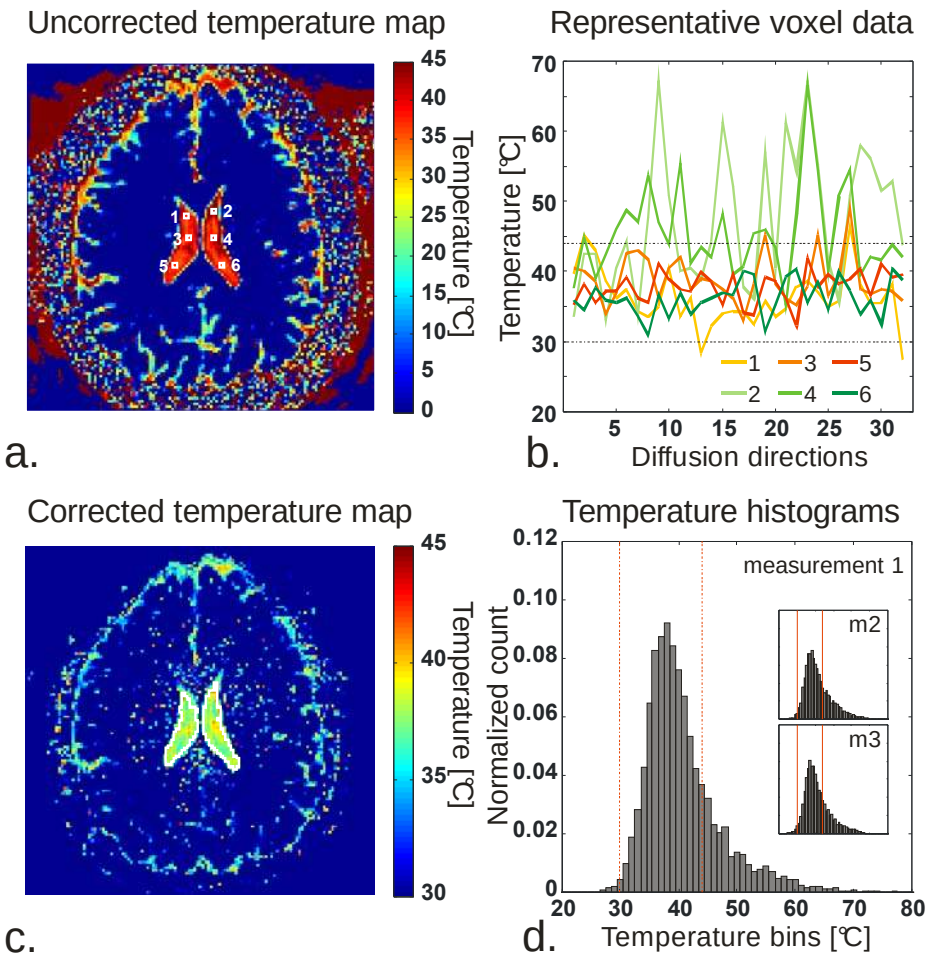
Upon calibration and CSF-pulsation correction, ventricular temperatures can be estimated in vivo.

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

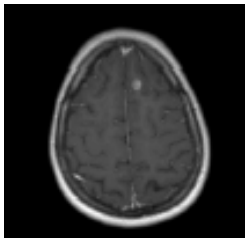
As water diffusivity depends on the balance of extracellular and intracellular factors, any pathology affecting these compartments (e.g. stroke, lymphoma, etc.) can cause changes in diffusivity, thus DWI can be used for diagnostic and prognostic purposes.

Arterial Spin Labeling (ASL)

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

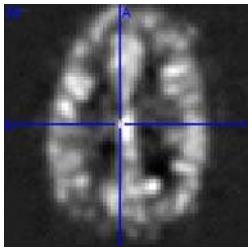
Invasive:

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



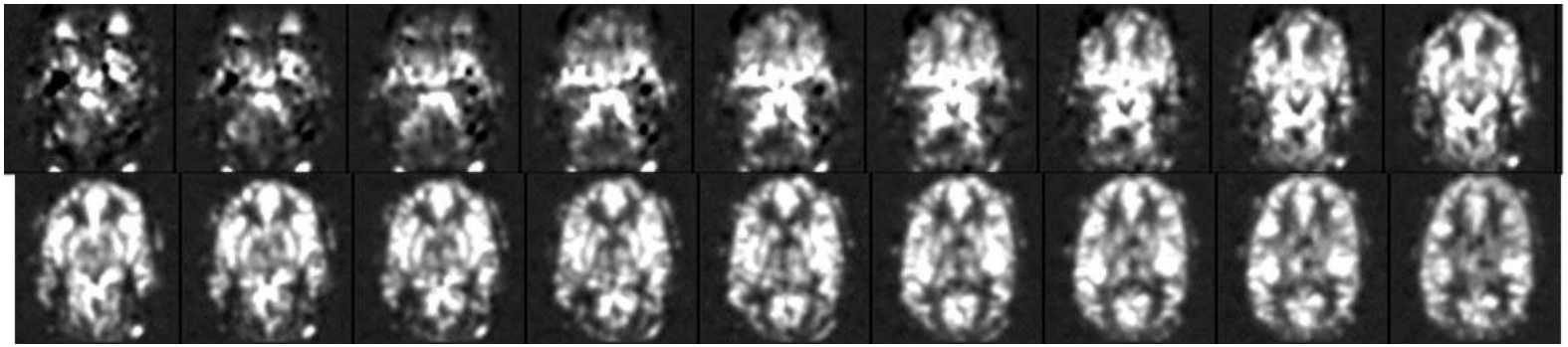
Noninvasive:

Arterial Spin Labelling (**ASL**)



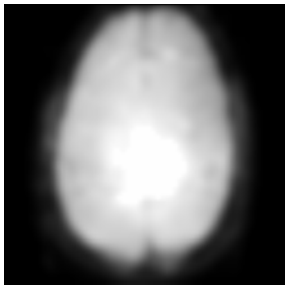
Principles of ASL

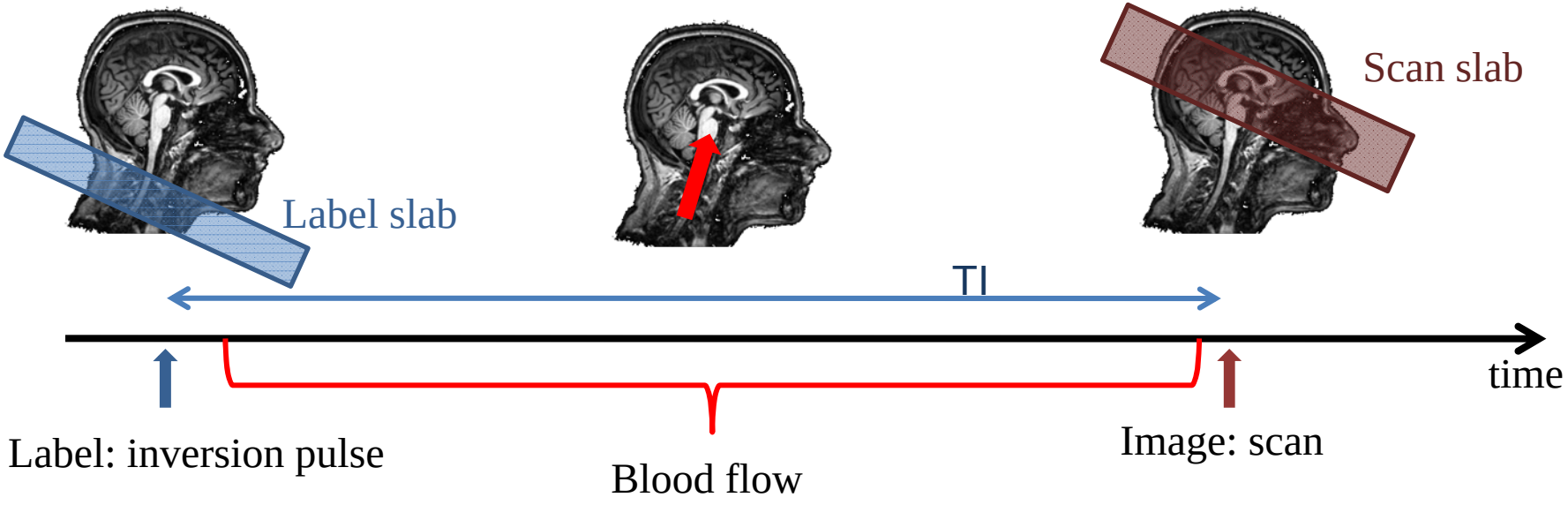
- PET-like for direct CBF measurement (but not CBV as with vascular contrast agents)
- Measurement of slow neural changes
- Absolute quantification of blood flow



Principles of ASL: acquiring tagged image

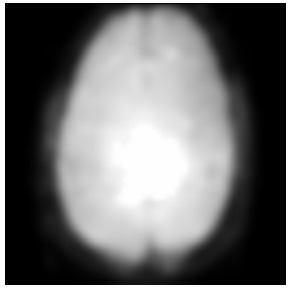
- Tag/label (with inversion) water in the blood proximal of imaging plane
- Wait predefined period of time for blood to arrive
- Acquire tagged image

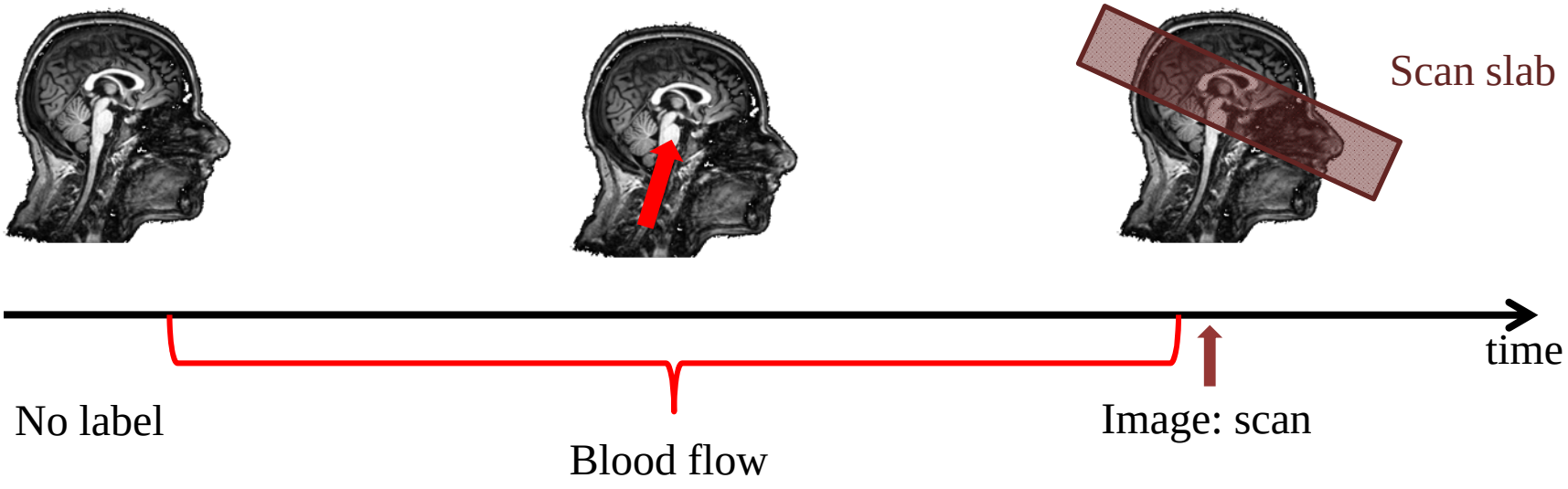




Principles of ASL: acquiring control image

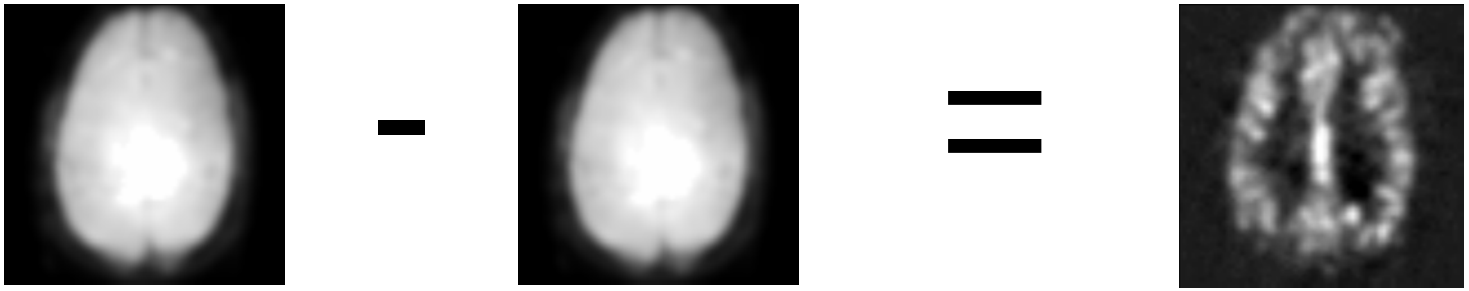
- Do not tag (or use altered, ineffective tag) water in the blood proximal of imaging plane
- Wait predefined period of time for blood to arrive
- Acquire control image



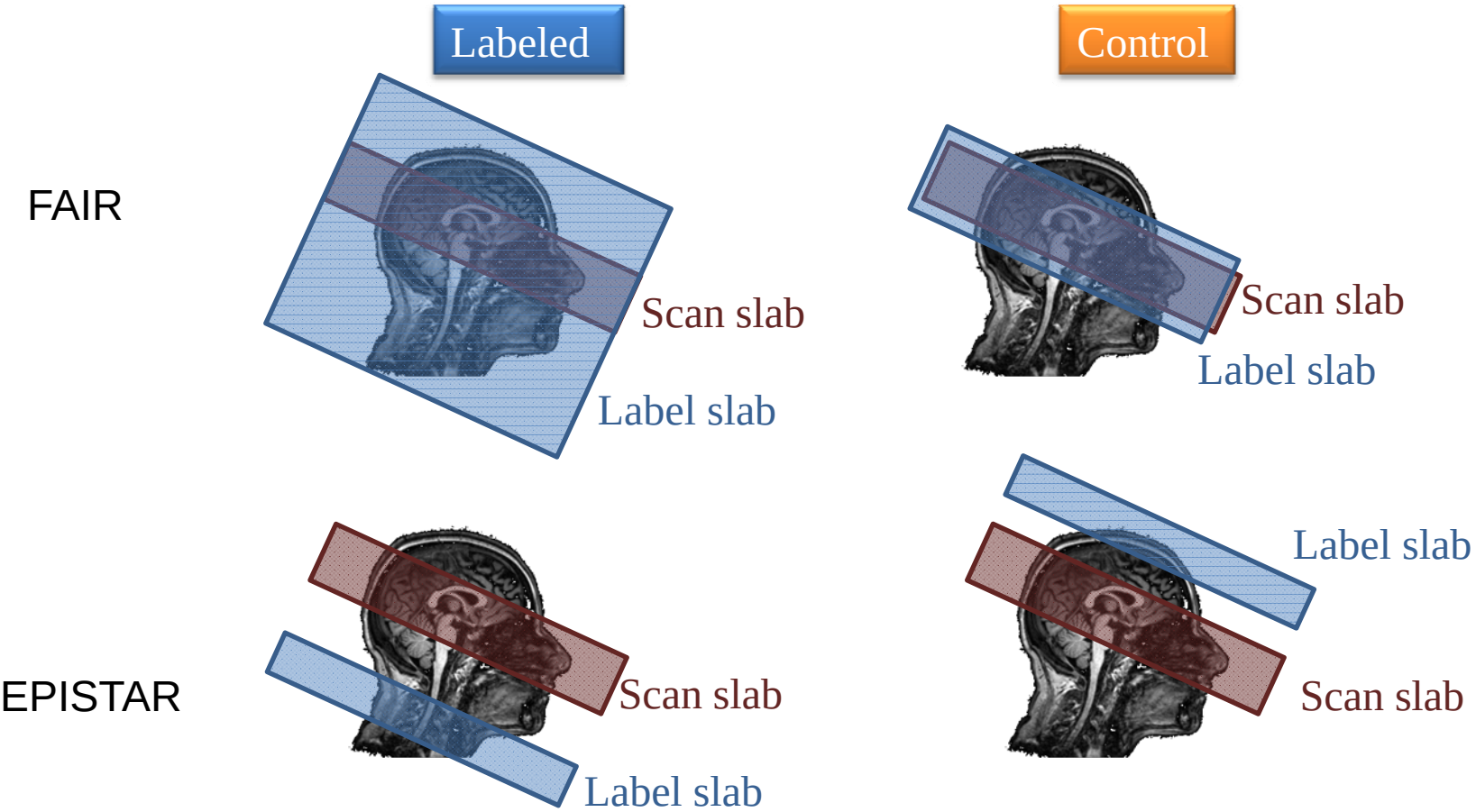


Principles of ASL

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

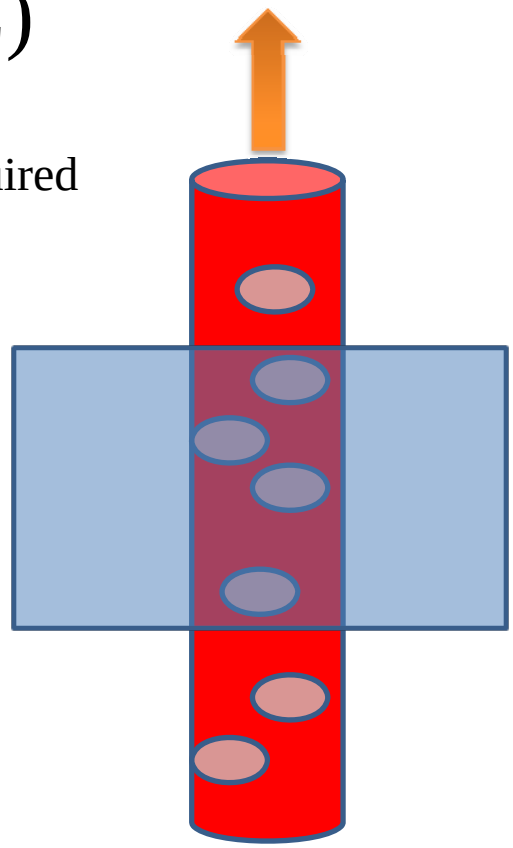


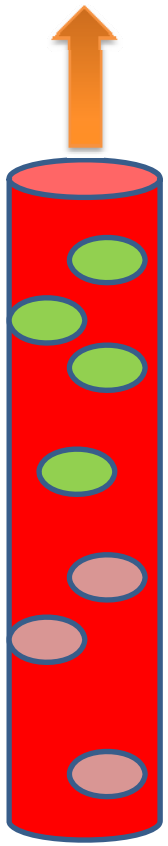
Pulsed ASL (PASL) variants



Pulsed ASL (PASL)

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



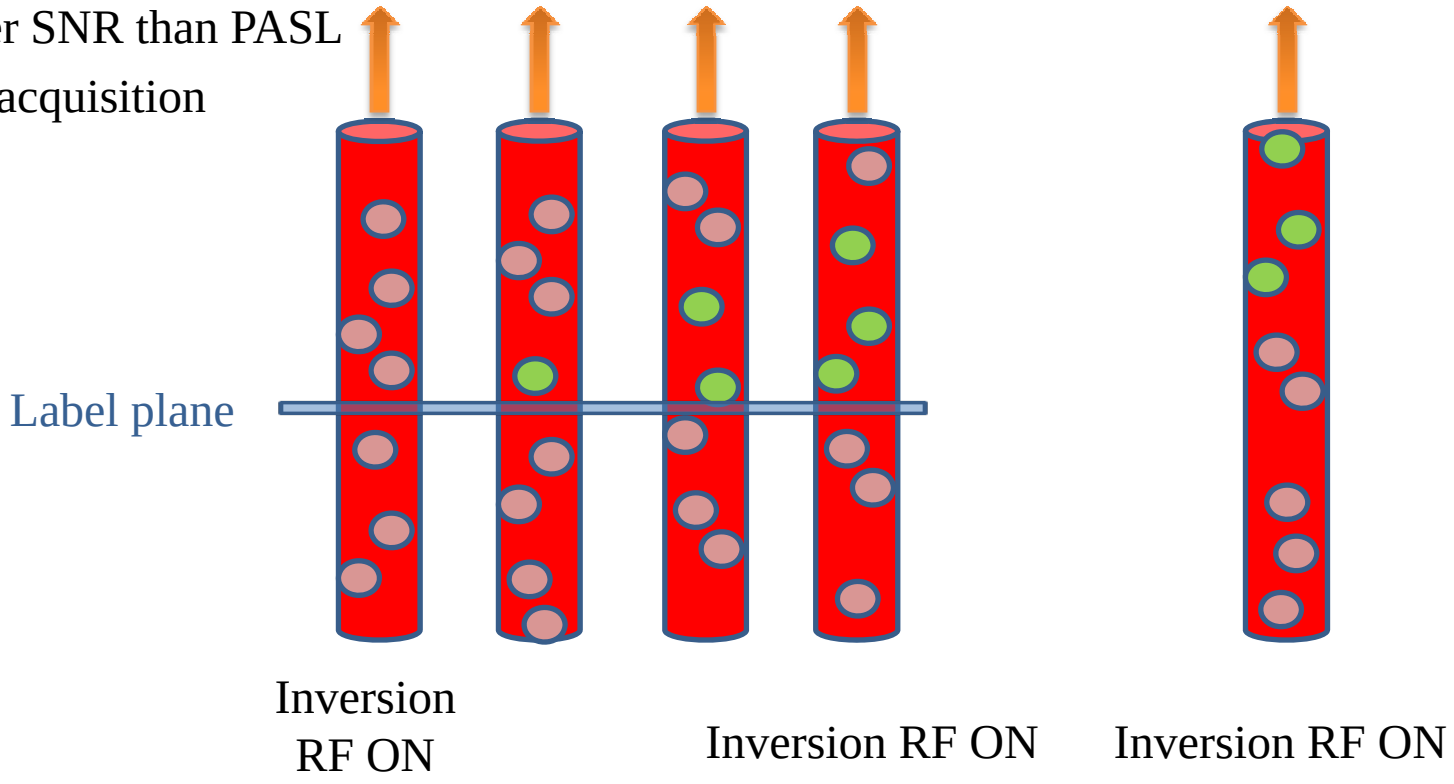


Inversion pulse ON

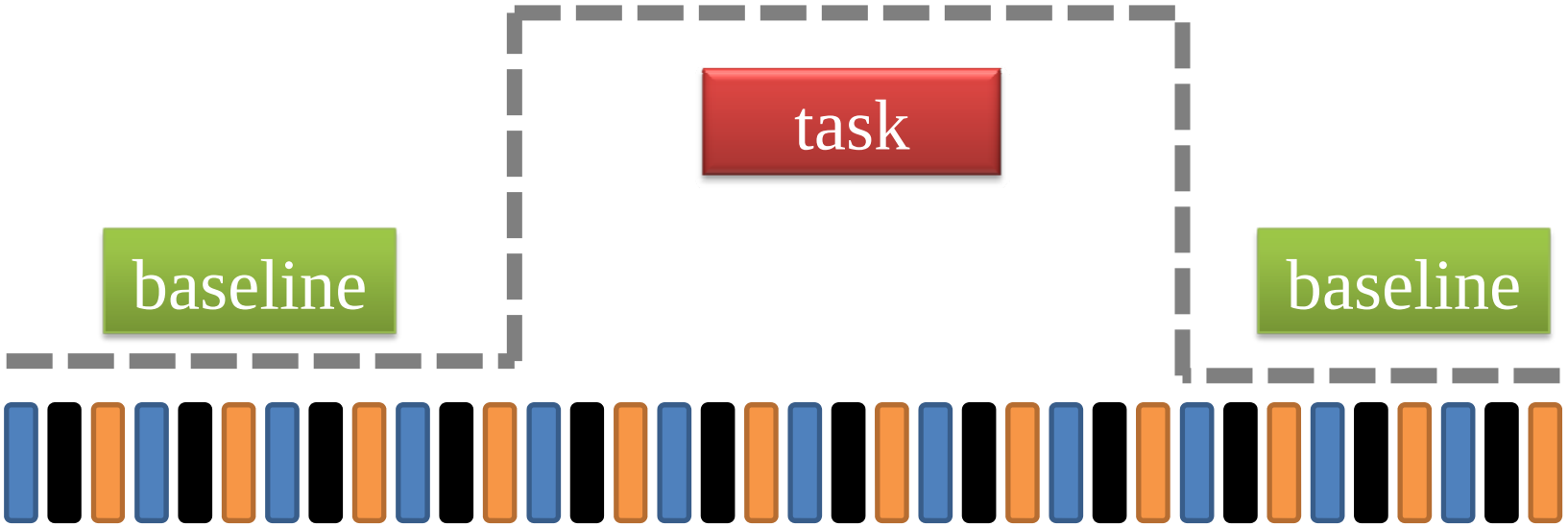
Inversion pulse OFF

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



Labelled
BOLD
Control

- 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

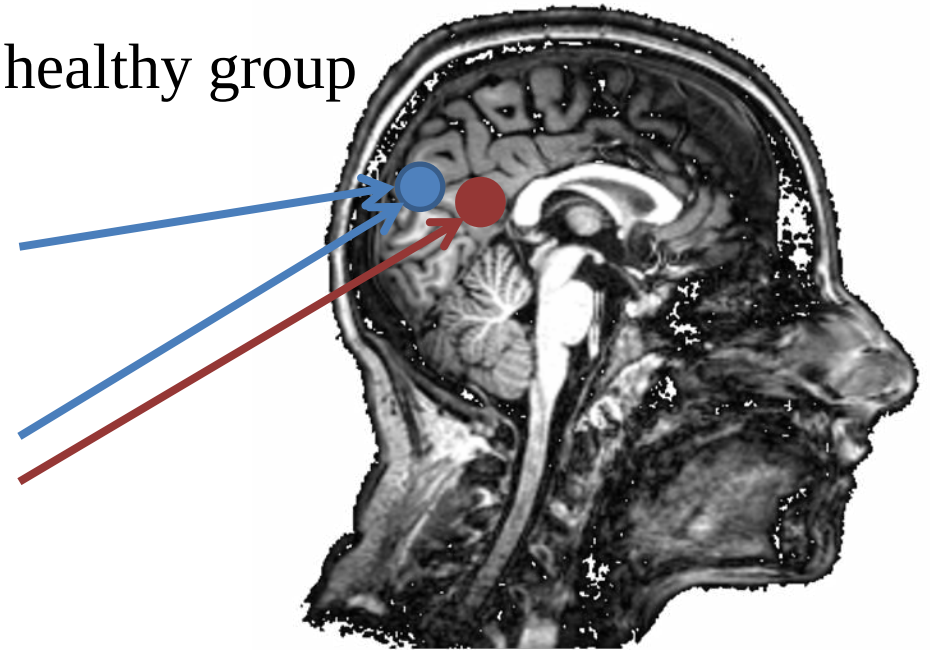
- Motion correction
  - separate (labelled-unlabelled)
  - combined
- Spatial smoothing & normalization
  - before or after subtraction
- Global spike elimination
- Normalization by CBF (calculation based on intesity difference)
  - global signal as covariate
- Spike (jump in average intensity) detection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

Clinical example: amnestic mild cognitive impairment (aMCI).

Direct comparison of patient and healthy group

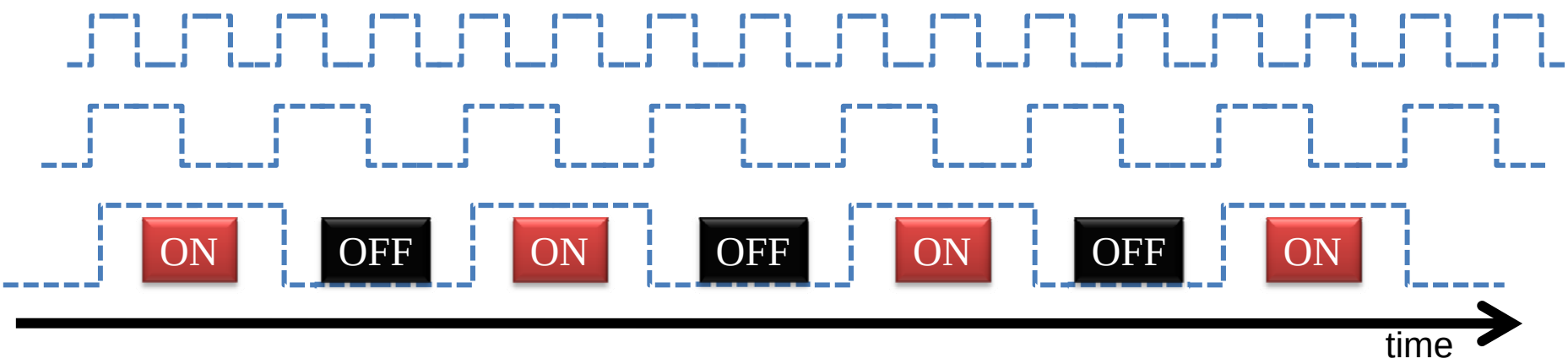
Hypo-perfusion (aMCIs<Controls) in control condition

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



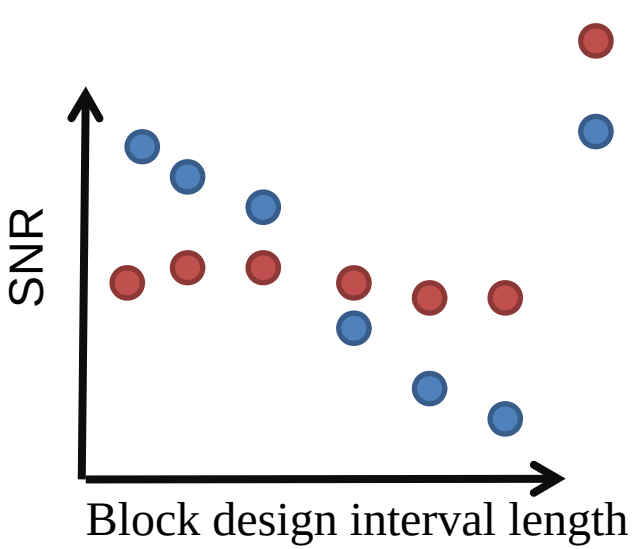
Block type motor task with different alternating time periods (0.5min, 1min .. 20min)

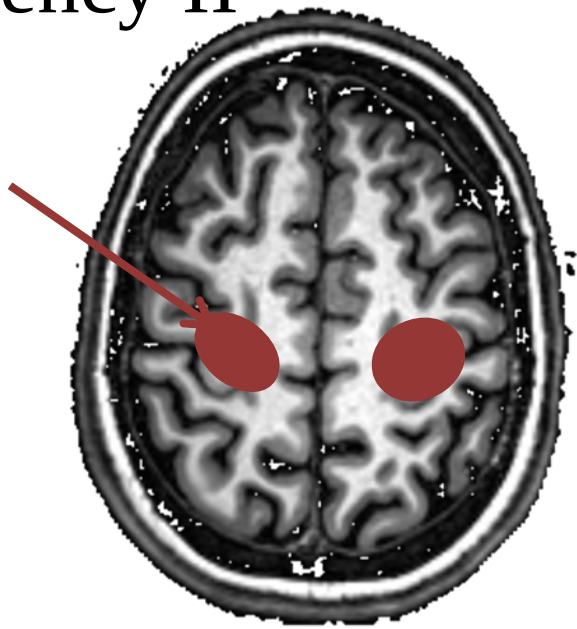
In some cases even 1 hour or a whole day separated the active and rest periods!!!

(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	+	+/-