BOLD Physiology

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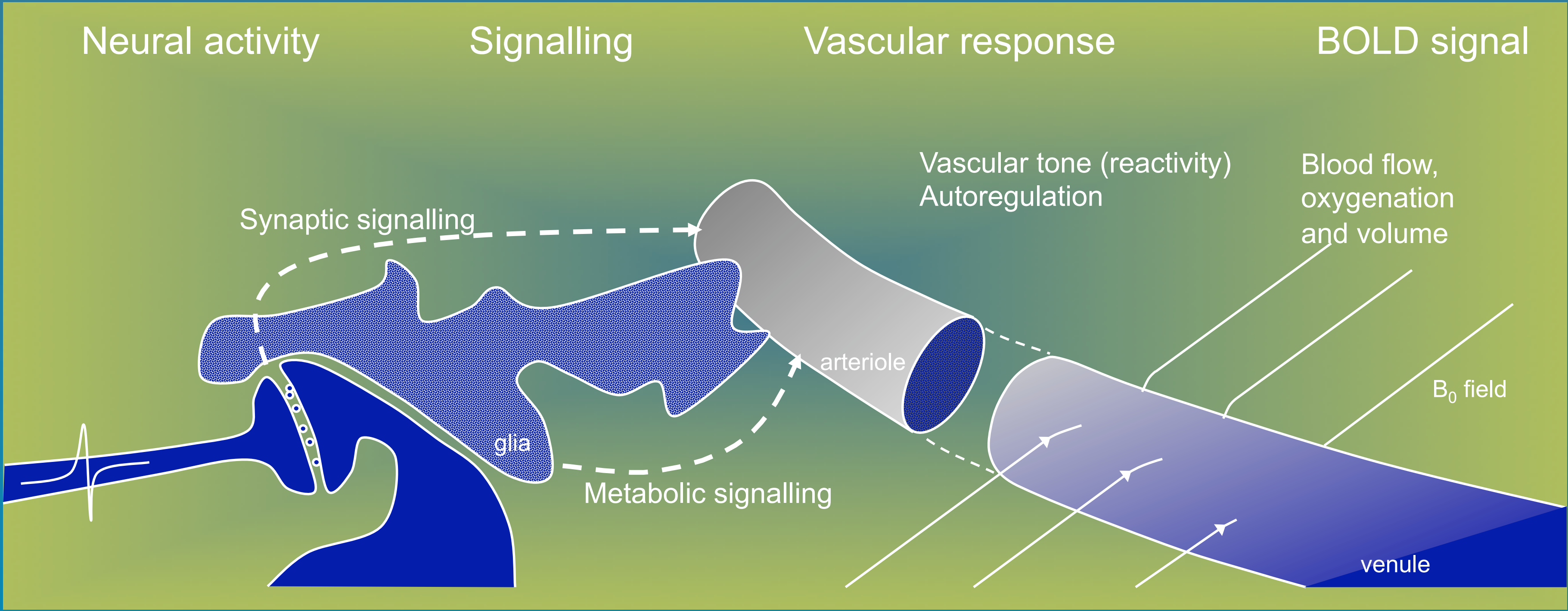
Overview

- BOLD Contrast
  - Metabolic and cerebral blood flow response
  - Mechanism of MR signal change
- Neurovascular coupling
- Noise
- Factors affecting BOLD
  - More detail
  - Changing physiological baseline
- Metabolic modelling

Blood
Oxygen
Level
Dependent
signal

T_2* change from the haemodynamic perturbation associated with neural activation

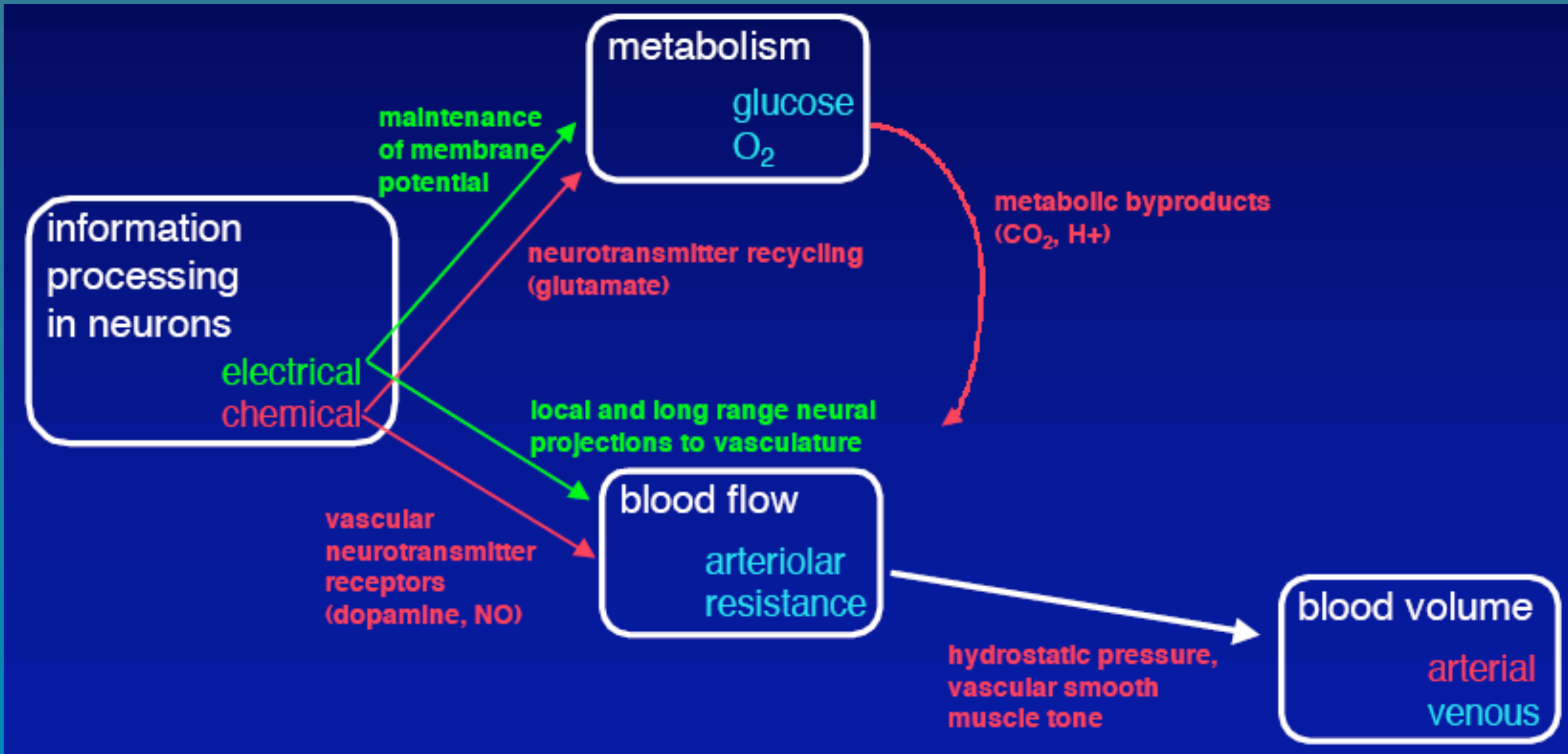
From neural activity to BOLD signal



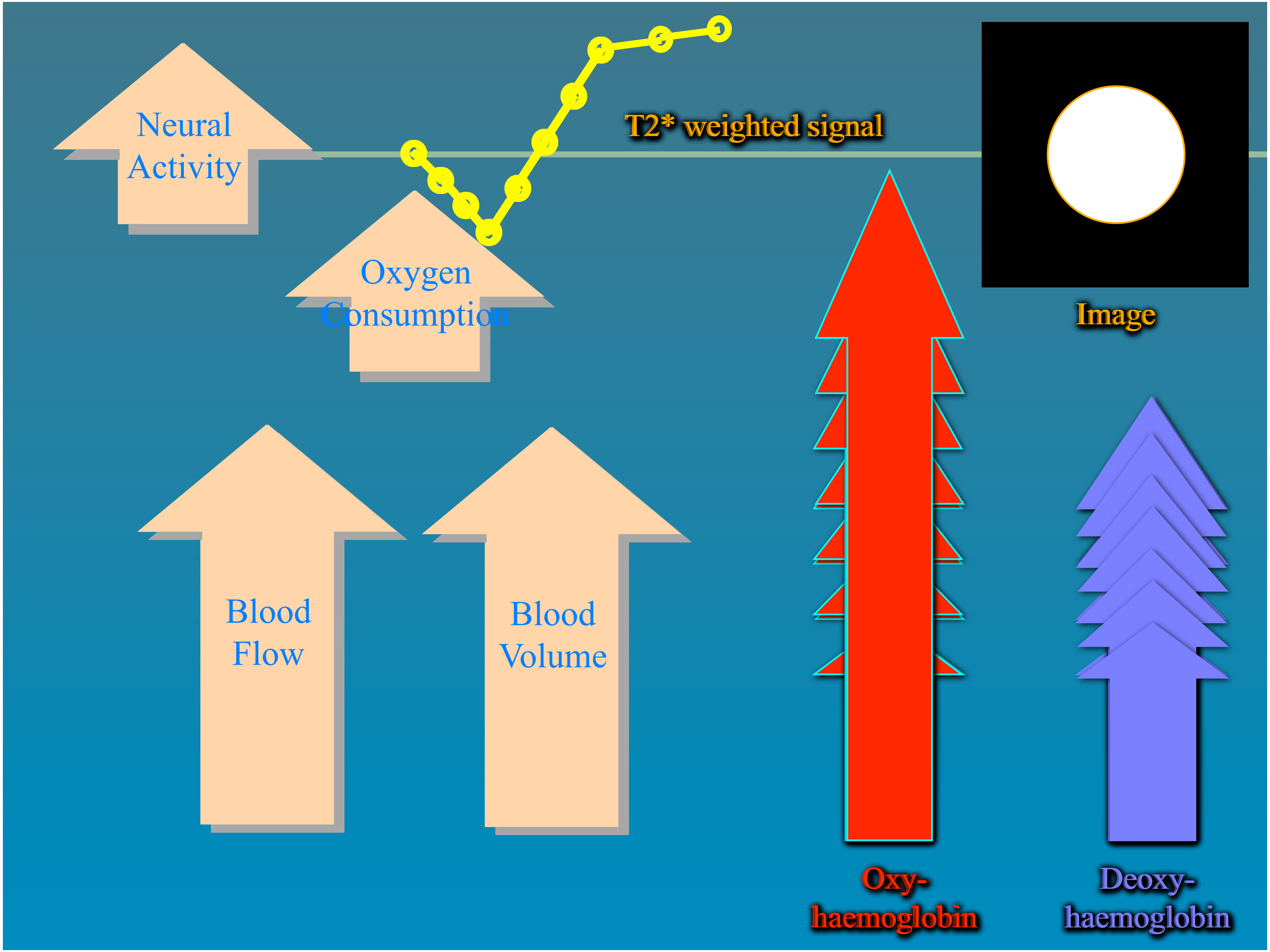
Factors affecting BOLD signal?

- Physiology
  - Cerebral blood flow (baseline and change)
  - Metabolic oxygen consumption
  - Cerebral blood volume
- Equipment
  - Static field strength
  - Field homogeneity (e.g. shim dependent T2*)
- Pulse sequence
  - Gradient vs spin echo
  - Echo time, repeat time, flip angle
  - Resolution

“Activation”

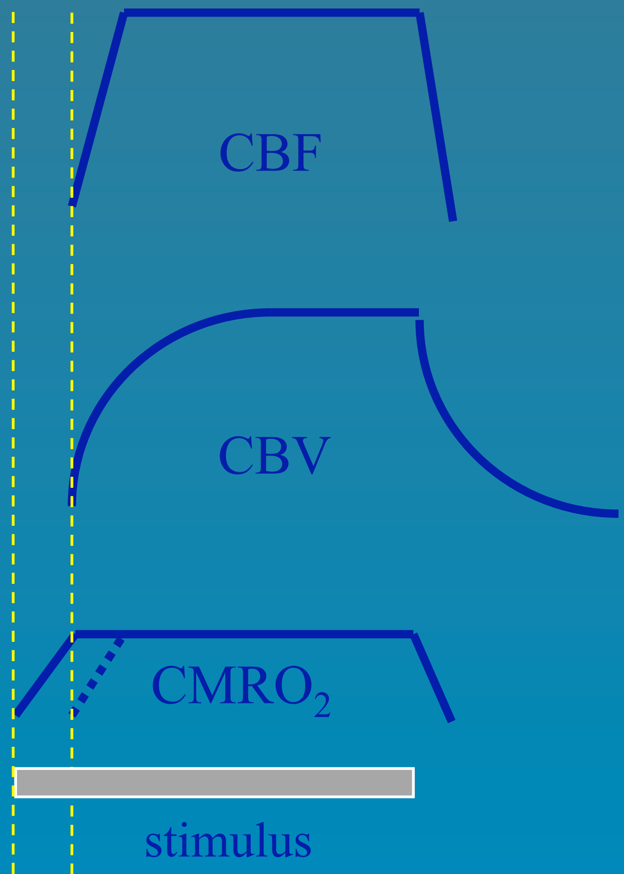


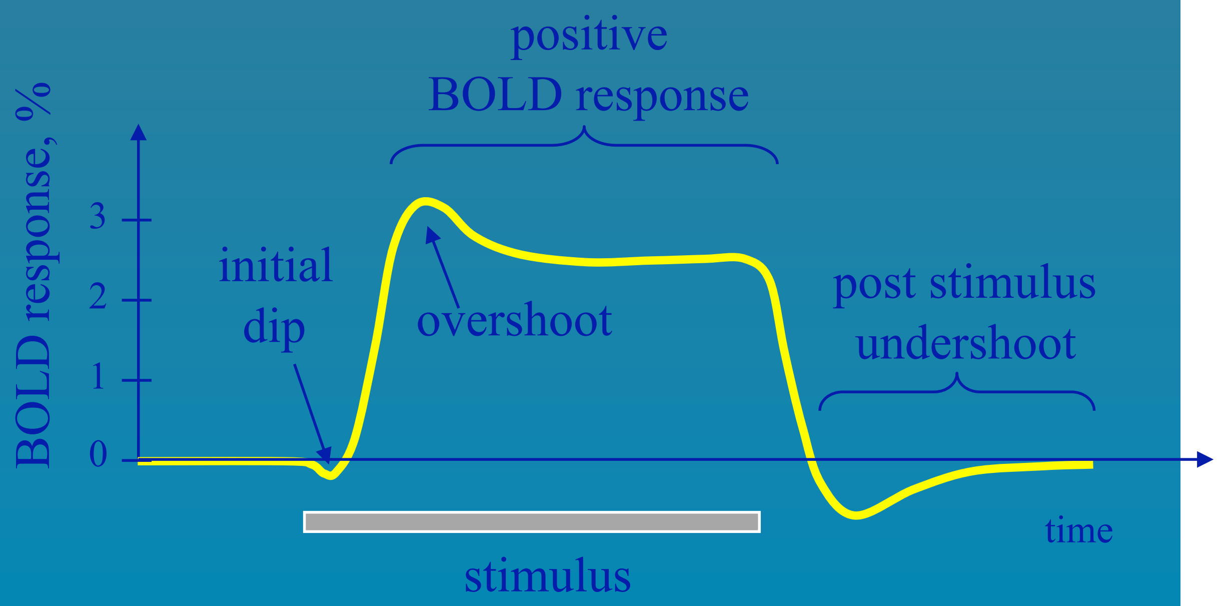
metabolism
glucose
O_2
maintenance of membrane potential
information processing in neurons
electrical
chemical
neurotransmitter recycling (glutamate)
metabolic byproducts (CO_2, H+)
local and long range neural projections to vasculature
blood flow
arteriolar resistance
vascular neurotransmitter receptors (dopamine, NO)
hydrostatic pressure, vascular smooth muscle tone
blood volume
arterial
venous



Neural Activity
Oxygen Consumption
T2* weighted signal
Image
Blood Flow
Blood Volume
Oxy-haemoglobin
Deoxy-haemoglobin

Heamodynamic changes underlying BOLD





BOLD contrast

- Transverse relaxation
  - Described by a *time constant*
  - Time for NMR signal to *decay*
    - Loss of spins phase coherence (out of step)
  - Spin echo, T2
    - Time varying field seen by diffusing spins
  - Gradient echo, T2*
    - Time varying field seen by diffusing spins
    - … plus spatial field variation across voxel
- Why is magnetic field non uniform?

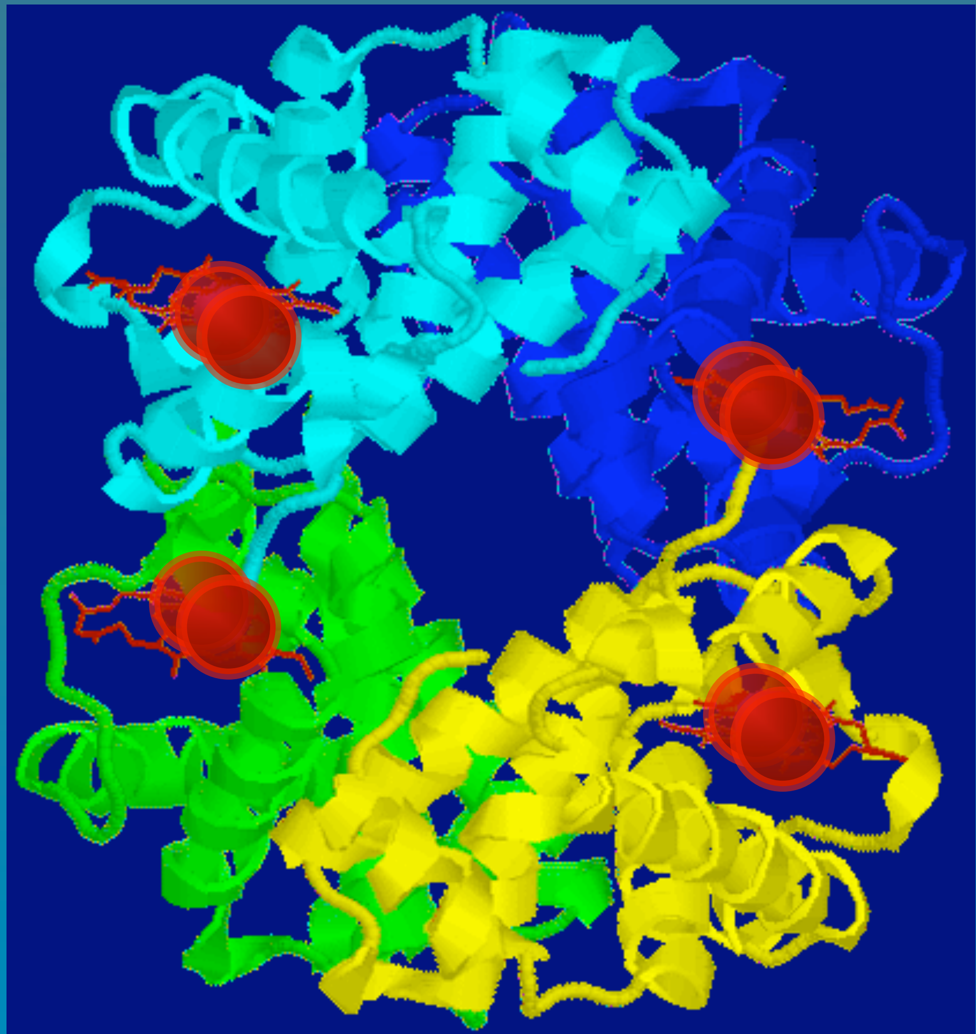
Deoxy-Haemoglobin

paramagnetic

different to tissue

$\Delta\chi$=0.08ppm

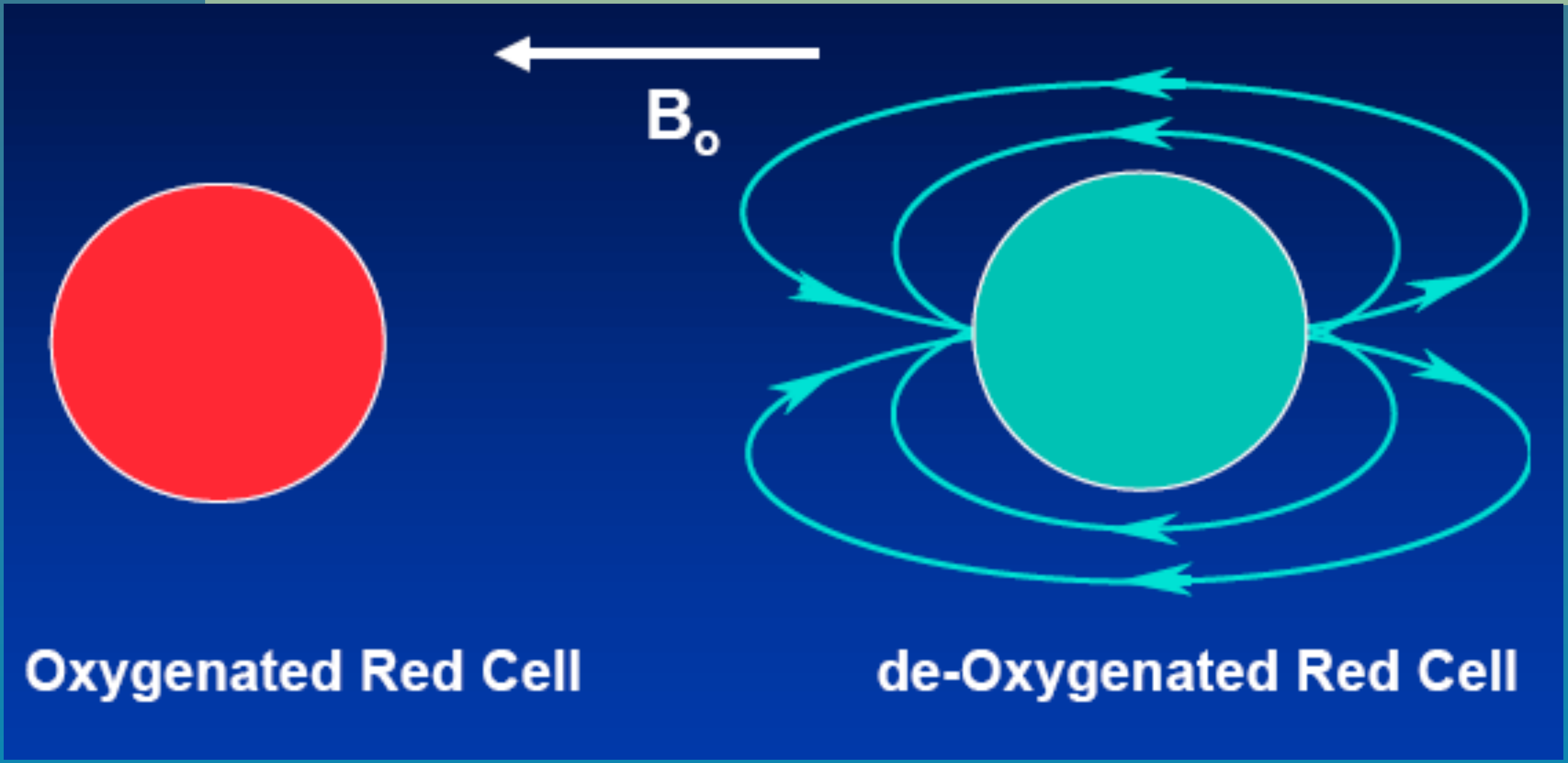
Oxy-Haemoglobin



diamagnetic

same as tissue

Field homogeneity & oxygenation state

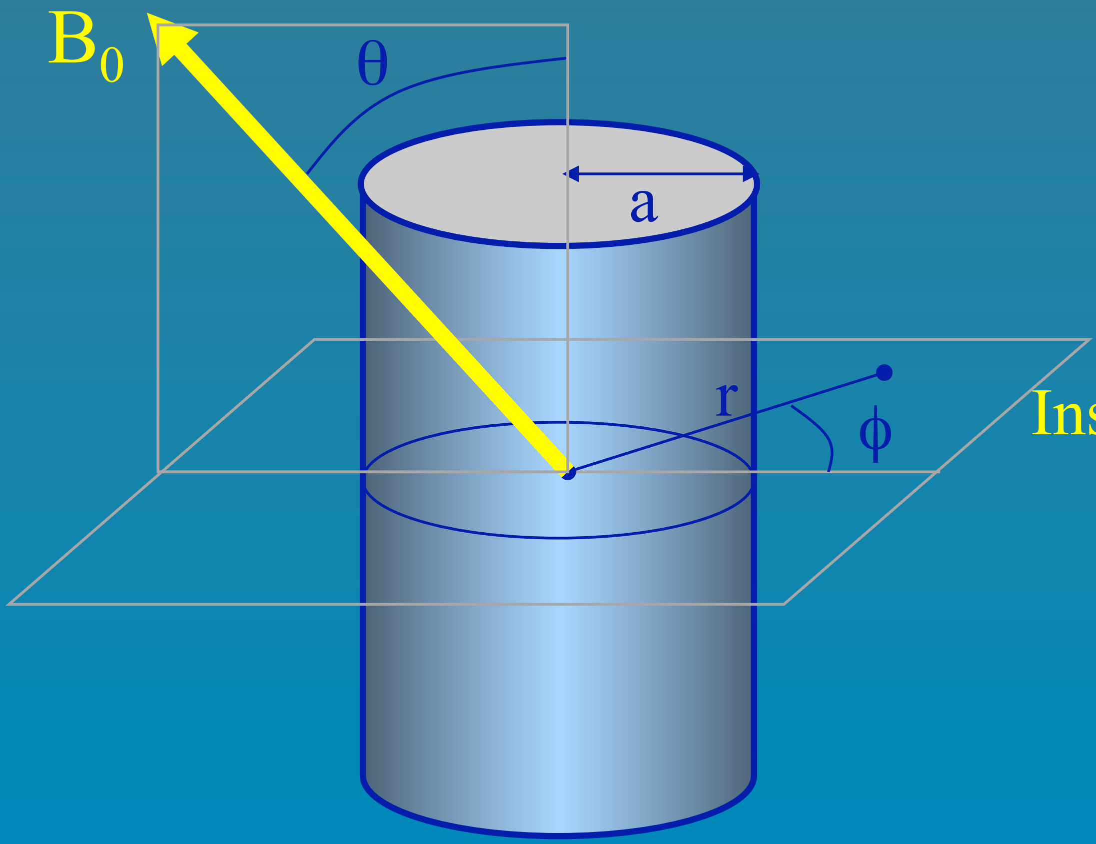


- Red blood cell
  - 6 μm diameter, 1-2 μm thick
- Susceptibility
  - An object with differing magnetic properties distorts the field

Water

- Freely diffusing water is the source of image signal
- Two water spaces
  - Intravascular (blood)
    - Capillaries and venules
  - Extravascular - a larger pool
    - In 50ms (FMRI TE) water diffuses 4 capillary diameters

Magnetic field in a vessel

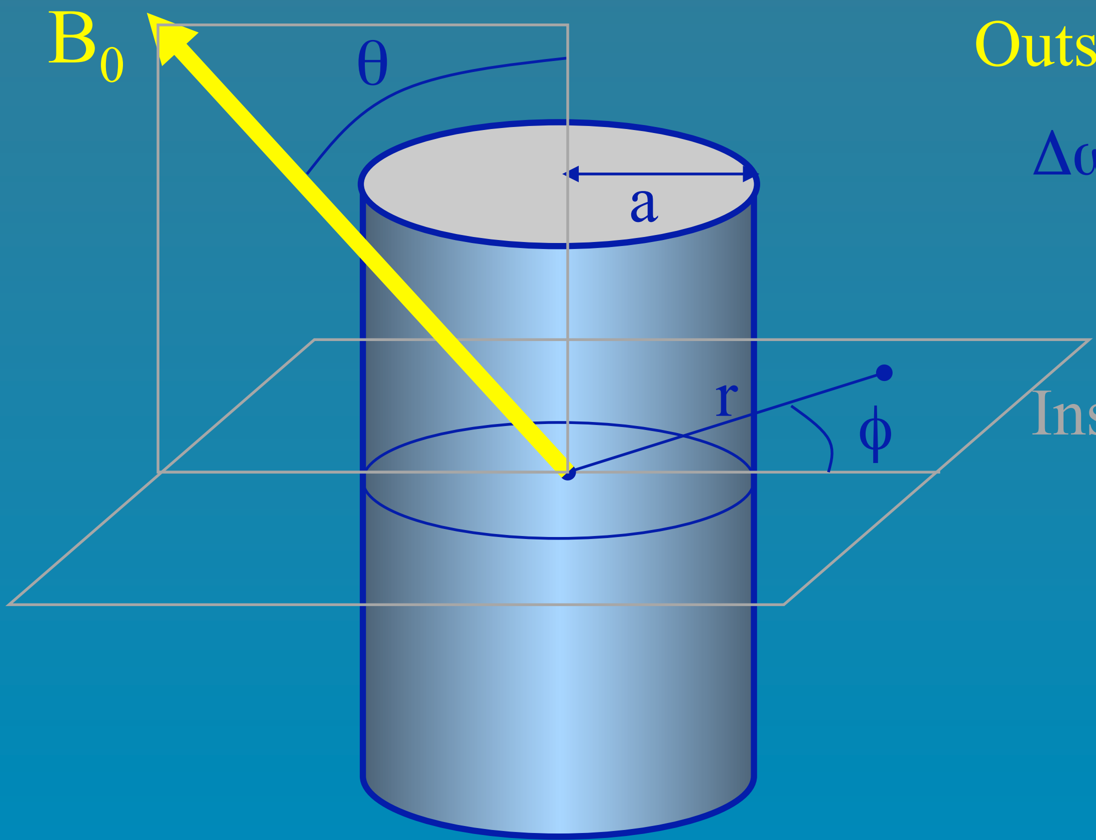


Inside Cylinder

$$\Delta\omega(\theta)=\Delta\omega'[3\cos^2(\theta)-1]/3$$

$$\Delta\omega' = 2\pi(1-Y)\,\Delta\chi'$$

Magnetic field around a vessel



Outside Cylinder

$$\Delta\omega(r,\theta,\phi) = \Delta\omega' \sin^2(\theta)(a/r)^2\cos(2\phi)$$

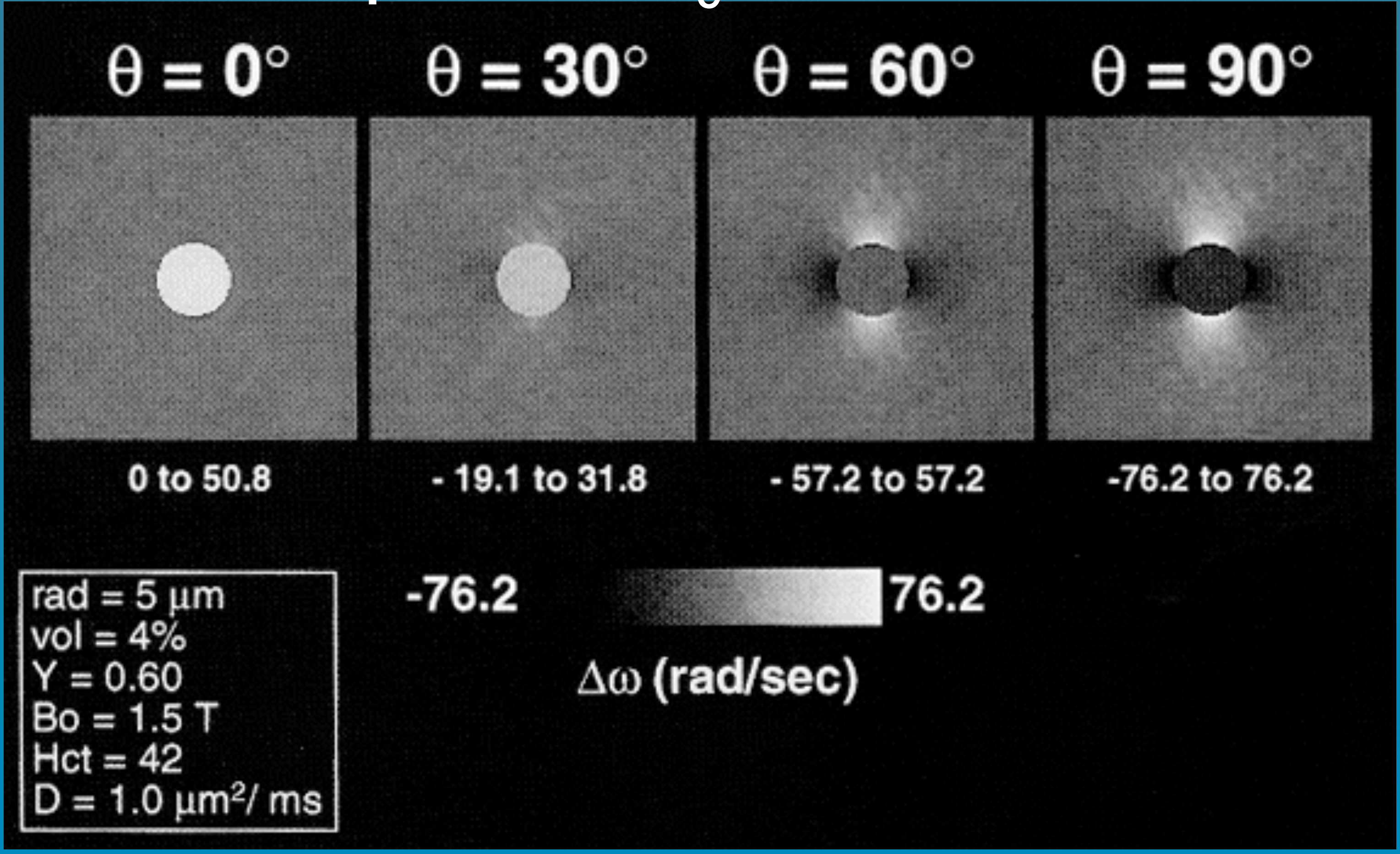
Inside Cylinder

$$\Delta\omega(\theta) = \Delta\omega'[3\cos^2(\theta)-1]/3$$

$$\Delta\omega' = 2\pi(1-Y)\,\Delta\chi'$$

Vessel orientation

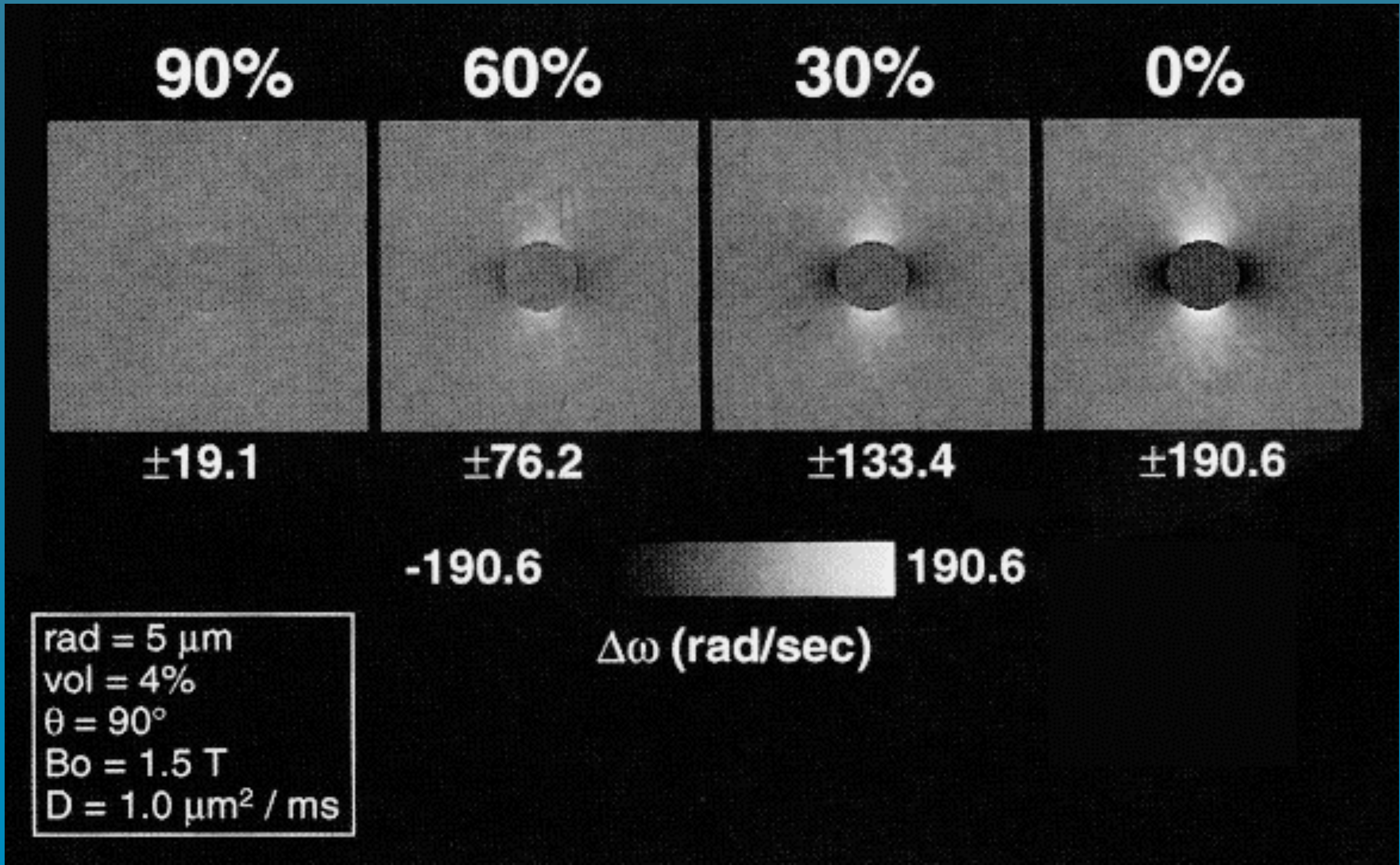
- Field inside and outside depends on angle θ with respect to B_0



Bandettini and Wong. Int. J. Imaging Systems and Technology. **6:**133 (1995)

Blood oxygenation

- Field inside and outside depends on Y, oxygenation



Bandettini and Wong. Int. J. Imaging Systems and Technology. **6:**133 (1995)

Signal dependence

- Macroscopic behaviour of NMR, gradient echo signal
- More extravascular at high field
- BOLD signal depends on the amount of dHb in the voxel

$$\Delta R2^* = 4.3\ \gamma\Delta\chi(1\text{-}Y)\ B_0\ CBV$$

(venules, larger vessels)

$$\Delta R2^* = 0.04\ \{\gamma\Delta\chi(1\text{-}Y)\}^2\ B_0^2\ CBV$$

(smaller capillaries)

Modelling of the BOLD effect

- Effects of oxygenation on T2*
  - Ogawa et al., J. Biophys., 64:803-812 (1993)
  - Kennan et al., MRM, 31:9-21 (1994)
  - Boxerman et al., MRM, 34:4-10 (1995)
- Flow and oxygenation coupling
  - Buxton and Frank, JCBFM, 17:64-72 (1997)
- CBV effects
  - Buxton et al., MRM, 39:855-864 (1998)
  - Mandeville et al., JCBFM, 19:679-689 (1999)

Signal evolution

- Monte Carlo simulation
  - Signal dephasing in the vascular tree amongst vessels of differing size, oxygenation and orientation
  - Boxerman J. *et al*. MRM 1995
- Deoxy-Hb contribution to relaxation

$$\Delta R2^* \propto (1\text{-}Y)^{\beta}\ CBV$$

$Y = O_2$ saturation

b~1.5

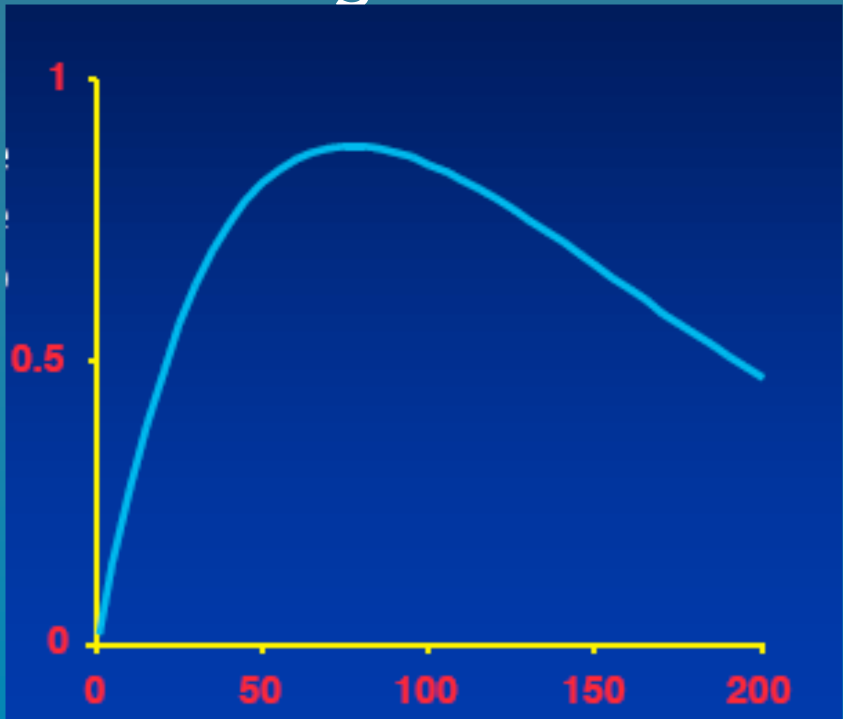
- Gradient echo

$$S = S_{max} \cdot e^{-TE/R2^*}$$

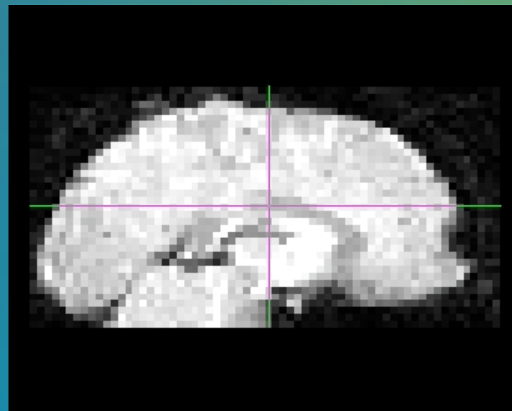
Echo time and BOLD sensitivity

- BOLD contrast-to-noise optimised when TE~T2*
- T2* shorter at high field

Relative CNR

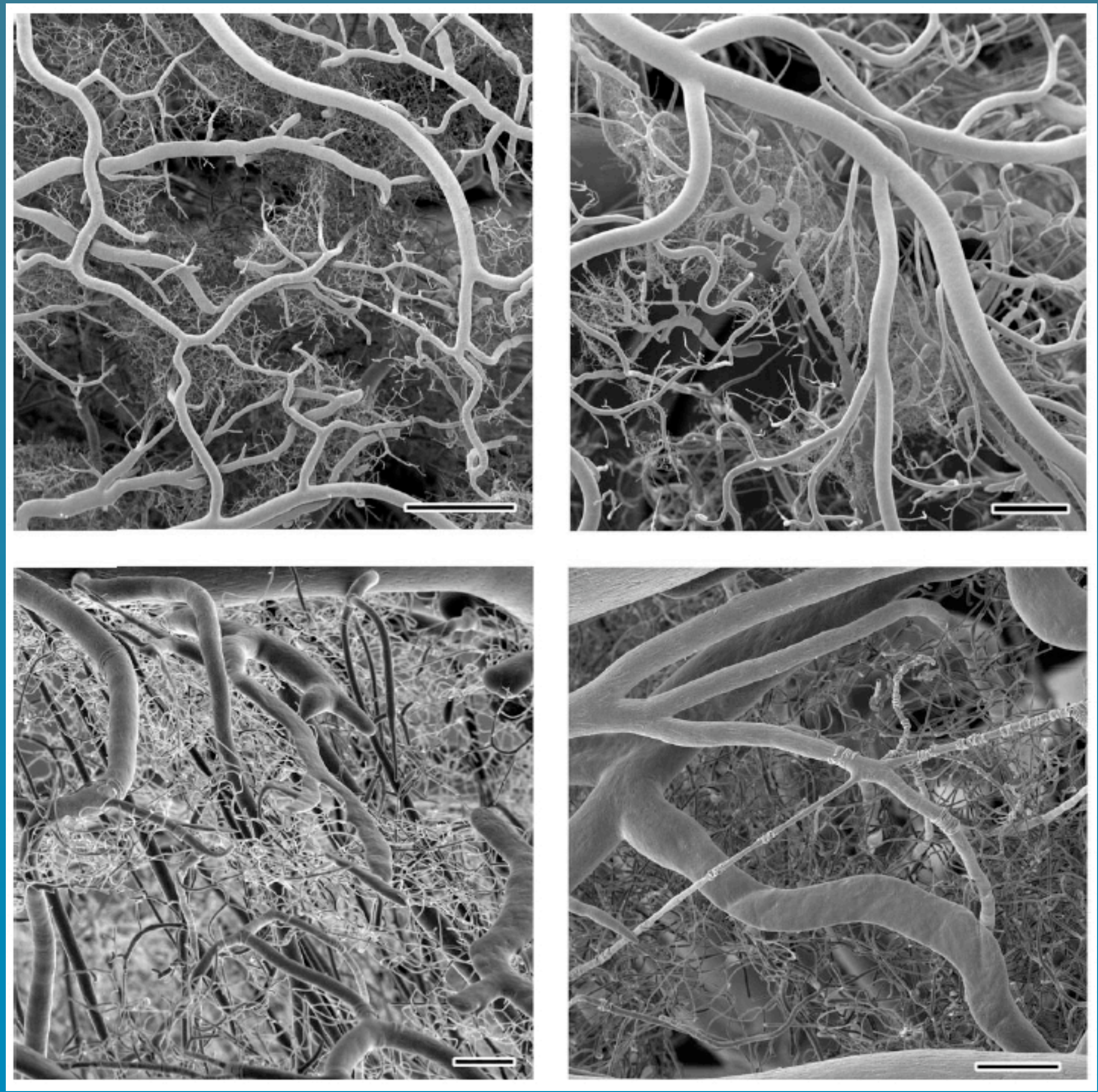


TE (ms)



$T_o2^* > T_f2^*$

Vessel density

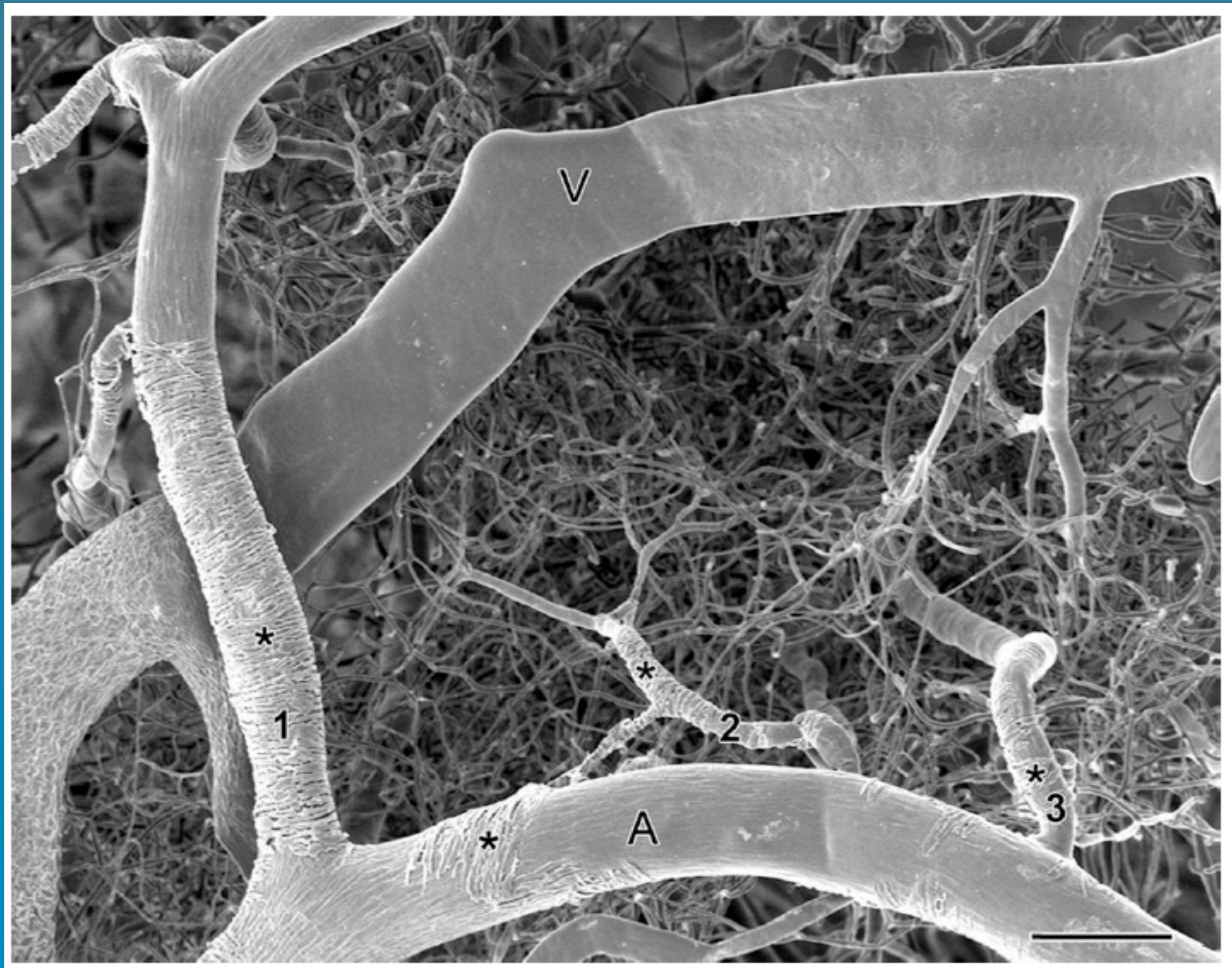


500 μm

100 μm

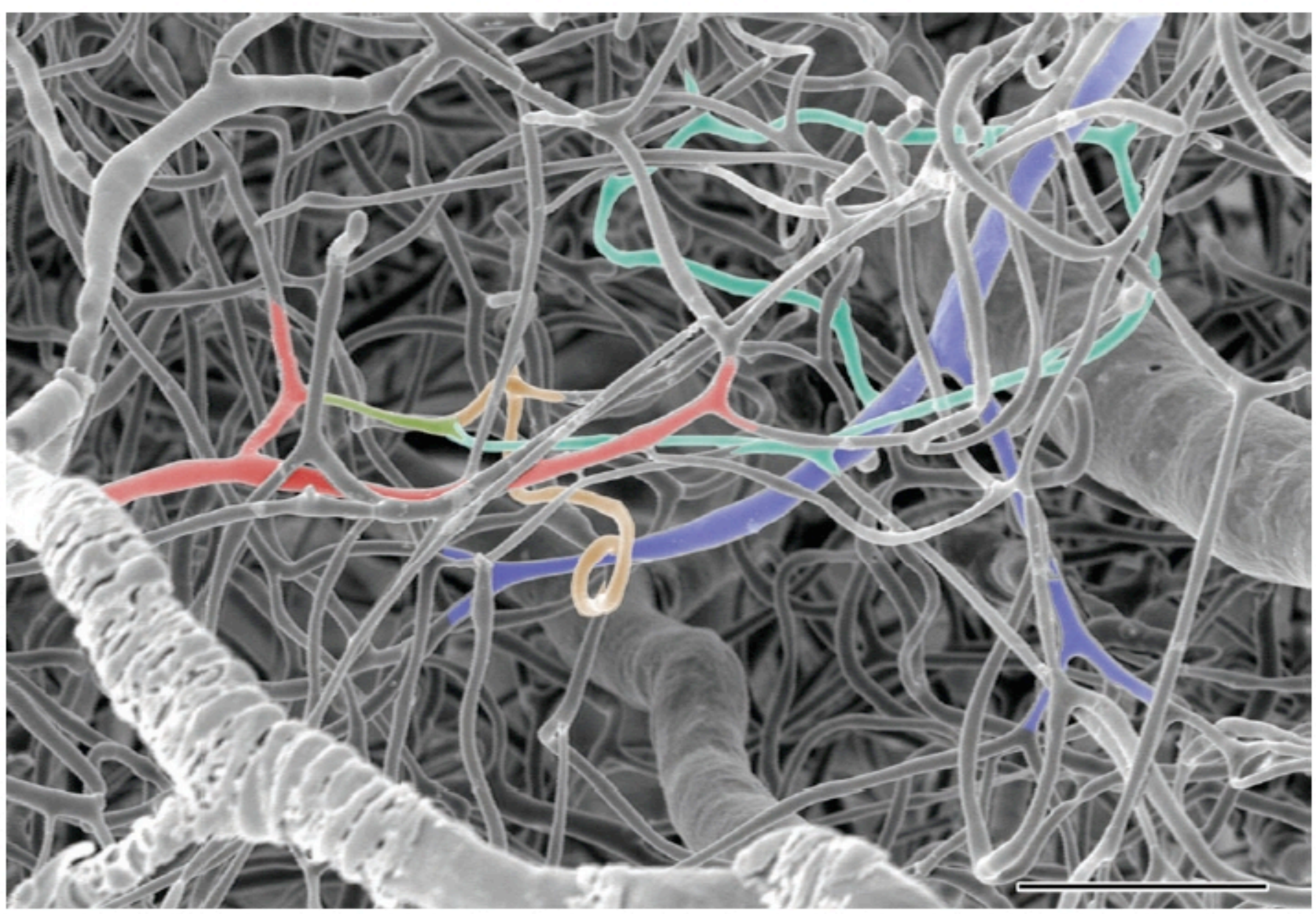
Harrison RV et al. Cerebral cortex. 2002

Arteriole



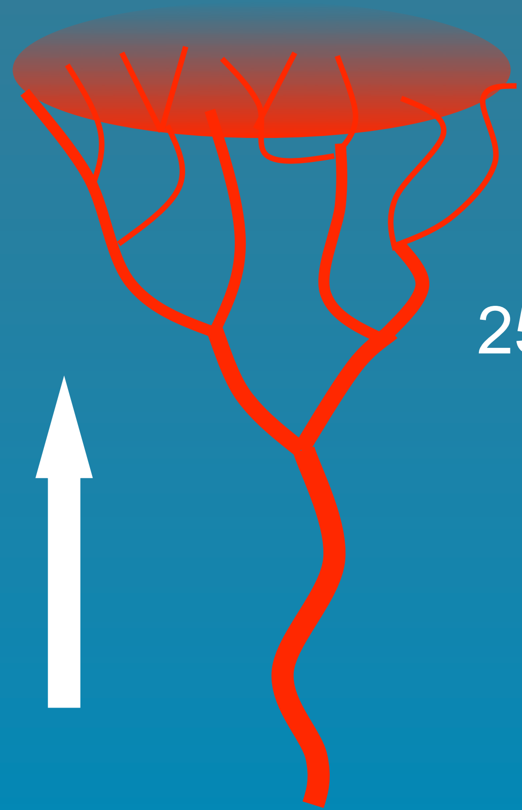
100 μm

Even smaller



50 μm

Arterial side



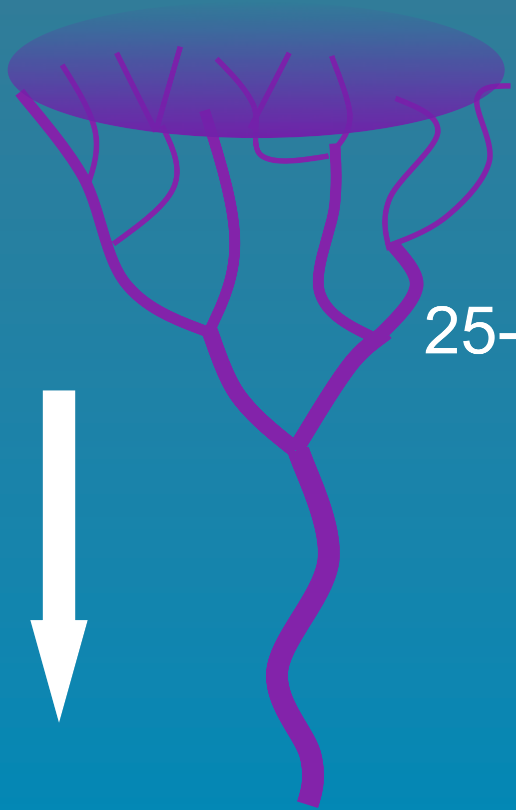
Capillaries
8 μm 40% CBV

Arterioles
25 μm 15% of CBV

Artery
Blood oxygen saturation, 98-100%

- Capillaries are randomly orientated
- Oxygen exchange in capillaries
- Arterioles perform local CBF control

Venous side



Capillaries

Venules
25-50 μm 40% of CBV

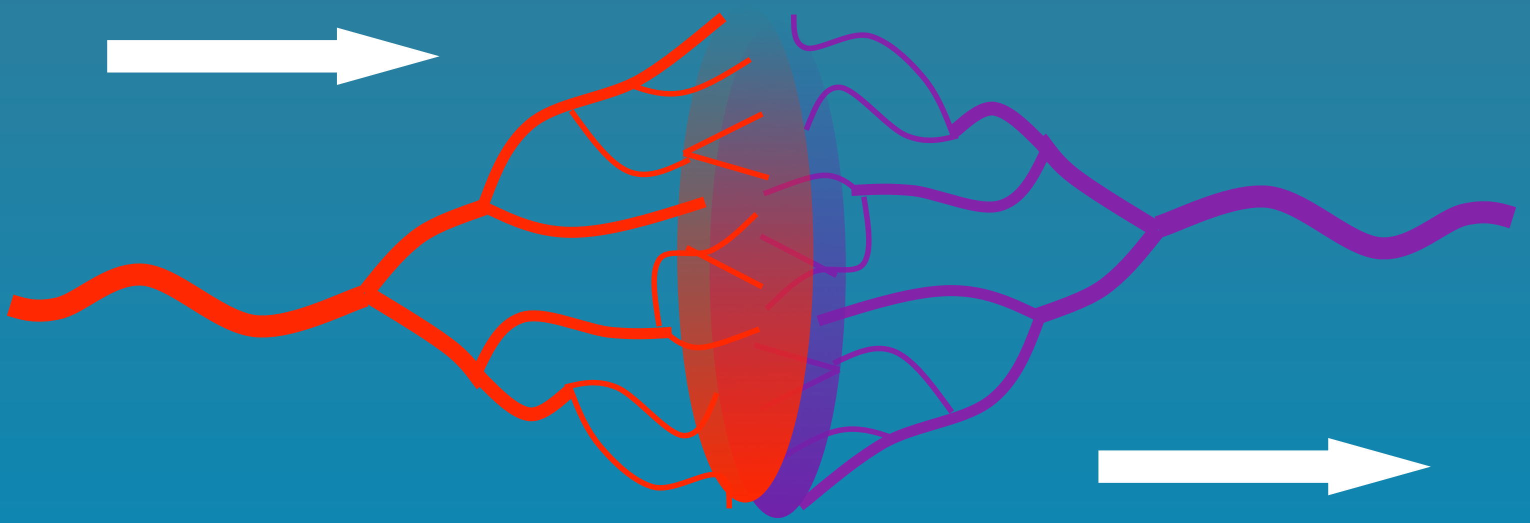
Vein
Blood oxygen saturation (resting), 60%

- Venules
  - are (approx) randomly orientated
  - have the same blood volume as capillaries
  - have twice the deoxyHb concentration of capillaries
  - are more (para)magnetic than capillaries and arteries

Activation

Rest

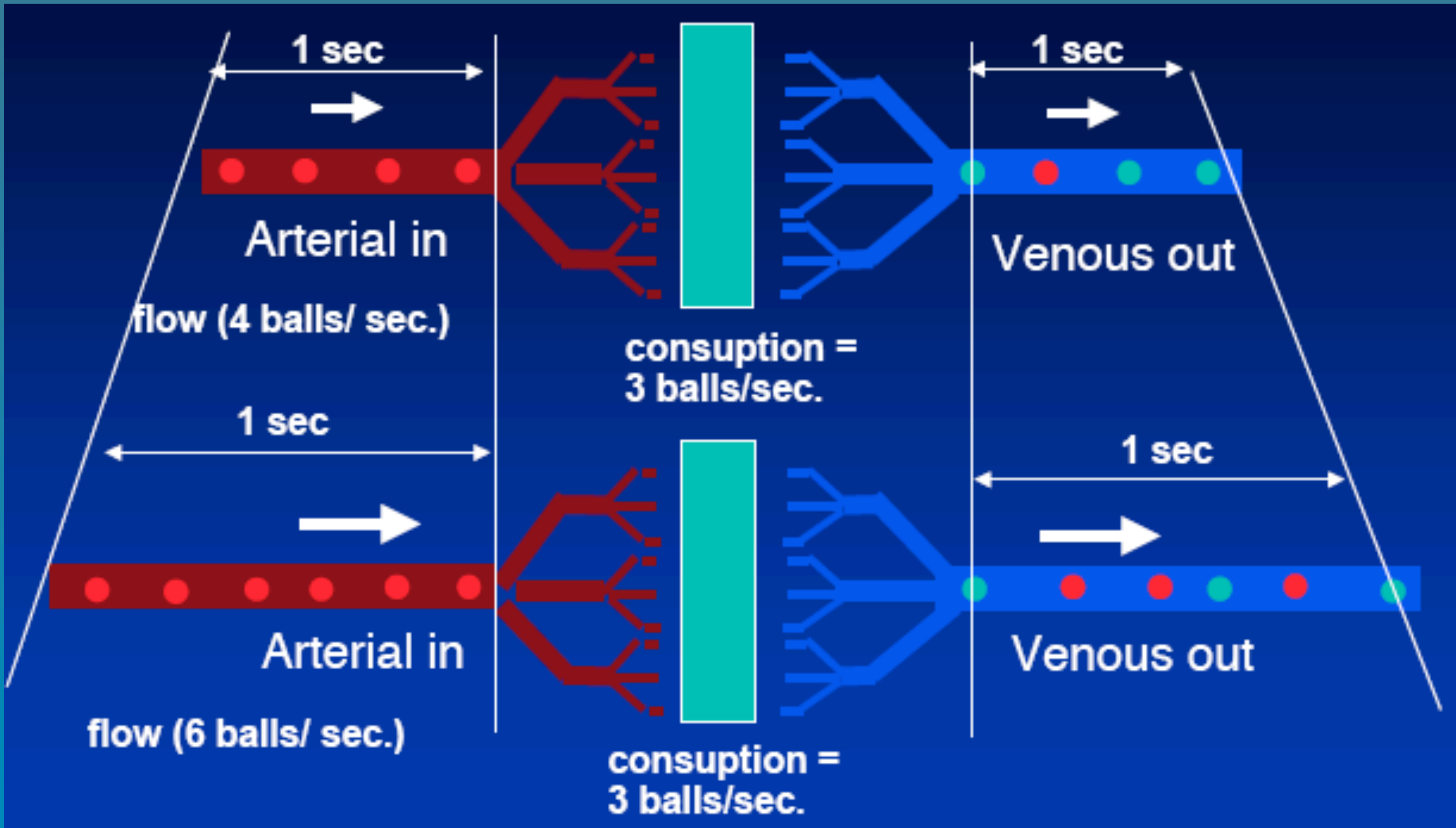
O2 Sat 100% 80% 60%



Active: 50% increase in CBF, 20% increase in CMRO2

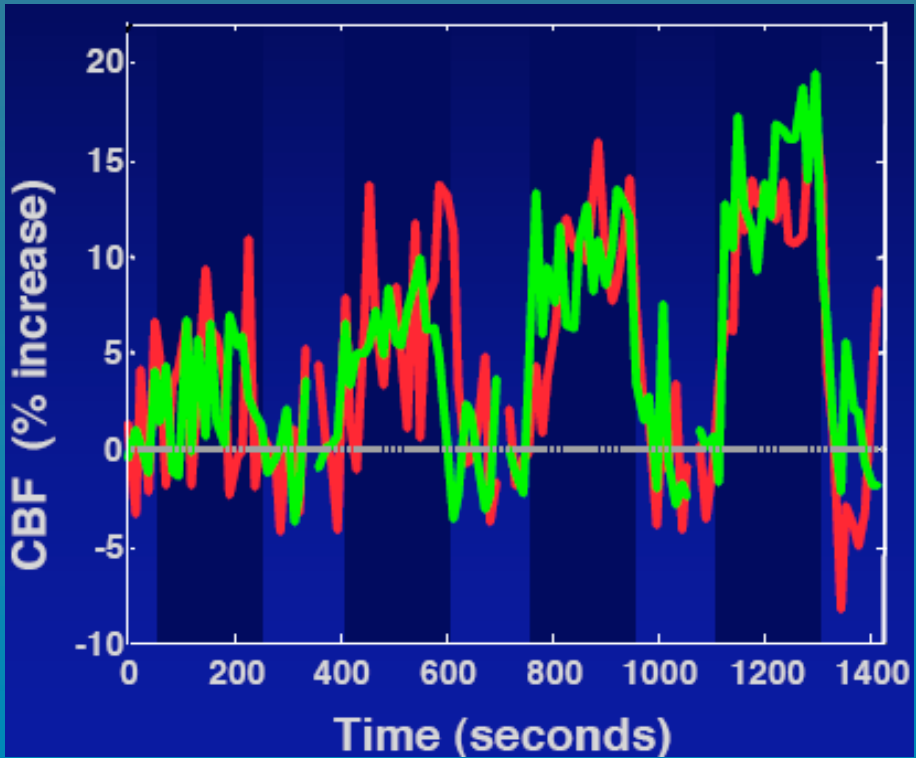
O2 Sat 100% 86% 72%

Decrease in deoxy-Hb concentration

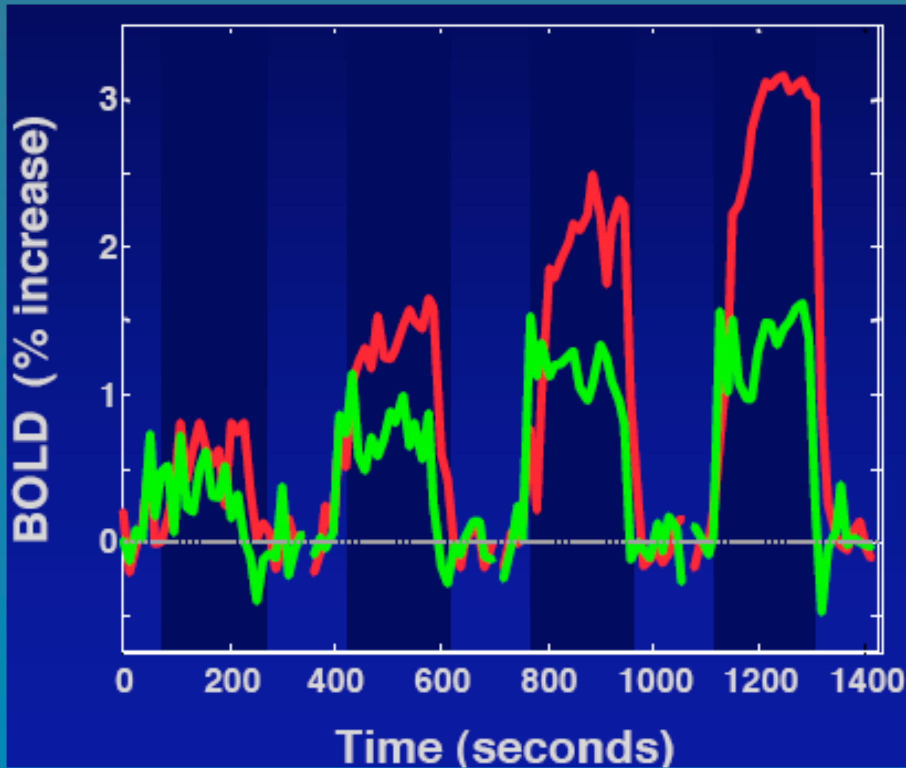


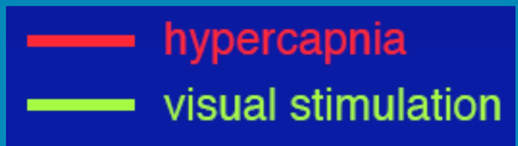
Oxidative metabolism attenuates BOLD signal

CBF



BOLD



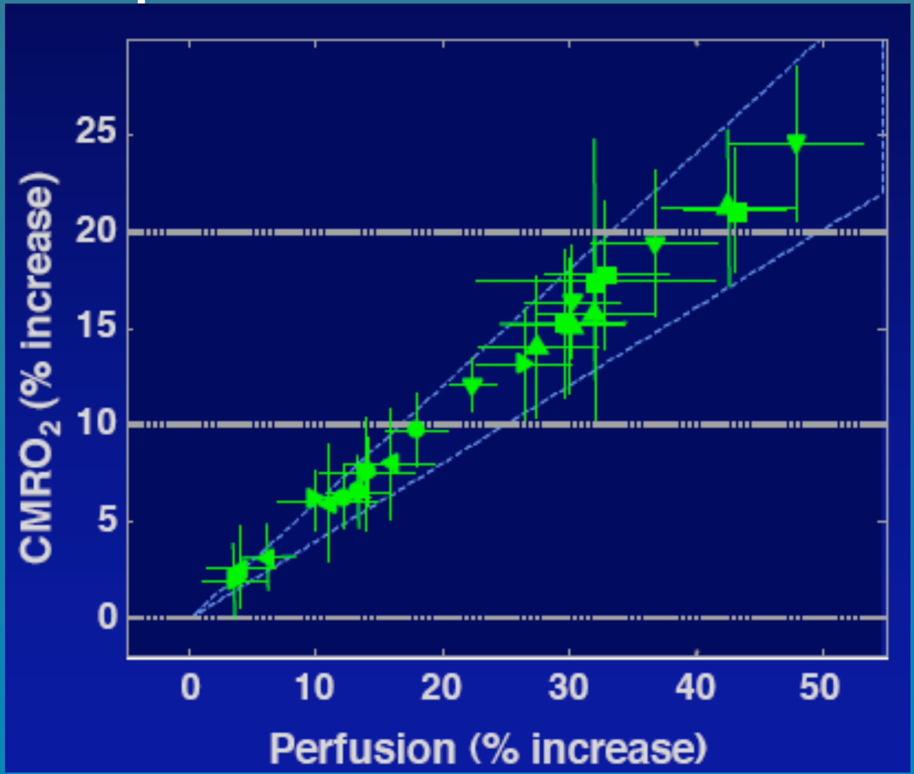


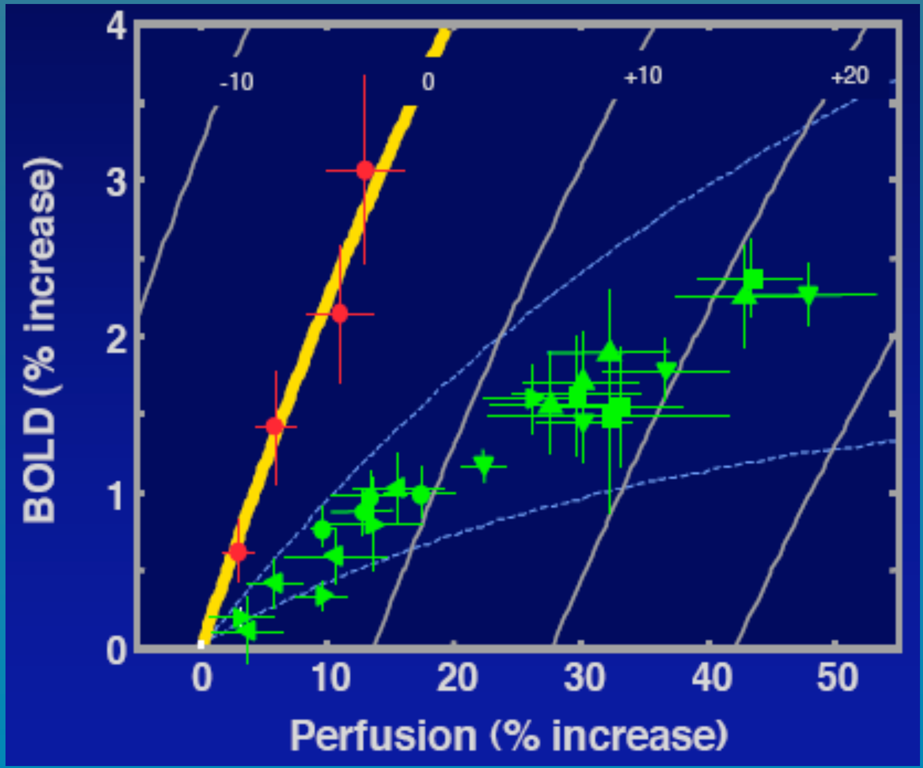
- Hoge R *et al*

$CMRO_2$-CBF ratio determines the BOLD signal

CMRO2-CBF coupling: slope ~2

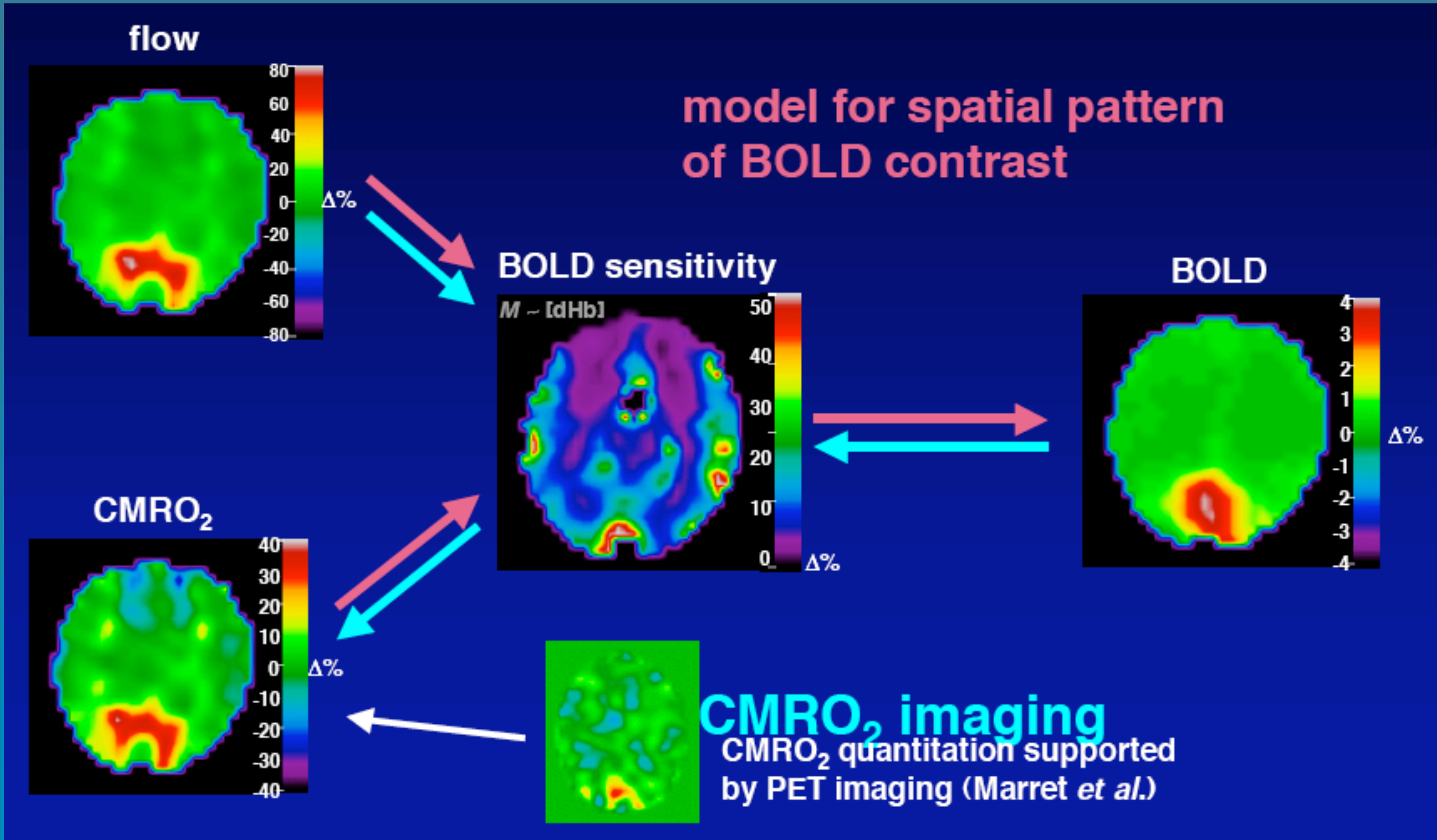
Calibrated BOLD



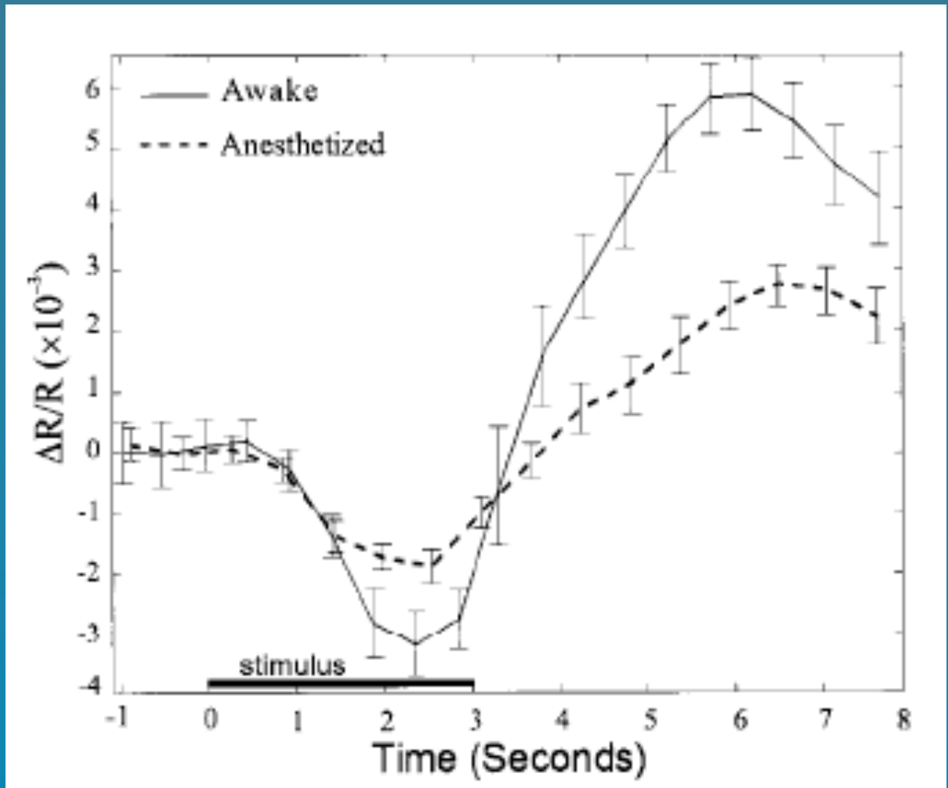


- Why is the flow increase larger than the CMRO2 increase?
- … lecture 2
- Hoge R *et al*

Spatial dependency of BOLD contrast



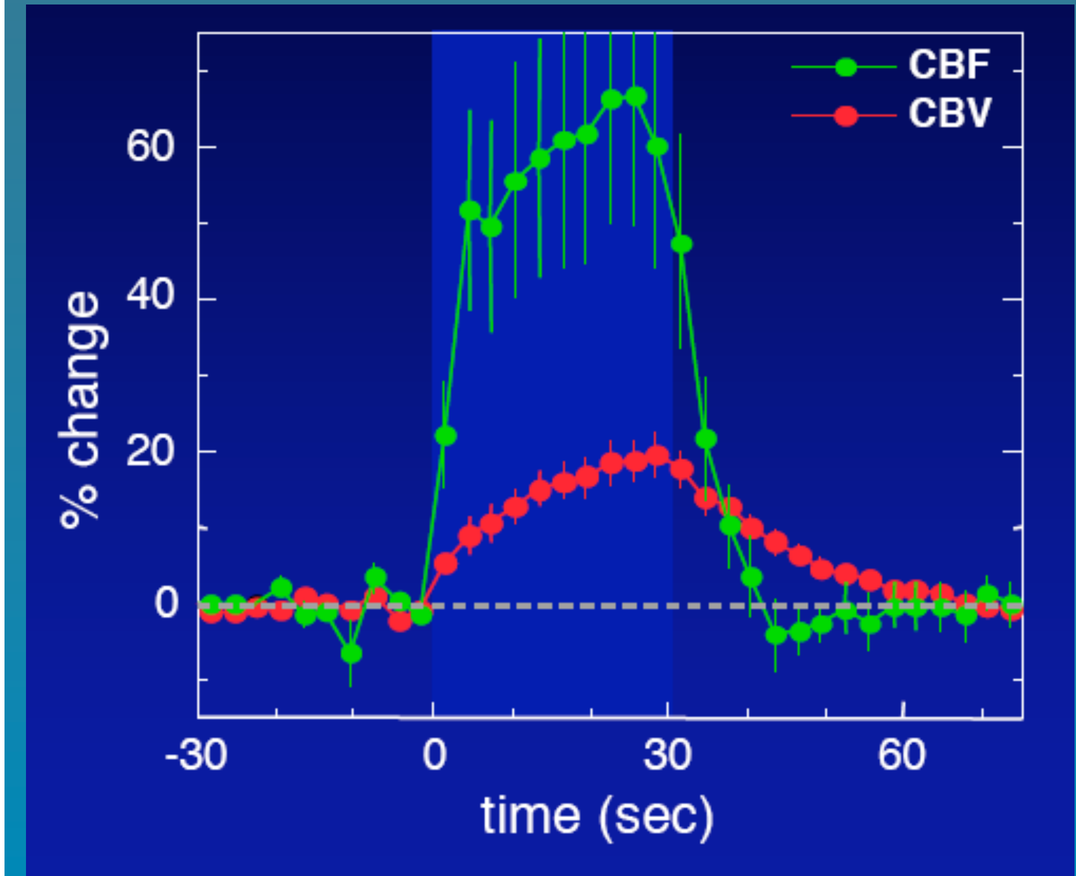
Initial dip



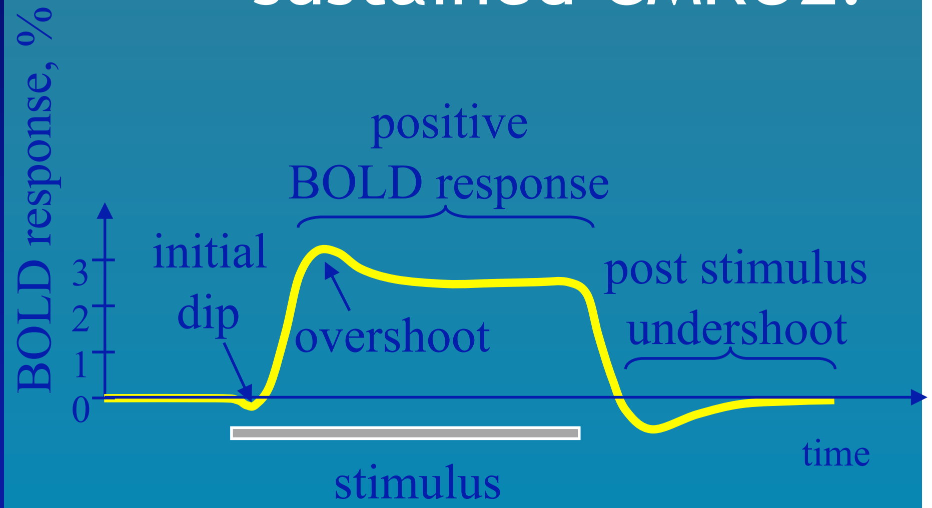
- Metabolic response (deoxyHb surge) preceding CBF increase
- Highly spatially localised (cortex)
- Seen in some areas (e.g. visual)
- Not observed by everyone

Shtoyerman, Grinvald *et al*

Post-stimulus undershoot



- Slow recovery of CBV?
- … or is it sustained CMRO2?



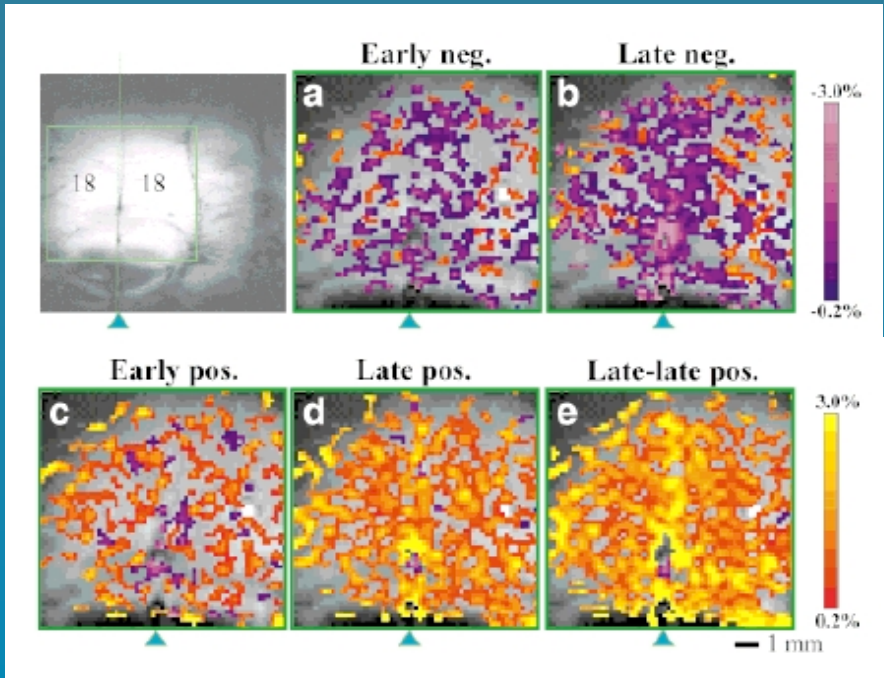
Mandeville *et al* MRM 1999

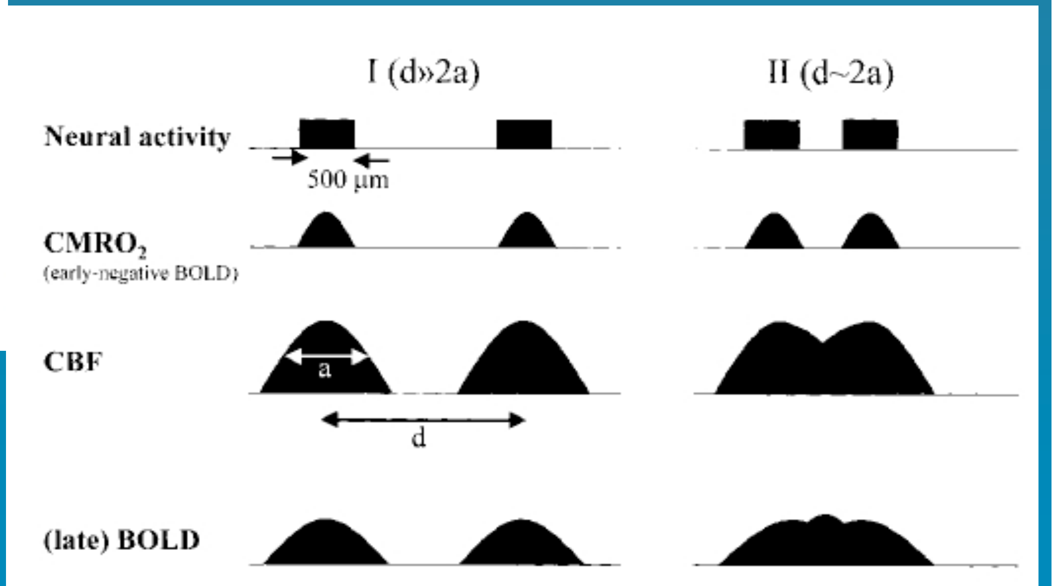
Purer physiological measures

- Perfusion and perfusion change
- $CMRO_2$ change
- Cerebral blood volume
- Oxygen extraction fraction

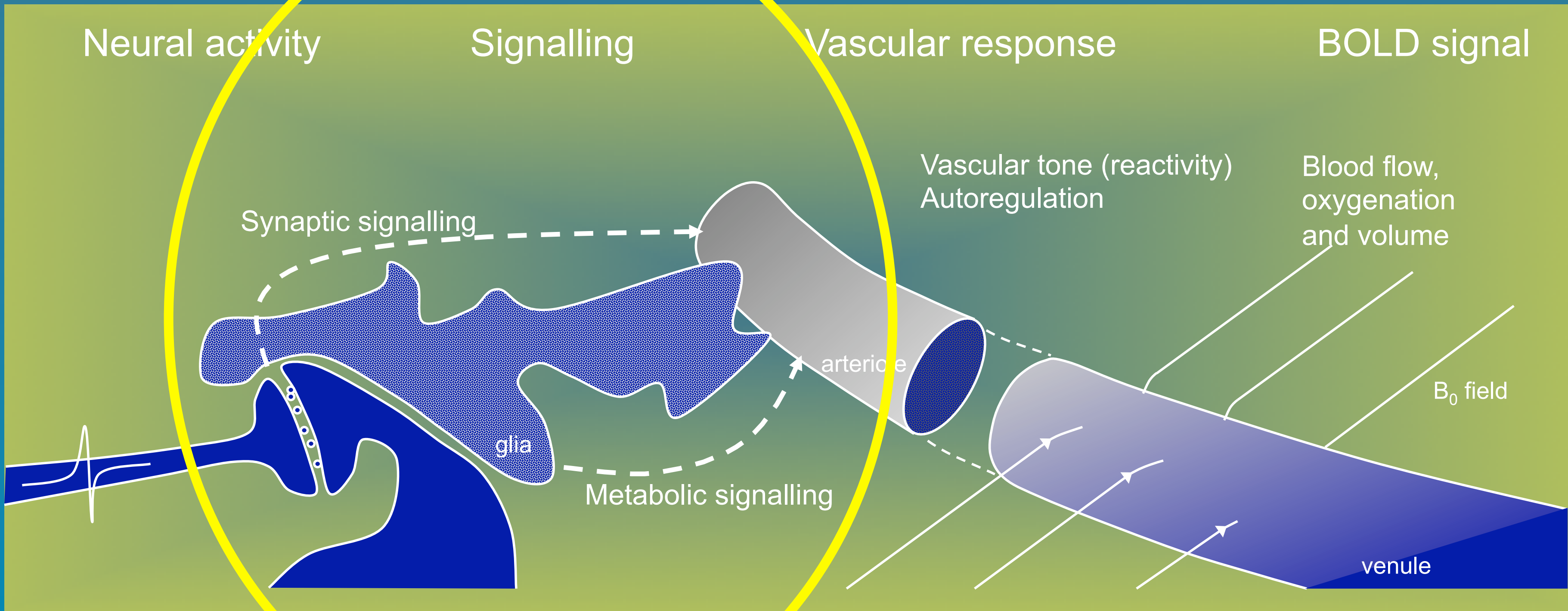
BOLD signal localisation

- Weighted towards draining veins
- Duong *et al* MRM 2000





Neurovascular coupling

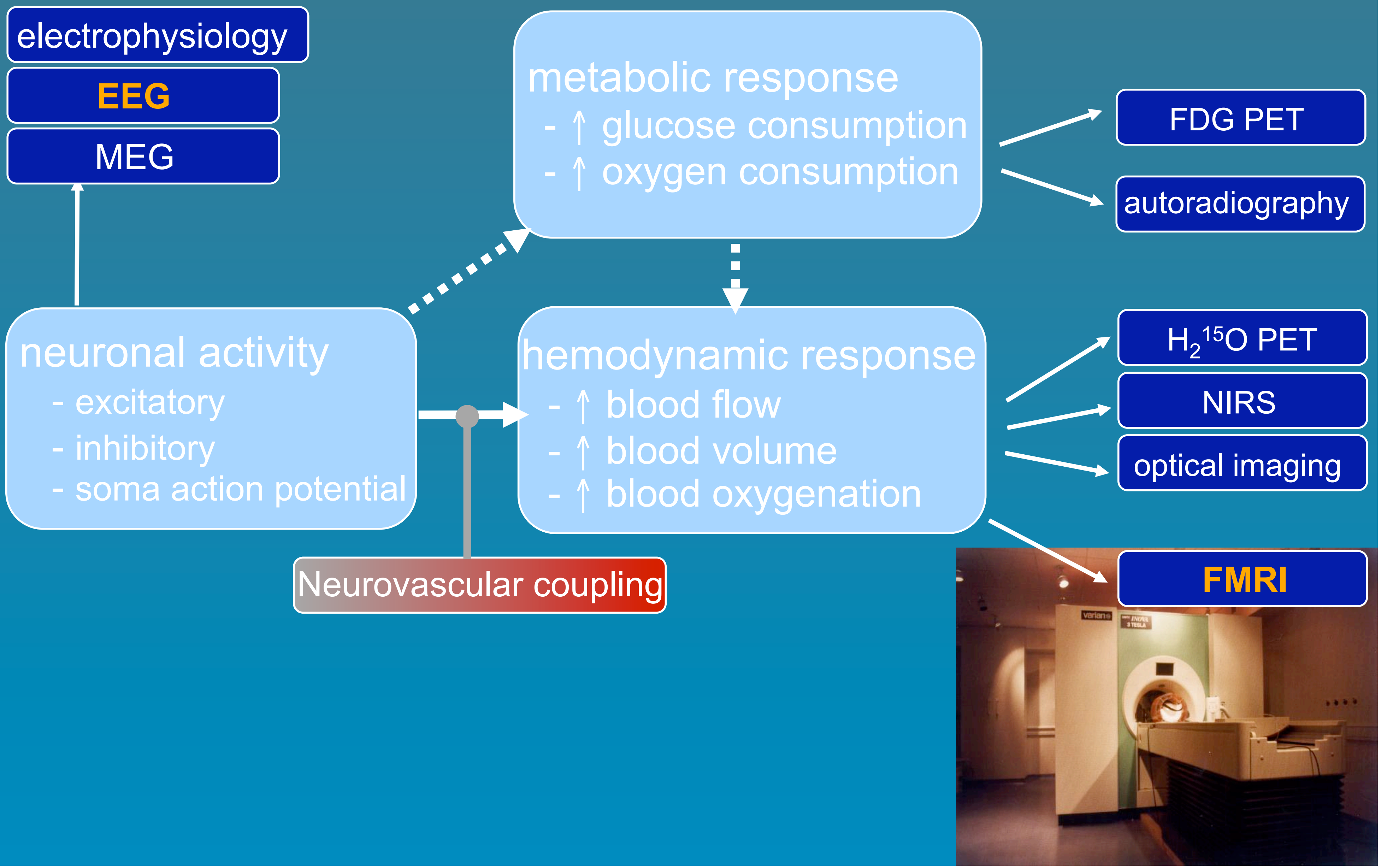


Energy consumption   CBF ↑

NO, K+, vasoactive neurotransmitter

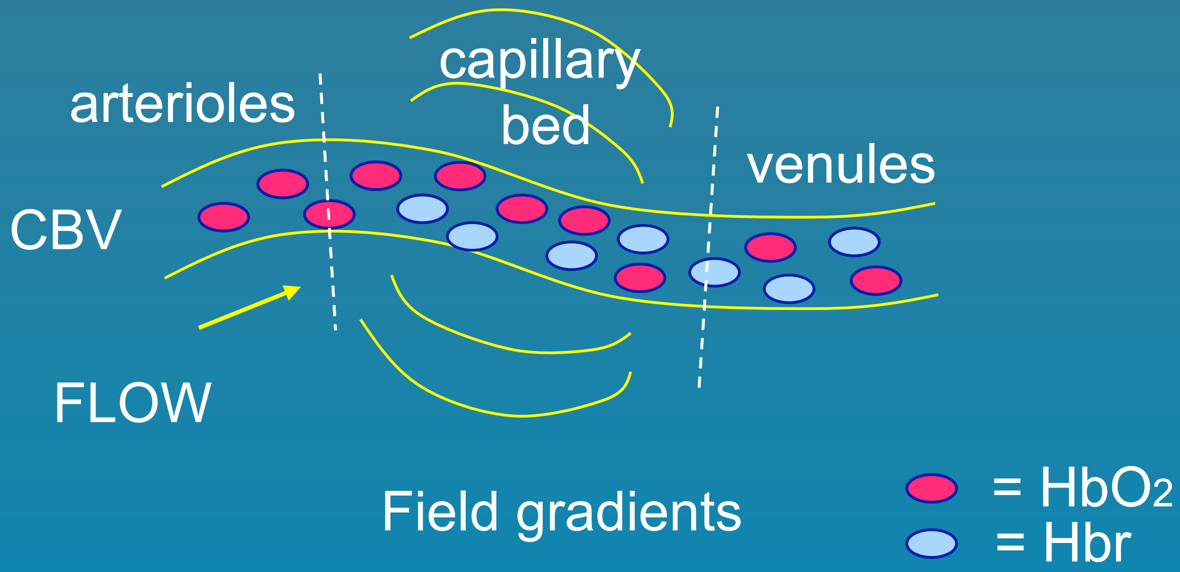
Neurotransmitters   Vessel innervation

Correlates of brain activity

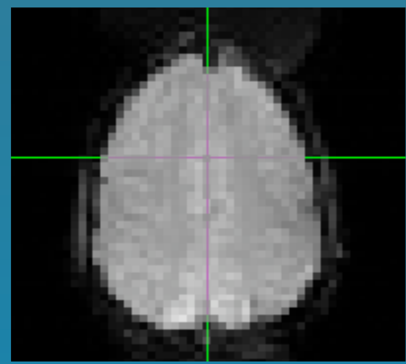


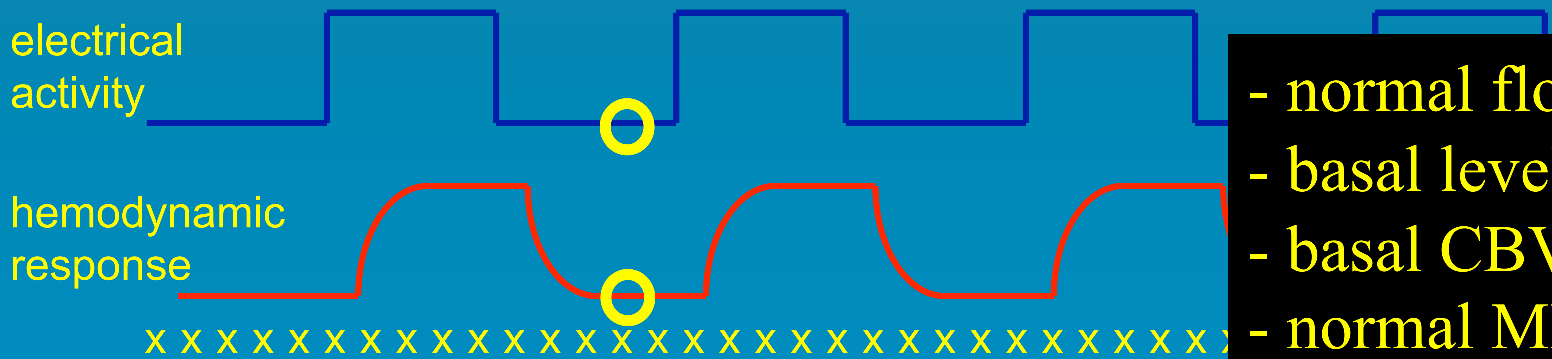
BOLD FMRI

Basal (resting) state



MRI signal

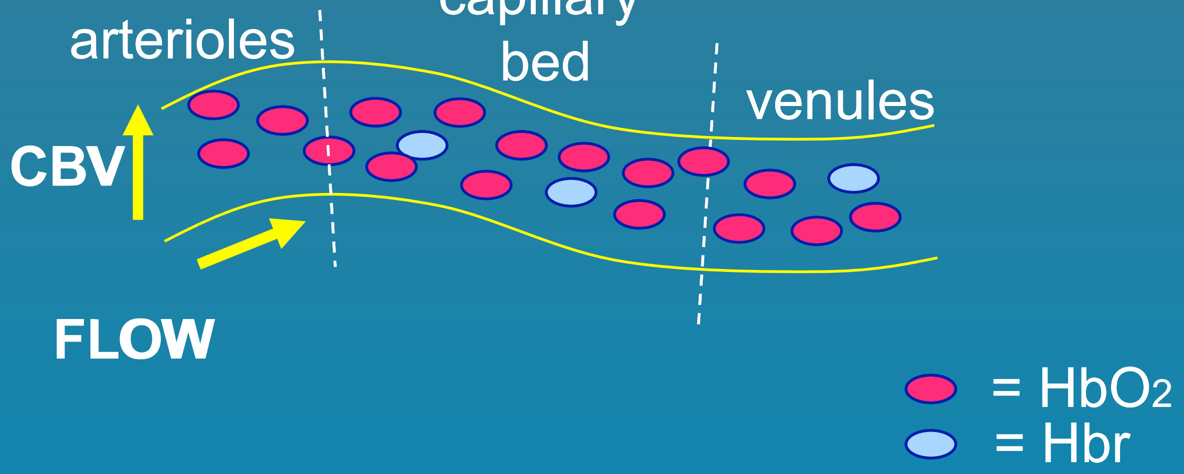




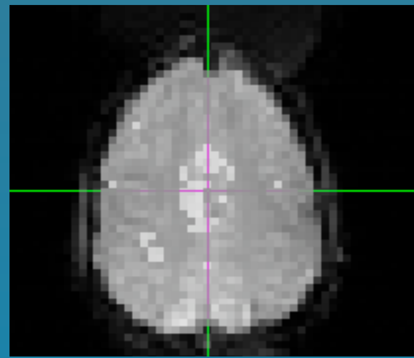
- normal flow
- basal level [Hbr]
- basal CBV
- normal MRI signal

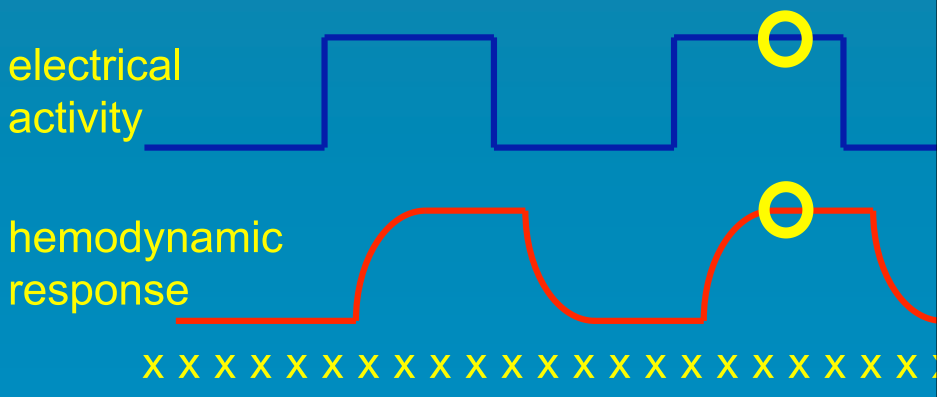
BOLD FMRI

Activated state



MRI signal

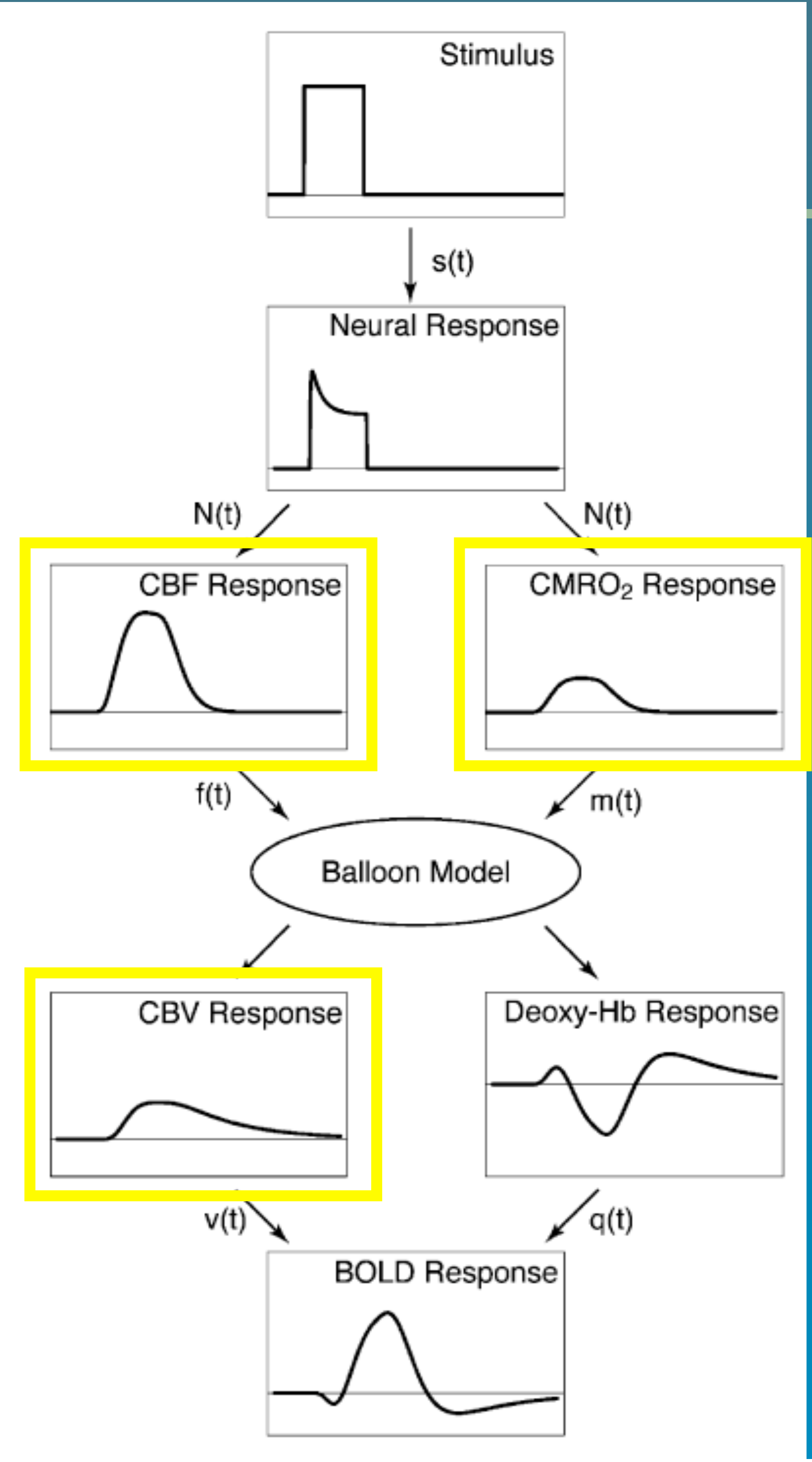




- increased flow
- decreased [Hbr] (*lower field gradients around vessels*)
- increased CBV
- increased MRI signal

(*from lower field gradients*)

Dissecting BOLD

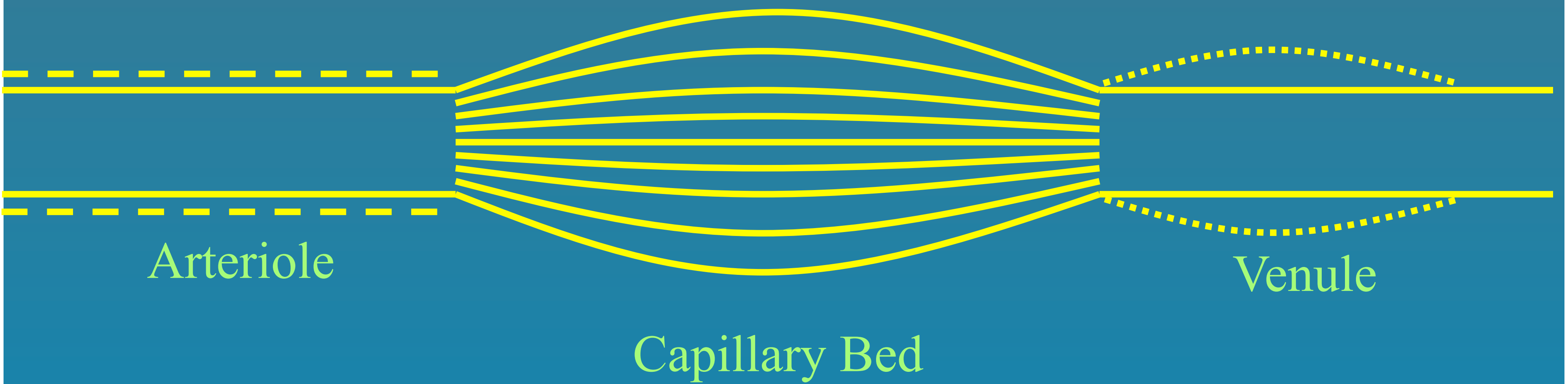


$$S_{BOLD}=f(CBV,CBF,CMRO_2)$$

Purer measures of neuronal activity?

Buxton et al. Neuroimage 2004

Balloon model of CBV changes



- rCBV increase is a *mechanical* consequence of CBF increase
- elastic properties of venous bed induce transient mismatches between CBV and CBF which does not require uncoupling of CBF and $CMRO_2$

$CMRO_2$ measurement

Measured

BOLD

$$R2^*_{(BOLD)} = k\, CBV^{\alpha}\, [dHb]^{\beta}$$

- k = field dependent constant
- CBV = cerebral blood volume fraction
- [dHb] = concentration of dHb in blood
- α = theoretical CBV dependence (α=1)
- β = theoretical [dHb] dependence
  - $\beta \approx 1.5$ (1.5T) [Boxerman et al, 1995]
  - $\beta \approx 1$ (>3T) [Ogawa et al, 1993]

$CMRO_2$ measurement

Substitutions:

$$CMRO_2 = CBF \cdot OEF \cdot C_a$$

$$[dHb] = CMRO_2 / CBF$$

(Fick's principle)

$$\frac{CBV}{CBV_0} = \left(\frac{CBF}{CBF_0}\right)^{\alpha}$$

(Grubb et al., 1974)

α = 0.38 (steady state value)

ASL measured

$CMRO_2$ measurement

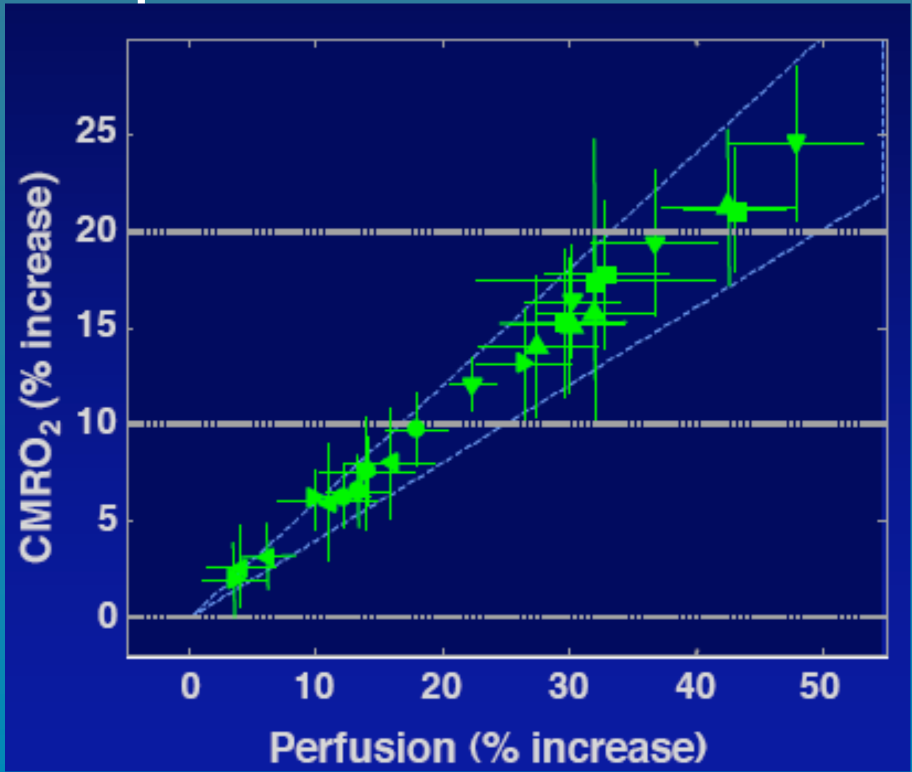
$$\frac{\Delta R2^*_{(BOLD)}}{R2^*_{0(BOLD)}} = \left[1 - \left(\frac{CMRO_2}{CMRO_{2(0)}}\right)^{\beta} \left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right]$$

Calibrate $R2^*_0$ using a hypercapnia challenge

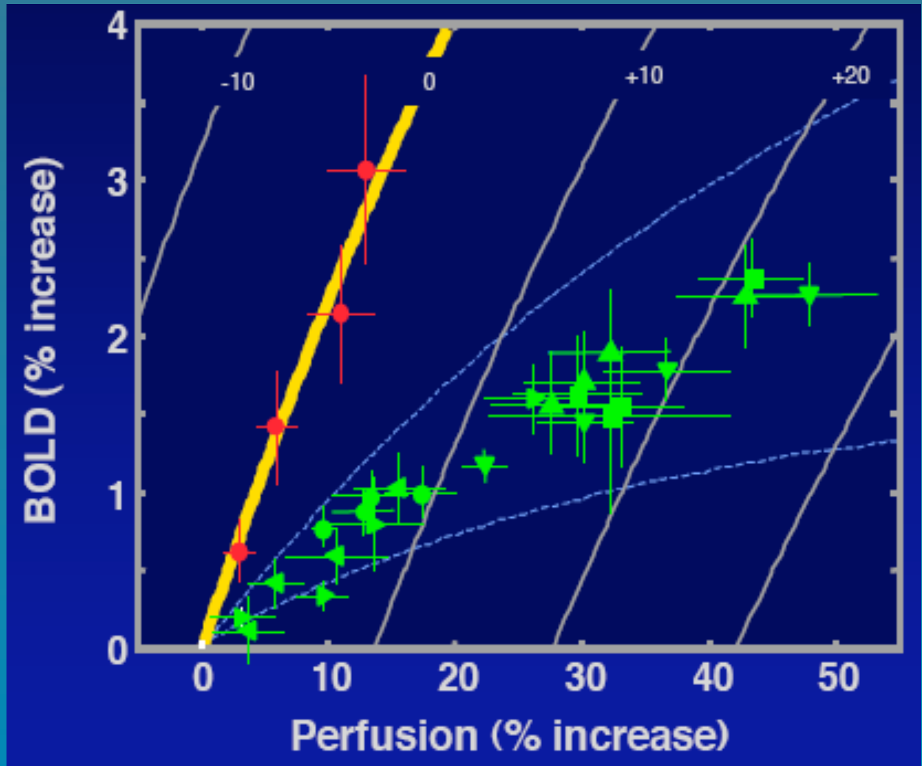
A flow increase without increase in $CMRO_2$

Calibrated BOLD for measuring $CMRO_2$

CMRO2-CBF coupling: slope ~2



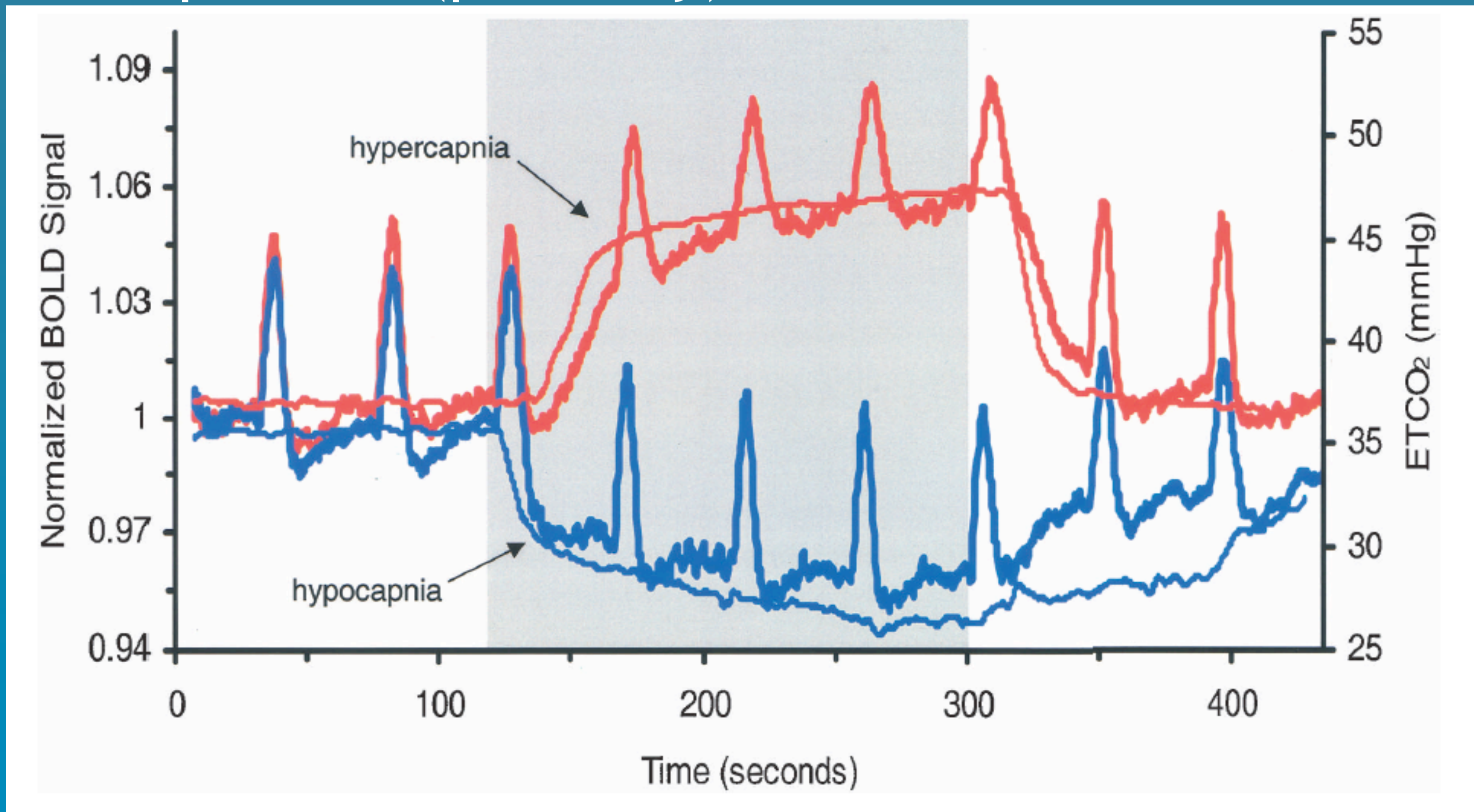
Calibrated BOLD



- Hoge R et al

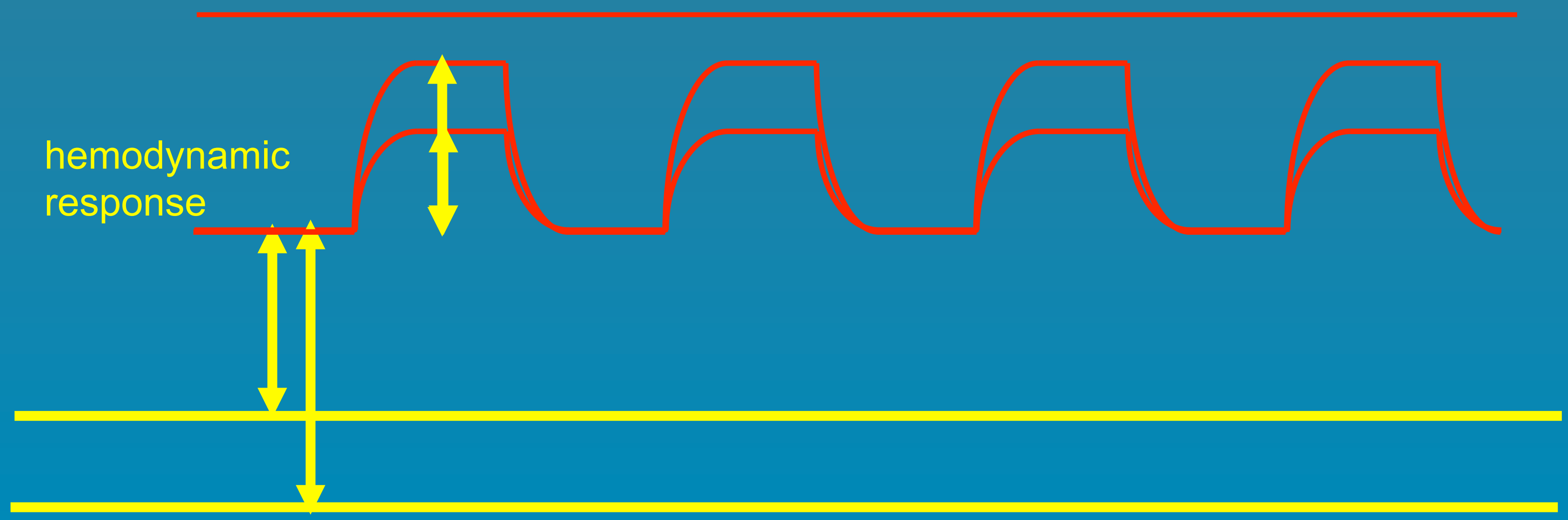
Physiological baseline

- Baseline CBF↑,
- But ΔCBF $\Delta CMRO_2$ unchanged (probably) (Brown et al JCBFM 2003)
- BOLD response ↓ (probably)



Cohen et al JCBFM 2002

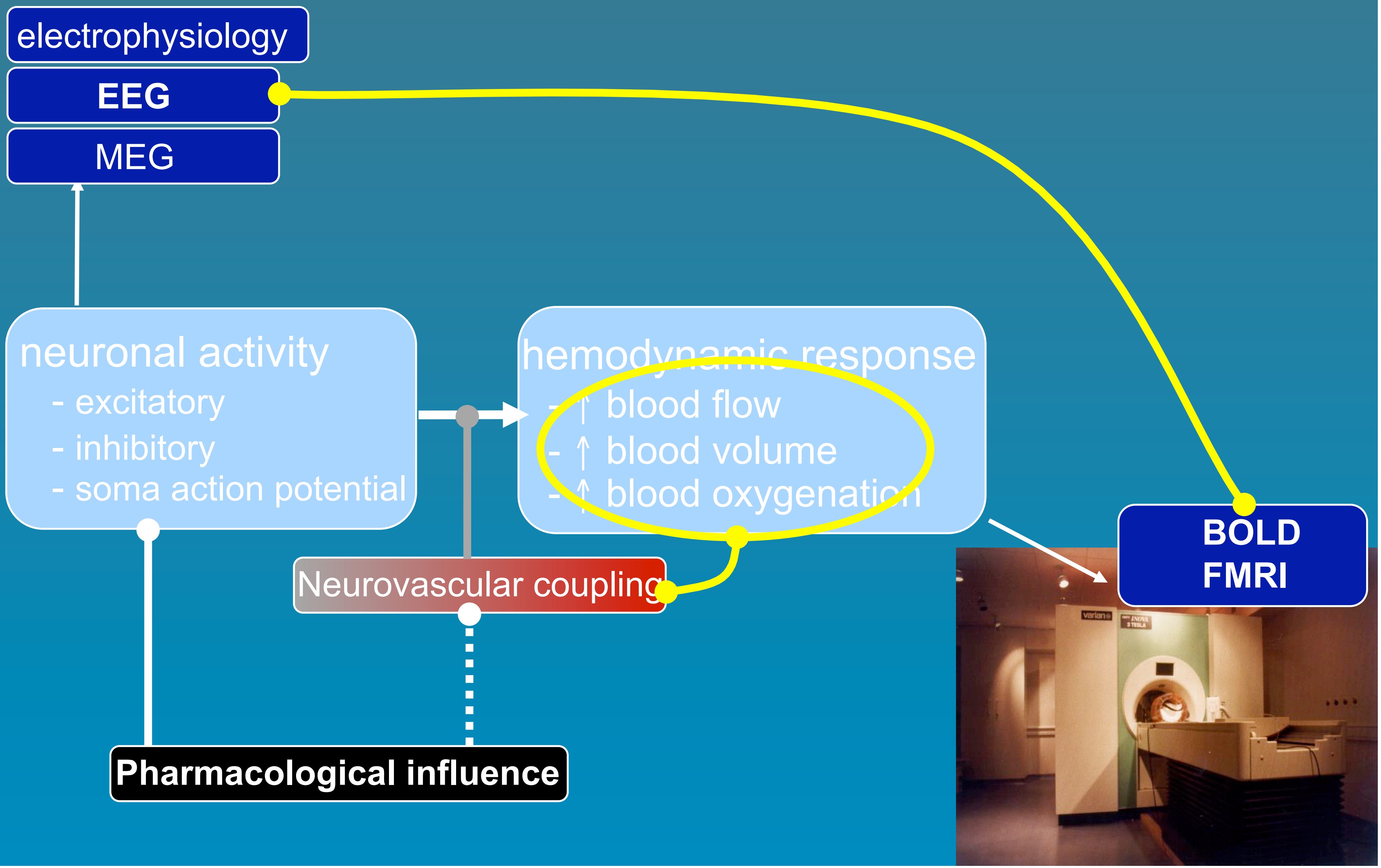
A bit about baselines



Implications

- Factors altering baseline state
  - Disease
  - Sedation
  - Anxiety
  - Vasoactive medications
    - Global and local
- ΔCBF (ASL) may be more robust?

Investigating NV coupling



Investigating NV coupling

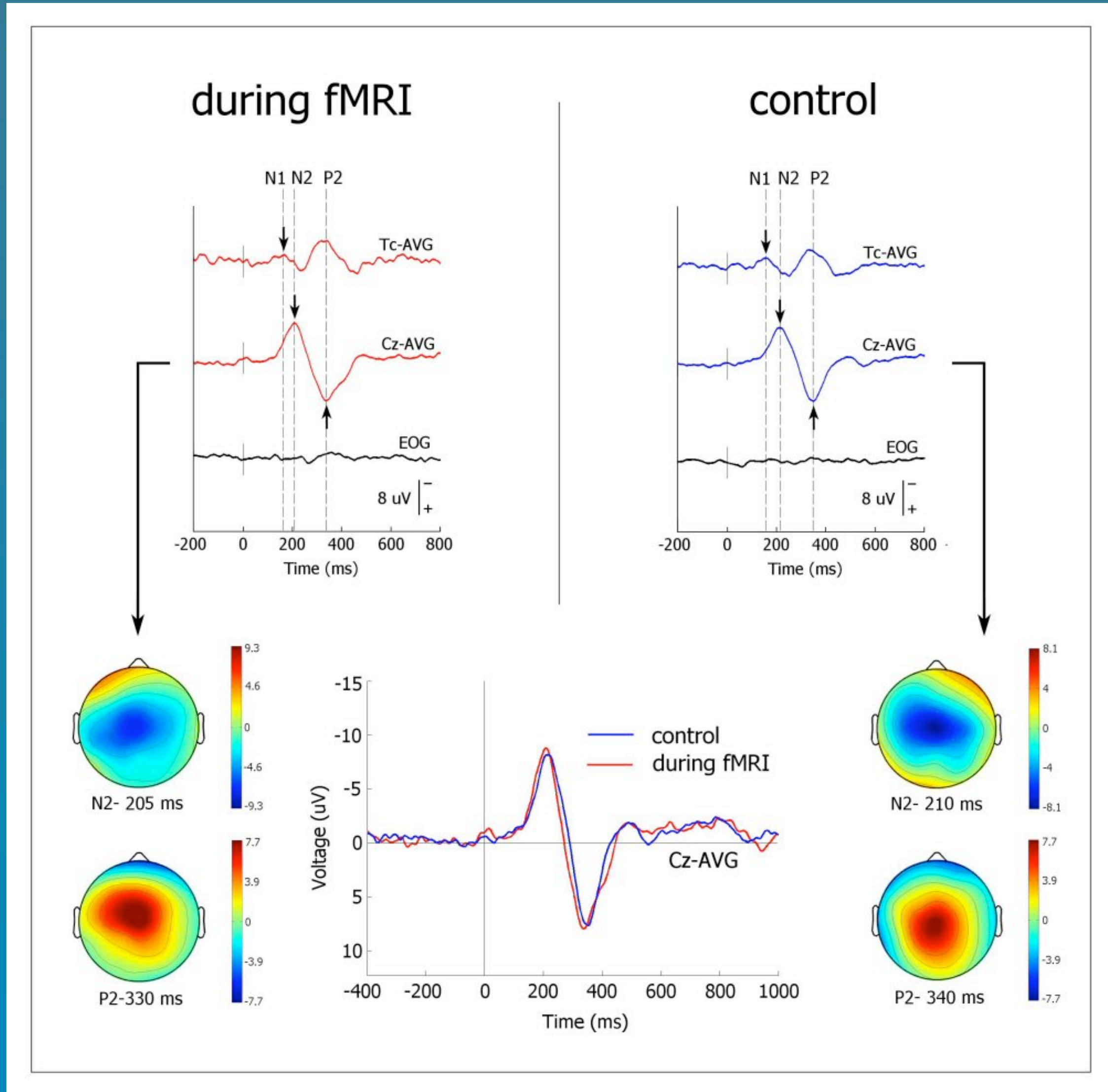
EEG

- How do pharmacological and physiological challenges modify the coupling between human brain activity measured electrophysiologically and haemodynamically (neurovascular coupling)?

BOLD
FMRI

Investigating NV coupling

- Simultaneous EEG-FMRI
  - Laser evoked potentials
- Advantages
  - High temporal **and** spatial resolution
  - Identical mental state
  - Single trial analysis
  - Spontaneous EEG



Courtesy of GD Iannetti

Noise sources

- What is noise in a BOLD experiment?
  - Unmodelled variation in the time-series
  - Intrinsic MRI noise
    - Independent of field strength, TE
    - Thermal noise from subject and RF coil
  - Physiological noise
    - Increases with field strength, depends on TE
    - Cardiac pulsations
    - Respiratory motion and B0 shift
    - Vasomotion, 0.1Hz
    - Blood gas fluctuations
    - “Resting state” networks
  - Also
    - Scanner drift (heating up)

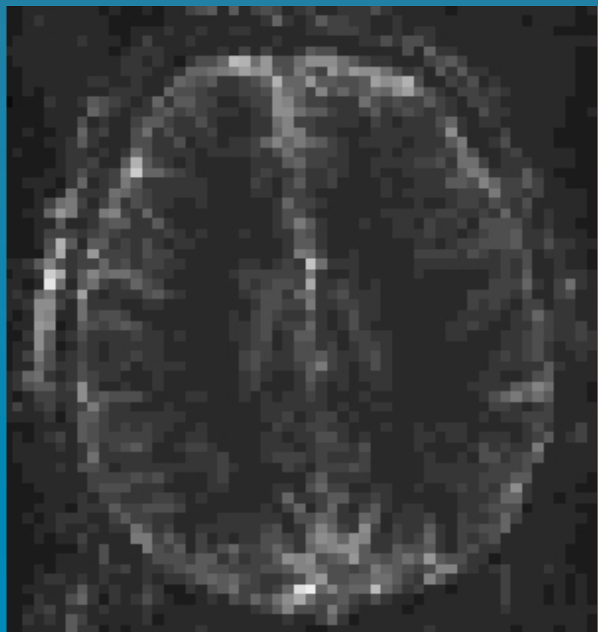
At 3Tesla

Physiological noise >
scanner + thermal noise

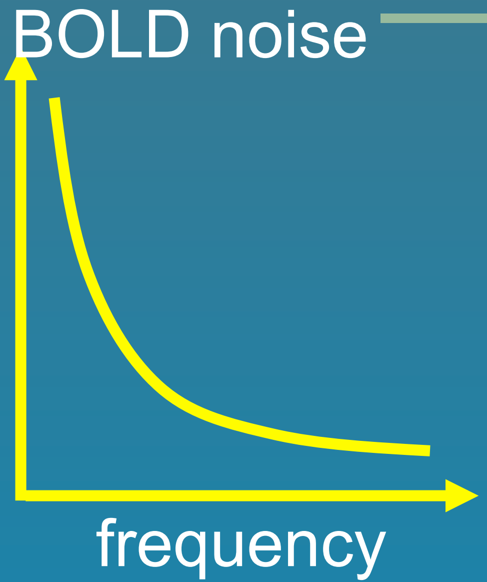
Physiological noise GM >
Physiological noise WM

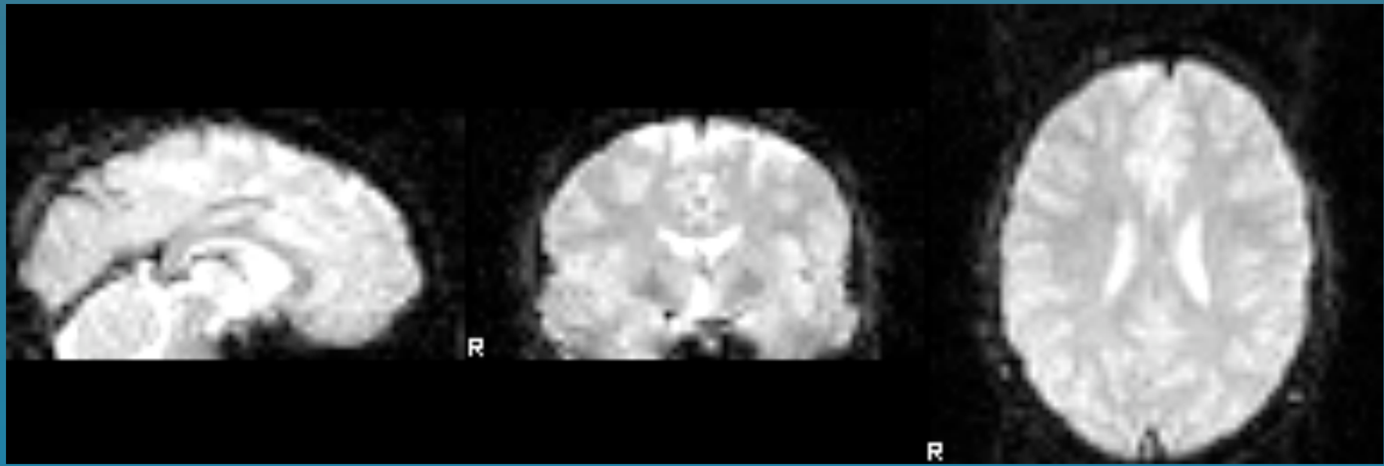
Spatial distribution of noise

- Motion at intensity boundaries
  - volunteer
  - Respiratory B0 shift
- Physiological noise in blood vessels and grey matter



Noise structure





- 1/f dependence
  - BOLD is bad for detecting long time-scale activation
- Next lecture
  - Is there signal in the noise?
  - Correcting physiological noise

Noise or signal?

- Noise is unmodelled signal
  - Spatially structured
  - Temporally structured
- "Physiological" signal
  - Vascular properties
- "Neuronal" signal
  - Resting state networks
  - Resting fluctuations
  - Stimulus induced deactivation

Separation: all haemodynamic

Physiological noise

- Motion
  - McFLIRT correction
- Cardiac
  - Pulsations (aliased)
- Respiratory
  - Motion
  - B_0 shift

} RETROICOR correction (Jon Brooks)

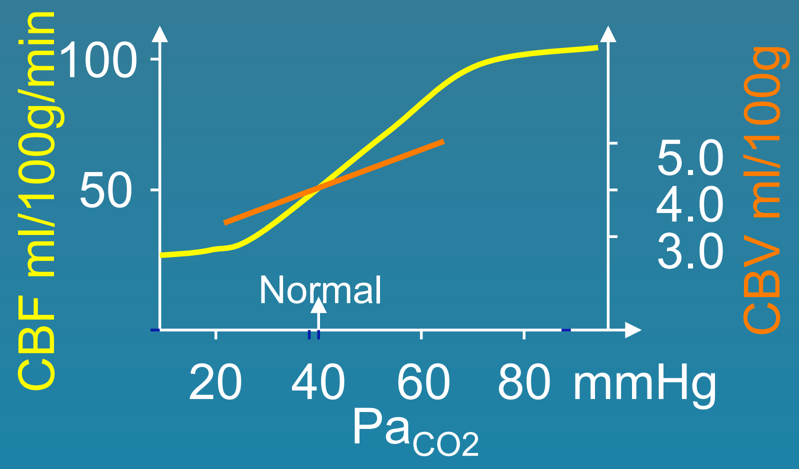
Physiological signal

- Low frequency haemodynamic oscillations
  - Information about vascular properties
  - CO_2 reactivity
  - Autoregulation

- Is it a problem?
- Can we use it?

BOLD response to CO_2

- CO_2 is a potent vasodilator



Hypercapnia:

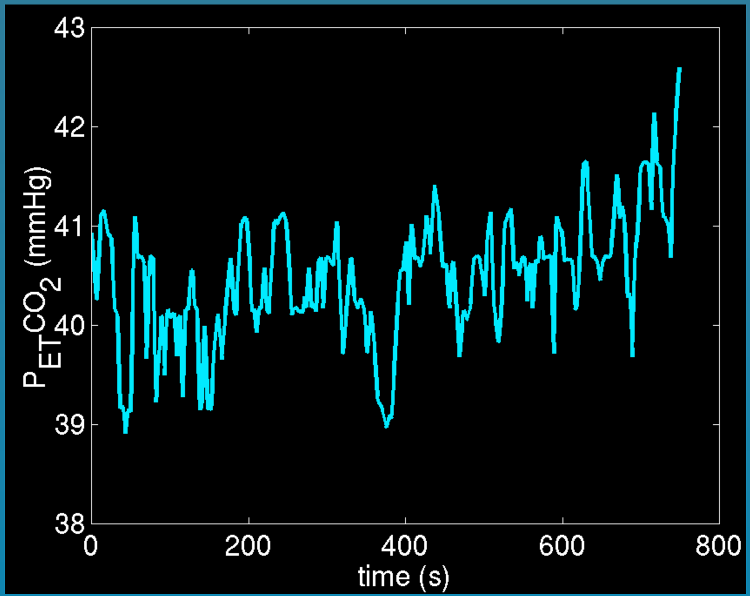
CBF, CBV ↑ → [deoxyHb] ↓ → T2* ↑ → S_{BOLD} ↑

- Previous investigations use sustained hyper/hypocapnia challenges to investigate regional sensitivity (1.5T)

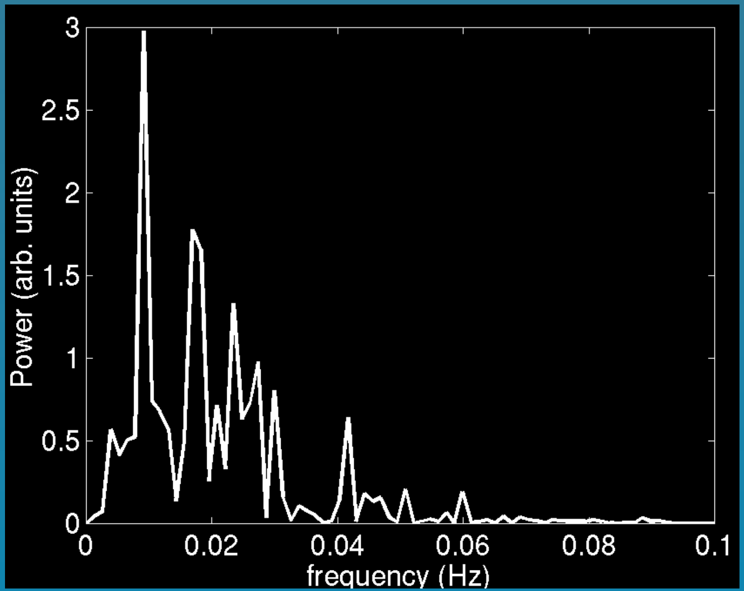
  e.g. Posse et al. 1997, 2001, Rostrup et al. 2000

Spontaneous CO_2 fluctuations

Resting $P_{ET}CO_2$



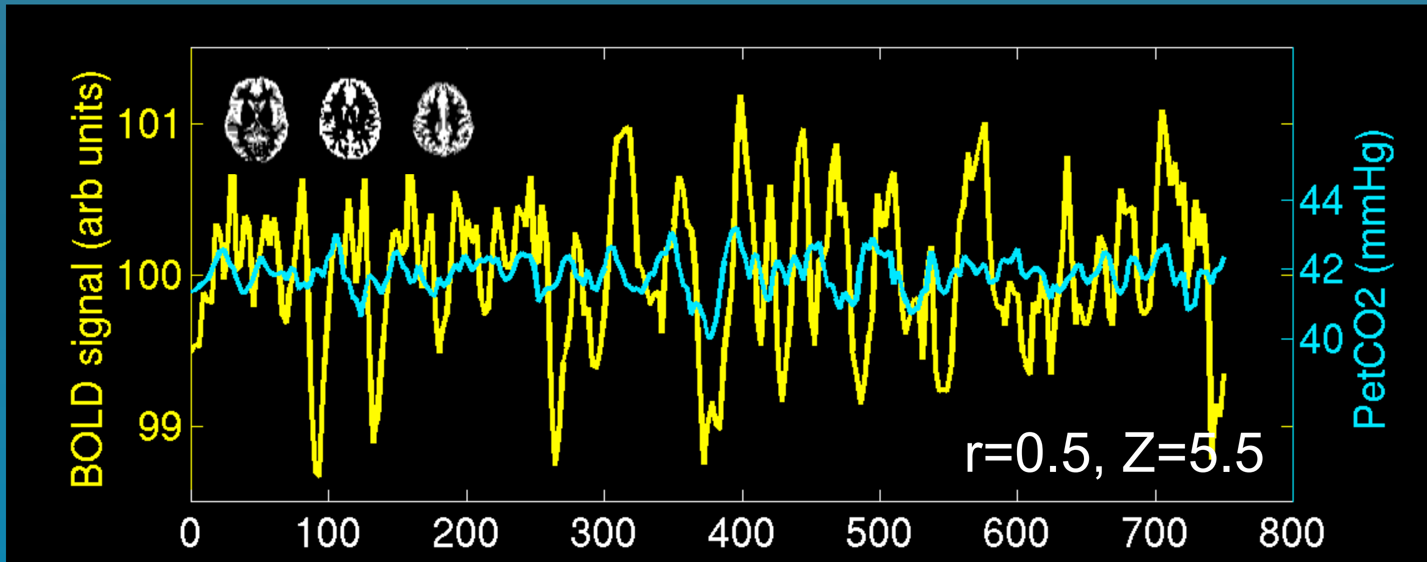
$P_{ET}CO_2$ power spectrum



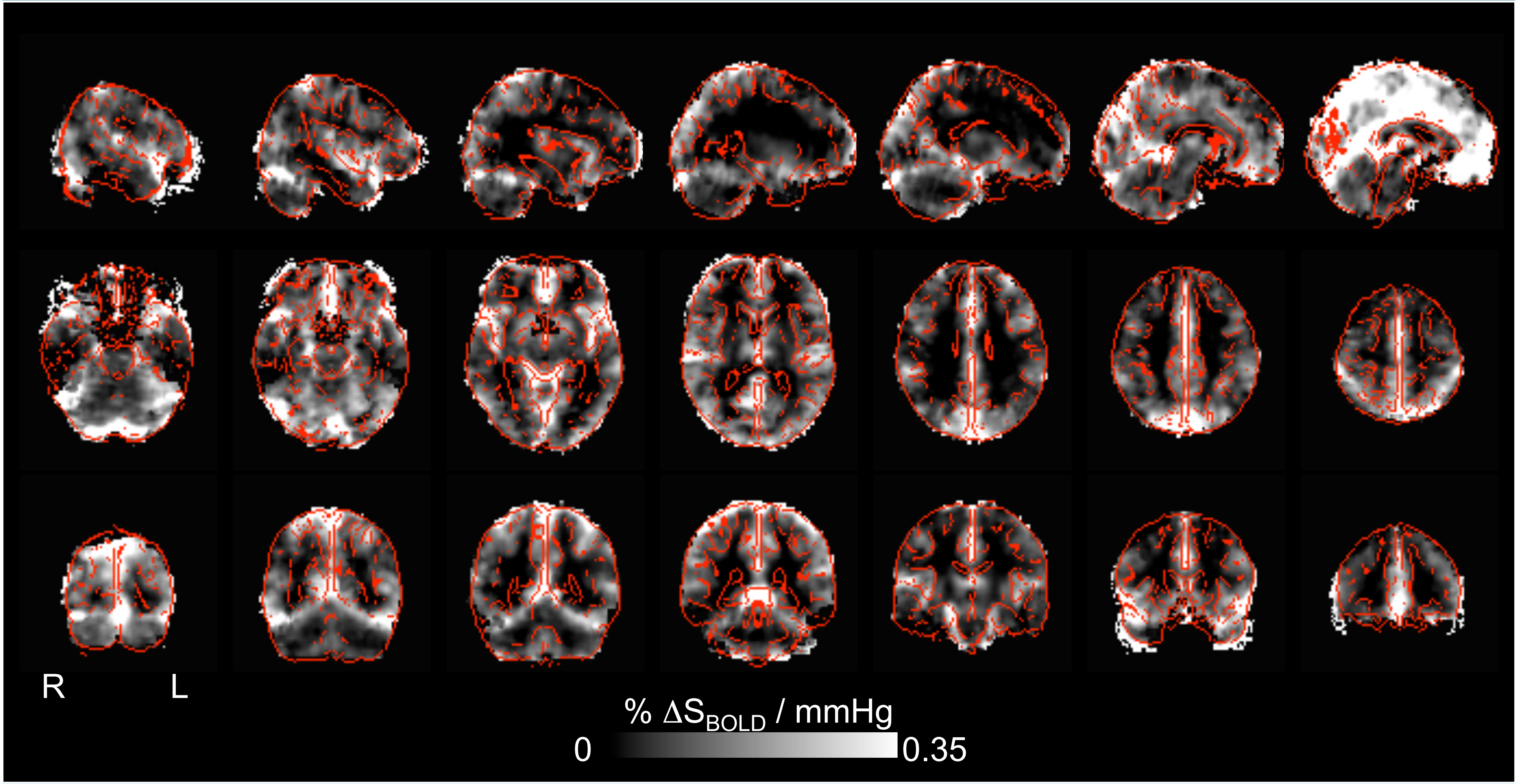
- End-tidal CO_2 ($P_{ET}CO_2$) is a good measure of arterial CO_2
- Fluctuations 0 - 0.05 Hz (Van den Aardweg & Karemaker, 2002)
- Overlaps with stimulus frequencies
- Can correlate with stimulation

Wise et al Neuroimage 2004

BOLD-CO_2 (resting) correlation



BOLD reactivity to resting CO_2



Practical questions

- What does BOLD signal mean in physiological terms?
- What factors affect BOLD signal sensitivity?
- How can I compare BOLD responses
  - Within regions (different conditions)
  - Across regions

Harder practical questions

- How does the temporal BOLD response relate to underlying neurophysiology
- Which features of the BOLD response are general and which are idiosynchratic?
  - Dips
  - Over/undershoots
- How specific is BOLD contrast as a marker for neuronal activation?
  - Spatial resolution
  - Is CBF better?
  - Physiological BOLD “noise”

Factors affecting BOLD signal

- Physiology
  - Cerebral blood flow (baseline and change)
  - Metabolic oxygen consumption
  - Cerebral blood volume
- Equipment
  - Static field strength
  - Field homogeneity (e.g. shim dependent T2*)
- Pulse sequence
  - Gradient vs spin echo
  - Echo time, repeat time, flip angle
  - Resolution

http://www.fmrib.ox.ac.uk/Members/bulte/

Extra Reading:

Buxton *et al*. Modeling the hemodynamic response to brain activation. NeuroImage 23 (2004) S220–S233

Raichle & Mintun. BrainWork and Brain Imaging. Annu. Rev. Neurosci. 2006. 29:449–76