

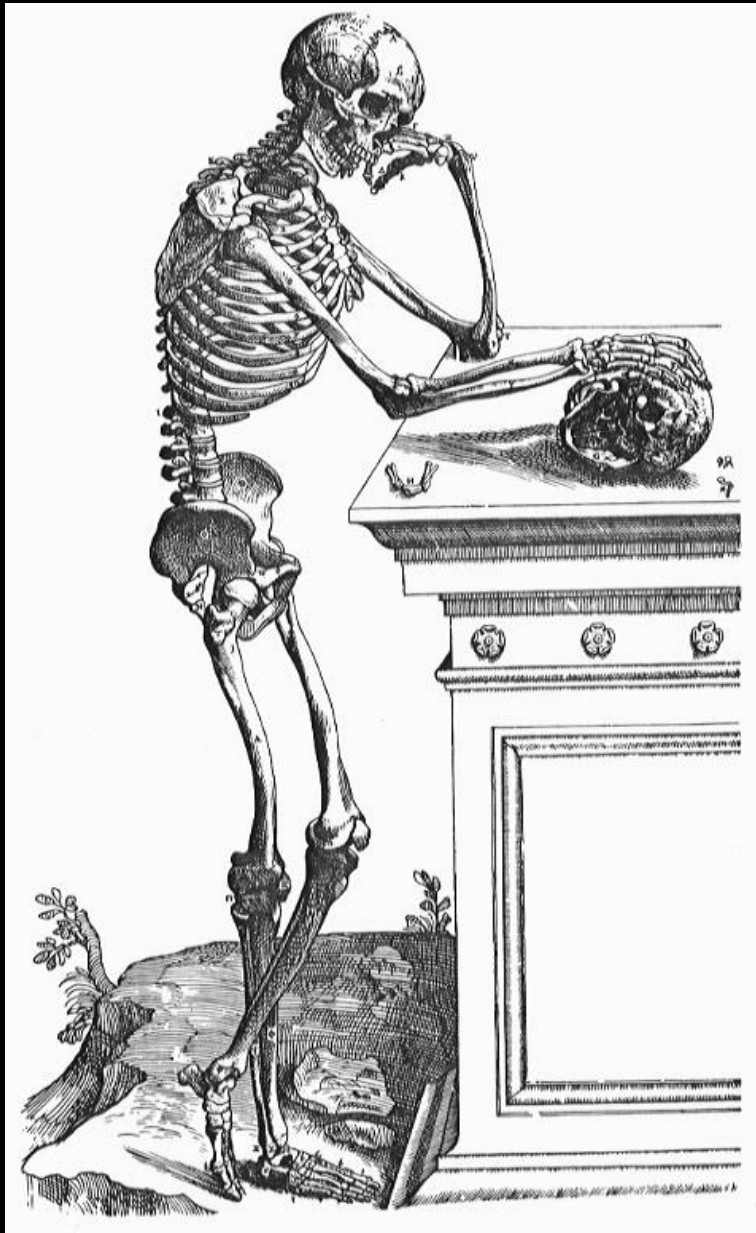
# **Tubes, Streams, and Arcs**

## **How Stem Cells Build the Brain**

**Rebecca Ihrie**

**Cell & Developmental Biology and  
Neurological Surgery**

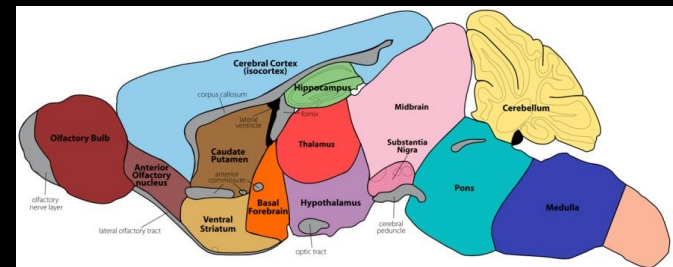
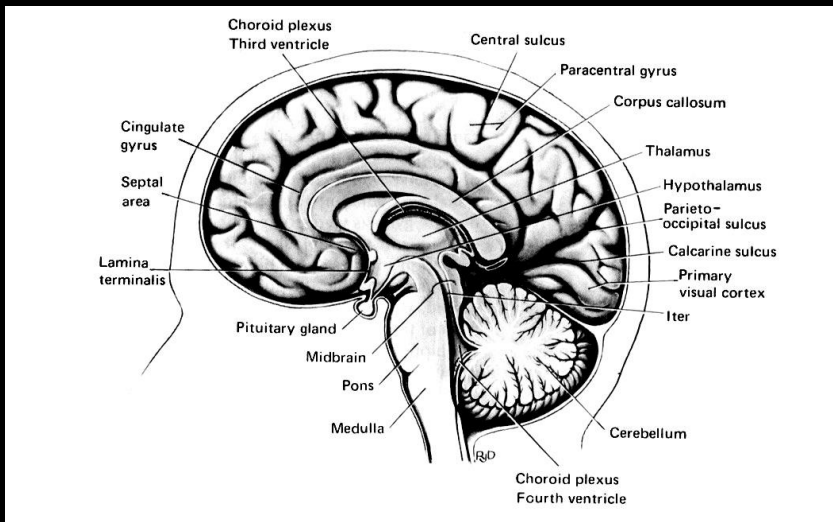
**[rebecca.ihrie@vanderbilt.edu](mailto:rebecca.ihrie@vanderbilt.edu)**



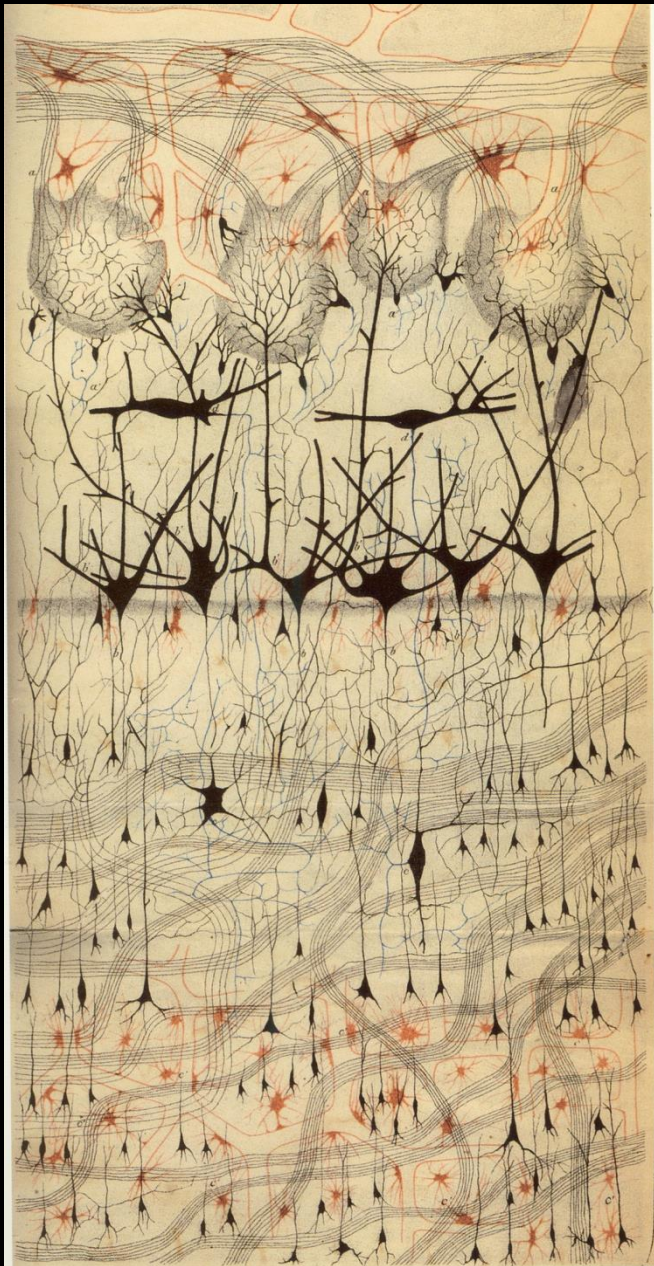
- Origins of the CNS (with a focus on cortex)
- Differences across species
- Disease states
- What about stem cells in adult brain?

# The Brain is Highly Organized

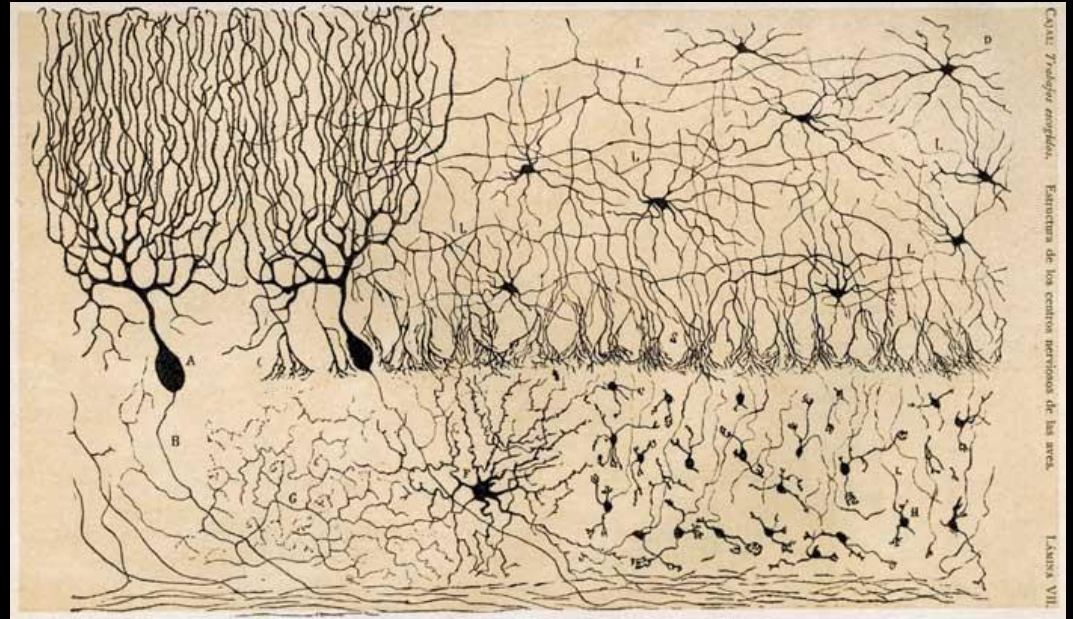
(and different across species)



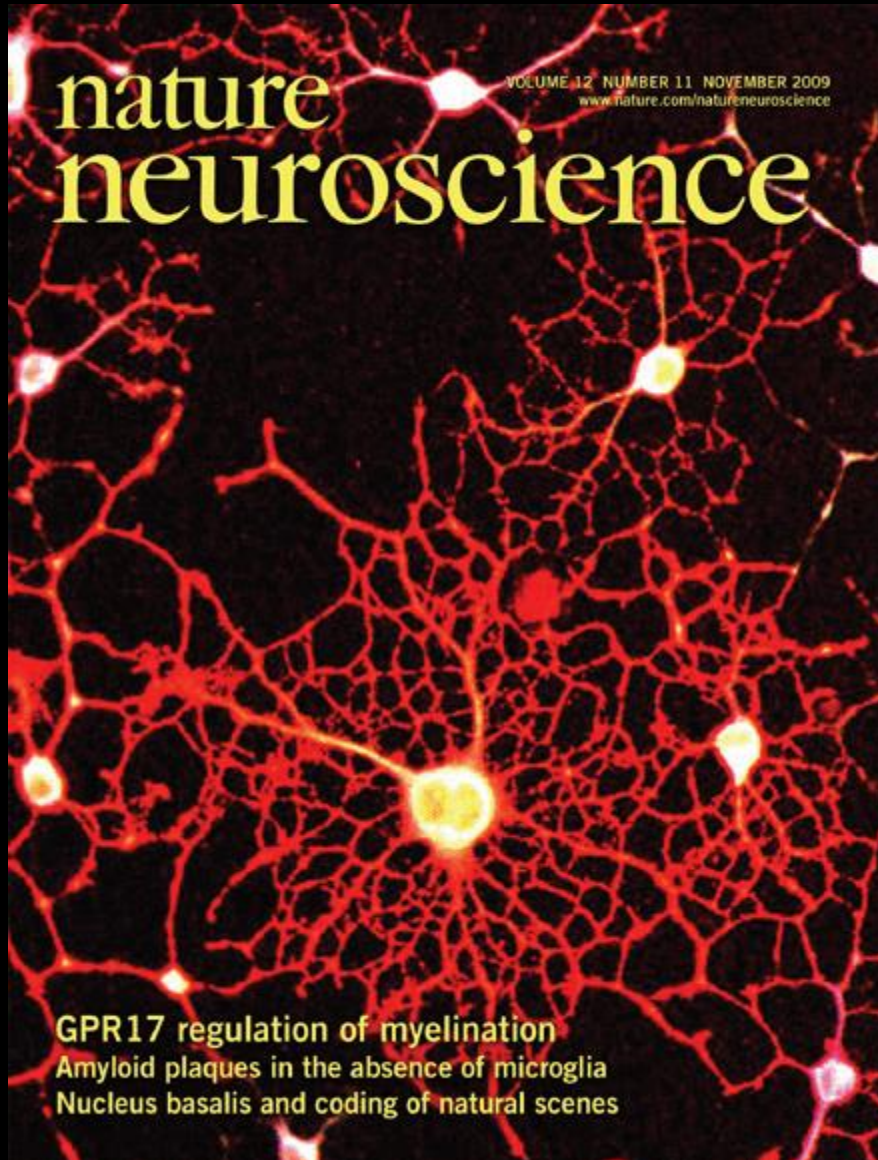
# Neurons: information and electrical signal carriers



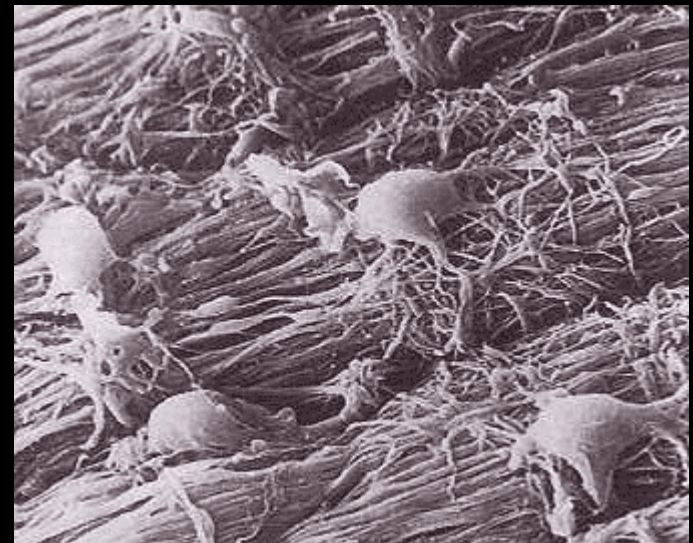
olfactory bulb – Golgi, 1875



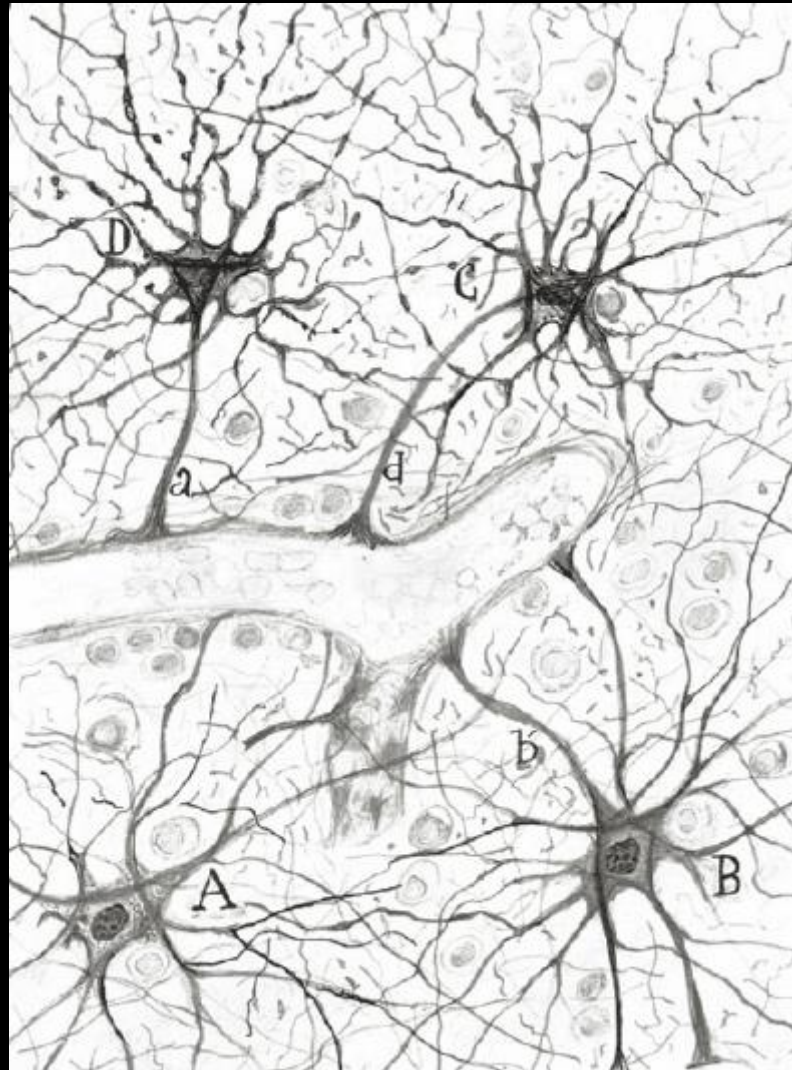
Santiago Ramon y Cajal, "Estructura de los centros nerviosos de las aves", 1905.



## Glia - Oligodendrocytes: insulators and dynamic movers



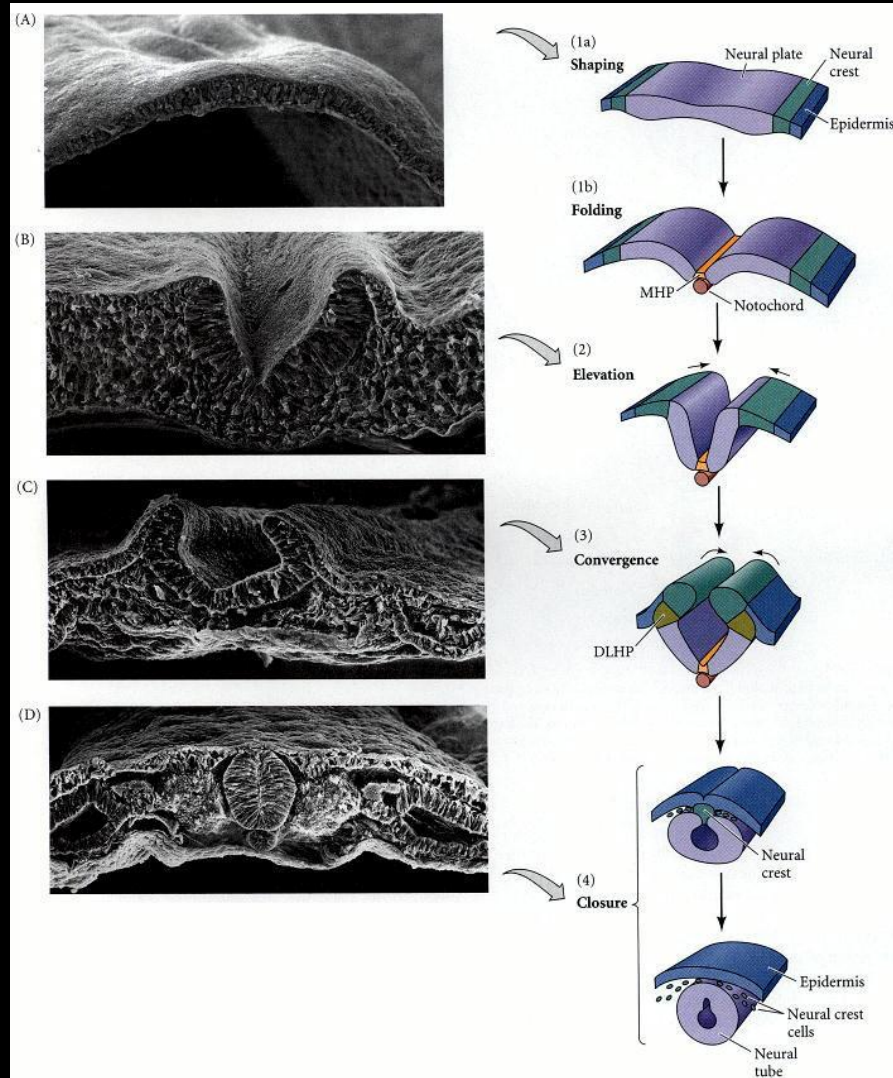
# Glia - Astrocytes: Energy providers and barrier makers



Ramon y Cajal, reprinted in Garcia-Marin et al, Trends Neurosci 2007

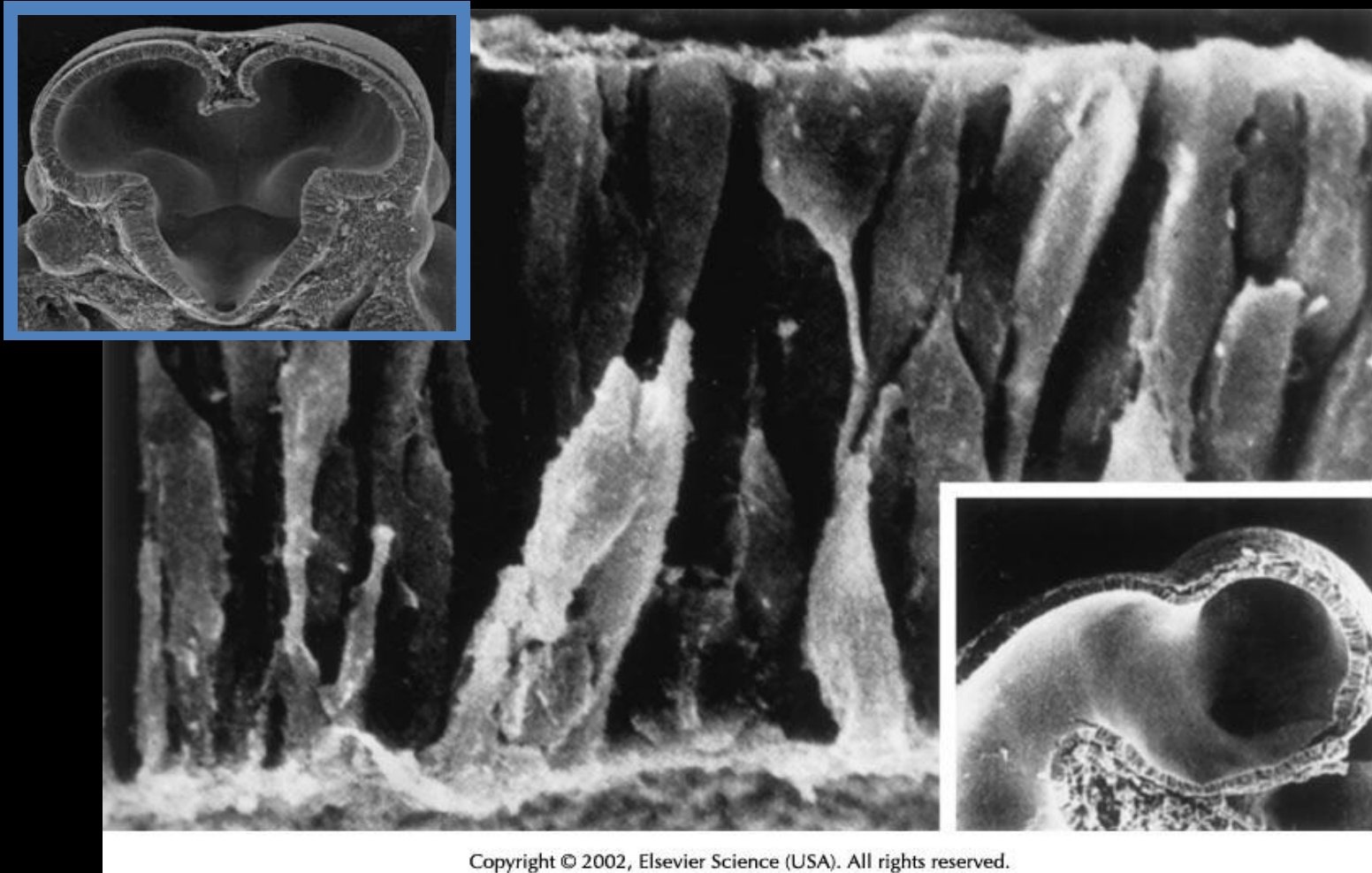
**In the beginning....**

# Neurulation: generation and closing of the neural tube

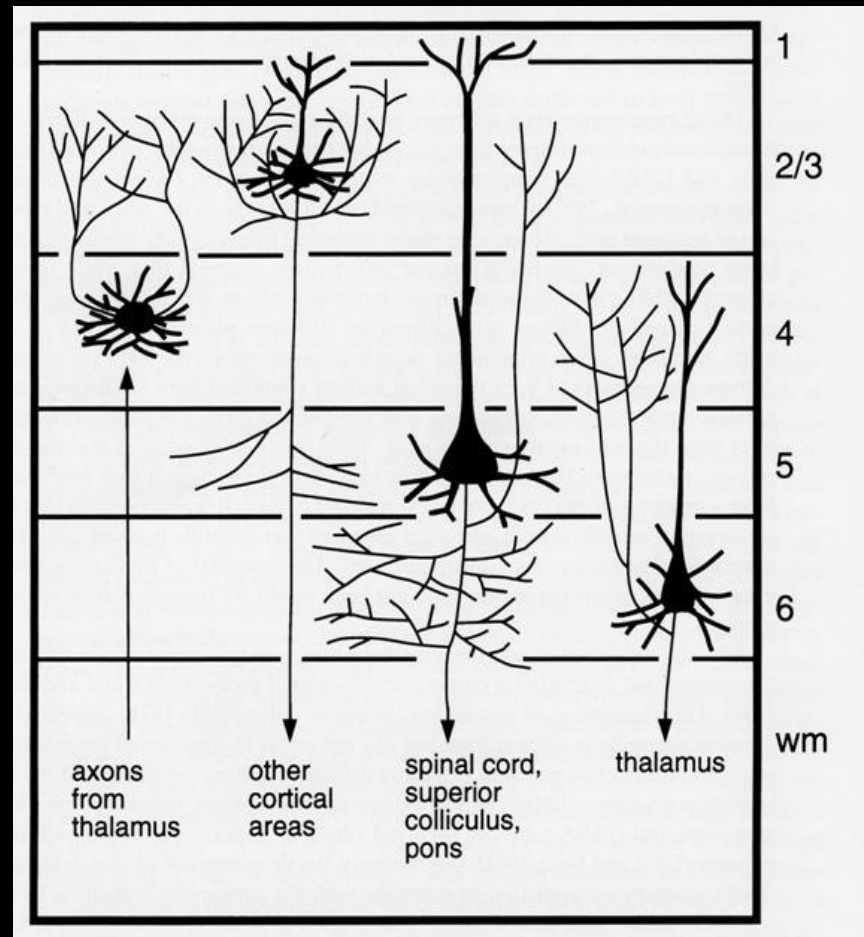
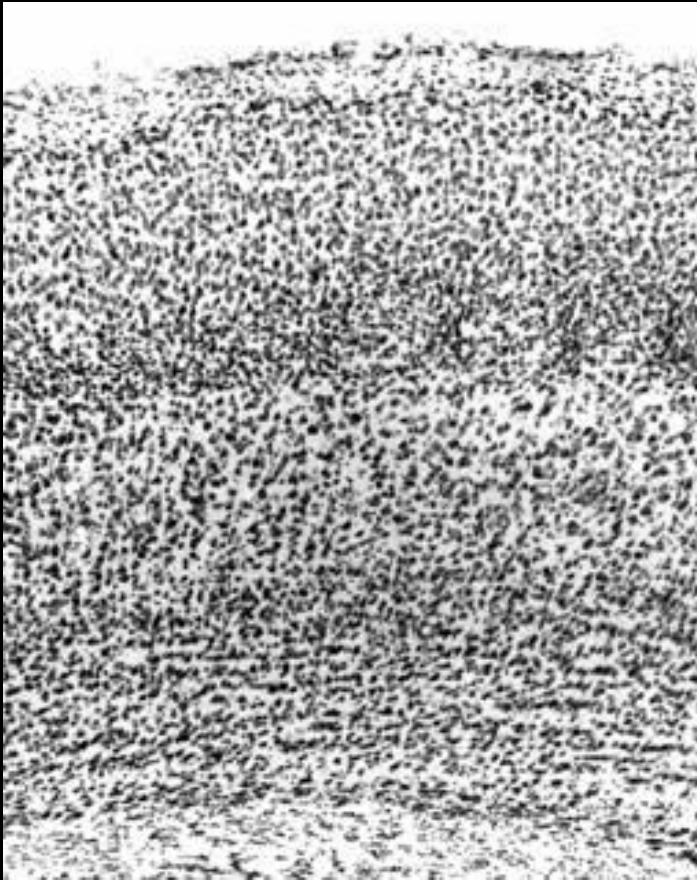


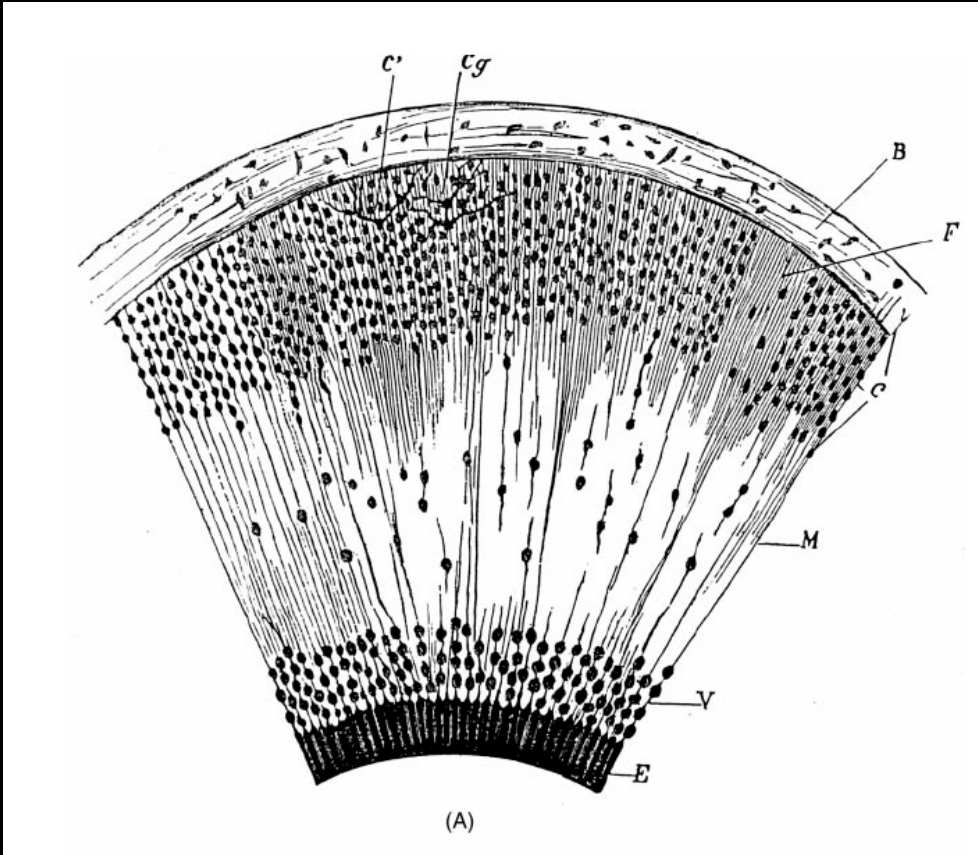


# After neural tube closure, we see ventricular zone progenitors

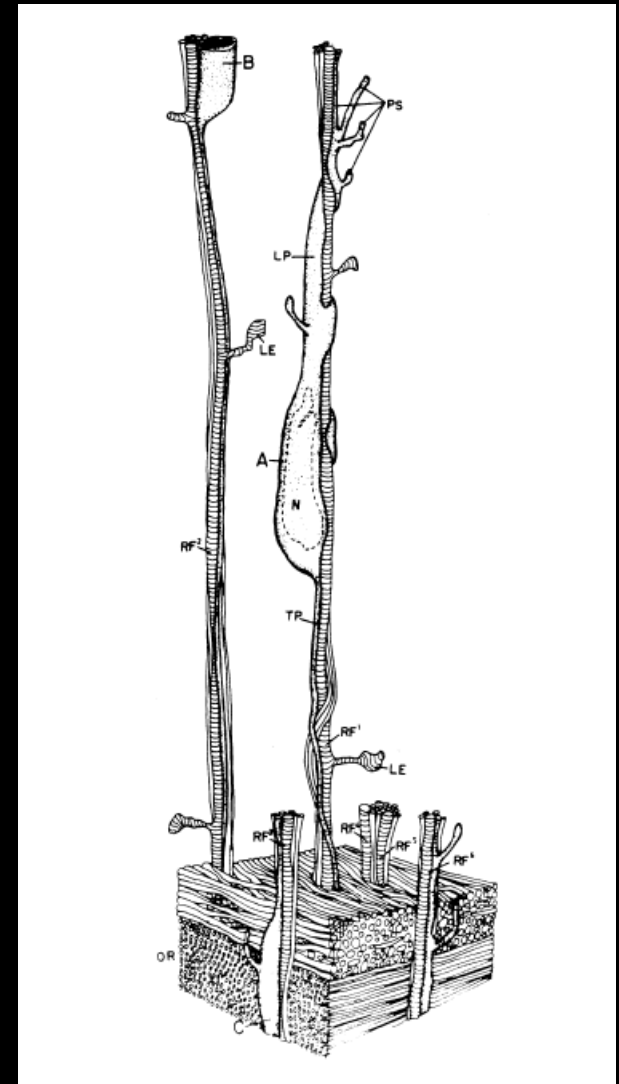


# Neurons in the cortex have different cell body locations, shapes, and connections





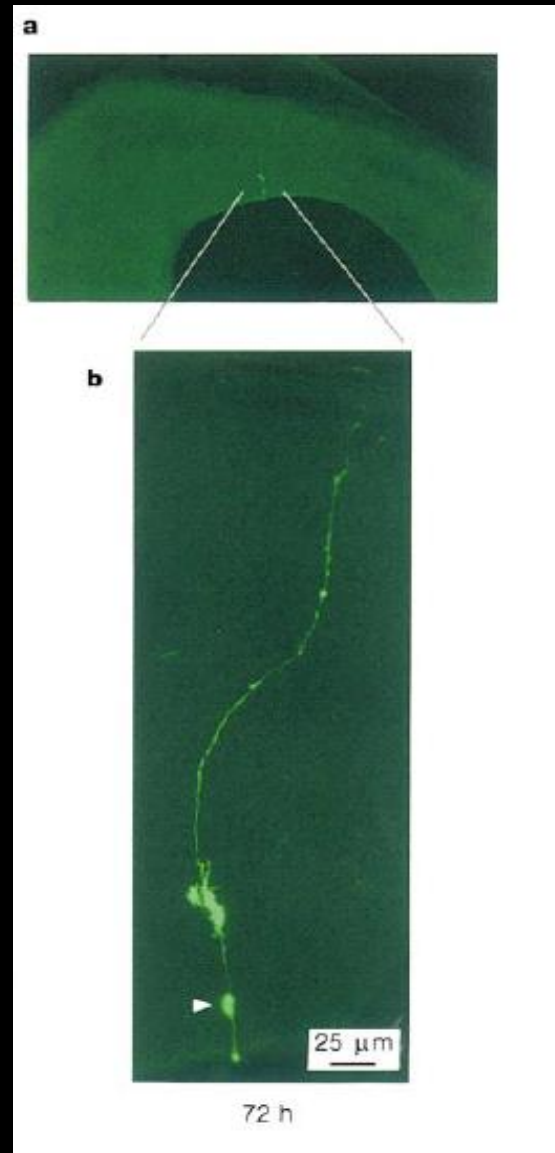
Cajal

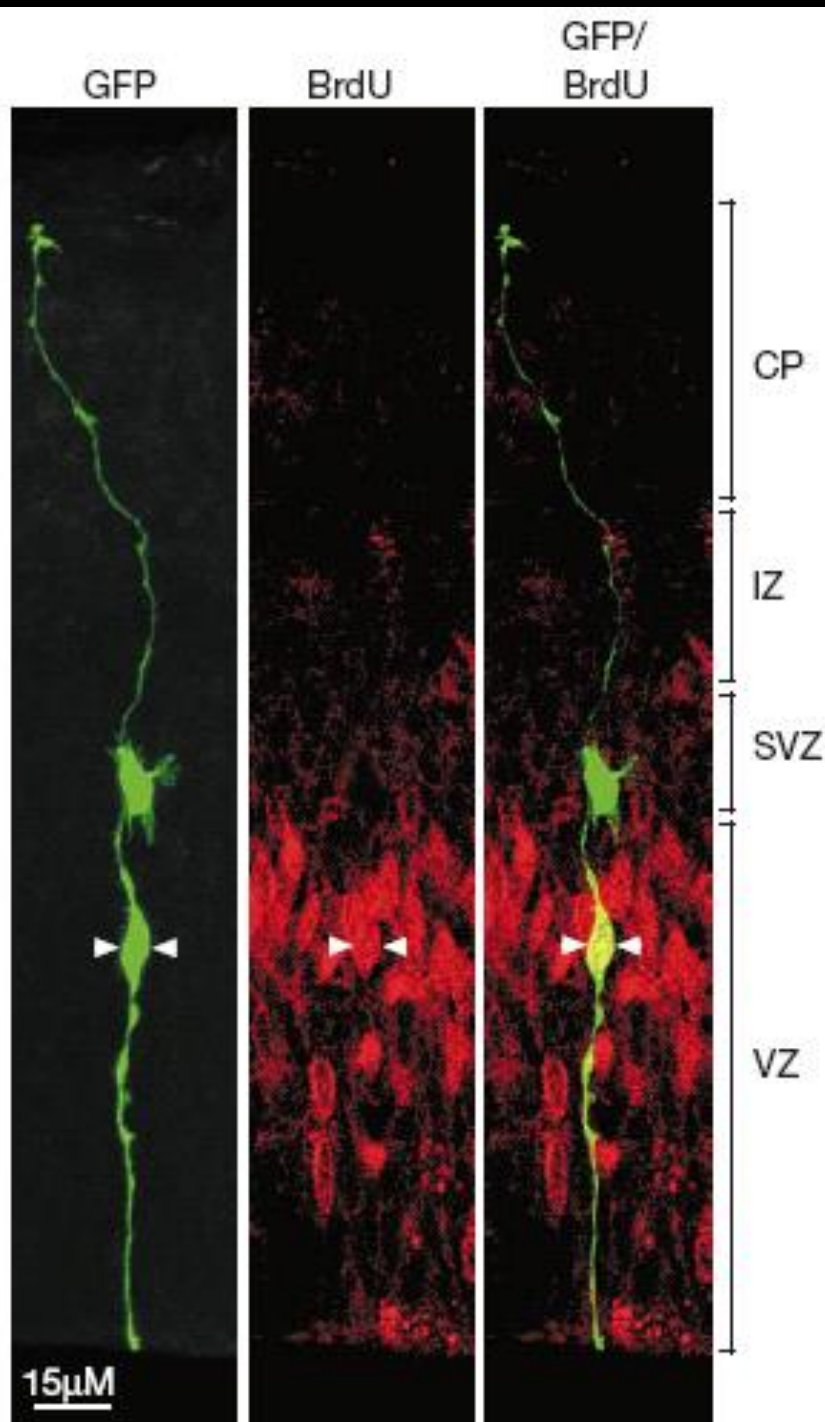


Rakic

(Science 1988 and others)

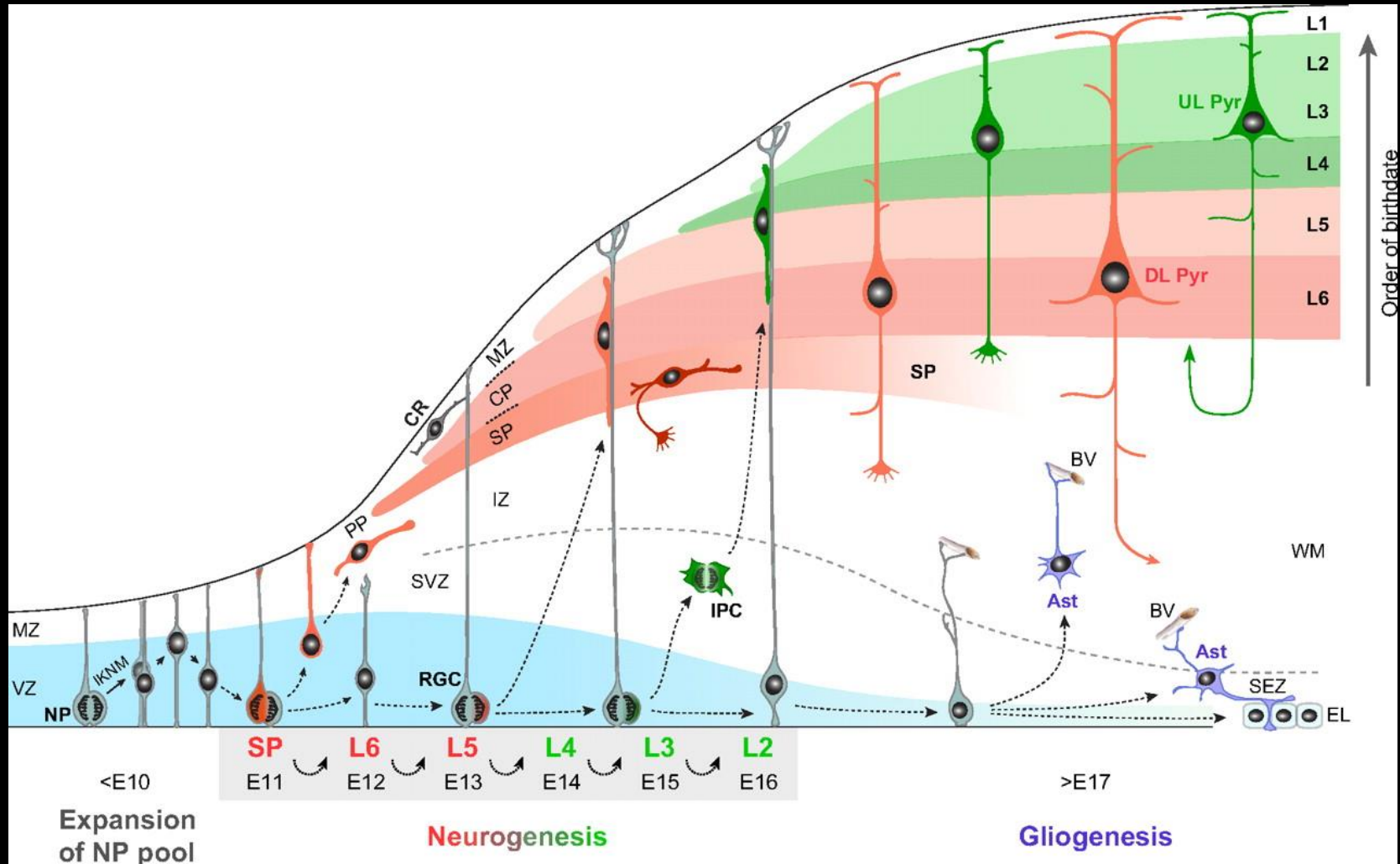
How can we *experimentally* show that these cells make the cortex?





Combinations of labels help us find actively dividing cells and see what they make

# Cortical neurogenesis: early radial glia and inside-out patterning



# Relative Sizes and Timing Across Species

**mouse: ferret: human**

Surface Expansion

~1:100:1000

Neuronogenesis

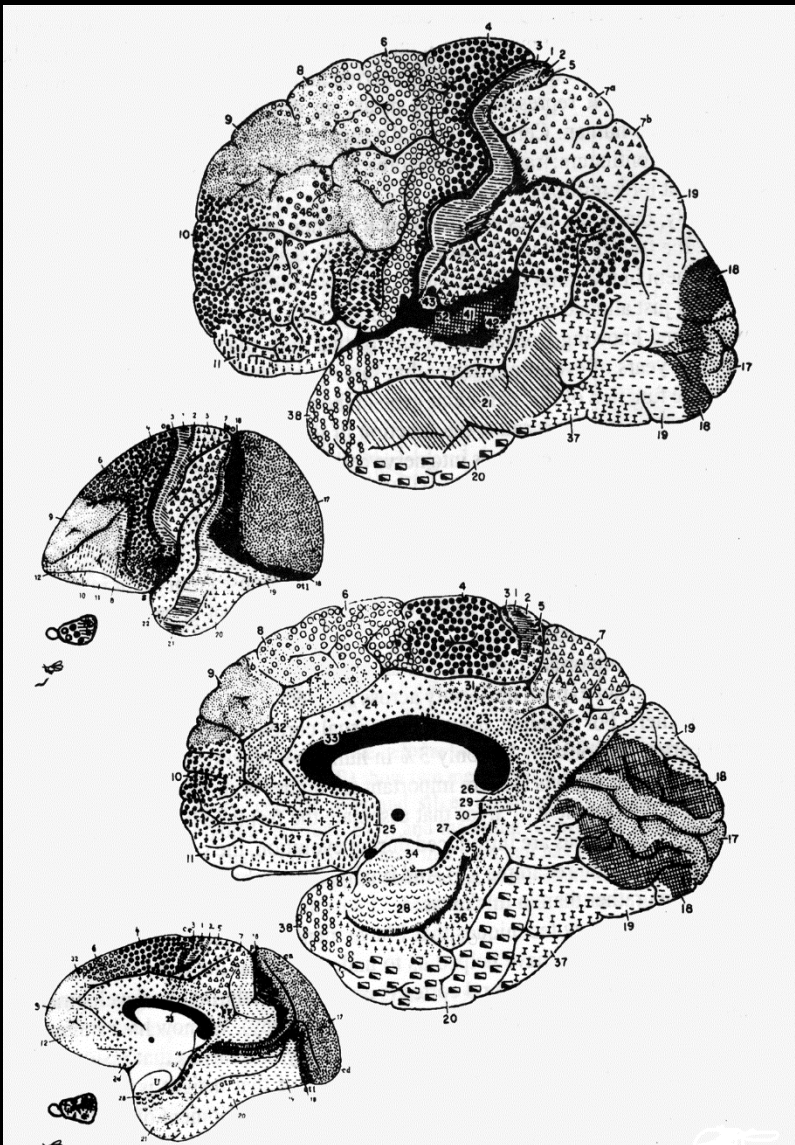
7:60:120 days

Gestation (d)

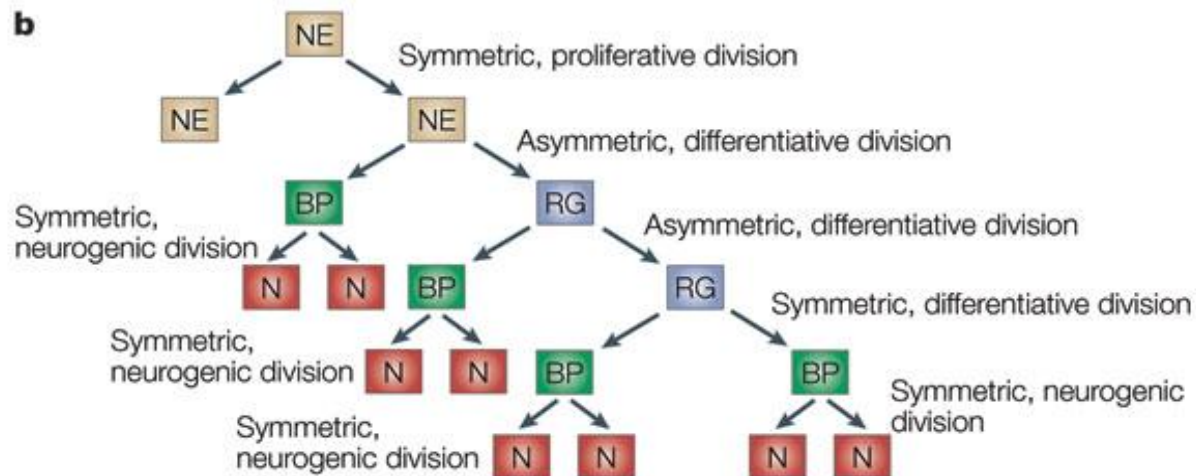
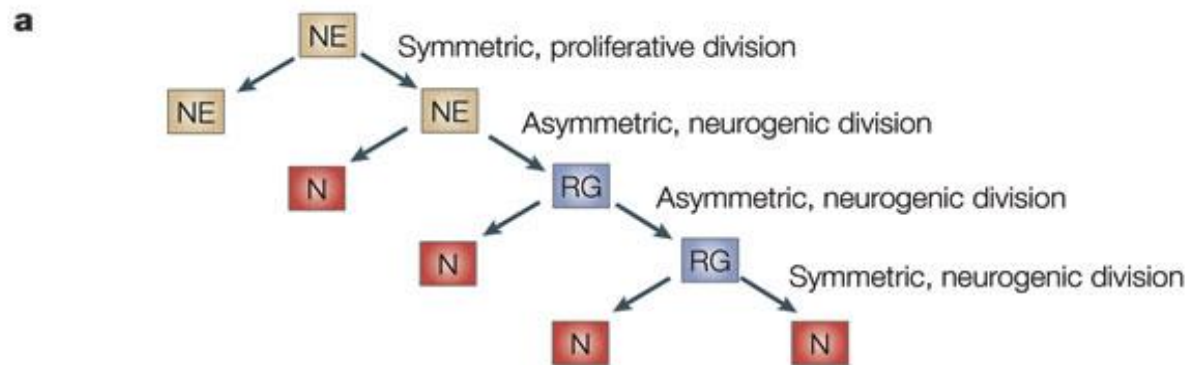
19:165:280

Cell Cycle

**4X longer**

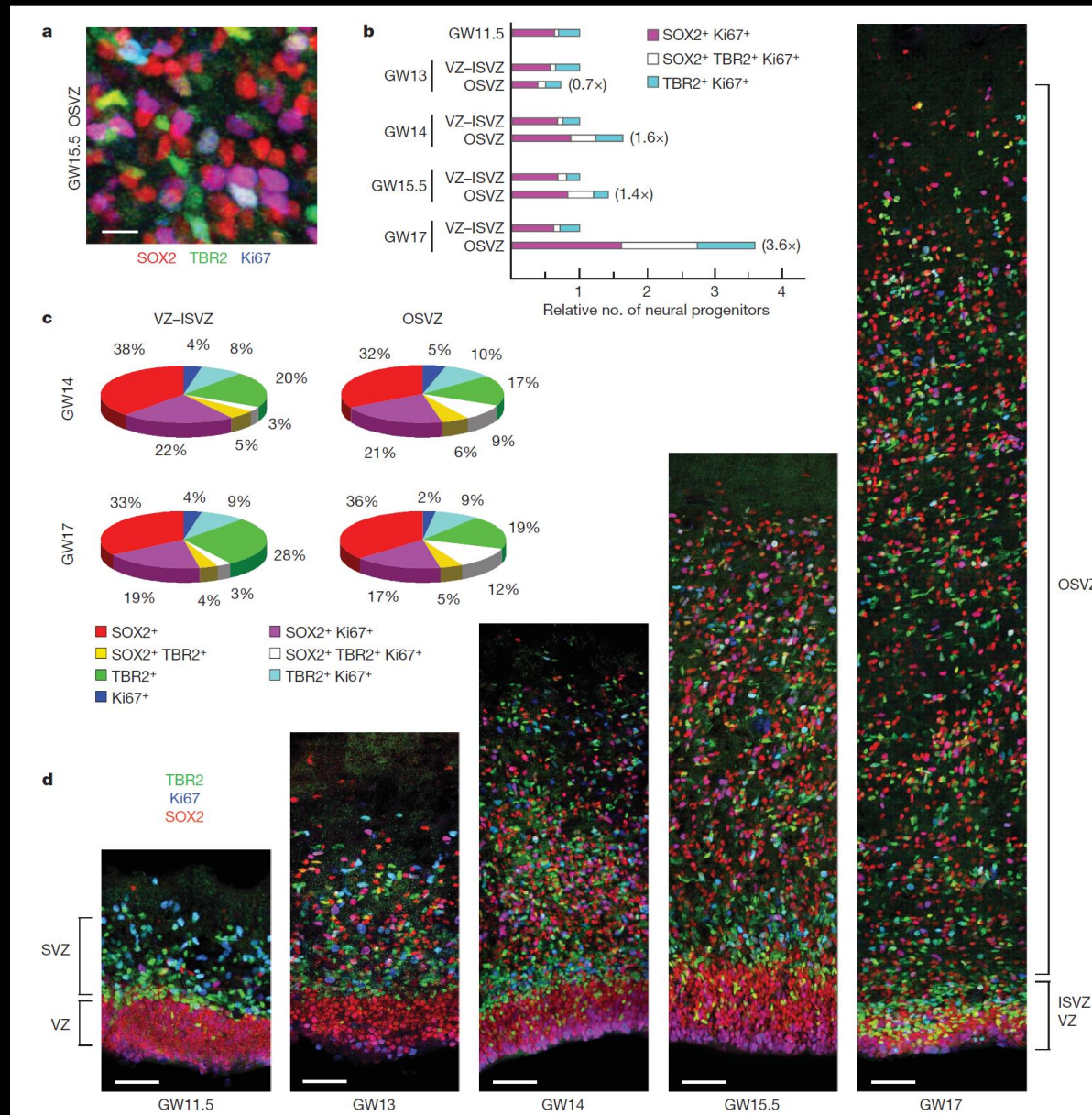


# Making a Bigger Brain: More Cells, More Time, and Bigger Cells

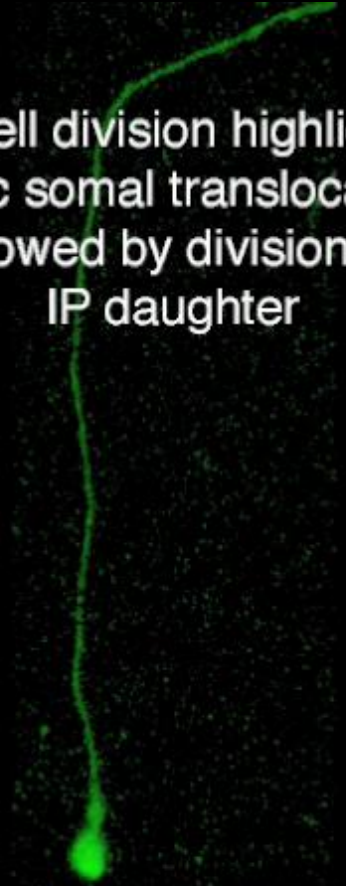




# “OSVZ Cells” Outnumber Classic Radial Glia

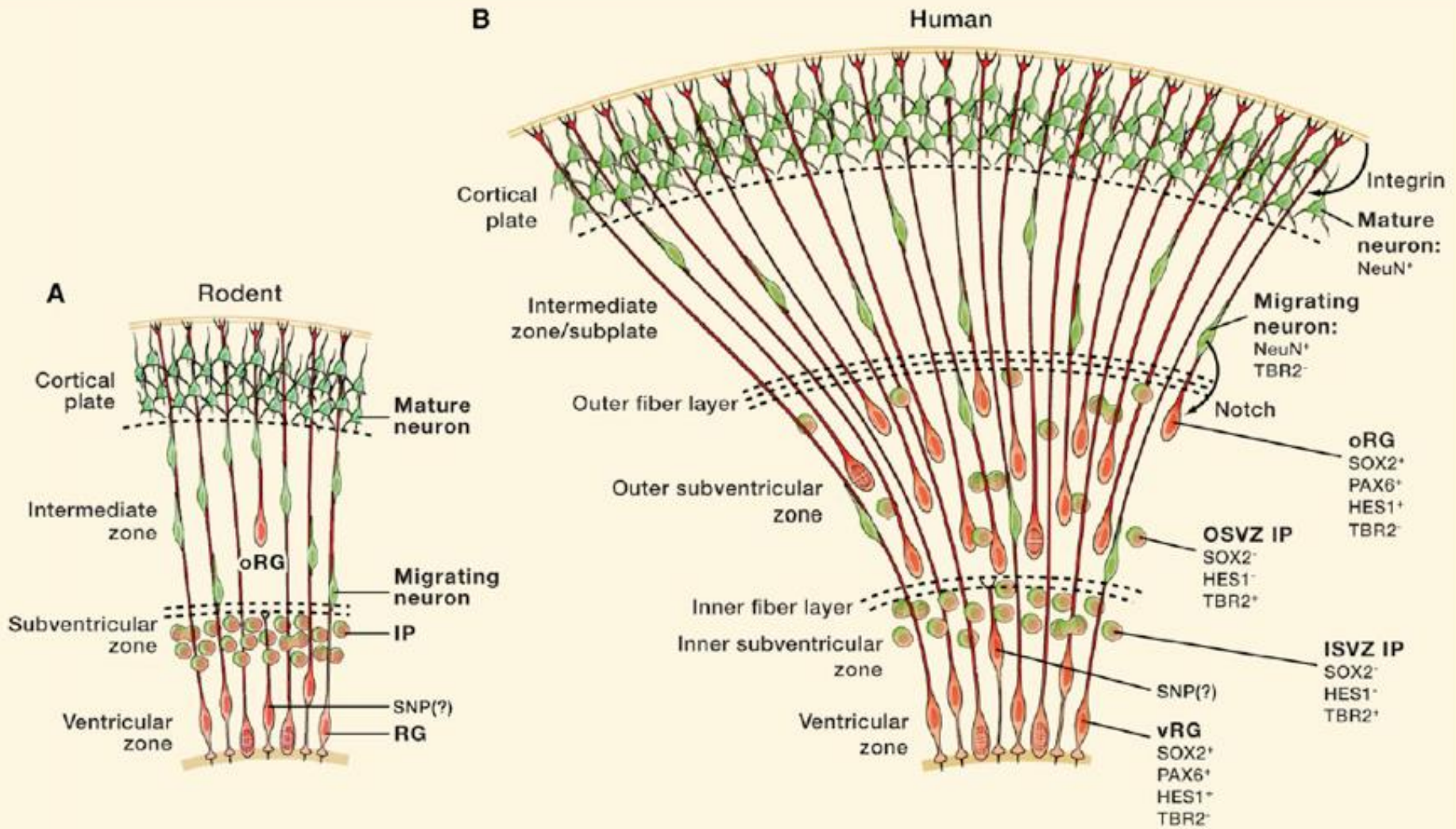


# These “Extra” Progenitor Cells Can Divide



oRG cell division highlighting  
mitotic somal translocation,  
followed by division of  
IP daughter

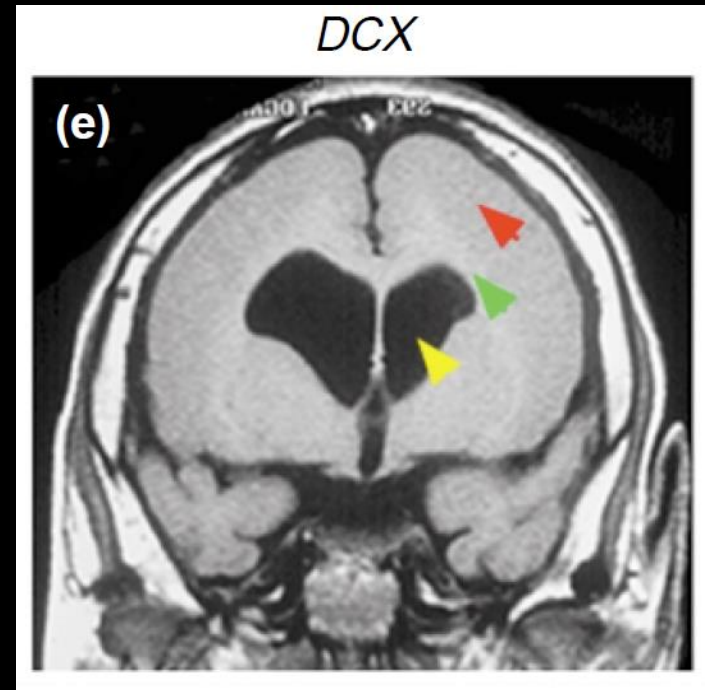
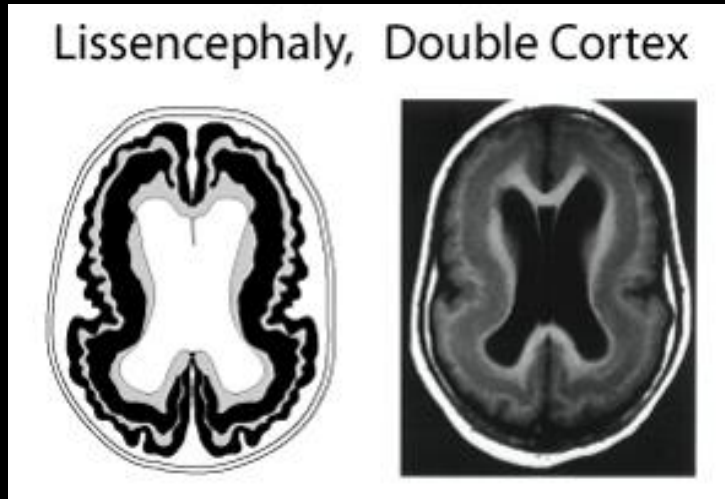
# Revising the Model for Which Cells Divide



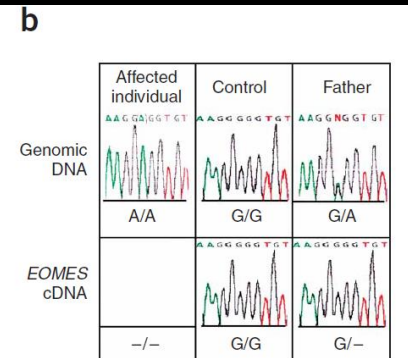
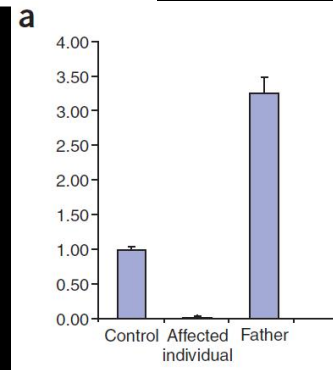
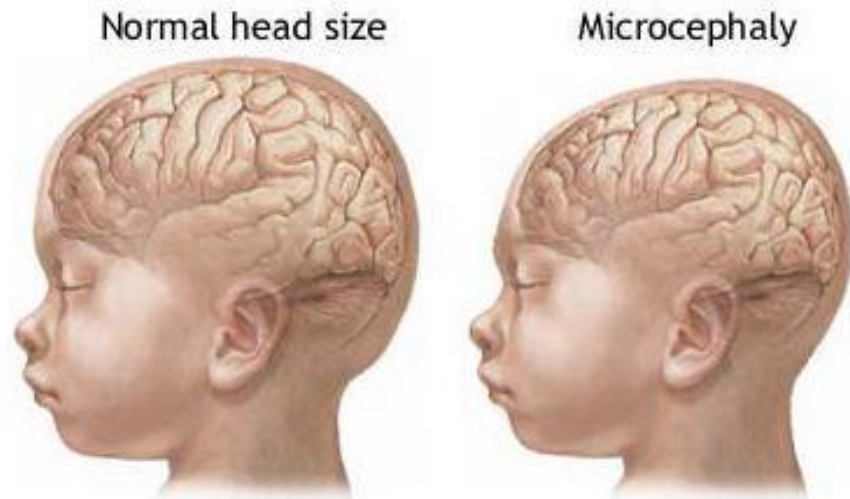
# What happens when it goes wrong?

- Defects in patterning (regions missing)
- Defects in migration (cells in the wrong place)
- Defects in differentiation (small or less “folded” brain)
- Selective loss of progenitors (Zika)

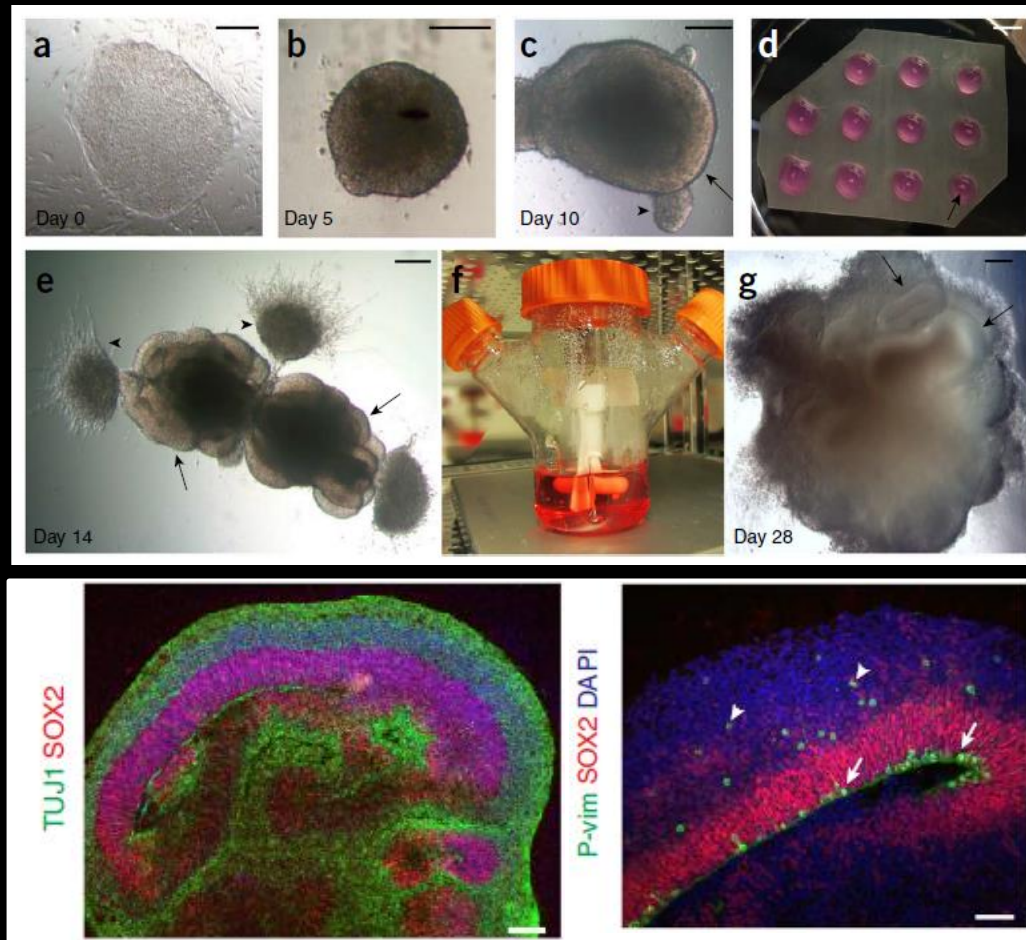
# Disrupted migration – smooth or “doubled” cortex



# Too few progenitors – a smaller cortex



# Cerebral organoids or “mini brains”: modeling development in the dish



So...what happens *after* birth??



# A Casual Summary of Adult Neural Stem Cell Research Across Species

*Does adult neurogenesis exist?* No, yes, no, yes, yes, no, yes, yes, yes, YES!

*Does adult neurogenesis exist in primates?* No, no, yes, maybe, yes, yes, YES!

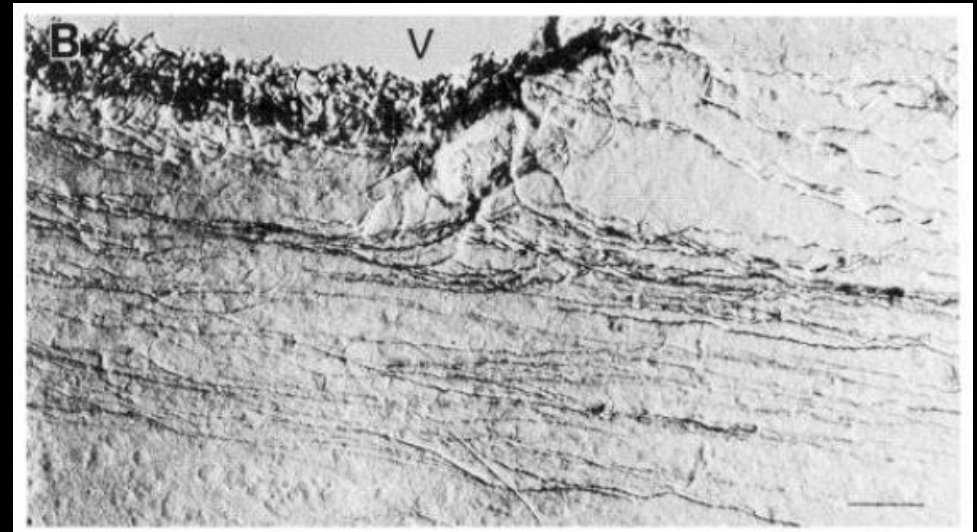
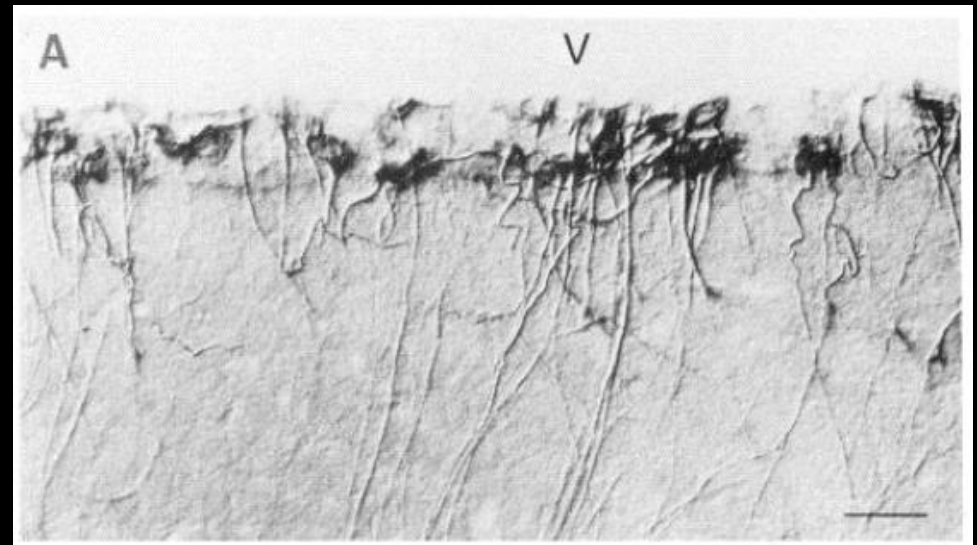
*Does neurogenesis occur in the neocortex?* No friggin way, yes, no way, yes, no way

Jose, yes, DEPENDS WHO YOU ASK.

*Does adult neurogenesis happen in humans?* Yes, yes, yes, no, WAIT WTF\* DID YOU SAY NO???

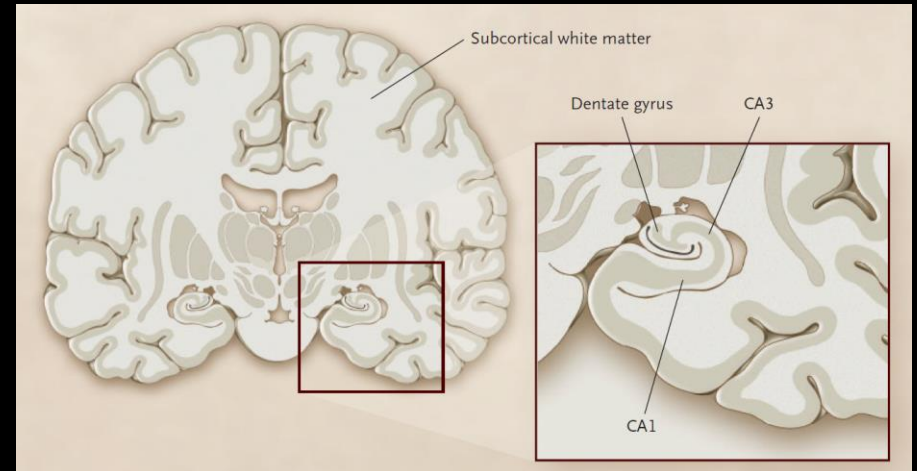
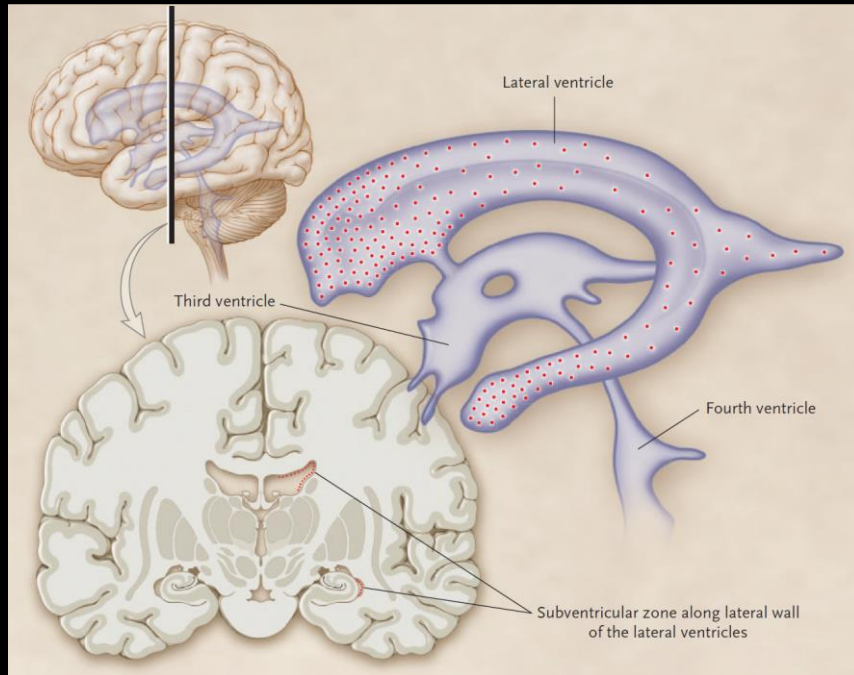
<http://snyderlab.com/2018/03/07/wtf-no-neurogenesis-in-humans/>

# Songbird Learning: a Catalyst for the Field



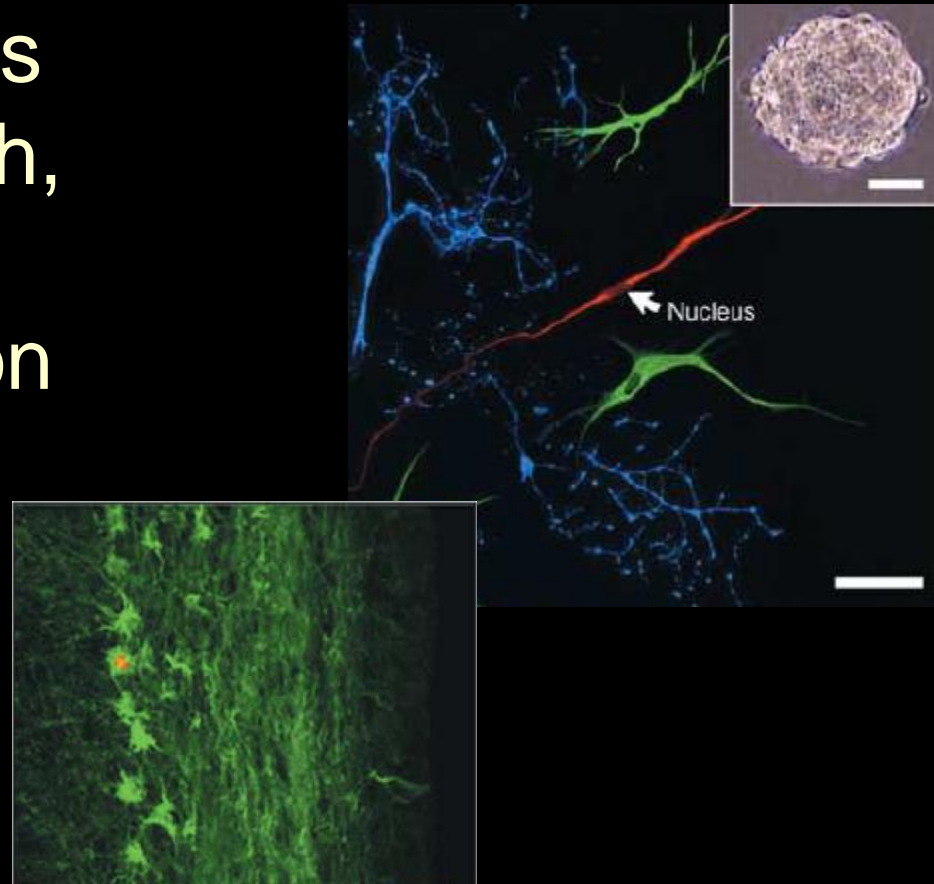
*J Neurosci*, 1988

# Adult Neurogenesis: Two Major Zones



# Adult Human SVZ is not Highly Proliferative

Although these cells can grow in a dish, it's very rare to detect proliferation in tissue



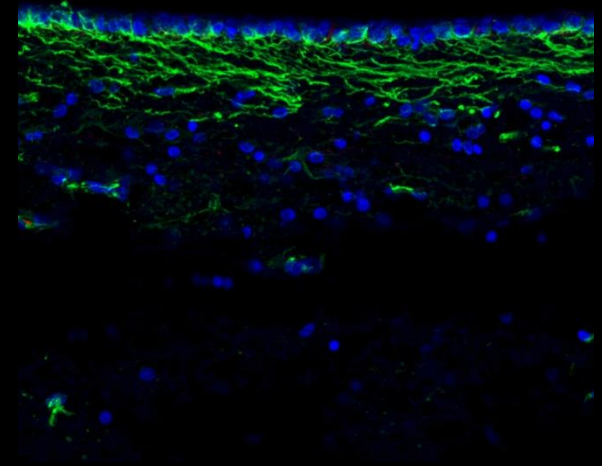
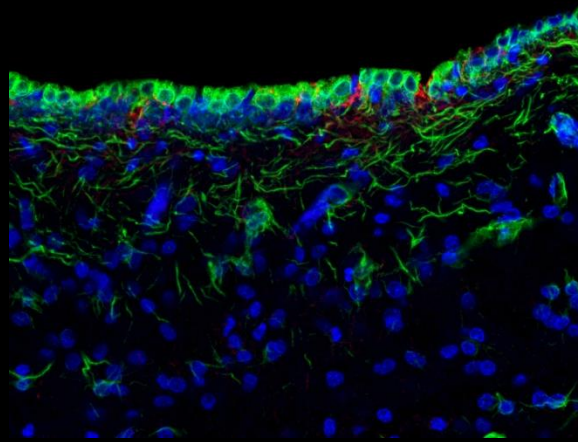
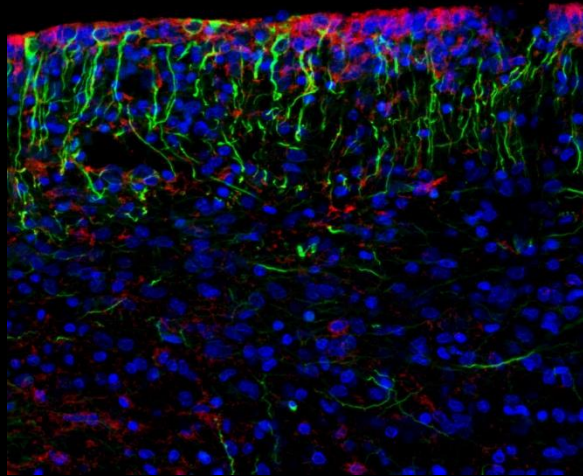
GFAP, Ki67, DAPI

# Proliferation and Immature Cells Disappear Quickly After Birth

1 day

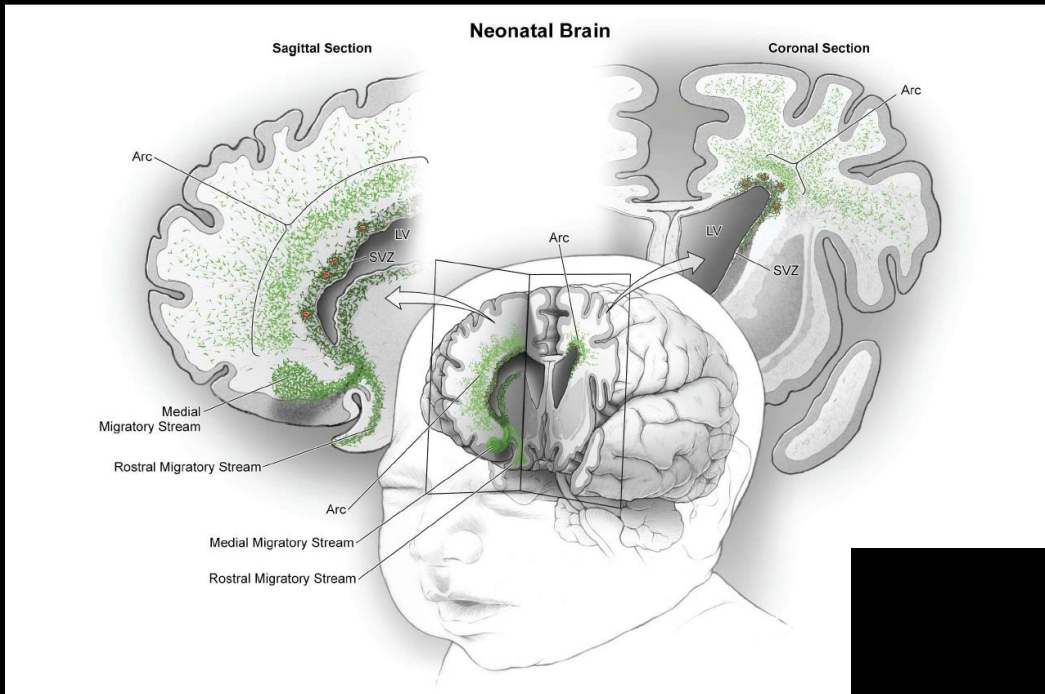
6 months

32 months

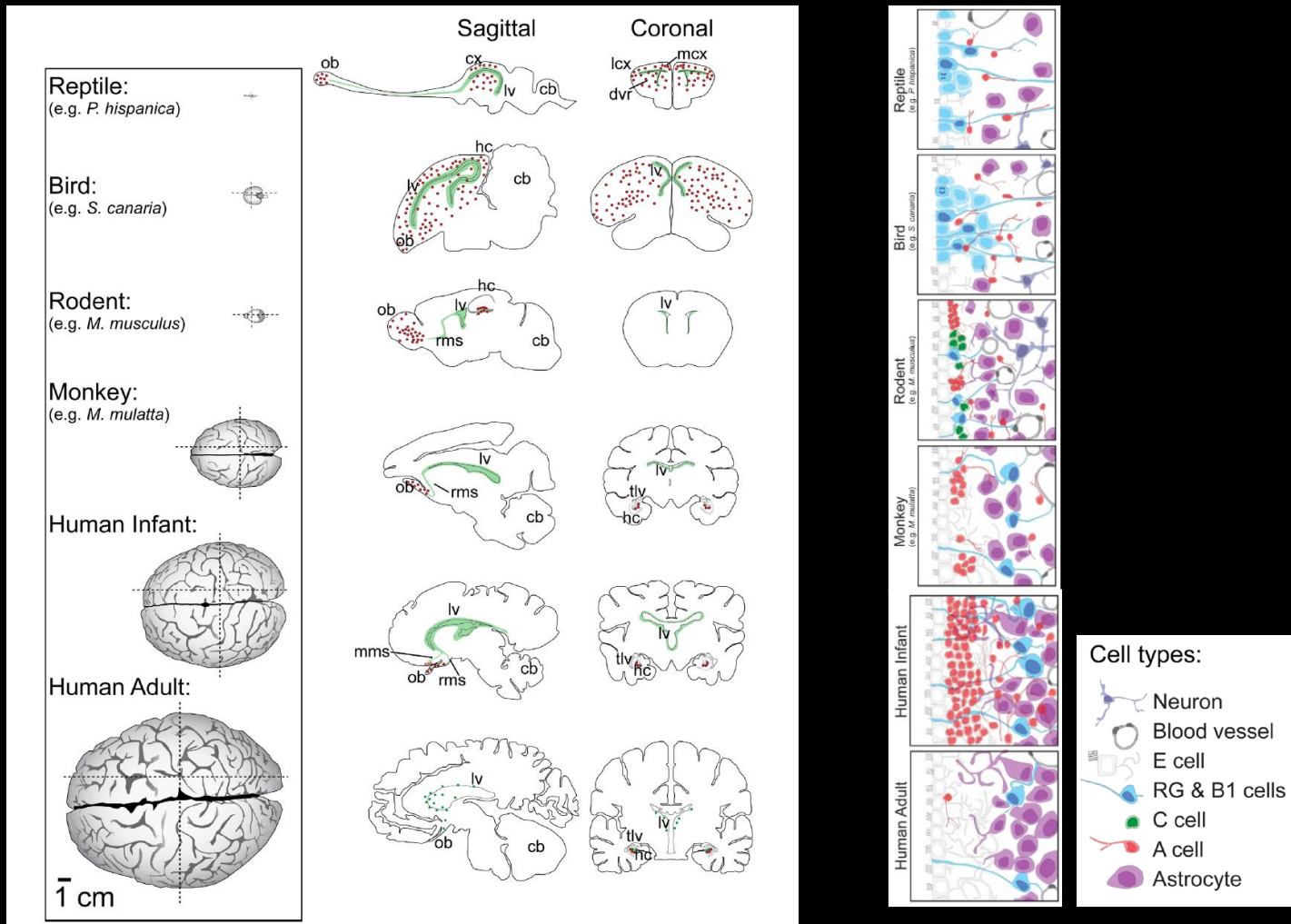


vimentin / Ki67 / DAPI

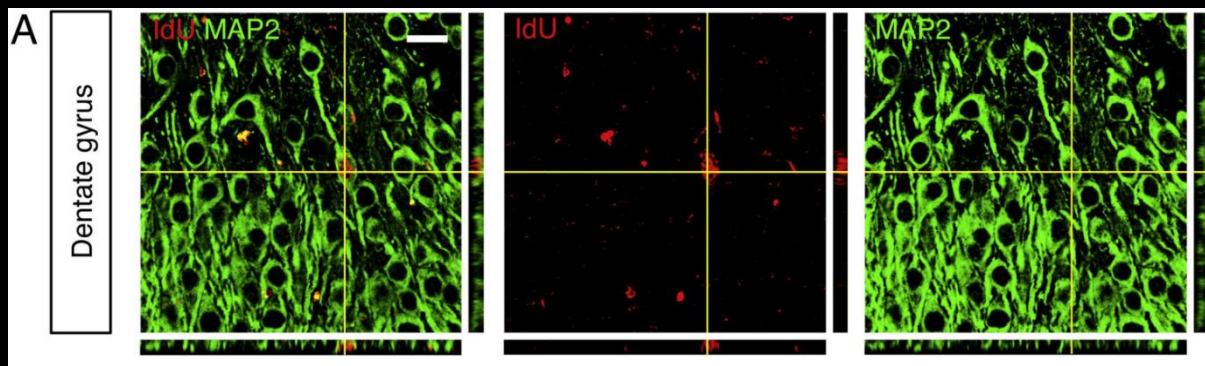
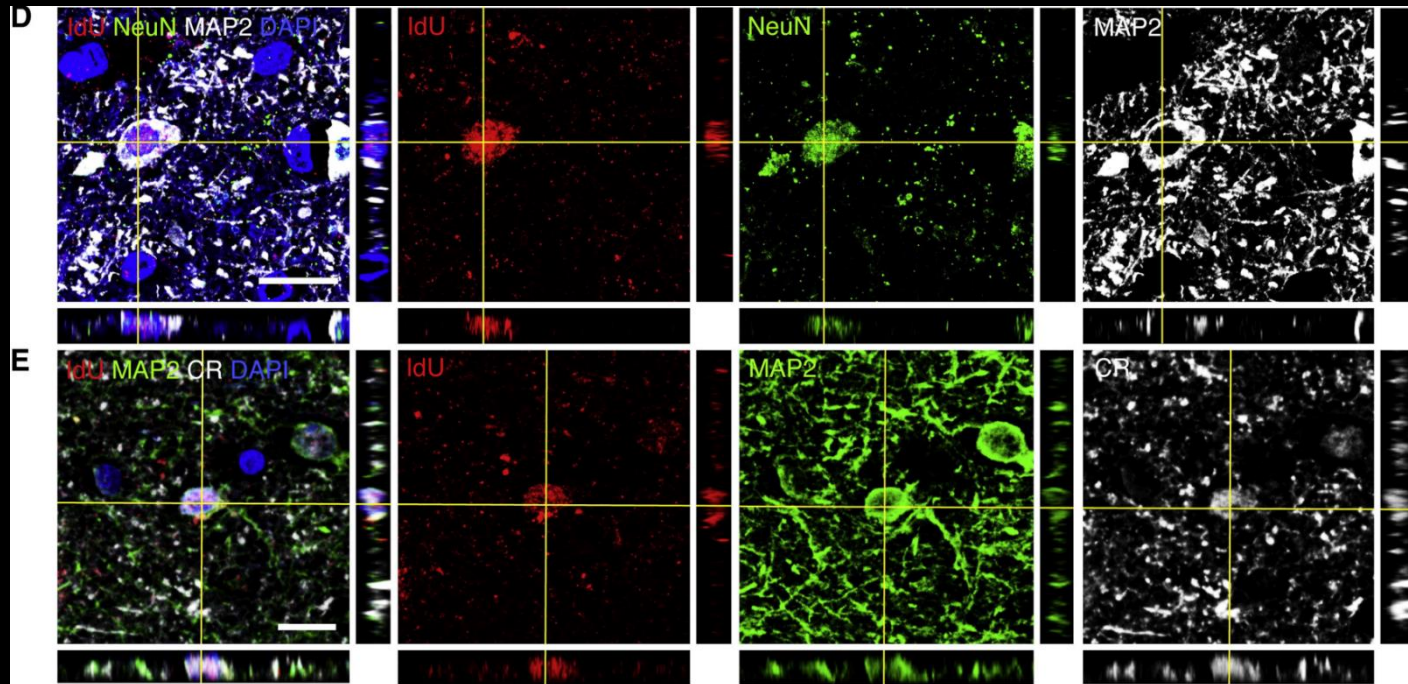
# Streams and Arcs As Proliferation Declines



# Does increased “complexity” mean less neurogenesis?

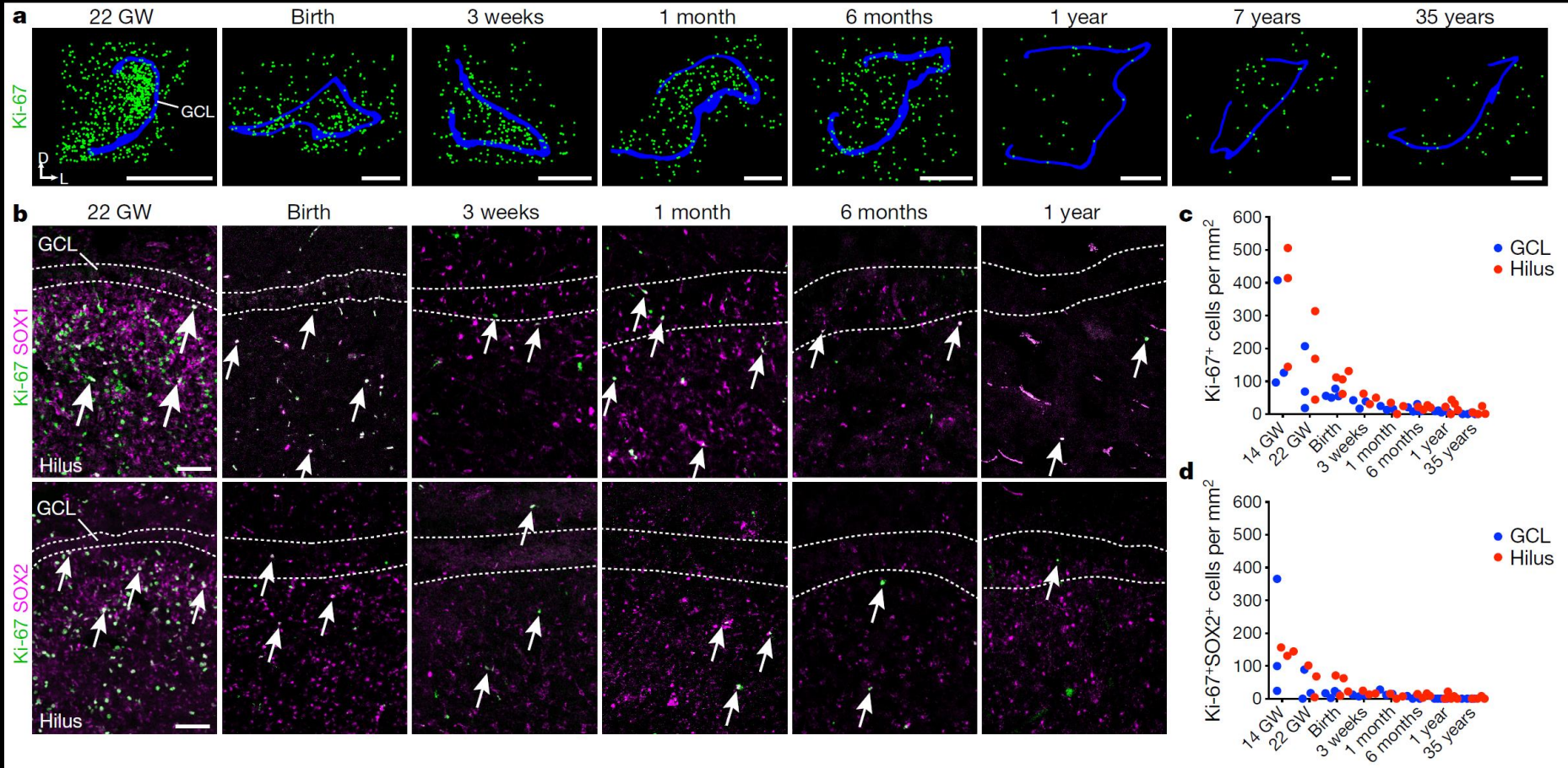


# How much neurogenesis happens in adult human brain?





# How much neurogenesis happens in adult human brain?



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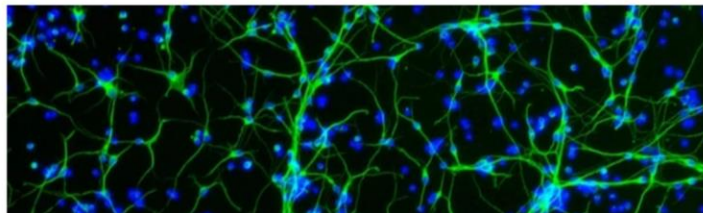
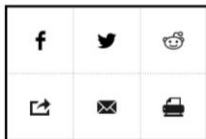
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NEUROSCIENCE

# Does the Adult Brain Really Grow New Neurons?

A new study stirs up debate over a long-held finding, and could dim hopes for the treatment of neurodegenerative diseases

By Helen Shen on March 7, 2018



# Take Home Points

- Patterning and control of cell division and movement over time are essential to building the brain
- The dynamics of division, growth, and persistence of dividing cells vary across species
- “Basic research” can have not-so-basic implications

Thank you for your attention!