MASTER IN CELLULAR AND MOLECULAR BIOLOGY
Developmental Neurobiology -Cortical Development
May 2020 - Week 1

Tuesday 5th of May:

Lecture 1: Cellular and molecular organization of the cerebral cortical progenitors in mammals

*11:00-13:00 – **Personal Introduction** + **Lecture + Questions***

Thursday 7th of May:

*14:00-16:00 - **Novel technologies used in neurobiology** - (i) 3D whole brain imaging; (ii) rabies virus tracing and optogenetics; (iii) scRNAseq & cell lineage tracking; (iv) IPSCS & brain organoids; (v) in vivo & in vitro reprogramming.*

Tasks for students:

1) Read the article that will be presented on Week 2 (prepare questions)
2) Work on the articles related to the novel technologies (presentation due in Week 3)

Developmental Neurobiology - Cortical Development
Week 2

Monday 11th of May:

Lecture 2: Acquiring neural diversity in the developing cerebral cortex

*14:00-16:00 – **Lecture and questions***

Tuesday 12th of May:

Lecture 3: Presentation of a scientific paper:
initial hypothesis and final product

*11:00-13:00 - **Lecture and questions***

14:00-16:00 - **Introduction to the task of writing a fellowship proposal**

Tasks for students:

1) *Work on the articles related to the novel technologies (presentation due in Week 3)*
2) *Choose the article for the fellowship proposal presentation (presentation due in Week 4)*

Developmental Neurobiology - Cortical Development
Week 3

Monday May 18th

Lecture 3: Brain disease modelling for understanding neurodevelopmental disorders in humans.

14:00-16:00 – ***Lecture and questions***

Tuesday May 19th

11:00-13:00 – **Student presentation on novel technologies**
(5 groups - 2-3 per group → 15-20' per group + questions)

Task for students:
Work on the fellowship proposal

Developmental Neurobiology - Cortical Development

Week 4

Monday May 25th

14:00-17:00 – Discussion with each group separately to give feedback on the fellowship proposal (*15-20' per group)*

Thursday May 28th

10:00-13:00 – Student presentation of the fellowship proposal by the different groups (*15-20' per group)*

Scientific cursus

Michèle Catherine STUDER married MENEGHELLO
1 child born in 2003

POSITION: Research Director Inserm since 2009
at the Institute of Biology Valrose, iBV
University de Nice Sophia-Antipolis (UNS)
Nice, France

Group Leader (PI) of the "*Development and Function of Brain Circuits Lab";*

EDUCATION: 1987: ***"Laurea 110/110 cum laude" in Biological Sciences***
at the University of Pisa, Pisa, Italy.
Work on "*Population cytogenetics of Albanians in the province of Cosenza: frequency of Q and C band variants.*"

1990: ***PhD in Molecular Biology***
at the "Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy".
Work on **"***Transcriptional regulation of the mouse liver/bone/kidney-type alkaline phosphatase gene in vitro.*"

1989: Visiting Research Fellow at ***Fidia S.P.A.*** 'Research Laboratories' , Abano, Italy
1990: Visiting Research Fellow *at* ***Research Institute of Molecular Pathology (IMP),*** *Vienna, Austria*

Scientific cursus

1991-1997: POST-DOC Research Fellow at:
Division of Developmental Neurobiology,
MRC/National Institute for Medical Research, London, UK.
Head of Laboratory: Robb Krumlauf

Work on: "*In vivo genetic interactions and functional characterization of the mouse homeotic gene Hoxb1 in the developing hindbrain*".

1994: ***Visiting Research Fellow at Baylor College of Medicine,***
Houston, USA; Head of Laboratory: Alan Bradley

1997-2001: ***MRC Research Group Leader/ Junior Lecturer***
MRC Centre for Developmental Neurobiology, King's College, Guy's Campus, London, UK.
Centre Director: Andrew Lumsden

Work on: "*Role of retinoic acid signaling during forebrain patterning*".

2000: ***Visiting Research Fellow at* UCSF,** San Francisco, USA
Head of Laboratory: John Rubenstein

Scientific cursus

2001-2009: ***Full Investigator*** and **Responsible of the Transgenic and Knock-out Core Facility** at TIGEM (Telethon Institute of Genetics and Medicine), Napoli, Italy.
Institute Director: Andrea Ballabio

Work on: "*Functional and genetic characterization of area patterning genes during cortical development* ".

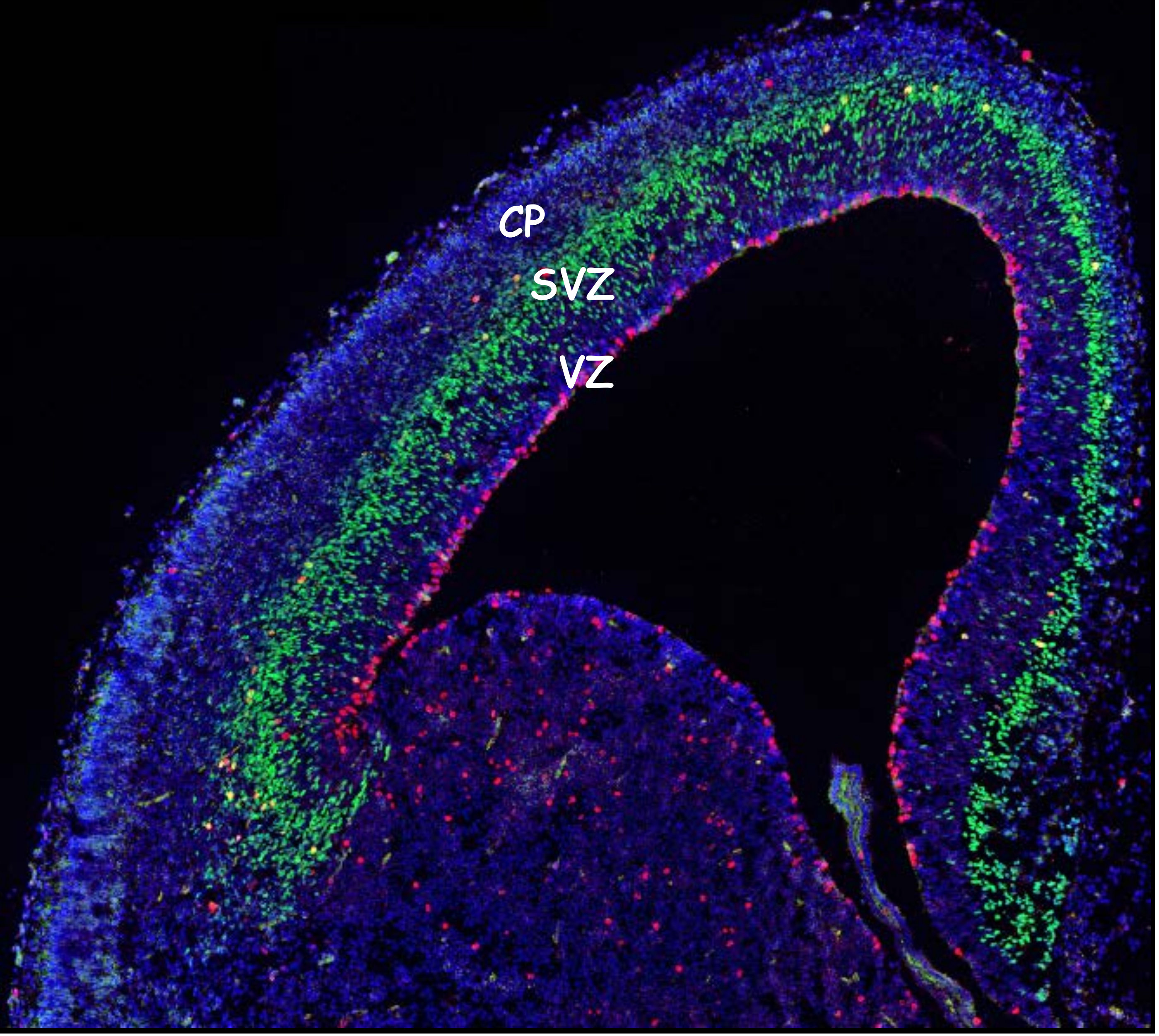
Since 2009: ***Directeur de Recherche (DR2-DR1) Inserm;*** University of Nice Sophia-Antipolis, Valrose Campus, Nice, France.

Work on: "*Molecular and cellular mechanisms during assembly of brain circuits*". http://ibv.unice.fr/research-team/studer/

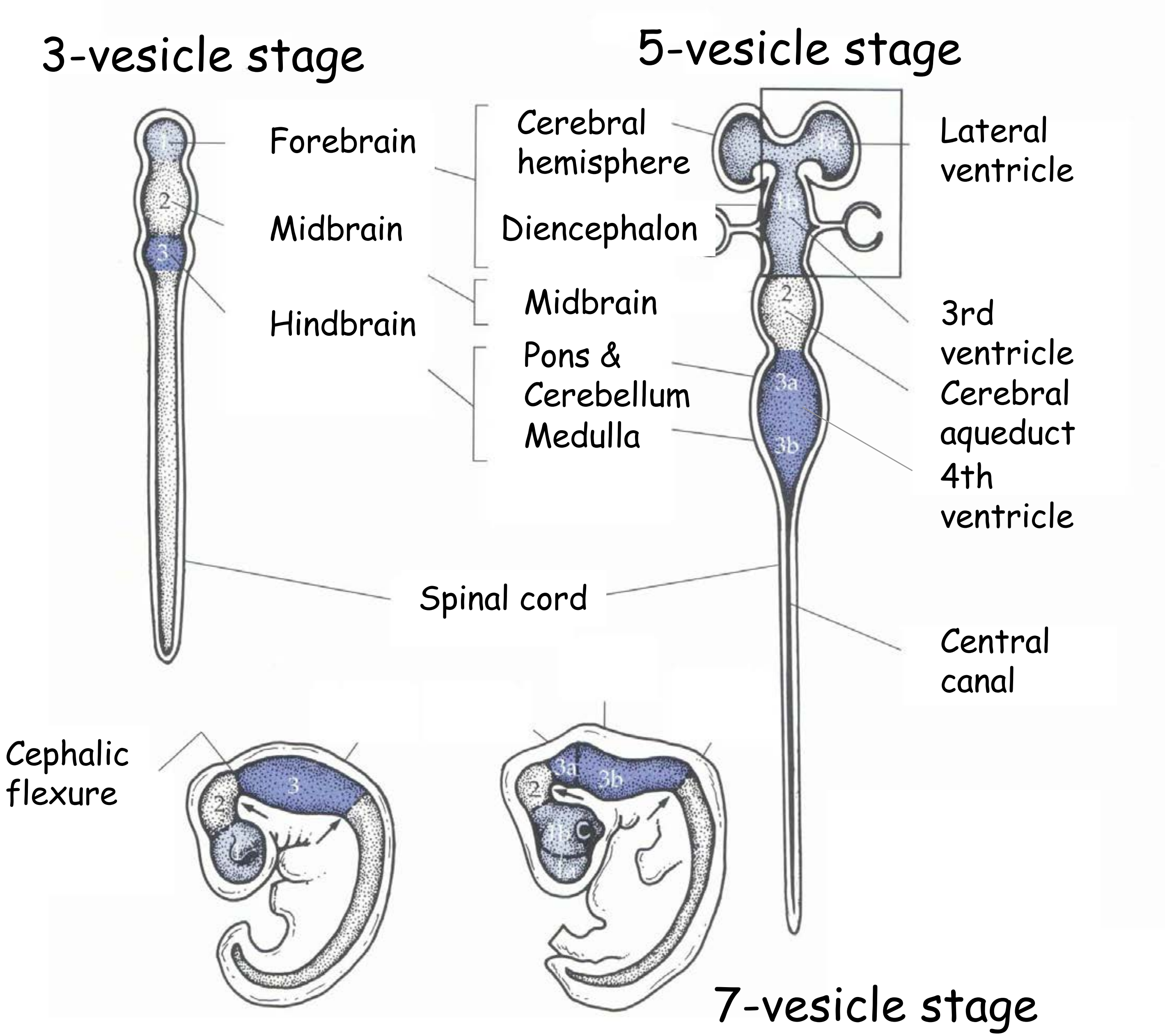
Cellular and molecular organization of the cerebral cortical progenitors in mammals

May 5th 2020

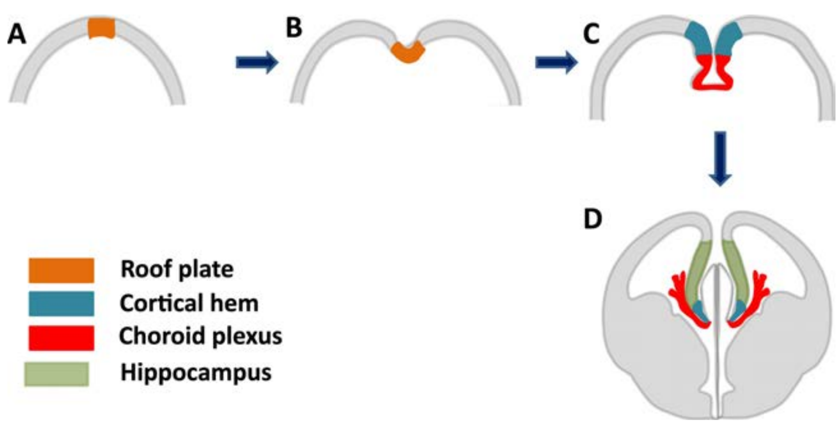
11:00-13:00

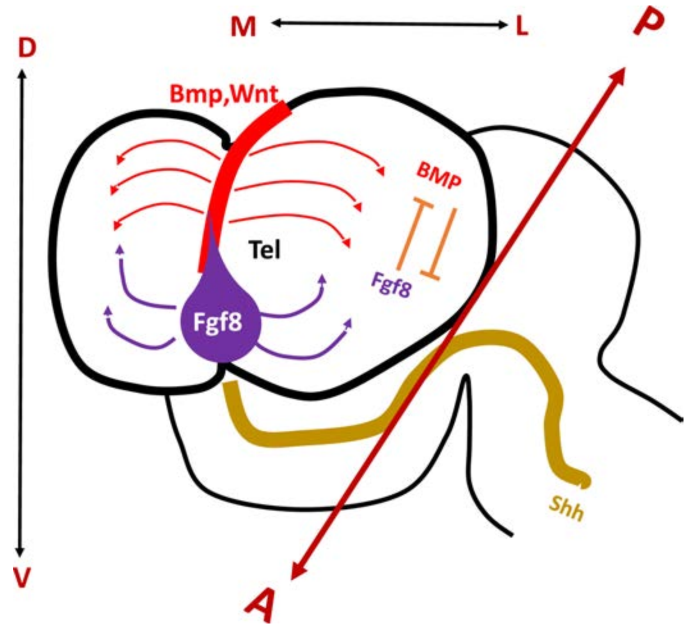


Neural Regionalization

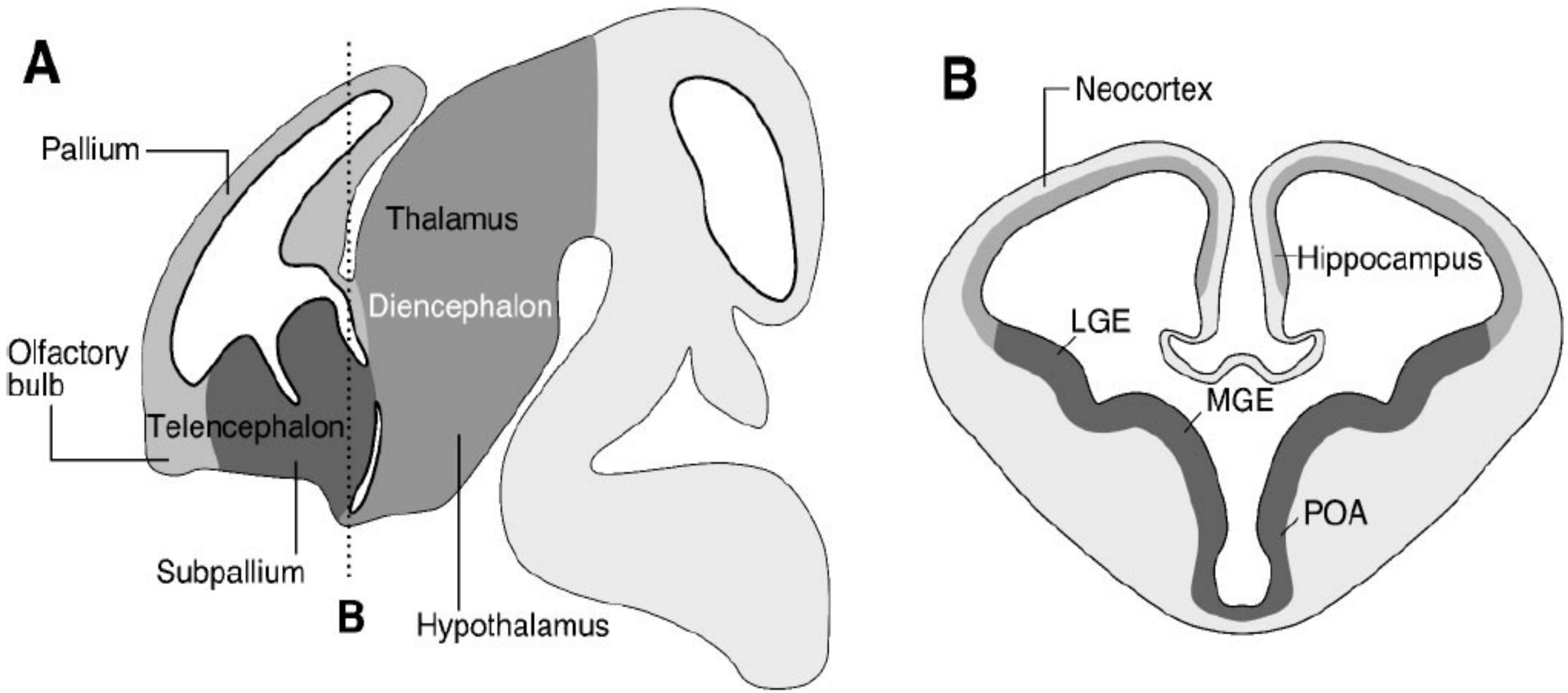


Regional signalling centres in the developing forebrain

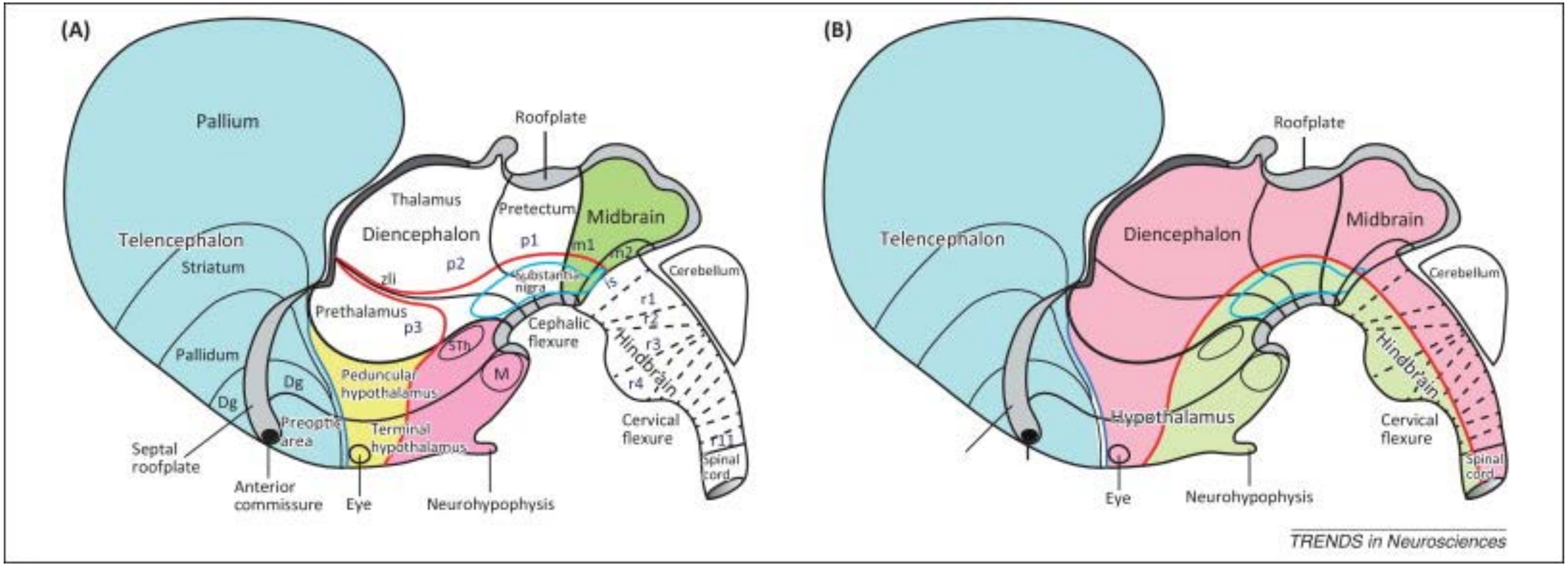




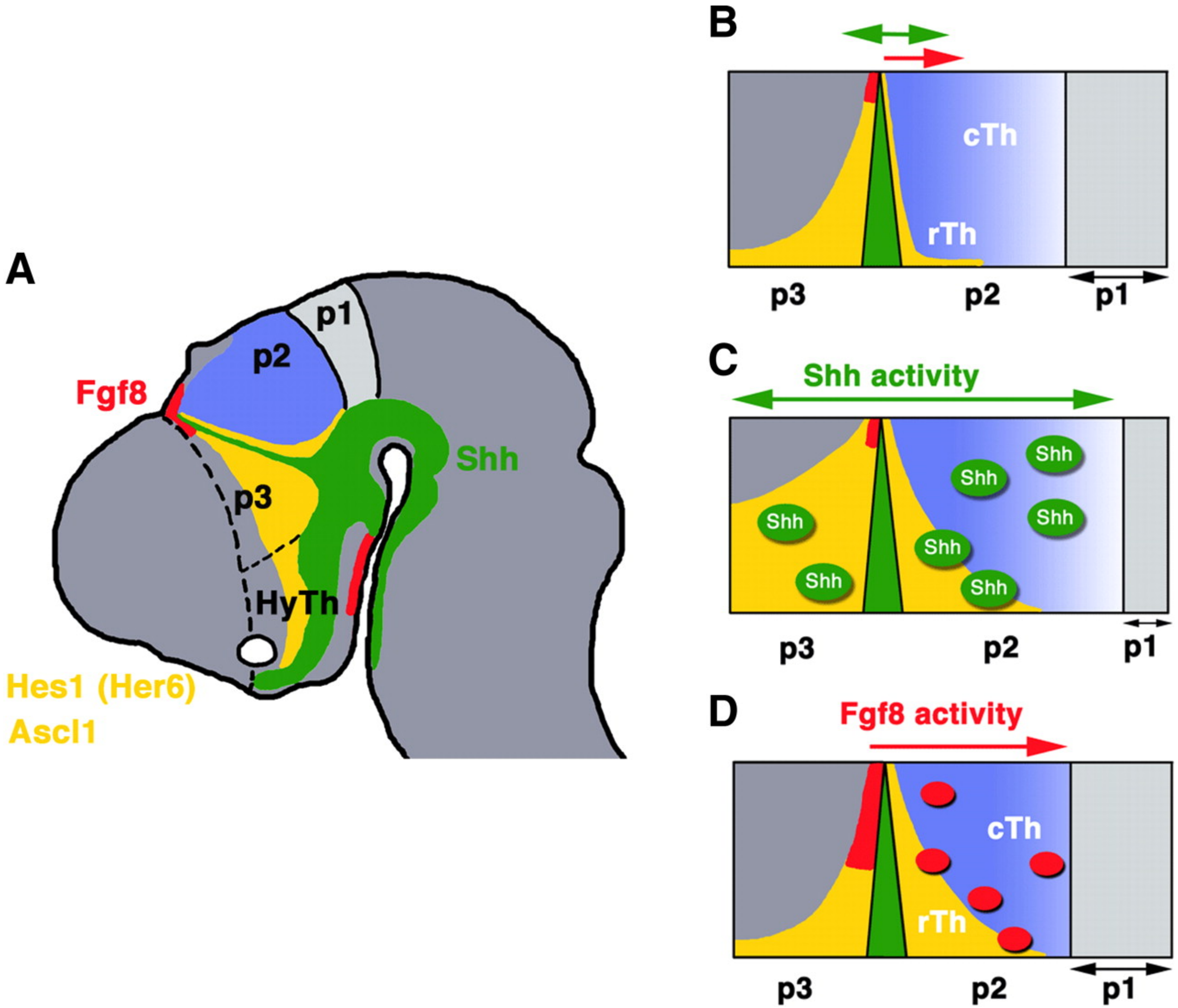
Antero-Posterior (AP) and Dorso-Ventral (DV) regionalization of the forebrain



The mammalian brain based on the prosomeric model



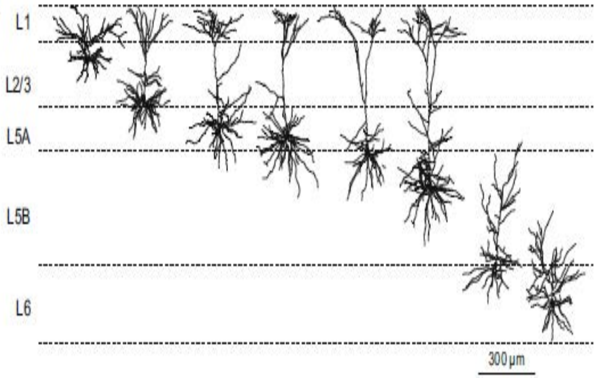
Localized signalling in the forebrain

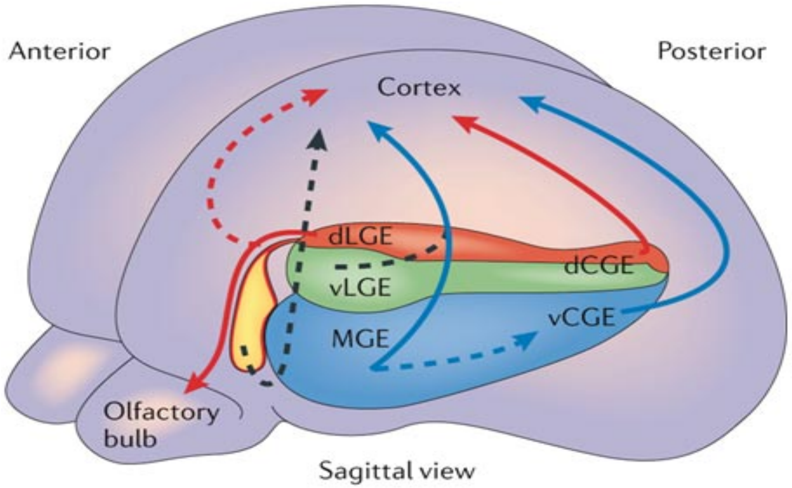


Seth Blackshaw et al. J. Neurosci. 2010;30:14925-14930

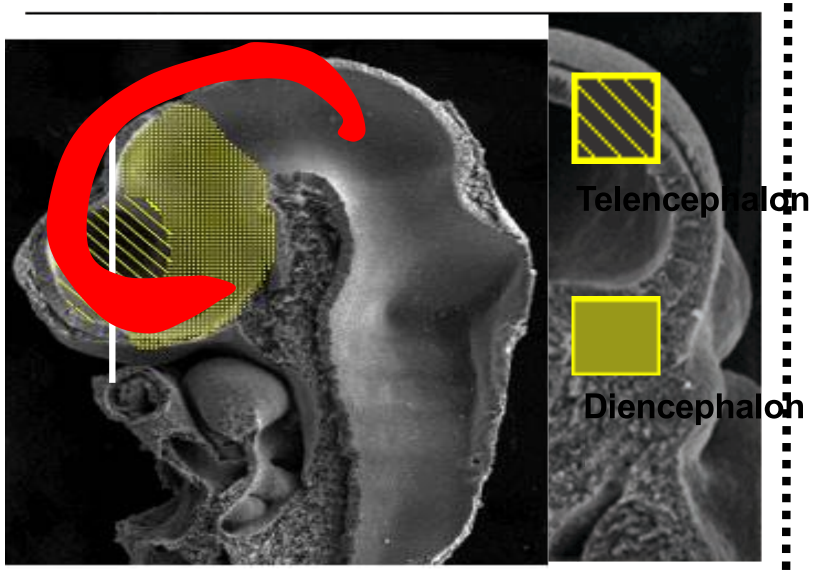
Cortical Projection neurons and Interneurons are born from different D/V regions of the telencephalon

Glutamatergic projection neurons



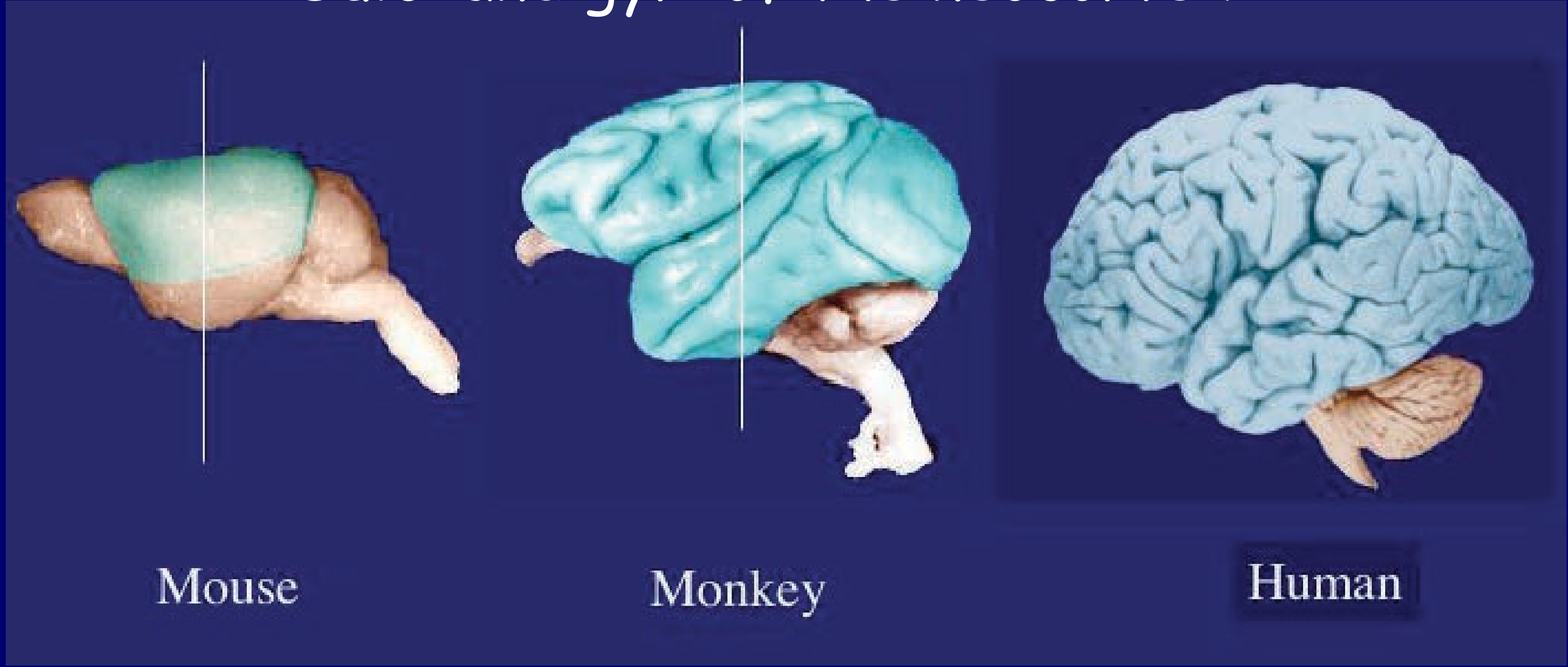


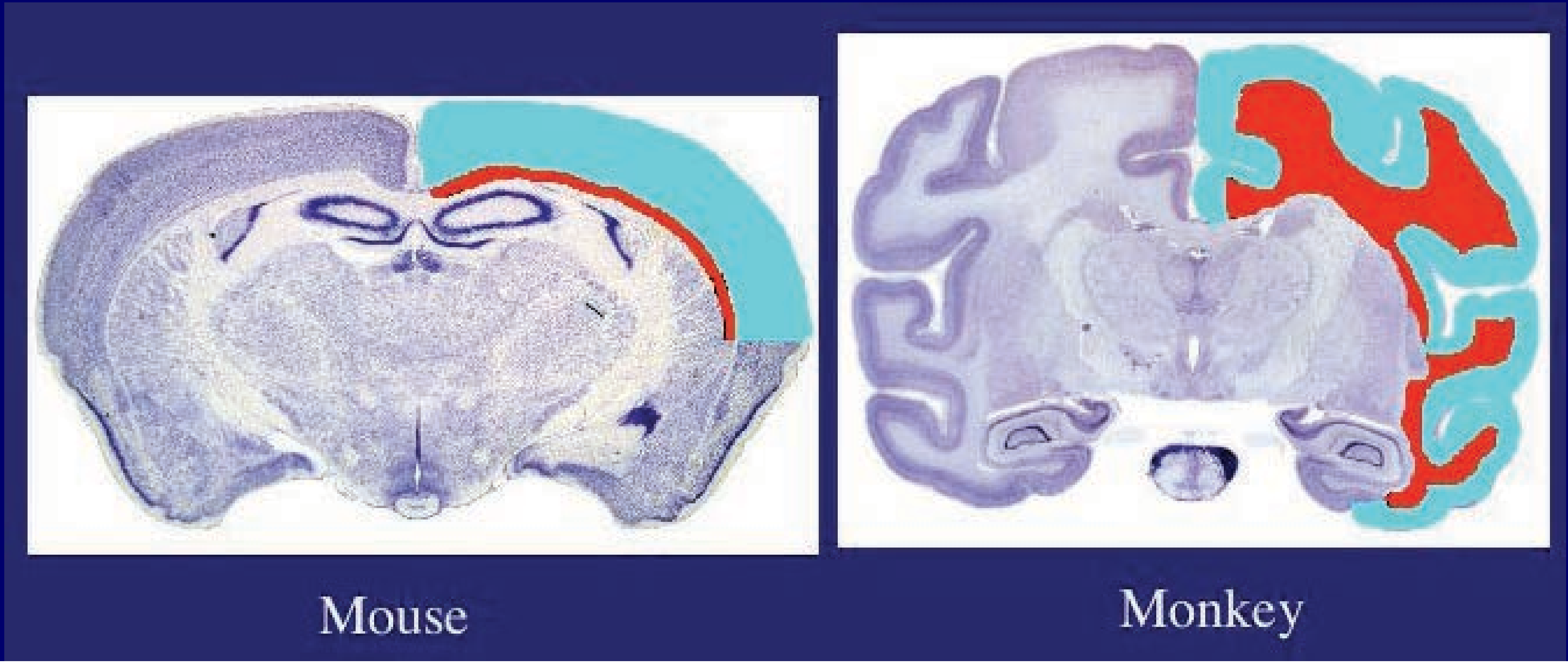
Dorsal (pallium)



Ventral (subpallium)

Sulci and gyri of the neocortex

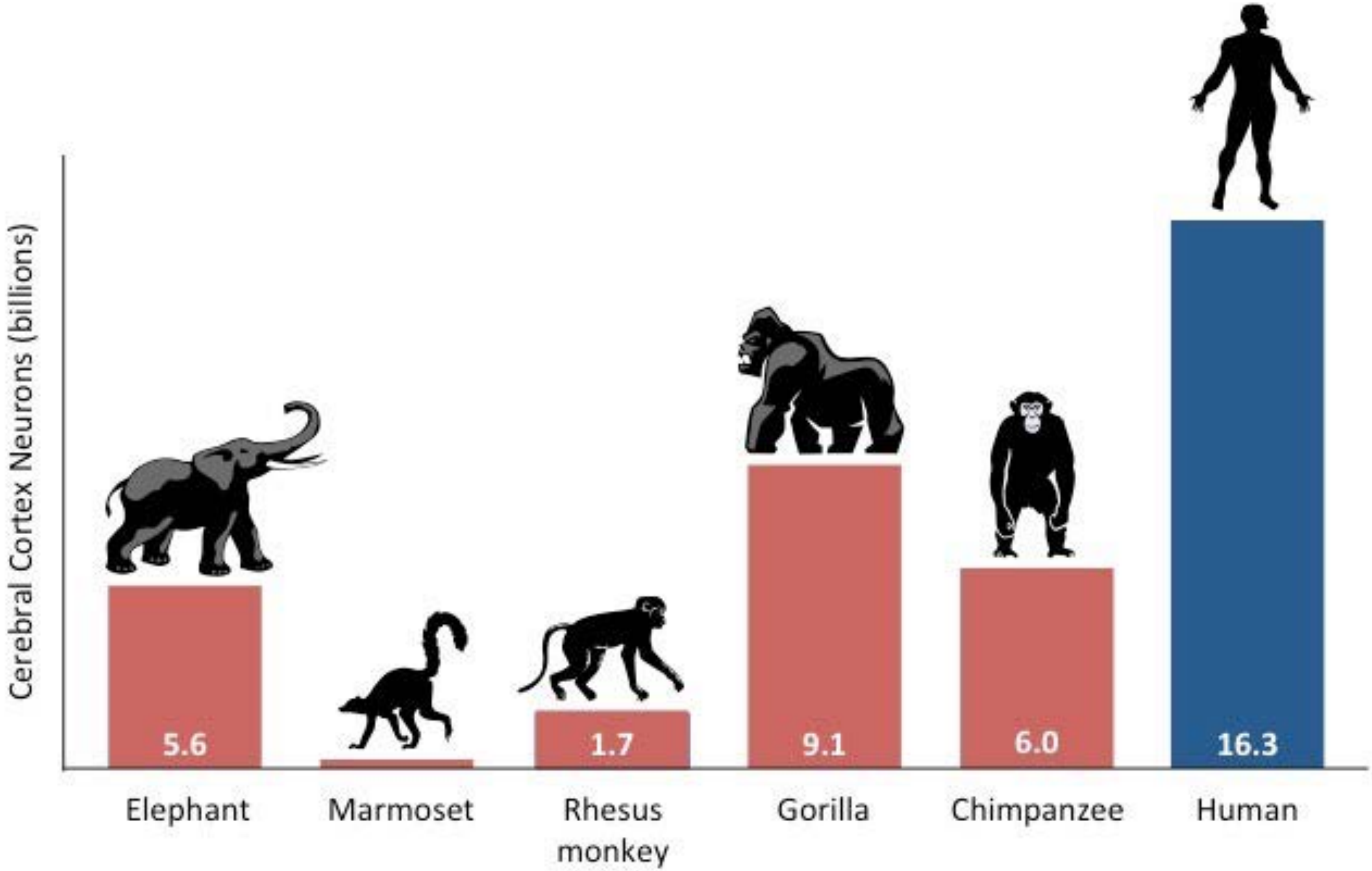




BRAIN SIZE AND NEURON COUNT

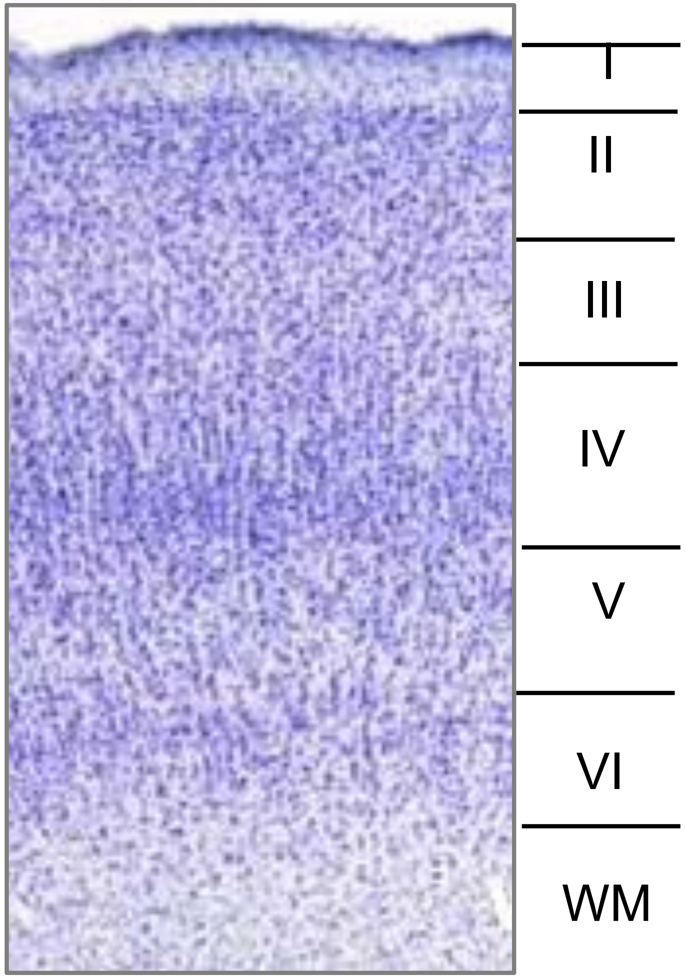
Cerebral cortex mass and neuron count for various mammals.

Capybara	Rhesus Macaque	Western Gorilla	Human	African Bush Elephant
non-primate	primate	primate	primate	non-primate
48.2 g	69.8 g	377 g	1232 g	2848 g
0.3 billion neurons	1.71 billion neurons	9.1 billion neurons	16.3 billion neurons	5.59 billion neurons

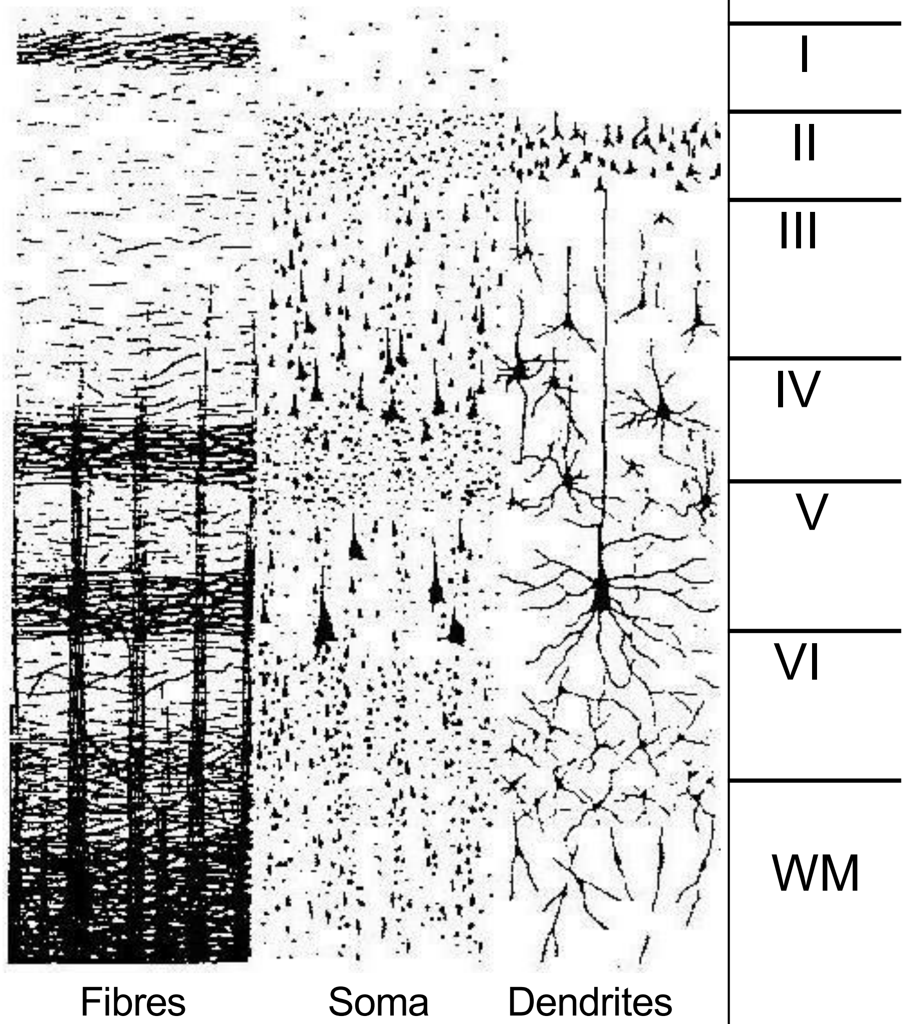


Cerebral Cortex Neurons (billions)
5.6
1.7
9.1
6.0
16.3
Elephant
Marmoset
Rhesus monkey
Gorilla
Chimpanzee
Human

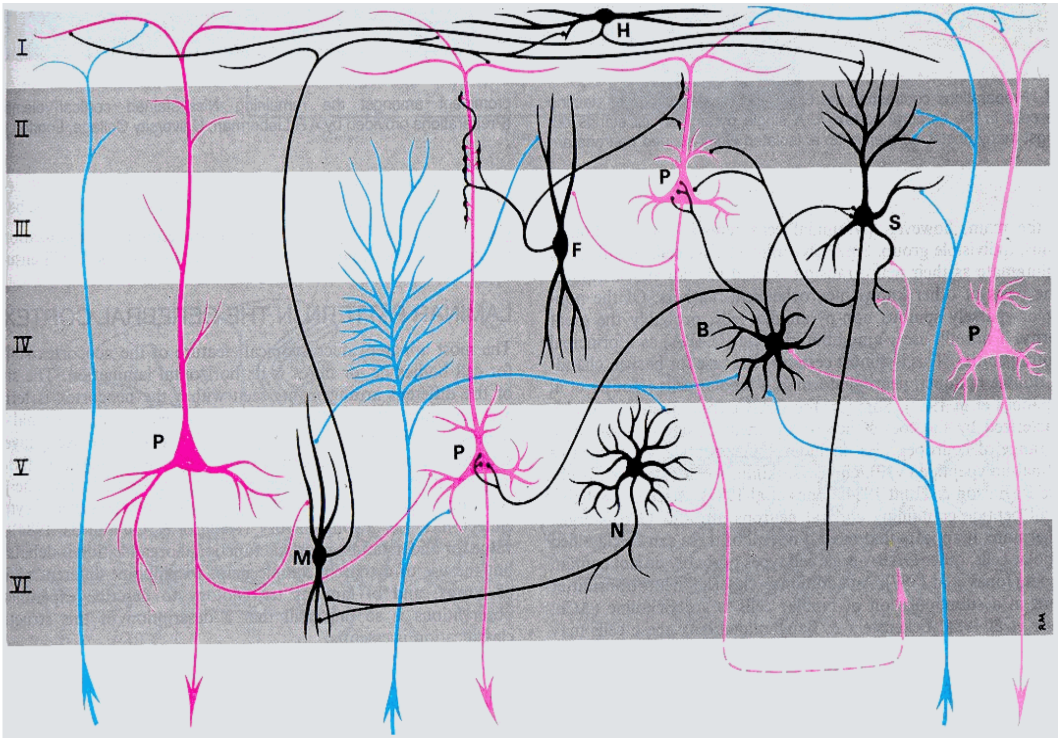
The cortex is subdivided into six distinct layers



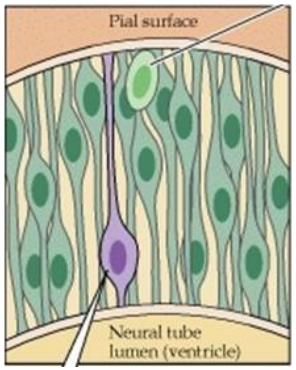
Nissl staining

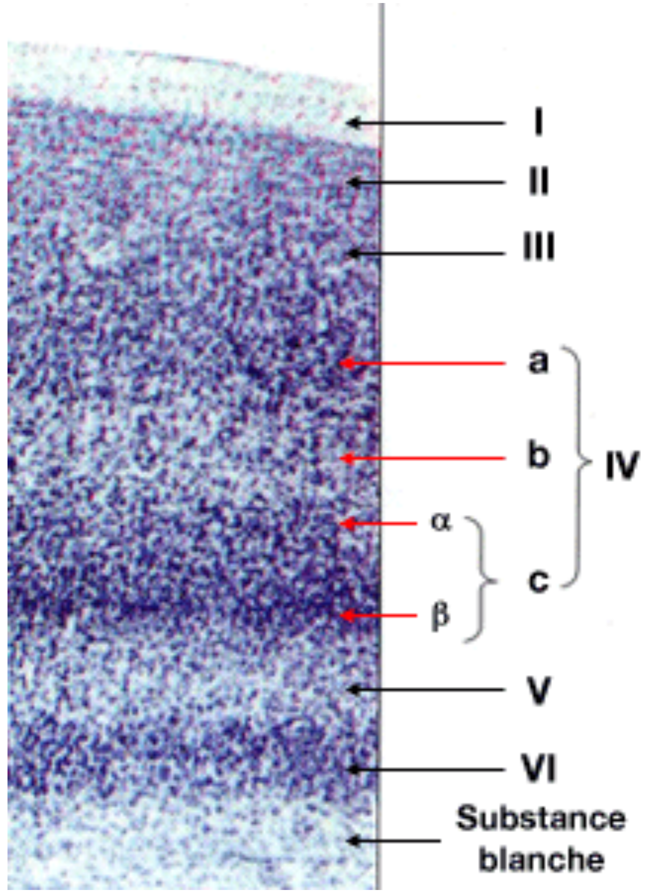


Morphological heterogeneity of cortical neurons

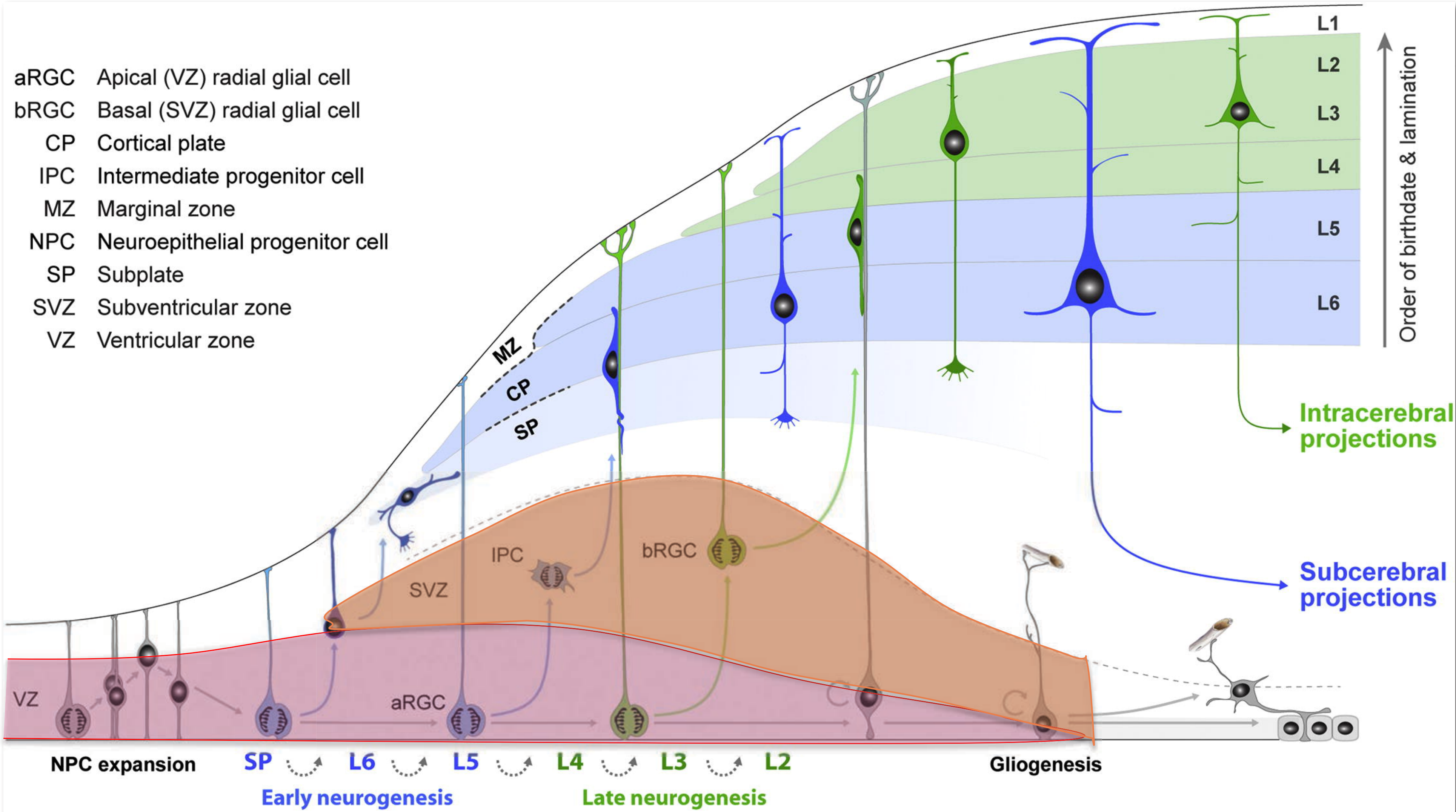


How can a relatively simple pseudostratified neuroepithelium transform into a complex structure organized into layers?

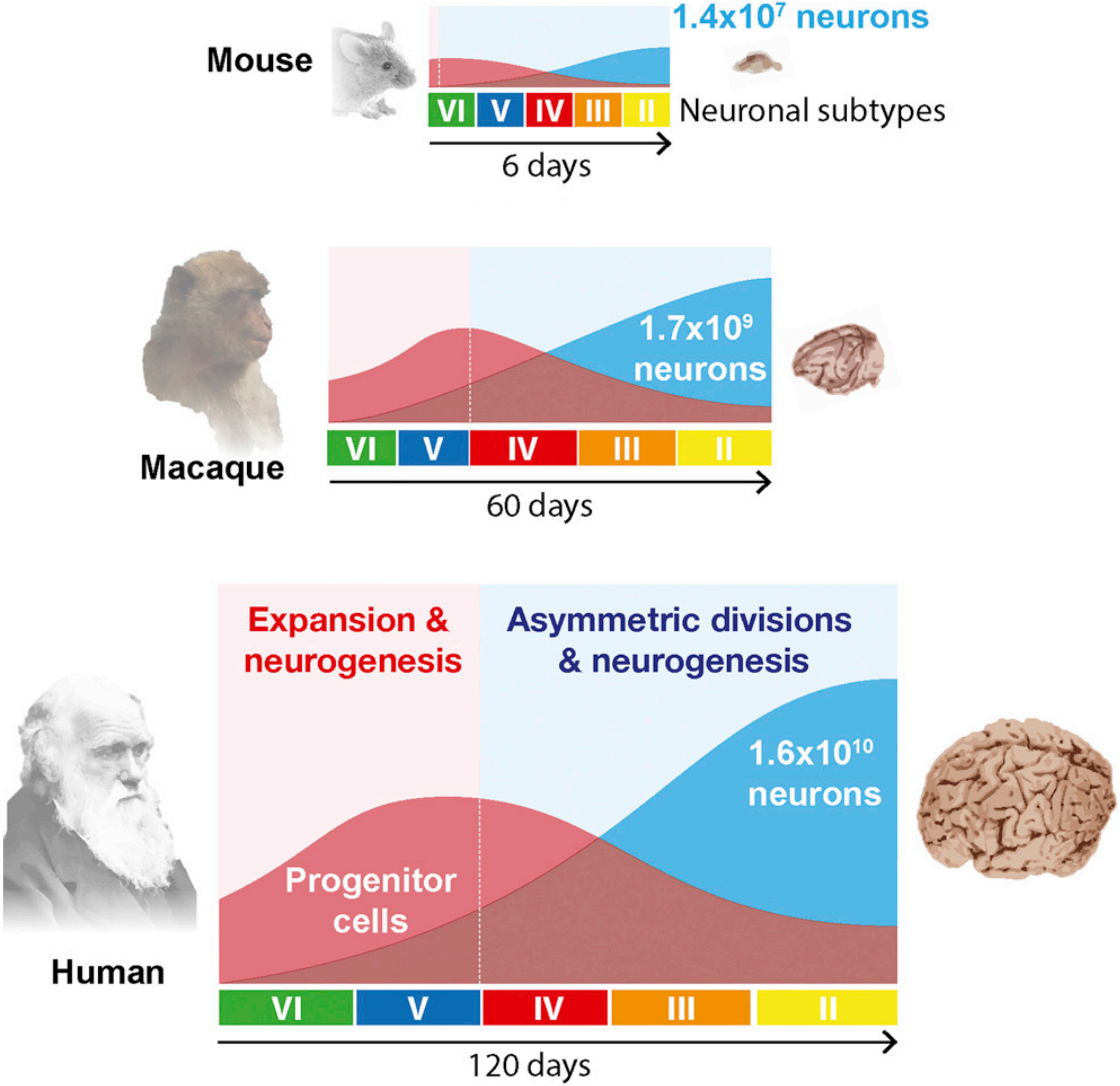




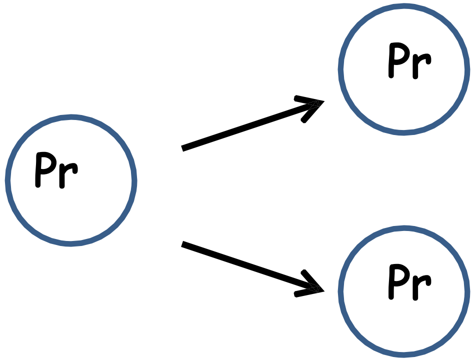
Mammalian corticogenesis



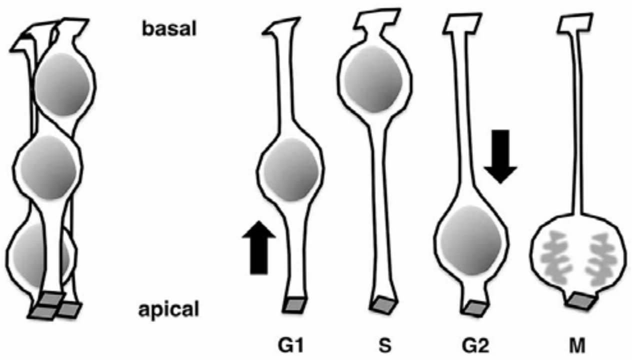
modified from Kwan et al., 2012

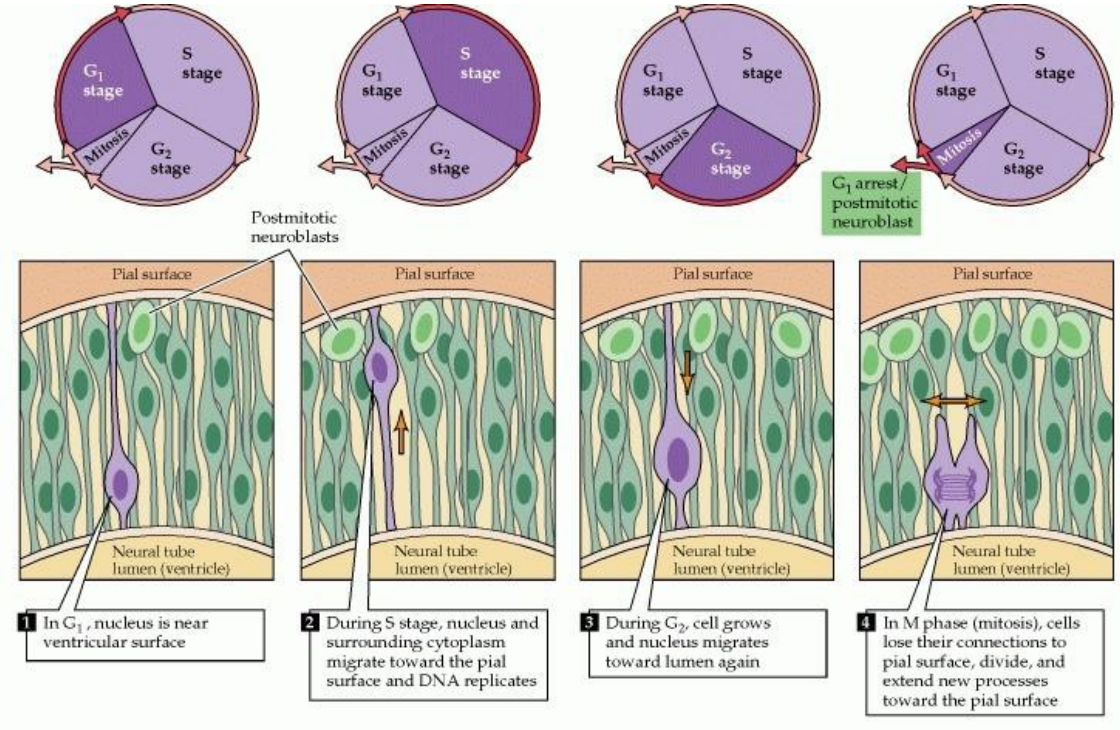

Mouse
$1.4x10^7$ neurons
VI V IV III II
Neuronal subtypes
6 days
Macaque
$1.7x10^9$ neurons
VI V IV III II
60 days
Expansion & neurogenesis
Asymmetric divisions & neurogenesis
$1.6x10^{10}$ neurons
Progenitor cells
Human
VI V IV III II
120 days

First stage: proliferation *via* symmetric division

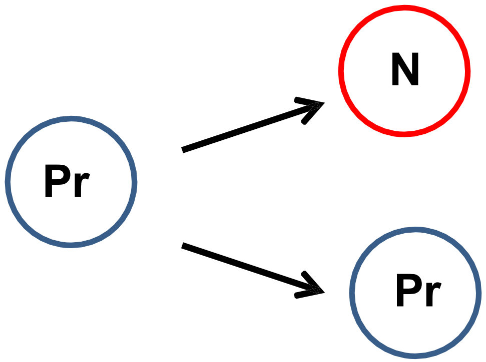


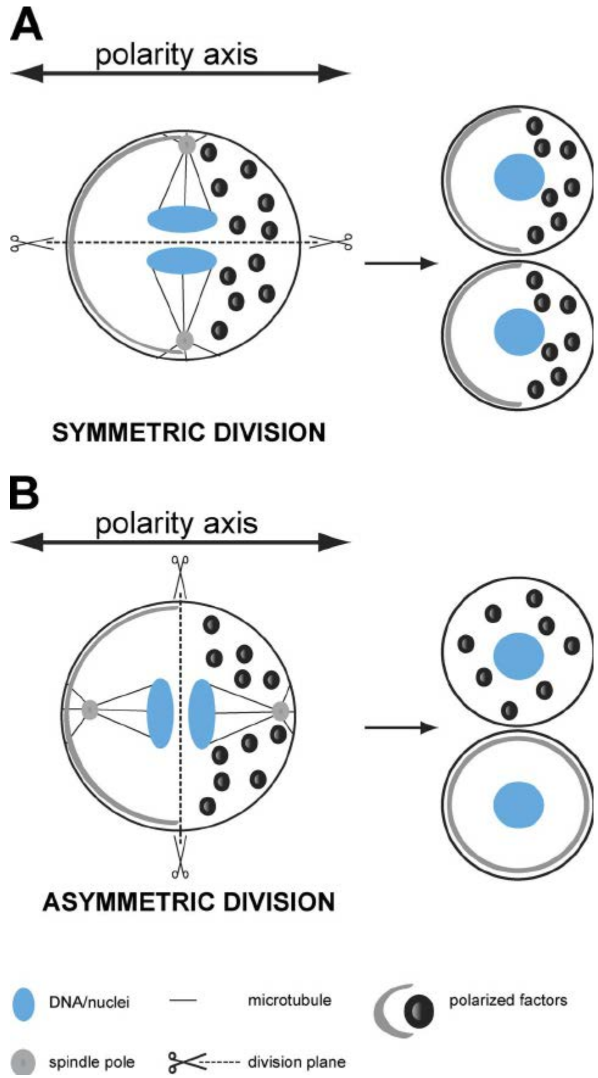
Interkinetic nuclear migration



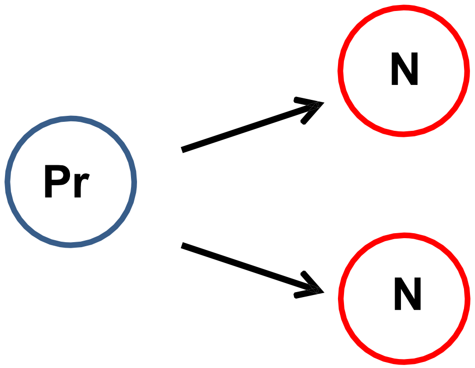


Second stage: proliferation *via* asymmtric division

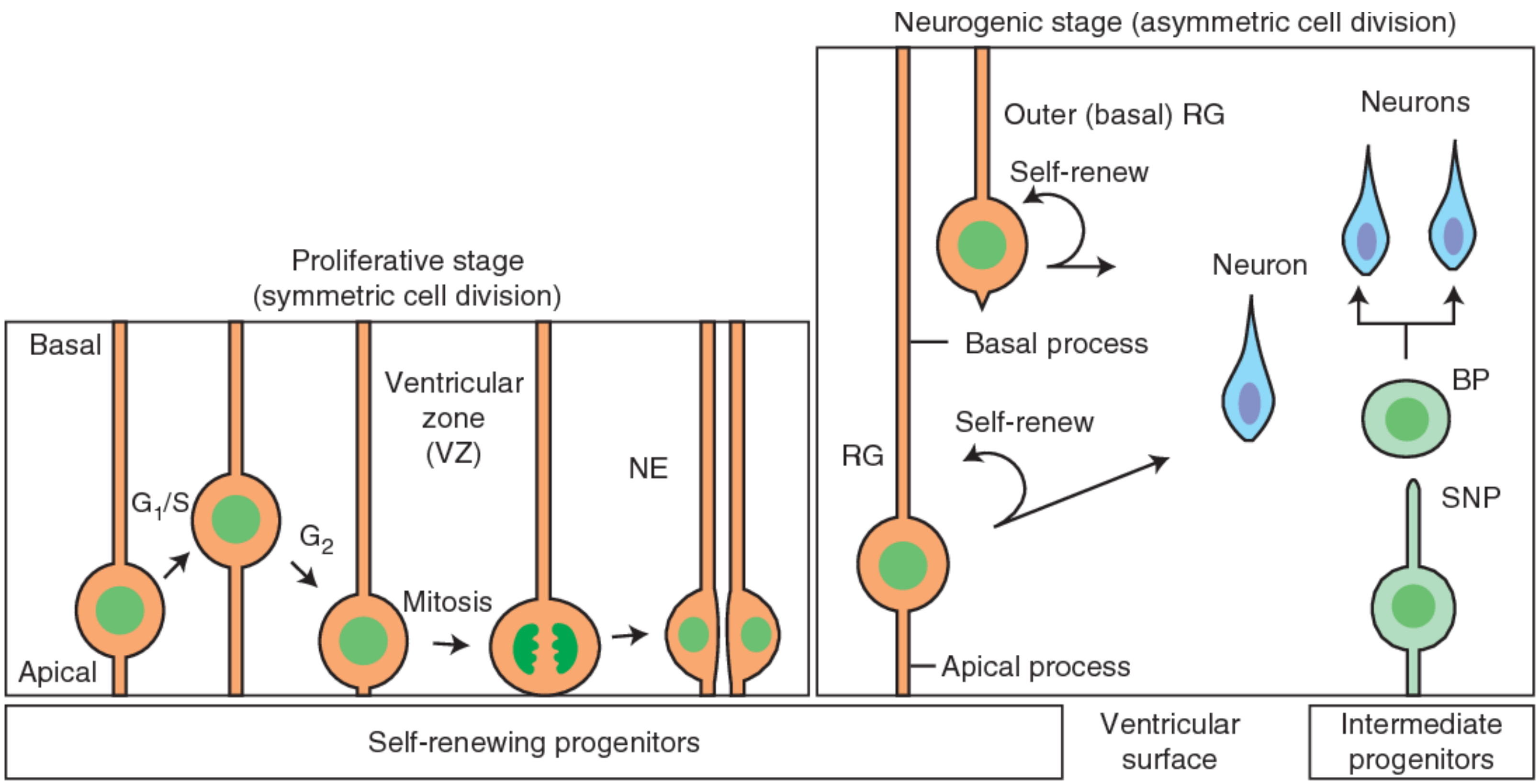




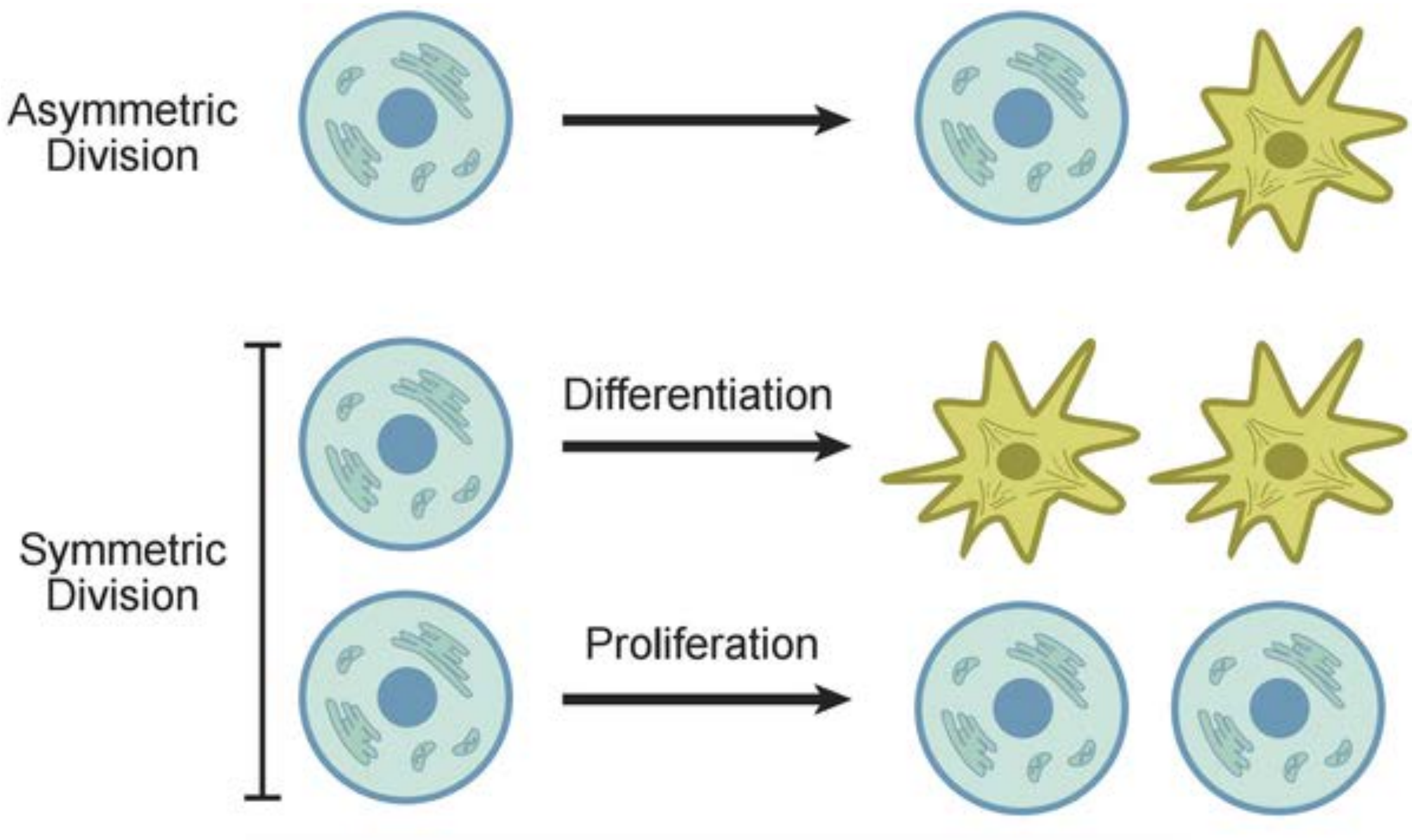
Third stage: neurogenesis via symmetric division



Self-renewing and intermediate progenitors in the developing mammalian neocortex

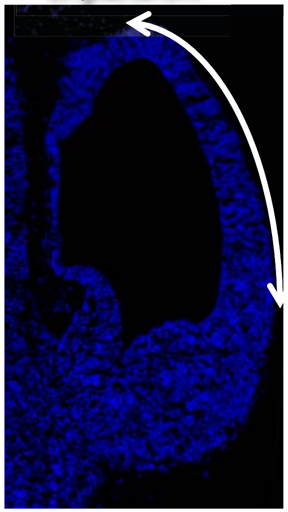


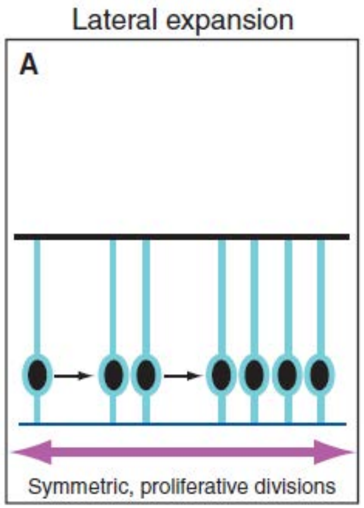
Symmetric and asymmetric progenitor divisions



Differences in cell division modes during lateral versus radial expansion

Lateral expansion

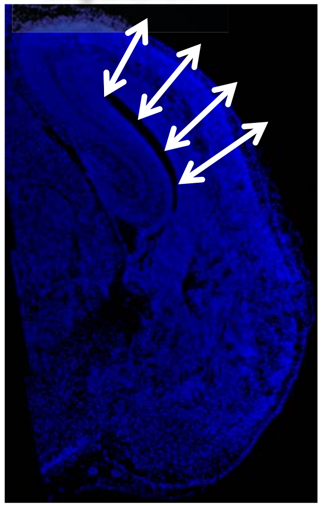


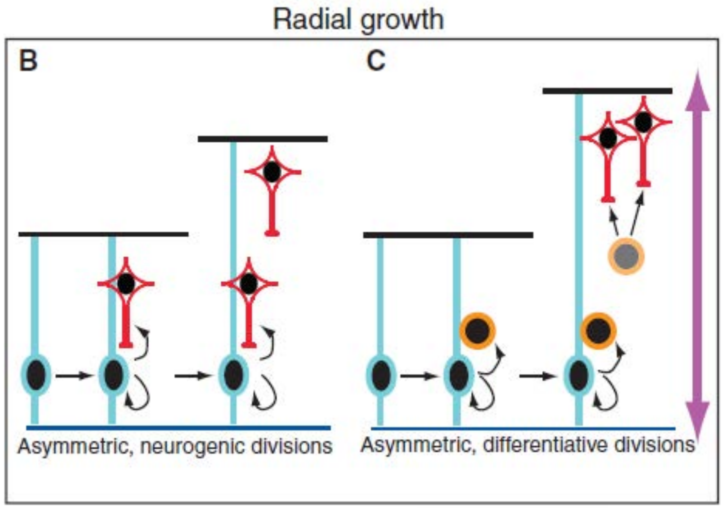


VZ

Symmetric: increase in number of radial columns + surface expansion of the cerebral cortex

Radial expansion

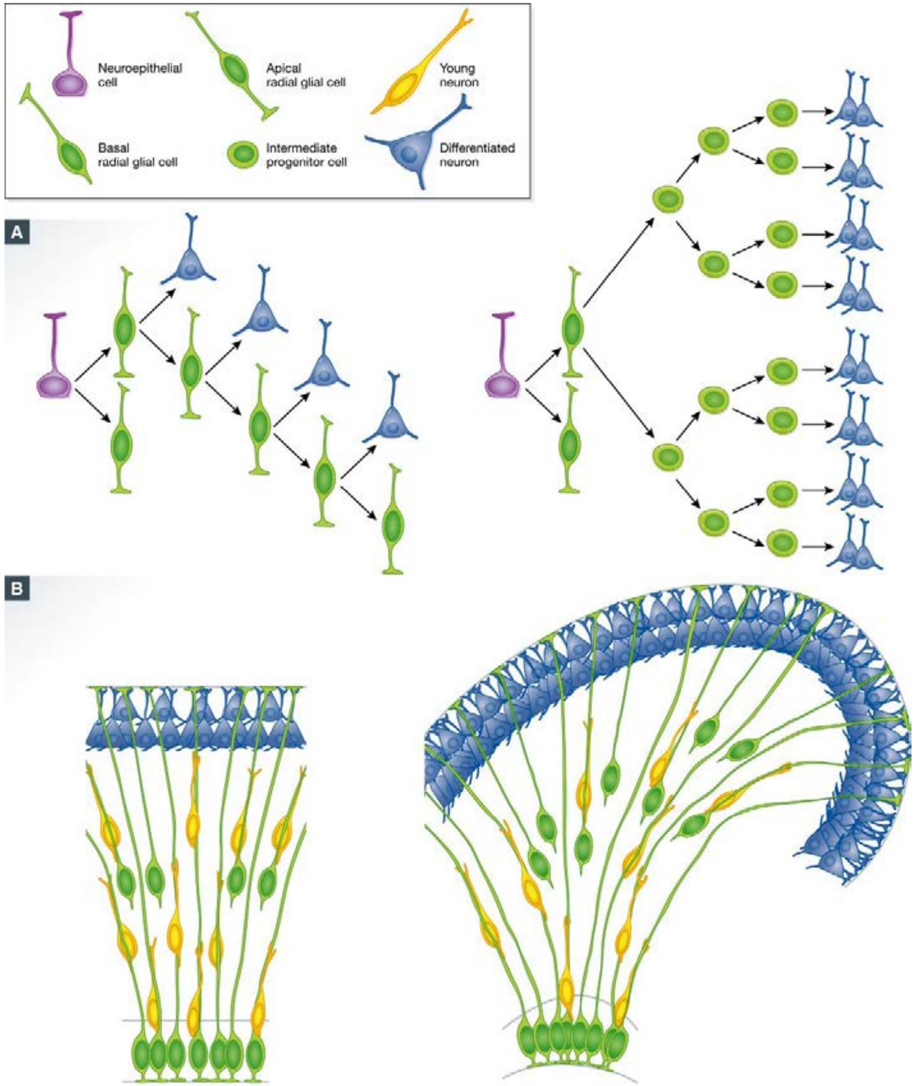




SVZ

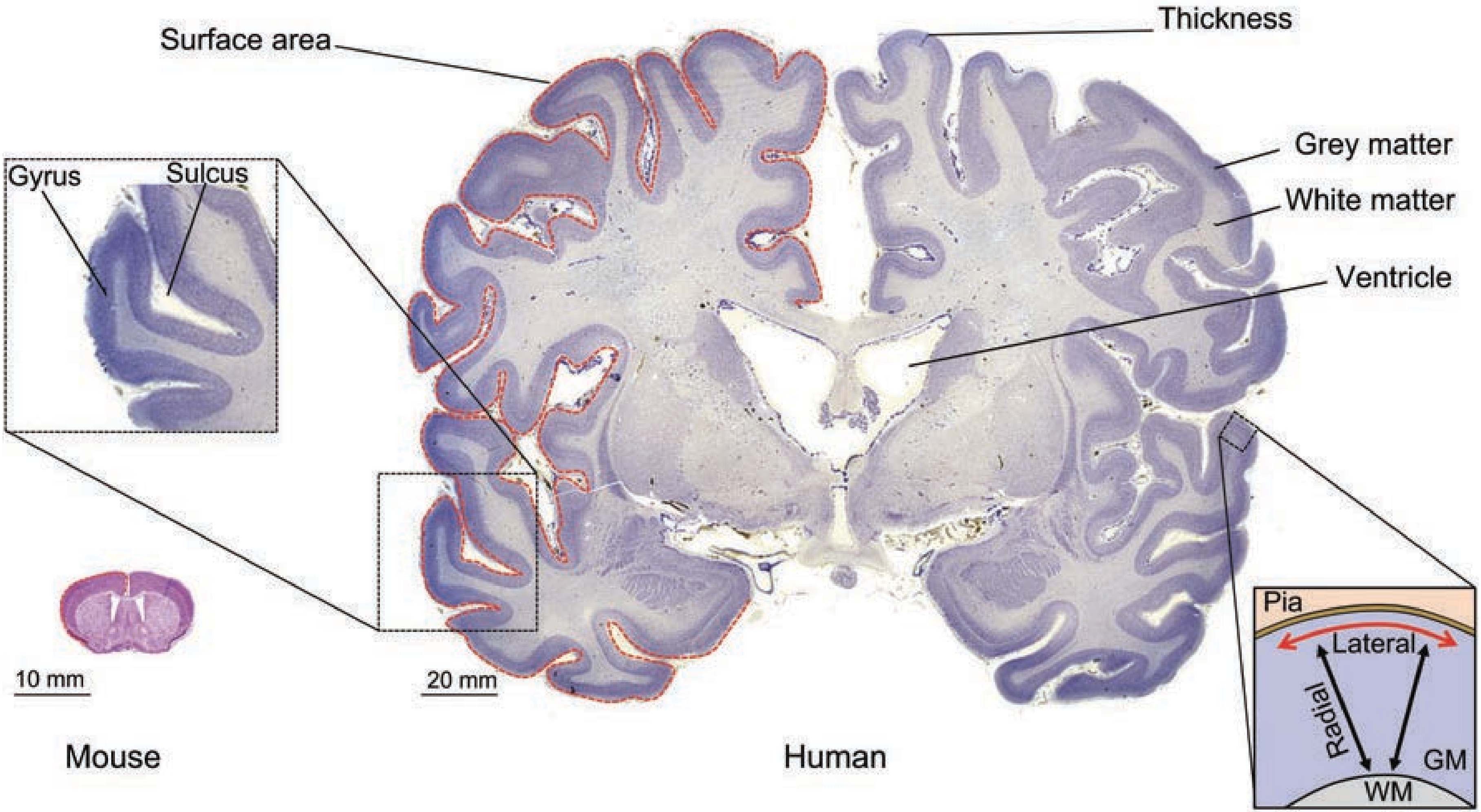
Asymmetric: increase in number of neurons within radial columns without a change in the cortical surface area (radial)

Differences in cell number for lateral vs radial expansion



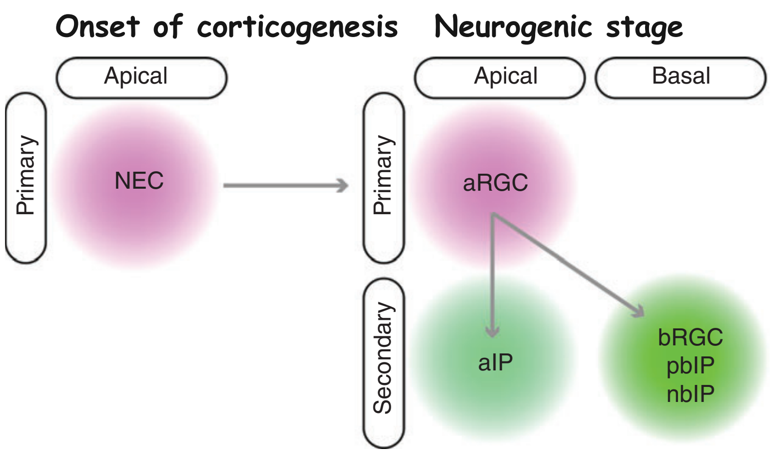
Virginia Fernández et al. EMBO J. 2016

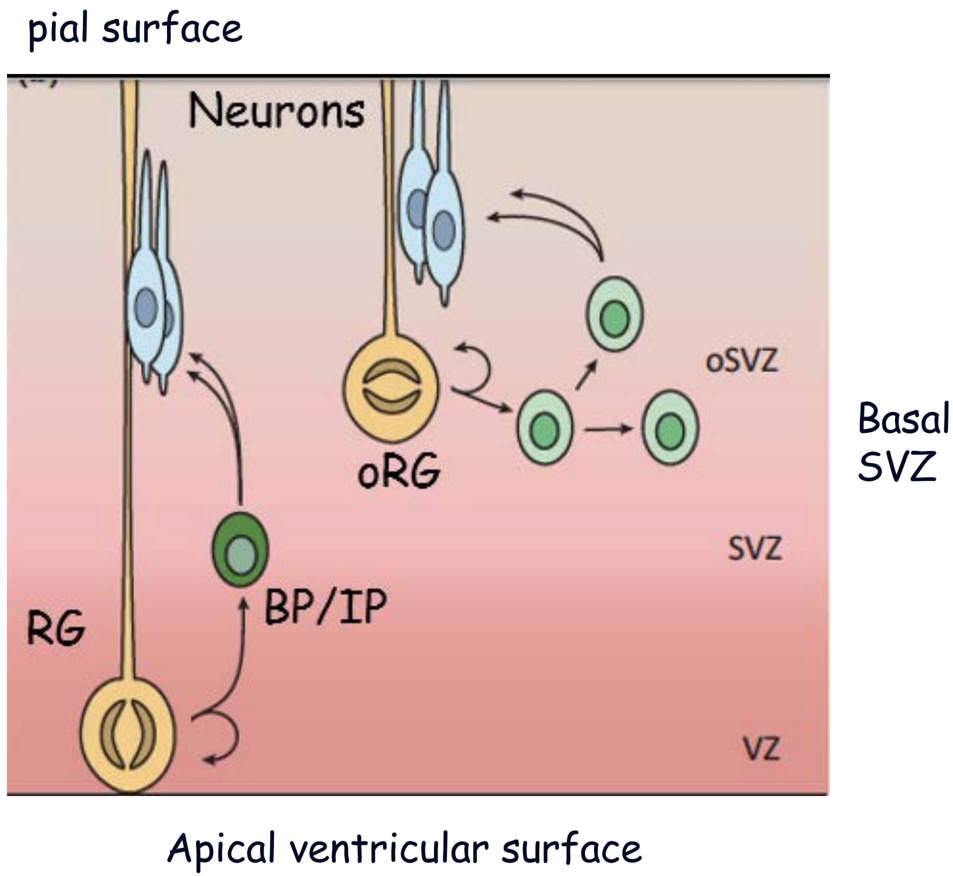
Sulci and gyri in primates



Florio & Huttner, Development, 2014

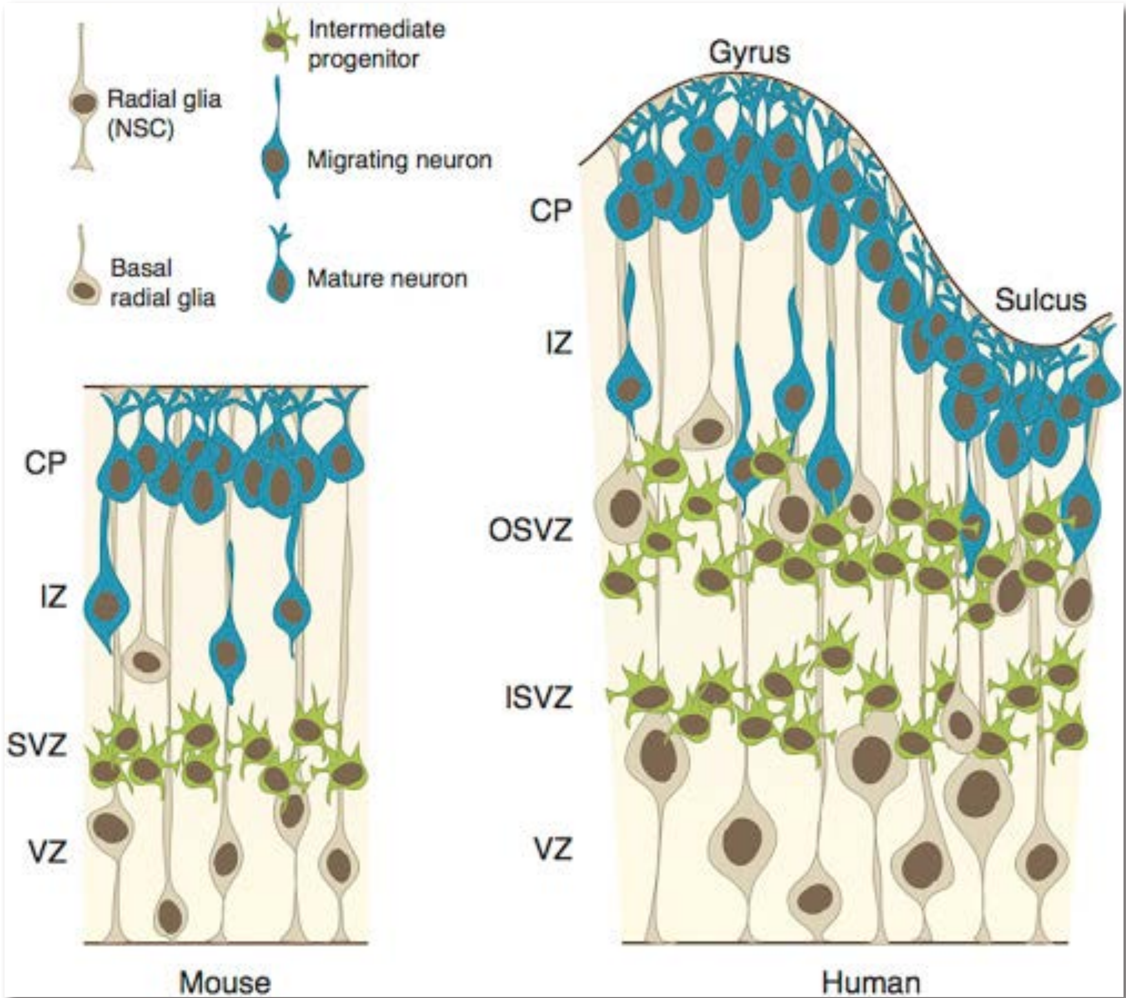
Different types of progenitors in VZ and SVZ





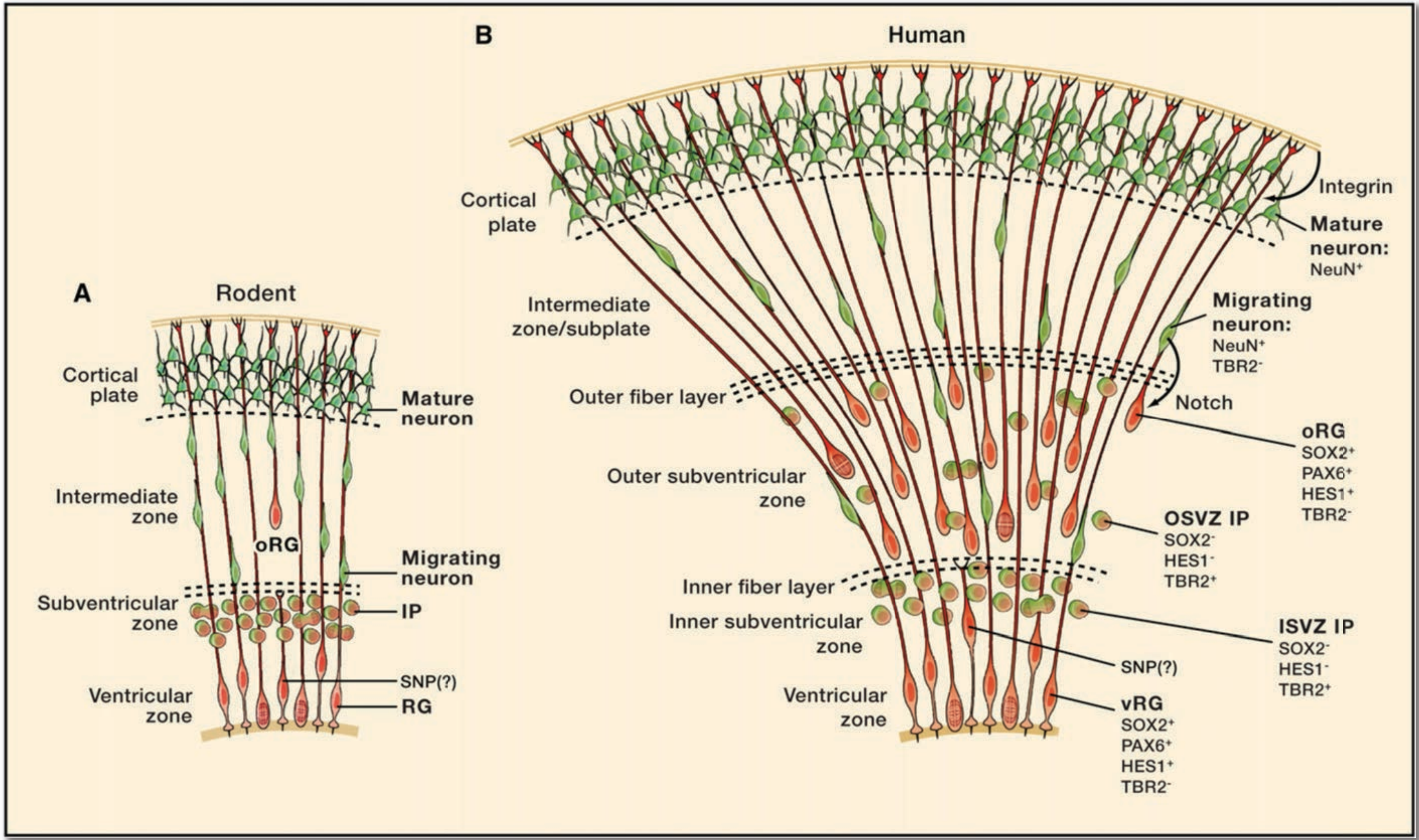
Namba & Huttner, 2016

Mouse vs human progenitor expansion



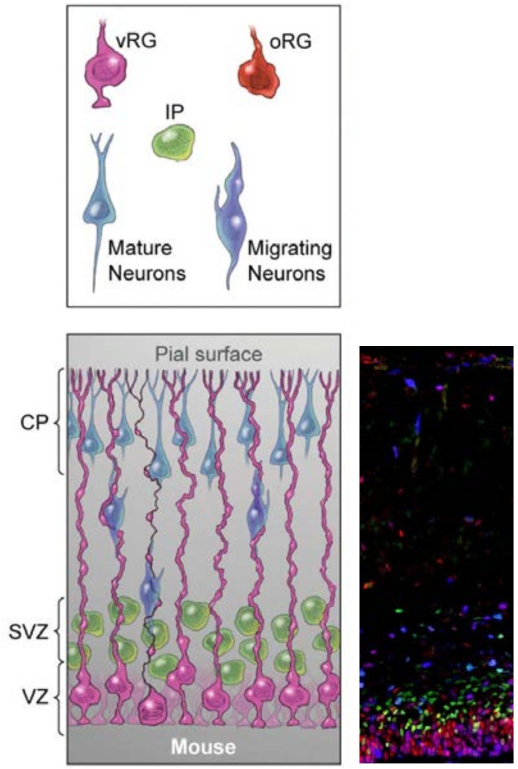
Iva Kelava, Madeline A. Lancaste, 2016

Molecular characterization of the different cell types



Lui et al., Cell, 2011

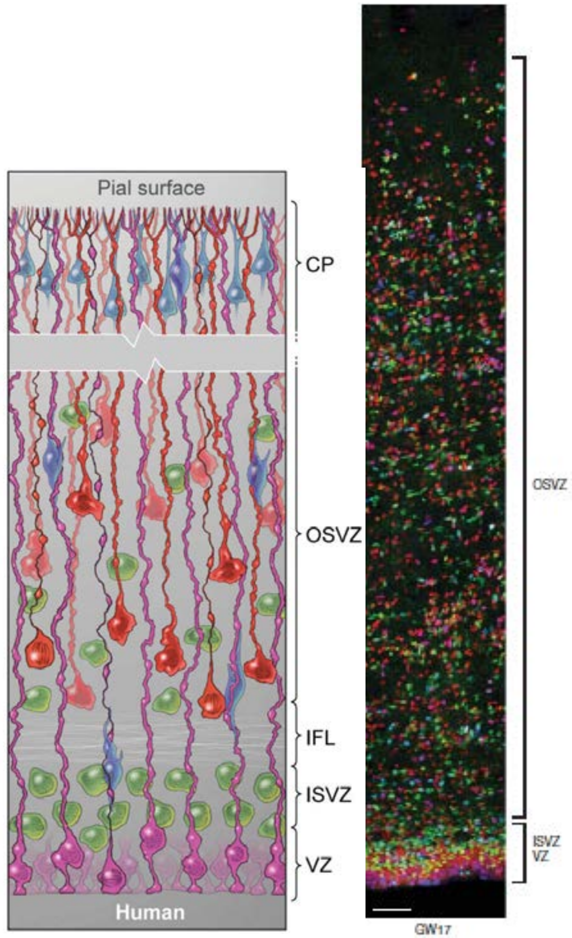
The human cortex generates more basal radial glia (OSVZ)



SVZ

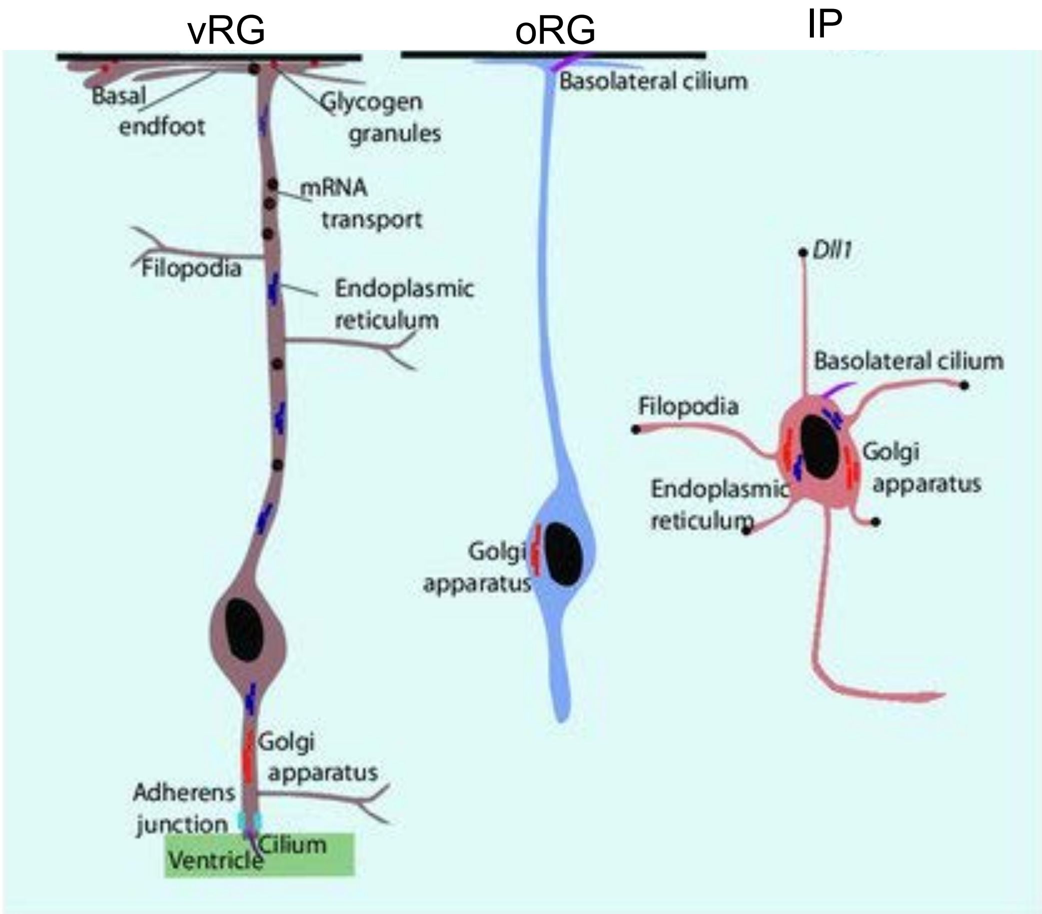
VZ

Tbr2
Sox2
Ki67



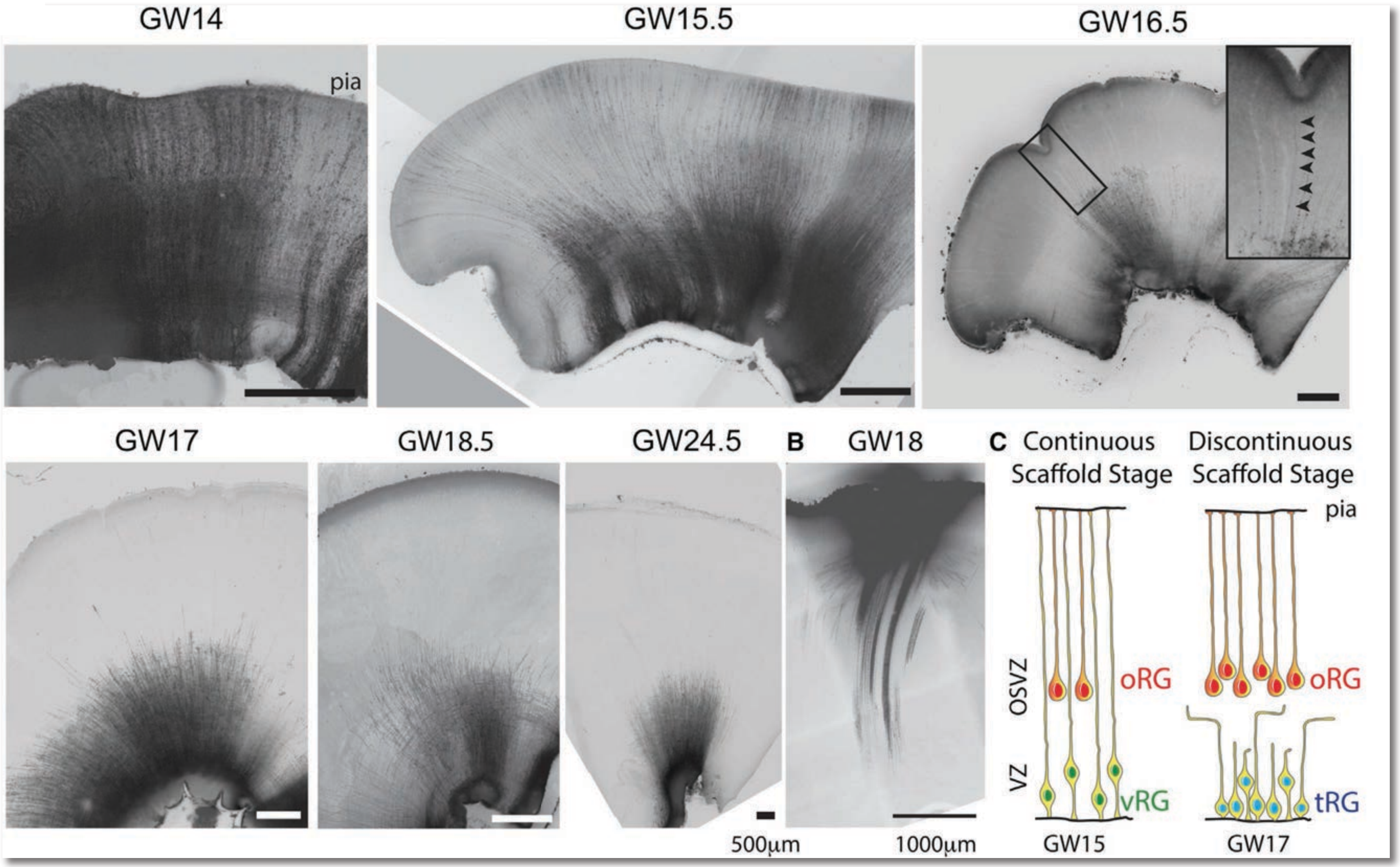
(Hansen et al.,Nature, 2010)

Morphological and cellular features of cortical progenitors



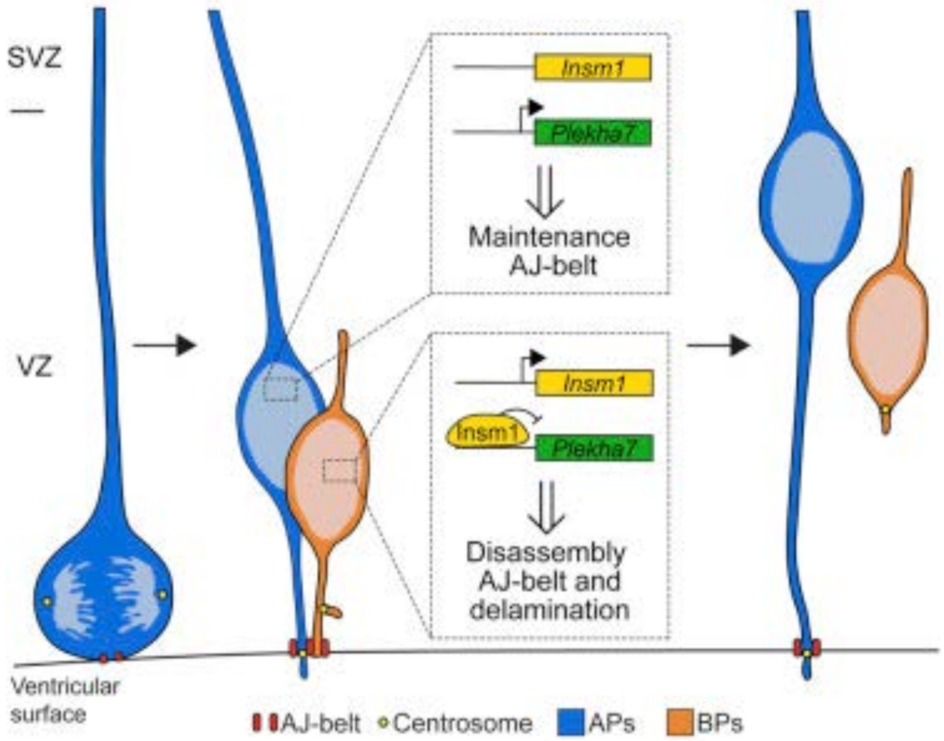
Govindan & Jabaudon, 2017

Morphological transition of radial glia subtypes



Nowakowski et al., 2016

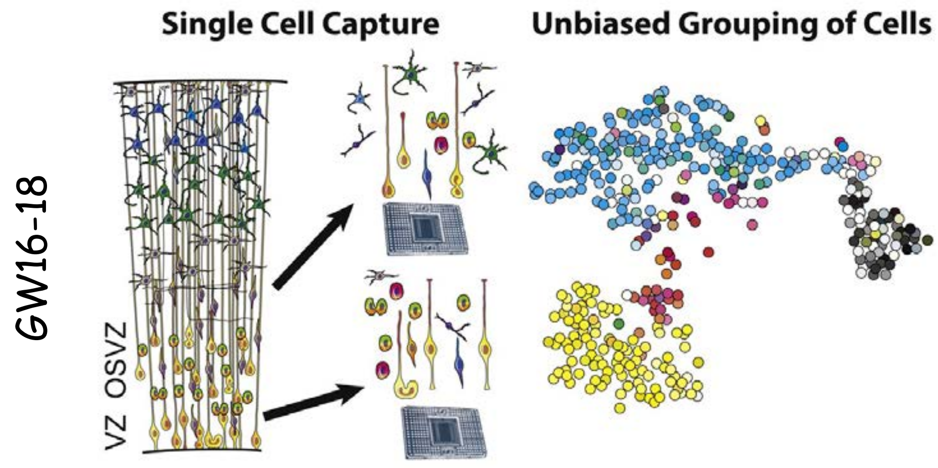
Delamination of neural progenitors via adherens junction proteins

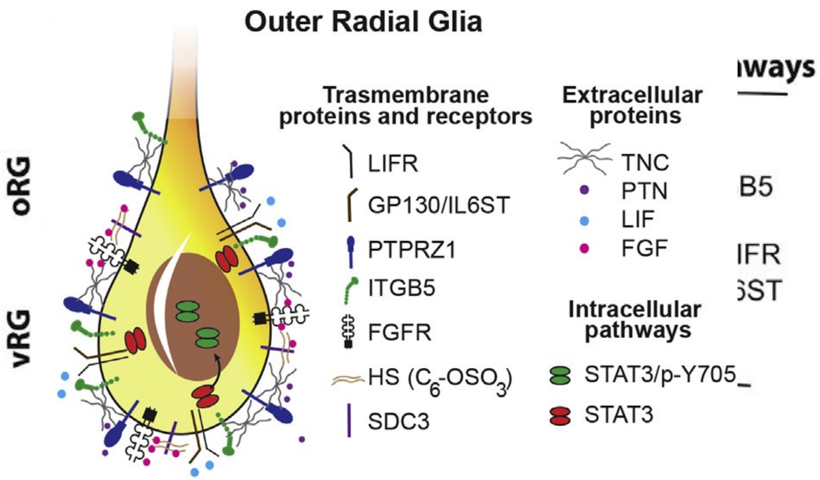


<u>Plekha7:</u> adherens junction belt-specific protein

Tavano et al., 2018

Human outer Radial Glia (oRG) cells retain a distinct molecular identity



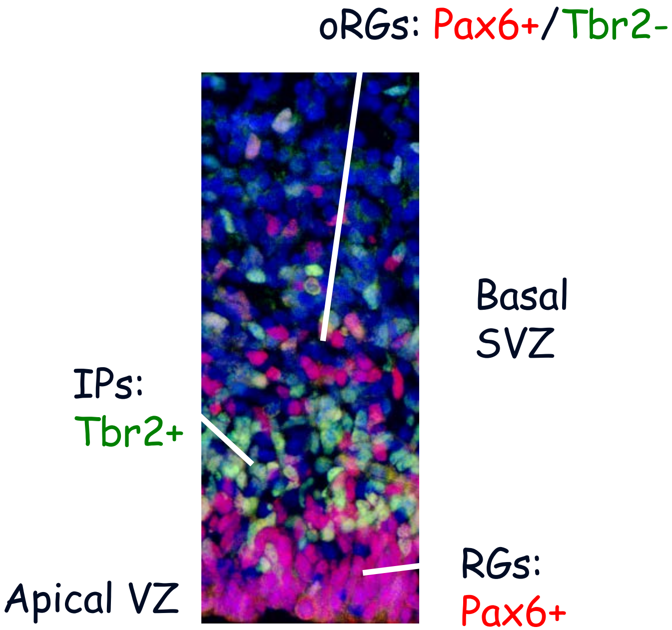


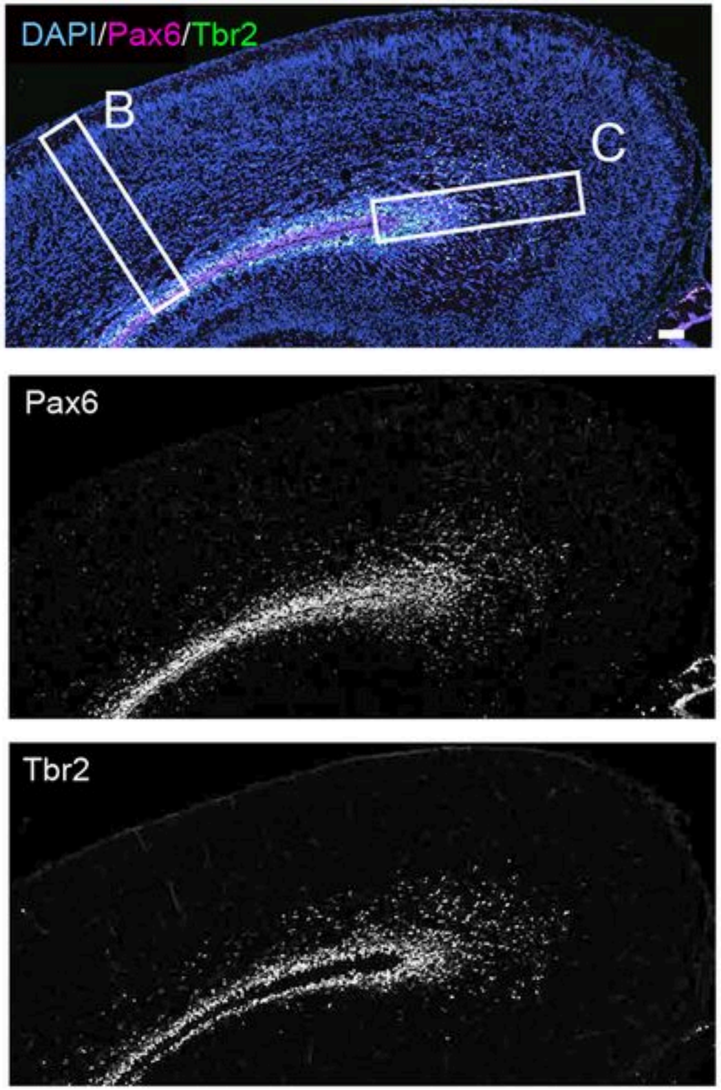
Signalling pathways:
- Growth factors (maturation)
- Integrin (promotes RG identity)
- LIFR/STAT3 (maintain RG ientity)
- pY705/STAT3 (cell cycle progression)

Pollen et al., 2015

An oRG population in the mouse

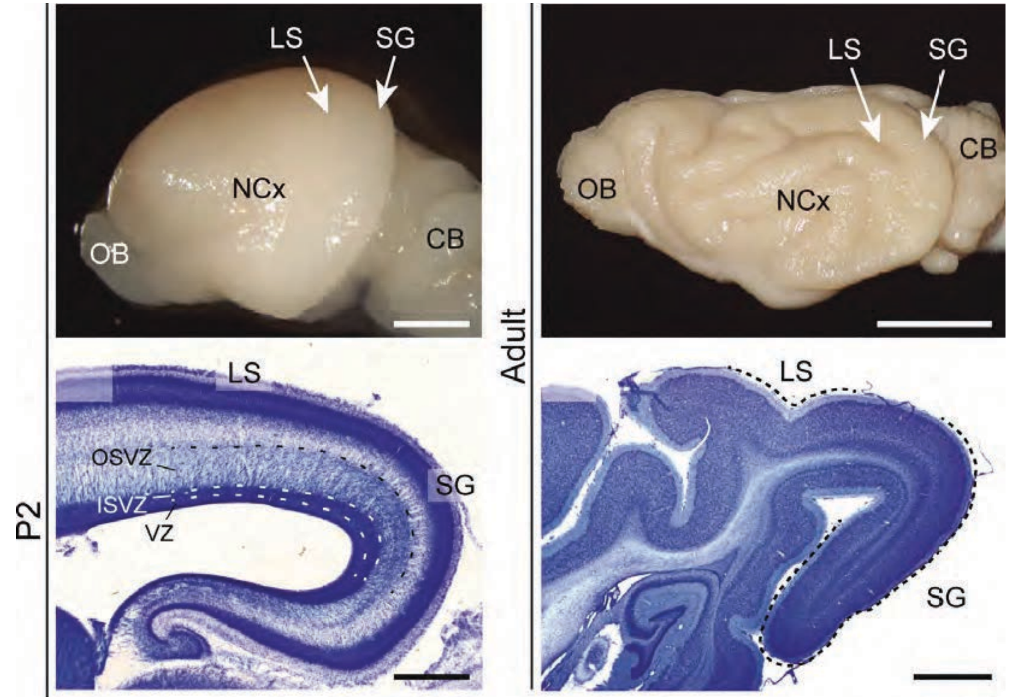
	RG	BP/IP	oRG
Sox2	+	-	+
Pax6	+	-	+
Tbr2	-	+	-
P-Vim	+	-	+
Hopx	+	-	+





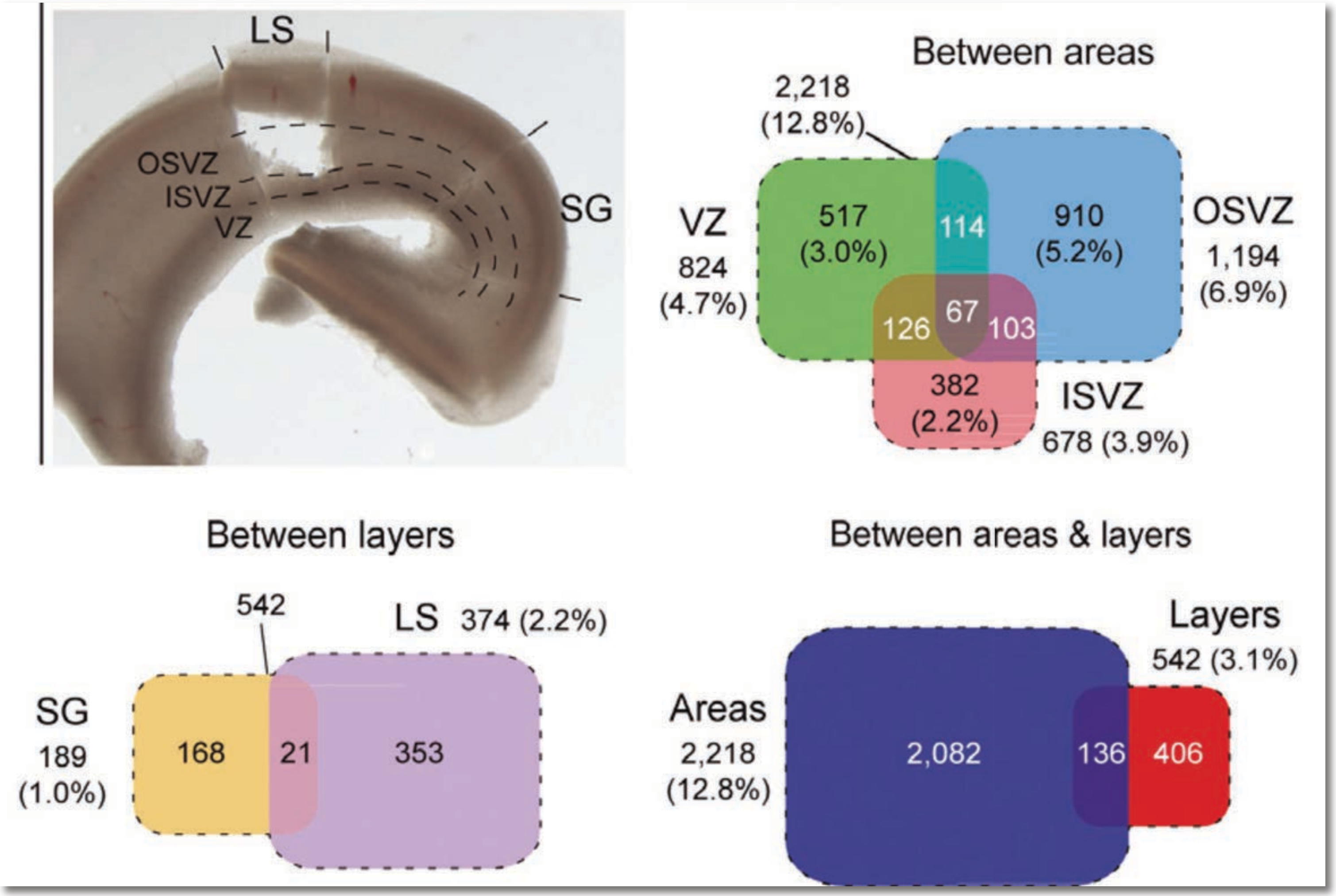
Vaid et al., 2018

The ferret: an ideal animal for studying mechanisms leading to cerebral cortical gyrencephaly



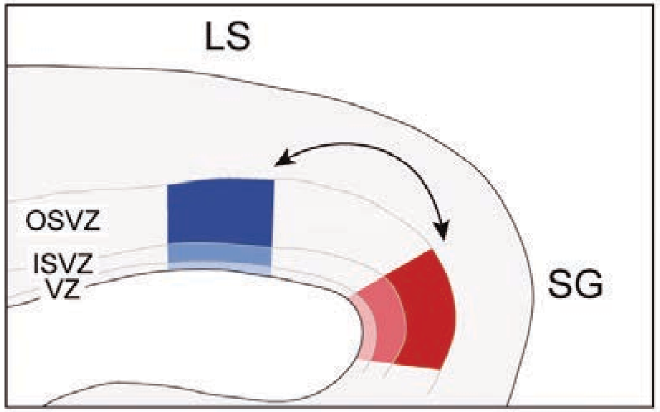
De Juan Romero et al., 2015

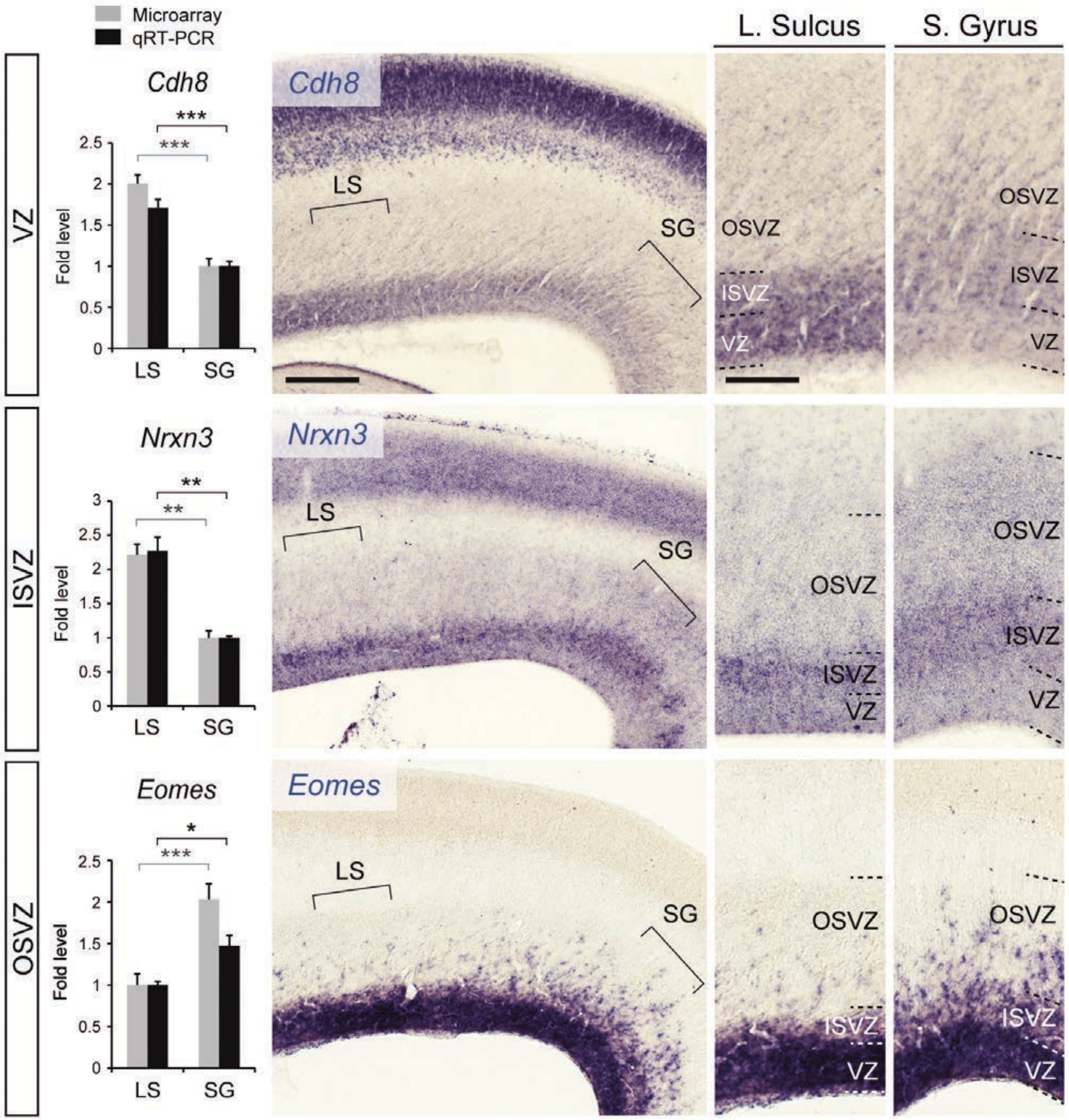
Looking for genes involved in cortical folding in the ferret



De Juan Romero et al., 2015

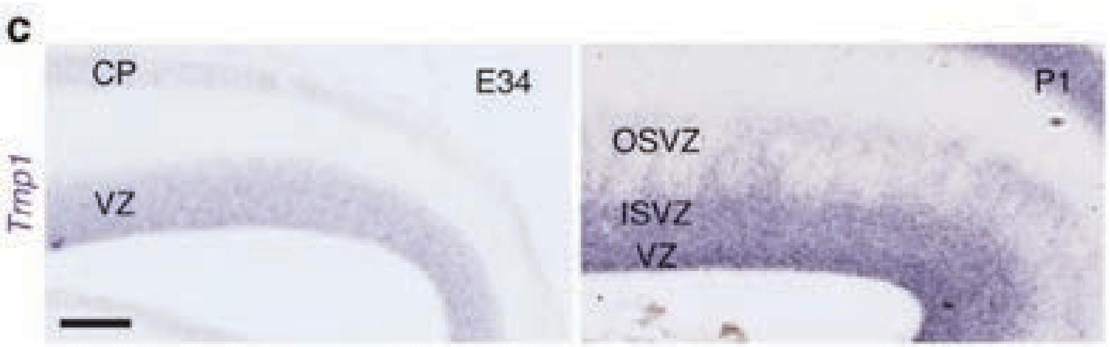
Differential gene expression between splenial gyrus (SG) and lateral sulcus (LS) along germinal layers





Expression of Trnp1 in Ferret and Mouse

Ferret

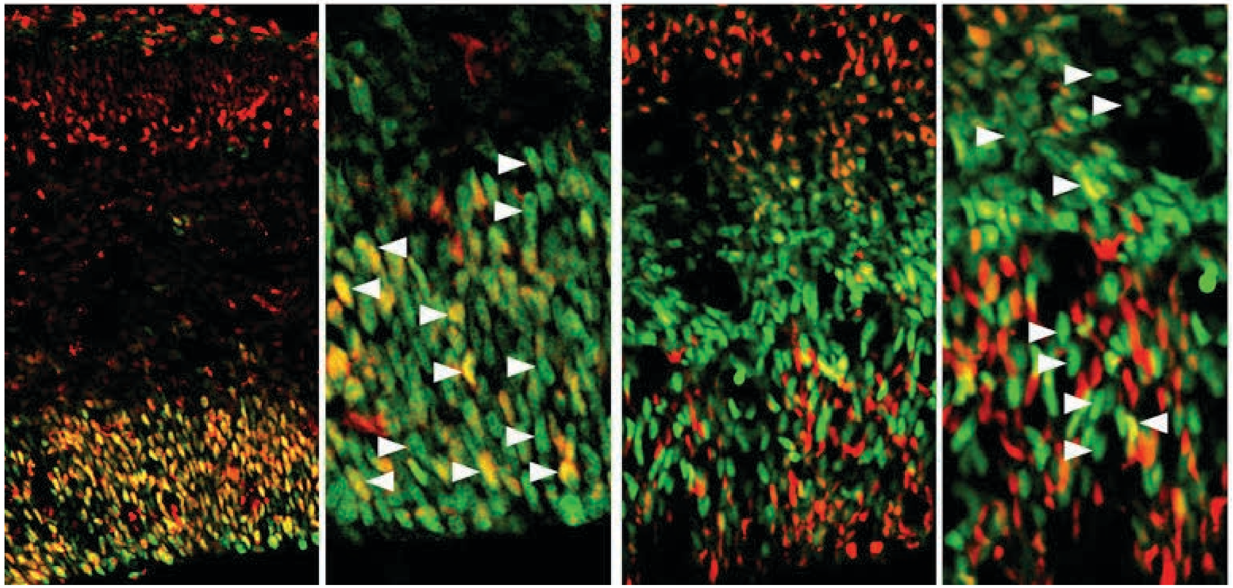


Different expression levels between OSVZ and VZ/SVZ

Mouse

E14 - Pax6 / Trnp1

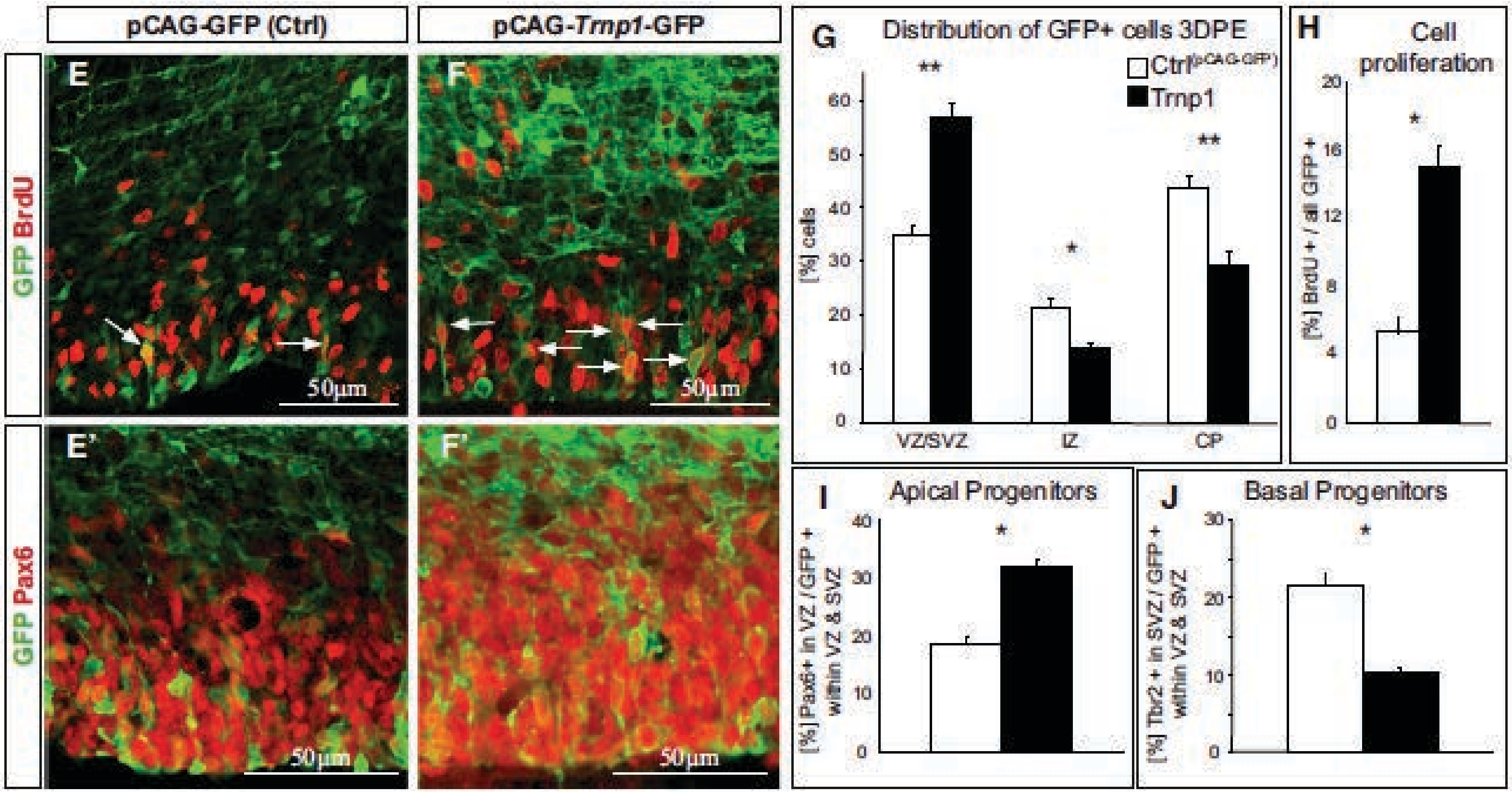
Tbr2 / Trnp1



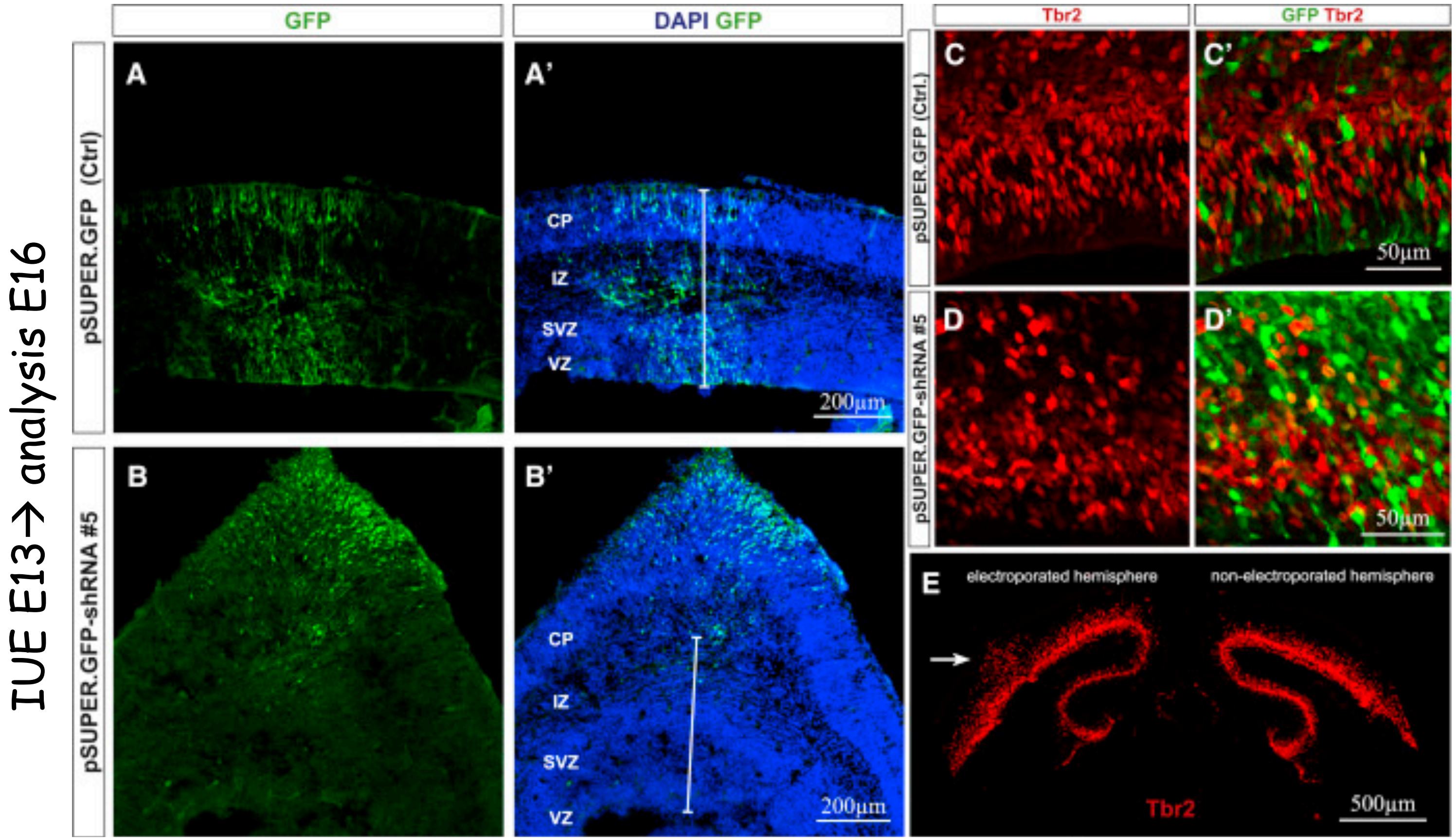
high in aRG
low in bRG

Stahl et al., 2013

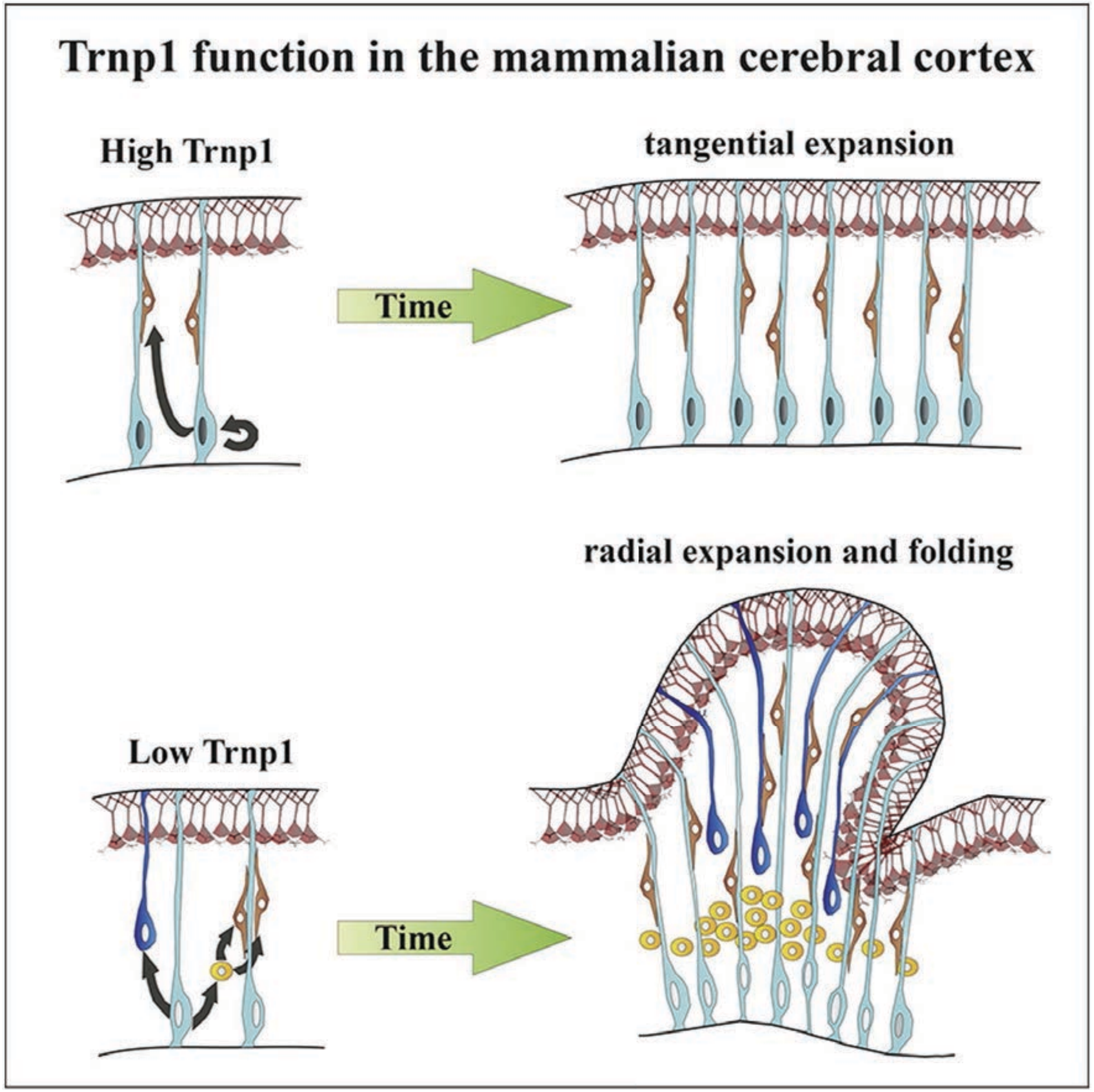
Overexpression of Trnp1 in vivo Increases the Number of Apical Progenitors and Promotes Lateral Expansion



Knockdown of Trnp1 In Vivo Increases the Number of Basal Progenitors and Promotes Radial Expansion



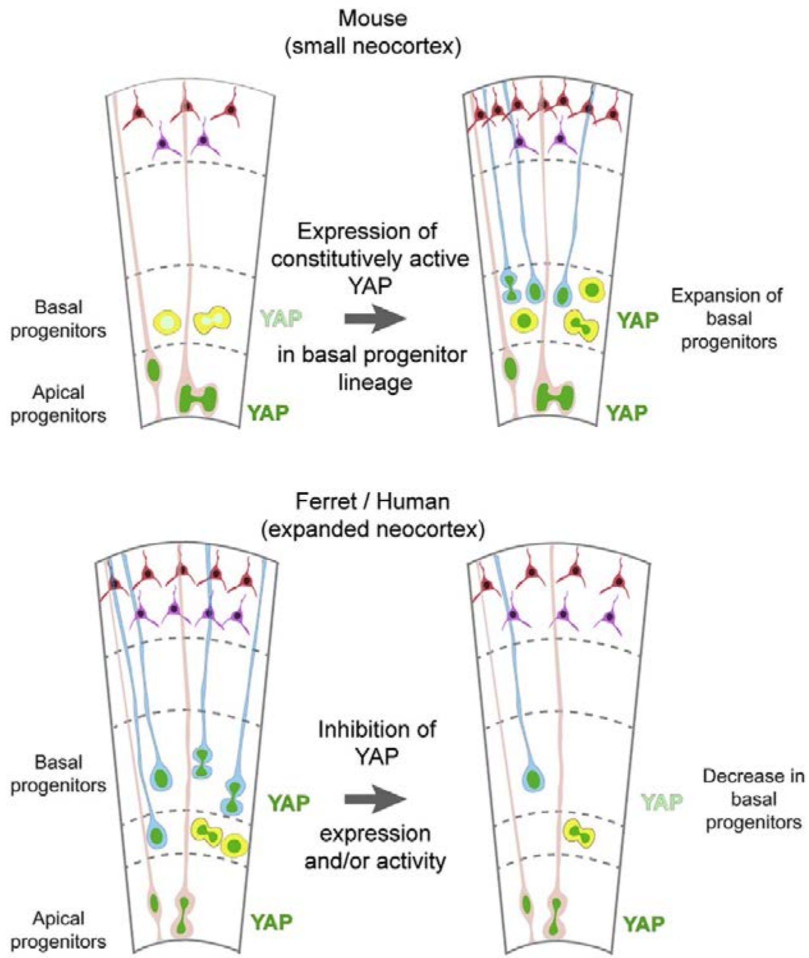
Stahl et al., 2013



Stahl et al., 2013
Martinez et al., 2016

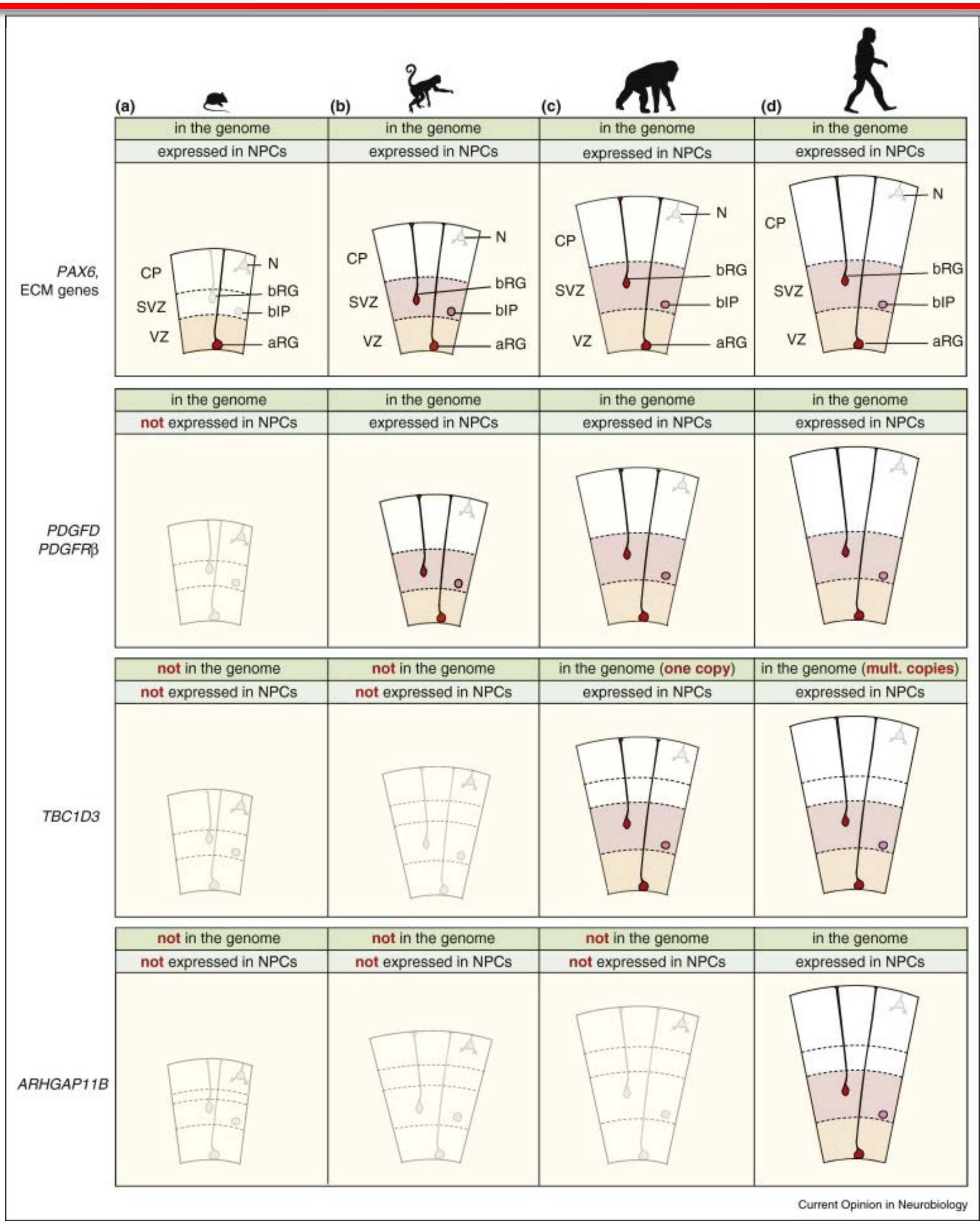
High levels of Hippo-YAP signalling pathway expands oRG

The Hippo-YAP pathway coordinates growth-factor-mediated signalling pathways.



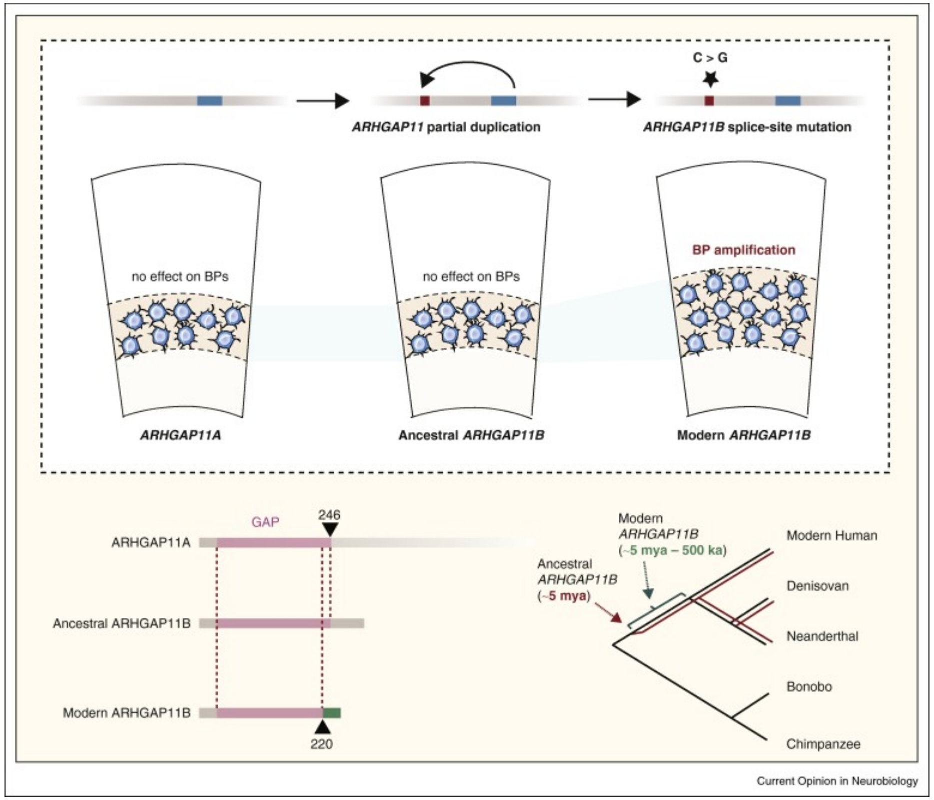
Kostic et al., 2019

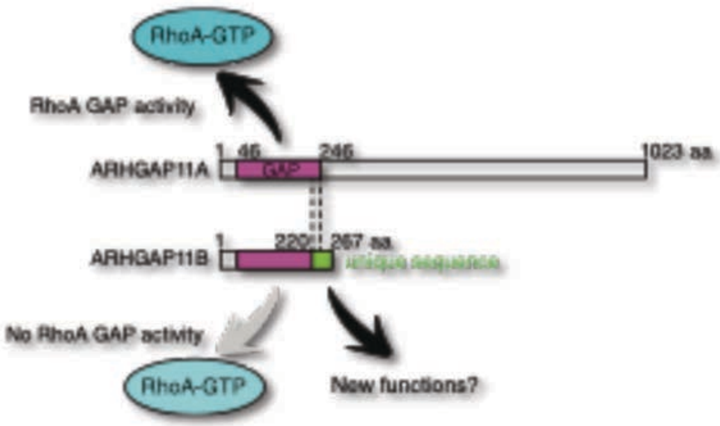
Gene expression changes affecting neural progenitor cells

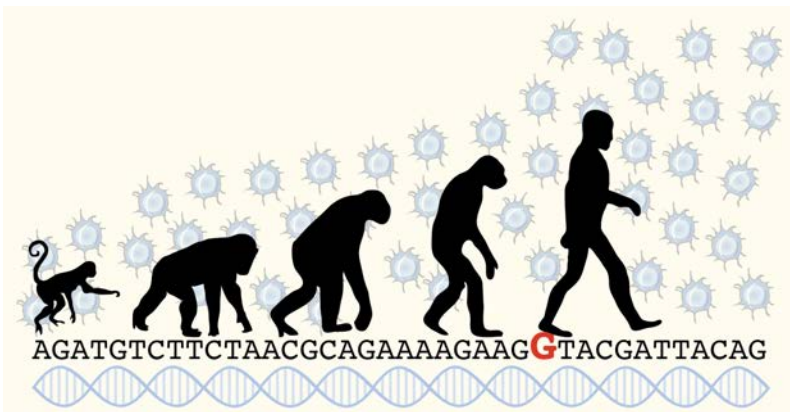


Florio et al., Science 2015

Evolution of the Rho-GTPase gene ARHGAP11B

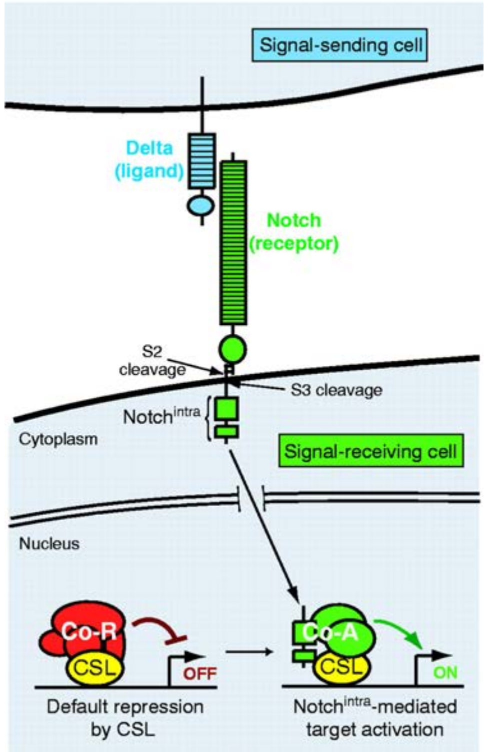




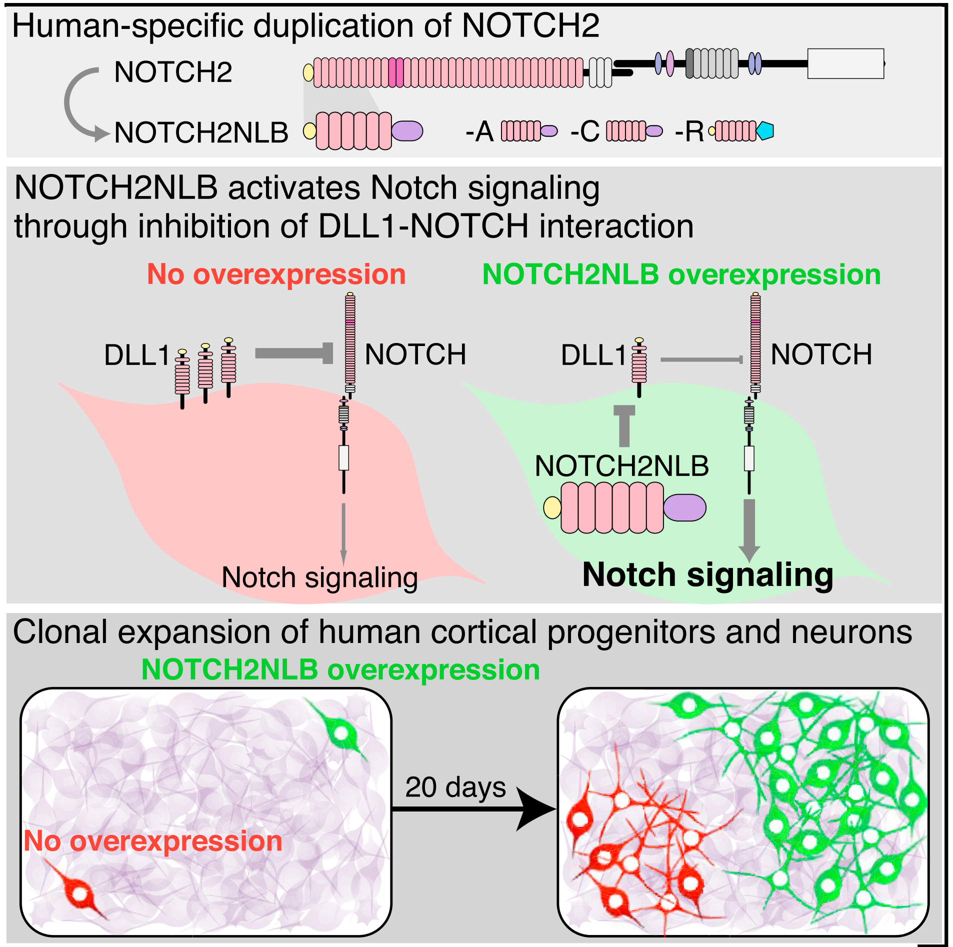


Florio & Hutner, 2017

Human-Specific NOTCH2NL Expand Cortical Neurogenesis through Delta/Notch Regulation

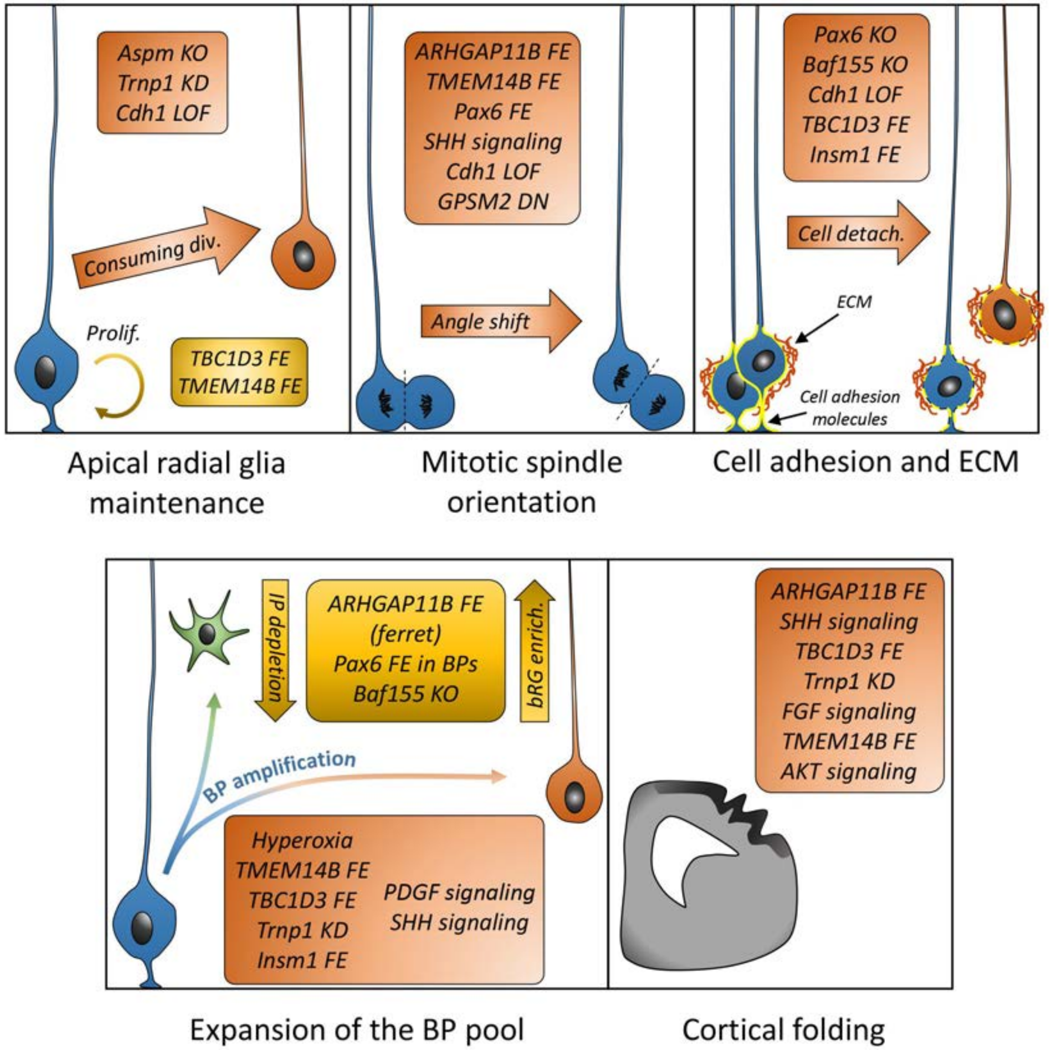


Notch signaling promotes proliferative signaling during neurogenesis



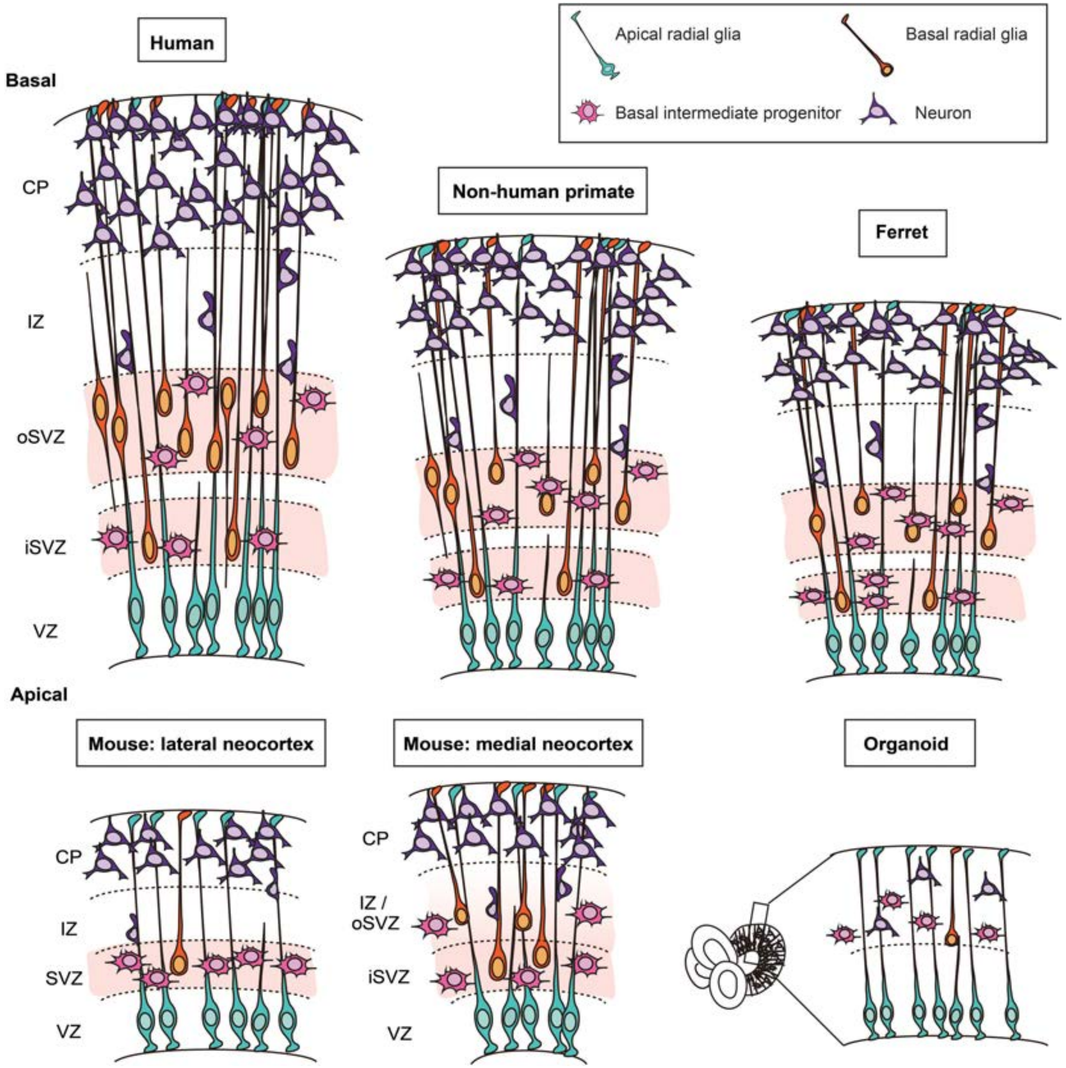
Suzuki et al., 2018

Mechanisms and genes associated with bRG generation/amplification



Penisson et al., 2019

Cytoarchitecture and cell types in the developing mammalian neocortex



Pinson et al., 2019