HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

Functional Magnetic Resonance Imaging (fMRI)

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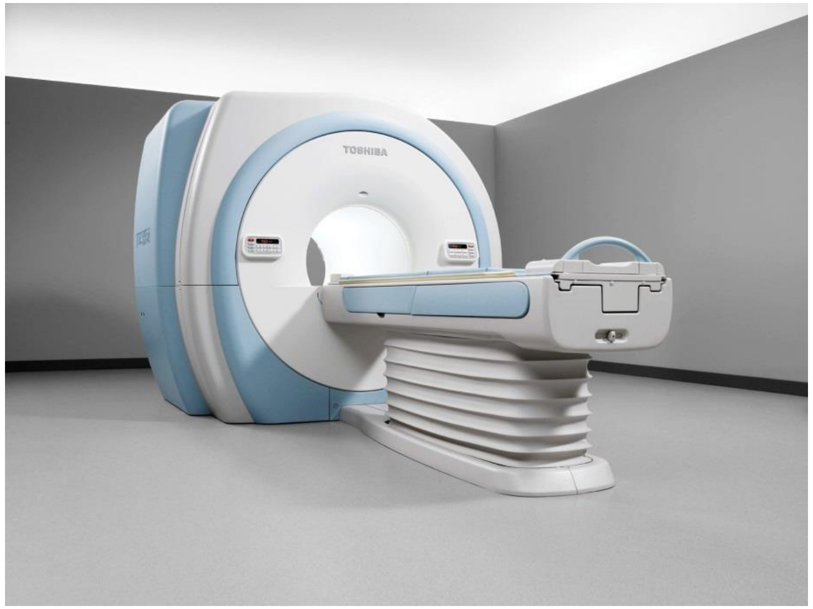
DRESDEN concept

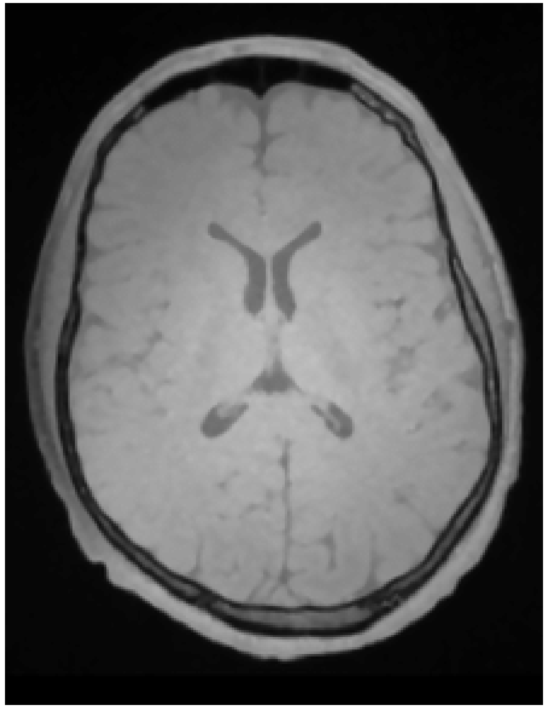
MRI quick summary

- Spin property of hydrogen atoms
- Using strong B_0 magnetic field
  - 1.5 T, 3T – clinical scanners
  - 7T – experimental scanners

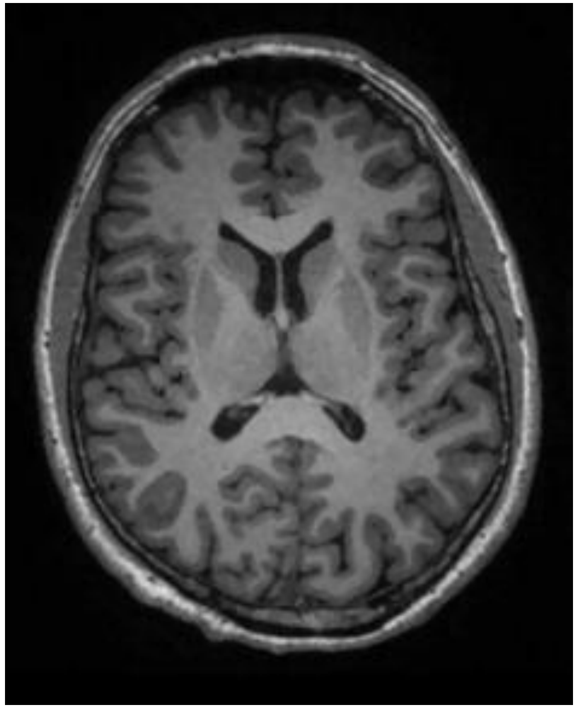


MRI quick summary

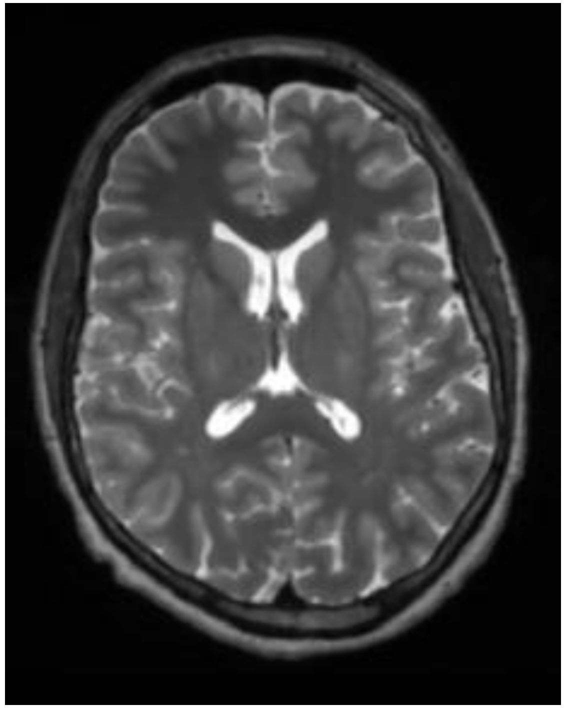
- Imaging magnetic properties of tissue
  - Proton density
  - T1-weighted relaxation
  - T2-weighted relaxation



PD



T1



T2

Brain imaging with different modalities

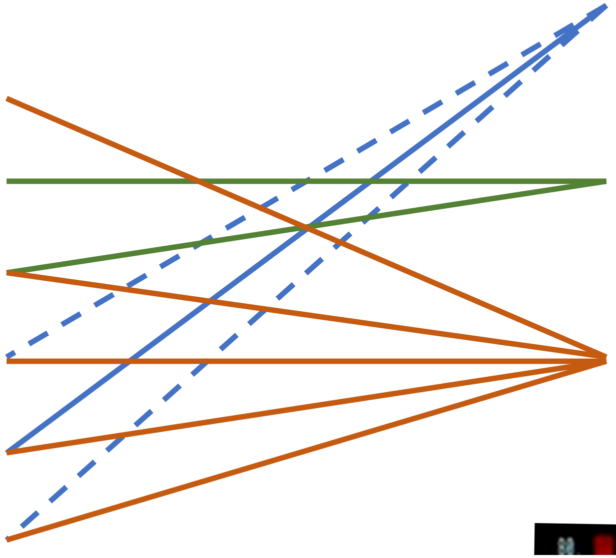
Structure

- Soft tissue
- Bones
- Vessels

Physiology

Metabolism

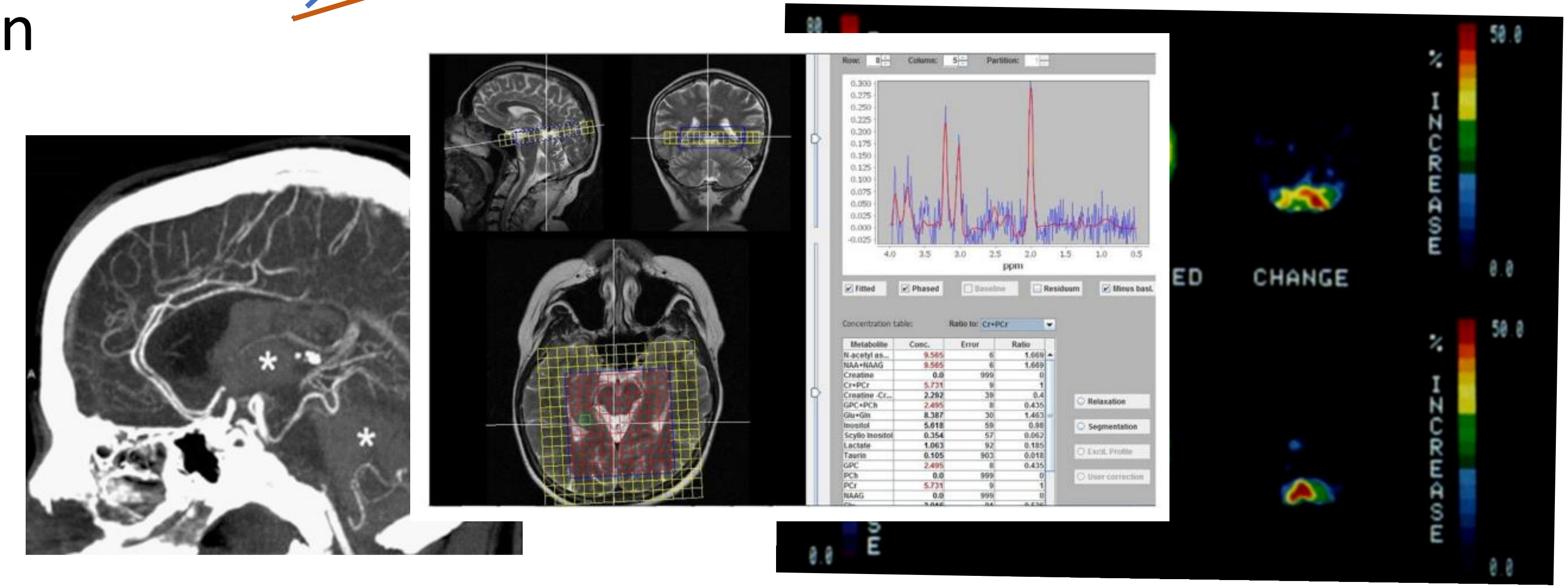
Function

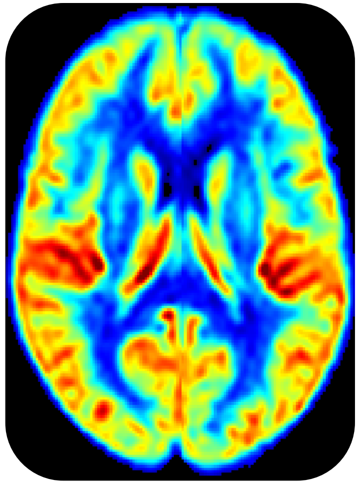


PET (Positron emission tomography)

CT (Computed tomography)

MRI



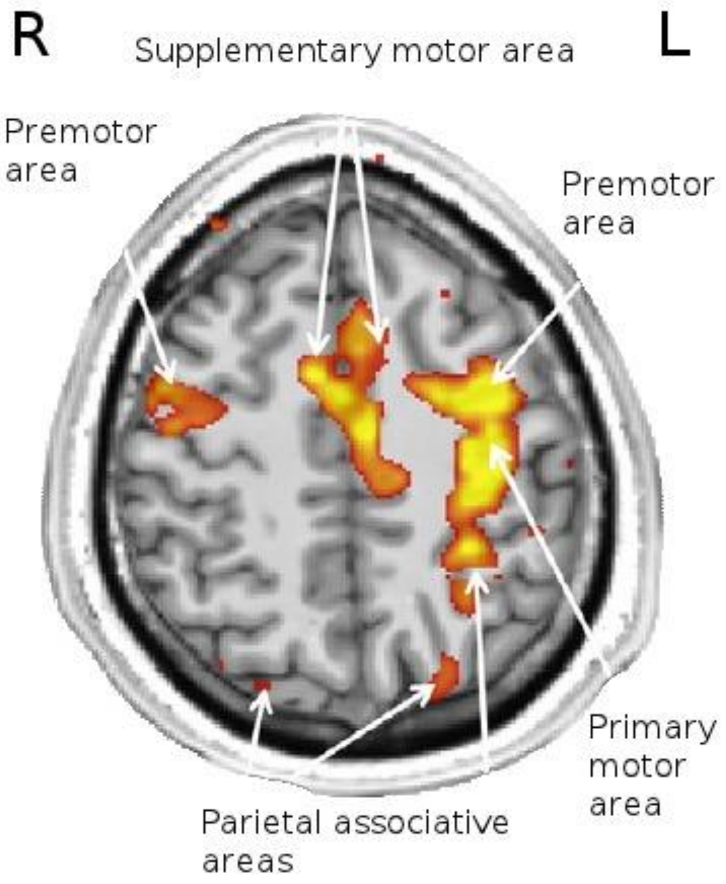


DRESDEN concept

HZDR

Functional MRI

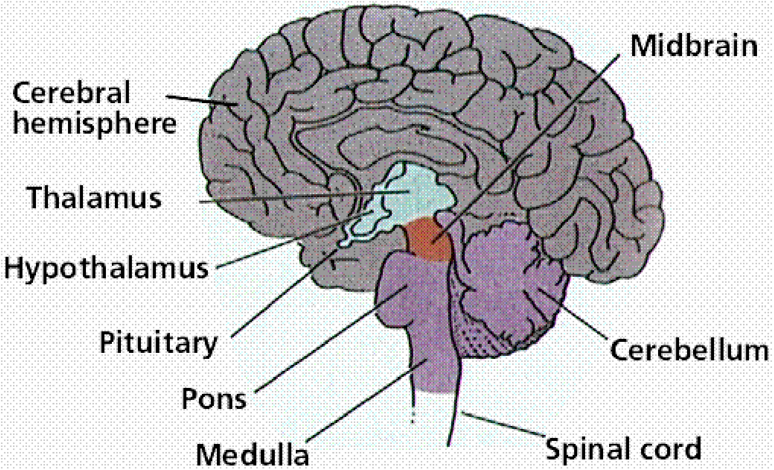
- Image brain activity
- Spatial resolution ~mm
- Temporal resolution ~s

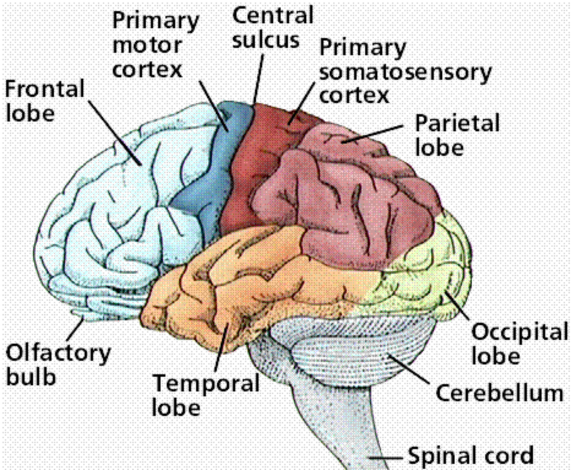


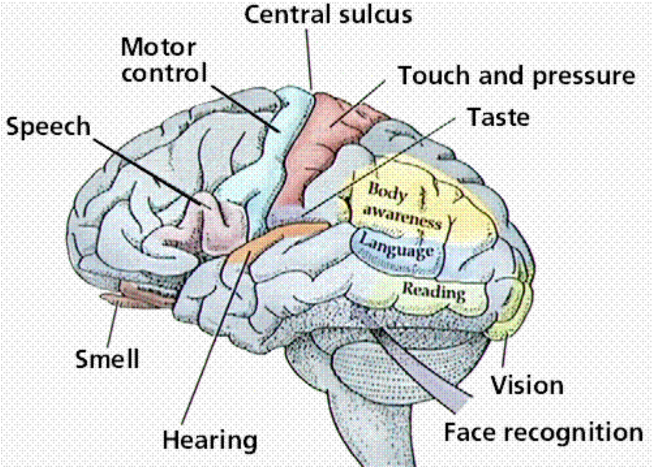
DRESDEN concept HZDR

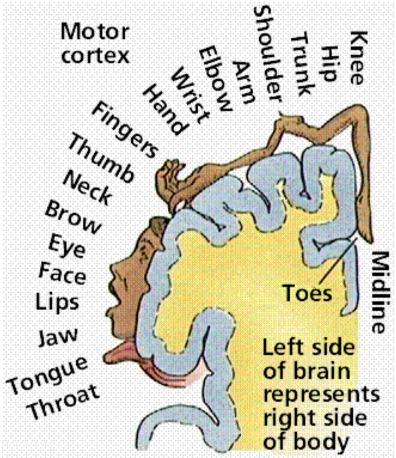
Brain regions

- Anatomical regions
- Individual difference
  - size?
  - shape?
  - topology?
- Functional regions





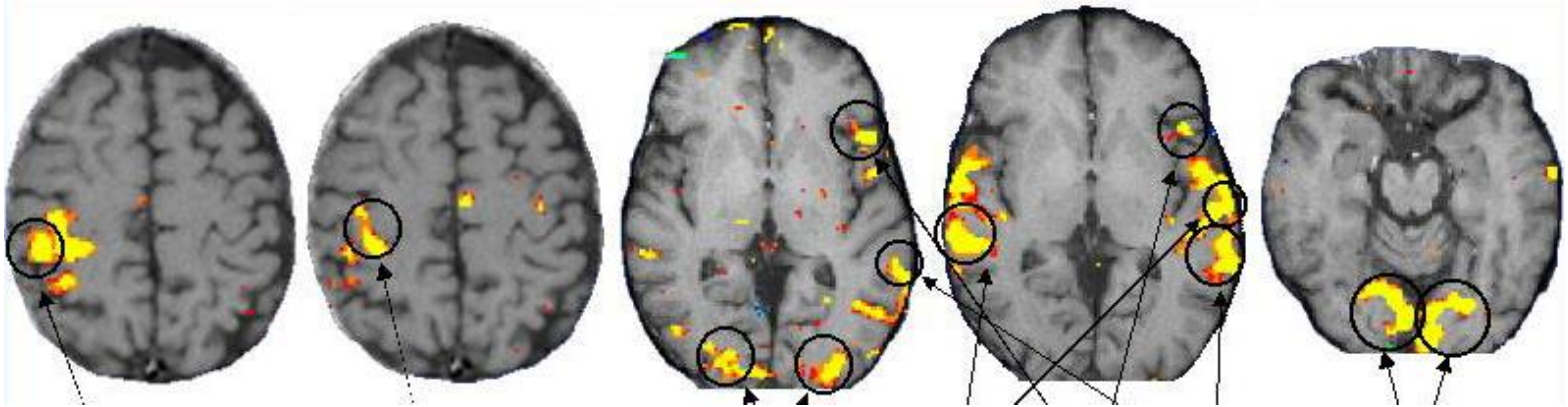




Brain regions

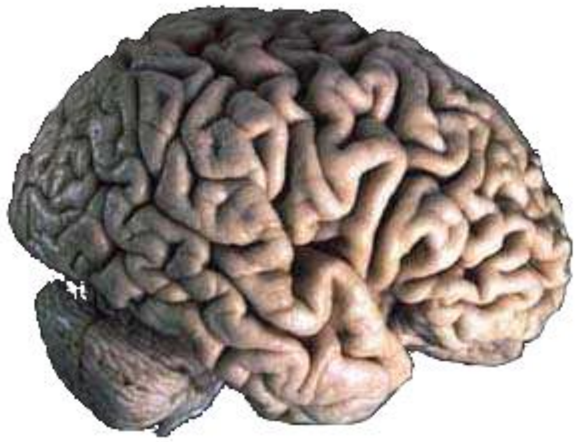
- Examples of brain activation regions

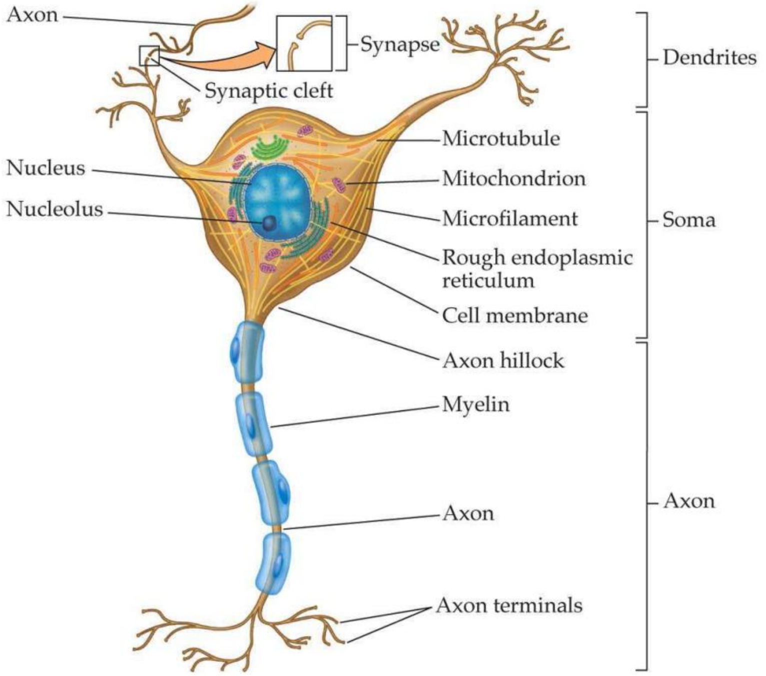
Sensory	Motor	Language		Vision
Touch	Finger tapping	Picture naming	Listening to words	Reversing checkerboard
Passive	active	active	passive	passive



Brain anatomy

- Neurons and glial cells
- Neurons communicate through axons
  - Through electrochemical processes

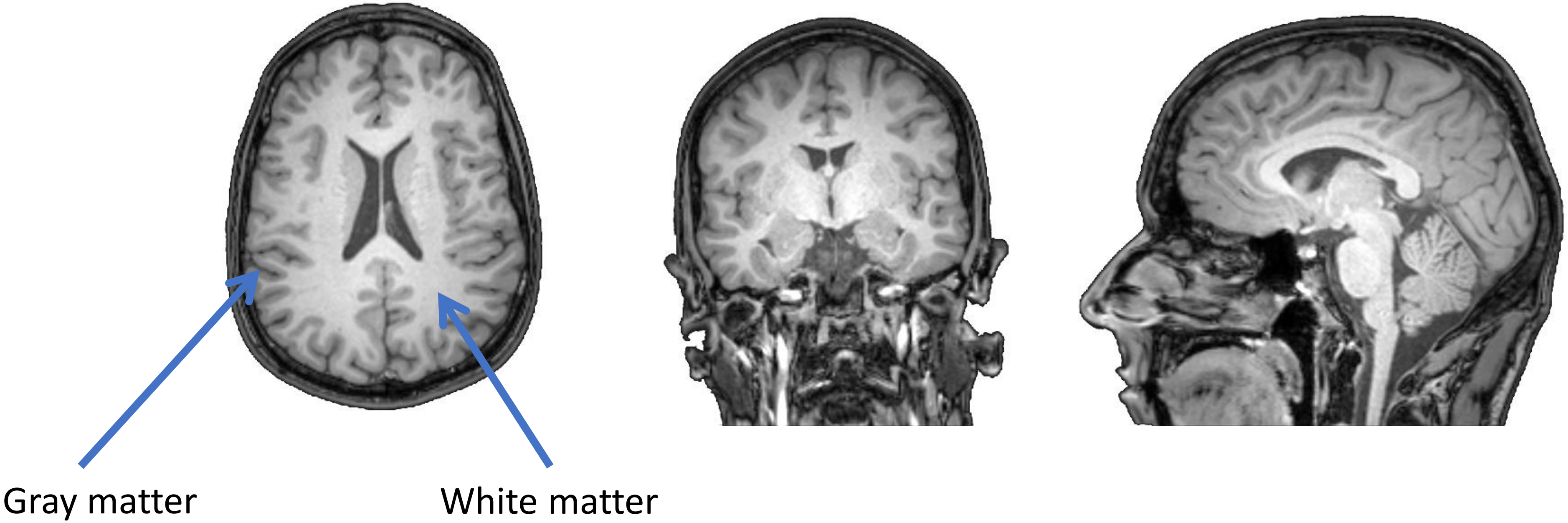




FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 6.2

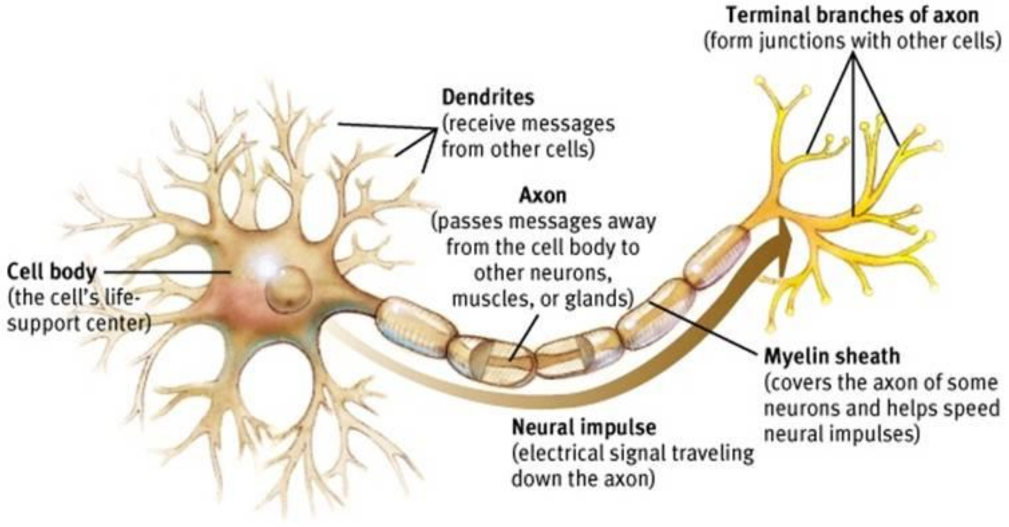
Brain anatomy

- Gray matter
  - Consists mostly of neurons
- White matter
  - Consists mostly of axons



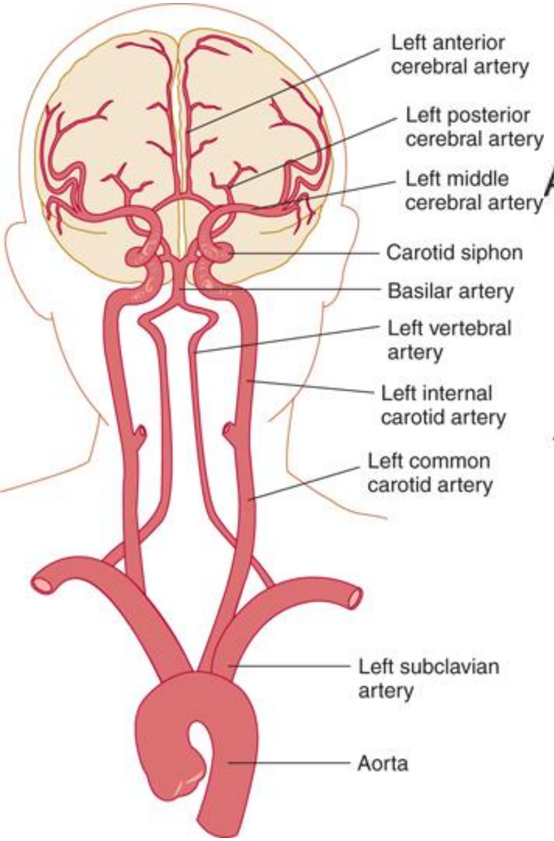
Neuronal activation

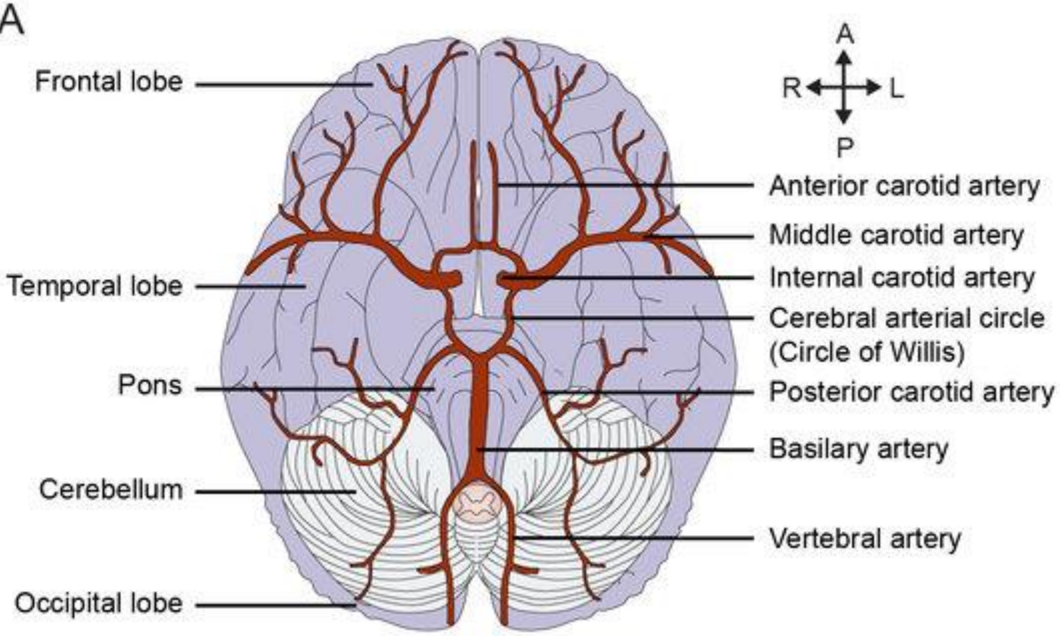
- Integrative and signalling activity
  - Change cell membrane potential
  - Release of neurotrasmitters
- Ionic pumps to restore concentration gradients
  - Requires glucose and oxygen

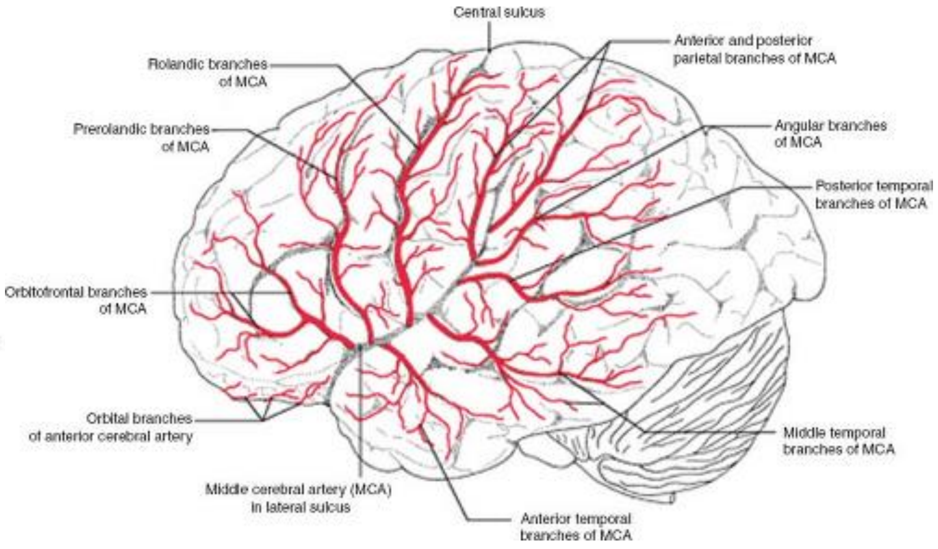


Brain vasculature

- Blood supplies brain with oxygen and glucose
- Internal carotid and vertebral arteries
- Further branching to microvessels and capillaries



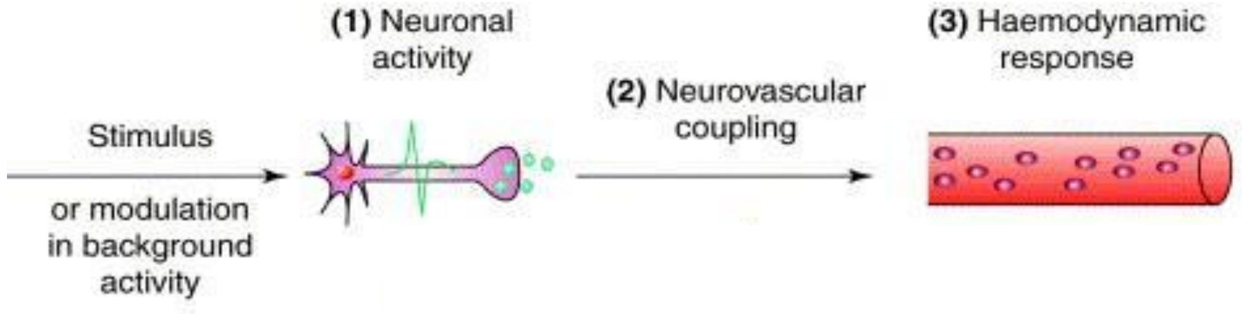




DRESDEN concept HZDR

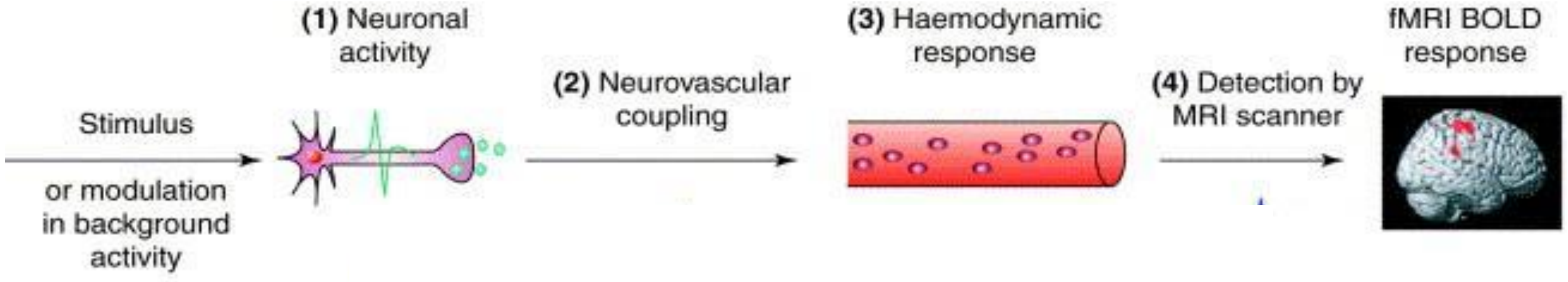
Neurovascular coupling

- Neurovascular coupling
  - Vasoactive substances → Dilate vessels
  - → Reduces resistance
  - → Increase blood flow



fMRI physiology

- What is measured in fMRI?
  - Electrical impulses?
  - Neurotransmitters?
  - Blood perfusion?
- Blood perfusion through the level of oxygenation



History of BOLD imaging

- BOLD – Blood Oxygenation Level Dependent
- Ogawa et al., 1990
  - Mice and rats at 7T MRI
  - Contrast on gradient-echo images influenced by proportion of oxygen in breathing gas
  - Increasing oxygen content → increased contrast
- Ogawa et al., 1992
  - Humans at 4T MRI
  - Visual stimulation
  - Changes of contrast in visual cortex

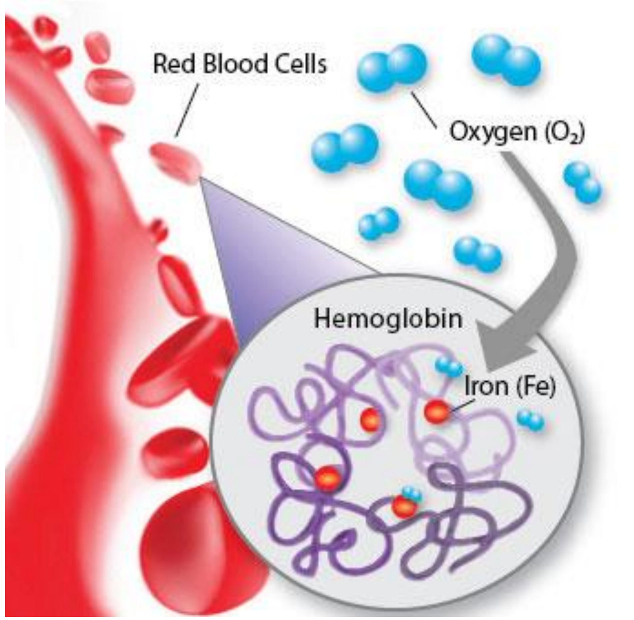
BOLD signal and T_2*

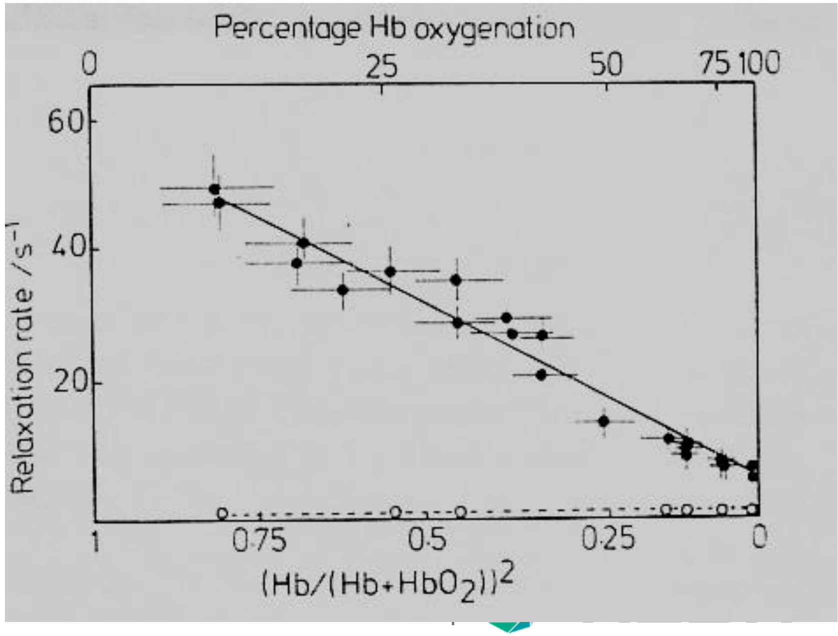
- T_2^* relaxation – decay of signal after excitation
- Two components of T_2^* :
  - Intermolecular interactions
    - → dephasing → T_2 signal decay
  - Macroscopic magnetic field inhomogeneity
    - → dephasing → T_2' decay.

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

BOLD signal and T_2^*

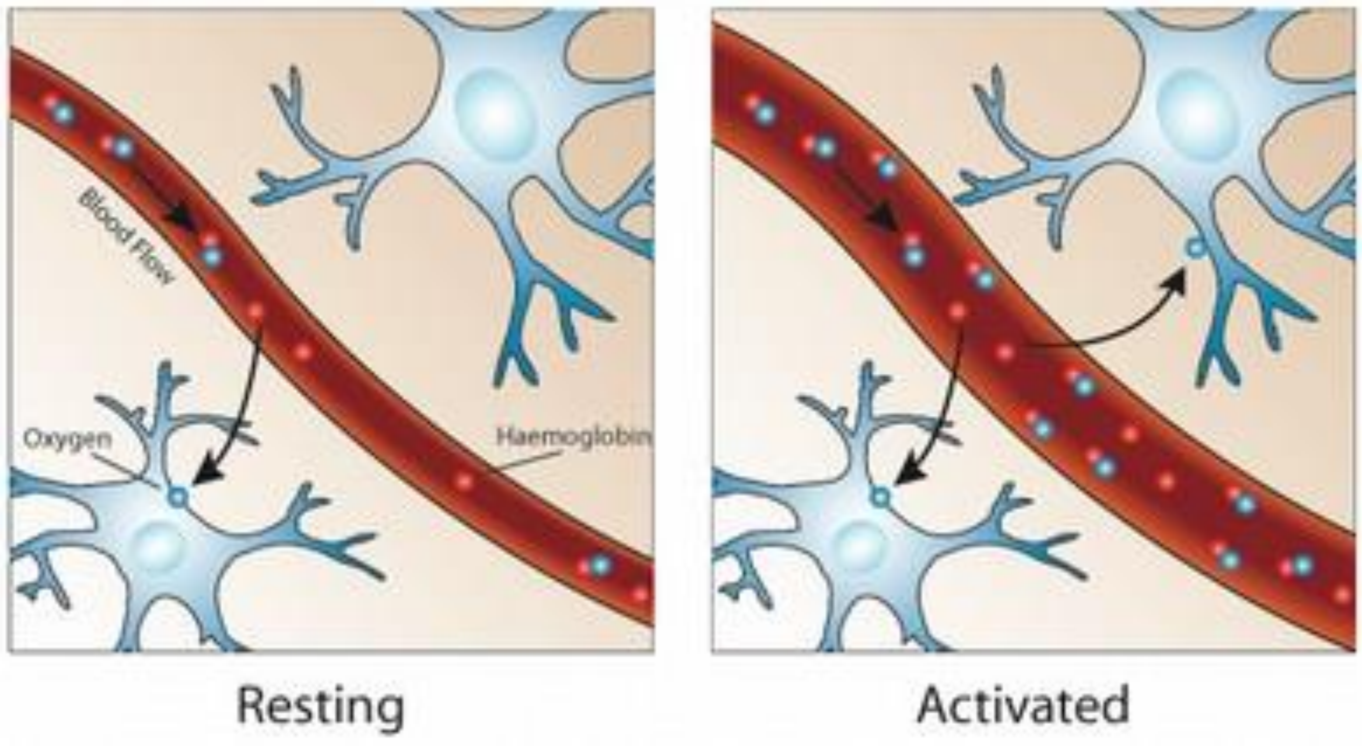
- Why does blood oxygenation affect the BOLD MRI signal?
- Hemoglobin contains iron to bind the oxygen
  - Oxyhemoglobin (oxHb) is diamagnetic
  - Deoxyhemoglobin (dxHb) is paramagnetic
- Higher dxHb concentration
  - → increased magnetic susceptibility
  - → increased magnetic field inhomogeneities
  - → decrease T_2^*
  - → lower BOLD MRI signal



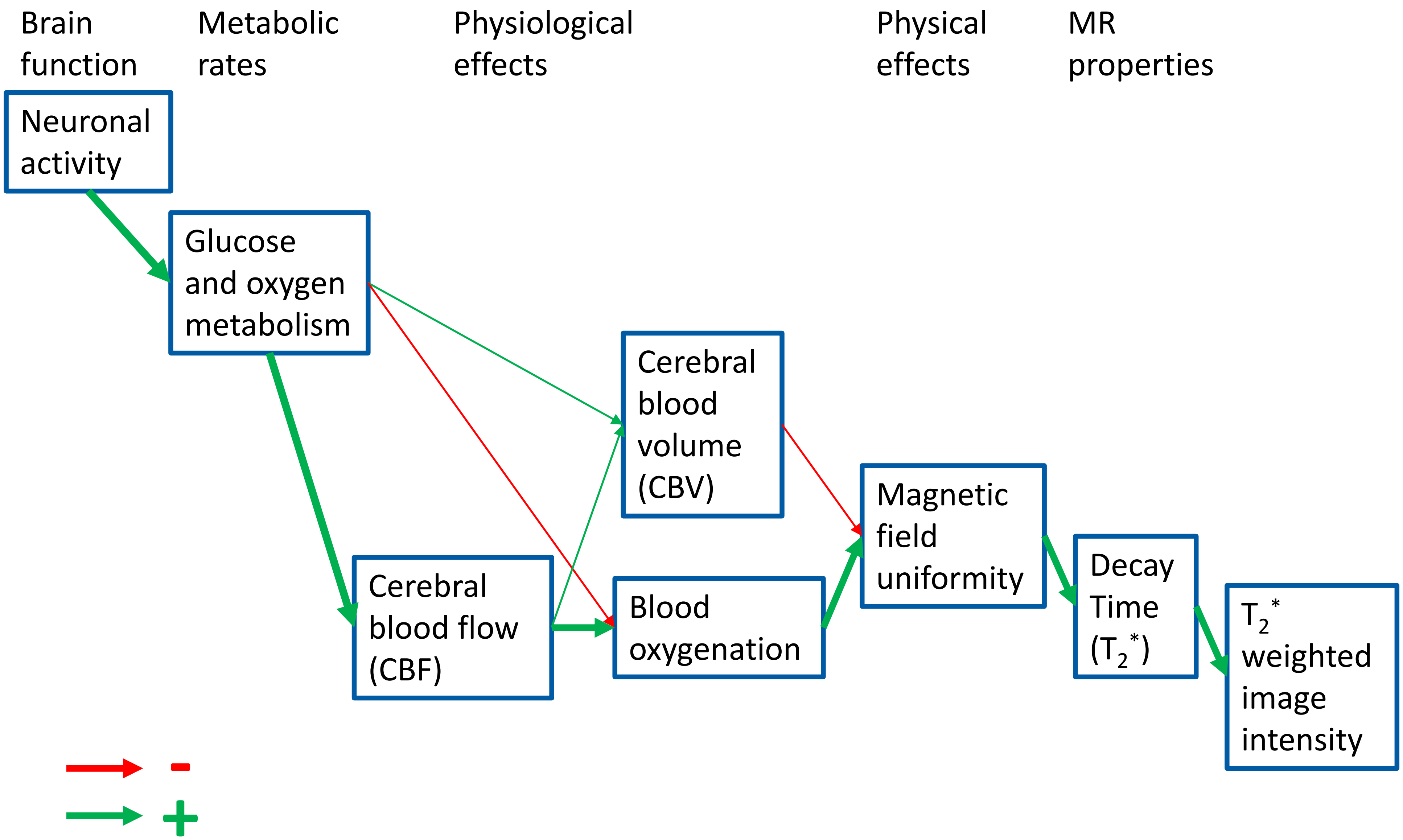


Hemodynamic response

- Neuronal activity
  - → Increased O_2 metabolism → Increased dxHb → lower BOLD signal?
  - → Neurovascular coupling → Vessel dilation → increased CBF
- → dxHb concentration decreases → higher BOLD signal

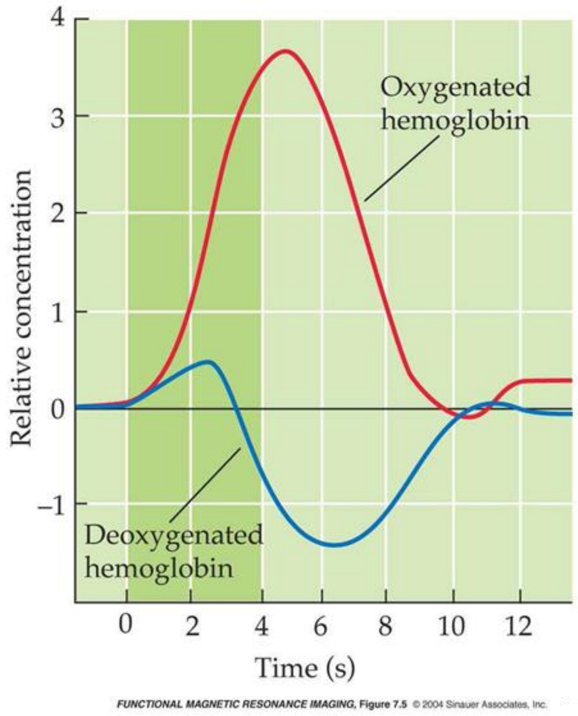


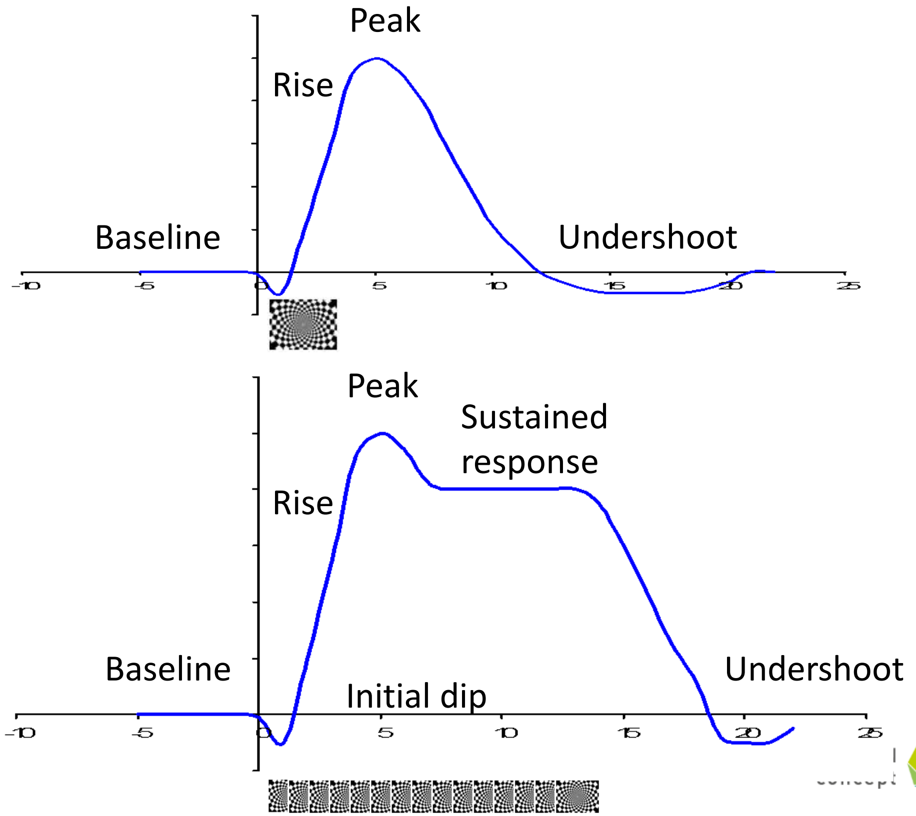
Hemodynamic response



Hemodynamic response

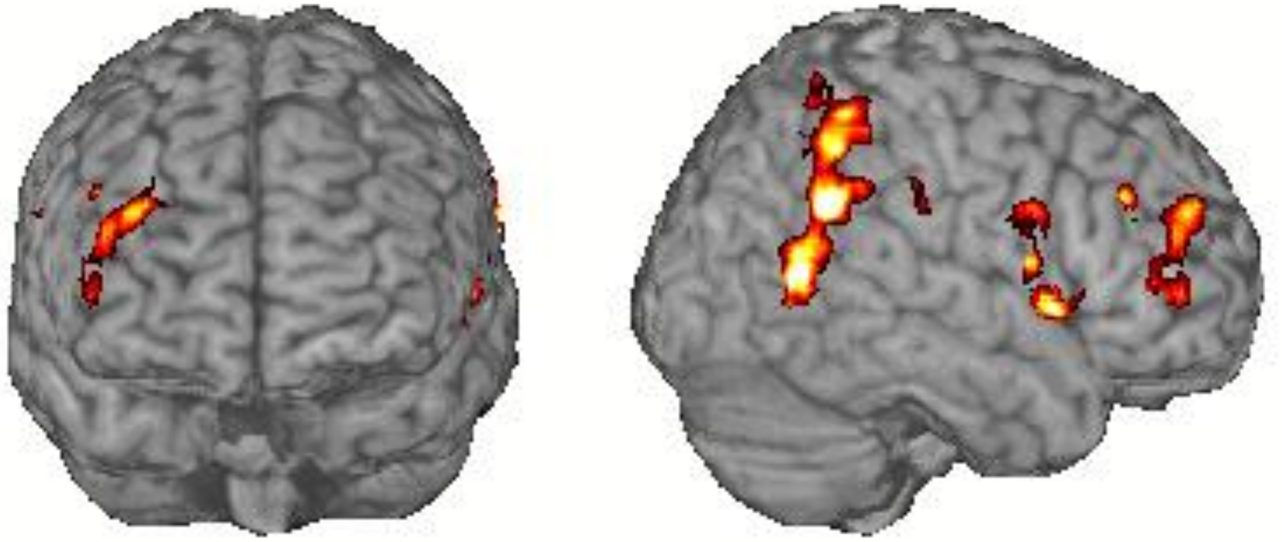
- Delay in BOLD signal change after activation
- Initial dip – increase in oxygen consumption before CBF increase
- Undershoot – CBF decrease faster than CBV





fMRI experimental design

- Goal: To detect what regions/voxels are active during a specific task



What sequence should be used for fMRI

- Neuronal response - 200-500ms
- Hemodynamic response – ~s

- Standard whole brain sequence
  - ~1mm spatial resolution
  - Time resolution ~mins

- Fast single shot sequences
  - Echo planar imaging (EPI)
  - 500ms-2s acquisition

fMRI task design

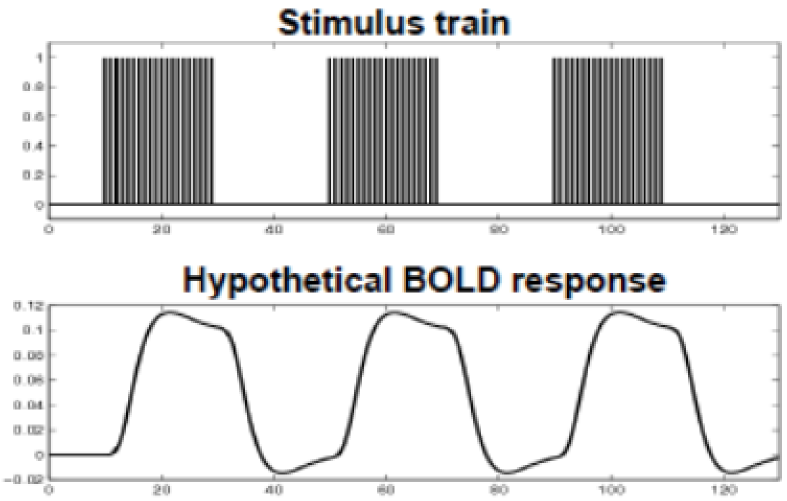
Create a desired cognitive state

Detect brain signals associated with that state

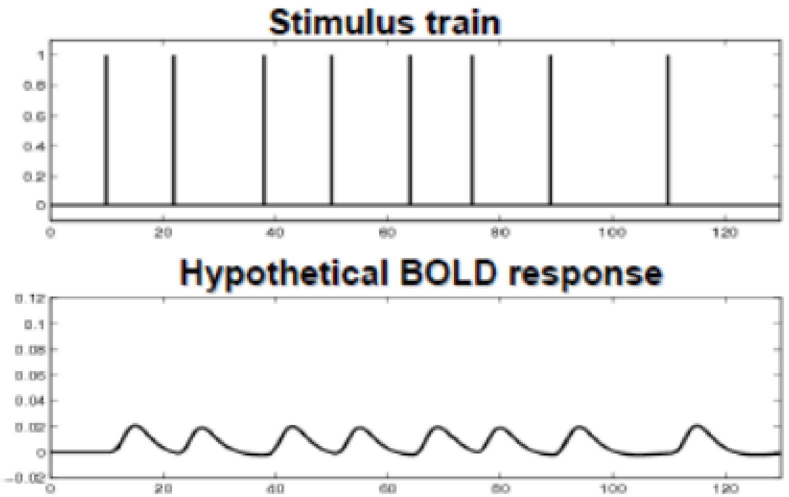
Types of fMRI designs

- Block-design
  - Detection power
- Event-related design
  - More flexible
- Mixed design

Block design

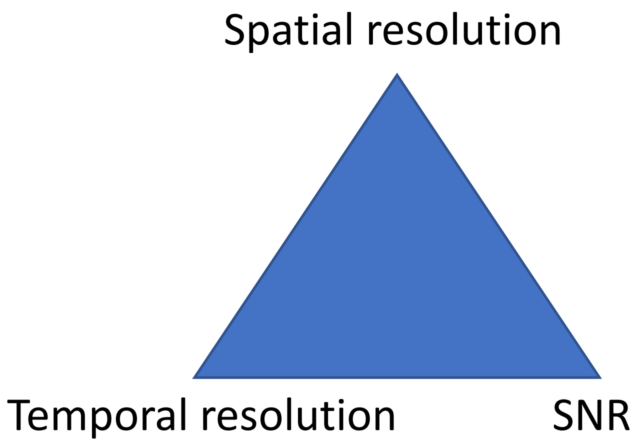


Event-related design



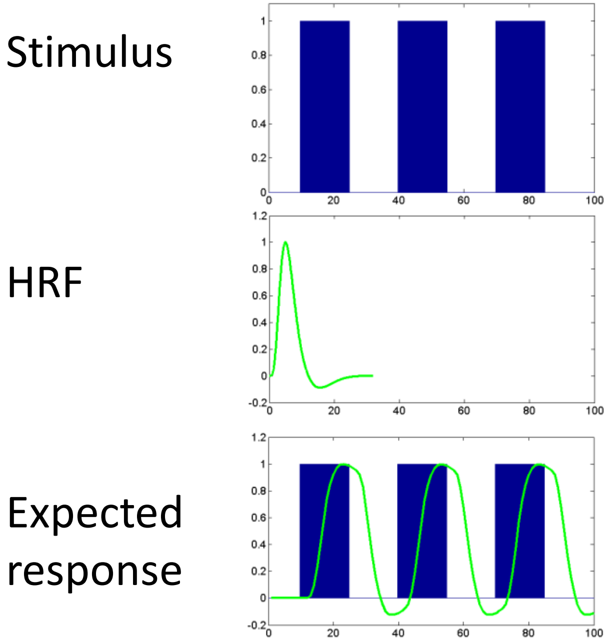
Readout in fMRI design

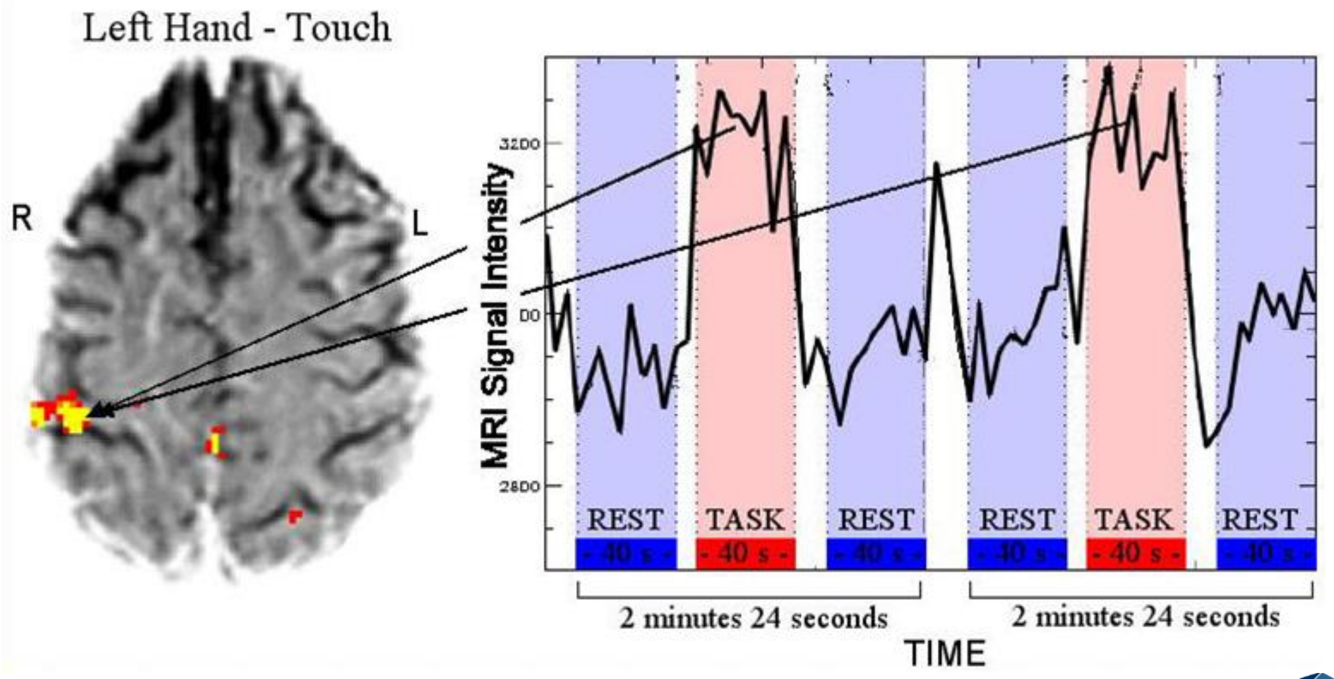
- ↑ spatial resolution:
  - ↓ time resolution
  - ↓ coverage (number of slices)
- ↑ temporal resolution requires:
  - ↓ spatial resolution
  - ↓ coverage (number of slices)
- ↑ SNR (signal-to-noise ratio):
  - ↓ Decreased spatial resolution
  - ↑ Increased scan time via averaging



fMRI study design

- BOLD signal – combination CBV, CBF, $CMRO_2$
- Observe change of BOLD signal as a reaction on a task or event





I have my data, now what?

- Data pre-processing

Structural MRI

functional MRI

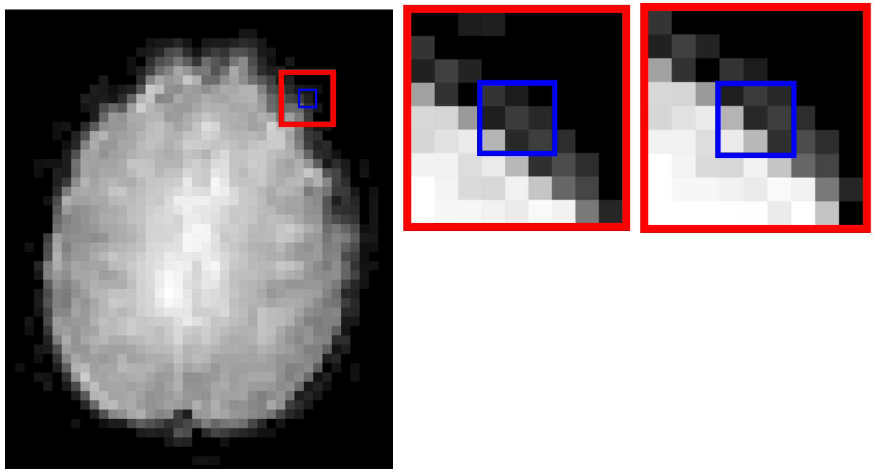
Why pre-process fMRI data

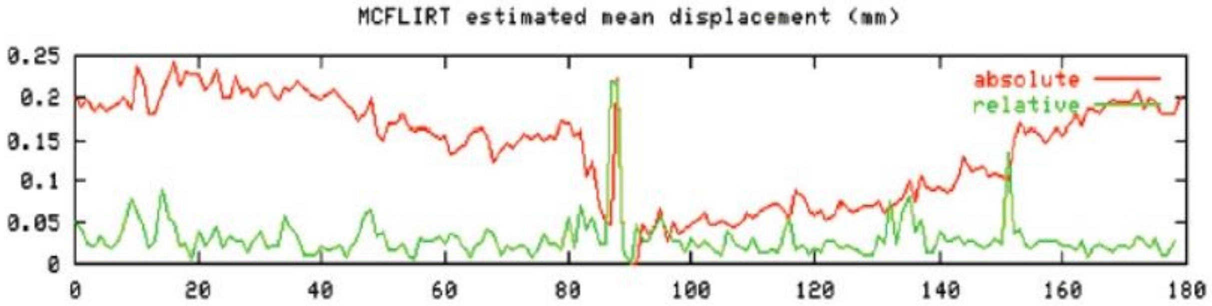
- Data are noisy (task-related change <5%)
- Subjects move
- Things change during the experiment

- Preprocessing:
  - → Increase signal to noise ratio
  - → Helps to meet assumptions for statistical analysis

Subject motion

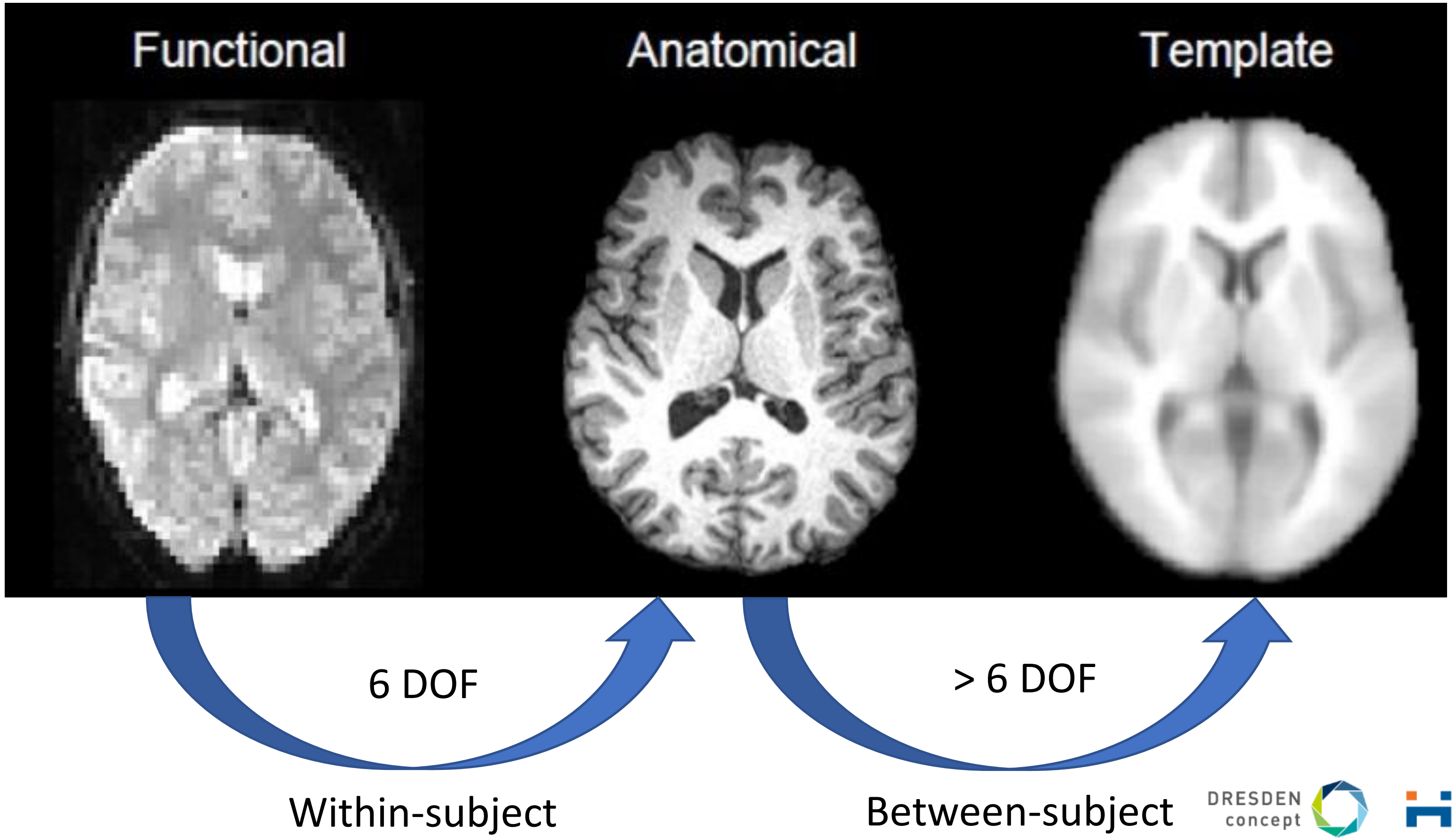
- Correct for head motion
  - 6 parameters rigid transformation
    - 3 rotations
    - 3 translations
- Lie very still
- Exclude subjects





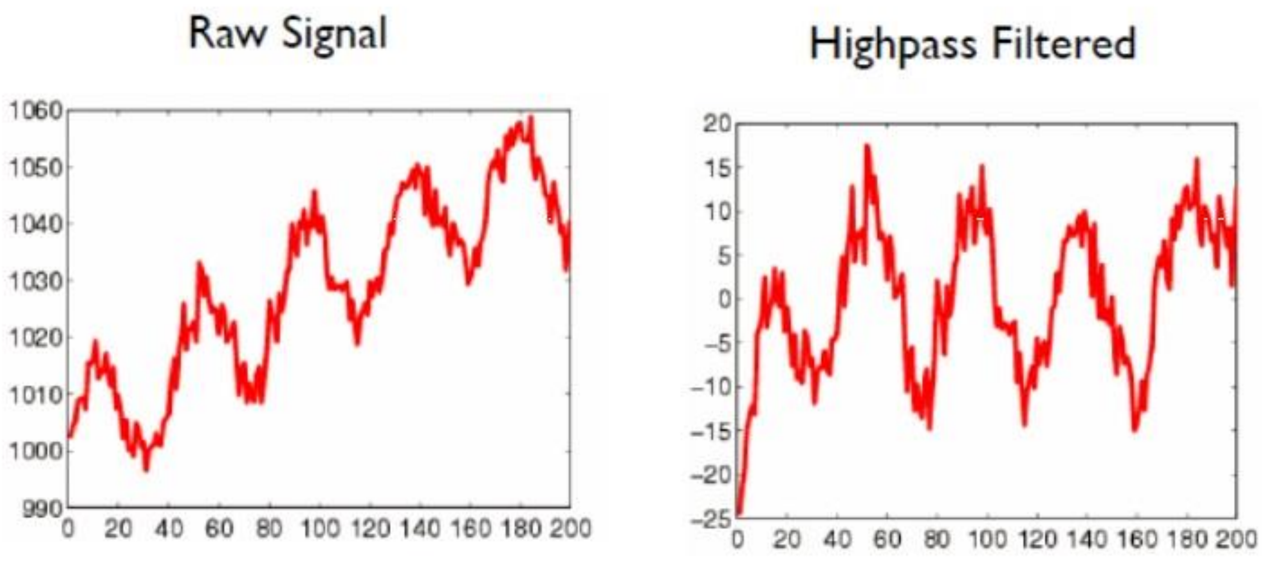
Spatial normalization

- Register functional vs. anatomical per subject
- Register to average brain (MNI)
- Larger population
  - Higher power



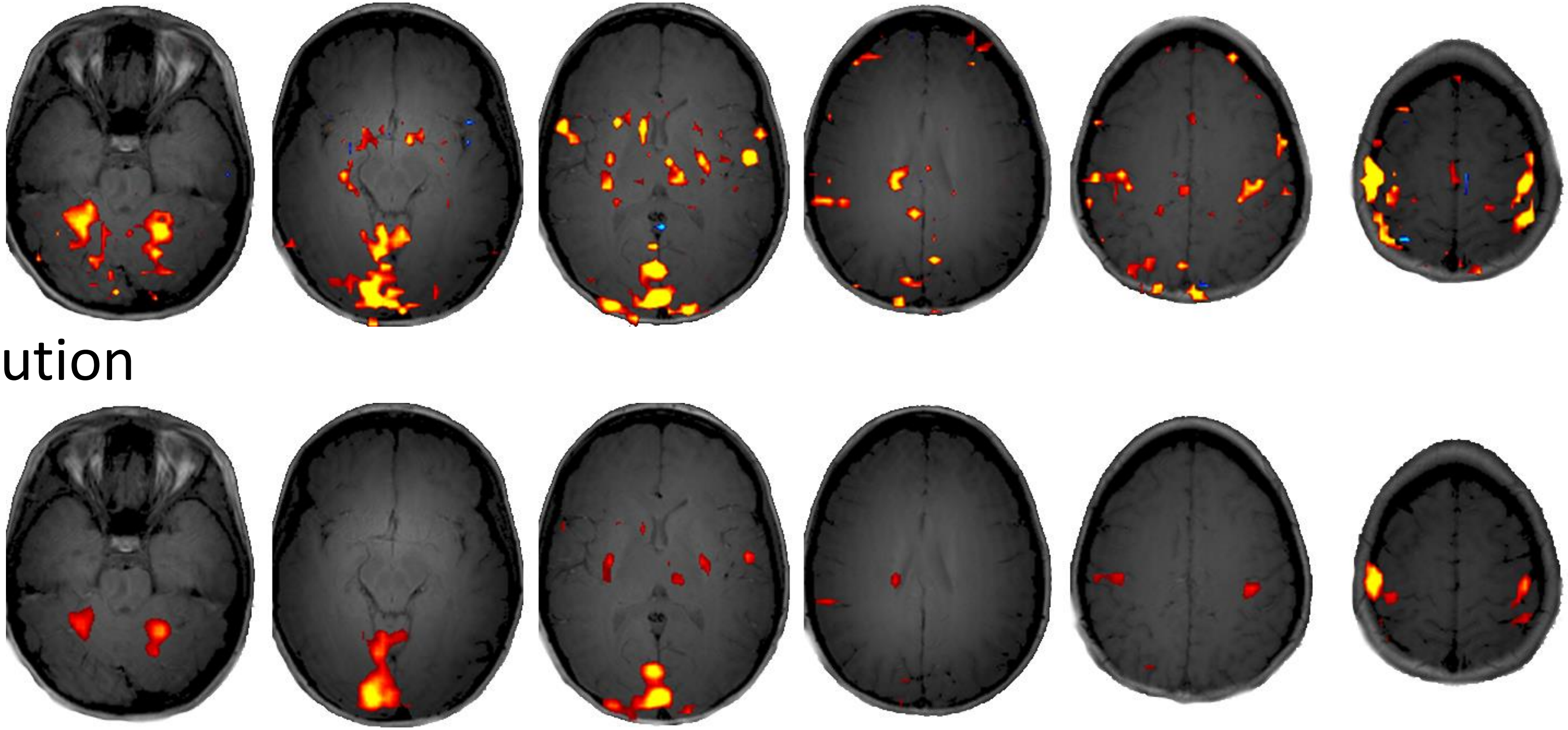
Temporal filtering

- Temporal drift from scanner
  - High-pass filter
- Physiological cycles (cardiac, respiratory)



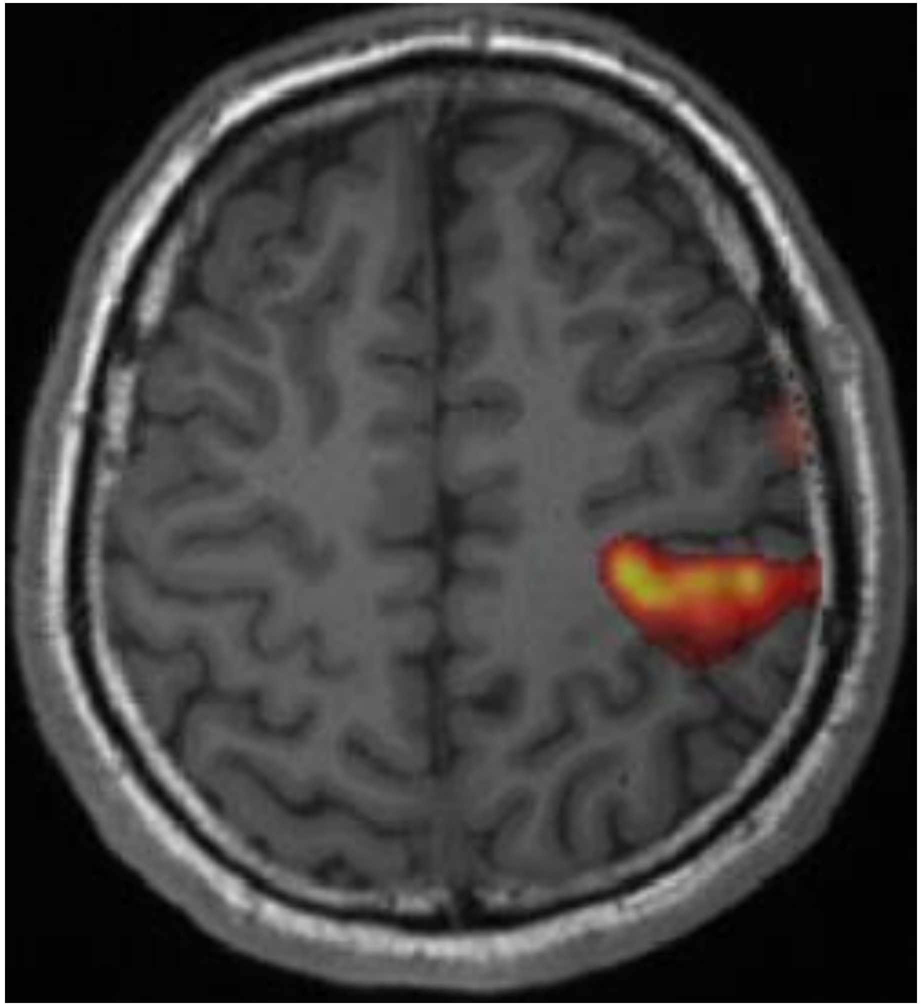
Spatial filtering

- Convolution with a Gaussian kernel
  - Improves
    - SNR
    - Specificity
  - Reduces
    - Spatial resolution
    - Sensitivity



Is there an activation?

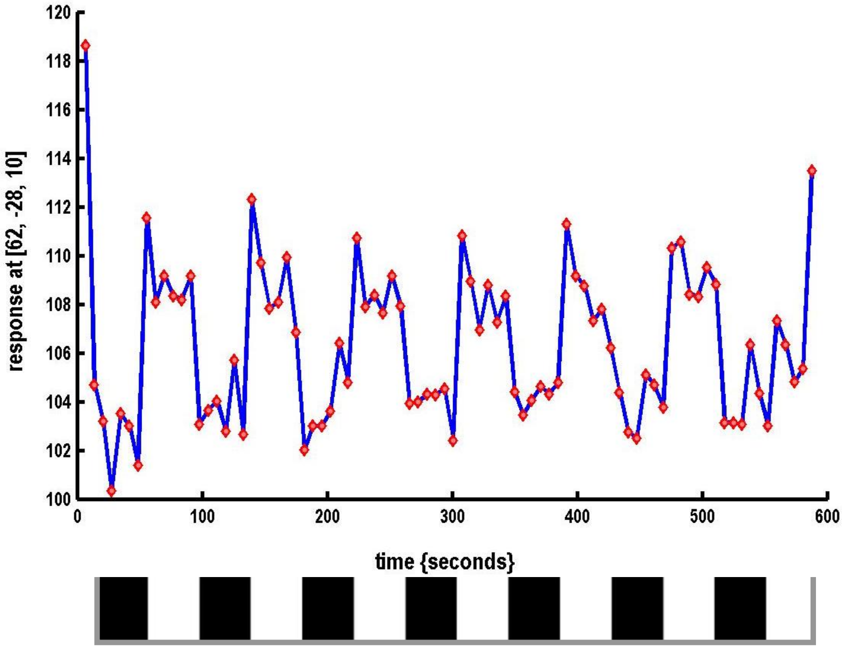
- A finger tapping example



A simple fMRI experiment

- Passive tapping vs rest (7 cycles)
- Blocks of 6 scans per cycle

- **Is there a change in the BOLD response between finger tapping and rest?**

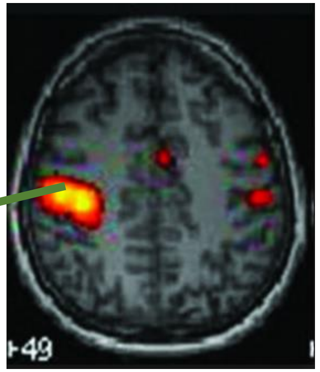


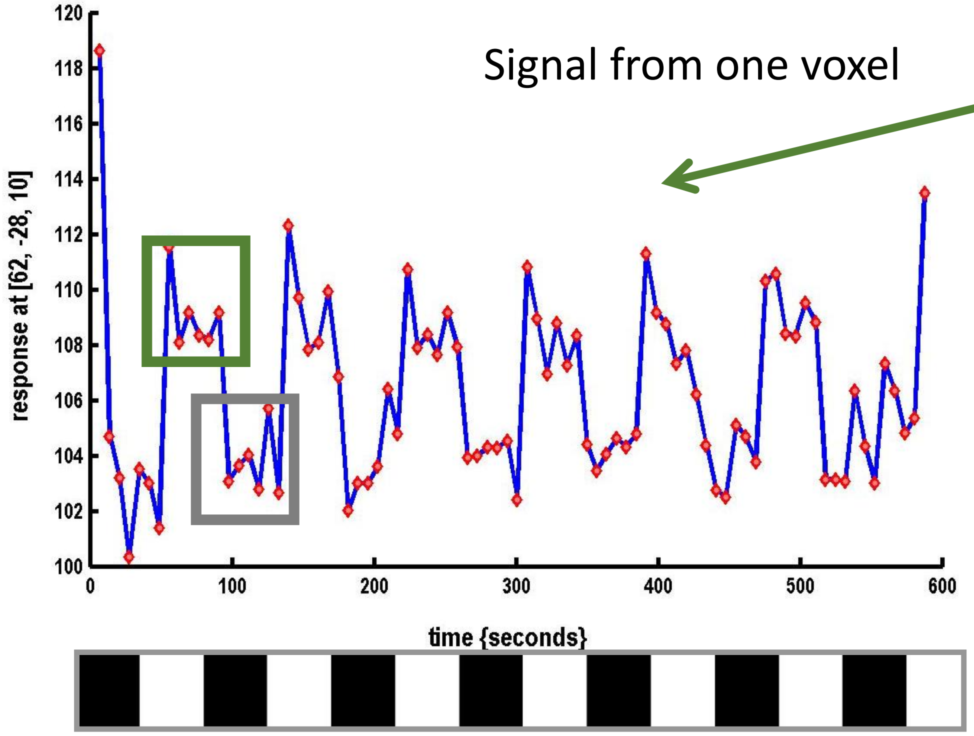
Stimulus function

A simple fMRI experiment

- Activation → compare:
  - Magnitude of response
  - Measurement noise
- T-test

Signal from one voxel





Stimulus function

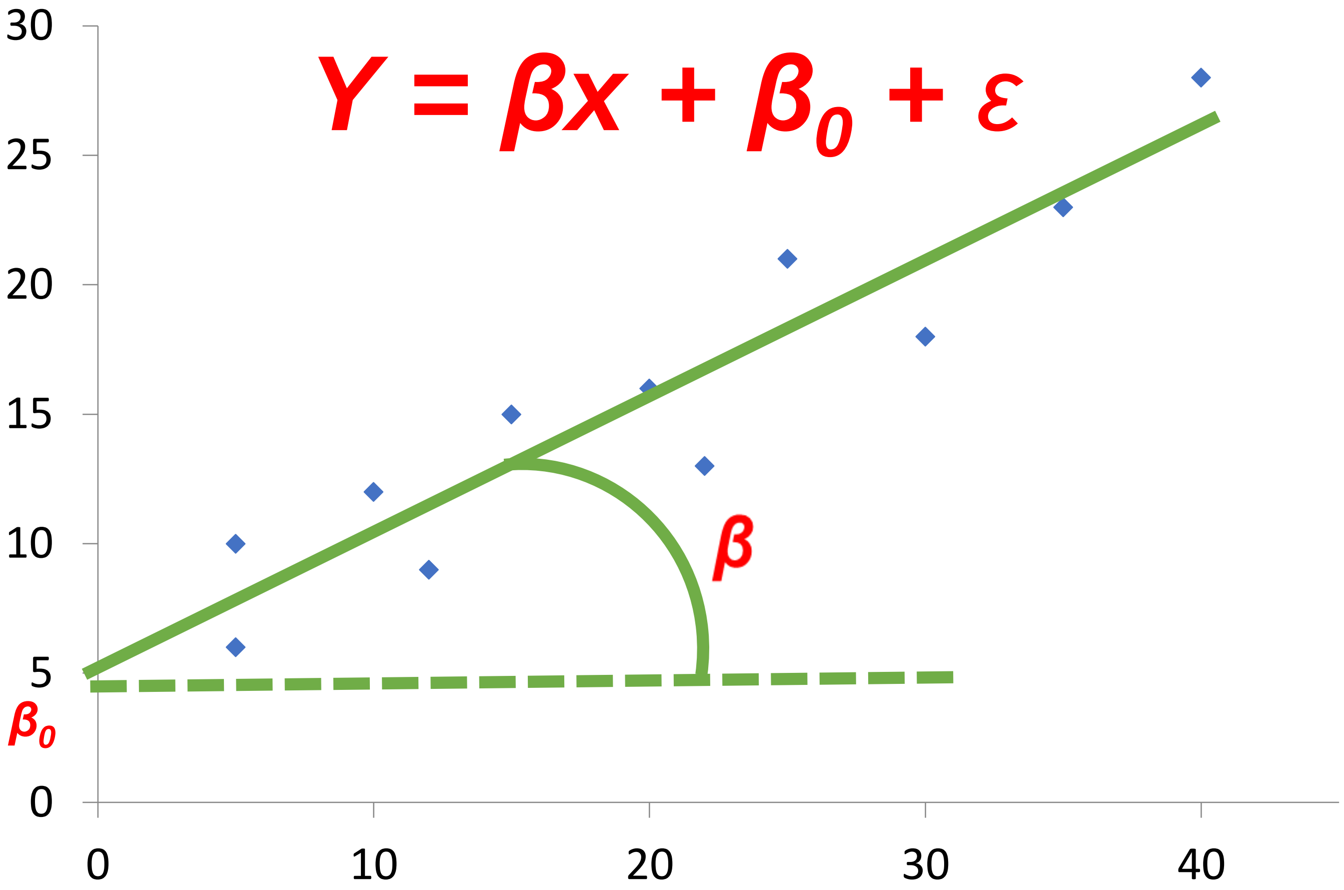
$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

$$s = \sqrt{\frac{\sum(x - \bar{x})^2}{n - 1}}$$

Compare tap in green vs rest

General linear model

- Experimental data (Y) - linear combination (β) of different model factors (x), along with uncorrelated noise (ε)
- Testing slope (β) against null hypothesis



General linear model for fMRI

$$Y = X * \beta + \varepsilon$$

timepoints

$$\begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{bmatrix} = \begin{bmatrix} 1 & X_{11} & \cdots & X_{1p} \\ 1 & X_{21} & \cdots & X_{2p} \\ \vdots & \vdots & & \vdots \\ 1 & X_{np} & \cdots & X_{np} \end{bmatrix} \times \begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{bmatrix} + \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{bmatrix}$$

Observed data (known)
BOLD signal in a single voxel

Design matrix (known)
Components that can explain the data

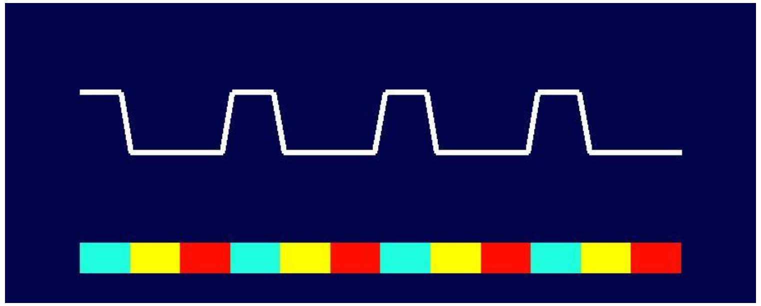
Model parameters (unknown)
Contribution of each component of X to Y

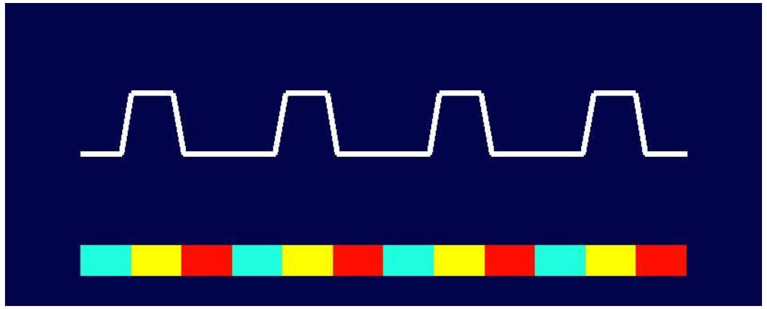
Error
Difference between the observed data and model prediction

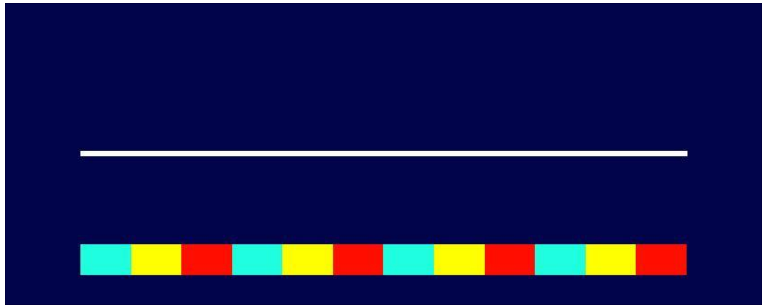
GLM example: Design

- Block design, language task
  - Word generation (noun presented, verb generated)
  - Word shadowing (verb presented, thinking on it)
  - Rest

- Design matrix:

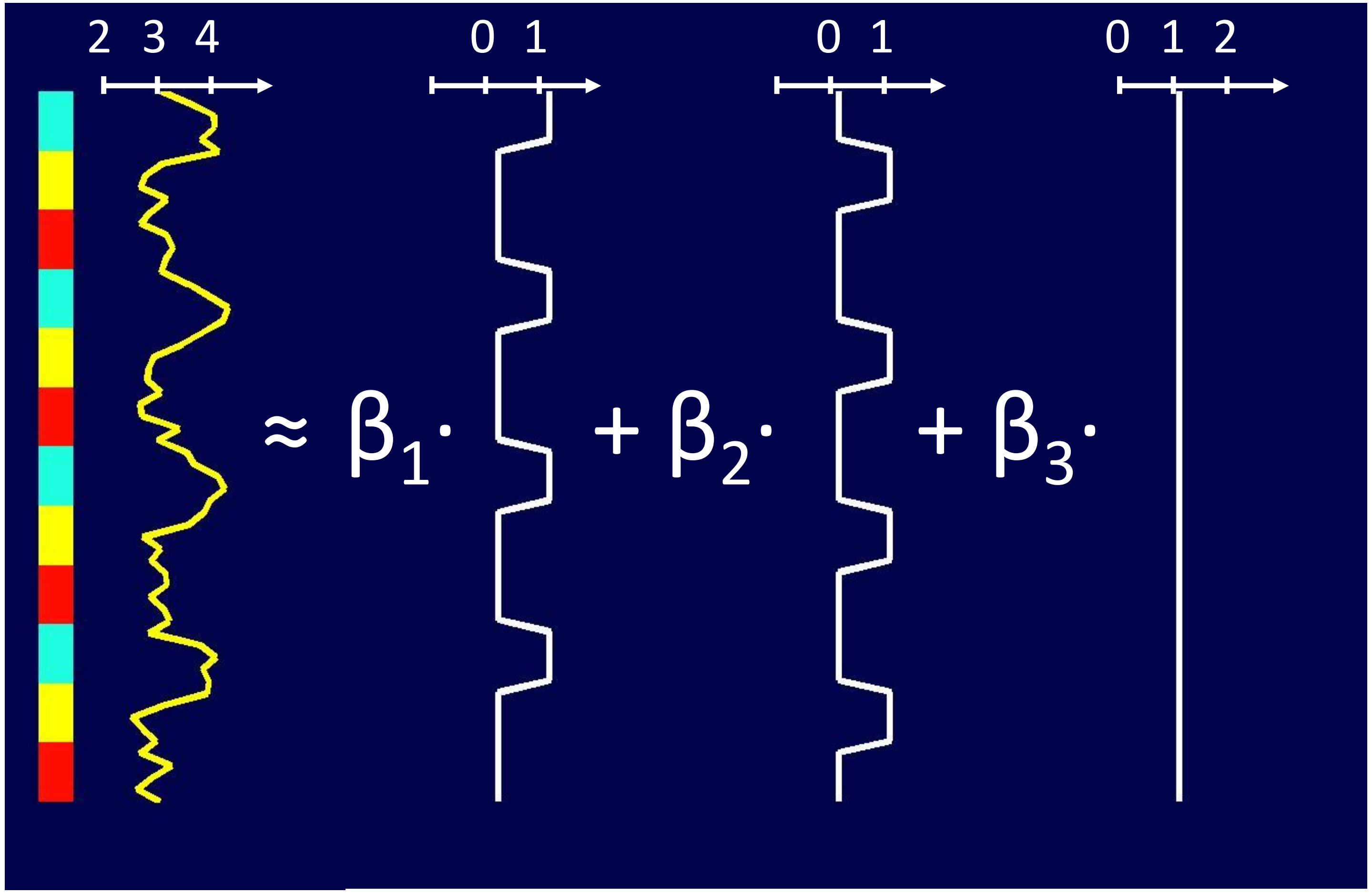

generation


shadowing


rest

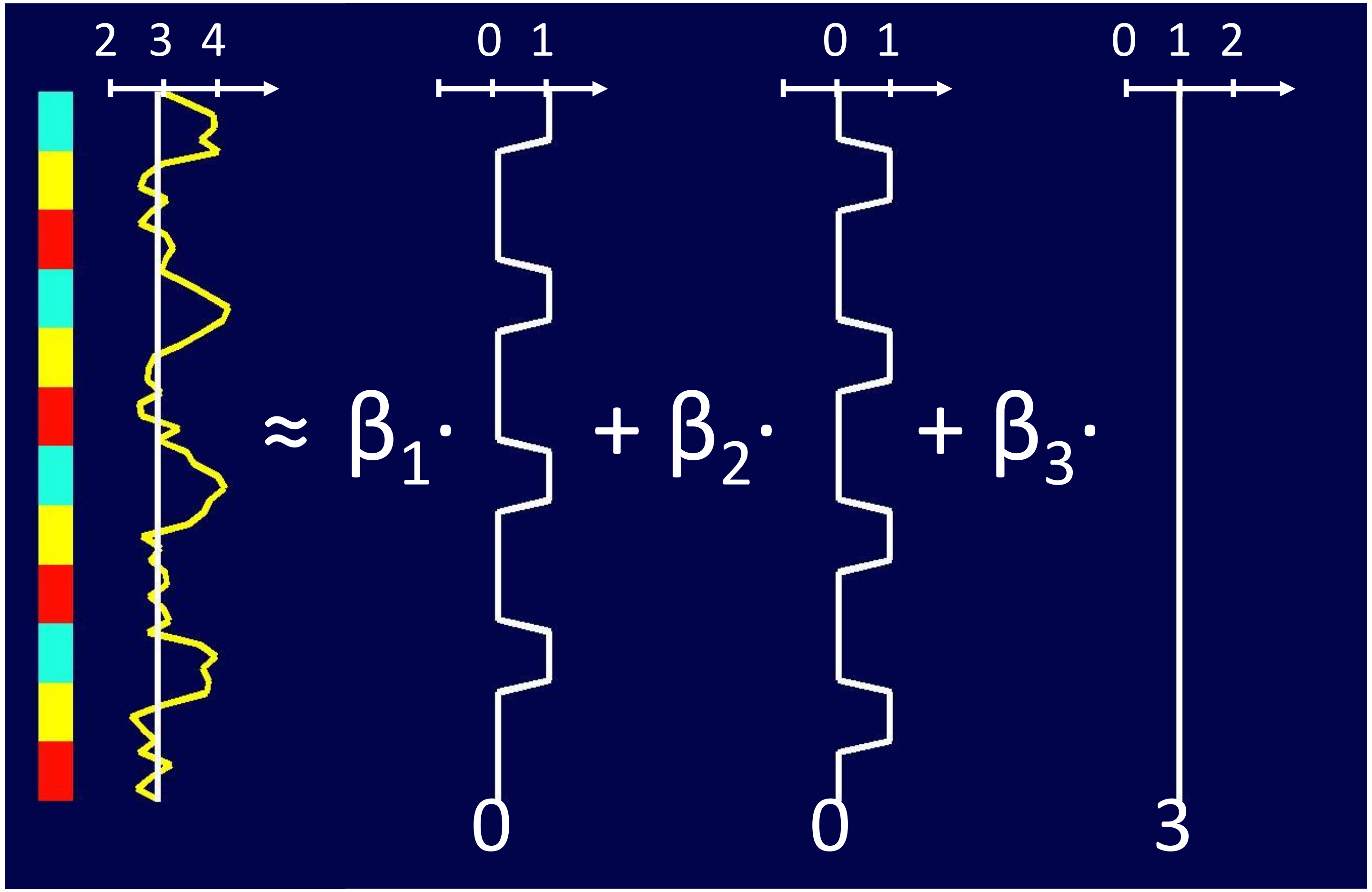
GLM example: Estimating betas

- Fitting model to data – ordinary least squares – minimizing $\varepsilon^T\varepsilon$
- $y = X\beta + \varepsilon$
- $\hat{\beta} = (X^TX)^{-1}X^Ty$



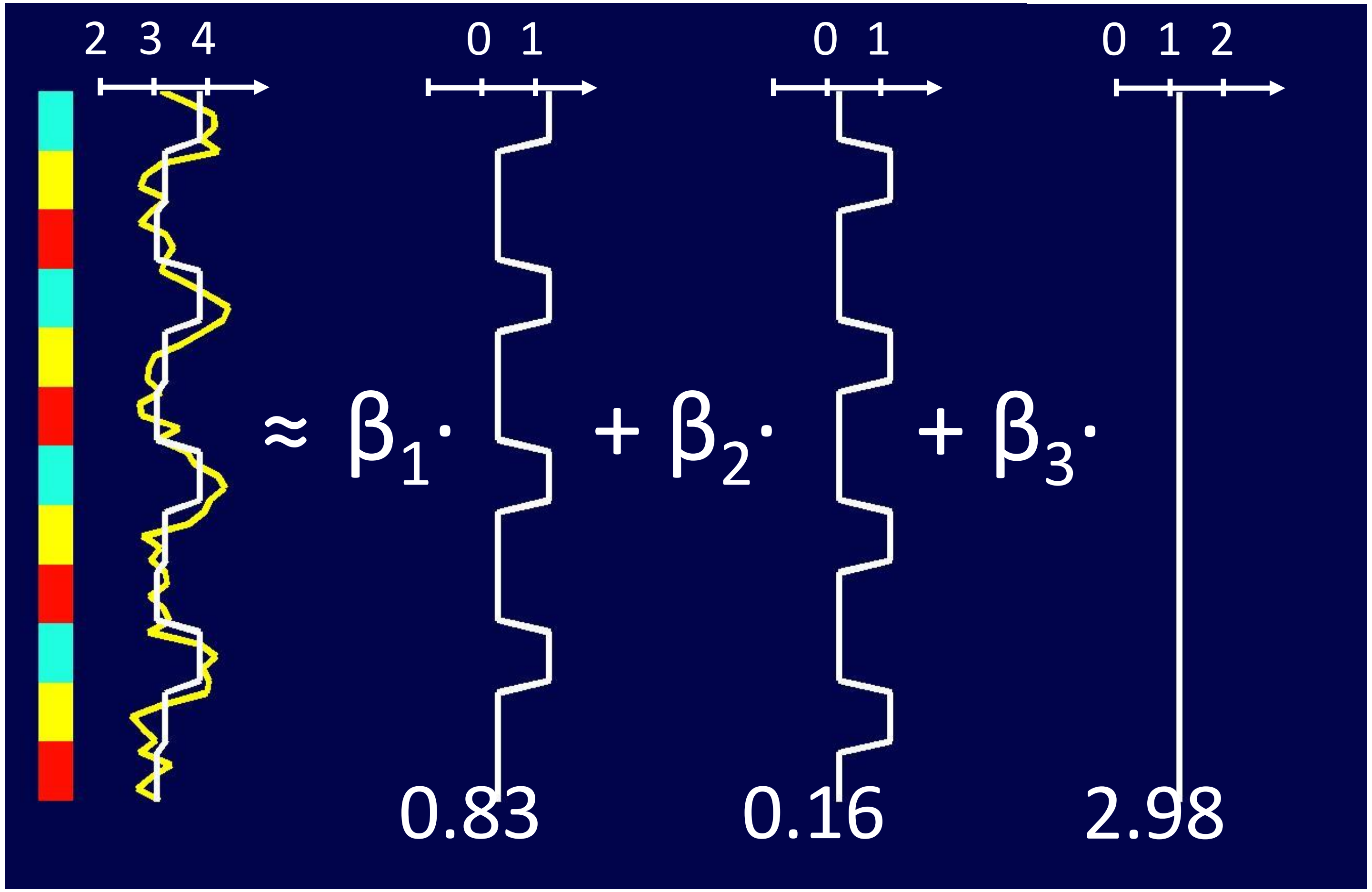
GLM example: Estimating betas

- Suboptimal fit
- $\beta = [0,0,3]$



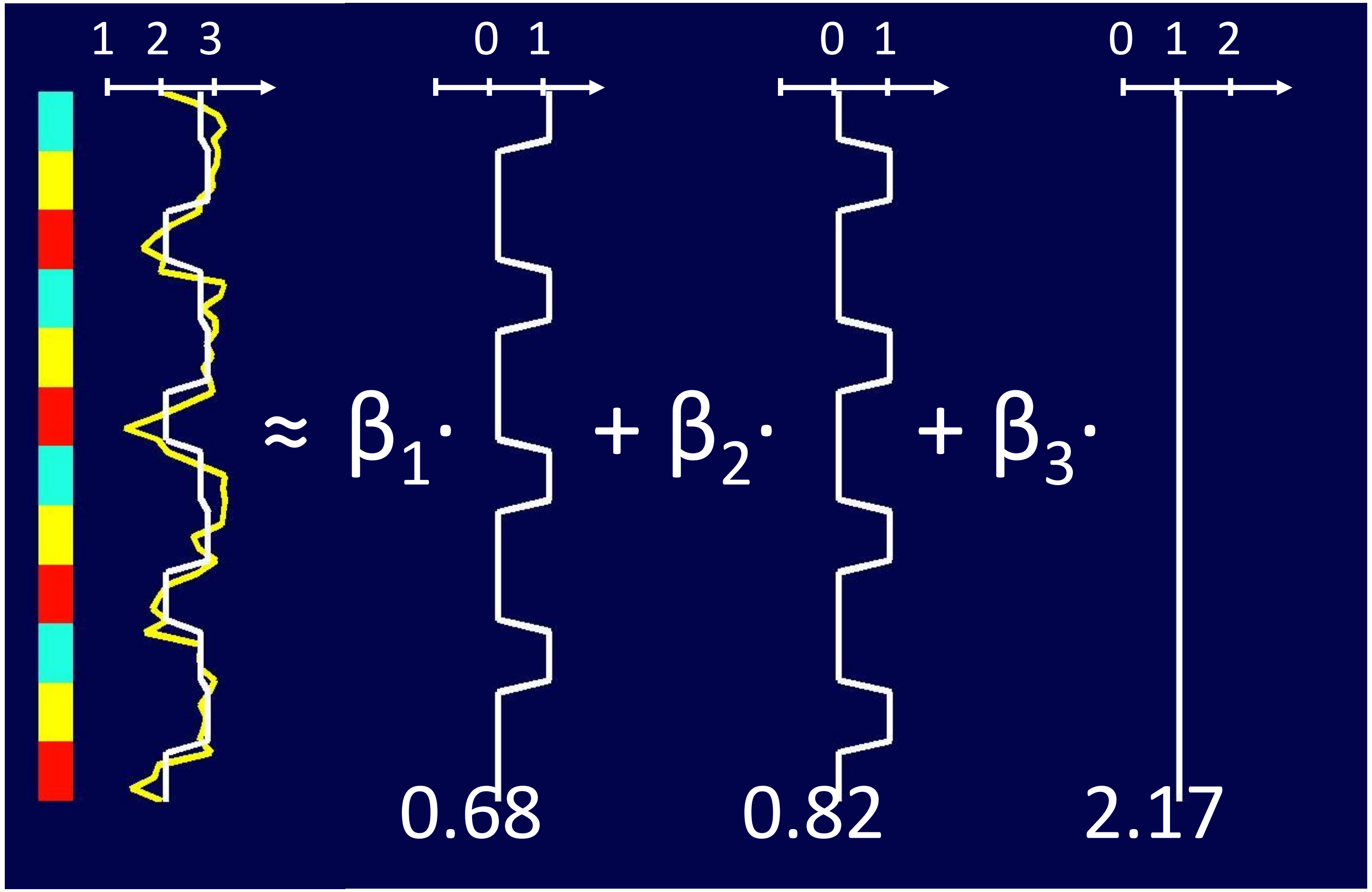
GLM example: Estimating betas

- Active in word generation $\beta = [0.83, 0.16, 2.98]$



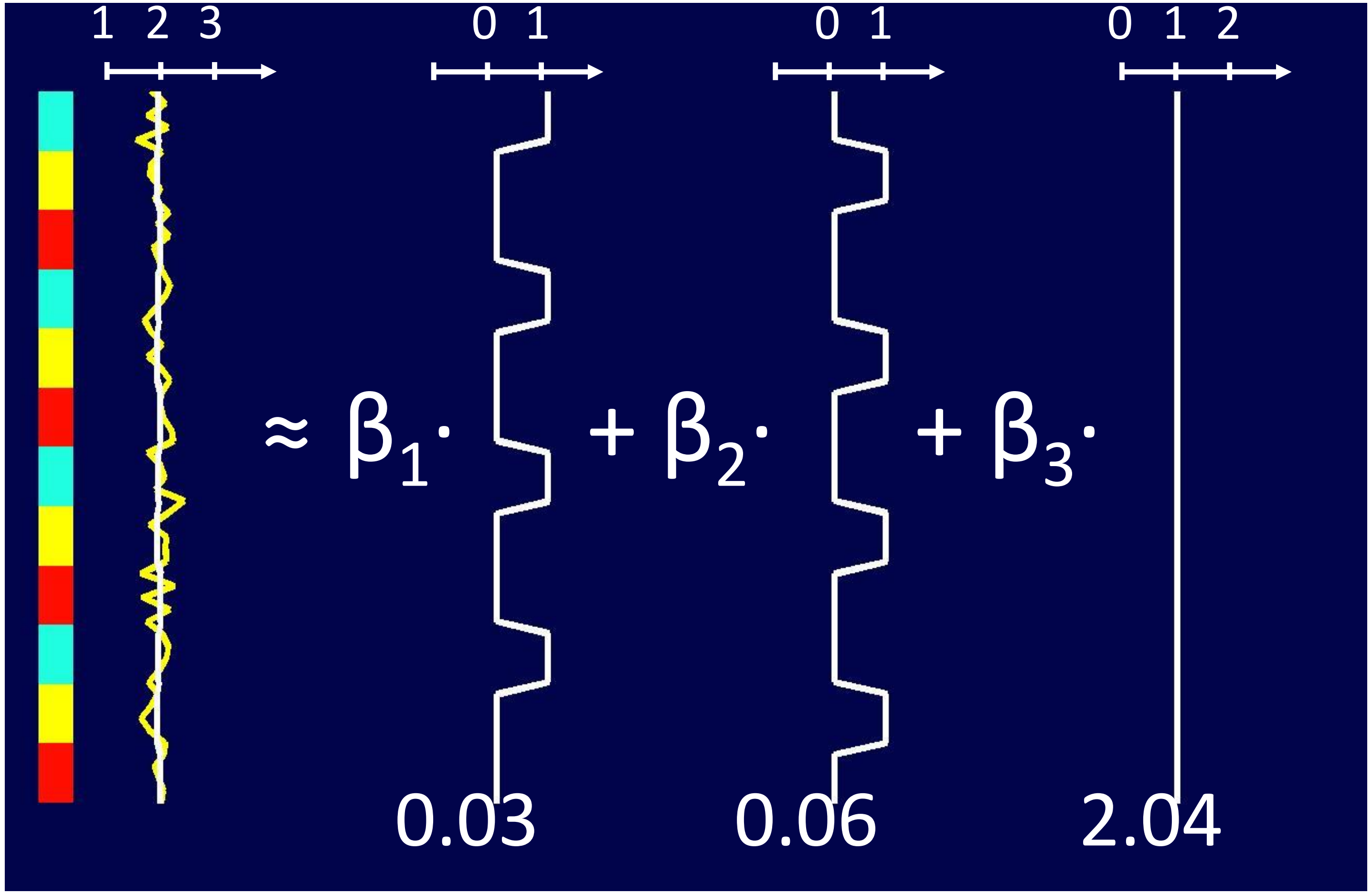
GLM example: Estimating betas

- Active in word generation and shadowing β=[0.68, 0.82, 2.17]



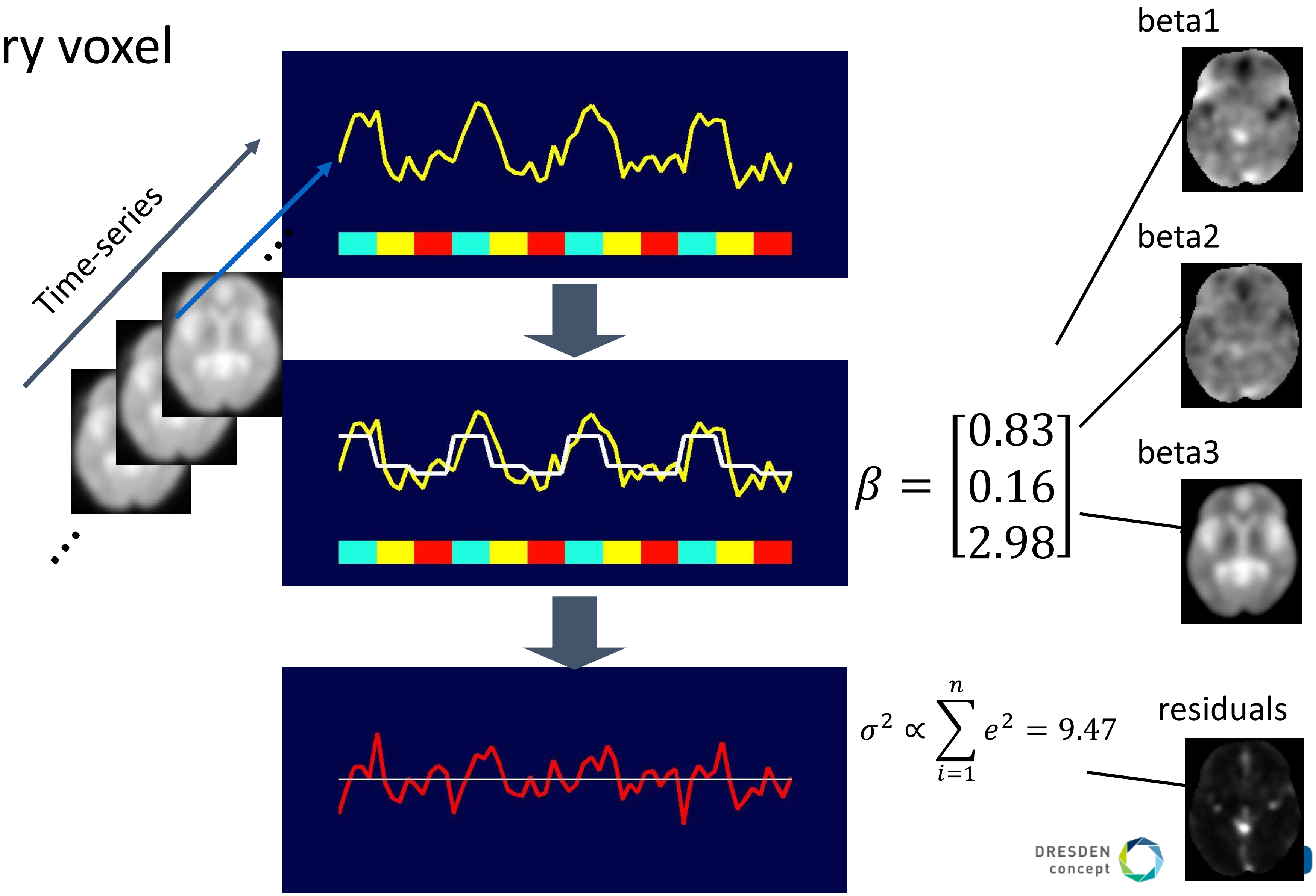
GLM example: Estimating betas

- Voxel not active β=[0.03, 0.06, 2.04]



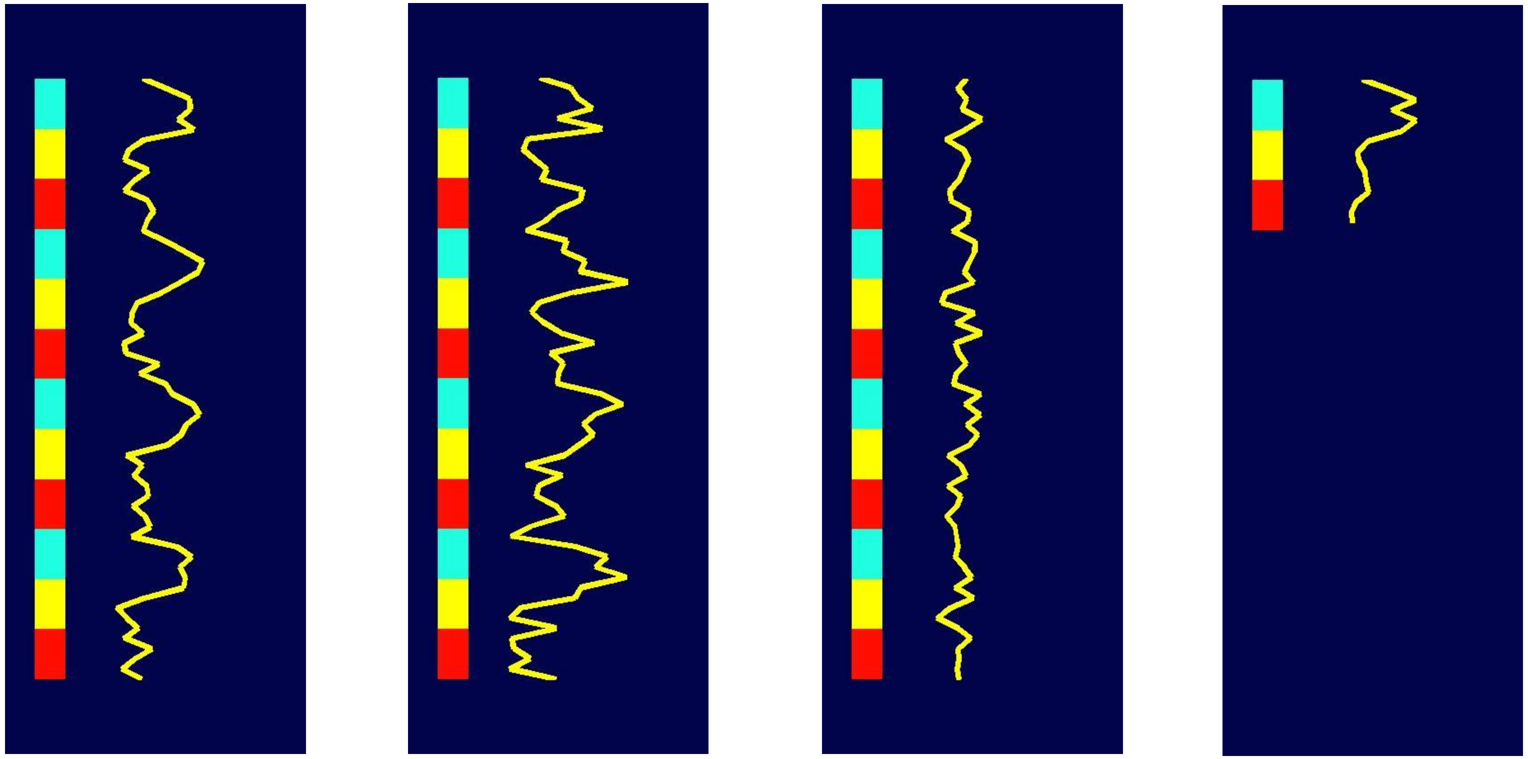
GLM example: Voxelwise fit

- Calculate fit for every voxel



GLM example: Significance

- Which of these series should we trust?
- Noise, effect size, number of measurements



$\beta_1=1$
$\sigma=0.2$
$n=60$

$\beta_1=1$
$\sigma=0.5$
$n=60$

$\beta_1=0.3$
$\sigma=0.2$
$n=60$

$\beta_1=1$
$\sigma=0.2$
$n=15$

GLM example: Contrast

- Weights *c* of model parameters β
  - $c = [c_1\ c_2\ c_3]$ for $\beta = [\beta_1\ \beta_2\ \beta_3]$
- c = [1 0 0]
  - Active in word generating
- c = [1 -1 0]
  - More active in generating than in shadowing

GLM example: Hypothesis testing

- Null hypothesis (H_0) – there is no effect
- Alternative hypothesis (H_a) – we find the effect in data
- Reject the null hypothesis → activation

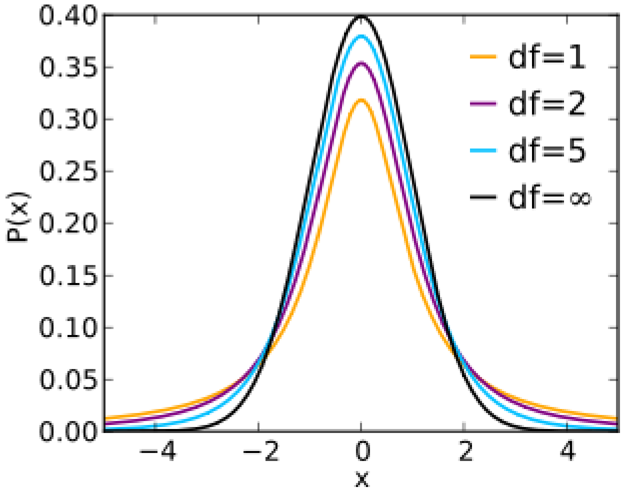
$$c^T\beta = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} 0.83 \\ 0.16 \\ 2.98 \end{bmatrix} = 0.83$$

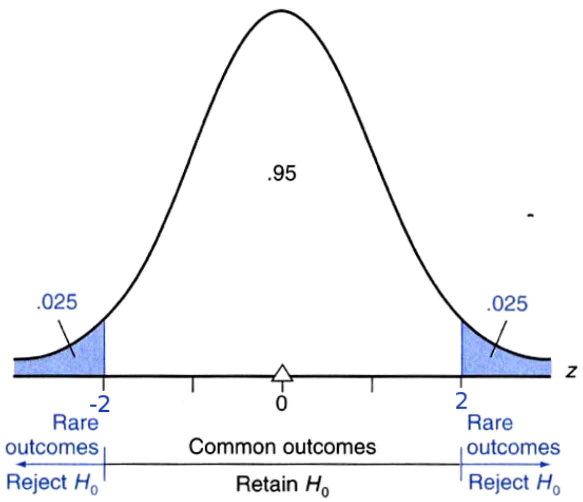
$$H_0: \quad c^T\beta = 0$$

$$H_a: \quad c^T\beta \neq 0$$

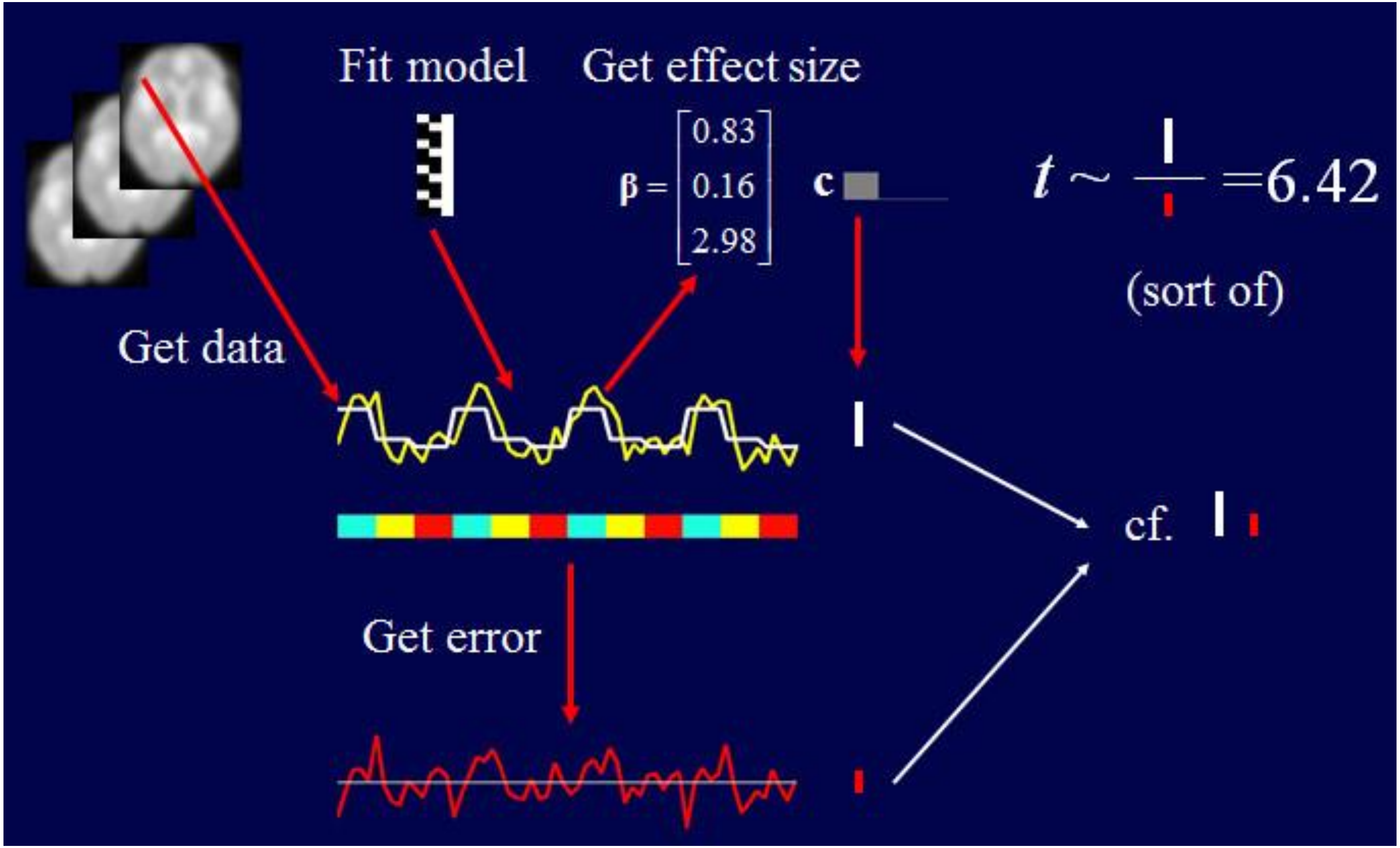
GLM example: t-contrast

- $t = \frac{c^T \beta}{\sigma \sqrt{c^T (X^T X)^{-1} c}}$
- follows Student's distribution (N-1 degrees of freedom)
- Probability that the null hypothesis is true
- p-value <0.05 we reject the null hypothesis



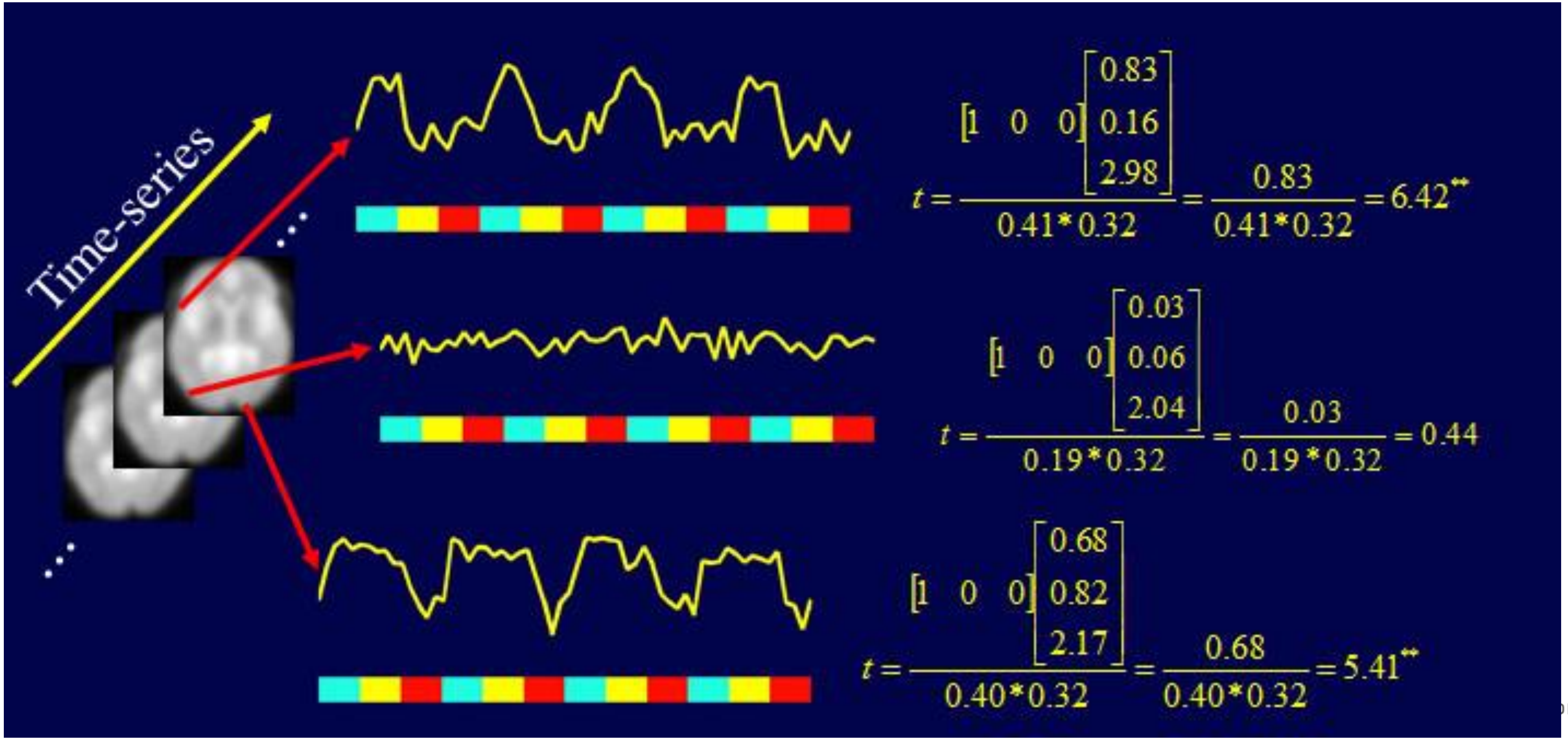


GLM example: t-contrast example



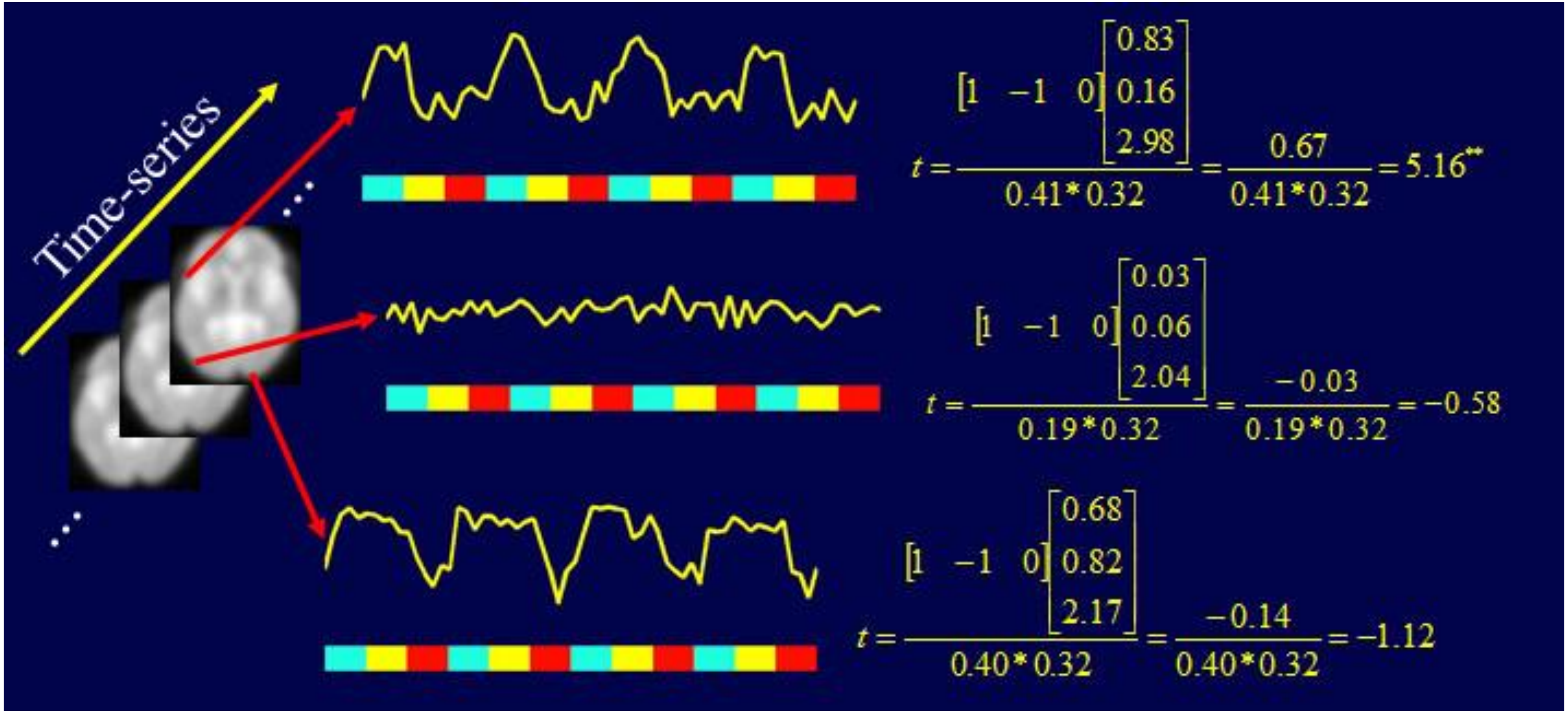
GLM example: t-contrast example

- Voxels active in word generation
- c=[1 0 0]



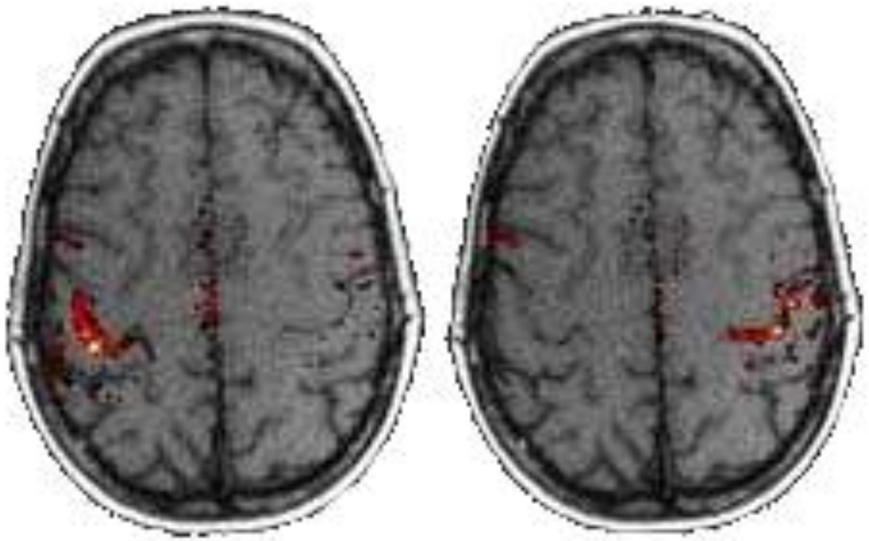
GLM example: t-contrast example

- Voxel active more in generating than shadowing
- c=[1 -1 0]



fMRI applications

- Surgery planning



Volunteer

Patient with glioblastoma

DRESDEN concept HZDR

fMRI application

- Addiction
  - Understanding of brain effects of long-term use
  - Development of treatment strategies for abusers
- Pharmacological studies
  - Effects on cognition
- Neuropsychological disorders
  - Disease markers may help in treatment
- Aging and brain development
  - Normal and pathological changes

fMRI summary

- Simple and non-invasive
- Very good time and spatial resolution
- Wide range of applications

- Problems with noise
- Limited clinical use