MRI *in a nutshell* (1)

- protons oscillate in external magnetic field
  (precession of nuclear spin)

- oscillation frequency depends on magnetic field strength
  Larmor frequency: $\omega_0 = \gamma B$; γ = gyromagnetic ratio
  protons: ω_0 = 42.58 MHz/T

- protons absorb energy, if exposed to electromagnetic energy
  at oscillation frequency (resonance)

- relaxation to equilibrium state via emission of that energy
  (= MRI signal)

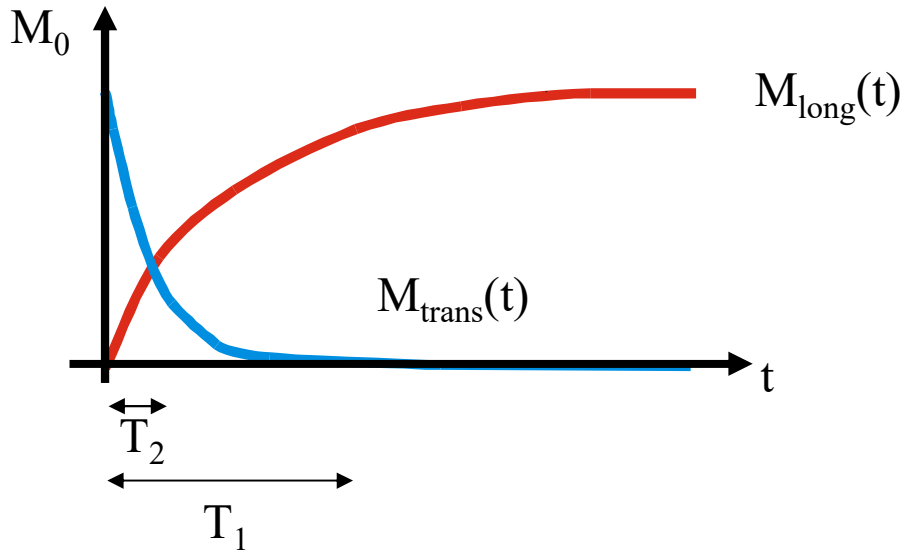
- relaxation to equilibrium state not instantaneous,
  requires certain time

MRI *in a nutshell* (2)

relaxation to equilibrium state determined by two physical processes:

(1) nuclear magnetization parallel
to magnetic field
(spin-lattice relaxation)
longitudinal relaxation time T1

(2) nuclear magnetization
perpendicular to magnetic field
(spin-spin Relaxation)
transversal relaxation time T2



effective transversal relaxation time: 1/T2* = 1/T2 + 1/T2(inhom.)

MRI *in a nutshell* (3)

MRI **signal amplitude** depends on:

(1) ***proton density (PD) in tissue***
(the higher the density the higher the signal amplitude)

(2) ***T1 time***
(relaxation time of magnetization parallel to external field)

(3) ***T2 time***
(relaxation time of magnetization perpendicular to external field)

MRI *in a nutshell* (4)

MRI **image contrast** depends on PD, T1, T2 of different tissues

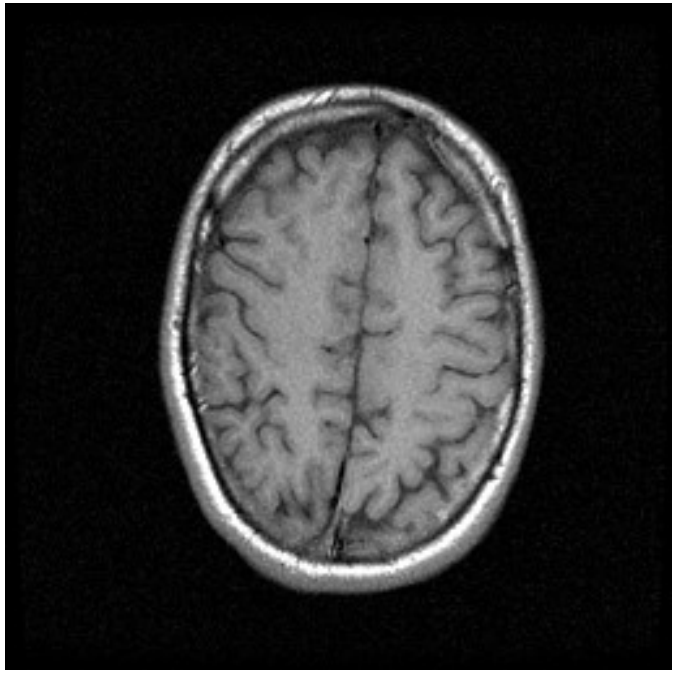
soft matter in body:
- PD extremely homogeneous (contributes weakly to signal difference)
- T1 and T2 differ strongly (main contrast)
- T1 and T2 depend on viscosity/stiffness of tissue

-in general: the more stiff resp. doughy the tissue
the shorter T1 and T2

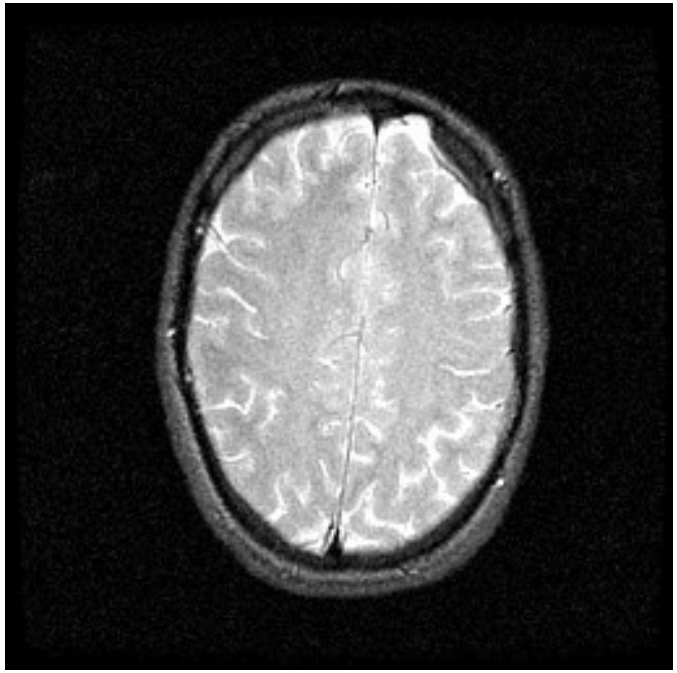
different images by accentuating different tissue properties
(proton density-, T1 - , T2 - weighting)

MRI *in a nutshell*

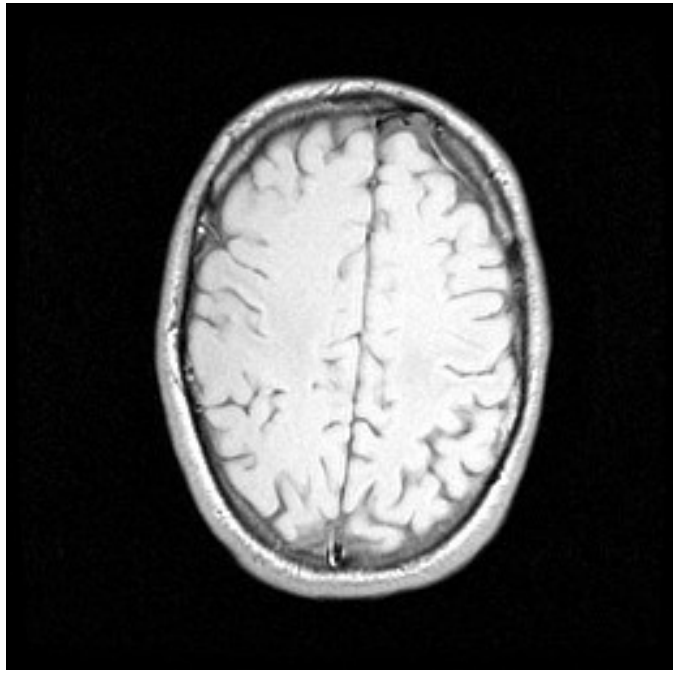
T1 contrast



T2 contrast



proton density



from MRI to fMRI

MRI

tomographic images based on magnetic properties of tissue

- non-ionizing
- non-invasive
- use as often as needed

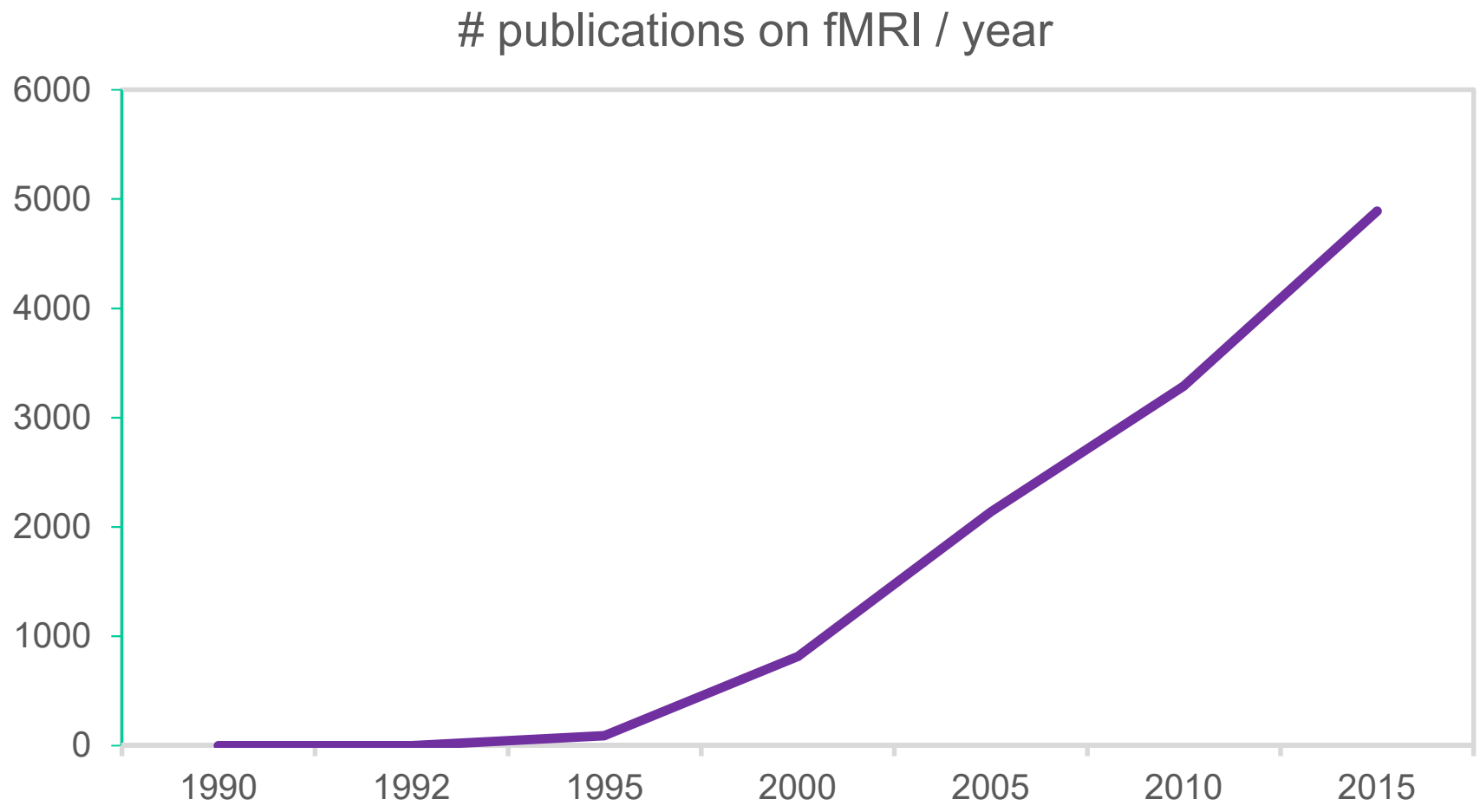
fMRI

differentiation of active and less/not active brain regions

basics:
hemodynamic processes
BOLD effect =
Blood Oxygenation Level Dependent

T2*-weighted images

functional MRI (fMRI)



source: web of knowledge; keywords: functional magnetic resonance imaging

functional MRI (fMRI)

BOLD =
Blood Oxygenation
Level Dependent

Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 9868–9872, December 1990
Biophysics

Brain magnetic resonance imaging with contrast dependent on blood oxygenation

(cerebral blood flow/brain metabolism/oxygenation)

S. OGAWA, T. M. LEE, A. R. KAY, AND D. W. TANK

Biophysics Research Department, AT&T Bell Laboratories, Murray Hill, NJ 07974

- blood contains oxygenated and deoxygenated hemoglobin

- ***oxy-hemoglobin (Hb) is diamagnetic****
  paired e^-; sum of magnetic moments vanishes (= 0)
  does not affect MR signal

- ***deoxy-hemoglobin (dHb) is paramagnetic****
  free e^-; sum of magnetic moments $\neq 0$
  changes in susceptibility lead to local field inhomogeneities
  reduced MR-signal amplitude (shortened T2* time)
  dHb as body-intrinsic contrast agent!

* Pauling, L. and Coryell, C. D. (1936) The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin *Proc. Natl. Acad. Sci. USA* **22,**210-216.
(physical reasons for different magnetic properties still unknown. configuration change? structural change? other ?)

functional MRI (fMRI)

hemoglobin

- blood-inherent protein

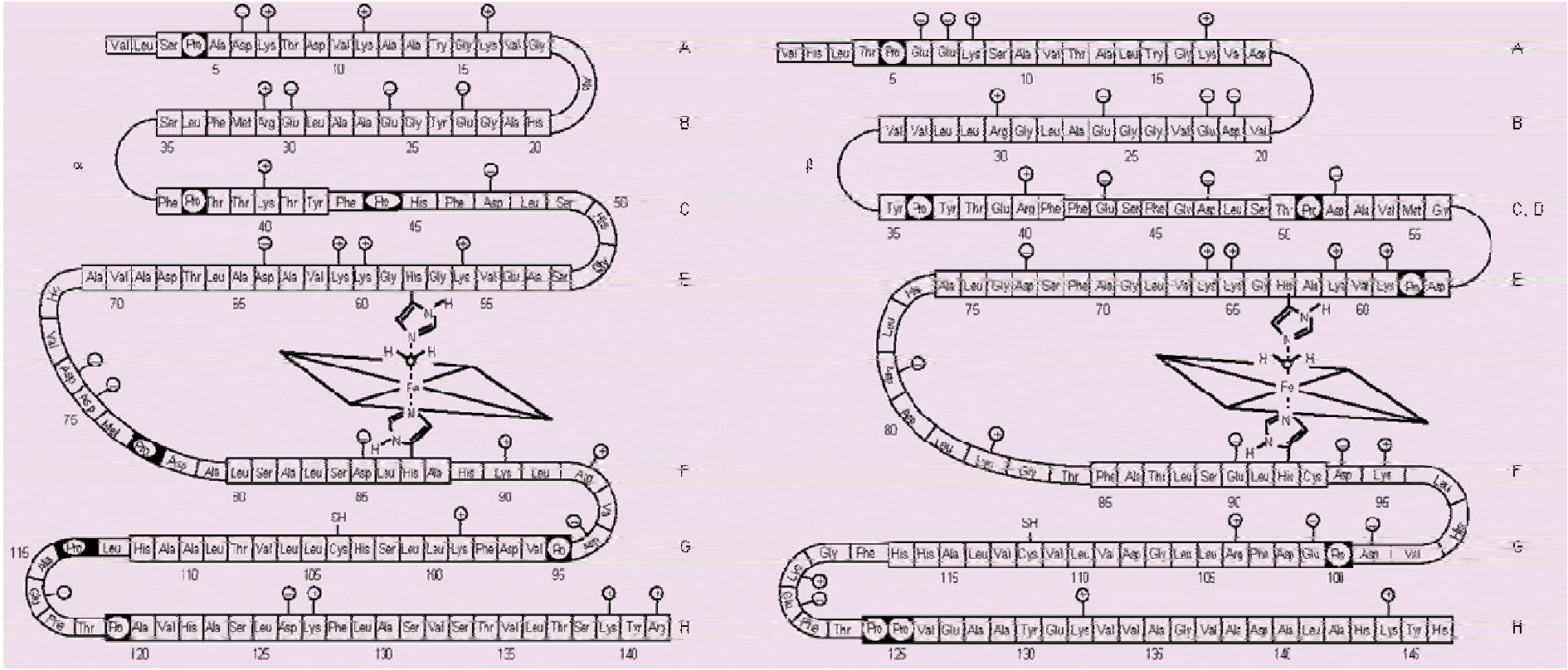
- binds oxygen

- relevant contribution:
iron bound into organic structure
(red color of blood)

- oxy-hemoglobin: with bounded oxygen

- deoxy-hemoglobin: without oxygen

hemoglobin



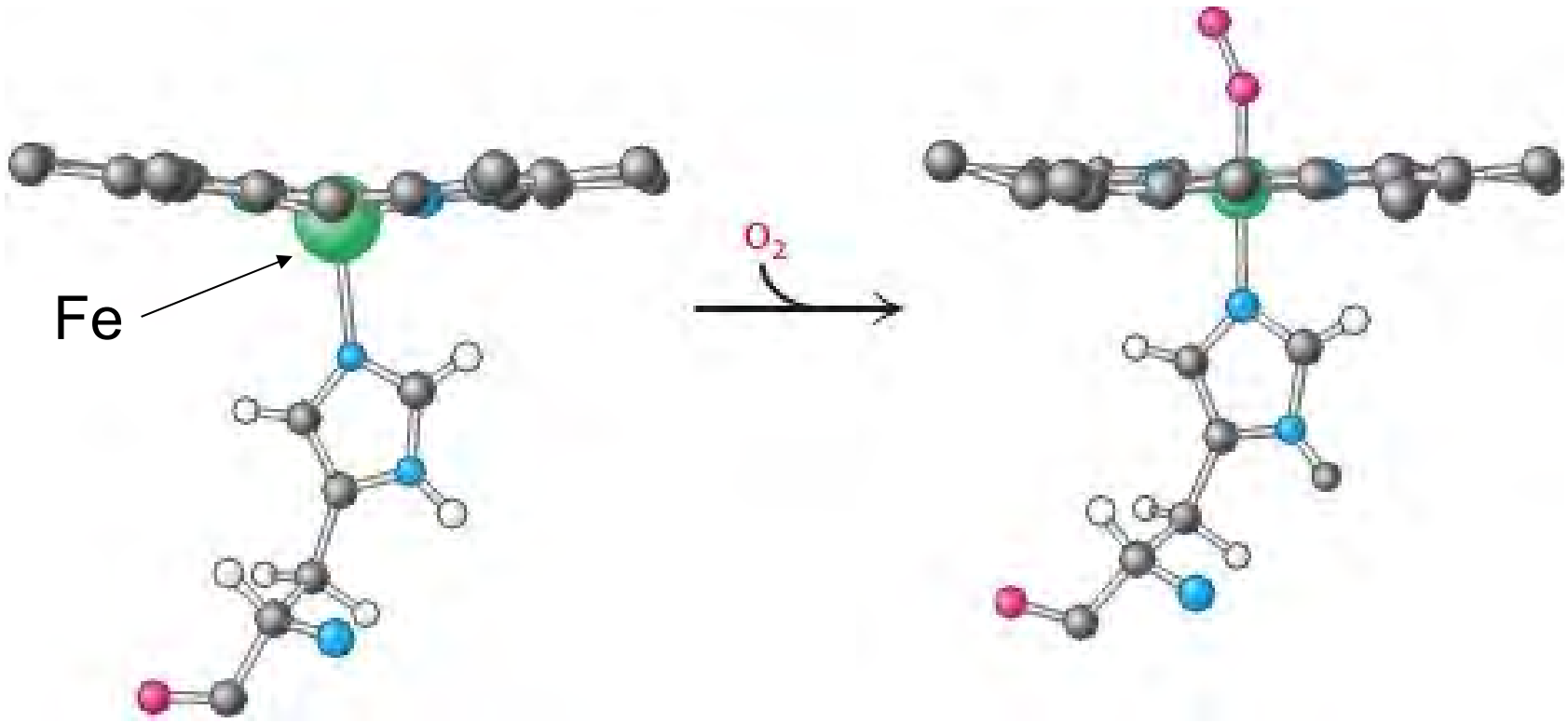
hemoglobin: amino-acid sequence of α- + β-chain: **Ala** = alanine, **Gly** = glycine, **Val** = valine, **Glu** = glutamine acid, **Thr** = threonine, **Cys-SH** = cysteine, **His** = histidine, **Lys** = lysine, **Asp** = asparagine acid, **Leu** = leucine, **Pro** = proline, **Phe** = phenylalanine, **Met** = methionine, **Try** = tryptophan, **Arg** = arginine, **Ser** = serine, **Tyr** = tyrosine

functional MRI (fMRI)

hemoglobin

deoxygenated

oxygenated



free e^- due to configuration change ?

functional MRI (fMRI)

basics

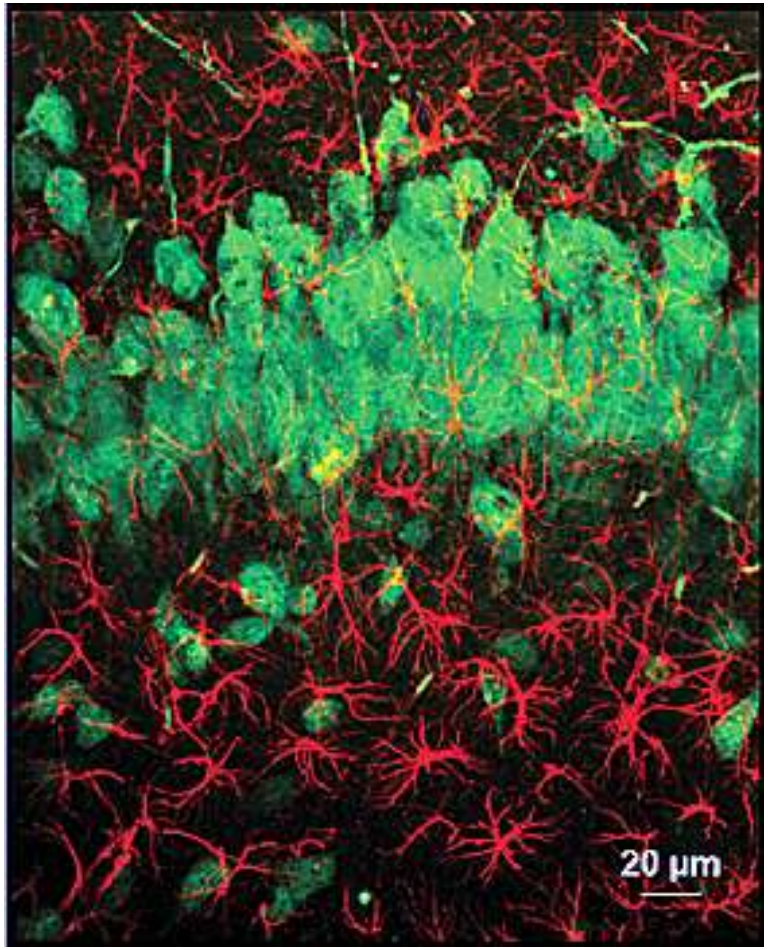
neuronal activity

neurons	glia cells	other cells
~10^{12}	x3	>>>
processing storage transmission of information	surround neurons support cells biochemical synthesis energy buffering electric isolation preserve ionic equi- librium	supply: oxygen sugar amino acids etc.

information processing

(Bezzi et al., Nature Neurosci 2004)

basics **neuronal activity**

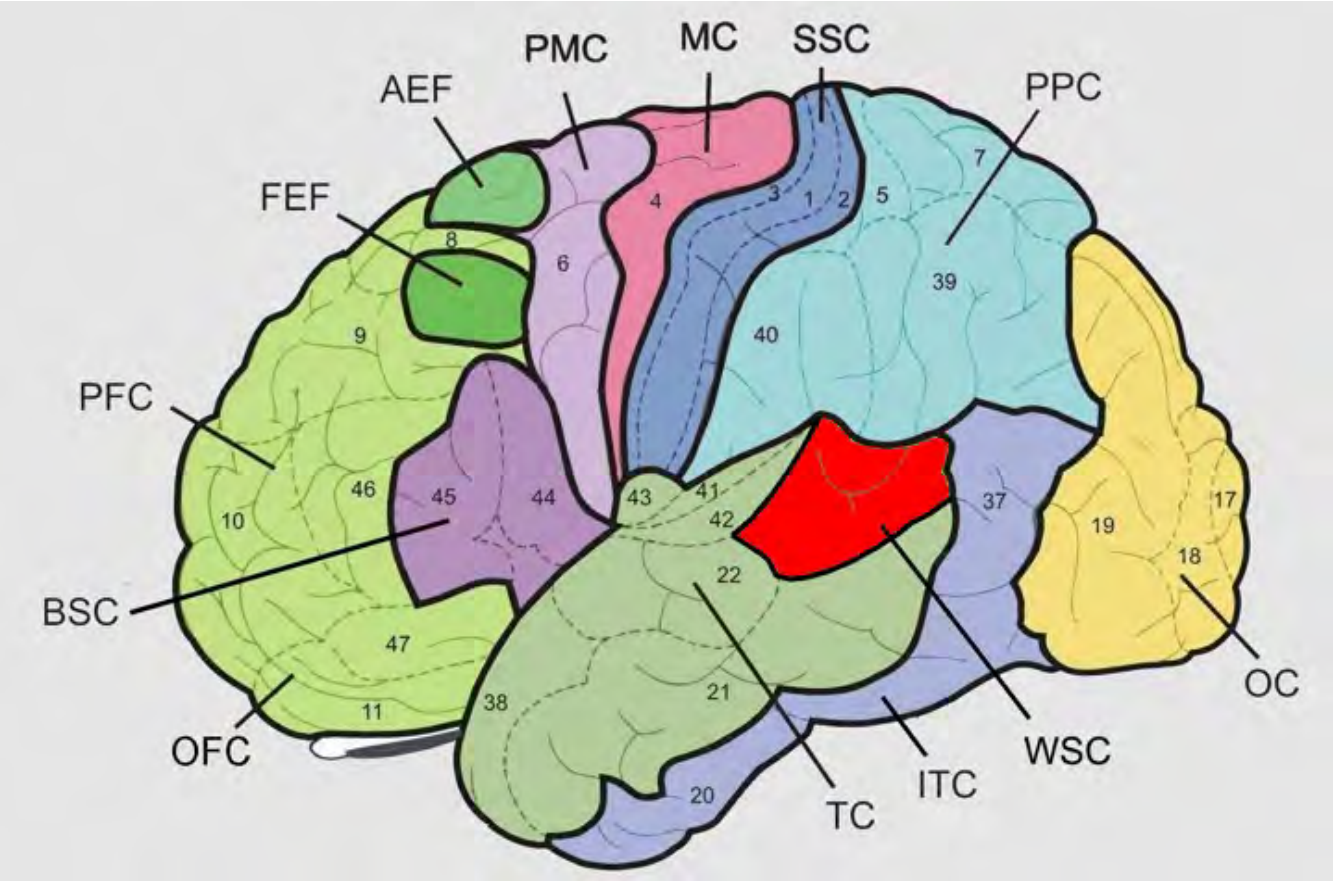


hippocampus (rat)

red: glia (GFAP)
green: cell body of neuron (NeuN)

basics

functional units of the brain



AEF = anterior eye field

FEF = frontal eye field

MC = motor cortex

OFC = orbital frontal cortex

PFC = prefrontal cortex

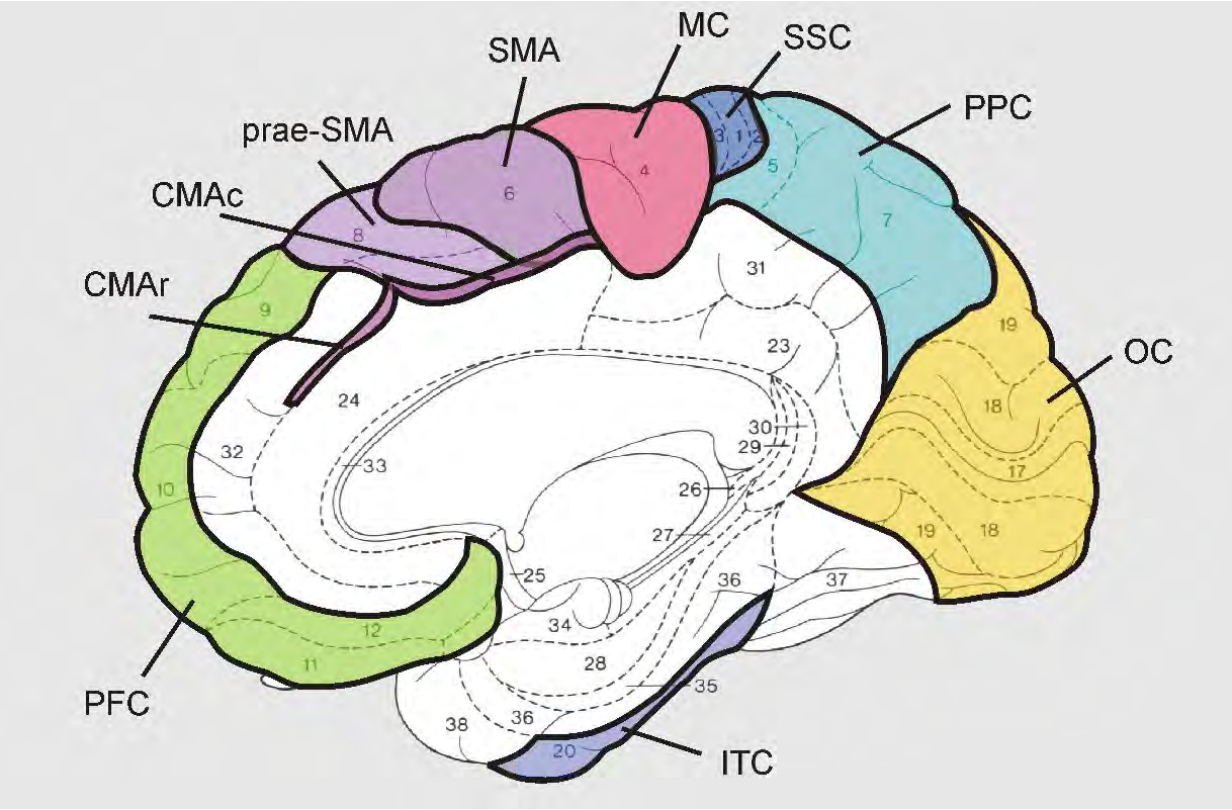
PMC = dorsolateral pre-motor cortex

PPC = posterior parietal cortex

SSC = somatosensory cortex

basics

functional units of the brain



MC = motor cortex

OFC = orbital frontal cortex

prae-SMA = pre-supplementary motor area

PFC = prefrontal cortex

PPC = posterior parietal cortex

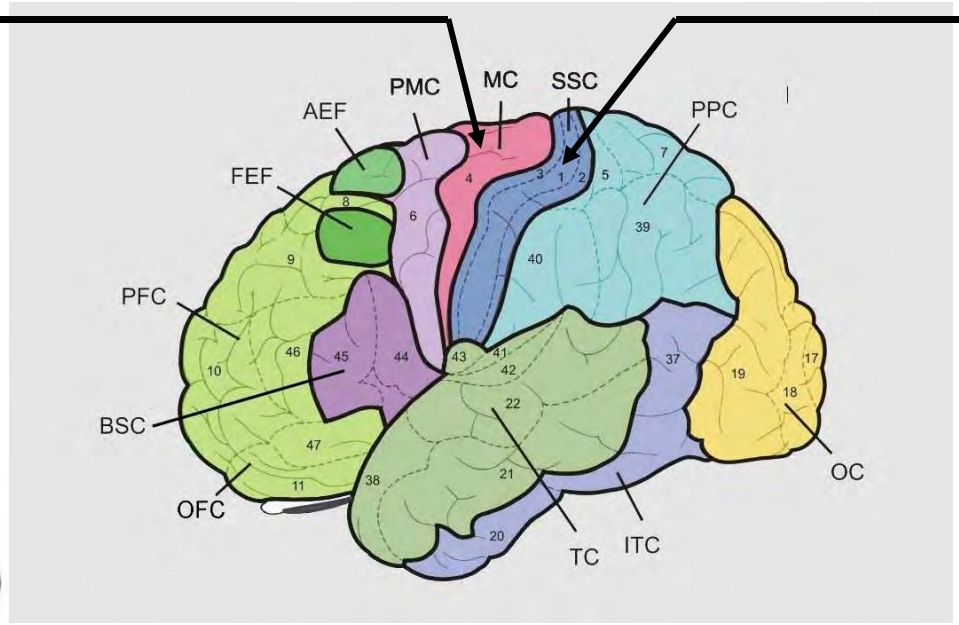
SMA = supplementary motor area

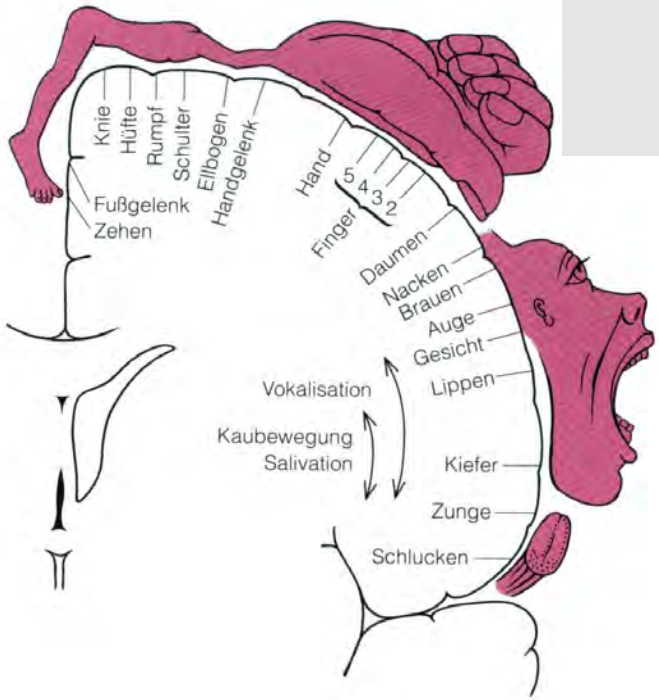
SSC = somatosensory cortex

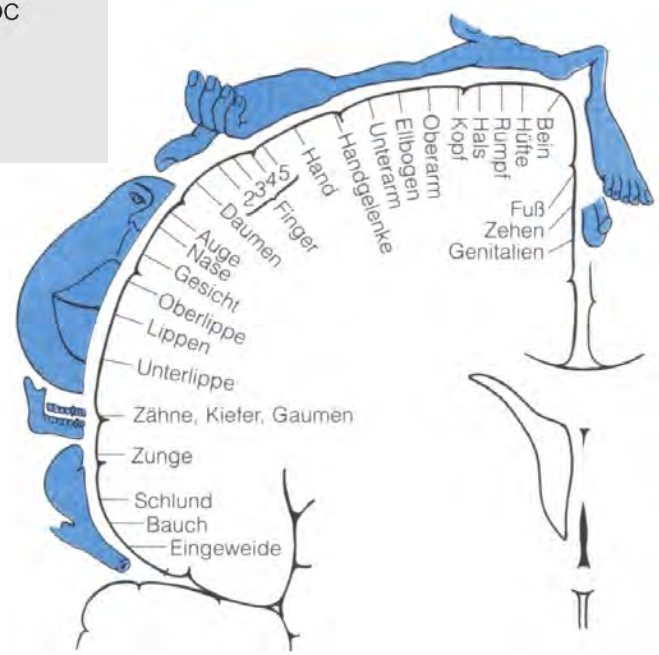
functional MRI (fMRI)

basics

functional units of the brain



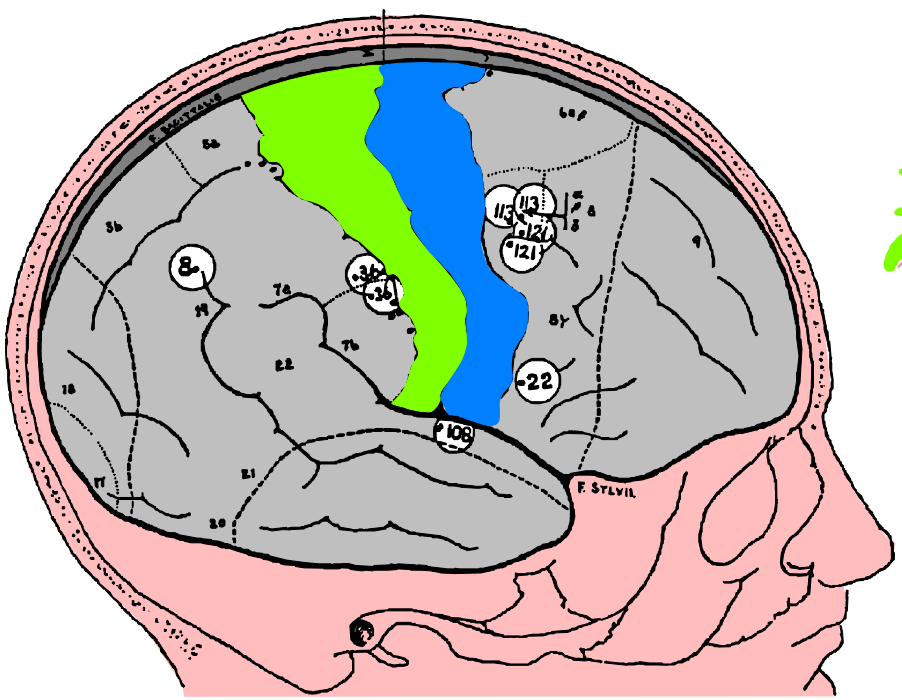


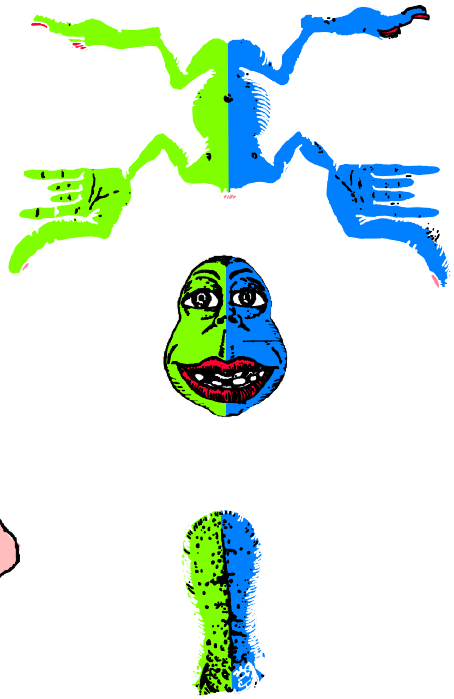


functional MRI (fMRI)

basics

functional units of the brain





Penfield and Jasper, 1954

basics **energy consumption of brain**

brain: **about 2 % of body weight**

oxygen consumption: **about 20 % of total consumption**

blood flow: **about 15 % of total blood flow**

blood flow (per unit volume) towards grey matter (synapses) about 10x higher than to white matter (cells)

regulation of blood flow no fully understood !!

basics **blood flow and hemodynamic response**

Roy and Sherrington (1890): "On the regulation of blood supply of the brain"

hypothesis (neurovascular coupling):

regional cerebral blood flow (rCBF) adjusts to metabolic requirements of neuronal activity

observations with neuronal activity:

- increase of local oxygen consumption by about 5 %
- increase of rCBF by 30 - 50 % (reason?)
- increase of regional cerebral blood volume by about 10%

spatial resolution of rCBF: ~ 1.5 – 3 mm^3

deoxy-hemoglobin concentration

***influencing factors*:**

(1) oxygen consumption of neurons (and glia)
increased consumption $\Rightarrow$ increased dHb concentration
in surrounding blood vessels

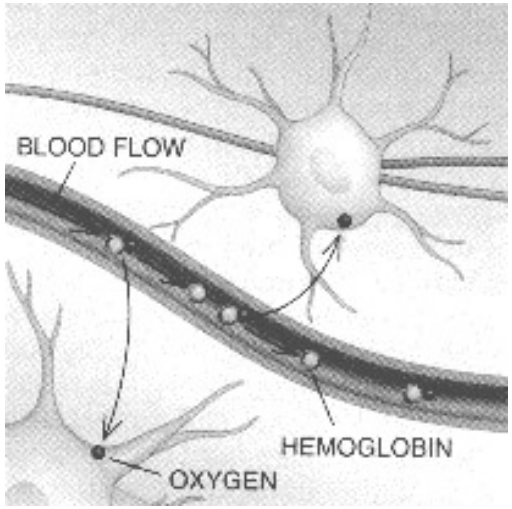
(2) blood flow
increased blood flow $\Rightarrow$ wash-in of oxygen-enriched blood;
wash-out of oxygen-depleted blood $\Rightarrow$
decreased dHb concentration

(3) change in blood volume
increased blood volume $\Rightarrow$ increased dHb concentration
however: (2)

BOLD-fMRI as "indirect" tracer of neuronal activity

- dHb in blood vessels
  susceptibility difference between
  vessels and surrounding tissues

"at rest"



- dephasing of proton MR-signal
  $\Rightarrow$ reduction of T2* time

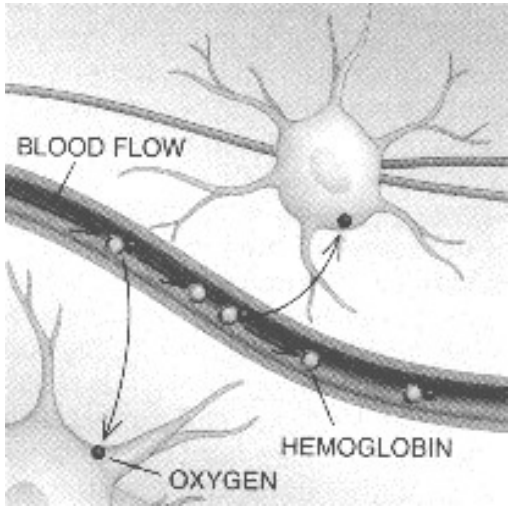
- T2*-weighted images:
  $\Rightarrow$ decreased signal intensity in voxel
  containing blood vessels (dark)

$\Rightarrow$ change in oxygenation can be observed
as signal changes in T2*-weighted images

BOLD-fMRI as "indirect" tracer of neuronal activity

naive ansatz for neuronal activity:
⇒ increased oxygen consumption
⇒ increased dHb concentration in blood
⇒ reduced MR-signal

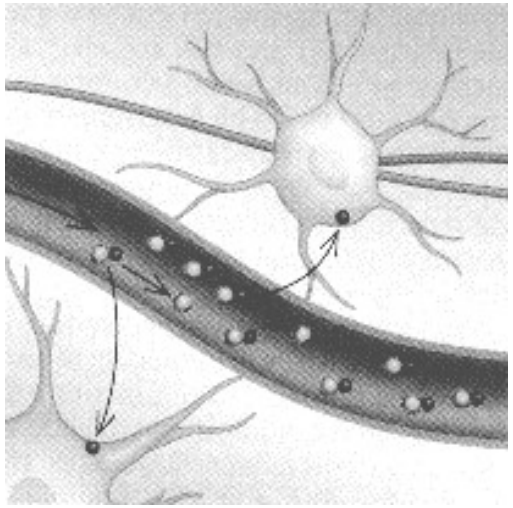
"at rest"



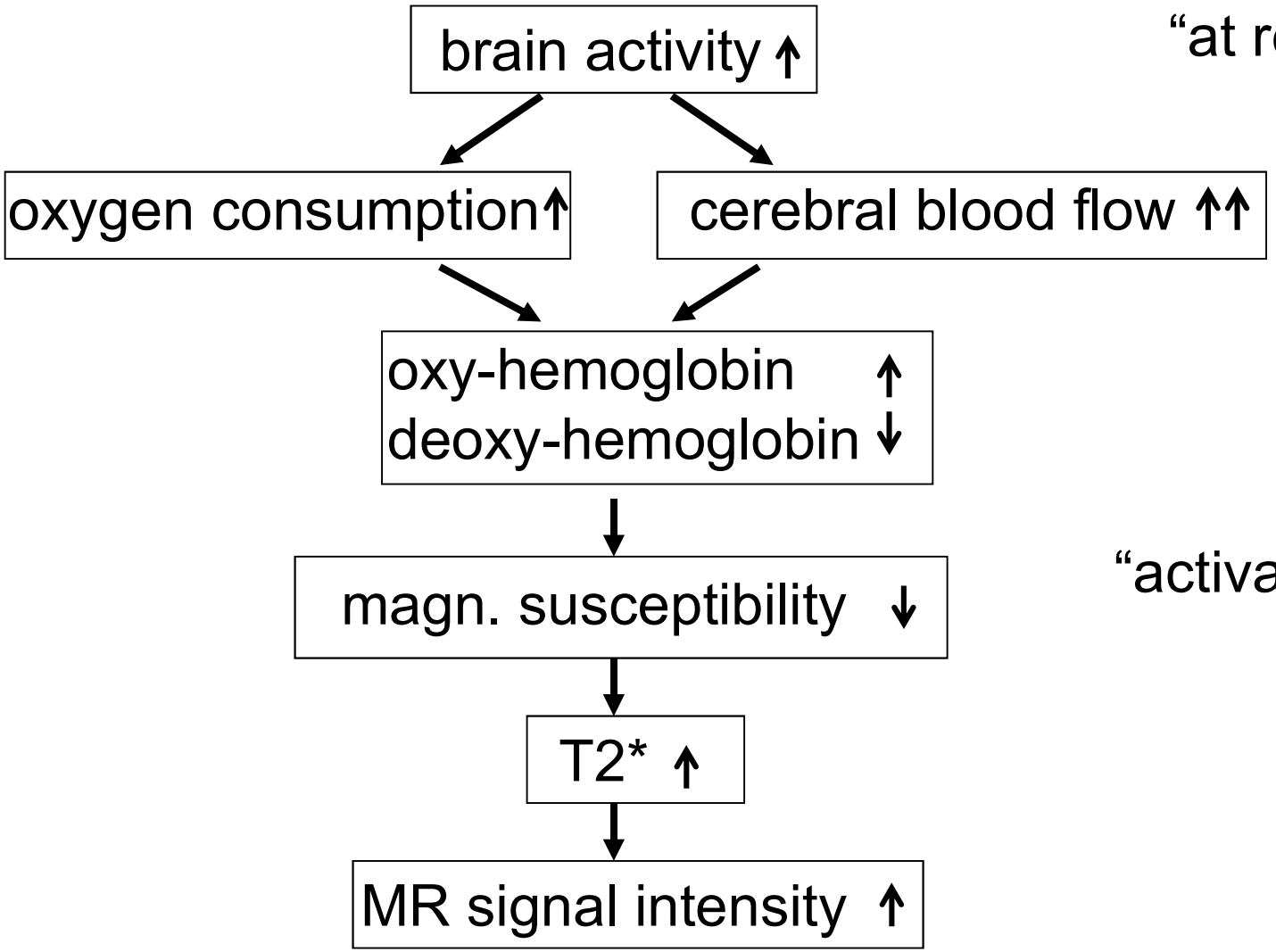
observation:
⇒ increased MR-signal !!
⇒ reduced dHb concentration (?)

reason:
- slightly enhanced oxygen extraction
- but: more profound increase of rCBF
⇒ increased oxy-hemoglobin (Hb)
⇒ mass effect: regional decrease of dHb
⇒ increased MR-signal

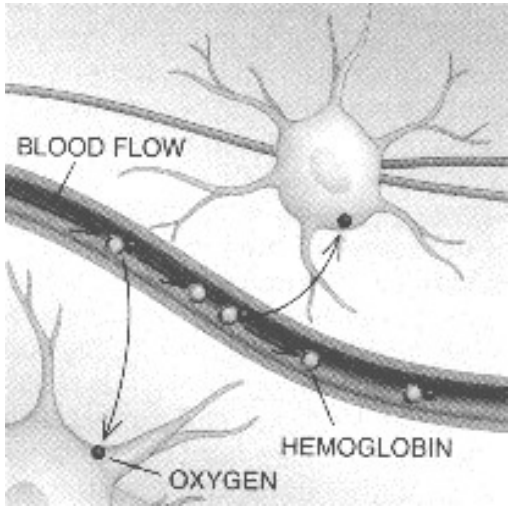
"activated"



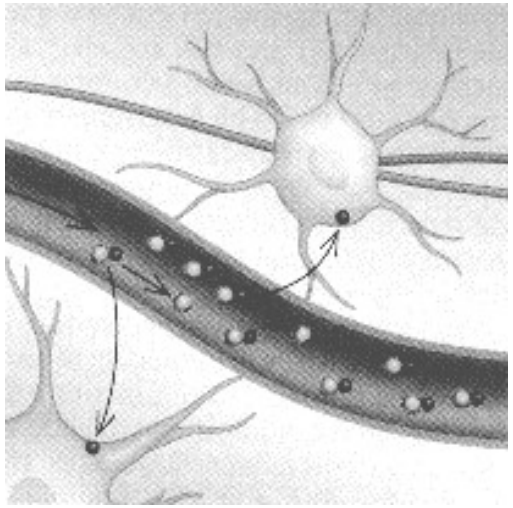
BOLD-fMRI as "indirect" tracer of neuronal activity



"at rest"



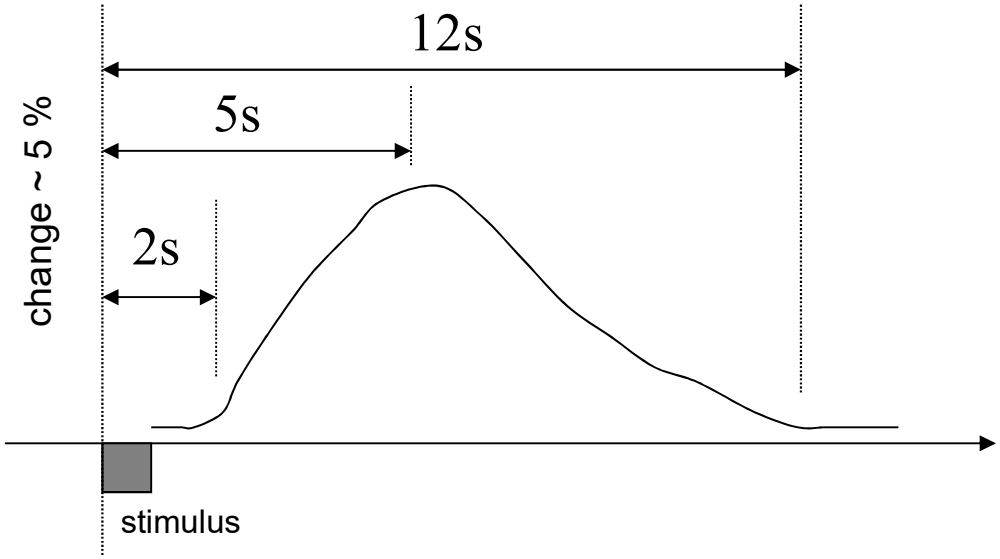
"activated"

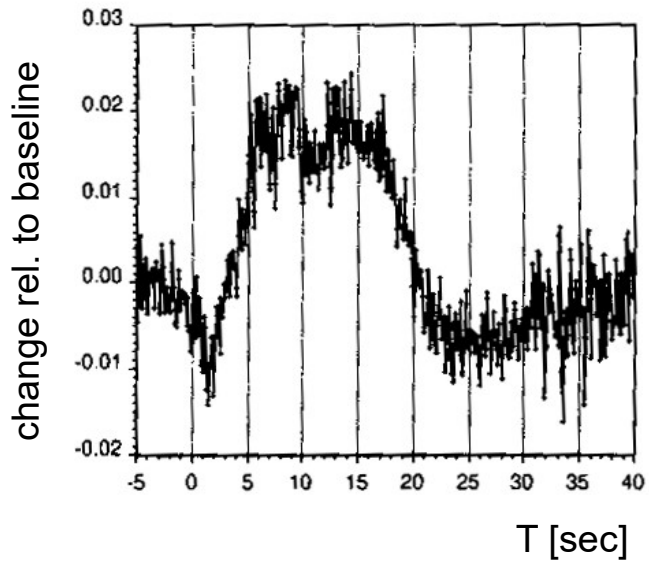


temporal course of BOLD effect

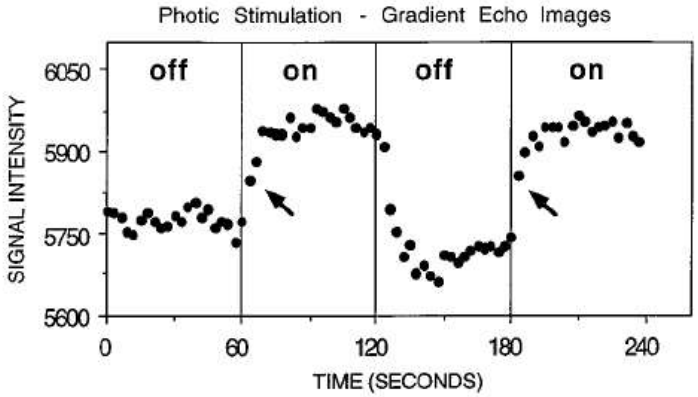
hemodynamic response:

1. **"initial dip"**
   slight decrease of
   MR signal at onset of
   neuronal activity (why?)
2. **progression**
   maximum increase after about
   4-6 s
3. **plateau**
   habituating static signal
4. **relaxation**
   return to resting level
   (possibly post stimulus undershoot)



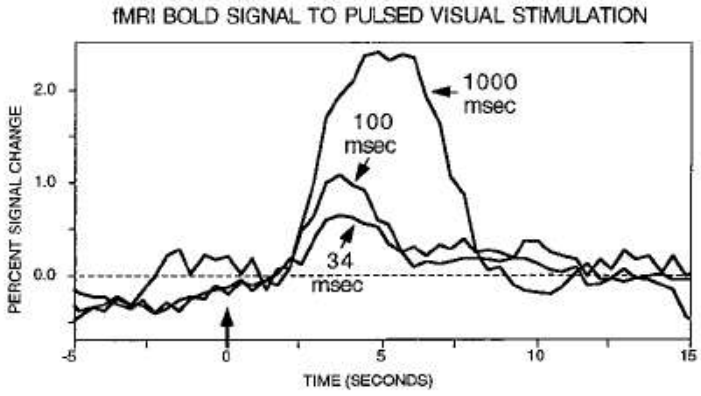


functional MRI (fMRI)



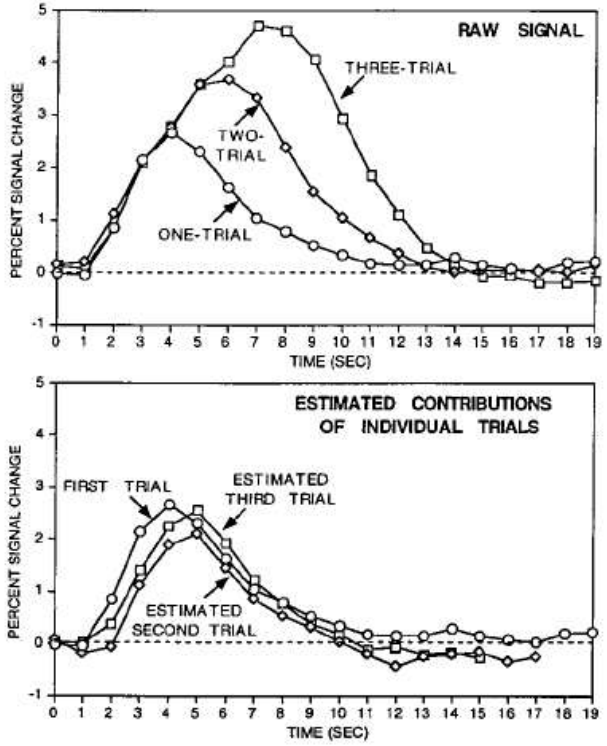
1992

FIG. 1. Adapted from Kwong *et al.* (20). BOLD contrast signal change is shown for a region of visual cortex during stimulation (on) and during rest (off). These data originally were used to demonstrate the application of BOLD contrast fMRI in normal human subjects. As can be seen, the rise time of the signal (indicated with arrows) is very rapid and has occurred after just a few seconds of stimulation, indicating that shorter stimulus events should be detectable.



1995

FIG. 2. Data from Robert Savoy and Kathleen O'Craven (25). BOLD contrast signal change are shown for visual stimuli of various brief durations. The three curves represent signal change for 34 msec, 100 msec, and 1,000 msec of stimuli, respectively. Importantly, clear signal change can be observed for events lasting as briefly as 34 msec.



1997

FIG. 3. Adapted from Dale and Buckner (31). (*Upper*) The raw BOLD fMRI signal evoked when either one, two, or three trials of visual checkerboard stimulation are presented. The trials were each 1 sec in duration and separated by 1 sec. The response increases and is prolonged with the addition of multiple trials, indicating it does not saturate going from one to three trials. (*Lower*) The explicit contribution of each individual trial by subtracting the one-trial condition from the two-trial condition (yielding the estimated response of the second trial) and the two-trial condition from the three-trial condition (yielding the estimated response of the third trial). The three estimated trials are roughly similar, although subtle but clear departures from linearity can be observed. This finding suggests the bold response can be shown to add linearly over trials, although the generalization of this finding to other brain regions and trial types is still an open question.

(from: Rosen et al., PNAS, 95, 773, 1998)

amplitude of BOLD effect

depends on:

- field strength (amplitude ~ B_0^{α}, $1 < \alpha < 2$)
  characteristic: B_0 = 1.5 – 3 T; experimental: 4 - 7 T

- echo time (TE) and repetition time (TR)
  ideally: TE and TR large
  $\Rightarrow$ gradient-echo sequence (slice-by-slice)
  $\Rightarrow$ EPI-sequence (multi-slice technique)

single-shot EPI ~10-15 slices/s
whole head: (~30x4 mm-slices): 2-3 s

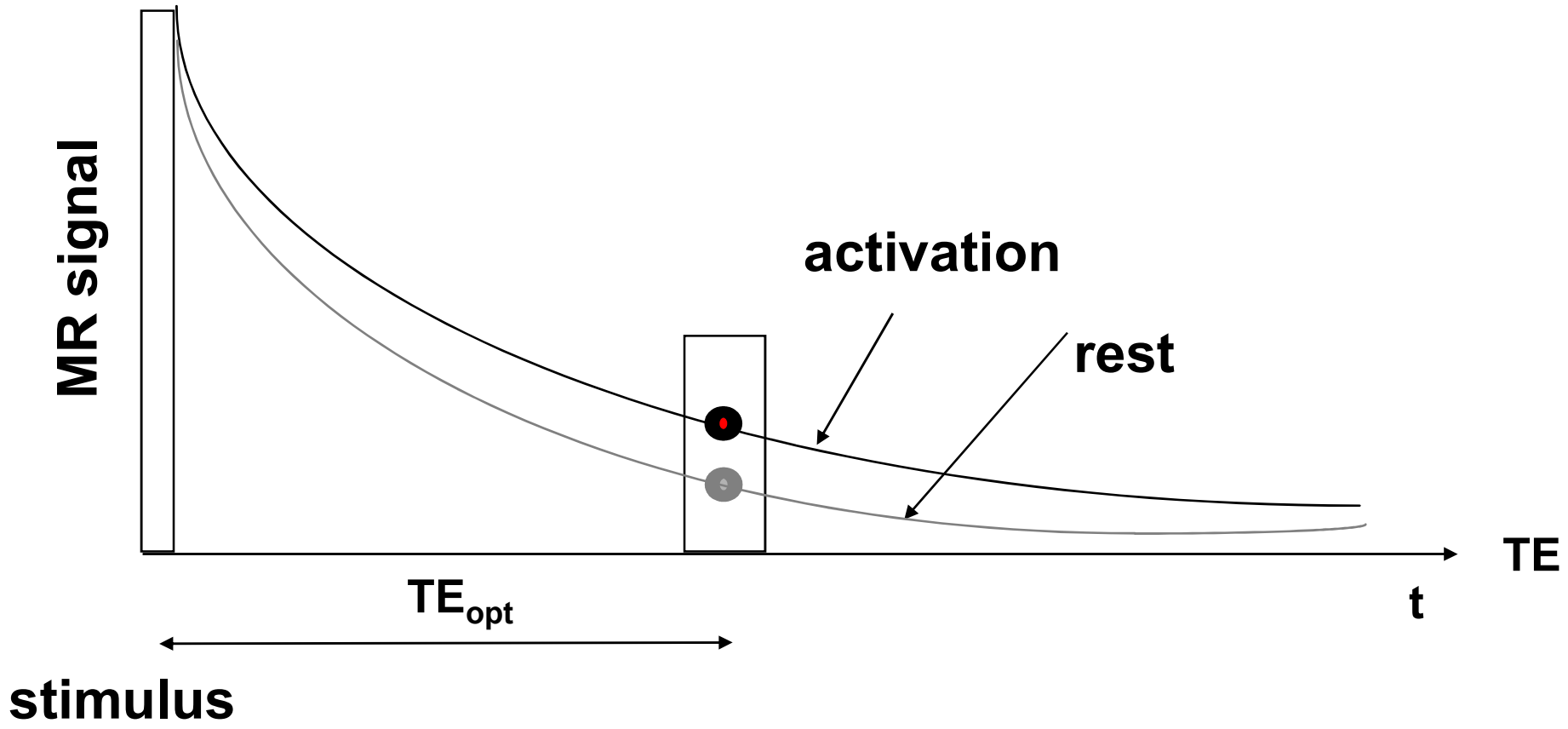
- blood volume

- +large number of physiologic and physical parameter (e.g. voxel size; slice thickness) !

$\Rightarrow$ T2*-weighted images !

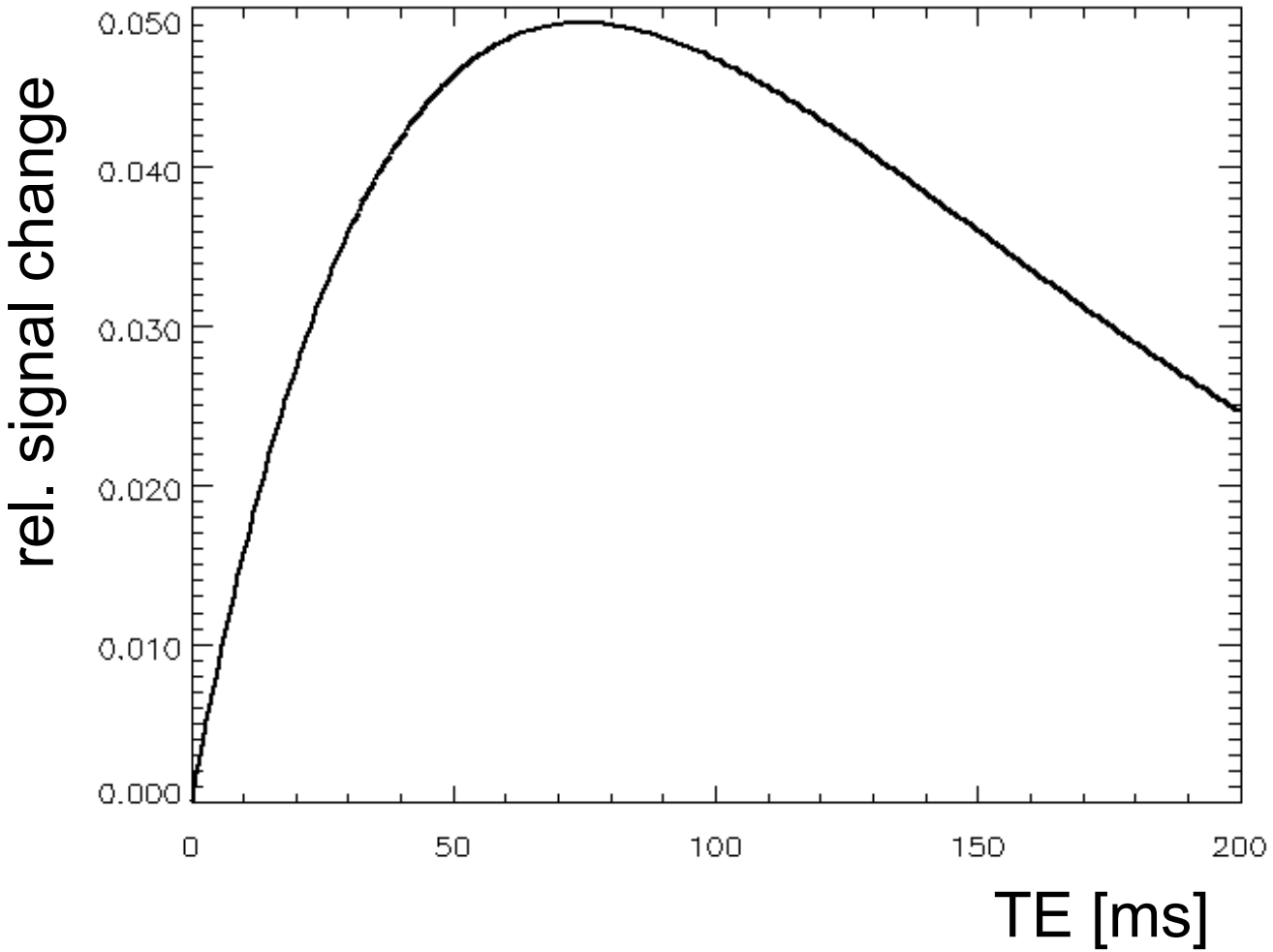
amplitude of BOLD effect

optimum echo time (TE) = maximum signal difference



amplitude of BOLD effect

optimum echo time (TE) = maximum signal difference



spatial resolution

- **BOLD point spread function**
  spatial extent of neuronal activity, of cerebral blood flow, and of BOLD effect

- **image resolution**
  64x64 with 240 mm FOV: 3.75 mm
  128x128 with 240 mm FOV: 1.875 mm

- **signal-noise-ratio**
  single-shot EPI @ 4x4x4 mm^3 voxel size: **~100** !!!

functional MRI (fMRI)

problems

- **sensitivity**

$$\text{contrast-to-noise ratio} = \frac{\text{activity-related signal changes}}{\text{temporal fluctuations of image intensity}}$$

BOLD signal changes: ~1-2% @ 1.5 T

signal-noise ratio (single-shot EPI) ~100 $\Rightarrow$ averaging !

physiologic pulsations (heart and breathing) $\Rightarrow$ co-registration

movement artifacts; instabilities of device $\Rightarrow$ signal analysis

- **specificity**

origin of activation – neurons or blood vessels ?

- **susceptibility artifacts**

functional MRI (fMRI)

problems

- **temporal resolution**

  limited by BOLD effect, image sampling rate,

  spin relaxation times

- **spatial resolution**

  limited by BOLD point spread function, SNR, image sampling rate

- **nonlinearities**

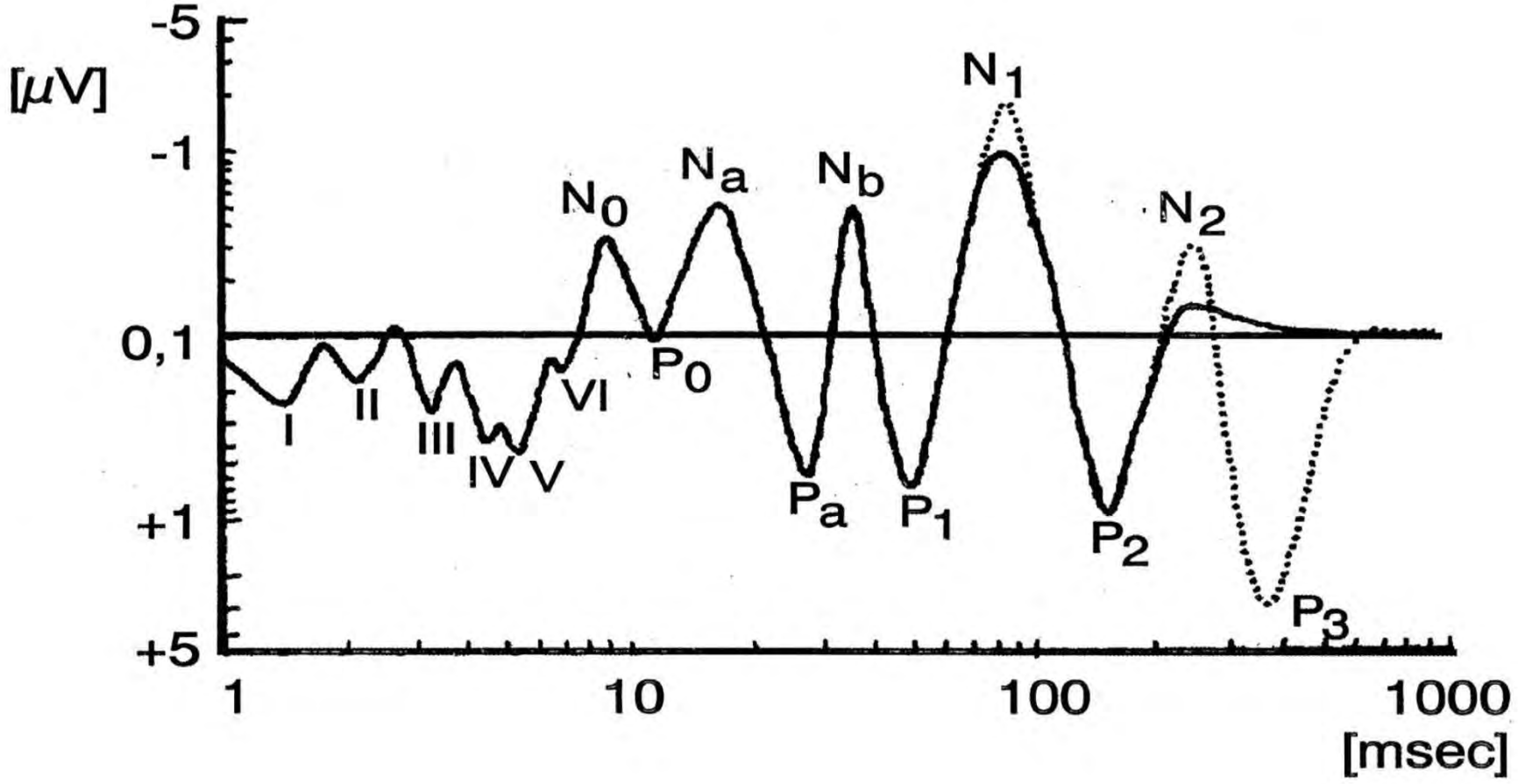
  neuronal and hemodynamic effects

- **acoustic noise**

functional MRI (fMRI)

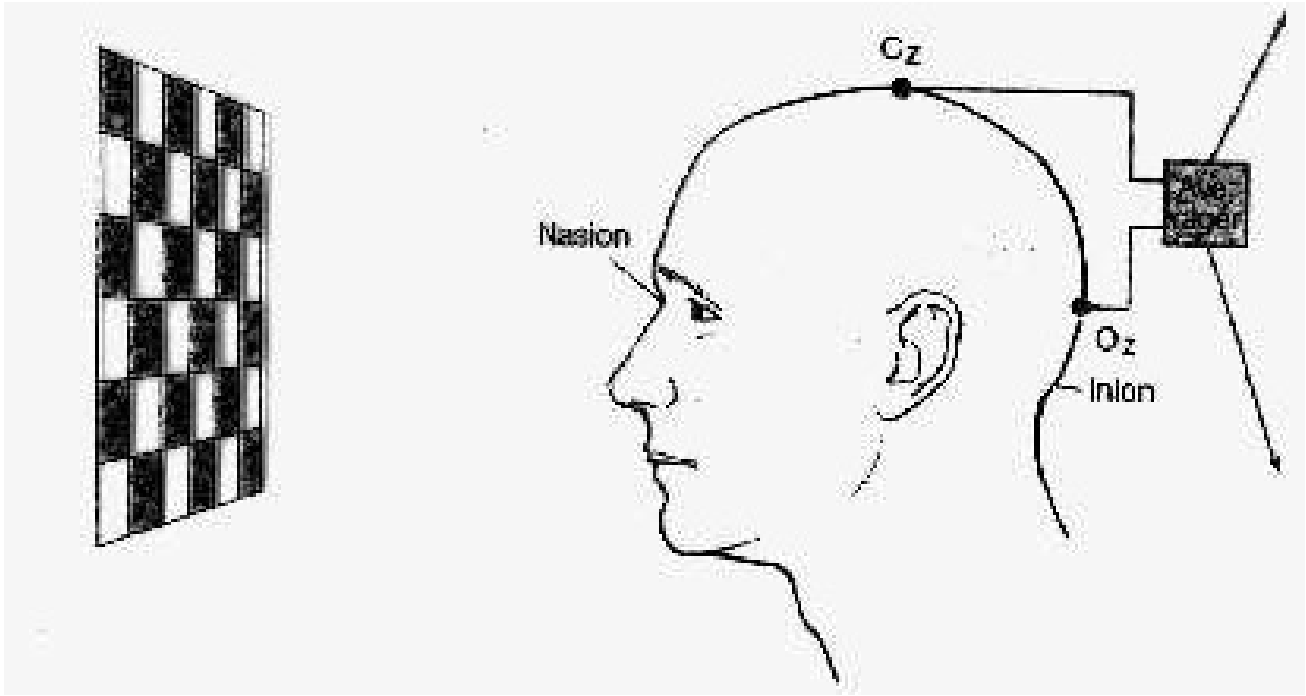
does BOLD effect capture neuronal activity ?

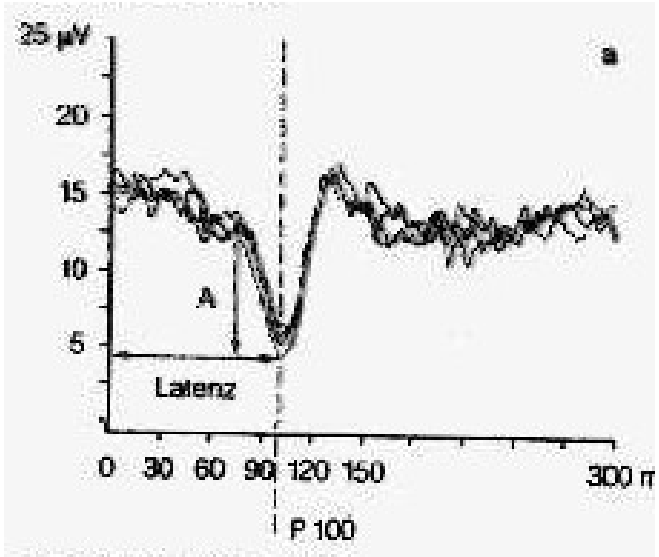
auditory evoked potentials (AEP)



does BOLD effect capture neuronal activity ?

visual evoked potentials (VEP)





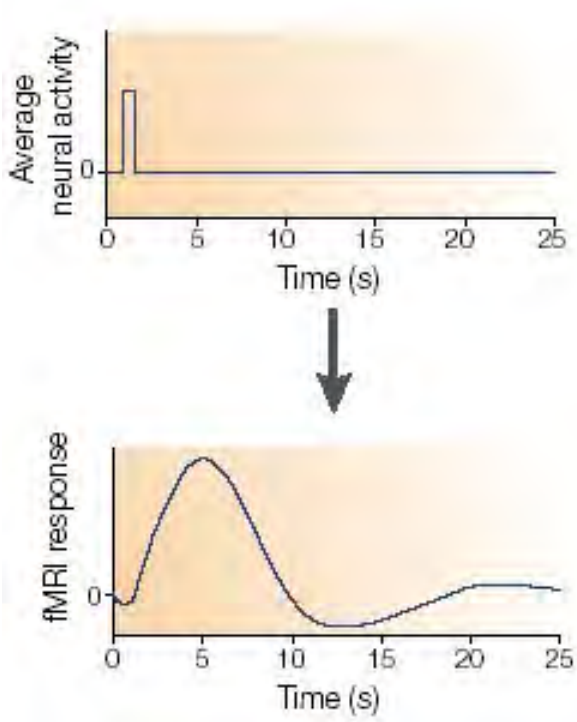
cortical activity: ~ 50 – 200 ms

functional MRI (fMRI)

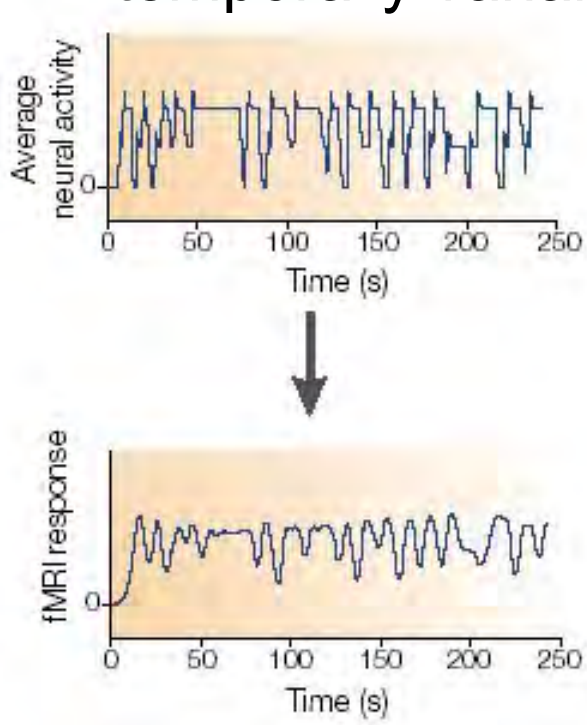
does BOLD effect capture neuronal activity ?

linear transformation model

Dirac-like



temporally variable



convolution with (hypothetical) hemodynamic response function

convolution with inverse function

functional MRI (fMRI)

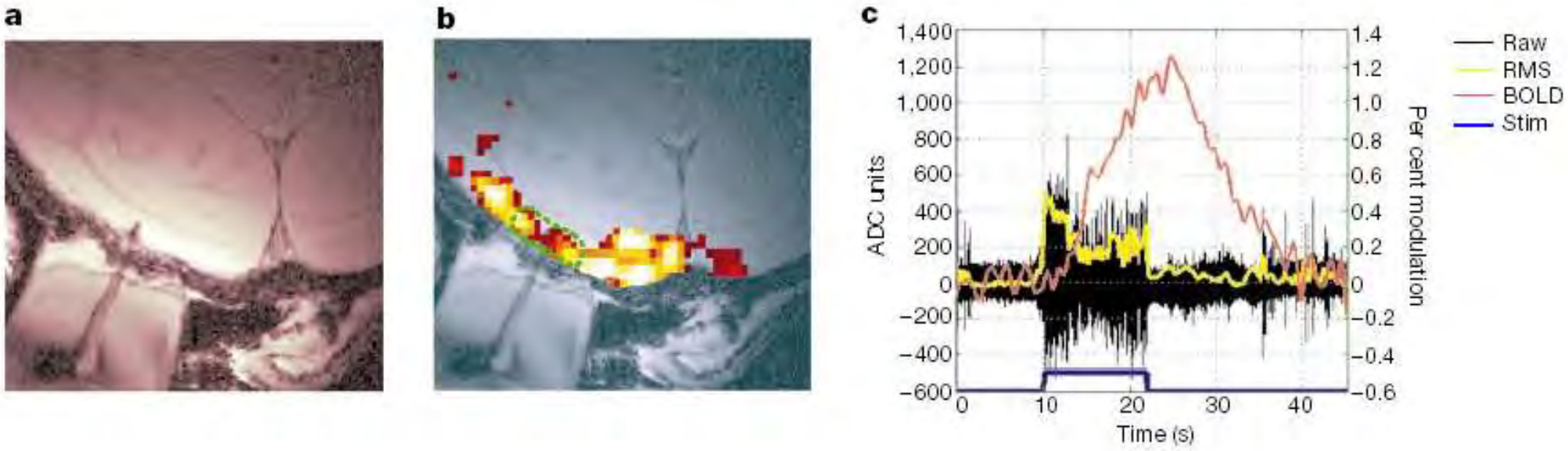
does BOLD effect capture neuronal activity ?

Neurophysiological investigation of the basis of the fMRI signal

Nikos K. Logothetis, Jon Pauls, Mark Augath, Torsten Trinath & Axel Oeltermann

Max Planck Institute for Biological Cybernetics, Spemannstrasse 38, 72076 Tuebingen, Germany

NATURE | VOL 412 | 12 JULY 2001



does BOLD effect capture neuronal activity ?

prediction of BOLD signal from local field potentials (LFP)
and multi unit activity (MUA)

- prediction quality depends on recording site (max. 90% of variance)
- LFP is best predictor

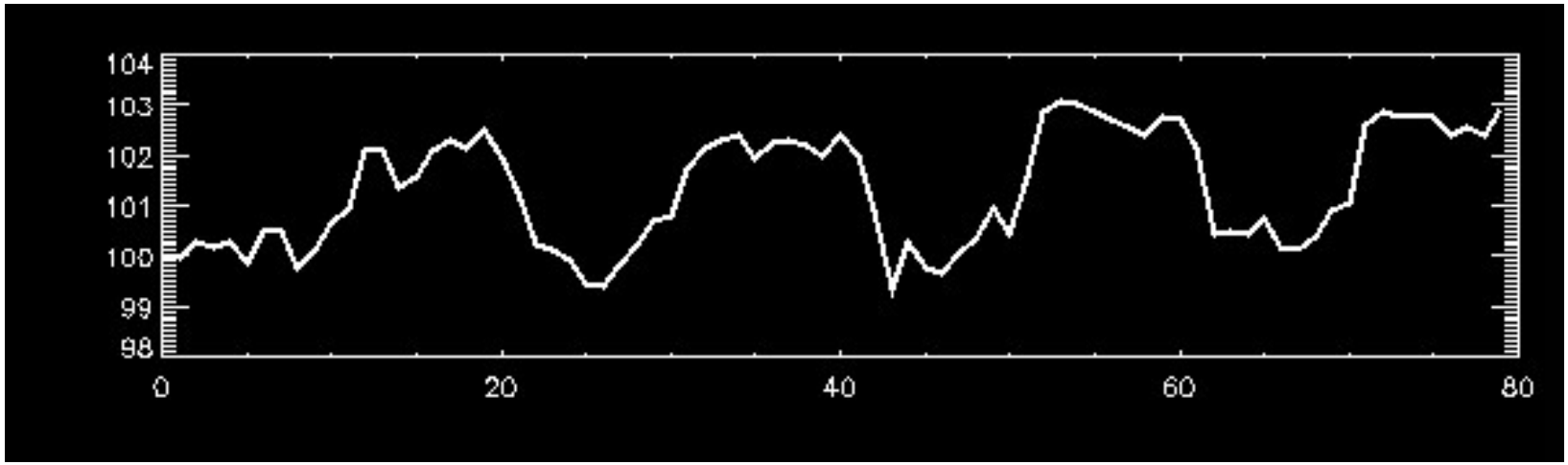
BOLD signal more likely reflects input and intracortical processing

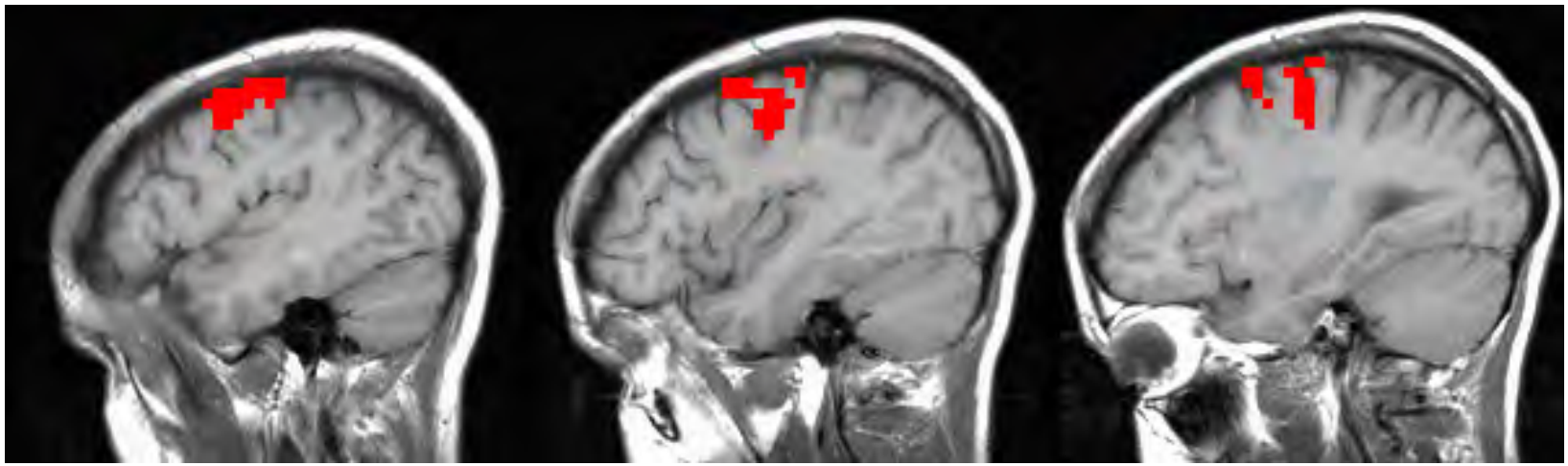
electrophysiology more likely reflects output (projections to other areas)

interpretability of fMRI data depends on extent of interactions between cortical outputs and intracortical activity

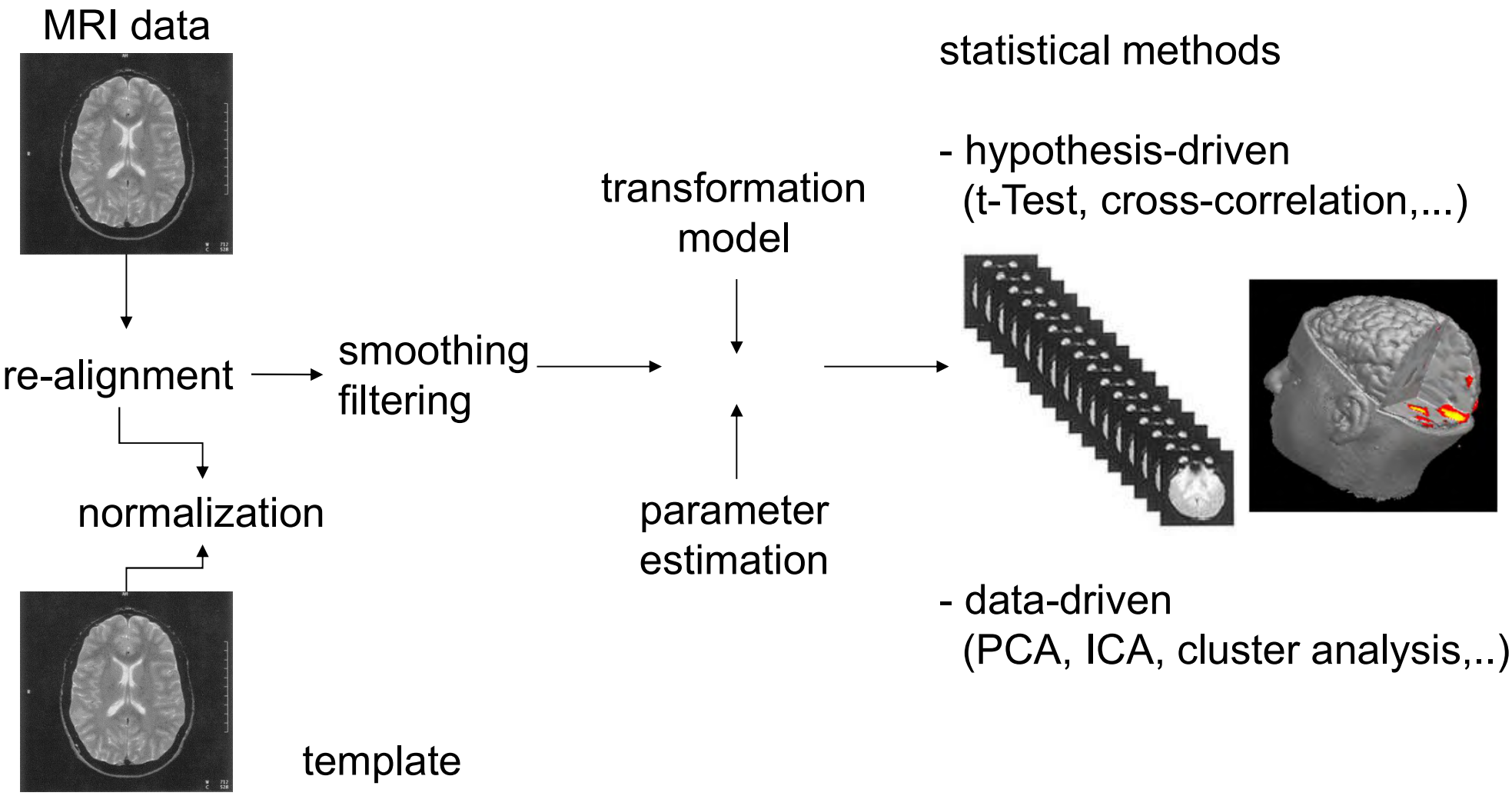
BOLD and neuronal activity:
monotonic but nonlinear relationship

BOLD time series and activation maps

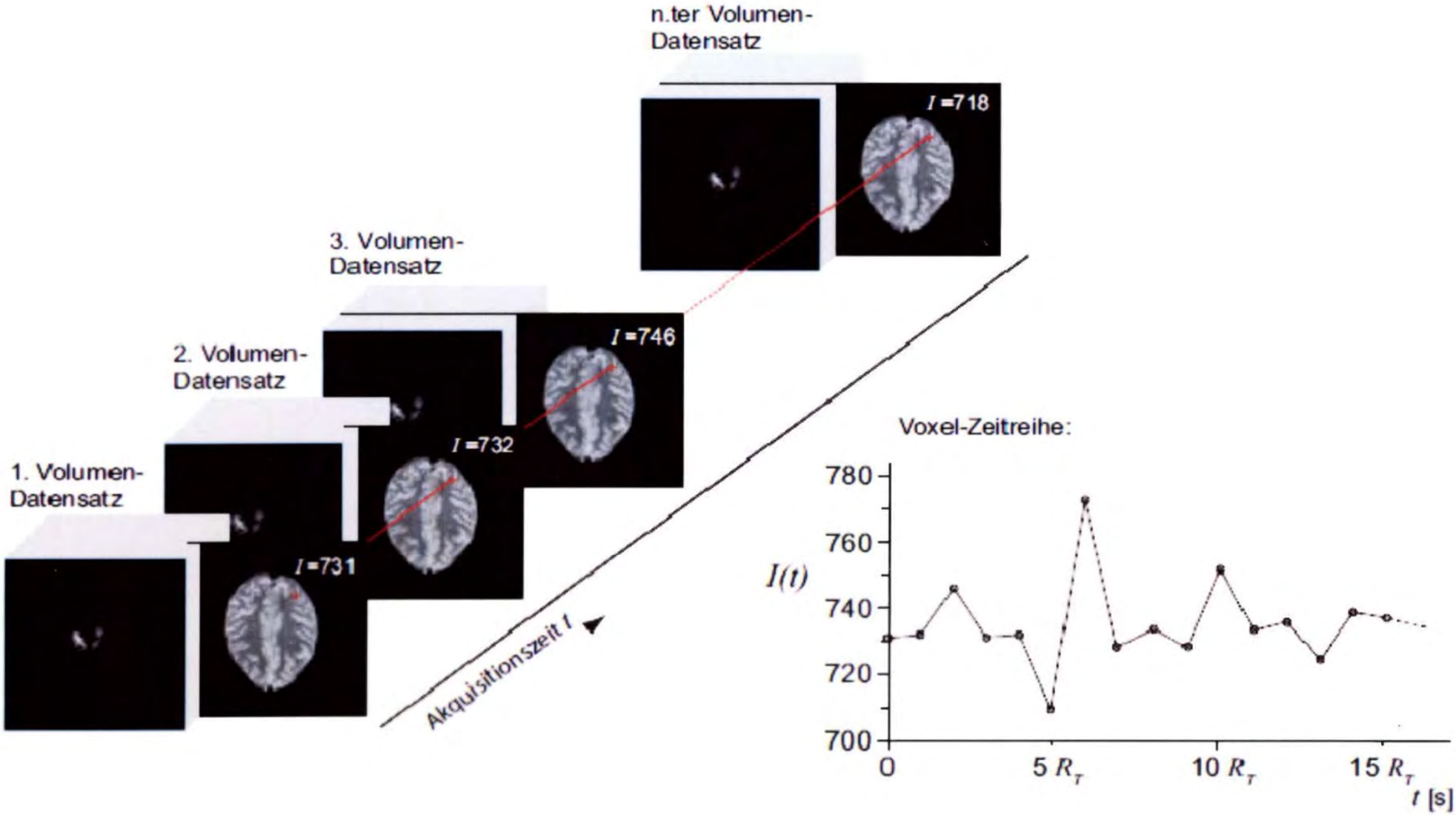




data analysis



data analysis

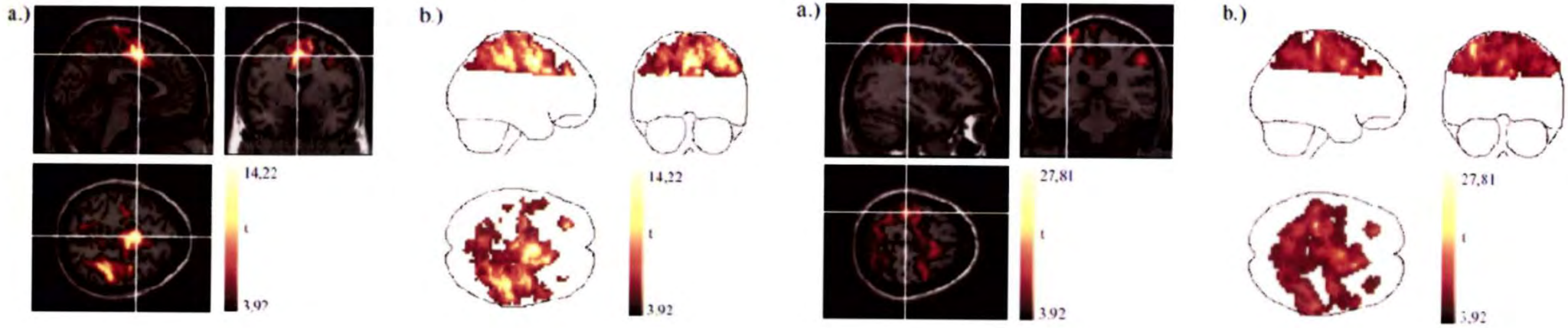


functional MRI (fMRI)

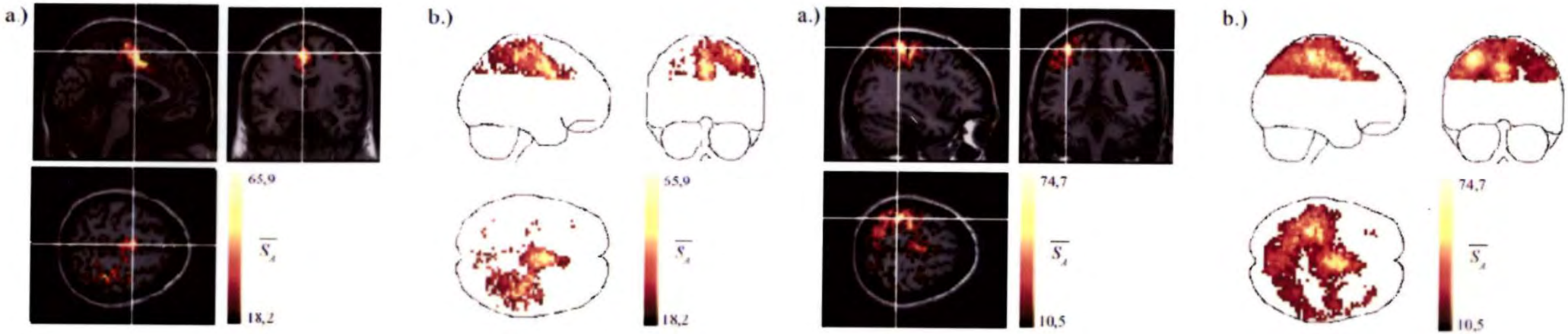
data analysis

Clustering

Statistical parametric mapping - hypothesenbasiert



Hierarchisches Mutual-Information Clustering - (nahezu) hpothesenfrei



Spreizen/Ballen der linken Hand

Spreizen/Ballen der rechten Hand

functional MRI (fMRI)

data analysis

Journal of Serendipitous and Unexpected Results

Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Proper Multiple Comparisons Correction

Craig M. Bennett [1*], Abigail A. Baird [2], Michael B. Miller [1] and George L. Wolford [3]

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[2]Department of Psychology, Blodgett Hall, Vassar College, Poughkeepsie, NY 12604
[3]Department of Psychological and Brain Sciences, Moore Hall, Dartmouth College, Hanover, NH 03755

J Serendipitous Unexpected Result 2009; 1: 1–5.

study was awarded IgNobel Prize in Neuroscience in 2012

multiple comparisons

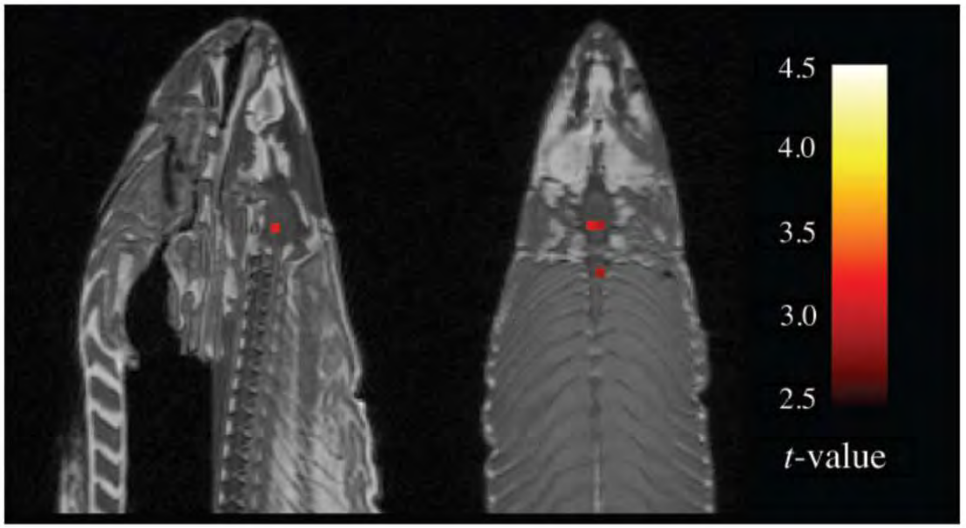


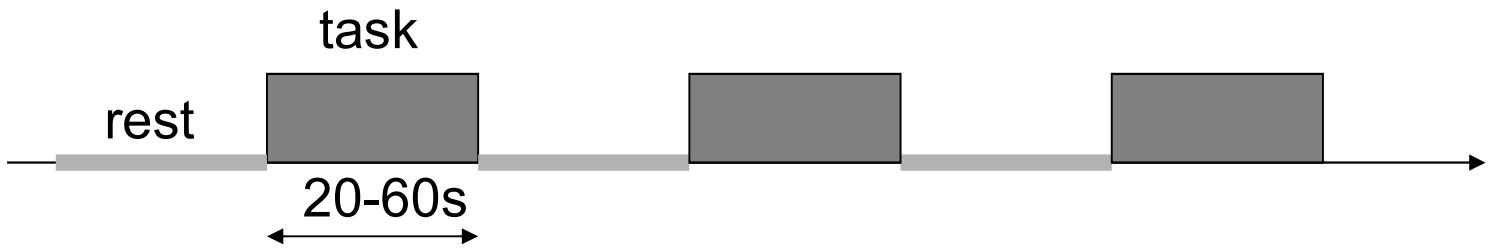
Fig. 1. Sagittal and axial images of significant brain voxels in the task > rest contrast. The parameters for this comparison were $t(131) > 3.15$, $p(\text{uncorrected}) < 0.001$, 3 voxel extent threshold. Two clusters were observed in the salmon central nervous system. One cluster was observed in the medial brain cavity and another was observed in the upper spinal column.

One mature Atlantic Salmon (Salmo salar) participated in the fMRI study. The salmon measured approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning. It is not known if the salmon was male or female, but given the post-mortem state of the subject this was not thought to be a critical variable.

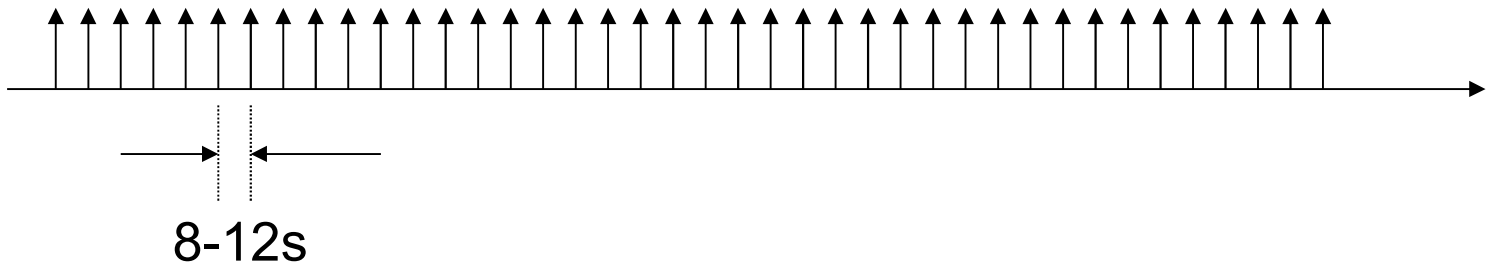
typical fMRI data set
~ 130.000 voxel
~ multiple comparisons (false positives)
correction schemes: family-wise error rate, false discovery rate
~ application of correction schemes in only 60-70% of publications in relevant journals in year 2008

experiment design

block design fMRI

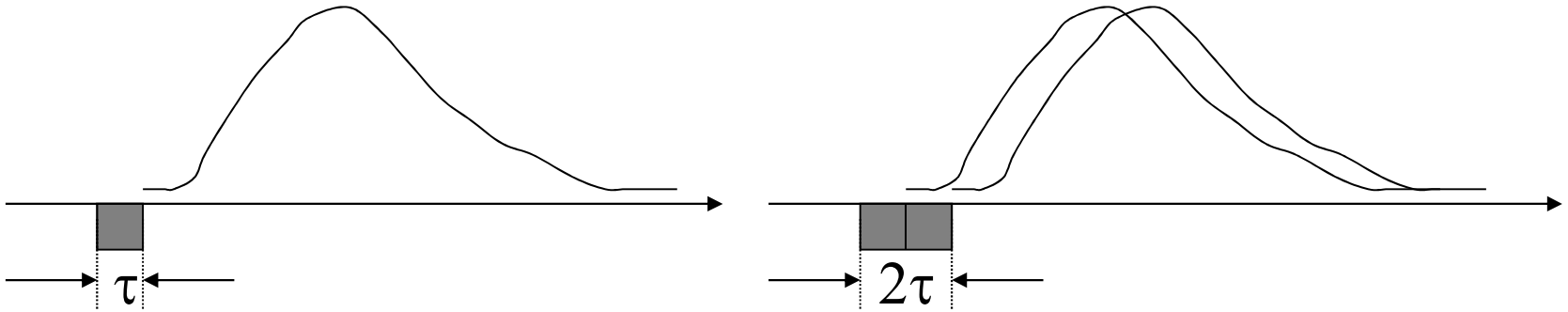


event-related fMRI

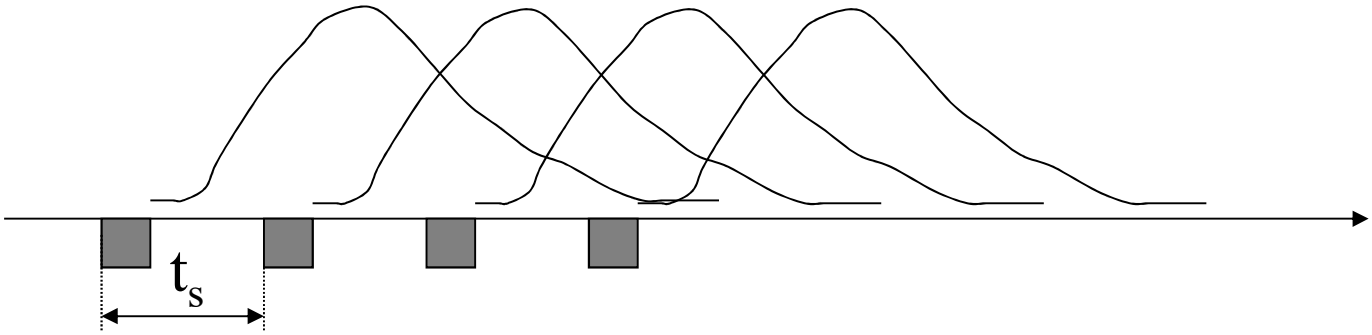


nonlinearity of BOLD effect

BOLD response vs. stimulus duration



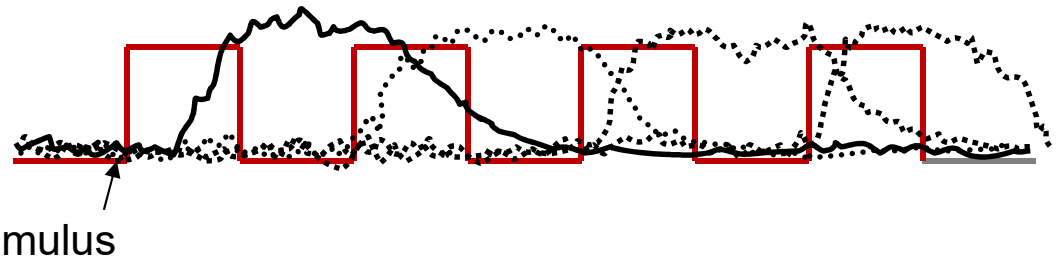
BOLD response when stimulating at high repetition rate



nonlinearity of BOLD effect

hemodynamic response and inter stimulus interval (ISI)

short ISI

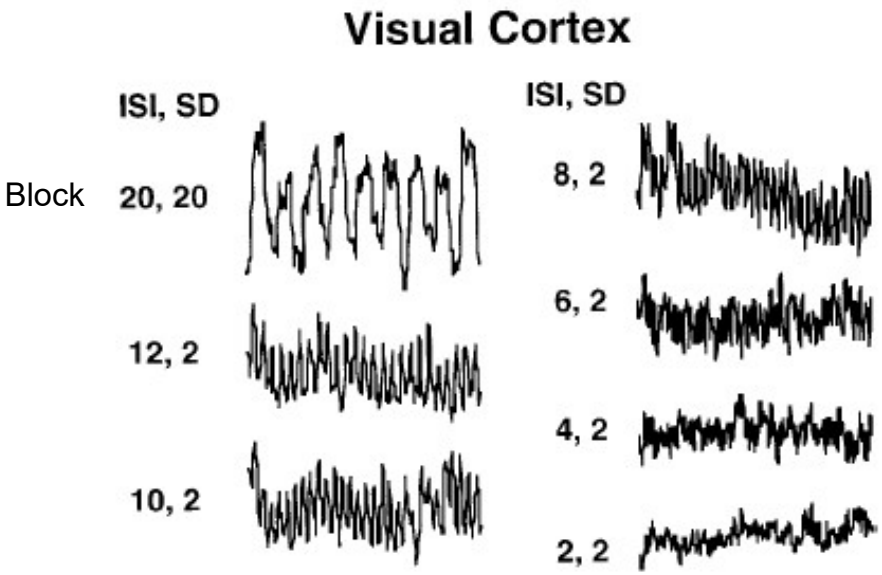


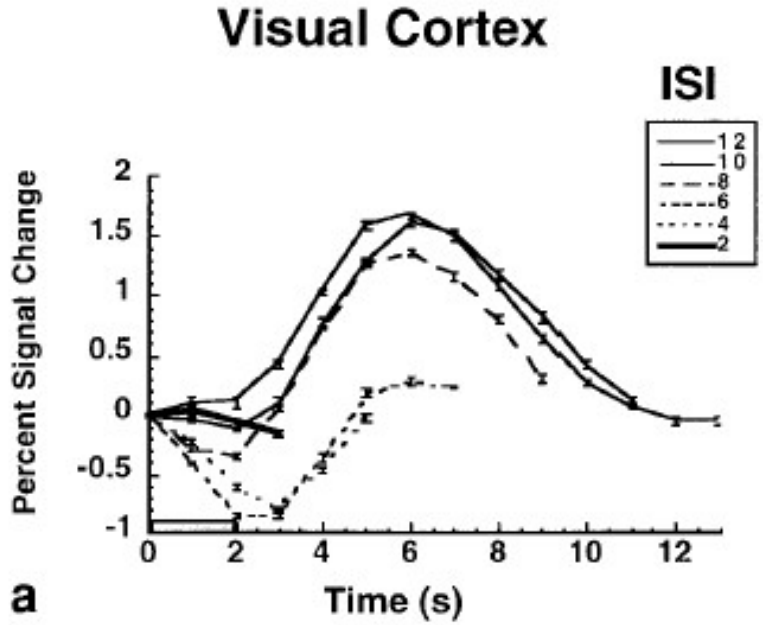
long ISI

- experiment duration
- SNR
- habituation
- adaption
- resolution
- spatial variability

nonlinearity of BOLD effect

hemodynamic response and inter stimulus interval (ISI)





SD: stimulus duration

functional MRI (fMRI)

experiment design

baseline

(PNAS, 98, 12760, 2001)

When zero is not zero: The problem of ambiguous baseline conditions in fMRI

Craig E. L. Stark† and Larry R. Squire†‡§¶‖

Departments of †Psychiatry, ‡Neurosciences, and §Psychology, University of California at San Diego, La Jolla, CA 92093; and ¶Veterans Affairs Medical Center, San Diego, CA 92161

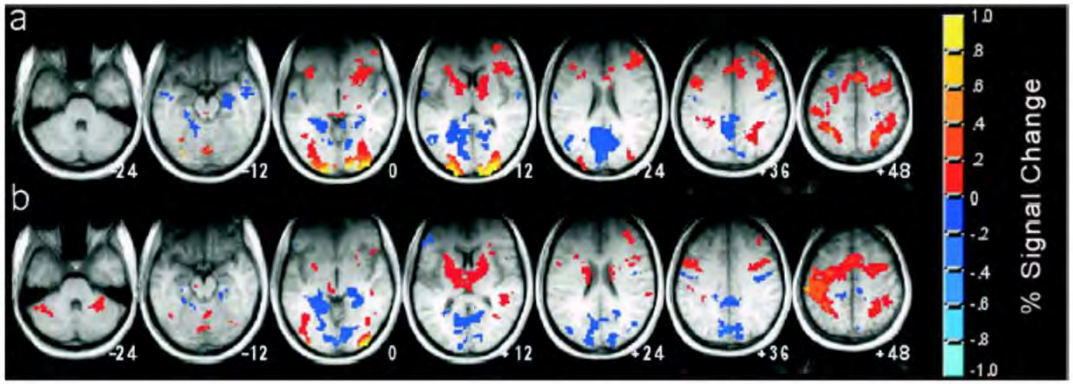


Fig. 3. fMRI data from two of the baseline tasks used in experiment 1, Noise Detection (*a*) and Odd/Even Digits (*b*), are shown in axial sections as colored overlays on the average structural images (transformed to the atlas of Talairach and Tournoux, ref. 22). Regions shown in yellow and orange exhibited greater activity in the baseline task than in Rest. Regions shown in blue exhibited greater activity in Rest than in the baseline condition. Deactivations relative to rest were observed not only in the medial temporal lobes, but in many regions throughout the brain. The relative absence of significant activity in the frontal lobe may be the result of the limited coverage of the radio frequency (RF) coil that was used.

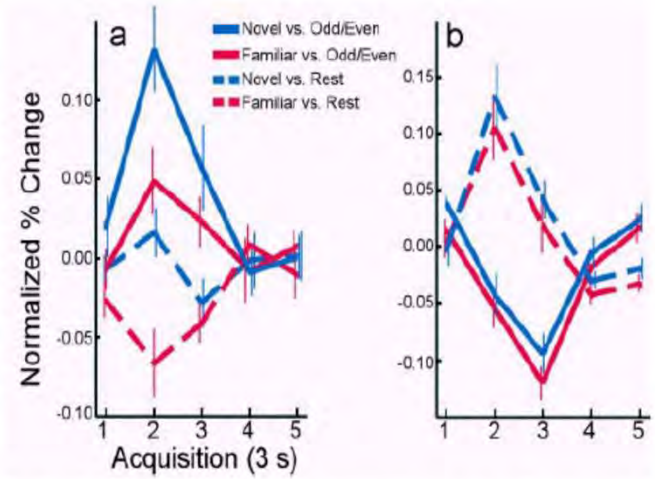


Fig. 2. Hemodynamic response showing activity over time (3 s per sample) within functionally defined ROIs in experiment 2. (*a*) Activity in a subregion of the left parahippocampal cortex functionally defined from experiment 1 (see text). When the Odd/Even Digit task was used as the baseline for activity in a rapid event-related design, both Novel and Familiar Pictures were associated with increased activity. When Rest was used as a baseline for activity, Novel Pictures were not associated with detectable activity, and Familiar Pictures were associated with decreased activity. (*b*) Activity in a subregion (see text) of the left motor cortex where the button pushes in the Odd/Even Digit task would be expected to be associated with significant activity. Here, the activity associated with Novel and Familiar Pictures was greater when Rest was used as a baseline than when the Odd/Even Digit task was used as a baseline. Thus, the effect of activity during a baseline task can be to reduce, eliminate, or even reverse the sign of the activity during the conditions of interest.

fields of application

cognitive neuroscience

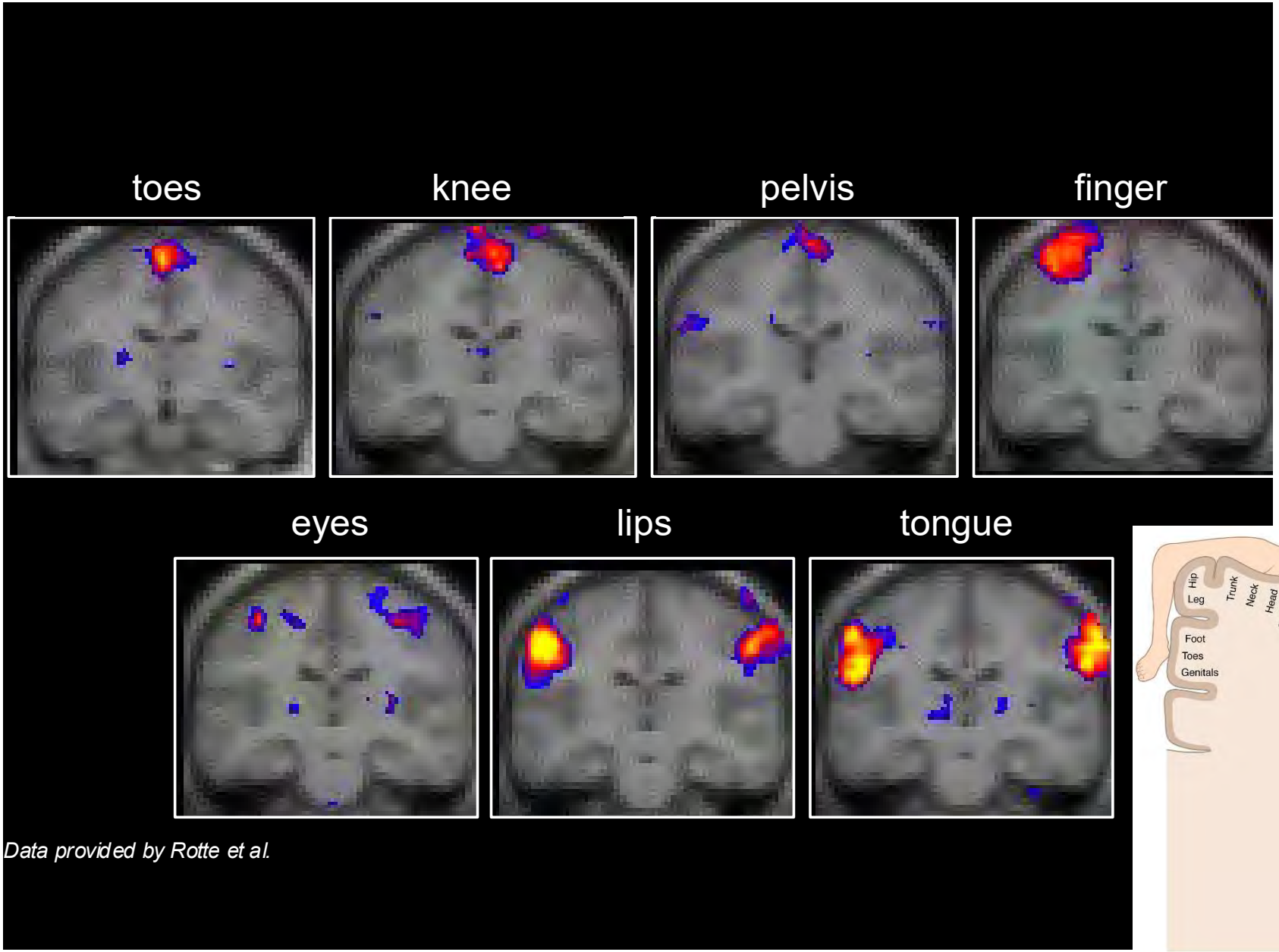
movement
perception
attention
learning, memory
remembrance, knowledge
emotions, motivation
language
thinking, planning
personality, self-identity
consciousness
....

diagnosis of diseases of CNS

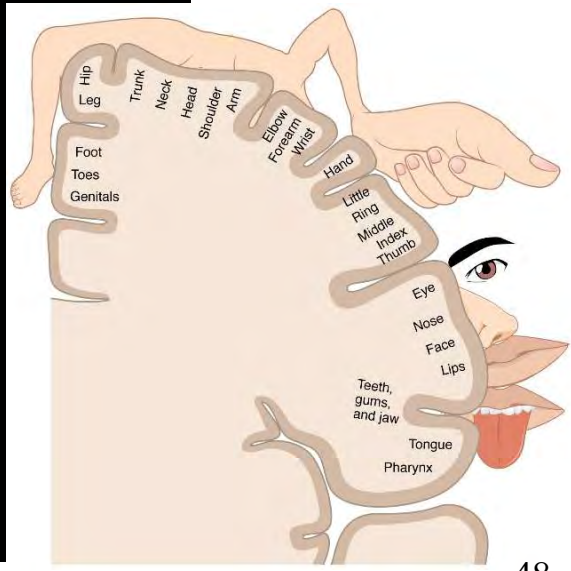
Alzheimer
Parkinson
multiple sclerosis
psychiatric diseases
epilepsy
malformation
stroke
...

presurgical planning

functional MRI (fMRI) — *motor cortex*



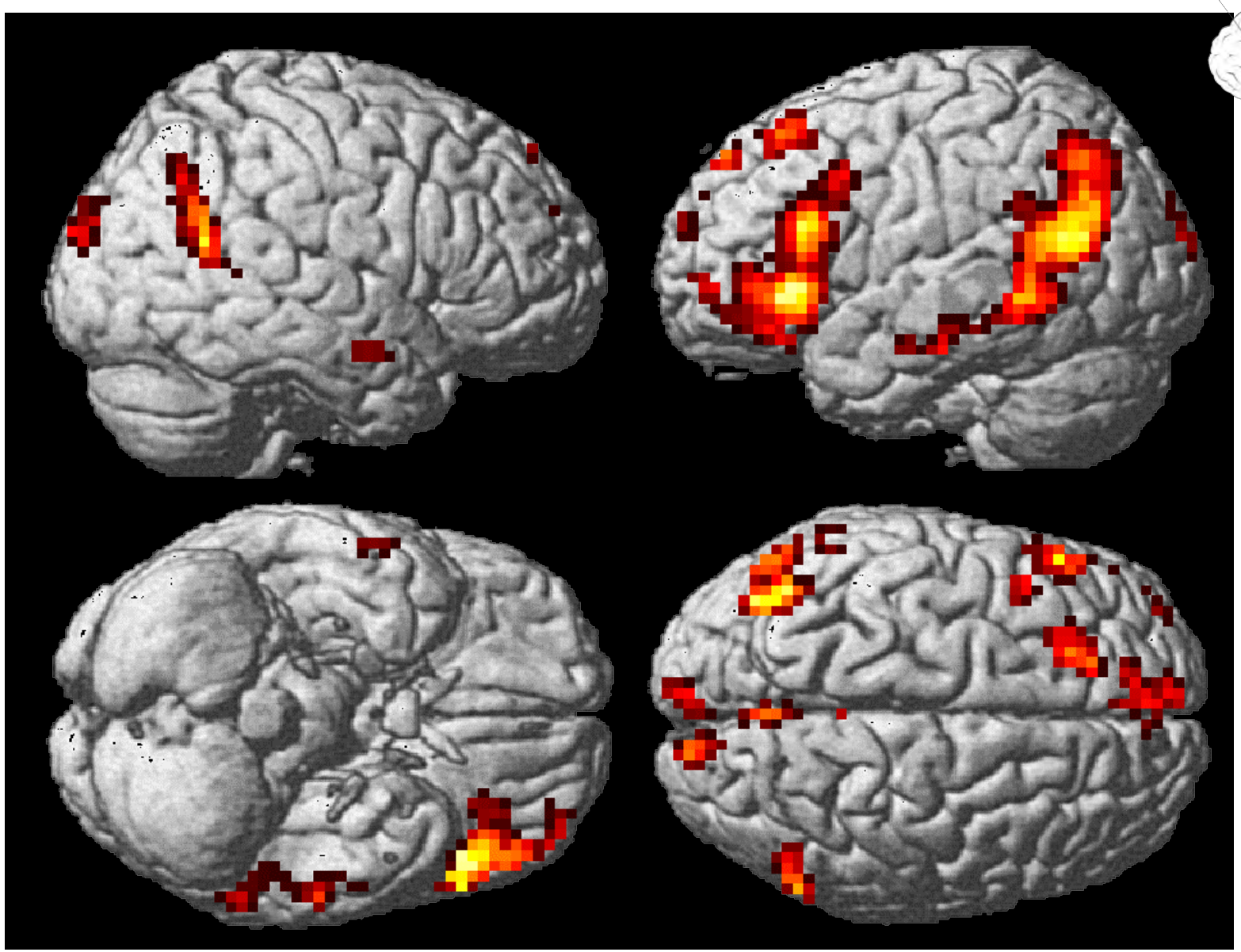
Data provided by Rotte et al.

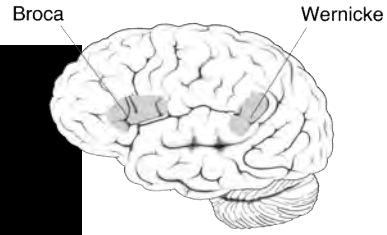


functional MRI (fMRI) *auditory cortex*

from: Rosen et al, PNAS, 95, 1998

functional MRI (fMRI) *language*





functional MRI (fMRI) *language/hormones/plasticity*

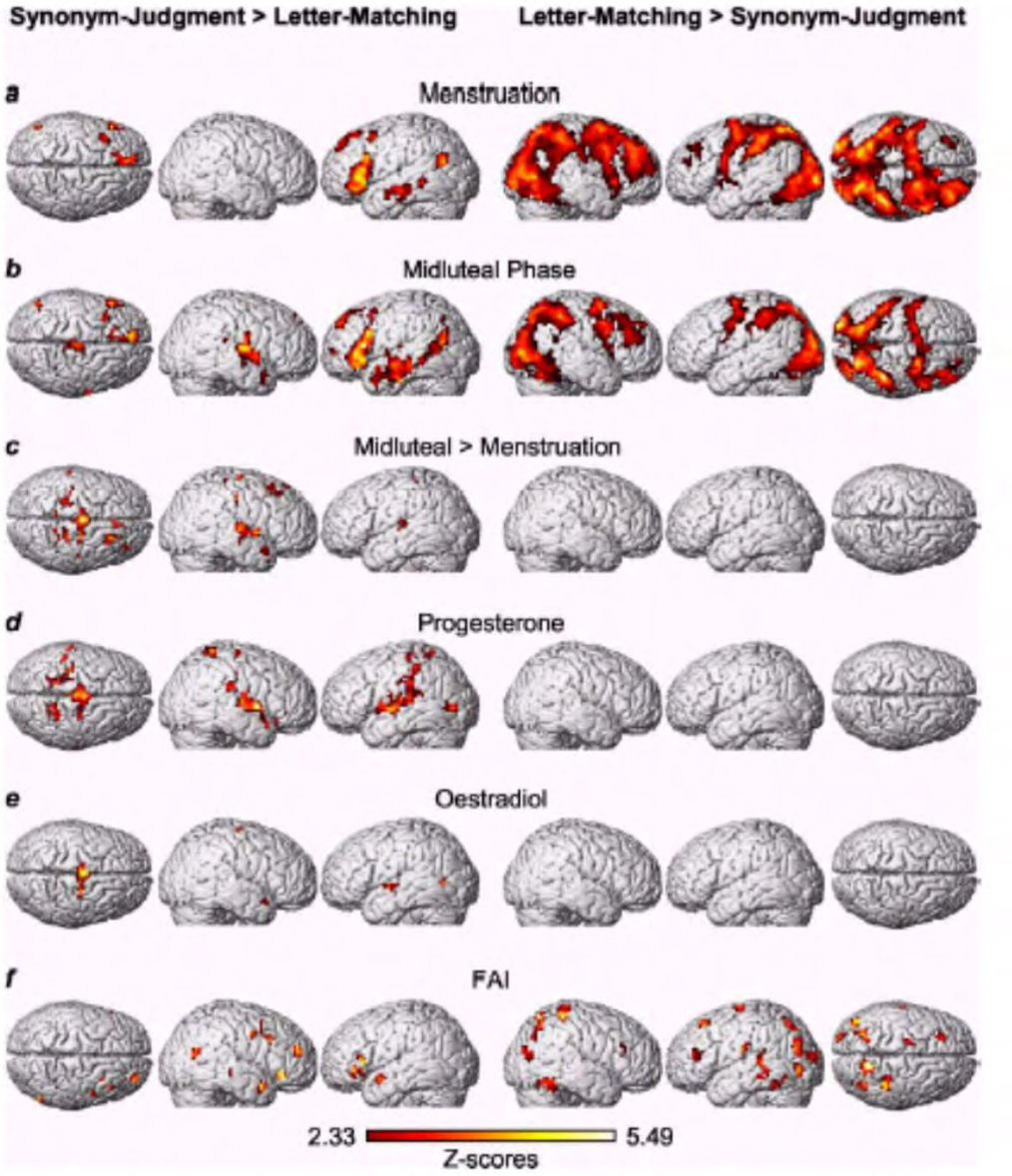
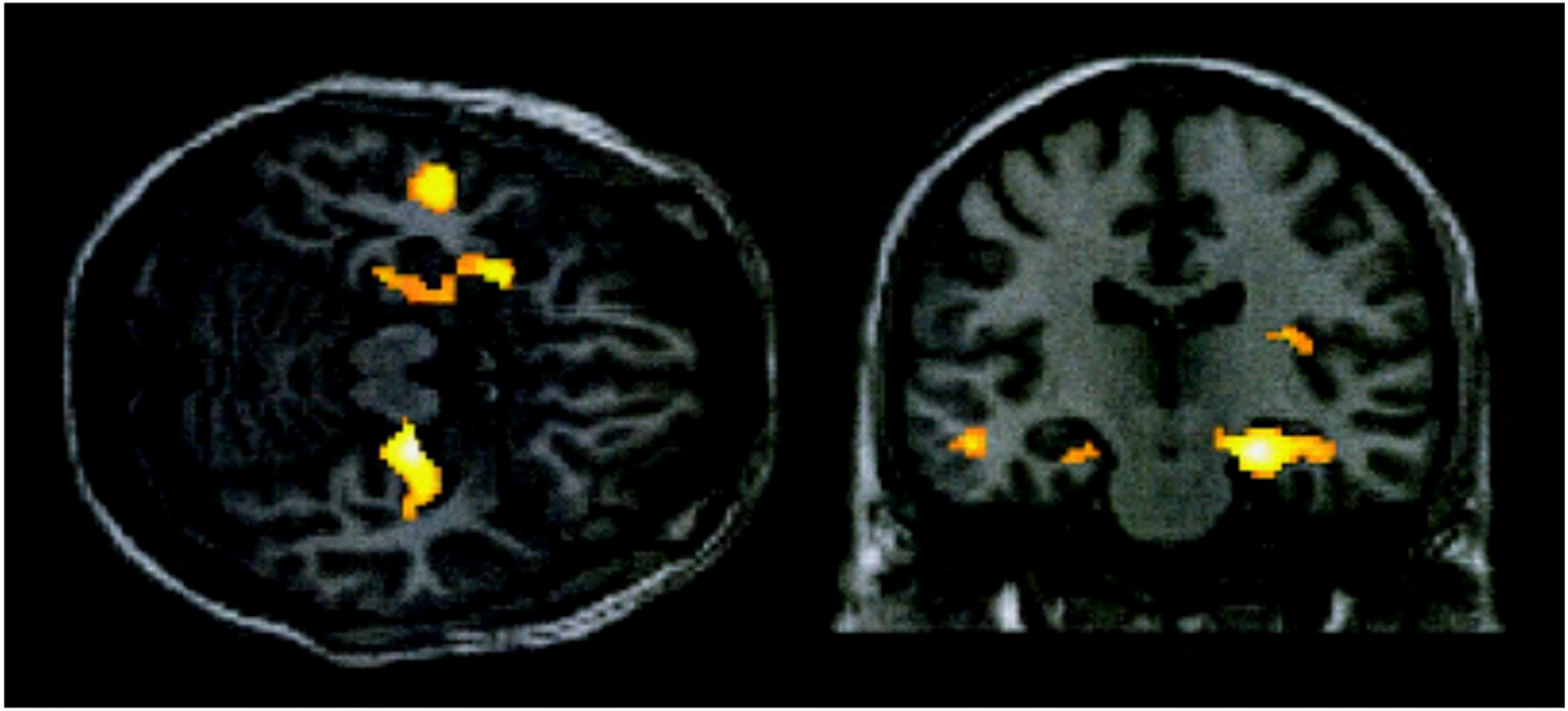


Figure 1. Brain regions significantly activated in all women (random effects model) in response to the synonym-judgment task contrasted with the letter-matching task (left columns) and to the letter-matching task contrasted with the synonym-judgment task (right columns) were overlaid onto an individual, randomly selected brain. *t* maps are thresholded at $p = 0.01$, and only clusters with an extent of >15 voxels are shown. Results are depicted separately for menstruation (*a*) and the midluteal phase (*b*) and their second-level comparison (*c*). The three bottom rows depict activity in cerebral areas significantly correlated with hormone serum levels: progesterone (*d*), estradiol (*e*), and FAI (*f*).

from: Fernandez et al.,
Menstrual Cycle-Dependent Neural Plasticity in the Adult Human Brain Is Hormone, Task, and Region Specific.
J. Neurosci, 23(9):3790 –3795, 2003

functional MRI (fMRI) *Alzheimer*



from: Grön et al, Ann. Neurol, 51, 2002

functional MRI (fMRI)

advantages

- non-invasive
- non-ionizing (cf. PET)
- whole-brain imaging
- relatively fast: ER-fMRI
- high spatial resolution
- assesses almost all cortical and subcortical structures

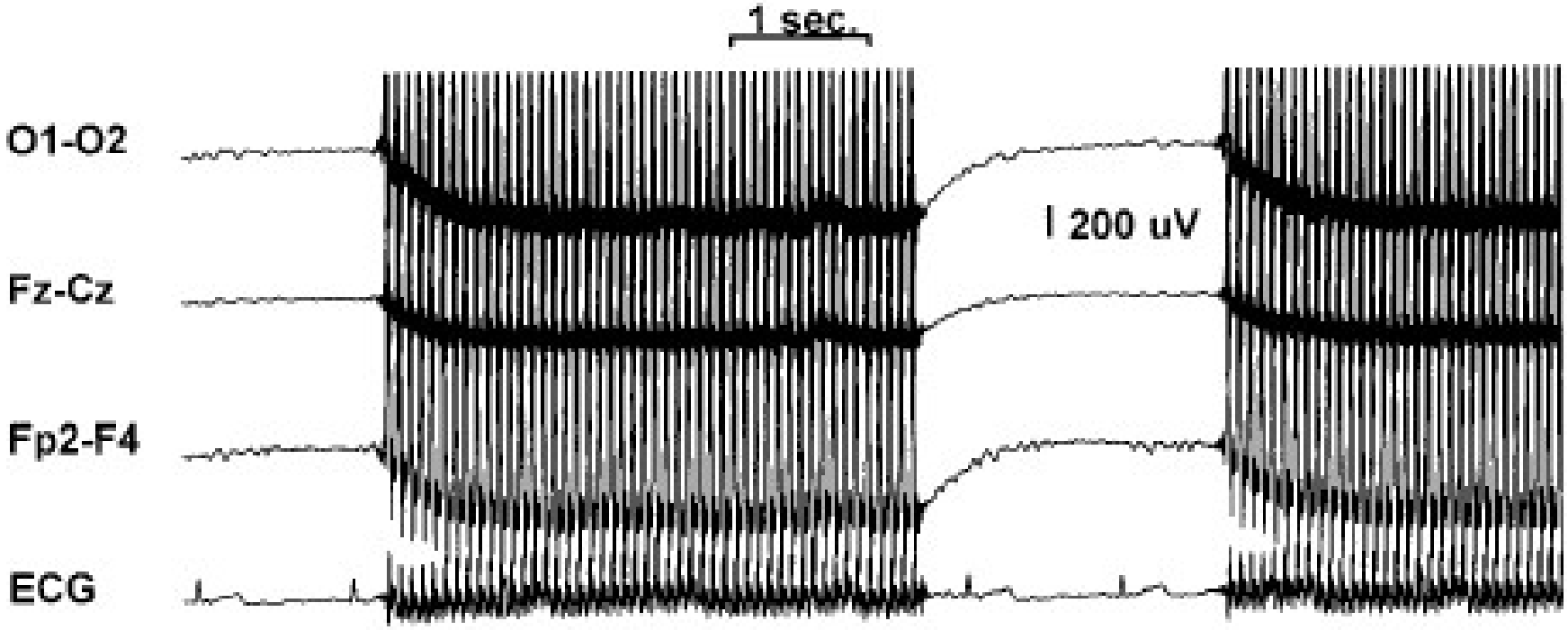
- improvement:
  - better SNR through higher field strengths (>8T)
  - faster sequences
  - „direct“ measurement (e.g. arterial spin labelling ASL)

problems

- safety (high field strengths) (stimulation peripheral nerves?)
- field inhomogeneities -> small brain volumes not depictable
- acoustic noise (100dB SPL, 1-2 kHz)
- susceptibility- (macroscopic) and movement artifacts, distortions (EPI), “Nyquist ghosts” (EPI)
- temporal resolution (100 ms - s)

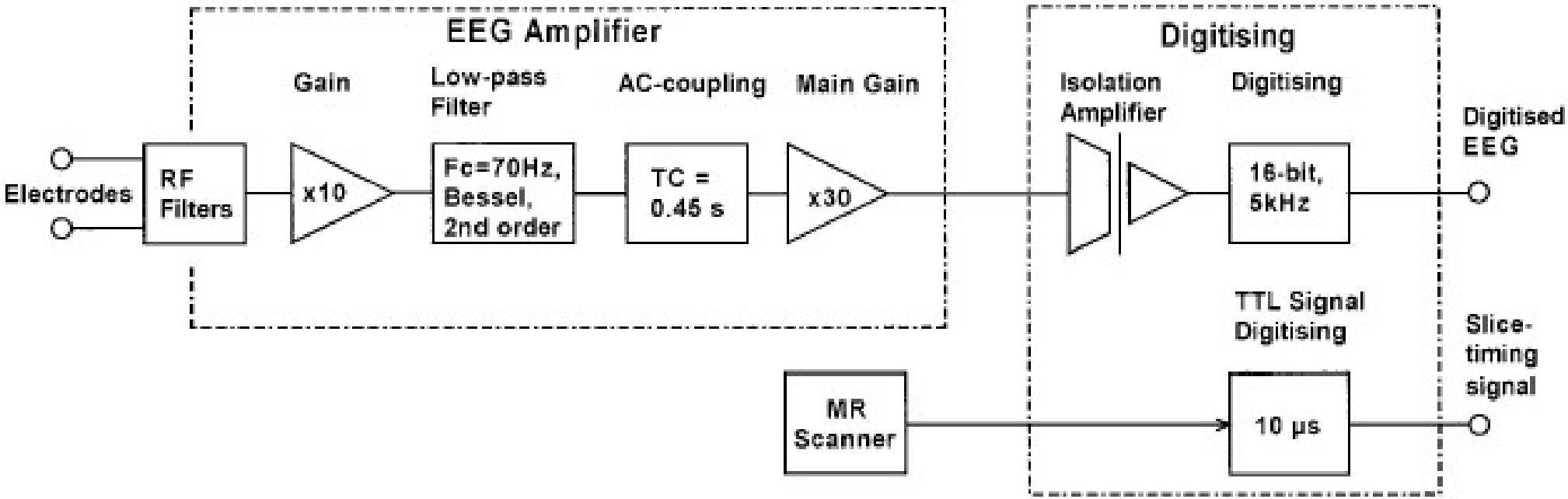
- BOLD <-> neuronal activity
  - linear relationship?
    - nonlinear contributions
    - saturation effects
    - spatial-temporal complexity
- relative measurements (baseline)

simultaneous EEG and fMRI recording



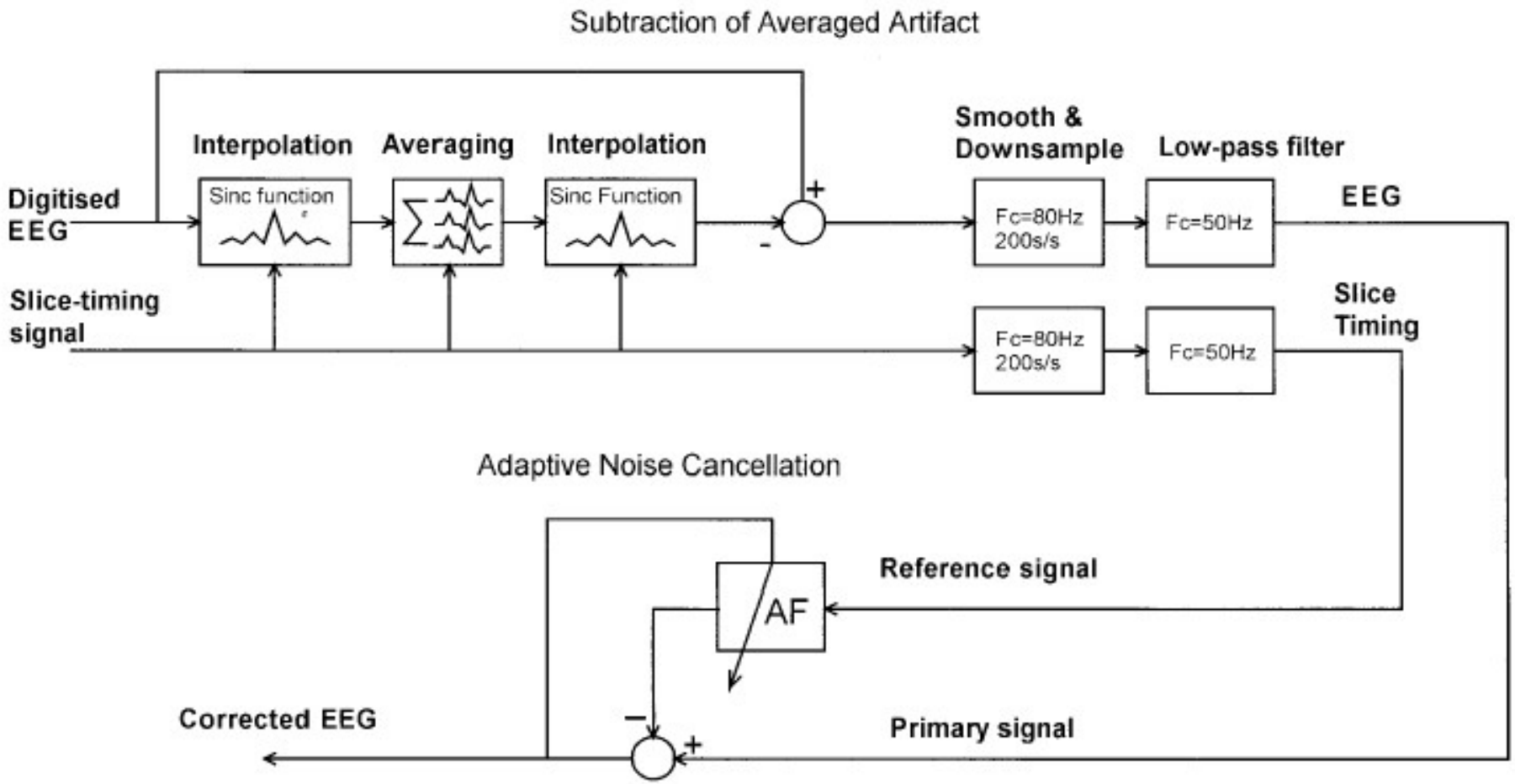
(from: Allen et al., Neuroimage, 12, 230, 2000)

simultaneous EEG and fMRI recording



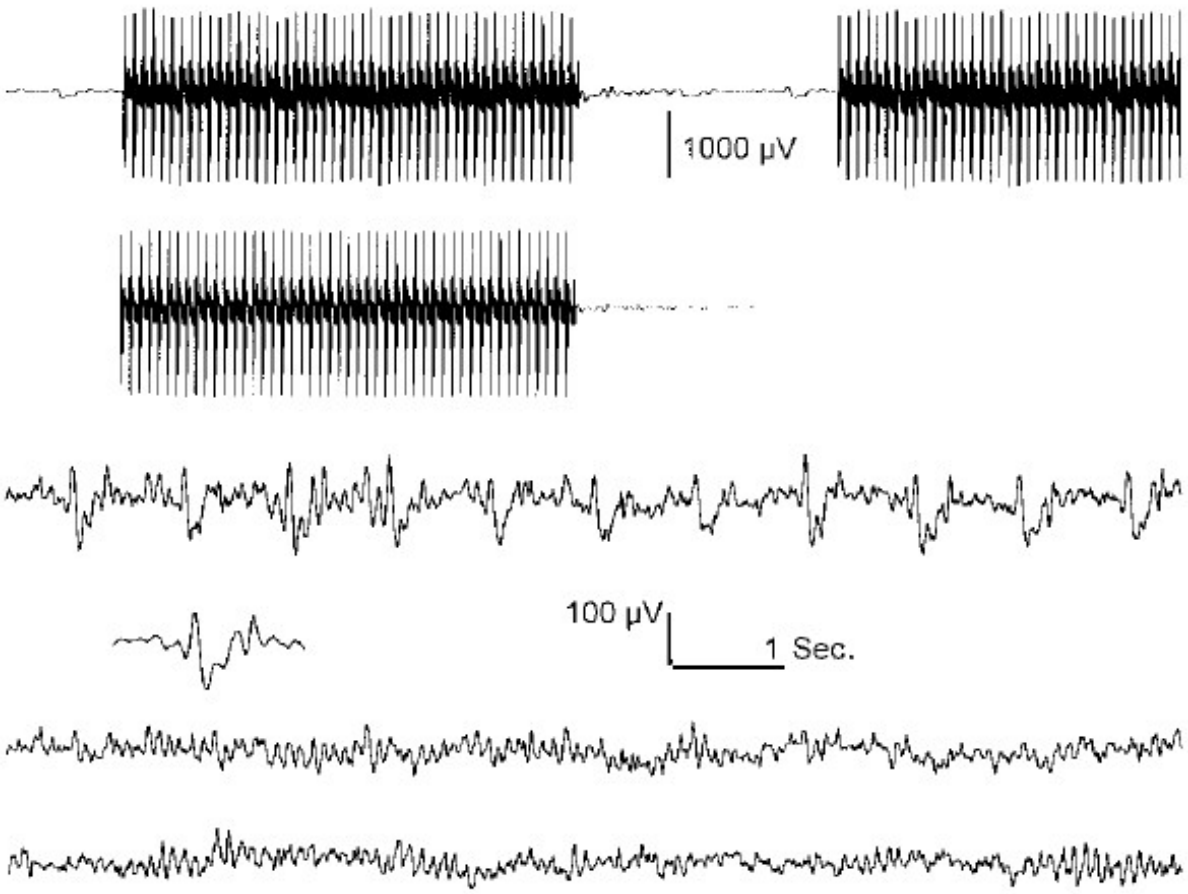
(from: Allen et al., Neuroimage, 12, 230, 2000)

simultaneous EEG and fMRI recording



(from: Allen et al., Neuroimage, 12, 230, 2000)

simultaneous EEG and fMRI recording



EEG during MRI acquisition

averaged acquisition artifact

after subtraction

averaged heart rate artifact

after subtraction

EEG of same person but recorded outside of MRI scanner

(from: Allen et al., Neuroimage, 12, 230, 2000)

simultaneous EEG and fMRI recording

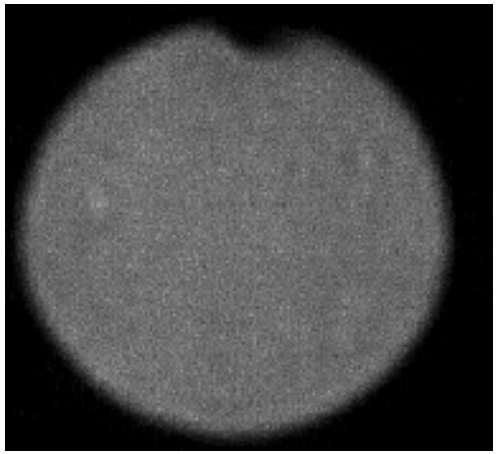
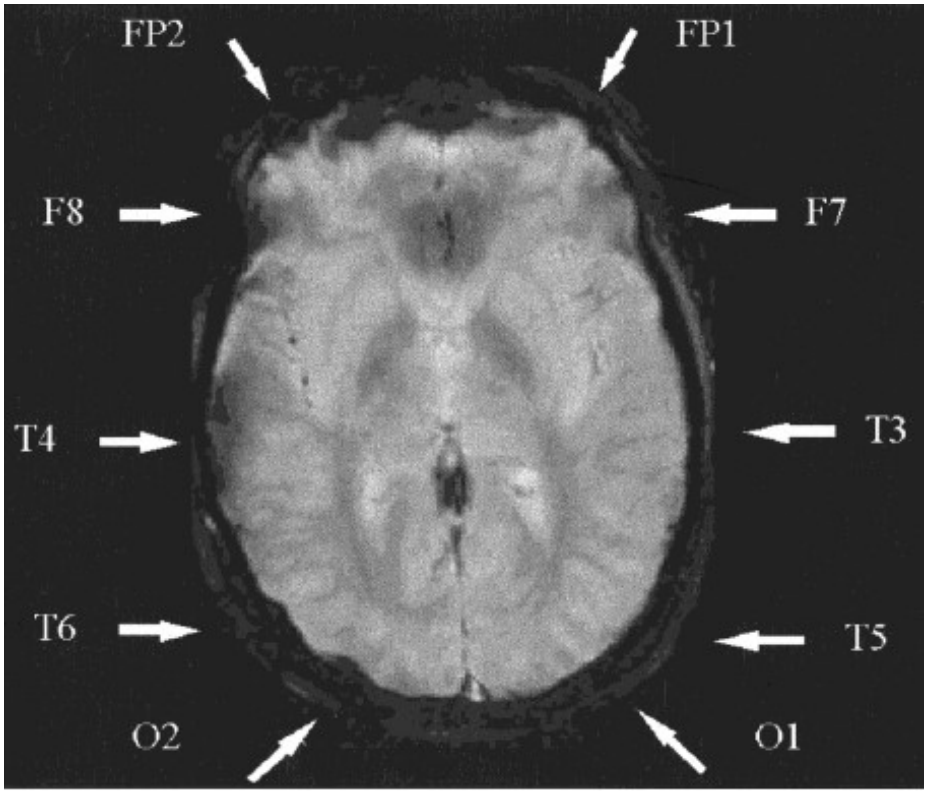


image artifact from
non-MRI-compatible
EEG-electrodes
(head phantom)



non-MRI-compatible
EEG-electrodes

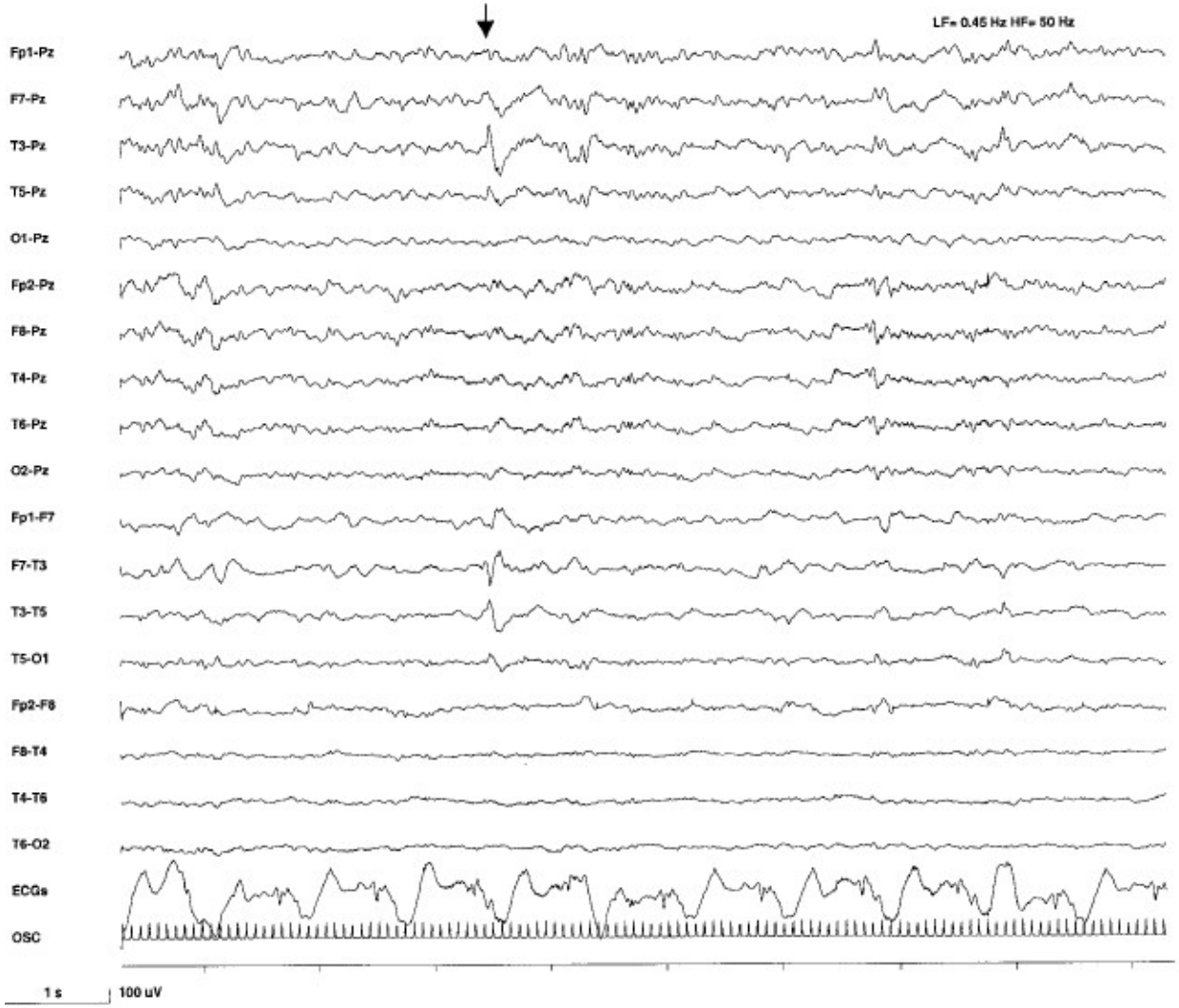
MRI-compatible
EEG-electrodes

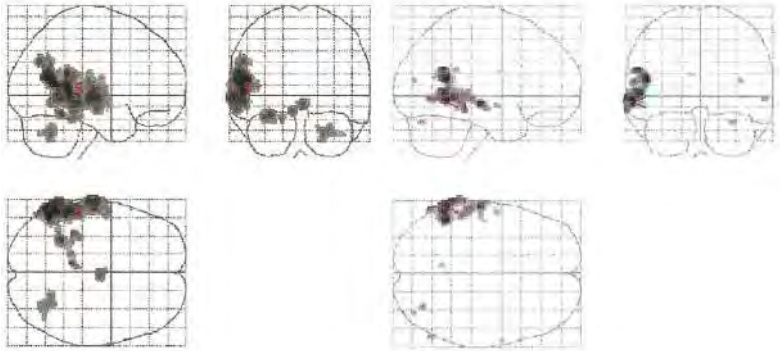
(from: Krakow et al., Human Brain Mapping, 10, 10, 2000)

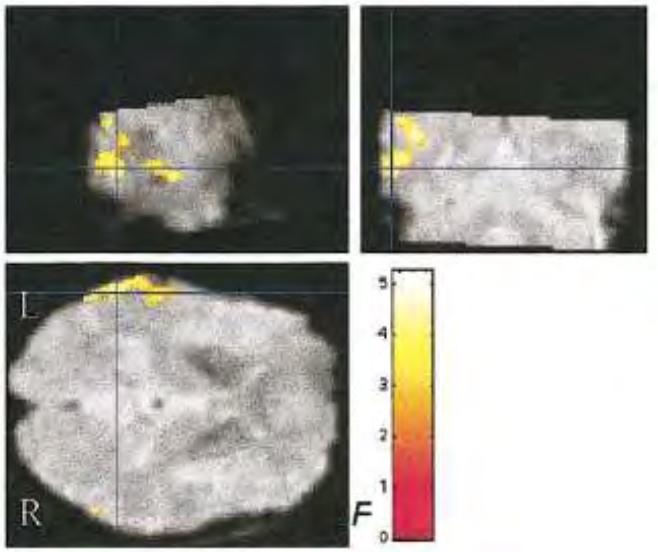
functional MRI (fMRI)

EEG-triggered fMRI

epileptic spikes



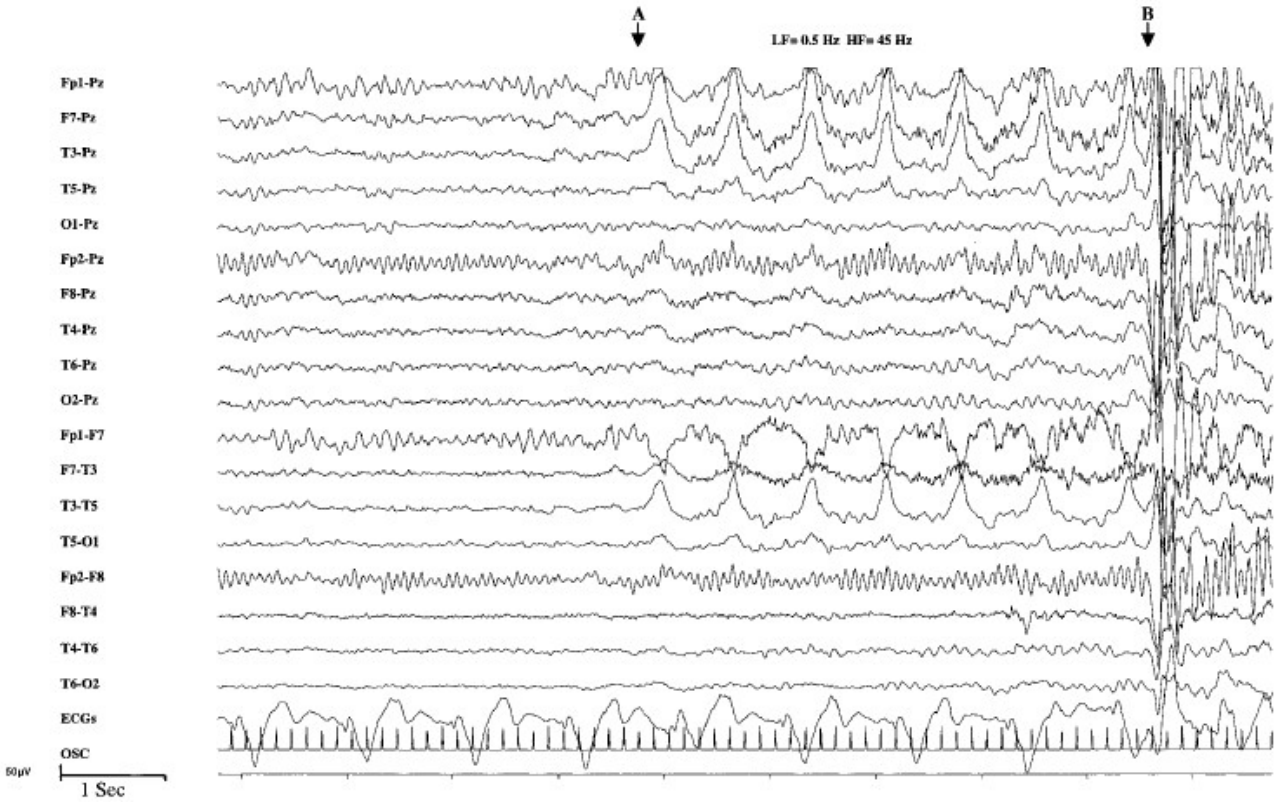


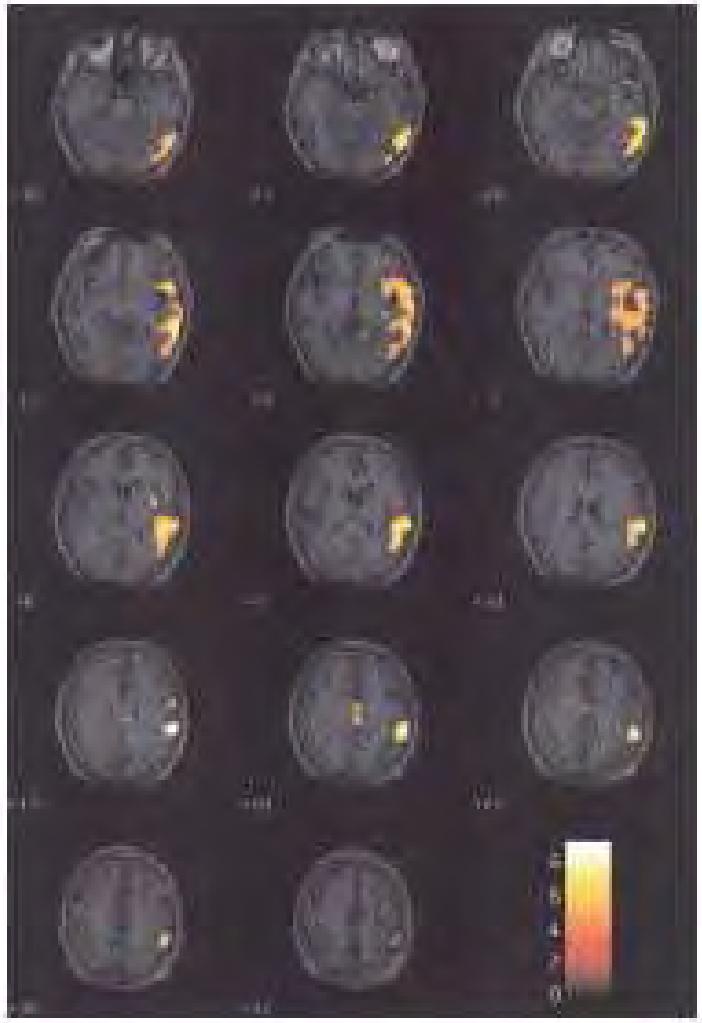


(from: Lemmieux et al., Neuroimage, 14, 2001)

EEG-triggered fMRI

epileptic seizure





(from: Salek-Haddadi et al., Neuroimage, 16, 2002)

comparison of functional imaging techniques