UCLA NITP

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Neurovascular Coupling

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Cerebral Blood Flow and Brain Activation

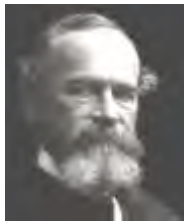
"... The subject to be observed lay on a delicately balanced table which could dip downwards either at the head or the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system. ..."

William James (Principles of Psychology, 1890)

Mosso's experiment?

Figure courtesy of Olaf Paulson

Cerebral Blood Flow and Brain Activation



"... We must suppose a very delicate adjustment whereby the circulation follows the needs of the cerebral activity. Blood very likely may rush to each region of the cortex according as it is most active, but of this we know nothing. "

William James (Principles of Psychology, 1890)

The Hemodynamic Response to Brain Activation

Motor task, human subjects, CBF measured with arterial spin labeling (data from Miller et al, 2001)

A

Basic questions:
Why is the flow change so quick?
Why is the flow change so large?

Buxton, *Frontiers in Neuroenergetics*, 2:8, 2010

Blood Flow and O_2 Metabolism

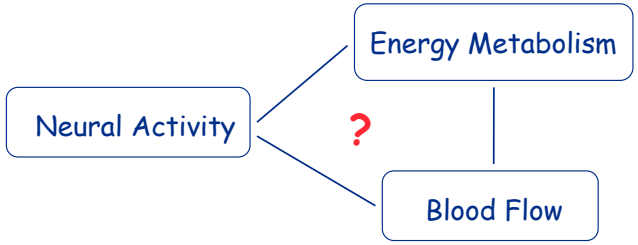
Blood flow delivers O_2 and glucose and clears CO_2

$$CMRO_2 = E\ CBF\ [O_2]_a$$

Key players:		Normal Value	Activation
$CMRO_2$	cerebral metabolic rate of O_2	1.6 µmol/ml tissue-min	+12%
E	O_2 extraction fraction	0.4	0.34
CBF	cerebral blood flow	0.5 ml/ml tissue-min	+30%
CBV	cerebral blood volume	0.05 ml/ml tissue	+10%
CMRGlc	cereb. Metb. Rate of Glucose	0.3 µmol/ml tissue-min	+25%
$[O_2]_a$	total arterial O_2	8 µmol/ml	---

E decreases with activation!

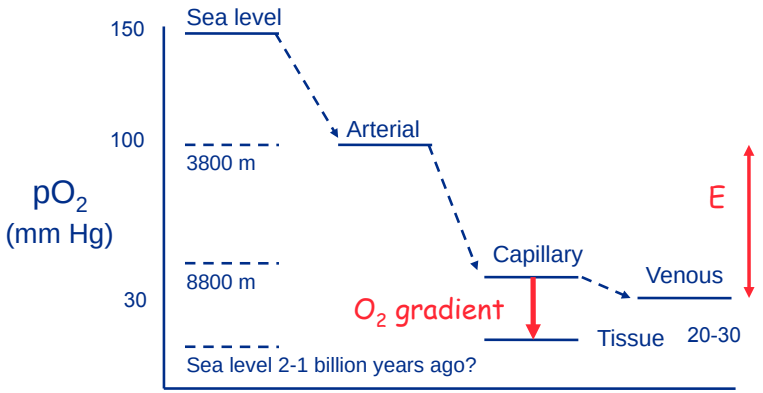
How does it all fit together?

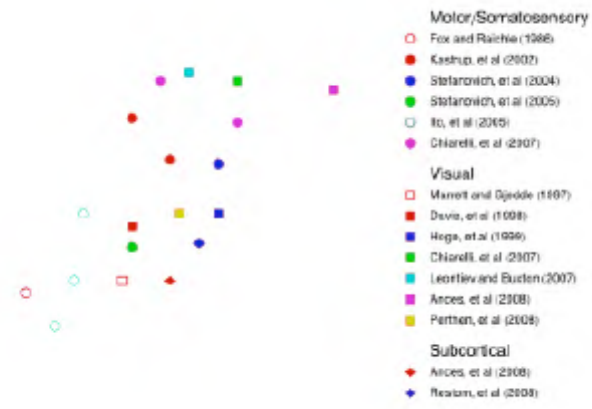


"The view that the hemodynamic response is coupled to signaling processes represents a conceptual shift from the traditional idea that the energy demands of the tissue directly determine the flow increase associated with neural activation."
Attwell and Iadecola (2002)

"Future issues to be resolved: 1) What function(s) does regional brain-blood flow perform when neuronal activity changes?"
Raichle and Mintun (2006)

Oxygen Concentration





Buxton, *Frontiers in Neuroenergetics*, 2:8, 2010

$$n = \frac{\%\Delta CBF}{\%\Delta CMRO_2}$$

Does the brain try to maintain tissue pO_2 as $CMRO_2$ increases?

A

Potential answer to basic questions:

Why is the flow change so large?
CBF change needs to be ~2–3 times larger than the $CMRO_2$ change to maintain constant tissue pO_2.

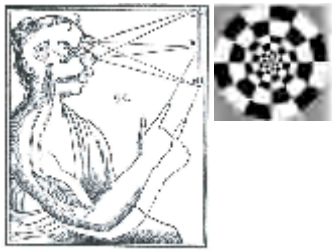
Why is the flow change so quick?
O_2 in brain: concentration ~ 0.3 mM (mostly in blood)
metabolic rate ~ 1.6 mM/min
depletion time ~ 10 sec

Why does blood oxygenation change?
Allows the capillary/tissue O_2 gradient to increase without changing the tissue pO_2.

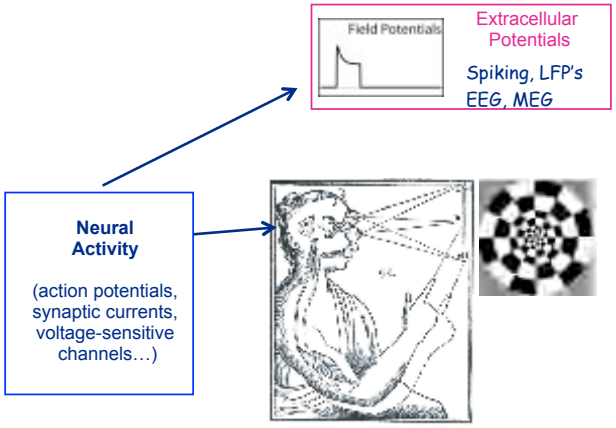
But the pO_2 itself is probably not the signal for changing CBF

Buxton, *Frontiers in Neuroenergetics*, 2:8, 2010 Devor et al, *J Neurosci*, 31:13676, 2011

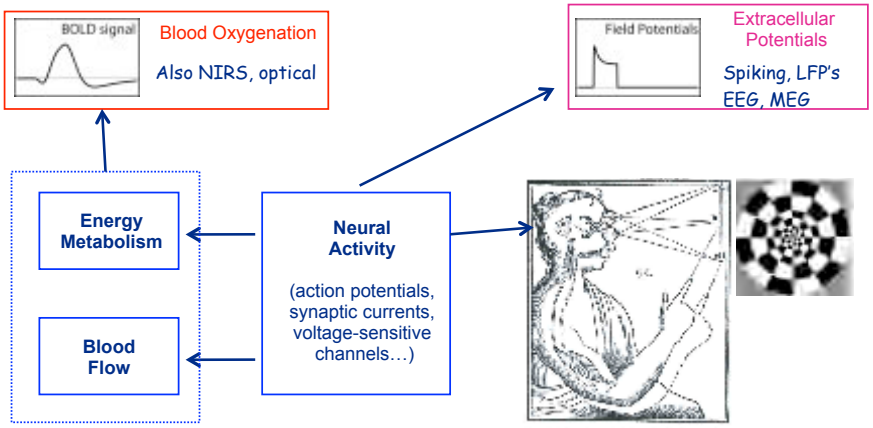
Neural activity and the BOLD response



Neural activity and the BOLD response

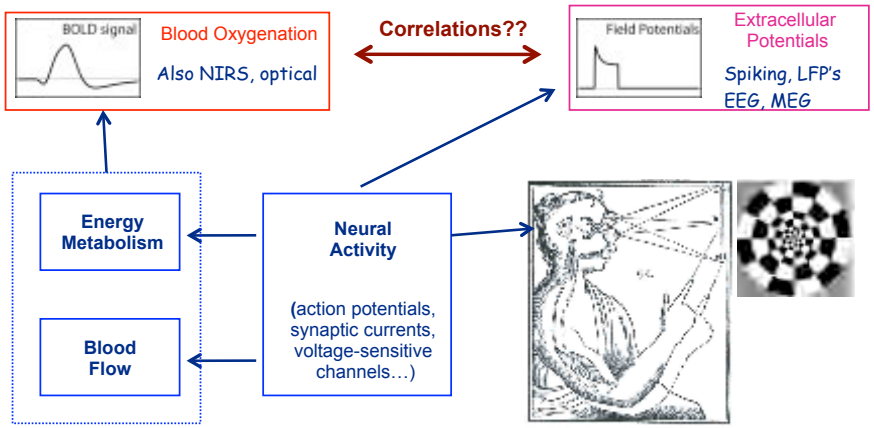


Neural activity and the BOLD response



Neural activity and the BOLD response

Ekstrom, *Brain Research Reviews*, 2010



Energy Metabolism

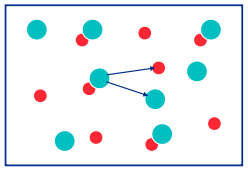
Biological energy sources

The brain needs sources of free energy (-ΔG) to drive uphill reactions and for signal amplification

Systems far from equilibrium:

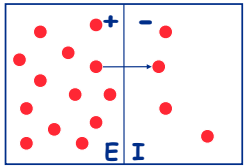
ATP system: $ATP \rightarrow ADP + Pi$

$$\frac{[ATP]}{[ADP]\,[Pi]} >> \text{equilibrium}$$

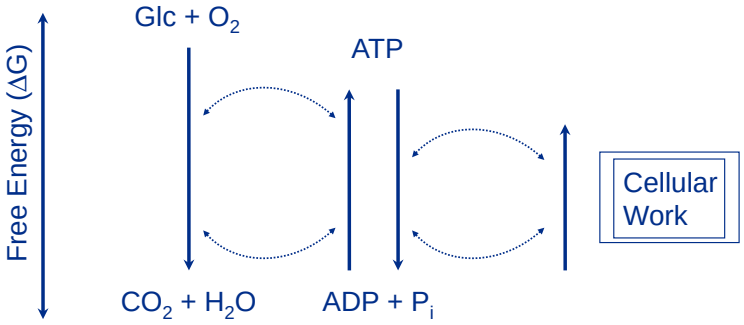


Sodium gradient across a membrane:

$$\frac{[Na^+]_E}{[Na^+]_I} >> \text{equilibrium}$$



Bioenergetics

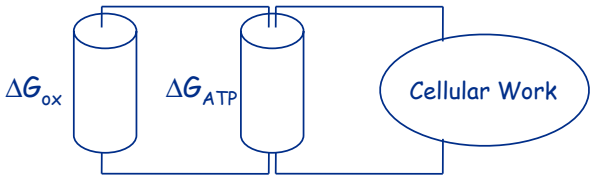


Glycolysis (cytosol): Glucose → 2 Pyruvate + 2 ATP

Oxidative metabolism (mitochondria):

$2\ Pyruvate + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O + 34\ ATP$

Biological Batteries



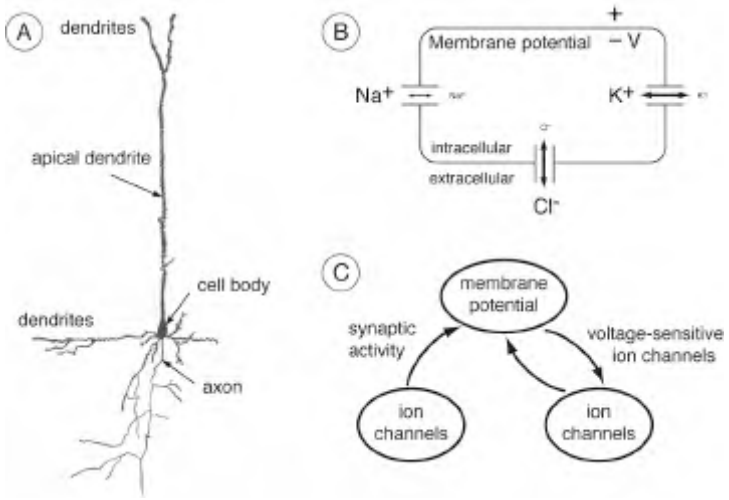
Free energy, either to drive uphill reactions or for signaling, is available from subsystems that are far from equilibrium:

$\frac{[Pyr][O_2]^3}{[CO_2]^3}$	$\frac{[H^+]_O}{[H^+]_I}$	$\frac{[ATP]}{[ADP][P_i]}$	$\frac{[Na^+]_E}{[Na^+]_I}$	$\frac{[Ca^{++}]_E}{[Ca^{++}]_I}$
Environment	Mitochondria	Cell	Cell Membrane	

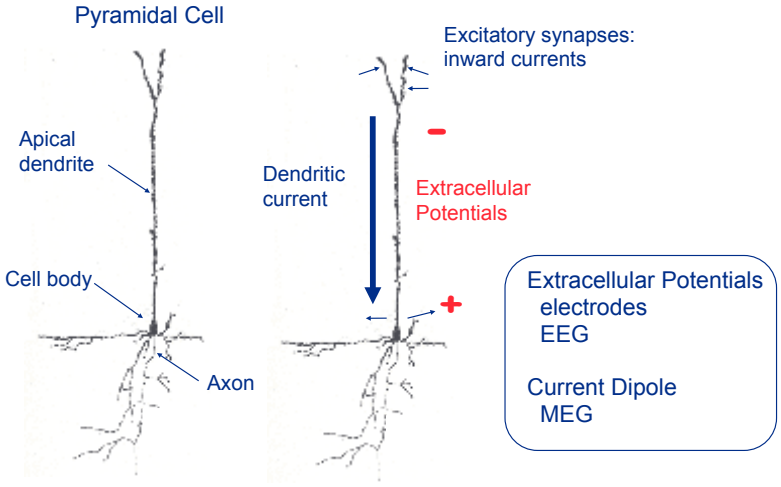
Sodium/Potassium pump

The Energy Cost of Neural Activity

Neuronal Signaling



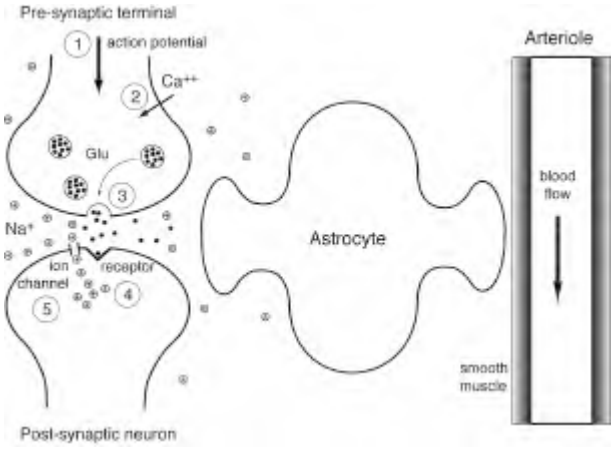
Electrophysiology Signals



Synaptic activity initiates ion fluxes

Pre-synaptic Activity:
1. Arrival of an action potential
2. Opens Ca^{++} channels
3. Ca^{++} influx causes vesicles to release glutamate

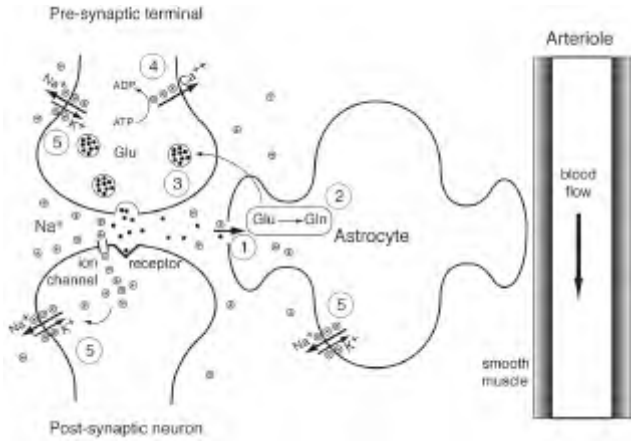
Post-synaptic Activity:
4. Glutamate binds to post-synaptic receptor
5. Binding opens Na^{+} channel, and many sodium ions flow into the cell down their gradient

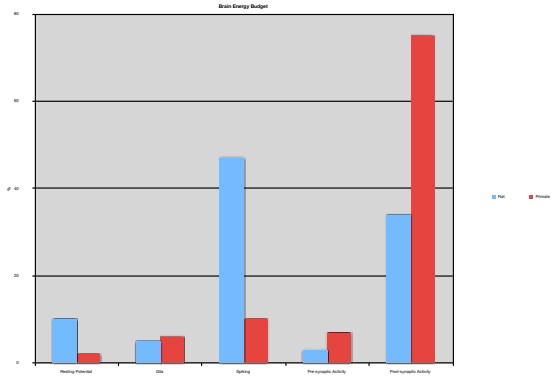


Pumping back the ions costs energy

Glutamate recycling:
1. Astrocyte takes up glutamate
2. Converts it to glutamine
3. Glutamine is transported back to the pre-synaptic neuron

Restoring ion gradients requires free energy
4. Ca^{++} moved out in exchange for 3 Na^{+} moving in (down the gradient)
5. Na^{+} transported by the Sodium/Potassium Pump





Most of the ATP is consumed by the Na/K pump in recovering from post-synaptic excitatory activity

Attwell and Laughlin (2001)

Glucose metabolism increases more than oxygen metabolism during activation

Lactate Shuttle Hypothesis (Magistretti, et al): Glycolysis increase is more prominent in astrocytes, producing lactate that is transported to the neurons as fuel for oxidative metabolism

Key questions:

Do CBF and Glucose metabolism always vary together? (usually, but not always)

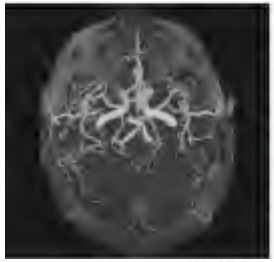
Does CBF need to increase to support Glucose metabolism? (no)

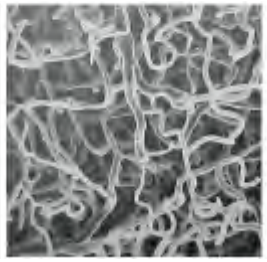
Is glycolysis preferred for providing ATP for synaptic activity? (maybe)

Do neurons primarily use lactate for oxidative metabolism? (maybe)

Cerebral Blood Flow

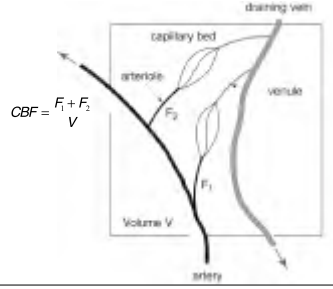
Cerebral Blood Flow





Duvernoy, et al 1981

Zheng, et al 1991



CBF = Rate of delivery of arterial blood to an element of tissue:

Human brain: CBF ~ 60 ml/(100 g)-(min)
~ 0.6 ml/ml-min

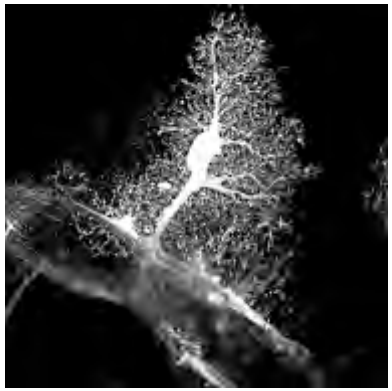
Control of CBF

Systemic: hormonal and neural effects control the distribution of blood flow to different parts of the body while maintaining CBF

Autoregulation: If blood pressure drops, cerebrovascular resistance decreases to maintain CBF

Functional activity: Local neural activity increases CBF, but function is still unclear

Astrocytes bridge neurons and vessels

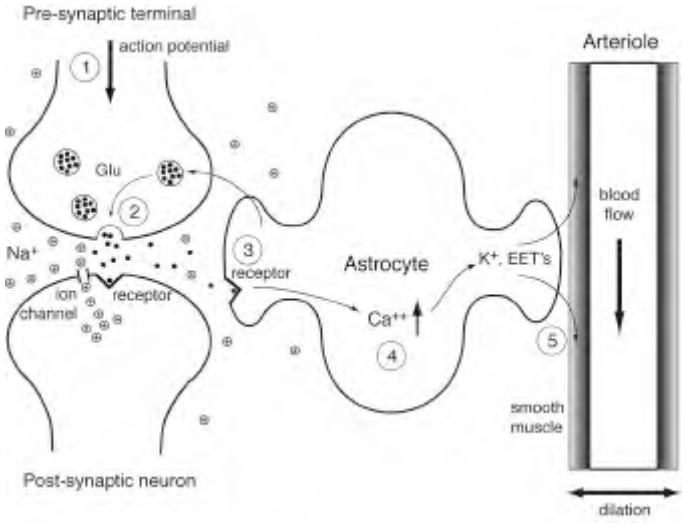


Single astrocyte expressing GFP, 2-photon imaging

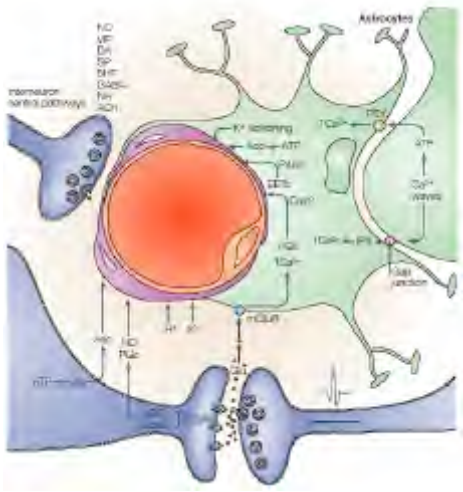
Schematic of astrocytes organized along vessels

Nedergaard et al, 2003

Blood flow changes with neural activation



Mechanisms of CBF Control



Vasoactive ions:
K^+, H^+, Ca^{++}

Diffusible gases:
Nitric oxide (NO),
Carbon monoxide (CO)

Metabolic factors:
lactate, CO_2, hypoxia,
adenosine

Vasoactive neurotransmitters:
dopamine, GABA,
acetylcholine,
Vasoactive intestinal peptide

Arachadonic acid pathways
COX, P450, EET's, HETE's

Girouard and Iadecola 2006

No simple relation between blood flow and inhibitory neural activity

Inhibitory interneurons can drive (Cauli, 2004)

constriction with release of: somatostatin (SOM)
neuropeptide Y (NPY)

dilation with release of: nitric oxide (NO)
vasoactive intestinal peptide (VIP)

Astrocytes can constrict or dilate through multiple released agents, possibly depending on current tone or pO_2. (Gordon, 2008)

Adenosine inhibits neural activity but dilates vessels. Caffeine blocks adenosine receptors and: (Griffeth, 2011)

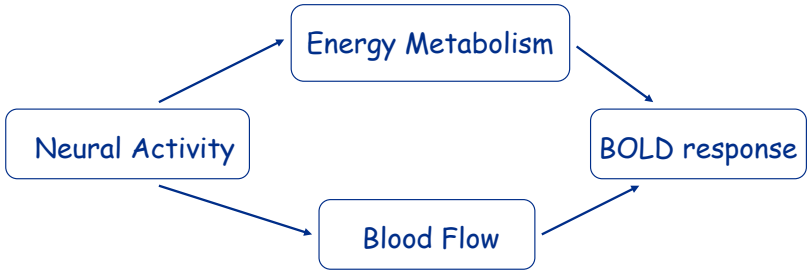
lowers baseline CBF
raises baseline $CMRO_2$
alters CBF/$CMRO_2$ activation coupling

Current Ideas: CBF and energy metabolism responses

Initial CBF response:
Feed-forward, driven by neural activity, rather than a feed-back response to the increased energy demand.
Strongly driven by excitatory synaptic activity.
Feed-back control related to metabolism operates more slowly (?).

Energy metabolism response:
Major energy cost is related to pumping sodium after excitatory activity.
CMRGlc also may be strongly driven by synaptic activity to provide energy for recycling neurotransmitter.
$CMRO_2$ increases to cover total energy costs.

Working Hypothesis



CBF driven primarily by local synaptic activity.
$CMRO_2$ driven by total energy costs (synaptic plus spiking).
BOLD response depends on both!