BENG 280A 2014

Functional MRI

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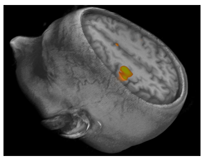
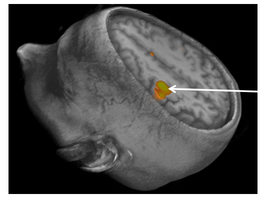


W. M. Keck Center for Functional MRI, UCSD

Mapping Brain Activation



Right handed finger tapping

Activated brain region

The *blood oxygenation level dependent* (BOLD) effect:

The MR signal is slightly stronger when blood is more oxygenated, and blood oxygenation *increases* when neural activity increases

Blood Flow and O_2 Metabolism

Blood flow delivers O_2 and glucose and clears CO_2

Key players:

$CMRO_2$ = cerebral metabolic rate of O_2	1.6 micromol/g-min
E = O_2 extraction fraction	40%
CBF = cerebral blood flow	0.5 ml/g-min
$[O_2]_a$ = total arterial O_2	8 micromol/ml

$$CMRO_2 = E\ CBF\ [O_2]_a$$

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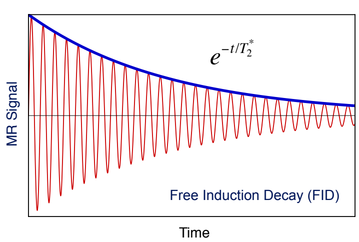
$$\uparrow CMRO_2 = \downarrow E\ \Uparrow CBF\ [O_2]_a$$

E decreases with neural activation! [Fox and Raichle, *PNAS* **83**:1140 (1986)]

Venous deoxy-hemoglobin = $E\ [O_2]_a$ ↓

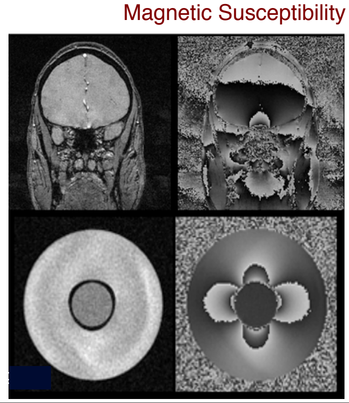
Key properties of the NMR signal



Resonant Frequency: $\nu_0 = \gamma B_0$ (128 MHz at 3T)

Relaxation Time: T_2^* (~50 ms at 3T)

Magnetic Susceptibility Effects

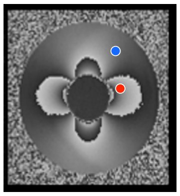


Large scale field gradients:
Susceptibility differences between air, water and bone

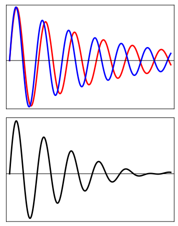
$\Delta B \approx \Delta X\ B_0$

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

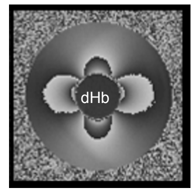


Magnetic field variations within a voxel lead to protons precessing at slightly different rates

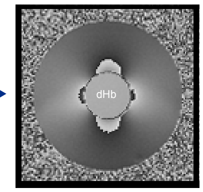
Deoxy-hemoglobin distorts the magnetic field around blood vessels, reducing the MR signal

The BOLD response to activation

Blood flow increases more than O_2 metabolism, increasing venous oxygenation (less deoxy-hemoglobin)

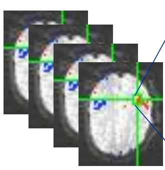


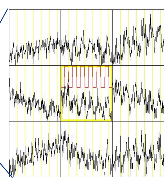
Neural Activation

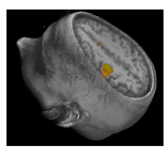


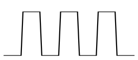
Magnetic field is less distorted, and the MR signal increases

The basic fMRI experiment







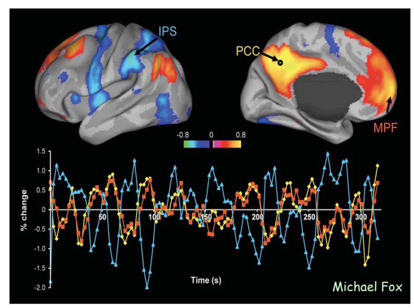


Dynamic imaging during "on" and "off" blocks of the stimulus

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

Map areas of significant correlation overlaid on the anatomical image

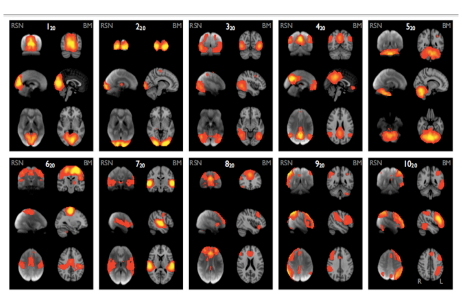
Brain networks from resting state correlations



Functional Connections

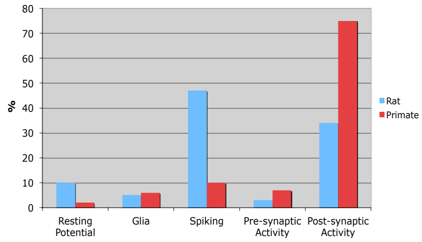
Correspondence of activation maps and resting correlation patterns

(Smith et al, PNAS 2009)



The physiological basis of the BOLD effect

An energy budget for the brain



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)]

The importance of continuous delivery of metabolites

Brain energy metabolism

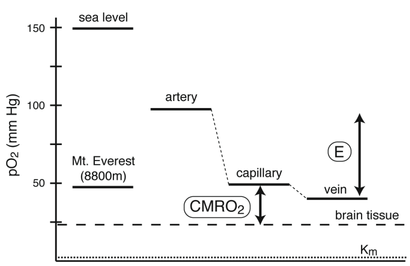
Glycolysis: Glc ⟶ 2 ATP

Oxidative metabolism: Glc + ~6 O_2 ⟶ ~34 ATP

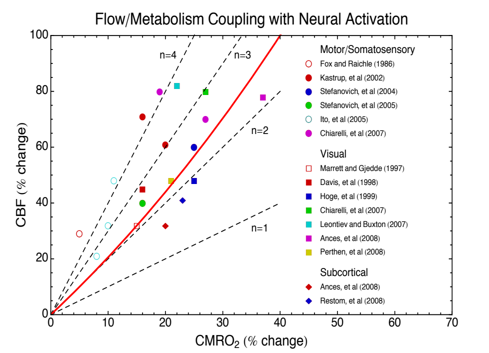
Metabolite	Metabolic rate	Tissue concentration	Lifetime
Glucose	0.3 mM /min	2.0 mM	~7 min
O_2	1.6 mM/min	0.03 mM (tissue only)	~1 sec
O_2		0.3 mM (plus blood)	~10 sec

There is very little reserve of O_2 in the brain, requiring a responsive blood flow

Why is the blood flow change so large?



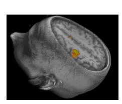
A large blood flow change prevents tissue pO_2 from dropping during neural activation



Buxton, *Frontiers in Neuroenergetics*, 2:8, 2010

$$n = \frac{\%\Delta CBF}{\%\Delta CMRO_2}$$

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



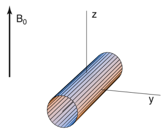
Neural Activity → Energy Metabolism → BOLD response

Neural Activity → Blood Flow → BOLD response

BOLD signal is:
increased by an increase of CBF
decreased by an increase of $CMRO_2$

The physical basis of the BOLD effect

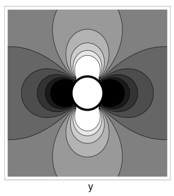
Signal changes when T_2^* changes



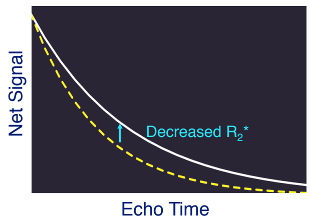
Relaxation rate: $R_2^* = \frac{1}{T_2^*}$

For a small change in R_2^*, the signal change is:

$$\frac{\Delta S}{S_0} = e^{-TE \cdot \Delta R_2^*} - 1 \approx -TE \cdot \Delta R_2^*$$



Magnetic field variations



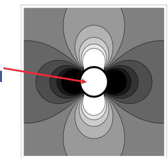
Sources of the BOLD signal

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

deoxy-Hb ↓ MR signal ↑

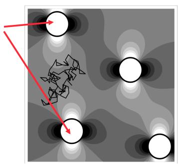
Extravascular

Blood vessel

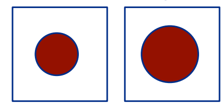


Intravascular

Red cell

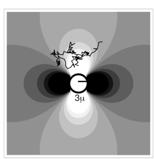


Volume exchange

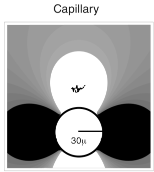


Griffeth and Buxton (2010)

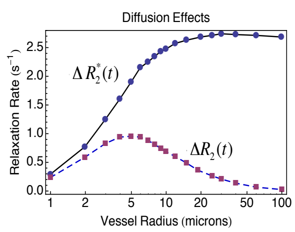
Gradient echo and spin echo BOLD effects



Capillary



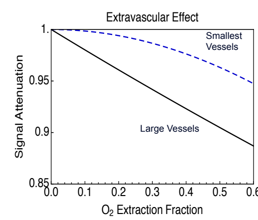
Venule

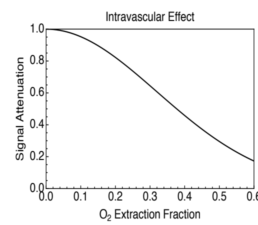


Due to water diffusion, there is an SE-BOLD effect, but weaker than the GE-BOLD effect

Buxton, *Rep Prog Physics*, 2013

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)

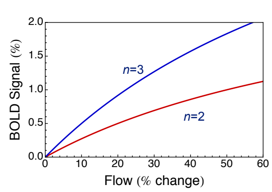
Scaling parameter ↓ Fractional CBF change ↓

$$\frac{\Delta S}{S_0} \approx M \cdot \left(1 - \frac{F_0}{F}\right) \cdot \left(1 - \alpha_V - \frac{1}{n}\right)$$

Correction for CBV change ↑ Coupling parameter ↑

$$M \propto [dHb]_0$$

$$n = \frac{\%\Delta CBF}{\%\Delta CMRO_2}$$



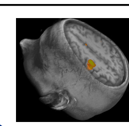
BOLD response is primarily driven by CBF change, but strongly modulated by:

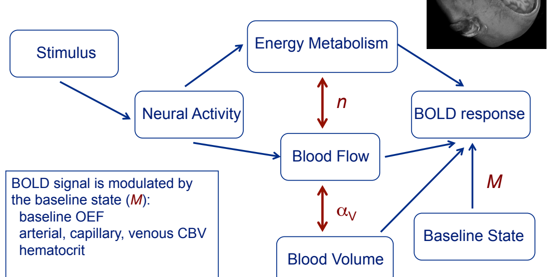
M, a scaling factor that depends on:
- baseline deoxyhemoglobin
- TE, field strength

n, the ratio of fractional changes in CBF and $CMRO_2$
- depends on brain region and/or stimulus (and baseline state?)

Griffeth et al (2013)

The BOLD effect



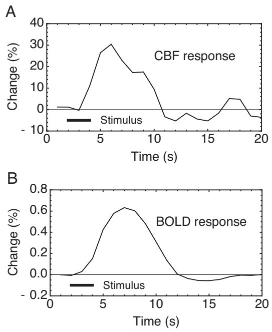


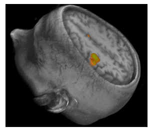
BOLD signal is modulated by the baseline state (*M*):
- baseline OEF
- arterial, capillary, venous CBV
- hematocrit

And the combination of changes:
- venous CBV change (α_V)
- CBF/$CMRO_2$ coupling ratio (*n*)

BOLD signal: $\frac{\Delta S}{S_0} \approx M \cdot \left(1 - \frac{F_0}{F}\right) \cdot \left(1 - \alpha_V - \frac{1}{n}\right)$

Response to a brief stimulus





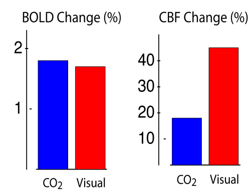
Motor cortex response to 2 sec of finger tapping

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

The Calibrated BOLD Experiment

(Davis, et al 1998)

Increased arterial CO_2 (hypercapnia) raises CBF with no change in $CMRO_2$.
Neural activation raises CBF but also raises $CMRO_2$ (less, but not zero).



$$\frac{\Delta S}{S_0} \approx M \cdot \left(1 - \frac{F_0}{F}\right) \cdot \left(1 - \alpha_V - \frac{1}{n}\right)$$

Measure CBF and BOLD responses to:

Hypercapnia: assume no change in $CMRO_2$ (*1/n=0*), calculate *M*

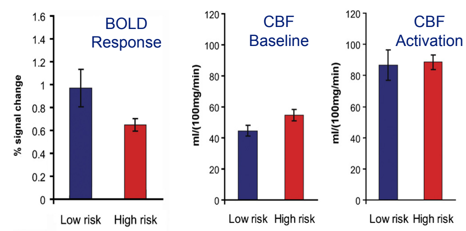
Activation: use *M* to calculate *n*

Combined measurements of BOLD and CBF changes allow calculation of the change in $CMRO_2$ with activation

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

Separating Baseline and Activation Effects

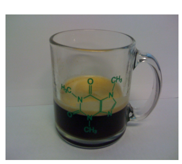
Comparison of hippocampal activation to a memory task in low risk controls with subjects at risk of AD (family history plus at least one copy of the APOE4 gene)



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

AS Fleisher, et al, *Neurobiology of Aging* (2008)

Caffeine



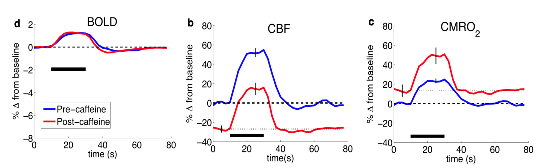
Caffeine blocks adenosine receptors

Adenosine has two effects on the brain:
- inhibits neural activity
- increases blood flow

Basic questions about CBF and $CMRO_2$:
- How does caffeine alter the baseline state?
- How does caffeine alter the response to a stimulus?

Quantitative fMRI: effects of caffeine

CBF and $CMRO_2$ responses to 200 mg caffeine in 9 abstaining caffeine users



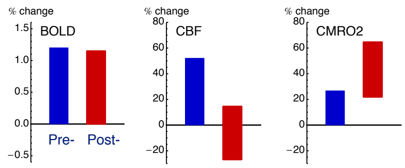
Absolute physiological changes

Baseline:	CBF ↓27%	$CMRO_2$ ↑22%
Stimulus response:	ΔCBF ↓20%	$\Delta CMRO_2$ ↑61%

V Griffeth, et al *Neuroimage* (2010); J Perthen et al *Neuroimage* (2008)

Variability of CBF/$CMRO_2$ coupling

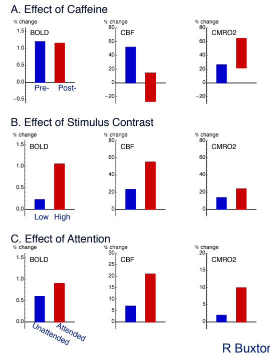
Effect of Caffeine



Griffeth et al, *Neuroimage* 57:809 (2011):
Visual stimulus before and after caffeine
Caffeine blocks adenosine receptors
Adenosine inhibits neural activity but increases flow

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

Variability of CBF/$CMRO_2$ coupling

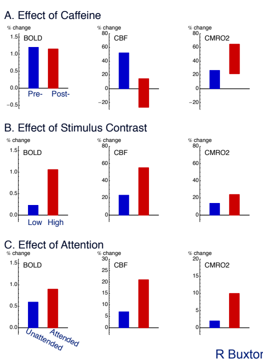


Basic pattern of our findings:

1. Increasing stimulus strength modulates CBF more than $CMRO_2$
2. Changing the brain state (attention, adaptation and caffeine) to respond differently to a standard stimulus modulates $CMRO_2$ more than CBF

R Buxton et al, *Frontiers in Neuroscience* (2014)

Variability of CBF/$CMRO_2$ coupling



Does CBF/$CMRO_2$ coupling vary with the balance of inhibitory/ excitatory activity?

Caffeine: higher *n* when adenosine is more active (higher I/E)

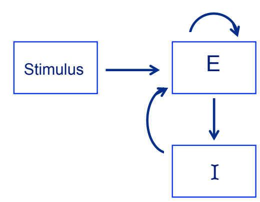
Stimulus Contrast: higher *n* with increasing contrast (electrophys. suggests I/E increases, Contreras and Palmer, 2003)

Attention: higher *n* when unattended (higher I/E?)

R Buxton et al, *Frontiers in Neuroscience* (2014)

What are the roles of excitatory and inhibitory activity?

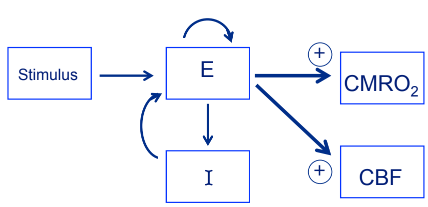
Excitatory (E) and Inhibitory (I) activity



Nonlinear relationship: Net evoked E depends on the evoked I

What are the roles of excitatory and inhibitory activity?

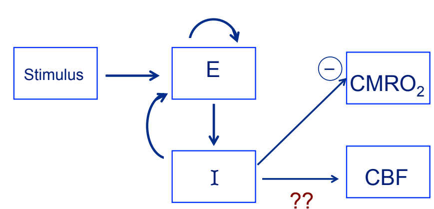
Excitatory (E) and Inhibitory (I) activity



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

What are the roles of excitatory and inhibitory activity?

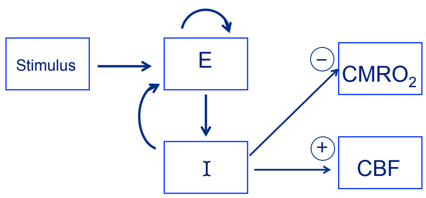
Excitatory (E) and Inhibitory (I) activity



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?

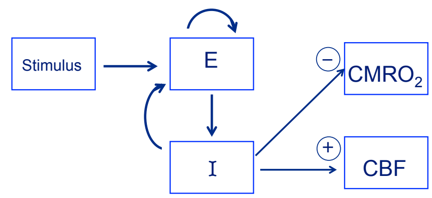
Excitatory (E) and Inhibitory (I) activity



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

What are the roles of excitatory and inhibitory activity?

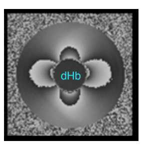
Excitatory (E) and Inhibitory (I) activity



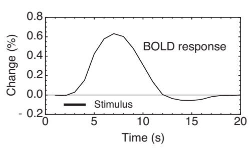
Hypothesis: E strongly drives up both flow and metabolism
I has opposite effects on flow and metabolism
CBF/$CMRO_2$ coupling depends on I/E

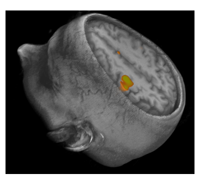
Summary: Brain mapping based on the BOLD effect

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

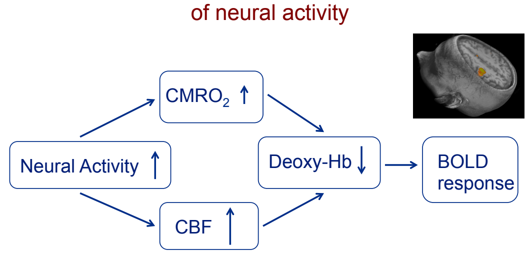


Physiology: The O_2 extraction fraction E *decreases* with activation, so the MR signal goes up





The BOLD response is a complex reflection of neural activity



$CMRO_2$ – Cerebral metabolic rate of oxygen
CBF – Cerebral blood flow

Linear reconstruction of perceived images from human brain activity

(Schoenmakers et al, Neuroimage 2013)