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

Methods and Models in fMRI, 20.09.2016

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K. E. Stephan for material
Overview of SPM

Image time-series → Realignment → Normalisation → Template

Kernel → Smoothing → General linear model → Parameter estimates

Design matrix → General linear model → Parameter estimates

Statistical parametric map (SPM) → Statistical inference

Gaussian field theory → p < 0.05
A very simple experiment

- One session
- 7 cycles of rest and listening
- Blocks of 6 scans with 7 sec TR
How is brain data related to the input?

What we know.

What we measure.
Statistical maps

Glass brain

Sections
Indirect relationship between cognitive processes, neural processing and fMRI

Cognitive processes (Sensory, motor, etc.)

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

Try to infer something about

Control and measure

Measured MRI signal
Indirect relationship between cognitive processes, neural processing and fMRI

1. What do we measure with MRI?

2. What do we measure with fMRI?

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

Cognitive processes (Sensory, motor, etc.)

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

Changes in blood flow, oxygen concentration, blood volume

Changes in MRI contrasts due to changes in relative hemoglobin concentrations

Control and measure

Try to infer something about

Measured MRI signal
1. What do we measure with MRI?

- Cognitive processes (Sensory, motor, etc.)
- Information processing in ensembles of neurons, e.g. synaptic processes and neural spiking
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Control and measure

Try to infer something about

Measured MRI signal
1. What do we measure with MRI?

• Magnetic resonance measures the collective signal of many spins (of protons, i.e. hydrogen atoms).

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

→ But how does it work?
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
Signal decay depends on tissue

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

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

- Fat has high signal → bright
- CSF has low signal → dark
- Fat has low signal → dark
- CSF has high signal → bright

Images: fmri4newbies.com
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?

- Fat has high signal $\rightarrow$ bright
- CSF has low signal $\rightarrow$ dark
- Fat has low signal $\rightarrow$ dark
- CSF has high signal $\rightarrow$ bright
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*.

• 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 with fMRI?

- Cognitive processes (Sensory, motor, etc.)
- Information processing in ensembles of neurons, e.g. synaptic processes and neural spiking
- Changes in blood flow, oxygen concentration, blood volume
- Changes in MRI contrasts due to changes in relative hemoglobin concentrations
- Measured MRI signal

Control and measure
Try to infer something about

2. What do we measure with fMRI?
fMRI uses T2* contrasts

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

Fast acquisition of T2*-weighted images (mostly echo planar imaging (EPI))

Spatial resolution: 1-3 mm (standard 3 T scanner)

Sampling speed: 1 slice: 50-100 ms → 2-4 secs per volume

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”?
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.

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

The BOLD effect

- BOLD (Blood Oxygenation Level Dependent) contrast measures inhomogeneities in the magnetic field due to changes in the level of O₂ in the blood.

**Oxygenated hemoglobin:**
- Diamagnetic (non-magnetic)
- → no signal loss!

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

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
Approximation of HRF with linear transform?

\[ F(ax+by) = aF(x) + bF(y) \]

Source: Huettel et al, 2004, fMRI (Book)
Although the HRF is non-linear, it is often a good approximation to consider the HRF being a linear transform.

Source: Dale and Buckner, Hum Brain Mapp, 1997; Boynton et al, J Neurosci, 1996
BOLD is a non-linear function of rCBF

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

stimulus function

neural state equation

hemodynamic state equations

- Blood volume and deoxy-hemoglobin concentration are important
- cf. DCM in part 2.

Source: Stephan et al., NeuroImage, 2007
3. How is the BOLD signal related to neural activity?

Cognitive processes (Sensory, motor, etc.)

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

Changes in blood flow, oxygen concentration, blood volume

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Control and measure

Try to infer something about

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

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

Three 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?
Where does the signal come from: Soma or synapse?

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

1% signal change ≈ 9 spikes/second

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

combined BOLD fMRI and electrophysiological recordings

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


→ found that BOLD activity is more closely related to LFPs than MUA
Dissociation between action potentials and rCBF

- GABA\(_A\) antagonist picrotoxine 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
Relation of BOLD and electrophysiology

Source: Maier et al, Nat Neurosci, 2008
The debate continuous

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

→ Spikes predict imaging better than LFP.

Source: Lima et al, J Neurosci, 2014
• The BOLD is correlated to both LFPs and spikes.
  • Controversy goes on: which of the two is more closely linked?
  • rCBF-increase can be independent from spiking activity, but so far no case has been found where it was independent of LFPs.

• Present conclusion of the field: BOLD more strongly reflects the input to a neuronal population as well as its intrinsic processing, rather than its spiking output.

→ Final decision is not taken yet.
Three 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?
What drives the BOLD signal?

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

[Diagram of neural activity and blood flow]
Cortical Metabolism

http://student.biology.arizona.edu/honors99/group7/glycolysis.jpg
Localisation of neuronal energy consumption

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
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
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 are important.

Source: Iadecola and Nedergaard, Nat Rev Neurosci, 2007
O₂ levels determine whether synaptic activity leads to arteriolar vasodilation or vasoconstriction (via prostaglandines).

Figure 1 | Lowering $p_{O2}$ converts vasoconstriction to vasodilation.

(a) Arteriole before and after synaptic activation in high O₂ (left) and low O₂ (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, $P < 0.01$.

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

Three 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

Stimulus a

Stimulus b

BOLD signal

Percent change

Correlation

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

**BOLD Summary**

- The BOLD signal seems to be more strongly related to LFPs than to spiking activity (ongoing controversy).
  - 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.

- We are far from completely understanding neurovascular coupling!
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 best correlated to the local field potential, which is itself highly correlated to spiking.
More Information

- 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](http://psychology.uwo.ca/fmri4newbies/Tutorials.html)