Activation processes consume energy (ATP)...
which comes from oxidative metabolism of glucose (+60-80%)...
supported by extravascular transport of nutrients and elimination of waste.

**BOLD Contrast**

- **Resting state**
  - arterial
  - $\text{HbO}_2$
  - $\text{Hb}$
  - venous

- **Stimulated state**

**BOLD ($\Delta T2^*$) Contrast**

- $T2^*$
- Activated ($\text{HbO}_2$)
- Resting ($\text{Hb}$)

Signal change maximized when $TE \sim T2^*$.
BOLD Contrast

\[ \text{BOLD signal is an epiphenomenological indicator of neural processing: many confounds to quantification} \]

- HRF characteristics
  - Amplitude
  - Latency
  - Baseline rCBF

- Physiological noise
  - Cardiac pulsation
  - Respiration
  - Head motion

\[ \rightarrow \text{calibration}\]

\[ \rightarrow \text{denoising}\]

fMRI Calibration: Motivation

Examples where quantifying activation may be important in drawing inferences about cognition:

- Inter-group comparisons
  - Age, health
- Longitudinal studies
  - Normal/abnormal development, therapy
- Multi-center studies
  - fBIRN schizophrenia fMRI trial

Working Memory

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial</strong></td>
<td><img src="#" alt="Spatial Low" /></td>
<td><img src="#" alt="Spatial Low" /></td>
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<tr>
<td></td>
<td><img src="#" alt="Spatial Medium" /></td>
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<tr>
<td></td>
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<td><img src="#" alt="Spatial High" /></td>
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<td><img src="#" alt="Verbal Medium" /></td>
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<tr>
<td></td>
<td><img src="#" alt="Verbal High" /></td>
<td><img src="#" alt="Verbal High" /></td>
</tr>
</tbody>
</table>

M. Thomason, NI 2009

Group comparisons

Do different z-scores represent:

- differences in signal (numerator)?
- differences in baseline brain noise (denominator)?
- hemodynamic differences?
- neural differences?
- other differences- e.g. behavioral?
Multicenter Neuroimaging Studies

- Potential use of MRI/fMRI as a biomarker
  - structural/functional differences may predict disease;
  - large study numbers are necessary for biodiversity
- ADNI study using VBM methods to study cortical thickness
- fBIRN schizophrenia study

Generate large data sets rapidly

Access wide or targeted demographic characteristics

Provide image databases for other analyses

Multicenter MRI/fMRI

- Desire to pool results across sites equally requires standardization
- Different vendors may have incompatible characteristics/ definitions- e.g.
  - pulse sequence contrast in FSPGR vs MPRAGE
  - meaning of BW/echo spacing in EPI imaging -> artifacts/SNR
  - k-space apodization filters -> smoothness/CNR
  - grad distortion correction
  - geometric calibration precision
  - temporal stability

Multicenter MRI

Goal: Develop methods for pooling fMRI data on 50 schizophrenics at each of 11 centers
  - load manipulation in emotional WM

Approaches: Reduce intersite/intersubject variability
  - scanner QA
  - measure/calibrate/normalize
    - BOLD sensitivity
    - HRF/vasoreactivity
fMRI Calibration: Motivation

What’s the problem?

Activation map derives from thresholding a statistical estimate of BOLD CNR:

$$y_{\text{meas}}(t) = \beta_{\exp} d_{\exp}(t) + \beta_{\text{cntl}} d_{\text{cntl}}(t) + \beta_0 + \epsilon(t)$$

GLM ⇒ β’s

$$t = \frac{\beta_{\exp} - \beta_{\text{cntl}}}{\sigma} = \frac{\text{effect}}{\text{resid}}$$

t_{\text{crit}} = \text{tpdf}(p, df)

What does it mean?

Does “activation” = metabolic up-regulation consequent to neural firing?

$$y_{\text{meas}}(t) = \beta d(t) + \epsilon(t)$$

No, not directly… HRF is in the way

$$y_{\text{meas}}(t) = \beta (d(t) * h(t)) + \epsilon(t)$$

General Linear Model

$$y = (\beta_1 d_1 + \beta_2 d_2 + \beta_3 d_3 \ldots + \beta_n d_n) * h + \beta_0 + \tilde{n}$$
**Hemodynamic Response Function**

- Definition: BOLD response to an impulsive stimulus
- may include neuronal and vascular responses
  - use a cognitively simple task to reduce neuronal component
- may be nonlinear
  - superposition does not hold

**Variability of HRF**

Miezen, et al. (2000)

M. Thomason

**Timing error**

- temporal differences in HRF important in event-related designs
- measure individual HRFs

**Individual differences: HRF**
Motivation for fMRI calibration

Methods for Calibration
- Measurement of HRF
- Measurement of vasoreactivity
- Measurement of latency

Physiological Noise

Outline

Measurement of HRF

Use short stimulus, long ISI:

HRF: Measure $h(t)$ with 1s task

- motor
- auditory

Finger tapping & tones at 3Hz, N=5

Glover, NI 1999

HRF: Measure $h(t)$ with 1s task

Effect of HRF on Activation

Canonical
Gamma variate

Linear HRF

Measured

Adult

Child
Measurement of HRF

- Event related designs are inefficient
  (T. Liu)

Detection or Estimation?

Jittered (random) designs → maximum estimation efficiency

Block designs → maximum detection power

Liu et al. NIM (2001)

Spectral content of \( h(t) \)

Fourier Measurement of HRF: (FHBF)

Design has on/off blocks of duration 4s, 6s, 8s, 10s, 12s, 16s, 20s, 30s, 40s, …4s
Fourier Measurement of HRF: (FHRF)

Model $h(t)$:

\[ h(t) = \sum_{i=1}^{3} a_i b_i(t) \]

\[ b_i(t) = \lambda_i e^{-\lambda_i t} / \Gamma(t + 1) \]

Then, calc. response is

\[ y_c(t) = d(t) * h(t) \]

\[ y_c(t) = \sum_{i=1}^{3} a_i [b_i(t) * d(t)] = \sum_{i=1}^{3} a_i x_i(t) \]

\[ Y_m = Y_c + \tilde{N} = AX + \tilde{N} \implies A = Y_m X^T (XX^T)^{-1} \]

GLM- Linear

Measurement Efficiency

<table>
<thead>
<tr>
<th>ER</th>
<th>FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\zeta = 0.32$</td>
<td>$\zeta = 1.85$</td>
</tr>
<tr>
<td>CNR(FM)/CNR(ER) = 6.1</td>
<td></td>
</tr>
</tbody>
</table>
**Measurement Efficiency**

- ER: 8 min
- FM: 6 min

**Key features**
- Requires a task
- May be difficult to obtain in relevant regions

**Measurement of HRF**

- Can provide characteristic info for each subject
  - Requires a task
  - May be difficult to obtain in relevant regions
- Key features are amplitude & latency
  - May be obtained without invoking a task

**Outline**

- Motivation for fMRI calibration
- Methods for Calibration
  - Measurement of HRF
  - Measurement of vasoreactivity
  - Measurement of latency
- Physiological Noise

**Vasoreactivity**

\[ \Delta R^2 = r_{CBF_a} [Hb]_a^\beta - r_{CBV_a} [Hb]_a^\beta \]

\[ BOLD = -TE \cdot \Delta R^2 \]

\[ r_{CBV} = r_{CBF}^\alpha \]

\[ BOLD_a = M[f]^\alpha (m[f])^\beta - 1] \]

\[ m = CMRO_2 / CMRO_2_0 \]

\[ f = r_{CBF} / r_{CBF_0} \]

\[ M \] represents a ‘gain’ factor related to vascular reactivity

---

Davis, PNAS (1998)
Buxton, 2003
Measuring vasoreactivity

Use a task that does not involve change in metabolism:

- Hypercapnia: O2 or CO2
- Breath holding

\[ \Delta R^2 \propto rCBV \left[ Hb \right] - rCBV_0 \left[ Hb \right] \]

\[ BOLD \propto -TE \cdot \Delta R^2 \]

\[ rCBV \propto rCBF^2 \]

\[ BOLD_m = M \left[ f \left( \frac{m}{f} \right) - 1 \right] \]

\[ m = CMRO2_m / CMRO2_0 \]

\[ f = rCBF_m / rCBF_0 \]

BH Task

Block trial: 15s off/on 8 cycles, 4 min, 15 s

breath 14s

Breath in & hold 2s

Hold 14s

BH-induced BOLD signal

Vascular Responsivity: BH

Thomason, et al., 2005

Vascular res. \( \downarrow \) HR \( \downarrow \) \( \downarrow \) CBF \( \Rightarrow \) hypoxia

Basal metab. \( \Rightarrow \) O\( \downarrow \), CO\( \downarrow \), NO, H\( \uparrow \)

\( \Rightarrow \) vasodilation \( \Rightarrow \) \( \uparrow \) rCBF
**BH Calibration Method**

- Use BH task (non-neuronal, no change in CMRO2) to normalize cognitive task
- Reduces signal change related to vasoreactivity
- Should reduce inter-subject variance
BH Calibration: Group Activation

No cal

Calib

vol = 1.0

vol = 1.24 @ p .001

3.5 ≤ t ≤ 10

Calibration: SWM

5 subjects, parietal

sd: p = 0.05 *

vol: ns

Activation volume

SWM

SWM calib

Activation Response

Correlation: WM & BH

SWM

BH

Top: adults
Bottom: children

Thomason, et. al, 2005
BH Task: Children vs. Adults

Motivation for fMRI calibration

Methods for Calibration
- Measurement of HRF
- Measurement of vasoreactivity
- Measurement of latency

Physiological Noise

Outline

Timing error

BH to measure vascular latency

Can a BH task be used to quantify relative differences in vascular latency across the brain?

BH causes activation “everywhere”
BH causes a BOLD signal response that is uncoupled from neural activation (CMRO2)
Latency Measurement

- Tone freq.
  - Normal breathing: 3.5s
  - Get ready
  - Deep breath: 11s

Latency Map

Validation: SM task

BH latency

Chang et al., 2008
Impact on default-mode network

Impact on Granger causality

Chang et al., 2008

Outline

• Motivation for fMRI calibration

• Methods for Calibration
  - Measurement of HRF
  - Measurement of vasoreactivity
  - Measurement of latency

• Physiological Noise

Resting State Networks
**fMRI signal: sources**

- Neuronal activation
- Respiration cycle
- Cardiac cycle
- Respiration volume ($\approx CO_2$)
- Heart rate

**Physio noise: reduction**

- Neuronal activation
- Respiration cycle
- Cardiac cycle
- Respiration volume ($\approx CO_2$)
- Heart rate

---

**Cardiac/Respiratory Noise**

[Graph showing Cardiac/Respiratory Noise]

**Retrospective sorting by cardiac phase**

[Graph showing Retrospective sorting by cardiac phase]

Glover, MRM 2000
**Cardiac/Respiratory Motion Correction**

Timeseries in a voxel

Before correction

after correction

TR 1000ms

**Retrospective Corrections**

<table>
<thead>
<tr>
<th>Before</th>
<th>K-space</th>
<th>I-space</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resp</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Resting State Brain**

Data from M. Greicius

uncorrected

retroicor

Data from M. Greicius- P26112: slice 10

3x3 pixel ROI frontal orbital area
**Physio noise: reduction**

- Neuronal activation
- Respiration cycle
- Cardiac cycle
- Respiration volume ($\approx$CO$_2$)
- Heart rate

**Physio noise: sources**

- Variation in respiration volume (per time)
  
  - Air intake is inversely related to the amount of CO$_2$ in your blood.
    - CO$_2$ is a vasodilator (causes blood vessels to expand); this decreases vascular resistance, causing blood flow to increase
    - Known to affect BOLD signal (Wise, 2004)

**Physio noise: RVHRCOR**

- Method to remove artifacts due to low-frequency respiration (RV) and heart rate (HR) (Chang et al, 2009, Birn et al., 2008)
- Model:
  
  $V_{voxel \ \text{time series}} = R V \otimes R R F + H R \otimes C R F + \text{(brain signal, etc.)}$

  - RRF and CRF are impulse responses that describe the mapping between RV $\leftrightarrow$ BOLD signal, and HR $\leftrightarrow$ BOLD signal, respectively (just like the hemodynamic response function (HRF) maps between stimuli $\leftrightarrow$ BOLD signal)
Deconvolve HR and RV response functions simultaneously

1. Compute RV from the raw respiration trace
   - Sliding window standard deviation

2. Convolve RV with the RRF

   • Correlation between RVx and each voxel
**RVHRCOR: RV**

**Why convolution?**

- RV waveform
- fMRI time series

**RVx CO2**

(after shifting CO₂ forward by about 10s)

- RV(T) ~ ventilation ~ 1/PaCO₂
- So, model could be: RV → CO₂ changes → BOLD changes

---

**RVHRCOR: HR**

1. Compute HR from the ECG/PPG triggers
   - average HR within a 6-sec sliding window

**Cardiac response function (CRF)**

- HR
- CRF(t)

---

Chang, 2009
Variance explained: RVx & HRx

RVHRCOR: Summary

Impact on activation: SM task

Impact on activation: WM task
Impact on resting-state networks

- Decreases “false” positive correlations w/ default-mode

Summary

BOLD contrast confounded by

- inter-subject, inter-regional variations in hemodynamic response amplitude/latency
- use hypercapnic calibration (e.g. BH) to reduce vasoreactivity ‘gain factor’ variance

- respiratory- and cardiovascular-induced BOLD signal changes
- use RETROICOR and RVHRCOR (must measure card. and resp. functions)

Summary

- Reduction of these confounds can improve confidence in activation maps

- important in group comparisons, longitudinal studies, RSN studies (no model)

Acknowledgements

C. Law
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NIH: National Center for Research Resources
Lucas Foundation, GE Medical Systems

Firenza
BOLD Contrast

↑ neuronal activation results in
• ↑ CBF (70%), CBV (30%)
  ... but
• ↑ CMRO₂ modest (5-30%)
  (4 unpaired electrons, S = 2)
• ↑ O₂ delivery ⇒ ↓ Hb, ↑ HbO₂
  (low spin state, S = 0)
• Reduced µ—gradients, increased T2*
• Increased signal

Spatial Working Memory

Nonlinearities- Motor

Measured - average of 5 subjects  Calculated using h(t)*rect(T)

Finger tapping at 3Hz: 1/3s, 2/3s, 1s, 2s, 4s, 8s, 16s

Nonlinearities- Auditory

Measured - average of 5 subjects  Calculated using h(t)*rect(T)

Finger tapping at 3Hz: 1/3s, 2/3s, 1s, 2s, 4s, 8s, 16s
**Nonlinearities**

Second order Volterra series (Friston, 1998)

\[ y_c(t) = h_0 + \int d(t') h^{(1)}(t - t') dt' + \int d(t') d(t'') h^{(2)}(t - t', t - t'') dt' dt'' \]

\[ h^{(1)}(t) = \sum_{i=1}^{3} d^{(1)}_i b_i(t') \]

\[ h^{(2)}(t', t'') = \sum_{i,j=1}^{3} d^{(2)}_{ij} b_i(t') b_j(t'') \]

\[ y_c(t) = \beta_0 + \sum_{i=1}^{3} \beta^{(1)}_i x_i(t') + \sum_{i,j=1}^{3} \beta^{(2)}_{ij} x_i(t') x_j(t'') \]

\[ x_i(t) = d(t) * b_i(t) \]

**Effect of HRF on Activation**

Linear HRF

Nonlinear HRF

**FHRF- Linear vs. Nonlinear**

**Vascular BOLD Uniformity**

Thomason, et. al, 2005
Calibration: WM

Raw

Calib

M. Thomason et al.

Calibration: WM

Raw

ROI

whole brain

pixel-wise

1 Slice for all subjects

M. Thomason et al.

Calibration: WM

Raw

pixel-wise

M. Thomason et al.

Calibration: WM

1 Slice for 3 subjects

BH Calibration

A. Correlation between signal amplitude in BH and WM scans

1 sub, voxels t > 6

r = 0.436

B. Breath holding BOLD signal

5 ROIs; 7 subs

r = 0.503

M. Thomason