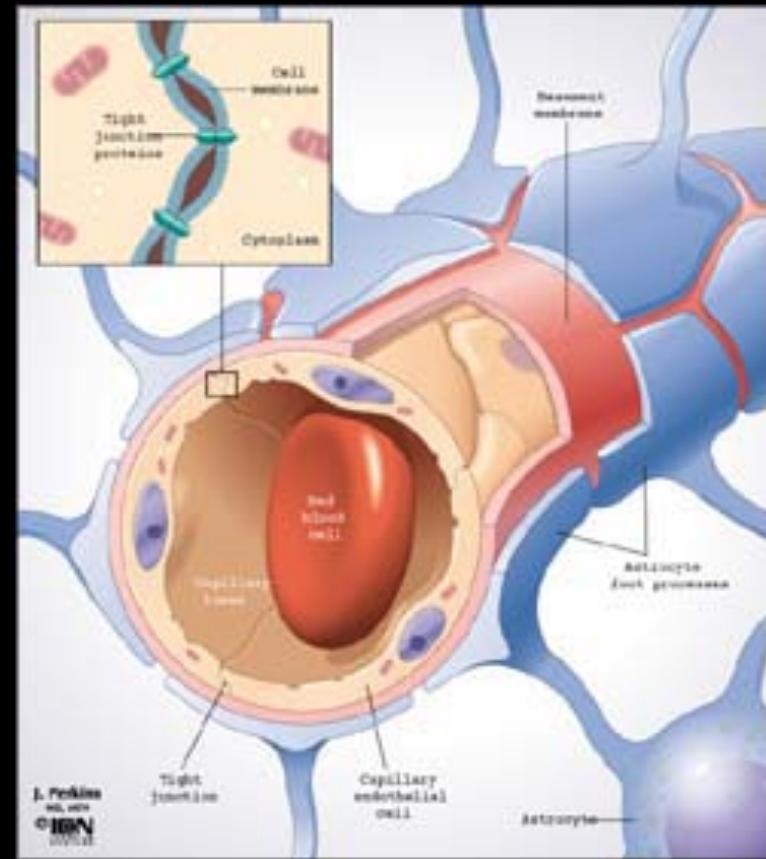
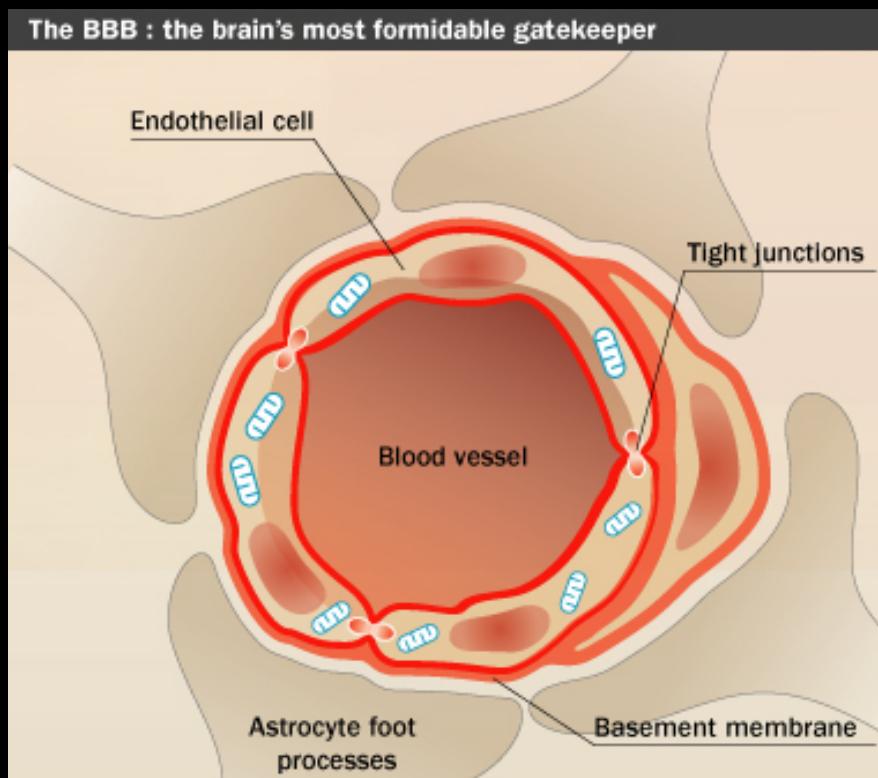


In vivo brain functional exploration

Why in vivo?

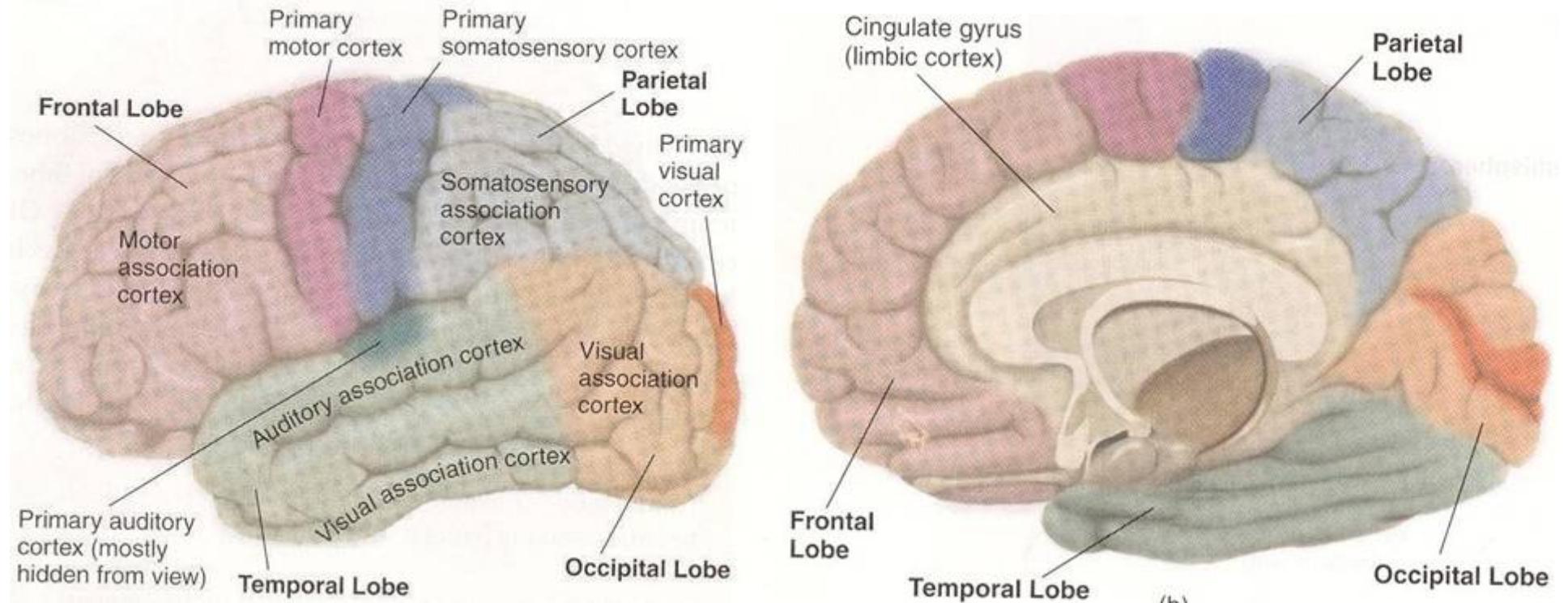
1. *in vitro* and *in vivo* differences
2. Anatomical 'constraints'



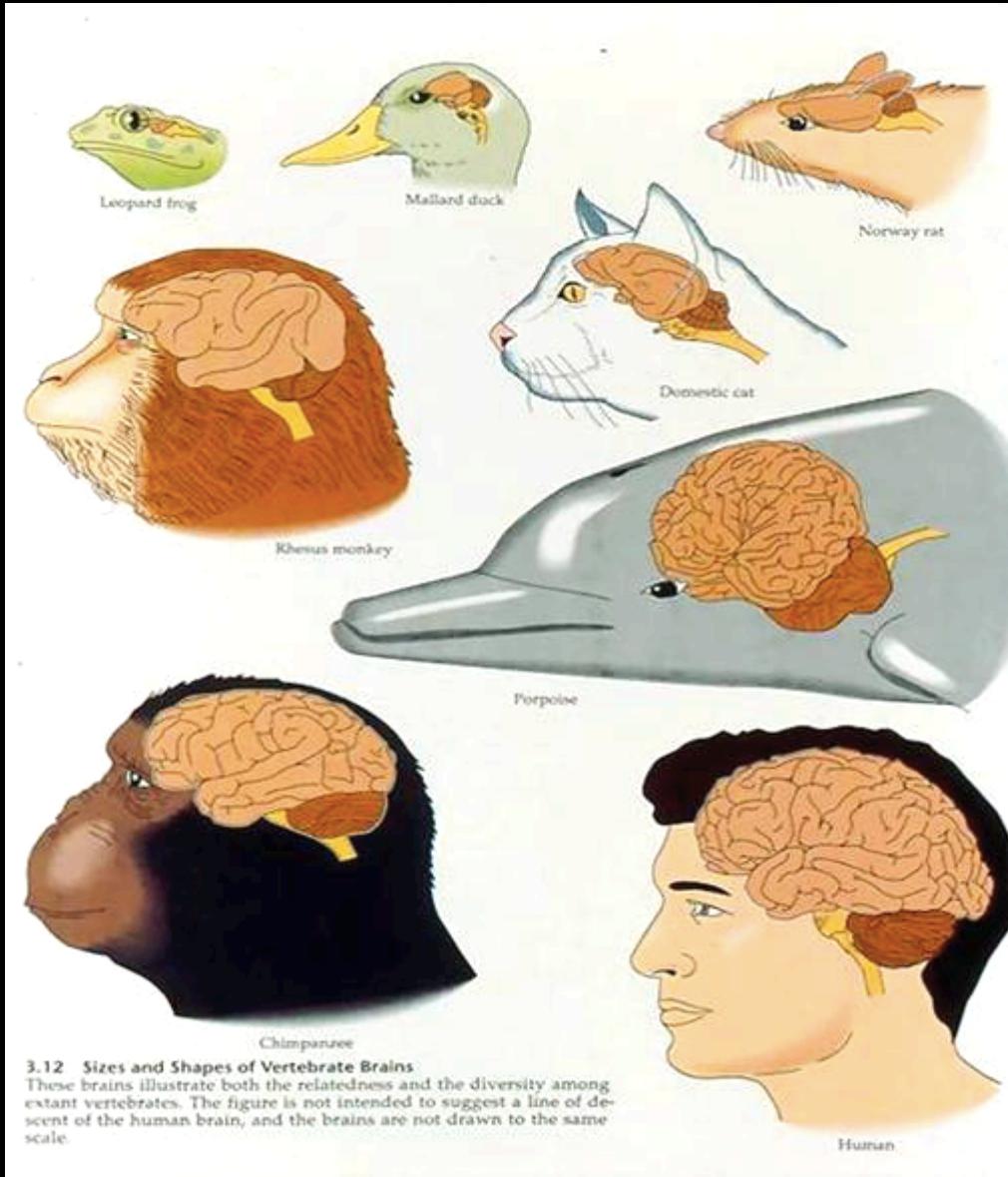
In vivo brain functional exploration

Why in vivo?

3. Functional segregation and integration



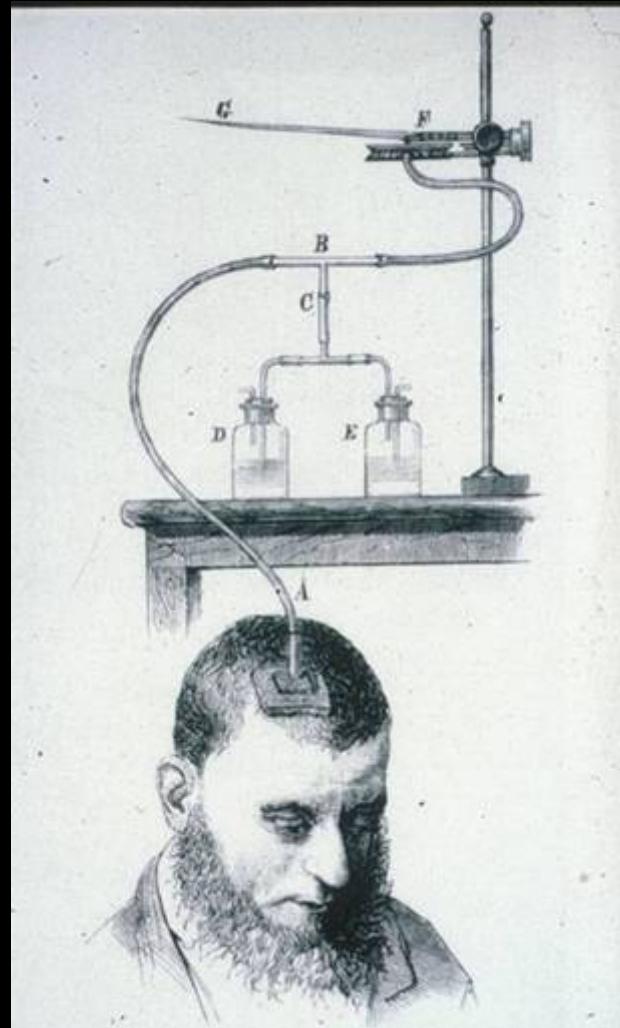
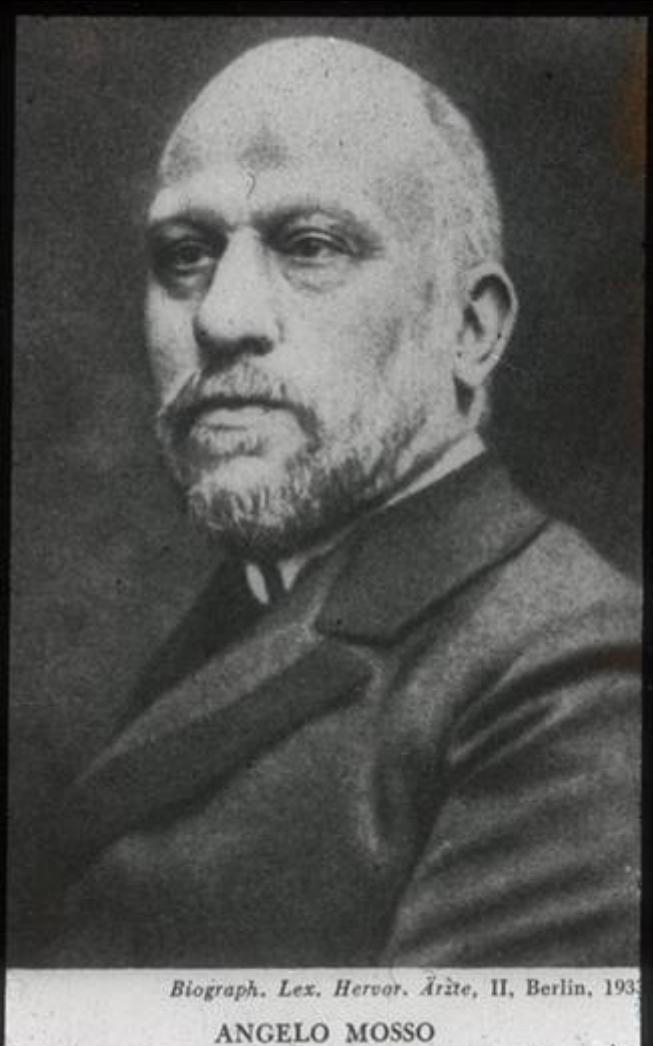
In vivo brain functional exploration



Why in vivo?
4. Limitations
of animal
models

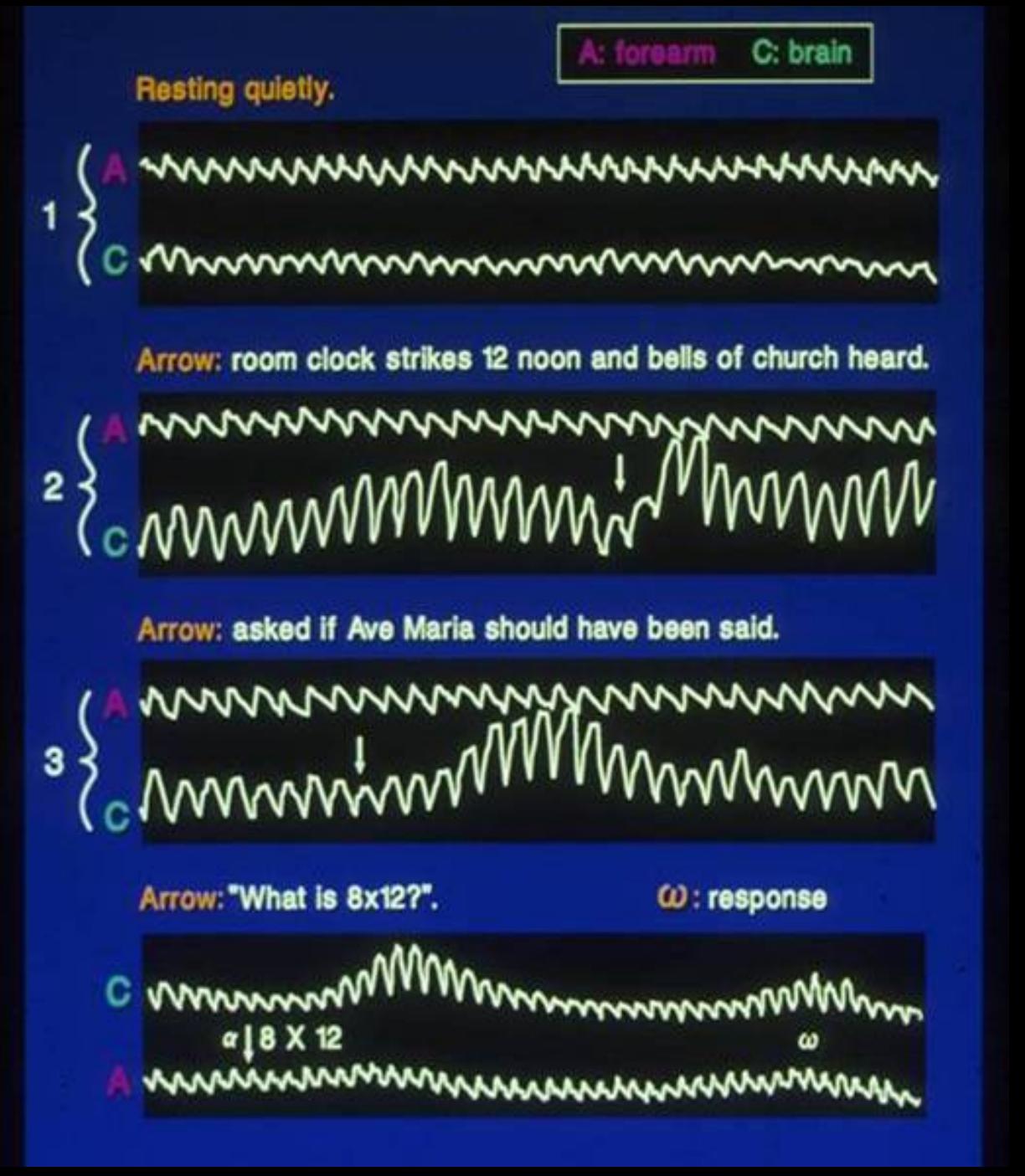
In vivo brain functional methodologies

The legacy of Angelo Mosso

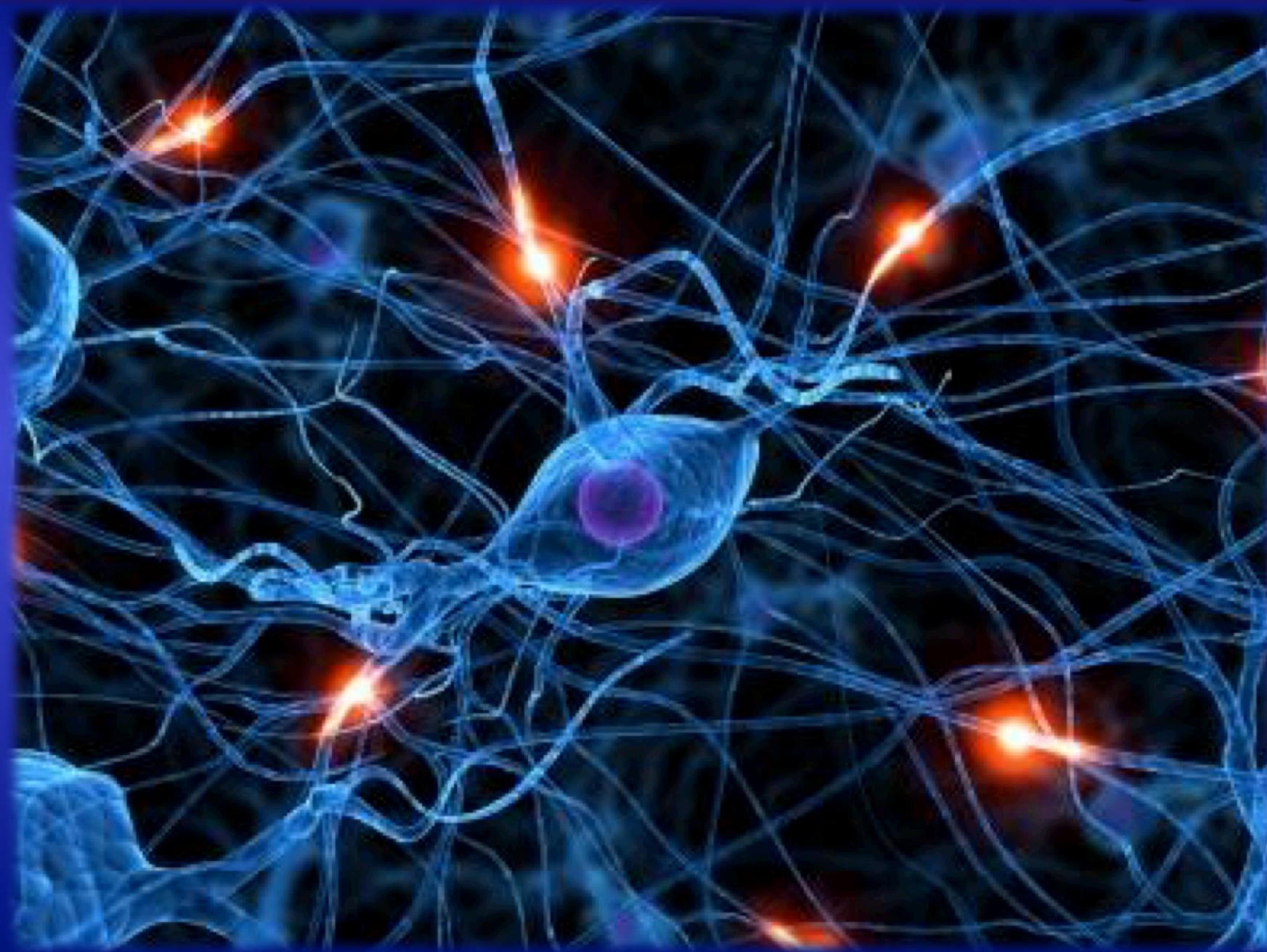


Angelo Mosso (1881): Concerning the Circulation of the Blood in the Human Brain

Verlag von Viet & Company:
Leipzig, pages 66-67

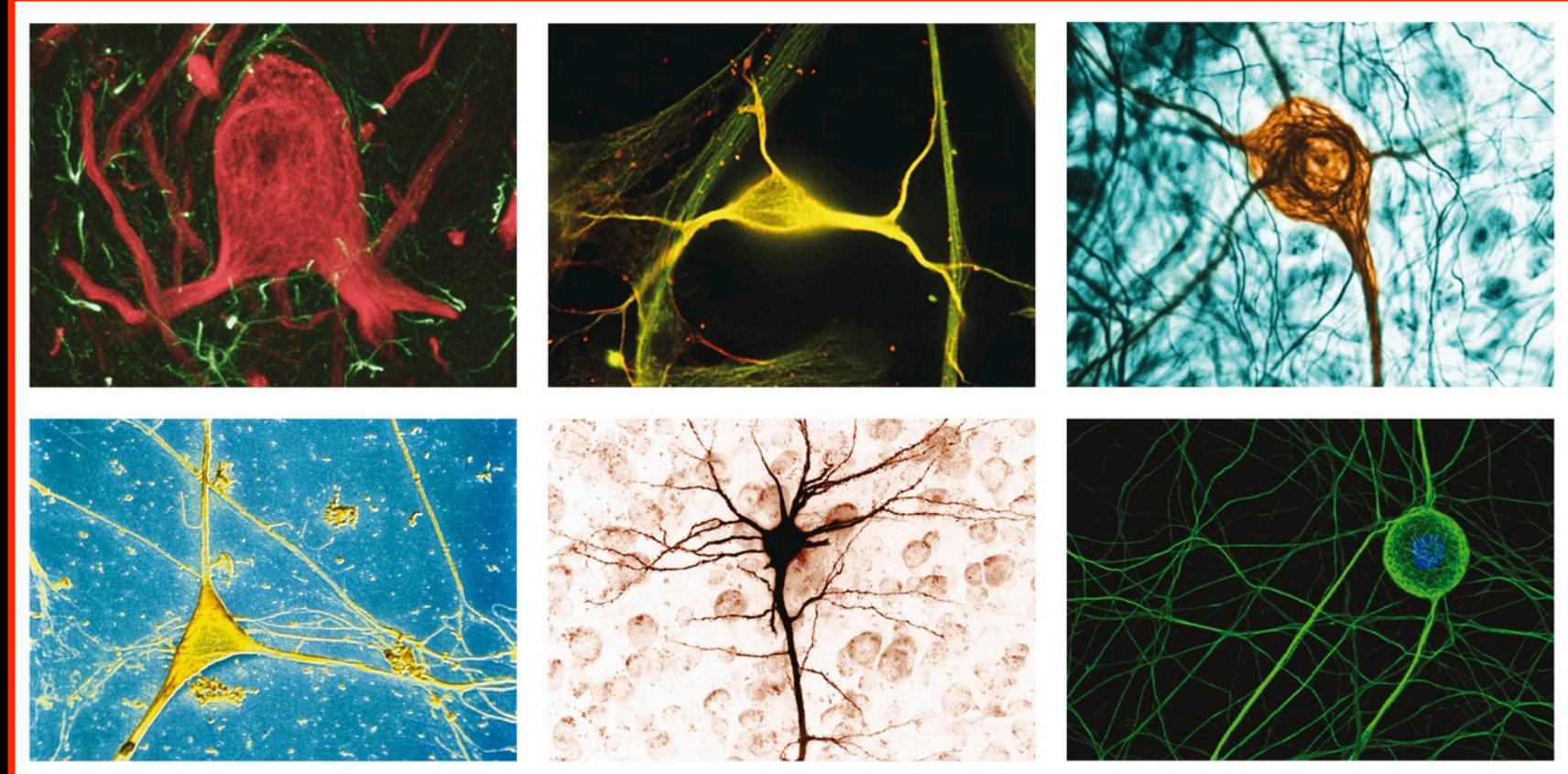


In vivo brain functional methodologies

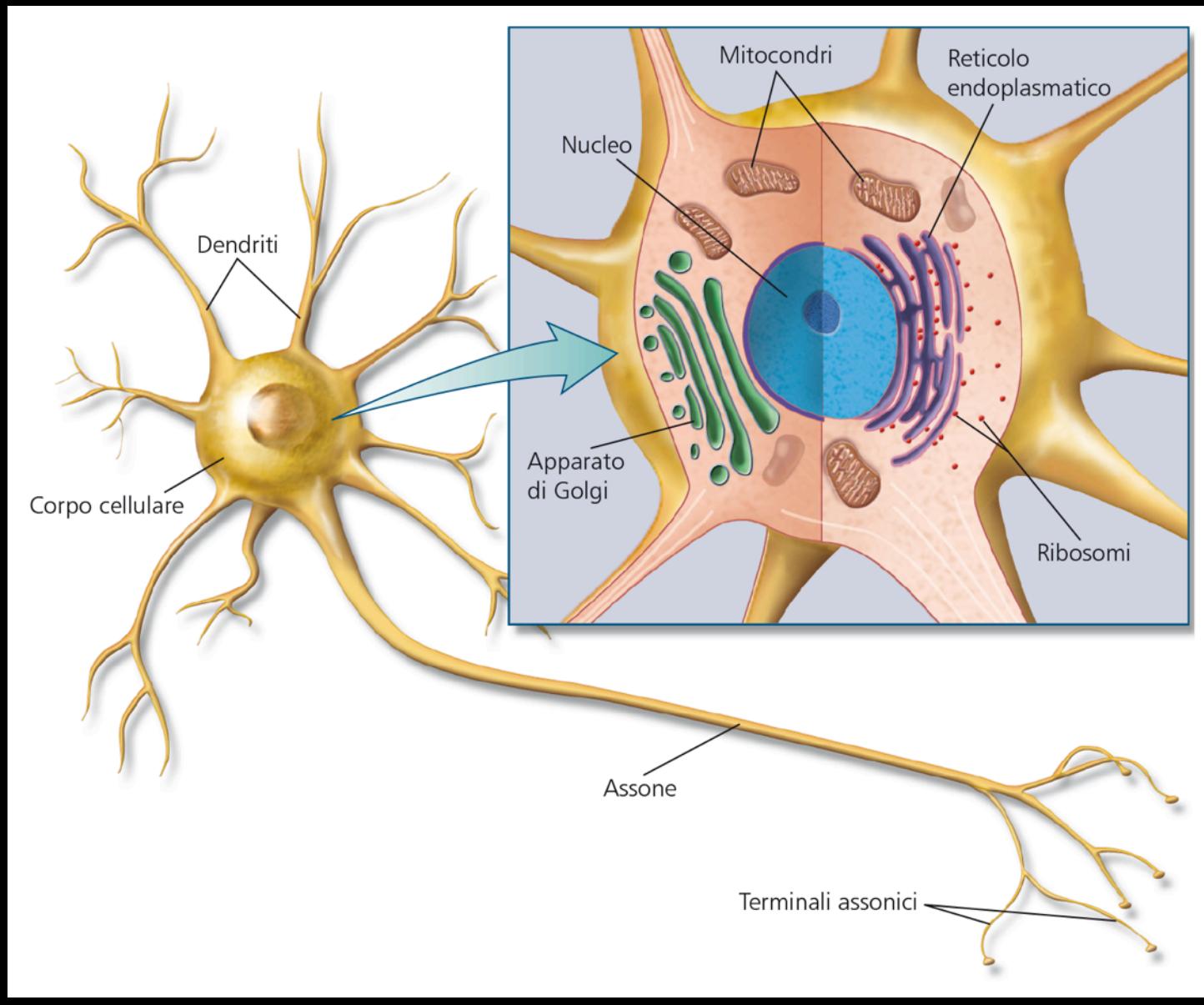


Cerebral metabolism of glucose

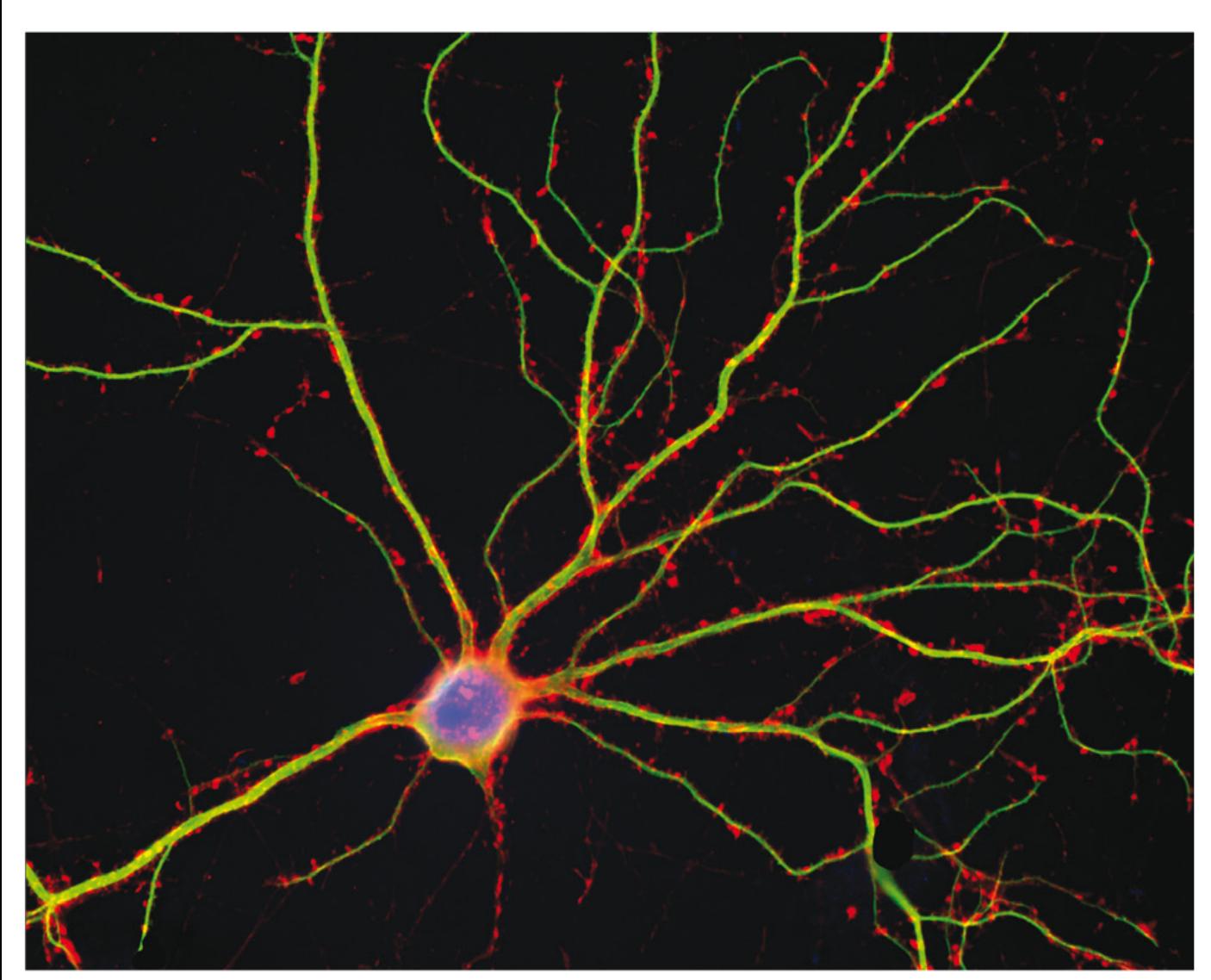
- Brain tissue includes neurons and glia cells

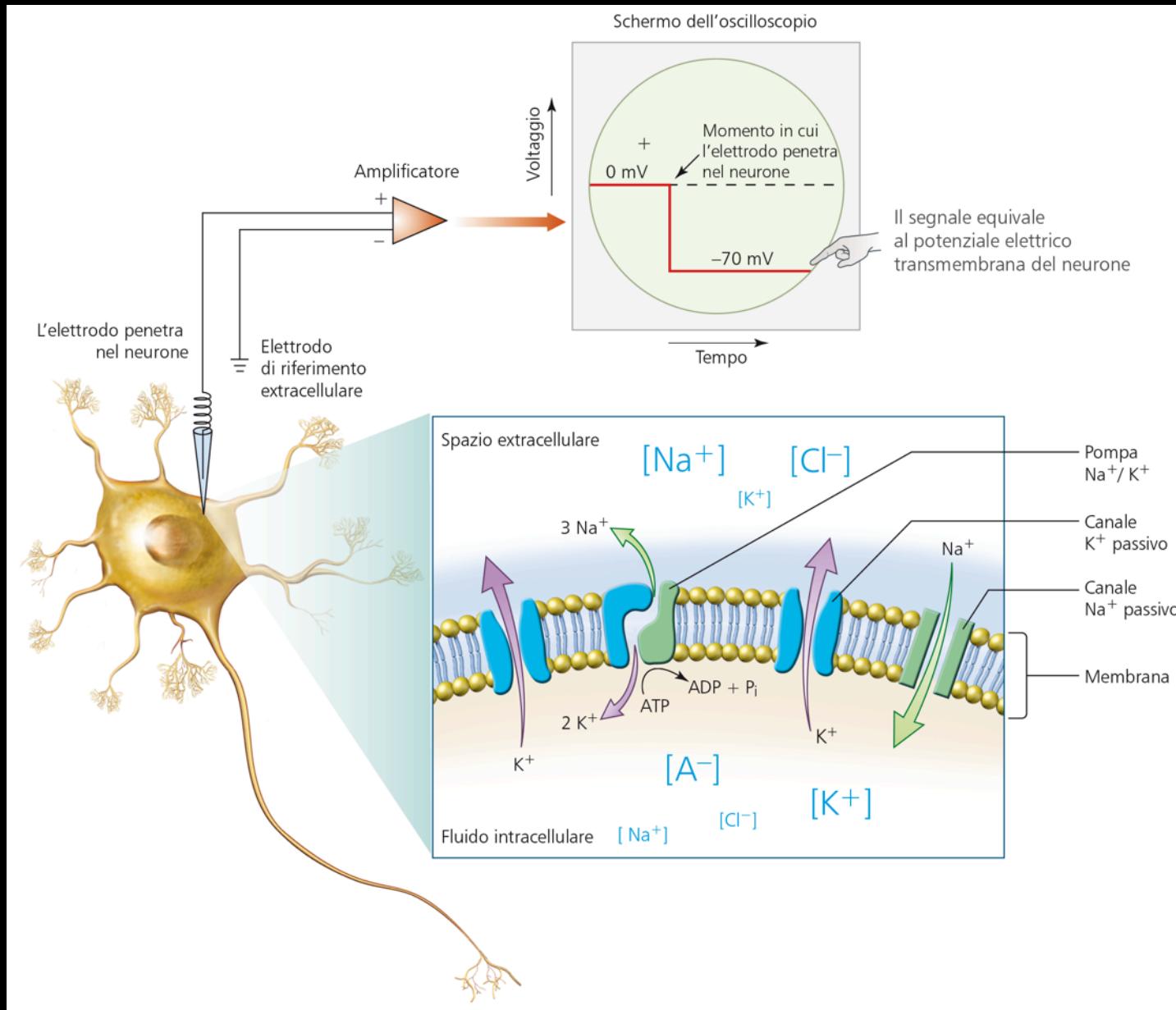


Neurons

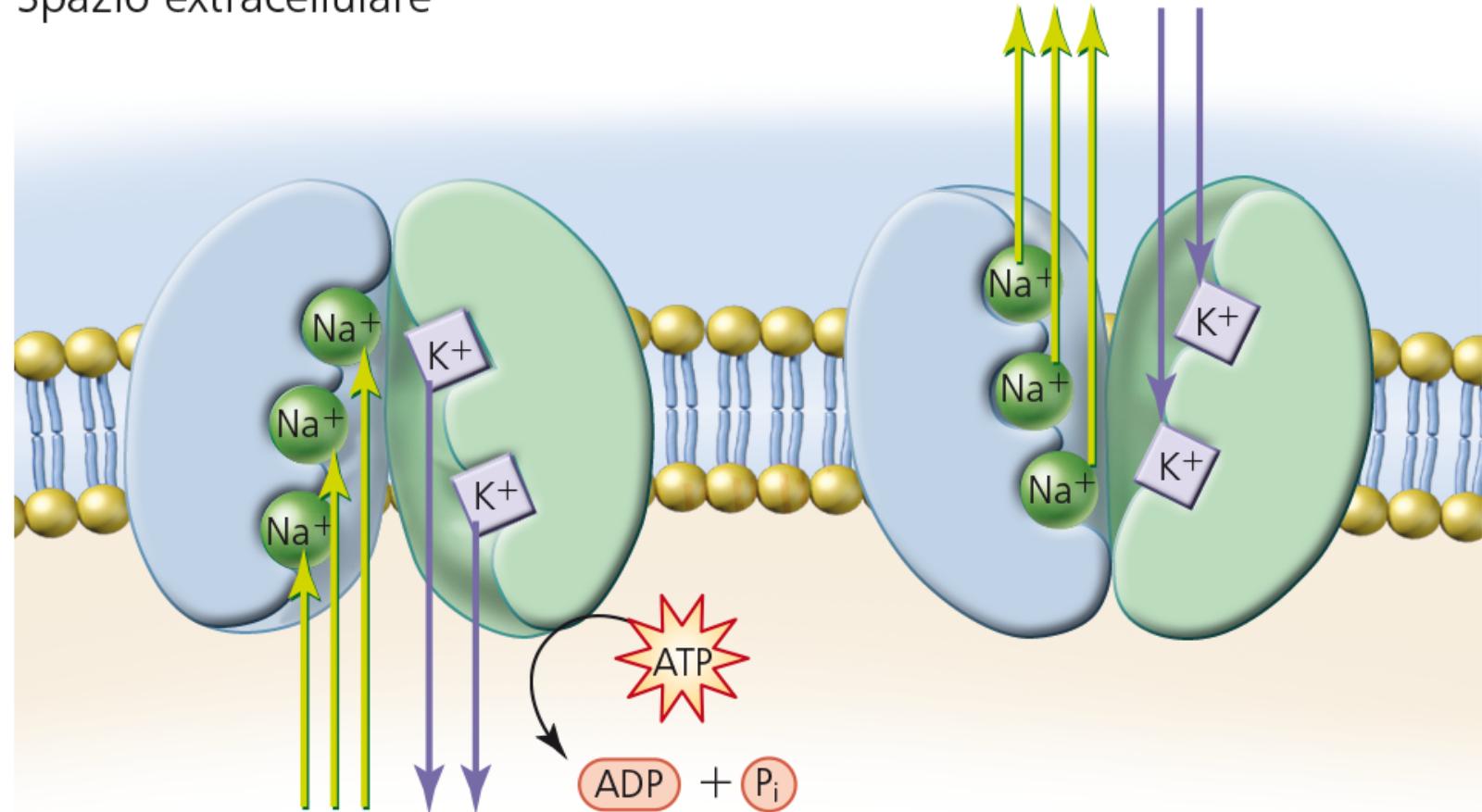


Neurons

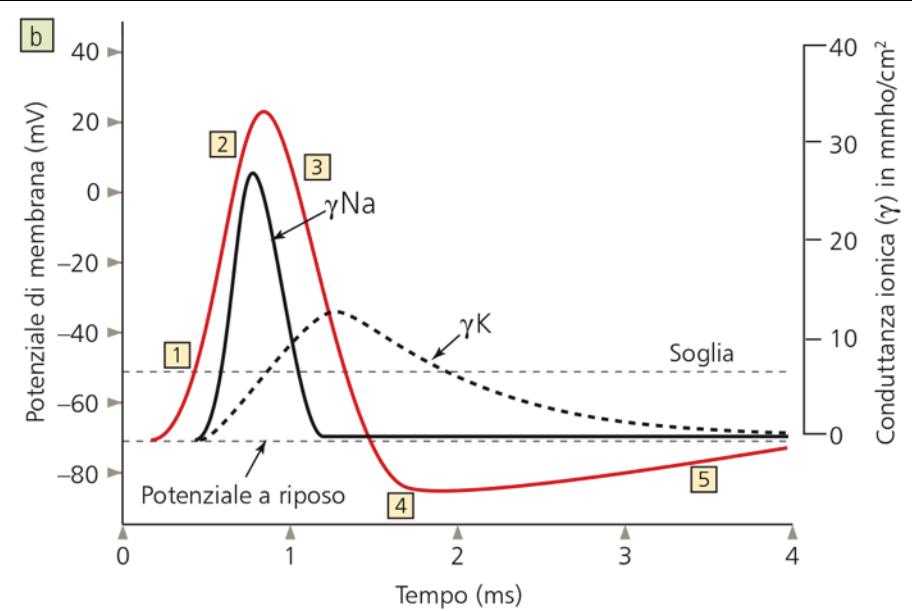
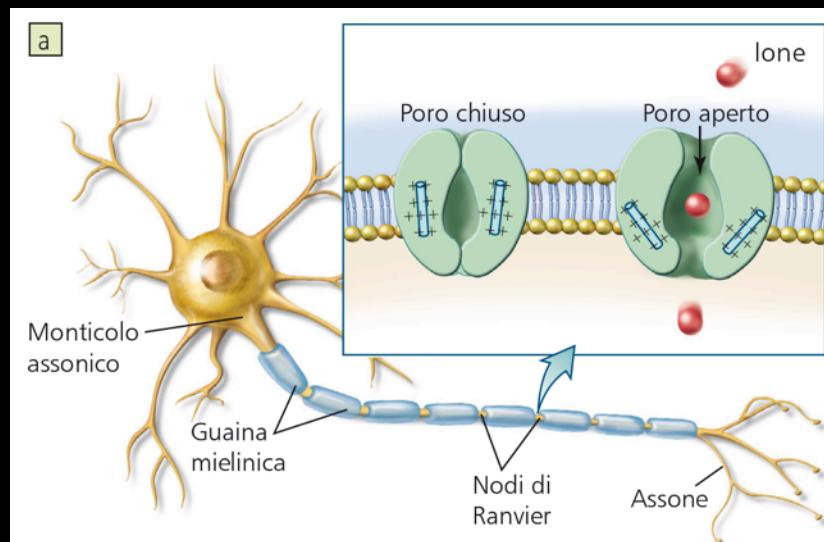


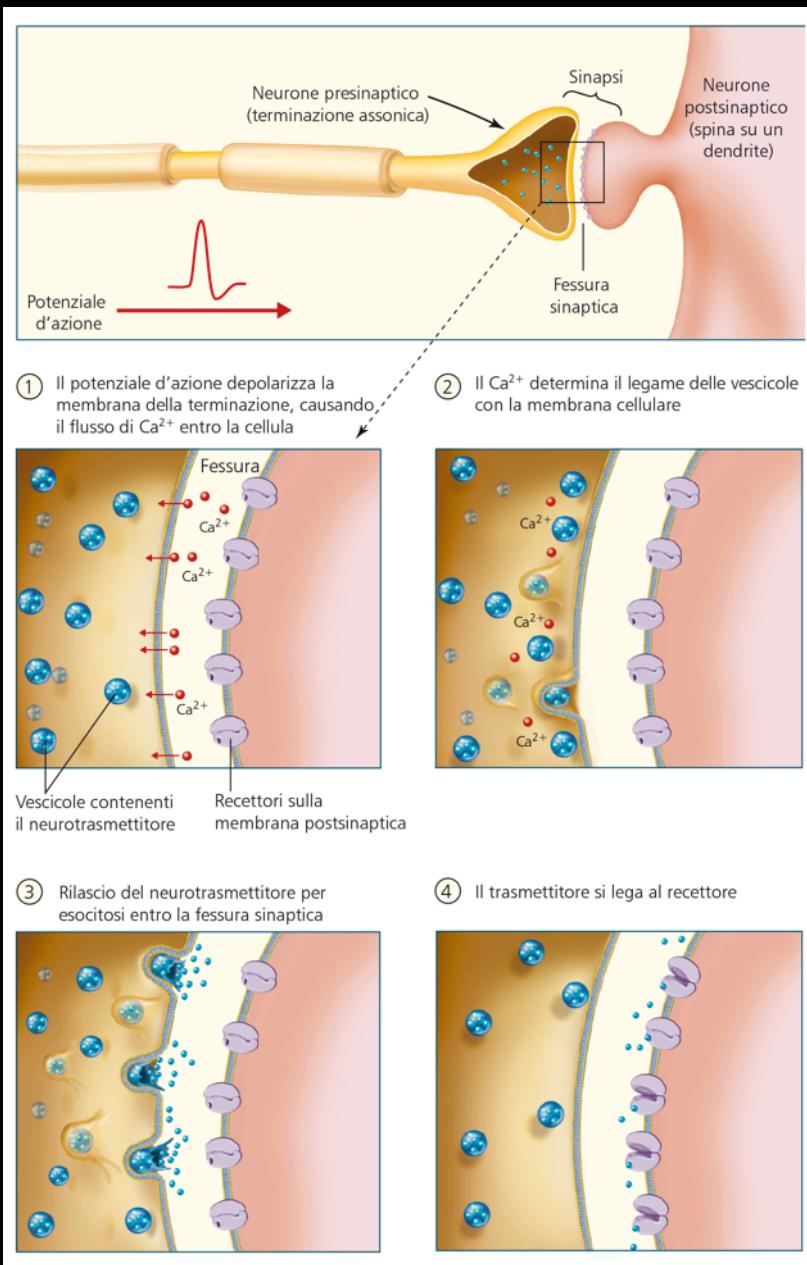


Spazio extracellulare

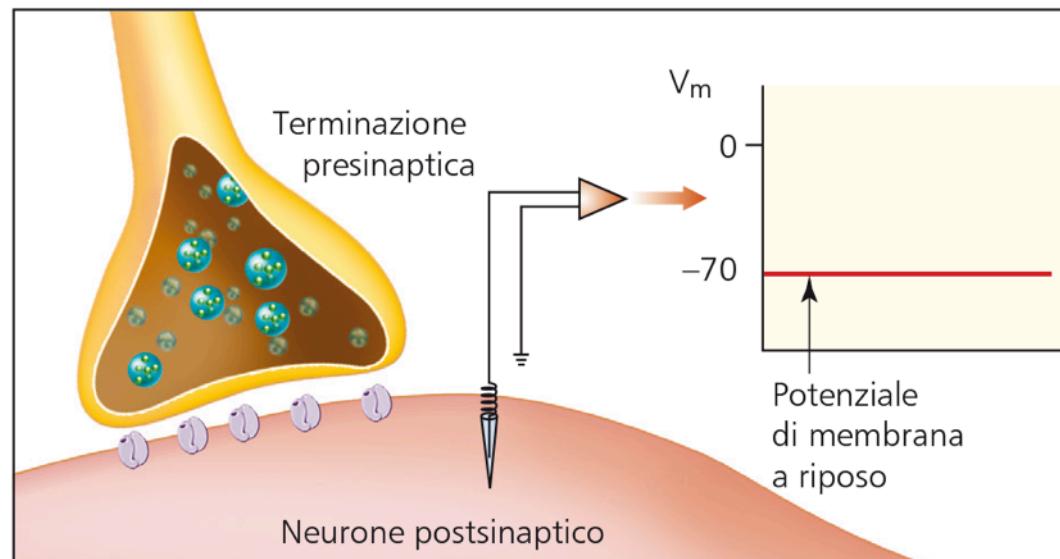


Fluido intracellulare

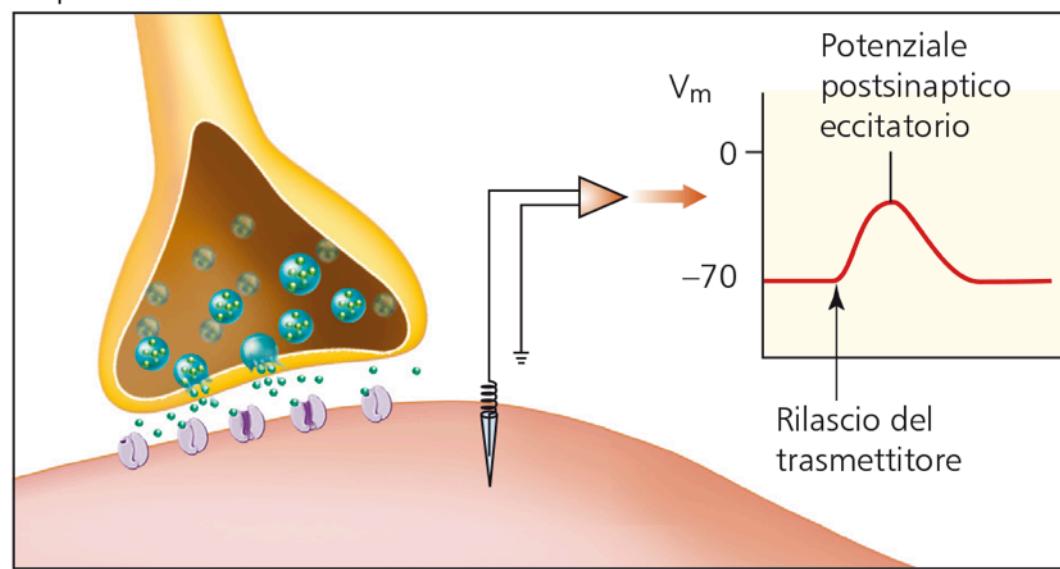




Prima del rilascio del trasmettitore



Dopo il rilascio del trasmettitore



THE STRUCTURES OF NEUROTRANSMITTERS

STRUCTURE KEY: ● Carbon atom ○ Hydrogen atom ○ Oxygen atom N Nitrogen atom R Rest of molecule

ADRENALINE

Fight or flight neurotransmitter



Produced in stressful or exciting situations. Increases heart rate & blood flow, leading to a physical boost & heightened awareness.

NORADRENALINE

Concentration neurotransmitter



Affects attention & responding actions in the brain, & involved in fight or flight response. Contracts blood vessels, increasing blood flow.

DOPAMINE

Pleasure neurotransmitter



Feelings of pleasure, and also addiction, movement, and motivation. People repeat behaviours that lead to dopamine release.

SEROTONIN

Mood neurotransmitter



Contributes to well-being & happiness; helps sleep cycle & digestive system regulation. Affected by exercise & light exposure.

GABA

Calming neurotransmitter



Calms firing nerves in CNS. High levels improve focus; low levels cause anxiety. Also contributes to motor control & vision.

ACETYLCHOLINE

Learning neurotransmitter



Involved in thought, learning, & memory. Activates muscle action in the body. Also associated with attention and awakening.

GLUTAMATE

Memory neurotransmitter



Most common brain neurotransmitter. Involved in learning & memory, regulates development & creation of nerve contacts.

ENDORPHINS

Euphoria neurotransmitters

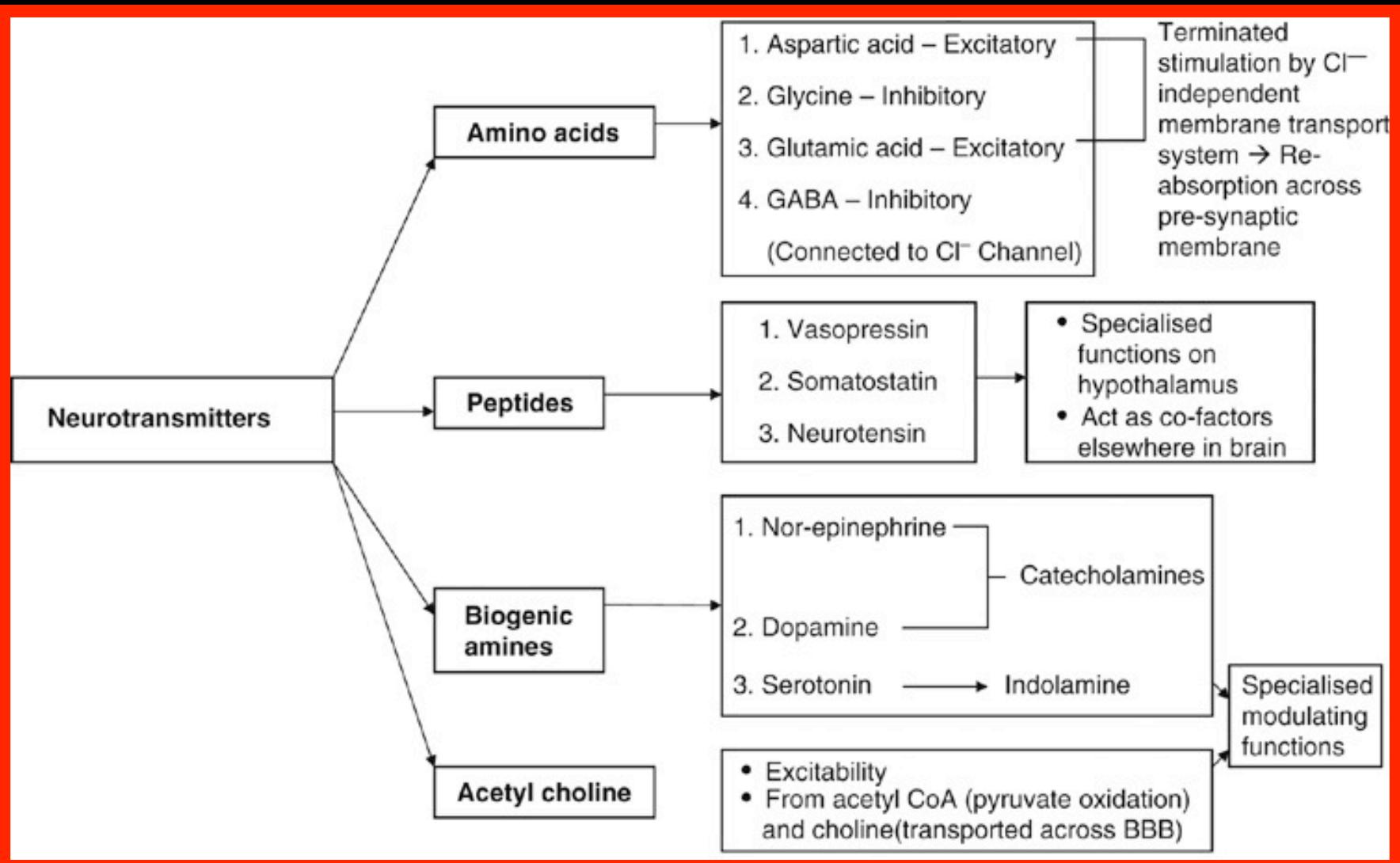


Released during exercise, excitement, & sex, producing well-being & euphoria, reducing pain. Biologically active section shown.

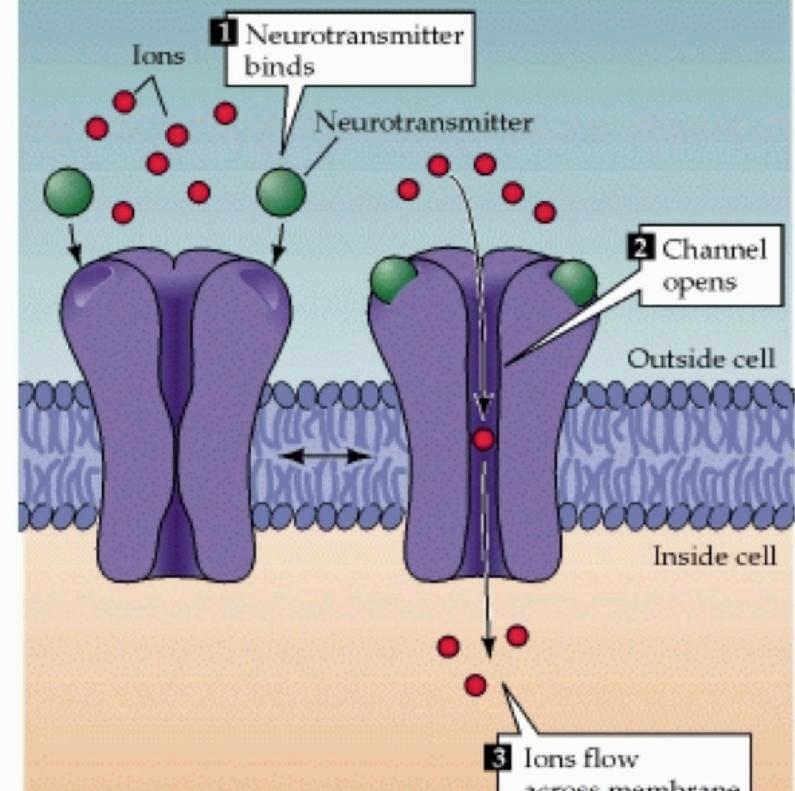


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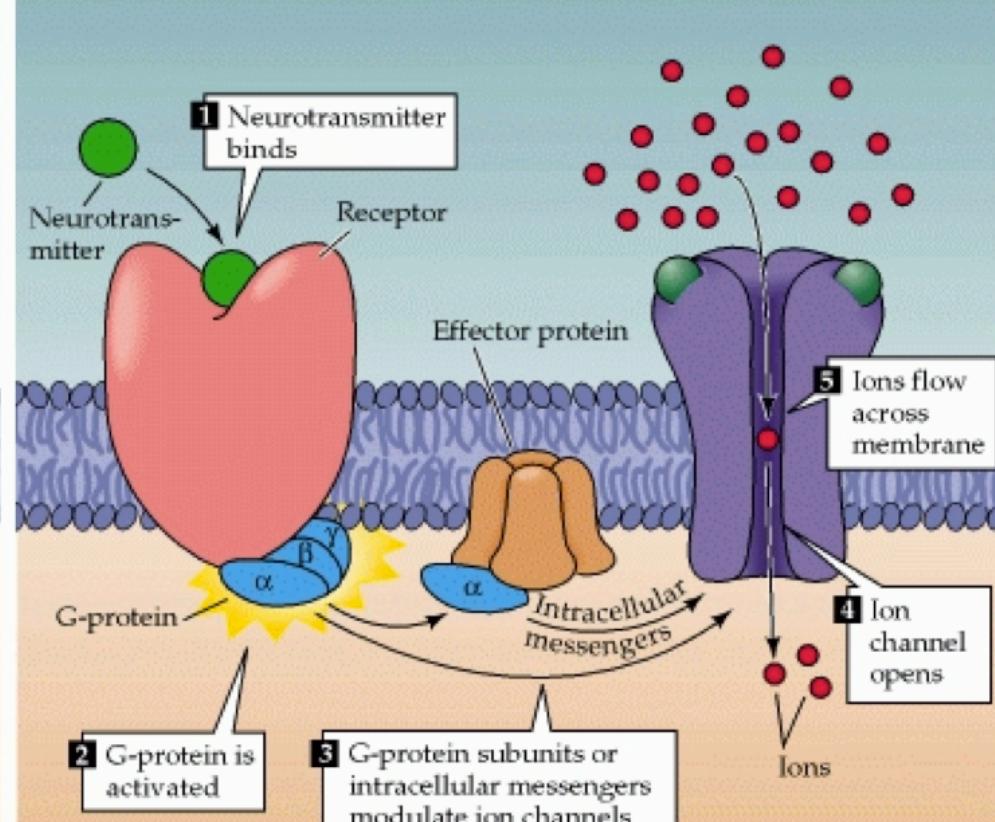




(A) Ligand-gated ion channels



(B) G-protein-coupled receptors



► Mechanisms of Drug Effects

Some Mechanisms of Drug Action

Agonistic Drug Effects

Drug increases the synthesis of neurotransmitter molecules (e.g., by increasing the amount of precursor).

Drug increases the number of neurotransmitter molecules by destroying degrading enzymes.

Drug increases the release of neurotransmitter molecules from terminal buttons.

Drug binds to autoreceptors and blocks their inhibitory effect on neurotransmitter release.

Drug binds to postsynaptic receptors and either activates them or increases the effect on them of neurotransmitter molecules.

Drug blocks the deactivation of neurotransmitter molecules by blocking degradation or reuptake.

Antagonistic Drug Effects

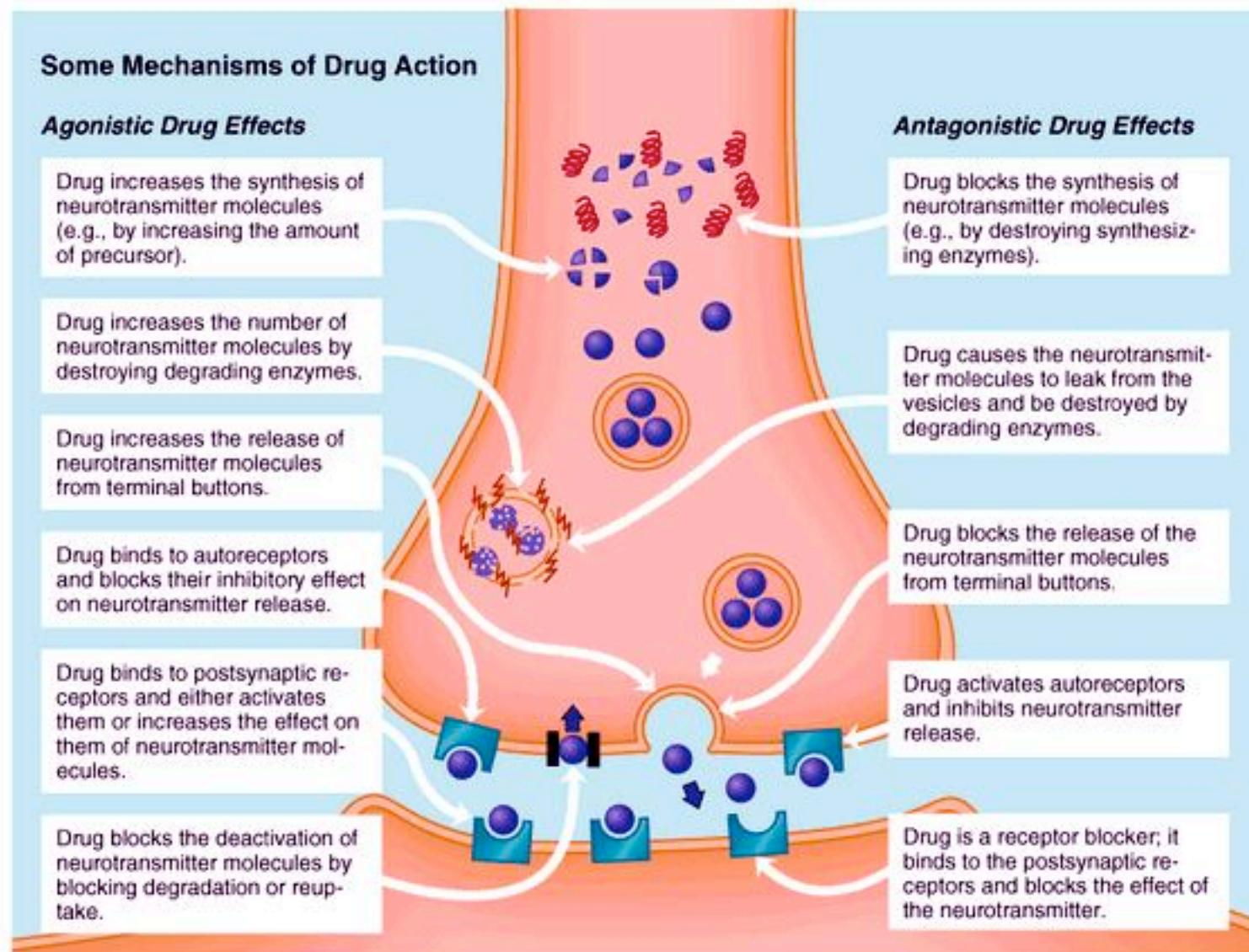
Drug blocks the synthesis of neurotransmitter molecules (e.g., by destroying synthesizing enzymes).

Drug causes the neurotransmitter molecules to leak from the vesicles and be destroyed by degrading enzymes.

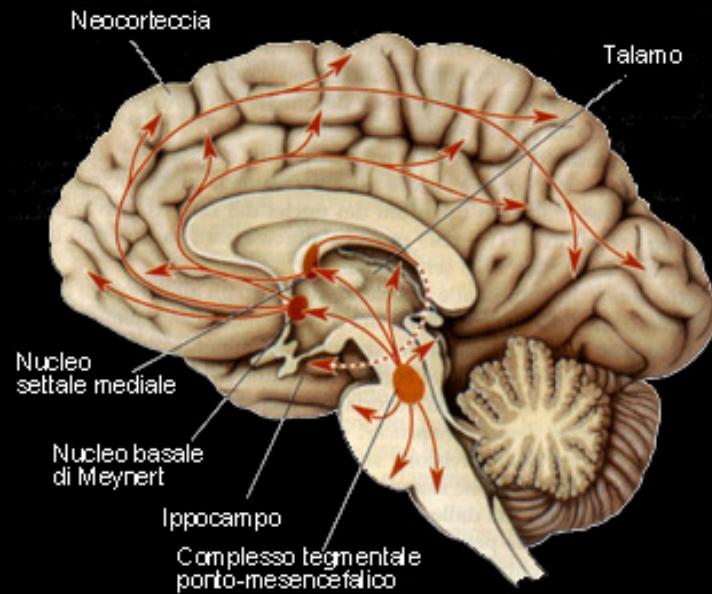
Drug blocks the release of the neurotransmitter molecules from terminal buttons.

Drug activates autoreceptors and inhibits neurotransmitter release.

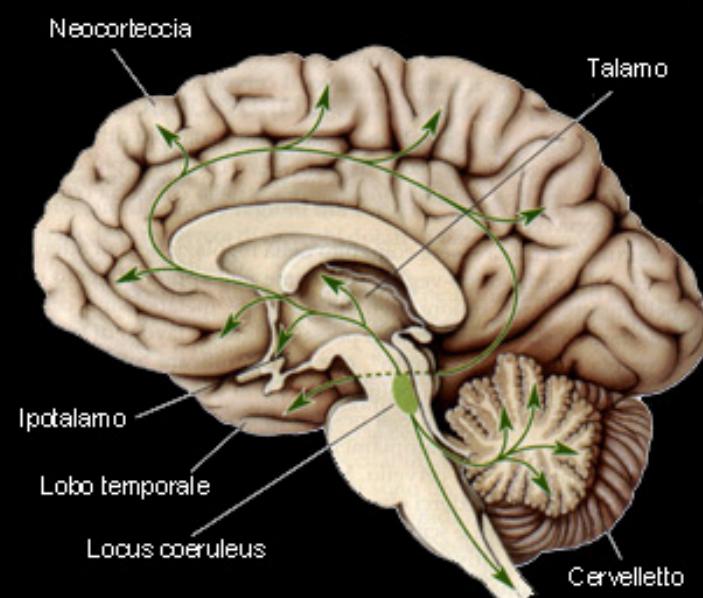
Drug is a receptor blocker; it binds to the postsynaptic receptors and blocks the effect of the neurotransmitter.



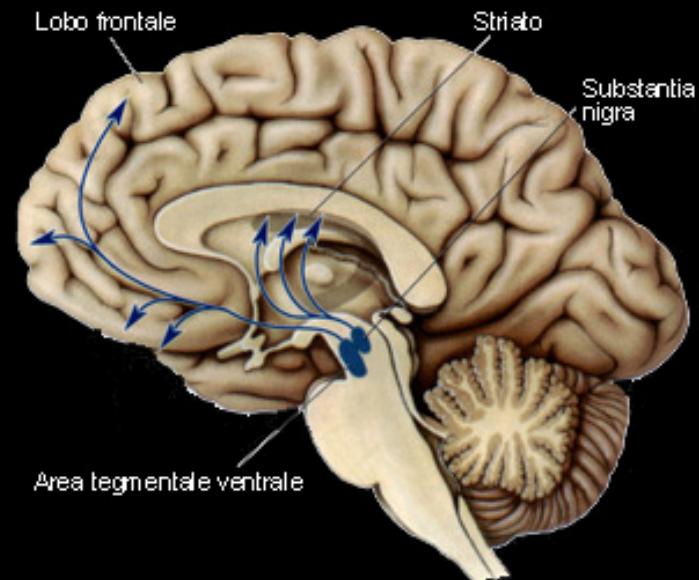
Sistema colinergico



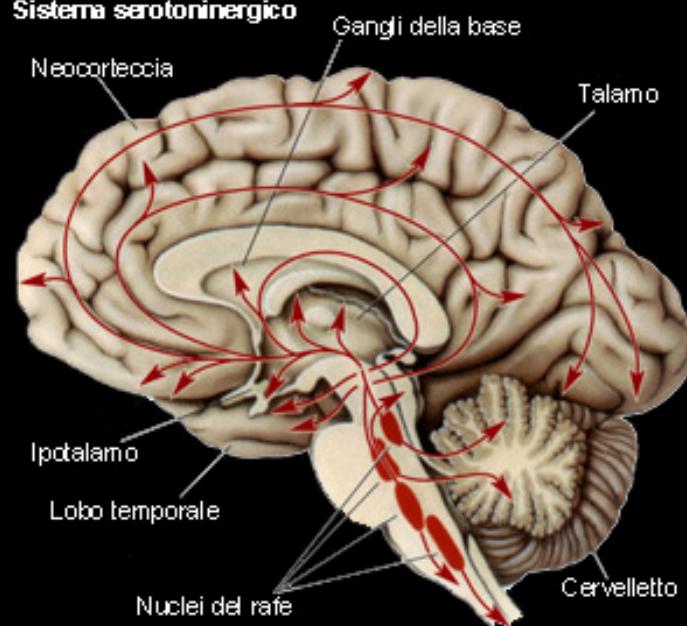
Sistema noradrenergico



Sistema dopaminergico

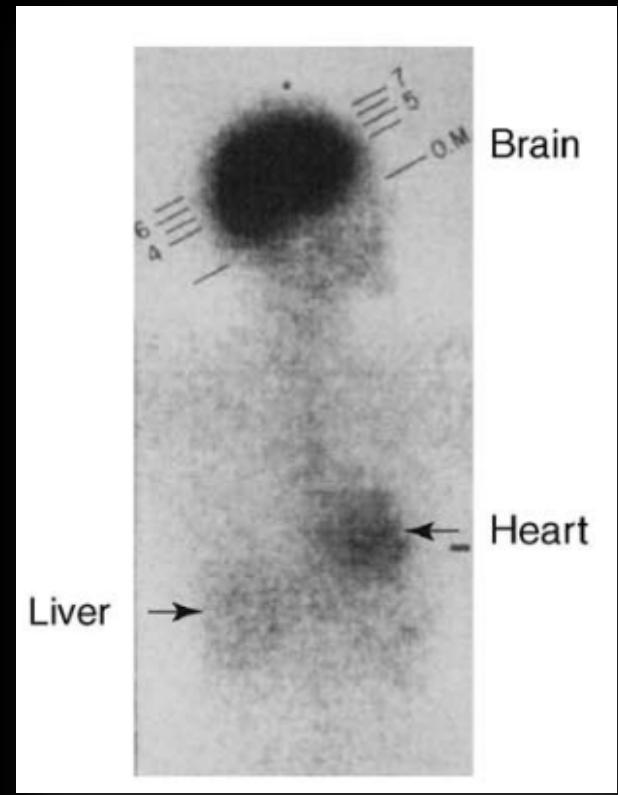


Sistema serotoninergico

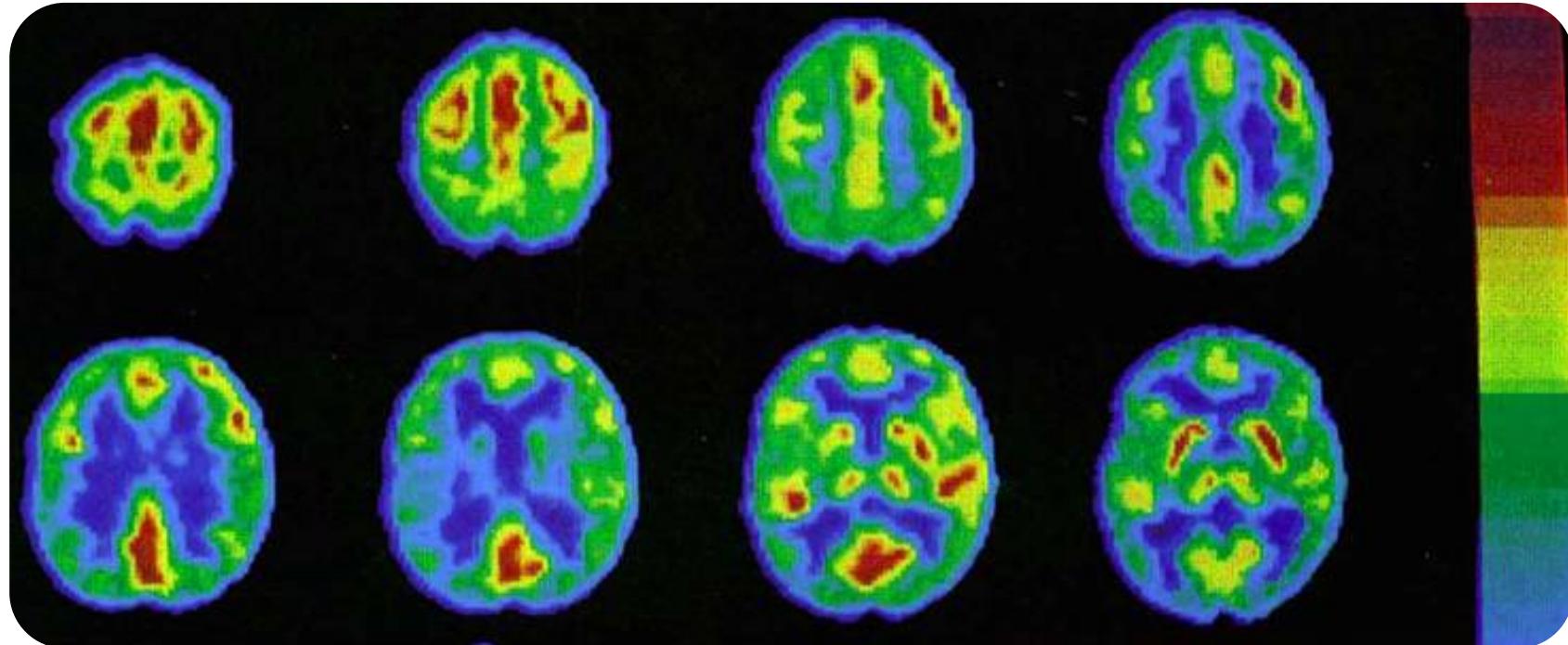


Cerebral metabolism of glucose

- Brain tissue includes neurons and glia cells
- In physiological conditions, glucose oxydation to CO_2 and H_2O is the unique metabolic pathway to produce ATP
- Glucose and oxygen supplies strictly rely on cerebral blood flow
- Human brain:
 - ~2% of total body weight
 - receives 15% basal cardiac output and consumes 20% of O_2
 - extracts about 10% blood glucose
 - limited glycogen storage
 - Blood supply increases in ‘activated’ brain regions

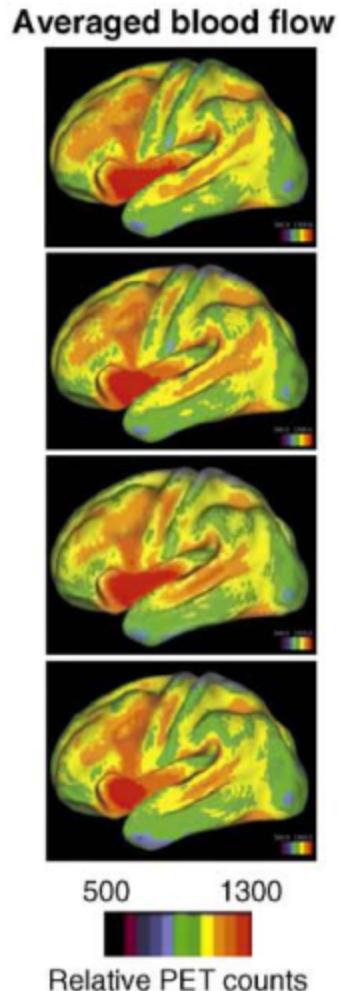


Our brain never rests...



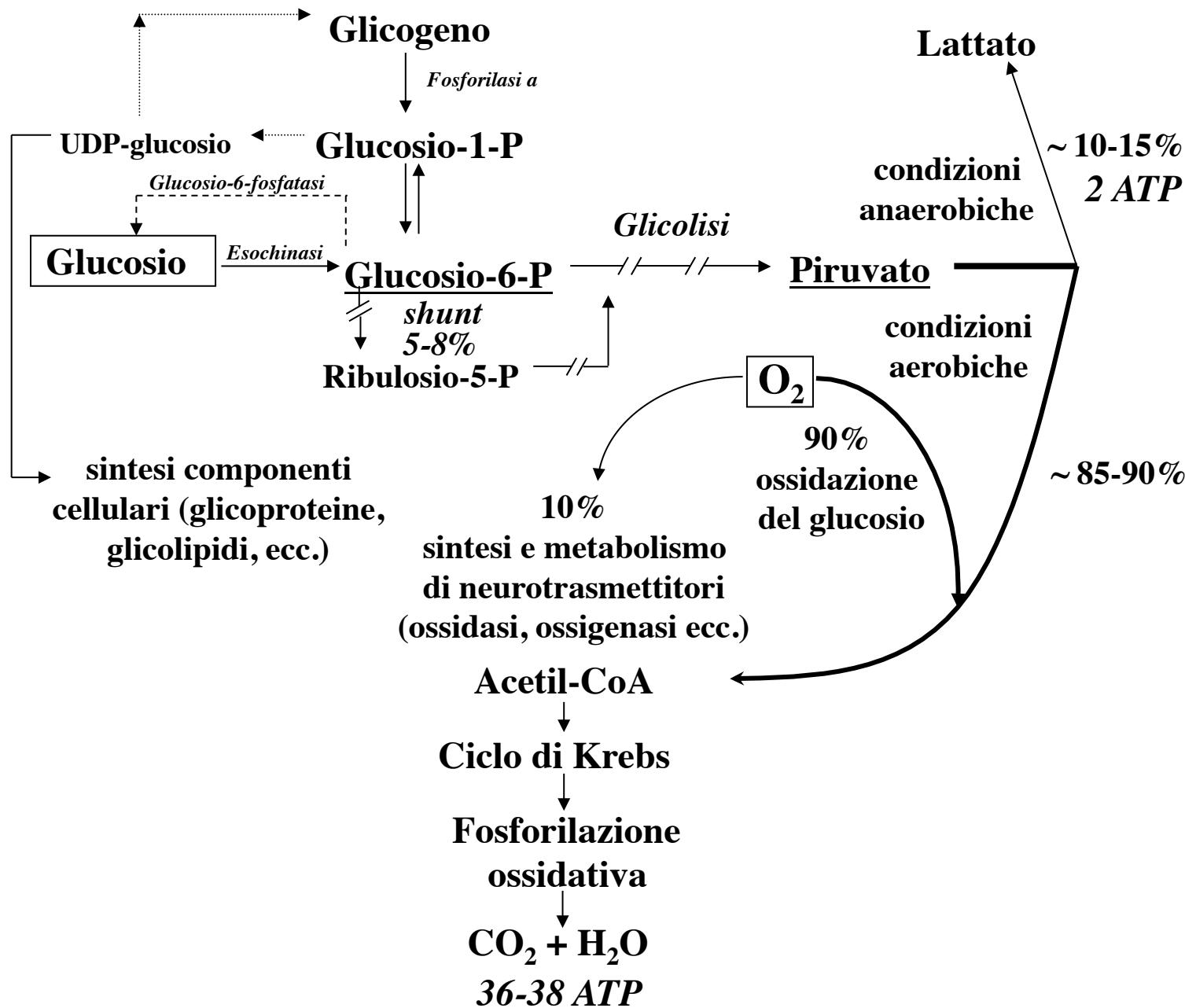
Glucose consumption at rest as measured by PET

Our brain never rests...



Which are the resting state or task-dependent responses?

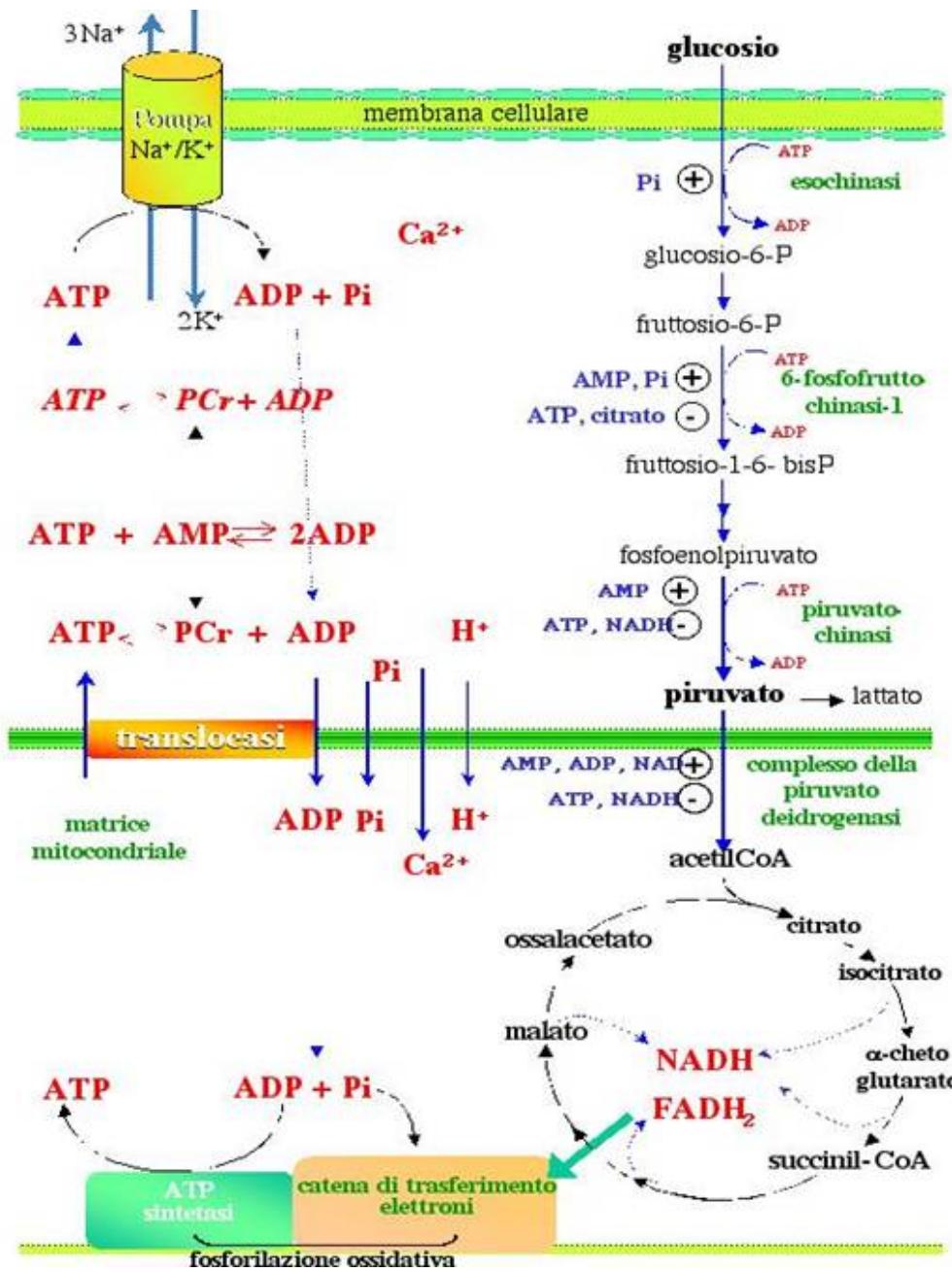
Metabolic fate of glucose and O₂



ATP brain consumption at rest

- 65% related to ionic fluxes:
 - Na^+/K^+ pump: maintenance of membrane negative potential; neurotransmitter reuptake
- 15% anabolic biochemical processes:
 - Proteins (6%)
 - Lipids (2%)
 - Nucleotides (1%)
 - Glycogensynthesis (2%)
 - Neurotransmitter turn-over
- 20% other neuronal processes:
 - Calcium reuptake
 - Phosphorilation processes
 - Synaptic vesicles transportation

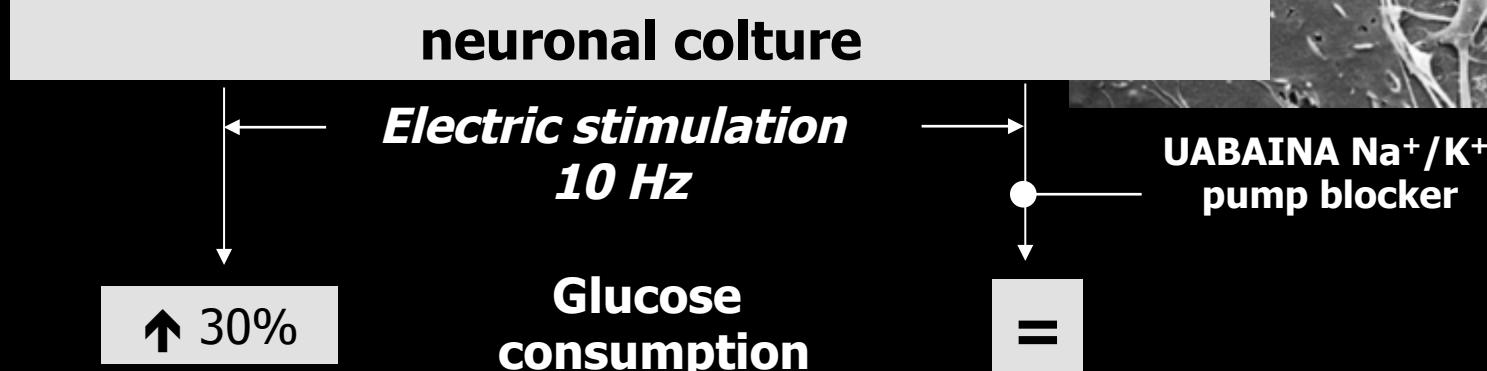
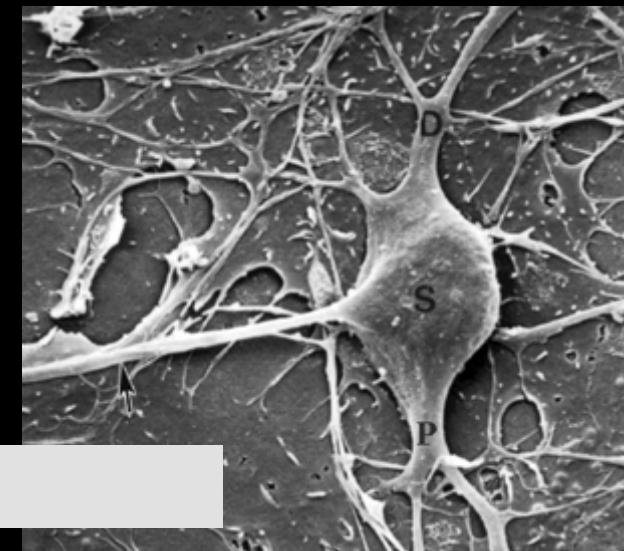
Metabolic fate of glucose and O₂



Neuronal activation

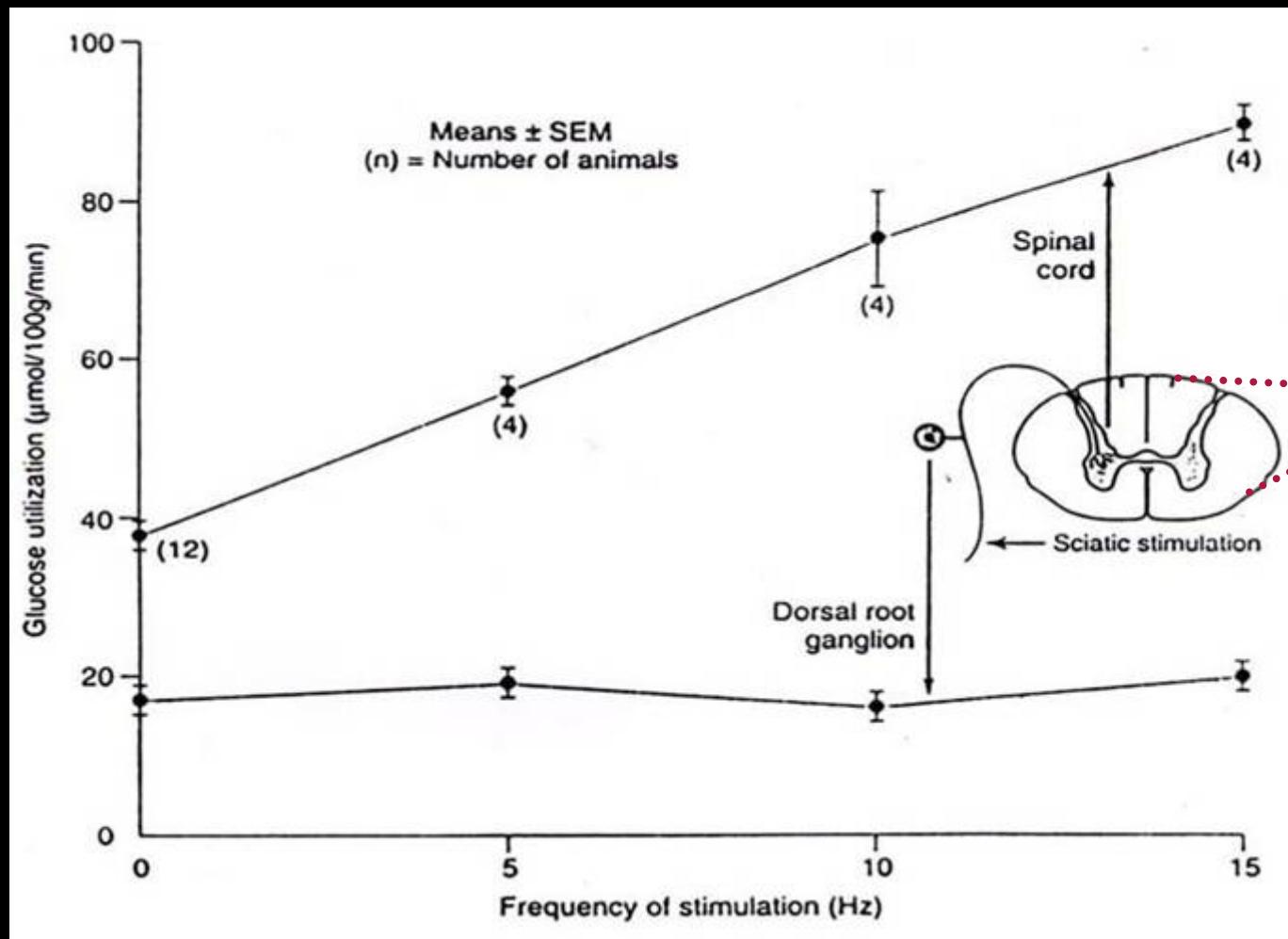
ATP production mainly subserves the functioning of Na^+/K^+ pump

Mata e coll., 1980
J Neurochem, 34: 213-215



Neuronal activation

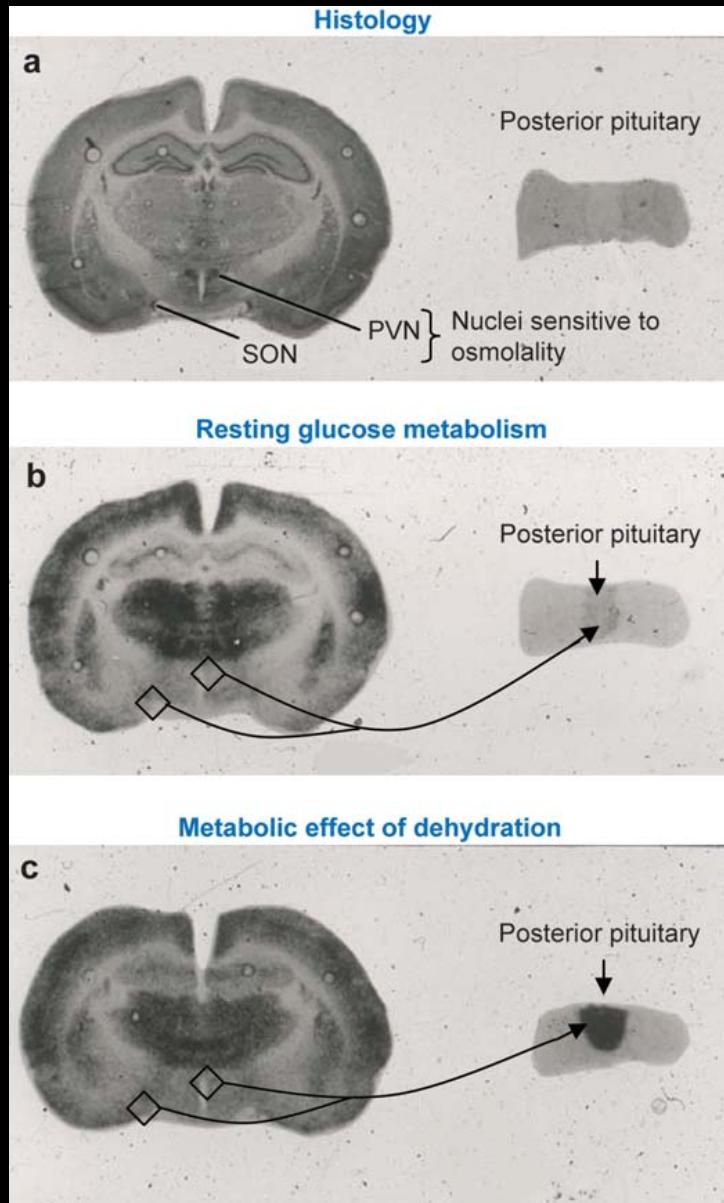
ATP consumption is specifically located at synaptic level



Kadekaro e coll., 1987 *Proc Natl Acad Sci USA*, 84: 5492-5495

Neuronal activation

Schwartz WJ, Smith CB, Davidsen L, Savaki H, Sokoloff L, et al. 1979. Metabolic map- ping of functional activity in the hypothalamo-neurohypophysial system of the rat. Science 205:723–25

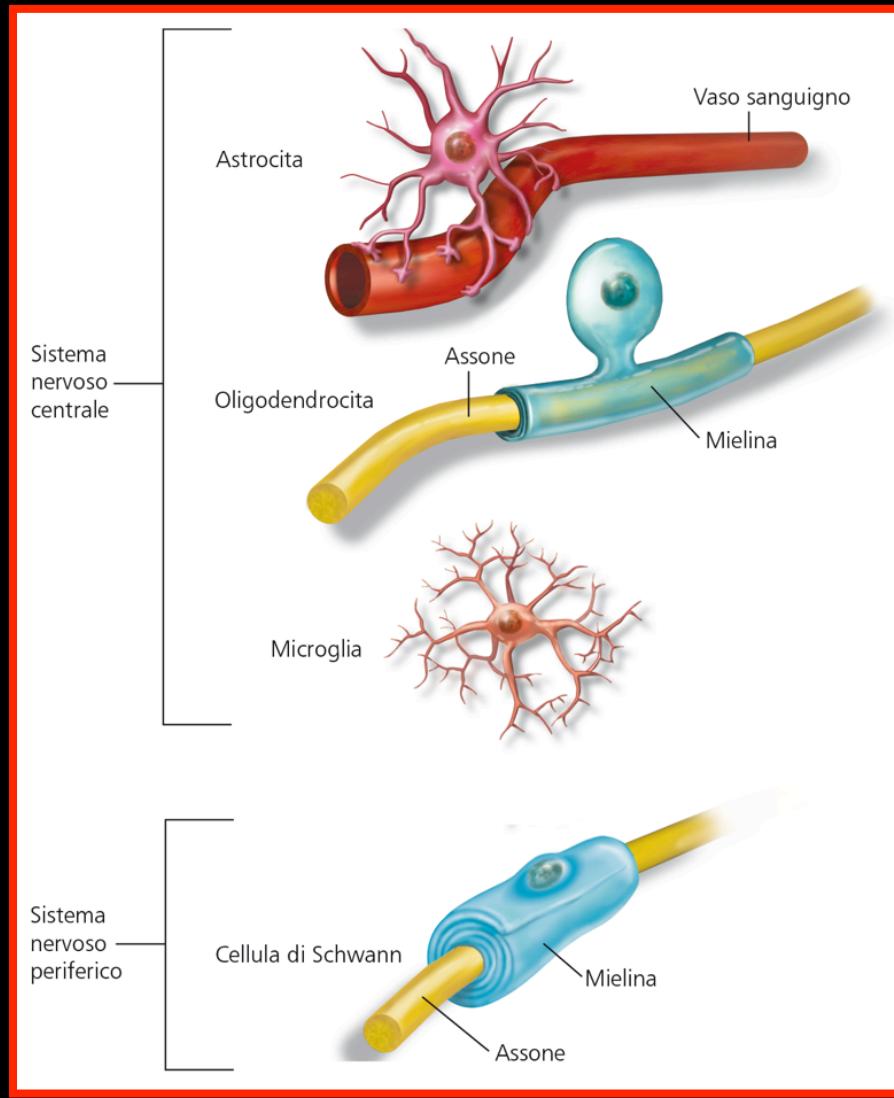


Neurovascular coupling

- Increases in neuronal synaptic activity are accompanied by increases in regional blood flow supply (coupling)
- Blood flow supplies glucose and oxygen to neurons
- In healthy conditions, glucose oxydation is the only metabolic pathway to produce ATP in the neuron
- ATP restores neuron membrane potential
- ATP consumption is located at a synaptic level
- Glucose consumption represents an indirect parameter to assess synaptic neuronal activity

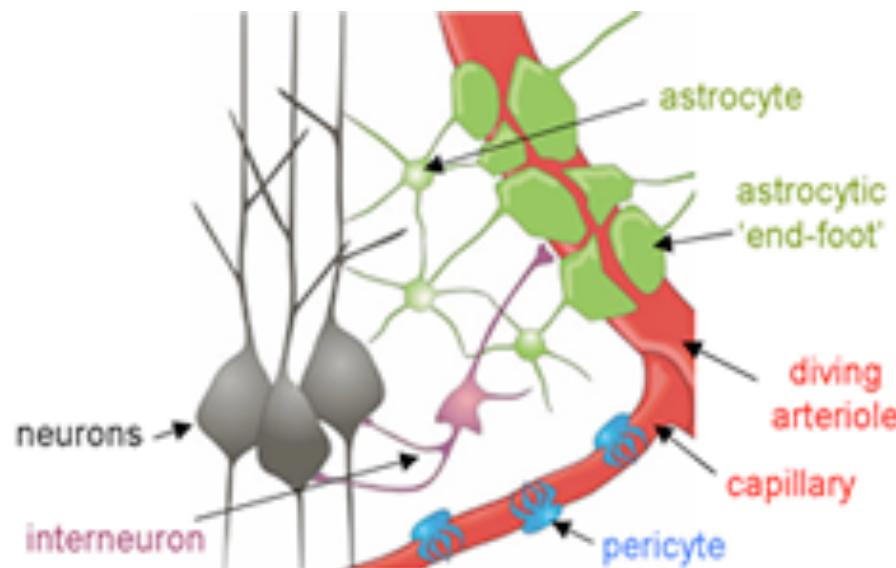
Neurovascular coupling

- Brain tissue includes neurons and glia cells



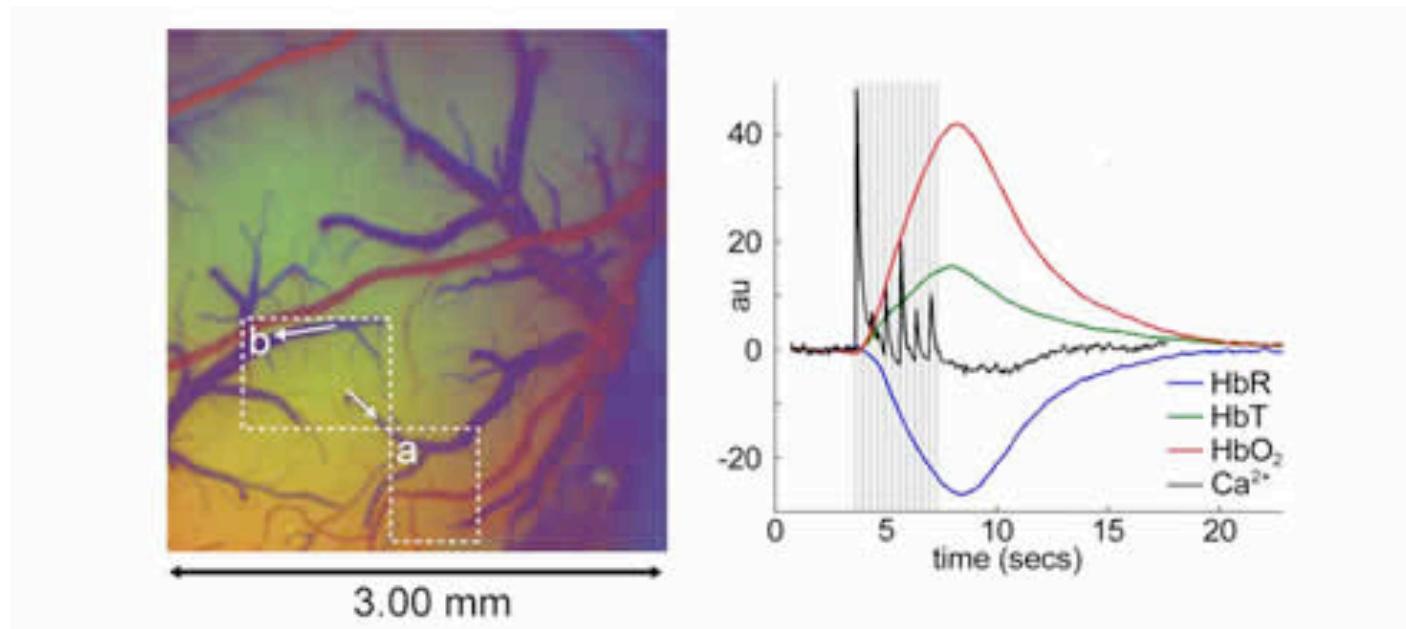
Neurovascular coupling (functional hyperemia)

- A local increase in cortical blood flow accompanies almost all neuronal responses to stimulus in the brain
- However, little is understood about the interrelation between blood flow and the neuronal activity that underlies it
- More importantly, normal functioning of the brain depends critically on the integrity of neurovascular coupling (e.g., Alzheimer's and age related neurodegeneration)



Neurovascular coupling

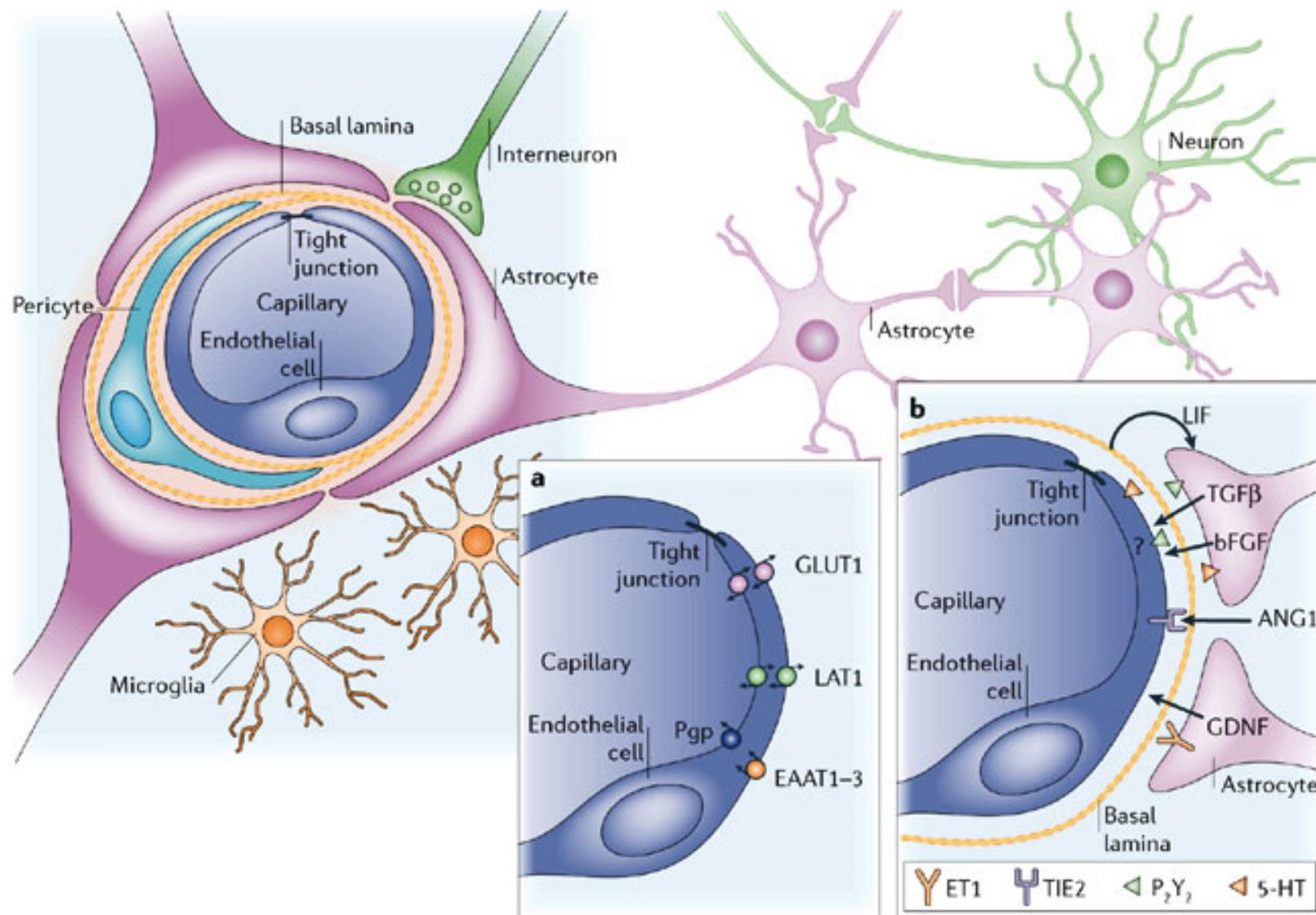
- The typical hemodynamic response consists of a rapid increase in HbT and HbO with a concomitant decrease in HbR.
- This response corresponds to a local increase in blood flow and in the amount of oxygenated blood present in the region, due to rapid dilation of the pial arterioles and little or no dilation (passive or active) of pial veins (so far, fMRI models assumed that the majority of HbT changes occurred in the venous compartment!)



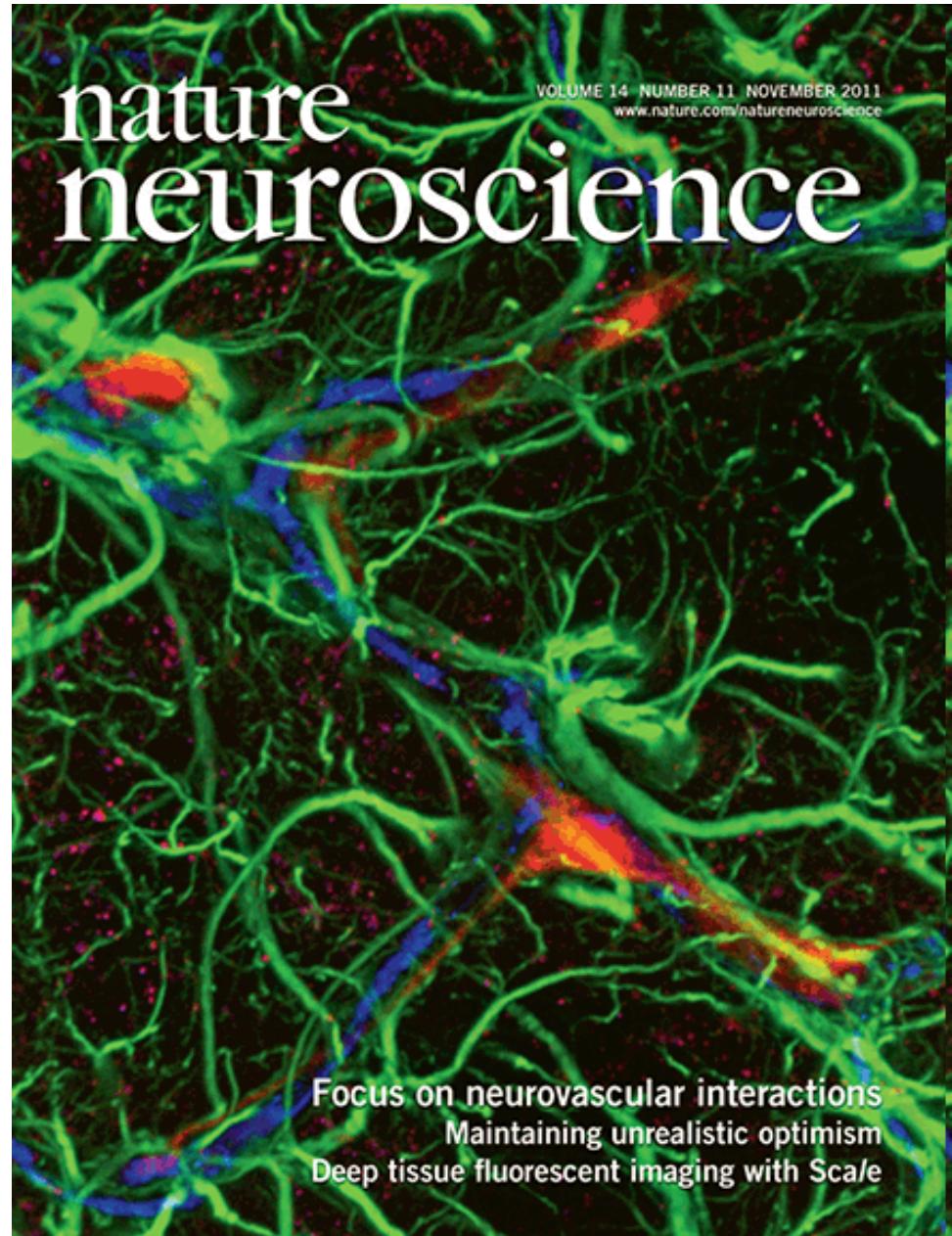
Neurovascular coupling

- Astrocytes possess many properties that make them attractive candidates for involvement in neurovascular coupling:
 - can sense the presence of local glutamate release via their metabotropic glutamate receptors
 - can release a range of vasoactive products including prostaglandins and potassium ions
 - are present around vessels in the brain
 - exhibit transient increases in intracellular calcium during stimulation
- Astrocytes ensheath all sub-pial vessels; diving arterioles, capillaries and ascending veins, but that they do not exhibit preferential relationships with diving arterioles and seem unlikely to be the primary mediators of long-distance, rapid dilation of pial arteriole branches... what about *endothelium*?

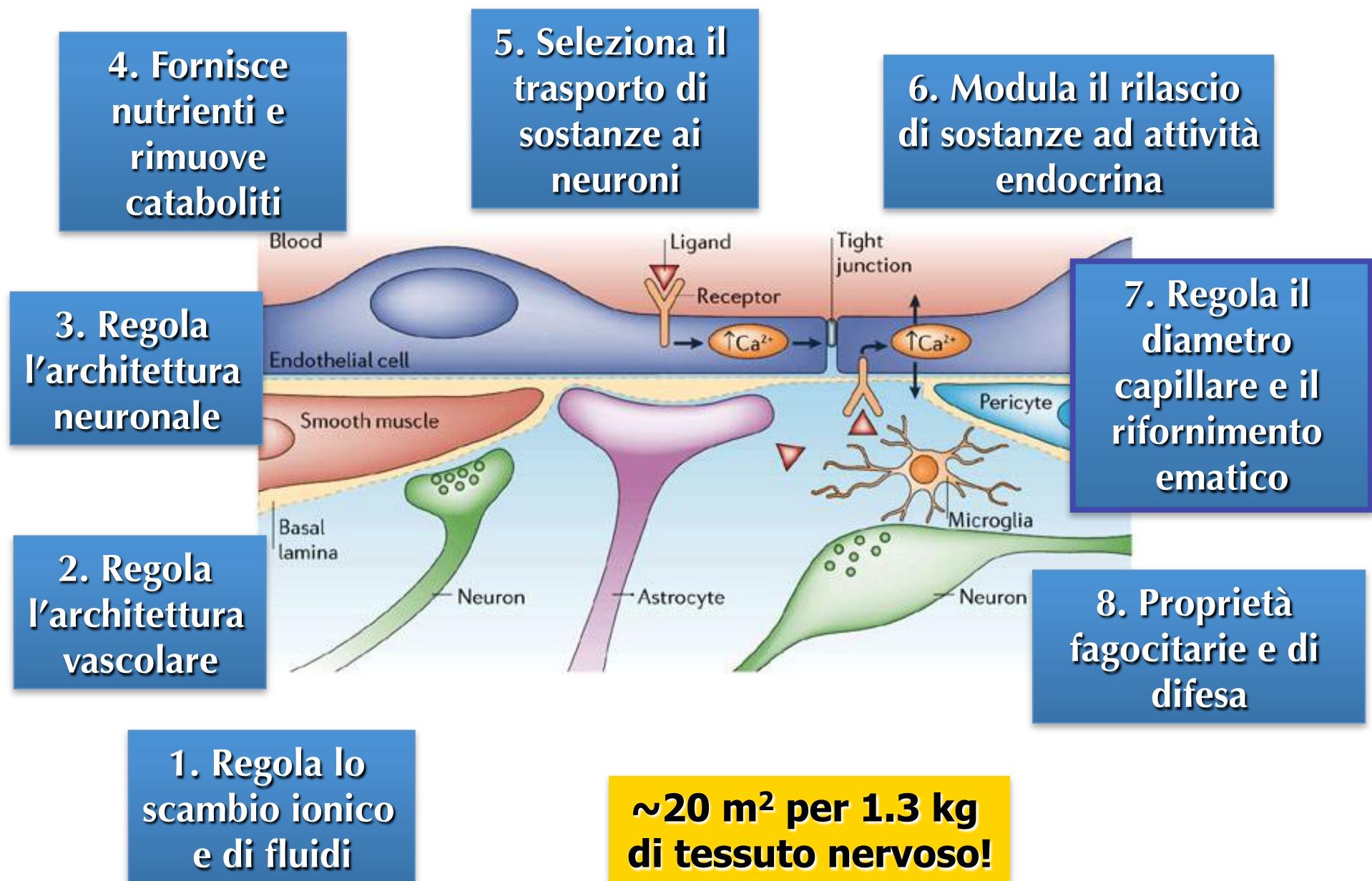
Neurovascular coupling



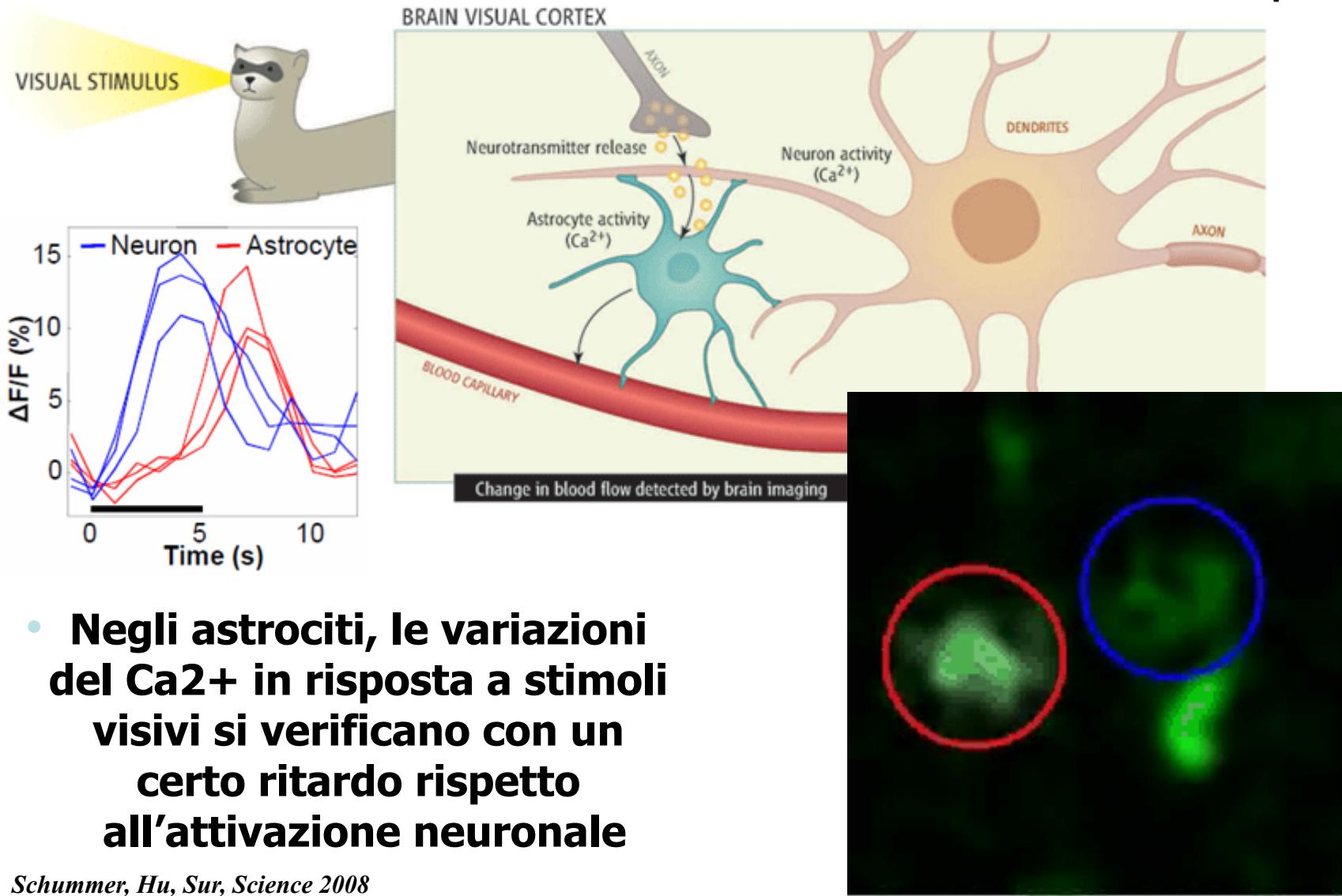
**“Interactions
between neurons,
glia and vasculature
are critical for the
maintenance of
normal brain
function”**



Il compito omeostatico della barriera emato-encefalico

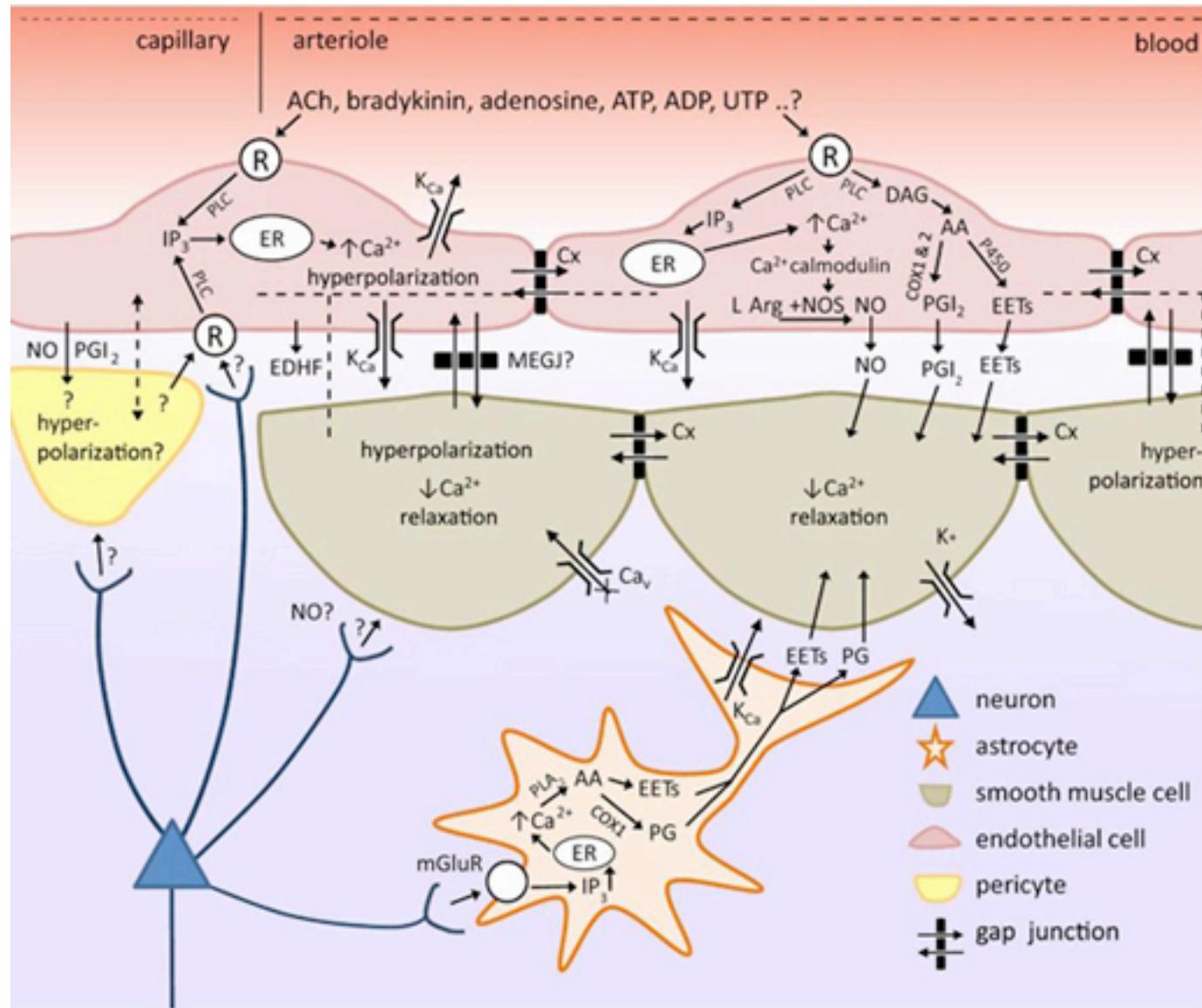


Gli Astrocyti della Corteccia Visiva Primaria rispondono a stimoli visivi



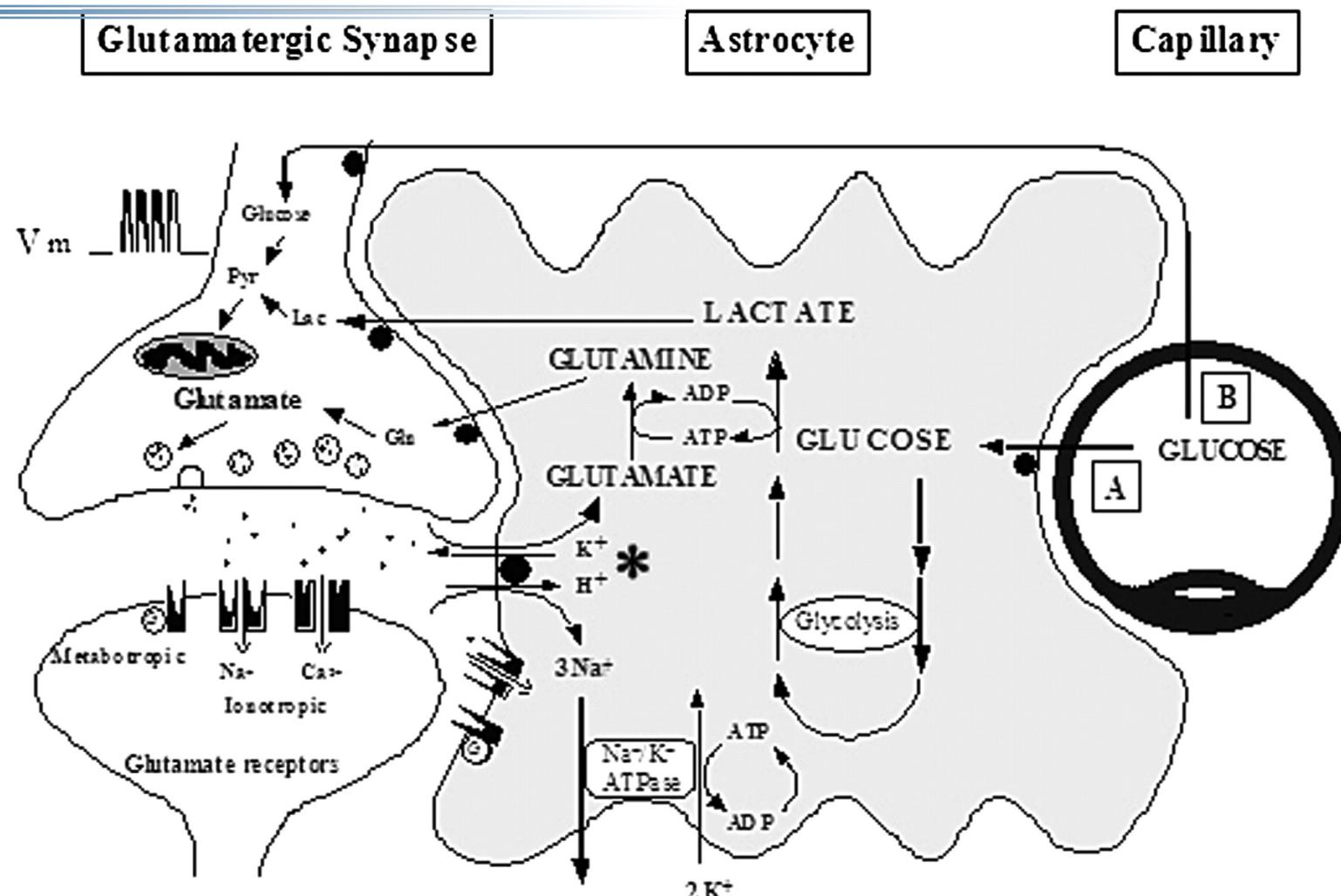
Schummer, Hu, Sur, Science 2008

Neurovascular coupling: endothelium



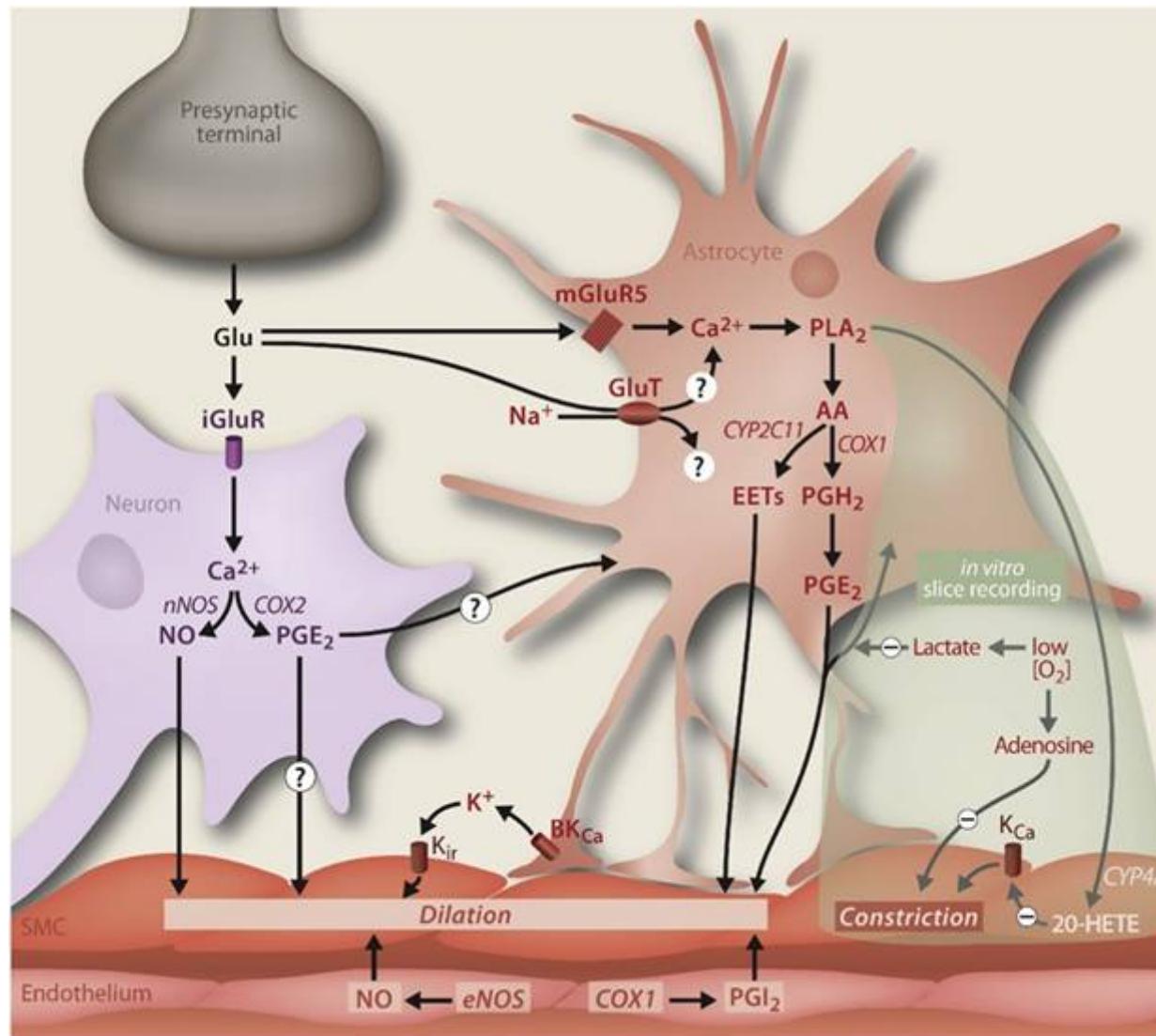
http://orion.bme.columbia.edu/~hillman/Brain_Imaging.html

Neurovascular coupling: where are the neurons?



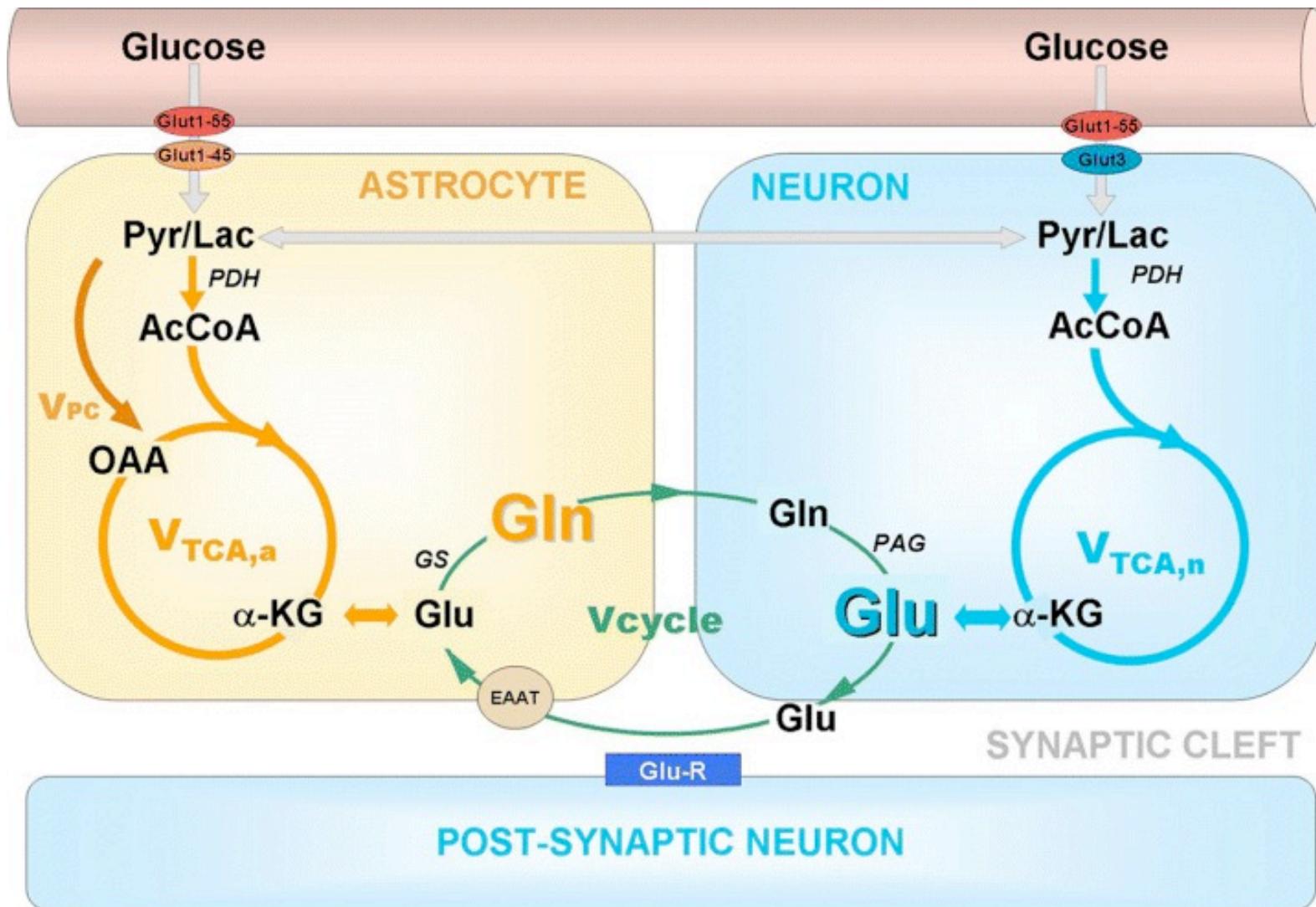
Pierre J Magistretti Am J Clin Nutr 2009;90:875S-880S

The cerebrovascular unit: where the 'signal' comes from



Petzold and Murthy, Neuron 2011

Neurovascular coupling: where are the neurons?

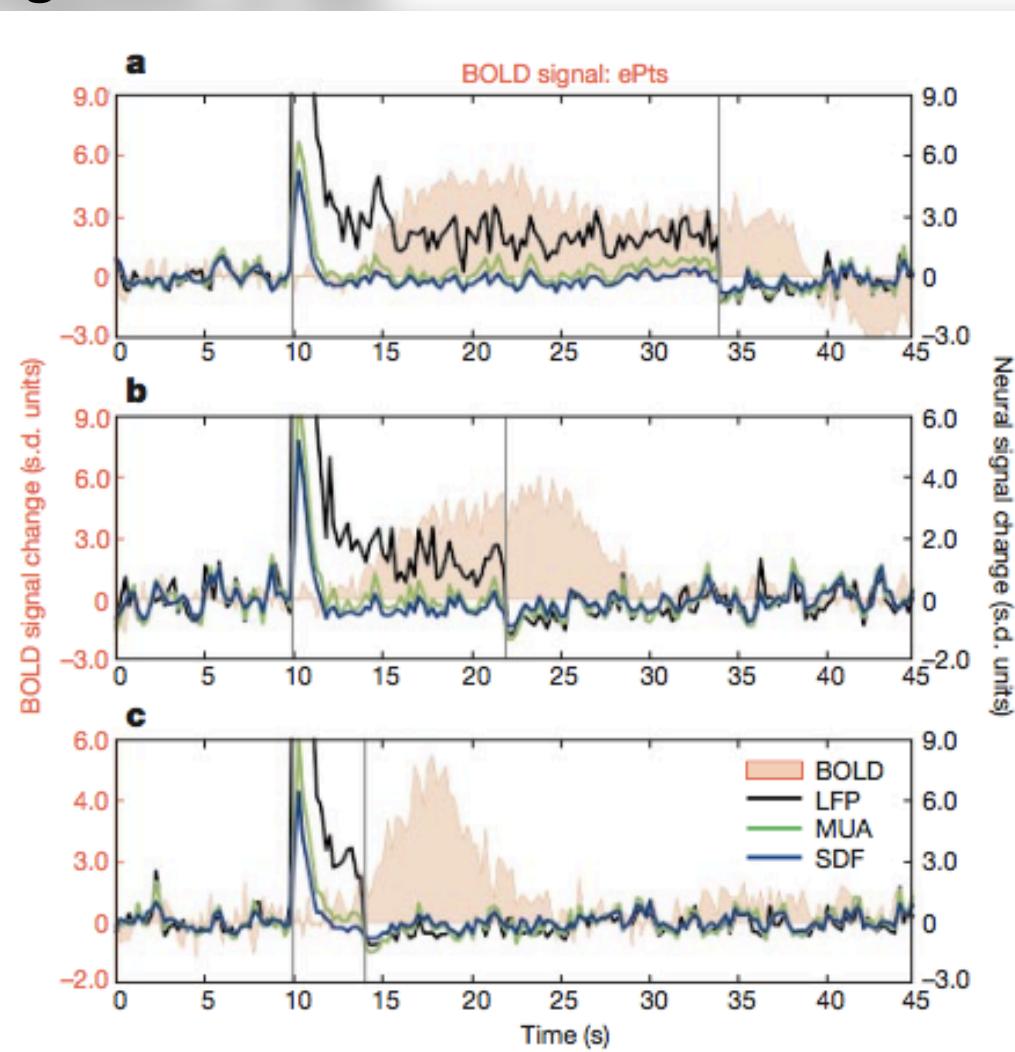


Coupling to synaptic and spiking neural activity

Neurophysiological investigation of the basis of the fMRI signal

Nikos K. Logothetis, Jon Pauls, Mark Augath, Torsten Trinath & Axel Oeltermann

Max Planck Institute for Biological Cybernetics, Spemannstrasse 38, 72076 Tuebingen, Germany



The cerebrovascular unit: where the 'signal' comes from

