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

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Overview

1. A brief introduction to MRI: What do we measure with MRI?
2. A brief introduction to fMRI: What do we measure in functional MRI?
3. An introduction to BOLD imaging: What does BOLD imaging tell us about neuronal processes?
1. What do we measure with MRI?

Magnetic resonance measures the magnetic properties of spins of nuclei.

The collective signal of many spins is measured.

The magnetic resonance depends on the properties of the nucleus and – most important – on its surrounding.

→ But how does it work?
Material in a magnetic field

Spin = rotation of a proton around some axis
Movement of a positive charge → magnetic moment

Protons align with the magnetic field. We can measure average magnetization.

Images: www.fmri4newbies.com
Strong constant magnetic field

1 Tesla (T) = 10’000 Gauss
Earth = 0.5 Gauss
3 Tesla = 60’000 times earth magnetic field
At least 100 times toy magnet (fridge)
Protons in a static magnetic field

Without static field:

- $B = 0$
- $M = 0$

No net magnetization

$\Rightarrow$ no signal detection

With static field:

- $B$
- $M$

Net magnetization parallel to $B$

$\Rightarrow$ signal detection possible
Excite spins by an RF pulse – measure the energy RF they emit

1. Excite sample with RF pulse (radio wave) at «Larmor frequency» (42.6MHz/Tesla).
2. Magnetization is tilted by the RF pulse and precesses around the magnetic field.
4. The temporal properties of this signal are the cue to MRI.
Signal decay depends on tissue

\[ T_1 = \text{time constant of how quickly the protons realign with magnetic field} \]

\[ T_2 = \text{time constant of how quickly the protons emit energy when recovering to equilibrium} \]

Fat has high signal \( \rightarrow \) bright

CSF has low signal \( \rightarrow \) dark

Fat has low signal \( \rightarrow \) dark

CSF has high signal \( \rightarrow \) bright

Images: www.fmri4newbies.com

The physiology of the BOLD signal
T2* magnetization decay

- Two factors contribute to the decay of transverse magnetization: 1) molecular interactions (tissue properties) (T2) 2) local inhomogeneities of the magnetic field
- The combined time constant is called 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
2. What do we measure in fMRI?

• We measure T2* decay of protons.

• Depends on:
  • Molecular interaction
  • Local inhomogeneities of magnetic field
Functional MRI (fMRI)

Uses *echo planar imaging* (EPI) for fast acquisition of T2*-weighted images.

Spatial resolution: 1.5-3 mm (standard 3 T scanner)

Sampling speed: 1 slice: 50-100 ms

Problems:
- distortion and signal dropouts in certain regions
- sensitive to head motion of subjects during scanning

Requires spatial pre-processing and statistical analysis.

What makes T2* weighted images “functional”?
Magnetic properties of hemoglobin

The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin

By Linus Pauling and Charles D. Coryell

Gates Chemical Laboratory, California Institute of Technology

Communicated March 19, 1936
Magnetic properties of oxy- and deoxy-hemoglobin

The more oxy-hemoglobin the larger (slower) is T2*

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

We are still measuring the spin of hydrogen atoms!!!

But, the surrounding tissue can have strong effects.

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!

**Deoxygenated hemoglobin:**
Paramagnetic (magnetic)
→ signal loss!

Indirect relationship between cognitive processes and BOLD signal

Control and measure

Try to infer something

But what about these?

Relatively well understood (physics)

Measure

Source: Huettel et al, 2004, fMRI (Book)
The BOLD 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**
Increased blood flow

- neural activity ➞ ↑ blood flow ➞ ↑ oxyhemoglobin ➞ ↑ T2* ➞ ↑ MR signal

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.
BOLD is a non-linear function of rCBF

**Neural State Equation**

\[
\frac{dx}{dt} = \left( A + \sum_{j=1}^{n} u_j B^{(j)} \right) x + Cu
\]

**Hemodynamic State Equations**

\[
\dot{s} = x - KS - (f - 1) \]

**Vasodilatory Signal**

\[ f = s \]

**Flow Induction (rCBF)**

\[ f = s \]

**Balloon Model**

\[
\tau_v = f - v^{\alpha}\]

\[
\tau_q = f E(f, E_0) / E_0 - v^{\beta} q / v
\]

**BOLD Signal Change Equation**

\[
\lambda(q, v) = \frac{NS}{S_0} = V \left[ k_1(1-q) + k_2 \left( 1 - \frac{q}{v} \right) + k_3(1-v) \right]
\]

Source: Stephan et al., NeuroImage, 2007
Can we approximate the HRF as a linear transform?

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

\[ F(ax+by) = aF(x)+bF(y) \]
Summation of BOLD responses

Strong visual stimulation

ISI: 2 seconds

Source: Dale and Buckner, Hum Brain Mapp, 1997
Although it is clearly non-linear, it is often a good approximation to consider the HRF being a linear transform.

Source: Boynton et al, J Neurosci, 1996
3. How is the BOLD signal related to neural activity?

Some important questions:

Is the BOLD signal more strongly related to neuronal action potentials or to local field potentials (LFP)?

Does the BOLD signal reflect energy demands or synaptic activity?

What does a negative BOLD signal mean?
Where does the signal come from: Soma or synapse?

Source: http://psychology.uwo.ca/fmri4newbies/Tutorials.html
Comparing BOLD with electrophysiology – early experiments

Moving dot stimuli

Compare average monkey physiology to average BOLD signal in humans.

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

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

Source: Heeger et al, Nat Neurosci, 2000; Rees et al, Nat Neurosci, 2000
MUA/LFP and BOLD

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

BOLD & LFPs


The physiology of the BOLD signal
Dissociation between action potentials and rCBF

- GABA$_A$ antagonist picrotoxin increased spiking activity without increase in rCBF...
- ... and without disturbing neurovascular coupling per se

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

Source: Thomsen et al., J Physiol, 2004
Lauritzen & Gold, J Neurosci, 2003

The physiology of the BOLD signal
Relation of BOLD and electrophysiology

The physiology of the BOLD signal

Source: Maier et al, Nat Neurosci, 2008
The BOLD signal is correlated to postsynaptic activity

- BOLD can be correlated both to presynaptic activity (action potentials) and to postsynaptic activity (as indexed by LFPs).
- Indeed, 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 independent of LFPs.
- This justifies the (present) conclusion that BOLD more strongly reflects the input to a neuronal population as well as its intrinsic processing, rather than its spiking output.

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

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What does a negative BOLD signal mean?
The BOLD signal: Synaptic processes or energy demand?

- deoxy-Hb/oxy-Hb ↓
- CBF ↑↑
- ???
- neural metabolism ↑
- synaptic activity ↑

The physiology of the BOLD signal
Cortical Metabolism

http://student.biology.arizona.edu/honors99/group7/glycolysis.jpg
Salt loading in rats and 2-deoxyglucose mapping

→ glucose utilization in the posterior pituitary but not in paraventricular and supraoptic nuclei (which release ADH & oxytocin at their axonal endings in the posterior pituitary)

→ neuronal energy consumption takes place at the synapses, not at the cell body

Schwartz et al., Science, 1979

Localisation of neuronal energy consumption
Energy consumption by synaptic transmission
Excitatory action might directly regulate rCBF
Calcium signaling is important

NO (nitric oxid) and PG (prostaglandin) have vasodilatory effects but very little contact between neurons and vasculature.

Source: Lauritzen, Nat Rev. Neurosci, 2005
Forward control of blood flow

[Diagram showing the physiological processes involved in the control of blood flow.]

Courtesy: Marieke Scholvinck
Influence of oxygen on blood control

O$_2$ levels determine whether synaptic activity leads to arteriolar vasodilation or vasoconstriction (via prostaglandines).

**Figure 1** Lowering p$_O_2$ converts vasoconstriction to vasodilation.

a, Arteriole before and after synaptic activation in high O$_2$ (left) and low O$_2$ (right). Dashed vertical lines indicate the previous position of the vessel wall.
b, Top: vessel lumen diameter changes over time in the same vessel shown in a. Arrows indicate time of afferent stimulation. Bottom: two expanded timescales show the stimulation protocol (350-ms, 20-Hz train repeated 5 times at 0.75 Hz) and the first train of the field excitatory postsynaptic potentials evoked, verifying synaptic activity. c, Summary data (n = 6). In all figures, experimental values are the mean ± s.e.m. Double asterisk, P < 0.01.

Astrocytes and blood supply

Camillo Golgi, (1843-1926)

Source: Iadecola and Nedergaard, Nat Rev Neurosci, 2007
Glia cells and blood supply

Astrocytes have many contacts with blood vessels.

Glia limitans can regulate blood flow of larger vessels

Domains of astrocytes

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 are important.

Source: Iadecola and Nedergaard, Nat Rev Neurosci, 2007
3. How is the BOLD signal related to neural activity?

Some important questions:

Is the BOLD signal more strongly related to neuronal action potentials or to local field potentials (LFP)?

Does the BOLD signal reflect energy demands or synaptic activity?

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
Negative BOLD due to reduced calcium?

Source: Lauritzen, Nat Rev. Neurosci, 2005
Excitatory-inhibitory networks and BOLD

Summary

• The BOLD signal seems to be more strongly related to LFPs than to spiking activity.

• The BOLD signal may primarily reflect the input to a neuronal population as well as its intrinsic processing.

• Blood flow seems to be controlled in a forward fashion by postsynaptic processes leading to the release of vasodilators (e.g., NO and prostaglandines).

• Negative BOLD signals may result from IPSPs.

• Various drugs can interfere with the BOLD response.
McRobbie et al, From Picture to Proton, Cambridge University Press, 2007

Huettel et al, Functional Magnetic Resonance Imaging, Sinauer, 2004


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