Functional MRI

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BOLD effect:
The MR signal is slightly stronger when blood is more oxygenated, and blood oxygenation increases when neural activity increases.

Blood Flow and O₂ Metabolism
Blood flow delivers O₂ and glucose and clears CO₂

Key players:

<table>
<thead>
<tr>
<th>CMRO₂</th>
<th>cerebral metabolic rate of O₂</th>
<th>1.6 micromol/g-min</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>O₂ extraction fraction</td>
<td>40%</td>
</tr>
<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
<td>0.5 ml/g-min</td>
</tr>
<tr>
<td>[O₂]ₐ</td>
<td>total arterial O₂</td>
<td>8 micromol/ml</td>
</tr>
</tbody>
</table>

CMRO₂ = E CBF [O₂]ₐ

E decreases with neural activation!

[Fox and Raichle, PNAS 83:1140 (1986)]

Venous deoxy-hemoglobin = [O₂]ₐ

Key properties of the NMR signal

Resonant Frequency: ν₀ = γB₀ (128 MHz at 3T)
Relaxation Time: T²* (~50 ms at 3T)

MR Signal
Free Induction Decay (FID)

Magnetic Susceptibility Effects

Large scale field gradients:
Susceptibility differences between air, water and bone:

ΔB = ΔΧ B₀

Microscopic field gradients:
Deoxy-hemoglobin (dHb) alters the susceptibility of blood
Signal decay due to deoxy-hemoglobin

Local signals become out of phase, reducing the net signal

Magnetic field variations within a voxel lead to protons precessing at slightly different rates

Deoxy-hemoglobin distorts the magnetic field around blood vessels, reducing the MR signal

The BOLD response to activation

Blood flow increases more than O₂ metabolism, increasing venous oxygenation (less deoxy-hemoglobin)

Neural Activation

Magnetic field is less distorted, and the MR signal increases

The basic fMRI experiment

Dynamic imaging during “on” and “off” blocks of the stimulus

Correlation of each voxel’s time course with the stimulus pattern.

Map areas of significant correlation overlaid on the anatomical image

Brain networks from resting state correlations

Functional Connections

Correspondence of activation maps and resting correlation patterns

(Smith et al, PNAS 2009)

The physiological basis of the BOLD effect
Most of the ATP is consumed by the Na/K pump in recovering from post-synaptic excitatory activity.

[Data from Attwell and Laughlin, JCBF+M 21:1133 (2001)]

An energy budget for the brain

The importance of continuous delivery of metabolites

Brain energy metabolism

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Glycolysis:</th>
<th>Oxidative metabolism:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Glc → 2 ATP</td>
<td>Glc + →6 O₂ →34 ATP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Metabolic rate</th>
<th>Tissue concentration</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0.3 mM/min</td>
<td>2.0 mM</td>
<td>~7 min</td>
</tr>
<tr>
<td>O₂</td>
<td>1.6 mM/min</td>
<td>0.03 mM (tissue only)</td>
<td>~1 sec</td>
</tr>
<tr>
<td>O₂</td>
<td>0.3 mM (plus blood)</td>
<td>~10 sec</td>
<td></td>
</tr>
</tbody>
</table>

There is very little reserve of O₂ in the brain, requiring a responsive blood flow.

Why is the blood flow change so large?

A large blood flow change prevents tissue pO₂ from dropping during neural activation.

Blood flow and oxygen metabolism are driven in parallel by neural activity

BOLD signal is: increased by an increase of CBF decreased by an increase of CMRO₂

The physical basis of the BOLD effect
Sources of the BOLD signal

Deoxyhemoglobin is paramagnetic, distorting the local magnetic field and reducing the MR signal

Intravascular

MR signal

Red cell

Extravascular

Blood vessel

Volume exchange

Griffeth and Buxton (2010)

Intravascular and extravascular BOLD effects

Extravascular BOLD effect is primarily due to venous vessels rather than capillaries;

Intravascular signal change contributes to the net BOLD effect

Buxton, Rep Prog Physics, 2013

The BOLD signal

(simple model)

Scaling parameter

Fractional CBF change

\[ \Delta S = M \left( 1 - \frac{F}{F_0} \right) \left( 1 - \alpha_n - \frac{1}{n} \right) \]

Griffeth et al (2013)

BOLD response is primarily driven by CBF change, but strongly modulated by:

- M: a scaling factor that depends on: baseline deoxyhemoglobin - TE, field strength
- n: the ratio of fractional changes in CBF and CMRO
- depends on brain region and/or stimulus (and baseline state?)

The BOLD effect

BOLD signal is modulated by the baseline state (M):

- baseline OEF arterial, capillary, venous CBV hematocrit

And the combination of changes:

- various CBF change (\( \alpha_n \))
- CBF/CMRO coupling ratio (n)

\[ \Delta S = \sum M \left( 1 - \frac{F}{F_0} \right) \left( 1 - \alpha_n - \frac{1}{n} \right) \]
Response to a brief stimulus

Motor cortex response to 2 sec of finger tapping

[Math et al, Hum Brain Mapp 13:1 (2001)]
[Buxton, Front. Neuroenergetics 2:8 (2010)]

CBF response

BOLD response

Time (s)

Change (%)

Time (s)

Change (%)

A

B

The Calibrated BOLD Experiment

(Davis, et al 1998)

Increased arterial CO₂ (hypercapnia) raises CBF with no change in CMRO₂.
Neural activation raises CBF but also raises CMRO₂ (less, but not zero).

+ \frac{F}{\Delta F} \left(1 - \frac{F}{F_0} \right)

Measure CBF and BOLD responses to:

Hypercapnia: assume no change in CMRO₂ (1/n=0), calculate M
Activation: use M to calculate n

Combined measurements of BOLD and CBF changes allow calculation of the change in CMRO₂ with activation

Interpreting the BOLD Response:
How can we go beyond mapping where brain activity changes?

Comparing hippocampal activation to a memory task in low risk controls with subjects at risk of AD (family history plus at least one copy of the APOE4 gene)


Is the BOLD difference due to an acute or chronic aspect of disease?

Caffeine

Caffeine blocks adenosine receptors
Adenosine has two effects on the brain:
inhibits neural activity
increases blood flow

Basic questions about CBF and CMRO₂:
How does caffeine alter the baseline state?
How does caffeine alter the response to a stimulus?

Quantitative fMRI: effects of caffeine

CBF and CMRO₂ responses to 200 mg caffeine in 9 abstaining caffeine users

Absolute physiological changes

Baseline: CBF ↓ 27% CMRO₂ ↑ 22%
Stimulus response: ΔCBF ↓ 20% ΔCMRO₂ ↑ 61%

Variability of CBF/CMRO\textsubscript{2} coupling

**A. Effect of Caffeine**
- BOLD
- CBF
- CMRO\textsubscript{2}


Primary finding: No BOLD change, despite reduced baseline flow and increased neural excitability.

**B. Effect of Stimulus Contrast**
- BOLD
- CBF
- CMRO\textsubscript{2}

Basic pattern of our findings:
1. Increasing stimulus strength modulates CBF more than CMRO\textsubscript{2}.
2. Changing the brain state (attention, adaptation and caffeine) to respond differently to a standard stimulus modulates CMRO\textsubscript{2} more than CBF.

**C. Effect of Attention**
- BOLD
- CBF
- CMRO\textsubscript{2}

Low! High!

Attended! Unattended!

What are the roles of excitatory and inhibitory activity?

**Excitatory (E) and Inhibitory (I) activity**

- Stimulus
- E
- I

Nonlinear relationship: Net evoked E depends on the evoked I.

**Excitatory Activity:**
- High energy cost (sodium currents)
- Strong driver of blood flow (Attwell and Iadecola, 2002)

**Inhibitory Activity:**
- Much lower energy cost (no sodium currents)
- Could drive flow up or down (Cauli et al, 2004)
What are the roles of excitatory and inhibitory activity?

**Excitatory (E) and Inhibitory (I) activity**

**Inhibitory Activity:** Adenosine and Nitric Oxide (NO) increase flow (Estrade and DeFelipe, 1998)

**Hypothesis:**
- E strongly drives up both flow and metabolism
- I has opposite effects on flow and metabolism
- CBF/CMRO\(_2\) coupling depends on I/E

**Summary: Brain mapping based on the BOLD effect**

**Biophysics:** Deoxy-hemoglobin distorts the magnetic field around blood vessels, reducing the MR signal

**Physiology:** The O\(_2\) extraction fraction E decreases with activation, so the MR signal goes up

**The BOLD response is a complex reflection of neural activity**

CMRO\(_2\) ↑

Neural Activity ↑

Deoxy-Hb ↓

CBF ↑

BOLD response

CMRO\(_2\) – Cerebral metabolic rate of oxygen
CBF – Cerebral blood flow

**Linear reconstruction of perceived images from human brain activity** (Schoenmakers et al., Neuroimage 2013)