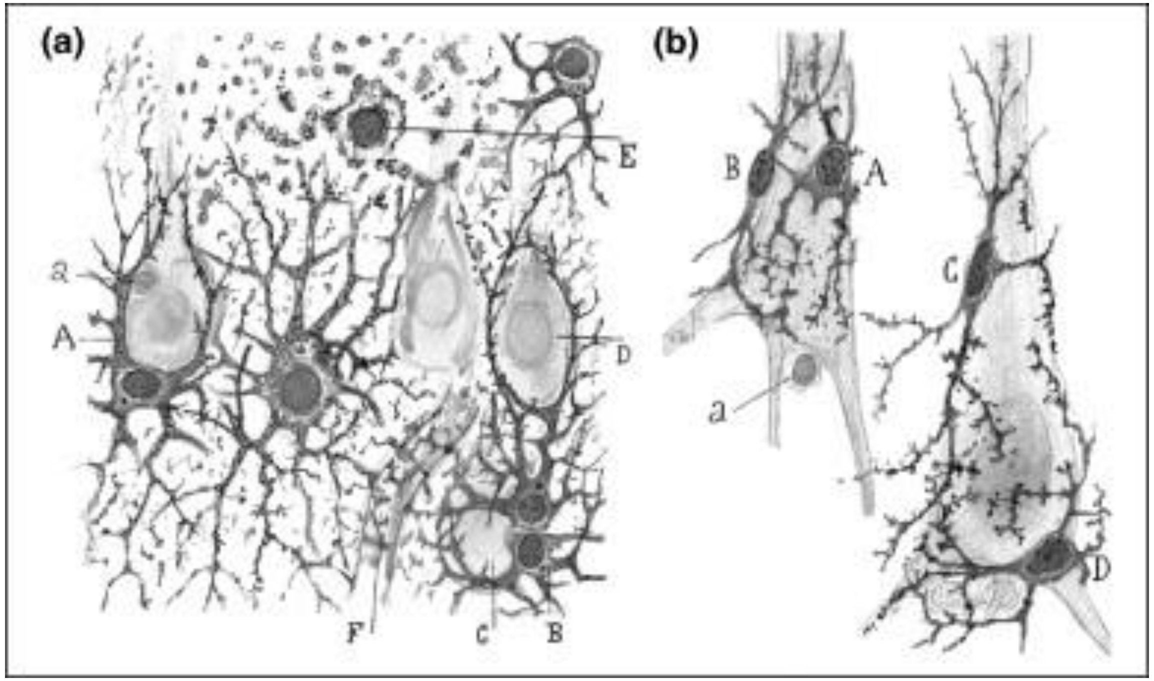
GLIAL CELLS

MYKHAILO BATIUK, PhD
Gräff lab, BMI, EPFL

Glia

- Long been neglected
- Name originated from “glue”
- But far more functions than just “glue”



Drawing from Santiago Ramon y Cajal

Glia/neuron ratio

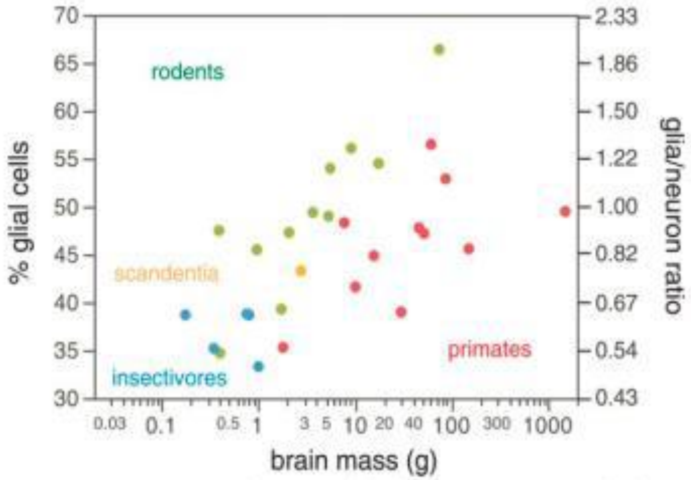


FIGURE 2: Variation in the overall glia/neuron ratio in the brain of 29 species of mammals according to brain mass. Each point represents the average proportion of glial cells (left axis) and the glia/neuron ratio (right axis) for one species, obtained by applying the isotropic fractionator separately to the cerebral cortex, cerebellum, and rest of brain of each specimen then pooling all structures together, and plotted against average brain mass for that species. Data from Herculano-Houzel et al. (2006, 2007, 2011), Azevedo et al. (2009), Sarko et al. (2009), and Gabi et al. (2010).

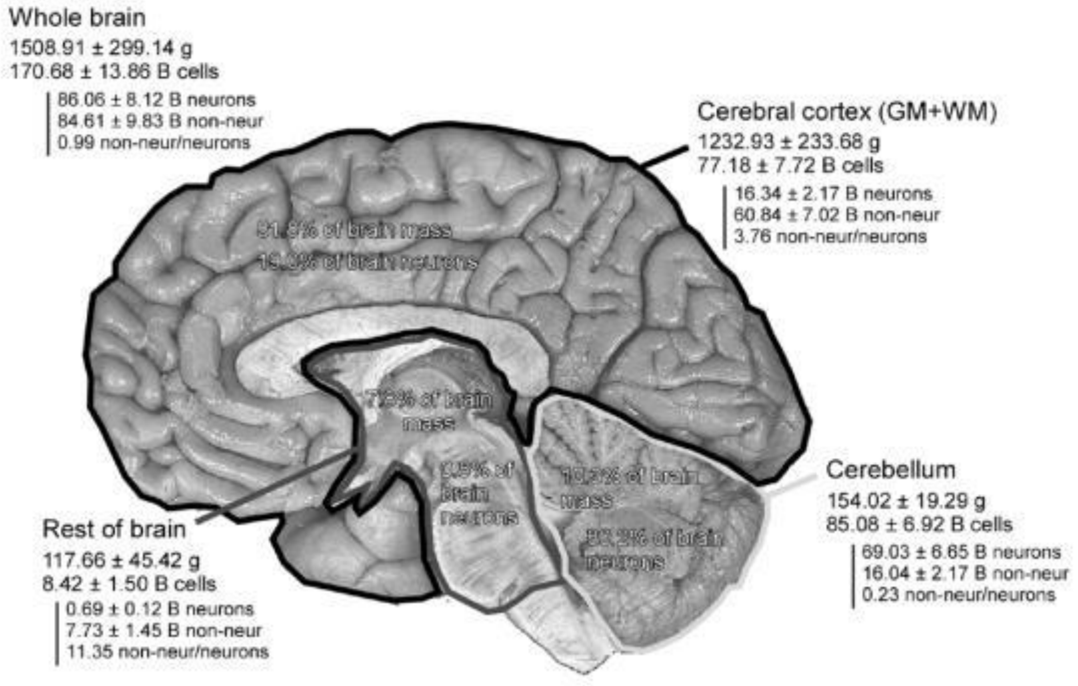


Figure 2.
Absolute mass, numbers of neurons, and numbers of nonneuronal cells in the entire adult human brain. Values are mean ± SD and refer to the two hemispheres together. B, billion.

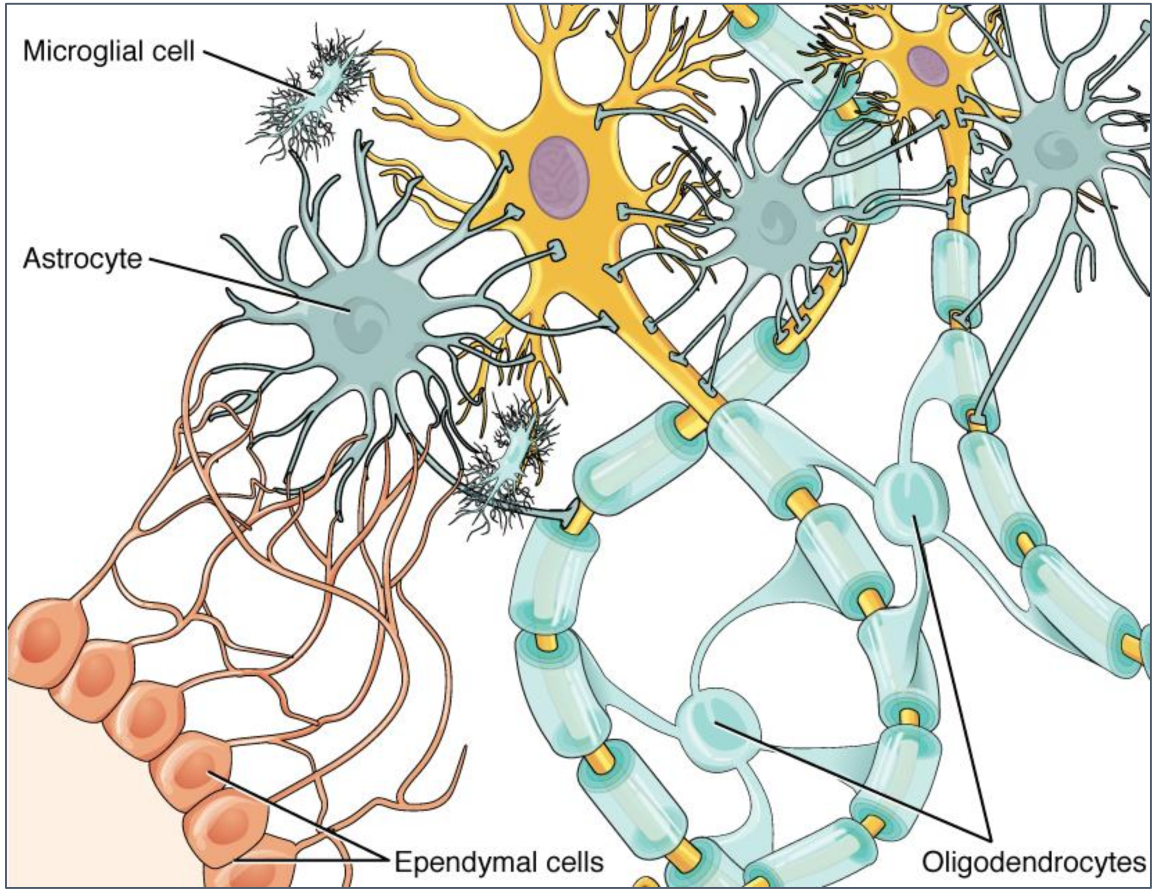
Herculano-Houzel S, Glia, 2014, 62:1377

Azevedo FAC et al, J Com Neurol, 2009, 513:532

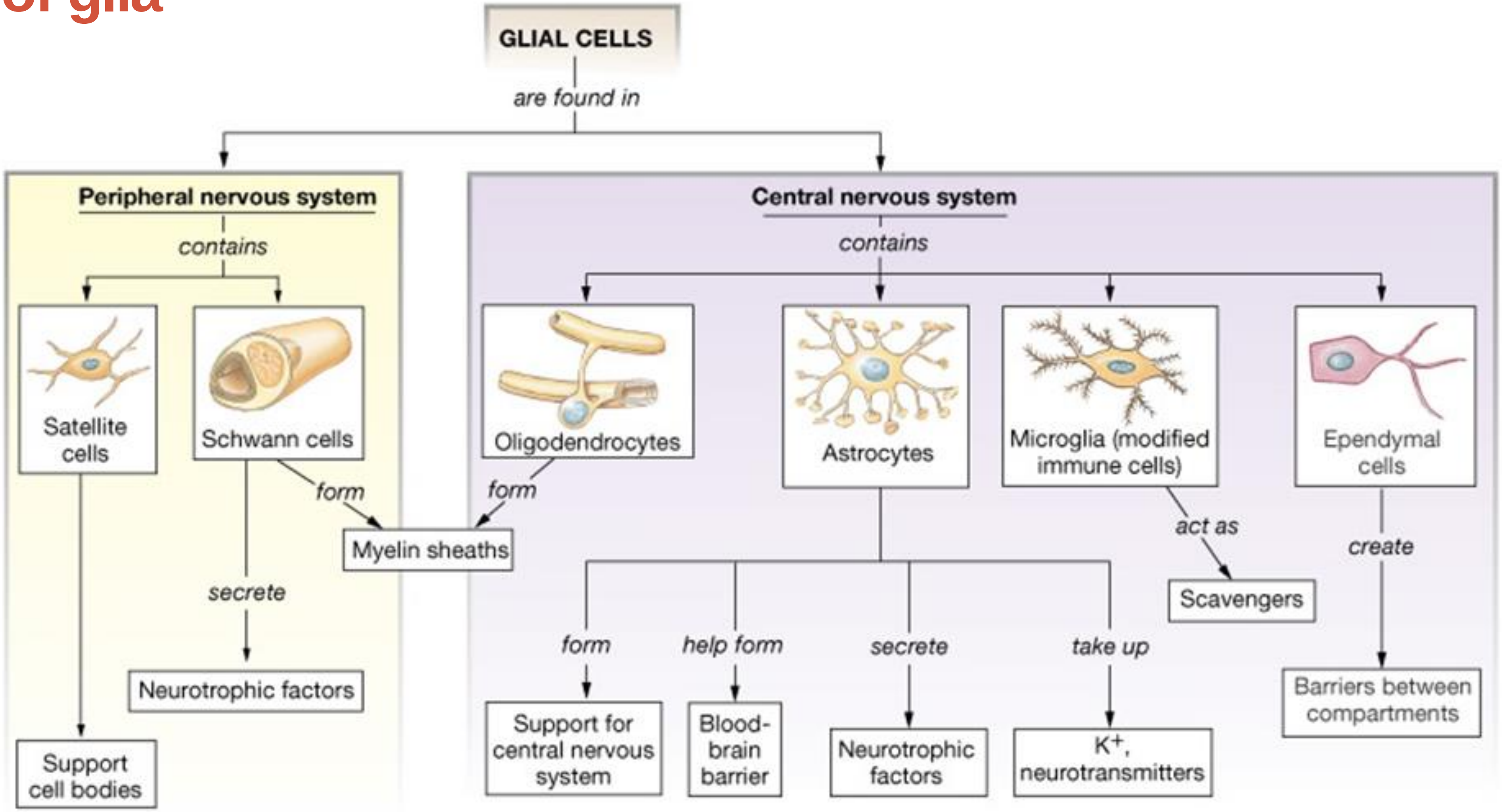
More glia to neurons in bigger brains . Glia to neurons is 1 to 1 in human

Type of glia

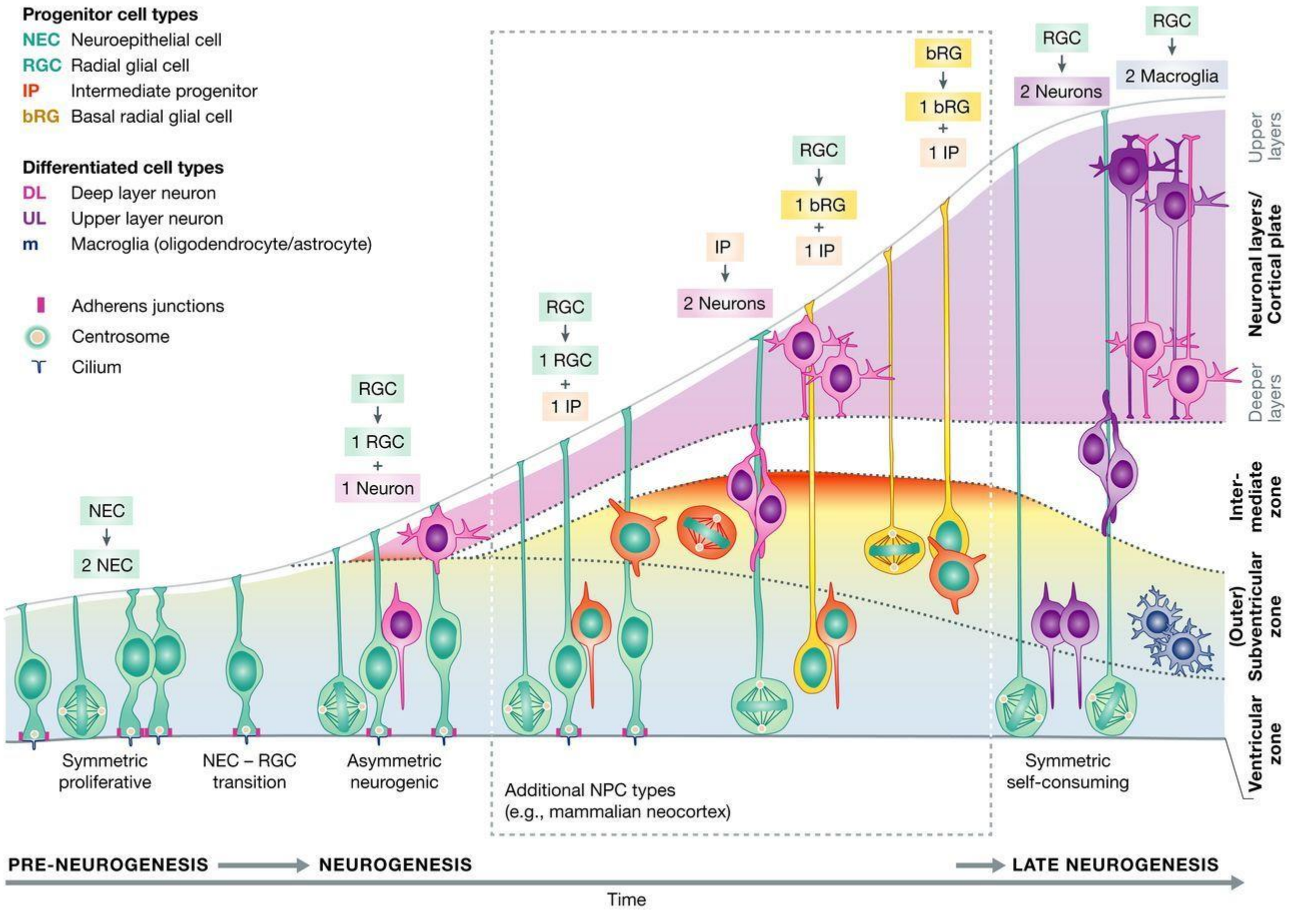
1) Astrocytes
2) Oligodendrocytes
3) Microglia
4) Ependymal cells



Type of glia


GLIAL CELLS
are found in
Peripheral nervous system
contains
Satellite cells
Schwann cells
form
Myelin sheaths
secrete
Neurotrophic factors
Support cell bodies
Central nervous system
contains
Oligodendrocytes
form
Astrocytes
Microglia (modified immune cells)
act as
Scavengers
Ependymal cells
create
Barriers between compartments
form
help form
secrete
take up
Support for central nervous system
Blood-brain barrier
Neurotrophic factors
K+, neurotransmitters

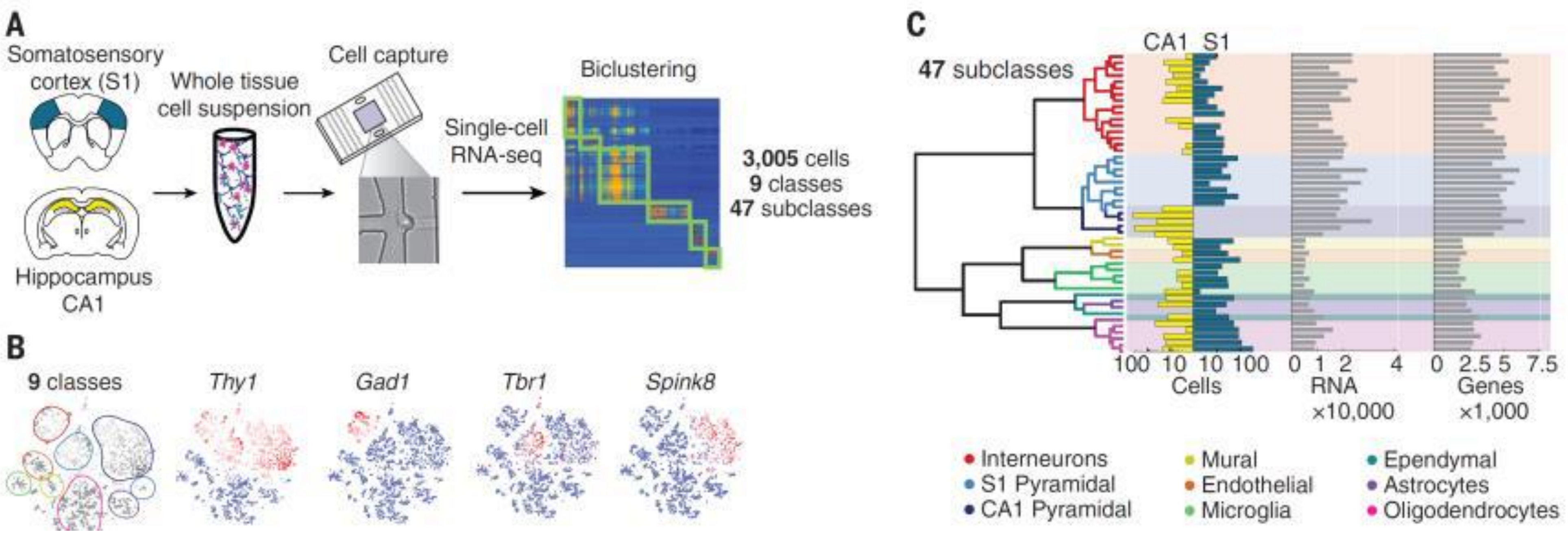
Origin of glia



Ernst Haeckel: embryogenesis often recapitulates evolution

Who appeared first in evolution?

Until recently glia was thought to be homogeneous



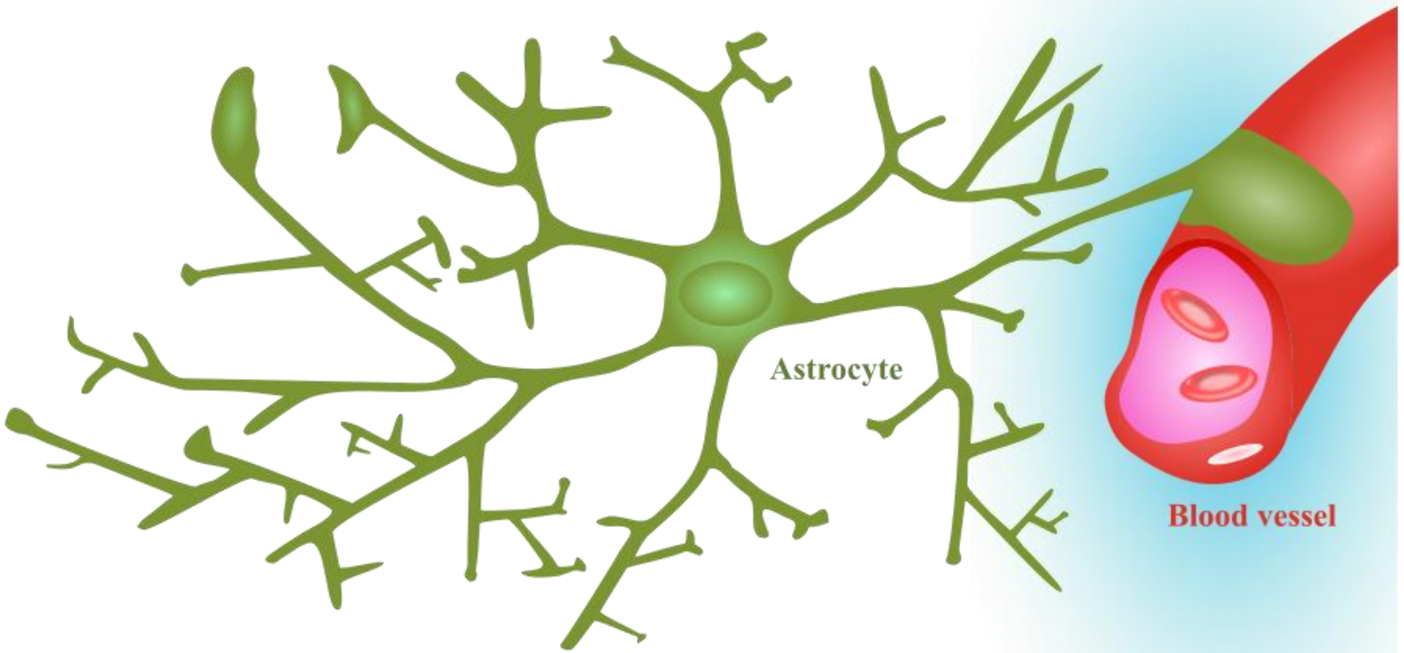
Subclasses:
Interneurons 16
Astrocytes 2
Microglia 2
Oligodendrocytes 6

Cell types in the mouse cortex and hippocampus in juvenile mice (21-21 days) revealed by single-cell RNA-seq.

Zeisel A et al, Science. 2015, 347:1138-1142.

1) Astrocytes

1) Astrocytes



Blood-brain barrier

Brain clean-up

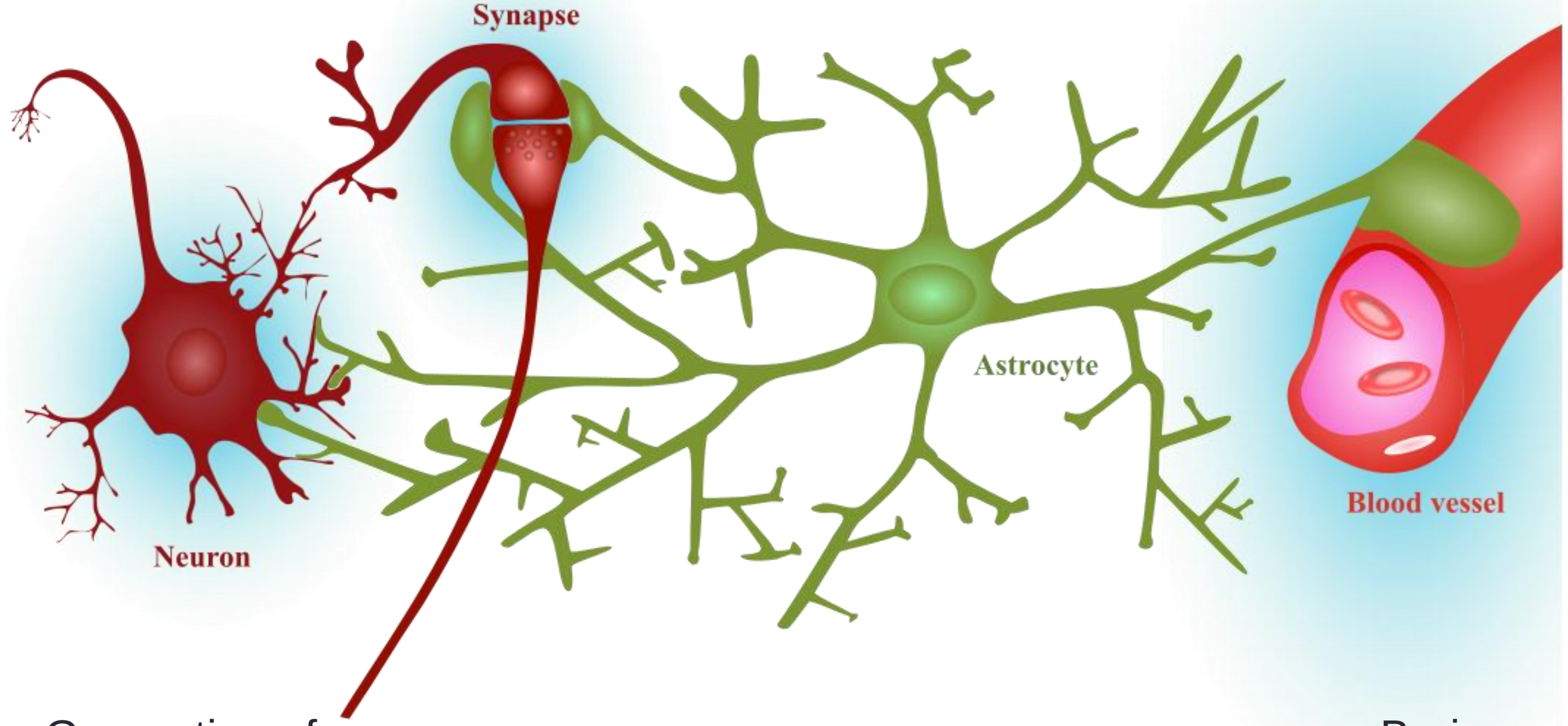
1) Astrocytes

Synapse biogenesis

Control of neurotransmission

Blood-brain barrier

Gliotransmission



Generation of new neurons

Brain clean-up

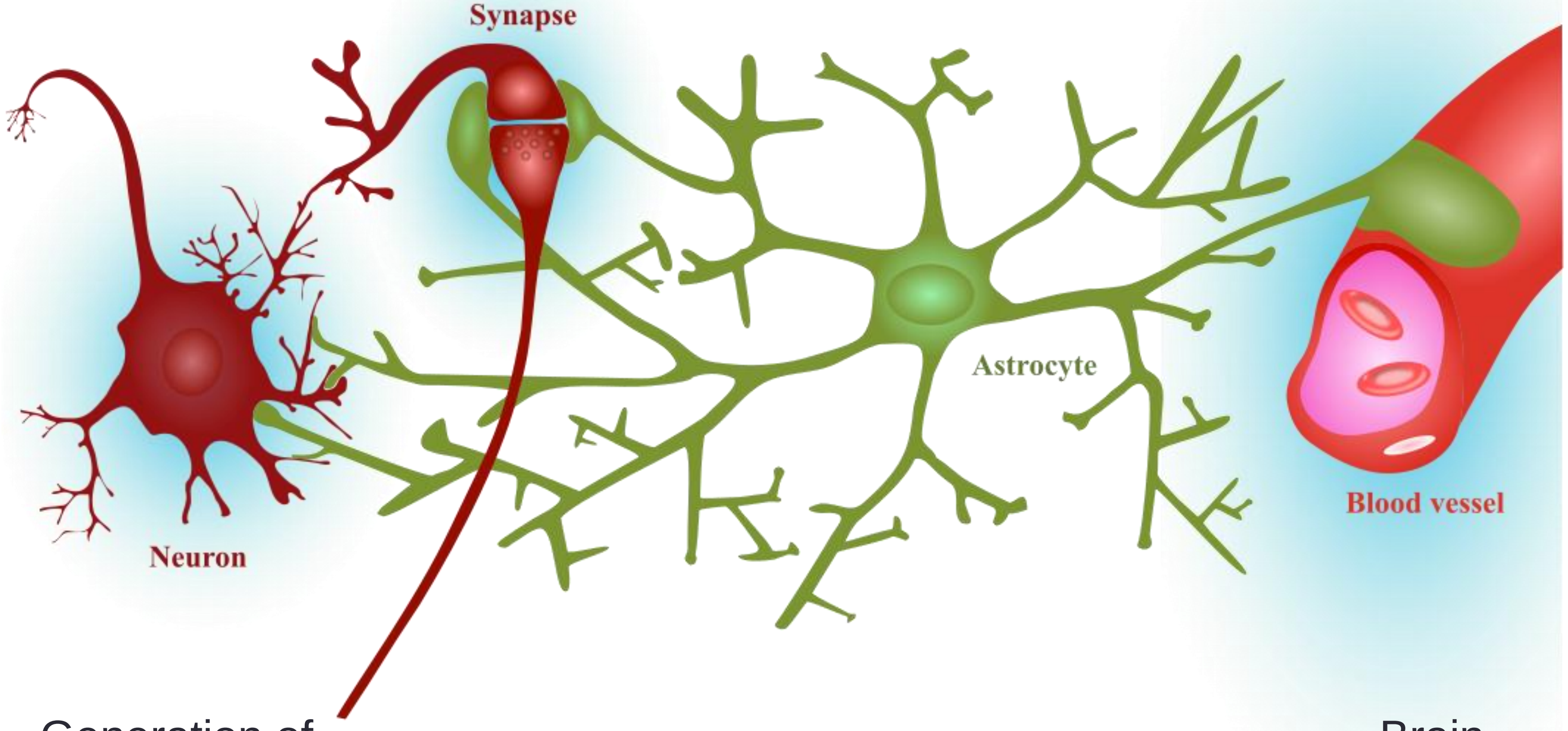
1) Astrocytes

Synapse biogenesis

Control of neurotransmission

Blood-brain barrier

Gliotransmission

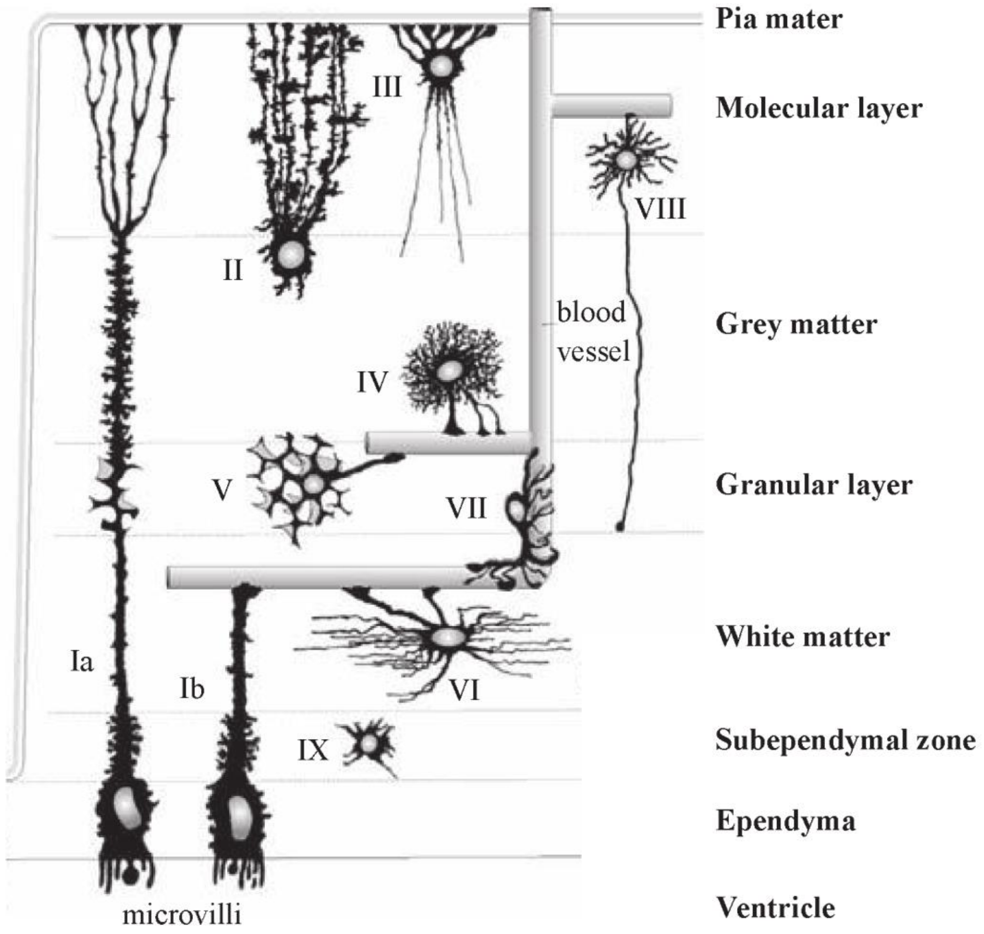


Generation of new neurons

Brain clean-up

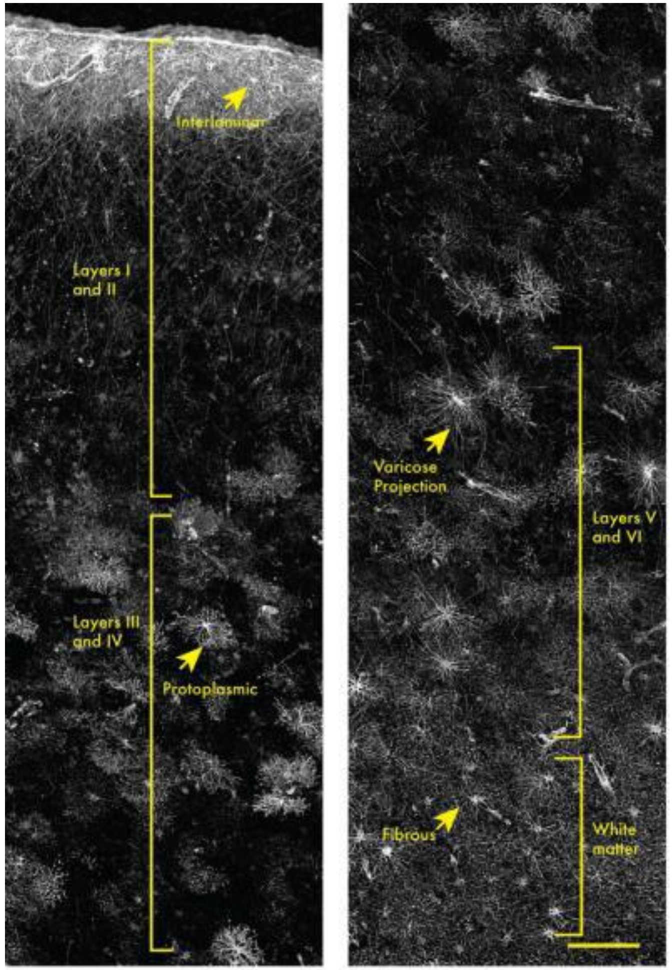
Neuron metabolic support
Blood flow regulation
Ion homeostasis

Morphologies of astrocytes

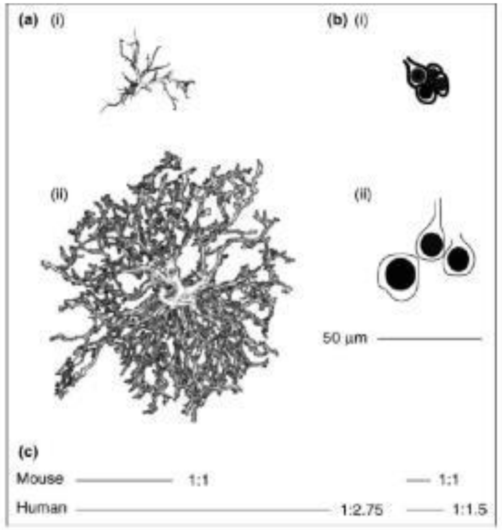


General classical subdivision – fibrous astrocytes in white matter, protoplasmic in grey matter

More complex astrocyte morphology in primates



Astrocytes Neurons



Mouse

Human

Figure 2. Evolution of astrocytes and neurons. (a) Graphical representation and GFAP immunostaining of mouse (i) and human (ii) cortical astrocytes. (b) Graphical representation and MAP2 immunostaining of mouse (i) and human (ii) cortical neurons. (c) Bars illustrating the sizes of human astrocytes (left) and neurons (right) relative to the sizes of these cells in mice. Human cortical astrocytes are almost threefold larger, have approximately tenfold more GFAP-positive processes, and are more symmetrical than mouse astrocytes. The increase in complexity and size of astrocytes from mouse to man is disproportionate to the evolution of neuronal structure, possibly reflecting the increasing importance of astrocytes in the brain function of higher organisms.

Mouse – Rhesus monkey - Human

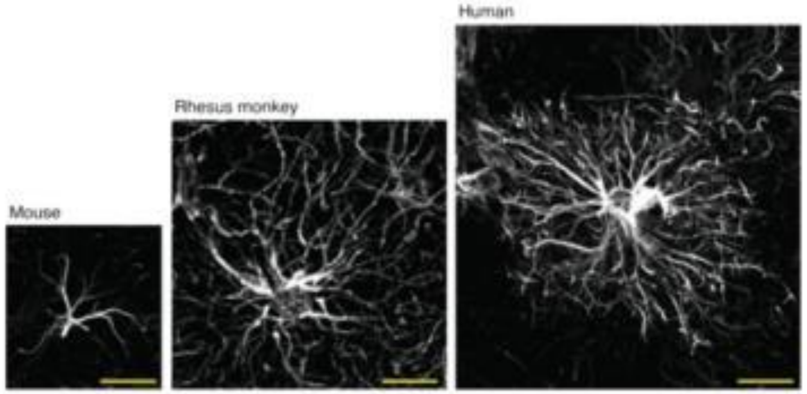


Fig. 6. Human astrocytes are larger and more complex than rodent and other primates. Mouse, Rhesus Monkey, and Human astrocytes are compared by GFAP staining (*white*). Scale = 20 µm.

Oberheim et al. 2009. J Neurosci 29:3276-87

Oberheim et al. 2006. TINS 29:547-553

Oberheim et al. 2012. Methods Mol Biol 814:23-45

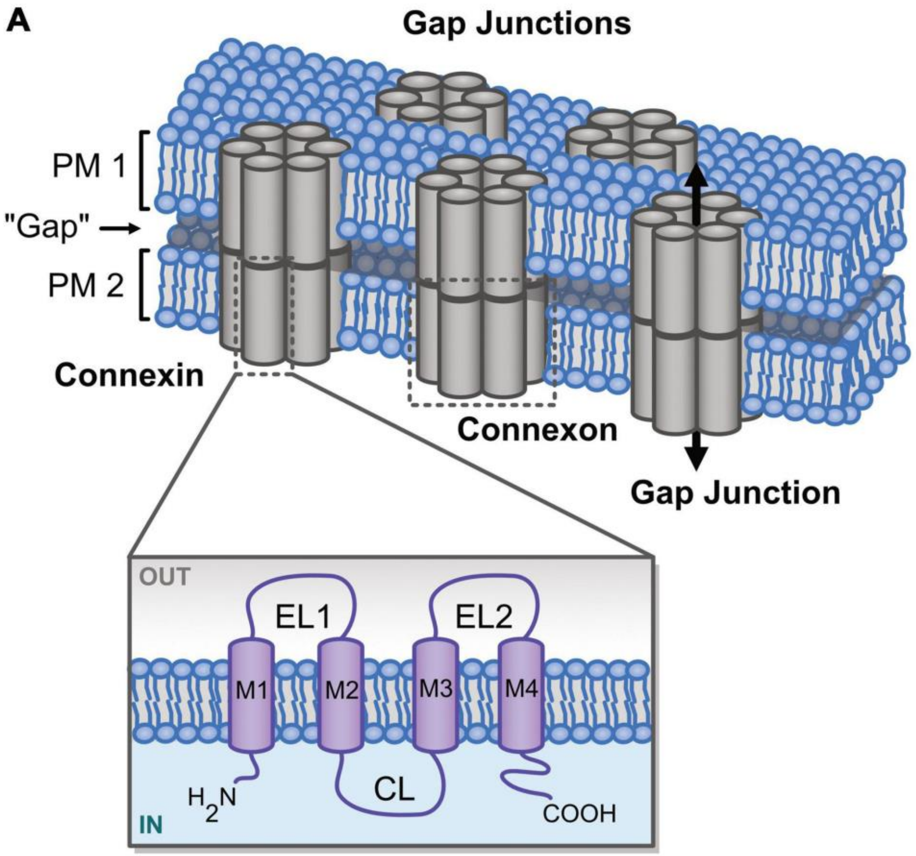
Human astrocytes in mouse brain

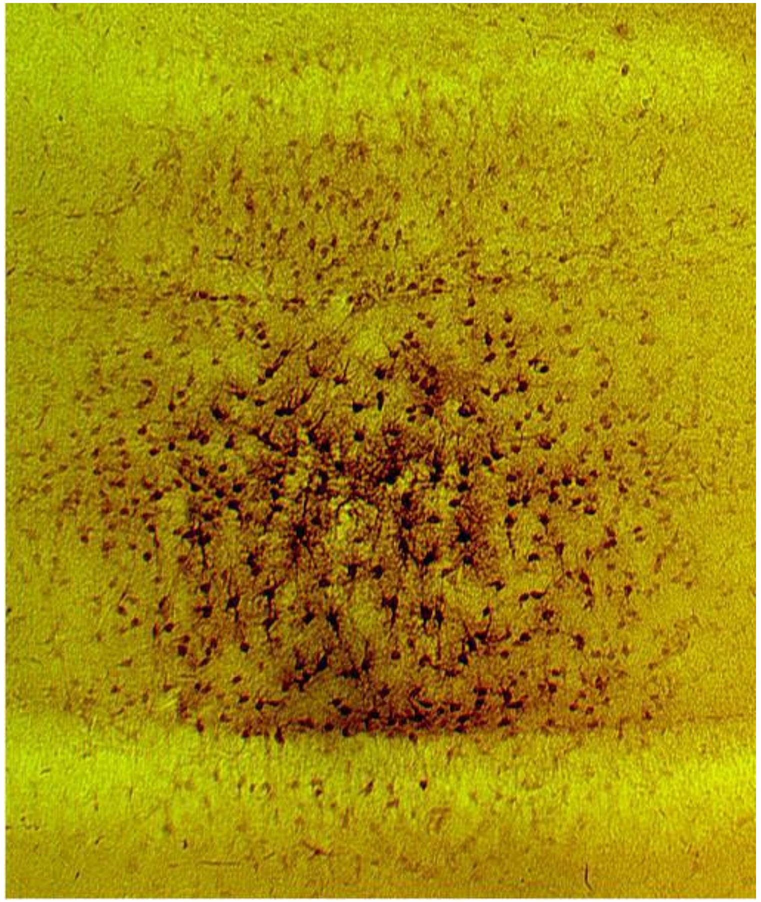
Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice

Xiaoning Han,[1,2] Michael Chen,[1,2] Fushun Wang,[1,2] Martha Windrem,[1,3] Su Wang,[1,3] Steven Shanz,[1,3] Qiwu Xu,[1,2] Nancy Ann Oberheim,[1,2] Lane Bekar,[1,2] Sarah Betstadt,[4] Alcino J. Silva,[5] Takahiro Takano,[1,2] Steven A. Goldman,[1,2,3,*] and Maiken Nedergaard[1,2,3,*]

Enhancement of mouse learning

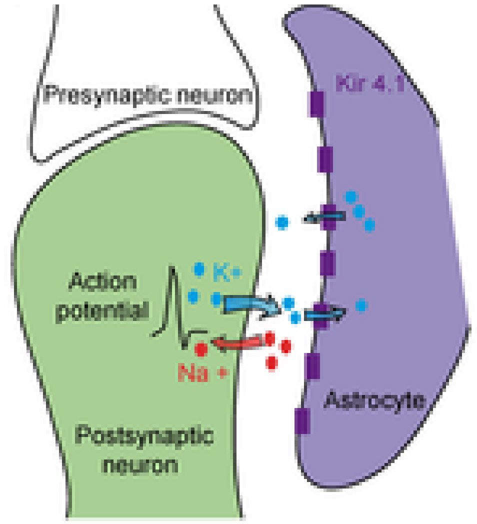
Astrocytes are connected through gap junctions





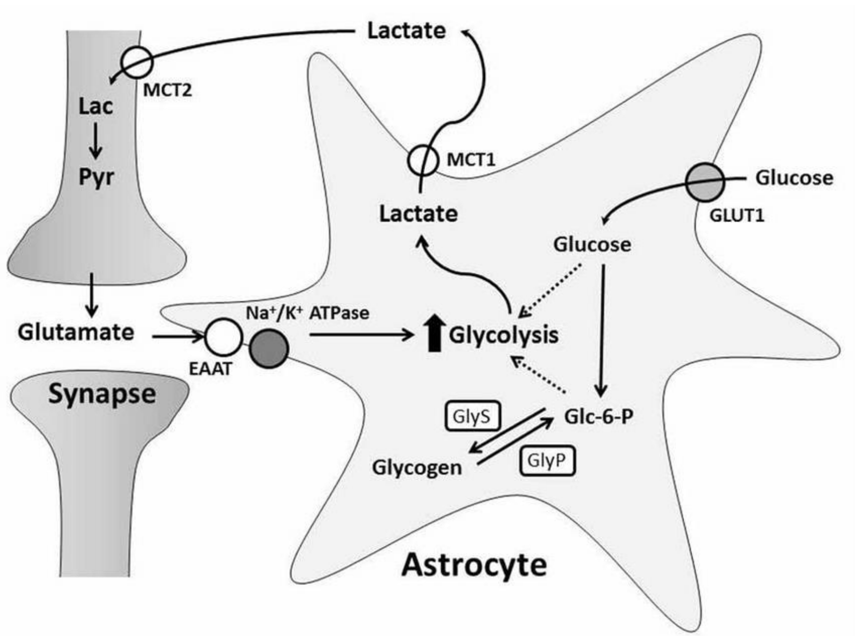
Tracer/dye injected in one astrocyte appears in other interconnected astrocytes

Regulation of extracellular K+ concentration and energy supply



- The generation of the electric signal results in increasing accumulation of K+ in the extracellular space, that is rapidly buffered by astrocytes

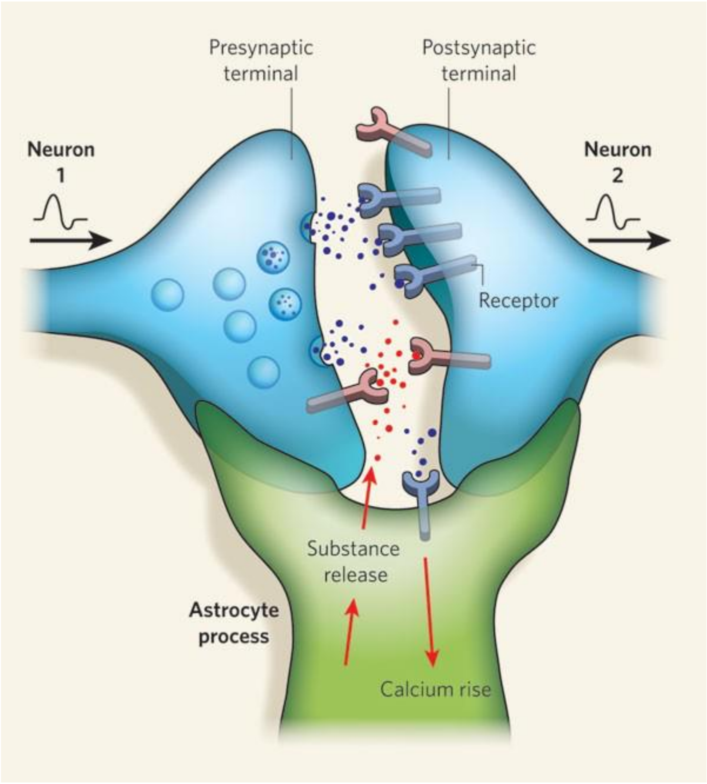
- Astrocytes can accumulate glycogen (polymers of glucose) for rapid energy supply in the form of lactate to highly active neurons

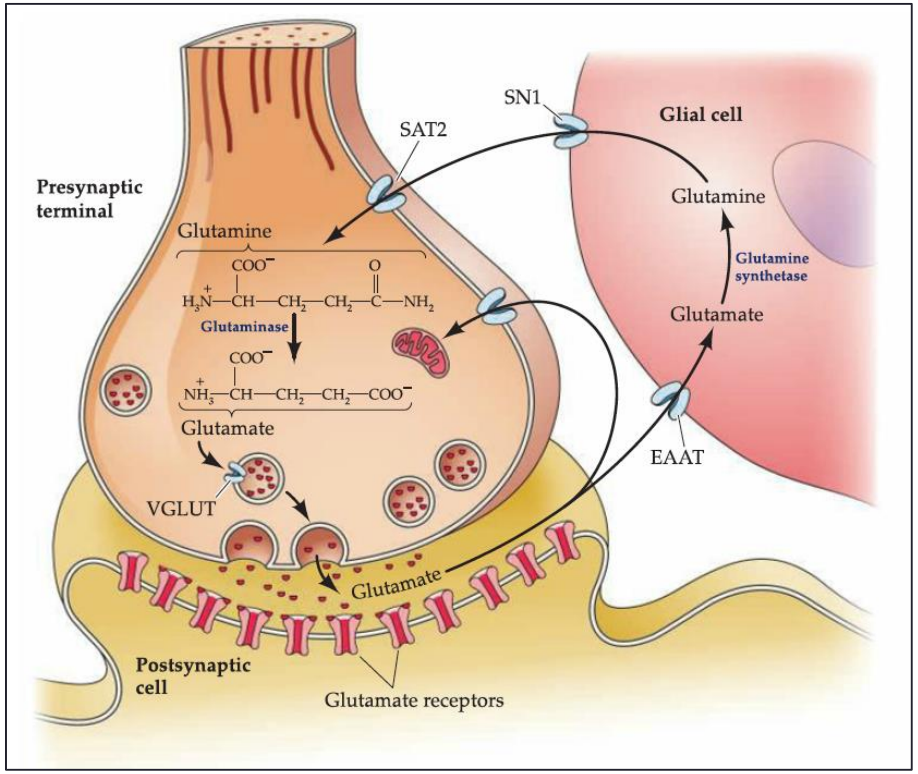


→ **Astrocytes can “sense” when neurons are active**

The tripartite synapse

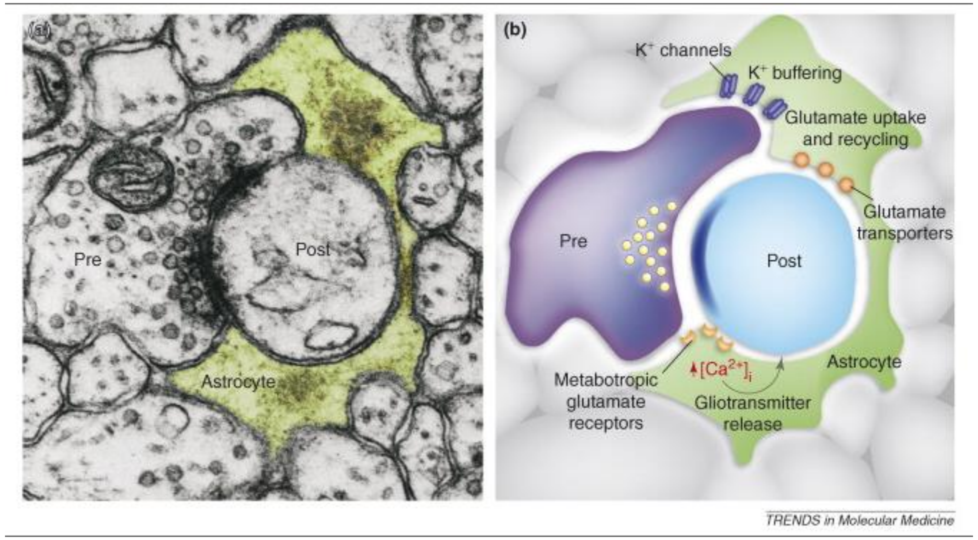
- Astrocytes processes are intimately associated with synapses
- Involved in neurotransmitter clearance through specific transporters (e.g., glutamate)

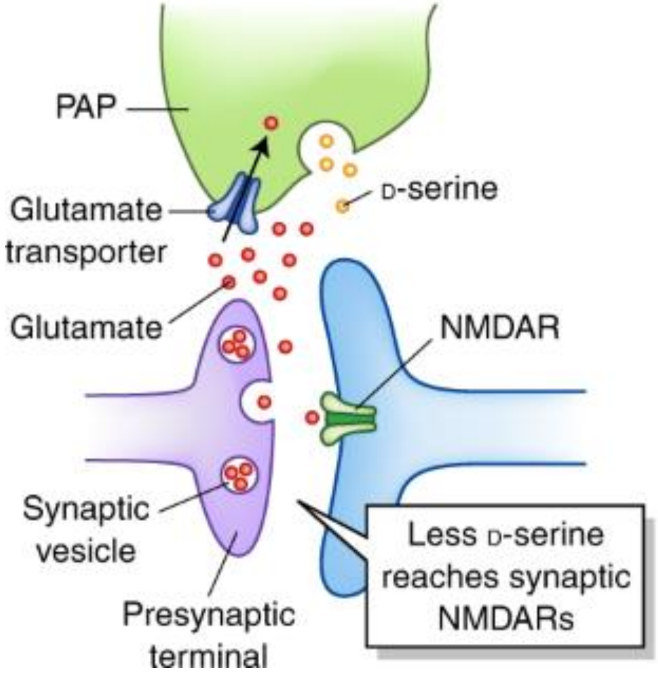




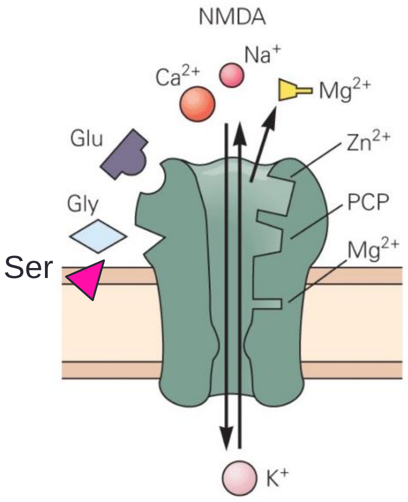
The tripartite synapse

- Neurotransmitter binding to astrocyte receptors leads to:
  - Increase in **calcium concentration**
  - Release of **gliotransmitters** (e.g., ATP, serine)
  - Role in cognition!!!





Serine is an allosteric modulator of NMDA receptor (**role in LTP**)



Article

Specialized astrocytes mediate glutamatergic gliotransmission in the CNS

https://doi.org/10.1038/s41586-023-06502-w

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Roberta de Ceglia[1], Ada Ledonne[1,2,10], David Gregory Litvin[1,3,10], Barbara Lykke Lind[1,4], Giovanni Carriero[1], Emanuele Claudio Latagliata[2], Erika Bindocci[1], Maria Amalia Di Castro[5], Iaroslav Savtchouk[1,9], Ilaria Vitali[1], Anurag Ranjak[1], Mauro Congiu[1], Tara Canonica[1], William Wisden[6], Kenneth Harris[7], Manuel Mameli[1], Nicola Mercuri[2,8], Ludovic Telley[1]✉ & Andrea Volterra[1,3]✉

From UNIL

Unique subtype of astrocytes exocytosing glutamate

Astrocytes react to neuronal activity by intracellular calcium elevation

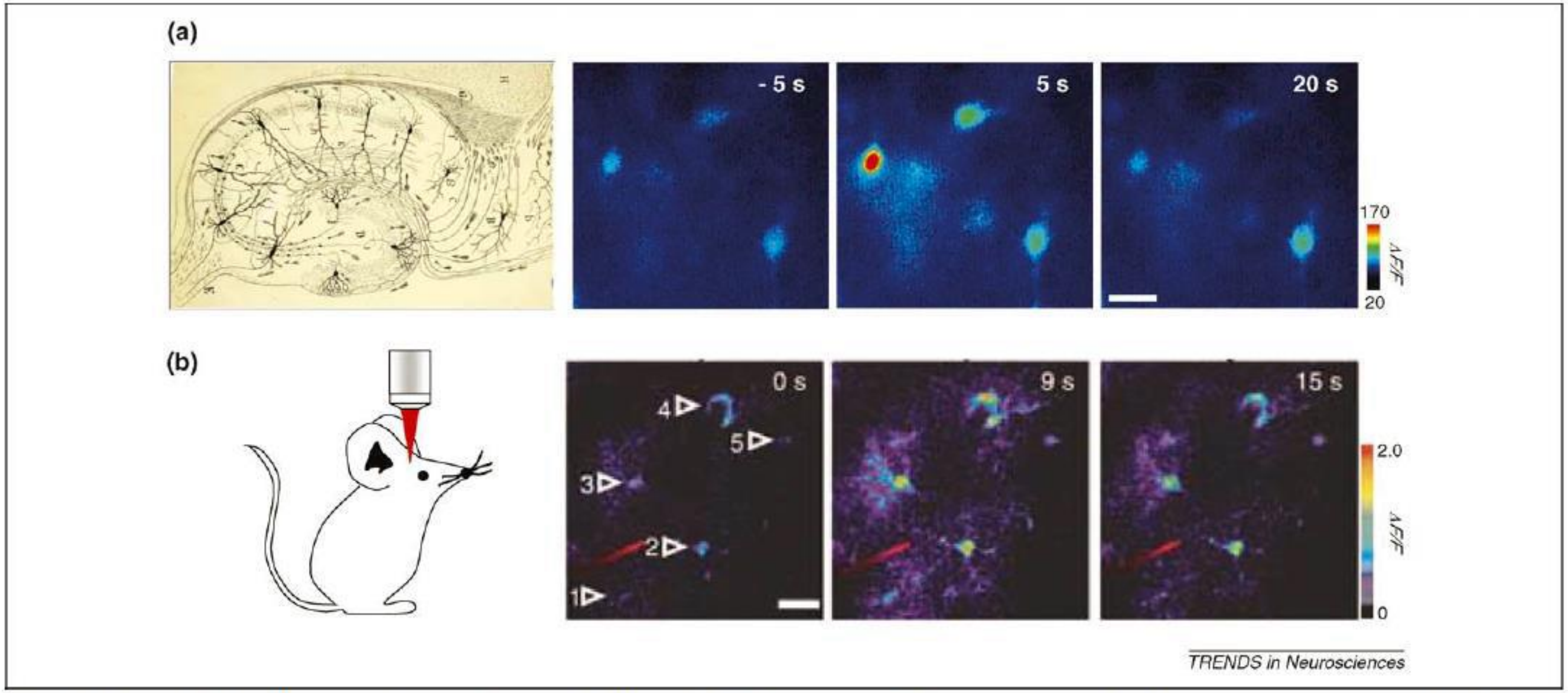
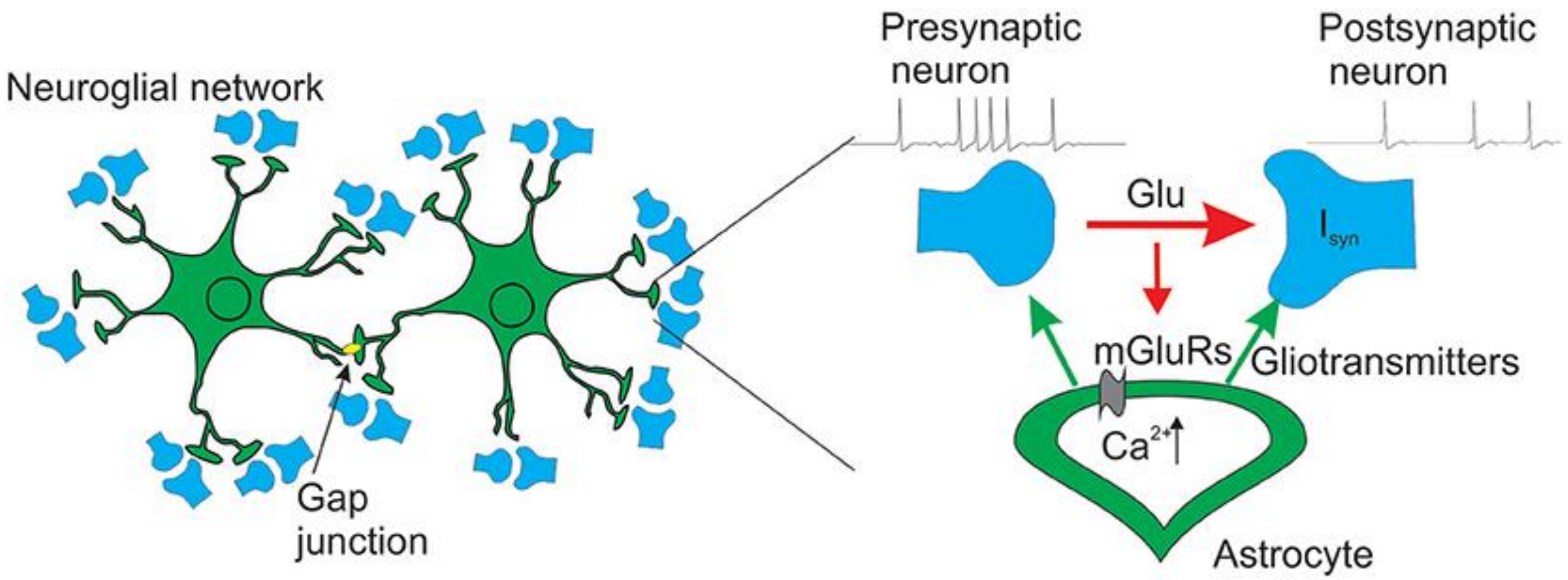


Figure 3. Astrocyte Ca^{2+} signaling in brain slices and *in vivo*. (a) Cajal's drawing of the mammalian hippocampus (reproduced from an original drawing with permission of the Instituto Cajal) and pseudocolor images from rat hippocampal slices representing fluorescence intensities indicative of astrocyte Ca^{2+} levels before (−5 s) and after (5 s, 20 s) electrical stimulation of Schaffer collaterals. Scale bar, 10 μm. (b) Two-photon microscopy images of the *in vivo* astrocyte Ca^{2+} signal in the barrel cortex. Pseudocolor images represent fluorescence intensities indicative of astrocyte Ca^{2+} levels before (0 s) and after (9 s, 15 s) evoked by whisker stimulation. Scale bar, 20 μm. Reproduced, with permission, from Ref. [33]. Note the astrocyte Ca^{2+} elevations evoked by electrical synaptic and sensory stimulation in hippocampal slices (a) and *in vivo* barrel cortex (b), respectively.

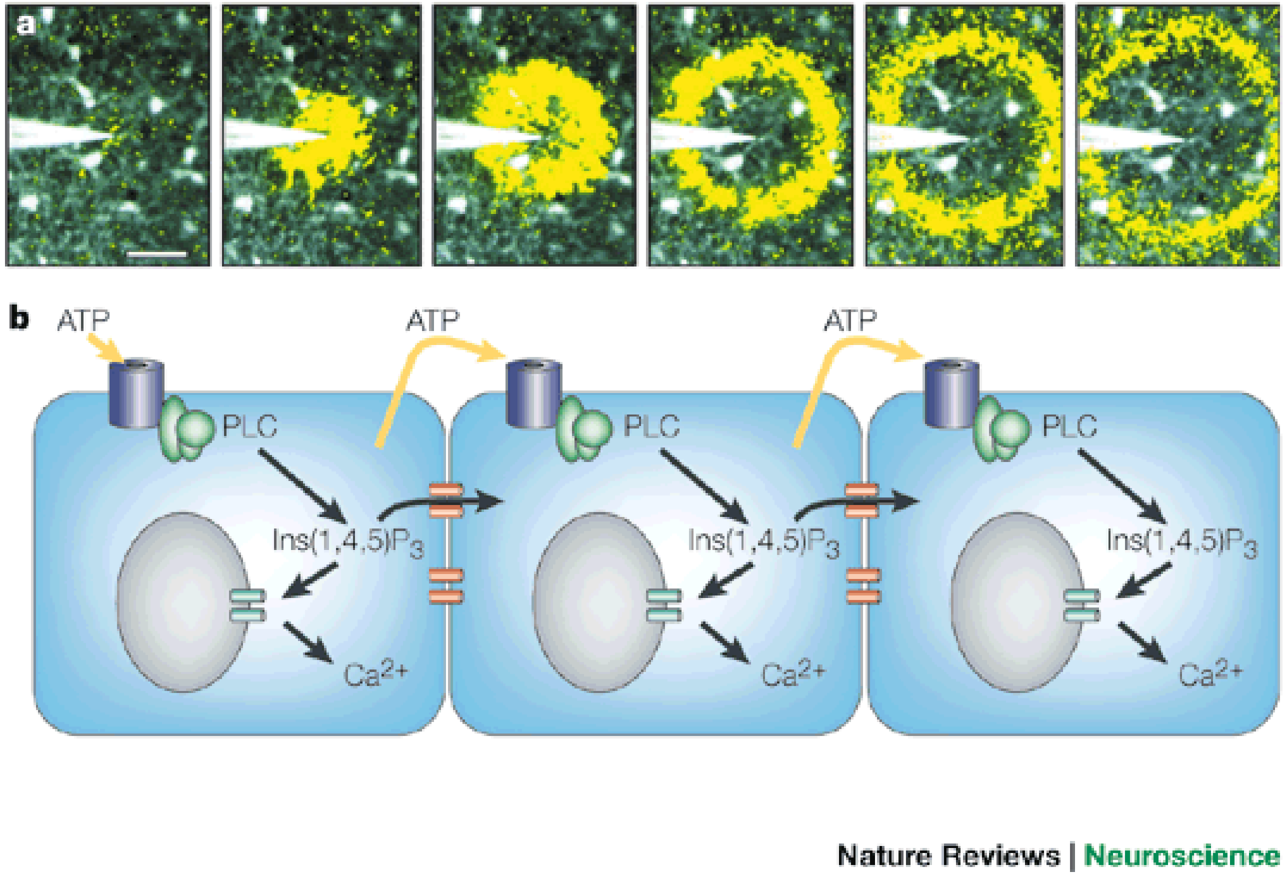
Perea et al, Trends Neurosci, 2009, 32:421

Calcium waves in astrocytes

- Calcium waves propagate through a network of interconnected astrocytes
- **Glia do not generate action potentials, but can send information (Ca2+)**



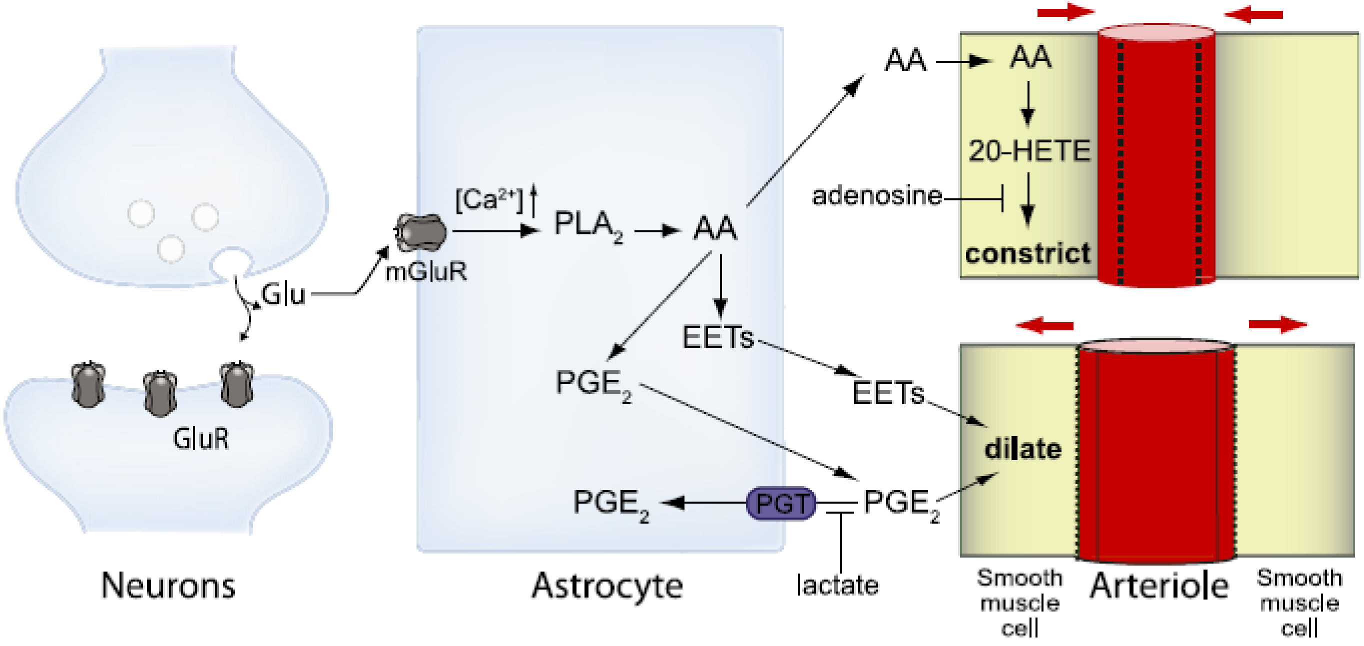
Calcium waves in astrocyte



Through gap junctions

Through release of signaling molecules (ATP) activating nearby astrocytes

Regulation of blood flow according to synaptic activity



Astrocytes sense neurotransmitter release during synaptic activity

Astrocytes increase intracellular calcium and free arachidonic acid

Astrocytes secrete prostaglandins and EETs

Blood vessels dilate

More oxygen and glucose from blood

Arachidonic acid can cause also vasoconstriction – depending on oxygen concentration

Belanger M et al, Cell metabolism, 2011, 14:724

Role for astrocytes in memory formation

nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-020-0679-6
Check for updates

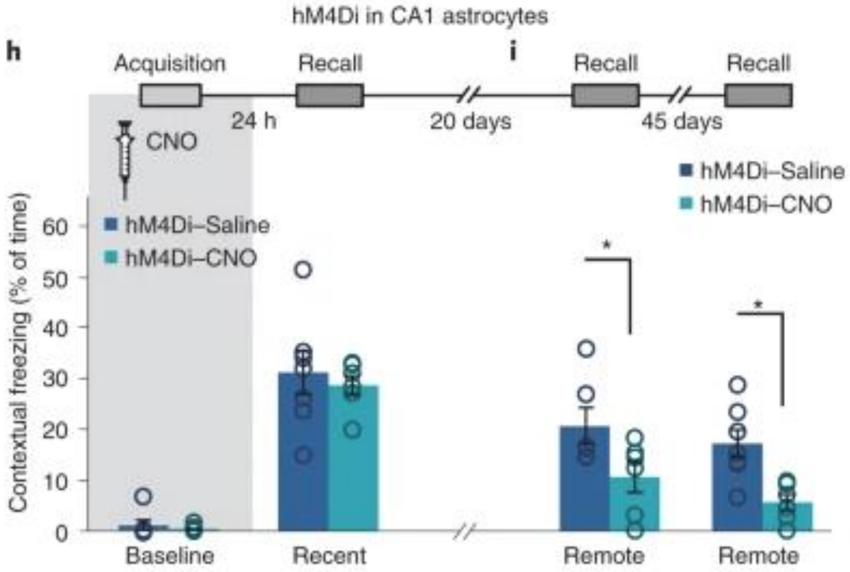
Astrocytes contribute to remote memory formation by modulating hippocampal-cortical communication during learning

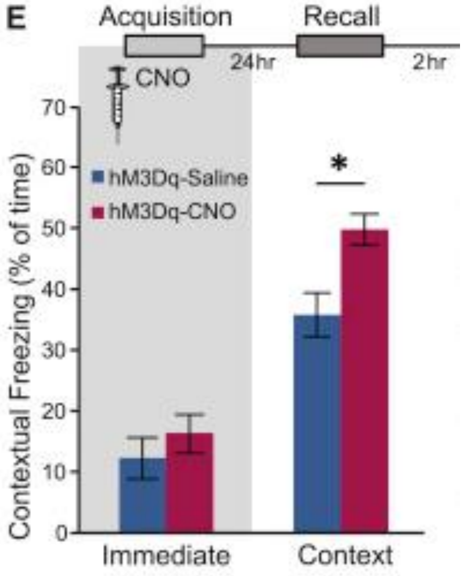
Adi Kol[1], Adar Adamsky[1], Maya Groysman[2], Tirzah Kreisel[1], Michael London[1,3] and Inbal Goshen[1]✉

Article
Cell

Astrocytic Activation Generates *De Novo* Neuronal Potentiation and Memory Enhancement

Adar Adamsky,[1,4] Adi Kol,[1,4] Tirzah Kreisel,[1] Adi Doron,[1] Nofar Ozeri-Engelhard,[1] Talia Melcer,[1] Ron Refaeli,[1] Henrike Horn,[1] Limor Regev,[1] Maya Groysman,[2] Michael London,[1,3] and Inbal Goshen[1,5,*]
[1]Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[2]ELSC Vector Core Facility, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[3]Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[4]These authors contributed equally





Role for astrocytes in memory formation

Learning-associated astrocyte ensembles regulate memory recall

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

Received: 27 December 2023

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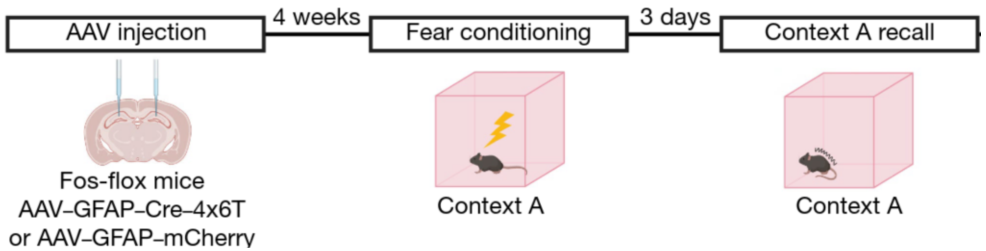
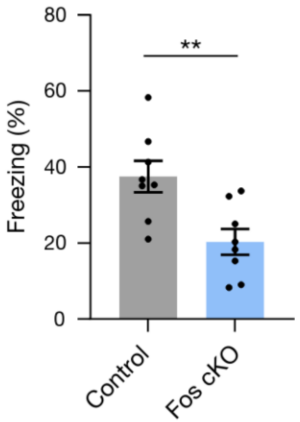
Michael R. Williamson[1,2,3,6], Wookbong Kwon[1,2,3,6], Junsung Woo[1,2,3], Yeunjung Ko[1,2,4], Ehson Maleki[1,2], Kwanha Yu[1,2,3], Sanjana Murali[1,2,5], Debosmita Sardar[1,2,3] & Benjamin Deneen[1,2,3,4,5]✉



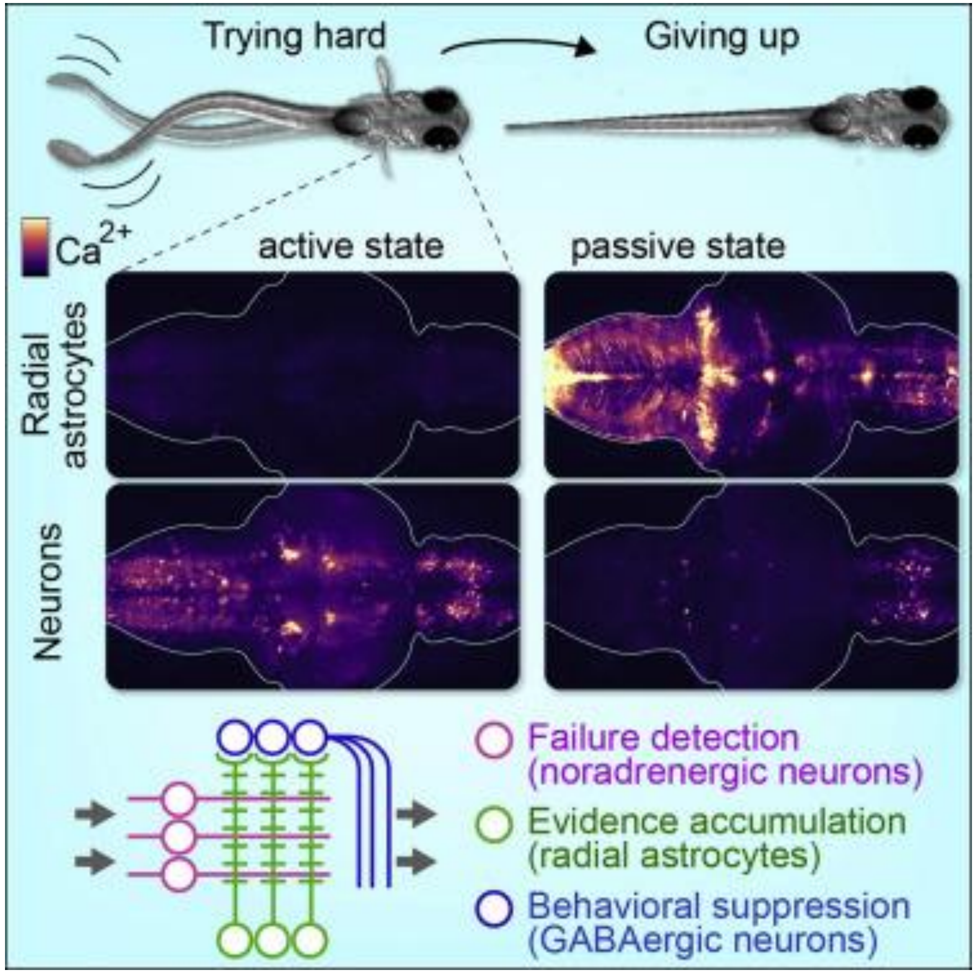


Learning-associated astrocytes participate in memory

Deletion of Fos (gene involved in memory) in astrocytes perturbs memory recall

Deletion of nuclear factor I-A in astrocytes also perturbs memory recall

Role for astrocytes in behavior



During unsuccessful swimming attempts:

Failure detection by noradrenergic neurons

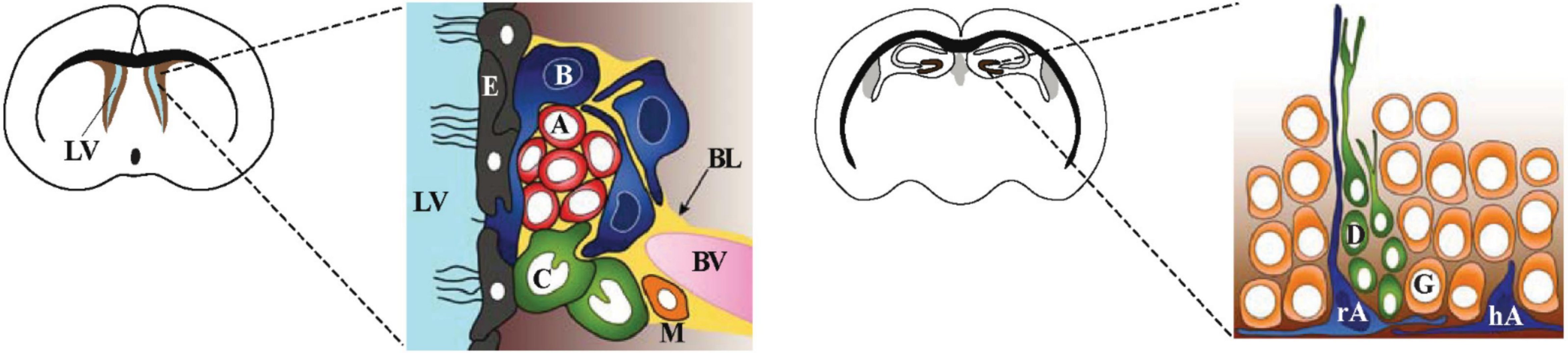
Integration of such signals by astrocytes over longer time

Astrocytes activate inhibitory neurons that block swimming

Neuron-Astrocyte-Neuron neural network!!!

Mu Y. Cell, 2019

Adult neural stem cells are considered as a special type of astrocytes



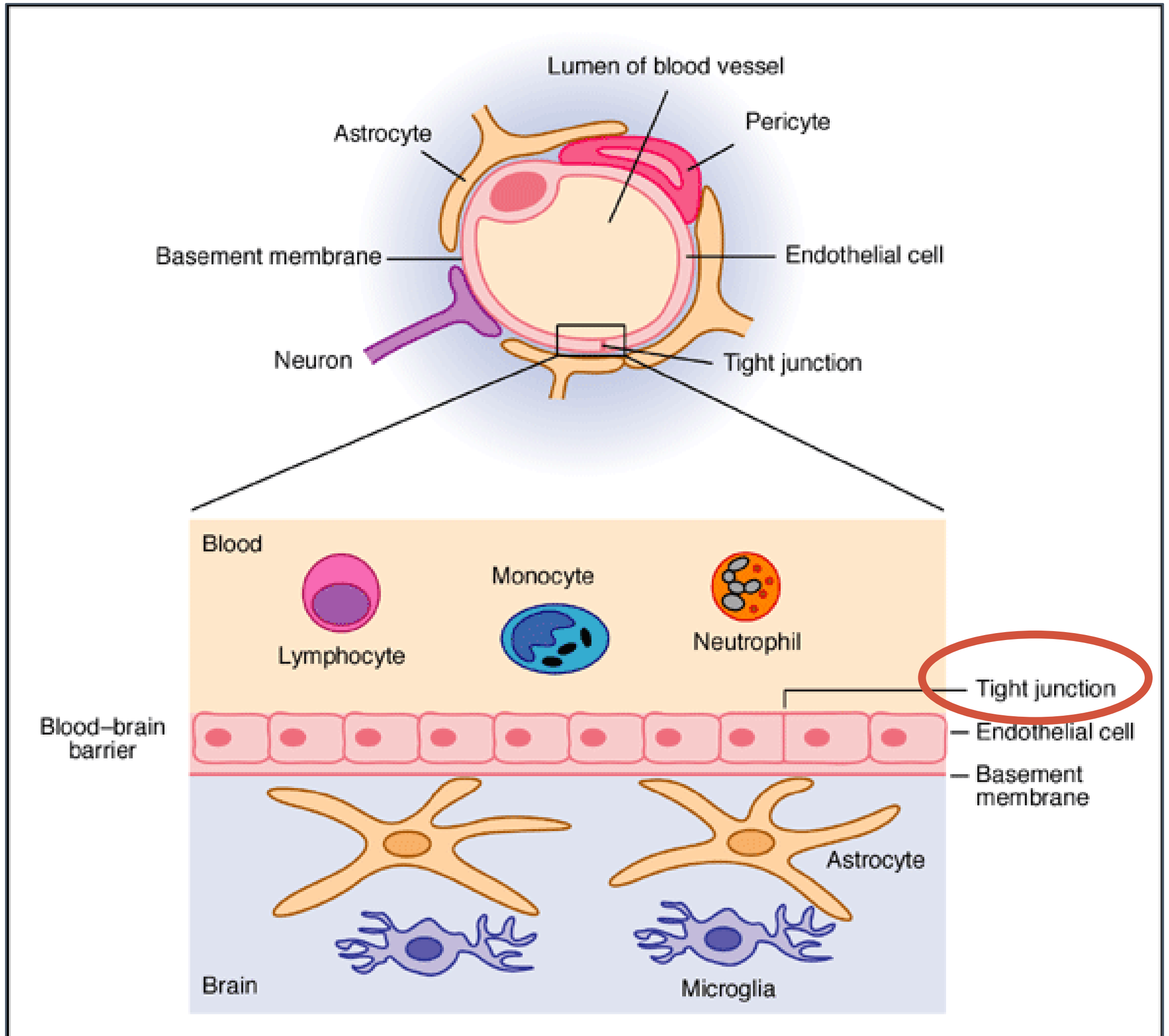
Wall of lateral ventricle (LV) and Dentate Gyrus (DG) in hippocampus – areas of adult neurogenesis
Contain adult neural stem cells

Upon physical activity adult neurogenesis is enhanced

The Blood-Brain Barrier (BBB)

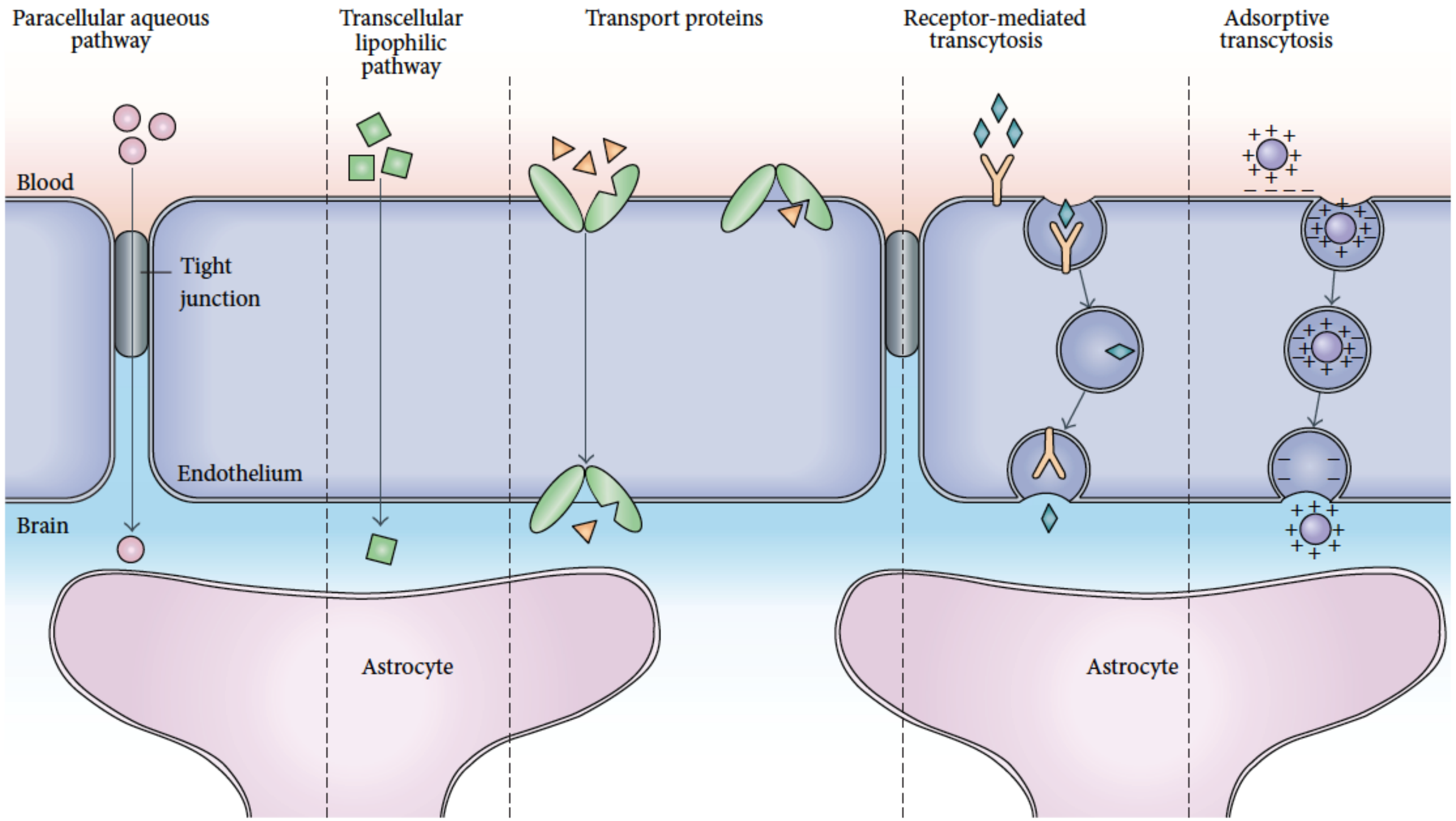
- Specialized structure preventing the entry of toxins (and drugs…) from the blood into the brain

- Composed of
  - Astrocytes
  - Basal membrane
  - Endothelial cells
  - Pericytes



The blood–brain barrier (BBB)

Pathways across the BBB

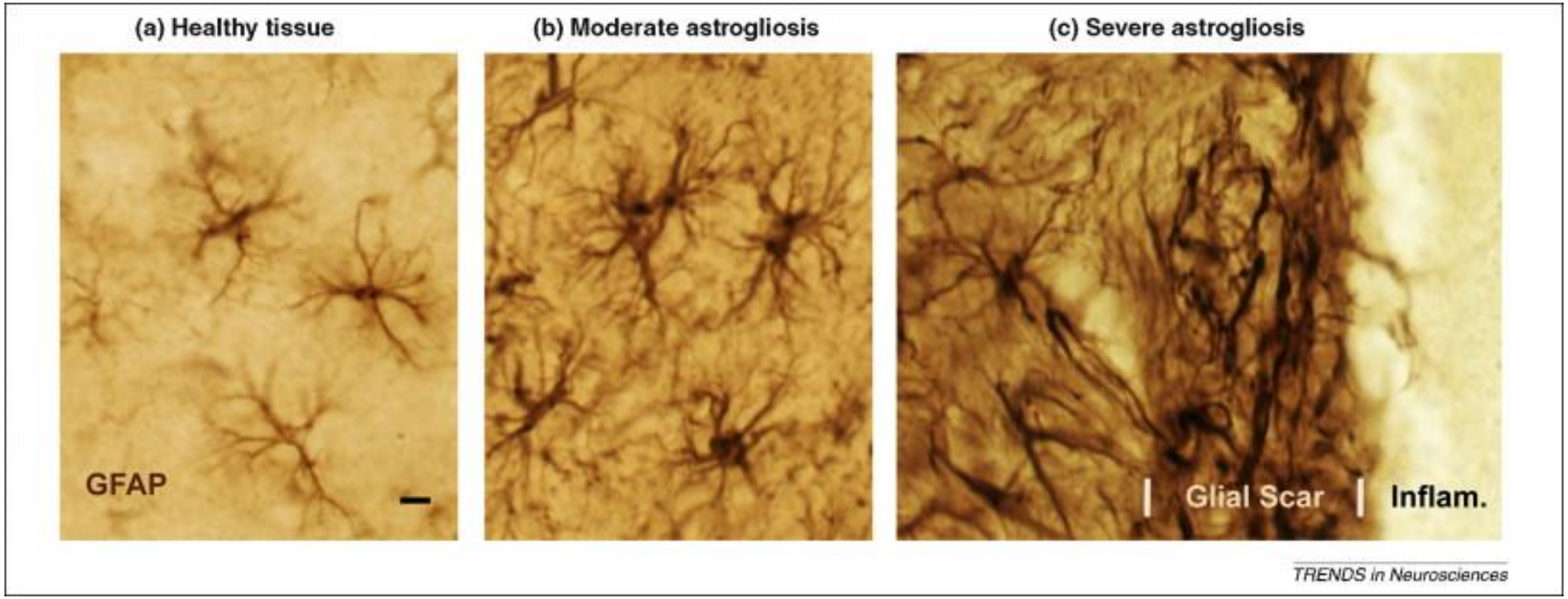


BBB dysfunction and consequences

Diseases	BBB proteins and affected mechanisms
Alzheimer's disease	BBB disruption and permit peripheral IgG to brain. Decrease P-gp and accumulate amyloid-β in brain [67].
Parkinson's disease	BBB disruption increases therapeutic agent concentration and reduces efficacy of Pgp [6].
Stroke	Astrocytes secrete TGFβ that downregulates tissue plasminogen activator (tPA) and anticoagulant thrombomodulin (TM) [68].
Epilepsy	Transient BBB opening and upregulation of multiple drug resistance (MRD1) Pgp [69].
Trauma	Opening of BBB, release of IL-6 from astrocytes, and neuroinflammation [70].
HIV	BBB TJ disruption. Loss of glycoproteins and apoptosis of endothelial cell lead to increase diameter of cortical vessels [71].
Infectious processes	Increase CSF/serum albumin ratio. Bacterial lipopolysaccharides affect BBB TJ [72].
Brain tumours	Breakdown of BBB TJ, overexpress folate, insulin, and transferrin receptor, and downregulation of claudin 1/3 [73].
Ischaemic brain oedema	BBB breakdown due to MMP9 release by neutrophils and degradation of occludin, claudins, and JAM [74].

Astrocytic response to injury

- Astrocytes can react to several brain insults → astrogliosis
- During stroke, hypoxia, Alzheimer's, Parkinson's, traumatic brain injury, etc.
- Characterized by strong GFAP upregulation, hypertrophy and proliferation



Astrocytes perturbation during psychiatric disorders

A concerted neuron–astrocyte program declines in ageing and schizophrenia

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Emi Ling[1,2]✉, James Nemesh[1,2], Melissa Goldman[1,2], Nolan Kamitaki[1,2,3], Nora Reed[1,2], Robert E. Handsaker[1,2], Giulio Genovese[1,2], Jonathan S. Vogelgsang[4,5], Sherif Gerges[1,2], Seva Kashin[1,2], Sulagna Ghosh[1,2], John M. Esposito[4], Kiely Morris[4], Daniel Meyer[1,2], Alyssa Lutservitz[1,2], Christopher D. Mullally[1,2], Alec Wysoker[1,2], Liv Spina[1,2], Anna Neumann[1,2], Marina Hogan[1,2], Kiku Ichihara[1,2], Sabina Berretta[1,4,5,6,7]✉ & Steven A. McCarroll[1,2,7]✉

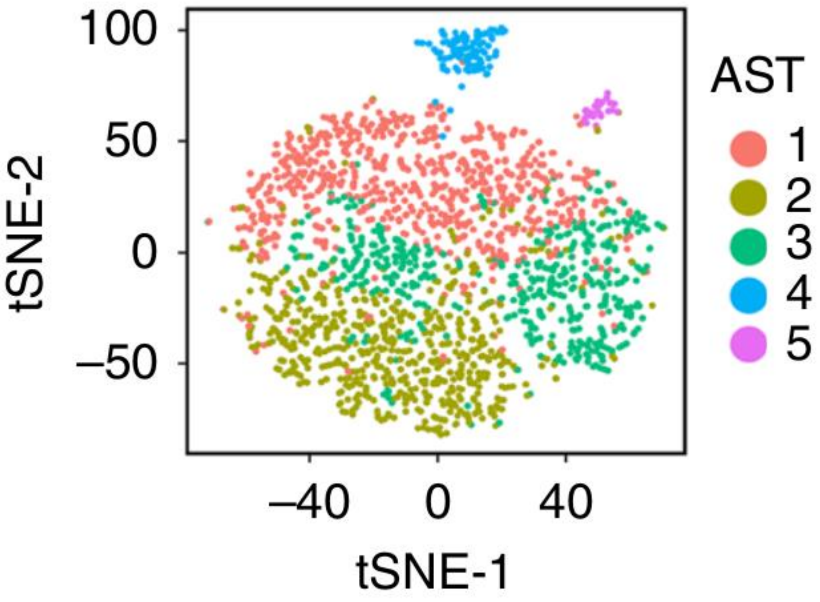
Perturbation of expression of astrocytic and neuronal synaptic genes correlates with cognitive decline during schizophrenia and aging

Astrocyte heterogeneity

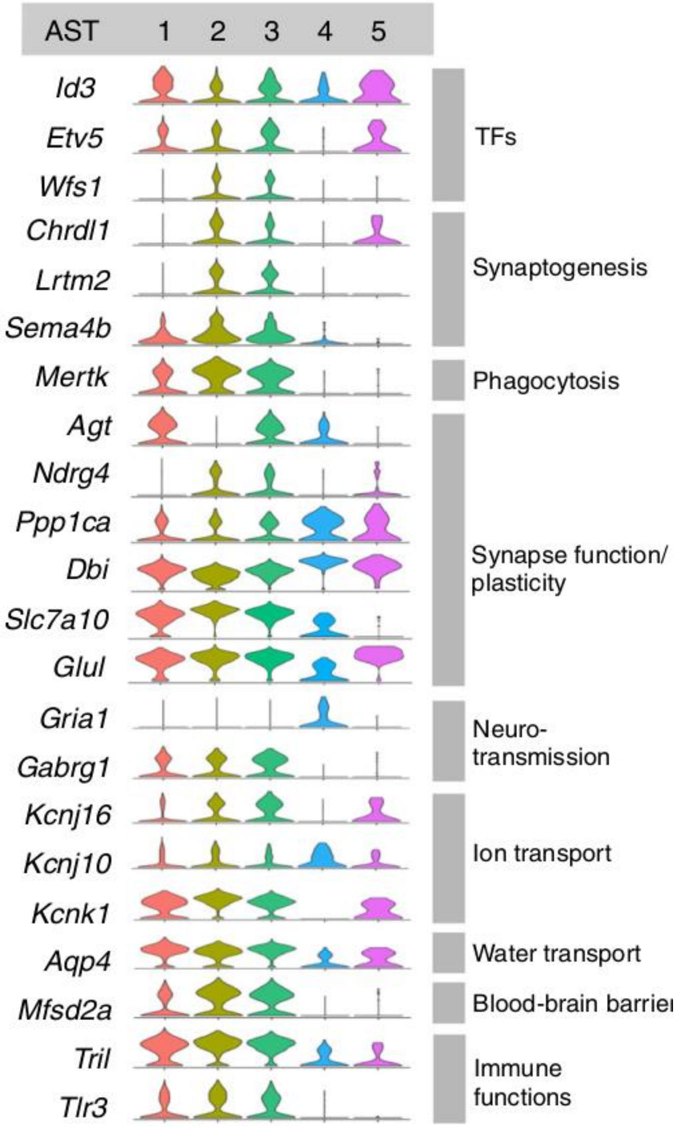
Previously knowledge of astrocyte heterogeneity was limited

Are all astrocyte function mentioned before performed by a single astrocyte?

Single cell RNA-sequencing of astrocytes in mouse cortex and hippocampus



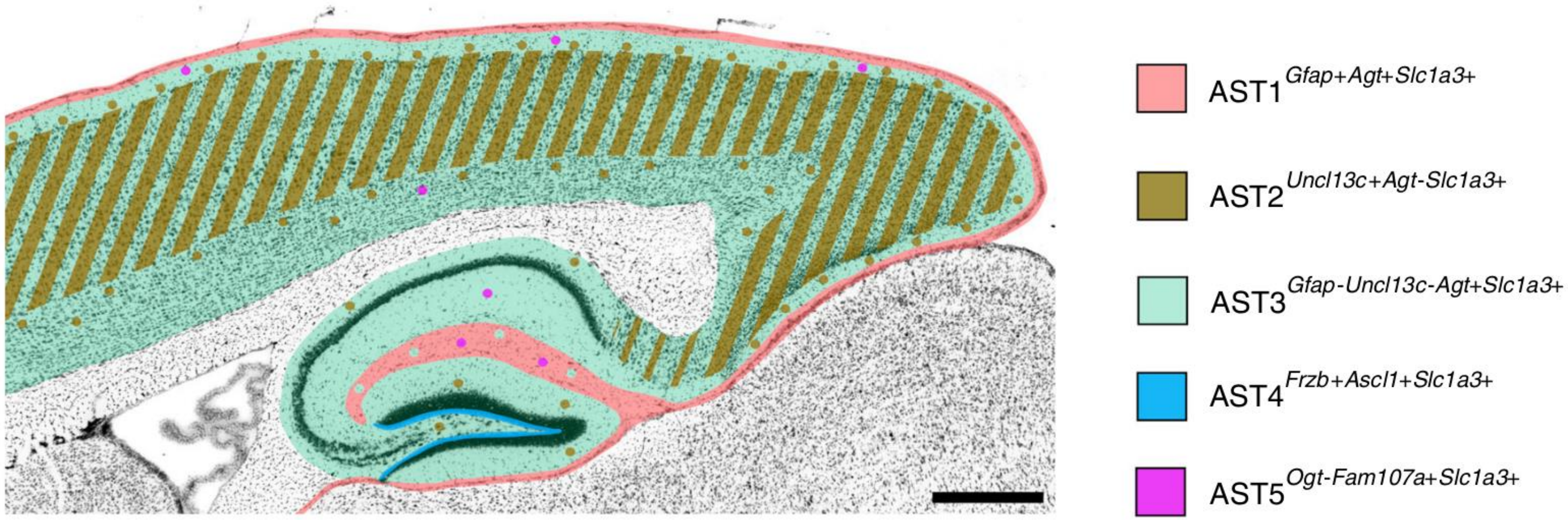
Astrocyte clustering based on transcriptome
5 subtypes identified



Astrocyte subtypes differ in gene expression

Batiuk et al., 2020

Spatial location of astrocyte subtypes



AST1 – mature marginal astrocytes (next to pia and hippocampal SLM)

AST2 – mature cortical protoplasmic astrocytes

AST3 – mature cortical and hippocampal protoplasmic astrocytes

AST4 – hippocampal stem cells

AST5 – possibly transitioning from immature to mature state

Astrocyte heterogeneity field expanded in recent years

RESEARCH ARTICLE

CELLULAR NEUROSCIENCE

Molecular basis of astrocyte diversity and morphology across the CNS in health and disease

Fumito Endo[1], Atsushi Kasai[2], Joselyn S. Soto[1], Xinzhu Yu[1]†, Zhe Qu[3], Hitoshi Hashimoto[2,4,5,6,7], Viviana Gradinaru[3], Riki Kawaguchi[8], Baljit S. Khakh[1,9]*

nature neuroscience

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

Astrocyte heterogeneity reveals region-specific astrogenesis in the white matter

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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 Sirko[1,2], Magdalena Götz[1,2,8,10] & Judith Fischer-Sternjak[1,2,10]

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Dual lineage origins contribute to neocortical astrocyte diversity

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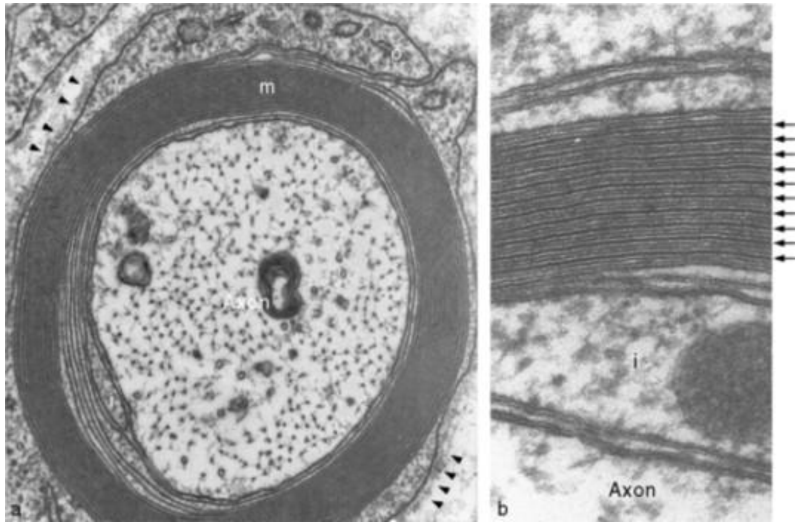
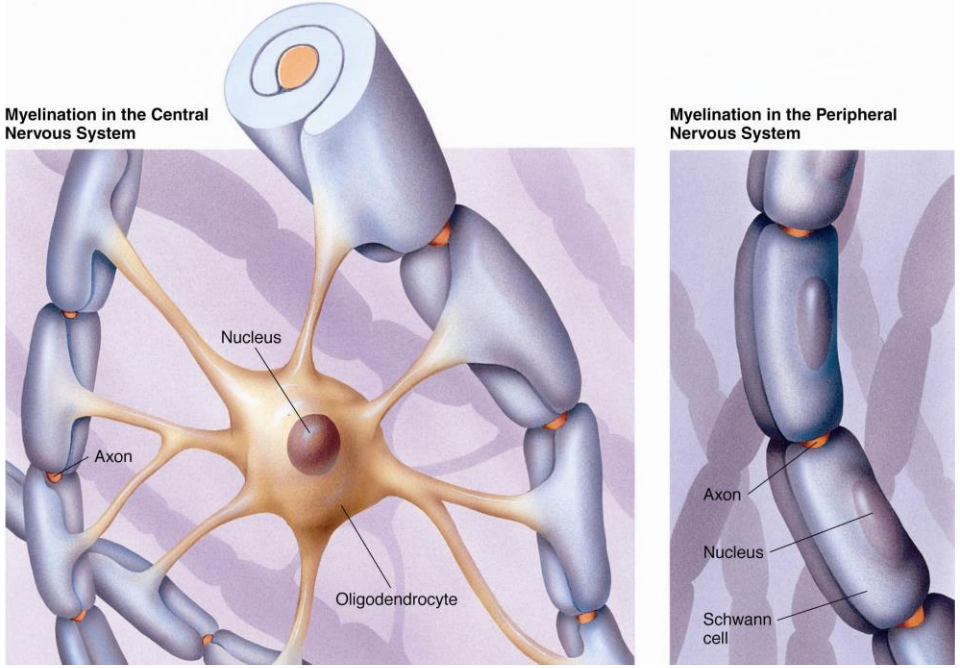
2) Oligodendrocytes

- Myelination in CNS and PNS
  - CNS: Oligodendrocytes
    - One oligodendrocyte can myelinate many neurons

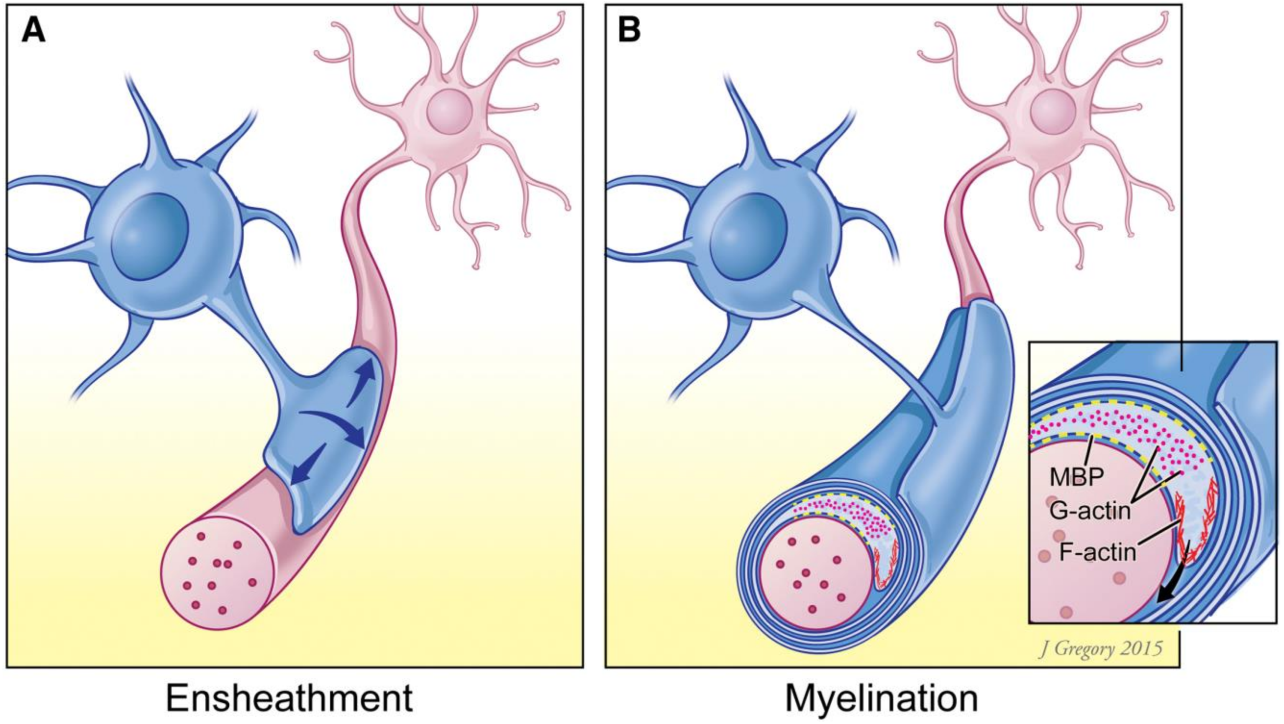


  - PNS: Schwann cells
    - One Schwann cell/neuron



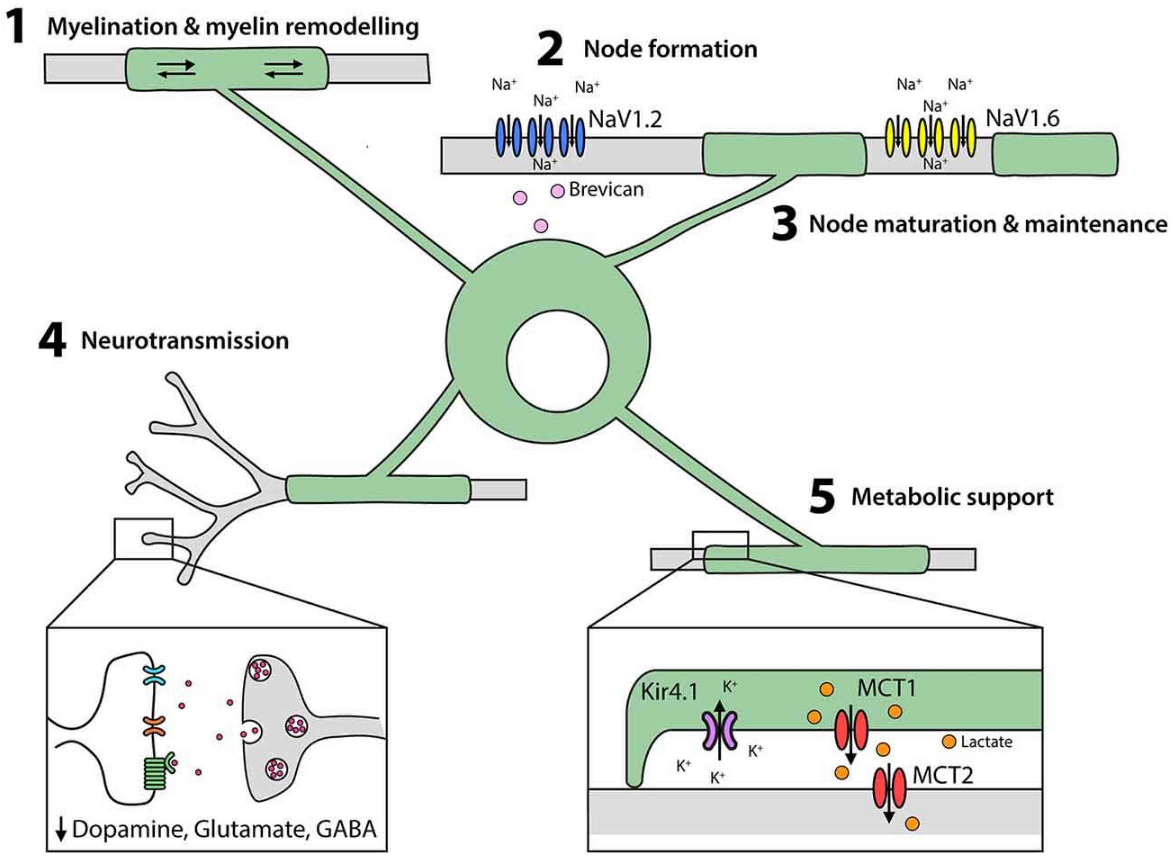
2) Oligodendrocytes

- Formation of myelin sheath



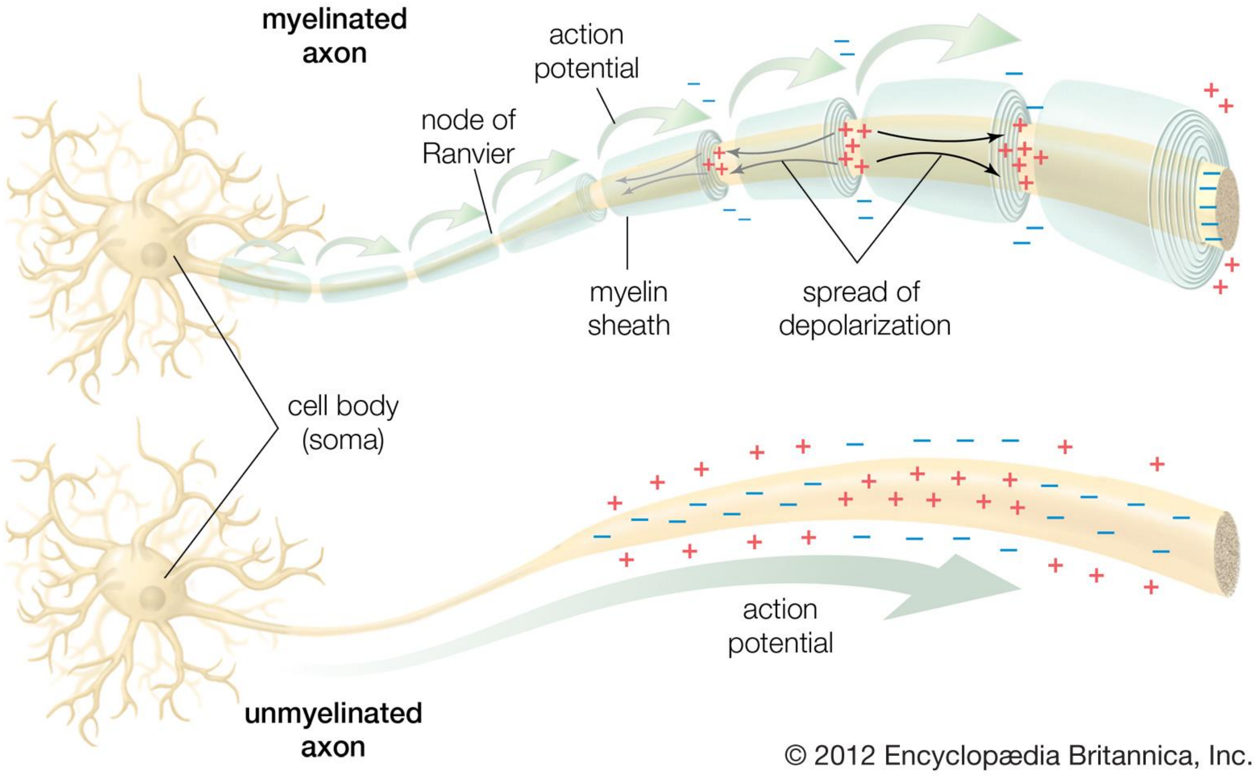
2) Oligodendrocytes

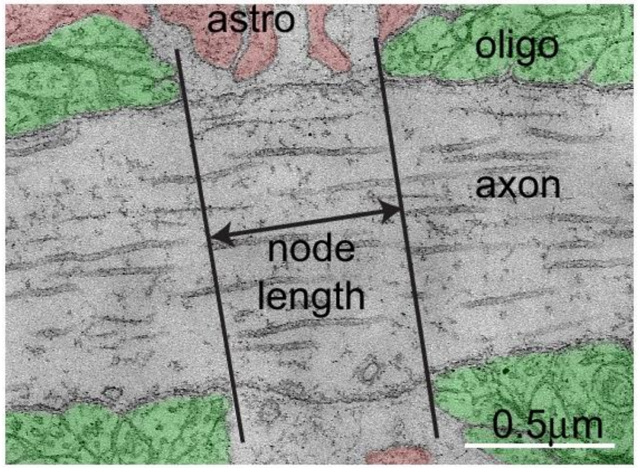
- Functions:
  - Myelination
    - Node of Ranvier formation and maintenance
    - Regulation of action potential conduction
  - Metabolic support

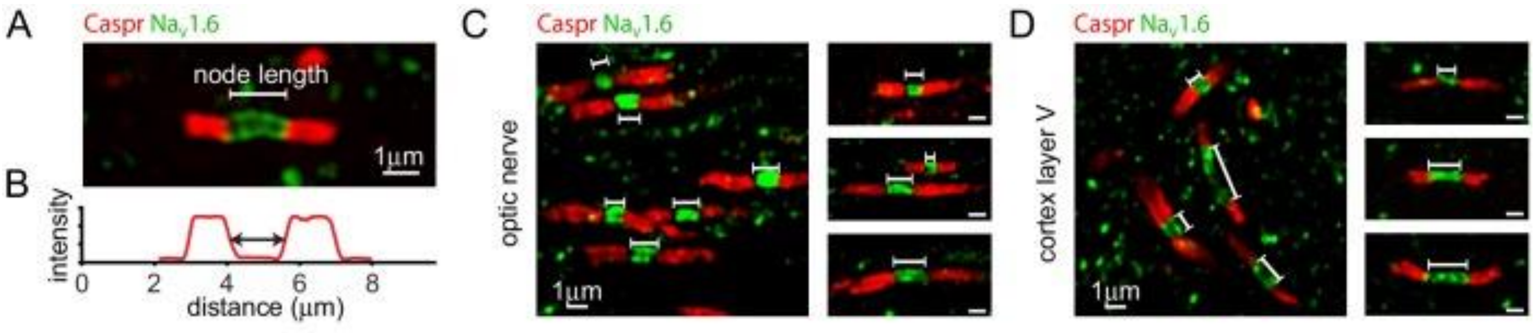


Saltatory conduction

- Action potential can only be regenerated at the Node de Ranvier
- Increases signal's propagation speed
  - myelinated axons → 150m/s
  - unmyelinated axons → 0.5-10m/s



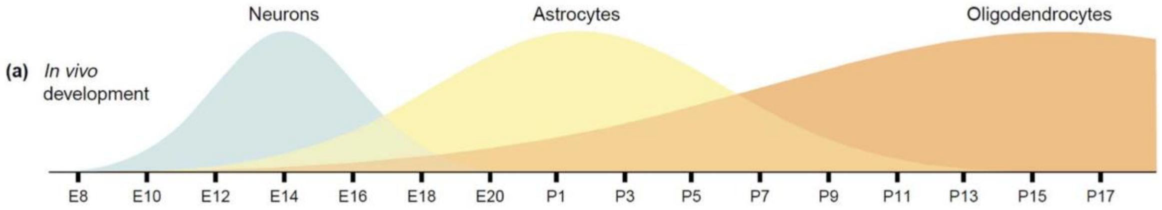


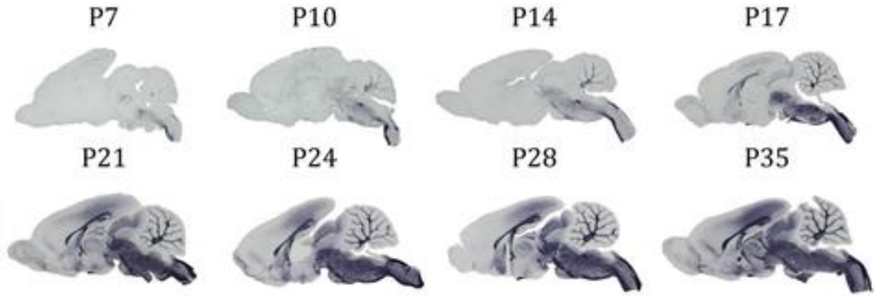


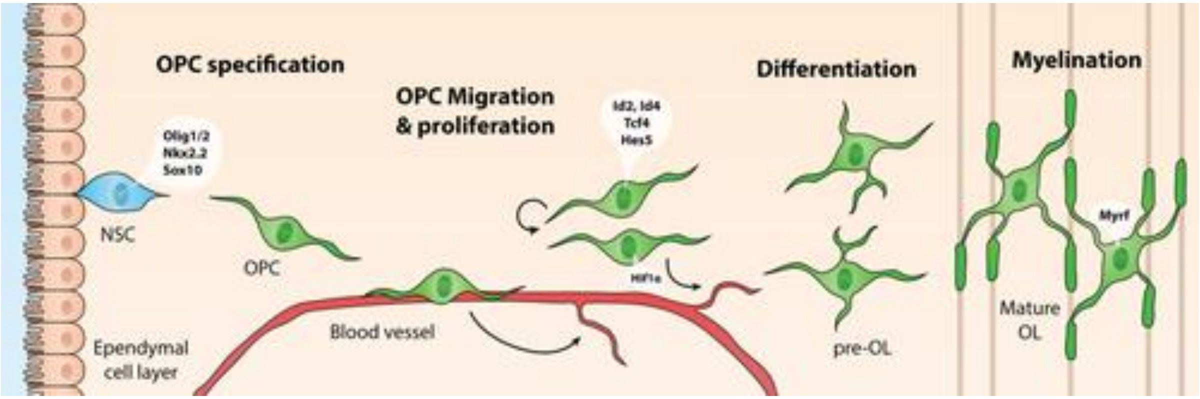
Arancibia-Carcarmo et al., 2017

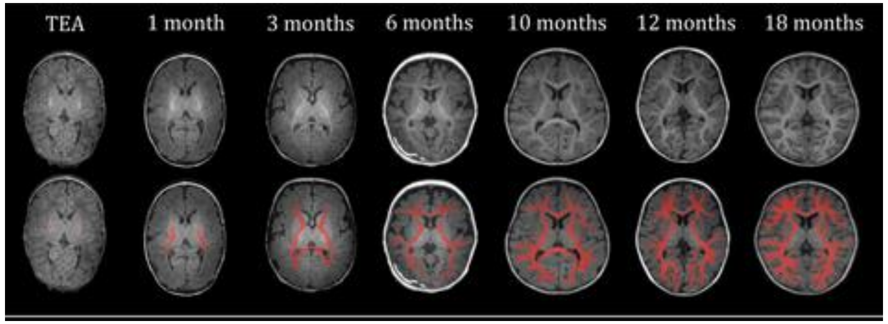
Oligodendrocytes and OPCs

- Only mature oligodendrocytes produce myelin
- Myelination occurs after birth
- OPCs = oligodendrocyte precursor cells = NG2 glia









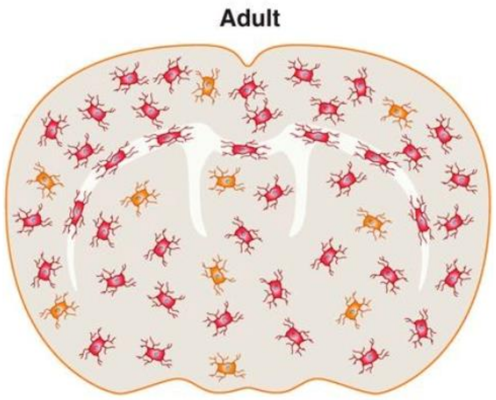
Human myelination finishes in the mid-late 20th

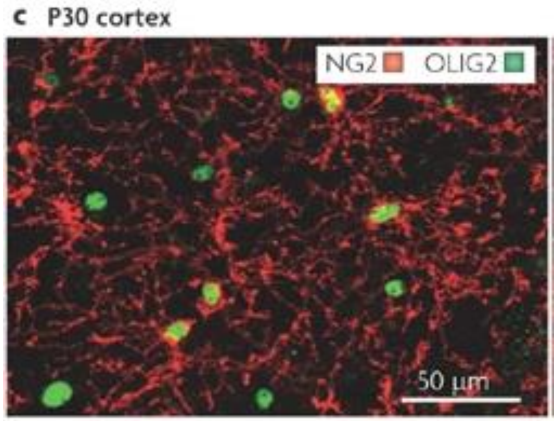
Why they giving a car to a teenager is a bad idea?

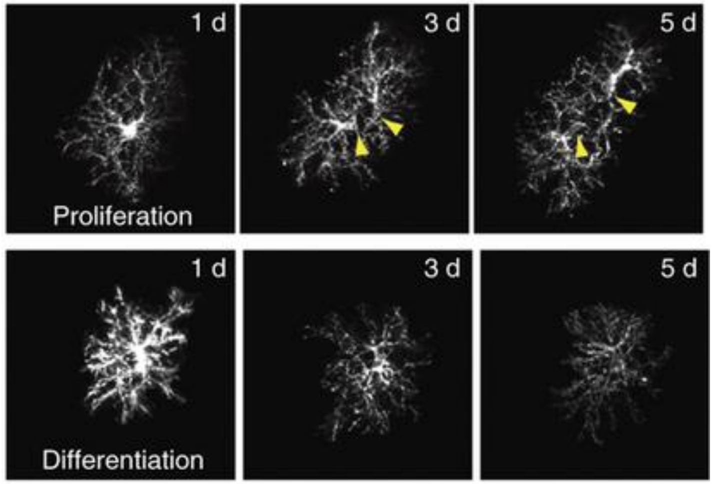
OPCs (NG2 cells)

- Oligodendrocyte precursor cells (OPCs) remain in the brain as the main progenitor cell population

- OPCs can proliferate and differentiate into oligodendrocytes during adulthood in response to stimulation





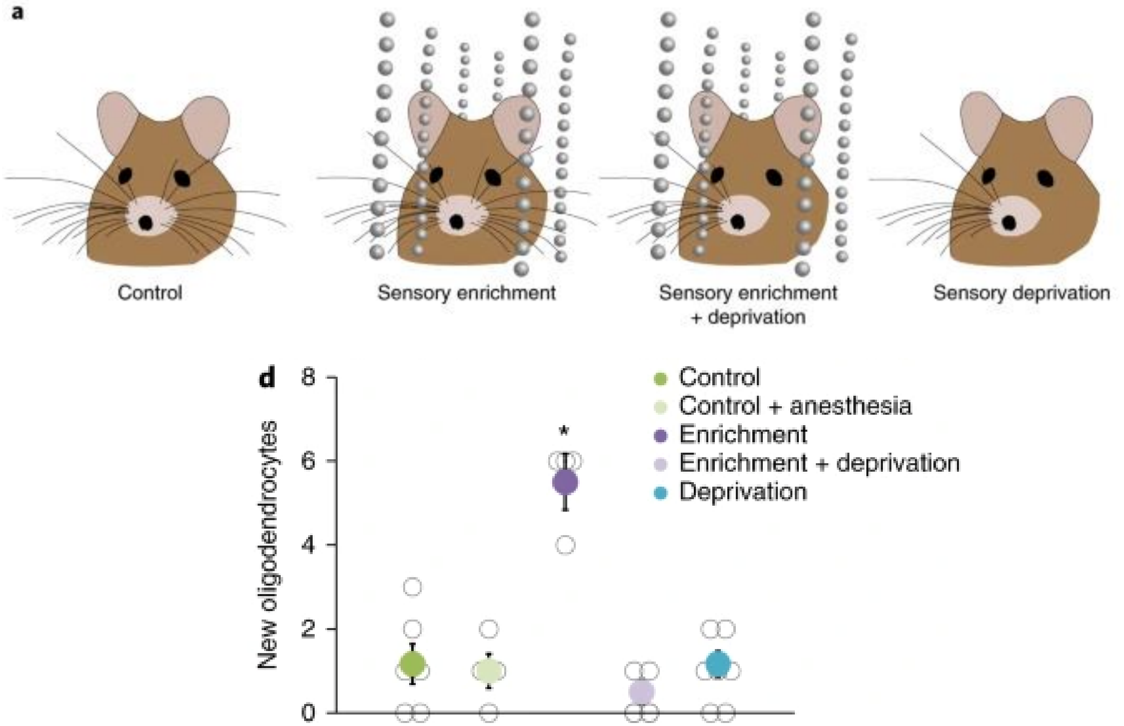


Nishiyama et al., 2009; Dimou&Goetz, 2014

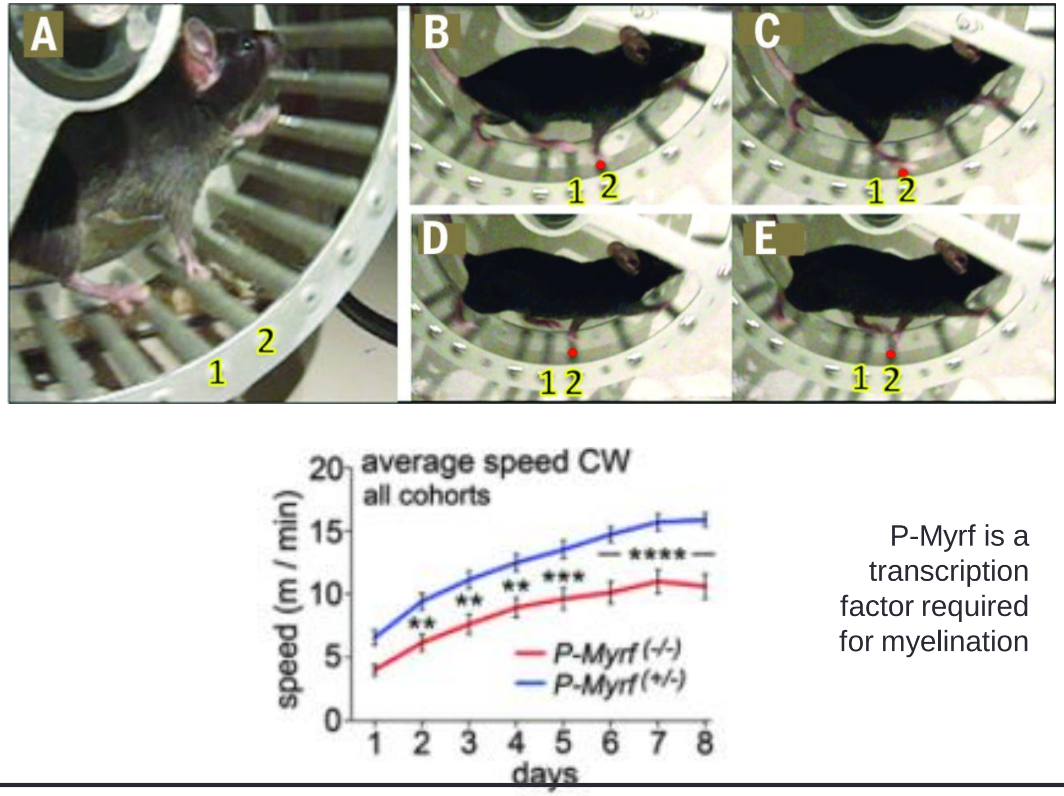
OPCs and "myelin plasticity"

OPCs generate oligodendrocytes in response to stimulation, and are needed for certain forms of learning

Sensory enrichment



Complex running wheel



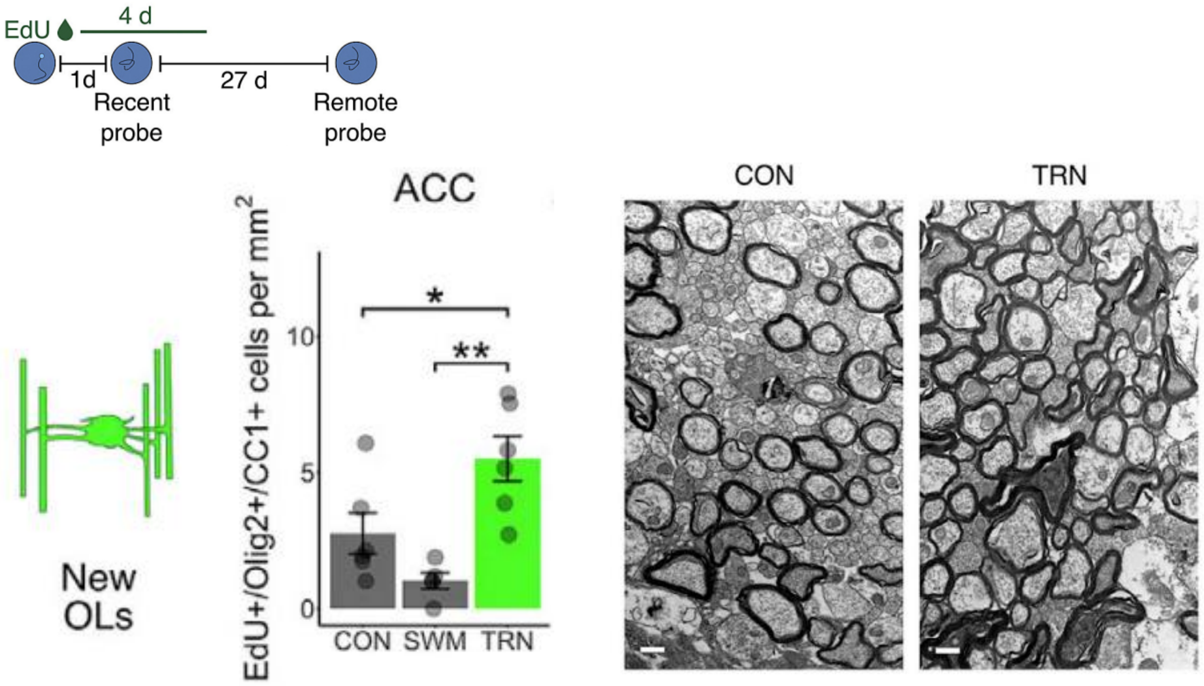
P-Myrf is a transcription factor required for myelination

Hughes et al., 2018

McKenzie et al., 2014

Oligodendrogenesis and memory

Memory consolidation induces oligodendrogenesis and myelination in the cortex



NG2/OPCs sense neuronal activity through neuron-NG2 cell synapses

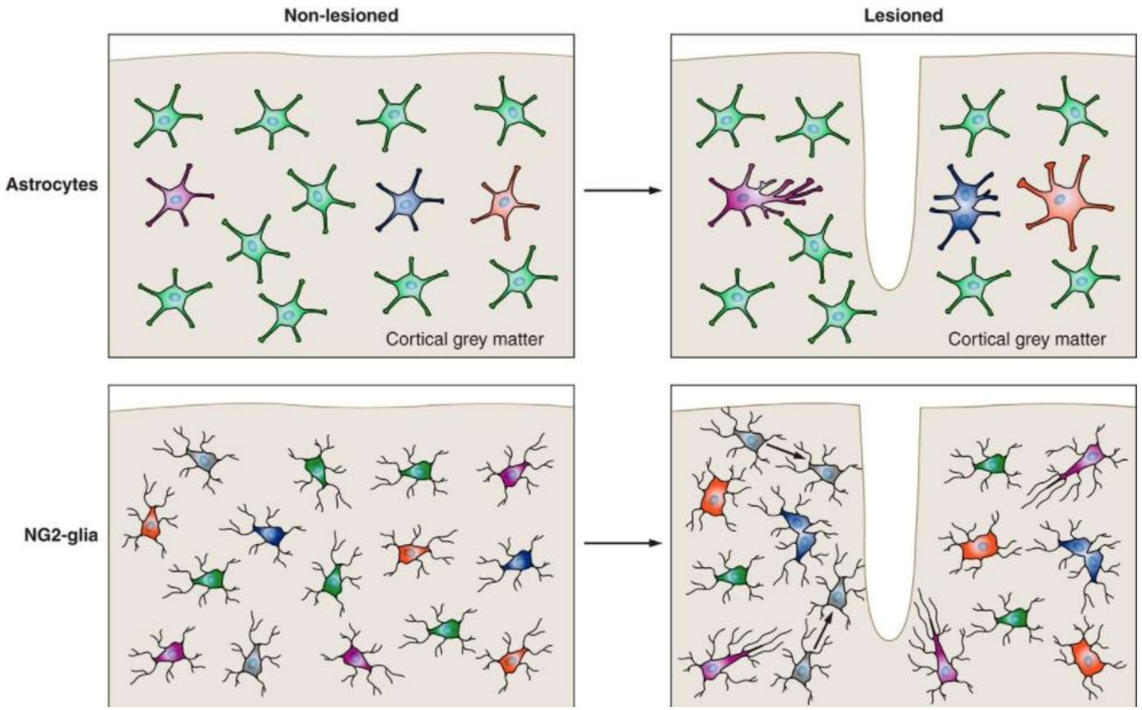
In accordance with neuronal activity NG2 cells proliferate and myelinate axons

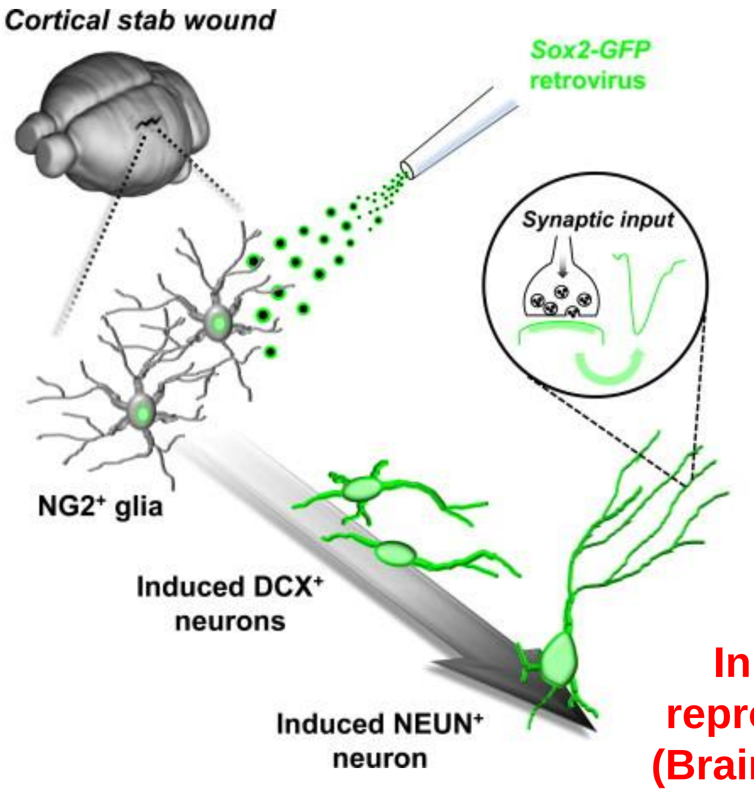
Myelination is required for memory

Speadman et al., 2020

Reprogramming of NG2 glia

- OPCs (also referred to sometimes as NG2-glia) can also react to injuries and are being used as vehicles for neuronal replacement therapies



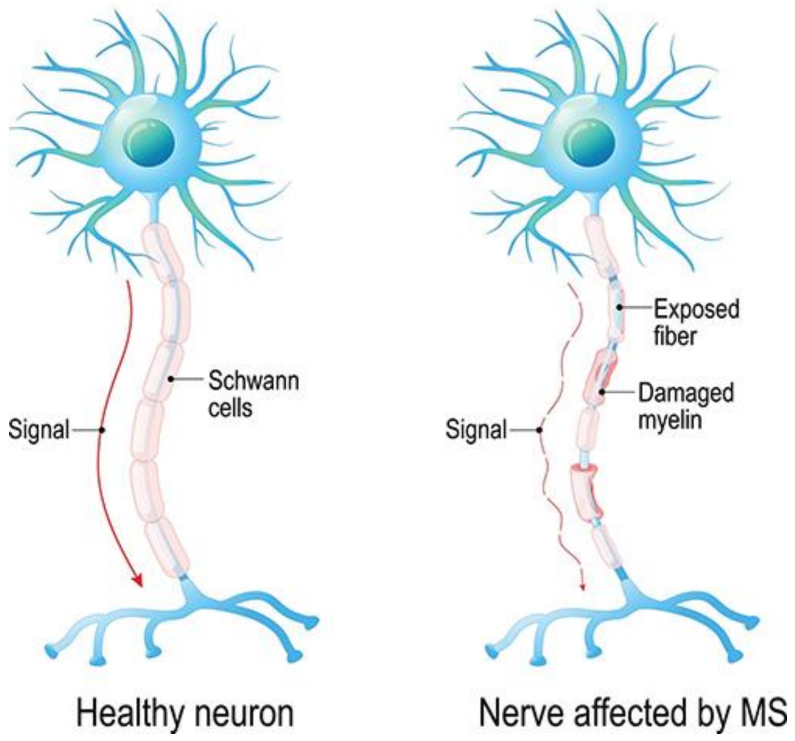


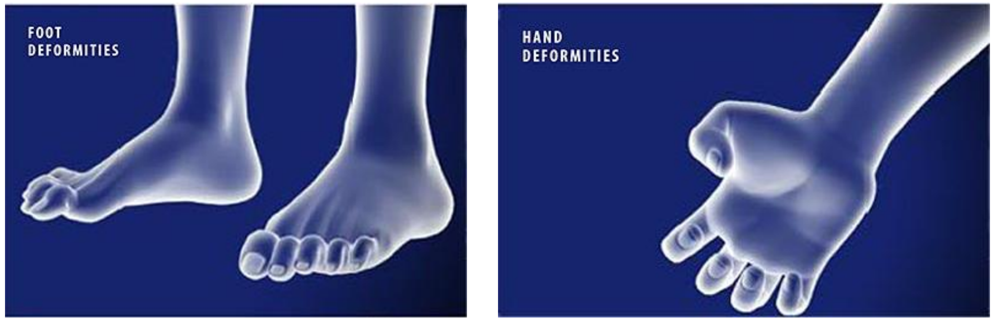
In vivo cell reprogramming (Brain injury, AD, PD, SCI)

Dimou&Goetz, 2014; Heinrich et al., 2014

Demyelinating diseases

- **Multiple Sclerosis**
  - Autoimmune disease with not known genetic cause
  - Numbness and weakness in limbs, unsteady gait
  - Vision problems
  - Slurred speech, fatigue
- **Charcot-Marie-Tooth Disease**
  - Hereditary mutations in PMP22 gene (peripheral myelin protein 22)
  - Reduced myelination and functioning in motor neurons
  - Muscle atrophy



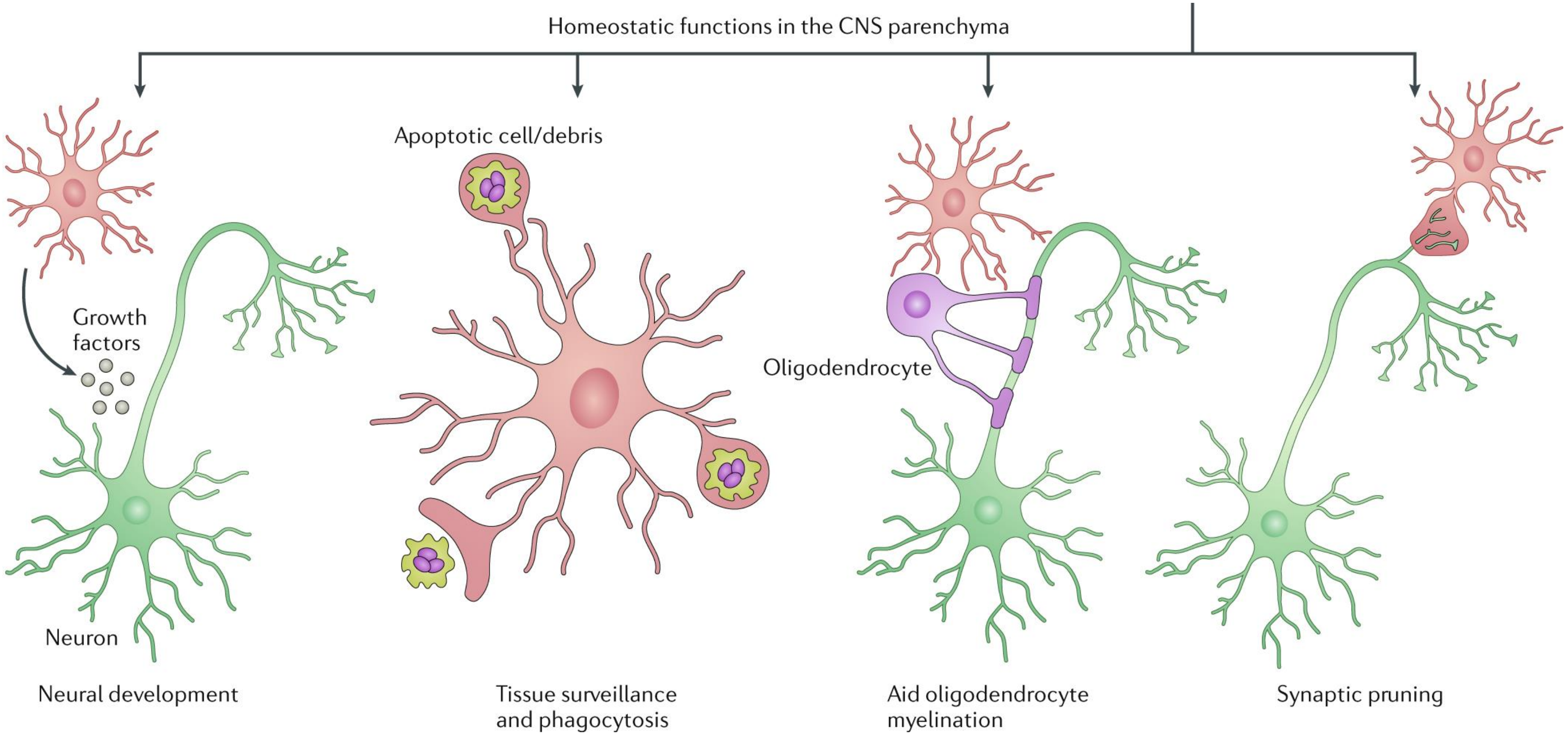


Hammer toes

3) Microglia

- Macrophages of the nervous system → <u>immunological surveillance</u>
  - Become activated following aberrant protein processing (e.g. Alzheimer's) and general tissue damage (neurodegeneration)

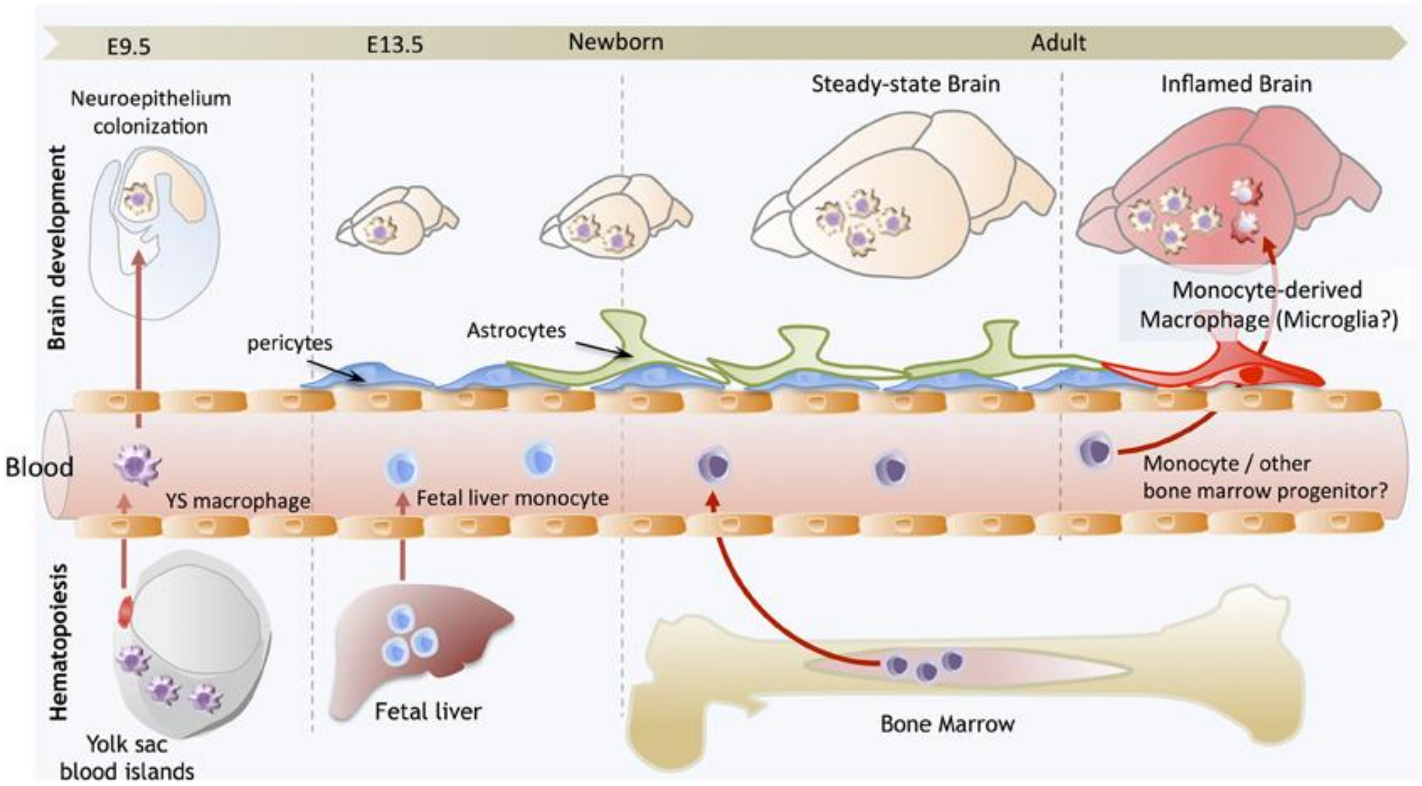
- Support functions



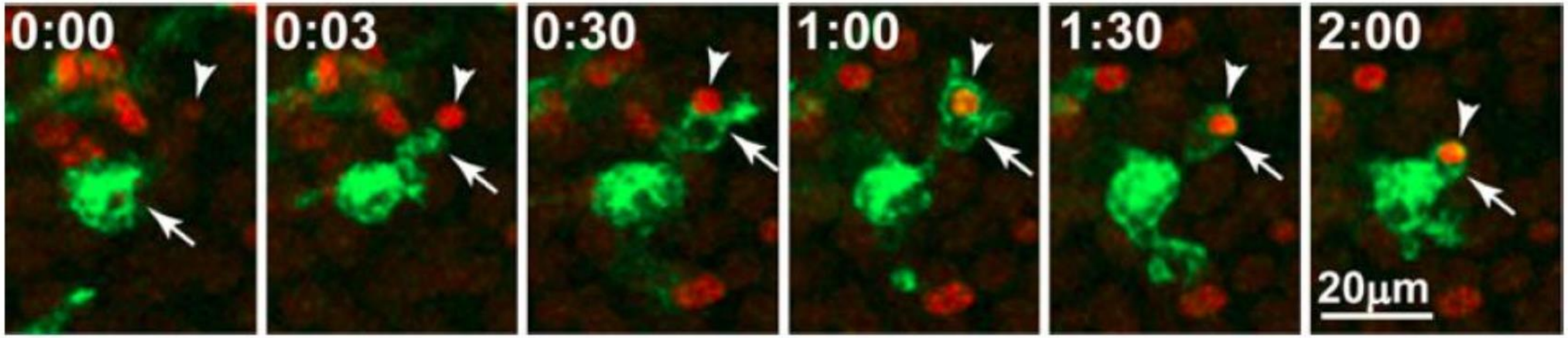
Microglial cells have a different developmental origin

- Yolk sac macrophages colonize the neural tube at early stages (E9 in mice / GW4.5 in humans), where they differentiate into microglial cells

- Whether or not blood-borne progenitors contribute to maintain the microglial compartment during adulthood is debated



Microglia in action

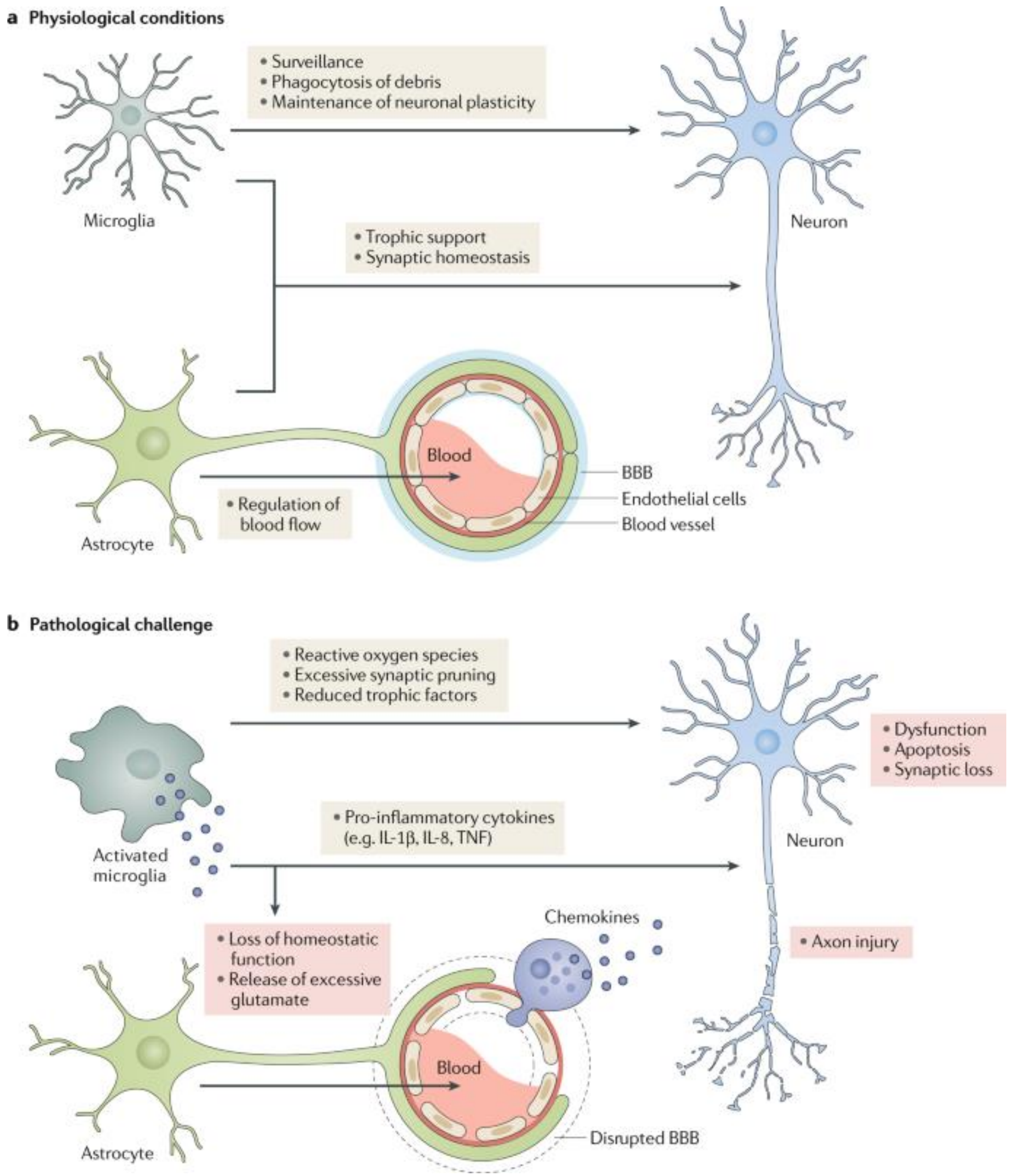


Activated microglia
Dead neuron

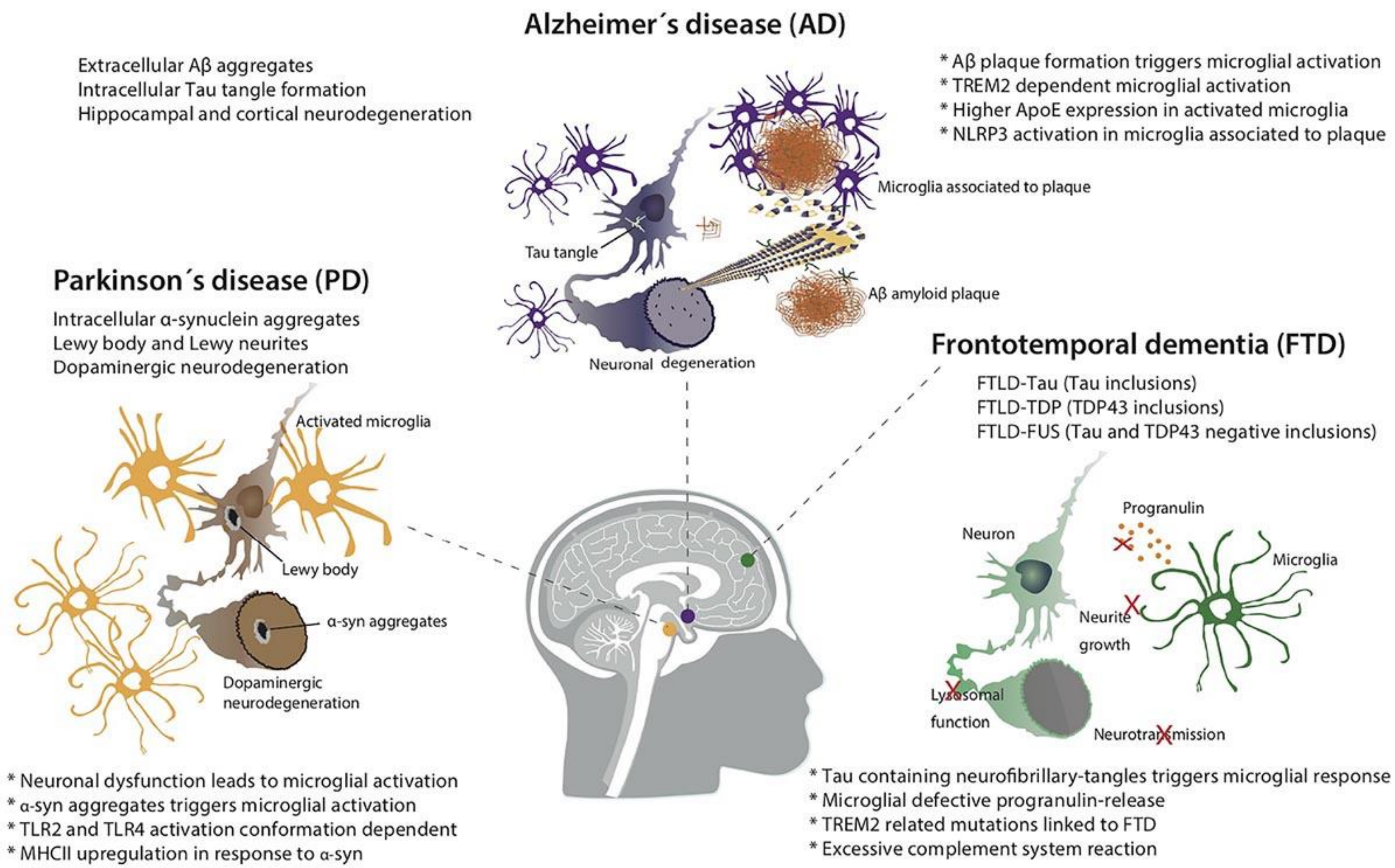
Microglia activation

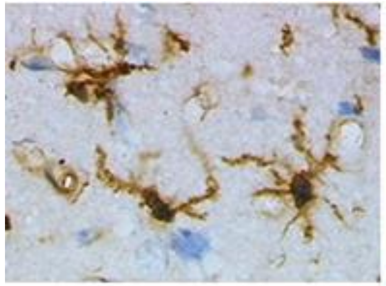
- Inflammatory response in the brain is mediated by microglia, which turn into an activated state in the presence of damage

- Activated microglia proliferate and release several factors
  - M1 activation: Pro-inflammatory
  - M2 activation: Anti-inflammatory

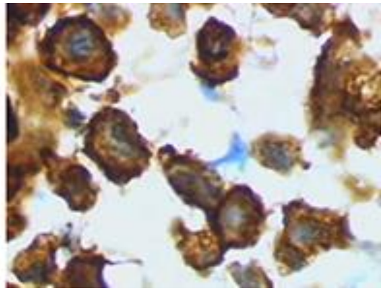


Microglia and neurodegenerative disorders

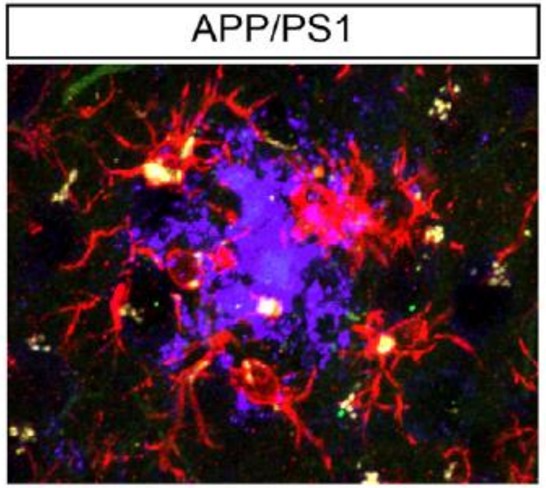




Resting microglia



Activated microglia

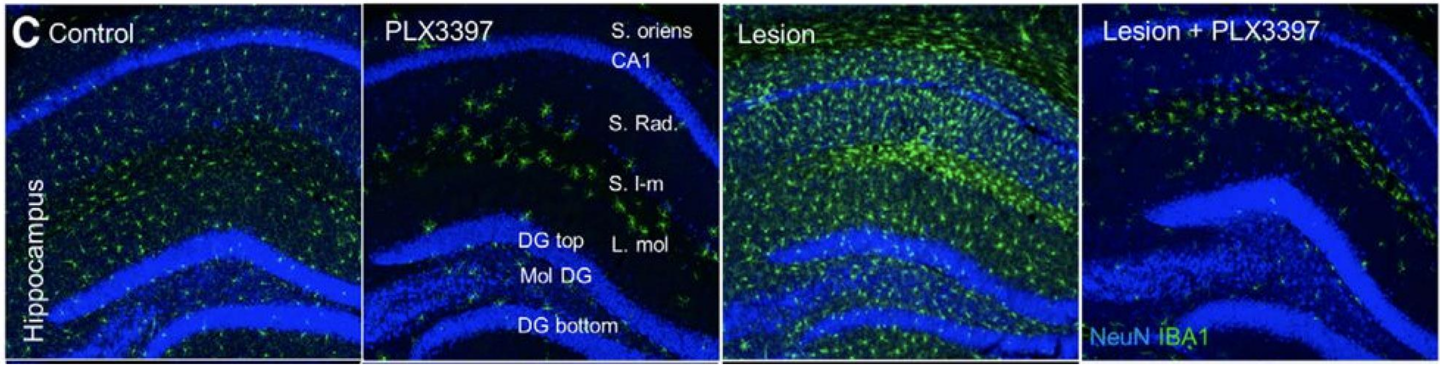


Amyloid plaque
Microglia

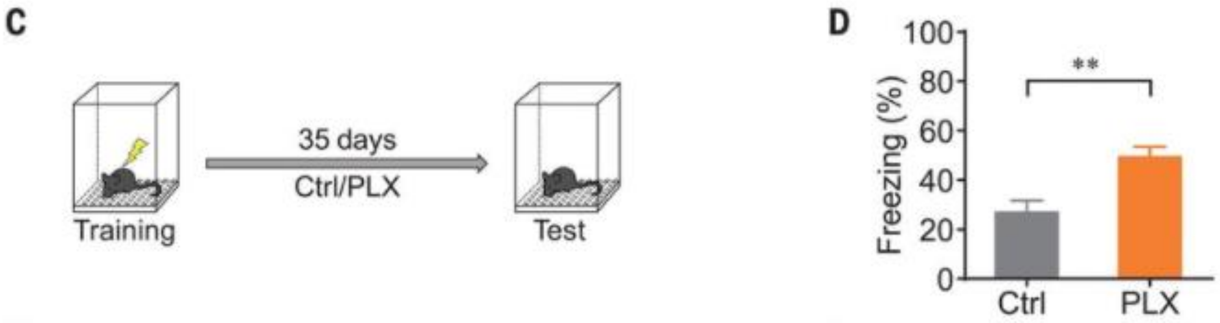
Role of microglia on synaptic pruning and memory

- PLX depletes microglia

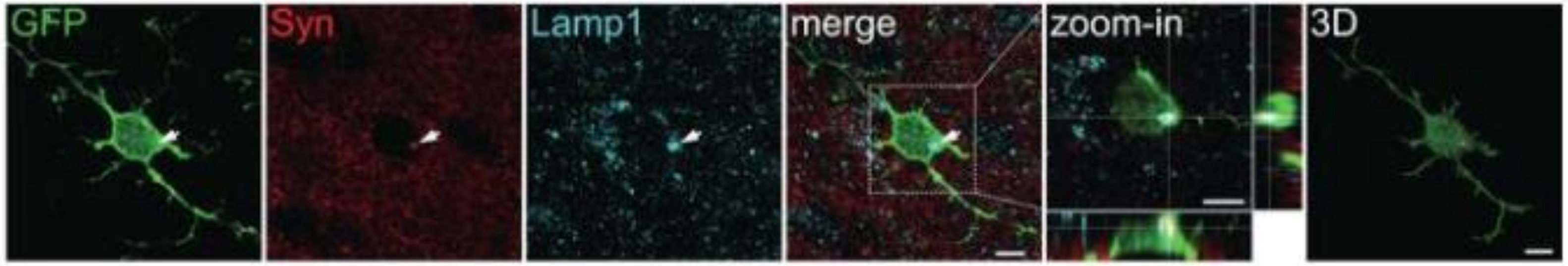
(antagonist of a receptor important for survival)



- Depleting microglia improves memory



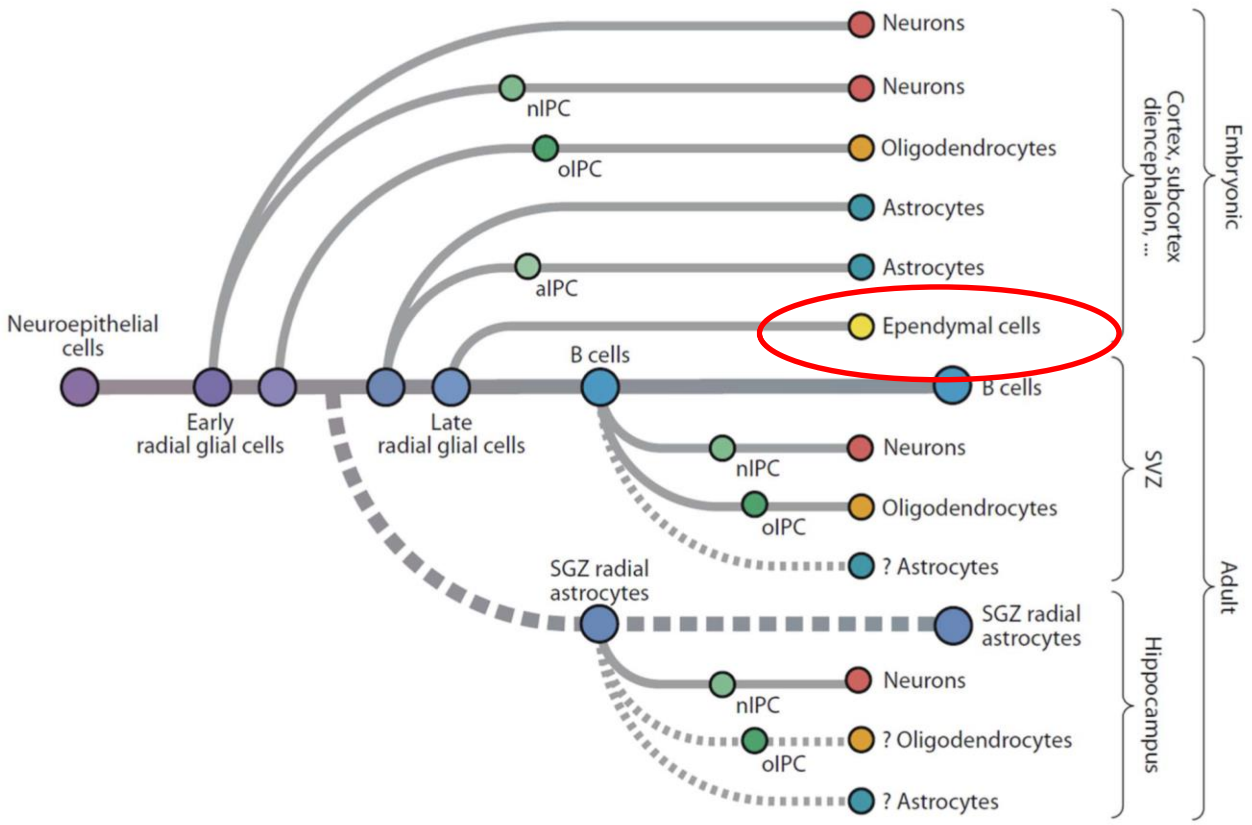
- Microglia mediates synaptic pruning

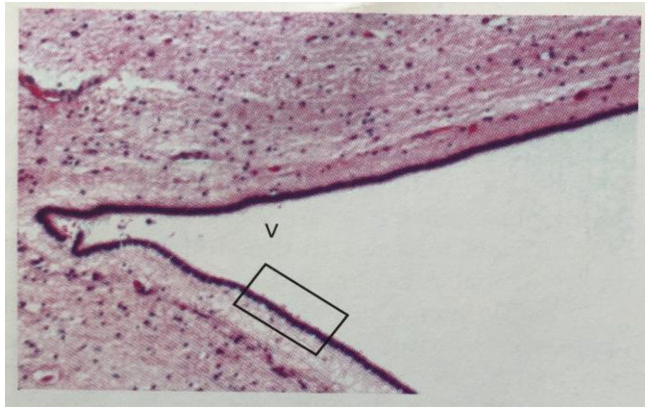


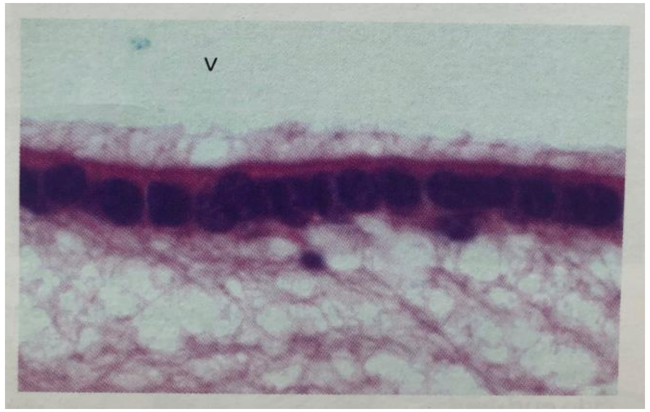
Rice et al., 2015; Wang et al., 2020

4) Ependymal cells

- Derive from radial glia cells
- Lining the ventricles
- Celia-like appendixes
- Function:
  - Cerebrospinal fluid (CSF) movement
  - CSF production (choroid plexus)

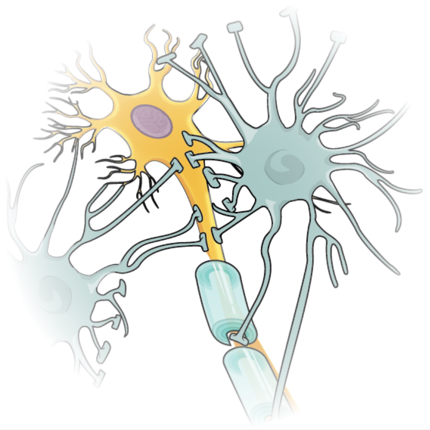
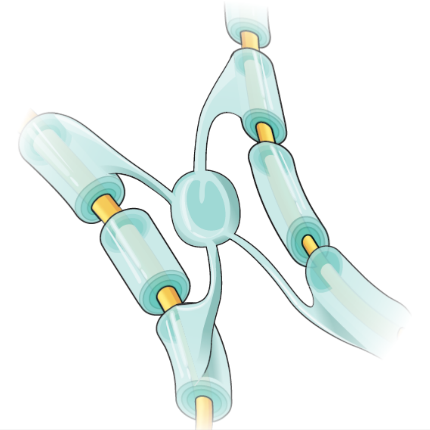
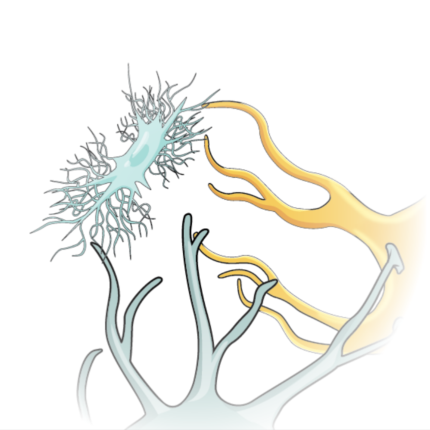
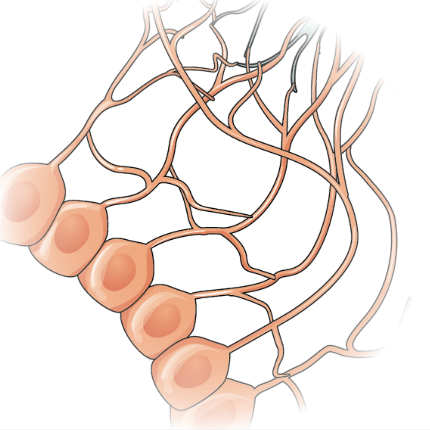






Glial cells – Overview

Table 2. Glial Cell Types by location and Basic Function

CNS glia				
	Astrocyte	Oligodendrocyte	Microglia	Ependymal cell
PNS glia	Satellite cell	Schwann Cell	--	--
Functions	Maintain extracellular environment, remove excess neurotransmitter, direct neural growth, induce blood-brain barrier in CNS (astrocyte only)	Create myelin	Immune surveillance and phagocytosis	Create and circulate Cerebrospinal fluid (CSF)