

LECTURE 22:

Modeling Neuron-Glia Interactions 1

Marja-Leena Linne

Tampere University

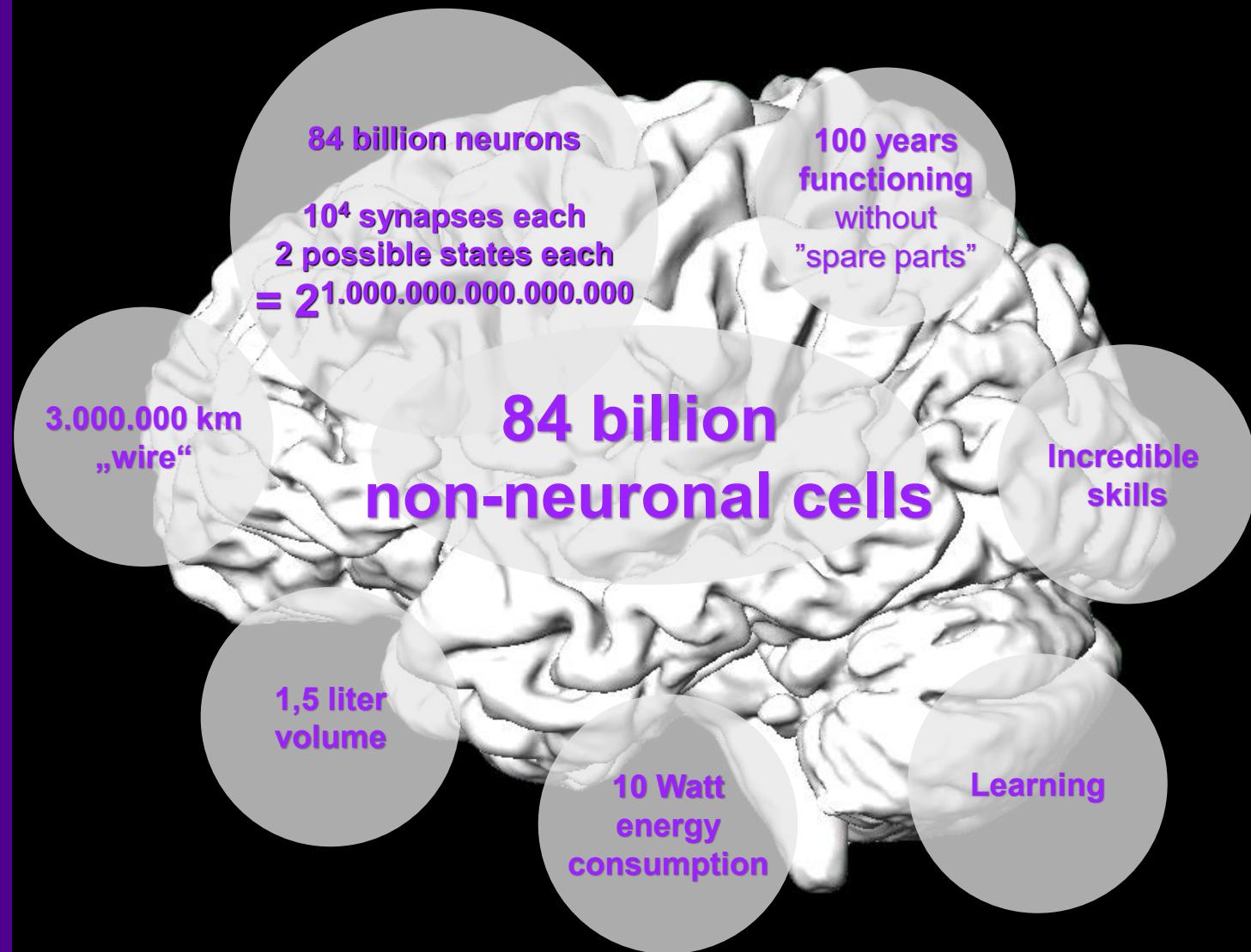
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<https://research.tuni.fi/computational-neuroscience/>



LASCON X: Three lectures and one tutorial

1. **Modeling Neuron-Glia Interactions 1: Biology of the Glial Cells & Background to Modeling**
2. Modeling Neuron-Glia Interactions 2: Modeling Single Cells
3. Modeling Neuron-Glia Interactions 3: Modeling Networks with Neuron-Glia Interactions
4. Tutorial: NEST Astrocyte Modeling Tool

From physics and electrical engineering to neuroscience

Studies (1990s):



Master of Science (Tech), Physics/Electrical Engineering

Work in medical technology

Neurobiology studies in Finland and abroad (FI, BE, IT, US)

Doctor of Science (Tech), Computer Science & Neuroscience (2001)

Research group leader (2004-):



Academy Research Fellow (2004–)

Docent, Signal Processing (2009); Computational Neuroscience (2016)

Co-PI Centre of Excellence (2004–2010)

Co-PI EU Human Brain Project (2013–2023)



Tampere, Finland

- Tampere is the second-largest urban area in Finland and the **largest inland city** in the Nordic Countries.
- **Tampere University** is the second largest university in Finland.



Tampere city region (Pirkkala, a small town)



October 2023

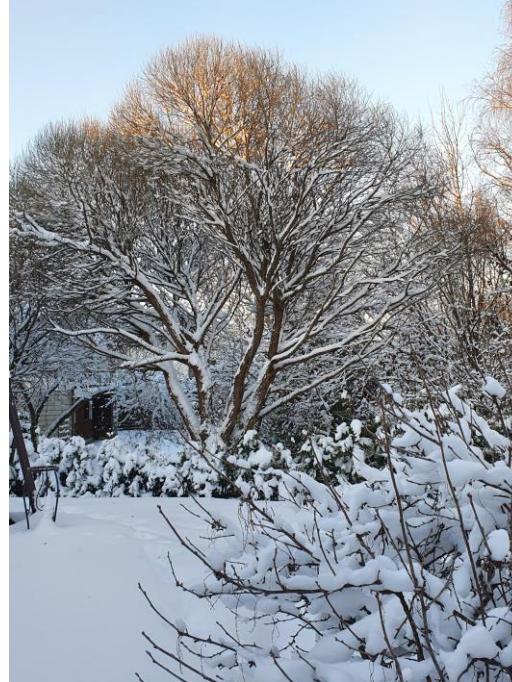
-5C



December 2023

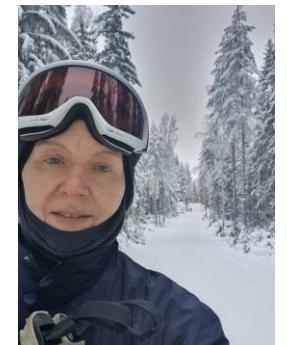
at noon

-20C



January 2023

-25C



We develop and apply **bottom-up** and **top-down** models

to understand the role of neuron-astrocyte interactions and the underlying cell and molecular biological mechanisms

in brain activity and functions

Reviews:

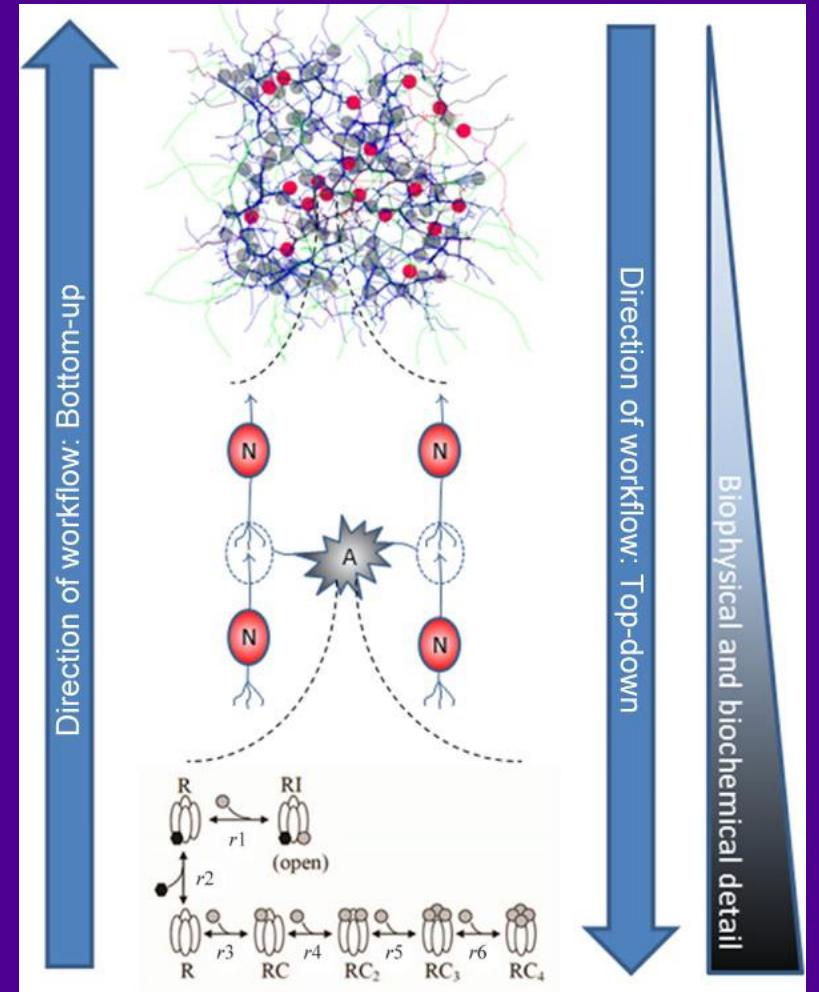
- Linne and Jalonens (2014) Prog. Mol. Biol. Transl. Sci.
- Linne et al. (2022) Adv. Exp. Med. Biol. (Book chapter)
- Linne (2024) Curr. Opin. Neurobiol.

Analysis of cellular level models:

Manninen, Havela, Linne (2018) Front. Comput. Neurosci.

Analysis of network level models:

Manninen, Acimovic, Linne (2023) Neuroinformatics



A – astrocyte, N - Neuron

Research group, funding and collaborations

Group

PhD Tiina Manninen
PhD Tuomo Mäki-Marttunen
PhD Jugoslava Acimovic
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Funding

EU FET Human Brain Project
EU Horizon EBRAINS
EU ERANET NEURON SYNCHIZ
Academy of Finland
Finnish technology foundations



Collaborations

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Lecture 22: Biology of the Glial Cells

Marja-Leena Linne

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Faculty of Medicine and Health Technology

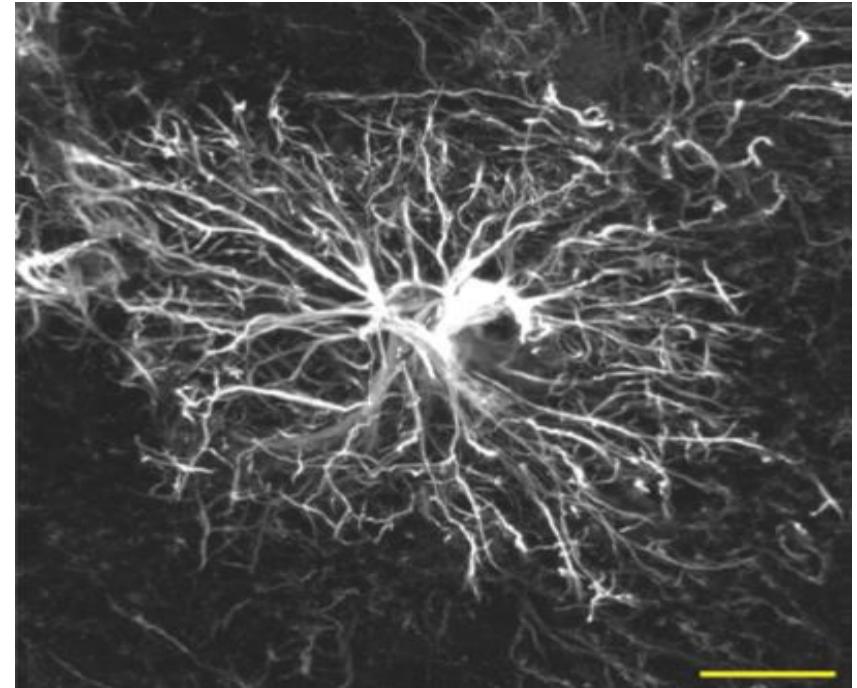
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Contents

1. Glial cell types
2. Astroglial morphology, activity and roles
3. Astrocytic calcium signaling



Cortical astrocyte *in vivo*

**How many of you had
an introduction to glia
in your studies?**

**How many of you have
done research on glia?**

1.

Glial Cell Types

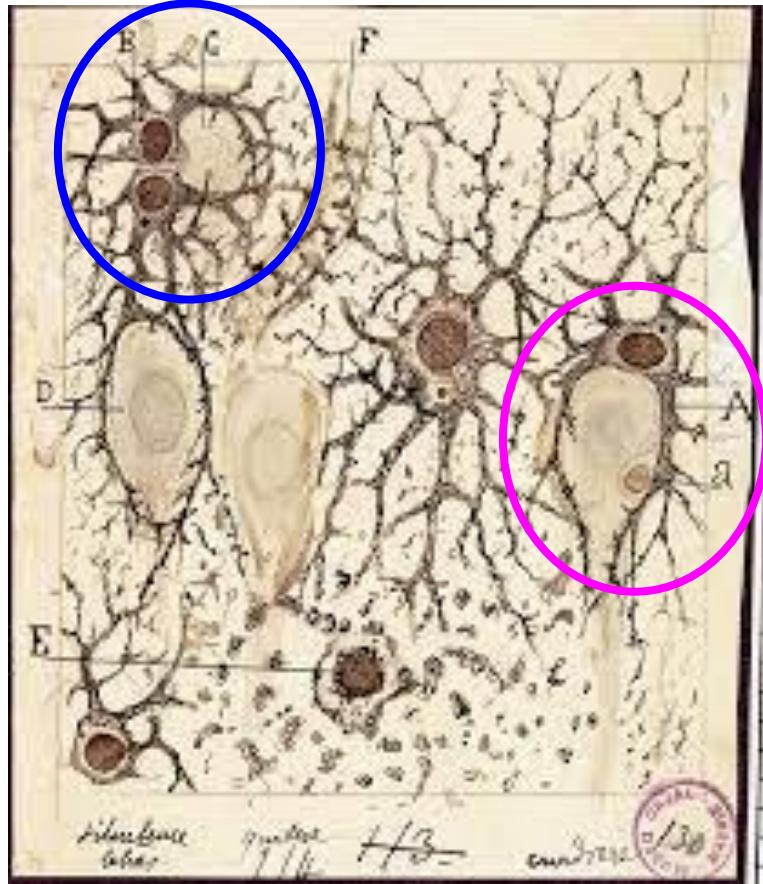
What are glial cells?

- Discovered in 1856 by a pathologist Rudolf Virchow
- Non-neuronal cells in the central and peripheral nervous system that contribute to various functions in the developing and adult brain
- As nervous systems shifted from diffuse to centralised structures, neurons became interconnected through the emergence of supportive glial cells.
- Glial complexity and number increases with the overall complexity of the nervous system.



Rudolf
Virchow

Cajal: Neuroglia-neuron interactions 100 years ago



Neuroglia (dark brown cells):

Small soma

Thick processes

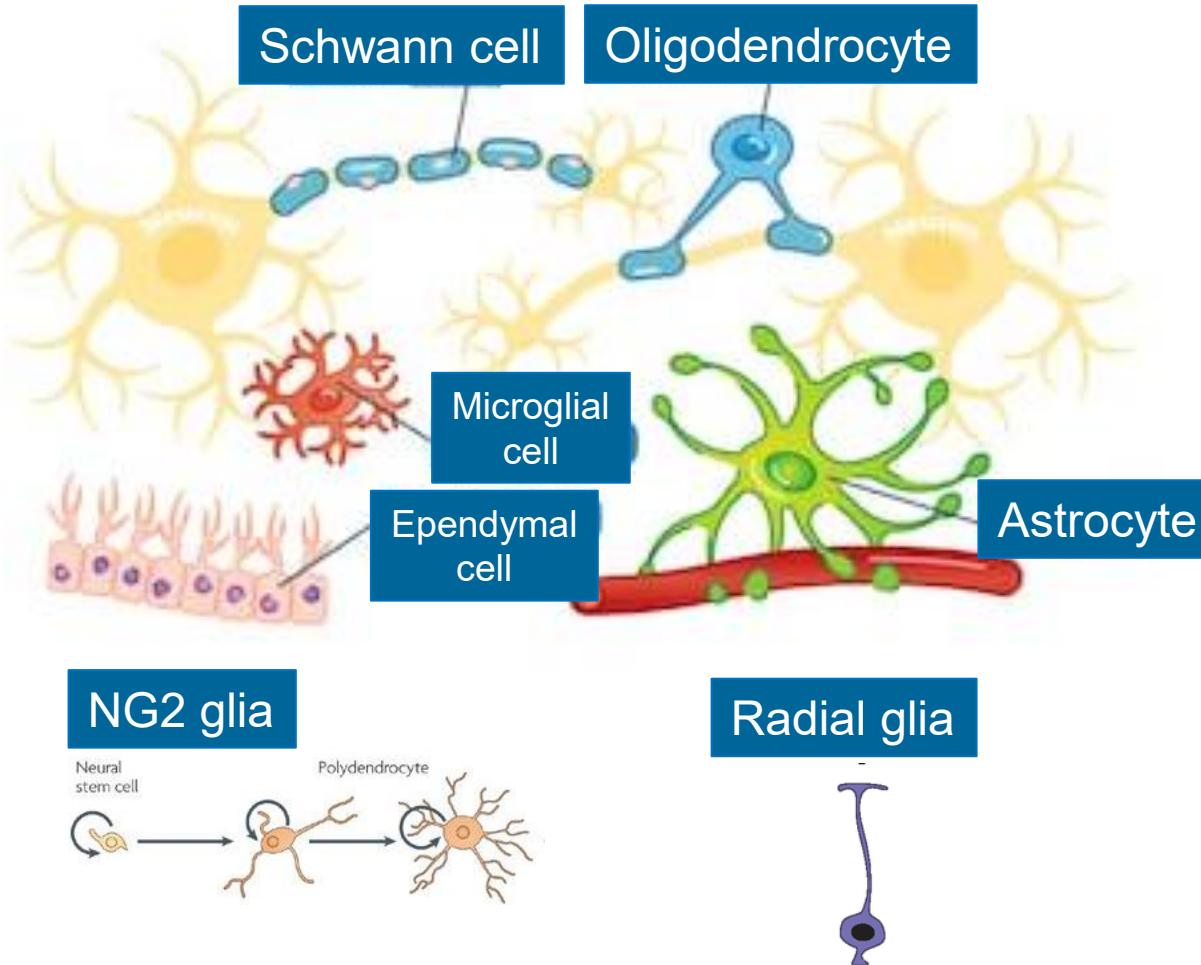
Fine distal processes surround Pyramidal neurons

Big astrocyte embracing a pyramidal neuron.

Twin astrocytes forming a nest around a pyr neuron.

Figure from Cajal Institute, Madrid, Spain

Glial cell types



Schwann cells – Axonal conduction

Oligodendrocytes – Axonal conduction

Astrocytes – Neuronal and vascular control

Microglia - Maintenance

Ependymal cells – Cerebrospinal fluid control

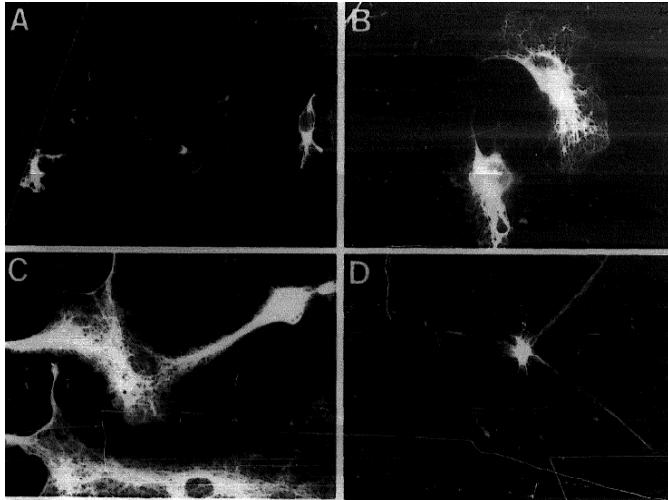
Radial glia – Guidance of neuronal development

NG2 glia – "Multipotent" cells

2.

Astroglial Morphology, Activity and Roles

In vitro cultured astrocytes: "Pancake" appearance



Rat acutely isolated cortical astrocytes stained for glial fibrillary acidic protein (GFAP).

A: P7 rat, acutely isolated cortical astrocyte, fixed at 4h after isolation.

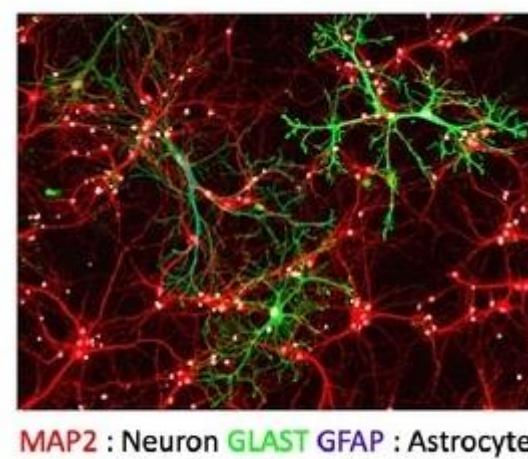
B: P6 rat, cultured for 3 days.

C: P6 rat, cultured for 20 days (HS).

D: P6 rat, cultured for 20 days in CDM.

20x magnification in all images.

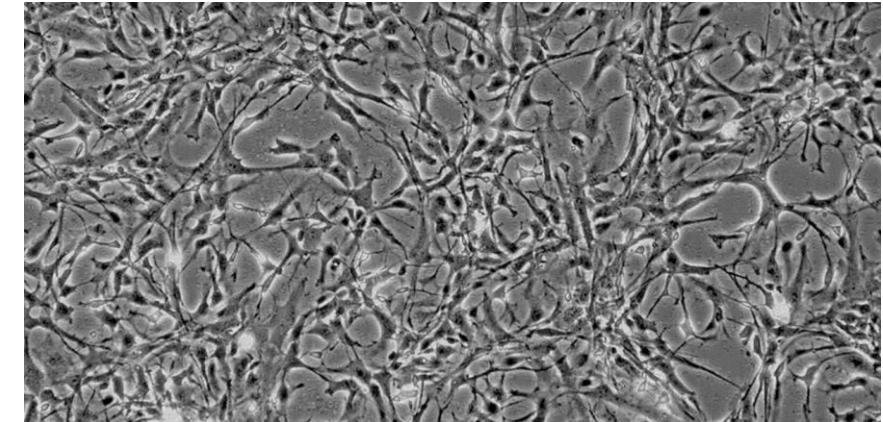
Jalonen, Linne, Kimelberg et al. 1997.



Rat co-culture with neurons and astrocytes:

Rat astrocytes in *in vitro* cell culture form high-order branches when they are grown with neurons ("co-cultures").

Hayashi et al. 2021

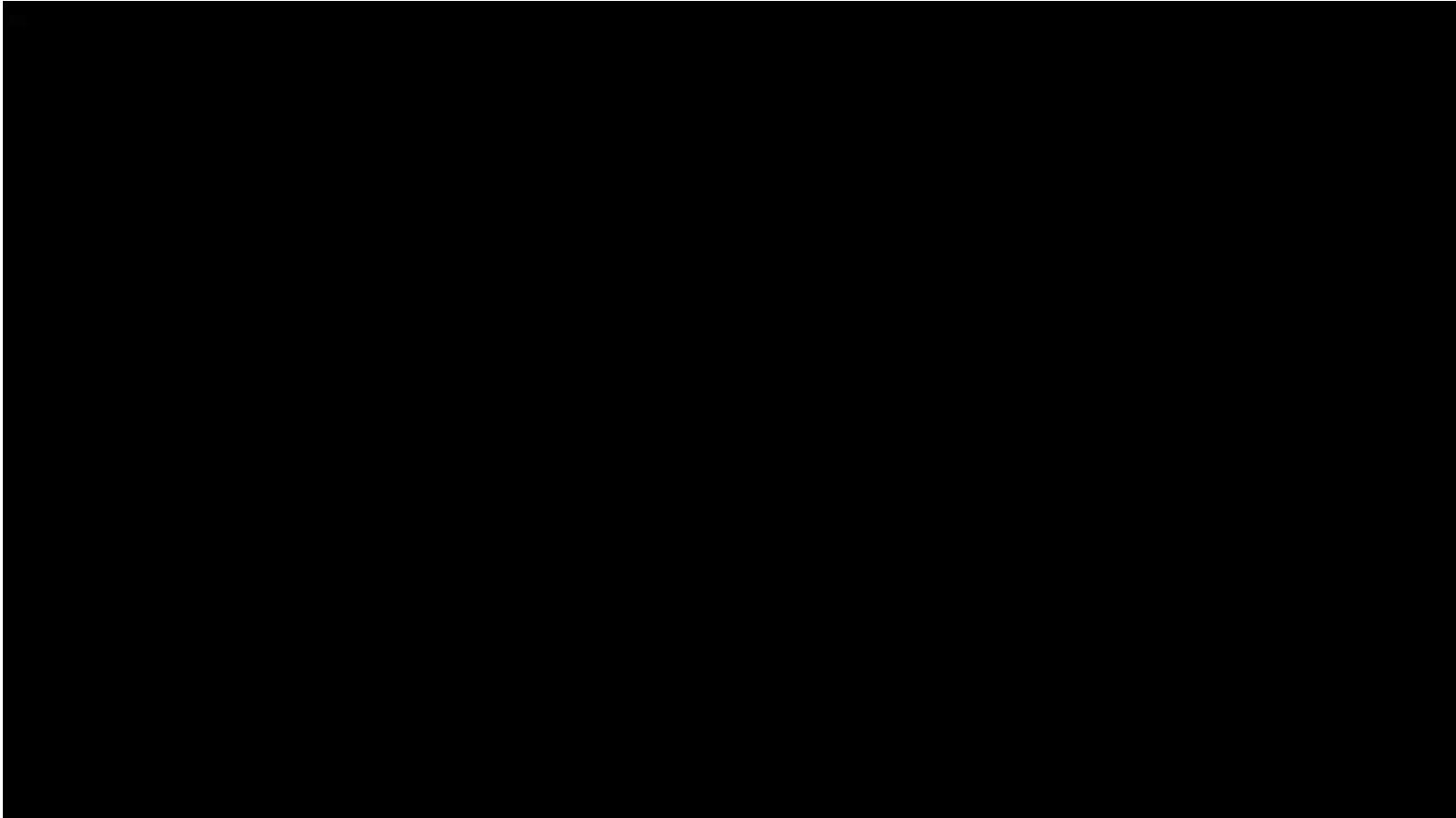


Cryopreserved Human Astrocytes are isolated from human brain of cerebral cortex and grown in culture (without neurons → "pancake")

Human Astrocytes are cryopreserved at P1 and delivered frozen.

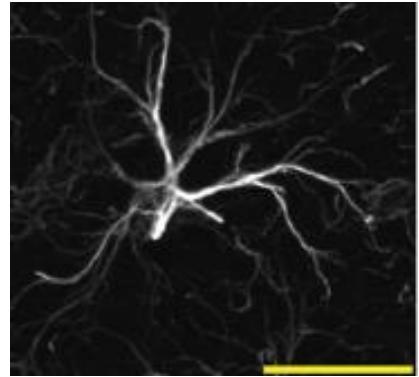
@3H Biomedical company

Comparative morphology of an astrocyte in 3D vs. 2D



Protoplasmic astrocytes (grey matter)

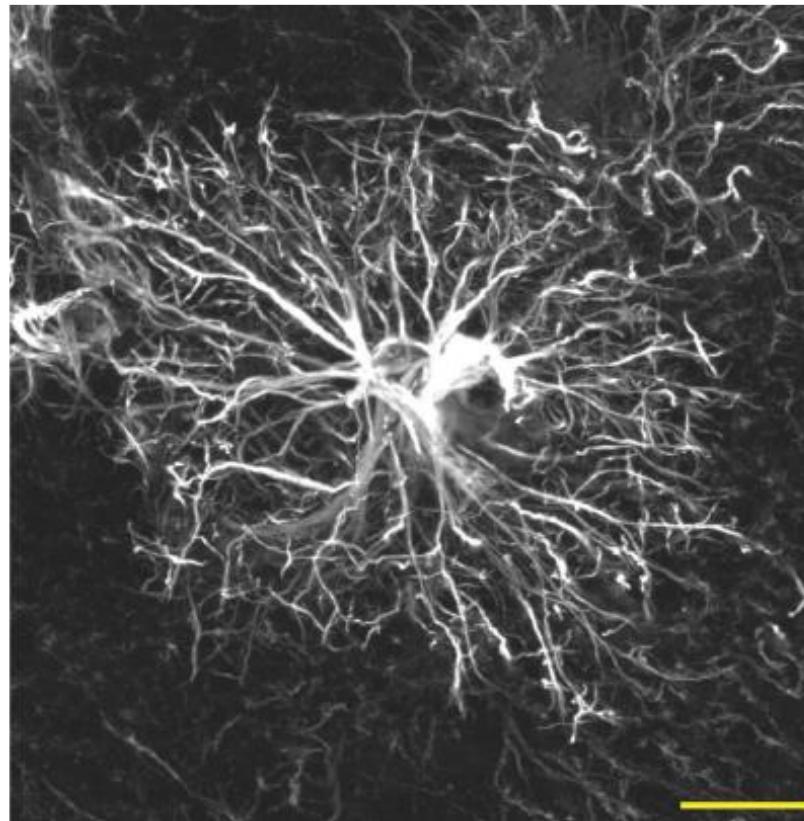
MOUSE



Oberheim et al. J Neurosci. 2009.

20 µm

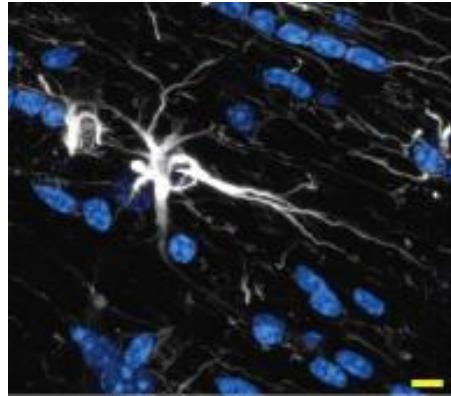
HUMAN



Oberheim et al. J Neurosci. 2009.

Fibrous astrocytes (white matter)

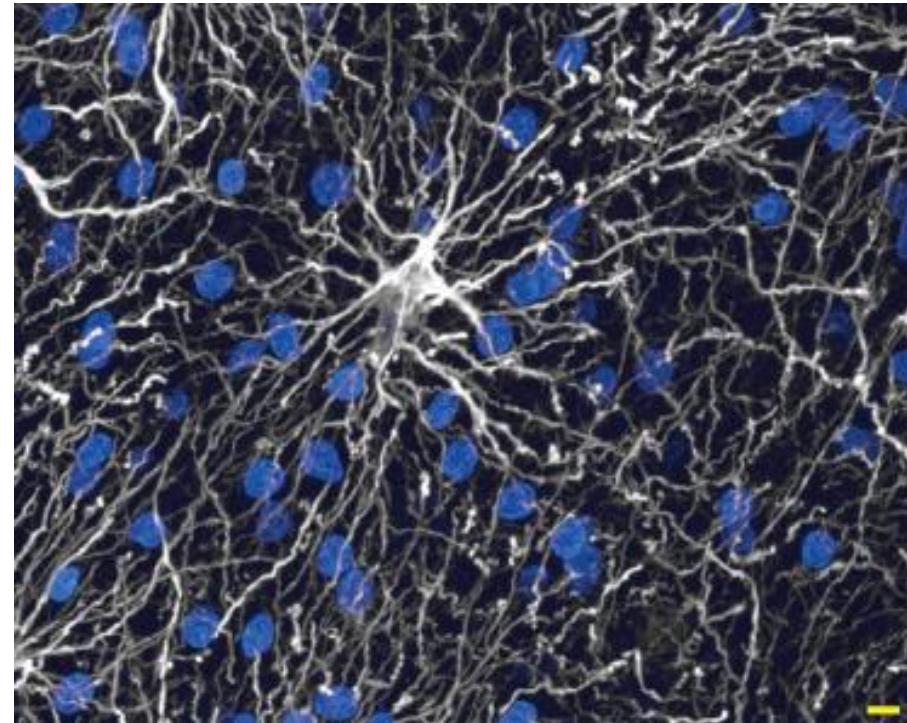
MOUSE



Oberheim et al. J Neurosci. 2009.

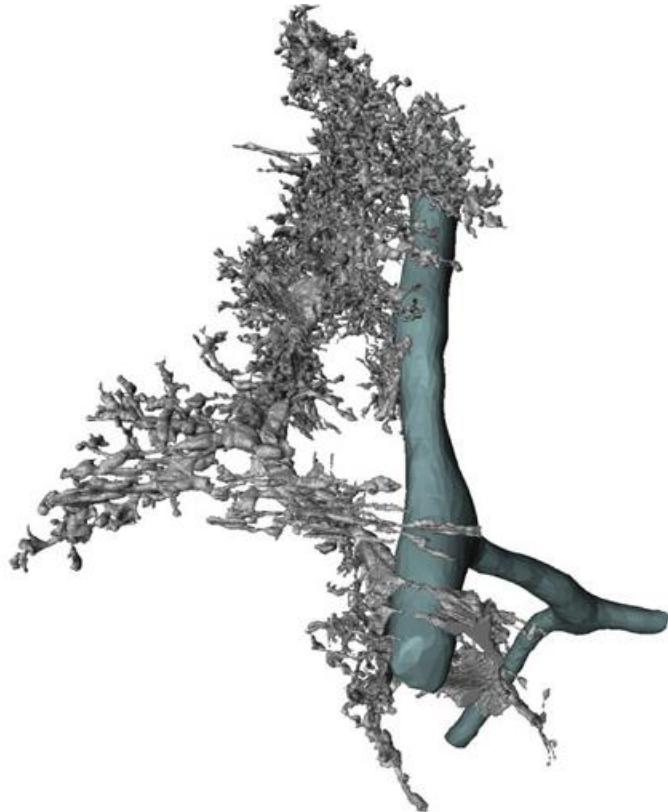
10 µm

HUMAN



Oberheim et al. J Neurosci. 2009.

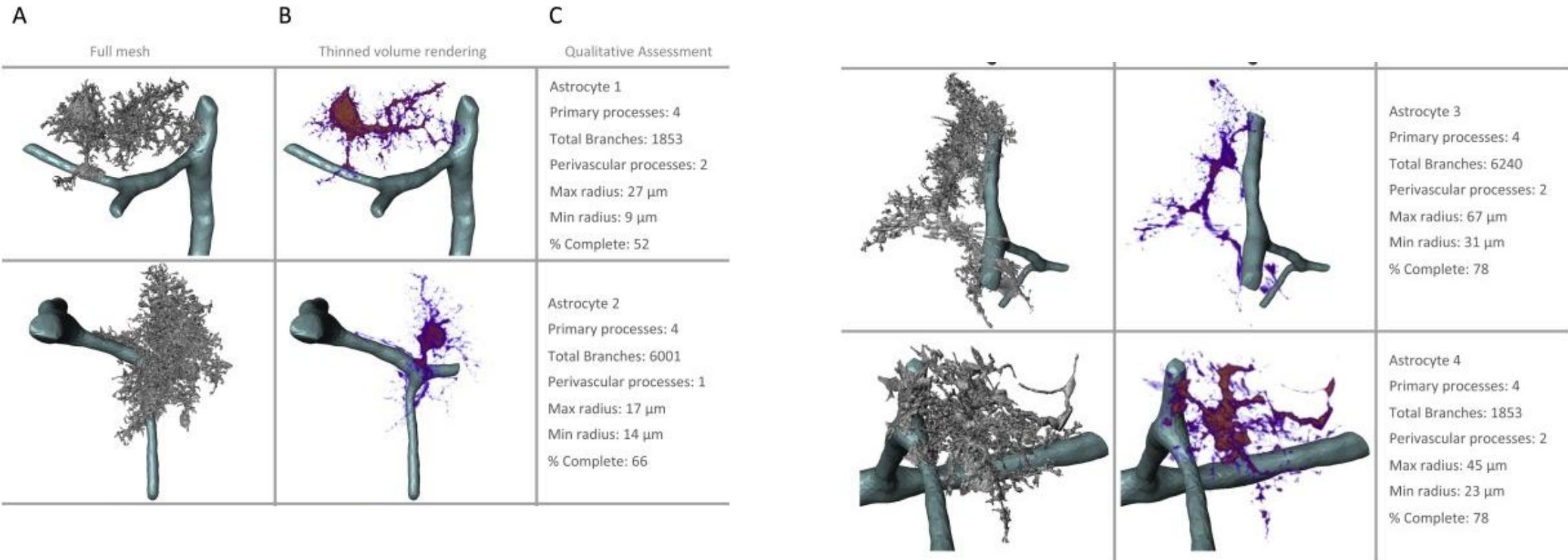
Reconstructed astrocyte morphology *in vivo*



Tissue imaging: Serial block face scanning
electron microscopy.

Image reconstruction: Manual and
machine learning based approaches.

I: Astrocytes are morphologically heterogenous



Assessment of astrocytes morphology from their 3D reconstruction.

(A) Full mesh rendering extracted from volume segmentation.

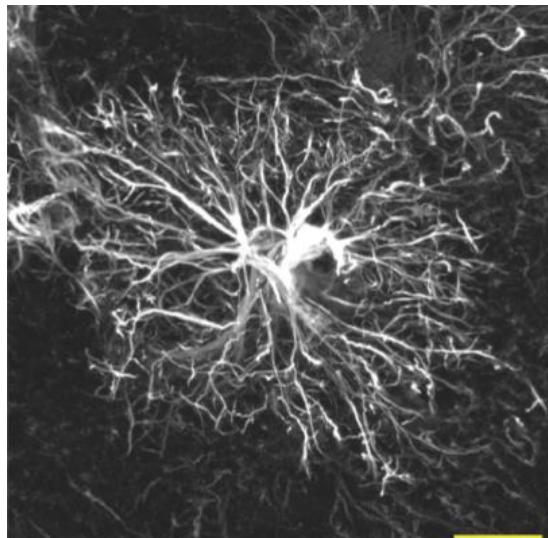
(B) Volume rendering from thinning procedure to highlight primary processes.

(C) Quantification of morphological parameters.

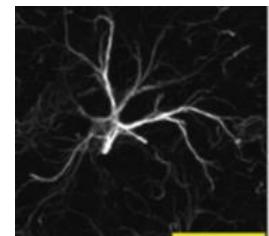
II: Human astrocytes are far more complex and larger than their rodent and primate counterparts

PROTOPLASMIC ASTROCYTE

Grey matter in cerebral cortex



Human

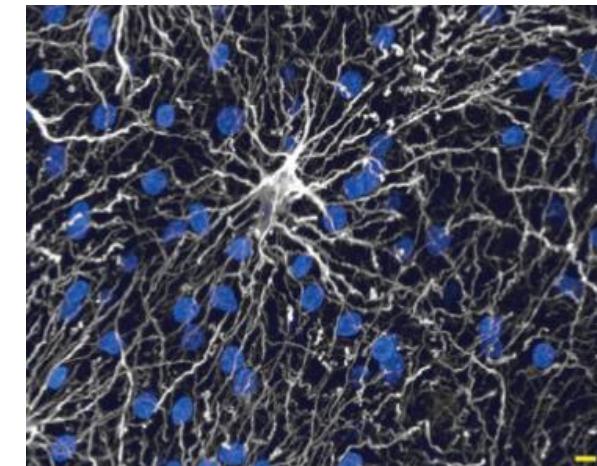


Mouse

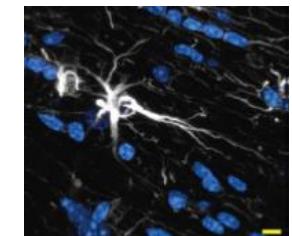
20 µm

FIBROUS ASTROCYTE

White matter in cerebral cortex



Human

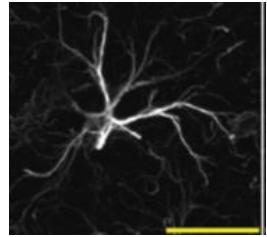


Mouse

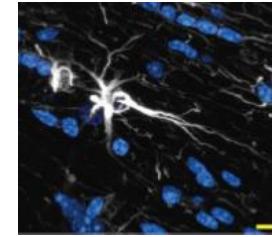
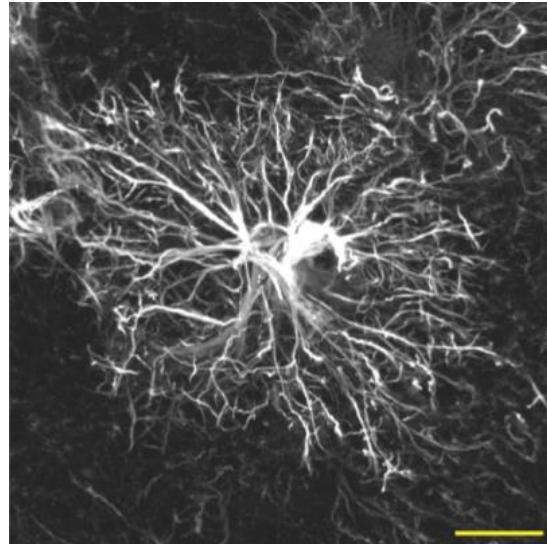
10 µm

Oberheim et al. (2009) *J. Neurosci.*

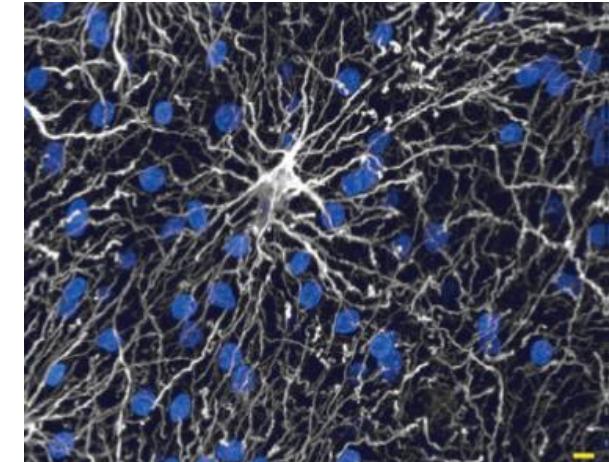
Additional details



20 μm



10 μm



Protoplasmic astrocyte
Grey matter
Mouse
Processes up to 150 μm

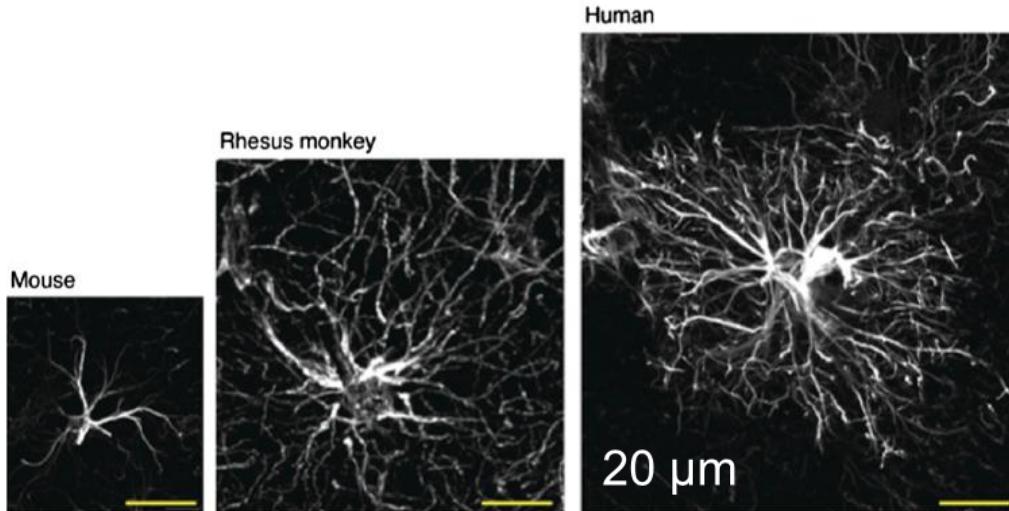
Protoplasmic astrocyte
Grey matter
Human

Fibrous astrocyte
White matter - Mouse
Processes from 150 μm
to 300 μm

Fibrous astrocyte
White matter
Human

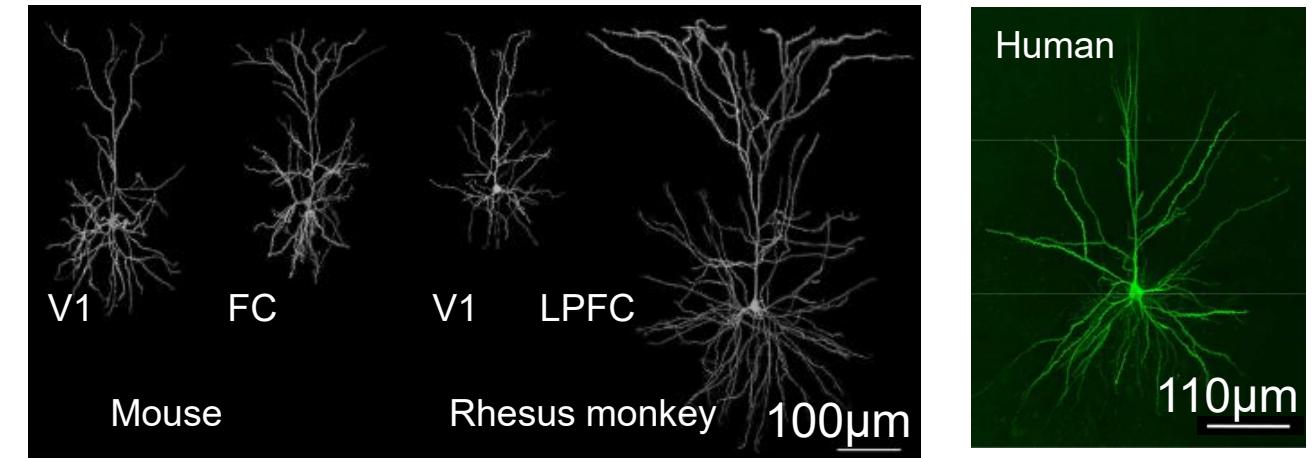
III: Larger increase in size and complexity of astrocytes from mouse to human brain - compared to neurons

PROTOPLASMIC ASTROCYTE



Oberheim et al. 2009
Kimelberg and Nedergaard, 2010

PYRAMIDAL NEURON



Gilman et al. (2017) Cereb. Cortex

Eyal et al. (2018) Front. Cell. Neurosci

IV: Estimated # of human glial cells vary between brain regions

Cerebral cortex (glia : neuron): ~ 4 : 1

Cerebellum (glia : neuron): ~ 0.2 : 1

Rest of the brain (thalamus etc.; glia : neuron): ~ 11 : 1

Note:

The above reflects my own interpretation based on multiple references and informal expert discussions.

Reported values vary across sources, and absolute figures remain unknown at this time.

Bartheld et al. (2016) *J. Comp. Neurosci.*

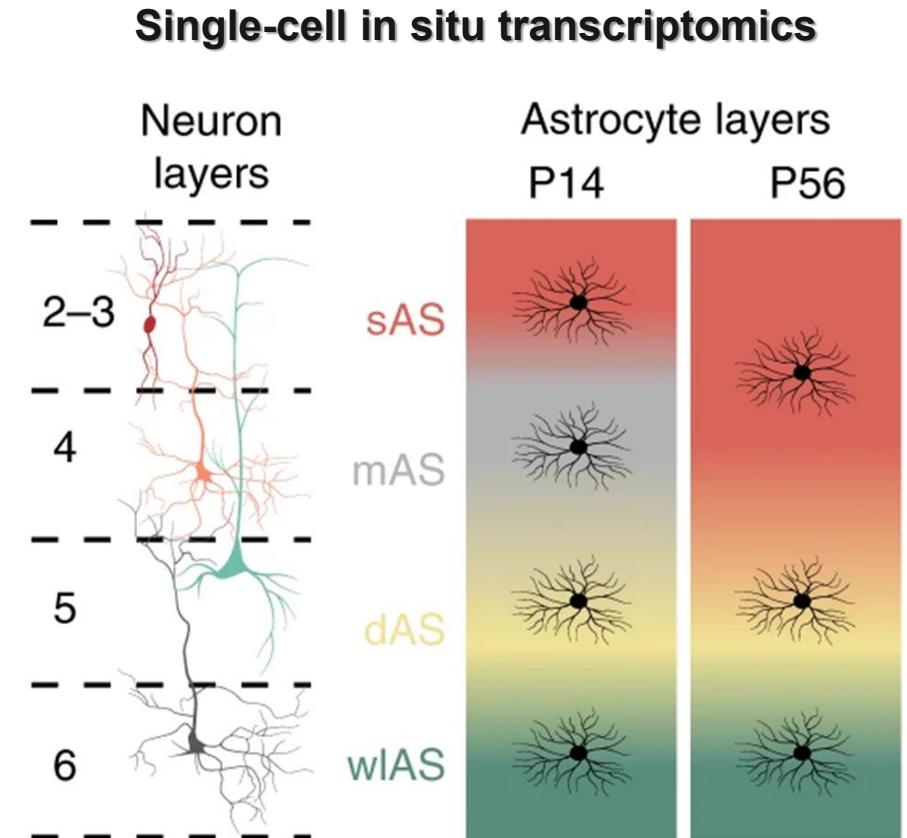
“More attention must ... be paid to quantitative studies of neuroglia and nerve cells, as opinions are often conflicting and frequently based on faulty technique.”

V: Cortical astrocyte layering is distinct from neurons (and astrocytes in each layer are heterogenous!)

P14: Superficial, mid and deep layer astrocytes during development

P56: Three grey matter layers merge into two in adulthood.

White matter layer (L6) astrocytes are maintained into adulthood.



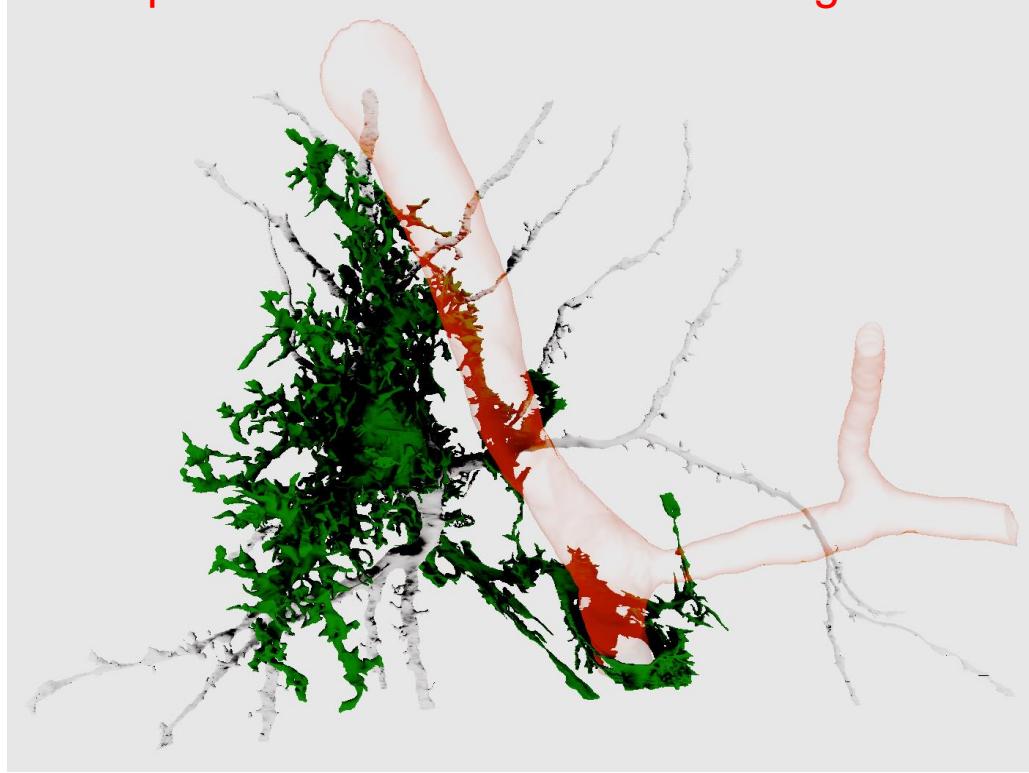
Bayraktar, Rowitch et al. (2020) Nature Neurosci.
See also: Cai et al. (2017) Neuron.

VI: Astrocytes have local and global projections

- The density of **protoplasmic astrocytes** is estimated to range between **10,000 and 30,000 per mm³** in the different brain areas of rodents (Verkhratsky and Nedergaard, 2018).
- The surface area of one **protoplasmic astrocyte** can be even **80,000 µm²** (Verkhratsky and Nedergaard, 2018).
- A single **protoplasmic astrocyte** in the rodent cortex can:
 - contact an average of **4–8 neurons** (Bushon et al. 2002, Halassa et al. 2007).
 - surround about **300–600 neuronal dendrites** (Bushon et al. 2002, Halassa et al. 2007).
 - cover for up to **20,000–120,000 synapses** residing within its domain (Bushon et al. 2002, Halassa et al. 2007).
- **Fibrous astrocytes** populating the white matter of the brain have long processes but less complex morphology with fewer fine processes compared to protoplasmic astrocytes.

VII: Astrocytes cover blood vessels and neuronal dendrites

Copyright by Corrado Cali,
please do not distribute the image!!!



Green – Full astrocyte

Red – Blood vessel

Grey – Full neuron

Imaging and tissue reconstruction reveal complex, **spongiform morphology** of cortical grey matter protoplasmic astrocytes (Cali et al., 2019).

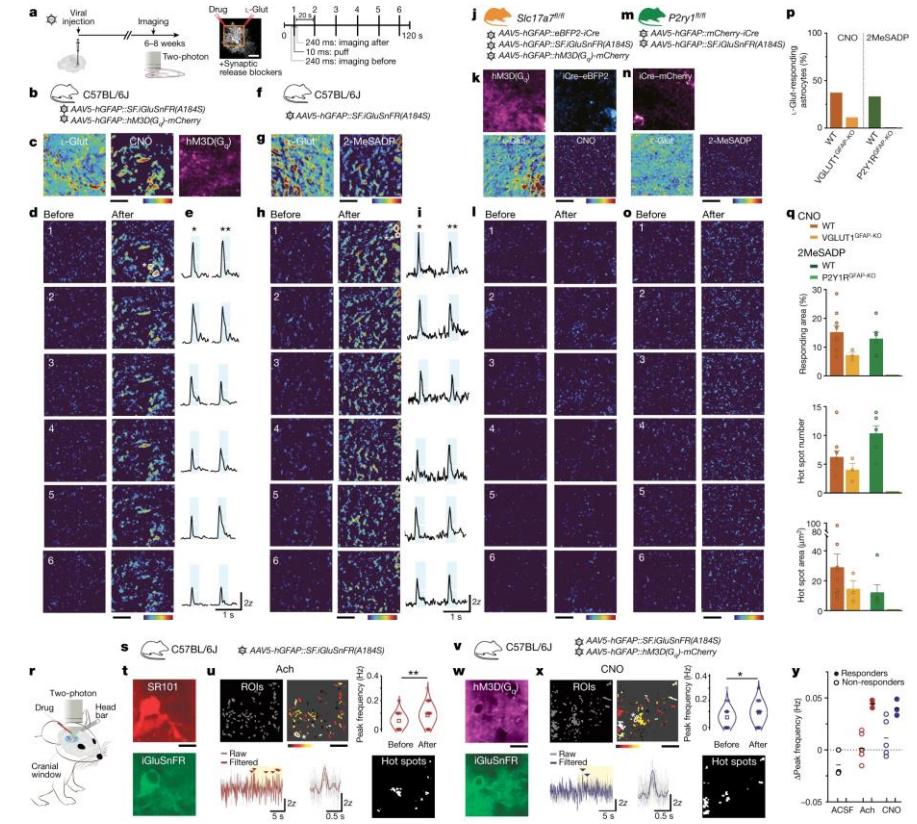
Compare with cell culture images!

Image Courtesy of: Corrado Calì (now: University of Turin, Italy)
Pierre Magistretti Lab
King Abdullah University of Science and Technology
Thuwal, Kingdom of Saudi Arabia

VIII: Astrocytes sense and control neurons

- Astrocytes' capacity to sense synapses has been known since 1990's.
- Astrocytes' capacity to **release "gliotransmitters"** to control synapses was proposed as early as in 1990's (**"Tripartite synapse concept, Araque et al. 1999**).
- Ca²⁺-dependent release of gliotransmitters from astrocytes and, hence, **glutamatergic gliotransmission** (first proposed by Araque et al. 1999) has been controversial
 - Both supporting and opposing evidences...
 - Transgenic animals were part of the controversy...long story (see e.g. Sloan and Barres 2015, Linne et al. 2022)
- **Debate resolved in 2023, by Andrea Volterra's group:**
 - Ca²⁺-dependent release of glutamate and gliotransmission from a subset of hippocampal astrocytes.
 - Exocytosis mechanism: **Vesicular** (similar to neuronal release of glutamate).

Glutamate sensor SF-iGluSnFR
to visualize release events:



De Ceglia...Volterra (2023) Nature

Astrocytes have important roles in many brain functions

Pre- and postnatal development

Initiate neurogenesis

Structure the brain

Mature and prune synapses

Energy metabolism

Support blood-brain barrier functions

Control glucose

Provide nutrients

Homeostasis and survival

Maintain extracellular ionic balance

Take up neurotransmitters

Neurology and neuropsychiatry diseases

Epilepsy

Schizophrenia

Parkinson's disease

Dementias, Alzheimer's

Plasticity learning memory cognition

Synaptic transmission (controversy)

Synaptic plasticity (controversy)

Astrocytes modulate network activity, brain oscillations, state transitions and sensory processing

[Lee et al. (2014) *PNAS*, Poskanzer and Yuste (2016) , Lines et al. (2020) *Nature Comm.*]

Astrocytes modulate cognition, behavior and sleep

[Barca-Mayo et al. (2017) *Nature Comm.*, Petrelli et al. (2020) *Molecular Psychiatry*, Halassa, Haydon et al. (2009) *Neuron*]

Astrocytes modulate synaptic plasticity, learning and memory

[Navarrete, Araque et al. (2012) *PLoS Biol.*, Min and Nevian (2012) *Nature Neurosci.*]

Astrocyte studies in Nature and Nature Neuroscience in 2024-25

nature neuroscience

Article

<https://doi.org/10.1038/s41593-025-01878-6>

Astrocyte ensembles manipulated with AstroLight tune cue-motivated behavior

Received: 10 October 2023

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Published online: 3 February 2025

Irene Serra  ¹, Cristina Martín-Monteagudo  ^{1,2,4}, Javier Sánchez Romero  ¹, Juan P. Quintanilla  ¹, Danny Ganchala  ^{1,3}, María-Angeles Arevalo  ^{1,3}, Jorge García-Marqués  ¹ & Marta Navarrete  ^{1,2}

Article

Learning-associated astrocyte ensembles regulate memory recall

<https://doi.org/10.1038/s41586-024-08170-w>

Michael R. Williamson  ^{1,2,3,6}, Wookbong Kwon  ^{1,2,3,6}, Junsung Woo  ^{1,2,3}, Yeunjung Ko  ^{1,2,4}, Ehsan Maleki  ^{1,2}, Kwanha Yu  ^{1,2}, Sanjana Murali  ^{1,2,5}, Debosmita Sardar  ^{1,2,3} & Benjamin Deneen  ^{1,2,3,4,5}

w

Received: 27 December 2023

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The physical manifestations of memory formation and recall are fundamental

nature neuroscience

Article

<https://doi.org/10.1038/s41593-025-01878-6>

Astrocyte heterogeneity reveals region-specific astrogenesis in the white matter

Received: 14 August 2023

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 Check for updates

Riccardo Bocchi  ^{1,2,9}, Manja Thorwirth  ^{1,2}, Tatiana Simon-Ebert ^{1,2}, Christina Koupourtidou ³, Solène Clavreul  ^{1,2}, Keegan Kolf  ³, Patrizia Della Vecchia  ¹, Sara Bottes ⁴, Sebastian Jessberger  ⁴, Jiafeng Zhou  ⁵, Gulzar Wani  ^{1,2}, Gregor-Alexander Pilz  ³, Jovica Ninkovic ^{2,3}, Annalisa Buffo  ^{6,7}, Swetlana Sirk  ^{1,2}, Magdalena Götz  ^{1,2,8,10}  & Judith Fischer-Sternjak ^{1,2,10}

Article

<https://doi.org/10.1038/s41586-024-07109-5>

Received: 4 December 2022

Accepted: 23 January 2024

Published online: 6 March 2024

nature neuroscience

Article

Astrocyte transcriptomic changes along the spatiotemporal progression of Alzheimer's disease

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Published online: 11 November 2024

 Check for updates

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Article

Disease-associated astrocyte epigenetic memory promotes CNS pathology

<https://doi.org/10.1038/s41586-024-07187-5>

Received: 2 August 2023

Accepted: 9 February 2024

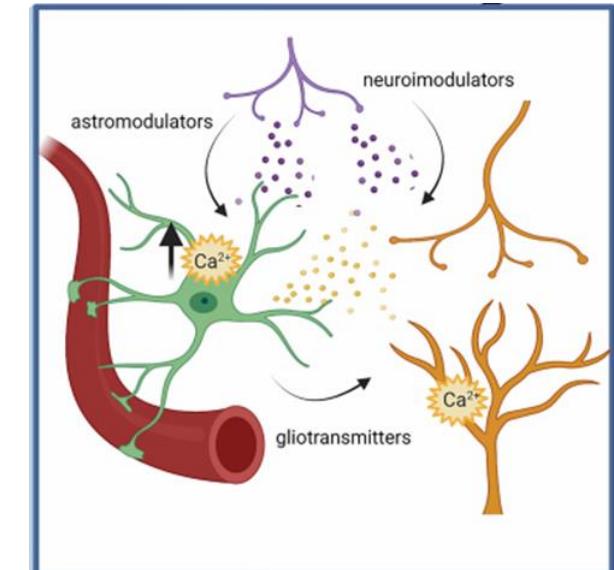
Published online: 20 March 2024

 Check for updates

Hong-Gyun Lee  ¹, Joseph M. Rose  ¹, Zhaorong Li  ^{1,2}, Camilo Faust Akli  ¹, Seung Won Shin  ³, Joen-Hyun Lee  ¹, Lucas P. Flausino  ¹, Florian Perrin  ¹, Chun-Cheh Chao  ¹, Kilian L. Kleemann  ¹, Lena Sun  ¹, Tomer Illoz  ¹, Federico Giovannoni  ¹, Marc Charbarat  ¹, Liliana M. Sammarco  ¹, Jessica E. Kenison ¹, Gavin Plester ¹, Stephanie E. J. Zandee ¹, Alexandre Prat ¹, Jain C. Clark ¹, Francisco J. Quintana ¹, Veit Rothhammer ¹, Michael A. Wheeler ¹, Veit Rothhammer ¹, Veit Rothhammer <img alt="ORCID icon" data-bbox="

Astrocytes have receptors to sense neuromodulators

- It has been assumed that neuromodulators alter neural circuit activity and behaviors by directly acting on neurons.
- Astrocytes (and other glia) express a diverse array of **neuromodulatory receptors** (known since 1990's).
- Example: Ma et al. Neuromodulators signal through astrocytes to alter neural circuit activity and behaviour, *Nature*, 2016.
- Lefton et al. Norepinephrine signals through astrocytes to modulate synapses, *Science*, 2024:
“Together, these findings fuel a new model wherein **astrocytes are a core component of neuromodulatory systems** and the circuit effector through which norepinephrine produces network and behavioral adaptations, **challenging an 80-year-old status quo**.”



Additional studies are required to better understand how astrocytes regulate brain activity and functions *in awake animals*

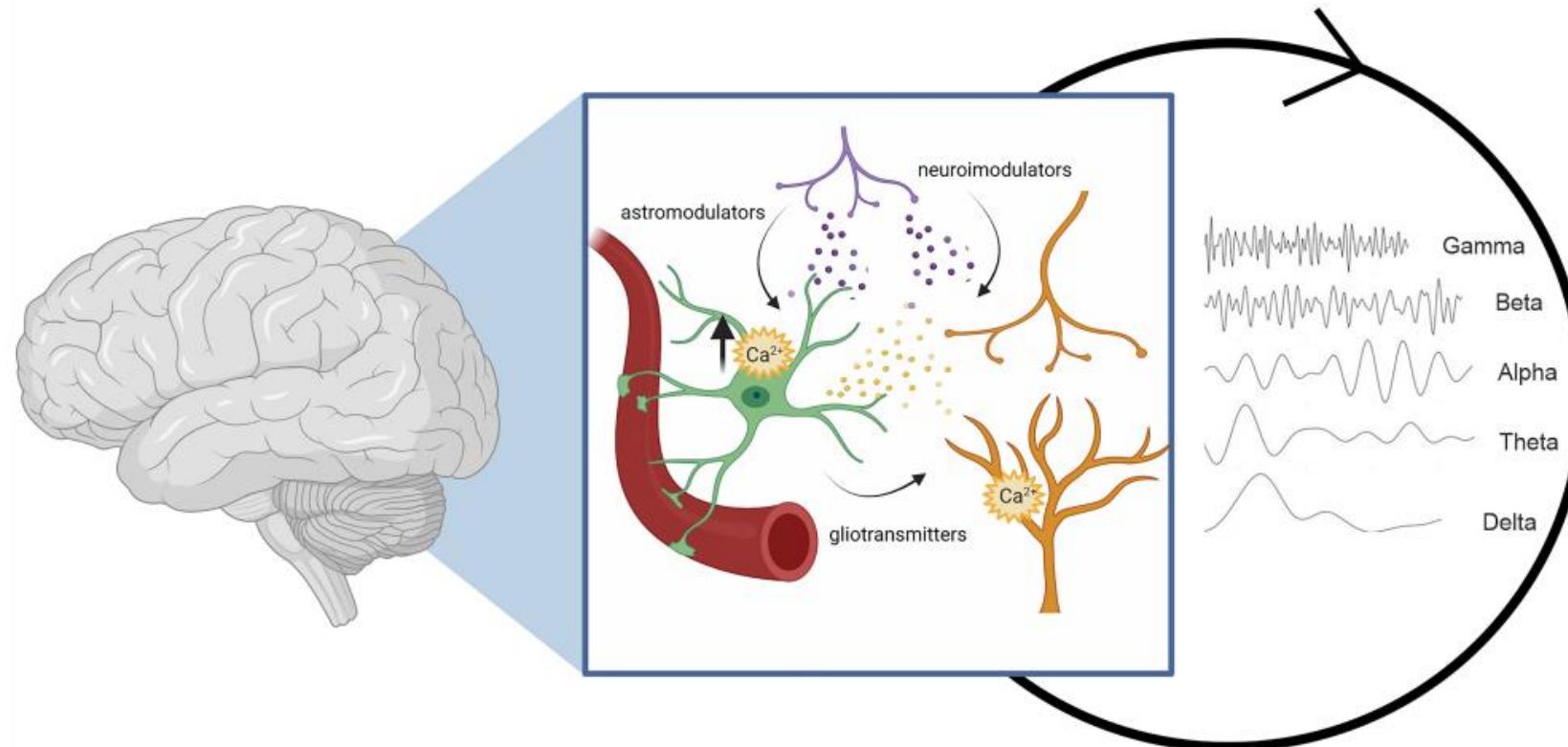


Figure from Van Horn et al. (2021) J. Neurophysiol.

Astrocytes modulate network activity, brain oscillations, state transitions and sensory processing

Lee et al. (2014) PNAS: Blocking astrocytic vesicular release in transgenic awake-behaving animals **reduced cortical gamma oscillations** and **impaired object recognition** (other forms of memory, including working memory and fear conditioning, remained unchanged).

Poskanzer and Yuste (2016) PNAS: Astrocytes, through regulation of extracellular glutamate, can **trigger a slow neuronal rhythm** in the brain that has been shown to be important in sleep and memory formation.

Lines et al. (2020) Nature Comm.: Astrocytes respond to sensory stimuli in a stimulus-dependent manner: sensory stimuli **increases neuronal network activity in the gamma range** (30–50 Hz), followed by a delayed astrocyte activity that dampens the steady-state gamma activity.

Astrocytes modulate cognition, behavior and sleep

Barca-Mayo et al. (2017) Nature Comm.: Deletion of astrocytic Bmal1-gene **alters circadian locomotor behavior and cognition** in mice through GABA signaling.

Petrelli et al. (2020) Molecular Psychiatry: Conditional deletion of astrocytic vesicular VMAT2-transporter produces **loss of prefrontal cortex dopamine homeostasis**, leading to **defective synaptic transmission and plasticity and impaired working memory and behavioral flexibility**.

Halassa, Haydon et al. (2009) Neuron: Astrocytes modulate the **accumulation of sleep pressure** and its cognitive consequences through a pathway involving Adenosine1 receptors.

Astrocytes modulate synaptic plasticity, learning and memory

Navarrete, Araque et al. (2012) PLoS Biol.: **Astrocyte Ca²⁺ signal is necessary** for cholinergic-induced **synaptic plasticity**, indicating that astrocytes are directly involved in brain storage of information.

Min and Nevian (2012) Nature Neurosci.: Astrocytes **modulate long-term depression** in developing mice.

3.

Astrocytic Calcium Signaling

Astrocytes cannot generate action potentials

- Reason: Not enough high density of voltage-gated Na^+ channels.
- However, astrocytes are electrically dynamic cells (cell membrane potential fluctuates, Ca^{2+} excitability).
- Astrocytes generate **Ca^{2+} signals (calcium excitability, calcium transients)**.

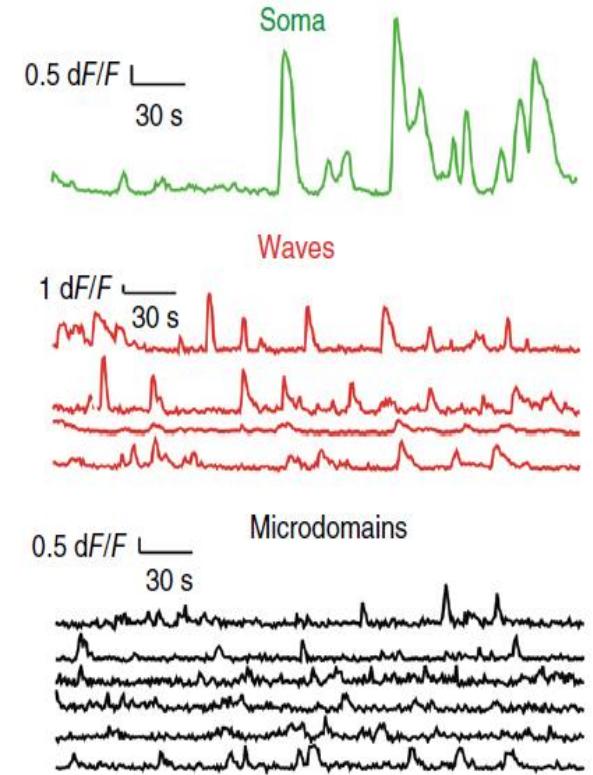
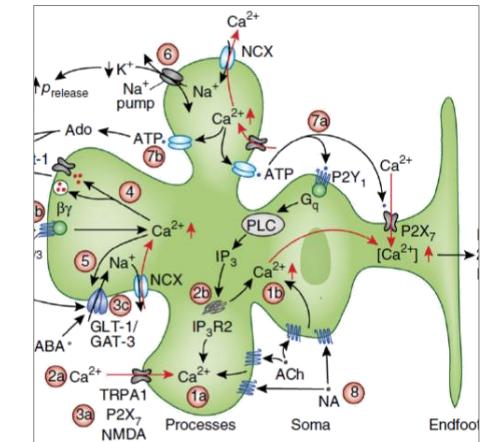


Figure from Srinivasan et al. (2015)
Nature Neurosci.

Astrocytes cannot generate action potentials

- Intracellular Ca^{2+} signals can depend on:
 - **Ca²⁺-Induced Ca²⁺ Release (CICR)** via IP_3 receptors (IP_3Rs) in the endoplasmic reticulum (ER)
 - Ca^{2+} influx, for example, via voltage-gated Ca^{2+} channels in the cell membrane
 - Mechanisms related to mitochondria.
 -
- Ca^{2+} signals are considered the **primary means of communication** between astrocytes and other cells.

Nimmerjahn, 2009; Volterra et al., 2014; Bazargani & Attwell, 2016



Astrocytic calcium activity in slice and in vivo

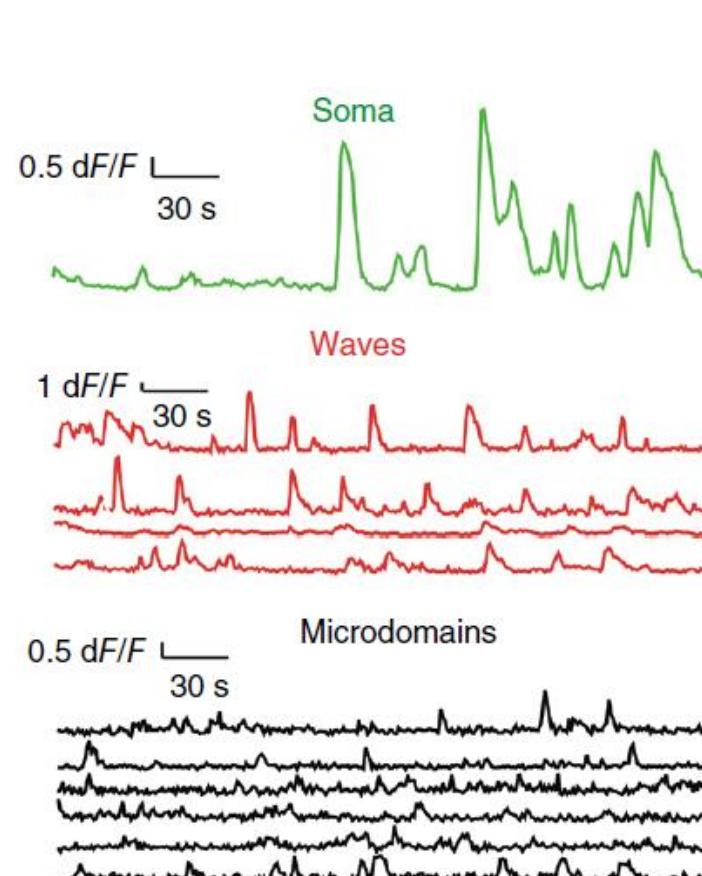


Figure from Srinivasan et al. (2015)

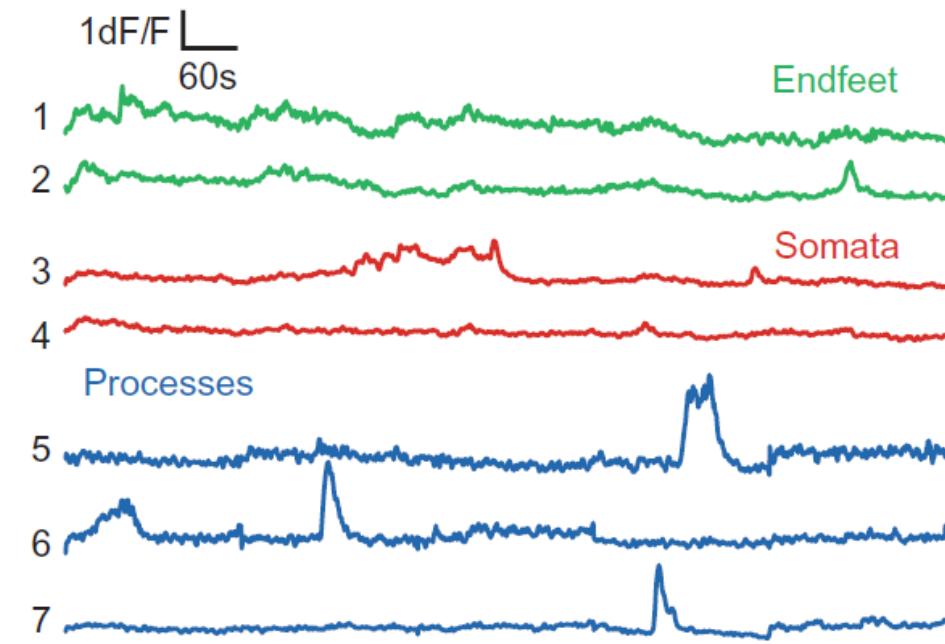
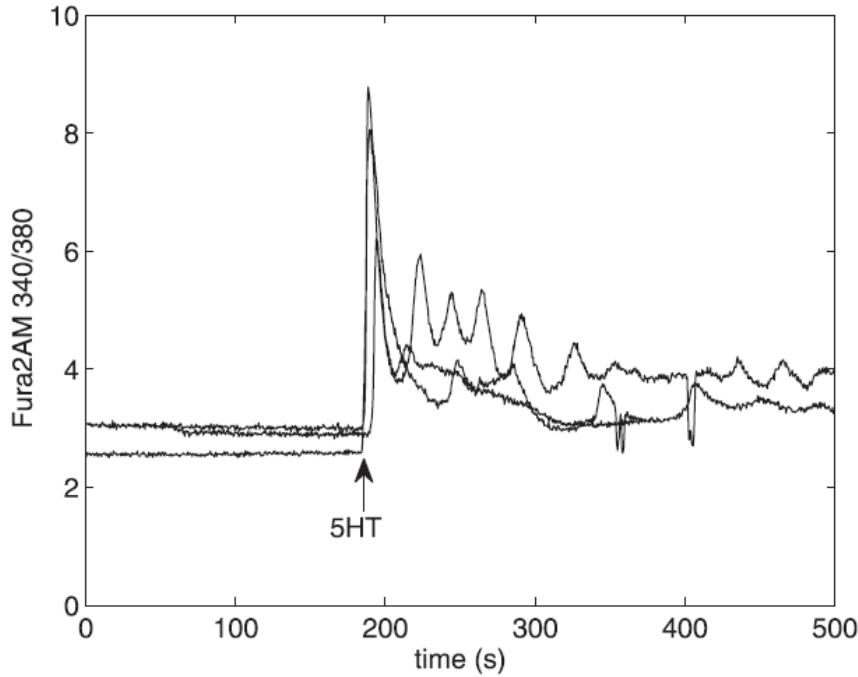


Figure from Stobart, Weber et al. (2018)

Astrocytic calcium activity in vitro

Stimulated by neuromodulator:

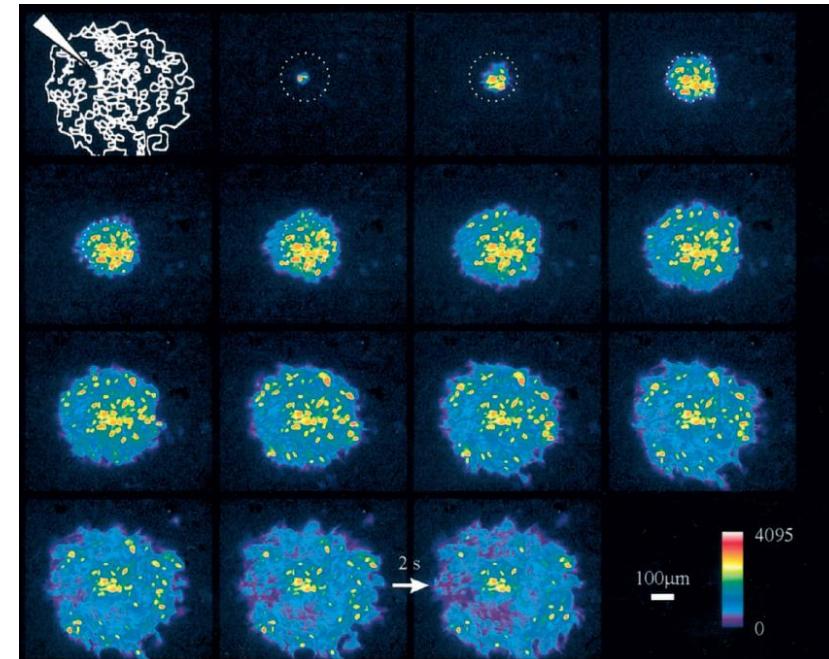
Acutely isolated cortical astrocytes (7 DIC)
(Fluorescent probe: Fura2AM)



Jalonen, Linne, Kimelberg et al. (1997) *Brain Res.*
Toivari, Manninen, Nahata, Jalonen, Linne (2011) *PLOS One*

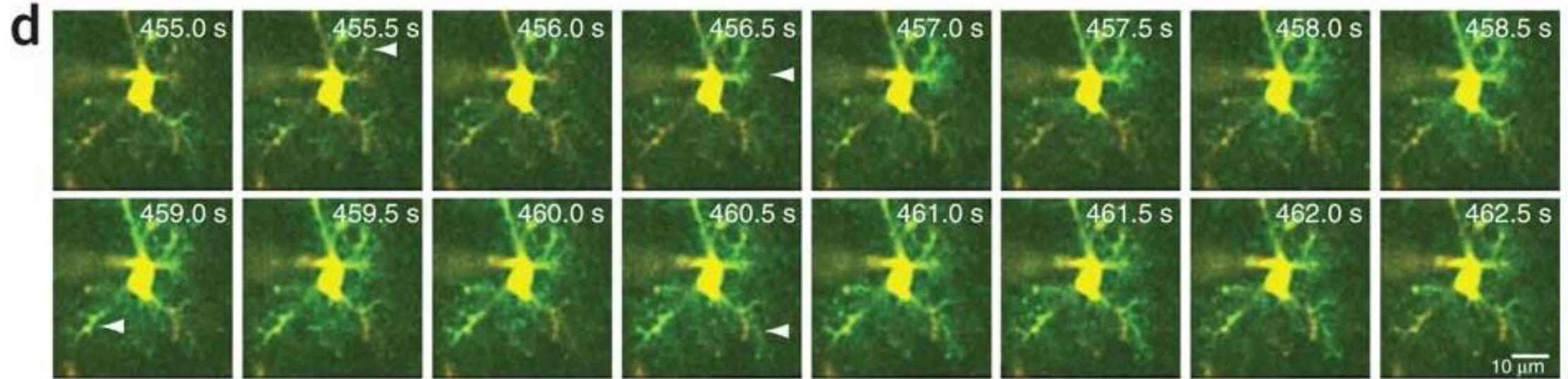
Stimulated by electricity:

Cortical astrocytes in cell culture (4 DIC)
(Fluorescent probe: Fluo-3, AM)



Innocenti et al. (2011) *J. Neurosci.*

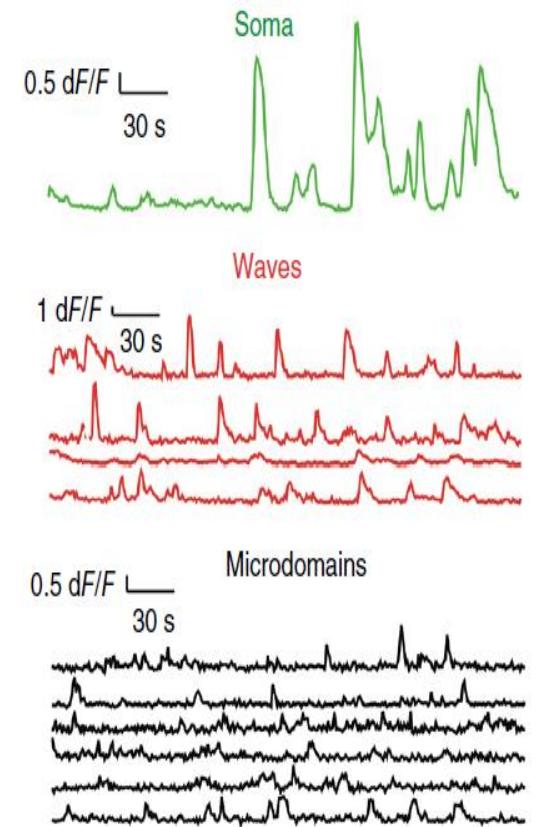
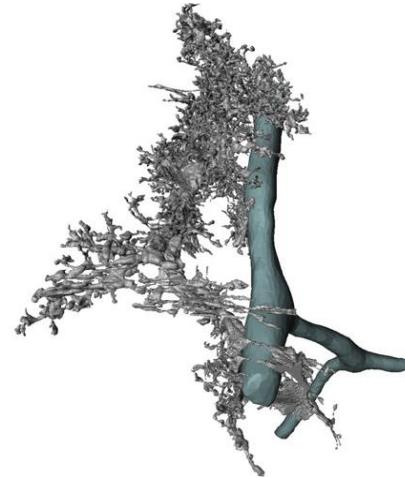
Astrocytic calcium activity in slice / in vivo



Two-photon time-lapse imaging of Ca^{2+} transients
in astrocyte processes
during induction of t-LTD
(spike-timing-dependent long-term depression).

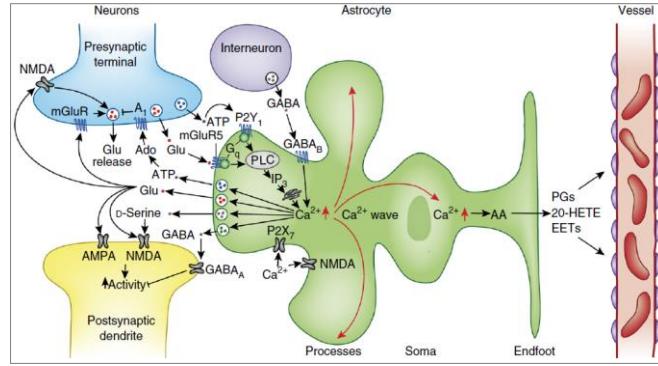
Calcium activity in soma vs. processes

Ca²⁺ signals in the
soma, processes / endfeet, and fine processes
of an astrocyte differ in
frequency, kinetics, and spatial spread.



Figures from:
Cali et al. (2019) Prog. Neurobiol.
Srinivasan et al. (2015) Nature Neurosci.

How our view of astrocyte calcium signaling has evolved

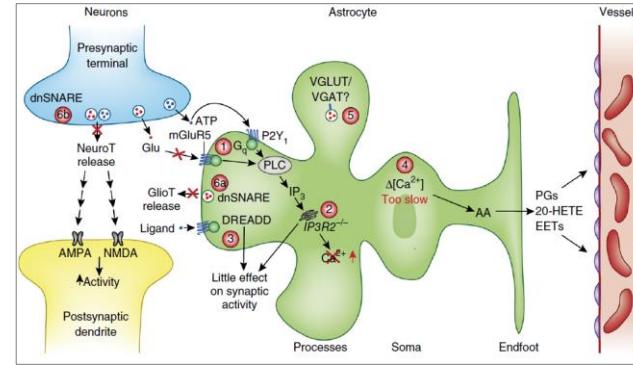


1990 →

In vitro

Ca^{2+} ↑ by G-protein coupled receptor-channels

→ Active sensing and modulation of neuronal activity



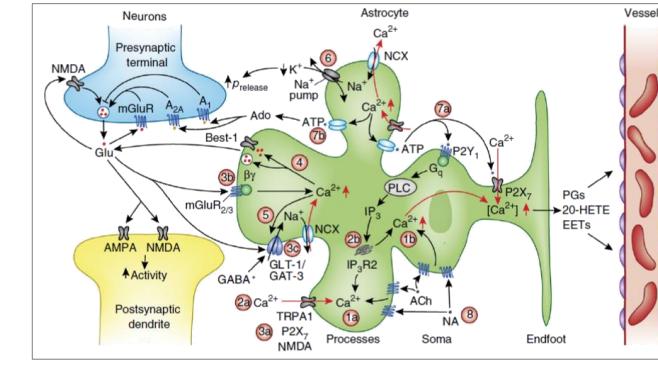
2000 →

In vitro/slice

Ca^{2+} too slow

No GlioT release

→ No direct modulation of neuronal activity



2010 →

In vivo

Complexity of signaling

The tripartite synapse concept remained controversial for decades but was largely resolved in 2023.

Astrocytic ion channels and transporters

- Astrocytes express all major types of **ion channels**, such as:
 - K^+ , Na^+ , and Ca^{2+} channels
 - Anion and chloride (Cl^-) channels
 - Aquaporins
 - Transient receptor potential channels
 - Non-selective channels.
- Astrocytes express adenosine and adenosine triphosphate (ATP)-dependent **transporters** and **pumps** on the plasma and ER membranes, such as:
 - Na^+/K^+ -ATPase pump
 - Plasma membrane Ca^{2+} -ATPase (PMCA)
 - Sarcoplasmatic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) on the ER.
- **Secondary transporters** include
 - Glutamate transporters, such as excitatory amino acid transporters
 - Gamma-aminobutyric acid (GABA) transporters
 - Glycine transporters, Na^+/Ca^{2+} exchangers, $Na^+/K^+/Cl^-$ cotransporters,

Astrocytic receptors

- Ionotropic & metabotropic receptors:
 - Neurotransmitters: glutamate, GABA, glycine, acetylcholine
- Neuromodulators:
 - Adrenergic (norepinephrine/adrenaline), serotonin, histamine, cannabinoid
- Purinergic receptors:
 - ATP, adenosine
- Neuropeptide receptors

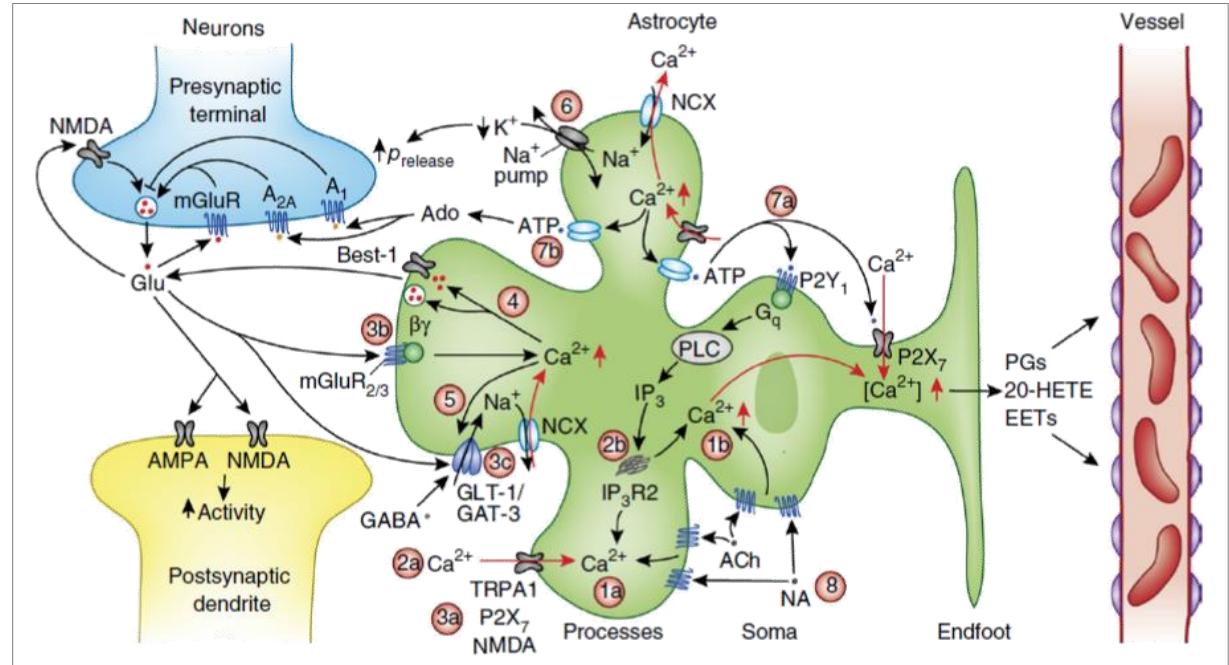


Figure from Bazargani and Attwell (2016)

Complex signaling mechanisms are responsible for Ca^{2+} signals in astrocytes – modeling is necessary!

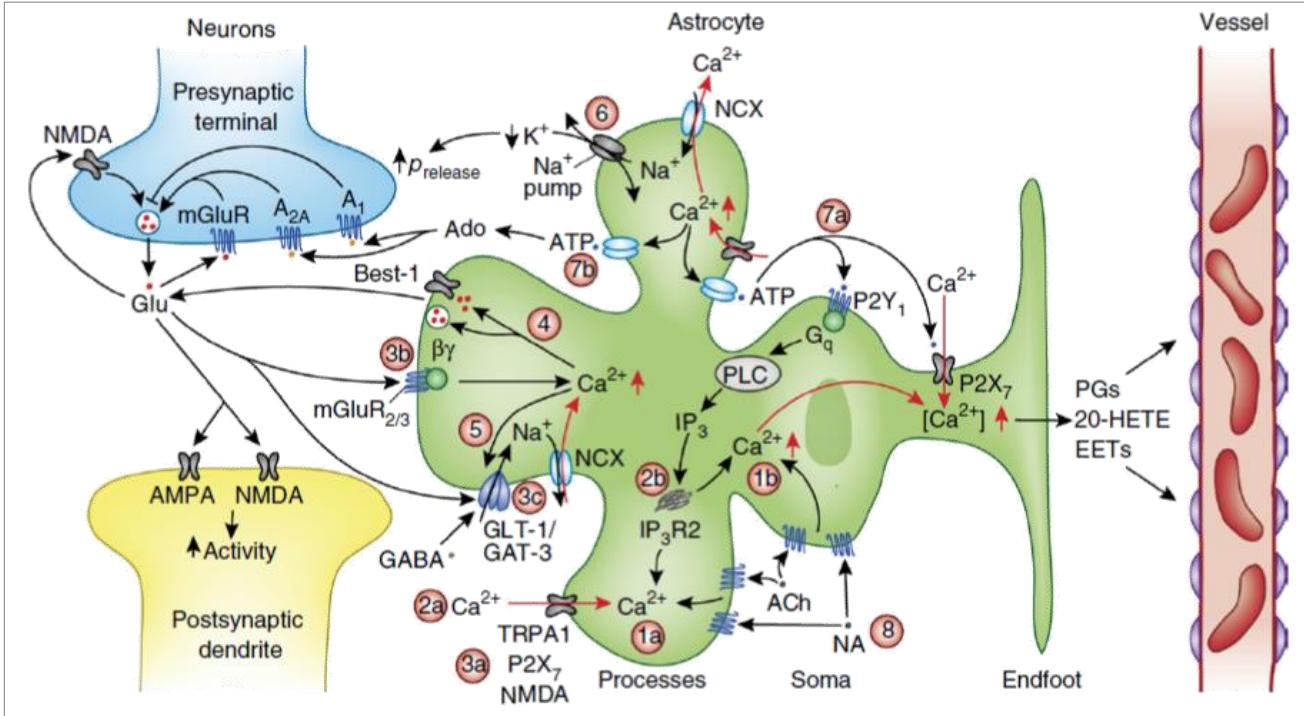


Figure from Bazargani and Attwell (2016)

Astrocyte calcium signaling: the third wave

Narges Bazargani & David Attwell

The discovery that transient elevations of calcium concentration occur in astrocytes, and release ‘gliotransmitters’ which act on neurons and vascular smooth muscle, led to the idea that astrocytes are powerful regulators of neuronal spiking, synaptic plasticity and brain blood flow. These findings were challenged by a second wave of reports that astrocyte calcium transients did not correlate with neuronal activity and did not contribute to synaptic plasticity. Recent studies have now turned again the most important calcium transients occur in fine astrocyte processes not resolved in earlier studies, and new mechanisms have been discovered by which astrocyte $[\text{Ca}^{2+}]_i$ is raised and exerts its effects. Here we review how this third wave of discoveries has changed our understanding of astrocyte calcium signaling and its consequences for neuronal function.

The first wave: astrocytes also process information

The discovery that glutamate evokes a calcium concentration rise in astrocytes^{1–4} (in culture, in brain slices, in whole retina and in vivo), which can propagate along astrocyte processes and even between glial cells, was the first to demonstrate that astrocytes can contribute to an extracellular signaling system in the CNS⁵. The subsequent demonstration that rises in intracellular $[\text{Ca}^{2+}]_i$ in astrocytes in response to a $[\text{Ca}^{2+}]_i$ rise in adjacent neurons^{1,17} sparked a flurry of studies that redefined the concept of gliotransmission. Increases of astrocyte $[\text{Ca}^{2+}]_i$ evoked by receptor agonists such as glutamate and GABA, or by uncaging of Ca^{2+} or inositol 1,4,5-triphosphate (IP_3) released from internal stores, trigger signaling cascades in the astrocyte that produce gliotransmitters, such as extracellular glutamate^{1,18–21}, ATP^{22–24}, D-serine^{22–24} and GABA^{25–28}. It is unknown whether $[\text{Ca}^{2+}]_i$ also regulates the release of slower acting astrocyte-derived factors that regulate receptor expression and shape each other in a feedback loop, with transforming growth factor $\beta 1$ and glycophipans^{29–31}. The release of these gliotransmitters has been reported to generate a wide range of effects on neurons (summarized in Fig. 1 and described at length in ref. 32). Glutamate release evokes an inward membrane current in neurons, mediated by NMDA receptors, and increases the excitability of neurons and induces long-term potentiation^{32–35}. Release of glutamate and GABA, and of ATP (which is converted to adenosine by extracellular ecto-ATPases), regulates synaptic and release probability by activating presynaptic receptors^{36–38}. The resulting changes in synaptic strength regulate whether synaptic plasticity can occur^{39–41}, as does the release of D-serine, which controls the amount of NMDA receptor activation occurring when glutamate is released at synapses^{32,33}. These changes of neuronal function are likely to be specific to individual neurons, but a major high-level function of gliotransmitter release was suggested to be modulation of sleep induction, produced by the accumulation of adenine nucleotides in the astrocyte-rich region⁴².

In addition to altering neuronal information processing, calcium-evoked release of messengers from astrocytes was suggested to regulate the energy supply to the brain in three important ways. First, increases of astrocyte $[\text{Ca}^{2+}]_i$ lead to the release of arachidonic acid (AA) from the membrane, which promotes the production of eicosanoids (PGs and 20-hydroxyeicosatetraenoic acid (20-HETE)) that modulate the contraction of vascular smooth muscle⁴³. This provides a mechanism by which the polarized morphology of astrocytes—with their processes extending into the extracellular space and their cell bodies—could regulate cerebral blood flow and energy supply⁴⁴ according to the activity of synapses, the main consumers of energy in the brain. Second, glutamate-evoked rises in astrocyte $[\text{Ca}^{2+}]_i$ trigger the uptake of glucose from the blood into the astrocyte, facilitating glucose uptake from the blood when synapses are active⁴⁵. Third, regulation of oxygen supply to the whole body may involve the activation of brainstem astrocytes by CO_2 , which leads to a $[\text{Ca}^{2+}]_i$ rise and a P2X receptor-mediated increase in blood flow⁴⁶.

All this work led to the idea that astrocytes constitute a network of cells that process information and regulate brain energy supply in parallel with neurons. It culminated in the proposal that an increase in the number of astrocytes in the brain is associated with the increased neural processing power that has occurred during hominid evolution⁴⁷. This idea was reinforced by an increase in synaptic plasticity and learning seen in mice seeded with human astrocytes⁴⁸, which

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Astrocytic perisynaptic process: Four major mechanisms to interact with neurons

1. Extracellular ion (K^+ , Ca^{2+} , ...) regulation (some modeling studies)
2. Neurotransmitter (glutamate, GABA) uptake via transporters (some modeling studies)
3. Sensing of glutamate by metabotropic glutamate receptors (most often modeled, NEST TUTORIAL)
4. Gliotransmission, ie. release of gliotransmitters and gliomodulators (many modeling studies, NEST tutorial)

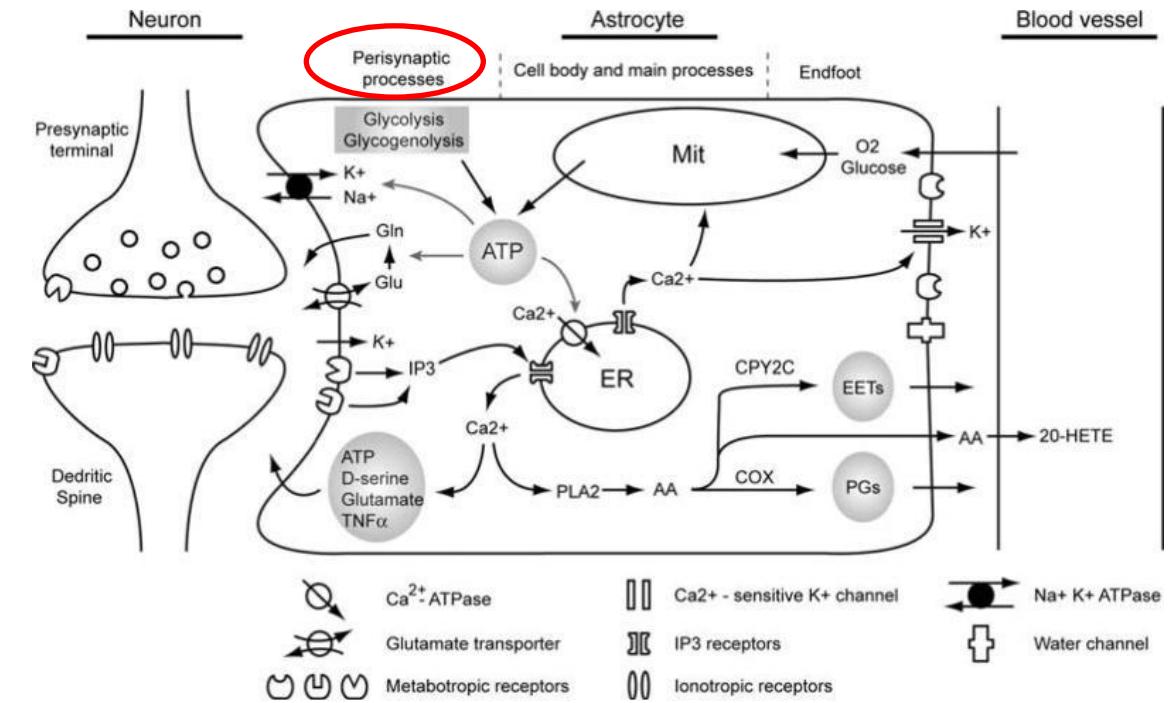


Figure from Wang et al. (2013)

Two fundamental (cell level) CNS models for neurons

ANALYTICAL / SIMULATION MODEL

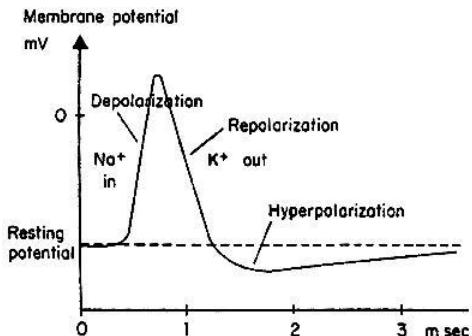
"THEORY MODEL"

Hodgkin-Huxley model:

- Mathematical model for action potential initiation and propagation
- Set of nonlinear differential equations
- Conductance-based



Alain Hodgkin
1914-1998 Andrew Huxley
1917-2012



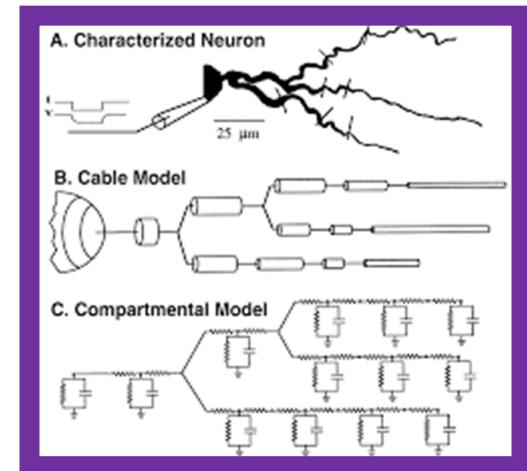
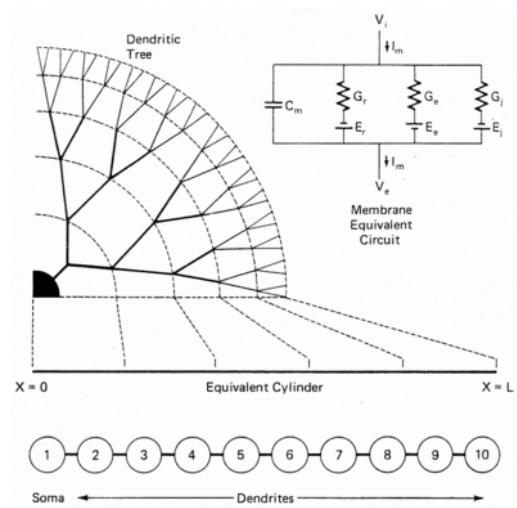
$$\begin{aligned}C \frac{dv}{dt} &= I - g_{Na}m^3h(V - V_{Na}) - g_Kn^4(V - V_K) - g_L(V - V_L) \\ \frac{dm}{dt} &= a_m(V)(1-m) - b_m(V)m \\ \frac{dh}{dt} &= a_h(V)(1-h) - b_h(V)h \\ \frac{dn}{dt} &= a_n(V)(1-n) - b_n(V)n \\ a_m(V) &= .1(V + 40)/(1 - \exp(-(V + 40)/10)) \\ b_m(V) &= 4 \exp(-(V + 65)/18) \\ a_h(V) &= .07 \exp(-(V + 65)/20) \\ b_h(V) &= 1/(1 + \exp(-(V + 35)/10)) \\ a_n(V) &= .01(V + 55)/(1 - \exp(-(V + 55)/10)) \\ b_n(V) &= .125 \exp(-(V + 65)/80)\end{aligned}$$

Rall model:

- Biophysical-mathematical model of neurons with dendritic trees
- Cable model



Wilfrid Rall
1922-2018

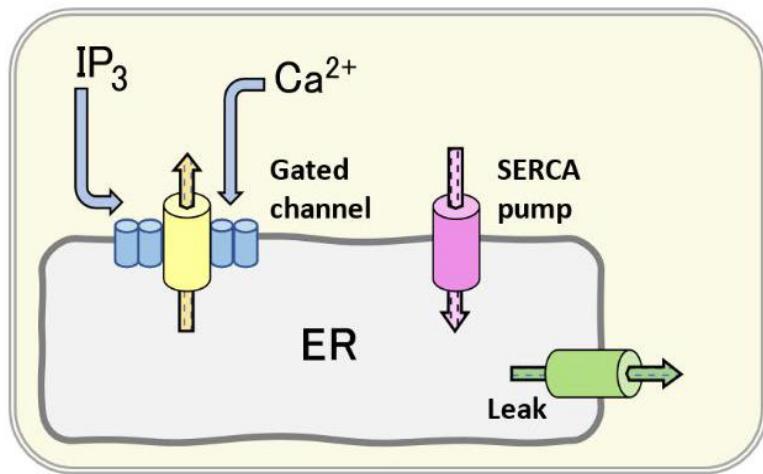


Hodgkin and Huxley, 1952

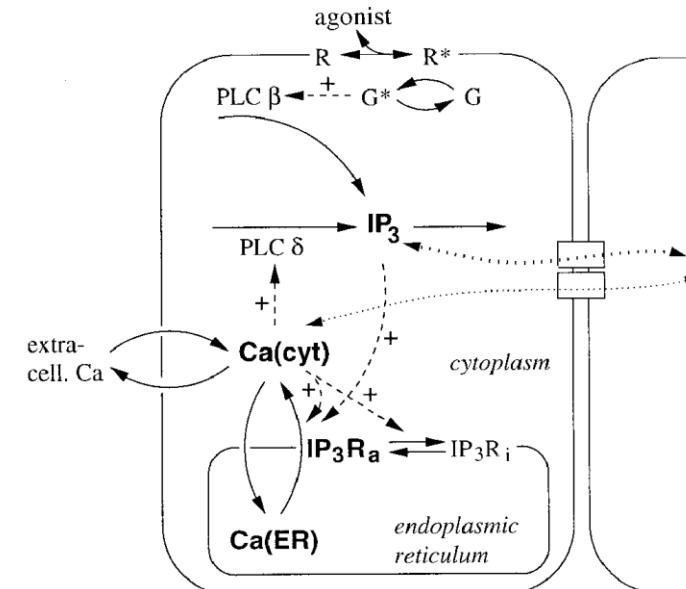
www.scholarpedia.org/article/Rall_model

Two generic astroglia models

- Two models are commonly used as basic building blocks of all published astrocyte models
 - **Li and Rinzel (1994)**: Equations for IP₃-receptor mediated $[Ca^{2+}]_i$ oscillations derived from a detailed kinetic model: A Hodgkin-Huxley like formalism (J. Theor. Biol.).
 - **Höfer et al. (2002)**: Control and Plasticity of Intercellular Calcium Waves in Astrocytes: A Modeling Approach (J. Neurosci.).



Li and Rinzel (1994) J. Theor. Biol.



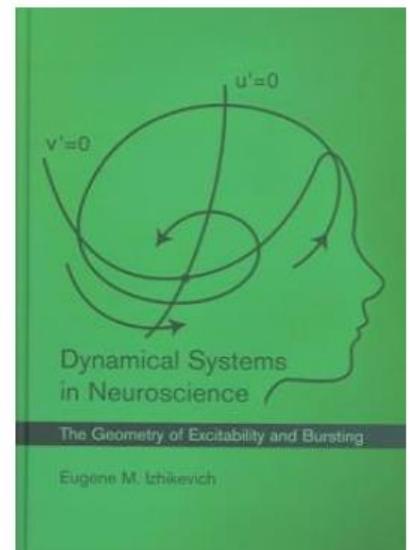
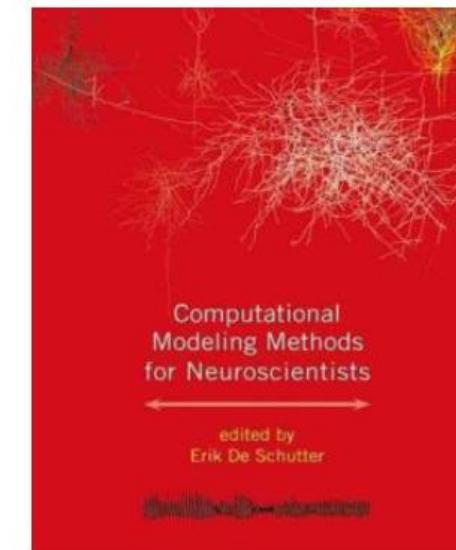
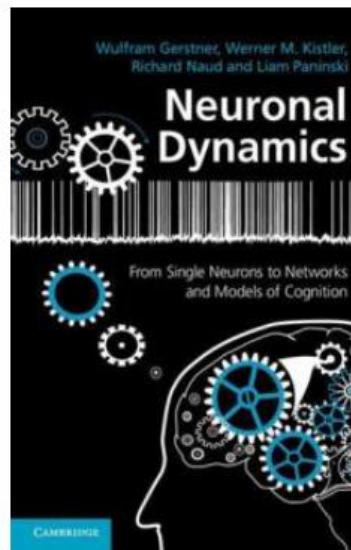
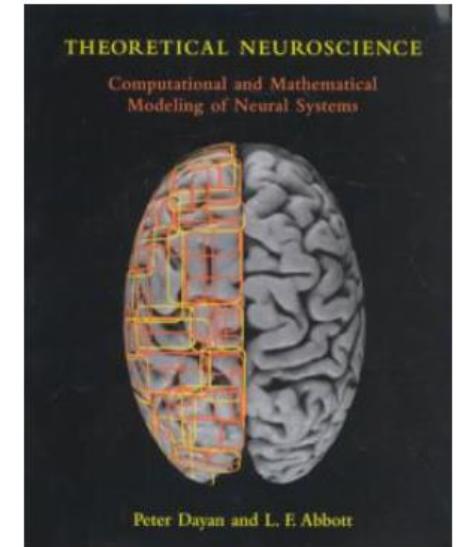
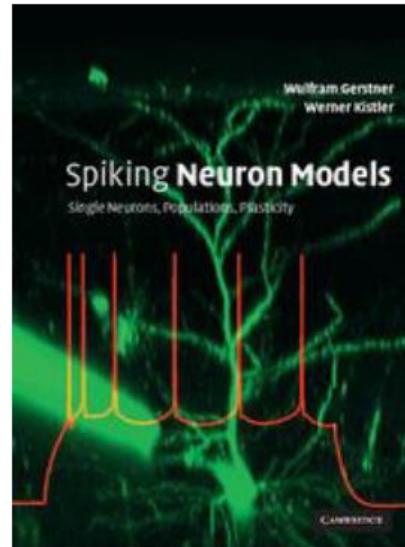
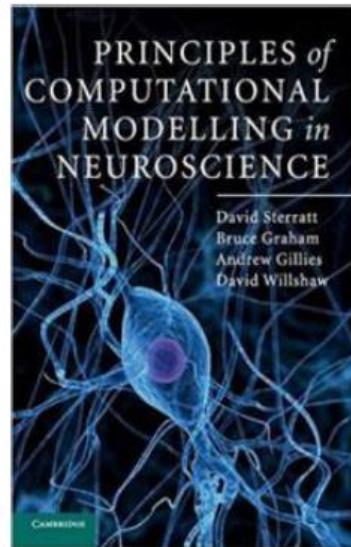
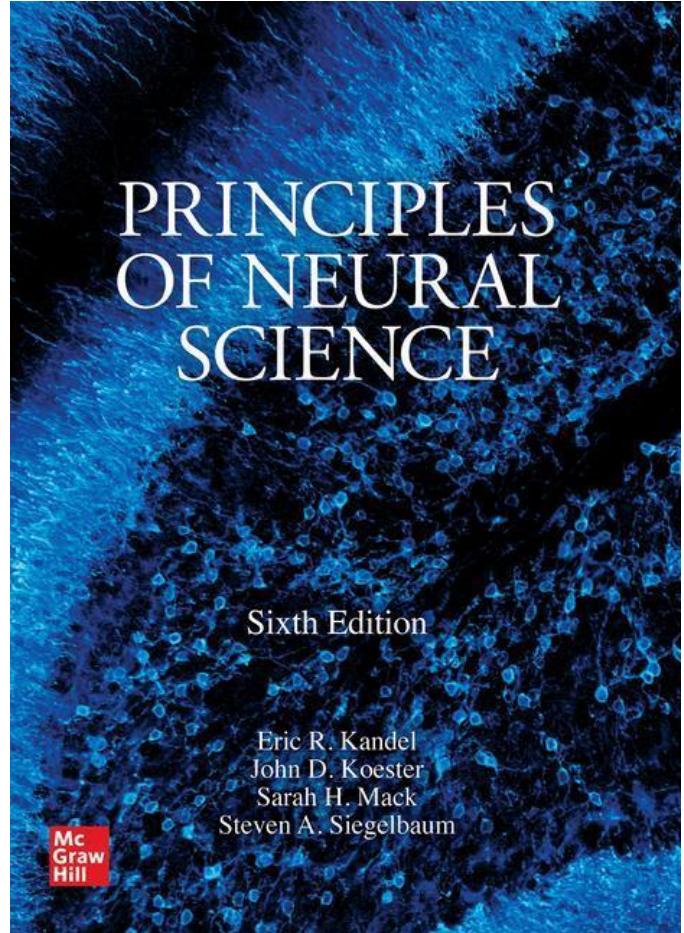
Höfer et al. (2002) J. Neurosci.

Take-home message I

Astrocyte cell biology

- Astrocytes are **morphologically very complex cells**.
- Unlike neurons, astrocytes **do not possess a clear-cut 'ground truth' signal**, like the action potential in neuronal activity.
- Astrocyte **calcium signaling exhibits significant variability**, depending on factors such as **brain region, astrocyte subtype, developmental stage, and the underlying mechanisms** driving the signal.
- **Somatic** calcium signals differ from the calcium signals observed in **processes** and **fine processes**.

Textbooks



Edited textbooks

