

Functional Brain MRI

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Outline

- BOLD

fMRI vs. MRI

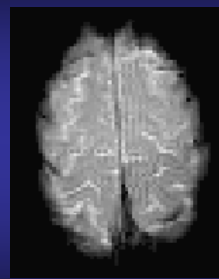


Functional MRI (fMRI)
studies brain function.

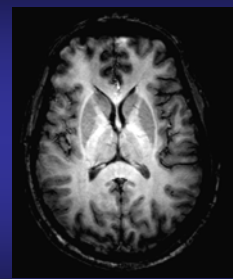


MRI studies
brain anatomy.

Images



Functional Image
(EPI)



Anatomical Image
(MPR)

Developments allowing functional MRI

- Discovery of BOLD contrast mechanism
- Ready availability of high-field scanners
 - Technological developments
- Echoplanar imaging methods
 - Proposed by Mansfield in 1977

MR Contrast Agents

- Defined: Substances that alter magnetic susceptibility of tissue or blood, leading to changes in MR signal
 - Affects local magnetic homogeneity: decrease in T_2^*
- Two types
 - Exogenous: Externally applied, non-biological compounds (e.g., Gd-DTPA)
 - Endogenous: Internally generated biological compound (e.g., dHb)

External Contrast Agents

- Most common are Gadolinium-based compounds introduced into bloodstream
 - Very large magnetic moments
- Create field gradients within/around vessels
 - What type of contrast would this generate?
- Large signal changes: 30-50%
 - Delay in activation change until agent bolus passes through MR imaging volume
 - Width of activation change depends on delivery of bolus and vascular filtering
 - Degree of signal change depends on total blood volume of area

Common Contrast Agents

Compound	Longitudinal Relaxivity	Transverse Relaxivity	Magnetic Susceptibility
GdCl ₂	1	1	1
MnCl ₂	0.96	3.83	0.51
GdDTPA	0.52	0.5	1
DyDTPA	0.03	0.04	1.78
GDTPA albumin	1.6	-	-
Iron oxide particle (3nm)	0.41	0.63	40.7
Iron oxide particle 253nm)	4.4	15.5	148

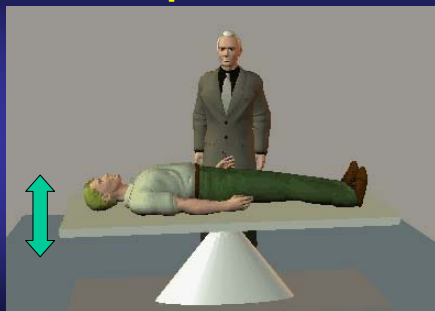
History of BOLD fMRI

Does blood flow serve function?

“These facts seem to us to indicate the existence of an **automatic mechanism** by which **the blood supply of any part of the cerebral tissue is varied in accordance with the activity** of the chemical changes which underlie the functional action of that part. Bearing in mind that strong evidence exists of localisation of function in the brain, we are of opinion that an automatic mechanism, of the kind just referred to, is well fitted to provide for a **local variation of the blood supply in accordance with local variations of the functional activity.**”

- Roy and Sherrington (1890)

A Simple Brain Activation Experiment

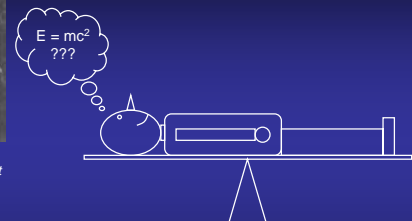


Apparatus of Angelo Mosso, as described by James (1890)

A Simple Brain Activation Experiment



Angelo Mosso
Italian physiologist
(1846-1910)

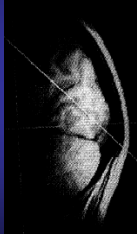


- “[In Mosso’s experiments] the subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either end were increased.
- The moment emotional or intellectual activity began in the subject, down went the balance at the head-end,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

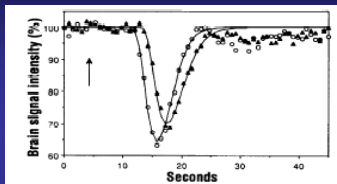
-- William James, *Principles of Psychology* (1890)

fMRI with contrast agent Belliveau et al., 1990

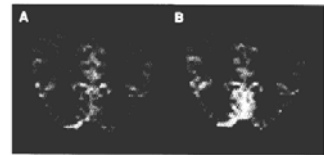
Slice Location



NMR intensity change
(CBV)



CBV Maps (+2.4%)



BOLD History

- **1990:** BOLD effect seen in rat brain @ 7T for the first time (Ogawa et al, PNAS)
- **1991:** in the human brain using contrast agent @ 1.5T (Belliveau et al, Science)
- **1992:** BOLD and perfusion fMRI in the human brain (Bandettini et al MRM; Frahm et al JMRI; Kwong et al PNAS, Ogawa et al, PNAS; Detre et al; Williams et al)
- **1993:** BOLD fMRI @ 4T (Ugurbil et al, MRQ)
- **2001:** BOLD fMRI @ 7T (Yacoub et al, MRM)

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CHEMISTRY: PAULING AND CORYELL Proc. N. A. S.

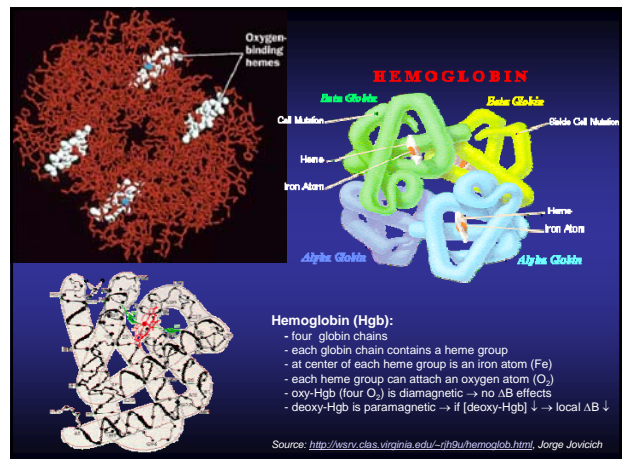
THE MAGNETIC PROPERTIES AND STRUCTURE OF HEMOGLOBIN, OXYHEMOGLOBIN AND CARBONMONOXYHEMOGLOBIN

BY LINUS PAULING AND CHARLES D. CORYELL

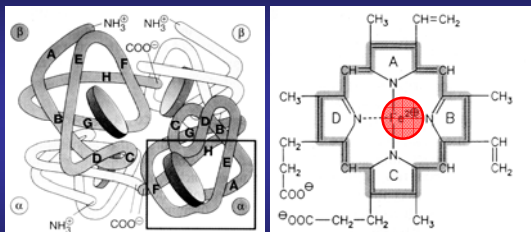
GATES CHEMICAL LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated March 19, 1936

Over ninety years ago, on November 8, 1845, Michael Faraday investigated the magnetic properties of dried blood and made a note "Must try recent fluid blood." If he had determined the magnetic susceptibilities of arterial and venous blood, he would have found them to differ by a large amount (as much as twenty per cent for completely oxygenated and completely deoxygenated blood); this discovery without doubt would have excited much interest and would have influenced appreciably the course of research on blood and hemoglobin.¹



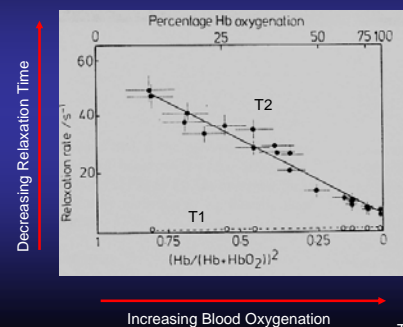
Haemoglobin



Haemoglobin

Heme

Blood Deoxygenation affects T2 Recovery



Increasing Blood Oxygenation

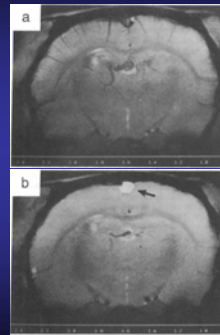
Thulborn et al., 1982

Ogawa et al., 1990a

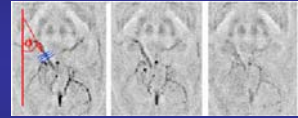
- **Subjects:** 1) Mice and Rats, 2) Test tubes
- **Equipment:** High-field MR (7 T)
- **Results 1:**
 - Contrast on gradient-echo images influenced by proportion of oxygen in breathing gas
 - Increasing oxygen content → reduced contrast
 - No vascular contrast seen on spin-echo images
- **Results 2:**
 - Oxygenated blood in tube leads to little signal change, either on spin- or gradient-echo images
 - Deoxygenated blood leads to large susceptibility effects on gradient-echo images

Ogawa et al., 1990b

100% O₂



Under anesthesia, rats breathing pure oxygen have some BOLD contrast (black lines).



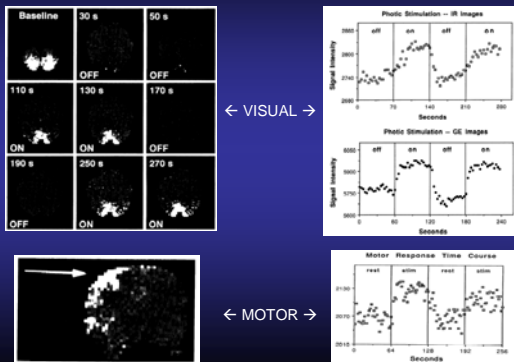
Breathing a mix including CO₂ results in **increased blood flow**, in turn **increasing blood oxygenation**.

There is no increased metabolic load (no task).

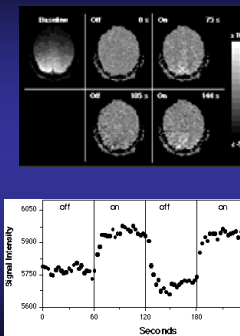
Therefore, BOLD contrast is reduced.

90% O₂, 10% CO₂

Kwong et al., 1992

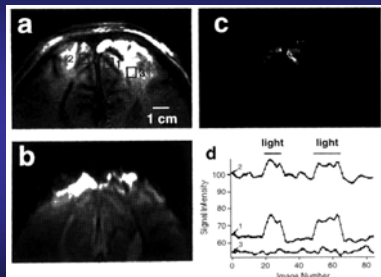


Kwong et al., 1992



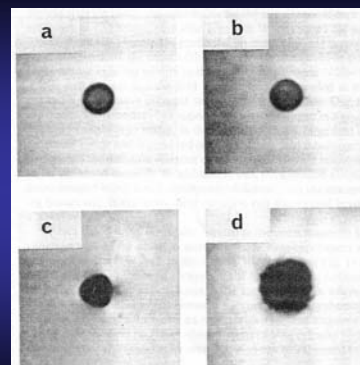
Source: Kwong et al., 1992

Ogawa et al., 1992



- High-field (4T) in humans
- Patterned visual stimulation at 10 Hz
- Gradient-echo (GRE) pulse sequence used
 - Surface coil recorded
- Significant image intensity changes in visual cortex

Spin Echo Gradient Echo

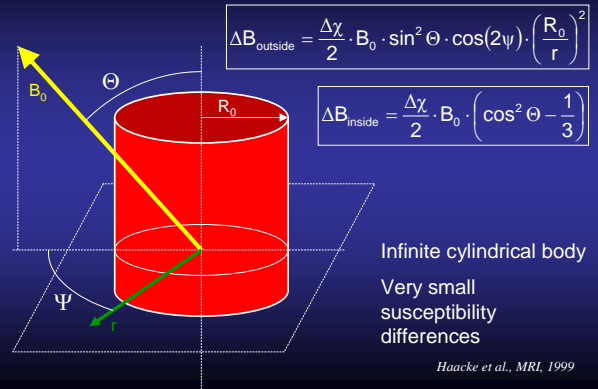


Ogawa 1990b

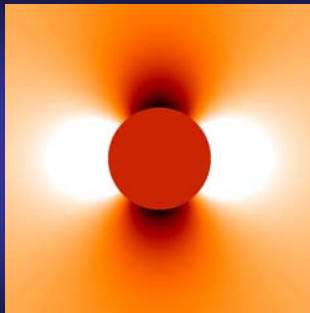
Susceptibility and BOLD fMRI

- **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).

Field Distortions

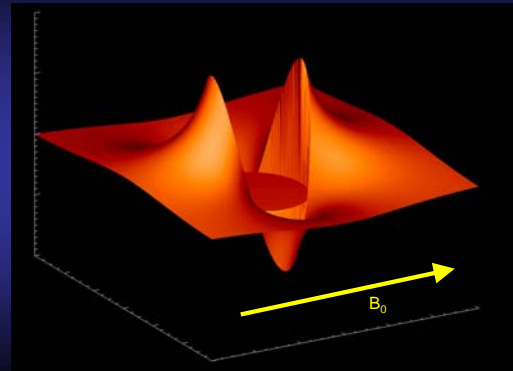


Field Distortions

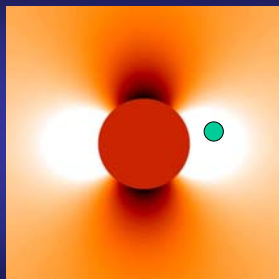


Magnetic field distribution within and around a vessel perpendicular to the external magnetic field B_0 .

Field Distortions



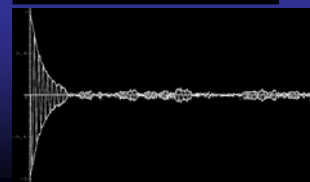
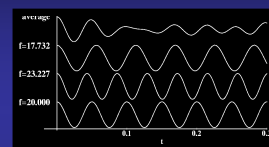
Why do field distortions change the NMR signal?



Spins feel different field strengths over time
 ↓
 Dephasing
 ↓
 More rapid signal decay
 ↓
 NMR signal decrease

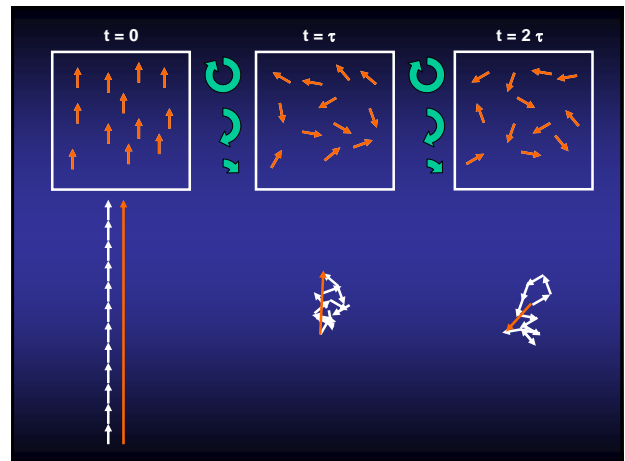
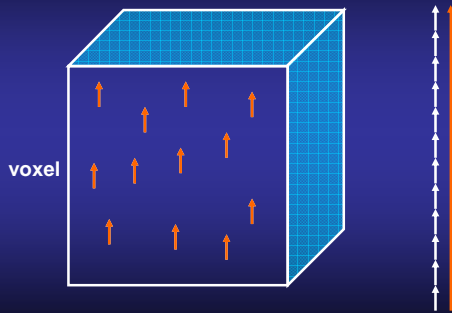
How Susceptibility Affects Signal

Susceptibility \rightarrow nonuniform precession frequencies
 RF signals from different regions that are at different frequencies will get out of phase and thus tend to cancel out



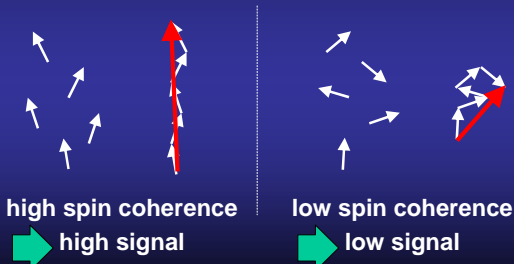
Robert Cox's web slides

Spin Summation

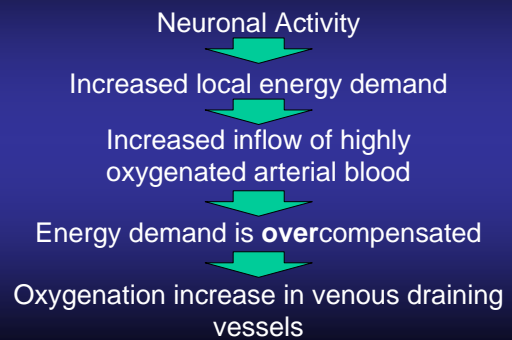


Spin Dephasing

- The signal in a voxel is the geometric sum of all individual spin signals



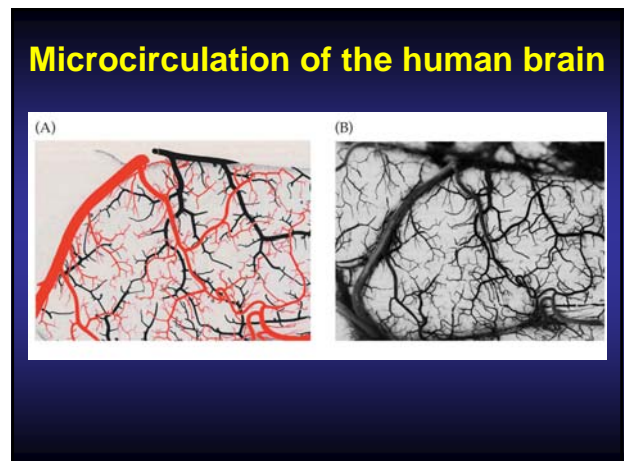
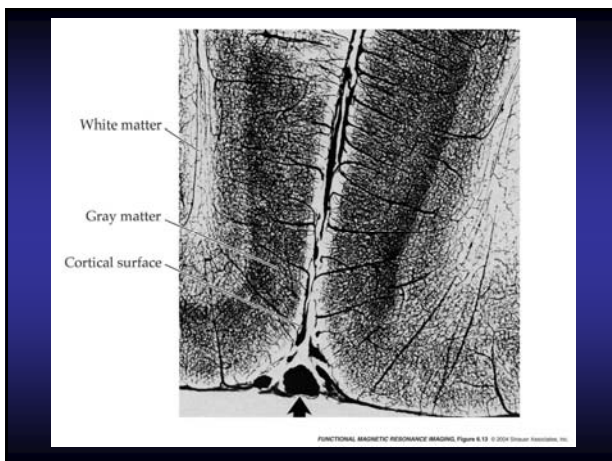
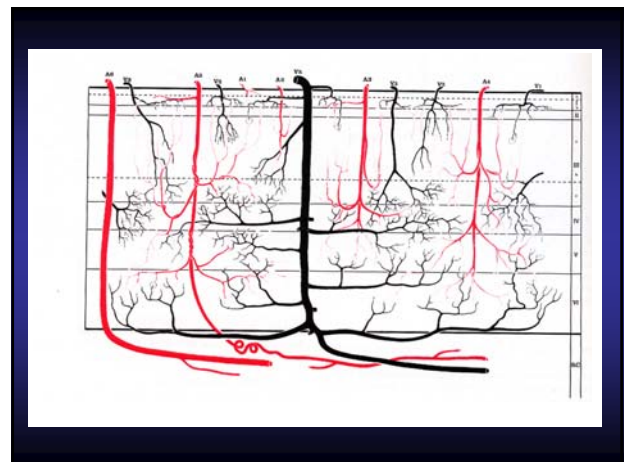
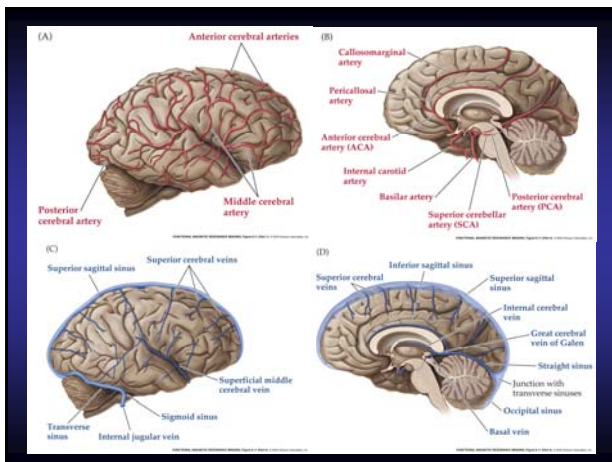
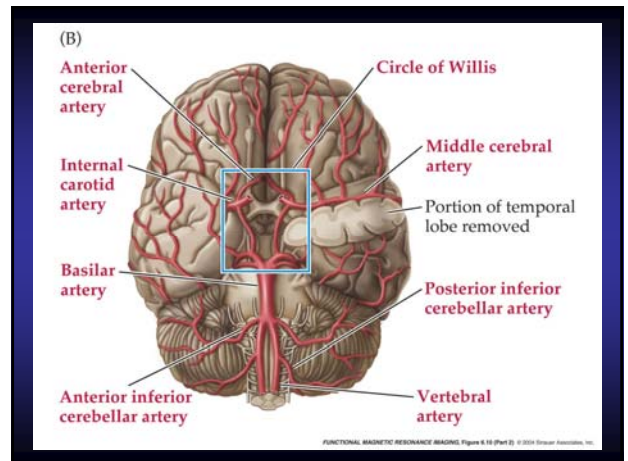
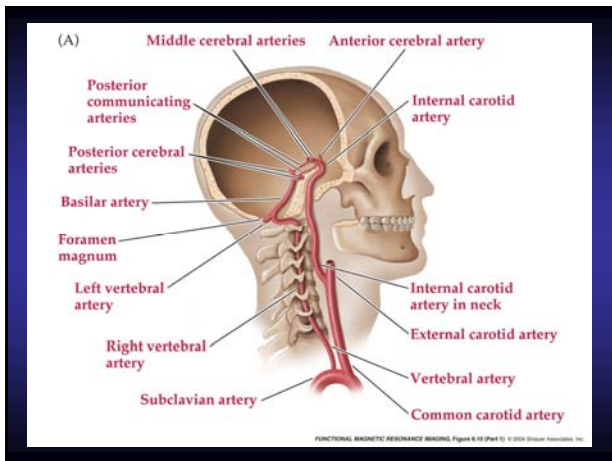
fMRI Physiology



Why do we need to know physics/physiology of fMRI?

- To understand the implications of our results**
 - Interpreting activation extent, timing, etc.
 - Determining the strength of our conclusions
 - Exploring new and unexpected findings
- To understand limitations of our method**
 - Choosing appropriate experimental design
 - Combining information across techniques to overcome limitations
- To take advantage of new developments**
 - Evaluating others' approaches to problems
 - Employing new pulse sequences or protocols

Cerebral Vasculature



Arterioles

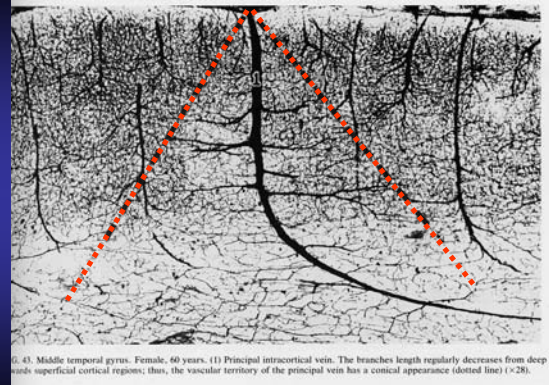
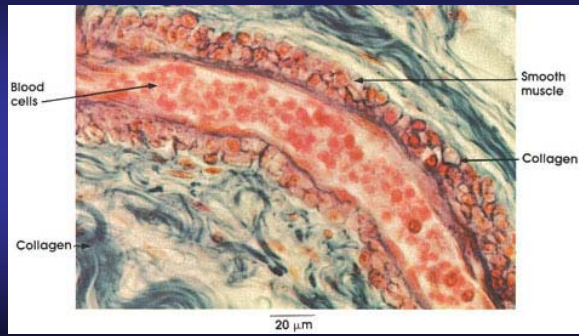
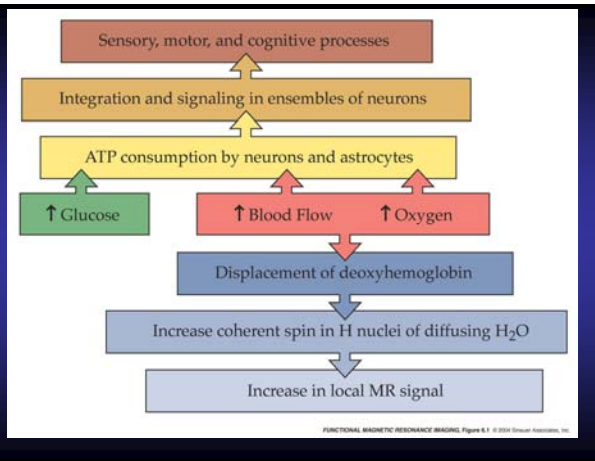


Fig. 43. Middle temporal gyrus. Female, 60 years. (1) Principal intracortical vein. The branches length regularly decreases from deep towards superficial cortical regions; thus, the vascular territory of the principal vein has a conical appearance (dotted line) ($\times 28$).



The relation between sensory stimulation and local blood flow changes

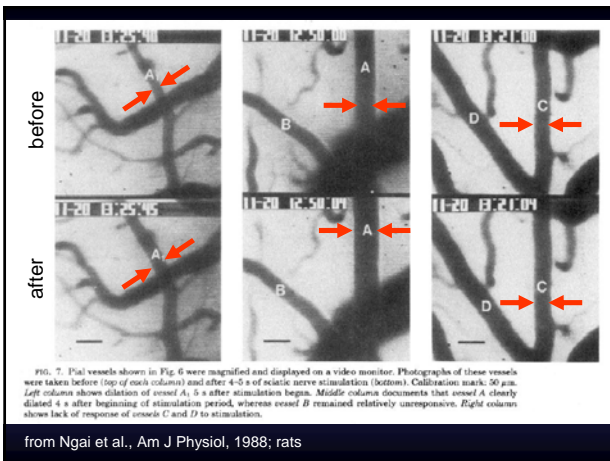
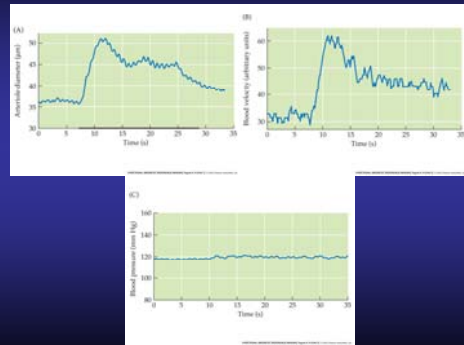
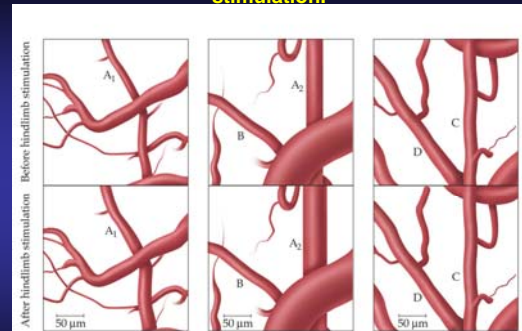


FIG. 7. Pial vessels shown in Fig. 6 were magnified and displayed on a video monitor. Photographs of these vessels were taken before (top of each column) and after 4-5 s of sciatic nerve stimulation (bottom). Calibration mark, 50 μ m. Left column shows dilation of vessel A, 5 s after stimulation begins. Middle column documents that vessel A clearly dilated 4 s after beginning of stimulation period, whereas vessel B remained relatively unresponsive. Right column shows lack of response of vessels C and D to stimulation.

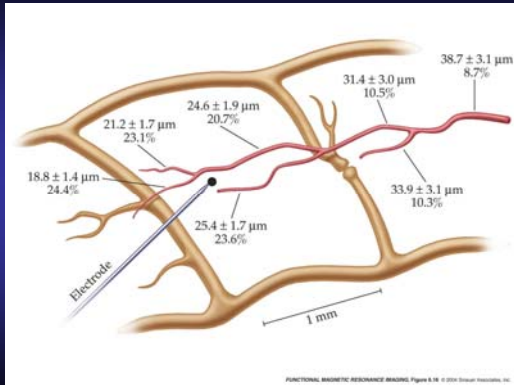
from Ngai et al., Am J Physiol, 1988; rats

The change in diameter of arterioles following sciatic stimulation.



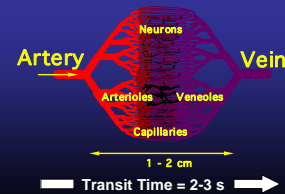
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 8.1

Change in arteriole dilation as a function of distance from active neurons.



Vascular Network

- Arterioles**
 - Y=95% at rest.
 - Y=100% during activation.
 - 25 μm diameter.
 - <15% blood volume of cortical tissue.
- Venules**
 - Y=60% at rest.
 - Y=90% during activation.
 - 25-50 μm diameter.
 - 40% blood volume of cortical tissue.
- Red blood cell**
 - 6 μm wide and 1-2 μm thick.
 - Delivers O₂ in form of oxyhemoglobin.
- Capillaries**
 - Y=80% at rest.
 - Y=90% during activation.
 - 8 μm diameter.
 - 40% blood volume of cortical tissue.
 - Primary site of O₂ exchange with tissue.

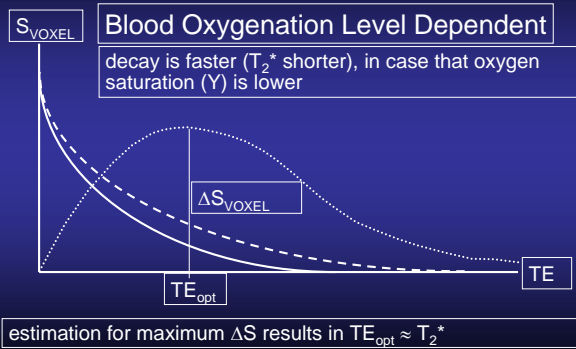


Source: Chris Thomas' Slides

BOLD Endogenous Contrast

- Blood Oxygenation Level Dependent Contrast**
 - Deoxyhemoglobin is paramagnetic, oxyhemoglobin is less so.
 - Magnetic susceptibility of blood increases linearly with increasing oxygenation
- Oxygen is extracted during passage through capillary bed**
 - Arteries are fully oxygenated
 - Venous (and capillary) blood has increased proportion of deoxyhemoglobin
 - Difference between oxy and deoxy states is greater for veins → BOLD sensitive to venous changes

BOLD contrast

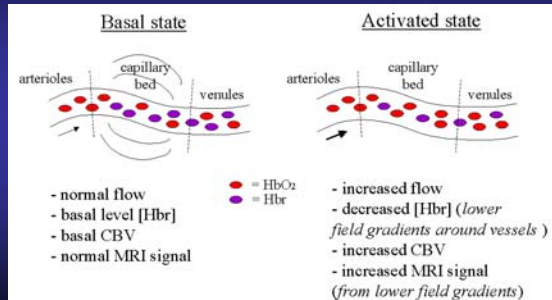


BOLD Physiology

BOLD signal

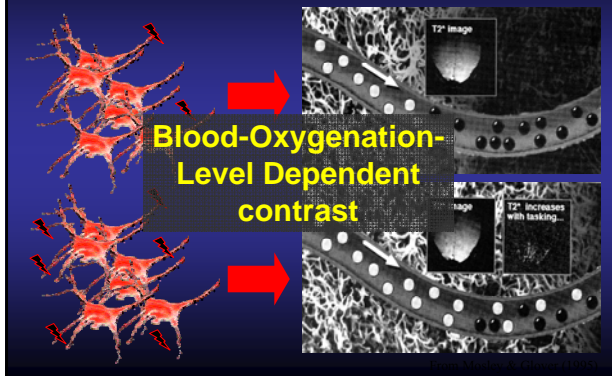
Blood oxygen level dependent signal

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

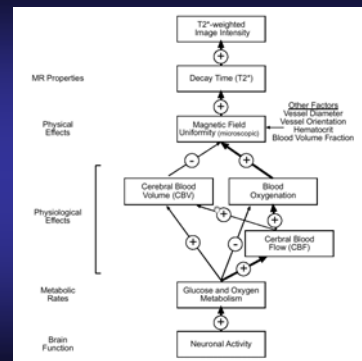


[MRIB] Brief Introduction to fMRI

Physiology (BOLD Contrast)



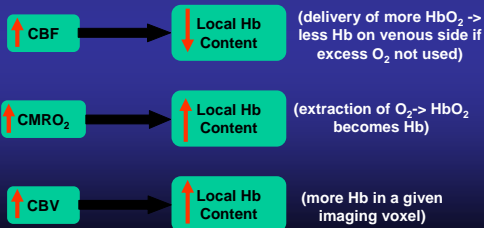
BOLD signal



BOLD signal

Blood Oxygen Level Dependent signal

- CBF, CBV, and CMRO₂ have different effects on HbO₂ concentration:



Models to account for decoupling

- 'Watering the whole garden for the sake of one flower' (Grinvald)
- Astrocyte shuttle (Shulman, Magestretti)
- Transit time (Buxton)
- Temperature regulation (Yablonskiy)
- 'the rose bush is being overwatered for the sake of one hungry root' (Mayhew)

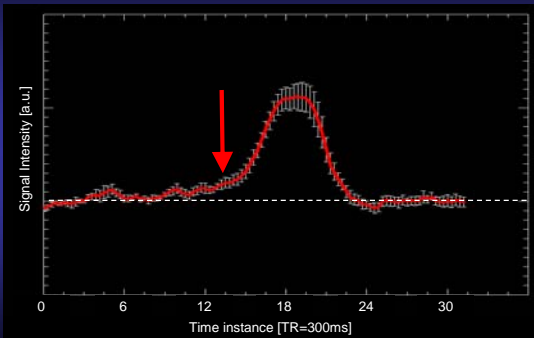
BOLD-fMRI at a Glance

- Water molecules diffuse in and around erythrocytes
- Paramagnetic deoxyhaemoglobin causes field distortions
 - Phase coherence of hydrogen nuclei decreased
 - Overall signal within a voxel decreased
- Activated regions show increased oxygenation, i.e. less deoxyhaemoglobin

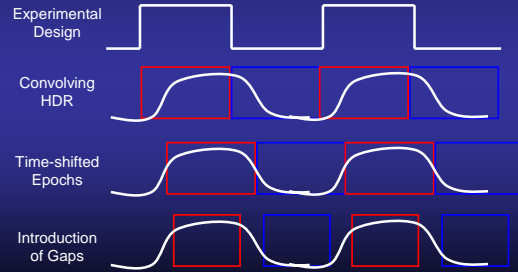
➔ NMR signal in "activated" regions increases

Haemodynamic Response

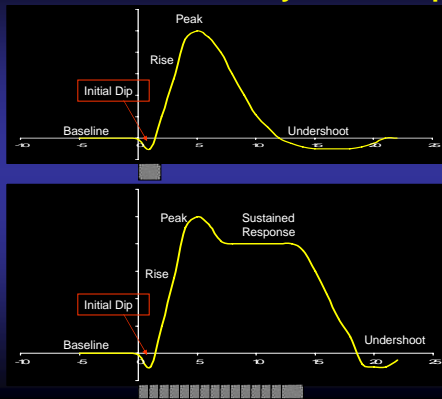
Haemodynamic Response



The Hemodynamic Response Lags Neural Activity

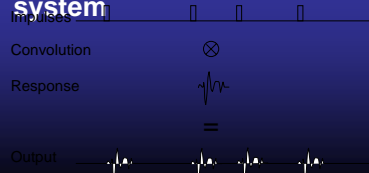


Basic Form of Hemodynamic Response

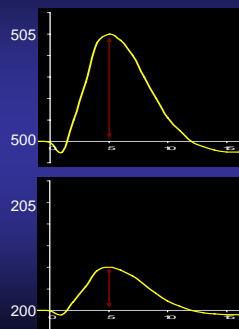


Impulse-Response Systems

- **Impulse:** single event that evokes changes in a system
 - Assumed to be of infinitely short duration
- **Response:** Resulting change in system



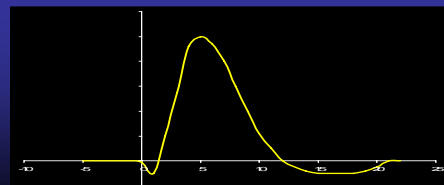
Percent Signal Change



- Peak / mean(baseline)
- Often used as a basic measure of “amount of processing”
- Amplitude variable across subjects, age groups, etc.

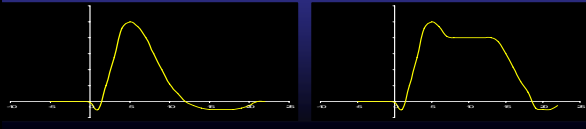
Rise (Hyperoxic Phase)

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



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



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

Issues in HDR Analysis

- **Delay in the HDR**
 - Hemodynamic activity lags neuronal activity
- **Amplitude of the HDR**
- **Variability in the HDR**
- **HDR as a relative measure**

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

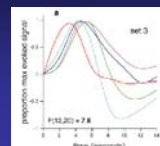
Variability in the Hemodynamic Response

- **Across Subjects**
- **Across Sessions in a Single Subject**
- **Across Brain Regions**
- **Across Stimuli**

Variability of HRF: Evidence

Aguirre, Zarahn & D'Esposito, 1998

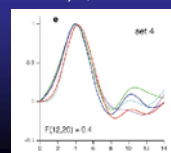
- HRF shows considerable variability between subjects



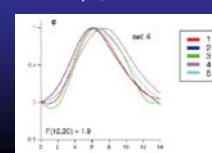
different subjects

- Within subjects, responses are more consistent, although there is still some variability between sessions

same subject, same session



same subject, different session

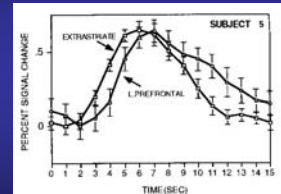


Variability of HRF: Implications

- Aguirre, Zarahn & D'Esposito, 1998
 - Generic HRF models (gamma functions) account for 70% of variance
 - Subject-specific models account for 92% of the variance (22% more!)
 - Poor modelling reduces statistical power
- Less of a problem for block designs than event-related
- Biggest problem with delay tasks where an inappropriate estimate of the initial and final components contaminates the delay component
- Possible solution: model the HRF individually for each subject

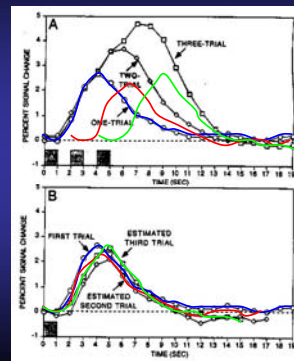
Variability of HRF: Implications

- Possible caveat: HRF may also vary between areas, not just subjects
- Buckner et al., 1996
 - noted a delay of .5-1 sec between visual and prefrontal regions
 - vasculature difference
 - processing latency?
- Bug or feature?
 - Menon & Kim – mental chronometry



Linearity of BOLD response

Dale & Buckner, 1997



Linearity:
"Do things add up?"

red = 2 - 1
green = 3 - 2

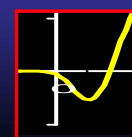
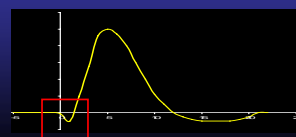
Sync each trial response to start of trial

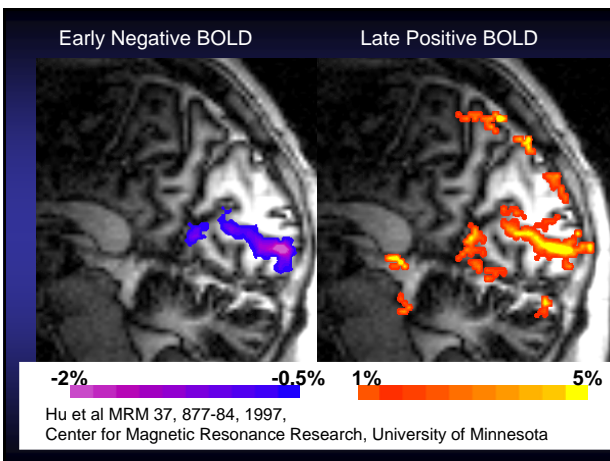
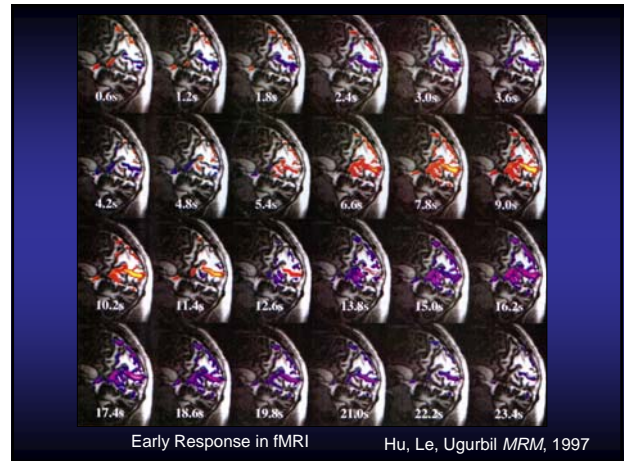
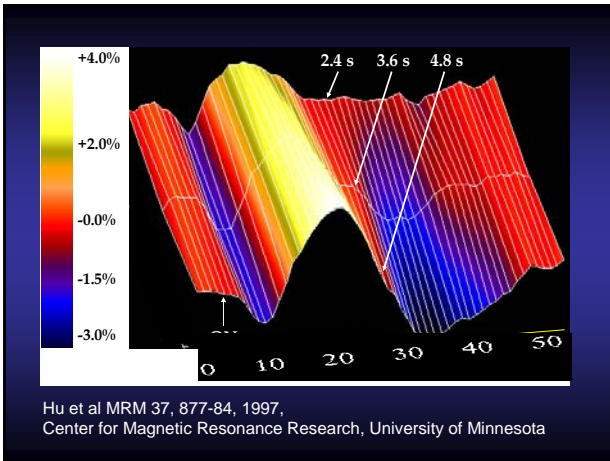
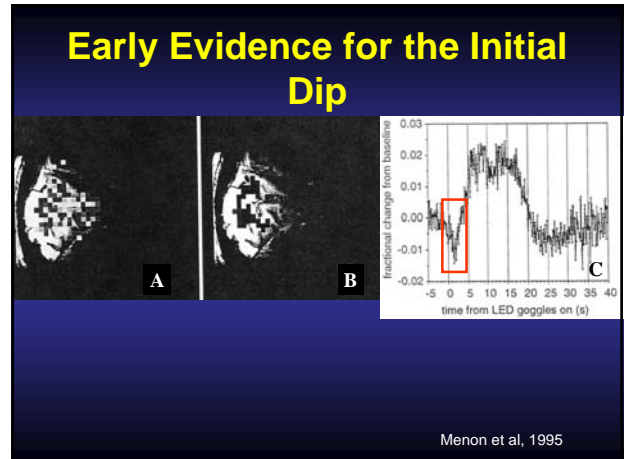
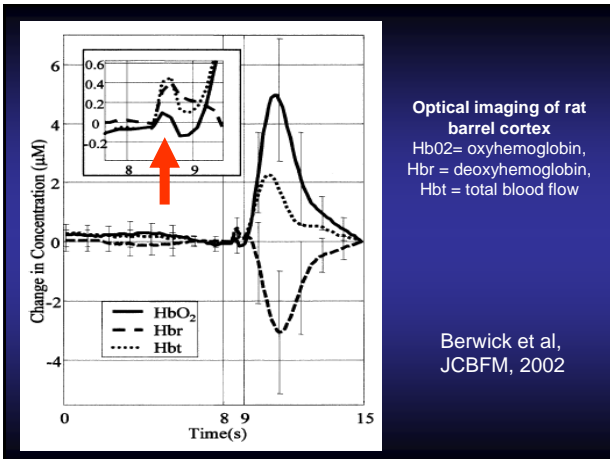
Not quite linear but good enough

Initial dip

Initial Dip (Hypo-oxic Phase)

- Transient increase in oxygen consumption, before change in blood flow
 - Menon et al., 1995; Hu, et al., 1997
- Shown by optical imaging studies
 - Malonek & Grünvald, 1996
- 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 perfusion response





Brain or Vein?

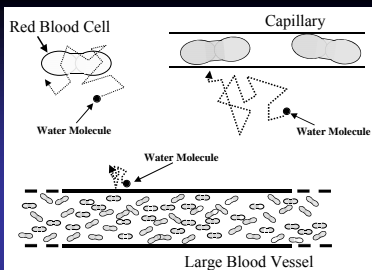
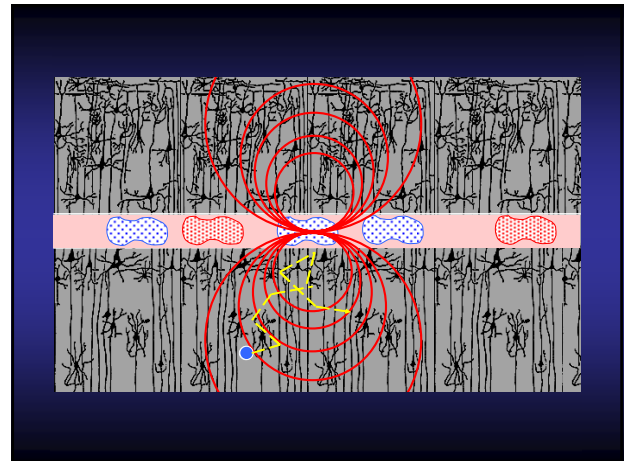
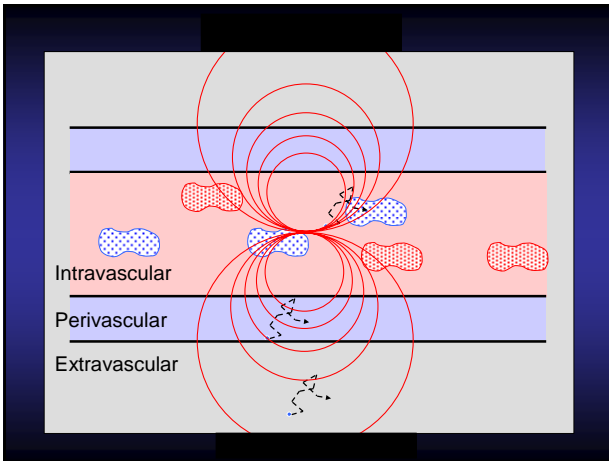
BOLD-fMRI at a Glance

- Water molecules diffuse in and around erythrocytes
- Paramagnetic deoxyhaemoglobin causes field distortions
 - Phase coherence of hydrogen nuclei decreased
 - Overall signal within a voxel decreased
- Activated regions show increased oxygenation, i.e. less deoxyhaemoglobin

➔ NMR signal in “activated” regions increases

Intra-, extravascular

- Two vascular spaces which do not easily exchange water ($> 0.5s$):
 - Extravascular (tissue)
 - Intravascular (blood)
- Two vascular regimes with different magnetic field characteristics:
 - capillary network (very small, randomly oriented vessels, diameter $\sim 7\mu m$)
 - Venules (oriented vessels, diameter $\sim 50-200\ \mu m$)



Field outside large “magnetized” venule is approx. constant on length scale of water mean path

- **Water diffuses freely in extravascular space**
 - In 50ms, water diffuses $25\ \mu m$ on average, thus moves $\sim 4x$ diameter of capillary
- **Diffusion is restricted in vascular space**
 - Water diffuses readily in and out of red blood cells. (spends about 5ms in a red blood cell)

T_2 or T_2^* changes?

- **Static dephasing regime: $\delta\omega \cdot \tau_D \gg 1$**
 - Diffusion is very slow compared to the change of the local field distribution (non-reversible)
 - This is the case for larger veins (venules)
 - \Rightarrow mainly T_2^* change
- **Dynamic averaging regime: $\delta\omega \cdot \tau_D \ll 1$**
 - water molecules dynamically move in a strong local field inhomogeneity
 - This is the case for capillaries
 - \Rightarrow Also T_2 change

$\delta\omega$... distribution of local Larmor frequencies
 τ_D ... average time of diffusion

Water Diffusion

For signal acquisition periods typical in fMRI

- **Intra-vascular water molecules**
 - diffuse unhindered between blood plasma and erythrocytes
 - do not leave the vasculature
- **Extra-vascular water molecules**
 - diffuse between intra- and extra-cellular space
 - do not enter the vasculature

Multiple Sites of the BOLD Effect

$$S = |S_{\text{tissue}} + S_{\text{vessel}}|$$

- **Intra-vascular**
 - Blood T_2 -changes
 - T_2' effects due to vessel orientations
- **Extra-vascular**
 - spin coherence changes due to extra-vascular field distortion

Blood T_2 -Changes

- Water diffuses between plasma and erythrocytes.
- Field distortions around erythrocytes
 - cause a loss of phase coherence
 - more rapid signal decay, T_2 -shortening
 - depending on oxygenation status
 - not compensated by spin-echo sequences

$$\frac{1}{T_2} = \frac{1}{T_{2,0}} + \alpha(1-Y) + \beta(1-Y)^2$$

T_2' -Effects due to Vessel Orientations

- All protons within a vessel segment sense a magnet field different from the surrounding tissue, according to

$$\Delta B_{\text{inside}} = \frac{\Delta\chi}{2} \cdot B_0 \cdot \left(\cos^2 \Theta - \frac{1}{3} \right)$$

- This field is constant throughout the vessel segment and does not lead to a loss of phase coherence within the vessel

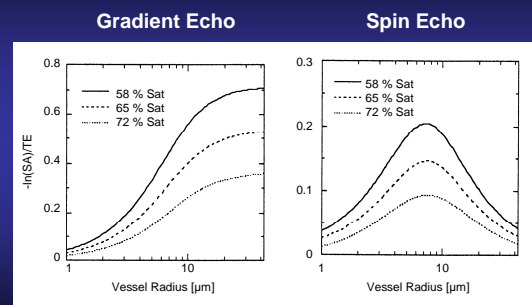
Extra-Vascular Effects

- Field distortions around vessels vary considerably

$$\Delta B_{\text{outside}} = \frac{\Delta\chi}{2} \cdot B_0 \cdot \sin^2 \Theta \cdot \cos(2\psi) \cdot \left(\frac{R_0}{r} \right)^2$$

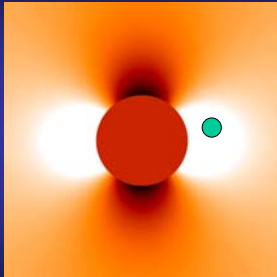
- Monte-Carlo simulations are used to quantify extra-vascular effects
- Sensitivities of GE and SE sequences depend on the vessel size

Extra-Vascular Effects at 1.5 T



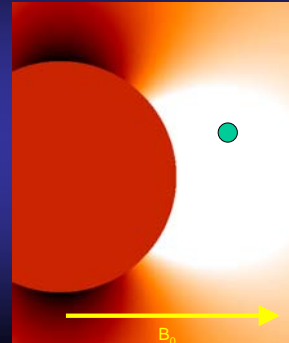
After Boxerman et al., MRM, 1994

Extravascular: small vessels



Spins feel different field strengths over time
 ↓
 Dephasing
 ↓
 More rapid signal decay
 ↓
 NMR signal decrease

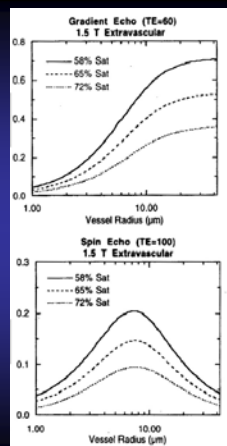
Extravascular: large vessels



Spins feel rather constant field strengths over time
 ↓
 Dephasing can be compensated with SE
 ↓
 SE sequences are not sensitive to oxygenation changes in large vessels

- T_2^* effects (gradient echo) are ~3-4x larger
- T_2^* effects are originate from bigger vessels

Boxerman et al. MRM 1995

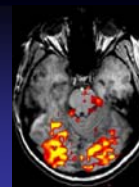


Spin Echo

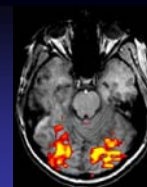
- for spin echoes ΔR_2 is relevant:
 - R_2 is also dependent on blood oxygenation
 - more specific to microvasculature (small veins) compared to gradient echoes
 - BUT: less sensitive than gradient echo

Diffusion weighting

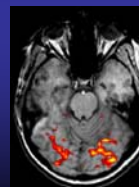
- Add a bipolar diffusion gradient to GE BOLD to remove signal from intravascular incoherent motion (IVIM), i.e. flowing spins
 - Range of flow velocities crushed can be adjusted spoiling venule flow (>10mm/s) eliminates 30% of BOLD, spoiling capillary (>0.5mm/s) eliminates 60% of signal
 - spoiling eliminates ~2/3 of the BOLD effect at 1.5T, ~1/2 at 3T and has no effect at 9.4T
- => BOLD signal becomes more extravascular at high field.



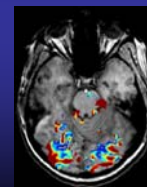
BOLD activation (b factor = 0)



Diffusion-weighted (b factor = 54)



Diffusion-weighted (b factor = 108)



ADC masked by BOLD activation

Large vessels

How to get rid of large vessels?

- **large arteries**
 - long TR \Rightarrow NO in-flow effect
- **large draining veins**
 - use perfusion
 - use spin echoes
 - use initial dip information
 - use diffusion weighting
 - use high field
 - use multiple gradient echoes

