Cellular components of CNS

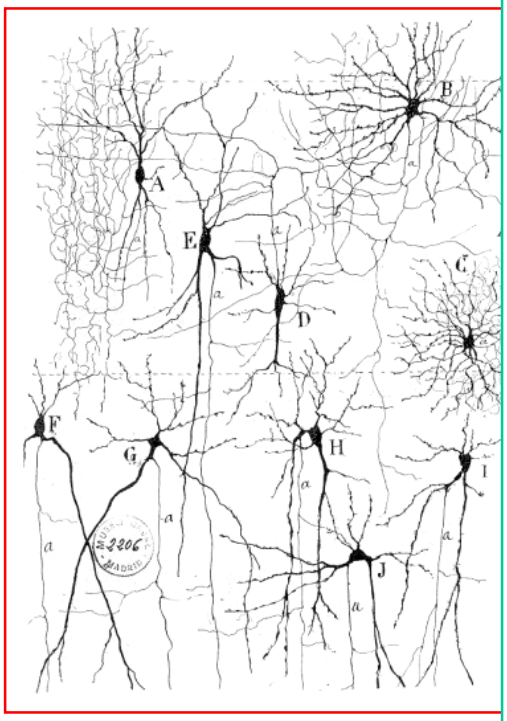
- Neurons
- Glial cells:

Astrocytes (including radial glia), oligodendrocytes, microglia, (ependymal cells)

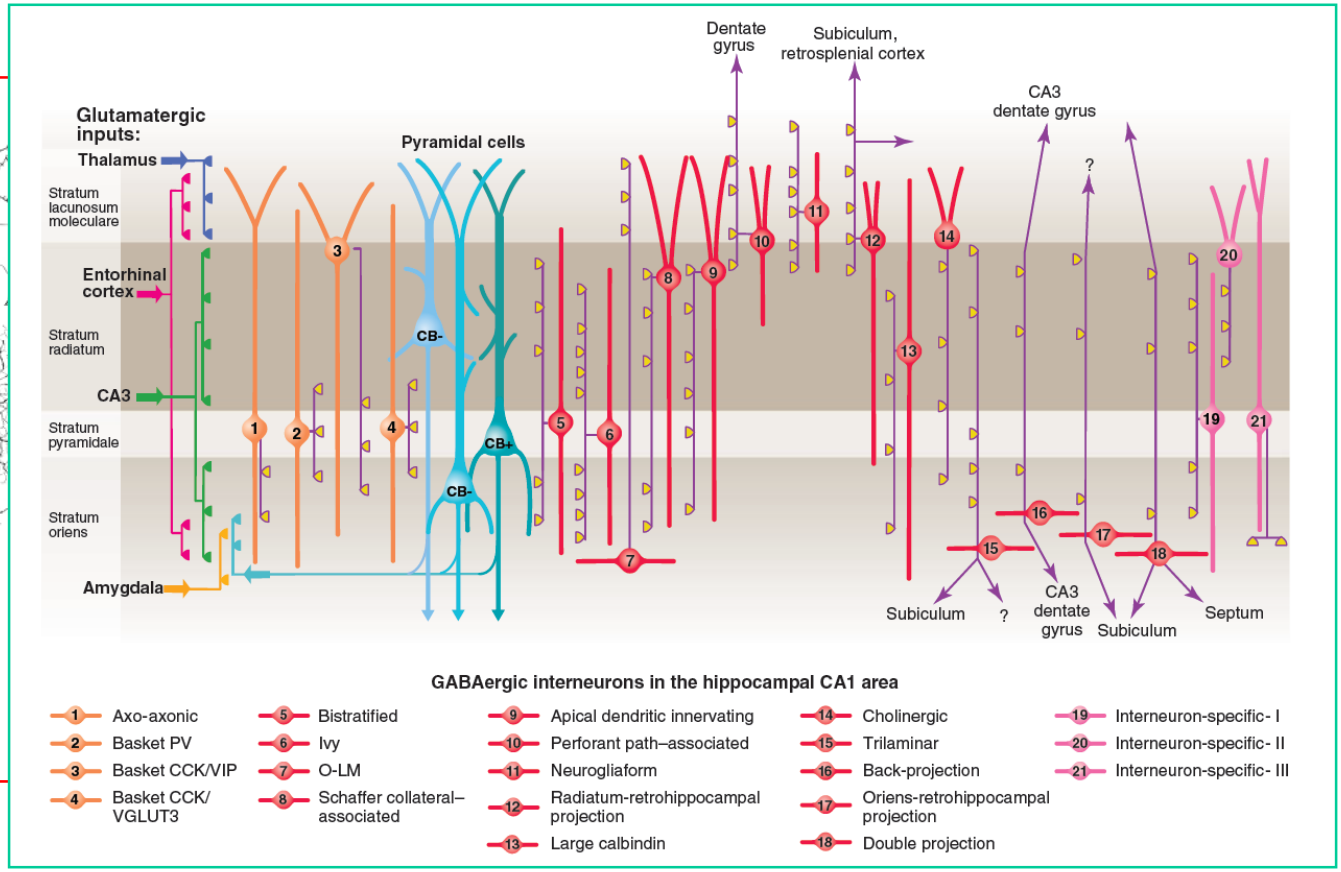
- Epithelial cells of choroid plexus
- Endothelial cells of CNS capillaries

The neuron is the basic functional unit of the nervous system

Neurons come in many different shapes and functions……



(Cajal, 1905)

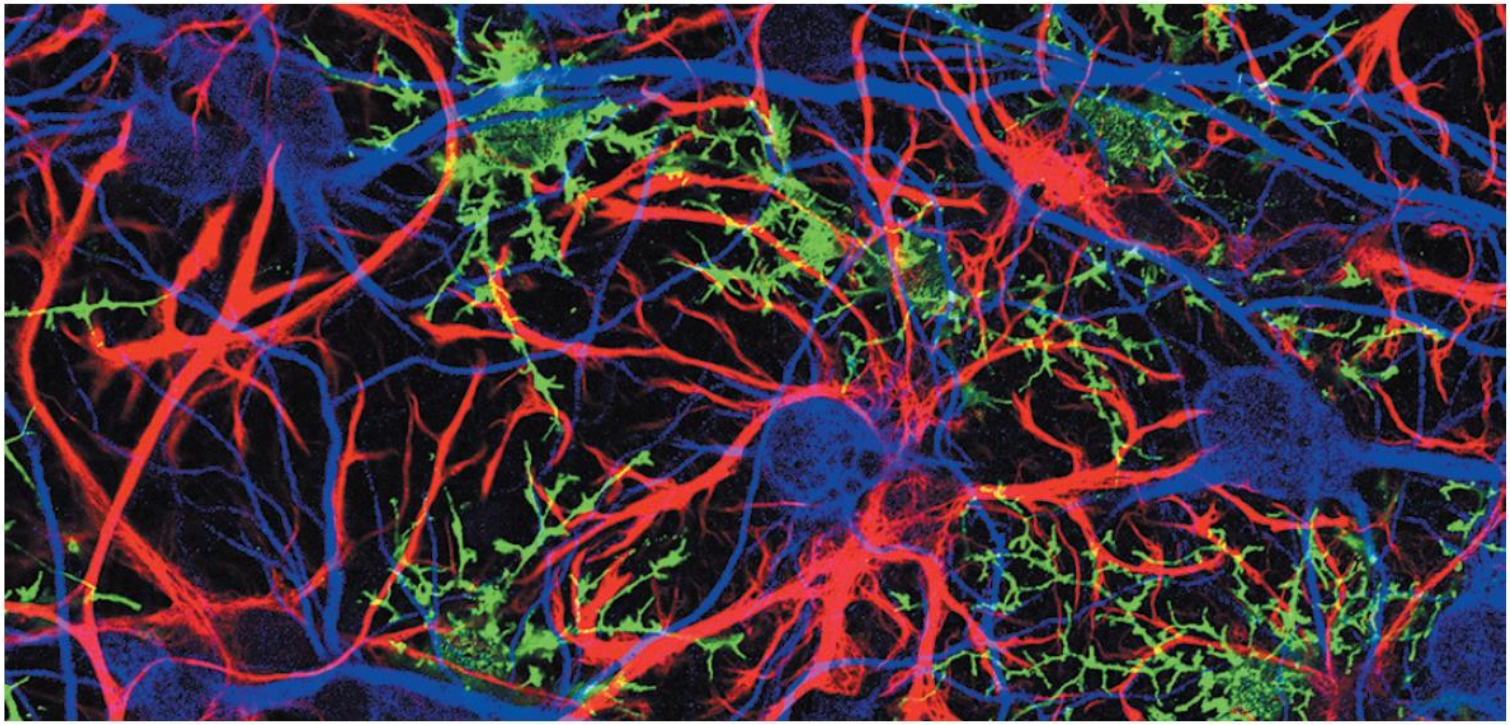


Thomas Klausberger[1,2]* and Peter Somogyi[1]*

SCIENCE VOL 321 4 JULY 2008

…yet, GLIA constitute roughly <u>half</u> of the cells of the central nervous system (CNS)

GLIA



More importantly, our understanding of <u>one half</u> of the brain (the part comprised of **astrocytes, oligodendrocytes and microglia**) lags **<u>a century behind</u>** our knowledge of neurons.

R. Douglas Fields

Neurons vs. glia

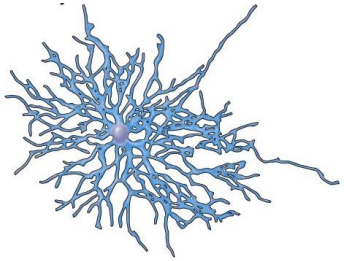
- The defining characteristic of a **neuron** is…
  its ability to transmit rapid electrical signals in the form of action potentials.

- All other neural cells that lack this property are broadly called **glia**.
  - Traditionally, glia have been viewed as passive cells that help to maintain the function of neurons.

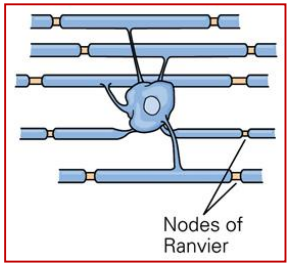
CLASSIFICATION OF GLIAL CELLS

MACROGLIA

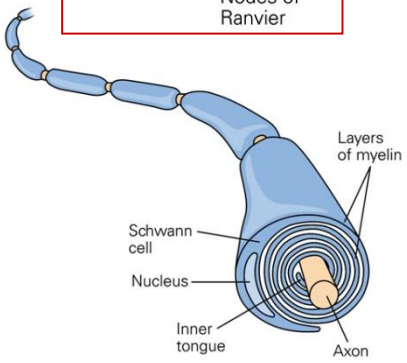
- Astrocytes (SNC)



- Oligodendrocytes (SNC)

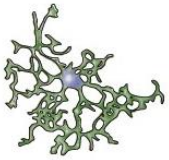


- Schwann cells (SNP)



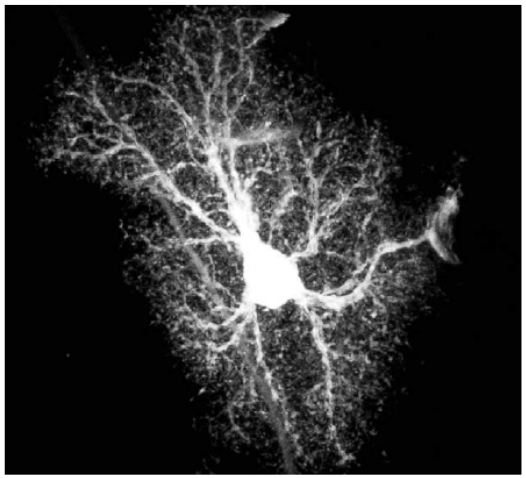
ectodermal origin

MICROGLIA

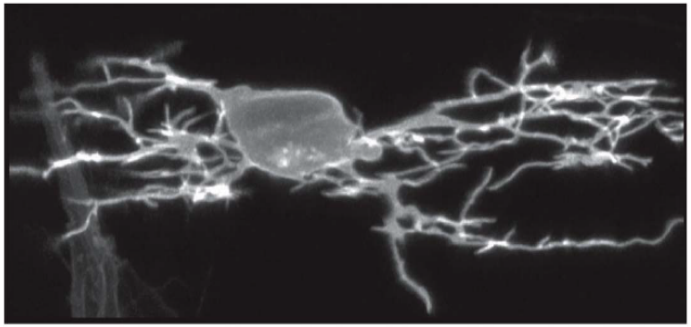


mesodermal origin

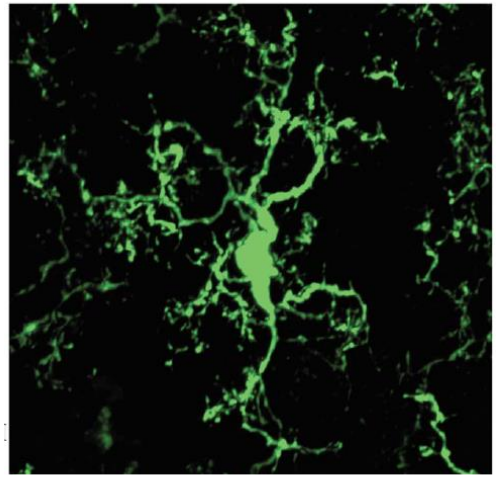
ROLES OF GLIAL CELLS?



Astrocytes



Oligodendrocytes



Microglia

ROLES OF GLIAL CELLS: ASTROCYTES

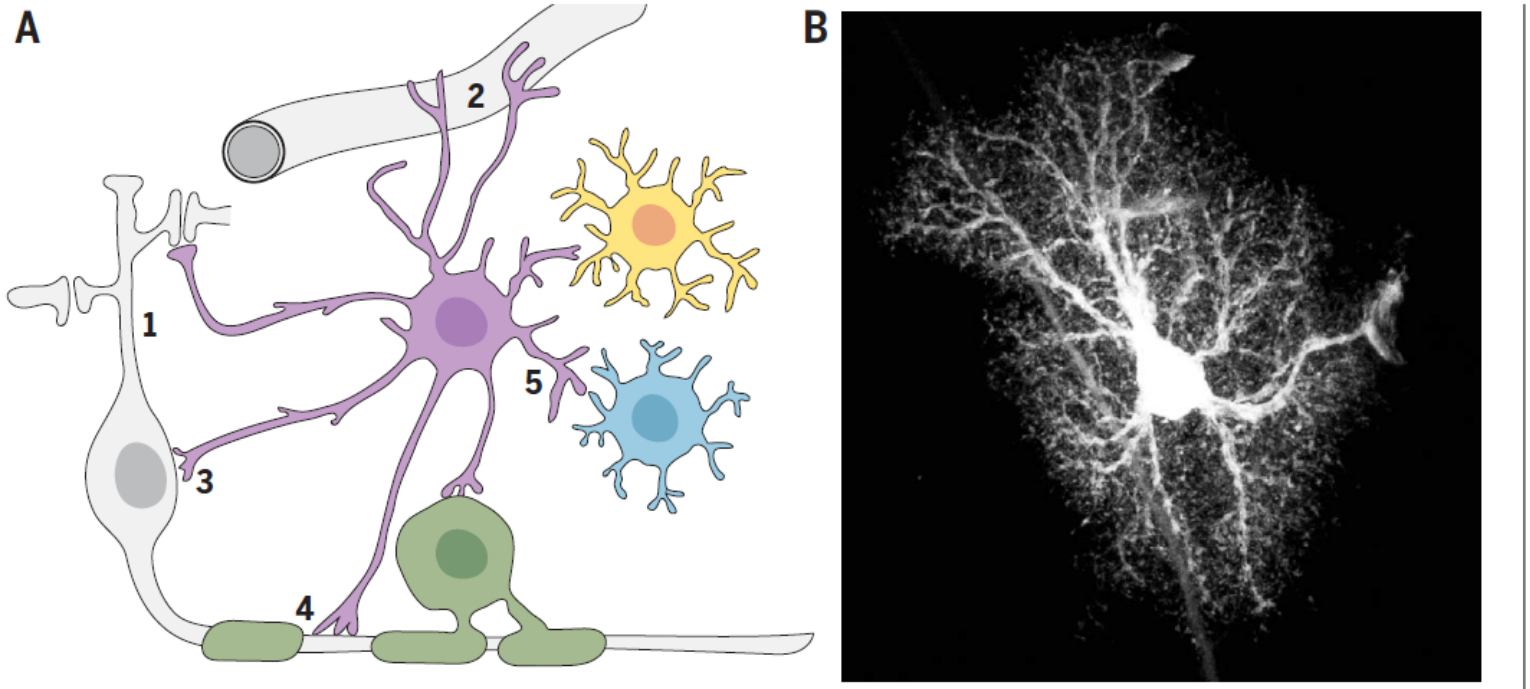
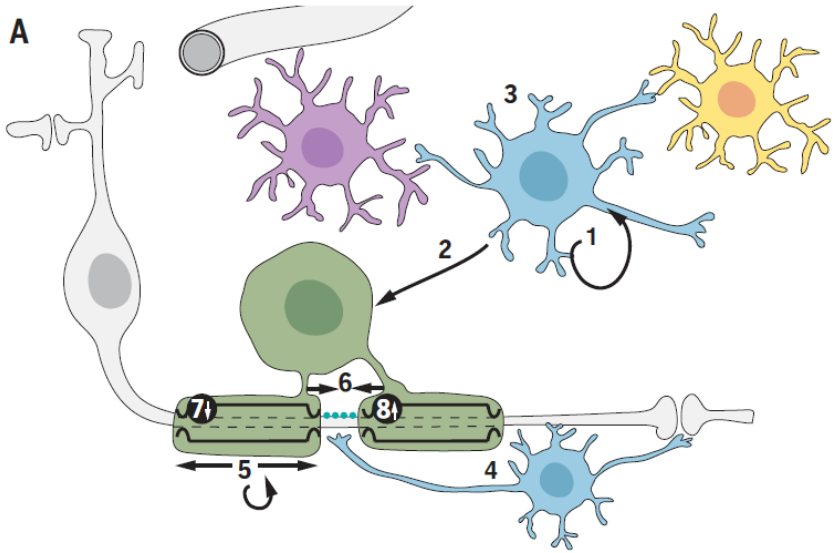


Fig. 2. Astrocytes. (**A**) Astrocytes (purple) have a characteristic star-like morphology and send out multiple branches that terminate in thousands of fine processes that interact with synapses, blood vessels, and other cells. Astrocytes regulate synapse formation, elimination, and function (1); have endfeet that ensheath CNS vasculature (2); contribute to metabolic support and homeostatic function; and have reciprocal interactions with neurons regulating circuit function (3). Astrocytes also make contact with nodes of Ranvier (4), the function of which is unclear, and interact bidirectionally with OPCs, oligodendrocytes, and microglia (5), the relevance of which is emerging. (**B**) Astrocyte confocal image. [Photo credit: The Cell Image Library, image CIL 48001; available at www.cellimagelibrary.org/images/48001]

Allen & Lyons, 2018
Science **362** (6411), 181-185.
DOI: 10.1126/science.aat0473

ROLES OF GLIAL CELLS: OLIGODENDROCYTES



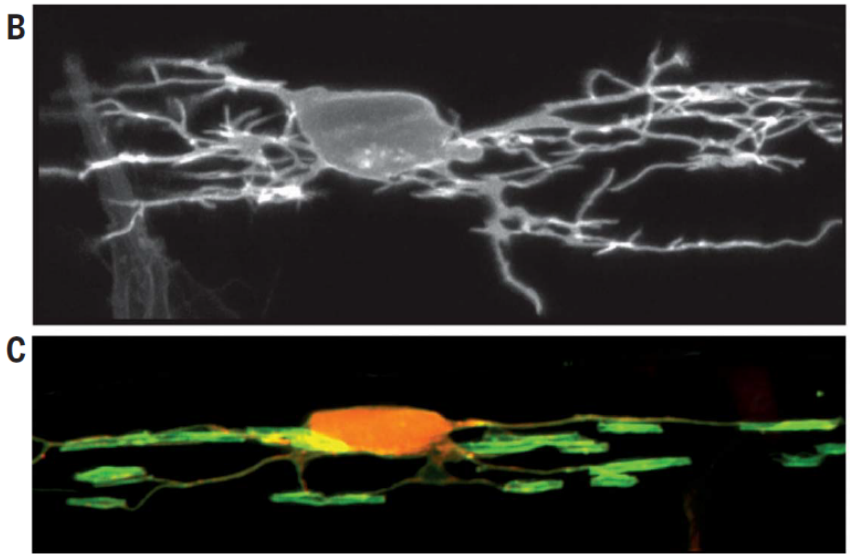


ILLUSTRATION: N. DESAI/*SCIENCE*

Fig. 3. OPCs and oligodendrocytes. (**A**) OPCs (blue) are the most proliferative cells of the CNS (1) and generate mature myelinating oligodendrocytes throughout life (2). OPCs interact with many other cells of the CNS (3), particularly in disease. OPCs extend processes that contact nodes of Ranvier, receive synapses from axons, and regulate synaptic function (4). Whether there are distinct subtypes of OPCs or simply different functional states remains unclear. Oligodendrocytes (dark green) produce lipid rich myelin sheaths that wrap around axons and regulate action potential conduction velocity. Dynamic regulation of myelination in response to neuronal signals (5) may be a fundamental mechanism by which neural circuit function is fine-tuned. Myelinating oligodendrocytes organize axonal domains (6), including nodes of Ranvier, where the voltage-gated Na^{2+} channels that mediate action potential propagation are localized; provide metabolic support to axons (7); and facilitate ion homeostasis that is essential to normal action potential conduction, for example, the uptake of K^{+} ions by myelin (8). (**B**) Confocal image of an OPC expressing membrane-tethered fluorescent protein visualized in a living transgenic zebrafish larvae at 3 days postfertilization. (**C**) Confocal image of an oligodendrocyte expressing membrane-tethered GFP (green) and cytoplasmic red fluorescent protein (orange) visualized in a living transgenic zebrafish larvae at 4 days postfertilization. [Photo credit: Marion Baraban, Lyons lab]

Allen & Lyons, 2018
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ROLES OF GLIAL CELLS: MICROGLIA

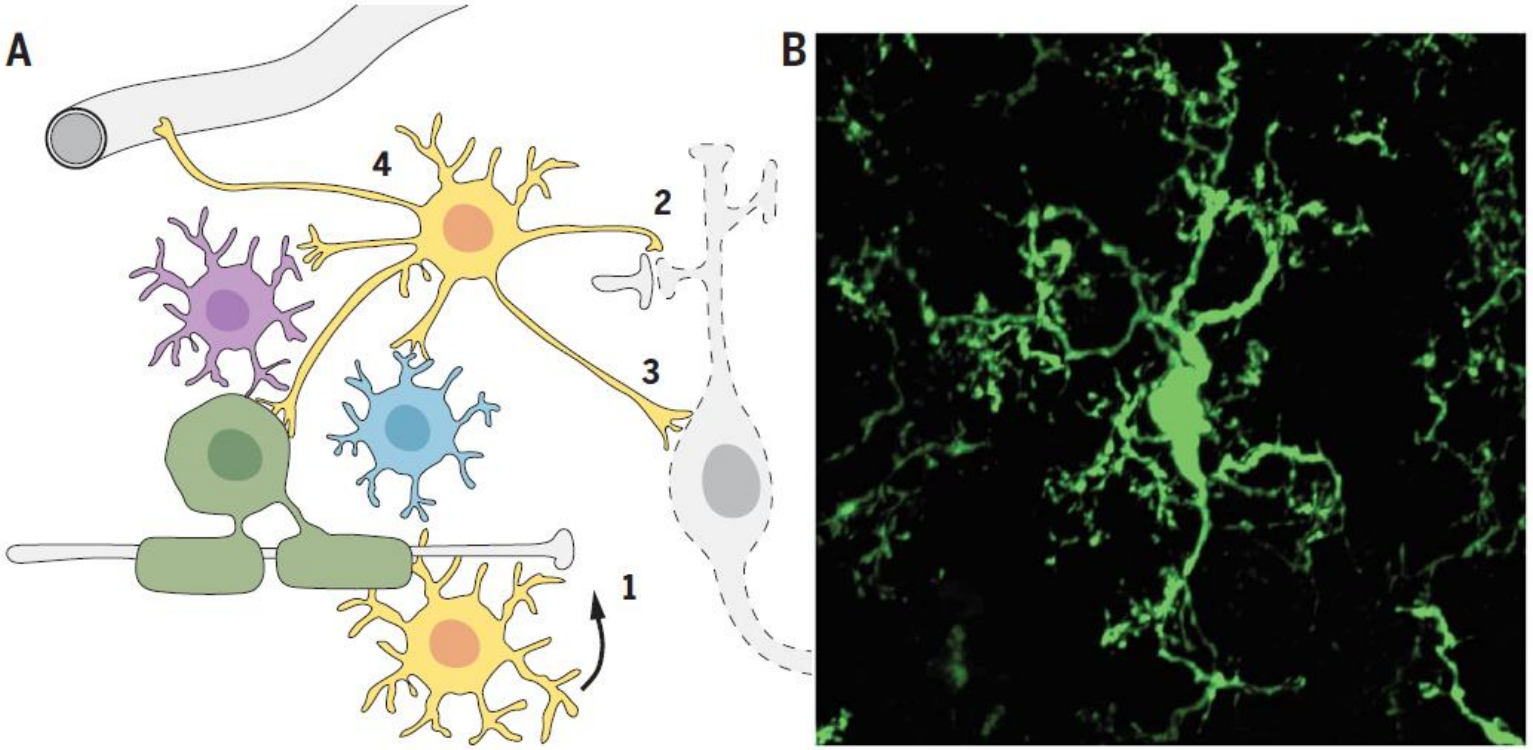

Fig. 4. Microglia. (**A**) Microglia (yellow) are the resident immune cells of the brain, entering during early development from the periphery (1). In addition to immune surveillance roles (not shown), microglia interact with multiple cell types of the CNS and regulate numerous developmental and functional processes, including synaptic pruning (2), clearing apoptotic neurons (3), and interacting with multiple CNS cell types, in health and disease (4). (**B**) Confocal image of microglia expressing GFP in mouse cortex (Cx3cr1-GFP). [Photo credit: Youtong Huang and Greg Lemke, Salk Institute]

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Brief history of glia

Glia have a long history: they were first noted in 1824 and first named in 1856.

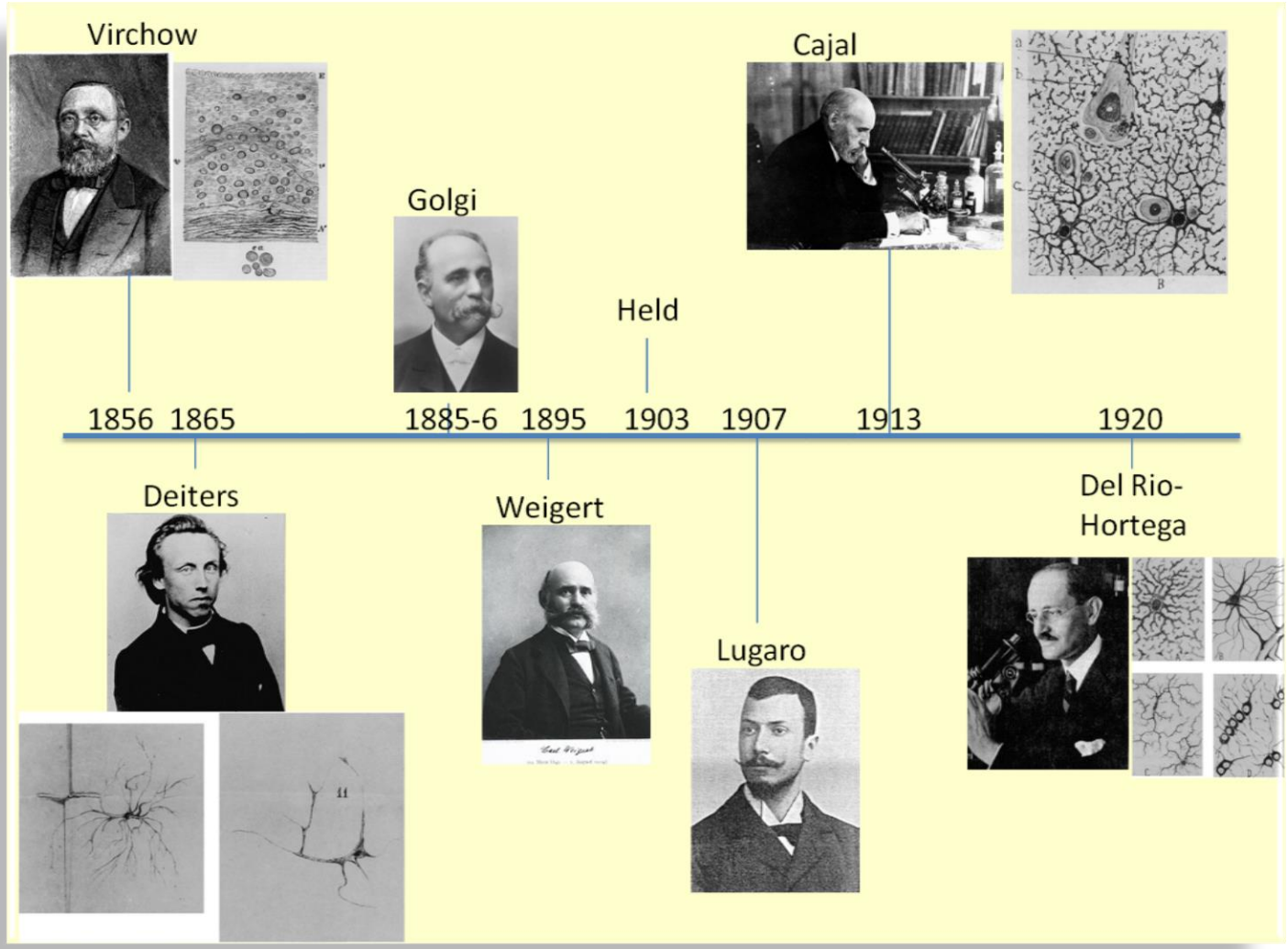
While never as studied as neurons, the early neuroscientists studied and debated glia's classification, morphology, and roles.

Very recently, more and more glial roles have been recognized and glia are being considered more active players in the nervous system than ever before.

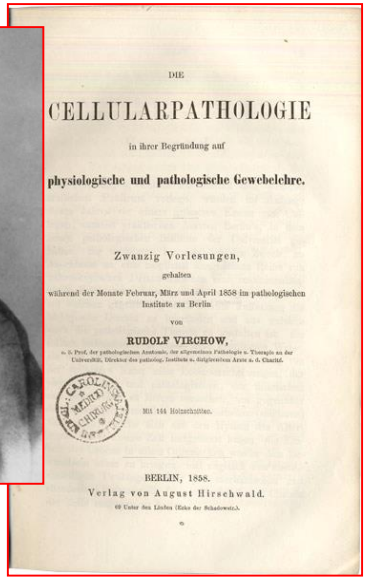
Many of the functions now recognized, however, were proposed by the earliest neuroscientists

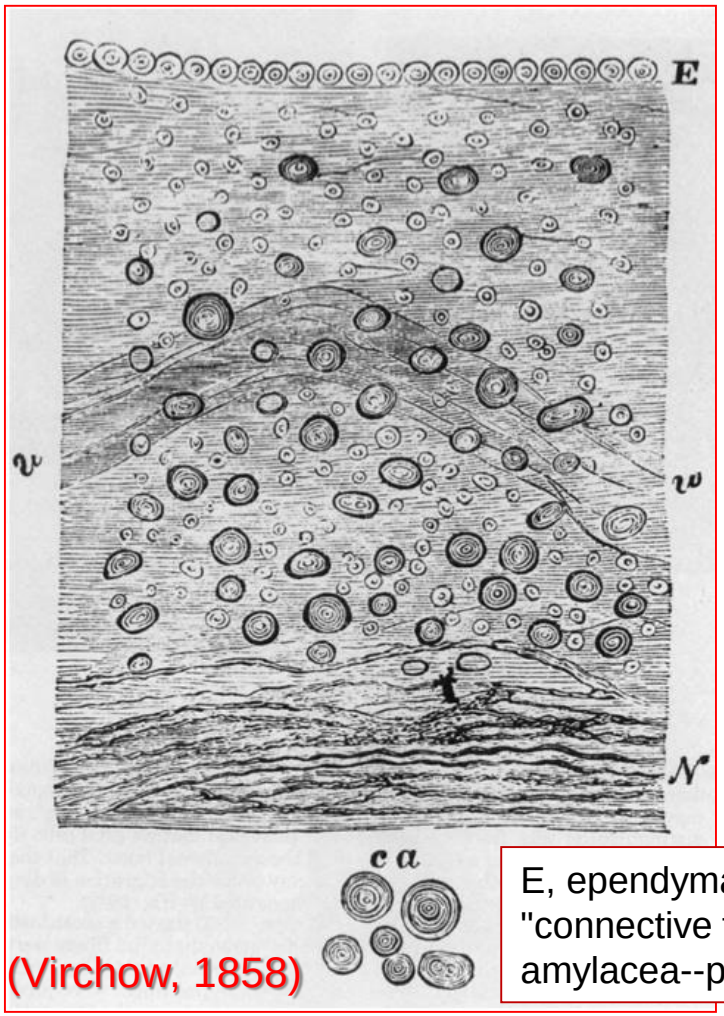
Brief history of glia

https://wiki.brown.edu/confluence/display/BN0193S04/History+of+Glia



Virchow (1821-1902)

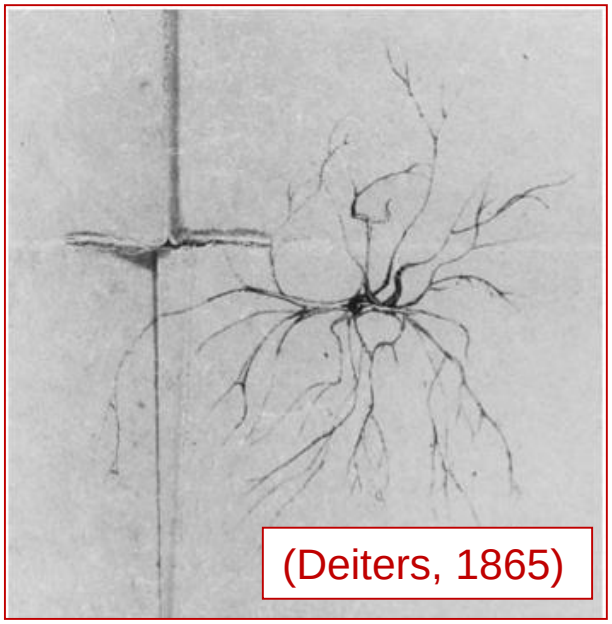




(Virchow, 1858)

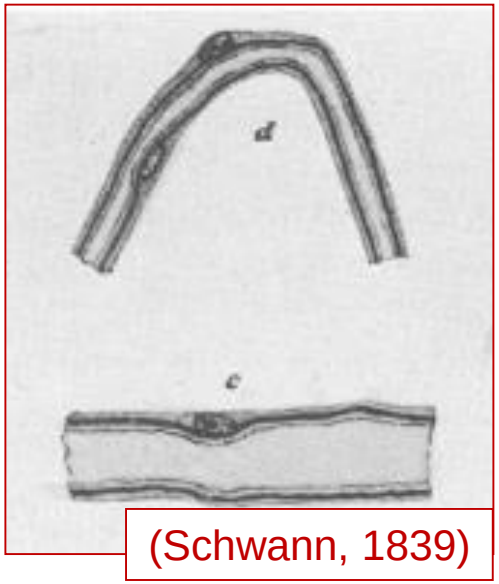
E, ependymal epithelium; v-w, blood vessel in "connective tissue"; N, nerve fibers; ca, copora amylacea--perhaps a staining artifact

- **Virchow** has been generally credited with the discovery of CNS glia (1856, 1858).
- Was actually arguing that there is a connective substance in the brain, *nervenkitt*, or neuroglia.



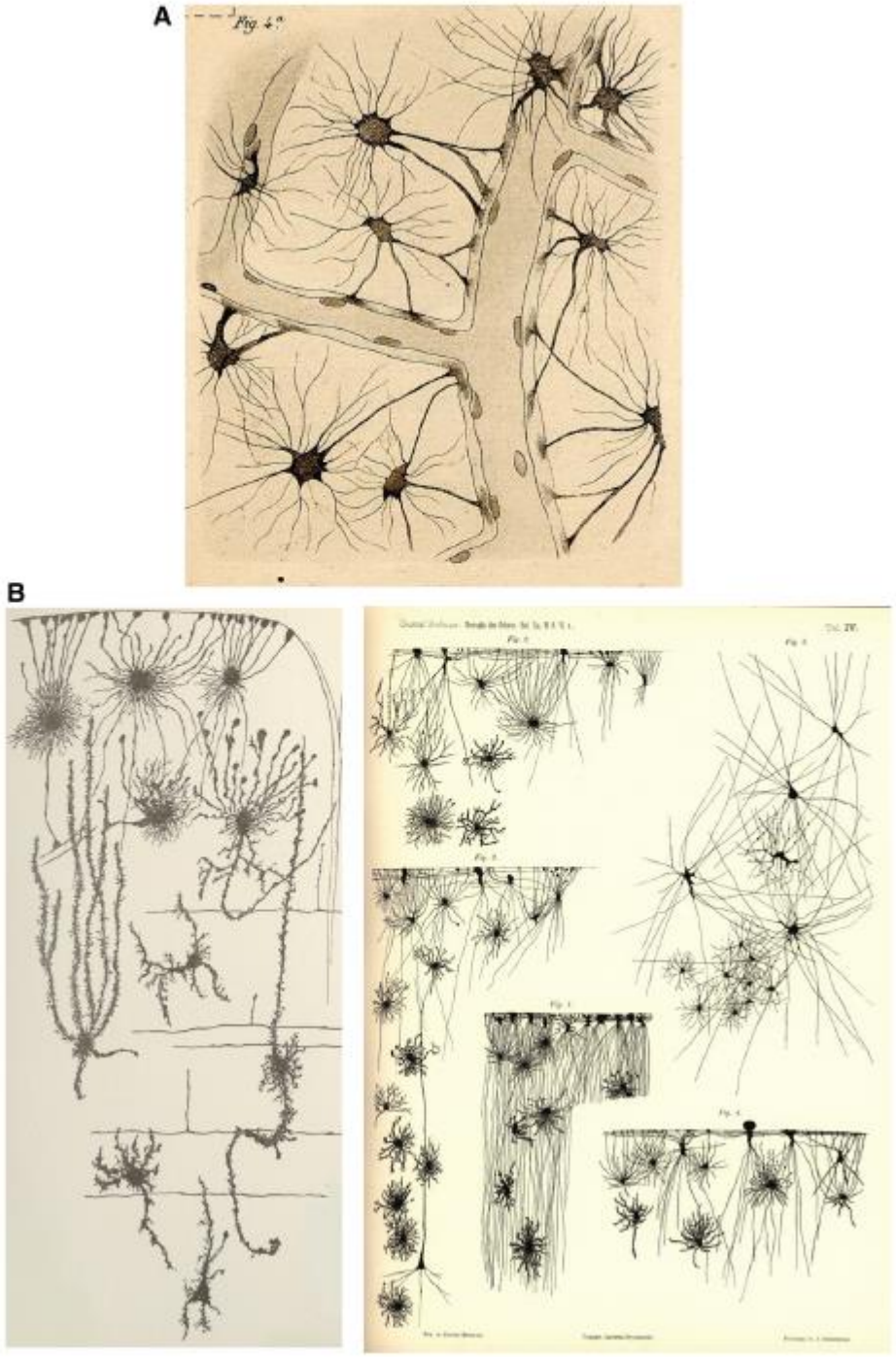
(Deiters, 1865)

Deiters (1865) first identified non-neuronal cells in the CNS as cells that lack axons.



(Schwann, 1839)

Schwann (1839) realized that the “white substance of nervous fibers” was associated with individual cells and identified Schwann cells in the PNS.



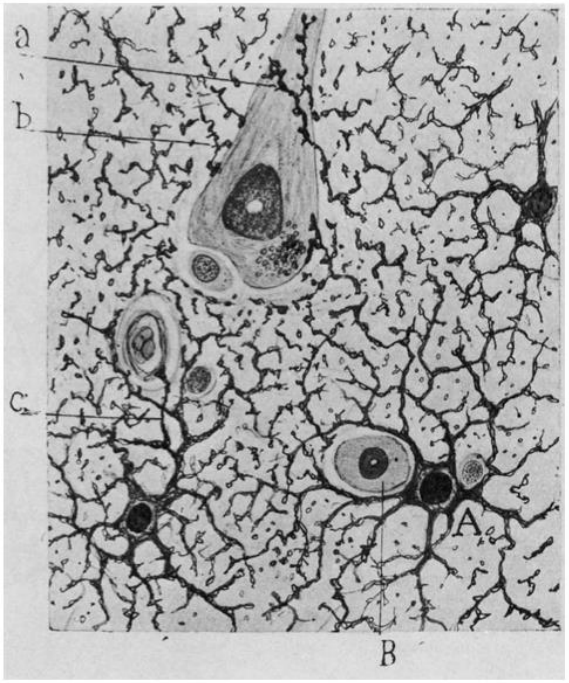
Astroglial cells stained by the silver-chromate technique.

A: **Protoplasmic astroglial cells** in the grey matter stained and drawn by Camillo Golgi; the astrocytes form numerous contacts (the endfeet) with brain capillaries (Golgi, 1883).

B. **Morphological heterogeneity of human astrocytes**. The astrocytes in the brain slices of human foetuses were stained by silver-chromate technique (Retzius, 1894).

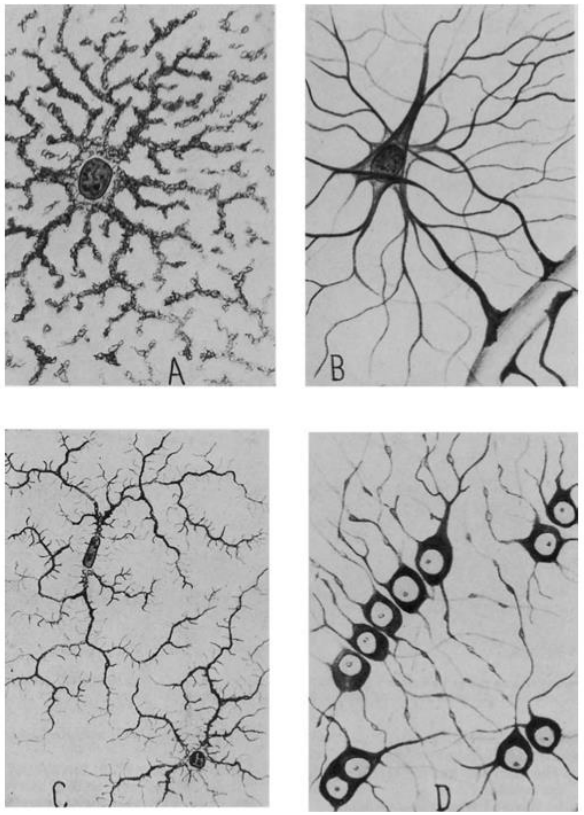
Verkhratsky et al., 2011
Brain Res Reviews
doi:10.1016/j.brainresrev.2010.05.002

By 1920, major classes of CNS glia had been indentified.

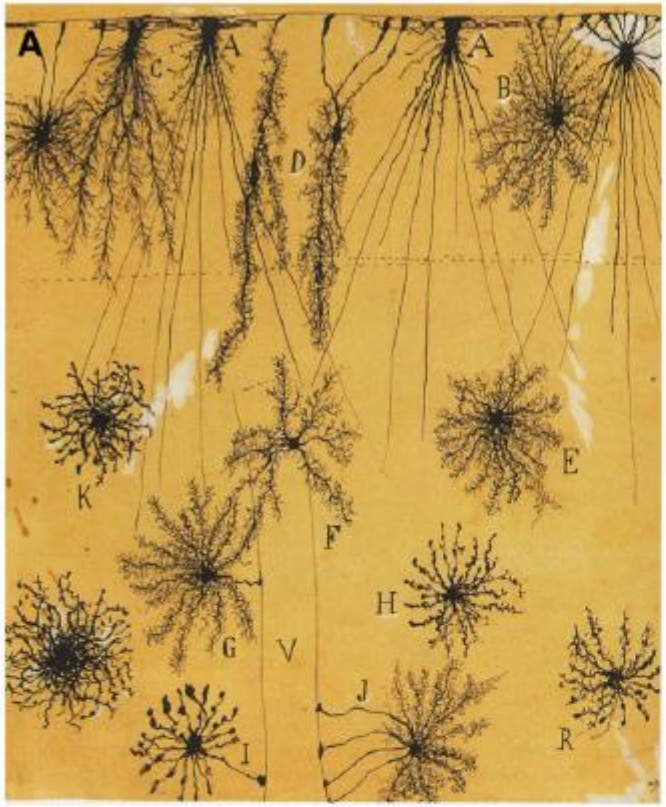


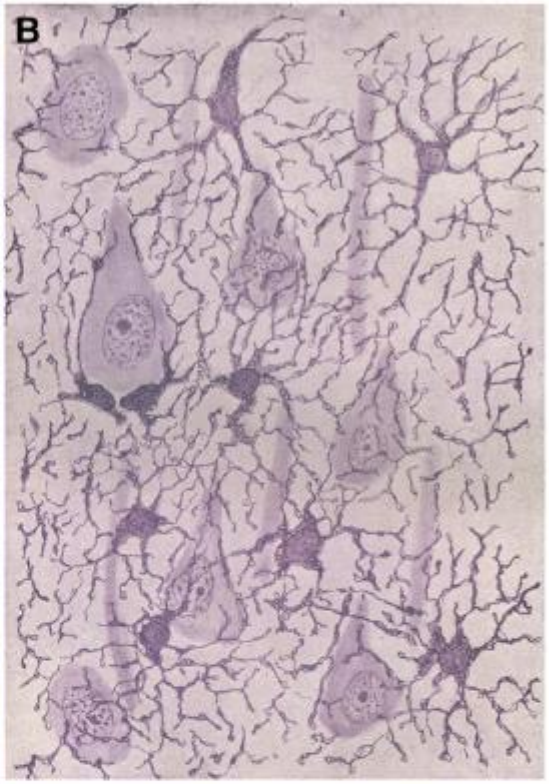
(Cajal, 1913)

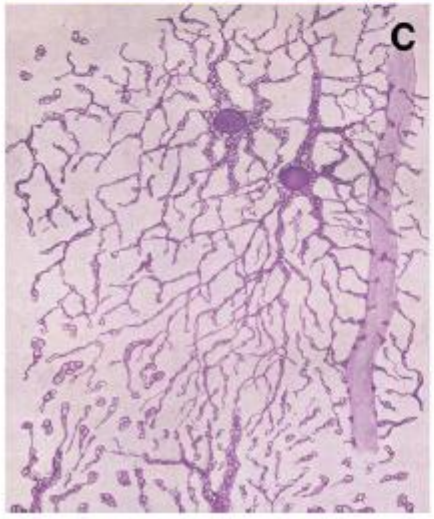
(Del Rio-Hortega, 1920)

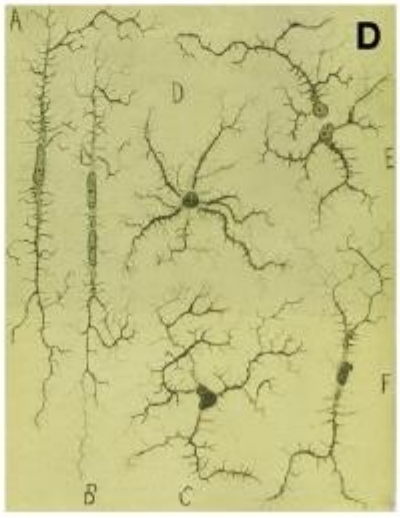


Del Rio-Hortega's four types of glia. A: Gray matter protoplasmic neuroglia. B: White matter fibrous neuroglia. C: Microglia. D: White matter interfascicular glia (oligodendrocytes) (Somjen 1988, Fig. 4)









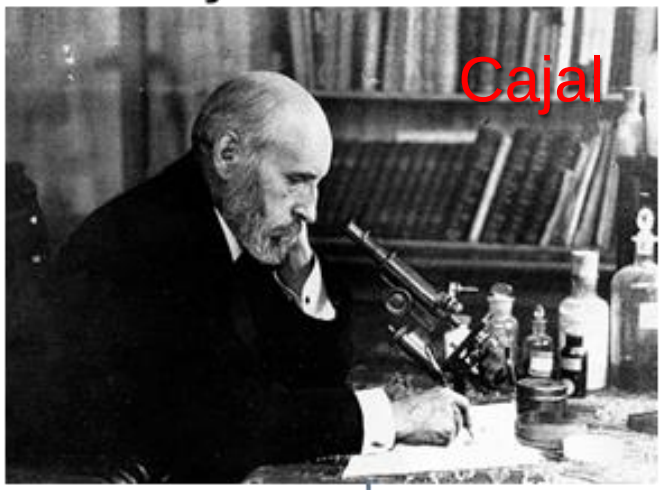
Glial cells by the eyes of Santiago Ramón y Cajal and Pío del Río-Hortega.

A: Cajal's drawing of Golgi impregnated glia showing human cortical neuroglial cells of the plexiform layer (A–D), cells of the second and third layers (E–H and K, R) and perivascular glia (I, J).

B, C: **Astrocytes** in the stratum lucidum of the human **CA1 area of the hippocampus** with particular emphasis on the anatomy of **perivascular astrocytes** in the CA1 stratum radiatum.

D, E: Drawings of **Pío del Río-Hortega** showing the different morphological types of **microglial cells** in the rabbit Ammon's horn and cortical perivascular neuroglia.

Verkhratsky et al., 2011
Brain Res Reviews
doi:10.1016/j.brainresrev.2010.05.002



Early functions of glia: a strong debate

Virchow named glia after what he thought was their main role – structural support –.
Golgi argued that glia served a nutritive role for neurons.
Santiago Ramon y Cajal, because he believed dendrites were involved in signaling and not just nutrients in neurons, disagreed with Golgi's hypothesis. Cajal also disagreed with Virchow's and Weigert's theory that glia simply filled the spaces in between neurons or left by dead neurons. Cajal believed instead that glia's main role was to provide insulation to protect neurons from incorrect electrical signaling. Cajal also proposed that glia could have a role in sleep by extending *"their processes into synapses, reducing their activity...when astrocytic processes retract, neurons would contact one another and thus become active again"*
Marinesco recognized in 1896 glia's role in the phagocytosis of neurons. **Nageotte** suggested in 1910 that glia were part of the endocrine system and could secrete substances into the blood stream. **Lugaro**, in 1907, suggested many roles glial cells, including guiding neuronal migration in development and maintaining and detoxifying the interstitial fluid. He even predicted a glial role in the synapse, suggesting that glia could terminate synaptic action by chemically altering or taking up neurotransmitters

The recent past…..

With the invention of the **electron microscopy**, investigations into the ultrastructure of astrocytes were undertaken by several scientists.

In terms of **chemical markers**, Eng et al. and Bignami et al. identified the glial fibrillary acidic protein, GFAP (1971 and 1972, respectively). This protein was found to be associated with astrocyte intermediate filaments, and though it is found not in all astrocytes, it has been particularly important in identifying astrocytes.

Additionally, Moore identified the S-100 protein, Sommer et al. identified the C1 antigen in Bergmann glia and retinal Muller cells, and Lagenaur et al. found the M1 antigen in protoplasmic and fibrous astrocytes, all of which help identify glia in immunocytochemistry today

(Macro)gliogenesis in Vertebrates

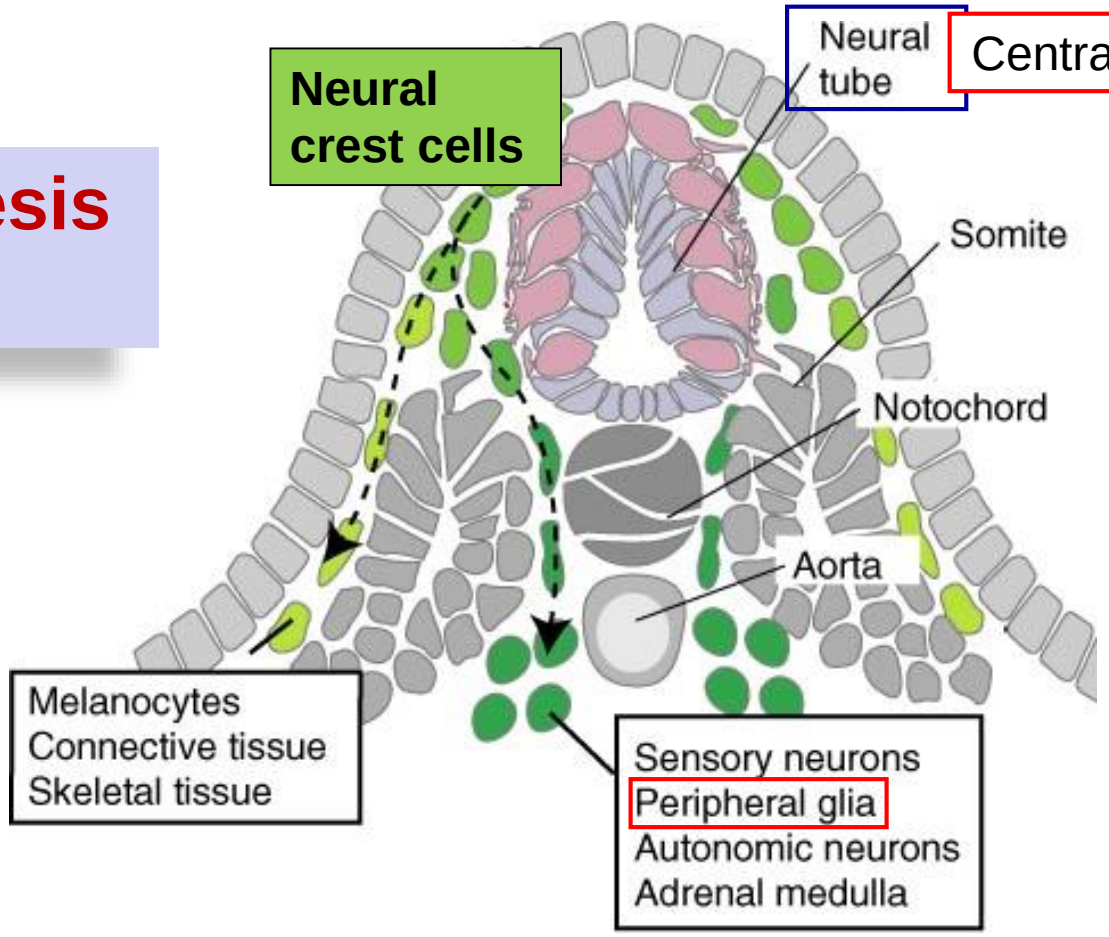
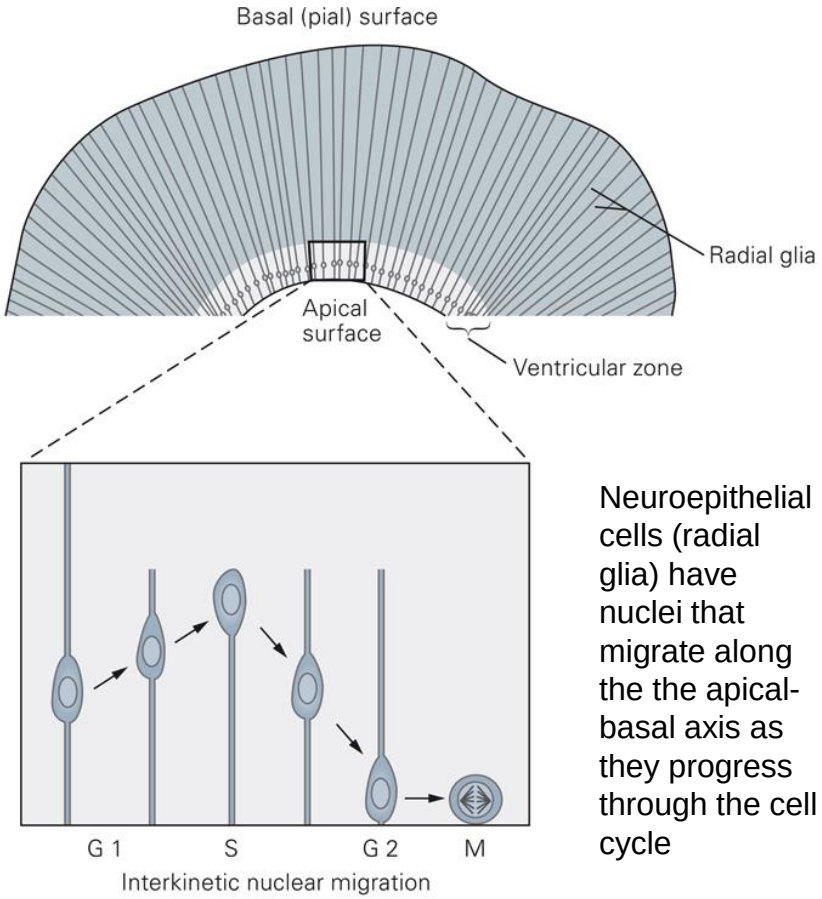


FIGURE 11 Neural crest lineages. Schematic cross section of vertebrate embryo in which migrating neural crest cells (green) are indicated. These cells follow two different pathways: a dorsal one (light green), giving rise to melanocytes, connective tissue, and skeletal tissue, and a ventral one, giving rise to sensory and autonomic ganglia, as well as adrenal medulla.

Development of macroglia in the CNS

All neurons and glia (except microglia) in the developing CNS develop from precursor cells derived from the neuroectoderm.

- **neuroepithelial cells** line ventricles and spinal canal
- the earliest morphologically distinguishable cell type to appear within the neuroepithelium are **radial glial cells**



Neuroepithelial cells (radial glia) have nuclei that migrate along the the apical-basal axis as they progress through the cell cycle

Developmental origin

During development of the cerebral cortex, radial glia generates neuronal and glial progenitors and guides their migration to the appropriate position

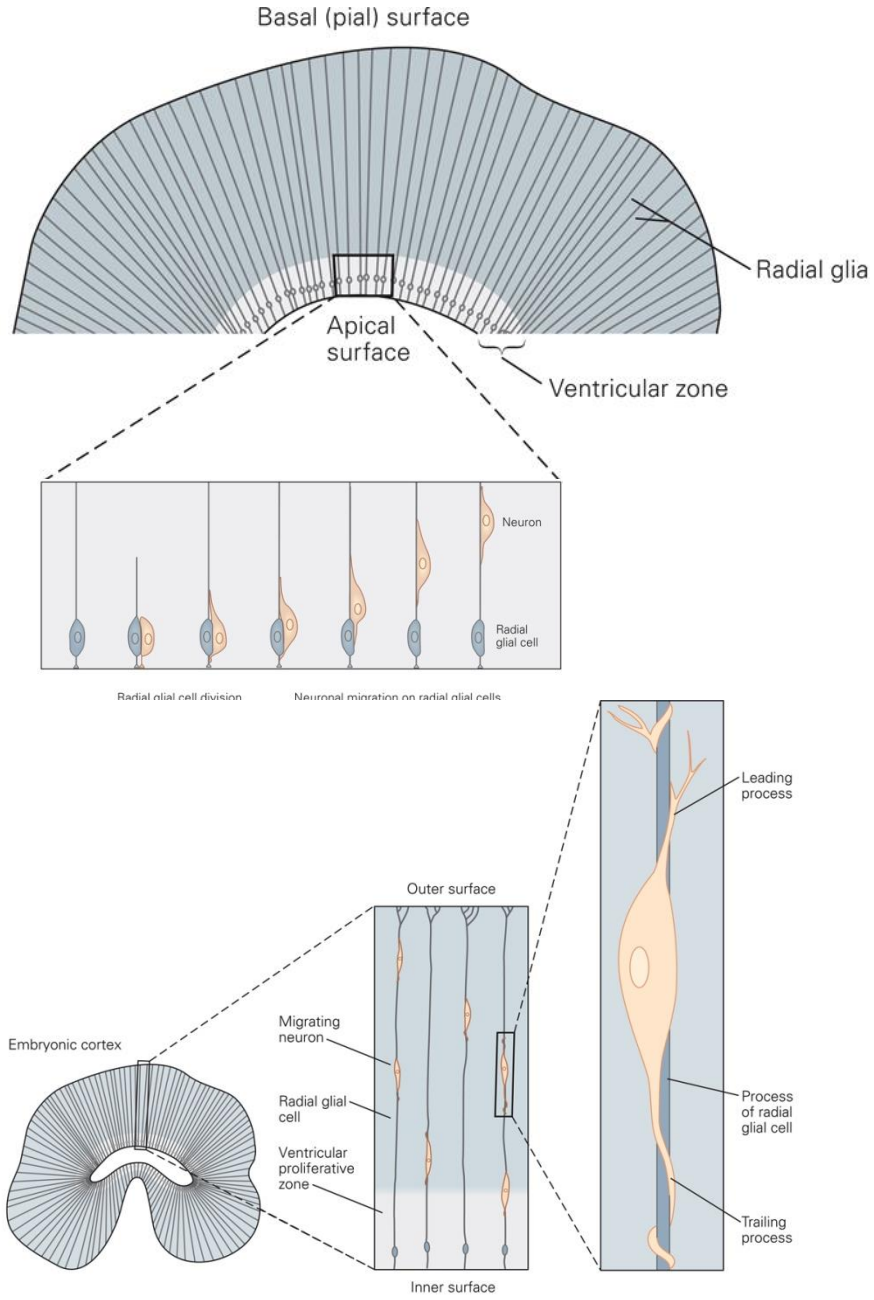


Figure 53–5 Neurons migrate along radial glial cells. After their generation from radial glial cells, newly generated neurons in the embryonic cerebral cortex extend a leading process that wraps around the shaft of the radial glial cell, thus using the radial glial cells as scaffolds during their migration from the ventricular zone to the pial surface of cortex.

Development of astrocytes, oligodendrocytes, (and neurons) from radial glia

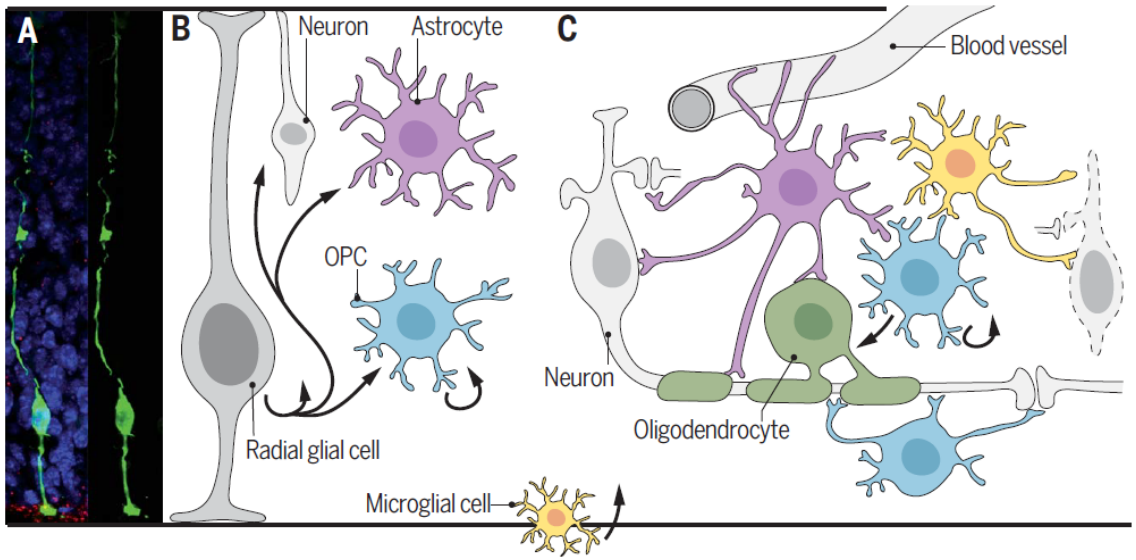


Fig. 1. Origin and overview of CNS glial cells. (**A**) Confocal image of a radial glial cell in an E14 mouse cortex, visualized after in utero electroporation of green fluorescent protein (GFP, green) (right) and costaining for apical centrosomes (pericentrin, red) and cell nuclei [4′,6-diamidino-2-phenylindole (DAPI), blue] (left). [Photo credits: Sven Falk and Magdalena Goetz, Helmholtz Centre, Munich] (**B**) Radial glial cells are the principal neuroepithelial progenitor cells of the central nervous system and generate the majority of CNS neurons and glia, either directly (e.g., neurons) or indirectly through intermediate progenitors (e.g., OPCs). Microglia (yellow) enter the CNS during embryonic development. (**C**) Neurons and glia interact in a myriad of ways (explained in text and subsequent figures). Dashed line indicates dying neuron.

Allen & Lyons, 2018
Science **362** (6411), 181-185.
DOI: 10.1126/science.aat0473

In the adult mammalian brain most radial glia disappears and neurogenesis persists only in few niches, those where radial glia-like cells (= neural stem cells) are still present

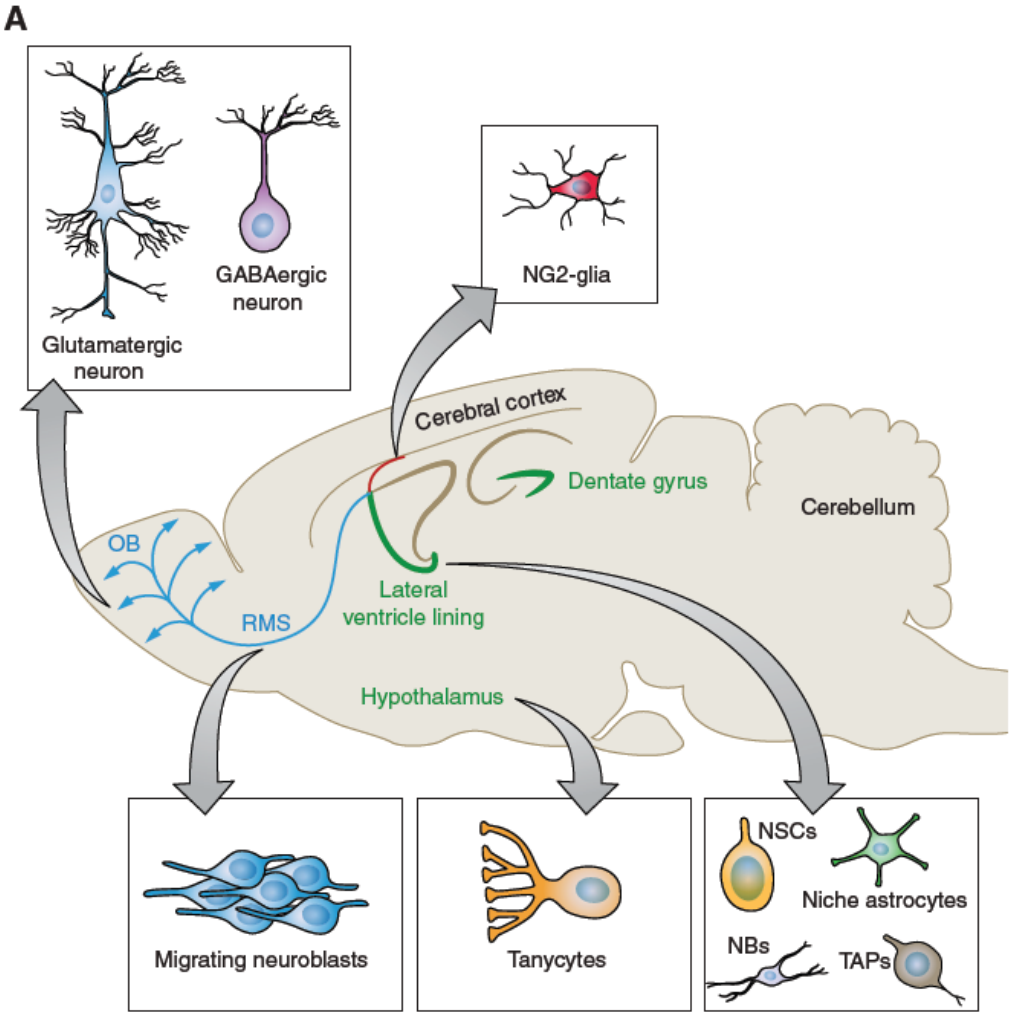
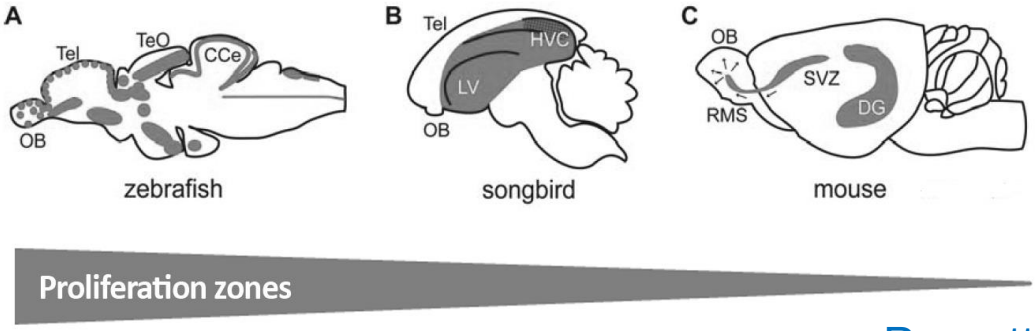


FIGURE 3. Glial cells as stem and progenitor cells in the healthy adult brain. *A*: endogenous neurogenesis still persists in the adult mammalian brain in few niches like the subependymal zone in the lateral wall of the lateral ventricle, the subgranular zone in the dentate gyrus, and the hypothalamus. Radial glial cells at the subependymal zone of the lateral ventricle divide and generate fast proliferating transit-amplifying progenitors (TAPs) and neuroblasts (NBs) that proliferate while they migrate through the rostral migratory stream (RMS) to their final destination, the olfactory bulb (OB), where they can differentiate to different neuronal types.

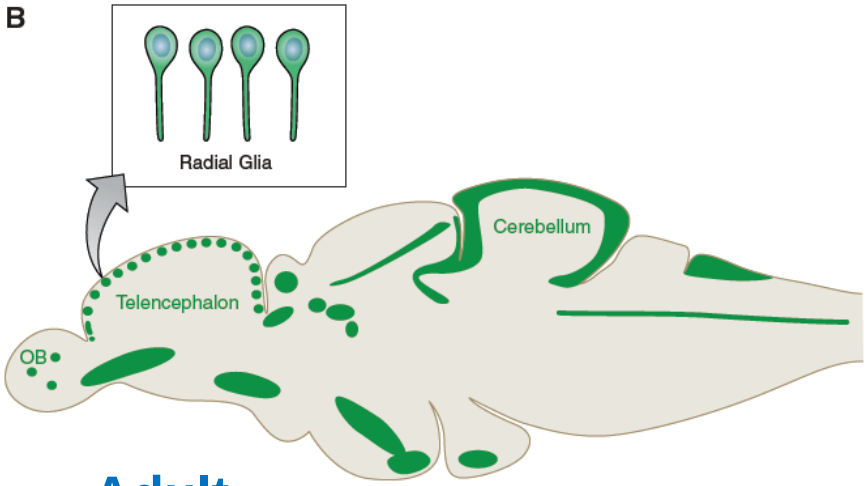
Leda Dimou and Magdalena Götz

Physiol Rev 94: 709–737, 2014
doi:10.1152/physrev.00036.2013

In many non-mammalian vertebrates (fish, amphibians and reptiles) radial glial cells remain abundantly present in a widespread manner in the adult CNS



Pomatto et al., 2013



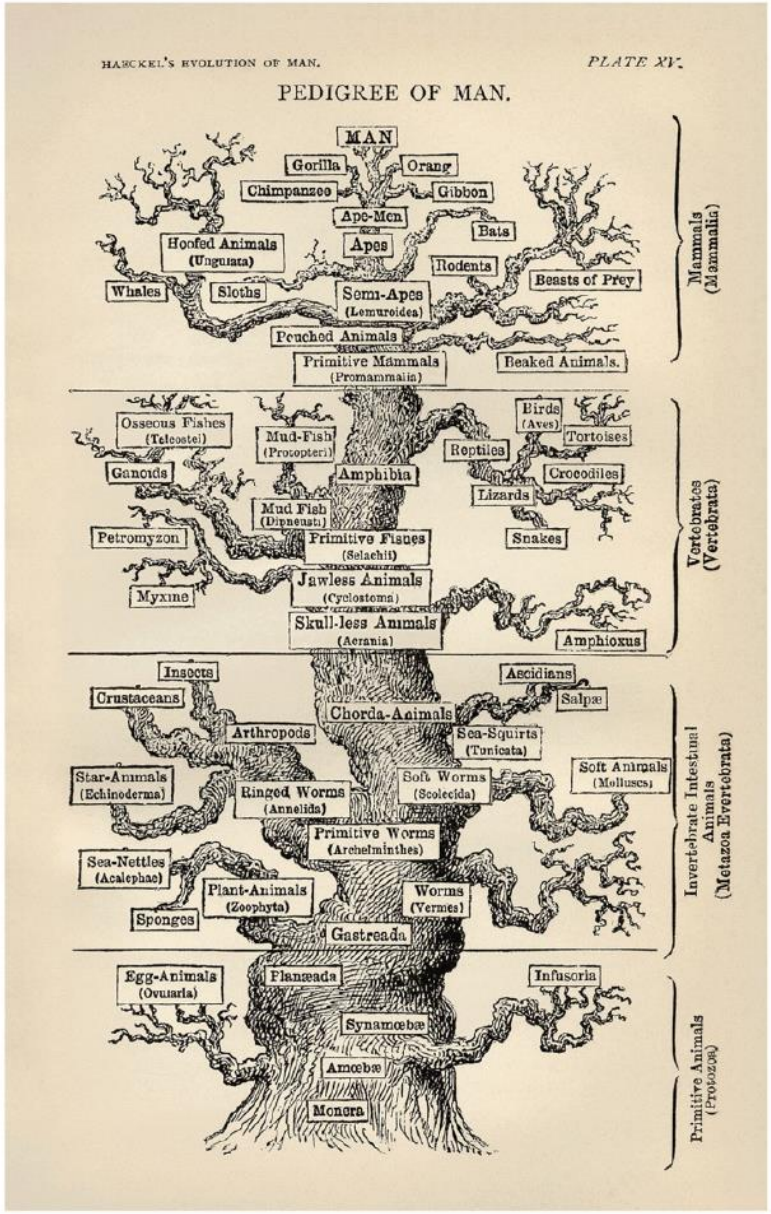
Adult zebrafish

B: radial glia cells in the adult zebrafish are more widespread than in mammals and are located along the ventricle. The zebrafish telencephalon is everted, with the ventricle lying between and above the two telencephalic hemispheres. Proliferating cells (green, based on data summary in Ref. 89) are located in distinct regions along the entire anterior-posterior axis.

Leda Dimou and Magdalena Götz

Physiol Rev 94: 709–737, 2014
doi:10.1152/physrev.00036.2013

Evolutionary aspects of glia



"Glial explosion" in the brains of hominides

Proto-myelinating cells appear and myelin sheath is formed around axons

Astrocytes make the primordial blood-brain barrier

Inmmune cells enter the neural ganglia and form the ancestral microglia

Appearance of glia

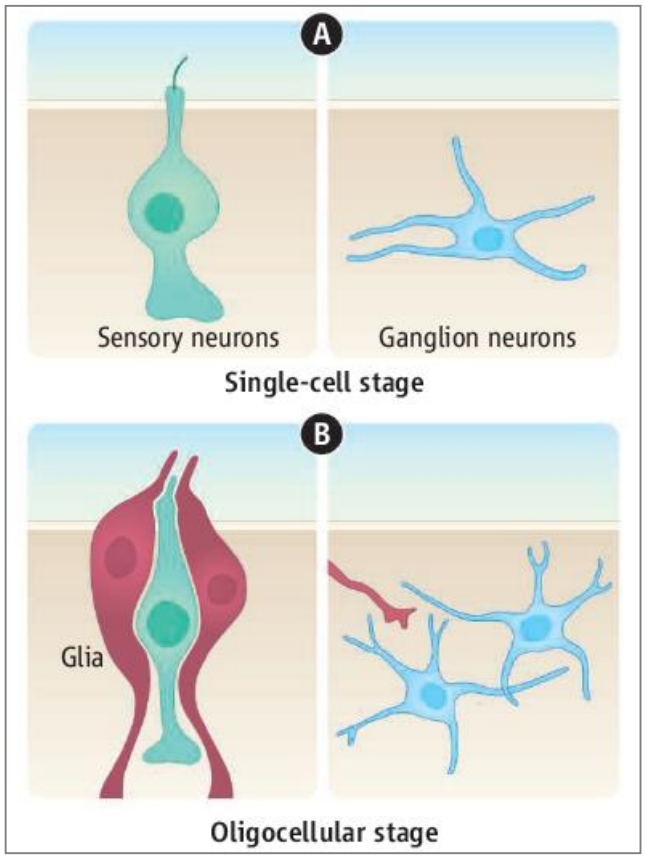
Verkhratsky et al., 2011
Brain Res Reviews
doi:10.1016/j.brainresrev.2010.05.002

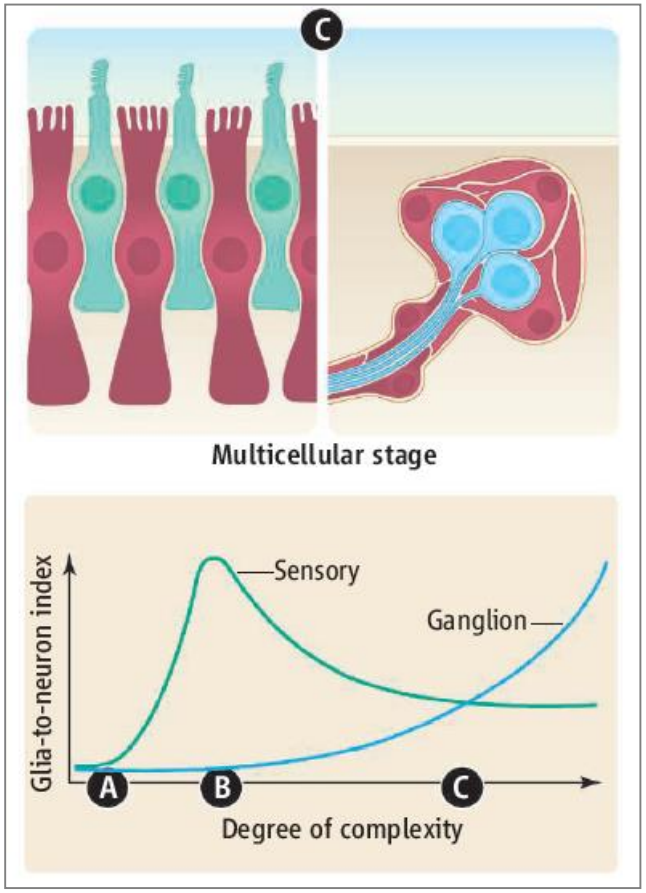
Fig. 4 – Evolution of the neuroglia; the tree of life is taken from Haeckel (1879).

Evolution of the glia-to-neuron index

Nerve net (most Cnidarians)

Primitive sensory organs & ganglions (C. elegans)





Sophisticated sensory organs & nervous centers (brains)

Glia, by complexity. A schematic survey of the differentiation stages of sensory (green) and ganglion (blue) neurons and glial cells (red). The numerical relation between glial and neuronal cells (glia-to-neuron index) is shown over the three stages of increasing nervous system complexity.

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SCIENCE VOL 322 31 OCTOBER 2008