The physiology of the BOLD signal
What do we measure with fMRI?

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Many thanks to
K. E. Stephan for material

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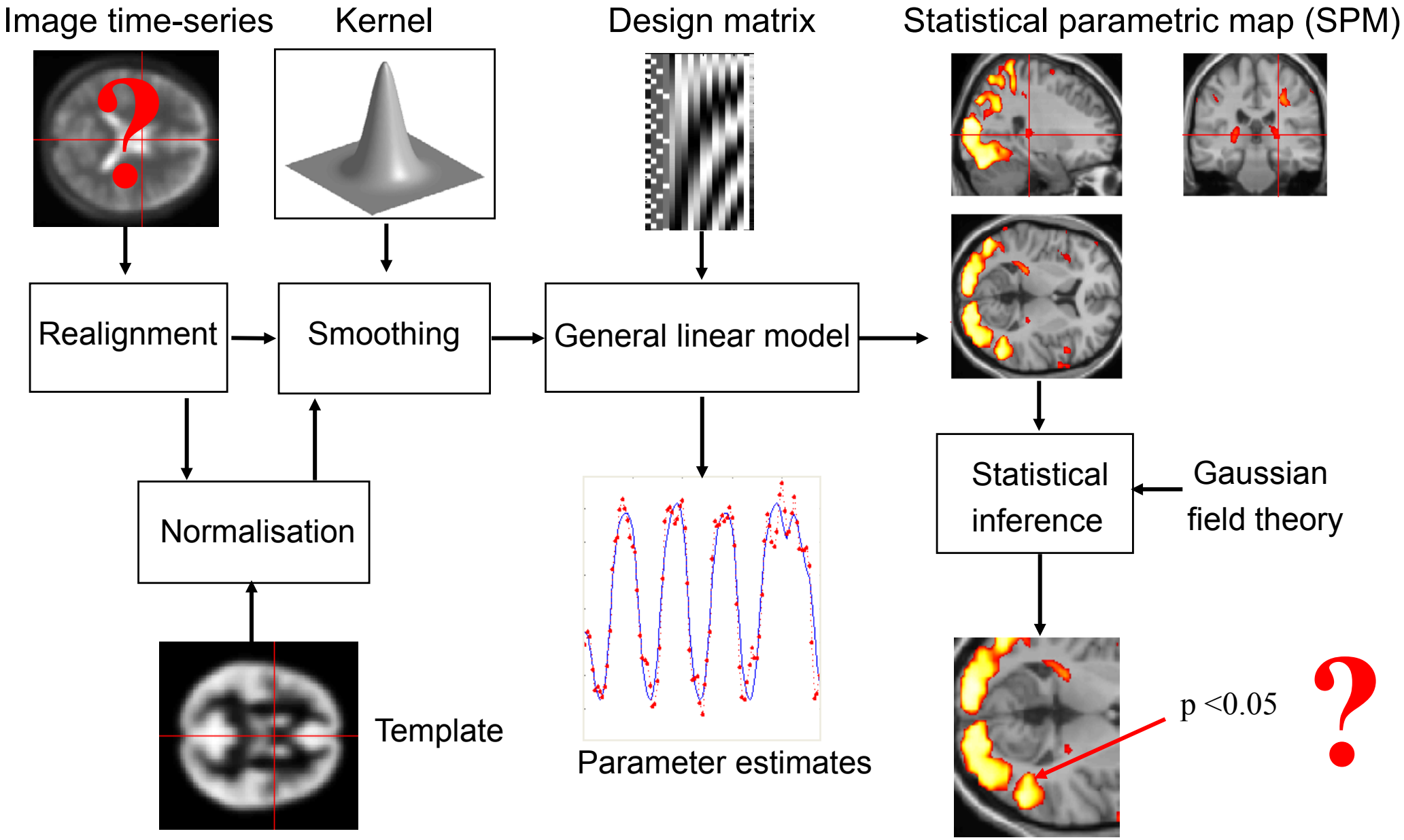
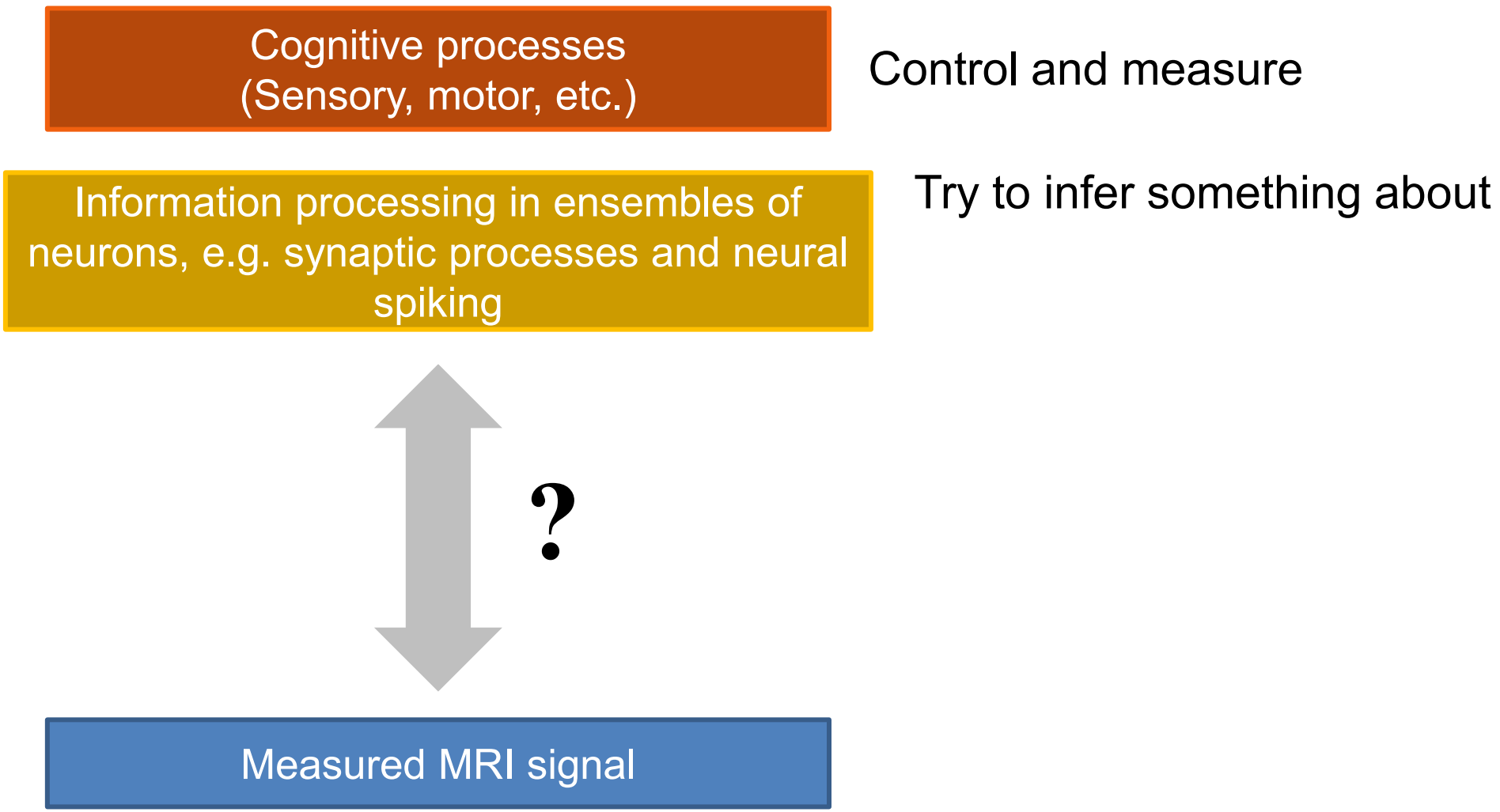
Overview of SPM

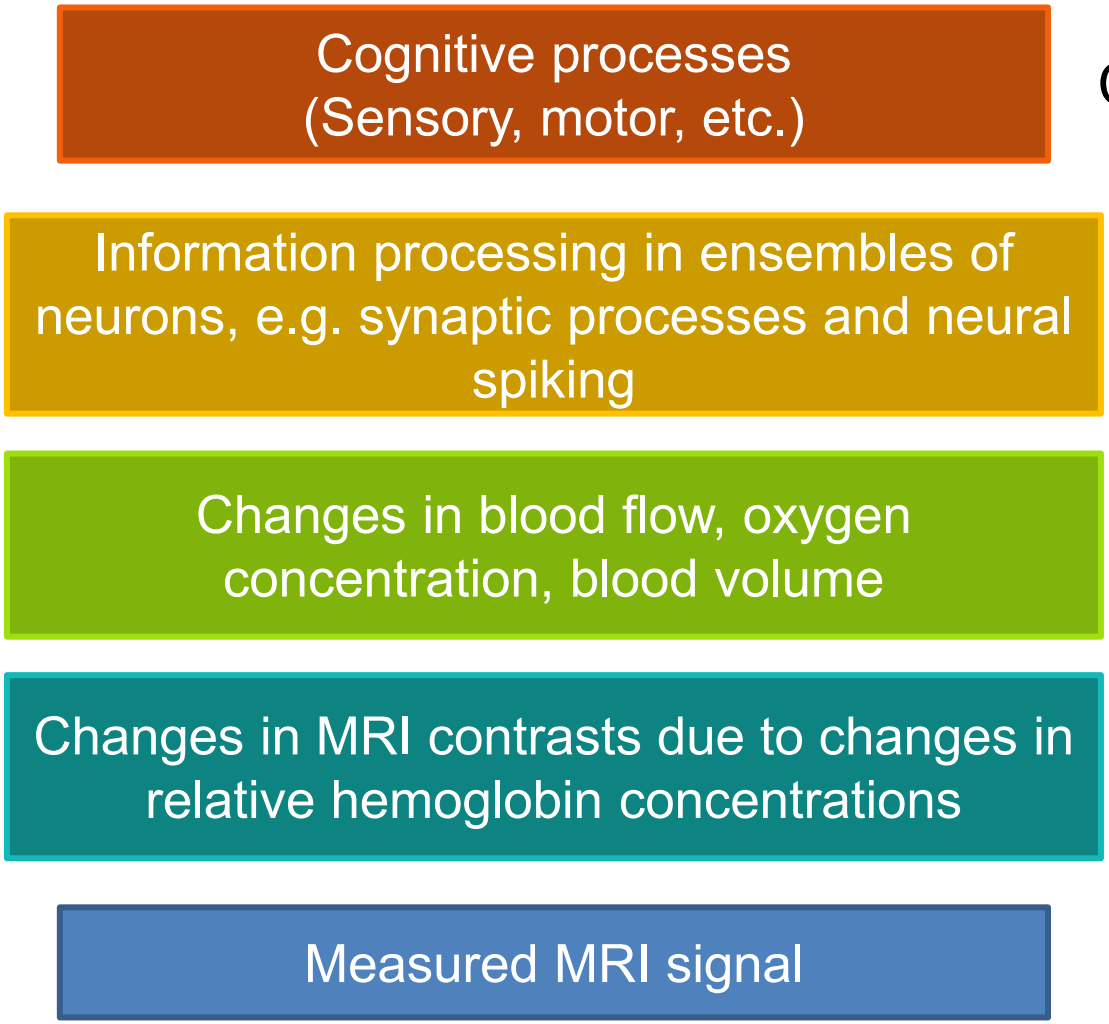


Indirect relationship between cognitive processes, neural processing and fMRI



Adapted from Huettel et al, 2004, fMRI (Book)

Indirect relationship between cognitive processes, neural processing and fMRI



Control and measure

Try to infer something about

3. How is the BOLD signal related to neural processing?

2. What do we measure with fMRI?

1. What do we measure with MRI?

Adapted from Huettel et al, 2004, fMRI (Book)

Material (hydrogen) in a magnetic field

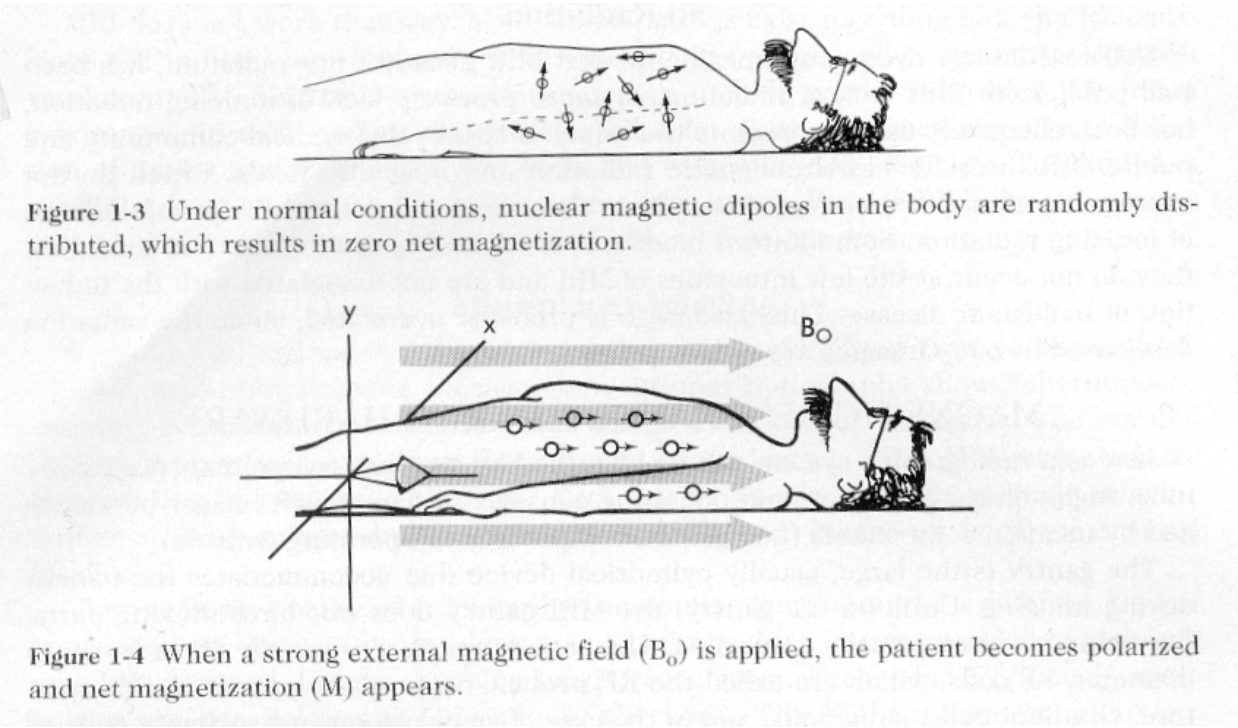
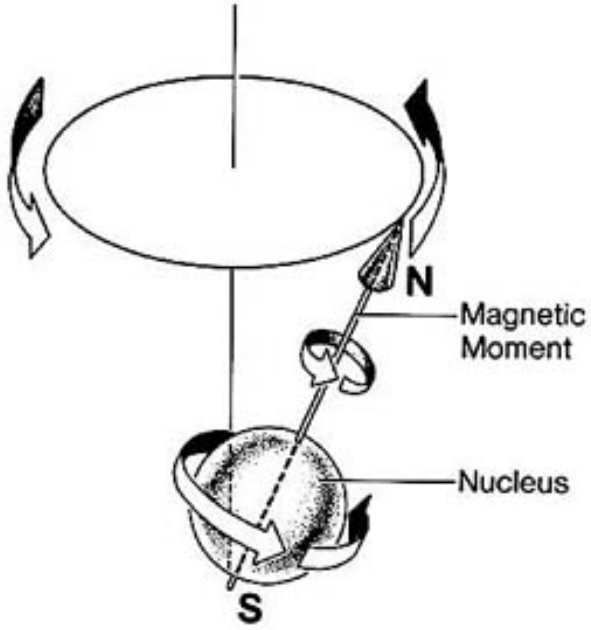


Figure 1-3 Under normal conditions, nuclear magnetic dipoles in the body are randomly distributed, which results in zero net magnetization.

Figure 1-4 When a strong external magnetic field (B_0) is applied, the patient becomes polarized and net magnetization (M) appears.

Protons align with the magnetic field.

We can measure the average magnetization.



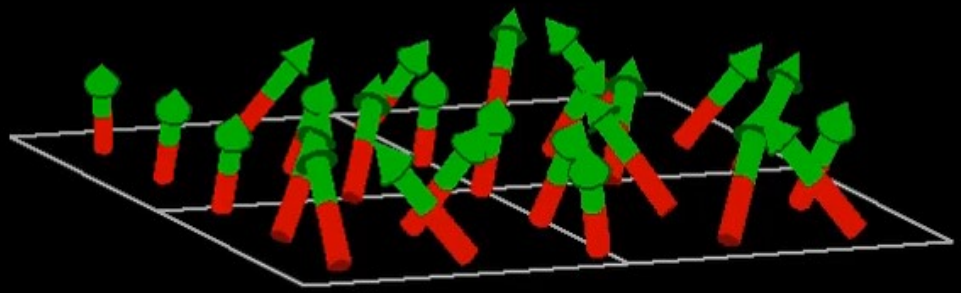
Spin = rotation of a proton around some axis

→ magnetic moment

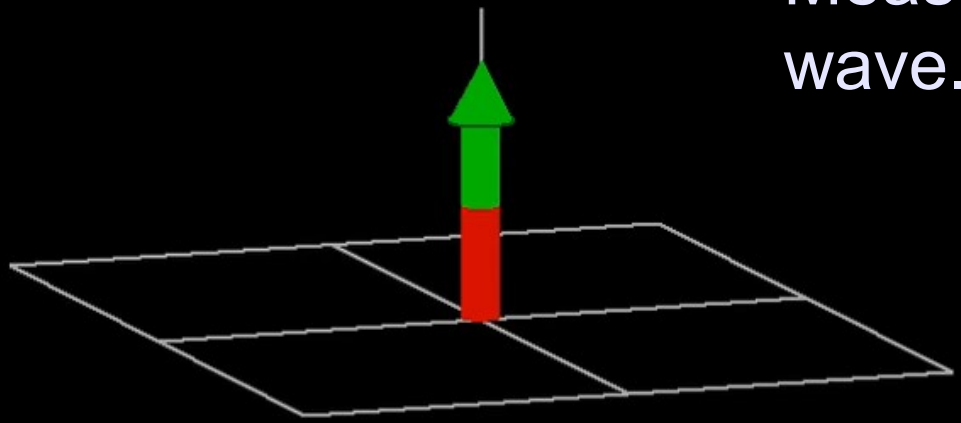
Images: www.fmri4newbies.com

Excitation and relaxation of spins

Excite sample with RF pulse (radio wave: 42.6MHz/Tesla).



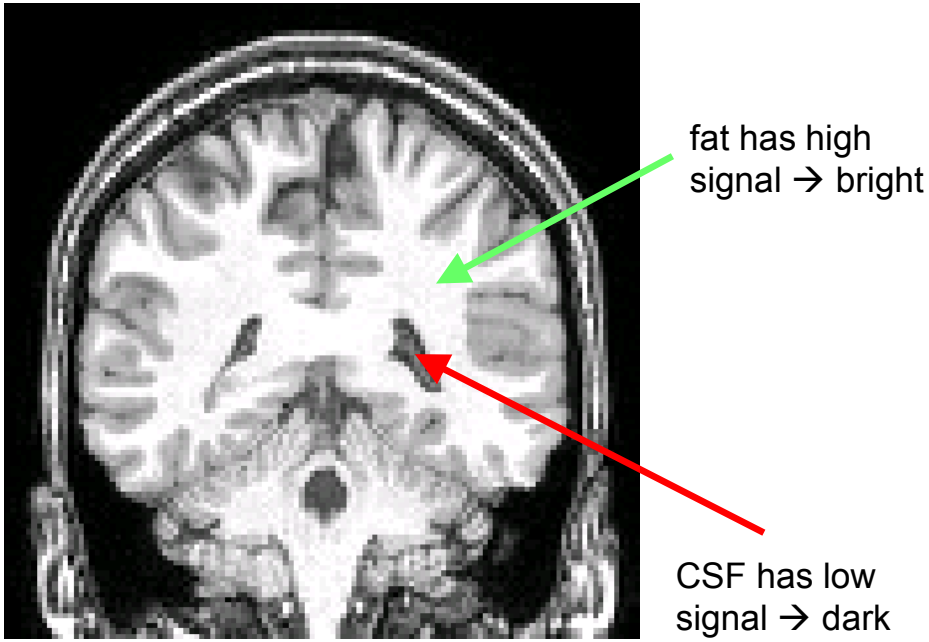
Measure the emitted radio wave.



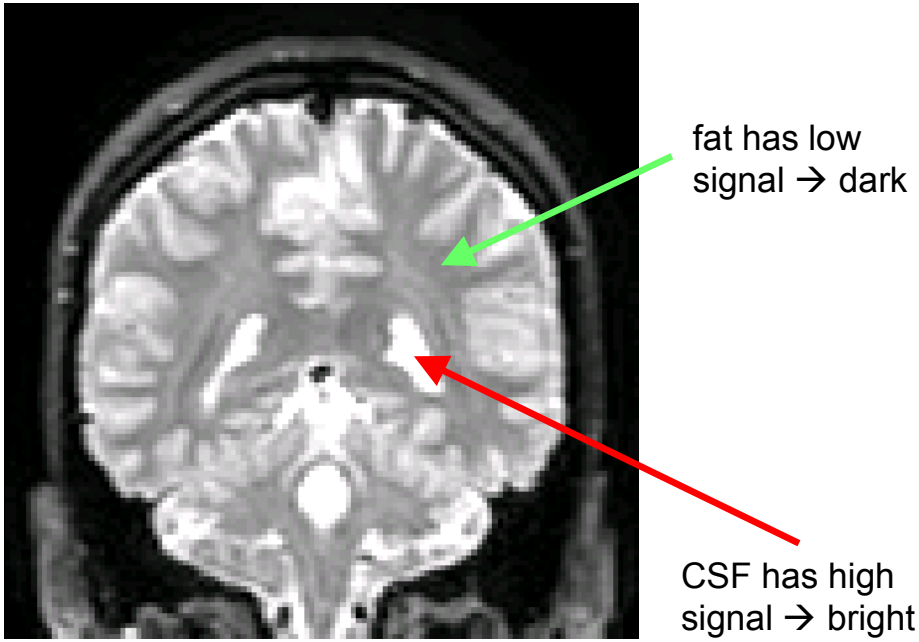
Movies: K. Prüssmann

Signal decay depends on tissue

T1 = How quickly do protons realign with magnetic field?



T2 = How quickly do protons emit energy (phase out) when recovering to equilibrium?



T2* magnetization decay

- Decay of transverse magnetization has two factors:

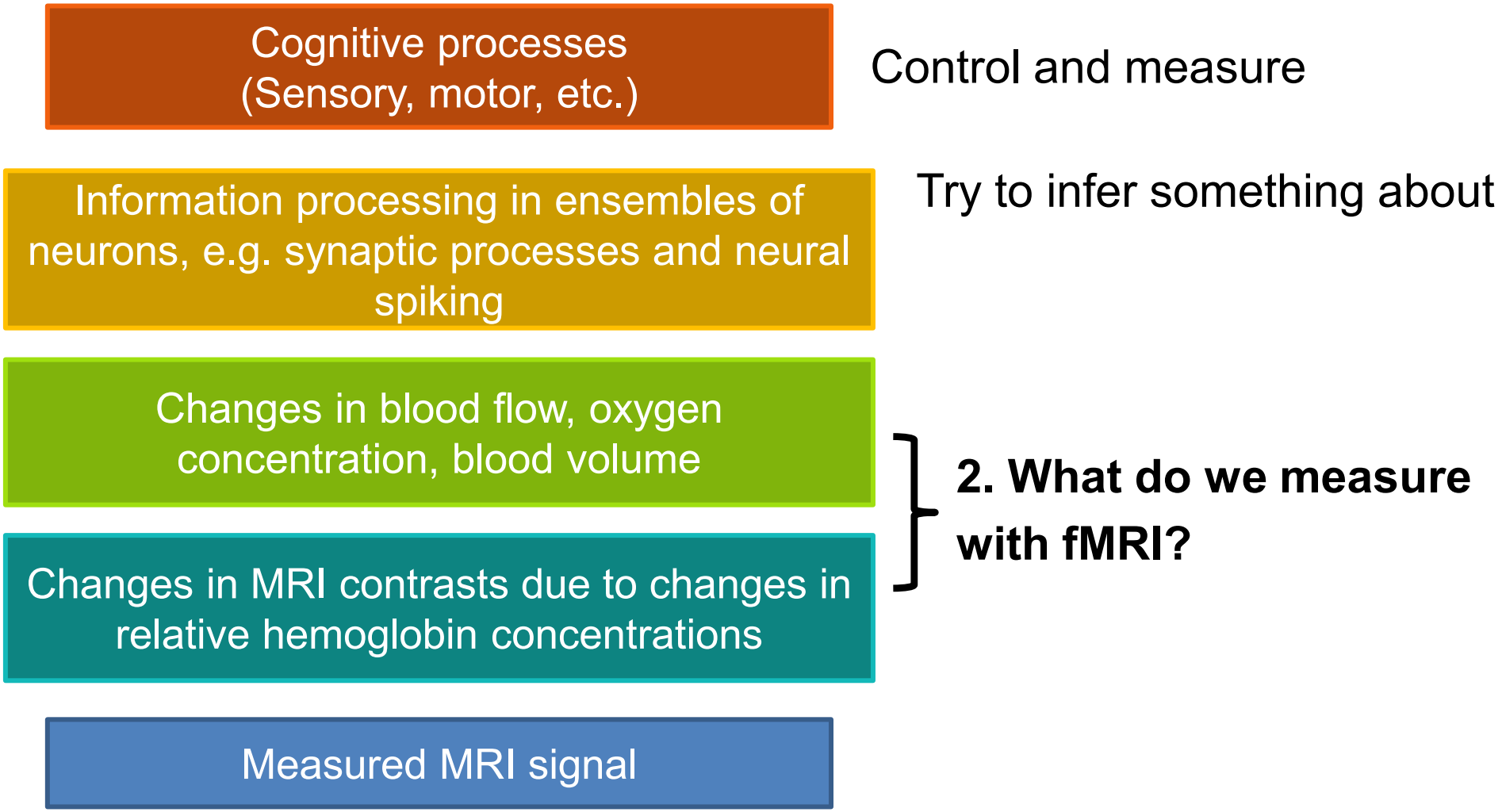
  1) molecular interactions (tissue properties) (T2)
  2) local inhomogeneities of the magnetic field

➢ The combined time constant is called T2*.

The general principle of MRI:

- excite spins in static field by RF pulses & detect the emitted RF
- use an acquisition technique that is sensitive to local differences in T1, T2 or T2*
- construct a spatial image

Indirect relationship between cognitive processes, neural processing and fMRI



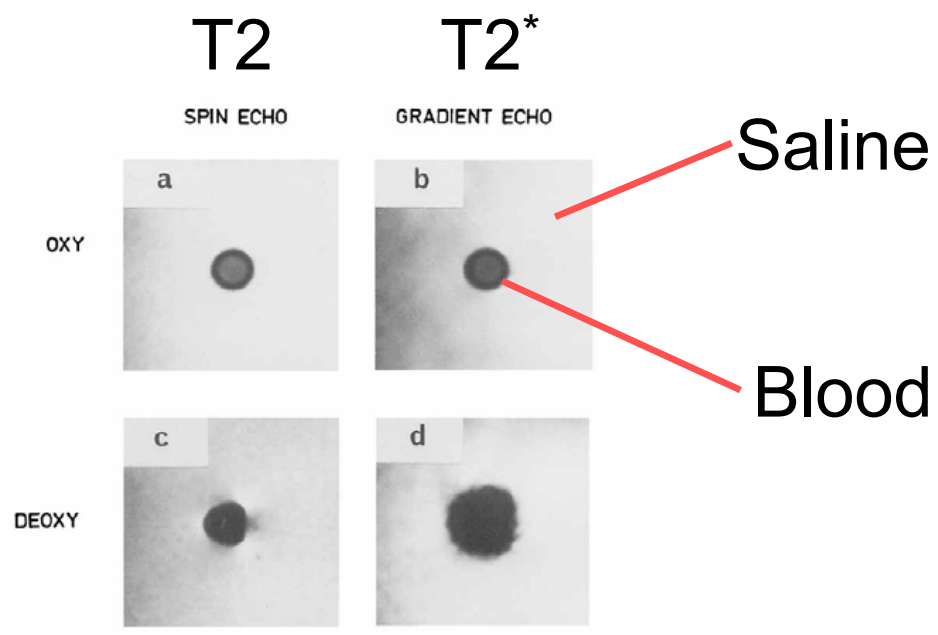
Adapted from Huettel et al, 2004, fMRI (Book)

fMRI uses T2* contrasts

- fMRI uses MRI sequences that measure T2* decay of protons.
- Depends on:
  - Molecular interaction
  - **Local inhomogeneities of magnetic field**

What makes T2* weighted images “functional”?

It’s the blood



The signal comes from the susceptibility change due to deoxy-Hb vs. oxy-Hb.

OxyHb (diamagnetic) vs. DeoxyHb (paramagnetic) effects on spin of hydrogen atoms in surrounding tissue.

Source: Ogawa et al, Magn. Res. Med., 1990

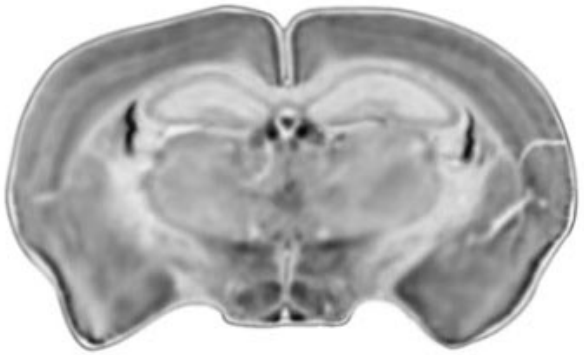
The BOLD effect

- BOLD (Blood Oxygenation Level Dependent) contrast measures inhomogeneities in the magnetic field due to changes in the level of O_2 in the blood

Oxygenated hemoglobin:

Diamagnetic (non-magnetic)

→ no signal loss!

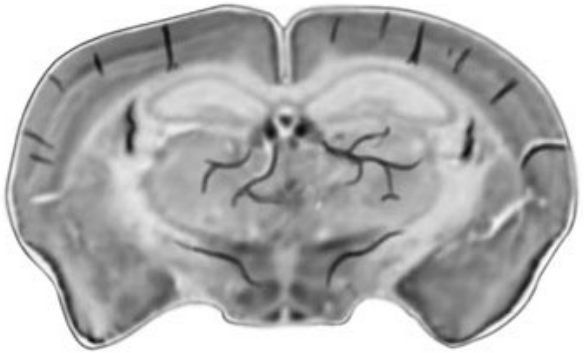


100 % O_2

<u>De</u>oxygenated hemoglobin:

Paramagnetic (magnetic)

→ signal loss!

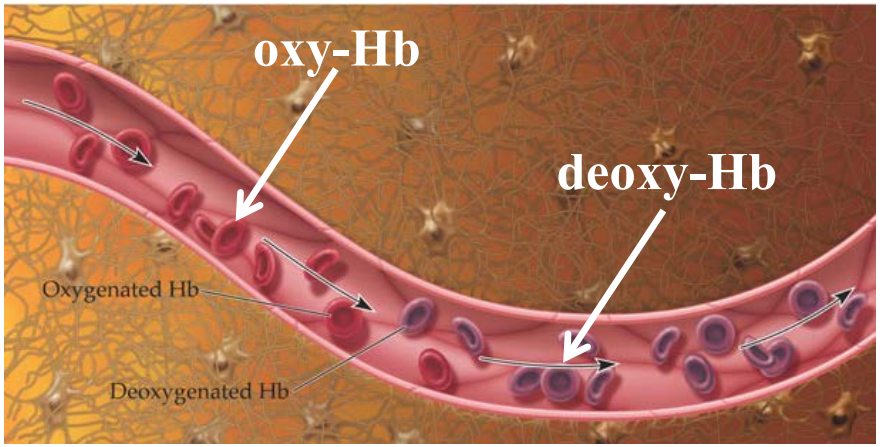


Normal air

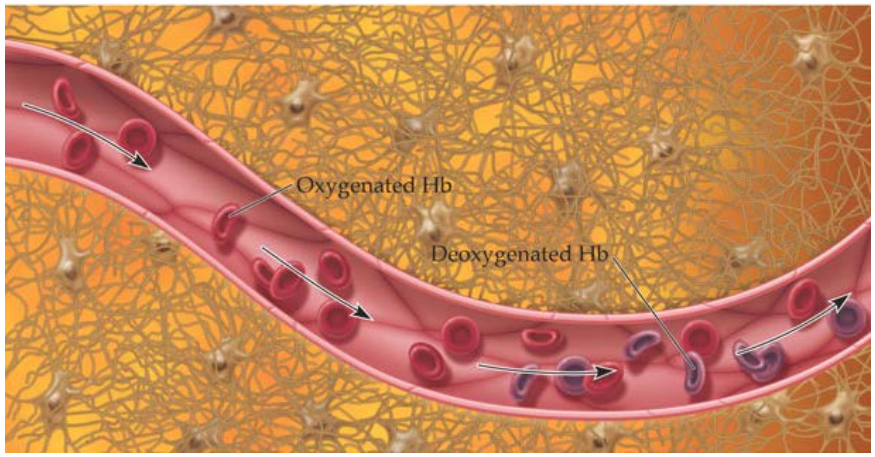
Source: Ogawa et al, Magn. Res. Med., 1990

Increased blood flow

Rest



Activity



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

Increased neural activity leads to an over-compensatory increase of regional CBF, which decreases the relative amount of deoxy-Hb → higher T2* signal intensity

Source: Huettel et al, 2004, fMRI (Book)

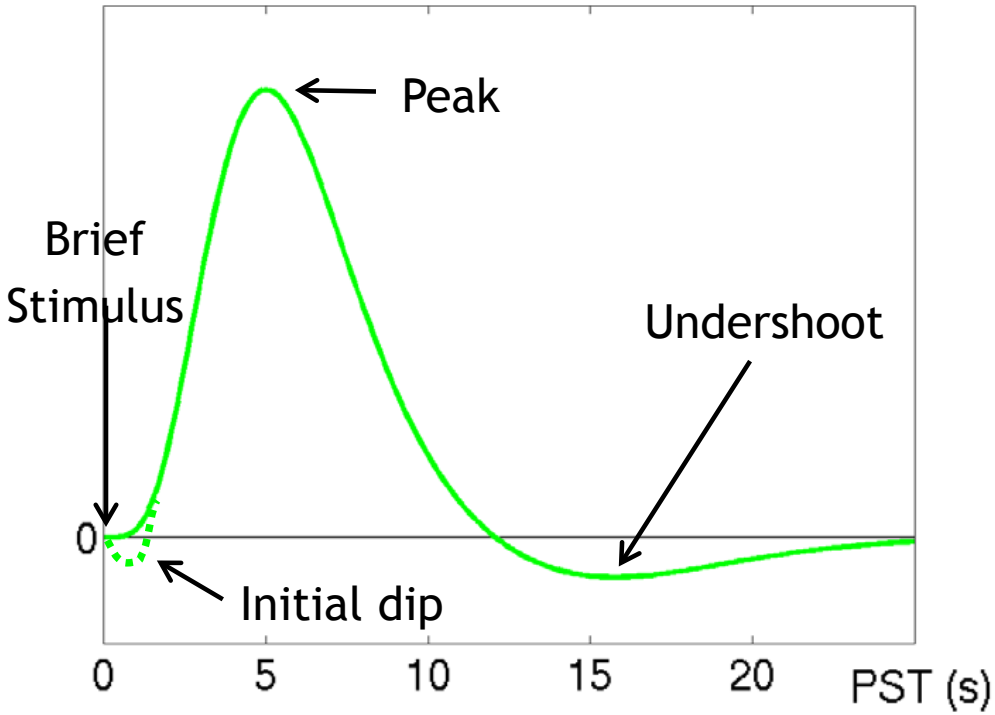
The hemodynamic response function (HRF)

sometimes shows initial undershoot → initial dip

peaks after 4-6 secs

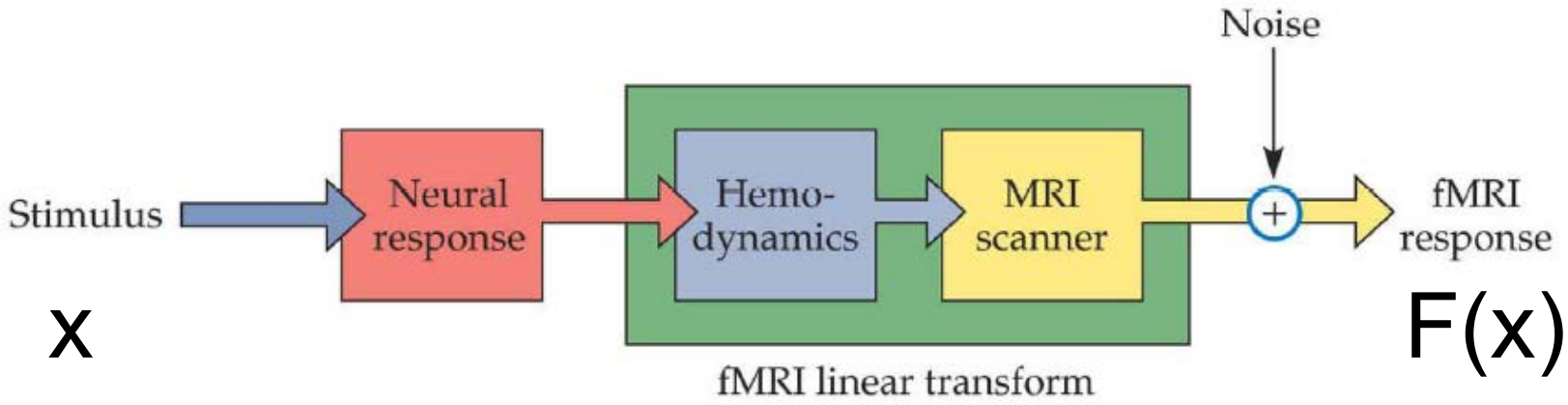
back to baseline after approx. 30 secs

can vary between regions and subjects



Hemodynamic response function = BOLD response to a brief stimulus

Approximation of HRF with linear transform?

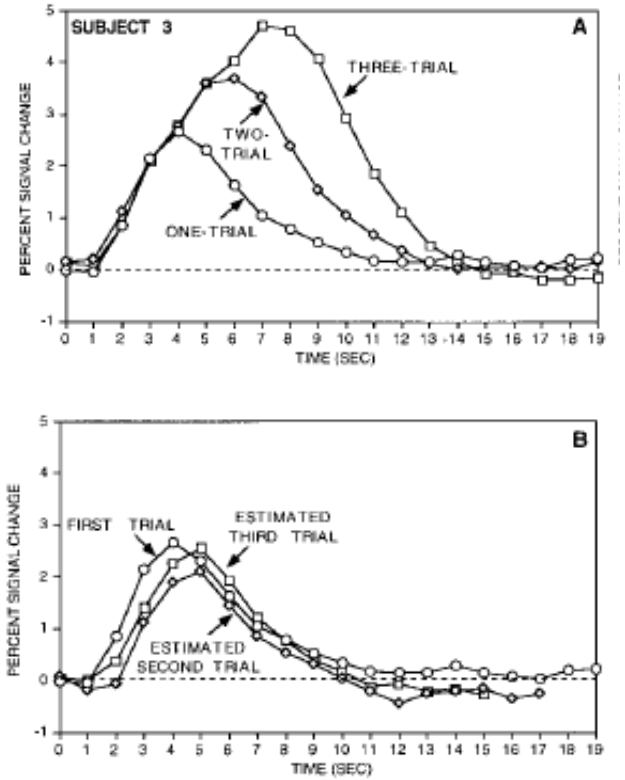


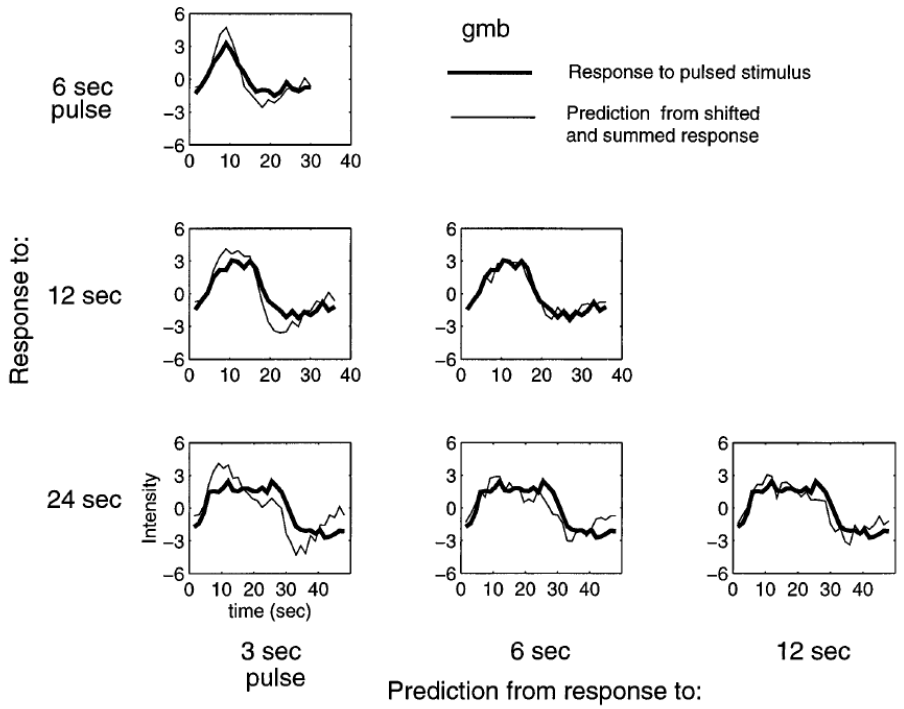
Linear transform: $F(ax+by)=aF(x)+bF(y)$

Important for data analysis, e.g. GLM!

Source: Huettel et al, 2004, fMRI (Book)

Evidence for linearity from early experiments

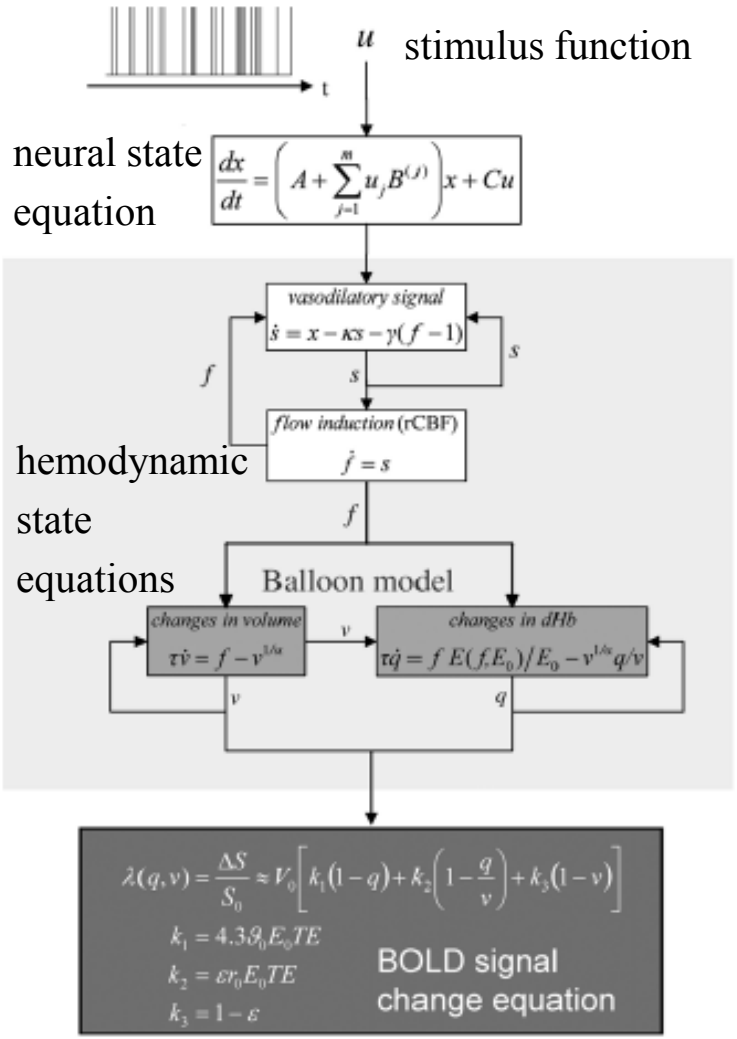


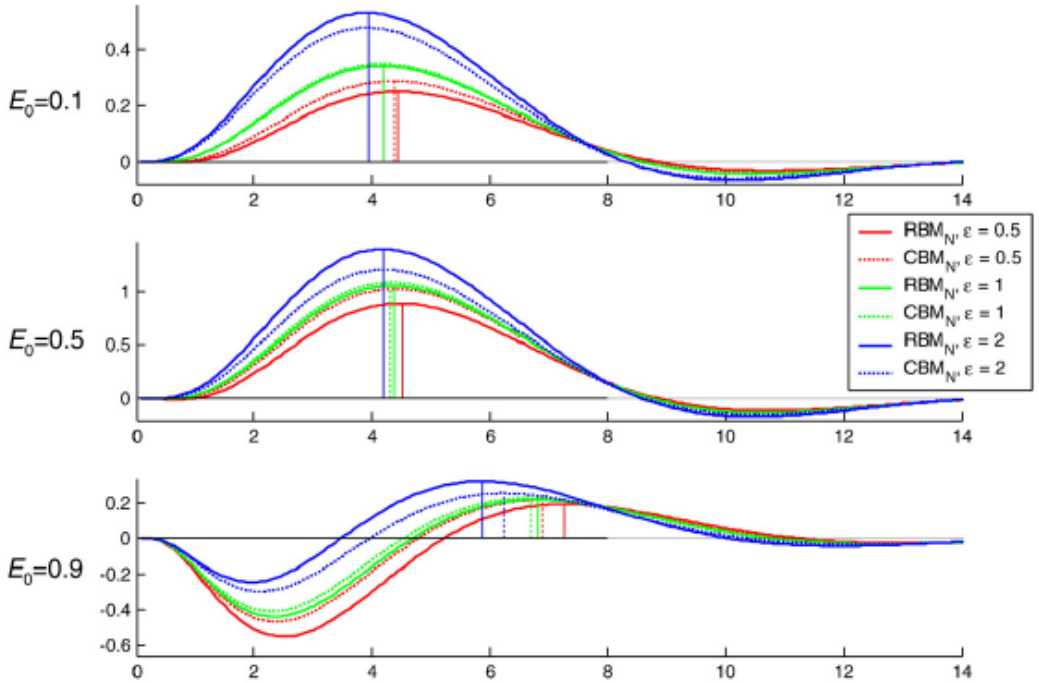


Often linear transform is a good approximation to HRF

Source: Dale and Buckner, Hum Brain Mapp, 1997; Boynton et al, J Neurosci, 1996

BOLD is a non-linear function of rCBF





BOLD is non-linear → cf. DCM!

Source: Stephan et al., NeuroImage, 2007

Indirect relationship between cognitive processes, neural processing and fMRI

Cognitive processes (Sensory, motor, etc.)

Control and measure

Information processing in ensembles of neurons, e.g. synaptic processes and neural spiking

Try to infer something about

Changes in blood flow, oxygen concentration, blood volume

3. How is the BOLD signal related to neural processing?

Changes in MRI contrasts due to changes in relative hemoglobin concentrations

Measured MRI signal

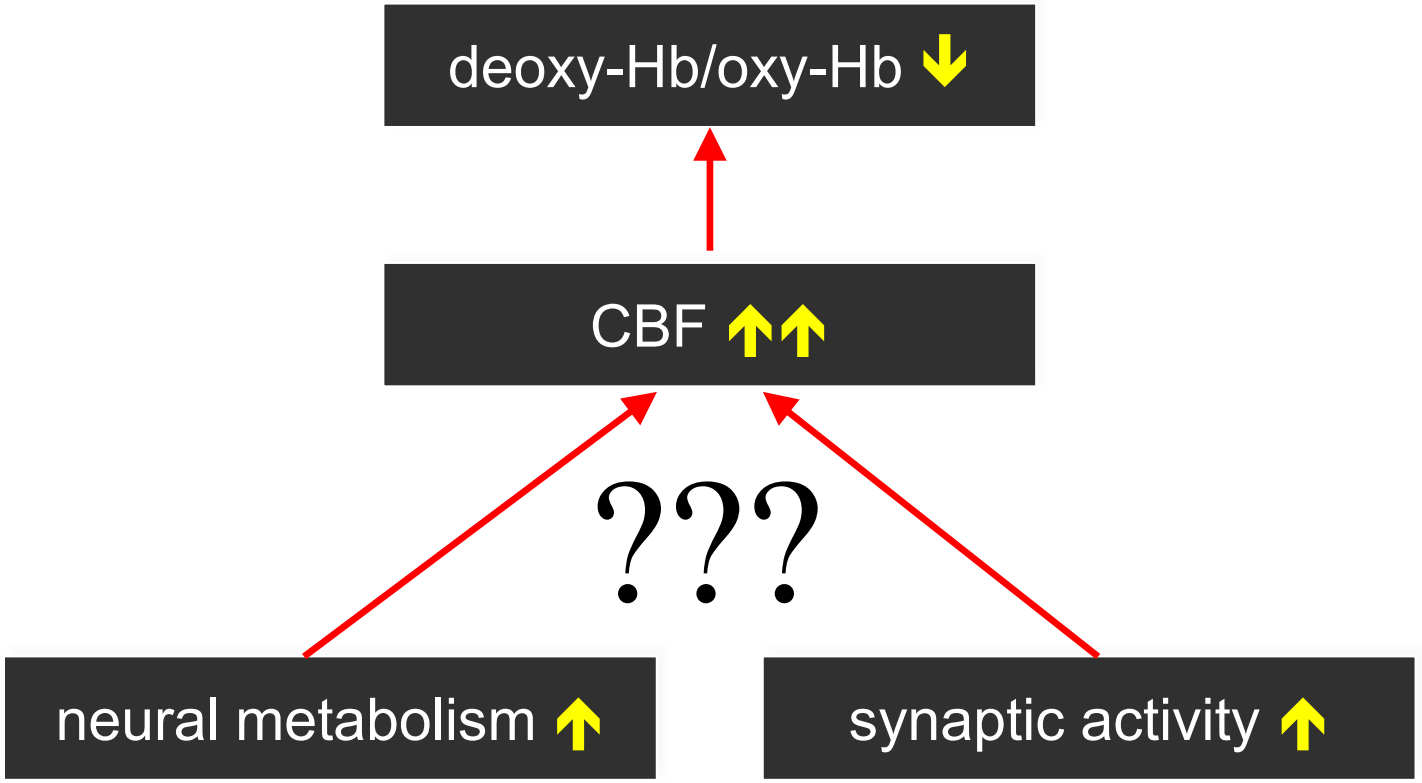
Adapted from Huettel et al, 2004, fMRI (Book)

3. How is the BOLD signal related to neural activity?

Some important questions:

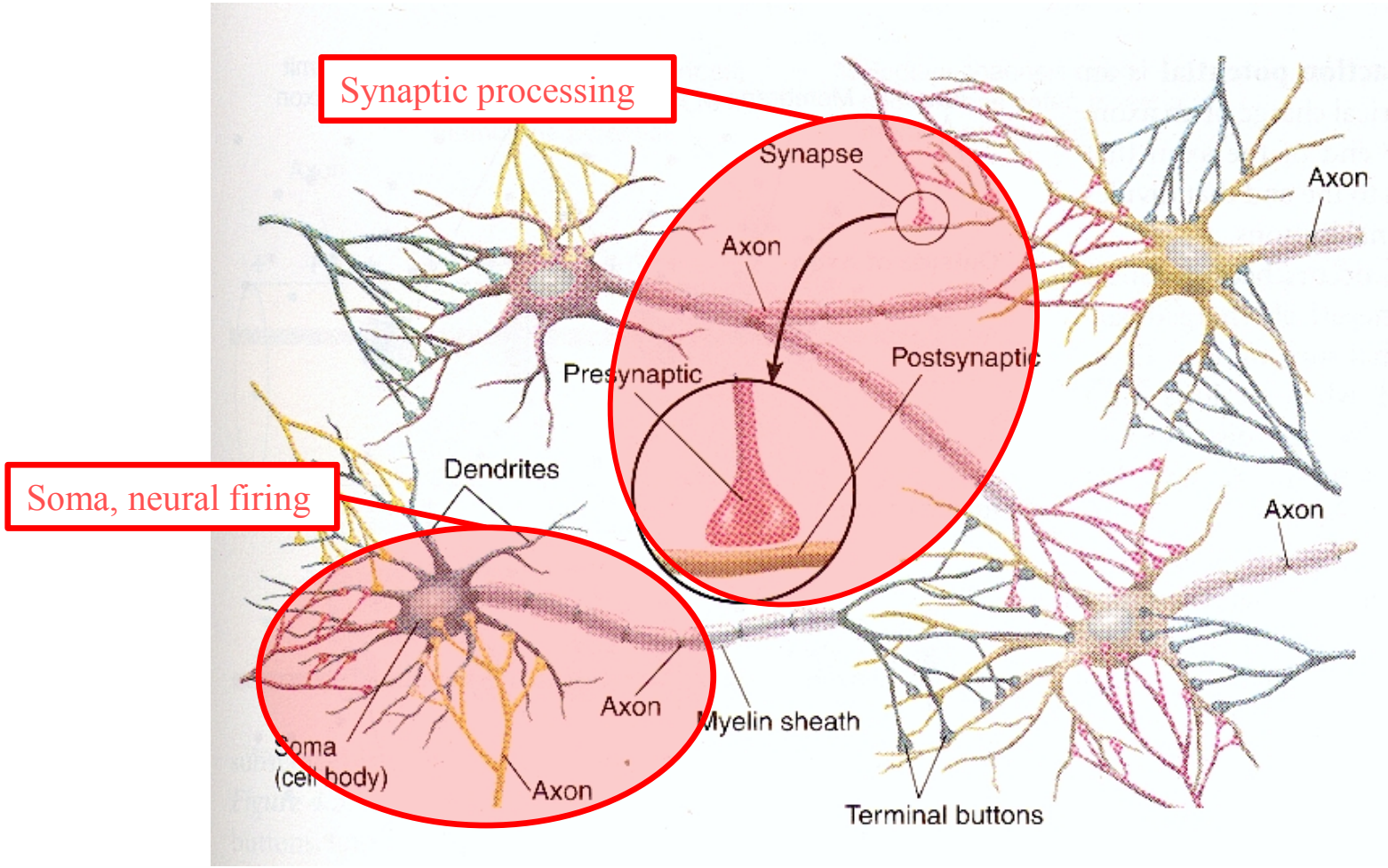
- What is the electrophysiological measure with the closest link to the BOLD signal?
- Does the BOLD signal reflect energy demands or synaptic activity?
- What does a negative BOLD signal mean?

What causes BOLD signal changes



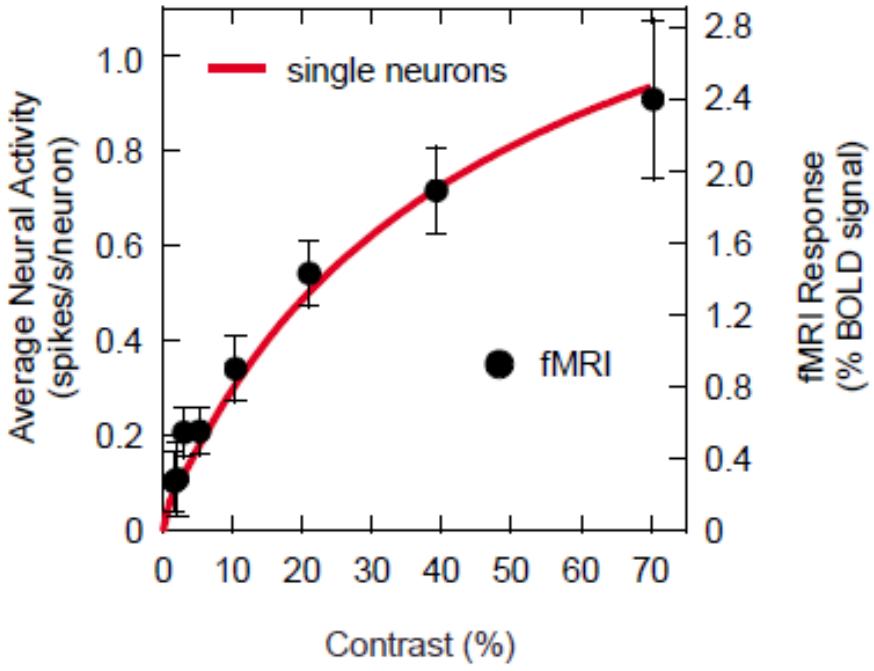
Neurovascular coupling?

Where does the signal come from: Soma or synapse?



Source: http://psychology.uwo.ca/fmri4newbies/Tutorials.html

Comparing BOLD with electrophysiology – early experiments



Idea:

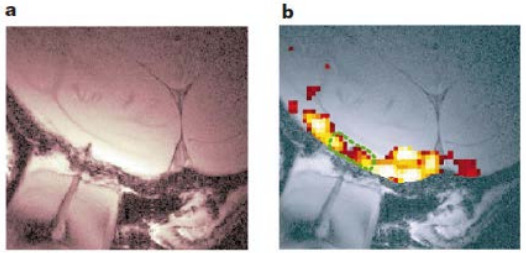
Compare average firing rate of cells in monkey MT to the BOLD activity measured in humans.

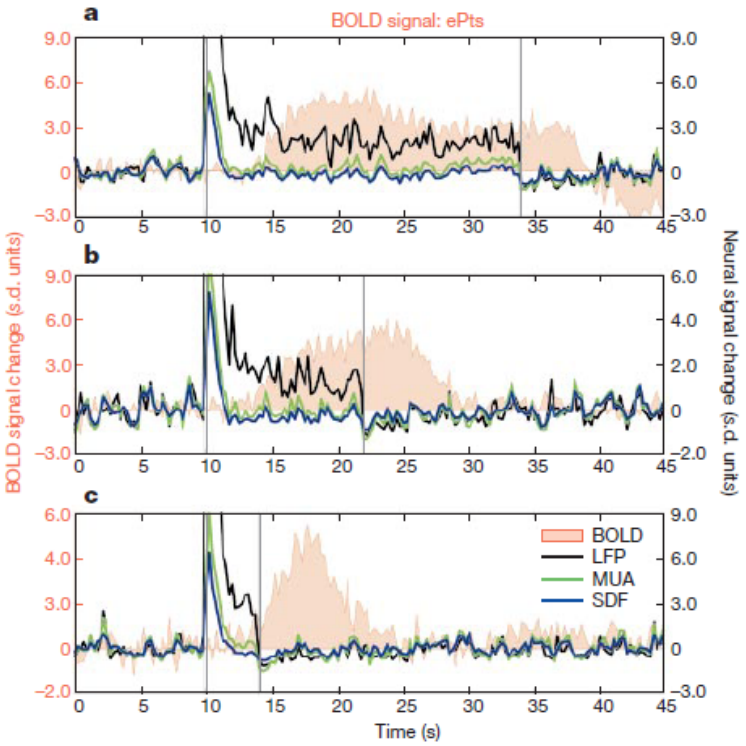
Conclusion:

There is a good agreement between spiking (firing rate) and BOLD.

Source: Heeger et al, Nat Neurosci, 2000
Rees et al, Nat Neurosci, 2000

LFP correlates best with the BOLD-signal





Local Field Potentials (LFP)

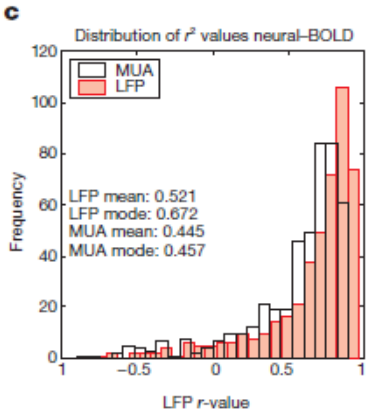
- reflect summation of post-synaptic potentials

Multi-Unit Activity (MUA)

- reflects action potentials/spiking

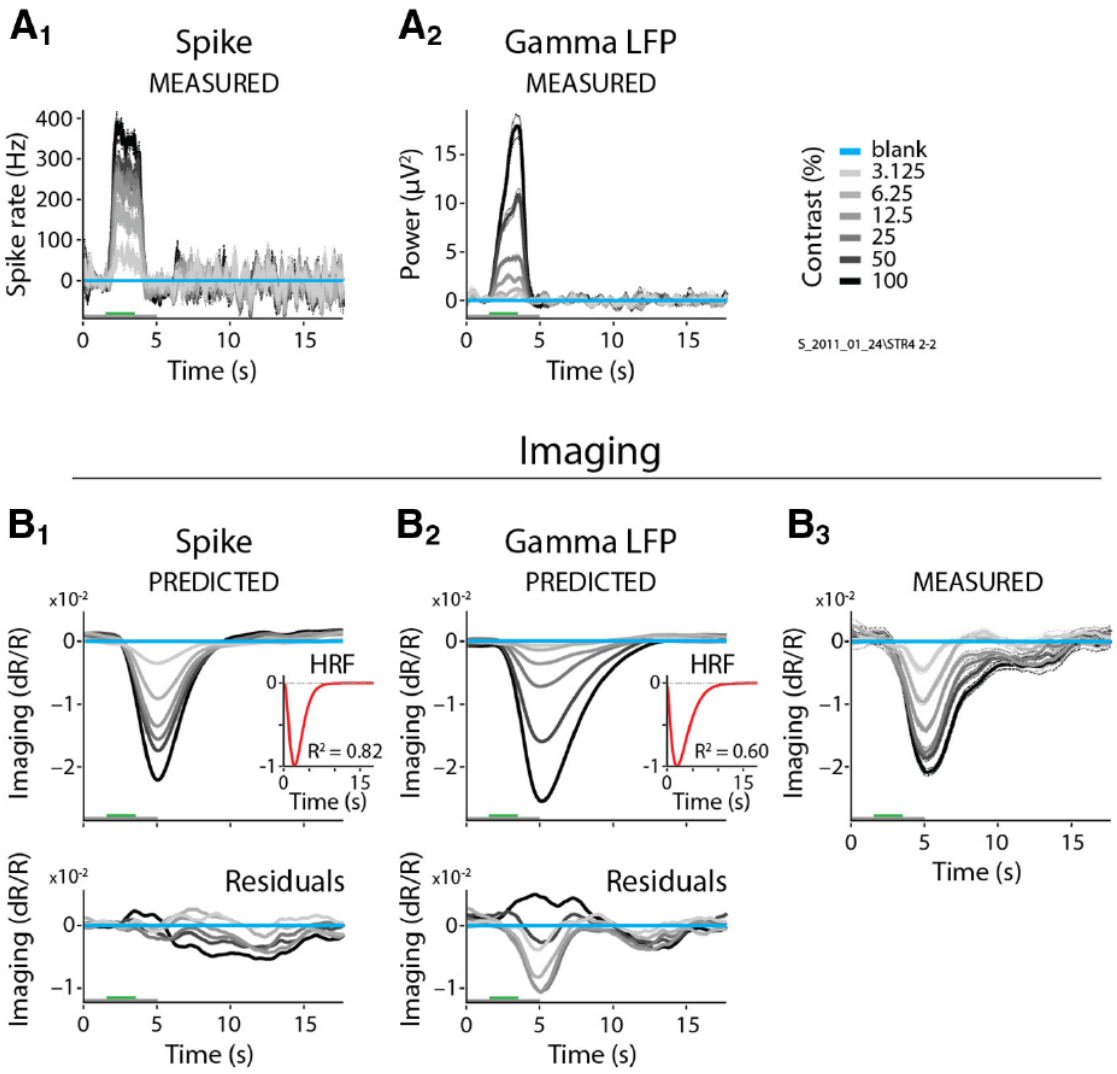
combined BOLD fMRI and electrophysiological recordings

→ found that BOLD activity is more closely related to LFPs than MUA



Source: Logothetis et al, Nature, 2001

But, also spikes can be better correlated with BOLD



- response to visual stimuli of varying contrast.
- used optical imaging instead of fMRI.
- removed blank trial baseline

→ Spikes predict imaging better than LFP.

Source: Lima et al, J Neurosci, 2014

The BOLD signal is correlated to postsynaptic activity

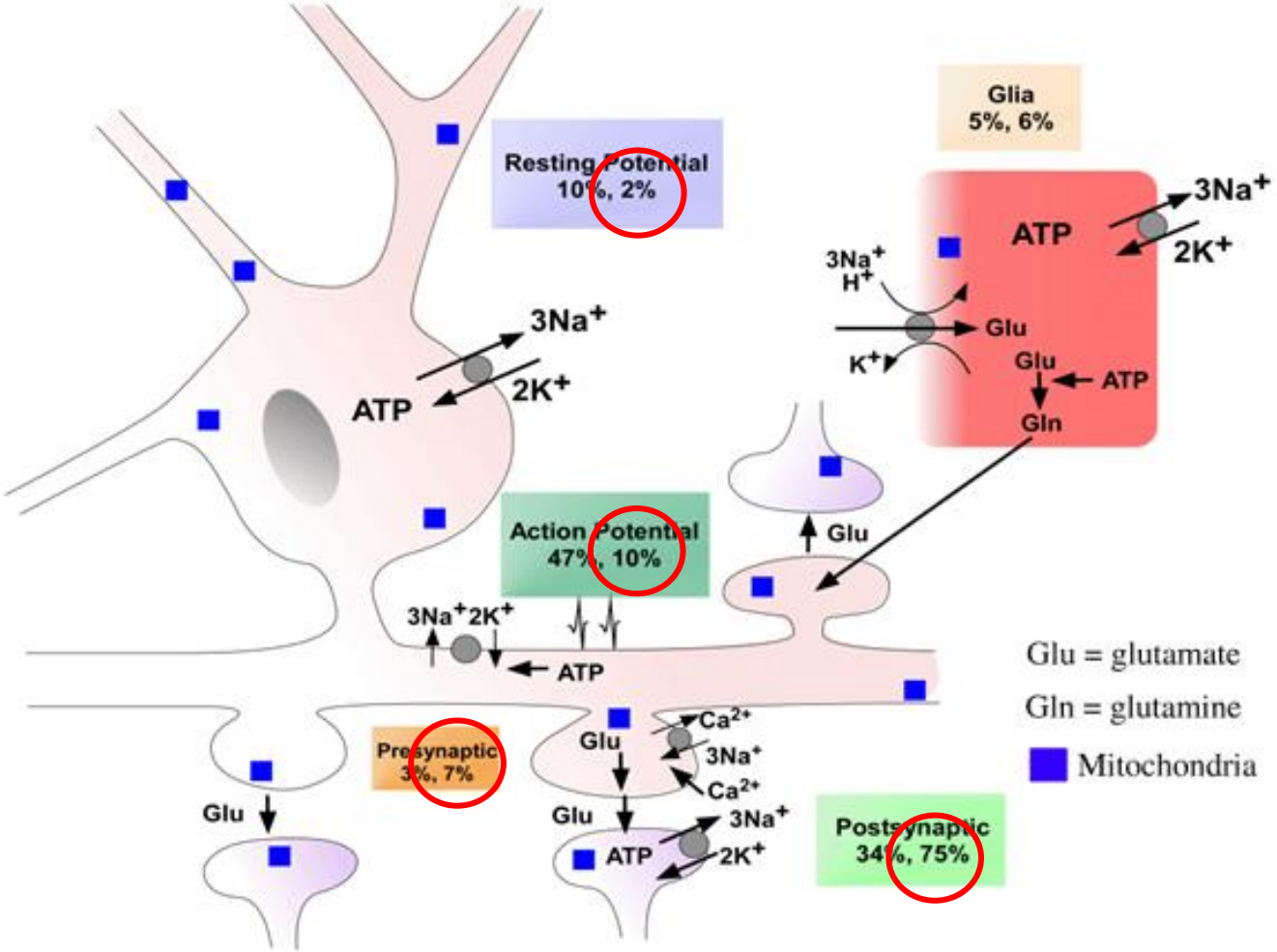
- The BOLD signal is best correlated to postsynaptic activity (as measured by LFPs)
  - In many cases action potentials and LFPs are themselves highly correlated.
  - rCBF-increase can be independent from spiking activity, but so far no case has been found where it was completely independent of LFPs.
- Present conclusion: BOLD more strongly reflects the **input to** a neuronal population as well as its **intrinsic (recurrent) processing**, rather than only its spiking output to other regions.

3. How is the BOLD signal related to neural activity?

Some important questions:

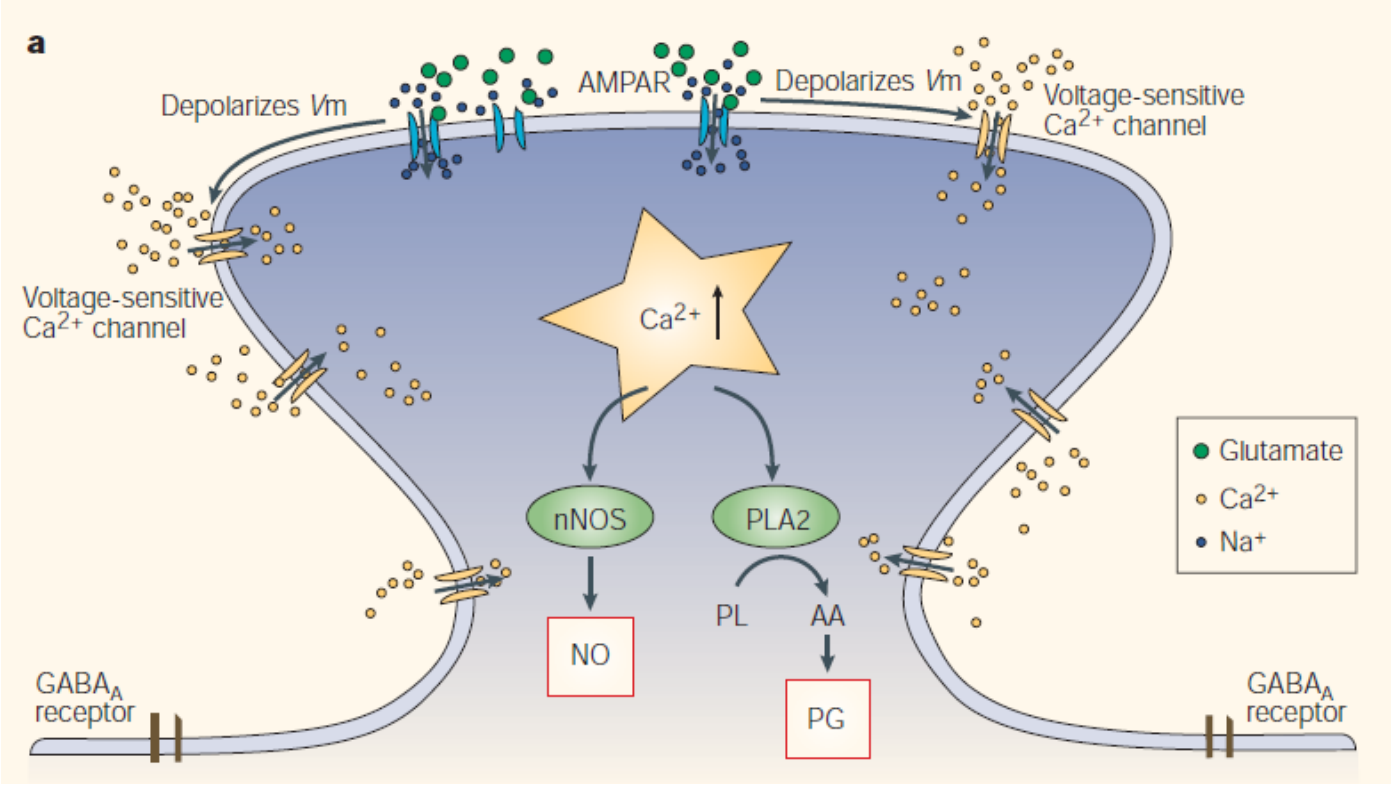
1. Is the BOLD signal more strongly related to neuronal action potentials or to local field potentials (LFP)?
2. Does the BOLD signal reflect energy demands or synaptic activity?
3. What does a negative BOLD signal mean?

Cortical Metabolism



http://student.biology.arizona.edu/honors99/group7/glycolysis.jpg
Based on: Attwell and McLaughlin, J Cer Blood Flow Metab, 2001

Excitatory action might directly regulate rCBF



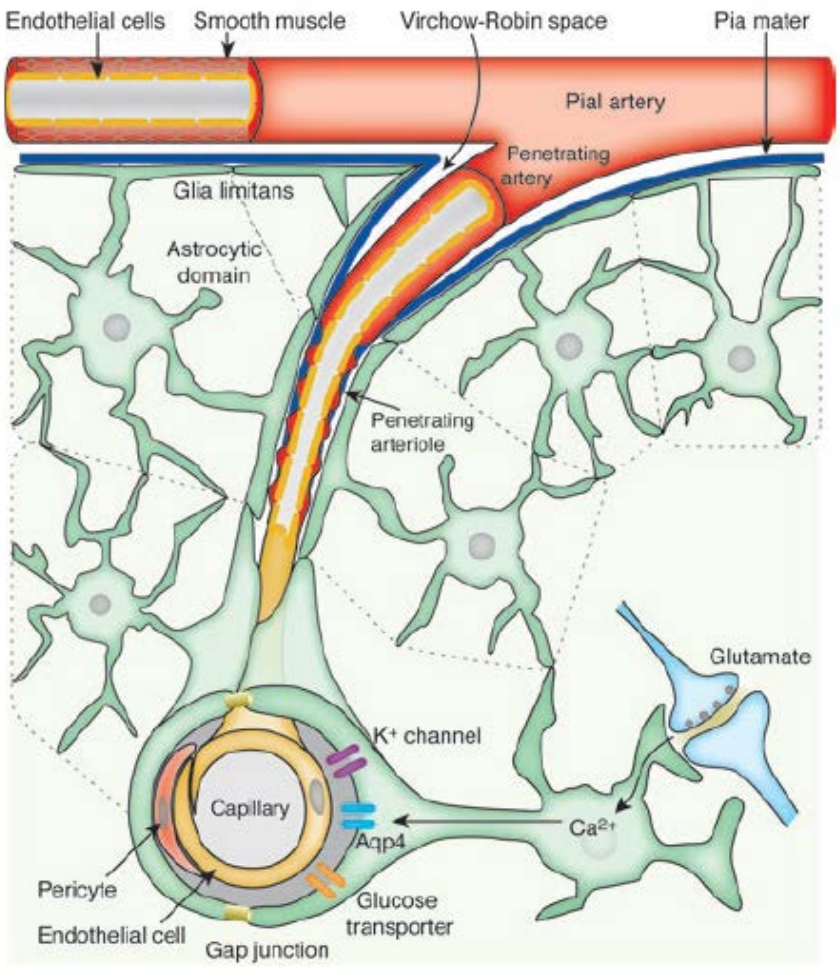
NO (nitric oxid) and PG (prostaglandin) have vasodilatory effects

→ Importance of Calcium

But: Very little contact between neurons and vasculature.

Source: Lauritzen, Nat Rev Neurosci, 2005

Glia cells and blood supply



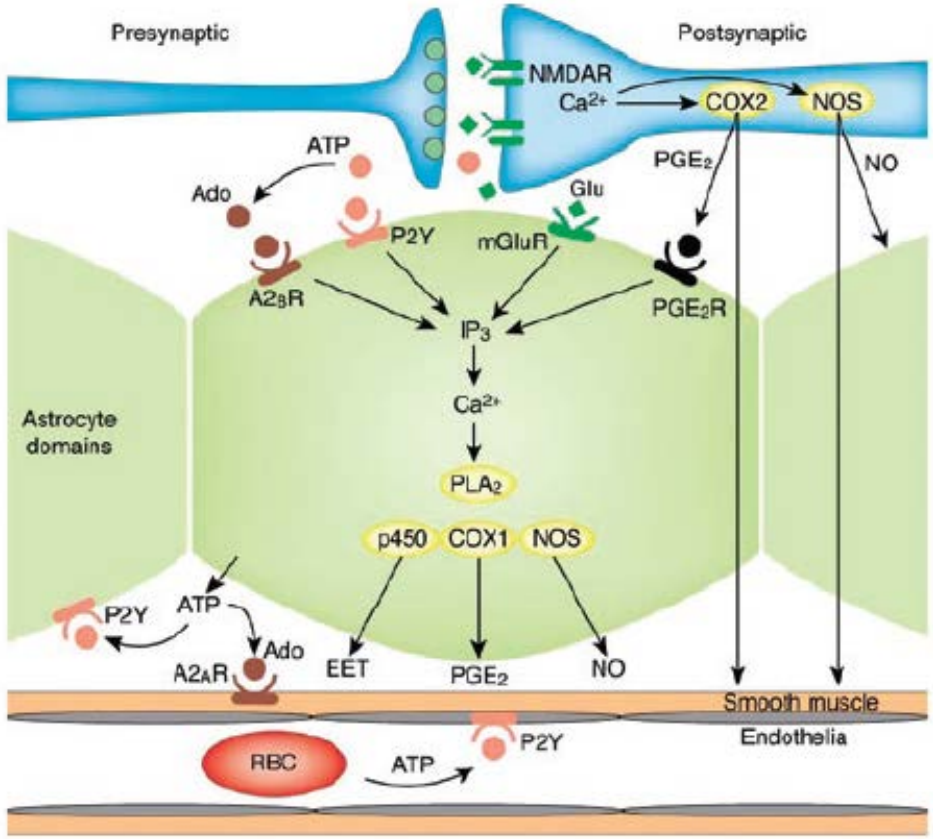
Astrocytes have many contacts with blood vessels.

Glia limitans can regulate blood flow of larger vessels

Domains of astrocytes are in line with a potential function in regulating blood flow.

Source: Iadecola and Nedergaard, Nat Rev Neurosci, 2007

Several pathways for blood flow regulation



Forward control of blood flow seems to occur via several mechanisms.

To date, two major pathways have been associated with NO and PG.

Astrocytes could be important.

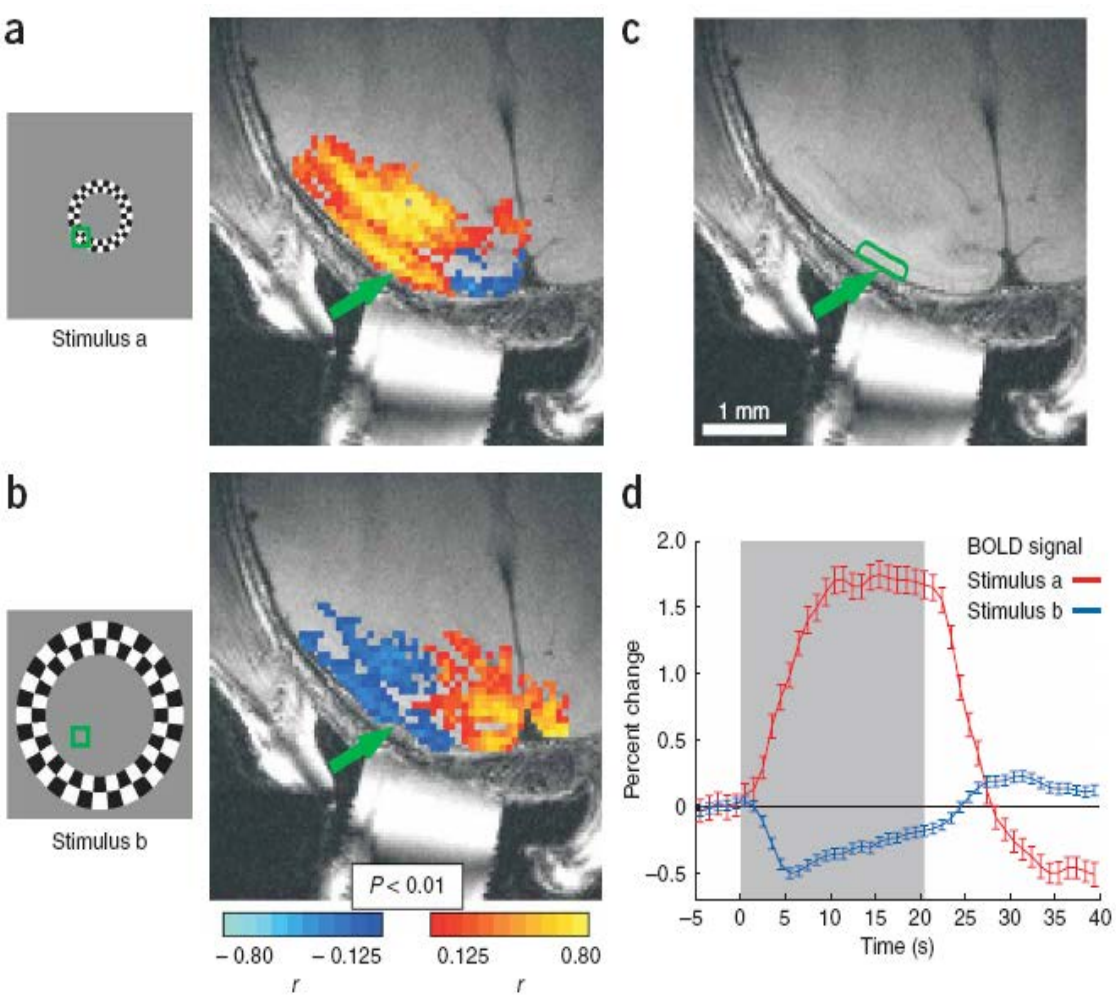
Source: Iadecola and Nedergaard, Nat Rev Neurosci, 2007

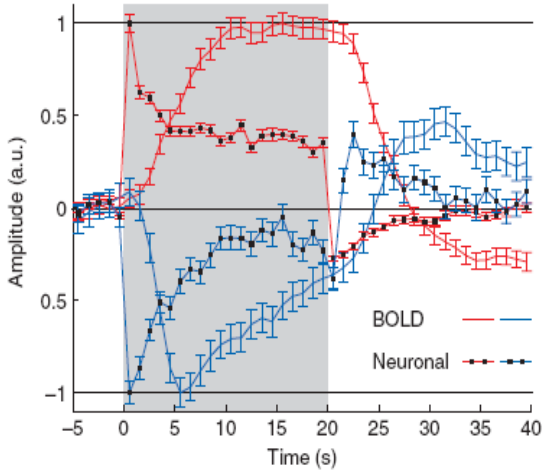
3. How is the BOLD signal related to neural activity?

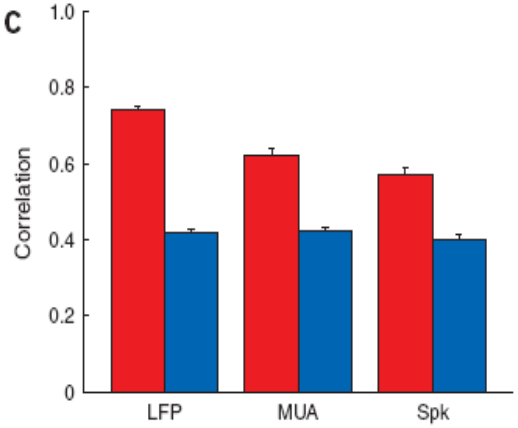
Some important questions:

1. Is the BOLD signal more strongly related to neuronal action potentials or to local field potentials (LFP)?
2. Does the BOLD signal reflect energy demands or synaptic activity?
3. What does a negative BOLD signal mean?

Negative BOLD is correlated with decreases in LFPs

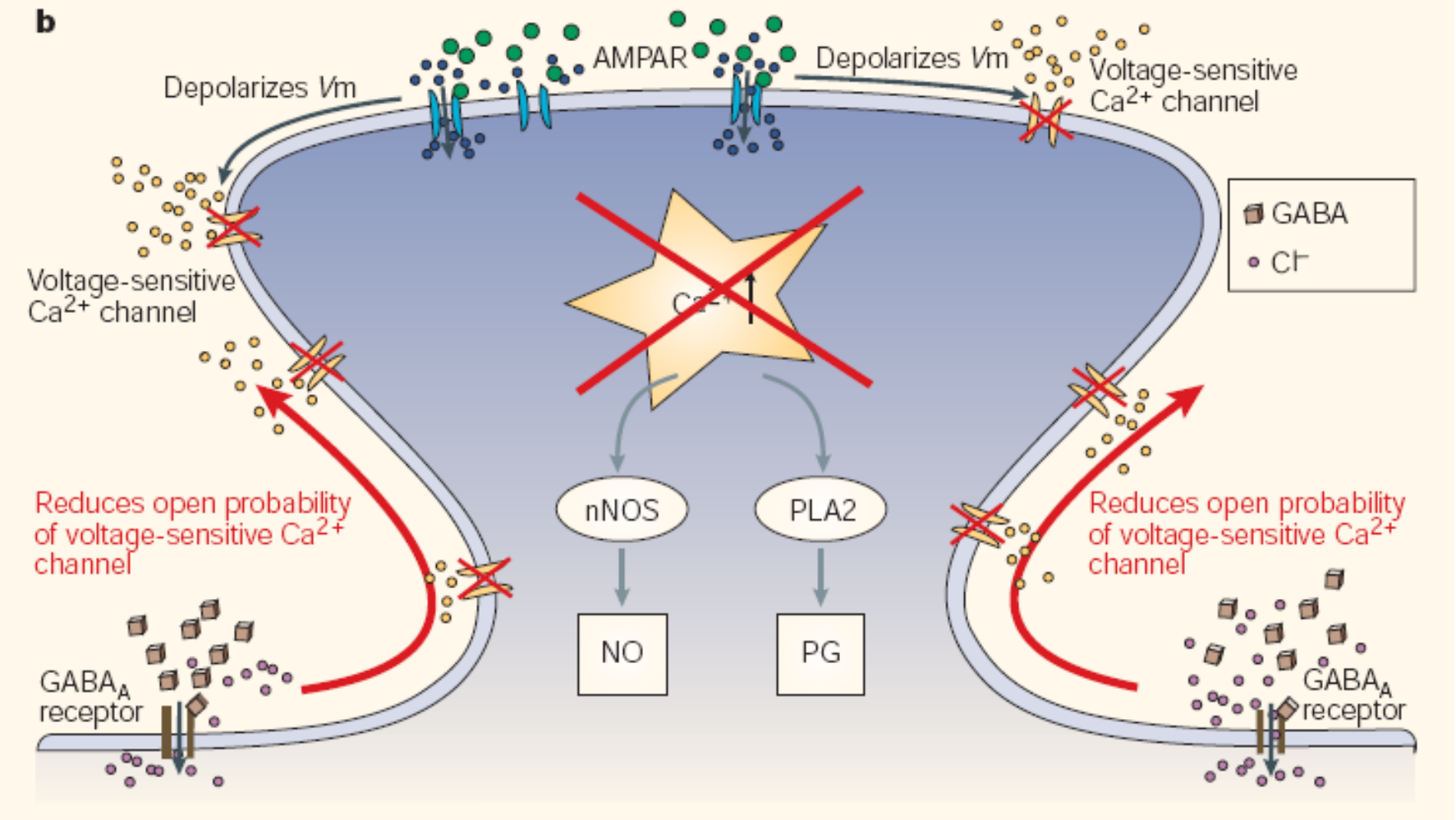






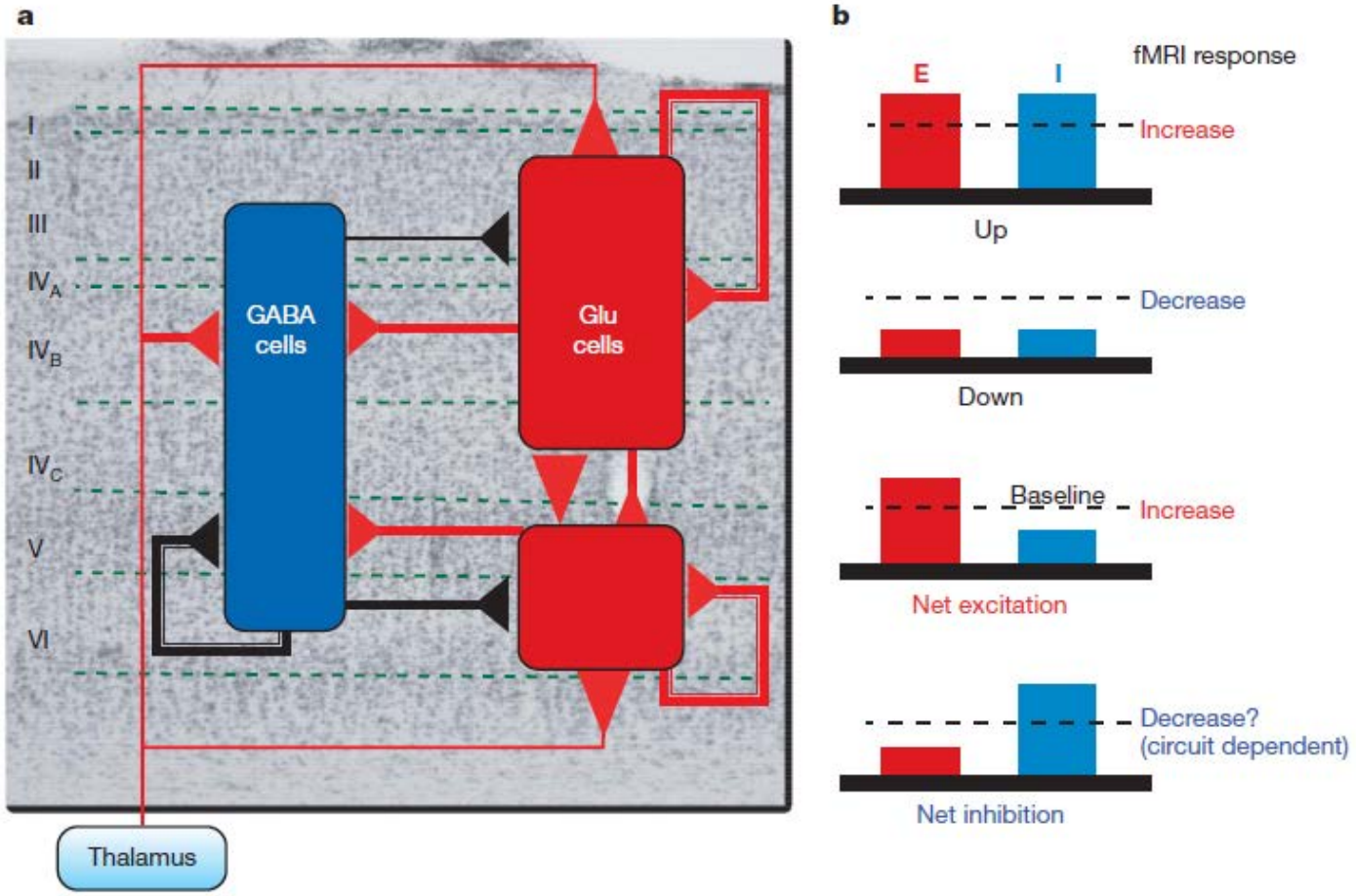
Shmuel et al., Nat Neurosci, 2006

Impact of inhibitory postsynaptic potentials (IPSPs) on blood flow



Source: Lauritzen, Nat Rev Neurosci, 2005

Excitatory-inhibitory networks and BOLD



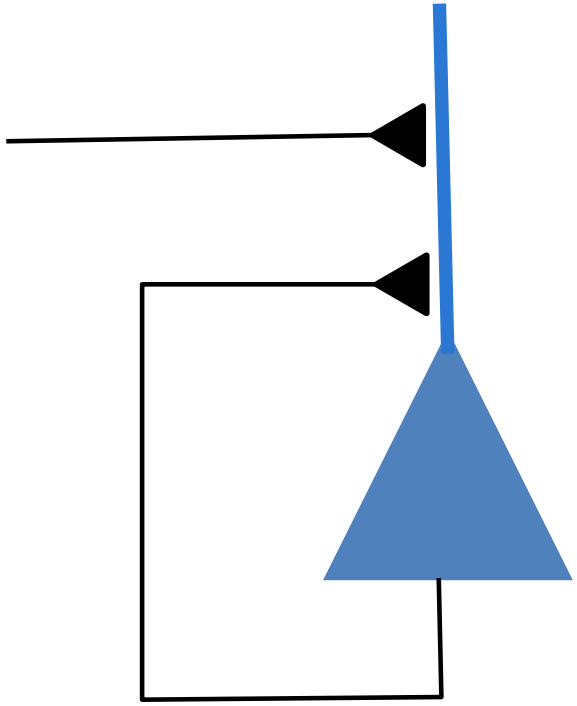
Source: Logothetis, Nature, 2008

BOLD Summary

- The BOLD signal seems to be strongly related to both LFPs and spiking activity.
  - The BOLD signal may primarily reflect the excitatory input to and recurrence of a neuronal population.
- Blood flow seems to be controlled in a forward fashion by postsynaptic processes at glutamatergic synapses leading to the release of vasodilators (e.g., NO and prostaglandines).
- Negative BOLD signals may result from IPSPs.
- We are far from completely understanding neurovascular coupling!

Summary - from a recent meeting

- Cellular neuroscientist say that cognitive neuroscientist oversimplify, but clearly the mechanisms are not fully understood.



Glutamatergic synapses are the main driver of vasodilation → blood flow changes → BOLD

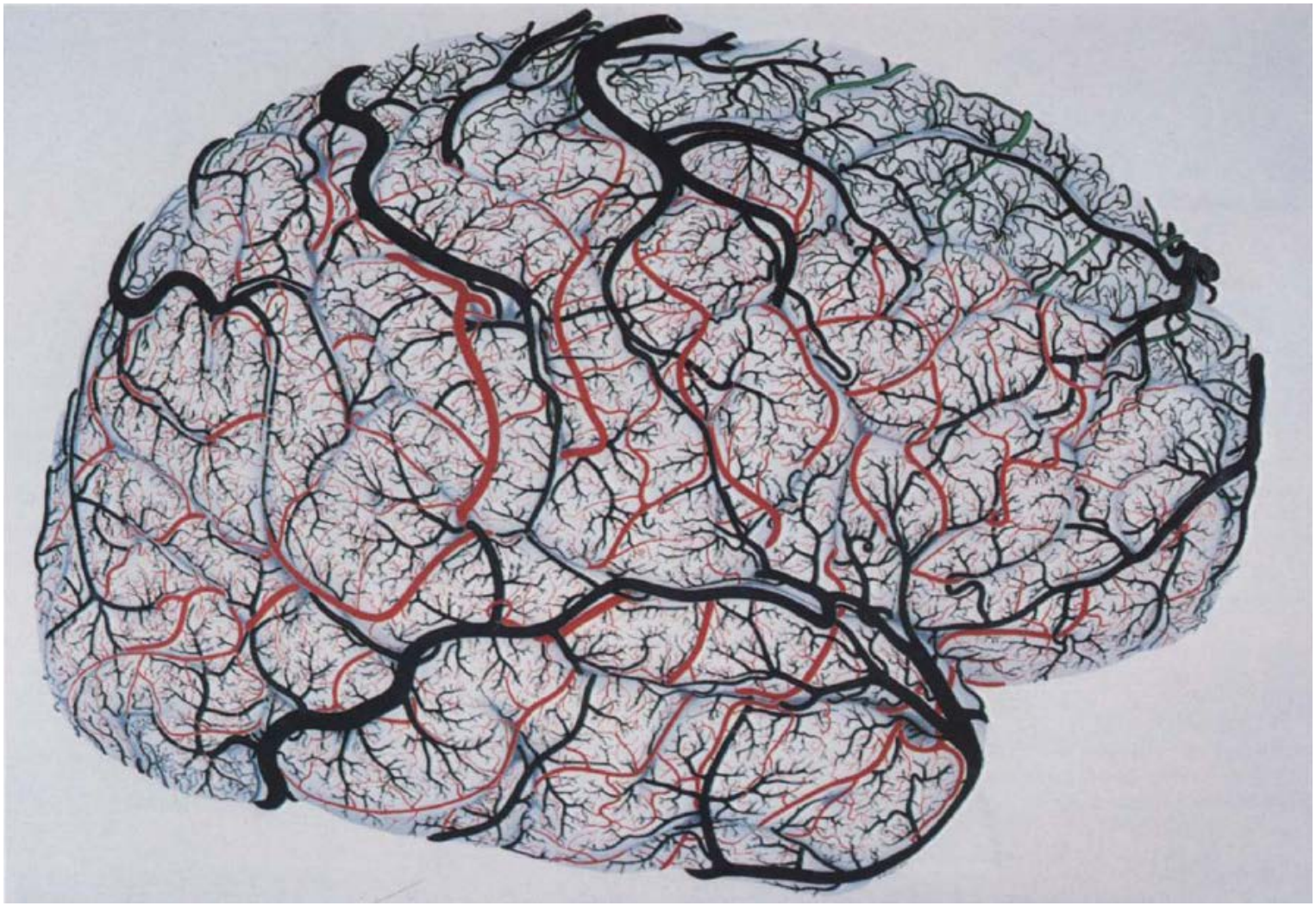
but, at least 80% of these synapses are recurrent, i.e. represent local firing.

Interpreting BOLD: a dialogue between cognitive and cellular neuroscience, Royal Society Meeting, 28.-29. Jan 2016

BOLD Summary

1. MRI measures the decay of magnetization of protons which depends on tissue properties.
2. fMRI measures changes in magnetic properties due to the ratio of oxy- vs. deoxy-hemoglobin in cerebral blood.
3. The BOLD signal is locally well correlated to the local field potential, which is itself highly correlated to spiking.

Thank you!



Source: Duvernoy et al, Brain Res. Bull., 1981

References

- McRobbie et al, From Picture to Proton, Cambridge Univesrity Press, 2007
- Huettel et al, Functional Magnetic Resonance Imaging, Sinauer, 2004
- Logothetis and Wandell, Ann. Rev. Neurosci., 2004 (BOLD in general)
- Logothetis et al, Nature, 2001 (LFP vs. BOLD)
- Logothetis, Nature, 2008 (What can we do with BOLD? What not?)
- Lauritzen, Nat. Rev. Neurosci., 2005 (Calcium, Bold in Cerebellum)
- Iadecola and Needergard, Nat. Neurosci., 2007 (Glia cells)
- http://psychology.uwo.ca/fmri4newbies/Tutorials.html