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.

The Activating Brain:

Brain physiology in response to external stimuli and Introduction to BOLD imaging

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What do we mean by brain "activation"?

- Even in its baseline state the brain is highly active (recall last lecture)
- "Activation" in the context of fMRI refers to an *evoked* neural (neuronal) response; i.e. ***an increase in neural activity in response to an external stimulus***
- Neural activity can be modulated in many ways

Examples of fMRI stimuli

Lecture Overview

1. Discuss changes in brain physiology during activation, as known from key experimental observations
2. Introduce how these changes lead to fMRI via **BOLD** imaging

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2. Introduce how these changes lead to fMRI via **BOLD** imaging

Physiological changes during activation

- Neuronal Changes
  - AP spiking activity, LFP
- Metabolic Changes
  - Glucose metabolism (CMRGluc)
  - Oxygen metabolism ($CMRO_2$)
- Vascular Changes
  - CBF, transit time
  - CBV

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  - *Oxygen metabolism ($CMRO_2$)*
- Vascular Changes
  - *CBF, transit time*
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Oxygen Extraction Fraction

Physiological changes during activation

Metabolic Changes

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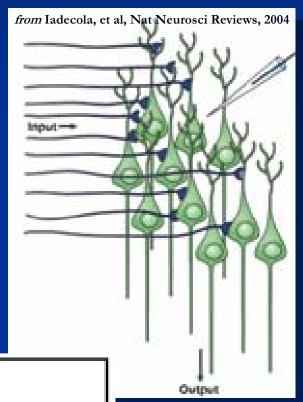


Neuronal Changes

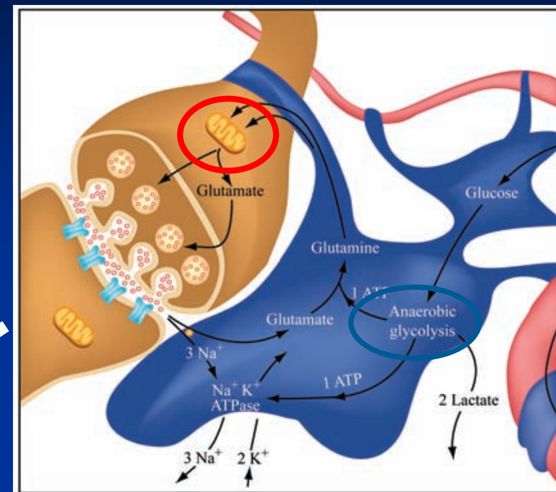
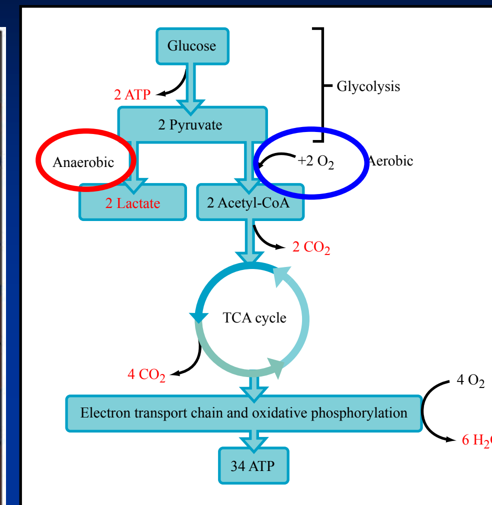


Figure by MIT OpenCourseWare.
After Huttel et al, *fRMI*, 2002.



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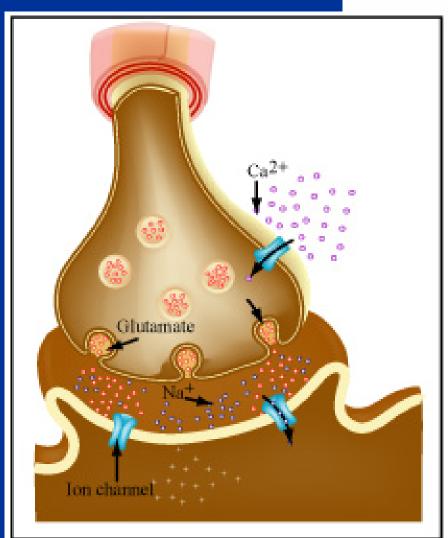
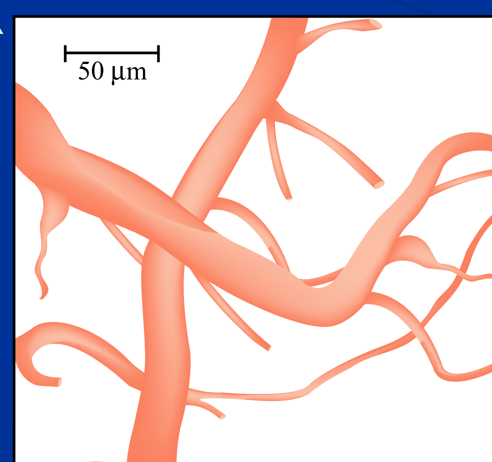


Figure by MIT OpenCourseWare.

Direct and Indirect Control

Vascular Changes



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Neuronal Changes

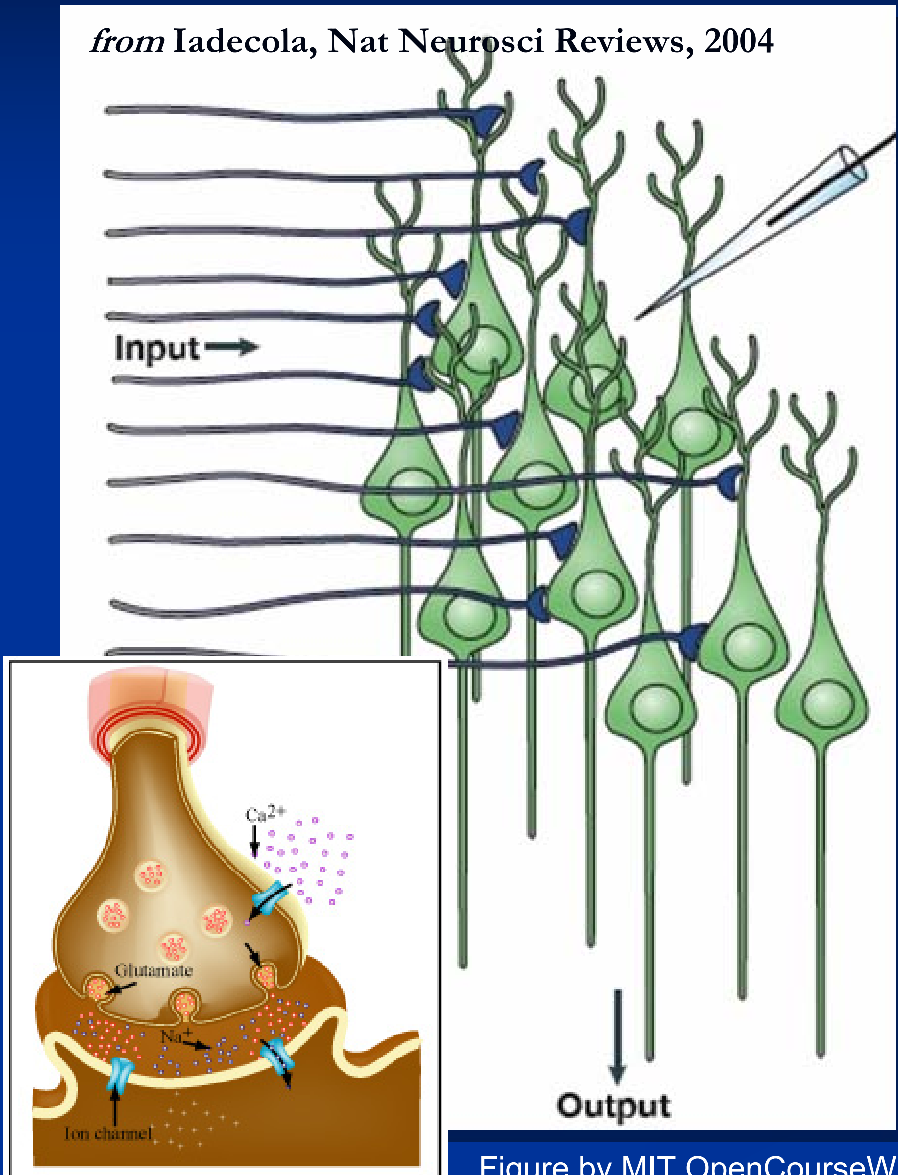
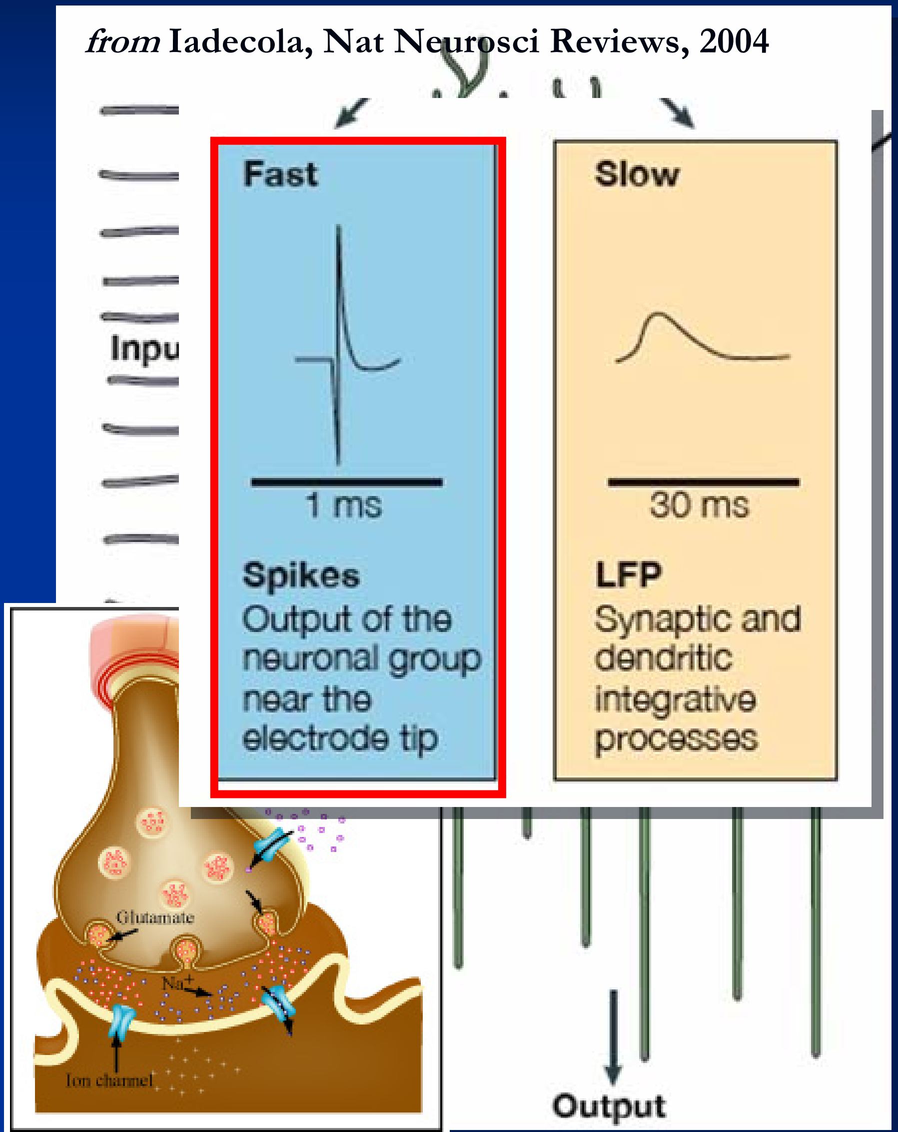


Figure by MIT OpenCourseWare.

- For fMRI, consider behavior of ***ensembles*** of neurons (hundreds)

Neuronal Changes



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- For fMRI, consider behavior of ***ensembles*** of neurons (hundreds)
- Increased action potential firing (output): ***multiunit spiking activity (MUA)****

Courtesy of Constantino Iadecola. Used with permission.

Neuronal Changes

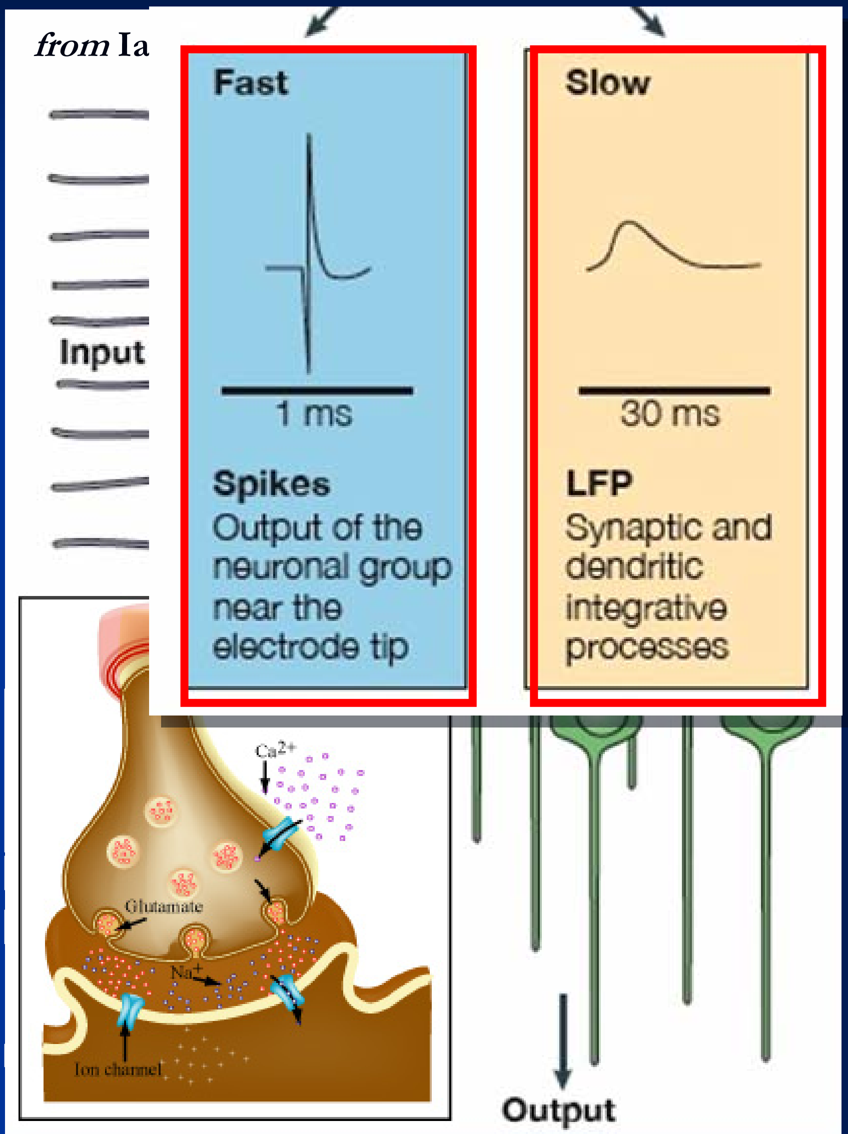
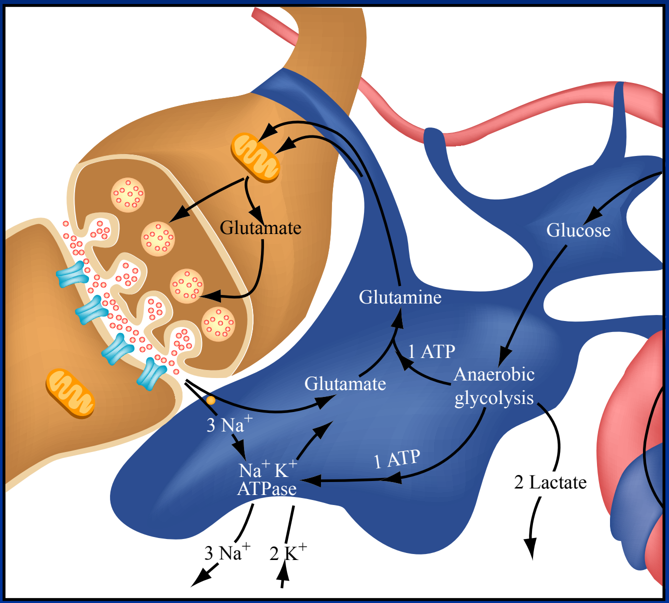


Figure by MIT OpenCourseWare.

- For fMRI, consider behavior of ***ensembles*** of neurons (hundreds)
- Increased action potential firing (output): ***multiunit spiking activity (MUA)****
- Increased synaptic & integrative activity (EPSPs, IPSPs); contributes to ***local field potential (LFP)***

Metabolic Changes



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After Huttel et al, *fRMI*, 2002.

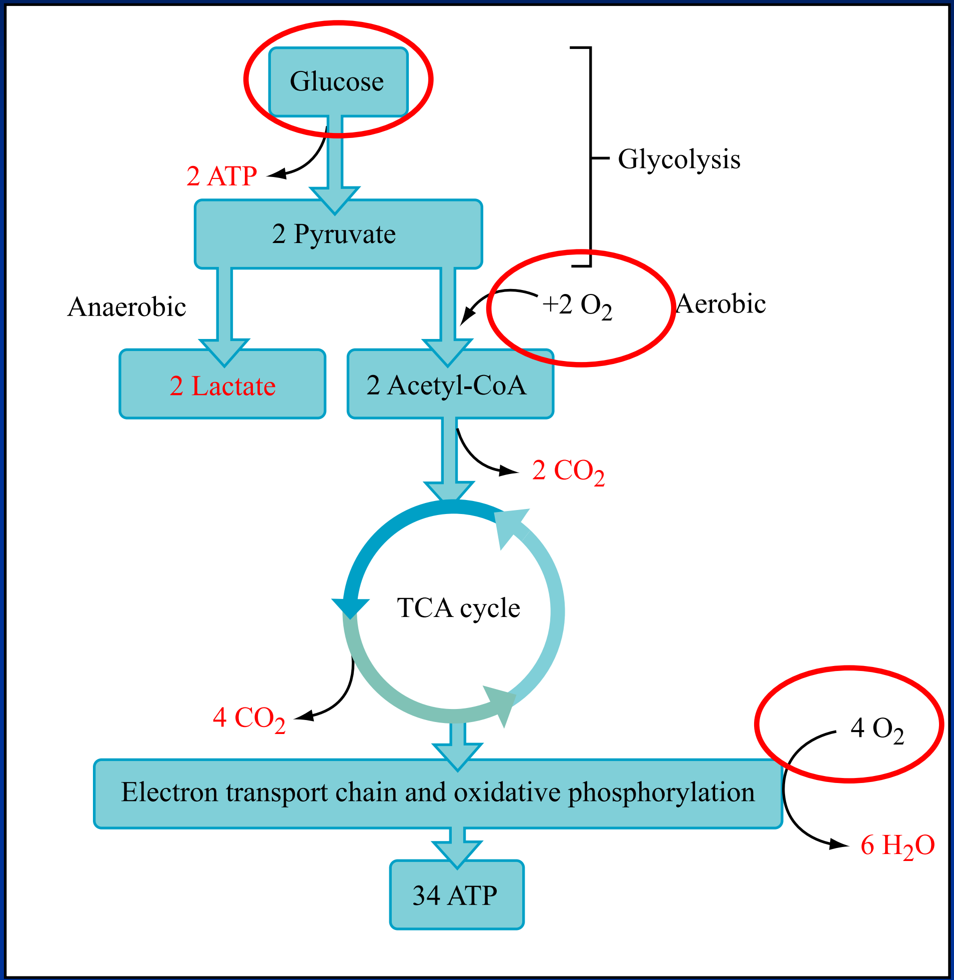


Figure by MIT OpenCourseWare.

- Glucose and oxygen metabolism both increase

Metabolic Changes

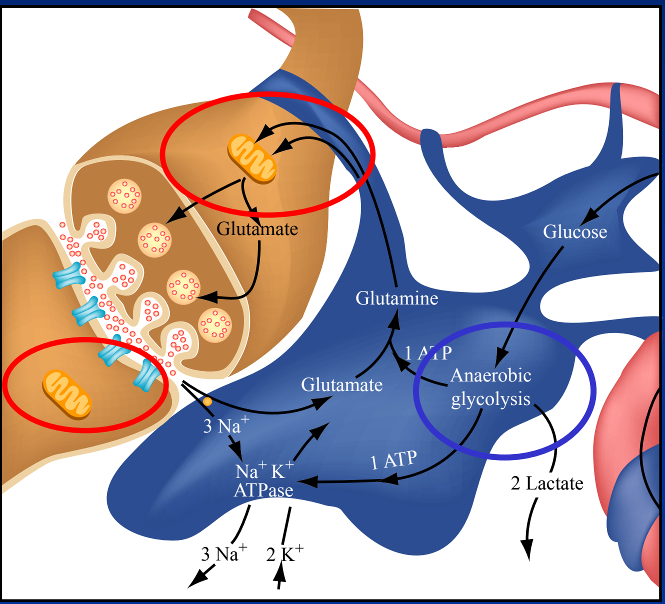
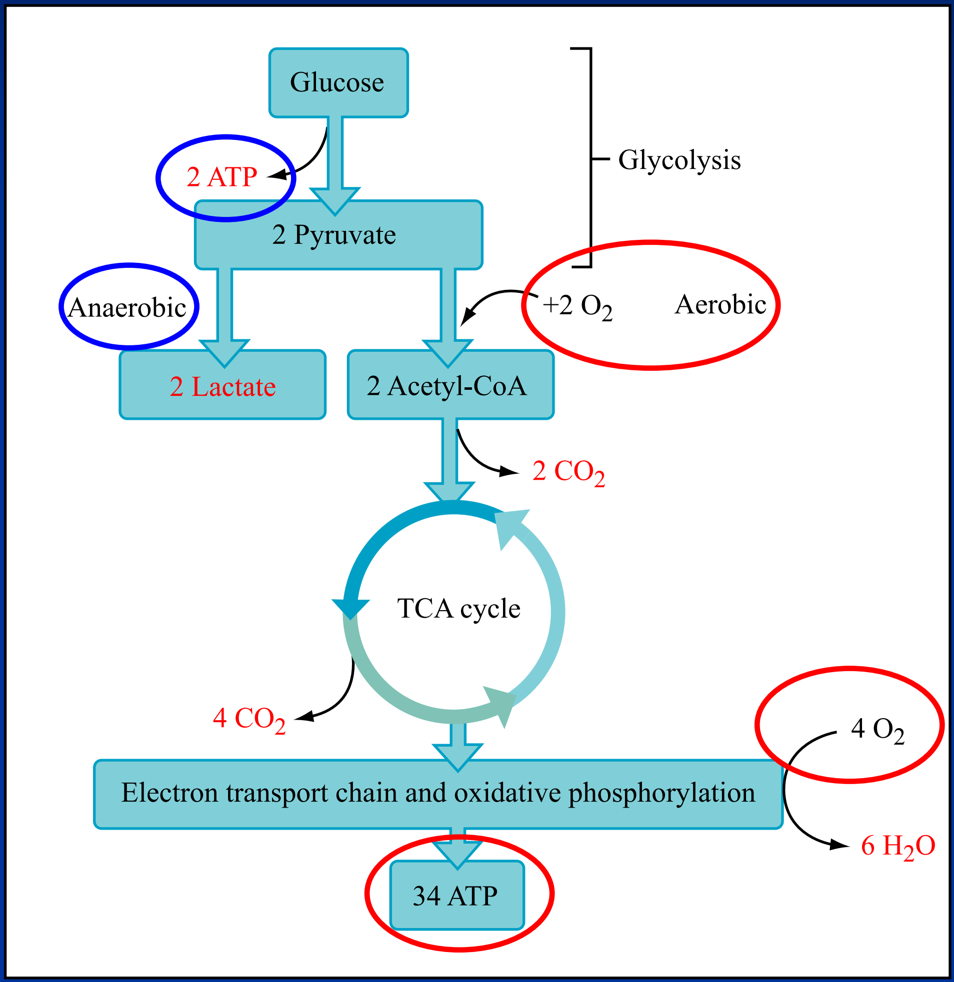


Figure by MIT OpenCourseWare.
After Huttel et al, *fRMI*, 2002.

- Slow Aerobic
  - **34 ATP**
- Fast Anaerobic
  - **2 ATP**



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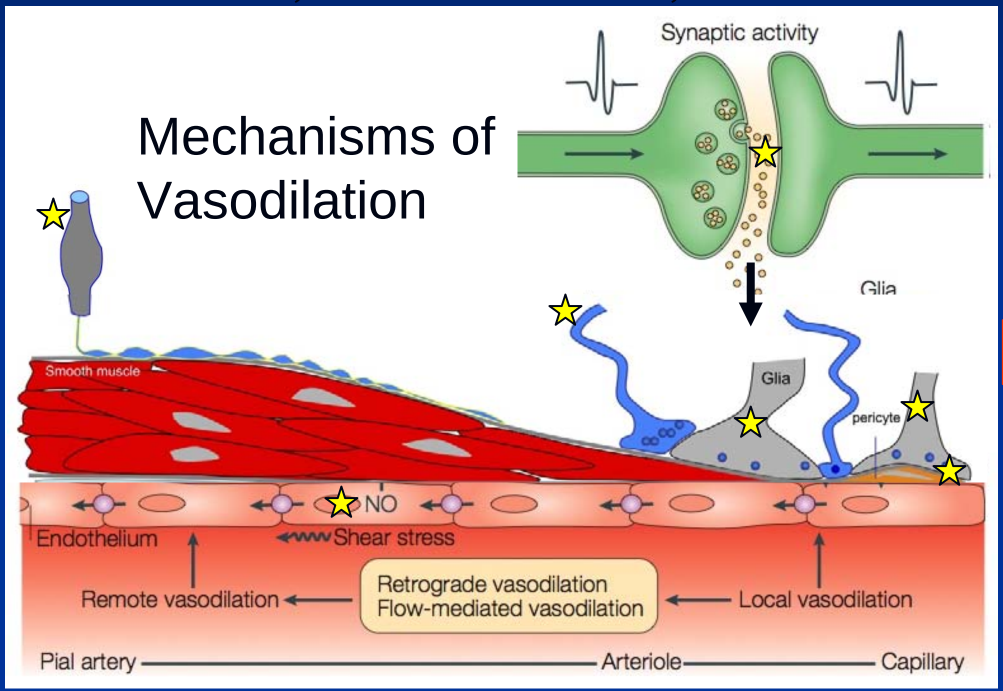
Vascular Changes

from Iadecola, Nat Neurosci Reviews, 2004



from Iadecola, Nat Neurosci Reviews, 2004 *and* Girouard and Iadecola, J Appl Physiol, 2006

Courtesy of Costantino Iadecola. Used with permission.

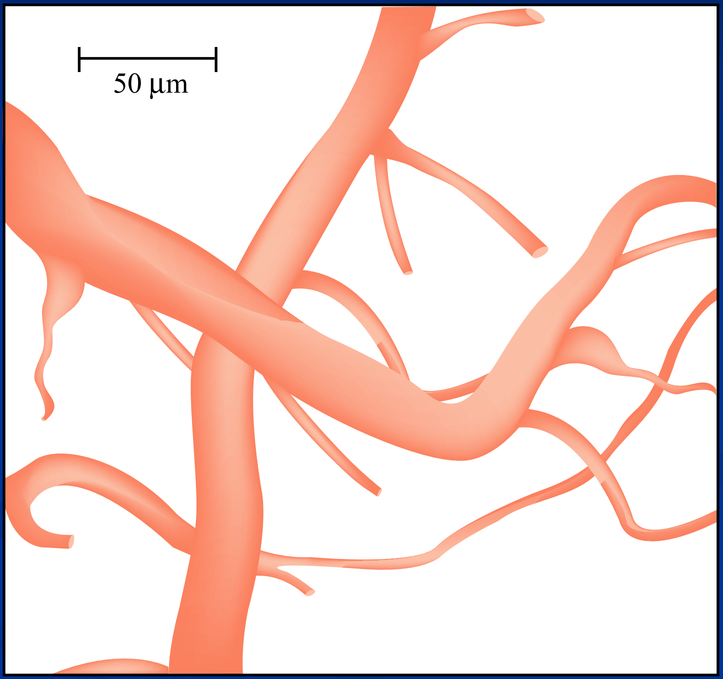


Figure by MIT OpenCourseWare.
After Huttel et al, *fRMI*, 2004.

- CBF increases during activation!
- CBF is proportional to (vessel radius)^4
- Small Δradius results in large ΔCBF
- CBV, MTT also modulated during activation

“Road Map” to Activation Physiology

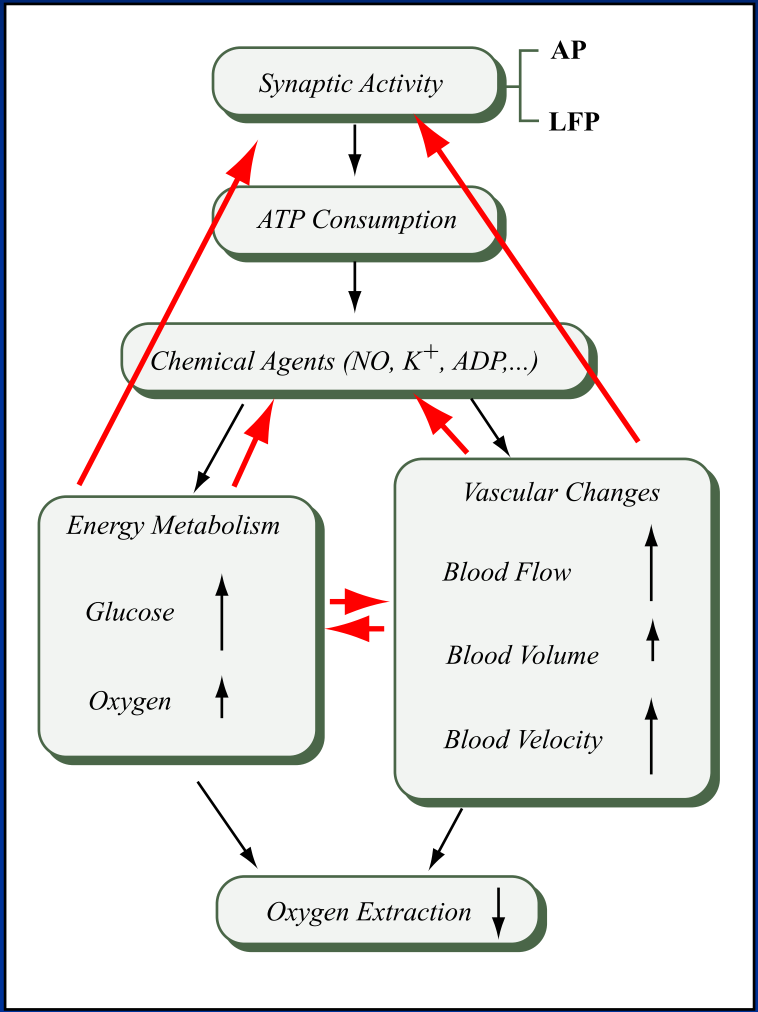


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

- Buxton presents a useful flow chart summarizing physiological changes accompanying activation
- In reality, this must be significantly modified; many new ideas have been introduced
- Coupling between these different physiological parameters is a vast area of research

"Road Map" to Activation Physiology

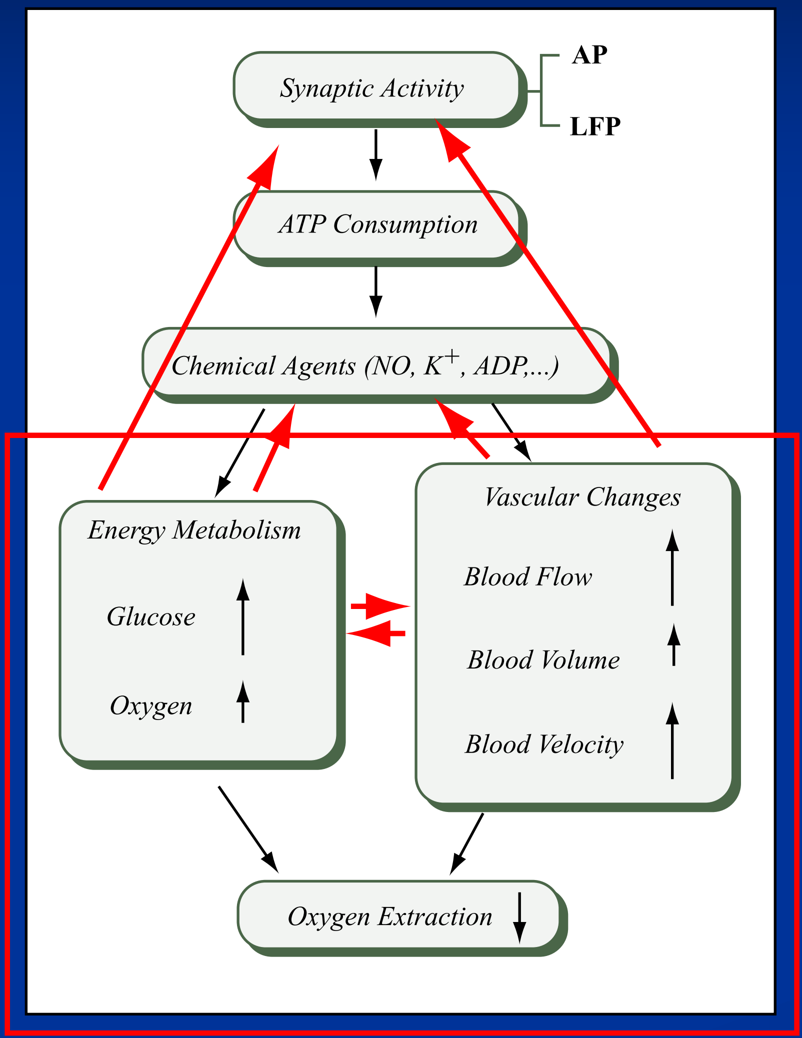


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

- Current fMRI techniques focus on the lower three blocks
- No method to directly measure with neuronal activity with fMRI

Physiological changes during activation

- While the physiological events presented in previous slides are correlated, they differ greatly in terms of spatiotemporal characteristics
- Correlation does not necessarily mean causality!
- ***What we do know comes from key experimental observations***

Key experimental observations during activation

1. Blood flow (CBF) and glucose metabolism (CMRGlc) increase substantially
2. Oxygen metabolism ($CMRO_2$) increases much less than CBF
3. Oxygen extraction fraction (OEF) decreases
4. CBV increases less than CBF, and temporally lags CBF response
5. CBF increases by increasing blood velocity, not by capillary recruitment
6. CBF increase correlates more strongly to LFP than MUA (spiking) activity

1. Blood flow and glucose metabolism increase substantially

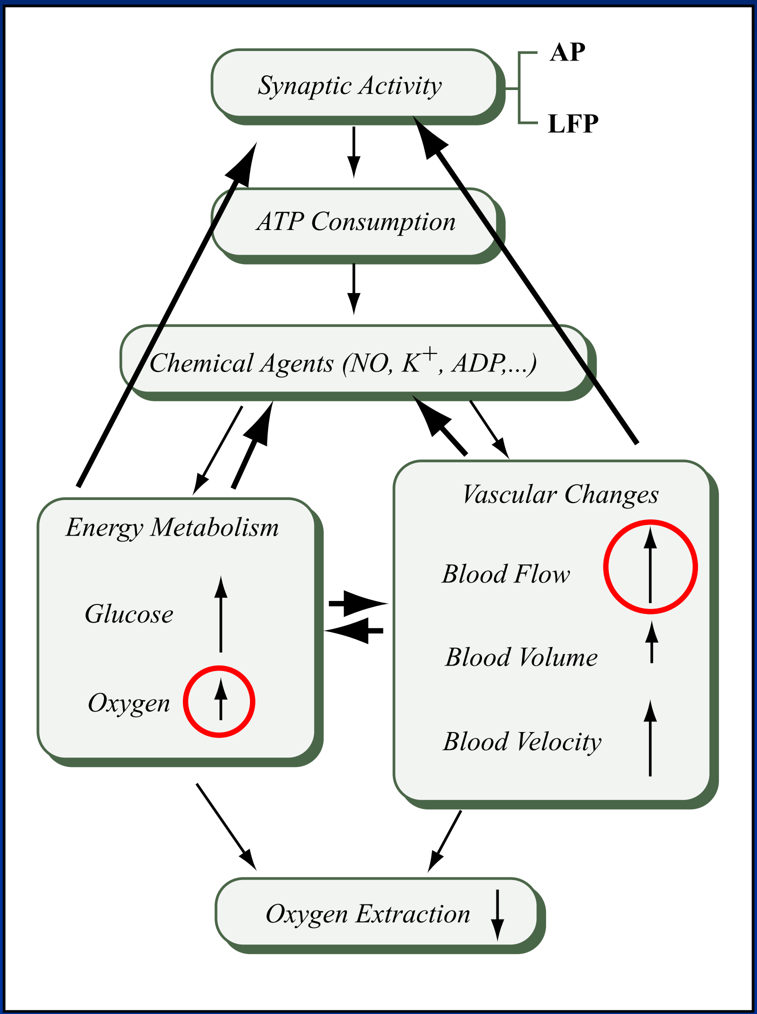


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

1. Blood flow and glucose metabolism increase substantially

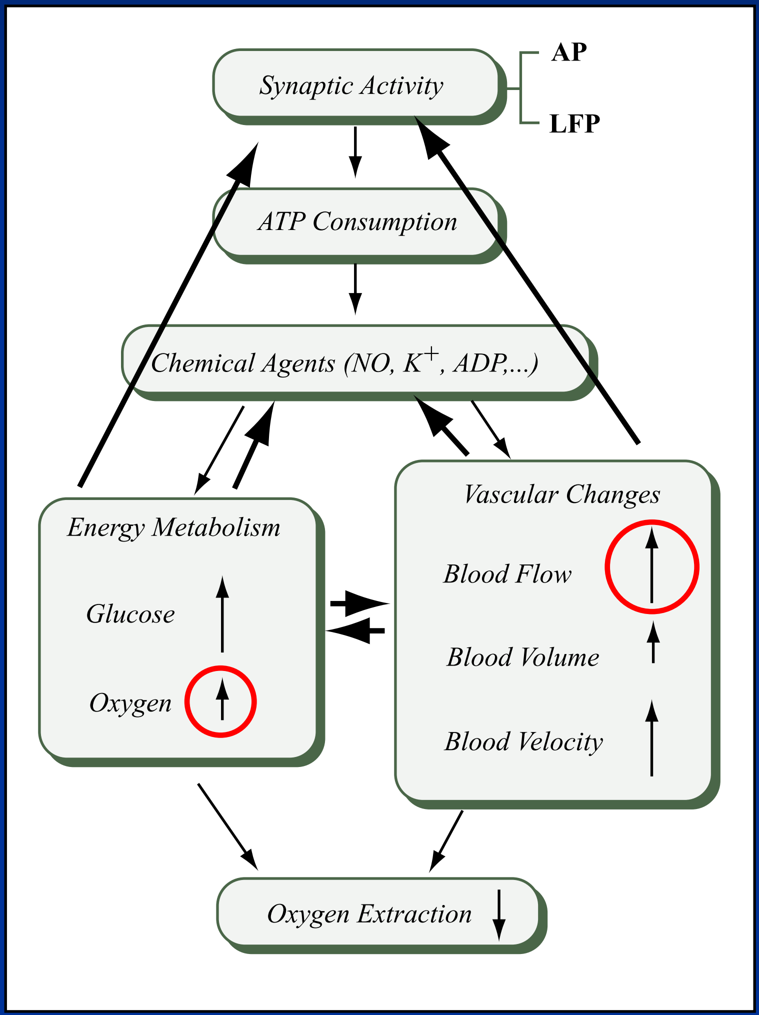
Set of MRI brain images
removed due to copyright restrictions.
See Fox et. al, *Science* 22 (1988): 462-464.

- Blood Flow and glucose metabolism (CMRGlc) increase substantially and are closely correlated to functionally active areas

- Despite correlation, causality is unlikely (i.e. flow does *not* increase to support change in CMRGlc)
- Suggests there is excess glucose around to support demand for increased glucose metabolism due to functional activity

Set of MRI brain images
removed due to copyright restrictions.
See Cholet et al, JCBFM 17 (1997): 1191-1201.

2. Oxygen metabolism ($CMRO_2$) increases much less than CBF



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After Buxton, *Introduction to fMRI*, 2002.

2. Oxygen metabolism ($CMRO_2$) increases much less than CBF

CBF

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See Fig. 1 in Fox, P. T., and M. E. Raichle. "Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects." *PNAS* 83, no. 4 (1986): 1140-1144.

$CMRO_2$

RESTING **STIMULATED**

- $CMRO_2$ increases less than CBF during activation (5% versus 30%)
- Mismatch corroborated since many times
- ***Why?*** Still remains of the largest questions in functional imaging….
- Ironically, **this mismatch is the basis of fMRI**

3. Oxygen extraction fraction (OEF) decreases

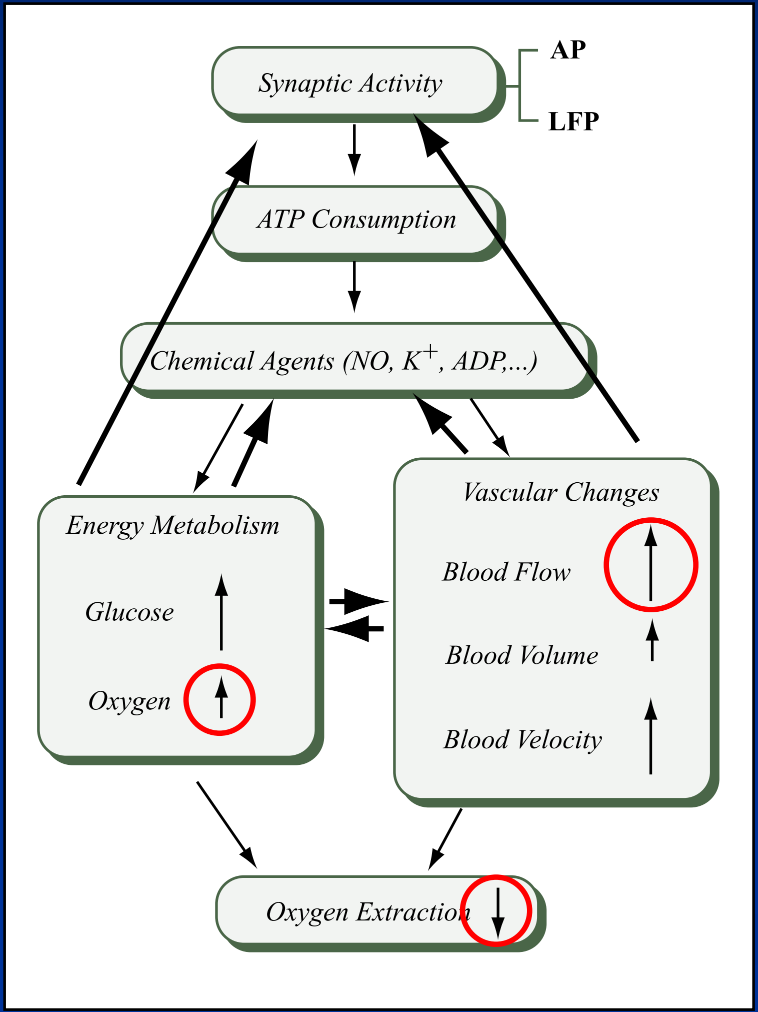

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

3. Oxygen extraction fraction (OEF) decreases

- OEF is oxygen consumption ($CMRO_2$): oxygen delivery (CBF), equivalent to:

$$OEF\downarrow = \frac{SaO_{2,arteriolar} - \uparrow SaO_{2,venular}}{SaO_{2,arteriolar}}$$

- Venous oxygen saturation ($SaO_{2,\ venous}$) increases during activation (Haacke, Oja)
- OEF decreases
- Consistent with CBF/ $CMRO_2$ observation:

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

Veins draining visual cortex

Images removed due to copyright restrictions.
Figure 2 in Oja et. al. “Determination of Oxygen Extraction Ratios by Magnetic Resonance Imaging.” JCBFM 19 (1999): 1289-1295.

4. CBV increases less than CBF, and temporally lags CBF response

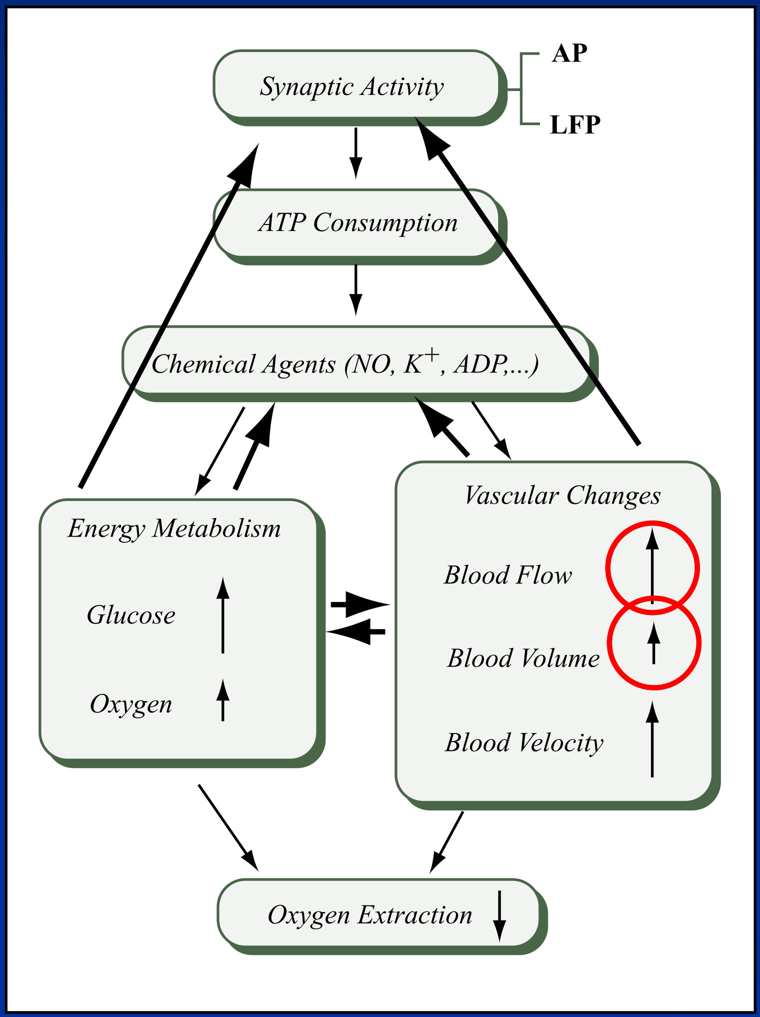

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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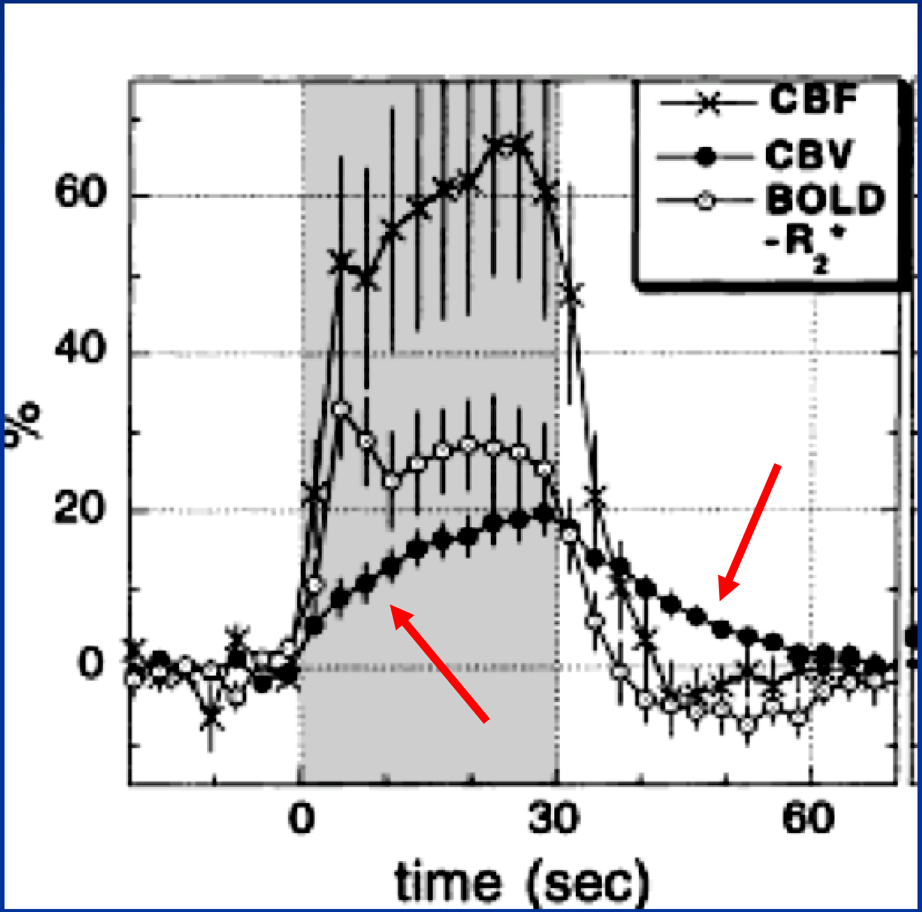
4. CBV increases less than CBF, and temporally lags CBF response



Mandeville et al, MRM, 1999

- CBV is delayed compared to initial CBF response to stimulus,
- CBV takes longer to return to baseline
- Hypothesized as *balloon effect* of venous vasculature
- If true, would lead to increased CBV_{venous} dynamically

5. Blood flow increases by blood velocity increase, not capillary recruitment

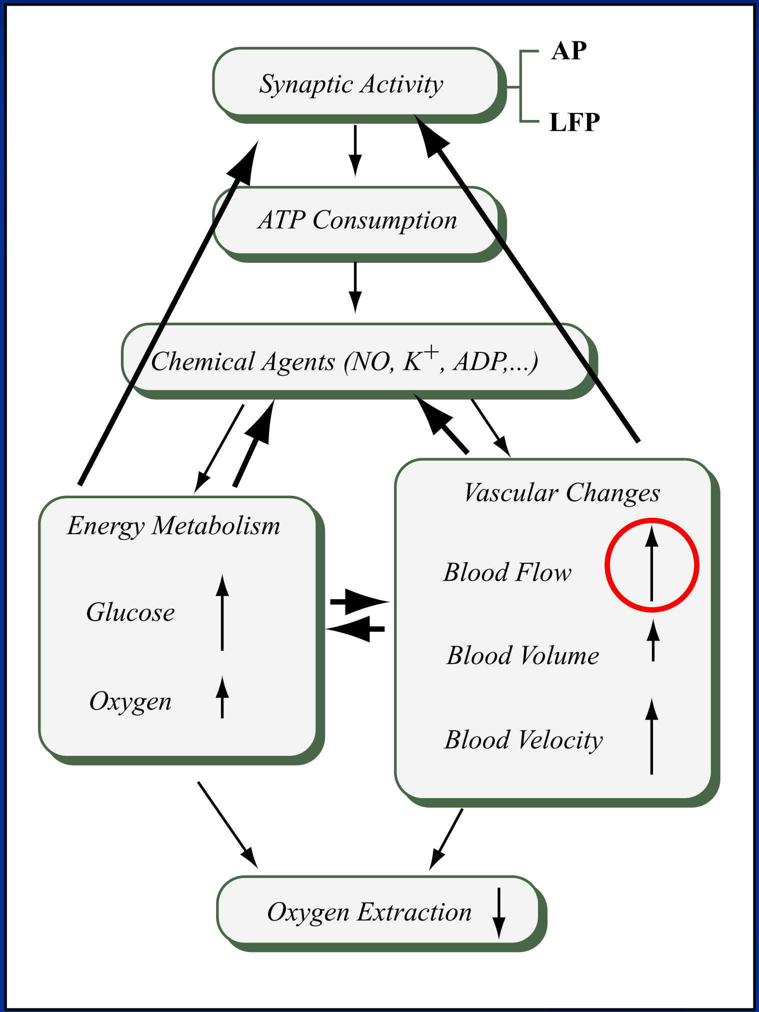


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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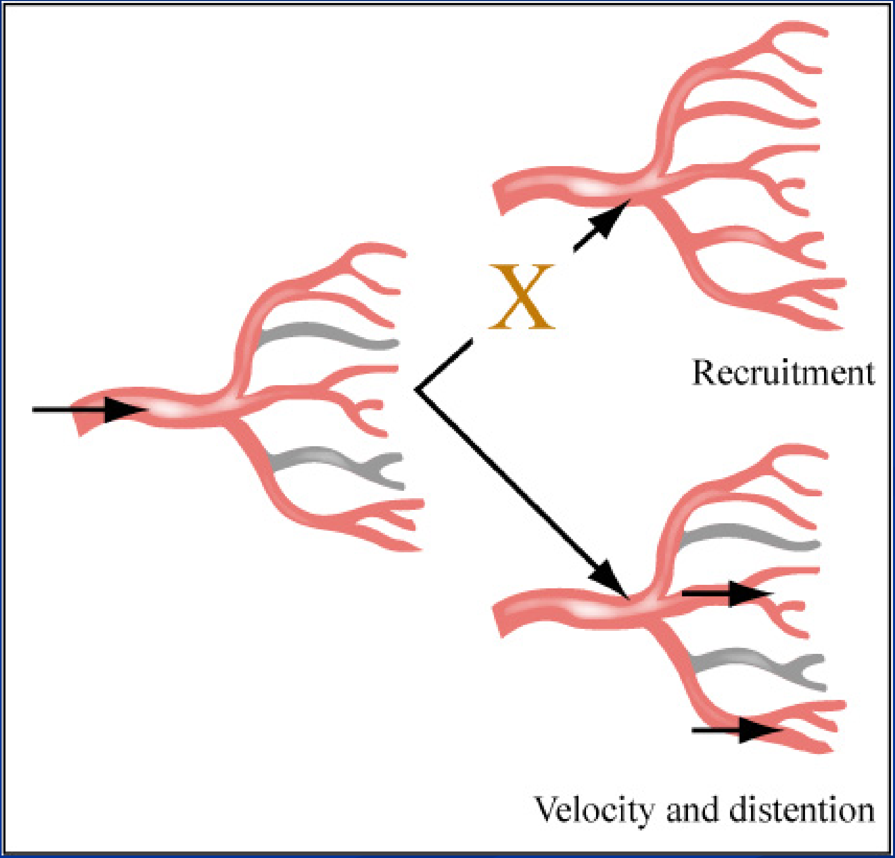
5. Blood flow increases by blood velocity increase, not capillary recruitment

- Increasing capillary flow involves either increasing total cross-sectional area or blood velocity:

$$flow = velocity \cdot cross\text{-}sectional\ area$$

- *Recruitment* involves opening up previously closed capillaries, increasing overall CS area (occurs in muscles)
- Several studies suggest that this does ***not*** happen in brain
- Brain capillary blood flow is primary increased by increasing blood velocity (although there may be slight distention)



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Velocity and distention

6. CBF increase better correlated to LFP than AP spiking

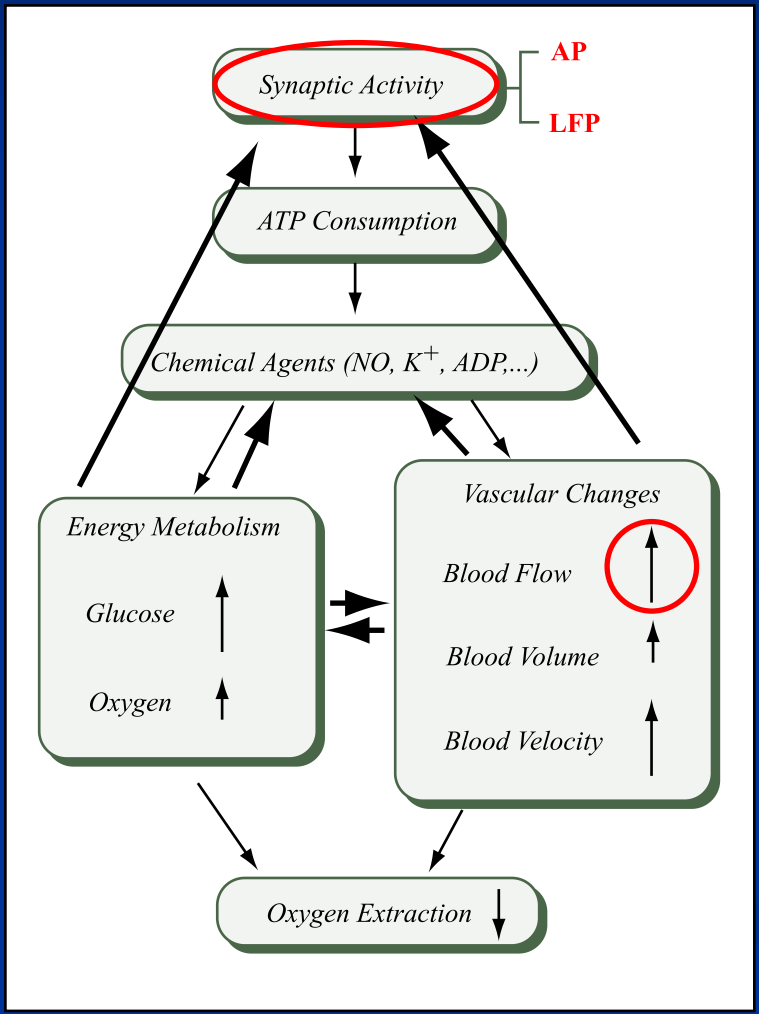
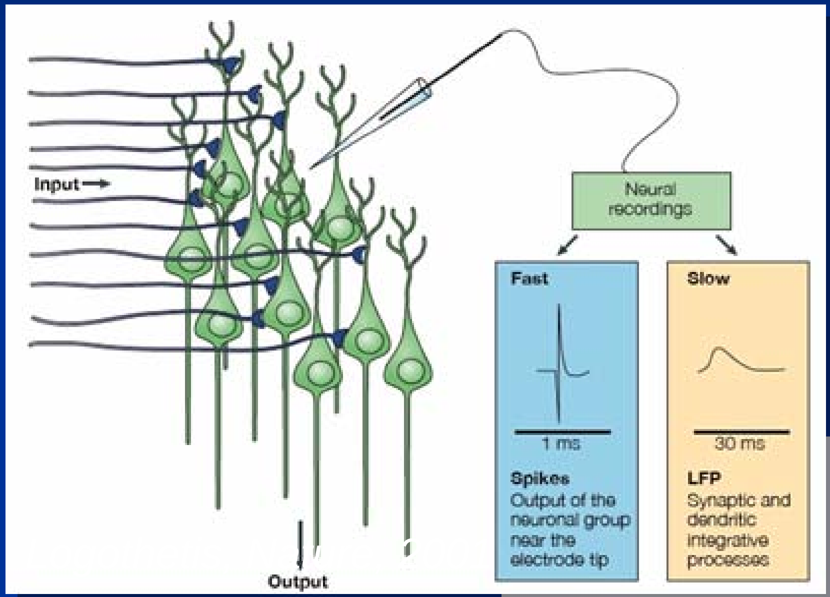


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

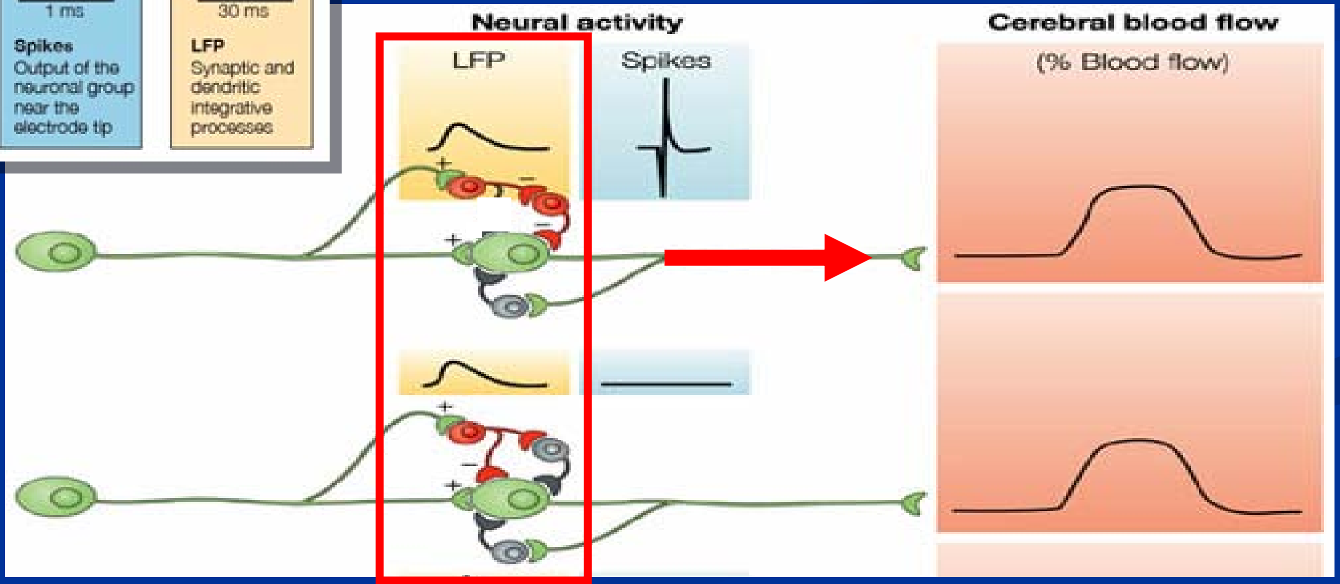
6. CBF increase more tightly correlated to LFP than AP spiking



- fMRI signals "reflect the **input** and intracortical processing of a given area rather than its spiking **output**."

Courtesy of Constantino Iadecola. Used with permission.

Both figures from Iadecola, Nat Neurosci Reviews, 2004



- LFP reflects ***input; i.e. synaptic activity***

Lecture Overview

1. Discuss changes in brain physiology during activation, as known from key experimental observations
2. Introduce how these changes lead to fMRI via **BOLD** imaging
3. Explore theories discussing metabolic and vascular coupling (i.e. flow-metabolism coupling)

Relevance for BOLD fMRI

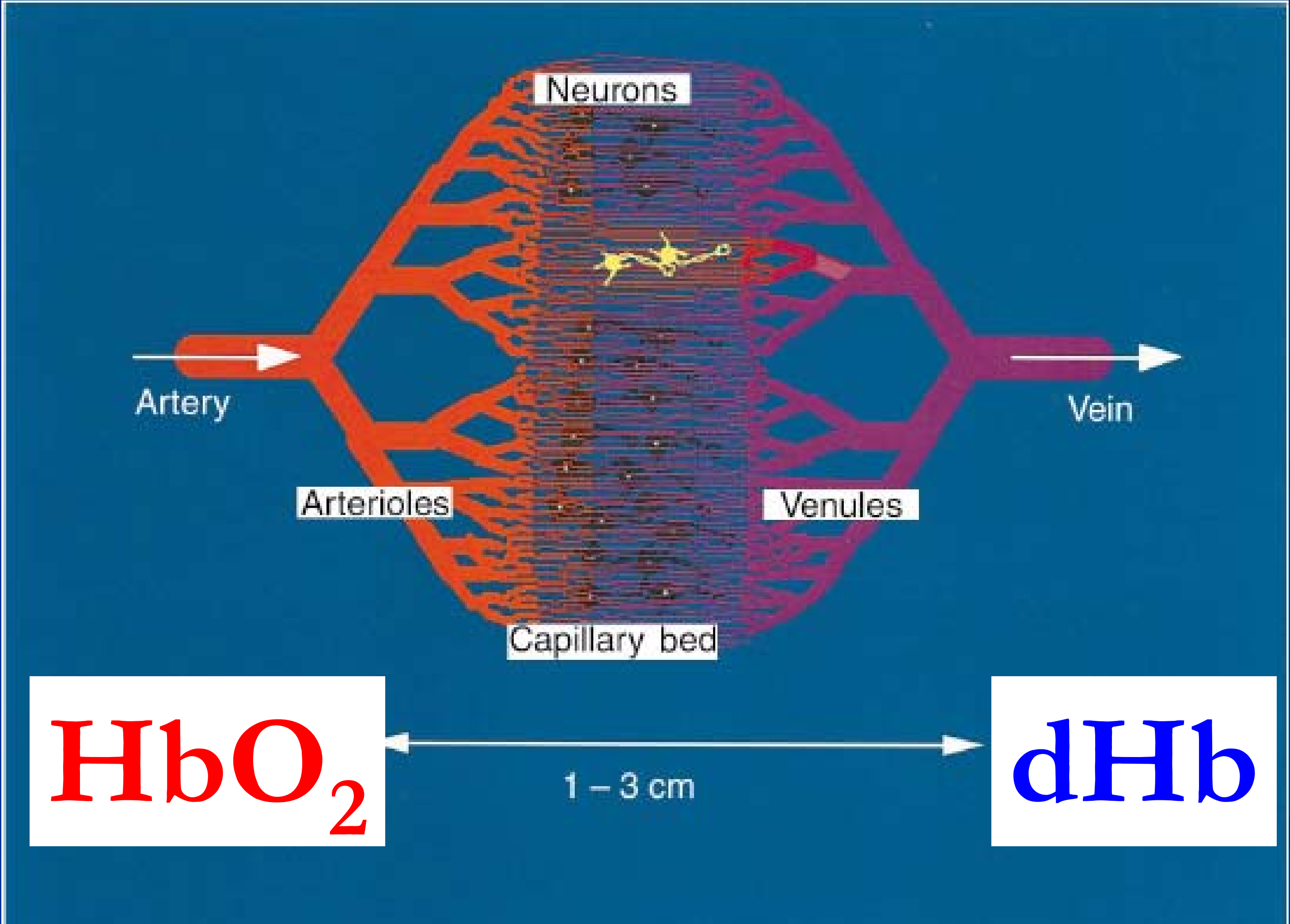
- These phenomena *in concert* lead to the BOLD fMRI response
- **Greatest contributor: *mismatch between CBF increase and CRMO$_2$ increase during activation***
- *CBF increase in response to functional activation is called "functional hyperemia"*
- ***Leads to less deoxygenated hemoglobin in blood and increase in BOLD fMRI signal***
- Other changes also contribute to BOLD response; details will be covered in next lecture

Birth of BOLD fMRI

- 1936: Linus Pauling discovered that oxygenated hemoglobin (HbO_2) is diamagnetic, deoxygenated hemoglobin (dHb) is paramagnetic
- 1982: Thulborn published seminal paper showing the dependence of the MRI T_2/T_2* relaxation parameter on blood oxygenation level (and hematocrit)
- Concluded that paramagnetic dHb reduces MR signal, and realized *hemoglobin as an intrinsic physiological agent that could alter MR signal*
- Possibility arose to use MRI to assay blood oxygenation

*Hemoglobin is the principal oxygen carrier in the blood for delivery to the tissues

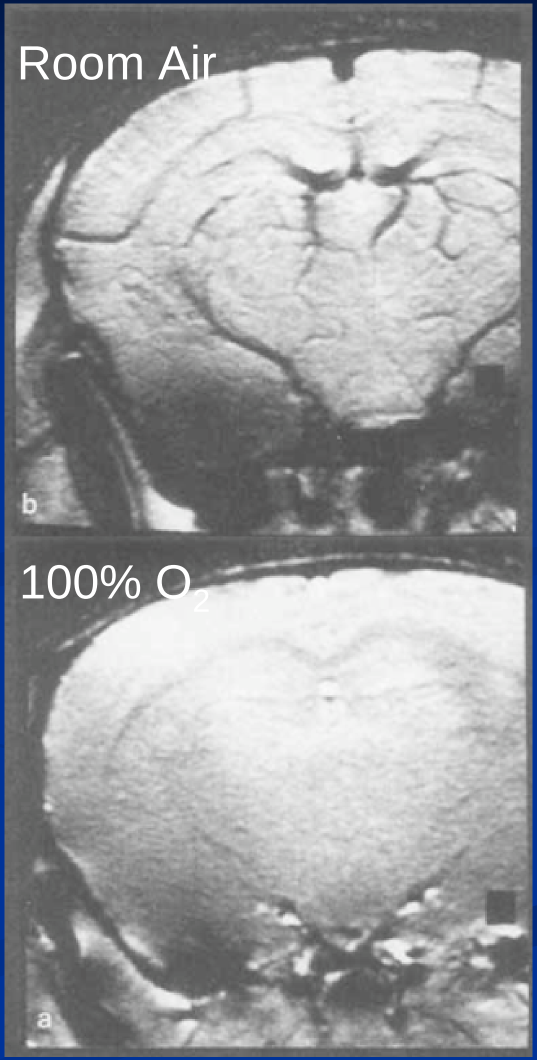
Hemoglobin in vascular system



from Menon & Kim. *TiCS* 3 no. 6 (1999): 207-216.

Birth of BOLD fMRI

- Late 80's: Ogawa postulated that MR signal dropouts in veins reflected the increased content of dHB in venous blood
- Imaged with GRE sequence as to target changes in T_2*
- Postulated that since paramagnetic dHb caused signal drop-out, dHb removal via hyperoxia would restore signal
- Had rat breathe 100% oxygen: ***Signal recovered!***
- ***Findings suggested that physiological processes that alter blood oxygenation could be detectable with MRI***

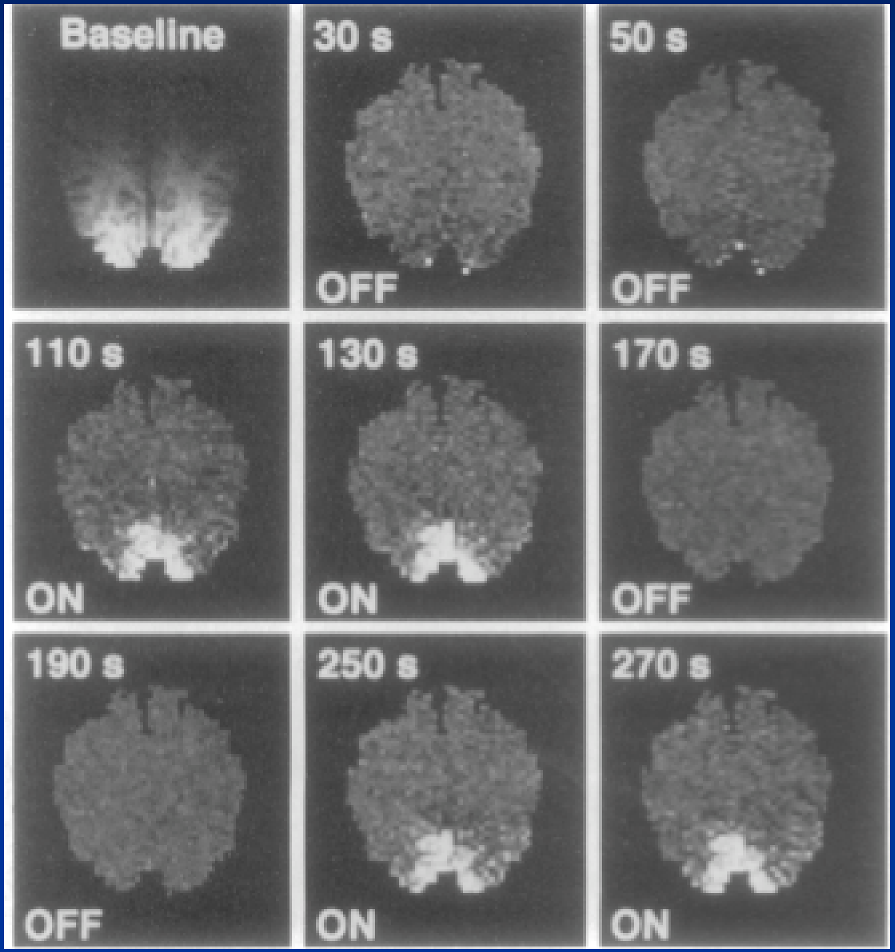


Ogawa et al, MRM & PNAS, 1990

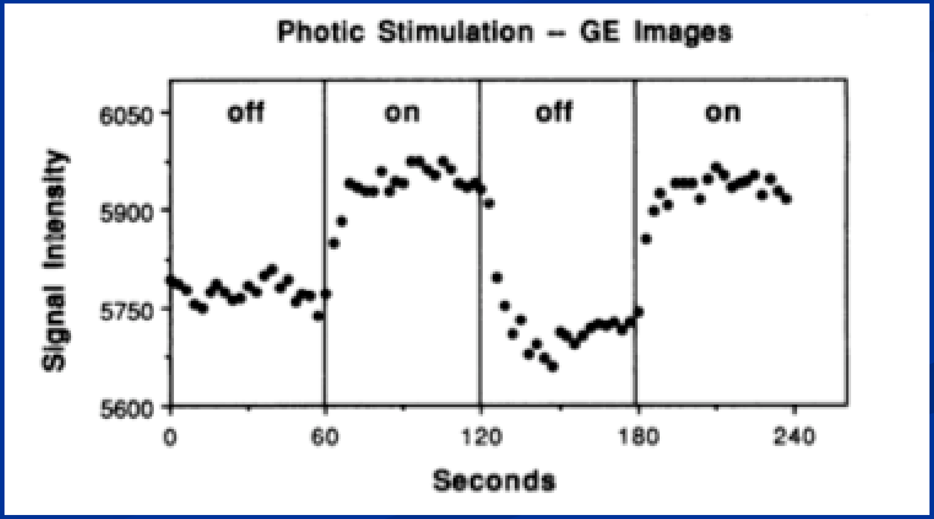
Using BOLD to image brain function

- In 1992 three groups independently used BOLD contrast to assay change in brain activity in response to a stimulus
- PNAS, Vol 89, June 1992: Ogawa, **Kwong (Martinos Center),** MRM 1992: Bandettini

Using BOLD to image brain function



Stimulus: Goggles containing array of 5x6 flashing red Light Emitting Diodes



Using BOLD to image brain function

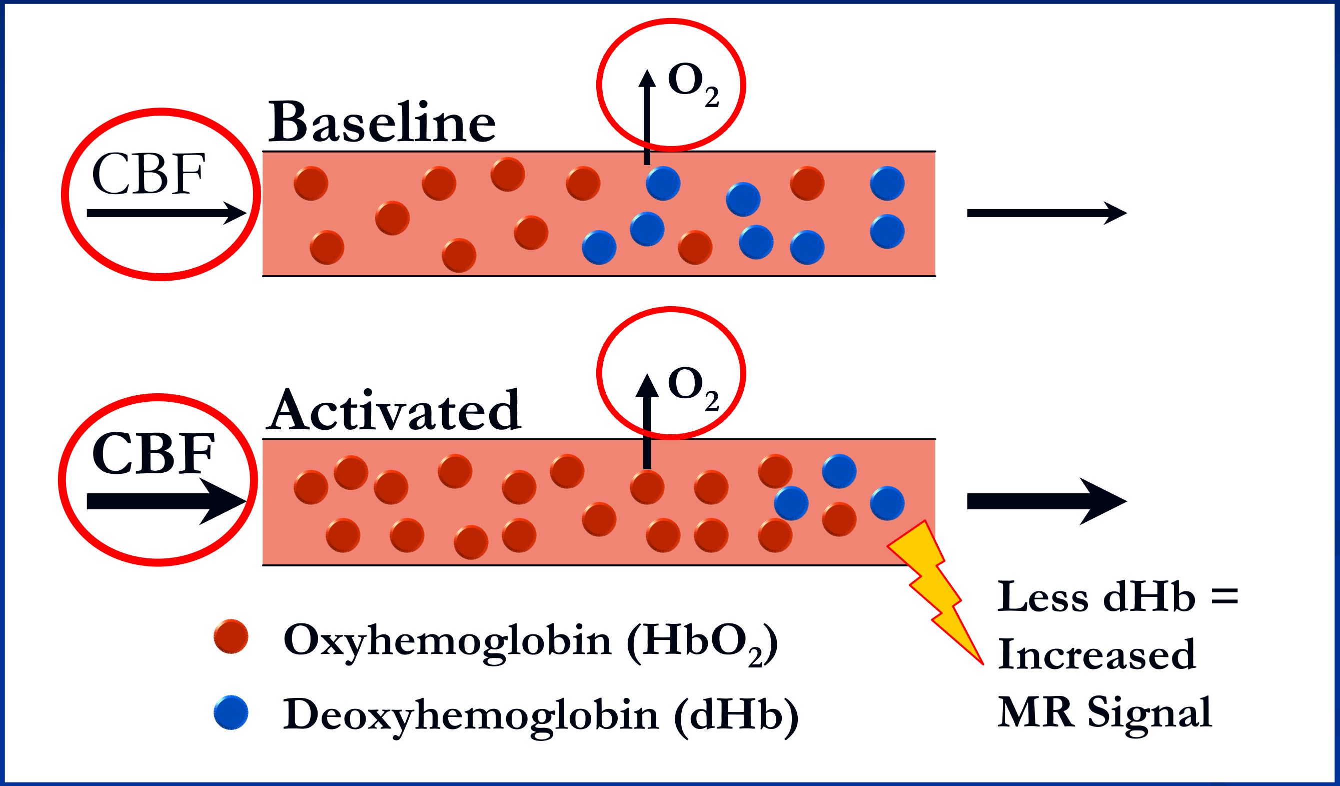
Image removed due to copyright restrictions.

Complete animation: http://www.e-mri.org/functional-mri/introduction.html

Using BOLD to image brain function

- Signal went UP in activated areas, suggesting *less* dHb in activated areas
- Consistent with Fox & Raichle PET observations: flow increase is much larger than increase in oxygen metabolism
- Since O_2 delivery (via flow) greatly exceeds consumption ($CMRO_2$), more oxygenated Hb returns to venous circulation
- Paramagnetic dHB is washed out and signal ***increases***

Basis of BOLD Contrast



- Increased blood flow relative to $CMRO_2$ flushes out dHb; causes increase in BOLD signal during activation

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Basis of BOLD Contrast

Image removed due to copyright restrictions.

Diagram of blood vessel through the brain.

See Huettel, Song, and McCarthy. *Functional Magnetic Resonance Imaging*. 2nd edition. Sunderland, MA: Sinauer Associates, 2008.

- Increased blood flow relative to $CMRO_2$ flushes out dHb; causes increase in BOLD signal during activation

Basis of BOLD contrast

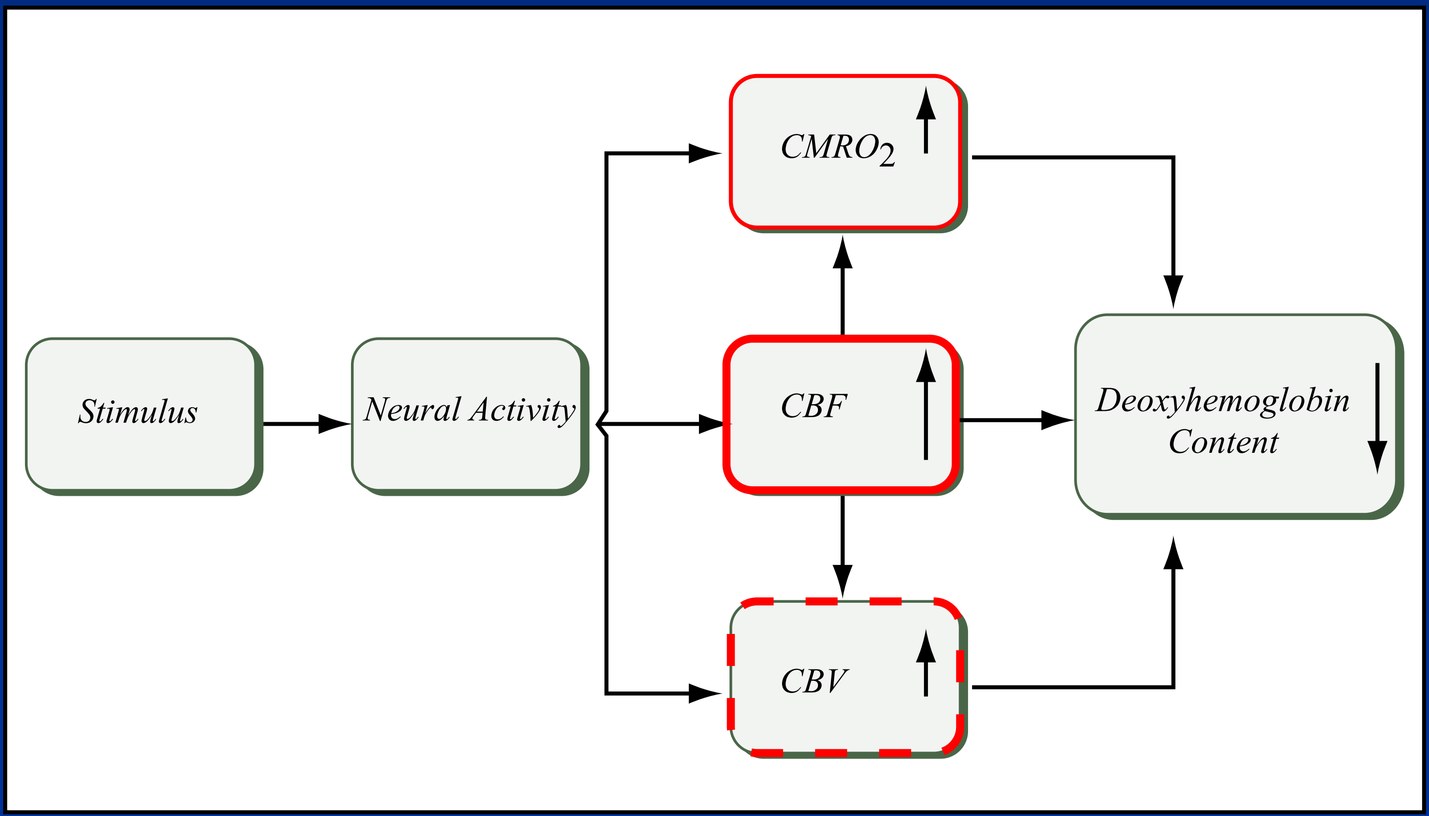
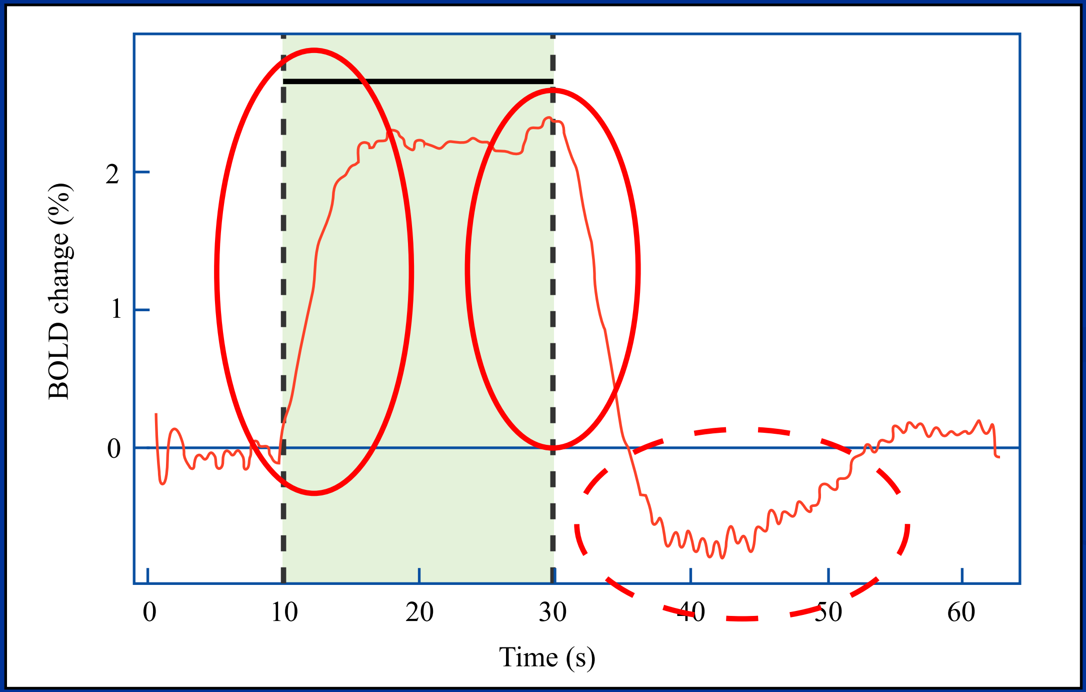


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

BOLD Imaging: Timing

- The BOLD response does not instantaneously follow neural activity; and occurs with delay and dispersion
- Since the BOLD response arises primarily from a CBF response, it typically referred to as the "hemodynamic response"
- The modulation of blood flow leads to the fMRI signal

BOLD Imaging: Timing



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After Buxton, *Introduction to fMRI*, 2002.

Using BOLD to image brain function

- Sophistication of imaging paradigms, hardware, software, and analysis techniques has increased substantially
- However, BOLD experiments done today are similar in many ways
- ***The BOLD phenomenon is basis of contrast for nearly all fMRI experiments***

Summary

- Key physiological (metabolic and vascular) changes follow neuronal activation
- BOLD contrast arises from these changes
- BOLD is primarily derived from a decrease of dHb during activation, due to a mismatch in flow/ $CMRO_2$ increase
- A simple block-design experiment can be used to detect activation with BOLD
- Basic physiological questions still remain, and *neurovascular coupling* very active area of study

Up Next:

- The BOLD hemodynamic response
- Linearity of BOLD response
- Modeling the BOLD signal: a deeper investigation into features and physiological correlates