BENG-280A
December 2013

Functional MRI

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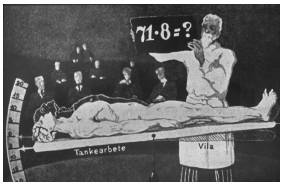
Cerebral Blood Flow and Brain Activation

"... The subject to be observed lay on a delicately balanced table which could dip downwards either at the head or the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system. ..."

William James (*Principles of Psychology*, 1890)



Mosso's experiment?

Figure courtesy of Olaf Paulson

Cerebral Blood Flow and Brain Activation

"... We must suppose a very delicate adjustment whereby the circulation follows the needs of the cerebral activity. Blood very likely may rush to each region of the cortex according as it is most active, but of this we know nothing. "

William James (*Principles of Psychology*, 1890)

Blood Flow and O_2 Metabolism

Blood flow delivers O_2 and glucose and clears CO_2

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

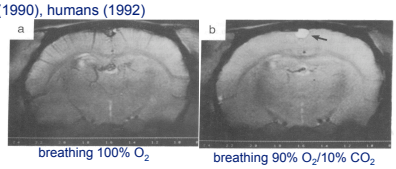
Key players:		Normal Value	Activation
$CMRO_2$	cerebral metabolic rate of O_2	1.6 μmol/ml tissue-min	+12%
E	O_2 extraction fraction	0.4	0.34
CBF	cerebral blood flow	0.5 ml/ml tissue-min	+30%
CBV	cerebral blood volume	0.05 ml/ml tissue	+10%
CMRGlc	cereb. metb. rate of Glucose	0.3 μmol/ml tissue-min	+25%
$[O_2]_a$	total arterial O_2	8 μmol/ml	---

E decreases with activation!

Fox and Raichle (1986)

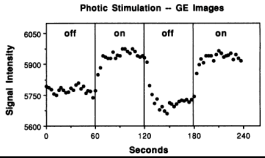
The Blood Oxygenation Level Dependent (BOLD) Effect

Seiji Ogawa: rat model (1990), humans (1992)

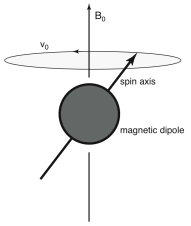


breathing 100% O_2 | breathing 90% O_2/10% CO_2

Ken Kwong (1992): humans

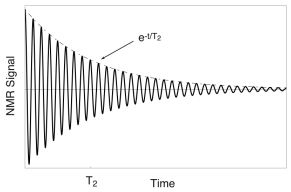


Nuclear Magnetic Resonance (NMR)



The MR Signal

Free Induction Decay (FID)



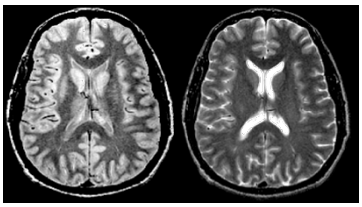
Precession

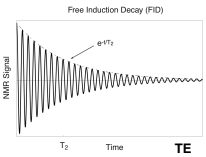
Resonant Frequency: $\nu_0 = \gamma B_0$
(128 MHz at 3T)

Relaxation

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

Image Contrast Depends on the Timing of Data Collection

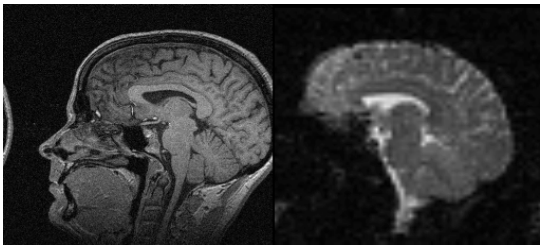




Short TE Long TE

The MR signal depends on the local relaxation time (T2*) and the delay (TE) between excitation and data collection

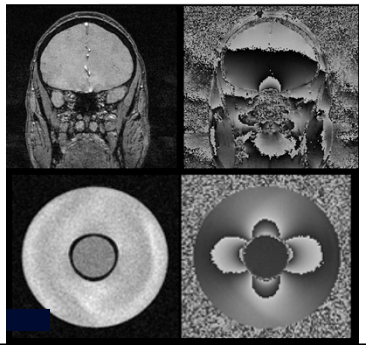
High spatial resolution High temporal resolution



MP-RAGE
Voxel volume: 1 mm^3
Imaging time: 6 min

EPI
Voxel volume: 45 mm^3
Imaging time: 60 msec

Magnetic Susceptibility Effects

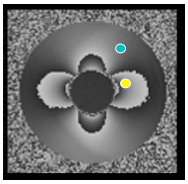


Large scale field gradients:
Susceptibility differences between air, water and bone

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

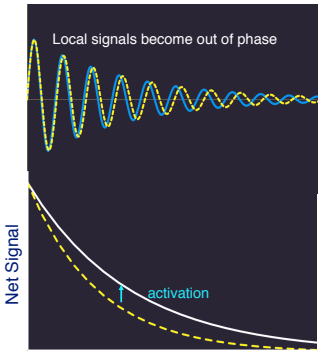
Microscopic field gradients:
Deoxy-hemoglobin alters the susceptibility of blood

T_2* Decay

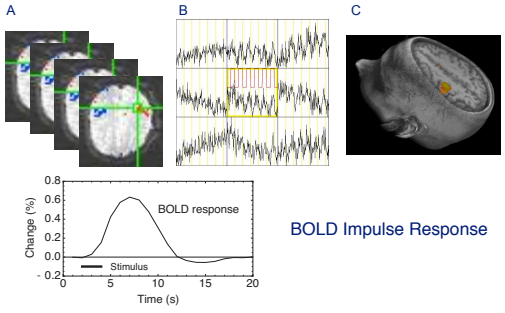


Magnetic field variations within a voxel

Deoxy-hemoglobin distorts the magnetic field around blood vessels



fMRI data acquisition and analysis

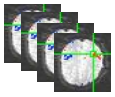


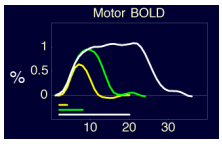
BOLD Impulse Response

Buxton, *Rep Prog Physics*, 2013

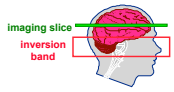
Measuring the Hemodynamic Response to Brain Activation

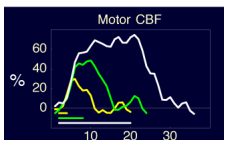
Blood Oxygenation Level Dependent (BOLD) Effect:
Small MR signal changes reflect altered blood oxygenation





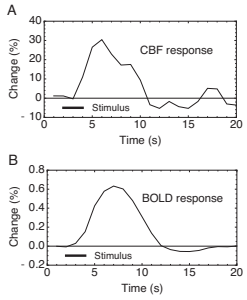
Arterial Spin Labeling (ASL):
Subtraction of tag/control images reflects cerebral blood flow (CBF)

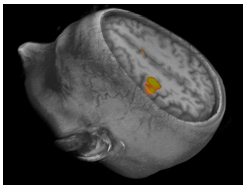




K. Miller, et al (2001)

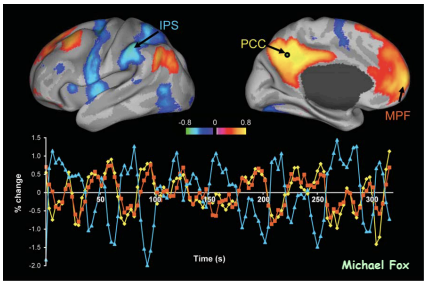
Human brain responses to 2s of finger tapping





Buxton, *Rep Prog Physics*, 2013

Brain Patterns



Functional Connections

Correspondence of activation maps and resting correlation patterns (Smith et al, PNAS 2009)

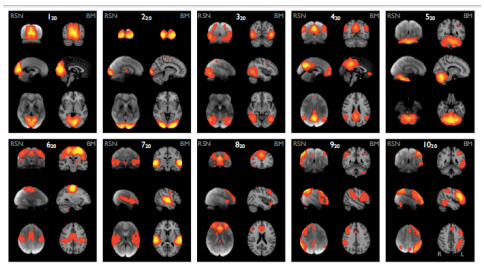
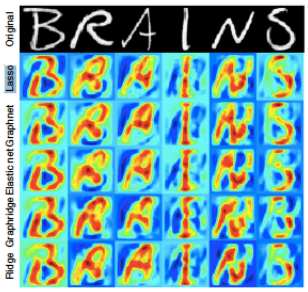


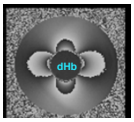
Fig. 1. Ten well-matched pairs of networks from the 20-component analysis of the 29,671-subject BrainMap activation database and (a completely separate analysis of) the 36-subject resting FMRI dataset. This figure shows the 3 most informative orthogonal slices for each pair. (Left column of each pair) Resting FMRI data, shown superimposed on the mean FMRI image from all subjects. (Right column of each pair) Corresponding network from BrainMap, shown superimposed on the MNI152 standard space template image. The networks were paired automatically by using spatial cross-correlation, with mean $r = 0.53$ (0.25:0.79); the weakest of these correlations thus has a significance of $P < 10^{-5}$ (corrected). All ICA spatial maps were converted to z statistic images via a normalized mixture-model fit, and then thresholded at $Z = 3$.

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

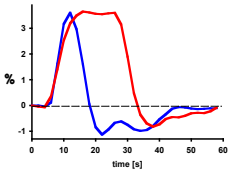


Blood Oxygenation Level Dependent (BOLD) Effect

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

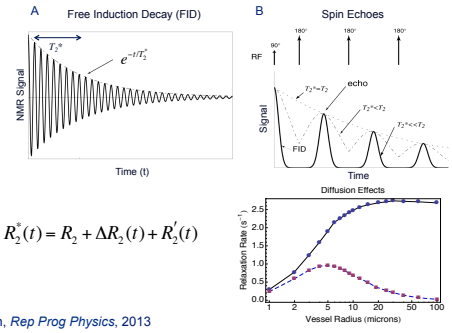


Physiology: The O_2 extraction fraction E *decreases* with activation, so the MR signal goes up



The physical basis of fMRI

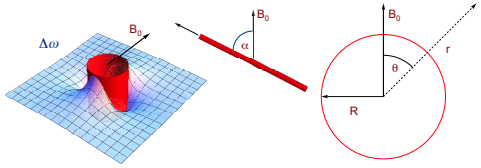
NMR signal decay



$$R_2^*(t) = R_2 + \Delta R_2(t) + R_2'(t)$$

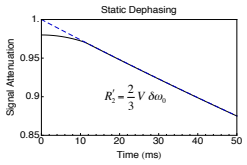
Buxton, *Rep Prog Physics*, 2013

Magnetic field distortions around a magnetized cylinder



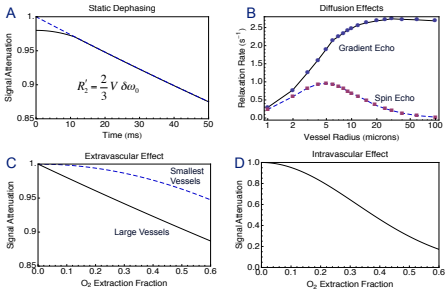
$$\Delta\omega(r,\theta) = \delta\omega_0 \left(\frac{R}{r}\right)^2 \sin^2\alpha \cos 2\theta$$

$$\delta\omega_0 = 2\pi\gamma B_0 \Delta\chi_0 Hct(1-Y)$$



Buxton, *Rep Prog Physics*, 2013

Signal decay due to magnetized blood vessels



Buxton, *Rep Prog Physics*, 2013

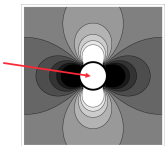
Sources of the BOLD signal

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

deoxy-Hb ↓ MR signal ↑

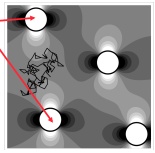
Extravascular

Blood vessel

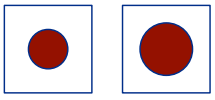


Intravascular

Red cell



Volume exchange



Griffeth and Buxton (2010)

The BOLD signal
(new simple model)

Scaling parameter

Fractional CBF change

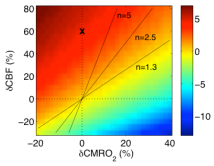
$$\frac{\Delta S}{S_0} \approx M \cdot \left(1 - \frac{F_0}{F}\right) \cdot \left(1 - \alpha_V - \frac{1}{n}\right)$$

Correction for CBV change

Coupling parameter

$$M \propto [dHb]_0$$

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



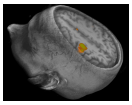
BOLD response is primarily driven by CBF change, but strongly modulated by:

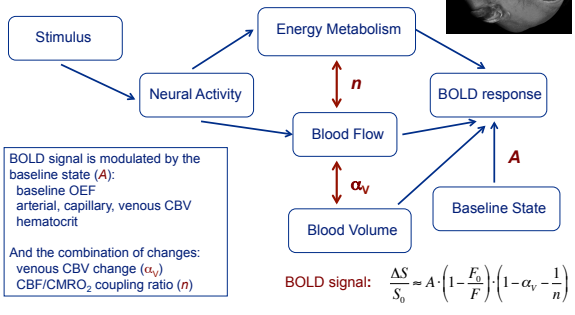
M, a scaling factor that depends on:
- baseline deoxyhemoglobin
- TE, field strength

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

Griffeth and Buxton (2010), Griffeth et al (2013)

The physiological basis of fMRI





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

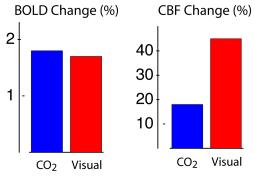
And the combination of changes:
- venous CBV change (α_V)
- CBF/$CMRO_2$ coupling ratio (*n*)

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

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).



$$\frac{\Delta S}{S_0} \approx M \cdot \frac{\Delta F}{F_0} \cdot \left(\frac{1}{1.3} - \frac{1}{n}\right)$$

Measure CBF and BOLD responses to:

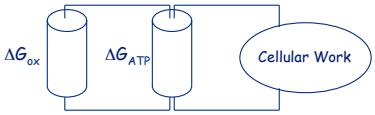
Hypercapnia: assume no change in $CMRO_2$ (*1/n=0*), calculate *M*

Activation: use *M* to calculate *n*

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

The physiological basis of fMRI

Biological Batteries



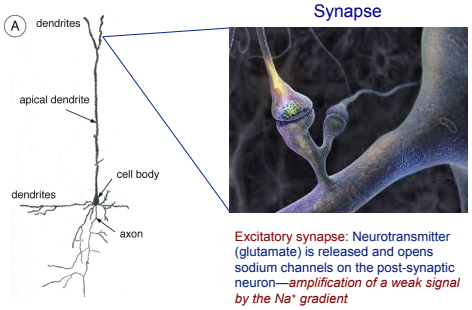
Free energy, either to drive uphill reactions or for signaling, is available from subsystems that are far from equilibrium:

$$\frac{[Pyr][O_2]^3}{[CO_2]^3} \quad \frac{[H^+]_o}{[H^+]_i} \quad \frac{[ATP]}{[ADP][P_i]} \quad \frac{[Na^+]_E}{[Na^+]_I} \quad \frac{[Ca^{++}]_E}{[Ca^{++}]_I}$$

Environment | Mitochondria | Cell | Cell Membrane

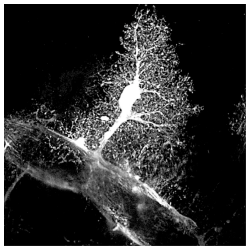
Sodium/Potassium pump

Neural Signaling

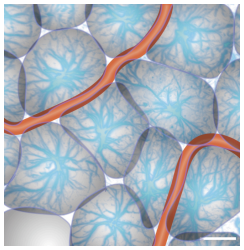


Excitatory synapse: Neurotransmitter (glutamate) is released and opens sodium channels on the post-synaptic neuron—*amplification of a weak signal by the Na⁺ gradient*

Astrocytes bridge neurons and vessels



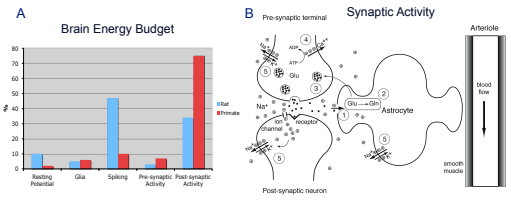
Single astrocyte expressing GFP, 2-photon imaging



Schematic of astrocytes organized along vessels

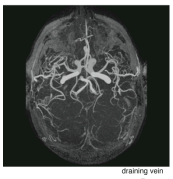
Nedergaard et al, 2003

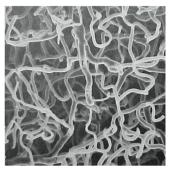
The energy cost of neural activity



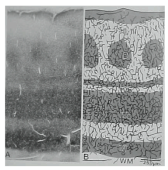
Buxton, *Rep Prog Physics*, 2013

Cerebral Blood Flow

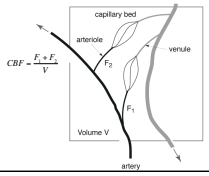




Duvernoy, et al 1981



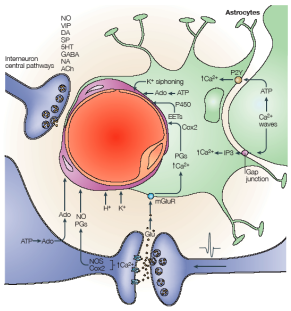
Zheng, et al 1991



CBF = Rate of delivery of arterial blood to an element of tissue:

Human brain: CBF ~ 60 ml/(100 g)-(min)
~ 0.6 ml/ml-min

Mechanisms of CBF Control



Vasoactive ions:
K^+, H^+, Ca^{++}

Diffusible gases:
Nitric oxide (NO),
Carbon monoxide (CO)

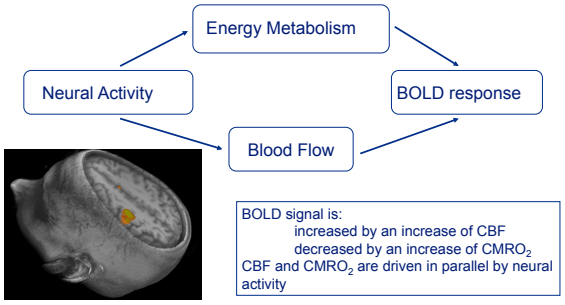
Metabolic factors:
lactate, CO_2, hypoxia,
adenosine

Vasoactive neurotransmitters:
dopamine, GABA, somatostatin,
acetylcholine, NPY, VIP…

Arachadonic acid pathways
COX, P450, EET's, HETE's

Girouard and Iadecola 2006

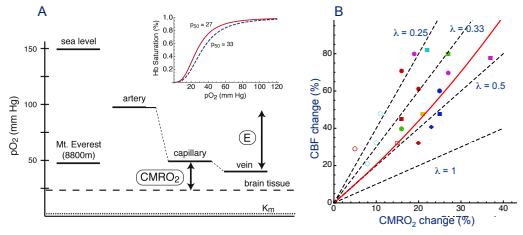
The BOLD response is a complex reflection of neural activity



BOLD signal is:
increased by an increase of CBF
decreased by an increase of $CMRO_2$
CBF and $CMRO_2$ are driven in parallel by neural activity

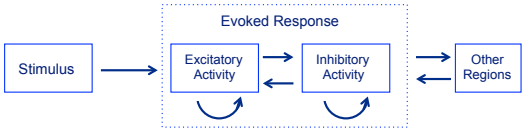
Challenges

Why is there a mismatch of blood flow and O_2 metabolism?

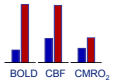


Buxton, *Rep Prog Physics*, 2013

Are flow and metabolism driven by different aspects of neural activity?

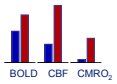


Modulations to produce a stronger response



↑ Stimulus Contrast
n ↑

Liang, et al (submitted)



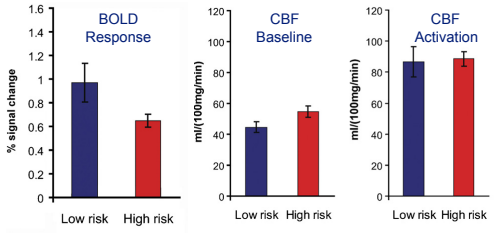
↑ Attention
n ↓

Moradi, et al (2011)

Possibly also modulated by:
stimulus frequency
adaptation
drugs (caffeine)
aging
disease

How can we interpret the BOLD response in disease?

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)

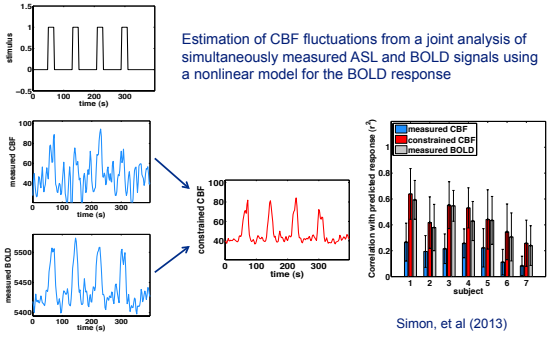


AS Fleisher, et al, Neurobiology of Aging (2008)

How can we make fMRI into a quantitative probe of physiology?

BOLD-Constrained Perfusion

Estimation of CBF fluctuations from a joint analysis of simultaneously measured ASL and BOLD signals using a nonlinear model for the BOLD response



Simon, et al (2013)