Neuroimaging and mathematical modelling
Lesson 6: functional MRI

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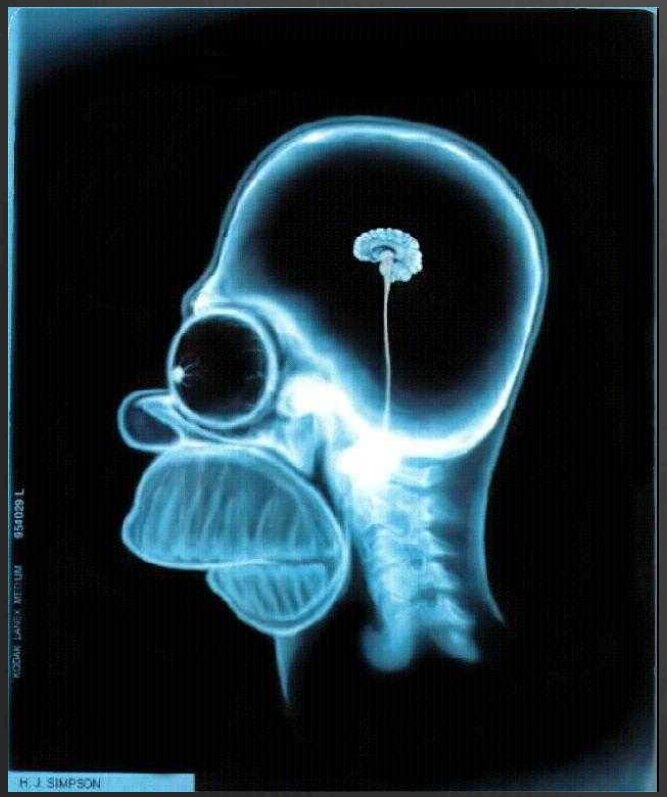
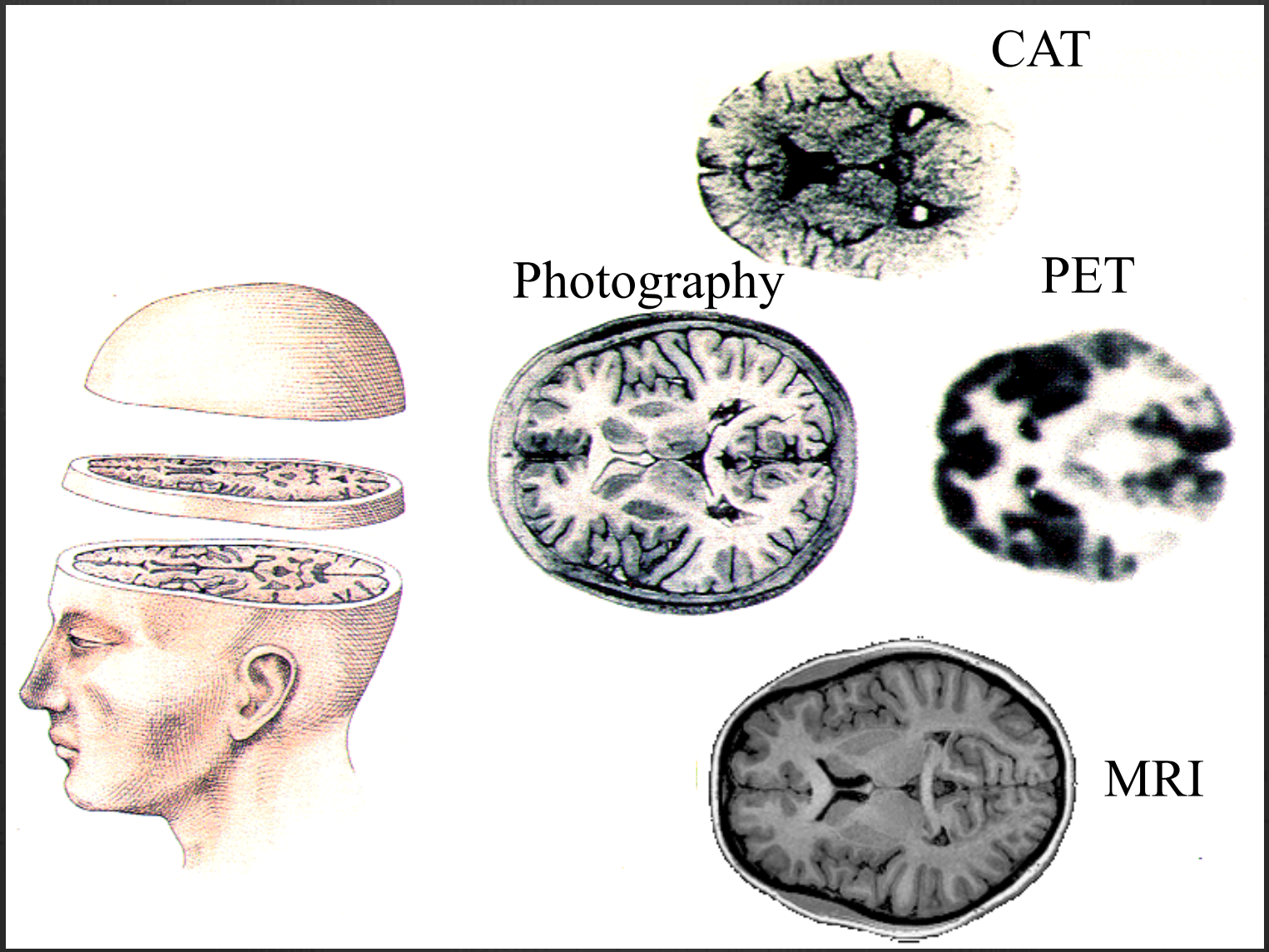
MRI vs. fMRI

MRI studies brain anatomy.



Functional MRI (fMRI) studies brain function.

Brain Imaging: Anatomy

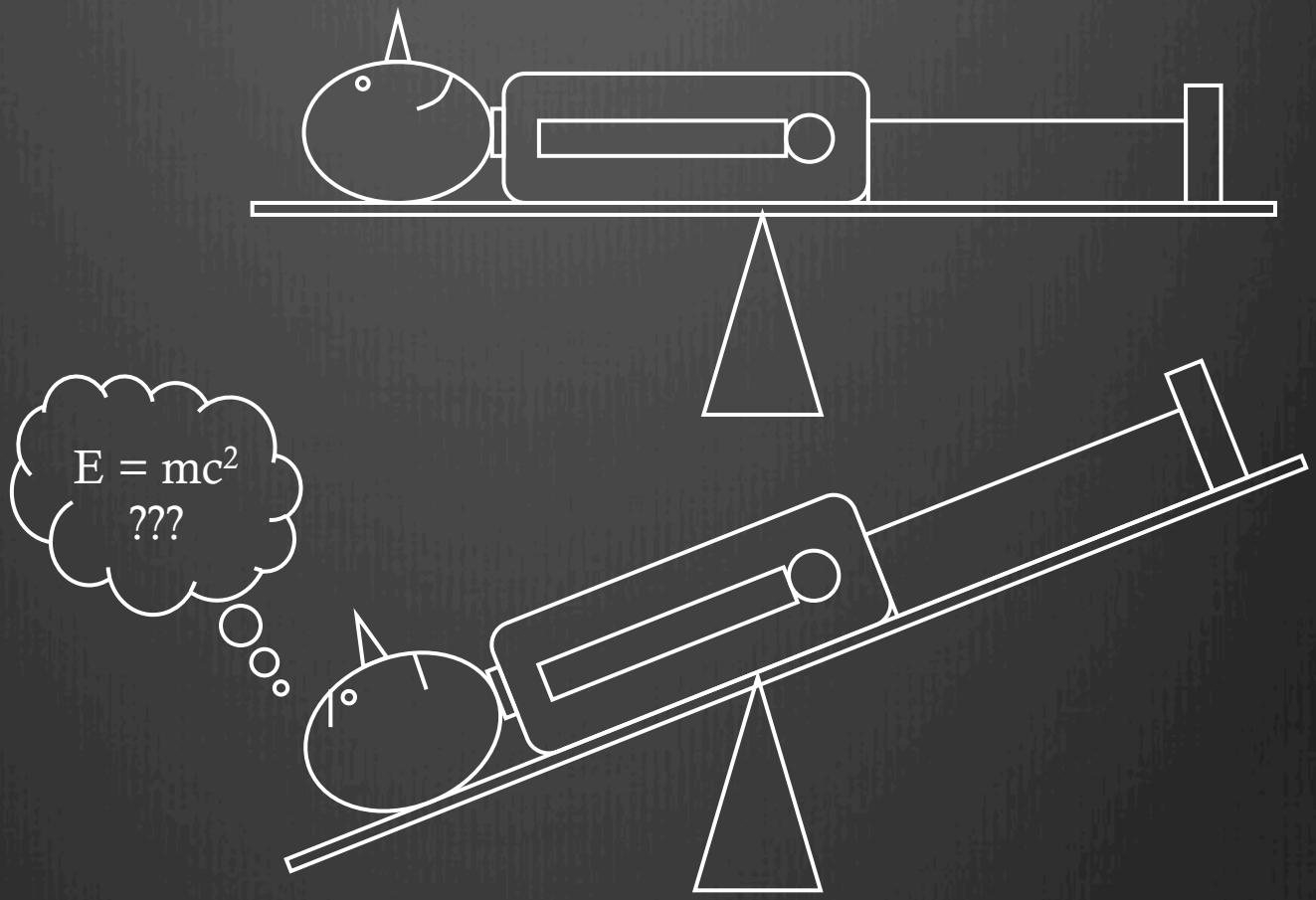


Source: modified from Posner & Raichle, Images of Mind

The First "Brain Imaging Experiment"

… and probably the cheapest one too!

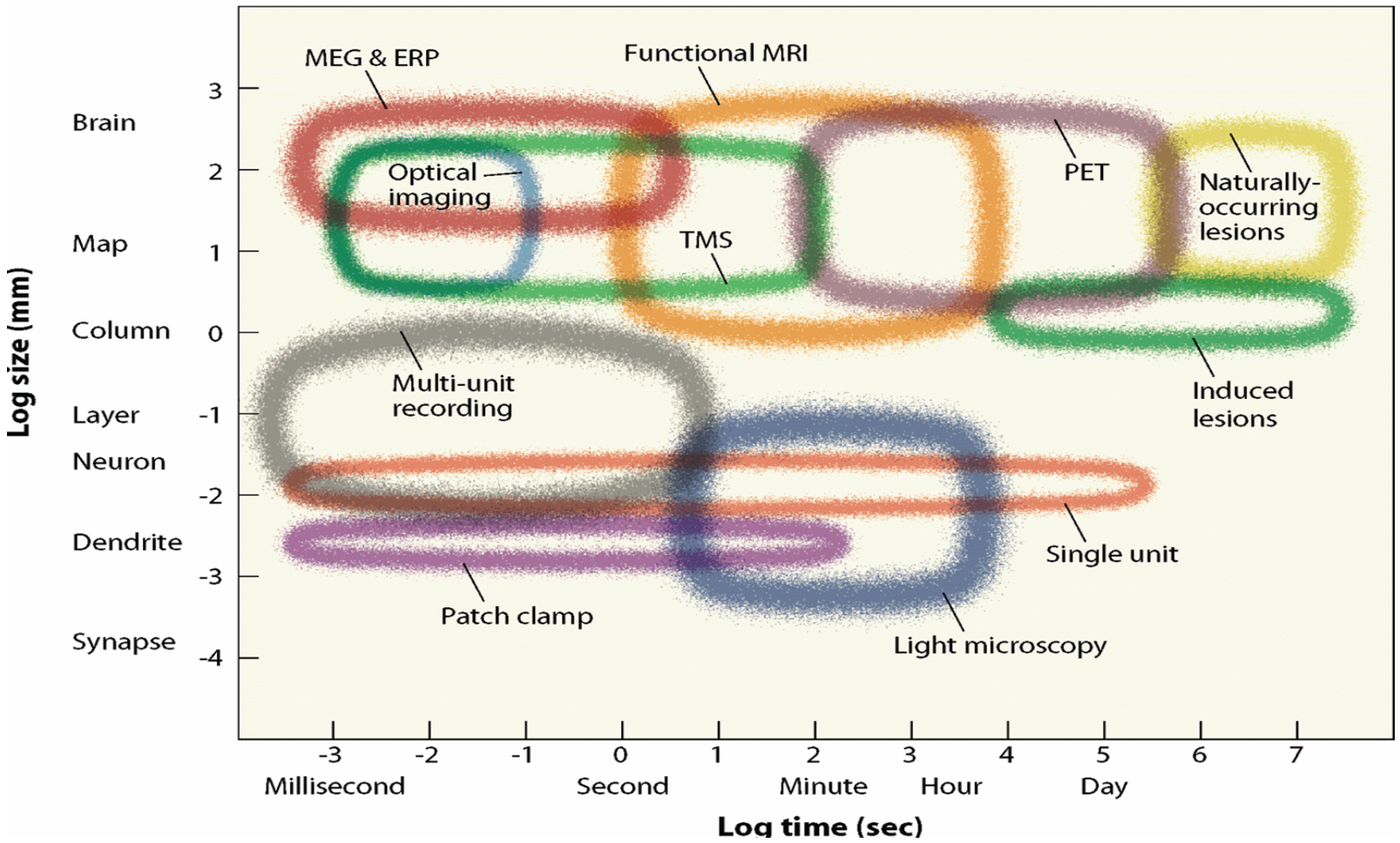
Angelo Mosso
Italian physiologist
(1846-1910)



"[In Mosso's experiments] the subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system."

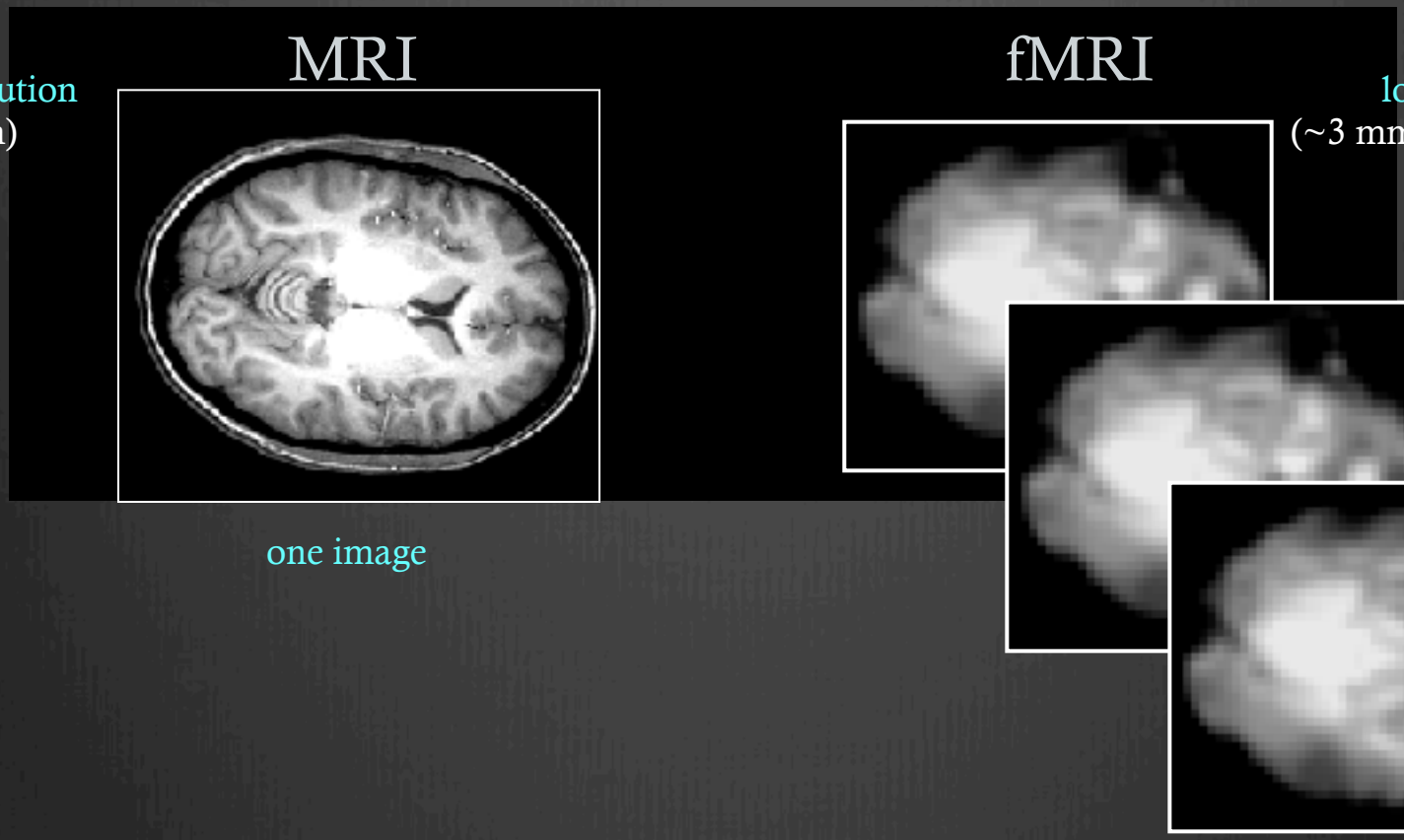
-- William James, *Principles of Psychology* (1890)

Spatial and Temporal Resolution



Gazzaniga, Ivry & Mangun, *Cognitive Neuroscience*

MRI vs. fMRI



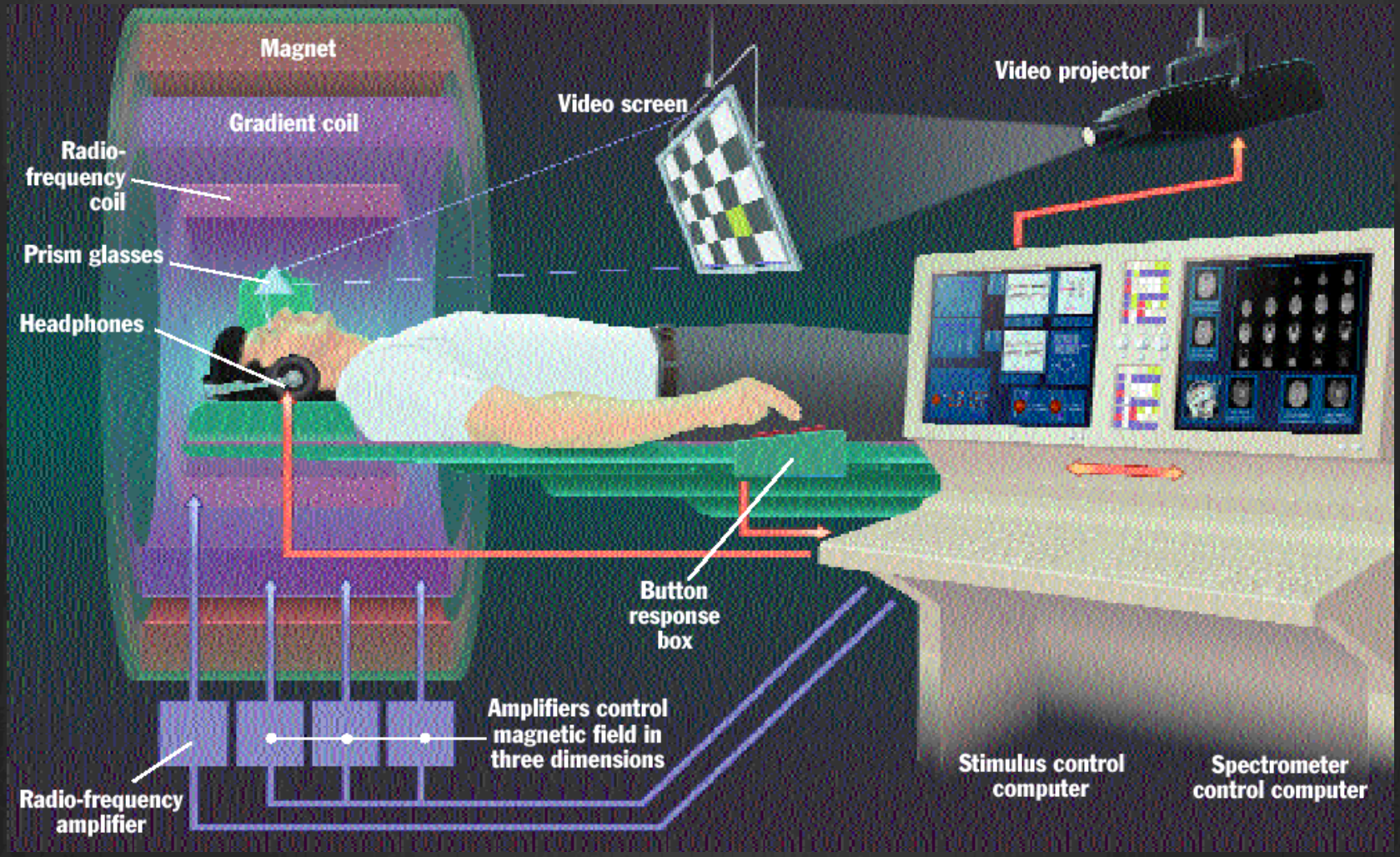
fMRI

Blood Oxygenation Level Dependent (BOLD) signal

indirect measure of neural activity

↑ neural activity ➔ ↑ blood oxygen ➔ ↑ fMRI signal

fMRI Setup


Magnet
Gradient coil
Radio-frequency coil
Prism glasses
Headphones
Video screen
Video projector
Button response box
Amplifiers control magnetic field in three dimensions
Radio-frequency amplifier
Stimulus control computer
Spectrometer control computer

History of fMRI

MRI
-1971: MRI Tumor detection (Damadian)
-1973: Lauterbur suggests NMR could be used to form images
-1977: clinical MRI scanner patented
-1977: Mansfield proposes echo-planar imaging (EPI) to acquire images faster

fMRI
-1990: Ogawa observes BOLD effect with T2*
blood vessels became more visible as blood oxygen decreased
-1991: Belliveau observes first functional images using a contrast agent
-1992: Ogawa et al. and Kwong et al. publish first functional images using BOLD signal

Ogawa

Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 9868–9872, December 1990
Biophysics

Brain magnetic resonance imaging with contrast dependent on blood oxygenation

(cerebral blood flow/brain metabolism/oxygenation)

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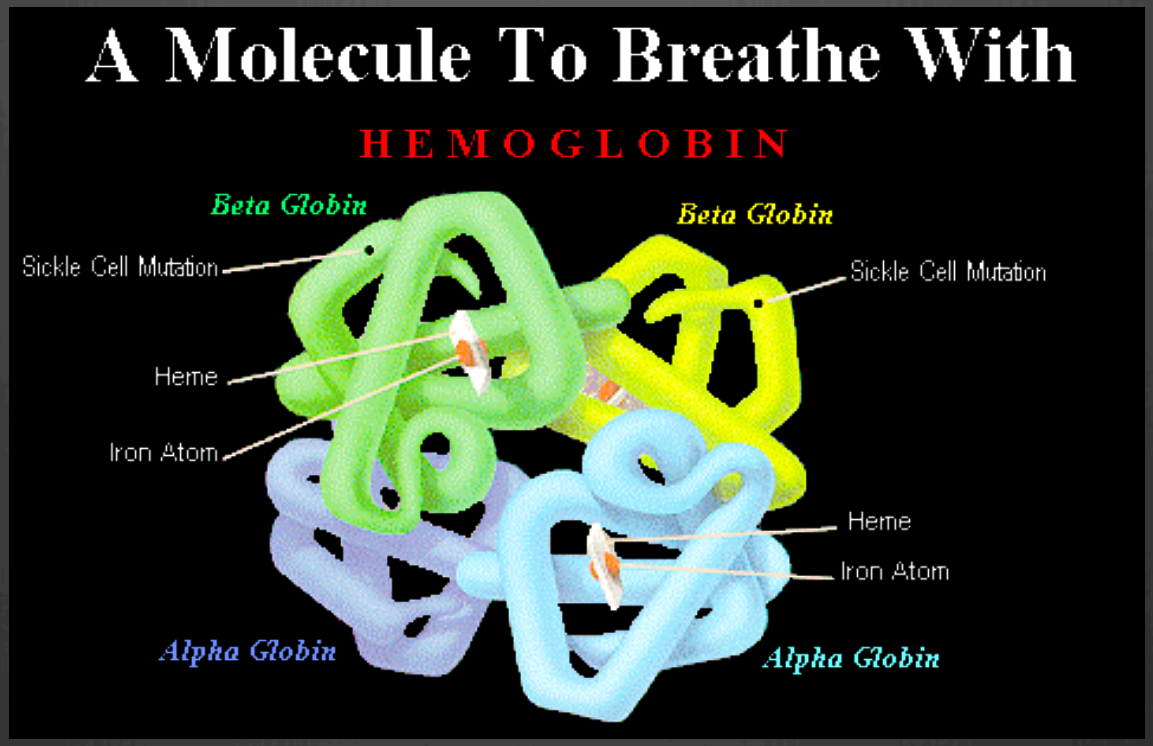
ABSTRACT Paramagnetic deoxyhemoglobin in venous blood is a naturally occurring contrast agent for magnetic resonance imaging (MRI). By accentuating the effects of this agent through the use of gradient-echo techniques in high fields, we demonstrate *in vivo* images of brain microvasculature with image contrast reflecting the blood oxygen level. This blood oxygenation level-dependent (BOLD) contrast follows blood oxygen changes induced by anesthetics, by insulin-induced hypoglycemia, and by inhaled gas mixtures that alter metabolic demand or blood flow. The results suggest that BOLD contrast can be used to provide *in vivo* real-time maps of blood oxygenation in the brain under normal physiological conditions. BOLD contrast adds an additional feature to magnetic resonance imaging and complements other techniques that are attempting to provide positron emission tomography-like measurements related to regional neural activity.

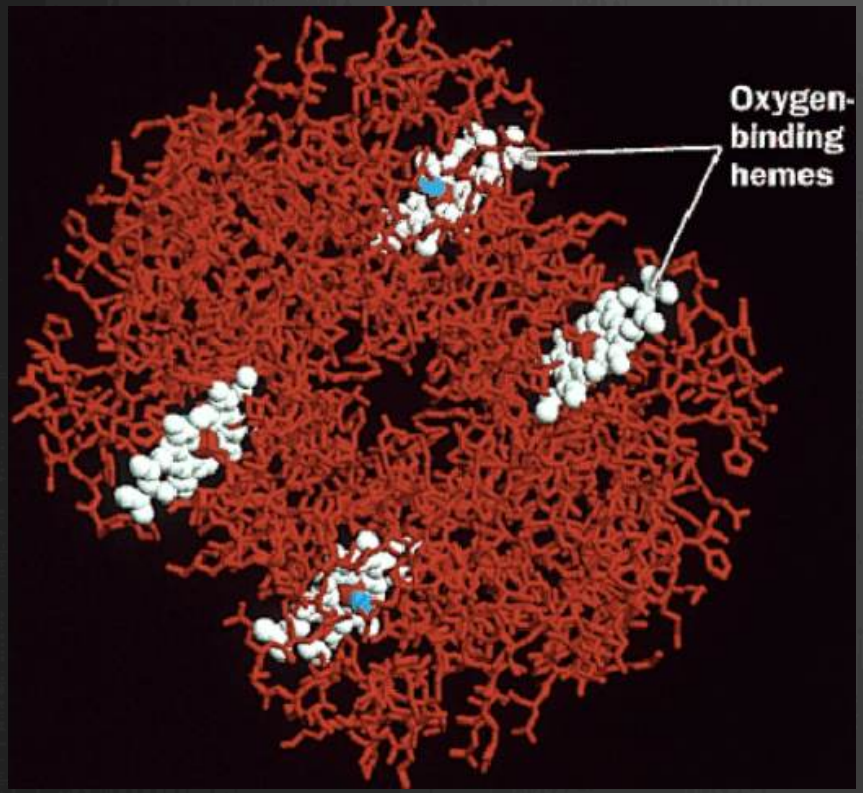
Hemoglobin

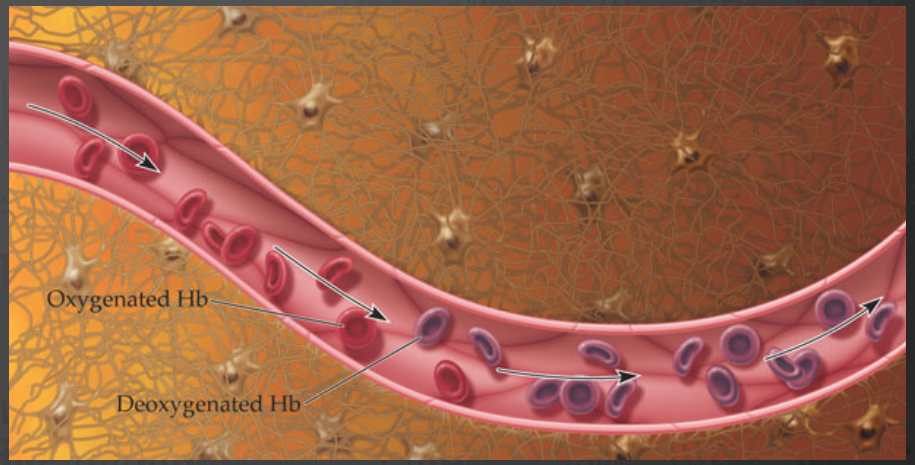


Hemoglogin (Hgb):

- four globin chains
- each globin chain contains a heme group
- at center of each heme group is an iron atom (Fe)
- each heme group can attach an oxygen atom (O_2)
- oxy-Hgb (four O_2) is diamagnetic → no ΔB effects
- deoxy-Hgb is paramagnetic → if [deoxy-Hgb] ↓ → local ΔB ↓

Hemoglobin





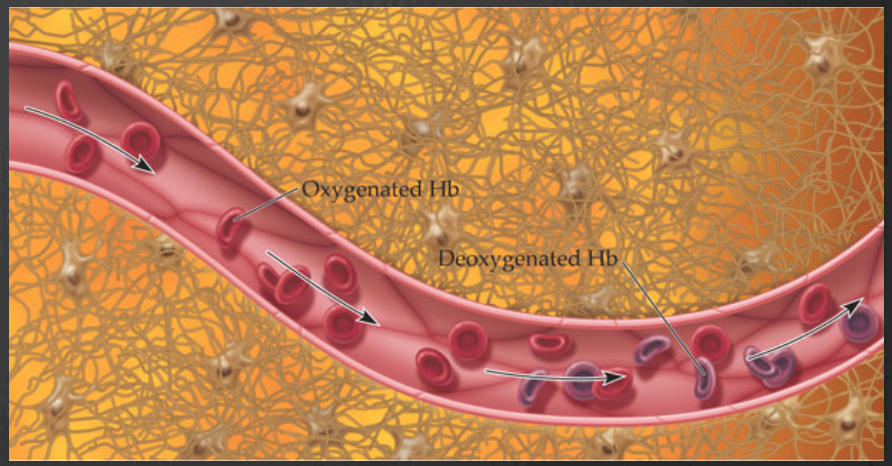
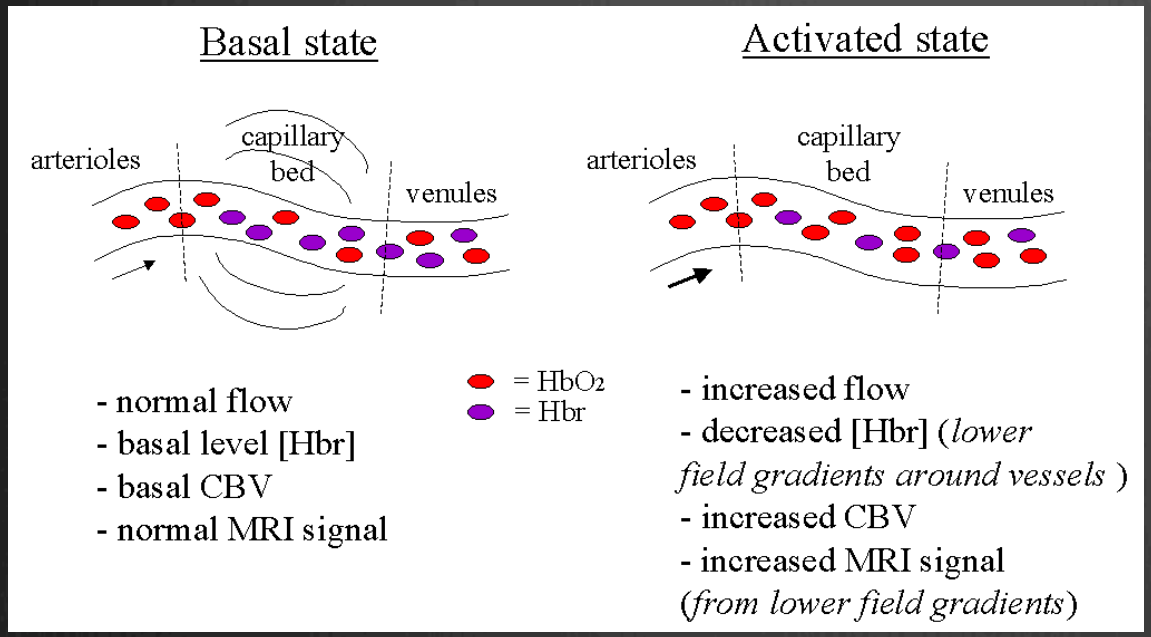


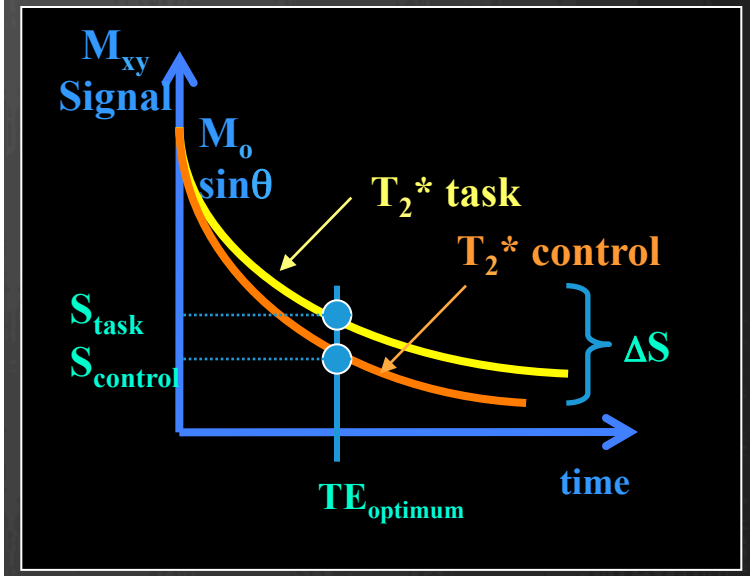
Figure Source, Huettel, Song & McCarthy, *2004,*
Functional Magnetic Resonance Imaging

BOLD signal

Blood Oxygen Level Dependent signal

↑neural activity ➔ ↑ blood flow ➔ ↑ oxyhemoglobin ➔ ↑ T2* ➔ ↑ MR signal





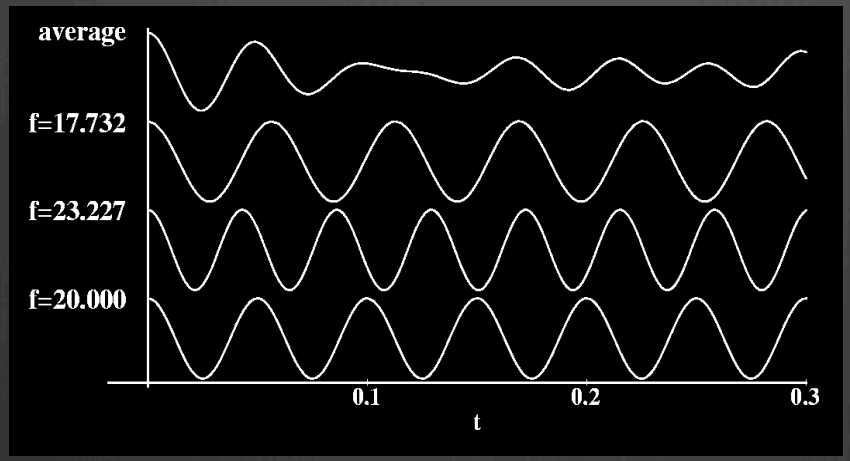
Susceptibility and BOLD fMRI

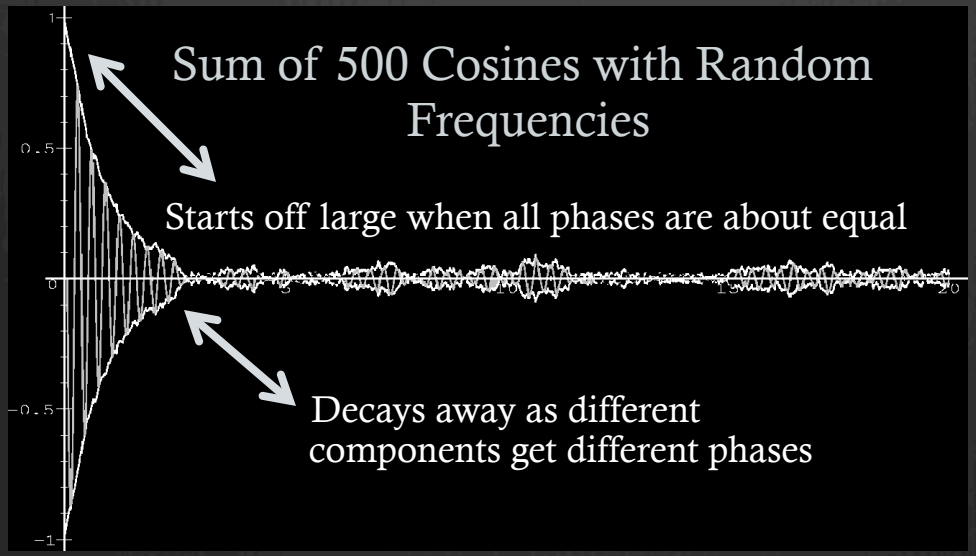
- Magnetic susceptibility (χ) refers to magnetic response of a material when placed in B_0.
- Red blood cells exhibit a change in χ during 'activation'
- Basically, oxyhaemoglobin in the RBC (HbO_2) becomes deoxyhaemoglobin (Hb):
  - Becomes paramagnetic.
  - Susceptibility difference between venous vasculature and surroundings (susceptibility induced field shifts).

How Susceptibility Affects Signal

Susceptibility ➔ nonuniform precession frequencies

RF signals from different regions that are at different frequencies will get *out of phase* and thus tend to cancel out





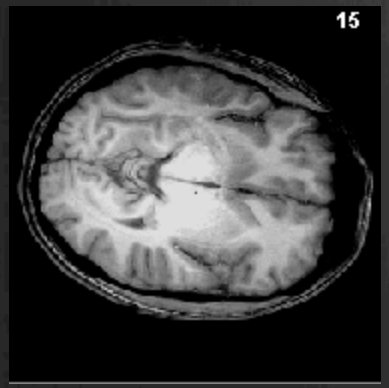
Source: *Robert Cox's web slides*

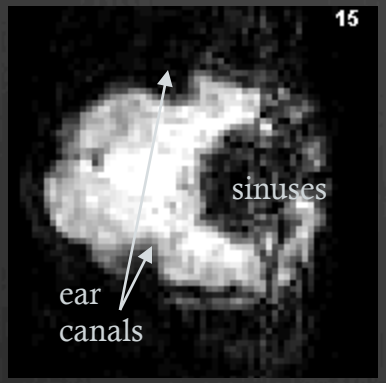
Susceptibility and Susceptibility Artifacts

Adding a nonuniform object (like a person) to B_0 will make the total magnetic field B nonuniform

This is due to *susceptibility*: generation of extra magnetic fields in materials that are immersed in an external field

For large scale (10+ cm) inhomogeneities, scanner-supplied nonuniform magnetic fields can be adjusted to "even out" the ripples in B — this is called *shimming*





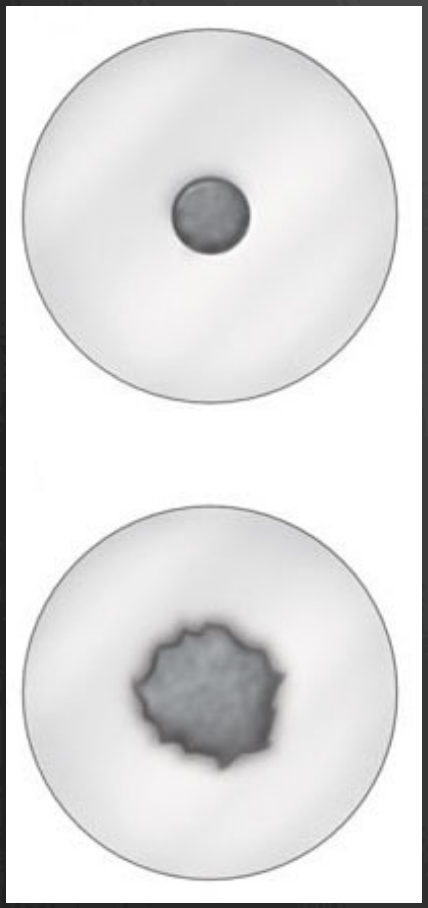
Susceptibility Artifact

-occurs near junctions between air and tissue

- sinuses, ear canals

Source: Robert Cox's web slides

Deoxygenated Blood → Signal Loss

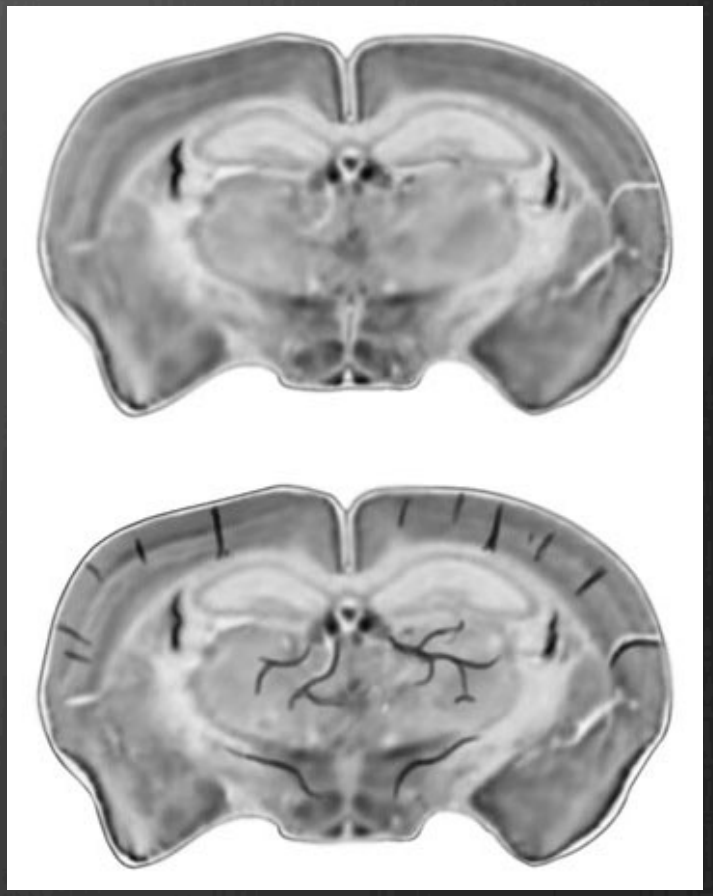


Oxygenated blood?

No signal loss…

Deoxygenated blood?

Signal loss!!!



Images from Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging

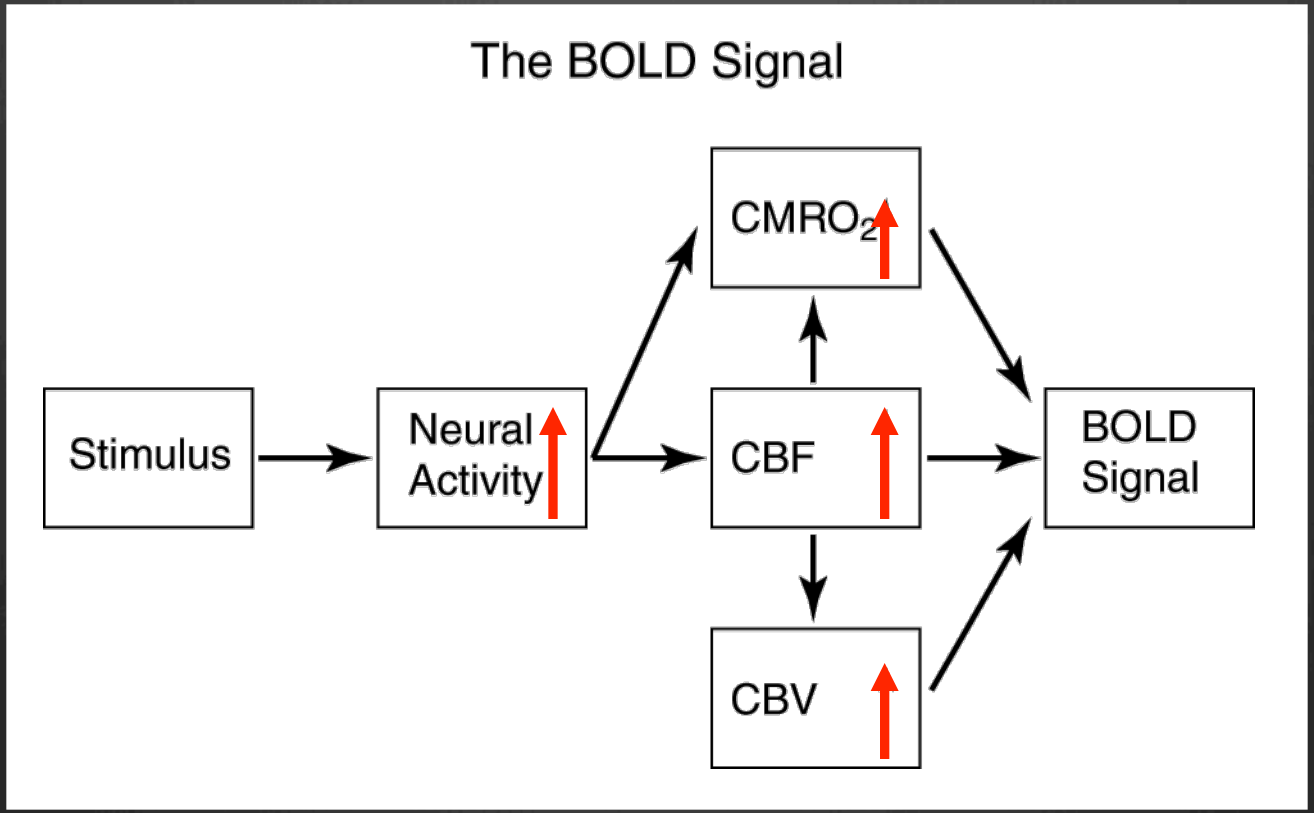
The Benefit of Susceptibility

Susceptibility variations can also be seen around blood vessels where deoxyhemoglobin affects T2* in nearby tissue

Modified from: Robert Cox's web slides

BOLD signal

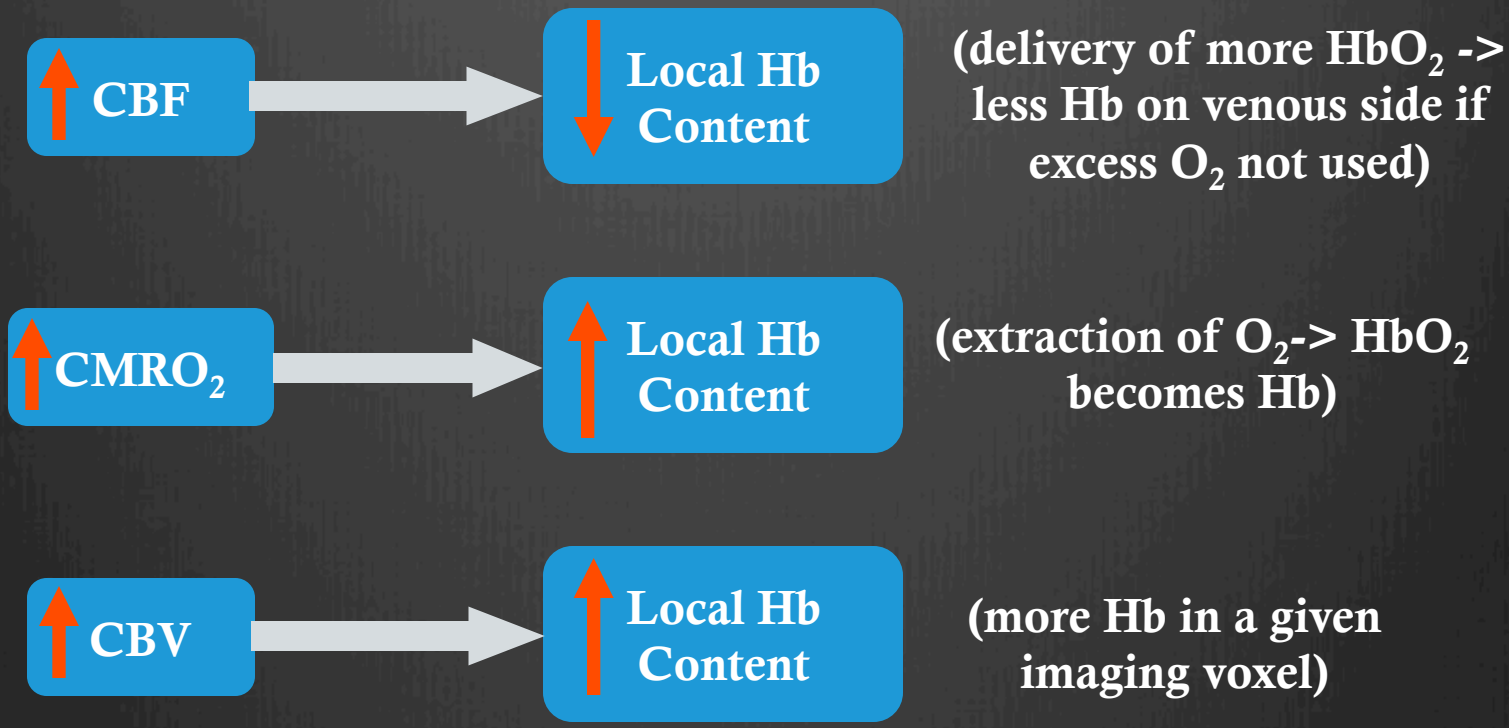
Blood Oxygen Level Dependent signal



Source: Buxton book Ch 17

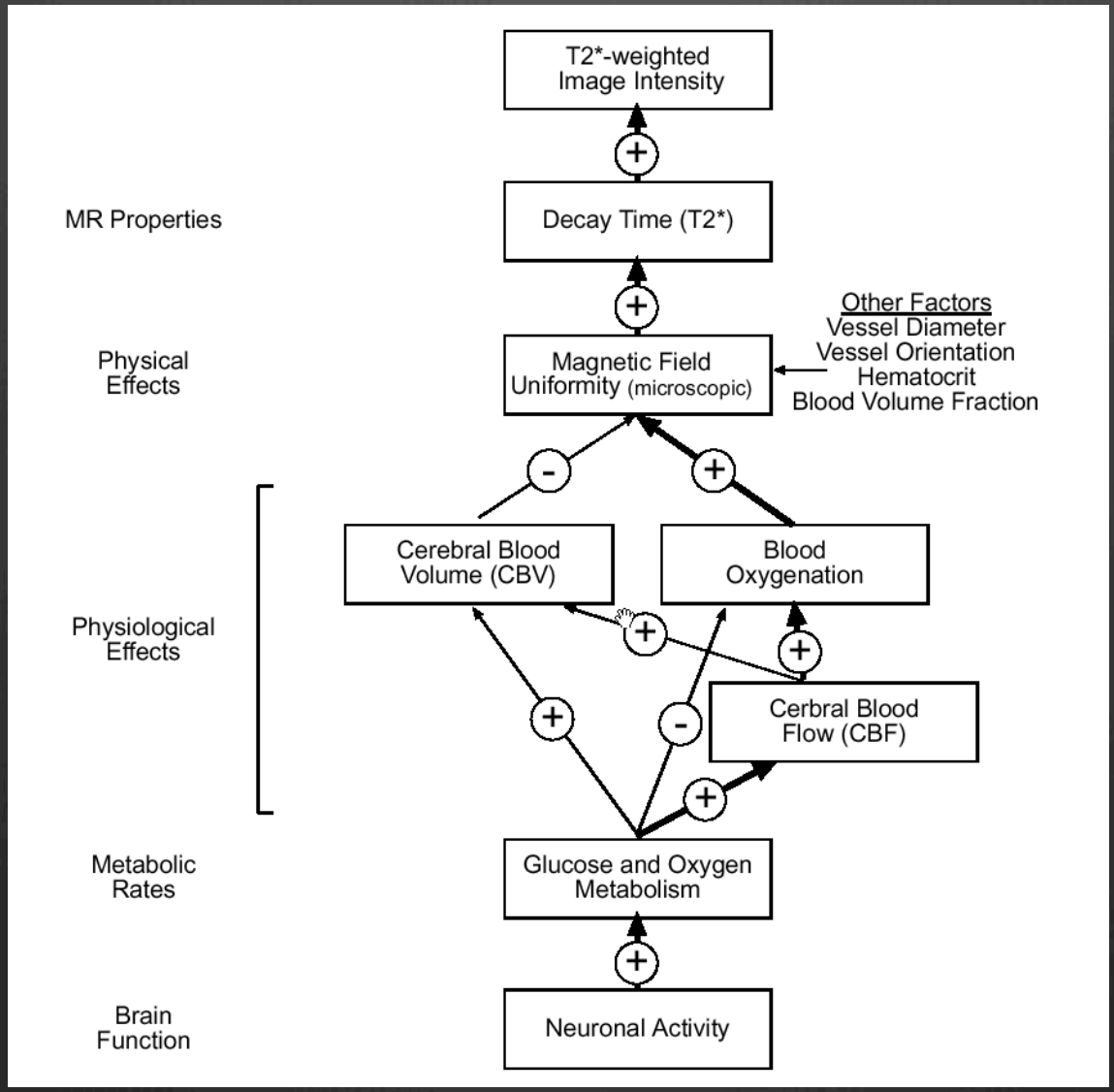
BOLD signal

- CBF, CBV, and $CMRO_2$ have different effects on HbO_2 concentration. Blood Oxygen Level Dependent signal



- Interaction of these 3 produce BOLD response
  - They change [Hb] which affects magnetic environment.

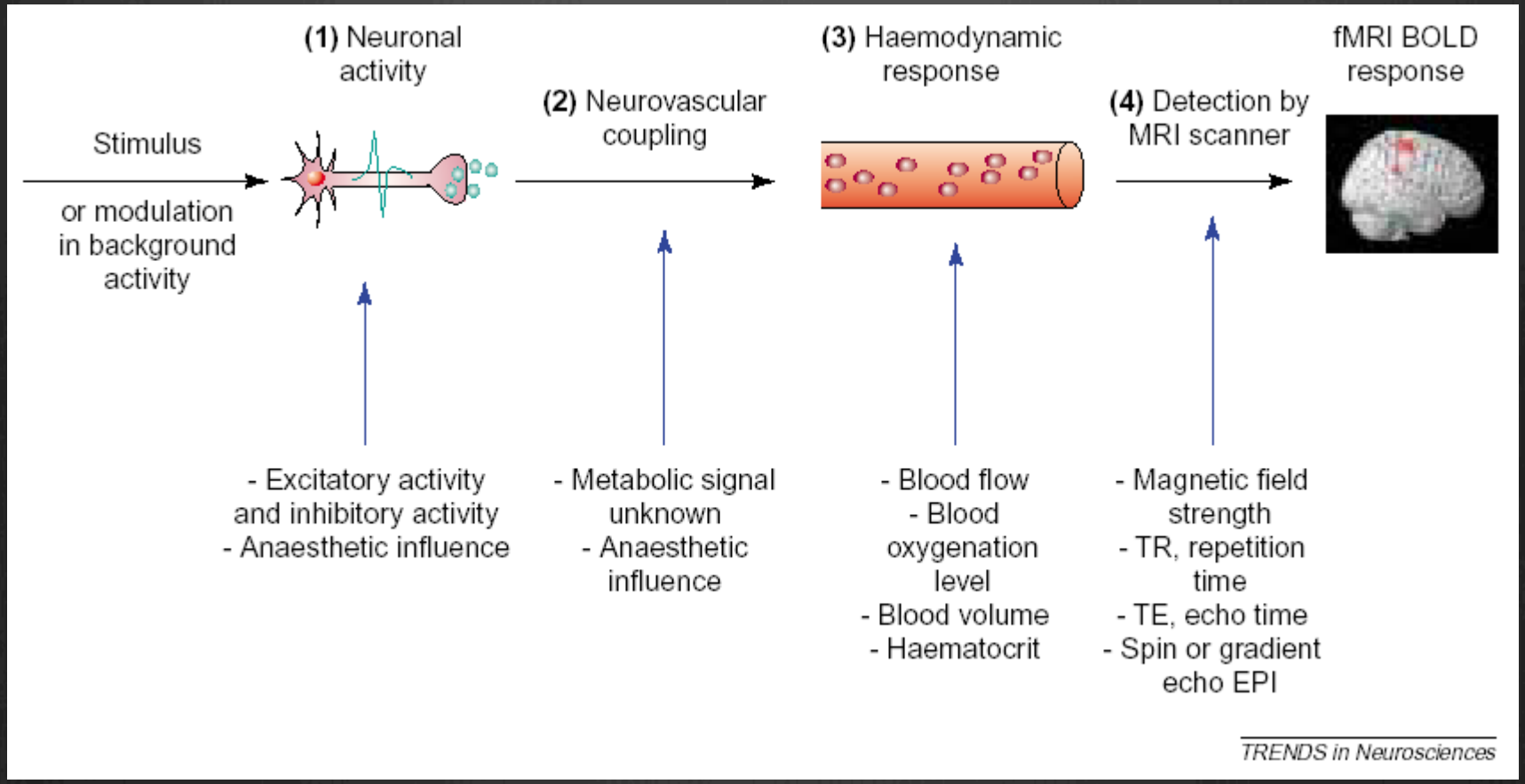
BOLD signal



Source: Doug Noll's primer

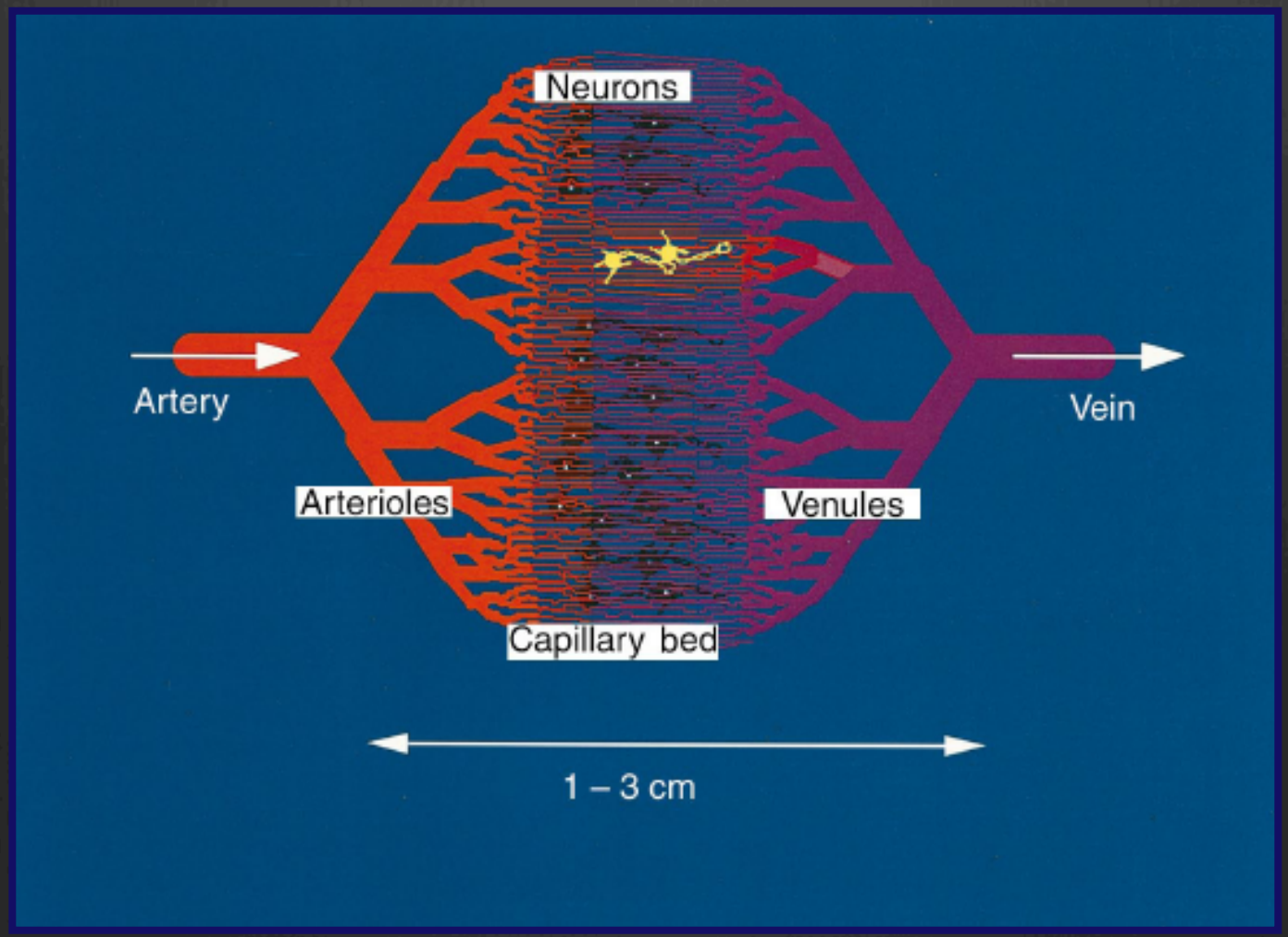
Neurons → BOLD

Stimulus to BOLD

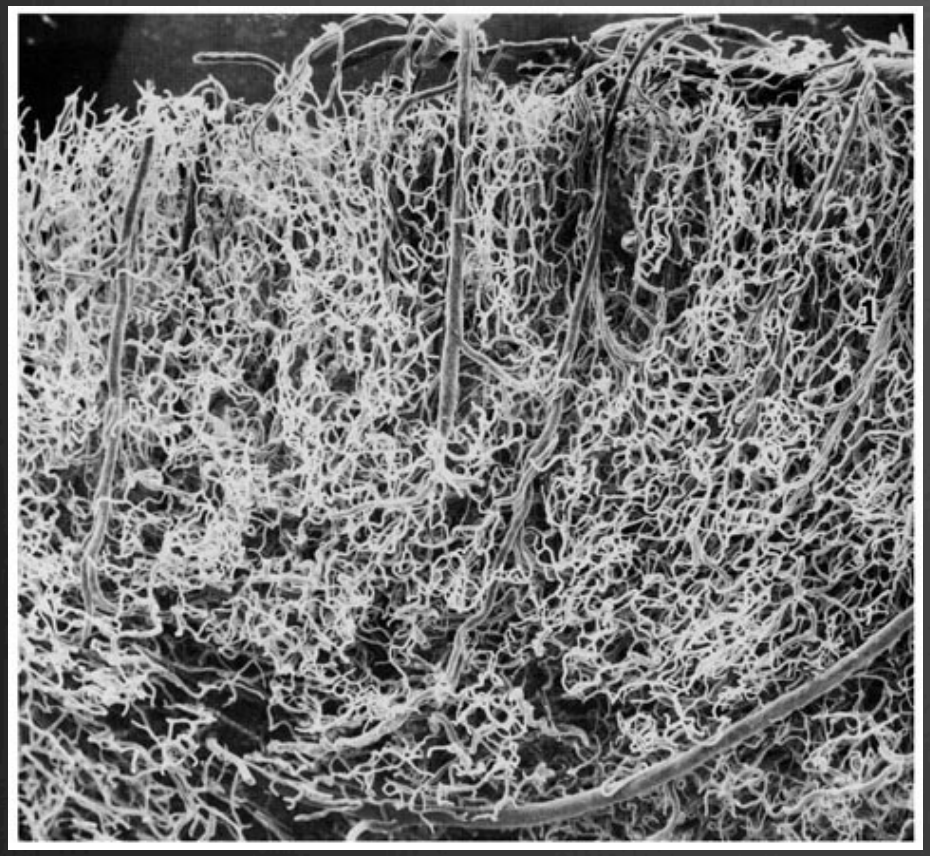


Source: Arthurs & Boniface, 2002, *Trends in Neurosciences*

Vasculature



Macro- vs. micro- vasculature



Capillary beds within the cortex.

Macrovasculature:

vessels > 25 μm radius
(cortical and pial veins)
⇒ linear and oriented
∴ cause both magnitude and phase changes

Microvasculature:

vessels < 25 μm radius
(venuoles and capillaries)
⇒ randomly oriented
∴ cause only magnitude changes

Neuron → BOLD?

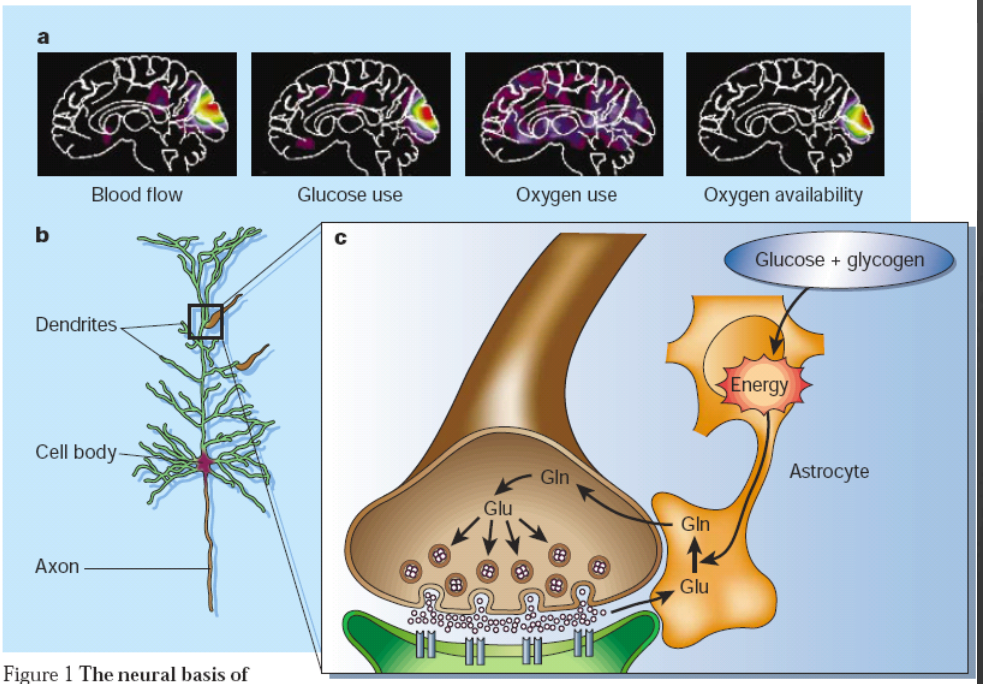
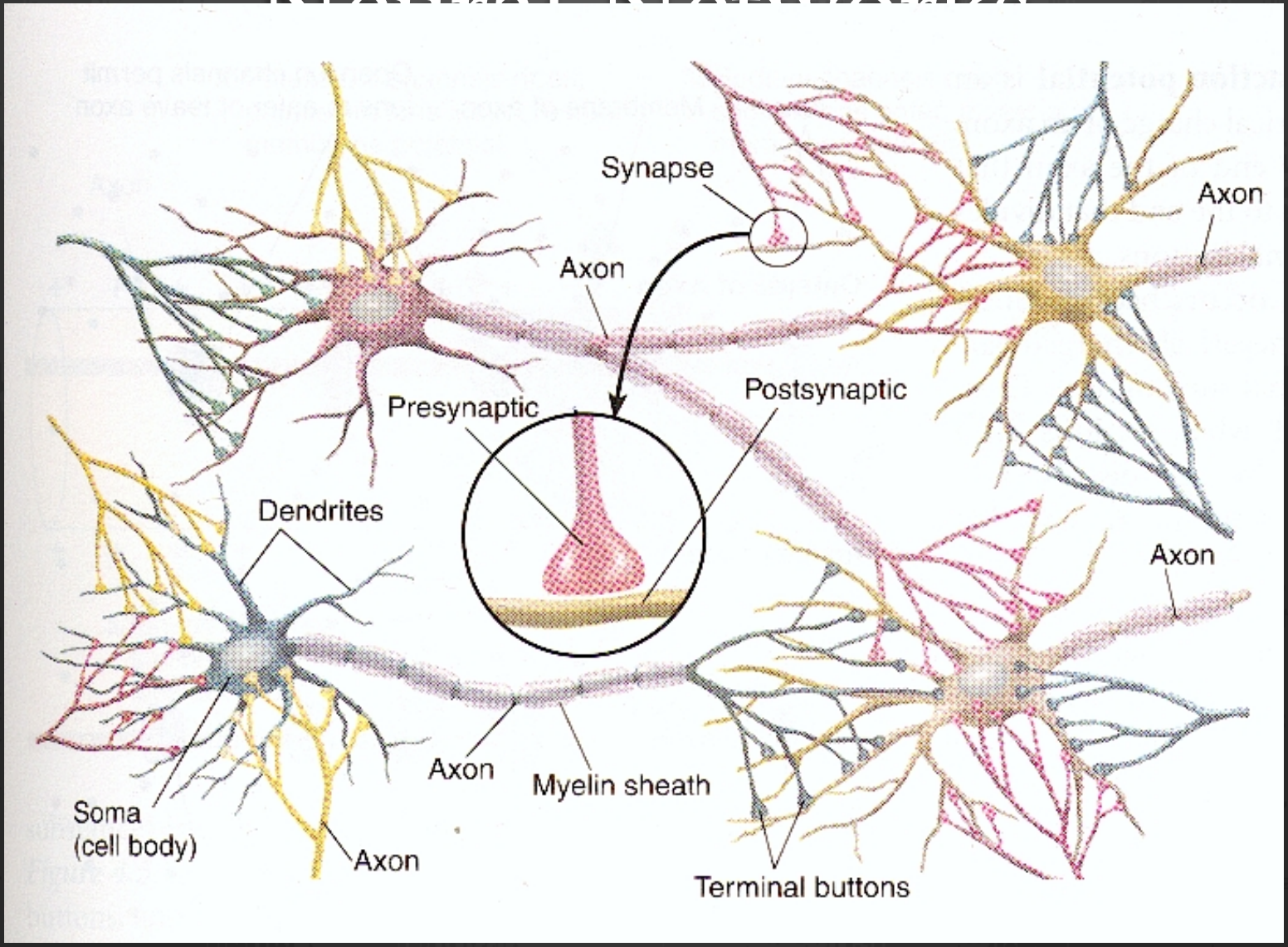


Figure 1 The neural basis of functional magnetic resonance imaging (fMRI). a, Viewing a stimulus such as a checkerboard produces marked changes in the areas of the brain that respond to visual stimuli, as seen in these positron-emission tomographic (PET) images. These changes include increases in glucose use and blood flow that are much greater than those in oxygen consumption. As a result there is an increase in the oxygen level in those areas (supply exceeds demand). PET is usually used to monitor blood flow. fMRI detects the changes in oxygen availability as a local change in the magnetic field. The resulting fMRI signal is a 'blood-oxygen-level-dependent' (BOLD) signal. b, As Logothetis *et al.*[2] show, these metabolic and circulatory changes are driven by electrical potentials arising from the input to, and information processing within, the dendrites of neurons. c, An attractive explanation for the BOLD signal invokes the preferential use of glycolysis in nearby non-neuronal cells (astrocytes) to handle an increase in the release of the neurotransmitter glutamate (Glu), which must be converted to glutamine (Gln) before it is returned to the neuron. Glycolysis consumes glucose to produce energy, but does not require oxygen.

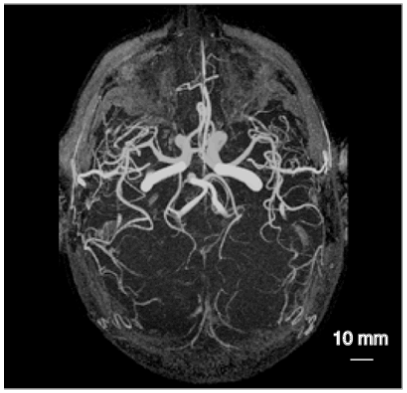
Raichle, 2001, Nature

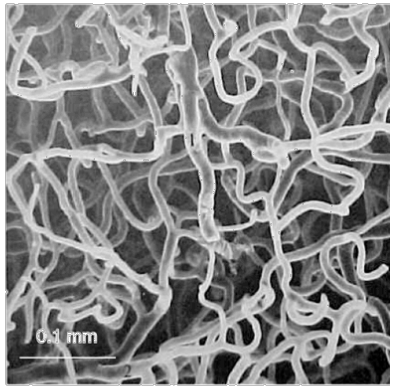
Neural Networks

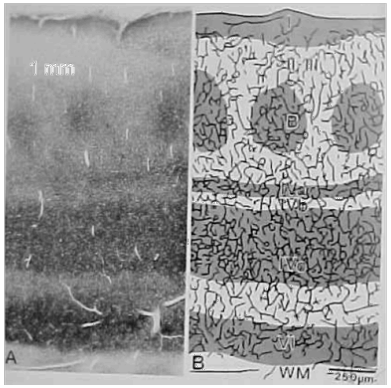


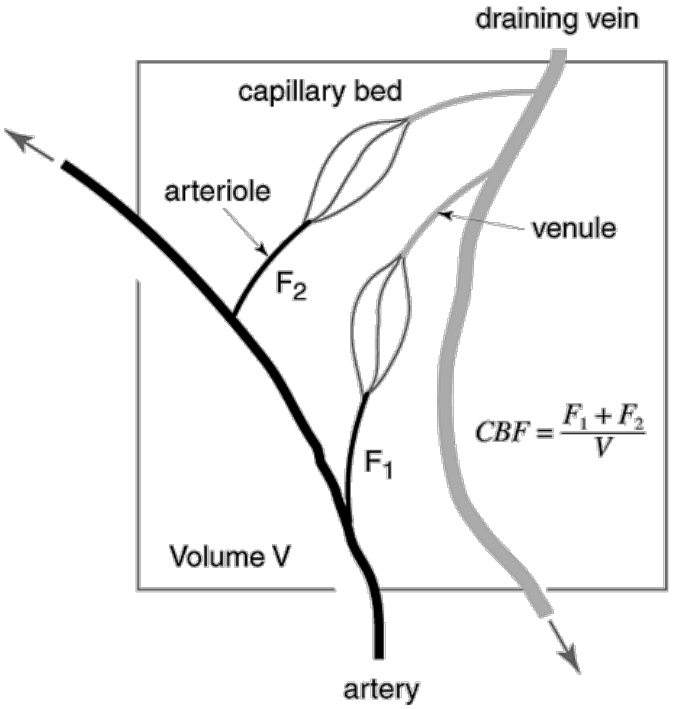
Vascular network and BOLD

Cerebral Vasculature



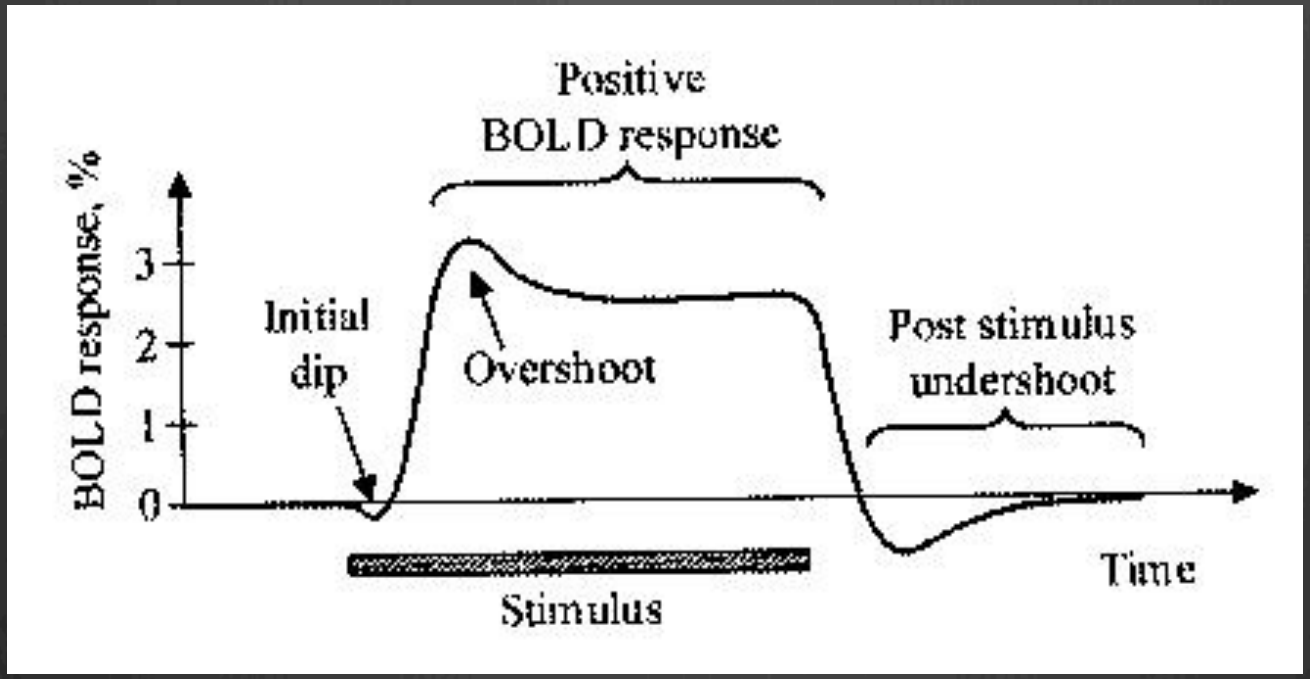






Source: Buxton book Ch 2

Hemodynamic Response Function



% signal change
= (point – baseline)/baseline
usually 0.5-3%

initial dip
-more focal and potentially a better measure
-somewhat elusive so far, not everyone can find it

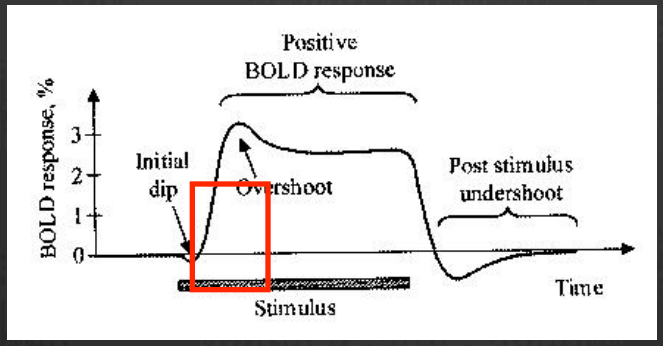
time to rise
signal begins to rise soon after stimulus begins

time to peak
signal peaks 4-6 sec after stimulus begins

post stimulus undershoot
signal suppressed after stimulation ends

Initial Dip (Hypo-oxic Phase)

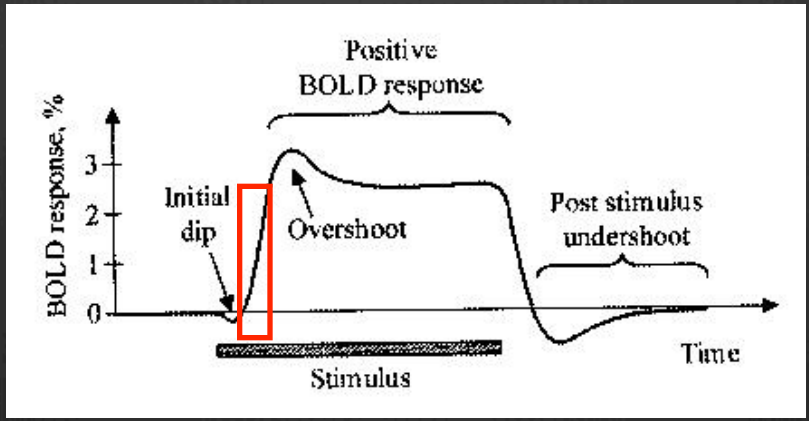
- Transient increase in oxygen consumption, before change in blood flow
  - Menon et al., 1995; Hu, et al., 1997
- Smaller amplitude than main BOLD signal
  - 10% of peak amplitude (e.g., 0.1% signal change)
- Potentially more spatially specific
  - Oxygen utilization may be more closely associated with neuronal activity than positive response



Slide modified from Duke course

Rise (Hyperoxic Phase)

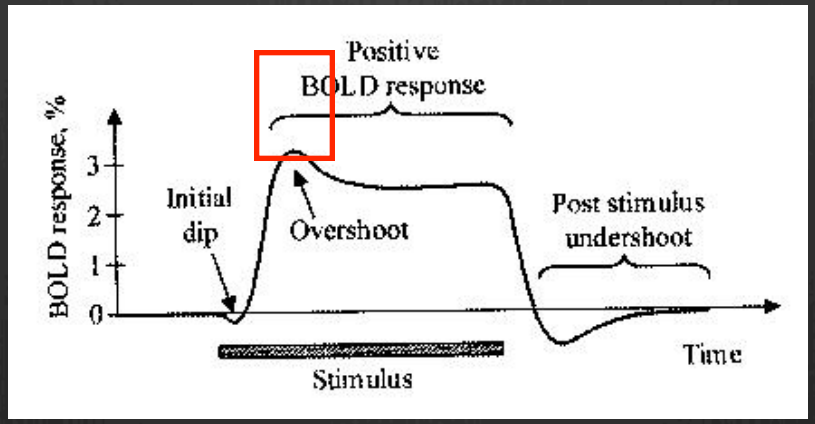
- Results from vasodilation of arterioles, resulting in a large increase in cerebral blood flow
- Inflection point can be used to index onset of processing



Slide modified from Duke course

Peak – Overshoot

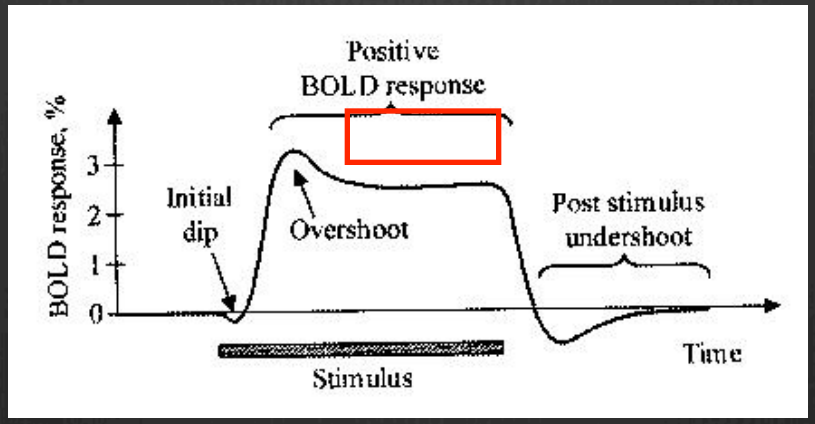
- Over-compensatory response
  - More pronounced in BOLD signal measures than flow measures
- Overshoot found in blocked designs with extended intervals
  - Signal saturates after ~10s of stimulation



Slide modified from Duke course

Sustained Response

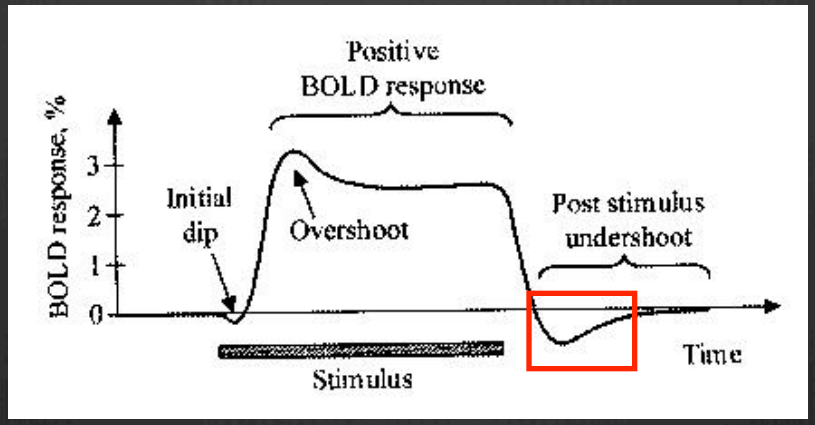
- Blocked design analyses rest upon presence of sustained response
  - Comparison of sustained activity vs. baseline
  - Statistically simple, powerful
- Problems
  - Difficulty in identifying magnitude of activation
  - Little ability to describe form of hemodynamic response
  - May require detrending of raw time course



Slide modified from Duke course

Undershoot

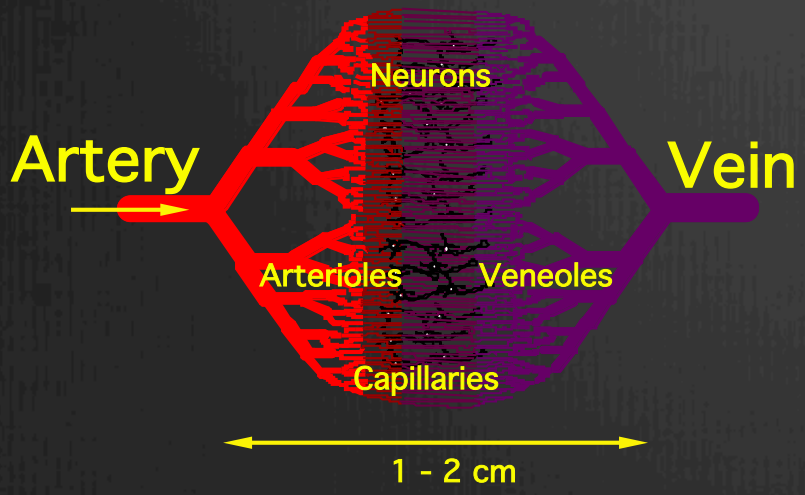
- Cerebral blood flow more locked to stimuli than cerebral blood volume
  - Increased blood volume with baseline flow leads to decrease in MR signal
- More frequently observed for longer-duration stimuli (>10s)
  - Short duration stimuli may not evidence
  - May remain for 10s of seconds

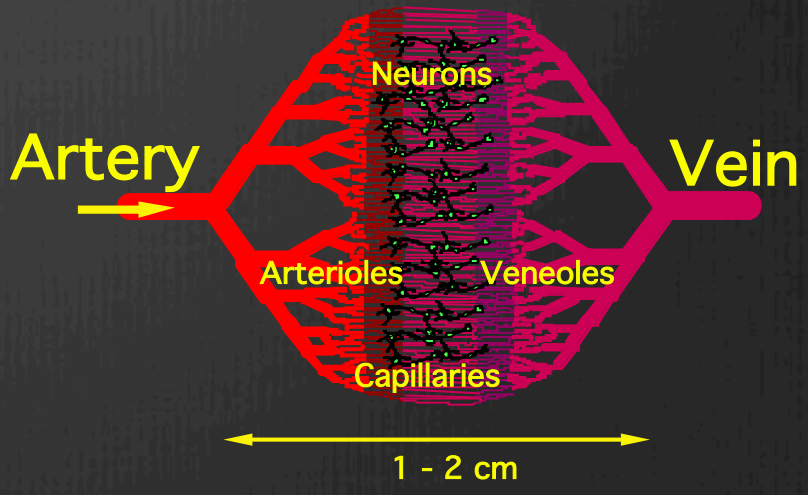


Slide modified from Duke course

Hyperoxygenation Phase

- Tightly coupled to neural metabolic activity (theoretically).
- Due to the imbalance of $\Delta CBF >> \Delta CMRO_2$
  - Results in increase in $[HbO_2]$ on venous side of capillary bed.
- Seen in both small and large vessels.
- Majority of fMRI studies are based on mapping of this response.





Fast Response

- Amplitude is independent of stimulus duration
  - Except for stimuli <2s.
- Correlates with optical measurements.
- Could reflect:

  1) initial $+\Delta CMRO_2$ and O_2 extraction from vasculature (✱).

  2) decrease in blood flow.

  3) or rapid increase in capillary and venous blood volume.
- Seen in small vessels and capillary bed
  - *Spatially closer to site of increased electrical activity and cellular metabolism*.
  - Mapping of fast/early reponse has potential to overcome some spatial specificity problems in fMRI.

Post-Response Undershoot

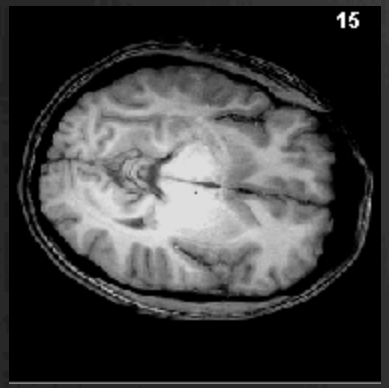
- Amplitude is dependent on duration of stimuli.
- *Very* slow to recover (eg.-1 minute!).
- Likely due to either:
  1) unbalanced metabolic energetics ($CMRO_2$ still elevated).
  2) or slow return of increased CBV fraction to basal state after end of stimulus (✱).
- Larger than fast response.
- Spatially, correlates more with hyperoxygenation phase.
- Seen in both large and small vessels (more so small).
- Does not reflect directly on energy metabolism.

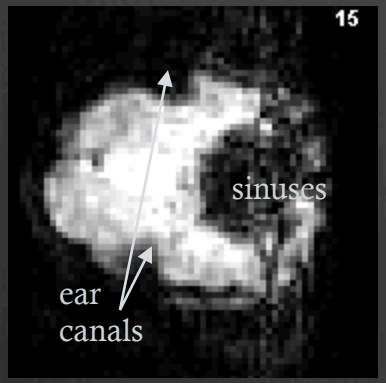
Susceptibility and Susceptibility Artifacts

Adding a nonuniform object (like a person) to B_0 will make the total magnetic field B nonuniform

This is due to *susceptibility*: generation of extra magnetic fields in materials that are immersed in an external field

For large scale (10+ cm) inhomogeneities, scanner-supplied nonuniform magnetic fields can be adjusted to "even out" the ripples in B — this is called *shimming*





Susceptibility Artifact

-occurs near junctions between air and tissue

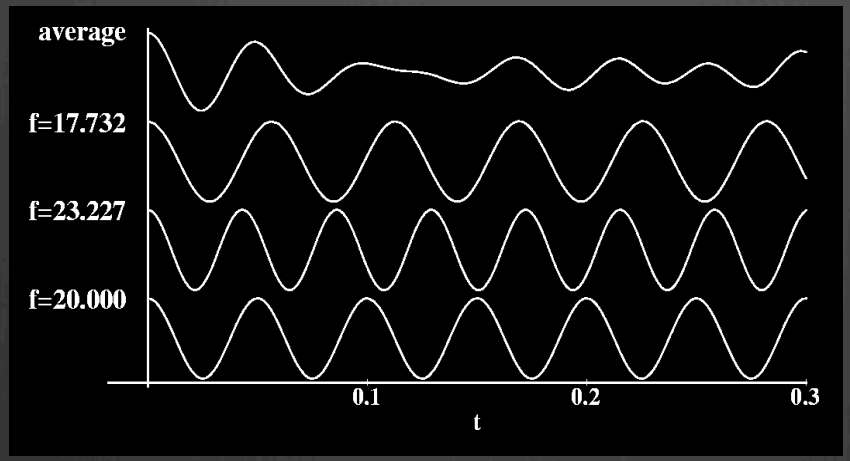
- sinuses, ear canals

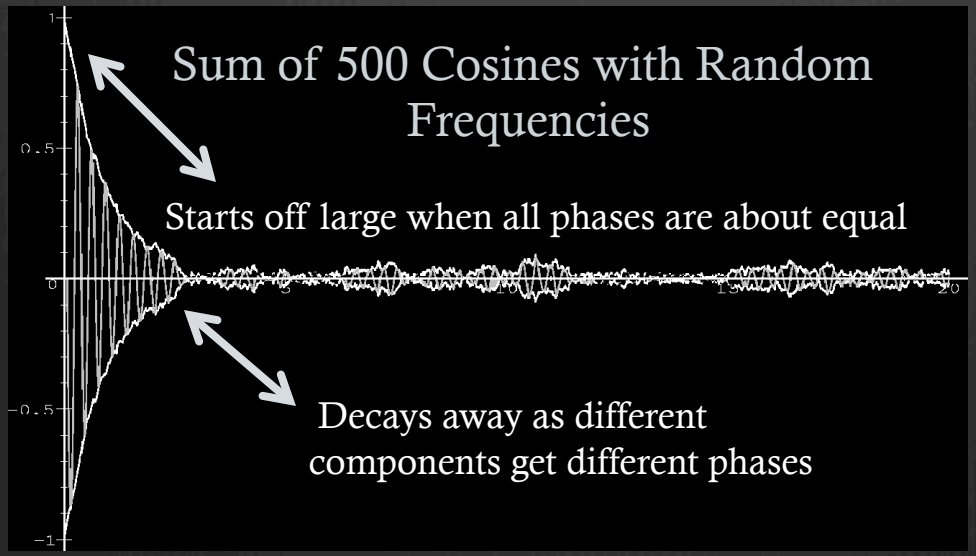
Source: Robert Cox's web slides

How Susceptibility Affects Signal

Susceptibility ➔ nonuniform precession frequencies

RF signals from different regions that are at different frequencies will get *out of phase* and thus tend to cancel out





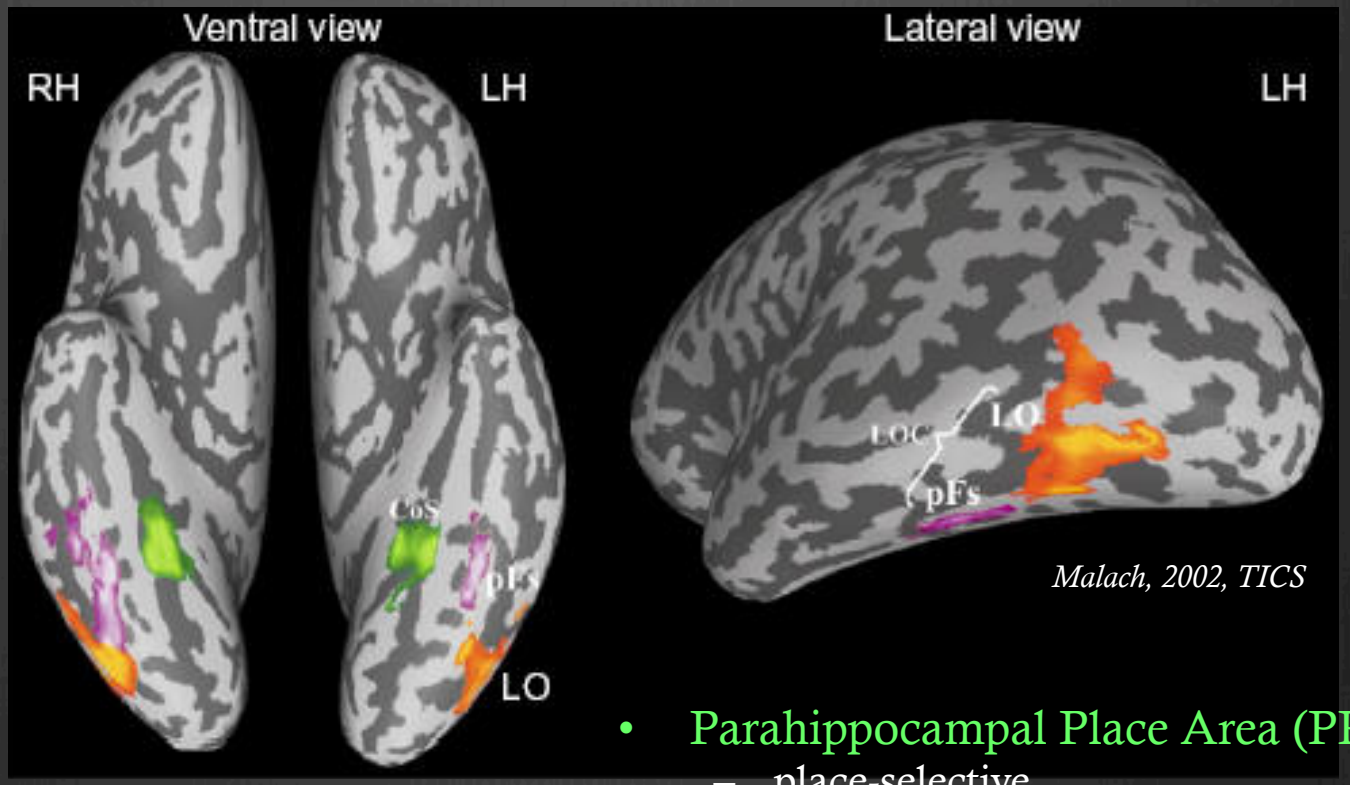
Source: *Robert Cox's web slides*

Category-Specific Visual Areas

objects

faces

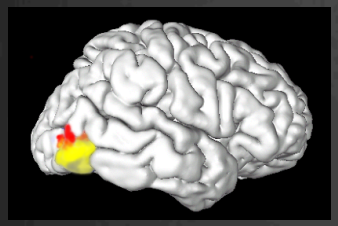
places



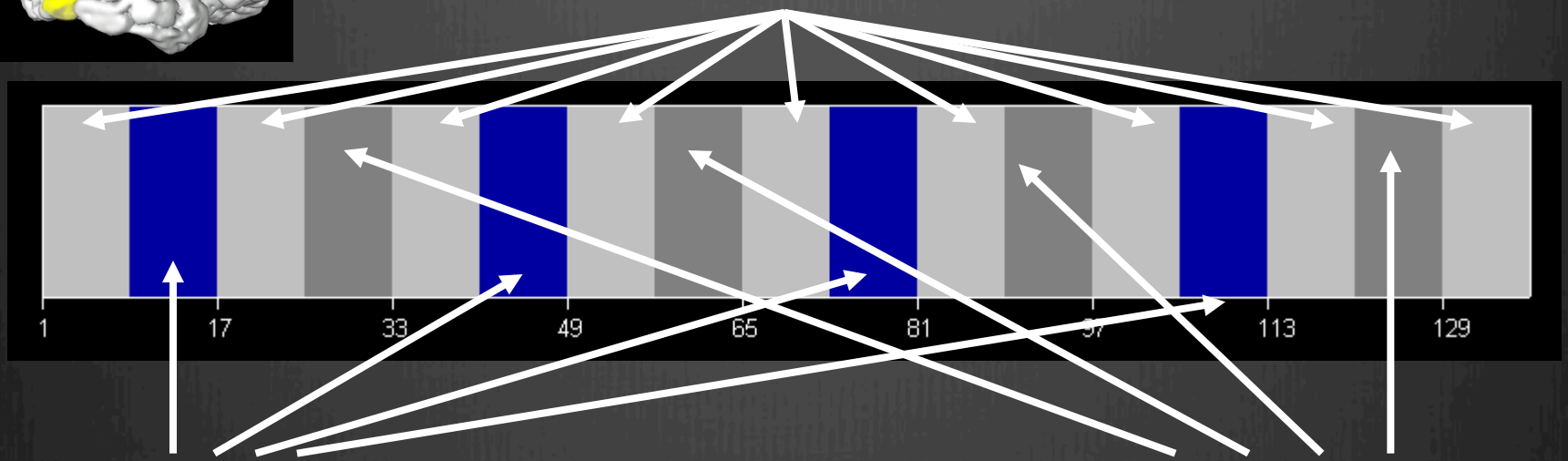
- Lateral Occipital (LO)
  - object-selective
  - objects > (faces & scenes)
  - objects > scrambled images

- Parahippocampal Place Area (PPA)
  - place-selective
  - places > (objects and faces)
  - places > scrambled images
- Fusiform Face Area (FFA) or pFs
  - face-selective
  - faces > (objects & scenes)
  - faces > scrambled images
  - ~ posterior fusiform sulcus (pFs)

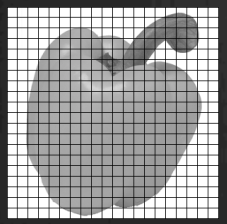
A Simple Experiment: LO Localizer



Lateral Occipital Complex
• responds when subject views objects

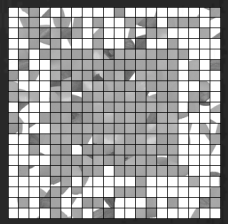


Intact Objects



TIME →

Scrambled Objects



One volume (12 slices) every 2 seconds for 272 seconds (4 minutes, 32 seconds)

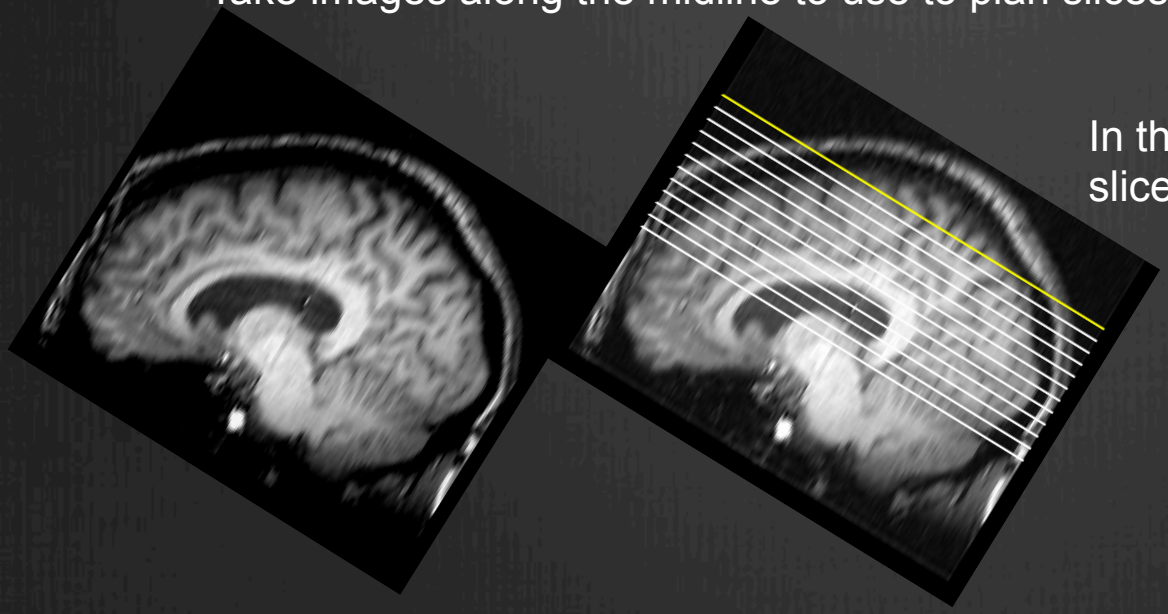
Condition changes every 16 seconds (8 volumes)

fMRI Experiment Stages: Prep

1) Prepare subject
   - Consent form
   - Safety screening
   - Instructions and practice trials if appropriate
2) Shimming
   - putting body in magnetic field makes it non-uniform
   - adjust 3 orthogonal weak magnets to make magnetic field as homogenous as possible
3) Sagittals

Note: That's one g, two t's

Take images along the midline to use to plan slices

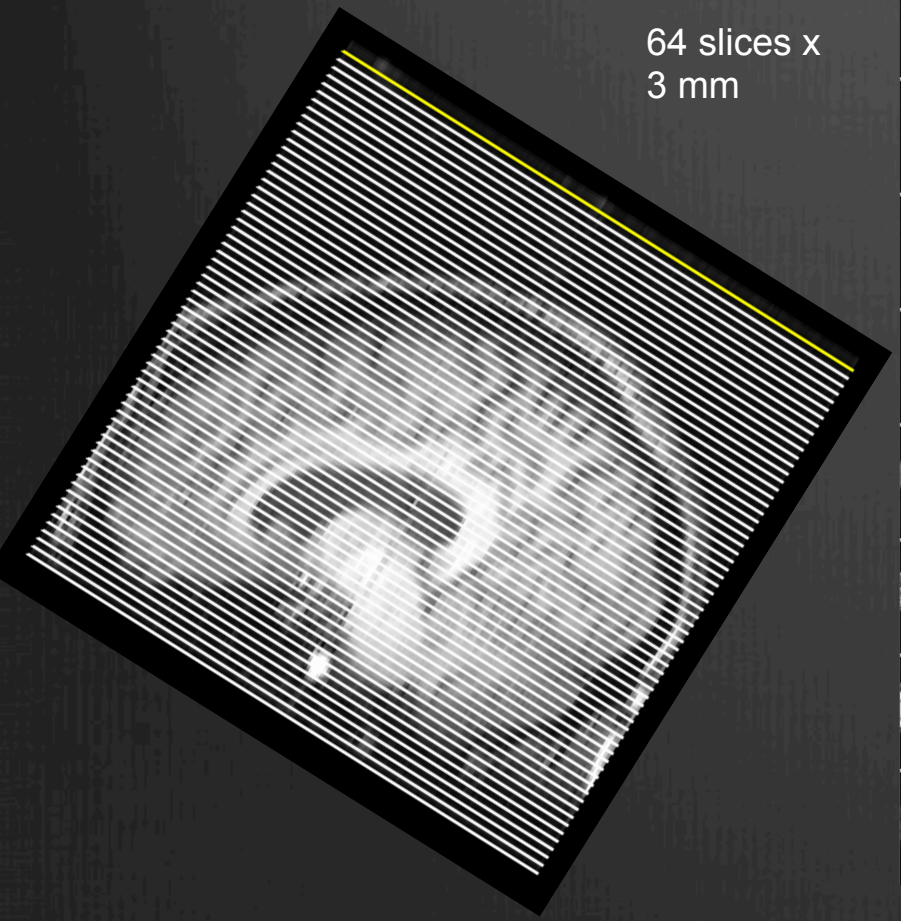


In this example, these are the *functional* slices we want: 12 slices x 6 mm

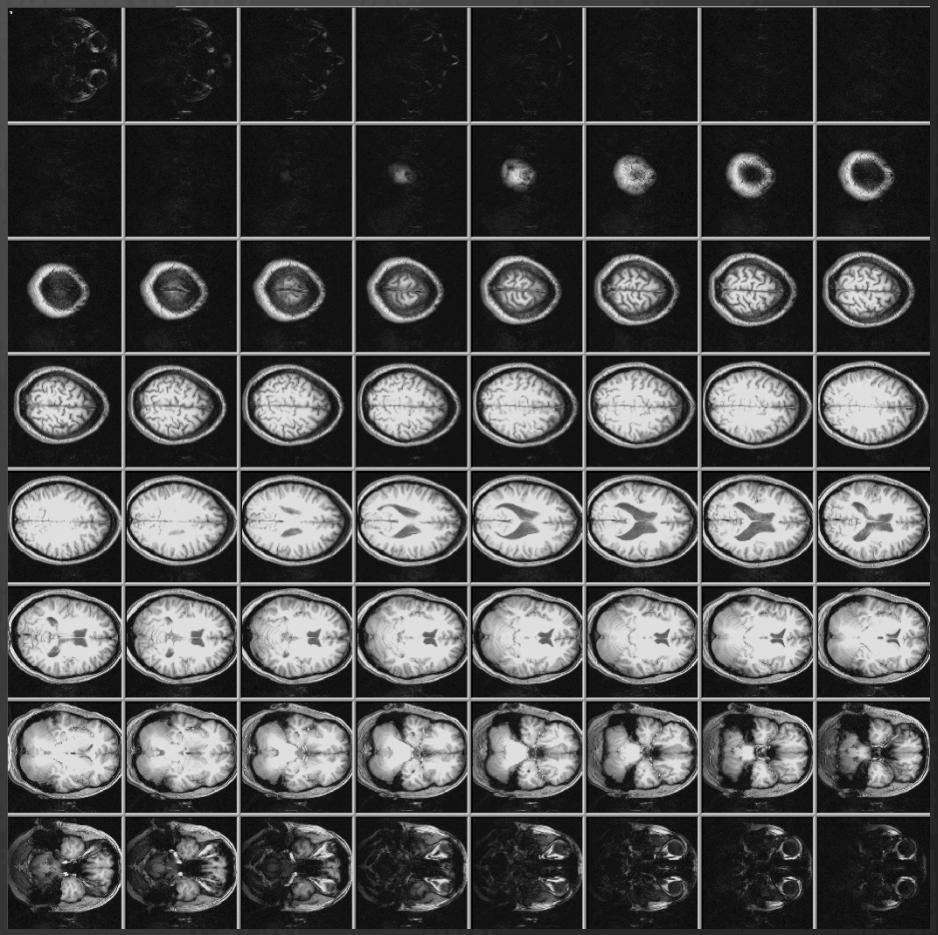
fMRI Experiment Stages: Anatomicals

4) Take anatomical (T1) images

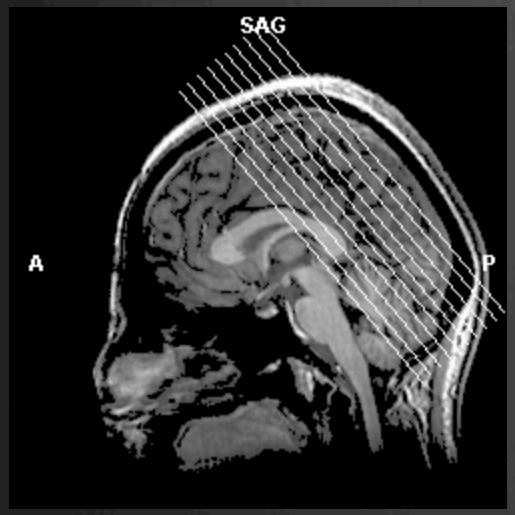
- high-resolution images (e.g., 0.75 x 0.75 x 3.0 mm)
- 3D data: 3 spatial dimensions, sampled at one point in time
- 64 anatomical slices takes ~4 minutes



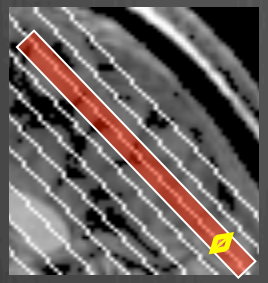
64 slices x
3 mm



Slice Terminology



SAGITTAL SLICE



Slice Thickness
e.g., 6 mm

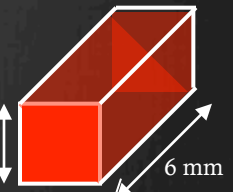
Number of Slices
e.g., 10

Matrix Size
e.g., 64 x 64

Field of View (FOV)
e.g., 19.2 cm

In-plane resolution
e.g., 192 mm / 64
= 3 mm

VOXEL
(Volumetric Pixel)

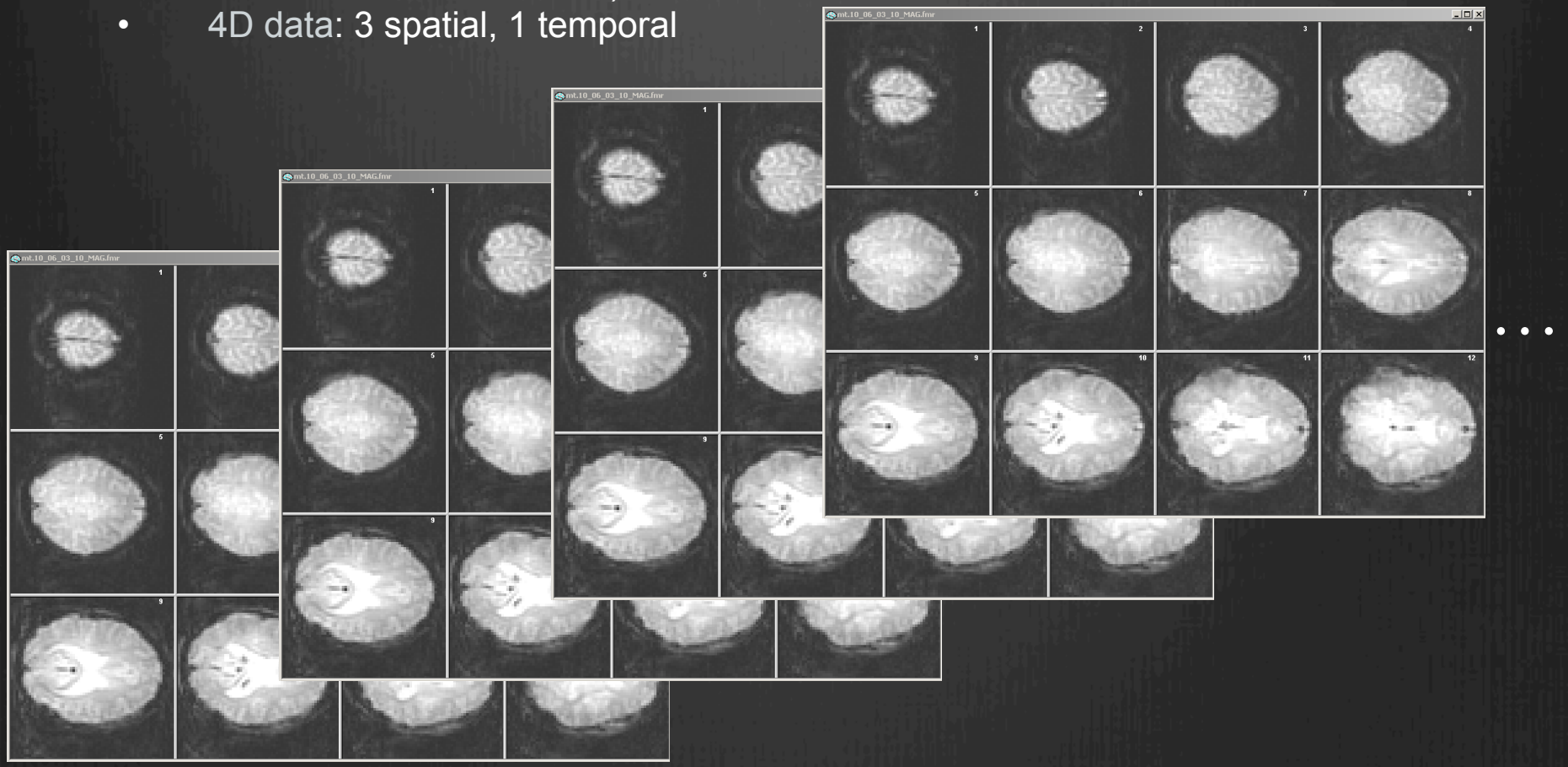


IN-PLANE SLICE

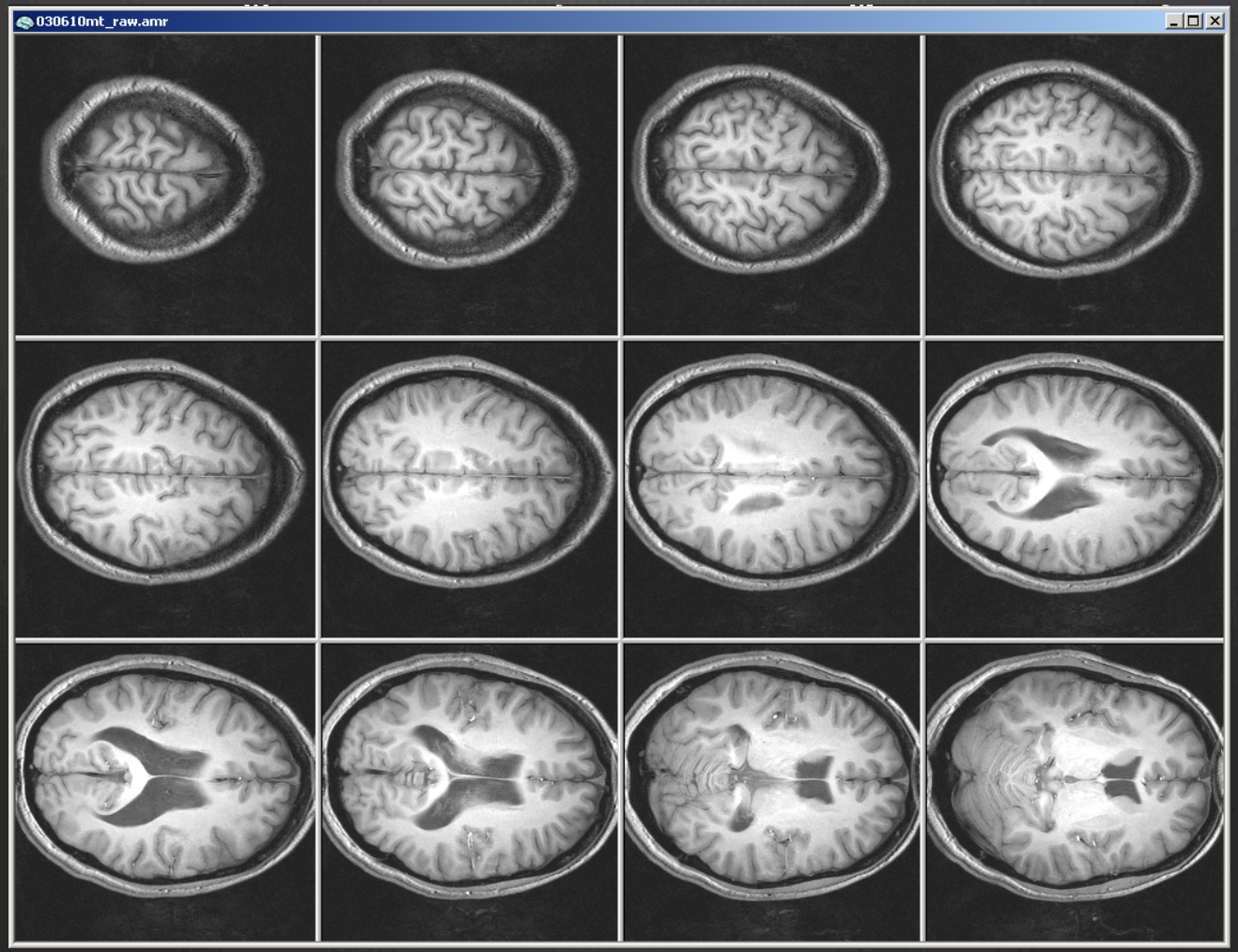
fMRI Experiment Stages: Functionals

5) Take functional (T2*) images

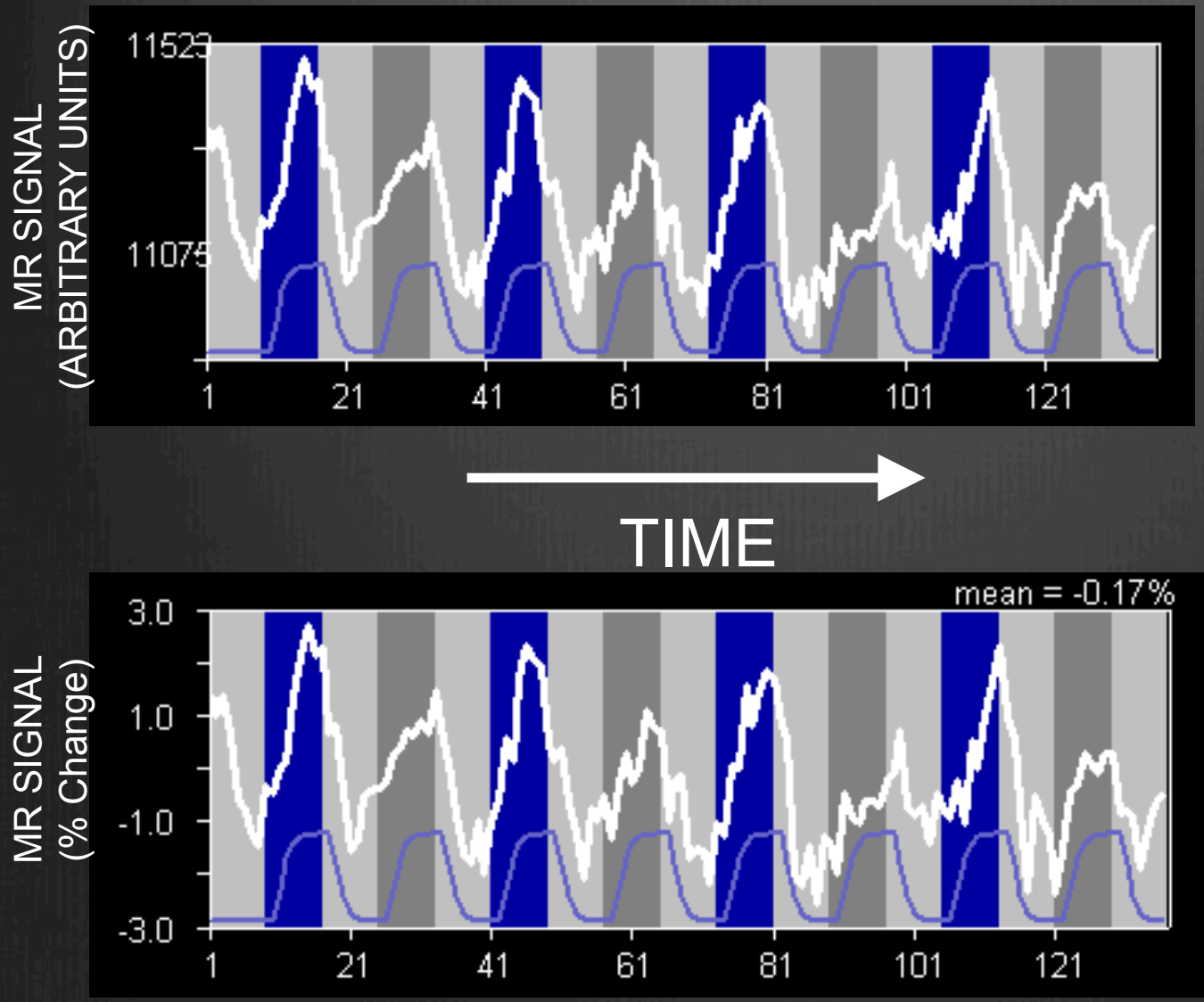
- images are indirectly related to neural activity
- usually low resolution images (3 x 3 x 6 mm)
- all slices at one time = a volume (sometimes also called an image)
- sample many volumes (time points) (e.g., 1 volume every 2 seconds for 136 volumes = 272 sec = 4:32)
- 4D data: 3 spatial, 1 temporal



Anatomic Slices Corresponding to Functional Slices



Time Courses



Arbitrary signal varies from voxel to voxel, day to day, subject to subject

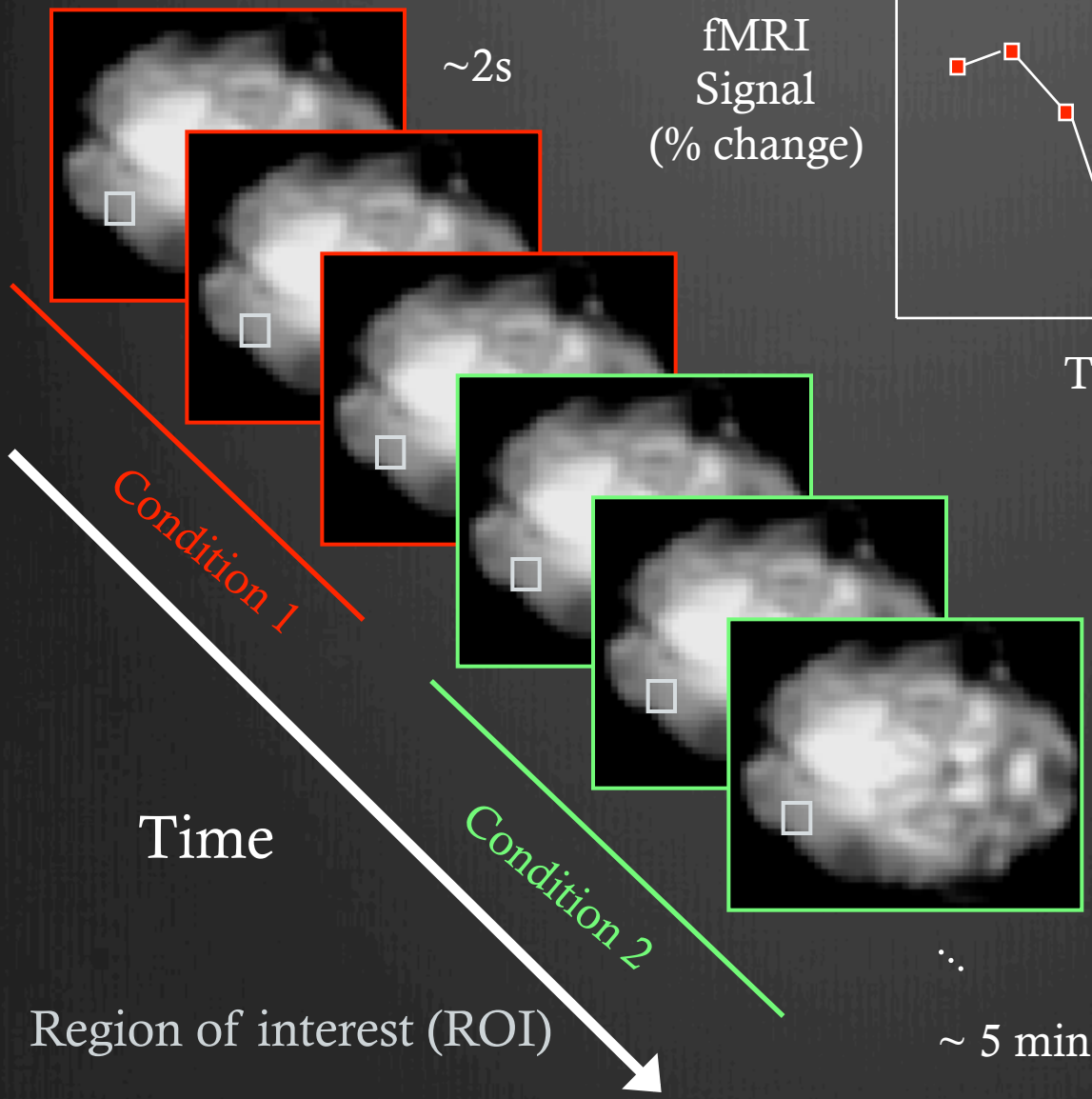
To make the y-axis more meaningful, we usually convert the signal into units of % change:

100*(x - baseline)/baseline

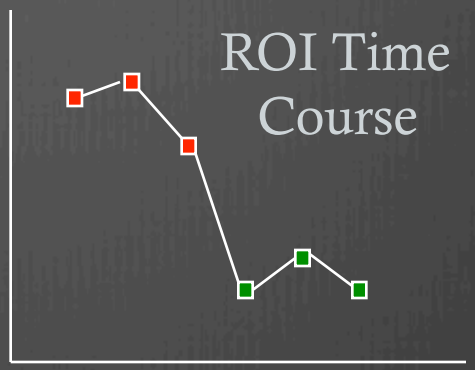
Changes are typically in the order of 0.5-4 %.

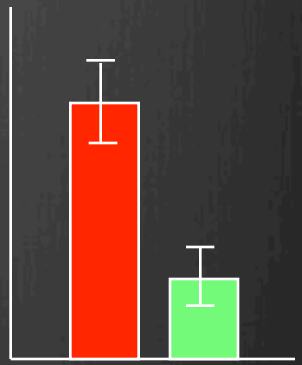
Activation Statistics

Functional images

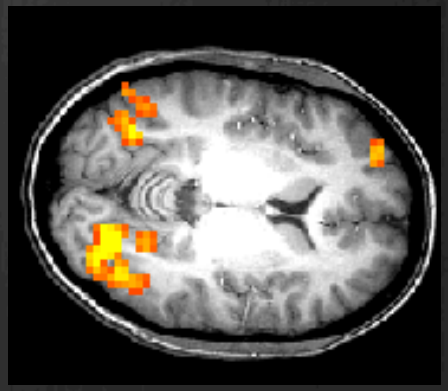


fMRI Signal (% change)

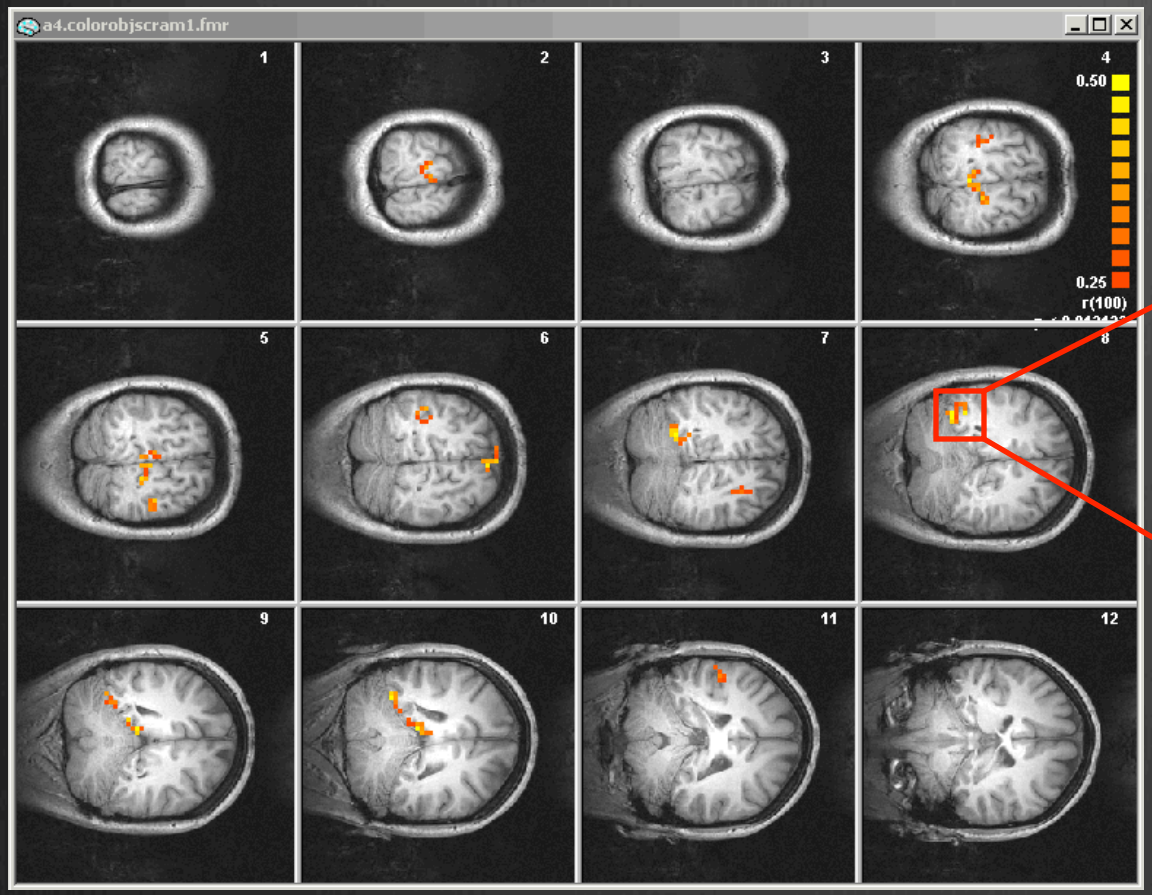




Statistical Map
superimposed on anatomical MRI image

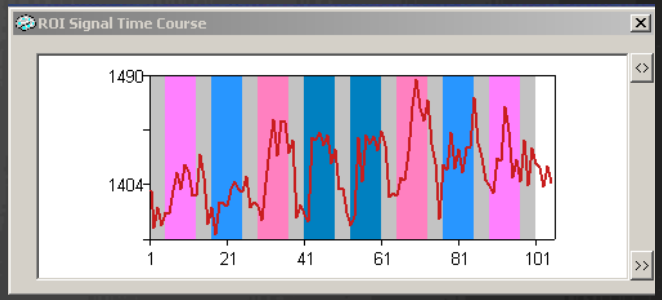


Statistical Maps & Time Courses

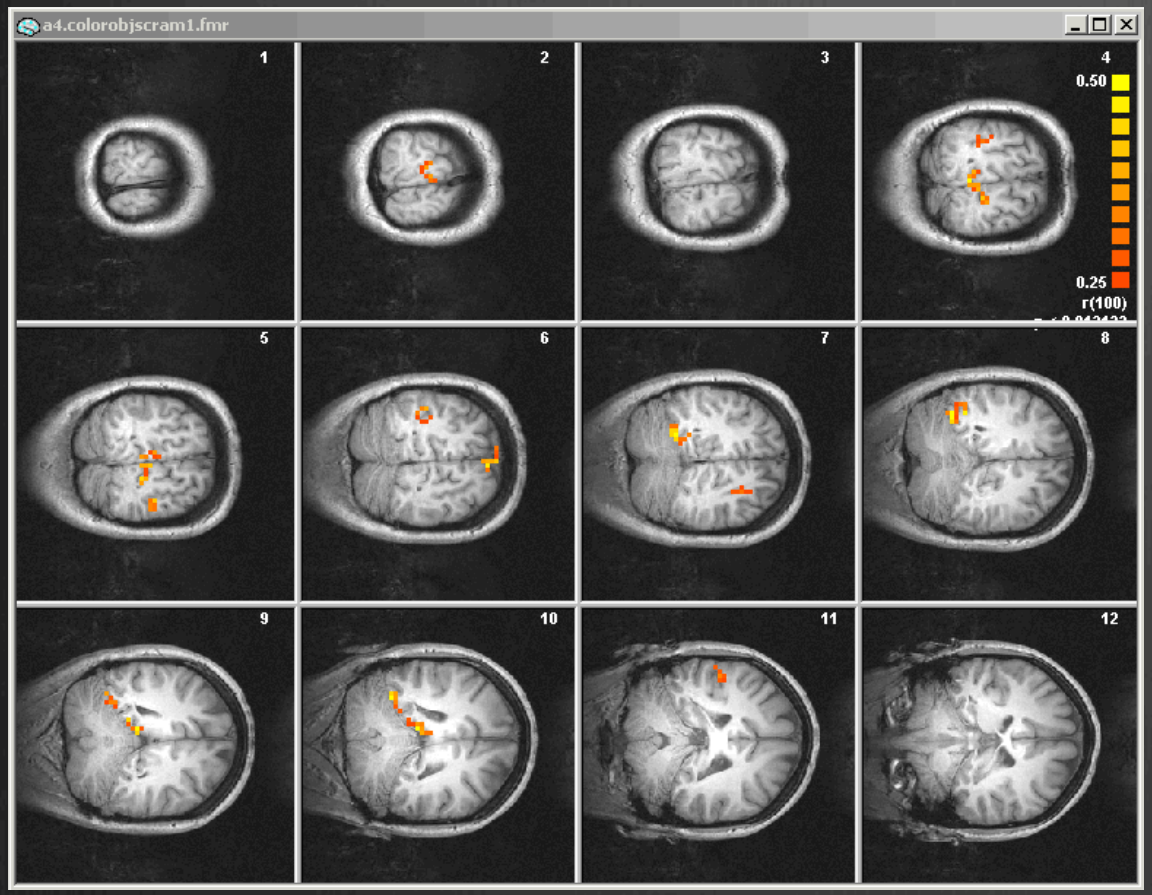


Use stat maps to pick regions

Then extract the time course



2D → 3D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3
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5
6
7
8
9
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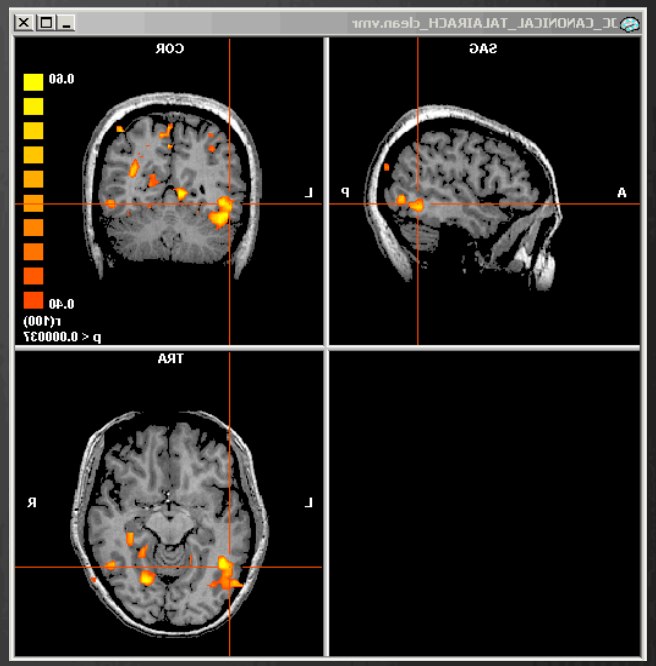
12


COR
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r(100)
p < 0.000037
L
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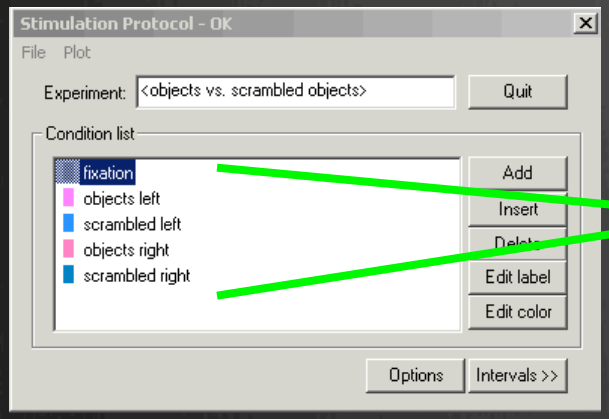
Design Jargon: Runs

session: all of the scans collected from one subject in one day
run (or scan): one continuous period of fMRI scanning (~5-7 min)
experiment: a set of conditions you want to compare to each other
condition: one set of stimuli or one task

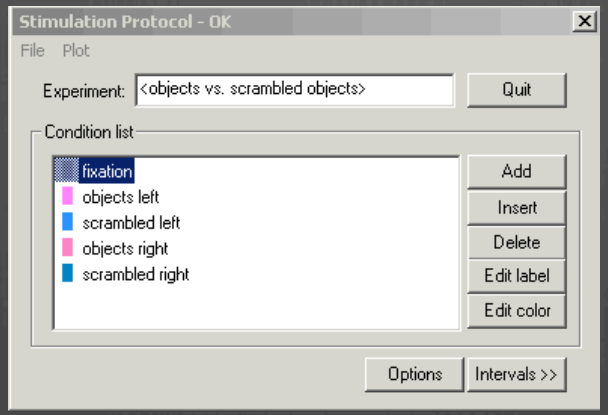
Note: Terminology can vary from one fMRI site to another (e.g., some places use "scan" to refer to what we've called a volume).



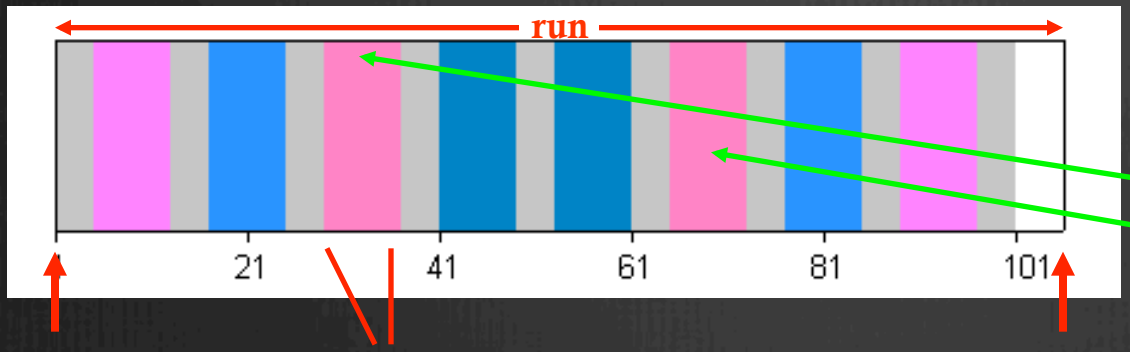
4 stimulus conditions
+ 1 baseline condition (fixation)

A session consists of one or more experiments.
Each experiment consists of several (e.g., 1-8) runs
More runs/expt are needed when signal:noise is low or the effect is weak.
Thus each session consists of numerous (e.g., 5-20) runs (e.g., 0.5 – 3 hours)

Design Jargon: Paradigm



paradigm (or protocol): the set of conditions and their order used in a particular run



epoch: one instance of a condition

first "objects right" epoch

second "objects right" epoch

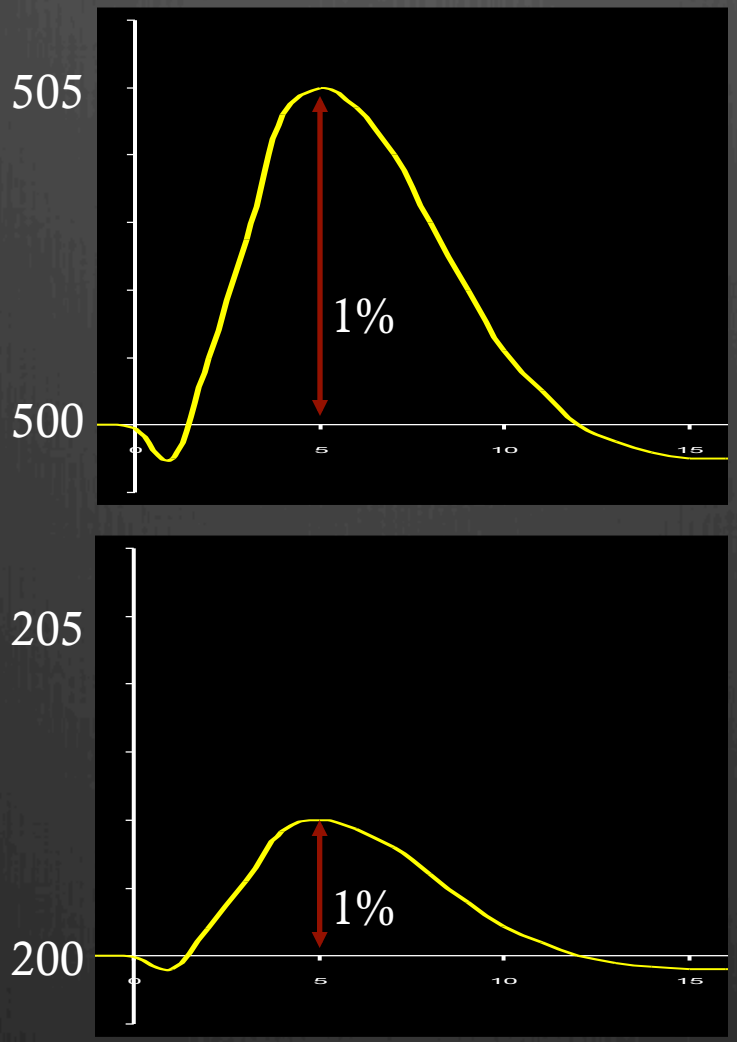
volume #1
(time = 0)

epoch
8 vol x 2 sec/vol = 16 sec

volume #105
(time = 105 vol x 2 sec/vol = 210 sec = 3:30)

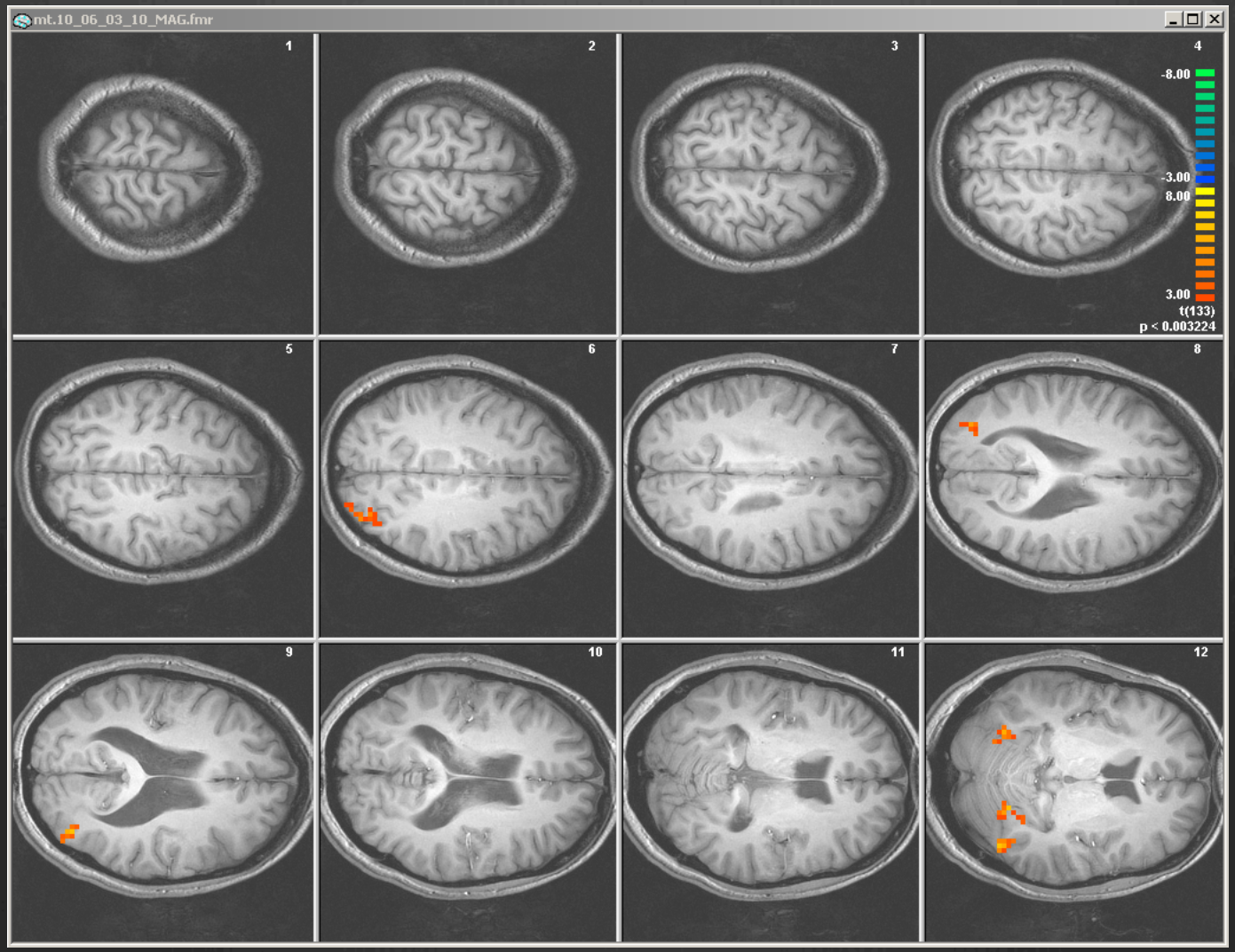
Time

Percent Signal Change

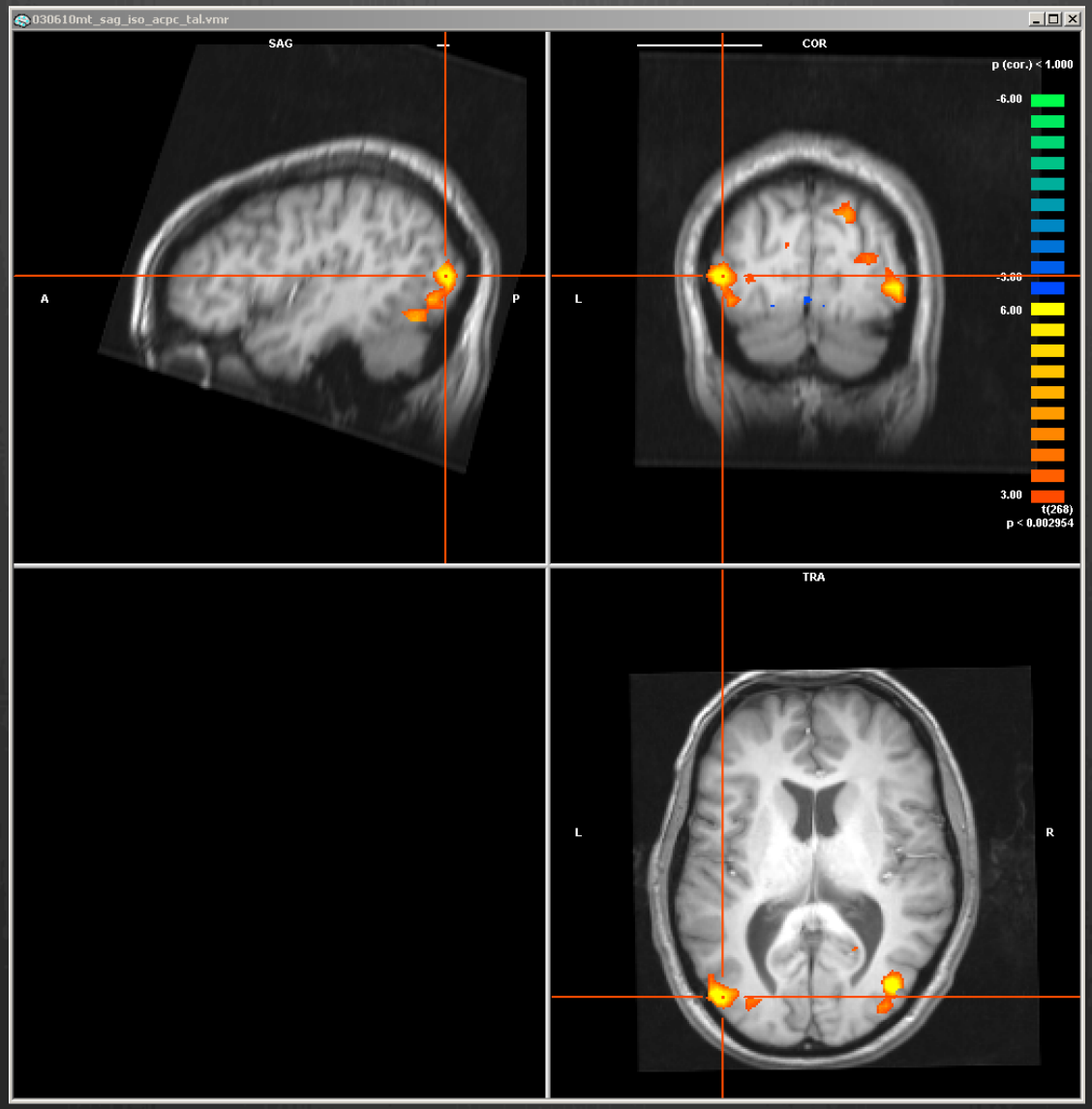


Slide from Duke course

Stats on Anatomical



2D ➔ 3D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