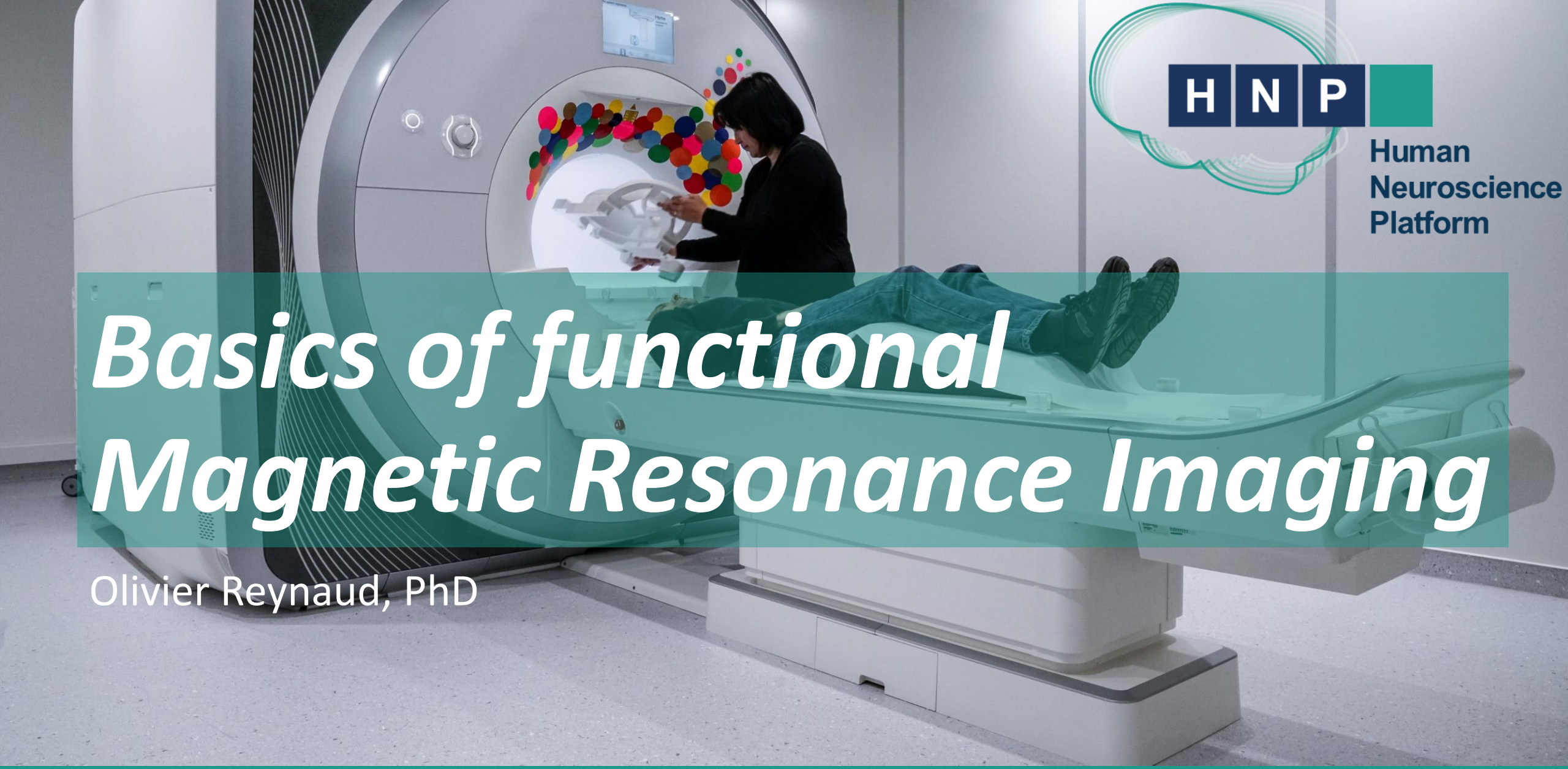


Basics of functional Magnetic Resonance Imaging

Olivier Reynaud, PhD

Advanced Biomedical Imaging Methods and Instrumentation course
EPFL, November 2021

Outline

0. MR signal & k-space

1. The BOLD contrast

- Biophysical mechanisms
- Spatiotemporal dynamics

2. fMRI data acquisition

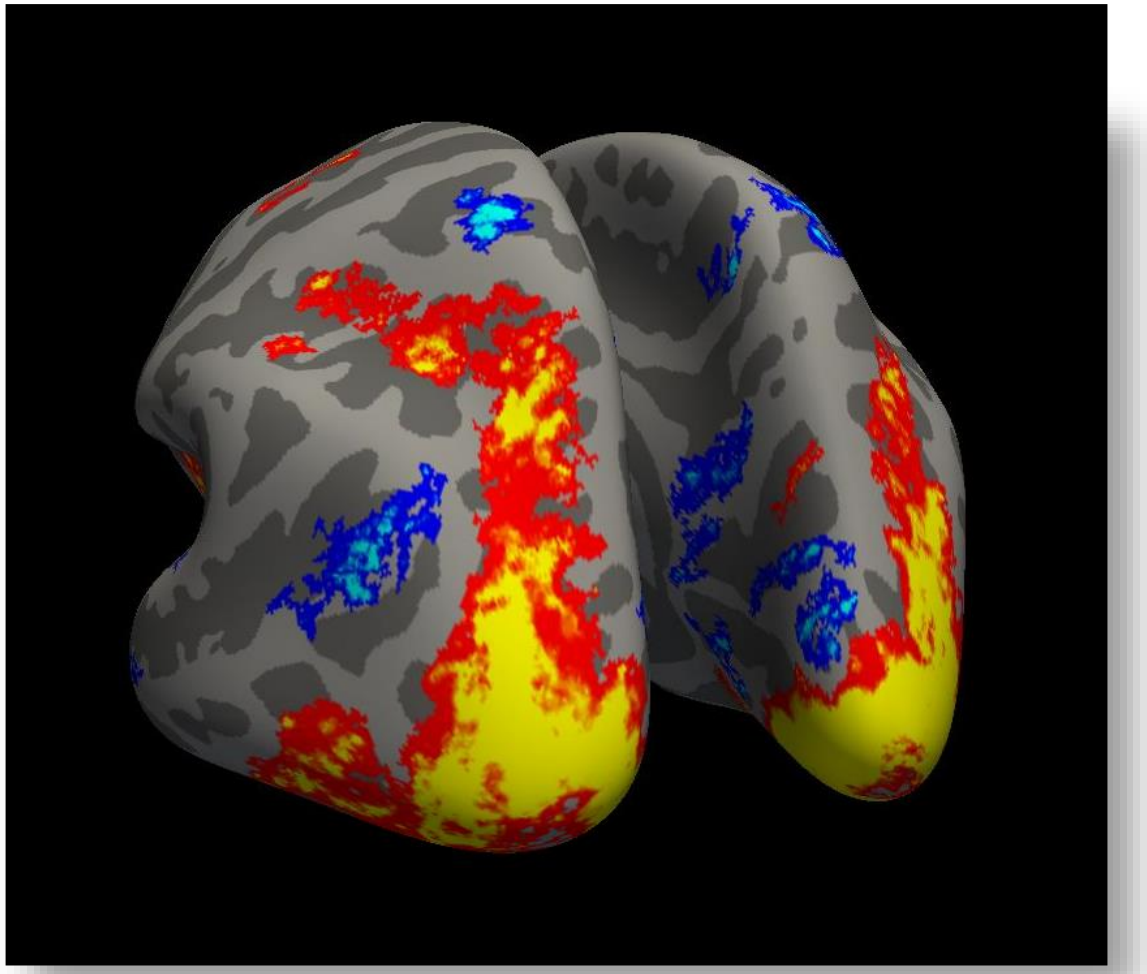
- Image acquisition
- Dependence on field strength

3. Non-BOLD fMRI

- ASL – measuring blood flow
- VASO – measuring blood volume

4. fMRI data analysis

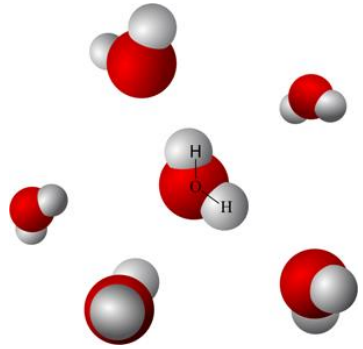
- Pre-processing
- Analysis: event-related activity
- Analysis: spontaneous activity

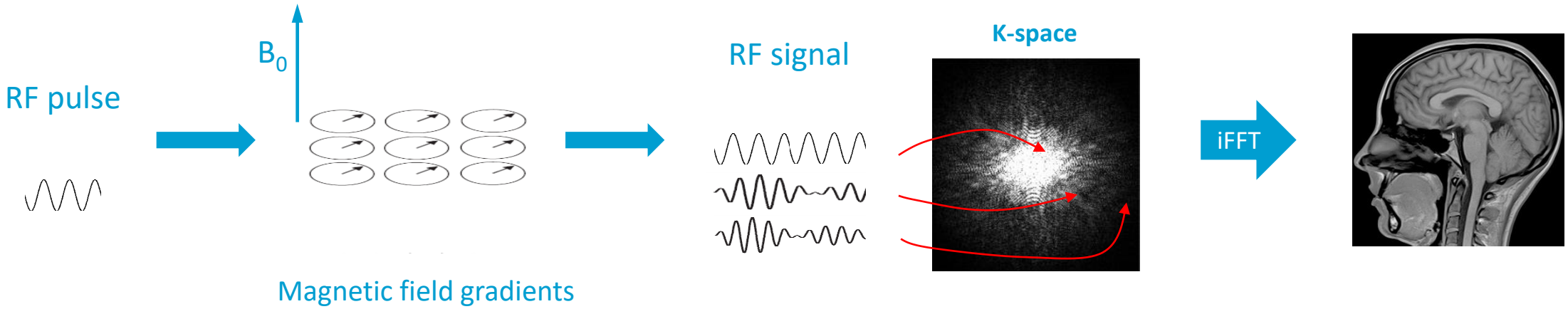


0. MR signal & k-space

Magnetic resonance imaging

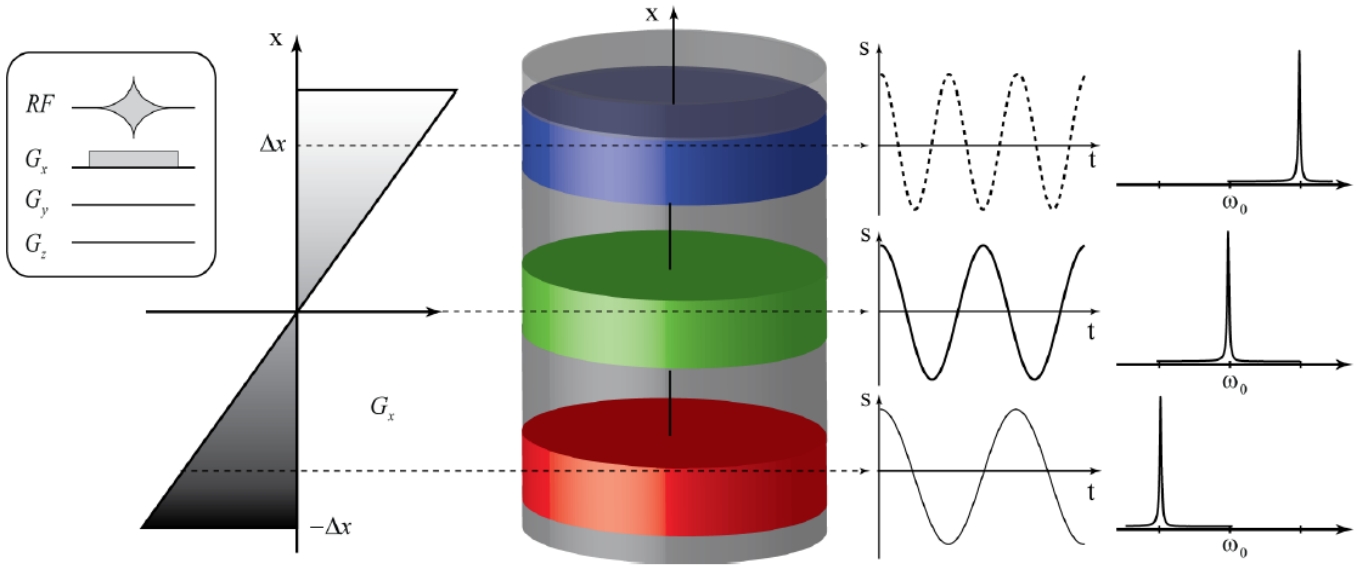
- Most MRI applications measure ^{1}H nuclei from water
- Imaging involves:
  - **Strong static field (B_0)** to separate nuclear magnetic states
  - **RF pulses** to excite the nuclei
  - **Magnetic field gradients** to differentiate the signal across space





- **Signal encoding in k-space**
  - Position is encoded via varying magnetic field gradients (slice, **frequency**, phase)
  - Acquired MR signal exists inside a Fourier (=frequency) space
  - Retrieving 2D/3D profiles is possible via Fourier transforms

Frequency encoding

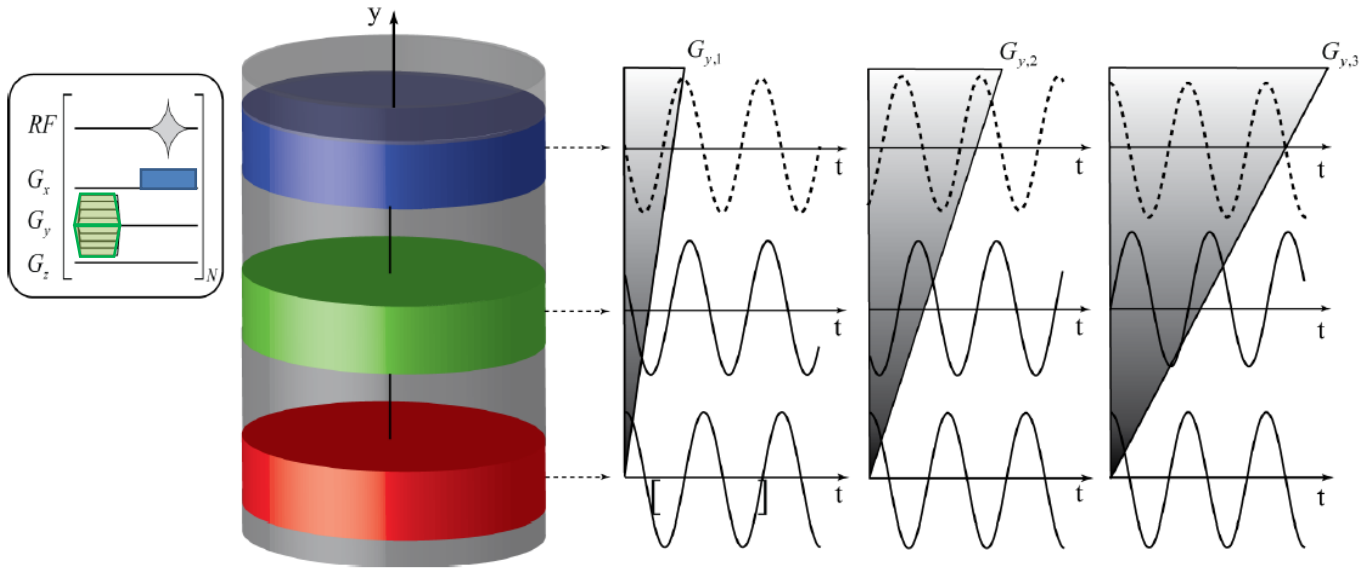


$$\rho(x = \frac{\omega}{\gamma G_x}) = \int_{-\infty}^{\infty} S(t) e^{i\omega t} dt$$

$$\vec{G}_x = x \cdot G \cdot \vec{e}_z$$

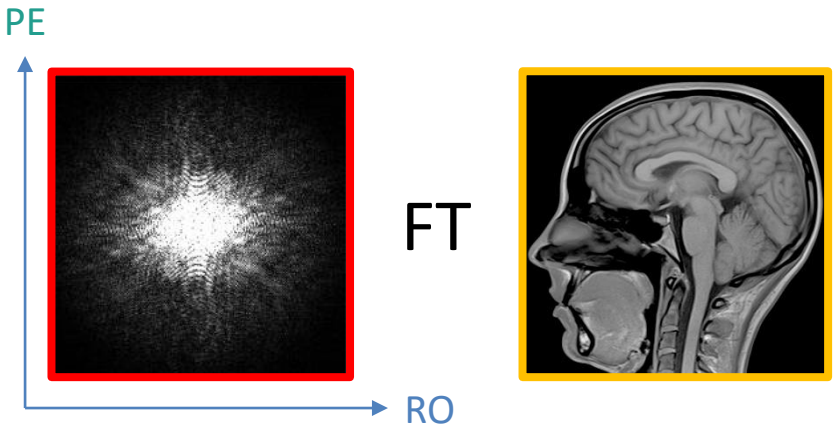
$$\omega = \gamma \cdot x \cdot G_x$$

Phase encoding



$$\phi(y) = \gamma \cdot n \cdot \Delta G_y \cdot y \cdot \tau$$

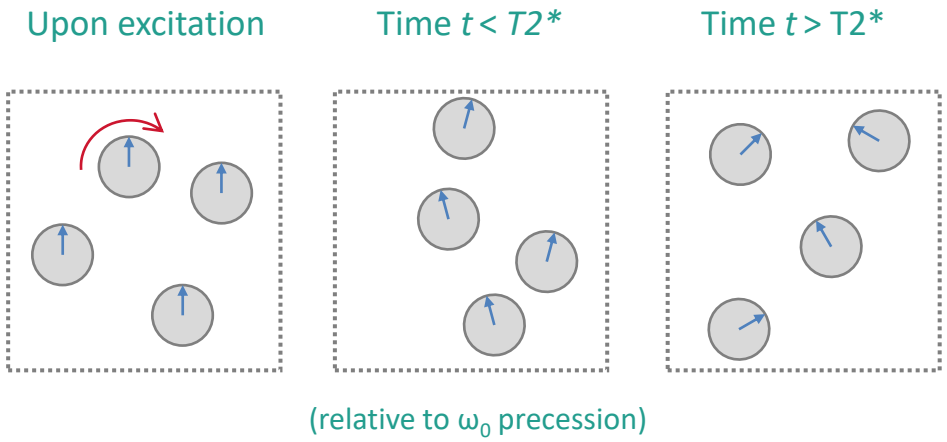
$$S^n(t) = \iiint_{sample} \rho(x,y,z) \cdot e^{-i\gamma \cdot G_x \cdot t \cdot x} \cdot e^{-i\gamma \cdot n \cdot \Delta G_y \cdot y \cdot \tau} \cdot dxdydz$$

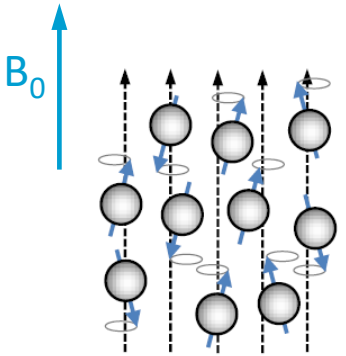


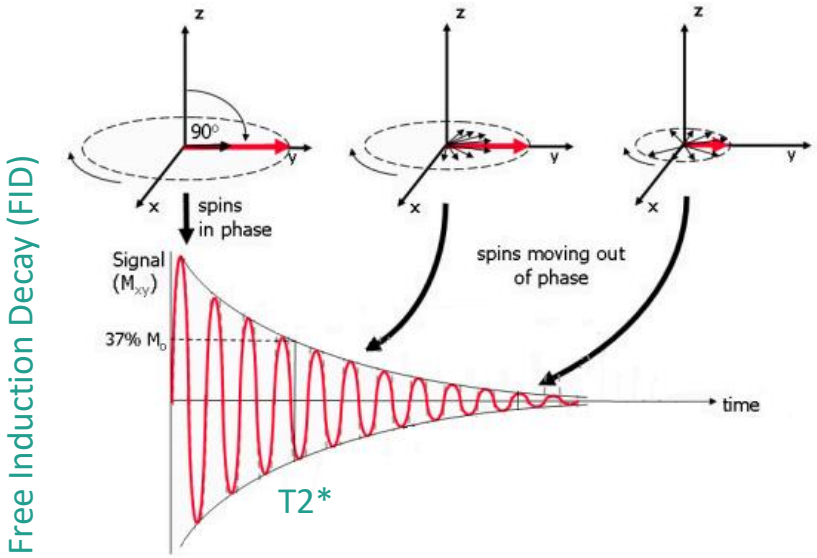
Spin relaxation

- After excitation, MR signal disappears in a few hundred milliseconds
- **T_1 or longitudinal relaxation (typically a few seconds)**
- Spins return to equilibrium state

- **T_2^* or transverse relaxation (tens of milliseconds)**
- Spins get dephased by local fluctuations in B_0
- Exponential decay in RF signal







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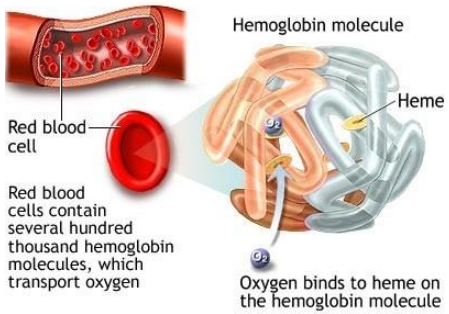
1. The BOLD contrast: biophysical mechanisms

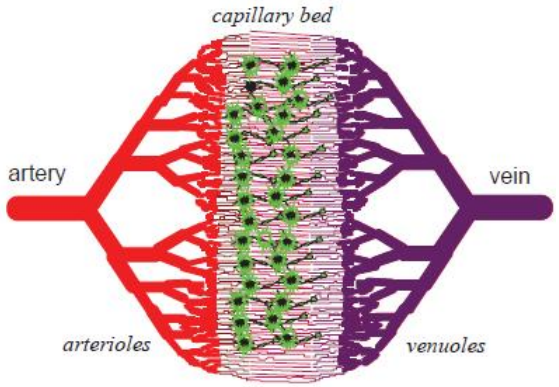
Magnetic properties of Hemoglobin (Pauling & Coryell, 1936)

- Most brain tissues are diamagnetic
- Hemoglobin has two states
  - **Diamagnetic** when oxygenated
  - **Paramagnetic** when deoxygenated

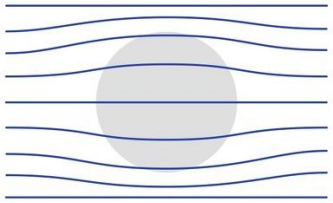
➢ creates B_0 inhomogeneities

➢ affects T_2^* relaxation

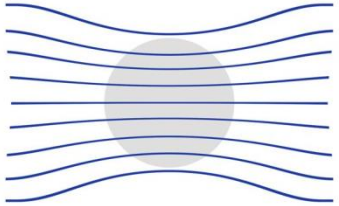




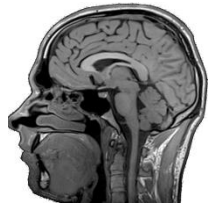
Diamagnetic materials
(oppose external field)



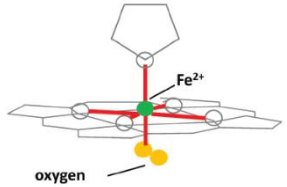
Paramagnetic materials
(enhance external field)



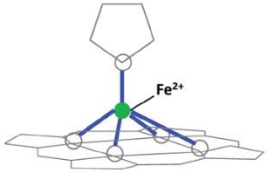
Ex:
- water
- most head tissues



Oxyhemoglobin (Hb)



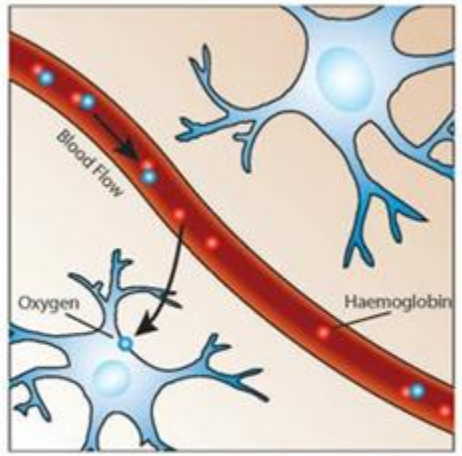
Deoxyhemoglobin (dHb)



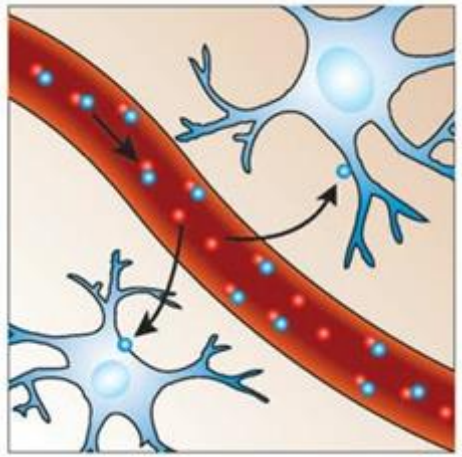
Blood oxygen level-dependent (BOLD) contrast (Ogawa et al. 1992)

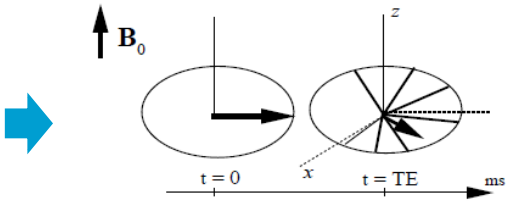
- Signal read at a long echo-time (TE) ⇨ to allow dephasing

Higher [dHB]/[Hb]

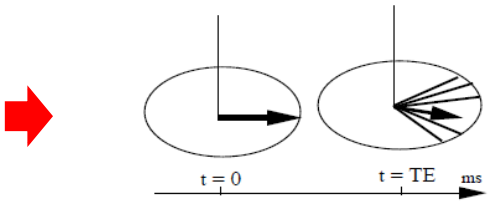


Lower [dHB]/[Hb]

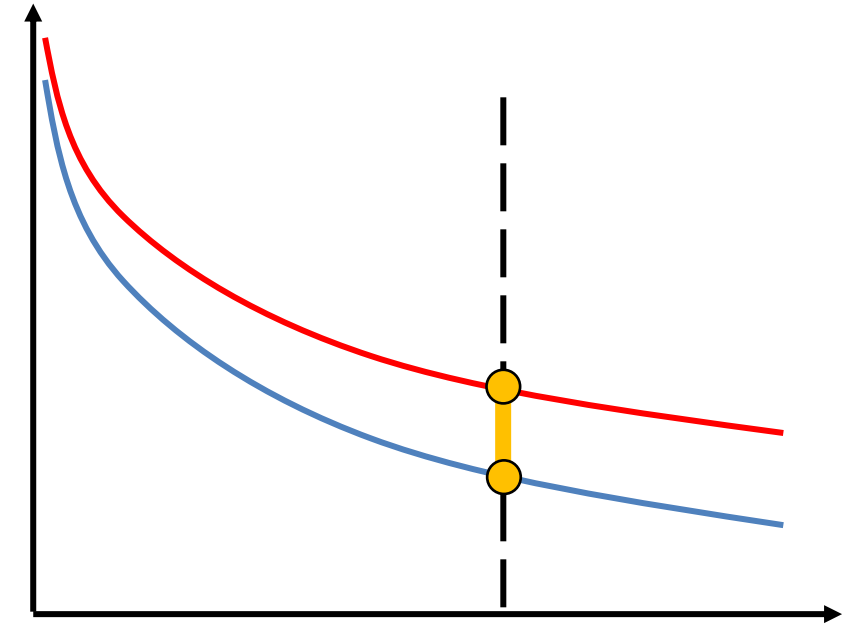




Local spins

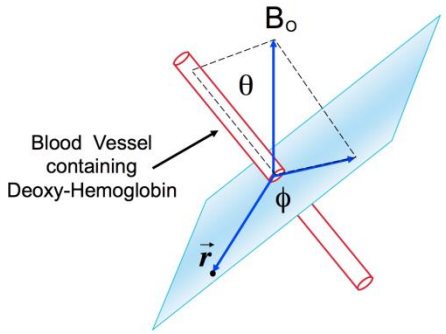


BOLD Signal Intensity



Does the BOLD functional MRI signal increase or decrease with brain activity?

local ↑neuronal activity ⇨ ↑O_2 consumption ⇨ ↑[dHB] ↓BOLD



Field shift due to venous compartment (Ogawa et al. 1993)

$$\Delta B(\mathbf{r}) = \begin{cases} \frac{\Delta\chi}{2} \cdot \left[\cos^2(\theta) - \frac{1}{3}\right] \cdot B_0 & \text{Inside cylinder} \\ \left[\frac{\Delta\chi}{2} \cdot \sin^2(\theta) \cdot \frac{a^2}{r^2} \cdot \cos(2\phi)\right] \cdot B_0 & \text{Outside cylinder} \end{cases}$$

where $\Delta\chi$ is the susceptibility difference between the intra and extravascular compartment, a is the radius of the cylinder

(Empirical) T_2^* dependence on [dHb] (Boxerman et al. 1995)

$$\frac{1}{T_2^*} = A\ CBV\ [dHb]^{\beta}$$

A is a field-strength and sample-specific constant, CBV is the local blood volume, β is a constant ($1 \leq \beta \leq 2$)

Does the BOLD functional MRI signal increase or decrease with brain activity?

local ↑neuronal activity	⇨ ↑O_2 consumption	⇨ ↑[dHB] ↓BOLD
	⇨ ↑ cerebral blood flow (CBF)	⇨ ↓[dHB] ↑BOLD
	⇨ ↑ cerebral blood volume (CBV)	⇨ ↑[dHB] ↓BOLD

Neurovascular coupling

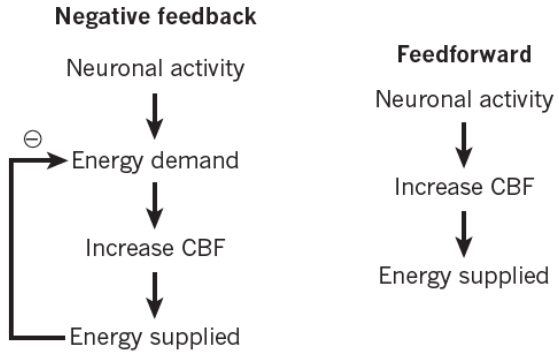
Components: neurons, glial cells (esp. astrocytes), muscle cells, vessels

Interactions: electrical, metabolic, vascular

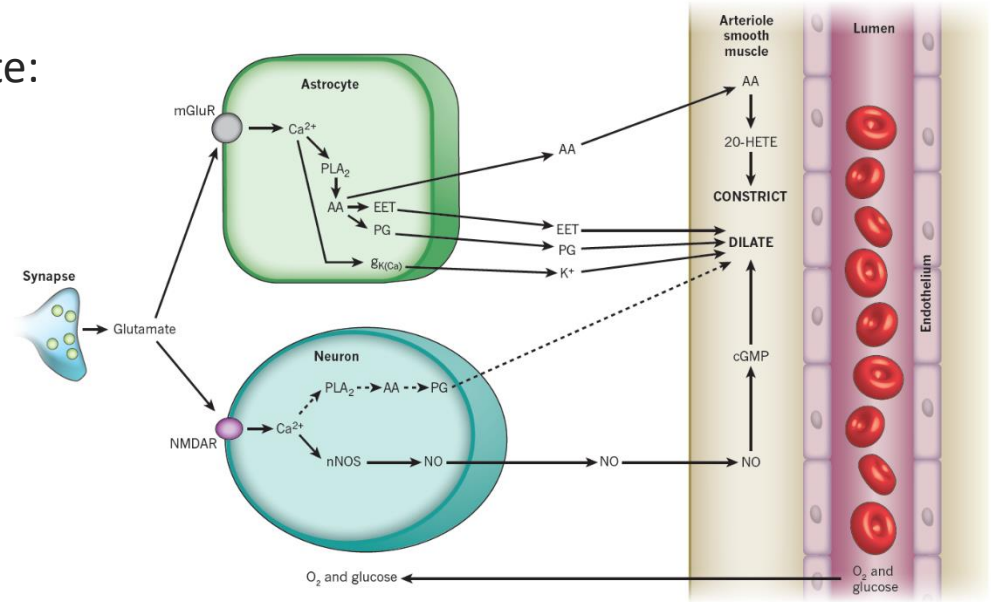
Neurovascular coupling

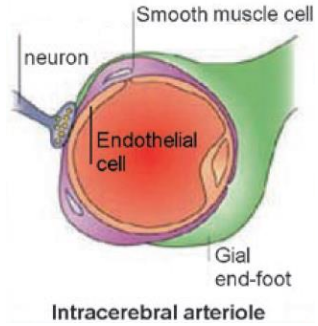
Various hypotheses

(Attwell et al., 2010)



Example for glutamate:





Does the BOLD functional MRI signal increase or decrease with brain activity?

local ↑neuronal activity ⇨ ↑O_2 consumption ⇨ ↑[dHB] ↓BOLD

⇨ ↑ cerebral blood flow (CBF) ⇨ ↓[dHB] ↑BOLD

⇨ ↑ cerebral blood volume (CBV) ⇨ ↑[dHB] ↓BOLD

Neurovascular coupling

Components: neurons, glial cells (esp. astrocytes), muscle cells, vessels

Interactions: electrical, metabolic, vascular

⇨ Still under active investigation (Logothetis 2008; Attwell et al, 2010; Hillman 2014)

Typically observed (for excitatory neuronal activity)

↑ excitatory activity ⇨ ↑↑ CBF (50–70%) ⇨ ↓ [dHB]/[Hb] ⇨ ↑ **local BOLD sign**

↑ $CMRO_2$ (2–5%)

BOLD response – temporal dynamics

Main positive peak

- 5–8 seconds after stimulus
- Due to increase in CBF

Return towards baseline

- Takes a few seconds

Negative undershoot

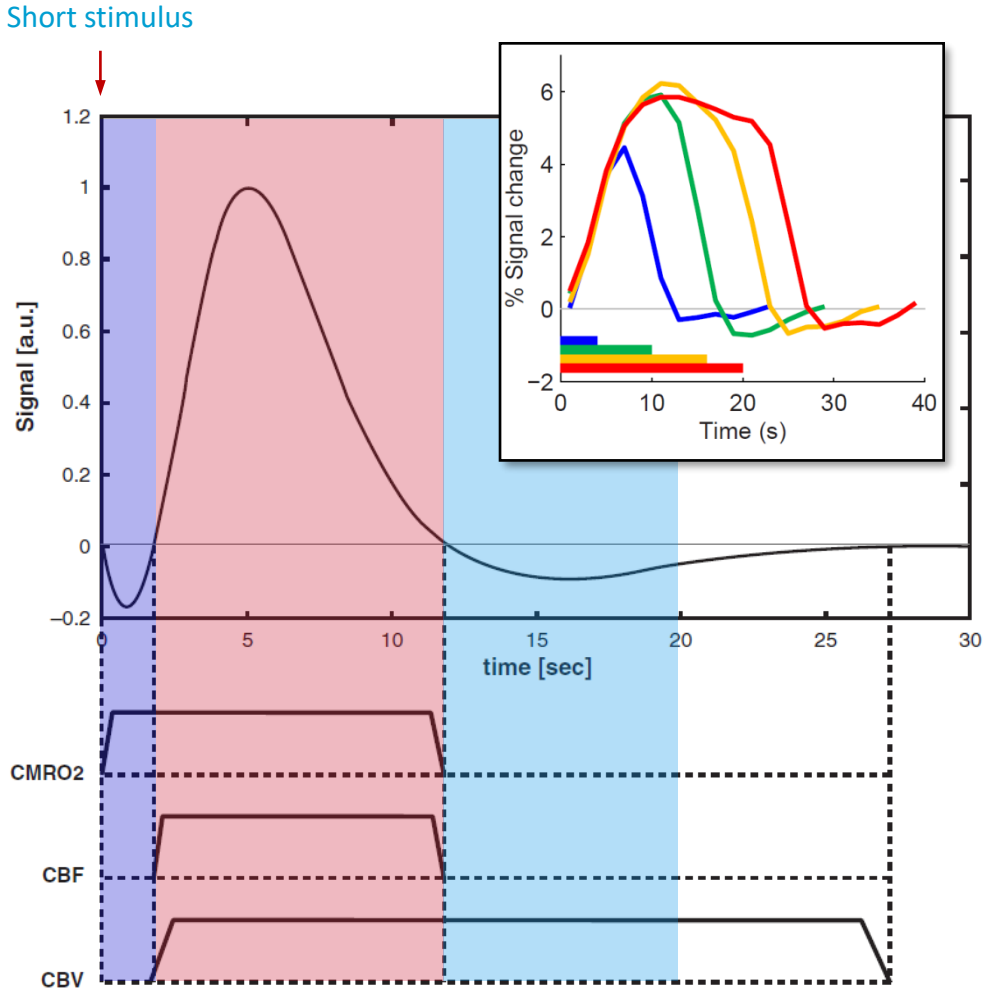
- Due to lagging increased CBV (?)

Return to baseline

- Takes 15–20 seconds

Initial dip (?) (Ernst & Hennig, 1994)

Overall: a delayed, smooth version of the underlying neuronal activity



BOLD response – spatial specificity

Response extends beyond activated region

BOLD response – technical aspects

Voxel size (1-3 mm, can reach sub-mm at 7T)

Spin refocusing: T_2^* effects can be partially cancelled

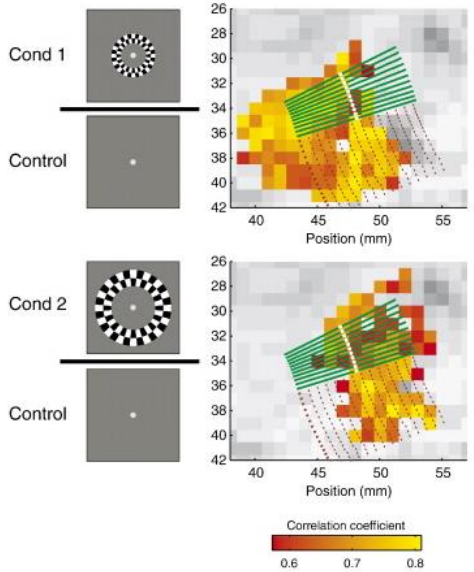
BOLD response – biophysical aspects

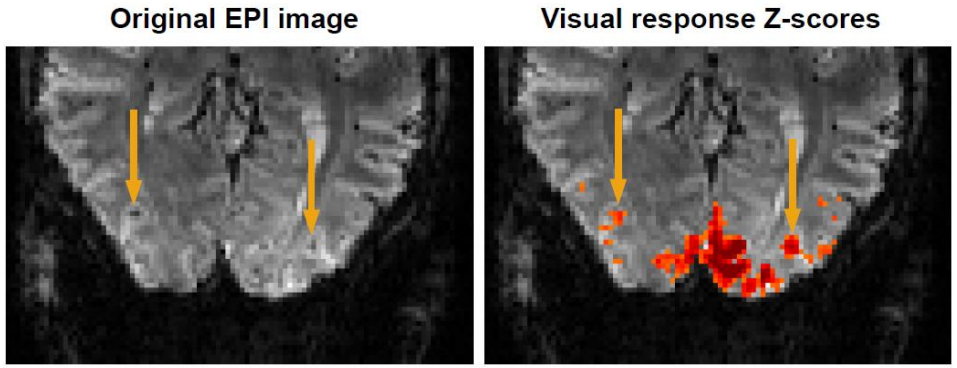
Extent of B_0 perturbations

Extent of capillary/arteriolar recruitment

BOLD contrast is strongest near veins

Bias towards large draining veins





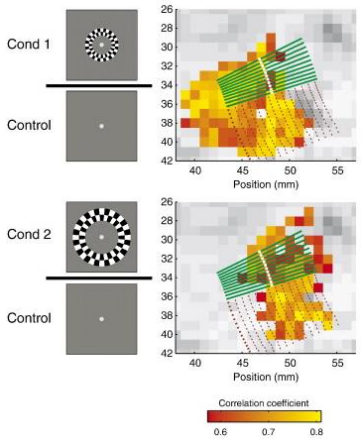
BOLD response – spatial specificity

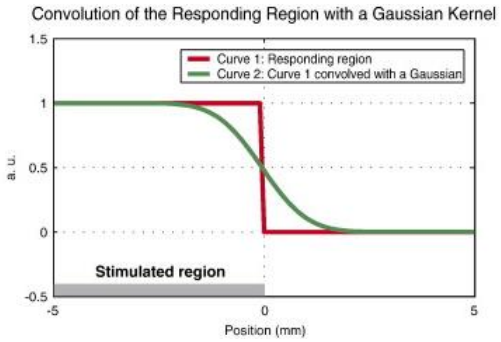
- BOLD point-spread-function in grey matter

  ~ 3.5 mm at 3T (Parkers et al. 2005)

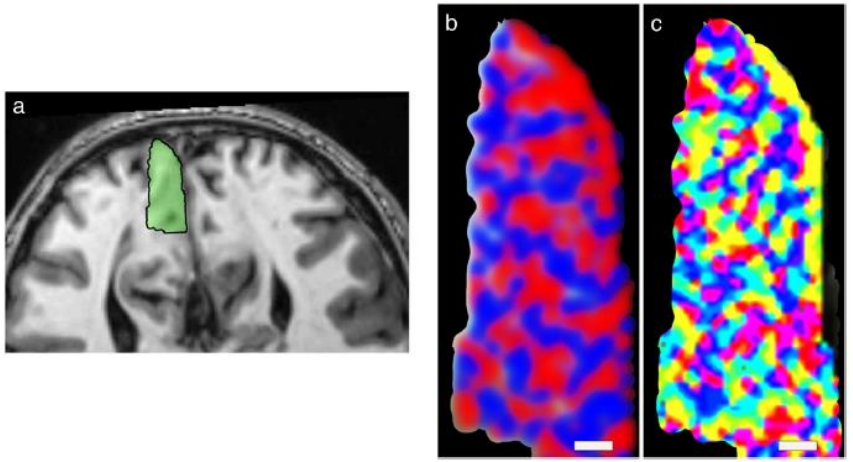
  ~ 2 mm at 7T (Shmuel et al. 2007)

- Comparing stimulus conditions enhances specificity

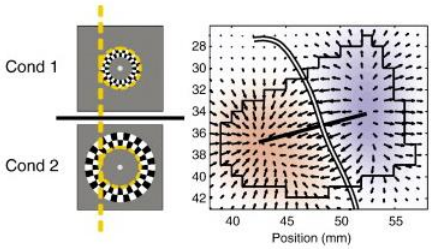




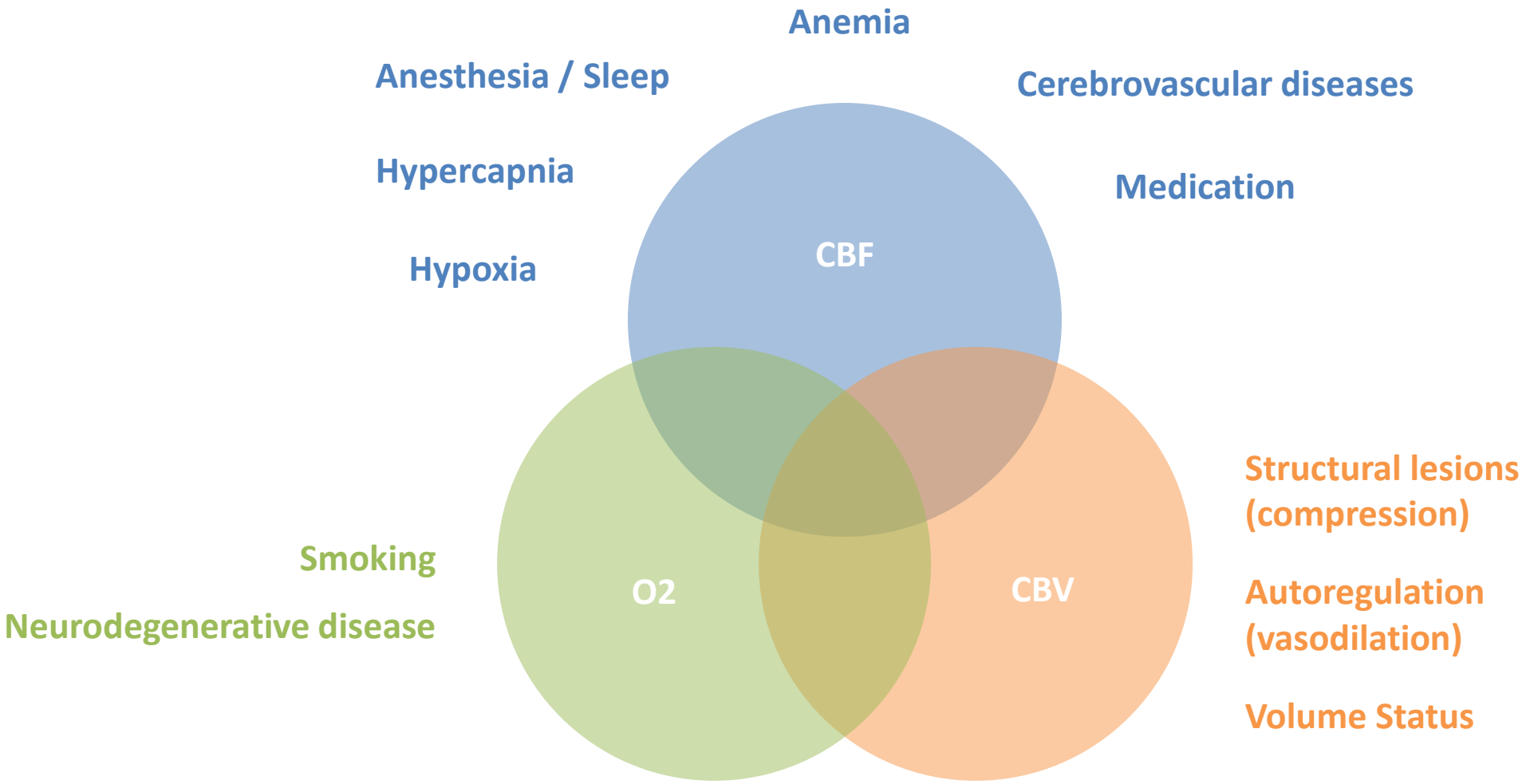
Example: occular dominance and orientation columns localized at 7T (Yacoub et al. 2007)



1 mm



Physiological influences on BOLD



➔ BOLD is qualitative, NOT quantitative

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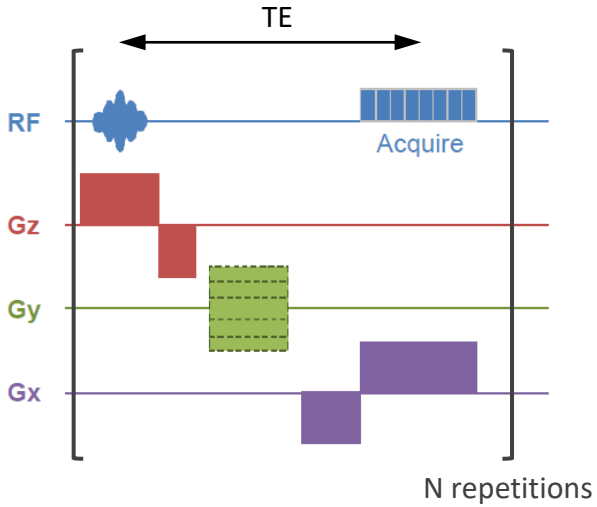
2. The BOLD contrast: image acquisition

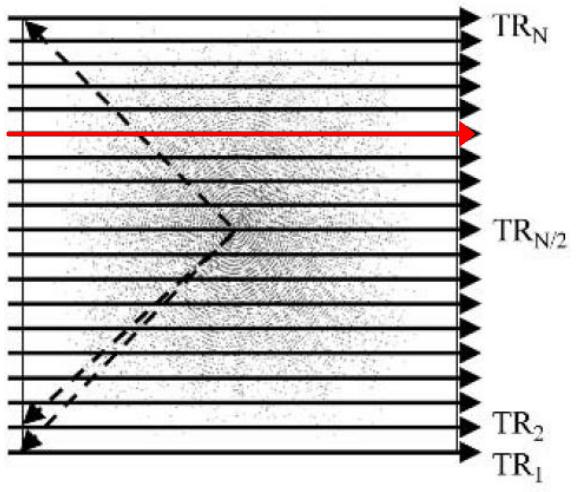
BOLD fMRI acquisition

- **Sensitivity:** need relatively long TE between excitation and readout
- **Temporal resolution:** need to acquire whole 3D images fast

Typical gradient-recalled echo (GRE) imaging

- TE can be made very short (nice for anatomical MRI, but not fMRI)
- Single k-space line per excitation – full volume takes too long



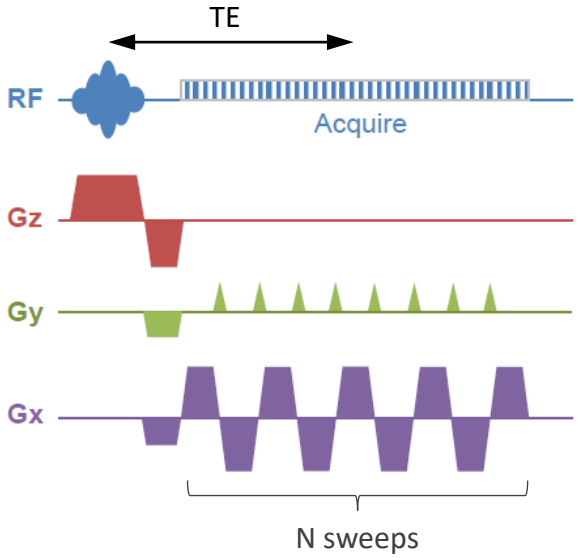


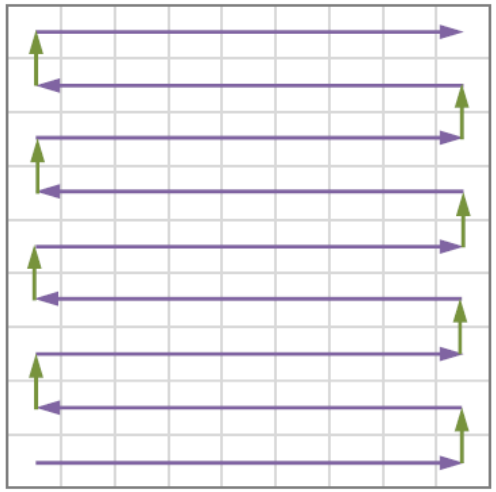
BOLD fMRI acquisition

- **Sensitivity:** need relatively long TE between excitation and readout
- **Temporal resolution:** need to acquire whole 3D images fast

Echo planar imaging (EPI) (Stehling et al. 1991)

- Full k-space plane per excitation
  - **2D–EPI:** one image slice per excitation (2D k-space)
  - **3D–EPI:** one k-space plane per excitation (3D k-space)





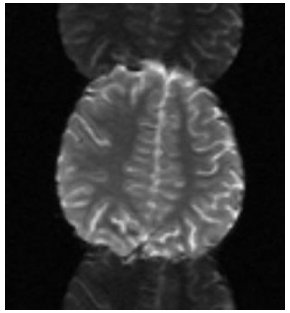
EPI – advantages

- Quite fast – whole-brain image in a few seconds
- Very efficient use of the long TE

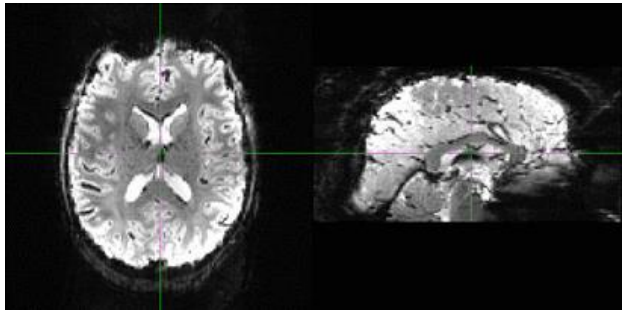
EPI – disadvantages

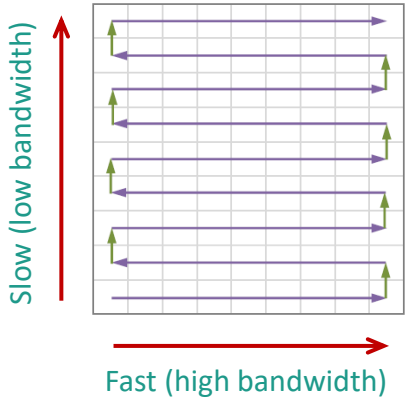
- **Ghosting artifacts** due to zig-zag trajectory
- **Spatial distortions** due to long encoding time
- Often quite **loud** due to intense gradient switching

Nyquist ghosting



Spatial distortions
(shown by reversing phase-encode direction)

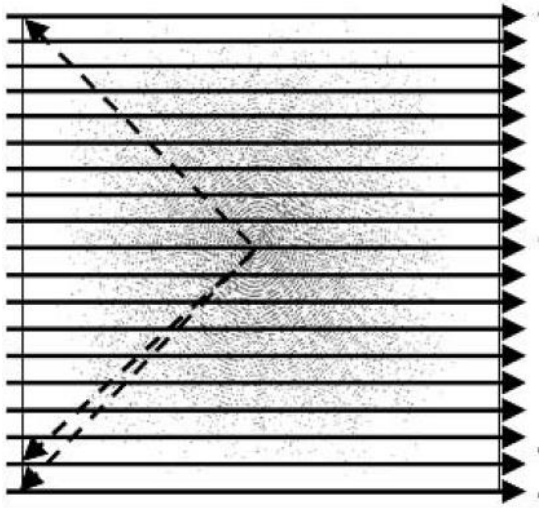




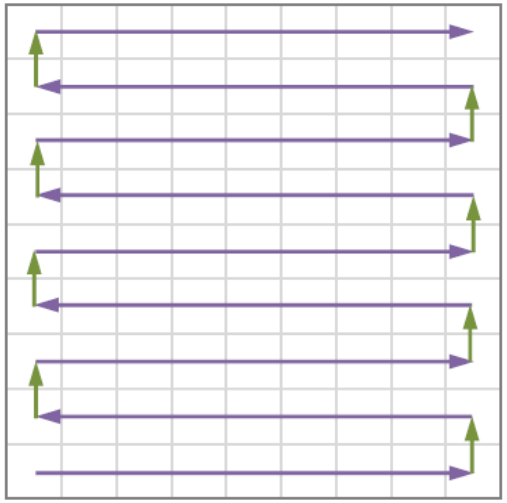
Other non-cartesian trajectories

- Spiral imaging
- Radial imaging

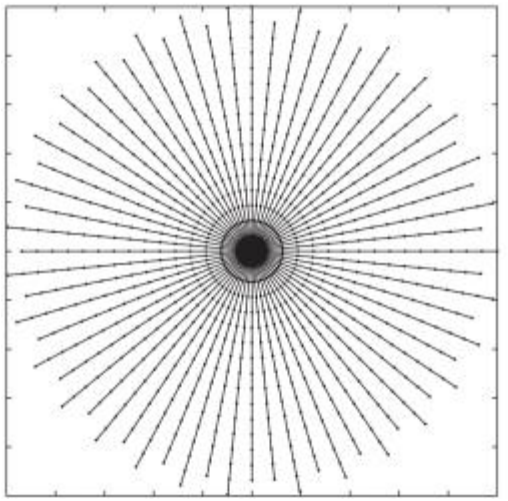
Linear Cartesian



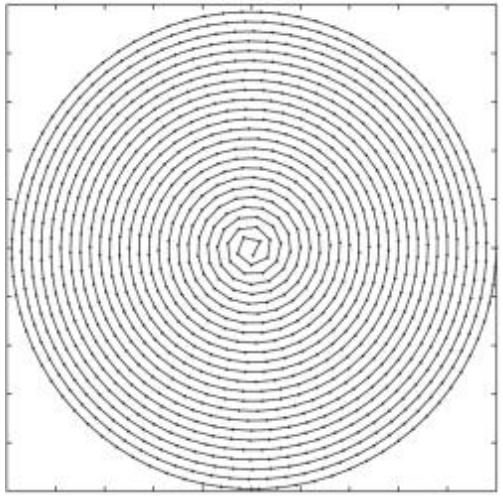
Echo Planar



Radial



Spiral



2. The BOLD contrast & field strength

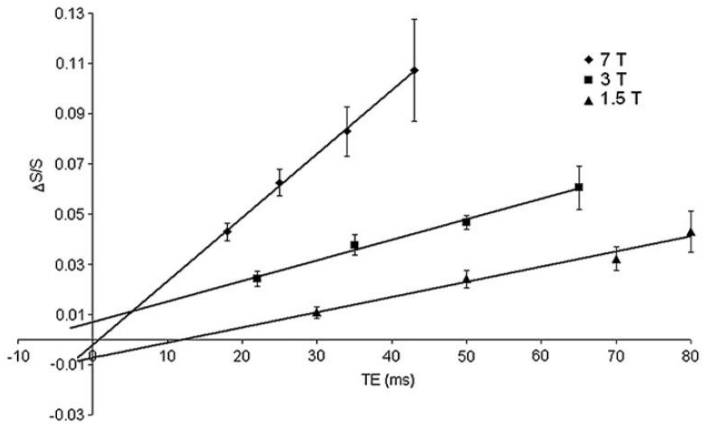
BOLD sensitivity

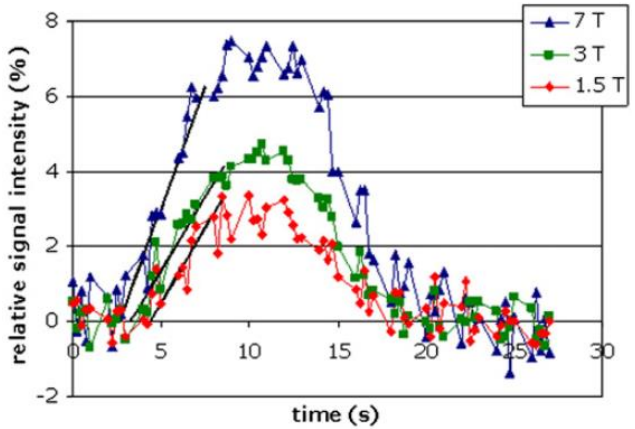
$\uparrow B_0$ ⇨ ↑MR signal $\quad SNR_{image} \propto {B_0}^{1.65}$ (Pohmann et al. 2016)

$\uparrow B_0$ ⇨ ↑field inhomogeneities ⇨ ↑BOLD contrast $\quad \Delta B_{dHb} \propto \chi_{dHb} B_0$

- Strong boost in BOLD sensitivity
  - Subtle responses easier to detect
  - Can be traded for higher spatial resolution, faster sampling, wider coverage

Example: responses in motor cortex at 1.5T, 3T, 7T





(van der Zwaag et al. 2009)

BOLD sensitivity

↑B_0 ⇨ ↑MR signal $SNR_{image} \propto B_0$ (Edelstein et al. 1986)

↑B_0 ⇨ ↑field inhomogeneities ⇨ ↑BOLD contrast $\Delta B_{dHb} \propto \chi_{dHb} B_0$

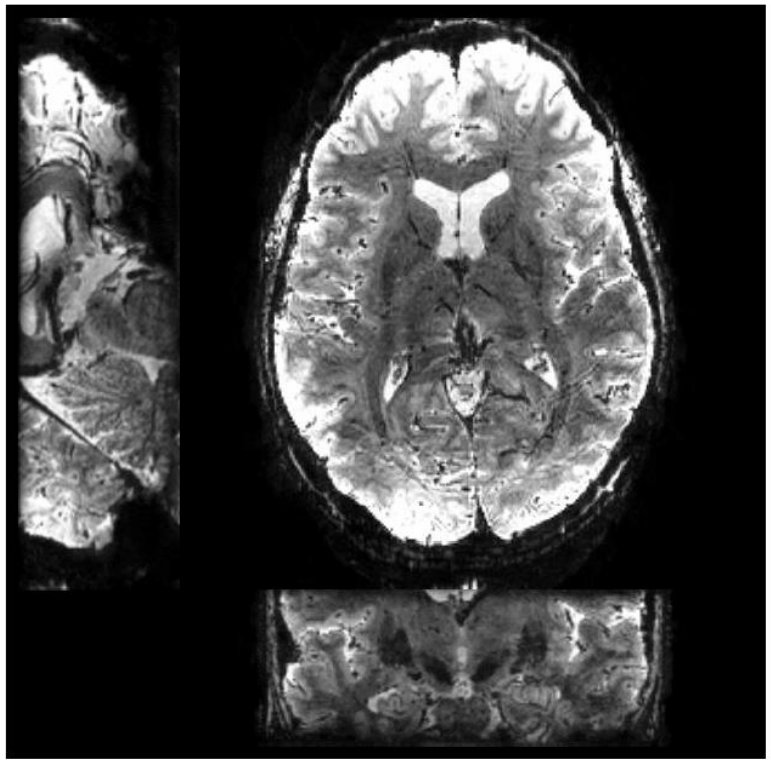
- Strong boost in BOLD sensitivity
  - Subtle responses easier to detect
  - Can be traded for higher spatial resolution, faster sampling, wider coverage

Also important with ↑B_0

- **Specificity:** ↓T_2 of venous signal ⇨ smaller venous contributions
- **↓ Optimal TE for BOLD** ⇨ less time for k-space readout, but faster volume sampling
- **↓ B_0 homogeneity** ⇨ ↑spatial distortions, ↑signal loss in certain regions
- **↓ B_1 homogeneity** ⇨ ↑heterogeneity in SNR across regions
- **↑ Relative sensitivity to non-white noise sources** (physiological noise, etc.)

The greater signal, BOLD contrast and spatial specificity at ultra-high field can be exploited to:

a. Improve the spatial resolution (i.e., smaller voxel size).
b. Reduce the number of trials to demonstrate robust activation.
c. Facilitate the study of the response to *rare events*
d. Investigate *subtle cognitive effects* (e.g., single subject differences).
e. Improve the temporal resolution (ie TR^{-1}, sampling rate)



Outline

0. MR signal & k-space

1. The BOLD contrast

- Biophysical mechanisms
- Spatiotemporal dynamics

2. fMRI data acquisition

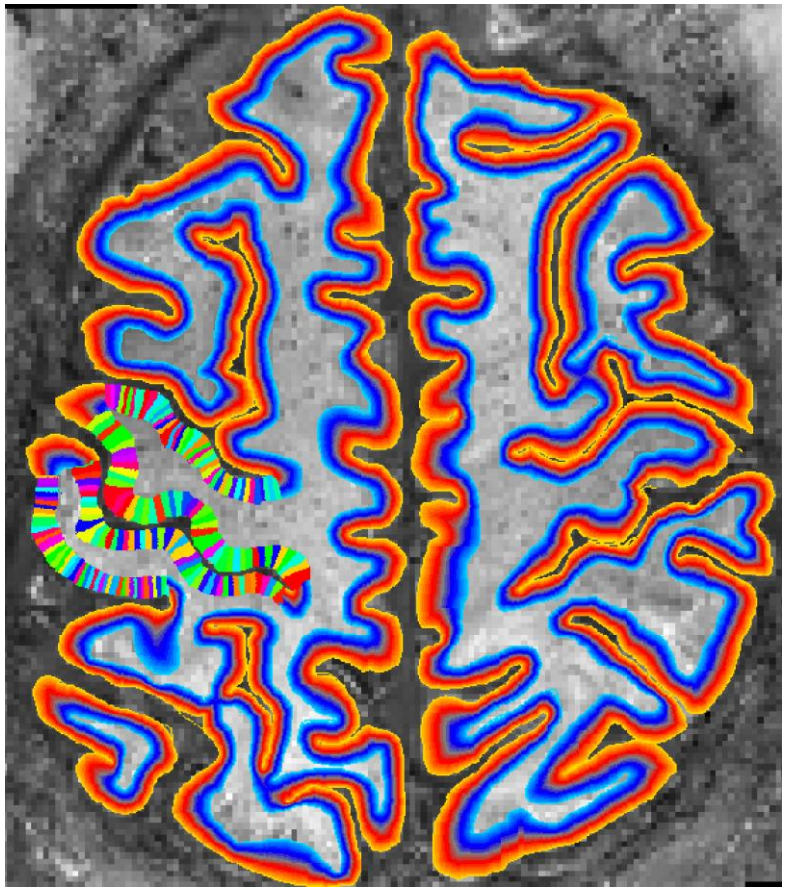
- Image acquisition
- Dependence on field strength

3. Non-BOLD fMRI

- ASL – measuring blood flow
- VASO – measuring blood volume

4. fMRI data analysis

- Pre-processing
- Analysis: event-related activity
- Analysis: spontaneous activity



3. Non-BOLD fMRI

Limitations of the BOLD contrast

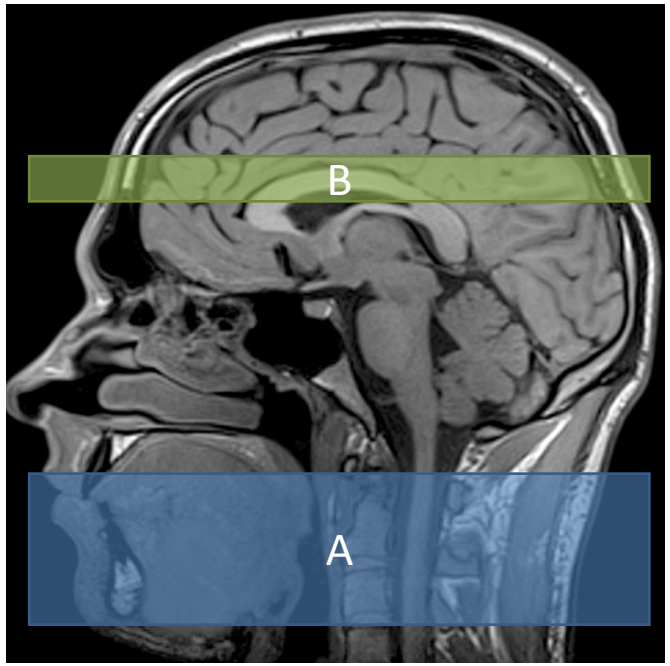
- Non-quantitative
- Complex and poorly understood combination of parameters ($CMRO_2$, CBF, CBV)
- Unclear result for combinations of excitation, deactivation, inhibition

ASL

Arterial spin labeling (ASL) to measure CBF

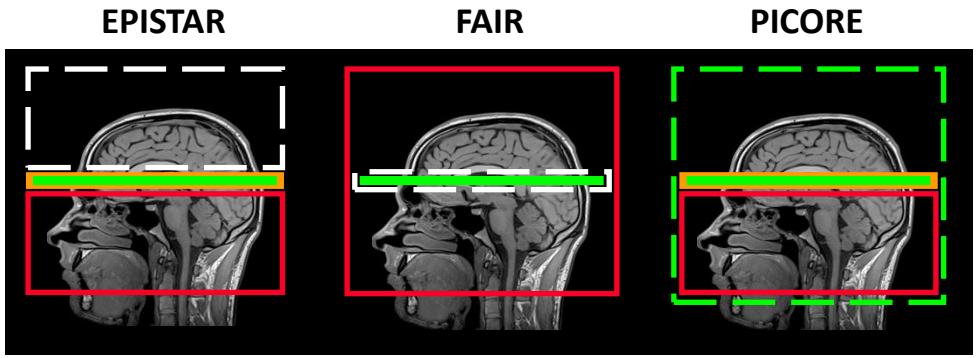
- Acquire “tag” image Im_T
  - Inversion pulse in neck region **A** (for ex.)
  - EPI slab in brain region **B = [brain – blood]**
- Acquire “control” image Im_C
  - No inversion pulse
  - EPI slab in brain region **B = [brain + blood]**
- Subtract both
- Repeat for more timepoints

$$Im_T - Im_C \propto CBF$$



Many variants

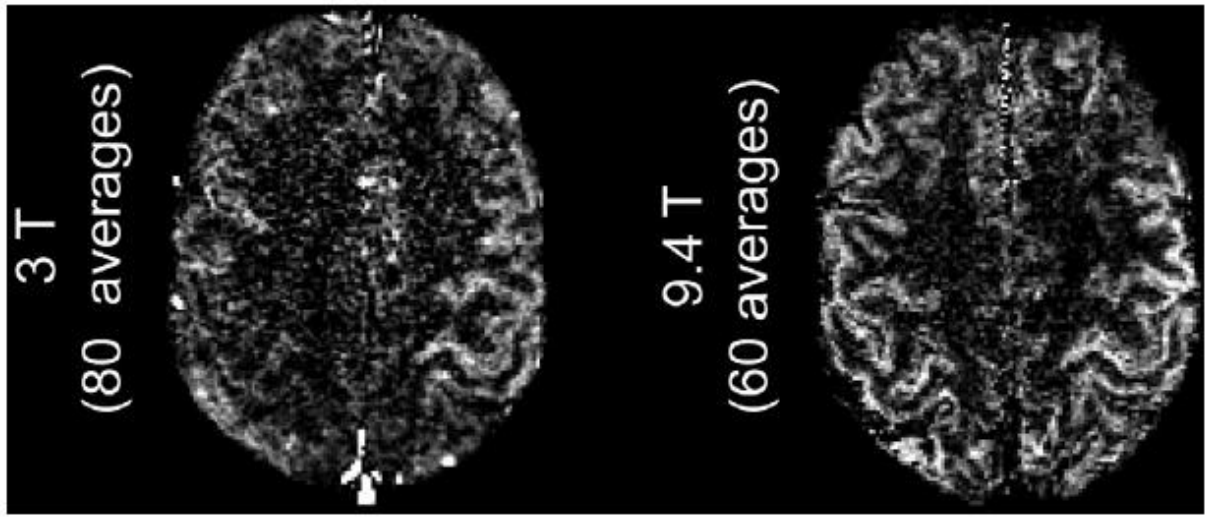
- **Tagging schemes**
  - Pulsed
  - Continuous
  - Pseudo-continuous



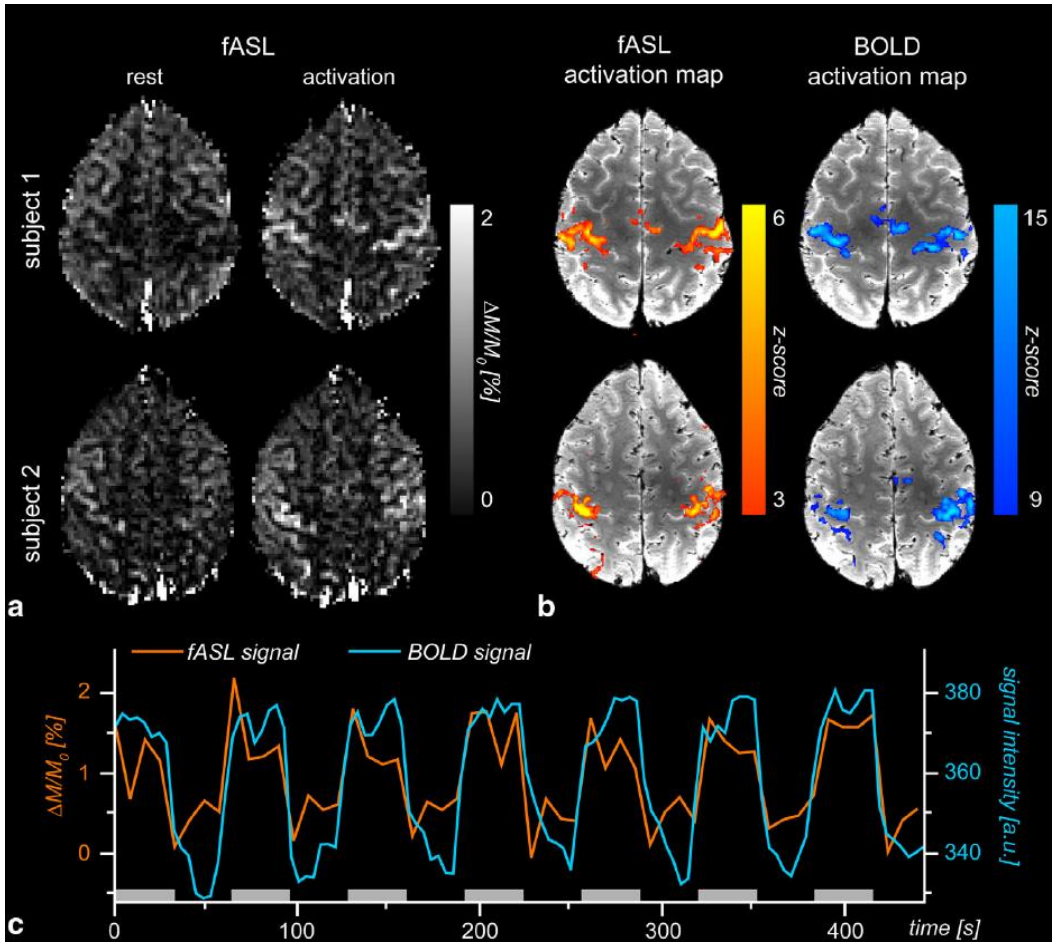
Arterial Spin Labeling at UHF

Quantitative and Functional Pulsed Arterial Spin Labeling in the Human Brain at 9.4 T

Jonas Bause,[1,2] Philipp Ehses,[1,3] Christian Mirkes,[1,3] G. Shajan,[1] Klaus Scheffler,[1,3] and Rolf Pohmann[1]*



3 T 9.4 T



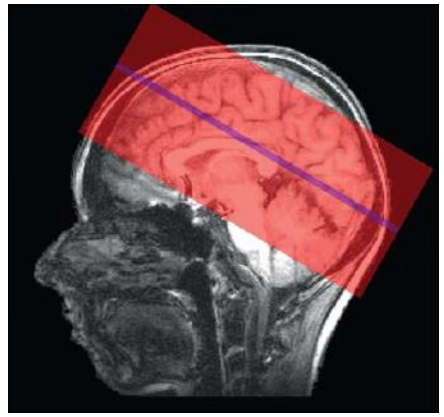
Voxel size: 1.2 x 1.2 x 4 mm3

VASO

Vascular space occupancy (VASO) to measure CBV (Lu et al. 2003)

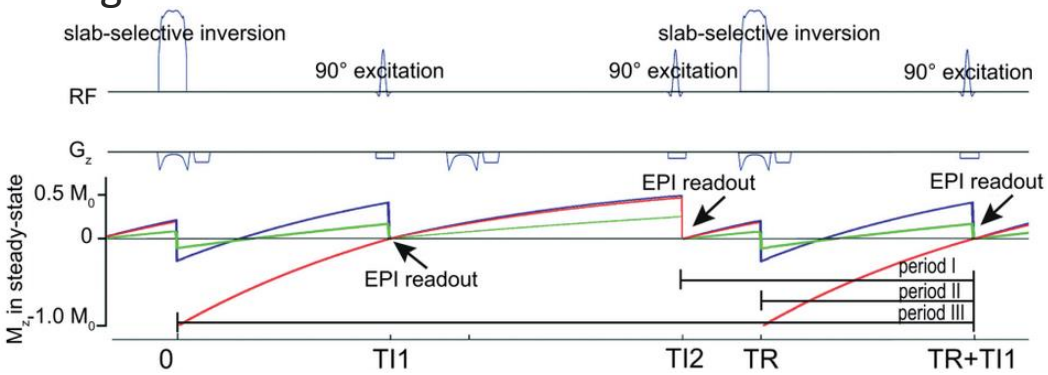
- 180° pulse inverts all spins
- Acquire image when blood signal is “null”
- Grey matter and blood have slightly different T_1 relaxation

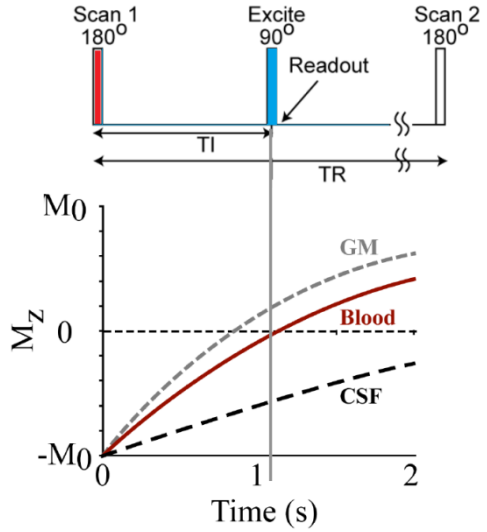
- Image is sensitive to changes in the CBV fraction
- Extravascular BOLD neglected (short TE, low field strength)



Slice-saturation, slab-inversion VASO at 7T (Huber et al. 2013)

- Additional readout per inversion
- Increases GM signal at blood-null time
- Combination of images cancels out BOLD effects





3. Non-BOLD vs BOLD: comparison

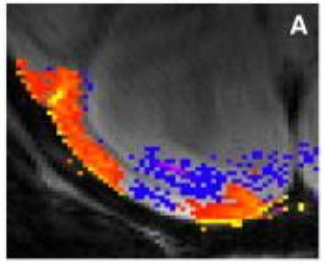
ASL & VASO – advantages

- CBF & CBV are direct physiological quantities
- More closely related to brain function
- Can be made quantitative
- Less biased towards veins

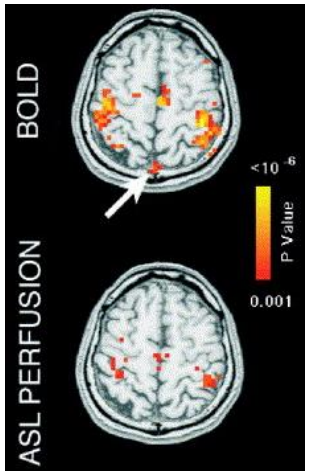
ASL & VASO – limitations

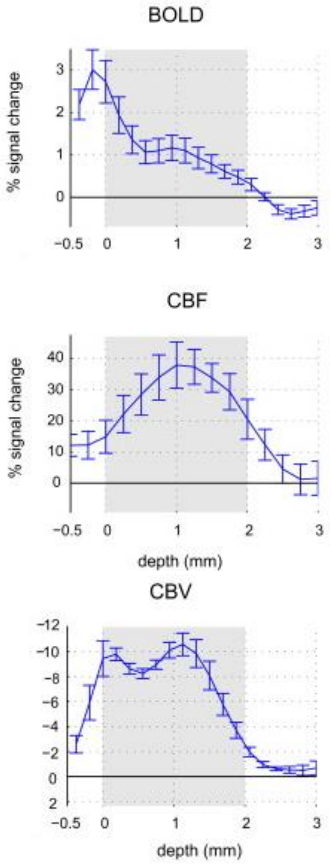
- Lower SNR than BOLD ⇨ require larger voxels
- Inversion efficiency ⇨ requires good transmit B_1
- Higher SAR due to inversion pulse
- Coverage and timing constraints
- Need to wait for bolus transit / blood-nulling
- More assumptions than BOLD

Ex: visual responses across cortical layers



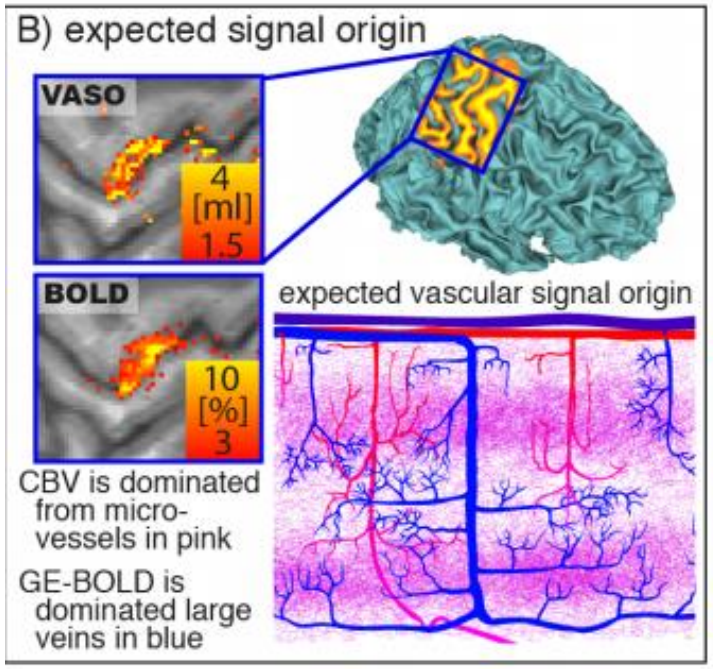
(Goense et al. 2012)

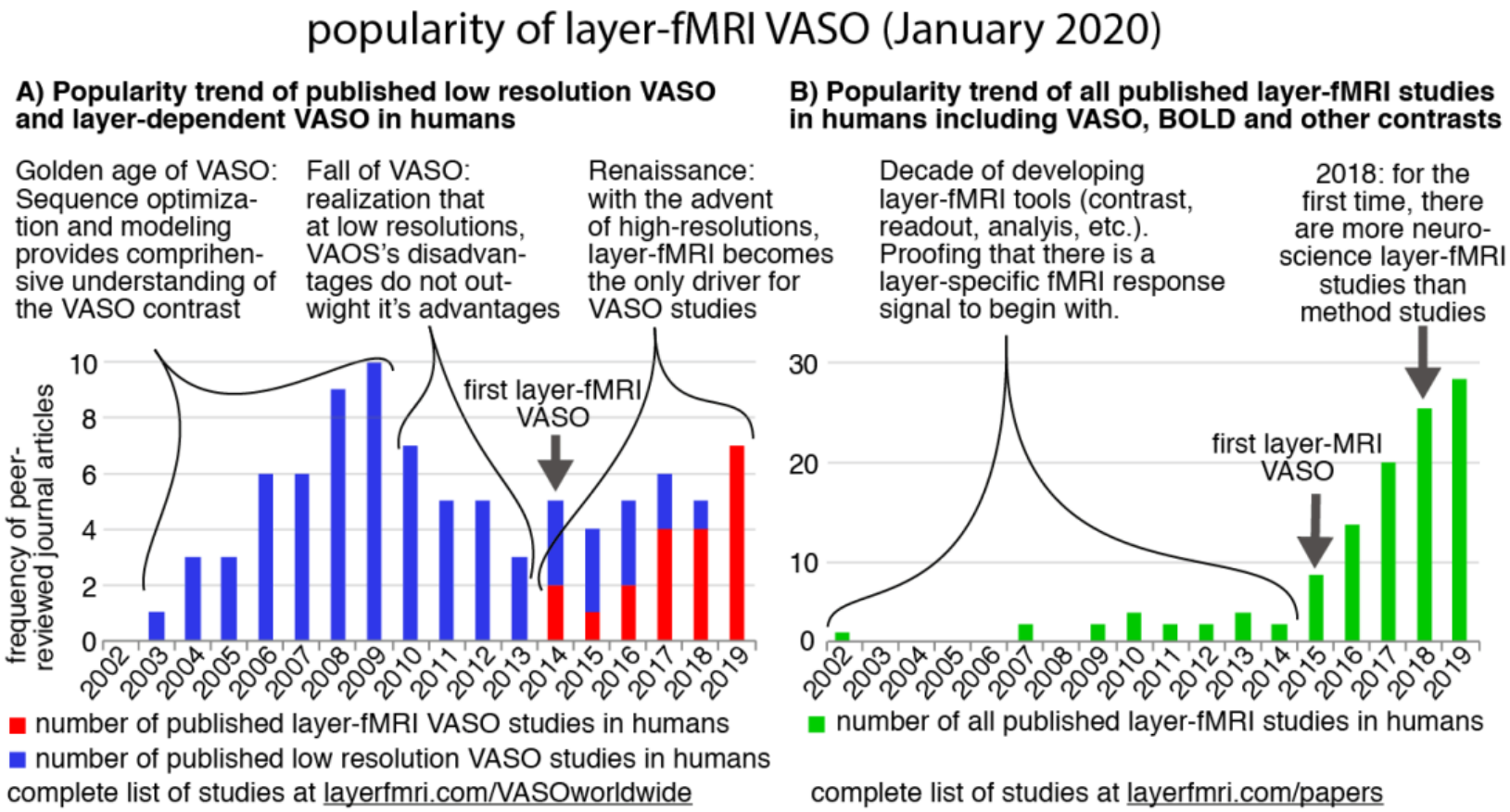




VASO is expanding rapidly

layer fMRI blog

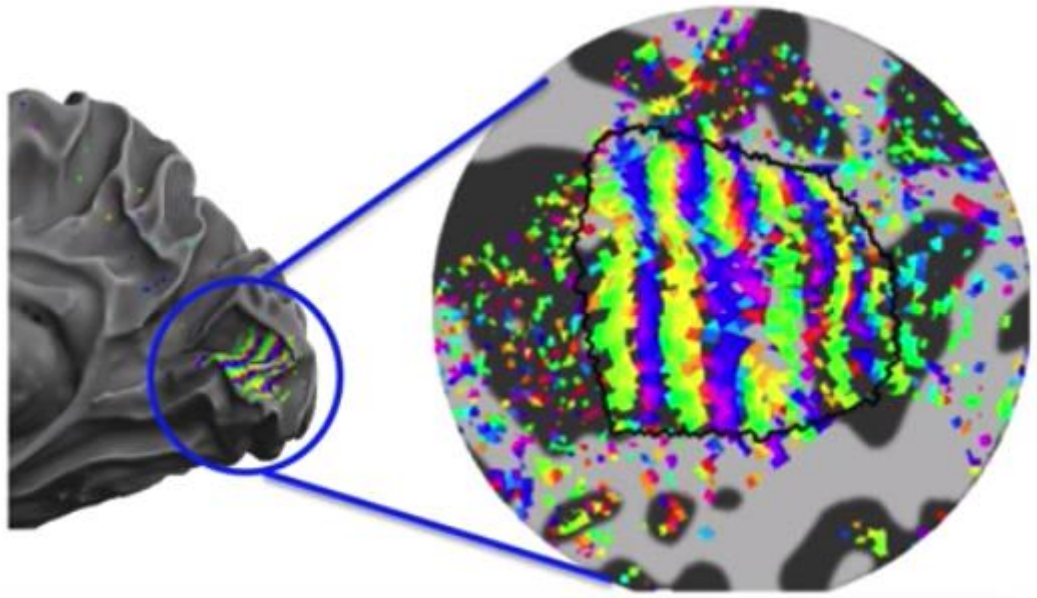




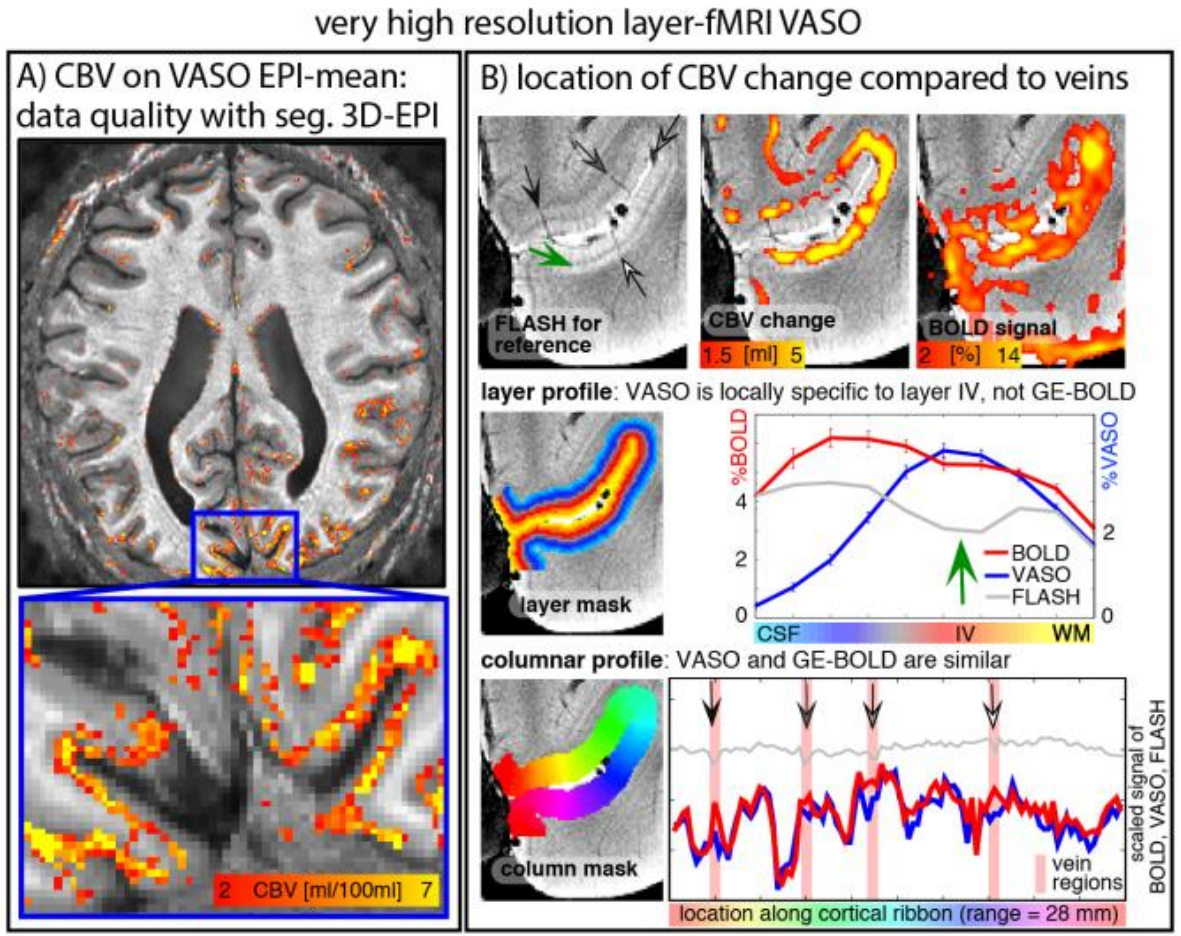
Laurentius Huber et al. (2020, February 4). Layer-dependent functional connectivity methods. Zenodo. http://doi.org/10.5281/zenodo.3635355

Layer-fMRI VASO at UHF

layer fMRI blog



sub-millimeter VASO to map the visual topography, Eli Merriam and Zvi Roth



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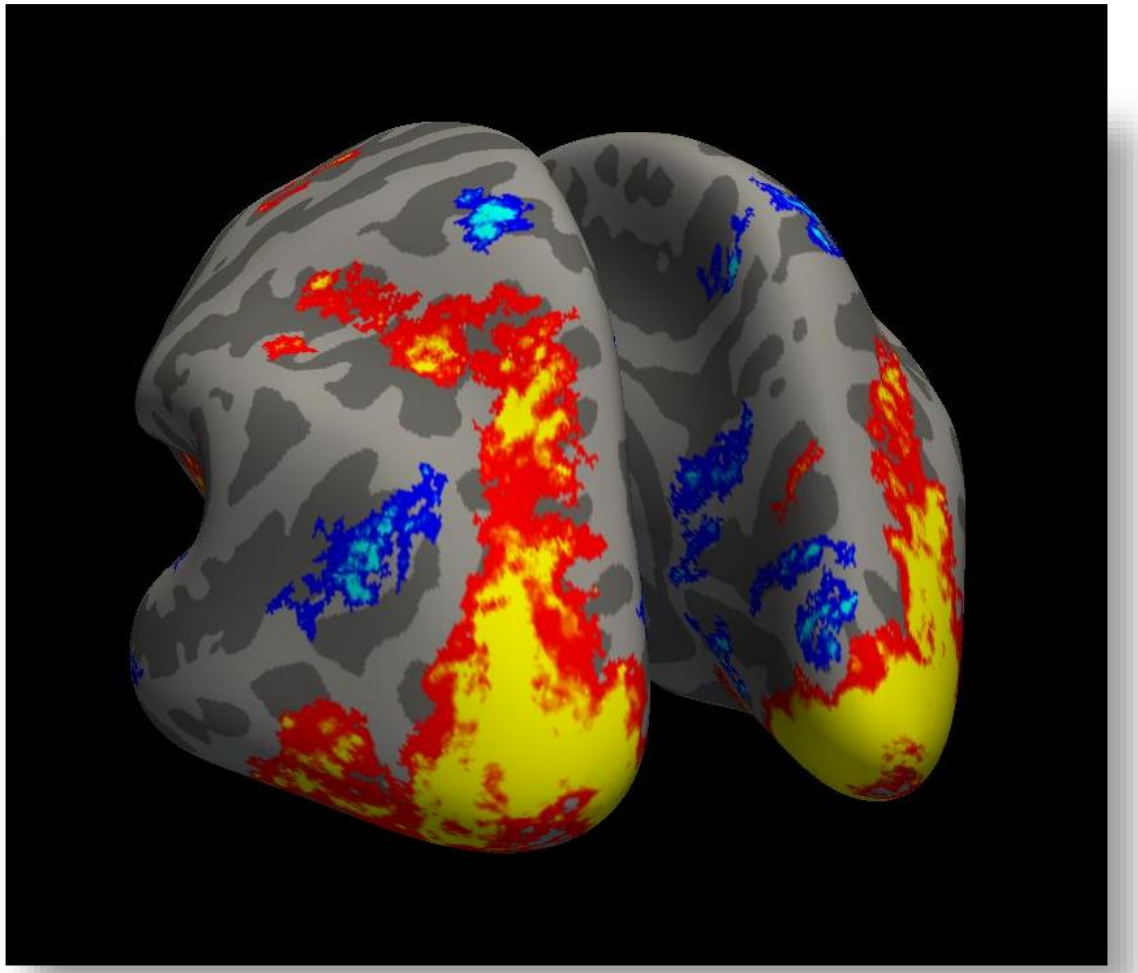


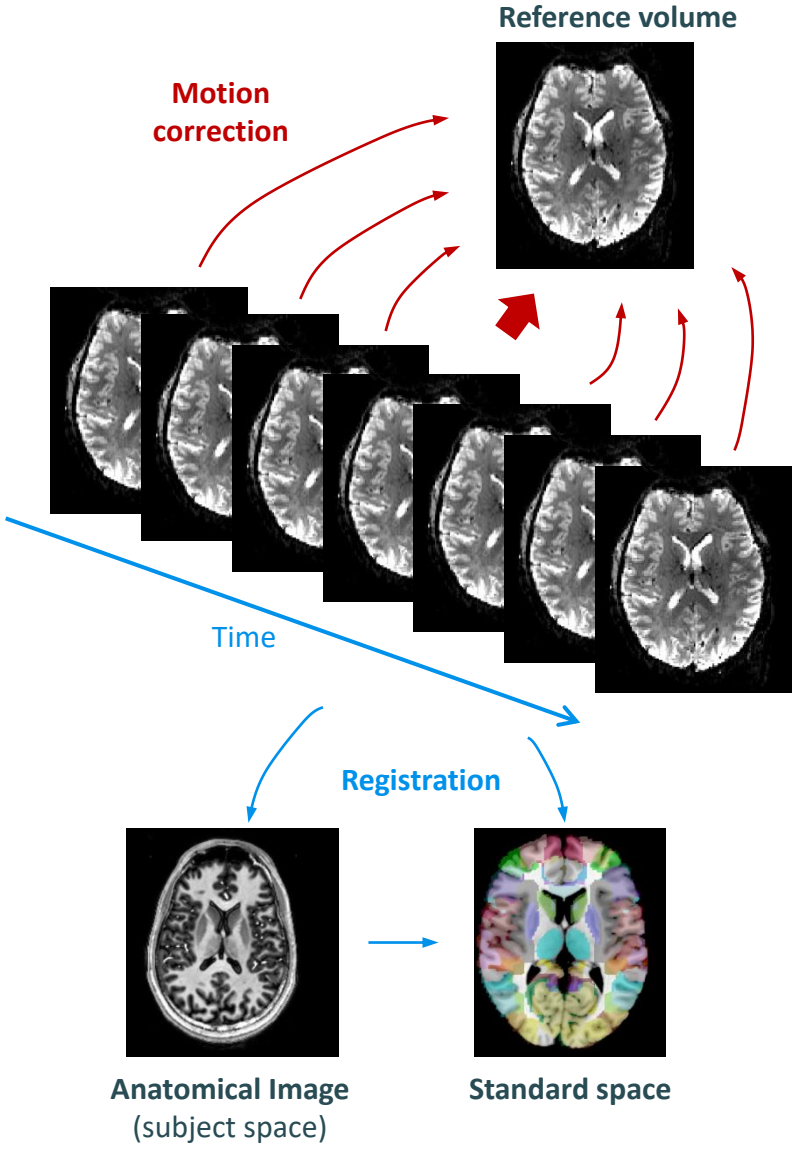
4. fMRI data: pre-processing

After fMRI acquisition

- 4D data (a timecourse of 3D volumes)
- Typical dimensions:
- In the order of 100 000 voxels × 100 timepoints
- Most methods available in toolboxes
  - **FSL** from Oxford
  - **SPM** from London
  - **AFNI** from Wisconsin / NIH
  - **Freesurfer** from Harvard

Pre-processing

- Prepares data for analysis & inference
- Typical steps:
  - Motion correction
  - Brain segmentation
  - Registration to anatomical, standard space



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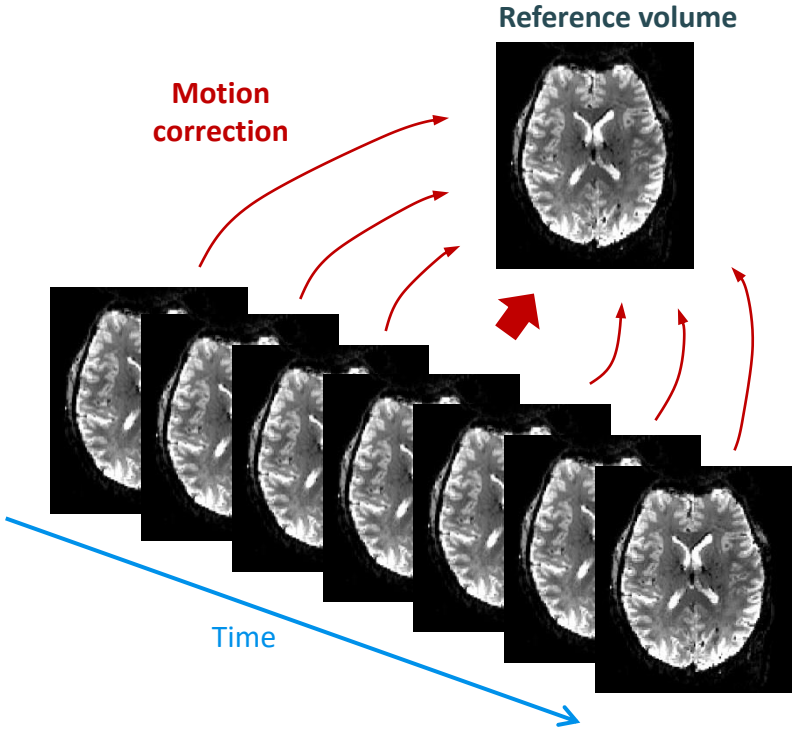
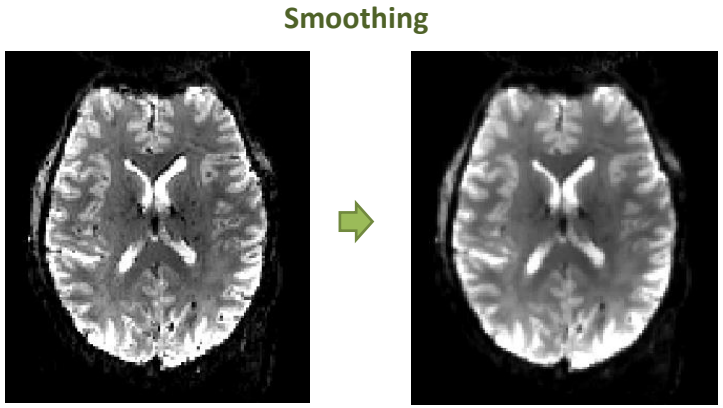


Pre-processing

- Prepares data for analysis & inference
- Typical steps:
  - Motion correction
  - Brain segmentation
  - Registration to anatomical, standard space
  - Spatial smoothing



4. fMRI data: stimulation/task studies

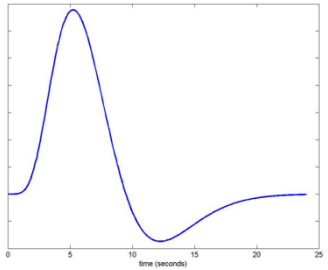
Brain responses to stimuli/tasks

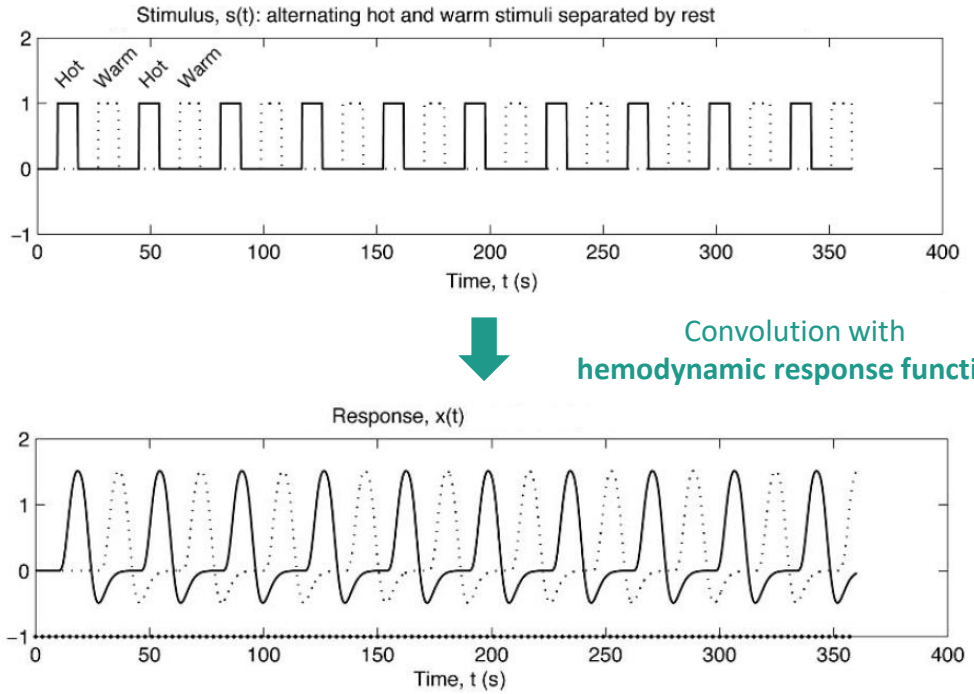
- Experimenter controls the stimuli / tasks / conditions
- Certain brain regions can respond, positively or negatively

A model for elicited responses

- Needs to account for BOLD temporal dynamics

Ex: combination of two gamma functions





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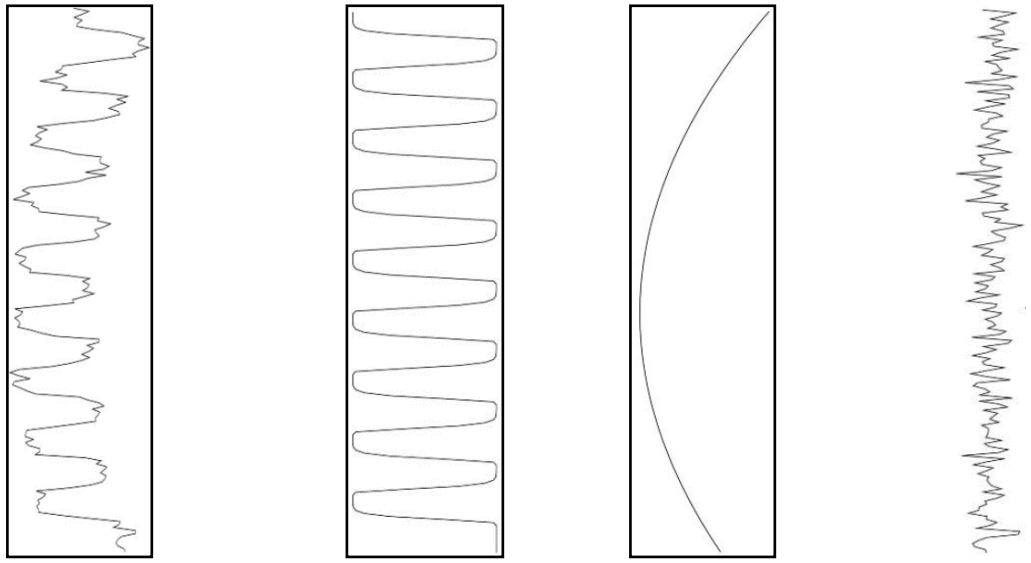
A model for the measured signals

- **General linear model (GLM)** analysis

$$Y = \beta_1 * X_1 + \beta_2 * X_2 + \varepsilon$$



Measured signal | **Response of interest** | **Confounds**

- slow drift, motion, cardiac & respiratory noise, and so on…

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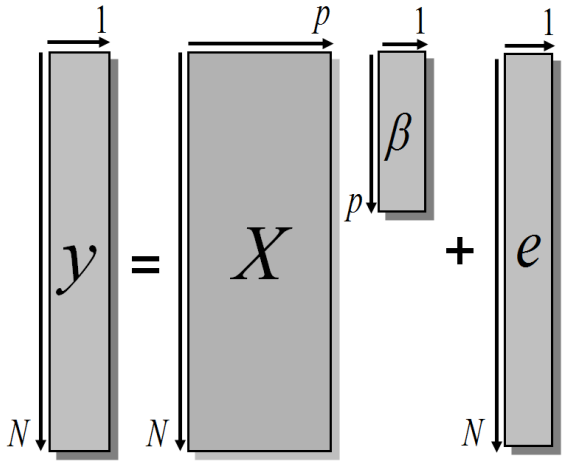
Matrix form

$$y = X\beta + e$$

$$e \sim N(0, \sigma^2 I)$$

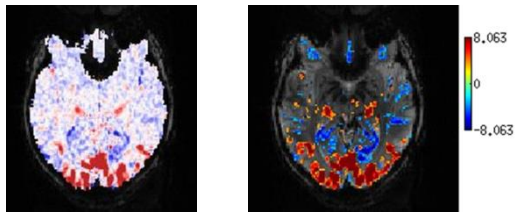


Statistical inference

- Which voxels/regions significantly respond to the paradigm?

- **For each voxel:**
  1. Estimate β
  2. Determine estimation uncertainty σ (noise modeling, based on *e*)

$$Tvalue = \frac{\beta}{\sigma}$$



- Account for **multiple comparisons** (testing many voxels)

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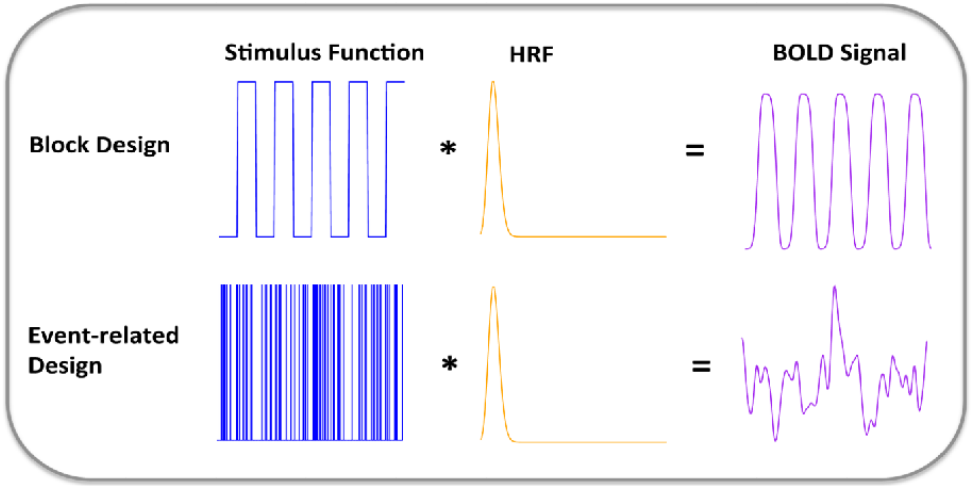
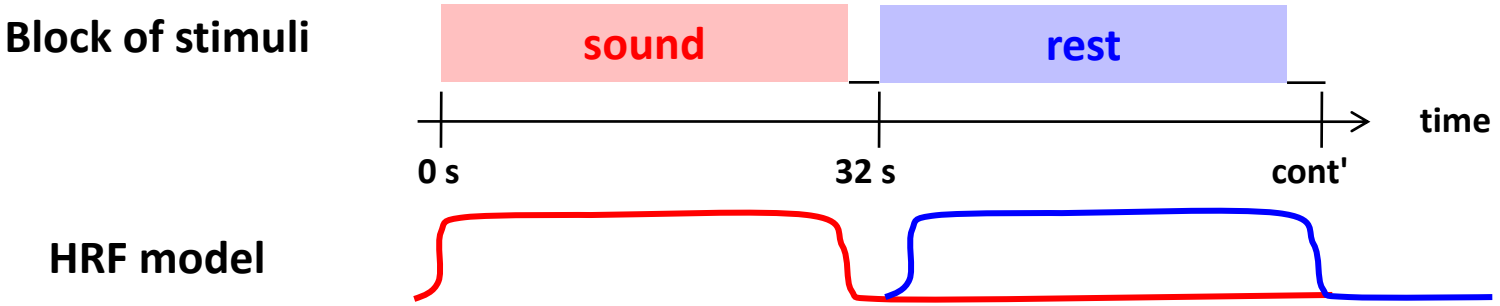
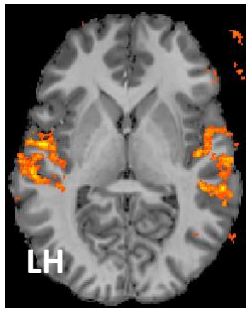






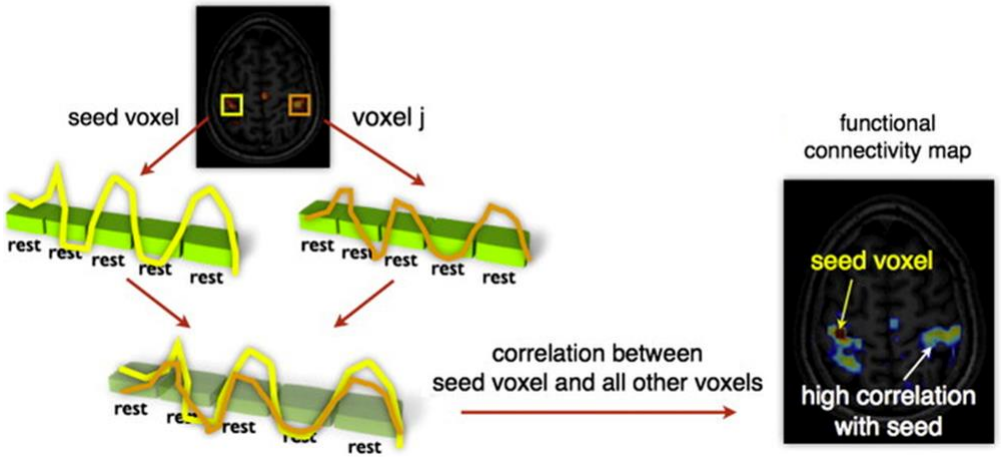
4. fMRI data: resting-state studies

Resting state activity

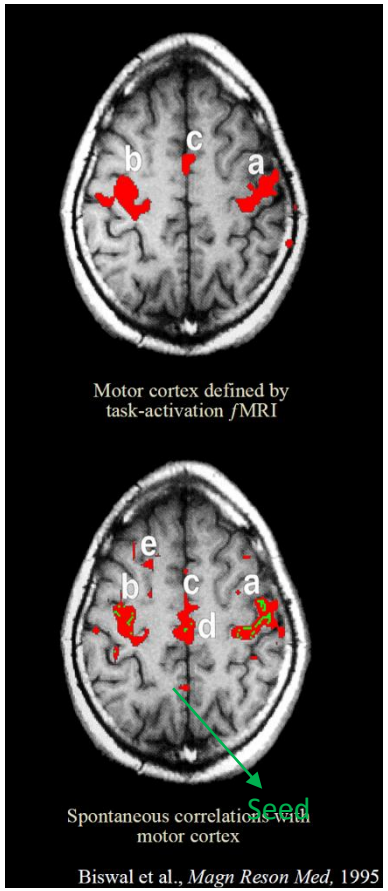
- No external control, no model
- Correlated fluctuations within and across regions (also termed **functional connectivity**)

Seed-based correlation analysis

- Pick a voxel or region
- Compute correlation to every other voxel/region
- Threshold correlation map



Example: motor cortex connectivity



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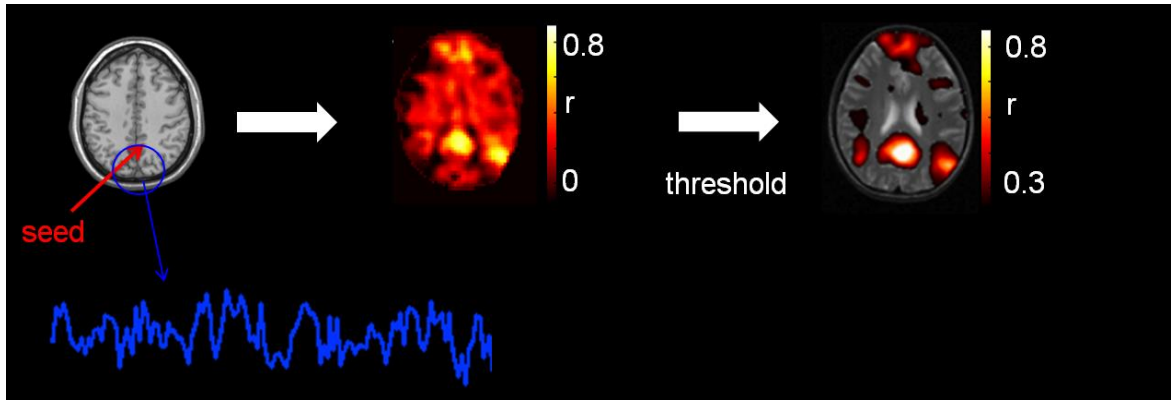
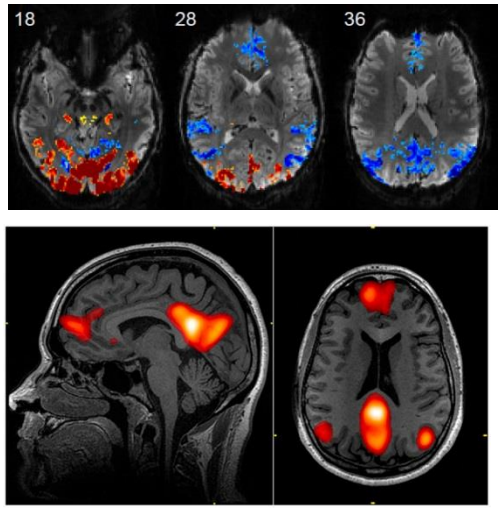
Example: "default mode network" or "task-negative network"



Negative response under visual stimulation



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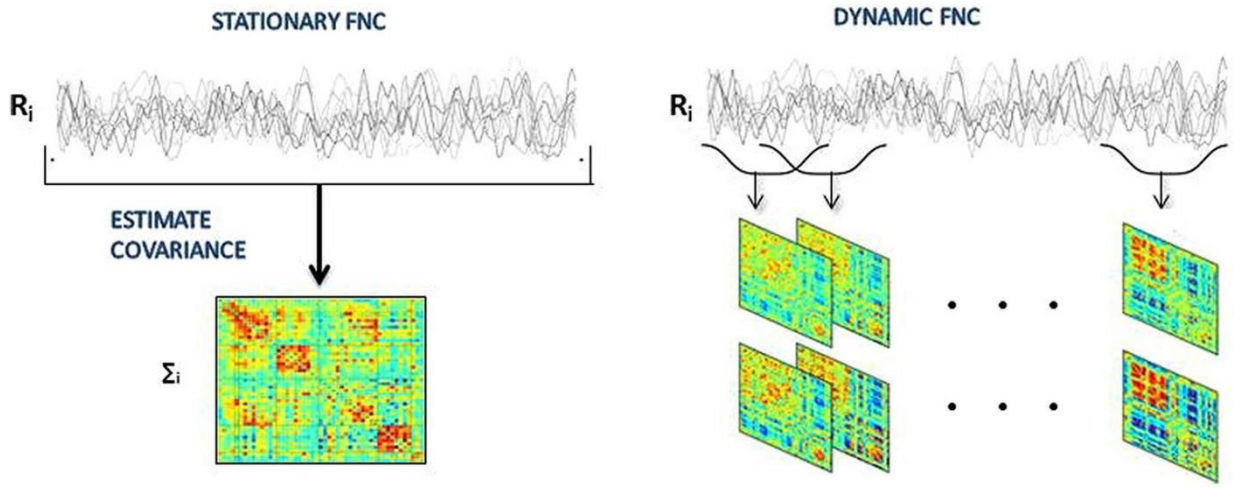
Sliding-window correlation for dynamic connectivity studies



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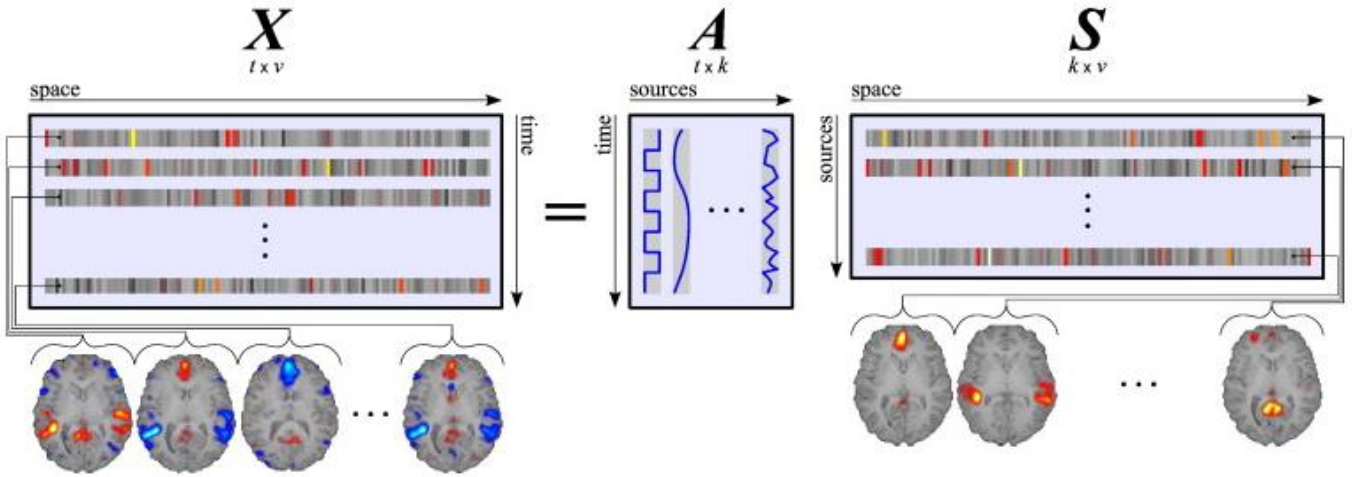
Independent component analysis

- Decomposes the data in statistically-independent components
- Each component comprises a **map** and its fluctuation **timecourse**
- Linear combination of all components spans the original data



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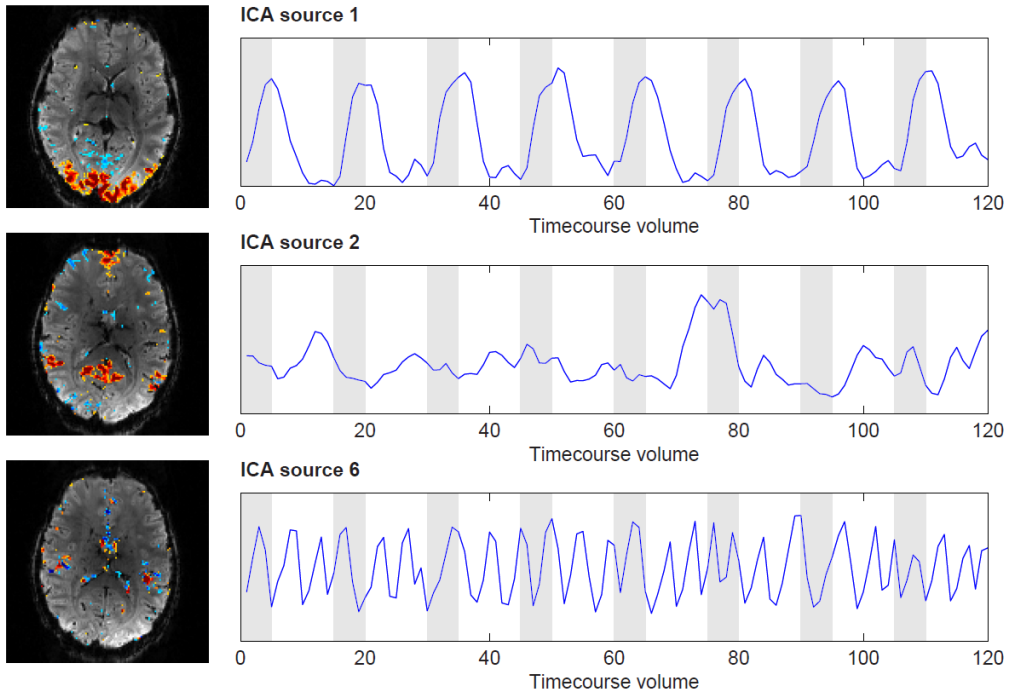
Example: visual stimulation data (no model-free specification)



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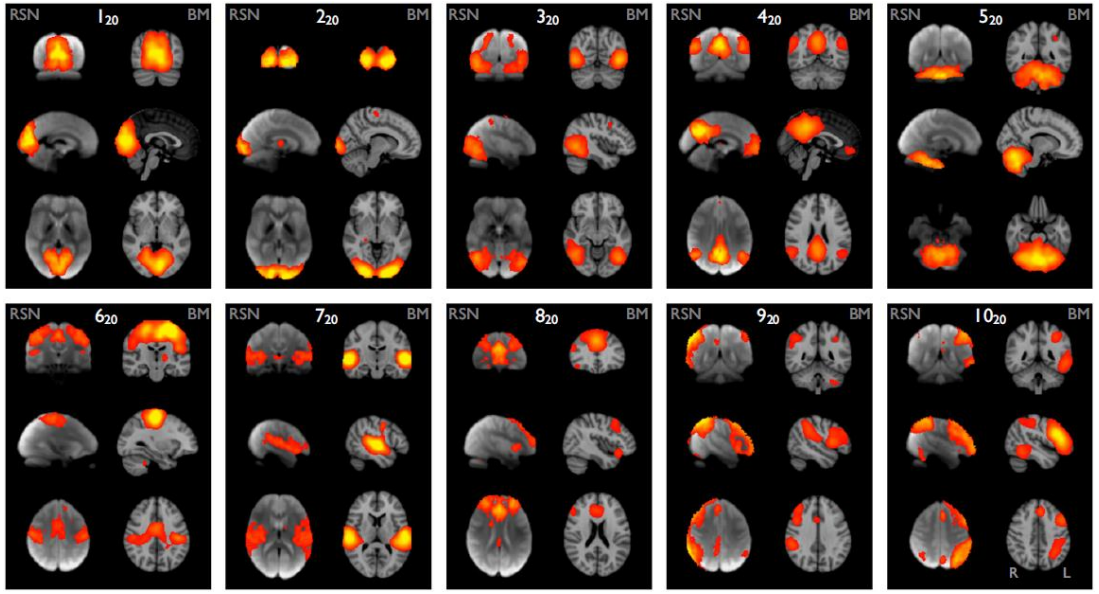
- Linear combination of all components spans the original data

(Smith et al. 2009)



Example: resting state data

Summary

0. MR signal & k-space

1. The BOLD contrast

- Biophysical mechanisms
- Spatiotemporal dynamics

2. fMRI data acquisition

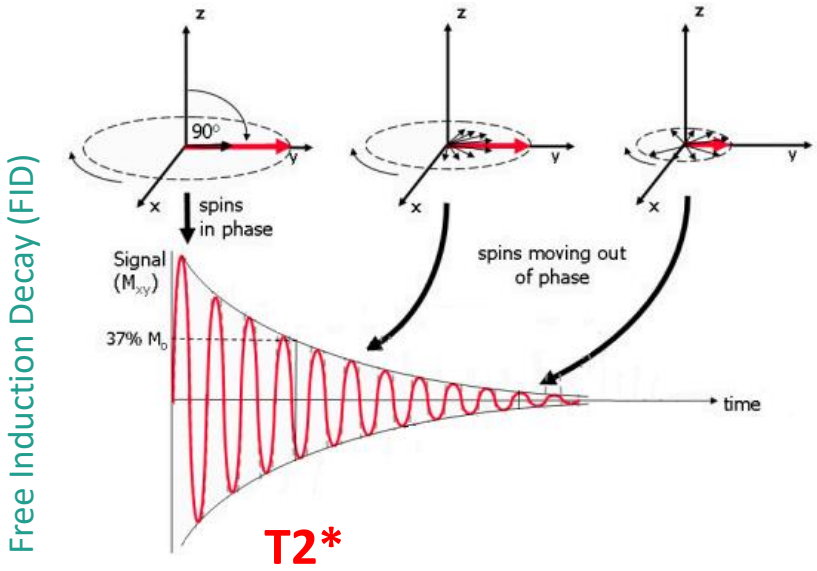
- Image acquisition
- Dependence on field strength

3. Non-BOLD fMRI

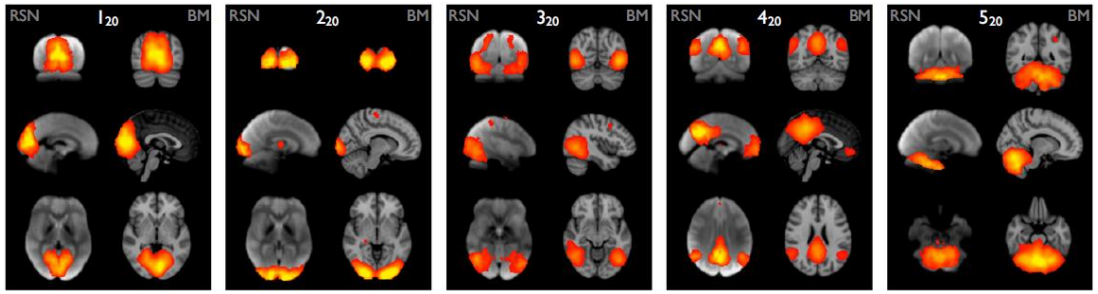
- ASL – measuring blood flow
- VASO – measuring blood volume

4. fMRI data analysis

- Pre-processing
- Analysis: event-related activity
- Analysis: spontaneous activity



Youtube > Renzo Huber: Layer dependent VASO in the Visual system



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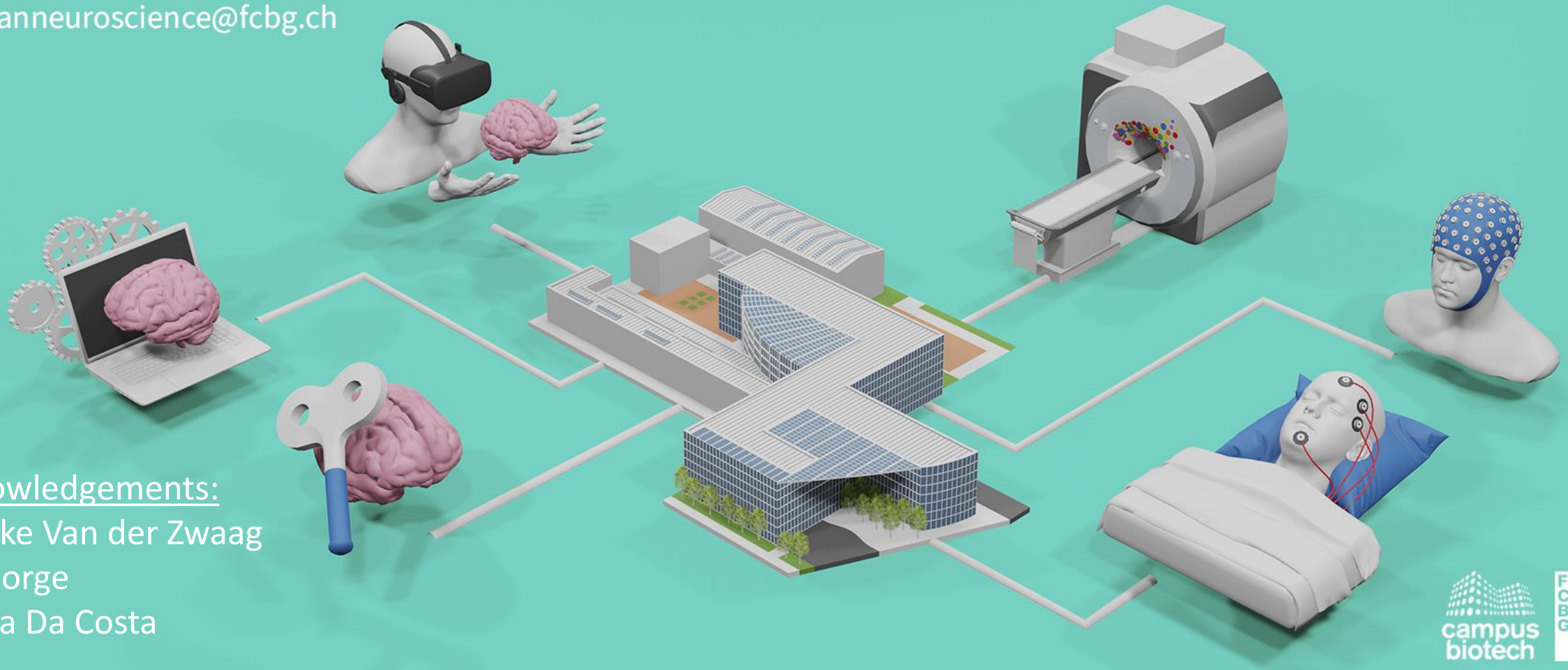

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