

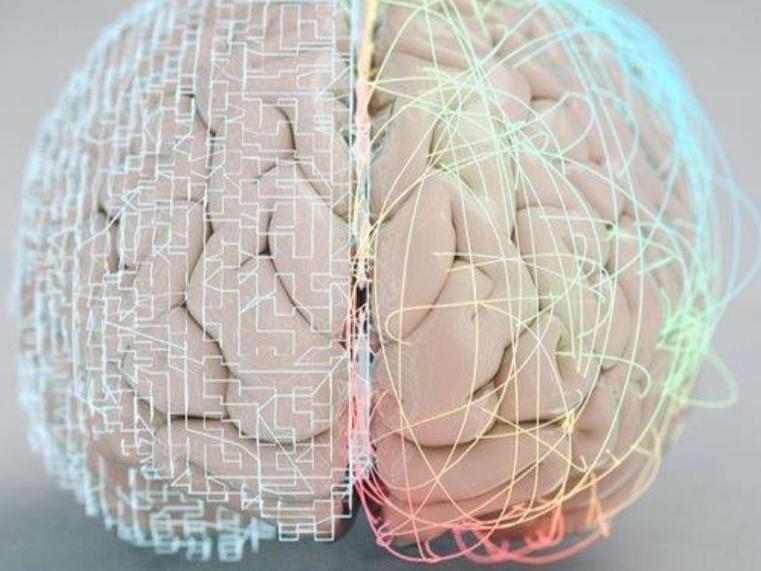


**UNIVERSITÀ
DEGLI STUDI
DI TRIESTE**



Dipartimento di
Scienze della Vita

COMPARATIVE BRAIN EVOLUTION



Comparative Histogenesis (III) Neurogenesis and forebrain evolution in amniotes

Neurogenesis and forebrain evolution in amniotes

1. Evolutionary origin of Tbr2+ precursors and SVZ

2. Forebrain evolution

Evolutionary Origin of Tbr2-Expressing Precursor Cells and the Subventricular Zone in the Developing Cortex

Verónica Martínez-Cerdeño,^{1,2,6*} Christopher L. Cunningham,³ Jasmin Camacho,¹ Janet A. Keiter,³ Jeanelle Ariza,¹ Matthew Lovern,⁴ and Stephen C. Noctor^{5,6*}

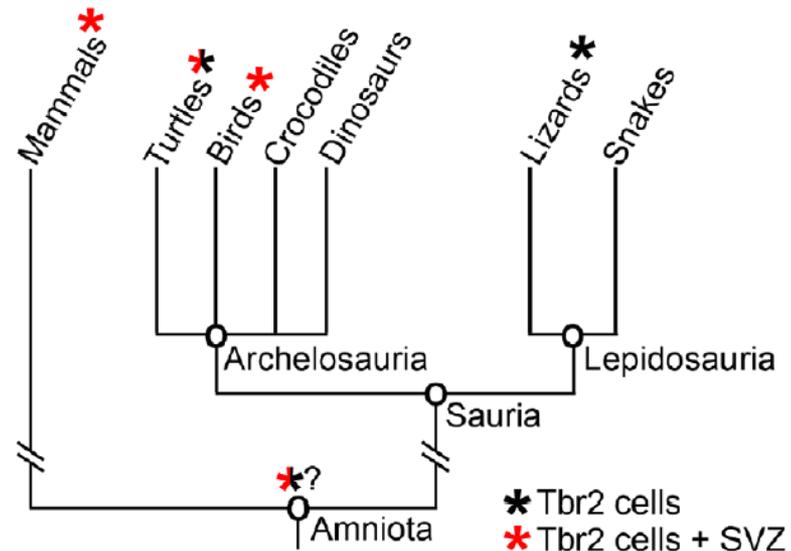
Species in this study

Turtle (*Trachemys scripta elegans*)

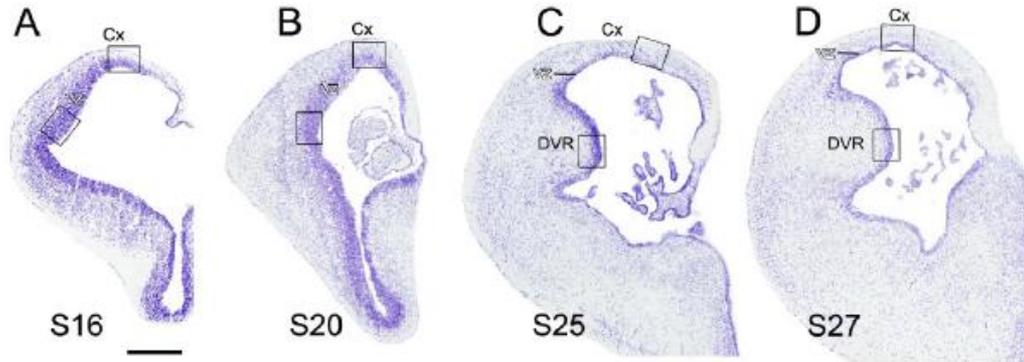
Chicken (*Gallus gallus domesticus*)

Dove (*Zenaida macroura*)

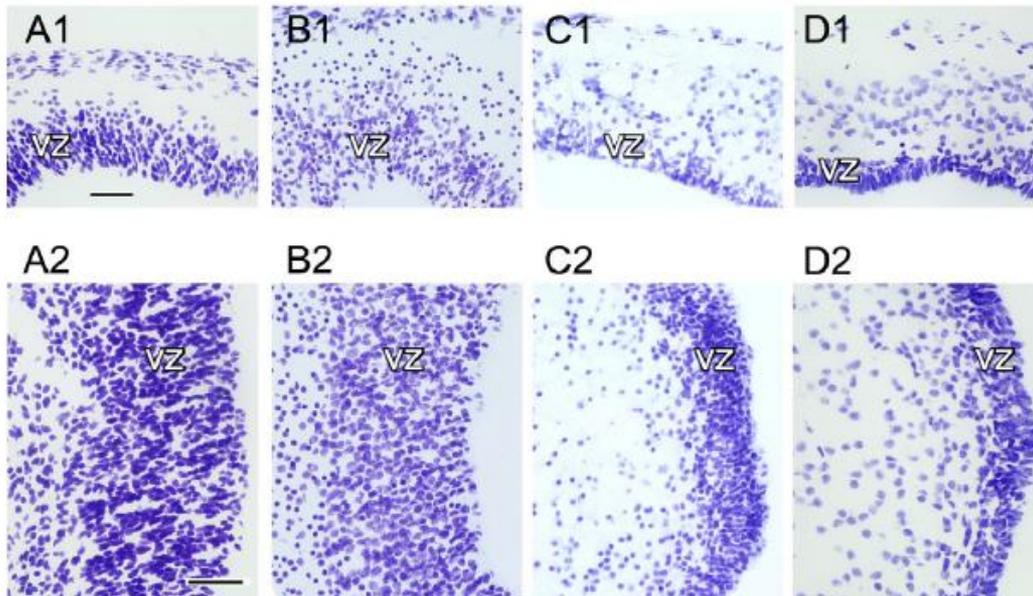
Lizard (*Anolis carolinensis*)



Development of the dorsal cortex and DVR in turtle



Nissl-stain of developing cortex in turtle

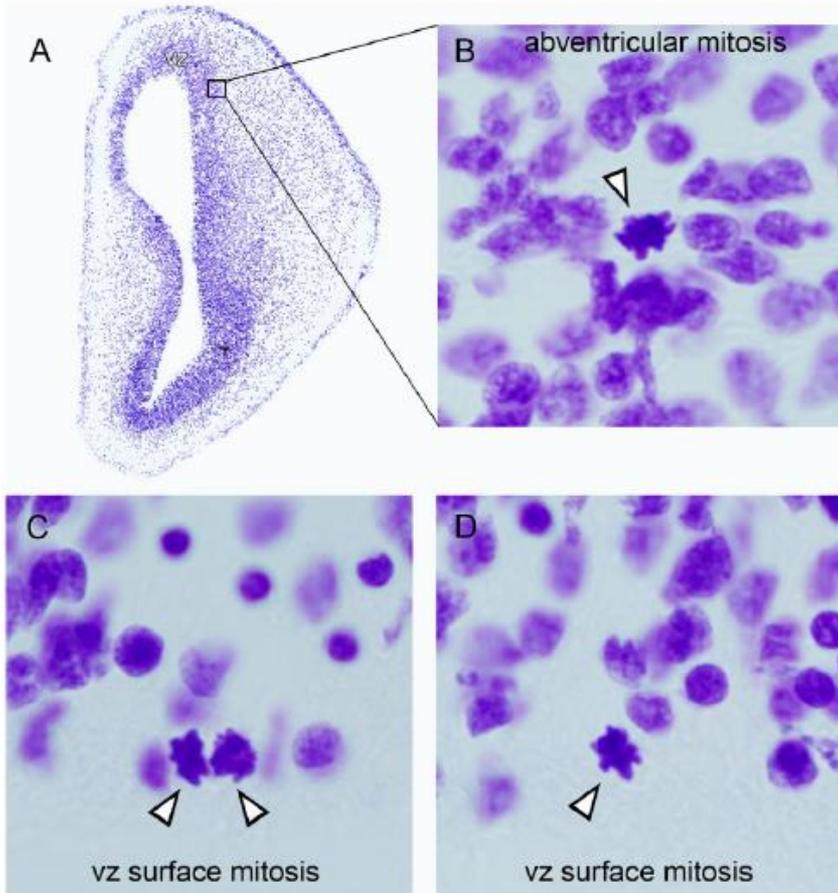


Dorsal cortex

DVR

VZ is thicker in the DVR

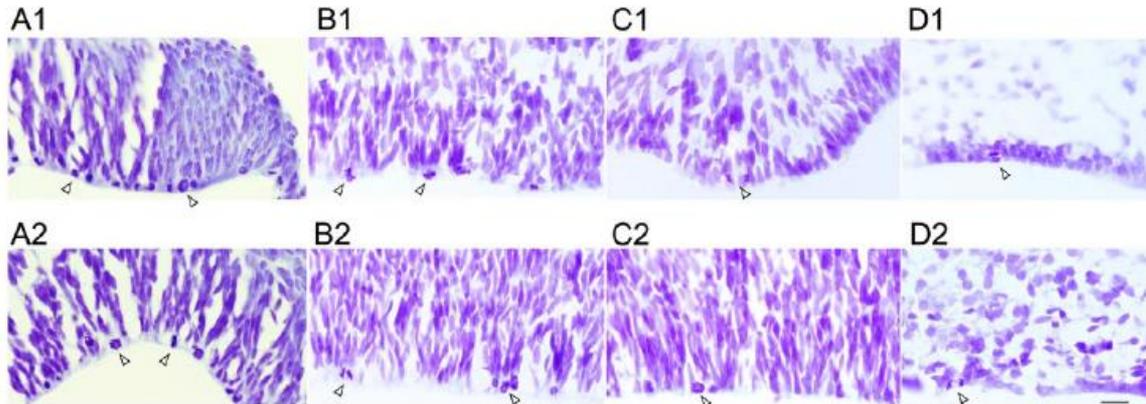
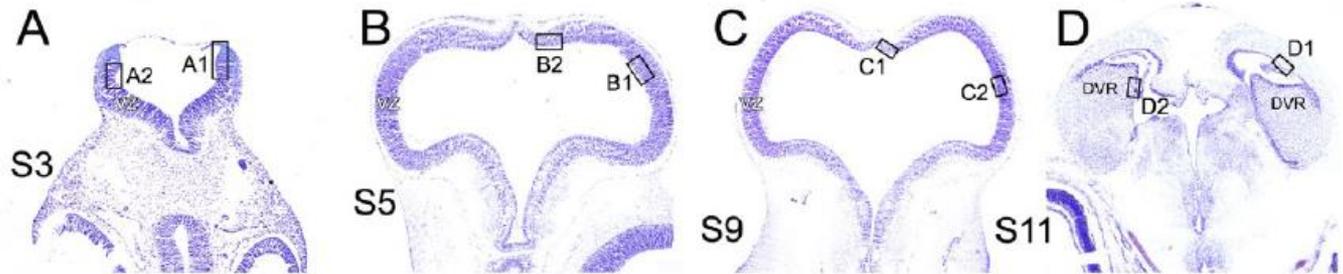
Mitotic cells in the developing turtle cortex



Mitotic cells both close to VZ and away from the ventricle (**abventricular mitosis**)

Mitotic cells in the developing lizard cortex

Lizard VZ thinner than turtle VZ



Very few **abventricular mitosis**

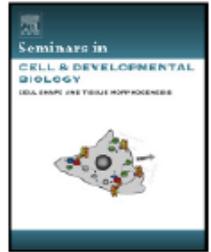


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journal homepage: www.elsevier.com/locate/semcdb



Review

Update on forebrain evolution: From neurogenesis to thermogenesis



Verónica Martínez-Cerdeño^{a,b,c,**}, Fernando García-Moreno^d, Maria Antonietta Tosches^e,
András Csillag^f, Paul R. Manger^g, Zoltán Molnár^{h,*}

Progenitor cells in the VZ/SVZ of the developing cerebral cortex

turtle

Tbr2⁺ cells as SVZ in the DVR (similar to mammal cortex)

chick/dove

Tbr2⁺ cells as SVZ in the dorsal forebrain

lizard & crocodile

Few Tbr2⁺ cells scattered in VZ
No SVZ

snake

Tbr2⁺ cells as SVZ

Conclusions

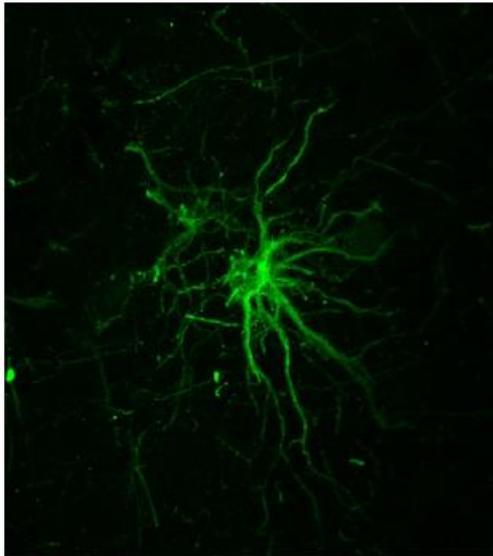
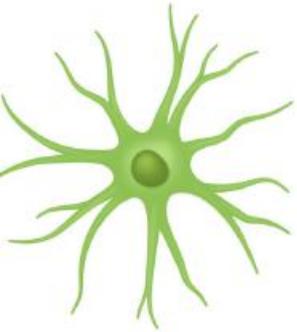
- Principal cellular elements of the mammalian SVZ evolved prior to the appearance of the modern day mammals (present in the ancestor of amniotes)
- Early in mammalian radiation, a subset of progenitors experienced a delay in the neurogenic period (heterochronic compared to the reptiles)
- Great heterogeneity of excitatory and inhibitory neuron types in the turtle and lizard pallia

The origin of glia: insights from invertebrates

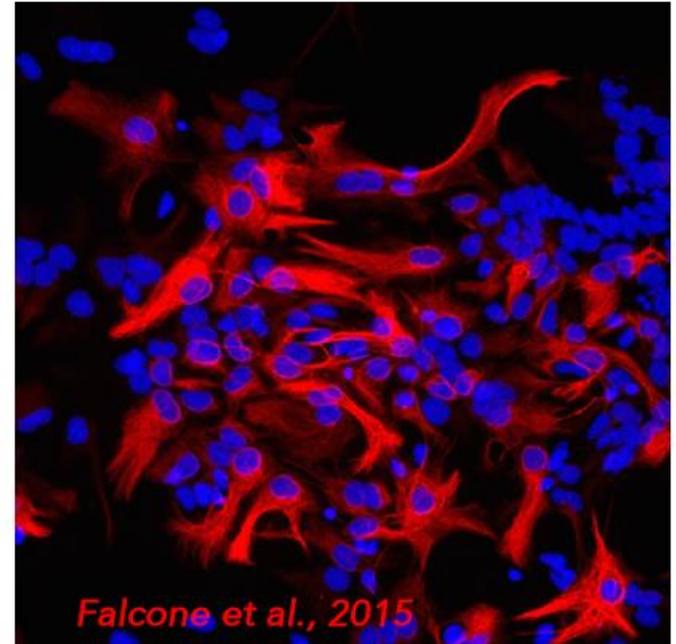
Astrocyte evolution across vertebrates

Astrocytes

- «Star shaped»
- Projections to neurons and blood vessels



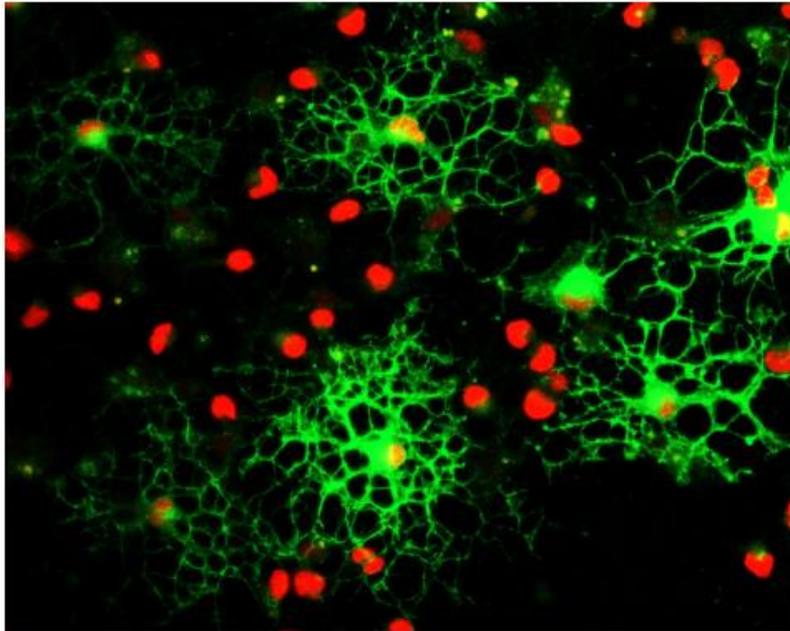
*GFAP⁺ astrocytes, chimpanzee
PFC
Ciani et al. (unpublished data)*



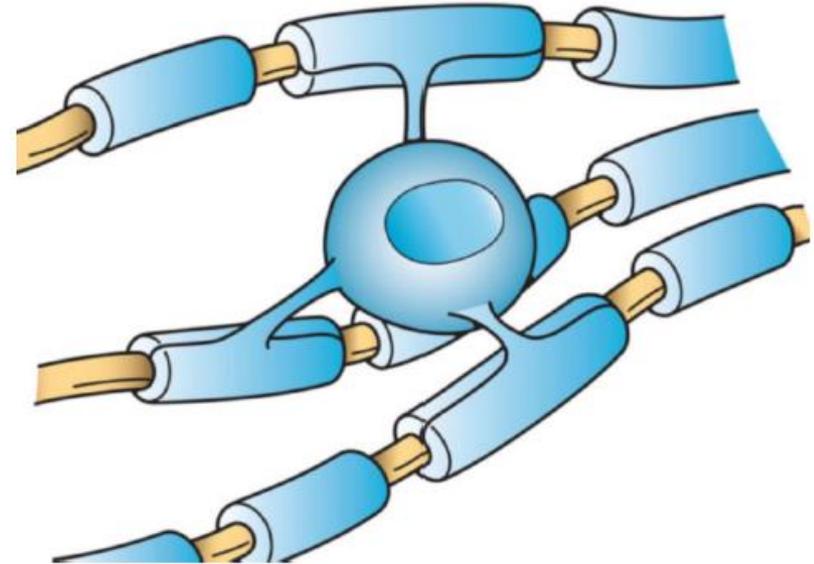
- Roles?
 - structural support
 - metabolic support
 - blood brain barrier
 - neurotransmitter uptake and release
 - regulation of ion concentration
 - role in neurodevelopment

Oligodendrocytes

- Roles: - myelin production
- metabolic support

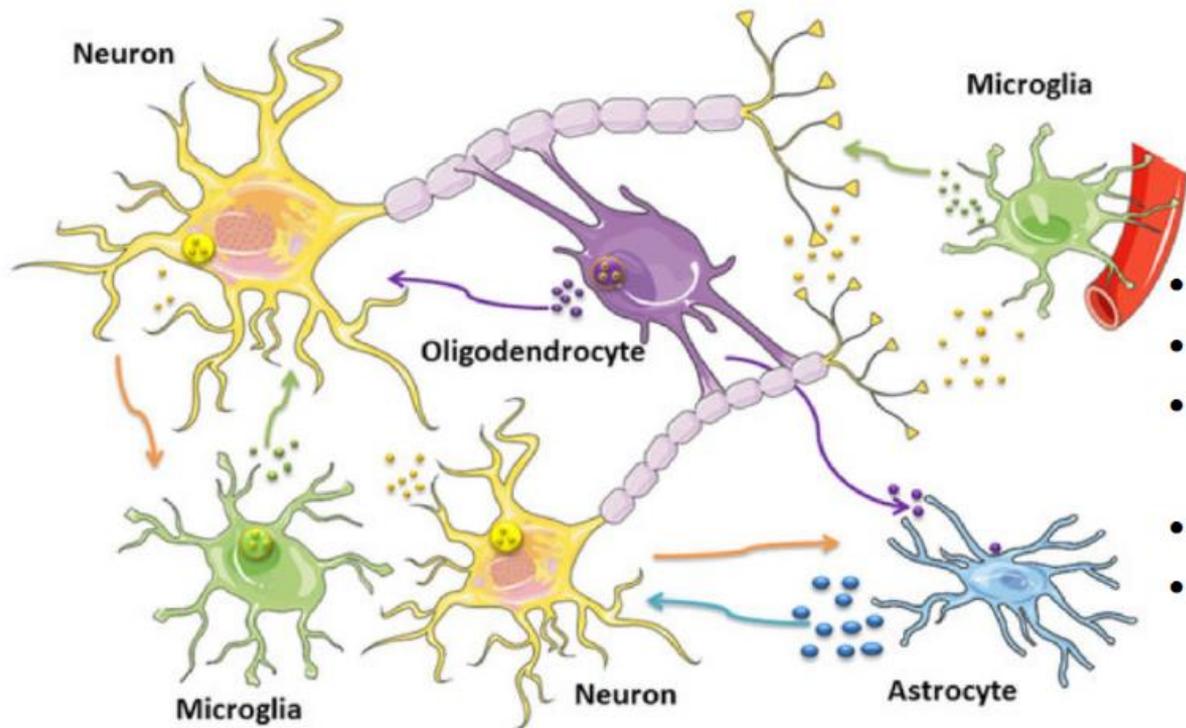


Ding et al. 2020



- 1 oligodendrocyte myelinates multiple axons

Neuron and glia cross-talk



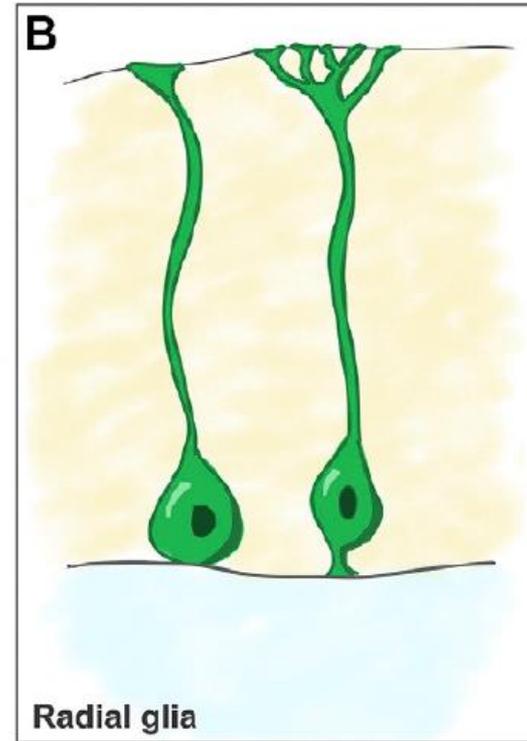
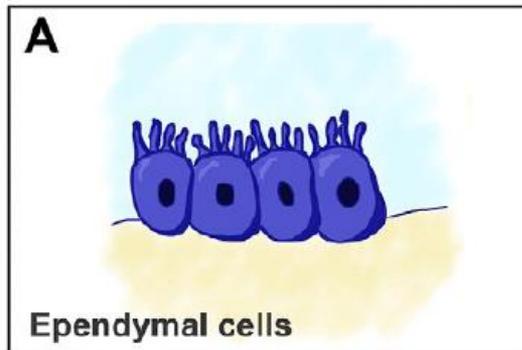
- Neurons-astrocytes
- Neurons-oligodendrocytes
- Neurons-microglia

- Astrocytes-oligodendrocytes
- Astrocytes-microglia

Riva et al. 2019

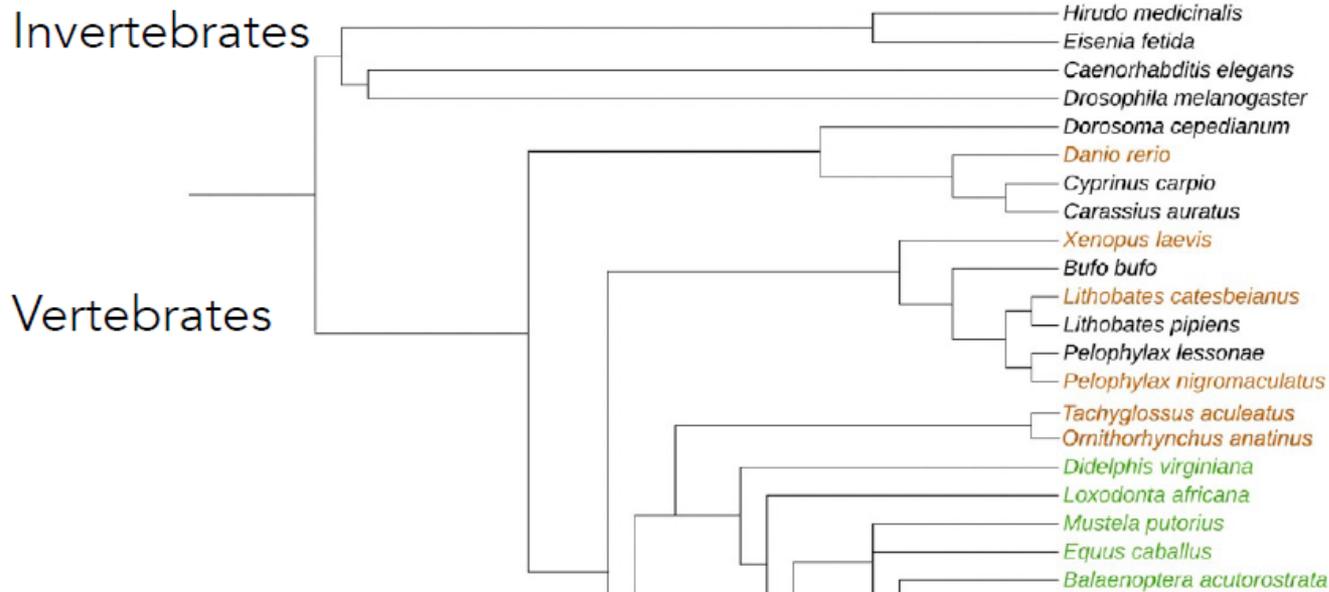
Where do glia come from in the CNS?

First types of glial cells



Falcone et al. 2022

First types of glial cells in the invertebrates



Flatworms:
The first Bilateria to show
a CNS

Glia-like mesenchymal
Cells
(long processes
contacting neurons)

First types of glial cells in the invertebrates

Nematodes (*C. elegans*):

Proto-astrocytes

- no functions in blood brain barrier because no circulatory system
- No mammalian astrocyte markers

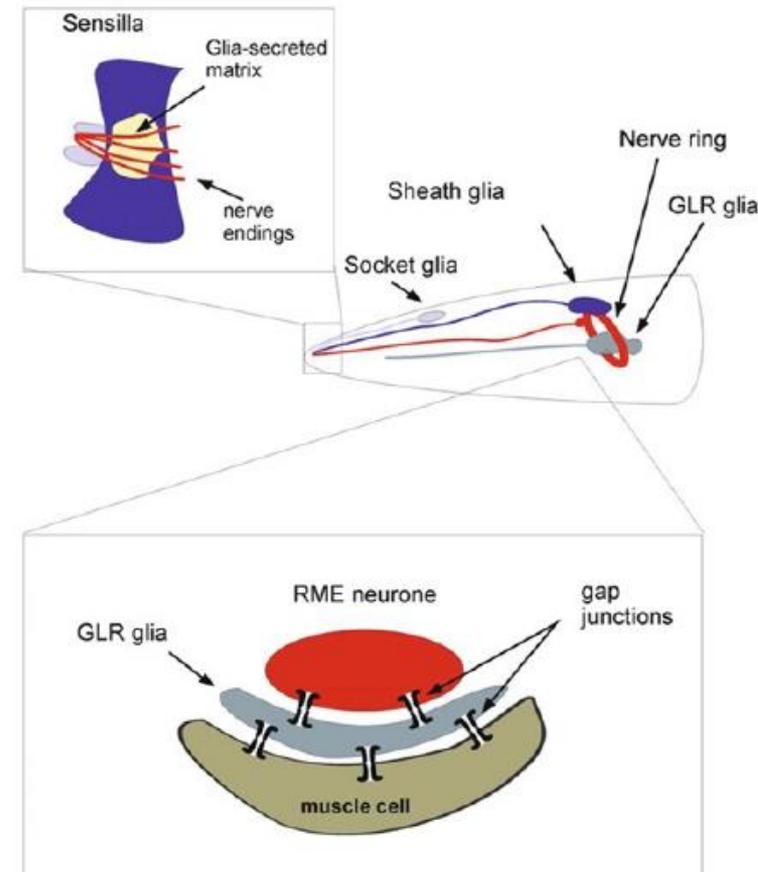
Different types:

- Cephalic sheath glia (in the nerve ring)

CEPsh

Functions in regulating neuronal development

Suppressing locomotion during sleep

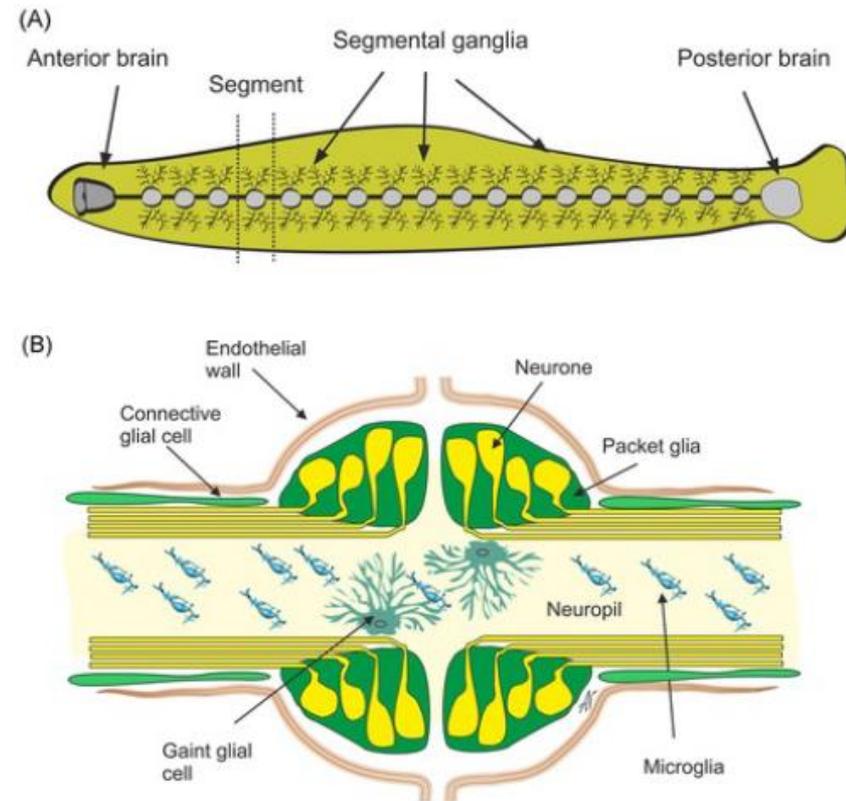


First types of glial cells in the invertebrates

Anellida (e.g. leech):
Homeostatic proto-astrocytes

Different types:

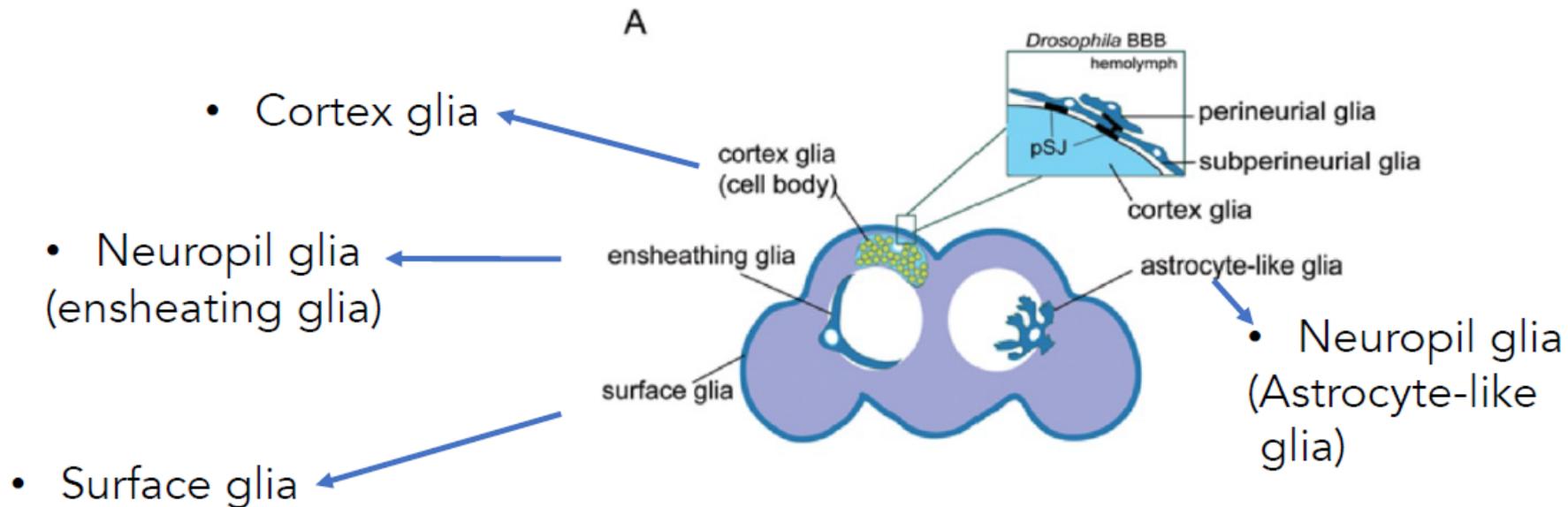
- Packet glial cells Buffer extracellular K^+
- Giant glial cells Processes contact dendrites



First types of glial cells in the invertebrates

Insects (e.g. *Drosophila melanogaster*)

Proto-astrocytes with a higher degree of specialization (vs. other invertebrates)



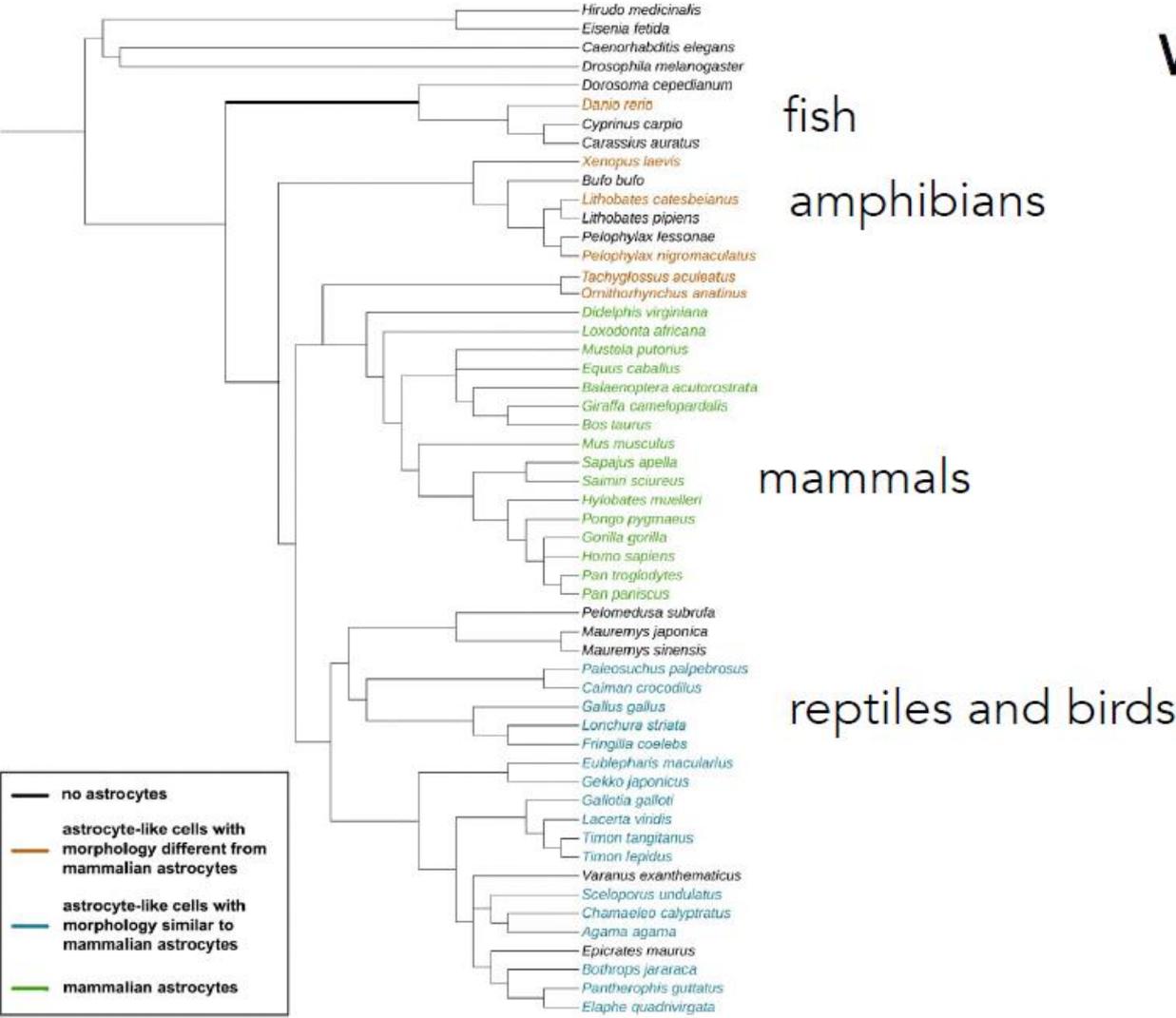
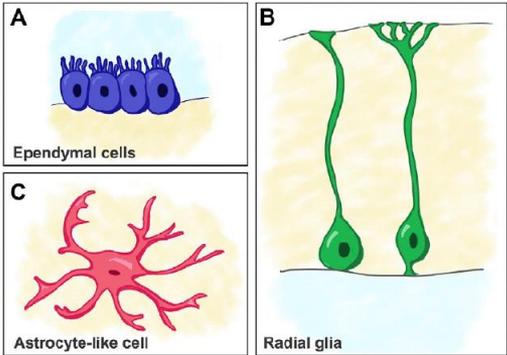
Astrocyte evolution across vertebrates

Where do astrocytes come from?

What is an astrocyte?

Where do astrocytes come from?

Who were the astrocytes' predecessors?



— no astrocytes

— astrocyte-like cells with morphology different from mammalian astrocytes

— astrocyte-like cells with morphology similar to mammalian astrocytes

— mammalian astrocytes

Falcone, 2022



Methods for conducting comparative studies on astrocytes?

- Immunohistochemistry/immunofluorescence on postmortem tissue
- In vitro studies
 - With primary cultures from model organisms
 - With iPSCs derived from different specie
- *In vivo* functional studies (with model organisms or with chimera mice)
 - IHC
 - Circuits/Electrophysiology
 - Behavior

Similarities among Zebrafish astrocyte-like cells and mouse astrocytes

nature
neuroscience

RESOURCE

<https://doi.org/10.1038/s41593-020-0703-x>



Live-imaging of astrocyte morphogenesis and function in zebrafish neural circuits

Jiakun Chen^{1,2,5}, Kira E. Poskanzer^{2,3}, Marc R. Freeman¹ and Kelly R. Monk^{1,2,5}

Astrocytes in human and non-human primates

Received: 25 September 2018 | Revised: 28 November 2018 | Accepted: 30 November 2018
DOI: 10.1002/cne.24605

WILEY **JCN** Journal of Comparative Neurology

RESEARCH ARTICLE

Cortical interlaminar astrocytes across the therian mammal radiation

Carmen Falcone^{1,2} | Marisol Wolf-Ochoa^{1,2} | Sarwat Amina^{2,3} | Tiffany Hong^{1,2} |
Gelareh Vakilzadeh^{1,2} | William D. Hopkins⁴ | Patrick R. Hof⁵ | Chet C. Sherwood⁶ |
Paul R. Manger⁷ | Stephen C. Noctor^{3,8} | Verónica Martínez-Cerdeño^{1,2,3}

Received: 12 May 2021 | Revised: 2 September 2021 | Accepted: 2 September 2021
DOI: 10.1002/glia.24093

GLIA WILEY

WILEY

RESEARCH ARTICLE

Redefining varicose projection astrocytes in primates

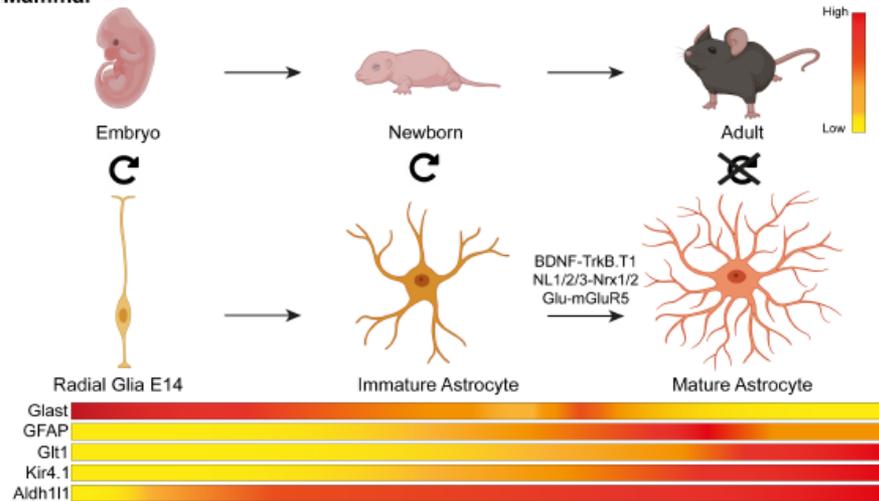
Carmen Falcone^{1,2} | Erin L. McBride^{1,2} | William D. Hopkins³ | Patrick R. Hof⁴ |
Paul R. Manger⁵ | Chet C. Sherwood⁶ | Stephen C. Noctor^{7,8} |
Verónica Martínez-Cerdeño^{1,2,7}

INTRODUCTION

Ballester et al, 2020

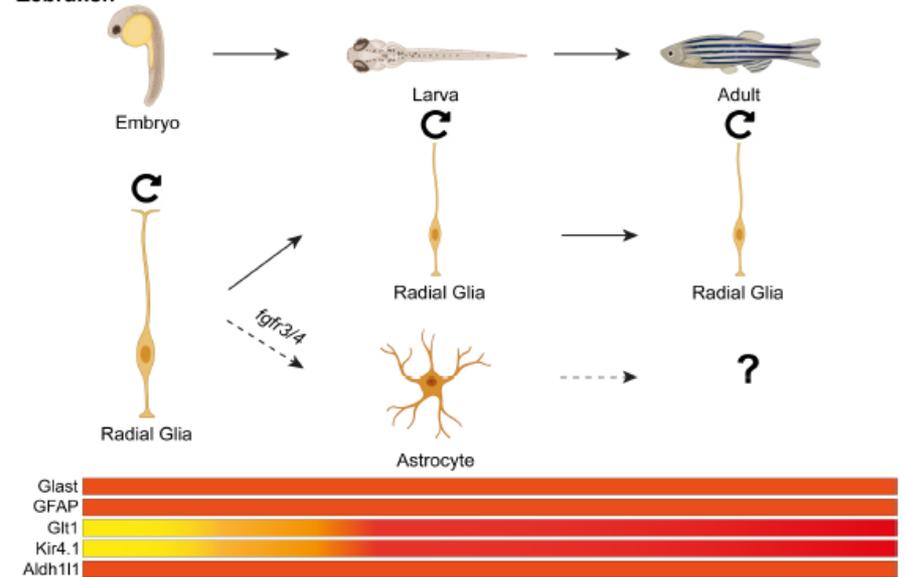
Spinal cord

Mammal



- Radial glia in mammals
- Astrocyte complexity
- Astrocytes → astrocytes in adults
- RG and astrocytes: shared expression of markers

Zebrafish



- Radial glia in zebrafish → neurons in adults
- Astrocytes (?)

SIGNIFICANCE:

They showed that zebrafish spinal cord radial glia differentiate into cells that are similar to mammalian astrocytes.



Validity of the zebrafish model for discovering molecular mechanisms governing astrocyte function.

Different types of astrocytes in the mammalian cerebral cortex

Two major types of astrocytes:

protoplasmic

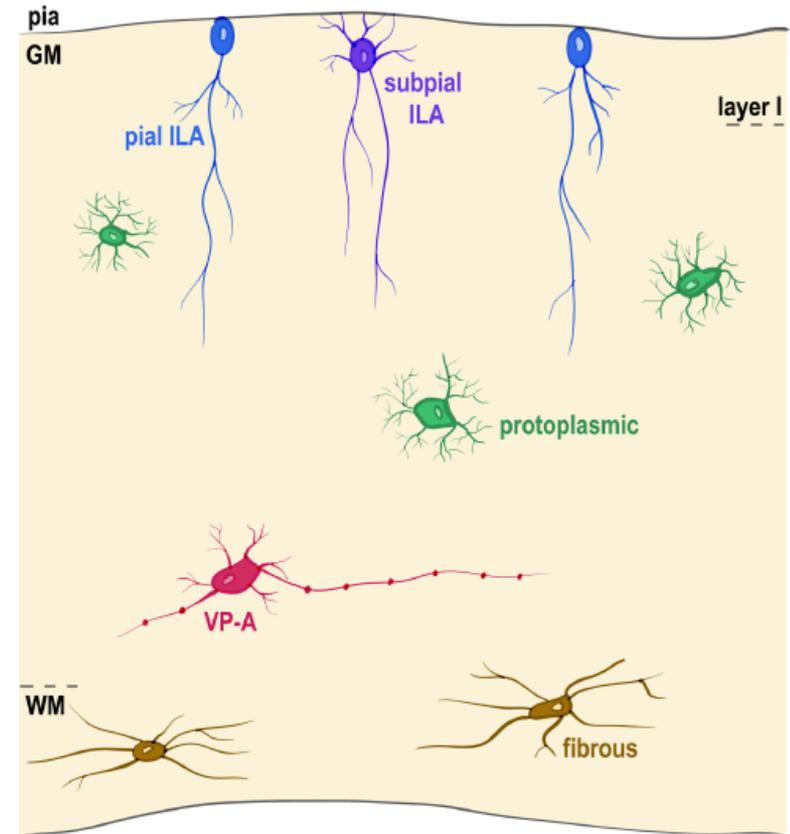
fibrous

IN ALL
MAMMALS

Other types of astrocytes:

Interlaminar (ILAs) Special features in PRIMATES

Varicose-projection (VP-As) Special features in
HUMAN & GREAT APES

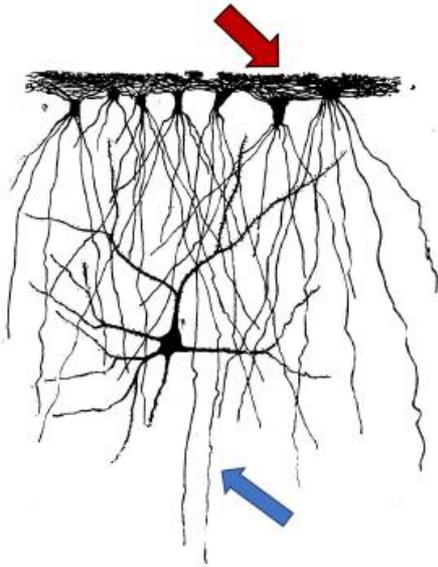


Falcone et al., 2022

Astrocytes with special features in primates

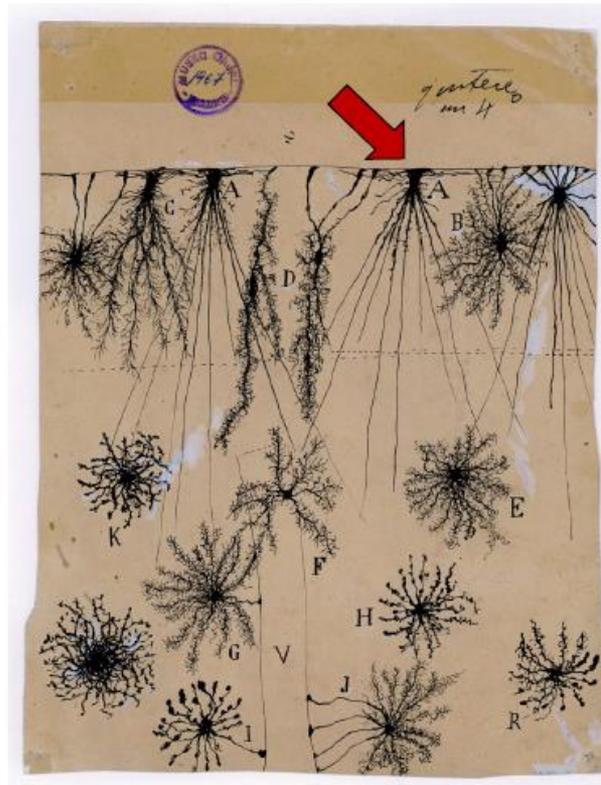
- 1) Interlaminar astrocytes: evolution
- 2) Varicose-projection astrocytes: evolution and implications for diseases

Interlaminar Astrocytes: a primate specific cell type?

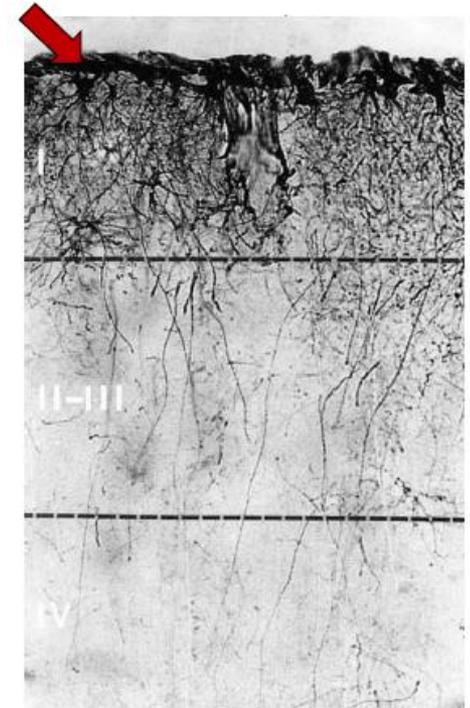


Andriezen, 1893, Golgi stain

Columnar organization?

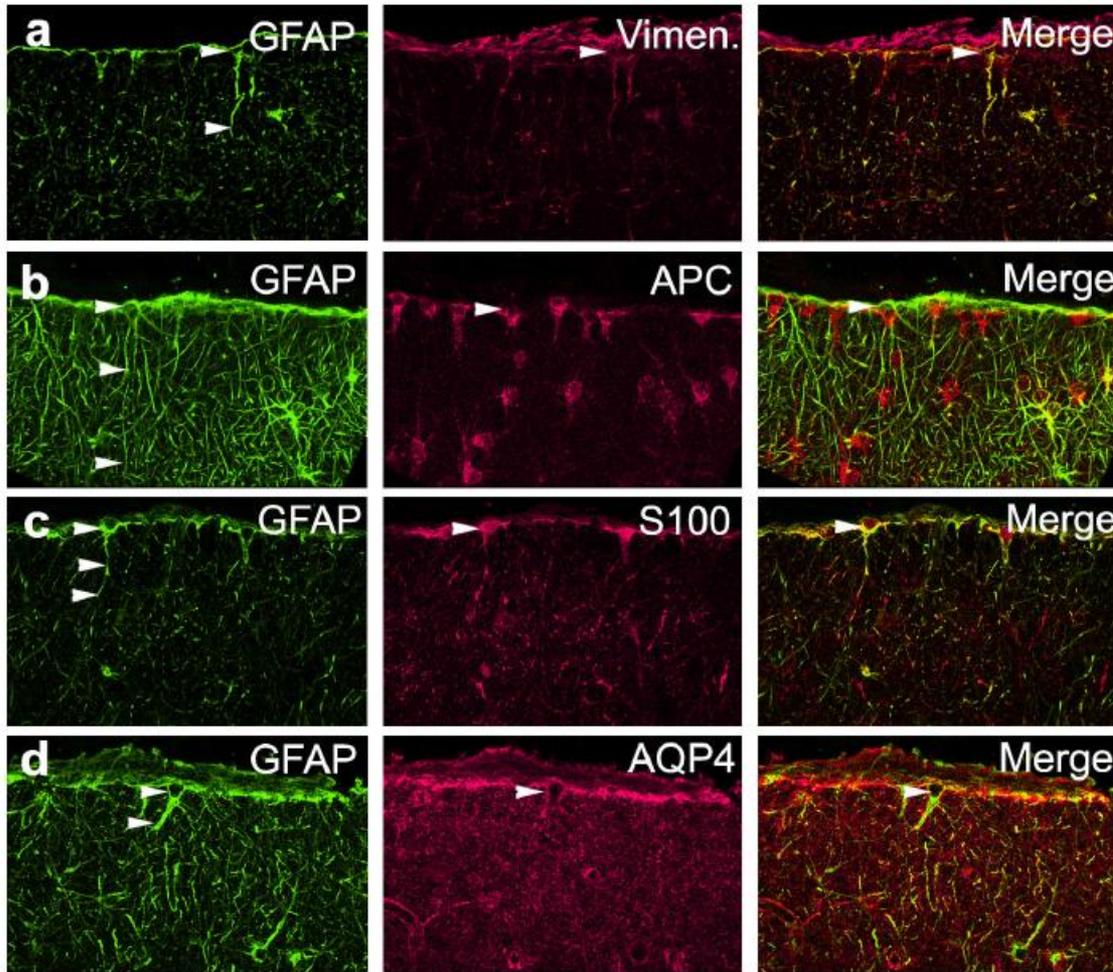


Human
Ramón y Cajal, 1904



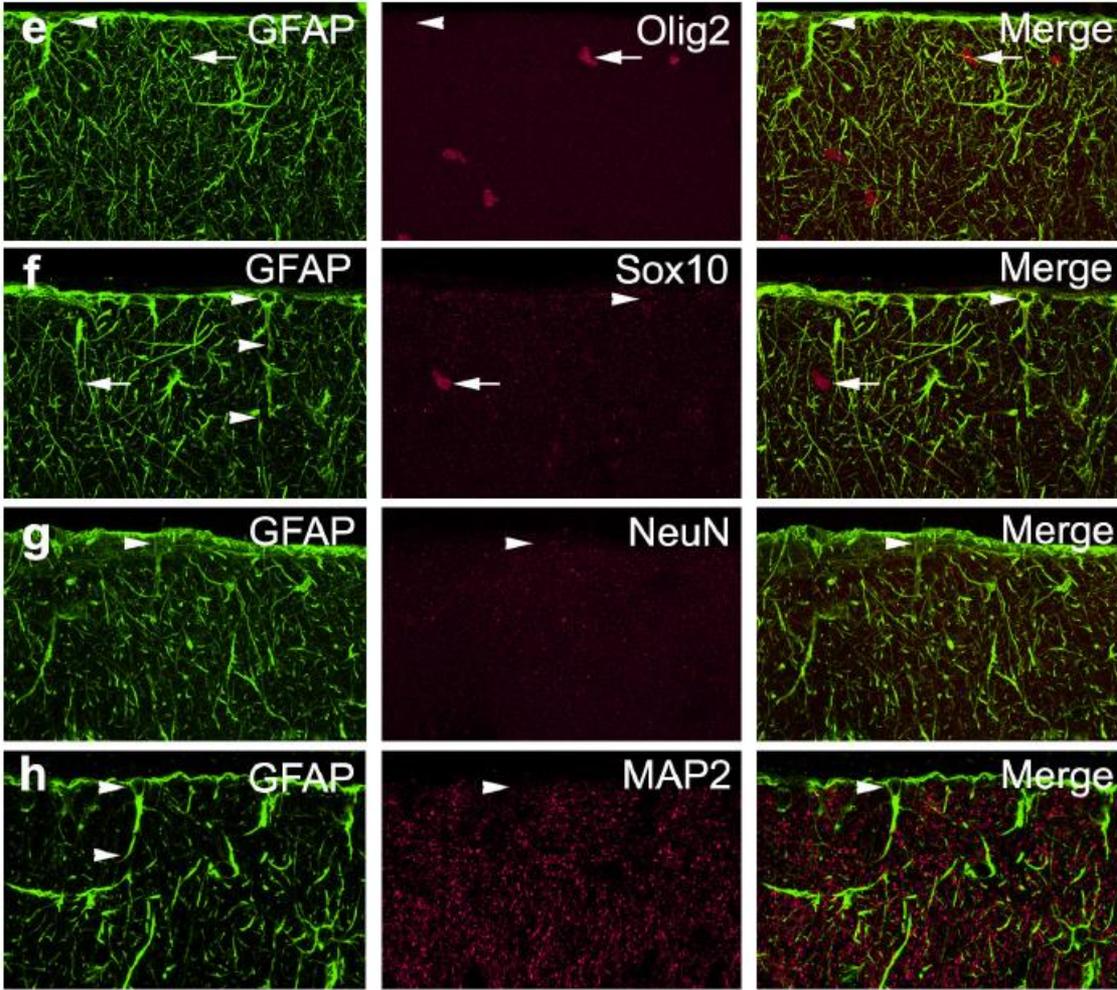
Adult capuchin monkey
(*Cebus apella*)
Colombo, 1994

Which marker do ILAs express?



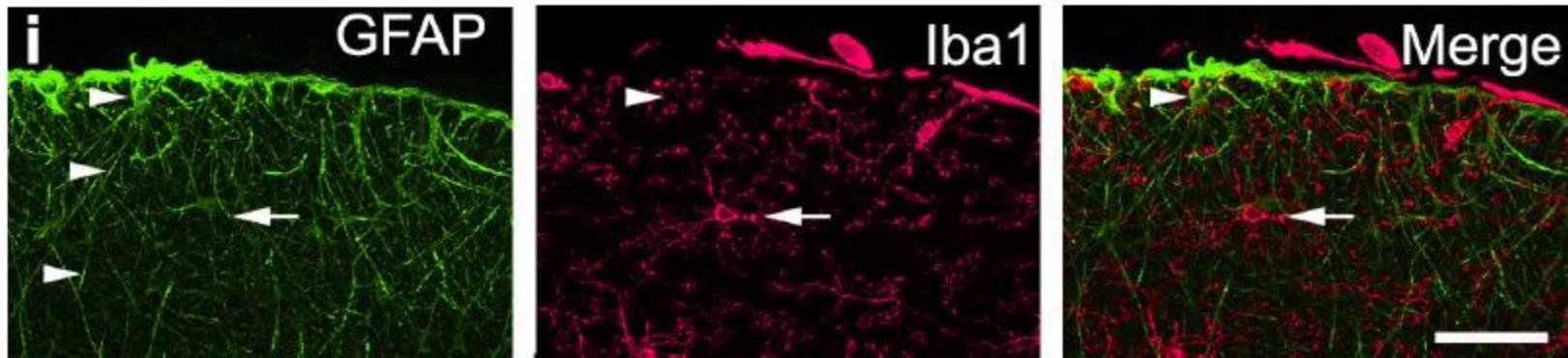
ILAs express astrocytic markers.

Falcone et al., J Comp Neurol 2018



ILAs do NOT express oligodendroglial nor neuronal markers.

Falcone et al. 2018



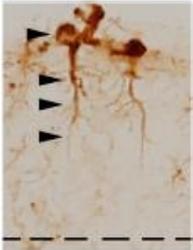
Astrocyte markers: GFAP+, S100+ , AQP4+, APC+
 Oligodendrocyte markers: Olig2-, Sox10-
 Neuron marker: NeuN-, MAP2-
 Microglia marker: Iba1-

ILAs show ASTROCYTE identity.

Interlaminar Astrocytes (ILAs)

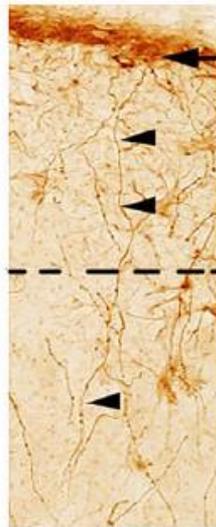
1. Evolution: *When did they appear?*
2. Development: *When are they born?*
3. Function: *What do they do?*

All mammals have ILAs



Some have rudimentary
ILAs
(= not crossing layer I)

Mus musculus
(mouse)



Procavia capensis
(rock hyrax)



Some have typical ILAs
(=crossing layer I).



Falcone et al., *J Comp Neurol* 2018

ILA linear density across evolution

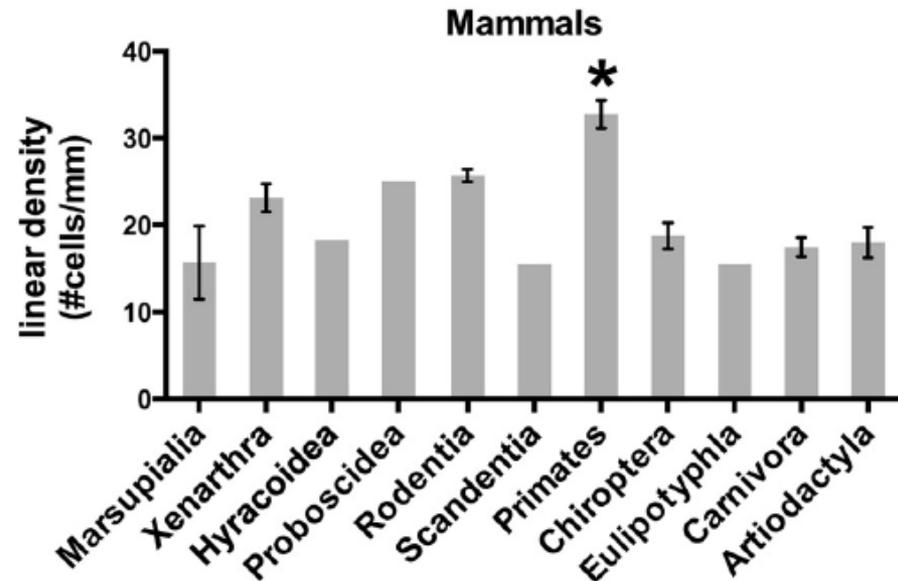


Methods

- IHC anti-GFAP (DAB)
- Pictures 40x oil
- Count cells
- Measure #cells/mm pial

ILA linear density across evolution

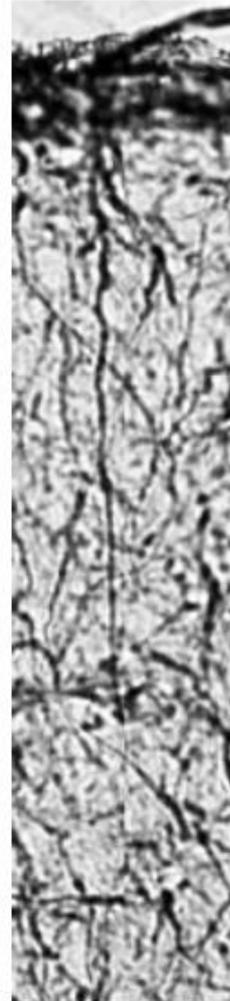
Primates have higher ILA density.



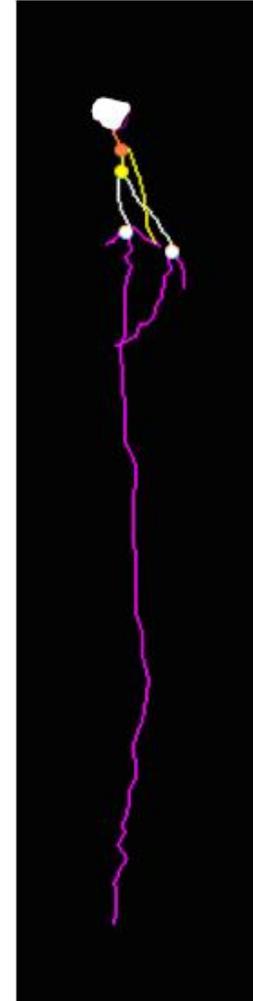
ILA morphology across evolution

Methods

- IHC anti-GFAP (DAB)
- Imaging in real time (Z-stack)
- Neurolucida 8 software
- 3D traces reconstruction
- Analysis of:
 - # primary processes
 - # total processes (branching)
 - Total length
 - Complexity index



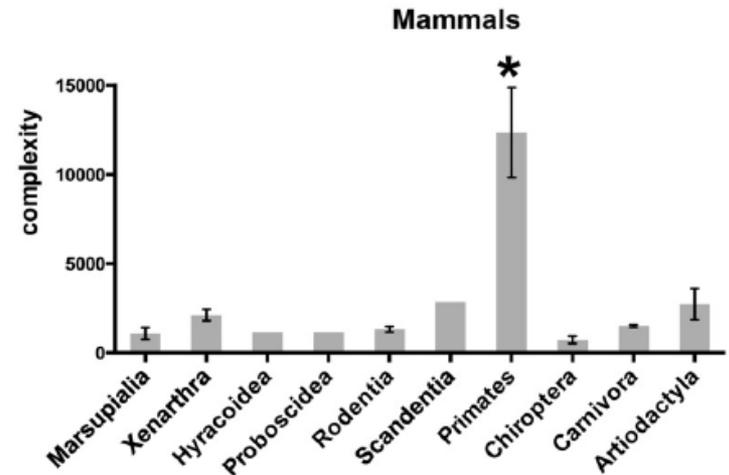
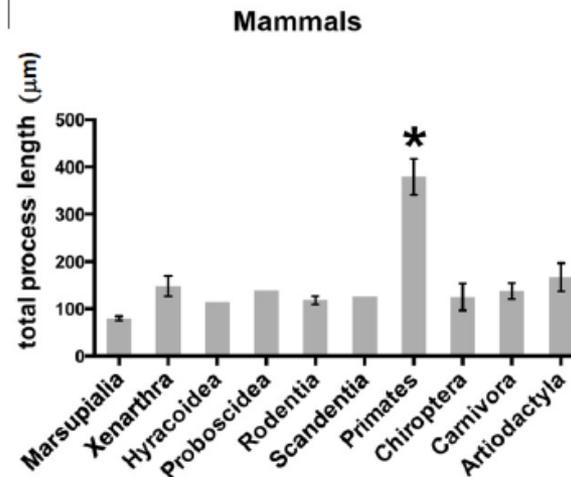
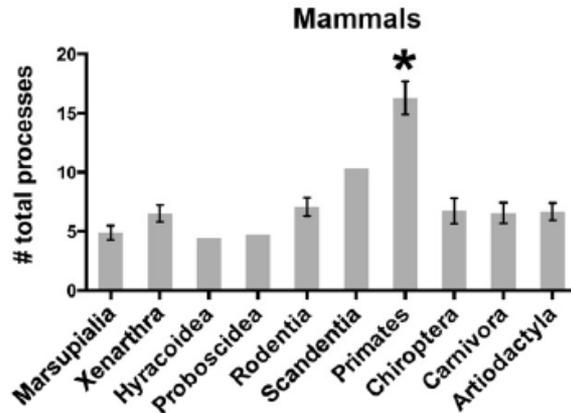
Live imaging



Neurolucida reconstruction

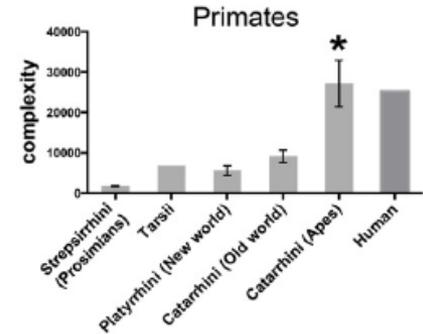
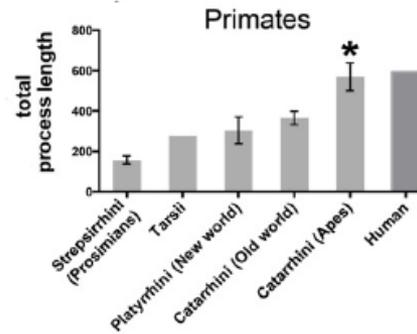
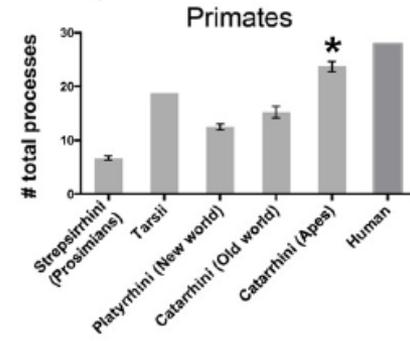
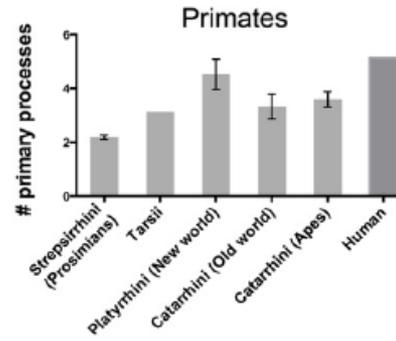
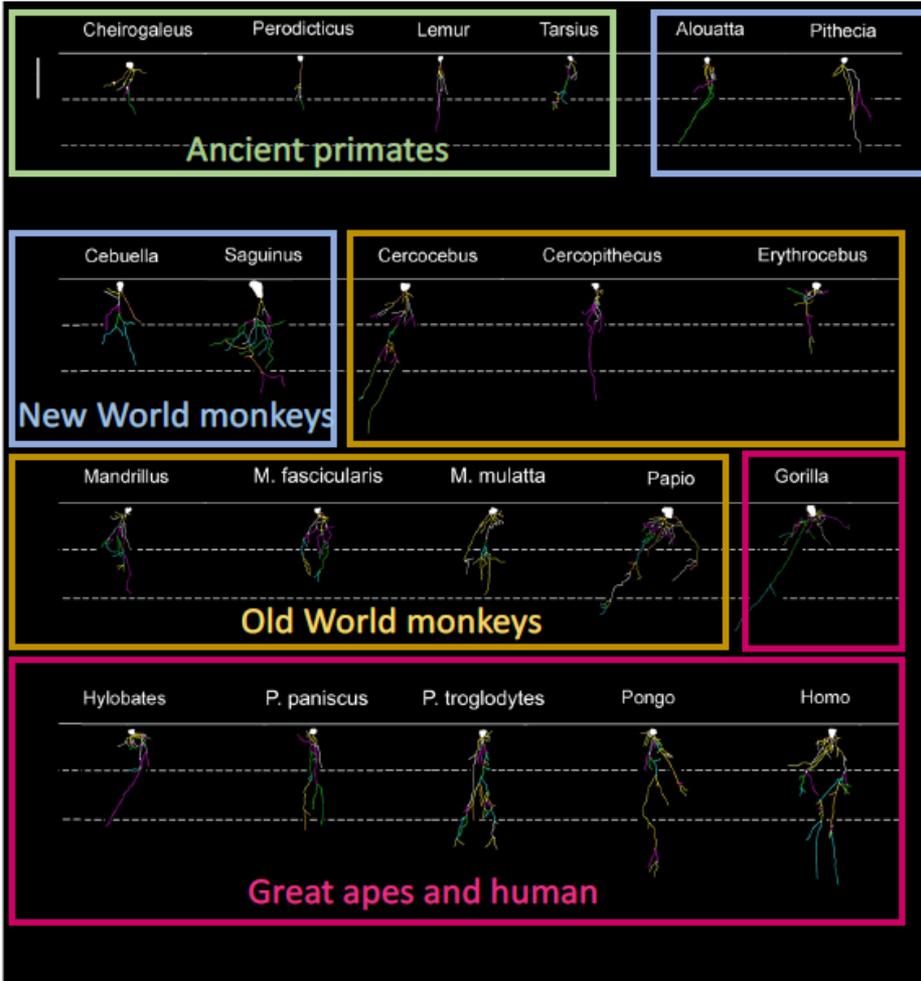
Why are ILAs morphologically special in Primates?

Primate ILA processes are more numerous, longer and more complex.



Falcone et al., 2018

PRIMATES



Among primates, **great apes** show ILAs with more branching and longer processes.

Falcone et al., 2018

The hypothesis

ILAs can be crucial players in regulating inter-layer connectivity by modulating synaptogenesis.



Oligodendrocyte evolution

Oligodendrocyte functions

Many of the functions are related to myelin

Myelin-related functions

1. To protect nude axons

Virchow (1854): « It serves as an isolating mass, that confines electricity within the nerve» (comparison with under sea cables)

Ranvier (1878): «Electrical wires immersed in a conductive medium need to be Protected from this medium by a non-conductive sheath.»

Myelin-related functions

2. To accelerate the speed of nerve conduction

To accelerate: increase axon diameter or wrap the axon with myelin

non-myelinated invertebrate axons
(1m/s in 10 μ m diameter axons) \rightarrow OK for small size animals

In vertebrates, rigid bony structures \rightarrow Increase diameter is not possible;
Myelin is needed for bigger size/longer distance

Myelin-related functions

3. To provide nutrient and support to axons

Transport along axons can be fast or slow

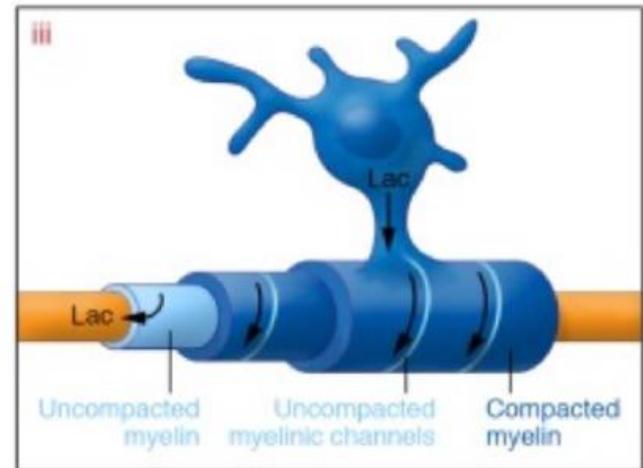


Soluble molecules
e.g. Glucose, lactate



Traffic vesicles

Oligodendrocytes transfer lactate to axons through monocarboxylate transporter (at the paranodal loops)



Morrison et al., 2013

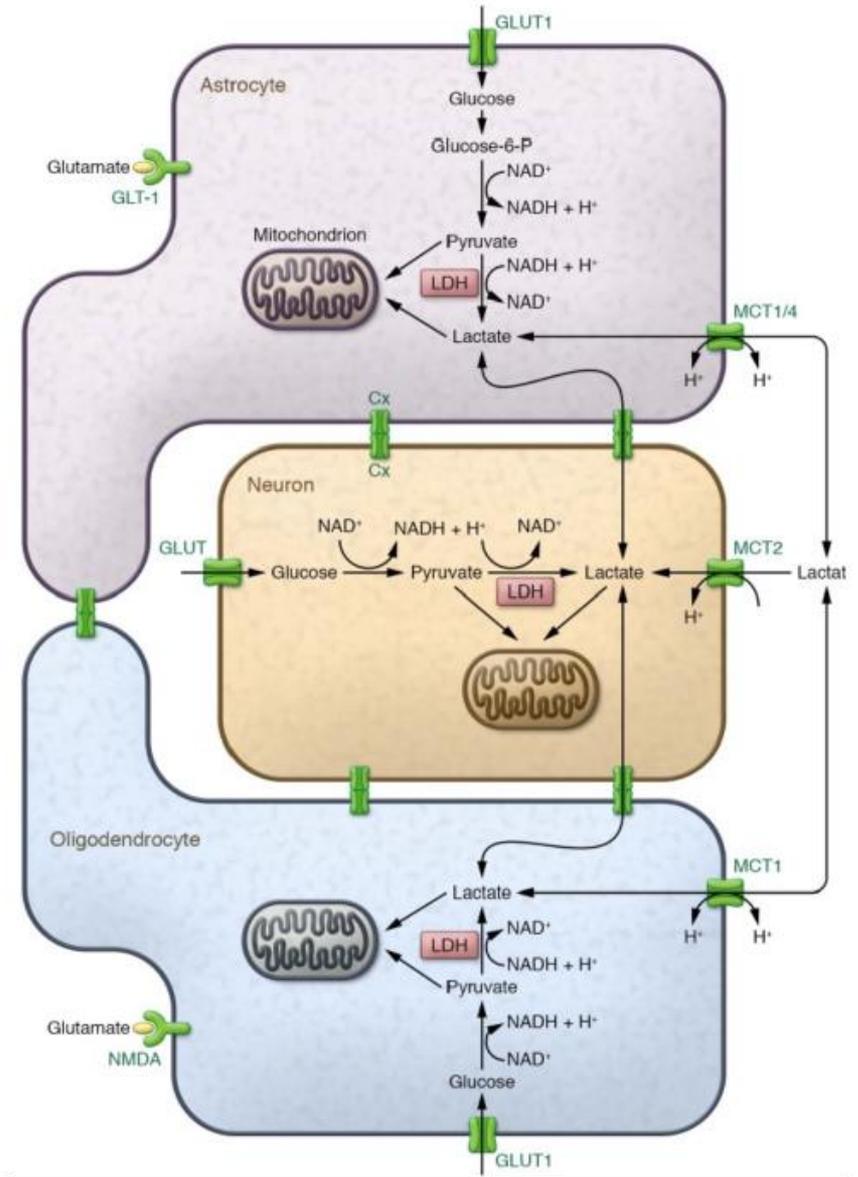
Myelin-related functions

3. To provide an additional form of neural plasticity

Experience-dependent adaptations to myelination

Hines et al., 2021

Crosstalk neurons-astrocytes-oligodendrocytes



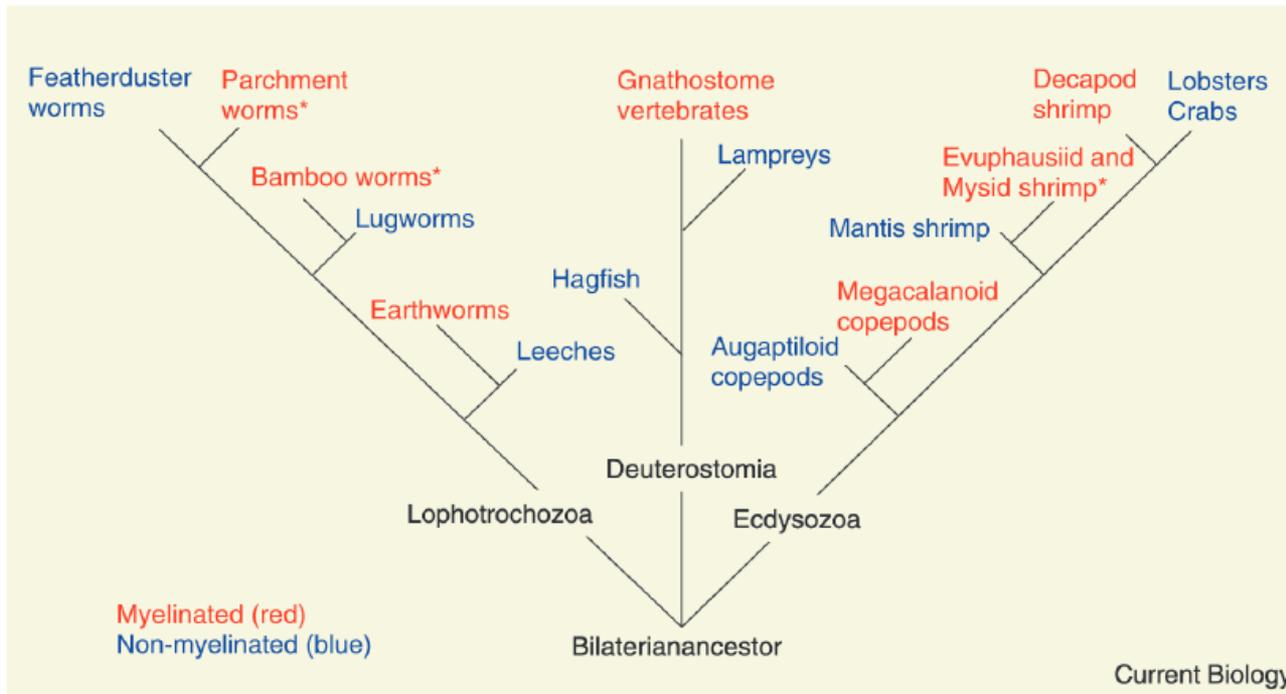
When during evolution has myelin first appeared?

Ensheathing glia in invertebrates

First observed in the living vertebrates

Possibly a prerequisite to permit larger size.

Are only vertebrates myelinated?



- Reports of myelin-like structures in anellid and crustaceans (not all of them..)
- Myelin-like: concentrically arranged membranes, incomplete compactness

Hartline et al., 2007

Myelin-like structures (invertebrates) vs myelin (vertebrates)

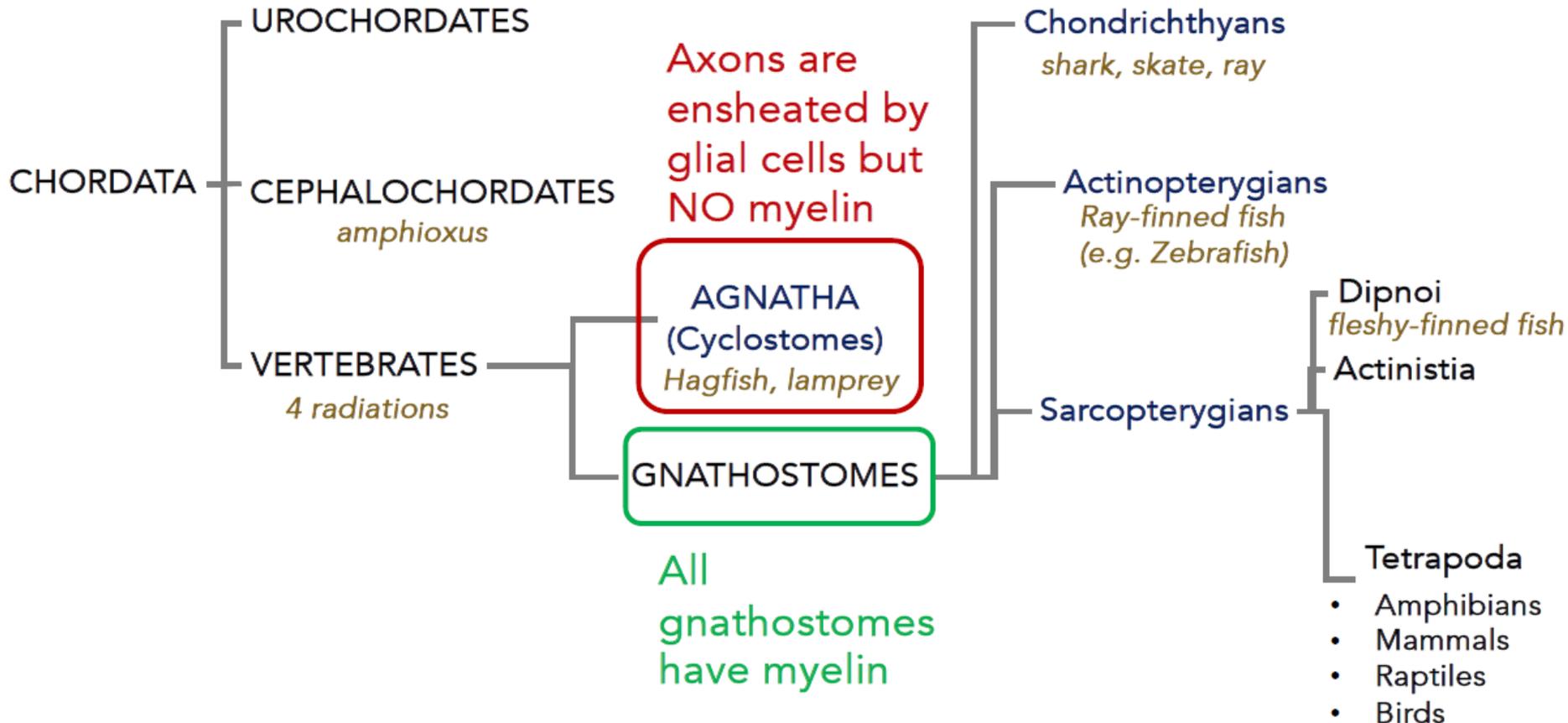


Concentrically deposited membranes
Less compact
Not present in all the species
(separate/convergent evolution)



Spirally wrapped
Adopted by many species

Are all vertebrates myelinated?



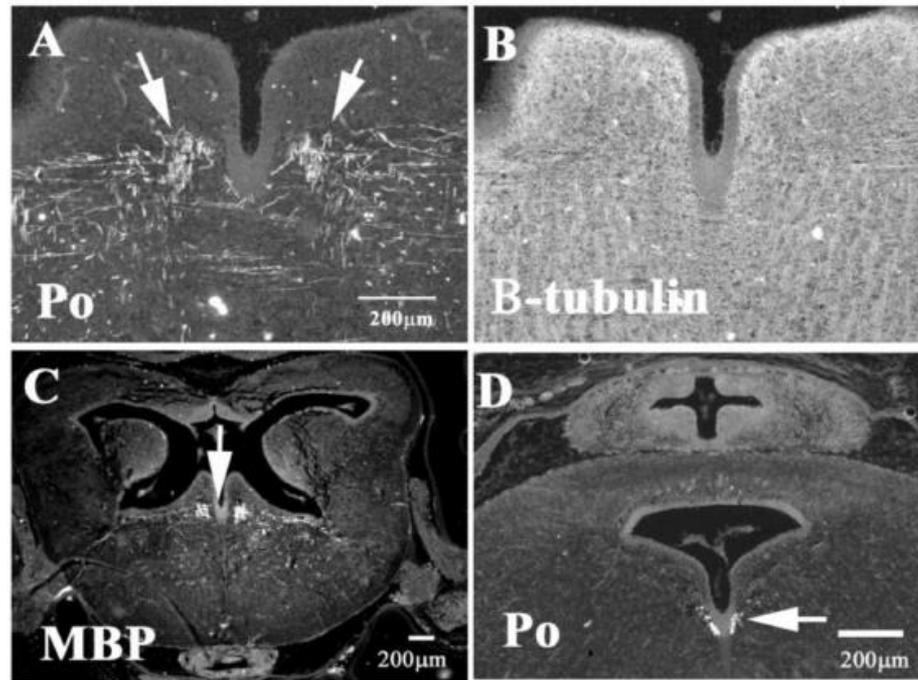
Are all vertebrates myelinated?

- Chondrichthyans are the most ancient living species with myelin

Both in CNS and PNS

Cellular similarities

Sequence homologies with mammalian myelin



Rotenstein et al., 2008

Myelin composition across species

- Similarities: galactosphingolipids (galactocerebroside and sulfatide)
- Differences:
 - P0 : main protein in fishes
 - PLP and MBP: major protein in amphibian and all others..

When during evolution has myelin first appeared?

First myelin observations In the living vertebrates

NO myelin
lamprey



Fully myelinated
sharks

Fossils?

Compared
nerve imprints
in fossilized
skulls of
ostracoderms
and placoderms

Myelin first acquired 425 MY
ago by placoderms
(early hinge-jaw fishes)

Zalc et al., 2016

Where has myelin initially appeared: CNS or PNS?

Fibers are myelinated by Schwann cells in PNS and oligodendrocytes in CNS.

If cell were myelinated in one system and not the other, Signals would have slowed down abruptly

Hp: Once the myelinating program started to evolve in one cell type, all or part of the program could have been activated in other cells, given the appropriate cues. (Li & Richardson, 2008)

Simultaneously in CNS and PNS

Myelination depends on an axonal signal

In co-culture of neurons and oligodendrocytes: oligos myelinate only axons

Not all axons are myelinated



Specific attracting signals on axons
to be myelinated

Neuregulin-1 type III for Schwann cells;
For Oligodendrocytes?

A new cell type dedicated to myelination: Oligodendrocytes have a multiple origin

Myelin look the same, oligodendrocytes are different depending on the developmental origin.

- PDGFRa signaling dependence
- Molecular cues to induce oligodendrogenesis (only ventral, or dorsal too? – not all dependent on Shh signaling)
- Dependence on Hox gene family

Other oligodendrocyte functions

Possible also without myelin

- Provide metabolic support
- Influence axonal and dendritic growth
- Regulate inflammation and angiogenesis
- Produce extracellular matrix to form perineuronal nets
- Influence BBB function

Hines et al., 2021

Evolutionary origins of oligodendrocytes

Where do oligodendrocytes come from?

Did they appear concomitantly with myelin?

Much less is known about evolution of oligodendrocyte cell types.
Evolutionary origins are unknown, different models.

e.g., teleost OPCs regulate circuit development in visual system.

Possible ancestral oligodendrocytes: Axial glia in amphioxus

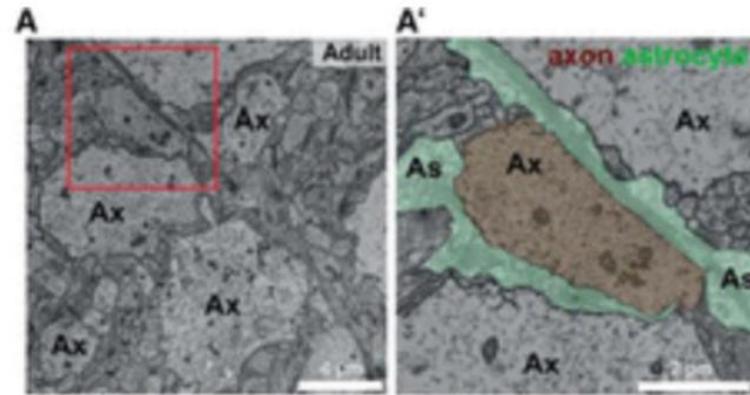
Axial glia: structure similar to gnathostome OPCs and non-myelinating oligodendrocytes

Molecular signatures and functions are still under investigation (they found astroglial gene and RG expression in amphioxus)

Possible ancestral oligodendrocytes: Multifunctional glia in lamprey

Cells that wrap axons
Express molecular markers similar to astrocytes

Multifunctional glial cell



Possible ancestral oligodendrocytes: SoxE factors

SoxE factors (homologous to gnathostome Sox8, Sox9 and Sox10)
Expressed in ventral spinal cord glia in lamprey

..and in developing hagfish and amphioxus spinal cord

Importance to look into the spinal cord!

Yuan et al., 2018; Ota et al., 2007; Jandzik et al. 2015

Defining the gnathostome oligodendrocyte cell type

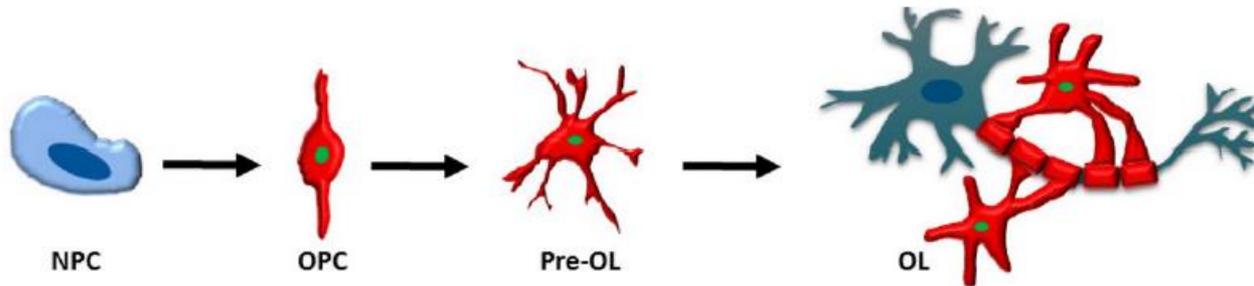
We need a comprehensive definition, unrelated to myelination

1. Morphology and functions
2. Genetic profile

1. Morphological properties of oligodendrocytes

- Simple bipolar morphology

- Complex/branchy morphology



- Ultrastructure for non-myelinating oligodendrocytes:
-unknown

- Ultrastructure for myelinating oligodendrocytes:
 - small size
 - chromatine density
 - no intermediate filaments
 - many microtubules

Kuhn et al., 2019

2. Genetic profile: a core genetic regulatory network (GRN)

- GRN that should be conserved across evolution...
- Hines proposes that GRN is likely conserved and therefore can be used as an identifier in the search for oligodendrocytes
- Alternative possibility: not conserved, oligodendrocytes in different species exhibit similar morphology/functions, with different GRNs

Looking for a core genetic regulatory network (GRN) in developmental programs

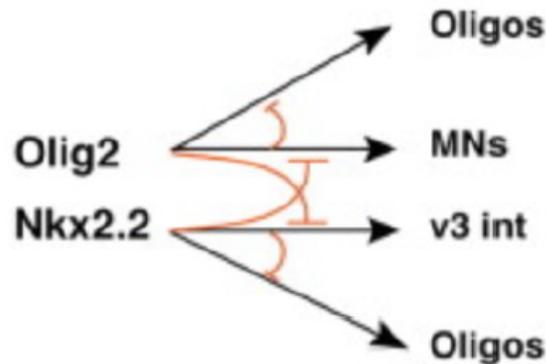
- *Olig2*

→ Oligodendrocyte production and differentiation (in mouse, zebrafish, chick, human)

→ in developing spinal cord:

→ KO in mouse

→ KO in zebrafish



Zhou et al, 2001

- SoxE group: Sox8, Sox9, Sox10

→ Both Oligodendrocyte specification and myelination

→ Sox10 role in development (expressed by OPCs and differentiating oligodendrocytes)

→ *sox10* mutants in zebrafish and mice: more OPCs but deficit in oligodendrocyte differentiation and myelination

→ SoxE in lamprey spinal cord development

Yuan et al, 2018

- Ascl1

→ Oligodendrocyte production in mice

Parras et al., 2004

- Ascl1a, Ascl1b

→ Oligodendrocyte production in zebrafish (?)

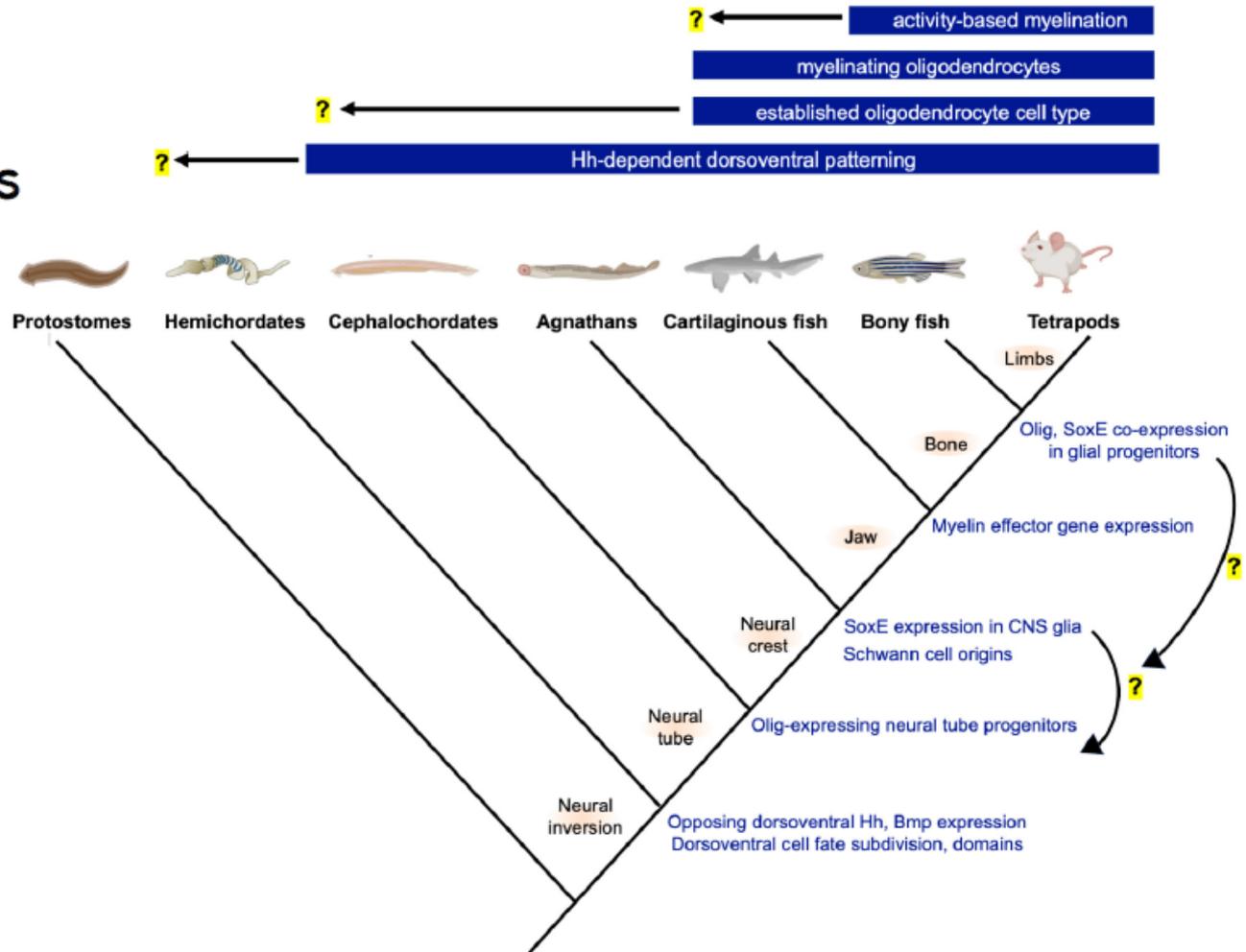
Scott et al., 2021

- Nkx6.1

→ Oligodendrocyte production in mice (by promoting Olig2)

Liu et al., 2003

Phylogeny and evolution of oligodendrocytes



Hines et al. 2021

Origins of vertebrate myelin and adaptive myelination

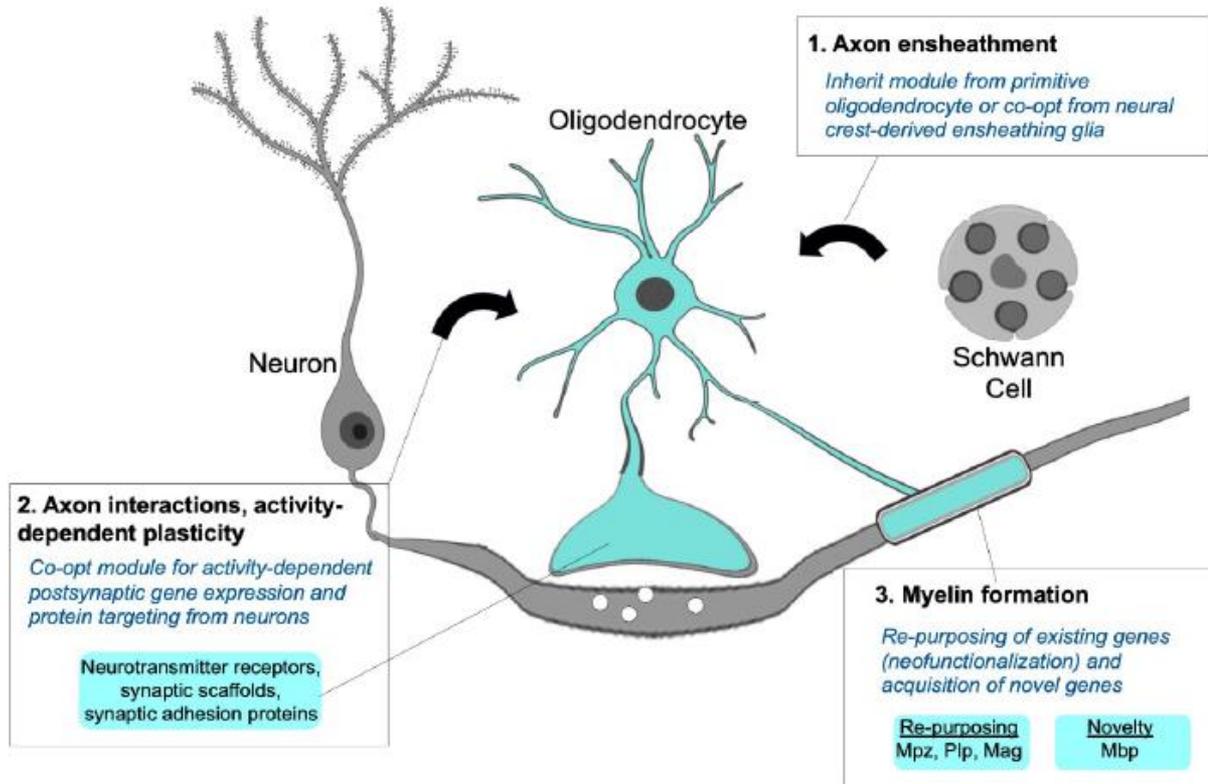


FIGURE 5 | Module integration responsible for the origins of the myelinating phenotype. A hypothetical model proposes the myelinating apomere integrating modules for axon ensheathment (1), activity-dependent axon interactions and structural remodeling (2), and formation of compact myelin sheaths (3). Primitive oligodendrocytes may not have possessed all modular components, but their novel and combined use for myelination can be explained through co-option from neurons and non-myelinating Schwann cells along with the recruitment and re-purposing of existing genes required to form myelin sheaths.

Hines et al. 2021

The acquisition of myelin: An evolutionary perspective

B. Zalc

Evolutionary Origins of the Oligodendrocyte Cell Type and Adaptive Myelination

*Jacob H. Hines**

Biology Department, Winona State University, Winona, MN, United States

Myelin proteins in land-living vertebrates

Myelin basic proteins (MBPs)

Structurally glue together myelin membrane leaflets at the cytoplasmic face

Protelipid protein (PLP) and DM-20

Effects on membrane fusion at the extracellular side

CNPase

(lipid-anchored membrane surface protein)

Only in oligodendrocytes, 2 isoforms: CNP1 and CNP2

Influence branching and process formation in oligodendrocytes

Myelin associated glycoprotein (MAG)

In the periaxonal membrane space of CNS and PNS myelin fibers

Accelerated evolution of oligodendrocytes in the human brain

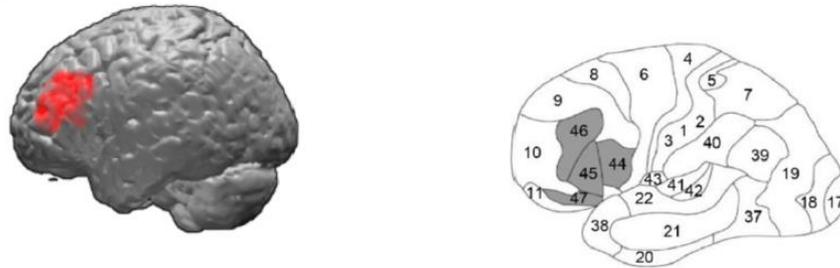
Stefano Berto^{a,1}, Isabel Mendizabal^{b,1}, Noriyoshi Usui^{a,c,d,1}, Kazuya Toriumi^{a,e,1}, Paramita Chatterjee^b, Connor Douglas^a, Carol A. Tamminga^f, Todd M. Preuss^{g,h,i}, Soojin V. Yi^{b,2}, and Genevieve Konopka^{a,2}

- Increased brain size + increased neuron numbers in primates (incl. humans)
- These changes alone cannot entirely account for the evolution of human cognitive abilities
- Changes in gene expression hypothesized as key in human brain evolution: previously shown extensive changes in neurons
- Oligodendrocytes show altered functional and disease-related patterns in humans vs. non-human primates

Methods

Sorted nuclei from humans, macaques and chimpanzees

Analyze genome-wide expression levels in adult human BA46 and homologous regions in chimpanzee and rhesus macaque



Conclusions

- Insights into cell-type, species-specific expression patterns during primate evolution
- Gene expression in the oligodendrocytes has undergone more dramatic acceleration in the human lineage compared with neurons
- Previous comparative primate gene expression studies were likely underpowered to detect these nonneuronal expression changes

Adult neurogenesis and regeneration in the vertebrate brain

1. Adult neurogenesis in vertebrates

2. Regeneration in vertebrates

Proliferation, neurogenesis and regeneration in the non-mammalian vertebrate brain

Jan Kaslin, Julia Ganz and Michael Brand*

Post-embryonic growth of the CNS in vertebrates

- In adult **mammalian** brain:
- low rate of gliogenesis
 - restricted neurogenesis
 - does not contribute to actual brain growth
- In adult **bird** brain:
- Max brain growth reached 1 month after birth (*exception: songbirds*)
- In adult **fish, amphibians & reptiles** brain:
- Number of brain cells increases with age, and body weight and size
 - specific brain regions have differential growth

In adult fish, amphibians & reptiles brain:

- Number of brain cells increases with age, and body weight and size
- specific brain regions have differential growth

In teleosts and amphibians:

Optic tectum and retina growth continuously during the lifespan

Some teleosts:

Lifelong differential growth-related shifts in relative sizes of sensory brain regions



related to the lifestyle!

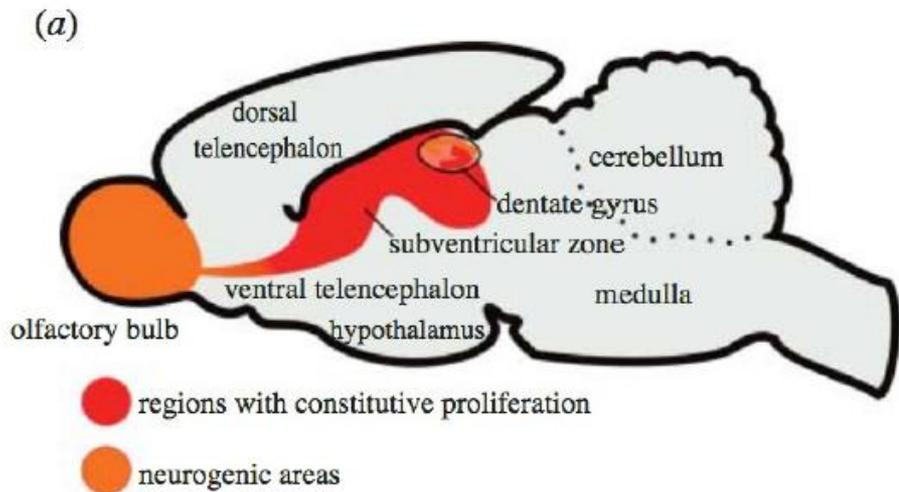
Post-embryonic growth of the CNS in vertebrates

A comparison of brain regions where constitutive adult neurogenesis occurs in vertebrates:

	mammals	birds	reptiles	amphibians	teleost fish
olfactory bulb	(+)	–	+	–	+
<i>telencephalon</i>					
ventral telencephalon/subpallium/SVZ	+	+	+	+	+
dorsal telencephalon/medial pallium/hippocampus	+	+	+	+	+
<i>diencephalons</i>					
preoptic region	–	–	–	+	+
epithalamus, habenula	–	–	–	–	+
thalamus	–	–	–	+	+
hypothalamus	–	(+)	–	+	+
pretectum	–	–	–	–	+
<i>mesencephalon and rhombencephalon and spinal cord</i>					
tectum	–	–	–	+	+
cerebellum	(+)	–	+	+	+
midbrain	(+)	–	–	+	+
vagal complex	(+)	–	–	–	+
spinal cord	(+)	–	–	–	+

Adult neurogenesis is restricted to proliferation zones in the CNS of vertebrates

Adult neurogenesis in mammals

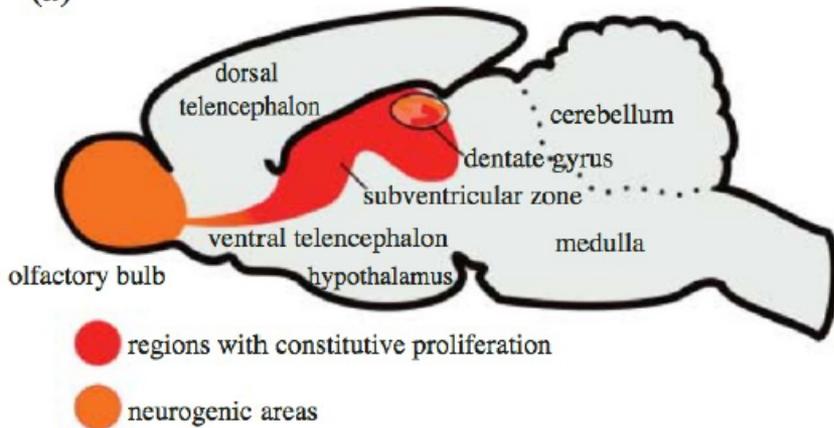


- 2 main regions of proliferation:
 - Subventricular zone (SVZ)
 - Subgranular zone (SGZ)

Transient proliferation in the cerebellum

Adult neurogenesis in mammals

(a)



➤ Subventricular zone (SVZ)

- most abundant
- neuroblasts migrate to the olfactory bulbs
 - Rostral migratory stream (RMS)
- differentiate into GABA-ergic interneurons
- astrocytes envelop the stream
- only a fraction mature, the rest die

➤ Subgranular zone (SGZ)

- In the innermost subgranular cell layer of dentate gyrus
- Neuroblasts migrate short distance (into the granular layer)
- Most of them die, the rest integrate into the circuit

Adult neurogenesis in mammals: other putative proliferative zones

- Amygdala
- Hypothalamus
- Midbrain
- Spinal cord

Unclear mechanism, needs more studies

Adult neurogenesis in non-mammalian vertebrates

Proliferation and adult neurogenesis occurs extensively in different brain regions in non-mammalian vertebrates.

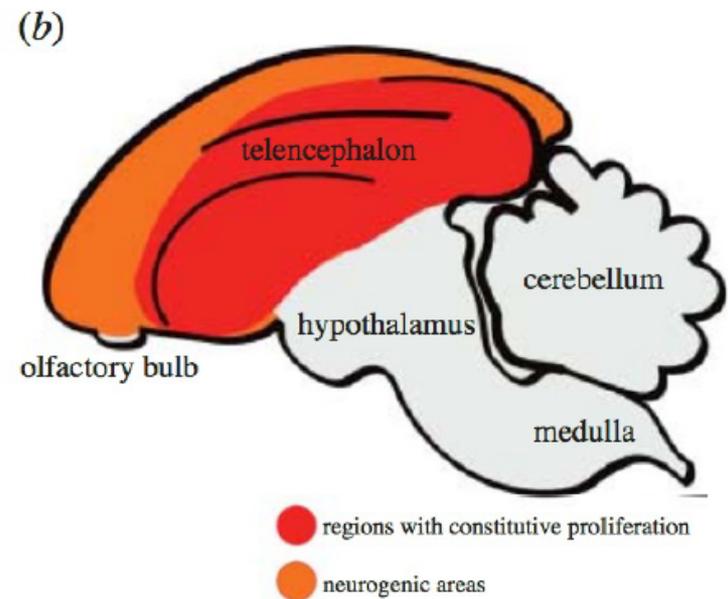
Details of mechanisms are still under investigation.

Adult neurogenesis in birds

- constitutive proliferation along the **telencephalic lateral ventricles**
 - “hot spots”

In adult **songbirds**

- neuroblasts migrate tangentially and then radially along RG scaffolds
- Many of them die (2/3)
- Neurons integrated into high vocal center circuitry (HVC)
- In hippocampus the newborn neurons replace the ones that die (no increase of neuron number)

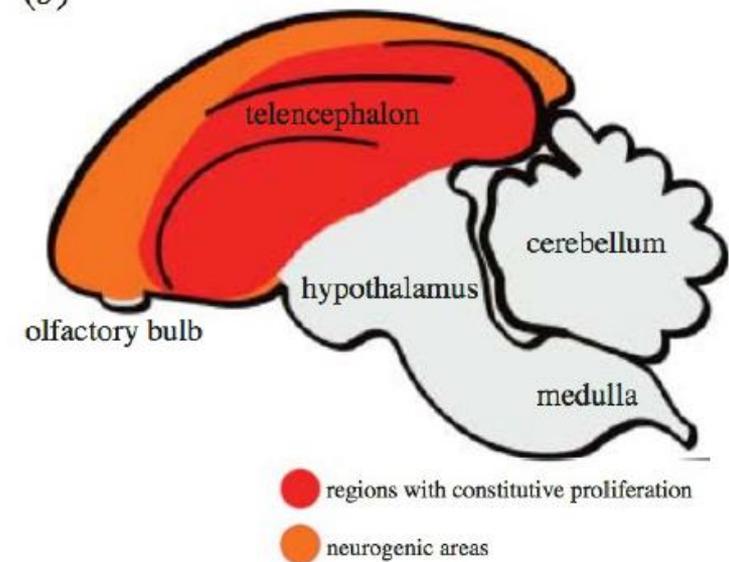


Adult neurogenesis in birds

In adult **dove**

- New neurons added to the forebrain (no specific nucleus destination)
- Age-related decline of neurogenesis

(b)



Lizard medial cortex

RG cells close to ventricle give rise to neuroblasts that migrate into granule cell layer (at random levels in the cortex).

Species difference in the number of cells that migrate along radial glia



Tropical lizard

<30% migrate along RG

European lizard

90% migrate along RG



Only a few newborn cells degenerate in reptile adult brain, most of them survive and integrate into circuits.

Adult neurogenesis in amphibians and fish

In adult **amphibians**, adult proliferation observed in:

- Telencephalon
- Preoptic region
- Thalamus
- Hypothalamus
- Midbrain
- Cerebellum

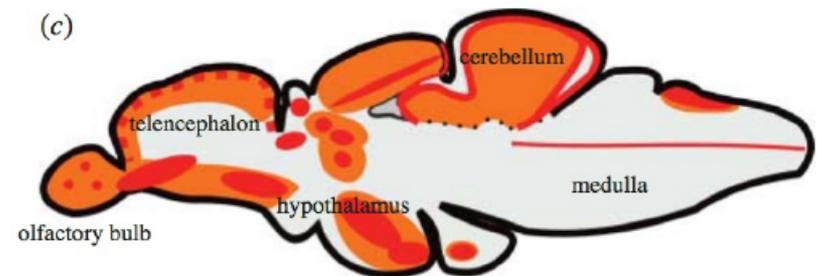
In adult **cyclostomes and chondrichthyans**:

- Rhombencephalon in the lamprey

Adult neurogenesis in amphibians and fish

In adult **teleost**, adult proliferation studied in 3 species only (including zebrafish):

- More than 10 distinct proliferative zones (along A/P axis)
 - Olfactory bulb
 - telencephalon,
 - Thalamus
 - Epithalamys
 - Preoptic region
 - Hypothalamus
 - Tectum
 - Cerebellum
 - Rhombencephalon
 - Spinal cord

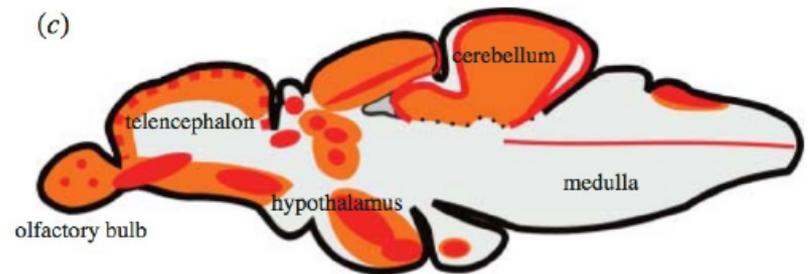


Adult neurogenesis in amphibians and fish

In adult **teleost**, adult proliferation studied in 3 species only (including zebrafish):

- More than 10 distinct proliferative zones (along A/P axis)

Adult zebrafish telencephalon express different TFs than embryo.



Most of the newly formed neuroblasts migrate slowly and differentiate into neurons (of different kinds: Glut, TH, PV)

Phylogenetic reduction of active proliferation zones

During evolution, the number of constitutively active adult proliferation has been reduced (transition between anamniotes-amniotes, and during mammalian radiation).

Why did this happen?

Phylogenetic reduction of active proliferation zones

Hypothesis 1

Loss of proliferative zones in mammals is an adaptation to keep neuronal population with their experience for the entire lifespan (e.g. primates).

AGAINST:

- Non mammalian vertebrates have high degree of neural complexity too
- Birds, fish, reptiles also live long

Phylogenetic reduction of active proliferation zones

Hypothesis 2

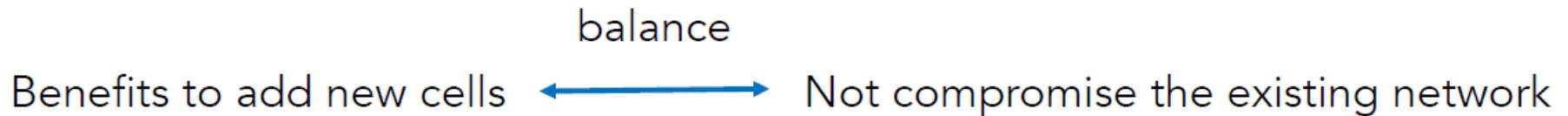
Non-mammalian vertebrate adult neurogenesis might be related to brain growth in response to growth of the sensory system.

- Need to increase CNS processing power for primary sensory input (e.g. retina and optic tectum in amphibians and fish)
- In "smell-oriented" mammals, more neurons added to the olf. bulb

Phylogenetic reduction of active proliferation zones

Hypothesis 3

Resistance to integrate new cells into a mature neural network.



- Newly born neurons in the adult may be more plastic (in both hippocampus and olfactory bulb)

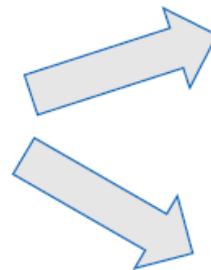
Phylogenetic reduction of active proliferation zones

Neurogenesis might be suppressed in adult mammalian brains, since it is possible to induce proliferation and neurogenesis in non-neurogenic brain regions (e.g. injury).

Compensatory neurogenesis and regeneration

- High capability of non-mammals to regenerate severe brain injuries
- Compensatory proliferation and neurogenesis in response to injury happen in all vertebrate CNS.

Different types of injuries



Ectopic neurogenesis

Enhanced proliferation at constitutive sites and migration to the injury site

Implications for therapies!

Compensatory neurogenesis and regeneration in mammals

- Compensatory proliferation and neurogenesis exist in mammals in response to an injury or disease
 - Alzheimer's, Huntington
 - Focal ischemia
 - stab wounds in mice
- Normally these precursors fail to generate neurons
- New promising results (glial cells)

Compensatory neurogenesis and regeneration in birds

- Compensatory proliferation and neurogenesis, and also functional integration of interneurons and long projecting neurons in birds.
 - After ablation of neurons
 - 3 types of neurons are regenerated: interneurons, HVC-RA and HVC-X long projecting neurons
 - recover singing abilities

Compensatory neurogenesis and regeneration in reptiles

- High capacity to morphologically and functionally regenerate severe lesioning
 - Lesioning with neurotoxins
 - 1-2 weeks after, newly produced cells from constitutively proliferating zones
 - 4-8 weeks functional restoration of the damaged area

Compensatory neurogenesis and regeneration in amphibians

- High regeneration of the peripheral nervous system, tail and limbs (newt, *Xenopus*)
- Morphological regeneration of optic tectum or telencephalo (in 3 months)
 - After lesions in telenc./ tectum, several proliferative zones activate to produce more cells and regenerate the lesion
 - Higher regeneration during larval stages, less after metamorphosis

Compensatory neurogenesis and regeneration in fish

- High capability for regeneration of the CNS (including spinal cord and retina) in teleosts
 - After incisions or ablation of whole parts
 - Stab wound example
 - If also constitutively active proliferative zones are removed, the level of regenerative capacity decreases

Induced proliferation and neurogenesis in the adult CNS

- EGF
- FGF2
- TGF- α
- EphB2
- VEGF



Increased proliferation and neurogenesis

If some vertebrates can regenerate CNS injuries why cannot we?

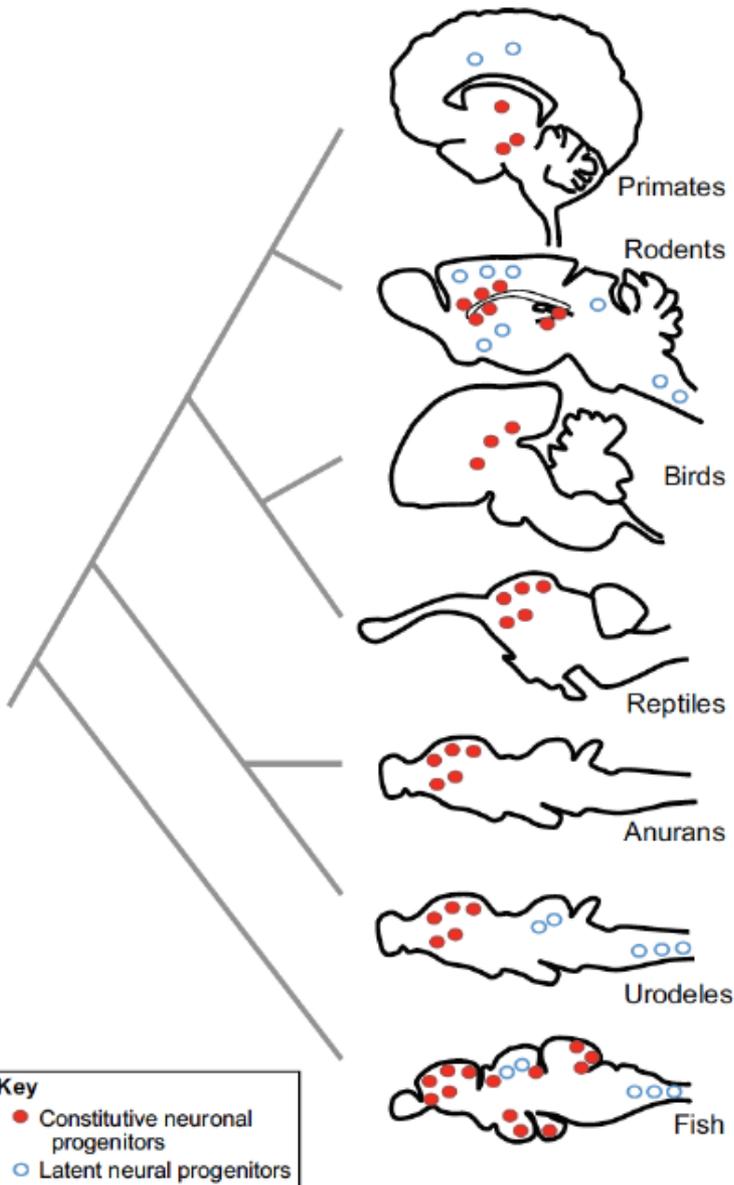
Adult stem cells and radial glia

In mammals

- A small fraction of RG persists in the adult
- astrocytes

In non-mammals

- RG is retained in the adult (in regions where constitutive neurogenesis takes place)
- E.g. birds, reptiles



Key

- Constitutive neuronal progenitors
- Latent neural progenitors

	Adult neurogenesis	Latent progenitors	Reparative neurogenesis
F	+	+	-
M	-	?	-
Sc	-	?	-
R	-	?	-
F	+	+	-
M	-	+	-
Sc	-	+	-
R	-	+	+/-
F	+	?	+
M	-	-	-
Sc	-	-	-
R	-	+	+
F	+	?	+
M	-	?	-
Sc	-	?	-
R	-	-	-
F	+	?	-
M	?	?	-
Sc	-	?	-
R	+	+	+
F	+	?	+
M	-	+	+
Sc	+	?	+
R	+	+	+
F	+	?	+
M	+	?	?
Sc	-	+	+
R	+	+	+

Summary

- Adult brain proliferation and neurogenesis are conserved characteristics of all vertebrates
- In mammals, adult neurogenesis occurs mainly in 2 regions, while non-vertebrates have a higher amount of adult neurogenesis in those and additional brain regions
- Fish, amphibians and reptiles display post-embryonic brain growth (e.g. sensory systems)
- Regeneration can occur to different extent in vertebrates after lesions or disease
- Different adult stem cells or glial cells are responsible for compensatory proliferation and regeneration after injury



Evolution and Adaptation of the Brain and Behavior

1. Phylogeny and adaptation

2. Complexity and evolution

3. Brain evolution and behavioral adaptation

Phylogeny and adaptation

adaptation: Process by which a species adjusts to environmental changes.

→ Evolutionary change



Random change in a population (that brings advantage)

How do we study evolution of the CNS behavior?

Comparative study on behavior of extant (living) animals (NOT fossils).

Phyletic vs adaptation studies

both comparative studies
SELECT THE RIGHT SPECIES TO STUDY!

Phyletic studies

Choose related species

WHAT changed?

Adaptation studies

Choose species with
common (behavior) features
(similar environment)

HOW changed?

Evolutionary change and development

Phyletic studies

Aim: reconstruct the evolutionary history of the development of some parts of the NS or a behavior pattern in a lineage.

Which species to choose?

- Descendant of a lineage
- Many species limited to a lineage

Adaptation studies

Commonality of lineage is not necessary for adaptation studies, WHY?



Species solve similar problems in a similar way.

Which species to choose?

- Species from similar environment
- Choose the process

Independent evolution

Independent evolution examples

- Comparative behavior of electroception
- Infrared detection

- No historical context, but provide info about structure-function relationship

If a behavior/structure is similar rank order, it does NOT mean that the species are in "historical sequence".

Similar adaptation \neq Similar history/phylogeny

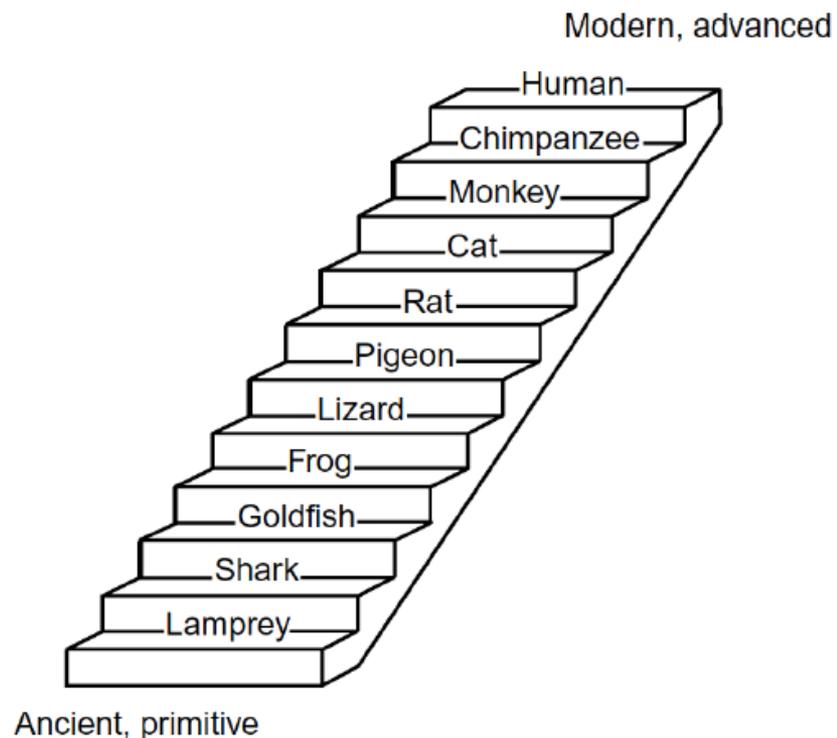
The phylogenetic scale

Old concept: WE DON'T USE IT ANYMORE

Animals were well-adapted at whatever geological age they existed.

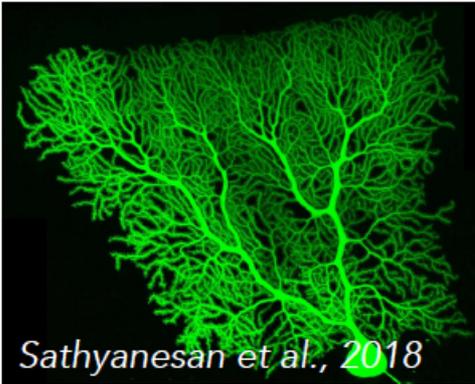
Primitive characters

~~Primitive species~~

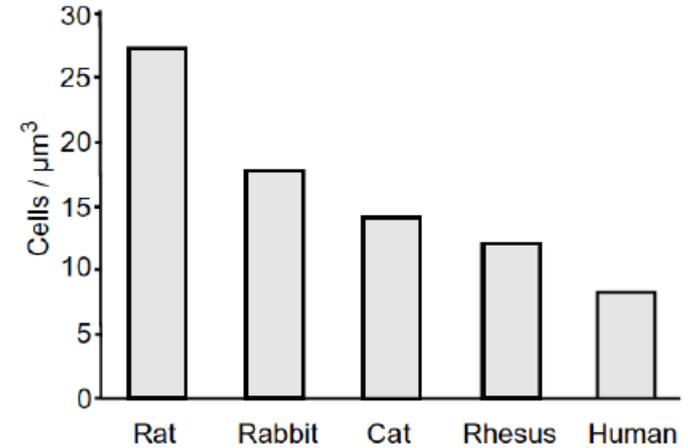


Complexity and evolution

Example: Purkinjee cells

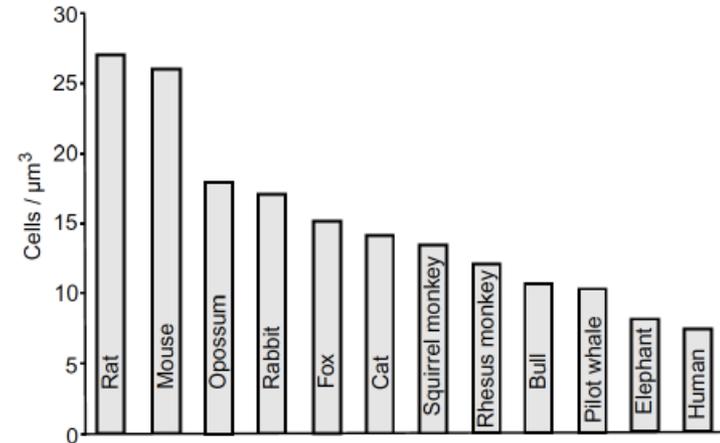


The relative number of **Purkinje** cells in the cerebellar cortex (seemed a progression..) *Lange (1975)*



If you increase the number of species...

Inverse relationship between relative Purkinjee cell number and the absolute size of the cerebellum.



Anagenesis

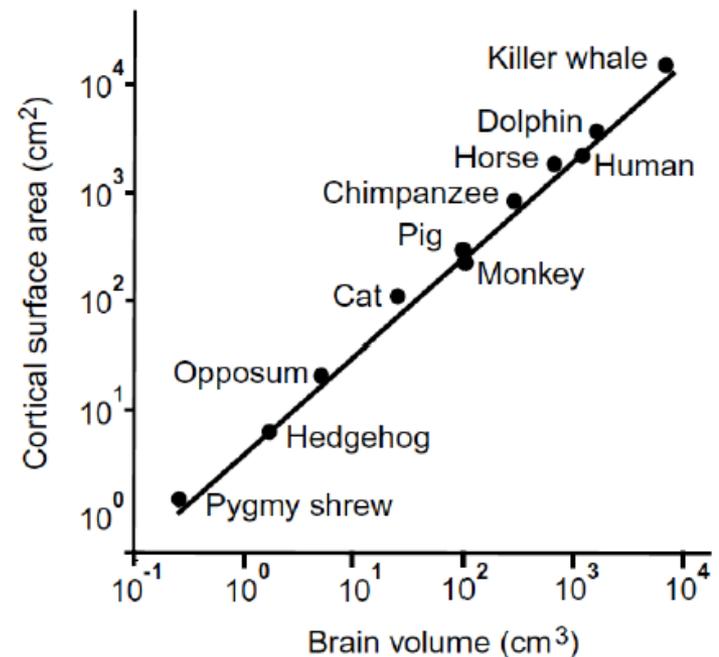
=progressive advancement/improvement through time in a given lineage.



Still derived from anthropocentric view.

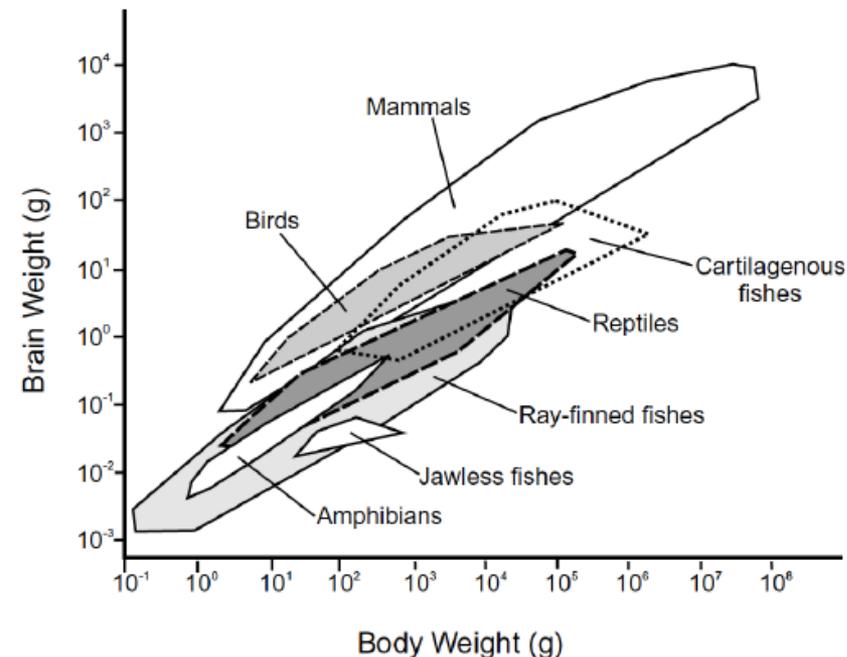
We have a large neocortex but no more neocortex than would be expected for a mammal with a brain of that size.

Adaptation and progression.



Brain size and brain allometry

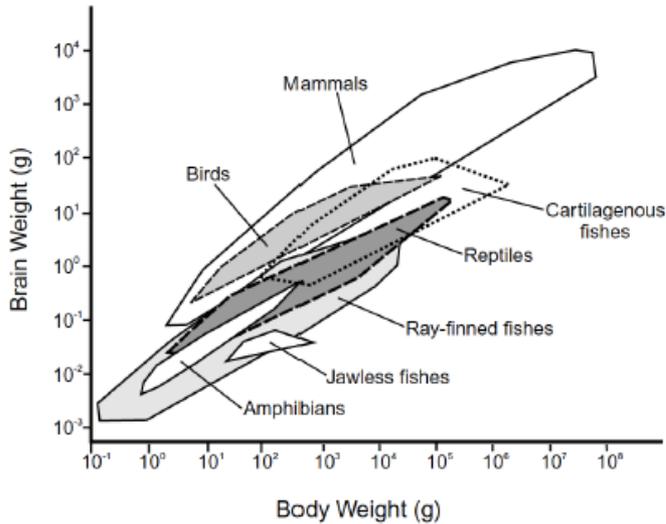
Allometry: mathematical method for allowing comparisons of the relative size of body parts by effectively removing the influence of the body size.



Useful to understand which animals have brains larger or smaller than expected for their body size.

WHICH CRITICISM?

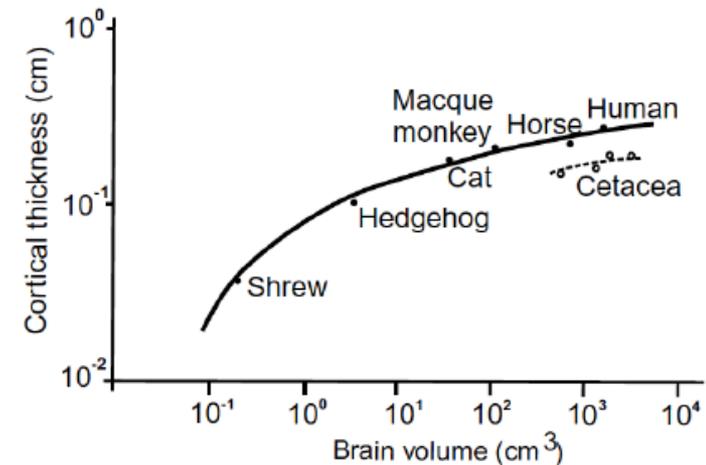
Brain size and brain allometry



Selection pressures for brain development not been uniform (complex organization).

WHICH CRITICISM?

selective pressure for body weight can be different (water vs. land)



Brain size and neuronal organization

More complex brains

Increased number of neural cells and more extensive dendritic organization

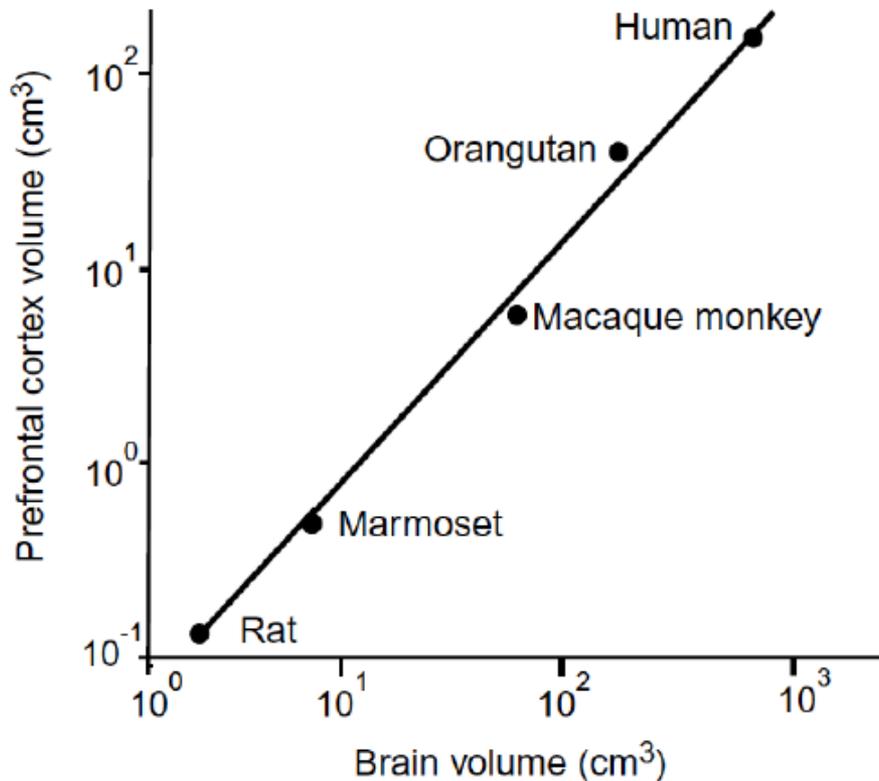
Local circuit arrangements (e.g. columnar organization of cells & fibers in the cerebral cortex)

Brain size and neuronal organization

Examples of more efficient packing and processing arrangements

- Gathering of scattered neurons → dense aggregations
- Segregation of myelinated axons from other axons and cell bodies (WM)
- Subdivision of neuronal masses into specialized components (different input/output)
- **Lamination** (separate layers of cells)

Relative size of the neocortex















**UNIVERSITÀ
DEGLI STUDI
DI TRIESTE**



Dipartimento di
Scienze della Vita

