认知心理学进阶第六讲：磁共振生理（一）

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Based on MIT MRI Open Course

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Before we begin: *What is functional MRI?*

- Broad sense: fMRI refers to any MR technique that goes beyond anatomy to measure aspects of local physiology.
- **Specific sense: fMRI refers to MR techniques that measure changes in brain function over time.**
- "Brain function" results from information processing activity of ensembles of neurons throughout the brain
- *Primary goal of fMRI is to detect signal changes corresponding to neuronal activity.*

Buxton RB. Introduction to Functional Magnetic Resonance Imaging, 2002.
Huettel S, Song AW, McCarthy G. Funcitonal Magnetic Resonance Imaging, 2004.

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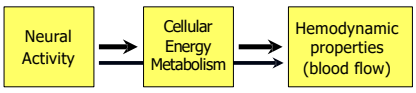
How do we measure neuronal activity with MRI?

- Currently not possible to directly measure neural activity (i.e. electrochemical activity) with MRI
- Can visualize downstream correlates of neural activity:

Simplified flowchart



- The following lectures will discuss the nature of these different aspects of neurophysiology, and to what extent MRI can be used to image them

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Overview of Imaging Physiology Block

- Lecture 6:
  - Brain at baseline: neural activity, energy metabolism, and cerebral blood flow
  - "Activated" brain: changes in brain physiology in response to external stimuli, and Introduction to BOLD fMRI

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Overview of Imaging Physiology Block

- Lecture 7:
  - BOLD fMRI in-depth
  - Beyond BOLD: state-of-the art fMRI techniques to directly image physiological parameters

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Brain at baseline: neural activity, energy metabolism, and cerebral blood flow

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Baseline Brain Activity

- *What do we mean by "brain at baseline"?*
  - Refers to the *intrinsic* functional activity of the brain, as opposed to activity *evoked* through stimulation
- Brain is *never* in zero-activity state; "resting" and "active" distinctions are actually misnomers
- Intrinsic functional activity far greater (60 – 80% of brain's energy budget) than evoked activity to external stimuli (0.5 to 1%)
- Next few slides will detail intrinsic processes that are occurring in the brain *all the time*.

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Overview

- Brain "activity" can be naturally divided into three points of study:
  - Neural Activity: electrochemical signal conduction
  - Metabolic Activity: energy production and consumption
  - Vascular Activity: cerebral blood flow and perfusion
- This is a very sophisticated system that is far from understood; we will present a simplified view.

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Overview

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  - Vascular Activity: cerebral blood flow and perfusion

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Neural Activity

- Let's begin with the smallest unit of functional activity in the brain: the neuron*
- Human brain has ~100 billion neurons
- Neural activity typically originates from ensembles of interconnected neurons communicating via electrical impulses
  - ***Integrative Processes***
  - ***Signaling Processes***

* *New research suggests that glial cells are more than just support cells; i.e. they have significant functional importance. Note that glial cells outnumber neurons by at least 10:1*

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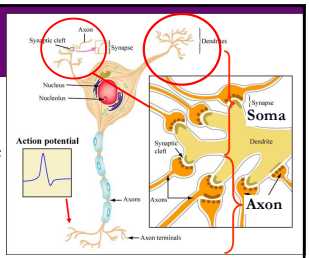
Neuronal Anatomy

- **Dendrite**: receiving end of neuron, receives and ***integrates*** input signals from other neurons
- **Soma**: provides metabolic and structural support for the neuron
- **Axon**: transmitting end of the neuron; ***signals*** elicited via *action potentials* to one or more neurons
- **Synapse**: Specialized junction between dendrite and axon through which information is transferred



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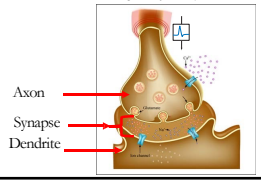

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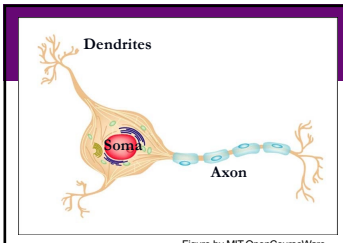
Signal Conduction



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Signal Conduction

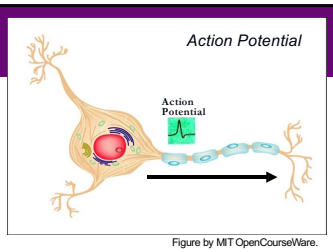

Figure by MIT OpenCourseWare.

- Signal conduction begins at base of axon with the *Action Potential*
- *Action Potential* is a wave of electrical activity that sweeps down axon

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Signal Conduction

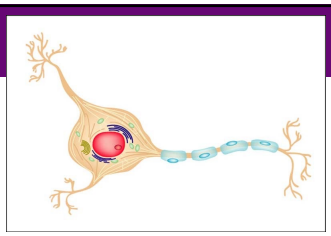

Figure by MIT OpenCourseWare.

- *AP* initiates when Na^+ channels open in axon base and allow Na^+ ions to flow in
- *Electrochemical gradient* drives Na^+ inflow:
  1. High concentration of Na^+ outside of neuron, low $[Na^+]$ inside
  2. Outside of neuron more electrically positive than inside
- Flow of positively charged Na+ into cell is energetically favorable process (does not require energy)

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Signal Conduction

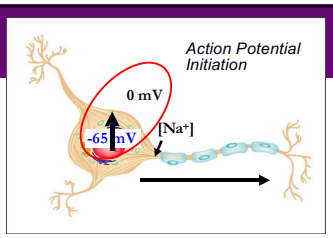

Figure by MIT OpenCourseWare.

- AP onset causes a *depolarization:*
- Decrease of the potential difference between the outside and inside of neuron
- Occurs since inside becomes *less negative* with Na^+ inflow

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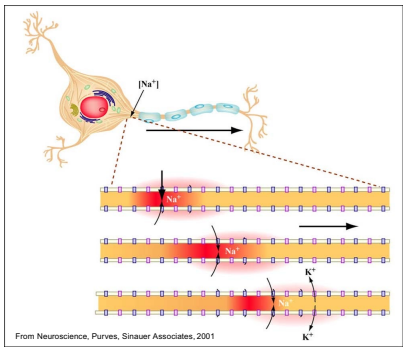
Signal Conduction

AP self-propagates and travels towards axon terminal



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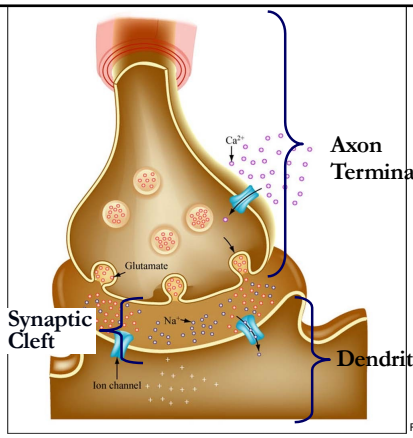

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Adapted from *fMRI*, Huettel, Song, McCarthy, Sinauer Associates, 2004.

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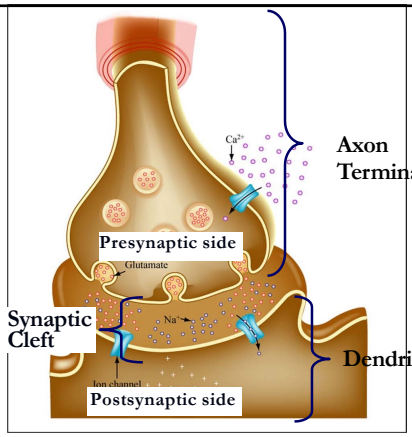

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Adapted from *fMRI*, Huettel, Song, McCarthy, Sinauer Associates, 2004.

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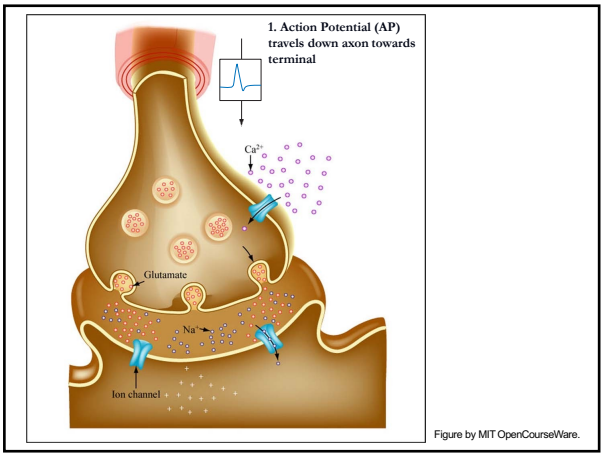

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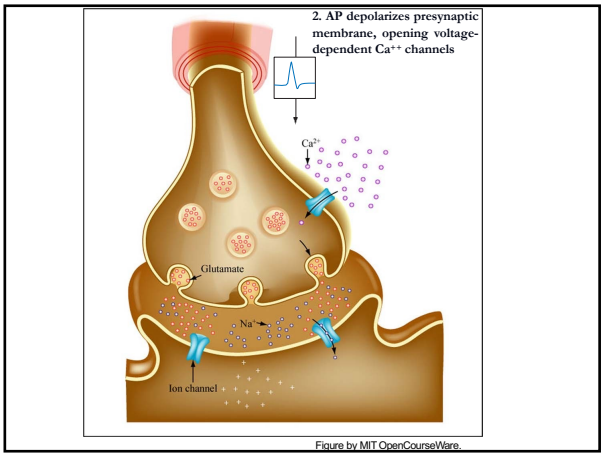

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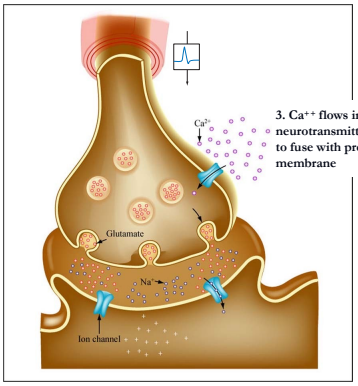

Neurotransmitter-filled vesicles populate the distal end of the axon

3. Ca^{++} flows into cell, causing neurotransmitter-filled vesicles to fuse with presynaptic membrane

Figure by MIT OpenCourseWare.

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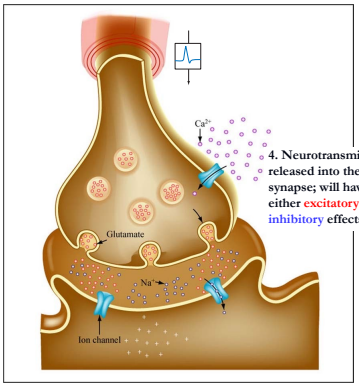

4. Neurotransmitter is released into the synapse; will have either excitatory or inhibitory effects

An excitatory or inhibitory effect depend on both neurotransmitter and receptor type

Glutamate is an abundant NT that primarily has excitatory effects

GABA is an abundant NT that primarily has inhibitory effects

Figure by MIT OpenCourseWare.

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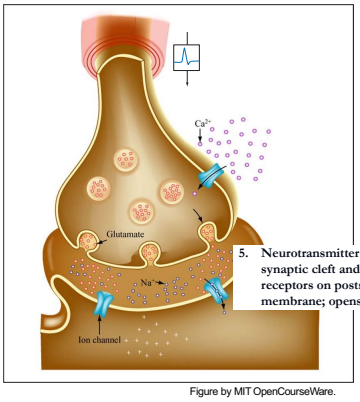

Neurotransmitter with excitatory effects binds to receptors on Na+ channels

Neurotransmitter with inhibitory effects bind receptors on Cl^- or K^+ channels

5. Neurotransmitter diffuses across synaptic cleft and binds with receptors on postsynaptic membrane; opens ions channels

Figure by MIT OpenCourseWare.

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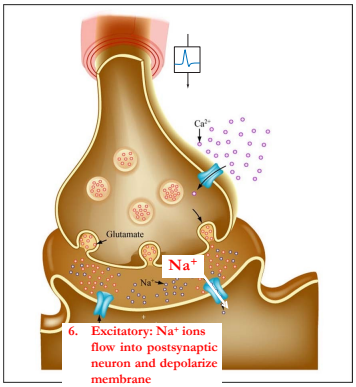

6. Excitatory: Na^+ ions flow into postsynaptic neuron and depolarize membrane

Excitatory effect leads to *Depolarization*:

Local decrease in the electrical potential between the inside and outside of the membrane

Figure by MIT OpenCourseWare.

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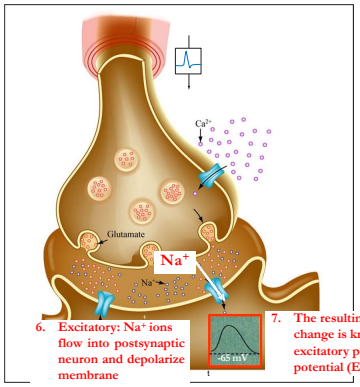

Excitatory effect leads to *Depolarization*:
Local decrease in the electrical potential between the inside and outside of the membrane

EPSPs *increase* probability that receiving cell will fire action potential

Figure by MIT OpenCourseWare.

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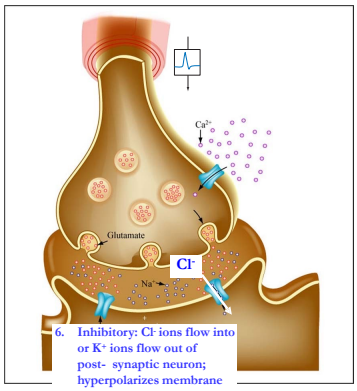

Inhibitory effect leads to *Hyperpolarization:*
Local increase in the electrical potential between the inside and outside of the membrane

Figure by MIT OpenCourseWare.

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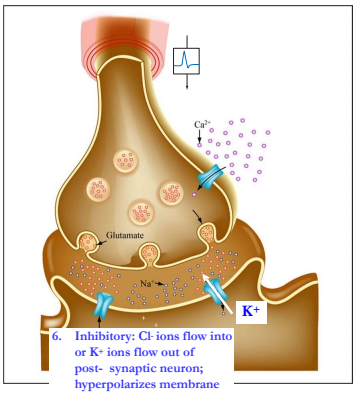

Inhibitory effect leads to *Hyperpolarization:*
Local increase in the electrical potential between the inside and outside of the membrane

Figure by MIT OpenCourseWare.

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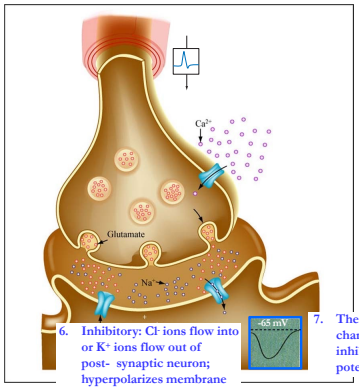

Inhibitory effect leads to *Hyperpolarization:*
Local increase in the electrical potential between the inside and outside of the membrane

IPSPs *decrease* probability that receiving cell will fire action potential

Figure by MIT OpenCourseWare.

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Integration leads to signaling

- Thousands of IPSPs and EPSPs are received by dendrites;
- **Integration** is the summation of these of these PSPs
- If the resultant voltage is beyond a threshold, an axon potential is elicited to continue **signaling**

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Summary of neural information processing

- Information processing is thus the combination of neuronal ***integrative*** and ***signaling*** roles
- ***Integration:*** The summation of EPSPs *(depolarizations)* and IPSPs *(hyperpolarizations)* from all incoming axons
  - Integration is affected by unique spatiotemporal characteristics of EPSPs and IPSPs
- ***Signaling:*** If summation results in a threshold potential being reached, a new action potential is elicited and sent down axon

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Overview

- Brain "activity" can be naturally divided into three points of study:
  - Neural Activity: electrochemical signal conduction
  - Metabolic Activity: energy production and consumption
  - Vascular Activity: cerebral blood flow and perfusion

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Energy requirements

- Postsynaptic potential (EPSPs, IPSPs) and action potential generation depend on electrochemical gradients, ion flow, & neurotransmitter release
- As signaling proceeds, the driving force behind AP/PSP generation is lost, as ion and neurotransmitter stores are depleted
- ***For neuronal signaling to continue:***
  1. ***Ion concentrations & electrochemical gradients must be re-established for continued ion flow, and***
  2. ***Neurotransmitter must be recycled returned to neuron***
- ***These processes require energy; the primary source of free energy in the brain is ATP!***

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Generation of ATP in the brain

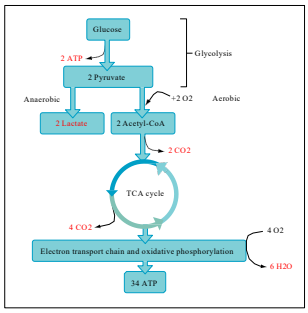

Figure by MIT OpenCourseWare.

- **Glycolysis**
  - Consumes glucose,
  - Produces 2 ATP, Acetyl CoA if O ; lactate if no O_2
- **TCA Cycle/ Ox Phos**
  - Consumes O_2
  - Produces CO_2, water and **LOTS of ATP**

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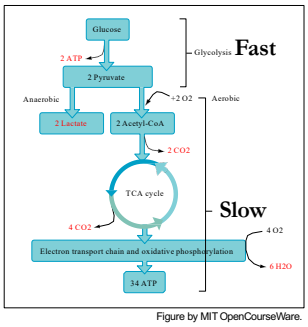
Generation of ATP in the brain



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- **Aerobic Respiration:** Requires oxygen, produces 34 ATP, *slow* process
  - Byproducts are CO_2 and H_2O
- **Anaerobic Respiration:** Does not require oxygen, produces only 2 ATP, but very *fast* process
  - Lactate is major byproduct

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Reestablishing ion concentrations & electrochemical gradients: Ion pumps

- Signal transduction requires ion flow
- As ions flow, intracellular and extracellular ion concentrations change
- Electrochemical gradient which drives ion flow gets depleted
- For signaling to continue, ion concentrations must be restored for
- This is done via ***ion pumps***

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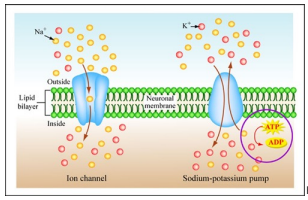
Ion Pumps

- Ion pumps restore electrochemical gradient by pumping ions into or out of neuron



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- Occurs in both presynaptic and postsynaptic neurons
- **This is a process that requires ATP**

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Neurotransmitter Recycling*

- Neurotransmitter glutamate is released into synapse during most excitatory signaling processes
- At this point two things must happen:
  1. Glutamate must be quickly removed to stop excitatory activity
     - Specific timing and duration of activity is critical for propoer information processing
     - Unchecked stimulation is neurotoxic
  2. Glutamate must be returned to presynaptic neuron for future signaling
- ***Astrocyte-Neuron Lactate Shuttle*** is a model that could explain glutamate cycling

* Will focus on glutamate; other NT beyond scope of lecture

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Neurotransmitter Recycling: Astrocyte-Neuron Lactate Shuttle

- NT glutamate is released into synapse after AP
- Na^+/Glutamate co-transporter on astrocyte *passively* removes glutamate from synapse
- *Anaerobic* glycolysis generates 2 ATP without O_2
- **One ATP** powers Na^+/K^+ pump to maintain membrane potential
- **One ATP** converts glutamate to inactive glutamine
- Glutamine is returned to neuron

Astrocyte is a *glial cell*, historically considered as primary neuronal support cell*

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Energy budget in the brain*

- Restoring presynaptic membrane ion concentrations following AP consumes **47%** of total energy expenditure
- Restoring postsynaptic membrane ion concentrations following PSPs consumes **34%**
- Glutamate cycling: **3%**

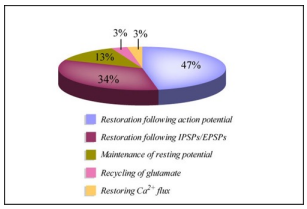

Figure by MIT OpenCourseWare.

* Data from rodent brain; Atwell & Laughlin, JCBFM 2001

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Overview

- Brain "activity" can be naturally divided into three points of study:
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  - Vascular Activity: cerebral blood flow and perfusion

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Cerebral Blood Flow (CBF)

- Supplies ***oxygen, glucose,*** and other nutritive elements to the brain, as needed for neuronal activity and energy metabolism
- Removes ***CO_2***, ***heat***, other byproducts and toxins
- Despite being only 2% of body's weight, the brain receives 20% of its blood flow

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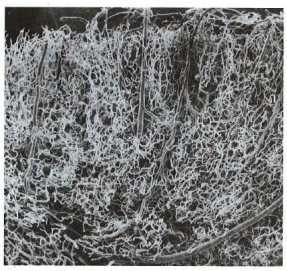
*Micro*vascular structure



- Vessels with radius ~3 um - ~500 um
- Capillaries
- Arterioles
- Venules

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Devernoy, Delon, Vannson. "Cortical blood vessels of the human brain." *Brain Research Bulletin* 7, no. 5 (November 1981): 519-579.

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Definition of terms

(in the context of fMRI)

- ***Perfusion*** describes nutritive delivery of arterial blood to a capillary tissue bed
- ***CBF*** is the rate of delivery of arterial blood to capillary beds of particular mass (or volume)
- ***CBV*** (cerebral blood volume) is the fraction of the tissue volume occupied by microvessels
- ***Mean transit time*** (τ) is the time it takes blood to flow through a defined volume; τ = CBV/CBF

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MRI definition of CBF

- Conventional definition of flow:

$$flow = \frac{volume}{time} = CS\ area \cdot velocity$$

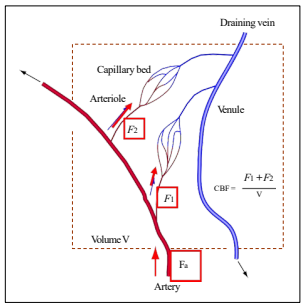

Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

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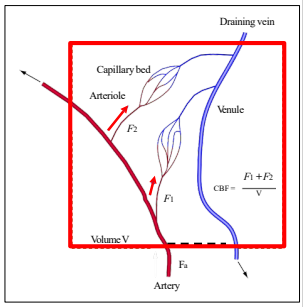
MRI definition of CBF

- Conventional definition of flow:

$$flow = \frac{volume}{time} = CS\ area \cdot velocity$$

- CBF does not report flow **through** a vessel, but rather flow **to** capillaries in an imaging volume
- MRI CBF depends on:
  1. Total flow ***to capillaries*** in **imaging voxel**
  2. Volume of imaging voxel



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After Buxton, *Introduction to fMRI* , 2002.

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MRI definition of CBF

- MRI CBF depends on:
  1. Total flow to ***capillaries*** in **imaging voxel**
  2. Volume of imaging voxel
- $CBF = \frac{Total\ flow\ to\ caps}{Voxel\ volume}$

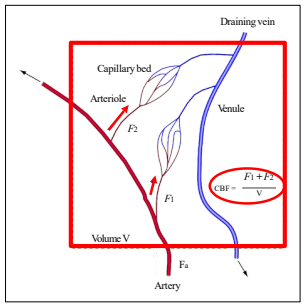

Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

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MRI definition of CBF

- MRI CBF depends on:
  1. Total flow to ***capillaries*** in **imaging voxel**
  2. Volume of imaging voxel
- $CBF = \frac{Total\ flow\ to\ caps}{Voxel\ volume}$
- Blood that flows *through* the imaging voxel does not count towards CBF!!
- This blood is destined for capillaries in other voxels and will contribute to CBF for that voxel

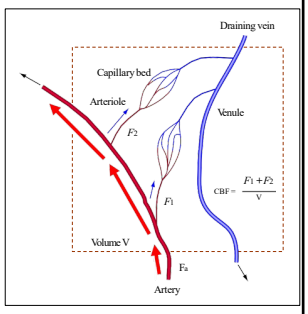

Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

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MRI definition of CBF

- Units of CBF:

$$\frac{ml}{ml\ of\ tissue\ -\ min}$$

- Density of brain tissue is ~1 gram/ ml
- More common units of CBF:

$$\frac{ml}{g\ of\ tissue\ -\ min}$$

- Typical gray matter CBF is 60 ml/(100g – min)

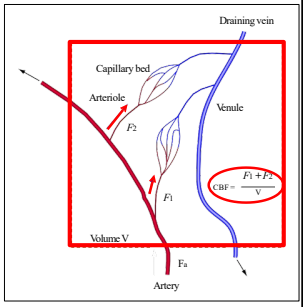

Figure by MIT OpenCourseWare. After Buxton, *Introduction to fMRI*, 2002.

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Regulation of CBF

- Modulation of vascular diameter (primarily arteriolar)
  - Vasodilatory substances (NO, CO_2, K^+, adenosine) bind with smooth muscle receptors and cause relaxation
  - Smooth muscle relaxation causes an increase in vessel radius; this increases flow by changing vascular resistance
  - **CBF is proportional to r^4**
- Secretion of vasodilatory substances by neuron during energy metabolism
- Direct neural innervation by afferents & interneurons
- Indirect control via astrocyte endfeet
- Pericyte constriction at capillary level
- ***Mechanisms of CBF regulation a highly active area of research!***

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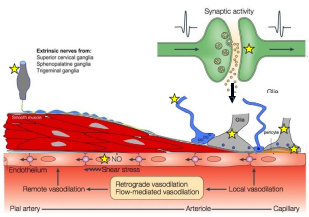
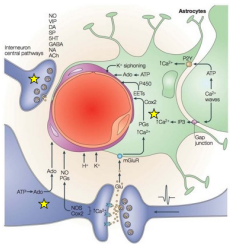
Regulation of CBF





- Direct afferent & interneuron innervation
- Indirect innervation via NT
- Glial (astrocyte) endfeet
- Capillary pericytes
- NO excreted by SM endothelial cells (retrograde vasodilation)

- Vasodilators secreted from neuron after energy metabolism
- Direct neurotransmitter action
- Indirect neurotransmitter action (via astrocyte)

From Iadecola, Nat Rev Neurosci, 2004

Courtesy of Costantino Iadecola. Used with permission.

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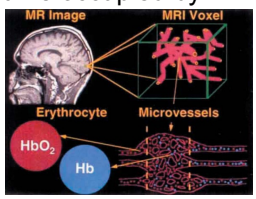
MRI definition of CBV

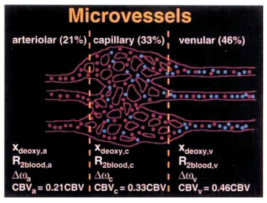
- Fraction of tissue volume occupied by microvessels



51

MRI definition of CBV

- Can divide CBV into capillary, arterial, and venous volumes



globin deoxygenation fraction $x_{deoxy,i}$ ($i \in a,c,v$) determines the local magnetic susceptibility shift differences ($\Delta\omega_i$) and spin-echo relaxation rates ($R_{2,blood,i}$) in the individual microvessels. These three blood relaxation rates are then combined with the tissue relaxation rate to determine the signal intensity in an MRI voxel. This is done by using the voxel composition (b) on the basis of microvessel and tissue morphometry data involving the individual microvessel blood volumes (CBV_i) and water densities for different tissues such as gray and white matter.

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Relating CBF to CBV

- CBV and CBF are independent physiological parameters, but are linked since CBF regulation occurs by dilating arterioles
- Grubb's Law, with alpha = 0.38:

$$\frac{V}{V_0} = \left(\frac{F}{F_0}\right)^{\alpha=0.38}$$

- **Implies that a only a small ΔCBV is required for a large ΔCBF (since CBF ∝ r^4)**

53

Mean Transit Time (τ)

$$\tau = \frac{CBV}{CBF}$$

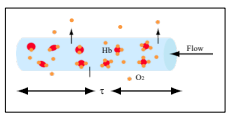

Figure by MIT OpenCourseWare.
From Introduction to *fMRI*, Buxton, Cambridge University Press, 2002

- Qualitatively: time it takes to cross vascular region
- Increasing flow, *decreases* transit time, since *velocity* increases
- A decrease in capillary transit time may result in decreased oxygen delivery to tissue

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Summary

- Three general categories of physiological parameters govern brain function
  - Electrical activity at the neuronal level
  - Energy metabolism at the cellular level
  - Hemodynamics at the microvascular level
- While these parameters are intimately related, they have *very* different spatiotemporal dynamics

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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
- "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

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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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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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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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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

} Oxygen Extraction Fraction

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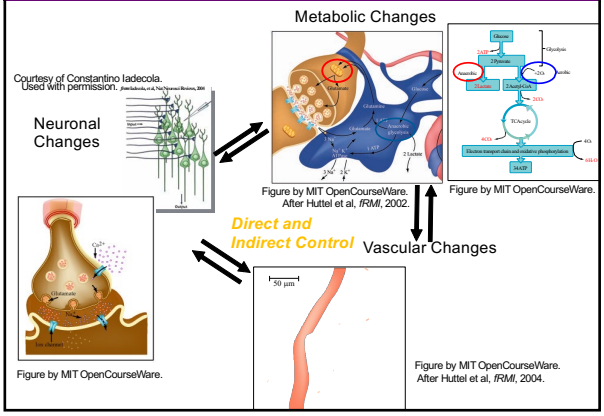
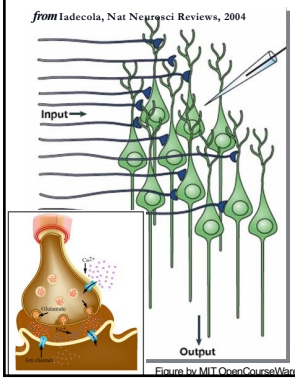
Physiological changes during activation



62

Neuronal Changes



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

Courtesy of Constantino Iadecola. Used with permission.

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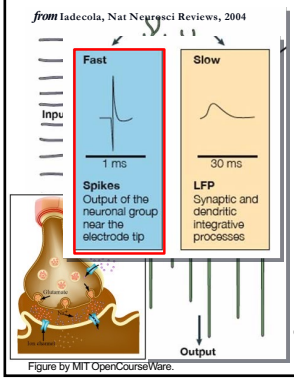
Neuronal Changes



- 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.

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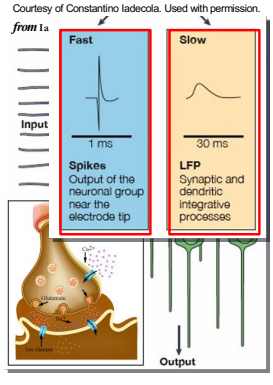
Neuronal Changes



- 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)***

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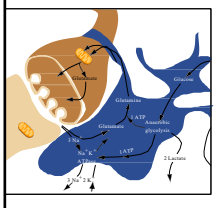
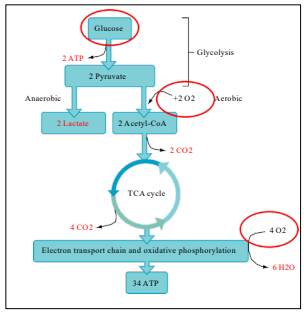
Metabolic Changes



- Glucose and oxygen metabolism both increase



66

Metabolic Changes

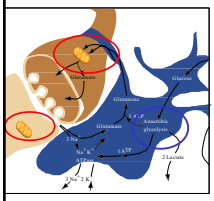


Figure by MIT OpenCourseWare.
After Huttel et al, *fMRI*, 2002.

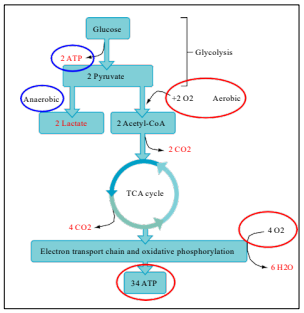


Figure by MIT OpenCourseWare.

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

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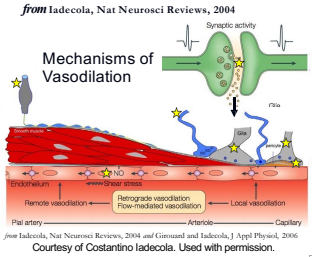
Vascular Changes



from Iadecola, Nat Neurosci Reviews, 2004 and Girouard and Iadecola, J Appl Physiol, 2006
Courtesy of Costantino Iadecola. Used with permission.

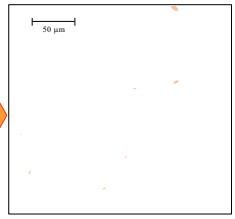


Figure by MIT OpenCourseWare.
After Huttel et al, *fRMI*, 2004.

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

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"Road Map" to Activation Physiology

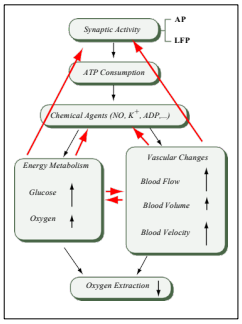

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

- 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

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"Road Map" to Activation Physiology

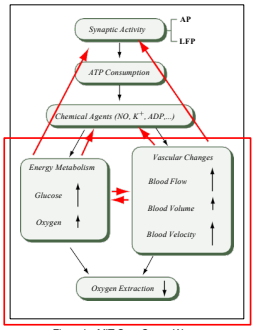

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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

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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***

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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

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1. Blood flow and glucose metabolism increase substantially

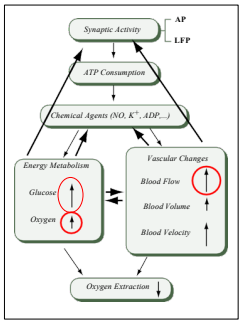

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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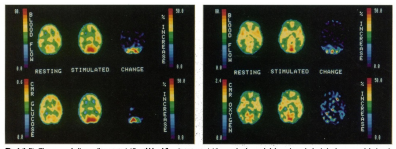
1. Blood flow and glucose metabolism increase substantially



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

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

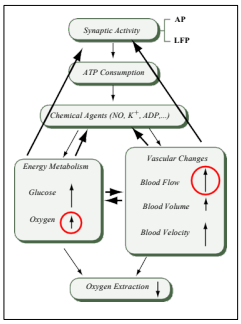
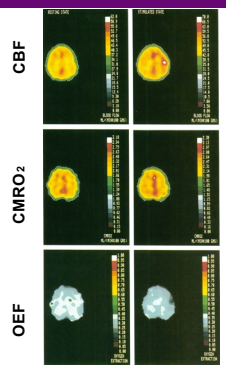


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

75

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



- $CMRO_2$ 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**

Fox, P. T., and M. E. Raichle. *PNAS* 83, no. 4 (1986): 1140-1144.

76

3. Oxygen extraction fraction (OEF) decreases

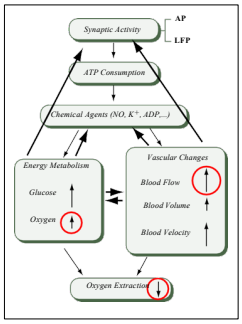


Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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3. Oxygen extraction fraction (OEF) decreases

- OEF is oxygen consumption ($CMRO_2$): oxygen delivery (CBF), equivalent to:
- OEF decreases
- Consistent with CBF/ $CMRO_2$ observation:

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

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

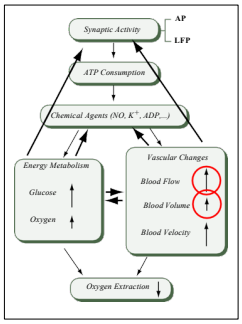

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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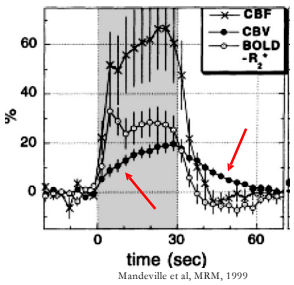
4. CBV increases less than CBF, and temporally lags CBF response



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

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

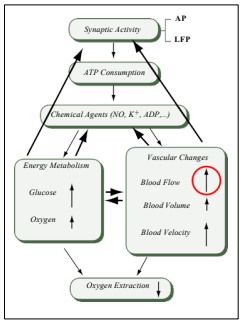

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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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)

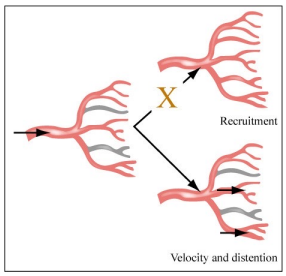

Figure by MIT OpenCourseWare.

Velocity and distention

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6. CBF increase better correlated to LFP than AP spiking

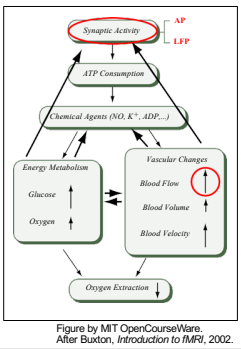

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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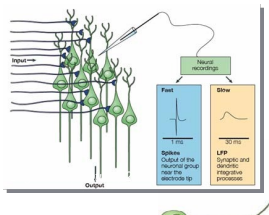
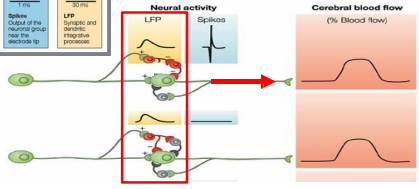
6. CBF increase more tightly correlated to LFP than AP spiking



- 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***

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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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Relevance for BOLD fMRI

- These phenomena *in concert* lead to the BOLD fMRI response
- **Greatest contributor: *mismatch between CBF increase and $CMRO_2$ 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

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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

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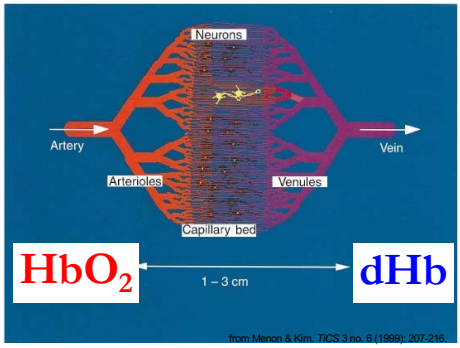
Hemoglobin in vascular system



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

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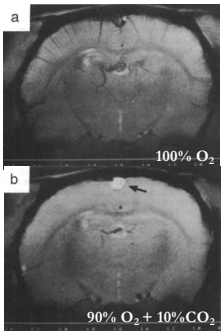
Birth of BOLD fMRI

- 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
- ***Findings suggested that physiological processes that alter blood oxygenation could be detectable with MRI***



Ogawa et al, MRM & PNAS, 1990

89

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

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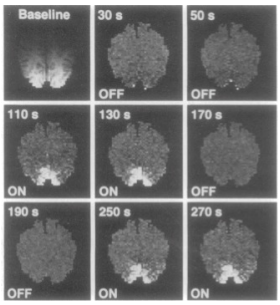
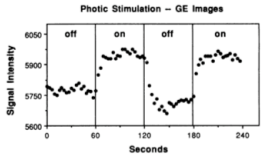
Using BOLD to image brain function



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



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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***

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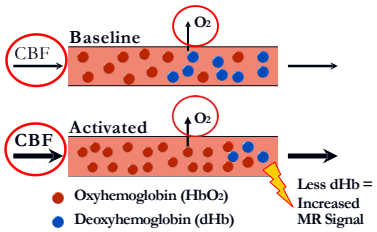
Basis of BOLD Contrast



- 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

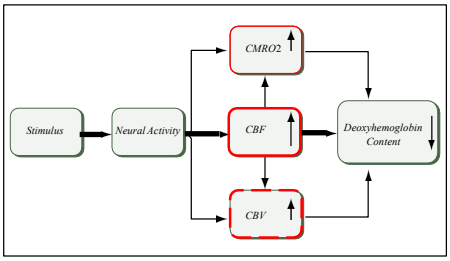

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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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

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BOLD Imaging: Timing

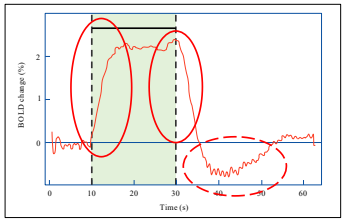

Figure by MIT OpenCourseWare.
After Buxton, *Introduction to fMRI*, 2002.

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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***

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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

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Up Next:

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

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感谢各位同学！

敬请批评指正！

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