Physiological Basis of the BOLD Signal

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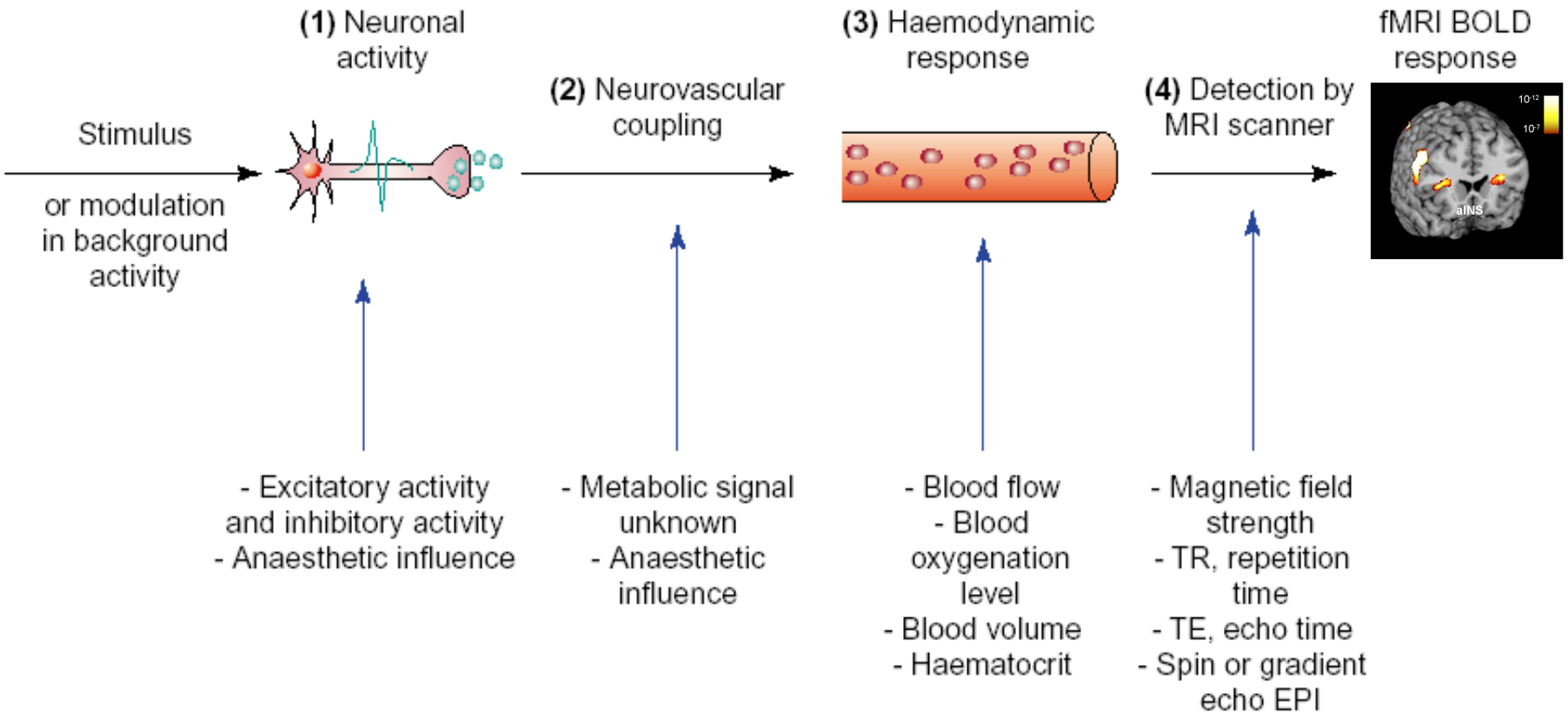
From Stimulus to Bold

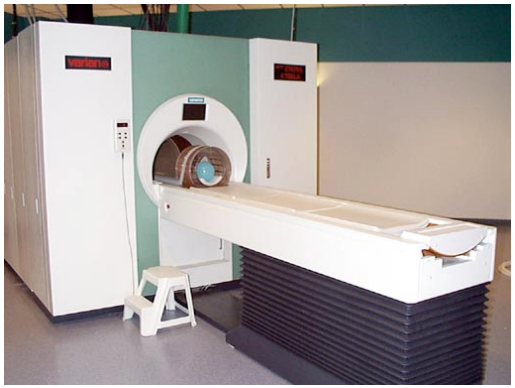


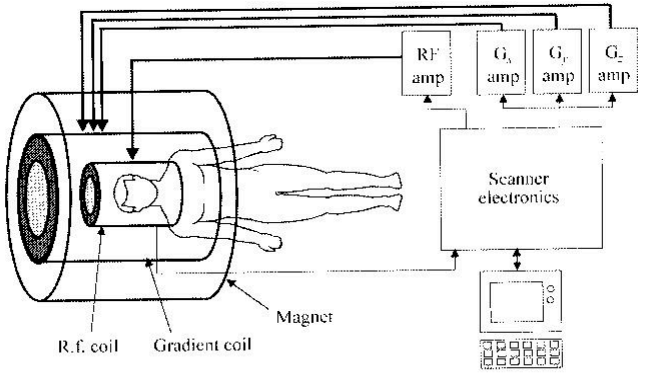
Source: Arthurs & Boniface, 2002

Overview

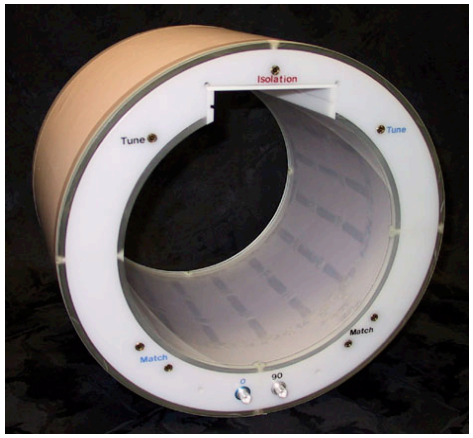
- Physics of BOLD signal
  - Magnetic fields and pulses
  - Magnetic properties of oxygen in blood
- Physiology of BOLD signal
  - Correlations with other measures or neural activity
  - How neurons cause blood flow increases

MRI Physics

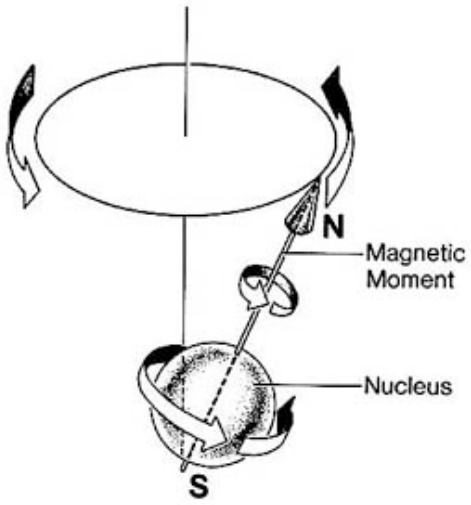




- Step 1: Place an object/subject in a big magnet
- Step 2: Apply radio waves
- Step 3: Measure emitted radio waves



Step 1: Place subject in a big magnet



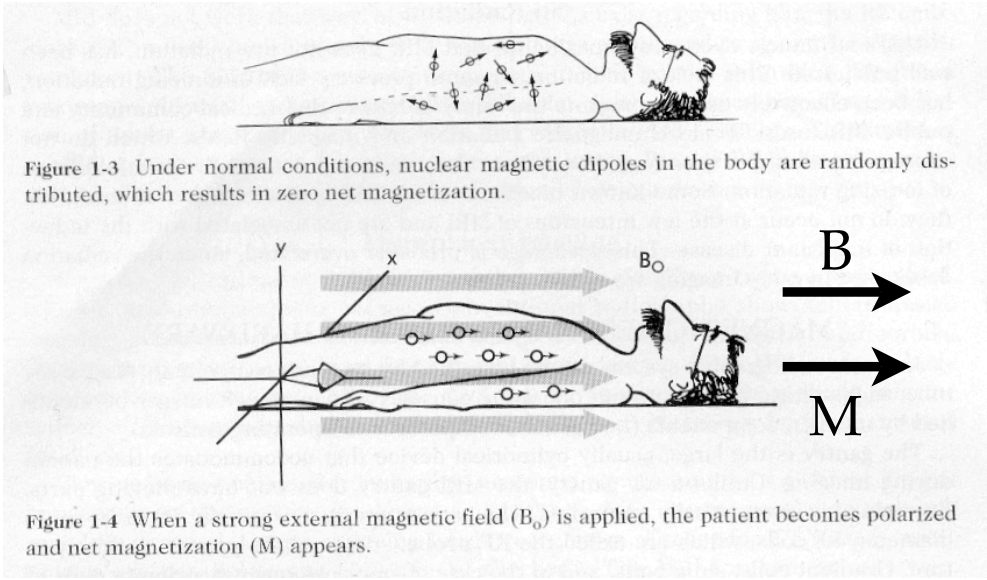


Figure 1-3 Under normal conditions, nuclear magnetic dipoles in the body are randomly distributed, which results in zero net magnetization.

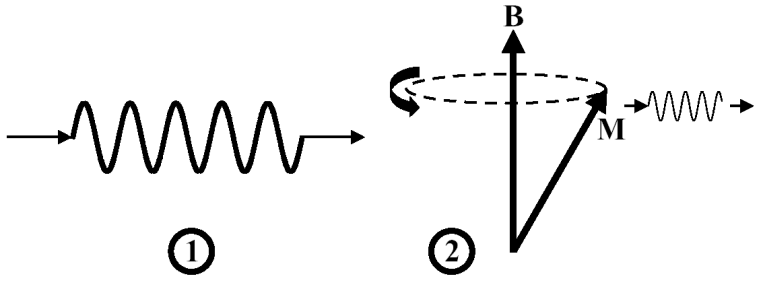
Figure 1-4 When a strong external magnetic field (B_0) is applied, the patient becomes polarized and net magnetization (M) appears.

Protons have "spins" (like gyroscopes). They have an orientation and a frequency.

When you put any material in an MRI scanner, the protons align with the direction of the magnetic field.

Images: www.fmri4newbies.com

Step 2: Apply radio waves



Send an *external radio signal*, *exactly* with the „Larmor frequency"

- Magnetization is tilted by signal
- Precesses around the magnetic field
- Emits a secondary radio signal

When you apply radio waves (RF pulse) at the appropriate frequency (Larmor frequency), you can change the orientation of the spins as the protons absorb energy.

Images: www.fmri4newbies.com

Step 3a: Turn off radio waves

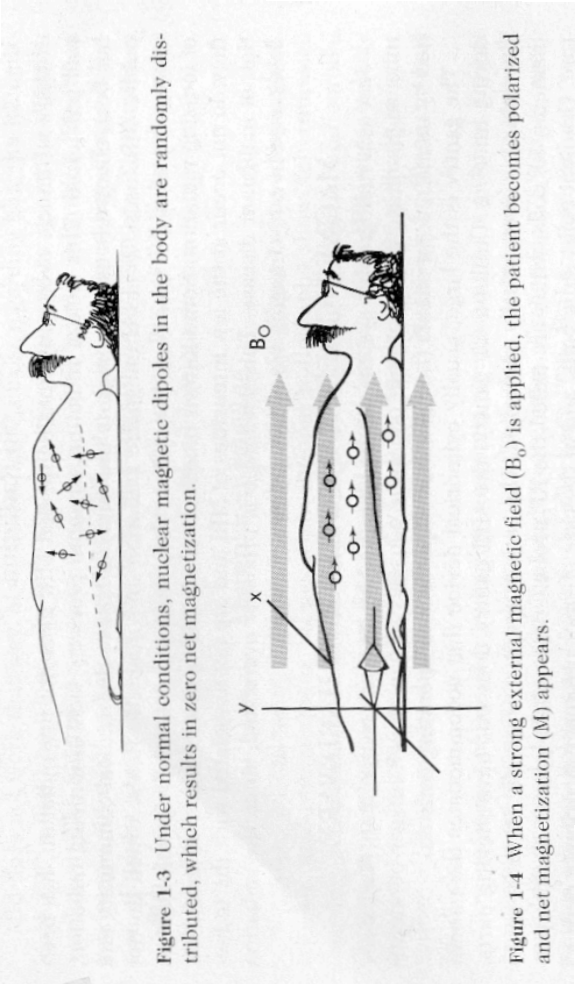
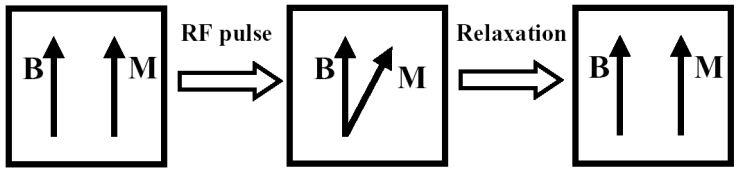
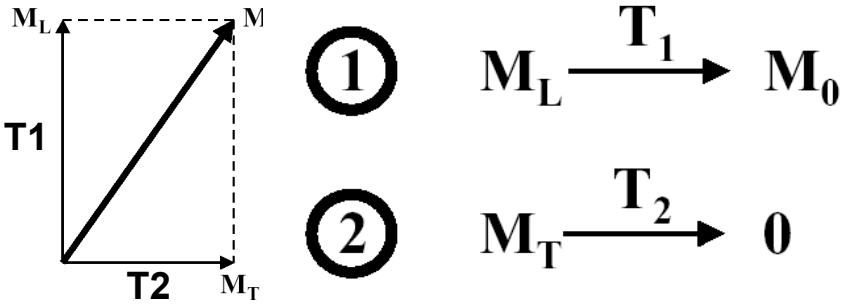


Figure 1-3 Under normal conditions, nuclear magnetic dipoles in the body are randomly distributed, which results in zero net magnetization.

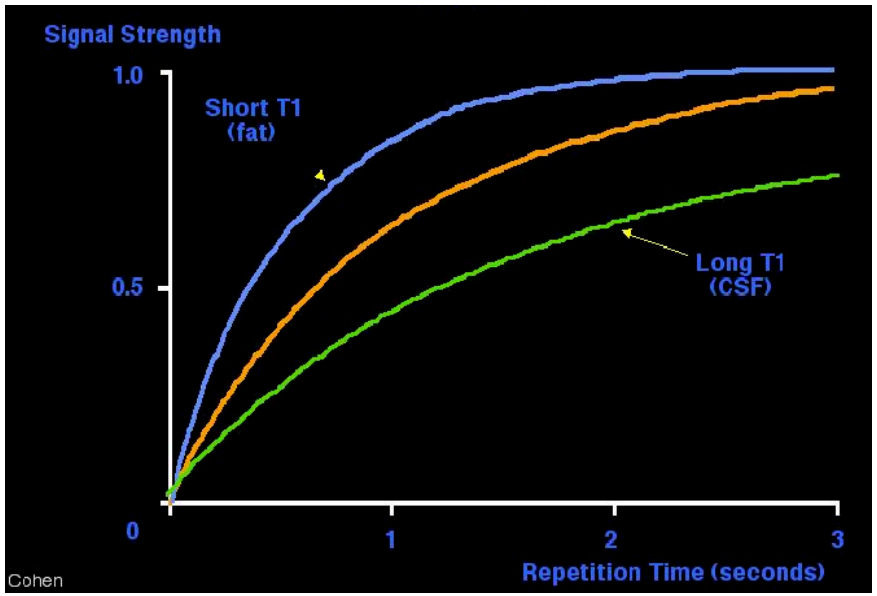
Figure 1-4 When a strong external magnetic field (B_o) is applied, the patient becomes polarized and net magnetization (M) appears.

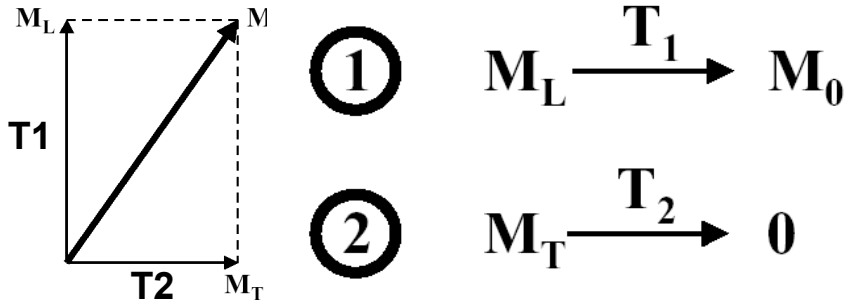




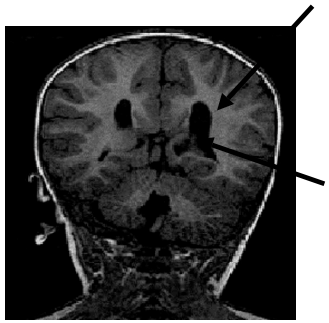
After you turn off the RF pulse, as the protons return to their original orientations, they emit energy in the form of radio waves.

Step 3b: Measure emitted radio waves (T1)





T1 = time constant of how quickly the protons realign with the magnetic field



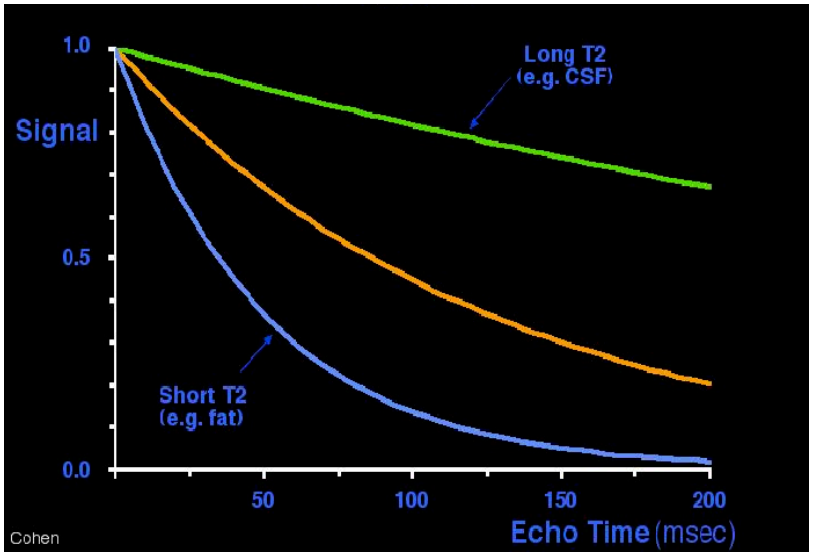
fat has high signal bright

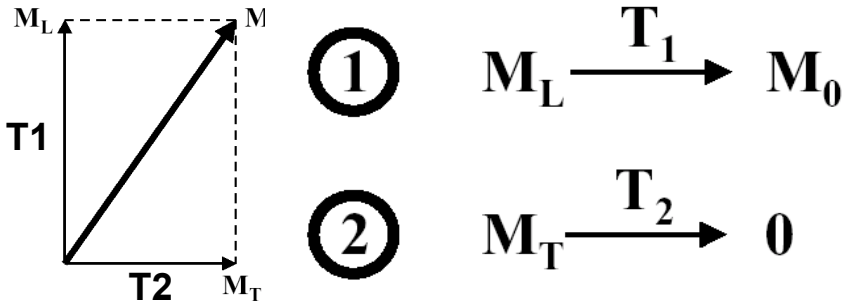
CSF has low signal dark

T1-WEIGHTED ANATOMICAL IMAGE

Images: fmri4newbies.com

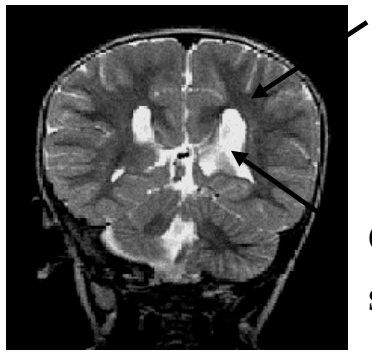
Step 3b: Measure emitted radio waves (T2 or T2*)





T2 = time constant of how quickly the protons emit energy when recovering to equilibrium

Images:
fmri4newbies.com



fat has low signal -> dark

CSF has high signal -> bright

T2-WEIGHTED ANATOMICAL IMAGE

T2* WEIGHTED IMAGES

- Two factors contribute to the decay of transverse magnetization:
  1. molecular interactions
  2. local inhomogeneities of the magnetic field (dephasing of spins)
- The combined time constant is called T2* (<T2).
- fMRI uses acquisition techniques (e.g. EPI) that are sensitive to changes in T2*.

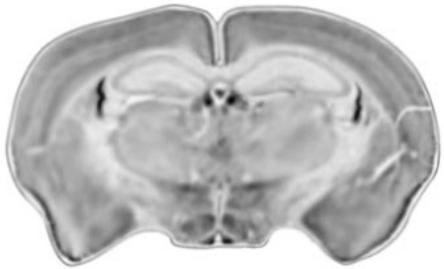
The general principle of MRI

- 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

The Bold Contrast

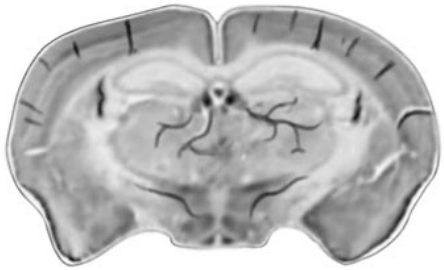
BOLD (Blood Oxygenation Level Dependent) contrast = measures inhomogeneities in the magnetic field due to changes in the level of O_2 in the blood

Oxygenated blood
is diamagnetic
-> no signal loss



Low ratio deoxy / oxygenated blood -> slow decrease in MRI signal

Deoxygenated blood
is paramagnetic
-> signal loss



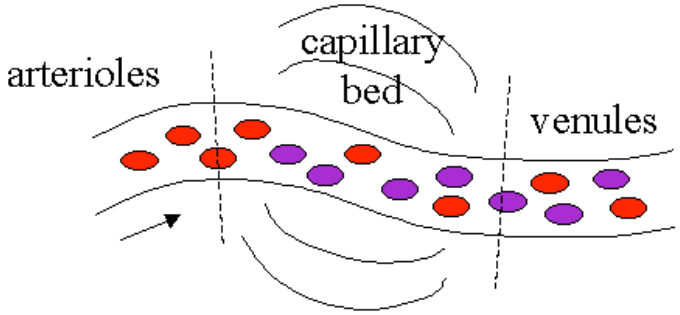
High ratio deoxy / oxygenated blood -> fast decrease in MRI signal

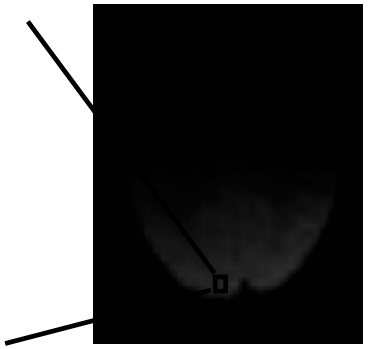
Huettel, Song, McCarthy, 2004

= HbO_2
= Hbr

The BOLD contrast

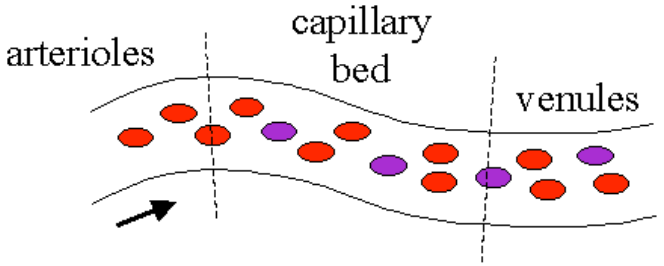
REST

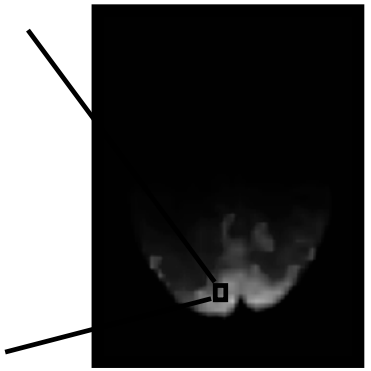




↑ neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal

ACTIVITY





Source: Jorge Jovicich, fMRIB Brief Introduction to fMRI

Summary MRI Physics

- Magnetic dipole moments of hydrogen nuclei align to magnetic field in scanner
- RF pulse causes them to spin, in phase
- Once pulse has stopped dipole moments realign to the magnetic field, dephasing as they do so
- Dephasing takes various amounts of time, depending in part on inhomogeneities in magnetic field
- Inhomogeneities are caused by variable ratio of deoxygenated : oxygenated blood
- Assumption: activity in brain area lowers this ratio and thereby decreases speed of decay of MRI signal

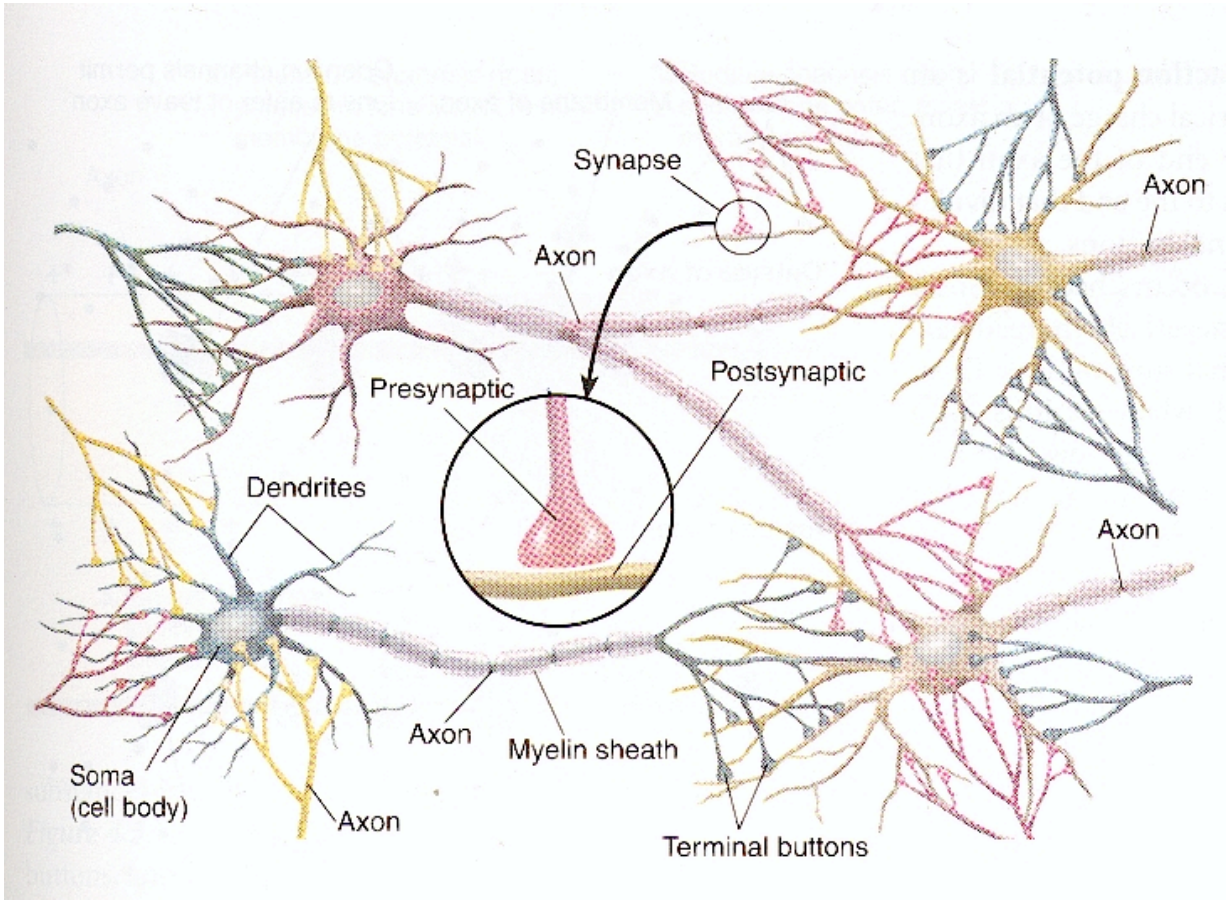
Overview

- Physics of BOLD signal
  - Magnetic fields and pulses
  - Magnetic properties of oxygen in blood
- Physiology of BOLD signal
  - Correlations with other measures or neural activity
  - How neurons cause blood flow increases

Three important questions

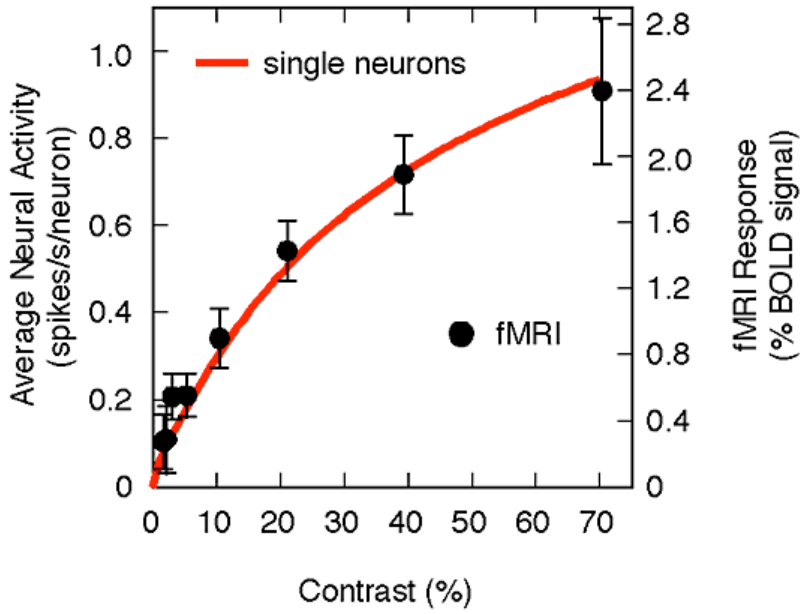
- Is the BOLD signal more strongly related to neuronal action potentials or to local field potentials (LFP)?
- How does the BOLD signal reflect the energy demands of the brain?
- What does a negative BOLD signal mean?

Neurophysiological basis of the BOLD signal: soma or synapse?



BOLD & ACTION POTENTIALS

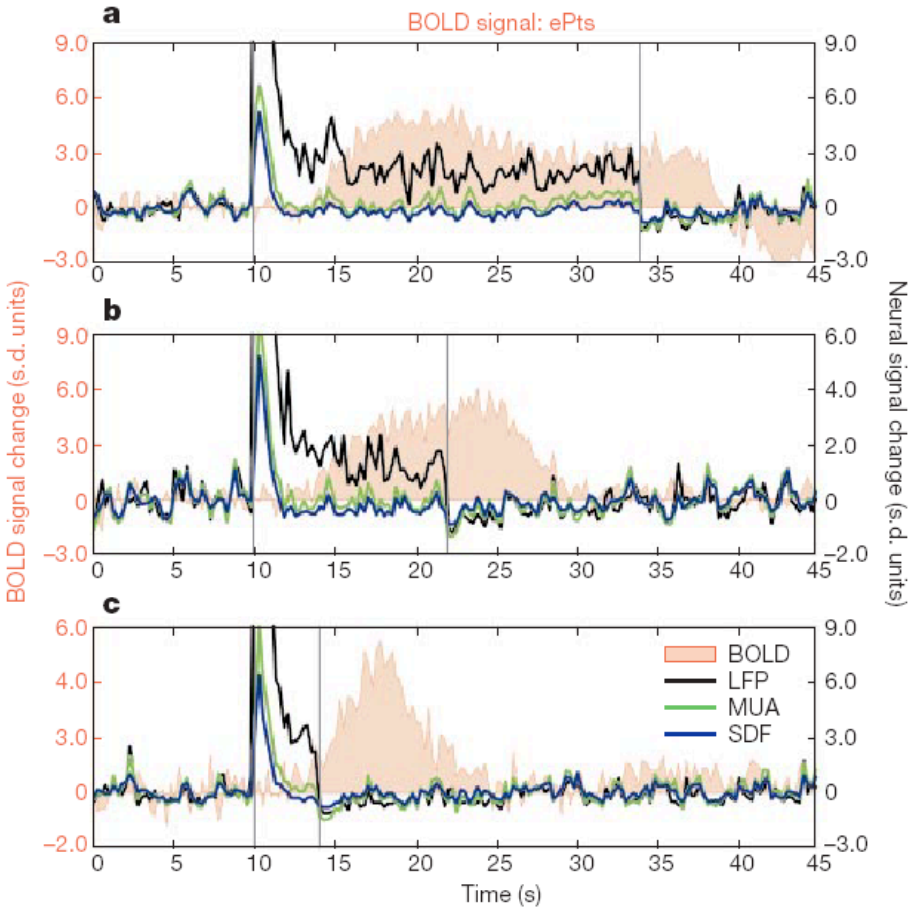
Red curve: "average firing rate in monkey V1, as a function of contrast, estimated from microelectrode recordings (333 neurons)."



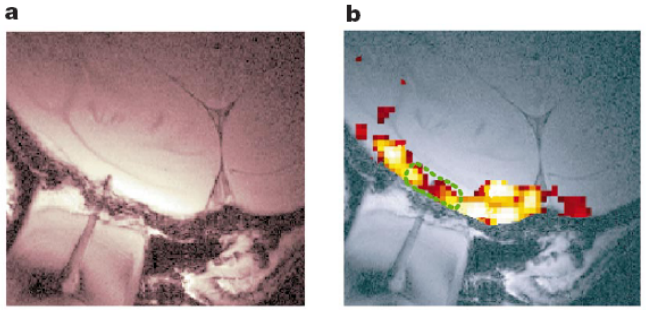
In early experiments comparing human BOLD signals and monkey electrophysiological data, BOLD signals were found to be correlated with action potentials.

Heeger et al 2000, *Nat. Neurosci.*
Rees et al. 2000, *Nat. Neurosci.*

Action potentials vs. postsynaptic activity



Logothetis et al., 2001, *Nature*



Local Field Potentials (LFP)

- reflect summation of post-synaptic potentials

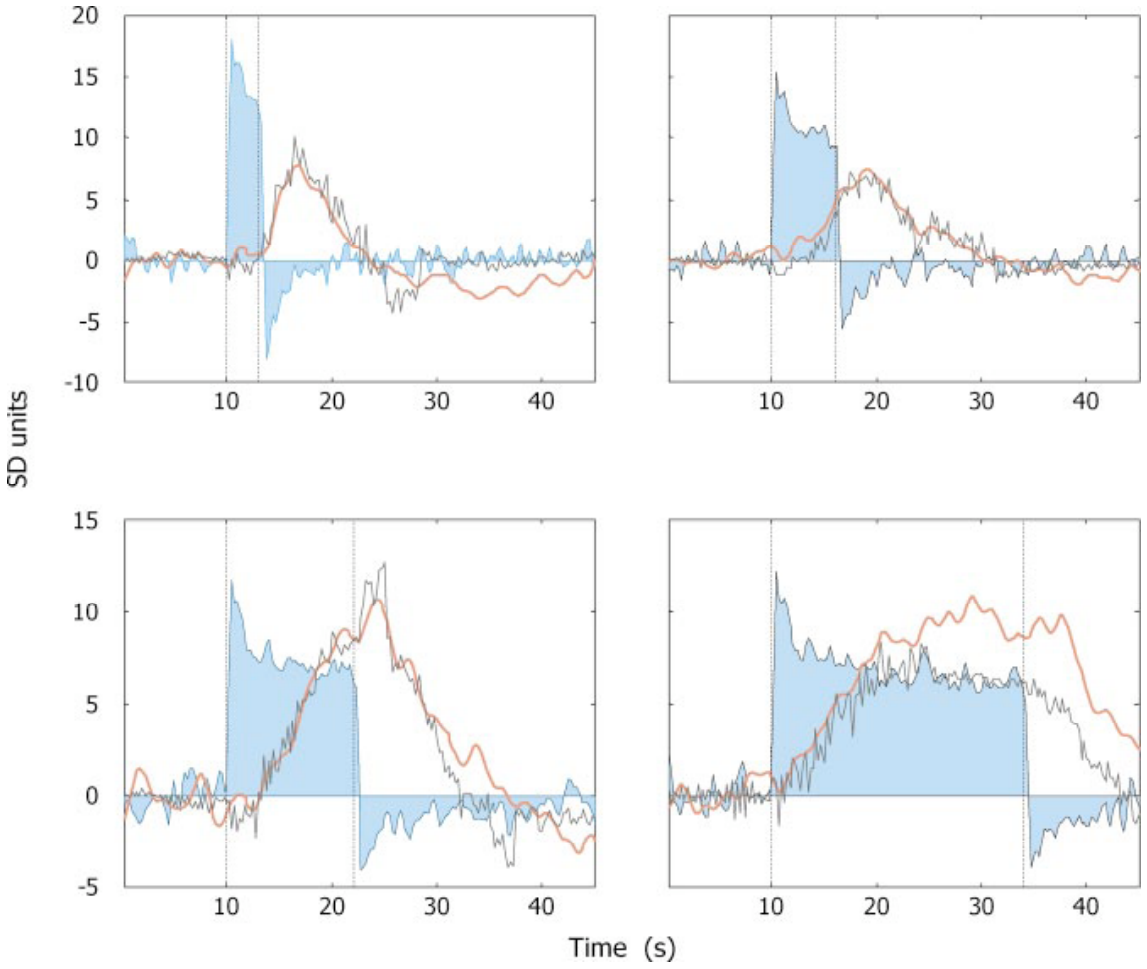
Multi-Unit Activity (MUA)

- reflects action potentials/spiking

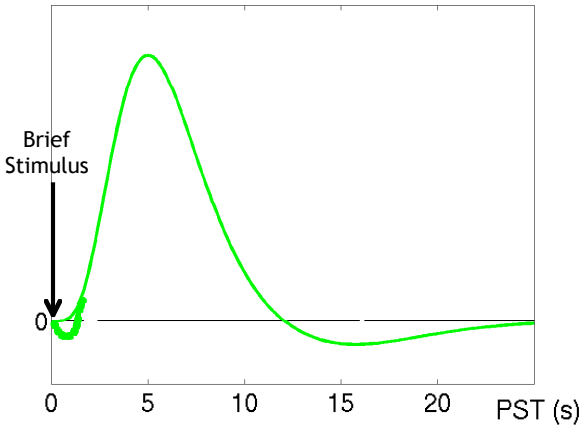
Logothetis et al. (2001)

- combined BOLD fMRI and electrophysiological recordings
- found that BOLD activity is more closely related to LFPs than MUA

BOLD & LFPs

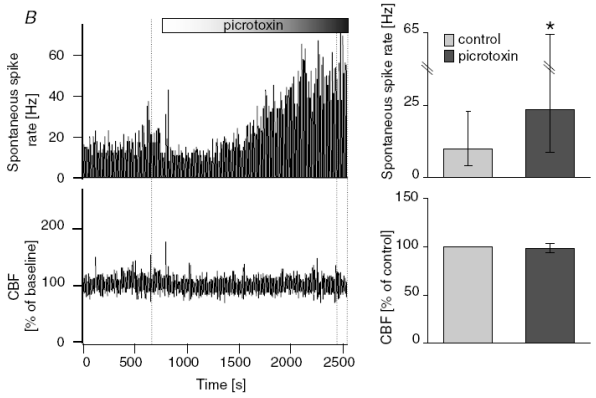


blue: LFP
red: BOLD
grey: predicted BOLD



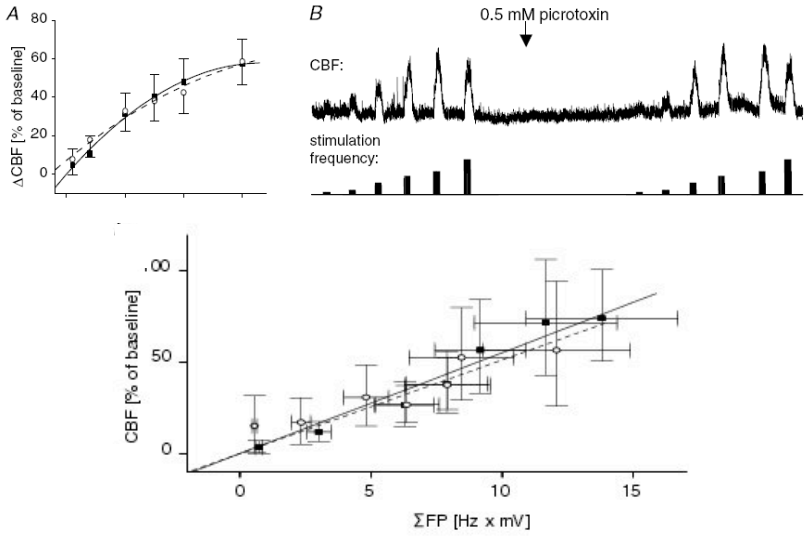
Logothetis & Wandell 2004, *Ann. Rev. Physiol.*

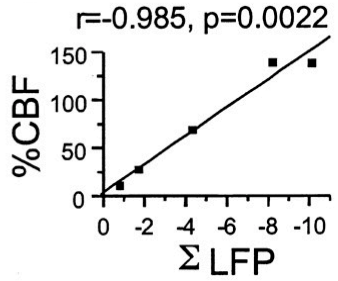
Dissociation between action potentials and rCBF



Thomsen et al. 2004, *J. Physiol.*

- $GABA_A$ antagonist picrotoxine increased spiking activity without increase in rCBF...
- ... and without disturbing neurovascular coupling per se

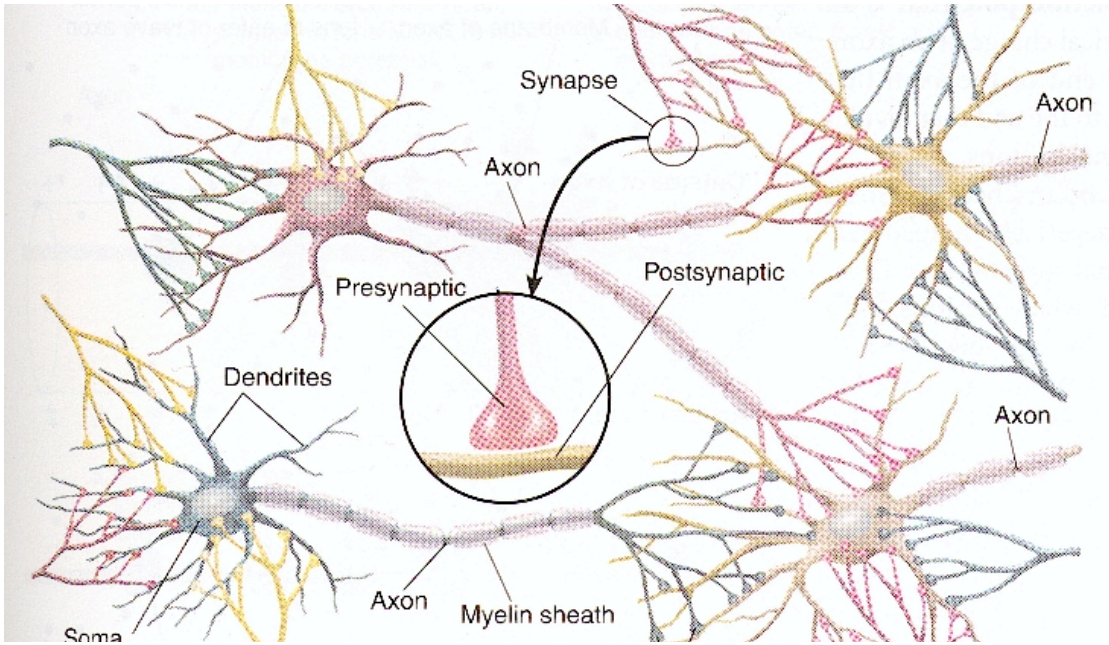




Lauritzen et al. 2003

⇒ rCBF-increase can be independent from spiking activity, but seems to be always correlated to LFPs

Current conclusion: BOLD signal seems to be more strongly correlated to postsynaptic activity



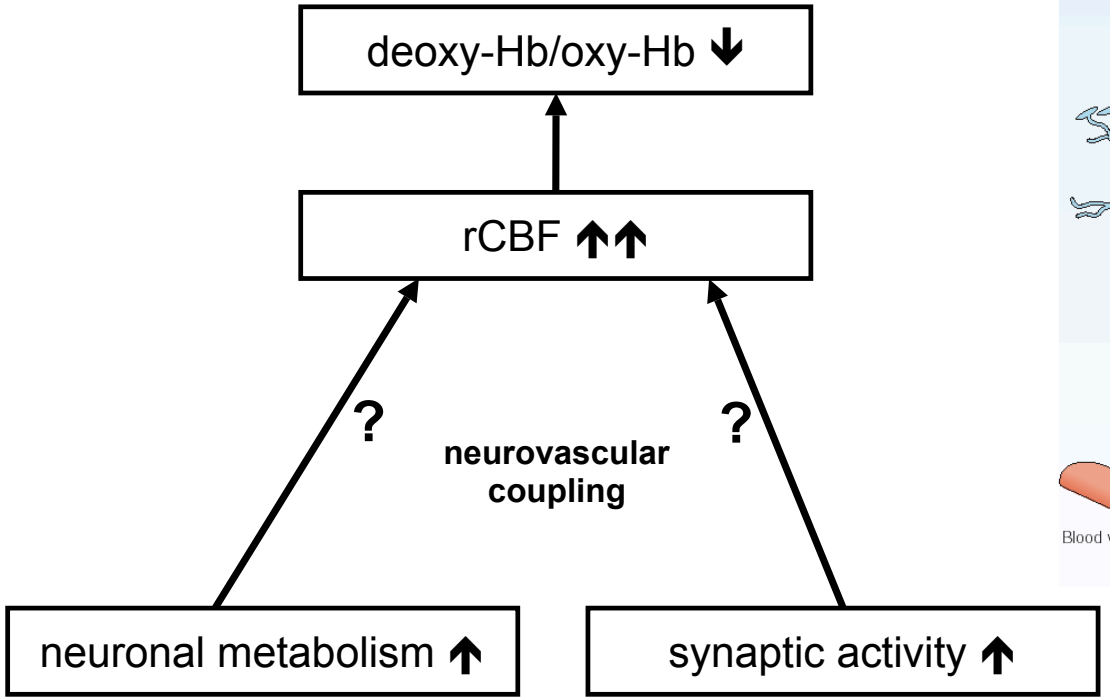
BOLD seems to reflect the input to a neuronal population as well as its intrinsic processing.

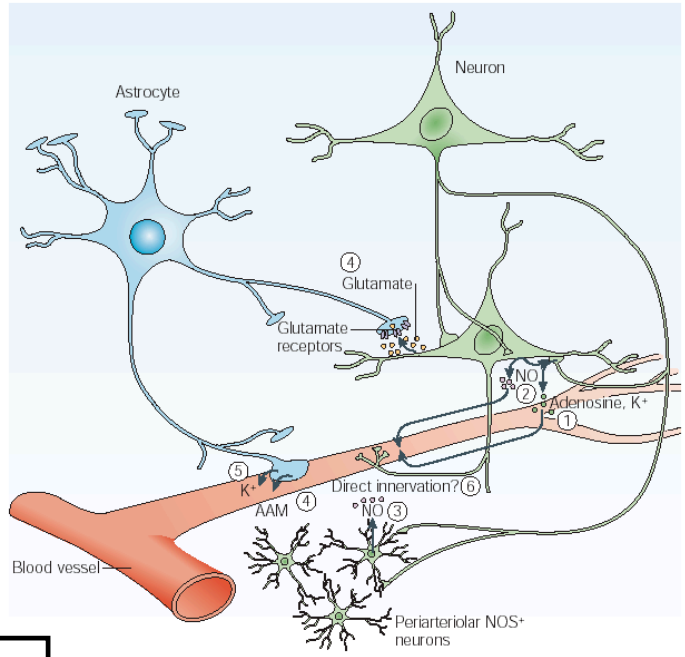
Lauritzen 2005, *Nat. Neurosci. Rev.*

Three important questions

- Is the BOLD signal more strongly related to neuronal action potentials or to local field potentials (LFP)?
- How does the BOLD signal reflect the energy demands of the brain?
- What does a negative BOLD signal mean?

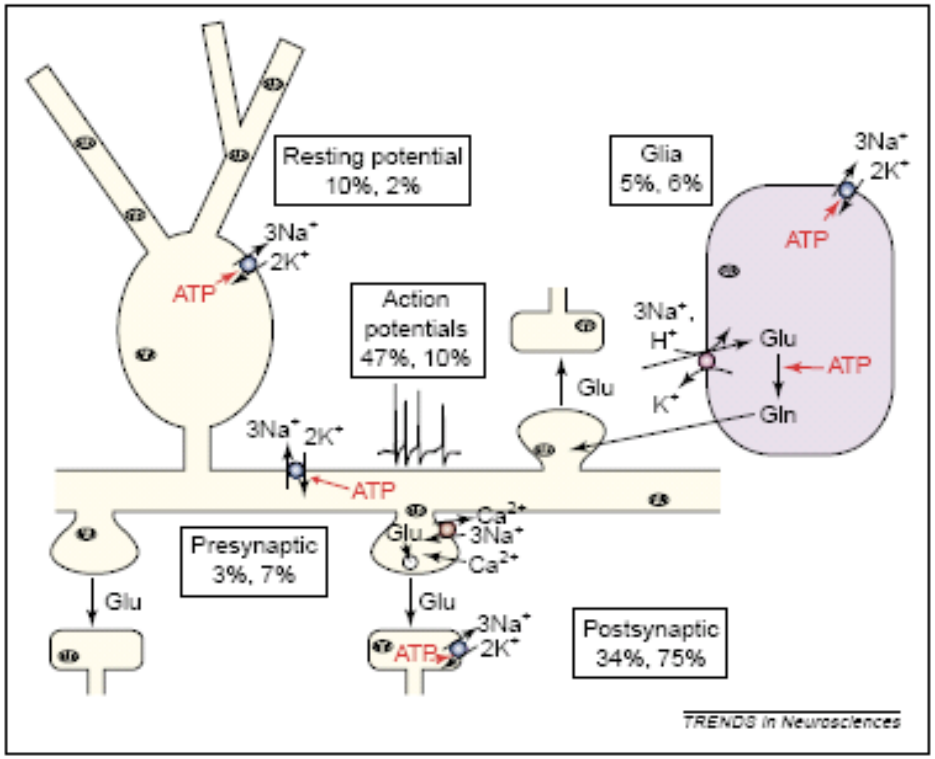
Is the BOLD signal driven by energy demands or synaptic processes?

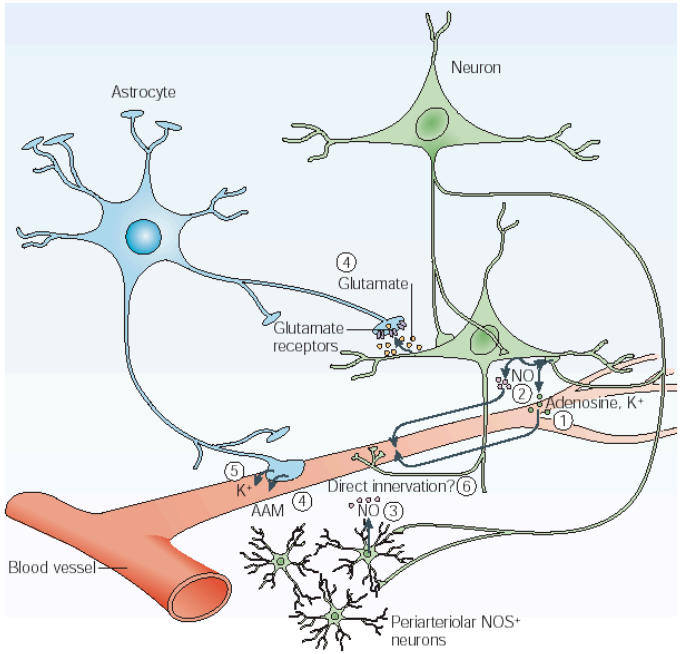




D'Esposito et al. 2003

Estimated Energy Consumption

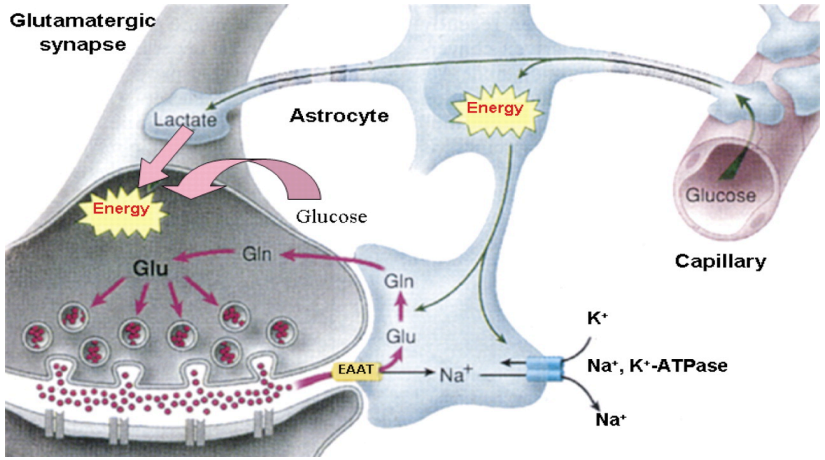




Energetic consequences of postsynaptic activity

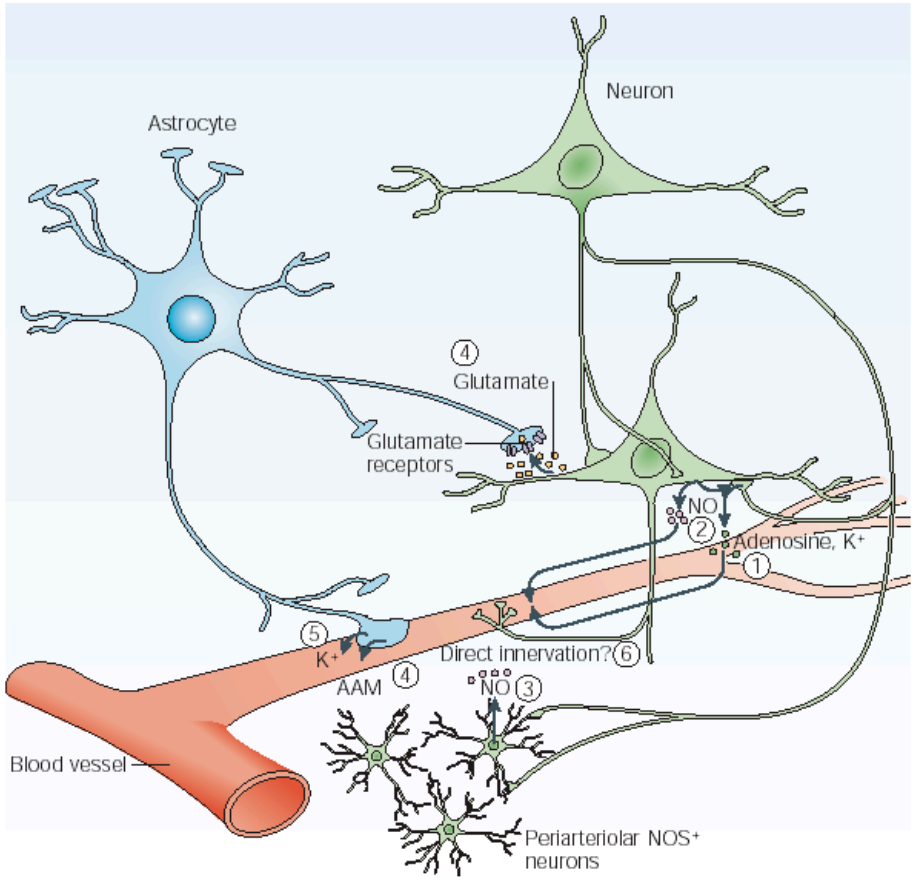
- action potentials at pre-synaptic cell
- release glutamate
- open ion-channels on post-synaptic cell
- re-uptake of glutamate by astrocytes triggers glucose metabolism
- pump ions out of cell again to restore ionic gradients
- uses energy (50-75% for glu re-uptake) and oxygen

➡ How does the energy and oxygen need affect the regional cerebral blood flow?

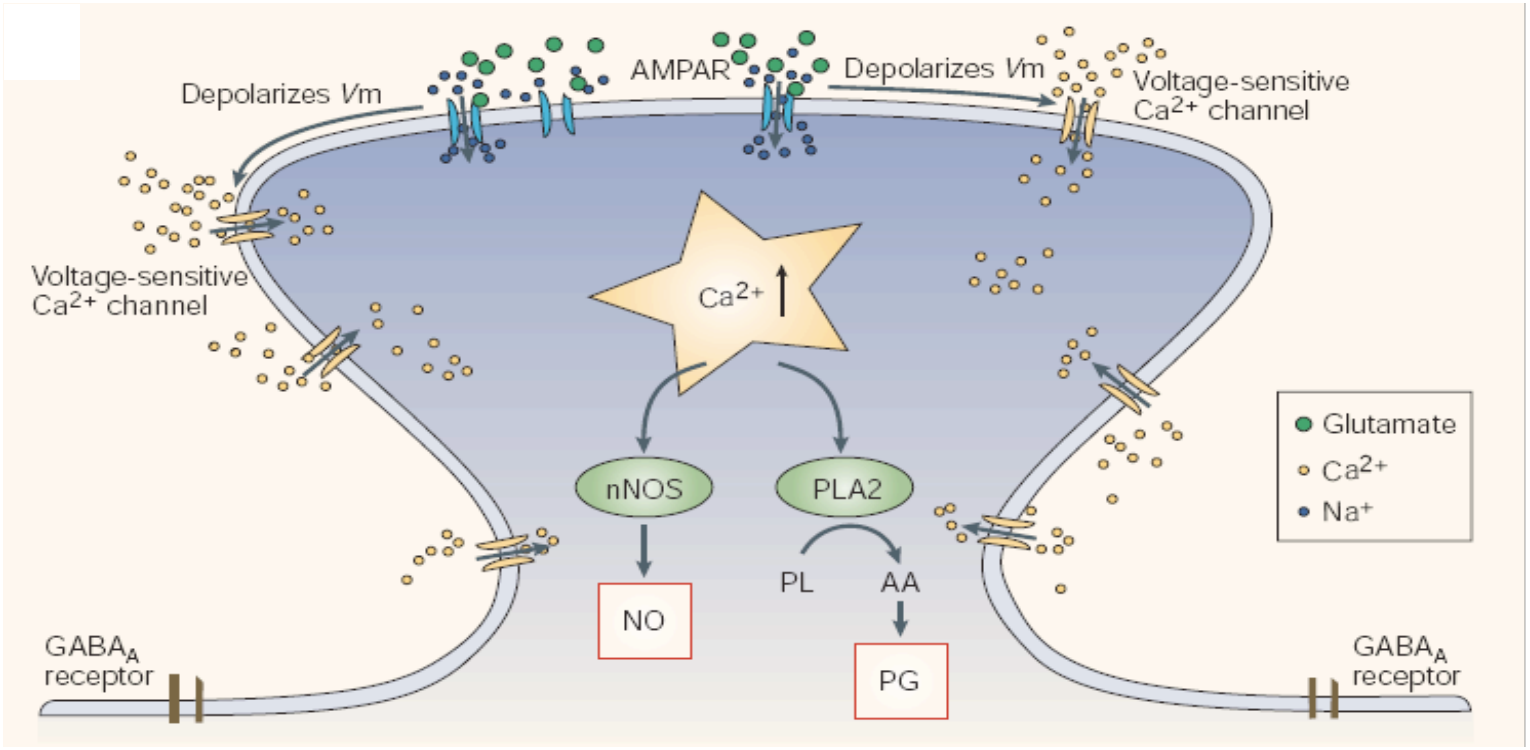


Attwell & Iadecola 2002, *TINS*.

Blood flow might be directly driven by excitatory postsynaptic processes

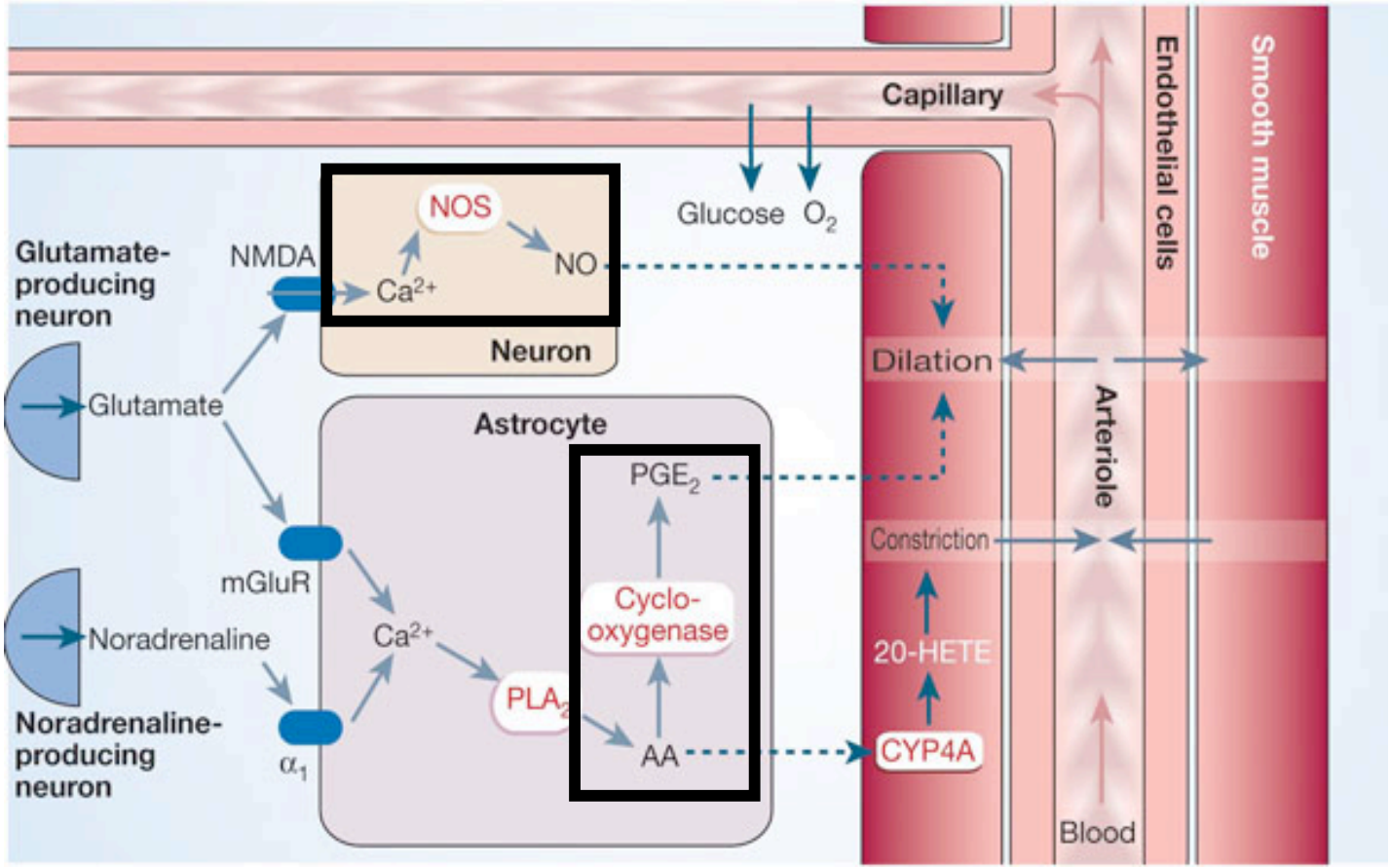


Glutamatergic synapses: A feedforward system for eliciting the BOLD signal?



Lauritzen 2005, *Nat. Neurosci. Rev.*

Forward control of blood flow



Peppiatt & Attwell, *Nature 2004;*
Zonta et al *Nature Neurosci 2003;*
Mulligan & MacVicar *Nature 2004*

Gordon et al *Nature 2008*

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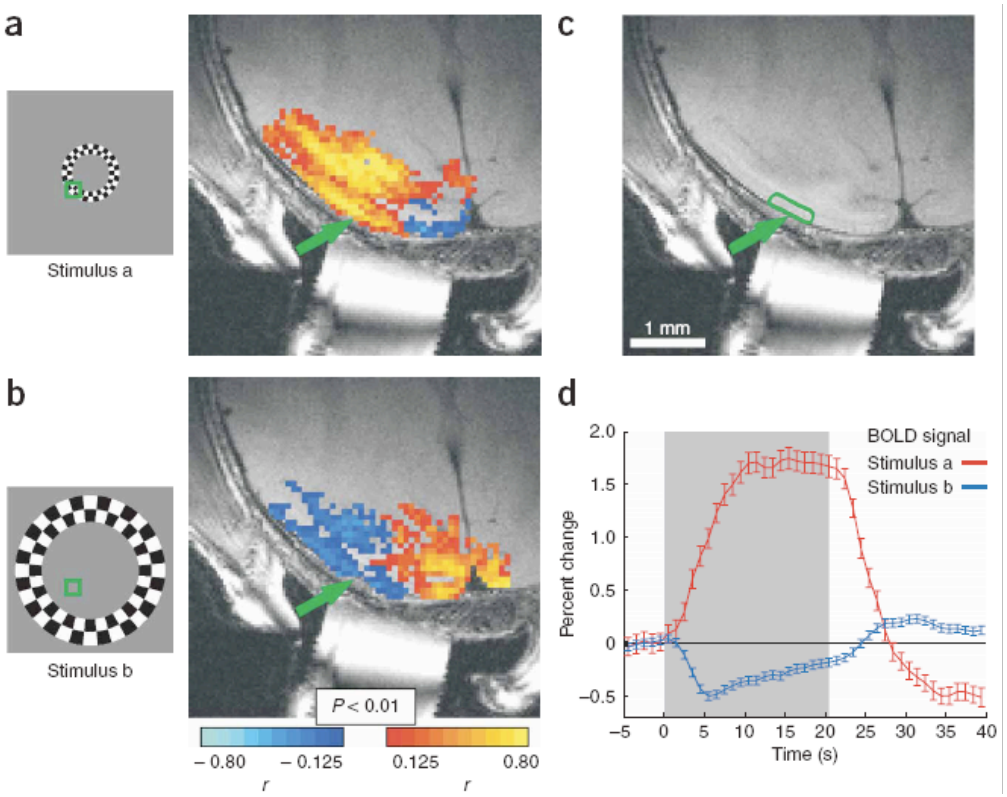
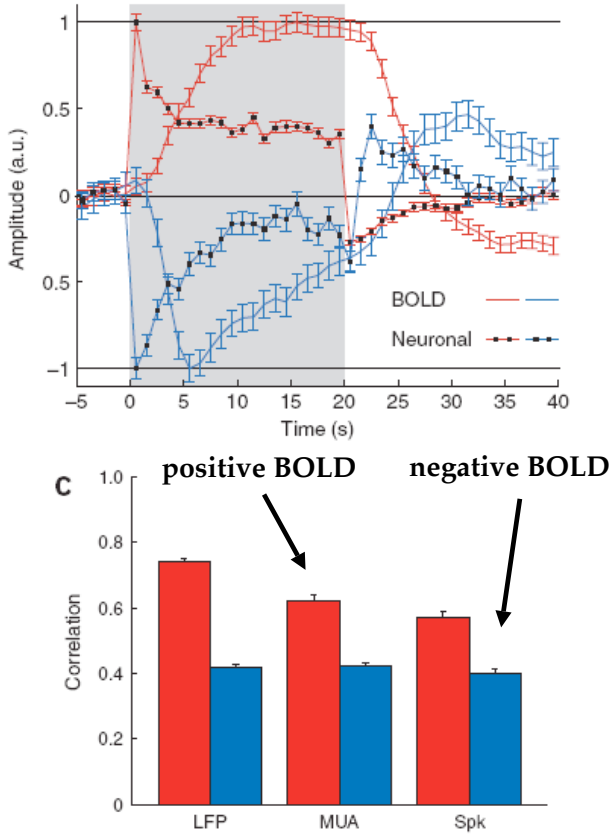
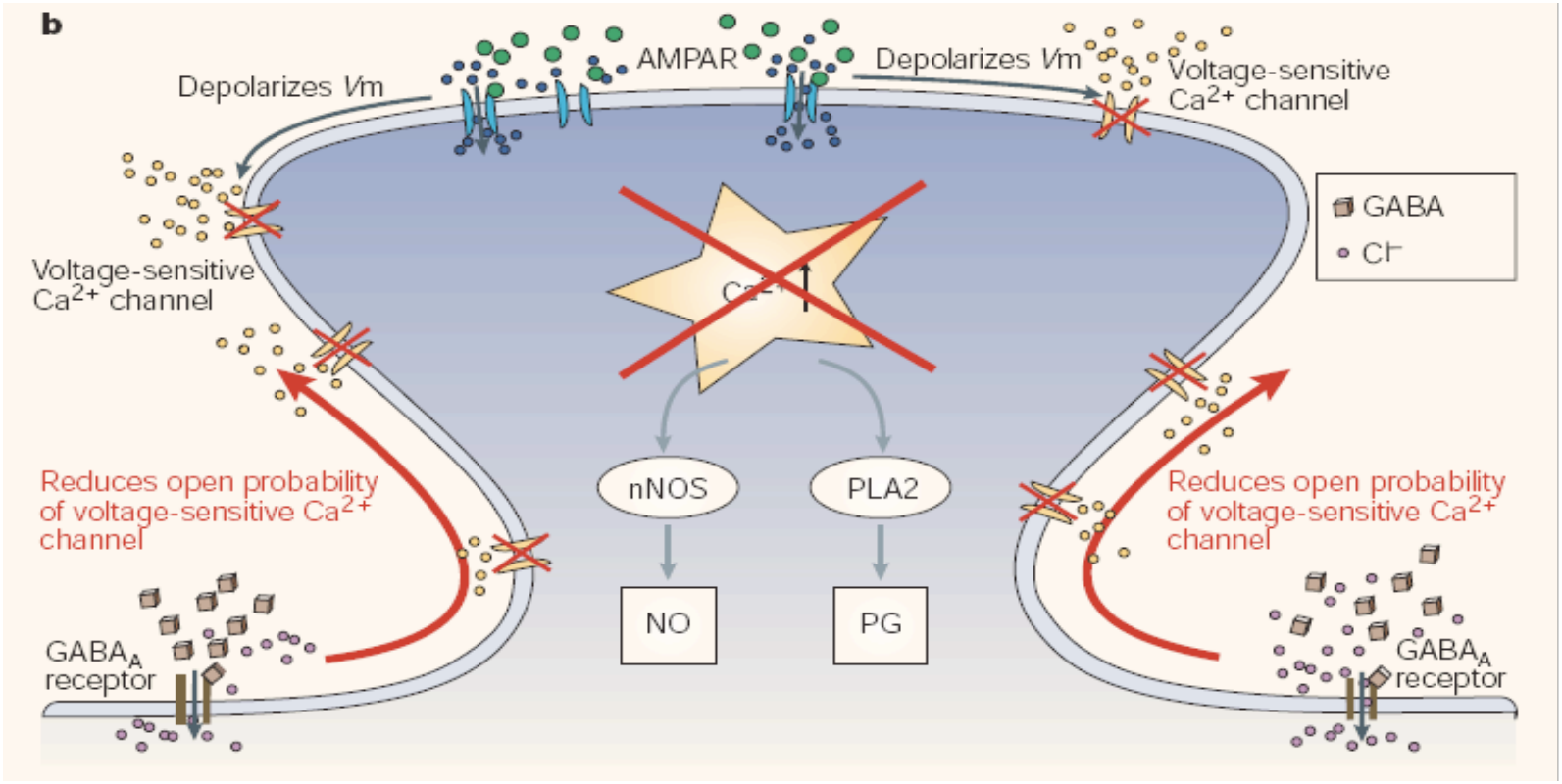
Negative BOLD is correlated with decreases in LFPs





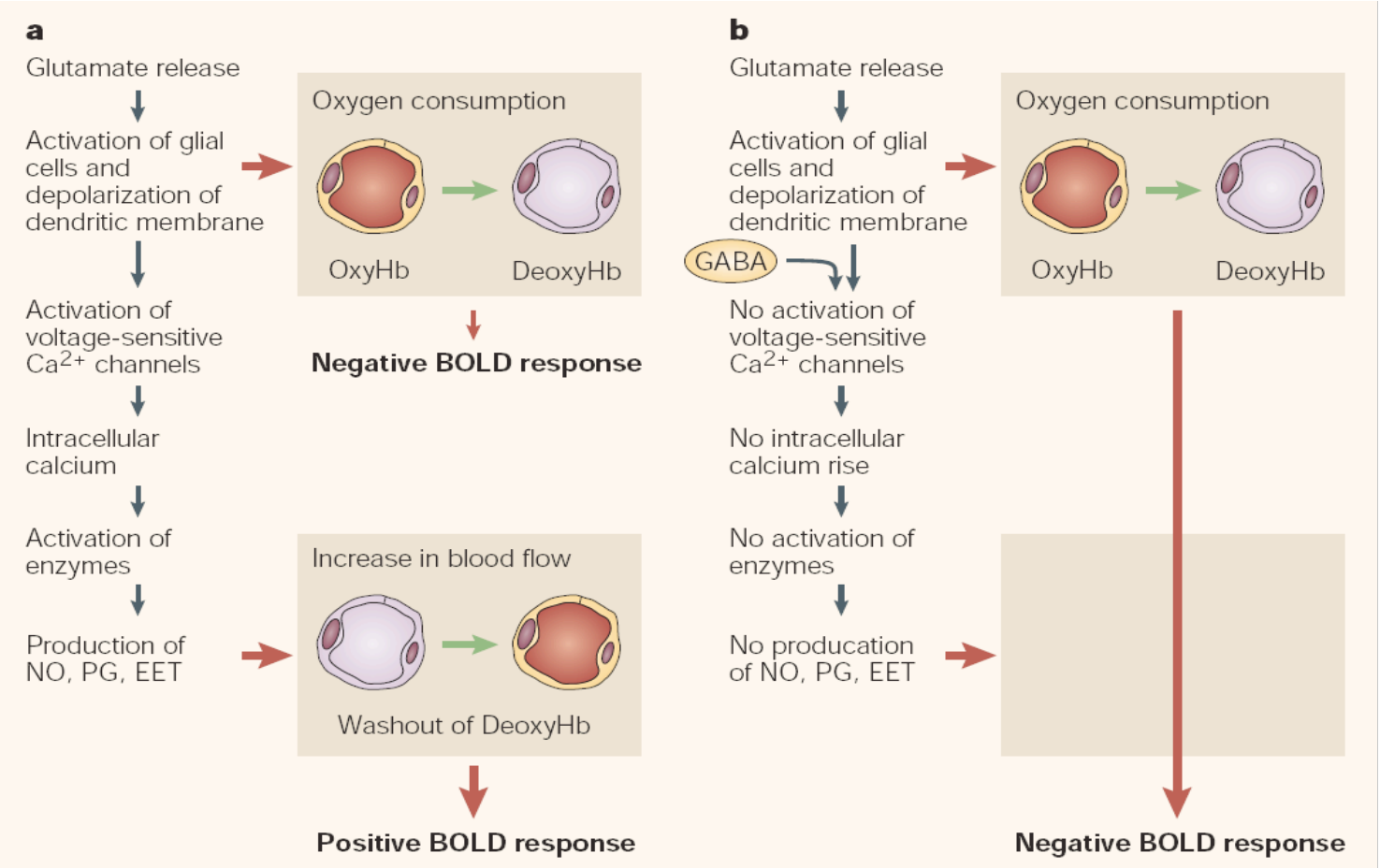
Shmuel et al. 2006, *Nat. Neurosci.*

Impact of inhibitory postsynaptic potentials (IPSPs) on blood flow



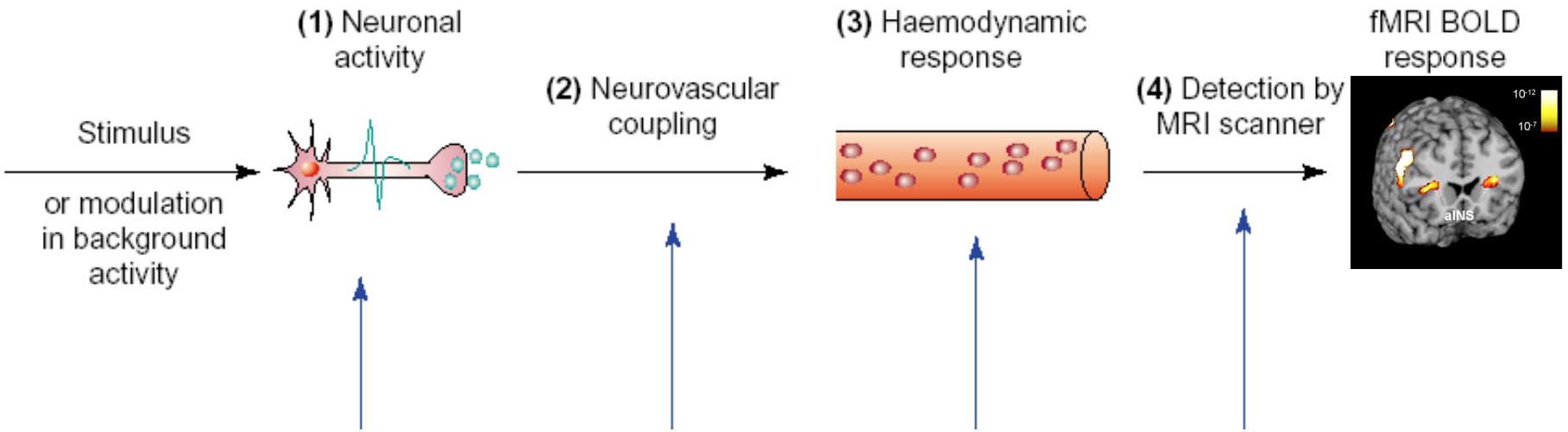
Lauritzen 2005, *Nat. Neurosci. Rev.*

Negative BOLD signals due to IPSPs?



Lauritzen 2005, *Nat. Neurosci. Rev.*

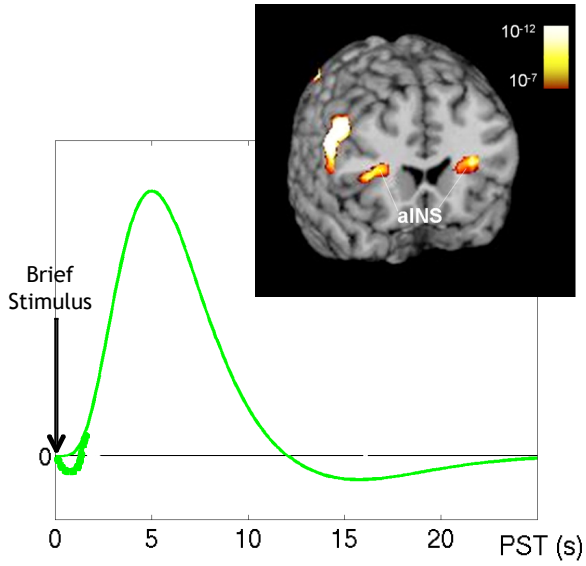
From Stimulus to Bold

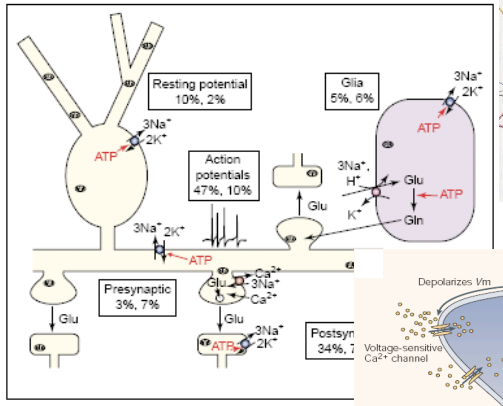


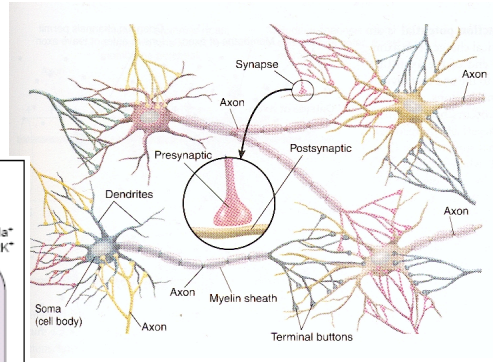
action potentials at pre-synaptic cell
-> release glutamate
-> open ion-channels on post-synaptic cell
-> re-uptake of glutamate & pump ions out of cell again
-> uses energy and oxygen

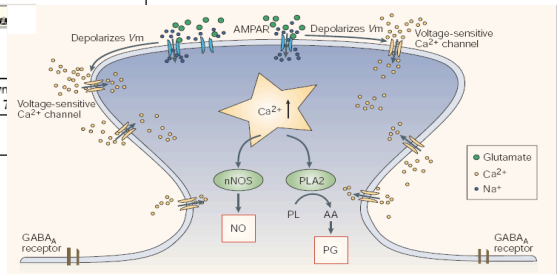
-> triggers blood vessel dilation
-> decrease ratio of deoxygenated/ oxygenated blood
-> decrease in paramagnetism
-> increase in T2*
-> increase in signal strength
-> more power to the SPM

Is this statistically significant?



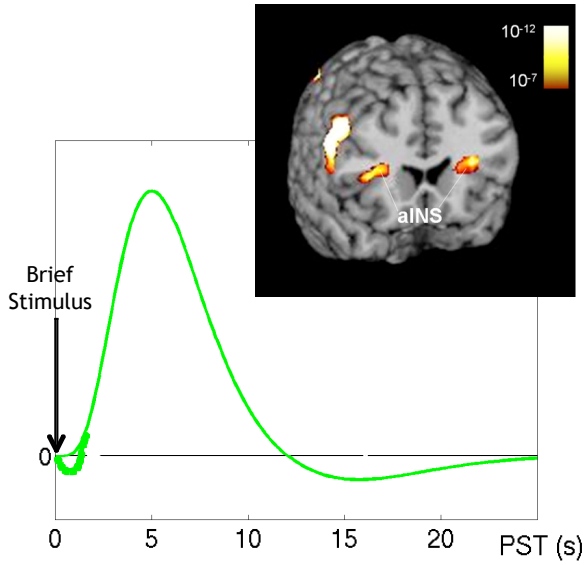


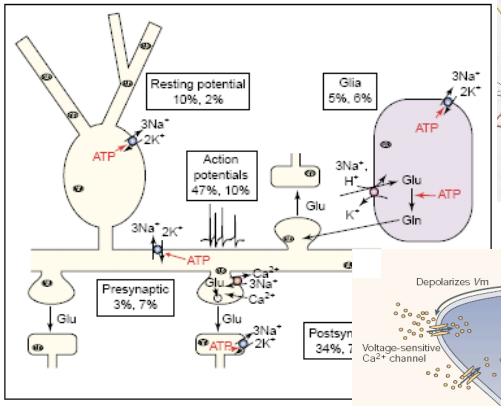


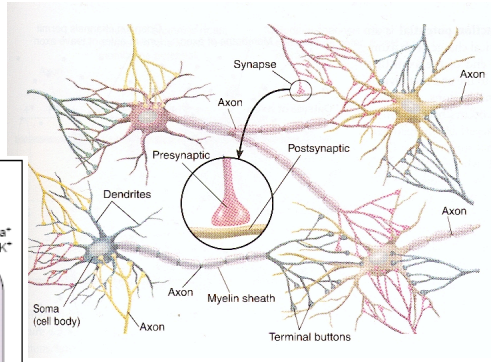


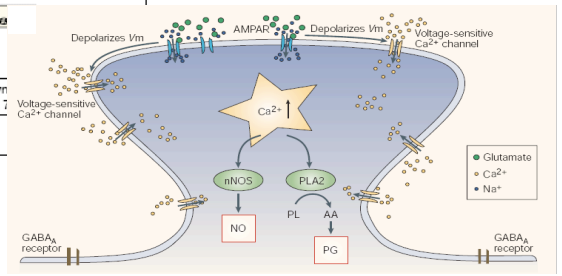
The BOLD signal

- seems to be more strongly related to LFPs than to spiking activity.
- seems to reflect a neuronal population's input as well as its intrinsic processing, and not its output.







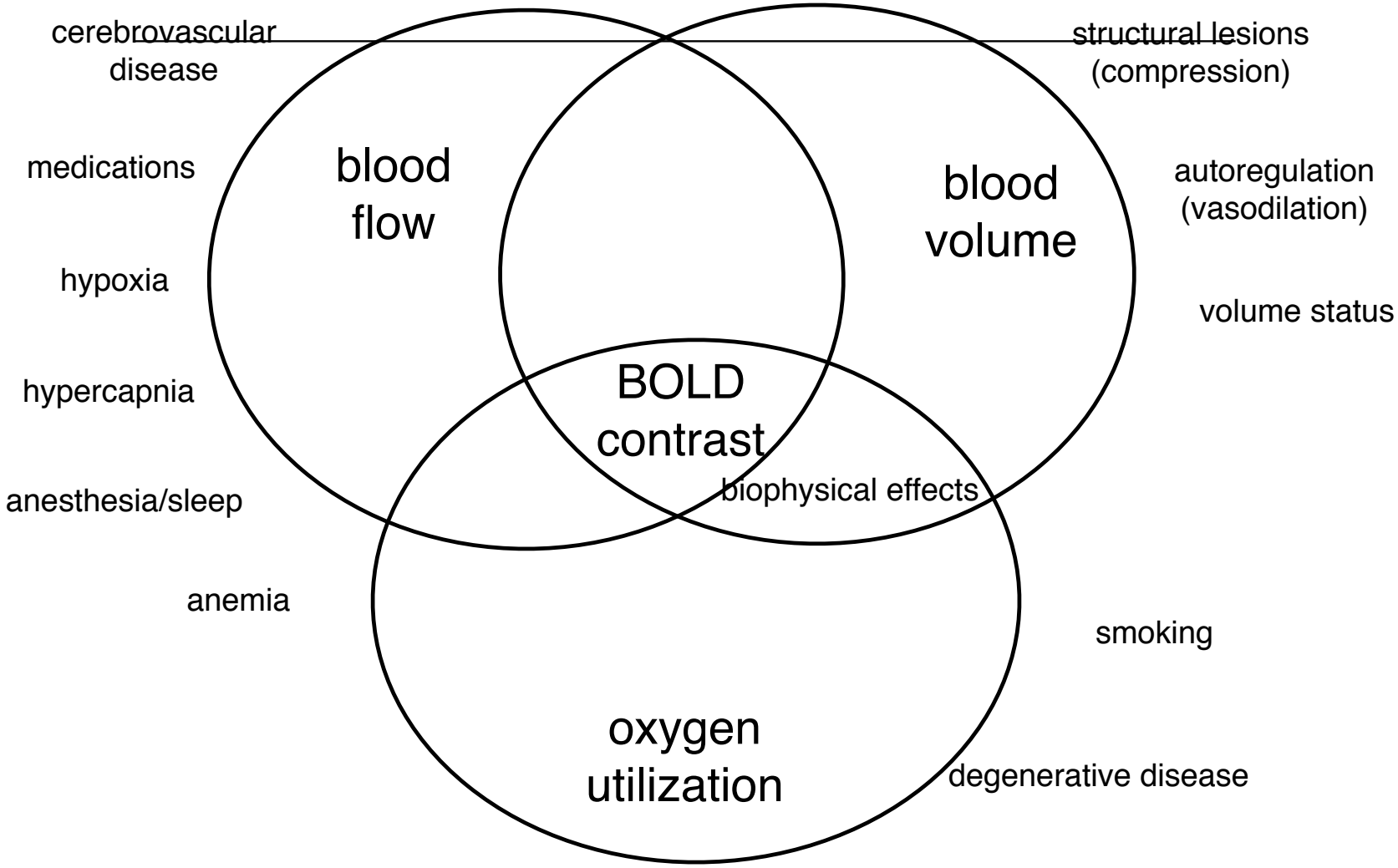


Blood flow seems to be controlled in a forward fashion by postsynaptic processes leading to the release of vasodilators.

Negative BOLD signals may result from IPSPs.

Various drugs can interfere with the BOLD response.

Potential physiological influences on BOLD



Thank you for your attention.