MASTER IN CELLULAR AND MOLECULAR BIOLOGY
Developmental Neurobiology
Cortical Development

I. Cellular and Molecular Organization of the Developing Cerebral Cortex

1st of April:

14:00-16:00 – ***Personal Introduction*** *+* ***Lecture and questions***

2nd of April:

11:00-13:00 → ***Lecture and questions (Room 1)***

14:00-16:00 → ***How to write a scientific paper (Room 5)***

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II. Neural Circuit Development in Health and Disease

15th of April:
14:00-16:00 – ***Lecture and questions***

16th of April: ***20 students/4→ 5 groups***

11:00-13:00 → ***Studer***: ***How to write a fellowship proposal*** (*Title; Background and Rationale; Research Question(s); Research Methodology; Plan of Work & Time Schedule; Bibliography*)

*14:00-16:00 →****Students***: ***Presentation of 5 emerging technologies*** in neurobiology/neuroscience: *(i) 3D whole brain imaging; (ii) optogenetics & functional whole brain imaging; (iii) scRNAseq & cell lineage tracking; (iv) IPSCS & brain organoids; (v) in vivo & in vitro reprogramming*.

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III. Genetics of Brain Disorders

29th of April:
14:00-16:00 – ***Studer & students***: Discussion on fellowship proposals

30th of April: 20 students/4→ 5 groups

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

*14:00-16:00 →****Students:*** Presentation of the fellowship proposal to the others

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 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* ".

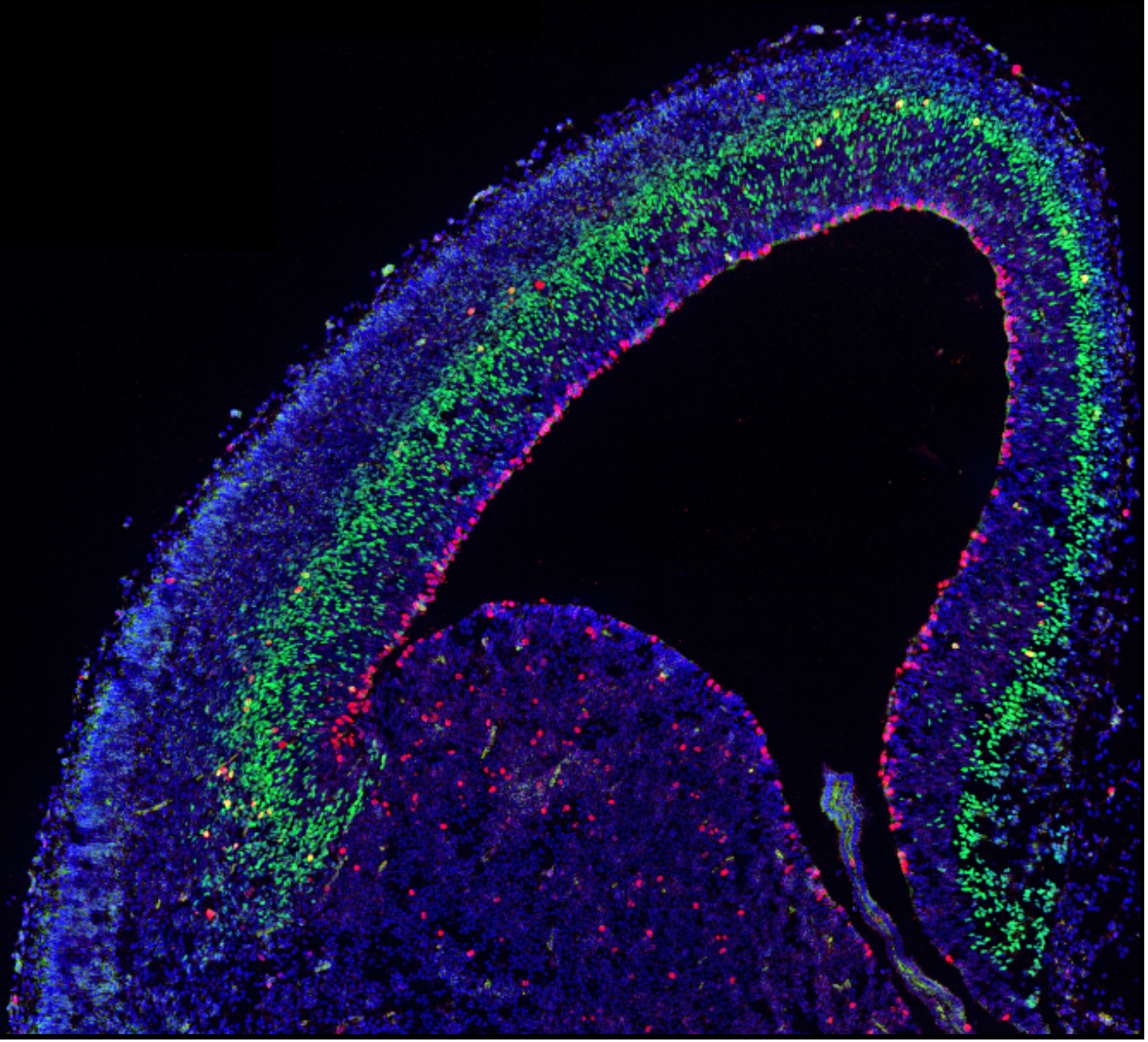
Since 2009: ***Directeur de Recherche (DR2-DR1) Inserm;*** University of Nice Sophia-Antipolis, Valrose Campus, Nice, France.

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

Cellular and Molecular Organization of the Cortex

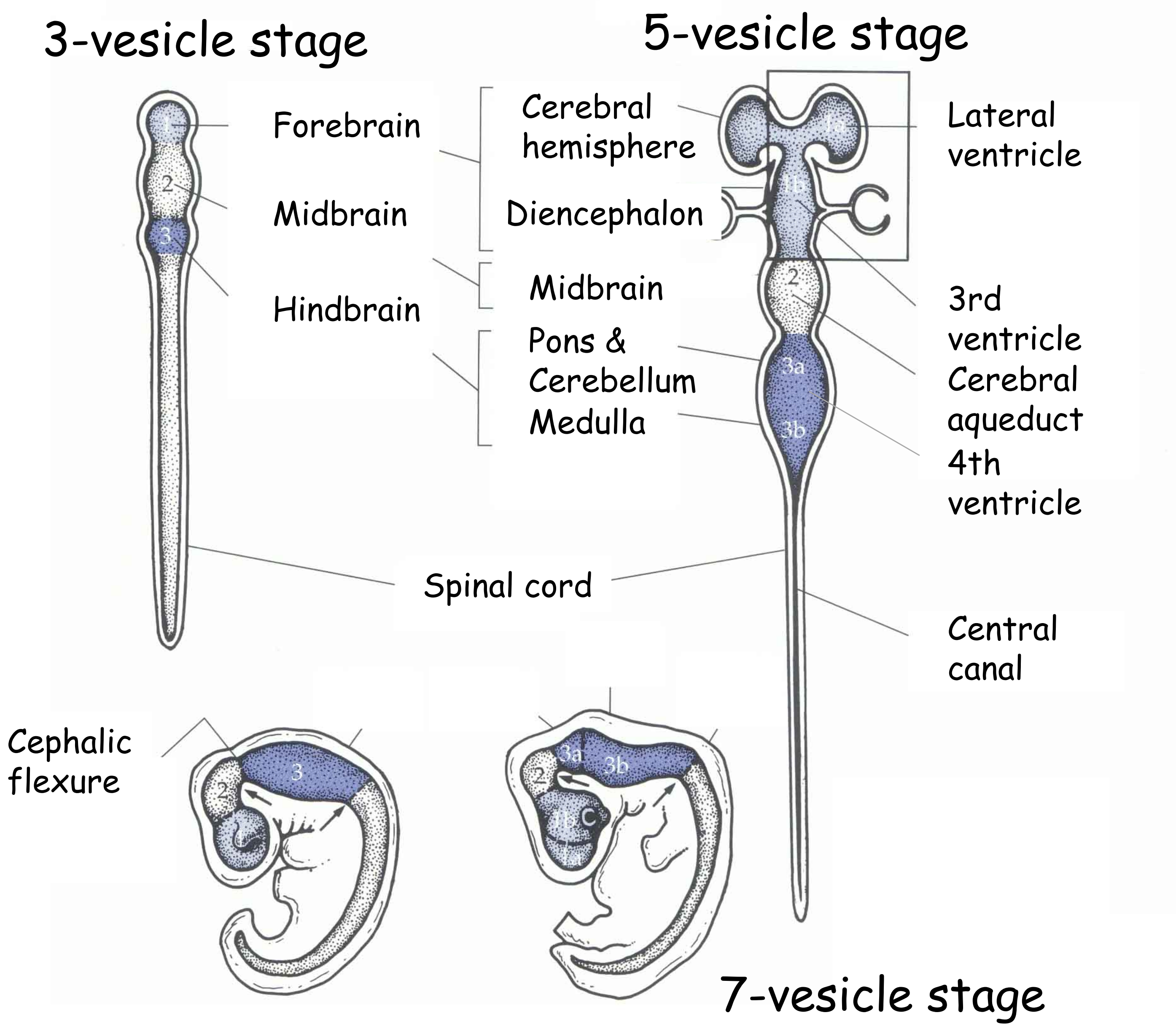
Michèle Studer
iBV, Nice,
France

institut Valrose Biologie

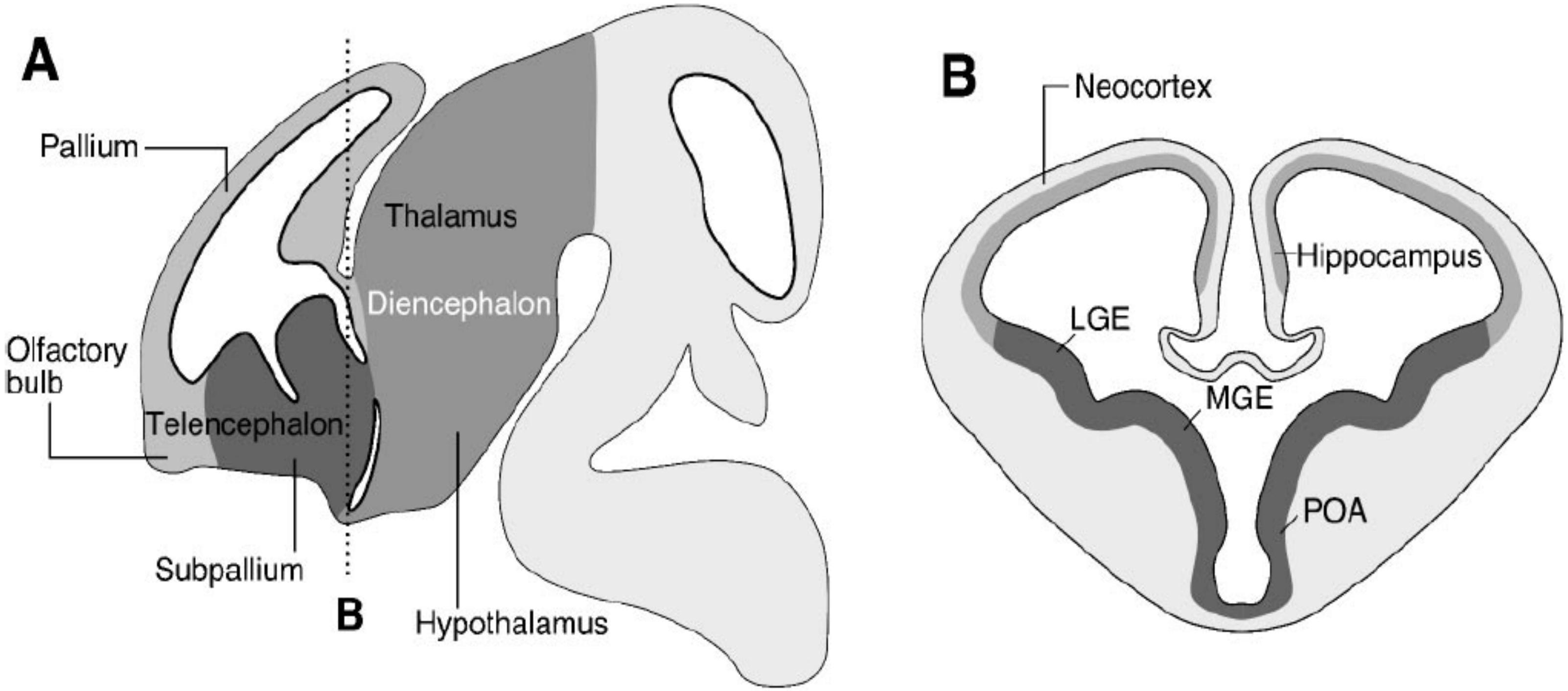


Torino
01/04/2019

Neural Regionalization

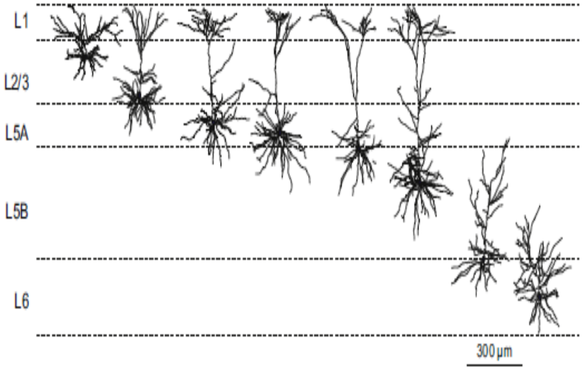


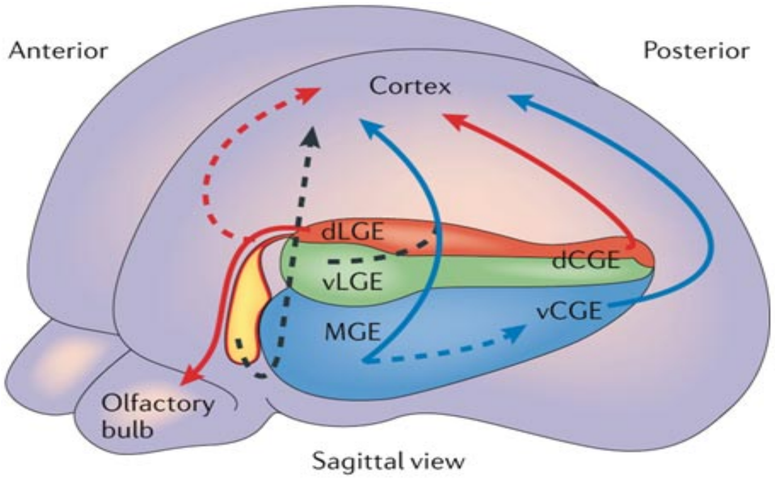
Antero-Posterior (AP) and Dorso-Ventral (DV) regionalization of the forebrain



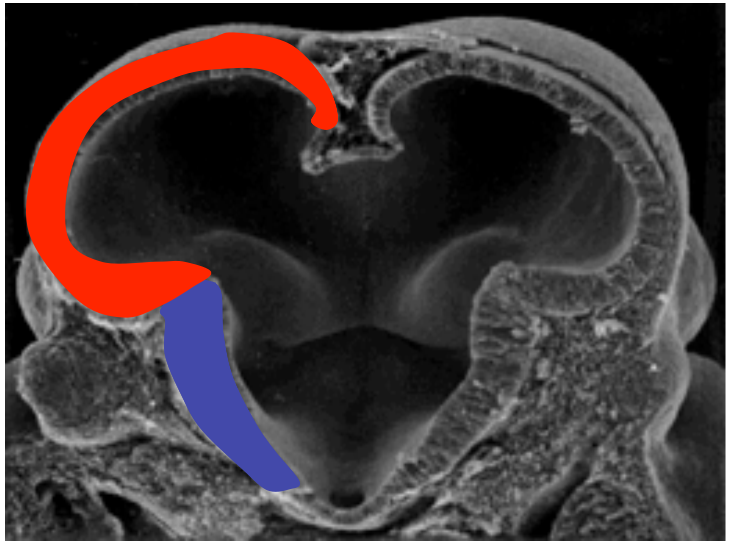
Cortical Projection neurons and Interneurons are born from different D/V regions of the telencephalon

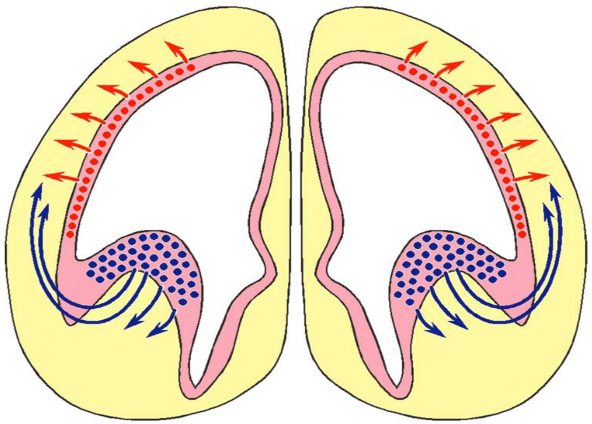
Glutamatergic projection neurons





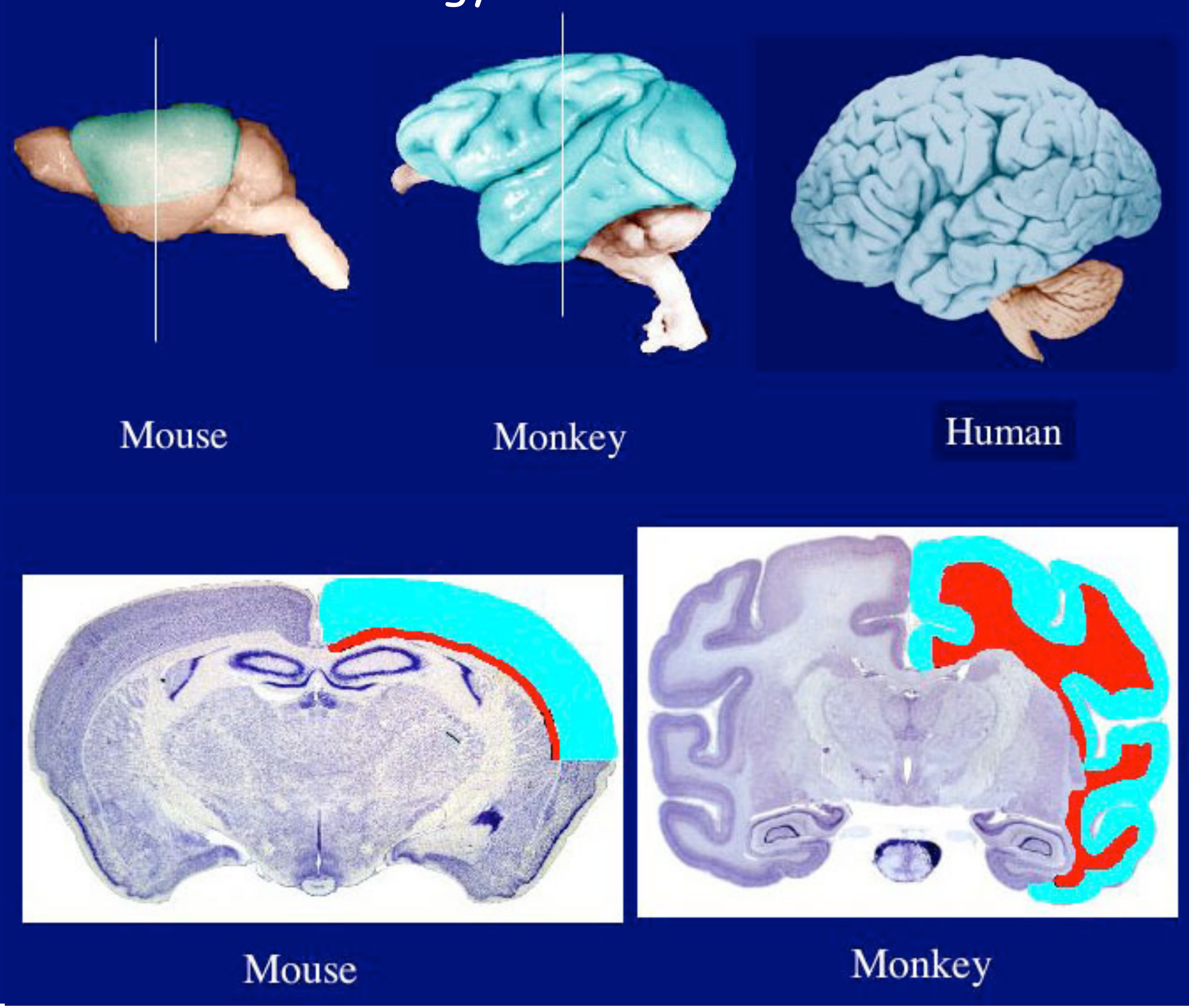
Dorsal (pallium)

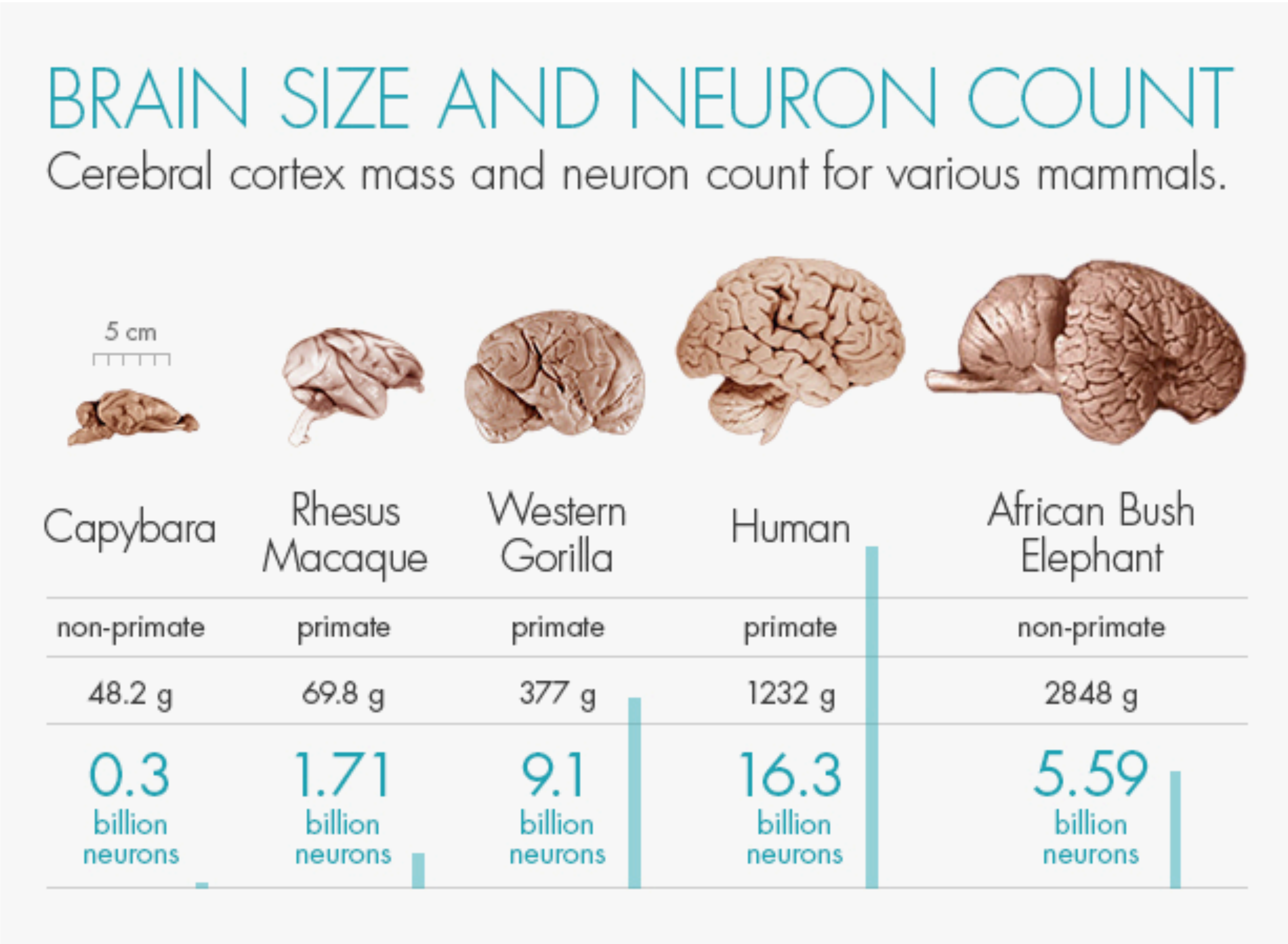




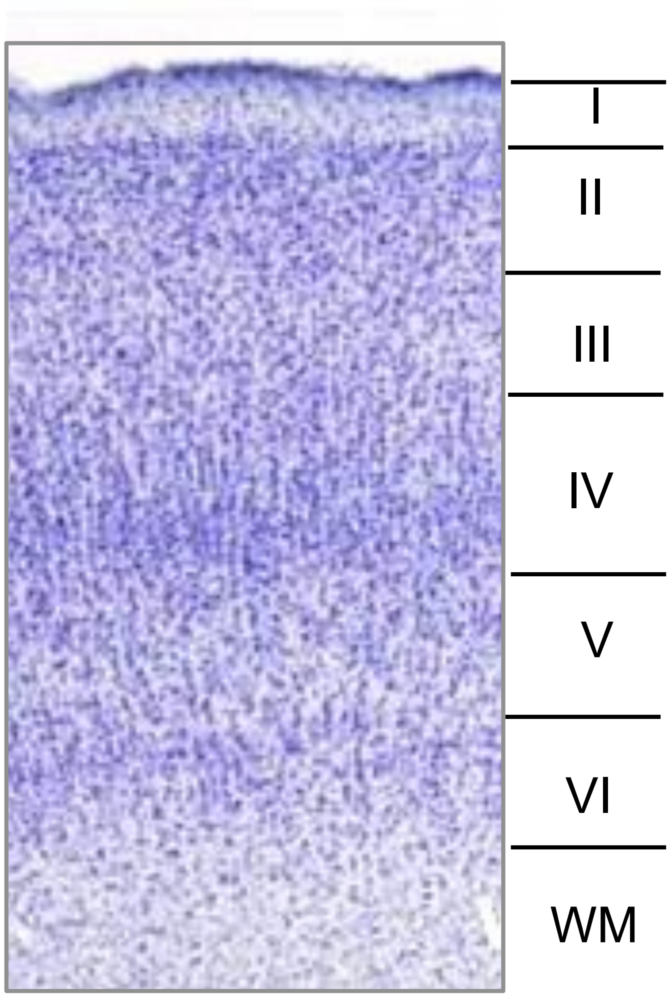
Ventral (subpallium)

Sulci and gyri of the neocortex

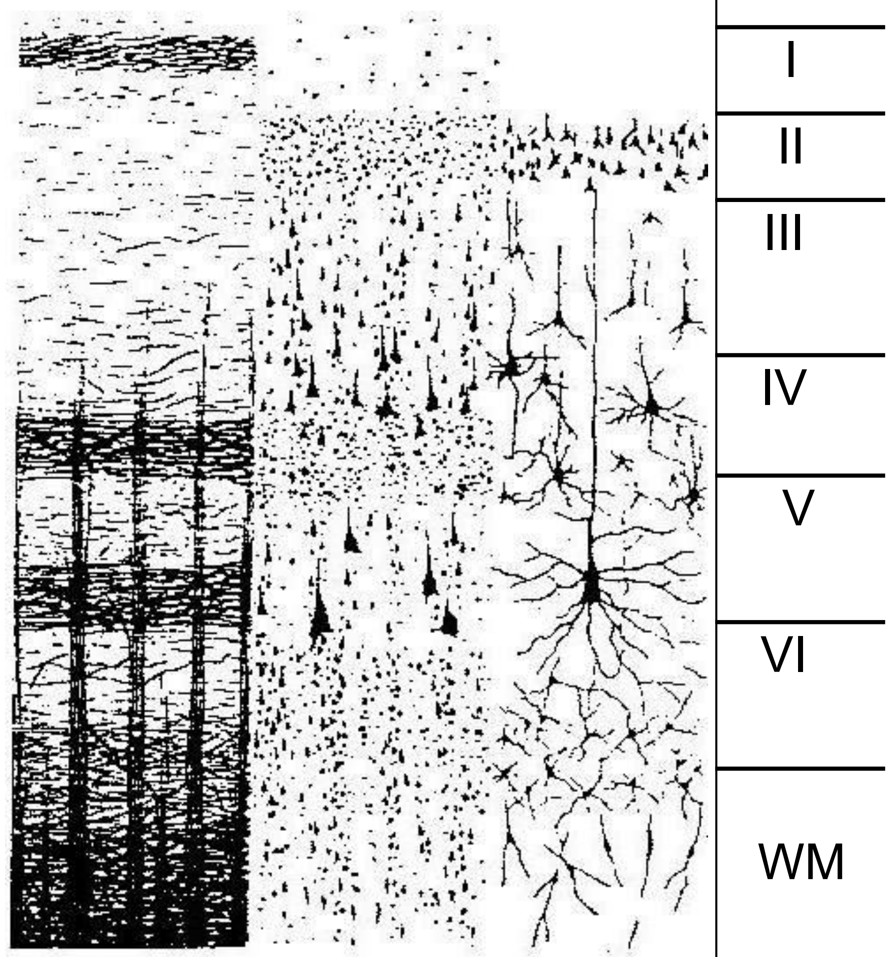



BRAIN SIZE AND NEURON COUNT
Cerebral cortex mass and neuron count for various mammals.
5 cm
Capybara
Rhesus Macaque
Western Gorilla
Human
African Bush Elephant
non-primate
primate
primate
primate
non-primate
48.2 g
69.8 g
377 g
1232 g
2848 g
0.3 billion neurons
1.71 billion neurons
9.1 billion neurons
16.3 billion neurons
5.59 billion neurons

The cortex is subdivided into six distinct layers

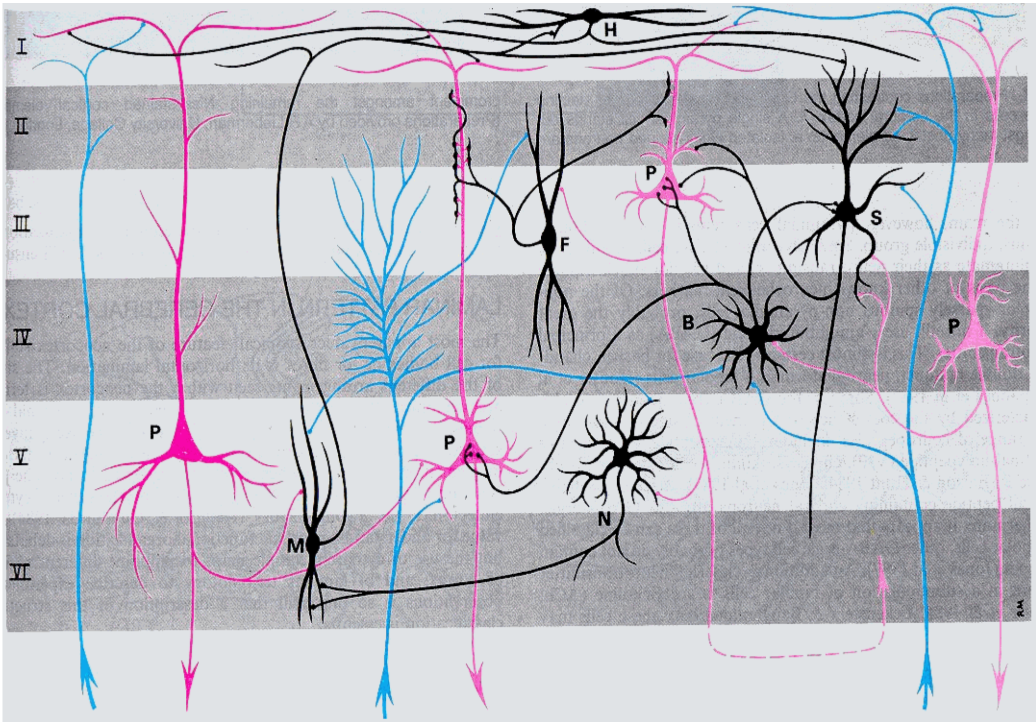


Nissl staining

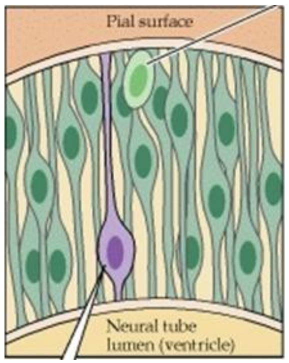


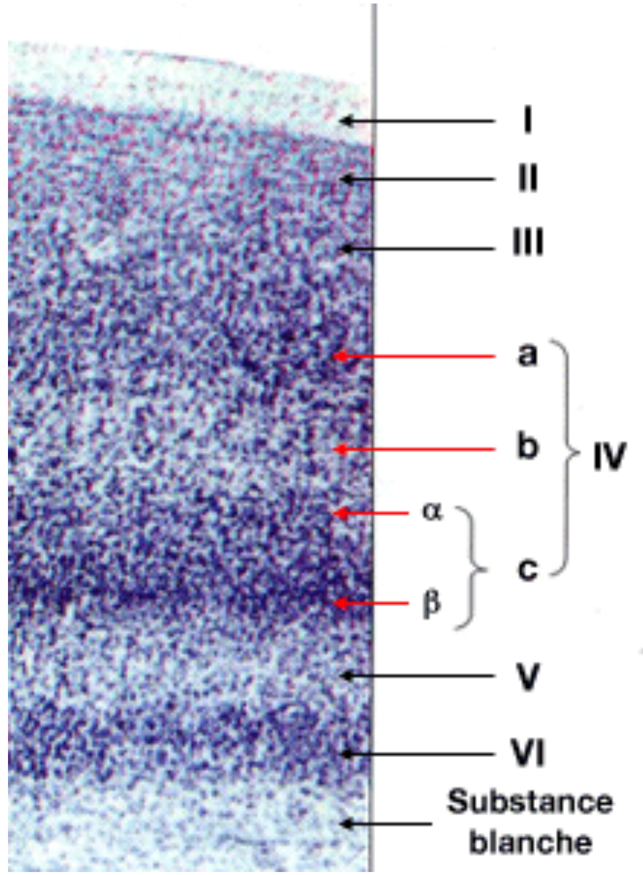
Fibres Soma Dendrites

Morphological heterogeneity of cortical neurons

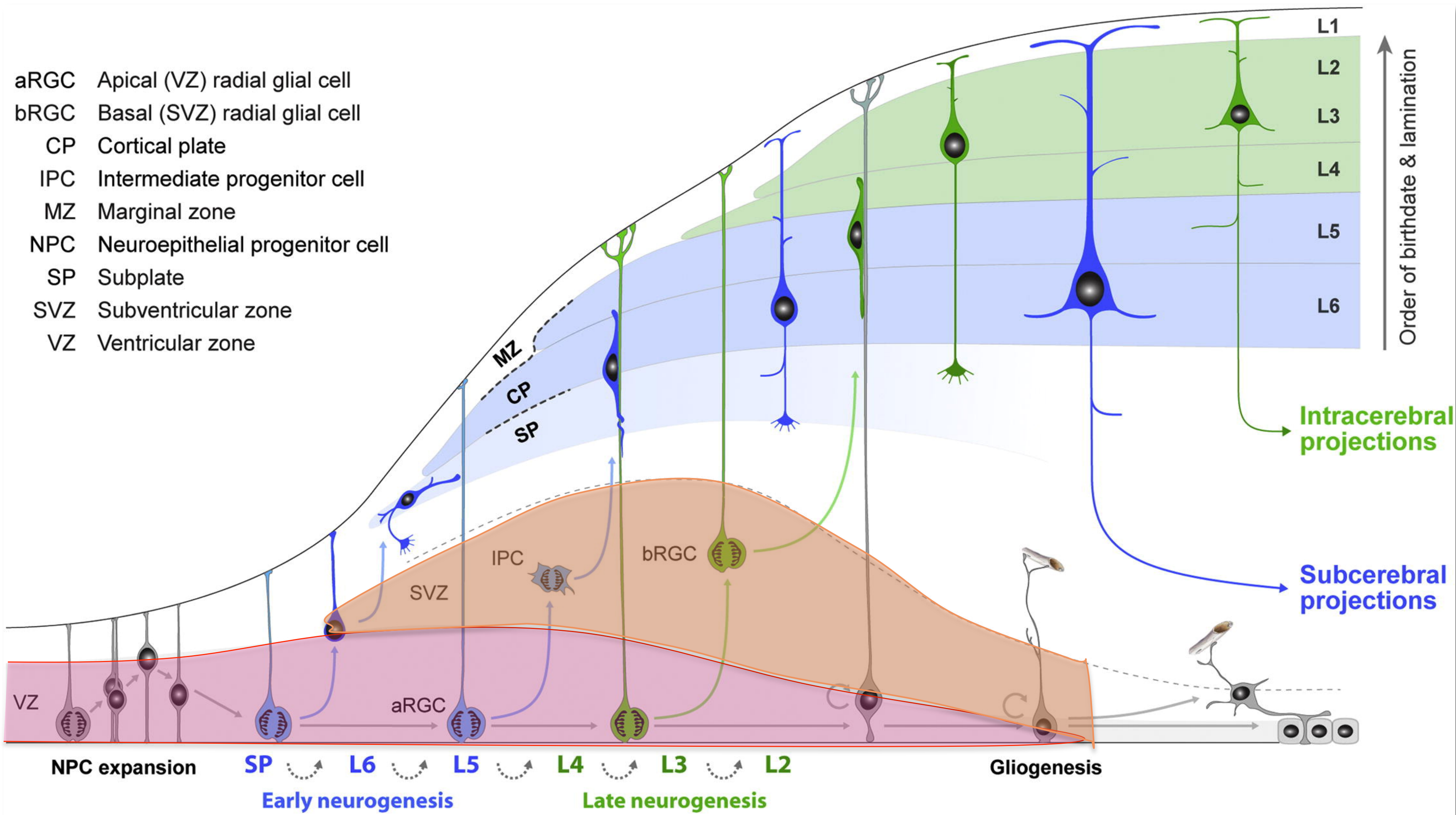


How can a relatively simple pseudostratified neuroepithelium transform into a complex structure organized into layers?

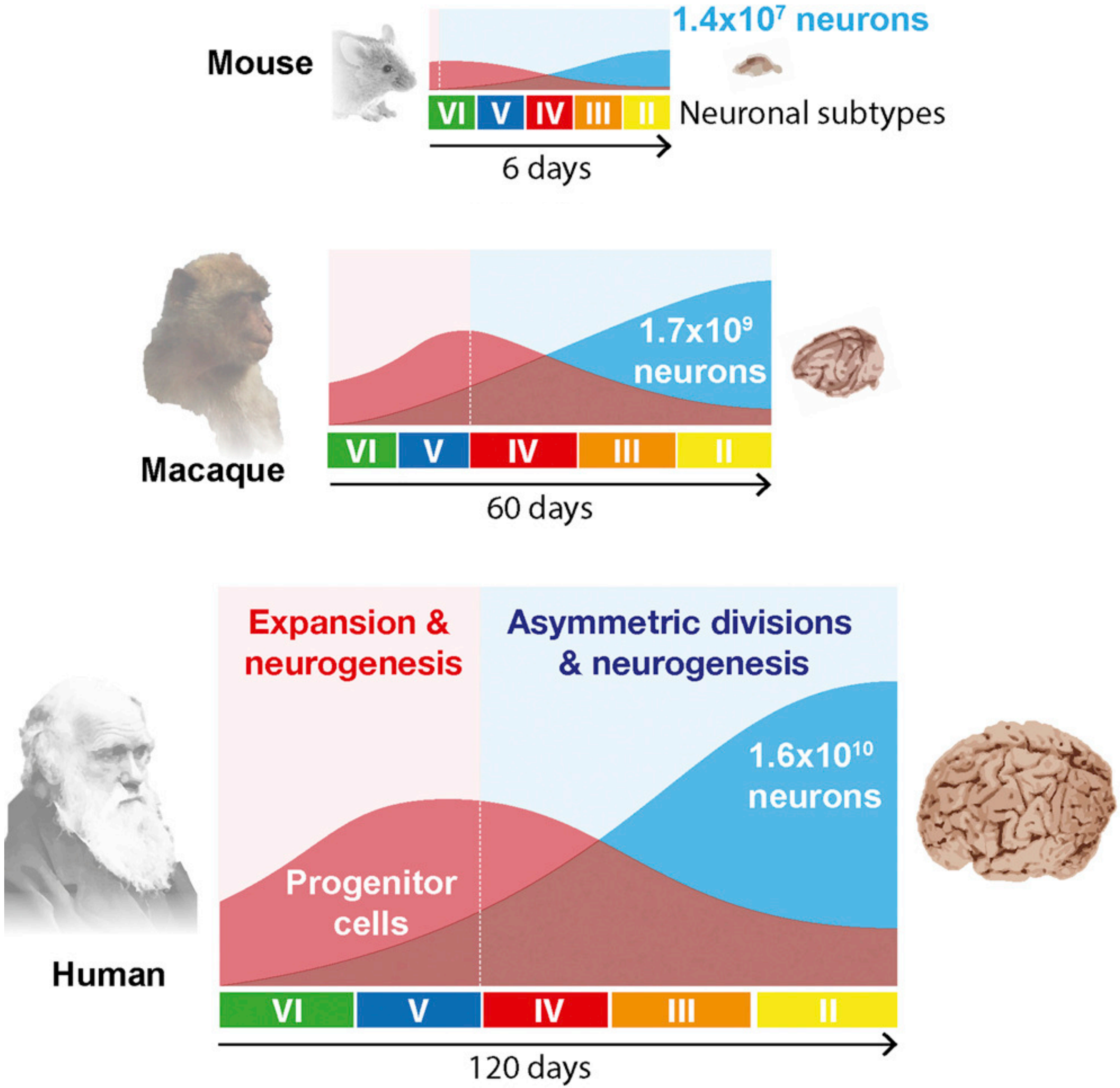




Mammalian corticogenesis

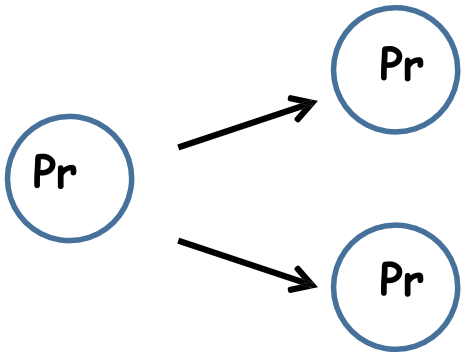


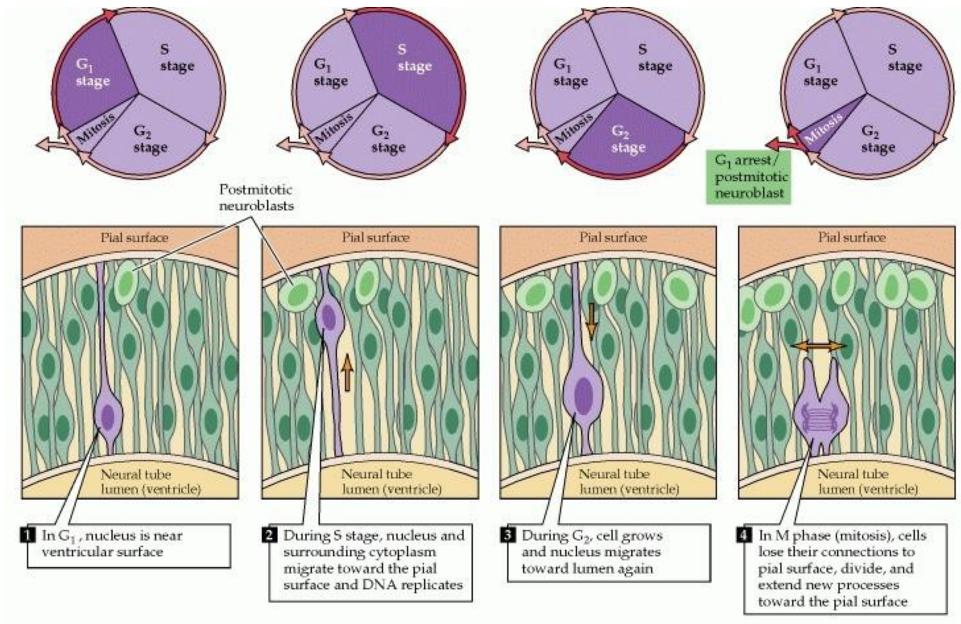
modified from Kwan et al., 2012



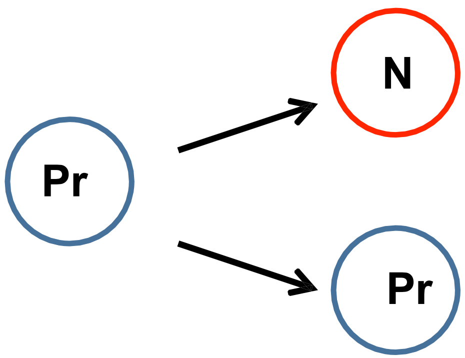
Mouse
1.4x10^7 neurons
VI
V
IV
III
II
Neuronal subtypes
6 days
1.7x10^9 neurons
Macaque
60 days
Expansion & neurogenesis
Asymmetric divisions & neurogenesis
1.6x10^10 neurons
Progenitor cells
Human
120 days

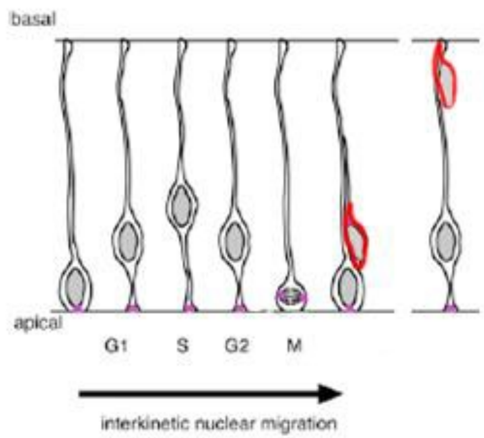
First stage: proliferation *via* symmetric division



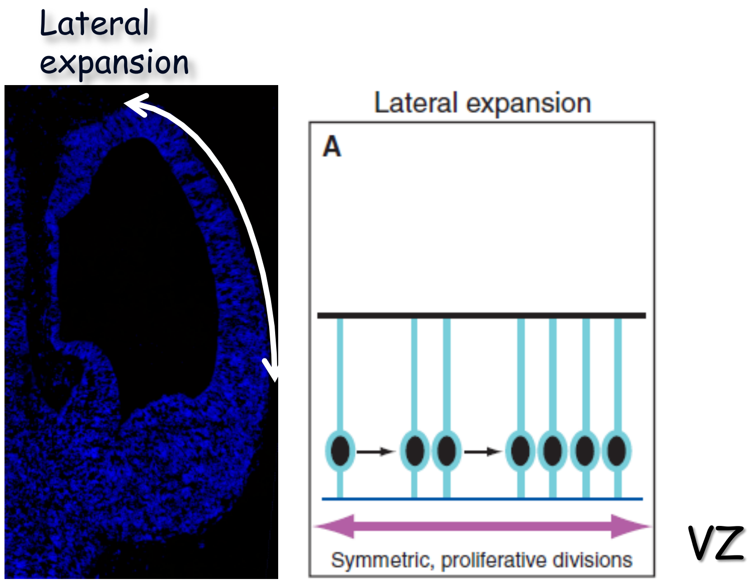


Second stage: proliferation *via* asymmtric division

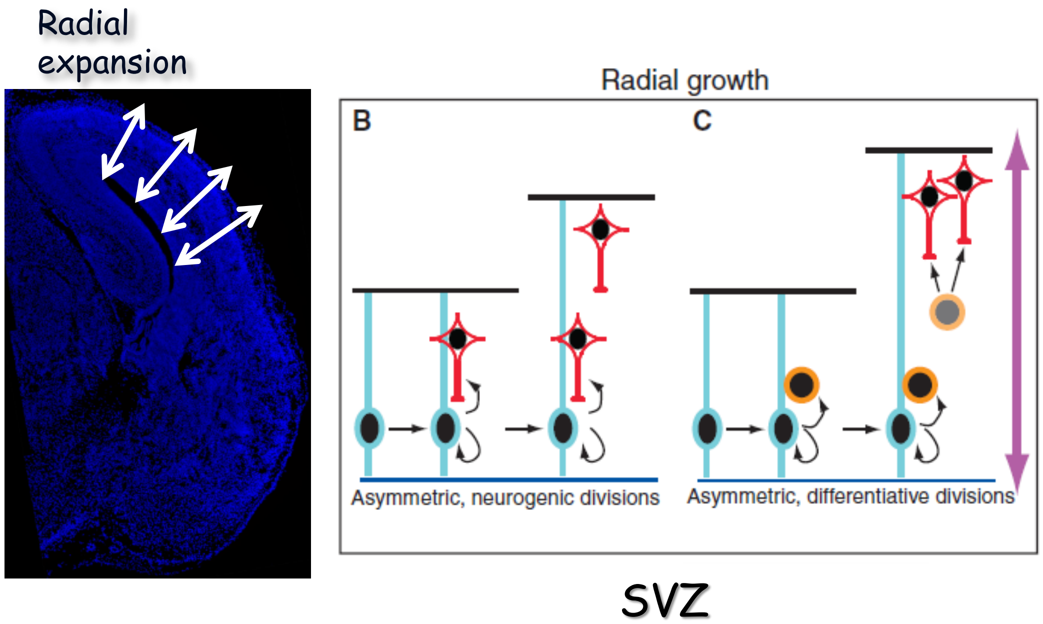




Differences in cell division planes during lateral versus radial expansion

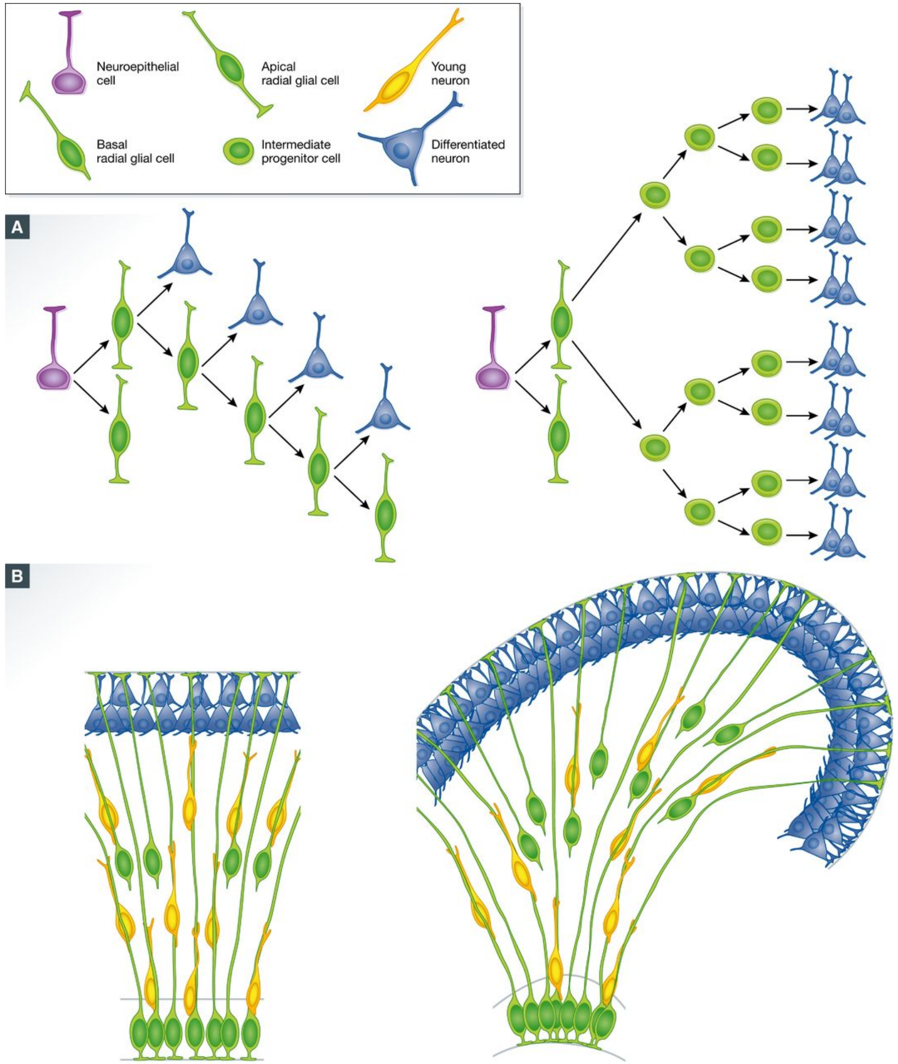


Symmetric: increase in number of radial columns + surface expansion of the cerebral cortex



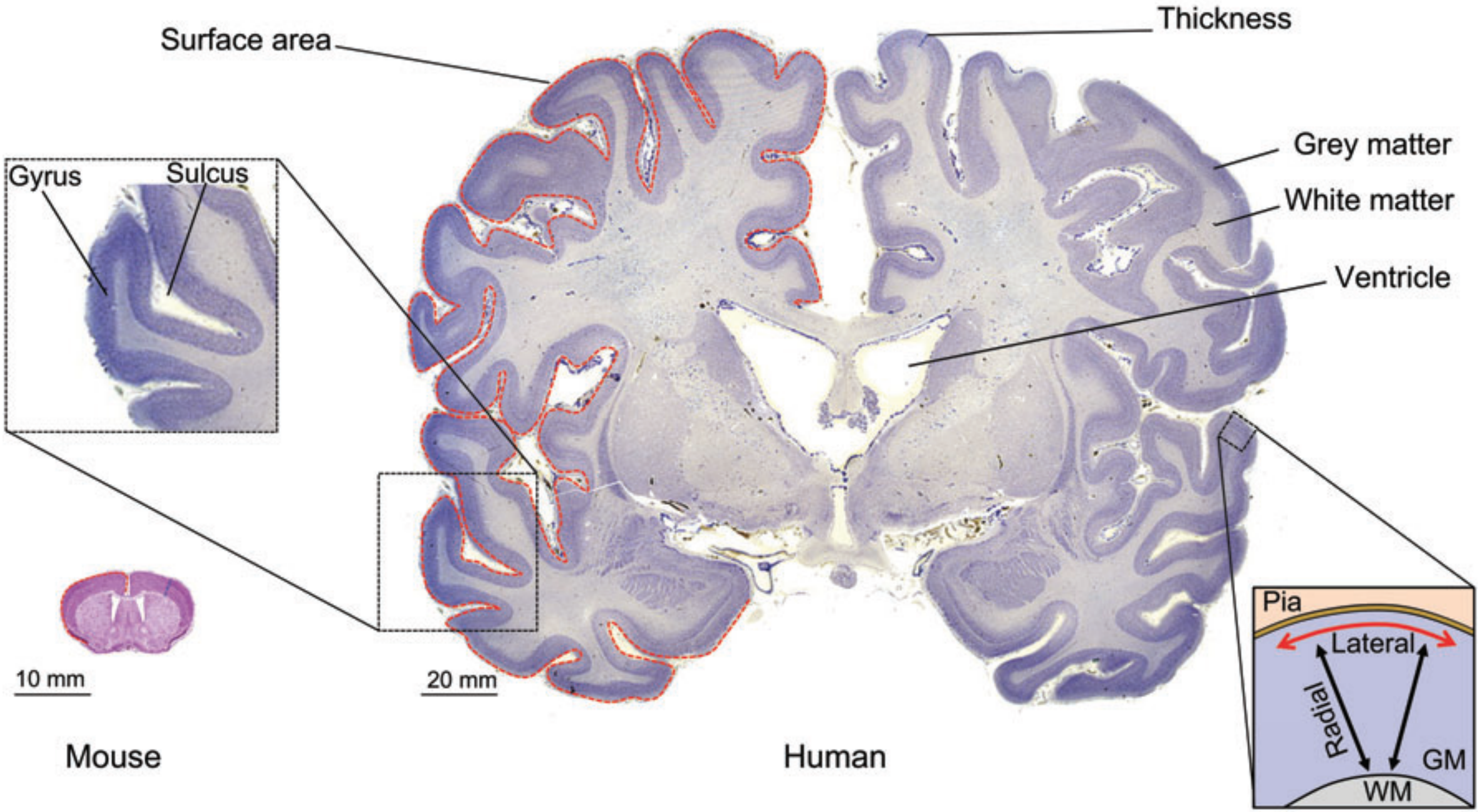
Asymmetric: increase in number of neurons within radial columns without a change in the cortical surface area (radial)

Differences in cell number for lateral vs radial expansion



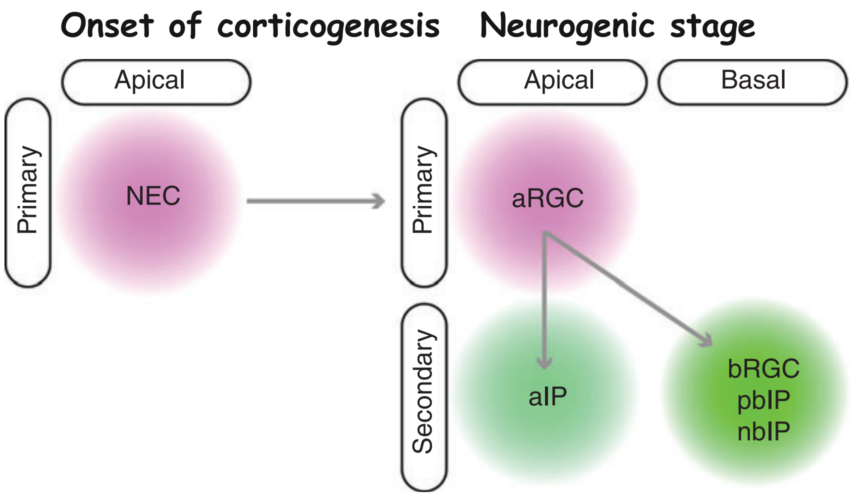
Virginia Fernández et al. EMBO J. 2016

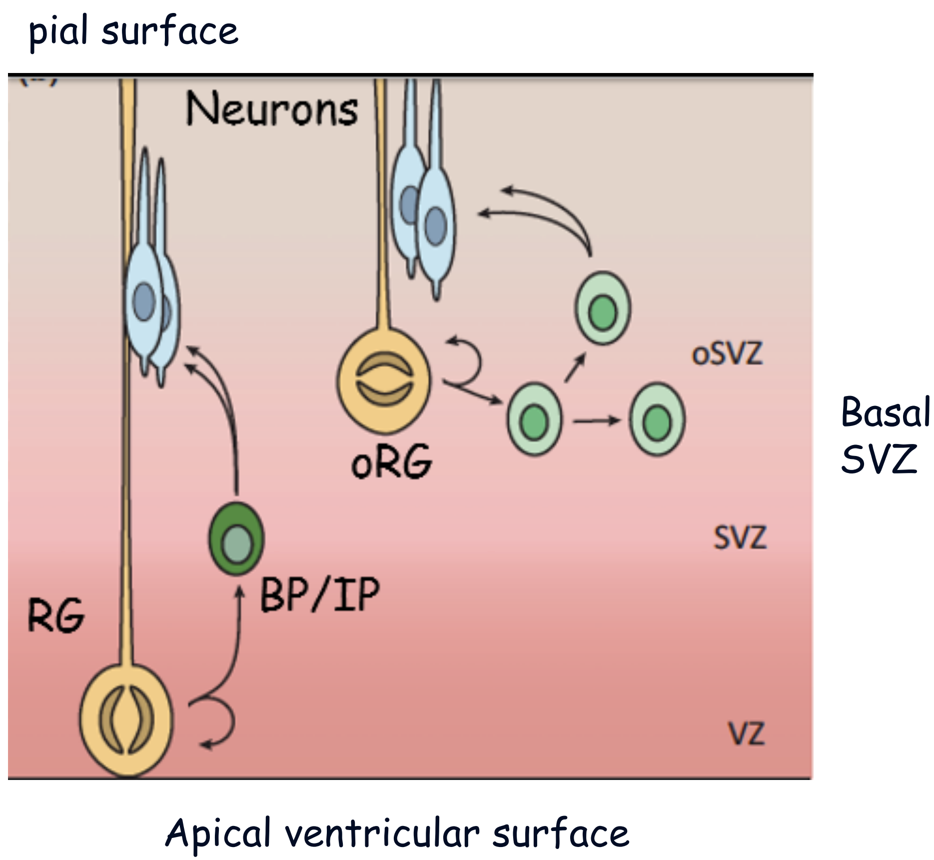
Sulci and gyri in primates



Florio & Huttner, Development, 2014

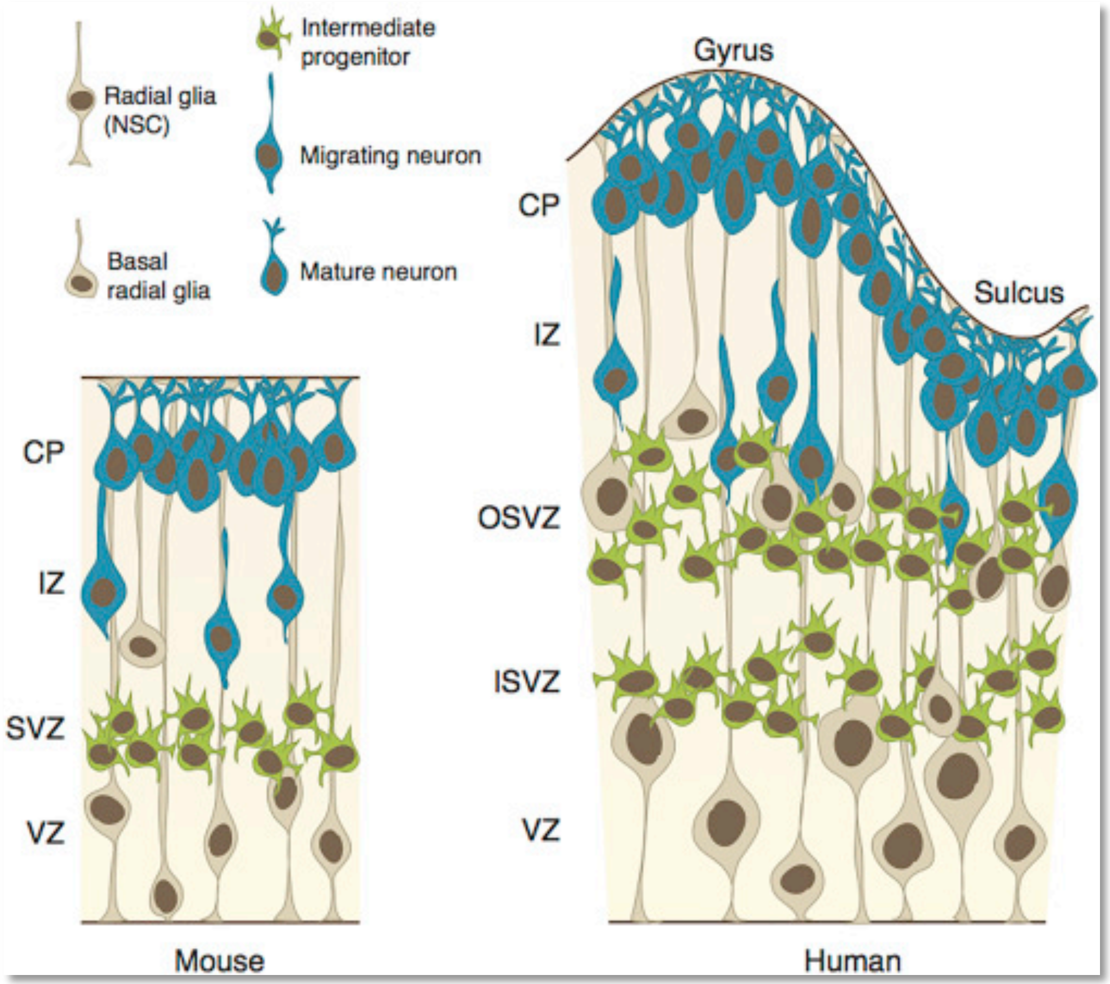
Different types of progenitors in VZ and SVZ





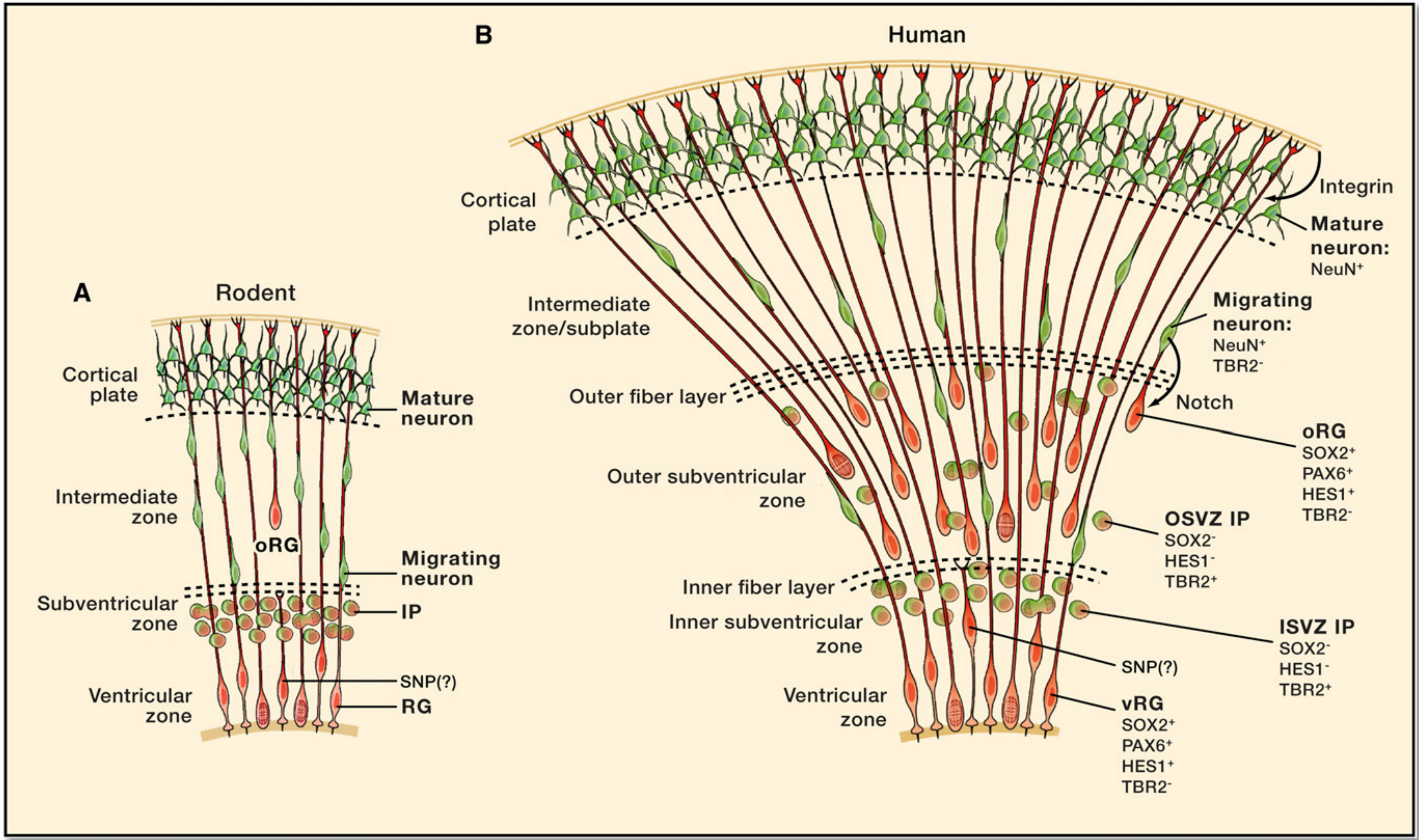
Namba & Huttner, 2016

Mouse vs human progenitor expansion



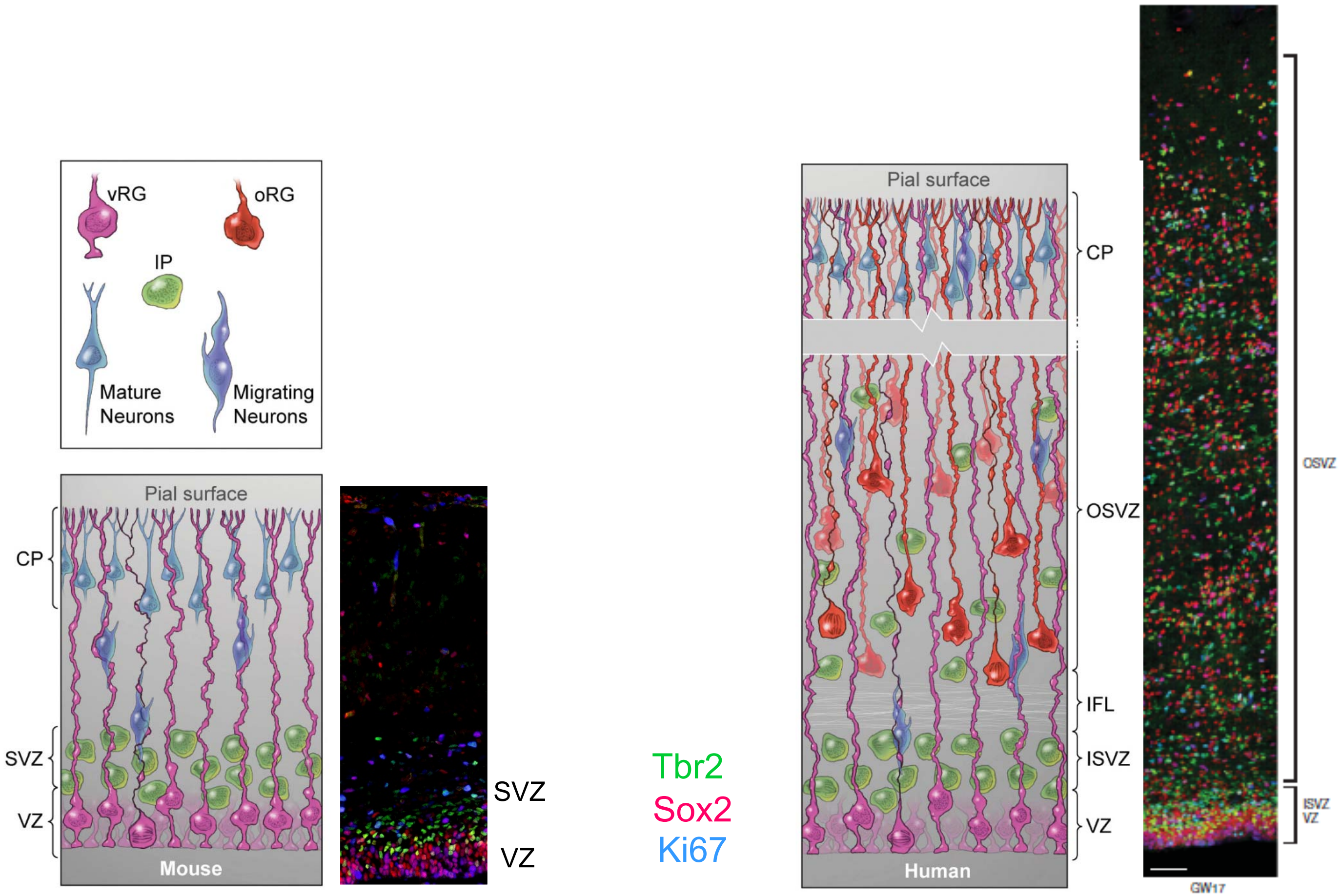
Iva Kelava, Madeline A. Lancaster

Molecular characterization of the different cell types



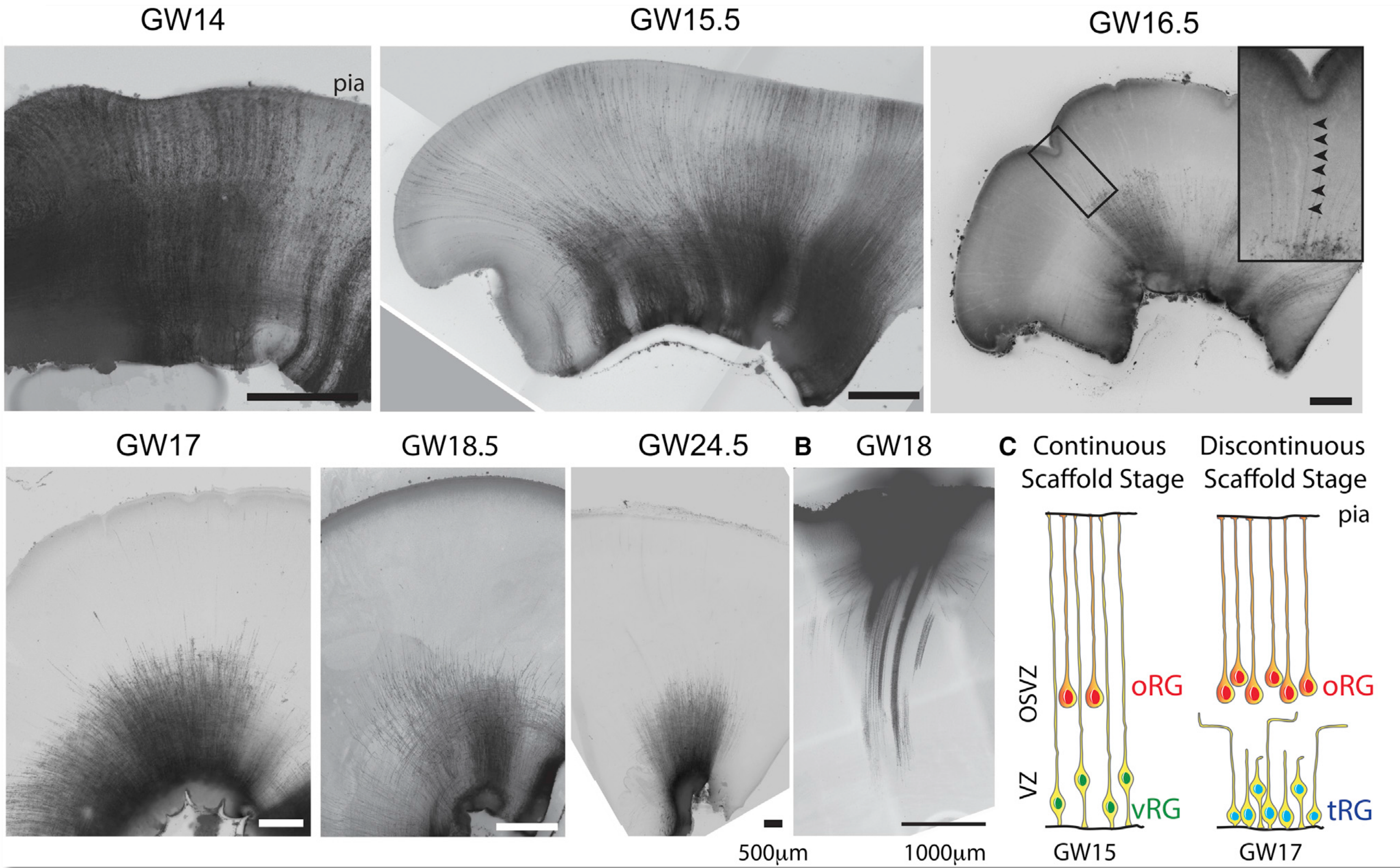
Lui et al., Cell, 2011

The human cortex generates more basal radial glia (OSVZ)



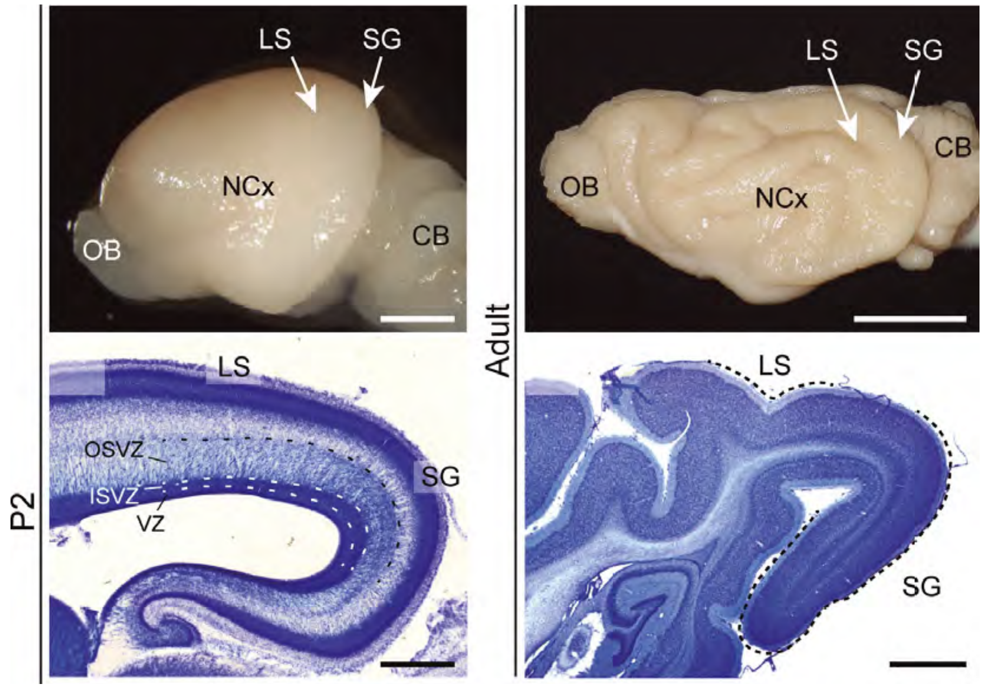
(Hansen et al.,Nature, 2010)

Morphological transition of the radial glia



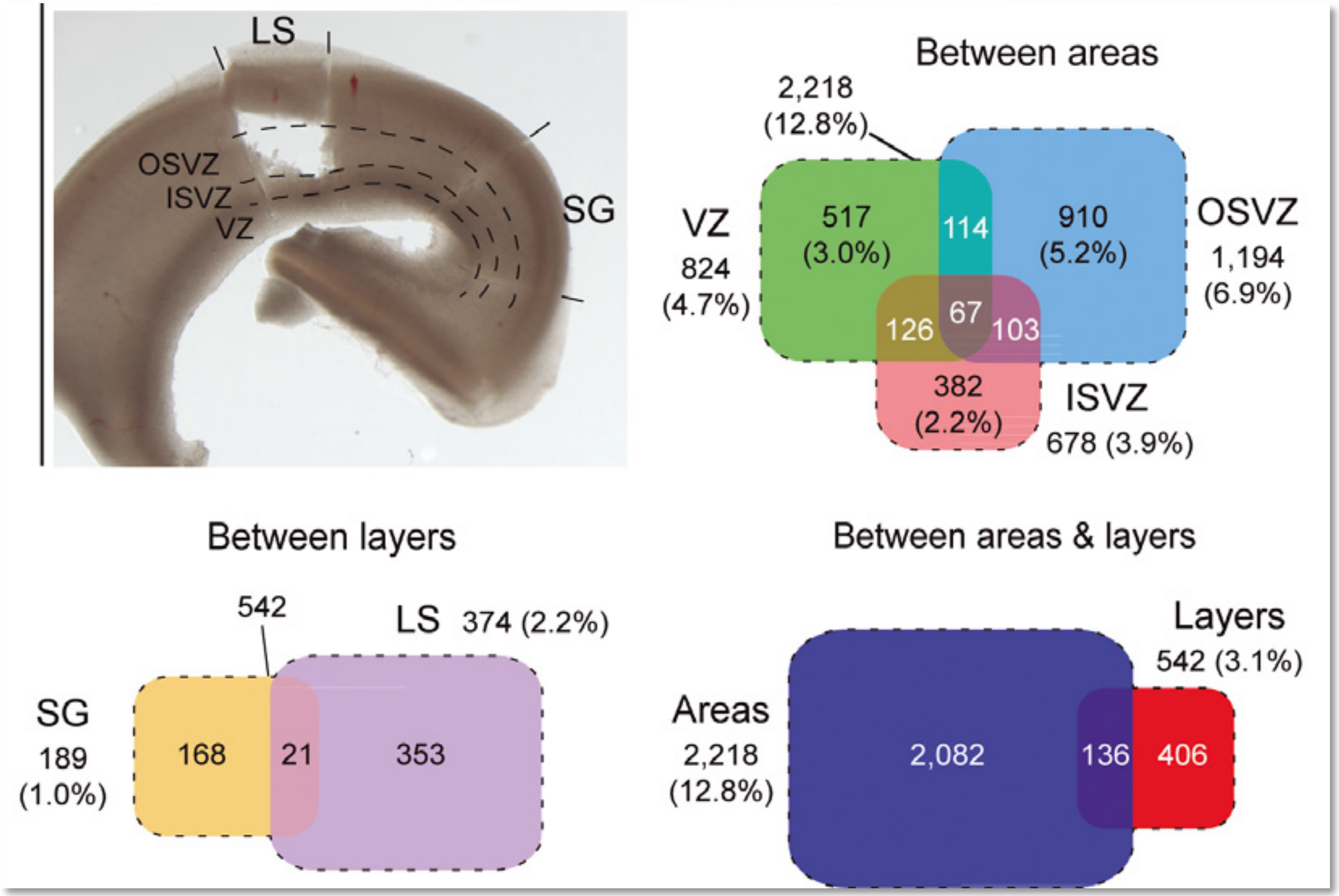
Nowakowski et al., 2016

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



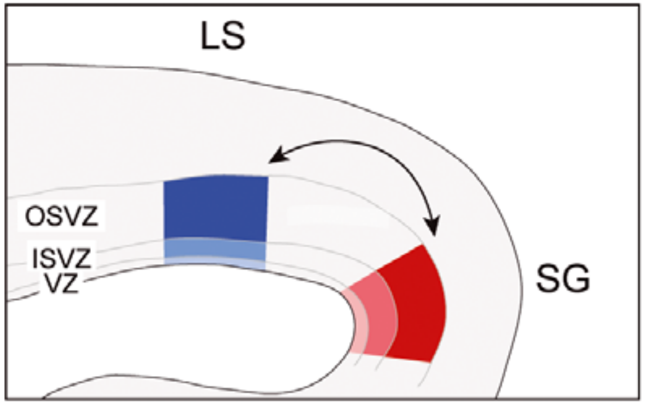
De Juan Romero et al., 2015

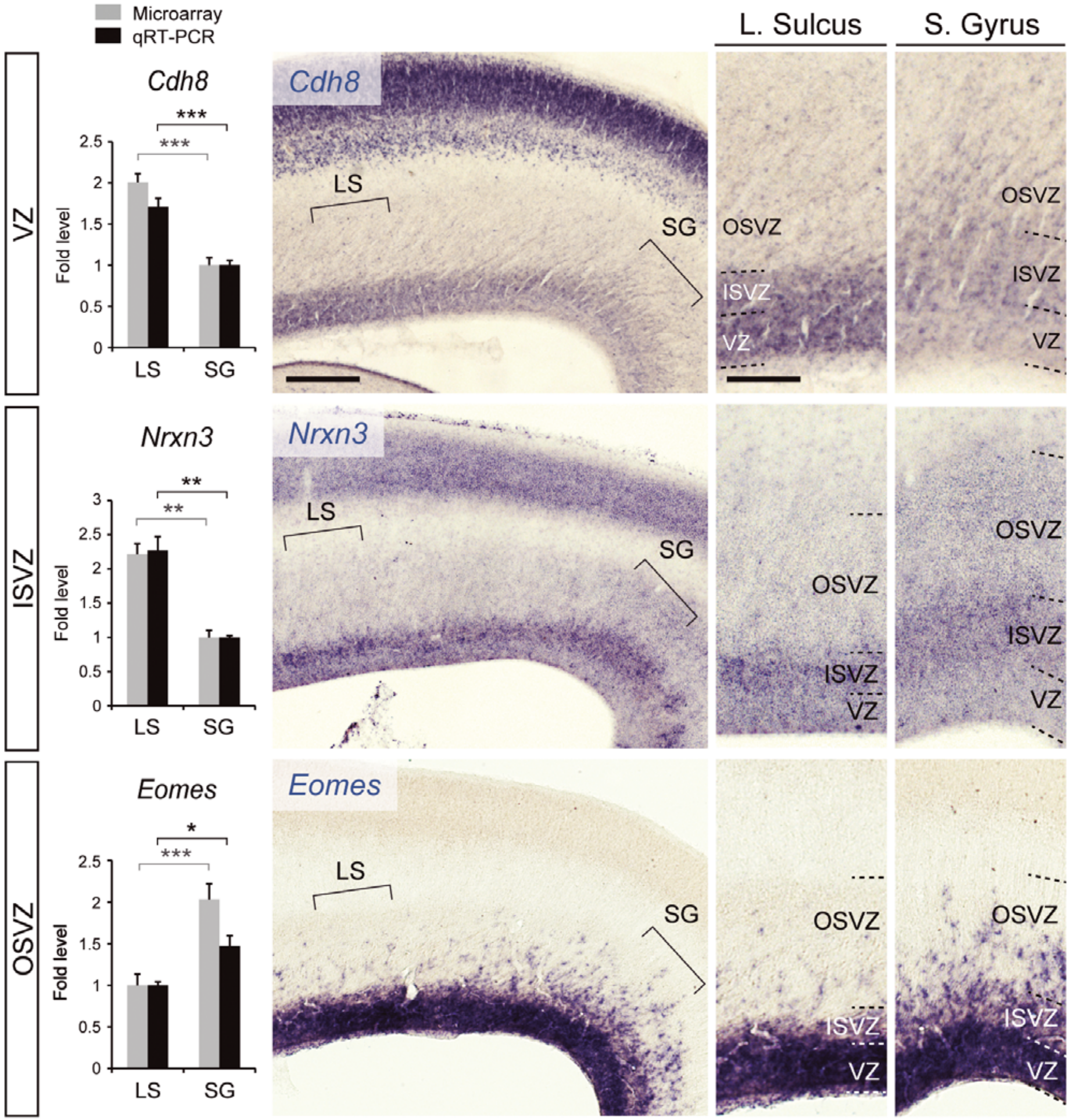
Looking for genes involved in cortical folding in the ferret



De Juan Romero et al., 2015

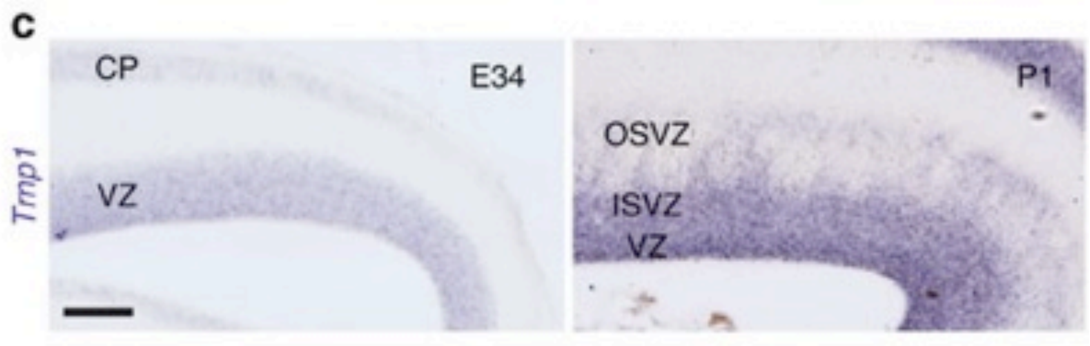
Differential gene expression between splenial gyrus (SG) and lateral sulcus (LS) along germinal layers





Expression of Trnp1 in Ferret and Mouse

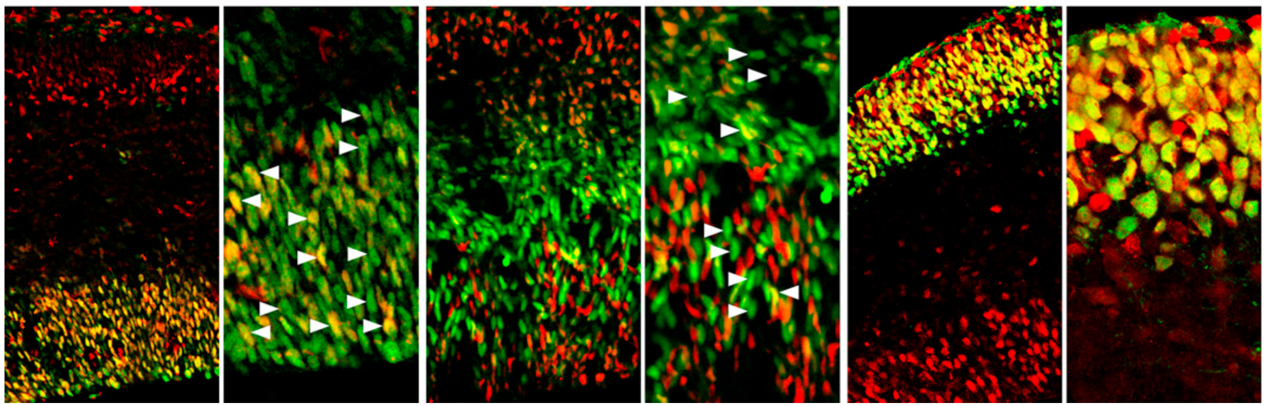
Ferret



Different expression levels between OSVZ and VZ/SVZ

Mouse

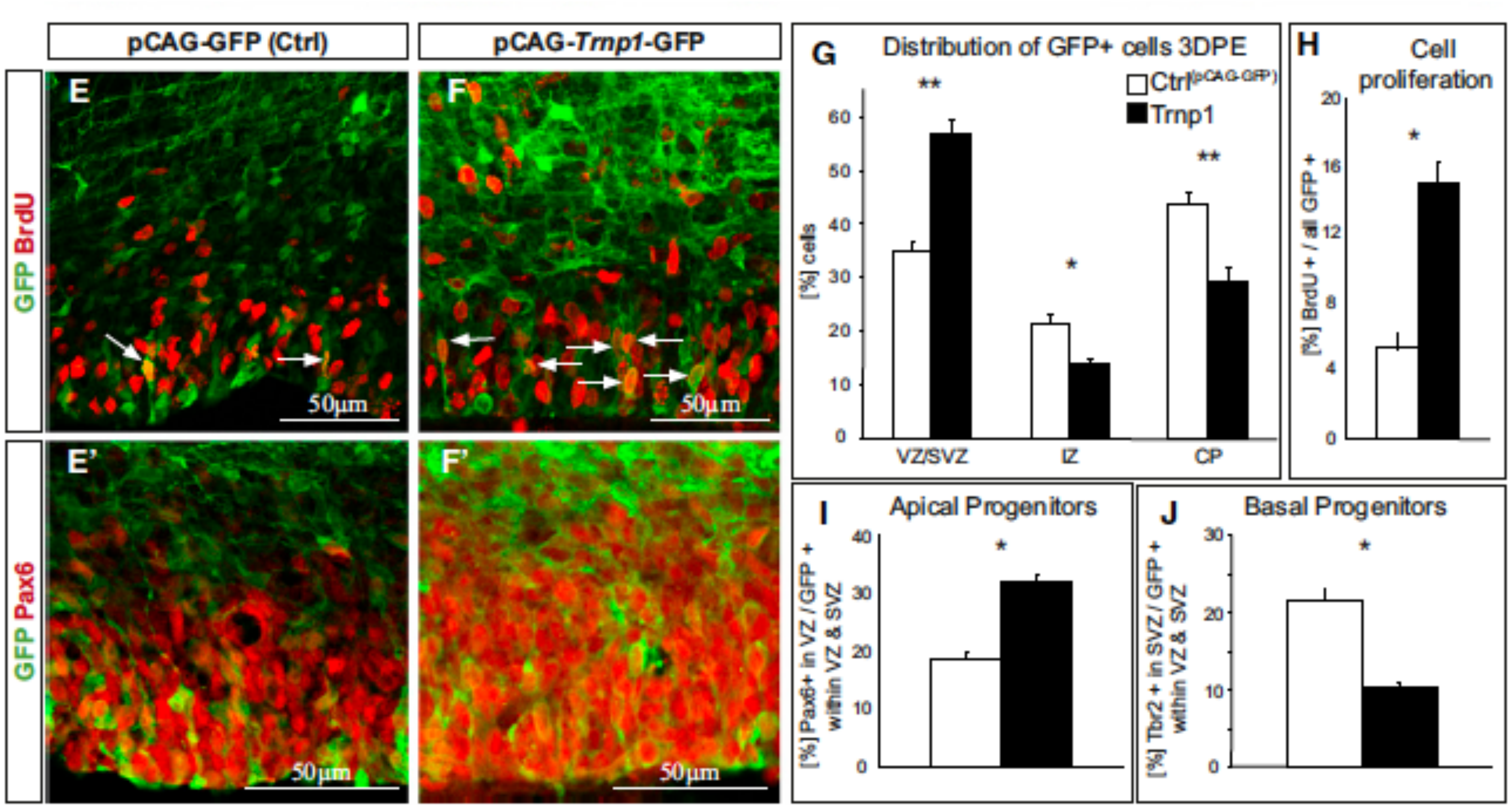
E14 - Pax6 / Trnp1 Tbr2 / Trnp1 Tbr1 / Trnp1



Similar expression levels between SVZ et VZ

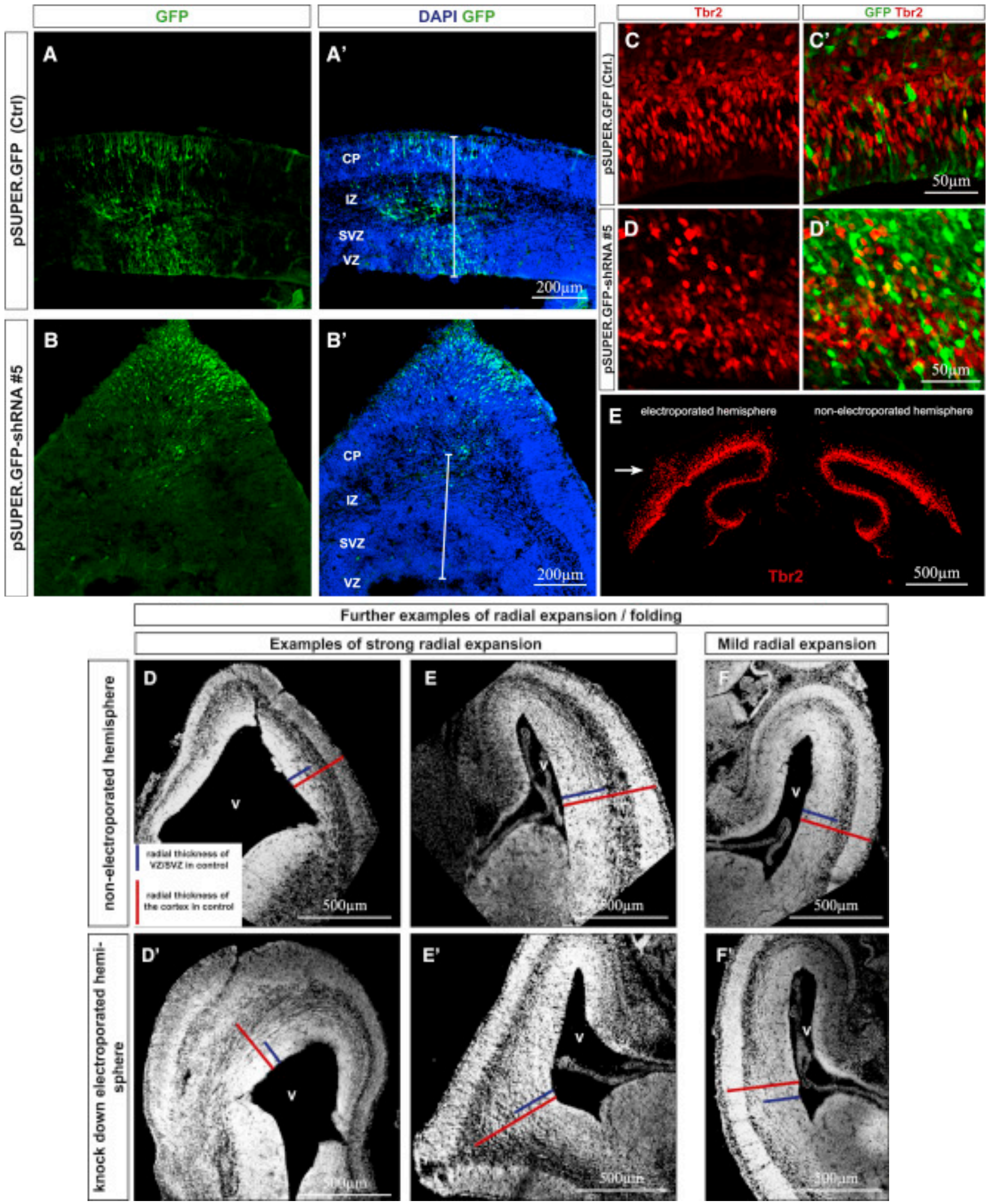
Stahl et al., 2013

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

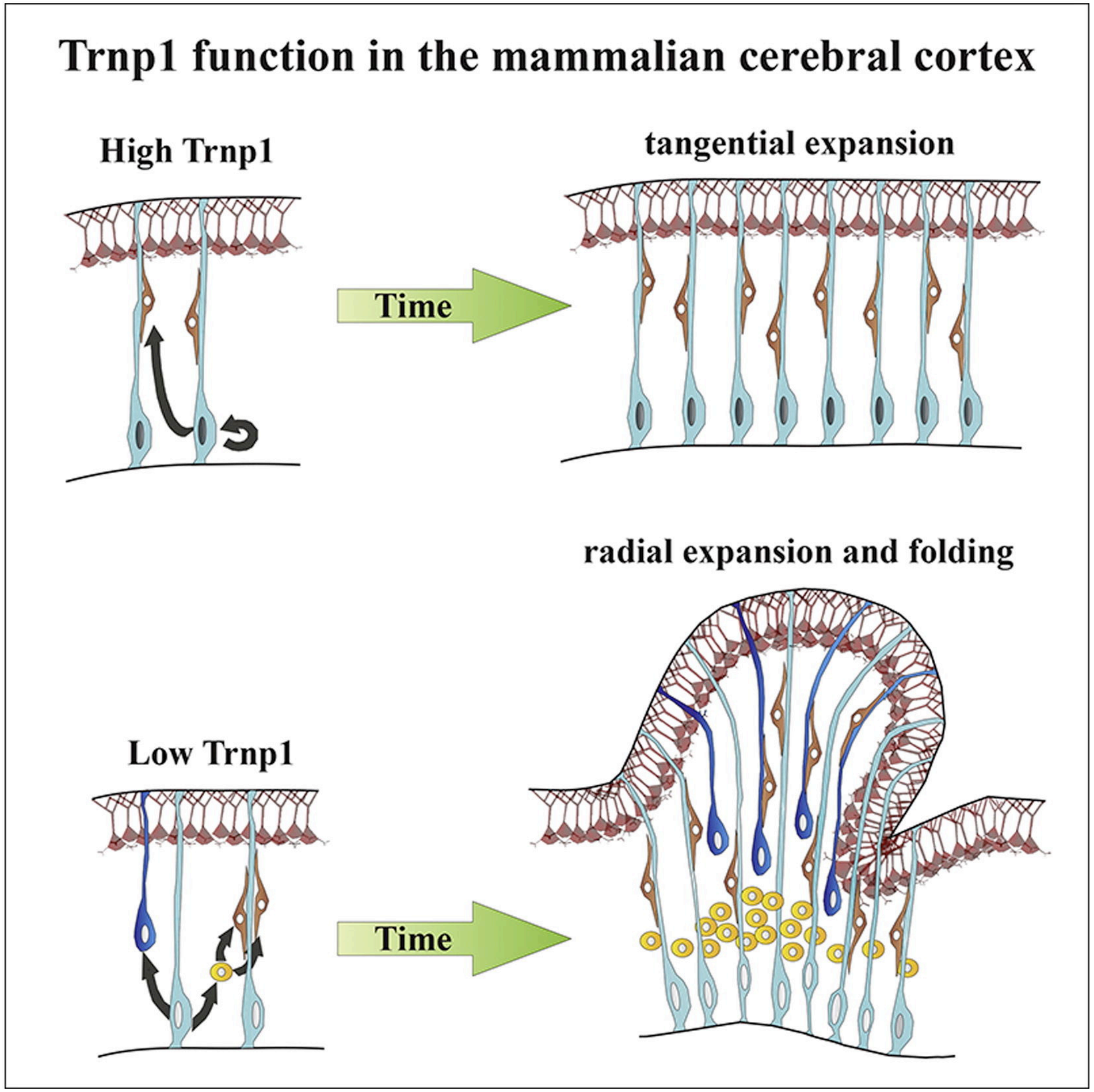


Knockdown of Trnp1 In Vivo Increases the Number of Basal Progenitors and Promotes Radial Expansion

IUE E13→ analysis E16

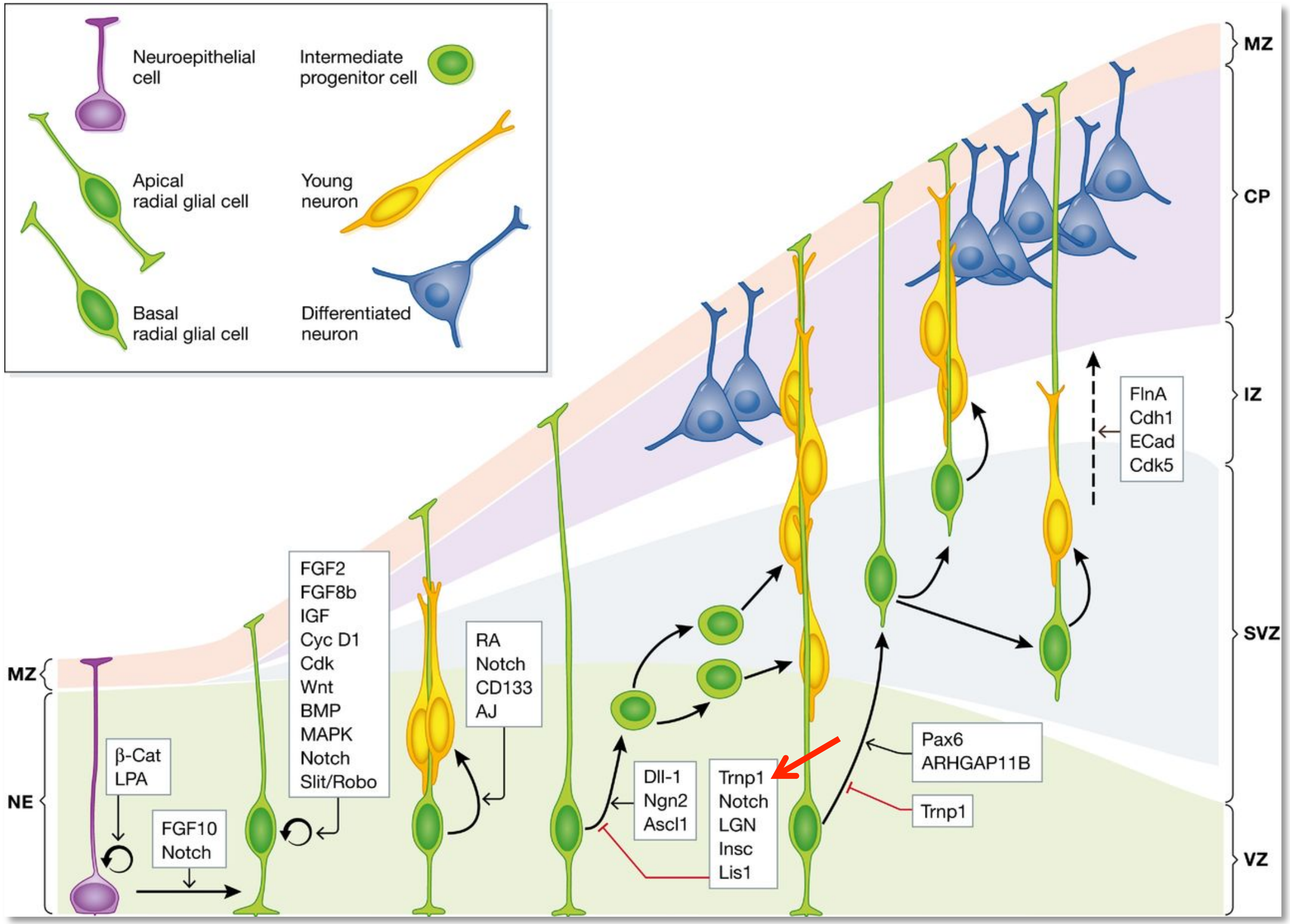


Stahl et al., 2013



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

Molecular regulation of stem cells in the developing cerebral cortex of gyrencephalic brains

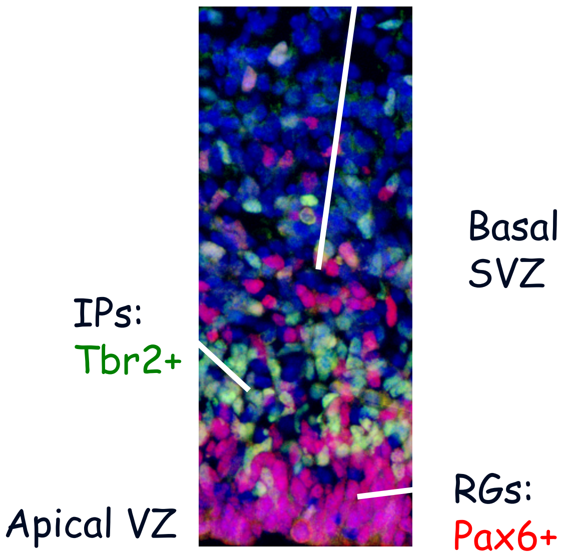


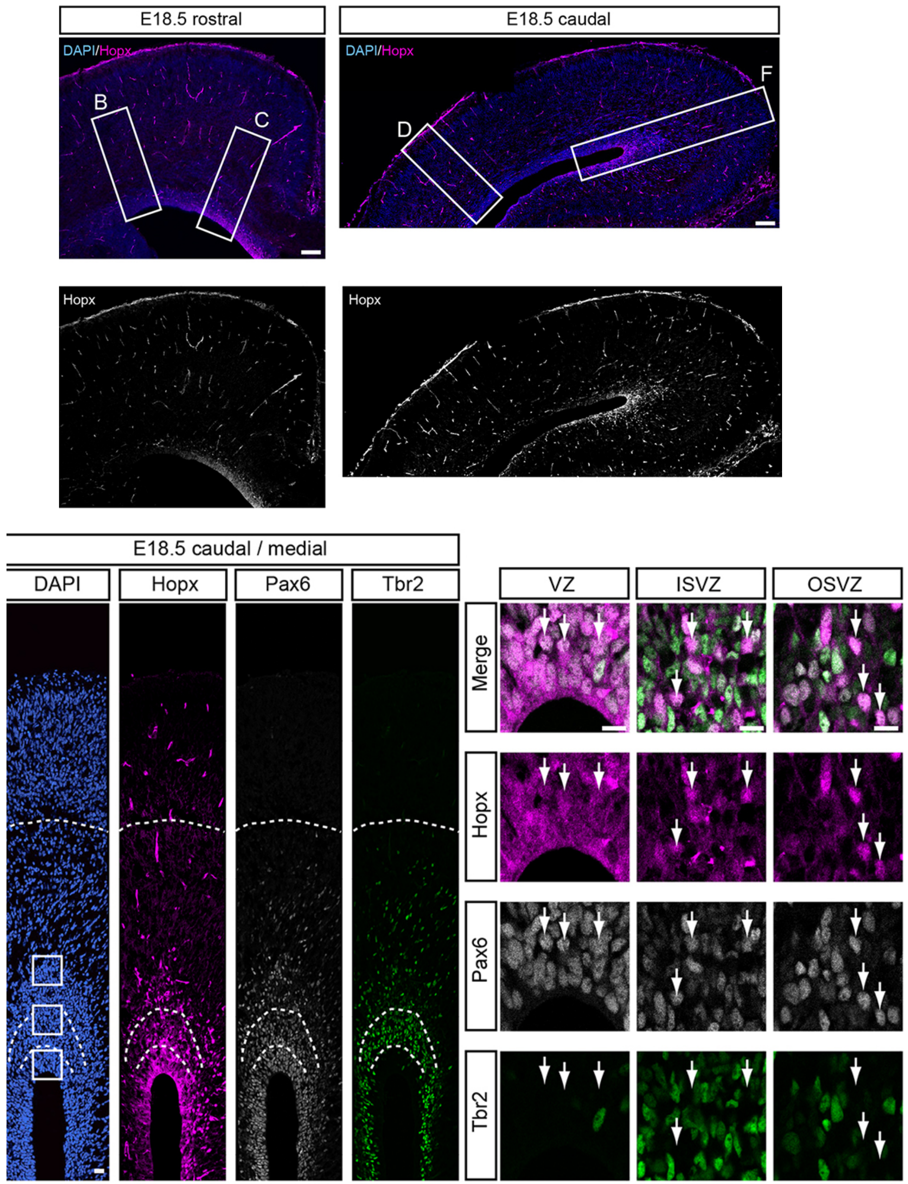
Virginia Fernández et al. EMBO J. 2016

An oRG population in the mouse

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

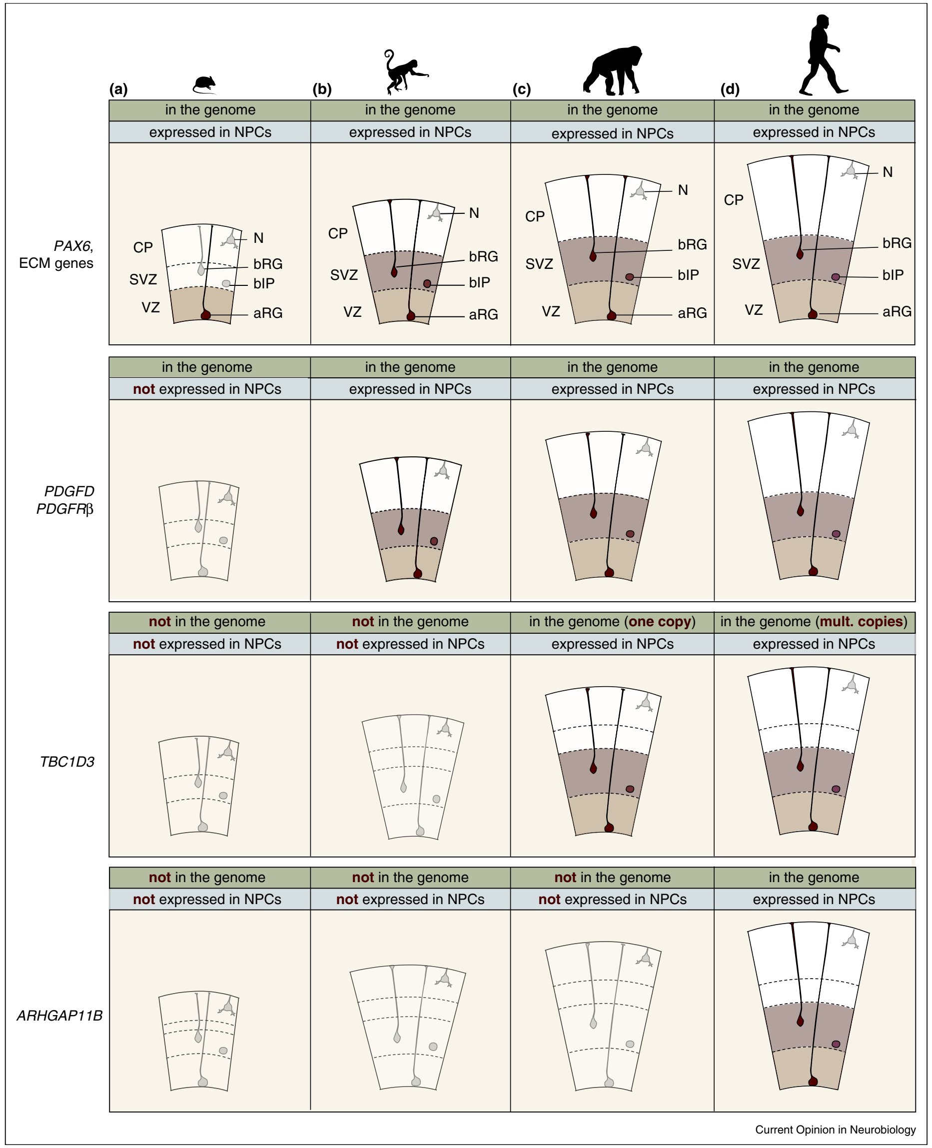
oRGs: Pax6+/Tbr2-





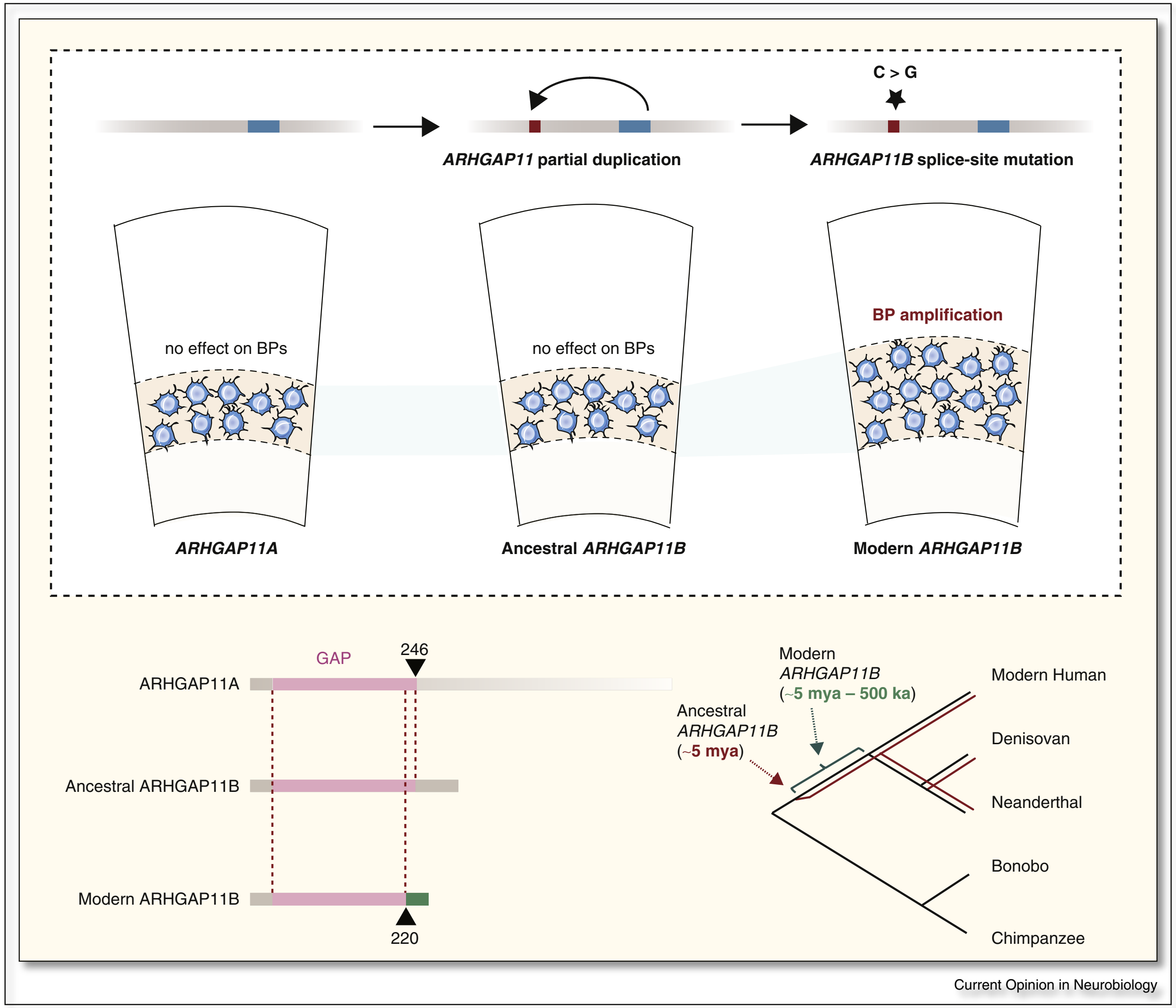
Vaid et al., 2018

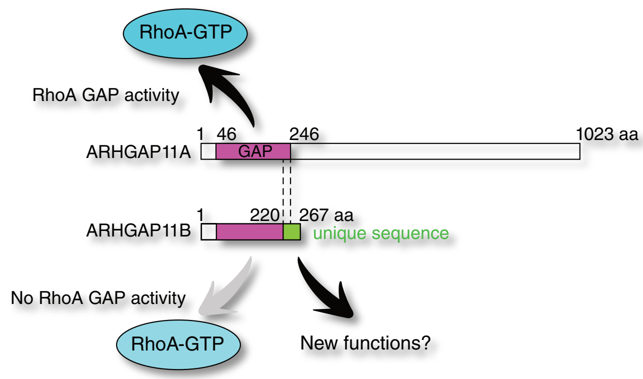
Gene expression changes affecting neural progenitor cells



Florio et al., Science 2015

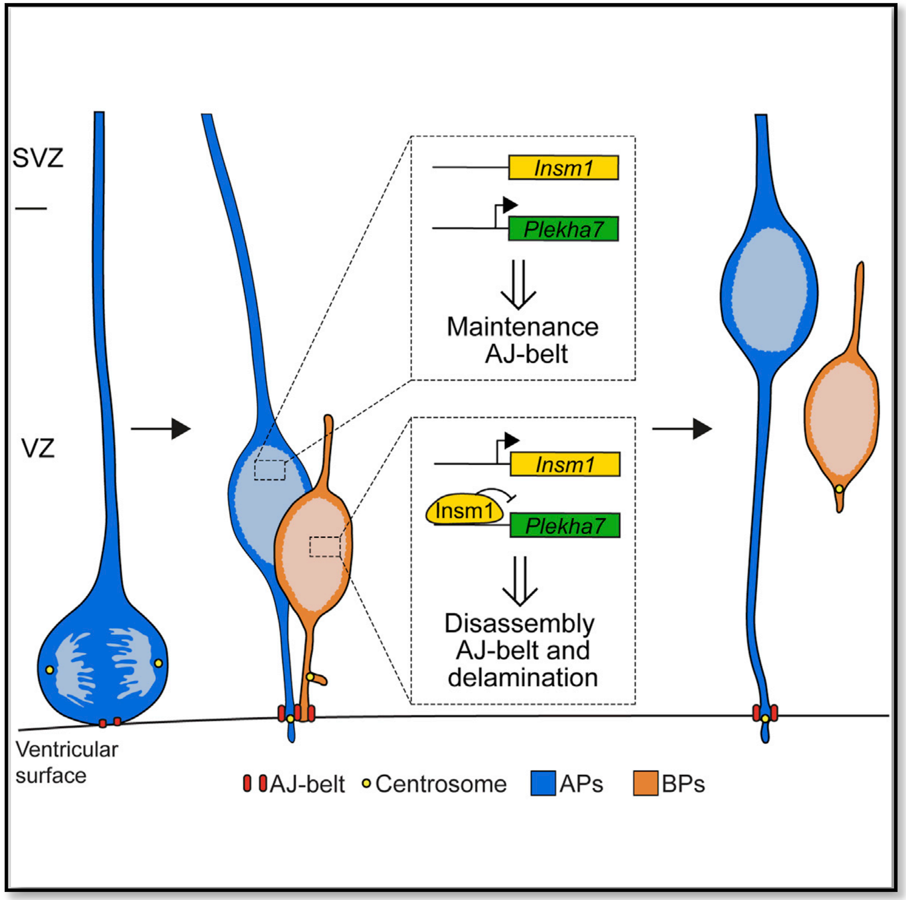
Evolution of the Rho-GTPase gene ARHGAP11B





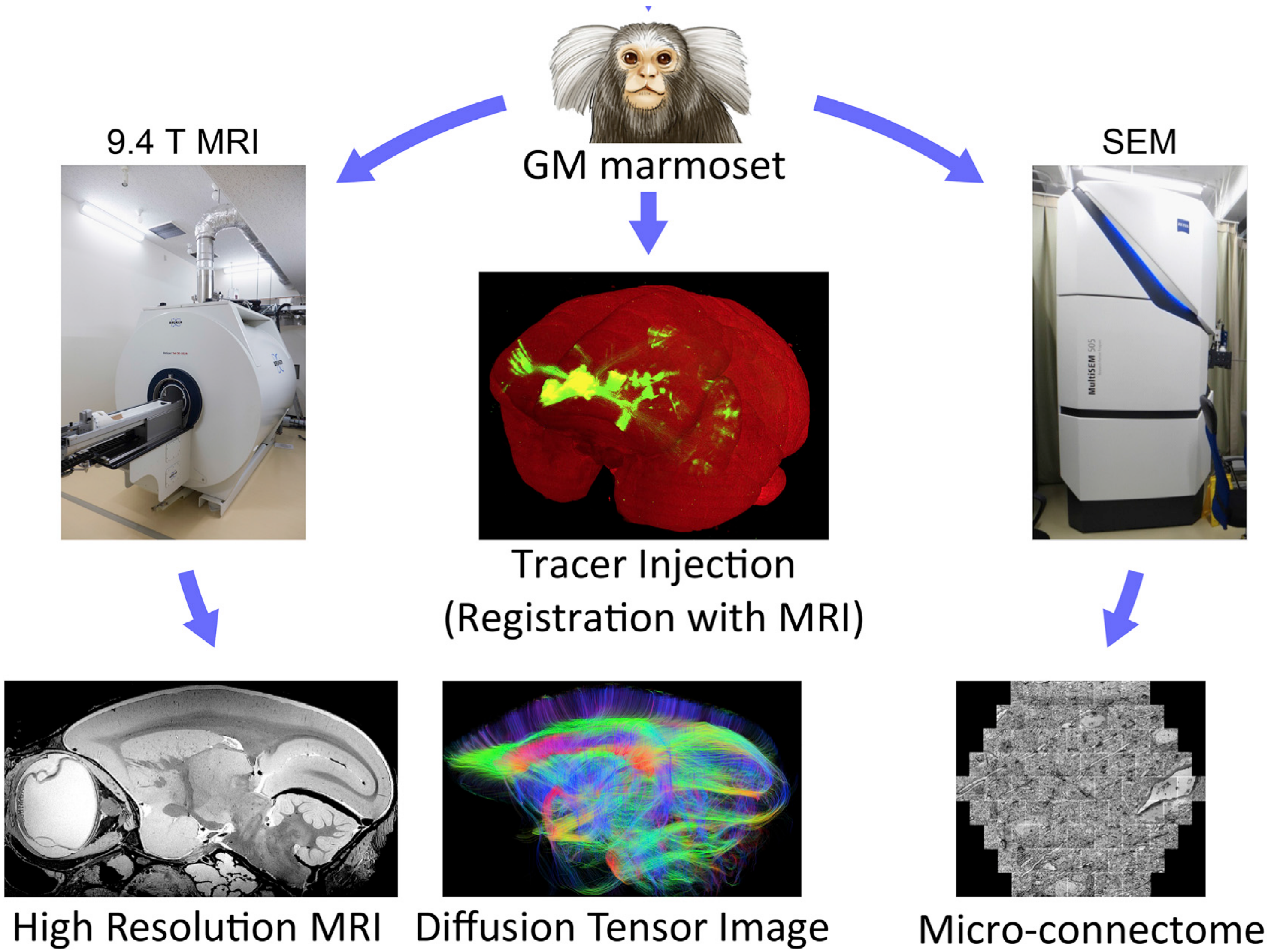
Florio & Hutner, 2017

Delamination of neural progenitors via adherens junction proteins

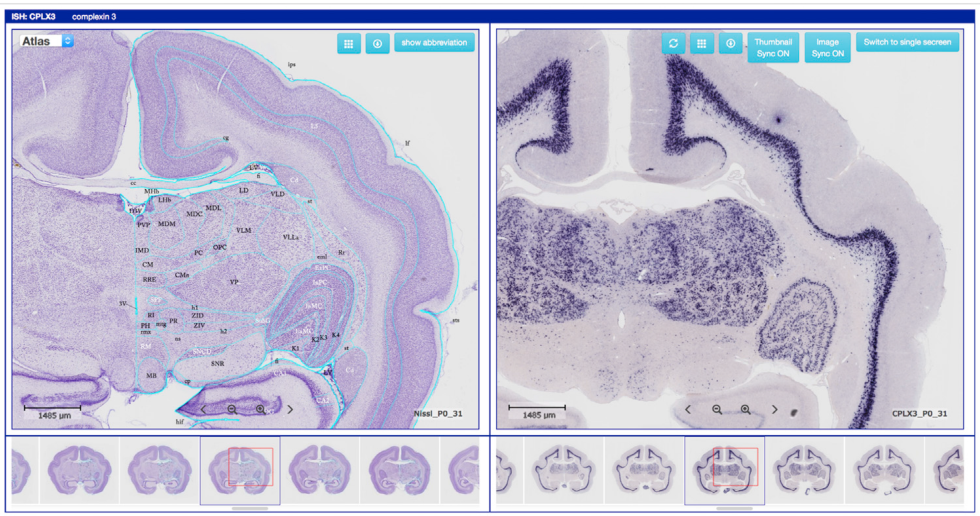


Tavano et al., 2018

The marmoset, a non-human primate recently used in neurosciences



Marmoset Gene Atlas



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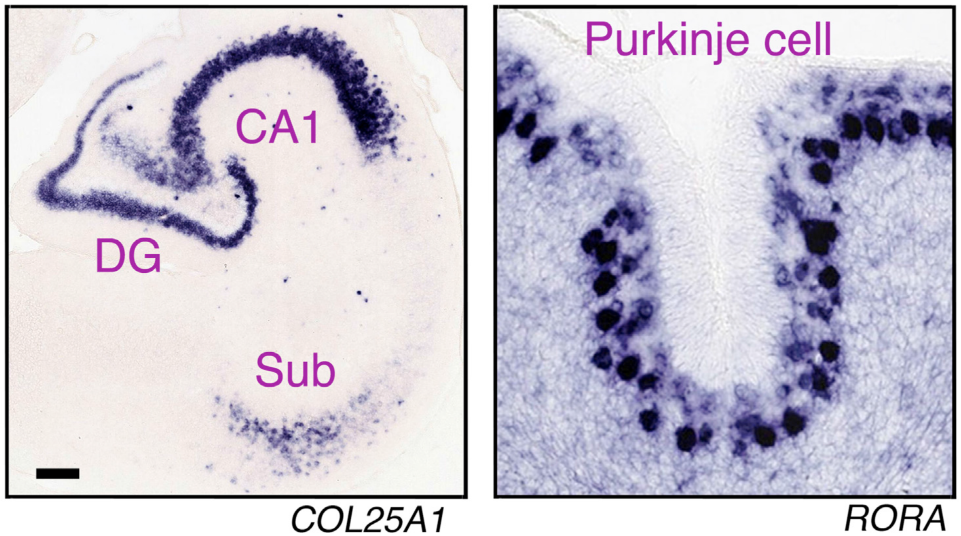
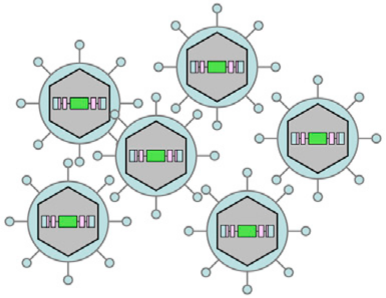
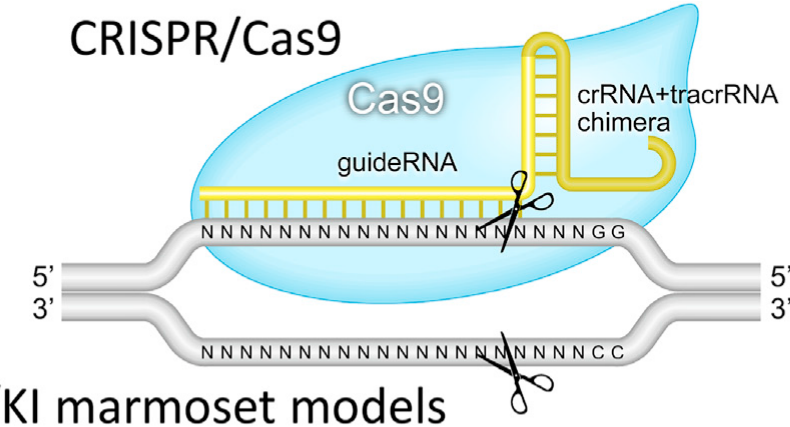
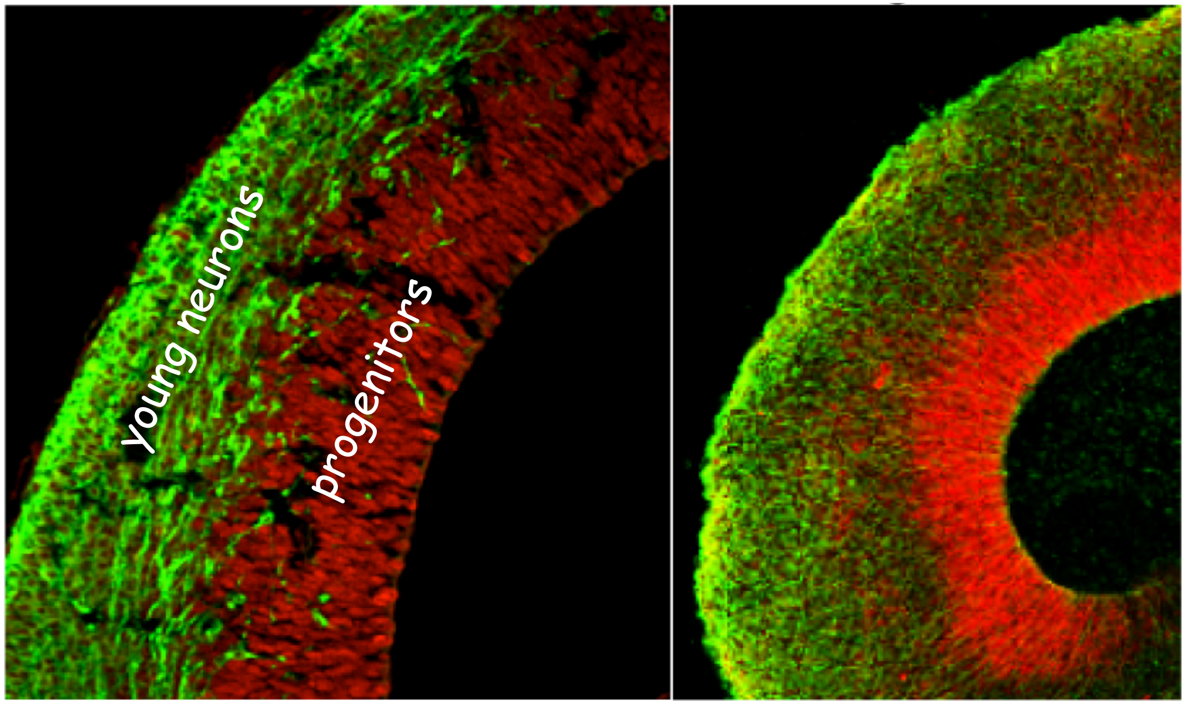




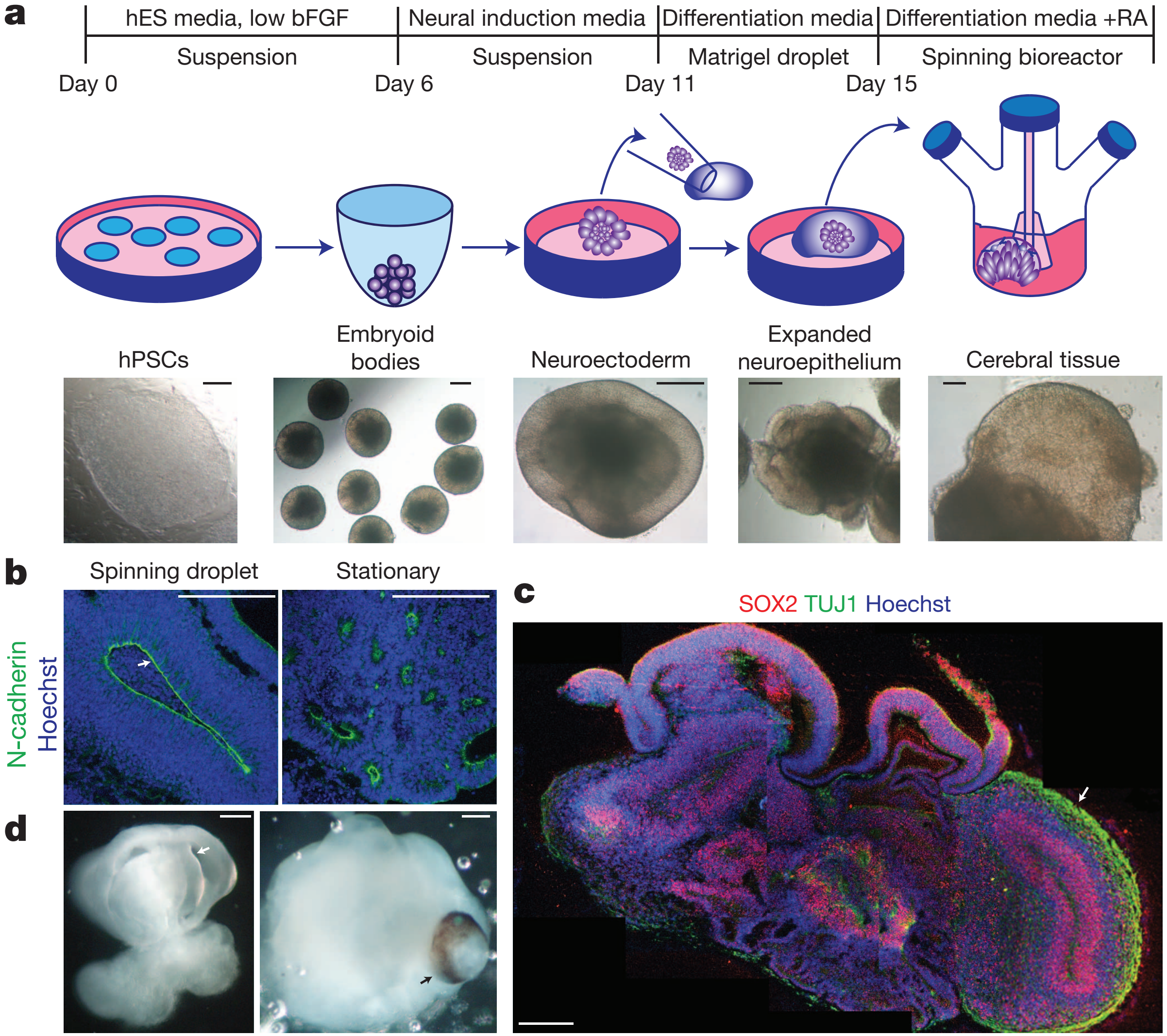


Transgenic/ target gene KO/KI marmoset models

"Learning from and for development":
using the knowledge from basic developing mechanisms to generate mini-brains in vitro

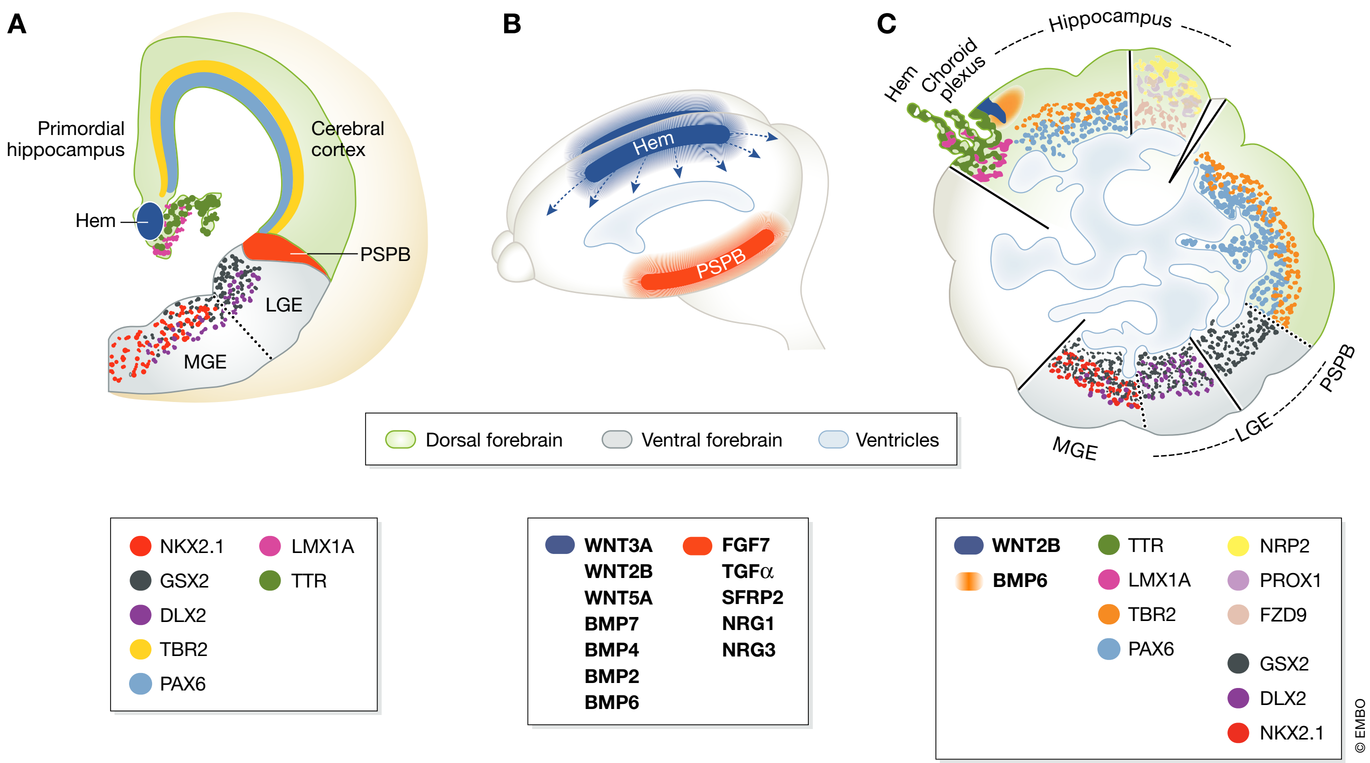


Culturing cerebral organoids in 3D



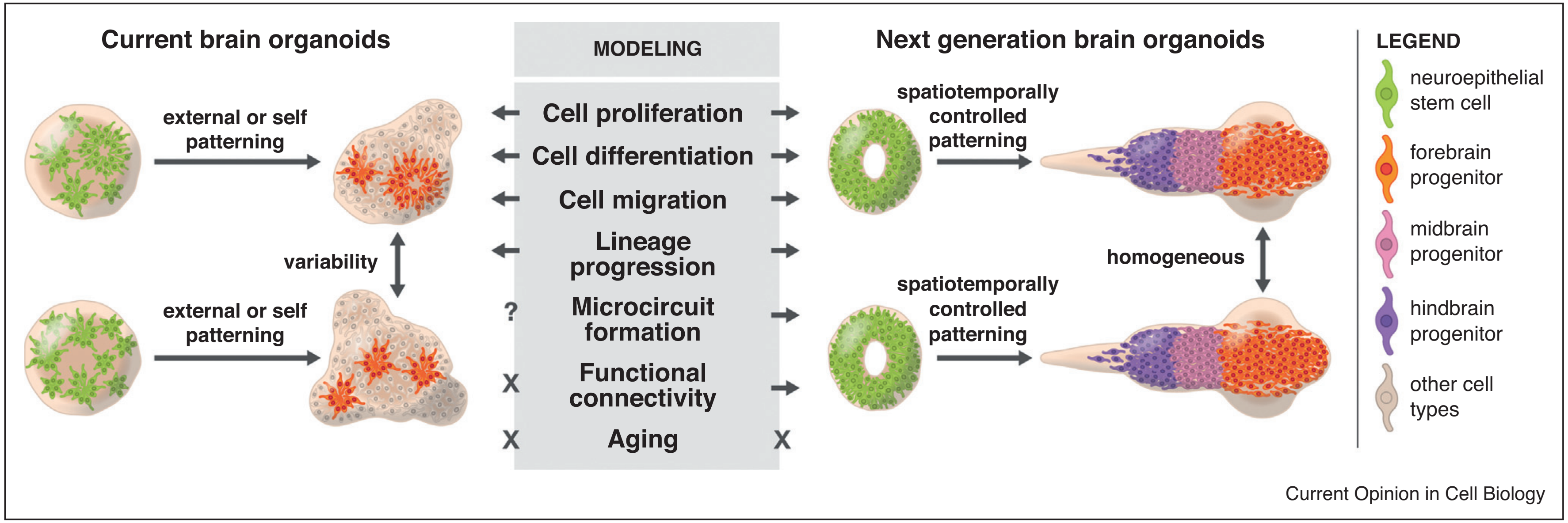
Lancaster M. et al., Nature, 2013

Major structural organization and regional differentiation are recapitulated in cerebral organoids



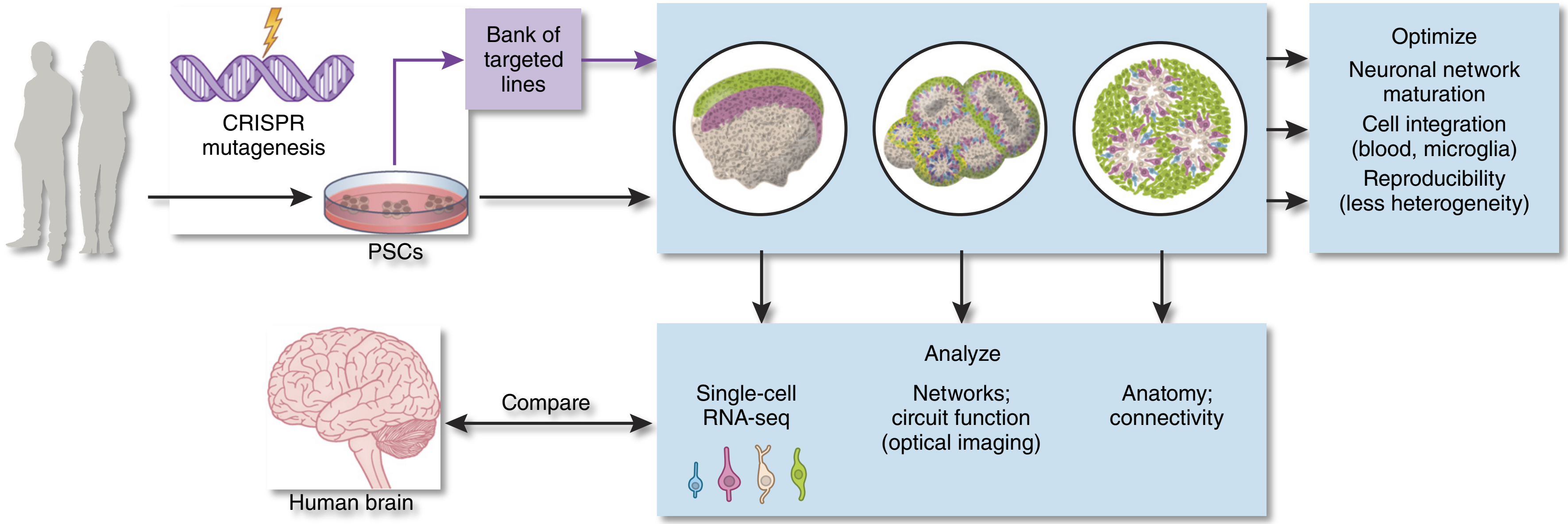
From Dias & Guillemot, EMBO J. 2017

Challenges in organoid production



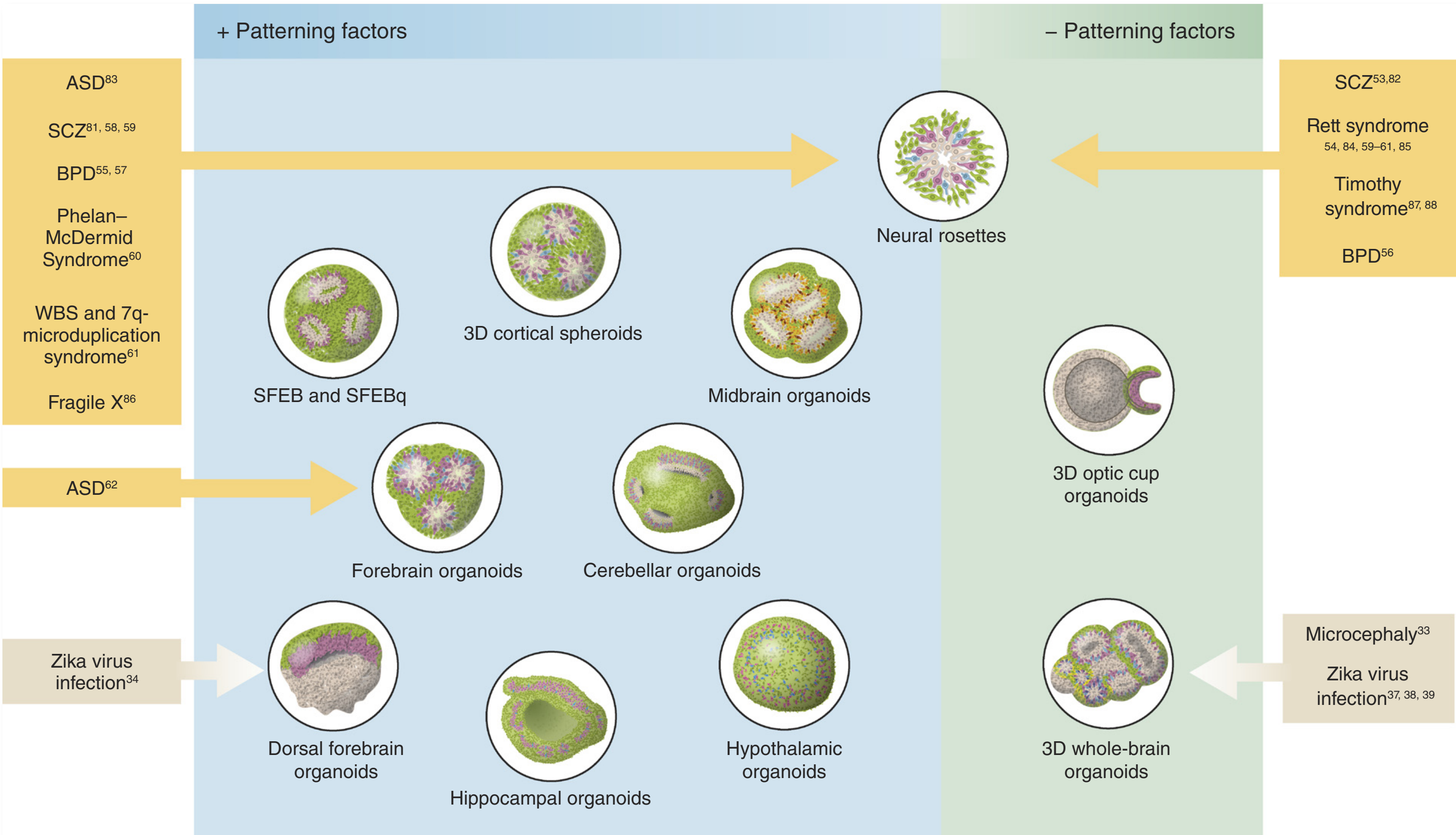
Quadrato & Arlotta, 2017

Generation, characterization and analysis of 3D cellular models of the human brain from induced pluripotent stem cells (iPSCs)



Quadrato et al., Nat Med, 2016

Cerebral organoids as models of neuropsychiatric diseases



Quadrato et al., Nat Med, 2016

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LETTERS

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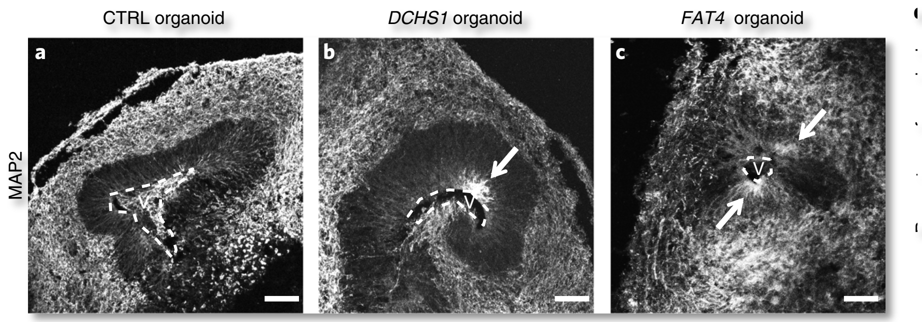
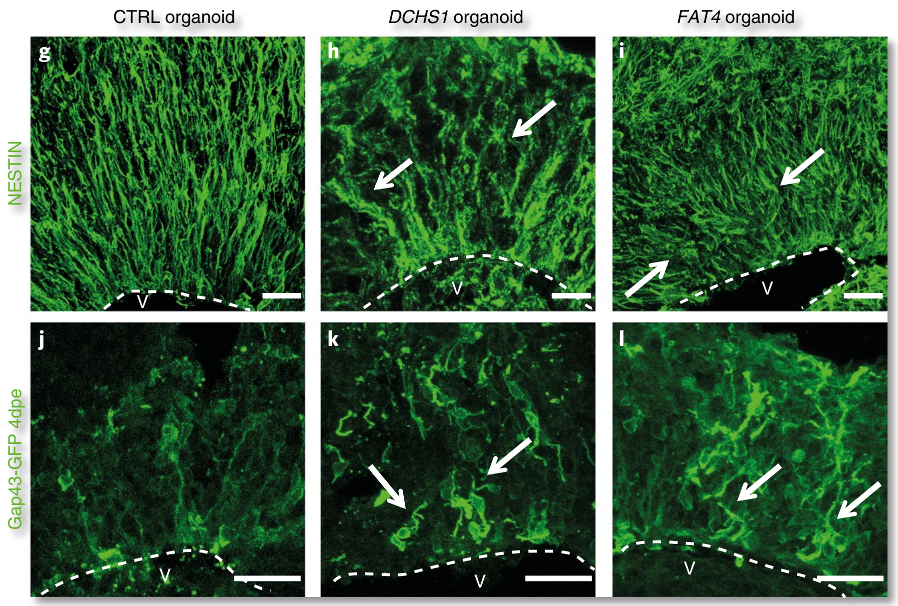
Altered neuronal migratory trajectories in human cerebral organoids derived from individuals with neuronal heterotopia

Johannes Klaus[1,11], Sabina Kanton[2,11], Christina Kyrousi[1,11], Ane Cristina Ayo-Martin[1,3], Rossella Di Giaimo[1,4], Stephan Riesenberg[2], Adam C. O'Neill[5,6], J. Gray Camp[2], Chiara Tocco[1], Malgorzata Santel[2], Ejona Rusha[7], Micha Drukker[7], Mariana Schroeder[1], Magdalena Götz[6,8], Stephen P. Robertson[5], Barbara Treutlein[2,9,10]* and Silvia Cappello[1]*

Mutations in the cadherin receptor-ligands pair DCHS1 and FAT4 cause neuronal heterotopia and abnormal morphology of NPC in cerebral organoids





Klaus et al., 2019