Overview of calibrated fMRI

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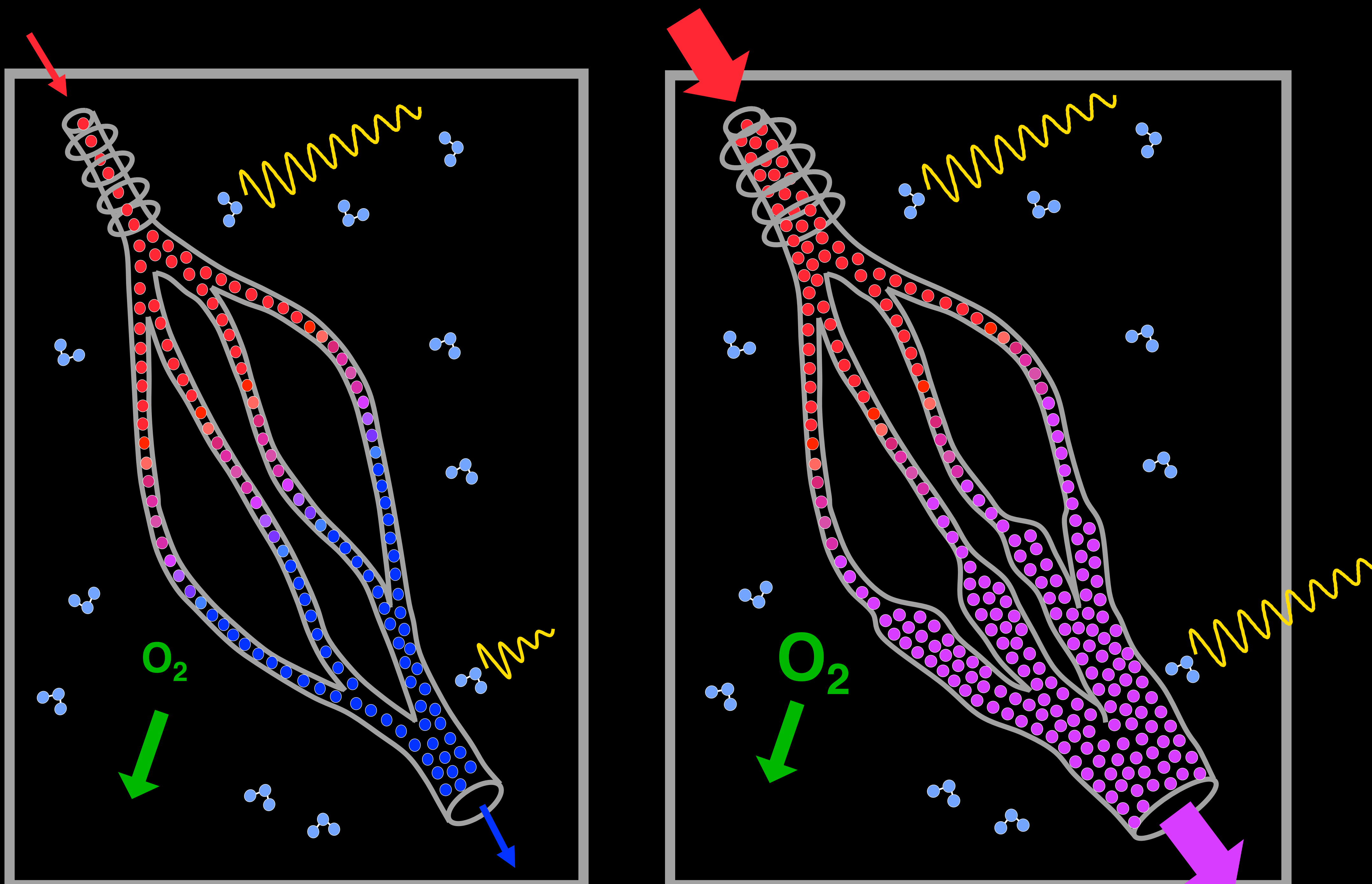
What do we mean by 'calibrated' ?

- the BOLD response has proven to be a sensitive marker for neuronal activation
- however, it's amplitude depends on many physiological variables that are generally unknown
- calibrated fMRI attempts to dissociate the key physiological inputs behind the BOLD response
  - cerebral blood flow (CBF)
  - cerebral blood volume (CBV)
  - cerebral metabolic rate of O_2 consumption ($CMRO_2$)
- most references to "calibrated fMRI" are talking about estimation of changes in $CMRO_2$

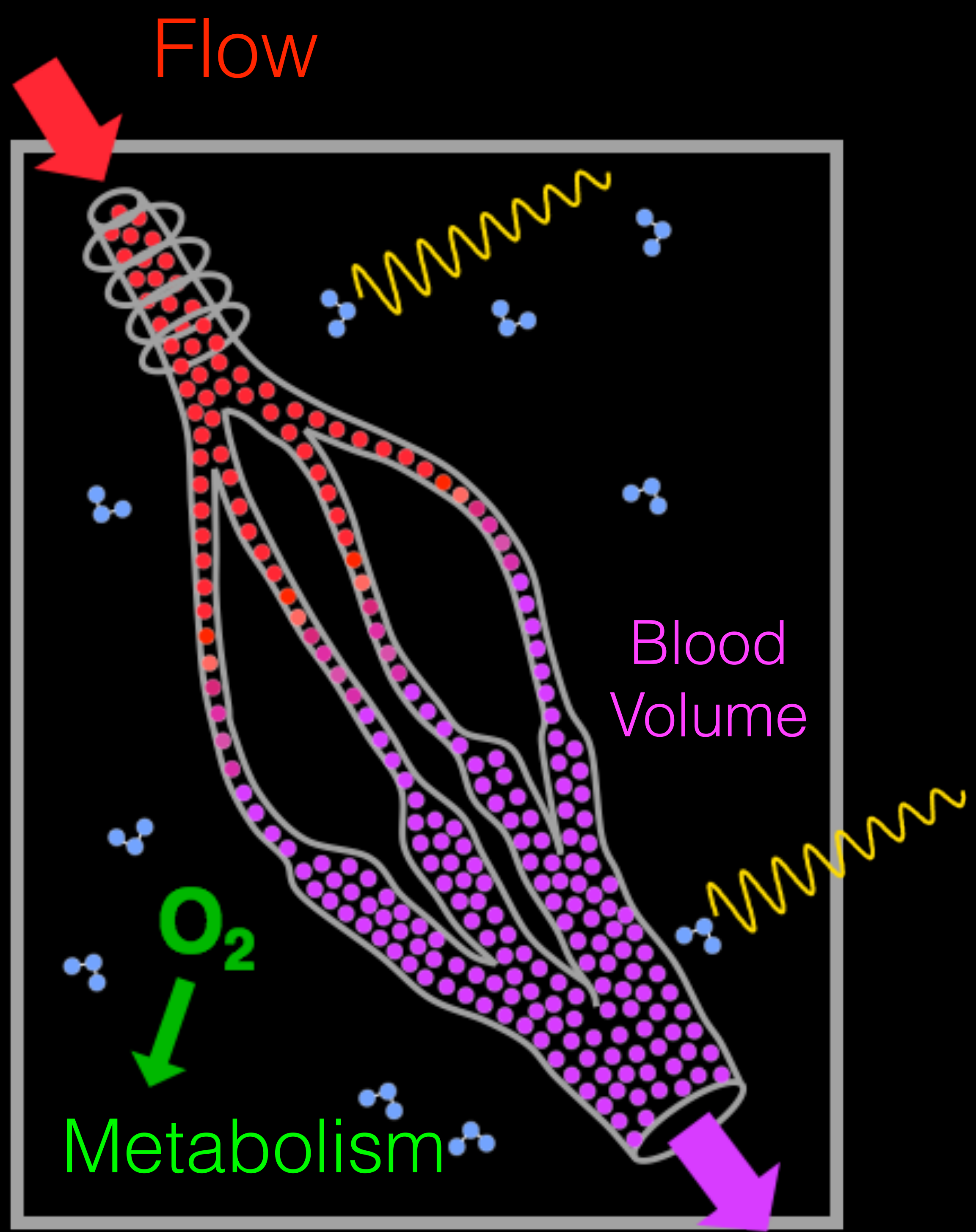
BOLD depends on multiple physiological variables



MRI voxel at rest

MRI voxel upon activation

BOLD depends on multiple physiological variables

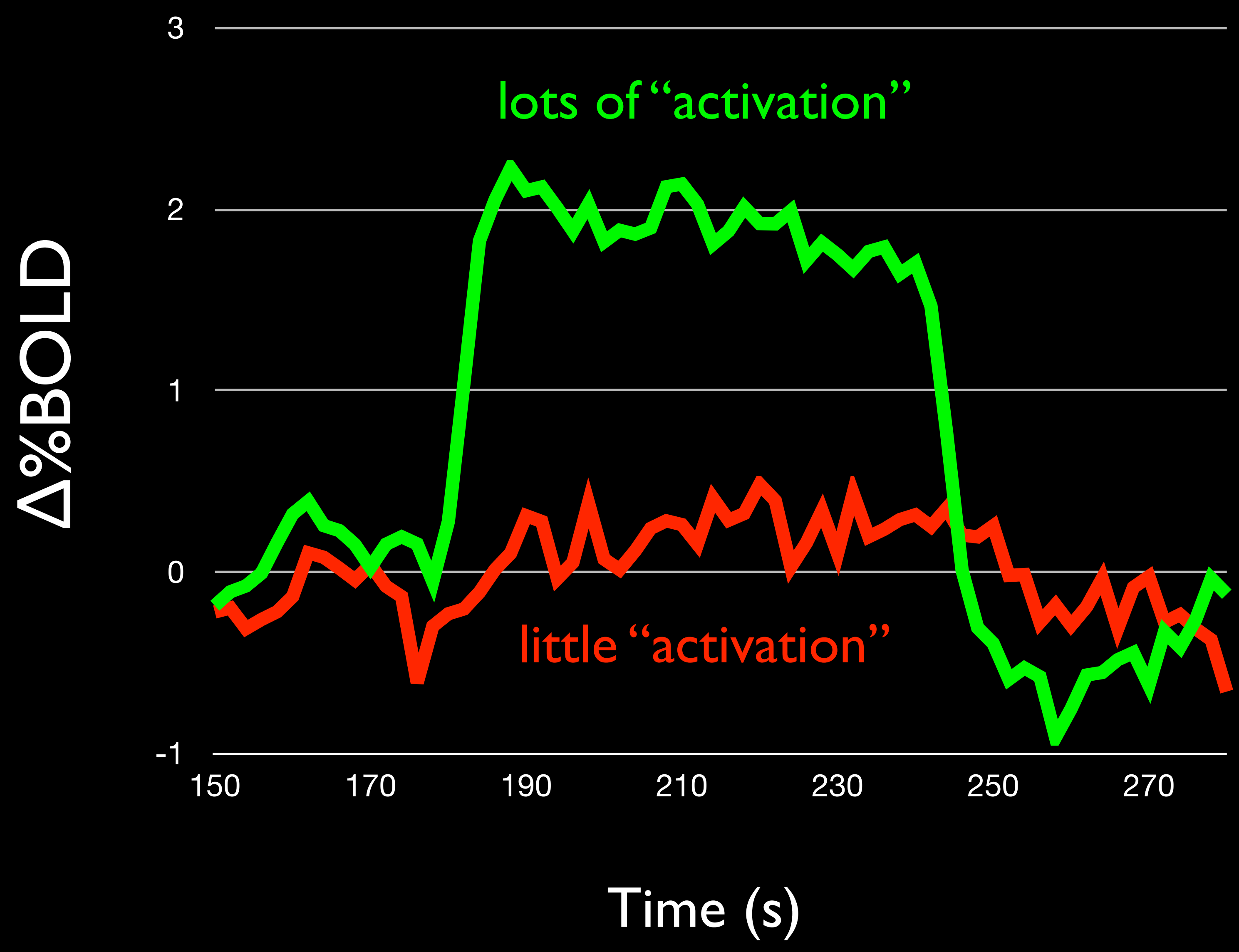


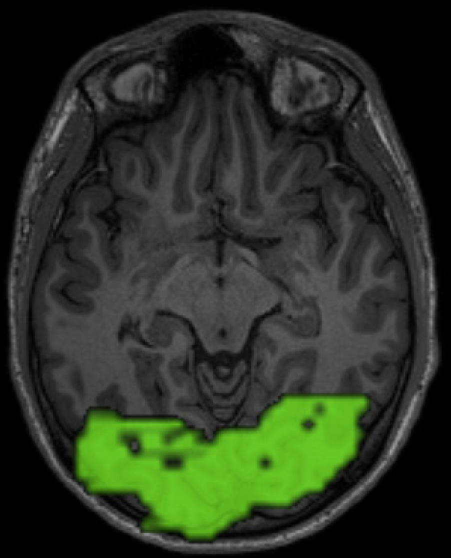
MRI voxel upon activation

When is calibrated fMRI useful?

- in situations where the response amplitude for BOLD alone could be biased by physiological differences between groups or conditions, e.g:
  - young vs. old
  - differences in physiological baseline (CBF, $CMRO_2$) associated with medication
  - healthy vs. vascular pathology

Example: BOLD responses to the same visual stimulus during two different physiological baselines

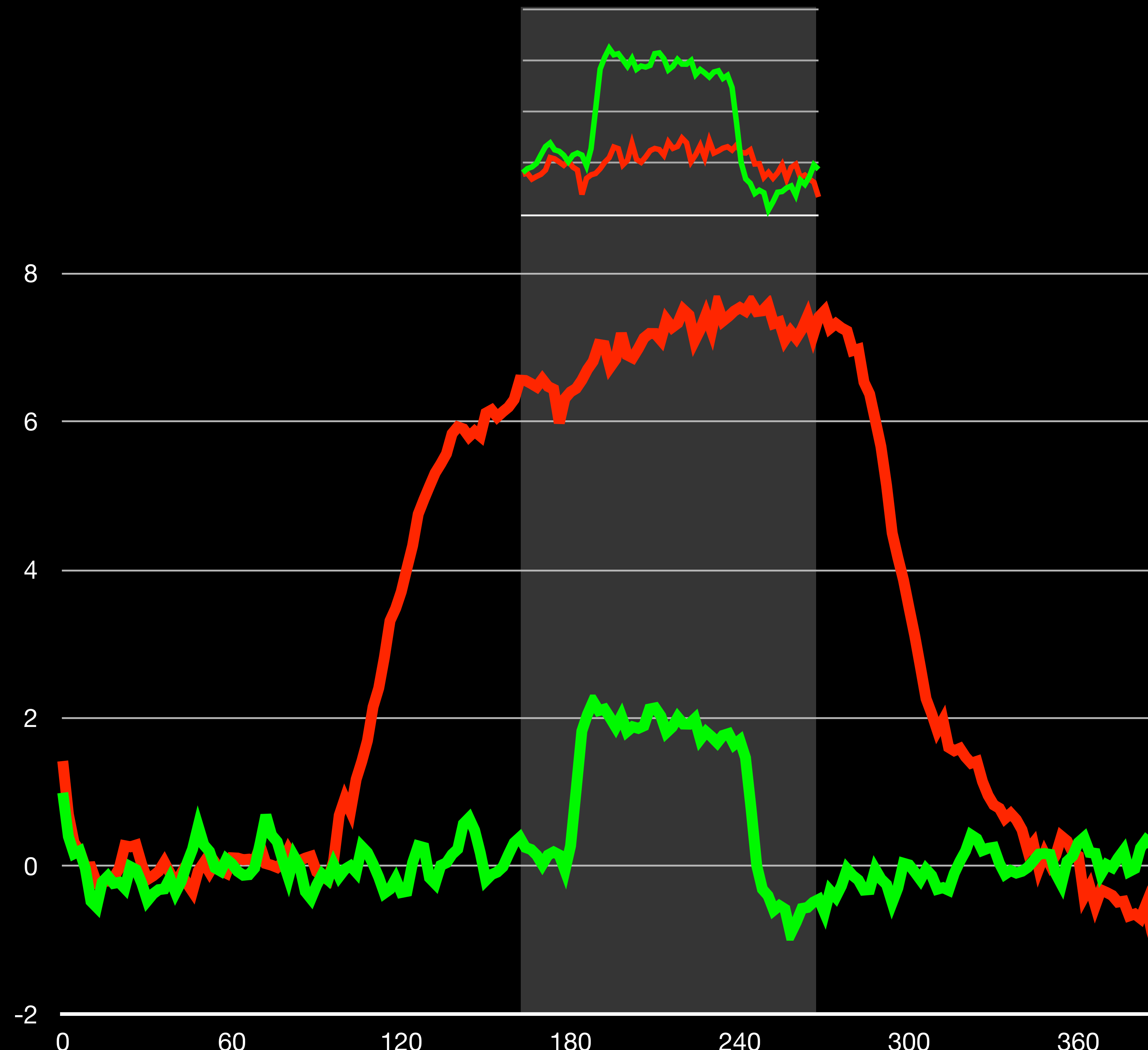




The whole picture

carbogen used to produce venous hypersaturation in red trace

air

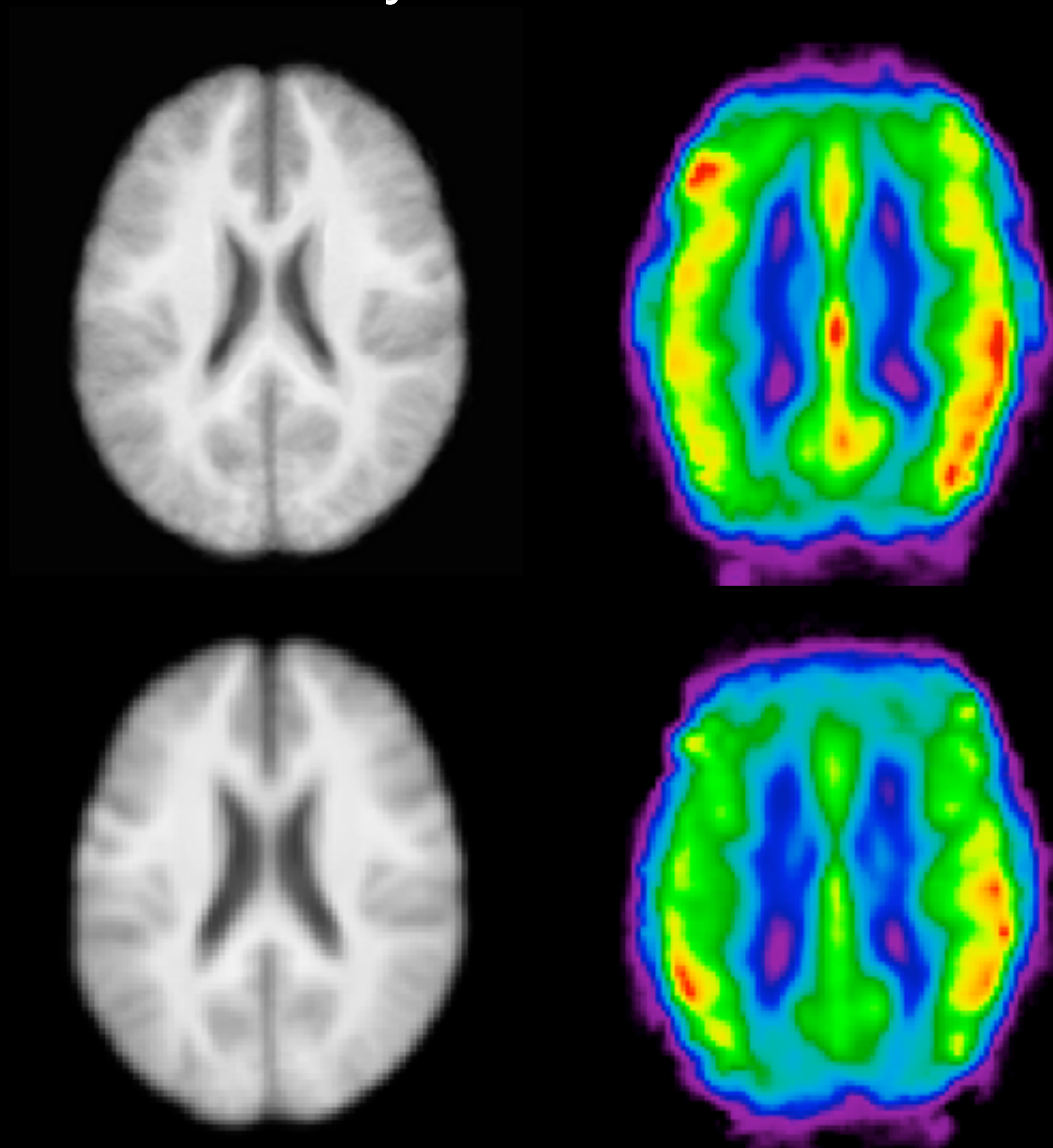


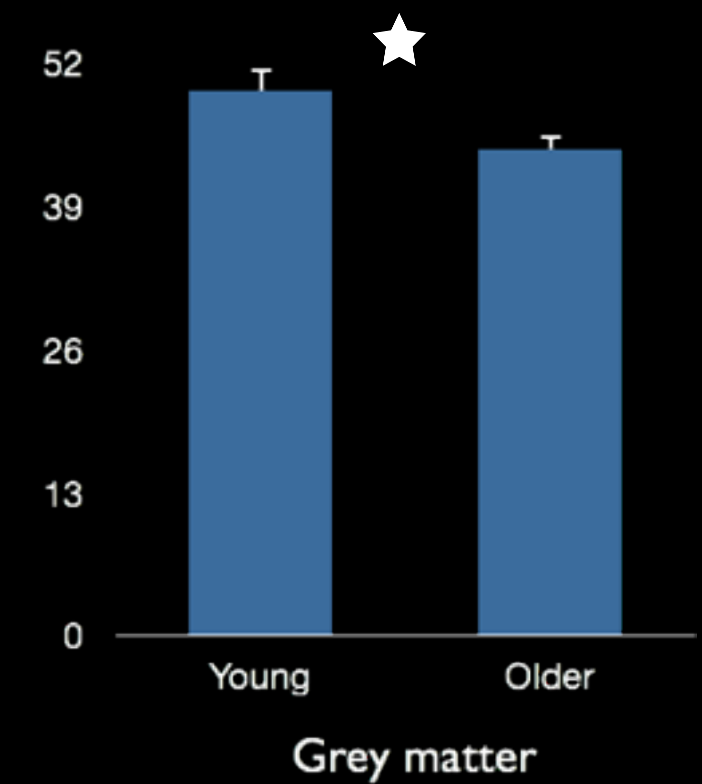
Example: age-related differences in resting brain perfusion

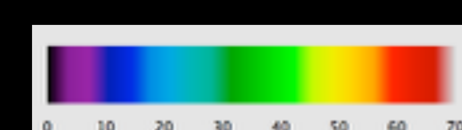
Anatomy | CBF

Young
N=31
24±3 yrs

Older
N=31
64±5 yrs



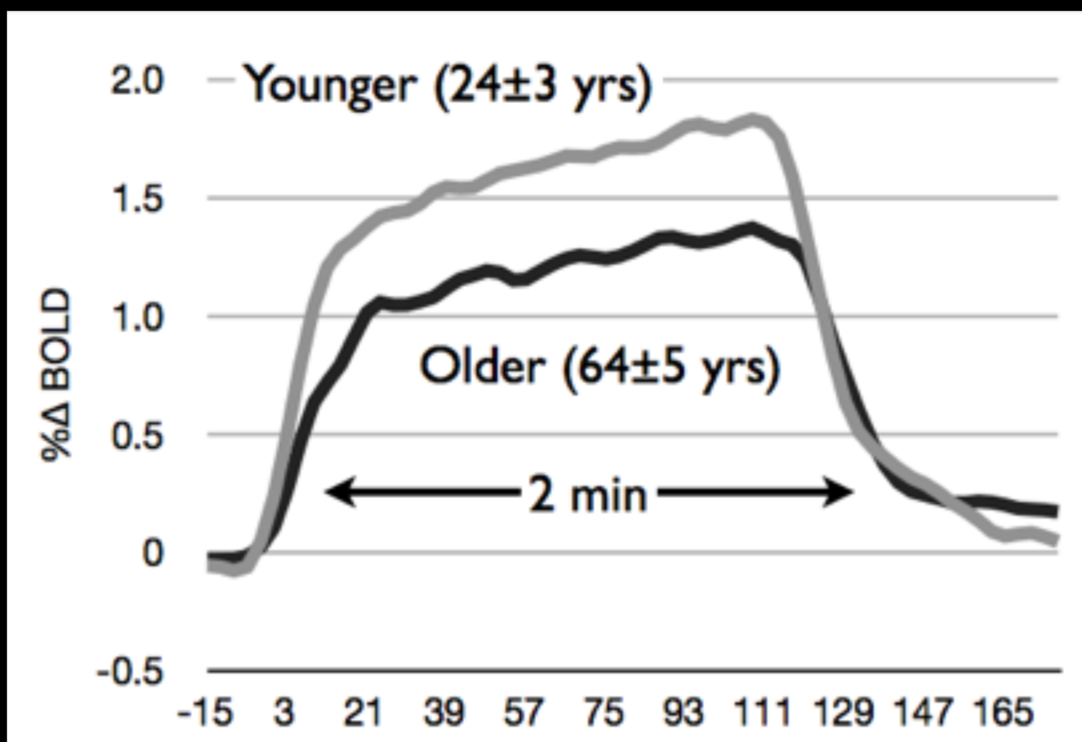




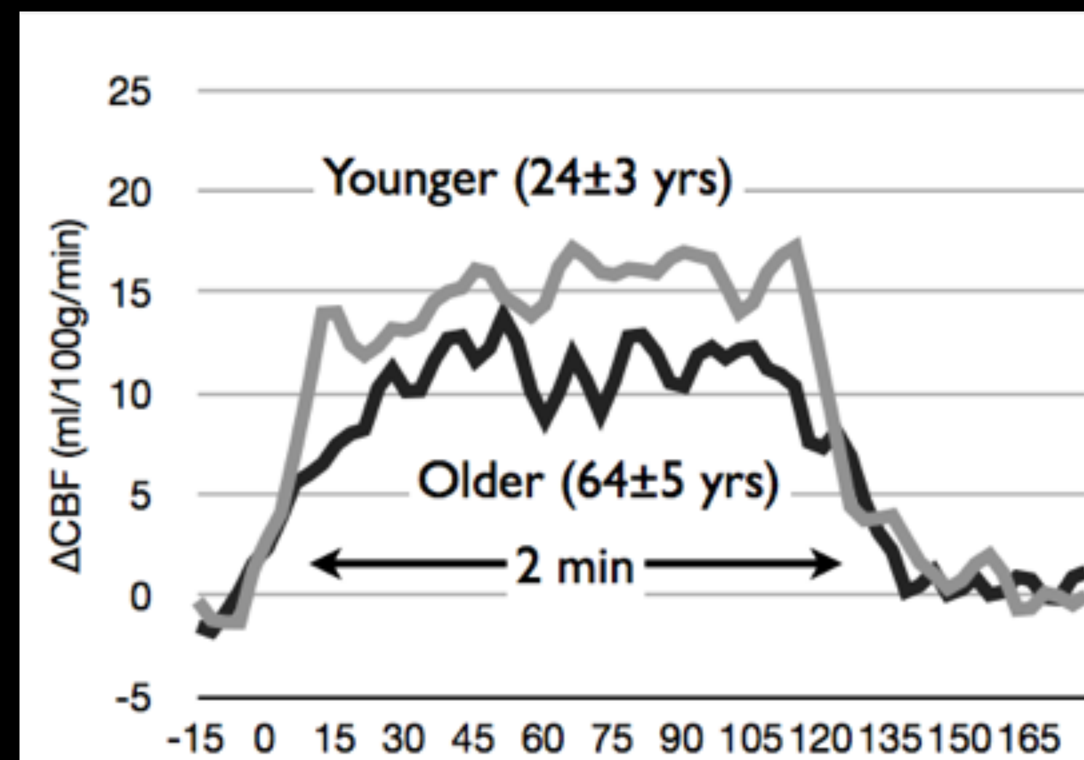
ml/100g/min

Gauthier et al. 2012

Example: age-related differences in hemodynamic response to controlled hypercapnia in cortical grey matter



BOLD



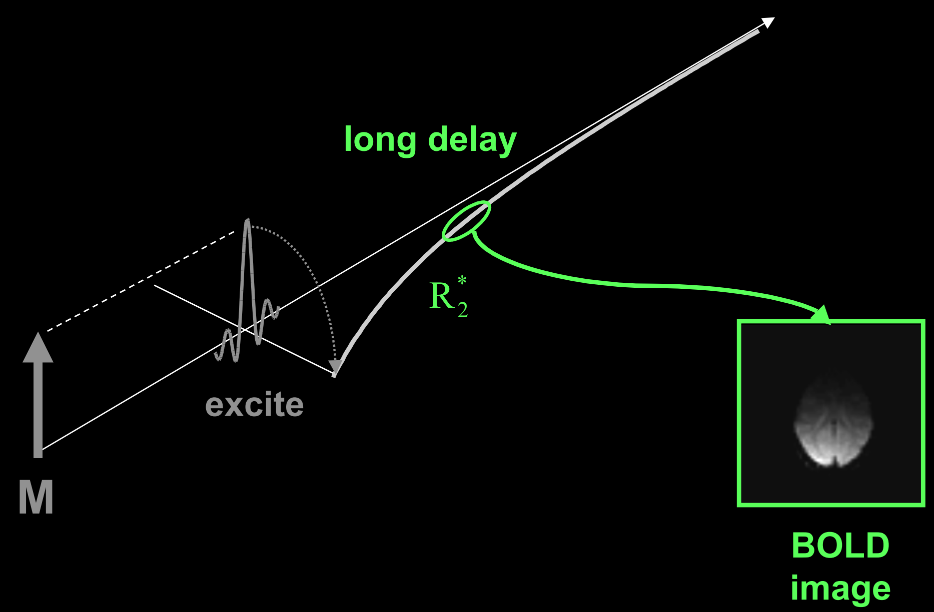
CBF

Gauthier, C. J., Madjar, C., Desjardins-Crépeau, L., Bellec, P., Bherer, L., & Hoge, R. D. (2013). Age dependence of hemodynamic response characteristics in human functional magnetic resonance imaging. Neurobiology of Aging, 34(5), 1469–1485. doi:10.1016/j.neurobiolaging.2012.11.002

How does calibrated fMRI work?

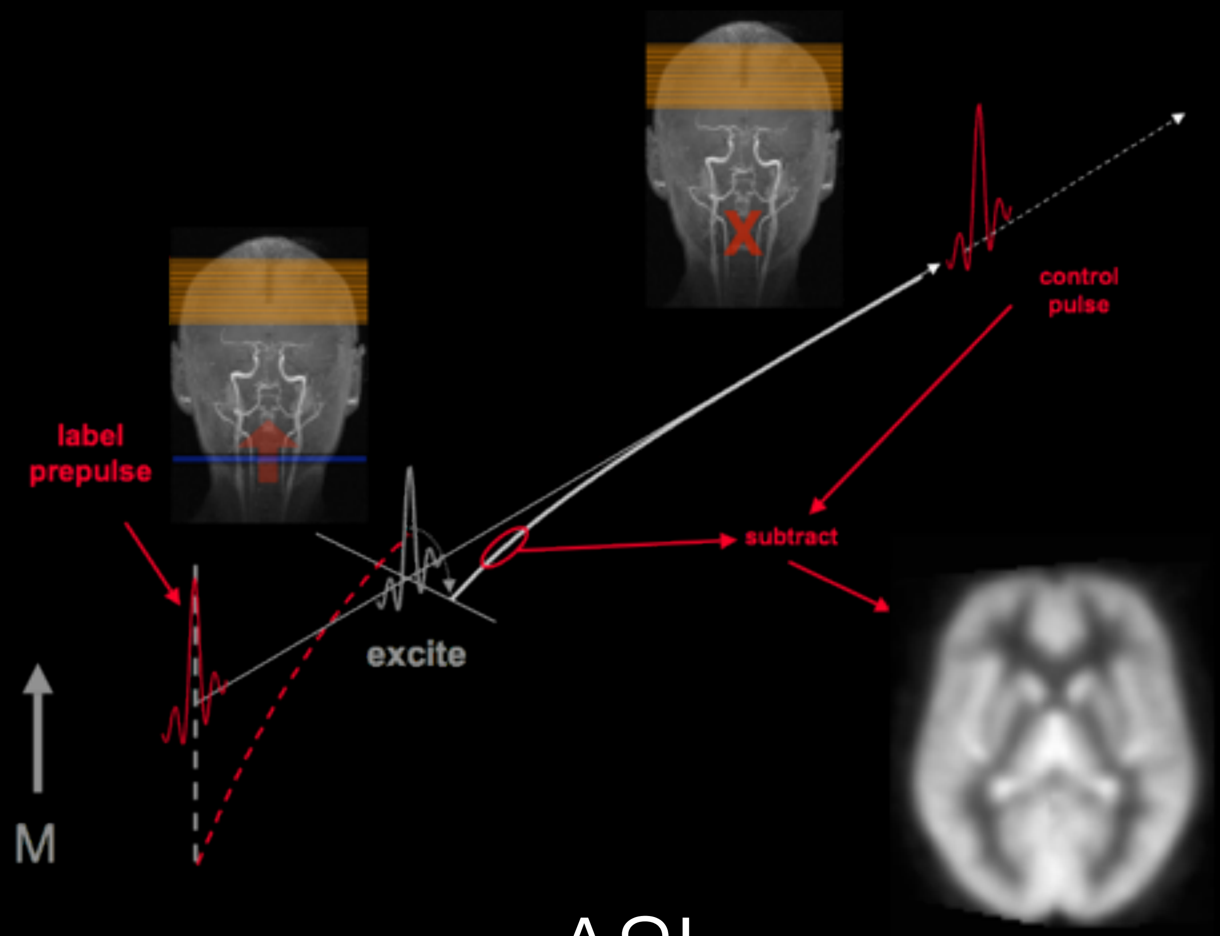
- Ingredients (for gas calibration methods):
  - an MR pulse sequence enabling simultaneous imaging of BOLD responses and cerebral blood flow
  - a biophysical model linking the BOLD signal to other measurable values like blood flow, exhaled gases
  - a manipulation that changes blood oxygenation and flow in a controlled or observable way
    - e.g. hypercapnia, hyperoxia

Simultaneous imaging of BOLD and CBF



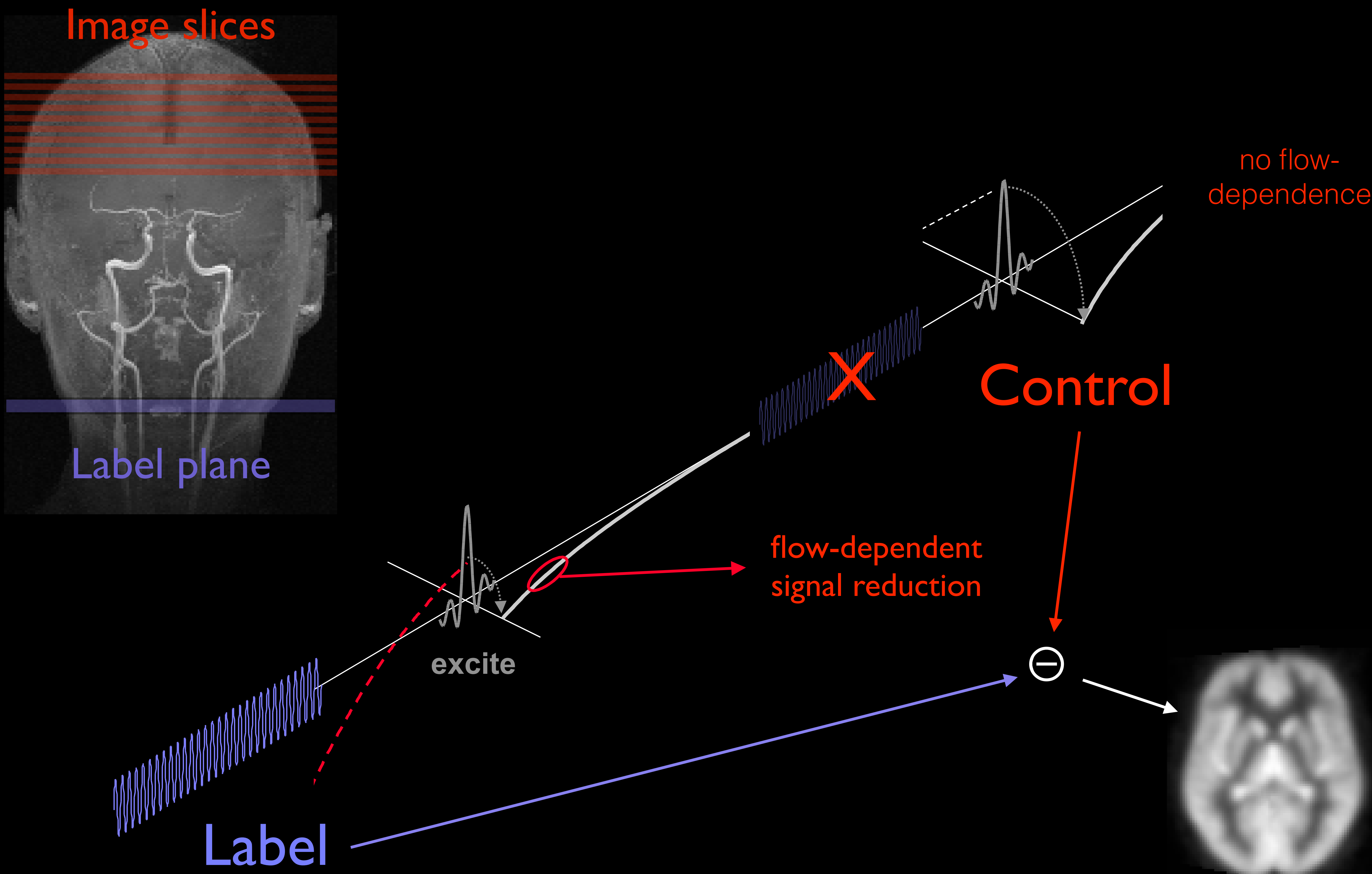
BOLD

+

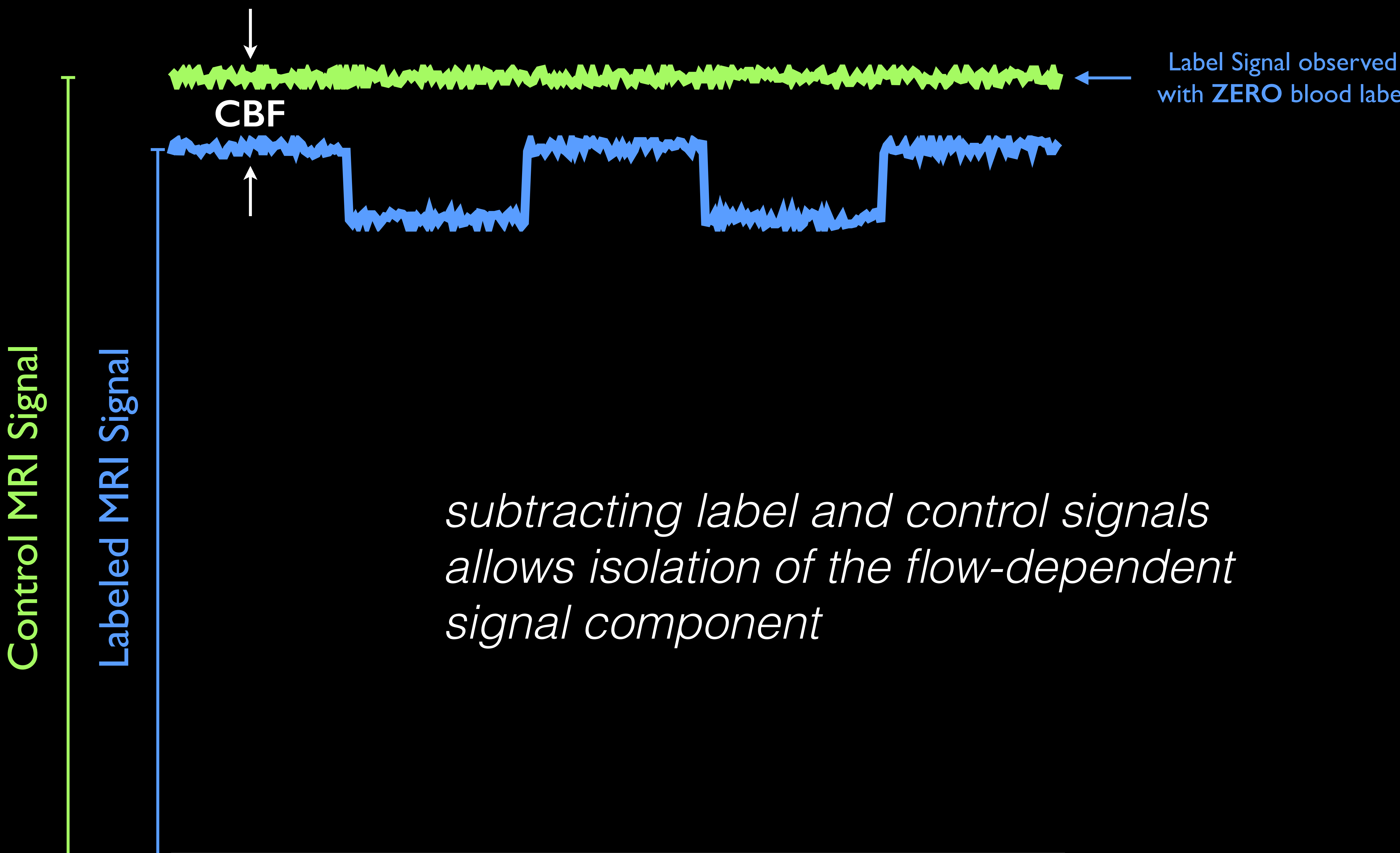


ASL

Arterial spin-labelling

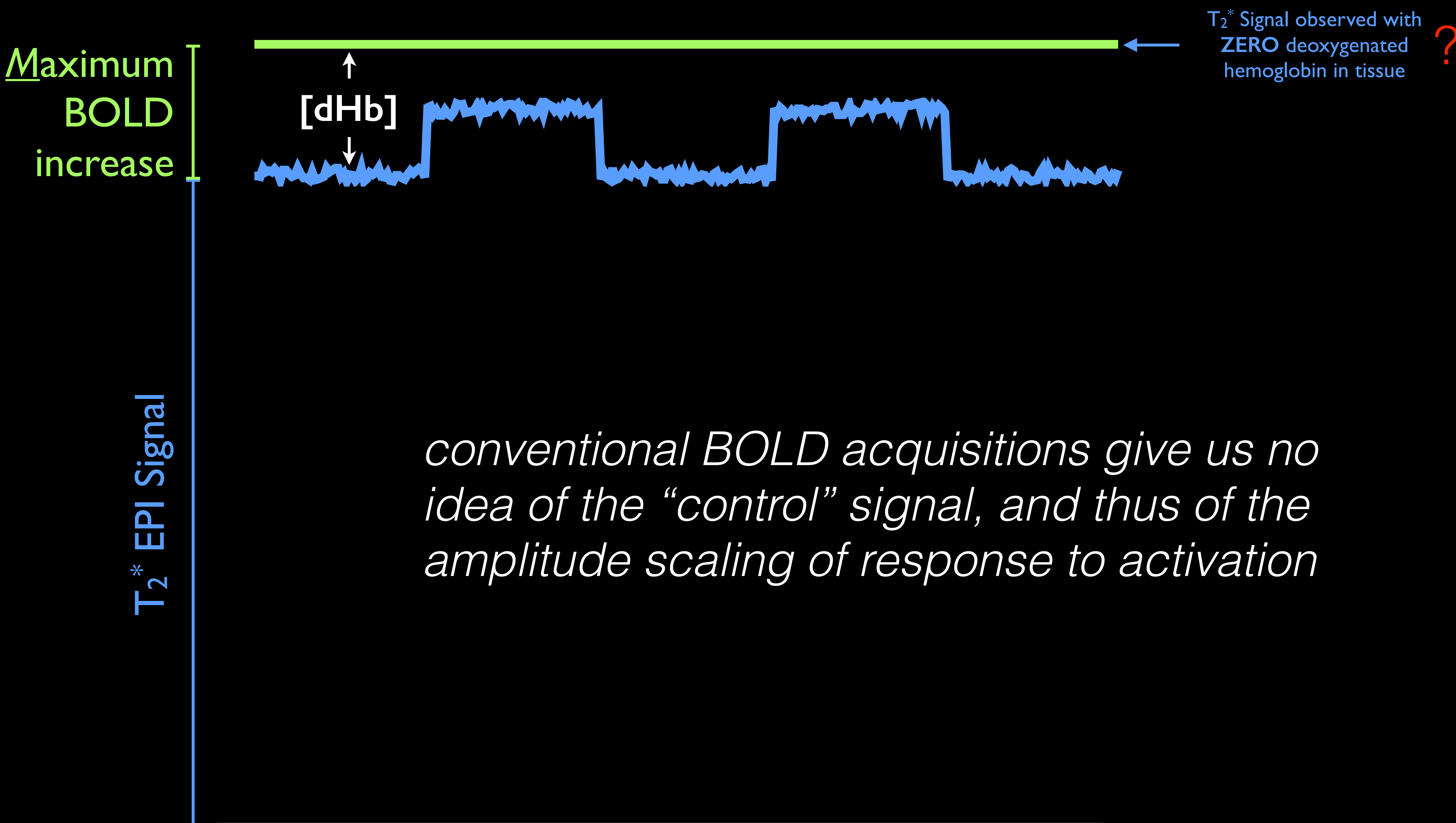


How ASL achieves physiological specificity



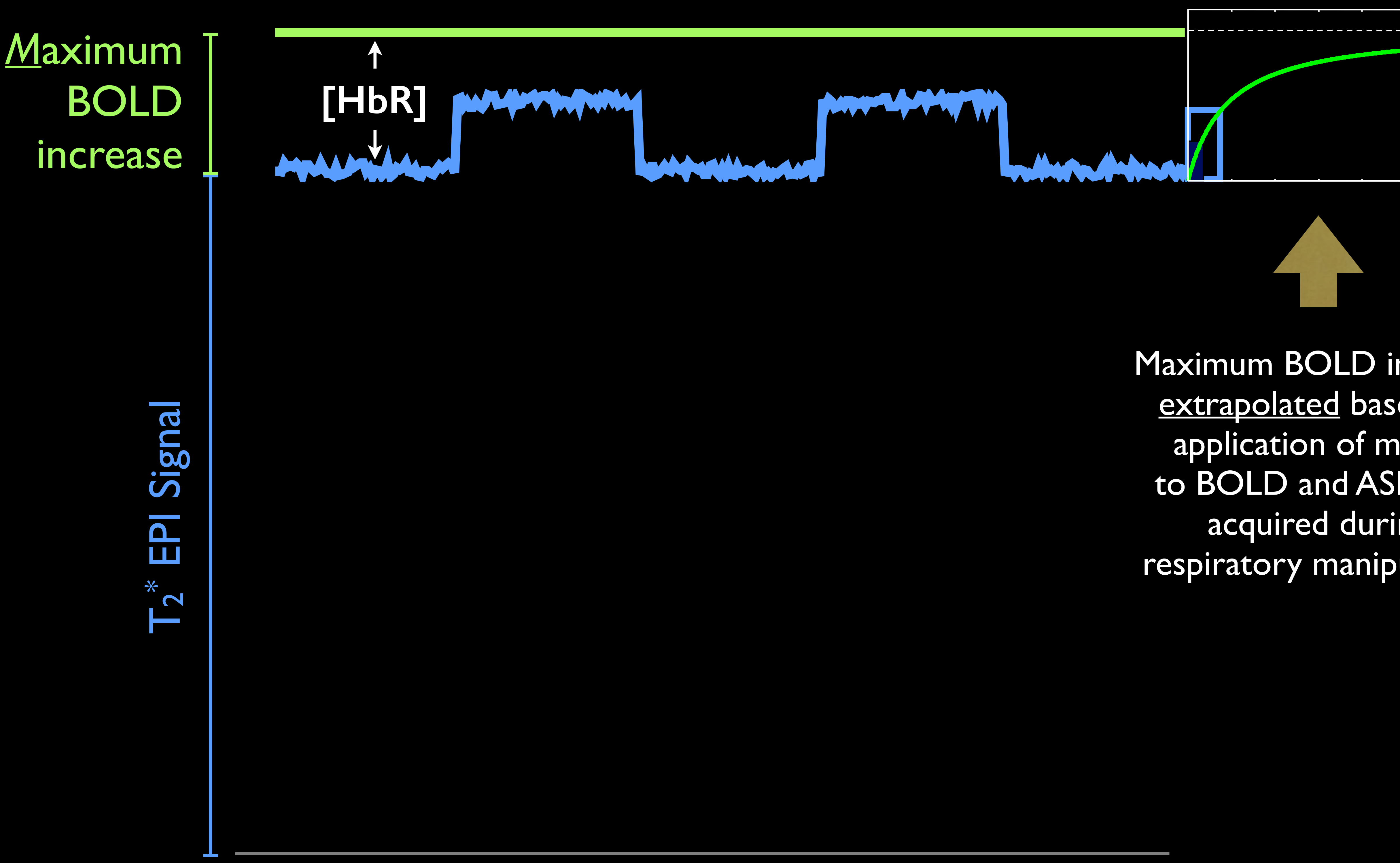
subtracting label and control signals allows isolation of the flow-dependent signal component

How can we make BOLD physiologically specific?



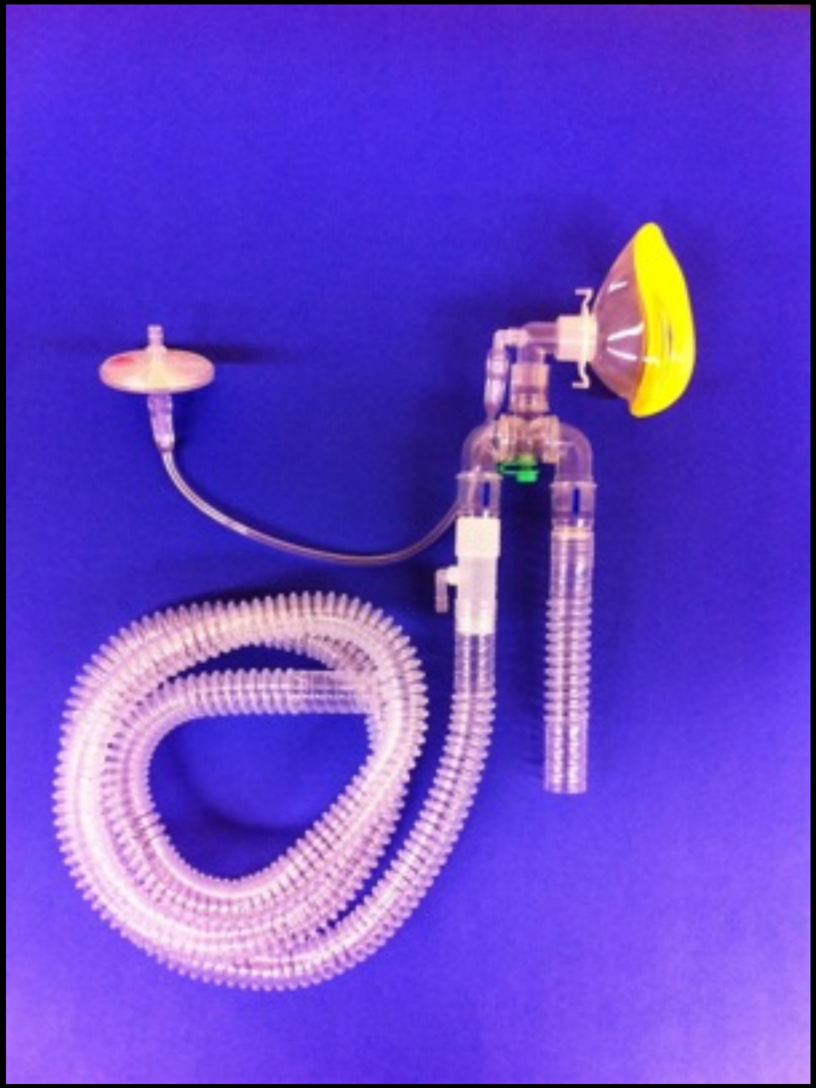
conventional BOLD acquisitions give us no idea of the "control" signal, and thus of the amplitude scaling of response to activation

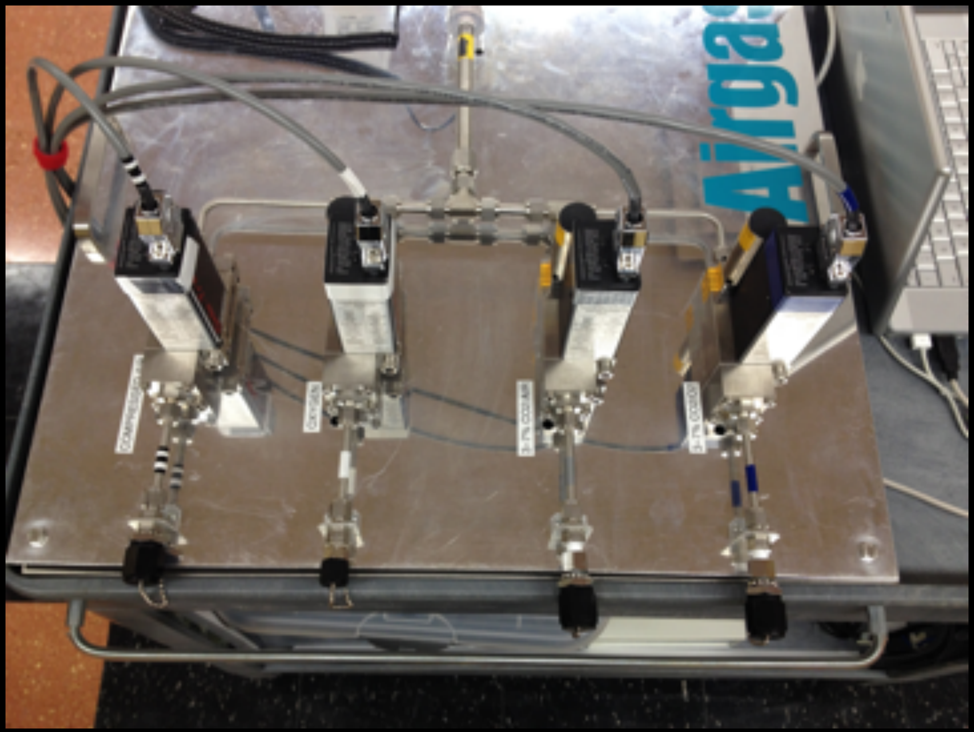
BOLD calibration: model and extrapolate



Maximum BOLD increase <u>extrapolated</u> based on application of model to BOLD and ASL data acquired during respiratory manipulation

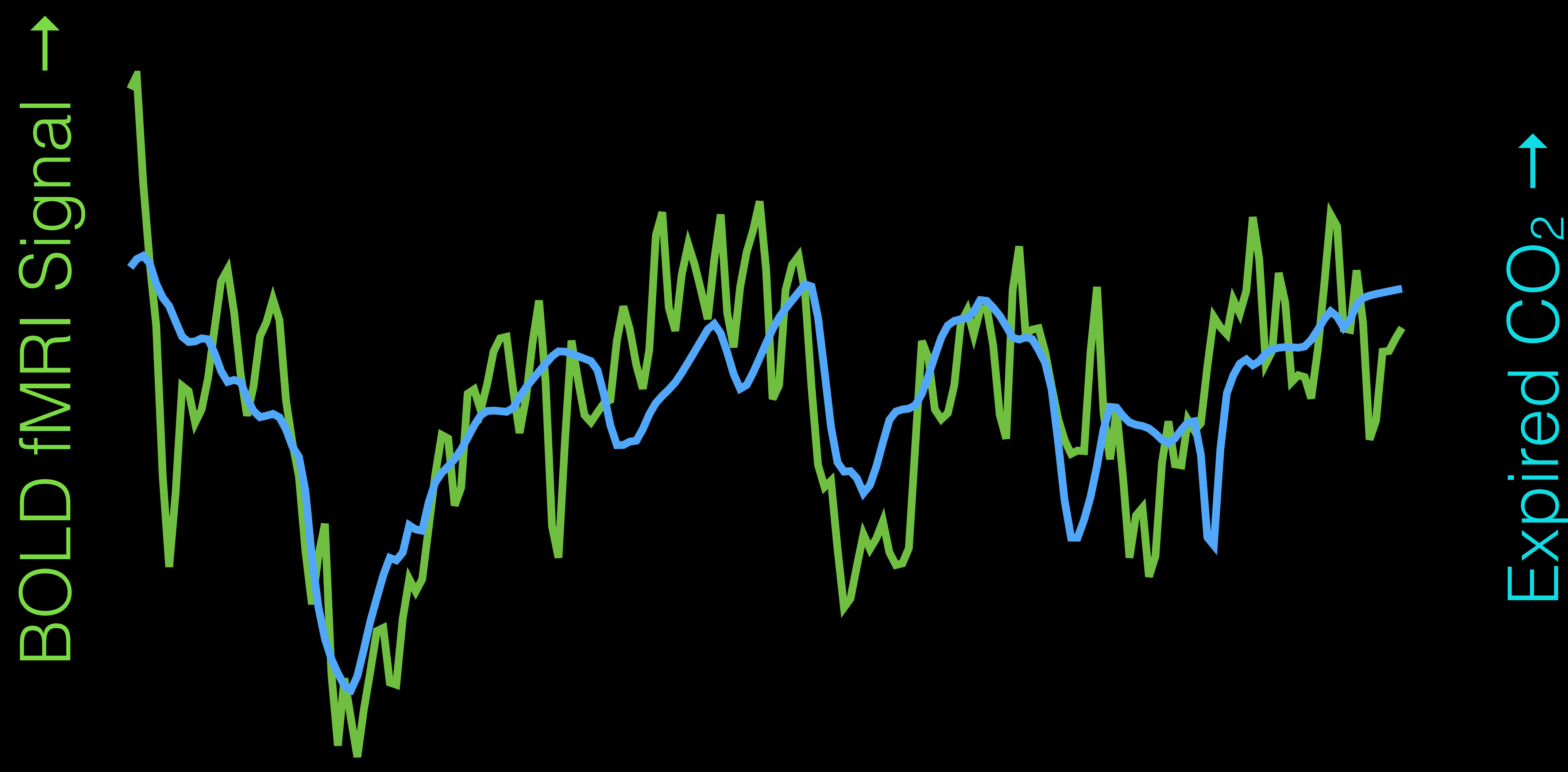
Induction of hypercapnia and hyperoxia for BOLD calibration





Tancredi, Lajoie, Hoge (2014). A simple breathing circuit allowing precise control of inspiratory gases for experimental manipulations. BMC Research Notes, 7:235.

BOLD signal is strongly correlated with blood CO_2 levels, due to vasodilatory effects

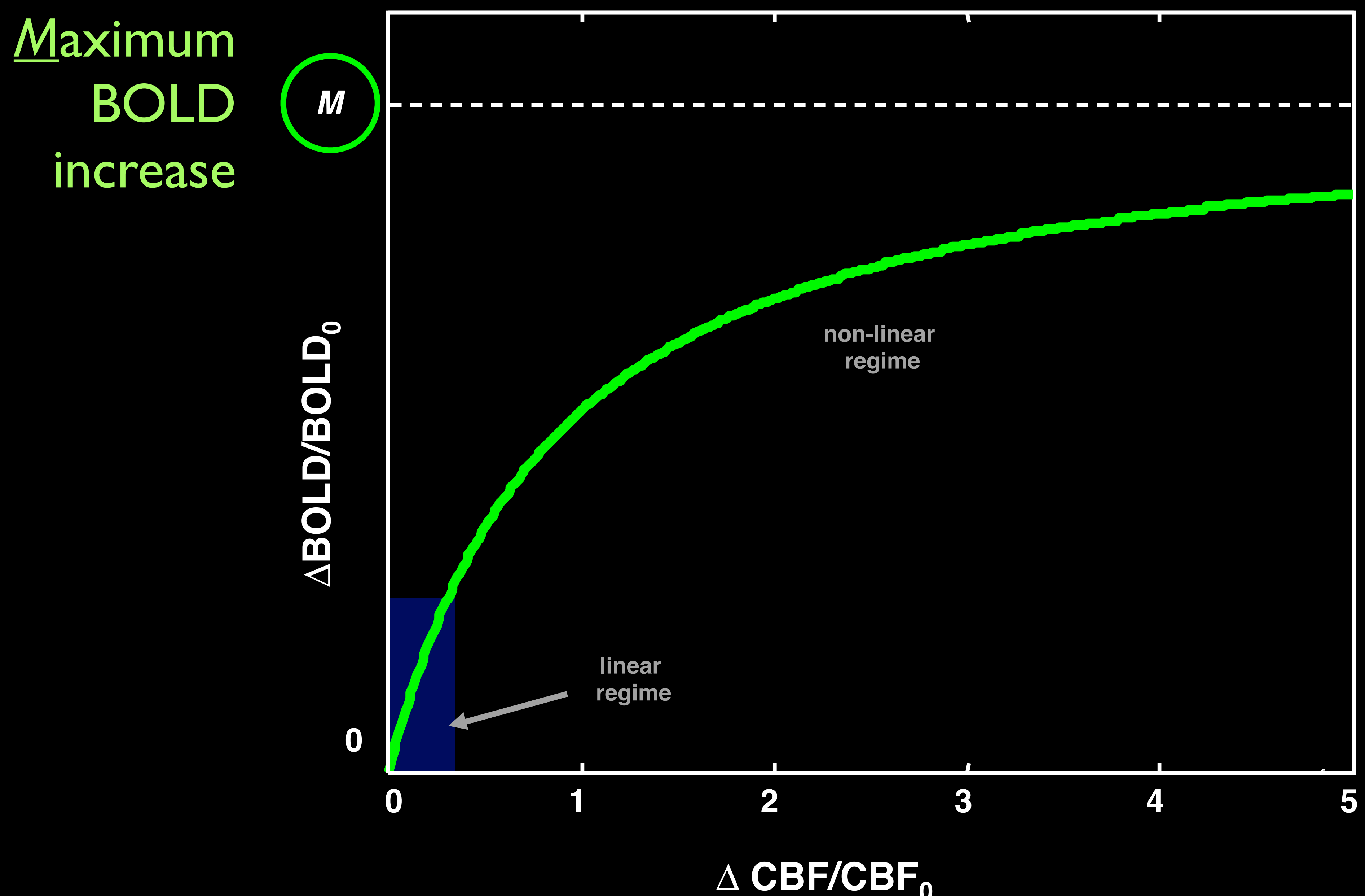


Spontaneous fluctuations in CO_2 and BOLD

Monitoring expired respiratory gases as a surrogate for blood gas

Sensor modules record end-tidal CO_2, O_2

Hypercapnic Calibration of BOLD



$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CBV_v}{CBV_{v_0}}\right)\left(\frac{[dHb]_v}{[dHb]_{v_0}}\right)^{\beta}\right)$$

Davis et al. 1998
Hoge et al. 1999

Knowing “*M*” allows computation of fractional change in CMRO2 during activation

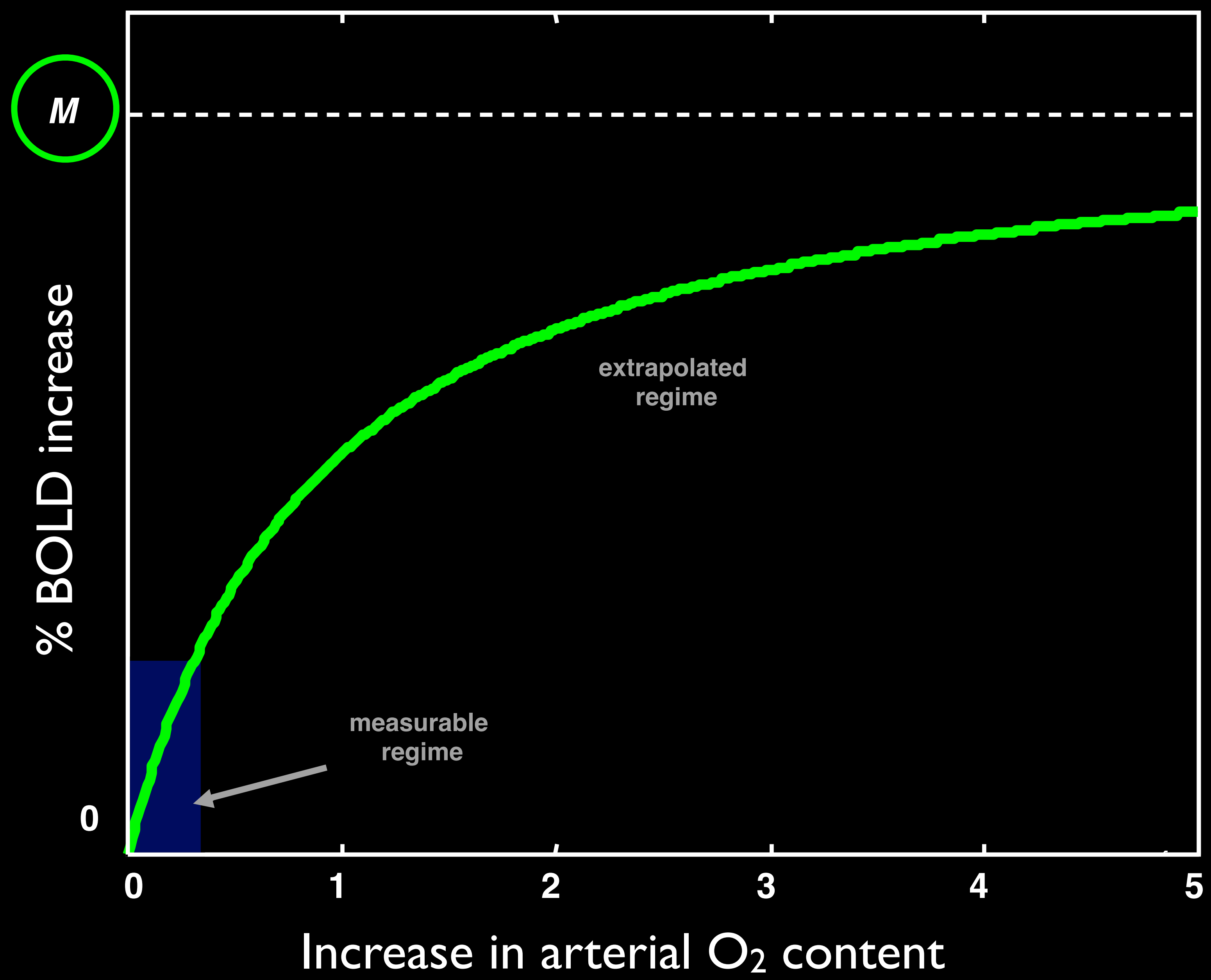
$$\frac{\mathrm{CMR}_{\mathrm{O}_2}}{\mathrm{CMR}_{\mathrm{O}_2}\big|_0} = \left(1 - \frac{\left(\frac{\Delta\mathrm{BOLD}}{\mathrm{BOLD}_0}\right)}{M}\right)^{1/\beta} \left(\frac{\mathrm{CBF}}{\mathrm{CBF}_0}\right)^{1-\alpha/\beta}$$

- only fractional *change* in $CMRO_2$
- baseline CMRO2 remains unknown

Davis, T. L., Kwong, K. K., Weisskoff, R. M., & Rosen, B. R. (1998). Calibrated functional MRI: mapping the dynamics of oxidative metabolism. Proceedings of the National Academy of Sciences of the United States of America, 95(4), 1834–1839.

Hyperoxic Calibration of BOLD

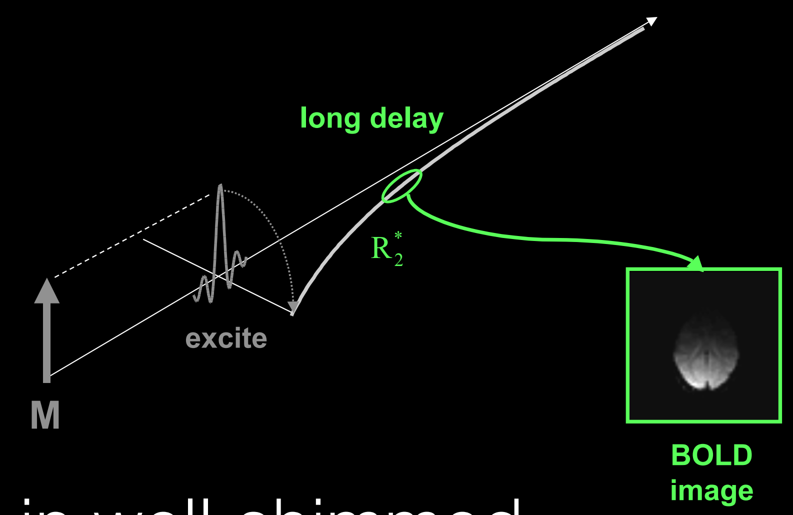
*M*aximum BOLD increase



Chiarelli, P. A., Bulte, D. P., Wise, R., Gallichan, D., & Jezzard, P. (2007). A calibration method for quantitative BOLD fMRI based on hyperoxia. NeuroImage, 37(3), 808–820. doi:10.1016/j.neuroimage.2007.05.033

$$\frac{\Delta BOLD}{BOLD} = M\left(1 - \left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]_v}{[dHb]_{v0}} + \frac{CBF_0}{CBF} - 1\right)^{\beta}\right)$$

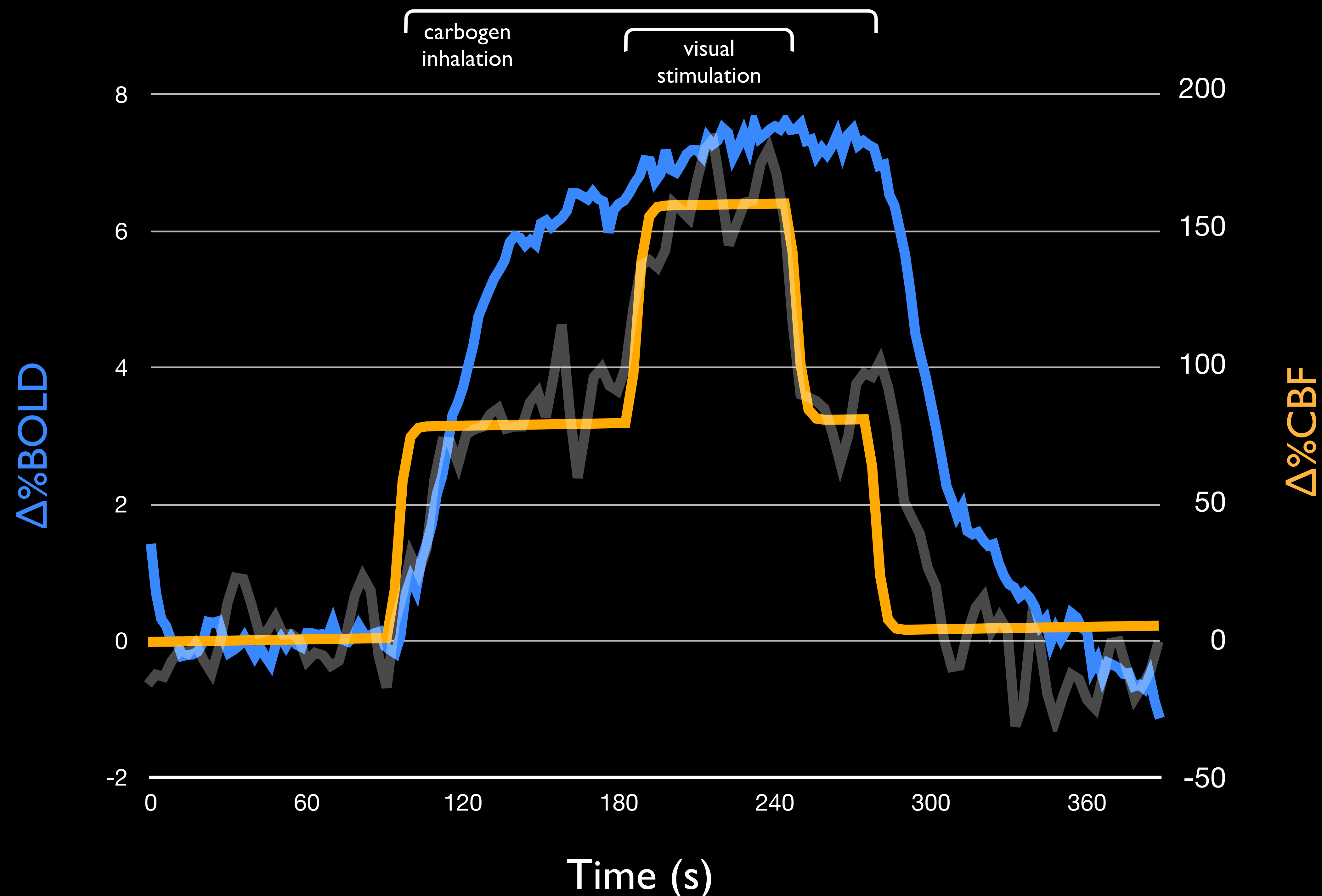
Non-respiratory calibration methods



- $R_2^* = R_2 + R_2'$
- reversible and non-reversible signal loss
- reversible signal loss (R_2') is largely due to dHb in well-shimmed brain tissue
- estimating R_2' in a voxel allows determination of M
- this is difficult in many brain regions due to large-scale susceptibility effects
- do not get vascular reactivity information available from hypercapnia

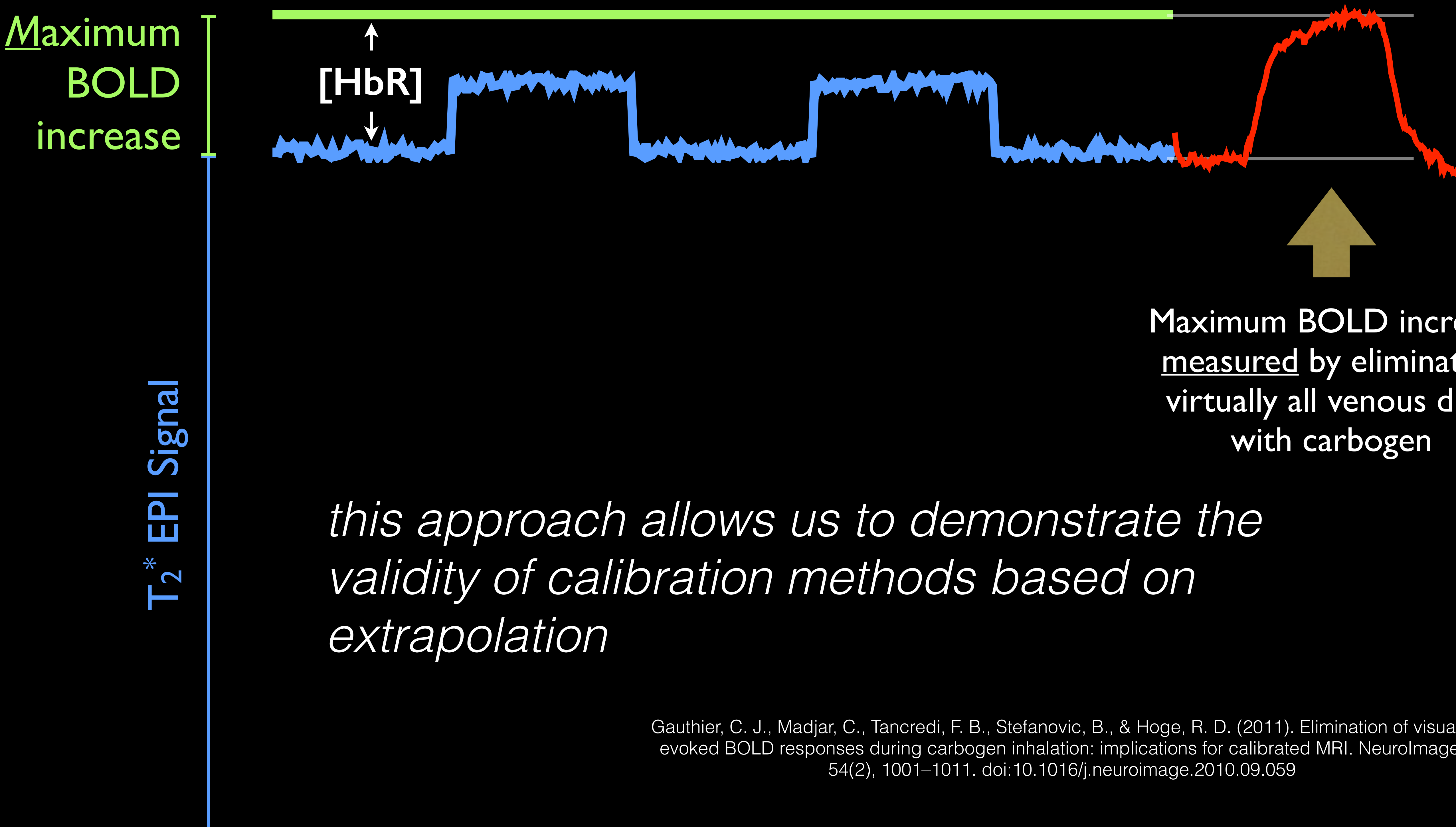
Blockley, N. P., Griffeth, V. E. M., & Buxton, R. B. (2011). A general analysis of calibrated BOLD methodology for measuring CMRO(2) responses: Comparison of a new approach with existing methods. NeuroImage, 60(1), 279–289. doi:10.1016/j.neuroimage.2011.11.081

"Brute force" calibration using carbogen



Gauthier *et al.*, 2011

“Brute force” calibration using carbogen



Maximum BOLD increase <u>measured</u> by eliminating virtually all venous dHb with carbogen

this approach allows us to demonstrate the validity of calibration methods based on extrapolation

Gauthier, C. J., Madjar, C., Tancredi, F. B., Stefanovic, B., & Hoge, R. D. (2011). Elimination of visually evoked BOLD responses during carbogen inhalation: implications for calibrated MRI. NeuroImage, 54(2), 1001–1011. doi:10.1016/j.neuroimage.2010.09.059

Generalized calibration model (GCM)

$$\frac{[\mathrm{dHb}]_v}{[\mathrm{dHb}]_{v_0}} = \underbrace{\left(\frac{\dfrac{\left.Ca_{O_2}\right|_0 \cdot OEF_0}{\varphi[\mathrm{Hb}]}}{1 - \dfrac{\left.Ca_{O_2}\right|_0}{\varphi[\mathrm{Hb}]}\left(1 - OEF_0\right)} \right)}_{X} \left(\frac{CBF_0}{CBF}\right) + \underbrace{\left(\frac{1 - \dfrac{Ca_{O_2}}{\varphi[\mathrm{Hb}]}}{1 - \dfrac{\left.Ca_{O_2}\right|_0}{\varphi[\mathrm{Hb}]}\left(1 - OEF_0\right)} \right)}_{Y}$$

Flow dilution of HbR delivered in arterial blood and generated through local metabolism

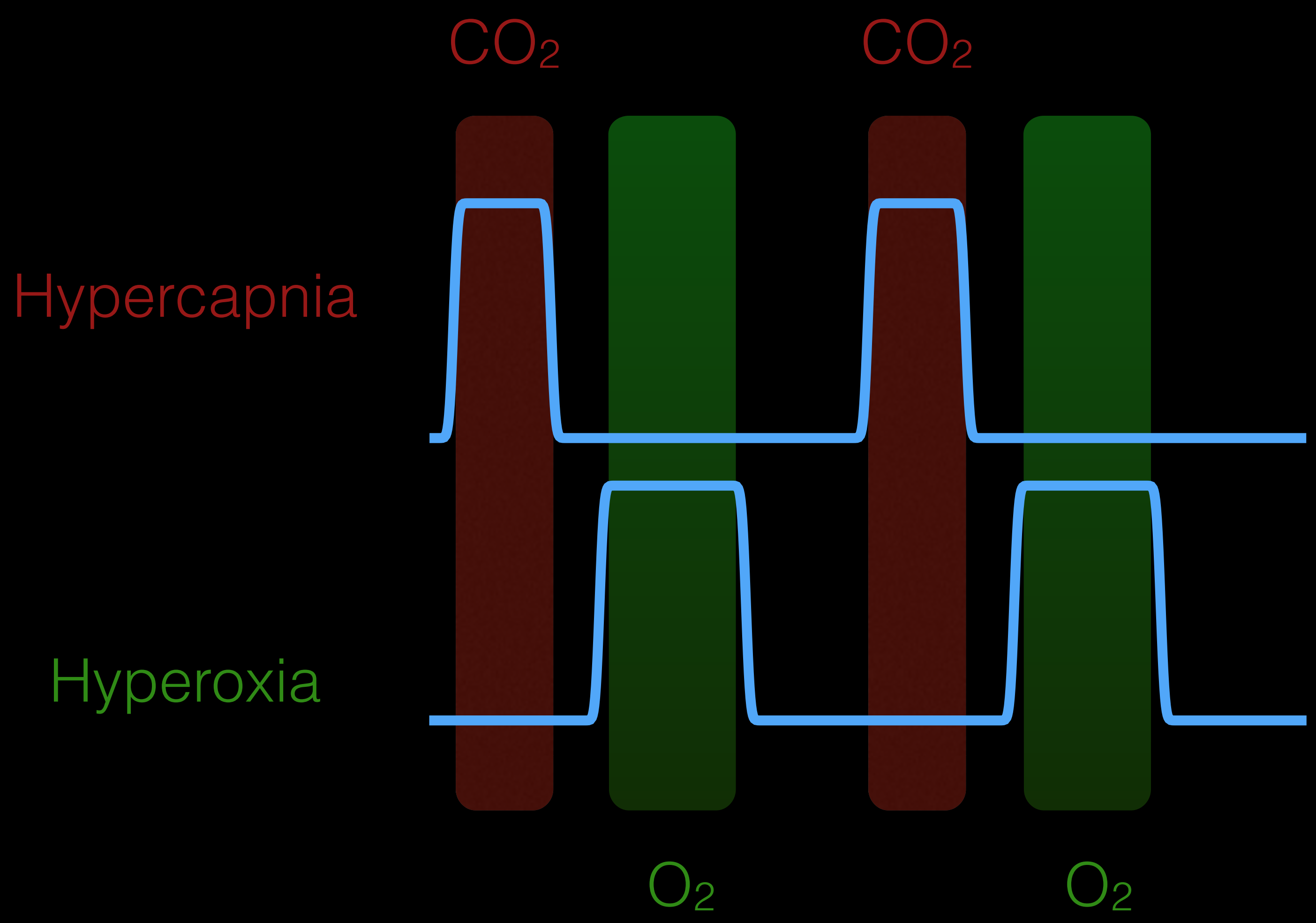
hypercapnia

Reduction of HbR from additional O_2 delivered in arterial blood

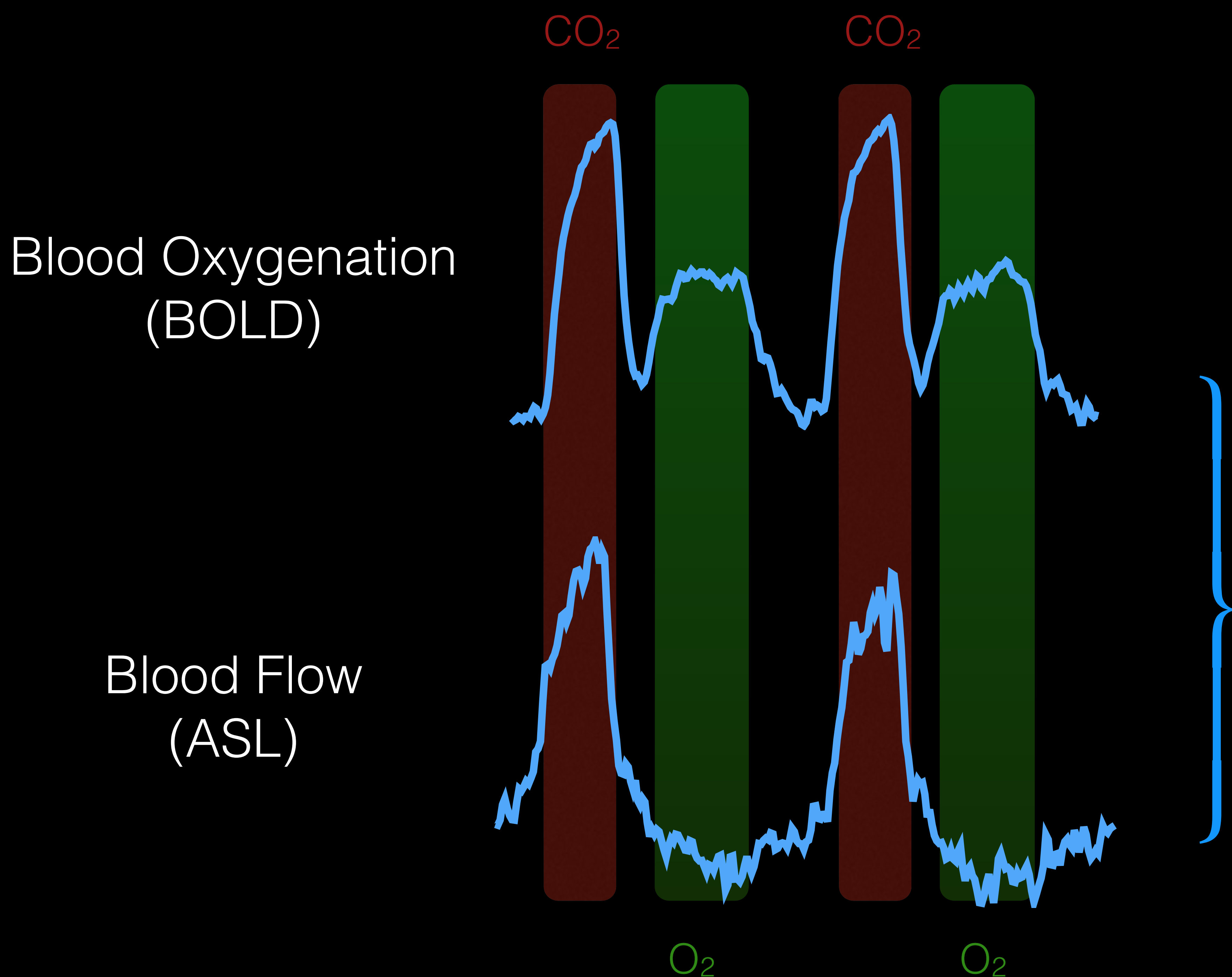
hyperoxia

Gauthier, C. J., & Hoge, R. D. (2011). Magnetic resonance imaging of resting OEF and CMRO(2) using a generalized calibration model for hypercapnia and hyperoxia. NeuroImage, 60(2), 1212–1225. doi: 10.1016/j.neuroimage.2011.12.056

Hybrid calibration with hypercapnia and hyperoxia

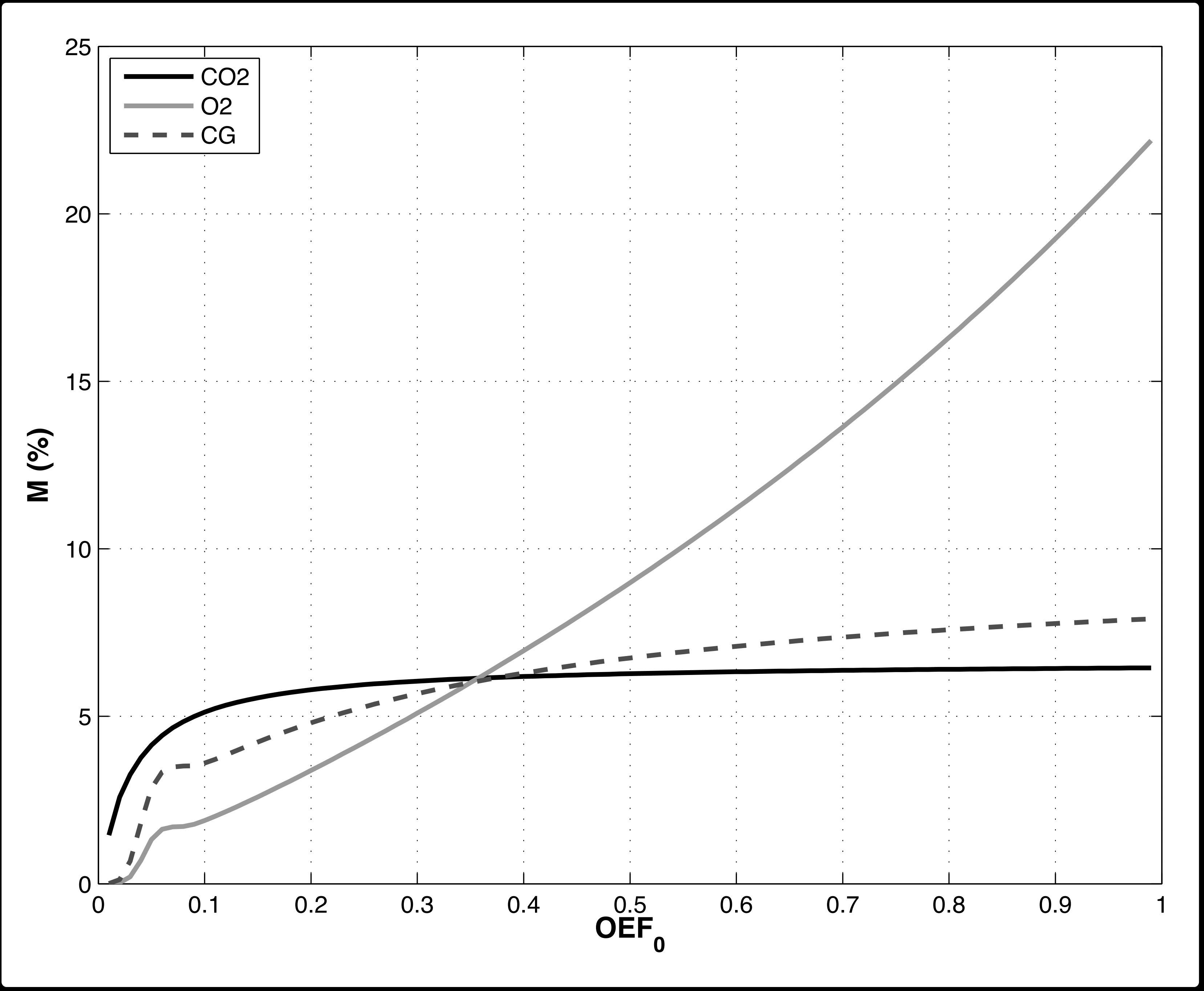


Controlled, orthogonal manipulations of blood flow and oxygenation



- Dual-echo pCASL MRI sequence
    - simultaneous flow and BOLD signals

M vs. OEF_0 curves for hyperoxia, hypercapnia, and carbogen



$$M = f(OEF_0\ ;\quad BOLD, CBF, PaO_2)$$

Gauthier and Hoge 2012

Reproducibility of M, CMRO2 and OEF measurements using QUO2 MRI and dual-echo pCASL

Isabelle Lajoie[1], Felipe B Tancredi[1], Danny J Wang[2], and Richard D Hoge[1]
[1]Centre de recherche de l'IUGM, Montreal, Quebec, Canada, [2]Neurology, University of California, Los Angeles, CA, United States

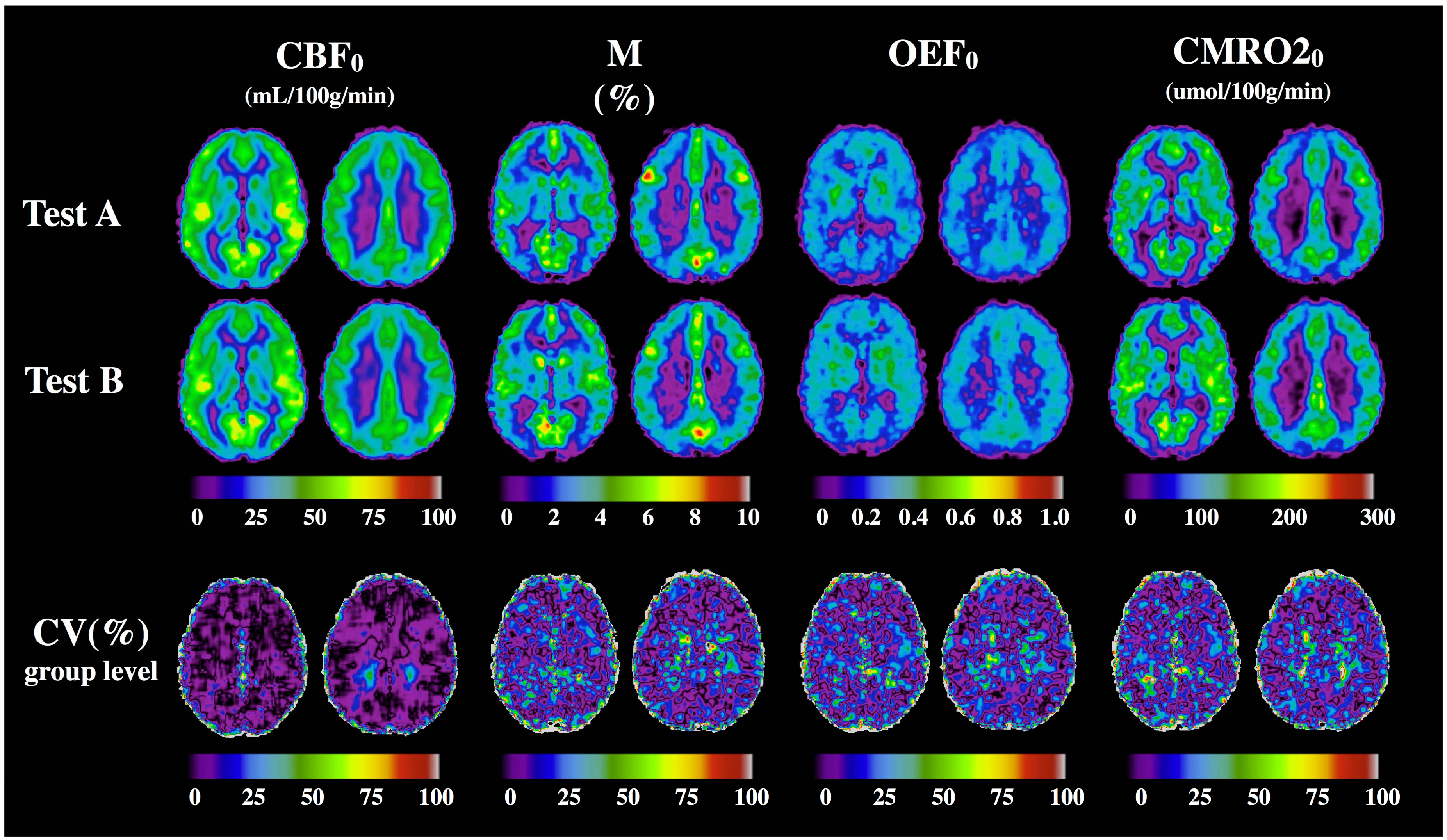


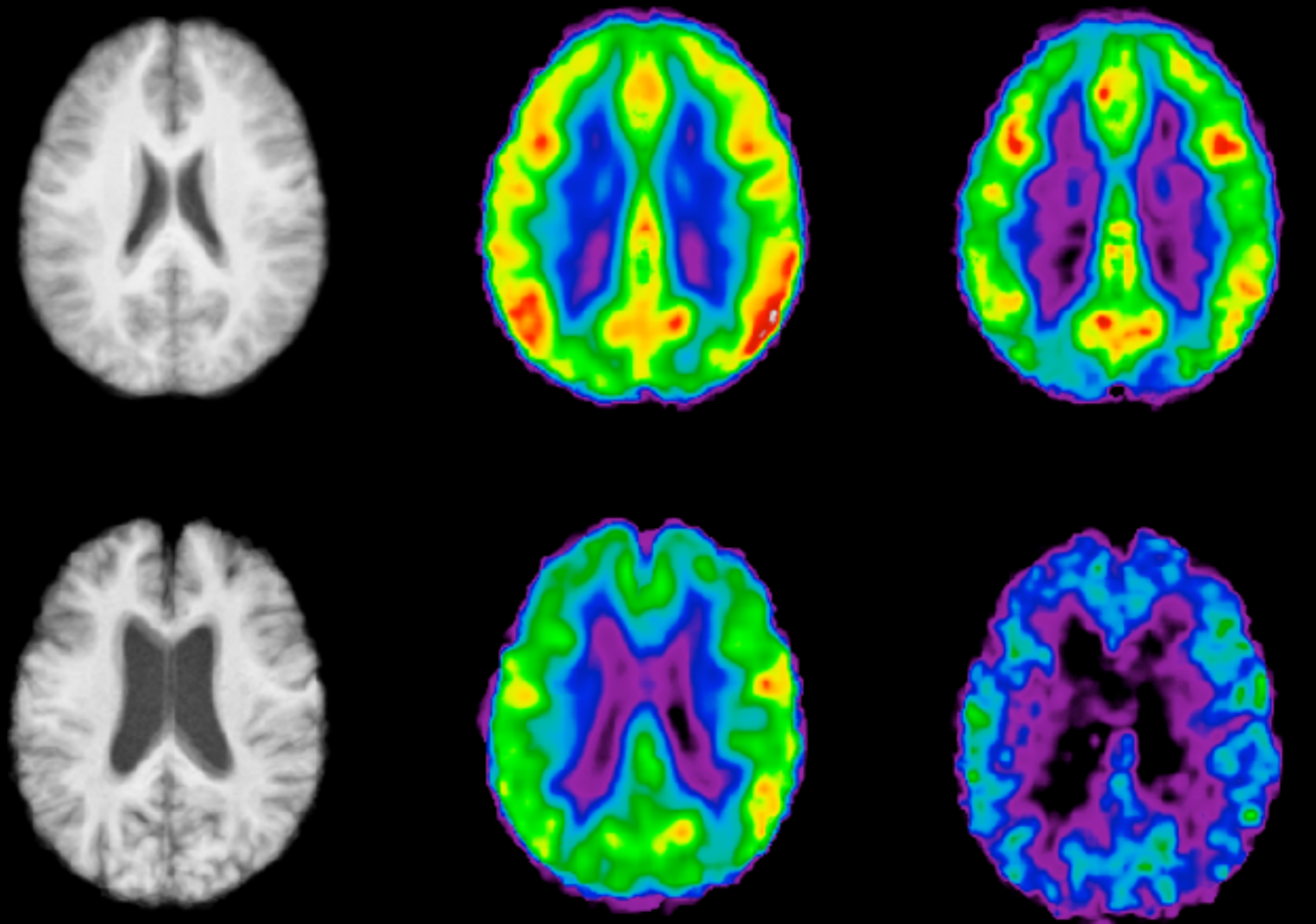
Figure 2. Two different slices of group-average maps for Test A and Test B, with corresponding CV% maps computed at group-average level

Preliminary resting $CMRO_2$ Data in Alzheimer's Disease

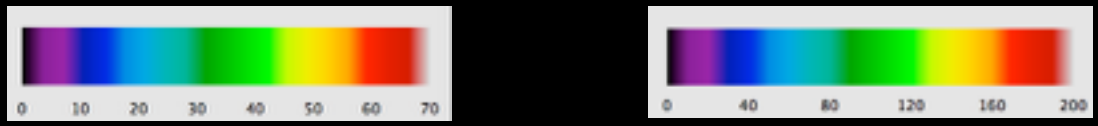
Anatomy | Blood Flow | Oxidative Metabolism

Control
n=6 average maps
*not demographically matched to patients

Alzheimer
n=6 average maps



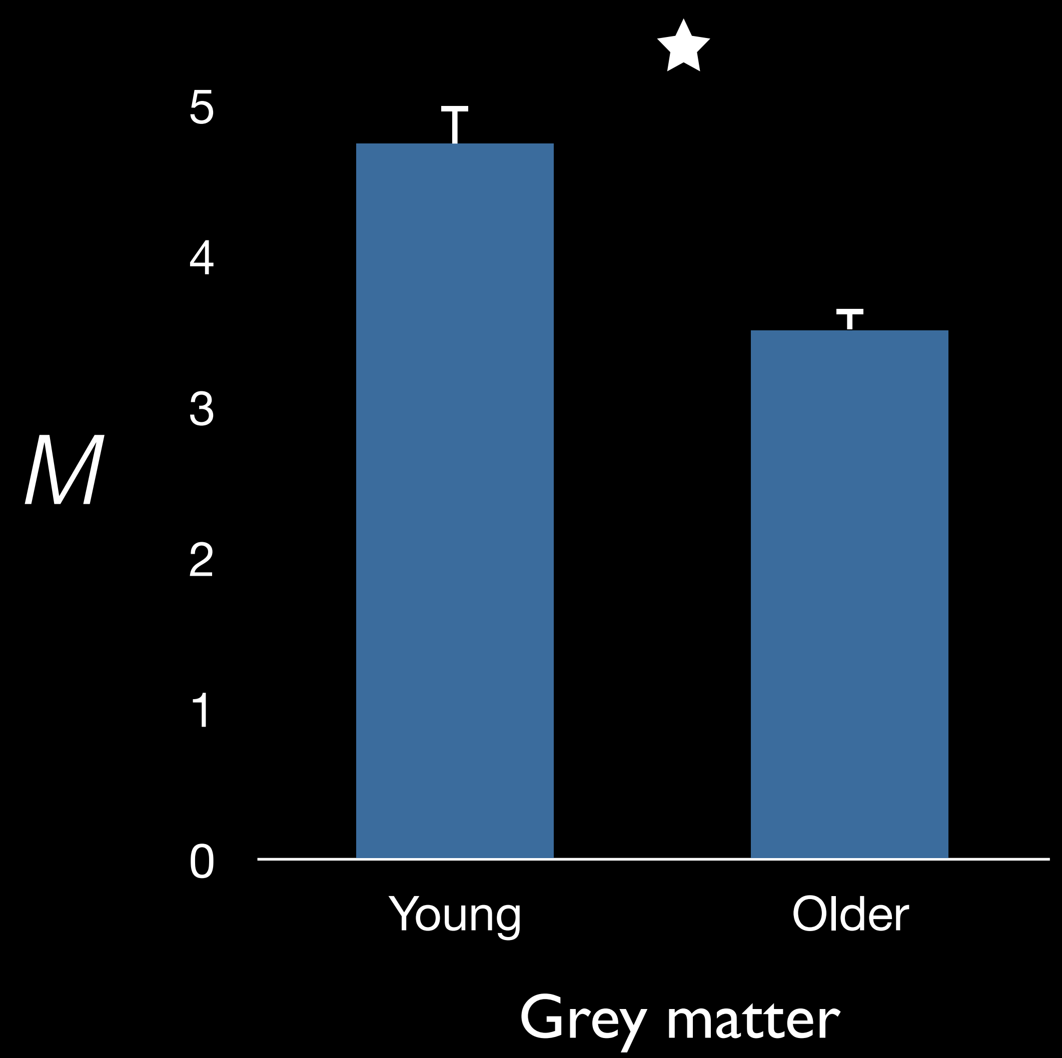
T1w MRI



ml/100g/min

μmol/100g/min

Example: implication for aging studies



- lower M value in older individuals leads to smaller BOLD change for a given physiological response (flow, metabolism)

Concerns related to gas methods

- comfort/safety
- complexity/availability of equipment
- does hypercapnia increase $CMRO_2$?

Current state of gas methods

- can be performed using pulse sequences that are readily available on all three major clinical MRI vendors (Siemens, GE, Philips)

- current protocols are comfortably tolerated by elderly individuals, including Alzheimer's patients

    - we have scanned over 100 individuals (young, elderly) using hypercapnic calibration, and the procedure is extremely well tolerated

    - we are now scanning 2-4 Alzheimer's patients per week with hybrid hyperoxia/hypercapnia calibration, also with excellent tolerability in patients

Current state of gas methods

- ASL response to hypercapnia (CO_2) provides an index of cerebrovascular reactivity, which is clinically and physiologically relevant

- hybrid hyperoxia and hypercapnia approaches provide resting $CMRO_2$ in micromolar units, plus a rich array of other data that may be useful (BOLD/ASL to CO_2/O_2)

- new experimental paradigms (carbogen, solution of generalized calibration model in overdetermined systems) have demonstrated the validity of these approaches

How can we make these technologies more accessible?

- low-cost breathing circuit
  - can be built from “off-the-shelf” components (~$30CDN/circuit)
  - excellent results can be achieved using manual flow control
  - BIOPAC or equivalent monitoring is required, but this is available at many research sites
- working on SOP documentation for a simple, low-cost implementation that we will share with neuroimaging community via open-access channels

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