NEW YORK INSTITUTE OF TECHNOLOGY

College of Osteopathic Medicine

Class of 2029

Introduction to the Nervous System

PPOM1

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Email with questions

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Do.
Make.
Heal.
Innovate.
Reinvent the Future.

Session Objectives

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- Describe the different types of neurons found in the CNS and PNS as well as the different parts of a neuron and the functions of these differ parts
- Describe the different types of glial cells found in the CNS and PNS and describe the basic function of these different glial cells.
- Describe the other type of supporting cells in the CNS and understand their function
- Describe the anatomy of chemical and electrical synapses.

Introduction to the Nervous System

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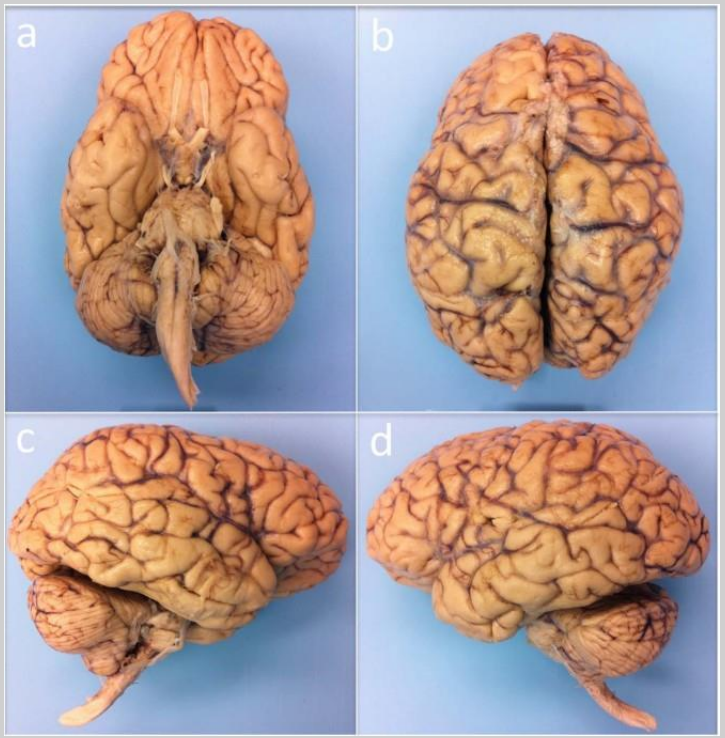
- Nervous system connections to… muscles, organs & glands, etc
- Neural control of behavior – *neural activity creates behavior (sensory & motor; cognitive & emotional, visceral, etc)*
- Changes in the brain (anatomical/physiological) cause behavioral change (development, aging, disease, injury, learning)
- Treatments for brain diseases must change the brain (back to normal or to stop further dysfunction) *ex. – neurodegeneration, demyelination, etc*

Cells of the Central Nervous System: NEURONS

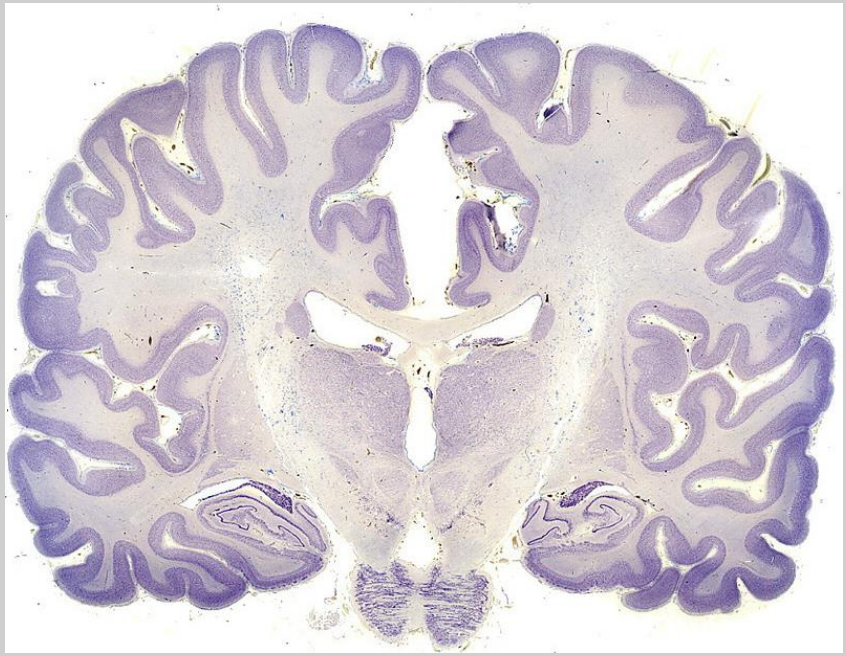
- characterized by the presence of soma (intracellular organelles), branching dendrites (often w/ spines), axon initial segment, branching axon, and axon terminals (synapses)
- electrically excitable cells that can release and respond to neurotransmitters via neuronal connections/synapses
- almost all neurons produced before birth and almost entirely non-renewable.

Clinical correlate:
Neurodegeneration or neuronal injury (stroke) results in permanent loss of neurons.

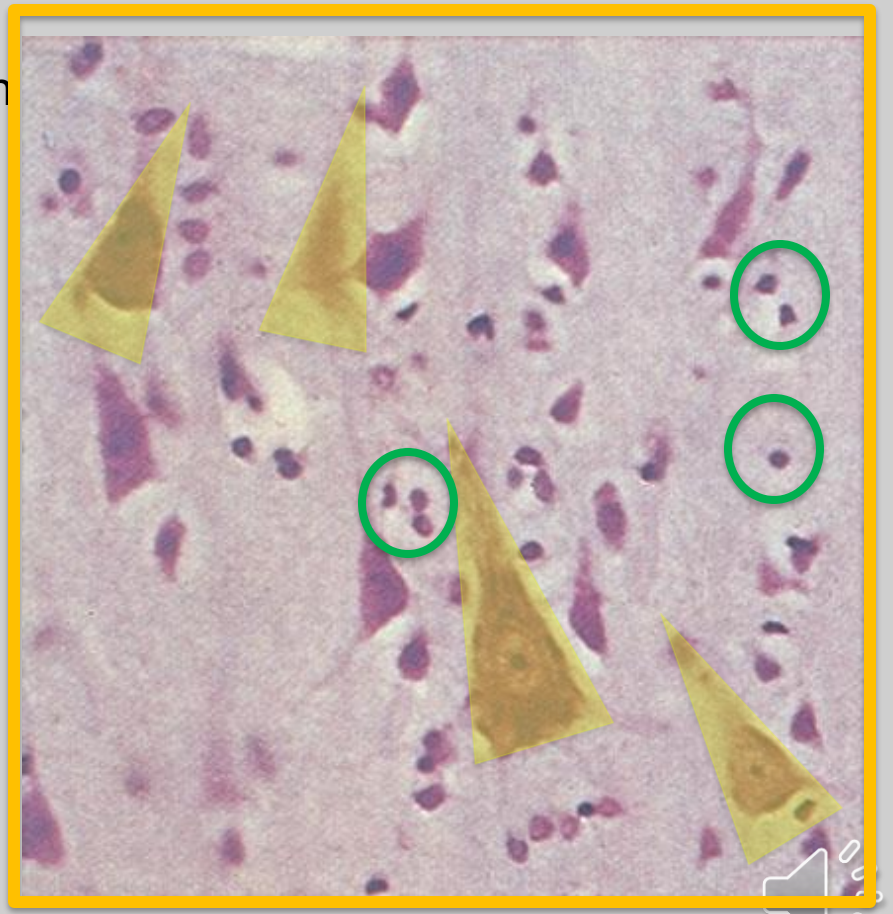


Edlow, B.L., Mareyam, A., Horn, A. *et al.* 7 Tesla MRI of the *ex vivo* human brain at 100 micron resolution. *Sci Data* **6,** 244 (2019). https://doi.org/10.1038/s41597-019-0254-8

Nissl stain



https://brains.anatomy.msu.edu/brains/human/coronal/2060_cell.html



Ch.5, Essential Neuroscience 2nd ed. Wolters Kluwer/Lippincott Williams

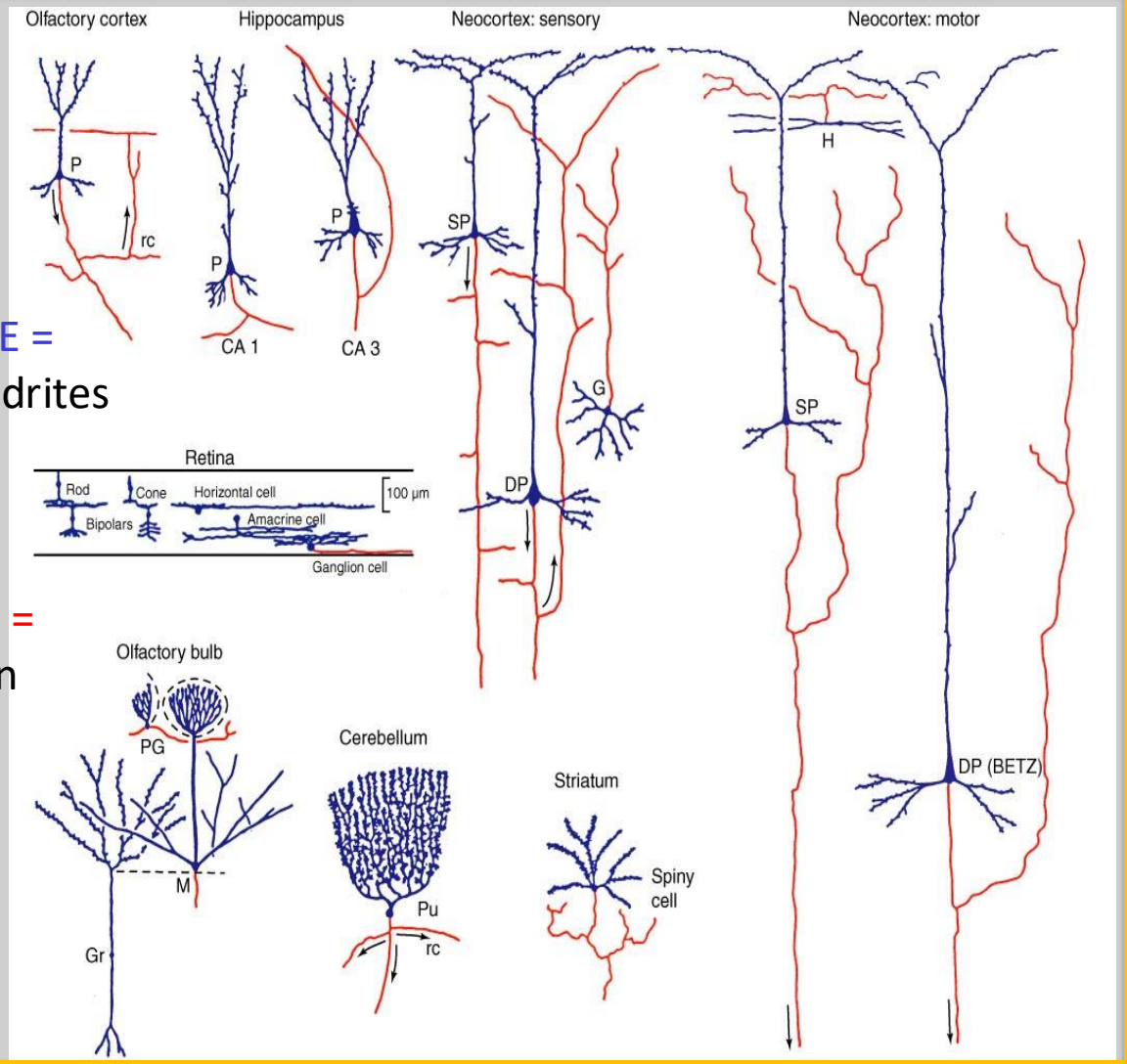
Major parts of NEURONS: *Dendrites and dendritic branches*

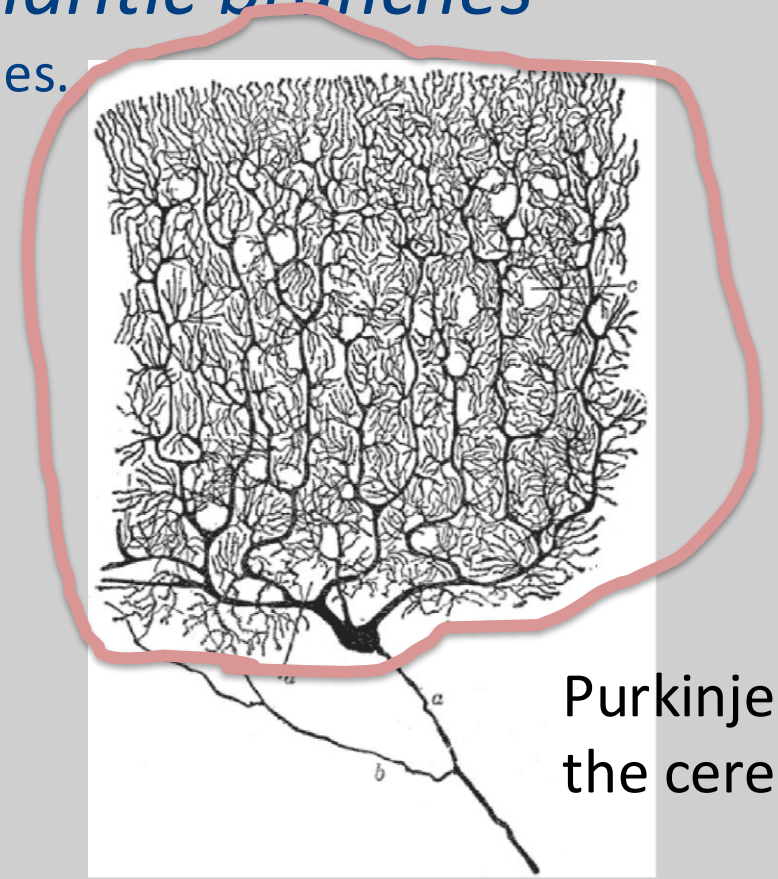
– Most neurons have elaborate dendrites w/ numerous branches.

– part of the neuron that performs the "hearing" part of a conversation between two neurons.

BLUE =
Dendrites

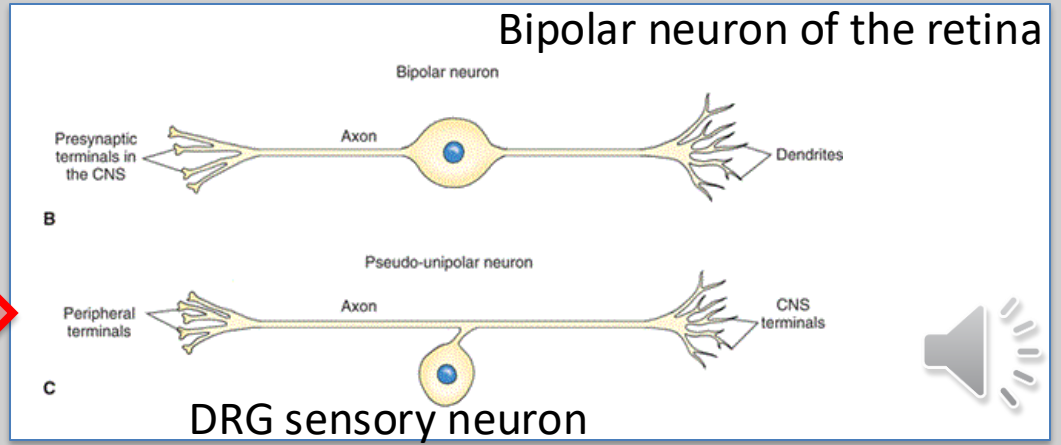
RED =
Axon





Purkinje cell of the cerebellum

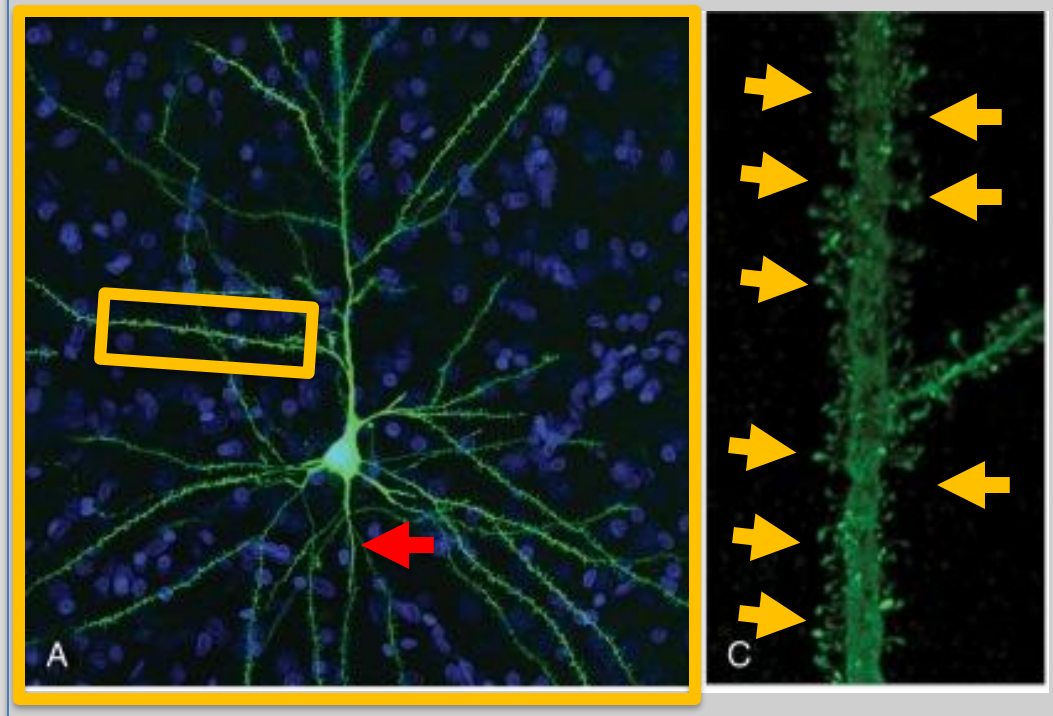
Bipolar neuron of the retina



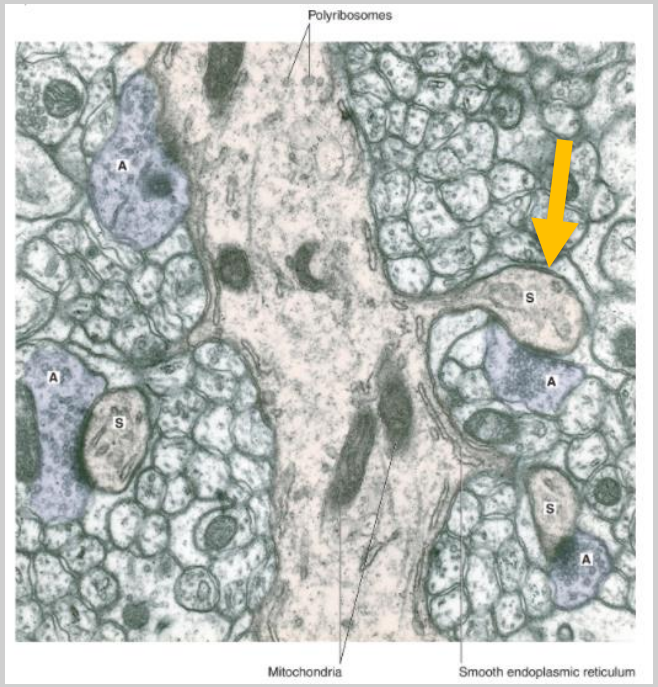
DRG sensory neuron

Parts of NEURONS: Dendrites & dendritic spines

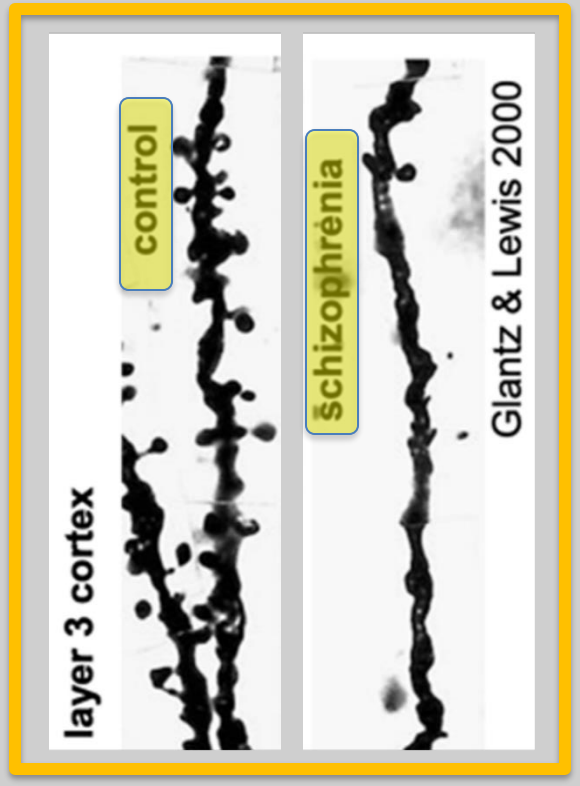
- spines found on the dendrites of many neurons such as neocortical neurons, Purkinje neurons, etc.
- synapses are preferentially made on spines



Human neocortical neuron (Benavides-Piccione et al. Cerebral Cortex 2013)



•Estomih Mtui MD, Gregory Gruener MD, MBA and Peter Dockery BSc, PhD Fitzgerald's Clinical Neuroanatomy and Neuroscience, 6, 63-74



Clinical correlate:

FMRP gene - that causes Fragile X syndrome- is important in dendritic spine development.
Patients with Fragile X syndrome have **increased** numbers of spines on neocortical neuron dendrites.

Clinical correlate:

Dendritic spines are **decreased** in neocortical neurons of patients w/ schizophrenia.
Mechanisms still unknown.

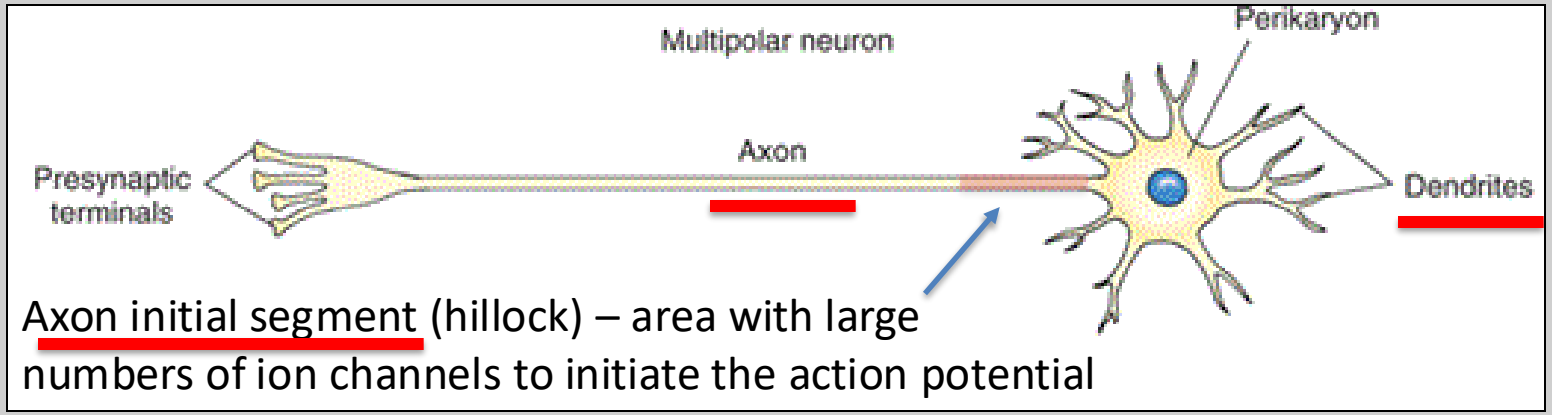
Parts of a NEURON: Axon, branches, terminals

- axons found on nearly all neurons

- axons can vary widely in length, shape, and number of branches (emanating from axon initial segment/hillock).

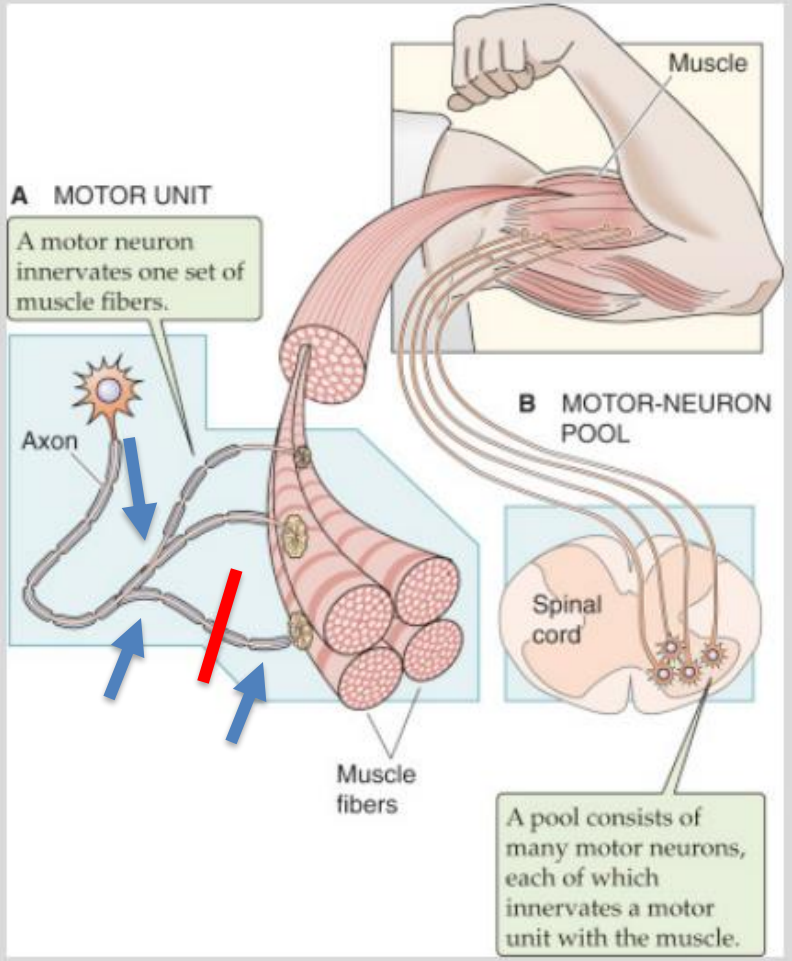
- axon terminals make "contact" with other neurons or muscle and form synapses

- communicating "wires" of neurons that do the "talking"



Axon initial segment (hillock) – area with large numbers of ion channels to initiate the action potential

Ch.5, Essential Neuroscience 2nd ed. Wolters Kluwer/Lippincott Williams



Medical Physiology by Boron and Boulpaep, Ch.9

Clinical correlate:

Severed or injured axons of neurons in the PNS can often grow back. Wallerian degeneration is the process of degenerating of axon distal to injury.

Cell body and dendrites

Yellow shows areas on axon where Na+ are localized.

High expression at the axon initial segment

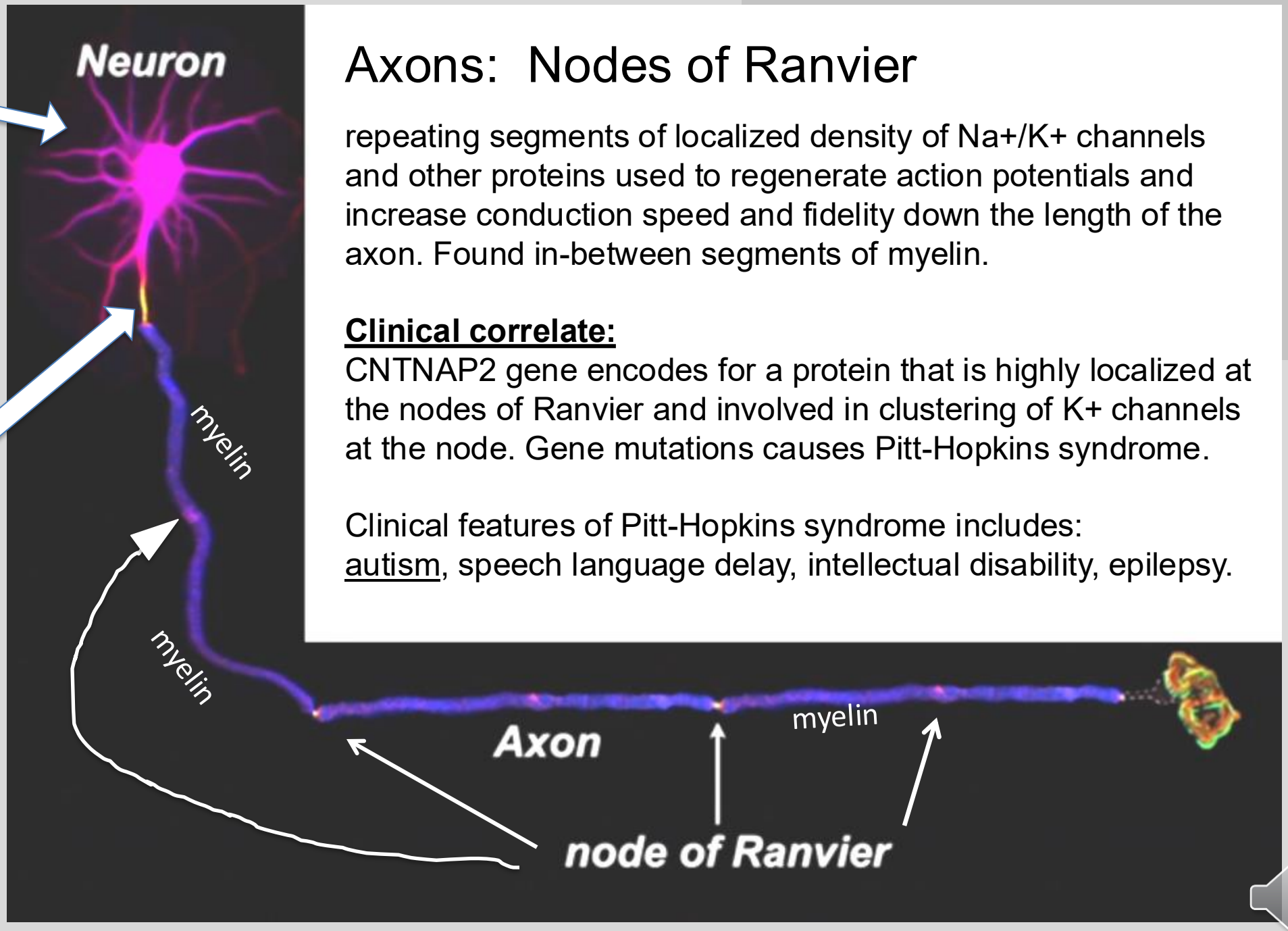
And at nodes of Ranvier

Axons: Nodes of Ranvier

repeating segments of localized density of Na+/K+ channels and other proteins used to regenerate action potentials and increase conduction speed and fidelity down the length of the axon. Found in-between segments of myelin.

Clinical correlate:
CNTNAP2 gene encodes for a protein that is highly localized at the nodes of Ranvier and involved in clustering of K+ channels at the node. Gene mutations causes Pitt-Hopkins syndrome.

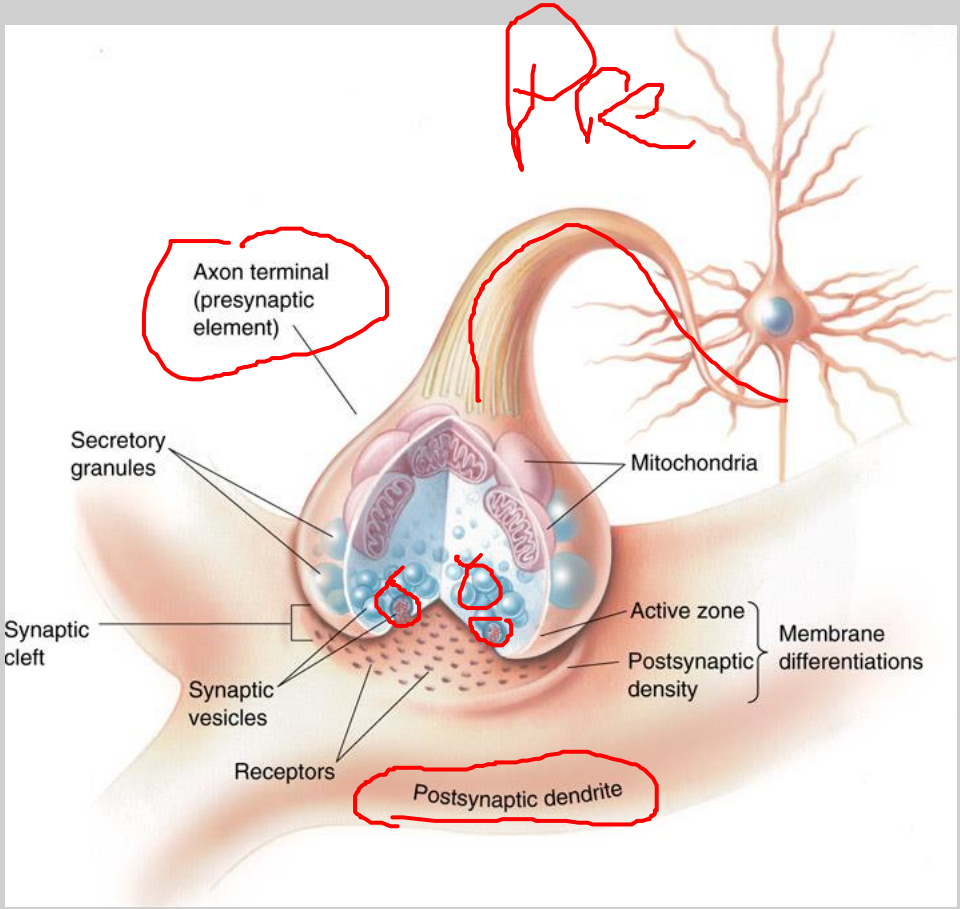
Clinical features of Pitt-Hopkins syndrome includes:
autism, speech language delay, intellectual disability, epilepsy.

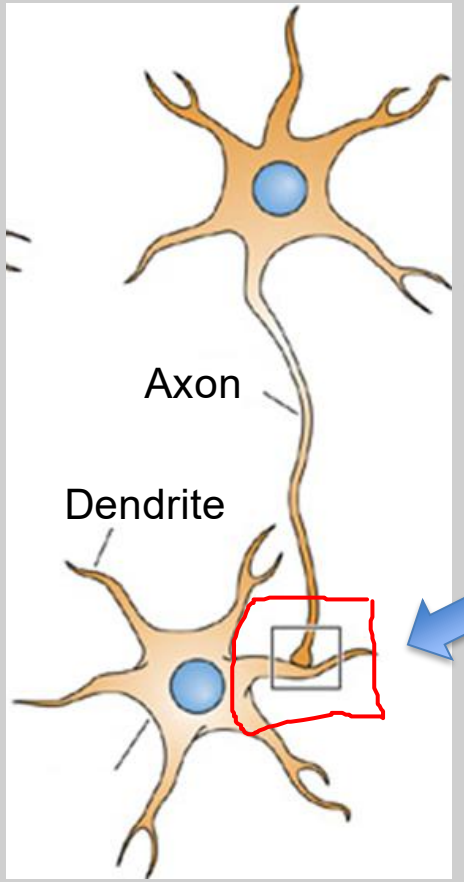


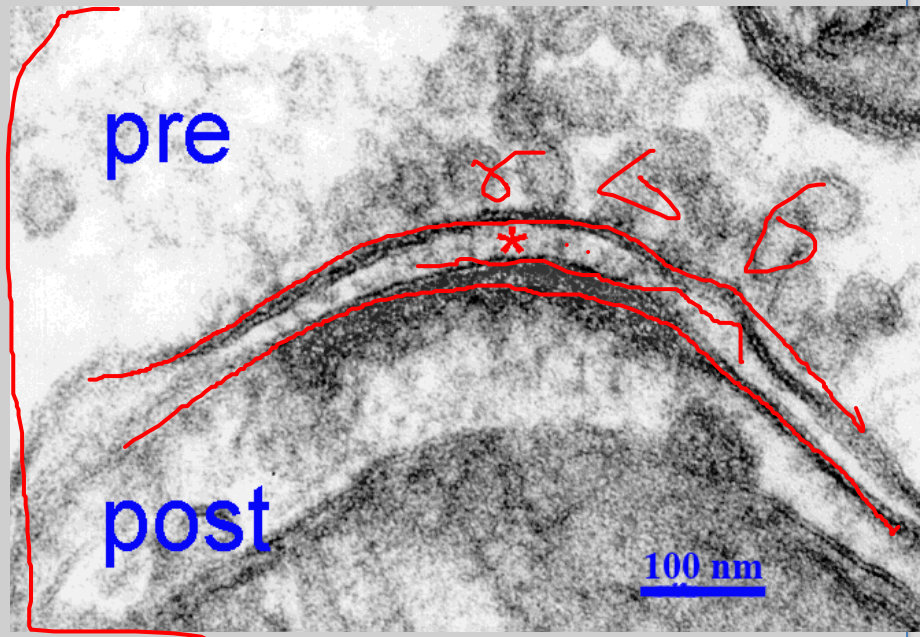
M. Rasband Baylor University, http://videocast.nih.gov/summary.asp?Live=17068&bhcp=1

Axon terminal (terminal bouton) forms the chemical synapse!

- site where neurons functionally communicate with one another via neurotransmitter release.







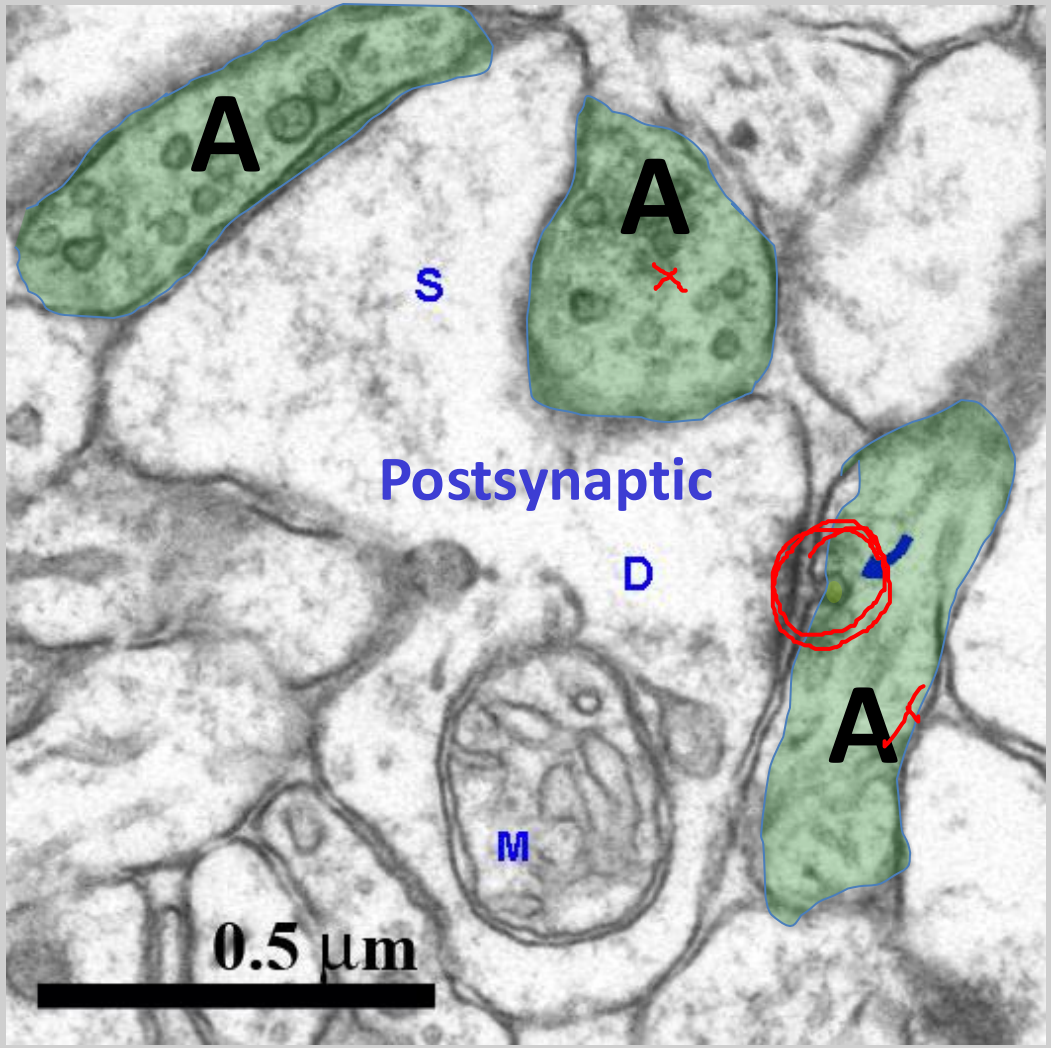
Presynaptic neuron – sending info/message

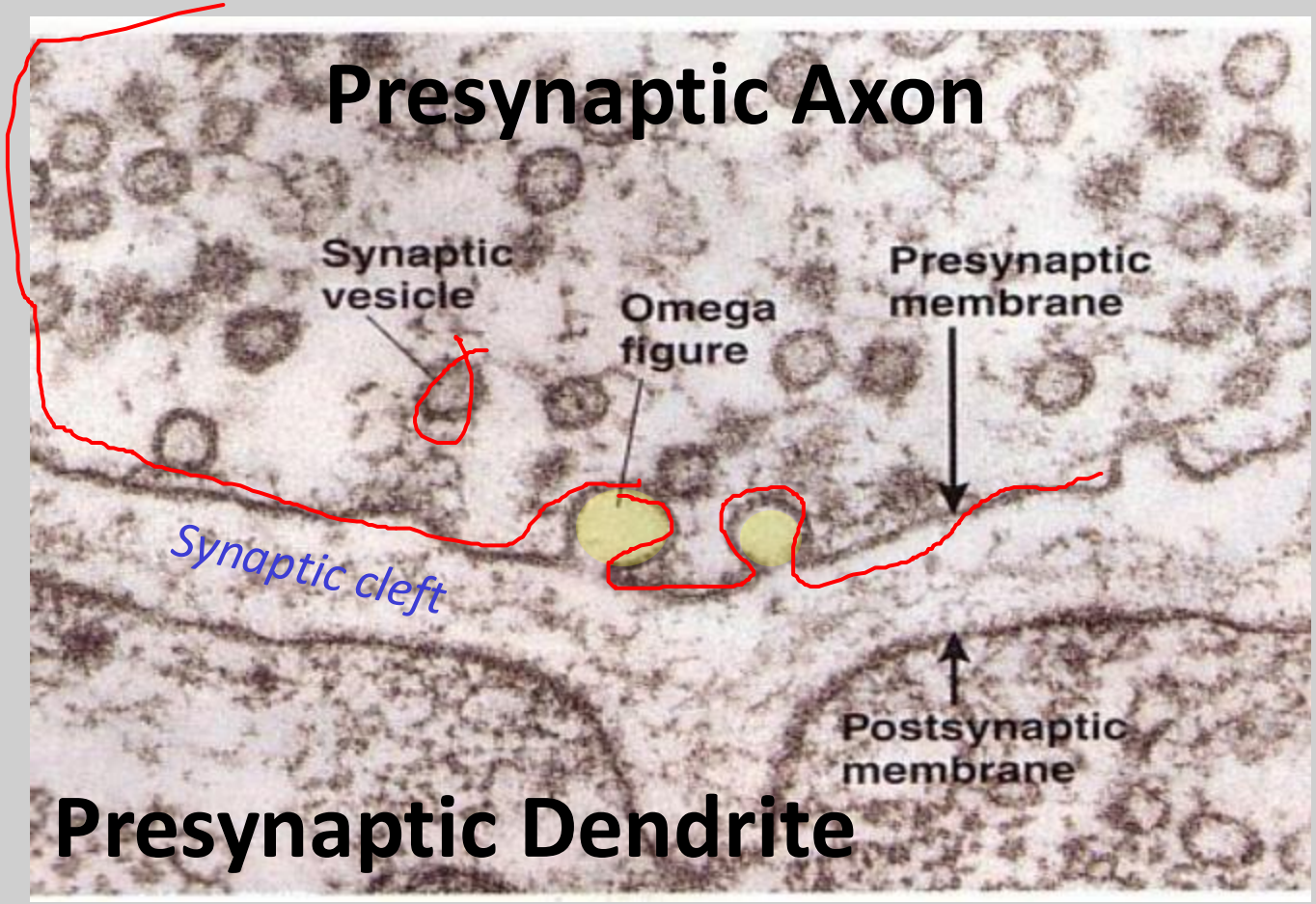
Postsynaptic neuron – receiving message

Clinical correlates – so many!
-neuro/psych disorders
-drugs of abuse/addiction
-sleep/wake, hunger/satiety
-SHANK3 mutations & autism

- Most common type of synapse
- Slower form of neural communication but still pretty fast ~1-5ms

Electron micrograph of the chemical synapse
- omega shapes structures show endocytosis of neurotransmitters



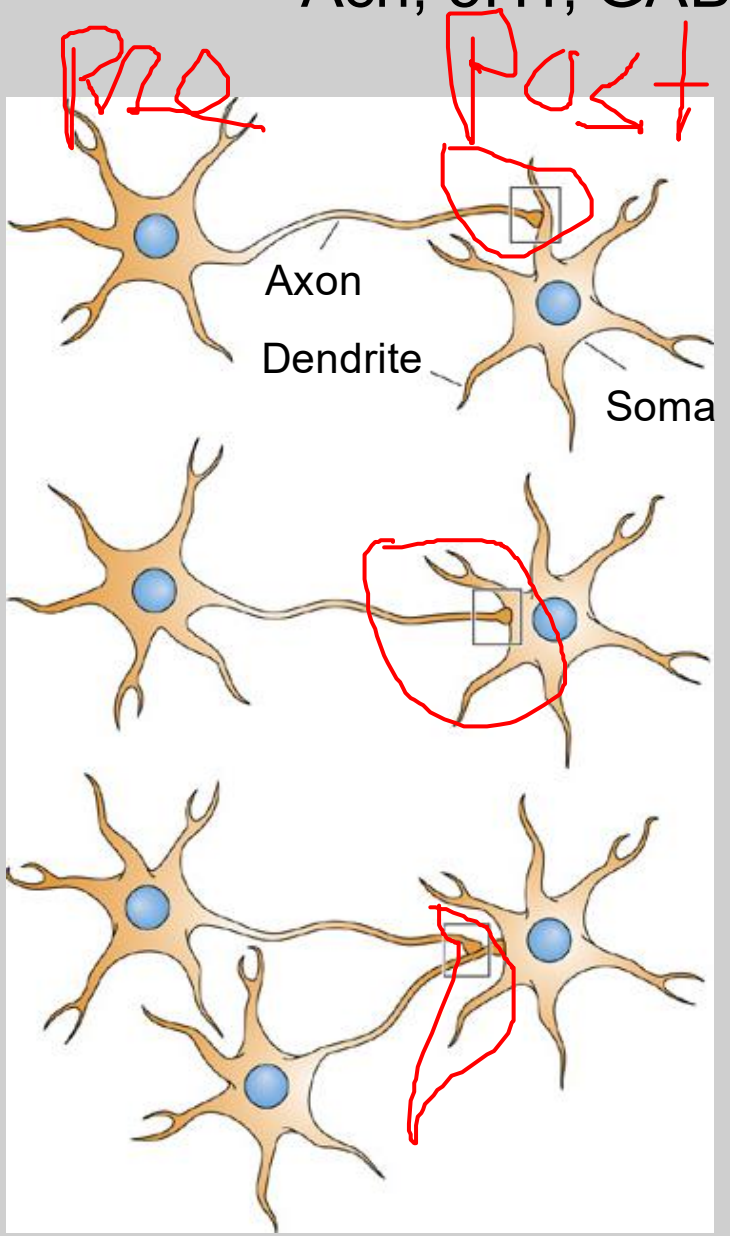


Heuser JE, Society for Neuroscience Symposia Vol 2; SFN 1997

S = dendritic spine D = dendrite A = axon

CHEMICAL SYNAPSES: mediated by neurotransmitters

- Ach, 5HT, GABA, glutamate, epinephrine, dopamine, neuropeptides

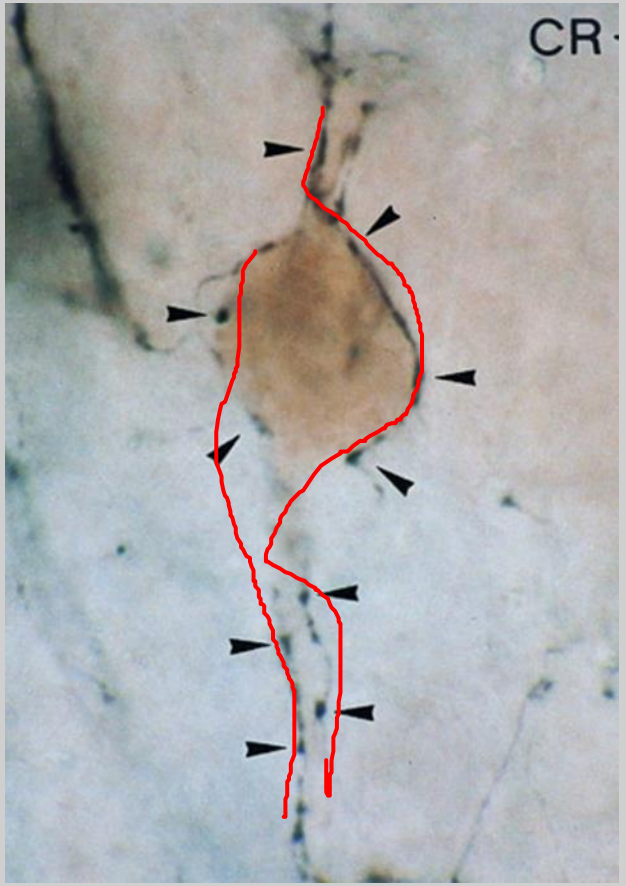


Different kinds of synaptic connections

Axo-dendritic:
Most common synapse type

Axo-somatic:
Common GABAergic synapse

Axo-axonic:
Least common synapse

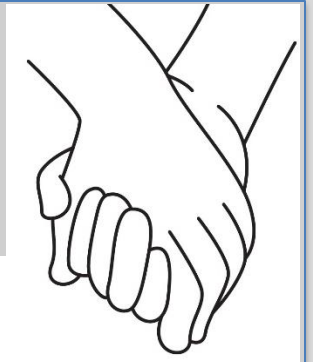


Gulyas et al 1996

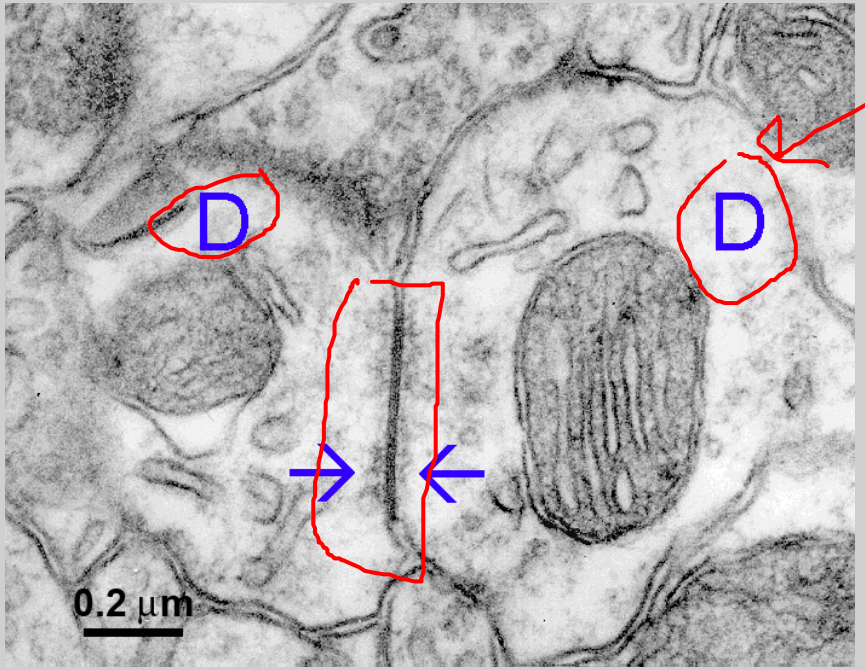
Axons can make synapses to multiple compartments of neurons

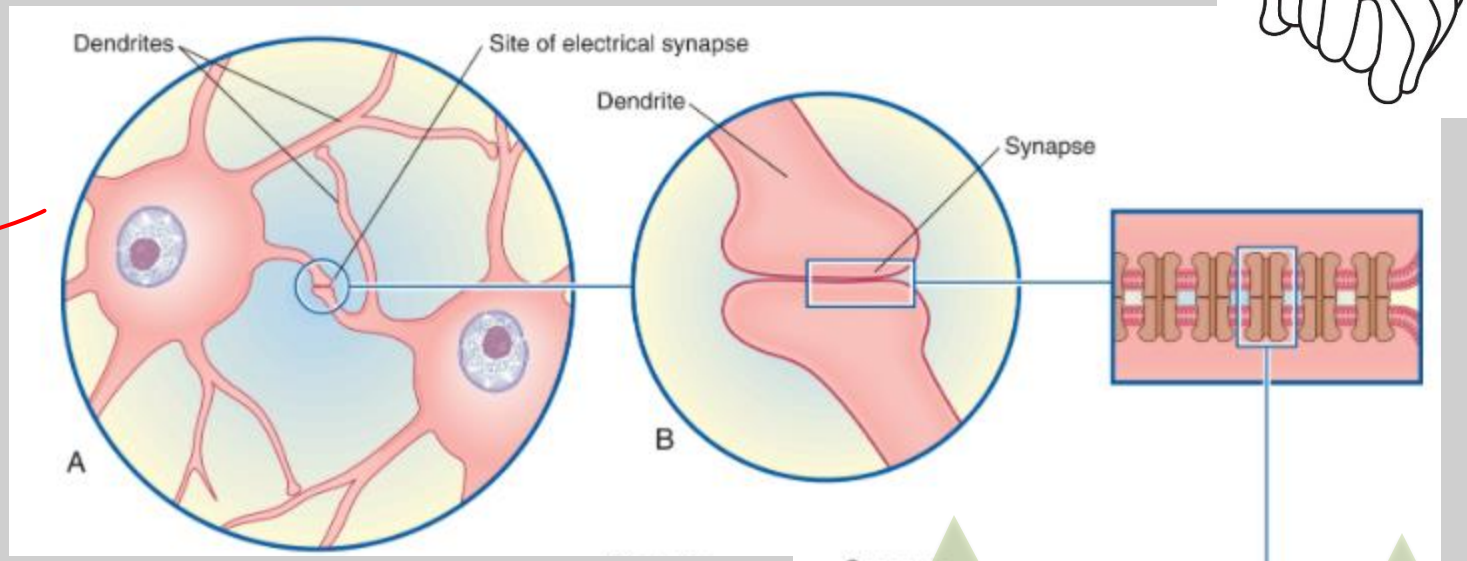
Neurons are “connected” to one another at the synapse

- the site where neurons functionally communicate with one another

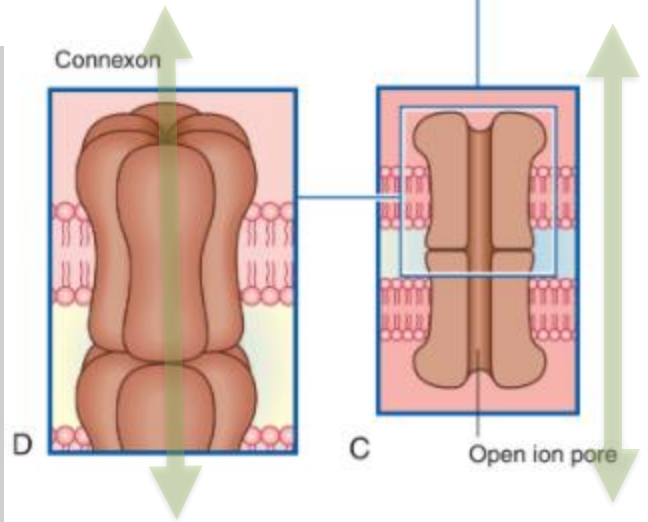


Electrical synapses:
Gap junctions/Connexons





Gap junctions allow direct ion & small molecule flow from one neuron to the other. Usually bidirectional.



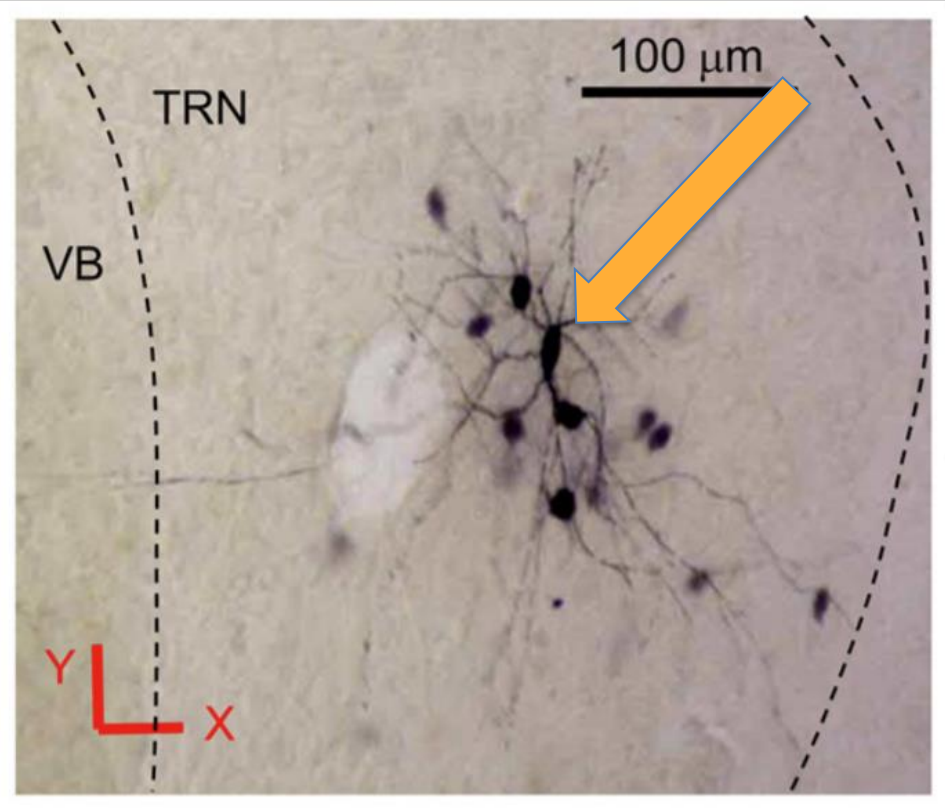
Clinical correlate:

Certain connexins expressed in specific cell types.

~30 disease due to connexin gene mutations.

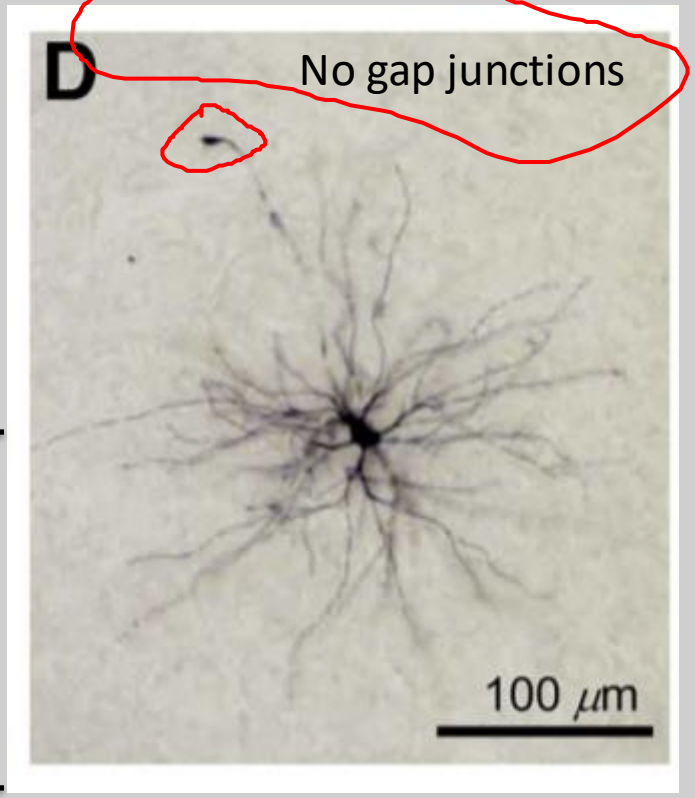
•E Mtui MD, G Gruener MD, MBA and P Dockery BSc, PhD Fitzgerald's Clinical Neuroanatomy and Neuroscience, 8; 85-101

Gap junctions & Electrical synapses in neurons



Inject dye into neuron labeled with orange arrow and dye travels through gap junctions to label neurons that are connected via electric synapses

Injection of dye only labels one neuron because the cell does not have any gap junctions.

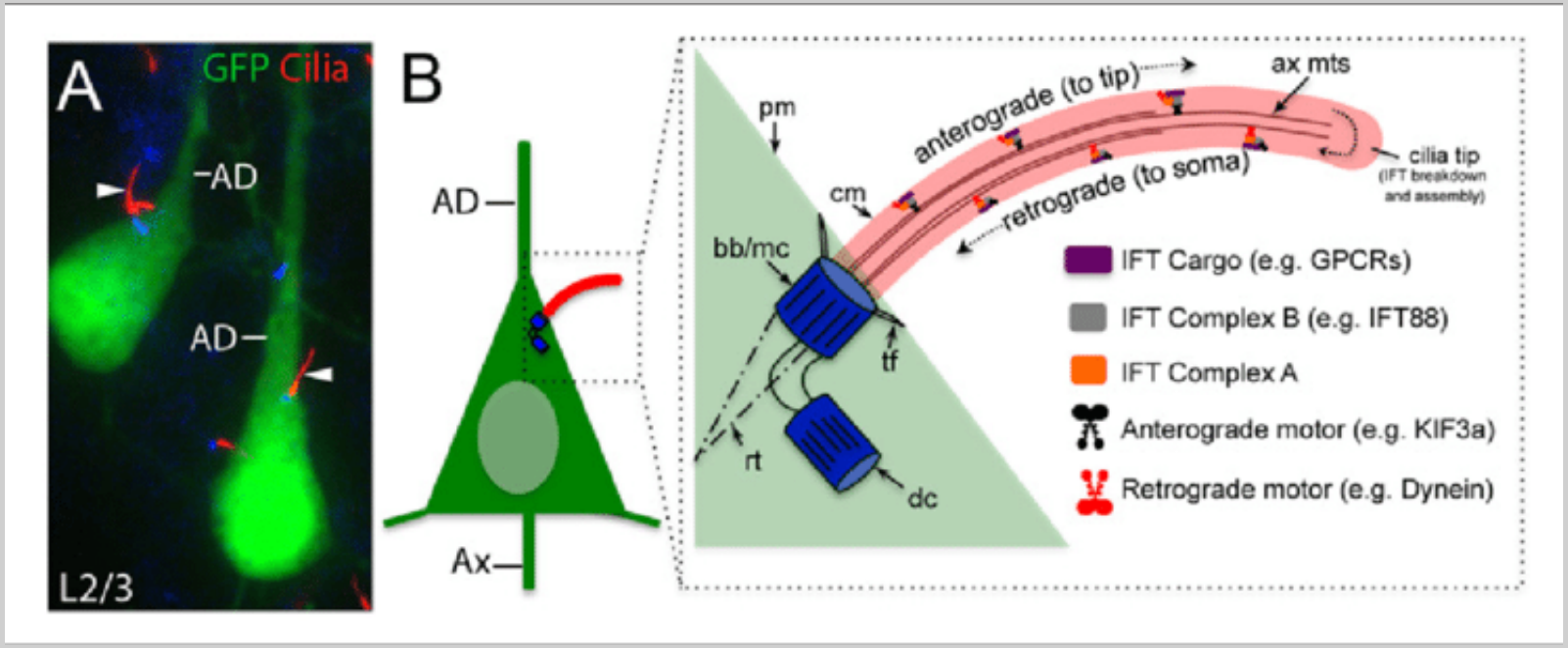


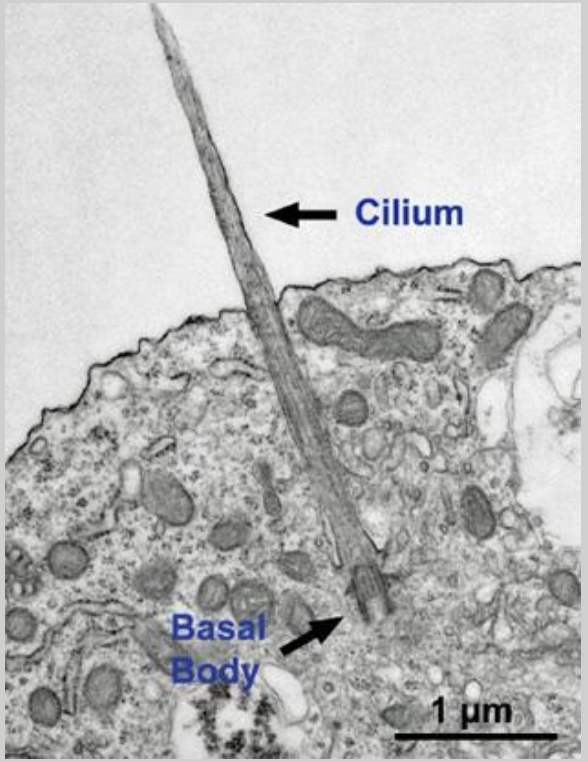
Lee et al. J Neurosci. 2014 Sep 24;34(39):13170-82. doi: 10.1523/JNEUROSCI.0562-14.2014.

- Gap junctions allow direct ion & small molecule flow from one neuron to the other.
- Usually bidirectional
- Fastest type of neural communication <1ms

Neuronal Cilia

- every neuron has a cilium (~2-4um long) which generally emerges from the cell body
- function of the cilium is poorly understood





Clinical correlate: serious neurodevelopmental disorders are associated with mutation of Genes important for cilia development.
ARL13B gene mutation causes defecitis in cilia development and Joubert Syndrome – characterized by midbrain & hindbrain malformations, intellectual disability, retinal dystrophy, cystic renal disease, congenital hepatic fibrosis and polydactyly

Sarkisian & Guadiana 2014

Neurons are the most diverse cells among all the organ systems due to diverse:

- Morphology: shape, size, dendritic/axonal features, spines,
- Connectivity: afferent/efferent projection ex. cortical neurons
- Neurotransmitter profile: Glutamate, GABA, Ach, 5HT, Epi
- Other molecular markers:
- Position within broader spatial area:

  motor cortex vs cerebellum vs amygdala

Glial cells (*by definition not neurons*)

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- Astrocytes
- Oligodendrocytes, Schwann cells
- Microglia

- *Supporting cells carrying different kinds of information about the environment and the internal state of the brain.*
- *Can communicate with other glia via electrical synapses.*
- *Can communicate with neurons but not via chemical or electrical synapses****

Astrocytes

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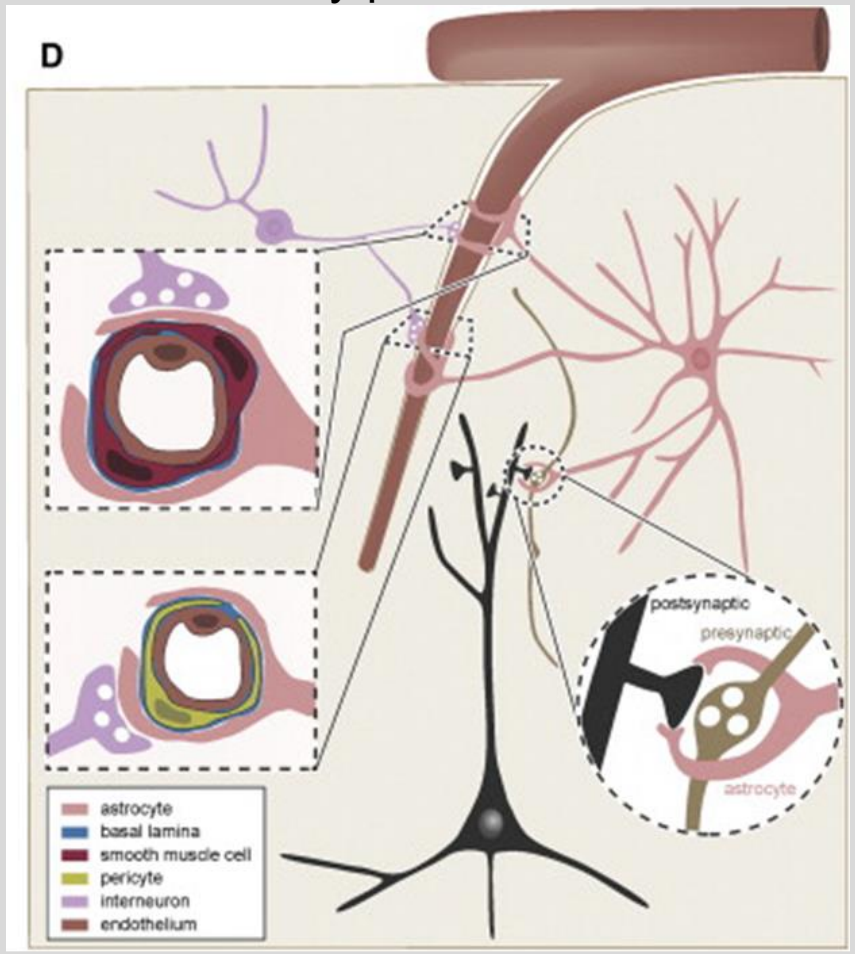
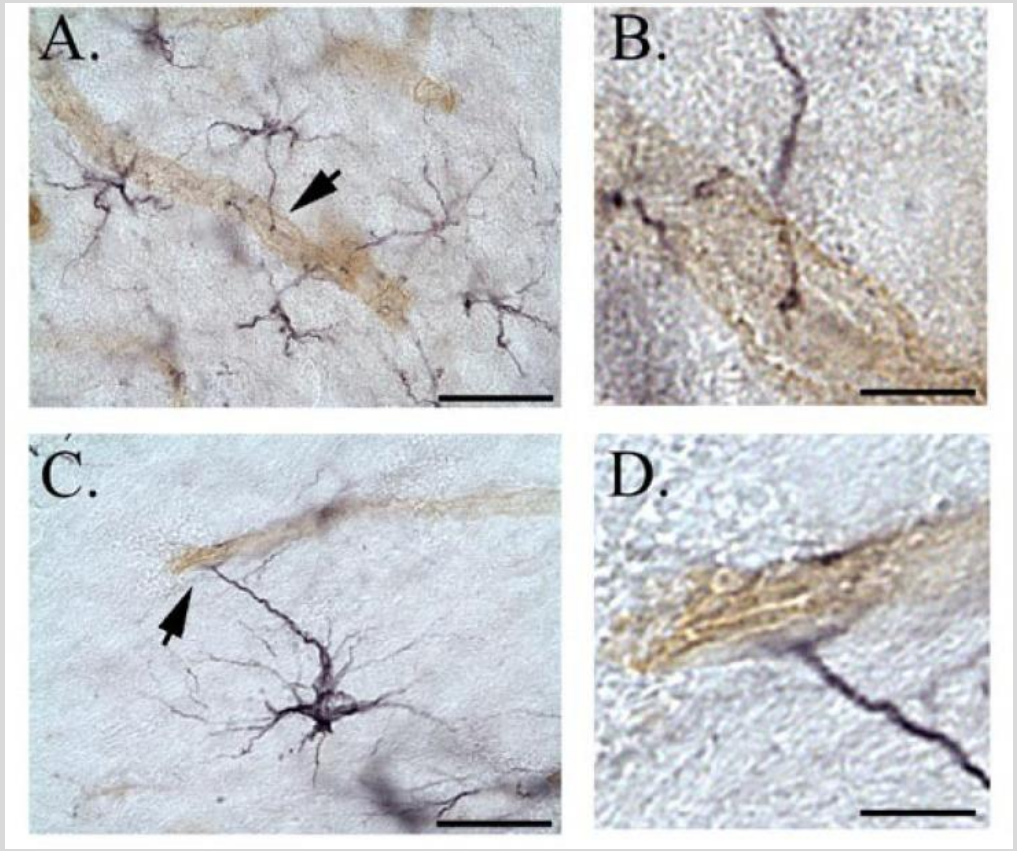
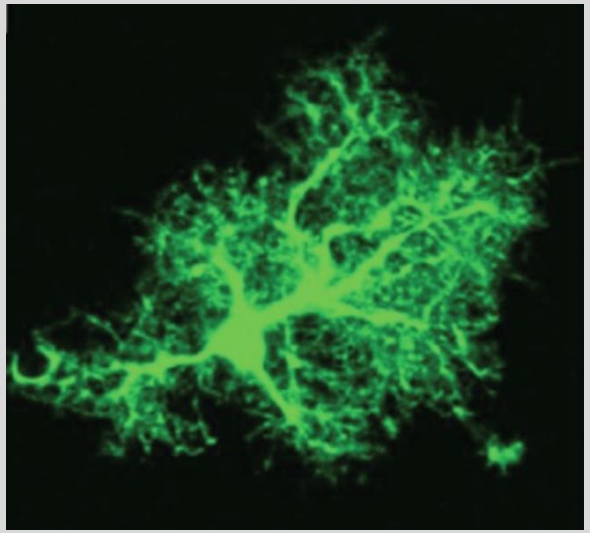
- structural partners at chemical synapses, capable of glutamate and K+ uptake
- form contacts with cerebral blood vessels (have aquaporin channels)
- continuously produced in the brain



Petzold and Murthy 2011



Ramos et al. 2008



Blood vessel and astrocyte communication

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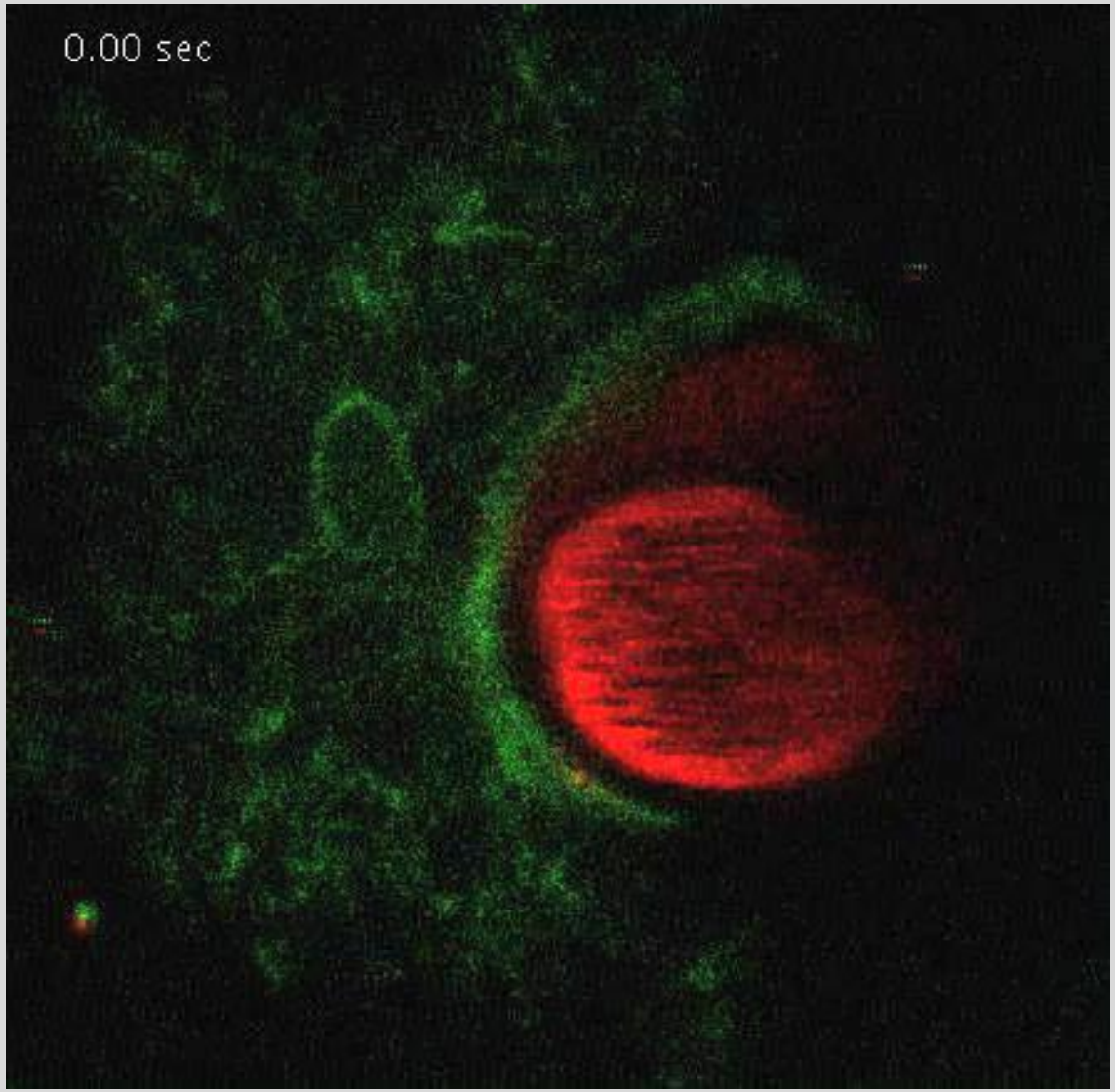
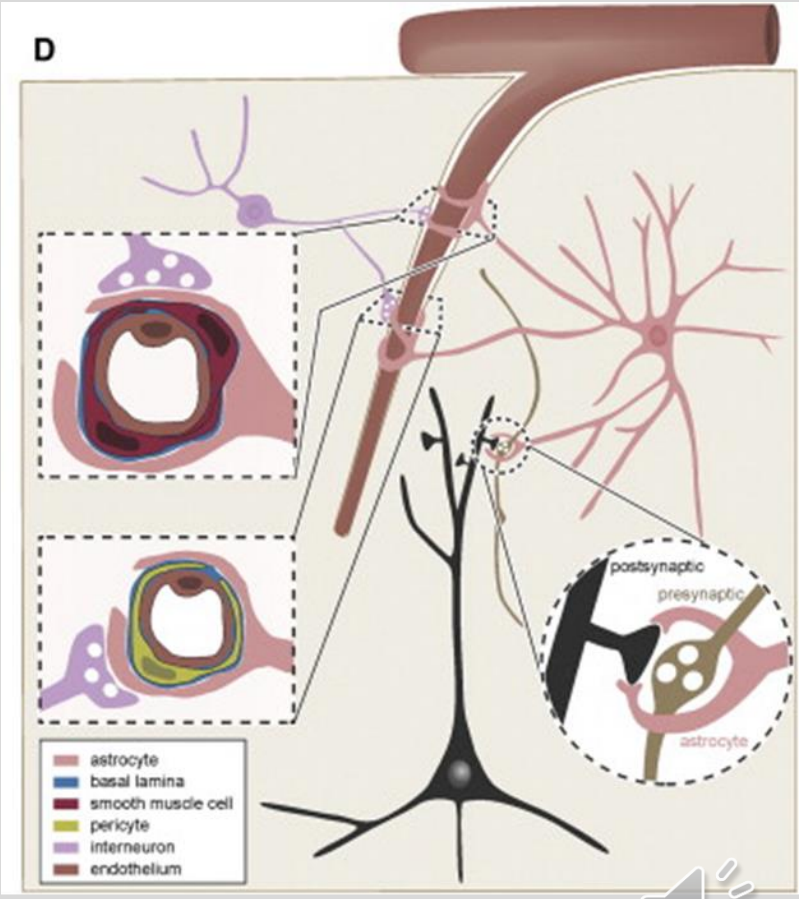


Green fluorescence shows depolarization/ calcium activity in astrocyte endfoot.

Red dye shows labels vessel and shows changes in vessel diameter



Tran et al. 2018 https://doi.org/10.1016/j.neuron.2018.09.045

Petzold and Murthy 2011

Gap junctions & Electrical synapses in Astrocytes

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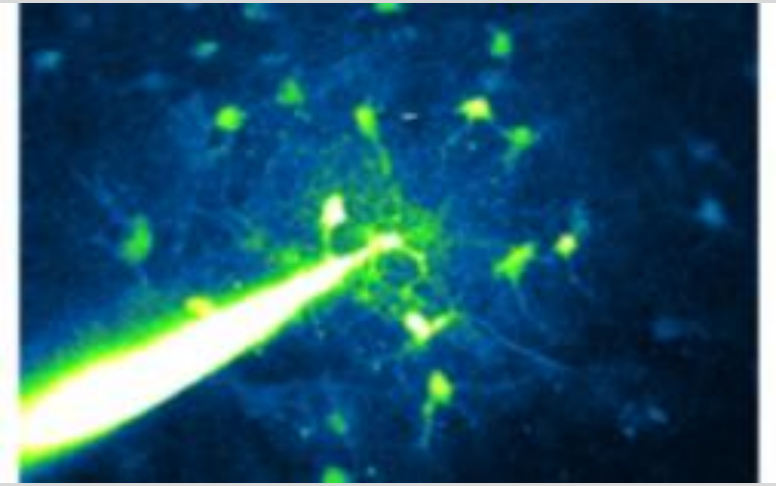
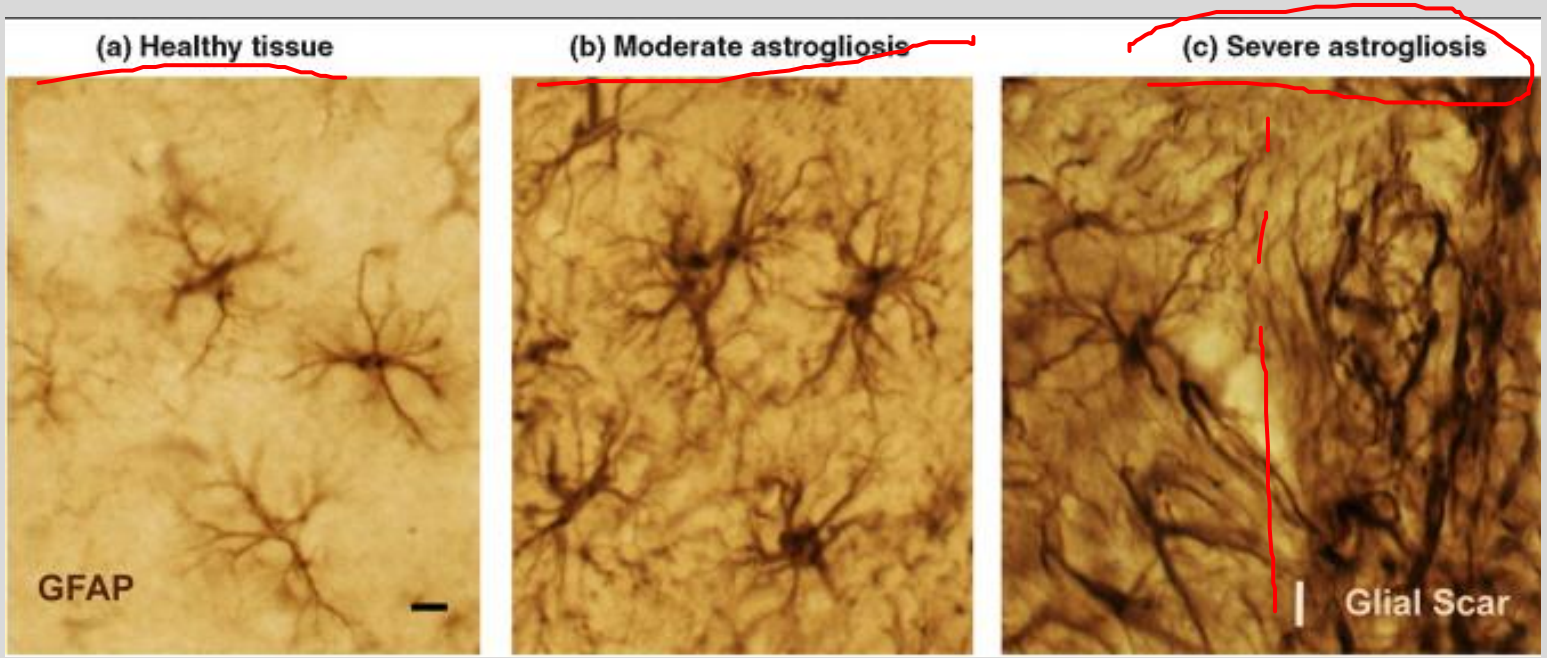
- Connected to other astrocytes as well as oligodendrocytes by gap junctions
- Can respond/"react" to tissue damage and form a glial scar but role not well understood (i.e. harmful or helpful such as in spinal cord injury)

Gap junctions in astrocytes





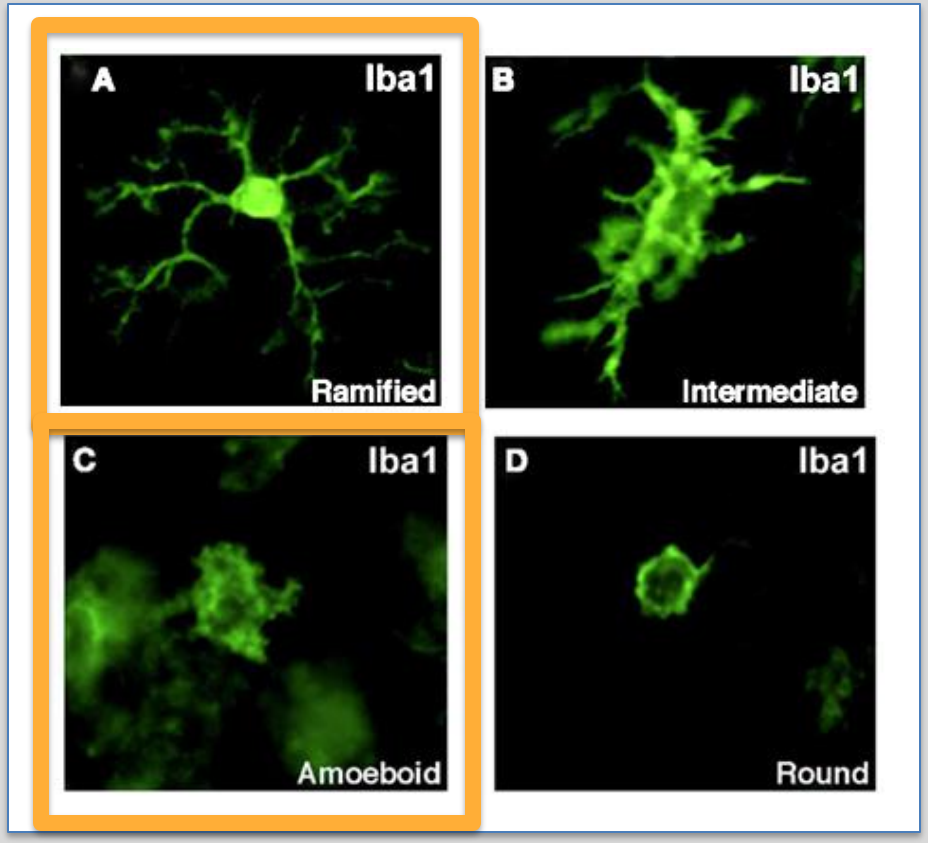
Clinical correlate:

Glial fibrillary acid protein (Gfap) is the gold standard molecular marker for reactive astrocytes and is used for detection of astro-gliosis (brain injury) and tumors made up of astroctyes (i.e. astrocytoma).

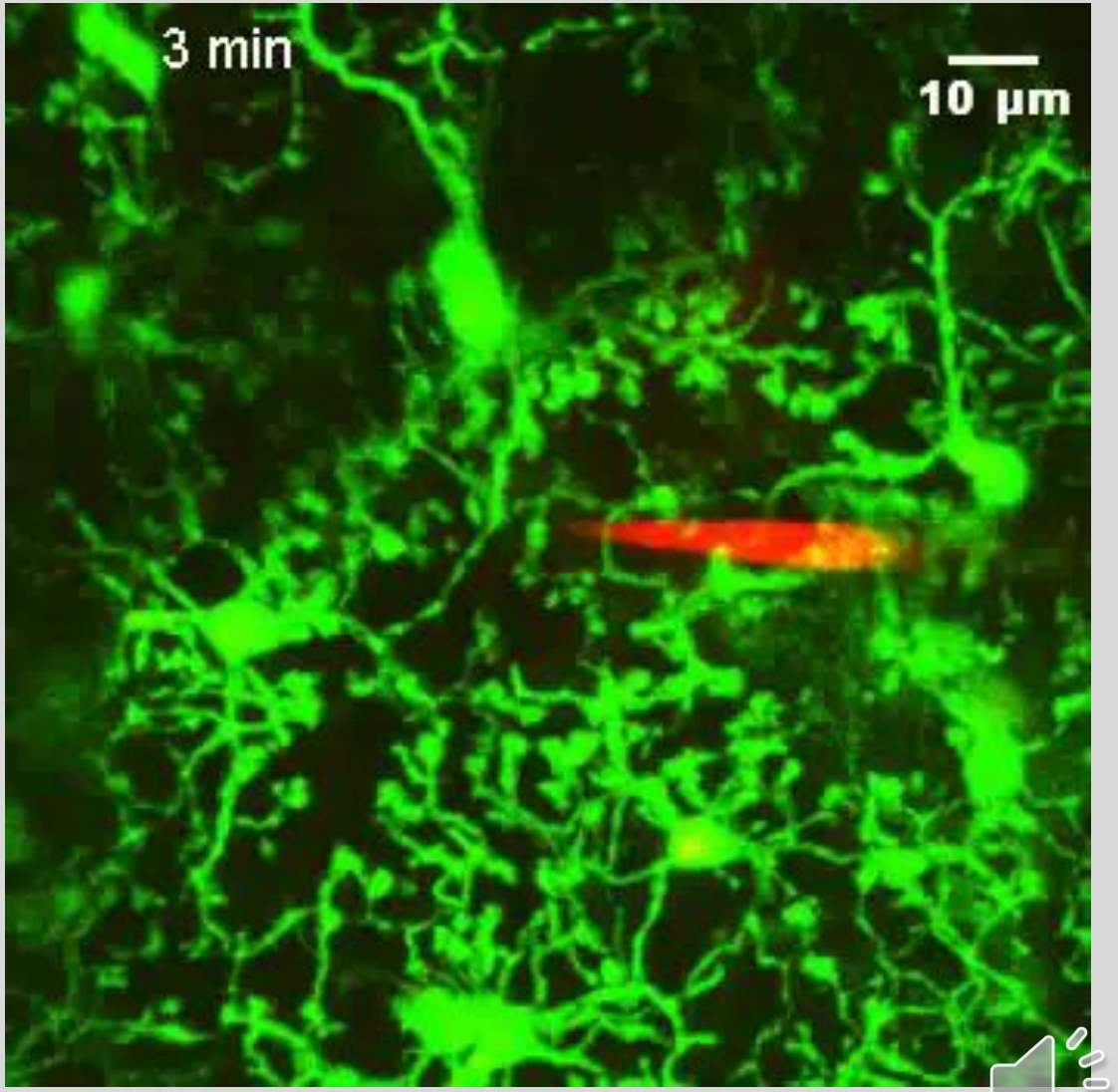
Mutation of the **GFAP** gene causes Alexander disease leukodystrophy which is characterized by childhood white matter development disruptions, and diverse symptoms such as cognitive and motor delays, loss of motor control.

Microglia

- immune cell of the nervous system
- capable of phagocytosis of cell debris or microbe
- capable of releasing cytokines and triggering inflammation
- change shape in response to injury, infection, inflammation
- continuously produced in the brain



Ekdahl 2012



Davalos et al. 2005

In vivo imaging of microglia phagocytosis of dying neurons

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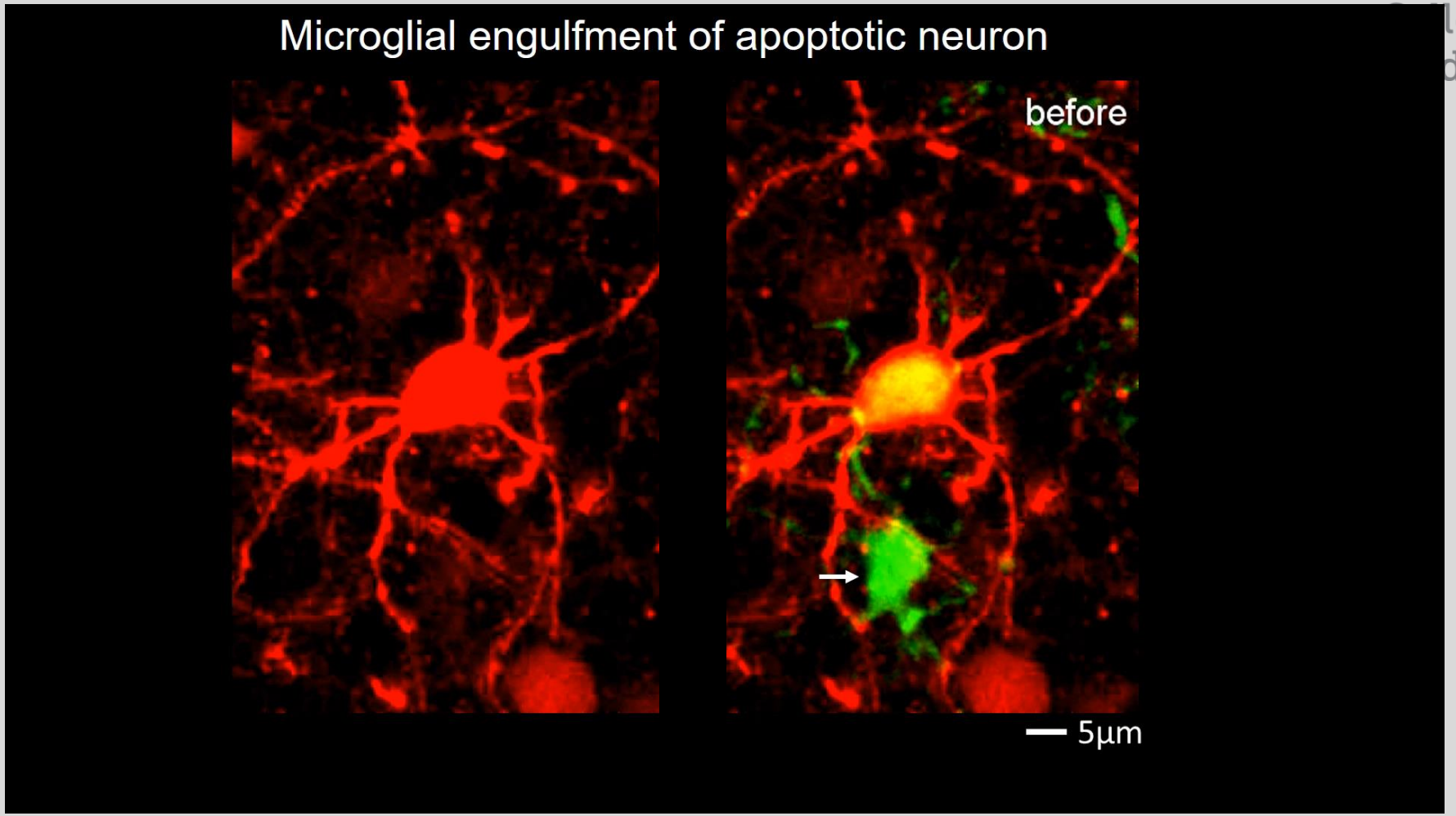

Damisah EC, Hill RA, Rai A, Chen F, Rothlin CV, Ghosh S, **Grutzendler J.** Sci Adv. 2020 Jun 26;6(26):eaba3239. doi: 10.1126/sciadv.aba3239.

Microglia response to injury

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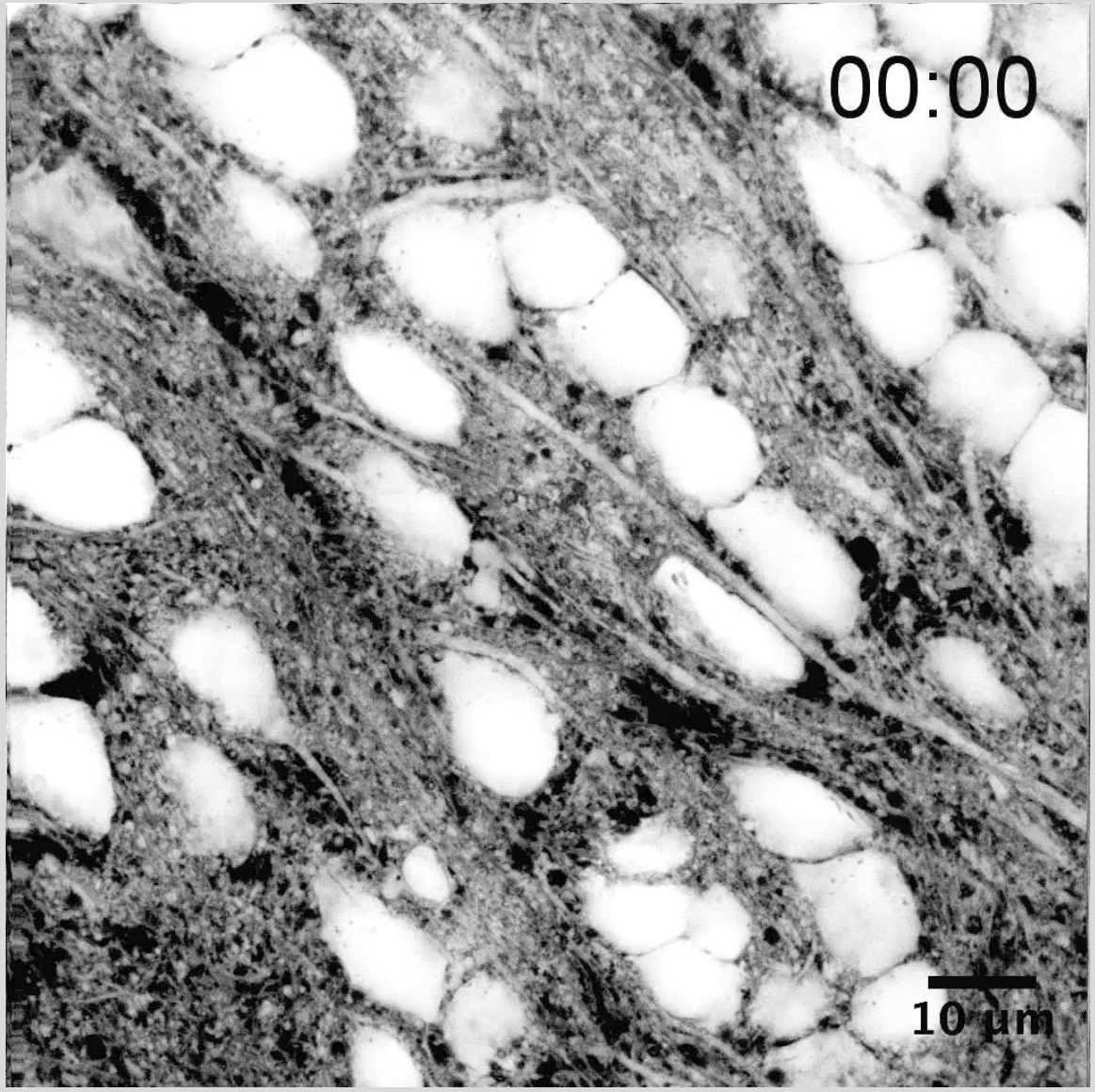

Tonnesen et al. Cell. 2018 Feb 22;172(5):1108-1121.e15.

Oligodendrocytes/Schwann cells

- myelin-producing cells of the CNS/PNS (respectively)
- differ in the number of axons that they envelop
  (i.e. oligos envelop more than one axon; Schwann cells envelop only one.)
- Both cell types causal to demyelinating and dysmyelinating diseases (e.g. Multiple Sclerosis)
- Continuously produced in brain

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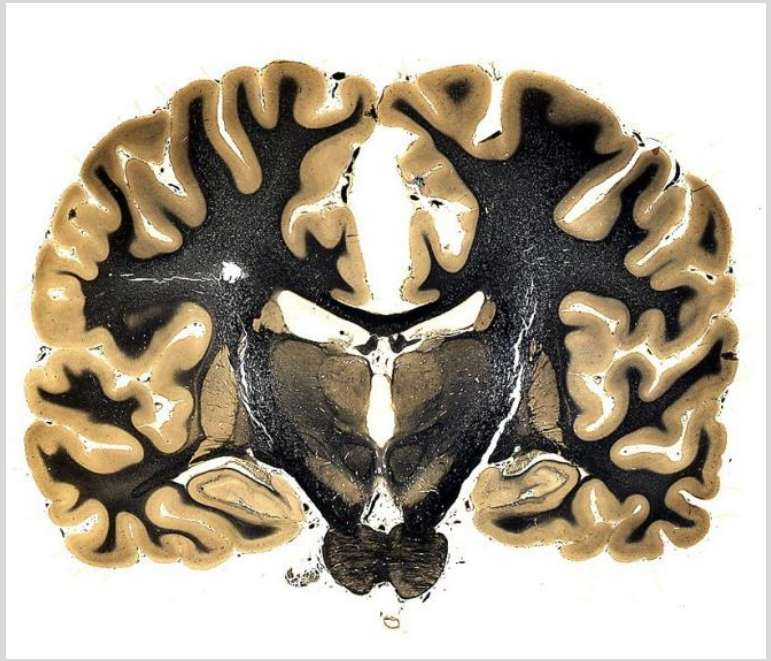
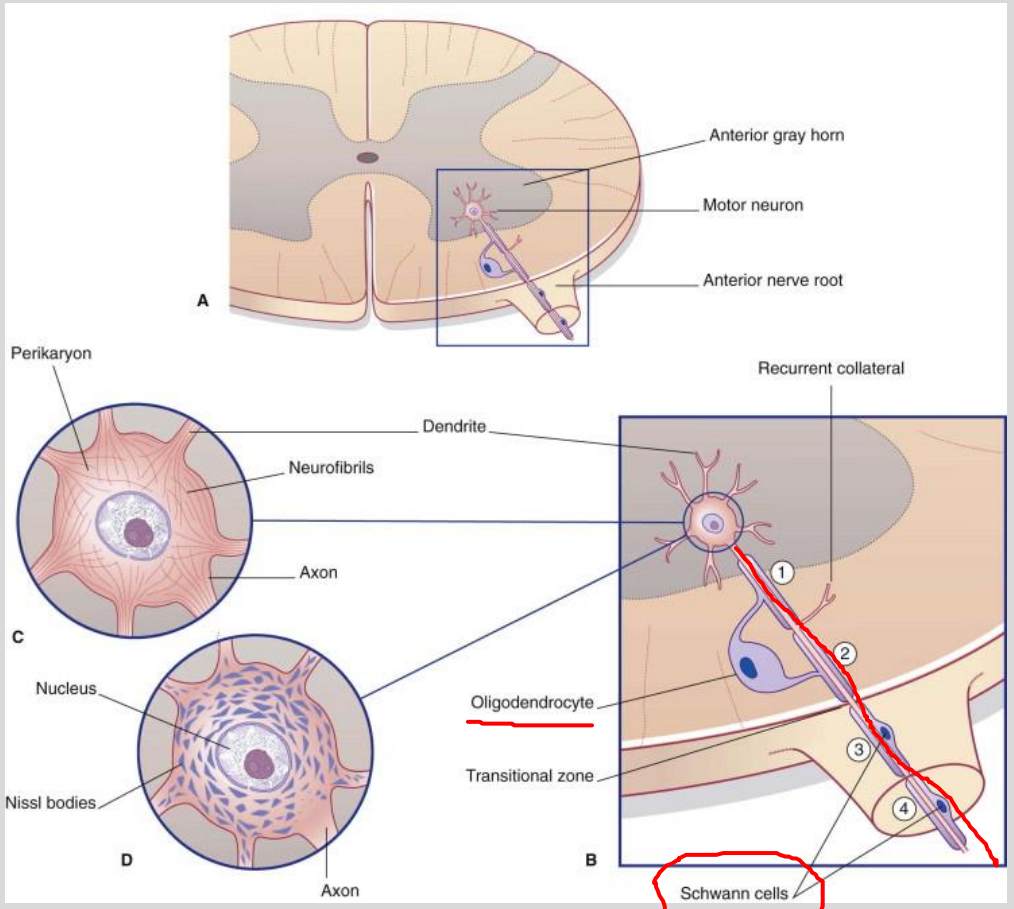
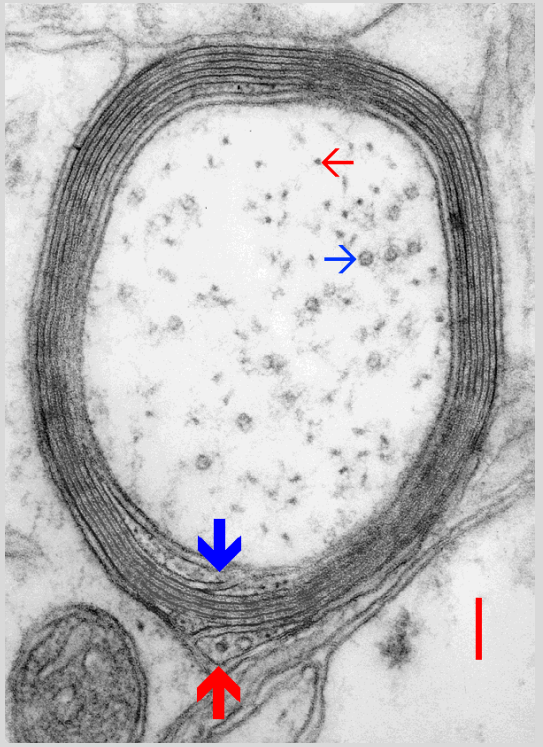


Myelin stain

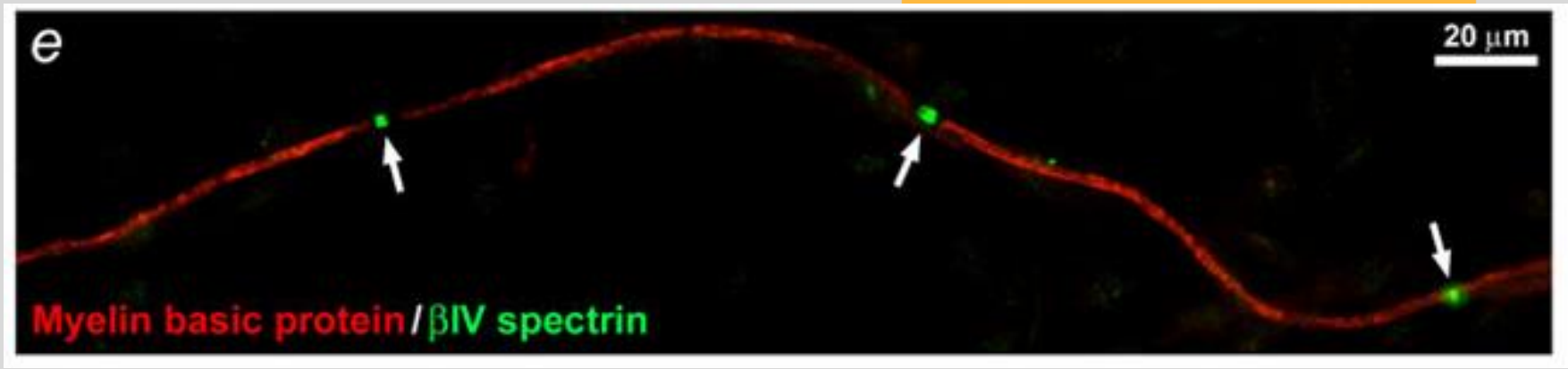


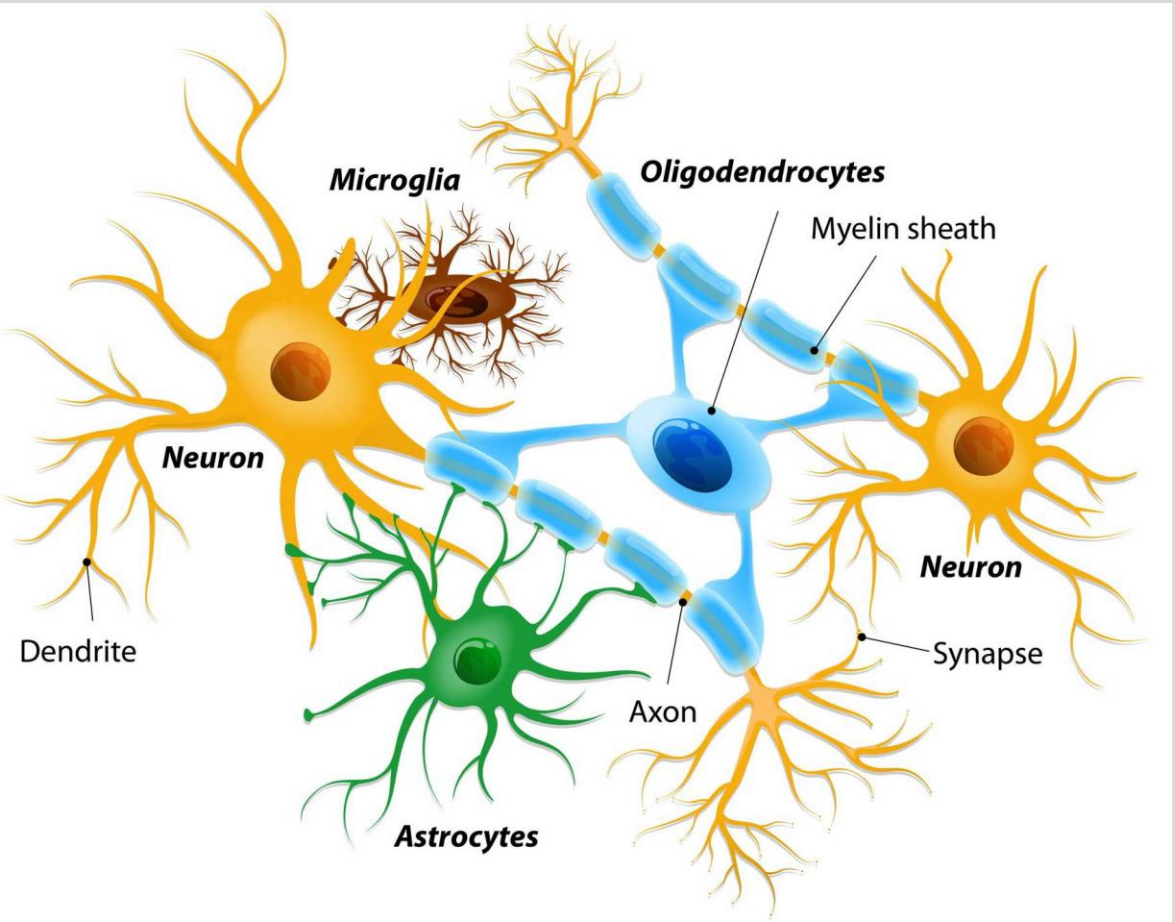
CH. 6, Clinical Neuroanatomy & Neuroscience, Saunders/Elsevier



Myelin found in between nodes of Ranvier

Oligodendrocytes ensheathe axons from more than one neuron. Schwann cells ensheathe only 1 neuron.





Clinical correlates

Autoimmune disorder where patients have IgG against **MOG - myelin oligodendrocyte glycoprotein**. MOG is a glycoprotein uniquely expressed in oligodendrocytes in the CNS**. MOG antibody disorder (MOGAD)** is an idiopathic, inflammatory, demyelinating disease of the central nervous system (CNS). Diverse peripheral and central symptoms including optic neuritis (loss or blurry vision, eye pain), transverse myelitis (weakness, numbness, pain, loss of bowel or bladder control).

Olig2 is a protein exclusively found in oligodendrocytes and is a maker for **oligodendroglioma** which can present with diverse symptoms such as headache, weakness, seizures, cognitive changes, etc.

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Non-neural & non-glial cells of the vasculature

- Endothelial cells (vessels) – blood brain barrier upcoming lecture
- Smooth muscle cell (vasodilation & vasoconstriction)
- Pericytes (wrap around vessels and are in direct contact with endothelial cells via gap junctions. Phagocytosis have been observed, suggesting that these cells also play macrophagic roles.)

Non-neural & non-glial cells of vasculature

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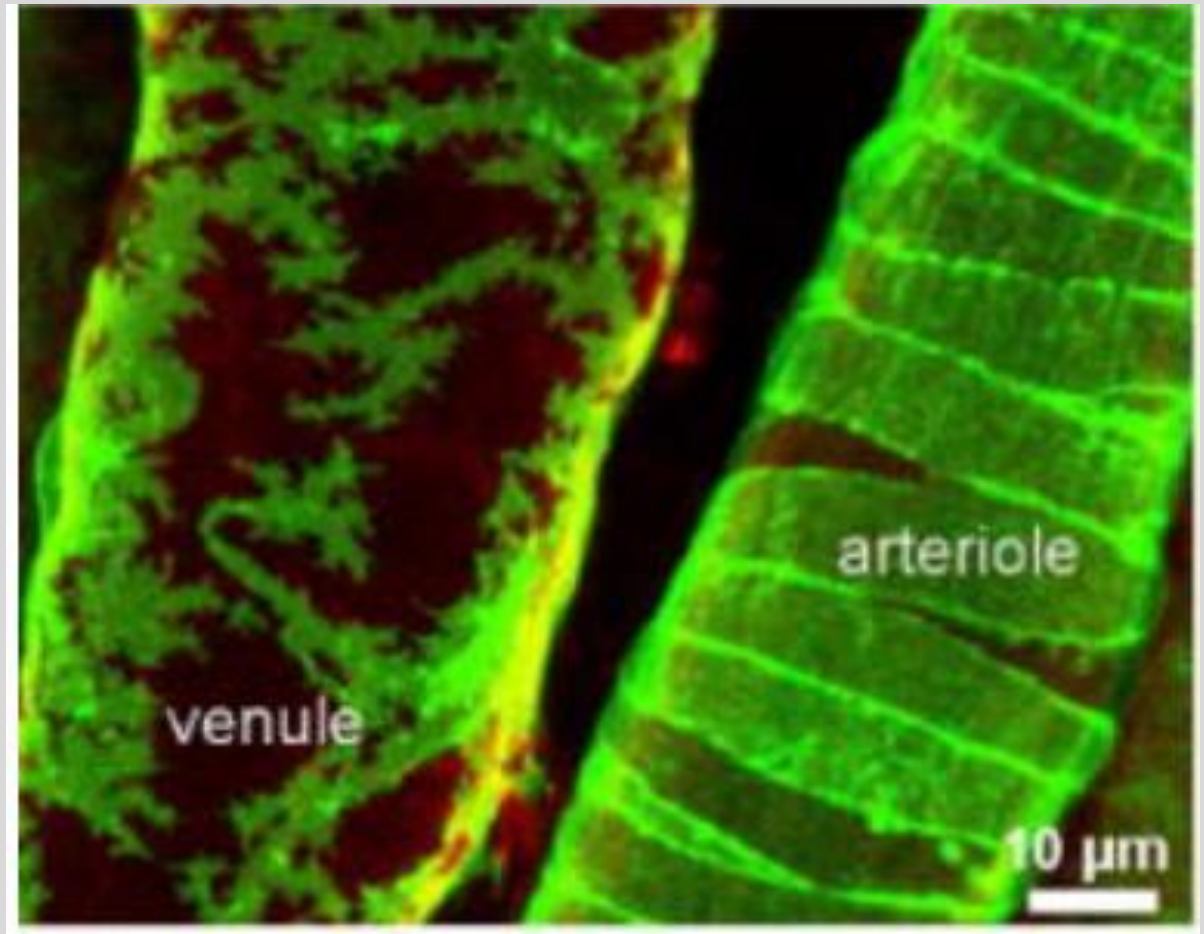
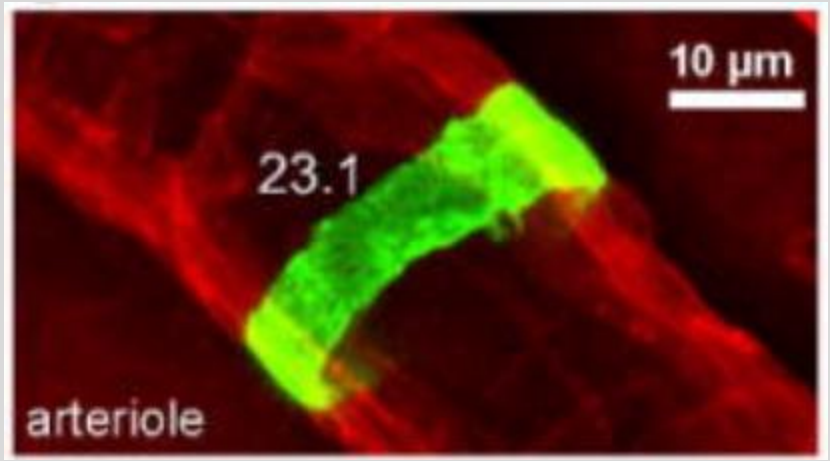


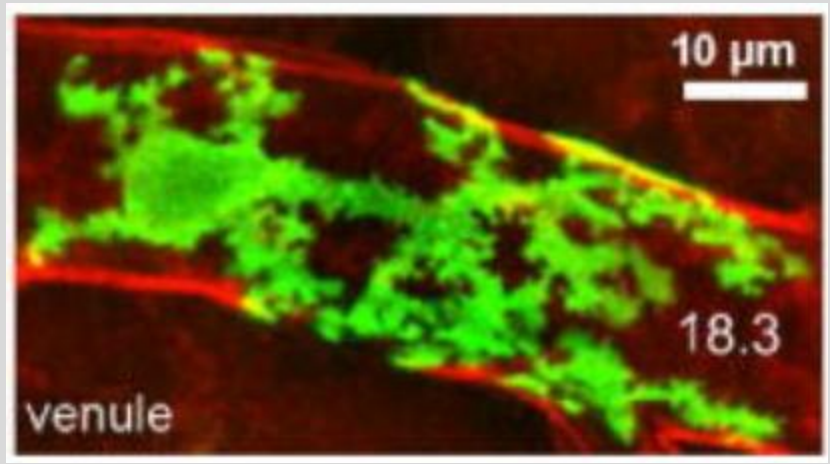
Pericytes
In venule

Smooth muscle
Cell in arteriole

Hill et al. 2015



Smooth muscle cell in arteriole



Pericytes in venule

Vasomotion and Smooth muscle cell

- Smooth muscle cell in green.
- calcium activity correlated with vasomotion

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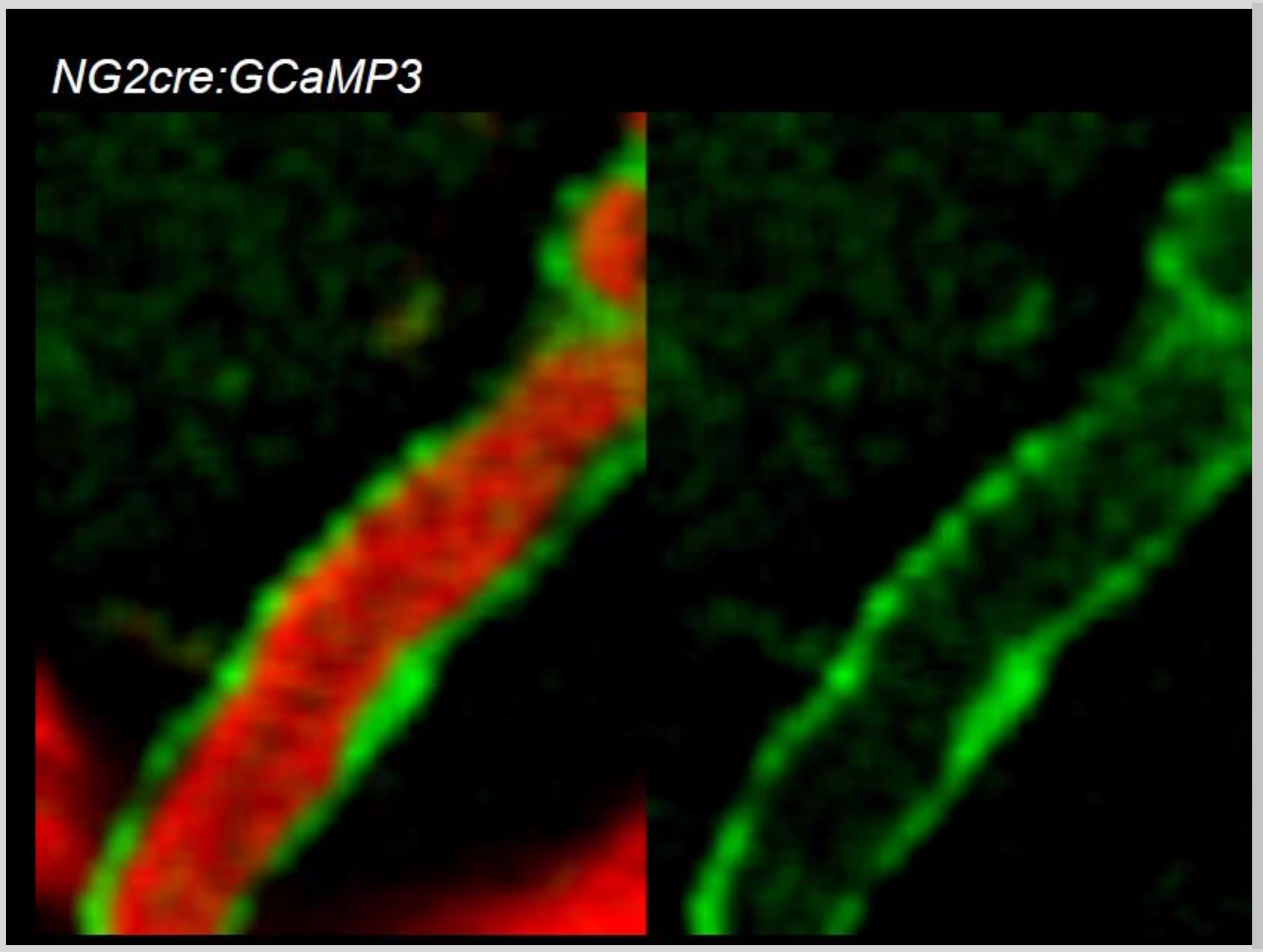

Hill et al. 2015 Neuron

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Non-neural & non-glial barrier cells

- Choroid plexus cells - epithelial and endothelial cells important for cerebral spinal fluid production

- Ependymal cells of the ventricles – important for circulation of the cerebral spinal fluid

- Lepto/Meningeal cells of the dura, arachnoid, and pia

Will be discussed in upcoming lectures.

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- The brain controls behavior via the activity of interconnected brain cells.
- There exist diverse cell types in the brain (neurons, glia, etc) with distinct functions, morphologies (structural components), connections (synapses) and clinical significance.

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