Functional MRI mechanism

Jun-Cheng Weng

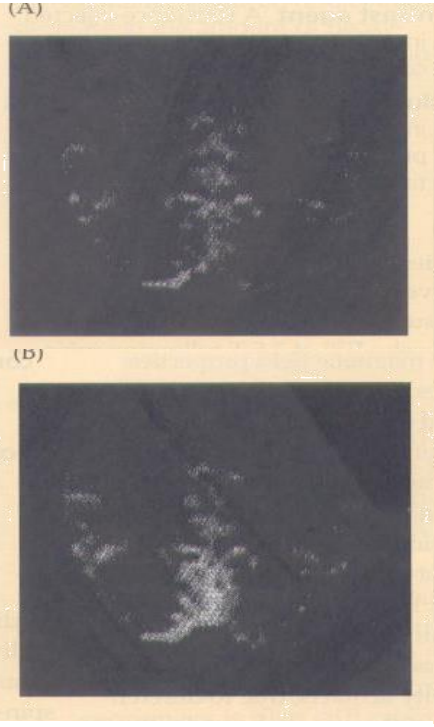
13 Dec 2014

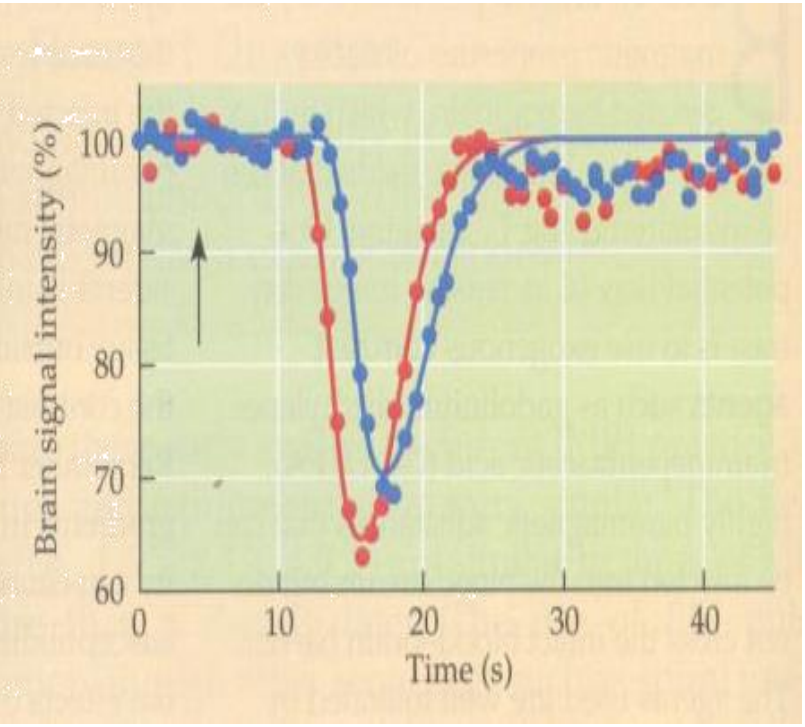
Outline

- BOLD fMRI review
- Imaging method
- Imaging parameter
- Temporal resolution limitation
- Spatial resolution limitation
- Other issues

First fMRI study

- Use Gd as exogenous tracer

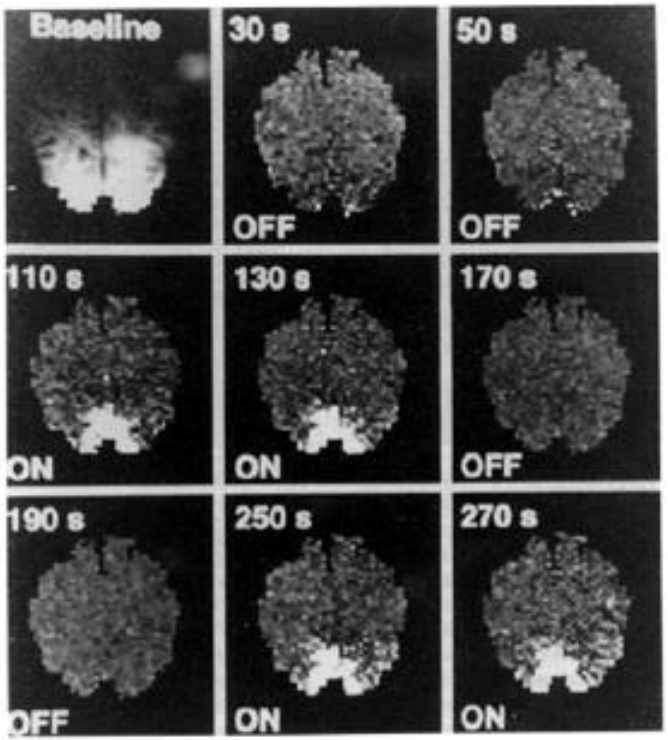




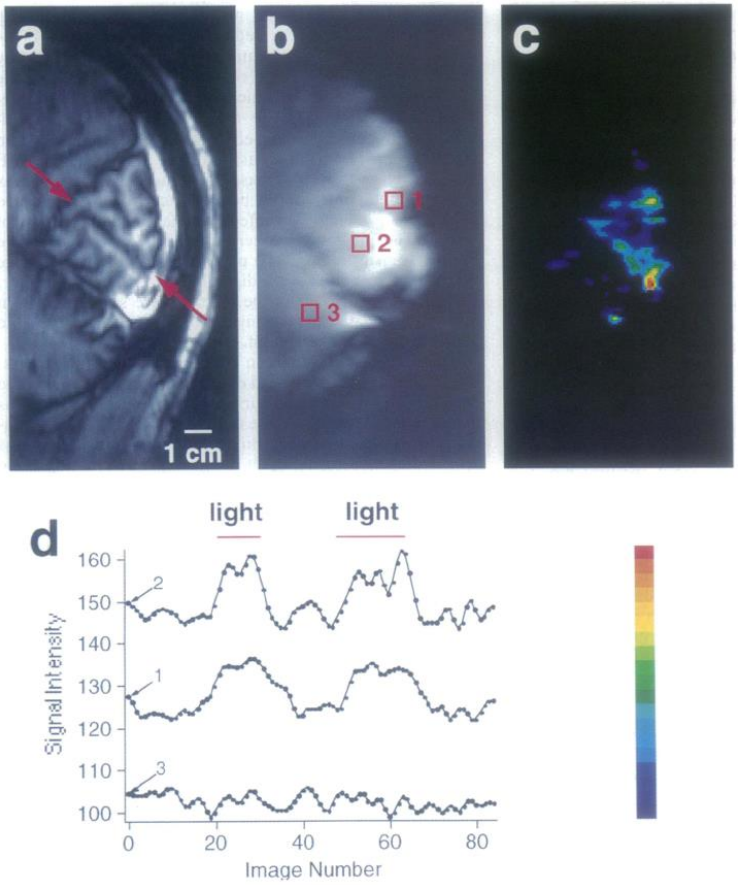
- Belliveau et al. ***Science*** 1990

First fMRI study

- Non-invansive

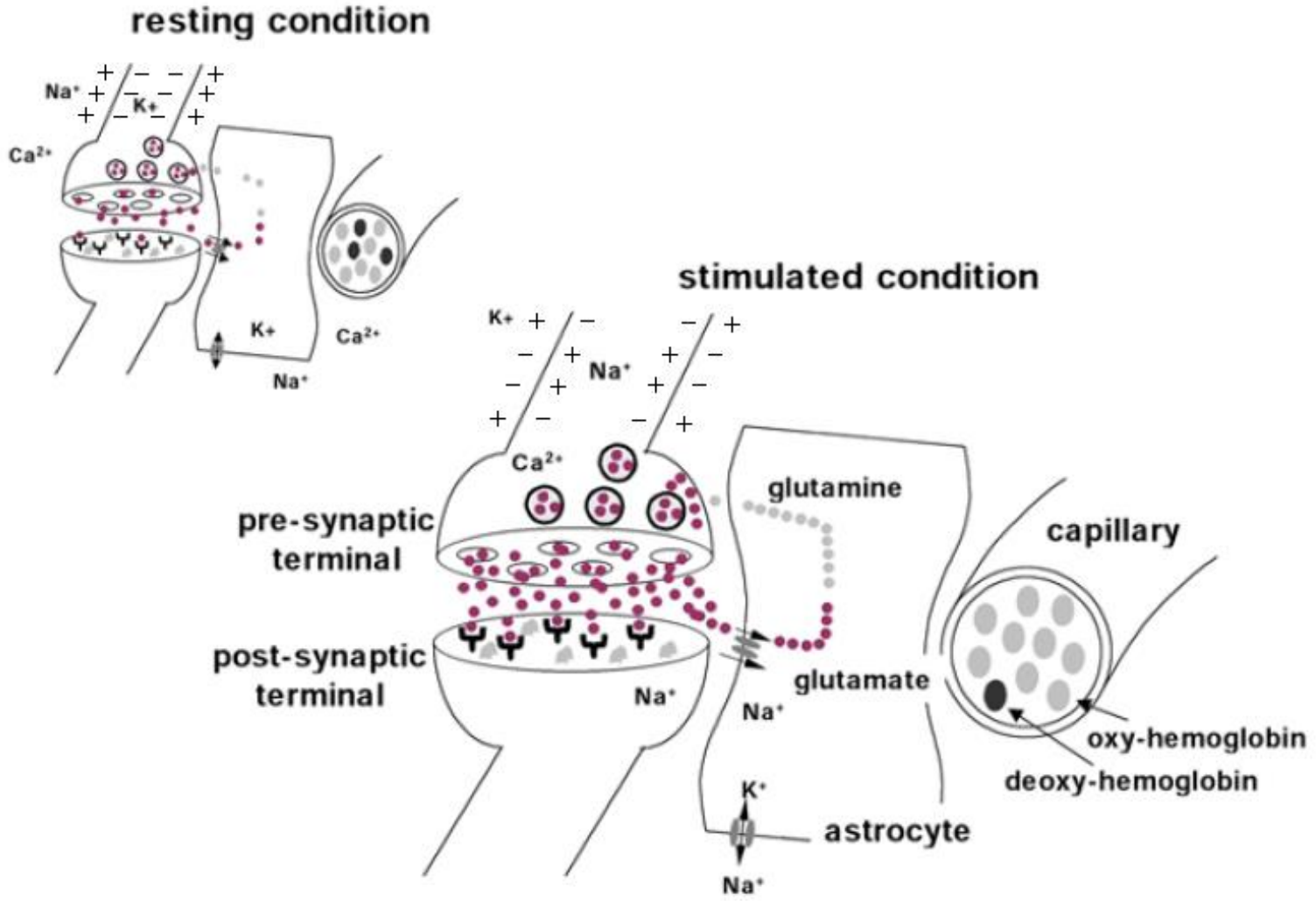


Kwong et al. ***PNAS*** 1992



Ogawa et al. ***PNAS*** 1992

Physiology during neural activation



Kida and Hyder, Magnetic Resonance Imaging Methods and Biologic Applications 2006; chapter 7.

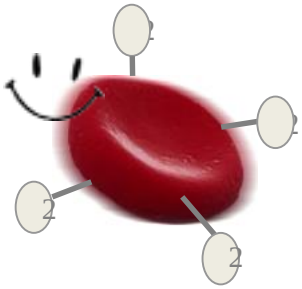
Energy during neural activation

- **Neuronal firing: electrical activity**
  - Excitatory and inhibitory
    - Neurotransmitter release and uptake
  - Action & graded potential
    - Ion flow
  - Hormone
- **Biochemical reaction: metabolic activity**
  - Active transport of ion pumps
  - Oxidative / non-oxidative glycolysis
- **Vascular response: hemodynamic activity**
  - Energy demand, clean up waste
  - Blood flow, blood volume, blood oxygenation

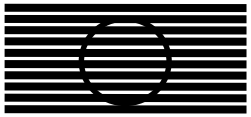
Blood oxygenation & MR signal

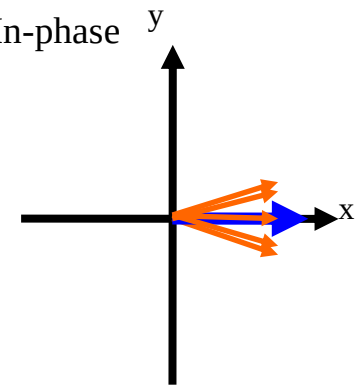
Oxygenated Hemoglobin

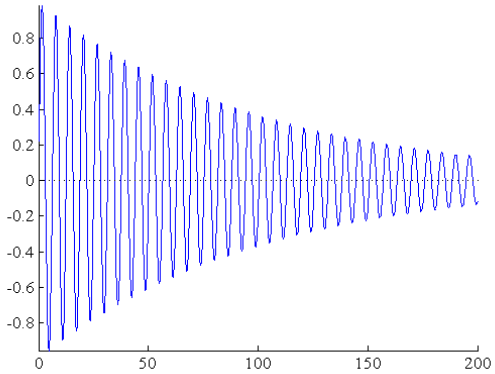
(Oxy-Hb)



Diamagnetic→
Same as body tissues
Homogeneous field



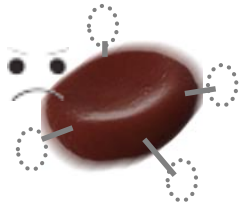




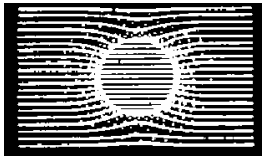
Oxy-Hb → MR signal increase!

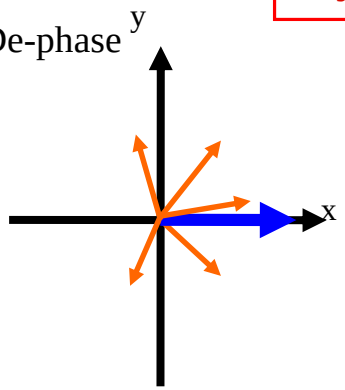
Deoxygenated Hemoglobin

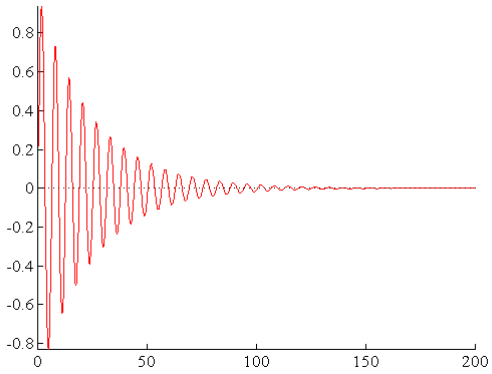
(Deoxy-Hb)



Paramagnetic→
Act as small magnet
Inhomogeneous field

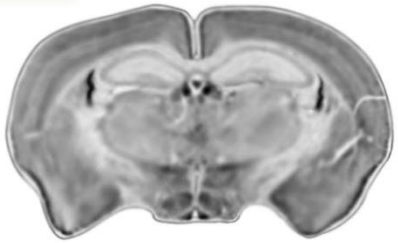




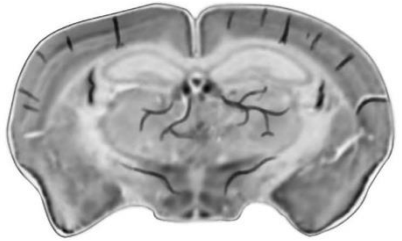


Blood Oxygenation Level-Dependent (BOLD)

Ogawa et al. ***PNAS*** 1990

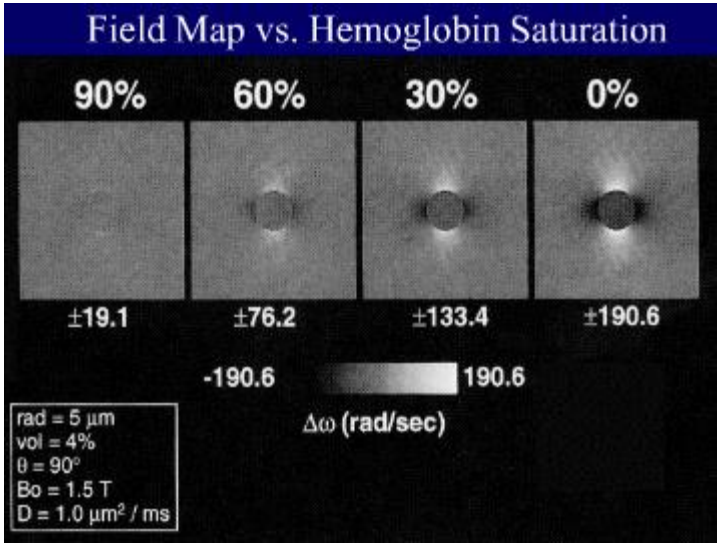


Inhalation of pure O_2



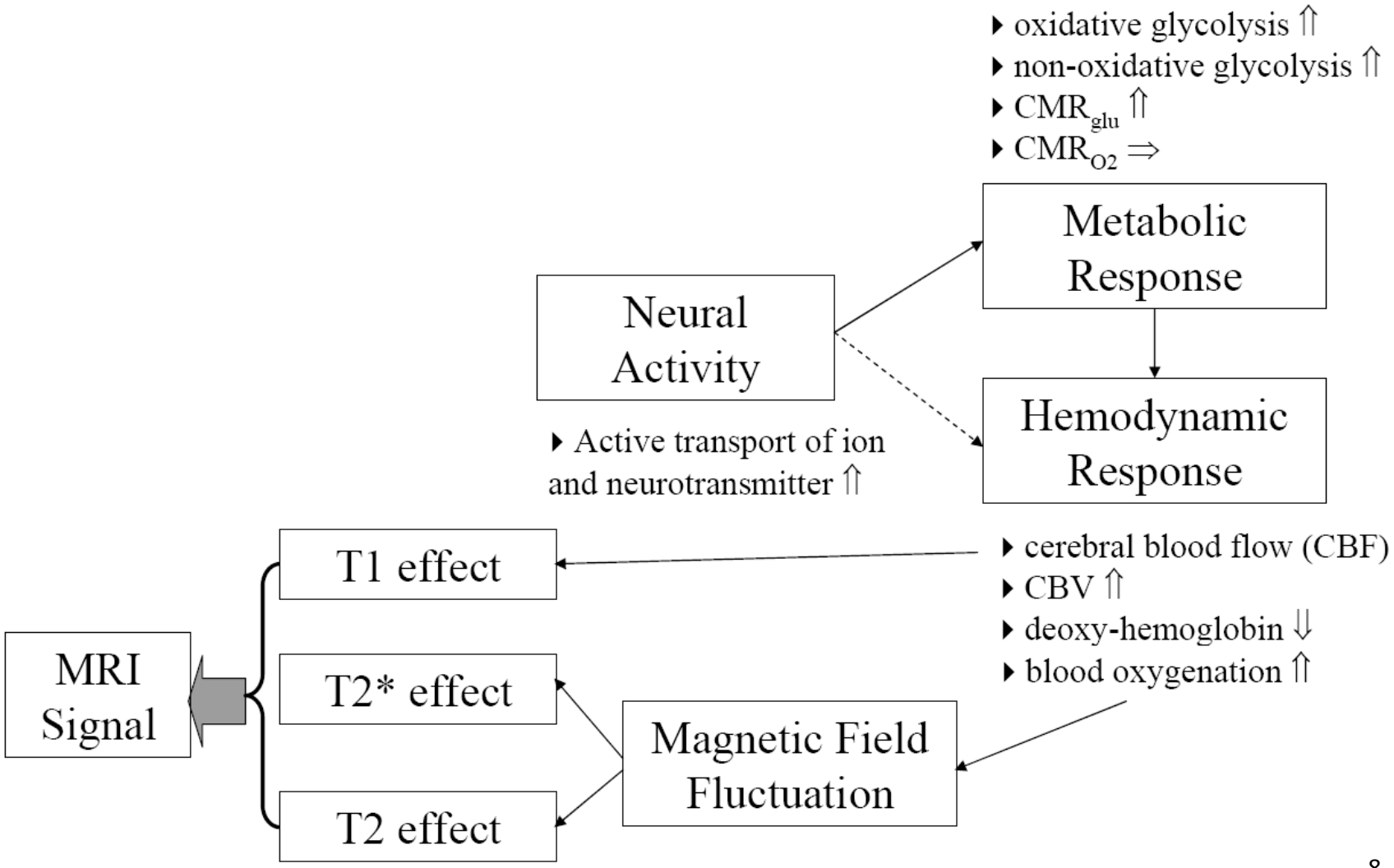
Inhalation of normal air

Hb Saturation (%, approx.)		
	resting	active
arterioles	90	90
capillaries	80	90
veins	60	90



Bandettini and Wong. ***Int'l J Imaging Systems and Technology*** 1995

BOLD fMRI physiology



Imaging method - contrast type

- **Gardient echo vs. spin echo**
  - Contrast: T2* vs. T2 sensitive
  - Singal: GE > SE (3-4 folds)
    - $\Delta R2^*/R2^* > \Delta R2/R2$
  - Localization: SE > GE
    - SE: micro-vasculartur e (capillary)
    - GE: macro-vasculartur e (draining vien, capillary)
  - Artifacts: GE > SE
    - susceptibility, distortion
  - Acquistion time: SE > GE

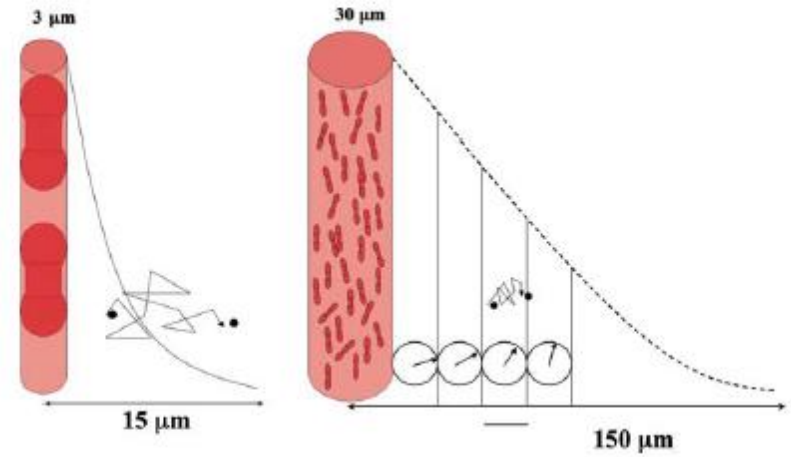
Blood vessel effect

- **Capillary**
  - Diffusion distance > gradient difference
  - Irreversible dephasing
  - T2 shorten by diffusion
  - Stronger T2 effect => SE

$$S(t) = S_0 e^{-t/T2}$$

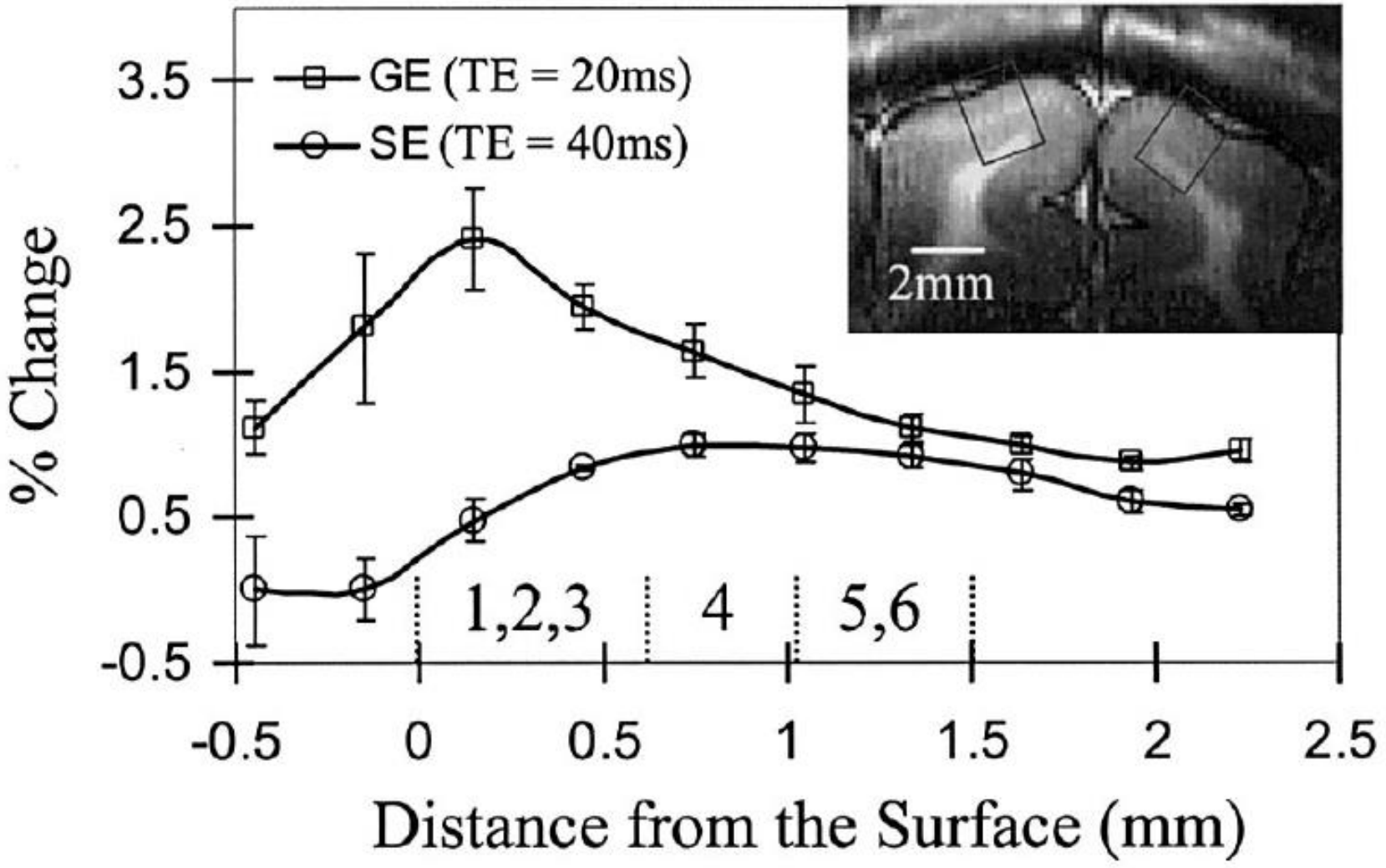
- **Large blood vessel**
  - Diffusion distance << gradient difference
  - Reversible dephasing
  - T2* shorten by average of spin
  - Stronger T2* effect => GE

$$S(t) = \sum_j S_{0j} e^{-t/T2_j} (e^{-i\omega_j t_j})$$



- Kim et al., Methods 2003; 30: 28-41.

GE vs. SE BOLD fMRI



- Zhao, et al., MRM 2004; 51: 518-524.

Imaging method - pulse sequence

- **k-trajectory**
  - Fast (s per slice): FLASH / FSE
    - Higher SNR, less off-resonance artifacts
  - Ultra-fast (0.1s per slice): EPI
    - Highly sensitive to T2* - > high BOLD signal
    - Subsecond resolution -> whole brain
    - Less physiological fluctuation
    - Less motion artifact
    - Less inflow artifact (infinite TR)
  - 2D /3D

Imaging method – 2D / 3D

- 2D multi-slice vs. 3D

	3D	2D
Benefit	• Rectangular slice profile • Thin slice / high resolution • Can generate arbitrary view from data • High SNR due to signal averaging of z axis (phase encoding)	• Faster • Less motion artifact
Pitfall	• Long scan time • Motion artifact • Aliasing artifact in z	• Imperfect slice profile (slice crosstalk) • Hard to get thin slice (anisotropic resolution)

Imaging parameters

- Important parameters:
  - TR, TE, slice thickness, matrix size, field-of-view, bandwidth, slice order, slice gap, flip angle
- Tradeoff among SNR, CNR, spatial/temporal resolution
  - BOLD contrast, imaging speed, volume coverage, spatial resolution, image SNR, sensitivity to physiological activity, motion

Tradeoff among SNR, CNR, resolution

- **TR:** temporal resolution, inflow effect, SNR, slice number
- **TE:** =T2*
- **FA:** inflow effect
- **BW:** SNR, image acquisition time; EPI: T2* blur, distortion, chemical shift
- **FOV:** spatial resolution, SNR
- **Matrix size:** spatial resolution, SNR, imaging time
- **Slice thickness:** spatial resolution, SNR, volume coverage, partial volume
- **Slice number:** volume coverage, temporal resolution
- **Slice order/gap:** slice cross-talk

SNR and CNR

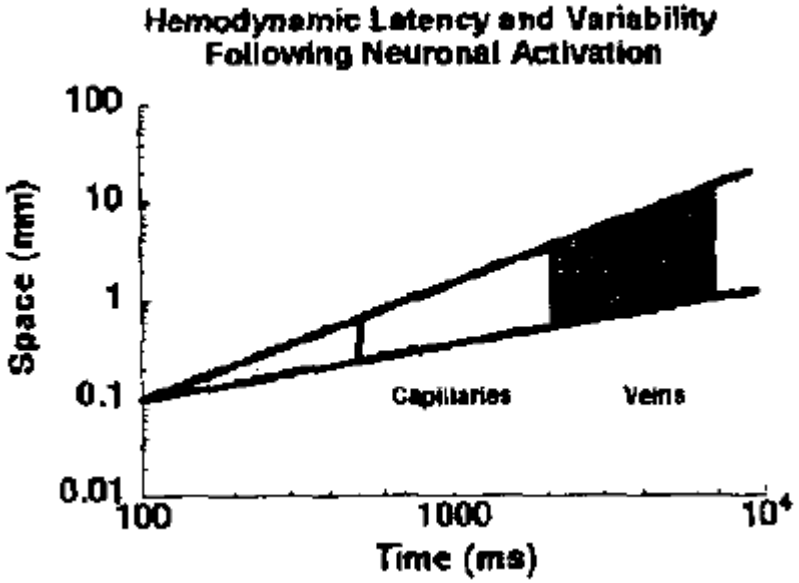
- **Signal-to-noise ratio (SNR)**
  - The most critical concern
  - Voxel size, BW, matrix, TR, FA
  - Optimal flip angle: Ernst angle $\alpha = cos^{-1}(e^{-TR/T1})$
- **Contrast-to-noise ratio (CNR)**
  - Voxel size: partial volume effect
  - Optimal TE = T2* of gray matter (30-40 ms @ 3T)

$$\frac{\Delta S}{N} = \frac{S_0}{N} e^{-TE\ R2^*}(TE\ \Delta R2^*)$$

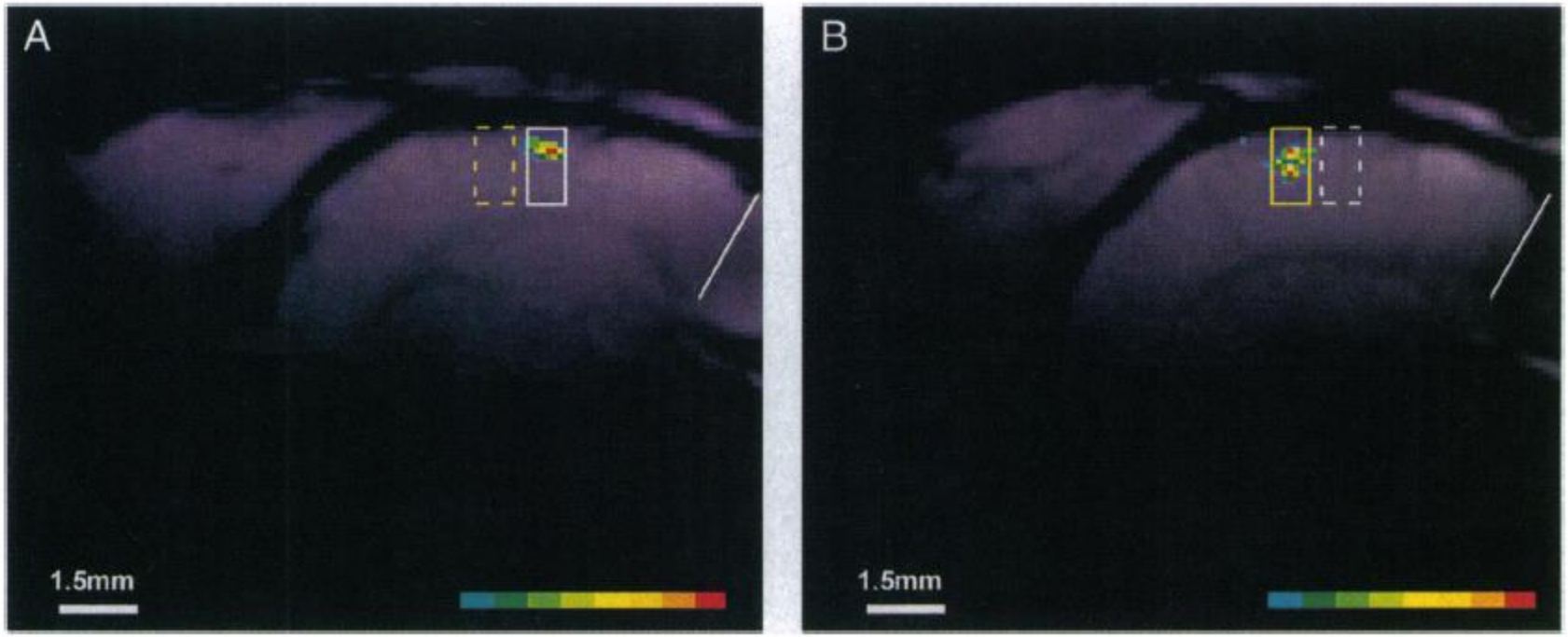
$$\propto \Delta R2^*/R2^* \quad \text{(when TE = T2*)}$$

Limitations

- Temporal
  - The shortest neural activity
- Spatial
  - The accuracy of spatial localization

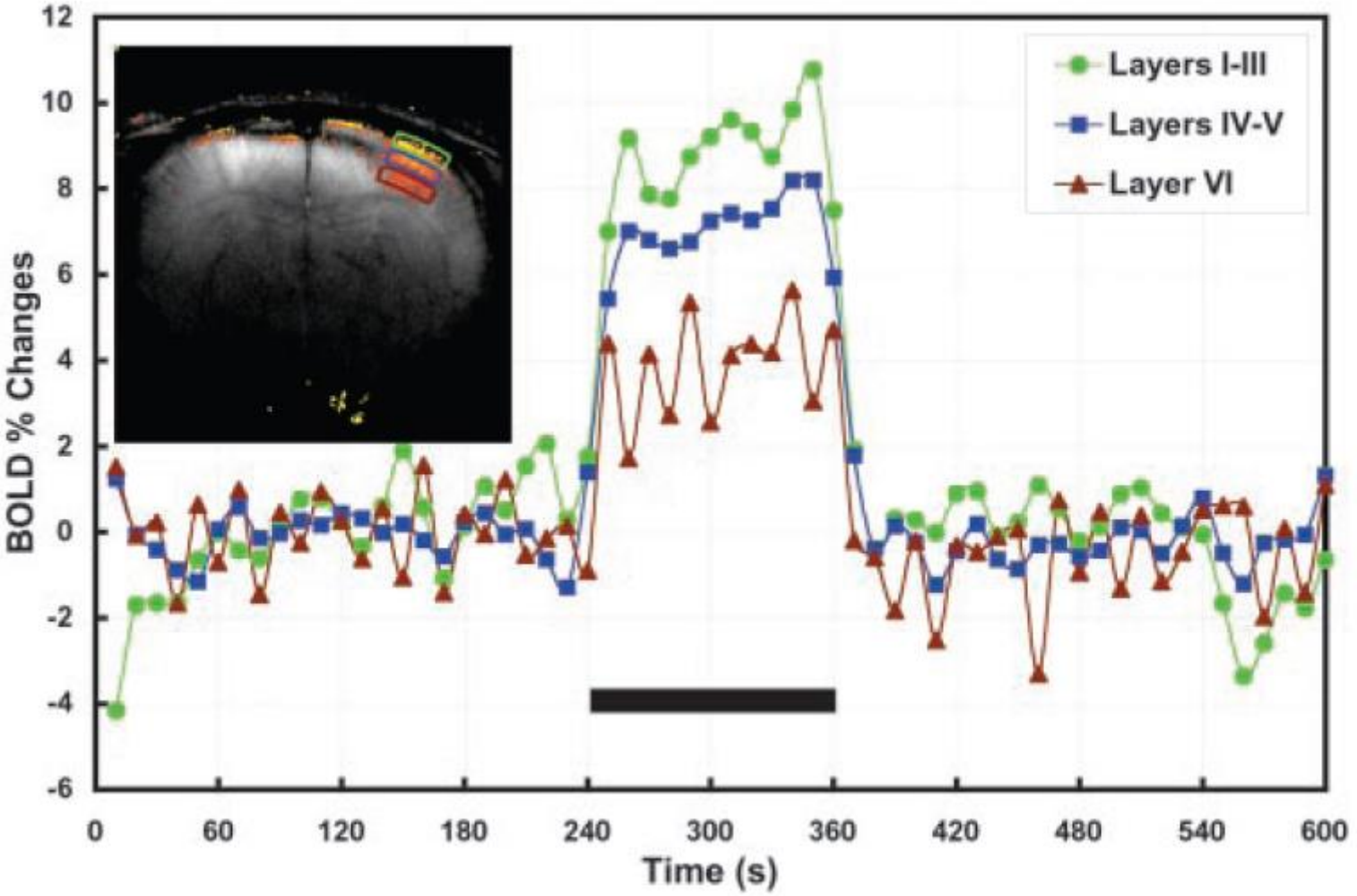


BOLD fMRI: rat whisker



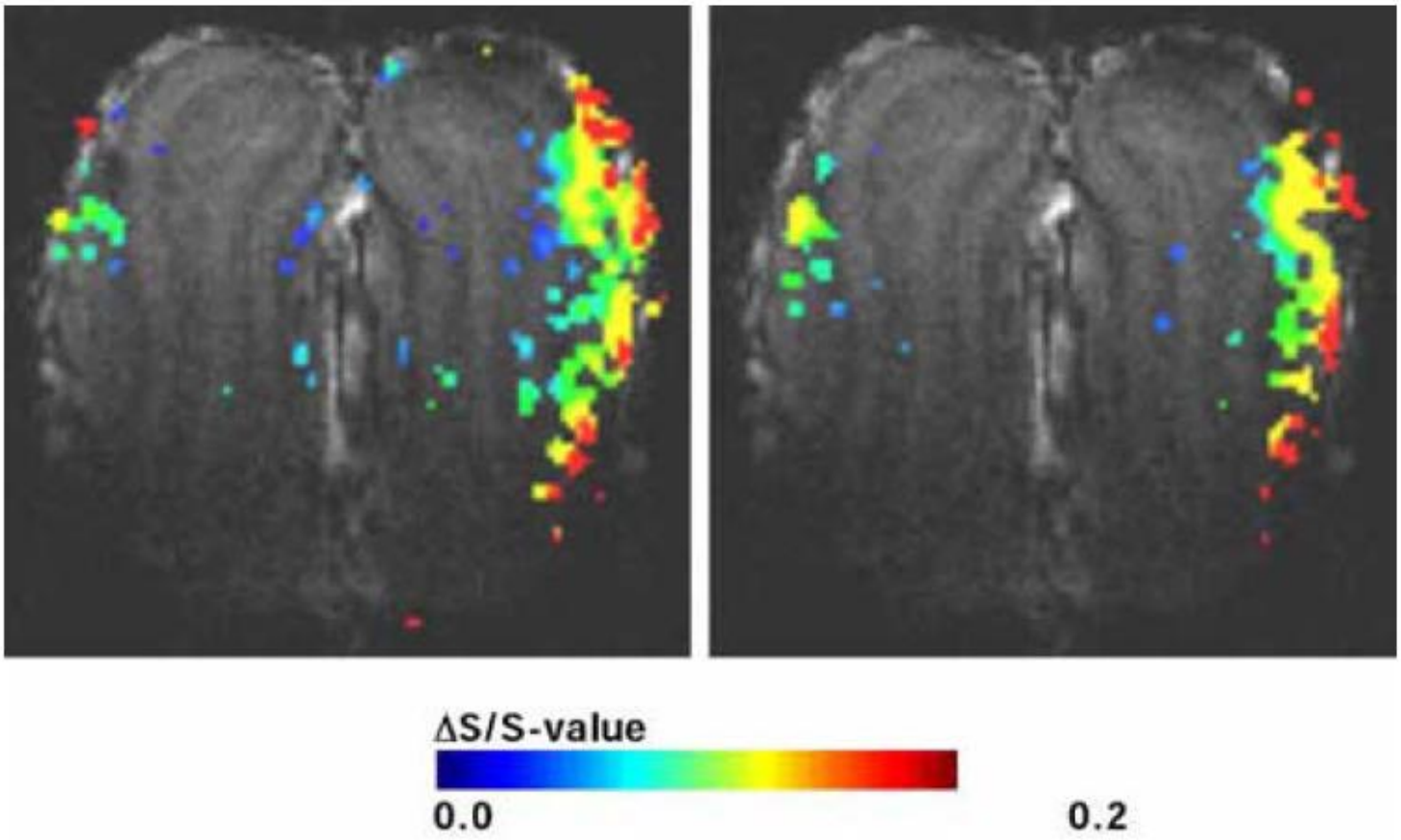
- Yang, et al., PNAS 1996: 93: 473-478.

BOLD fMRI: laminar layers



- Silva and Koretsky, PNAS 2002; 99(23): 15182-15187.

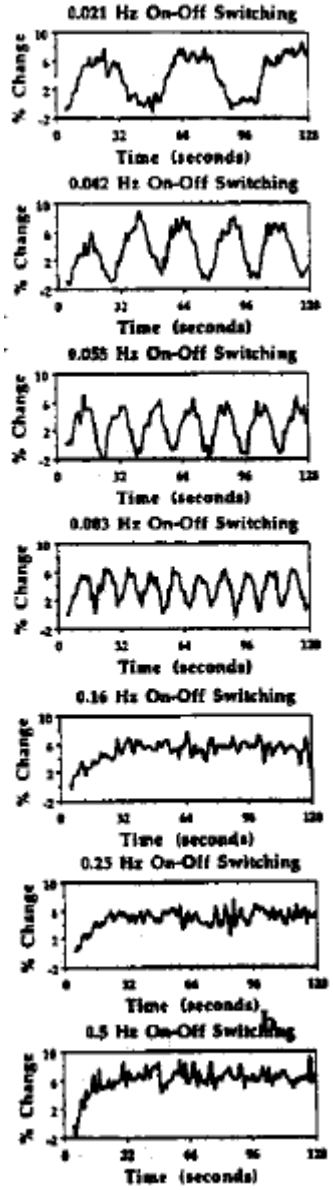
BOLD fMRI: olfactory bulb



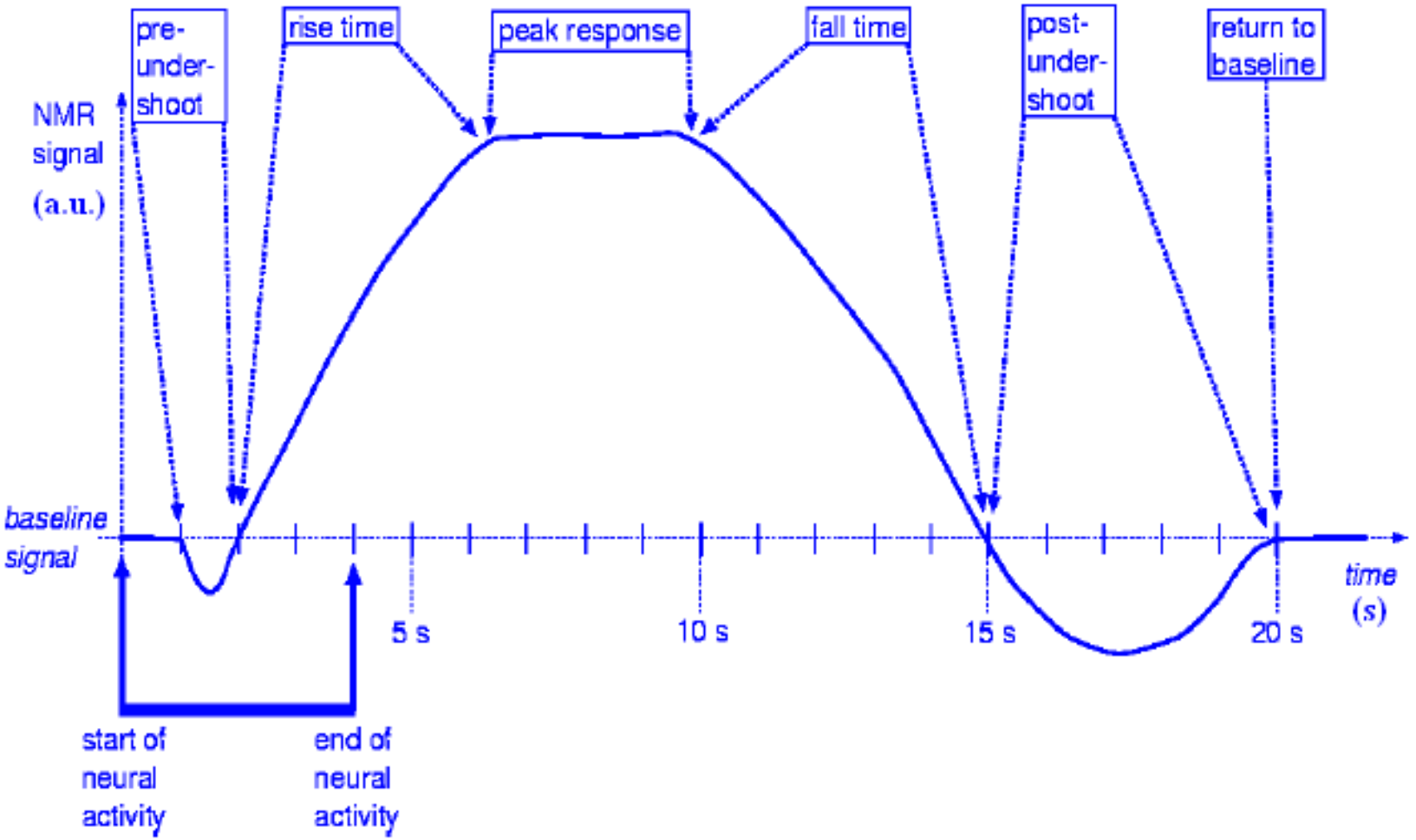
- Xu, et al., PNAS 2003; 100: 11029-11034.

Temporal resolution

- **Physiology**
  - Hemodynamic response resembles a low-pass filter
  - Time constant of the response function
  - Limit of stimulus duration
  - Detectability of difference in latency
    - Within one ROI
      - Deconvolution of HRF
      - Linear system assumption
    - Across ROIs
- **Hardware**
  - Image acquisition rate: tradeoff



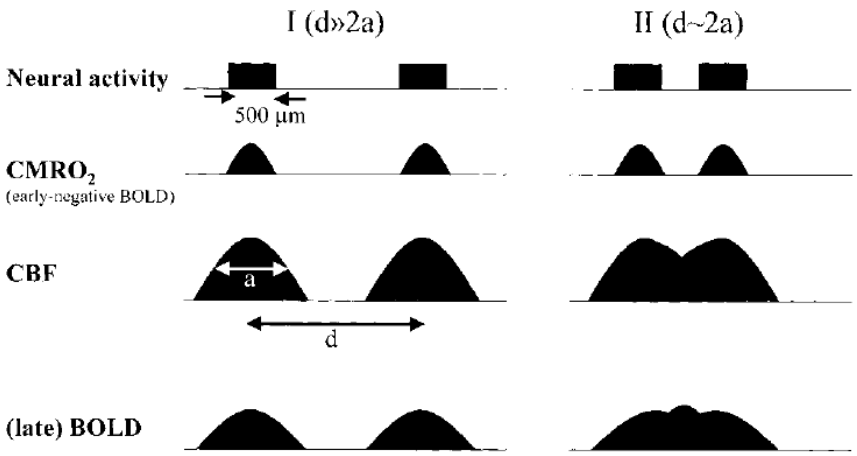
Hemodynamic response function

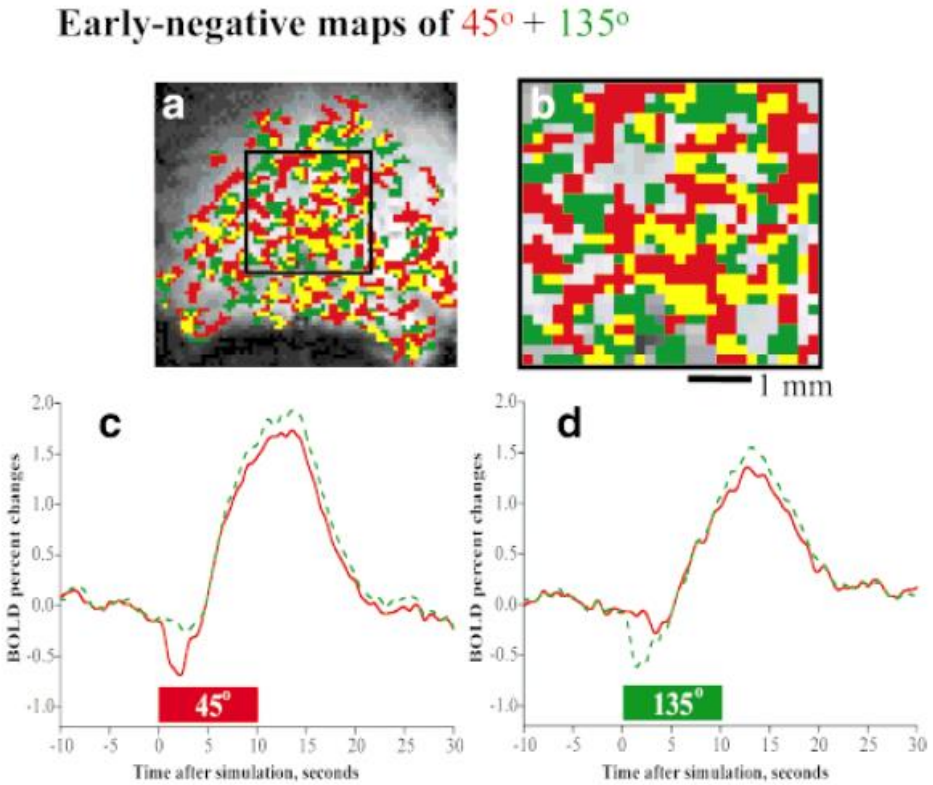


Variability of hemodynamics

- Temporal variability
  - Noise
    - 1% baseline fluctuation
  - HRF time constant variation
    - entire: 650ms; rise: 450ms; fall: 1250ms
  - Variation over space
    - +/- 2.5s

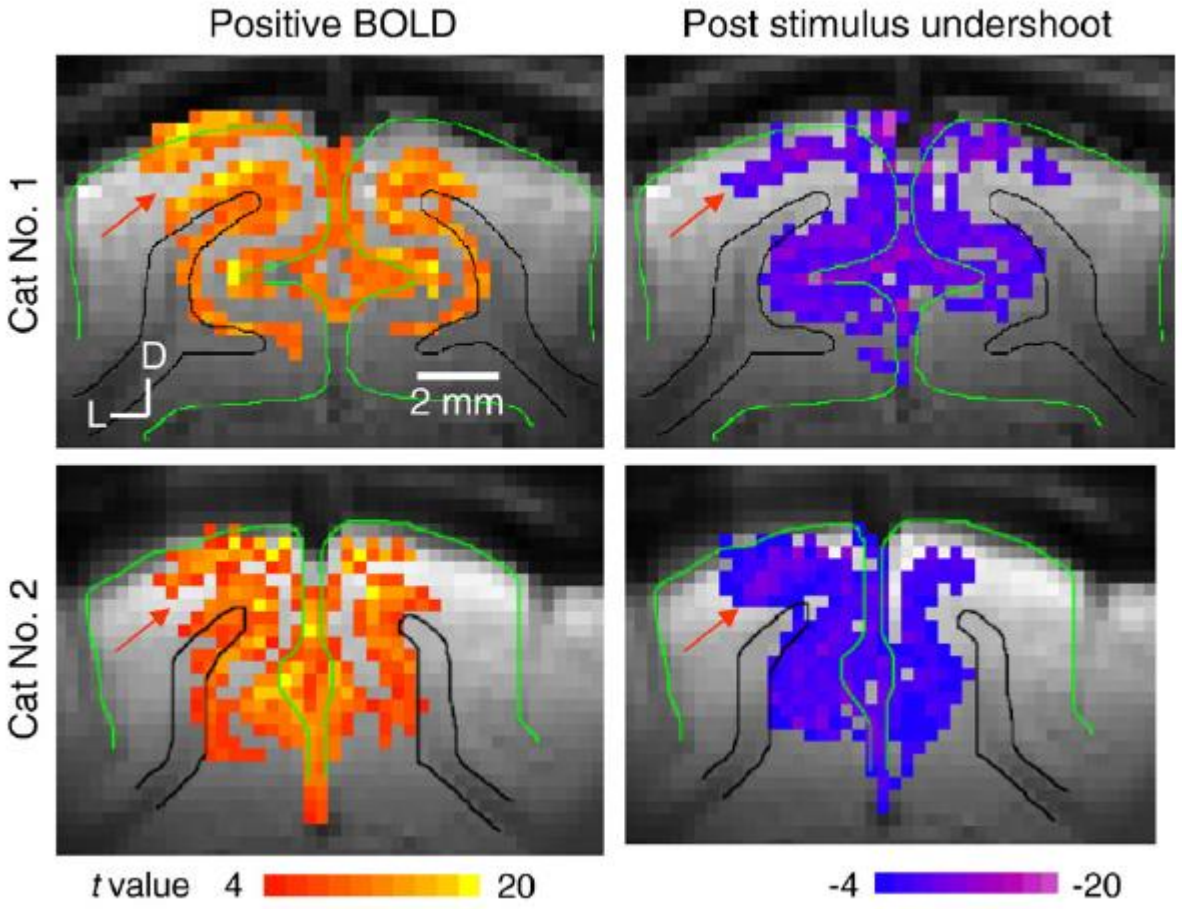
Initial dip: orientation columns in cat visual area





- Duong, et al., MRM 2000; 44:231-242

Undershoot: cat visual cortex



- Zhao, et al., NeuroImage 2007; 34: 1084-1092.

What's the temporal limit of

- Maximum on-off switch rate
- Minimum detectable activation duration
- Minimum detectable difference in activation duration or onset in same region
- Minimum detectable activation interval across separate brain regions
- Maximum image acquisition rate

Current temporal limit

- Maximum on-off switch rate
  - 4 s to 8 s duration cycles
- Minimum detectable activation duration
  - 30 ms
- Minimum detectable difference in activation duration or onset in same region
  - 100 ms
- Minimum detectable activation interval across separate brain regions
  - 100 ms with normalization
- Maximum image acquisition rate
  - 64 images per sec

Spatial resolution

- Consideration
  - CNR & SNR
  - Large vessel
    - Vessels that can not resolved by high resolution image
    - Large vein has larger signal change

      -> significant at low CNR/SNR
  - Spatial limitation of hemodynamic response
    - Point spread function

Spatial limit - CNR

- **Signal**

$$\Delta S = \rho S_0 (e^{-TE\Delta R2^*} - 1)$$

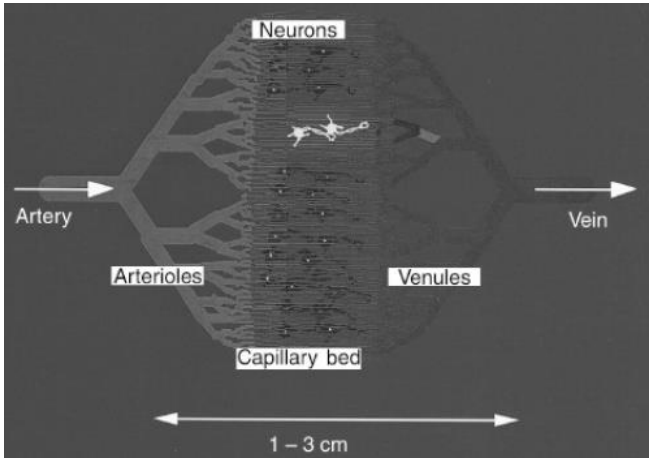
  - S_0: control state signal
    - Proportional to voxel volume
  - ρ: active volume
  - Solution: coil, higher-field
- **Noise**
  - Random noise
  - Physiological
  - Head motion
  - System instability

} location-dependent

Spatial limit - macrovasculature

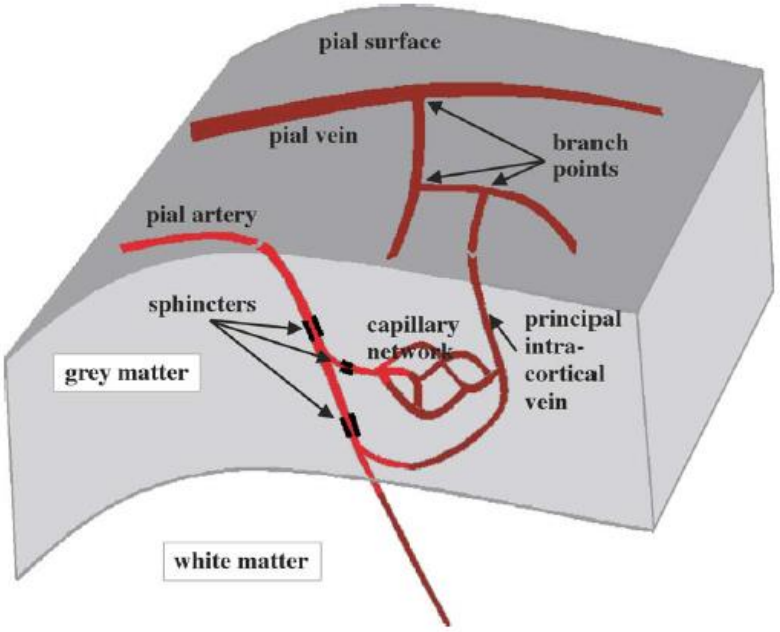
- **Inflow effect**
  - Esp for sequence using multiple excitation
  - Solution
    - Longer TR (full relaxation)
    - Shorter flip angle
    - Spin echo
- **BOLD (T2* effect)**
  - Venous T2/T2* will change during activation

    -> spin-echo also affected
  - Draining/large vein effect
  - Solution
    - Bipolar gradient -> suppress flowing spin in large vessels



Spatial limit - macrovasculature

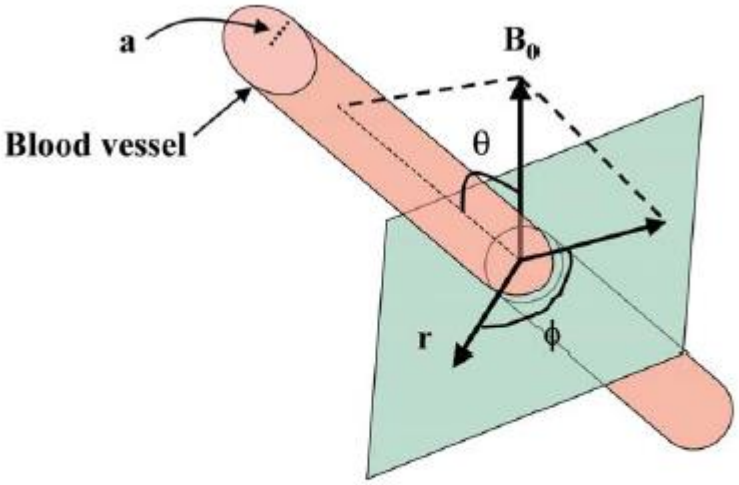
- Reduce signal from large draining vein
  - Spin-echo
  - Bipolar gradient



- de Zwart et al., NeuroImage 2005; 24: 667-677.

Blood vessel effect

- Susceptibility difference: $\Delta\chi(\fallingdotseq 0.27$ ppm at $37^{o}C)$
- Deoxy-Hb concentration: 1-Y
- Vessel size: a
- Vessel orientation: θ, ψ
- Distance: r

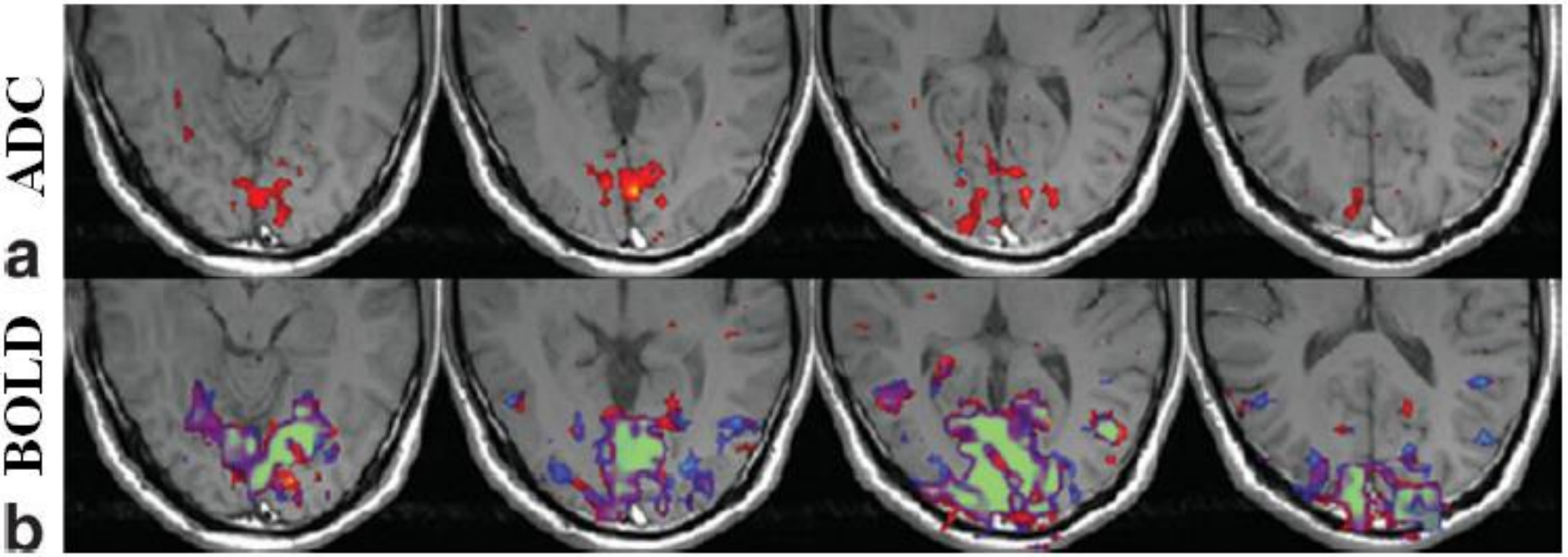


$$\Delta\omega_{in} = 2\pi\,\Delta\chi_0\,(1 - Y)\,\omega_0\,(\cos^2\theta - 1/3)$$

$$\Delta\omega_{out} = 2\pi\,\Delta\chi_0\,(1 - Y)\,\omega_0\,(a/r)^2\,(\sin^2\theta)\,(\cos 2\phi)$$

- Kim et al., Methods 2003; 30: 28-41.

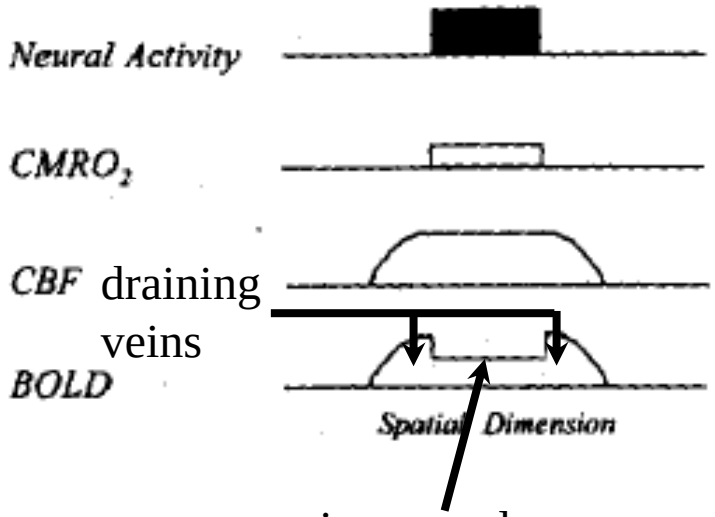
Biopolar gradient: human visual cortex



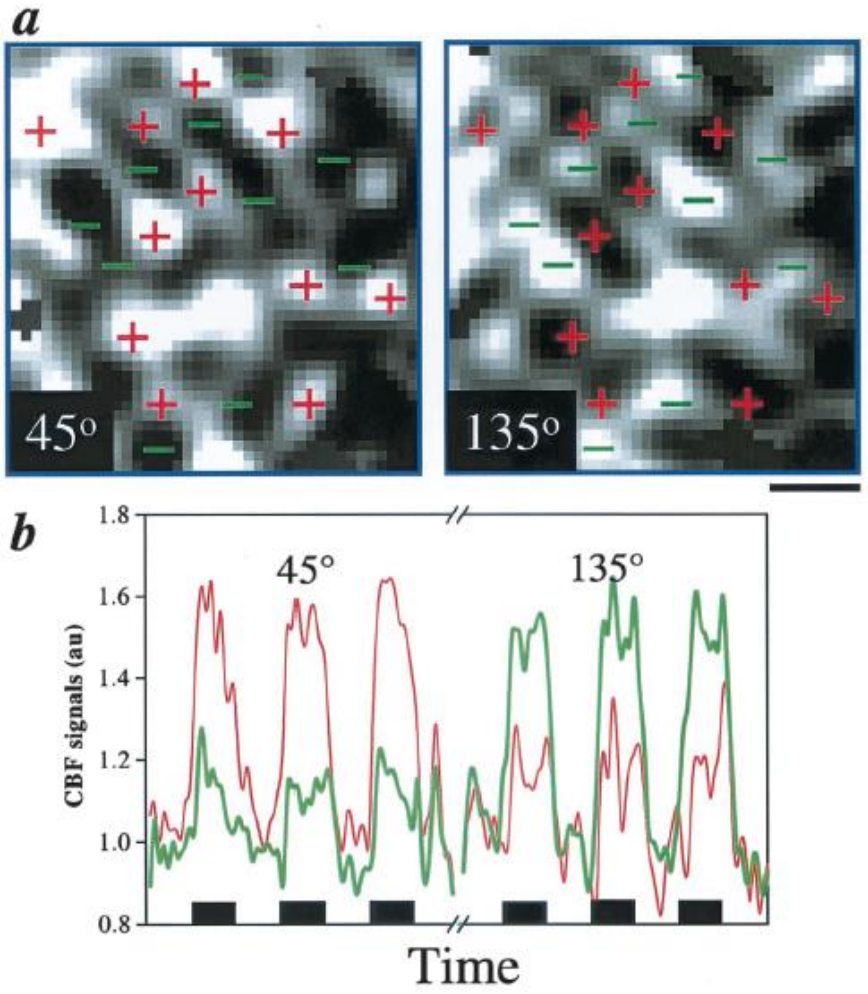
- Song, et al., MRM 2007 57: 417-422.

Spatial limit - hemodynamic

- Electrical activity
- Metabolic activity (closer)
  - Synaptic activity may increase in inactive neuron
- Hemodynamic activity (farther)
  - CBF
  - BOLD
    - Early negative response (closer)
    - Late positive response (farther)
- Assume CMRO2 is exact
  - Largest signal is away



CBF: orientation columns in cat visual area



- Duong, et al., PNAS 2001; 98: 10904-10909.

Interpretation of fMRI signal

- fMRI signal is an index of ensemble of neural activity
  - presumably monotonic relation
- Neural source of BOLD signal is not clear
  - spiking activities vs. synaptic activity
  - excitatory vs. inhibitory
- Difficult to compare fMRI signals across cortical regions and subjects
  - BOLD signal depend on vascular structure and volume

Other issues

- **Normal physiology condition**
  - Age
    - inferior vascular response for aged people (CBF decrease)
    - neonate: deoxyHb increase
  - Disease
    - transient global ischemia: vascular response abolished
    - carotid stenosis: vascular response diminish
  - Drug
    - alter vascular response, cardiopulmonary function,…
- **Meaning of negative response**
  - Negative response -> decreased activity?
  - Inhibitory activity also increase glucose uptake

Challenge of quantification

- **Electrical activity**
  - Tiny perturbation in magnetic field: MRI phase
  - Ca^{2+} : manganese (Mn^{2+}) enhanced MRI
  - Glutamate, GABA : H^1-MRS
- **Metabolic activity**
  - Lactate : H^1-MRS
  - $CMRO_2$: combine CBF and BOLD
- **Hemodynamic activity**
  - Oxygenation: BOLD fMRI
  - CBF: Arterial Spin Labeling (ASL) MRI
  - CBV: contrast-injection / VASO

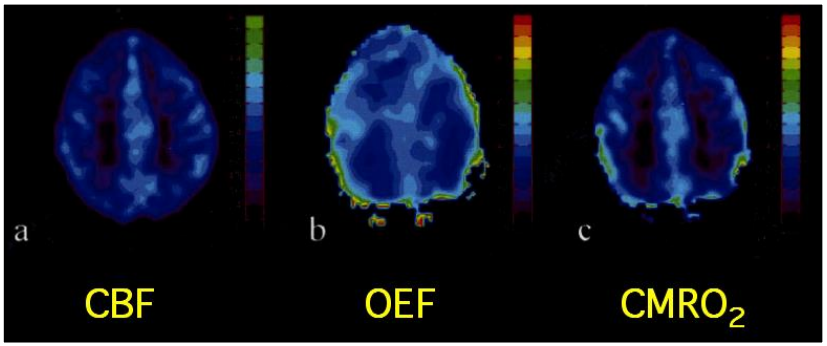
$CMRO_2$-based fMRI

- Biophysical modeling metabolism
  - Combine CBF (or CBV) & BOLD
  - *Fick's principle*

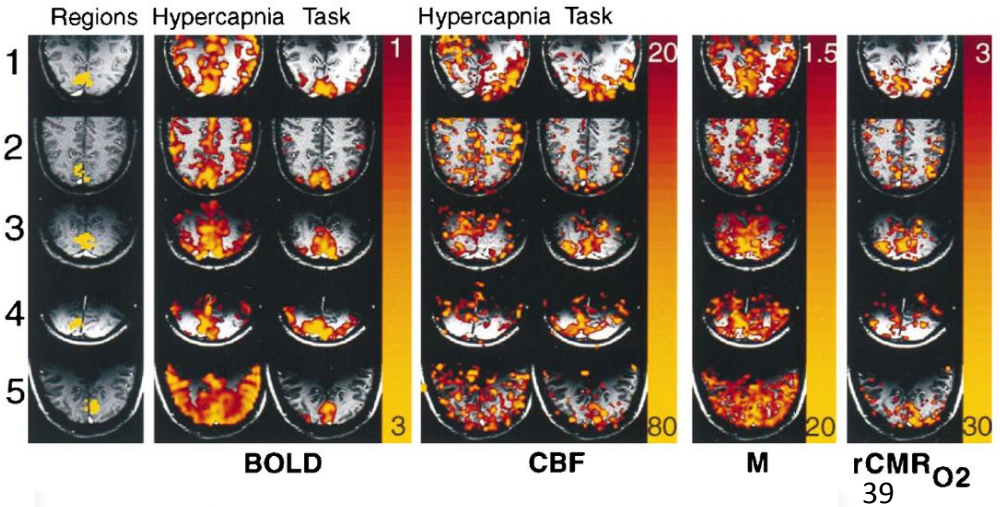
$$\frac{[\text{deoxy-Hb}]_v}{BOLD} = \frac{1}{4}\frac{CMR_{O_2}}{CBF}$$

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1 - \left(\frac{CMR_{O_2}}{CMR_{O_2}|_0}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right).$$

Hoge et al. ***Magn Reson Med*** 1999



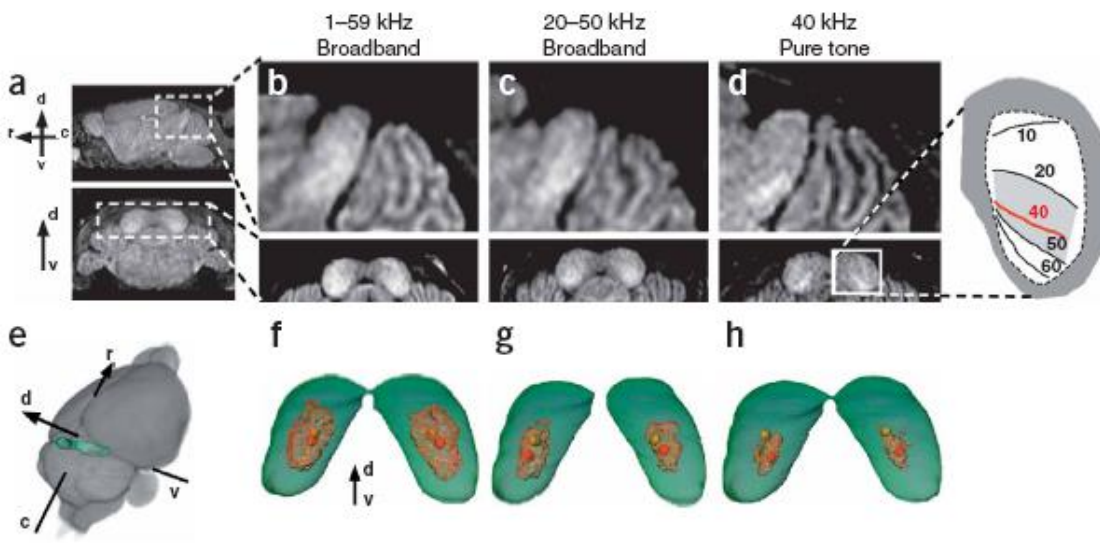
An et al. ***NMR Biomed*** *2001*



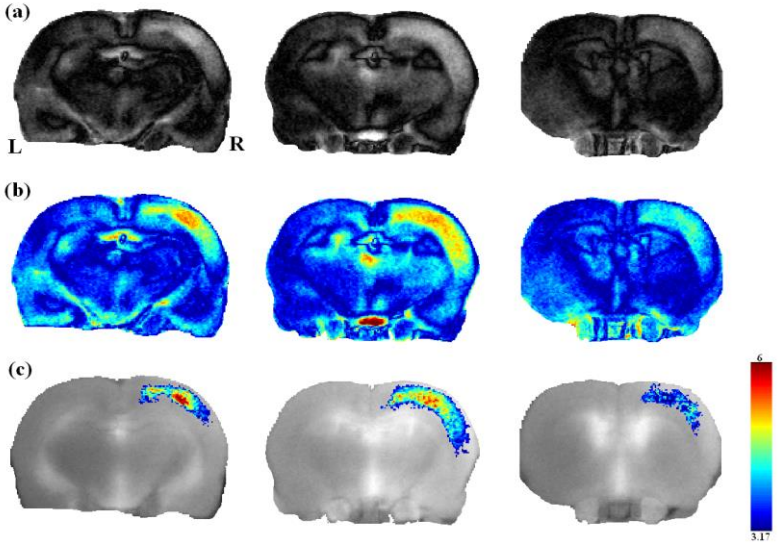
Davis et al. ***PNAS*** 1998

Manganese-enhanced MRI (MEMRI)

- Auditory and whisker stimulation studies



Yu, et al., Nature neuroscience 2005; 8: 961-968.



JC Weng et al., NeuroImage 2007; 36, 1179-1188.

Future of fMRI

Technology	Methodology	Neuroscience
High Spatial Resolution	**Pulse Sequence**	**Neurology**
Cortical layers Closer to neural activity	Diffusion fMRI msMRI Inverse imaging...etc	Aging Stroke Vegetative state / Coma
High Field Strength	**Experimental Design**	**Psychiatry**
Contrast / SNR Improvement	Freely-performing task fMR adaptation	Depression Autism Schizophrenia ...etc
Parallel Imaging	**Processing Methods**	**Social Neuroscience**
SNR / Resolution Enhancement	Multivariate Pattern Recognition (Brain Reading)	Attitude / emotion Interpersonal relations

- Bandettini et al. ***Int'l J. Psychophysiol.*** 2007

Take home message

- BOLD fMRI review
- Imaging method
- Imaging parameter
- Temporal resolution limitation
- Spatial resolution limitation
- Other issues

Thank you for your attention

May the force be with you