Physiology of BOLD

Dorothee P Auer

The University of Nottingham

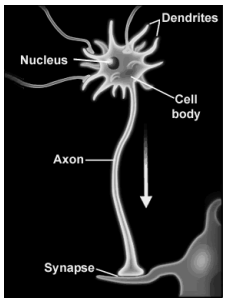
Institute of Neuroscience

Contents

Physiology of brain activation

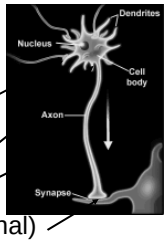
Primer on neurons

- Neurons are specialised cells to process and transmit electrical signals.
- There are ~ 10^{11} neurons in the human brain.
- Neurons are densely interconnected with signal transmission via 'synapses'.
- Neurons receive information via dendrites and soma, and transmit information via axonal connections.



http://www.morphonix.com/software/education/science/brain/game/specimens/images/neuron_parts.gif

Neuronal signaling

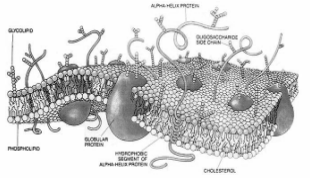


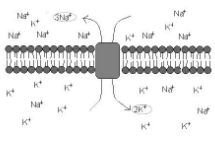
- Input signal (synaptic potential)
- Integrative signal (at axonal hillock)
- Conductive signal (action potential)
- Output signal (secretary synaptic signal)

➢ *Except for output all other signals represent a change in the electric properties of the cell membrane.*

Electric properties

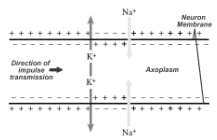
- There is a negative electric potential of ~ 70 mV across all cell membranes ('resting potential').
- The resting potential is maintained via active ion transport (Na^+/K^+ pump).
- Neurons can change their membrane potential.

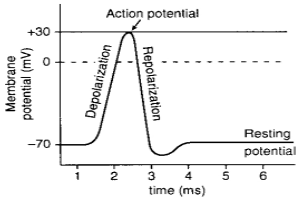




Action potential

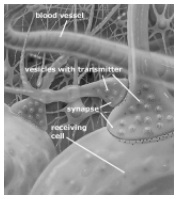
- AP describes short positive changes of the membrane potential due to Na+ influx.
- AP occurs after suprathreshold depolarisation – 50mV.
- AP is a uniform all or none reaction to suprathreshold stimulation.
- AP are self-propagating.

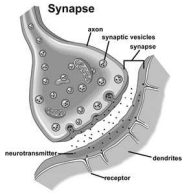




Synaptic transmission

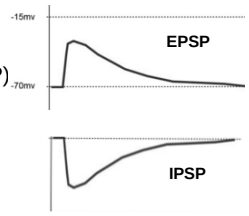
- There are ~ 10^{14} synapses in the adult human brain.
- Most synapses are chemical, i.e. signal transduction occurs via chemical neurotransmission.
- Synaptic transmission can be modulated by learning, i.e. sites of plasticity.





Post-synaptic potentials (PSP)

- Ion flow into the postsynaptic cell due to ligand sensitive channels leads to temporary changes in membrane potential.
- Influx of positively charged ions causes depolarisation, facilitating AP and is hence ***excitatory*** (EPSP)
- Influx of negatively or efflux of positively charged ions cause hyperpolarisation, hence are ***inhibitory*** (IPSP).



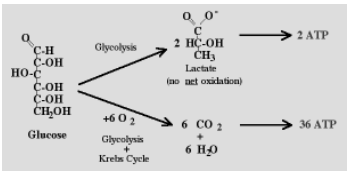
The energy cost of brain activation

- The brain consumes 20% of oxygen despite weighing only 2% of body weight.
- The metabolic activity of the brain is relatively constant.
- Most of the energy use appears related to active signaling.
- Na^+/K^+ ATPase pump may account for 80% of cerebral energy use.
- There are metabolic costs related to
  - Resting membrane potential (<15% in rodents)
  - Restoration after action potential (~ 50% in rodents)
  - Restoring postsynaptic ion fluxes (~1/3 in rodents)

Attwell &Laughlin 2001

How energy cost is met

- The brain has no energy stores, and depends on constant sufficient oxygen and glucose supply.
- ATP synthesis is the principle means to meet energy costs.
- ATP is synthetised via glycolysis, TCA cylce and oxidative phosphorylation.



ATP metabolism

ATP metabolism is regulated by ATPase and creatine kinase.

- All four fluxes can be measured in vivo by ^{31}P magnetization transfer spectroscopic experiments (*Du et al., MRM 2008*)
- ATP synthesis rate (~9 umol/g/min) reflects cerebral oxidative phosphorylation, and is tightly coupled to oxygen metabolism under physiological conditions.
- ATPase flux (^{31}P spectroscopy) is tightly coupled with brain activity in rats (*Du et al., PNAS 2008*)

Metabolism and brain activation

- Do you expect glucose and oxygen metabolism to be related to brain activity? If so, how?
- Do you expect oxygen and glucose metabolism to be coupled?

CMR_{O2} : cerebral metabolic rate for oxygen
CMR_{Glc} : cerebral metabolic rate for glucose

Metabolic uncoupling?

- If all glucose were oxidised, the oxygene to glucose ratio (index) would be 6:1, but only a 5.5:1 ratio has been observed at rest suggesting partial anaerobic glycolysis.
- During stimulation, cerebral blood flow and CMR_{Glc} are matched, whereas CMR_{O2} increased only 1/10 of CBF or $CMR_{Glc.}$ (Fox, Raichle et al., 1988).

➢ CMR_{Glc} and CMR_{O2} are hence stoichiometrically 'uncoupled'.

Metabolic uncoupling

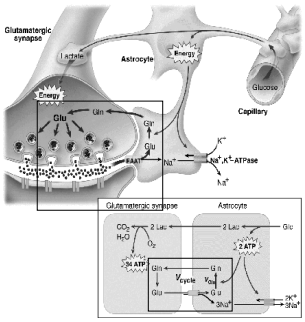
Nature of uncoupling of glucose and oxygen metabolism remains unclear.

Various explanations/models were proposed, i.e. uncoupling may result from:

- ➢ anaerobic glycolysis (Fox/Raichle, Magistretti/Pellerin Shulman/Rothman/Hyder).
- ➢ superfluous perfusion (Malonek & Grinvald).
- ➢ limited oxygen extraction/diffusion (Buxton, Gjedde).

The Astrocyte-Neuron Lactate Shuttle

- Glutamate uptake and recycling in astrocytes is energy depending at a cost of 2 ATP/glutamate.
- ATP cost is met by anaerobic glycolysis.
- Lactate is then released from astrocytes and taken up by neurons to be oxidised to yield further 36 ATP molecules.



after Magistretti et al, Science 1999

Limited oxygen delivery Models

Buxton/Frank 1998 (Transit-time model)

Assumptions

- Cerebral oxygen tension is low.
- Oxygen delivery is increased through perfusion.
- There is no capillary recruitment.

Predictions

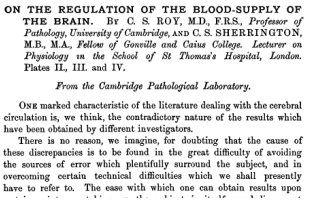
- Highly nonlinear relation CBF/CMR_{O2}
- Only small fractional CMR_{O2} / CBF increases

Explains Fox/Raichle data but conflicts with other data!

Gjedde 1997
Hyder et al., 1998

Blood flow and Brain activation

- Roy & Sherrington, 1890
  - Concept of functional local CBF regulation



ON THE REGULATION OF THE BLOOD-SUPPLY OF THE BRAIN. By C. S. ROY, M.D., F.R.S., *Professor of Pathology, University of Cambridge*, AND C. S. SHERRINGTON, M.B., M.A., *Fellow of Gonville and Caius College. Lecturer on Physiology in the School of St Thomas's Hospital, London.* Plates II., III. and IV.

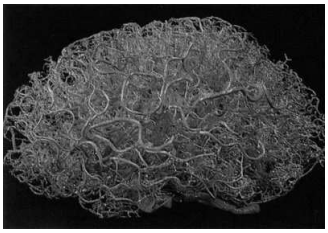
From the Cambridge Pathological Laboratory.

One marked characteristic of the literature dealing with the cerebral circulation is, we think, the contradictory nature of the results which have been obtained by different investigators.

There is no reason, we imagine, for doubting that the cause of these discrepancies is to be found in the great difficulty of avoiding the sources of error which plentifully surround the subject, and in overcoming certain technical difficulties which we shall presently have to refer to. The ease with which one can obtain results upon

CBF is tightly coupled to neuronal activation

Regulation of cerebral blood flow



Cerebral blood flow

Primer

CBF: Cerebral blood flow (perfusion)
(~50ml/100g/min)
vs. cerebral blood flow velocity
CBV: Cerebral blood volume (arterial/venous)
CPP: Cerebral perfusion pressure: MABP-ICP
MABP: Mean arterial blood pressure
ICP : Intracranial pressure
CVR: Cerebral vascular resistance

CBF regulators

CBF is regulated via changes in vascular resistance

- External chemical
  - $PaCO_2$
- Pressure
  - Pressure Autoregulation (60-150mmHg)
    CBF = CPP/CVR
- Metabolic
  - Functional hyperaemia
  - ? Adenosine, potassium, prostaglandine
- Neurogenic
  - Sympathetic activity

CBF regulation

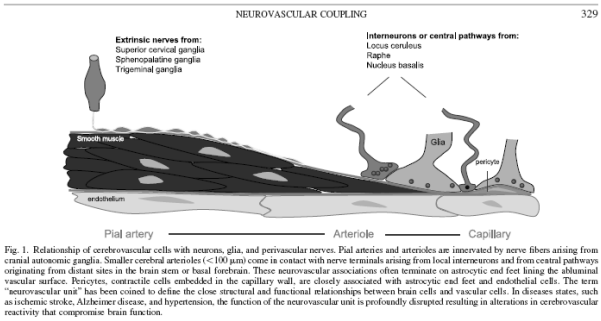
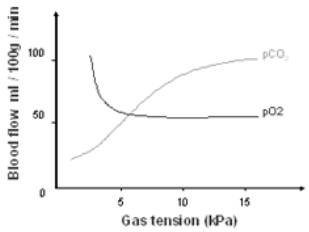


Fig. 1. Relationship of cerebrovascular cells with neurons, glia, and perivascular nerves. Pial arteries and arterioles are innervated by nerve fibers arising from cranial autonomic ganglia. Smaller cerebral arterioles (<100 μm) come in contact with nerve terminals arising from local interneurons and from central pathways originating from distant sites in the brain stem or basal forebrain. These neurovascular associations often terminate on astrocytic end feet lining the abluminal vascular surface. Pericytes, contractile cells embedded in the capillary wall, are closely associated with astrocytic end feet and endothelial cells. The term "neurovascular unit" has been coined to define the close structural and functional relationships between brain cells and vascular cells. In diseases states, such as ischemic stroke, Alzheimer disease, and hypertension, the function of the neurovascular unit is profoundly disrupted resulting in alterations in cerebrovascular reactivity that compromise brain function.

Girouard and Iadecola, J Appl Physiol 100:328-335, 2006

Chemical CBF regulation

- CO_2 is the most potent vasodilator
- Proportional CBF increase over range of pCO_2

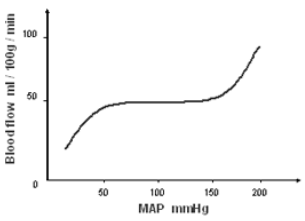


http://www.frca.co.uk/default.aspx

AnaesthesiaUK

Autoregulation

- Cerebral autoregulation is the process that maintains CBF constant over a range of pressure fluctuations (physiologically 50-150 mm Hg).



http://www.frca.co.uk/default.aspx

AnaesthesiaUK

Metabolic CBF regulation

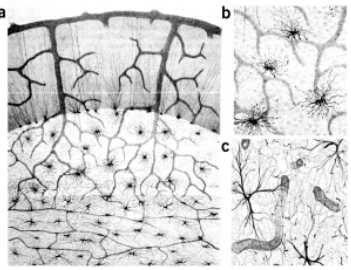
- Functional hyperaemia (Roy, Sherrington 1890)
- CBF is coupled with metabolism (Sokoloff 1977)

- CBF is tightly coupled with neuronal activation ('neuro-vascular coupling')

Mechanisms of metabolic CBF regulation remain poorly understood.

Functional hyperaemia

- Mismatch between arteriolar territories and functional neuronal ensembles
- Role o



Iadecola, Nat Neurosci 2007

Neurovascular coupling

Table 1. *Factors implicated in neurovascular coupling*

Agent	References
Vasoactive ions	
K^+	45
H^+	45
Ca^{2+}	28
Metabolic factors	
Lactate, CO_2	71, 73
Hypoxia	73
Adenosine	72
Vasoactive neurotransmitters	
Dopamine	43
GABA	22
Acetylcholine	74
Vasoactive intestinal peptide	83
Other	
NO	61
COX-2 products	55
P450 products	67
CO	51

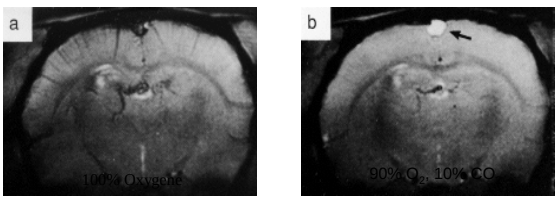
NO, nitric oxide; COX-2, cyclooxygenase-2; CO, carbon monoxide.

Girouard and Iadecola, J Appl Physiol 100:328-335, 2006

Physiological underpinnings of BOLD changes

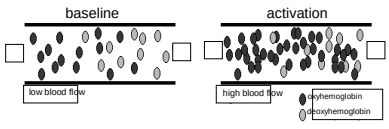
BOLD contrast

- Chemical regulation of CBF translates into signal change in T2* sensitive MRI.
- CBF increase leads to MRI signal increase reflecting increased ratio of oxyhaemoglobin/deoxyhaemoglobin (OxHb/DeOxHb).

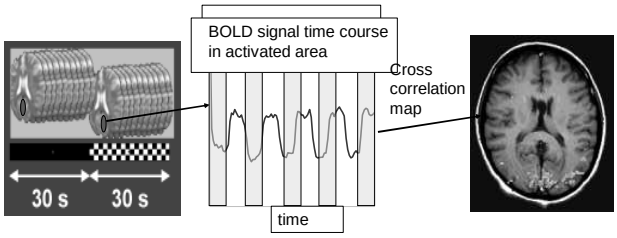


'Blood oxygenation level dependent contrast' *Ogawa et al., PNAS 1990*

The principle of f-MRI



BOLD signal increase correlates with local field potentials and spike frequency
(Logothetis et al., Nature, 2001; Smith et al., PNAS, 2002)

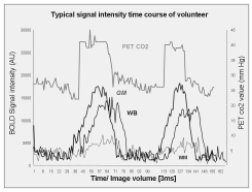


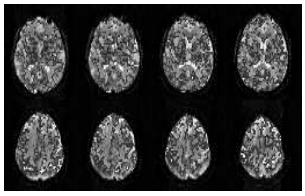
CBF, CBV and BOLD

- CBF increase induces BOLD increase.
- Venous CBV leads to decreased OxHb/DeOxHb ratio, i.e. reduced BOLD signal.
- Arterial CBV leads to increased OxHb/DeOxHb ratio, i.e. synergistic BOLD increase with CBF.
- Ratios of aCBV and vCBV and their dynamics in brain activation are largely unknown.

Hypercapnia and BOLD

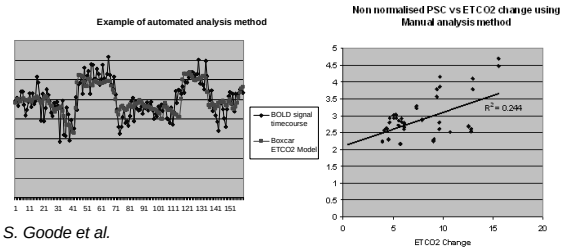
- CO_2 ↑ induces CBF↑ and CBV ↑
- No change in oxygen extraction
- No substantial change in metabolism
- Net increase in OxHb/deOxHb





Hypercapnia and BOLD

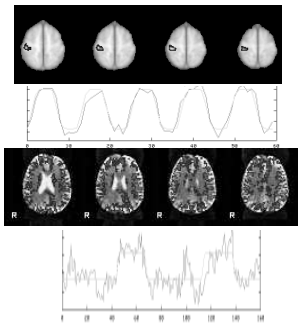
- Near linear relation between BOLD PSC and hypercapnia level.
- Still: physiological interpretation is limited by compounding effects of CBV.

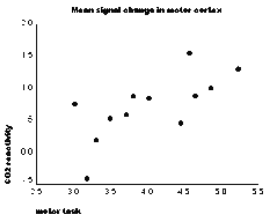


S. Goode et al.

Cerebro-vascular reactivity

Fully recovered patients with unilateral carotid disease (<60% stenosis), previous transitory symptoms, no stroke.





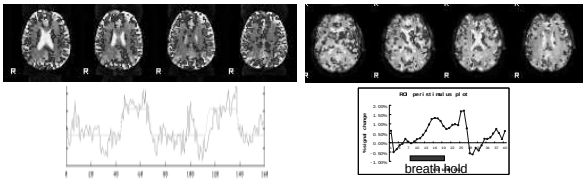
Pearson correlation coefficient =0.69 ~50% variance

Ojango, Goode et al., ECR 2007

Does physiological CO_2 fluctuation modulate BOLD ?

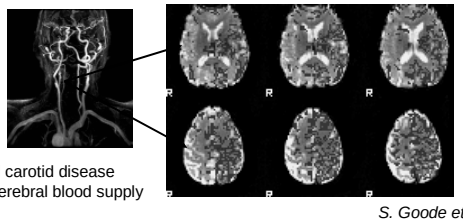
- CO_2 acts as strong vasodilator and varies with breathing contributing to spontaneous BOLD fluctuations. *(Wise et al., 2004)*
- Vasomotor reactivity induces further variance, and calibration using breath hold reduces ~25% *(Thomason et al., 2007)*

7% CO_2 inspiration (10' @ 1.5T) *20'' breath hold (4' @ 3T)*



Cerebrovascular reserve capacity

- Cerebrovascular reserve (CVR) - capacity of the cerebral circulation to adapt to vasodilatory stimuli (vasomotor reactivity).
- CVR is severely reduced in patients with e.g. carotid artery disease leading to haemodynamic impairment.

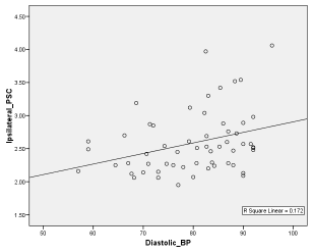


Unilateral carotid disease impairs cerebral blood supply

S. Goode et al.

CVR and autoregulation

- BOLD reactivity to hypercapnia was positively correlated with diastolic blood pressure in patients with carotid disease suggesting shifted autoregulation.

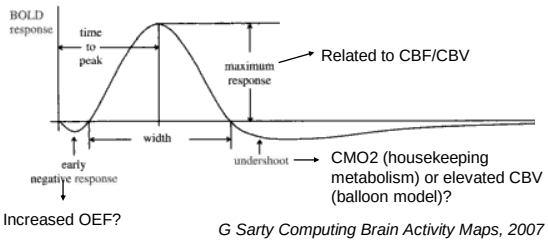


– Diastolic BP vs Ipsilateral %SC R^2 = 0.172 (p=0.006).
– Diastolic BP vs Contralateral %SC R^2 = 0.107 (p=0.047).

S. Goode et al.

Dynamic neuronal BOLD response

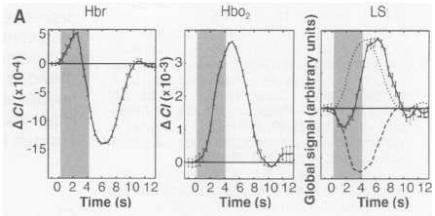
- Complex haemodynamic response to brief neuronal stimulation.



G Sarty Computing Brain Activity Maps, 2007

Haemoglobin changes

- Malonek and Grinvald, Science 1996



The initial dip

- Short-term BOLD signal decrease prior to positive response (Menon et al., 1995)
- May result from increased oxygen extraction
- Controversial as inconsistent experimental findings.

The undershoot

- BOLD signal decrease after end of stimulation
- Two prevailing theories:
  - Balloon Model (*Buxton, Mandeville*)
    - Slow return of CBV to baseline accounts for BOLD signal decrease
  - Metabolic Model (*Frahm*)
    - On-going metabolic demand (housekeeping) leads to increased oxygen metabolism lasting longer than haemodynamic response.

Logothetis, Nature 2001

Metabolic origin of undershoot ?

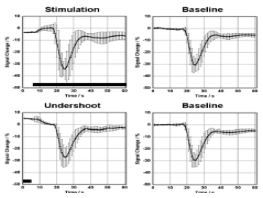
NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 40 (2008) 473–481

The post-stimulation undershoot in BOLD fMRI of human brain is not caused by elevated cerebral blood volume

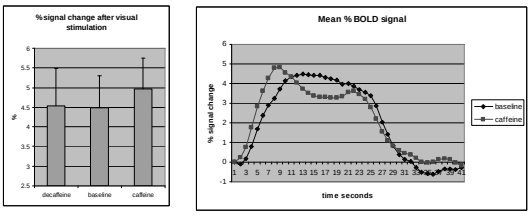
Jens Frahm,[a,*] Jürgen Baudewig,[b] Kai Kallenberg,[b,c] Andreas Kastrup,[d] K. Dietmar Merboldt,[a] and Peter Dechent[b]

Stimulus induces 31% increase in CBV, but no change in CBV was noted in undershoot period.



Caffeine and altered BOLD dynamics

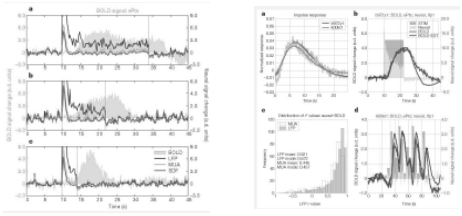
- Caffeine, an adenosine receptor antagonist causes vasoconstriction (CBF reduction).
- 3mg/kg caffeine increases visual BOLD response amplitude, and alters haemodynamic response function (abolishes undershoot).



Koumelis, Stewart et al.

BOLD and electrophysiology

- BOLD signal changes correlate better with local field potentials (LFP dendro-somatic input) than multi-unit activity (output) of a neuronal population.



Logothetis, Nature 2001