UCLA NITP

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Quantitative fMRI

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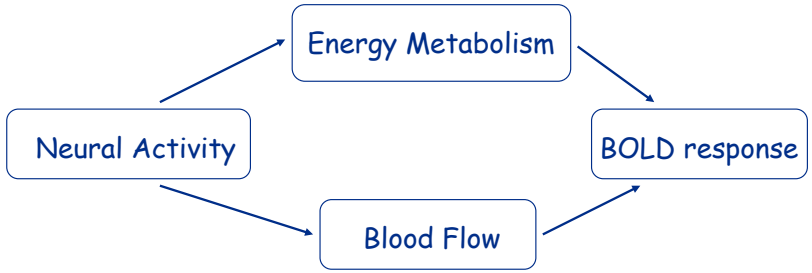
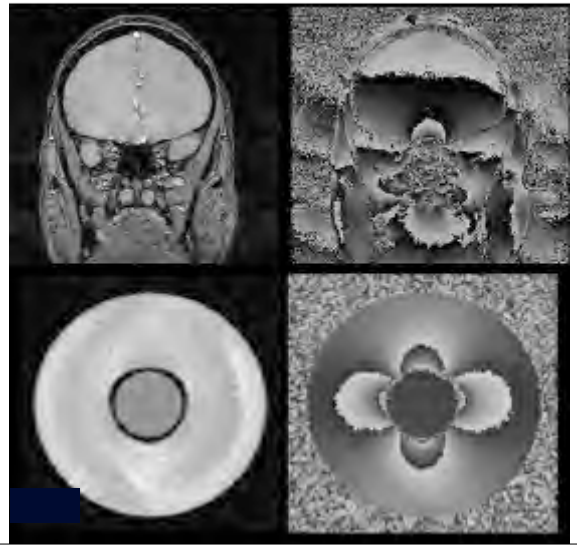
Working Hypothesis



CBF driven primarily by local synaptic activity.
$CMRO_2$ driven by total energy costs (synaptic plus spiking).
BOLD response depends on both!

The BOLD response

Magnetic Susceptibility Effects

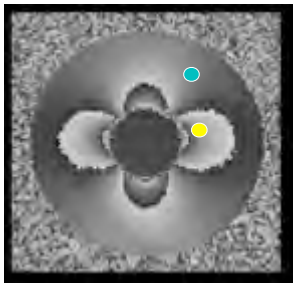


Large scale
field gradients:
Susceptibility differences
between air, water and bone

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

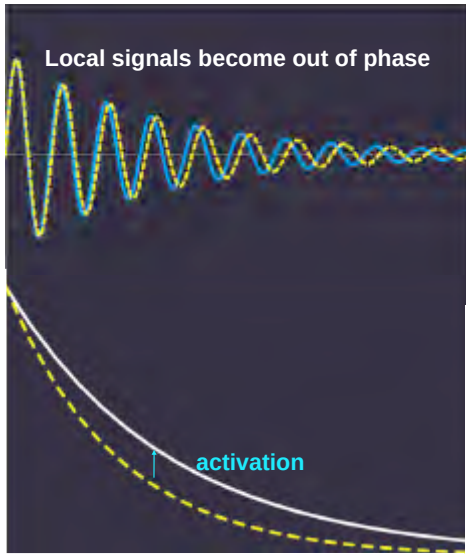
Microscopic
field gradients:
Deoxy-hemoglobin
alters the susceptibility
of blood

T_2* Decay



Magnetic field variations within a voxel

Deoxy-hemoglobin distorts the magnetic field around blood vessels



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

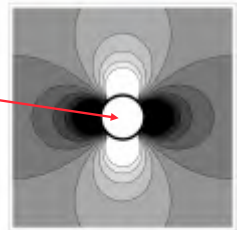
%

Sources of the BOLD signal

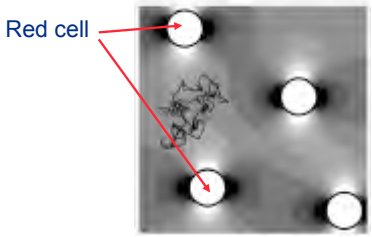
Deoxyhemoglobin is paramagnetic, distorting the local magnetic field and reducing the MR signal

deoxy-Hb ↓ MR signal ↑

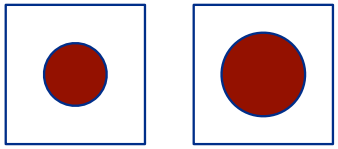
Extravascular



Intravascular



Volume exchange



Griffeth and Buxton (2010)

The BOLD signal
(new simple model)

Scaling parameter

Fractional CBF change

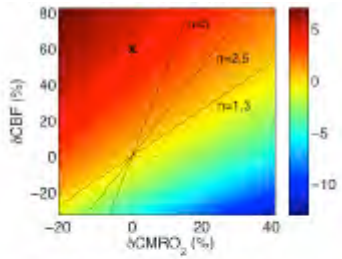
$$\frac{\Delta S}{S_0}$$

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 (in prep)

The BOLD signal (example)

A

Karla Miller, et al (2001)

Scaling parameter

Fractional CBF change

$$\frac{\Delta S}{S_0}$$

Correction for CBV change

Coupling parameter

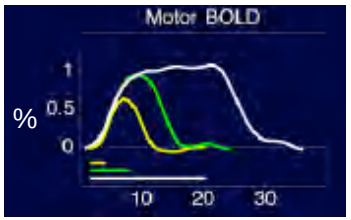
M = 0.1
$\Delta F/F_0$ = 25%
n = 2

BOLD response = 0.67%

Measuring the Hemodynamic Response to Brain Activation

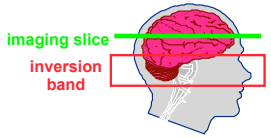
Blood Oxygenation Level Dependent (BOLD) Effect:

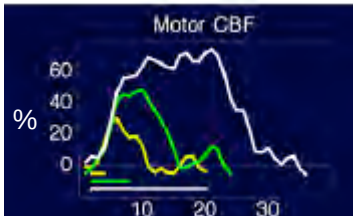
Small MR signal changes reflect altered blood oxygenation



Arterial Spin Labeling (ASL):

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

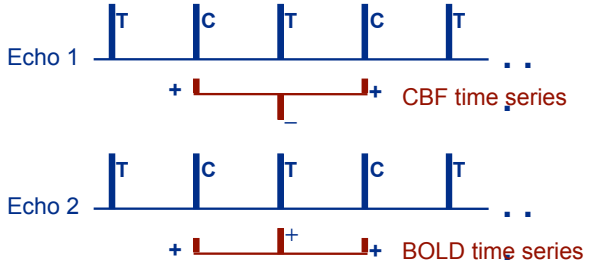




K. Miller, et al (2001)

Simultaneous Flow and BOLD with ASL

Dual-echo spiral acquisition, alternating Tag and Control images

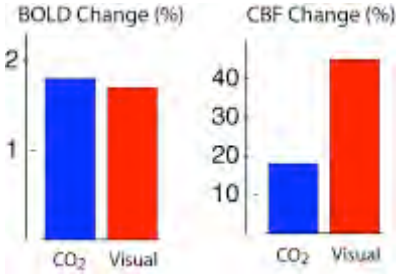


Drift of the BOLD signal is minimized by working with ΔR_2^* calculated from the two echoes of the BOLD time series

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).



$$\frac{\Delta S}{S_0}$$

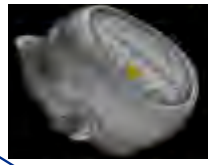
Measure CBF and BOLD responses to:

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

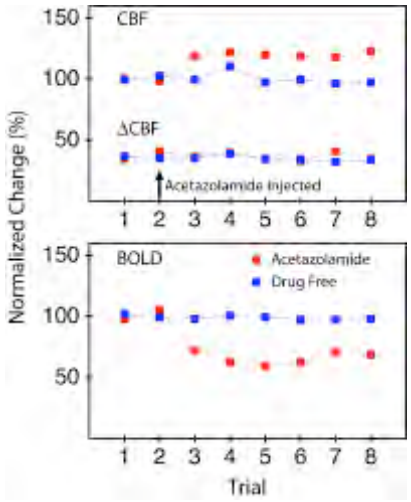
The BOLD response is a complex signal



BOLD signal is driven by CBF changes, but strongly modulated by:
- the baseline state (*M*)
- the CBF/$CMRO_2$ coupling ratio (*n*)

The importance of the baseline state

Changing the baseline state can change *M*



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%

Pre → Post-acetazolamide:

Baseline CBF ↑ M ↓ BOLD ↓

Changing the Baseline State: Control Condition

Activation: flickering checkerboard
Deactivation: eyes closed

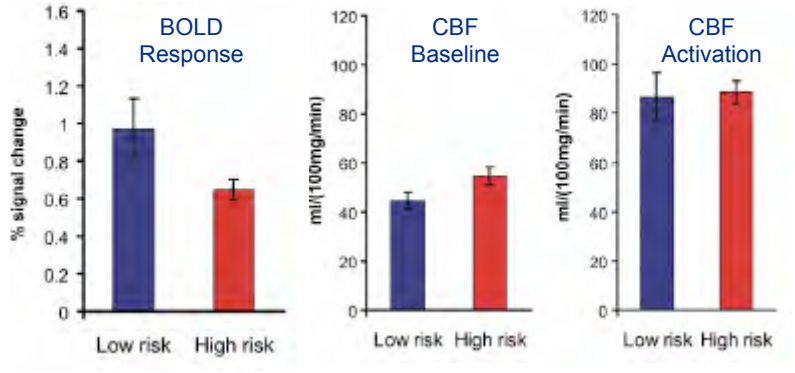
closed → open baseline:

Baseline CBF ↑ M ↓ BOLD ↓

K. Uludag et al, (2004)

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)



Baseline CBF↑ M ? BOLD↓

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

Variation of *M* with (slight) aging

Healthy younger subjects (average of 10, mean age 28 yrs) and older subjects (average of 10, mean age 52 yrs), visual cortex response (flickering checkerboard)

	Baseline CBF ml/100ml/min	% $CMRO_2$ change	*n*	*M* (%)
Younger (21-35 years old)	59.6 ± 9.1	32.3 ± 5.4	2.3 ± 0.2	6.5 ± 0.8
Older (45-60 years old)	*41.7 ± 4.8	32.1 ± 4.6	2.2 ± 0.1	*4.6 ± 0.4

* = p < 0.04

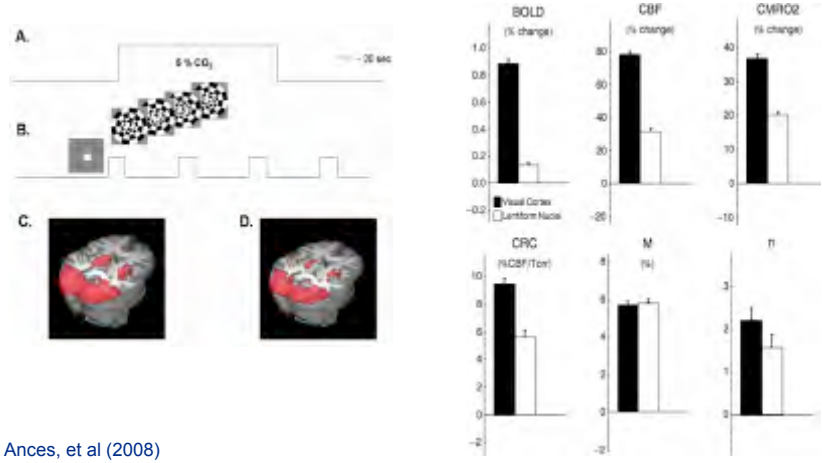
Baseline CBF↓ M↓ BOLD↓

B. Ances, et al (2009)

The variability of flow/metabolism coupling

Flow/metabolism coupling differences between visual cortex and basal ganglia (lentiform nuclei)

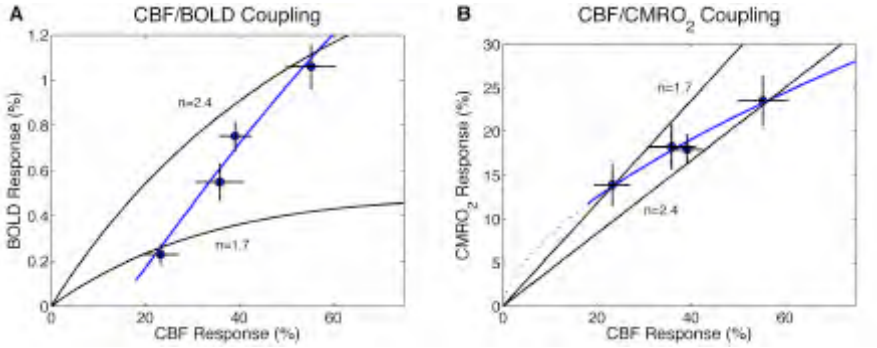
(13 subjects)



B. Ances, et al (2008)

Variability of CBF/CMRO$_2$ coupling with stimulus contrast

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



Response dynamic range: BOLD~4.3, CBF~2.4, CMRO$_2$~1.7

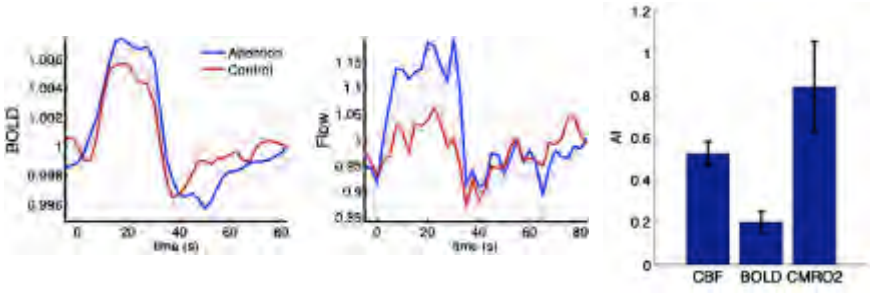
$$n = \frac{\%\Delta CBF}{\%\Delta CMRO_2}$$

Liang, et al, (submitted)

Attention modulates CMRO$_2$ more than CBF

Peripheral low-contrast visual stimulus, 6 subjects

(Moradi et al, Neuroimage 59:601, 2012)



Caffeine

Caffeine blocks adenosine receptors

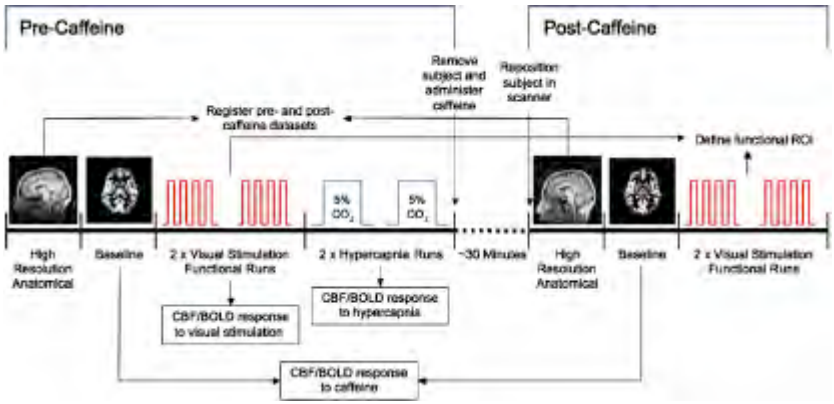
Adenosine has two effects on the brain:
- inhibits neural activity
- increases blood flow

Basic questions about CBF and CMRO$_2$:
- How does caffeine alter the baseline state?
- How does caffeine alter the response to a stimulus?

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

Effect of caffeine on CBF and CMRO$_2$

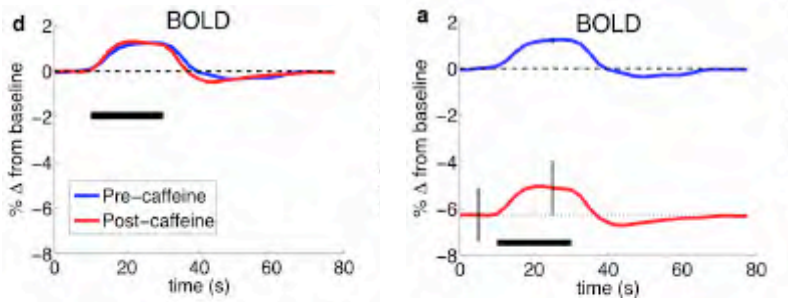
CBF and CMRO$_2$ responses to 200 mg caffeine in 9 abstaining caffeine users



J. Perthen et al (2008)

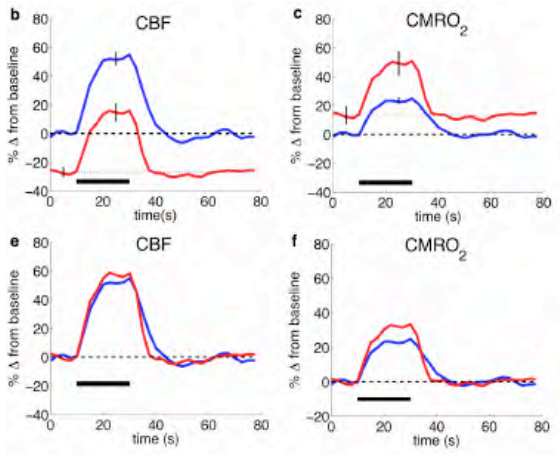
Quantitative fMRI: effects of caffeine

Little effect on the BOLD response except for a baseline shift



Griffeth, et al (2011); Perthen et al (2008)

Quantitative fMRI: effects of caffeine



Large effects on CBF and $CMRO_2$

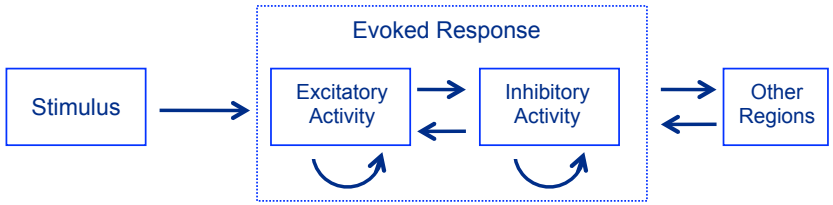
Baseline shifts:
reduced CBF
increased $CMRO_2$

Evoked response:
increased $\Delta CMRO_2$
(reduced *n*)

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

Baseline CBF ↓ M ↑ BOLD ---

Variability of flow/metabolism coupling

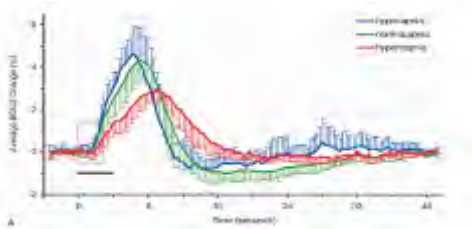


Modulations to produce a stronger response

Griffeth, et al (in prep.)

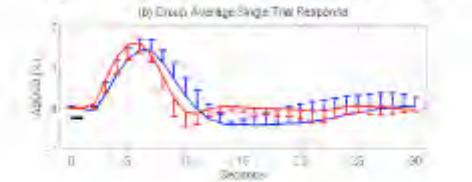
Dynamics of the BOLD response

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)

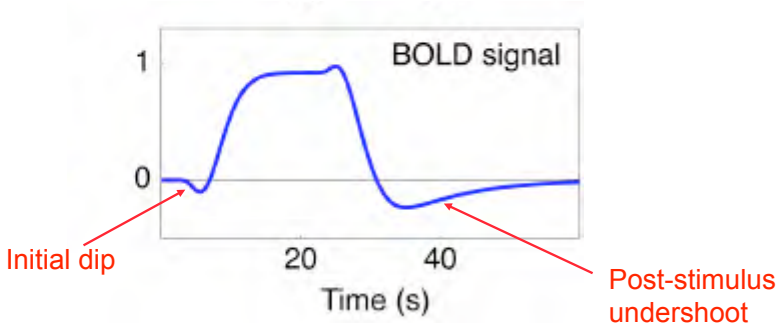
Vessel wall is analogous to two springs in parallel, representing the elastic connective tissue and the smooth muscle components.

Smooth Muscle

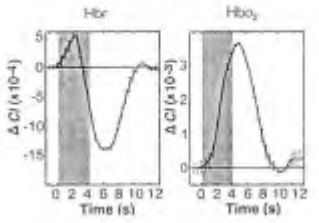
Elastic Components

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

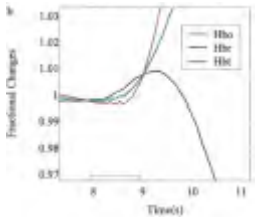
BOLD Transients



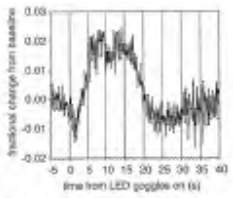
BOLD Dynamics: the Initial Dip



(Malonek and Grinvald, 1996)

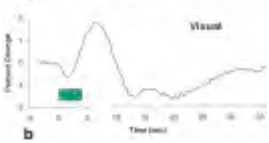


(Mayhew et al, 2001)



(Menon et al, 1995)

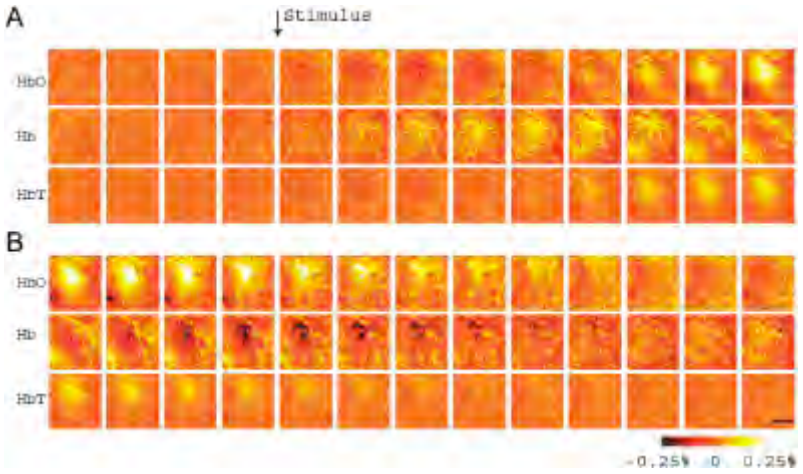
(Kim et al, 2000)



(Yacoub and Hu, 2001)

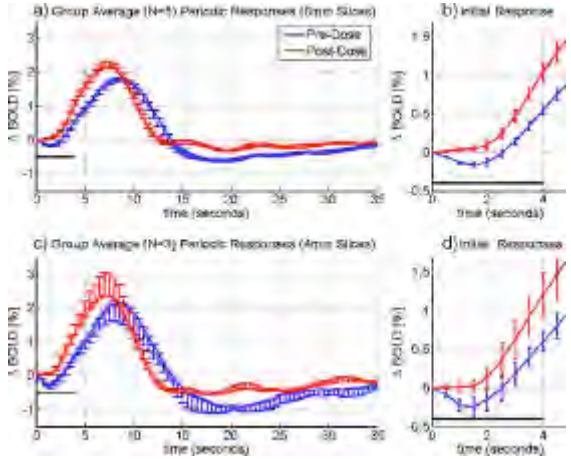
BOLD Dynamics: the Initial Dip

(Devor et al, 2003)

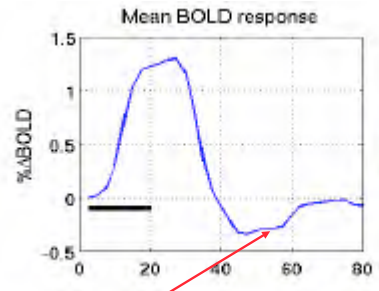


Caffeine Reduces the Initial Dip

(Behzadi and Liu, 2006)



The BOLD Post-Stimulus Undershoot



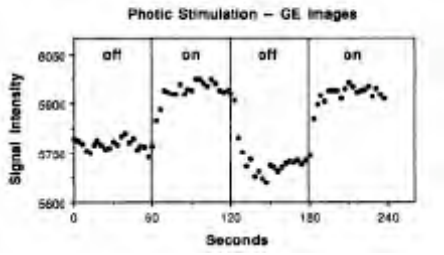
Post-stimulus undershoot

Possible origins:

Neural: coupled deactivation?

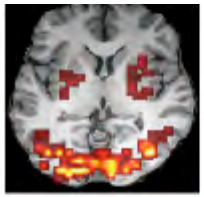
Vascular: elevated blood volume?
flow undershoot?

Metabolic: elevated O_2 metabolism?



(Kwong, et al, 1992)

Interpreting 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. Comparing 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).

Prospects for Quantitative fMRI

Baseline $CMRO_2$

Based on the sensitivity of the T2 of venous blood to oxygenation:
isolate signal of venous blood,
measure with different TE's
(Bolar et al, MRM 2011; Guo and Wong, MRM 2012)

Calibration without inspired gases

Based on T2 characteristics of tissue (R2'):
10 min measurement in the baseline state
(Blockley et al, Neuroimage 2012)

Dynamic CBF and $CMRO_2$ measurements

Quantitative physiological dynamics for complex stimuli

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 (in prep.)