

Edinburgh Imaging

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The BOLD signal

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Overview

1. MRI physics
2. Neurovascular coupling
3. Neural activity and BOLD
4. Experimental BOLD changes
5. Non experimental BOLD changes

The fMRI BOLD signal

Using MRI to measure a surrogate of neural activity, i.e. changes in blood flow ([Ogawa et al, PNAS 1990](#)).

The relationship between venous oxygenation and the MR signal strength corresponds to images called Blood Oxygenation Level Dependent (BOLD).



[Belliveau et al. 1991](#)

1 - MRI physics

BLOOD Flow vs. Metabolism

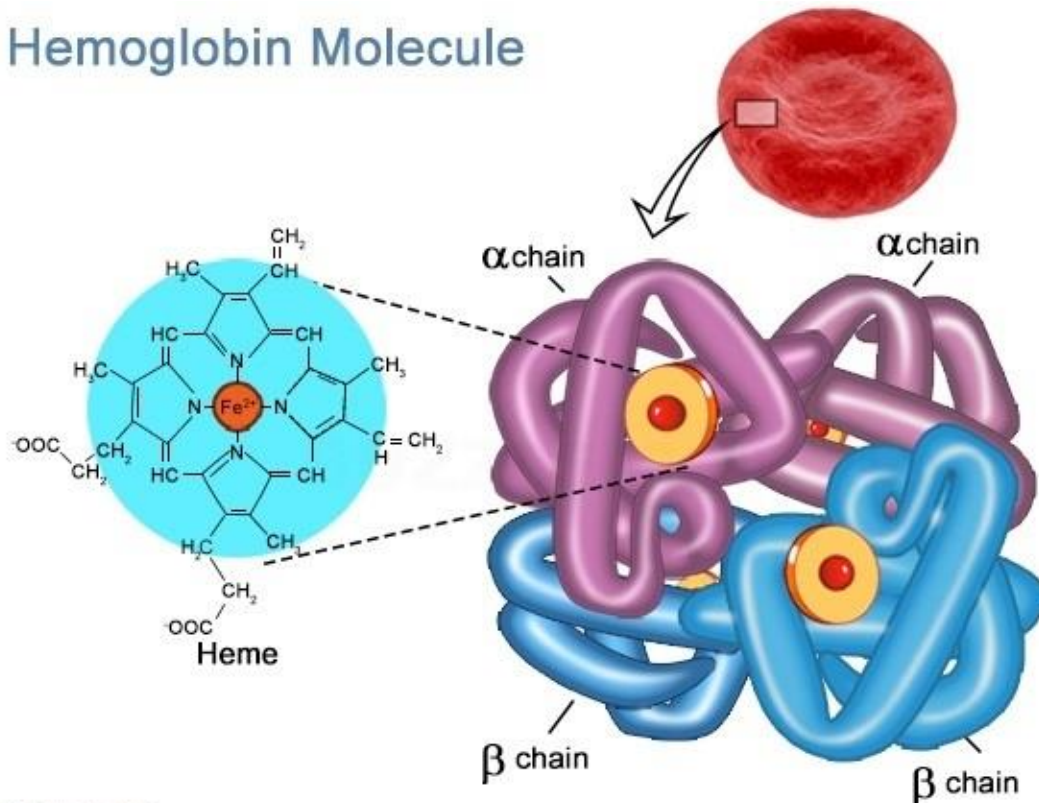
During information processing, there is an increase neuronal activity in different parts of the brain. This increase in neuronal activity elicits an increase in oxygen and glucose consumption supplied by the vascular system.

PET studies using $\text{H}_2\text{O}_{15}^*$ and FDG^* have shown that the regional cerebral blood flow (rCBF) and the regional cerebral metabolic rate (rCMR) increase during activation phases (neuronal stimulation). However, rCBF and rCMR are not completely coupled. During activations, the rCMRO_2 increase of 5% but the rCBF increase of 50% (Fox & Raichle, 1986).

The Magnetic property of Blood

❖ In 1936, [Linus Pauling*](#) discovered that the hemoglobin molecule has magnetic properties that differ depending upon whether or not it is bound to oxygen.

Hemoglobin Molecule



❖ Oxygenated hemoglobin (Hb) is diamagnetic as it has no unpaired electron and no magnetic moment.

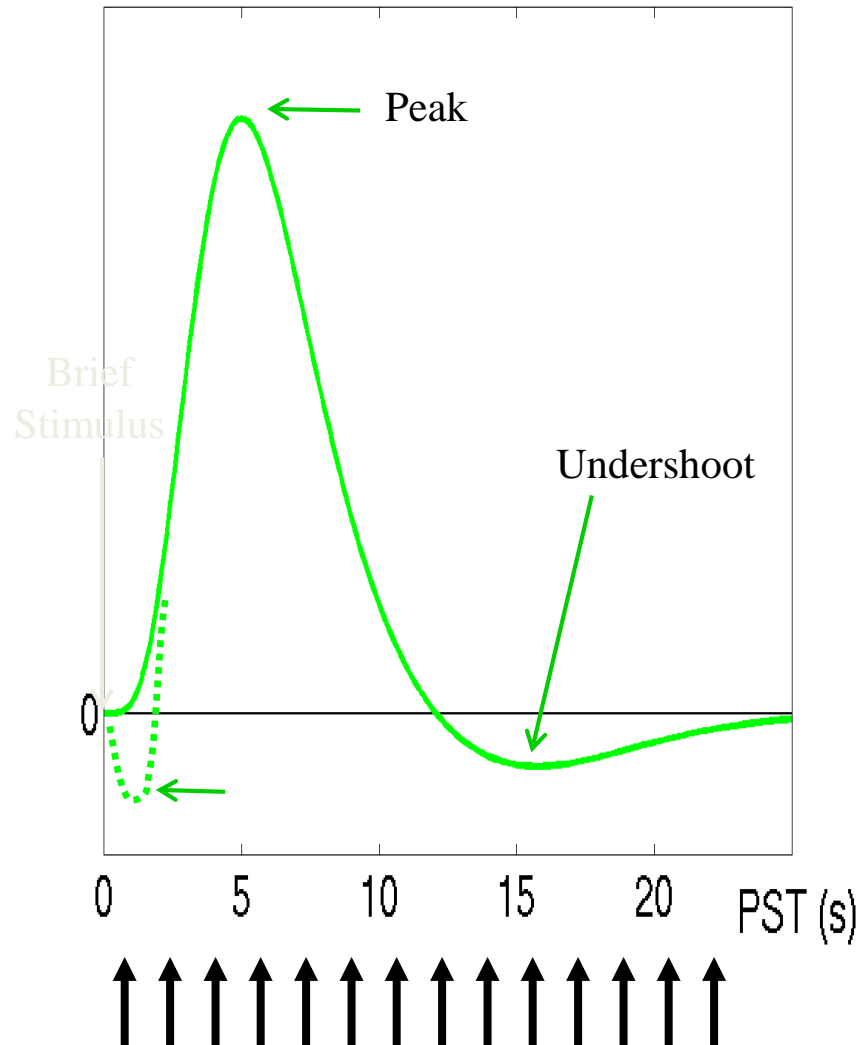
❖ Deoxyhemoglobin (dHb) is paramagnetic as it has unpaired electron and magnetic moment.

The BOLD contrast

- ❖ Because blood deoxygenation affects magnetic susceptibility, MR pulses used in fMRI should show more signal for blood with oxygen (Hb) and less signal for blood deoxygenated (dHb). How can we have more signal then?
- ❖ The MRI signal measured in functional imaging is usually a signal that measures changes in the microvasculature oxygenation. More precisely, it deals with venous oxygenation since oxygenation in arteries is always 90-100%, no matter if there is an increase in neural activity.
- ❖ Increase of the Hb / dHb ratio, i.e. we have, in proportion, less dHb → Slower phase decoupling = stronger T2*.

The BOLD signal

- The BOLD signal increases about 2 sec after the neural activity, it then reaches a plateau at about 5 – 8 sec. It will plateau if the neural activity continues. Once the neural activity stops, the signal returns to baseline 8 to 11 sec later. Finally, a transient change referred to as the undershoot can be observed.

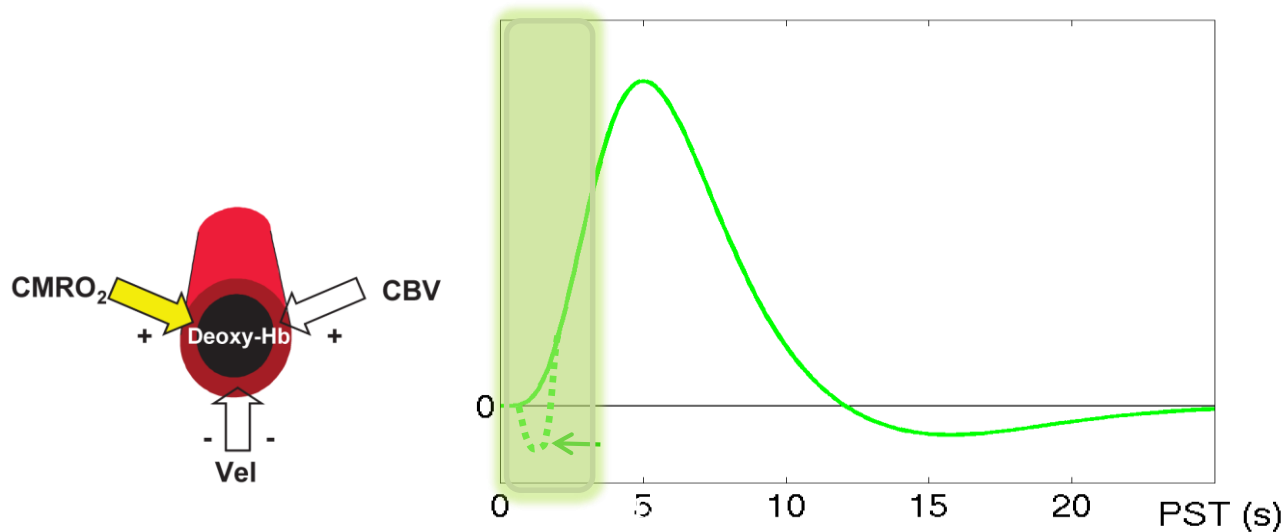


We need fast multiple acquisitions
= time series of 3D volumes

2 - Neurovascular coupling

What is driving the rCBF?

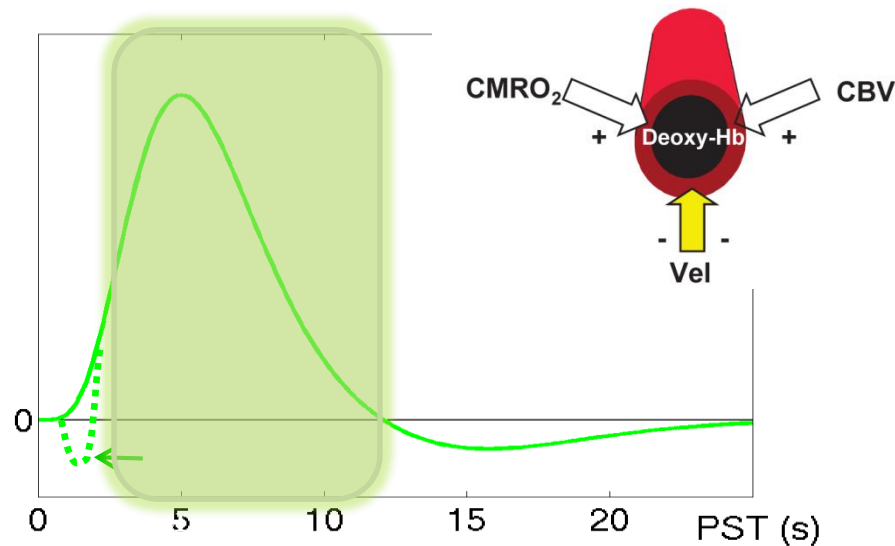
The shape of the BOLD signal, can easily be explained by oxygen metabolism.



At the onset of neural activity, dendrites rapidly consume O_2 (increase of the $CMRO_2$ - Kasischke et al, 2004) for glycolysis, leading to a reduction in oxygen pressure (pO_2 - Ances et al, 2001) and oxyhaemoglobin (Devor et al, 2005).

What is driving the rCBF?

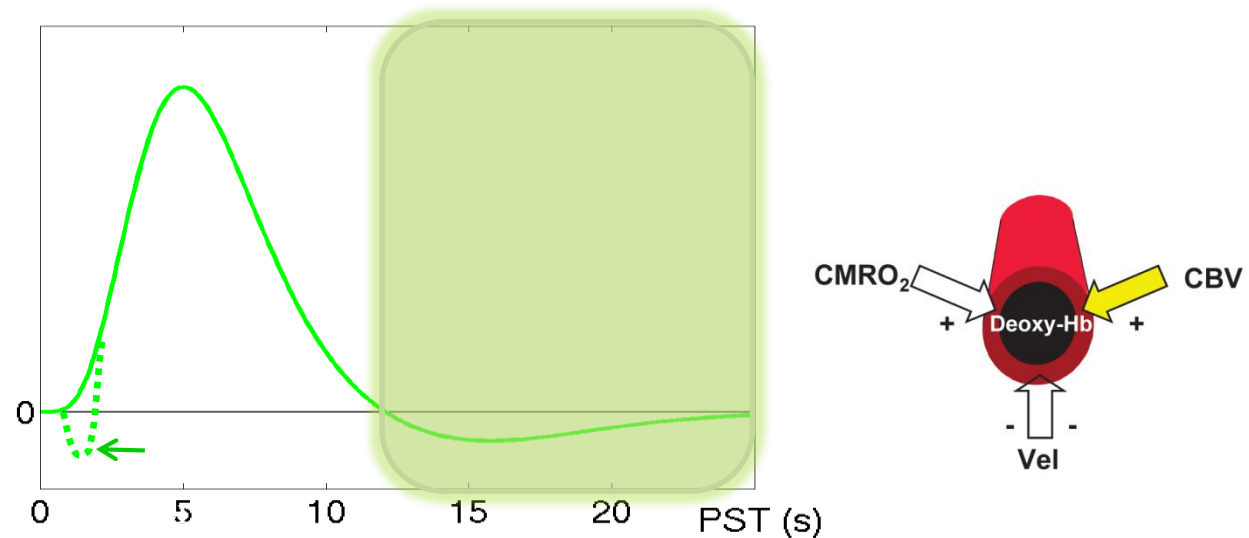
The shape of the BOLD signal, can easily be explained by oxygen metabolism.



Increase of the rCBF → more Hd supplied than consumed = increase of the signal. Villringer et al. (1994) showed that changes in the blood flow are linked to an increase in capillaries dilatation and/or blood cell velocity.

What is driving the rCBF?

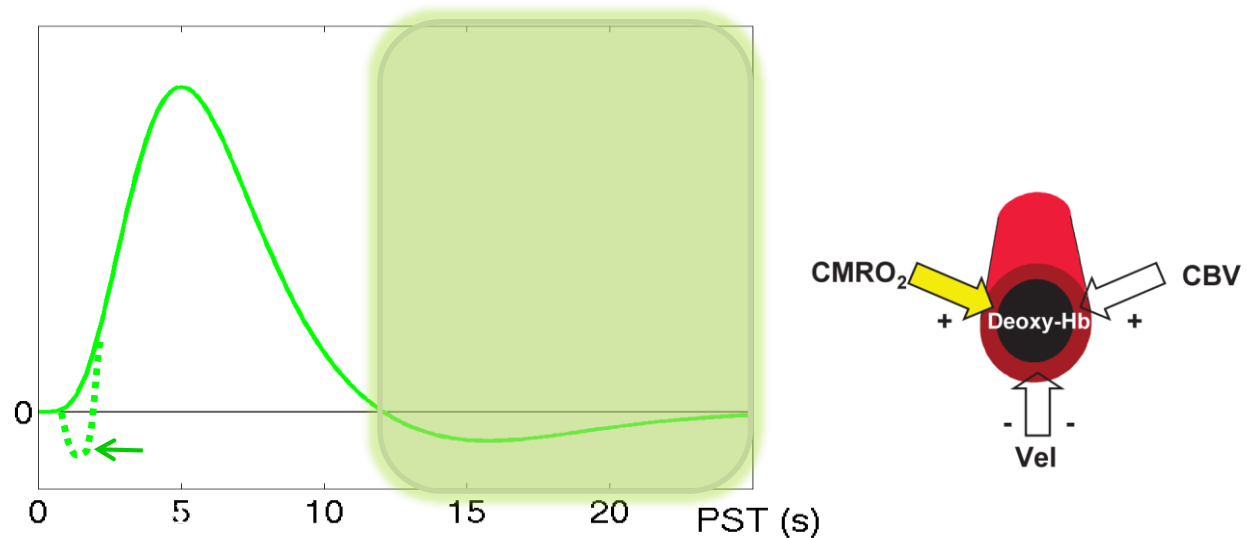
The shape of the BOLD signal, can easily be explained by oxygen metabolism.



Increased cerebral blood volume (CBV) due to differences between the active response of arteries (dilatation/constriction) and the passive venous response (Buxton et al. 1998, Mandeville et al., 1999a, 1999b, 2001)

What is driving the rCBF?

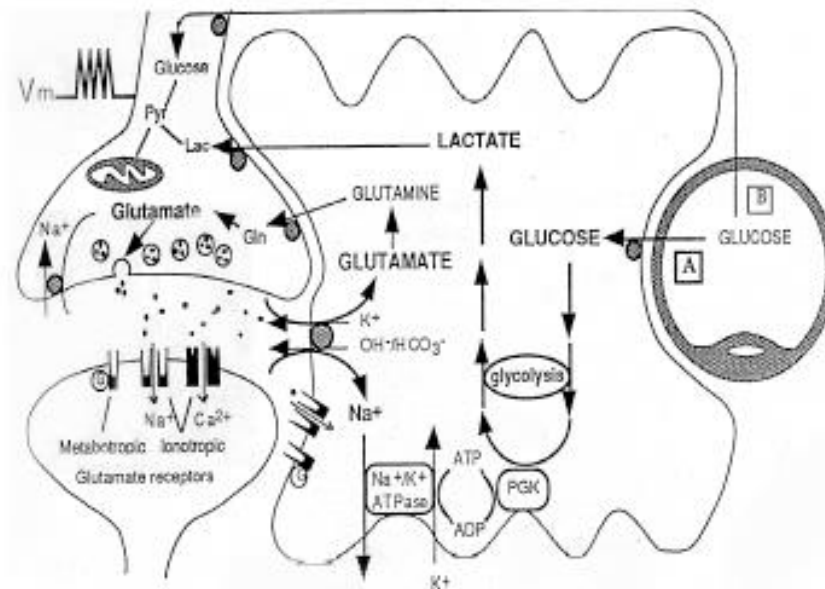
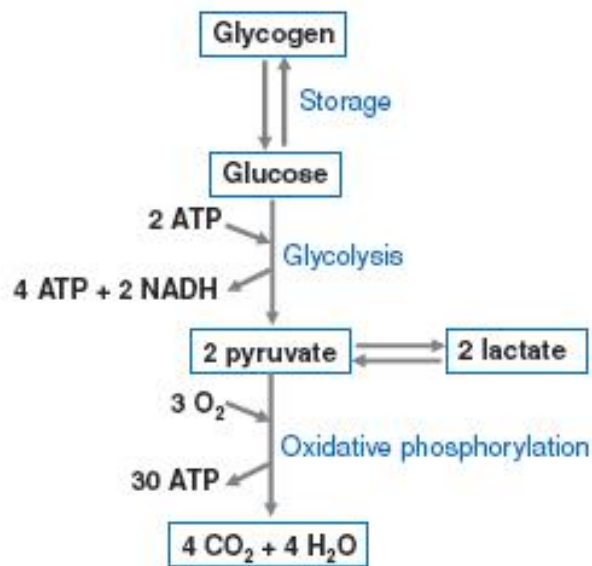
The shape of the BOLD signal, can easily be explained by oxygen metabolism.



OR uncoupling between normal CBF (returned to baseline) and post CBF increase related to CMRO₂ - Frahm et al (2008) for instance showed that in humans there was no change in CBV

What is driving the rCBF?

The energy produced for the brain relies mainly on glucose oxidation. There are evidences that the increase in rCBF is not driven by oxygen consumption and, arguably, it has been proposed that the main driver is glucose consumption.



Astrocyte-Neuron Lactate Shuttle hypothesis - Pellerin & Magistretti, 1994

Astrocytes not Neurons?

Astrocytes are an essential part of a *neuronal–glial–vascular unit*:

- Astrocytes control the local blood flow by releasing molecules acting on the dilatation or constriction of arterioles ([Gordon et al, Nature 2008, vol 546](#)).
- They therefore supply neurons with energy substrates (mainly lactate), which is *essential for information transmission* between neurons.
- Without the lactate (lactate is transformed in pyruvate in neurons which itself is oxidated by neural mitochondria) synaptic transmission is altered ([Rouach et al, Science 2008, vol 322](#)) which can lead to e.g. memory deficits ([Suzuki et al, Cell 2011, vol 810](#)).

Maybe neurons after all

Lundgaard et al. (2015 – Nat Communications) showed that neurons also transform glucose into lactate

Changes in neural activity correlated with changes in neural glucose consumption while the astrocyte glucose consumption remained constant

→ So still glucose as the metabolite behind the response, still neurons and astrocytes, but not too sure about the relative contributions

3 - Neural activity and BOLD

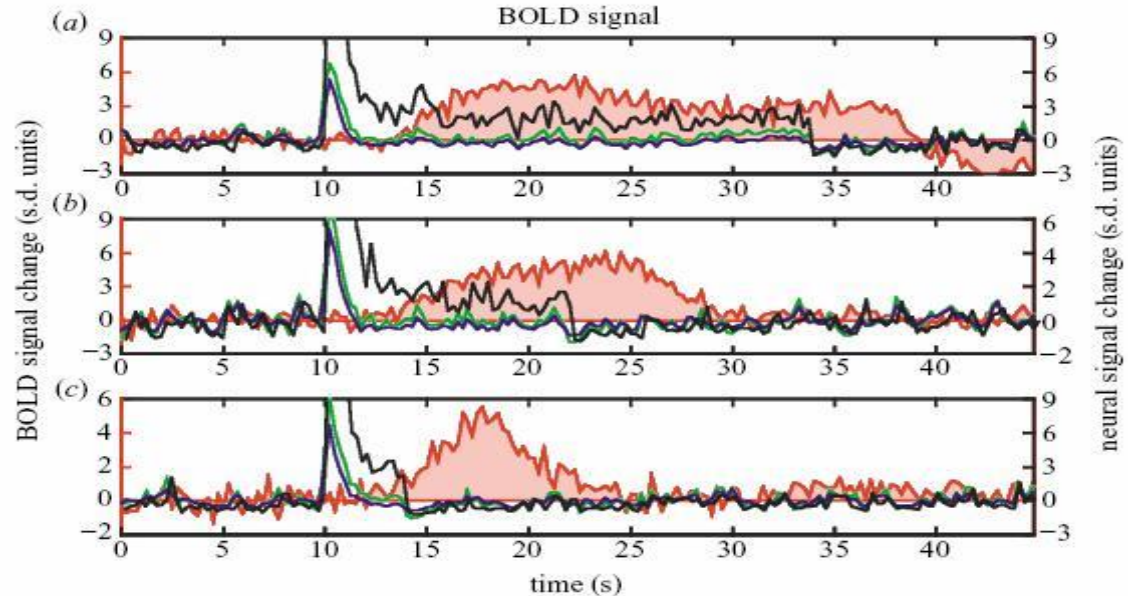
Neural activity and BOLD

- The BOLD signal reflects the firing of neural populations such as a strong correlation exists between the BOLD amplitude and local field potentials data (Logothetis, 2001)

24 sec stimulation

12 sec stimulation

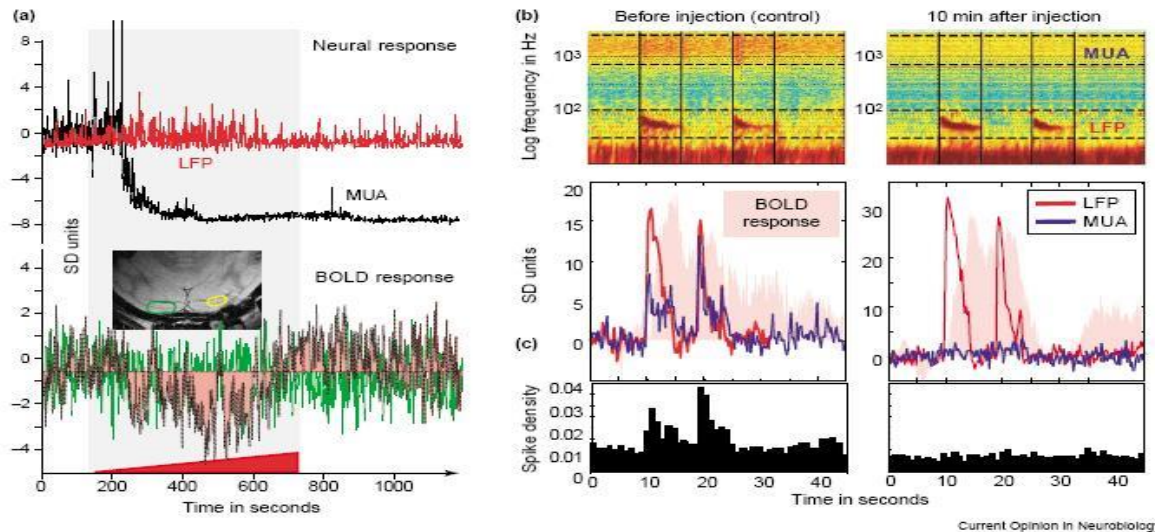
4 sec stimulation



- This means that BOLD is more related to synaptic activity than neural activity per se (i.e. the interplay of EPSP and IPSP)

Neural activity and BOLD

The relationship between neural spiking and BOLD signal is NOT straightforward because it reflects synaptic activity, which means one cannot really say if the BOLD signal relates to a neural excitation or inhibition.

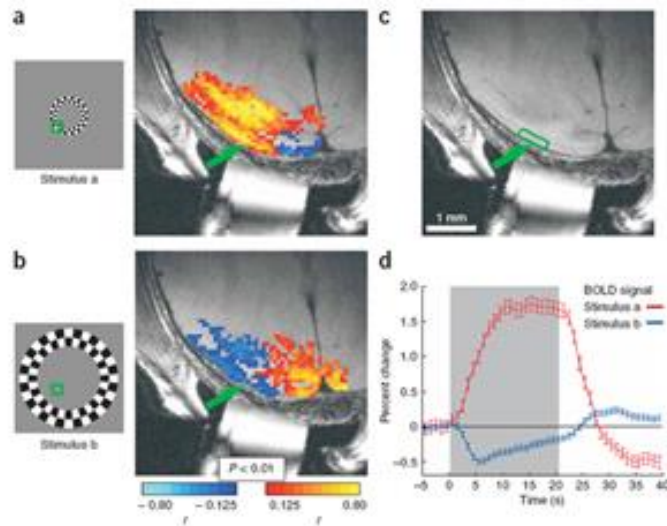


Serotonin (5HT) is injected during 10min (red) during a visual stimulation. Soon after injection, the multiunit activity decreases (inhibition) but both LFP and BOLD are clearly above baseline (Logothetis 2003).

The BOLD signal reflects mainly the input and processing of neural information

Neural activity and BOLD

- Synaptic activity related to excitatory (EPSP) and inhibitory (IPSP) potentials leads to observe a positive BOLD response.
- Decrease in local neural activity (e.g. Shmuel et al. 2006, Pasley et al., 2007 - see however Devor et al, 2005) leads to a negative BOLD response. Neural decrease most often relates to activity of inhibitory interneurons (Lauritzen, 2012).



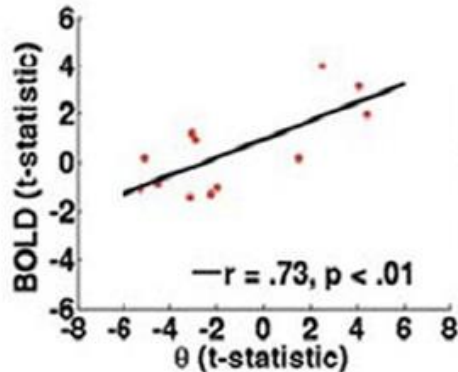
A negative BOLD response beyond the stimulated regions of visual cortex, associated with local decreases in neuronal activity below spontaneous activity, detected 7.15 ± 3.14 mm away from the closest positively responding region in V1. (Schmuel et al, 2006 Nat Neurosc 9)

Neural activity and BOLD

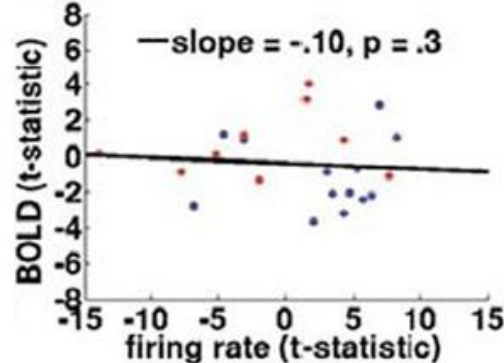
Hippocampal activations

Several researchers have observed a dissociation between spiking activity, LFP and BOLD signal in the hippocampus.

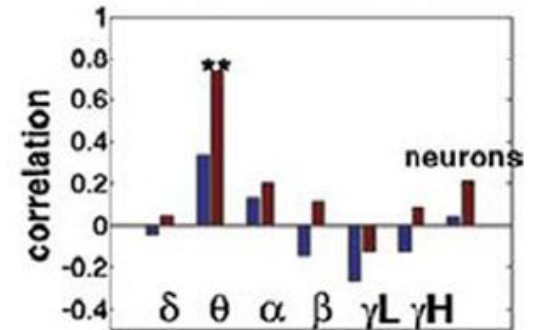
A.



B.



C.

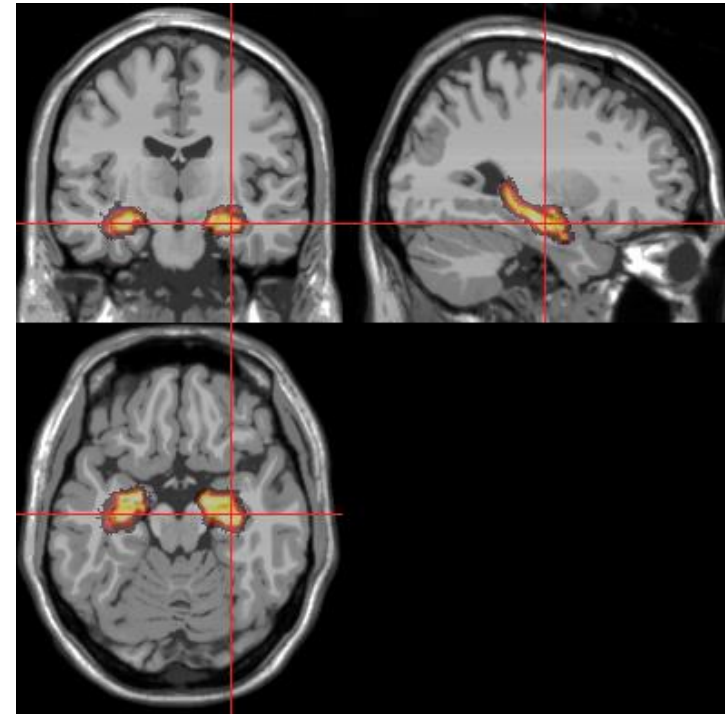


Neural activity and BOLD

Hippocampal deactivations

Negative BOLD responses compared to baseline are often observed in memory tasks.

One possible explanation relies on the particular low capillary vasculature of this region such as neural activity leads to an increase in oxygen consumption beyond the blood flow supply (Ekstrom 2010).

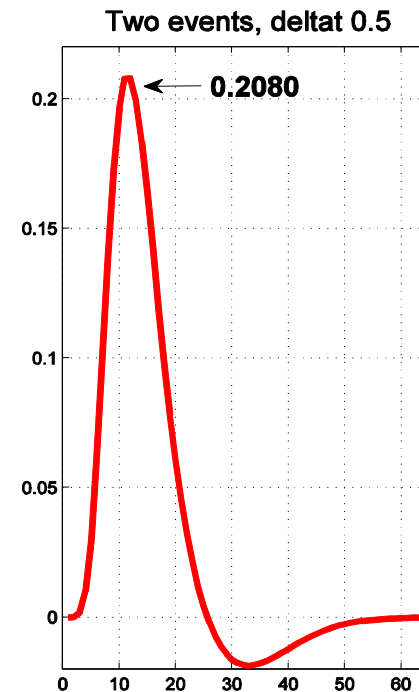
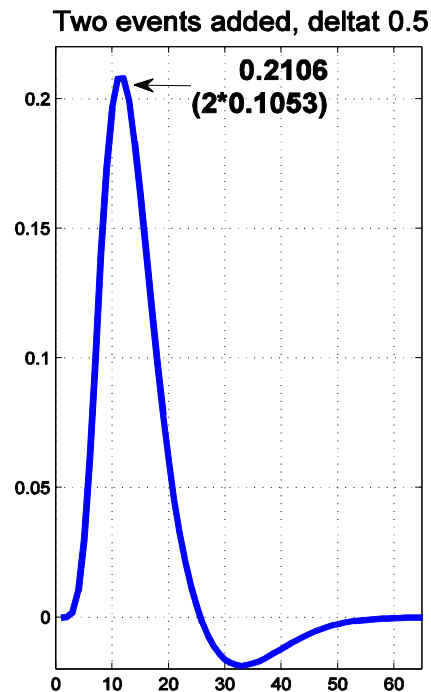
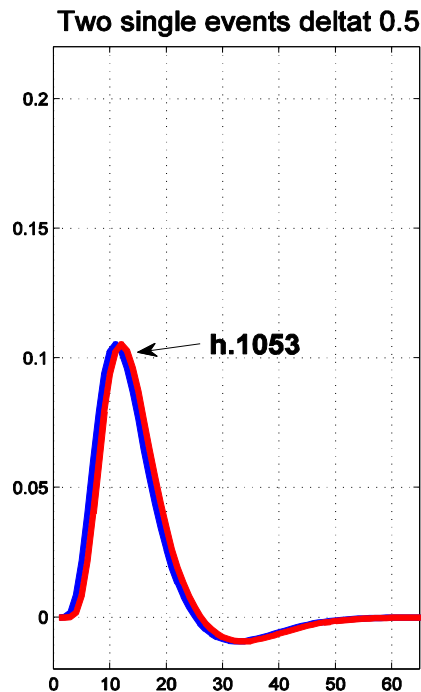


http://www.thomaskoenig.ch/Lester/Files/SPAMs_Hippocampus.jpg

4 – Experimental BOLD changes

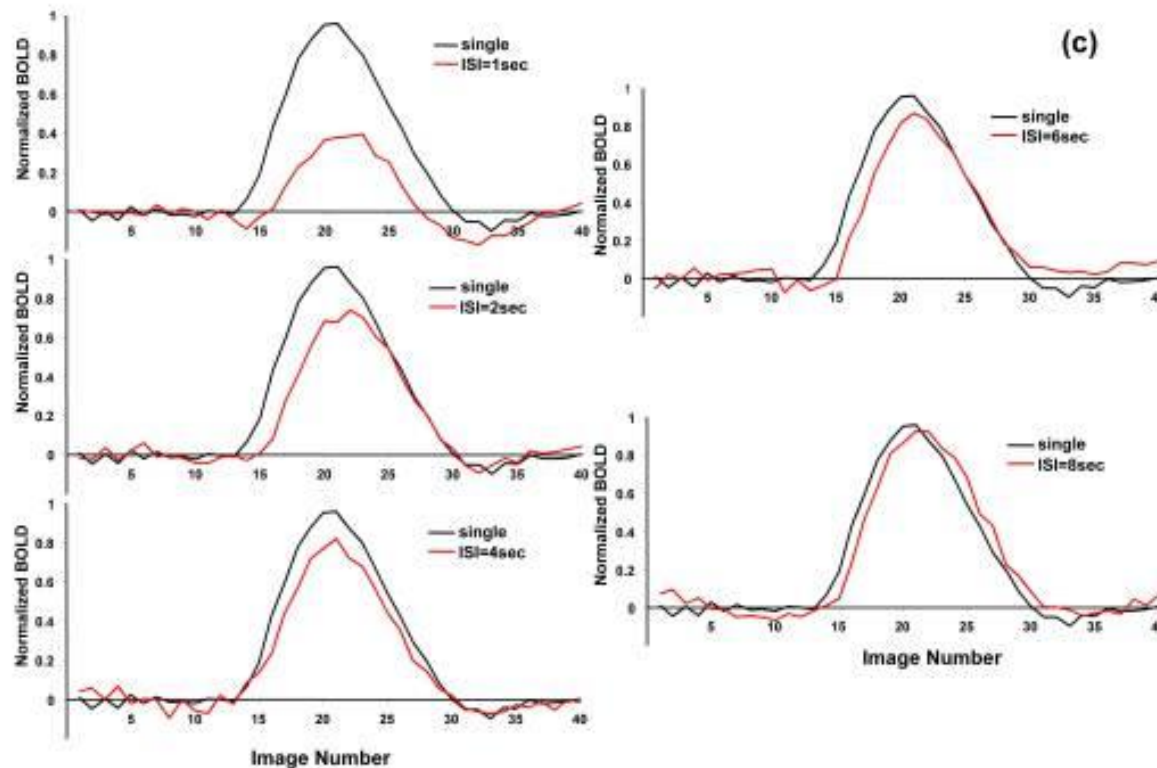
Non-Linearity

- Linearity means that for 2 events presented with a delay Δ , the total response equals = event 1 + event 2 at a delay Δ , and event 1 and 2 are the same as a single event.



Non-Linearity

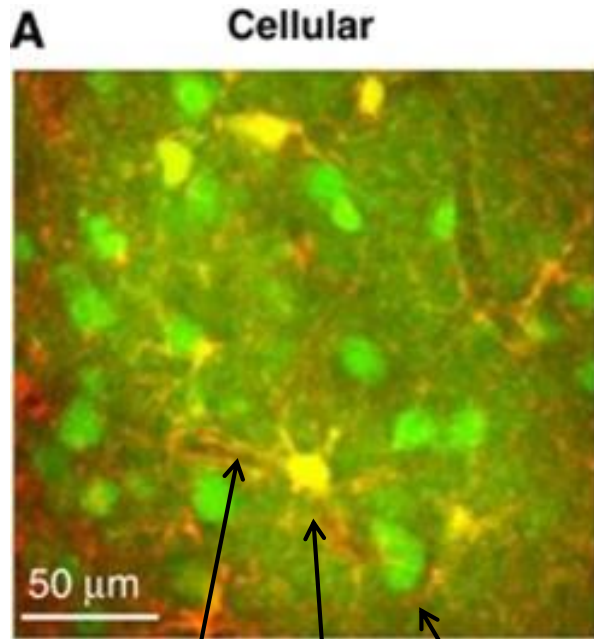
- Linearity is essential to the rapid ER fMRI design with stimuli presented at short ISI. At short ISI ($<4s$), the amplitude of the second event is shorter and the onset latency is delayed.



Zhang et al. 2009
NeuroImage, 43

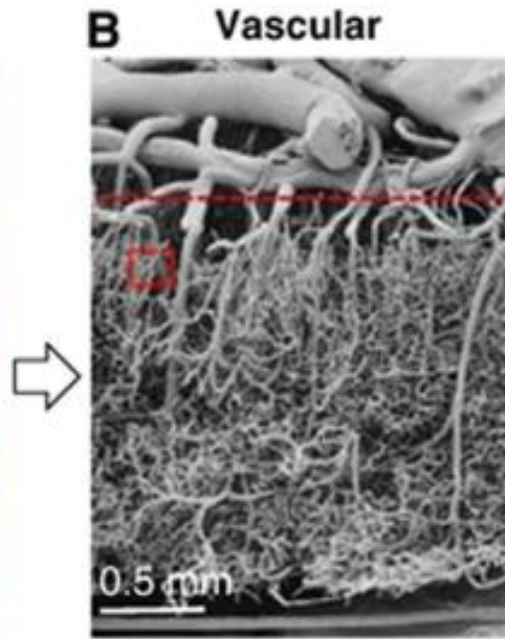
Non-Linearity

- Non-linearities seems to be caused by 'large' vessels and Spin-Echo fMRI (suppress larger vessel BOLD) at high field revealed a much more linear relationship between BOLD and stimulus repetition down to ISI of 1sec ([Zhang et al. 2009](#)).
- Non-linear responses are observed for stimuli that are repeated for ISI below 4 sec – pblm for event related designs.
- Non-linear responses are useful for [adaptation design](#): if an additive/linear response is observed vs. non-linear then it indicates a release from adaptation ; but effects needs to be controlled as to reflect neural and not vessel activity.



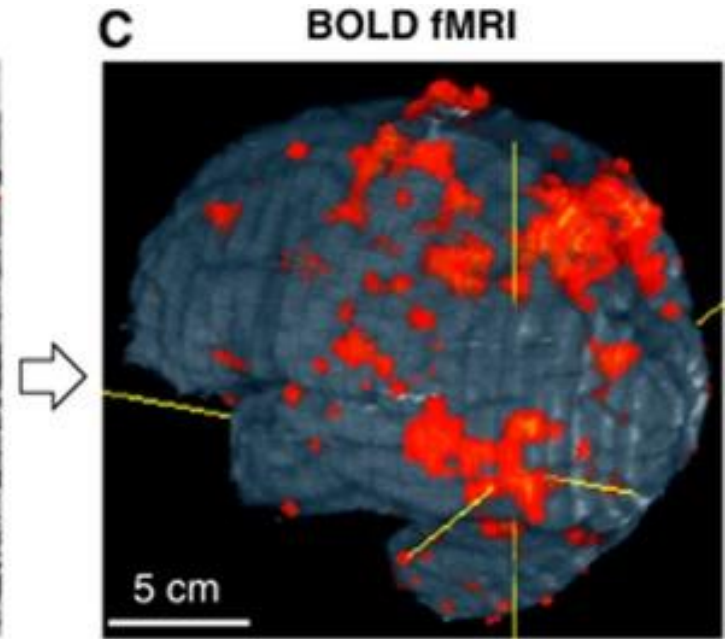
capillary astrocyte neuron

Increased activity in the neurons and astrocytes near and surrounding the capillaries induces an increase in capillary blood flow and dilation of upstream arterioles and/or increase blood cell velocity



Pial / Intracortical vessels

Non-linearity arises mainly from pial vessels



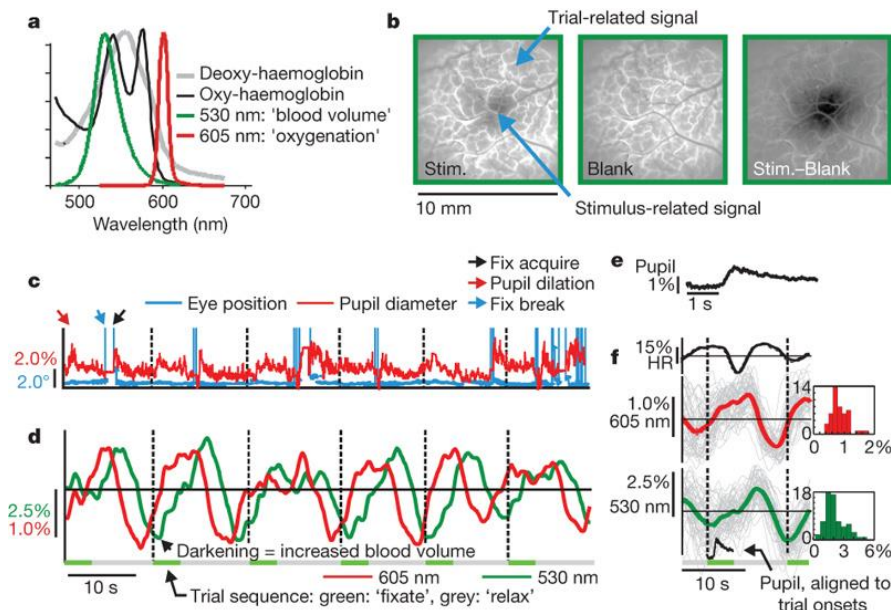
fMRI activations

BOLD amplitude depends on baseline CBV, and vasculature changes in space – comparison between voxels on absolute BOLD is not valid (area A > area B only for a condition relative to another/control).

5 – Non experimental BOLD changes

Trial, not stimulus, related changes

Sirotin & Das (2009 - *Nature* **457**) measured blood volume, oxygenation and electrical activity in a monkey performing a fixation/relax task and found trial changes in blood volume and oxygenation in regions not receiving any light !



Cardoso et al. (2012 - *Nat Neuro*, 15) showed that even for areas receiving light input, the BOLD response is better seen as a linear sum of stimulus induced spiking activity (~50% of the variance) and a trial-related signal, not related directly to the local spiking.

Trial, not stimulus, related changes

- *Design is key:*
- Rest or null events: removing effects of (blank) null trials or non specific form of global from local signal are not confounded by this trial-related signal.
- Factorial and/or parametric design: comparison of conditions within the same task structure or regression against a range of intensity also avoid confound from by this trial-related signal

Other known factors

- Hematocrit level (red blood cells)
 - Caffeine (vasoconstrictor – half life 6h)
 - Food (hypoglycemia)
 - Alcohol
 - and many more
-
- **A good subject: not hangover, no coffee on the day of scanning, possibly exercised in the morning / limited smoking, had food and no alcohol few hours before scanning.**

Selected References

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- Cardoso et al 2012 The neuroimaging signal is a linear sum of neurally distinct stimulus- and task-related components. Nat Neurosc 15