UCLA NITP
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Hemodynamics and fMRI Signals

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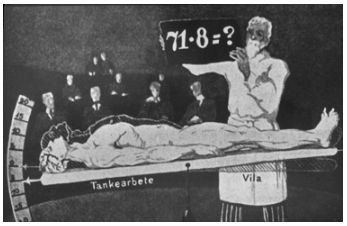
Cerebral Blood Flow and Brain Activation

"... 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

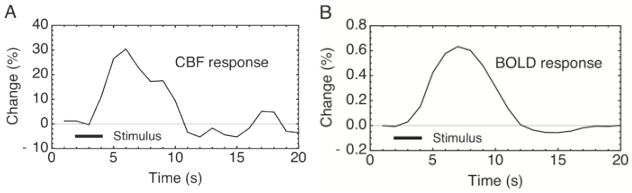
Cerebral Blood Flow and Brain Activation

"... 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)

The Hemodynamic Response to Brain Activation

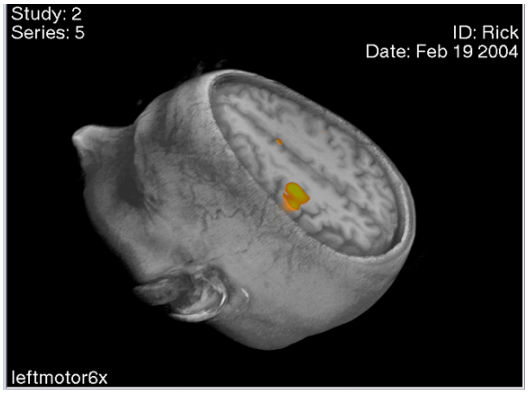
Motor task, human subjects, CBF measured with arterial spin labeling (data from Miller et al, 2001)



Basic questions:
- Why is the flow change so quick?
- Why is the flow change so large?
- Why does blood oxygenation change?

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

Mapping Brain Activation

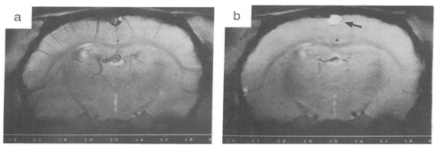


Outline

The BOLD response
The coupling of blood flow and oxygen metabolism
Effects of the baseline physiological state
Dynamics of the BOLD response

The BOLD response

The Blood Oxygenation Level Dependent (BOLD) Effect



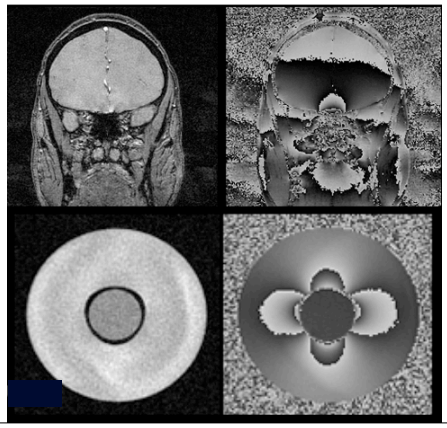
breathing 100% O_2 breathing 90% O_2/10% CO_2

Seiji Ogawa (1990):

Rat model, 7T

Increased blood flow → increased MR signal in and around veins

Magnetic Susceptibility Effects

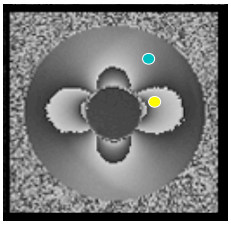


Large scale field gradients: Susceptibility differences between air, water and bone

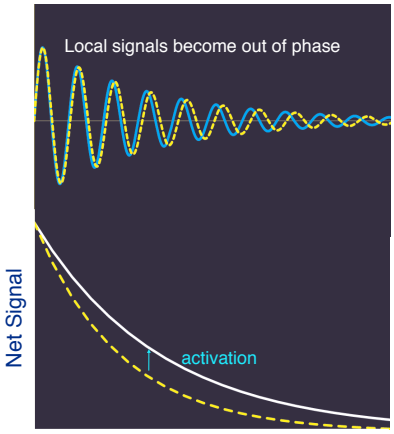
$$\Delta B \approx \Delta X \, B_0$$

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

T_2* Decay



Magnetic field variations within a voxel



Blood Flow and O_2 Metabolism

Blood flow delivers O_2 and glucose and clears CO_2

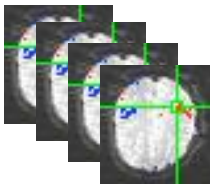
$$CMRO_2 = E \; CBF \; [O_2]_a$$

Key players:

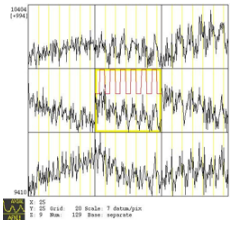
$CMRO_2$ = cerebral metabolic rate of O_2	1.6 micromol/g-min
E = O_2 extraction fraction	40%
CBF = cerebral blood flow	0.5 ml/g-min
CBV = cerebral blood volume	4%
$[O_2]_a$ = total arterial O_2	8 micromol/ml

E decreases with activation!

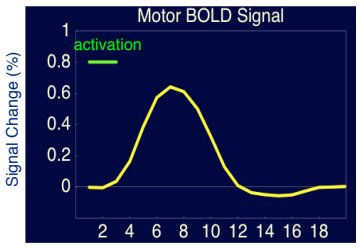
fMRI of Motor Stimulation



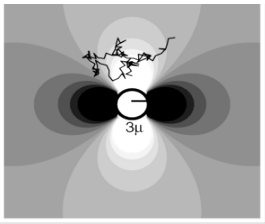
Dynamic Time Series



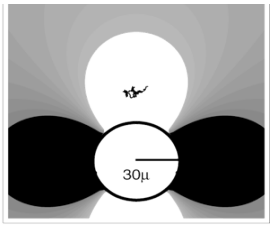
BOLD Impulse Response



Sources of the BOLD Signal Change



Capillary



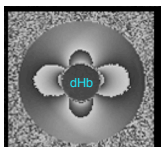
Venule

Signal changes around veins are much larger than the changes around capillaries.

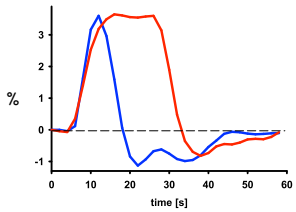
Intravascular signal changes also make a significant contribution to total signal change

Blood Oxygenation Level Dependent (BOLD) Effect

Biophysics: deoxy-hemoglobin is paramagnetic 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 increases

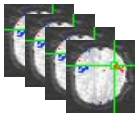


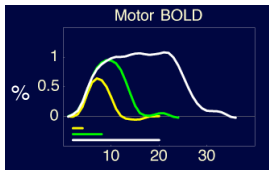
The coupling of blood flow and oxygen metabolism

Measuring the Hemodynamic Response to Brain Activation

Blood Oxygenation Level Dependent (BOLD) Effect:

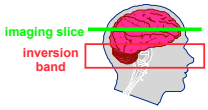
Small MR signal changes reflect altered blood oxygenation

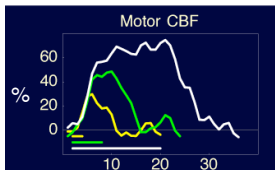




Arterial Spin Labeling (ASL):

Subtraction of tag/control images reflects cerebral blood flow (CBF)





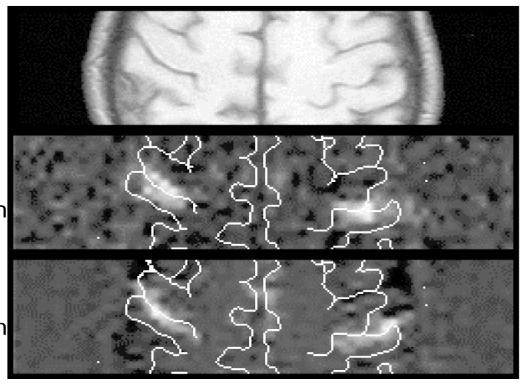
K. Miller, et al (2001)

Locations of BOLD and CBF Changes

Anatomy

Flow Activation

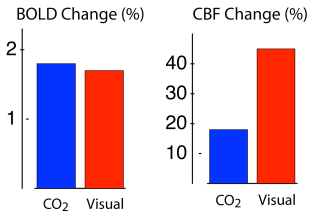
BOLD Activation



The BOLD signal depends on the changes in both CBF and $CMRO_2$

(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)



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

BOLD Signal Model

Davis (1998) Model: BOLD response is primarily driven by %ΔCBF, but strongly modulated by:

M: Scaling factor, proportional to $V_0E_0^{\beta}$

- depends on baseline state

n: the ratio of fractional changes in CBF and $CMRO_2$

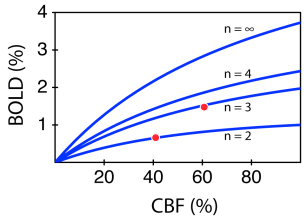
- depends on brain region and/or stimulus (and baseline state?)

Additional parameters are assumed to be constant and uniform:

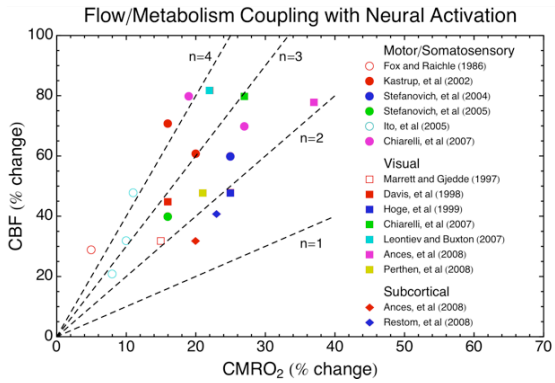
α = 0.4 (CBV/CBF coupling exponent)

β = 1.5 (nonlinear dependence on E)

$$\frac{\Delta BOLD}{BOLD_0} \approx M\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\frac{CMRO_2}{CMRO_{2,0}}\right)^{\beta}\right)$$



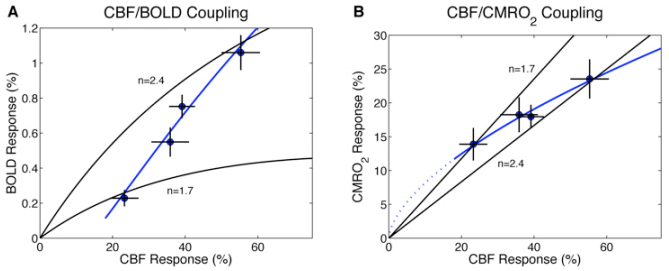
(points are for 20% change in $CMRO_2$)



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

Variability of CBF/$CMRO_2$ coupling with stimulus contrast

9 subjects, visual stimulus with 4 levels of contrast, calibrated BOLD

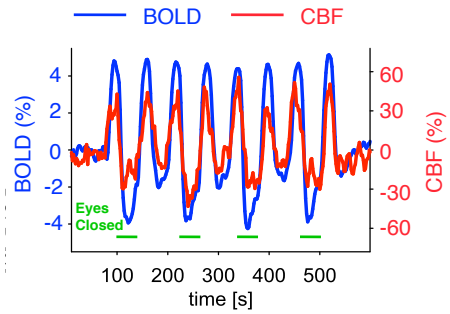


$$n = \frac{\%\Delta CBF}{\%\Delta CMRO_2}$$

Liang, et al, ISMRM (2009)

Effects of the baseline physiological state

Changing the Baseline State: Control Condition

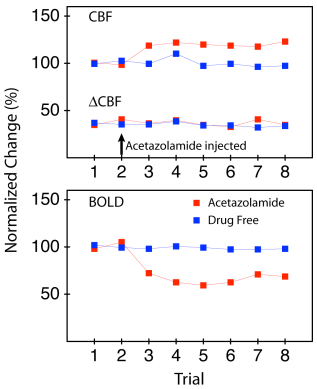


Activation: flickering checkerboard

Deactivation: eyes closed

K. Uludag et al, (2004)

Changing the Baseline State: Drug Response



Brown, et al (J CBF and Metab 23:829, 2003):

Human study of finger tapping response before and after acetazolamide.

BOLD + ASL

20% increase in baseline CBF

Activation response:

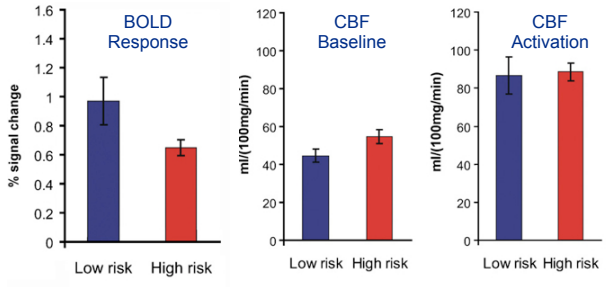
ΔCBF unchanged,

BOLD response reduced 35%

Feed-forward neurovascular coupling?

Separating Baseline and Activation Effects

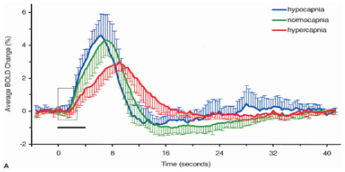
Comparison of hippocampal activation to a memory task in low risk controls with subjects at risk of AD (family history plus at least one copy of the APOE4 gene)



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

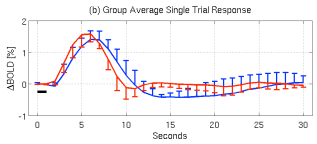
Dynamics of the BOLD response

Baseline Effects: BOLD Dynamics



Cohen, et al (J CBF and Metab 22:1042, 2002):

BOLD response after altering baseline state CO_2



Liu, et al (Neuroimage 23:1402, 2004):

BOLD response after altering baseline state with caffeine;

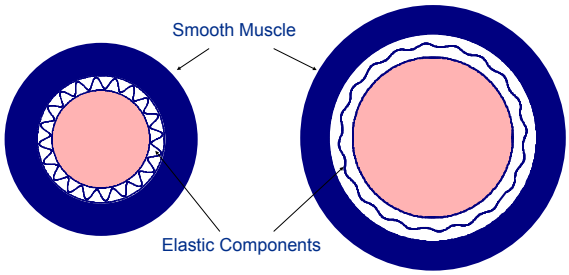
Baseline CBF decreased 24%

Slower dynamics with increased baseline CBF, faster dynamics with reduced baseline CBF

Arterial Compliance Model

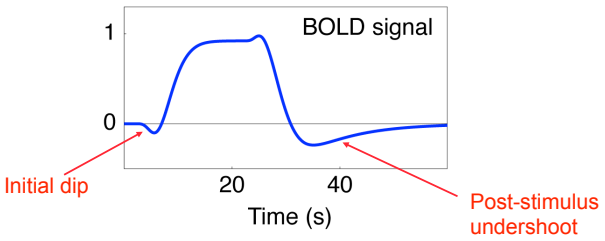
Behzadi and Liu, Neuroimage (2005)

Vessel wall is analogous to two springs in parallel, representing the elastic connective tissue and the smooth muscle components.

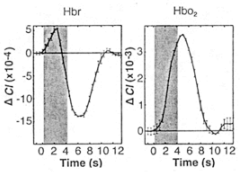


Vasodilators are more effective at lower CBF when compliance is dominated by smooth muscle

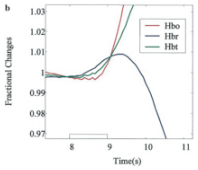
BOLD Transients



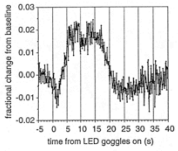
BOLD Dynamics: the Initial Dip



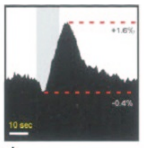
(Malonek and Grinvald, 1996)



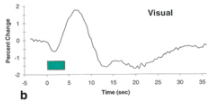
(Mayhew et al, 2001)



(Menon et al, 1995)



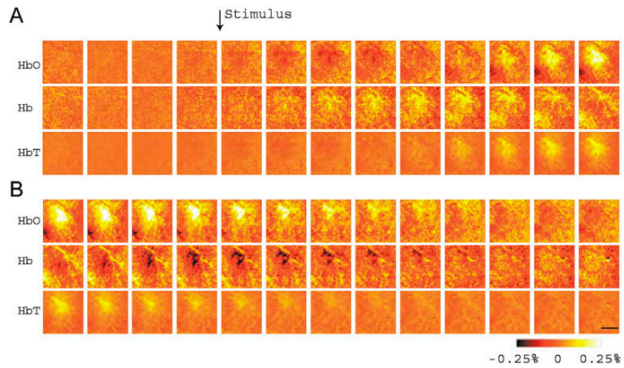
(Kim et al, 2000)



(Yacoub and Hu, 2001)

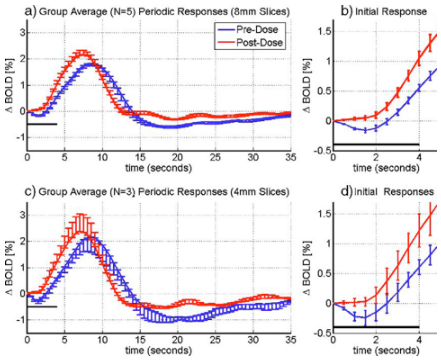
BOLD Dynamics: the Initial Dip

(Devor et al, 2003)

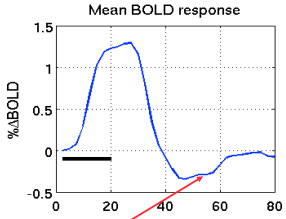


Caffeine Reduces the Initial Dip

(Behzadi and Liu, 2006)



The BOLD Post-Stimulus Undershoot



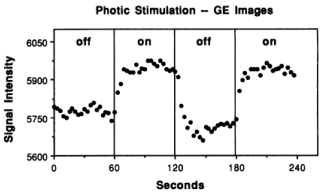
Post-stimulus undershoot

Possible origins:

Neural: coupled deactivation?

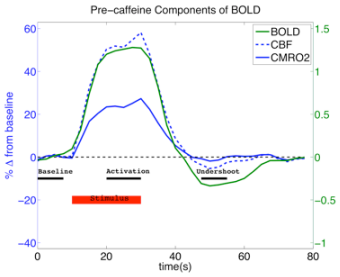
Vascular: elevated blood volume? flow undershoot?

Metabolic: elevated O_2 metabolism?



(Kwong, et al, 1992)

Can a weak CBF undershoot explain a pronounced BOLD undershoot in human studies?



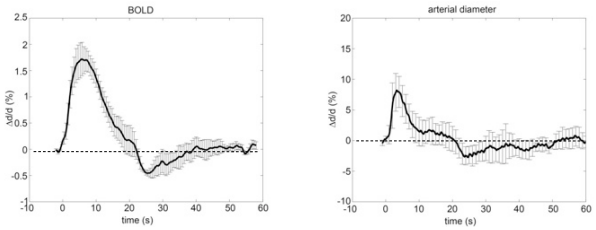
Davis model predicts that the BOLD/CBF response ratio is ~3-5 times larger for a weak CBF-only undershoot than for a large change in CBF (50%) accompanied by a change in $CMRO_2$ (20-25%).

Griffeth, et al (ISMRM 2009): visual stimulation in humans, calibrated-BOLD with dynamic calculation of $CMRO_2$ change

BOLD post-stimulus undershoot is consistent with a weak CBF undershoot that may not reach statistical significance in noisy ASL data

7T BOLD compared with 2-photon microscopy in a rat model

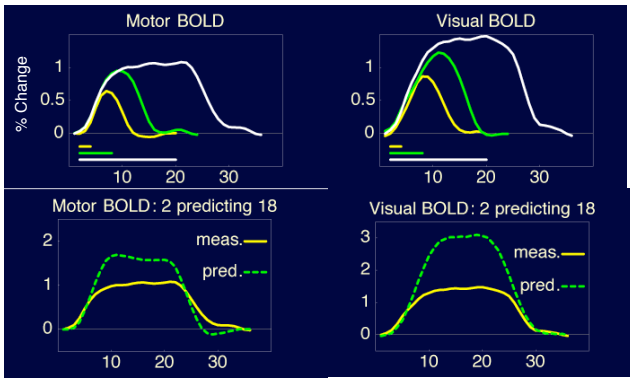
Devor, et al (ISMRM 2009)



The vascular response to activation takes 10's of seconds to settle back to baseline, consistent with the BOLD post-stimulus origin.

In this study, the BOLD undershoot is consistent with a CBF undershoot.

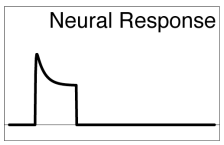
Nonlinearity of the BOLD Response



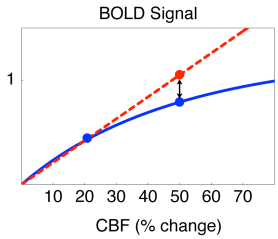
K. Miller, et al (2001)

Nonlinear Responses

Neural adaptation:



BOLD ceiling effect:



Both effects: response to a long stimulus is weaker than predicted from the response to a short stimulus.

Summary

BOLD response: Primarily reflects a change in CBF, but is strongly modulated by:

M, a scaling factor that depends on the amount of deoxy-Hb present in the baseline state and determines the ceiling for the BOLD effect; and,

n, the coupling ratio of blood flow and oxygen metabolism changes with activation.

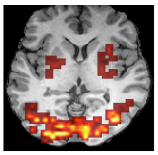
Dynamics: The BOLD response sometimes has transients, such as an initial dip or a post-stimulus undershoot, that are likely due to differences in the dynamics of the CBF, $CMRO_2$ and CBV responses.

Nonlinearity: The BOLD response to a sustained stimulus is weaker than predicted from the response to a brief stimulus, possibly due to neural adaptation or to the ceiling on the BOLD effect.

Baseline state: Physiological manipulations, drugs or disease that alter baseline CBF can affect both the magnitude and the dynamics of the BOLD response.

Interpreting the BOLD Response

The BOLD response depends on the baseline state as well as the activation state, and activation coupling of blood flow and oxygen metabolism may vary, with a significant effect on the magnitude of the BOLD response.

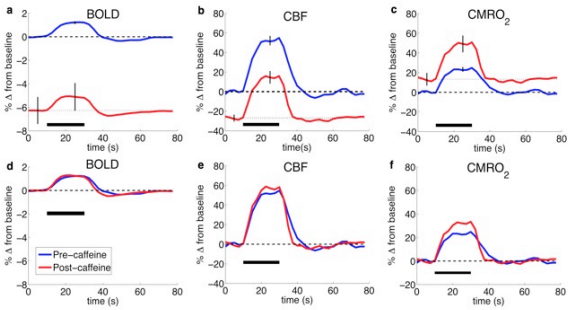


- The BOLD response is good for:
  1. Mapping where an activation occurs (stimulus correlation).
  2. Detecting patterns of coherent fluctuations (resting state networks).
  3. Measuring how the brain responds to different stimuli in the same brain region of a subject.

- But it is difficult to meaningfully compare the *magnitude* of BOLD responses across brain regions, subjects or disease states without additional information (e.g., CBF measurements).

Quantitative fMRI: effects of caffeine

9 subjects, dual echo spiral ASL for simultaneous CBF and BOLD acquisition, before and after caffeine caffeine administration



Griffeth, et al, ISMRM (2010); Perthen et al (2008)

The BOLD Response