HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2008

HST.583: Functional Magnetic Resonance Imaging: Data Acquisition and Analysis, Fall 2008
Harvard-MIT Division of Health Sciences and Technology
Course Director: Dr. Randy Gollub.

BOLD Imaging I

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Imaging Physiology Block

- Lecture 1: Neural activity, energy metabolism, and cerebral blood flow in the resting brain
- Lecture 2: Brain activation and intro to BOLD fMRI
- Lecture 3: BOLD Imaging I
- Lecture 4: Bold Imaging II and Beyond BOLD: State-of-the art fMRI techniques

Overview

- BOLD review
- BOLD response to *blocks* and *events*
- Linearity of BOLD response
- Modeling the BOLD signal
  - Main response
  - Post-stimulus undershoot
  - Initial Dip

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Review of BOLD fMRI

- dHb is paramagnetic agent; decreases signal in T_2/T_2^* -weighted MR imaging
- Neuronal activity leads to:
  - Small ↑ in $CMRO_2$ = Small ↑ in dHb
  - Large ↑ in CBF = Large ↓ dHb
  - **Net effect = ↑ in dHb:** *fresh oxygenated blood flushes out deoxygenated blood (dHB)*
  - ***MR signal increases***
- **This is BOLD in simplest terms**

Review of BOLD fMRI

1. External stimulus increases neural activity
2. $CMRO_2$ increases slightly, resulting in a transient *increase* in dHb, and a transient *decrease* in BOLD

Embedded animation removed due to copyright restrictions.
See http://www.sinauer.com/neuroscience4e/animations1.1.html
(Website for Purves et al. *Neuroscience*. 4th edition. Sunderland, MA: Sinauer Associates, 2008.)

Fast response: ↑ in $CMRO_2$ → ↑ dHb content → ↓ BOLD signal!

Review of BOLD fMRI

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See http://www.sinauer.com/neuroscience4e/animations1.1.html
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1. External stimulus increases neural activity
2. $CMRO_2$ increases slightly, resulting in a transient *increase* in dHb, and a transient *decrease* in BOLD
3. CBF begins to increase substantially, delivering more HbO_2
4. HbO_2 (now abundant) displaces dHb; BOLD signal *increases*

Slow response: ↑↑ CBF →

↓↓ dHb → ↑↑ BOLD signal!

Review of BOLD fMRI

- Thought question: *Ignoring timing, what if CBF and $CMRO_2$ both increased by the same percent? Would we see much of a BOLD effect?*
- Probably not; the increased dHb content (via oxygen removal from HbO_2 via metabolism) would be exactly compensated by fresh HbO_2 brought in by CBF
- dHb/HbO_2 ratio and thus dHb content would not appreciably change*

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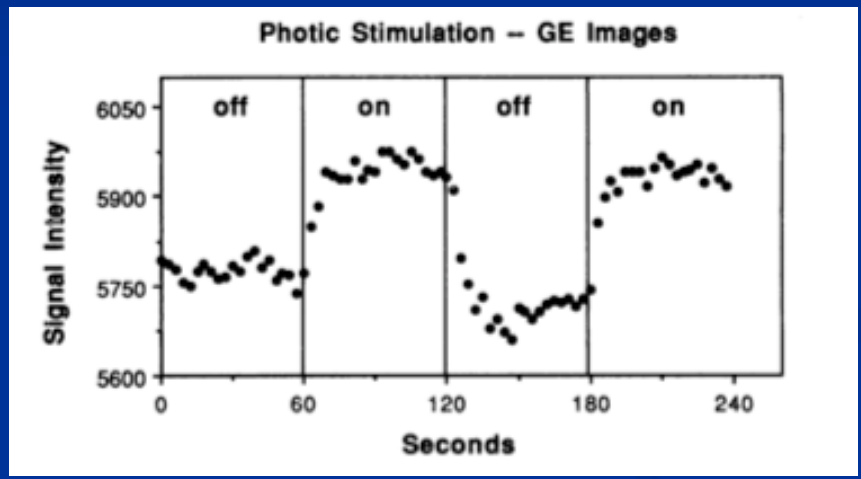
BOLD Response

- Recall first fMRI study



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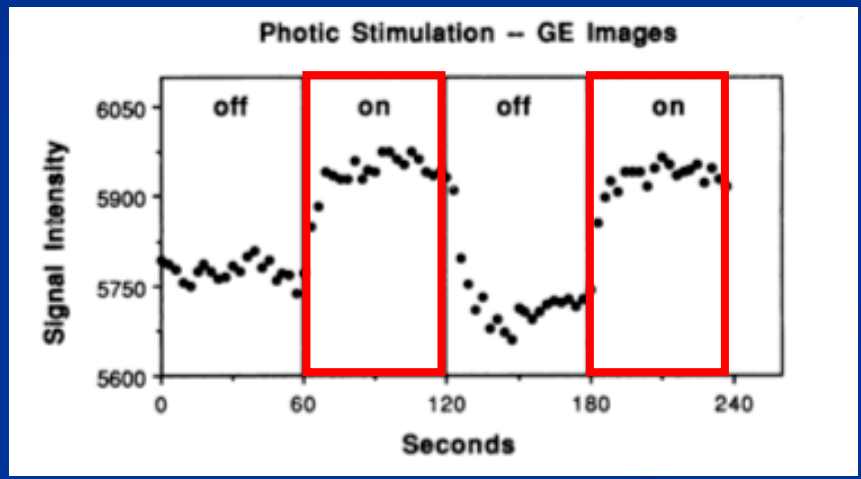

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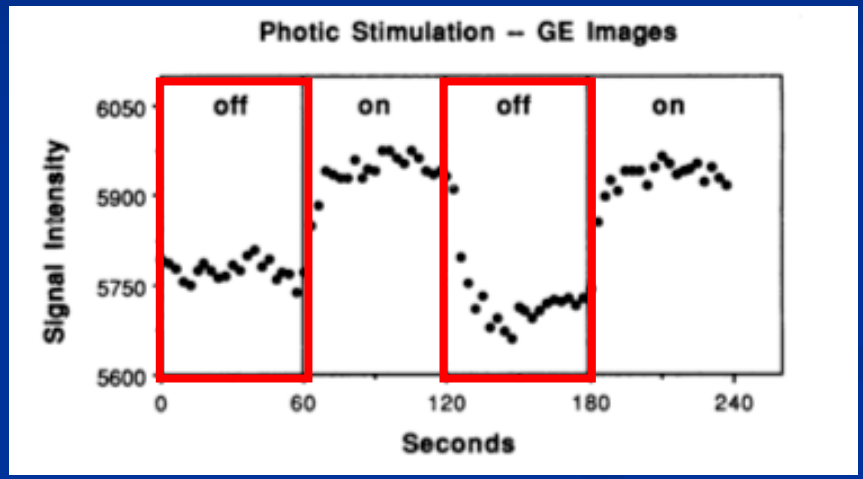
Kwong, K K, et al. "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." *PNAS* 89, no. 12 (1992): 5675-5679. Copyright © 1992, National Academy of Sciences, U.S.A.

- Experiment involved using a long duration visual stimulus (60 s), i.e. the “on” period

BOLD Response

- Recall first fMRI study



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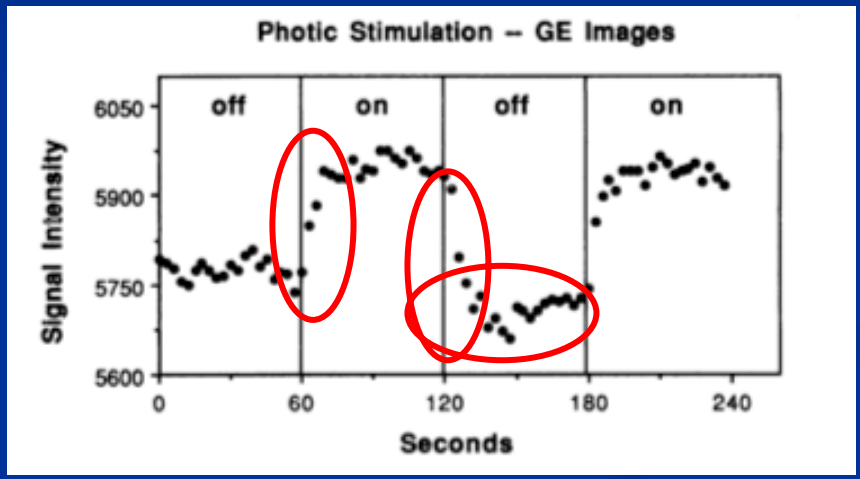
- Experiment involved using a long duration visual stimulus (60 s), i.e. the “on” period
- Interleaved with long “off” periods (60 s)

BOLD review

- Even earliest study revealed some characterisc features of the BOLD response:

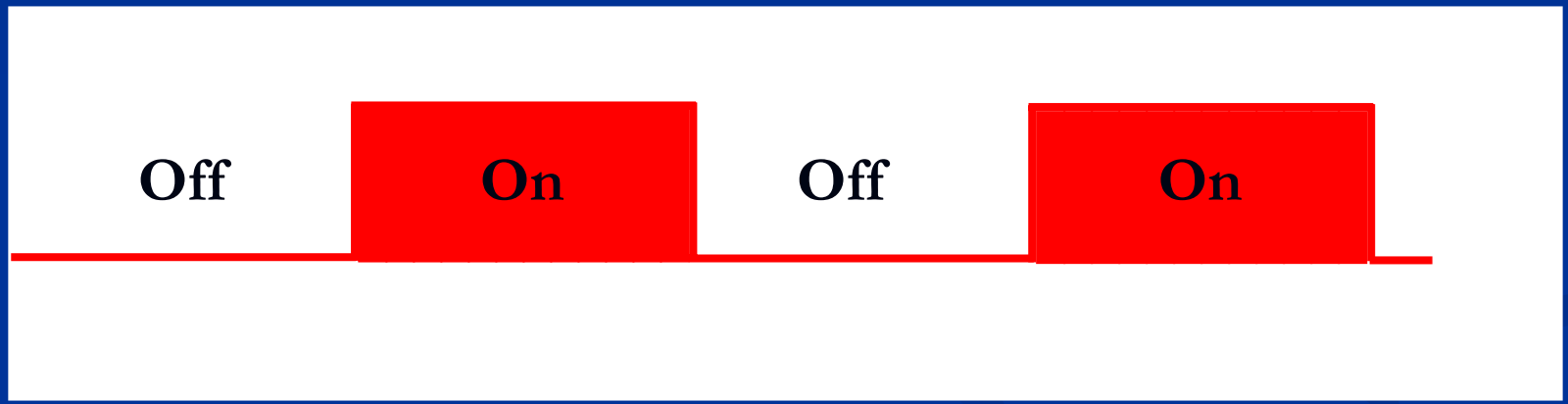


- *BOLD effect does not instantaneously follow stimulus*
- *There is a delay after stimulus onset and offset; undershoot after stimulus cessation*

BOLD: Epoch-related or blocked design

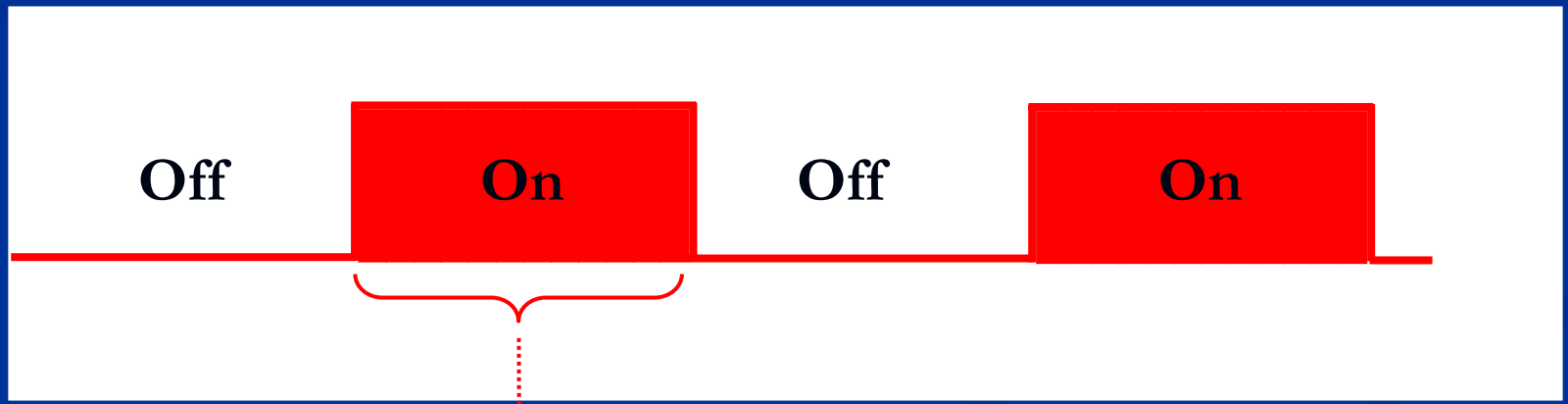
- This type of approach is known as a *blocked* or *epoch-related design*
- Sustained periods of stimulation produce sustained neural activity and a sustained BOLD response
- Employed by most early fMRI studies; provides a large response for maximal sensitivity

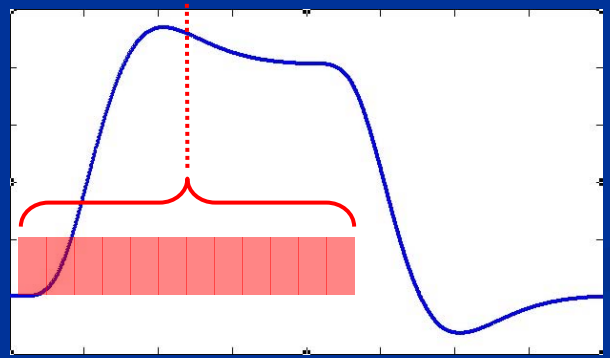
BOLD: Epoch-related or blocked design



Block stimulus yields strong BOLD response of extended duration

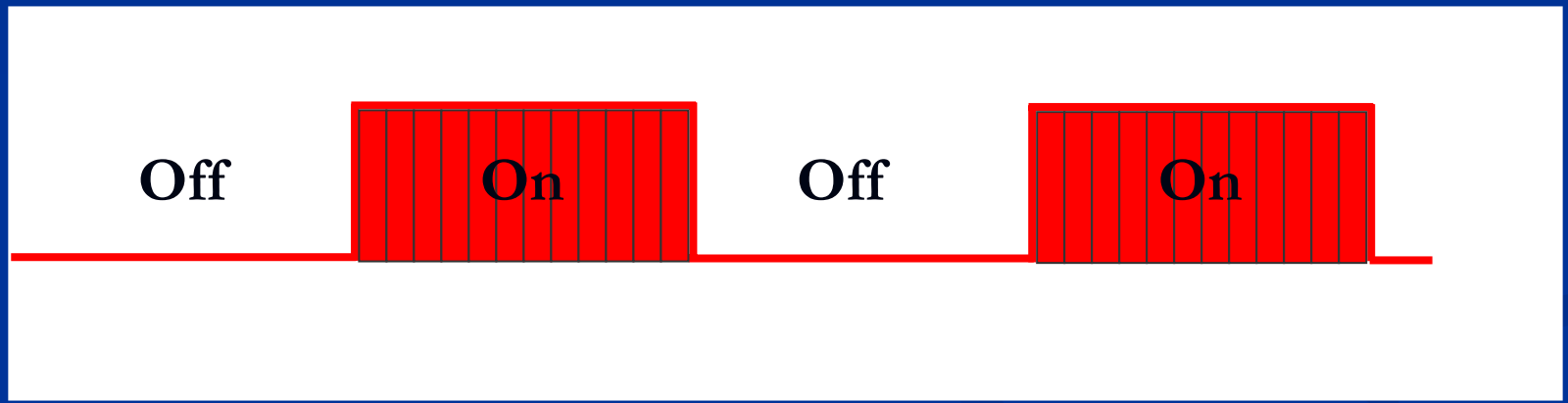
BOLD: Epoch-related or blocked design





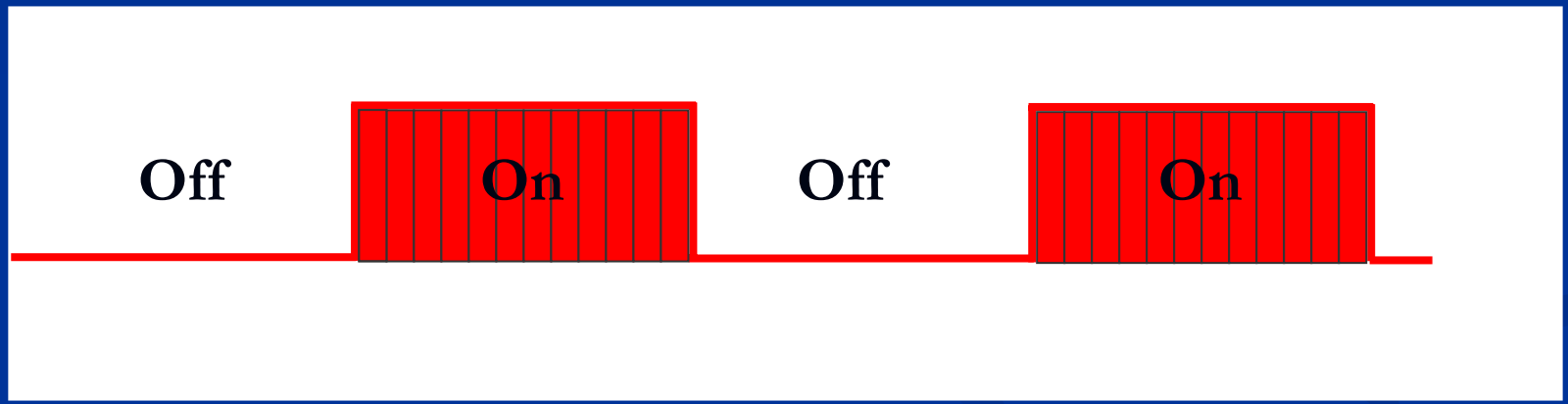
Block stimulus yields strong BOLD response of extended duration

BOLD: Epoch-related → Event-related



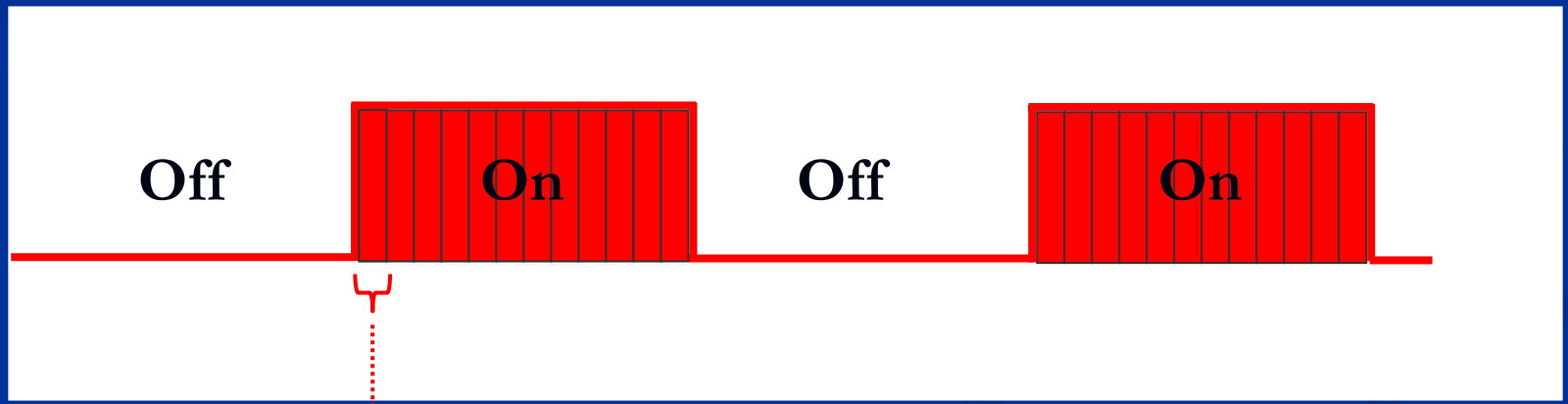
"On" period can also be thought of as being composed of many individual repeating *events*, clustered together

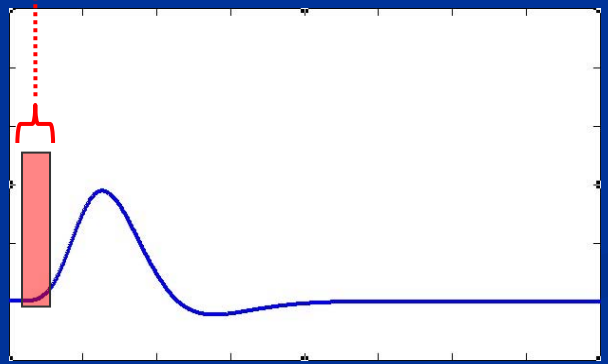
BOLD: Epoch-related → Event-related



Looking at the BOLD response from a *single* event …

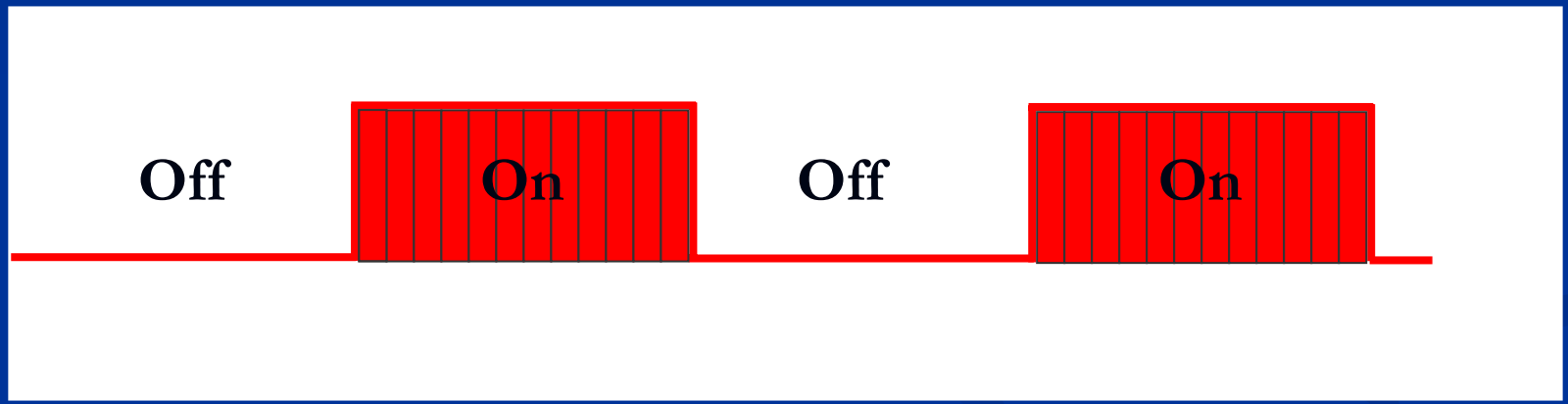
BOLD: Epoch-related → Event-related

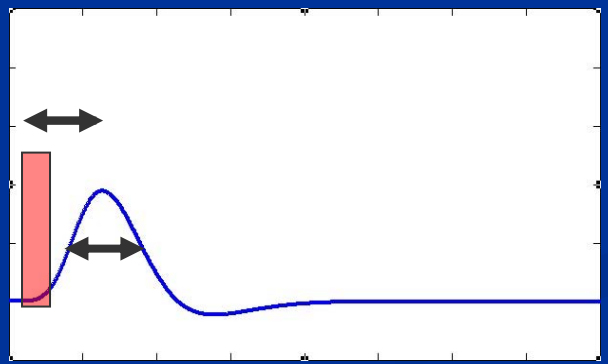




We'd see a much shorter, smaller amplitude response

BOLD: Epoch-related → Event-related

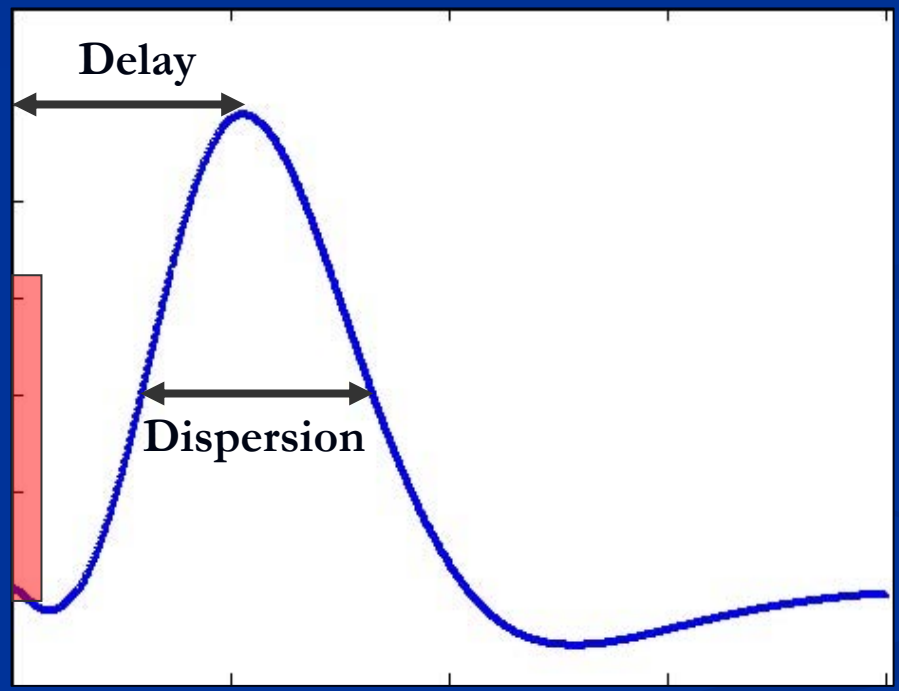




Notice both *delay* and *dispersion* from actual stimulus

BOLD: Event-related

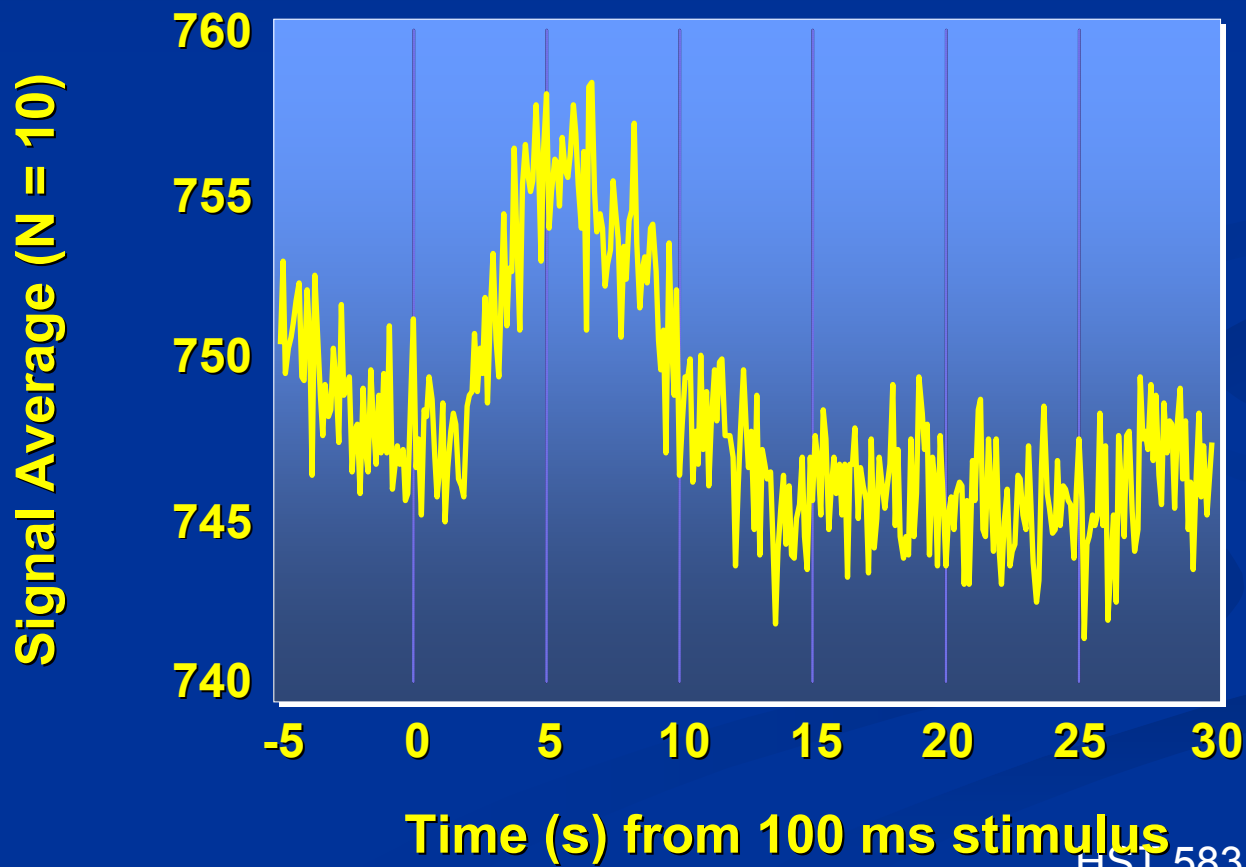
- BOLD response to event is known as the *impulse response* or *hemodynamic response*



- Many implications for fMRI design and analysis

BOLD: Event-related

- Experimentally measuring the hemodynamic response requires averaging to reduce noise



Courtesy of Robert Savoy, Ph.D., and Robert Weisskoff, Ph.D. Used with permission.

BOLD: Events and Epochs

- "*Event*" refers to a short-duration stimulus producing a *brief burst* of neural activity
- *"Epoch"* refers a block of consecutive events, clustered into "on" periods, interleaved with "off" periods, producing *sustained* neural activity

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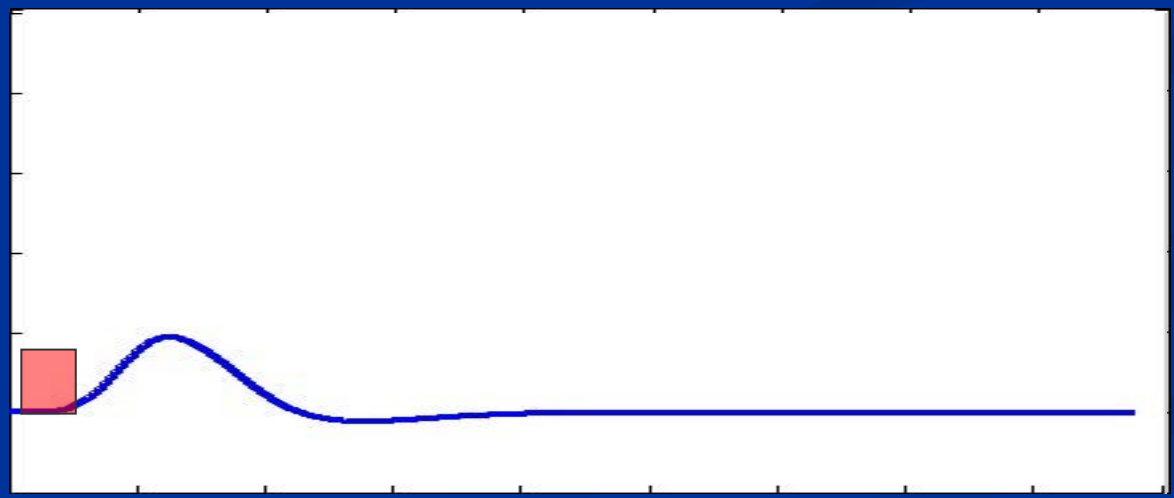
Linearity of BOLD hemodynamic response

- It has been shown that the BOLD hemodynamic response is roughly linear
- *Scaling* and *superposition* hold
- Scaling states that the output of a linear system is proportional to magnitude of its input
- Superposition states that the output of a linear system with more than one input is the sum of the responses to the individual inputs

Linearity of BOLD response

- *Scaling* property can be demonstrated by
  - Increasing stimulus intensity



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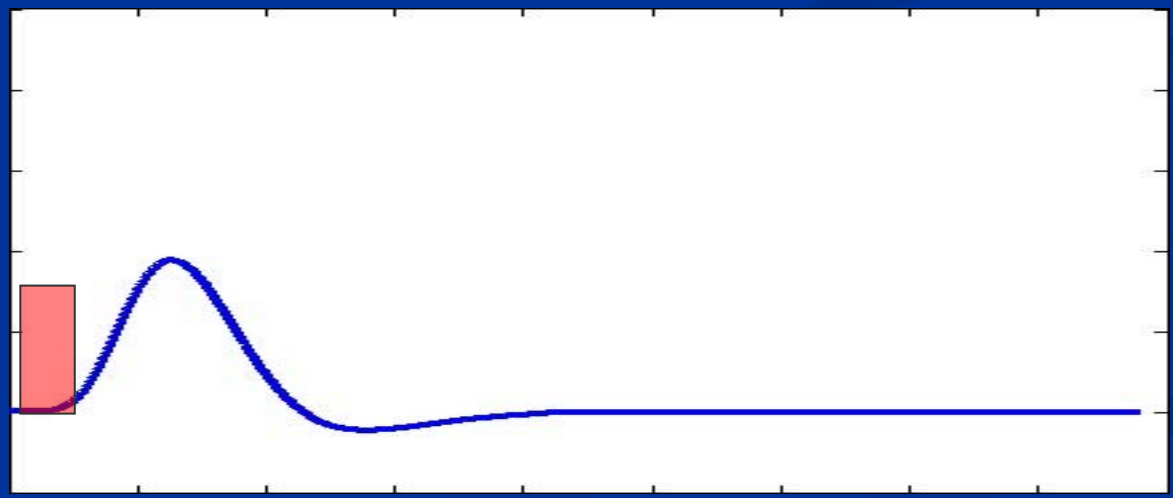

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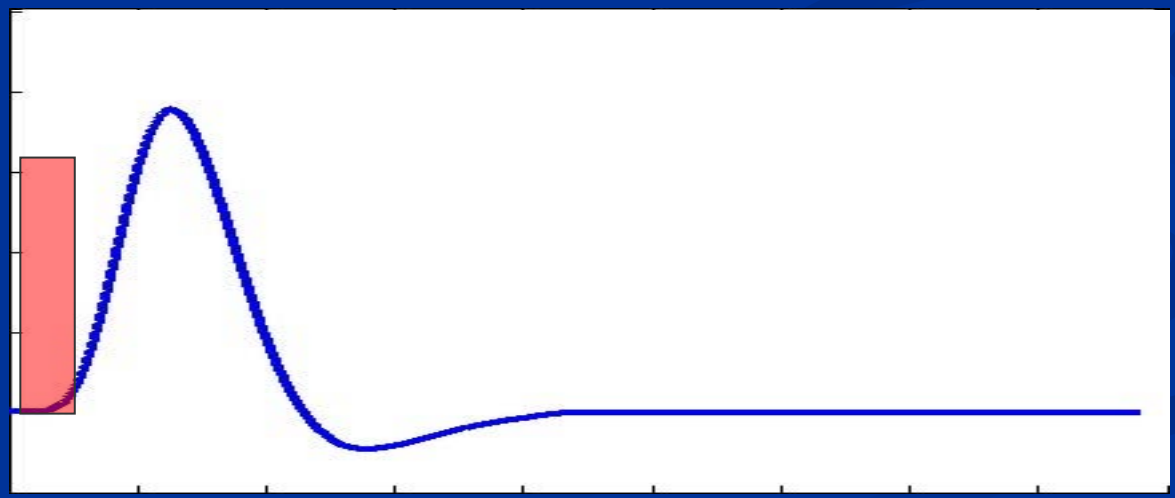
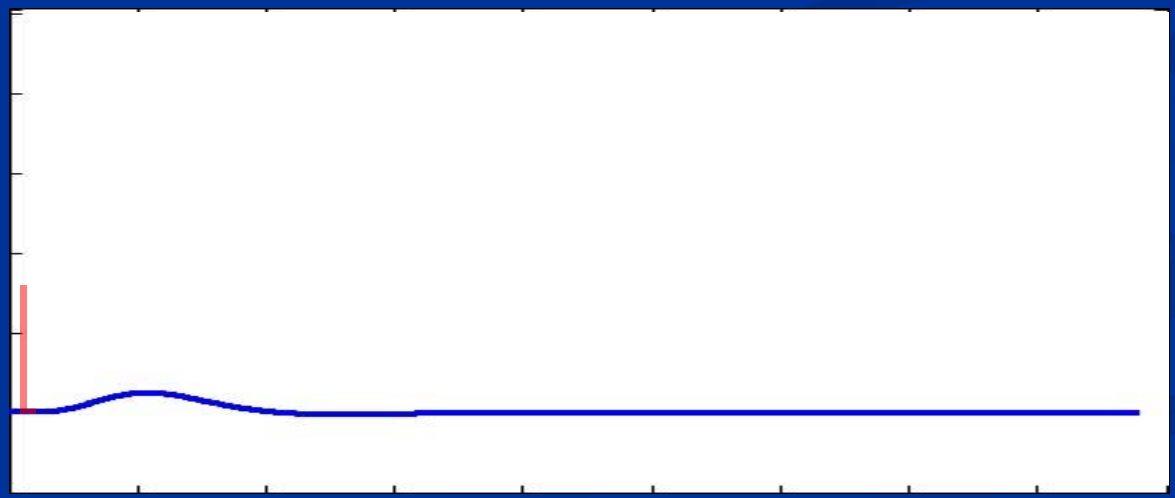


Linearity of BOLD response

- *Scaling* property can be demonstrated by
  - Doubling stimulus intensity
  - Doubling stimulus duration



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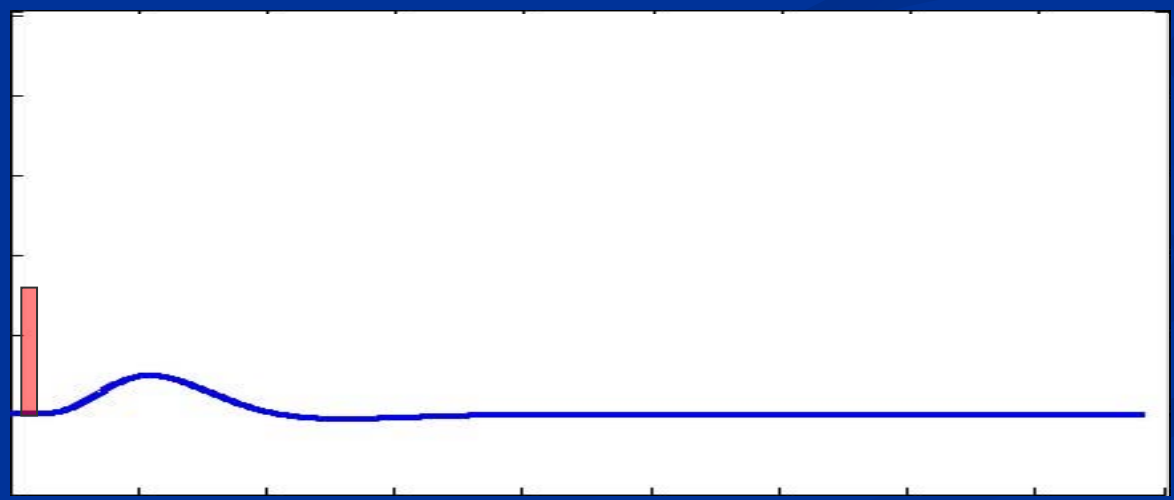

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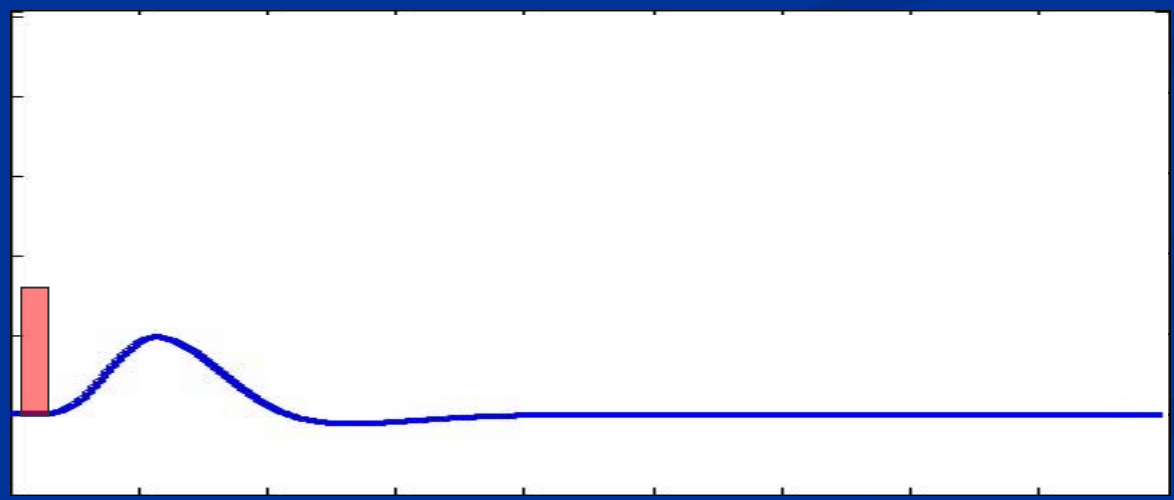
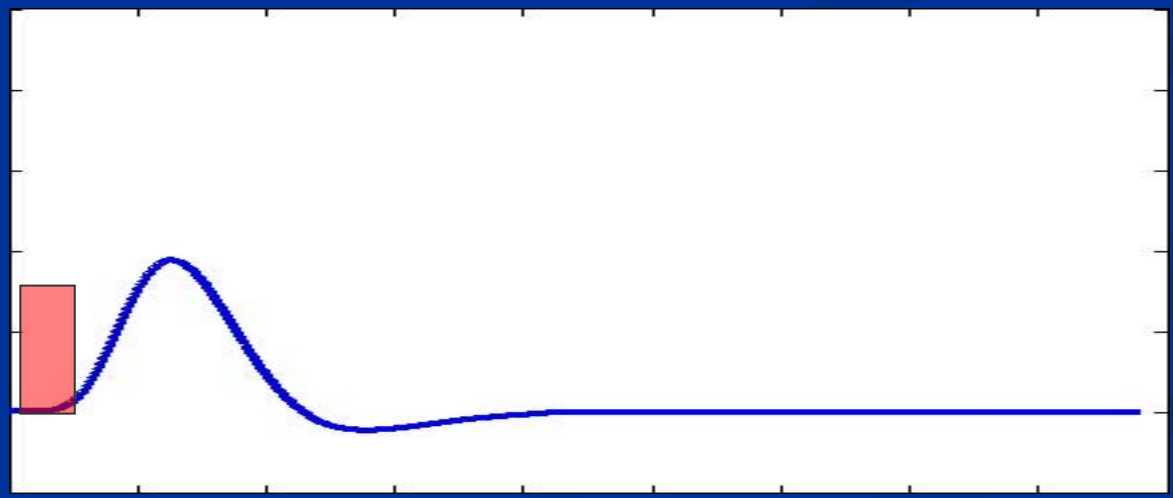


Linearity of BOLD response

- *Superposition* can be demonstrated by adding additional events at points in time
- Responses sum with appropriate lag



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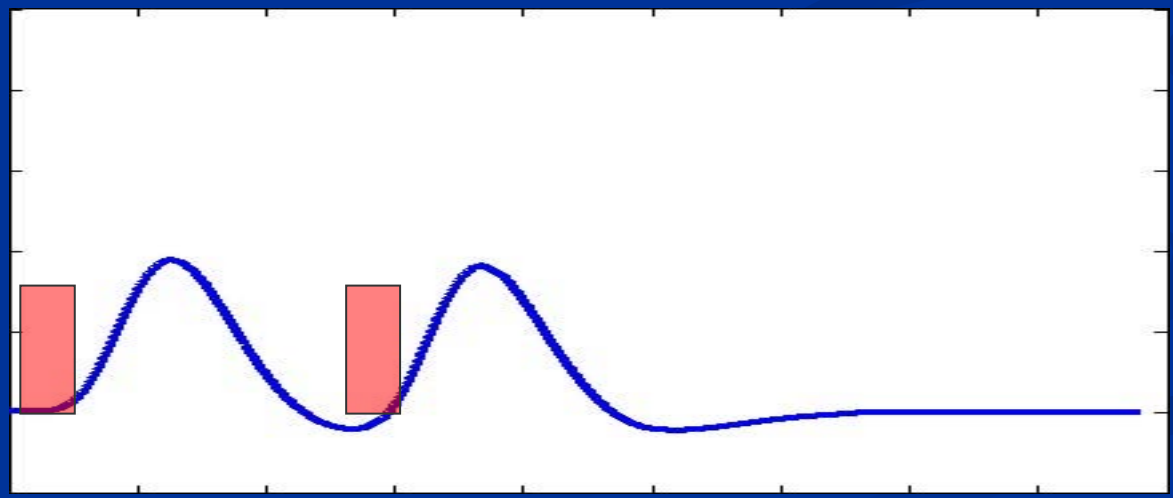

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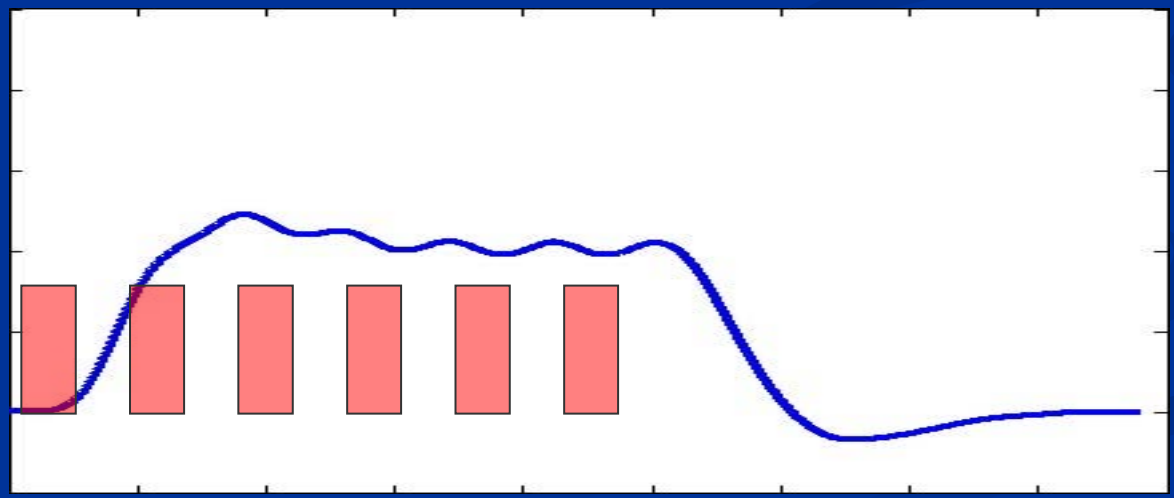

HST.583, Divya Bolar, 2008

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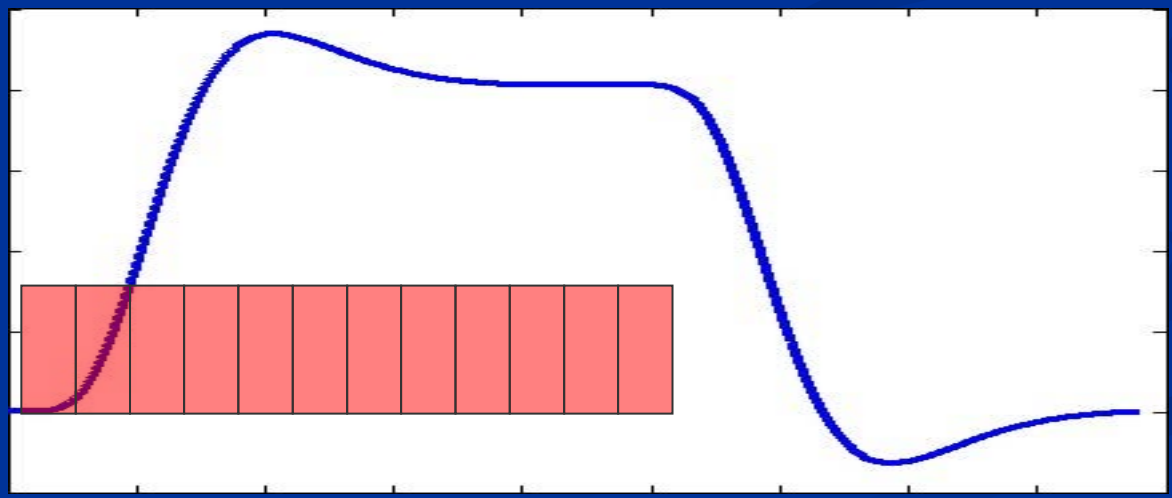
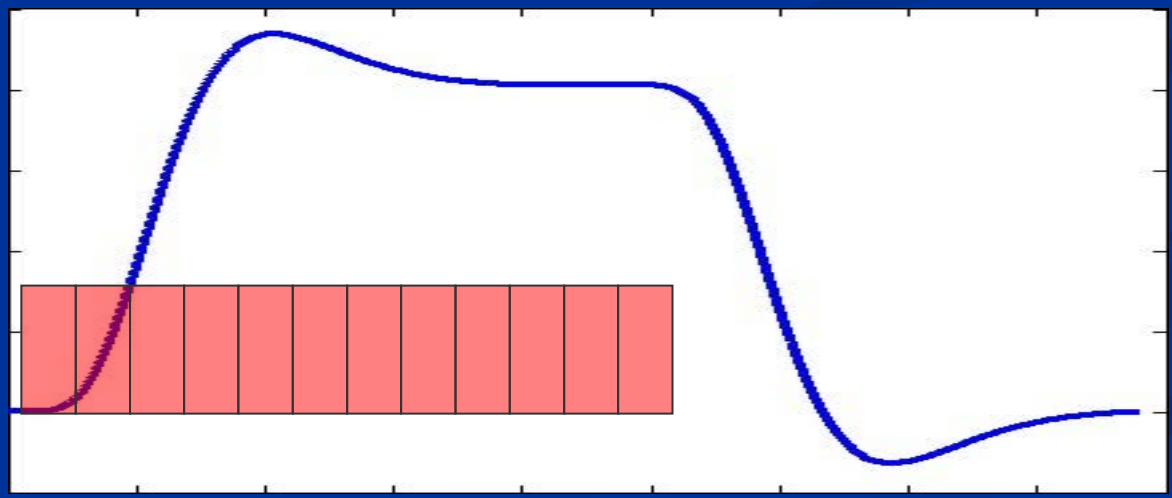


Linearity of BOLD response

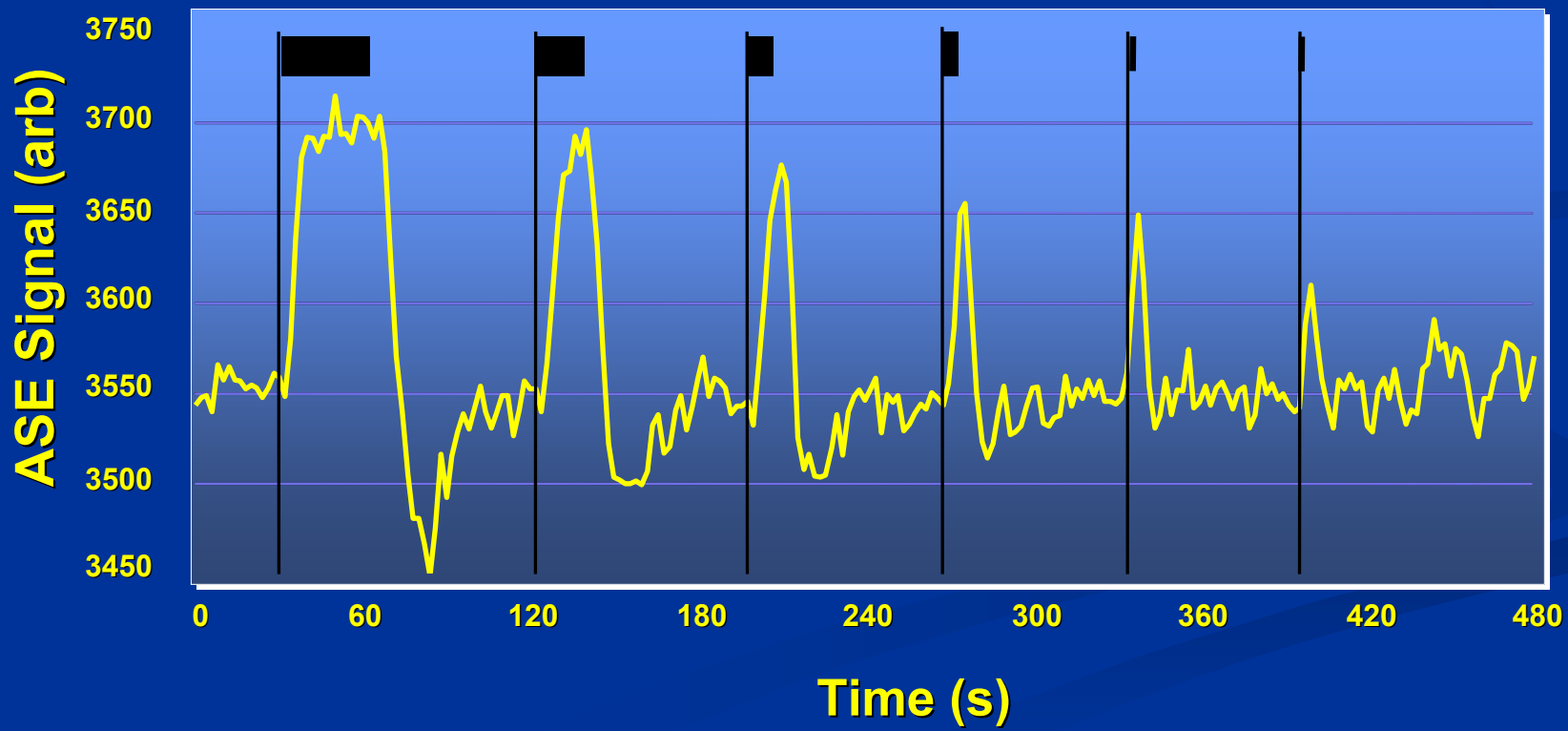
- Blocked design increase response amplitude significantly



HST.583, Divya Bolar, 2008

Linearity of BOLD response

- In reality, signal response to short stimuli can be lost in noise



Courtesy of Robert Savoy, Ph.D., and Robert Weisskoff, Ph.D. Used with permission.

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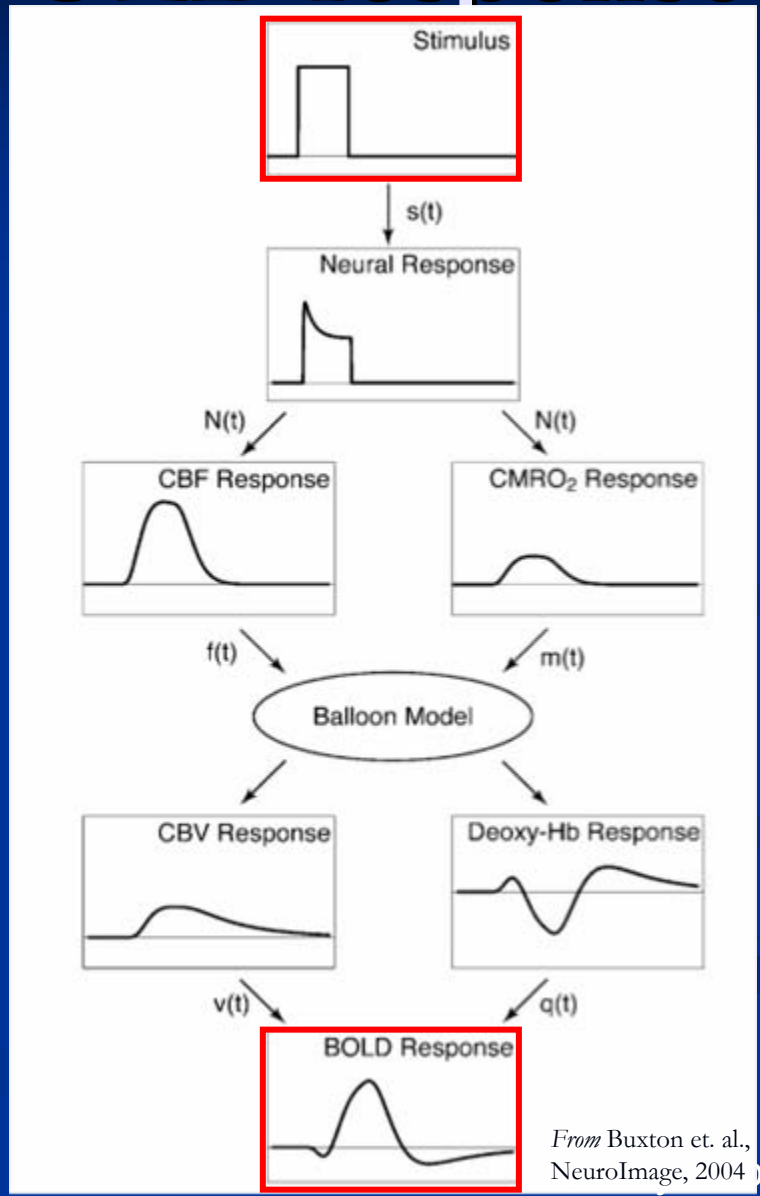
Modeling the BOLD response

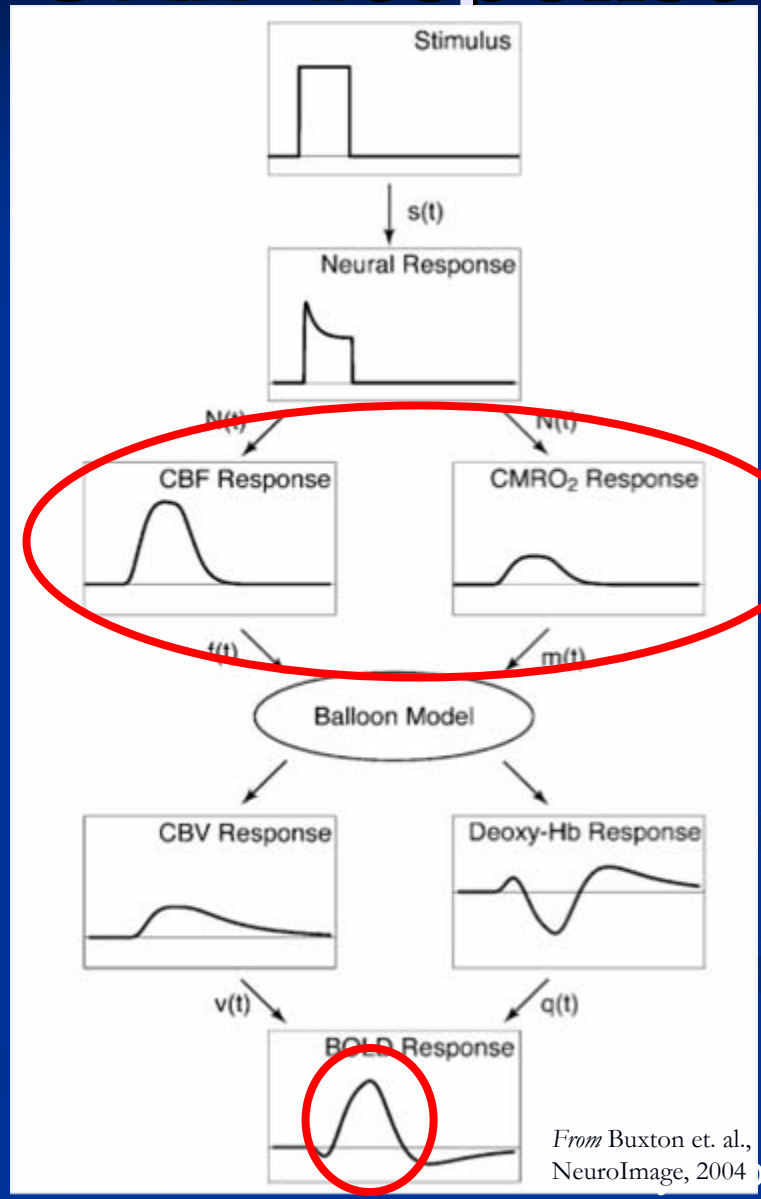
- Response arises from a culmination of different physiological responses secondary to stimulus
- The nature of these response and how they are linked is an active area of research



From Buxton et. al., NeuroImage, 2004

Modeling the BOLD response

- We have discussed the CBF/ $CMRO_2$ relationship
- Several competing hypotheses; difficult to test because imaging $CMRO_2$ difficult with MRI
- *Mismatch remains one of the most fundamental questions of functional neuroimaging*



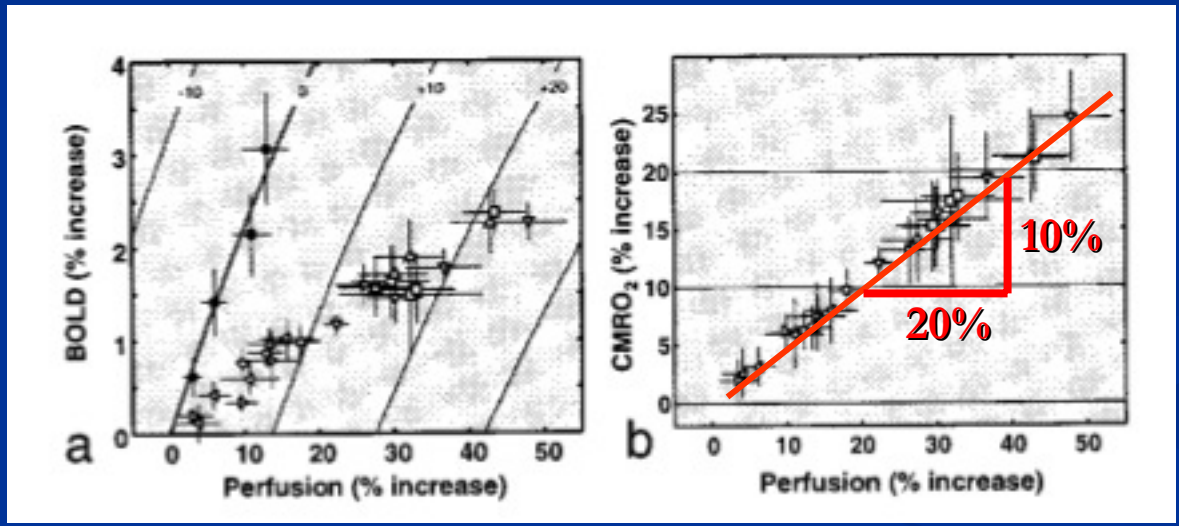
From Buxton et. al., NeuroImage, 2004

Why is increase in CBF so much larger than increase in $CMRO_2$?

1. Uncoupling between CBF and $CMRO_2$?
2. Coarse spatial control of CBF?
3. Oxygen limitation model?
4. Astrocyte-Neuron Lactate Shuttle Model?
5. Hemoneural hypothesis?
6. Other ideas?

1. Uncoupling between CBF and $CMRO_2$?

- Probably not; **Hoge et. Al showed a strong linear relatiobship between CBF and $CMRO_2$**



Courtesy of National Academy of Sciences, U. S. A. Used with permission.
Source: Hoge, R., et al. "Linear coupling between cerebral blood flow and oxygen consumption in activated human cortex." *PNAS* 96 no. 16 (August 3, 1999): 9403-9408.
Copyright (c) 1999, National Academy of Sciences, U.S.A.

- Graded hypercapnia was used to define isocontours of $CMRO_2$; graded visual stimulus experiments could be then used explore $CMRO_2$/ CBF relationship*
- Still doesn't explain why a much larger CBF change is *needed*; i.e. Rick's data shows a 2x increase in CBF versus $CMRO_2$!

2. Coarse spatial control of CBF?

- Malonek & Grinvald suggested that in fact a matching increase in oxygen delivery *is* required to support the small increase in $CMRO_2$ (oxygen consumption)
- However, vascular response is not precise enough to delivery CBF to *only* the region with increased $CMRO_2$
- Can only deliver CBF to a *larger containing area*, and thus a much larger than necessary response is required
- *"Watering the garden, for the sake of the thirsty flower"*

2. Coarse spatial control of CBF?

Image removed due to copyright restrictions.

Fig. 3 in Malonek, D. and A. Grinvald. "Interactions Between Electrical Activity and Cortical Microcirculation Revealed by Imaging Spectroscopy: Implications for Functional Brain Mapping." *Science* 272 (1996): 551-554.

- In other words, Malonek and Grinvald asserted that CBF is controlled on a *coarse* spatial scale, while areas of increased $CMRO_2$ occur on a *fine* spatial scale
- Using optical techniques found that initial *transient rise* in dHb mapped to fine columnar structure of visual cortex
- Suggested that increased dHb correlates to increased $CMRO_2$ oxygen metabolism ***before*** CBF increase
- The spatial map of HbO_2 (i.e. the effect behind BOLD) did *not* reveal columnar structure, suggesting only coarse control

Malonek & Grinvald, Science, 1996

2. Coarse spatial control of CBF?

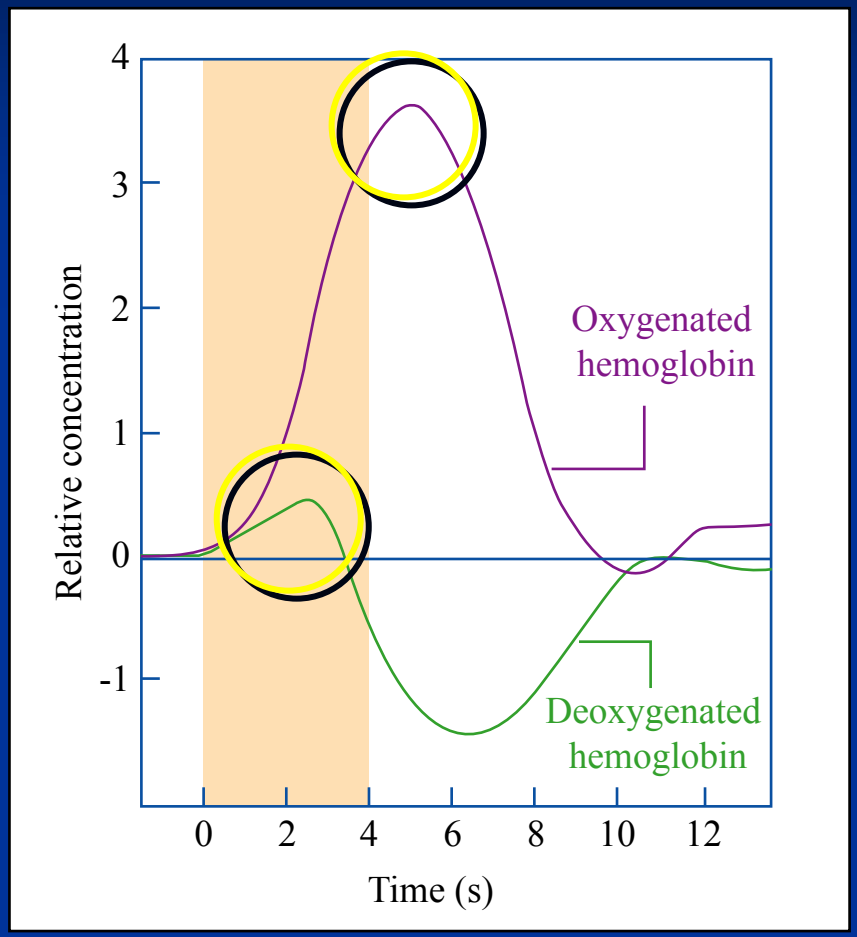


Figure by MIT OpenCourseWare.

After Malonek & Grinvald, Science, 1996

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2. Coarse spatial control of CBF?

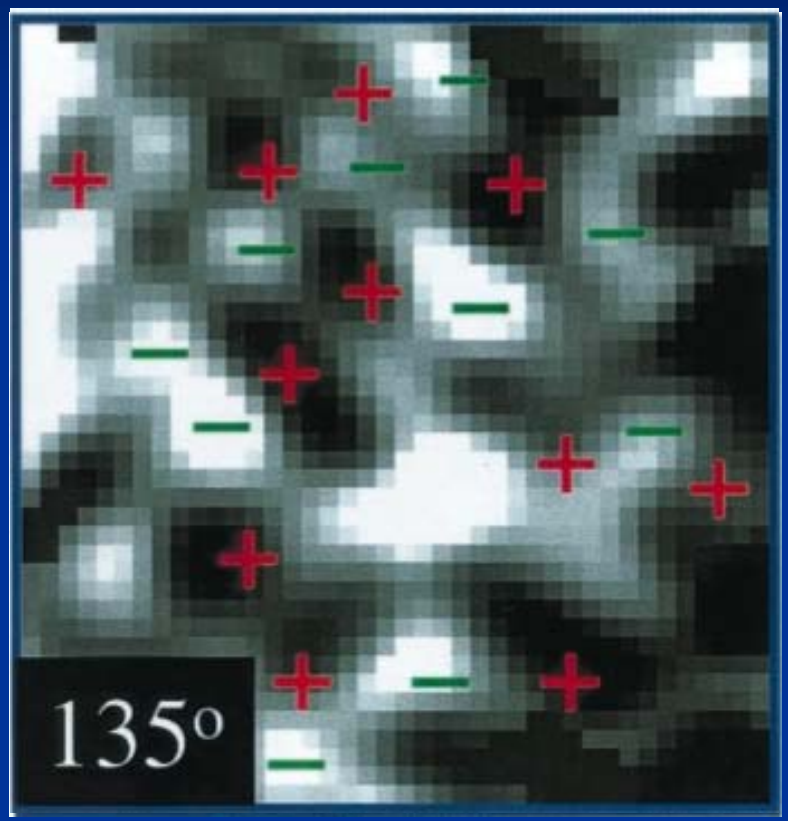
See accompanying video clip

"Screen Grating"

Orthogonal Stimuli at 45 and 135 degrees

- Duong and colleagues used CBF-mapping MRI (ASL) to delineate orientation columns in cat visual cortex
- Suggested that hemodynamic-based fMRI could indeed be used to individual functional columns
- *Non-BOLD approach; eliminates venous large-vessel contribution*

2. Coarse spatial control of CBF?



Duong et al, PNAS, 2001

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2. Coarse spatial control of CBF?

- In addition to Duong, several studies of provide contradictory evidence to Malonek & Grinvald theory
- Woolsey & Rovainen, 1991, rat barrel cortex.
- *However*, these specialized cortices (i.e. visual and barrel) may be unique cases; brain in general may not have such fine spatial control of blood flow
- *If Malonek and Grinvald are correct, what does this imply about spatial resolution of BOLD imaging??*
- ***Suggests limit of BOLD fMRI spatial resolution is physiological, not technological!***

3. Oxygen limitation model?

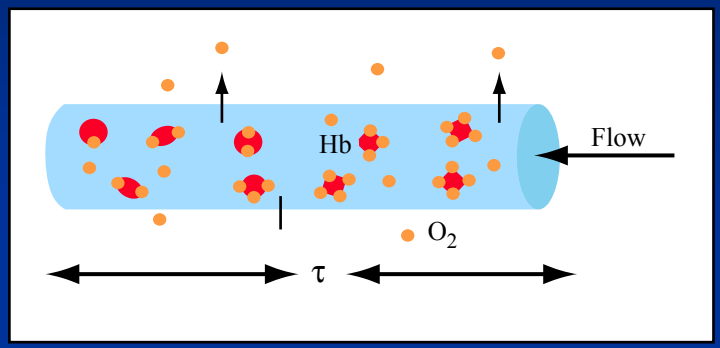


Figure by MIT OpenCourseWare.

Buxton & Frank, JCFMB, 1997
Buxton, Intro to fMRI, Cambridge 2002

- Assume O_2 extraction is limited at rest and CBF increases by increasing blood velocity (*not* by recruitment)

3. Oxygen limitation model?

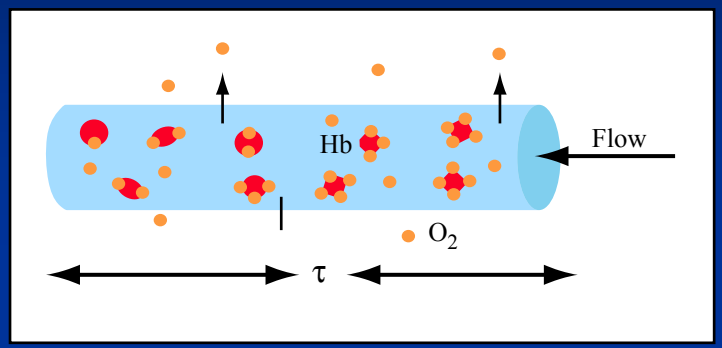


Figure by MIT OpenCourseWare.

ACTIVATION:
Increased capillary velocity
Reduced transit time
Decreased oxygen extraction

Buxton & Frank, JCFMB, 1997
Buxton, Intro to fMRI, Cambridge 2002

- Assume O_2 extraction is limited at rest and CBF increases by increasing blood velocity (*not* by recruitment)
- An increase in CBF will decreases capillary transit time
- A decrease in capillary transmit time will decrease O_2 extraction
- Results in nonlinear relationship between CBF and C
- Consistent with following equation:

$$CMRO_2 \uparrow \propto OEF \downarrow \cdot CBF \uparrow$$

- **Thus, a large increase in CBF is required to sustain a modest increase in $CMRO_2$!**

4. Astrocyte-Neuron Lactate Shuttle?

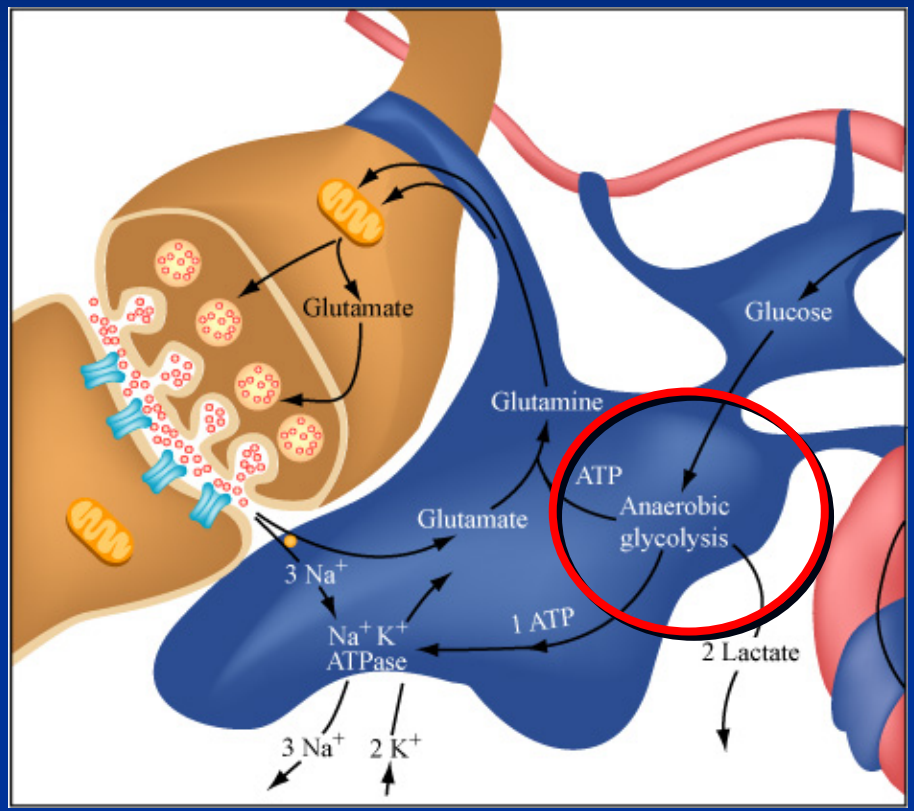


Figure by MIT OpenCourseWare.
After Huttel et al, *fRMI*, 2002.
After Magestretti et al, Science, 1999.

- Posits that initial increase in neuronal activity is followed by an immediate increase in *anaerobic respiration (*since it can respond faster)
- This suggests an ***initial uncoupling*** between CBF and $CMRO_2$; anaerobic respiration does not use O_2, so initial increase in $CMRO_2$ is small
- Using extended duration stimuli Mintun and colleagues have shown that $CMRO_2$ actually *increases* over time, perhaps ***recoupling*** with CBF
- ***Perhaps fast anaerobic response for immediate ATP demands, then slow aerobic response to sustain ATP demands***

5. Hemoneural hypothesis?

- While the increase in CBF is excessive from a metabolic standpoint, it may be appropriate if interpreted as having activity-dependent neuro-modulatory functions
- Authors posit that hemodynamics may impact neural activity through direct and indirect mechanisms
- Chris Moore spent a discussion section talking about these novel ideas, and will have another session later this fall

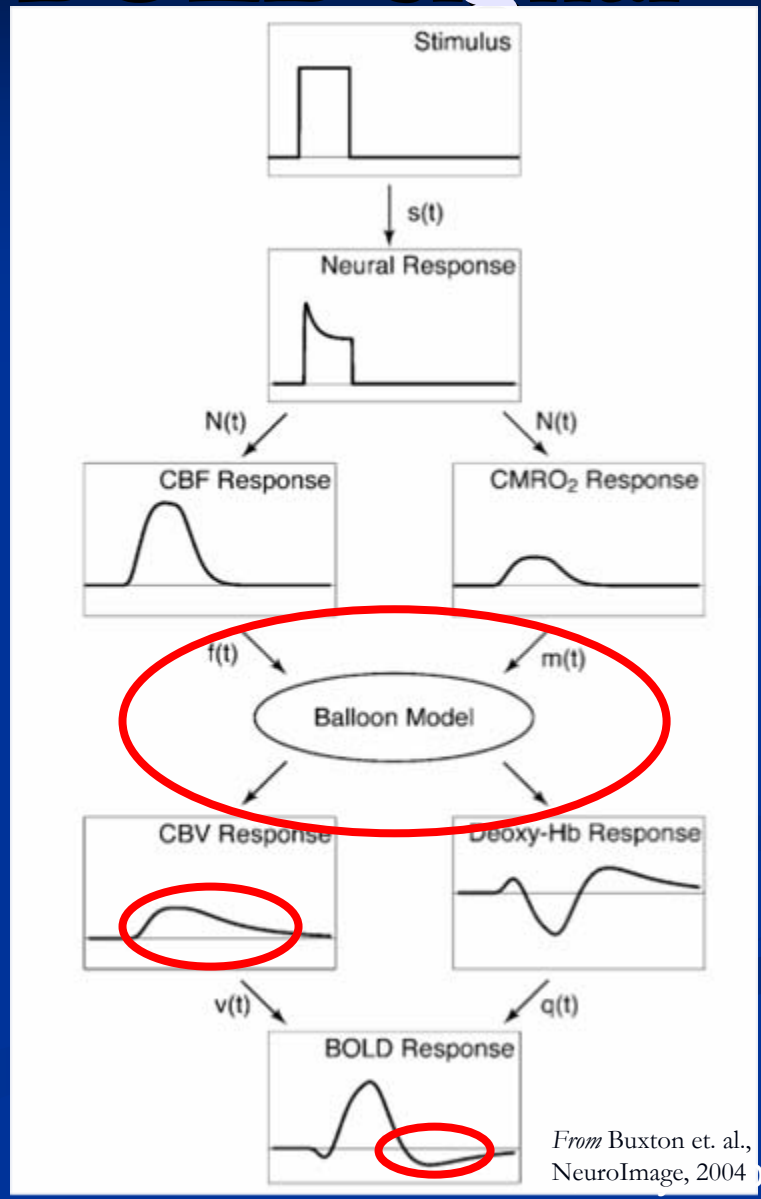
6. Other ideas (have any?!)

Overview

- BOLD review
- BOLD response to *blocks* and *events*
- Linearity of BOLD response
- Modeling the BOLD signal
  - Main response
  - Post-stimulus undershoot
  - Initial Dip

Modeling the BOLD signal

- Another key feature of the BOLD response is the *post-stimulus undershoot (PSU)*
- Until recently, two similar CBV models (i.e. the "balloon model" or "delayed venous compliance" model) were broadly accepted

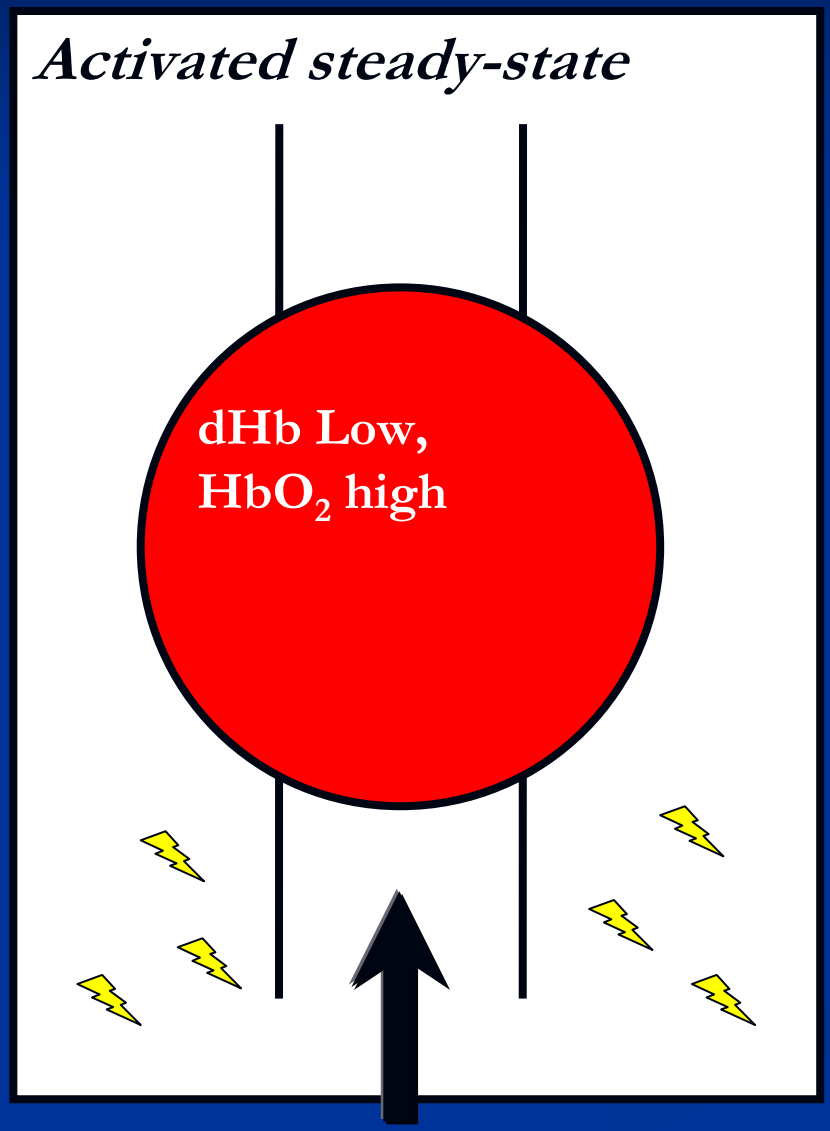


From Buxton et. al., NeuroImage, 2004

Balloon / Delayed Venous Compliance (DVC) Model

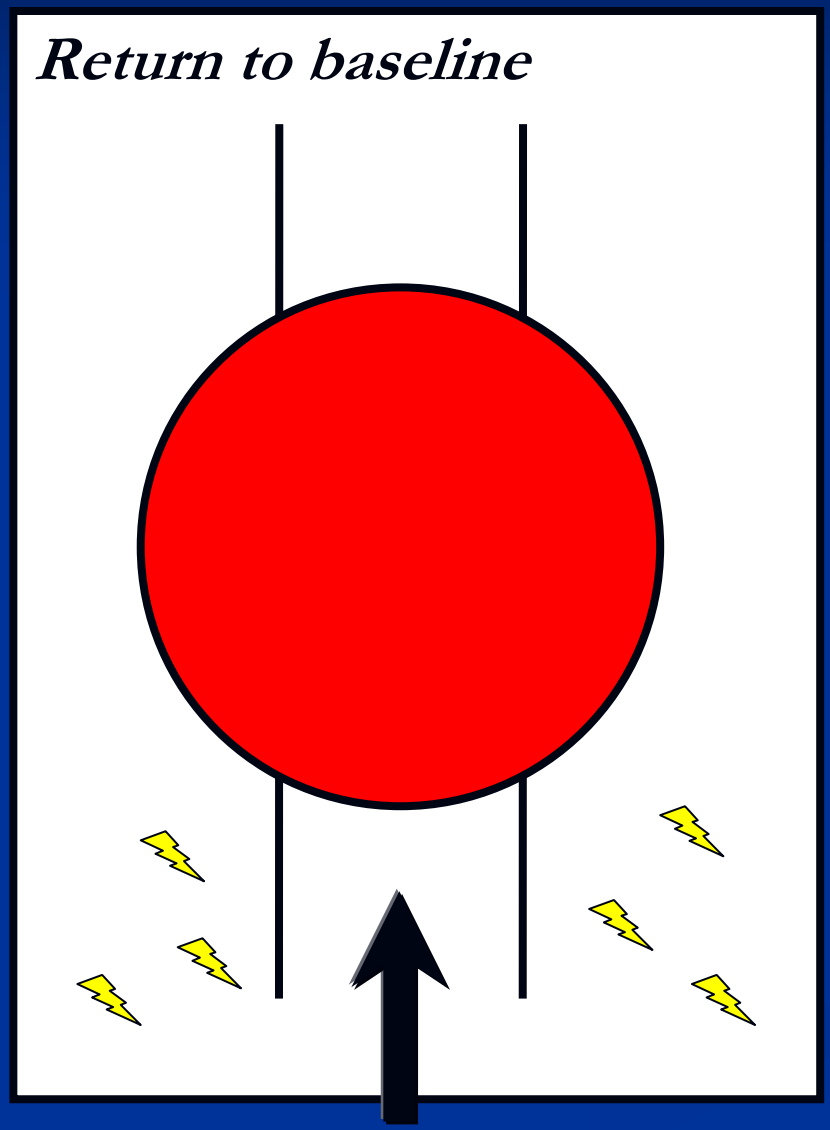
- Veins are compliant and distend in response to increased blood flow
- Distention leads to increased venous CBV, but CBV response lags CBF response
  - CBF returns to baseline quickly; thereby stops HbO_2 delivery and dHb flushing
  - dHb *concentration* starts returning to baseline
  - CBV_{venous} is still elevated, so *total* dHb *content* (content = CBV_{venous} ·[dHb]) is *increased* compared to baseline
- ***BOLD signal transiently decreases following stimulus cessation***

Balloon/DVC Model



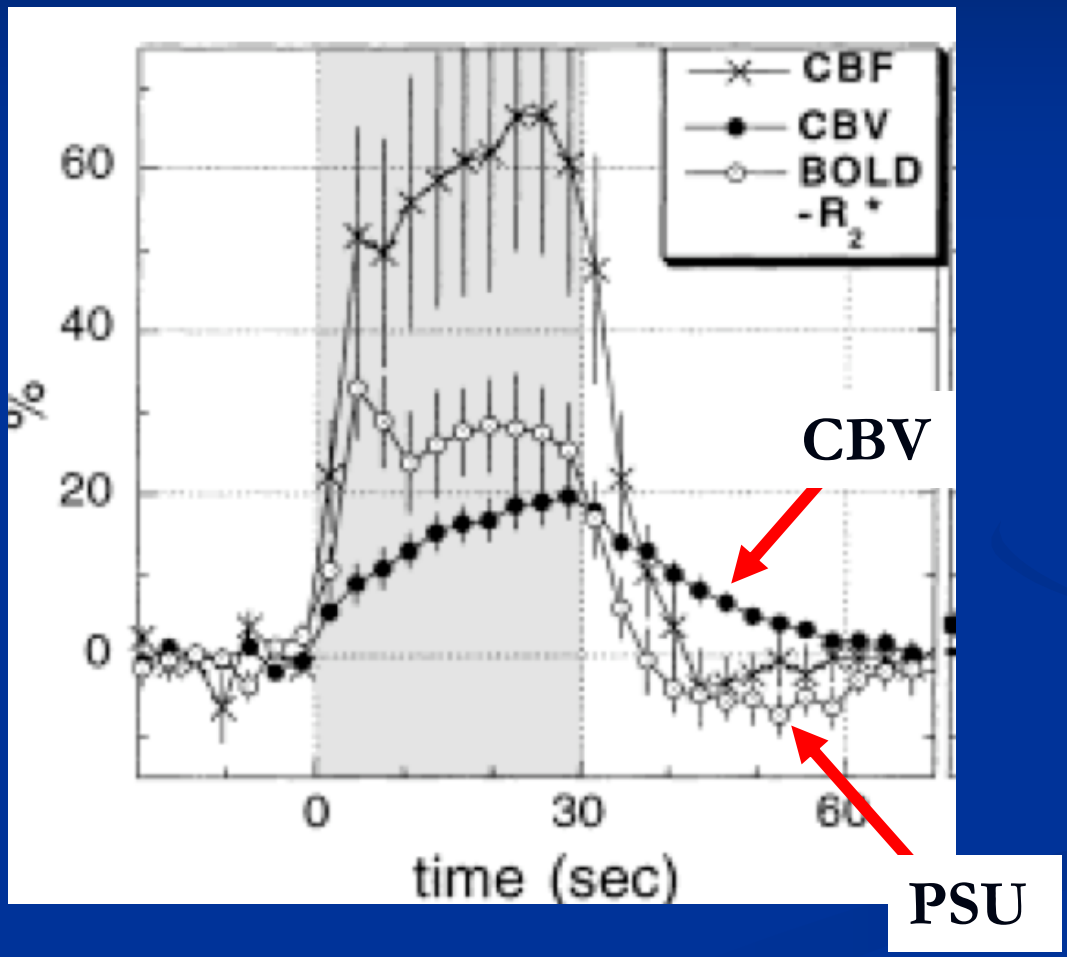
1. During activation both CBF and CBV are elevated; dHb is **low**

Balloon/DVC Model



1. During activation both CBF and CBV are elevated; dHb is **low**
2. After activation ceases, CBF returns to baseline quickly; [dHb] returns towards baseline
3. CBV takes much longer to return to baseline
4. Total dHb *content* increases; signal falls

Balloon/DVC Model



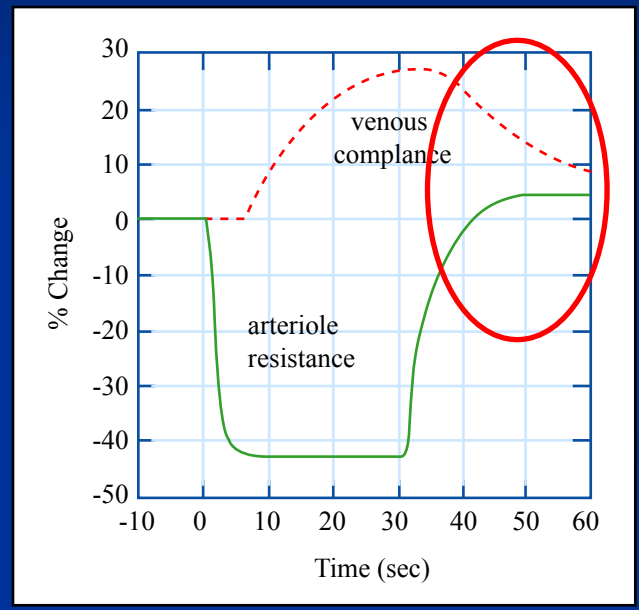
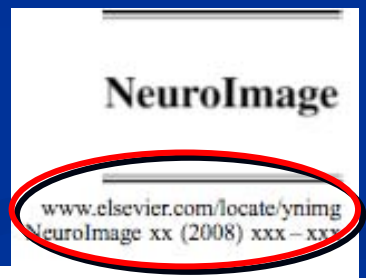


Figure by MIT OpenCourseWare.
After Mandeville et al, JCBFM, 1999.

PSU: *Not* a volume effect!?

- New evidence suggests post-stimulus undershoot is NOT caused by elevated CBV (not biomechanical)



The post-stimulation undershoot in BOLD fMRI of human brain is not caused by elevated cerebral blood volume

Jens Frahm,[a,*] Jürgen Baudewig,[b] Kai Kallenberg,[b,c] Andreas Kastrup,[d]
K. Dietmar Merboldt,[a] and Peter Dechent[b]

Another example of being on the edge of 50% right/ wrong!

PSU: Uncoupling of $CMRO_2$ and CBF?

- CBF returns to baseline quickly after stimulus ends, but $CMRO_2$ stays elevated.
- Oxygen consumption/ dHb production) > Oxygen delivery/ dHb removal)
- Net result: more dHb leading to transient decrease in BOLD signal
- Schroeter (NIRS), Frahm, Van Zijl (VASO), Devor

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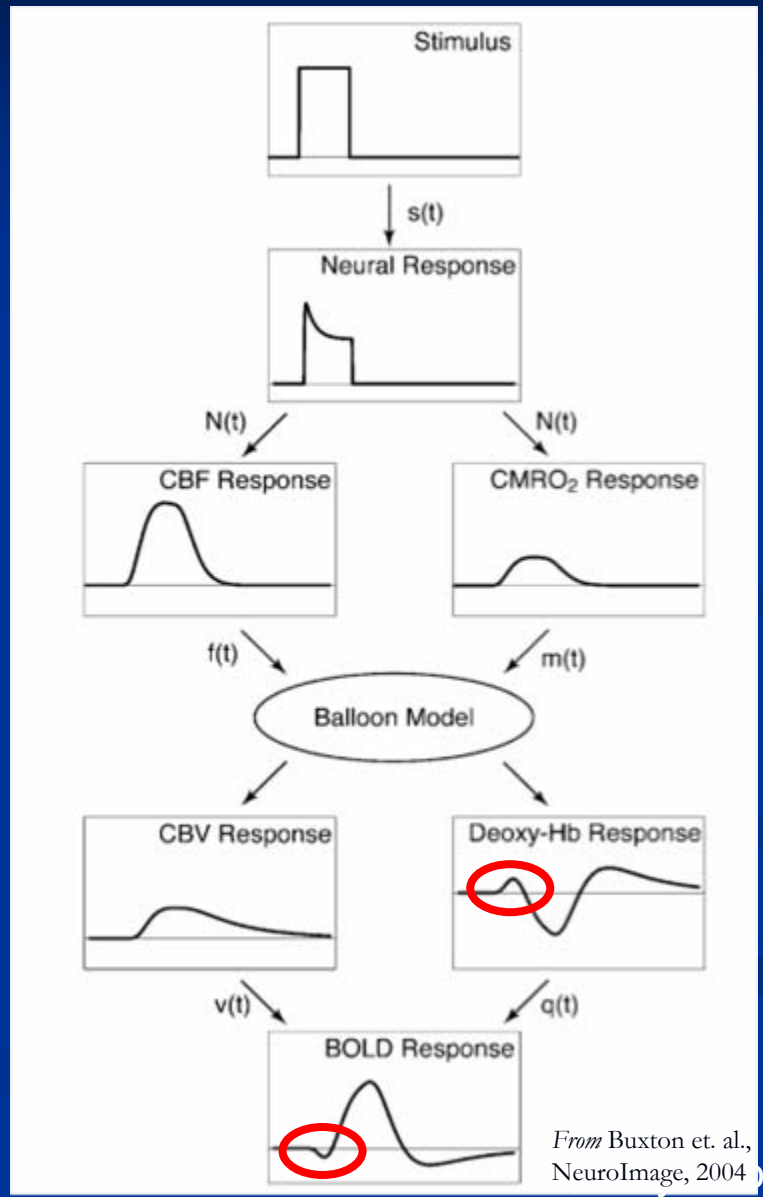
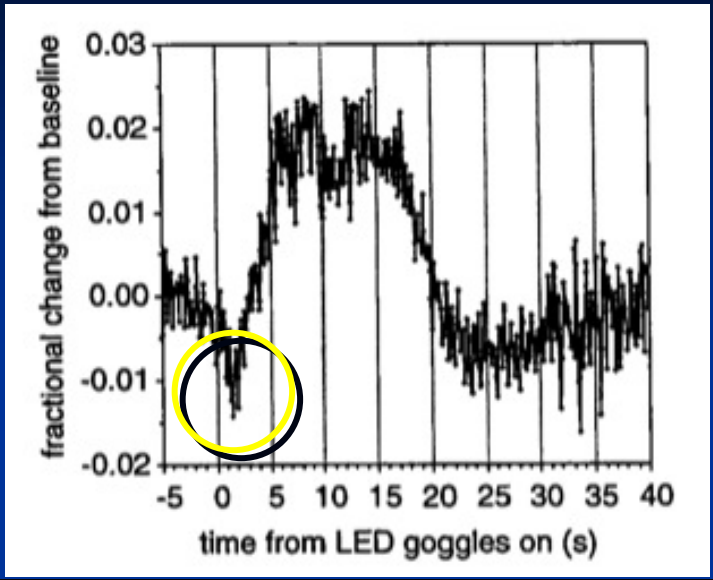
Modeling the BOLD signal

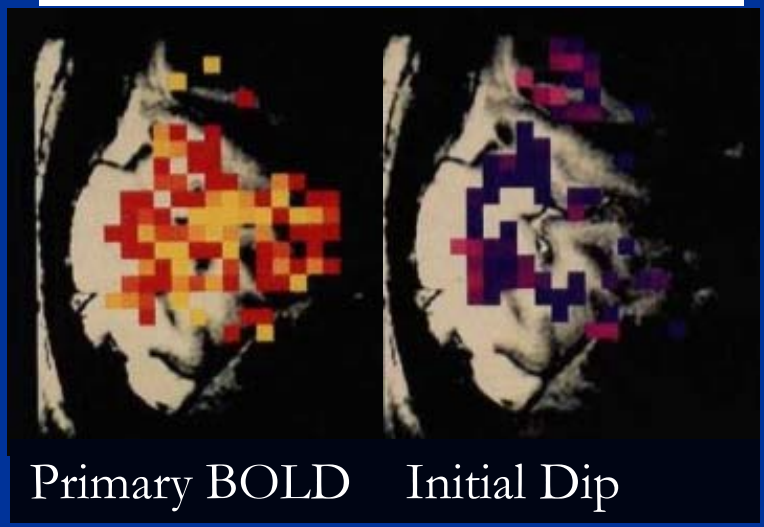
- An important, but controversial feature of the BOLD response is the *initial* or *early dip*.
- Initial *decrease* in dHb content, leading to initial *decrease* in BOLD
- Many groups do not see initial dip, but this may be due to decreased sensitivity at lower fields
- *As imaging hardware improves, the initial dip may become an important indicator of activation*



From Buxton et. al., NeuroImage, 2004

The Initial or Early Dip

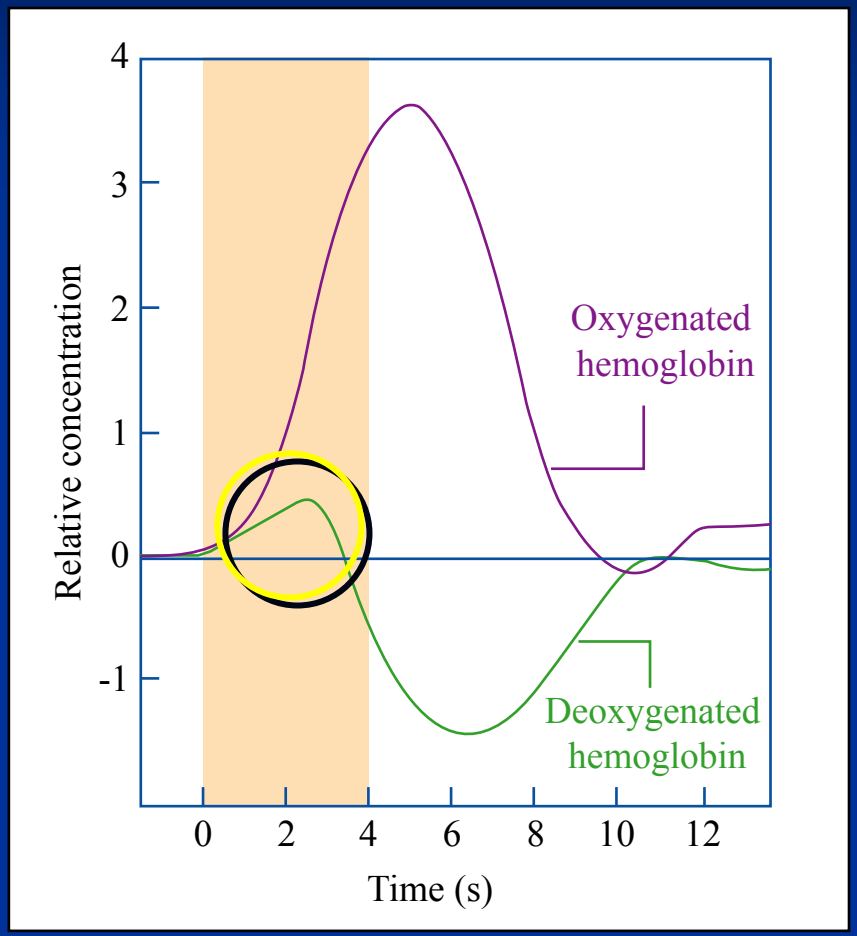




- Menon & colleagues reported first BOLD fMRI study at 4T
- Initial dip appeared more tightly correlated to cortical neurons than primary response
- Like Malonek & Grinvald, suggested that early surge in dHb was due to a fast increase in $CMRO_2$

Source: Menon, R.S. *MRM* 33, no. 3 (March 1995); 453-459.

The Initial or Early Dip



Malonek & Grinvald, Science, 1996

Figure by MIT OpenCourseWare.

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Summary: Some contributors to BOLD response

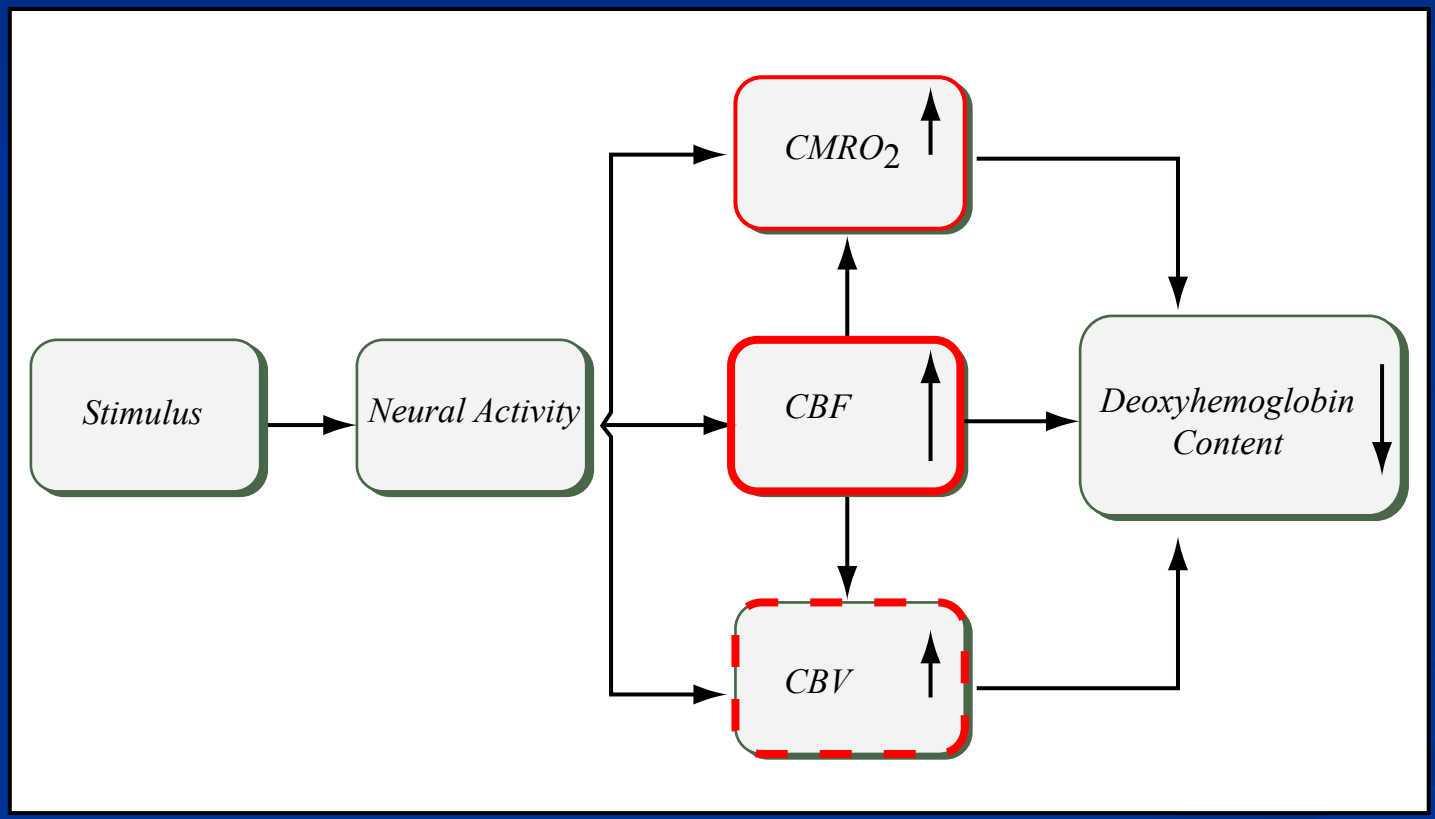

Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

Summary

- BOLD response to stimuli called hemodynamic response and is roughly linear
- Three main features of response: initial dip, primary positive response, and post-stimulus undershoot
- These features have different spatiotemporal properties, as they arise from different physiologic parameters

Up next:

- BOLD Imaging II
  - Effects of diffusion on BOLD signal
  - Spatial source of BOLD signal contribution (extravascular versus intravascular)
  - BOLD sequence variants and parameters
- Beyond BOLD: State-of-the-art techniques to image activation physiology
  - CBF techniques (ASL)
  - CBV techniques (VASO)
  - Calibrated BOLD/ rel $CMRO_2$ techniques