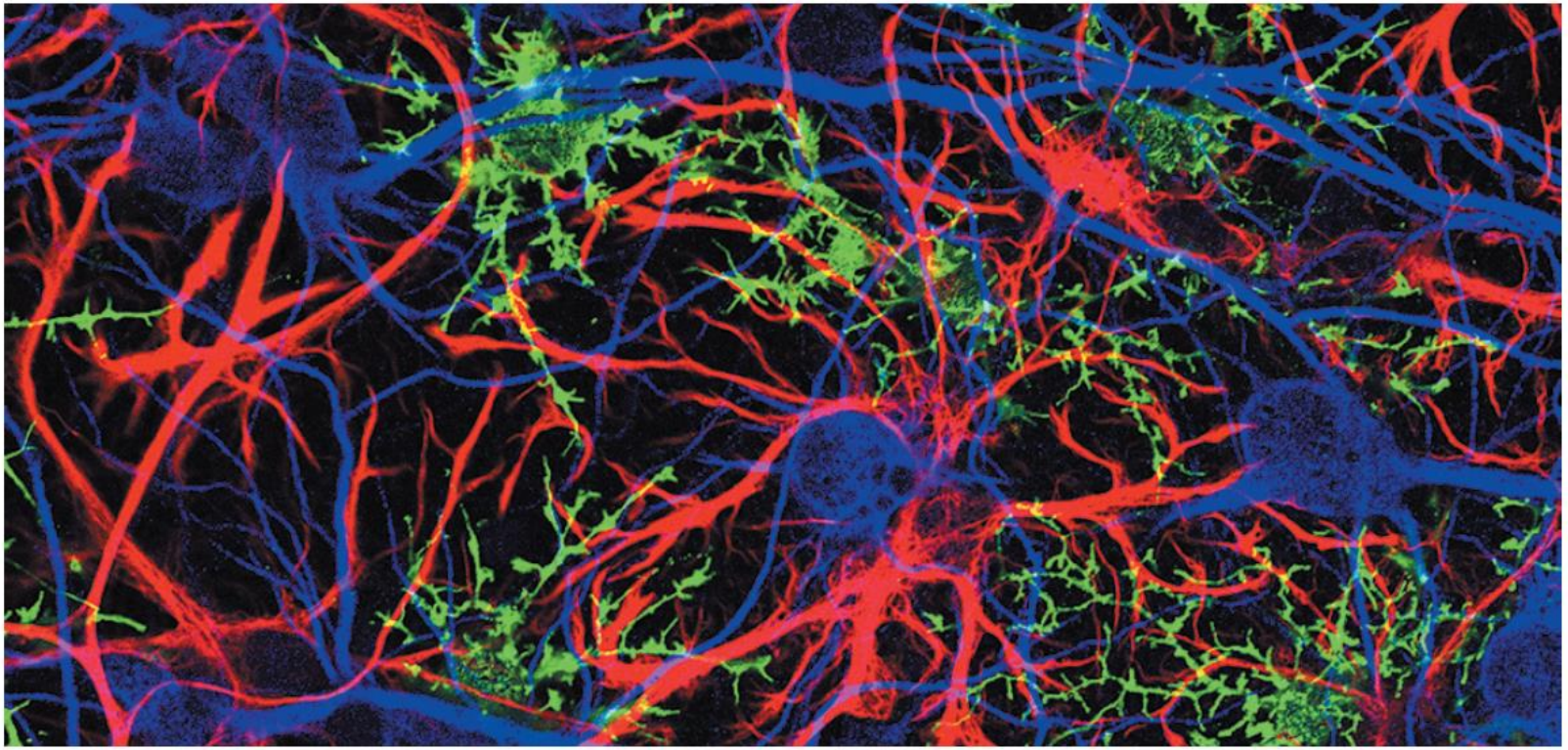
GLIA



Astrocytes (red) and immature oligodendrocytes (green), types of glial cell, intertwine with neurons (blue) from the brain's hippocampus.

R. Douglas Fields 5 SEPTEMBER 2013 | VOL 501 | NATURE | 25

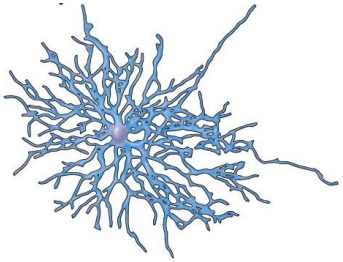
Neurons vs. glia

- 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.

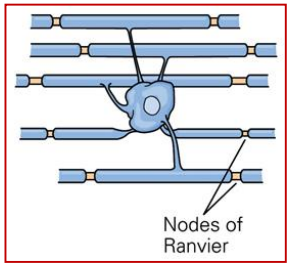
CLASSIFICATION OF GLIAL CELLS

MACROGLIA

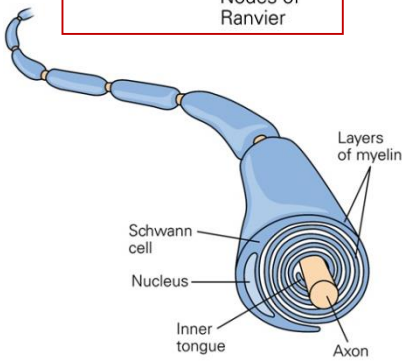
- Astrocytes (SNC)



- Oligodendrocytes (SNC)

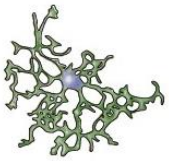


- Schwann cells (SNP)



ectodermal origin

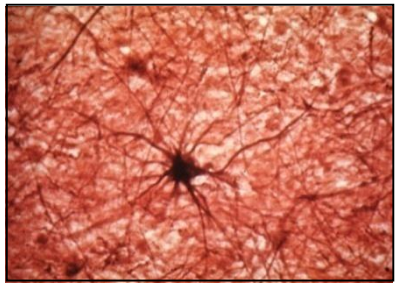
MICROGLIA



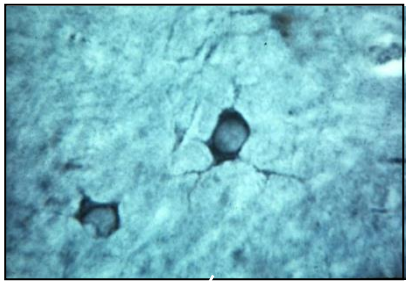
mesodermal origin

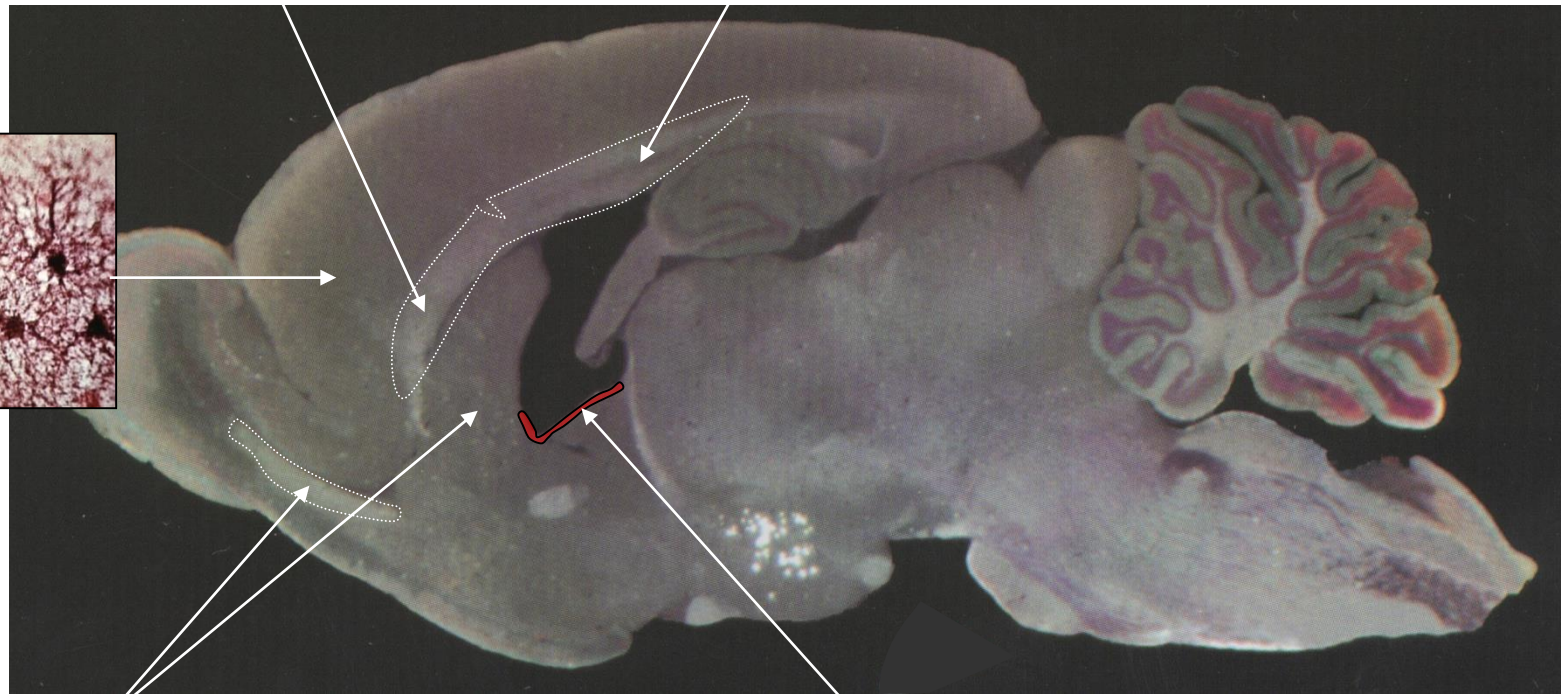
Glial cell distribution *in vivo* in the CNS

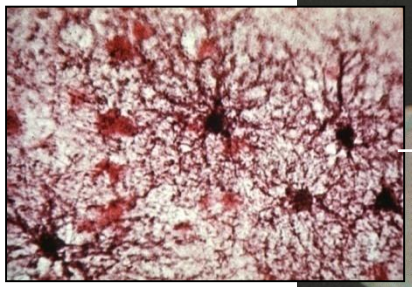
Fibrous astrocytes



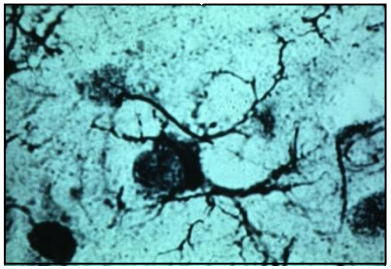
Oligodendrocytes



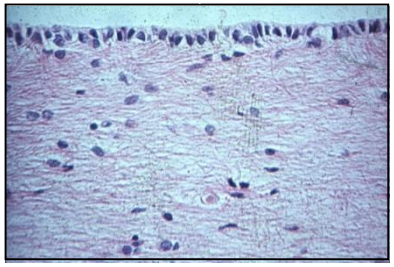




Protoplasmic astrocytes



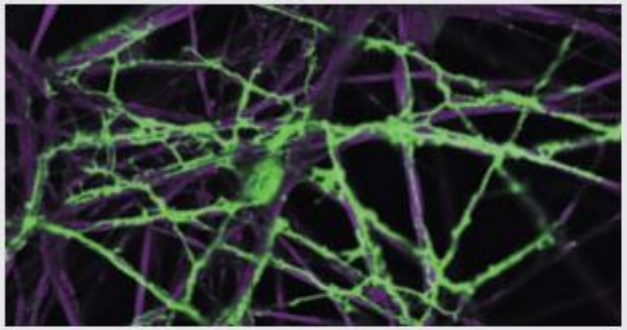
Microglial cells



Ependimal cells

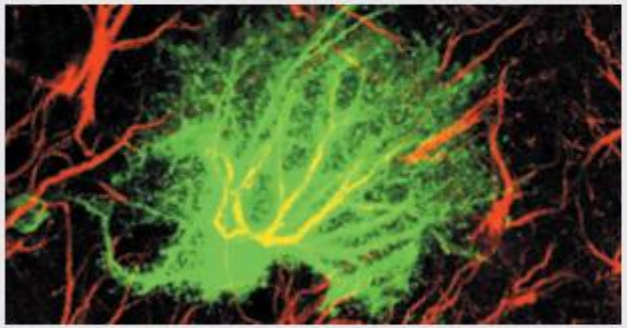
THE OTHER HALF OF THE BRAIN

Roles of glial cells



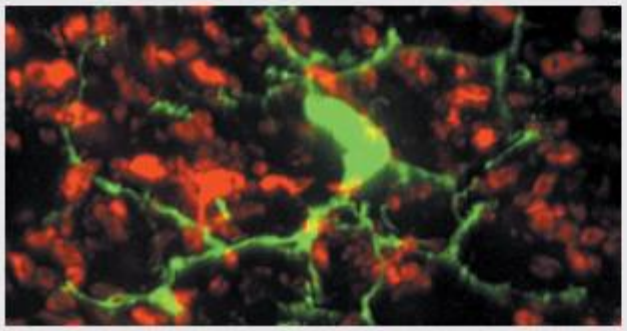
Oligodendrocytes (green)

- Form myelin electrical insulation, increasing conduction velocity by at least 50 times.
- Provide vital metabolic support for axons (purple).
- Involved in multiple sclerosis, amyotrophic lateral sclerosis and the inhibition of repair after spinal-cord injury.



Astrocytes (red and green)

- Ensheath synapses, regulate neuronal excitability and synaptic transmission.
- Respond to injury by secreting extracellular matrix proteins.
- Implicated in neurogenesis, cell migration, and many neurological and psychiatric disorders.



Microglia (green)

- Highly motile and responsive to nervous-system injury and infection.
- Monitor electrical activity in neurons and prune synaptic connections (red).
- Involved in almost all nervous-system diseases and in certain psychiatric conditions.

R. Douglas Fields

Brief history of glia

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

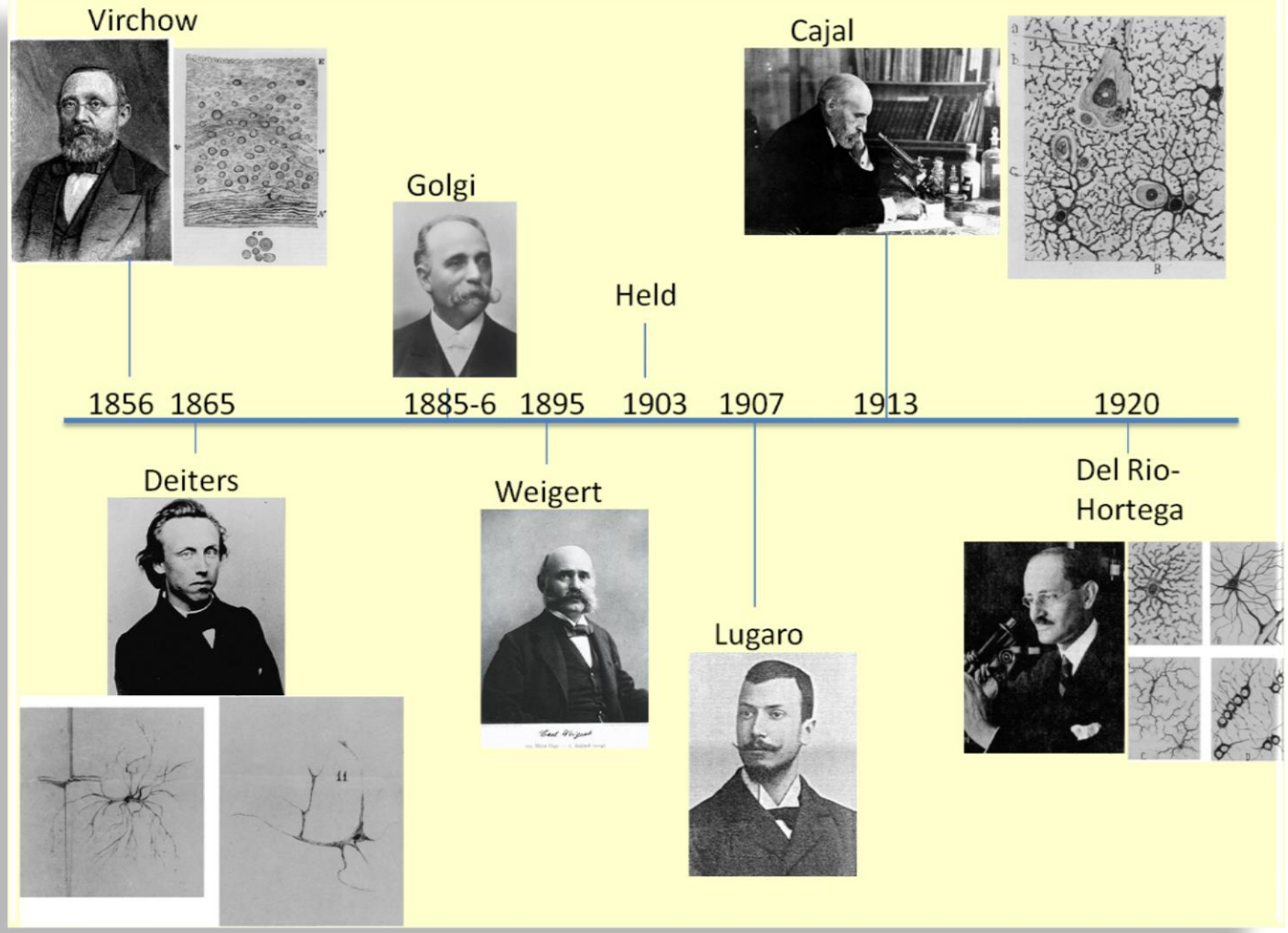
While never as studied as neurons, the early neuroscientists studied and debated glia's classification, morphology, and roles.

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.

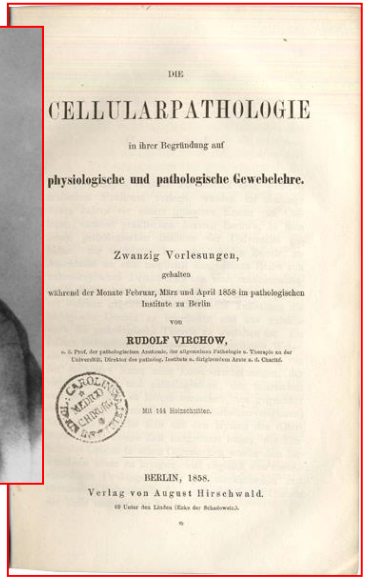
Many of the functions now recognized, however, were proposed by the earliest neuroscientists, such as glia's ability to secrete chemicals (Nageotte), their association with blood vessels (Golgi), their morphological plasticity (Cajal), their ability to electrically insulate (Cajal), their role in neurotransmitter uptake and termination (Lugaro), and role in pathology (Virchow).

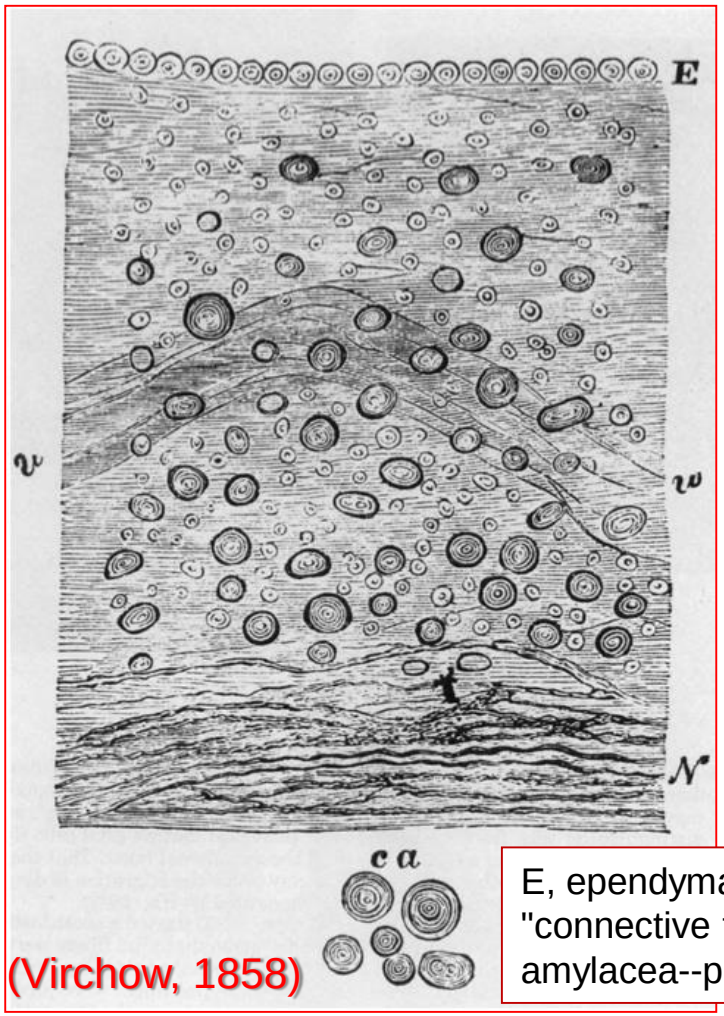
Brief history of glia

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



Virchow (1821-1902)

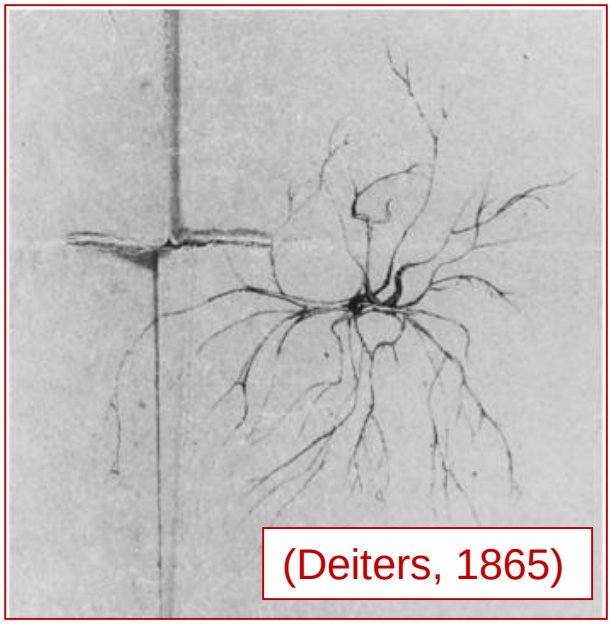




(Virchow, 1858)

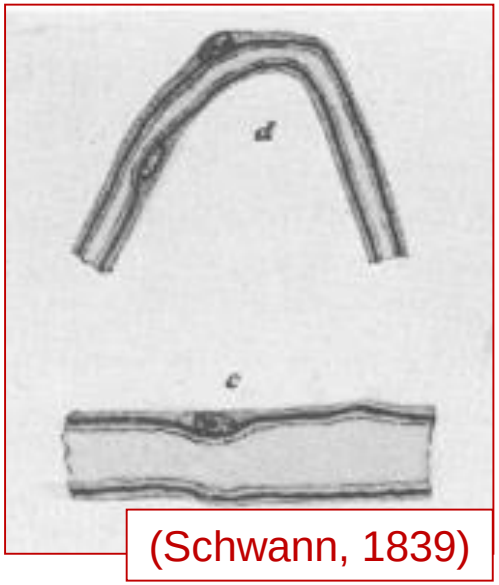
E, ependymal epithelium; v-w, blood vessel in "connective tissue"; N, nerve fibers; ca, copora amylacea--perhaps a staining artifact

- **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.



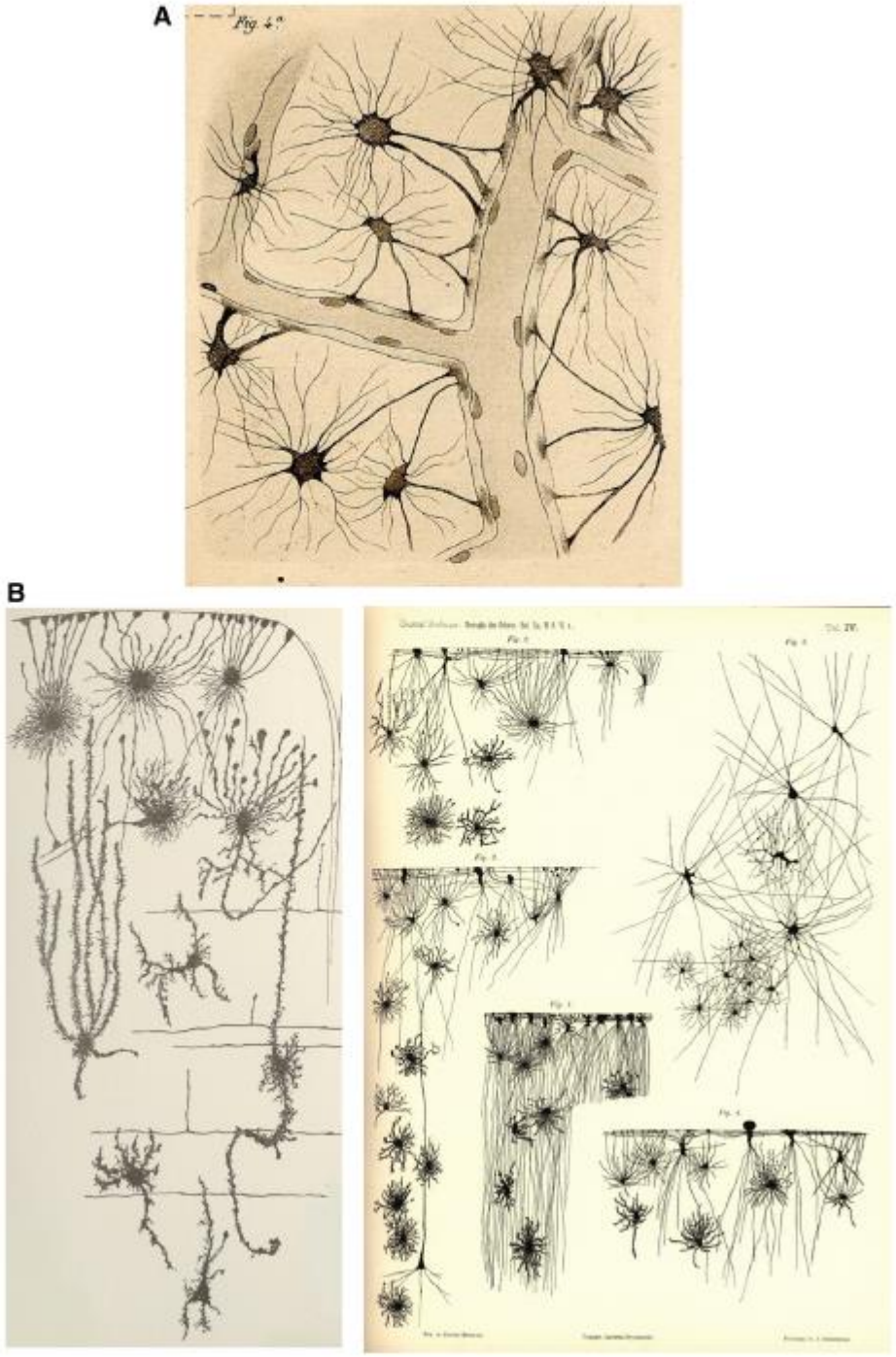
(Deiters, 1865)

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.



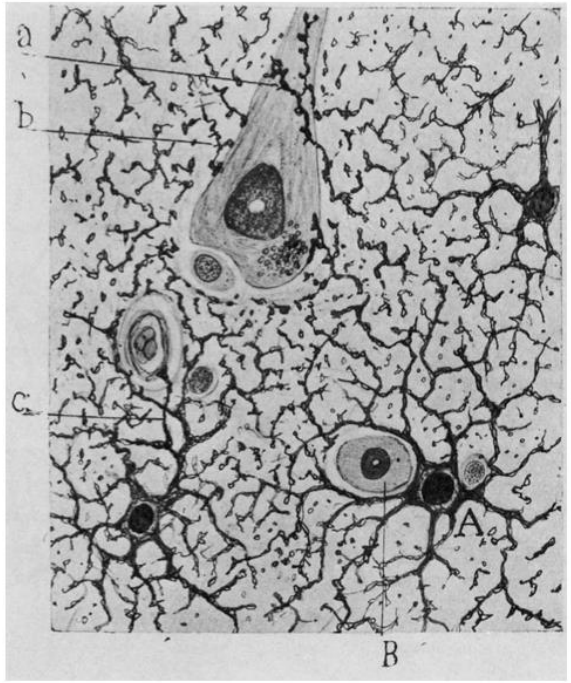
Astroglial cells stained by the silver-chromate technique.

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).

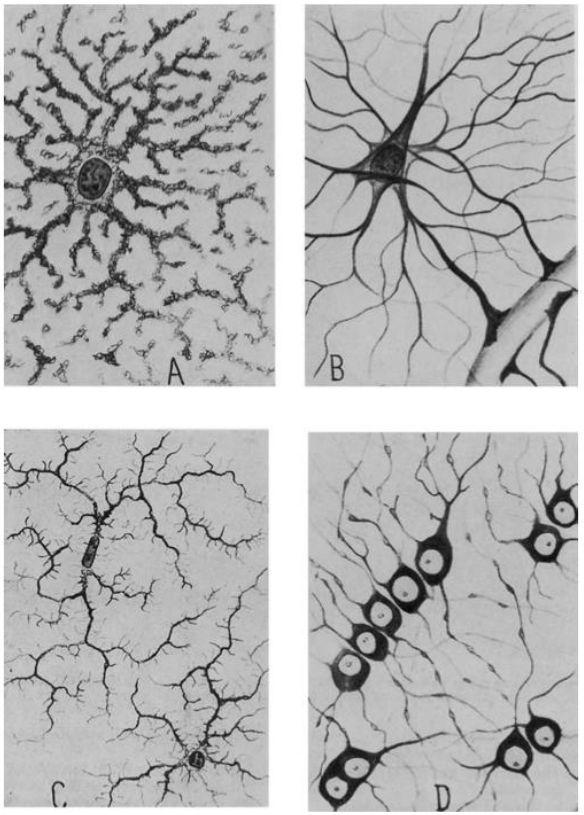
Verkhratsky et al., 2011
Brain Res Reviews
doi:10.1016/j.brainresrev.2010.05.002

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

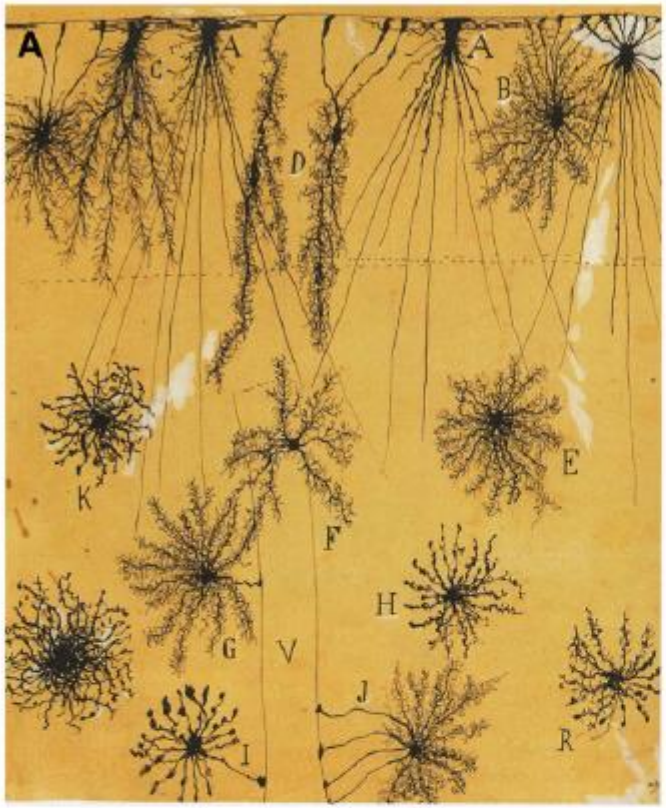


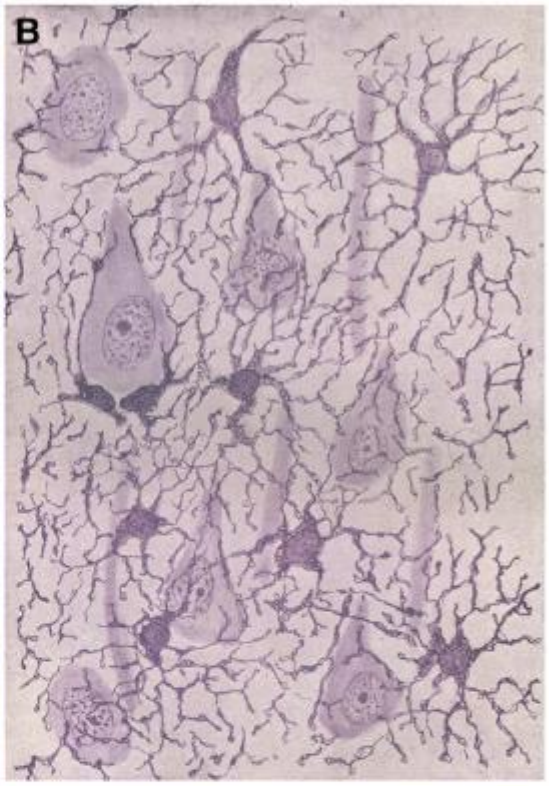
(Cajal, 1913)

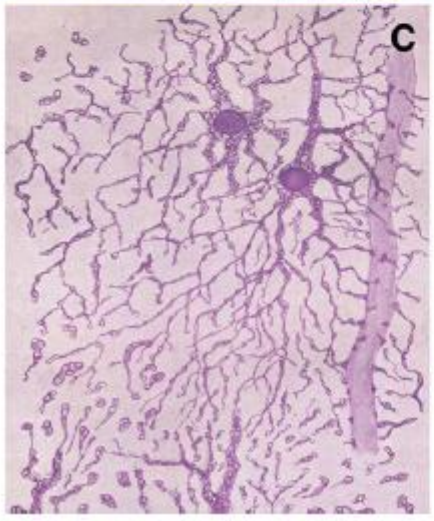
(Del Rio-Hortega, 1920)

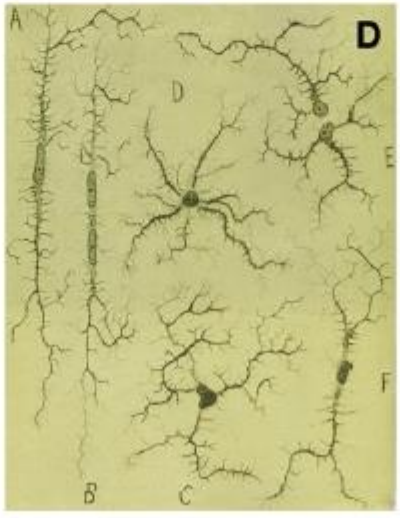


Del Rio-Hortega's four types of glia. A: Gray matter protoplasmic neuroglia. B: White matter fibrous neuroglia. C: Microglia. D: White matter interfascicular glia (oligodendrocytes) (Somjen 1988, Fig. 4)









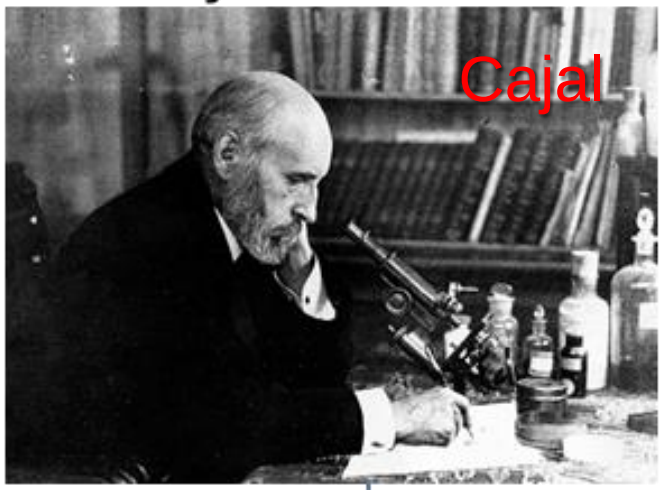
Glial cells by the eyes of Santiago Ramón y Cajal and Pío del Río-Hortega.

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 immuncocytochemistry today

Developmental origin

(Macro)gliogenesis in Vertebrates

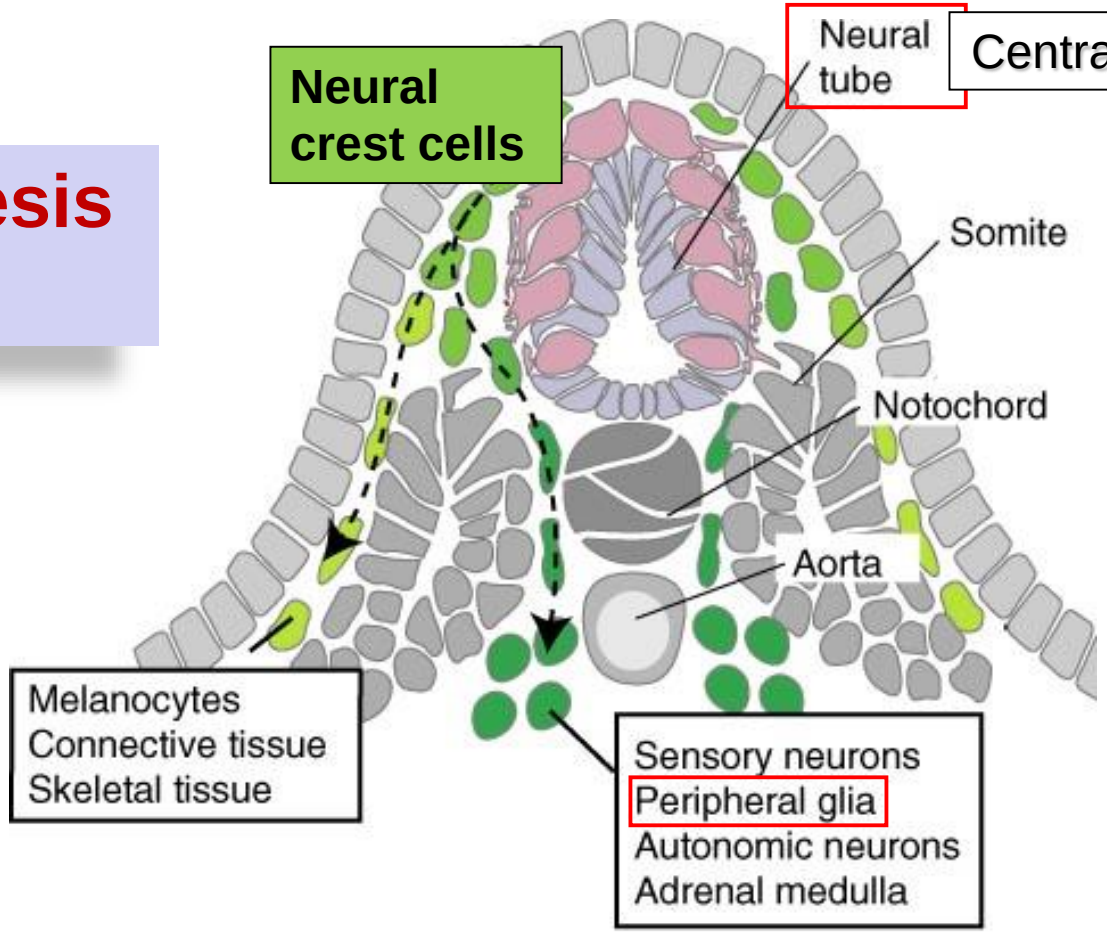
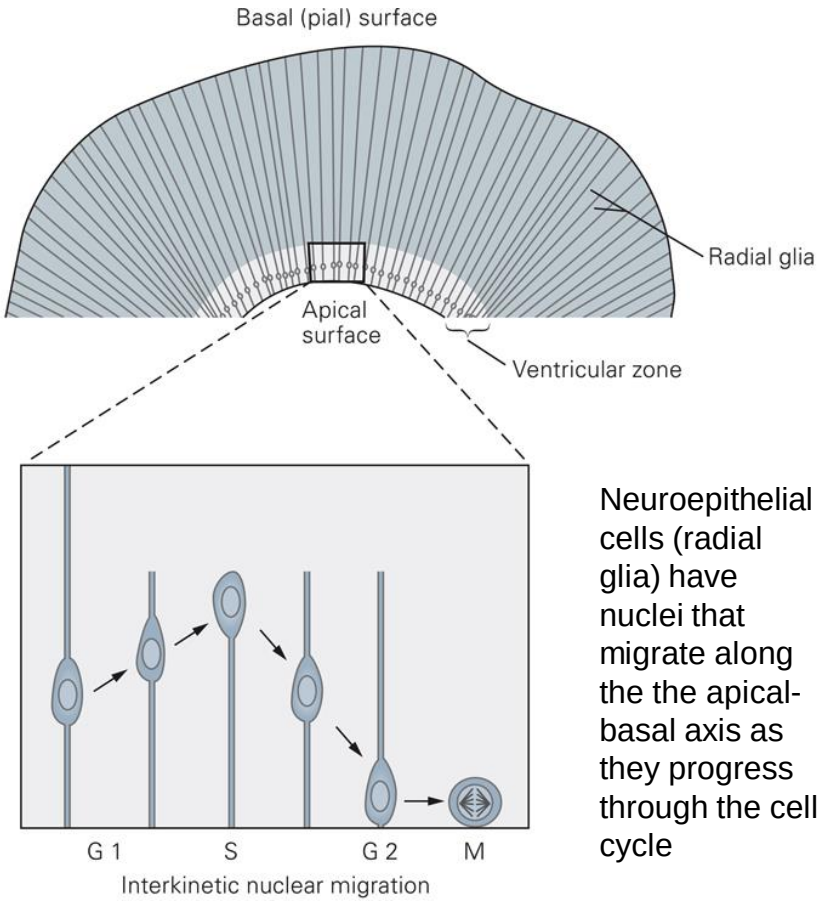


FIGURE 11 Neural crest lineages. Schematic cross section of vertebrate embryo in which migrating neural crest cells (green) are indicated. These cells follow two different pathways: a dorsal one (light green), giving rise to melanocytes, connective tissue, and skeletal tissue, and a ventral one, giving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

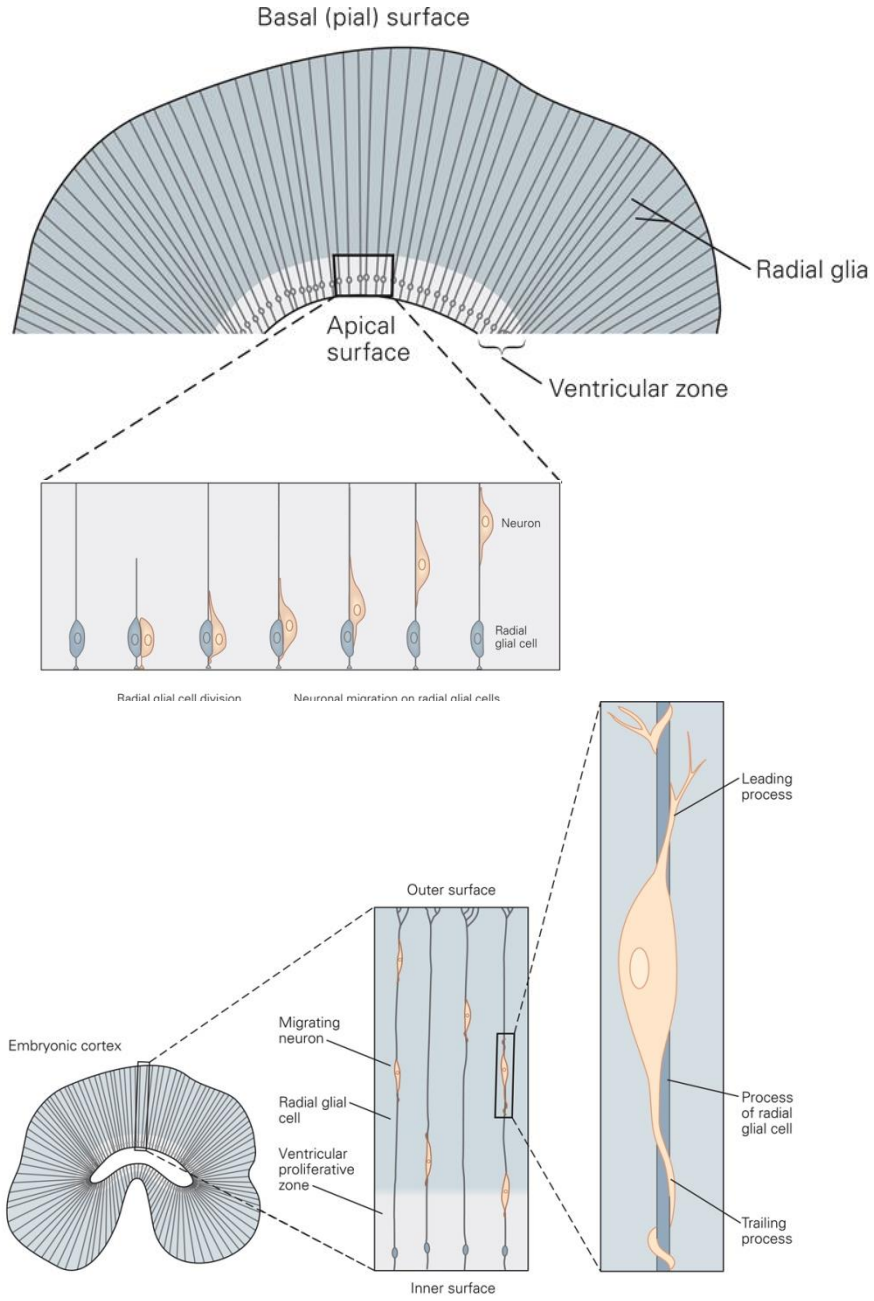
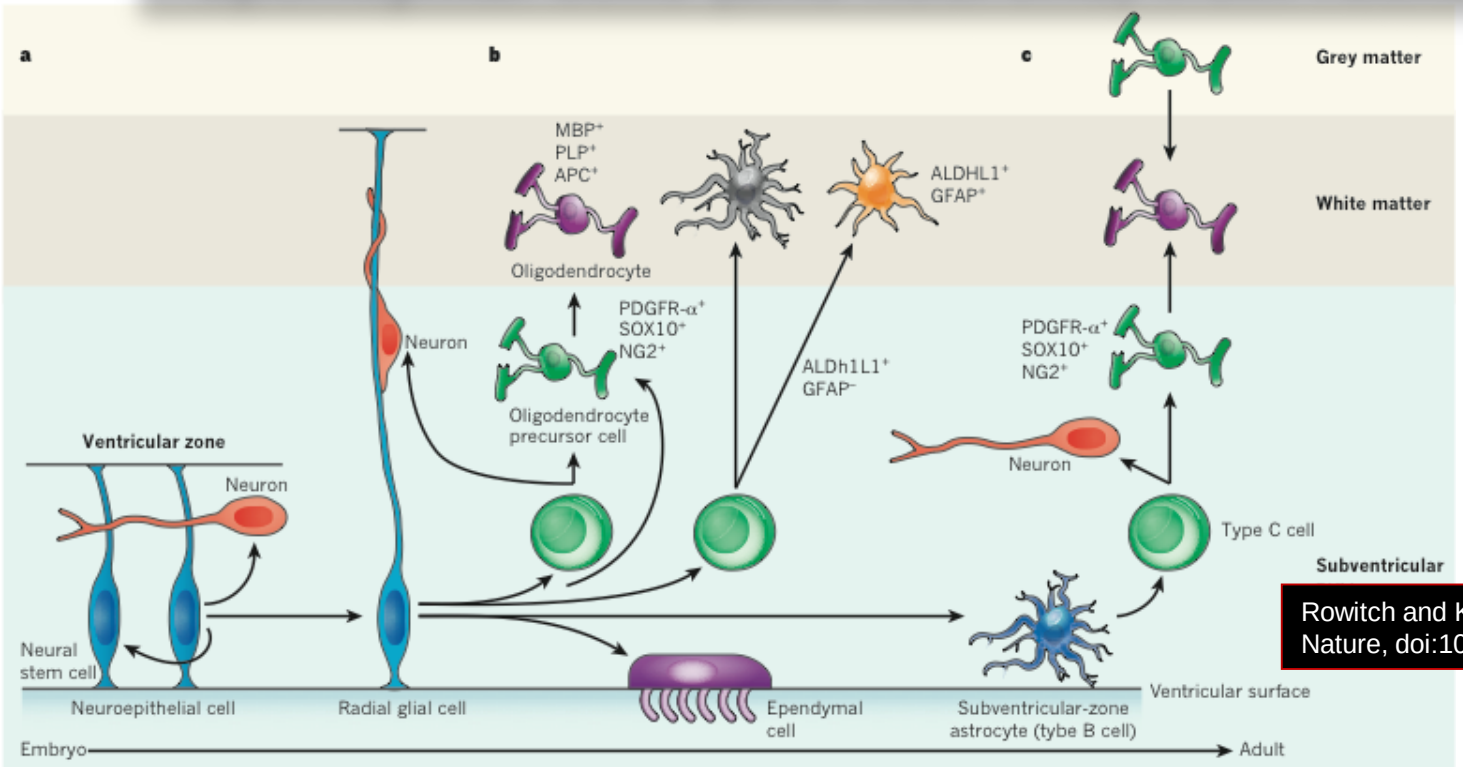


Figure 53–5 Neurons migrate along radial glial cells. After their generation from radial glial cells, newly generated neurons in the embryonic cerebral cortex extend a leading process that wraps around the shaft of the radial glial cell, thus using the radial glial cells as scaffolds during their migration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

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



Rowitch and Kriegstein, 2010
Nature, doi:10.1038/nature09611

Figure 1 | Patterns of gliogenesis in embryonic and adult progenitor zones. The progression from the embryo to the adult is shown from left to right (**a** to **c**). Black arrows indicate self-renewal or differentiation from one cell type to another. Markers of macroglia and their precursors are listed. **a**, Self-renewing neuroepithelial cells line the ventricles throughout the neuraxis at the stages of neural tube closure. These cells may generate some neurons. Neuroepithelial cells are transformed into radial glial cells as neurogenesis begins. **b**, Radial glia produce intermediate progenitor cells and oligodendrocyte precursor cells (OPCs), which in turn produce neurons and oligodendrocytes, respectively. Radial glia can also become astrocytes, as well as producing intermediate progenitors that expand in number before producing astrocytes. Protoplasmic astrocytes and fibrous astrocytes might arise from common or independent progenitors. Radial glia also produce ependymal cells. **c**, In adults, oligodendrocytes are produced by two independent pathways: type B cells in the cortical subventricular zone produce transit-amplifying cells (known as type C cells), which in turn produce OPCs as well as neurons. The OPCs subsequently generate oligodendrocytes, and OPCs that are already resident in the grey matter also produce oligodendrocytes. ALDH1L1, aldehyde dehydrogenase 1 family, member L1; APC, adenomatous polyposis coli; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; PDGFR-α, platelet-derived growth-factor receptor-α; PLP, proteolipid protein 1. All green cells are intermediate progenitors, with type C cells being a subset of these, and all blue cells are neural stem cells (even though each blue cell is a different type).

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

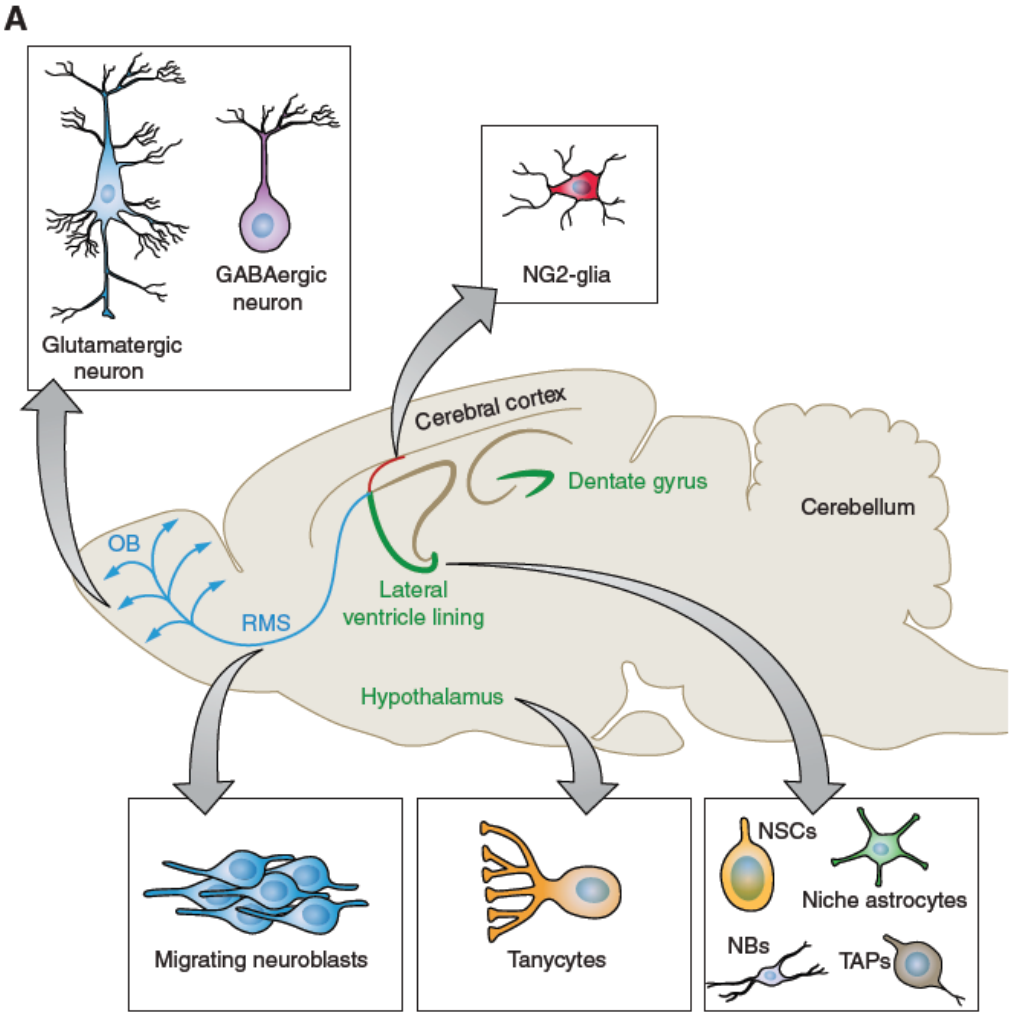
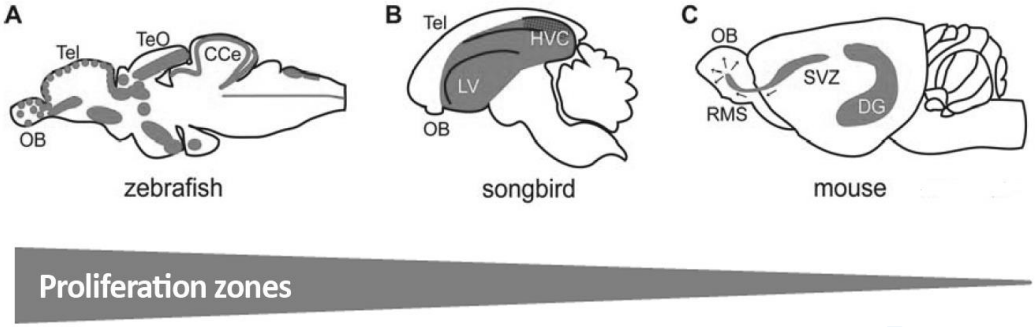


FIGURE 3. Glial cells as stem and progenitor cells in the healthy adult brain. *A*: endogenous neurogenesis still persists in the adult mammalian brain in few niches like the subependymal zone in the lateral wall of the lateral ventricle, the subgranular zone in the dentate gyrus, and the hypothalamus. 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.

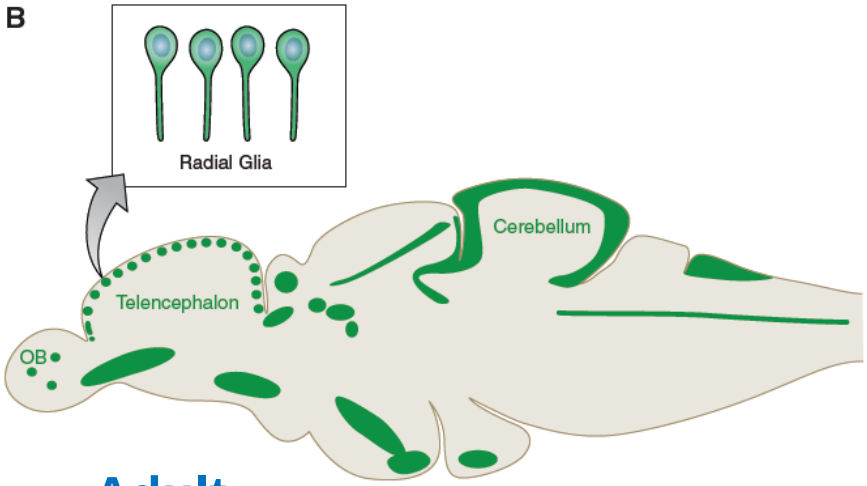
Leda Dimou and Magdalena Götz

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



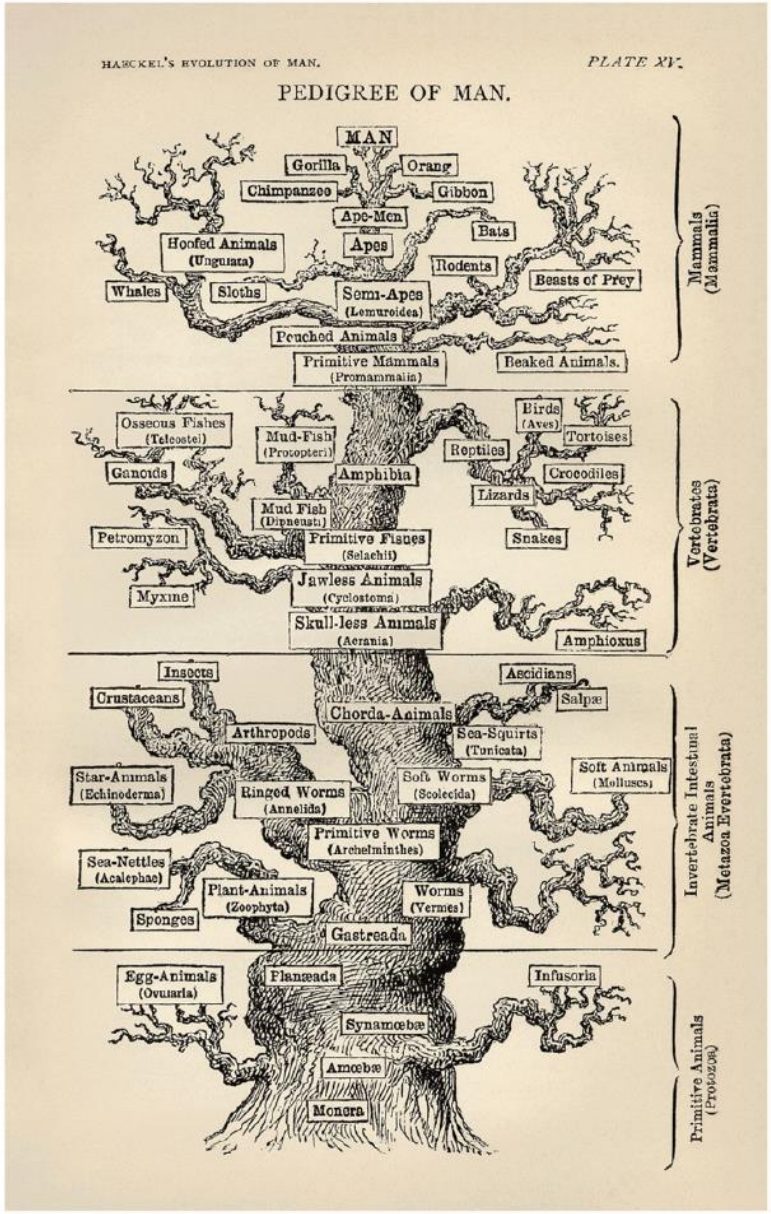
Adult zebrafish

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

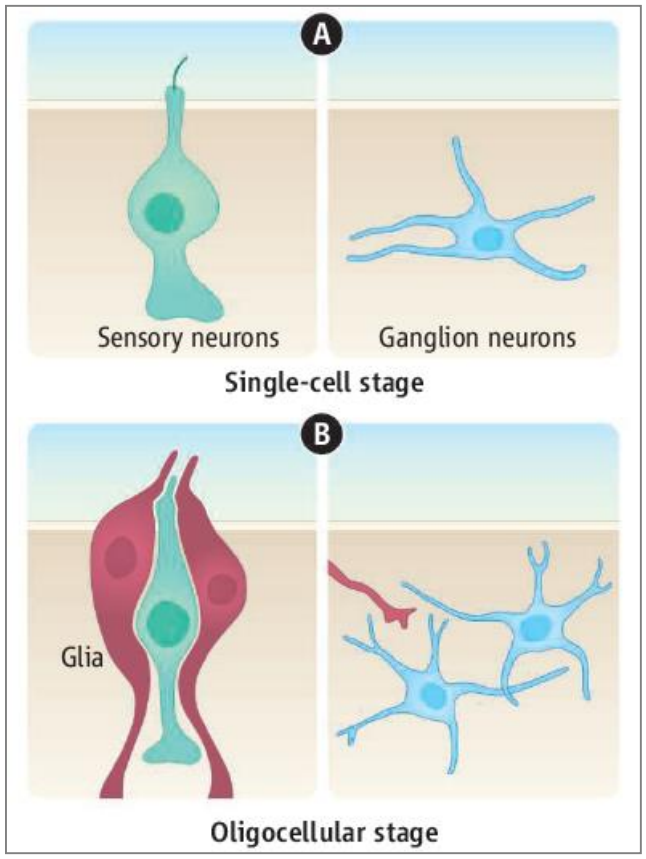
Verkhratsky et al., 2011
Brain Res Reviews
doi:10.1016/j.brainresrev.2010.05.002

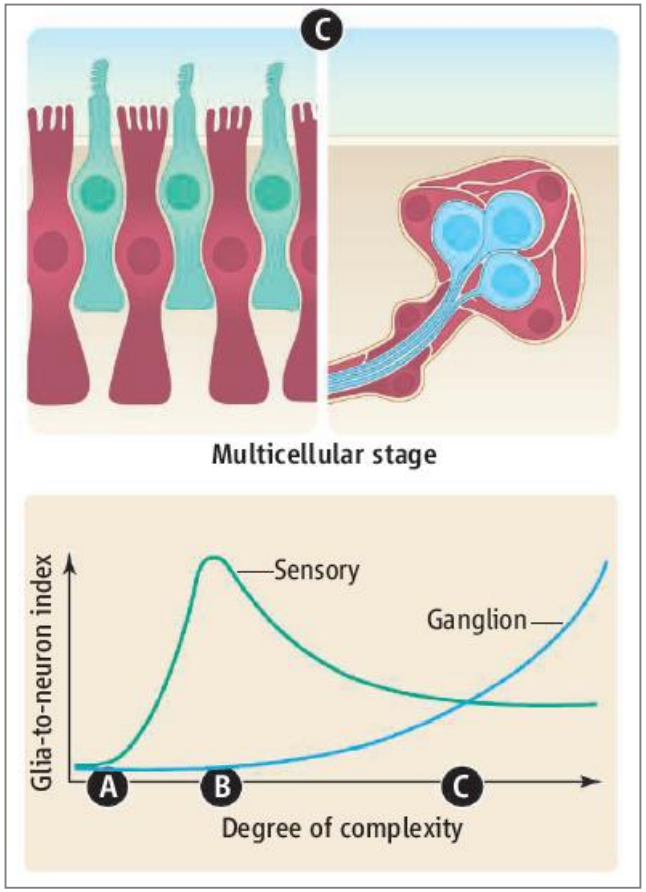
Fig. 4 – Evolution of the neuroglia; the tree of life is taken from Haeckel (1879).

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.

Andreas Reichenbach and Thomas Pannicke
SCIENCE VOL 322 31 OCTOBER 2008