Organization for Human Brain Mapping
Hamburg, Germany
June 9, 2014

Modeling and What We Have Learned About Calibrated fMRI From Studying Caffeine

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The question:

Can the effects of a drug on brain activity be measured using functional MRI?

We set out to look at the effects of caffeine and how well our current methods worked for determining changes in $CMRO_2$

Educational goals

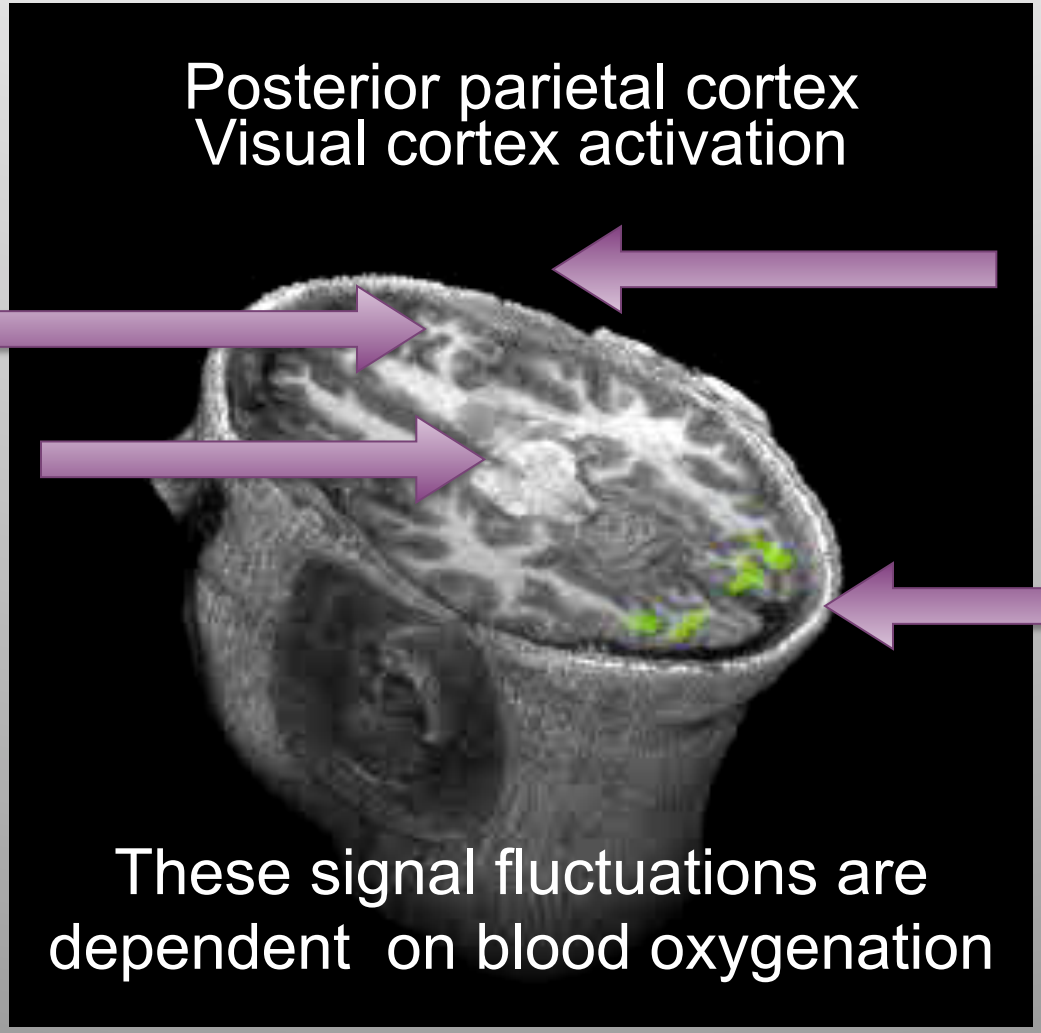
- Be able to explain differences between models of the BOLD signal and what different models can be used for

- Understand why effects of drugs on neural activity may not be apparent from measuring the BOLD signal alone and how this limitation can be overcome

Why MRI?

- Non-invasive and non-toxic
  - PET, X-ray and CT involve ionizing radiation
- Widely available in hospitals and imaging centers
- Capable of imaging large volumes of the brain
  - Better spatial resolution than EEG or MEG
- Limitations:
  - Temporal resolution, signal-to-noise, image artifacts
  - Time-consuming, expensive
  - Signals may not directly reflect physiology of interest

fMRI Maps Brain Activation



Current Applications of BOLD fMRI

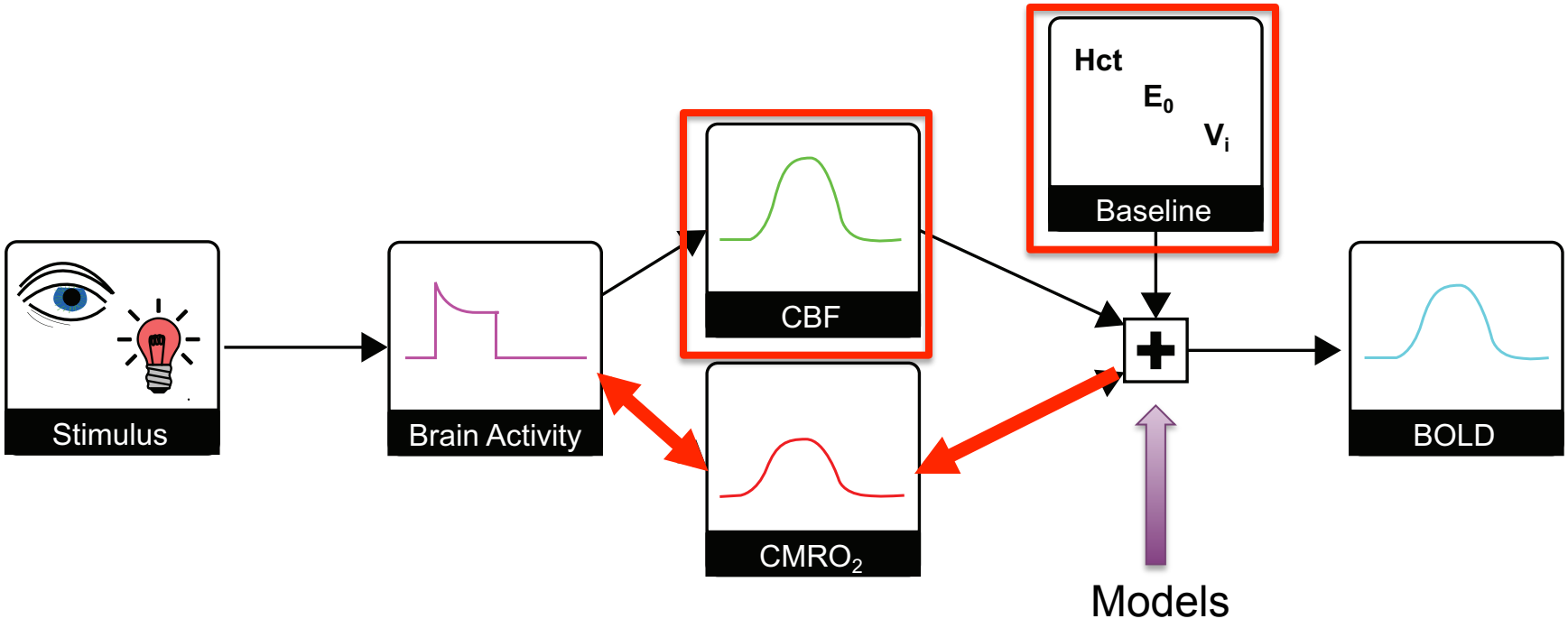
(Blood Oxygenation Level Dependent)

- Most fMRI studies examine healthy subjects
  - Mapping brain areas involved in different tasks
- Less common clinical applications:
  - Task response differences in disease
  - **Exploring drug effects on the brain**
- Resting state neural networks
- Brain connectome

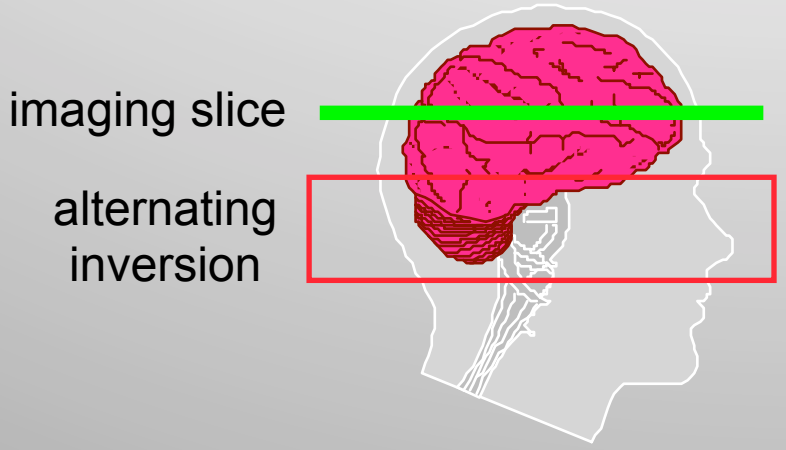
The BOLD effect and neural activity

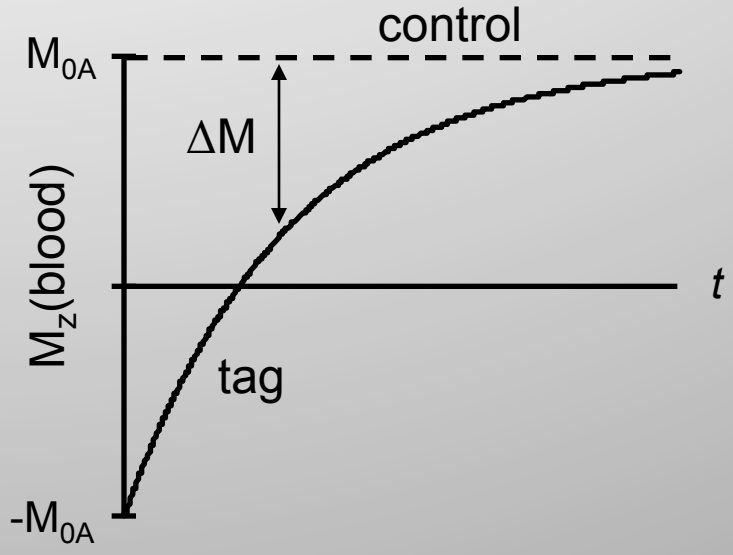
- The BOLD signal depends on the oxygenation of hemoglobin
- Neural activation changes blood oxygenation
  - Increases blood flow (CBF) more than oxygen metabolism ($CMRO_2$)
  - Decreases concentration of deoxyhemoglobin
    - This leads to a BOLD signal increase
- Dual dependence on CBF and $CMRO_2$ creates complexity in interpreting the BOLD signal quantitatively

Source of the BOLD signal



Arterial Spin Labeling (ASL):
Integral to calibrated BOLD





Tag image: Magnetization of arterial blood is inverted

Control image: Magnetization of arterial blood is fully relaxed

$$\Delta M = Control - Tag \propto CBF$$

Mathematical modeling of BOLD

- Historically very simple models have been proposed to relate the BOLD signal to ΔCBF and $\Delta CMRO_2$
- In the detailed BOLD model, we integrated knowledge of the underlying physiology to simulate the steady-state BOLD signal
- We applied this model to test:
  - The accuracy of simpler models (e.g. the Davis model)
  - A new heuristic model and ratio method
  - Issues related to calibration
  - Effects of blood gas manipulation
  - Improving signal to noise of CBF measurements

Testing accuracy of simpler models

- Davis model[1,2]

$$\delta S = BOLD(\%) = M\left[1-\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\frac{CMRO_2}{CMRO_{2,0}}\right)^{\beta}\right]$$

- Hoge model[3]

$$\delta S = TE\cdot A\cdot CBV_0\cdot\left[dHb\right]_{v_0}^{\beta}\left[1-\left(\frac{CBV}{CBV_0}\right)\left(\frac{\left[dHb\right]_v}{\left[dHb\right]_{v_0}}\right)^{\beta}\right]$$

- Heuristic model and ratio method[4]

$$\delta S(\%) = A\left(1-1/f\right)\left(1-\alpha_v-1/n\right)$$

- Testing of alternative calibration methods[5]
  - R_2' calibration

- Expanding model into dynamics of BOLD

[1]Davis et al., NIMG 1998; [2]Griffeth and Buxton, NIMG (2011); [3]Hoge et al., MRM (1999); [4]Griffeth et al., PLOS One (2013); [5]Blockley et al., NIMG (2012)

Assumptions of simple models

- The fractional BOLD signal change is proportional to the change in [dHb] (raised to a power β)

$$\delta S \simeq -TE \cdot \Delta R^*_{2,dHb} = -TE \cdot A \cdot \left(CBV \cdot [dHb]^{\beta}_{v} - CBV_0 \cdot [dHb]^{\beta}_{v_0} \right)$$

- CBV is exponentially related to CBF

$$\frac{CBV}{CBV_0} = \left(\frac{CBF}{CBF_0} \right)^{\alpha}$$

- Only two compartments (tissue and blood)

- The fractional change in tissue concentration of total dHb is equal to the fractional change of venous dHb (heuristic model only)

Steady-state detailed BOLD model

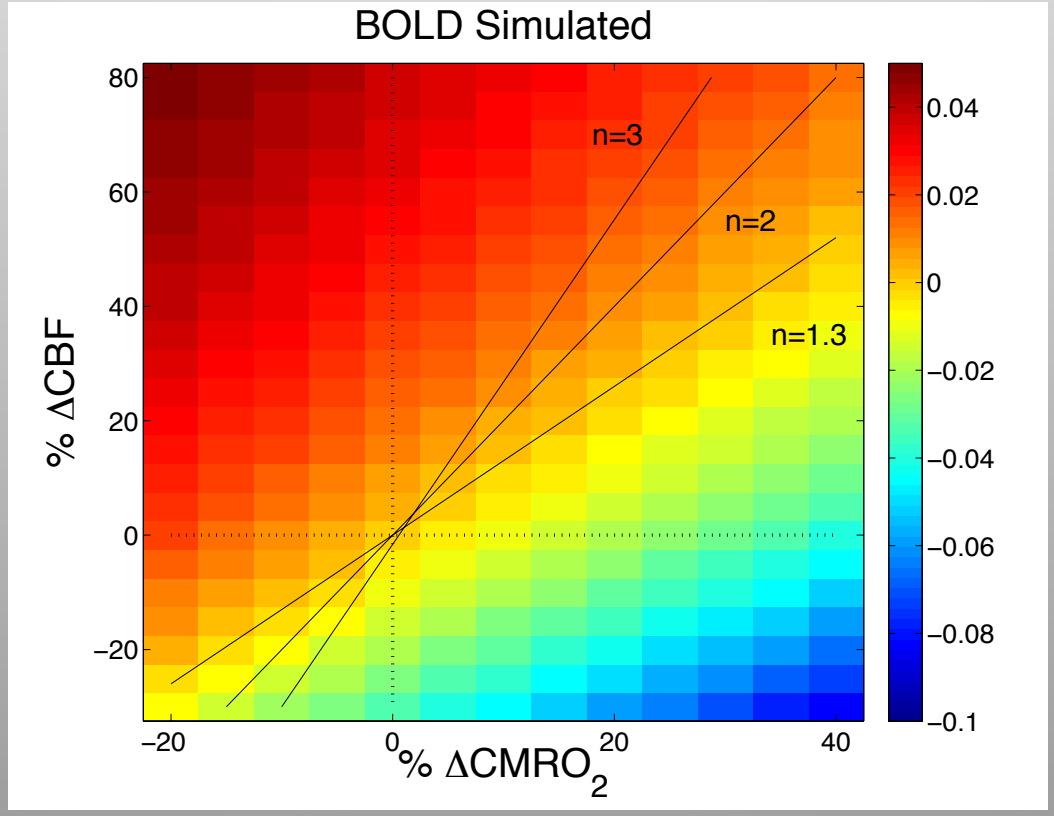
- Detailed analytic BOLD prediction model for arbitrary changes in CBF and $CMRO_2$
  - Synthesizes our knowledge of how changes in dHb create a BOLD signal response
- Model includes:
  - One tissue and three blood compartments
  - Extravascular and intravascular signal changes
  - Volume exchange effects
    - Volume changes mostly arterial[1]
  - Variable baseline and activation CBV distributions
  - Variable baseline Hct, S_aO_2, and OEF

[1]Lee et al. 2001, Chen and Pike, 2010; Jones et al., 2005; Sicard and Duong. 2005.

Steady-state detailed BOLD model

In one application, the model can generate surfaces of the BOLD signal in a ΔCBF-$\Delta CMRO_2$ plane:

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



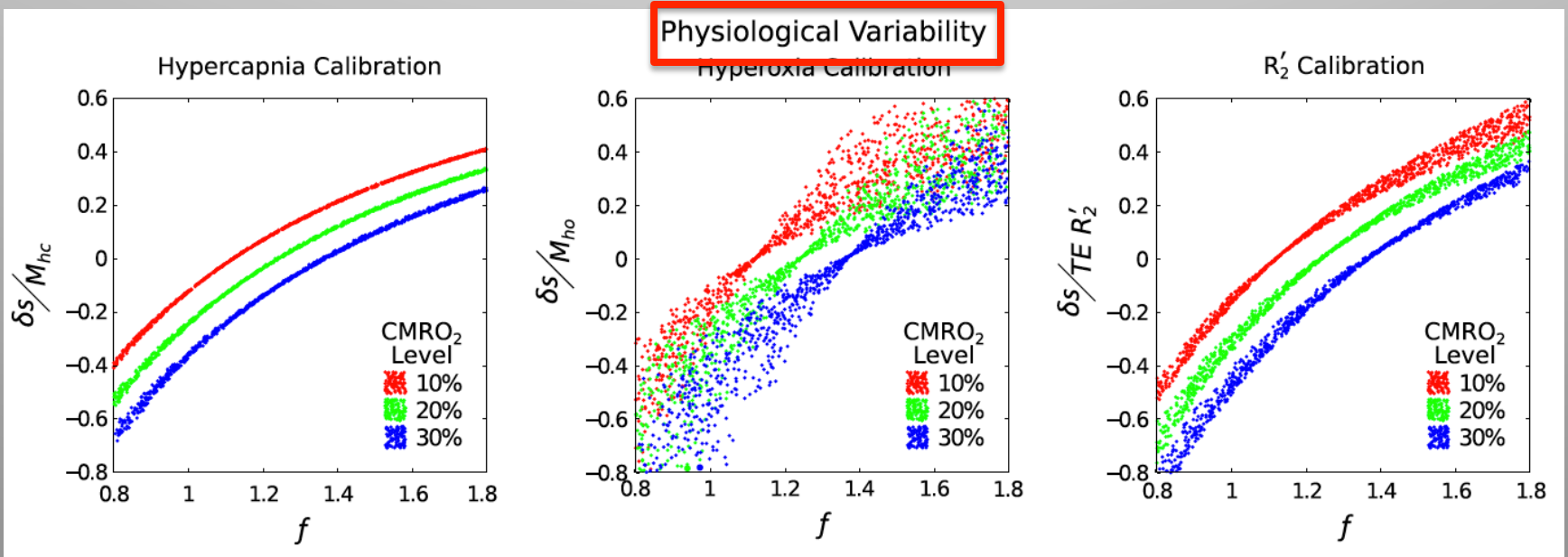
Calibration (brief notes)

- Limitations of inhaled gas calibration:
  - Time consuming
  - May not be accurate
  - Can also be uncomfortable

- R_2' offers a possible alternative
  - Need to better characterize this approach and examine different acquisition techniques

How accurate are calibration methods?

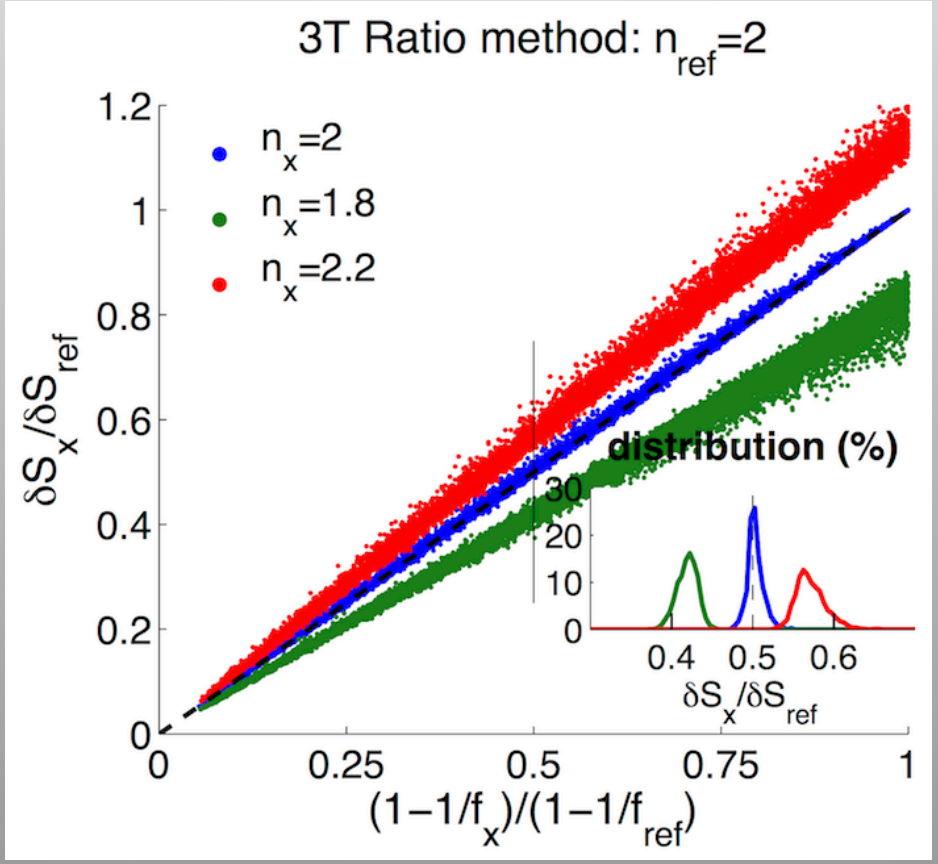
- Hypercapnia may not be isometabolic or could produce changes in CBV with a different dependence on CBF
- Other calibration procedures have been proposed:
  - Hyperoxia
  - A combination of hypercapnia and hyperoxia
  - Direct measurement of R_2' (the part of R_2* refocused by a spin echo)



Modeling the Ratio Method

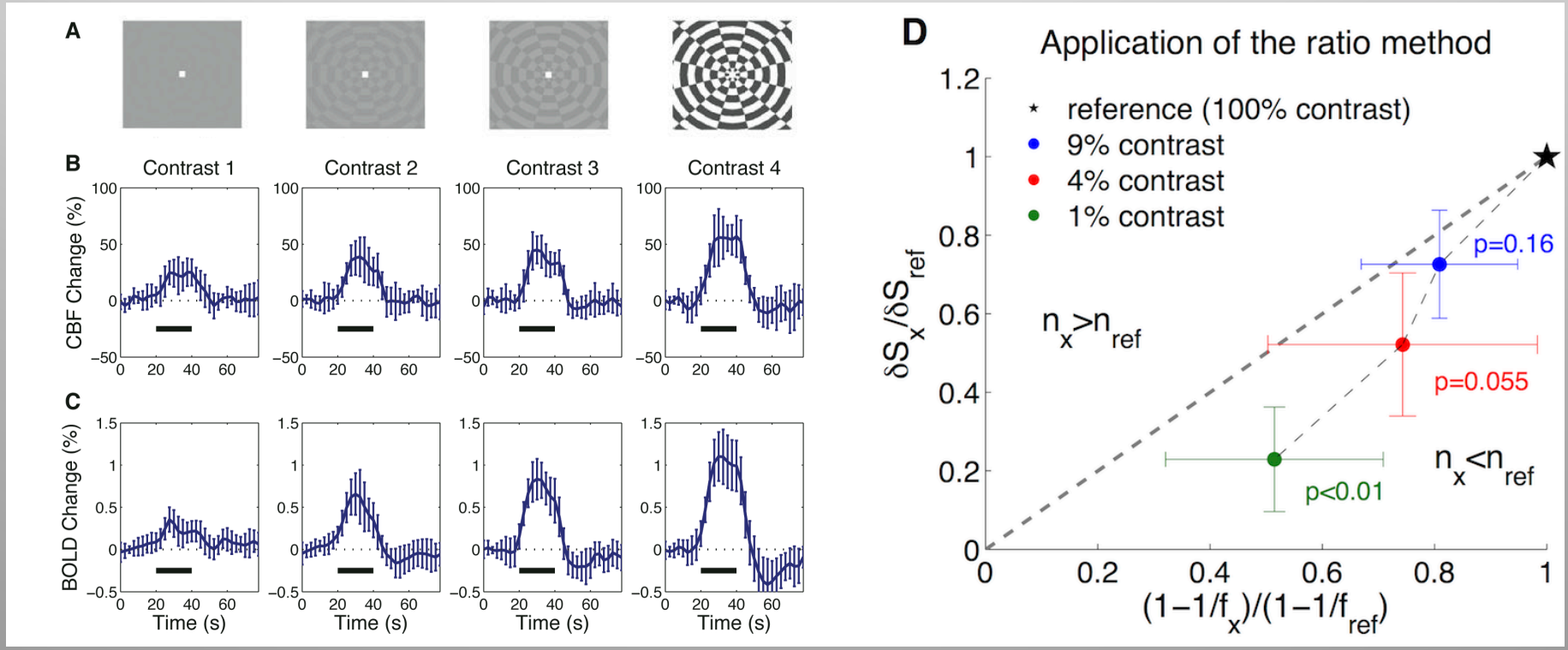
Heuristic model: $\delta S(\%) = A\left(1-1/f\right)\left(1-\alpha_v-1/n\right)$

Ratio method: $\delta S_x/\delta S_{ref} = \left(1-1/f_x\right)\Big/\left(1-1/f_{ref}\right)$



Variability of CBF/$CMRO_2$ coupling with stimulus contrast

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

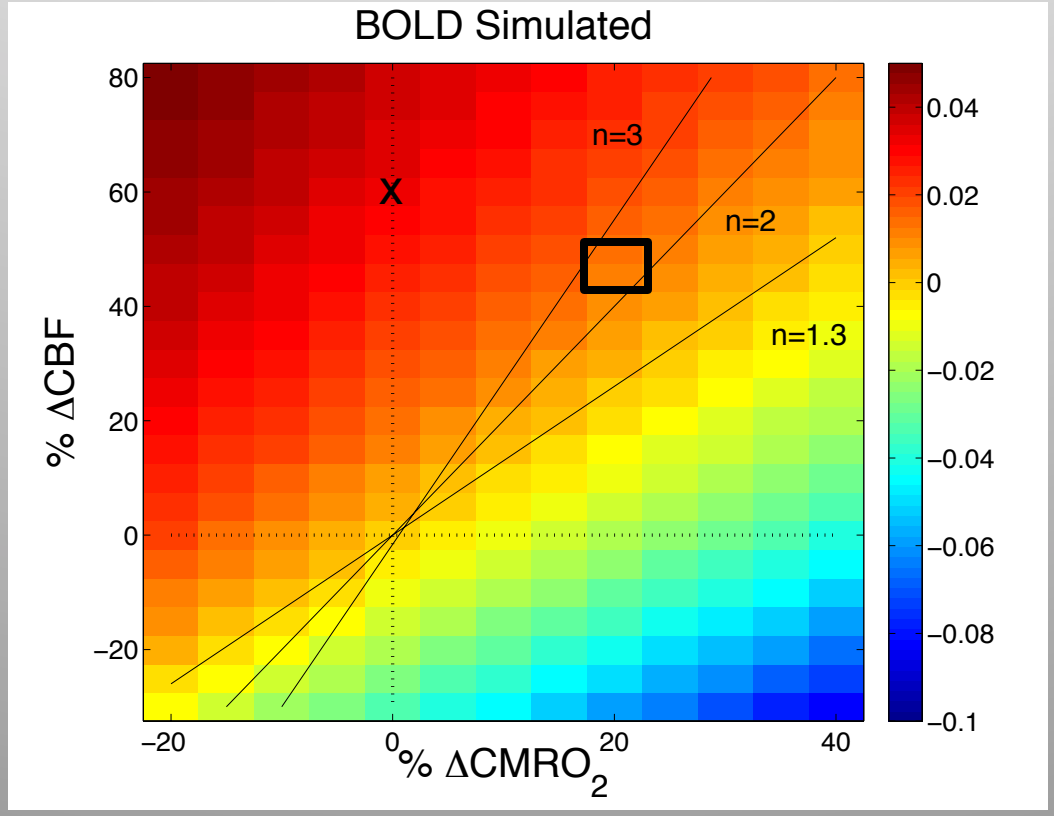


[1]Liang, et al, *Neuroimage* (2012); [2]Griffeth et al., 2013, PLOS ONE

Simulated calibrated-BOLD experiment

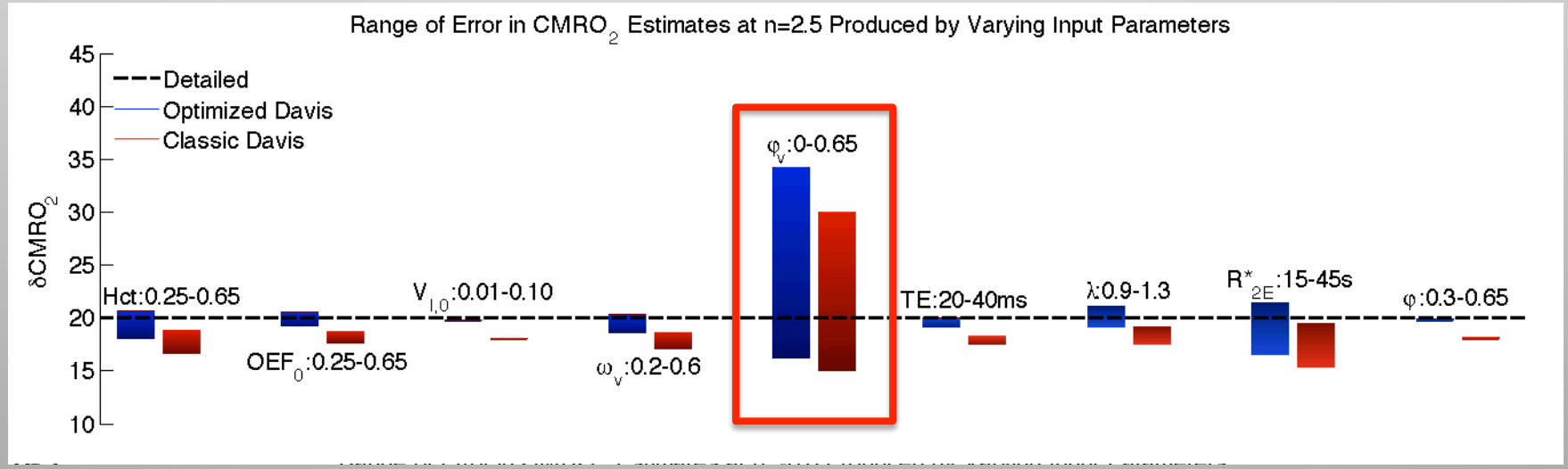
From the modeled BOLD data, a hypercapnia calibrated BOLD experiment can be simulated assuming n=2.5.

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



Error due to physiological variation

How well does the calibration experiment and scaling parameter, M, capture the effect of different physiological variables?

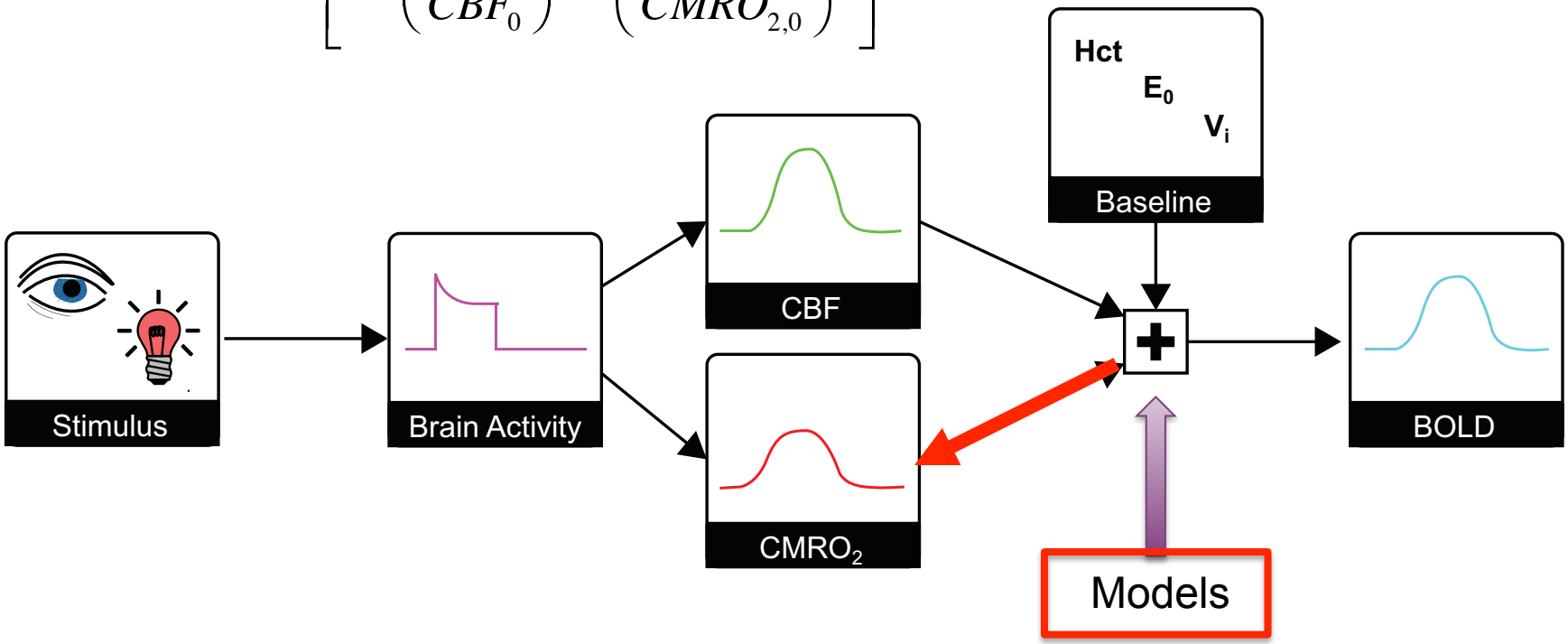


The Davis model appears to be most sensitive to variation in the dependence of the venous CBV change on the change in CBF

Hct: hematocrit
OEF_0: baseline oxygen extraction fraction
$V_{I,0}$: baseline blood volume fraction
ω_V: baseline venous blood volume fraction
ϕ_V: dependence of venous ΔCBV on ΔCBF
TE: echo time
λ: intravascular to extravascular proton density
$R_2{}^*_E$: baseline tissue signal decay rate
ϕ: dependence of total ΔCBV on ΔCBF

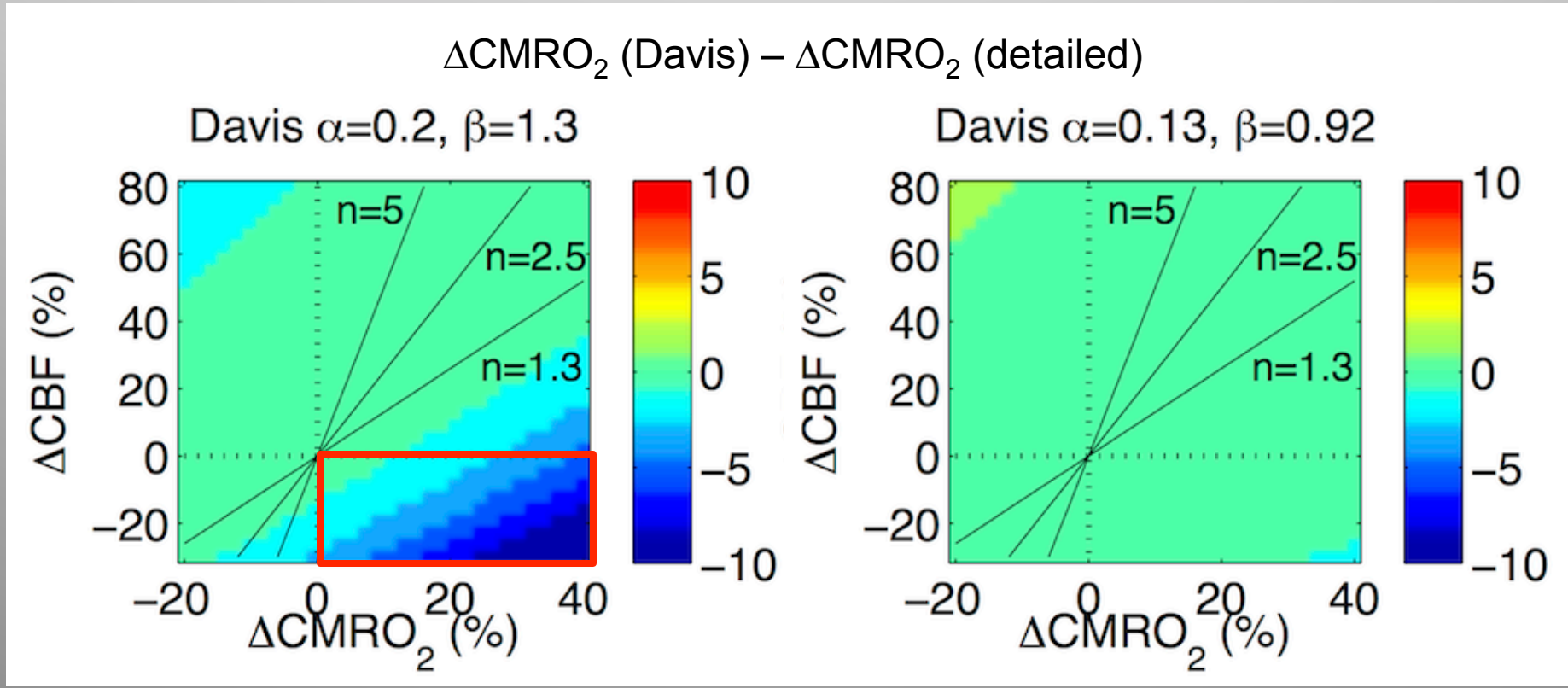
Simulating the Davis model analysis of calibrated BOLD data

$$BOLD(\%) = M\left[1 - \left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\frac{CMRO_2}{CMRO_{2,0}}\right)^{\beta}\right]$$

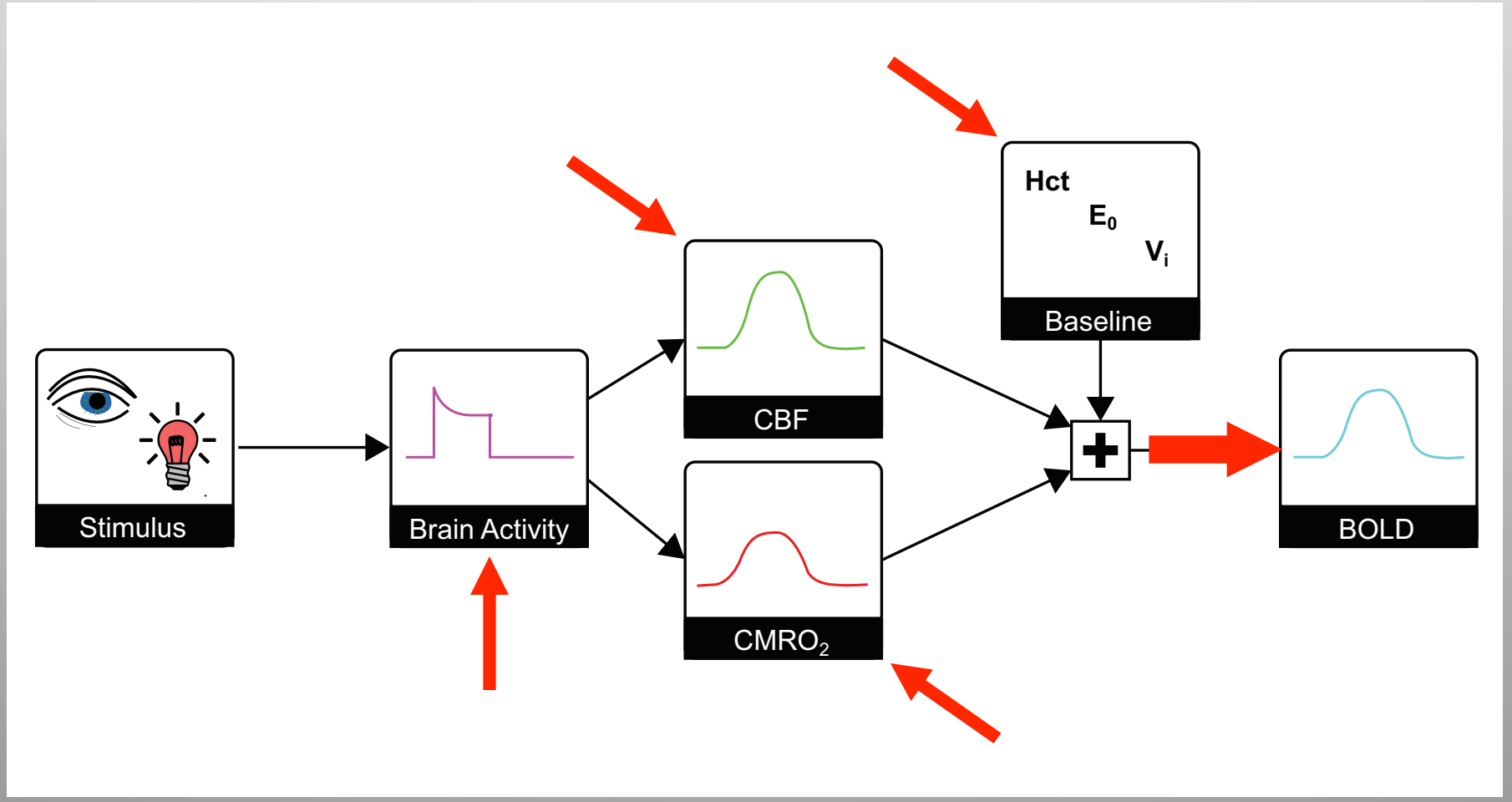


The Davis model is remarkably accurate

- At 3T and for typically ΔCBF-$\Delta CMRO_2$ coupling, error is small
  - Error much greater when CBF decreases and $CMRO_2$ increases
- Optimization improves Davis model accuracy across the full range of reasonable ΔCBF and $\Delta CMRO_2$



Effects of Caffeine



Nehlig et al., 1992

fMRI studies on caffeine

- Previous studies of caffeine effects:
  - Variable effect on BOLD and CBF responses[1,2,3,4]
  - Decreased baseline CBF, baseline BOLD[4,5] & insignificant increase in baseline $CMRO_2$[5]
  - Reduced time to peak and FWHM of BOLD[3,6]
  - Reduced coupling of ΔCBF and $\Delta CMRO_2$[4]
- Our study compared $CMRO_2$ responses to visual stimulus in an absolute sense

[1]Laurienti et al., 2003. [2]Mulderink et al., 2002. [3]Liau et al., 2008. [4]Chen and Parrish, 2009.
[5]Perthen et al., 2008. [6]Liu et al., 2004.

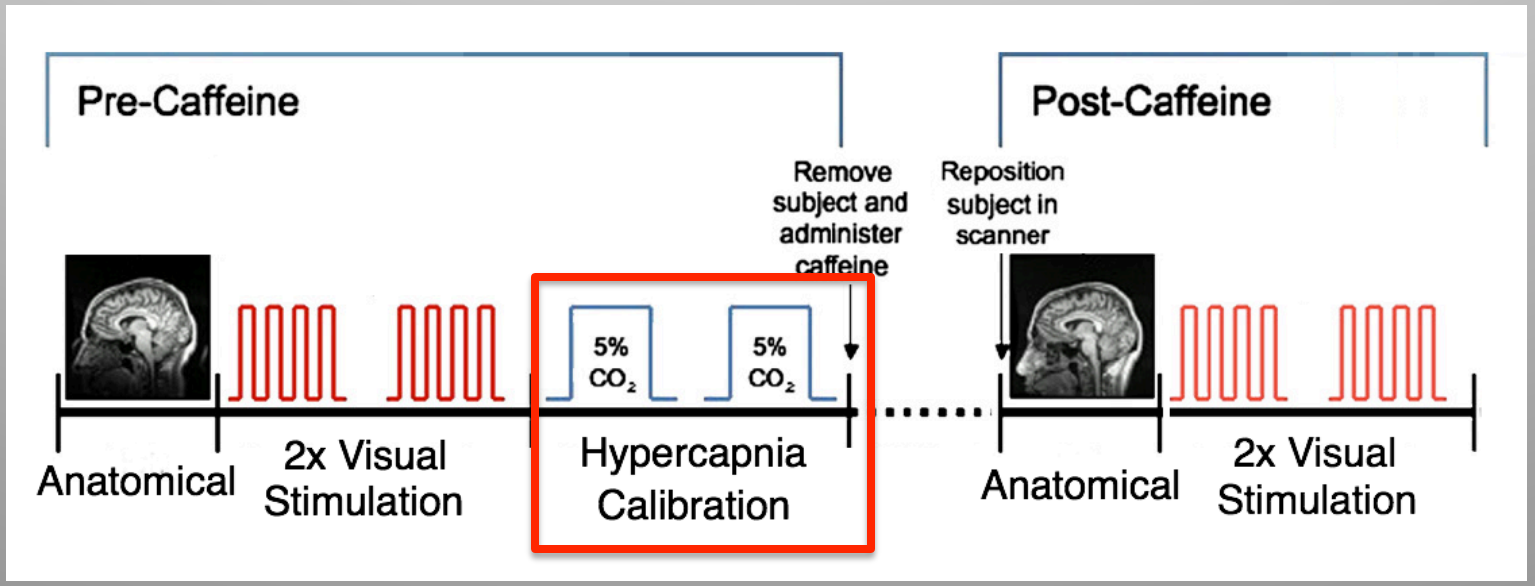
Applying optimized Davis to study of caffeine effects

- Quantitative fMRI can be used to increase reliability of drug studies
  - For example, studying the effects of caffeine on the visual response
- Dual echo acquisition and surround subtraction analysis allow assessment of both baseline and activation changes

Methods: Data Acquisition

- Imaging: Dual-echo spiral ASL technique provided simultaneous measurements of CBF and R_2*
  - PICORE QUIPSS2, TI_1/TI_2 600/1500ms, TE_1/TE_2 2.9/24ms

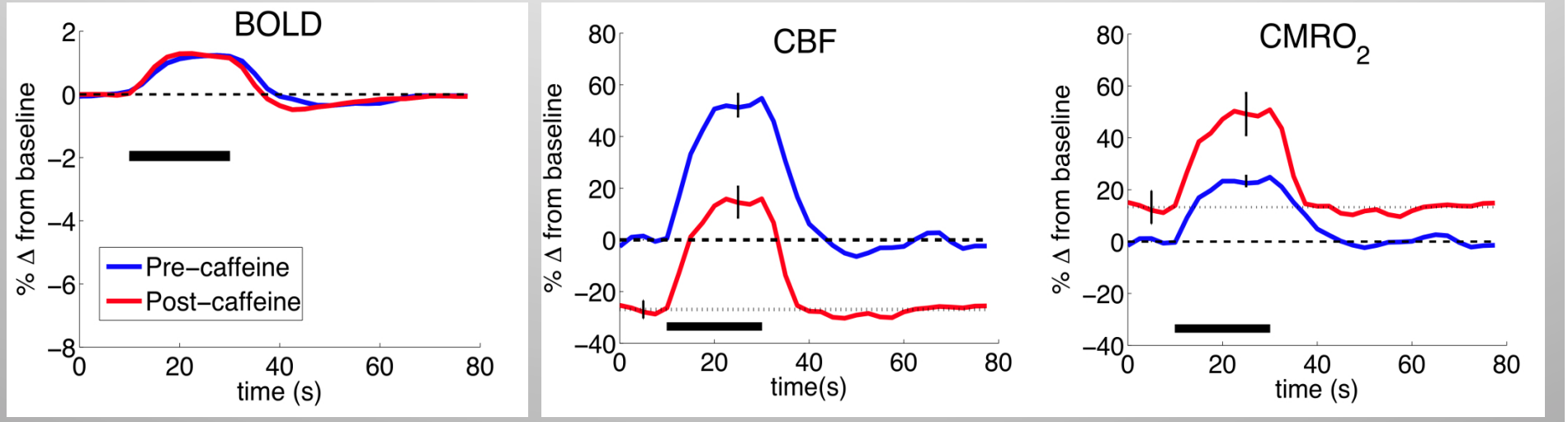
- Participants: 10 healthy, daily caffeine consuming adults who had abstained from caffeine for ≥12 hrs



Perthen et al., 2008

Quantitative fMRI

- CBF and $CMRO_2$ responses pre- and post-caffeine in 10 subjects



Absolute physiological changes

Baseline: CBF 27% ↓ $CMRO_2$ 22% ↑

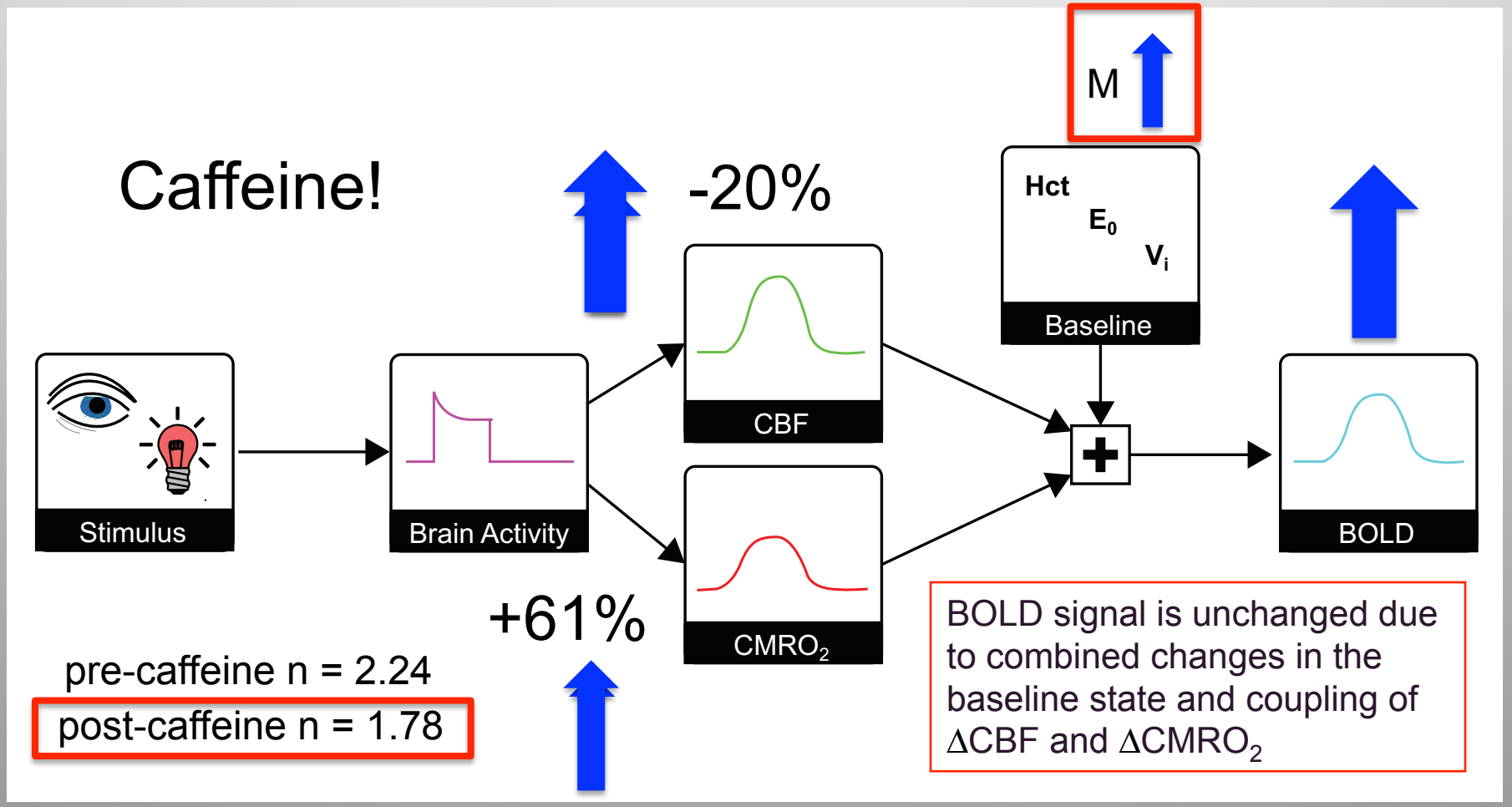
Stimulus response: ΔCBF 20% ↓ $\Delta CMRO_2$ 61% ↑ (↓n)

V Griffeth, et al., NIMG (2011); J Perthen et al., NIMG (2008)

Summary of Results

- Effects of caffeine on baseline and visual stimulus response:
  - Little to no effect on the BOLD signal response
  - **Big effects on both CBF and $CMRO_2$**:
    - Baseline CBF decreased (-27%) and ΔCBF decreased (-20%) post-caffeine
    - $\Delta CMRO_2$ increased (+61%) post-caffeine while baseline $CMRO_2$ increased (+22%)
  - Coupling parameter, *n*, decreased

Inferring Neural Activation from fMRI



Conclusions

- The BOLD signal is complicated
  - Depends on baseline physiology
  - Non-linear dependence on CBF and $CMRO_2$
    - Contributions to signal can be in opposition!
  - Is not a direct reflection of neural activity
- Calibrated BOLD allows $CMRO_2$ measurement
  - More reflective of underlying neural activity
  - With good experimental design also permit baseline measurement of $CMRO_2$

Acknowledgements

- Support provided by:
  - NIH/NINDS R01-NS036722
  - NIH/NIBIB R01-EB009380
  - NIH/NIMH F30-MH095298

- UCSD, Keck Center for Functional MRI
  - David Dubowitz
  - Eric Wong
  - Tom Liu
  - Miriam Scadeng
  - Mary O'Malley
  - Peggy Totzke
  - Kun Lu
  - David Shin
  - Bob Bussell
  - Larry Frank
  - Eman Ghobrial
  - Marianne Clark

- Buxton fMRI lab
  - Richard B. Buxton, PI
  - Aaron Simon
  - Nic Blockley
  - Farshad Moradi

Questions?

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