Neuroenergetics: How energy constraints shape brain function

Renaud Jolivet, PhD

EP-DI & University of Geneva

CERN, July 21, 2016

Outline

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- Neuroenergetics

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- Energy as a constraint on brain function

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Energy

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William Hamilton
(1805 – 1865)

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Brain energy

What is biological energy?

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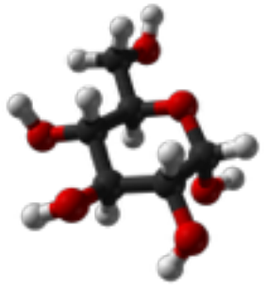

- In the brain, the vast majority of energy is produced from **glucose**.

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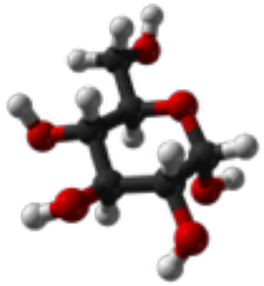

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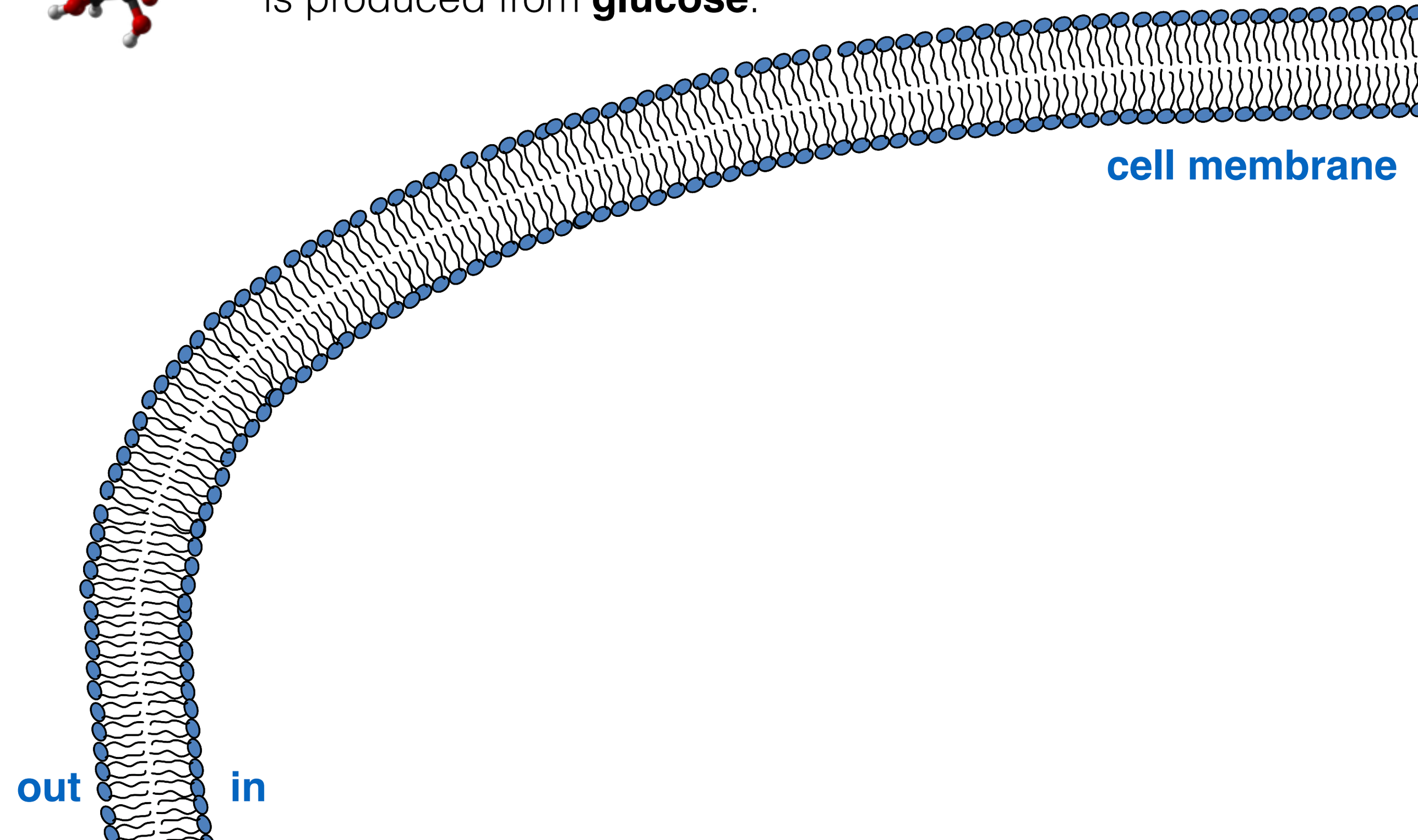

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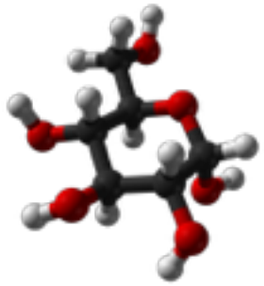

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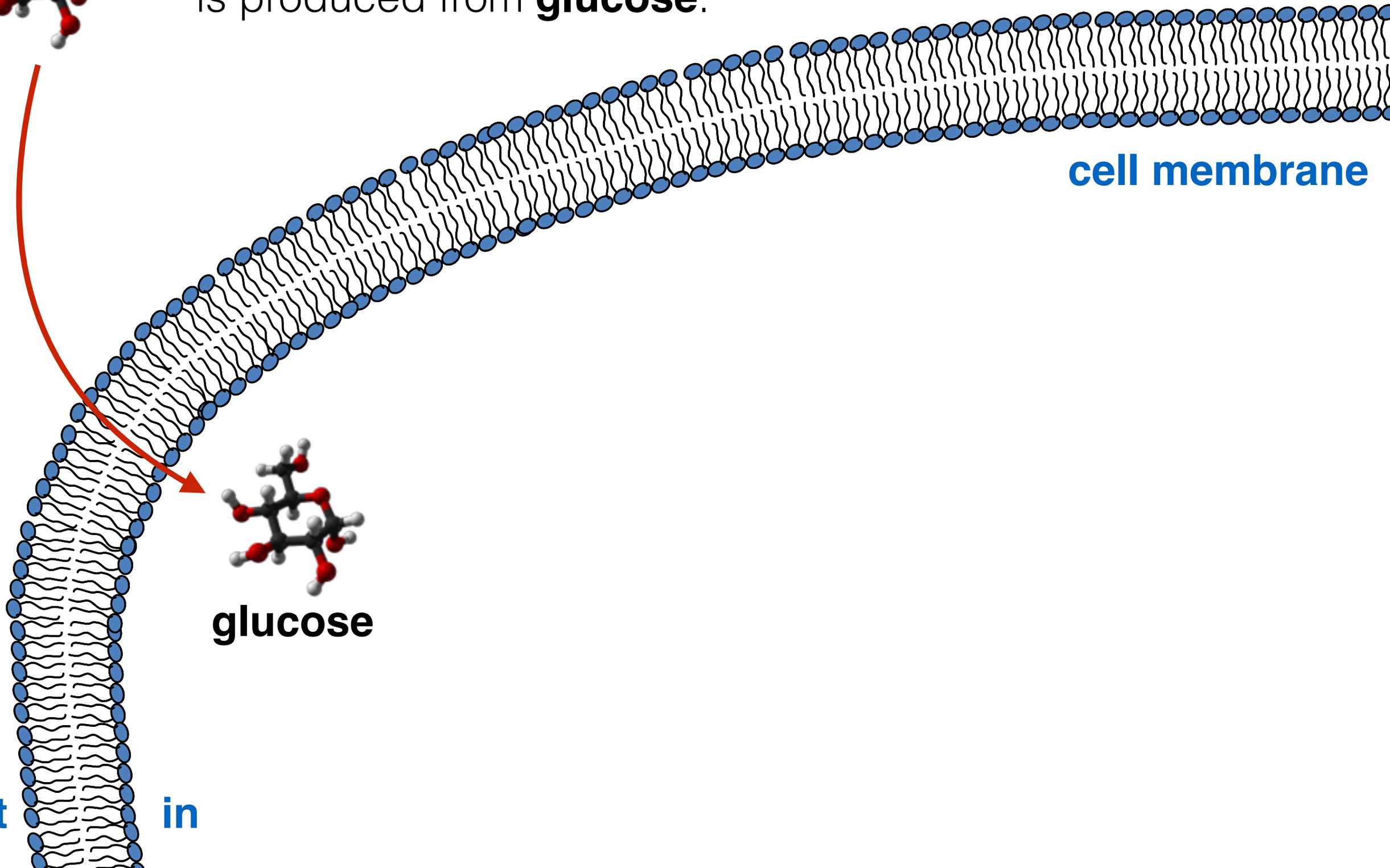

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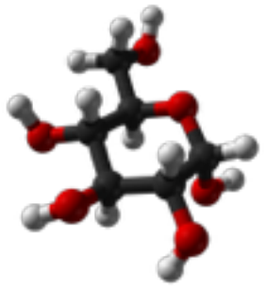

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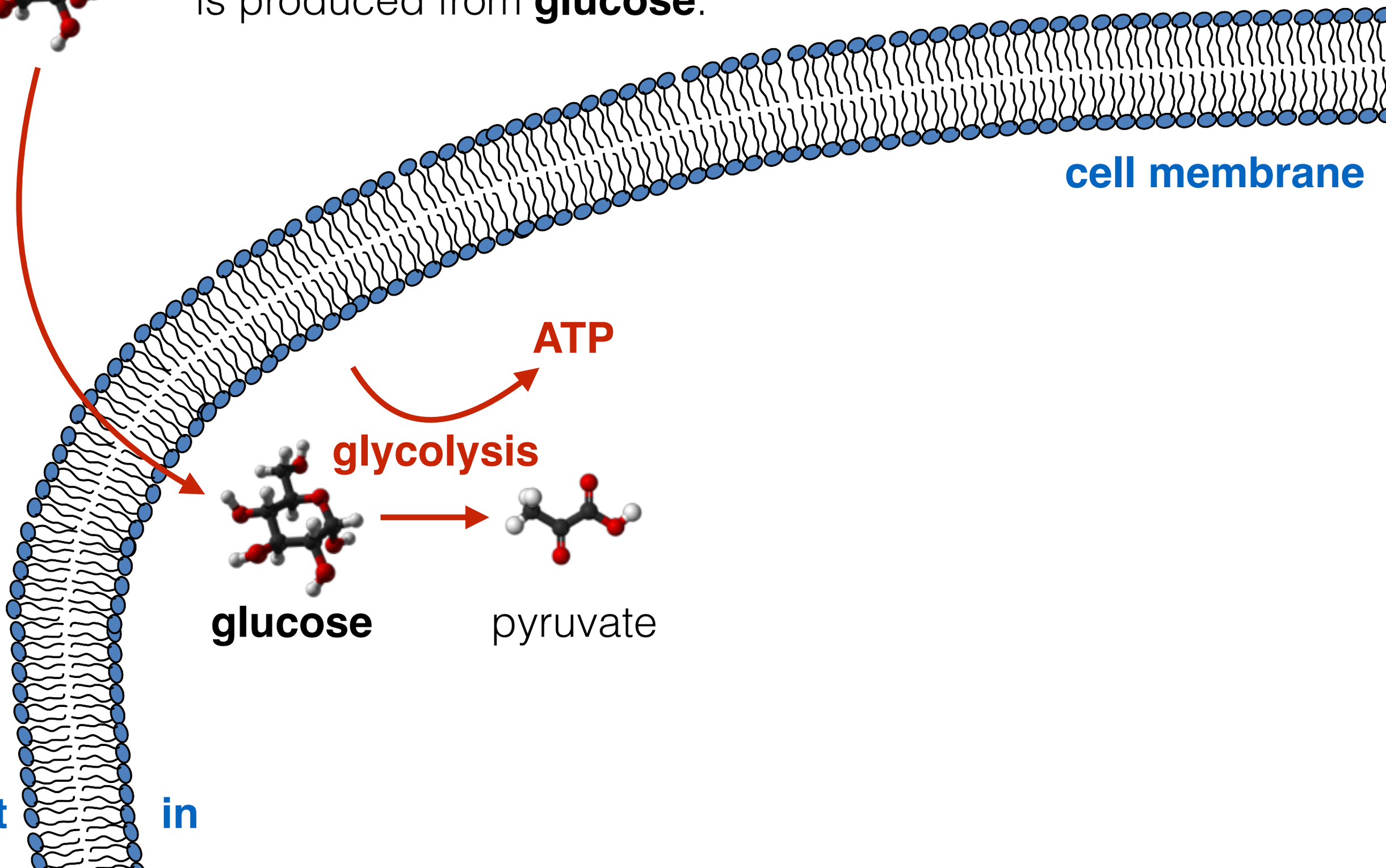

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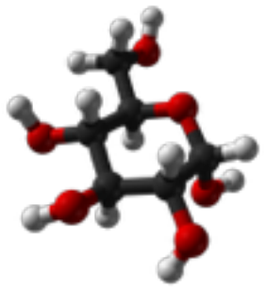

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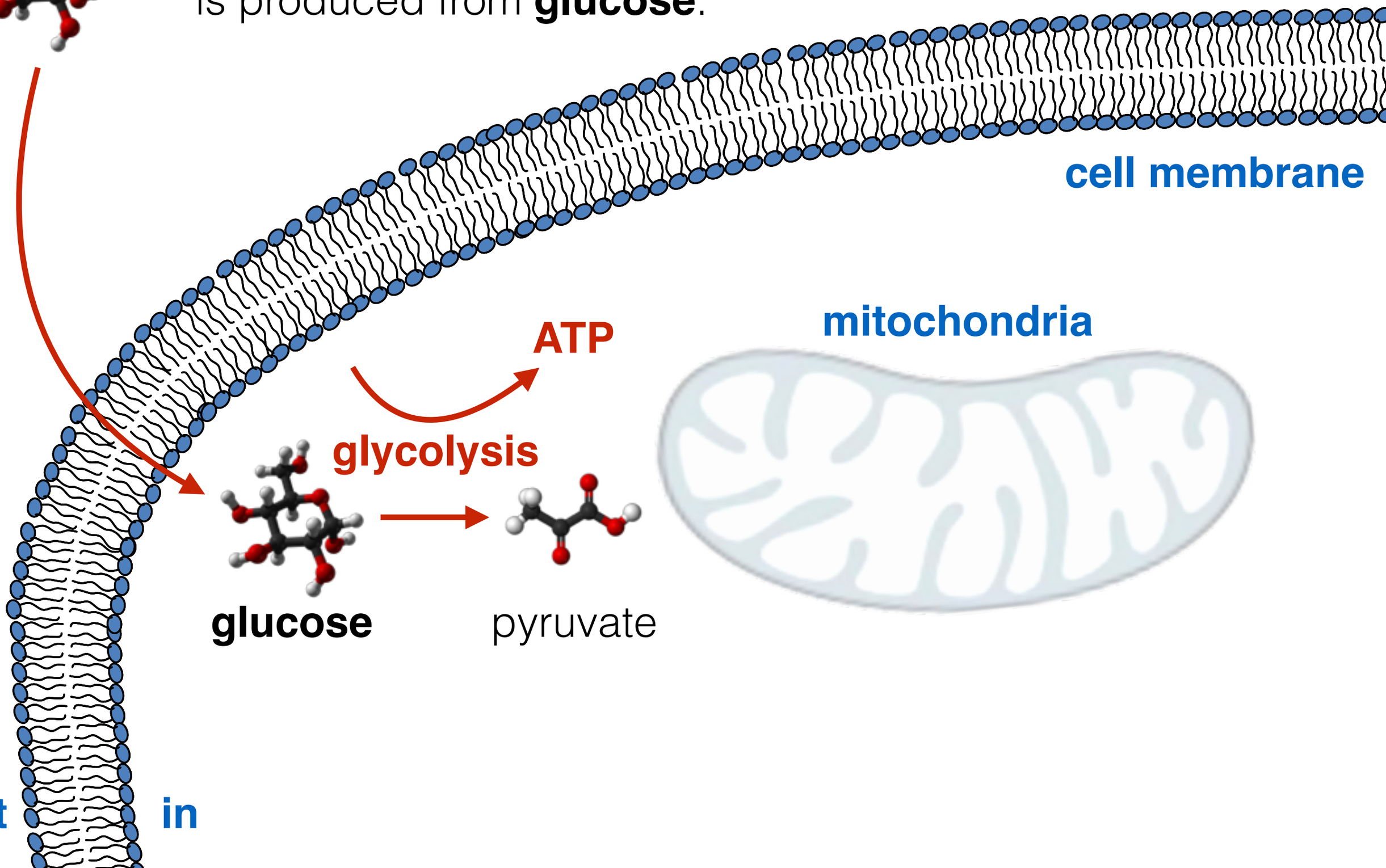

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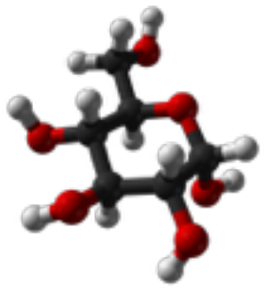

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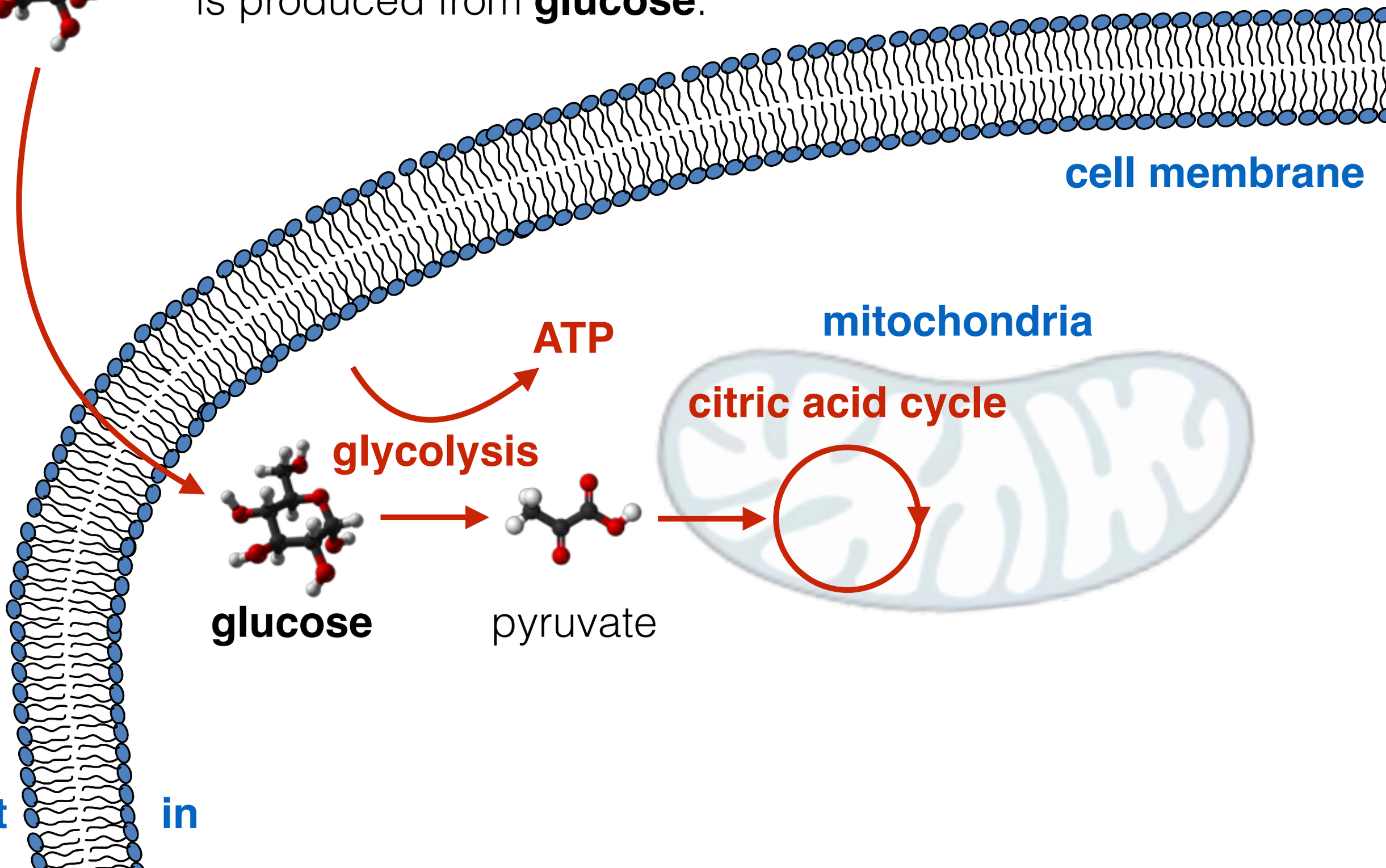

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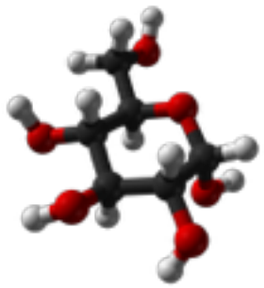

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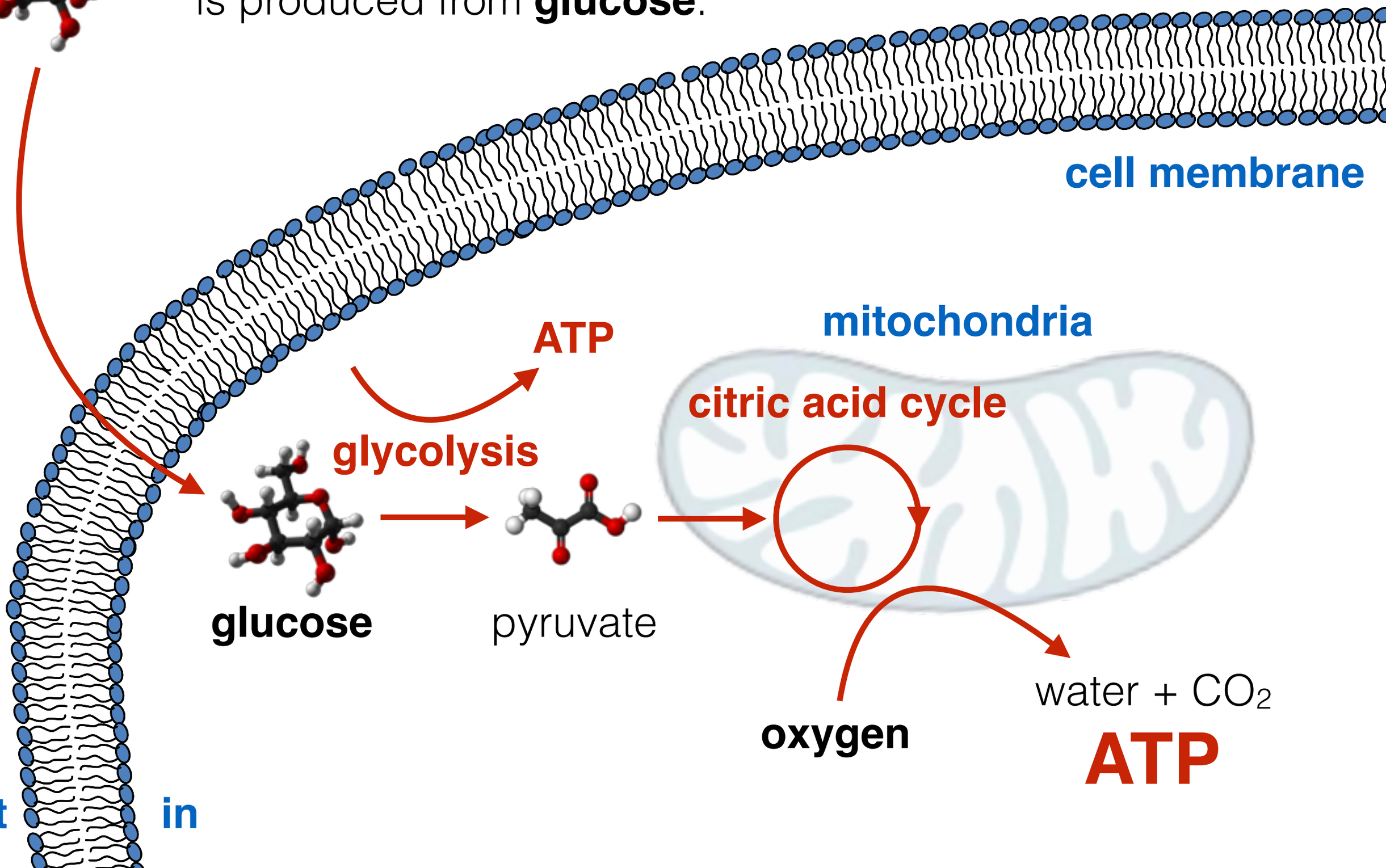

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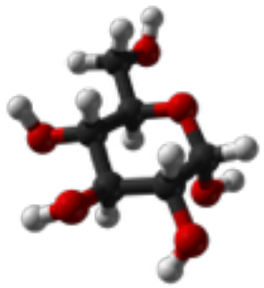

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cell membrane

ATP

mitochondria

citric acid cycle

glycolysis

glucose

pyruvate

oxygen

water + CO_2

ATP

out

in

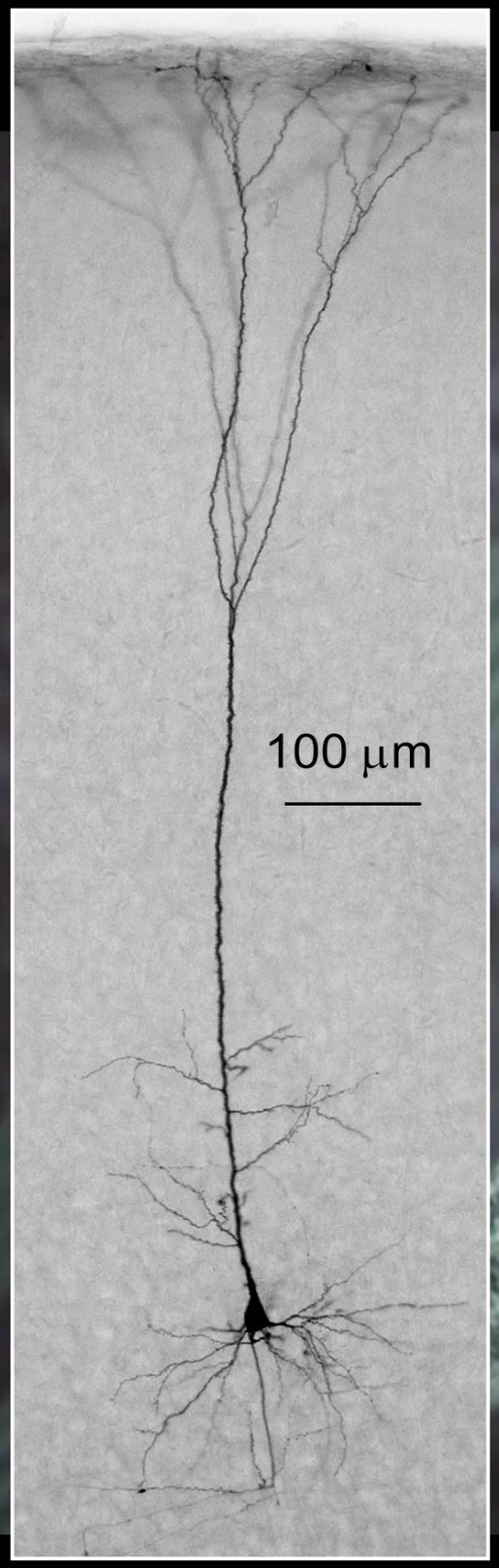
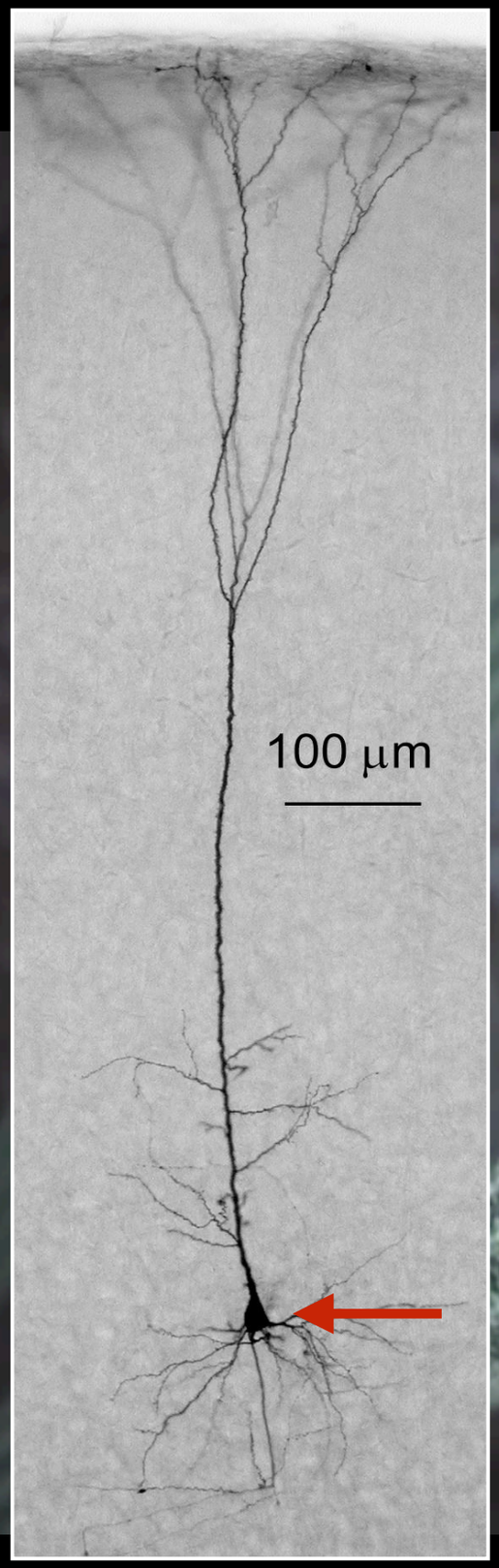


image courtesy of A. Rauch

The Inner Life of the Cell, Harvard



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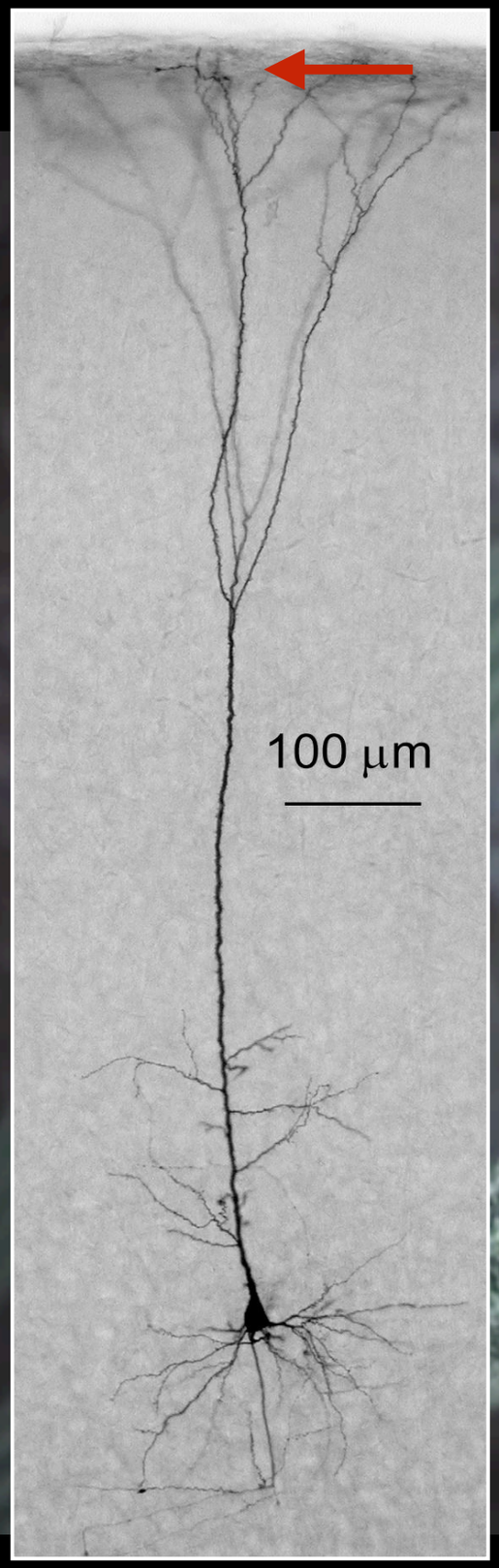

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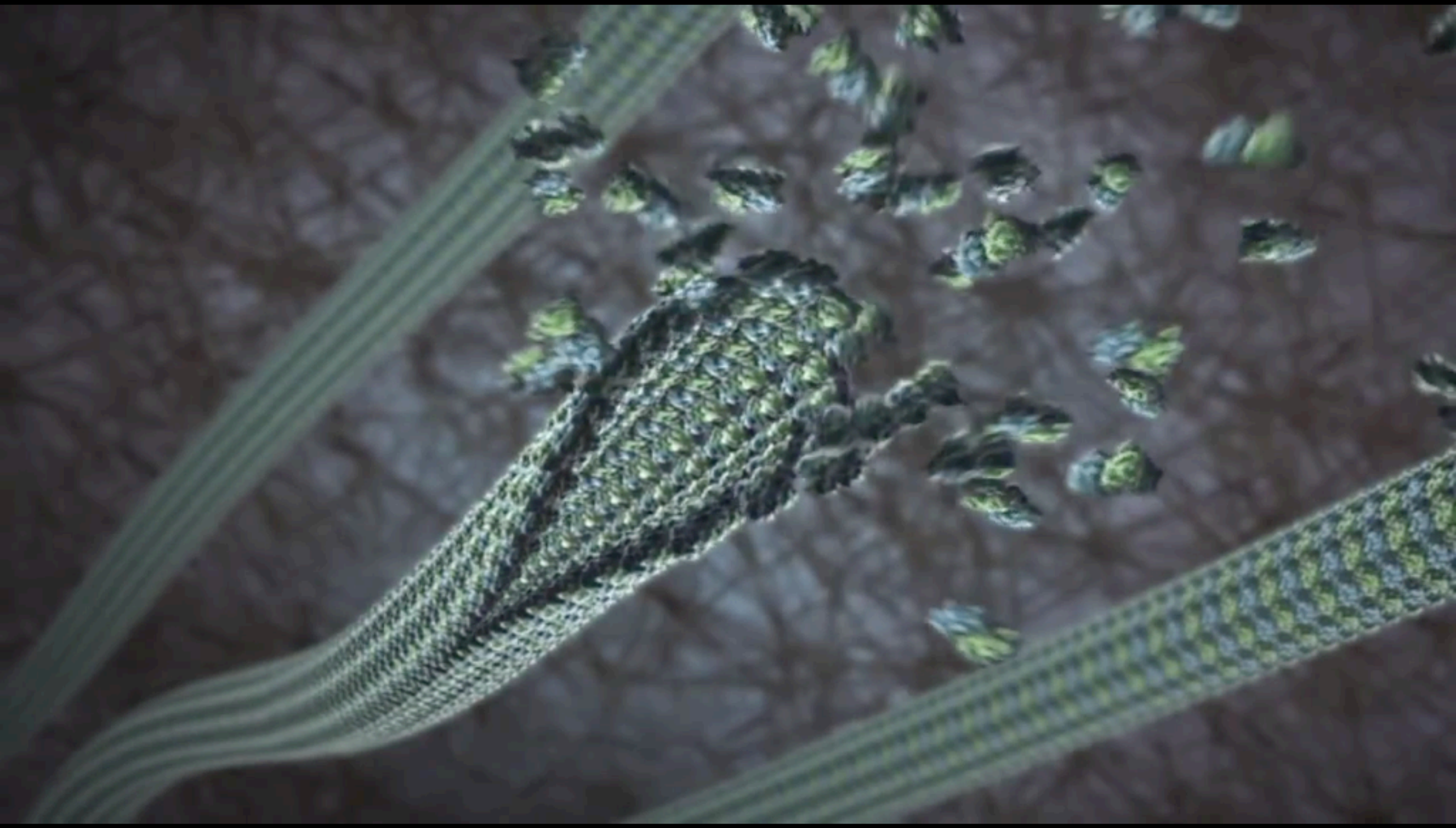

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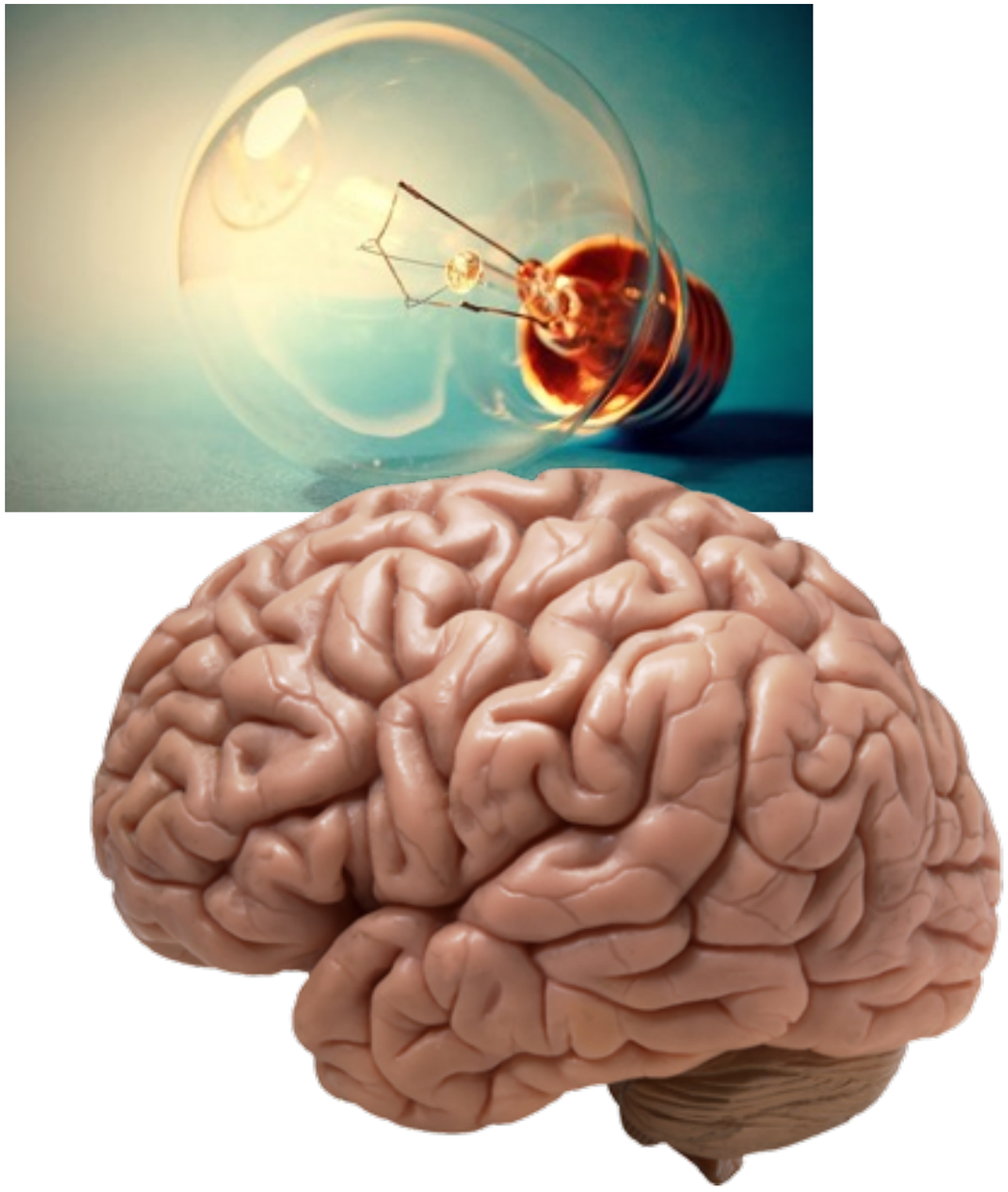
Your brain
~20 W



Your brain
~20 W

Your brain
~20 W

iMac
135 – 200 W

From your body's perspective,
your brain is rather expensive

From your body's perspective, your brain is rather expensive

^{18}F-fluorodeoxyglucose
(glucose utilisation)

image courtesy of M. T. Wyss

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- The brain accounts for approximately 2% of the total body weight but for about 20% of the whole body glucose utilisation.

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- Disruptions of the energy supply to the brain have rapid and dramatic consequences.

Interrupting the energy supply to the brain has dramatic consequences

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Stroke is the second leading cause of disability in Europe after ischaemic heart disease (IHD) and is the sixth leading cause worldwide (See Background Paper 6.6, Table 6.6.7). Women have a higher lifetime risk of stroke than men: about **one in five women** (20% to 21%) and **one in six men** (14% to 17%) **will suffer a stroke in their lifetime**, according to a 2006 study.[5,6] The prevalence of stroke events is expected to increase across the globe as the global population aged over 65 increases.[7,8] The number of stroke events in Europe is projected to rise from 1.1 million in 2000 to 1.5 million per year by 2025, largely due to the ageing population.[9] In the EU27 countries, the annual economic cost of stroke is an estimated €27 billion: €18.5 billion (68.5%) for direct costs and €8.5 billion (31.5%) for indirect costs. An additional €11.1 billion is calculated for the value of informal care.[10]

http://www.who.int/medicines/areas/priority_medicines/Ch6_6Stroke.pdf

From your body's perspective, your brain is rather expensive

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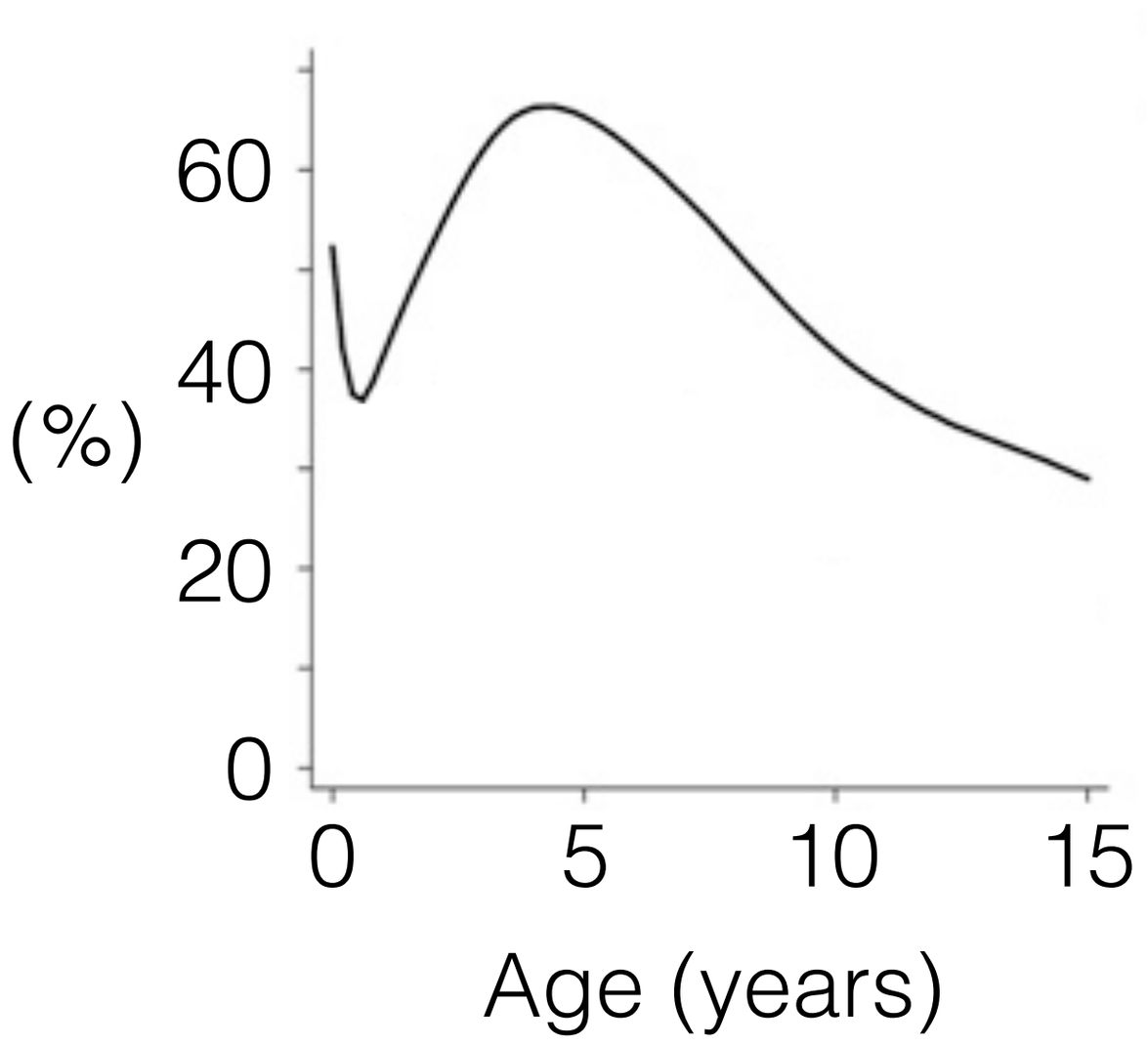
Brain glucose uptake to body's resting metabolic rate



Kuzawa et al., *PNAS* 2014

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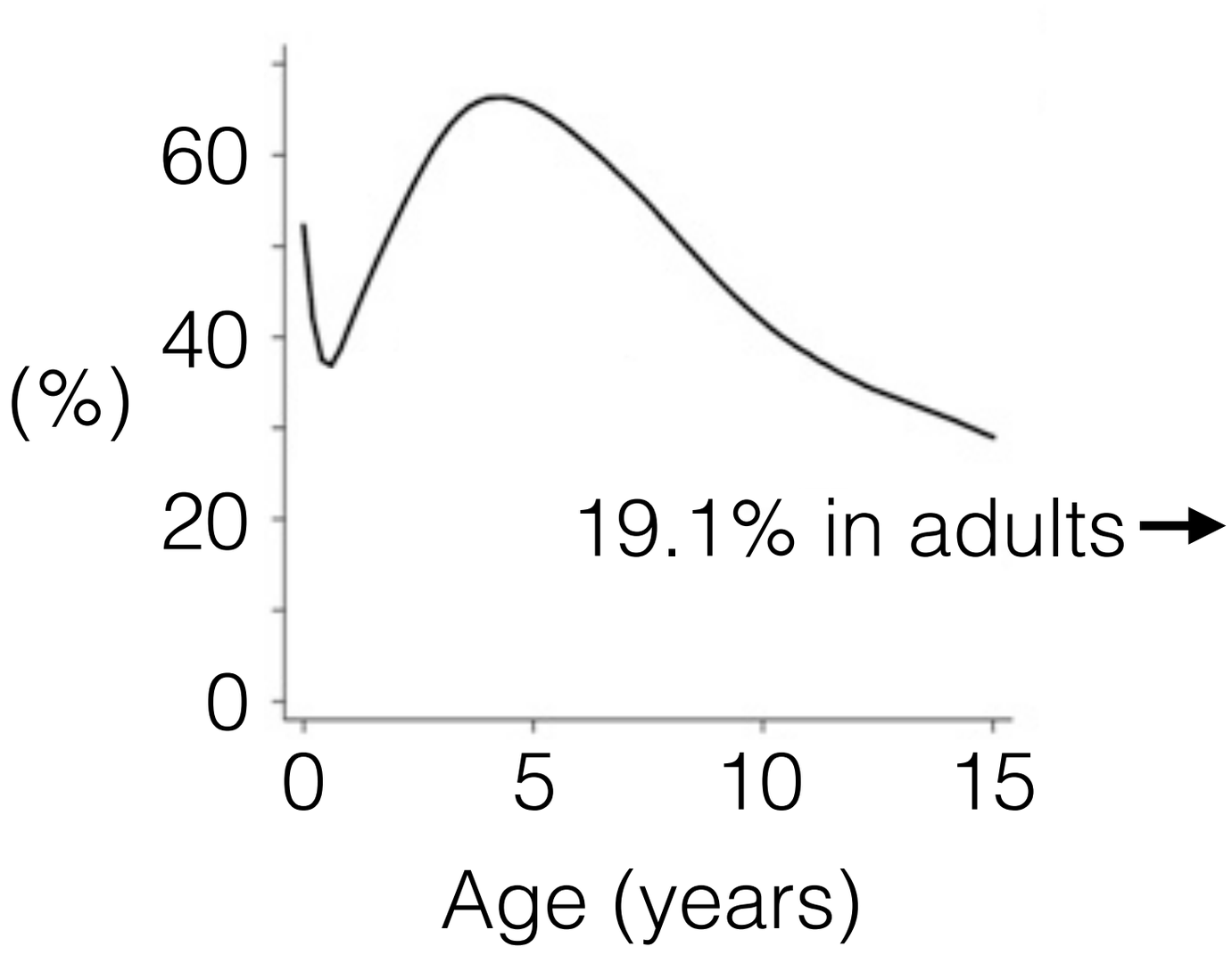

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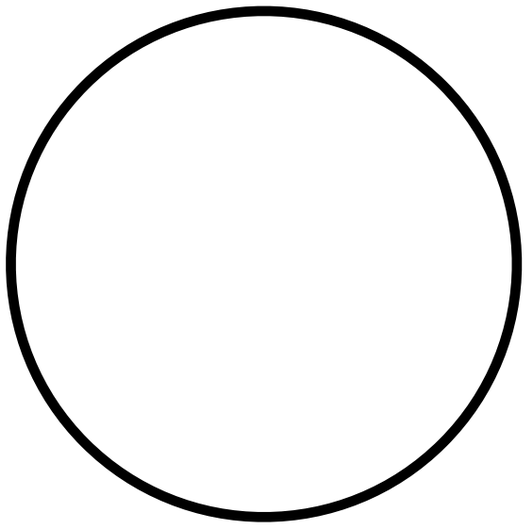
- The brain is energetically efficient when compared to man-made computing devices.

- The brain is an expensive organ from our body's perspective.

- Where is this energy being spent?

How do neurons work and spend energy?

Neuron



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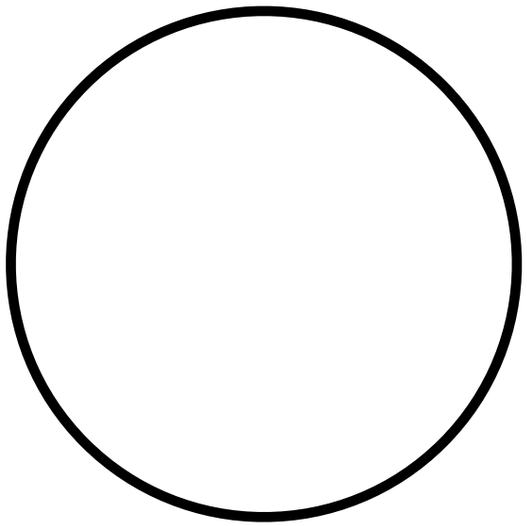

Na^+

K^+

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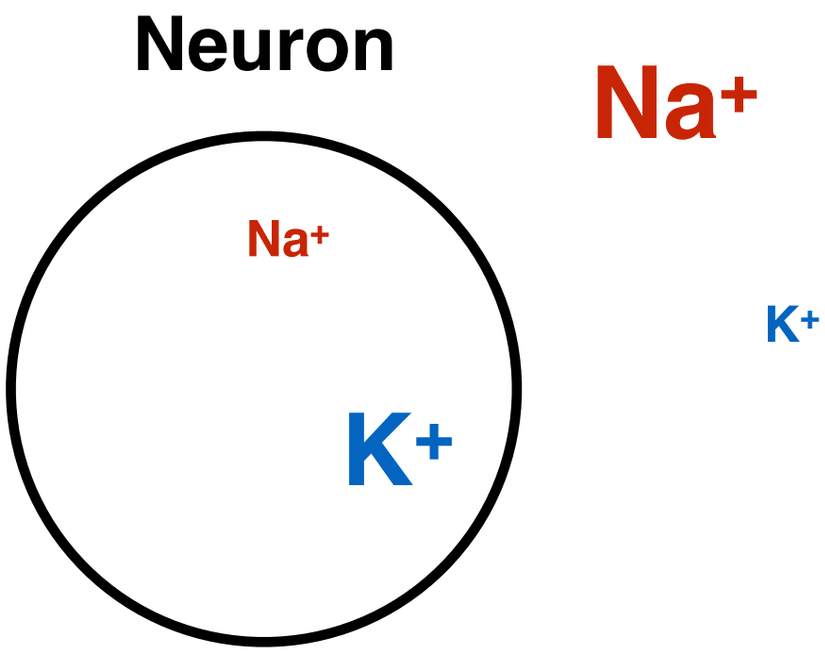

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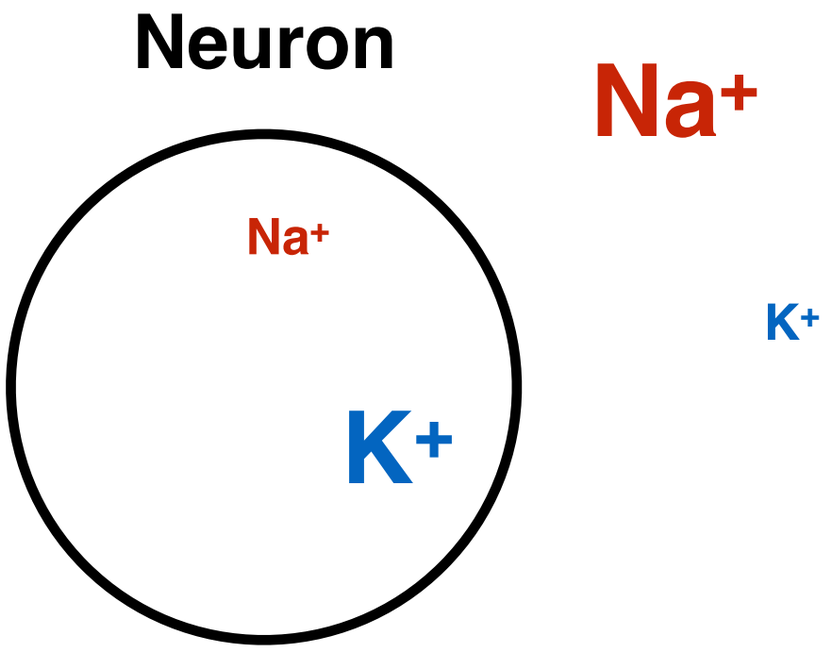

Establishes the resting membrane potential ~ -70 mV

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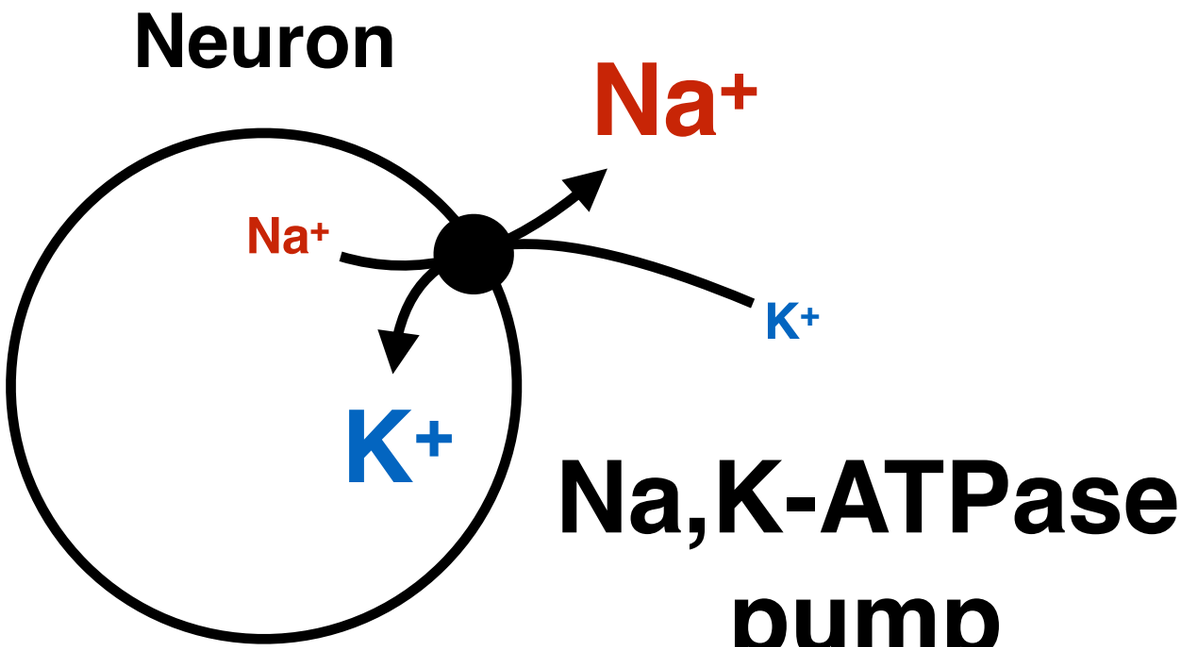

Na,K-ATPase pump

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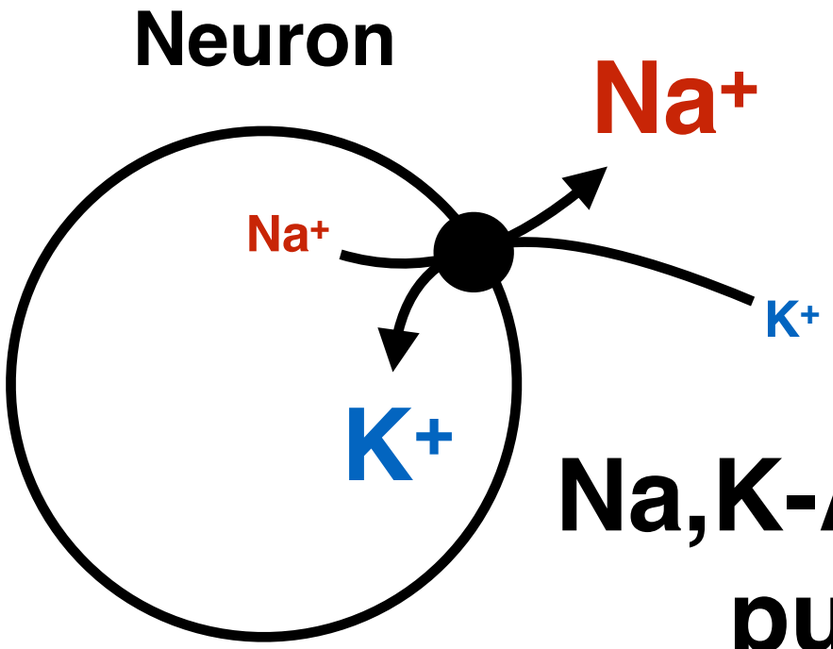
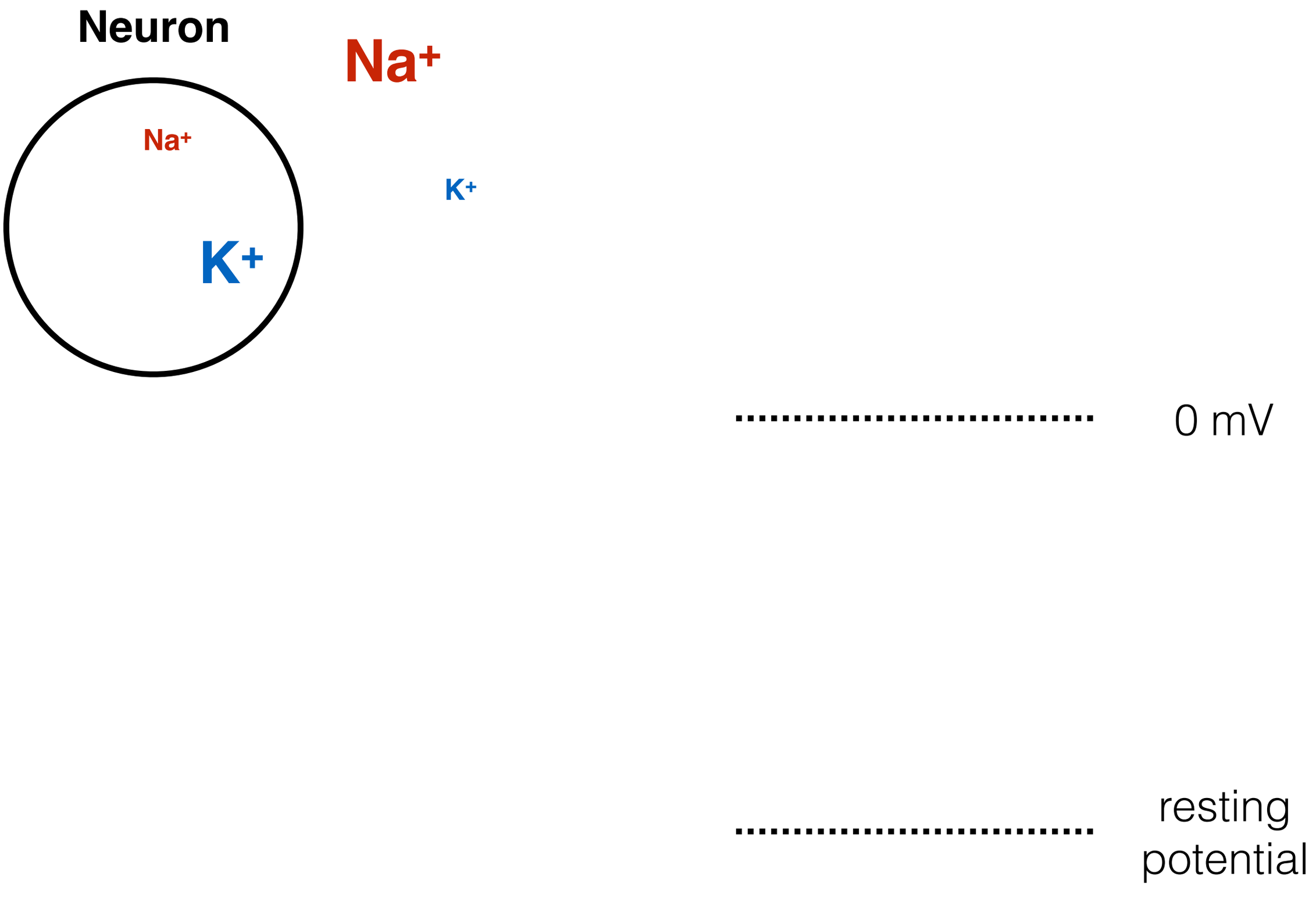


Na,K-ATPase pump

Establishes the resting membrane potential ~ -70 mV

Maintaining that status quo costs energy

How do neurons work and spend energy?



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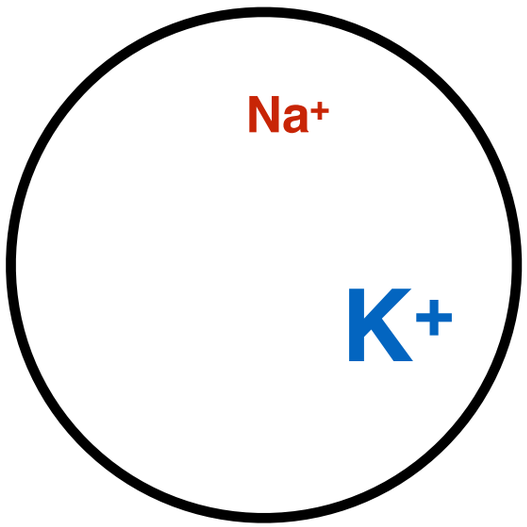


Na+

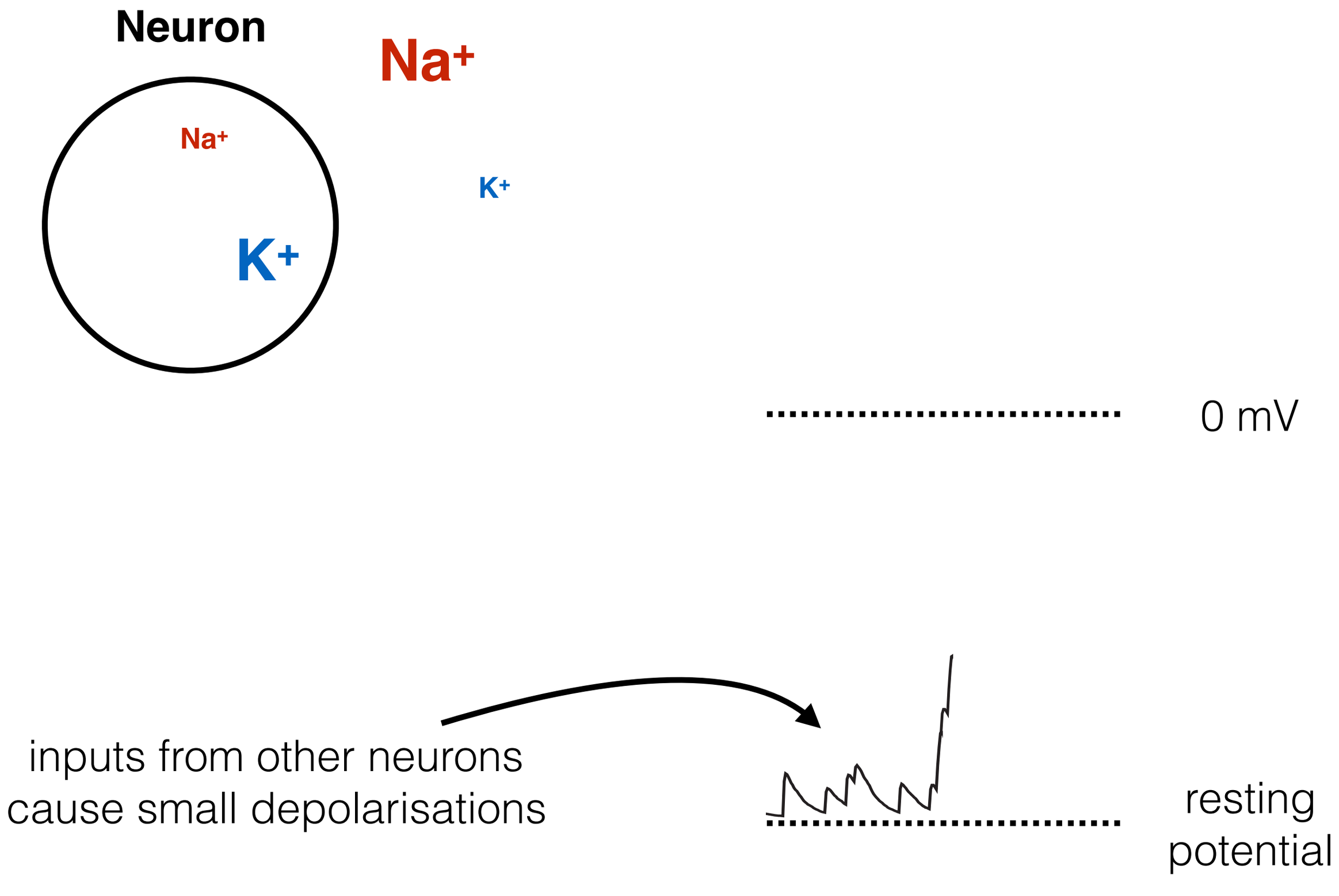
K+

0 mV

inputs from other neurons
cause small depolarisations

resting
potential

How do neurons work and spend energy?



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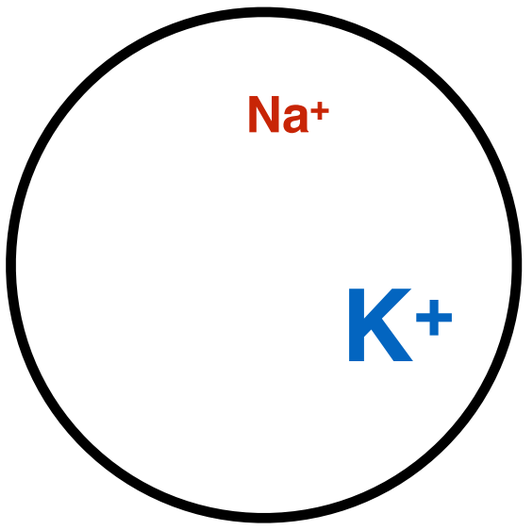

Na+

K+

0 mV

activation threshold

resting potential

inputs from other neurons cause small depolarisations

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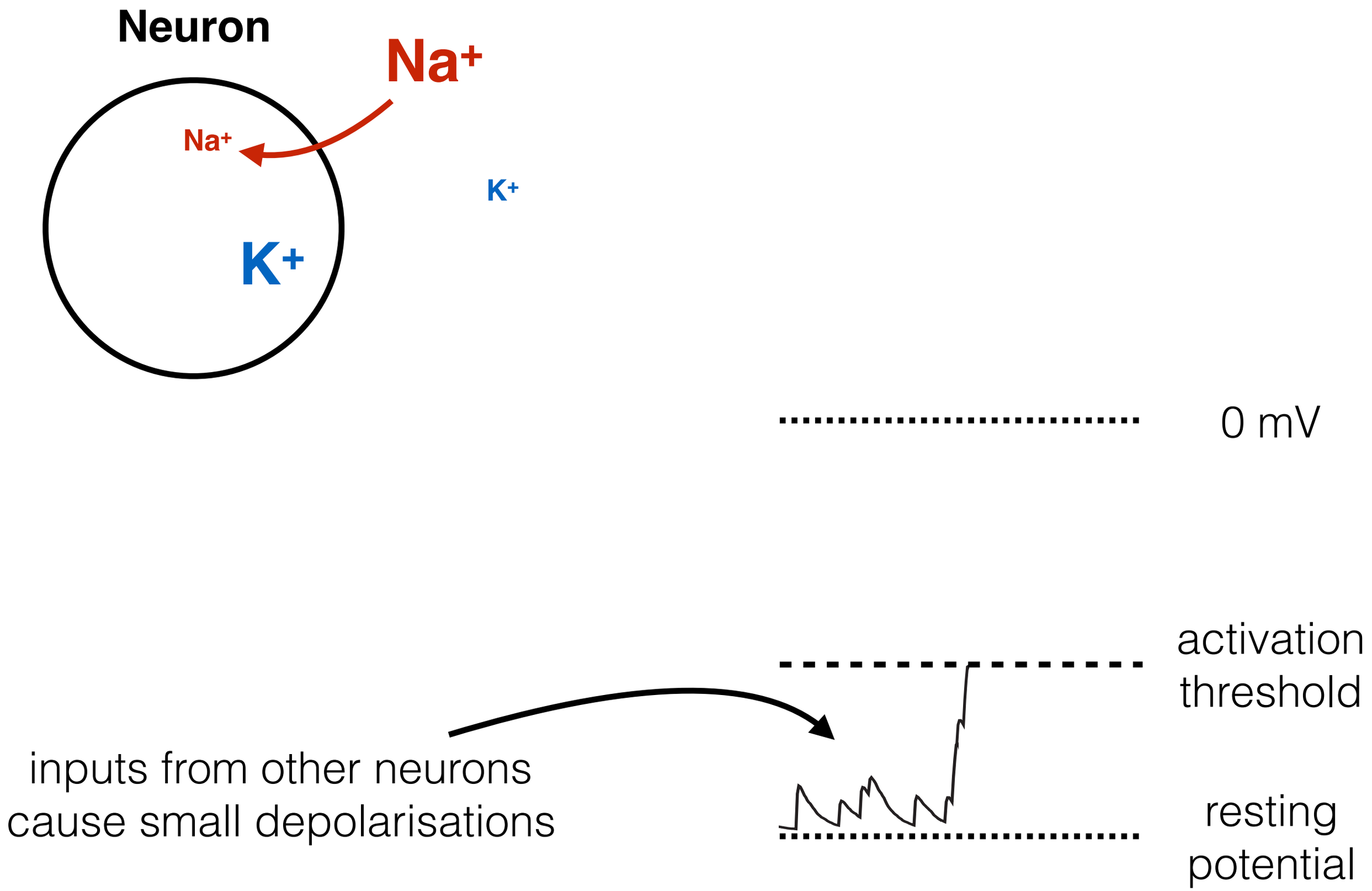

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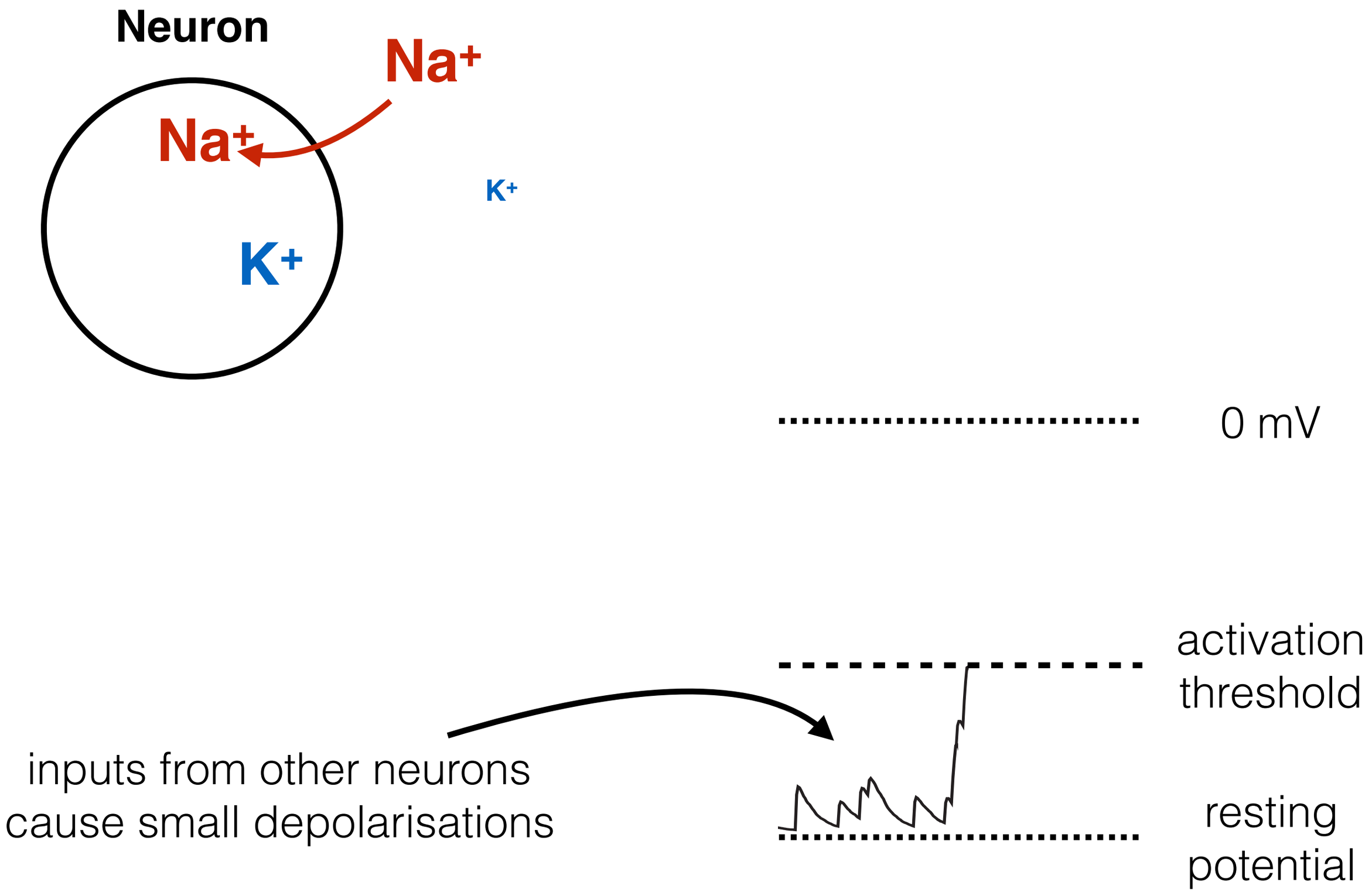

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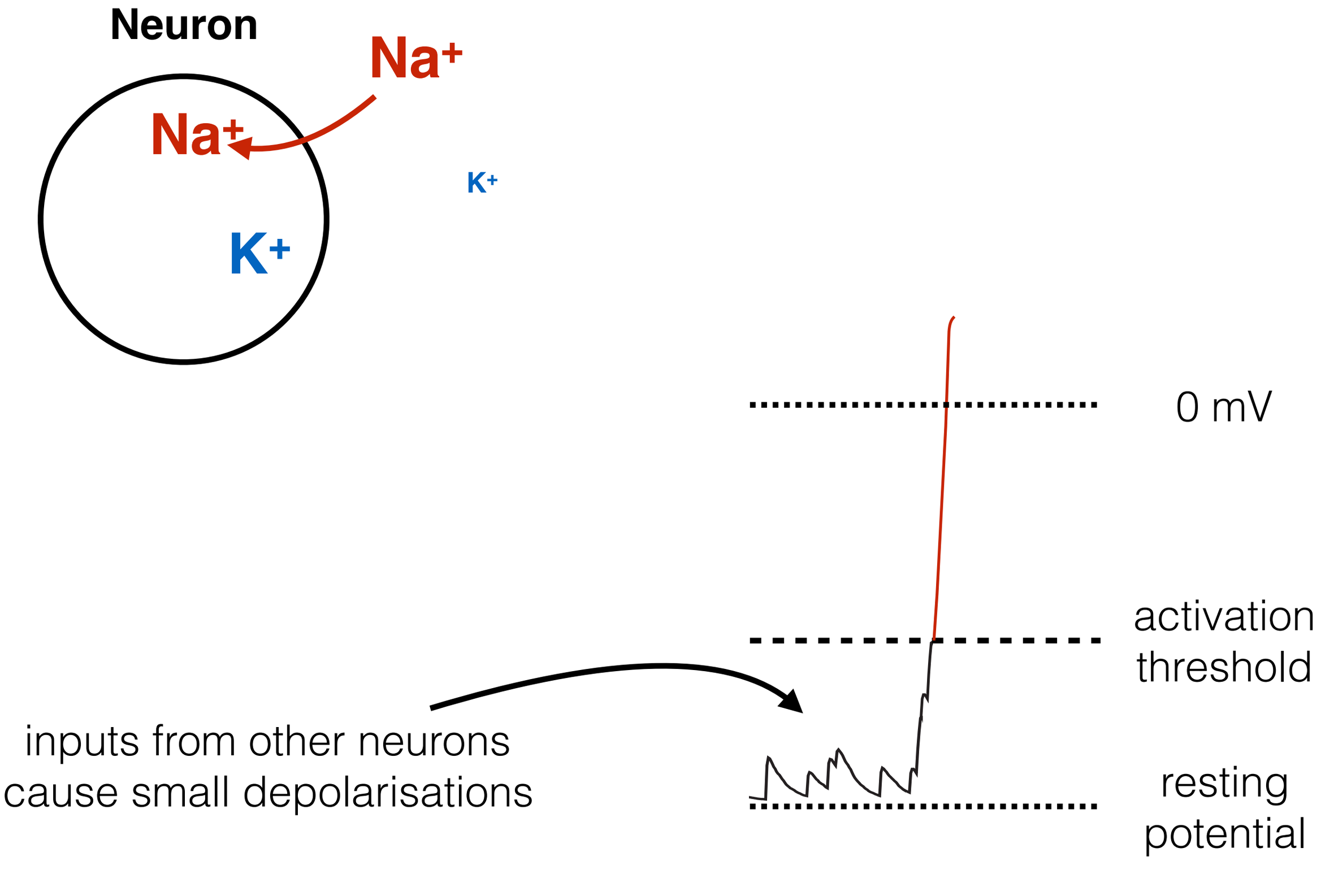

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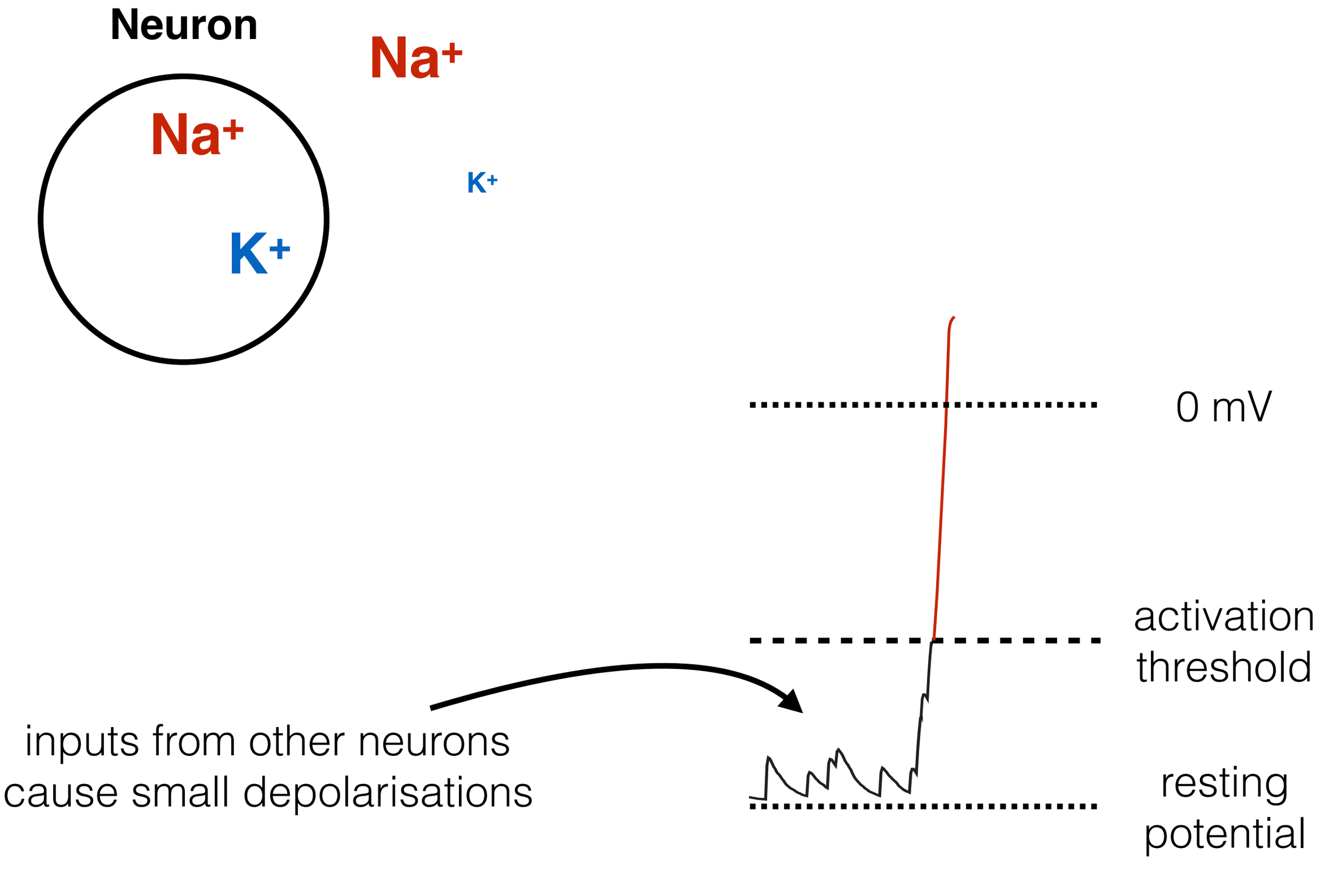

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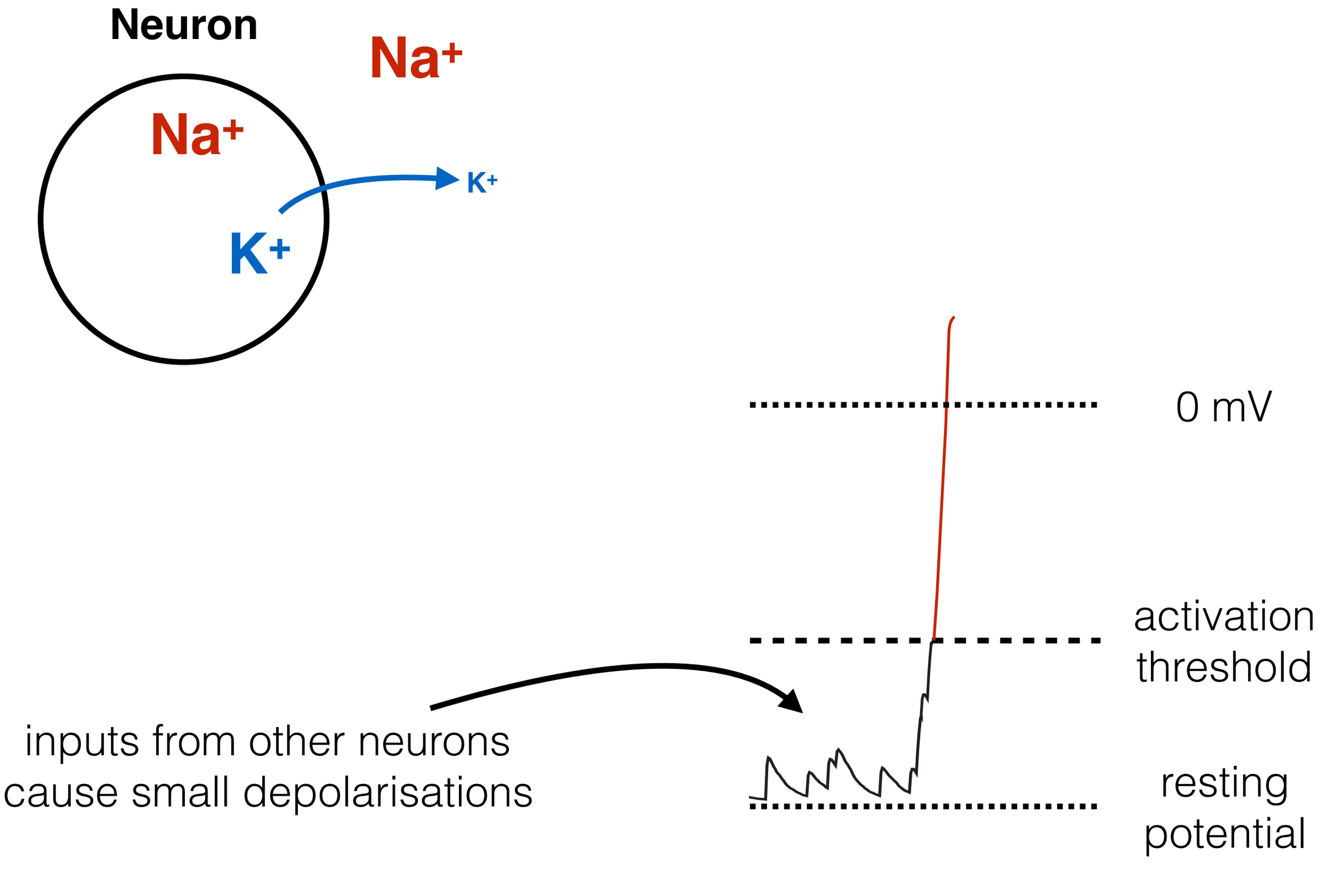

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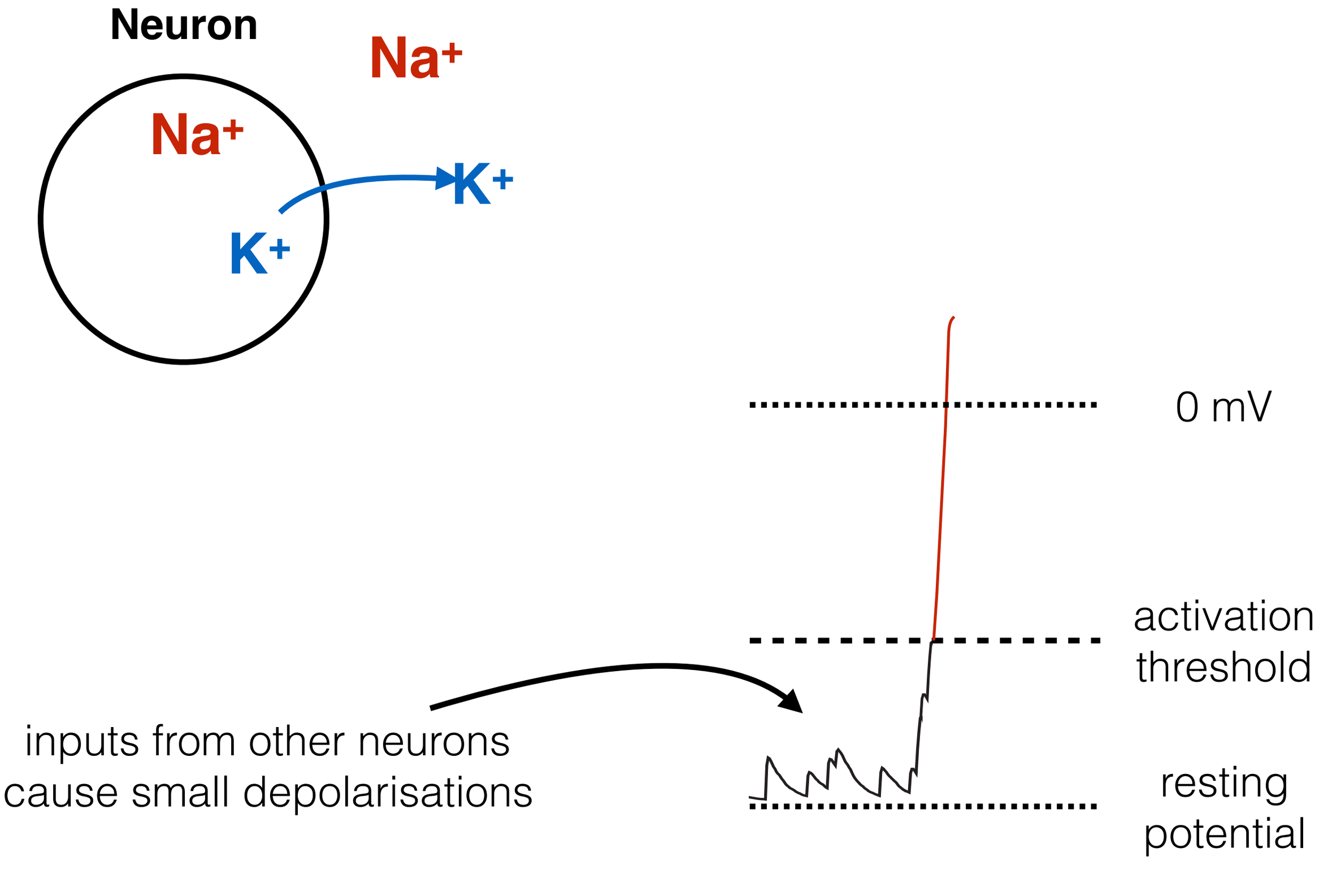

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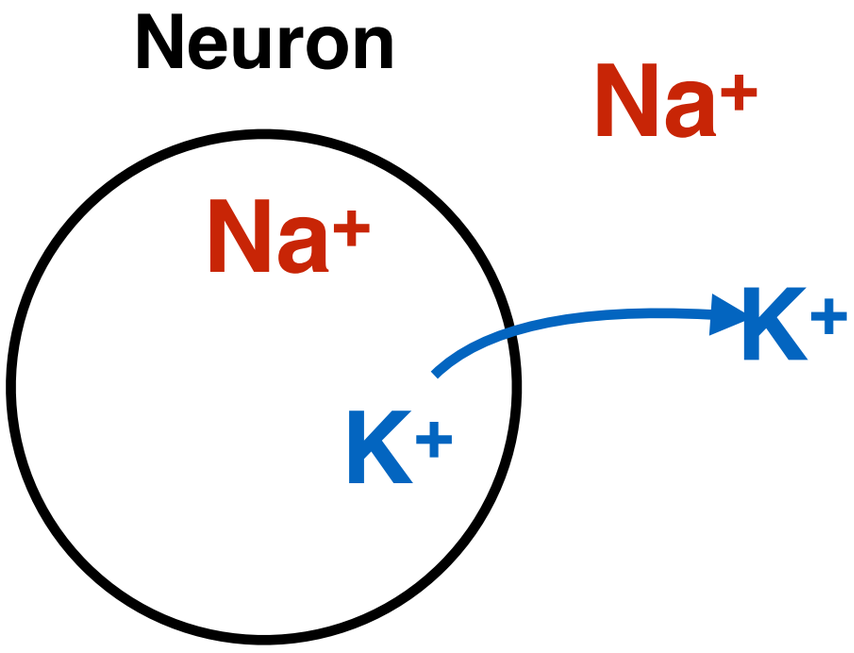

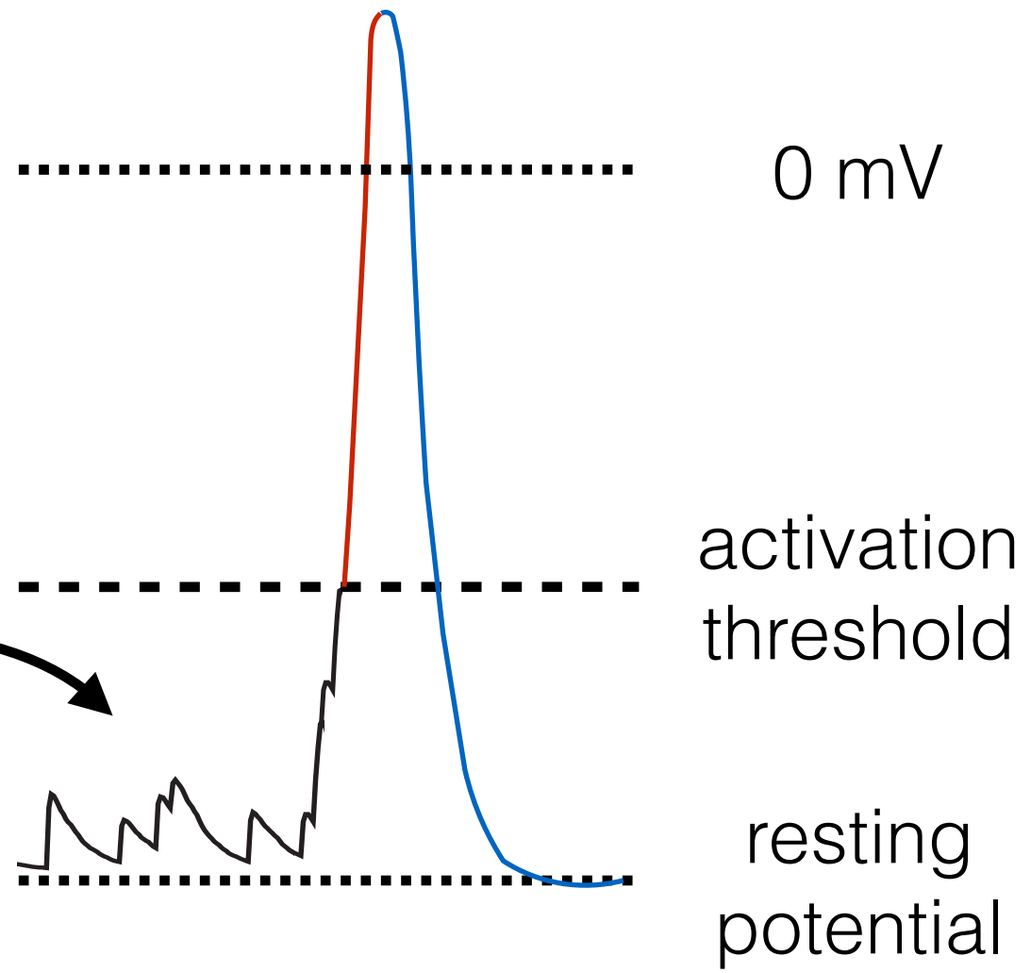

inputs from other neurons cause small depolarisations

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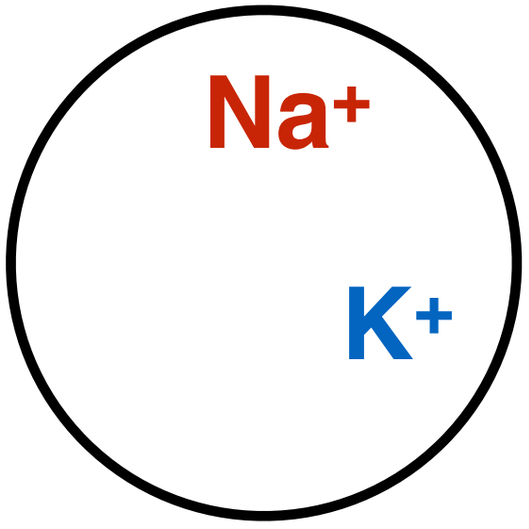
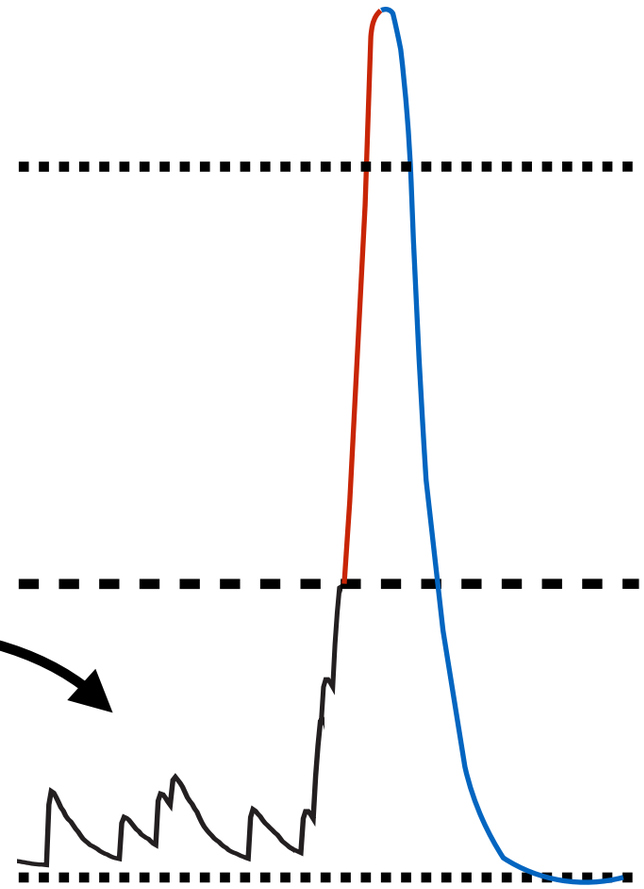


Na+

K+

Action potential



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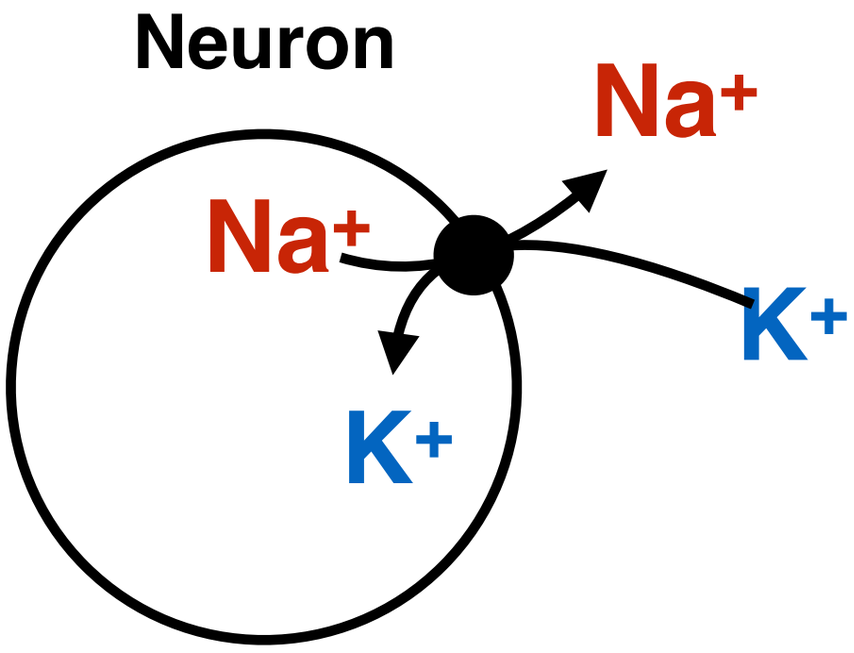

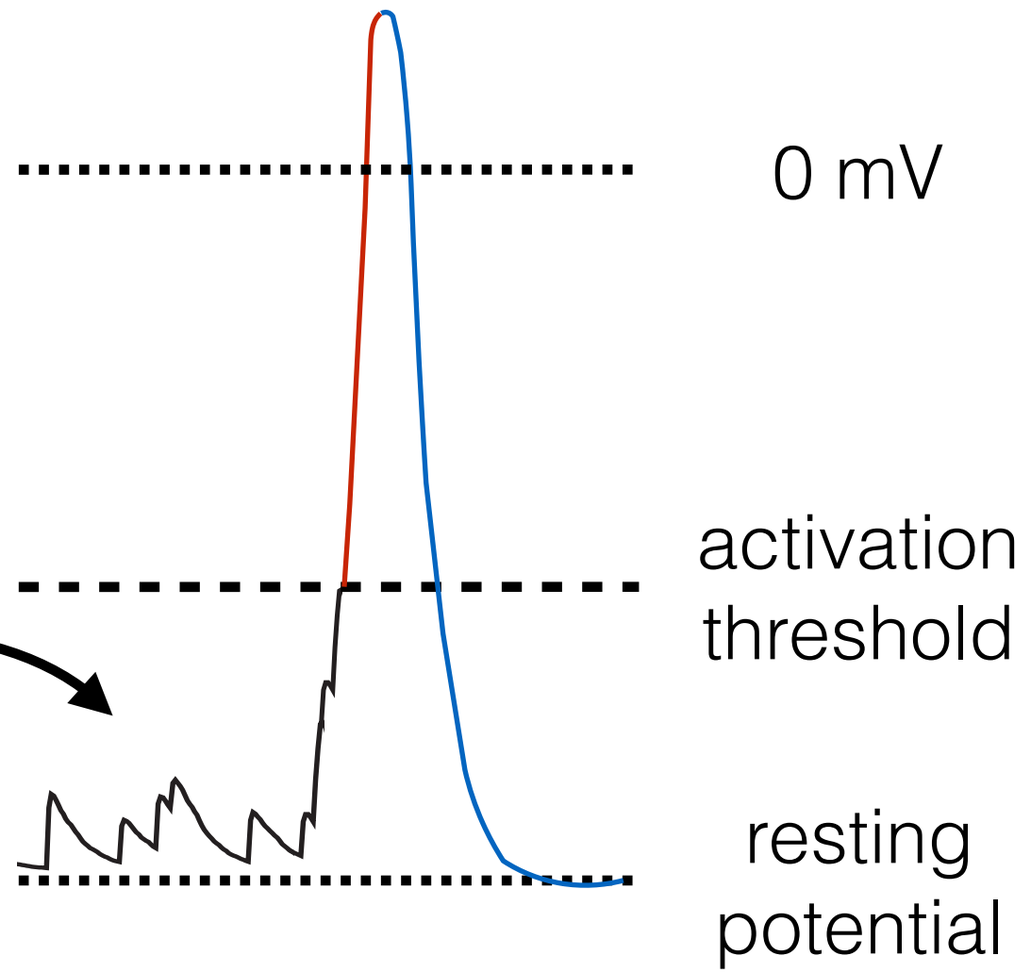

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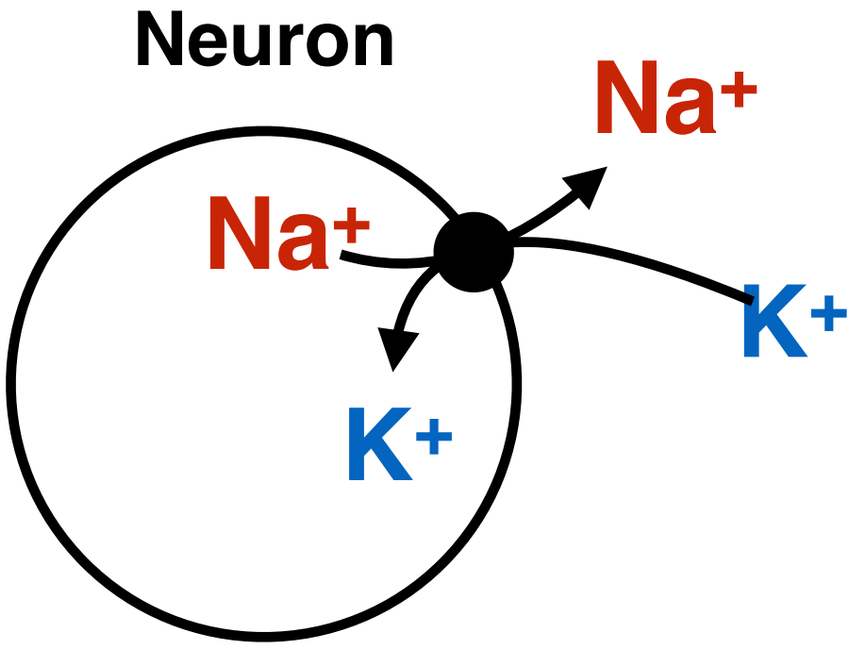
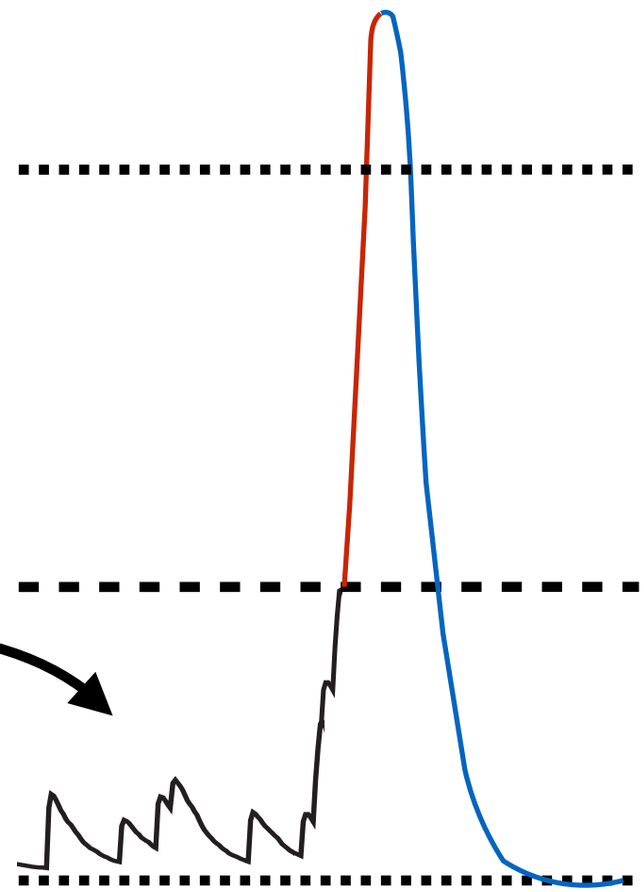


Restoring the status quo costs energy

Action potential



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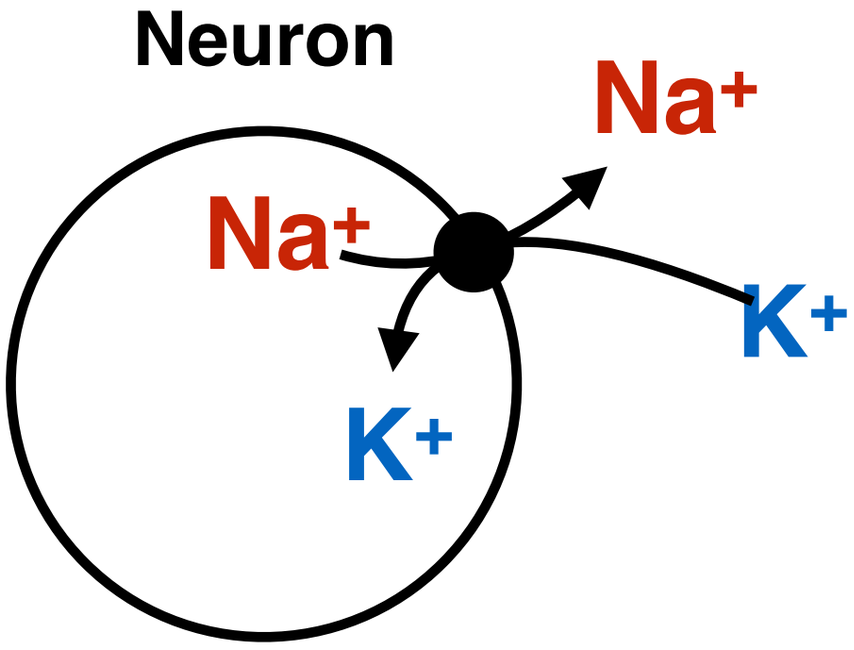

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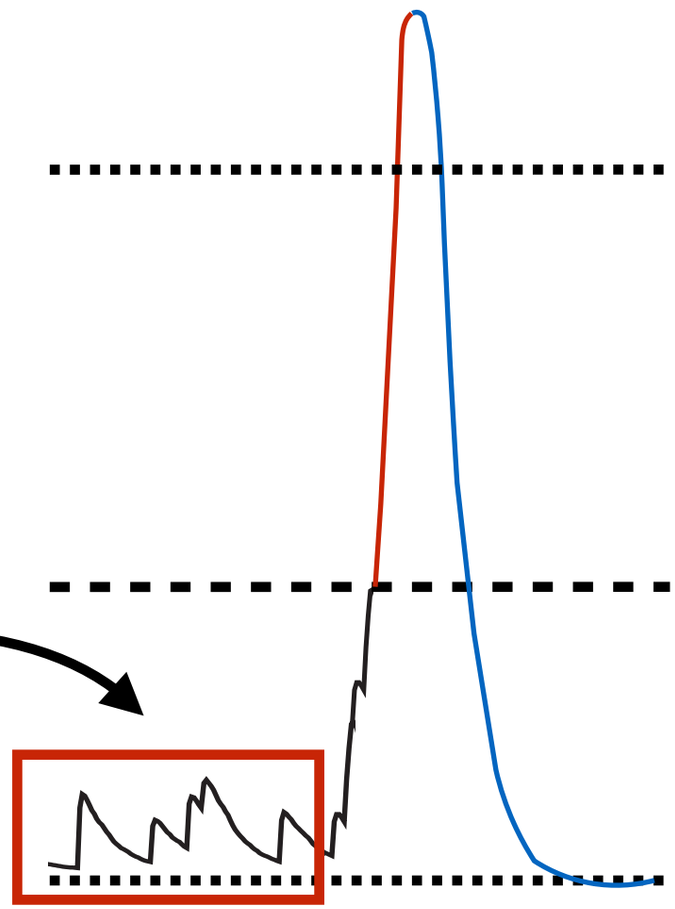

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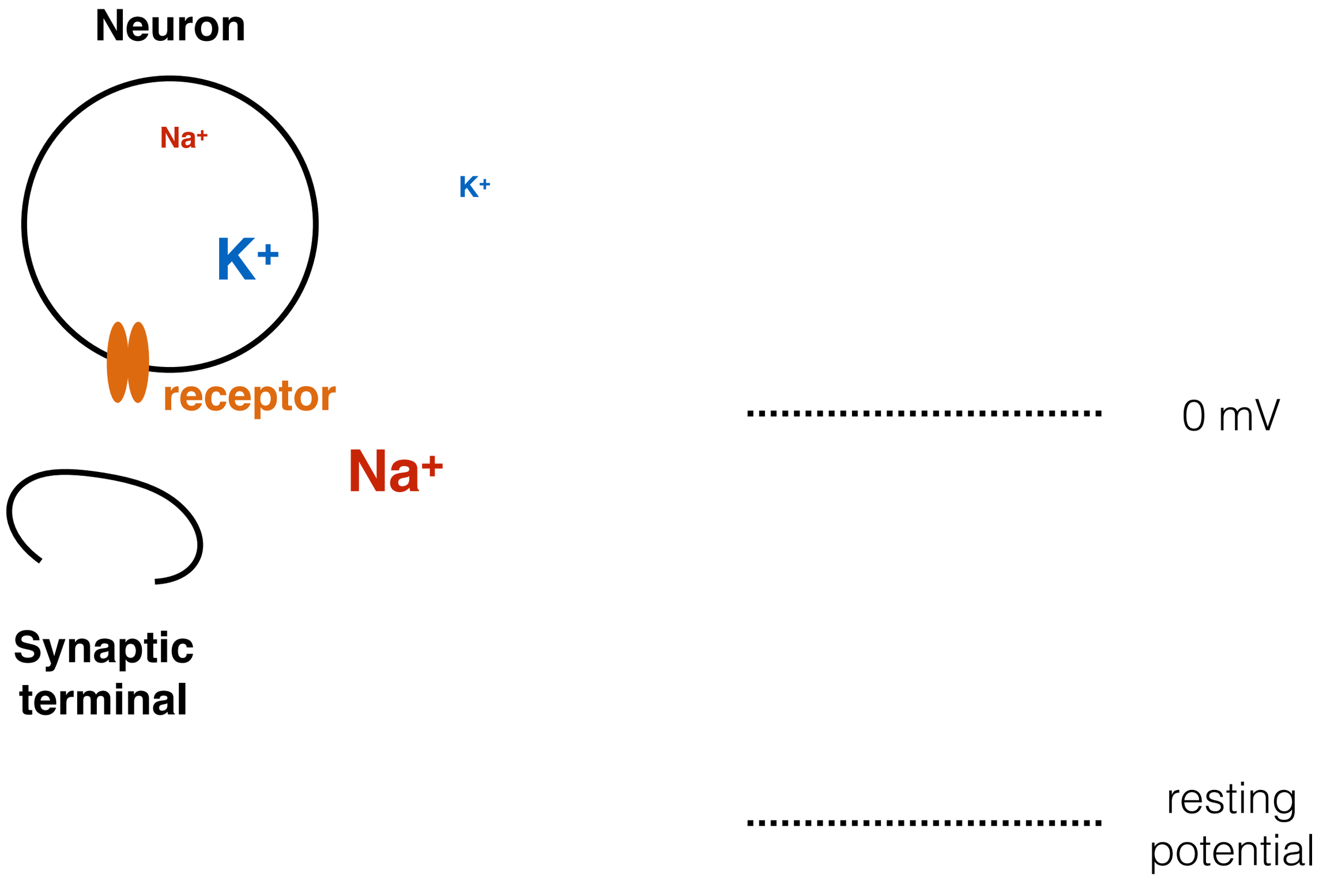

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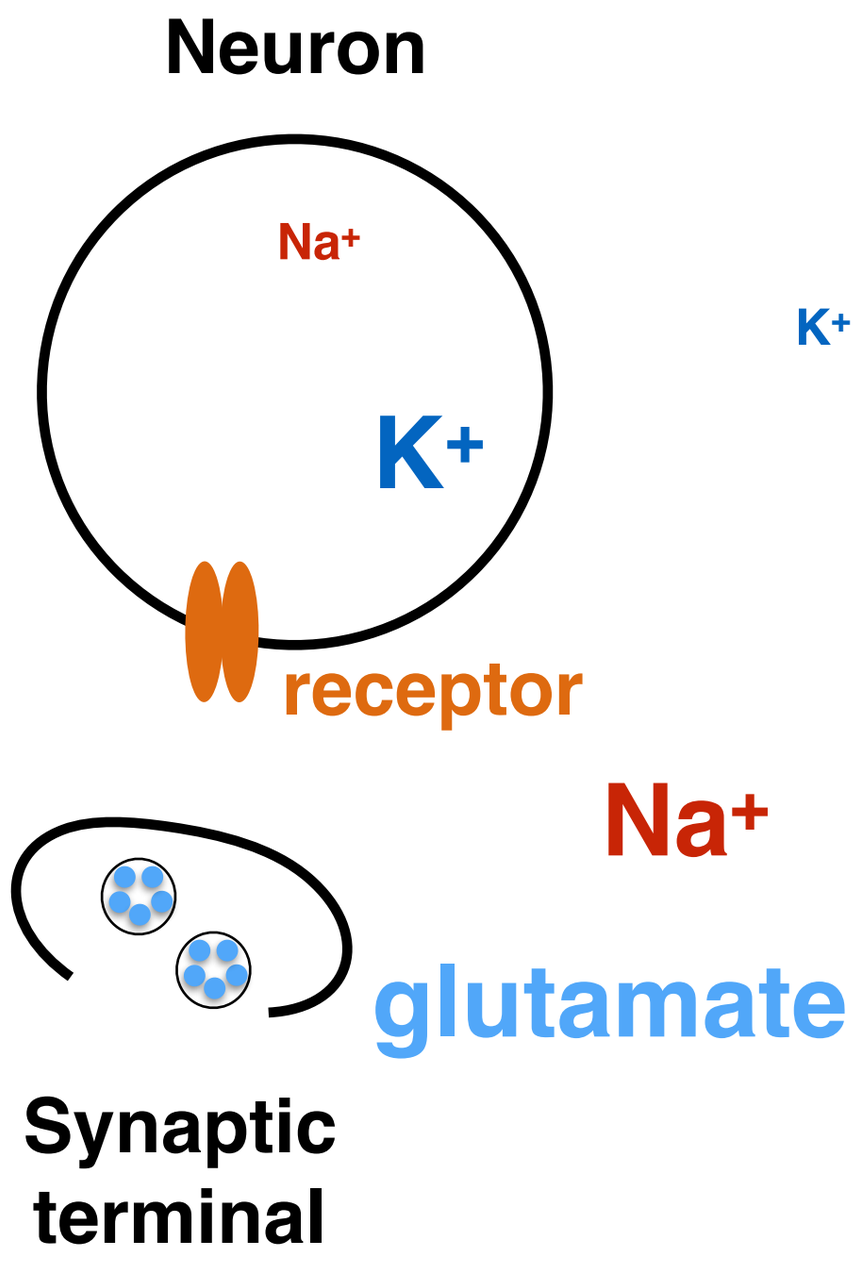

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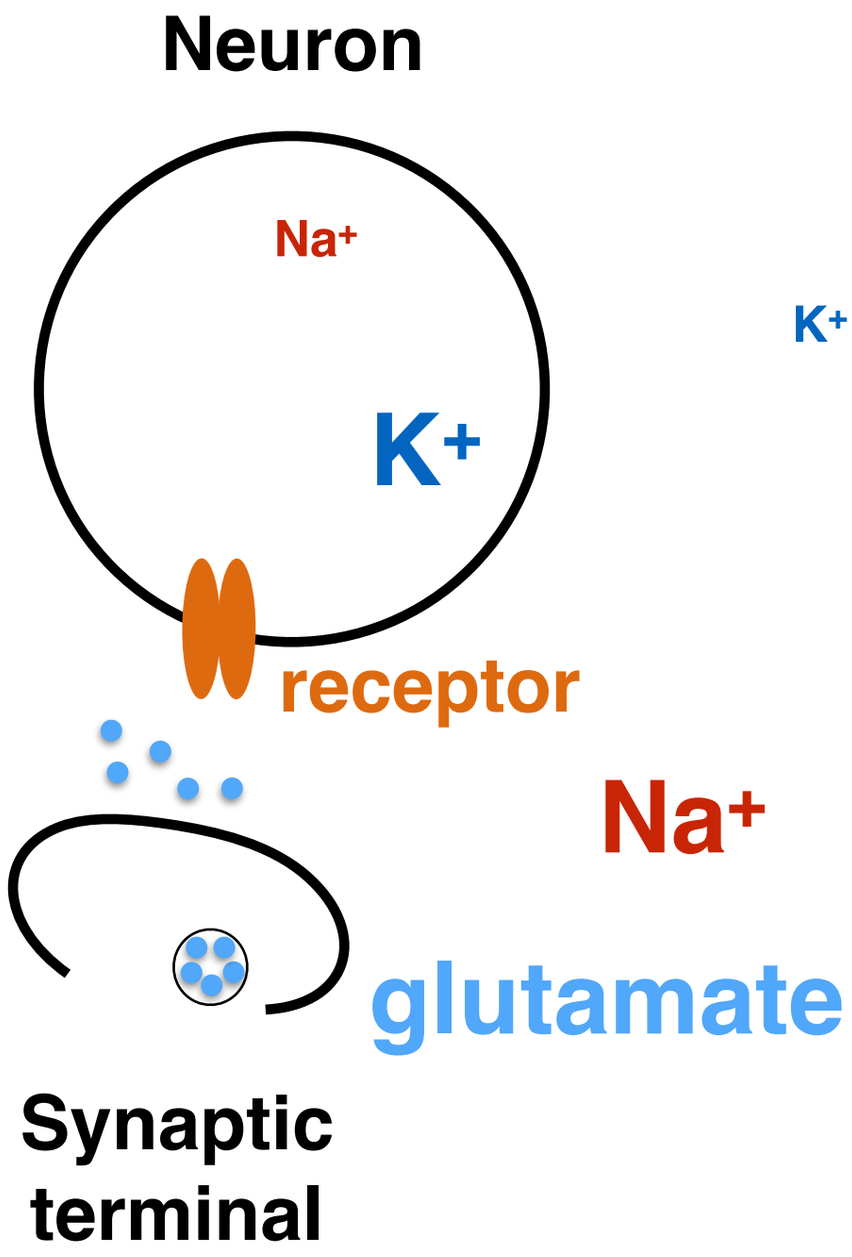

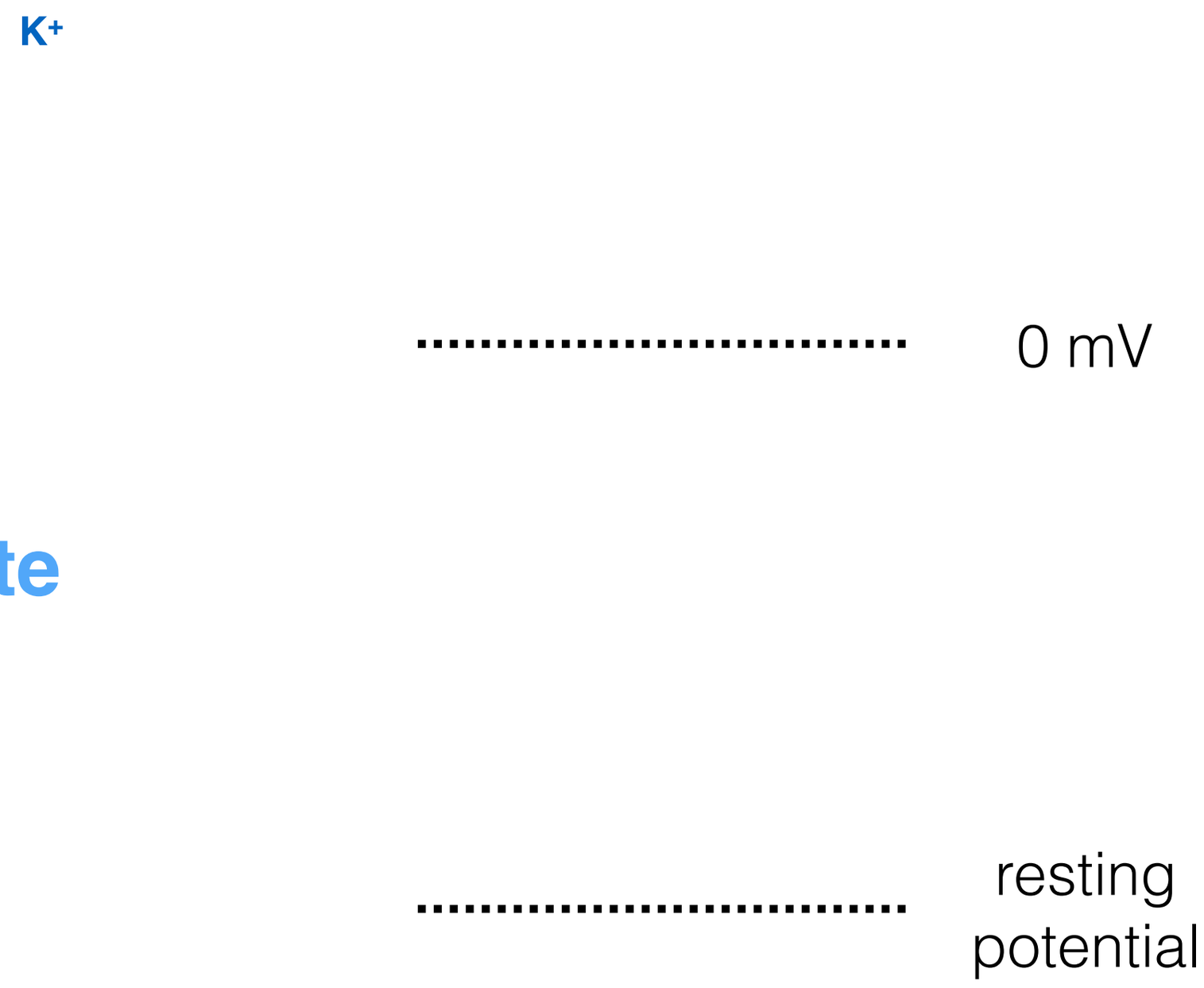

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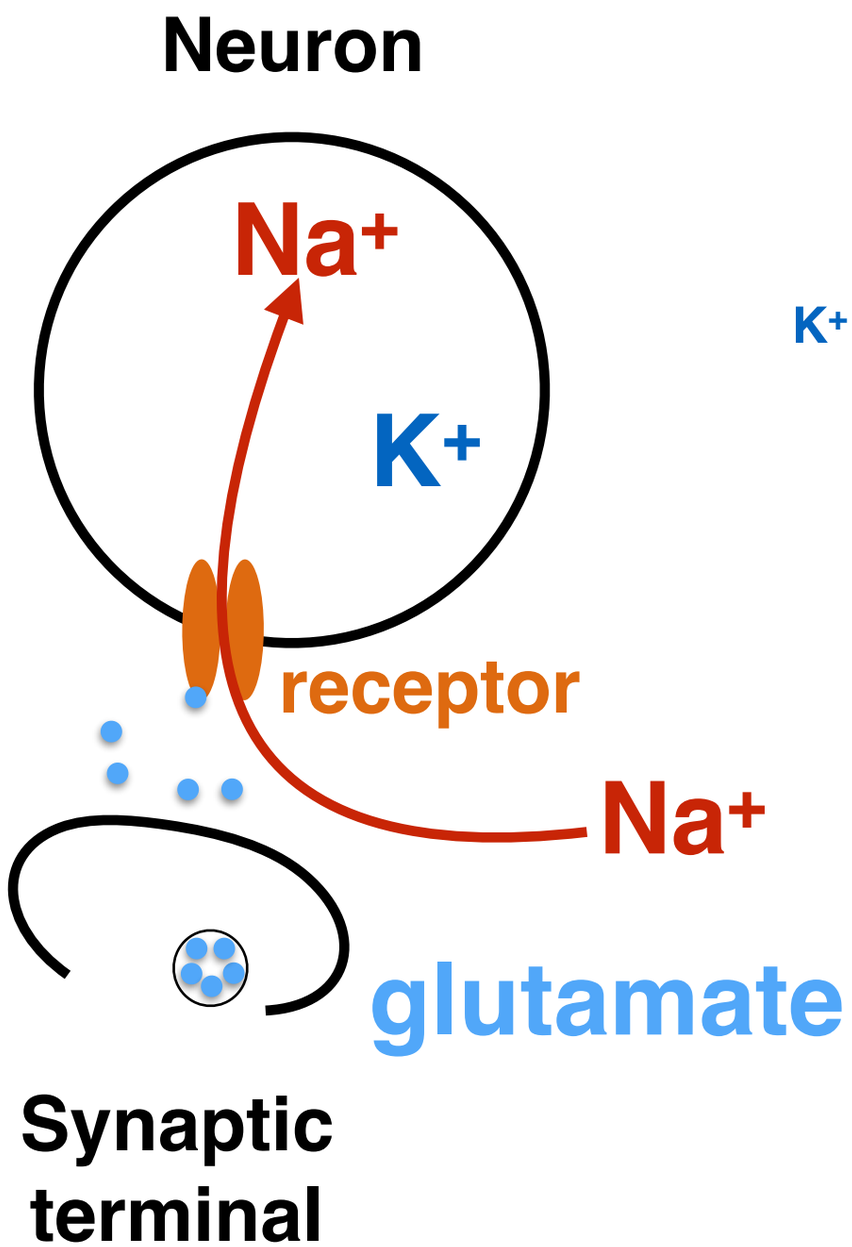
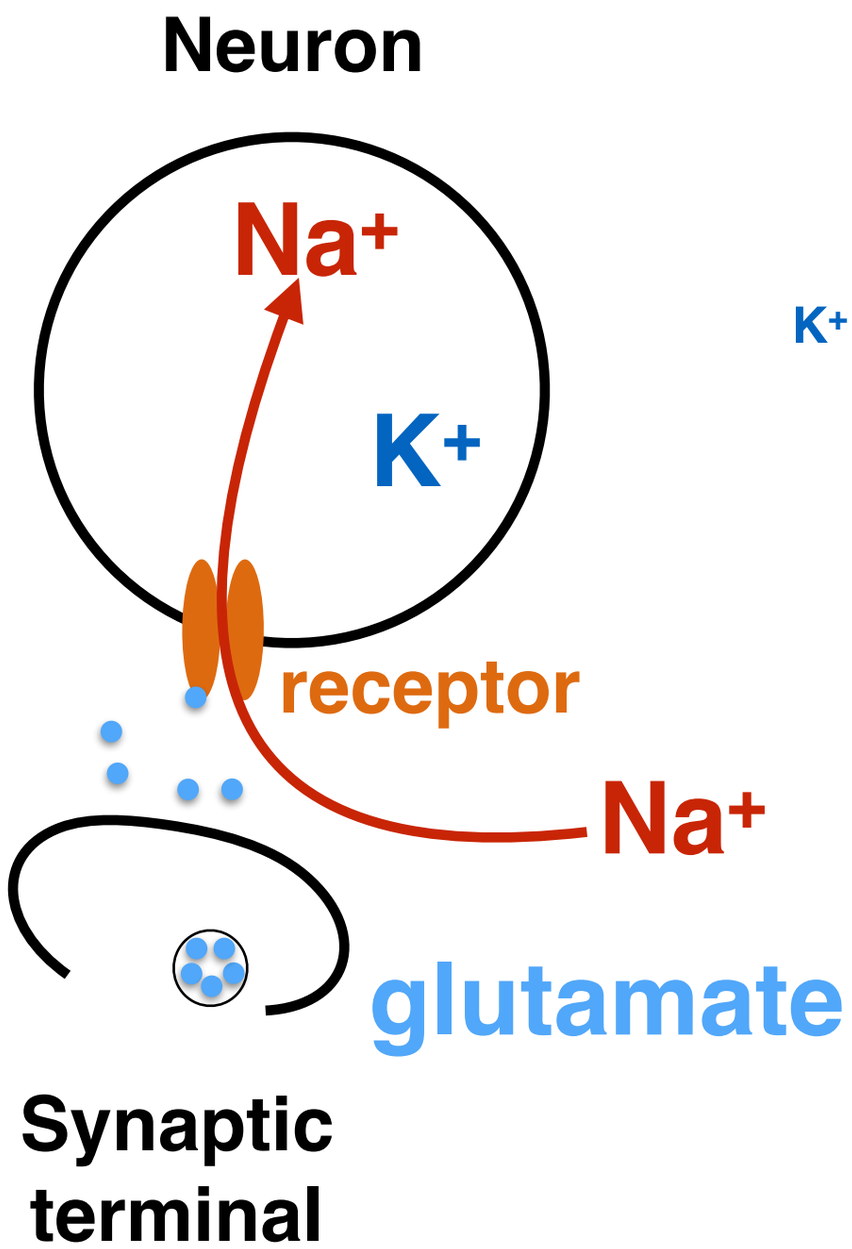


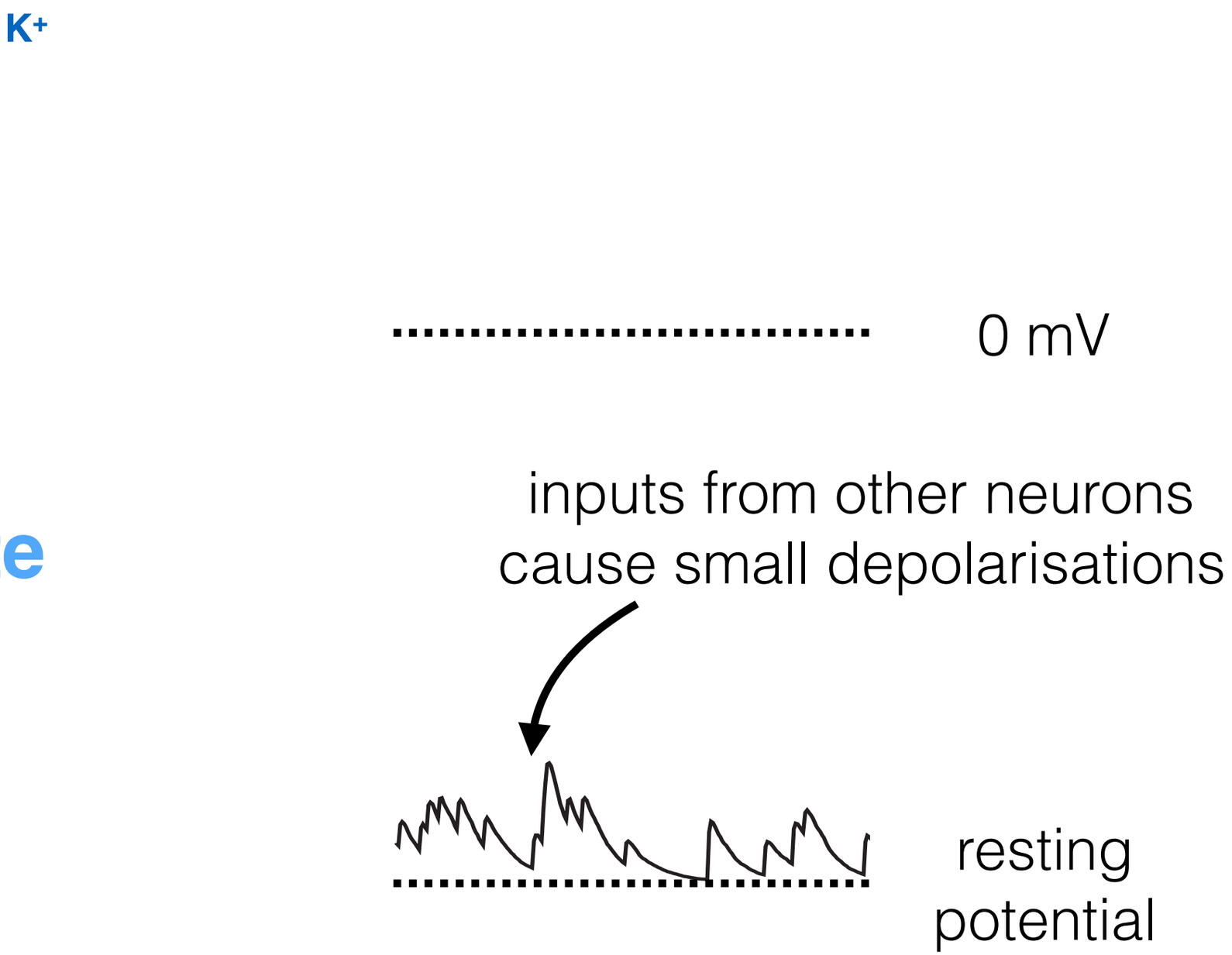
K+

..... 0 mV

..... resting potential

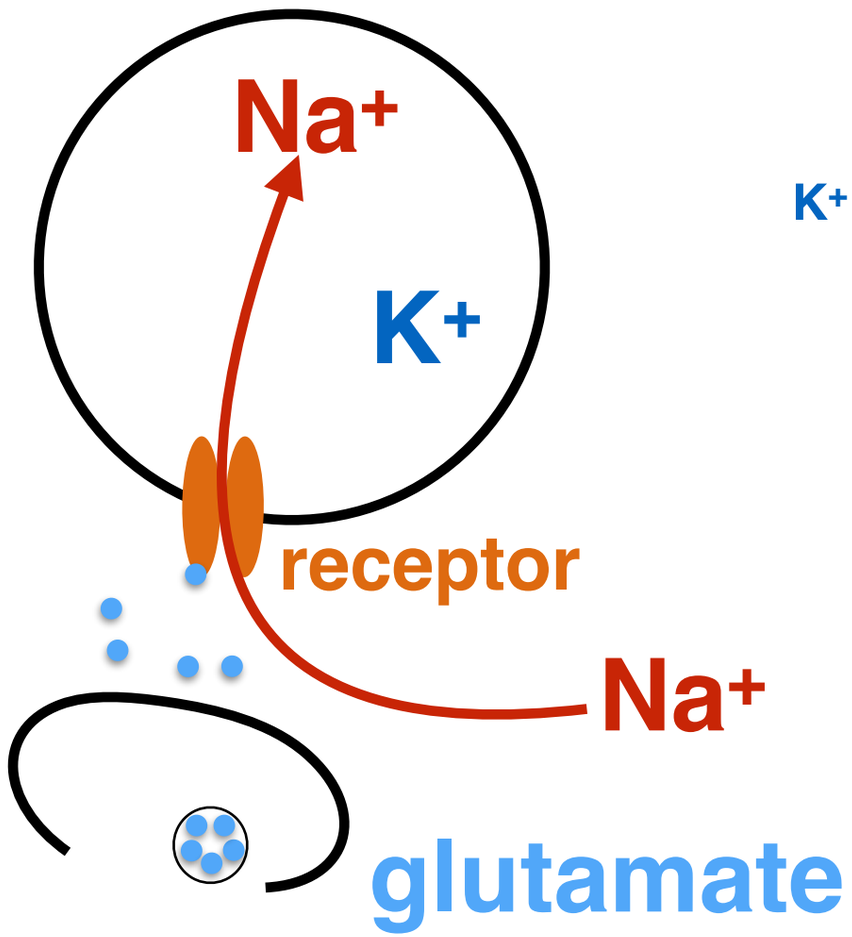
How do neurons work and spend energy?





How do neurons work and spend energy?

Neuron



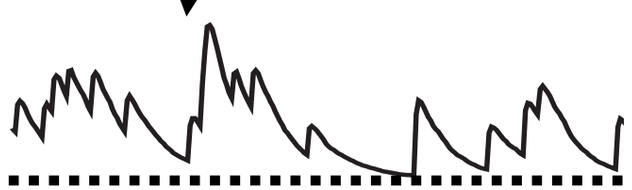
Synaptic terminal

K+

Restoring the status quo costs energy

0 mV

inputs from other neurons cause small depolarisations



resting potential

An energy budget for the CNS gray matter

Harris*, Jolivet* and Attwell, *Neuron* 2012
Jolivet et al., *Front Neuroenerg* 2009
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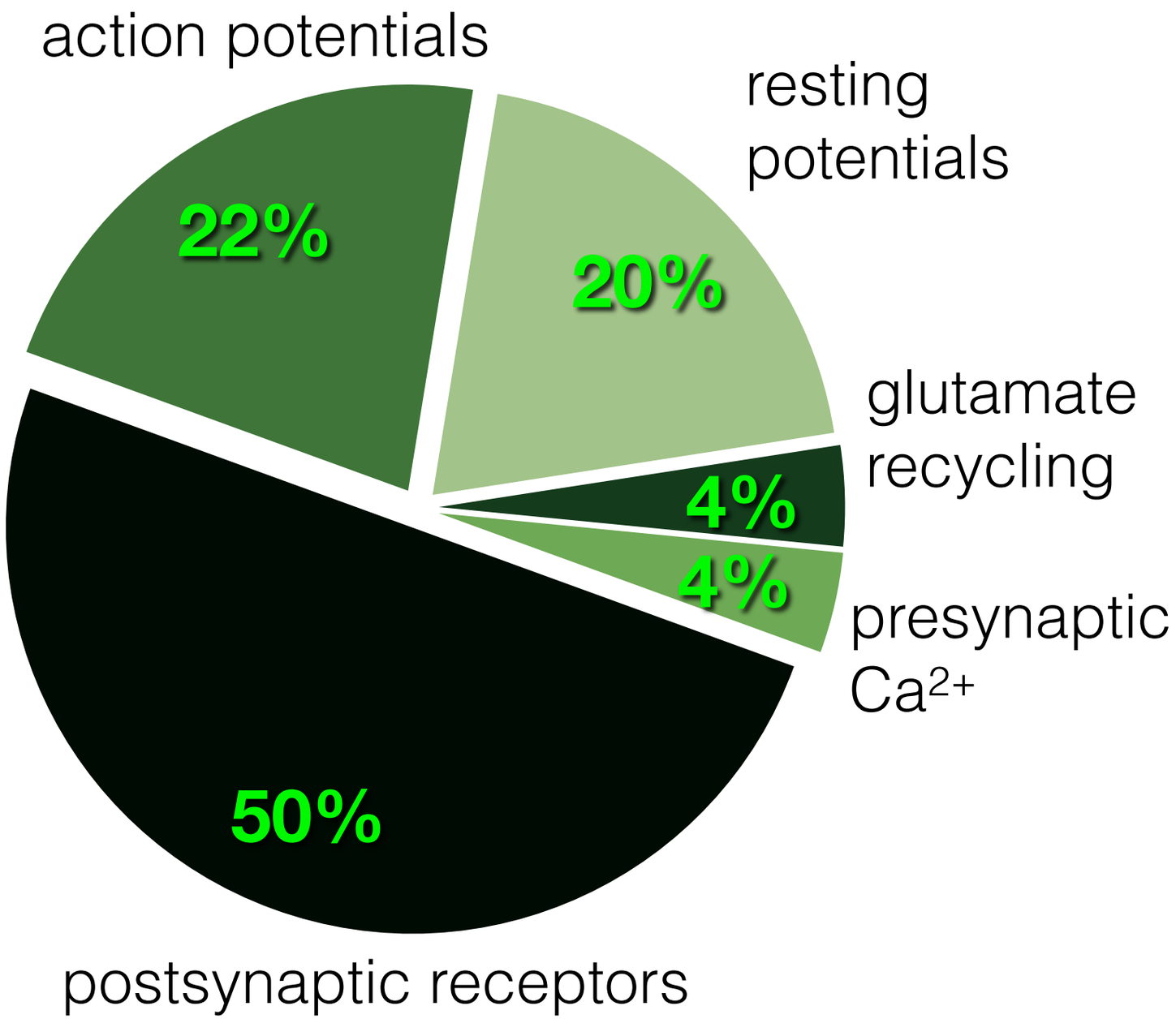

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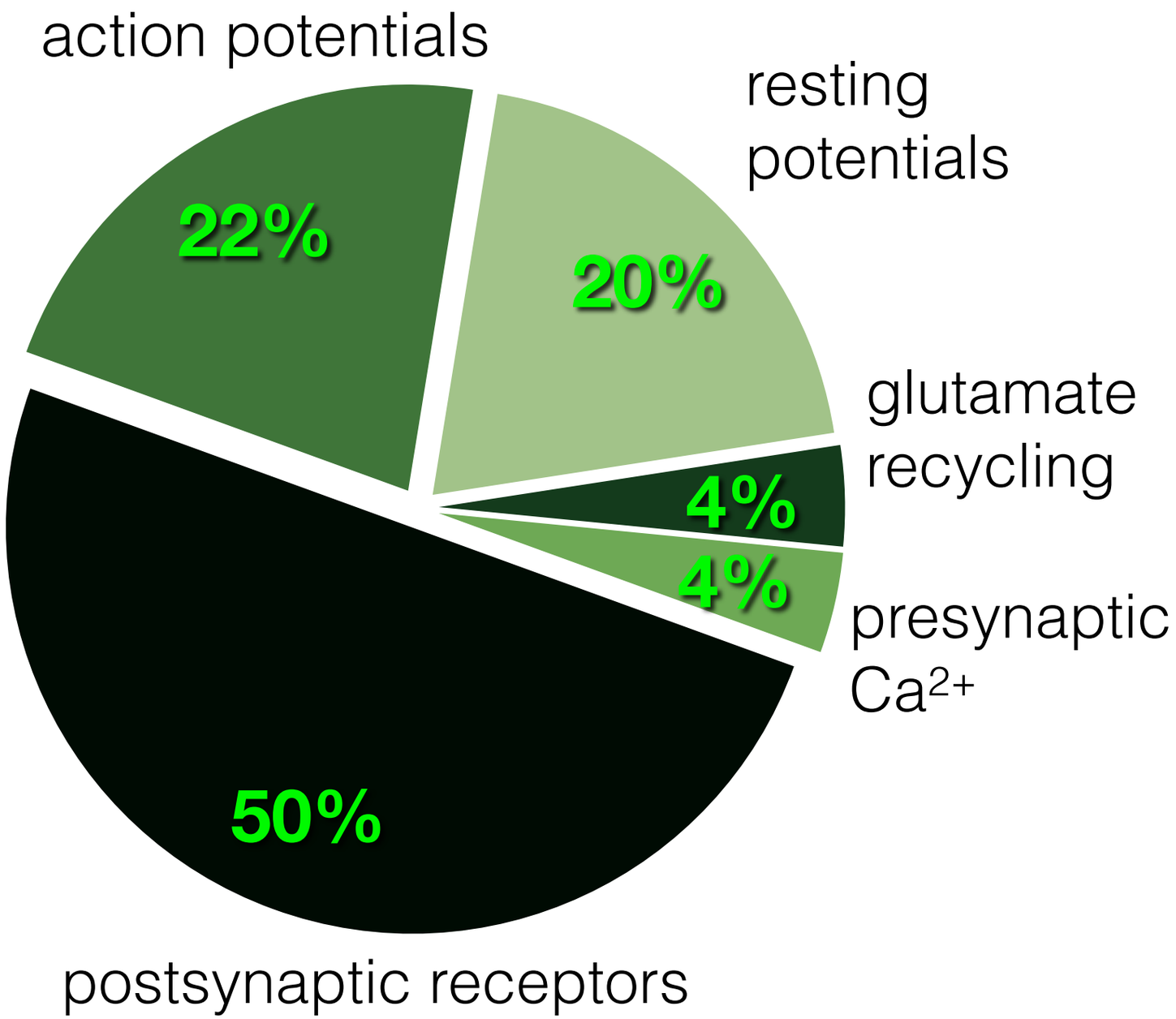

About 60% of energy is expended at synaptic connections

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- Cells extract energy from nutriments (glucose) and oxygen to produce their energy currency (ATP).

- The brain is energetically efficient when compared to man-made computing devices.

- The brain is an expensive organ from our body's perspective.

- Cells extract energy from nutriments (glucose) and oxygen to produce their energy currency (ATP).

- The brain is energetically efficient when compared to man-made computing devices.

- The brain is an expensive organ from our body's perspective.

- Most brain energy is spent on neural communication.

Original Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
0(00) 1–16

DOI: 10.1177/0271678X16648710
jcbfm.sagepub.com

SAGE

Non-signalling energy use in the developing rat brain

Elisabeth Engl[1], Renaud Jolivet[1,2], Catherine N Hall[3] and David Attwell[1]

Abstract

Energy use in the brain constrains its information processing power, but only about half the brain's energy consumption is directly related to information processing. Evidence for which non-signalling processes consume the rest of the brain's energy has been scarce. For the first time, we investigated the energy use of the brain's main non-signalling tasks with a single method. After blocking each non-signalling process, we measured oxygen level changes in juvenile rat brain slices with an oxygen-sensing microelectrode and calculated changes in oxygen consumption throughout the slice using a modified diffusion equation. We found that the turnover of the actin and microtubule cytoskeleton, followed by lipid synthesis, are significant energy drains, contributing 25%, 22% and 18%, respectively, to the rate of oxygen consumption. In contrast, protein synthesis is energetically inexpensive. We assess how these estimates of energy expenditure relate to brain energy use in vivo, and how they might differ in the mature brain.

Keywords

ATP, brain development, brain slice, energy metabolism, lipids

Received 12 January 2016; Revised 30 March 2016; Accepted 5 April 2016

Outline

- Neuroenergetics
- Energy as a constraint on brain function
- Energy as a signal for the brain's immune system
- CERN as a model for the neurosciences

CURRENT ANTHROPOLOGY Volume 36, Number 2, April 1995

The Expensive-Tissue Hypothesis

The Brain and the Digestive System in Human and Primate Evolution[1]

by Leslie C. Aiello and Peter Wheeler

Brain tissue is metabolically expensive, but there is no significant correlation between relative basal metabolic rate and relative brain size in humans and other encephalized mammals. The expensive-tissue hypothesis suggests that the metabolic requirements of relatively large brains are offset by a corresponding reduction of the gut. The splanchnic organs (liver and gastrointestinal tract) are as metabolically expensive as brains, and the gut is the only one of the metabolically expensive organs in the human body that is markedly small in relation to body size. Gut size is highly correlated with diet, and relatively small guts are compatible only with high-quality, easy-to-digest food. The often-cited relationship between diet and relative brain size is more properly viewed as a relationship between relative brain size and relative gut size, the latter being determined by dietary

Wood on the analysis of the postcranial fossils from Olduvai Gorge. She has published (with M. C. Dean) *An Introduction to Human Evolutionary Anatomy* (London: Academic Press, 1990), "Allometry and the Analysis of Size and Shape in Human Evolution" (*Journal of Human Evolution* 22:127–47), "The Fossil Evidence for Modern Human Origins in Africa: A Revised View" (*American Anthropologist* 95:73–96), (with R. I. M. Dunbar) "Neocortex Size, Group Size, and the Evolution of Language" (CURRENT ANTHROPOLOGY 34:184–93), and (with B. A. Wood) "Cranial Variables as Predictors of Hominine Body Mass" (*American Journal of Physical Anthropology*, in press).

PETER WHEELER is Director of Biological and Earth Sciences, Liverpool John Moores University. He was born in 1956 and educated at the University of Durham. His research focuses on physiological influences on human evolution and thermobiology. Among his publications are "The Influence of Bipedalism on the Energy and Water Budgets of Early Hominids" (*Journal of Human Evolution* 21:107–15), "The Influence of the Loss of Functional Body Hair on the Energy and Water Budgets of Early Hominids" (*Journal of Human Evolution* 23:379–88), "The Thermoregulatory Advantages of Large Body Size for Hominids Foraging in Savannah Environments" (*Journal of Human Evolution* 23: 351–62), and "The Influence of Stature and Body Form on Hominid Energy and Water Budgets: A Comparison of *Australopithecus* and Early *Homo* Physiques" (*Journal of Human Evolution* 24:13–28).

The present paper was sumitted in final form 15 VI 94.

Much of the work that has been done on encephalization in humans and other primates has been oriented toward why questions—why different primate taxa have different relative brain sizes or why the human line has undergone such a phenomenal increase in brain size during the past 2 million years. Hypotheses that have been put forward to answer these questions primarily invoke socio-ecological factors such as group size (Aiello and

Current Anthropology Volume 36, Number 2, April 1995

The Expensive-Tissue Hypot

The Brain System in Evolution

by Leslie
Peter Wh

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expensive-tissue h
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LETTER

doi:10.1038/nature10

Energetics and the evolution of human brain size

Ana Navarrete[1], Carel P. van Schaik[1] & Karin Isler[1]

The human brain stands out among mammals by being unusually large. The expensive-tissue hypothesis[1] explains its evolution by proposing a trade-off between the size of the brain and that of the digestive tract, which is smaller than expected for a primate of our body size. Although this hypothesis is widely accepted, empirical support so far has been equivocal. Here we test it in a sample of 100 mammalian species, including 23 primates, by analysing brain size and organ mass data. We found that, controlling for fat-free body mass, brain size is not negatively correlated with the mass of the digestive tract or any other expensive organ, thus refuting the expensive-tissue hypothesis. Nonetheless, consistent with the existence of energy trade-offs with brain size, we find that the size of brains and adipose depots are negatively correlated in mammals, indicating that encephalization and fat storage are compensatory strategies to buffer against starvation. However, these two strategies can be combined if fat storage does not unduly hamper locomotor efficiency. We propose that human encephalization was made possible by a combination of stabilization of energy inputs and a redirection of energy from locomotion, growth and reproduction.

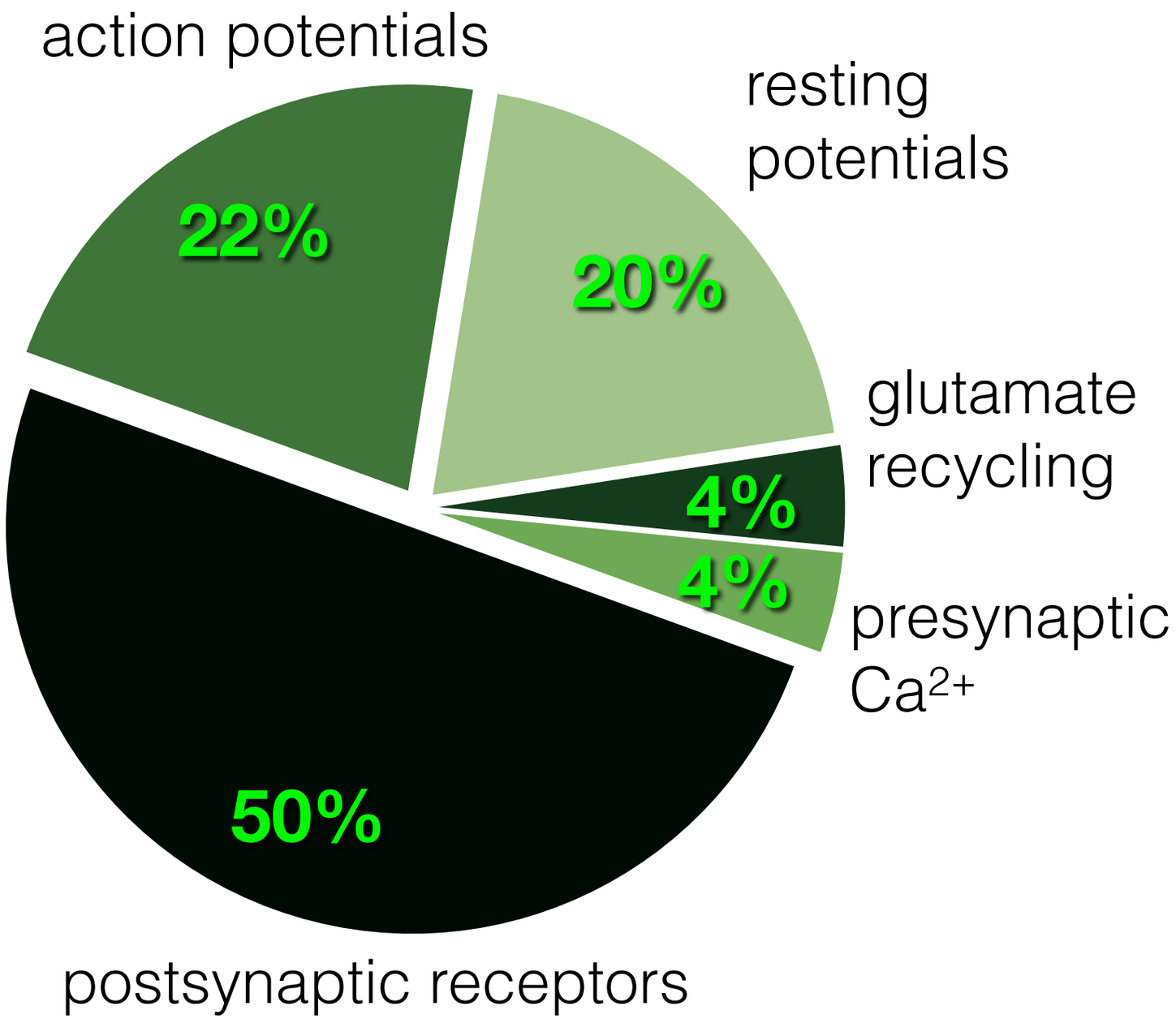
Brains are energetically expensive[2]. The human brain is about three

Data). In this analysis, it is crucial to control for body size, but the u
measure taken for this, body mass, is highly affected by variation in
size of adipose depots. This variation may confound or even reverse
direction of correlations among organs (Supplementary Fig. 2
Supplementary Table 4b). Here, we therefore used fat-free body m
as the best proxy for body size.

Contrary to the predictions of the expensive-tissue hypothesis
found no negative correlations between the relative size of the b
and the digestive tract, other expensive organs or their combined
among mammals or within non-human primates, controlling for
free body mass, even though statistical power was sufficient to de
these negative correlations if they existed (see Table 1). We also did
find any trade-offs among other expensive organs (Fig. 1). Th
results therefore refute the expensive-tissue hypothesis as a gen
principle to explain the interspecific variation of relative brain
in mammals. In our view, this finding reduces the plausibility of
argument that human encephalization was made possible by a red
tion of the digestive tract[1,5].

Energy trade-offs with other tissues that are less expensive but
abundant[7] may nonetheless explain part of brain size variation.
instance, adipose depots make up an appreciable proportion

An energy budget for the CNS gray matter



About 60% of energy is expended at synaptic connections

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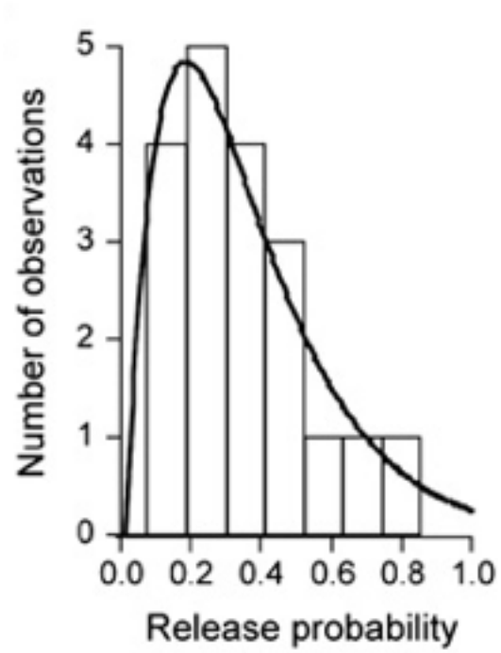

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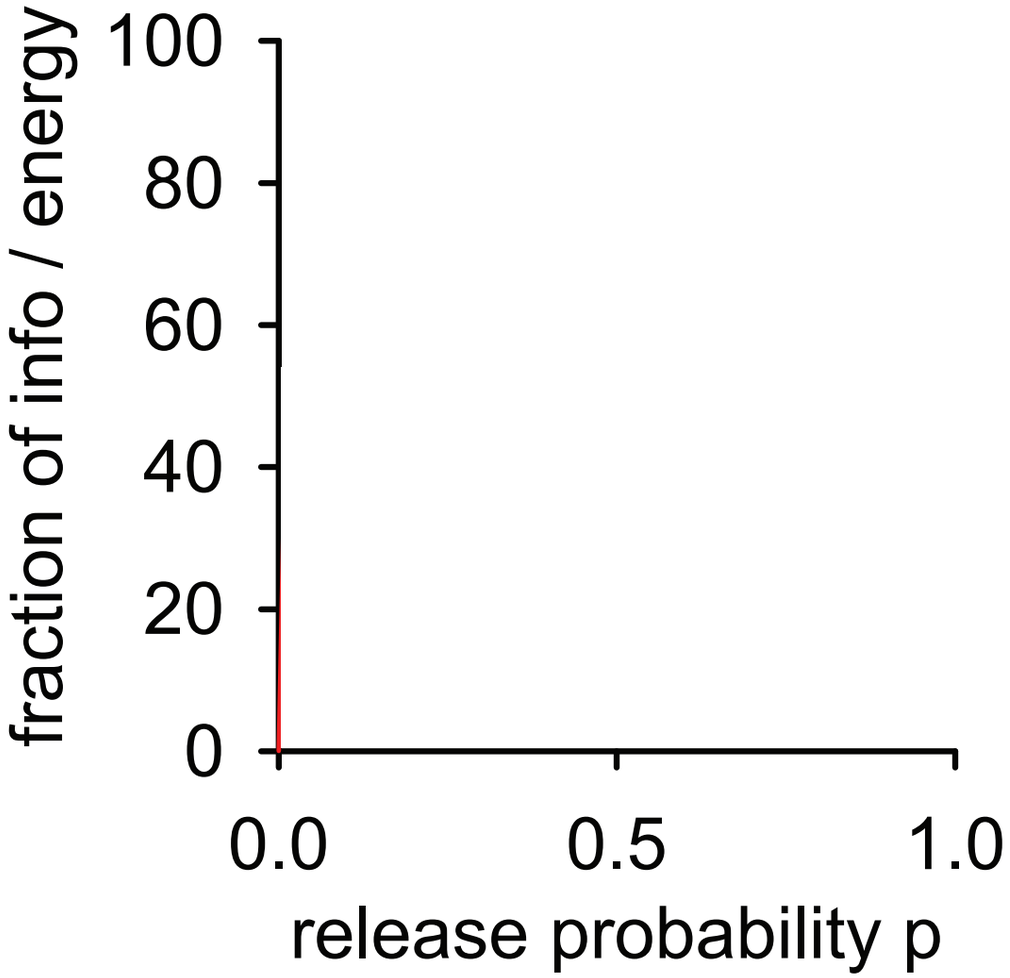

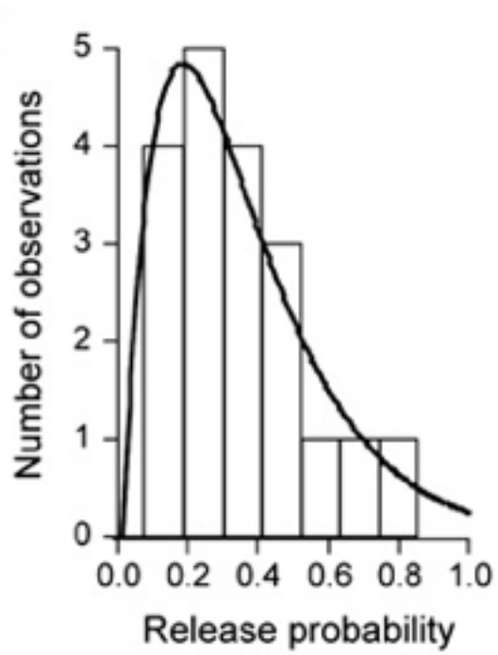

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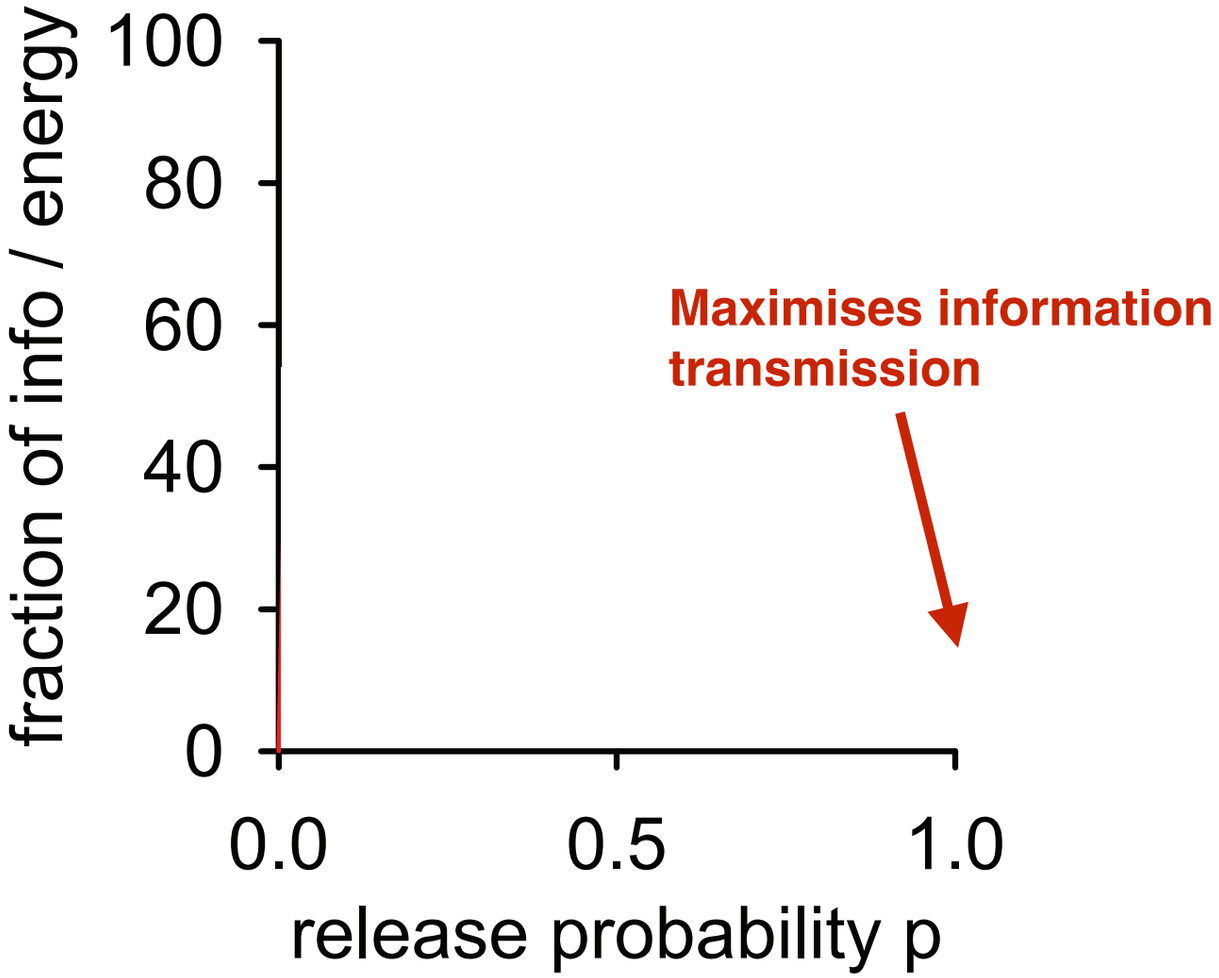

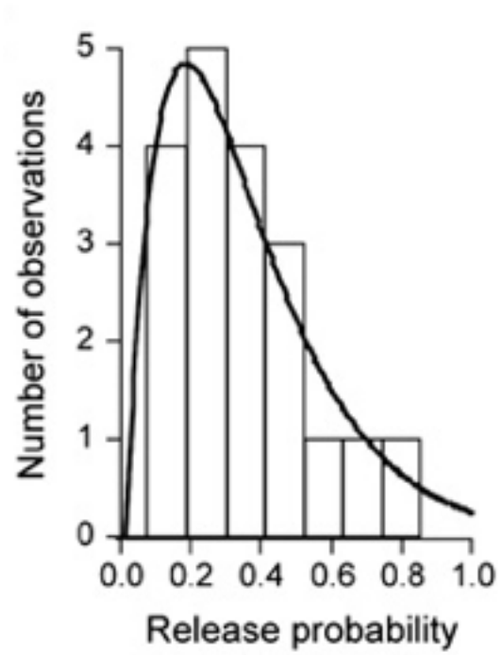

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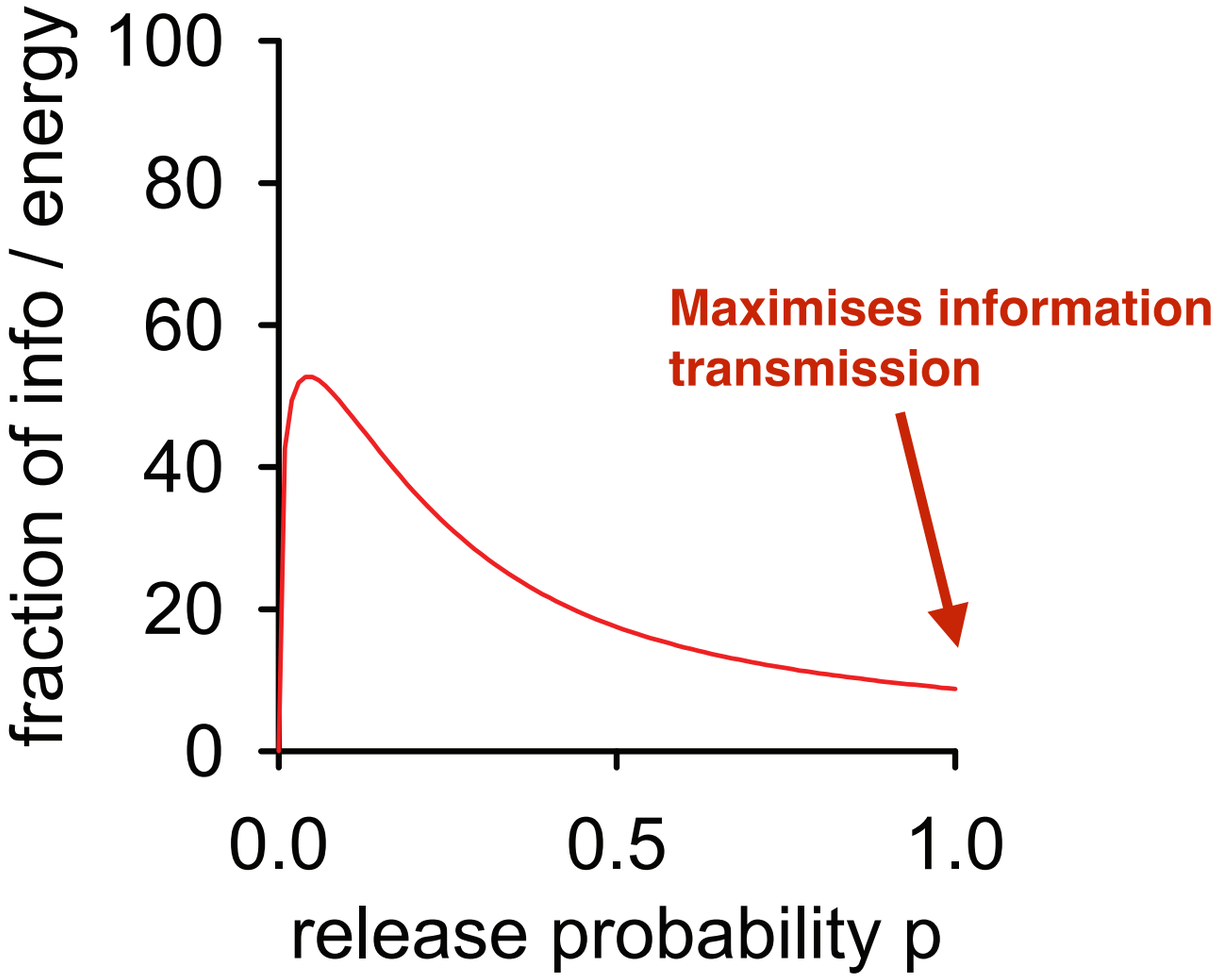

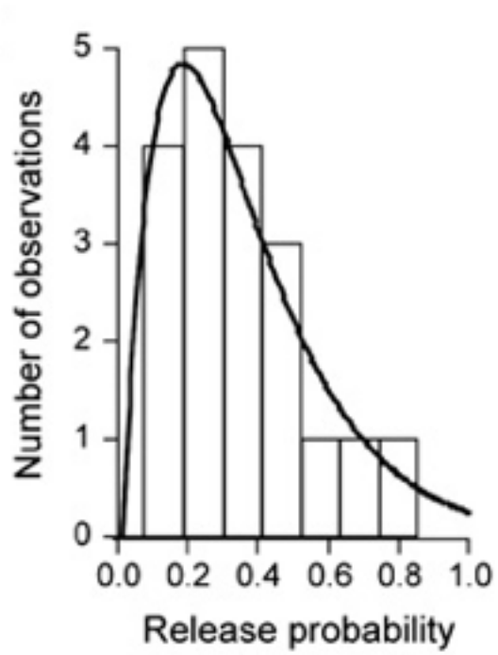

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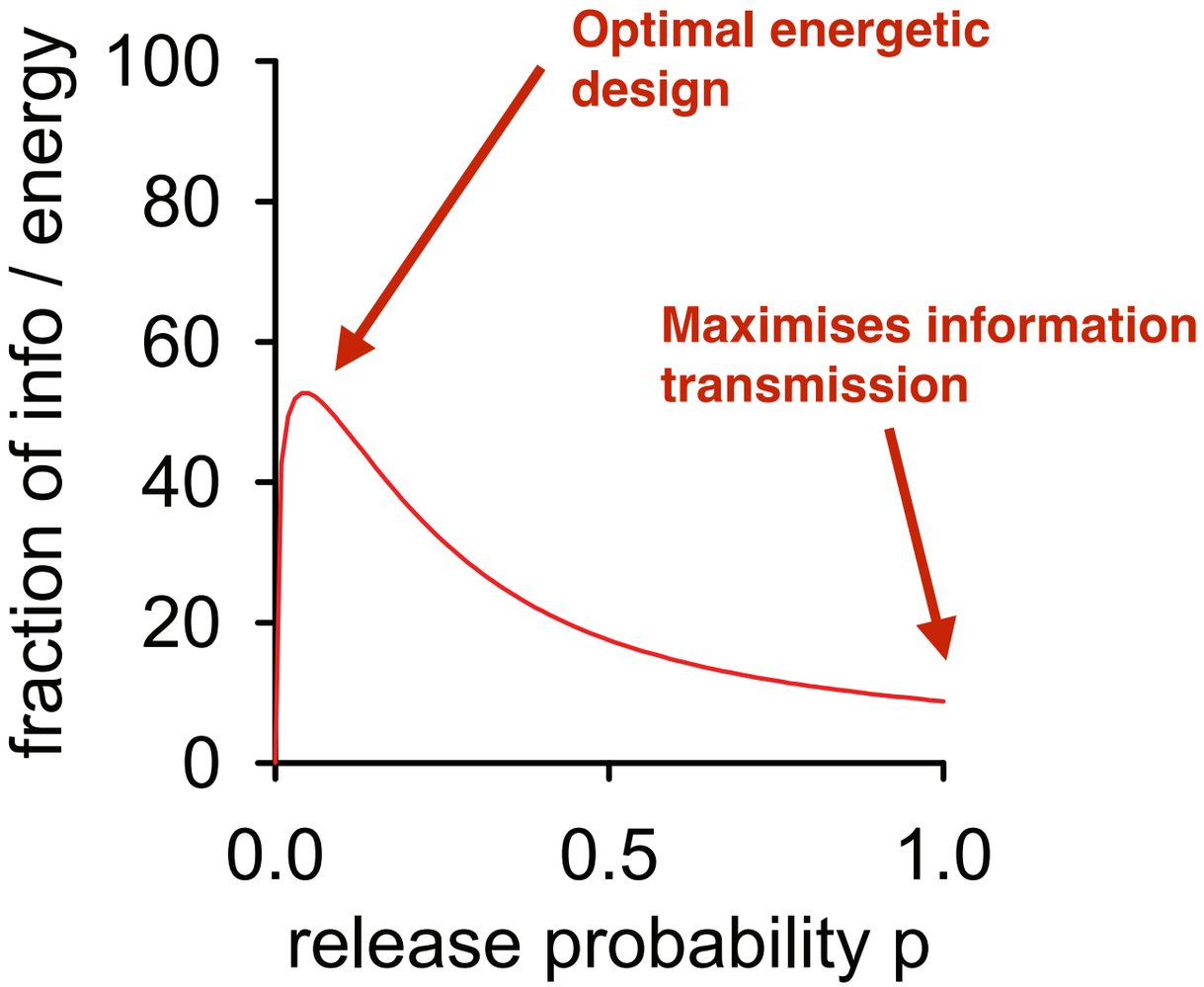

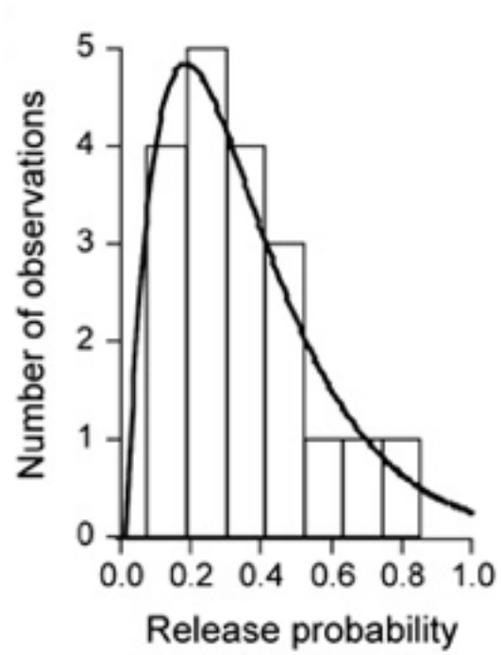

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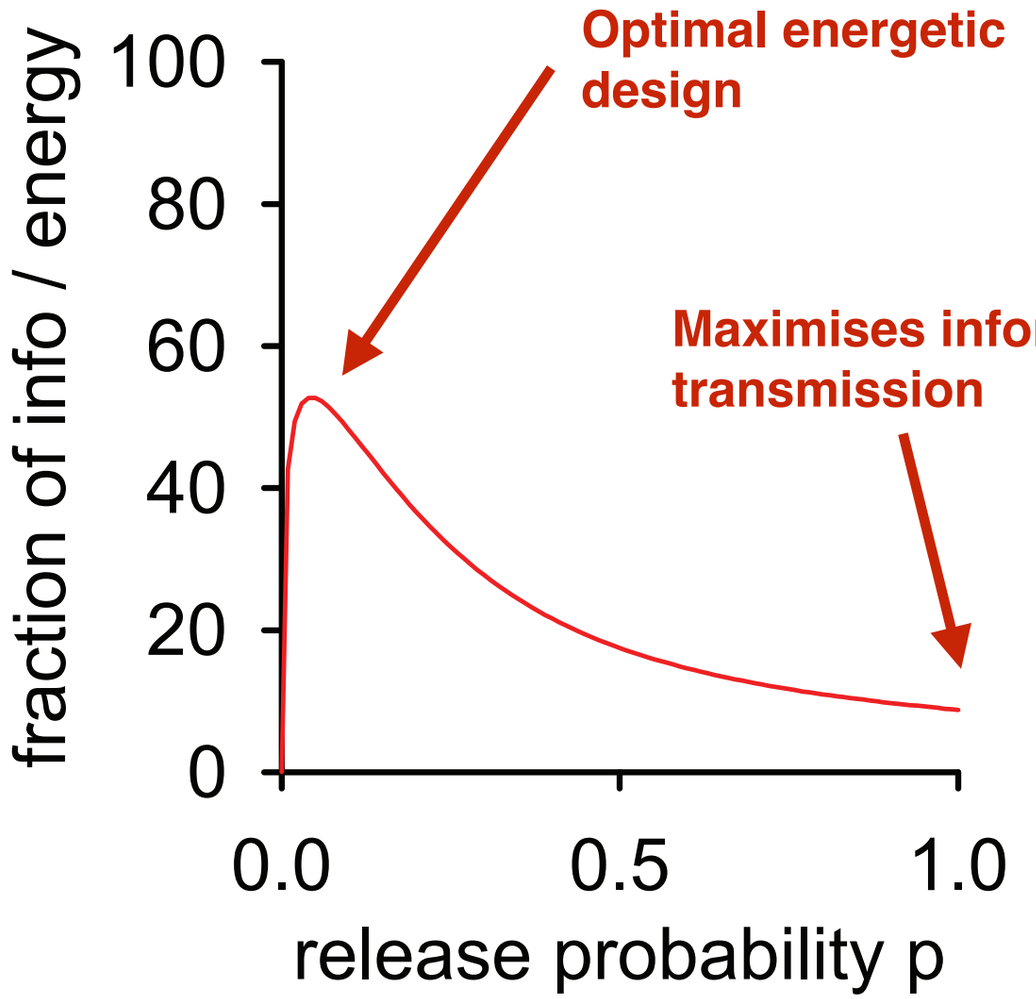
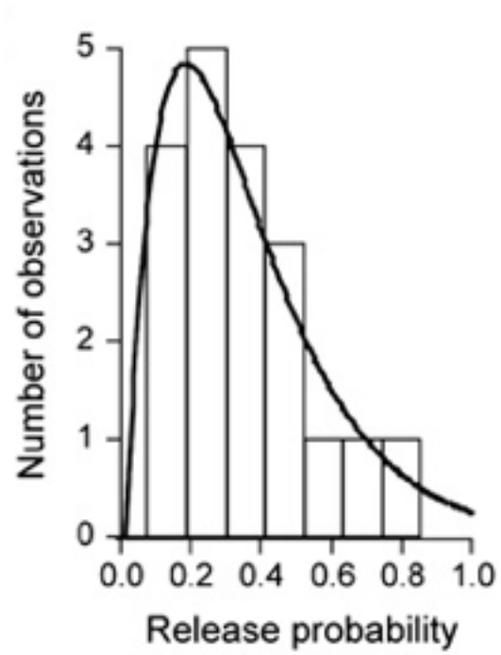




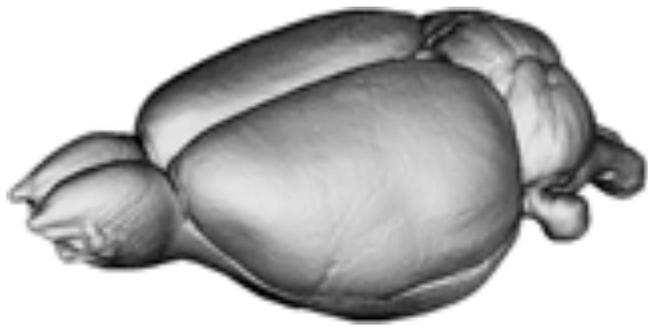
Branco et al., *Neuron* 2008

- This configuration can be explained by representing the optimal energetic design.

Harris*, Jolivet* and Attwell, *Neuron* 2012

Testing optimal energetic design in the visual pathway

Rat brain



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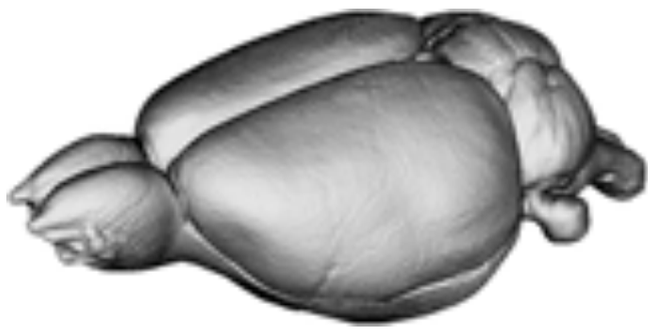

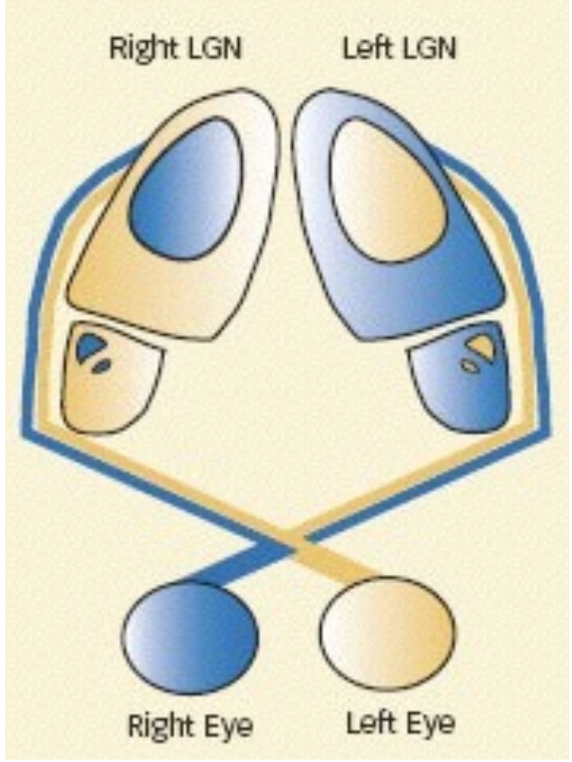

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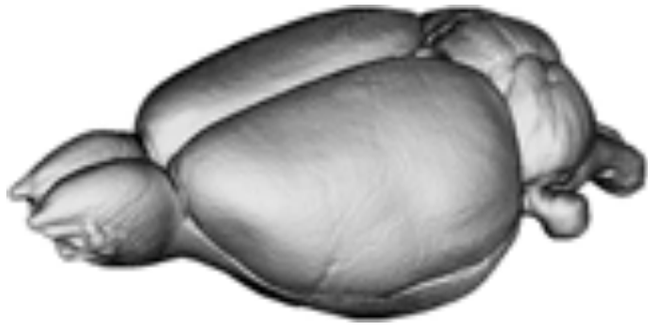

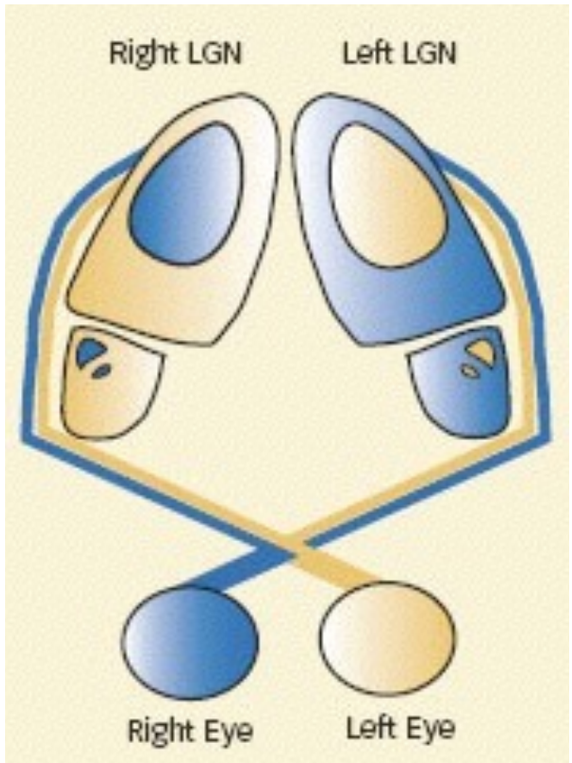

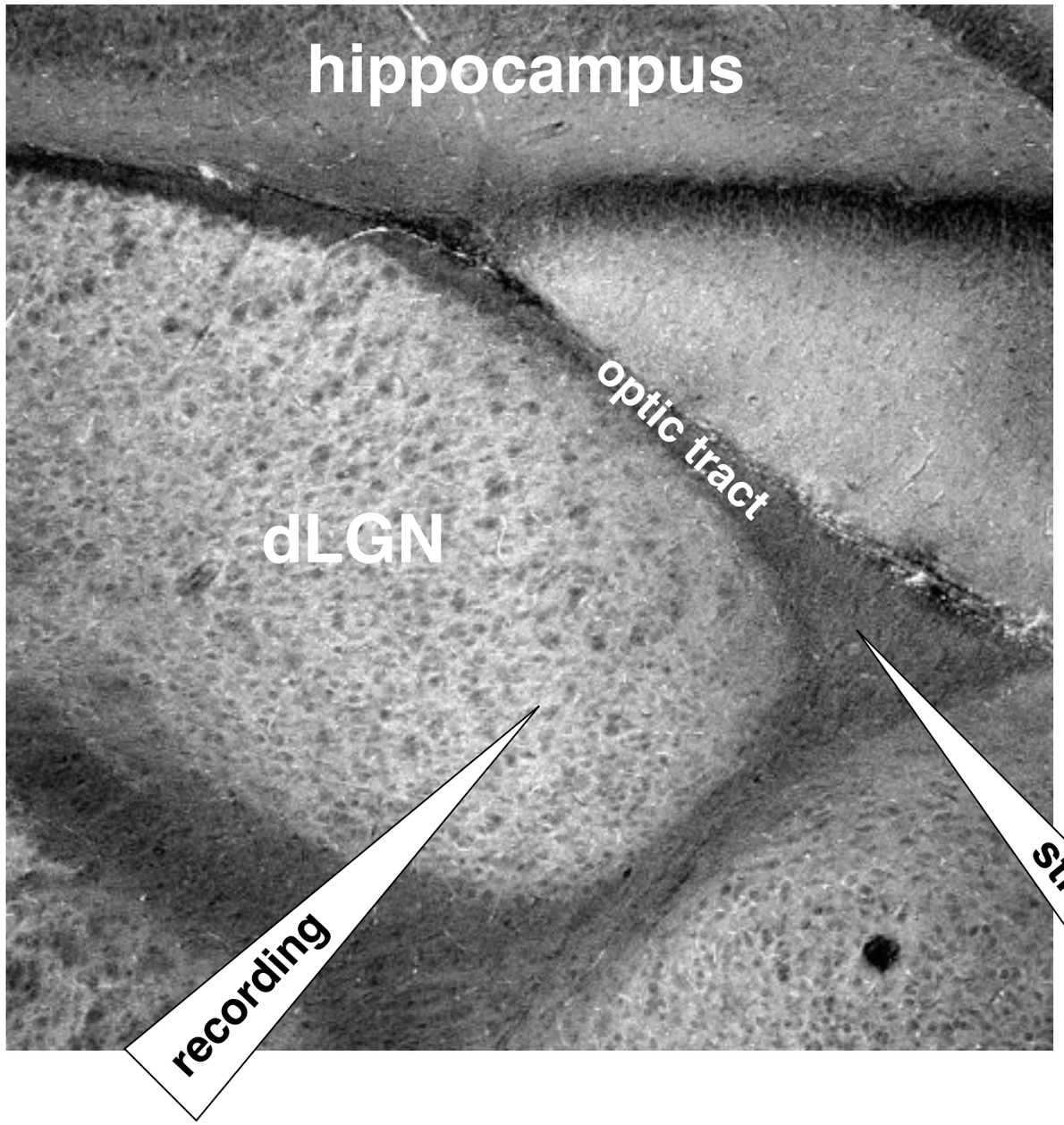

Circuit design

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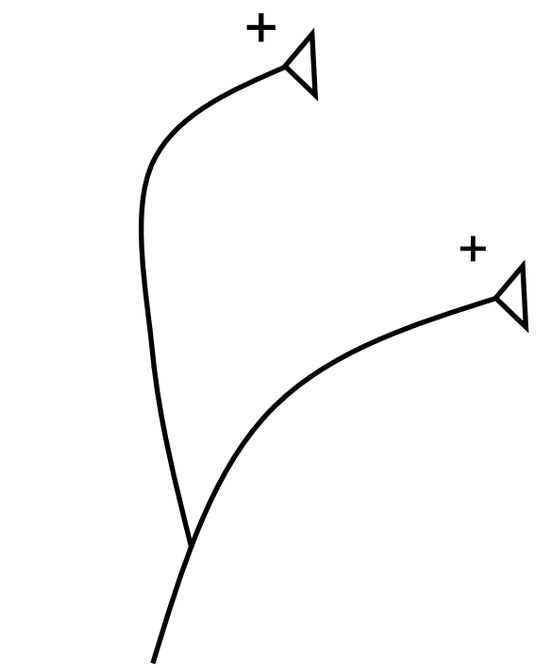

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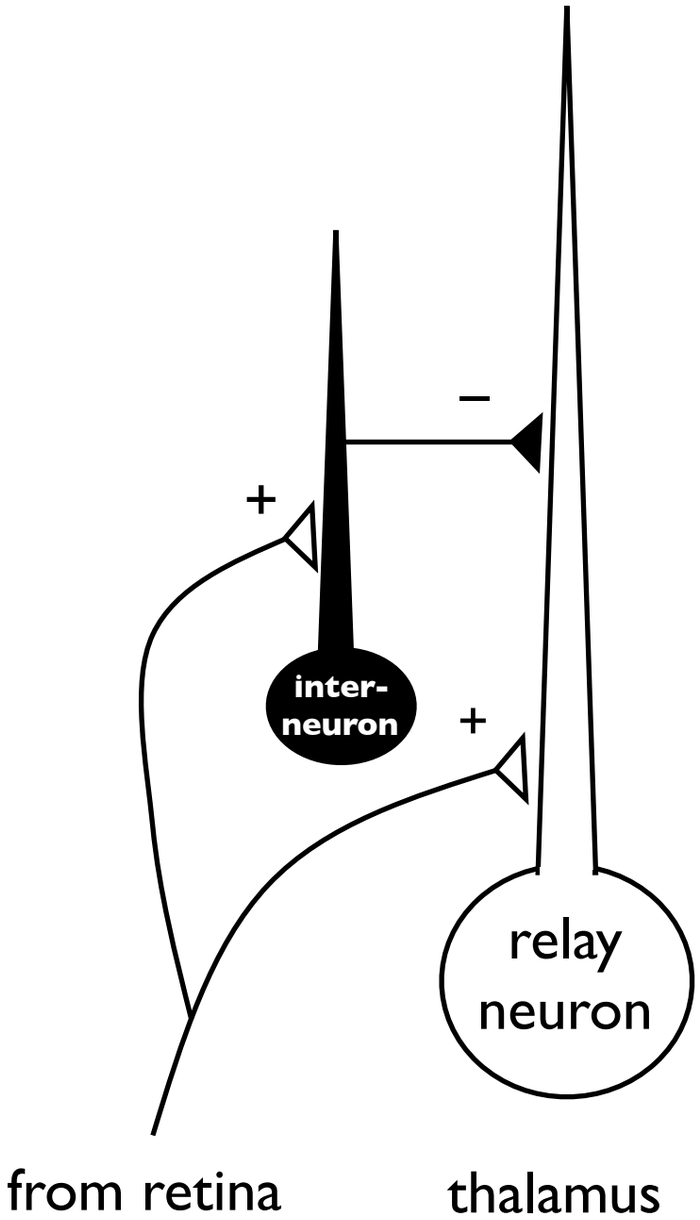

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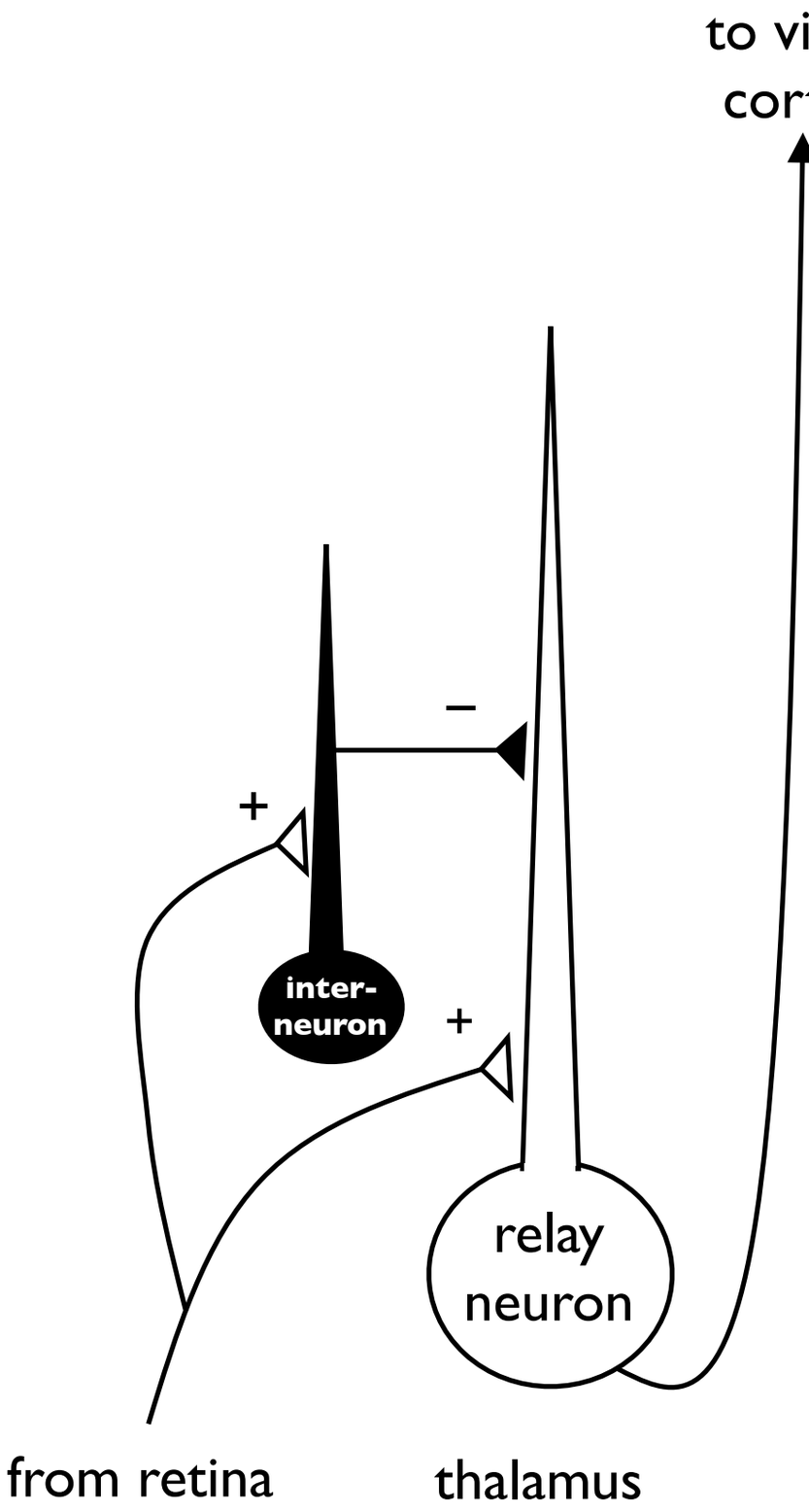

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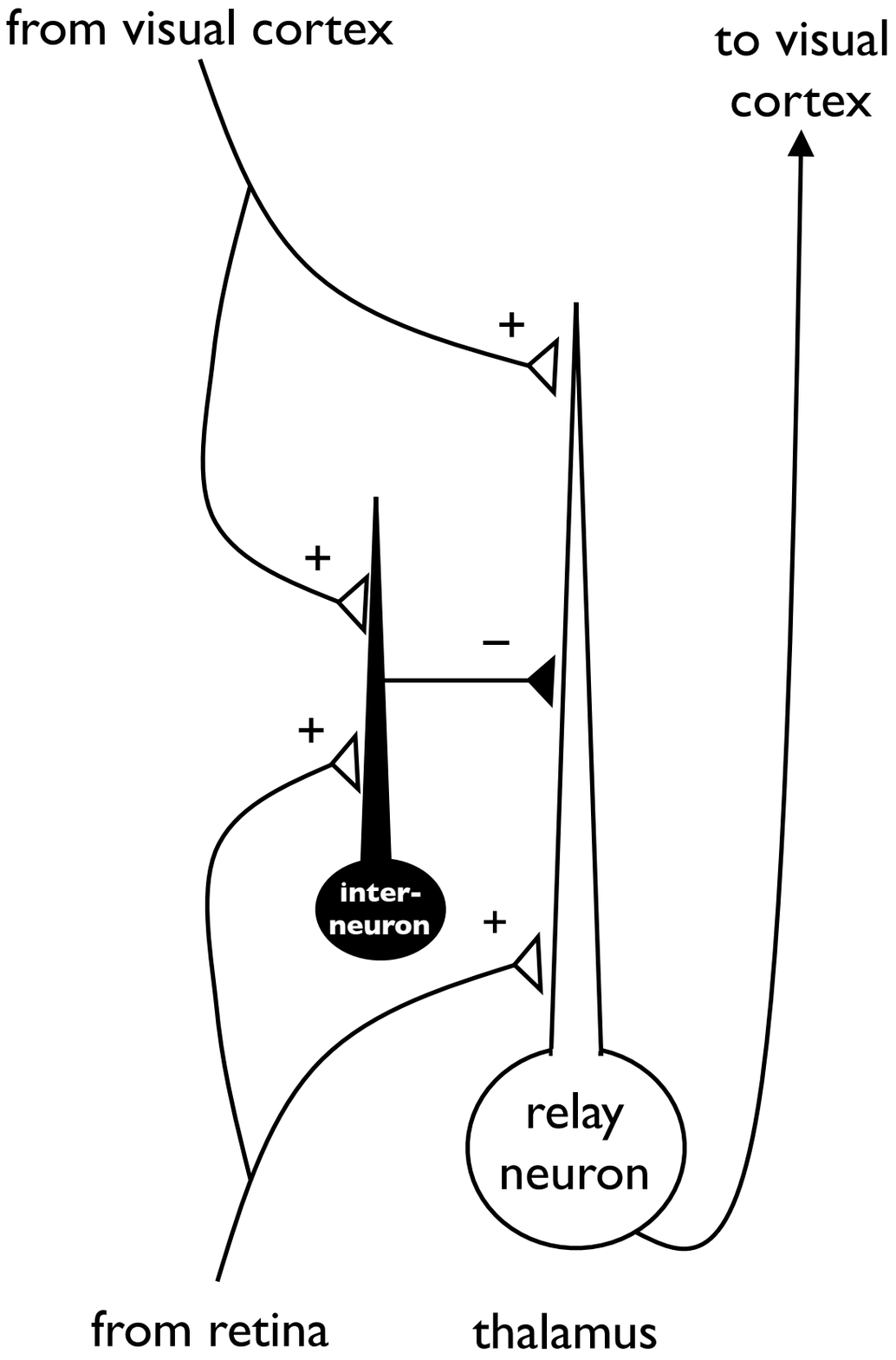

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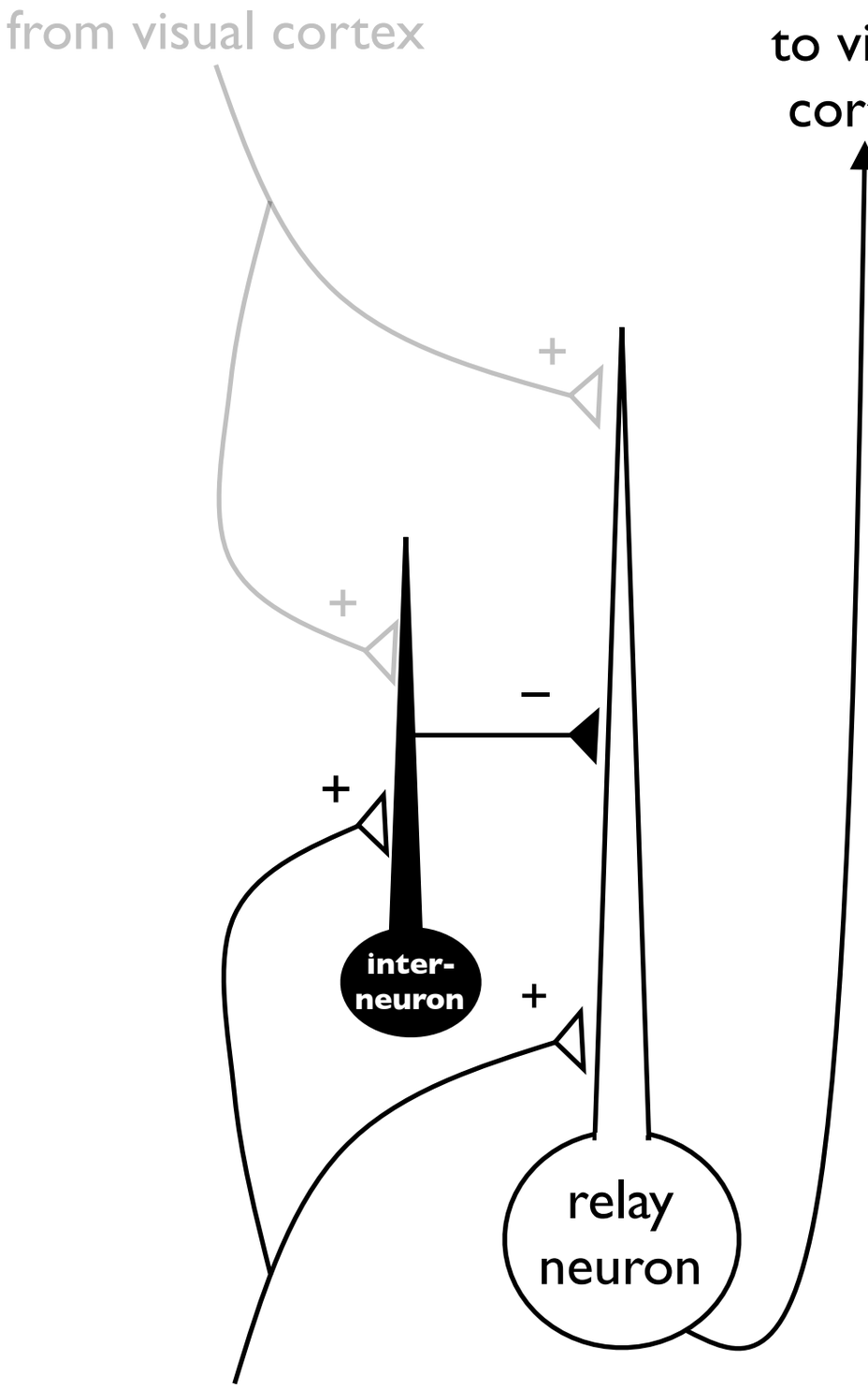
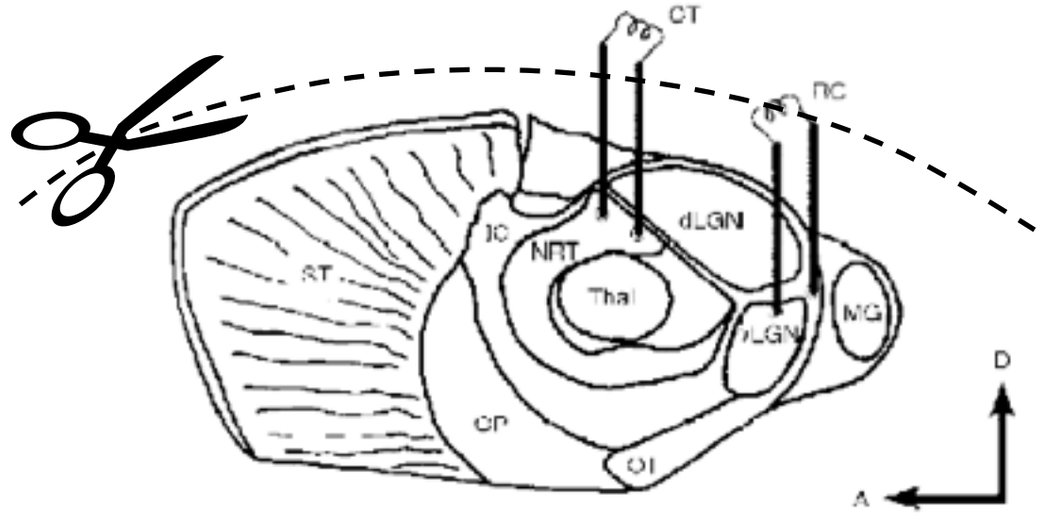


Sever cortex

- To remove cortical inputs



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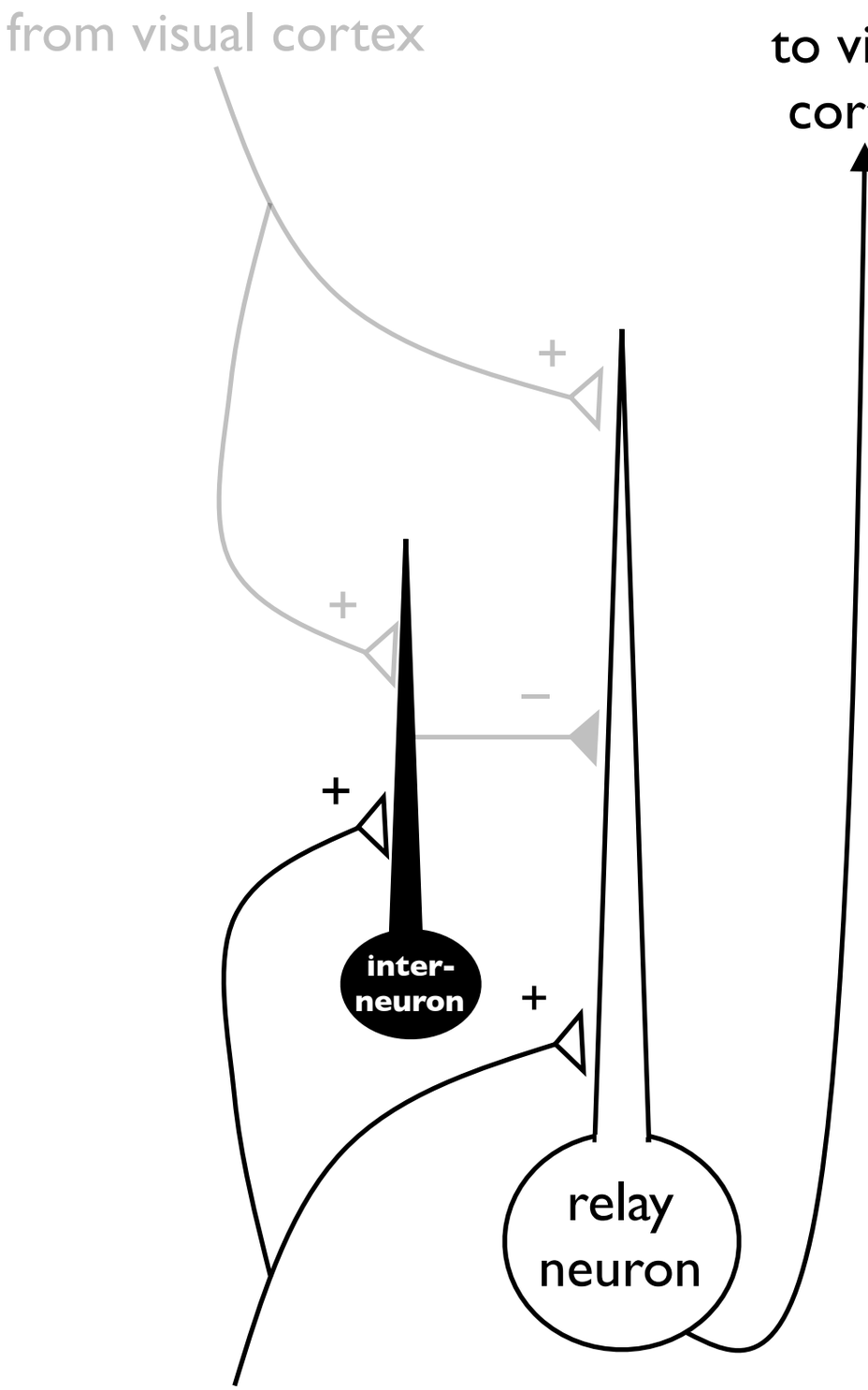

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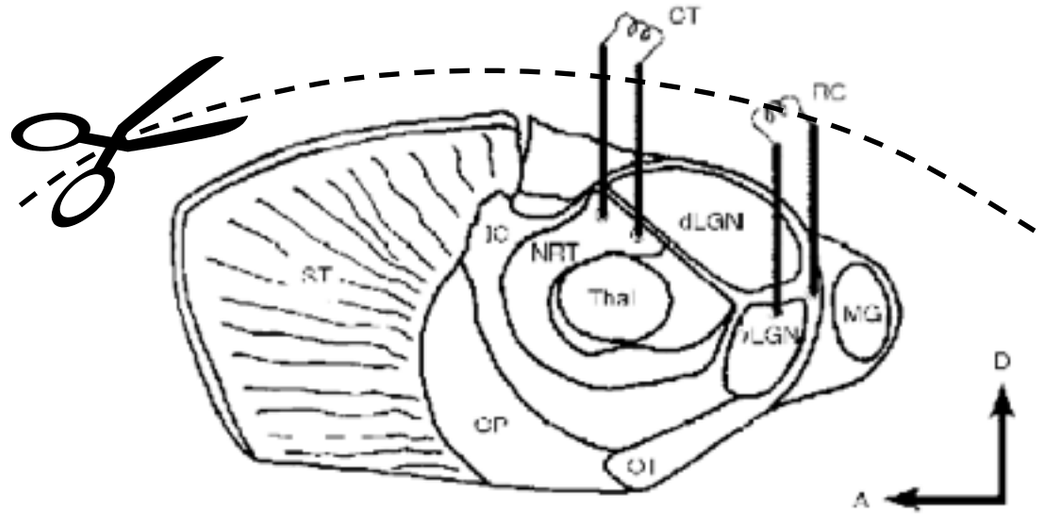
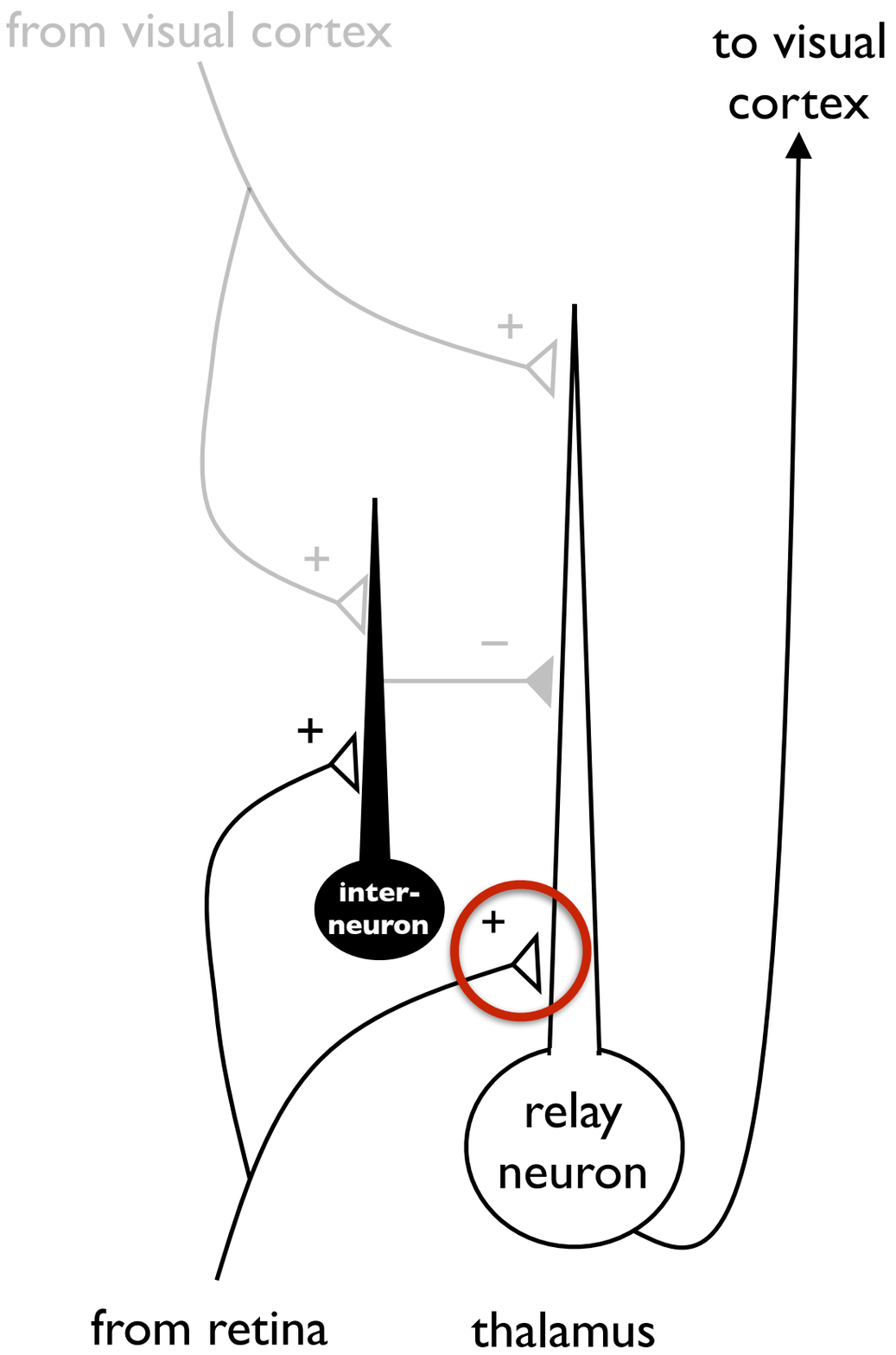


5 µM gabazine

- Block $GABA_A$ receptors
- To remove inhibitory input from interneurons

Circuit design



Sever cortex

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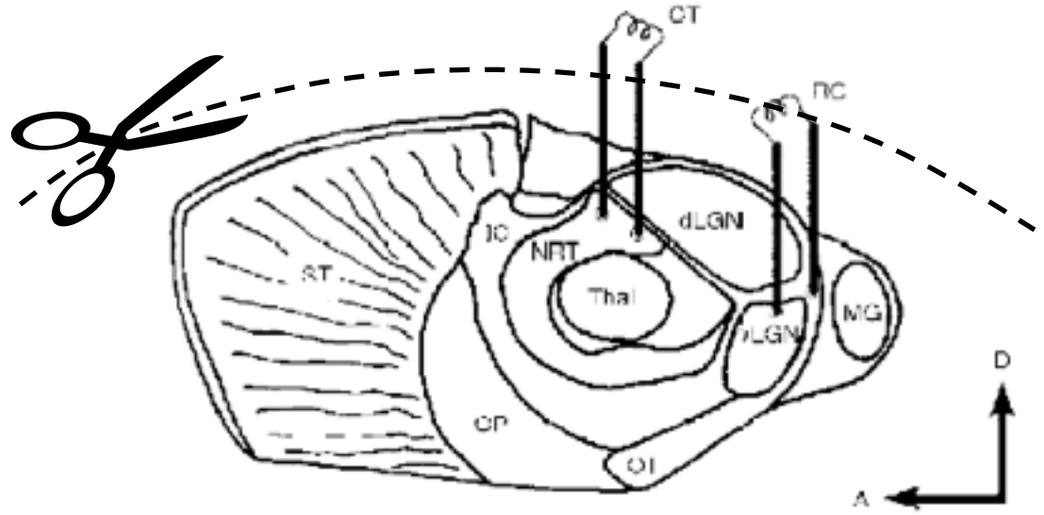


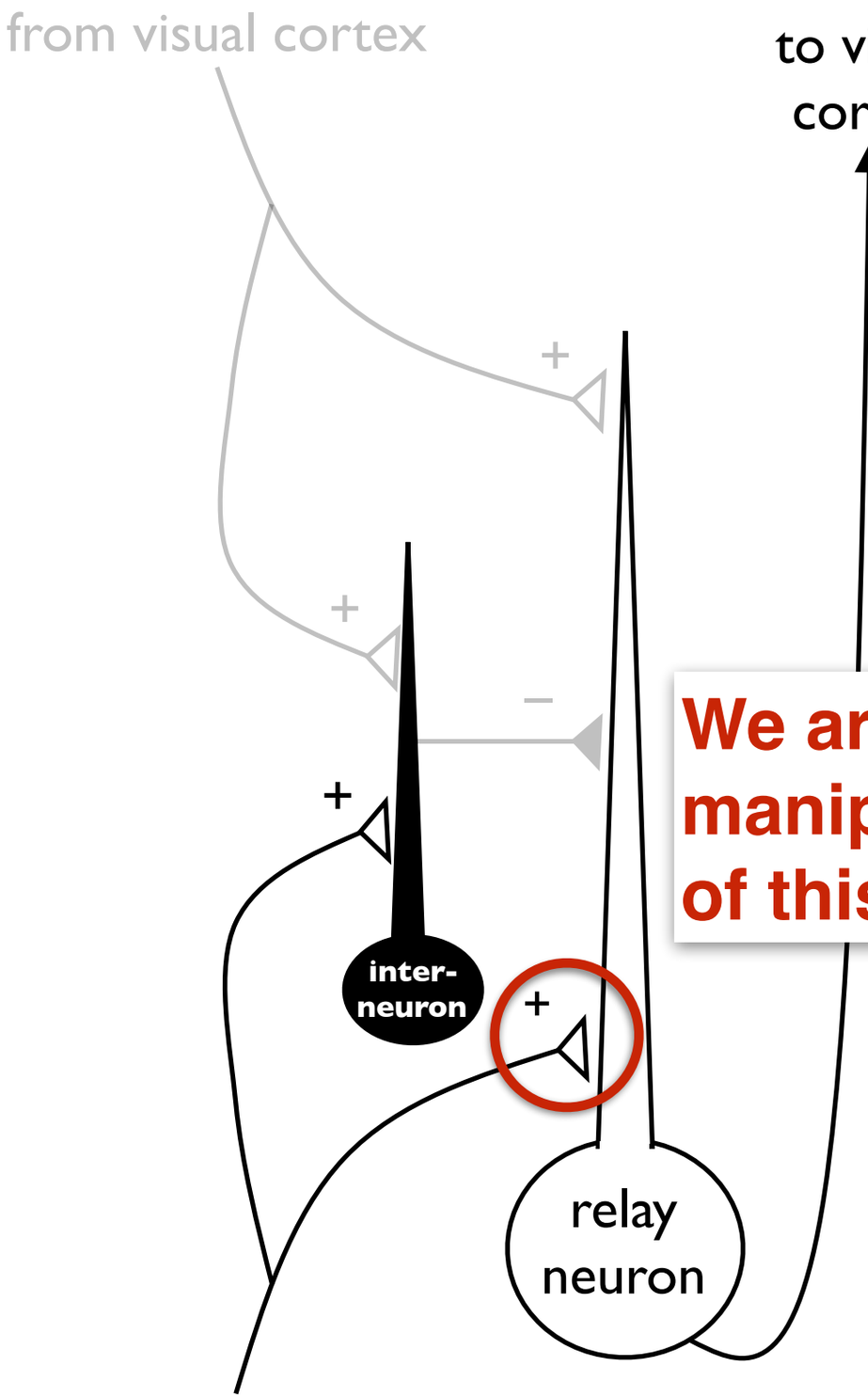
5 µM gabazine

- Block $GABA_A$ receptors
- To remove inhibitory input from interneurons

P28 rats

- Relay neurons receive input from only one RGC axon

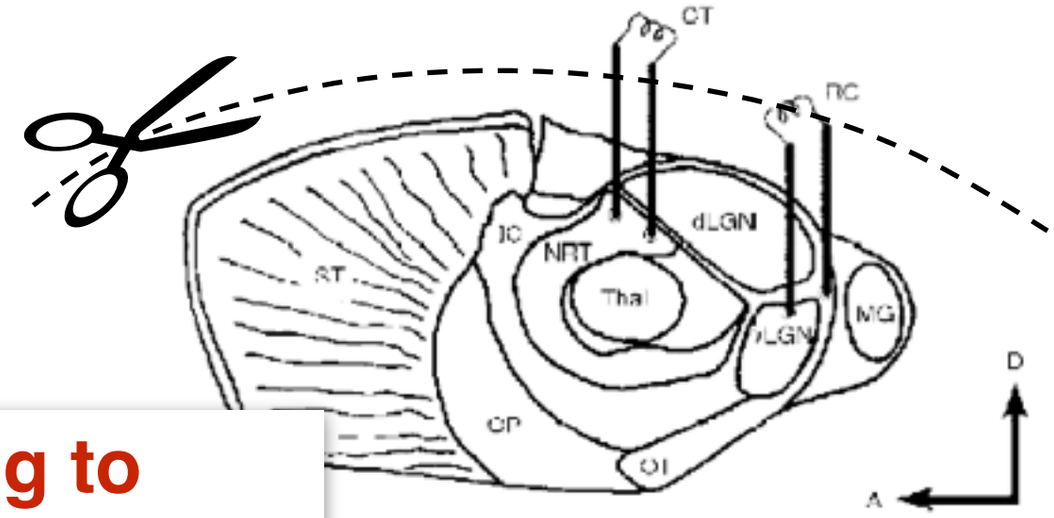
Circuit design



We are now going to manipulate the amplitude of this connection!

Sever cortex

- To remove cortical inputs



ine

BA_A receptors

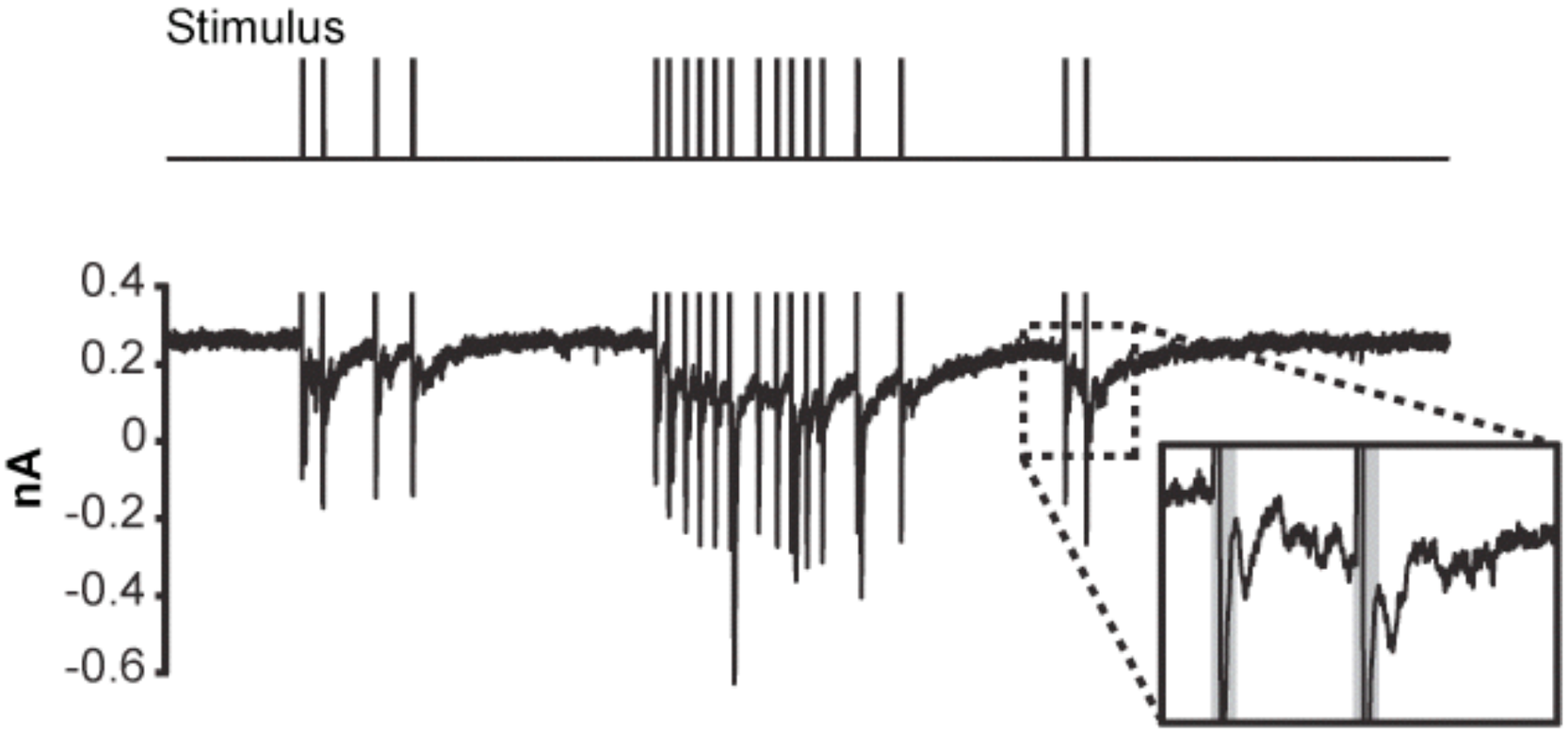
- To remove inhibitory input from interneurons

P28 rats

- Relay neurons receive input from only one RGC axon

Calculating energy and information

Calculating energy and information



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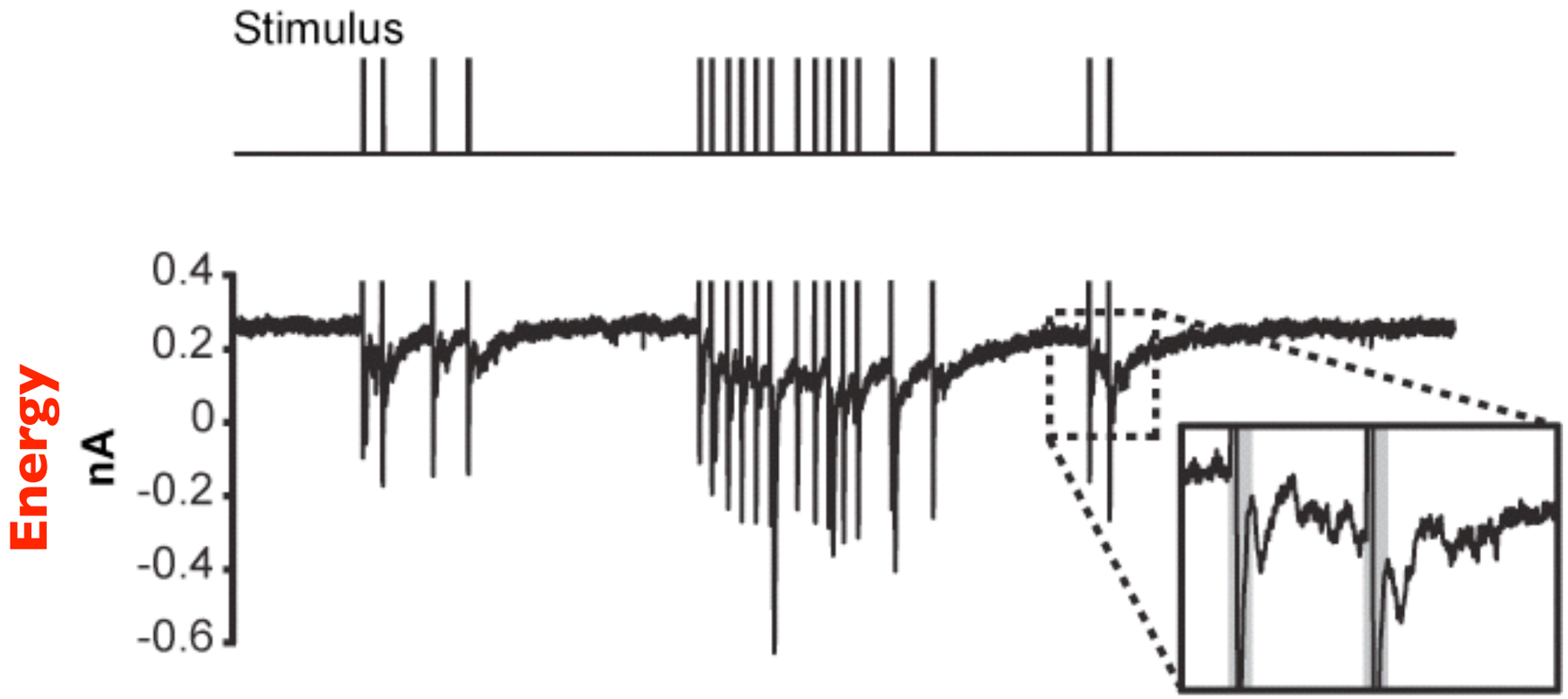
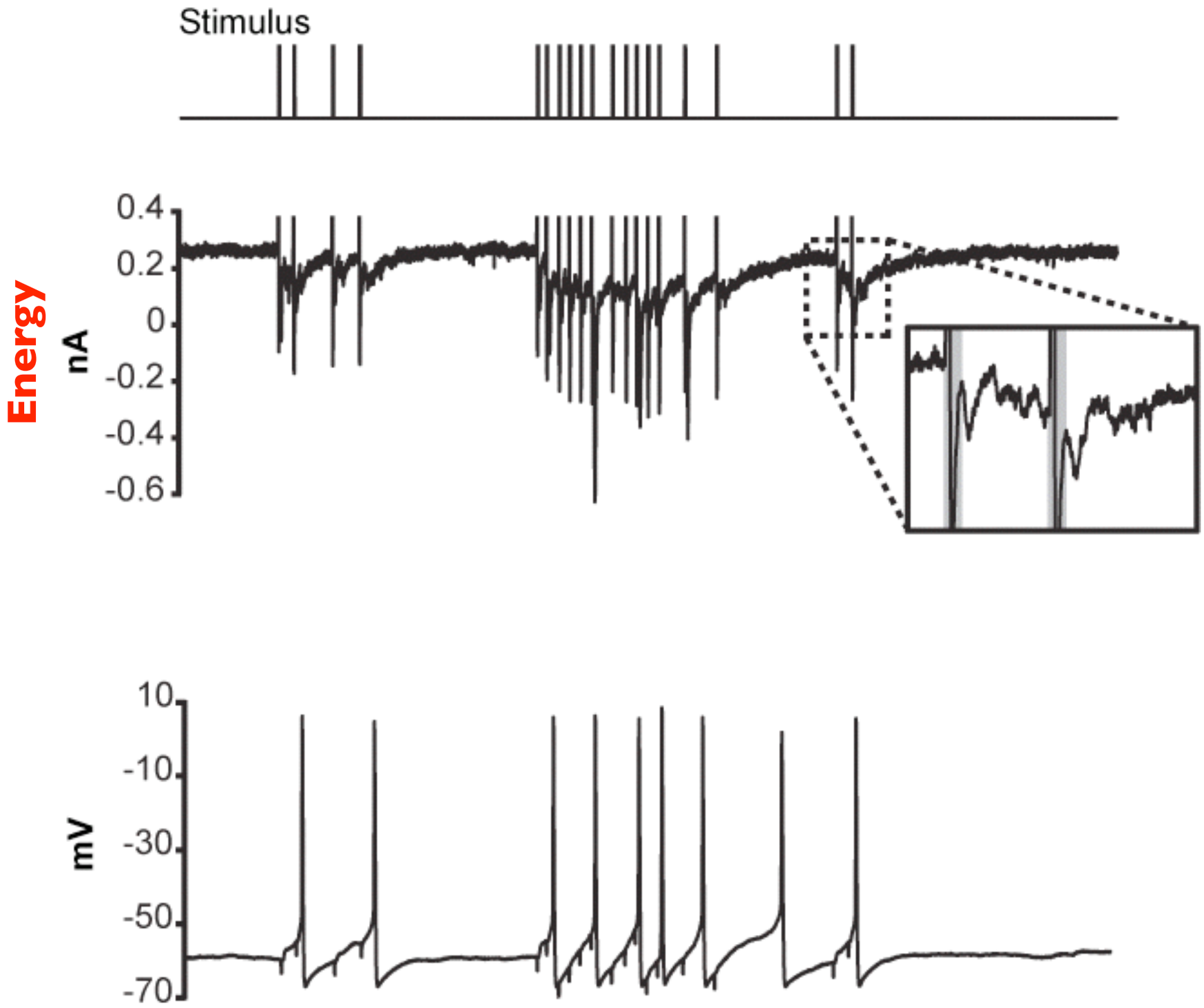


How much ATP is spent on synaptic transmission?

Calculating energy and information



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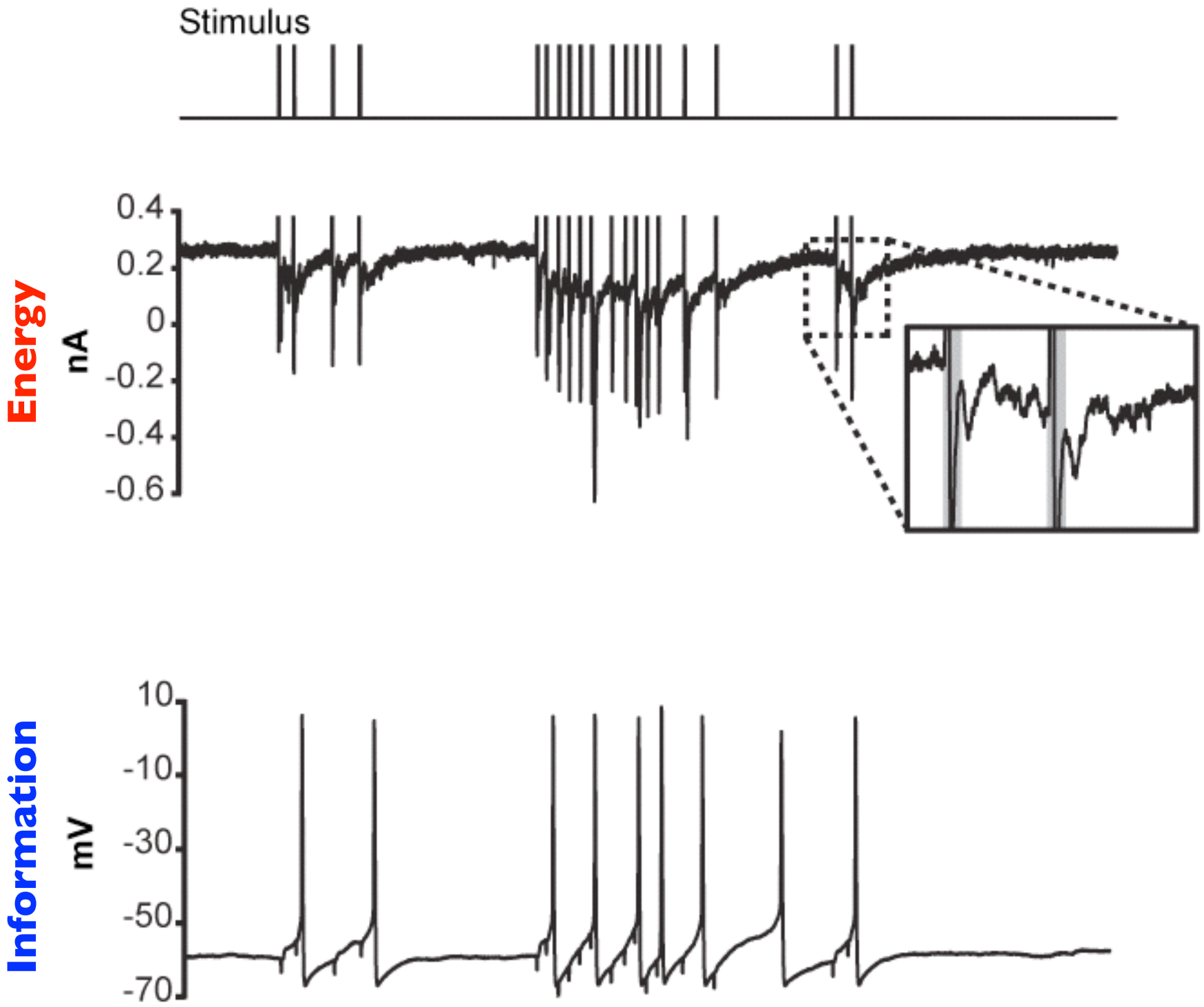
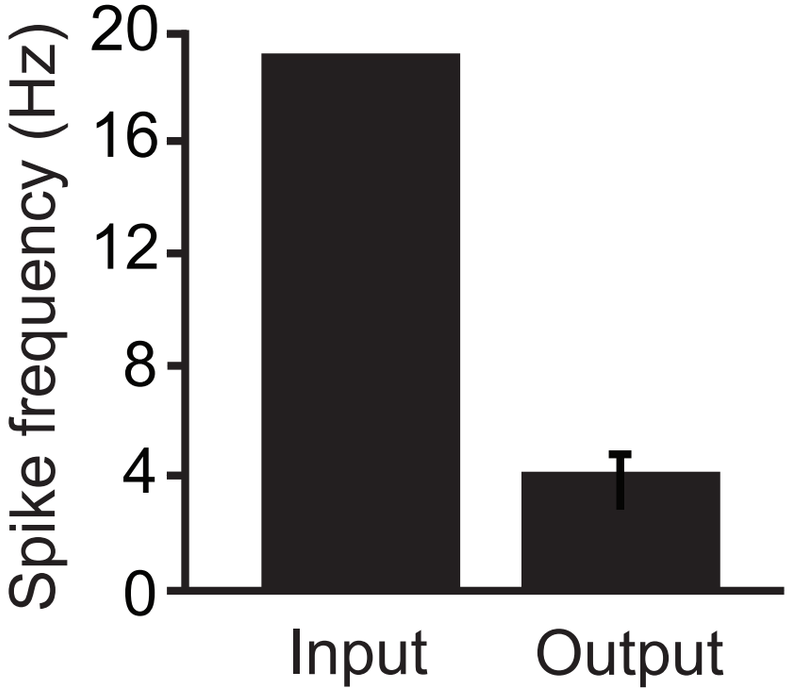


How much ATP is spent on synaptic transmission?

How well does the neural response describe the stimulus?

The retinogeniculate synapse does not maximise information transmission

Stimulation statistics



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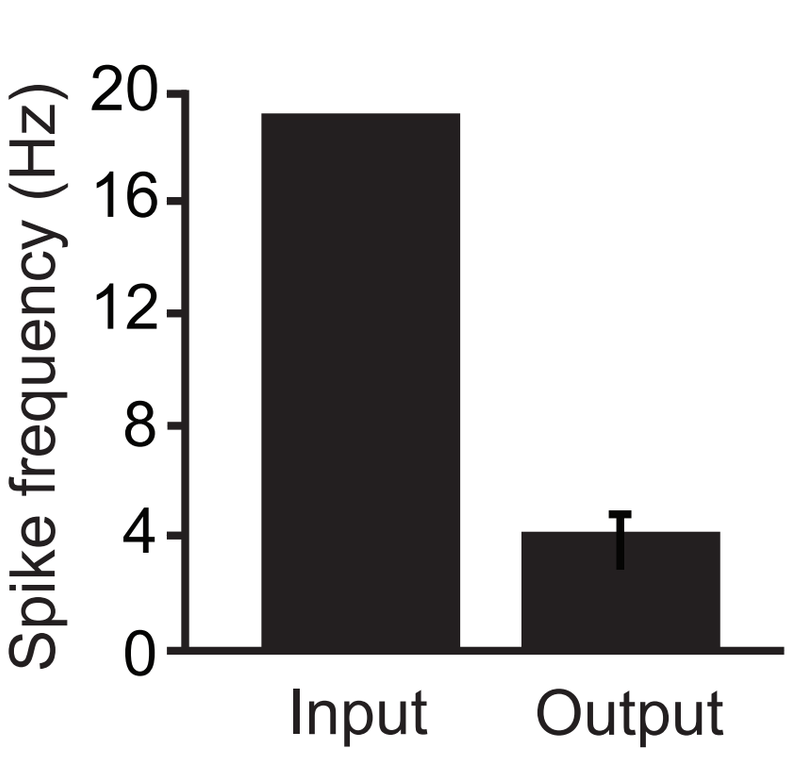
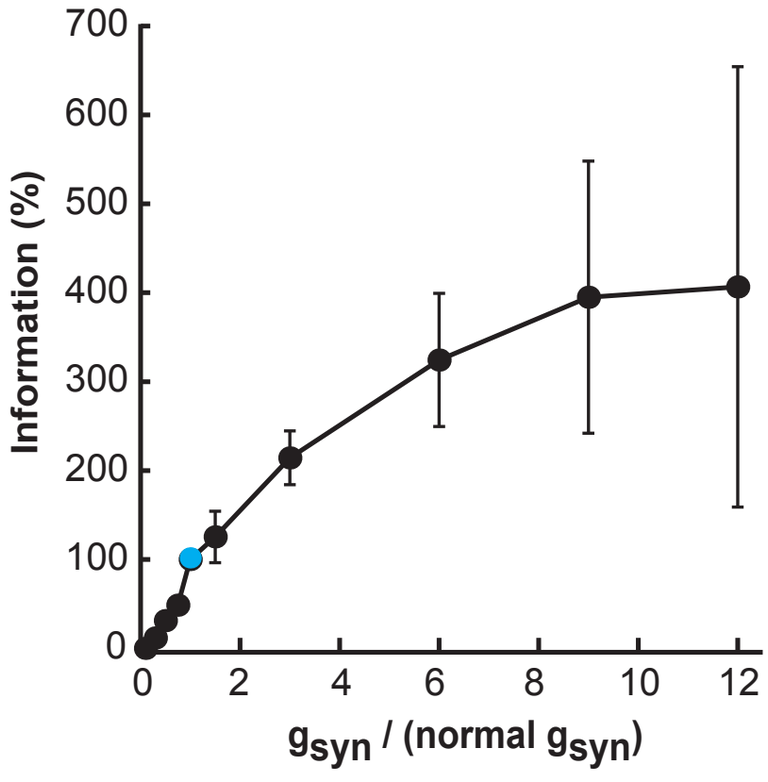


Increasing the synaptic connection's gain increases information transfer



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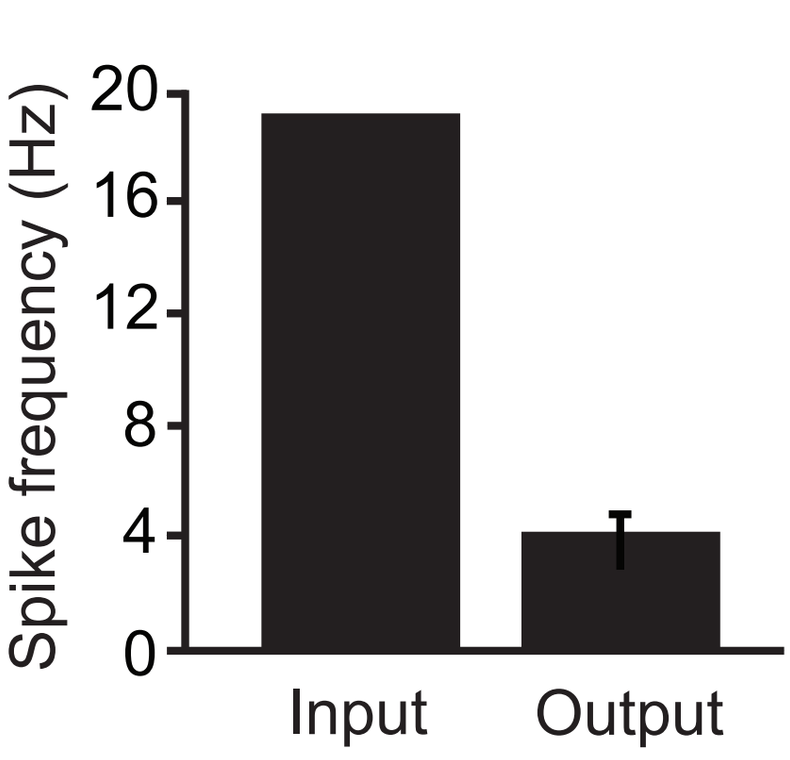

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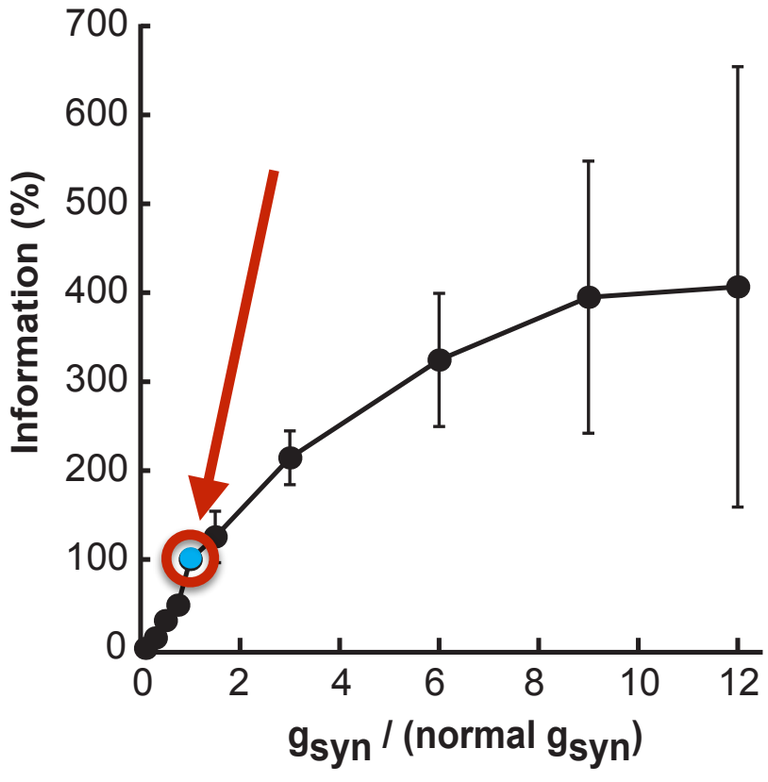
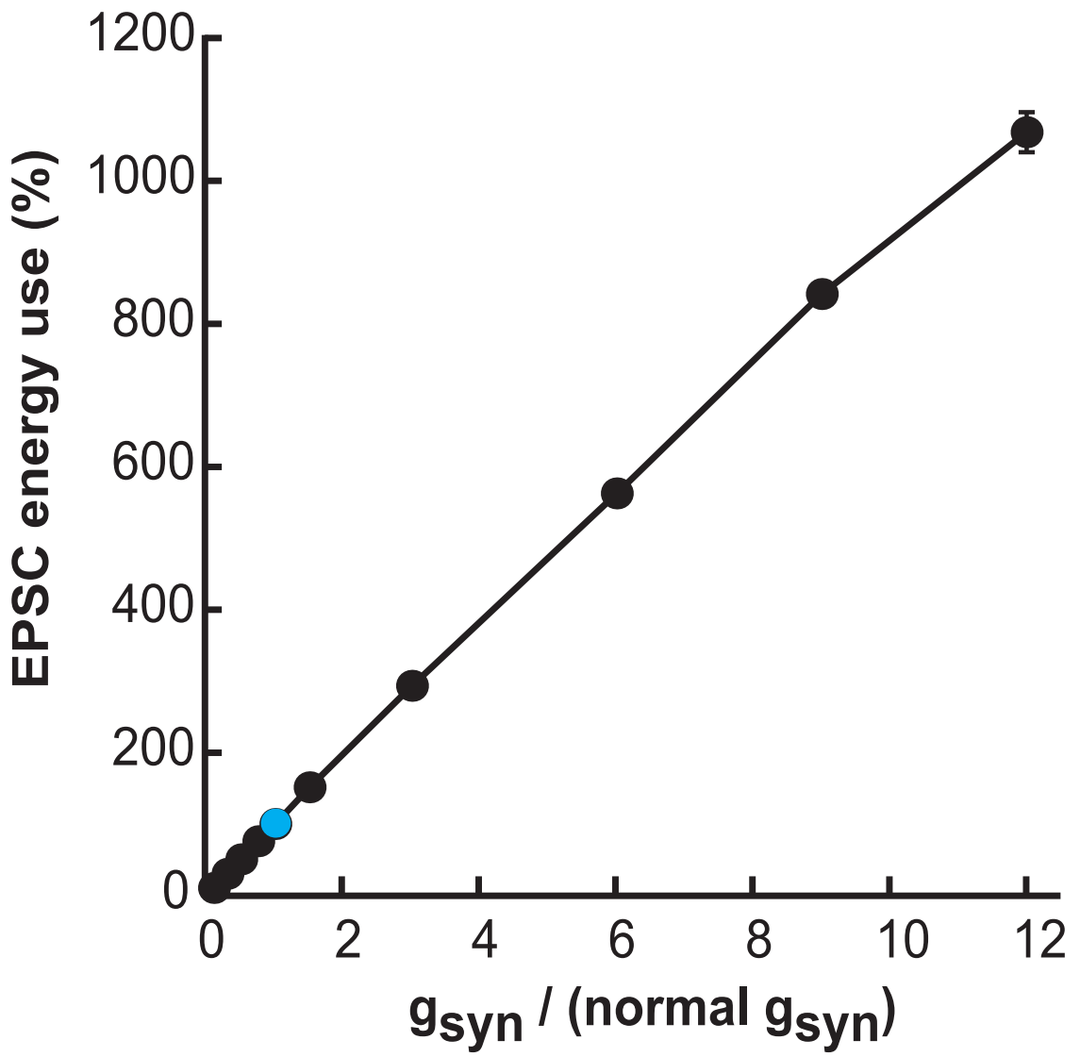
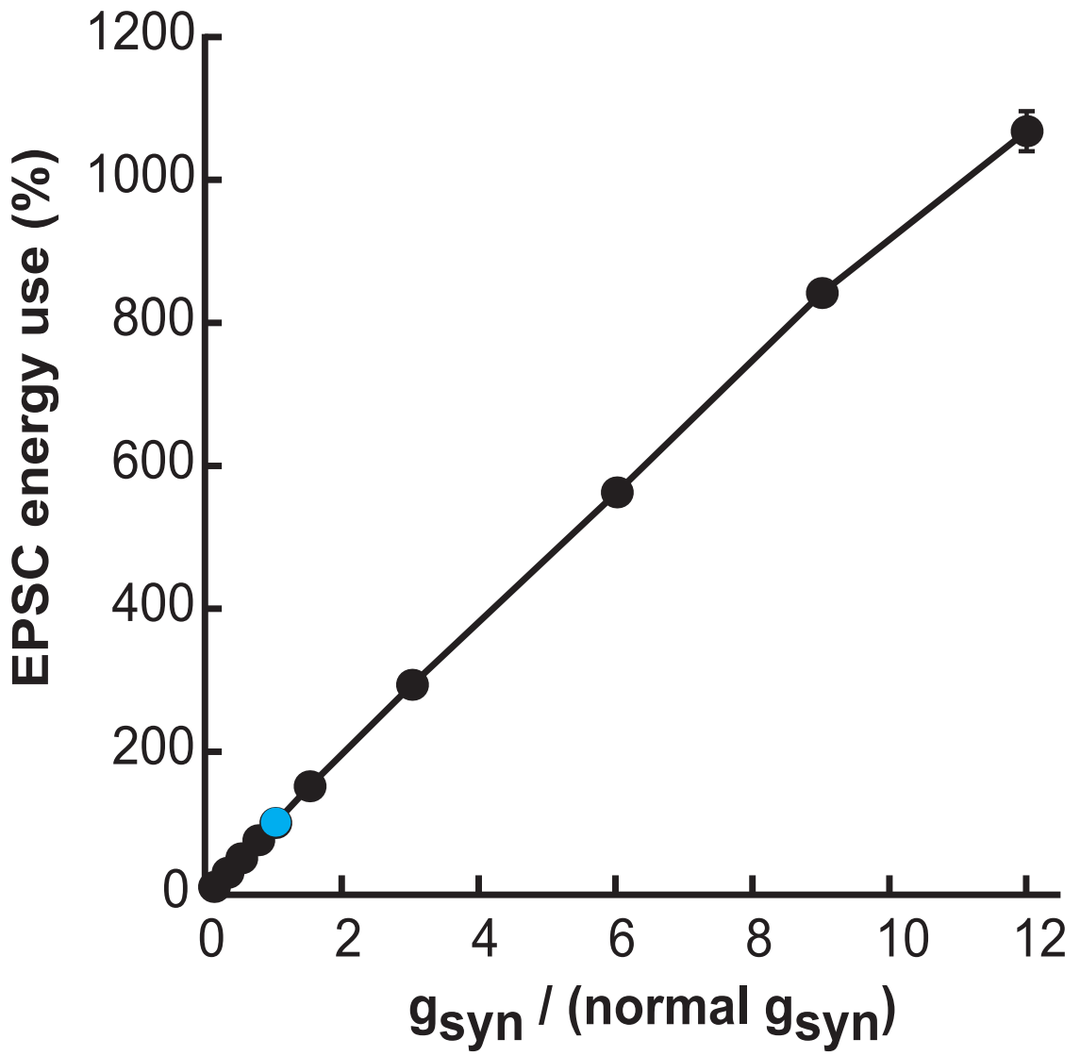
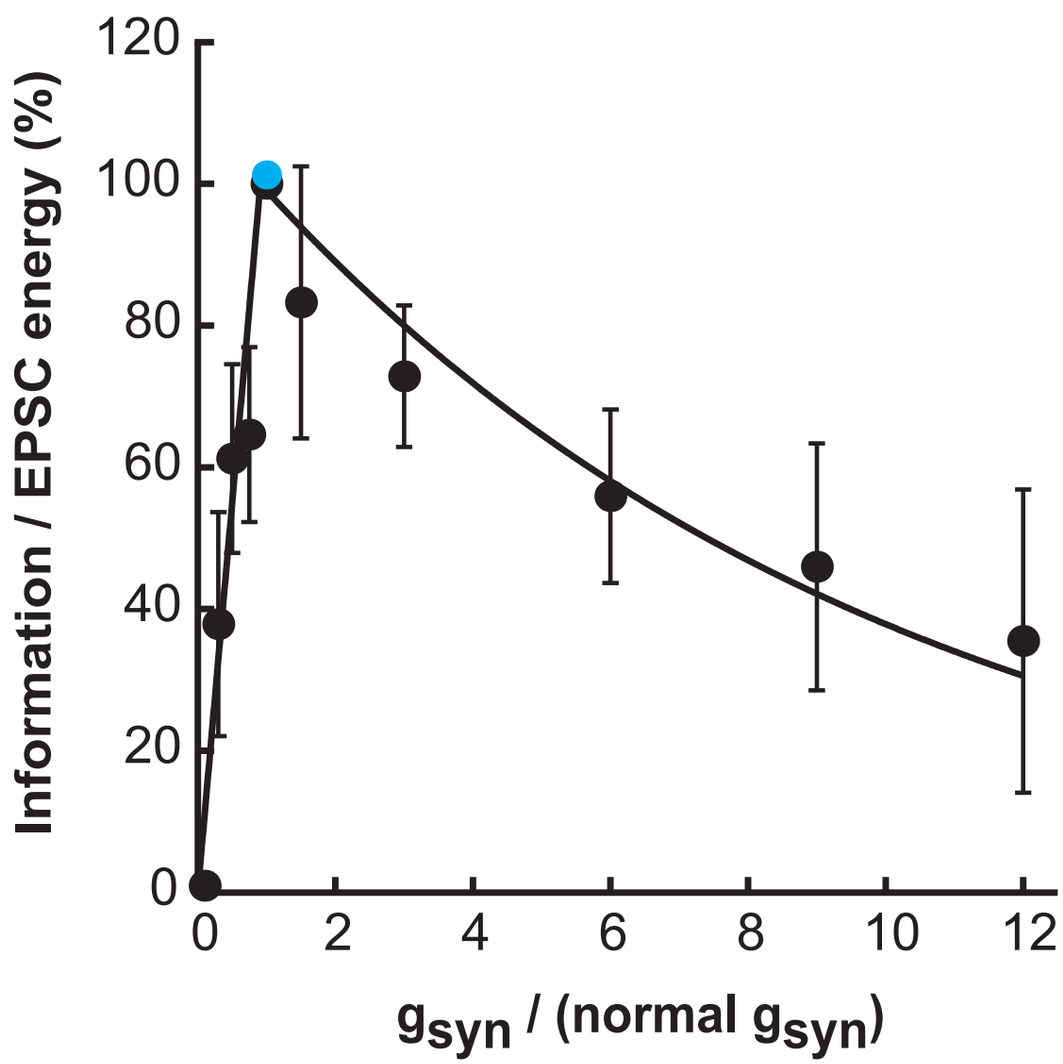


The retinogeniculate synapse maximises the energetic efficiency of information transmission



The retinogeniculate synapse maximises the energetic efficiency of information transmission





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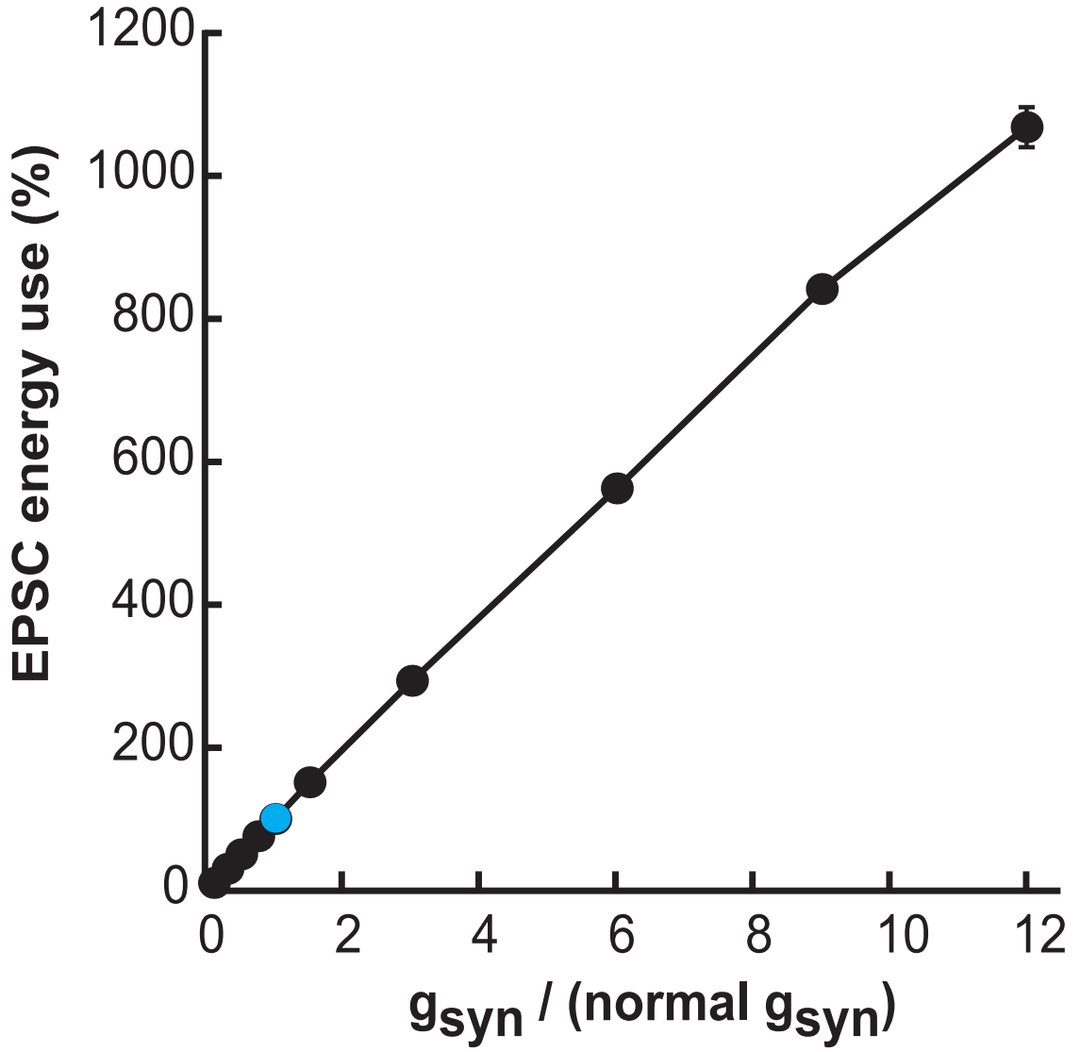

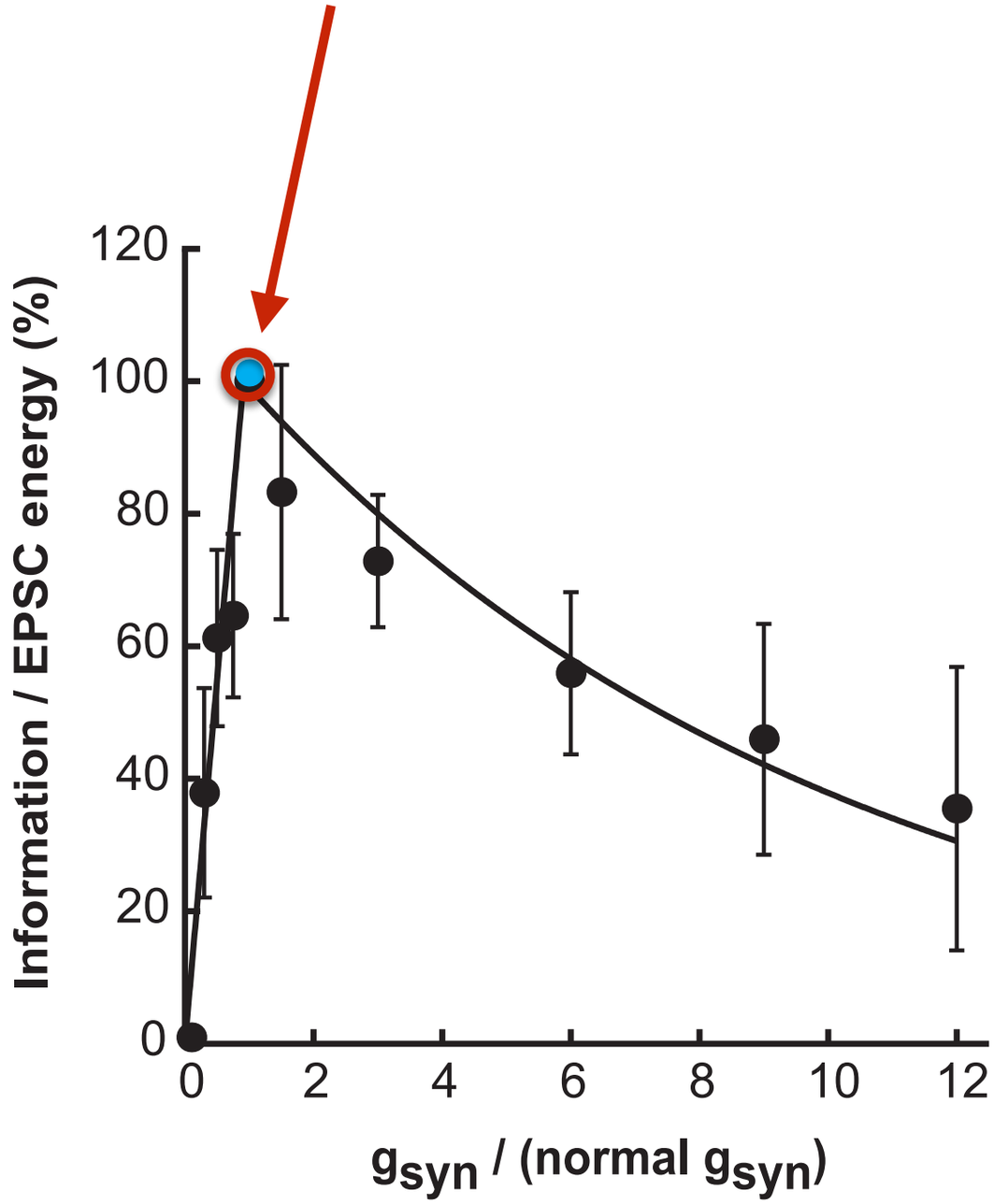

Harris*, Jolivet* et al., *Current Biology* 2015

This might be true for cortical connections as well

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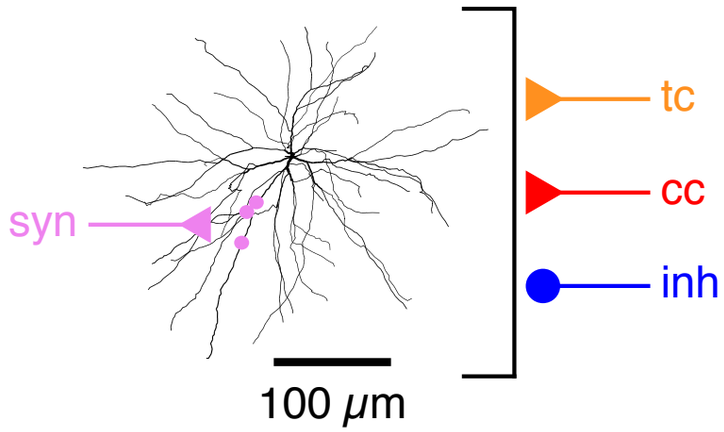
Multicompartment simulations
(layer 4 spiny stellate cells)



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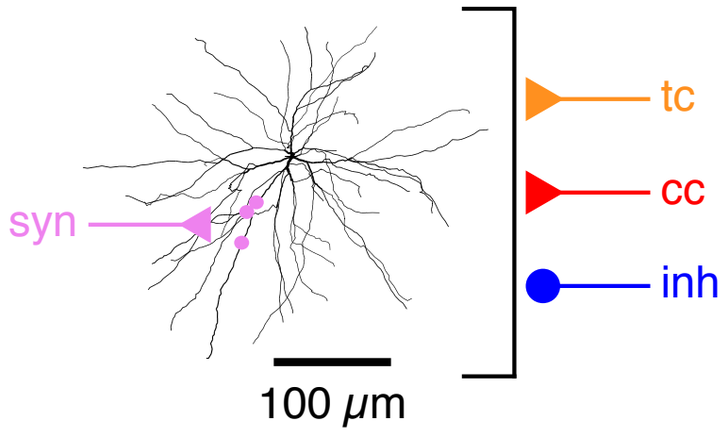
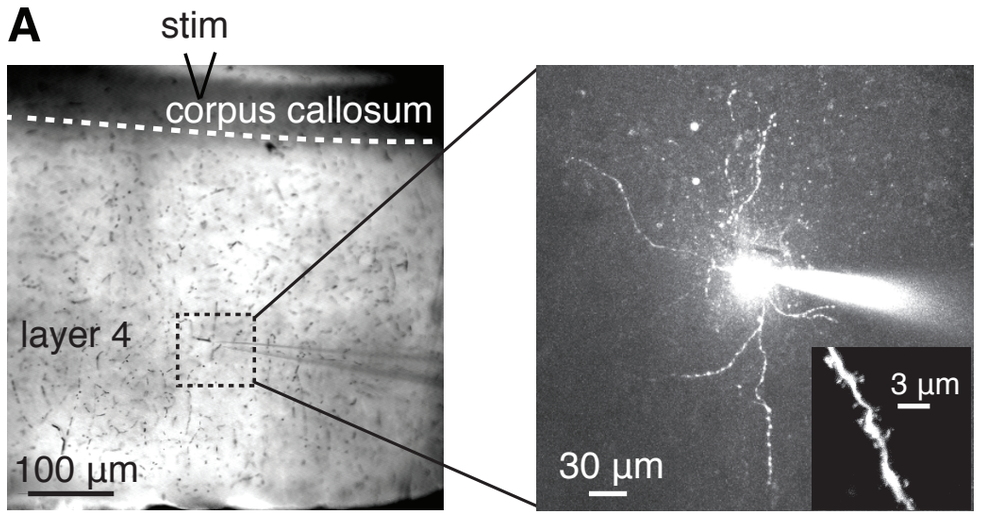


Electrophysiology experiments
(layer 4 spiny stellate cells)



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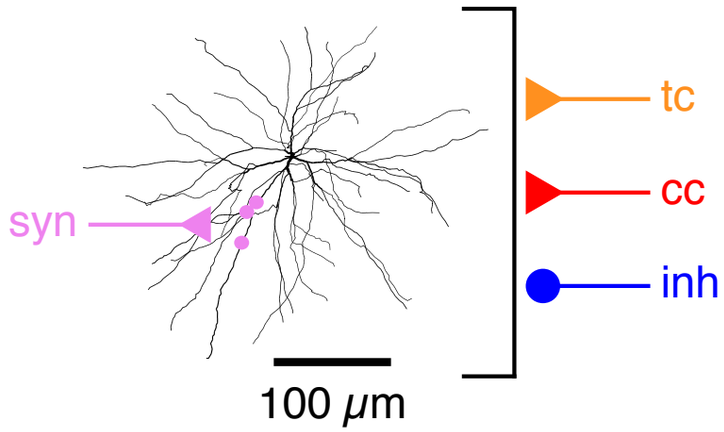

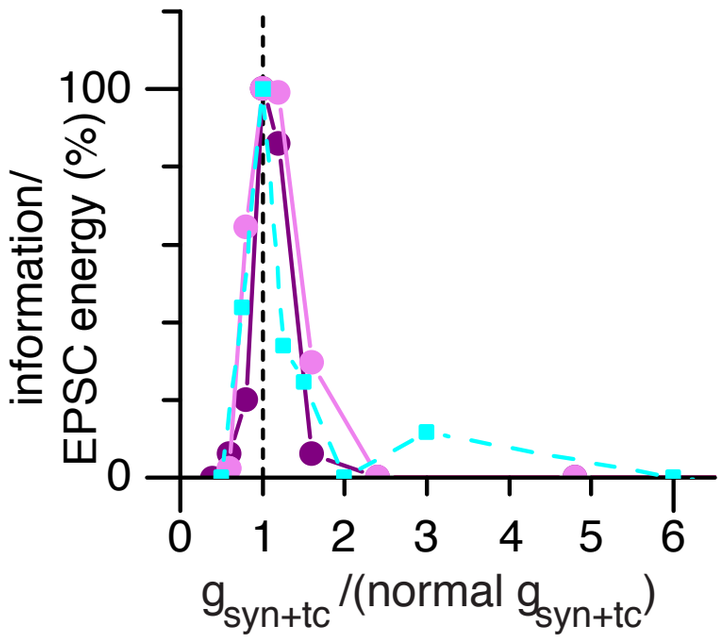

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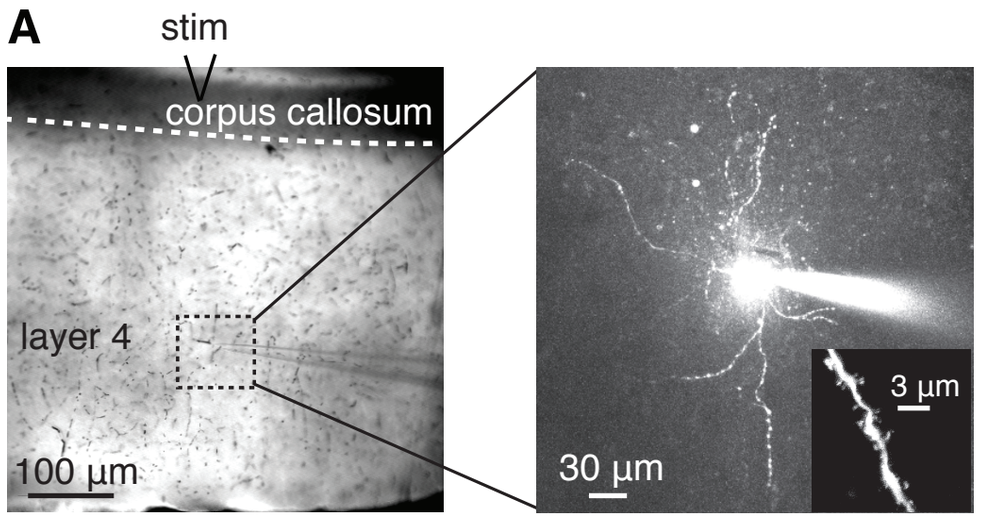

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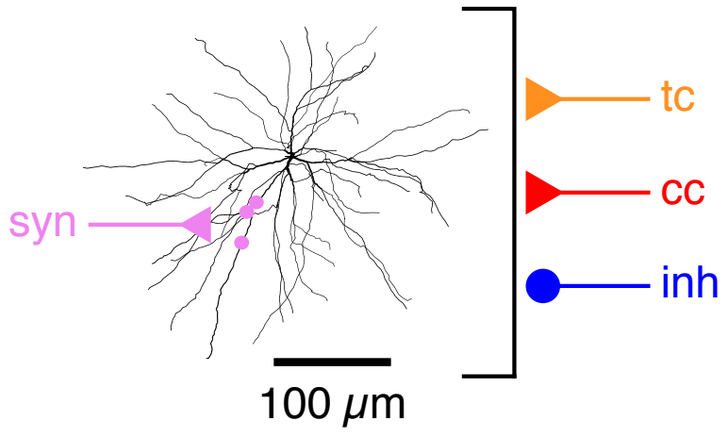

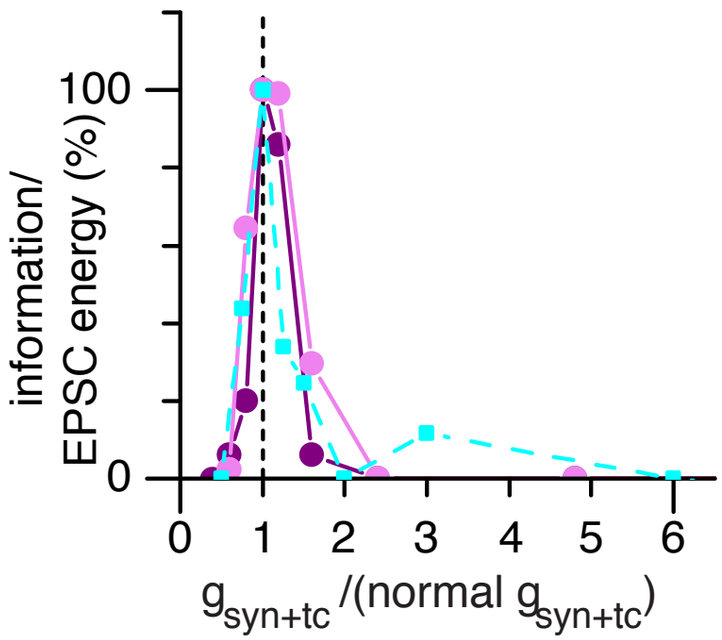

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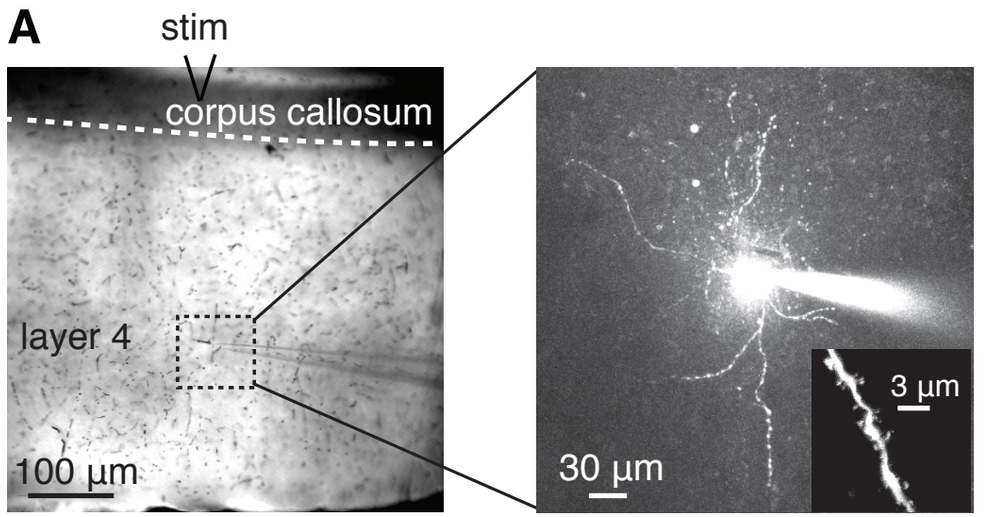

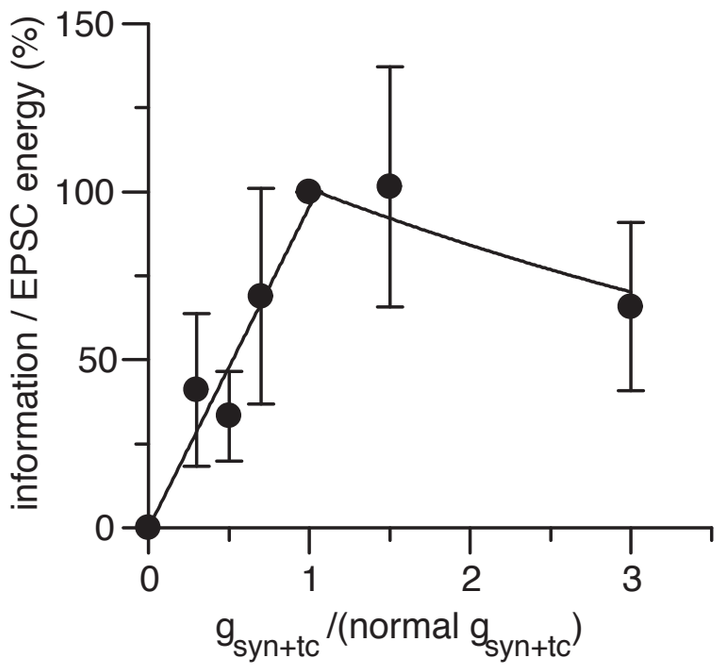

Jolivet*, Harris* et al., *in preparation*

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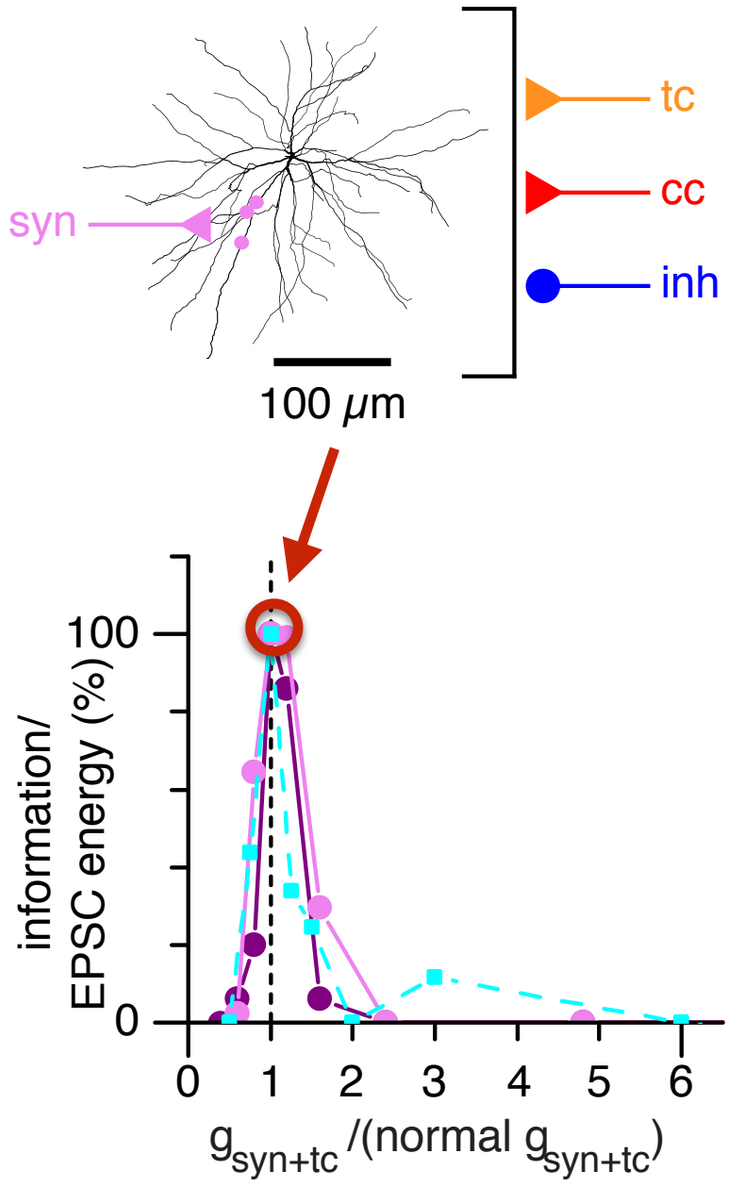

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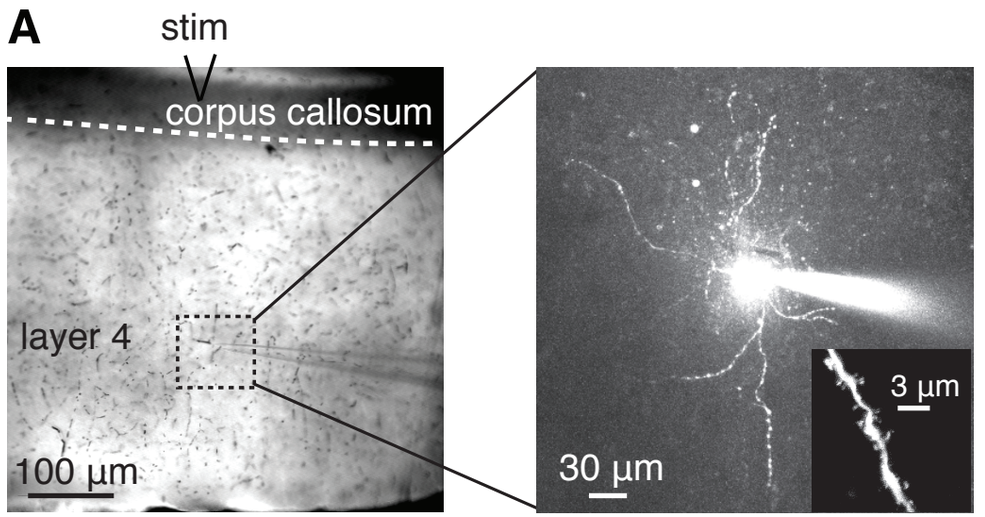

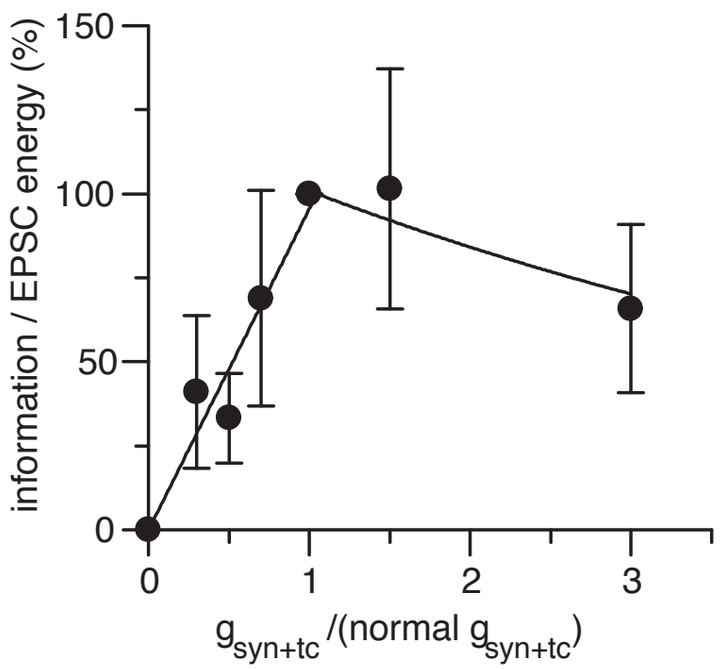

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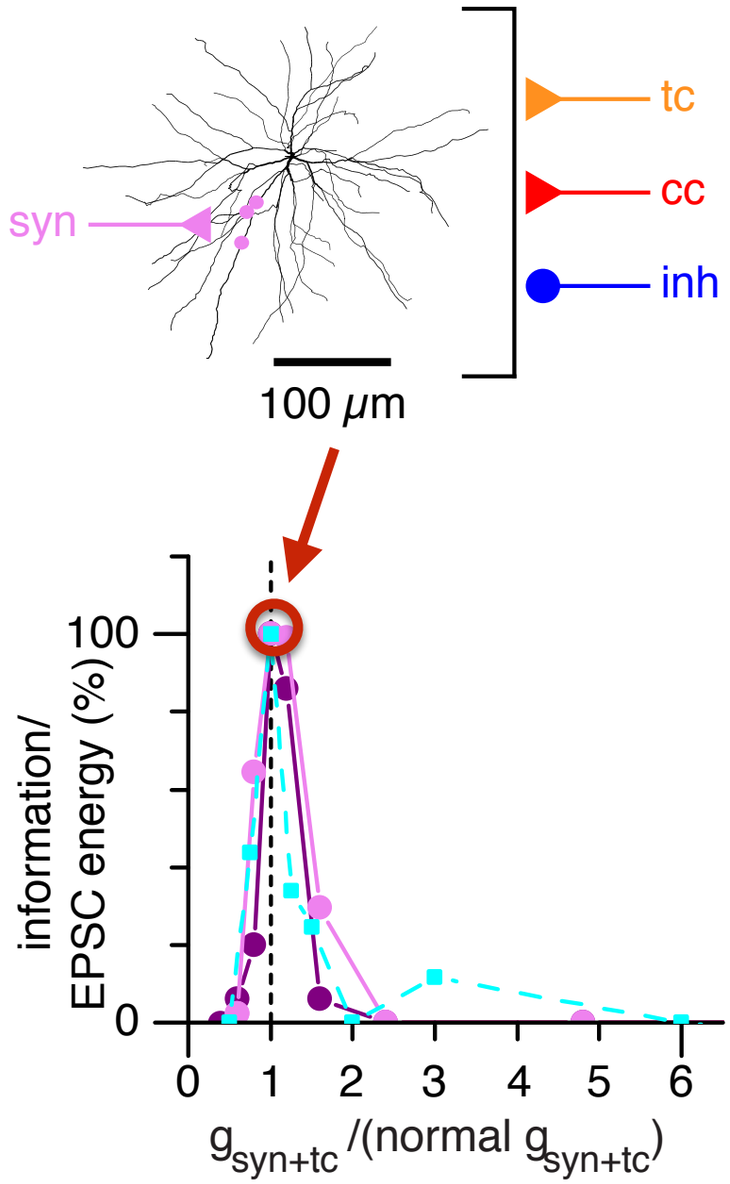

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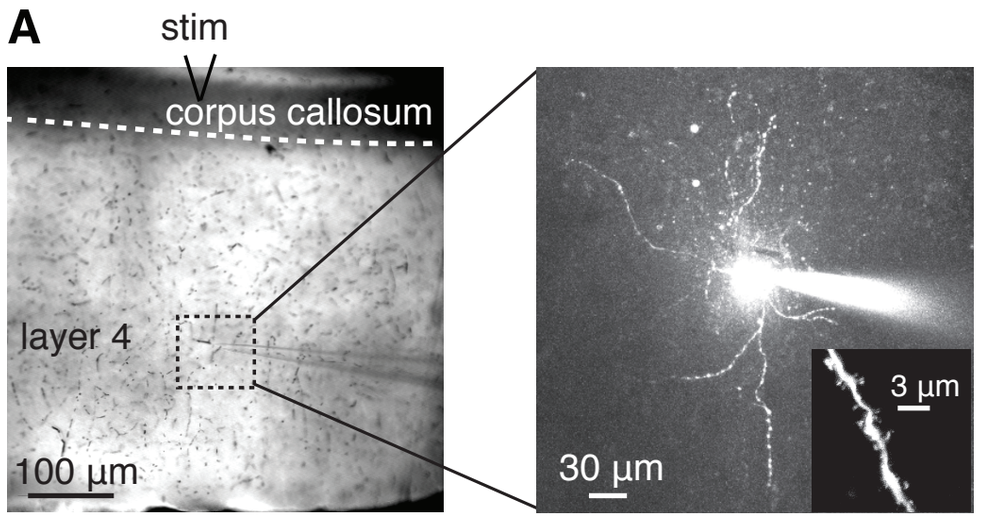

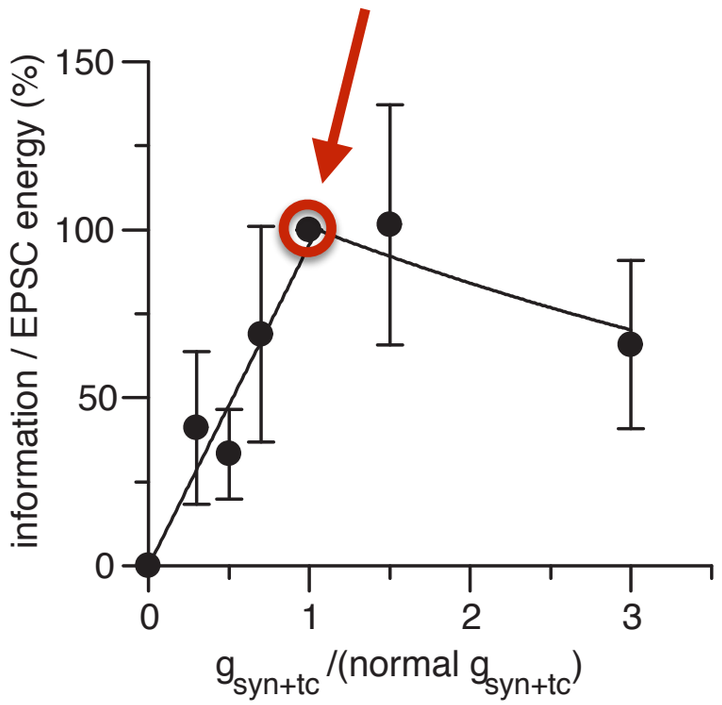

Jolivet*, Harris* et al., *in preparation*

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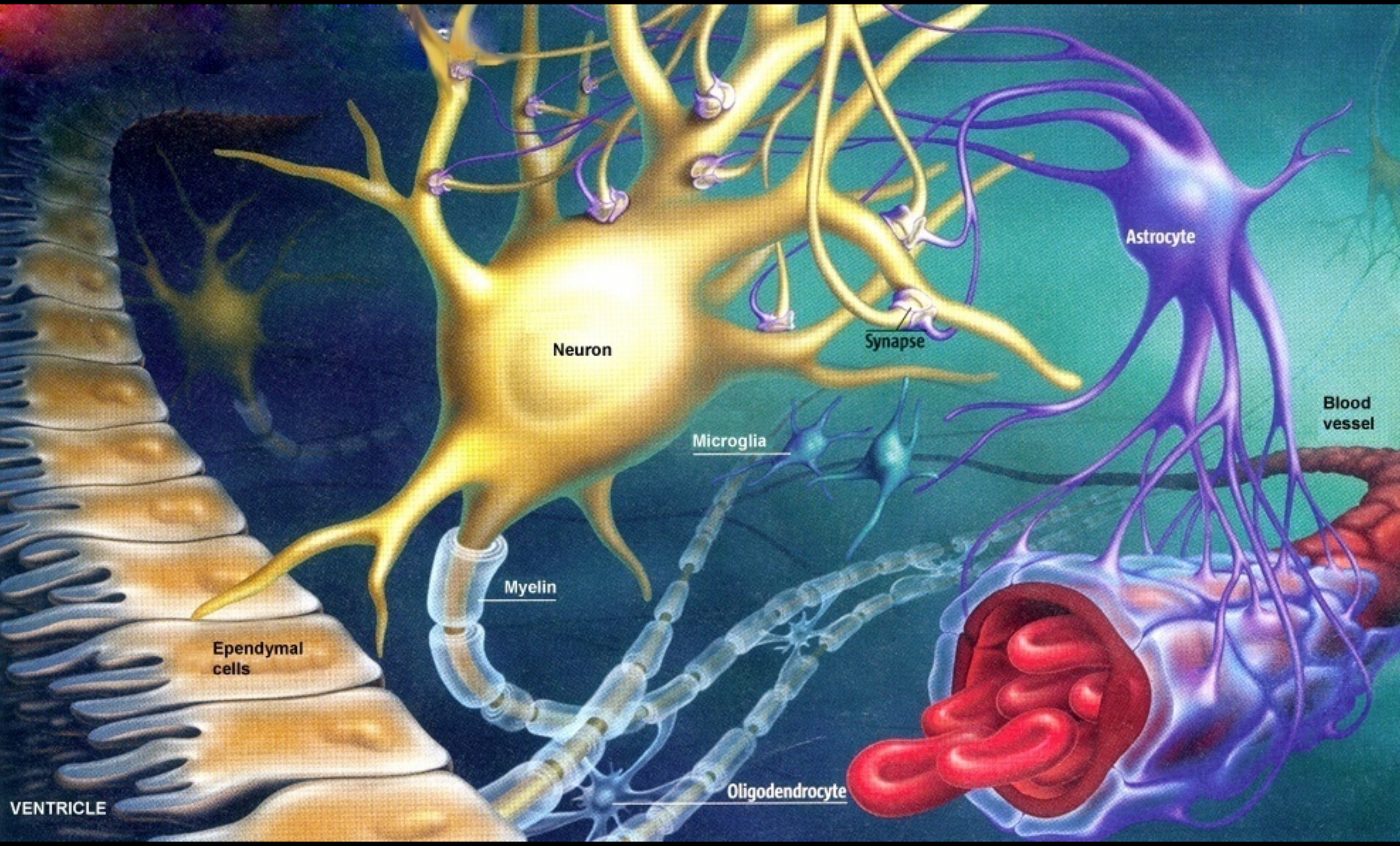
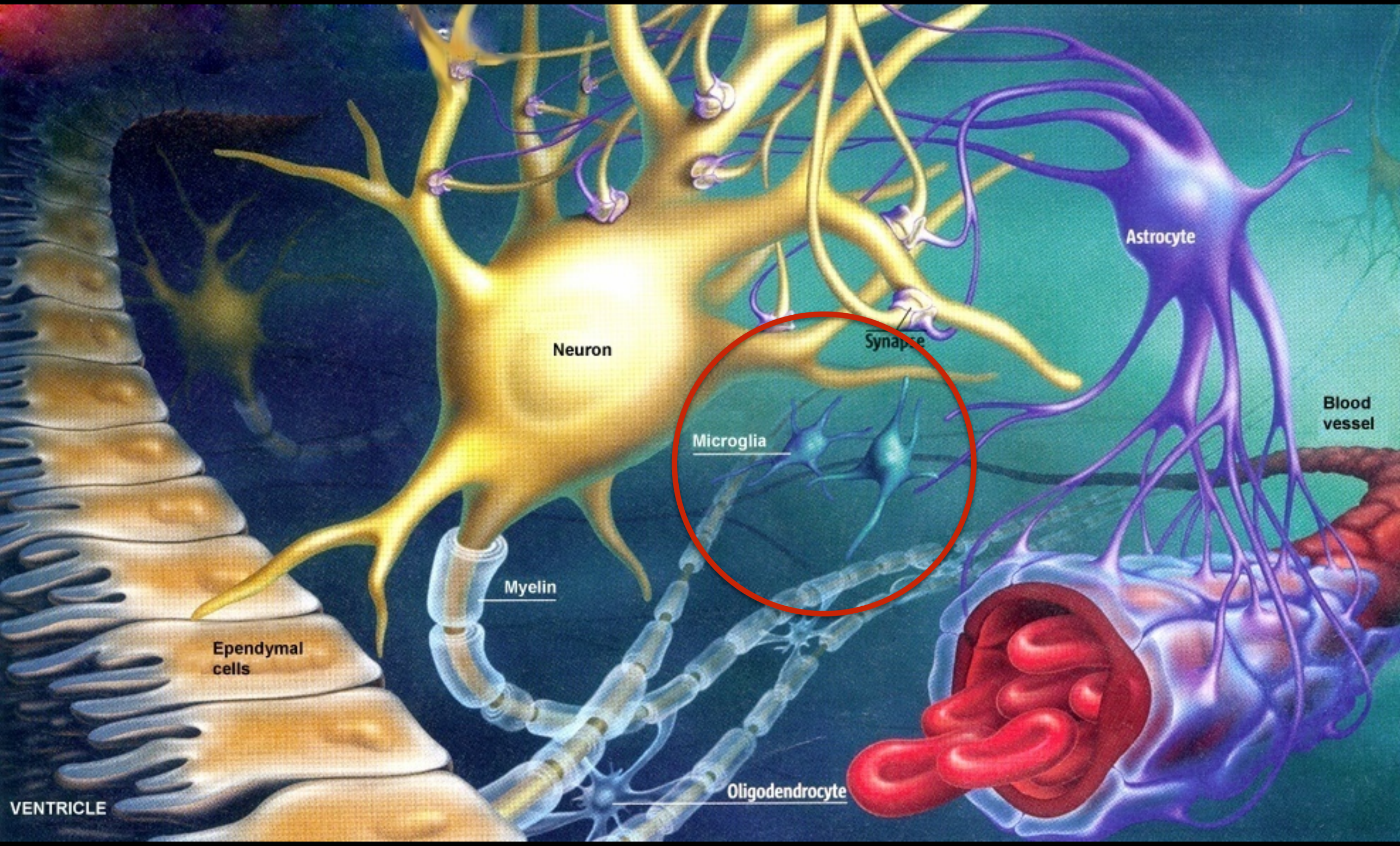
- How does it arise?

- Can it be applied outside of the brain?

Outline

- Neuroenergetics
- Energy as a constraint on brain function
- Energy as a signal for the brain's immune system
- CERN as a model for the neurosciences


Astrocyte
Synapse
Neuron
Blood vessel
Microglia
Myelin
Ependymal cells
Oligodendrocyte
VENTRICLE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Microglia are the brain’s resident immune cells

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Pio del Rio-Hortega
(1882 – 1945)

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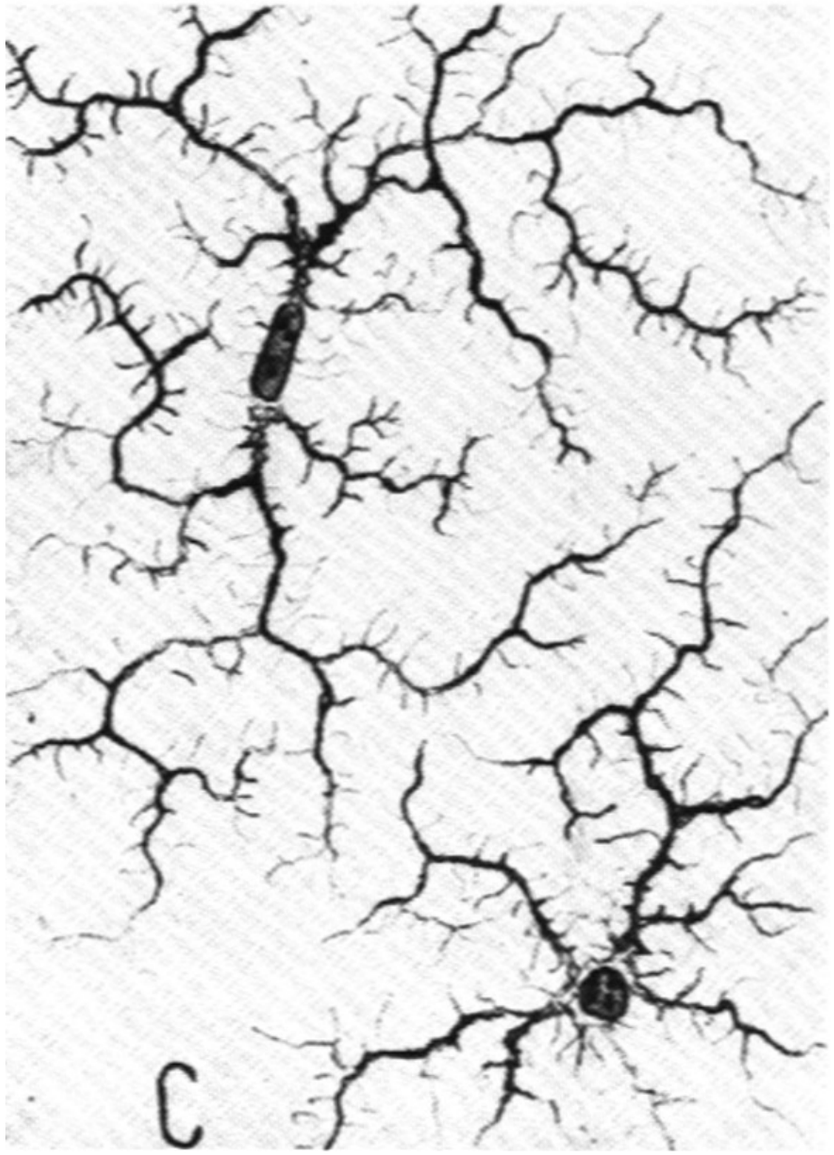
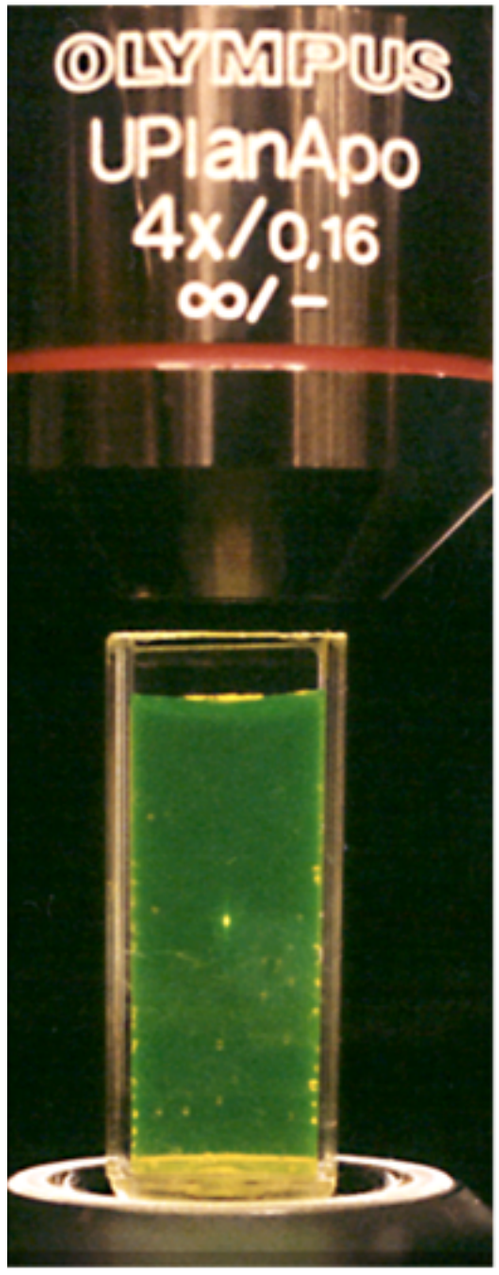


del Rio-Hortega, *Bol de la Soc esp de biol* 1919

Two-photon microscopy



900 nm pulsed excitation

Two-photon fluorescence

$$Signal \propto I^2$$

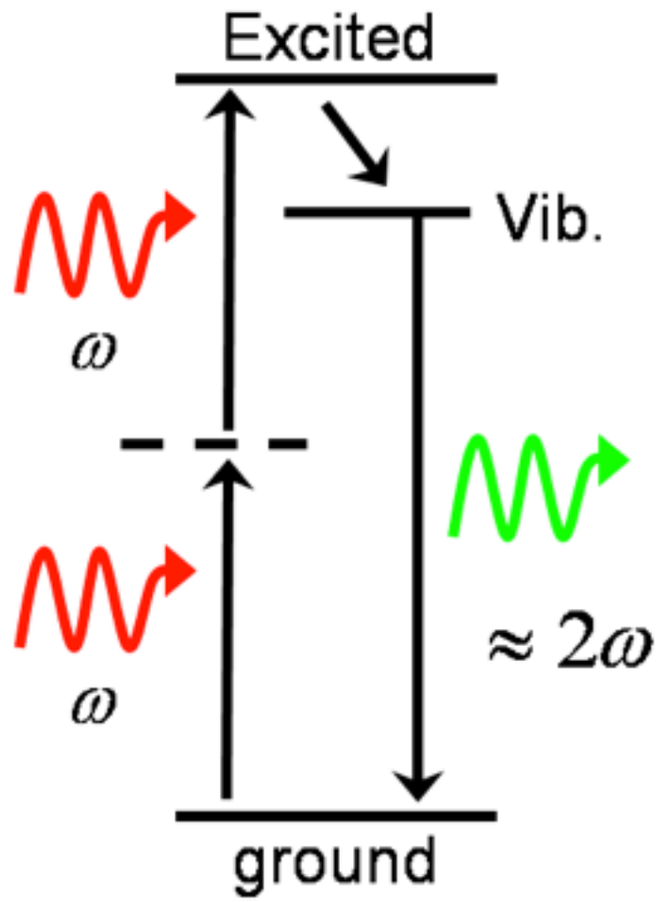
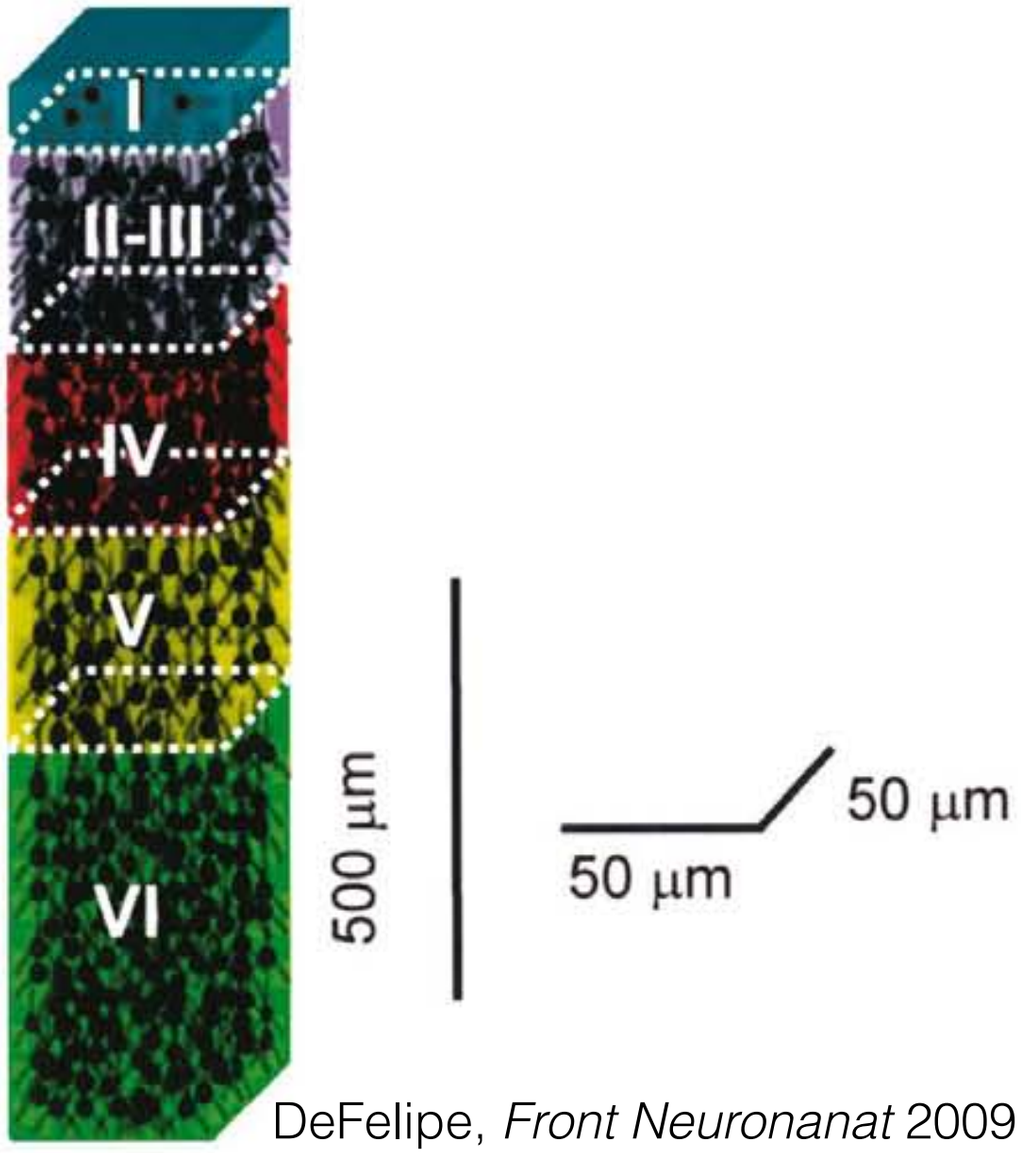


image Webb Lab

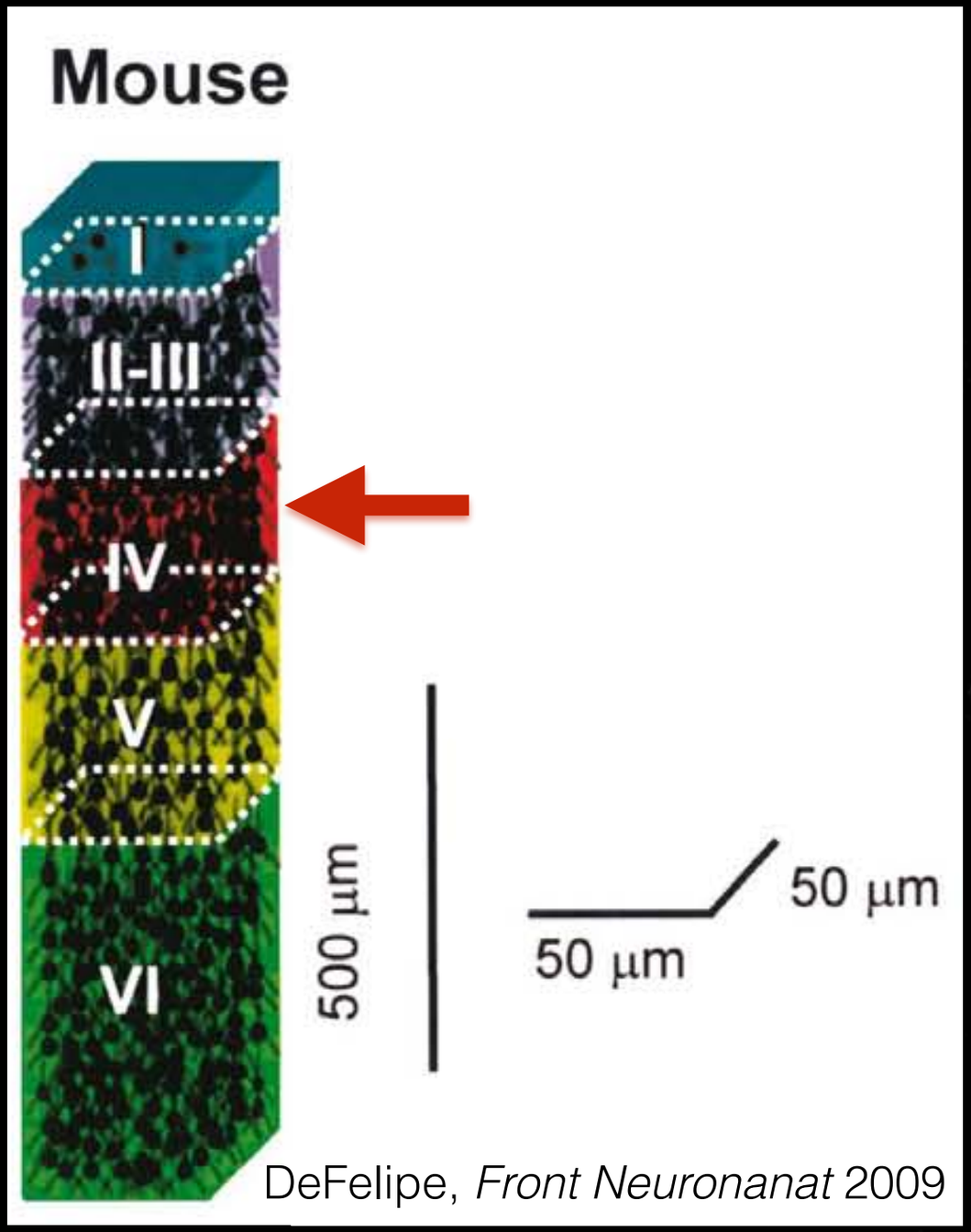
Mouse



DeFelipe, *Front Neuronanat* 2009

100 µm

Iba1-eGFP



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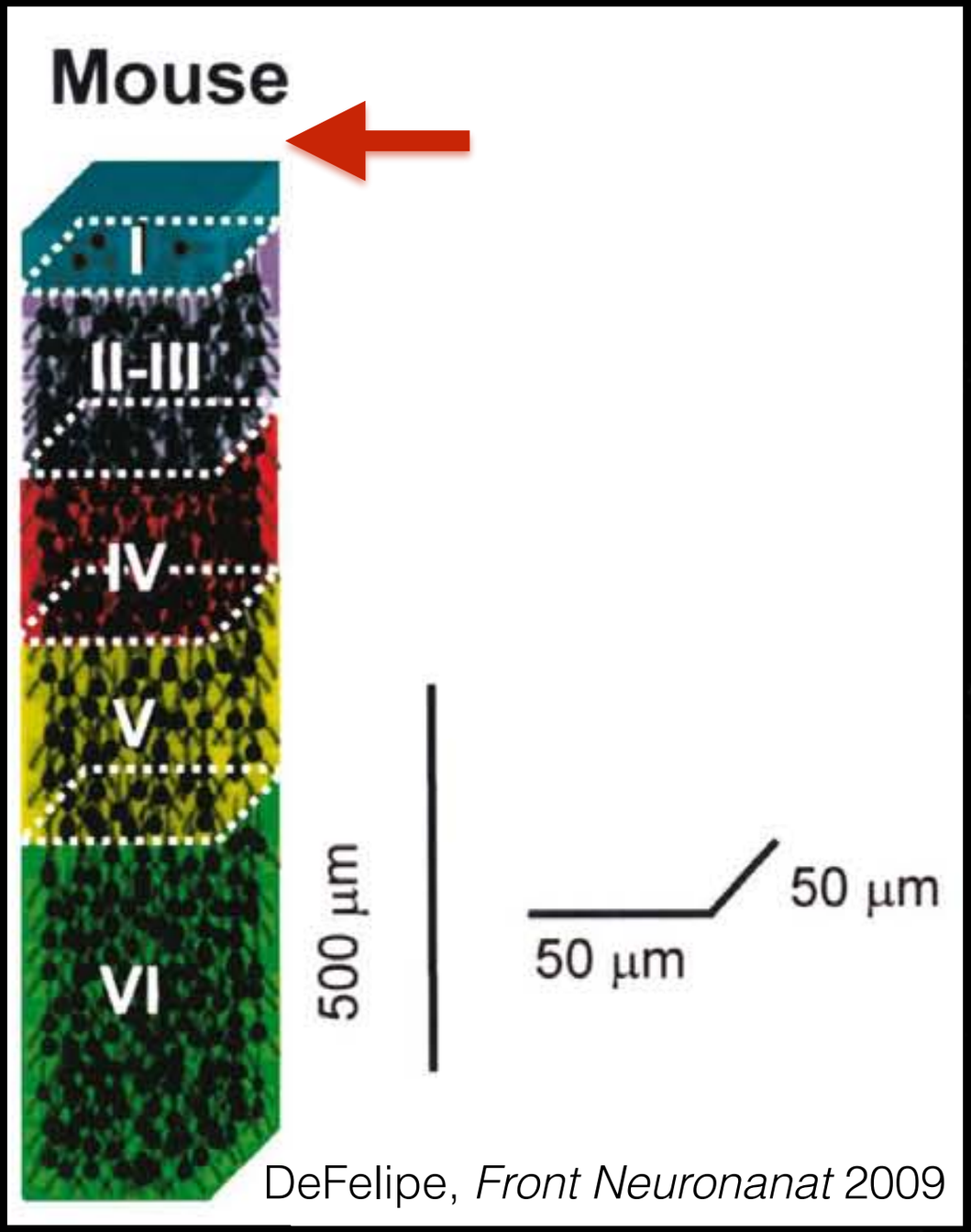

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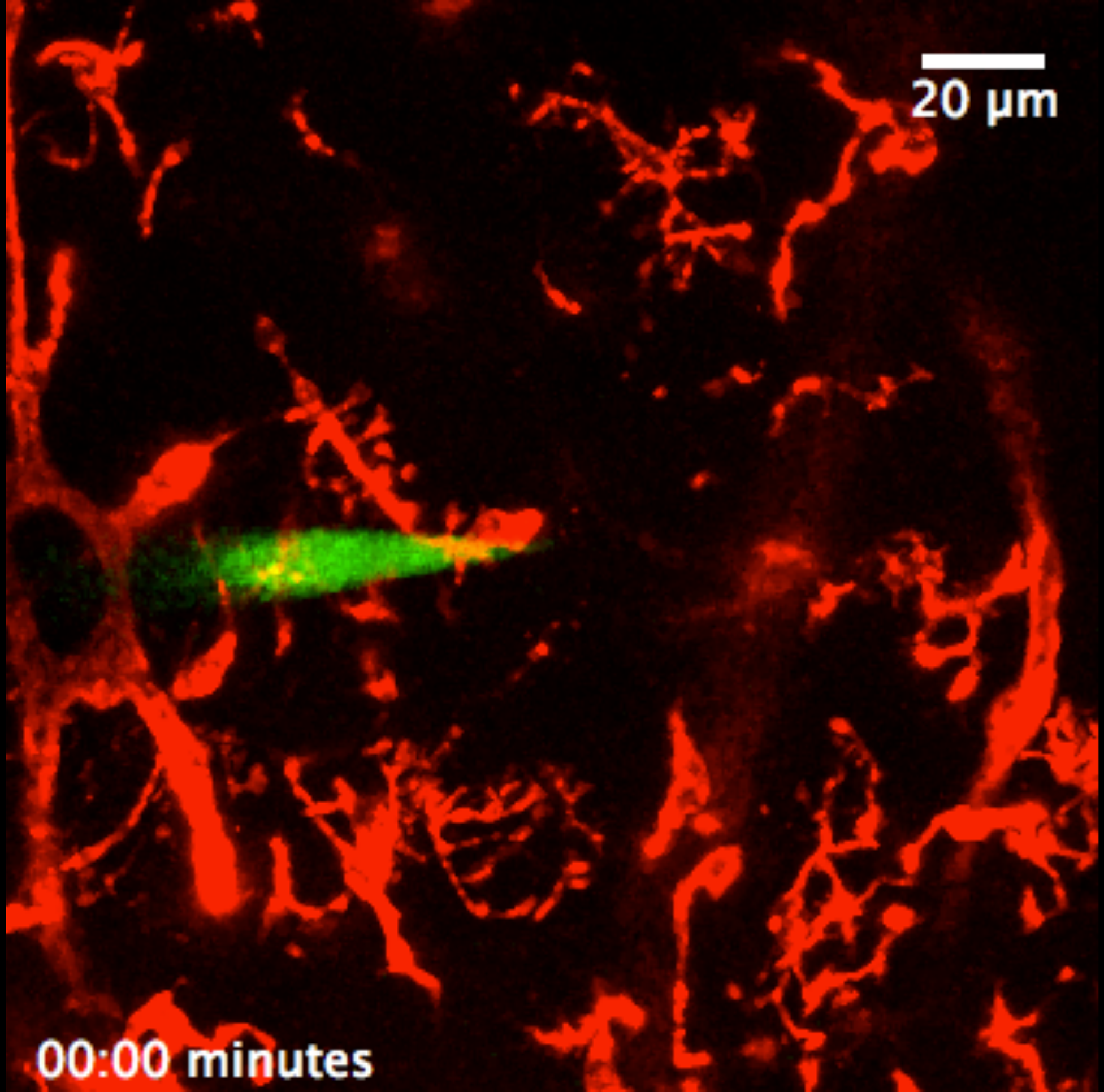
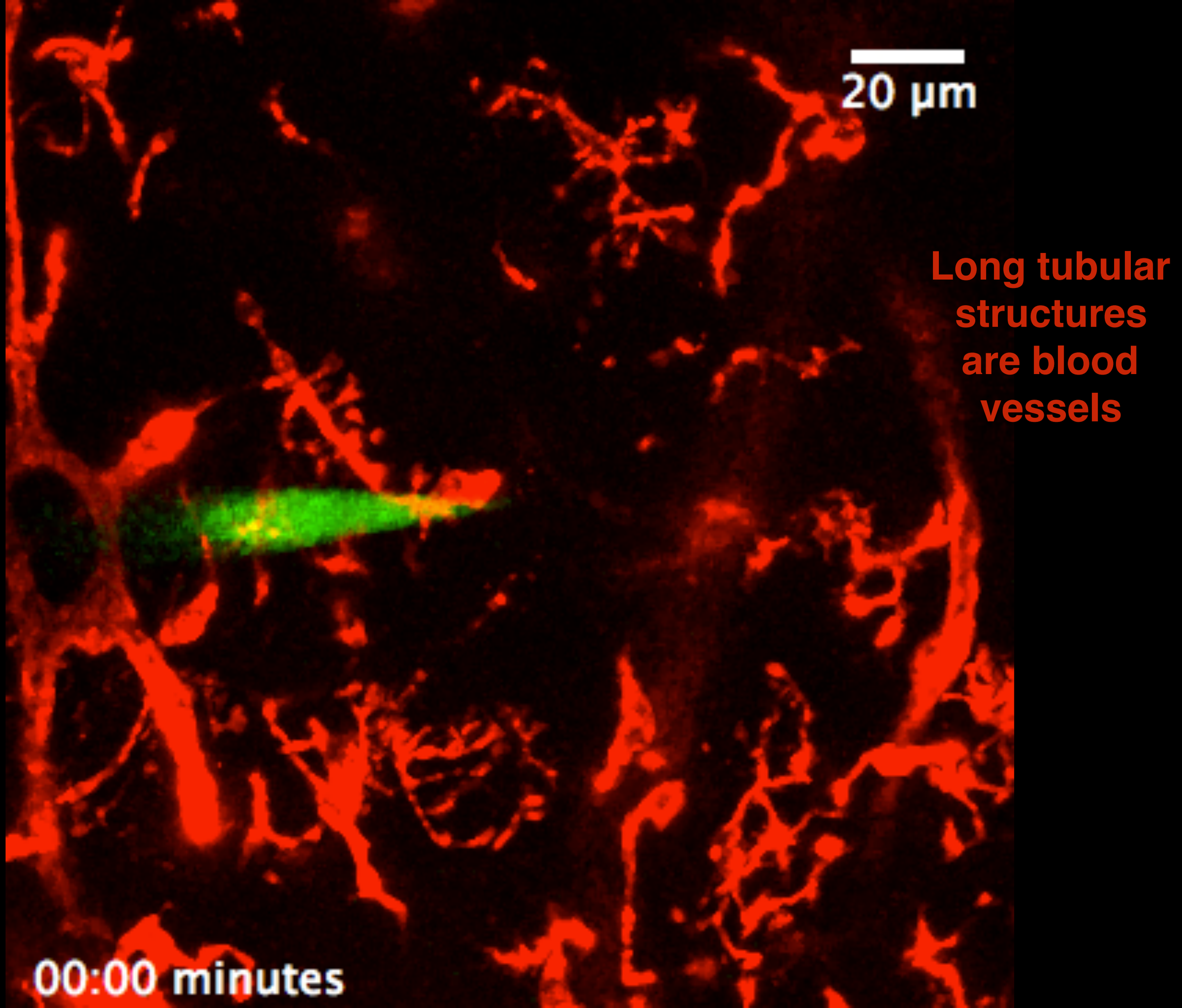
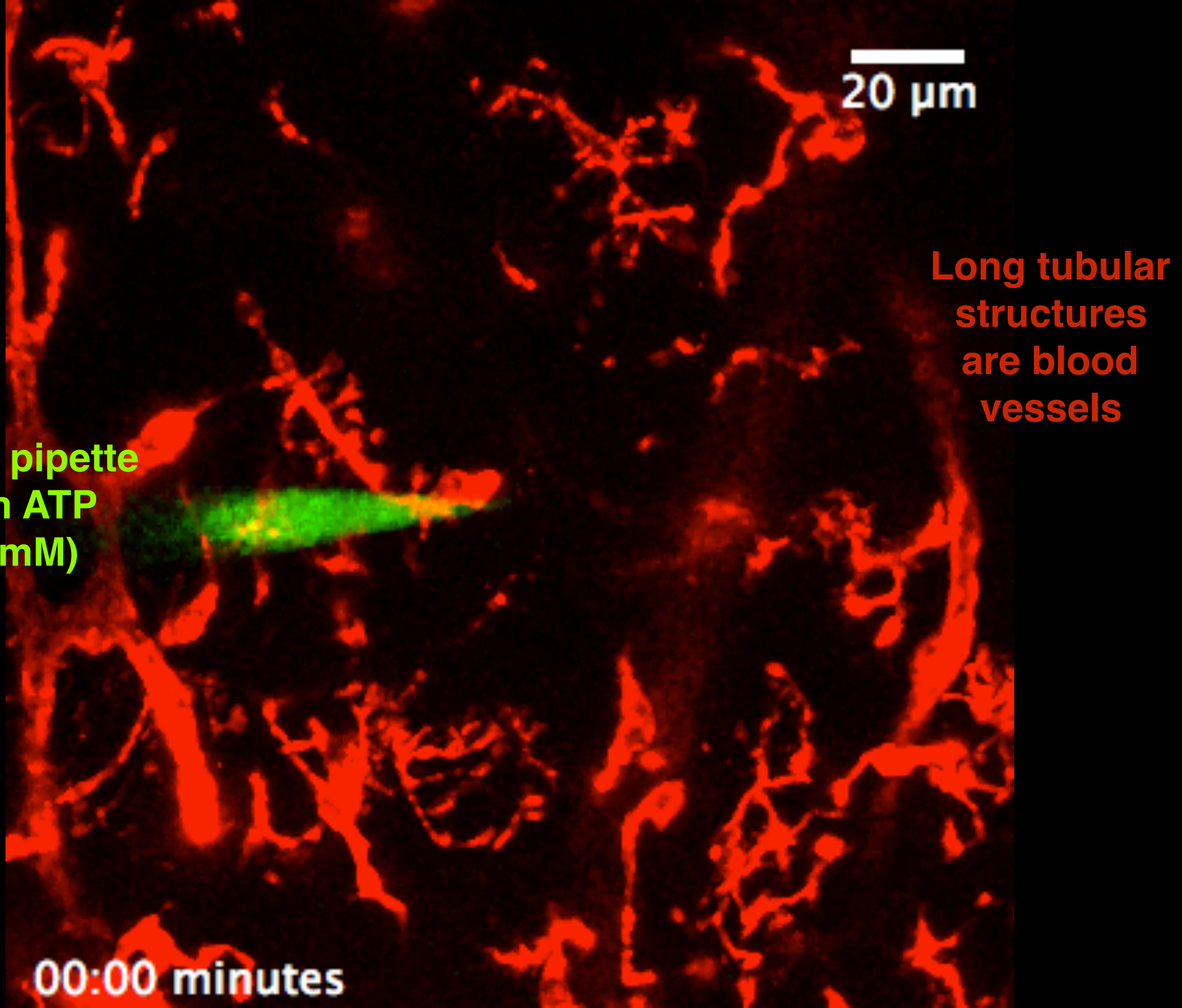

20 µm
00:00 minutes


20 µm
Long tubular structures are blood vessels
00:00 minutes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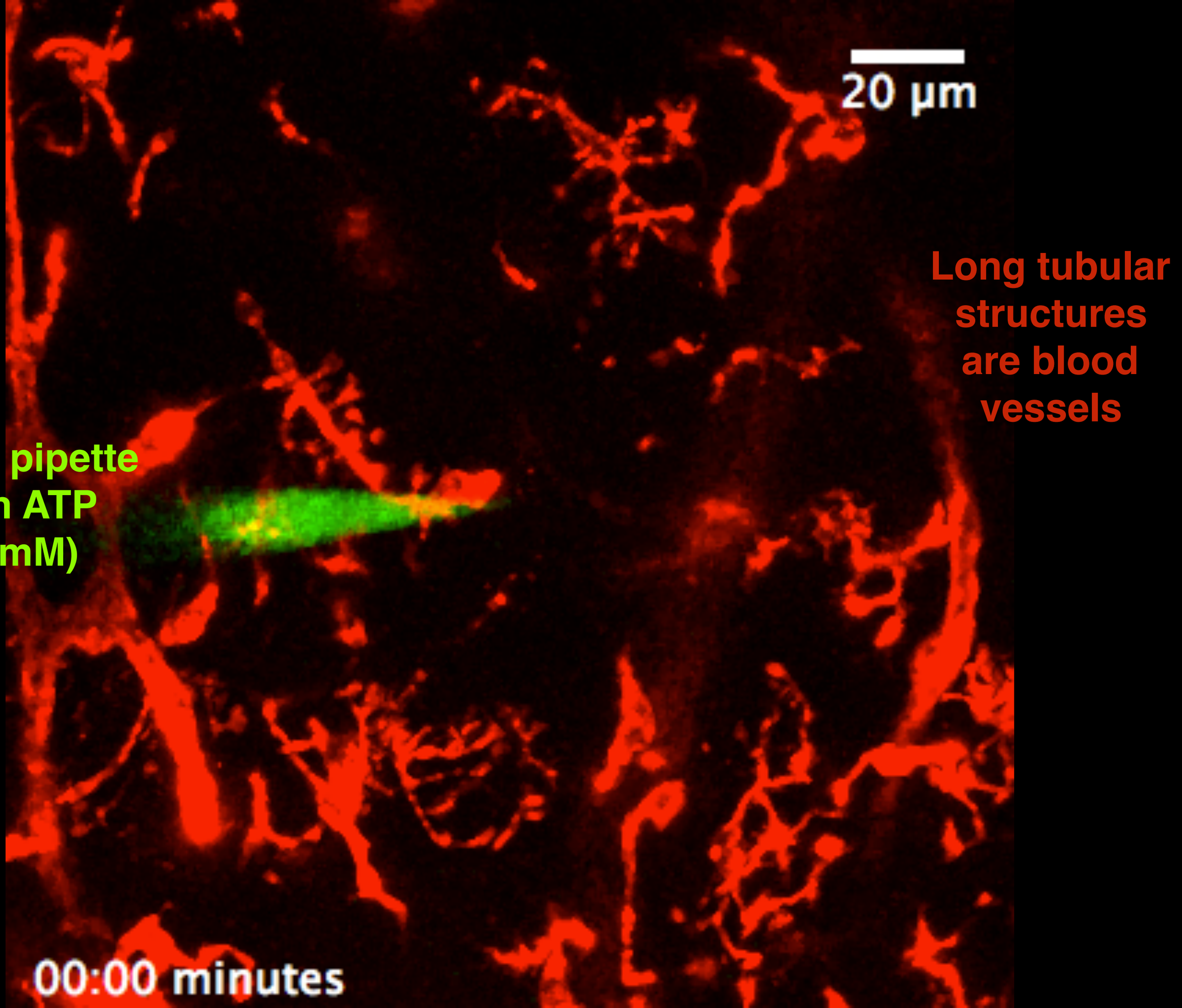
Long tubular structures are blood vessels
Glass pipette with ATP (1 mM)
00:00 minutes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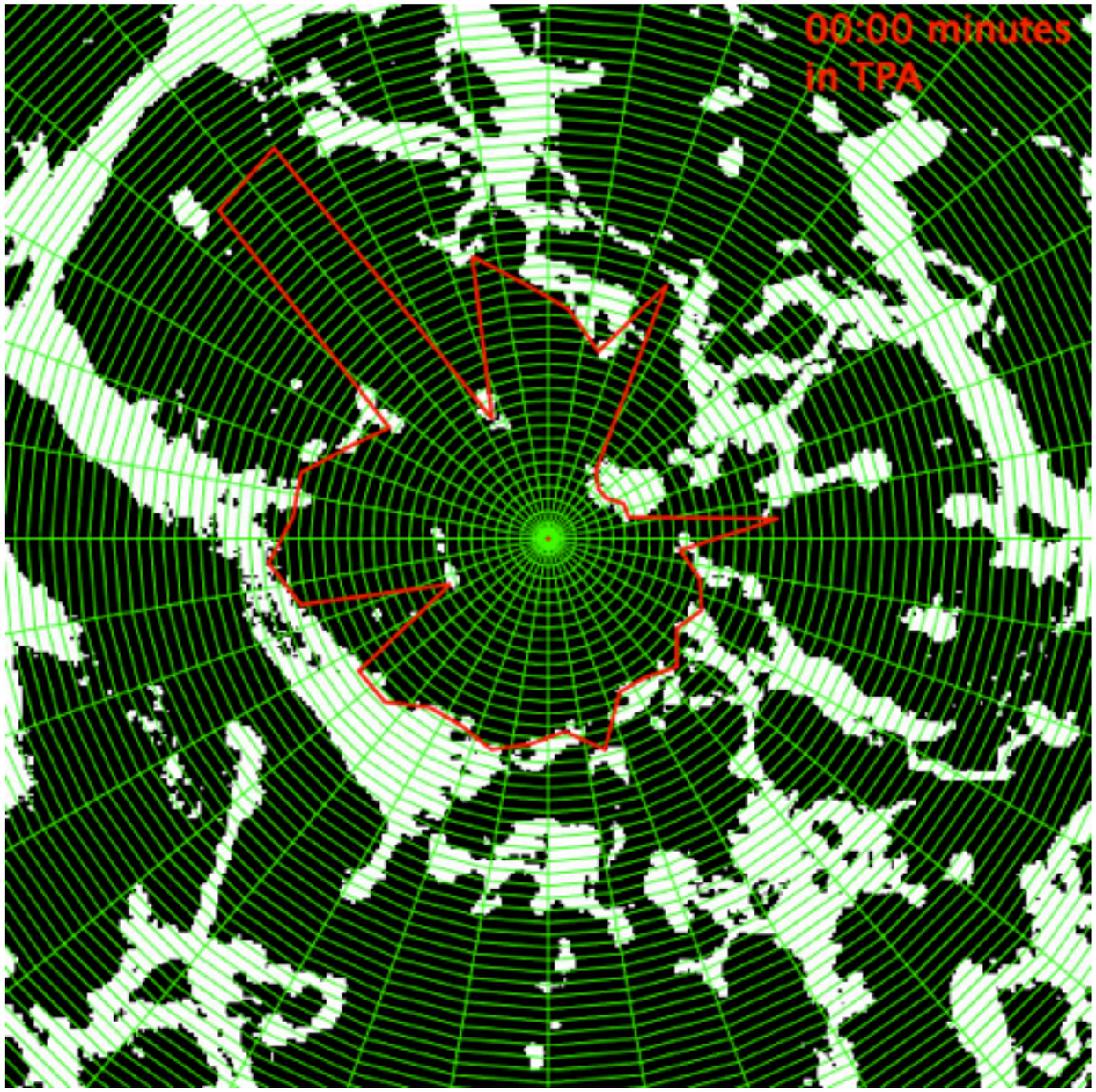
ATP, the energy currency of cells, mediates the response of the brain's immune cells to acute damage



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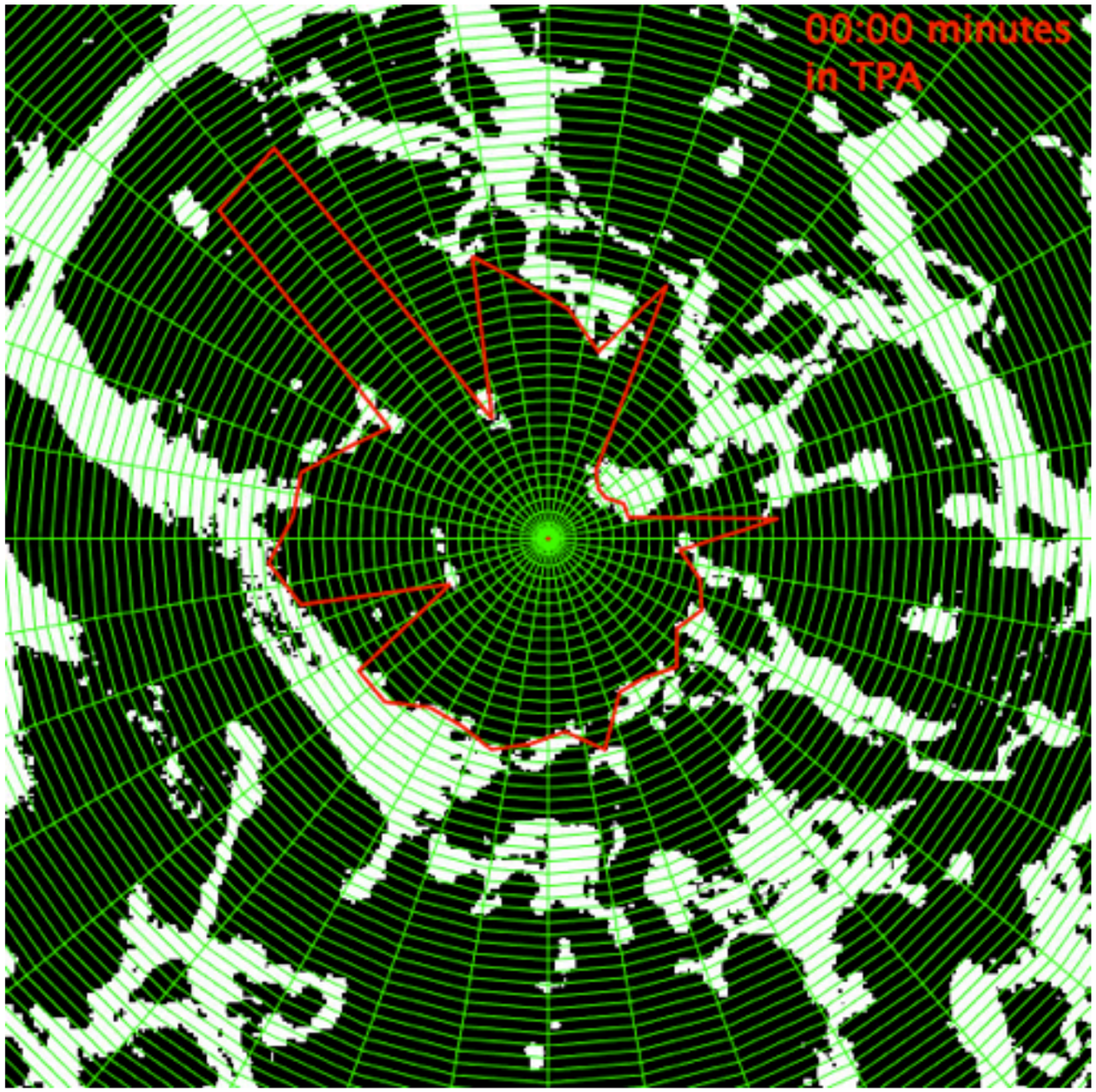

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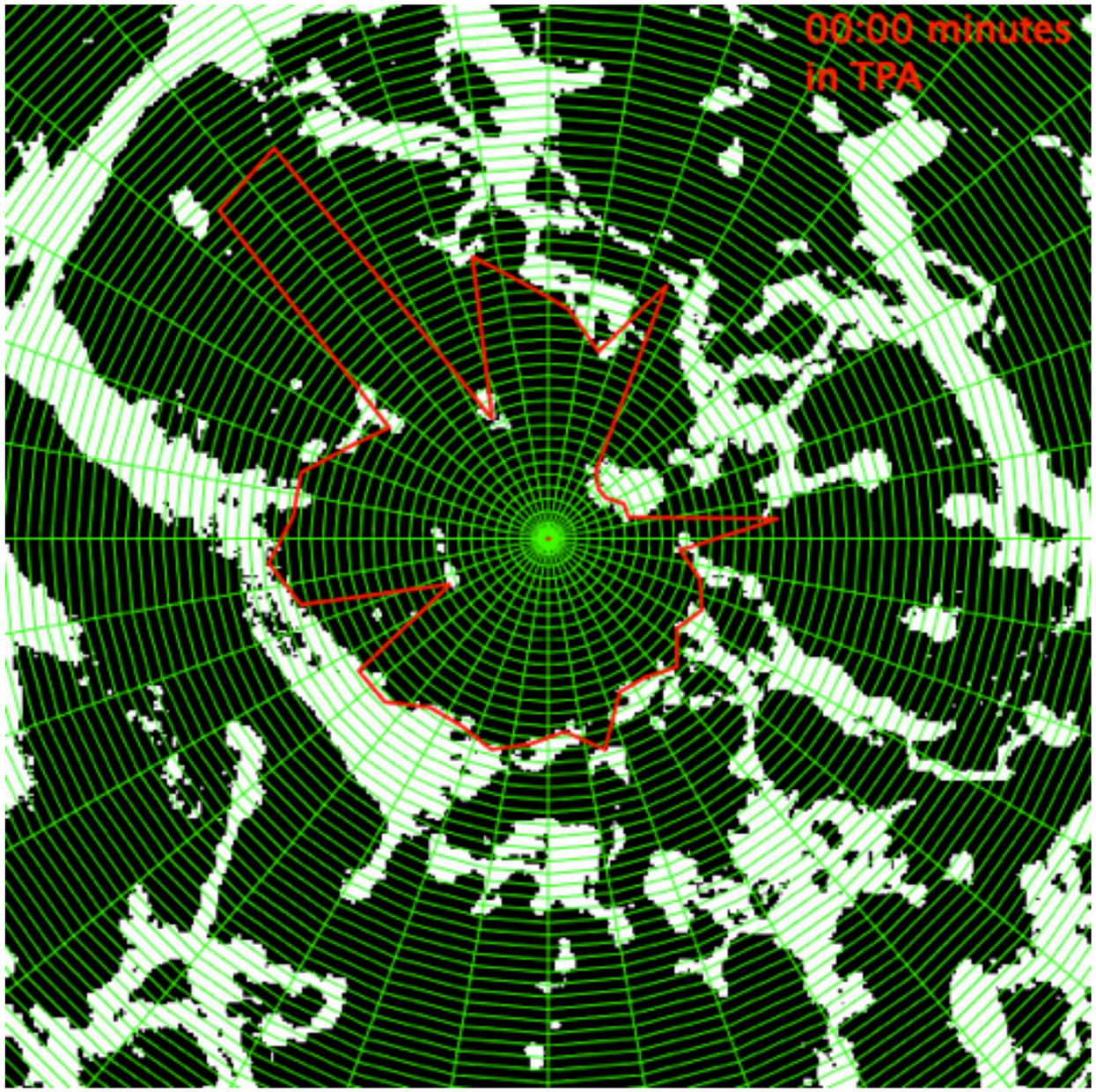

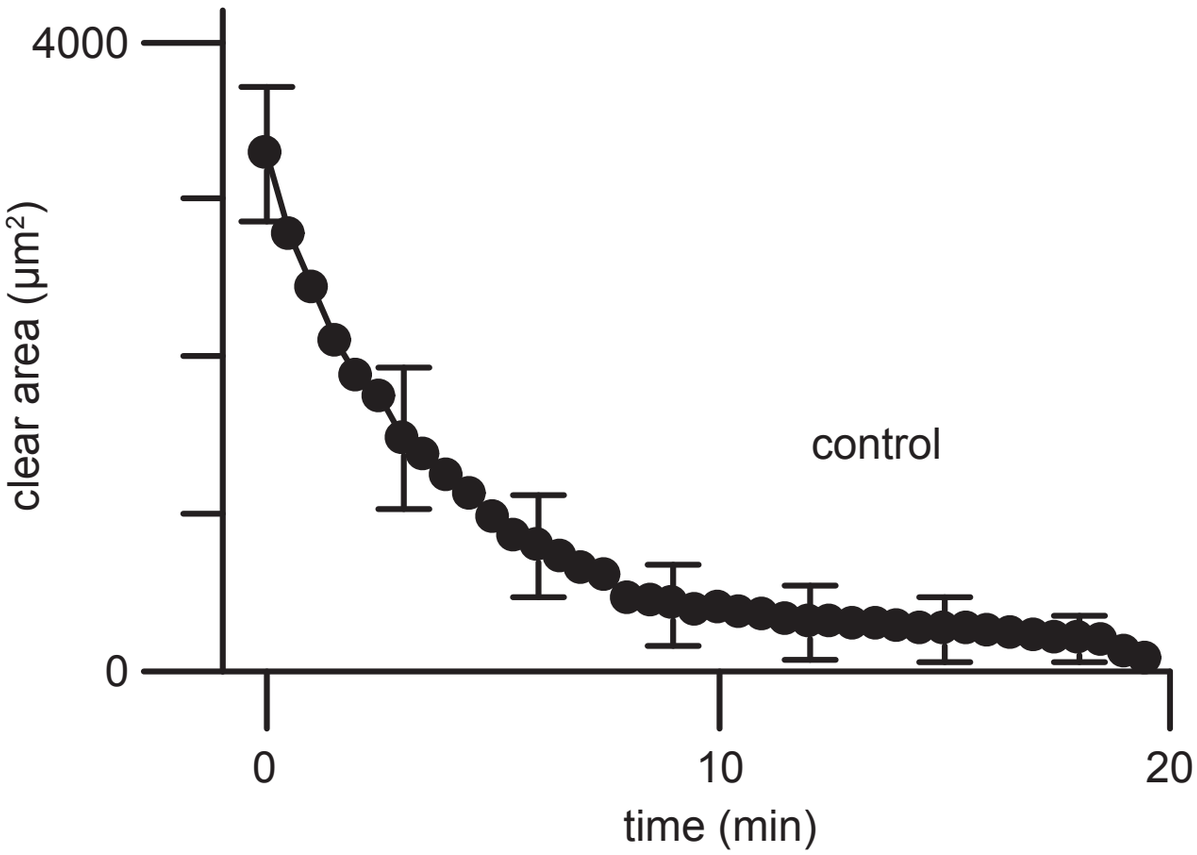

Haynes et al., *Nat Neurosci* 2006
Madry*, Jolivet* et al., *in revision*

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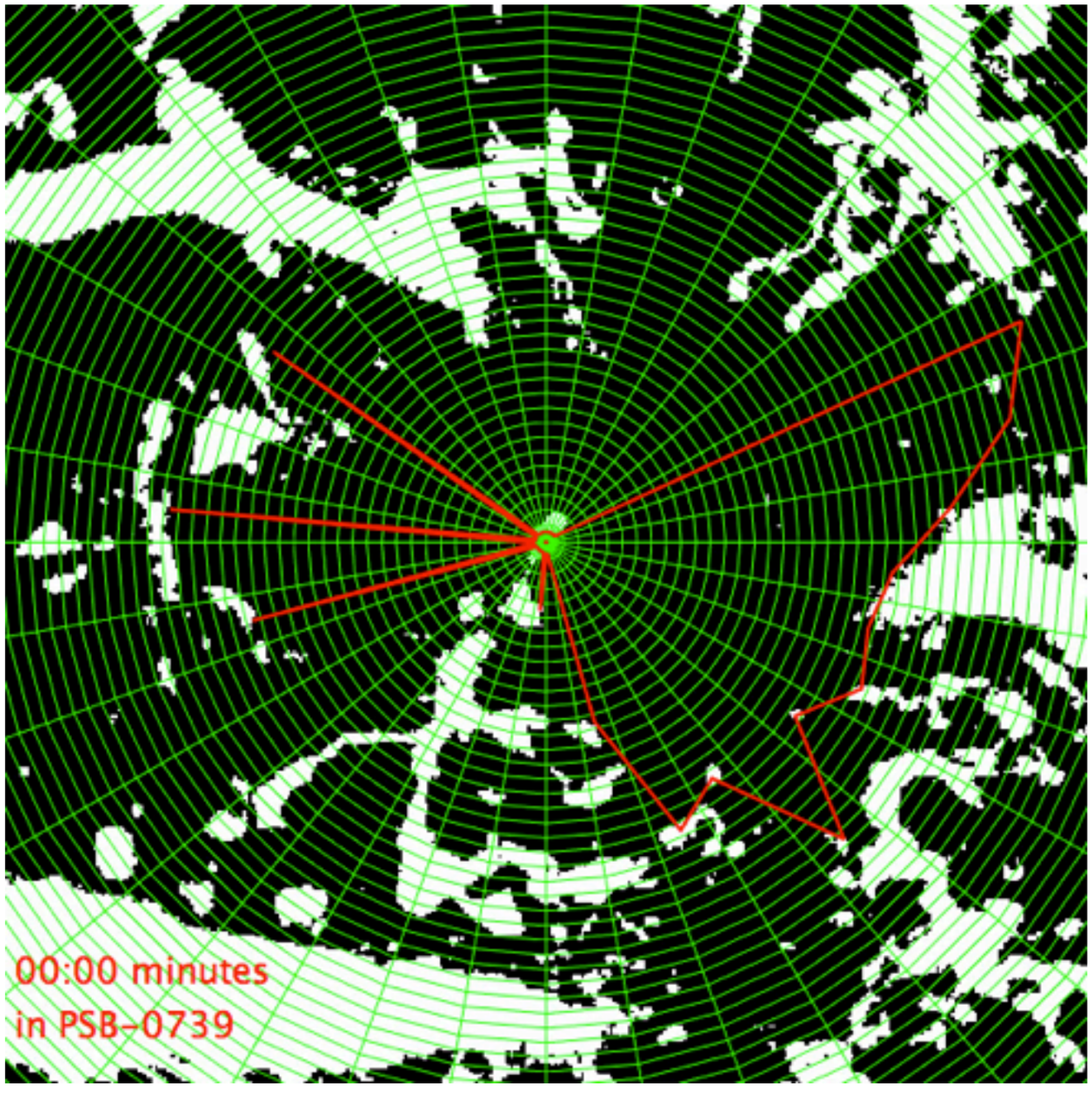
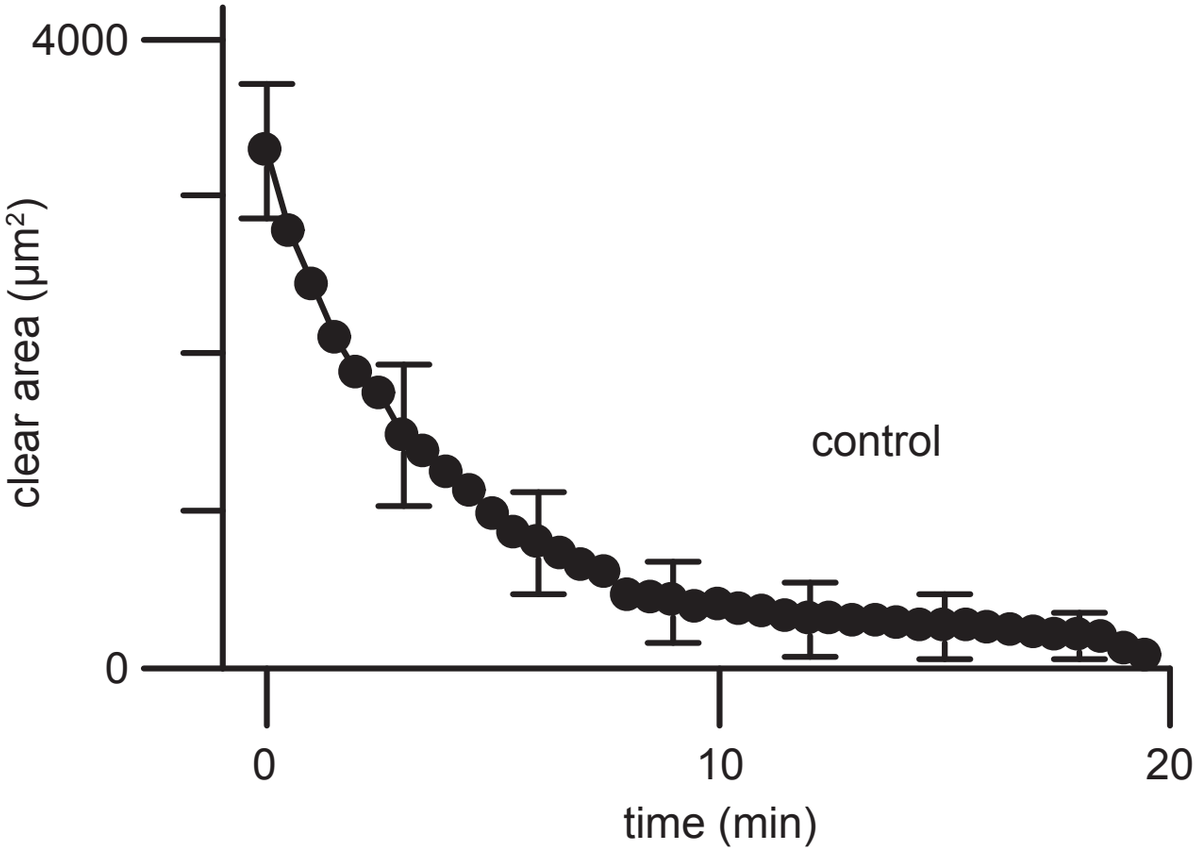


Block receptors for ATP (P2Y12)



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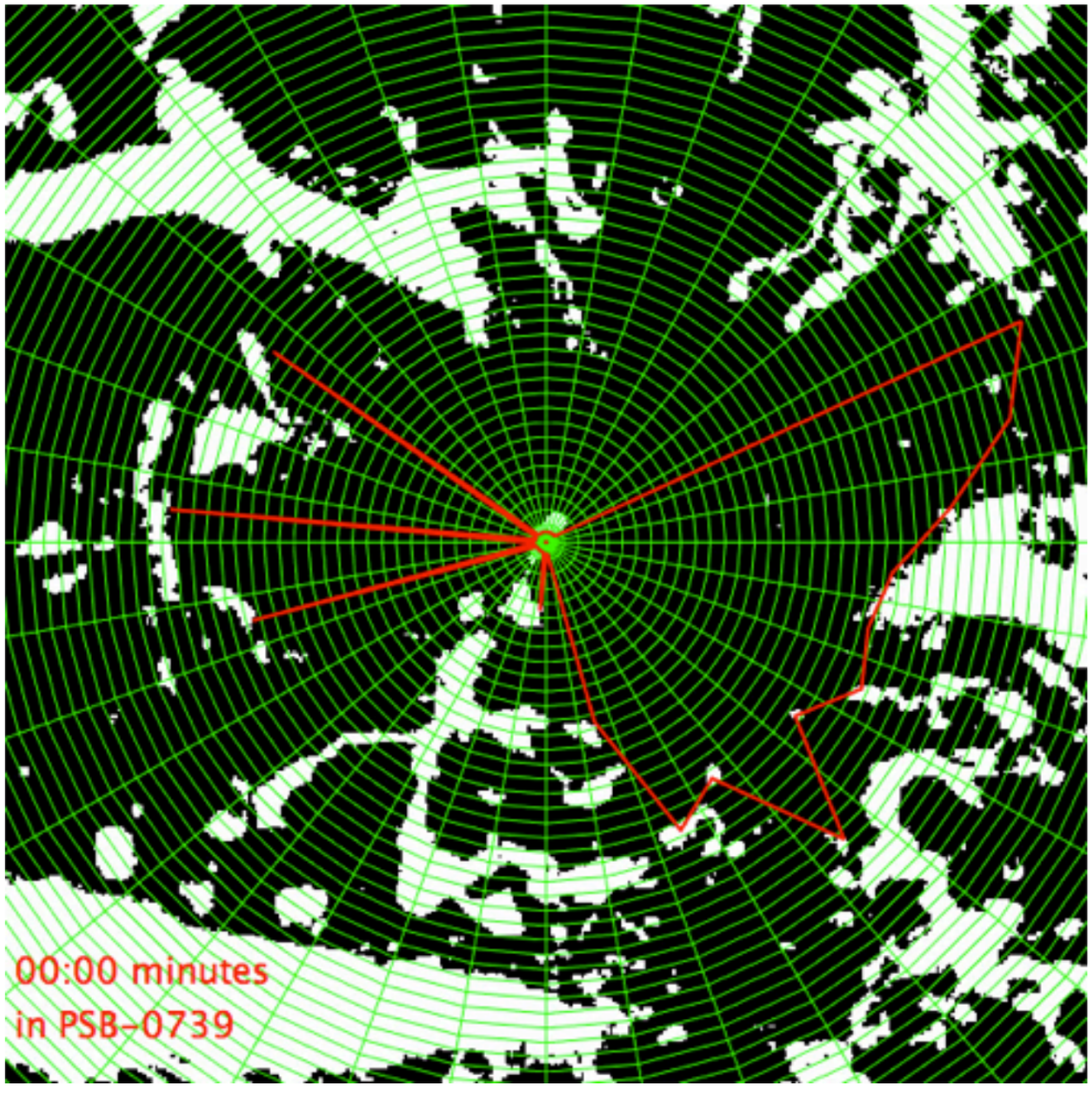

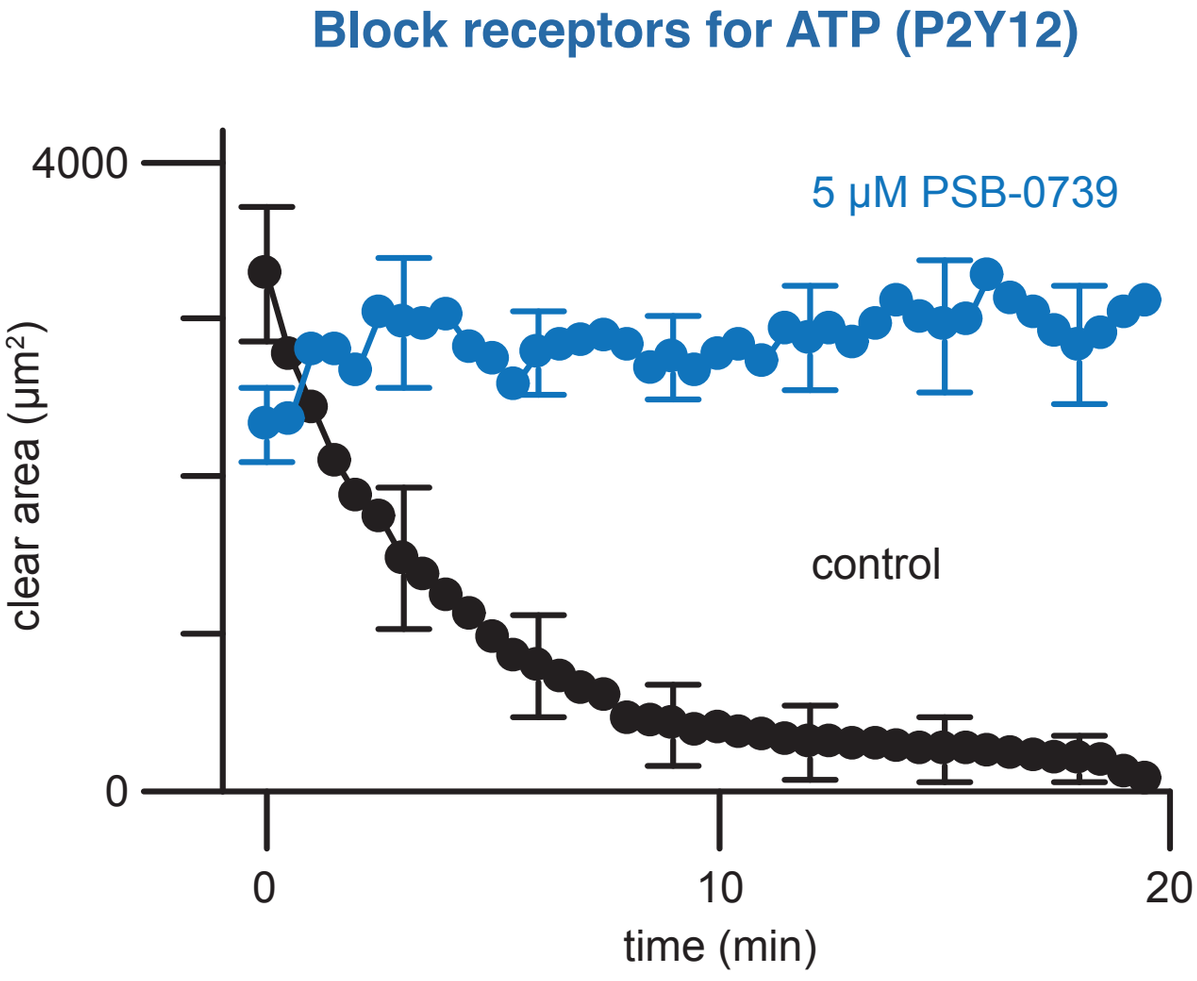

Haynes et al., *Nat Neurosci* 2006
Madry*, Jolivet* et al., *in revision*

Baseline immune surveillance of the brain

Data | Binarized image | Cumulative image

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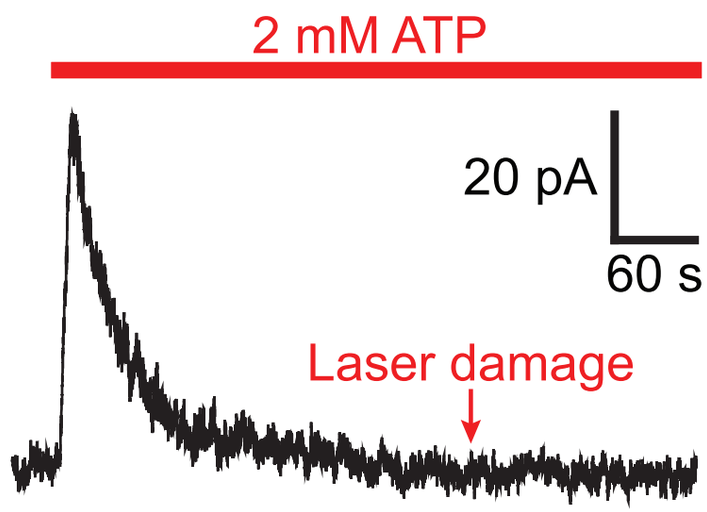
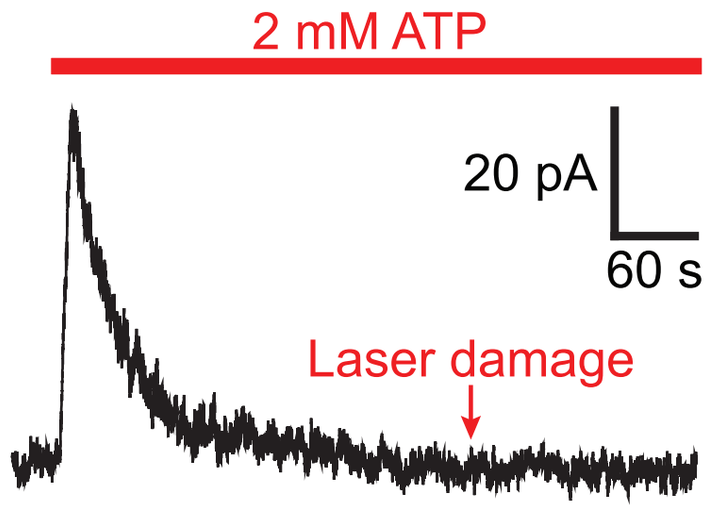
ATP, the energy currency of cells, triggers a potassium current in the brain's immune cells



ATP, the energy currency of cells, triggers a potassium current in the brain's immune cells

This is a small potassium current across the membrane



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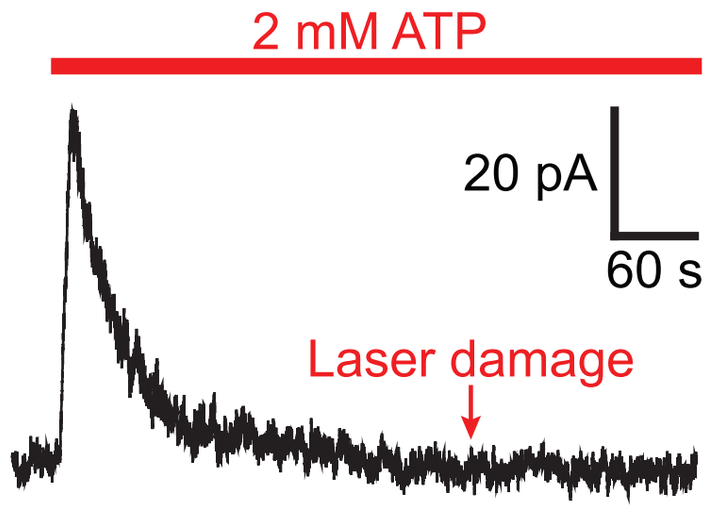

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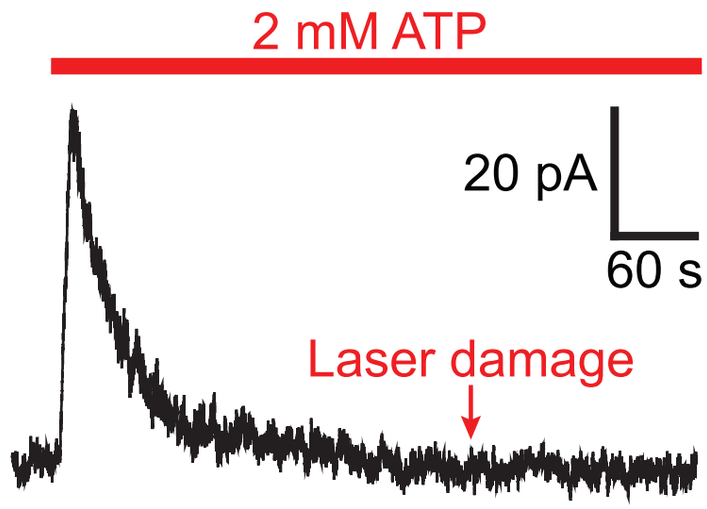

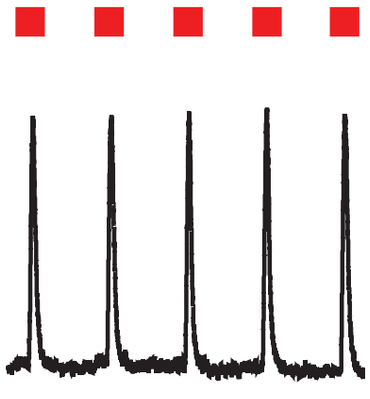

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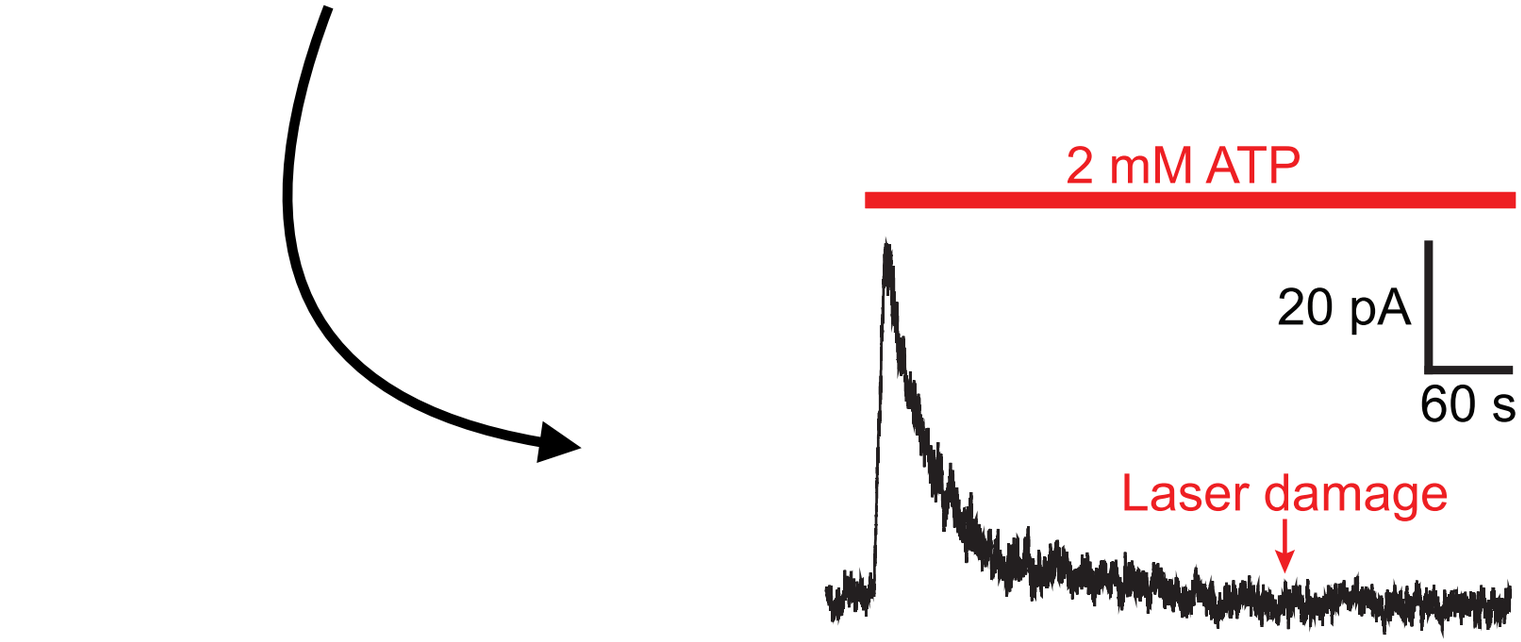

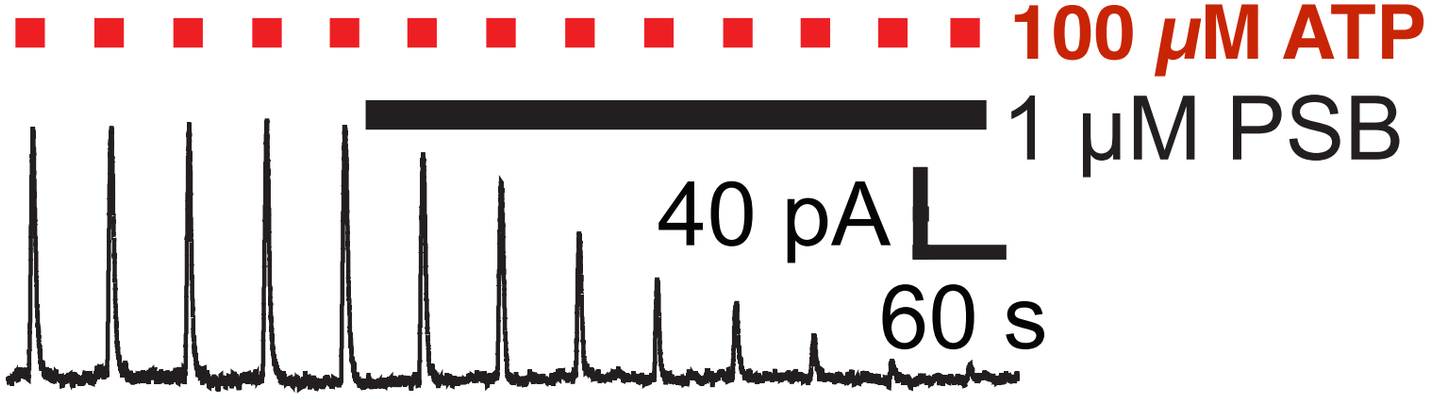

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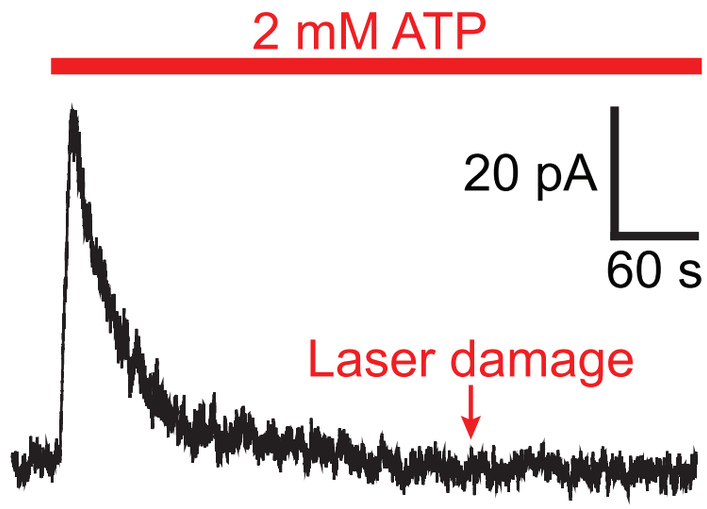
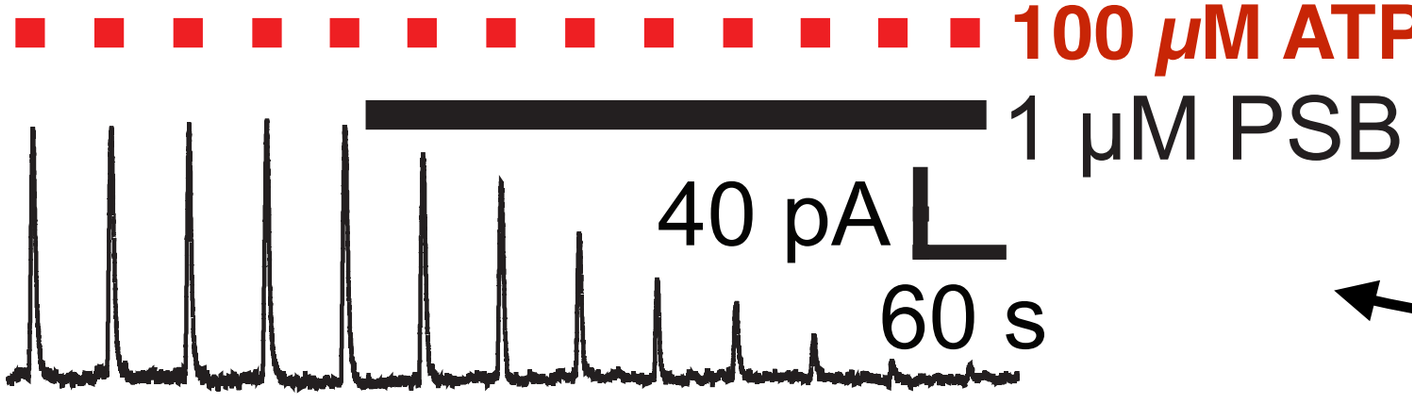


It is mediated by the same receptor than the centripetal movement of the cells



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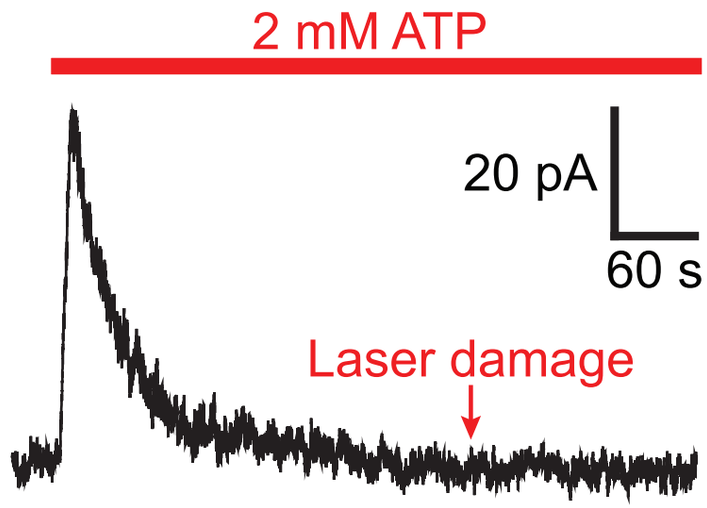

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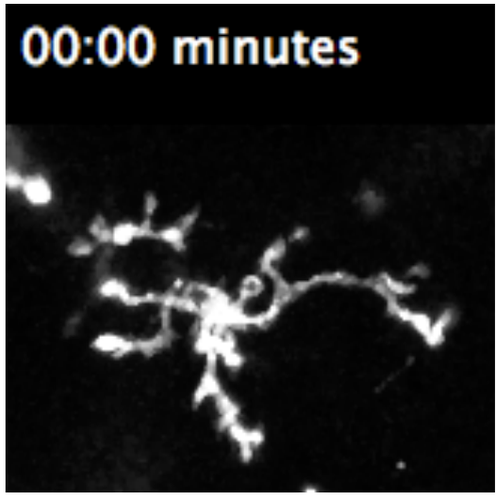

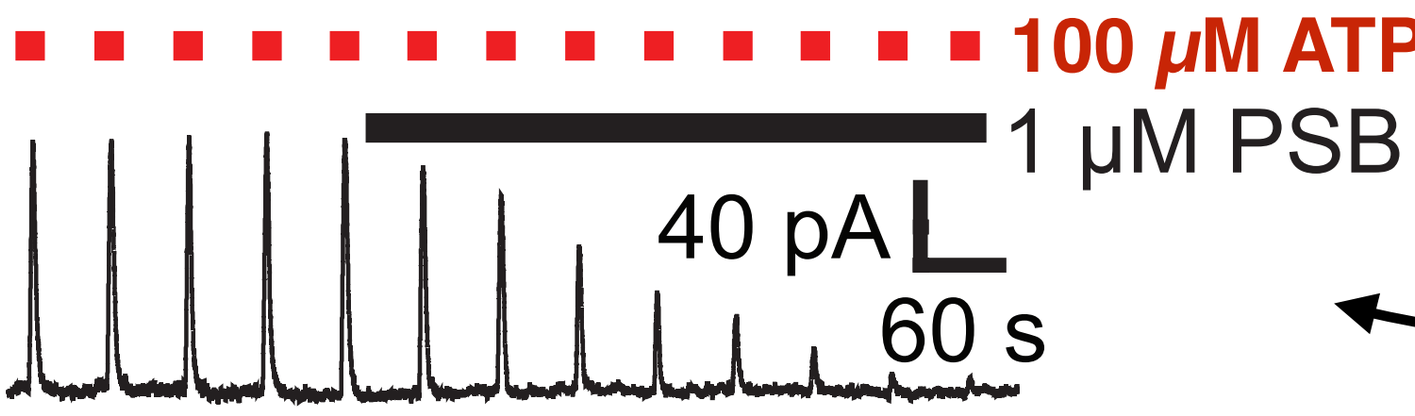

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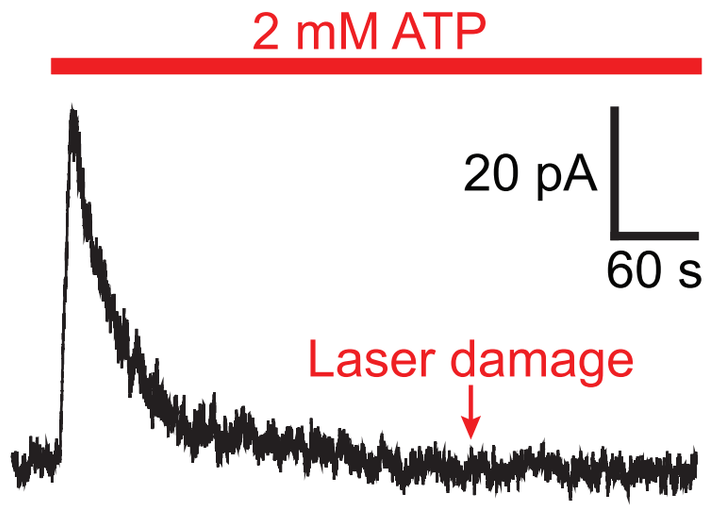

This current is mediated by a two-pore-domain potassium channel called THIK-1 (TWIK-related halothane-inhibitable K^+ channel-1)

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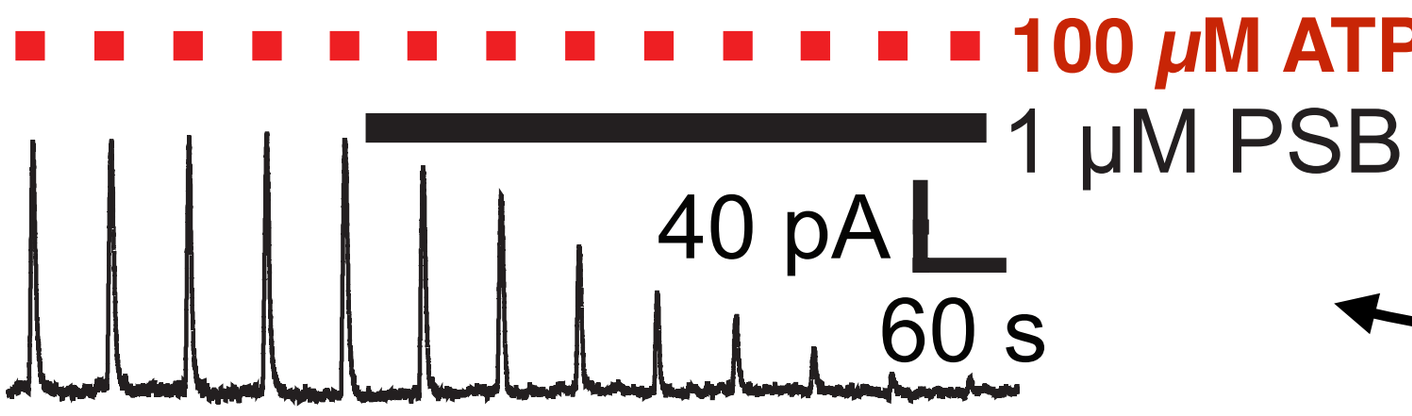
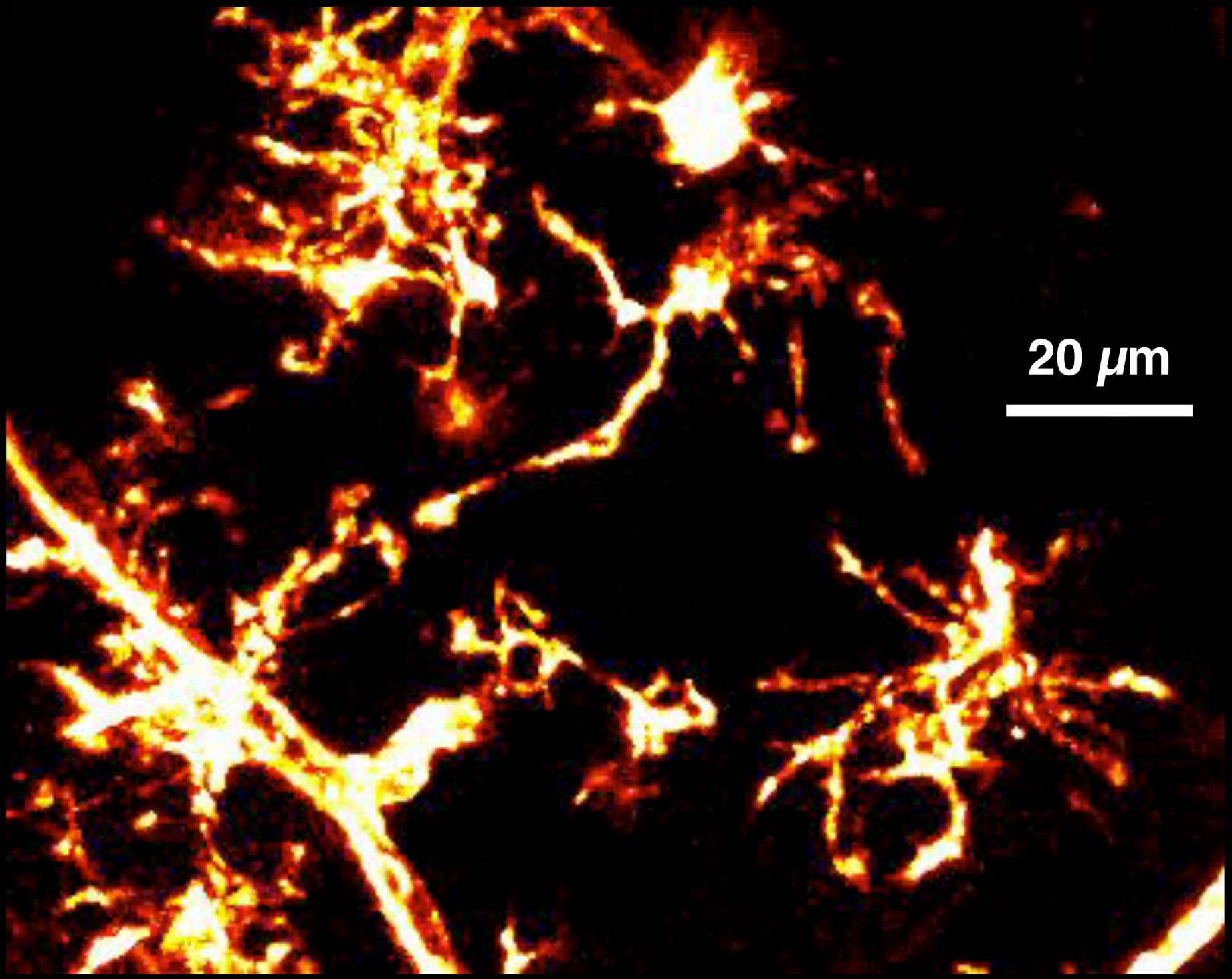


Isoflurane reversibly inhibits microglial resting surveillance and triggers deramification



Rat P12 hippocampal slice; 100 minutes; Isoflurane applied at saturating concentration for 20 minutes;

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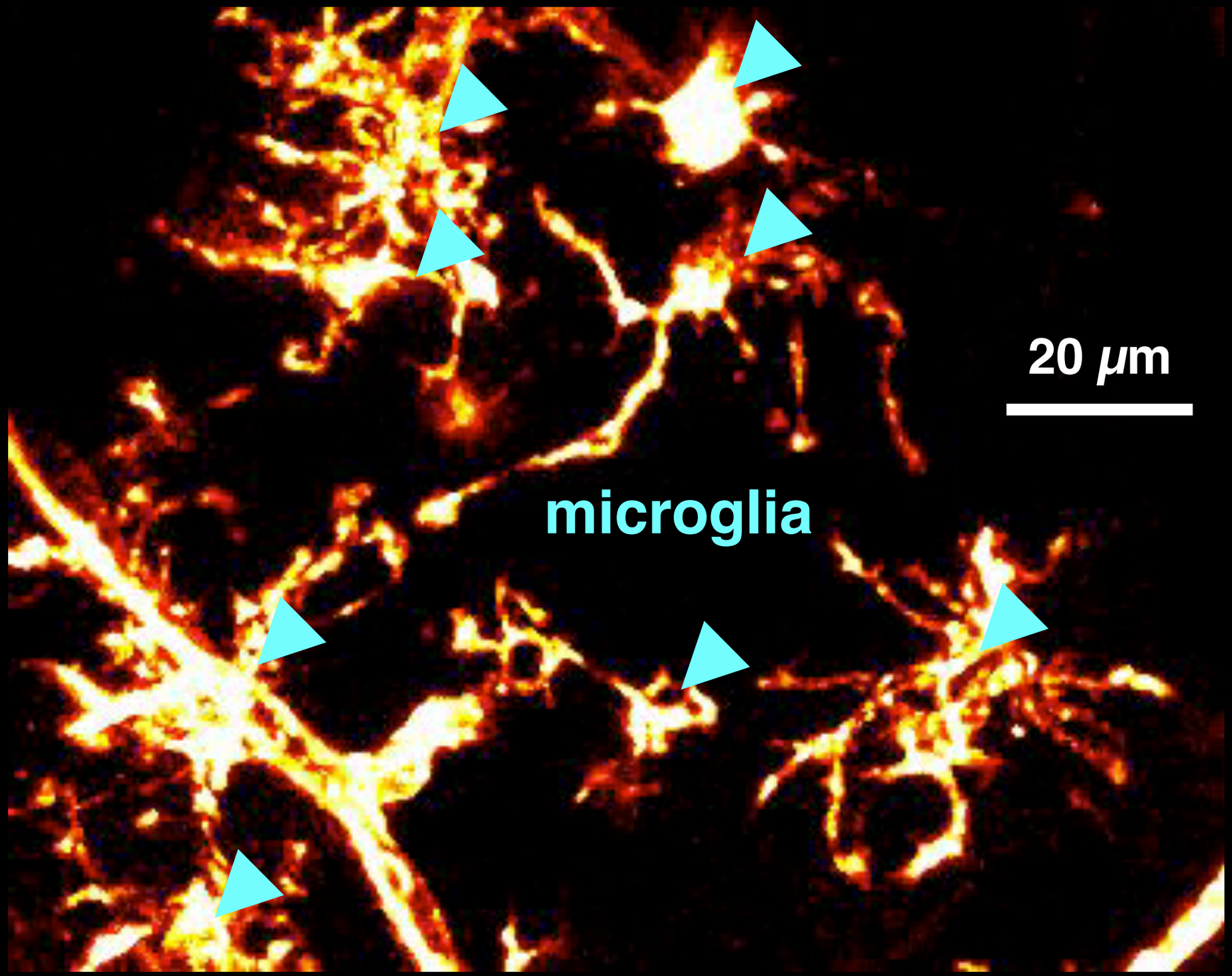

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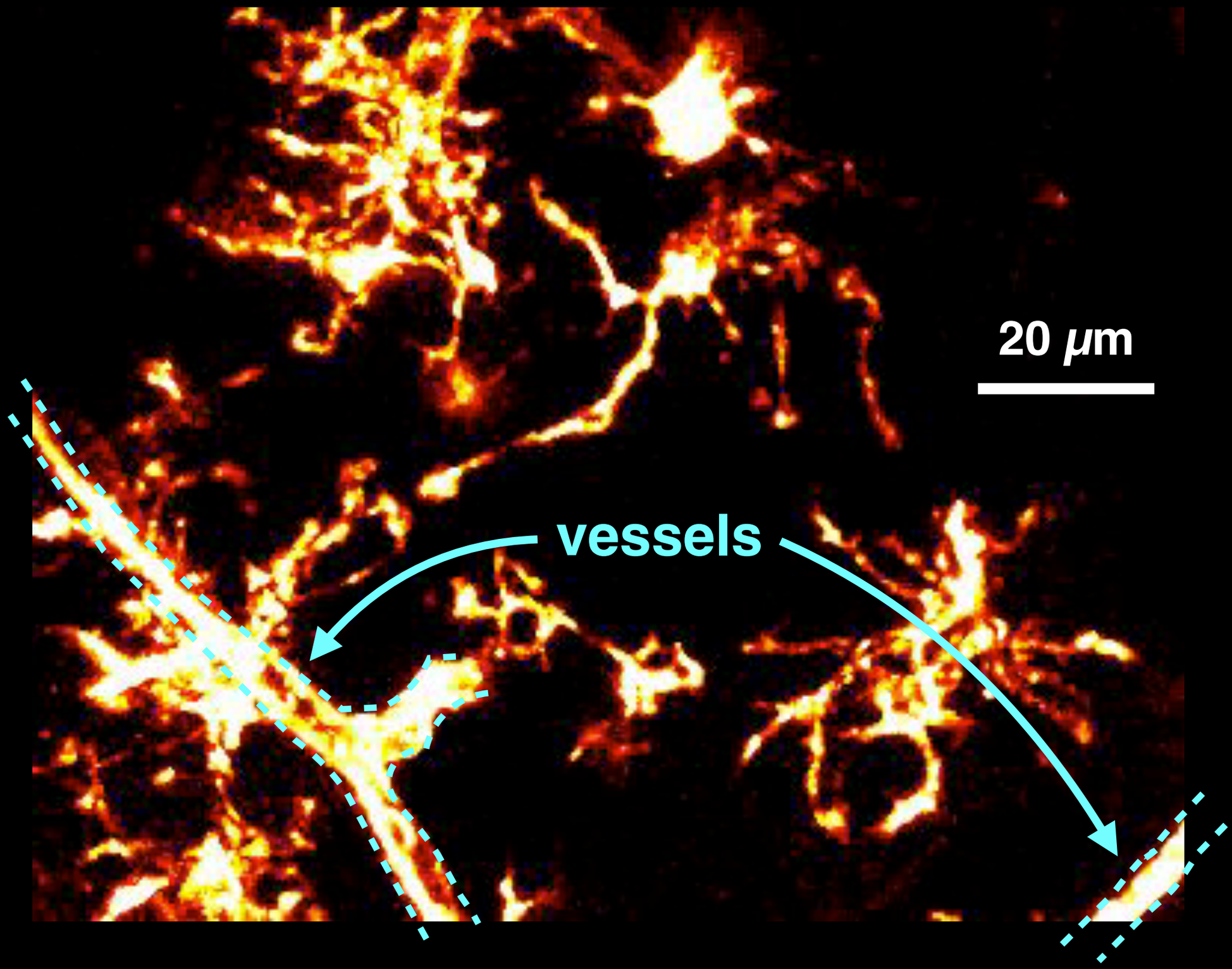

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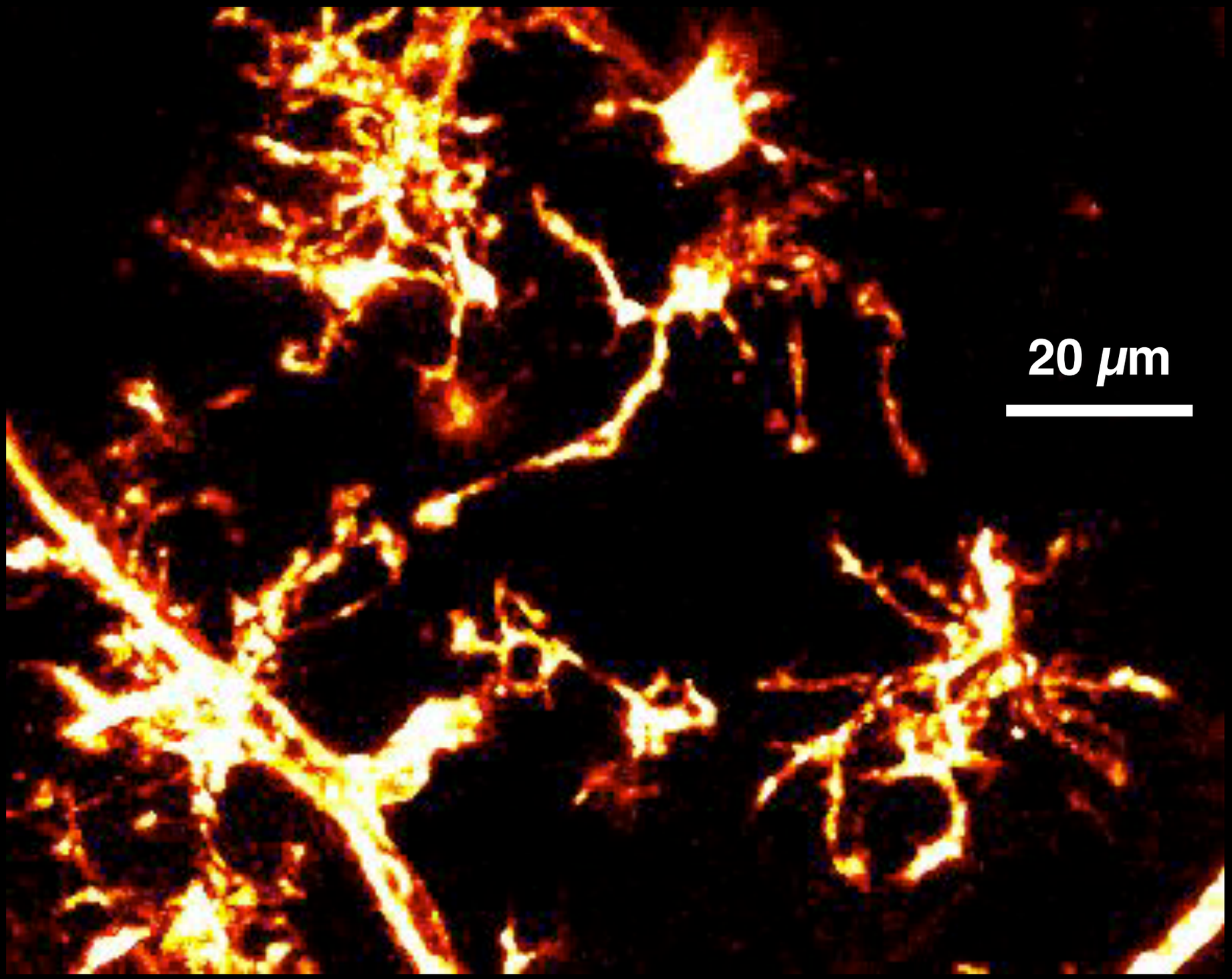

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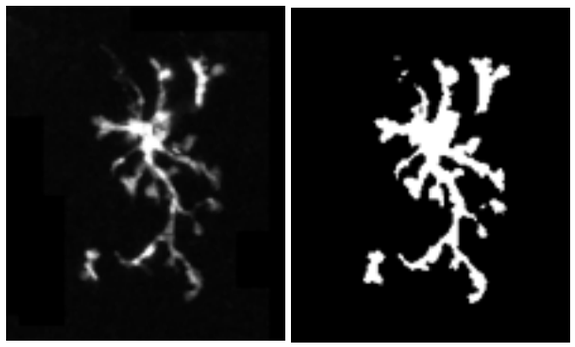
Blocking this potassium channel abolishes the baseline immune surveillance of the brain



initial image

thresholded image

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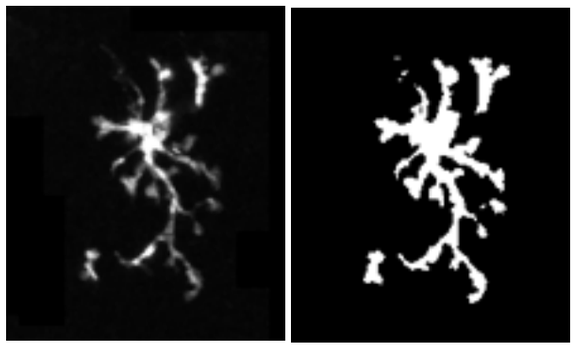

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- Motility: processes extensions + retractions (normalised by the cell area).

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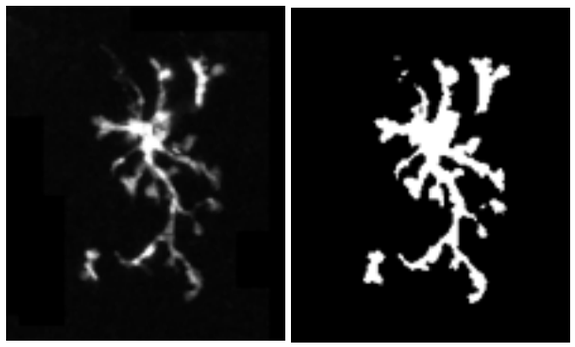

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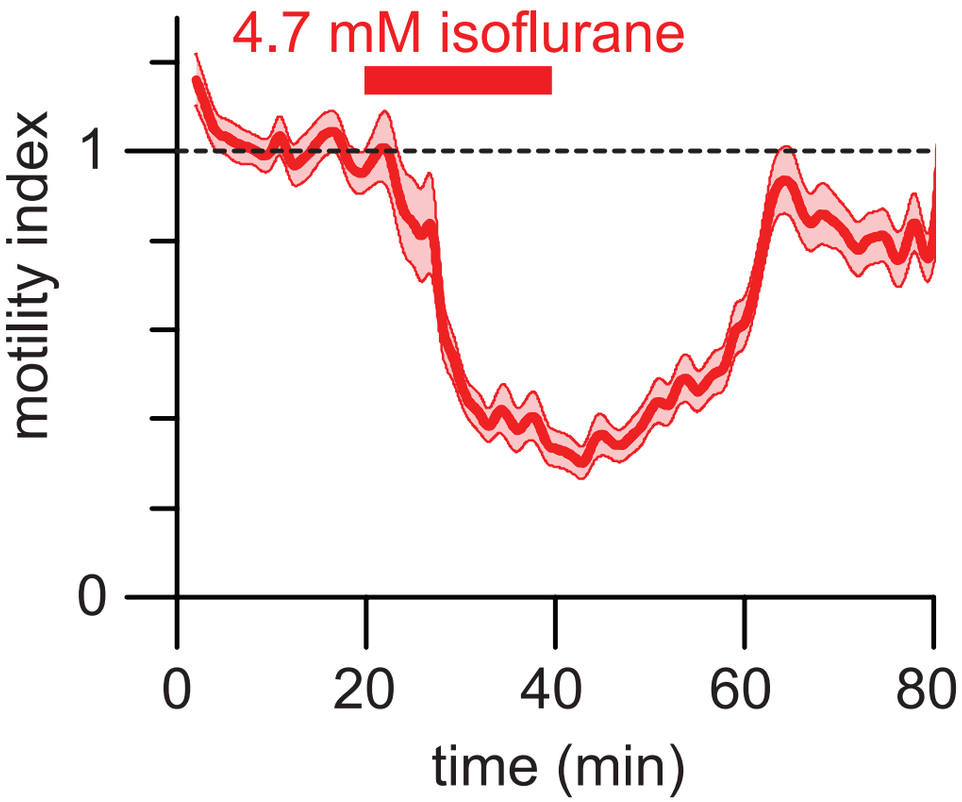

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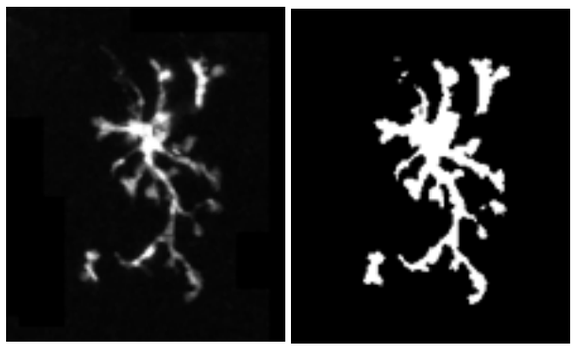

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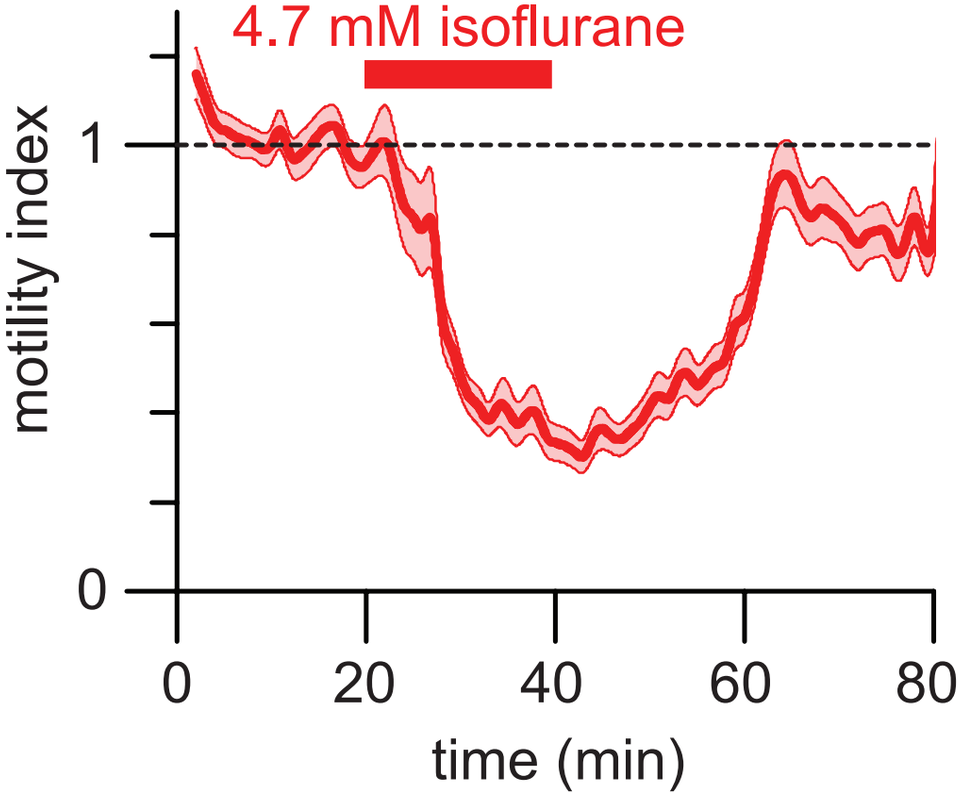

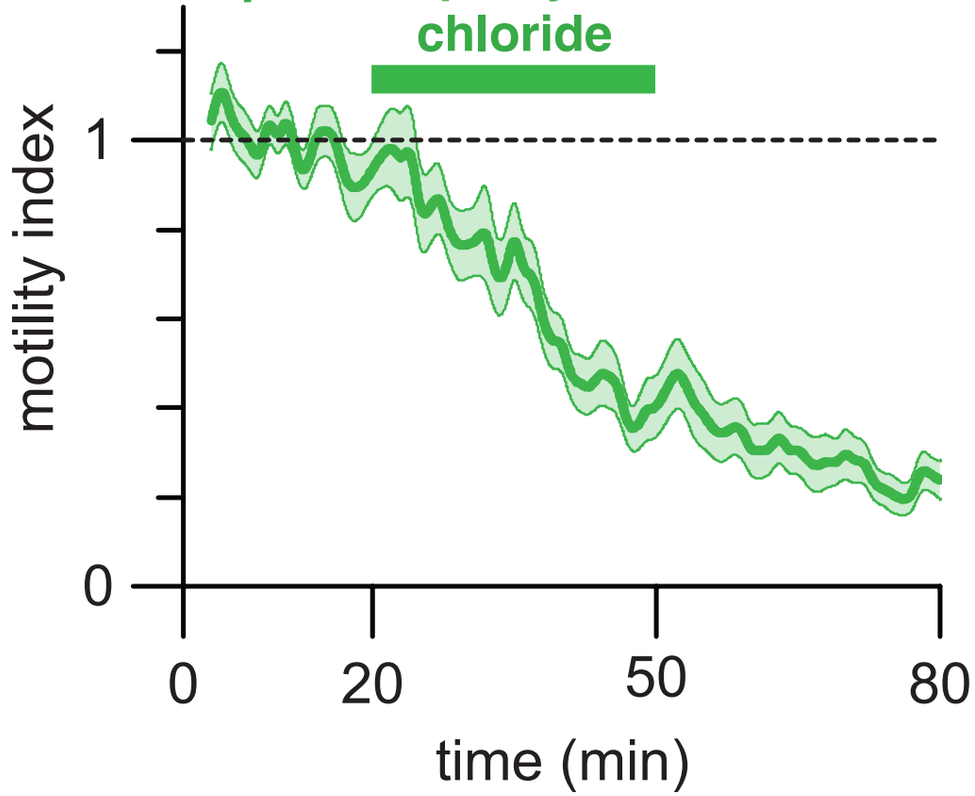

Madry*, Jolivet* et al., *in revision*

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- We have identified one of the components of the machinery that controls the baseline immune surveillance of the brain.

- Immune surveillance of the brain might be compromised during surgeries using volatile anaesthetics and in ageing.

Outline

- Neuroenergetics
- Energy as a constraint on brain function
- Energy as a signal for the brain's immune system
- CERN as a model for the neurosciences

Acknowledgments

@ KAUST, Saudi Arabia

Pierre Magistretti

@ EPFL, Switzerland

Igor Allaman

@ University of Zurich, Switzerland

Bruno Weber

@ University College London, UK

David Attwell
Lorena Arancibia Carcamo
Elisabeth Engl
Vasiliki Kyrargyri
Christian Madry

@ Imperial College London, UK

Julia Harris

@ National Institute of Neuroscience, Japan

Shinichi Kohsaka

UNIVERSITÉ DE GENÈVE

FACULTÉ DES SCIENCES

Thank you for your attention!