Calibrated BOLD fMRI in Disease: Applications to Aging and HIV

Beau M. Ances, MD, PhD, MSc
Assistant Professor
Department of Neurology
Washington University in St. Louis
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Disclosure of Interest

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Speakers Bureau
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Clinical Trials
Biogen

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None

Objective: To examine the role of functional magnetic resonance imaging (fMRI) in aging and HIV

I own no stocks or equity in any pharmaceutical company
Bad: What does conventional BOLD fMRI measure?

Ugly: What parameters should we consider when using fMRI in disease states?

Good: Can a calibrated BOLD fMRI be helpful?
   • Lessons learned from healthy aging and neuroHIV

Future: What is the role of multi-modal imaging
Conventional Blood Oxygen Level Dependent (BOLD) Reflects CBF, CBV, and CMRO$_2$ Changes

Buxton et al., *MRI*, 2007
Limitations of Conventional BOLD fMRI in disease states

- Magnitude of BOLD response ≠ quantitative measure of underlying neural activity, signaling, metabolism, or cerebral blood flow

Iannetti and Wise, MRI, 2007
Is There a Role for Calibrated BOLD?
Arterial Spin Labeling (ASL) Measures CBF

1: Tag by Magnetic Inversion

2: Control

Control - Tag $\propto$ CBF (mL/100mL/min)
Calibrated BOLD fMRI Calculates Functional CMRO$_2$ Changes

- Simultaneously measure CBF and BOLD.
- Mild hypercapnia (5%) raises CBF but not CMRO$_2$
Stimuli Activate Lenticular Nuclei (LN) and Visual Cortex (VC)
**Calibrated BOLD Calculations**

\[
\frac{\Delta S}{S_0} = M \left[ 1 - \left( \frac{CBF}{CBF_0} \right)^{\alpha - \beta} \left( \frac{CMRO_{O_2}}{CMRO_{O_20}} \right)^{\beta} \right]
\]

- **M**: Scaling factor that represents maximum achievable “ceiling” BOLD signal
- **n**: CBF/CMRO$_2$ coupling parameter

\[
n = \frac{\% \Delta CBF}{\% \Delta CMRO_{O_2}}
\]

*Davis et al., PNAS, 1998*
Calibrated BOLD in Healthy Controls

- Reproducibility
- Comparison between different brain regions
- Effects of “normal” aging
Reproducibility Between 1\textsuperscript{st} and 2\textsuperscript{nd} Day in Healthy Controls in the VC

![Graph showing functional changes in CBF and BOLD, and CMRO\textsubscript{2} changes.](image)

Leontiev et al., *NeuroImage*, 2007

(n=10)
Healthy Controls Have Comparable Intra-subject but Not Total Variability in the VC

Coefficient of Variation (CV)- a normalized measure of dispersion of a probability distribution.

\[ CV = \left( \frac{\sigma_i}{x_{avg}} \right)^*(100\%), \text{ where } \hat{\sigma}_i = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n - 1}} \]

and \( n \) = number of sessions compared

CV allows for comparison amongst different magnitudes (i.e. BOLD (1–2%) vs CBF (30–40%) vs CMRO2 (10-20%)).
CBF/CMRO$_2$ Coupling in the VC and LN are Different

(N=13 subjects)  
Effects of Aging in the VC Using Calibrated BOLD


- Older = > 50 years old (n=9)
- Younger = < 35 years old (n=10)
Calibrated BOLD Within in a Disease State (HIV)
Pathophysiology of HIV Associated Neurocognitive Disorders (HAND)

Modified from Kaul et al. *Nature*, 2001
HAND Consists of a Clinical Triad

- **Cognition**
  - Memory Loss
  - Concentration
  - Mental Slowing
  - Comprehension

- **Behavior**
  - Apathy
  - “Depression”
  - Agitation, Mania

- **Motor**
  - Unsteady Gait
  - Poor Coordination
  - Tremor
Reproducibility Between 1\textsuperscript{st} and 2\textsuperscript{nd} Day in HIV+ Subjects in the VC

**Functional Changes in CBF (%)**

![Graph showing functional changes in CBF on Day 1 and Day 2 with data points and a trend line.]

**Functional Changes in BOLD (%)**

![Graph showing functional changes in BOLD on Day 1 and Day 2 with data points and a trend line.]

**CMRO\textsubscript{2} Changes (%)**

![Graph showing CMRO\textsubscript{2} changes on Day 1 and Day 2 with data points and a trend line.]

*Ances et al. Brain 2009 Poster #263*
Functional Changes in BOLD May Not Distinguish HIV+ Patients

“A thought too BOLD, a dream too wild”

Ralph Waldo Emerson, 1837

* = p < 0.05

<table>
<thead>
<tr>
<th>Region</th>
<th>HIV-</th>
<th>HIV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenticular Nuclei</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Motor Hand Region</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Visual Cortex</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>
To BOLDly Go Not Alone Into the Future
Baseline CBF Can Assist in Disease State Diagnosis

Sensitivity of 88% (29/33)
Specificity of 88% (23/26)

Significant decreases in baseline CBF in AD (n=17) compared to controls (n=11)

Ances et al., Neurology, in press

Alsop et al., Ann Neurol, 2000
Aging and HIV: A Strain on the Brain

- Functional CBF changes for visual stimulation increased with age and HIV infection.
- No interaction was seen.
- HIV infection was equivalent to 15 years of brain aging

Ances et al. Brain 2009
Oral- BR-O05 Functional Brain Imaging
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Ances Bioimaging Laboratory (ABL) at Washington University in St. Louis

http://neuro.wustl.edu/research/researchlabs/anceslaboratory.htm

Please contact with questions or possible collaborations:

bances@wustl.edu
(314) 747-8423