General Linear Model for fMRI analysis

19.8.2021 Kerttu Seppälä

PhD Student, Turku PET Centre

kerttu.seppala@utu.fi

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
- 4 oxygen molecules in each hemoglobin molecule, 280 million hemoglobin molecules in each red blood cell

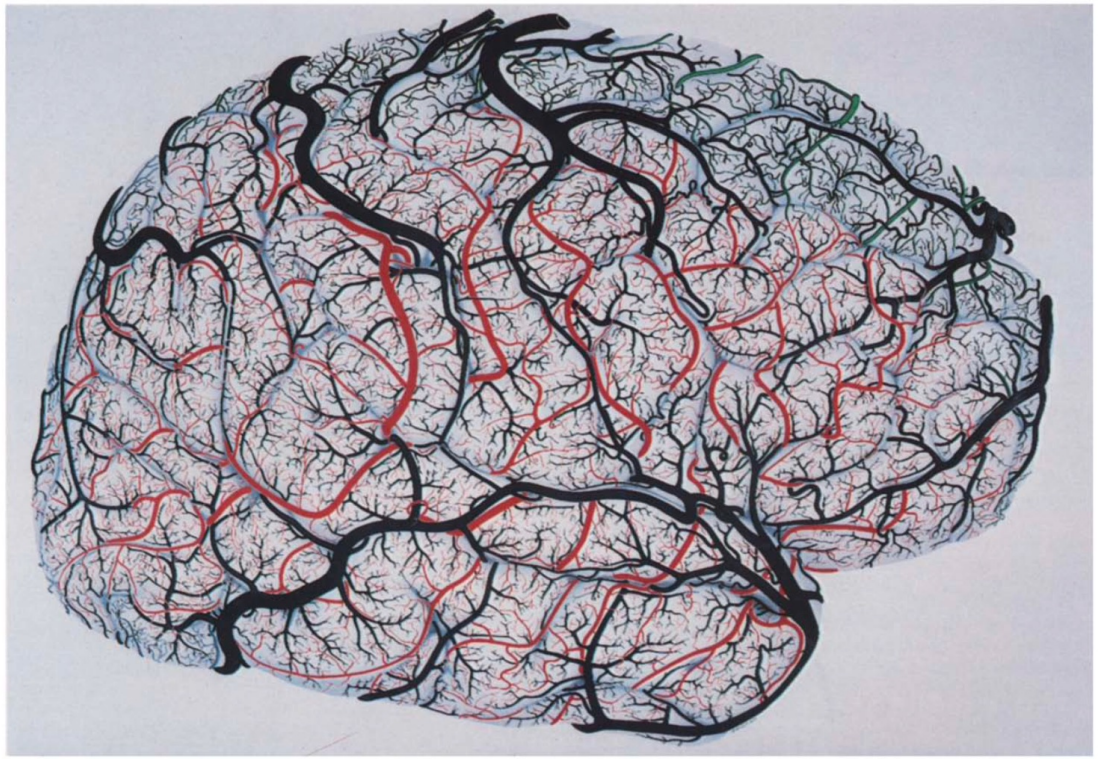
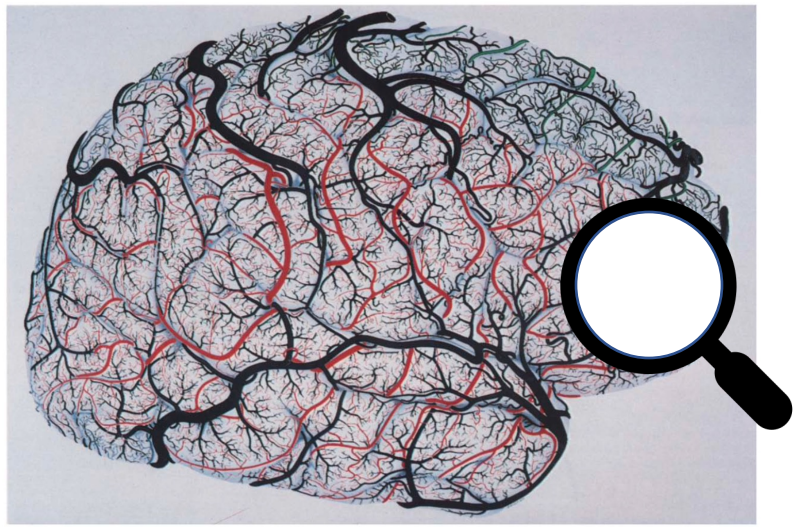


FIG. 1. Drawing of the cortical pial vessels. Right hemisphere. Female, 50 years. RED: Tributaries of the middle cerebral artery. GREEN: Tributaries of the anterior cerebral artery. BLUE: Tributaries of the posterior cerebral artery. Veins are shown in black.

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.



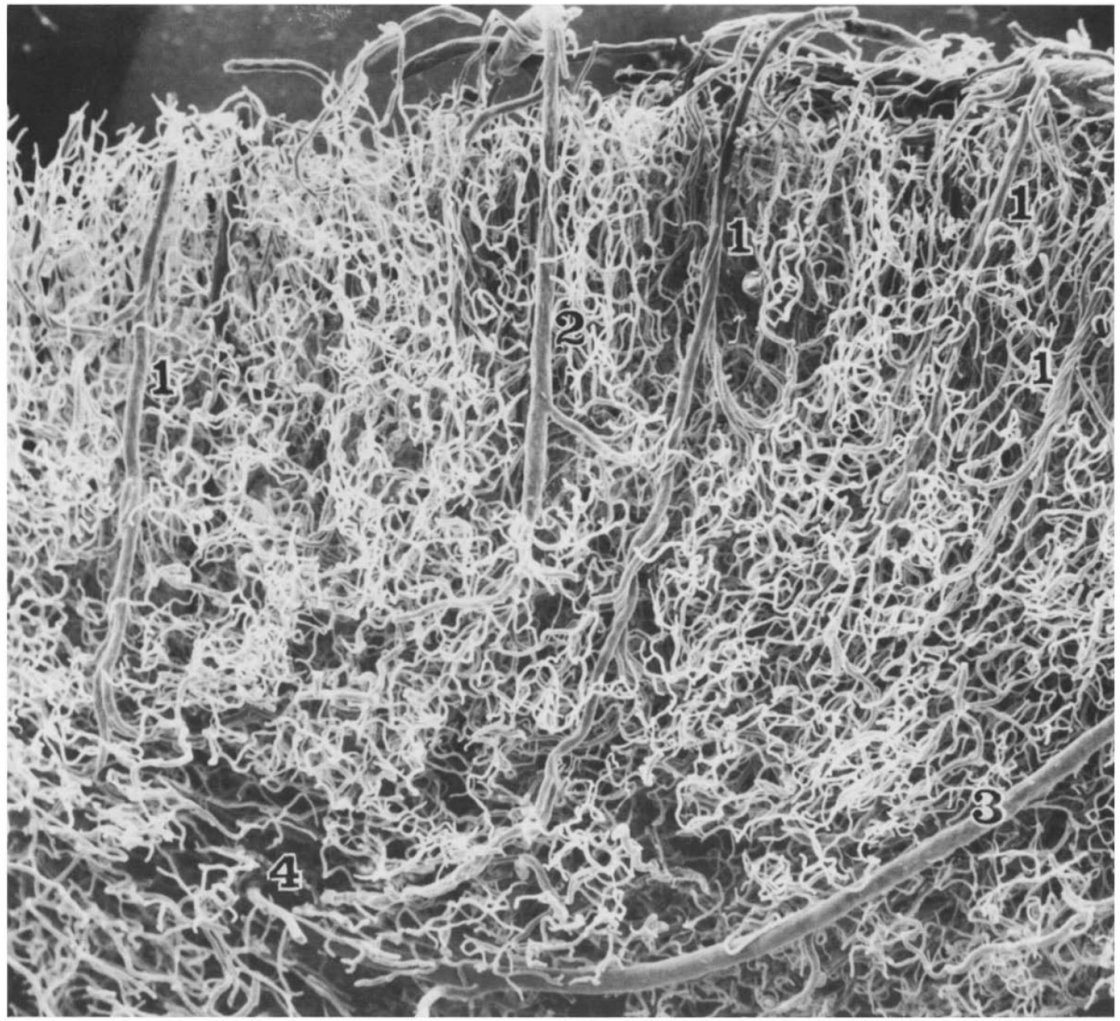
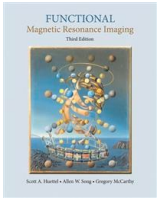


FIG. 60. Temporal pole (SEM). Male, 66 years. General view of the cortical vessels. (1) Cortical arteries. (2) Cortical vein. (3) Medullary artery (type A6). (4) Subcortical white matter (×40).

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

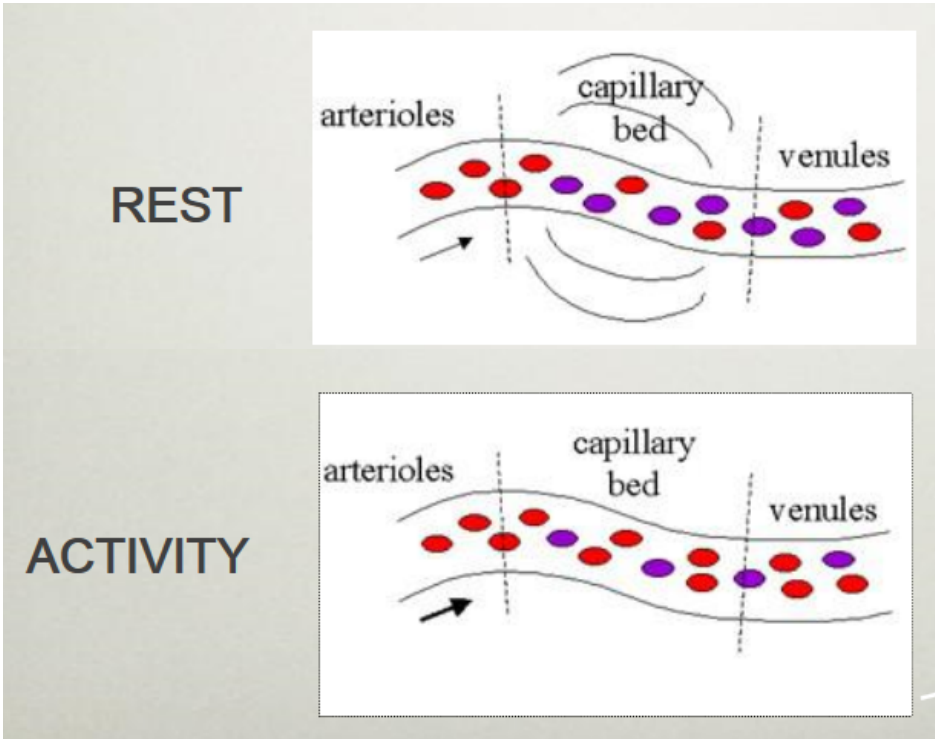


- fMRI does not measure neuronal activity!
- fMRI measures physiological changes correlated with neuronal activity
- BOLD: Blood-Oxygenation-Level Dependent contrast
  - Activity of neurons increase metabolic requirements; blood becomes briefly deoxygenated
  - Oxygen travels in hemoglobin
  - Vascular 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

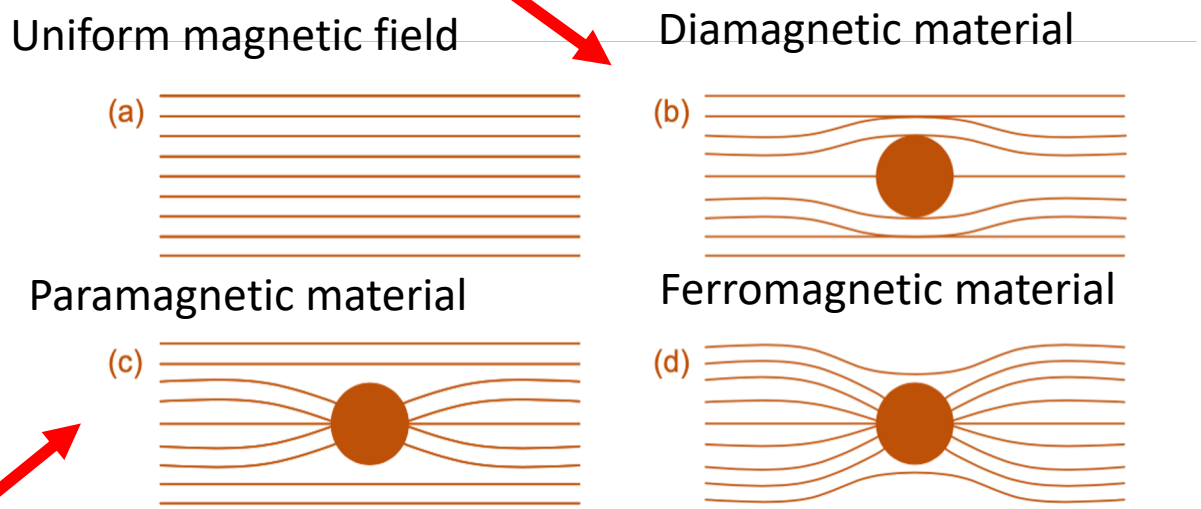
Effect of Hemoglobin in Magnetic Field

OxyHb: diamagnetic

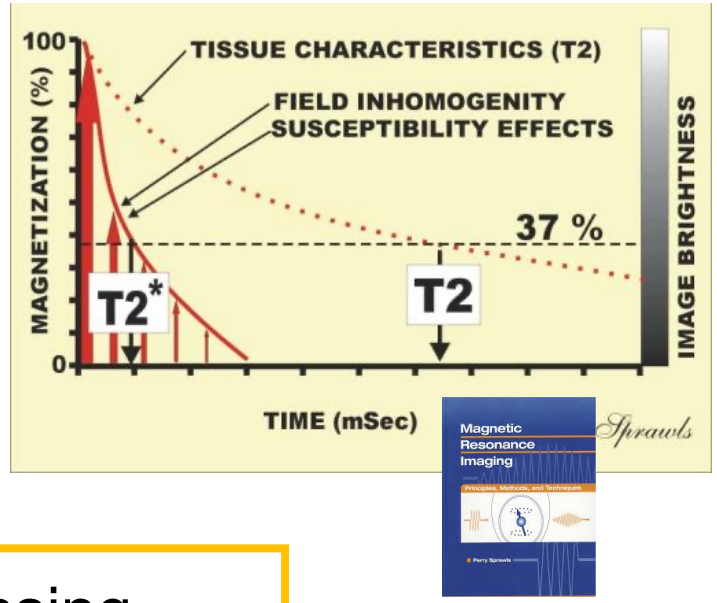
→ weak field inhomogeneities

→ 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

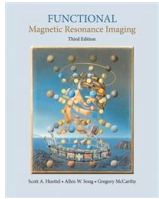
→ strong field inhomogeneities

→ Fast dephasing

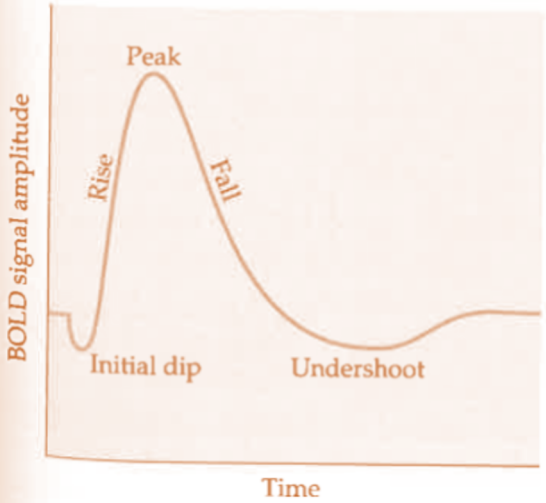
Fast T2*

BOLD signal and Hemodynamic Response?

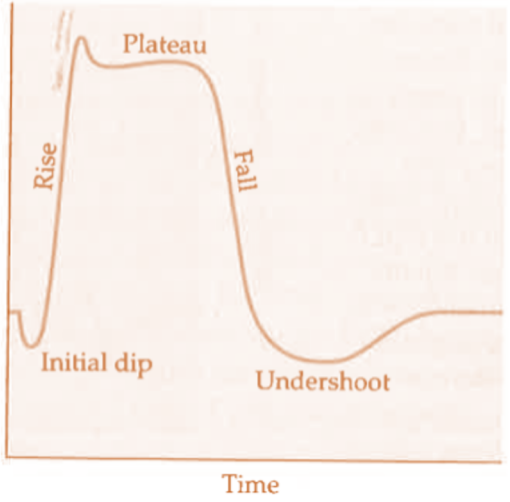
HDR: Hemodynamic Response



(A) HDR for a short stimuli



(B) HDR for a multiple and consecutive events



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***

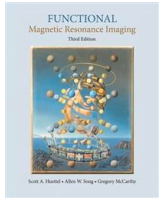
- Maximal amplitude of HDR
- The overcompensation of used oxygen from arteries to neurons
- Slow signal: 4-6 s delay

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

Fig. 7.10

The Actual Measured Signal



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

The units are arbitary

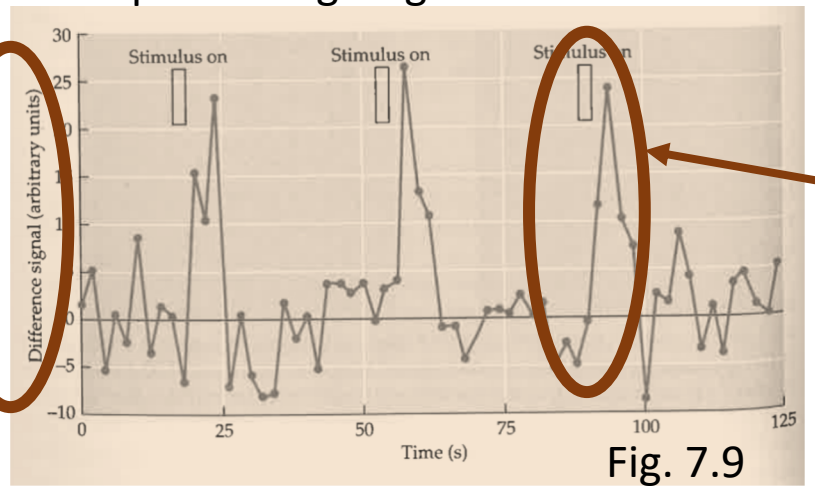
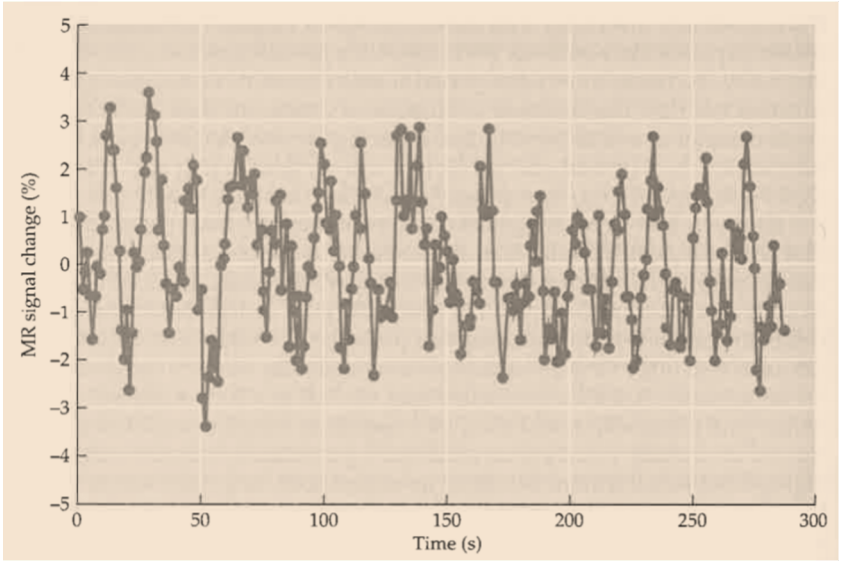
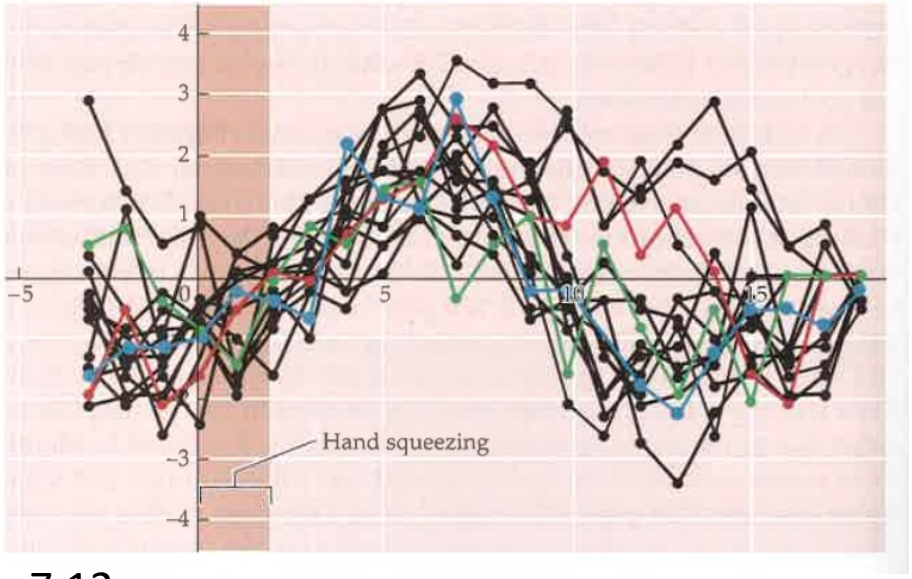


Fig. 7.9

Notice also the delay after the stimulus and before the peak

Example of BOLD hemodynamic response to a hand squeezing task

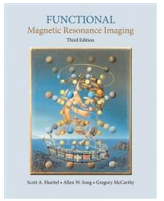




The same data as on the left but the timeseries has cut and organized timewise

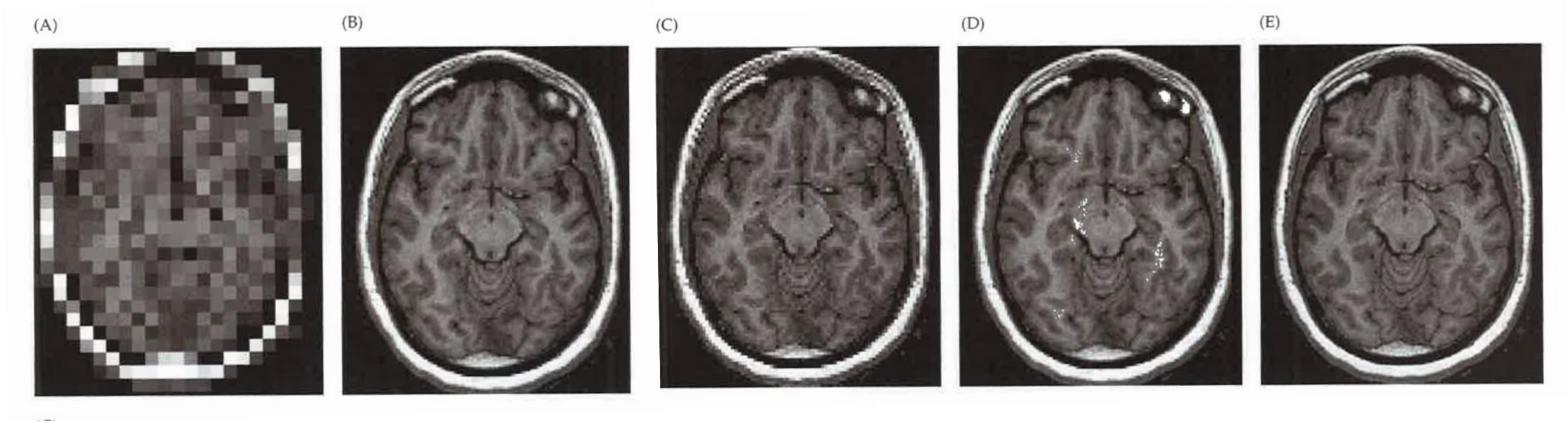
Fig. 7.12

Spatial Resolution



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

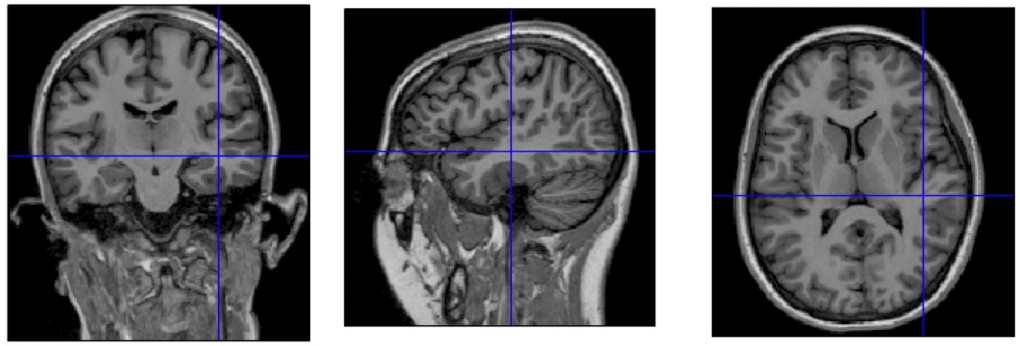
Figure 1.7 The human brain at different spatial resolutions. Spatial resolution refers to the ability to resolve small differences in an image. In general, we can define spatial resolution based on the size of the elements (i.e., voxels) used to construct the image. The images shown here present the 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.



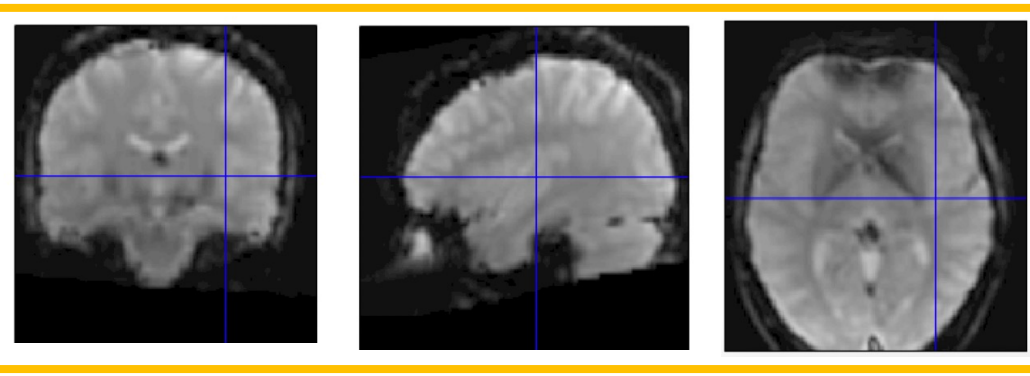
Spatial Resolution 2

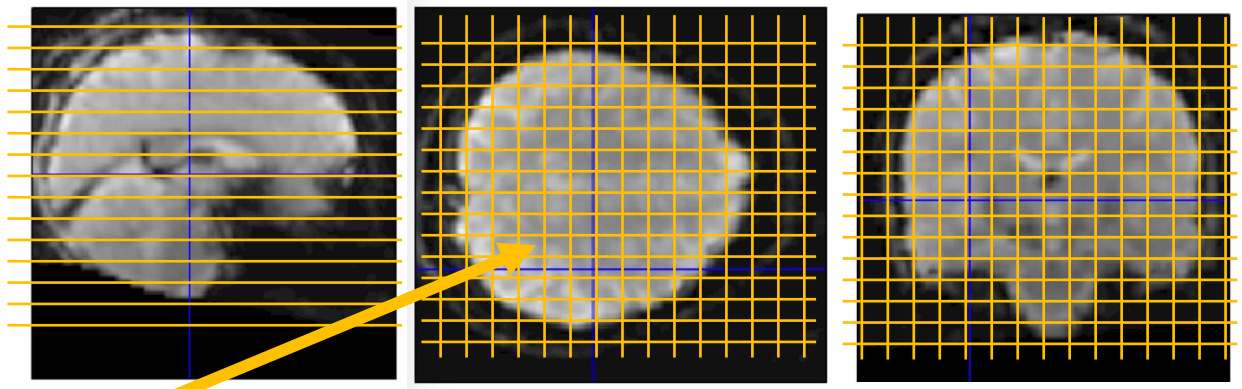
- Structural images voxels maybe
  1 x 1 x 1 mm
- Functional images voxels maybe
  3 x 3 x 3 mm (depends on the question)
- BOLD signal is direct measure of the amount of deoxyhemoglobin in a voxel
- Partial volume effects: combination of different tissue types within a voxel (effect from large arteries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

MRI



fMRI





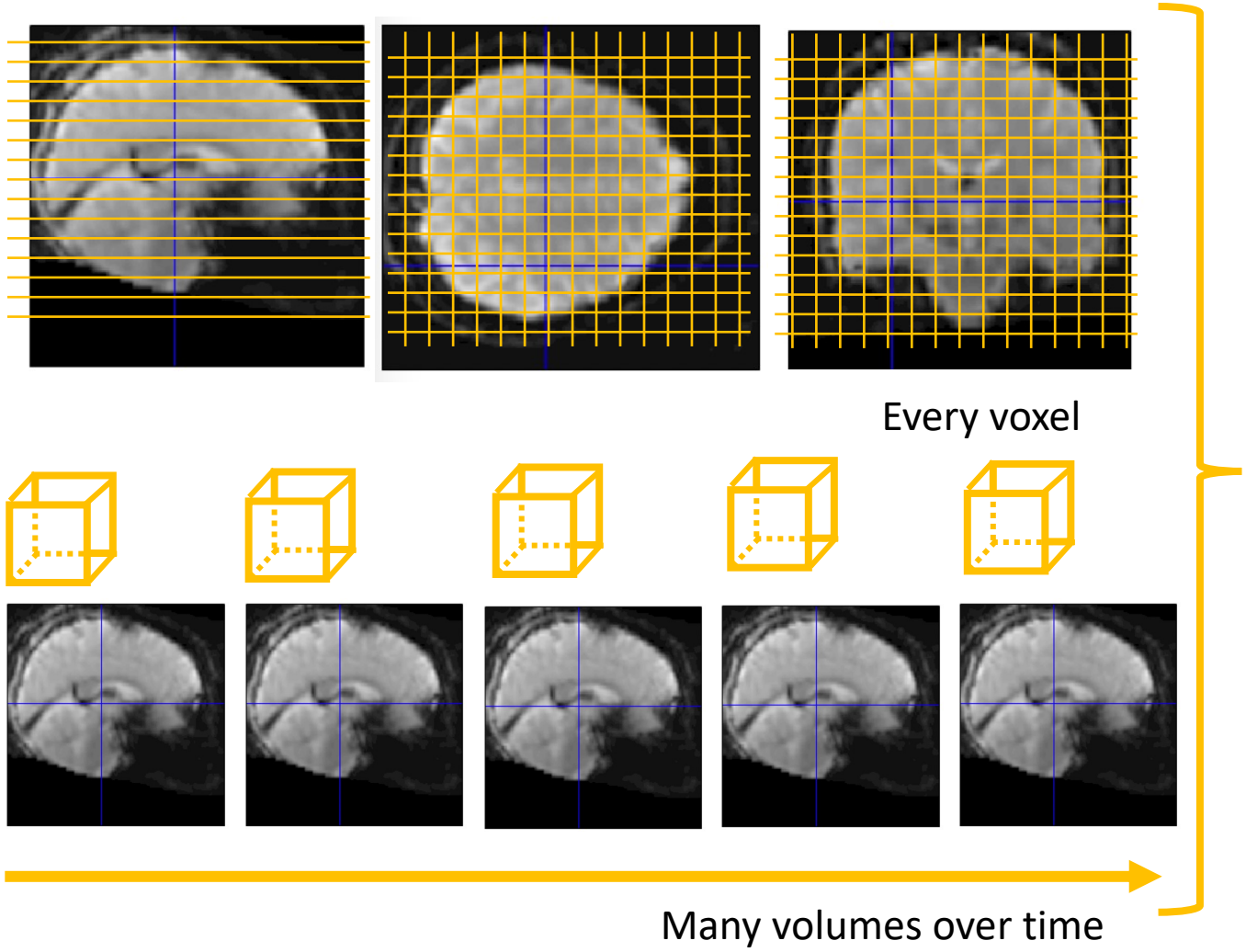
Voxel: 3D volume element

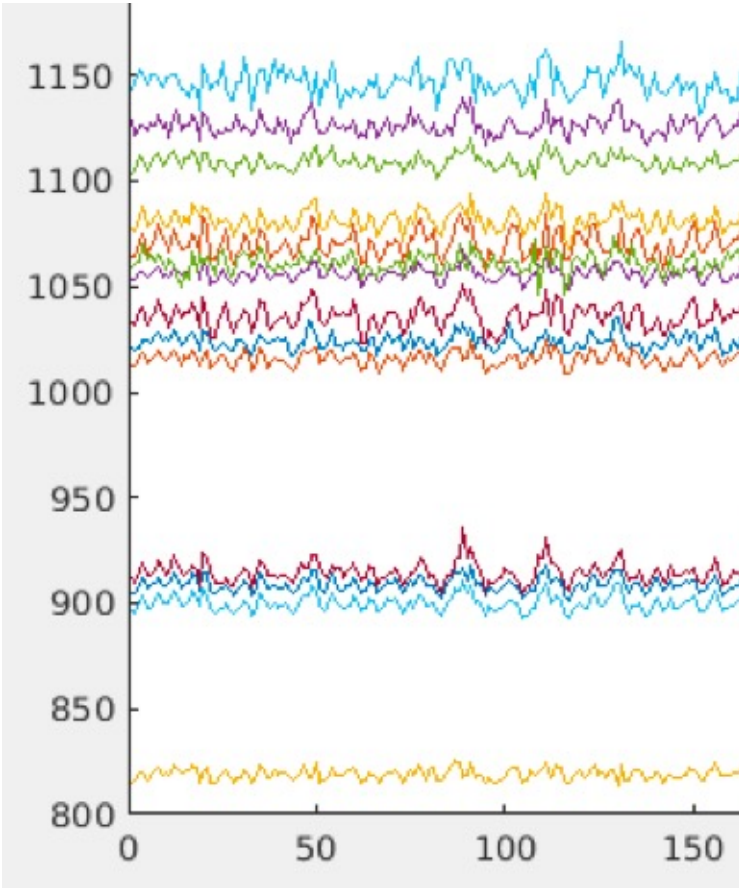
30 slices, 64 x 64 voxels per slice → 122800 voxels

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

Timeseries

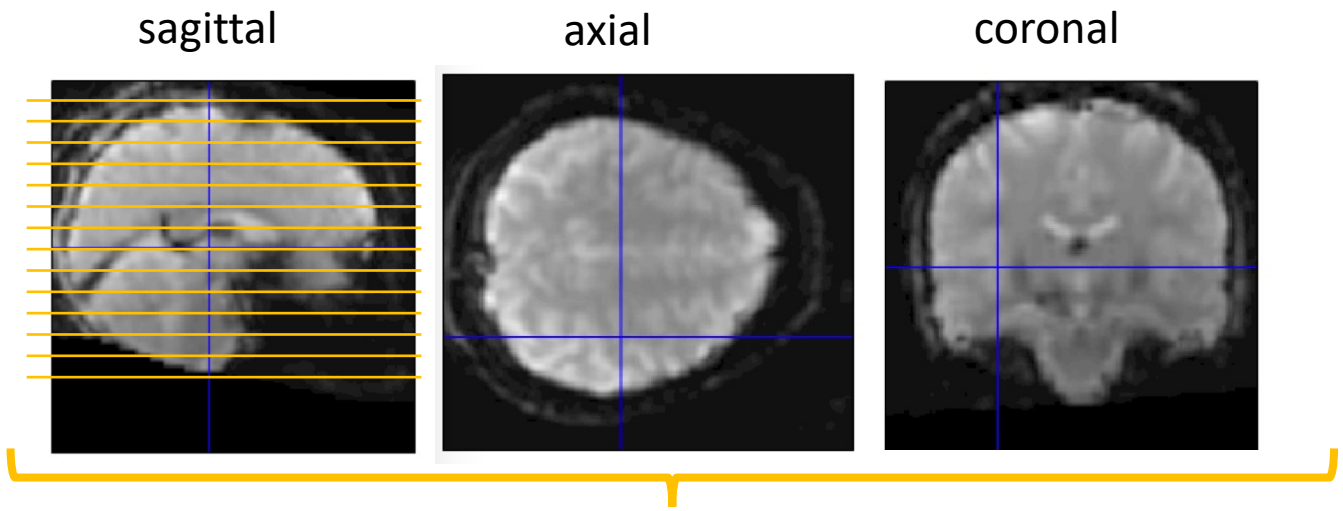

Every voxel
Many volumes over time


1150
1100
1050
1000
950
900
850
800
0
50
100
150

Temporal Resolution

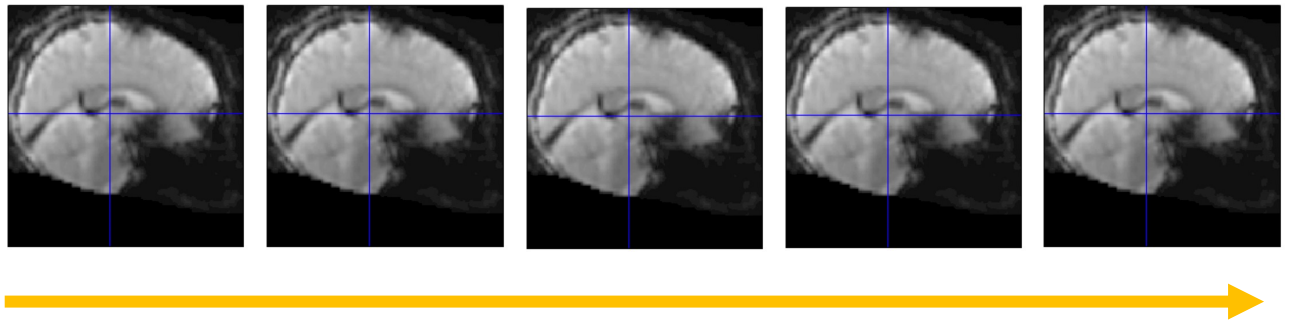
- Determined by TR and by limitations of vascular system
  - TR = time of repetition (time for a volume)
  - HDR rises and falls within 10-15 s
  - Duration of the stimulus does not necessarily correspond with duration of neuronal activity
- fMRI is slow
  - neuronal activity is short < 1s
  - no snapshot 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

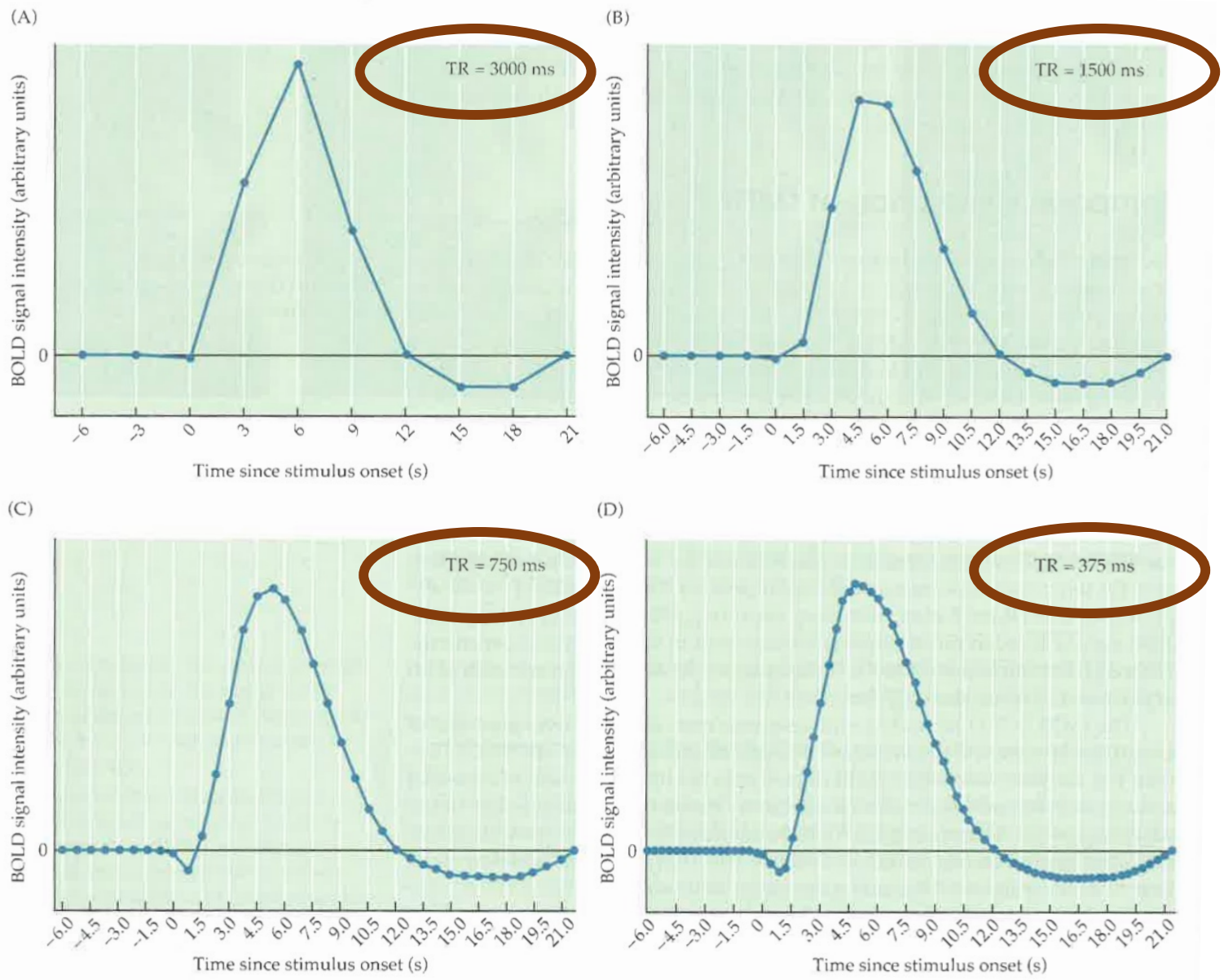
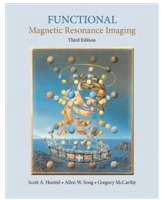
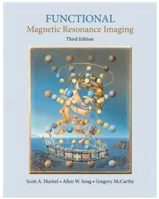


Figure 7.20 Effects of sampling rate (TR) on the measured hemodynamic response. In each figure, an idealized hemodynamic response is sampled at a different rate.



Linearity of the Hemodynamic Response



Linear system

- System: for a given input the system will respond with same output

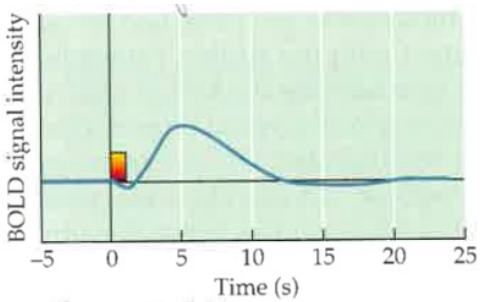
- Input: neuronal activity is a short-duration input
- Output: HDR

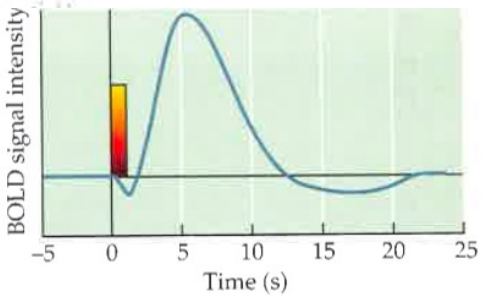
Principles of linear system

1) Scaling + 2) Superposition

1) Scaling

- The magnitude (amplitude) of the system output must one proportional to the system input
- Test condition and control condition:
  - neuronal activity in task required twice as much of work as in rest condition, so the amplitude of HDR is more in activation than in rest
  - if no interference, the brain areas are not activating so





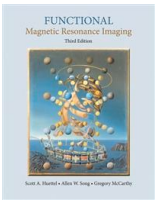
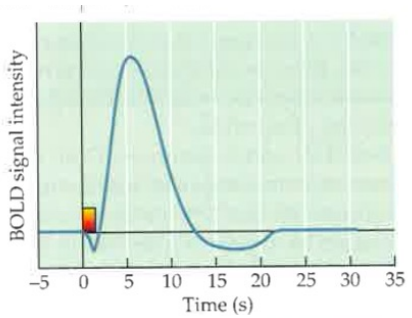
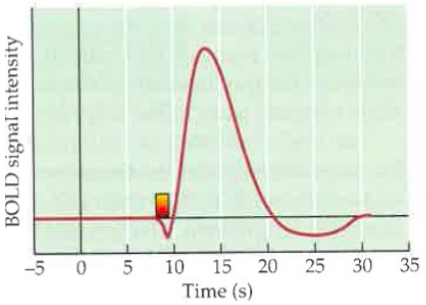


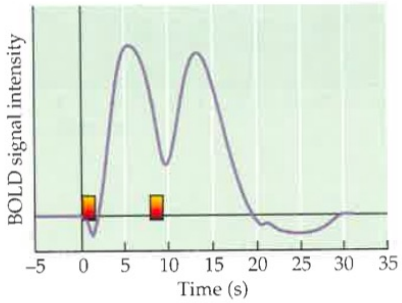
Fig 7.28

2) Superposition

- Total response to a set of imputes is equivalent to the summation of the independent responses to the inputs
- 1 event creates 1 HDR, 2 events create combined response equal to two individual responses added together







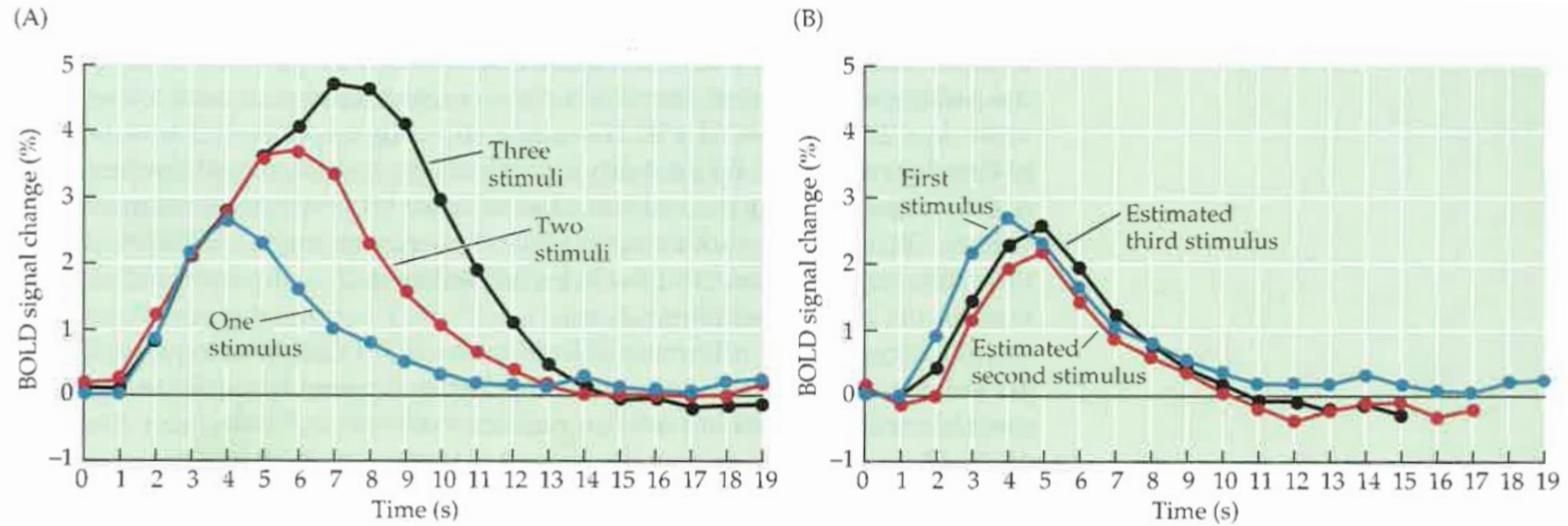
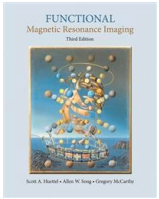


Figure 7.29 Linear addition of hemodynamic responses to individual stimulus events. (A) The hemodynamic responses evoked by presentation of one, two, or three identical stimuli (short-duration visual flashes) at short interstimulus intervals were measured. Shown here are data from a 2-s interval. The total hemodynamic response increased in a regular fashion as the number of stimuli in a trial increased. (B) By subtracting the one-stimulus trial from the two-stimulus trial and subtracting the two-stimulus trial from the three-stimulus trial, the contributions of the second and third stimuli in a trial were estimated. The responses to the second and third stimuli were generally similar to the response to the first stimulus, suggesting that the BOLD response scales in a roughly linear fashion. (From Dale and Buckner, 1997.)

Limitations in Linearity of HDR



- Limitation: short stimuli intervals create more deviation in HDR
→ less linear system, BUT more data and more statistical power

- Limitation coming from refractory period: a time period following the presentation of a stimulus during which subsequent stimuli evoke a reduced response, around 6 s

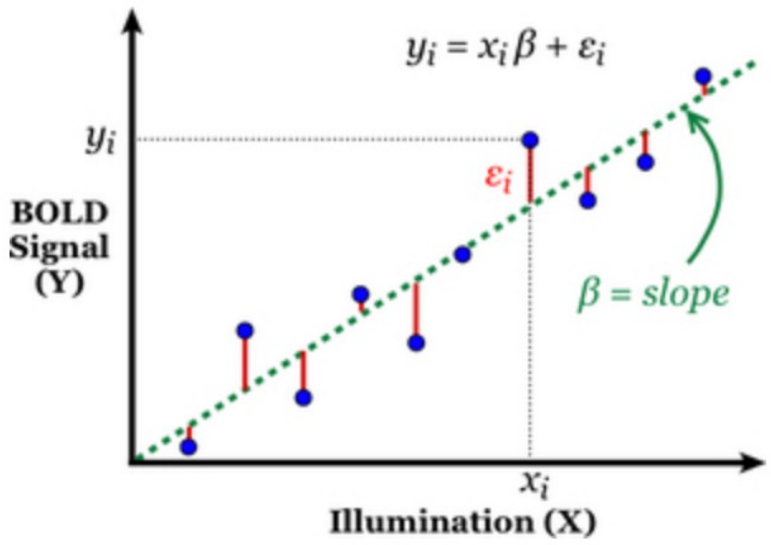
→ refractory period differs between the brain areas

→ However, offers possibility for further studies in brain science, but requires advanced modelling

GLM for fMRI

General Linear Model

- Because the system is linear, the modelling can be linear



Simplified linear regression example, adapted from data of Hansen et al (2004)

http://mriquestions.com/general-linear-model.html

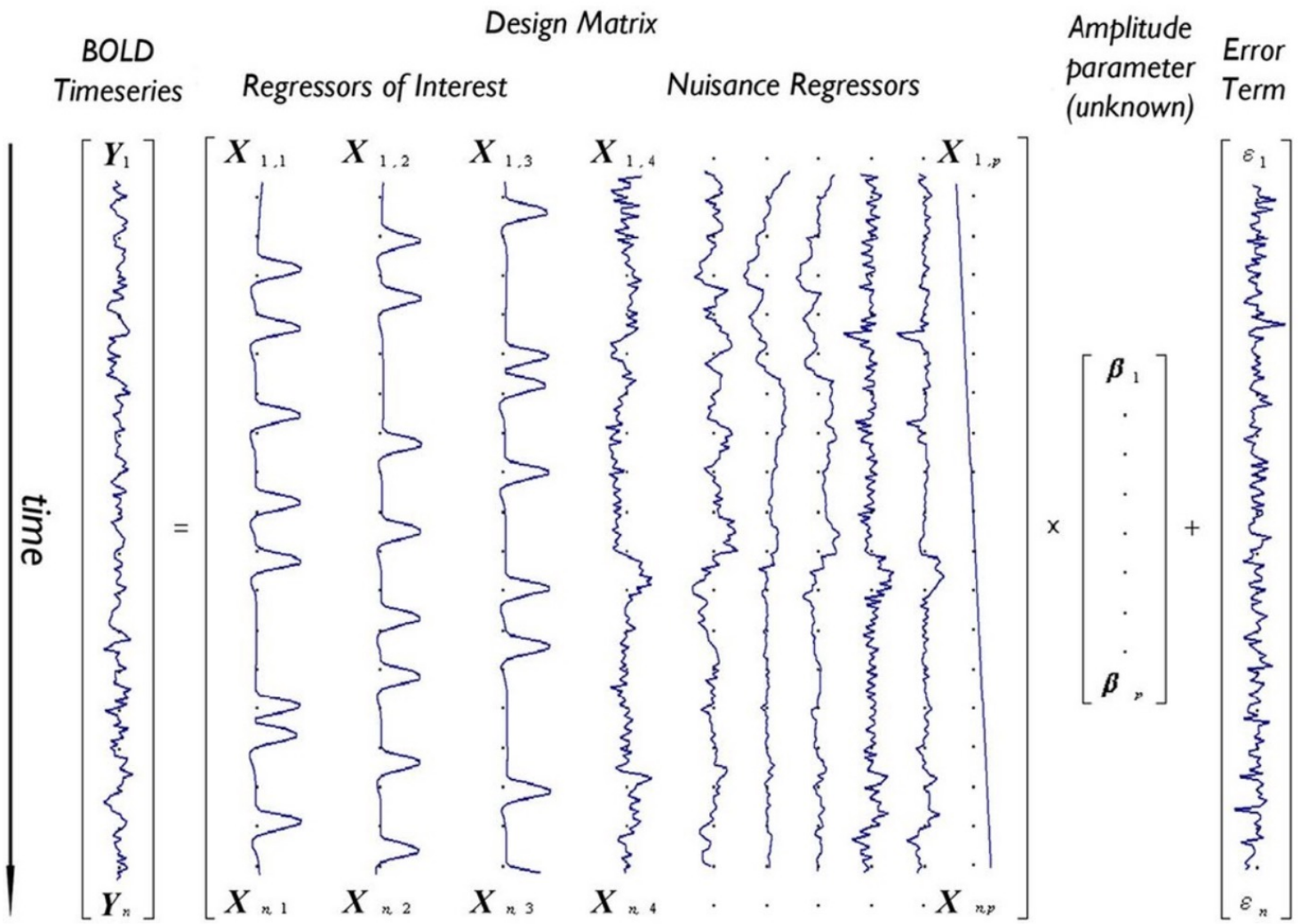
$$y = \beta X + \varepsilon$$

Y = measured signal (BOLD)
X = the stimuli for the subject

Because the system is linear, we hope that modelling it as such will explain the brain activity found, so:

B = find the best ones that leaves the error minimized
E = error

So: **1)** create a **model**, **2)** **fit** the model with the data and **3)** do the **statistical** tests → beautiful activation maps and pictures



Depiction of the General Linear Model (GLM) for a voxel with time-series **Y** predicted by a design matrix **X** including 10 effects (three regressors of interest – e.g., tasks A,B,C – and seven nuisance regressors – e.g., six motion parameters and one linear drift). Calculated weighting factors ($\beta_1 - \beta_{10}$) corresponding to each regressor are placed in amplitude vector **β** while column vector **ε** contains calculated error terms (ε_i) for the model corresponding to each time point *i*. (From Monti, 2011, under CC BY license)

”Stated in words, the GLM says that **Y** (the measured fMRI signal from a single voxel as a function of time) can be expressed as the sum of one or more experimental design variables (**X**), each multiplied by a weighting factor (***β***), plus random error (**ε**)”

http://mriquestions.com/general-linear-model.html

This is a quick overview about the topic, please think about this again, when you have learned to build 1st level models and design matrixes…

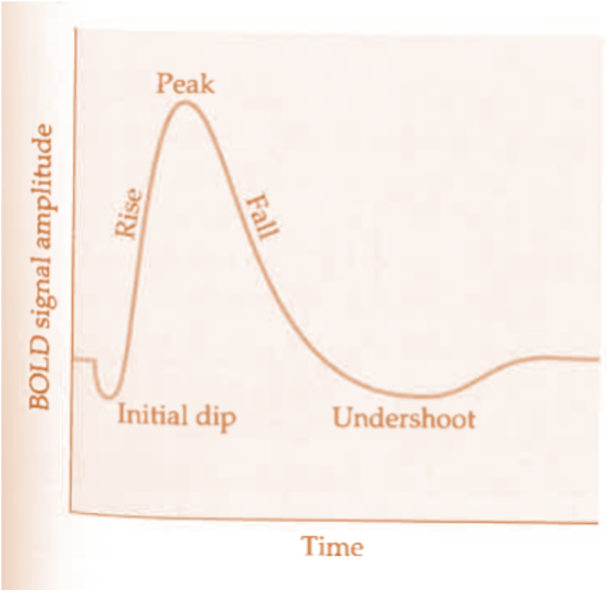
Summary

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

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

- HDR: Hemodynamic Response
- Linear System: for a given input the system will respond with same output
- GLM: General linear model

$$y = \beta X + \varepsilon$$



Question Time!