Physiology of the BOLD Signal

TURKU PET CENTRE NEUROIMAGING COURSE 2023

12.9.2023 Kerttu Seppälä

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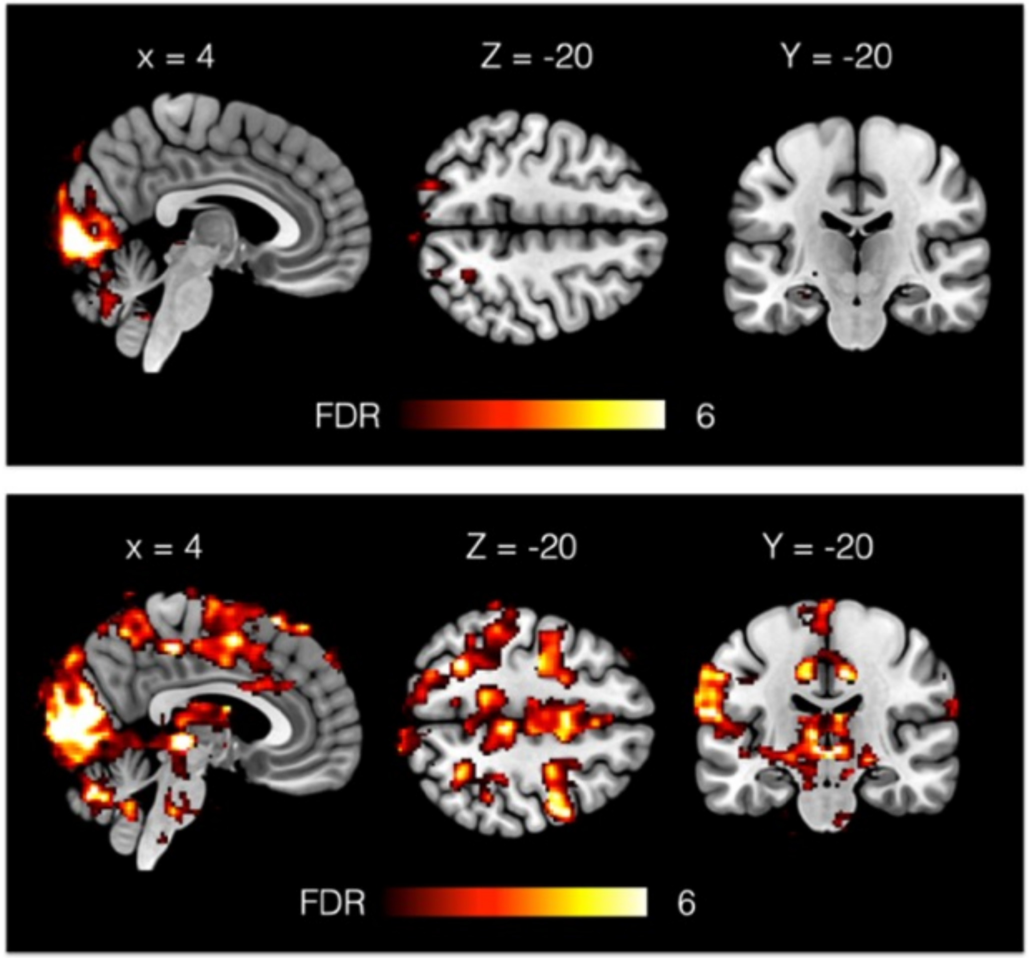
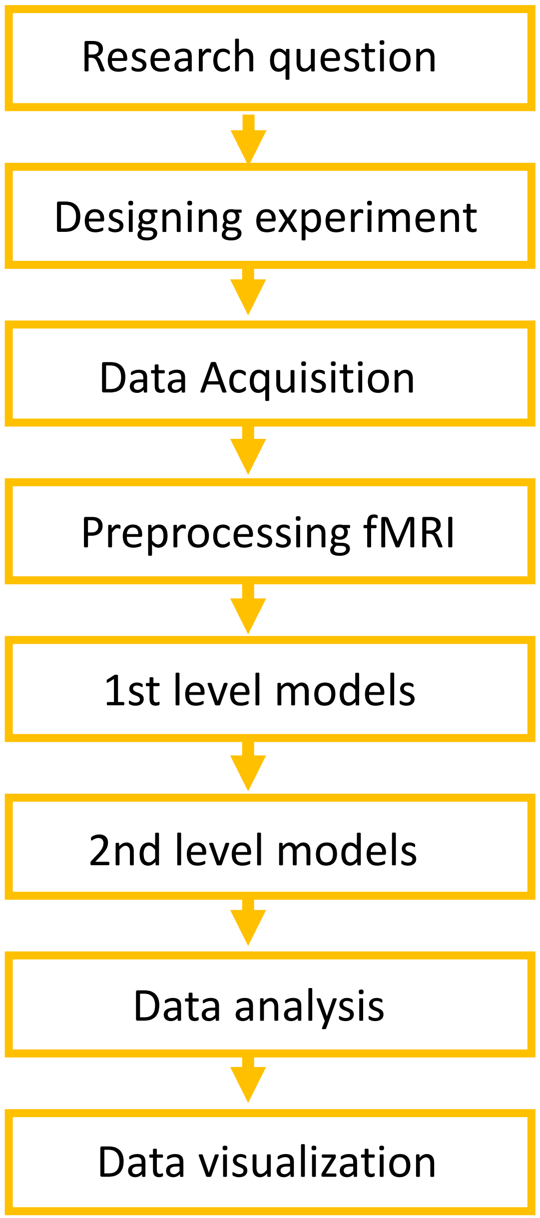
What is fMRI?





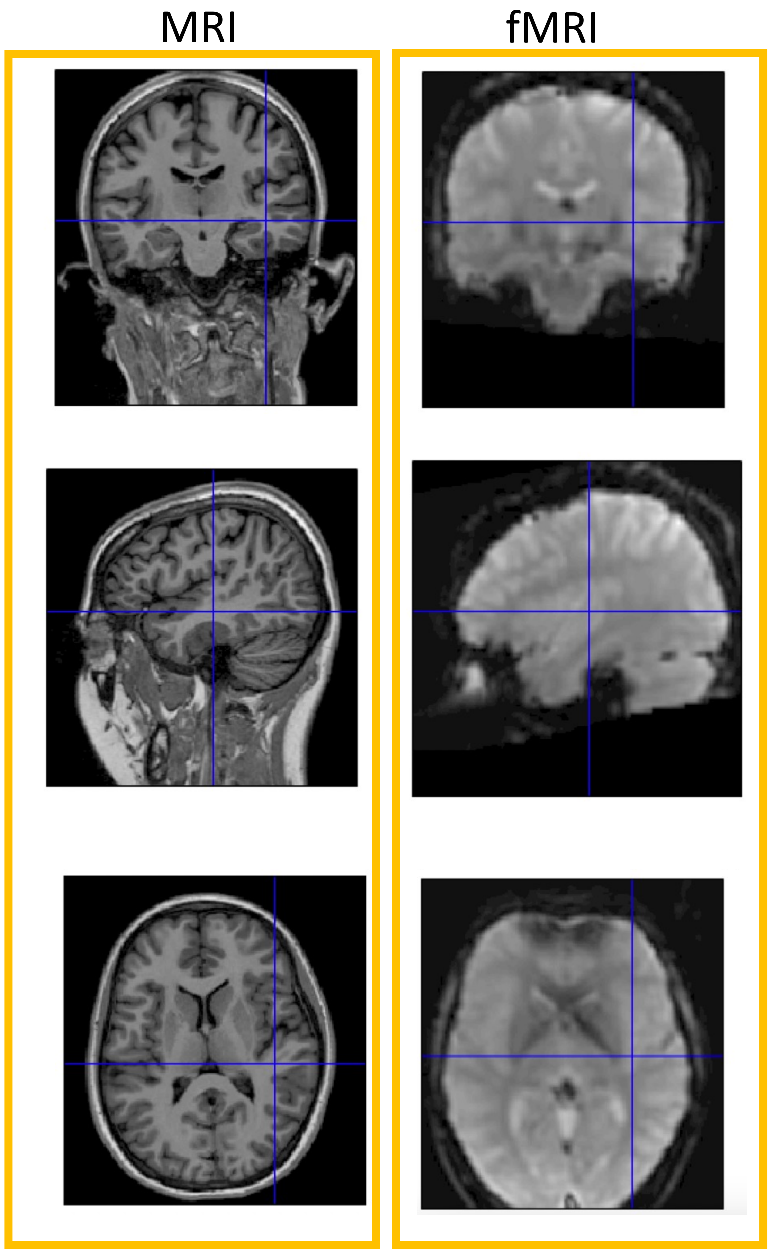
8:30–9:15	**Physiology of the BOLD signal and T2* image acquisition**
9:15–10:00	Experimental designs for fMRI
10:00–10:45	Preprocessing with fMRIprep
10:45–12:00	Lunch break
12:00–12:45	General Linear Model
12:45–13:30	First level models for fMRI
13:30–13:45	Coffee break
13:45–14:30	Second level models for fMRI
14:30–15:15	Region of interest analysis
15:15–16:00	Data visualization

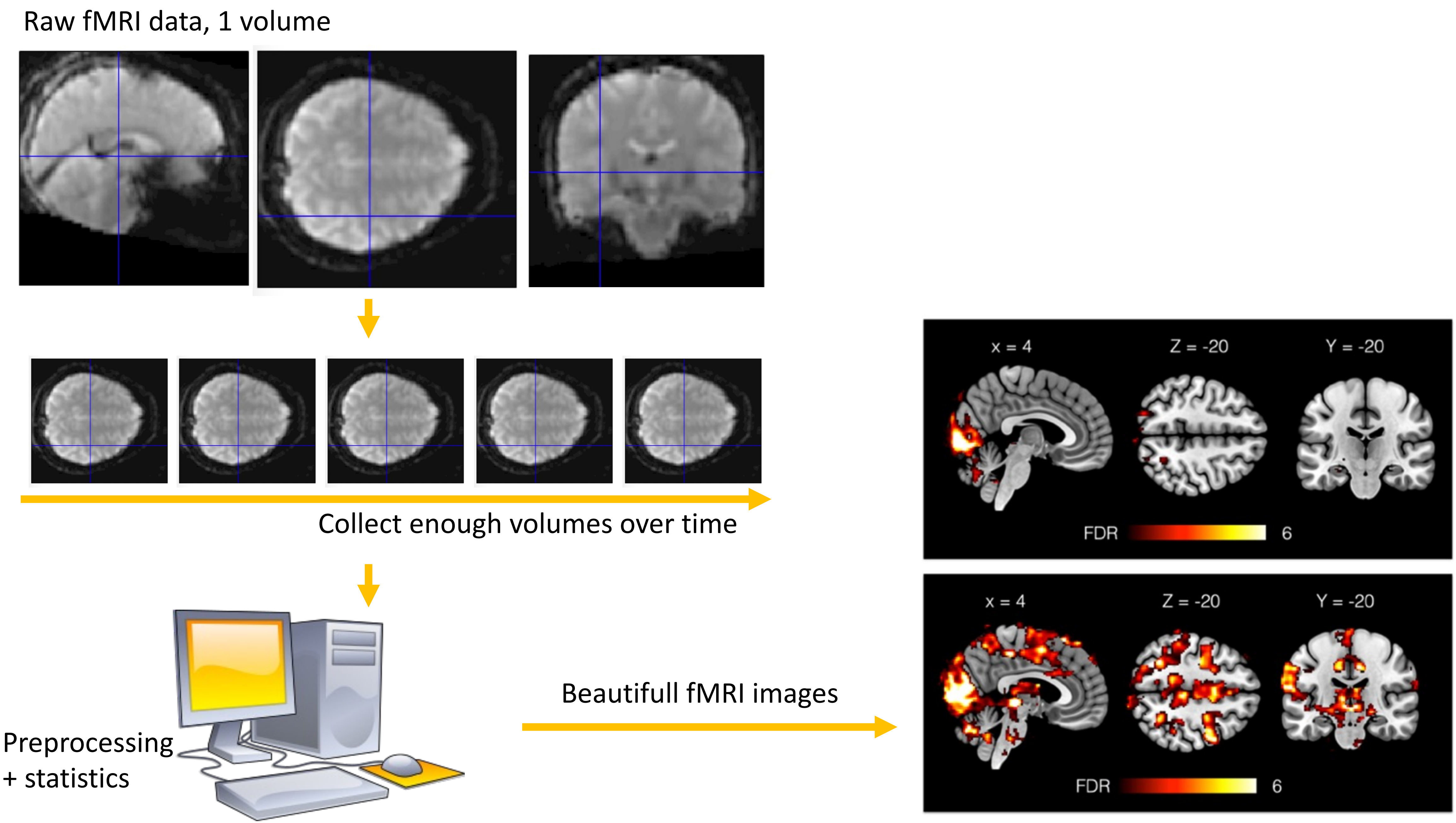
What is MRI and fMRI?

- Images taken with MRI scanner (Magnetic Resonance Imaging)

- **Anatomical MRI:** anatomical image gives structure (but they cannot reveal short-term physiological changes)

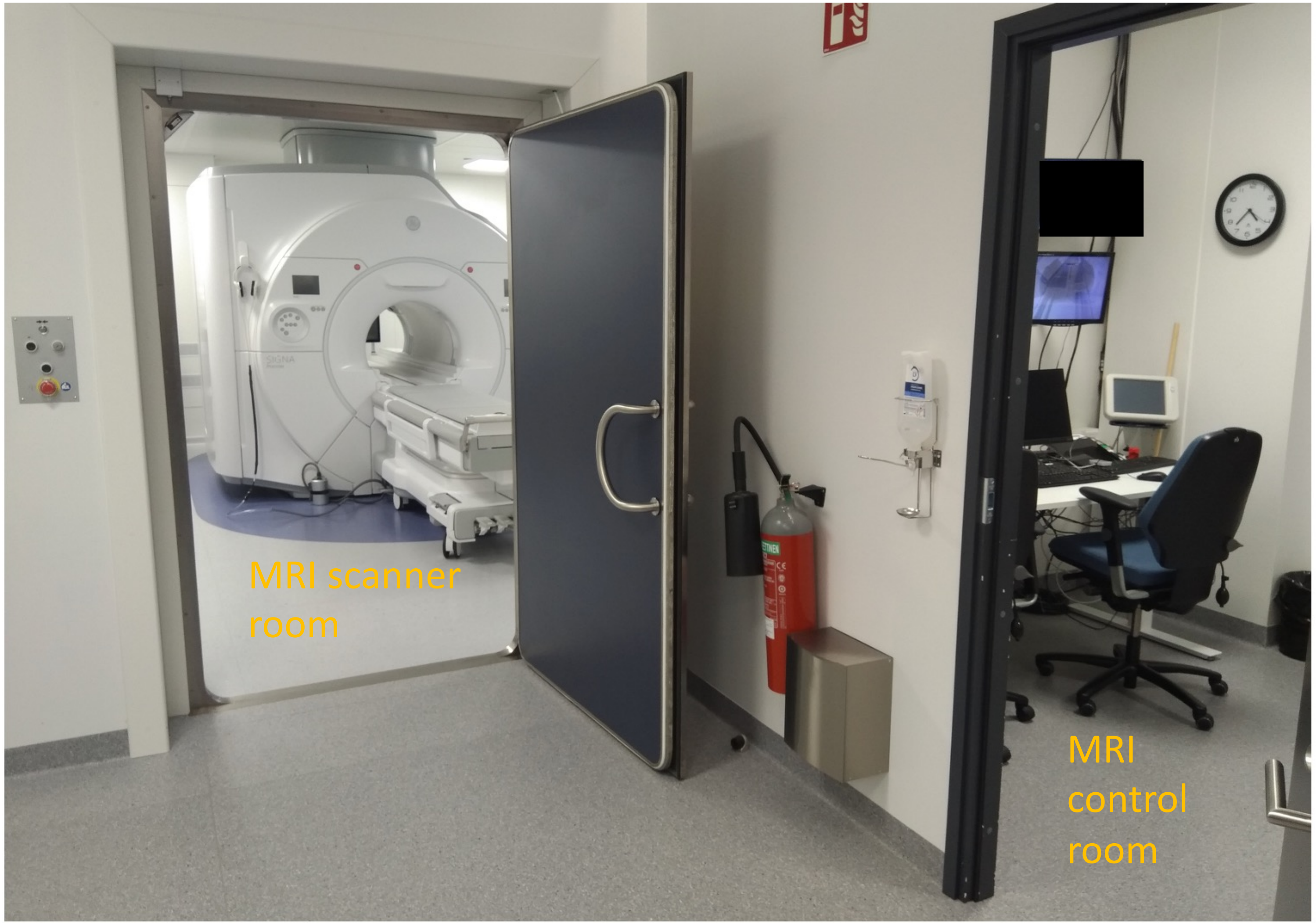
- **fMRI:** functional images
  - measure changes in subjects' brains function while they are focusing on a task in a MRI scanner or try not to do anything
  - Purpose
    - 1) fiding specific part of the brain where mental process happens
    - 2) patterns of brain activation associated with mental processes
  - signal based on rapid changes in blood oxygenation over time on specific areas
    - the signal is coming from nuclear level, fMRI measurements noninvasive and are not interfering with neuronal firing or blood flow

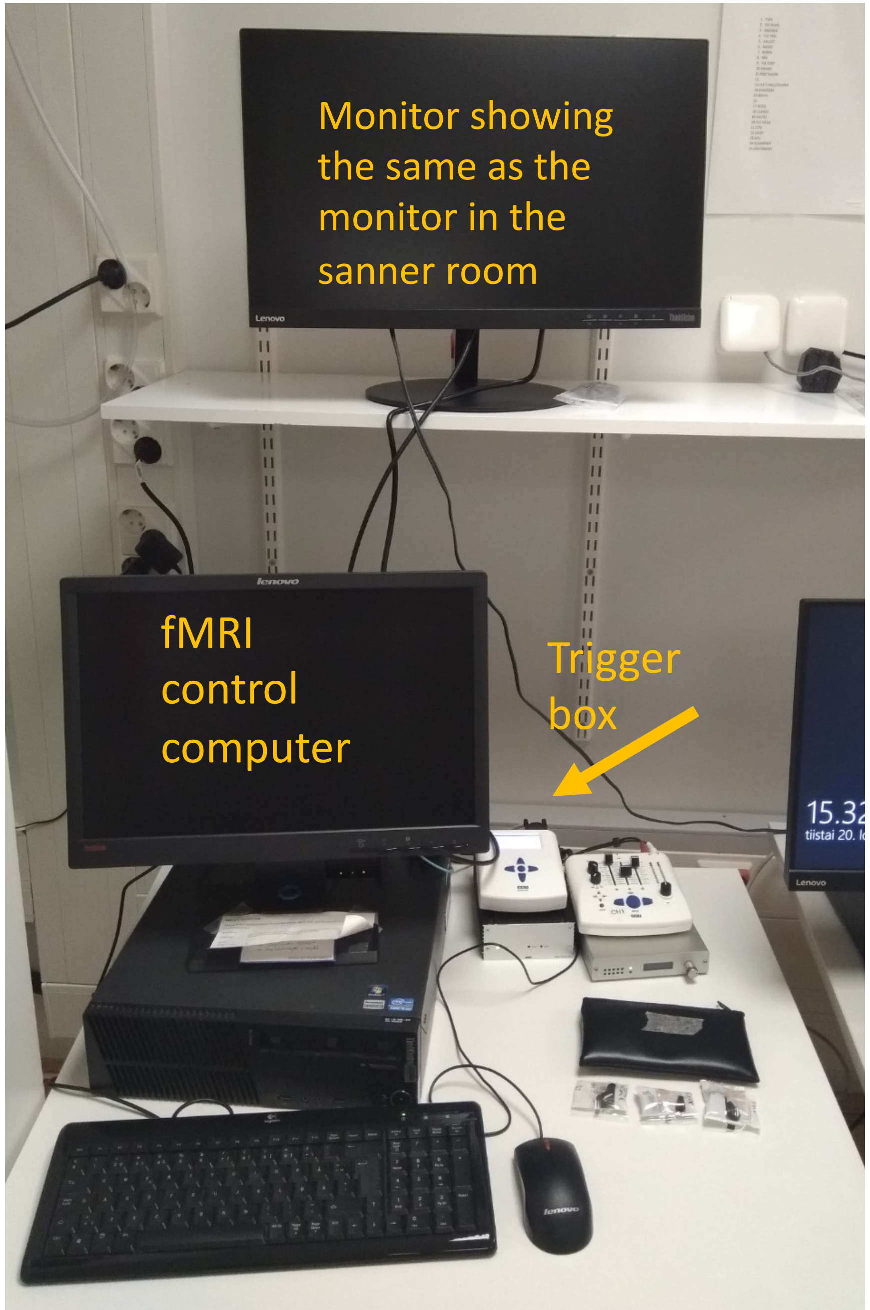




https://fi.wikipedia.org/wiki/Henkil%C3%B6kohtainen_tietokone

How to collect data?


MRI scanner room
MRI control room


Monitor showing the same as the monitor in the sanner room
fMRI control computer
Trigger box

Siemens MAGNETOM Sola 1.5 T

https://www.siemens-healthineers.com

Siemens MAGNETOM Vida 3 T

Philips Ingenia 1.5 T

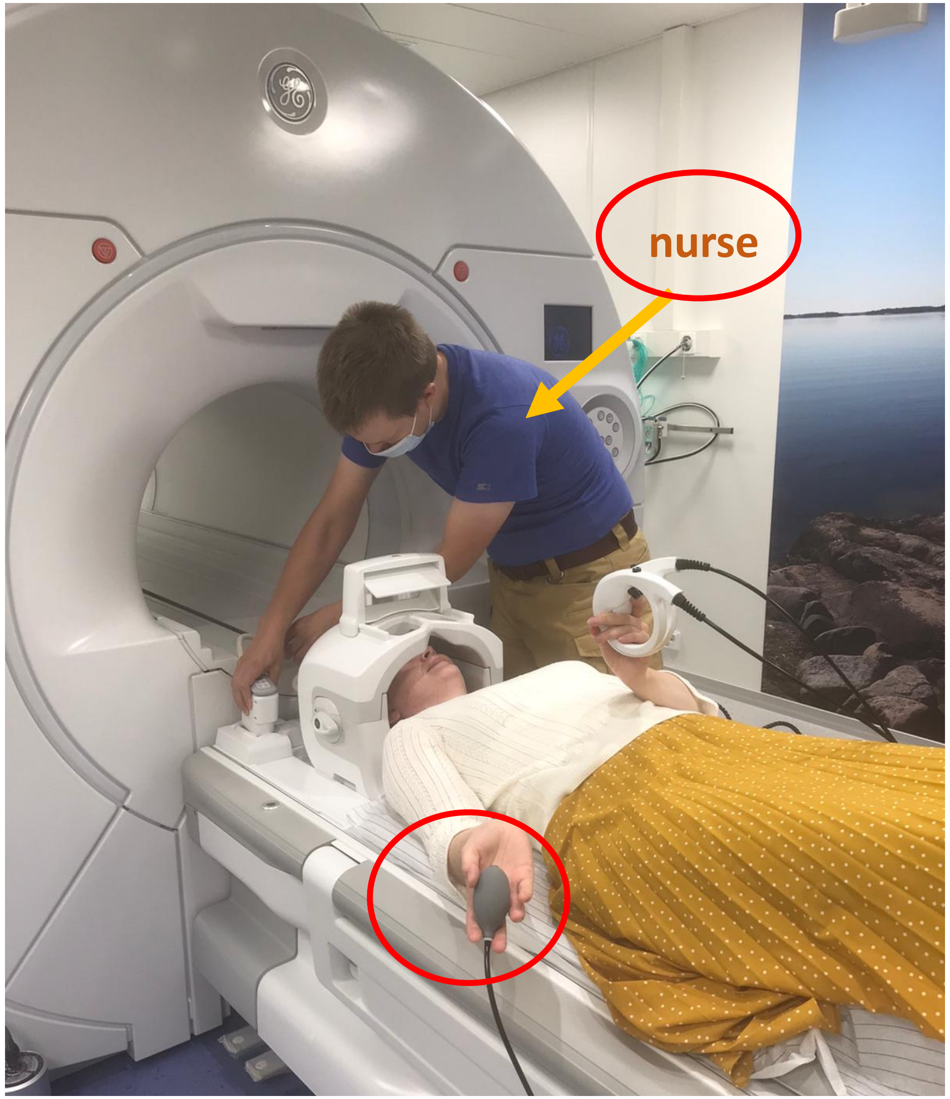
https://www.philips.fi/

Philips Ingenia 3 T

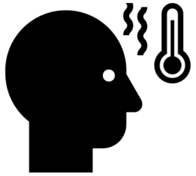
GE SIGNA 1.5 T

www.gehealthcare.com/products/magnetic-resonance-imaging/

GE SIGNA 3 T



While scanning:
- Noise → double ear protection
- Claustrophobia → communicate
- SAR (specific absorption rate) → no patients with fever
- Careful screening: no tattoos, implants, ear rings, etc. In the scanner.



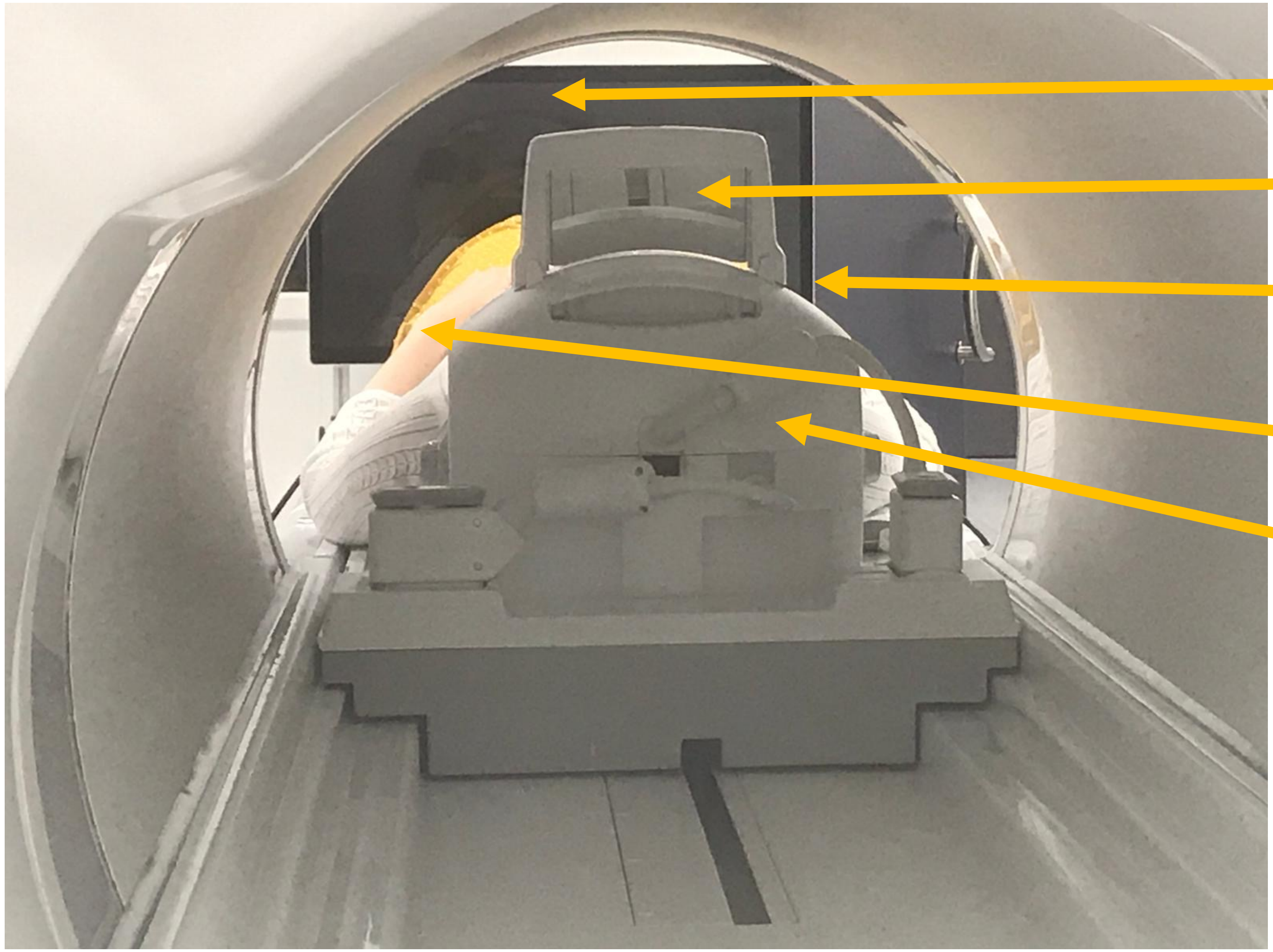
Prepare the subject on the table
Some sites ask the subjects to change clothes, some not, please follow the rules on your own laboratory

Place the subject into the scanner

Important: make the subject feel comfortable

Double hearing protection must be

Extra super important: the subject cannot move! There are selection of different pillows to gently prevent subjects' head from moving



Nice and comfortable positioning, the subject is ready to start the task

The magnet is always on

https://www.harveynorman.com.au/amable-office-chair-red.html

Safety first! The magnet is always on

- 1.5 T is 30 000 times stronger than earth magnetic field

https://www.harveynorman.com.au/amable-office-chair-red.html

IMPORTANT INSTRUCTIONS

Before entering the MR environment or MR system room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners, & clothing with metallic threads.

Please consult the MRI Technologist or Radiologist if you have any question or concern BEFORE you enter the MR system room.

True for everyone and everything entering the scanner room

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the MRI Technologist or Radiologist BEFORE entering the MR system room. The MR system magnet is ALWAYS on.

http://www.mrisafety.com/images/PreScrnF.pdf

http://www.mrisafety.com/

Please indicate if you have any of the following:

- ❒ Yes ❒ No Aneurysm clip(s)
- ❒ Yes ❒ No Cardiac pacemaker
- ❒ Yes ❒ No Implanted cardioverter defibrillator (ICD)
- ❒ Yes ❒ No Electronic implant or device
- ❒ Yes ❒ No Magnetically-activated implant or device
- ❒ Yes ❒ No Neurostimulation system
- ❒ Yes ❒ No Spinal cord stimulator
- ❒ Yes ❒ No Internal electrodes or wires
- ❒ Yes ❒ No Bone growth/bone fusion stimulator
- ❒ Yes ❒ No Cochlear, otologic, or other ear implant
- ❒ Yes ❒ No Insulin or other infusion pump
- ❒ Yes ❒ No Implanted drug infusion device
- ❒ Yes ❒ No Any type of prosthesis (eye, penile, etc.)
- ❒ Yes ❒ No Heart valve prosthesis
- ❒ Yes ❒ No Eyelid spring or wire
- ❒ Yes ❒ No Artificial or prosthetic limb
- ❒ Yes ❒ No Metallic stent, filter, or coil
- ❒ Yes ❒ No Shunt (spinal or intraventricular)
- ❒ Yes ❒ No Vascular access port and/or catheter
- ❒ Yes ❒ No Radiation seeds or implants
- ❒ Yes ❒ No Swan-Ganz or thermodilution catheter
- ❒ Yes ❒ No Medication patch (Nicotine, Nitroglycerine)
- ❒ Yes ❒ No Any metallic fragment or foreign body
- ❒ Yes ❒ No Wire mesh implant
- ❒ Yes ❒ No Tissue expander (e.g., breast)
- ❒ Yes ❒ No Surgical staples, clips, or metallic sutures
- ❒ Yes ❒ No Joint replacement (hip, knee, etc.)
- ❒ Yes ❒ No Bone/joint pin, screw, nail, wire, plate, etc.
- ❒ Yes ❒ No IUD, diaphragm, or pessary
- ❒ Yes ❒ No Are you here for an MRI examination?
- ❒ Yes ❒ No Dentures or partial plates
- ❒ Yes ❒ No Tattoo or permanent makeup
- ❒ Yes ❒ No Body piercing jewelry
- ❒ Yes ❒ No Hearing aid
  (Remove before entering MR system room)
- ❒ Yes ❒ No Other implant ________________________
- ❒ Yes ❒ No Breathing problem or motion disorder

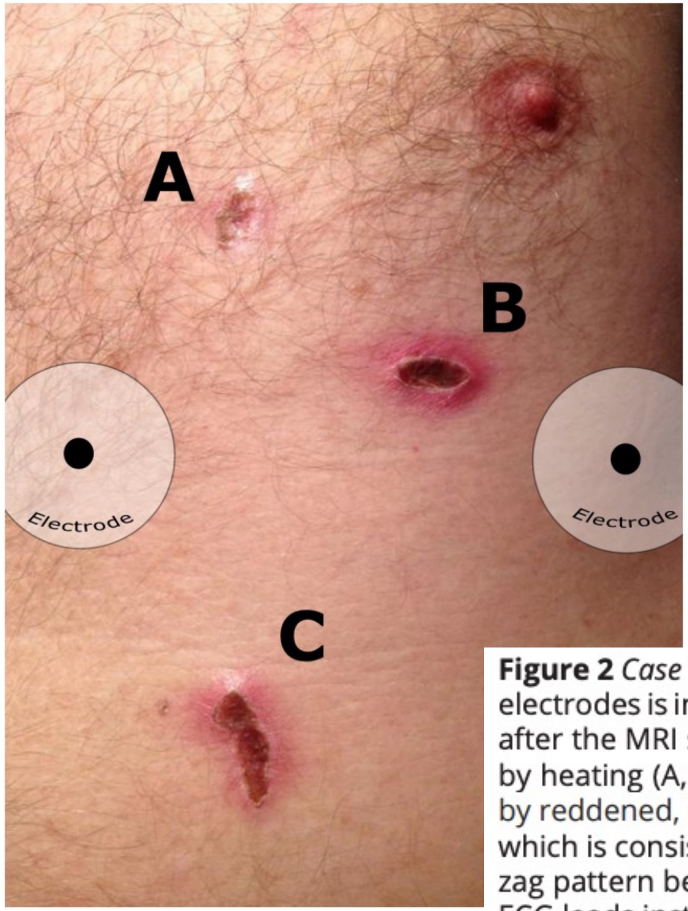


Figure 2 *Case 1:* Image of skin burns caused by ECG leads. Placement of the electrodes is indicated by the graphical overlay. The image is dated one week after the MRI scan and demonstrates three elongated burn lesions caused by heating (A, B & C). The lesions are covered with crusts and surrounded by reddened, inflamed skin and are therefore no longer in the acute phase which is consistent with the time of injury. The wounds are oriented in a zig zag pattern between the electrodes, which indicates trauma caused by the ECG leads instead of the ECG electrodes.

Brix et all., J Radiol Imaging, 2016, 1(4):29-32

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form: ____ Date _____/_____/_____

Signature

www.mrisafety.com/images/PreScrnF.pdf

When you know what to do, image acquisition is fun!

Where is the MRI signal coming from?

MR imaging is easy

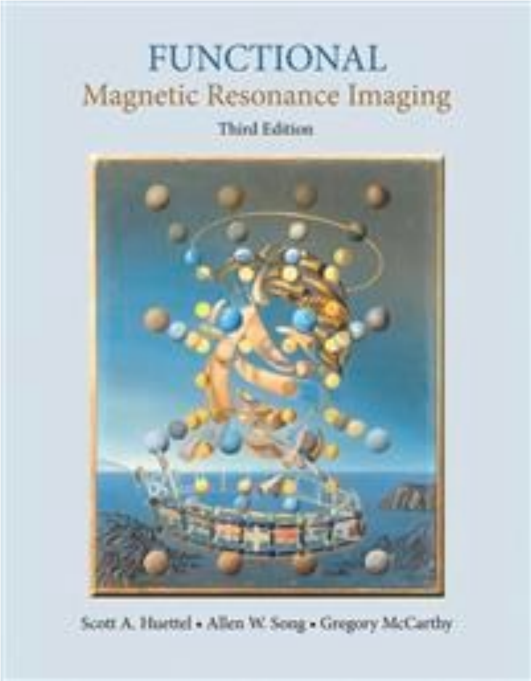
1) **Place the subject** into the MRI scanner in strong magnetic field

2) Sent a **radio wave in**

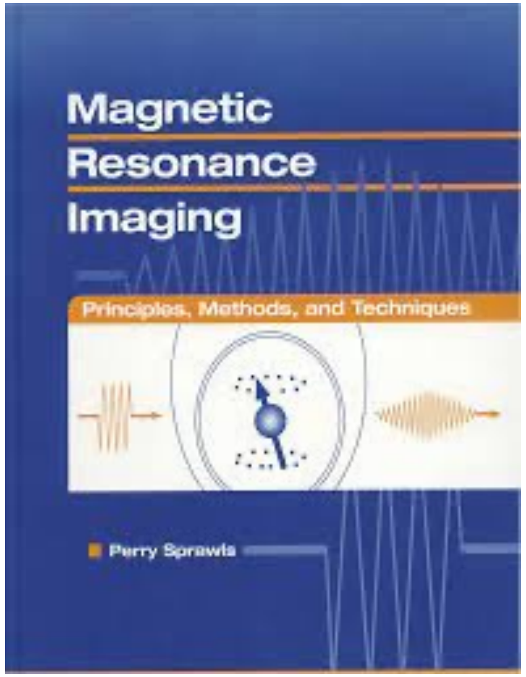
3) Turn the **radio wave off**

4) The **subject emits a signal** for head coil to catch

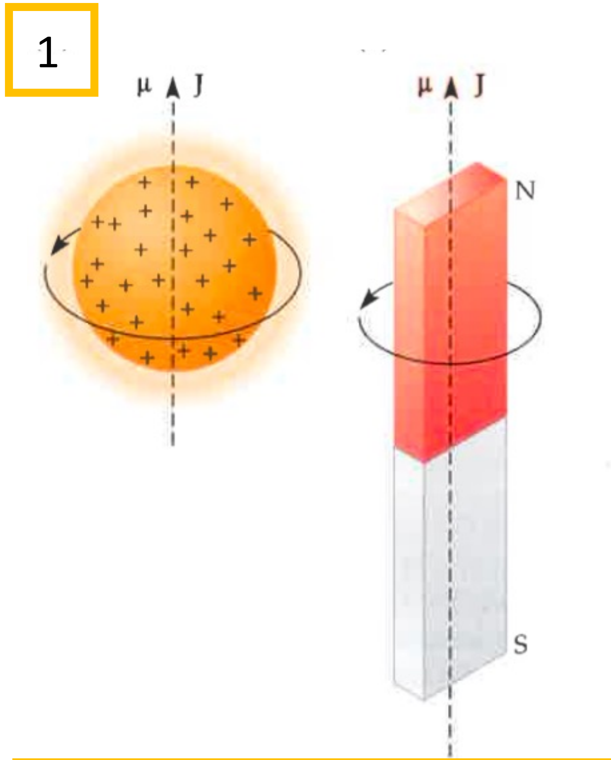
5) **Reconstruct** the image

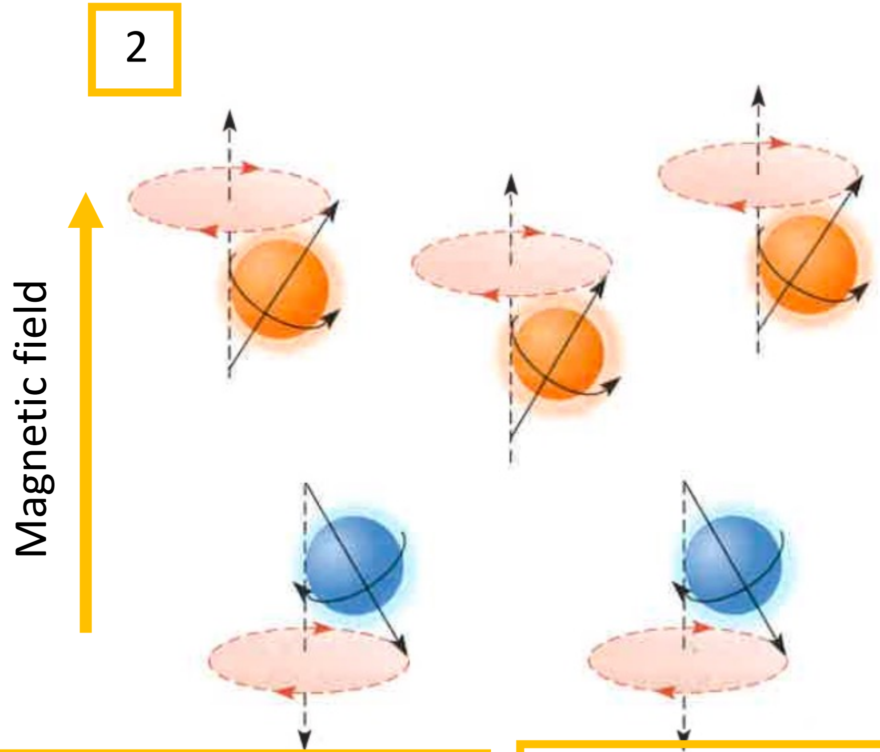


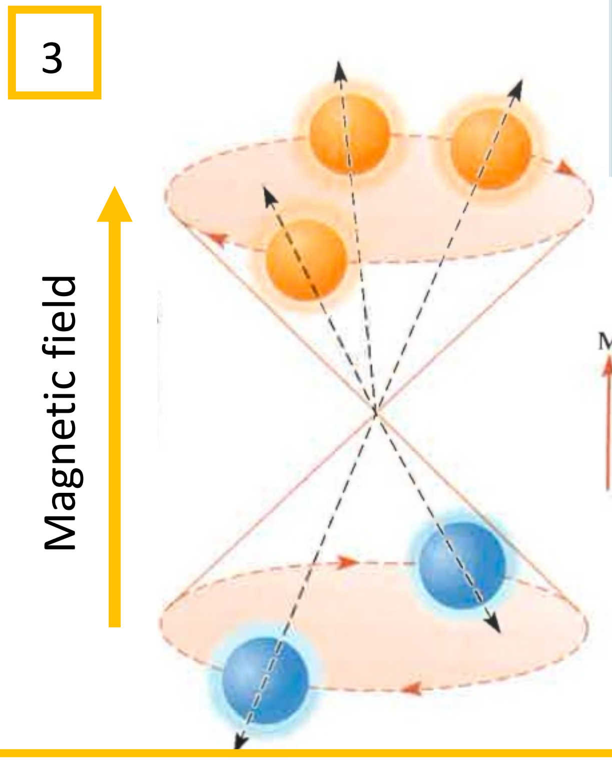
Huettel Scott A., Song Allen W., McCarthy Gregory: Functional Magnetic Resonance Imaging, 2014, Oxford University Press Inc

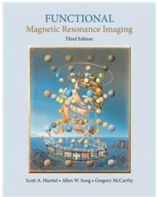


Sprawls, Magnetic Resonance Imaging, Online Edition, provided by Sprawls Educational Foundation http://www.sprawls.org









1. Spin:

- Intrinsic property
- Proton spinning on their axis

→ 1) because proton has positive charge, spin generates electrical current on it's surface

→ Magnetic moment in external magnetic field (μ)

→ 2) because proton has odd-numbered atomic mass and when spinning → moving mass results in angular momentum (J)

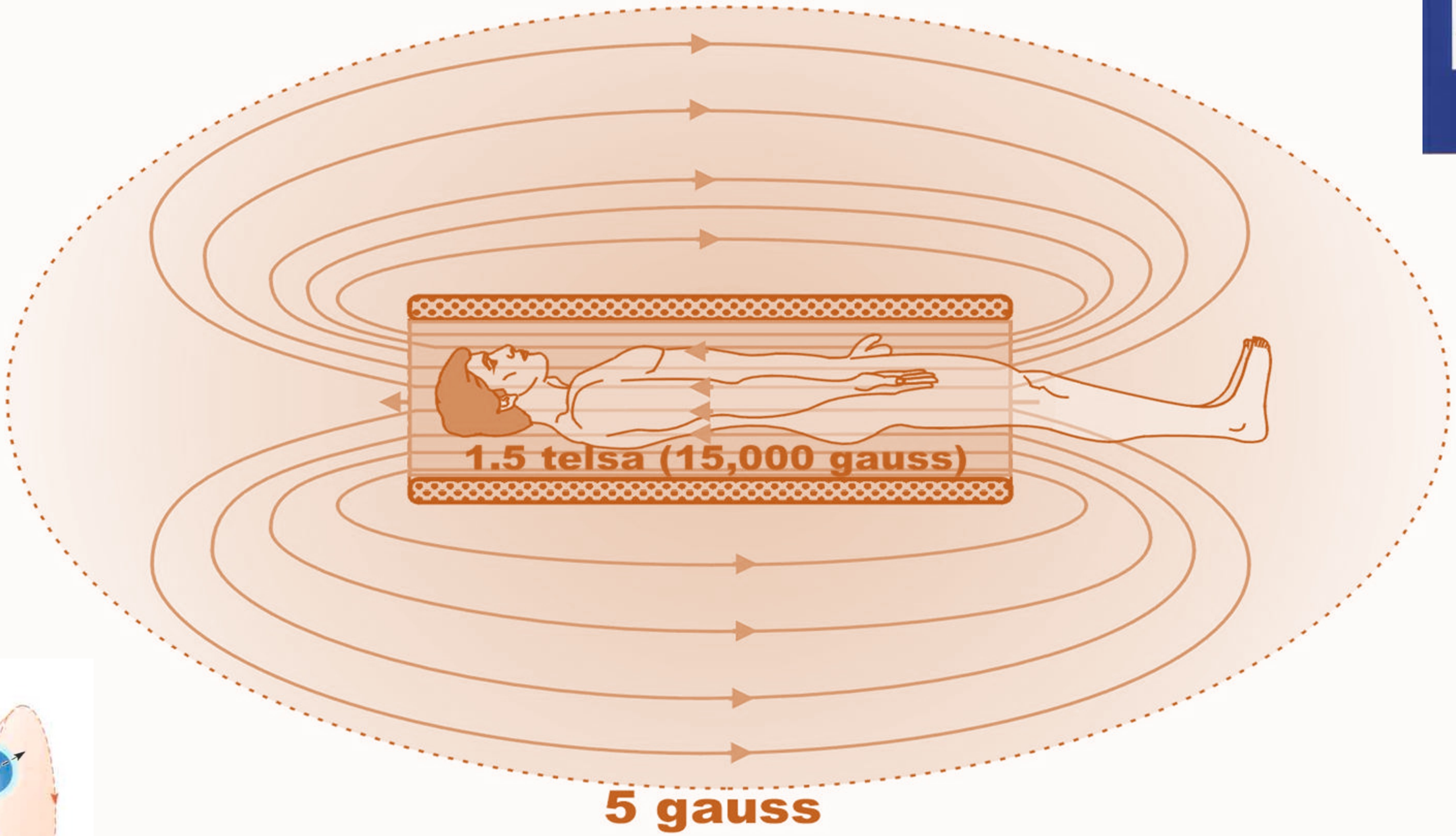
2. Precession

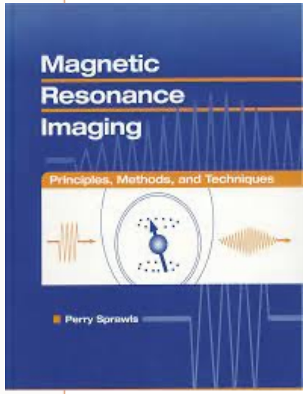
- Spins align within external magnetic field
- Orange spins on lower energy state = parallel state (the amount always more!)
- Blue spins on higher energy state = antiparallel state

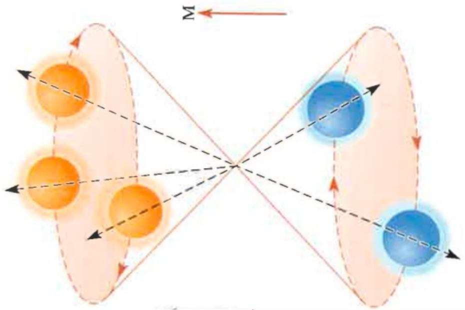
3. Net Magnetization (M):

- Difference between the number of spins in the parallel state and in the antiparallel state
- The more spins in the parallel state, the larger the M

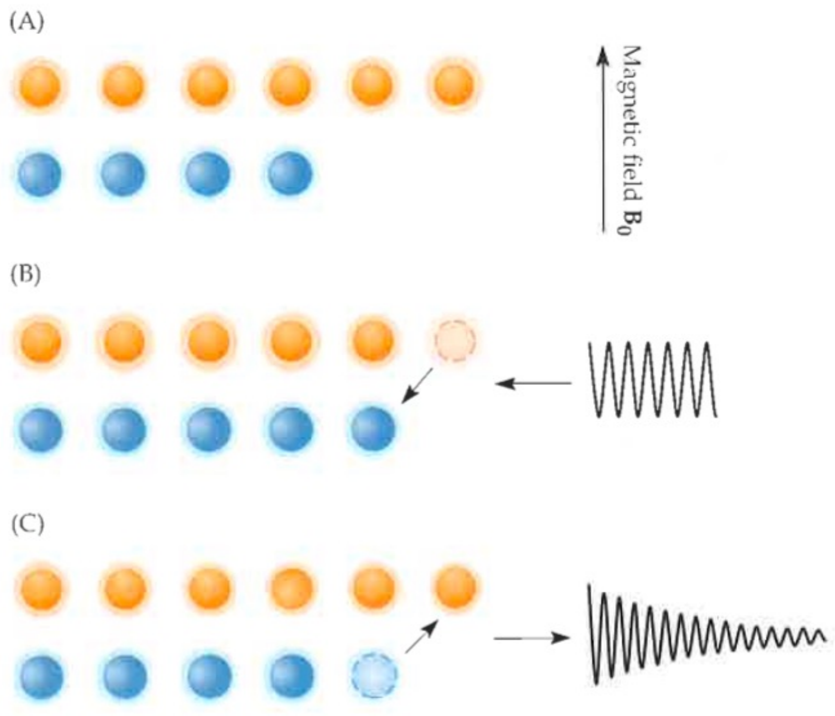
THE MAGNETIC FIELD





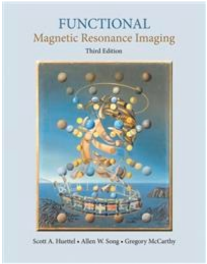


Sprawls



A)   A neutral situation:

Spins are in external magnetic field, orange lower energy state, blue higher energy state



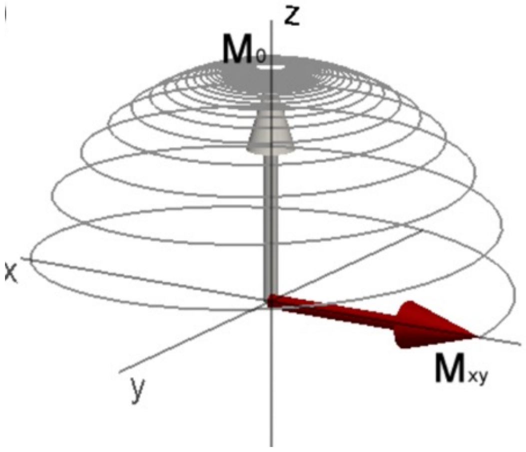
B) A radio wave comes in:

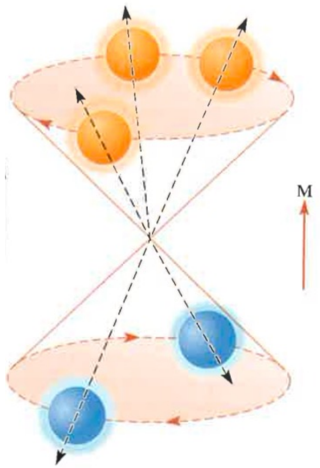
Some of the lower energy state spins jumps to higher energy state (orange spin into blue)

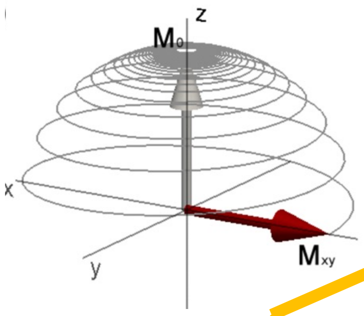
C) Incoming radio wave stops, outcoming starts:

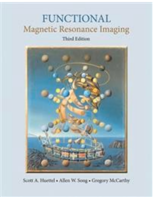
Some of the high-energy state spins return to the lower energy state and release the absorbed energy as a radiofrequency wave with the same frequency as the excitation pulse

In conceptual way of thinking: 90° excitation pulse tilts the Net magnetization









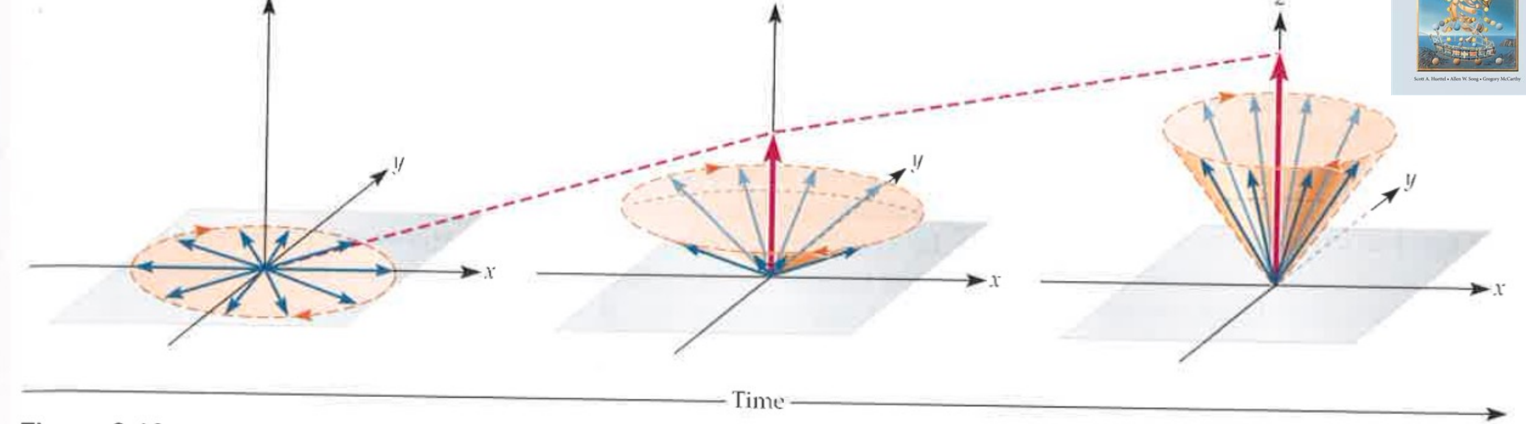


Figure 3.12 A conceptual overview of T_1 recovery. The net magnetization tips into the transverse plane as a result of the absorption of energy by some spins (i.e., those that have changed from low- to high-energy states). Once the excitation pulse ceases, spins begin to release energy back into the surrounding environment. This causes the net magnetization to recover along the longitudinal axis, often returning to near its original amplitude within a few seconds (red dashed line).

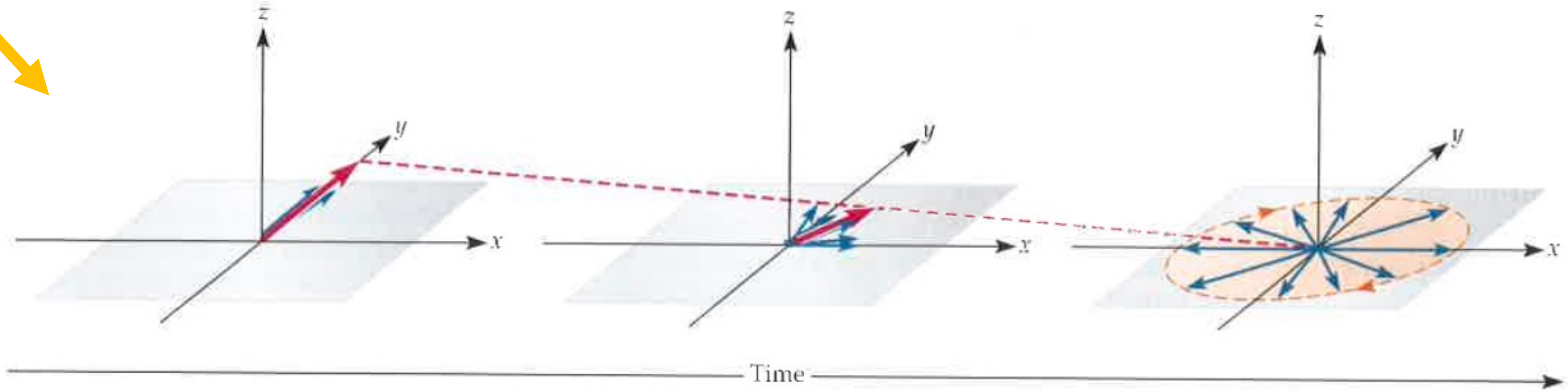
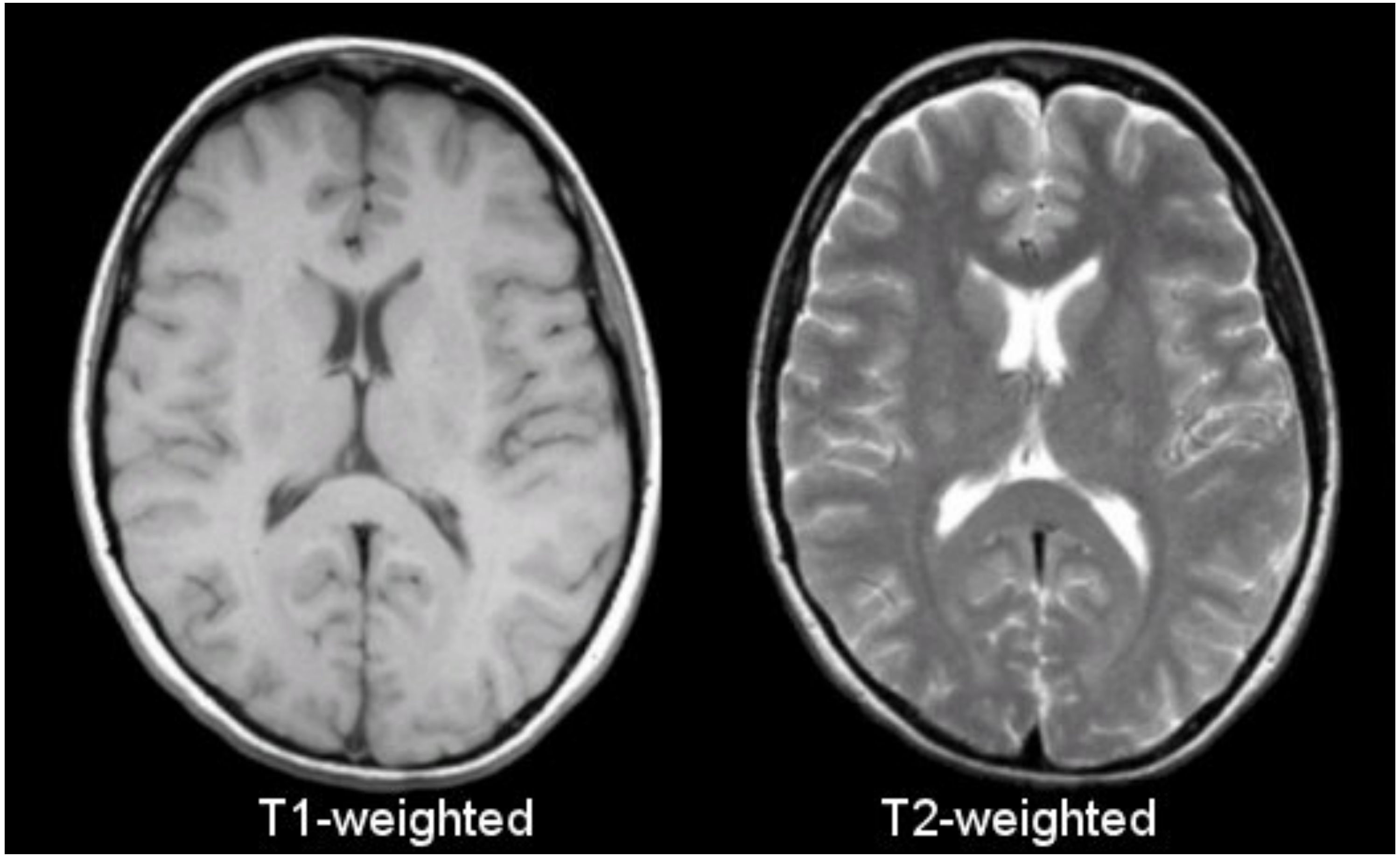


Figure 3.11 A conceptual overview of T_2 decay. After the net magnetization has been tipped into the transverse plane, it rapidly decays because of a loss of coherence among the spins. For most types of tissue, the net magnetization available to generate the MR signal decays to near zero within a few hundred milliseconds (red dashed line).

Contrast

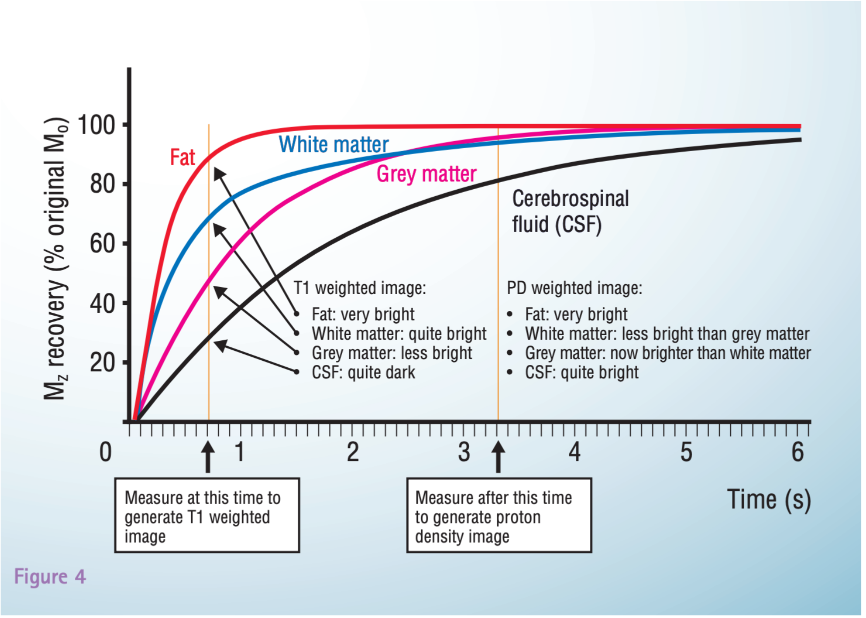
Contrast in medical imaging:

The intensity difference between different quantities (tissues)

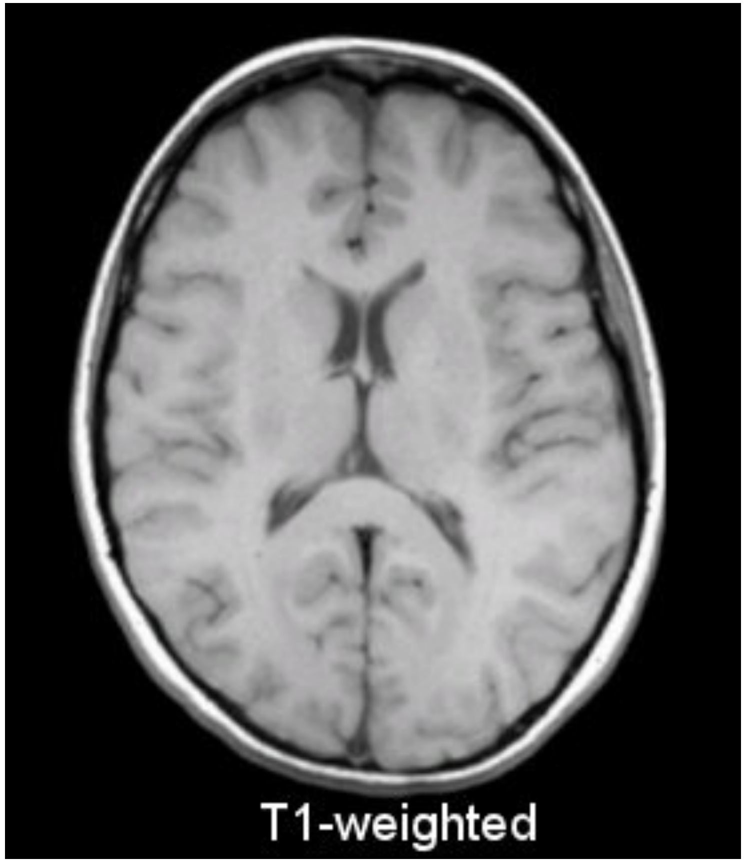


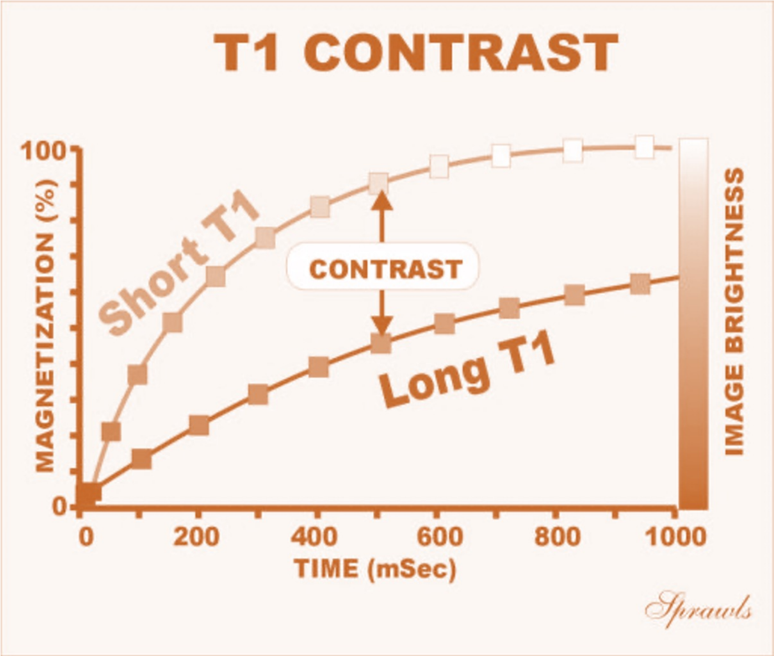
Case Western Reserve University
Magnetic Resonance Imaging (MRI) of the Brain and Spine: Basics
https://case.edu/med/neurology/NR/MRI%20Basics.htm

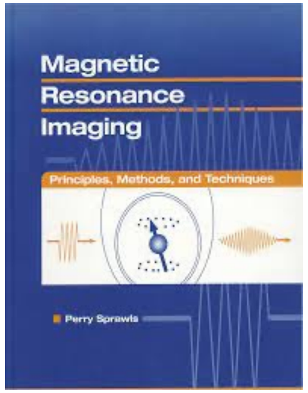
T1 relaxation and contrast



Farrall, Magnetic Resonance Imaging, Practical Neurology 2006; 6: 318-325

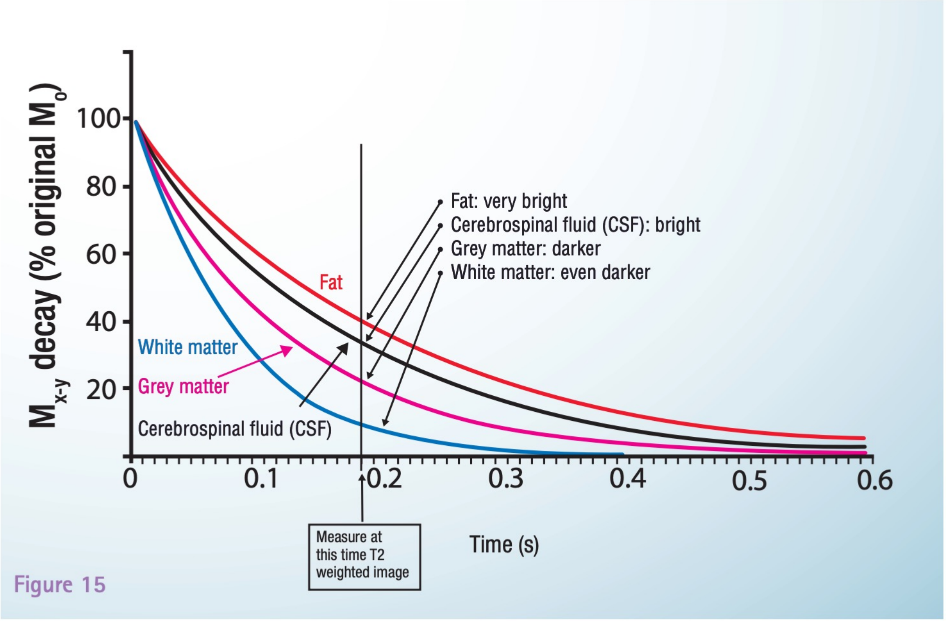






Case Western Reserve University
Magnetic Resonance Imaging (MRI) of the Brain and Spine: Basics
https://case.edu/med/neurology/NR/MRI%20Basics.htm

T2 relaxation and contrast



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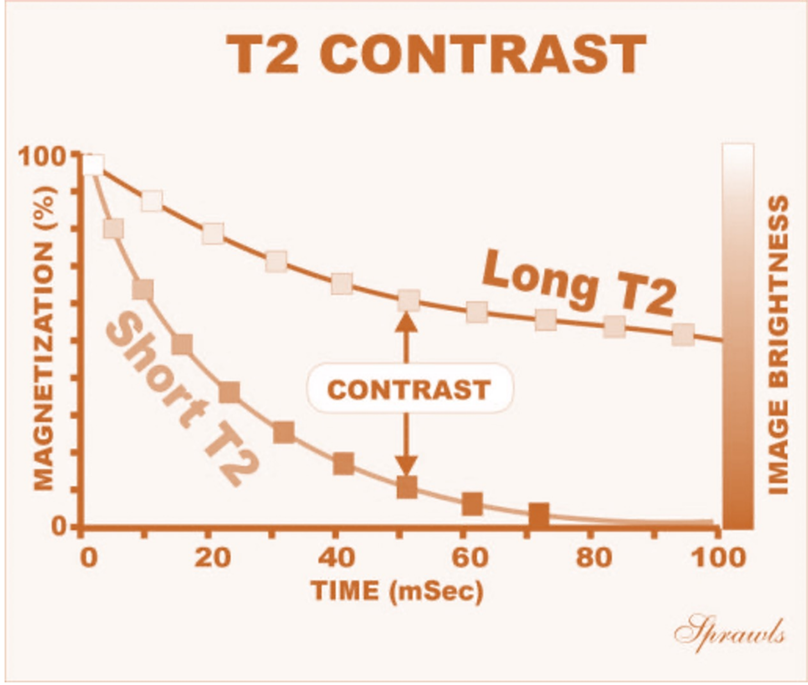

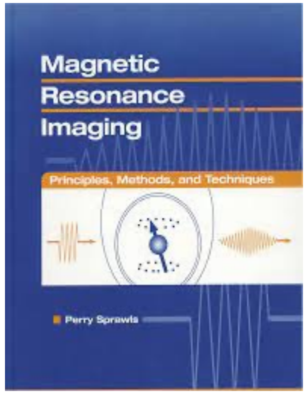

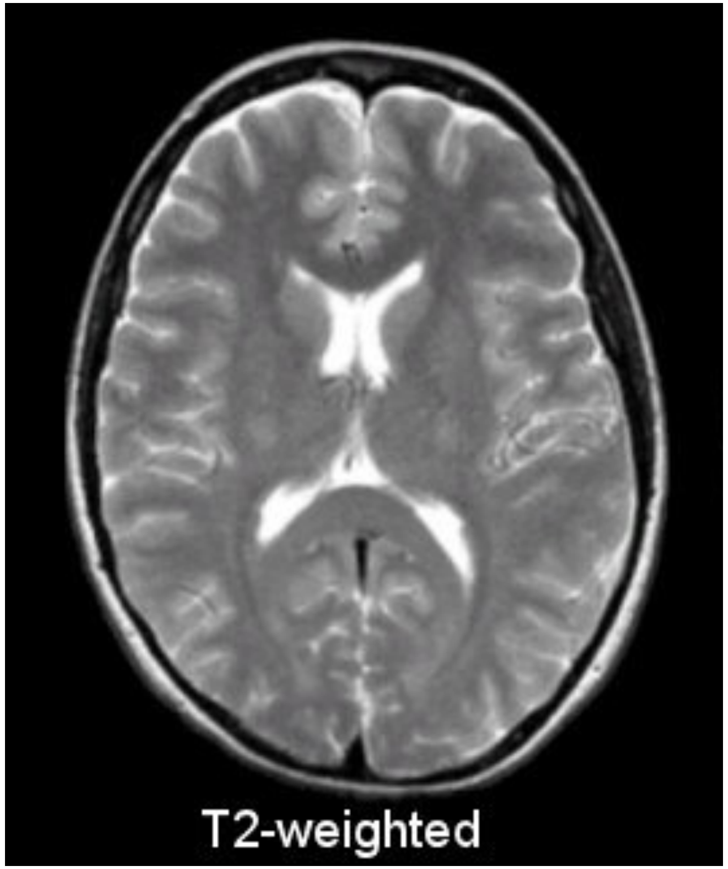

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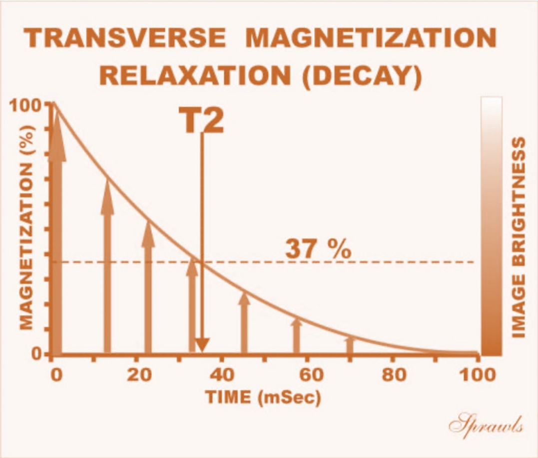
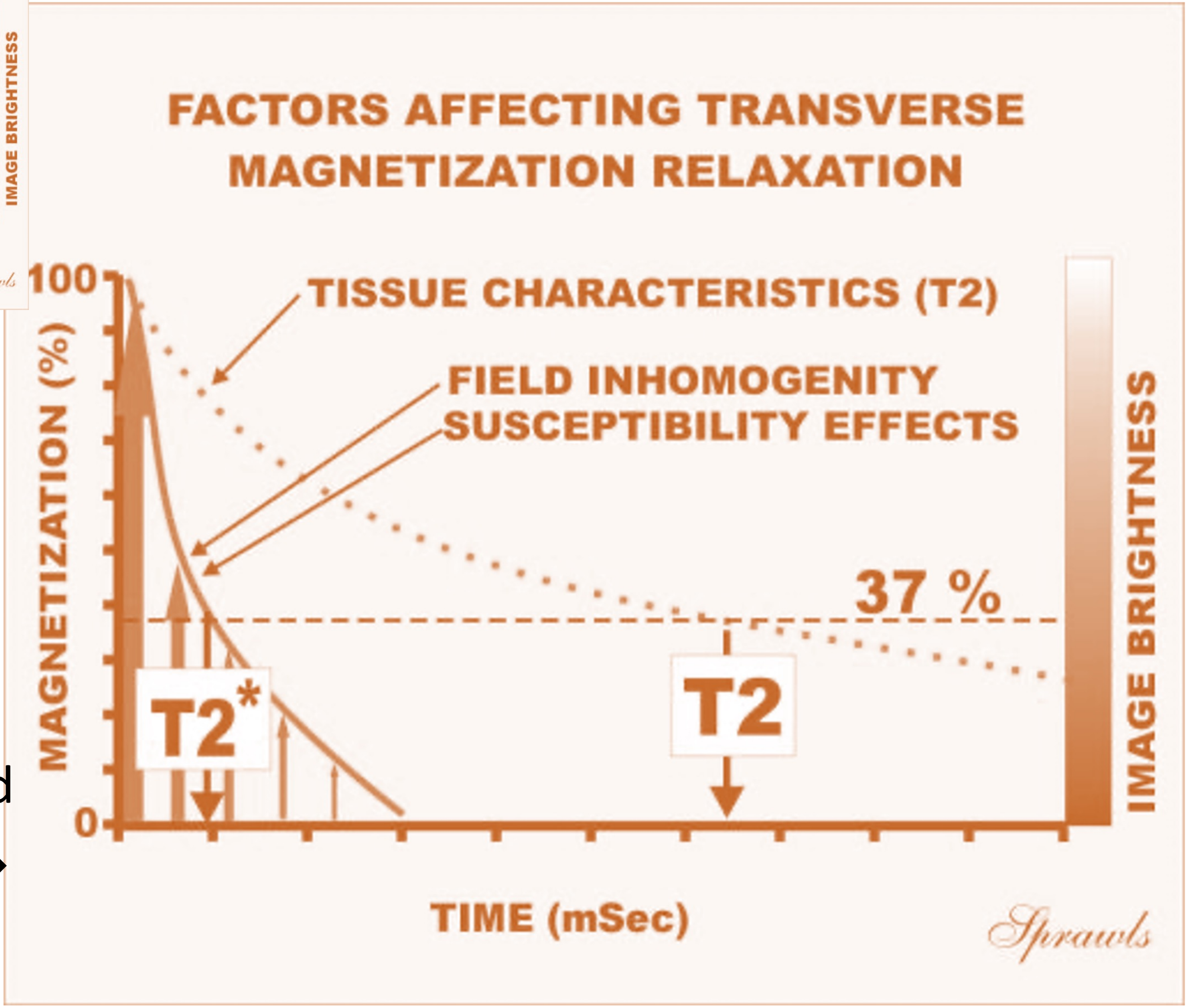
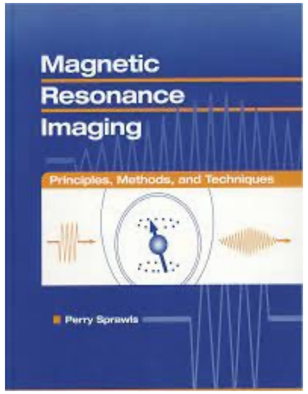
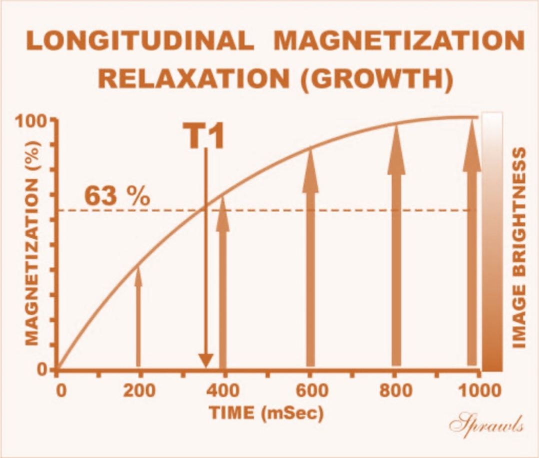
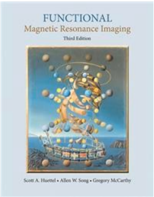








Local magnetic field inhomogeneities → **T2* contrast** (even faster decay)



Quantitative path

$$\mu = \gamma J$$

$$\frac{d\mu}{dt} = \gamma(\mu \times B_0)$$

$$M = \frac{\Delta E}{2k_B T} n\mu_z z$$

$$\omega_{rot} = \gamma B_{1eff} = \gamma B_1 \qquad emf = -i\omega_0 \int_v \overline{B_1} \cdot M(t)dv$$

$$\frac{dM}{dt} = \gamma M \times B + \frac{1}{T_1}(M_0 - M_z) - \frac{1}{T_2}(M_x + M_y)$$

Where is the fMRI signal coming from?

Brain is full of arteries, capillaries and veins

- Arteries (oxygen rich blood from heart) → capillaries (exchange of oxygen to carbon dioxide) → veins (back to lungs)
- 100 billion neuros, 20 billion within cortex
- 800 mL / min of blood through average 1400 g brain = 15%-20 % of the blood flow in human body. Brain takes 2-3% of the body weight but requires 20% of blood oxygen
- Oxygen travels in hemoglobin
- 4 oxygen molecules in each hemoglobin molecule, 280 million hemoglobin molecules in each red blood cell

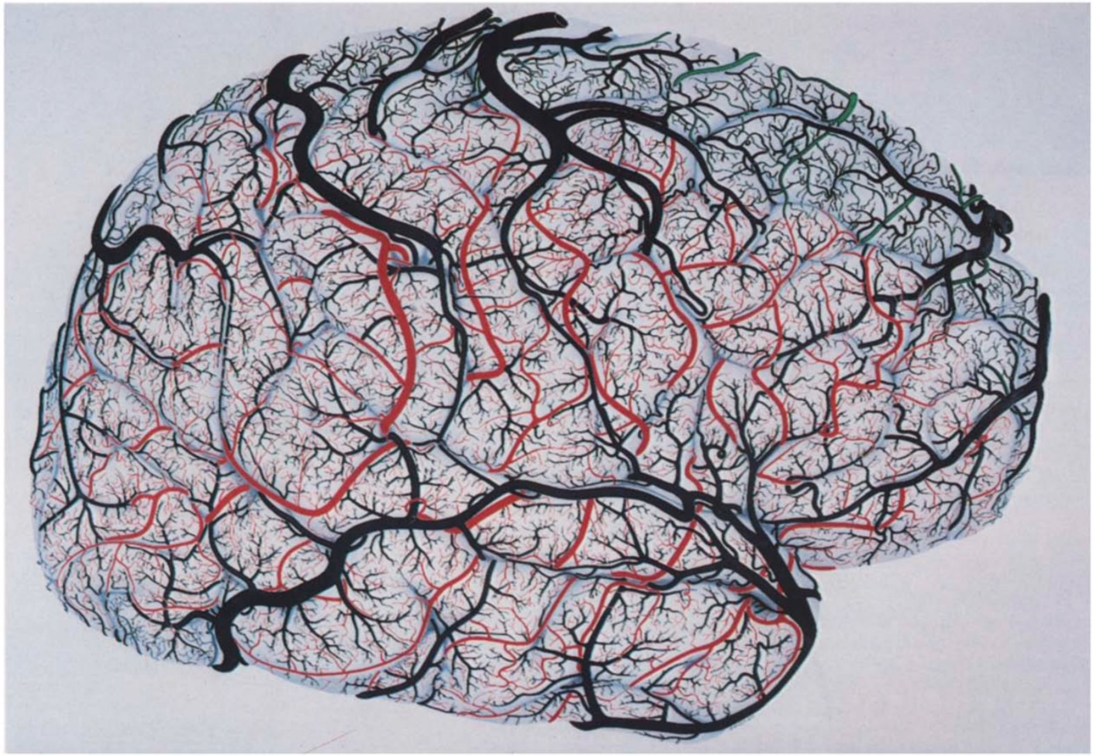
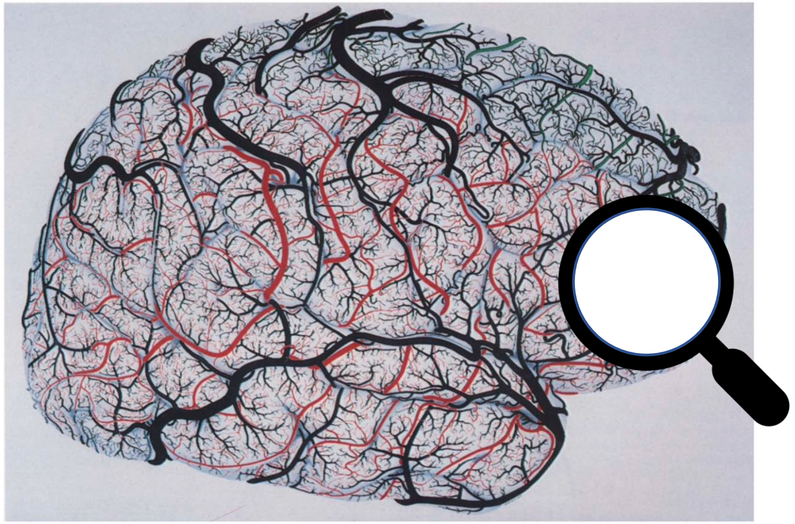


FIG. 1. Drawing of the cortical pial vessels. Right hemisphere. Female, 50 years. RED: Tributaries of the middle cerebral artery. GREEN: Tributaries of the anterior cerebral artery. BLUE: Tributaries of the posterior cerebral artery. Veins are shown in black.

Duvernoy HM, Delon S, Vannson JL. Cortical blood vessels of the human brain. Brain Res Bull. 1981 Nov;7(5):519-79. doi: 10.1016/0361-9230(81)90007-1. PMID: 7317796.



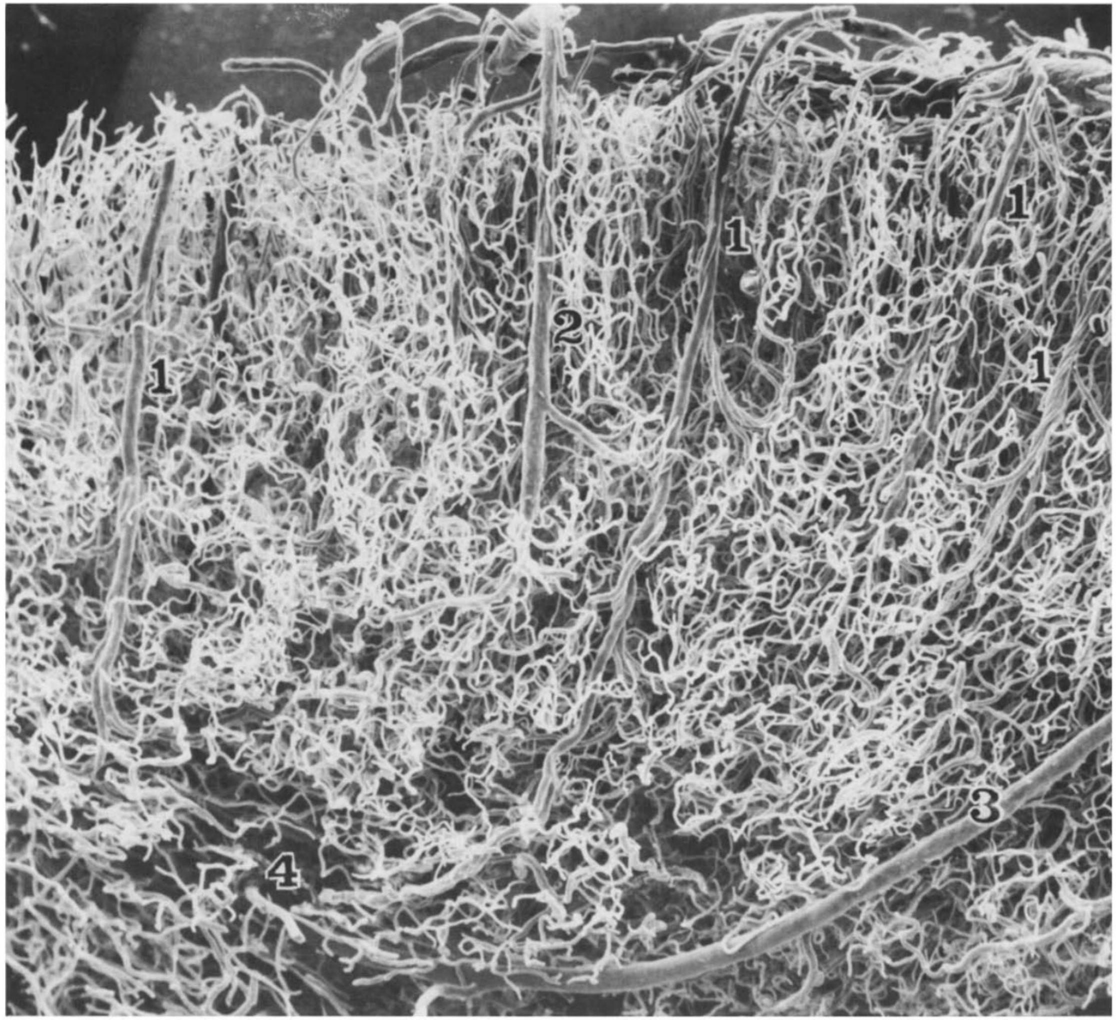
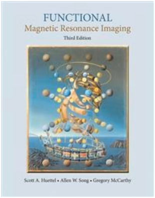


FIG. 60. Temporal pole (SEM). Male, 66 years. General view of the cortical vessels. (1) Cortical arteries. (2) Cortical vein. (3) Medullary artery (type A6). (4) Subcortical white matter (×40).

Duvernoy HM, Delon S, Vannson JL. Cortical blood vessels of the human brain. Brain Res Bull. 1981 Nov;7(5):519-79. doi: 10.1016/0361-9230(81)90007-1. PMID: 7317796.

fMRI and BOLD

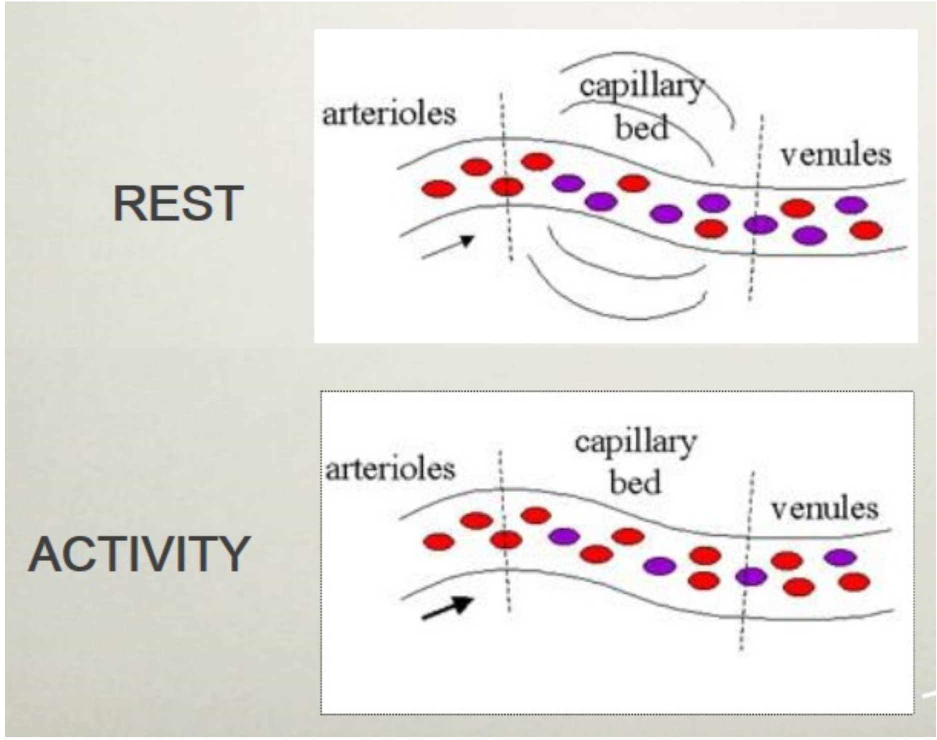


- fMRI does not measure neuronal activity!
- fMRI measures physiological changes correlated with neuronal activity
- BOLD: Blood-Oxygenation-Level Dependent contrast
  - Activity of neurons increase metabolic requirements; blood becomes briefly deoxygenated
  - Oxygen travels in hemoglobin
  - Vascular system provides glucose and oxygen refill: arterial supply of oxygenated hemoglobin increases; the amount of the oxygenated blood increases on broad area more than needed

  → amount of deoxygenated hemoglobin decreases compared to the normal conditions

  → measure with T_2*

  → brighter MRI



↑neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal

Effect of Hemoglobin in Magnetic Field

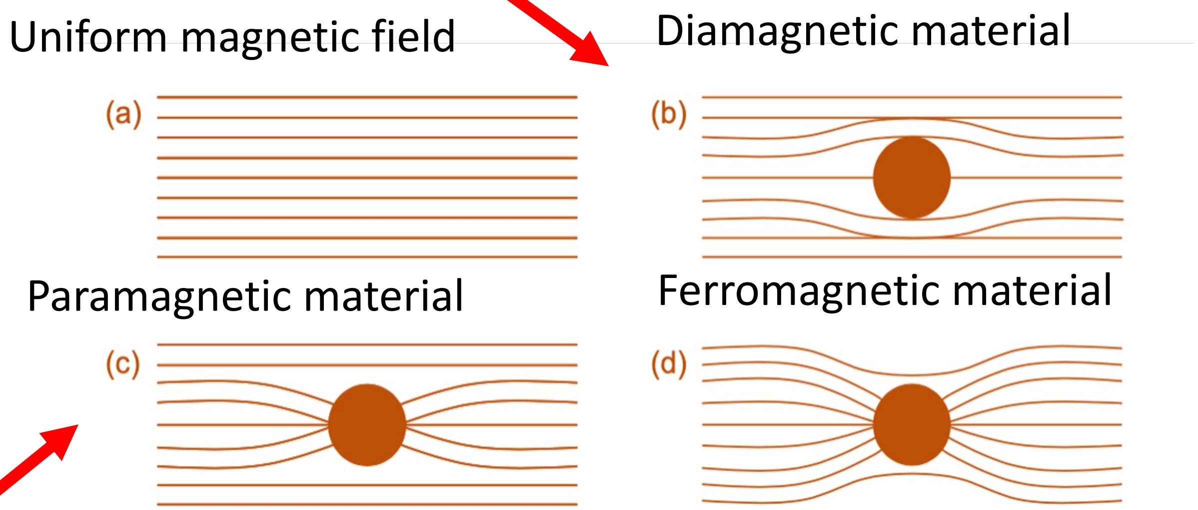
OxyHb: diamagnetic

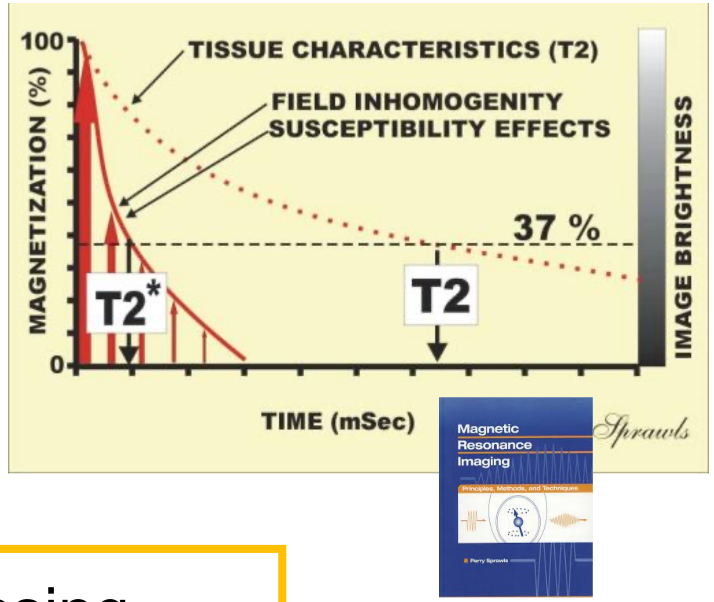
→ weak field inhomogeneities

Slower dephasing

slower T2*

Marijke Fagan-Endres, "Fundamental studies of heap leaching hydrology using magnetic resonance imaging, Theses, Jan 2013, DOI:10.17863/CAM.6692





DeoxyHb: paramagnetic

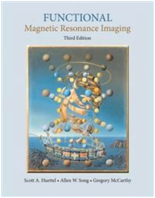
→ strong field inhomogeneities

Fast dephasing

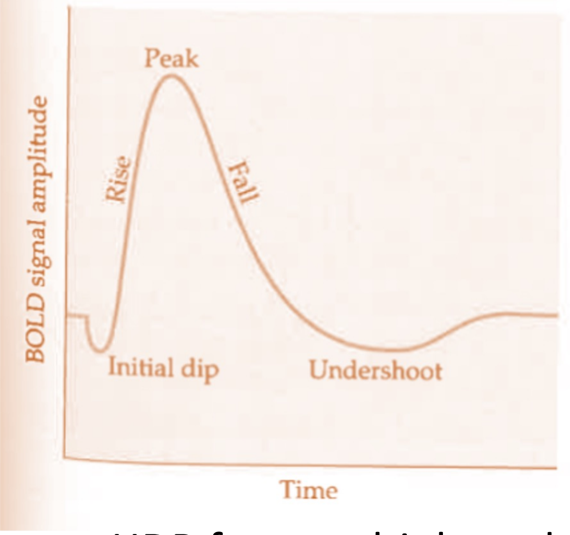
Fast T2*

BOLD signal and Hemodynamic Response?

HDR: Hemodynamic Response



HDR for a short stimuli



HDR for a multiple and consecutive events

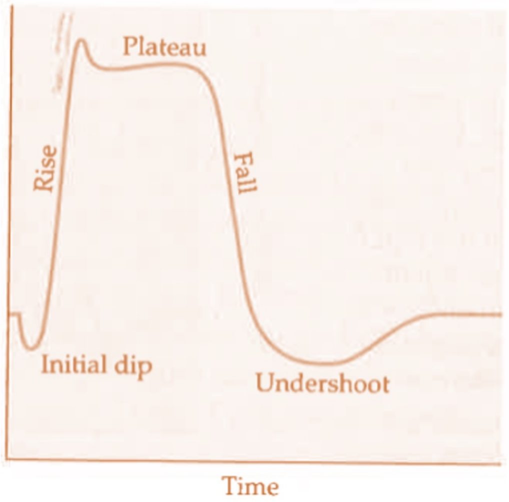


Fig. 7.10

The change in the MRI signal triggered by neuronal activity

The ***initial dip***

- Might reflect the decreased oxygenation before arteries provide more
- Is not detected in every study; Easier to detect on higher field (≥ 7 T)
- Allen Elster: Questions and Answers in MRI Website: BOLD and Brain Activity, http://mriquestions.com/does-boldbrain-activity.html: ”mechanism remains disputed: a) increased early metabolic extraction of blood oxygen, and/or b) increased local cerebral blood volume. ”

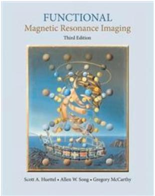
The positive ***dominant peak***

- Maximal amplitude of HDR
- The overcompensation of used oxygen from arteries to neurons
- Slow signal: 4-6 s delay

The ***post-stimulus undershoot***

- Happens most likely because combination of reduced blood flow and increased blood volume
- Easier to detect in block of multiple consecutive events

The Actual Measured Signal



Changes in BOLD activation after presenting single event stimuli for subject from a voxel

The units are arbitary

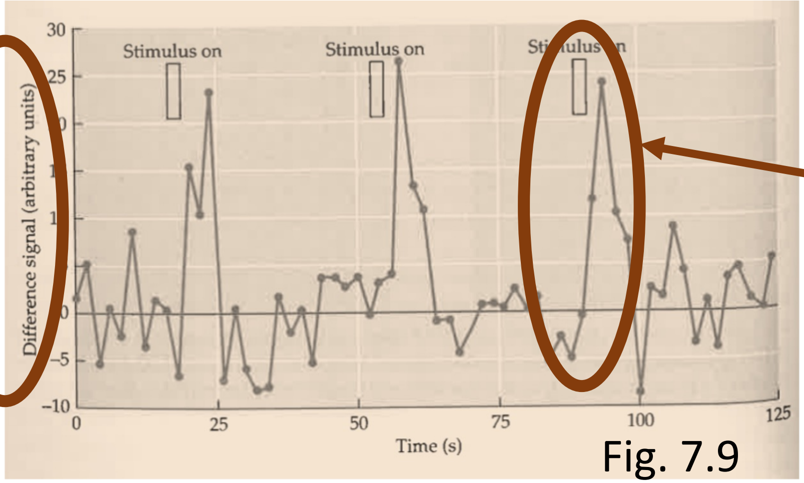
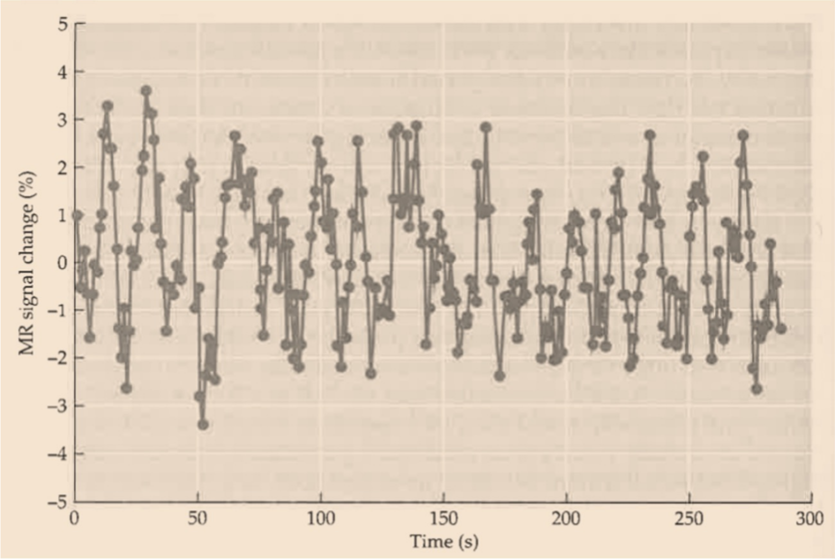


Fig. 7.9

Notice also the delay after the stimulus and before the peak

Example of BOLD hemodynamic response to a hand squeezing task



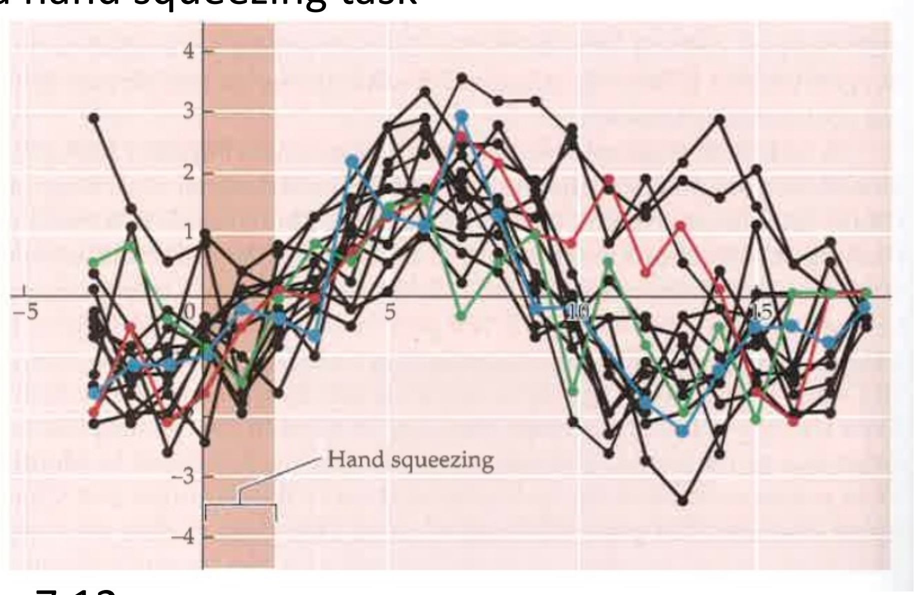
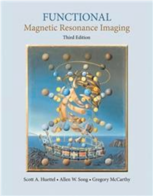


Fig. 7.12

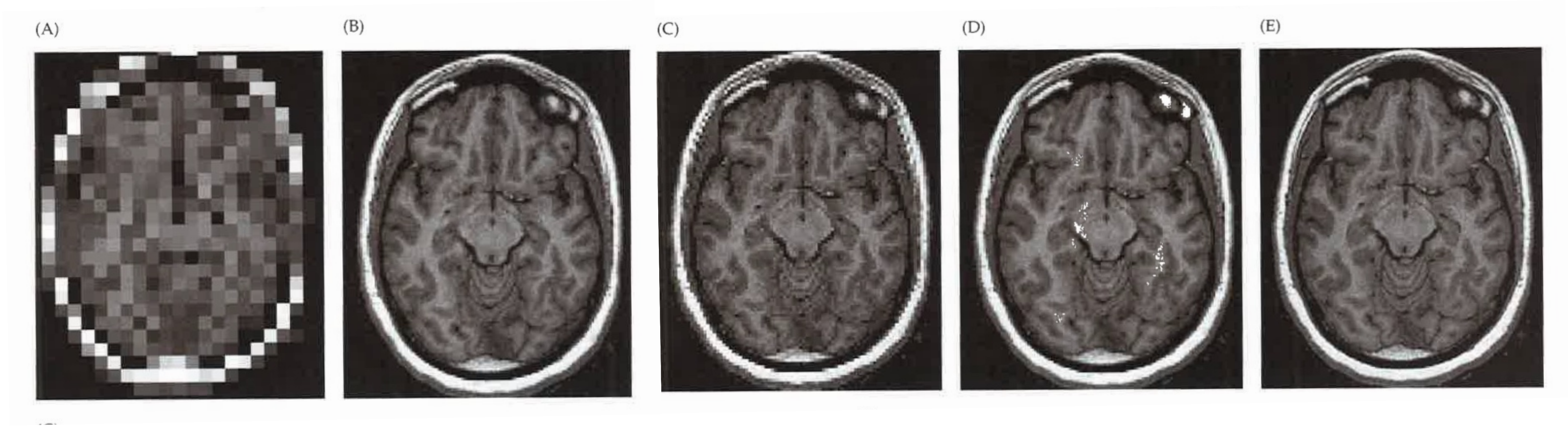
The same data as on the left but the timeseries has cut and organized timewise

Spatial Resolution



- Spatial Resolution: Ability to distinguish different locations within an image

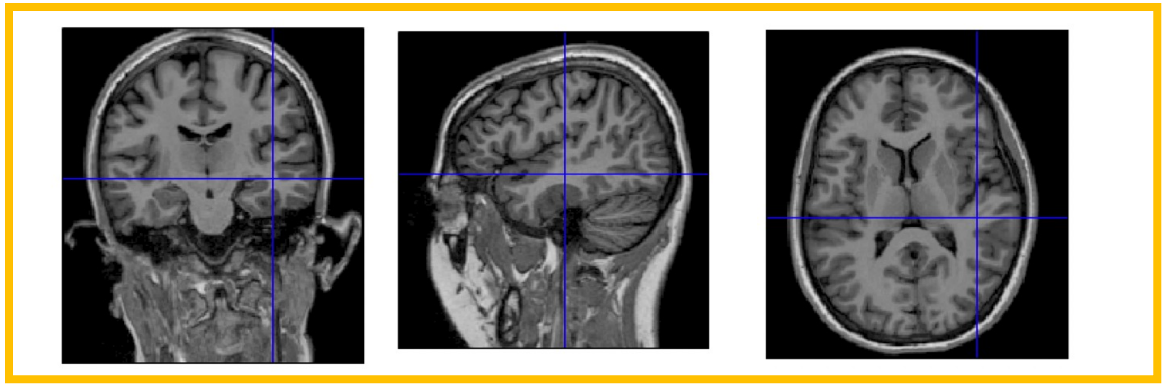
Figure 1.7 The human brain at different spatial resolutions. Spatial resolution refers to the ability to resolve small differences in an image. In general, we can define spatial resolution based on the size of the elements (i.e., voxels) used to construct the image. The images shown here present the same brain sampled at five different element sizes: 8 mm (A); 4 mm (B); 2 mm (C); 1.5 mm (D); and 1 mm (E). Note that the gray–white structure is well represented in the latter three images, all of which were produced using element sizes that were less than half the typical gray matter thickness of 5 mm.



Spatial Resolution 2

- Structural images voxels maybe
  1 x 1 x 1 mm
- Functional images voxels maybe
  3 x 3 x 3 mm (depends on the question)
- BOLD signal is direct measure of the amount of deoxyhemoglobin in a voxel
- Partial volume effects: combination of different tissue types within a voxel (effect from large arteries / small capillaries)
- → Spatial smoothing for statistics and better signal-to-noise ratio

MRI



fMRI

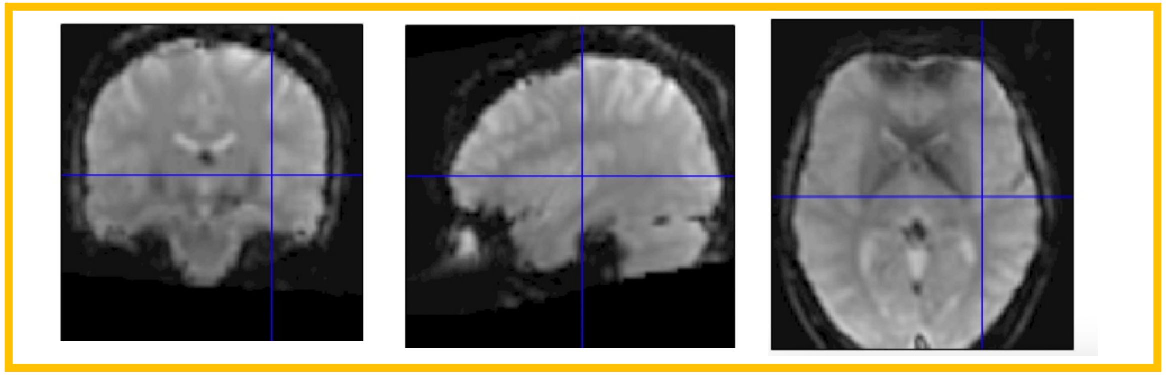
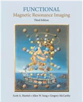
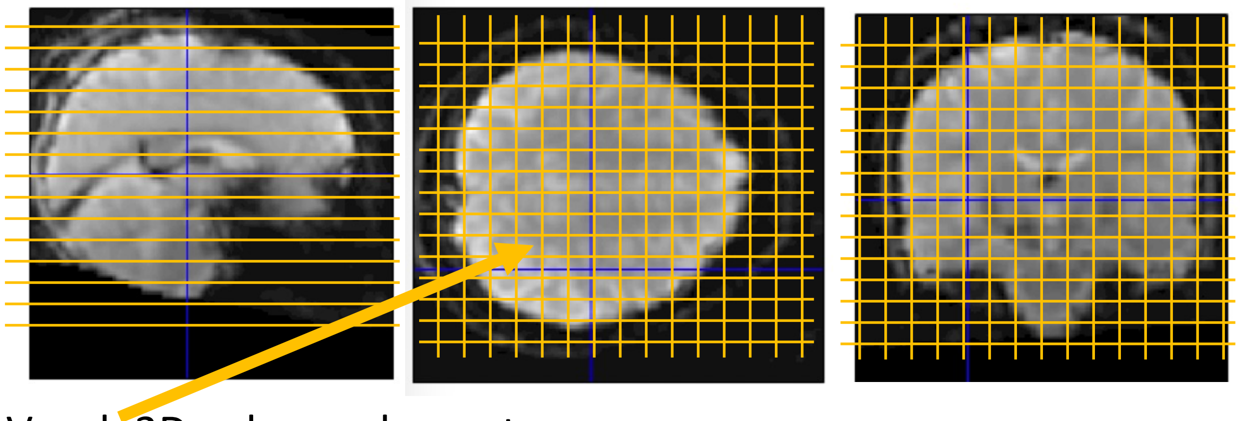
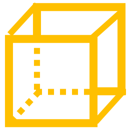


Table 7.1 Spatial Scales in the Human Brain



Structure	Scale (mm)
Brain	100
Gyri	10
Dominance column	1
Neuron	0.01
Synapse	0.001
Ion channel	0.00001





Voxel: 3D volume element

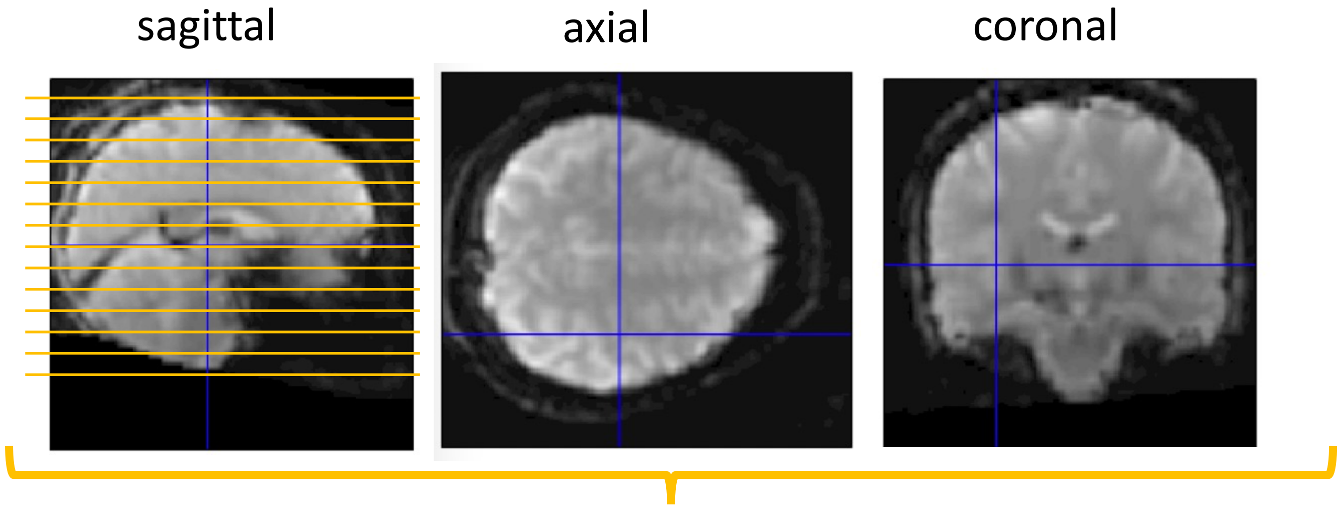
30 slices, 64 x 64 voxels per slice → 122800 voxels

Temporal Resolution

- Determined by TR and by limitations of vascular system
  - TR = time of repetition (time for a volume)
  - HDR rises and falls within 10-15 s
  - Duration of the stimulus does not necessarily correspond with duration of neuronal activity

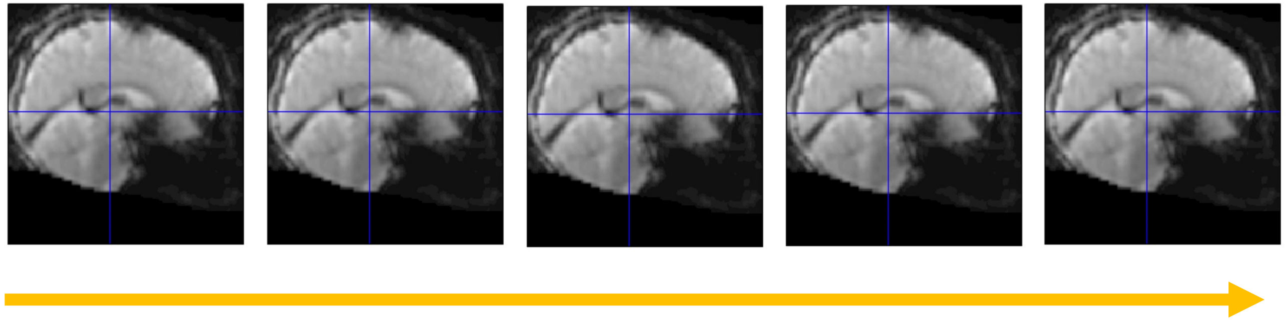
- fMRI is slow
  - neuronal activity is short < 1s
  - no snapshot of neuronal activity but an estimate of slower changes in vascular system

- Good TR?
  - Depending on the experiment (0,5 s – 3 s)
  - Smaller TR
    → more accurate estimation of HDR shape;
    not necessary effect on amplitude



One volume, takes TR to collect

30 slices, 64 x 64 voxels per slice → 122800 voxels



Many volumes over time

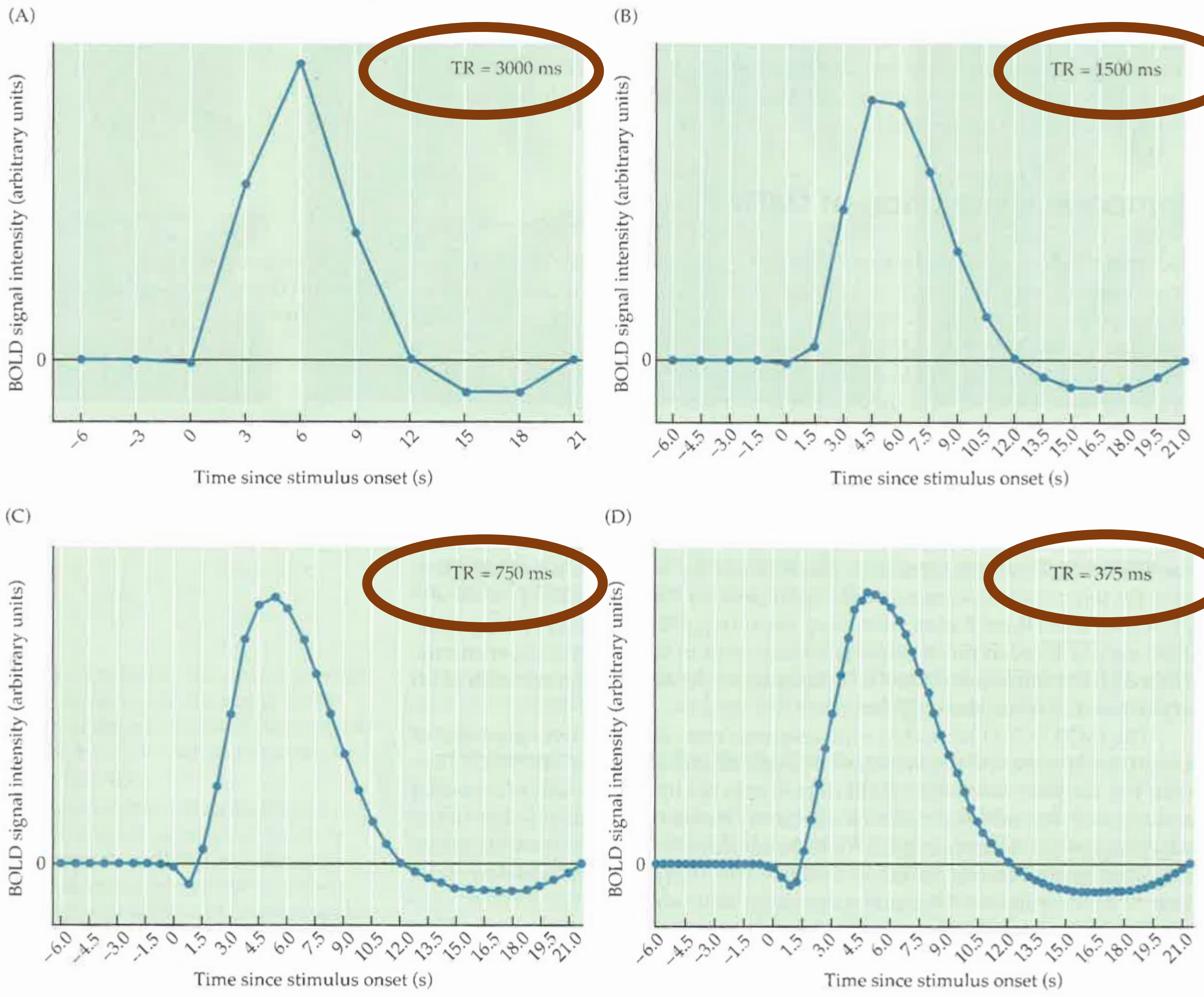
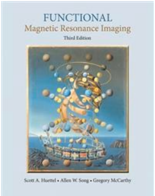
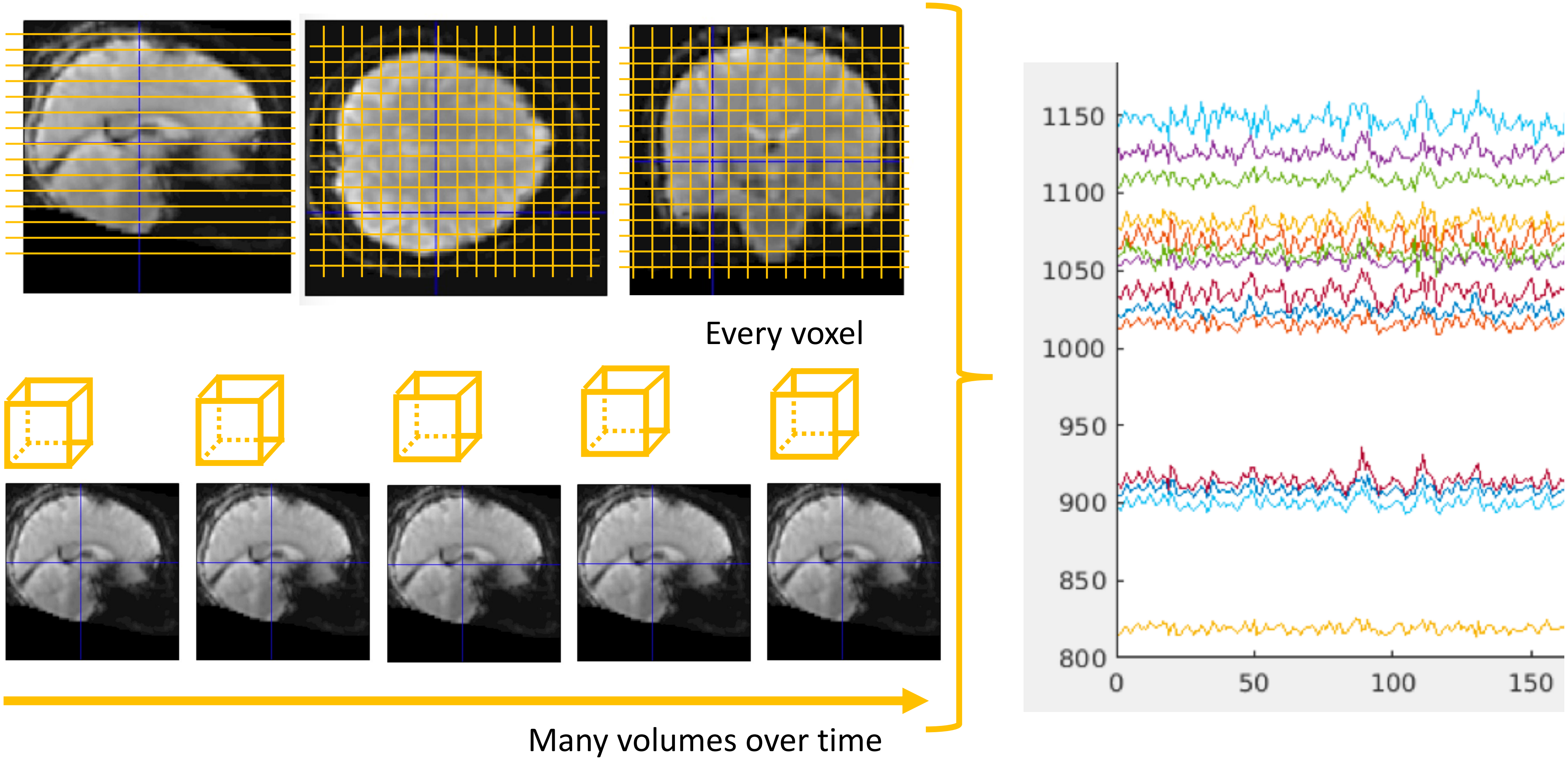


Figure 7.20 Effects of sampling rate (TR) on the measured hemodynamic response. In each figure, an idealized hemodynamic response is sampled at a different rate.



Timeseries

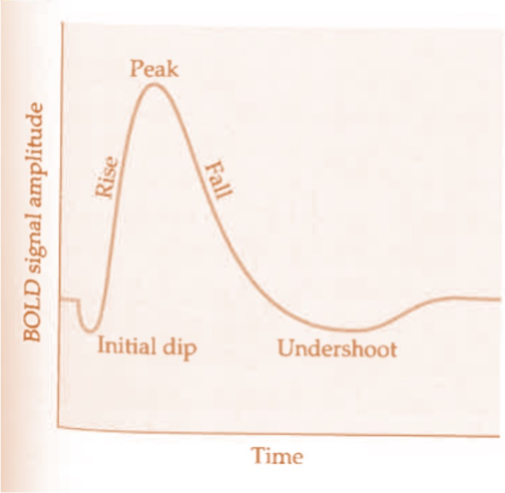

Every voxel
Many volumes over time
1150
1100
1050
1000
950
900
850
800
0
50
100
150

Summary

- fMRI:
  - neuroimaging technique with MRI scanners
  - measures physiological changes correlated with neuronal activity
  - Safe when used right, no ionizing radiation
- BOLD: Blood-Oxygenation-Level Dependent contrast

↑neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal

- HDR: Hemodynamic Response



Question Time!