Neurovascular Coupling 
and Methods

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Topics

• Neurovascular factors
• BOLD signal model
• Calibrated fMRI
• Resting State fMRI
• Multimodal Imaging
Test Slide

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Most fMRI studies assume that the BOLD signal is proportional to brain activity. This is a reasonable assumption for basic studies of healthy young unmedicated subjects. However, the assumption is less valid for studies where disease, medication, and age may be a factor.

Boynton et al, 1996
BOLD Signal Chain

Ianetti and Wise, MRI, 2007
Carbon Dioxide

Lower CBF

Higher CBF

Average BOLD Change (%)

Time (seconds)

Cohen et al 2002
(a) Hemodynamic Response Function

- Young; CBF = 65.7
- Old; CBF = 52.4
- Old w/caffeine; CBF = 37.4
Effects of Alzheimer’s Disease Risk

Fleisher et al 2008
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Key properties of the NMR signal

Free Induction Decay (FID)

$e^{-t/T_2^*}$

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

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

Buxton 2014
Signal Decay

Time

0

TE

Some inhomogeneity, Some dephasing

More inhomogeneity, More dephasing, Decrease in MR signal
The overall decay has the form.

$$\exp\left( -R_2^* (\bar{r}) t \right)$$

where

$$R_2^* = \frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T'_2}$$

Due to random motions of spins. Not reversible.

Due to static inhomogeneities. Reversible with a spin-echo sequence.
BOLD Signal Change

Baseline Signal
\[ S_B = M_0 \exp(-TE \cdot R^*_{2,B}) \]

Activation Signal
\[ S_A = M_0 \exp(-TE \cdot R^*_{2,A}) \]

\[ \frac{\Delta BOLD}{BOLD_0} = \frac{S_A - S_B}{S_B} \approx -TE \cdot \Delta R^*_2 \]
BOLD Contrast

Source: Ogawa et al., 1992

Fig. 3. Reducing TE reduces amplitude of the visual stimulation-induced intrinsic signal change. The time course of intrinsic signal changes observed at a fixed caudal position in primary visual cortex are shown for TE = 40 ms and TE = 8 ms. Other experimental conditions were as in Fig. 2, except that patterned-flash visual stimulation was provided between images 15–25 and 35–55.
Multiecho ICA (ME-ICA)

P Kundu et al, Neuroimage, 2012
R2* Depends on dHB

Oxygen binds to the iron atoms to form oxyhemoglobin HbO₂

Release of O₂ to tissue results in deoxyhemoglobin dHBO₂

Some dHB, Some dephasing

More dHB, More dephasing, Decrease in MR signal.
Higher R₂*
BOLD Signal Equation

\[ R_{2,dHB}^* \propto \text{Total dHb} \]

\[ R_{2,dHB}^* = A \cdot CBV \cdot [dHb]_v^\beta \]

Simulations suggest \( \beta \approx 1.5 \) is a reasonable overall value.

\( \beta \approx 2 \)

\( \beta \approx 1 \)

Cassot et al, 2006

Ogawa et al, 1993; Boxerman et al 1995; Hoge et al. 1999
Oxygen Extraction

\[[\text{dHB}]_{\text{venous}} = \text{OEF} \times [\text{O}_2]_{\text{arterial}}\]

OEF = Oxygen Extraction Fraction

Cassot et al, 2009
Blood Flow and Oxygen Metabolism

Cerebral Blood Flow

\[ \text{CBF} \ [O_2]_{\text{arterial}} \]

Oxygen extraction fraction (OEF)

Cerebral Metabolic Rate of Oxygen

\[ \text{CMRO}_2 = \text{OEF} \times \text{CBF} \times [O_2]_{\text{arterial}} \]
Deoxyhemoglobin

\[ [dHB]_{venous} = \text{OEF} \times [O_2]_{arterial} \]
\[ = \frac{\text{CMRO}_2}{\text{CBF}} \]

Cassot et al, 2009
Blood Flow and Oxygen Metabolism

\[ [dHB]_{venous} = \frac{\text{CMRO}_2}{\text{CBF}} \]

Cerebral Blood Flow

CMRO\textsubscript{2}

Cerebral Metabolic Rate of Oxygen

\[ \text{CBF} \quad \rightarrow \quad \text{CMRO}_2 \quad \rightarrow \quad [dHB]_{venous} \quad \leftarrow \quad \text{CBF} \]

Oxygen extraction fraction (OEF)

\[ [\text{dHb}]_{venous} = \frac{\text{CMRO}_2}{\text{CBF}} \]

[dHb]_{venous} = \frac{\text{CMRO}_2}{\text{CBF}}
BOLD Signal Path

\[ R_{2*}^{dHB} = A \text{ CBV} \left[ dHB \right]_{venous}^\beta \]

\[ \approx A \text{ CBV} \left( \text{CMRO}_2 / \text{CBF} \right)^\beta \]
fMRI: Spatial Temporal Dynamics

arteriole capillary bed venule

Neural activity $\rightarrow$ CMRO$_2$

CBF

oxyHb deoxyHb

Initial dip

Positive BOLD

CBF CMRO$_2$ CBV

Post-stimulus Response

CBF CMRO$_2$ CBV

dHb

CMRO$_2$

CBV

dHb
Questions

1. The magnitude of the BOLD signal change will ______ as a function of echo time (TE).

2. An increase in the functional CBF response will tend to ______ the BOLD signal.

3. An increase in the function CMRO$_2$ response will tend to ______ the BOLD signal.

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BOLD Signal Model

Neural Activity ➔ Cerebral Blood Flow (CBF)
Metabolism (CMRO$_2$) ➔ Cerebral Blood Flow (CBF)

deoxyHb ➔ BOLD Signal

\[
\frac{\Delta \text{BOLD}}{\text{BOLD}_0} = -TE \cdot \Delta R_{2,dHB}^* \approx M \left(1 - f^{\alpha-\beta} m^\beta \right)
\]

Grubb’s Relation; $\alpha \approx 0.38$

\[
\frac{\text{CBV}}{\text{CBV}_0} = \left(\frac{\text{CBF}}{\text{CBF}_0}\right)^\alpha
\]

\[
f = \frac{\text{CBF}}{\text{CBF}_0}; \quad m = \frac{\text{CMRO}_2}{\text{CMRO}_{2,0}}
\]

Davis et al. 1998; Hoge et al. 1999
\[ \frac{\Delta BOLD}{BOLD_0} \approx M \left( 1 - f^{\alpha - \beta} m^{\beta} \right) \]

Maximal BOLD signal

\[ M = TE \cdot A \cdot CBV_0 \cdot [dHb_0]^\beta \]
CBF/CMRO\textsubscript{2} Coupling Factor

\[ n = \frac{\% \Delta \text{CBF}}{\% \Delta \text{CMRO}_2} = \frac{f - 1}{m - 1} \]
Why is the blood flow change so large?

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

Buxton 2013
\[
\frac{\Delta \text{CBF}}{\text{CBF}_0} \approx M \left( 1 - f^{\alpha - \beta} m^\beta \right)
\]

CBF/CMRO\text{$_2$} Coupling Factor

\[n = \frac{\% \Delta \text{CBF}}{\% \Delta \text{CMRO}_2} = \frac{f - 1}{m - 1}\]
Different ways to accomplish the same change in BOLD

n=2.5; M = 8.0

n=2.50; M = 6.3

n=2.15; M = 8.0
Effect of Age on CBF and BOLD Responses in the Hippocampus

Restom et al, NIMG 2007
Neural Activity $\Rightarrow$ Cerebral Blood Flow $\Rightarrow$ Metabolism (CMRO$_2$) $\Rightarrow$ Cerebral Blood Volume $\Rightarrow$ deoxyHb $\Rightarrow$ BOLD Signal

**Graphs:**
- **CBF:**
  - Y-axis: % increase
  - X-axis: Time
  - Lines: Young (Exp) and Old (Exp)

- **BOLD:**
  - Y-axis: % increase
  - X-axis: Time
  - Lines: Young (Exp), Old (Exp), and Old (Sim)
Effect of age on CBF and BOLD

- (f) Baseline CBF
- (b) % ΔBOLD($R_2^*$)
- (c) % ΔCBF

ΔCMRO$_2$

Young | Old
Normalized CMRO$_2$
Young | Old
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Neural Activity $\rightarrow$ Metabolism (CMRO$_2$) $\rightarrow$ Cerebral Blood Flow $\rightarrow$ ASL Signal

Cerebral Blood Flow $\rightarrow$ Cerebral Blood Volume $\rightarrow$ deoxyHb $\rightarrow$ BOLD Signal
Calibrated fMRI (Davis et al 1998)

\[ b \approx M \left(1 - f^{\alpha-\beta} m^\beta \right) \]

Assume CO2 inhalation doesn’t change CMRO₂

\[ M = \frac{b_{CO₂}}{1 - f^{\alpha-\beta}} \]

\[ m^\beta = \left(1 - \frac{b}{M} \right) f^{\alpha-\beta} \]
Age dependence of hemodynamic response characteristics in human functional magnetic resonance imaging

Claudine J. Gauthier a,b,+, Cécile Madjar b, Laurence Desjardins-Crépeau b,c, Pierre Bellec b,d, Louis Bherer b,c, Richard D. Hoge a,b
\[ M = \frac{b_{CO_2}}{1 - f_{CO_2}^{\alpha-\beta}} \]

\[ m^\beta = \left( 1 - \frac{b}{M} \right)^{f_{\alpha-\beta}} \]

**A**

Bar graph showing differences in M (%): GM, LF, RF, P.

- Younger
- Older

**B**

Bar graph showing differences in %ΔCMRO2: LF, RF, P.

- Younger
- Older
Questions

1. If baseline CBF is increased and all other factors are relatively constant, then M will tend to _____

2. If M increases and all other factors are held constant, the BOLD signal will ______.

2. If M increases but the measured BOLD and CBF signal remains the same, then our estimate of the cerebral rate of oxygen metabolism (CMRO$_2$) would ______

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Emerging Methods

Hypercapnia/hyperoxia $\rightarrow$ estimates of absolute CMRO$_2$

QUIXOTIC: Venous T$_2$ $\rightarrow$ venous O$_2$

Bolar et al 2011
\[ R_2^* = R_2' + R_2 \]

Use asymmetric spin-echo to estimate \( R_2' \)
Then scale to estimate M without use of hypercapnia

Blockley et al 2015
Calibrated fMRI

- Calibrated fMRI based on the Davis model can provide quantitative measures of functional responses, but is sensitive to assumptions.

- Can be difficult to apply to cognitive tasks and special populations, due to low sensitivity of ASL CBF measures.

- The need for breathhold or hypercapnia can also be an issue. Hyperoxia-based methods have been proposed as an alternative.

- Emerging methods are aimed at (a) providing absolute measures of CMRO$_2$ and OEF or (b) simplifying the acquisition process (e.g. eliminate hypercapnia).
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Resting-State fMRI

Fox and Raichle 2005; Iannetti and Wise 2007; http://www.youtube.com/watch?v=VaQ66lDZ-08&feature=plcp
Resting-State BOLD Connectivity

Task-Related Motor Activation Map

Resting State Correlation Map

Resting State fMRI Signals From Left and Right Motor Cortices
Decrease in HDR amplitudes leads to a decrease in correlation between BOLD measures of 0.54 to 0.41.

Liu, NIMG 2013
Calibrated fMRI of Resting-state Connectivity

Wu et al, NIMG 2009
Calibrated fMRI of Resting-state Measures

As BOLD signals get smaller

\[
\left( \frac{CMRO_2}{CMRO_{20}} \right)^\beta = \left( \frac{CBF}{CBF_0} \right)^{\beta - \alpha} \left[ 1 - \left( \frac{\Delta BOLD}{BOLD_0} \right) \right]
\]

CMRO\textsubscript{2} estimates are driven primarily by the CBF measures

Restom et al 2008; Rack-Gomer 2011
Case Study: Effects of Hypercapnia on Functional Connectivity

Biswal et al, JCBFM 1997

Xu et al, JCBFM 2011
Chen and Pike, JCBFM, 2010

\[ \text{CBF}_0 \uparrow \rightarrow \text{dHB}_0 \downarrow \rightarrow \text{M} \downarrow \rightarrow \text{BOLD} \downarrow \]

\[ \Delta\text{CBF} \]

\[ \text{CMRO}_{2,0} \downarrow \]

CMBF Responses

\( r = 0.74; p = 1.50 \times 10^{-2} \)

\( r = 0.79; p = 6.31 \times 10^{-3} \)

Xu et al, JCBFM 2011

\( \Delta \text{CBF} \)

Liau et al NIMG 2009
**Case Study:** Effects of Caffeine on Functional Connectivity

Functional connectivity maps for representative subject

Wong et al; NIMG 2012; Rack-Gomer et al, NIMG, 2009
CBF₀ ↓ → dHB₀ ↑ → M ↑ → BOLD ↑
CMRO₂,₀ ↑ → ?

n ↓ → BOLD ↓

Chen and Parrish 2009; Rack-Gomer et al, NIMG, 2009; Griffeth et al 2011; Xu et al ISMRM2014, p. 4168
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Case Study: Effects of Caffeine Revisited

4 OR 6

PRE

Caffeine

OR

Placebo

POST
Inverse Model

Forward Model

Sensor Space

Source Space

Brookes et al 2011

Group Analysis

Single Subject Analysis
Higher vigilance $\rightarrow$ lower GS $\rightarrow$ more anticorrelation

Wong et al 2013
$\Delta$ vigilance = post dose - pre-dose vigilance

$\Delta$ GS Amplitude = post dose - pre-dose GS Amplitude

Wong et al 2013
Summary

• The BOLD signal is a complex function of the baseline state and changes in blood flow, volume, and metabolism.
• Differences in the BOLD signal do NOT always reflect differences in neural activity.
• Instead they make reflect differences in the baseline vascular or metabolic state.
• Calibrated fMRI can provide additional insights into differences in brain activity, especially in the presence of disease, medication, and age. However, it is a technically challenging method and may be difficult to apply in certain populations.
• Application of calibrated fMRI to resting-state fMRI needs further study.
• Multimodal imaging can provide insights that are not achievable with fMRI alone.
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Arterial spin labeling (ASL)

1: Tag by Magnetic Inversion

2: Control - Tag = ΔM ∝ CBF
Whole brain CBF Images from 1 subject scanned at each of the 4 sites are shown below. Grayscale bar indicates units of ml/(100g-min).
**ASL Time Series**

Wait →

- Tag by Magnetic Inversion
- Control

Image 1: 
-0.5

Image 2: 1
+0.5

Image 3: -0.5
-1

Image 4: +0.5

Perfusion Images

Raw ASL time series

-0.5 to +0.5