Dept of Veterinary Sciences

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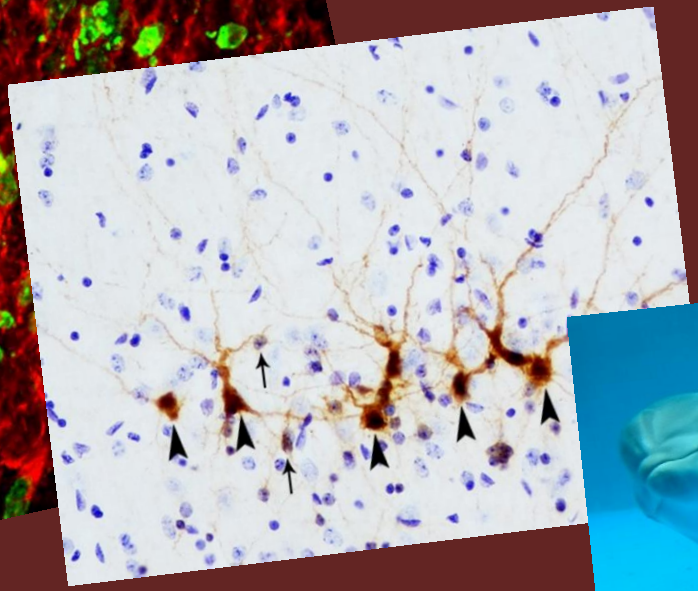
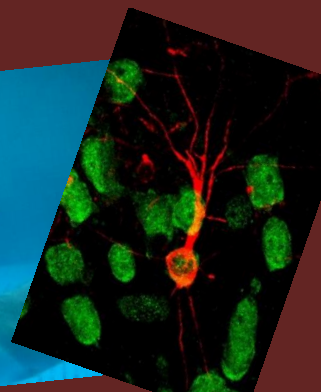
Adult neurogenesis:
from stem cells to immature neurons





Neurons expressing markers of «immaturity» in the adult sheep hippocampus

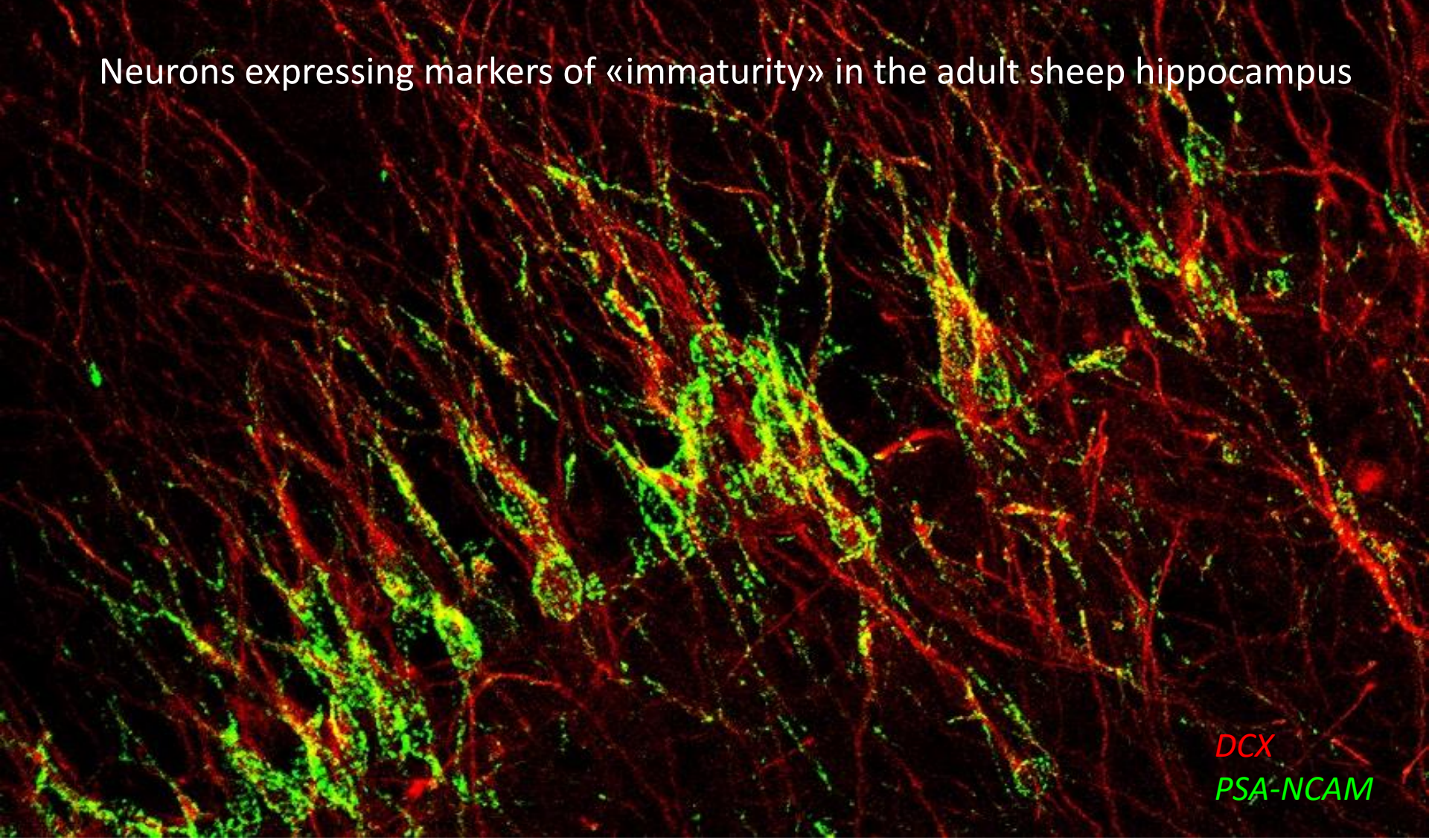


Foto: Ottavia Palazzo

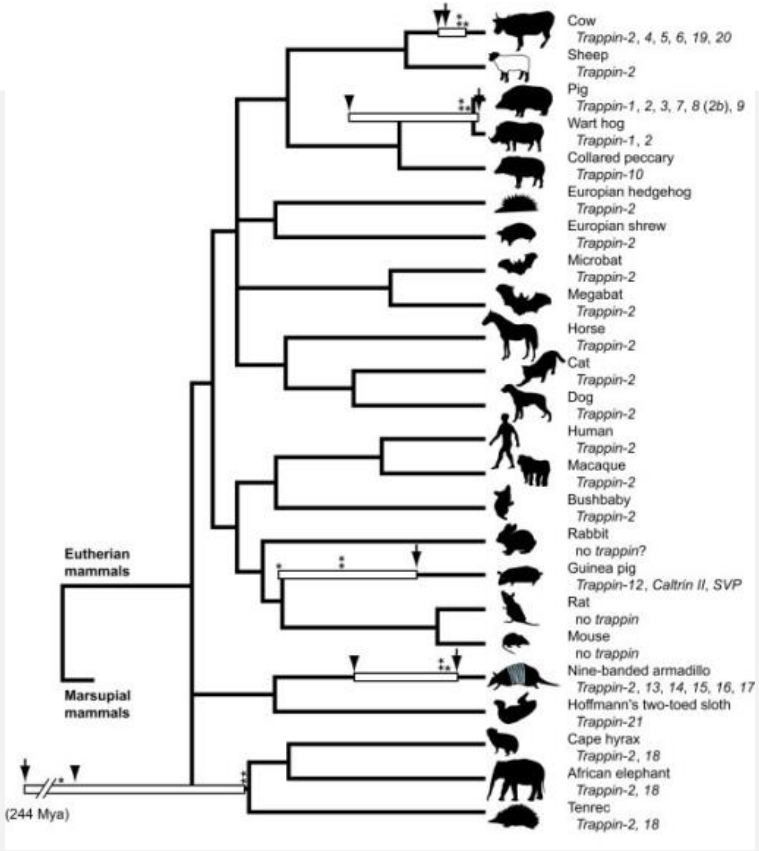
Published 3 days ago

NEUROSCIENCE

Adult neurogenesis in mammals

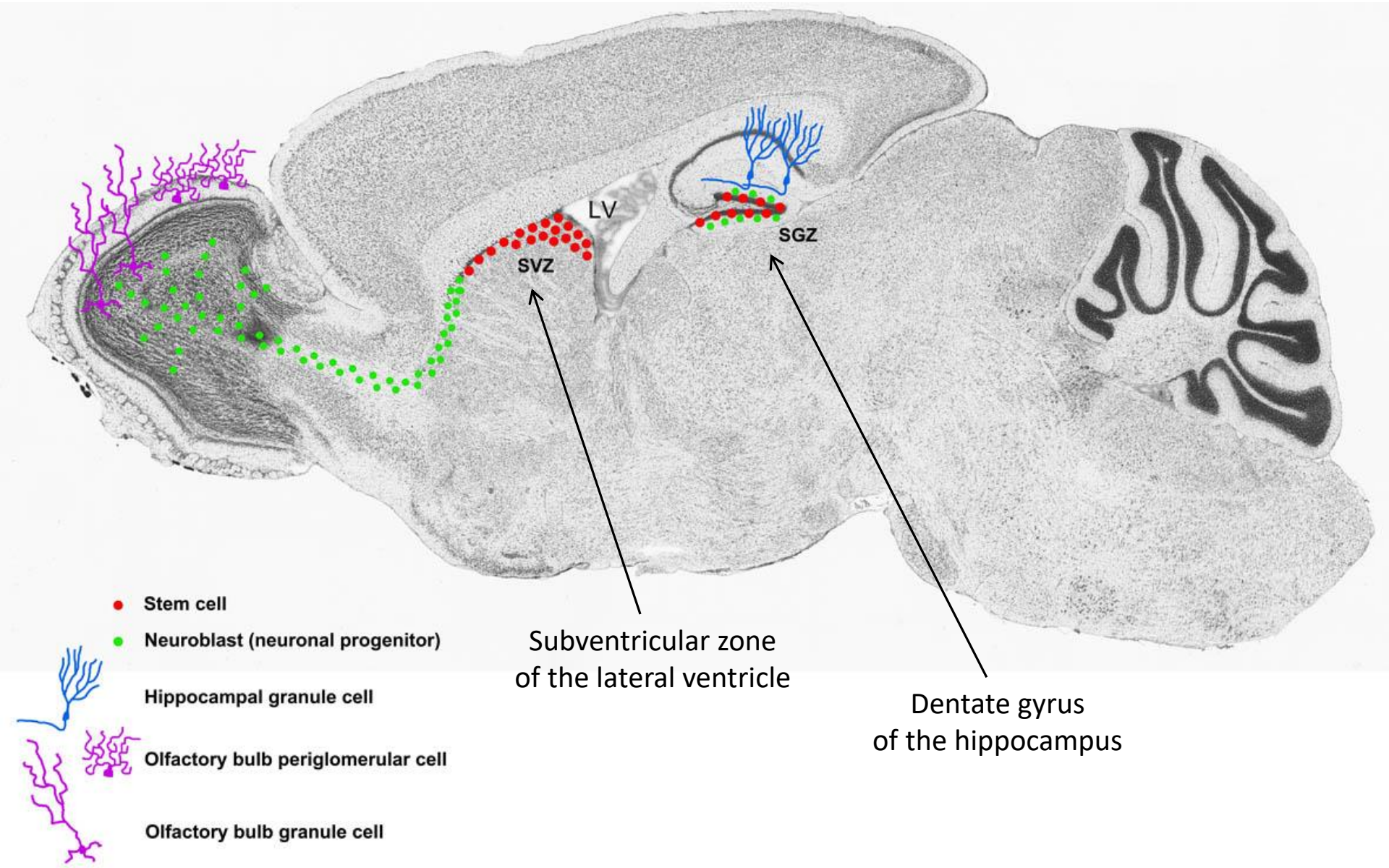
Neurogenesis in adulthood has implications for sense of self, memory, and disease

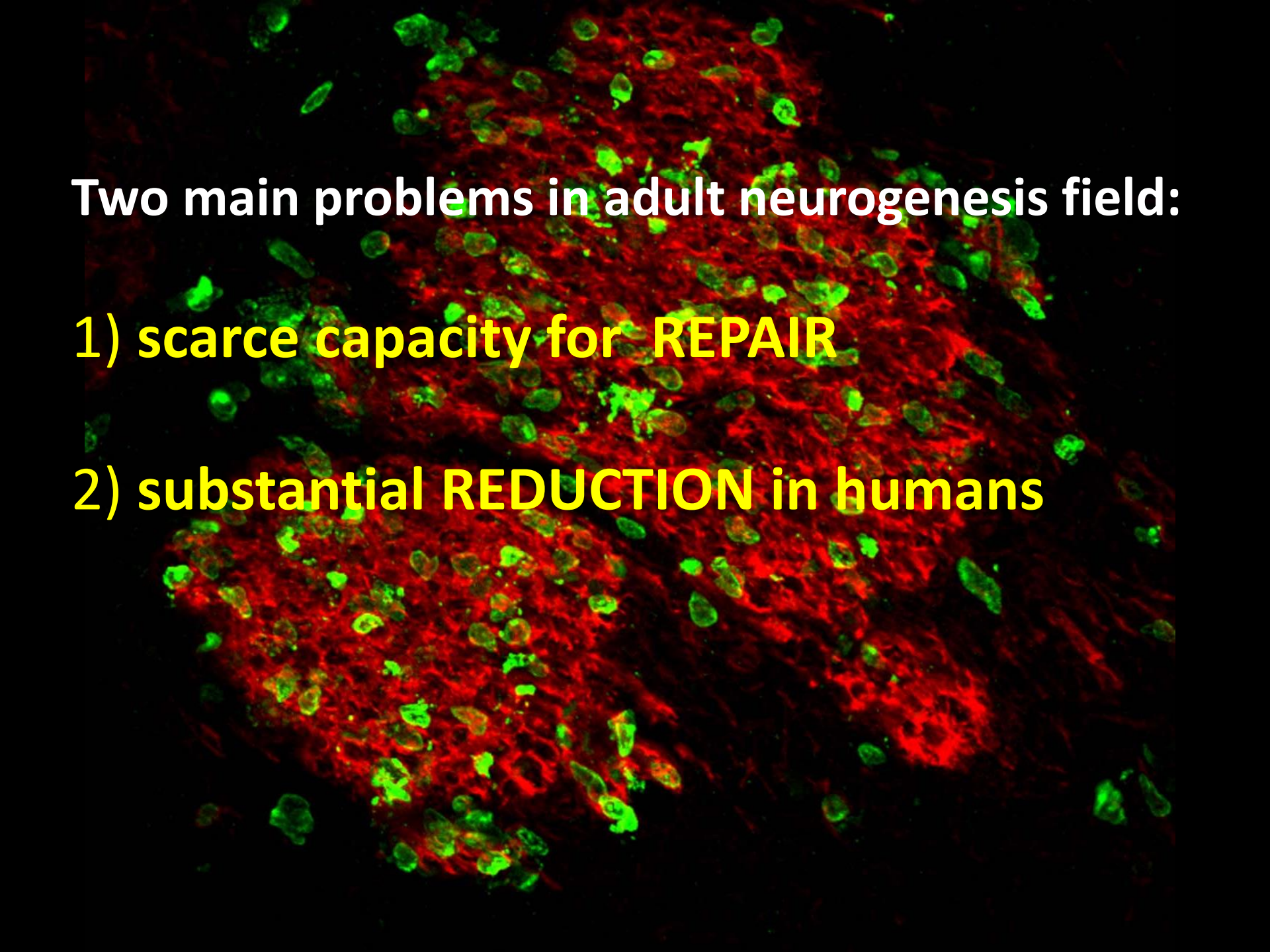
By **Fred H. Gage**



genesis, including proliferation, maturation, migration, differentiation, survival, and inte-

Neurogenic zones and their outcome





Two main problems in adult neurogenesis field:

1) **scarce capacity for REPAIR**

2) **substantial REDUCTION in humans**

NO REPAIR in mammals

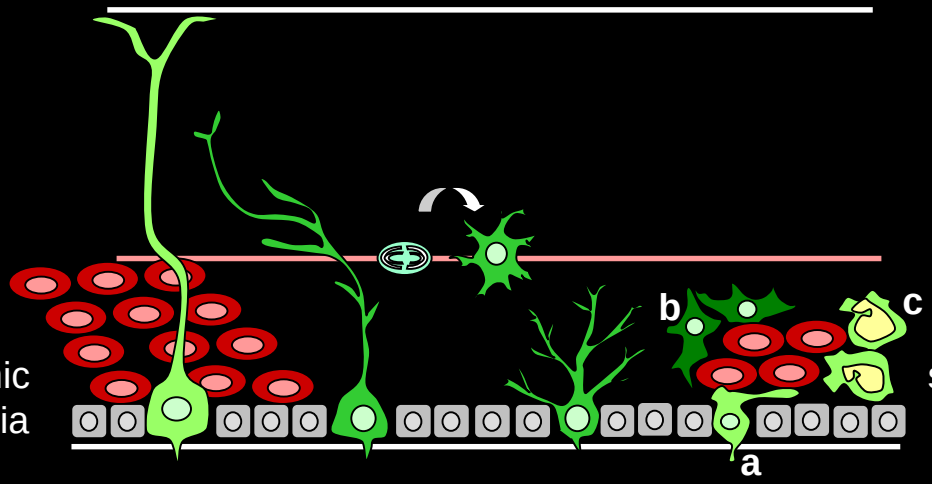
Strong reduction in mammals

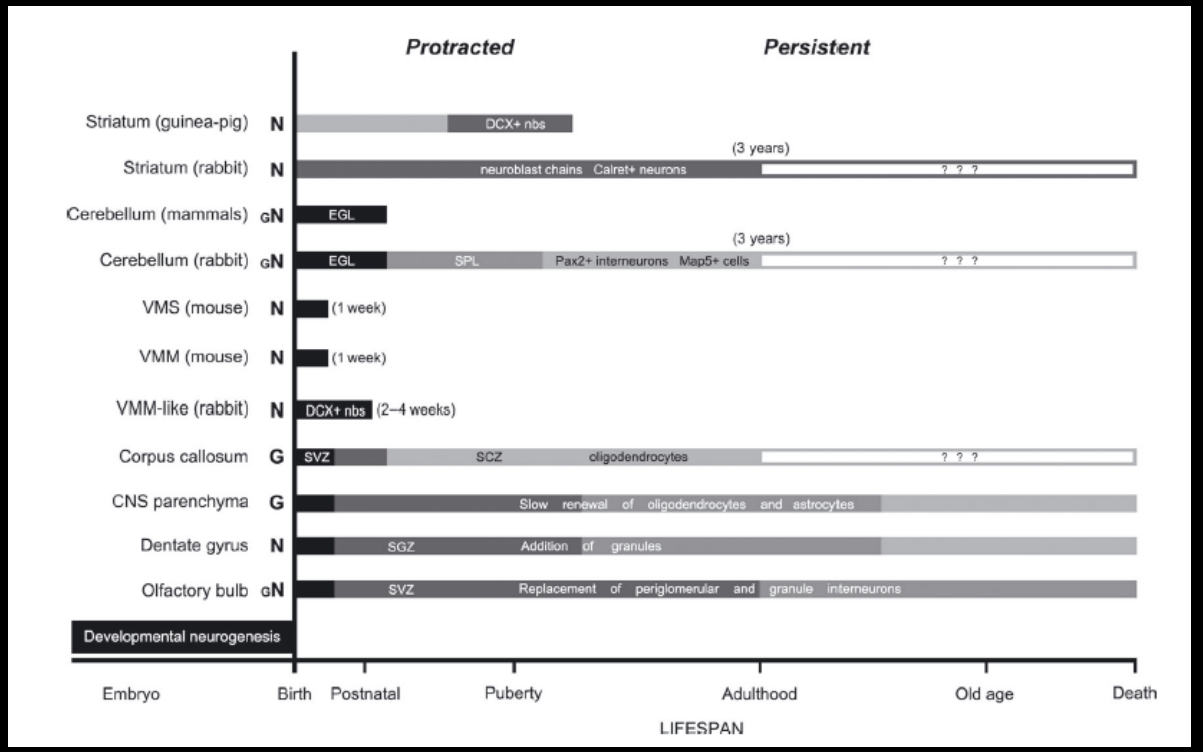
Adult neurogenesis, structural plasticity, repair

Plasticity + repair

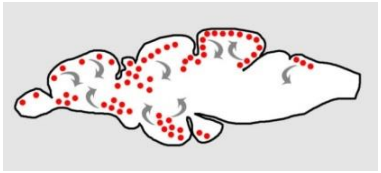
Plasticity

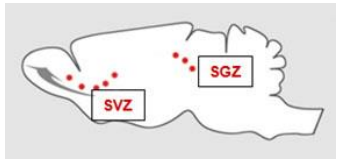
Adult neurogenesis is a **protracted DEVELOPMENTAL** process





Bonfanti & Peretto 2011 Eur J Neurosci



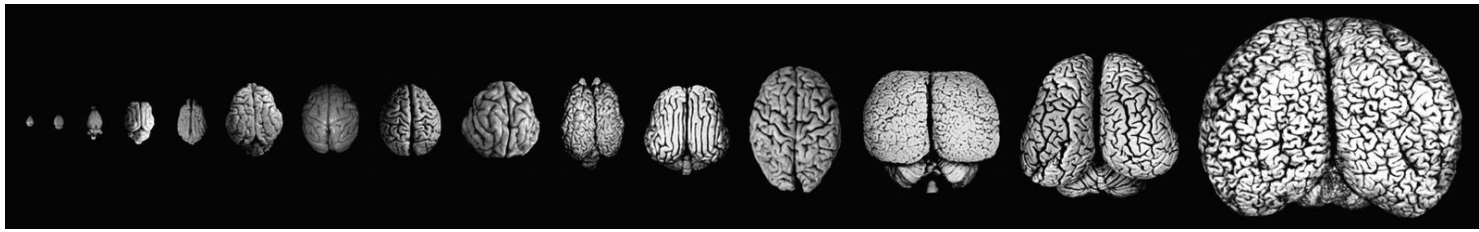


Non mammalian vertebrates

Mammals

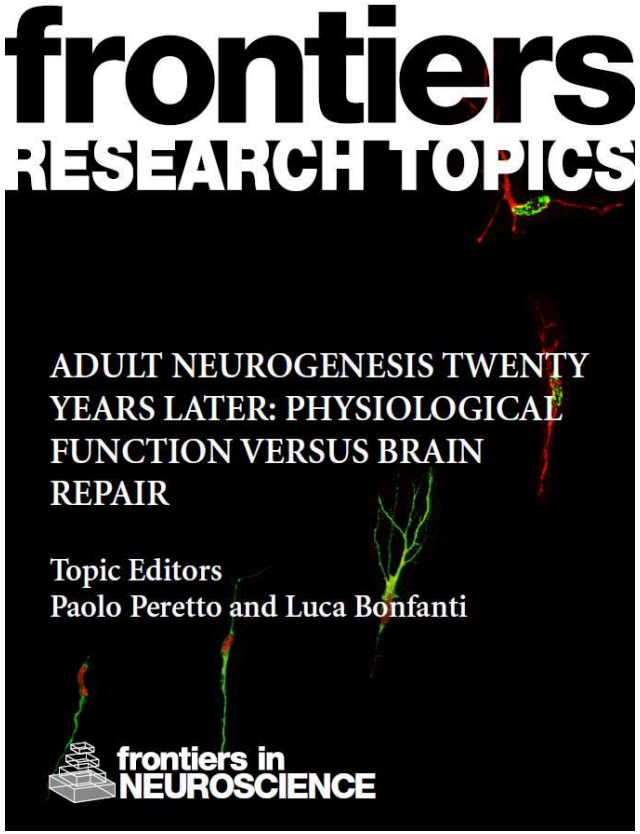
Reduction among mammals

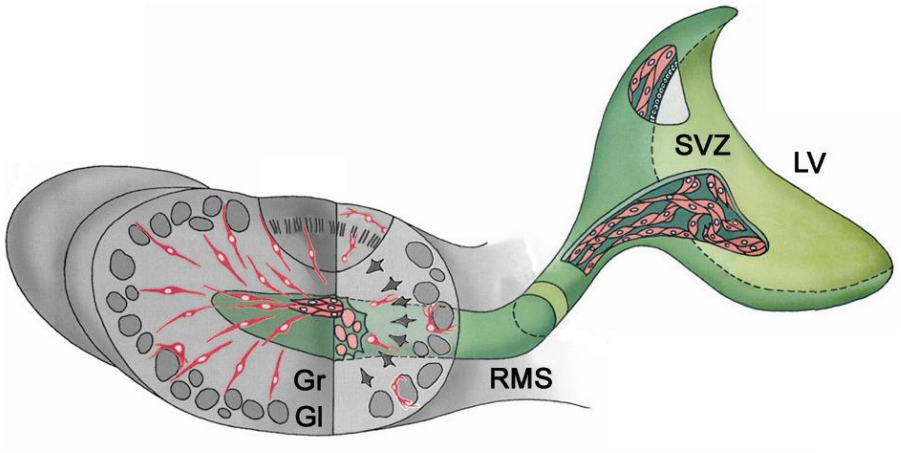
Repair (plasticity?)

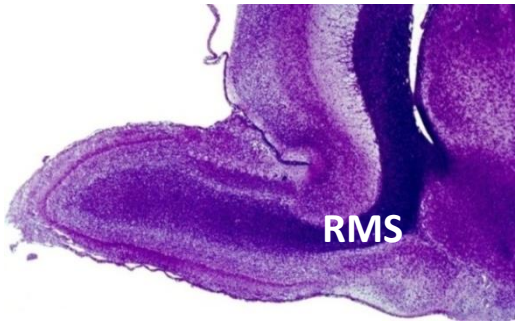


Brains in mammals are DIFFERENT

Adult neurogenesis: only physiological function in mammals?



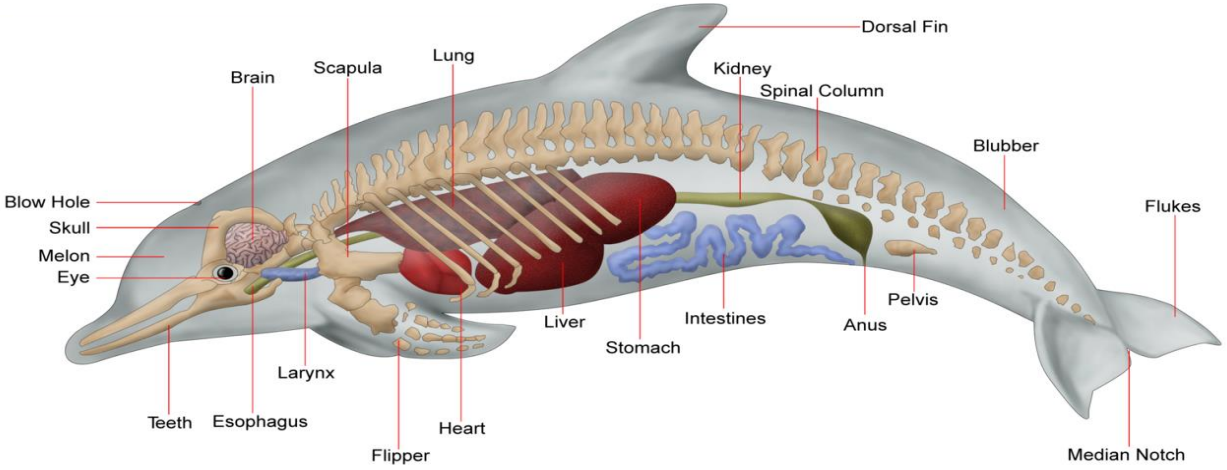




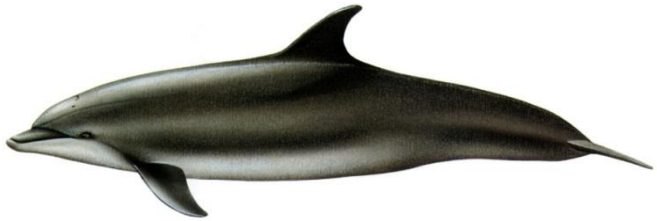
We need a mammal devoid of olfaction

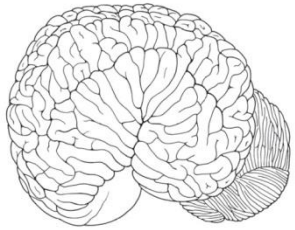
Dolphins

Aquatic mammals (cetacea)



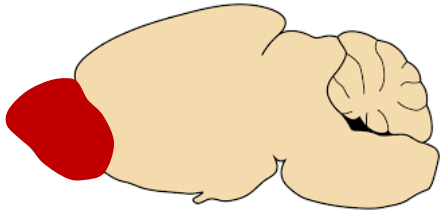
LARGE-BRAINED
CORTEX EXPANDED
HIGHLY GYRENCEPHALIC
LONG LIFESPAN
ECOLOCALIZATION

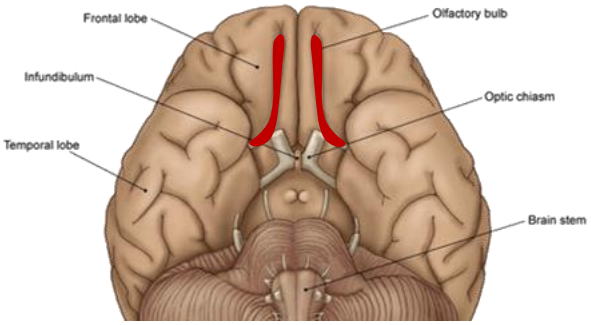


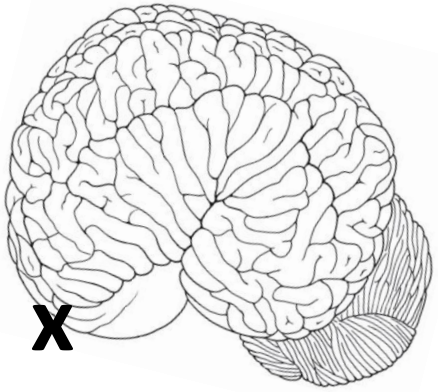


No olfaction. No olfactory bulb

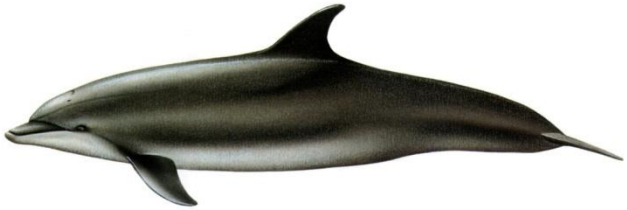
Mouse *(not in scale)* **Human** **Dolphin**





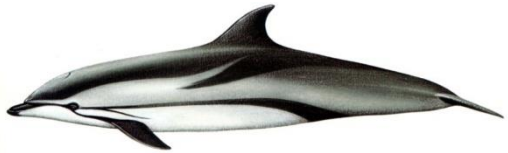


LARGE **SMALL** **ABSENT**



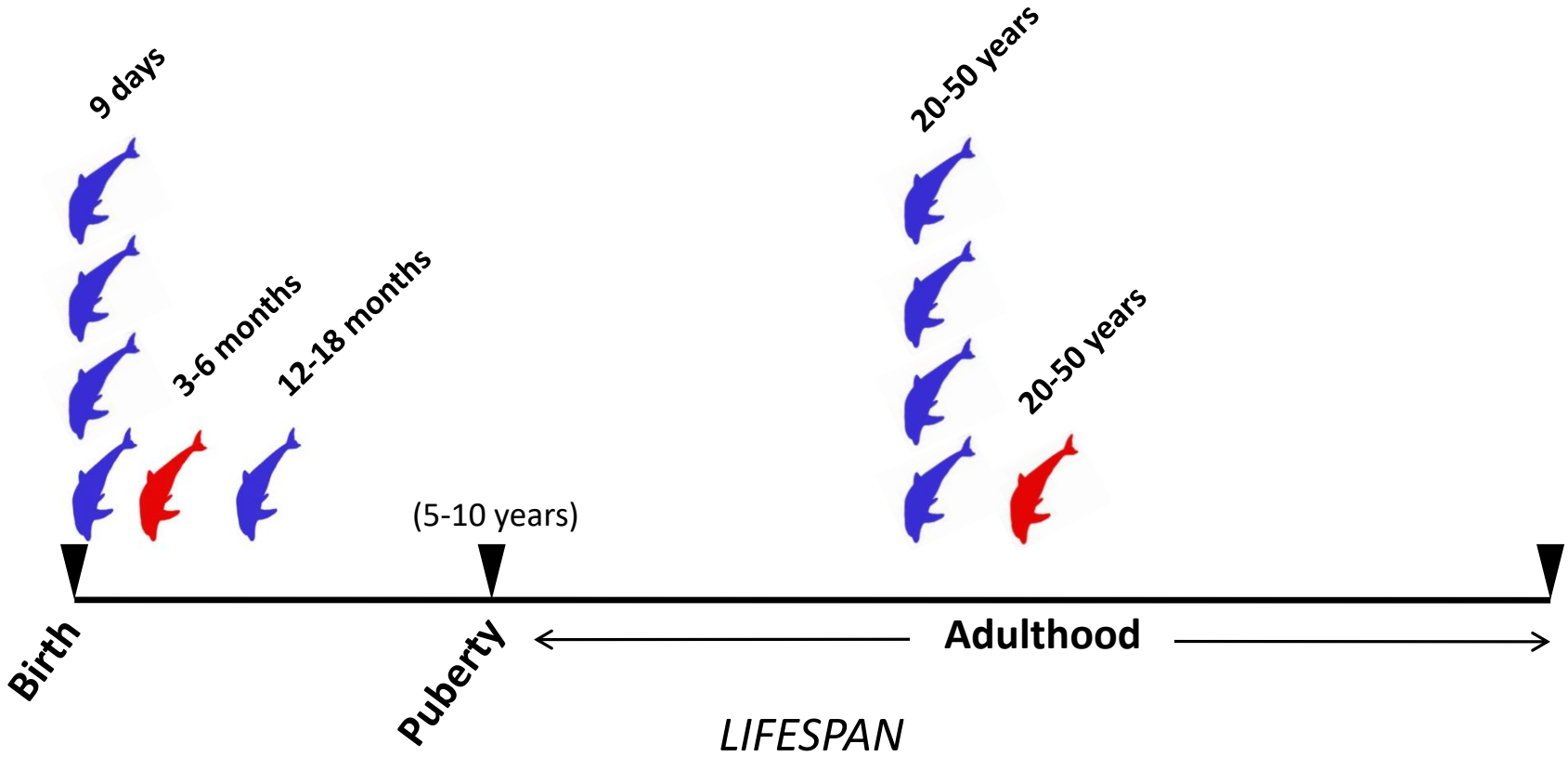
Tursiops truncatus

NEONATAL (9 days)
POSTNATAL (12-18 months)
ADULT (20-50 years)

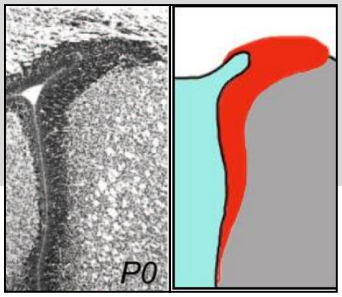


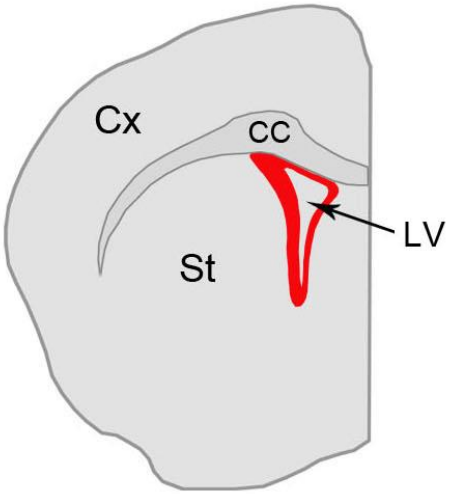
Stenella coeruloalba

EARLY POSTNATAL (3-6 months)
ADULT (20-50 years)

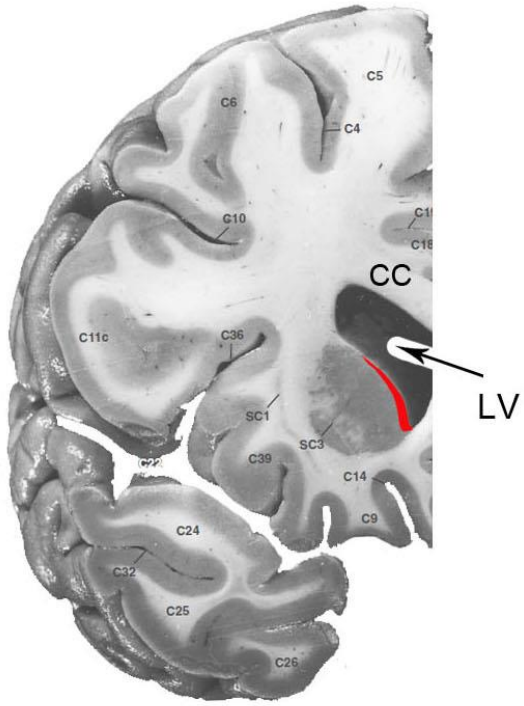


Parolisi et al., 2015 Front Neuroanat

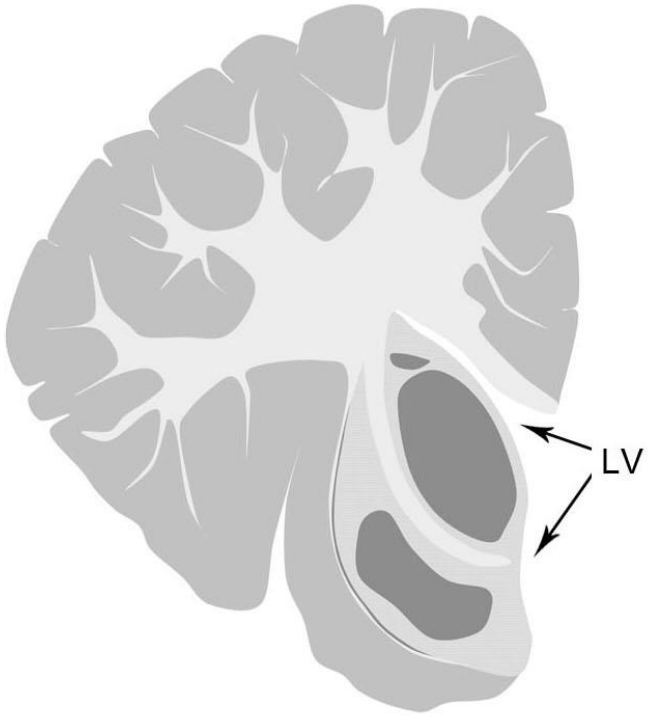




Neonatal mouse



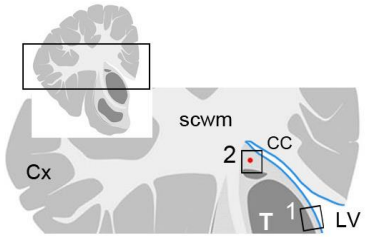
Neonatal human

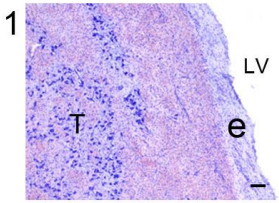


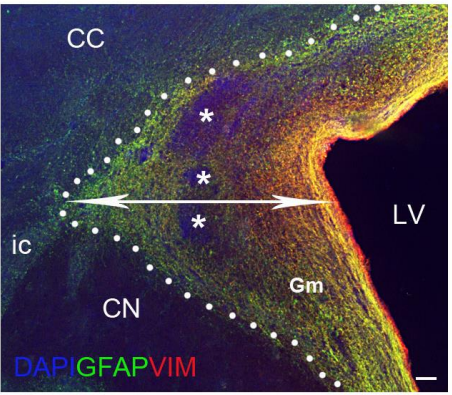
Neonatal dolphin

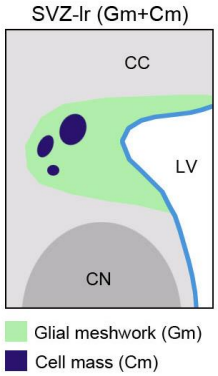
<u>Absence</u> of periventricular germinal layer at birth

T. Truncatus - **neonatal**



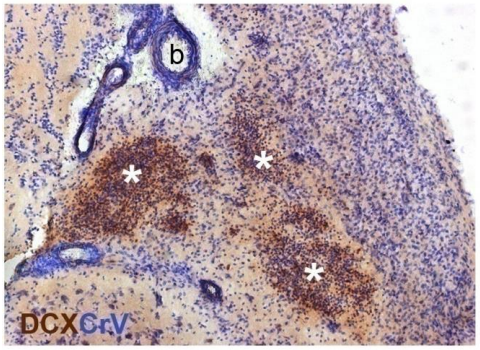


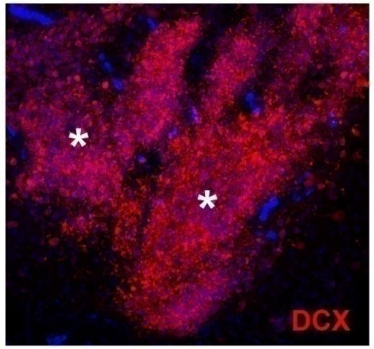


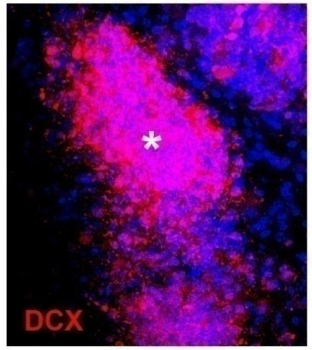


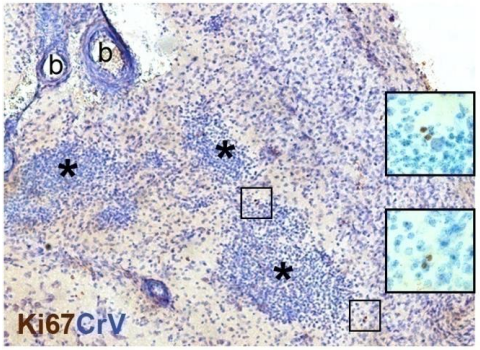
SVZ-like region

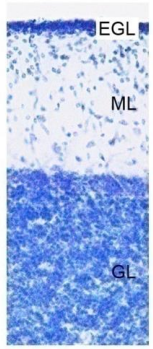
Already at birth, the SVZ is vestigial and does not work

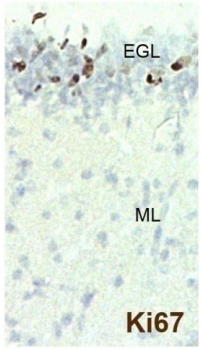


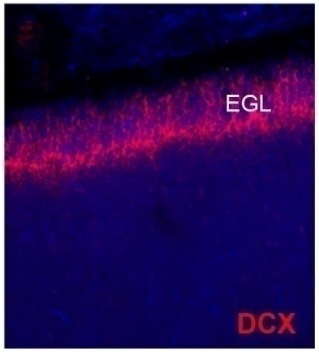












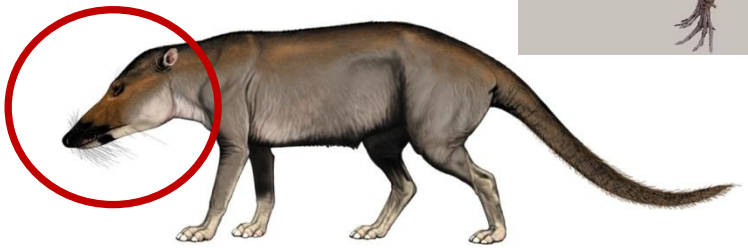
Cerebellum (internal control)

Parolisi et al., 2017 *Brain Struct Funct*

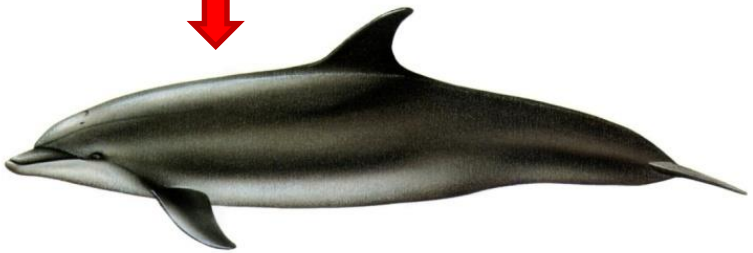
… many years ago

Kishida et al, 2015 *Zool Lett*

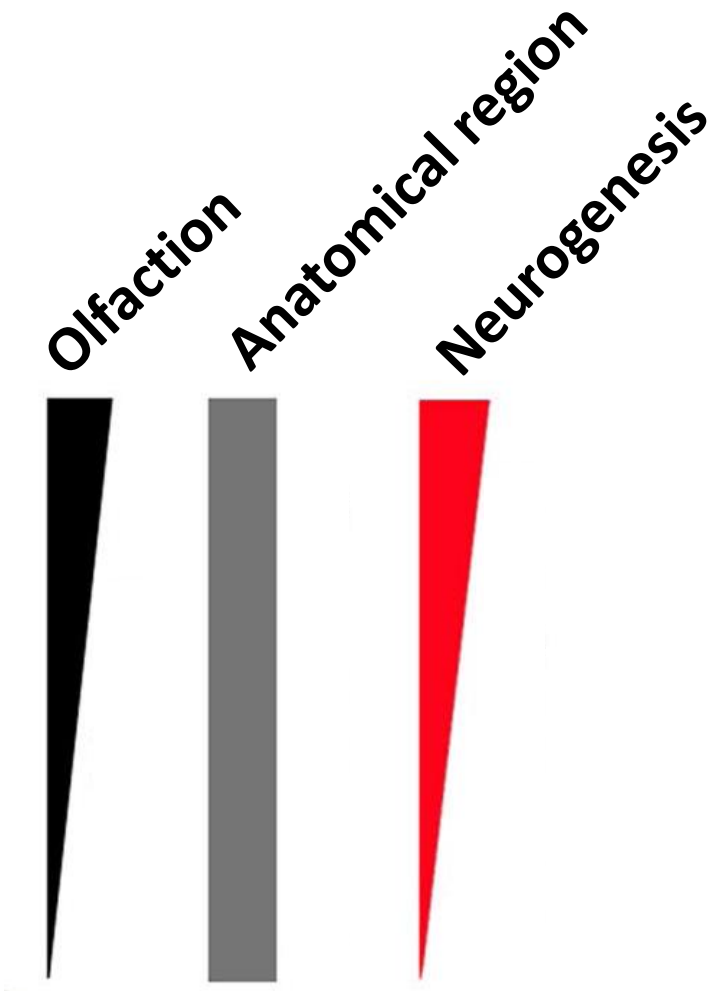
Olfaction



38 million years



No olfaction



Parolisi, Cozzi, Bonfanti, 2017 *Brain Struct Funct*

The trend seems confirmed

Vestigial SVZ?

Mammals

Vertebrates

Adult neurogenesis, structural plasticity, repair

What about Humans?

Sanai et al., 2011 *Nature*

Spalding et al., 2013 *Cell*

Sorrells et al., 2018 *Nature*

Cipriani et al., 2018 *Cereb Cortex*

Boldrini et al., 2013 *Cell Stem Cell*

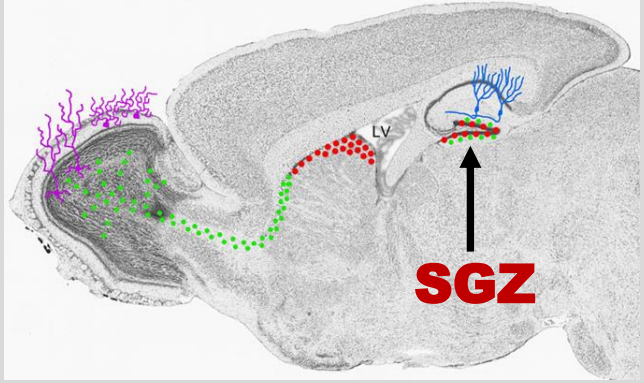
Tobin et al., 2019 *Cell Stem Cell*

Moreno-Jiménez et al., 2019 *Nature Med*

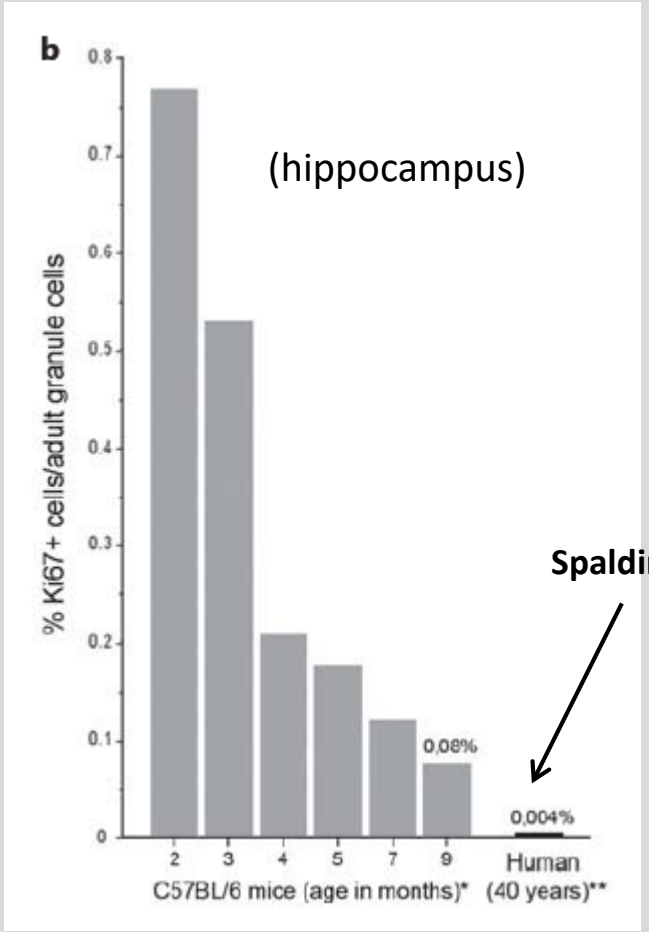
Brain, Behavior and Evolution 2016;87:205–221

Adult Neurogenesis in Mammals: Variations and Confusions

Hans-Peter Lipp[a–c] Luca Bonfanti[d, e]



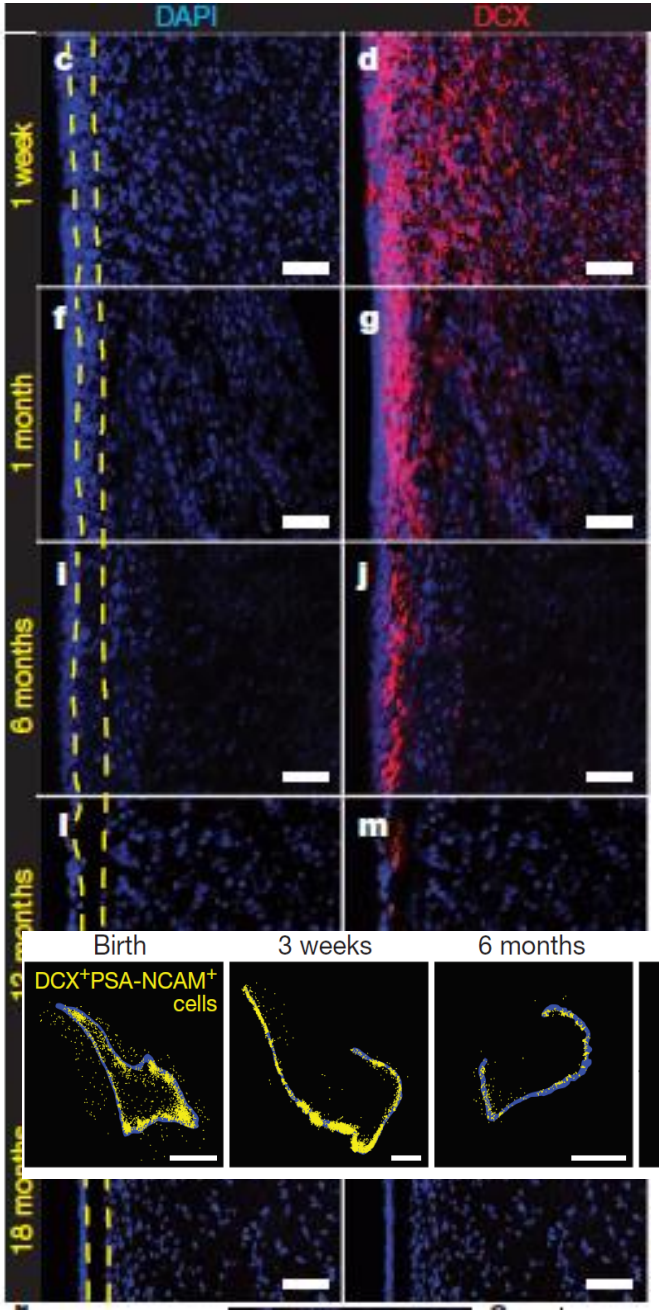
Comparative studies reveal that adult neurogenesis is quite different in humans and mice



(hippocampus)

Spalding et al., 2013 Cell

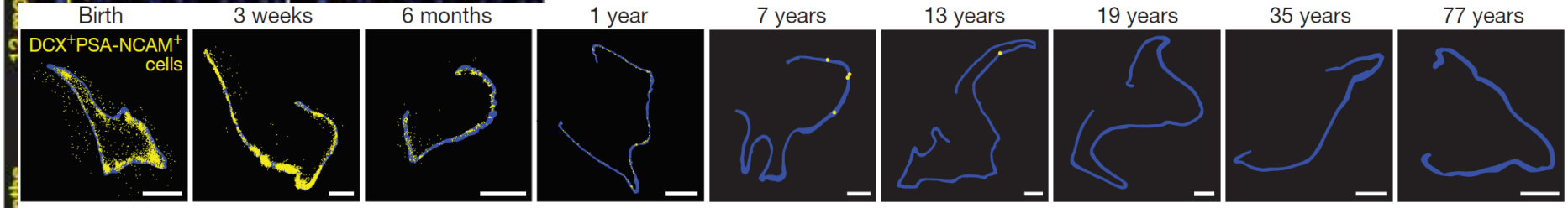
They claim 20-fold higher!



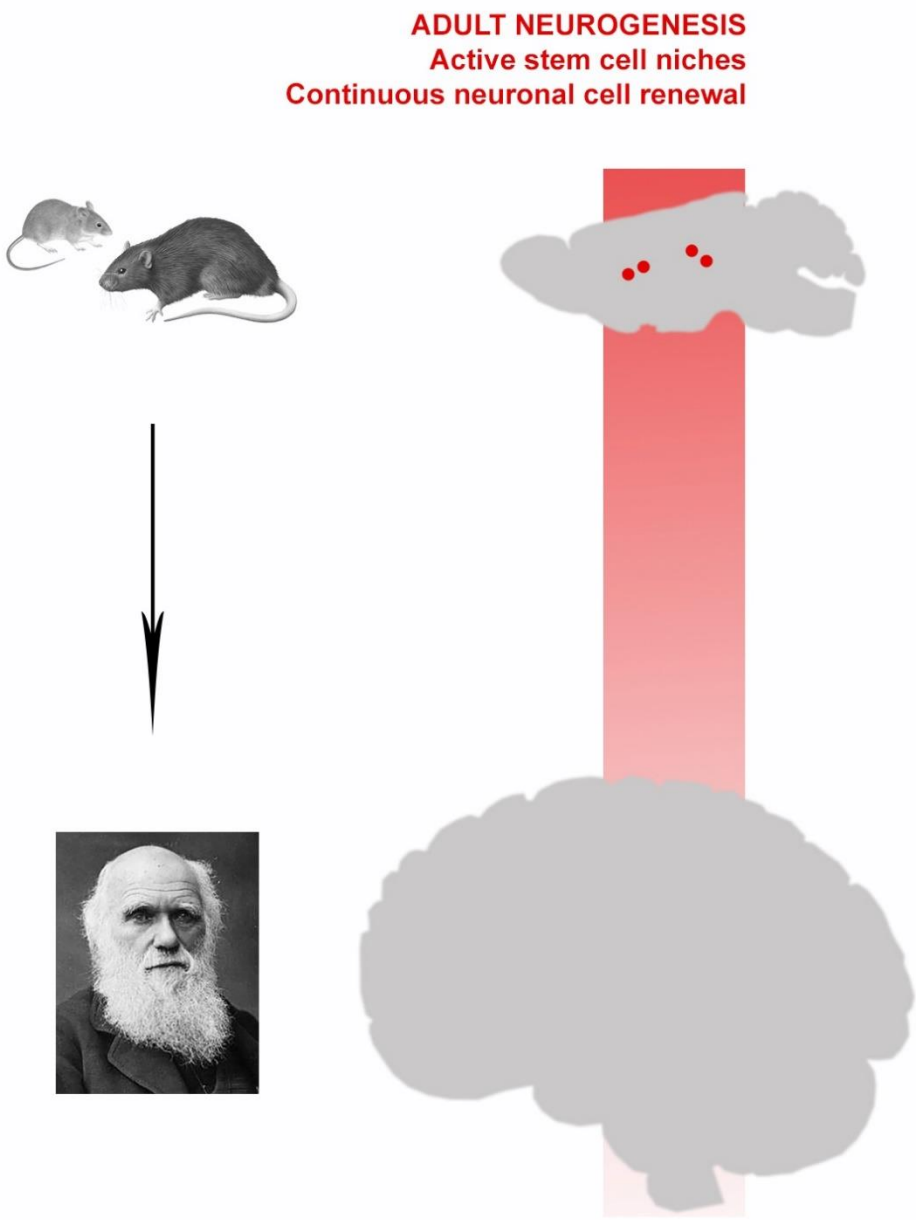
Sanai et al, *Nature* 2011

L'apporto di nuovi neuroni verso il BULBO OLFATTIVO nell'**uomo** scompare a **18 mesi**

Nell'ippocampo accade tra 7 e 13 anni

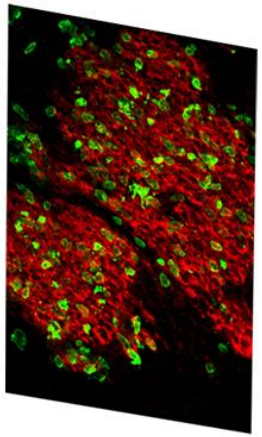


Sorrells et al., *Nature* 2018



Dal topo all'uomo
la neurogenesi adulta
si riduce di molto

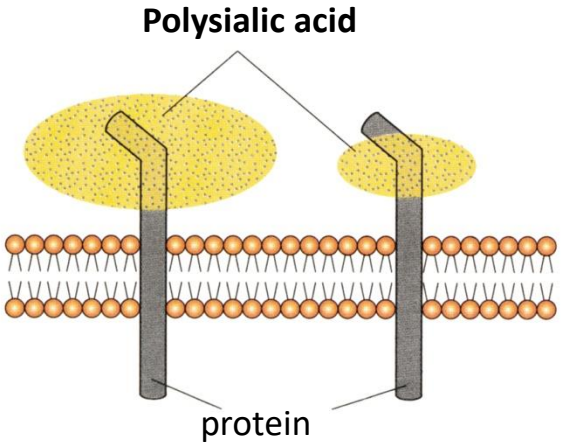
Alternatives?

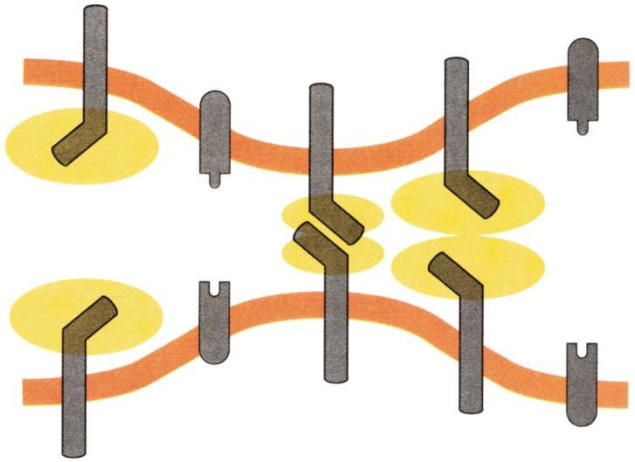


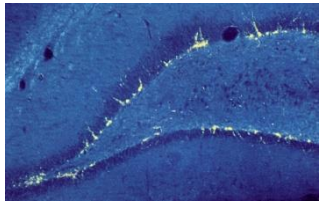
?

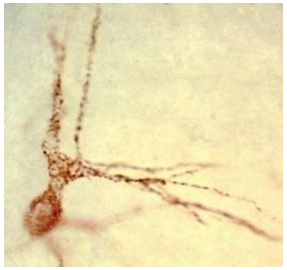
PSA-NCAM

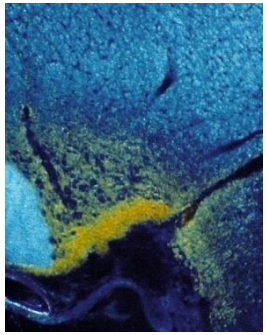
(low adhesive form of NCAM)

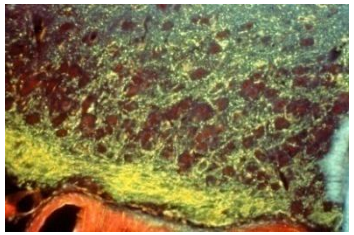


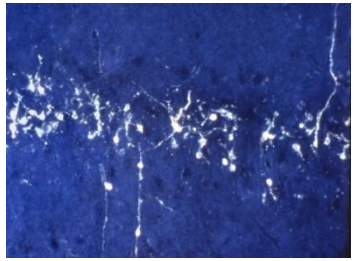








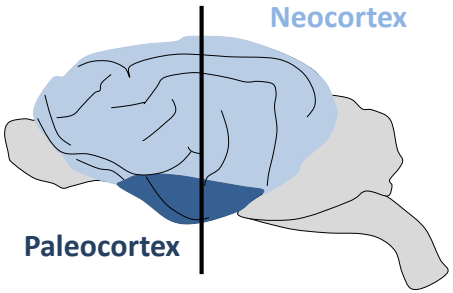


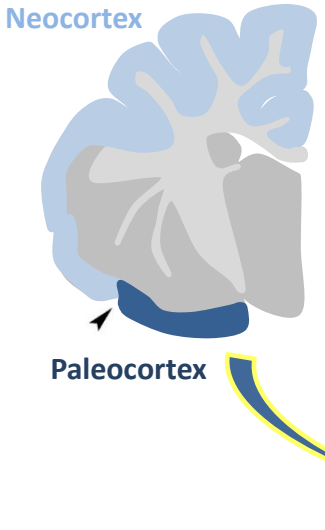


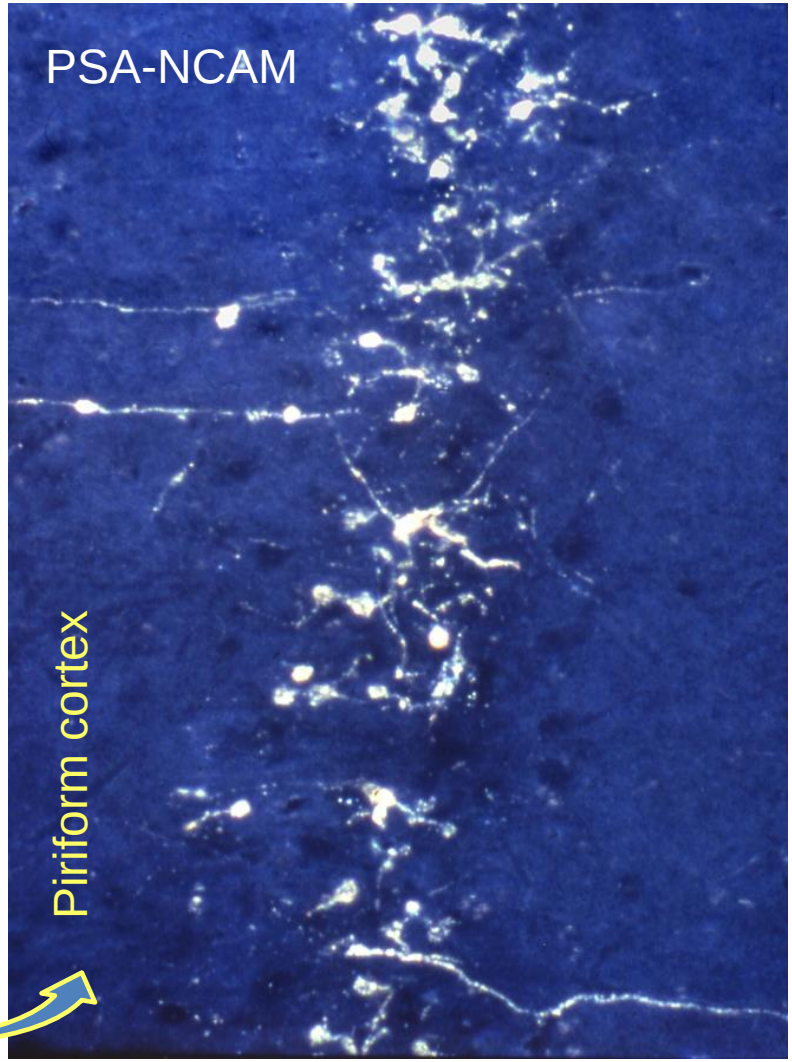
Brain regions showing PSA-NCAM staining

PSA-NCAM+ neurons in the adult rat paleocortex

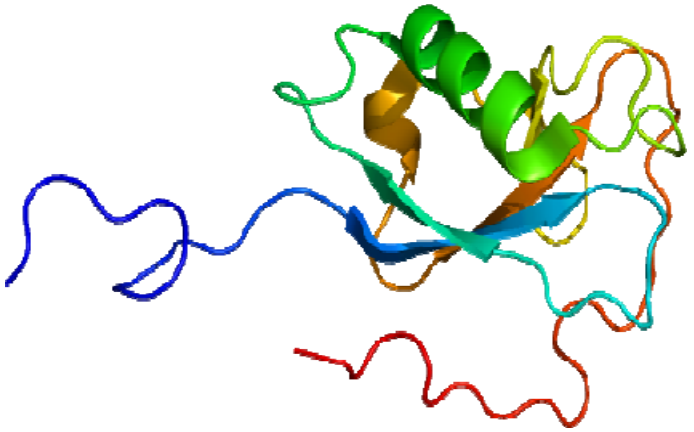
(Seki & Arai, Anat Embryol,1991) (Bonfanti et al., *Neuroscience*, 1992)



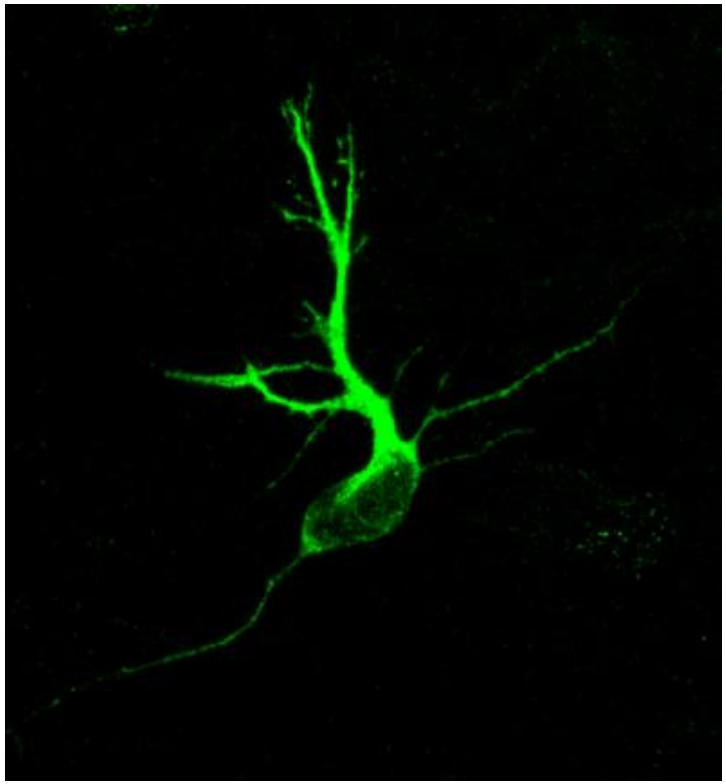




Doublecortin (DCX) as marker of structural plasticity



Microtubule-associated protein



Cytoskeletal protein indicator of strucural plasticity

Involved in:

Neuronal migration
Growth-cone dynamics
Gyrencephaly

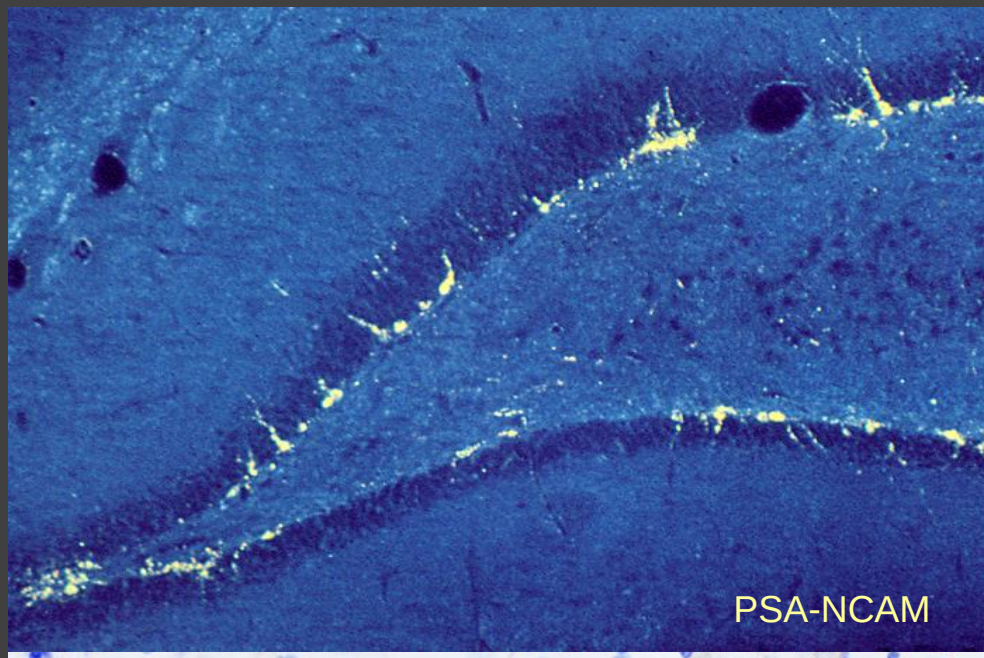
Francis et al , 1999, Neuron
Gleeson et al, 1999, Cell
Horesh et al, 1999, Hum mol Genet

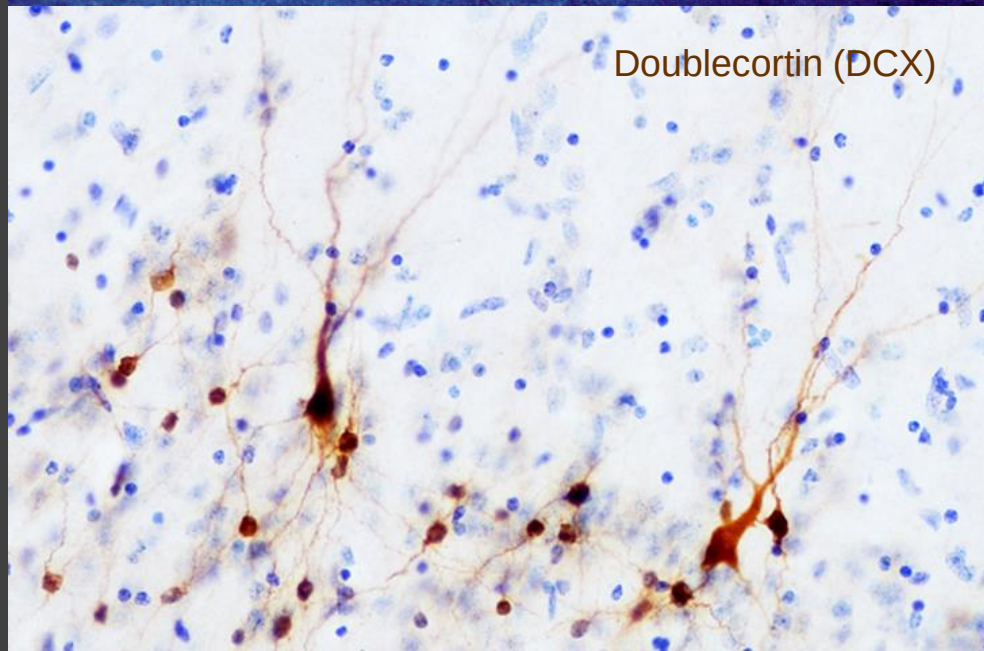
Neurogenic and non-neurogenic plasticity share some markers

Structural plasticity
with neurogenesis

PSA-NCAM
DCX

Structural plasticity
without neurogenesis





Neurons expressing markers of «immaturity» in the adult sheep hippocampus

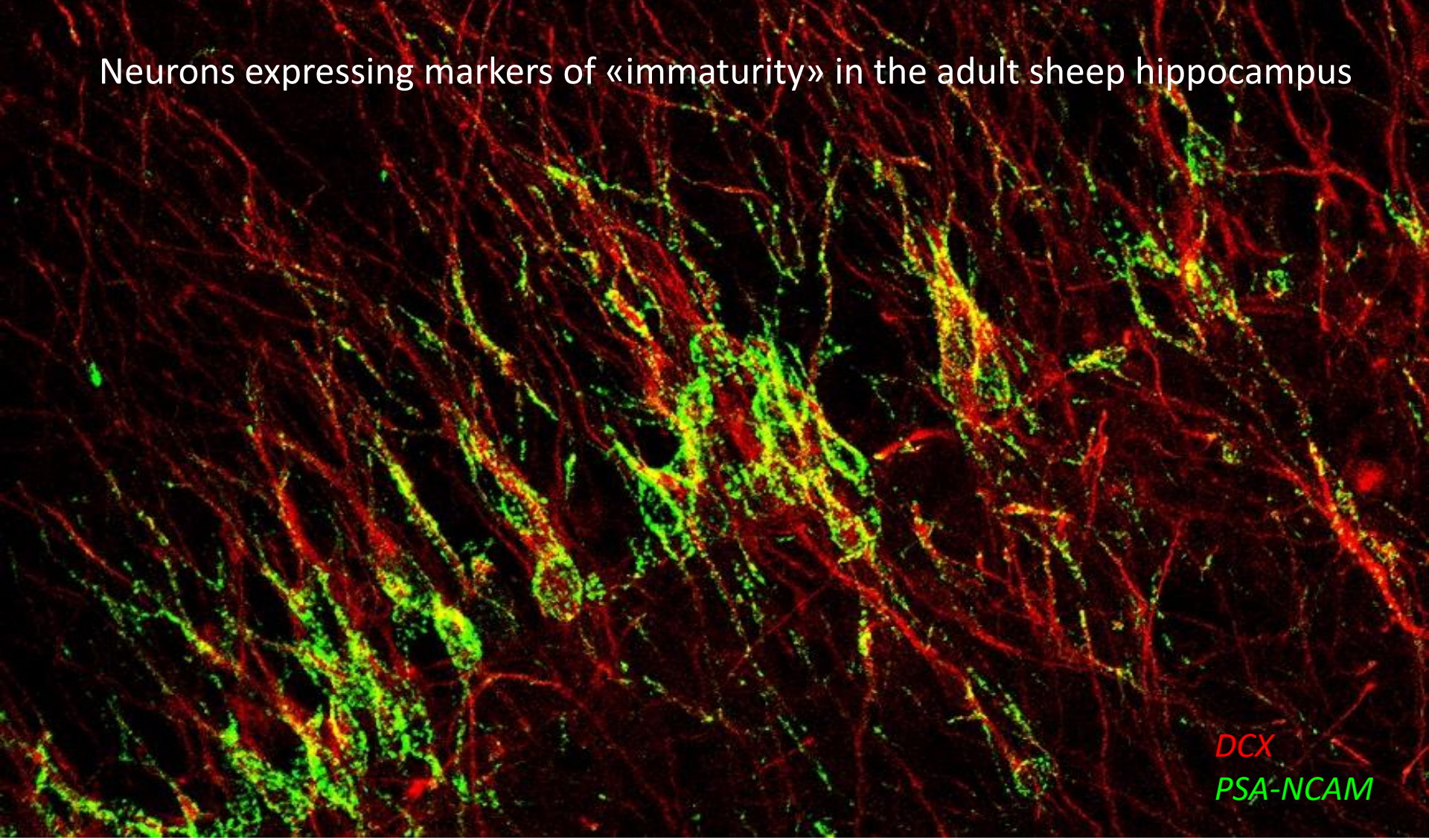


Foto: Ottavia Palazzo

Cerebral Cortex October 2008;18:2229-2240
doi:10.1093/cercor/bhm255
Advance Access publication January 31, 2008

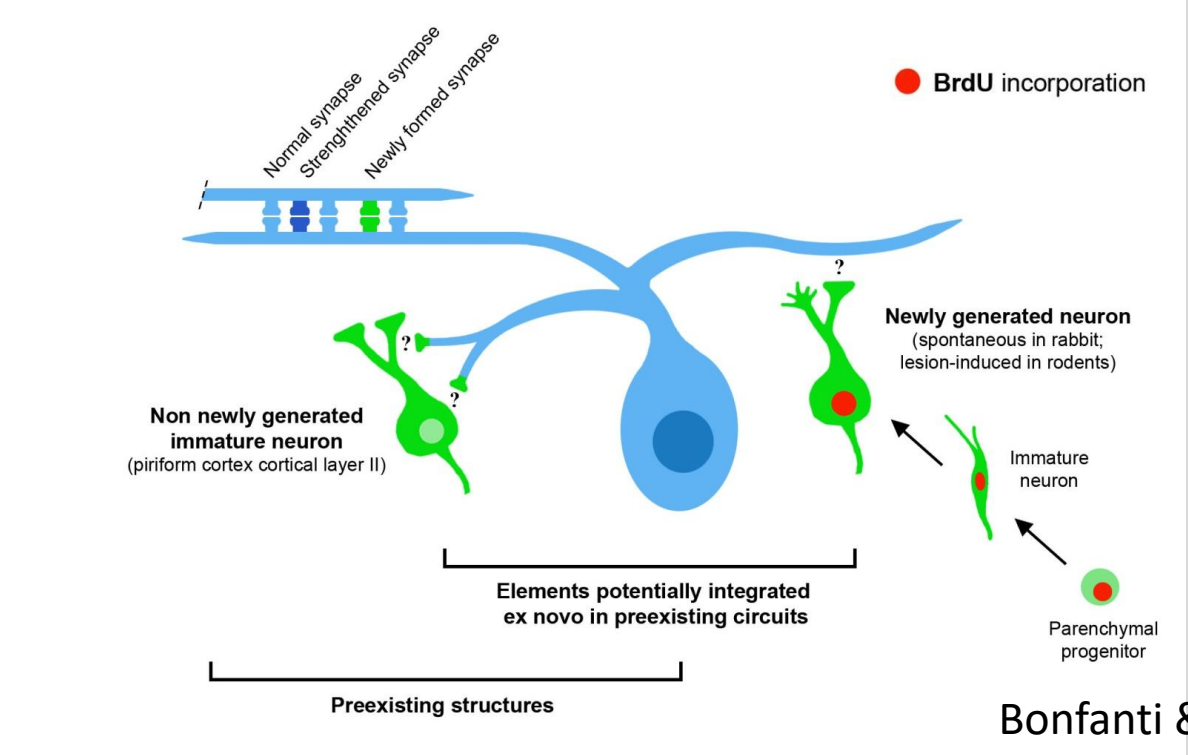
FEATURE ARTICLE

A Population of Prenatally Generated Cells in the Rat Paleocortex Maintains an Immature Neuronal Phenotype into Adulthood

María Ángeles Gómez-Climent, Esther Castillo-Gómez, Emilio Varea, Ramón Guirado, José Miguel Blasco-Ibáñez, Carlos Crespo, Francisco José Martínez-Guijarro and Juan Nácher

Neurobiology Unit and Program in Basic and Applied Neurosciences, Cell Biology Dpt., Universitat de València, Spain

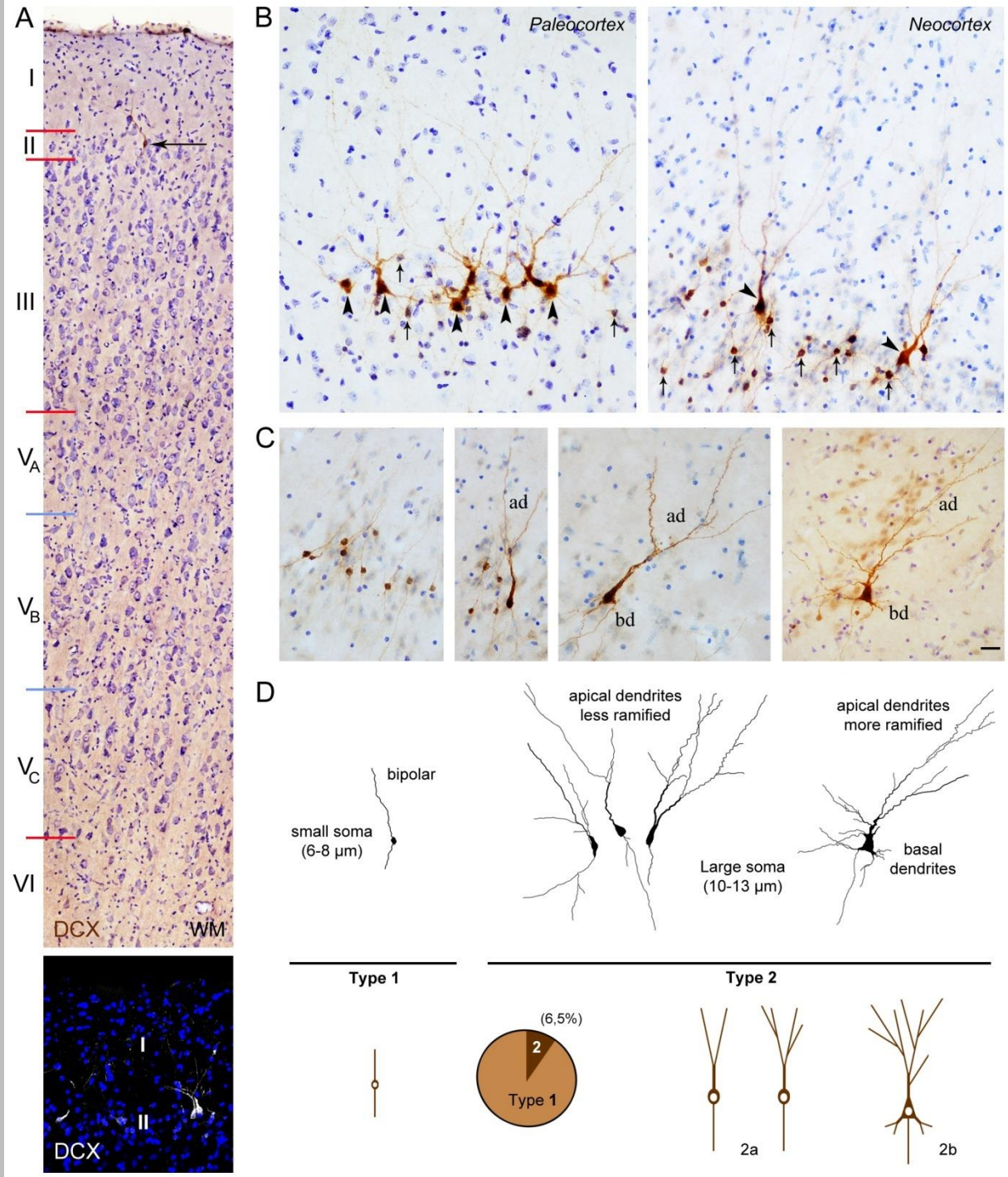
They express **immature markers**
They have **no synapses**
They are **covered by glial lamellae**



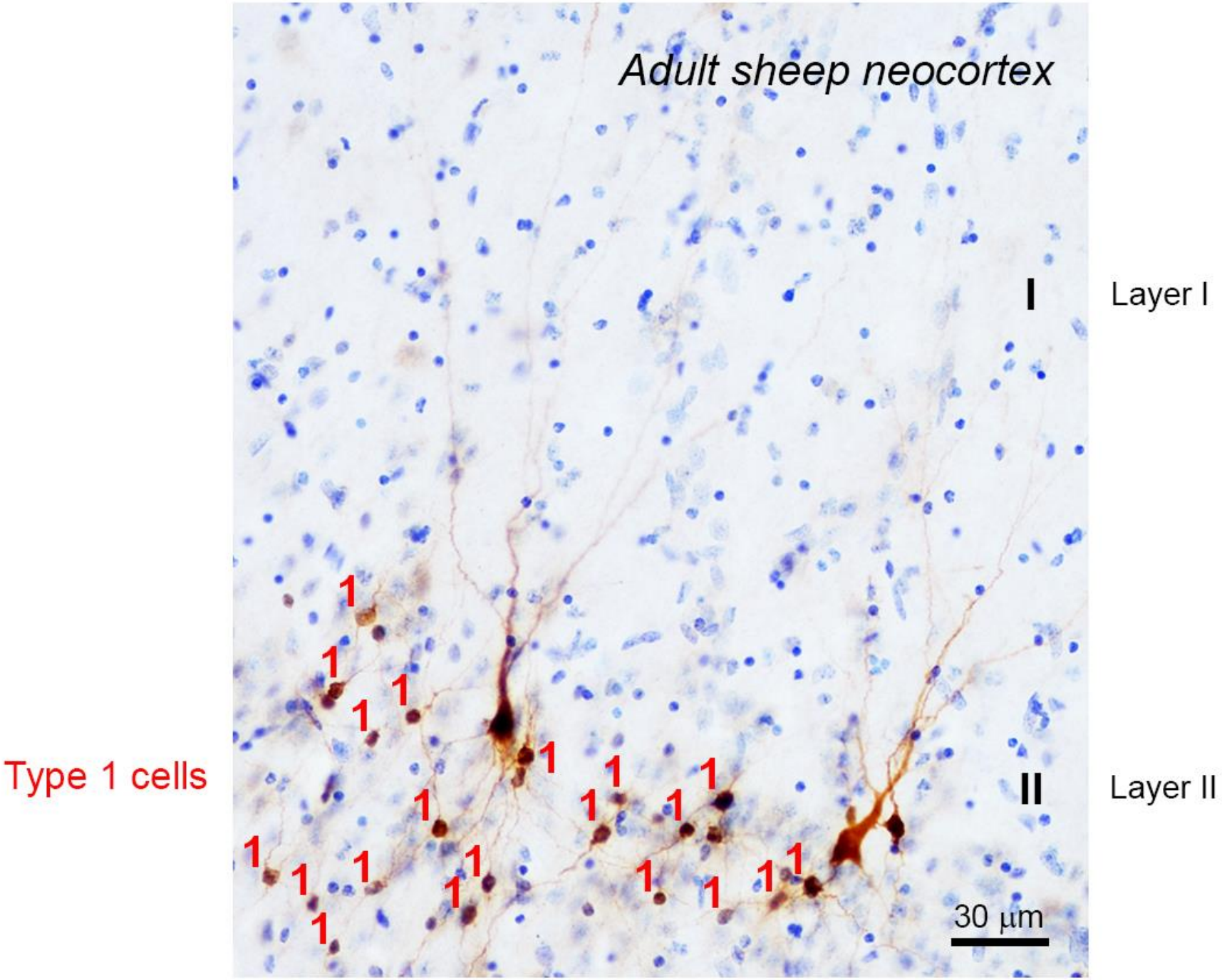
Bonfanti & Nacher 2012 Prog Neurobiol

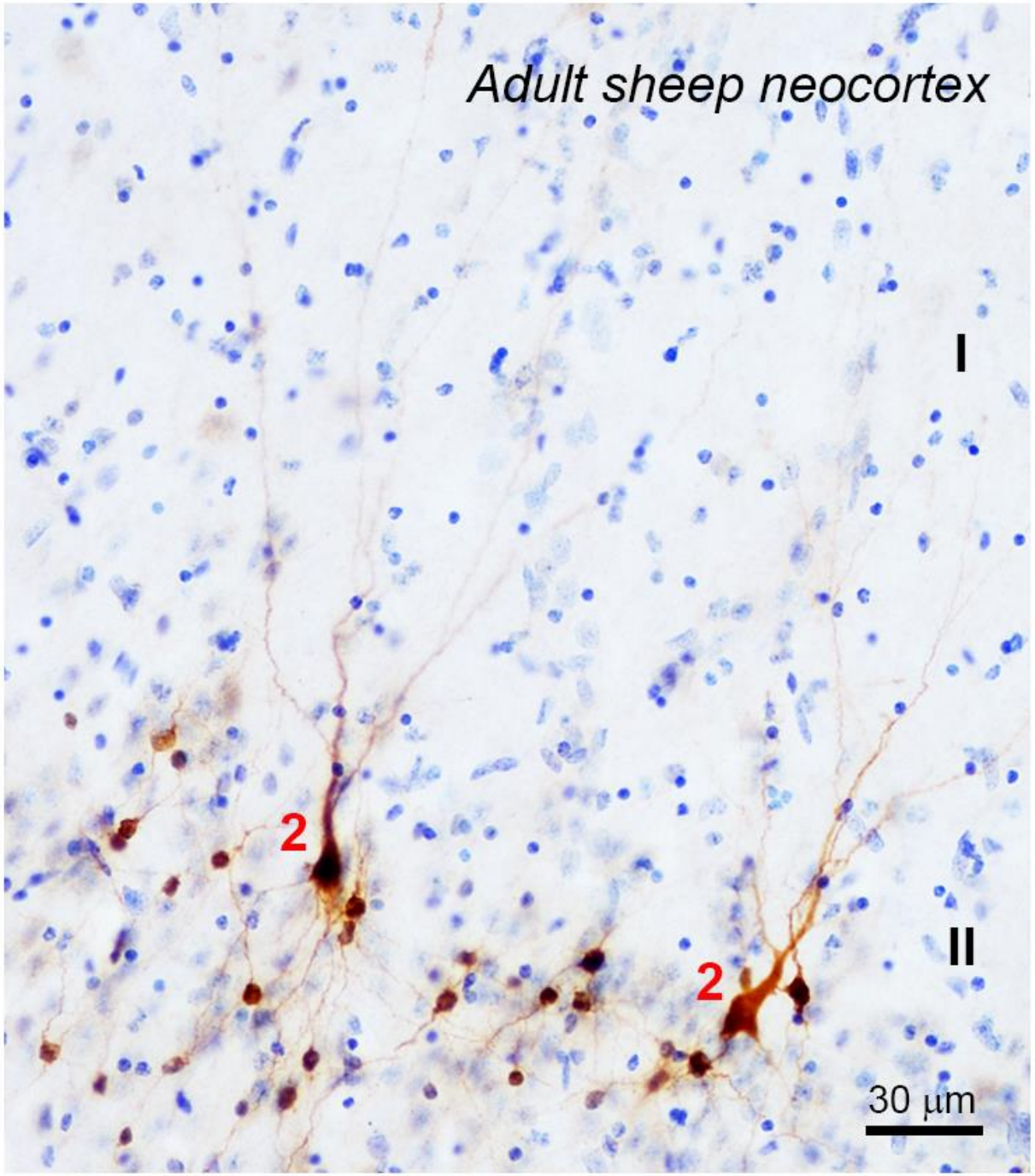
Immature neurons in the cortical layer II

(Sheep)



Piumatti et al 2017 *J Neurosci*


Adult sheep neocortex
I
Layer I
II
Layer II
Type 1 cells
30 μm



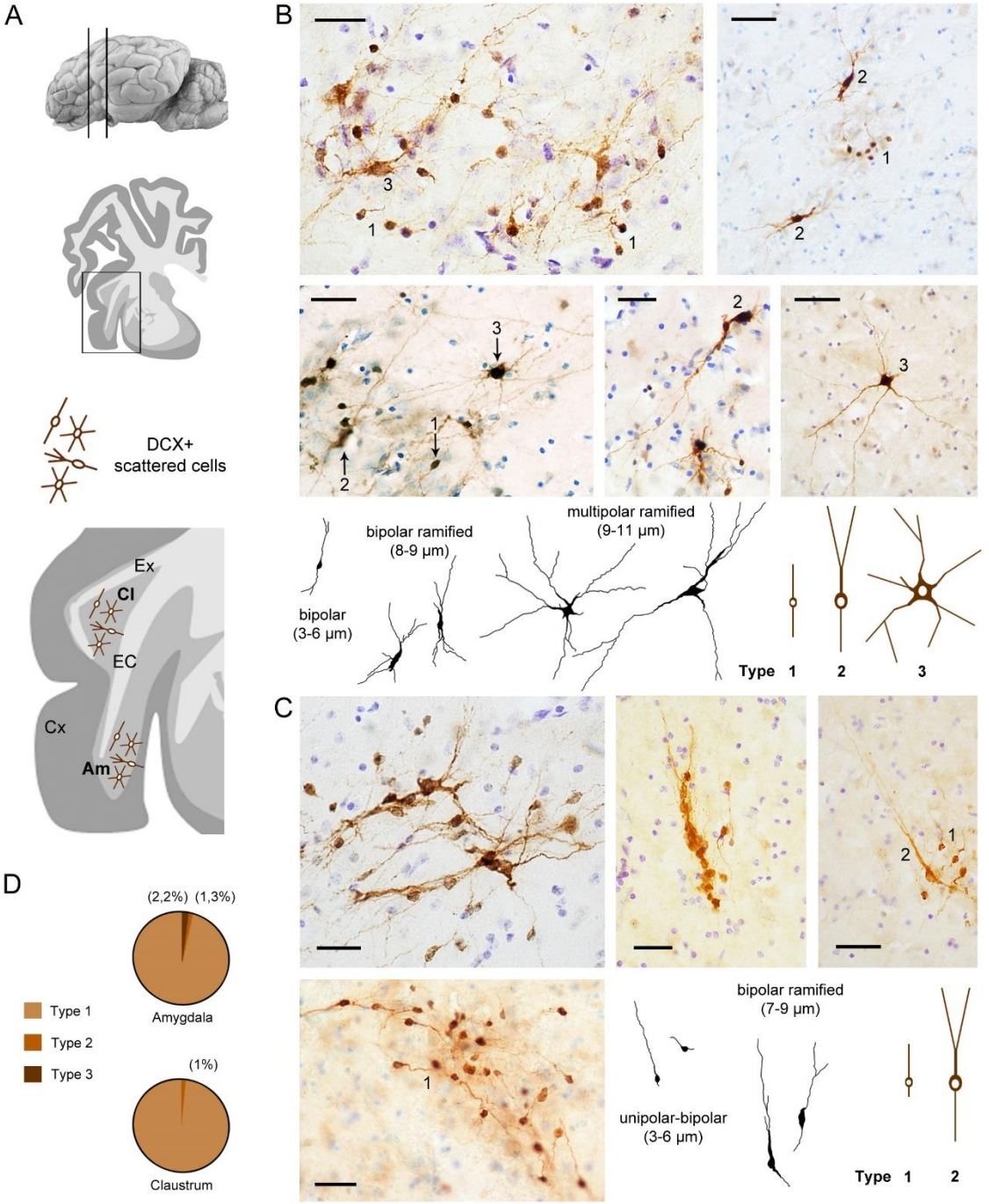
Type 2 cells

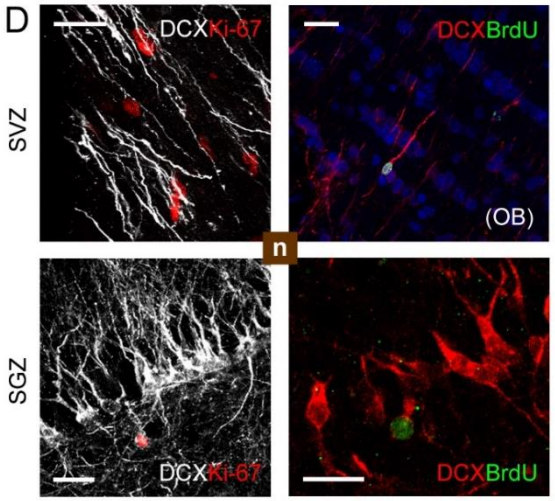
Adult sheep brain

Claustrum

Amygdala

Piumatti et al 2017 *J Neurosci*

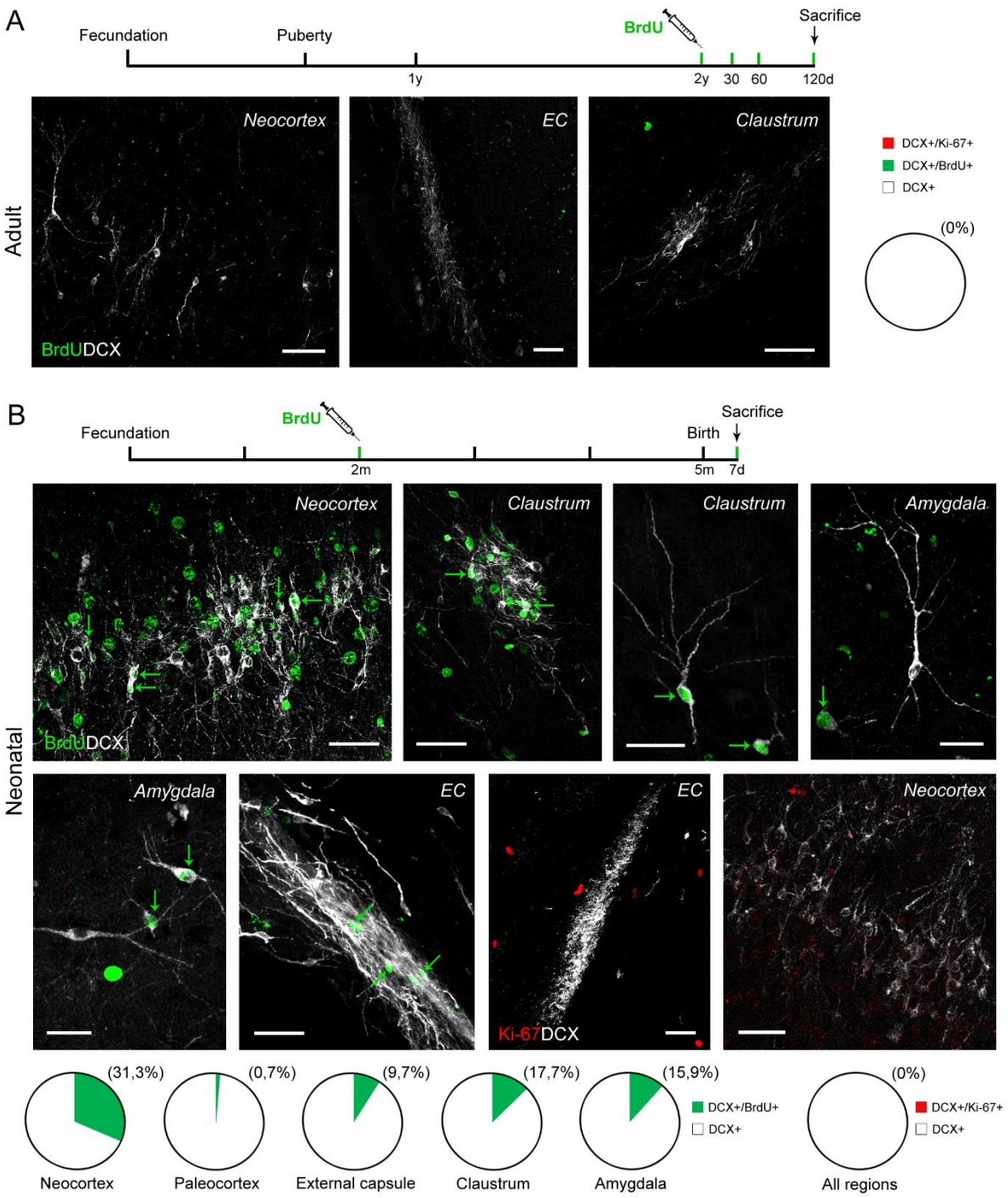




Internal controls
in neurogenic zones

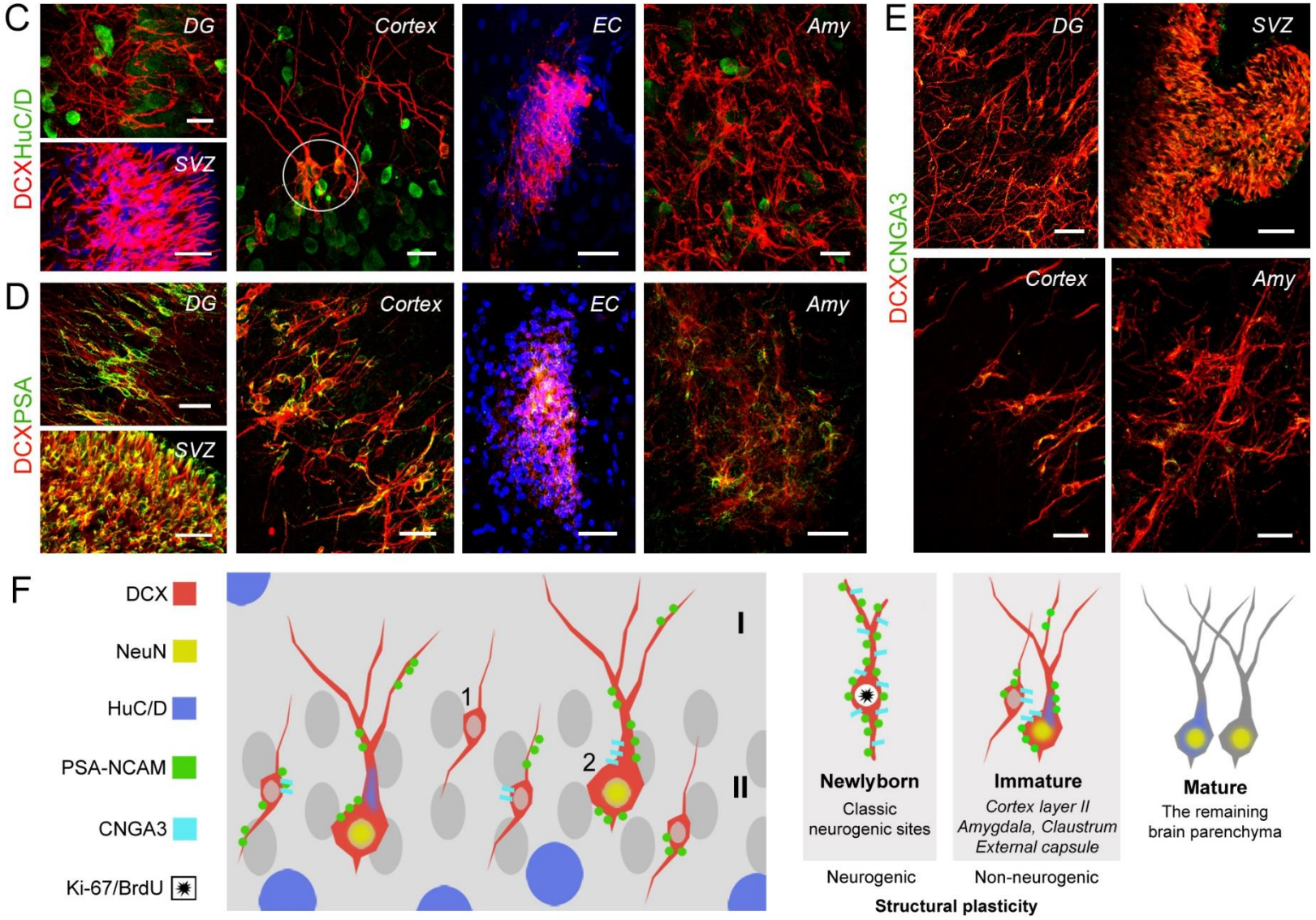
The DCX+ cells in cortex, amygdala, claustrum, external capsule are NOT newly generated but they are born prenatally

Piumatti et al 2017 *J Neurosci*



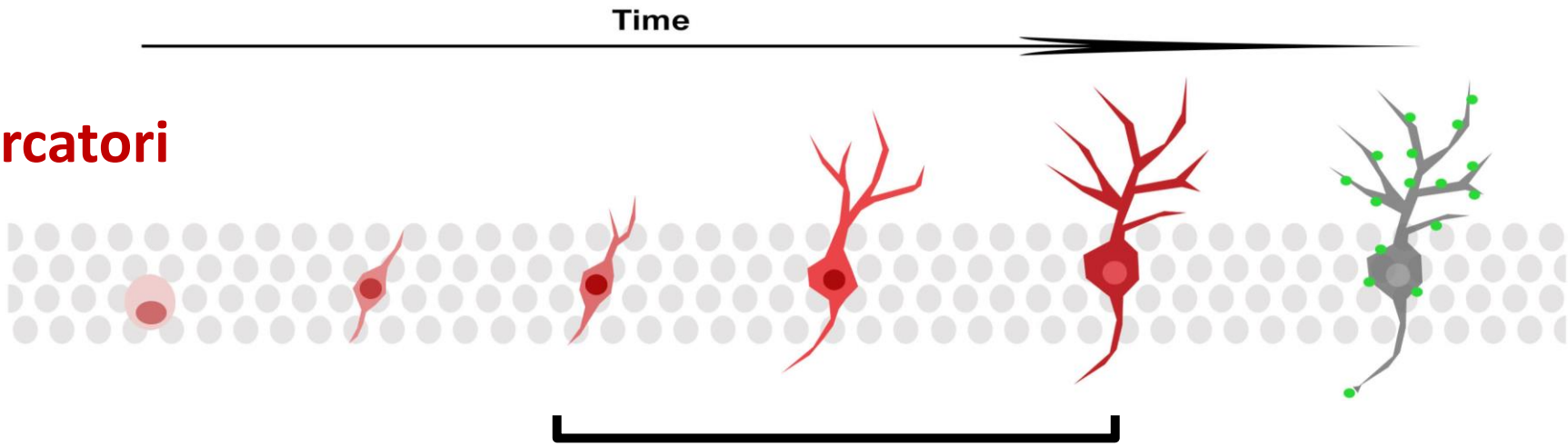
Piumatti et al 2017 *J Neurosci*

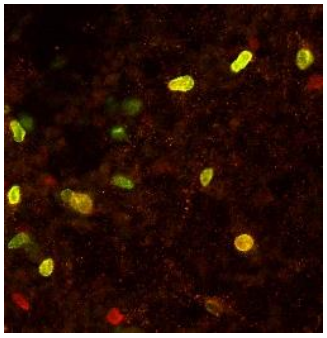
Markers of maturity/immaturity



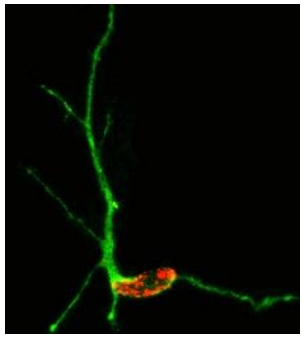
The DCX+ cells are in an intermediate state of immaturity

Marcatori

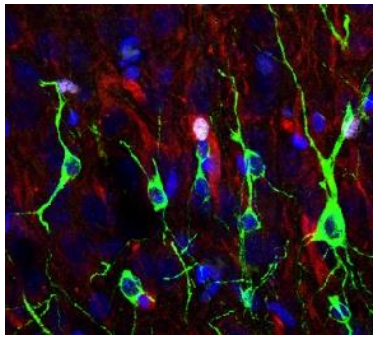




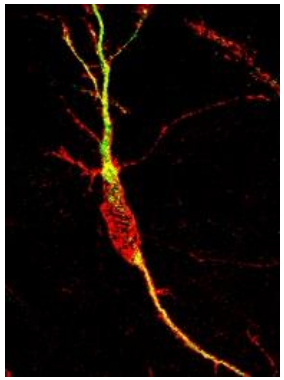
Ki-67 antigen
Nuclear protein
Cell proliferation



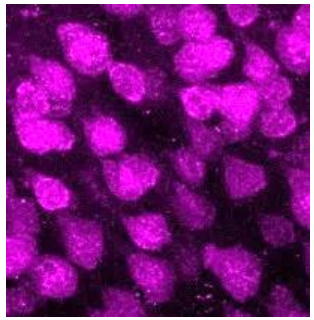
BrdU
(Bromodeoxyuridine)
Thymidine analog
Cell proliferation
(possibility to track progeny through time)



DCX (doublecortin)
Cytoskeletal protein
Migration/Cell shape



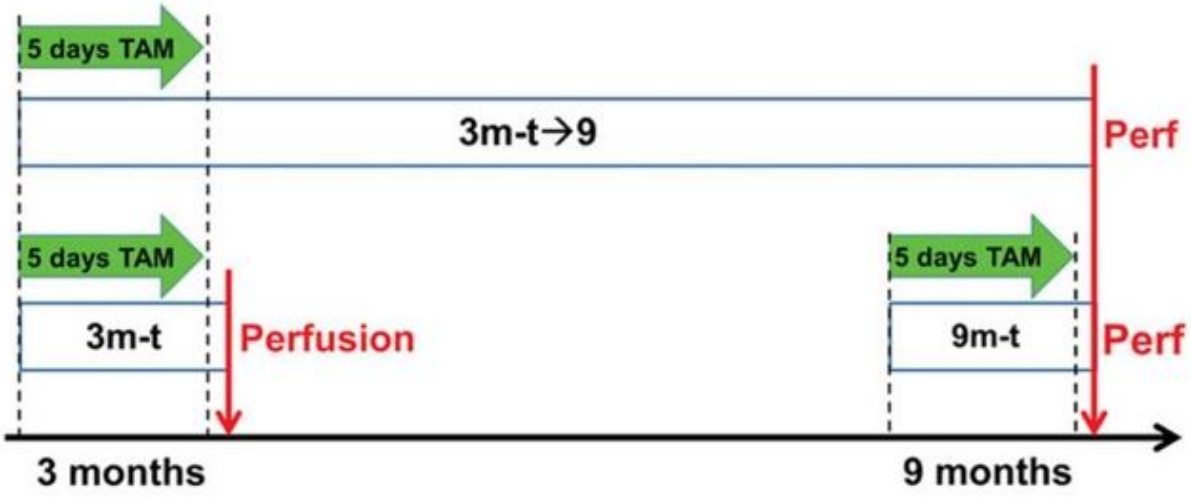
PSA-NCAM
Membrane carbohydrate
Anti-adhesive/Migration

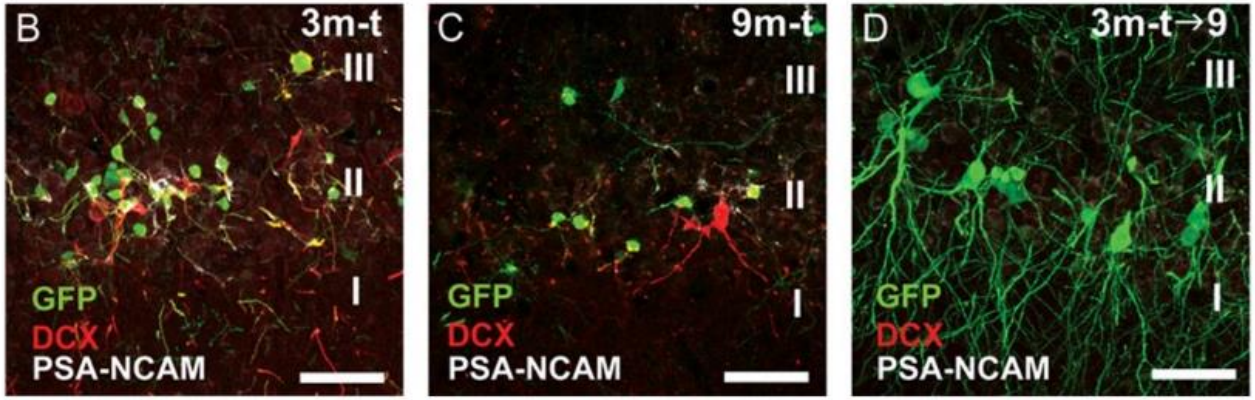


NeuN
(Neuronal nuclear protein)
Neuronal differentiation

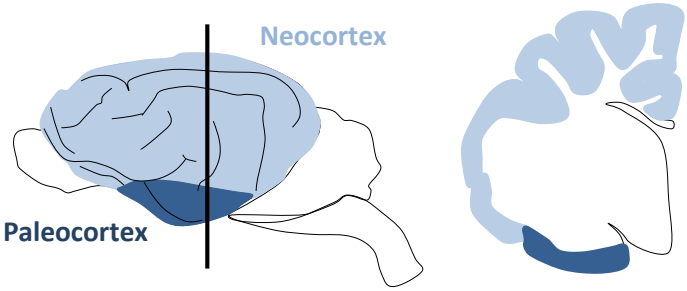
Immature neurons can mature through age

(Rotheneichner et al., 2018)

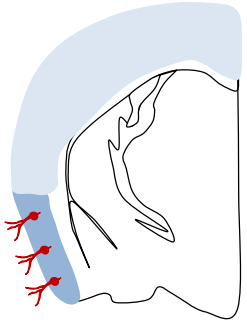




Forse i neuroni immaturi non sono limitati alla paleocortex

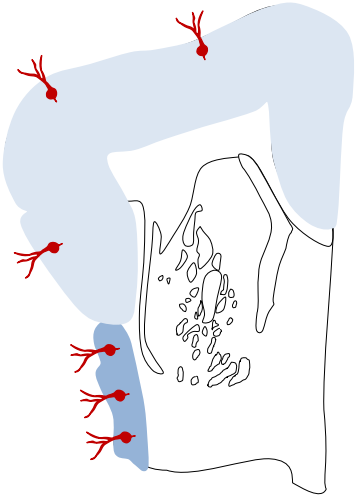


Topo



Immature neurons

Coniglio



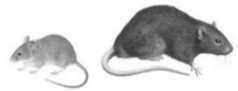
?

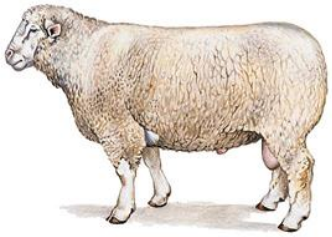
Xiong et al., 2008, Exp Neurol
Cai et al., 2009, Exp Neurol
Luzzati et al, 2009, Cereb Cortex
Zhang et al., 2009, Front Neuroanat

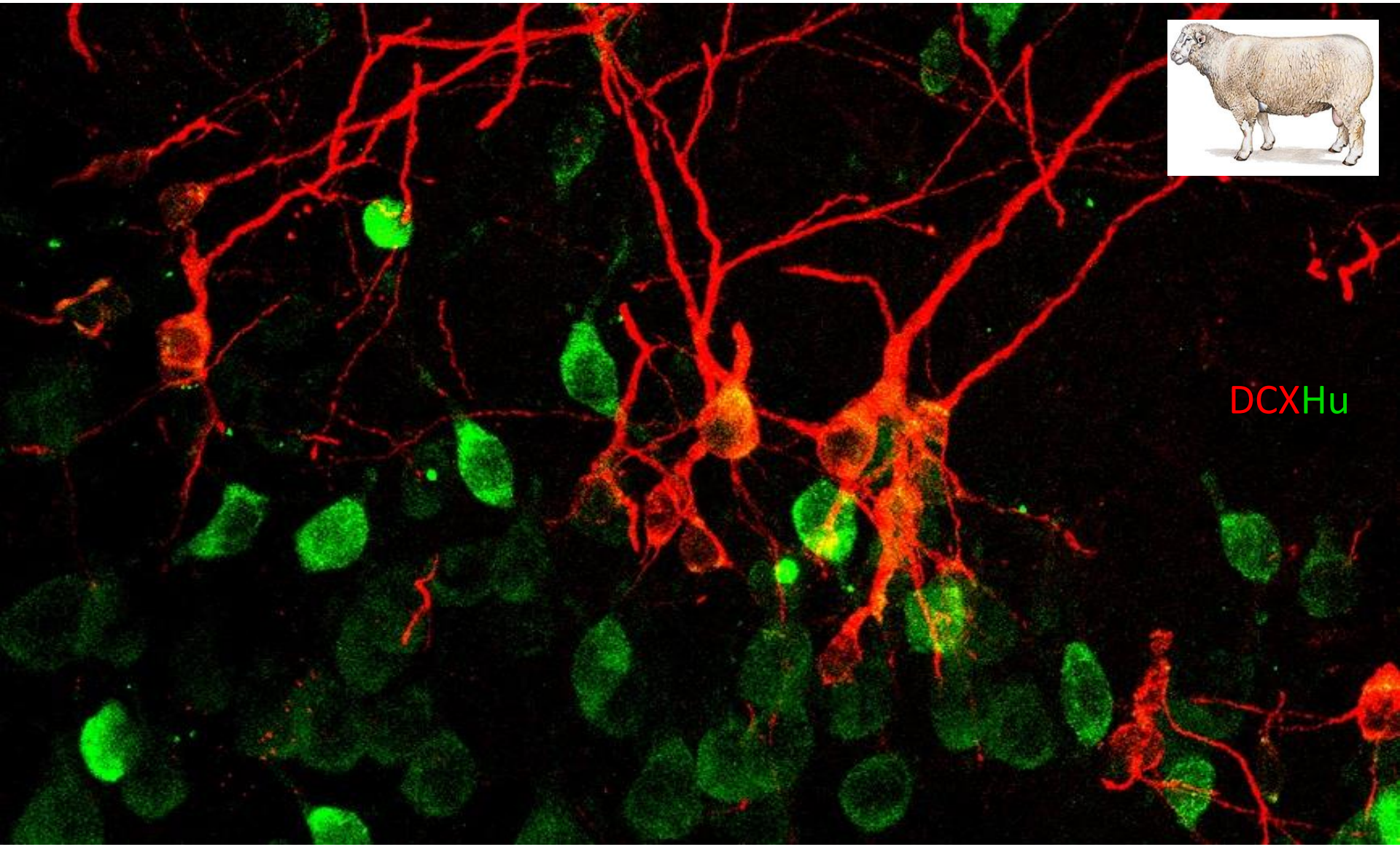
Aspettativa di vita:
15-25 anni

Cervello grande

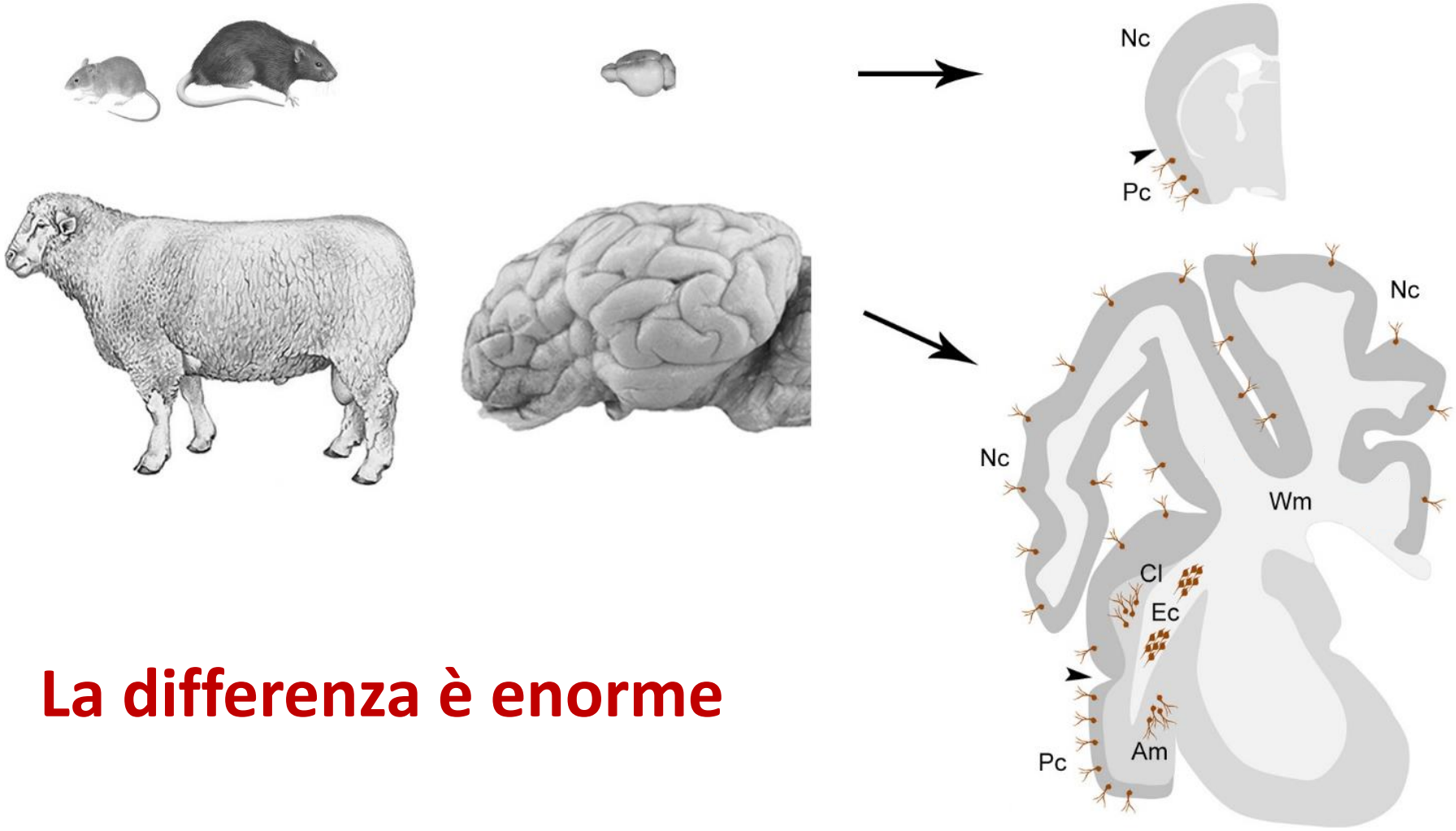
Girencefalia







Piumatti, Palazzo, La Rosa, Bonfanti et al, 2018, **J Neurosci**

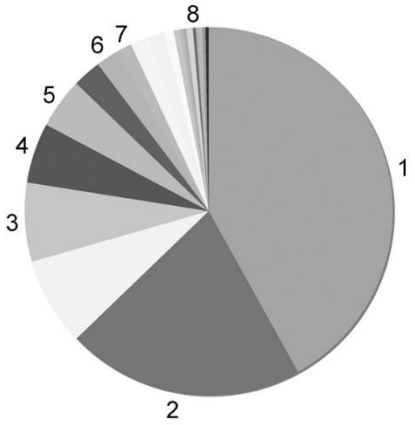


La differenza è enorme

Piumatti, Palazzo, La Rosa et al, 2018, J Neurosci

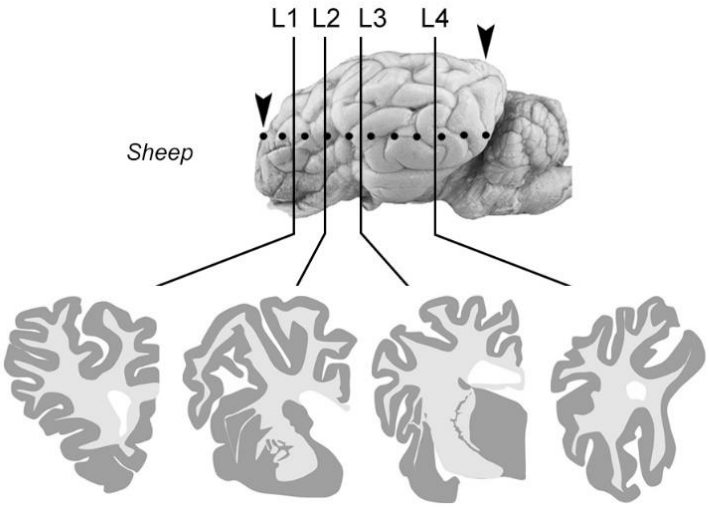
Is there a trend in the occurrence/type/distribution/amount of immature neurons among mammals?

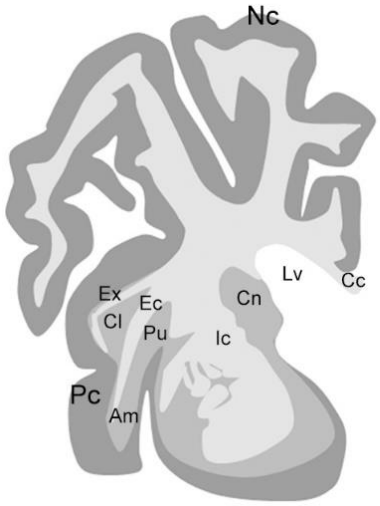
Study in 12 mammalian species



1 - Rodentia	*Mus musculus* (Mouse), *Heterocephalus glaber* (Naked mole rat)
2 - Chiroptera	*Eidolon helvum* (SC bat), *Epomophorus wahlbergi* (WE bat)
3 - Primates	*Callithrix jacchus* (Marmoset), *Pan troglodytes* (Chimp)
4 - Carnivora	*Vulpes vulpes* (Fox), *Felis catus domestica* (Cat)
5 - Artiodactyla	*Ovis aries* (Sheep)
6 - Lagomorpha	*Oryctolagus cuniculus* (Rabbit)
7 - Macroscelidea	*Elephantulus myurus* (Sengi)
8 - Perissodactyla	*Equus caballus* (Horse)

Establishment of 4 comparable brain levels





White matter
Cortical
Subcortical
Grey matter

Pc	Paleocortex
Nc	Neocortex
Ex	Capsula extrema
Ec	External capsule
Cl	Claustrum
Pu	Putamen
Am	Amygdala
Ic	Internal capsule
Cn	Caudate nucleus
Cc	Corpus callosum
Lv	Lateral ventricle

In collaboration with:

Irmgard Amrein
Brain tissues, data analises

Cozzi
ssues

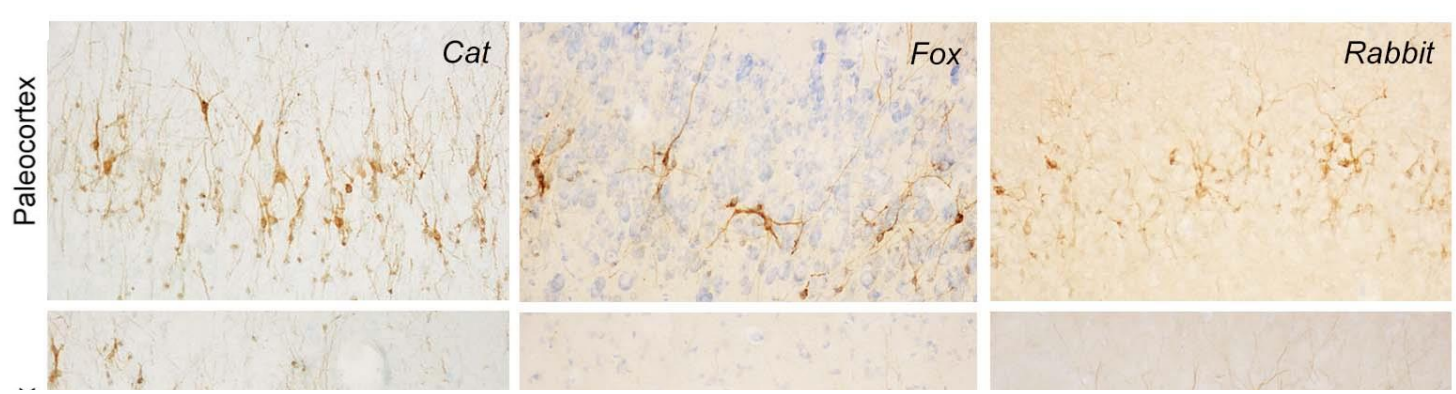
Chris Faulkes
Brain tissues

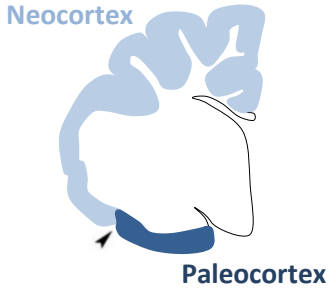
85 brains

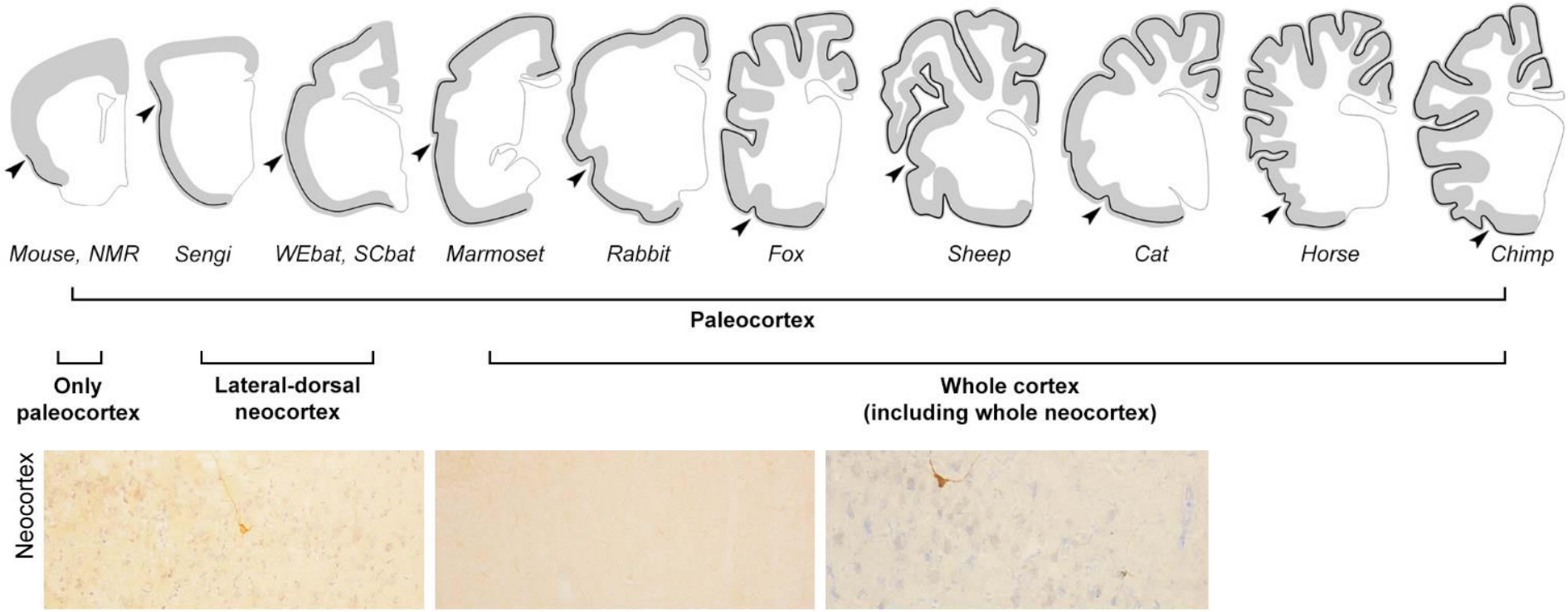
Frederic Levy
Brain tissues
BrdU treatments

Juan Nacher
Immature neurons expertise

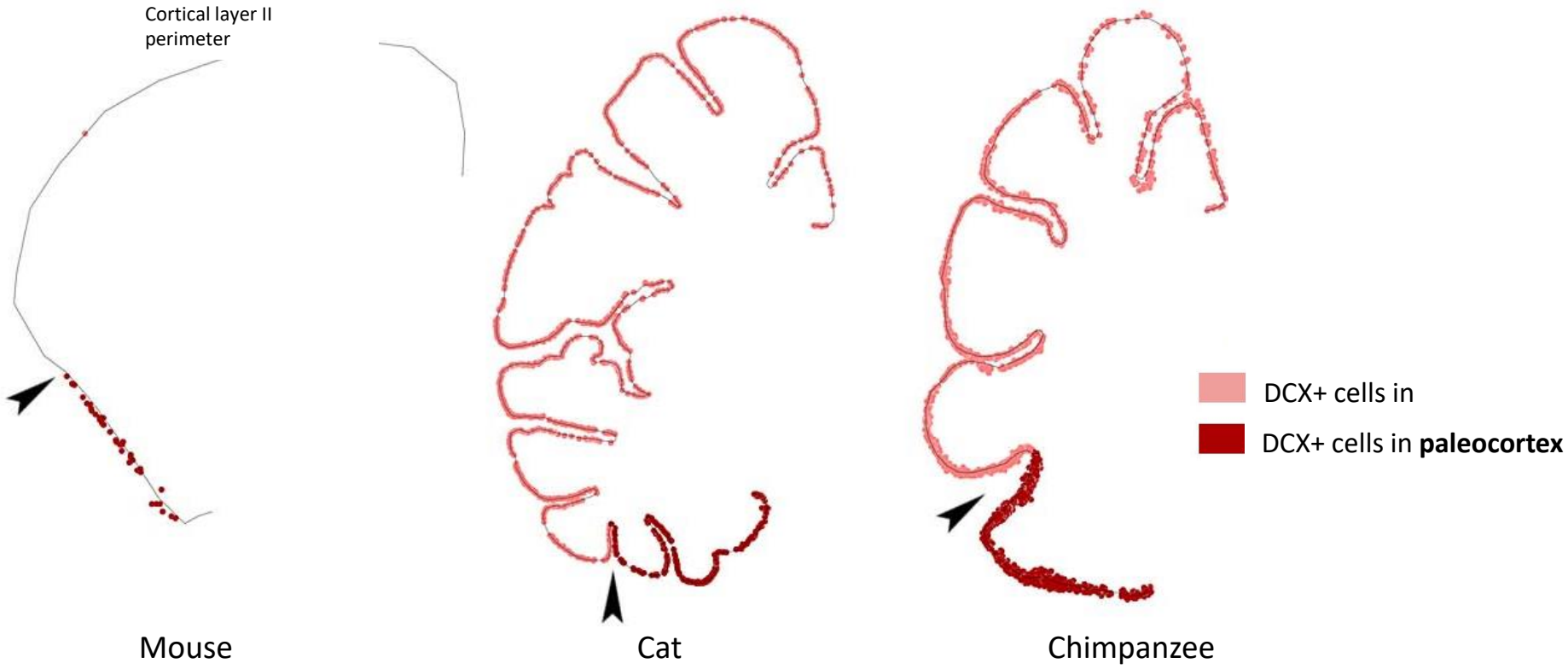
Chet Sherwood
Brain tissues


Paleocortex
Cat
Fox
Rabbit

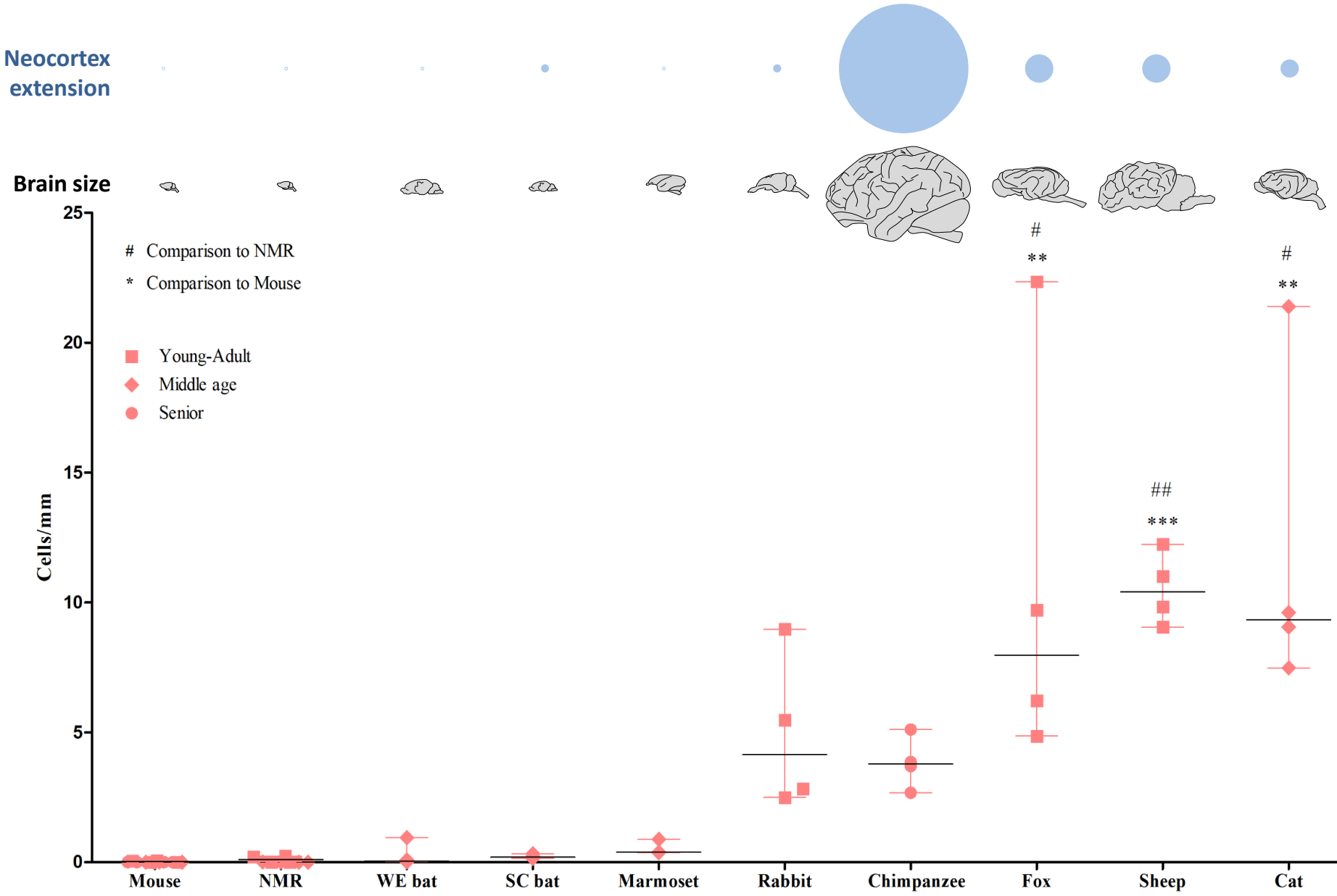

Neocortex
Paleocortex


Mouse, NMR
Sengi
WEbat, SCbat
Marmoset
Rabbit
Fox
Sheep
Cat
Horse
Chimp
Paleocortex
Only paleocortex
Lateral-dorsal neocortex
Whole cortex (including whole neocortex)
Neocortex

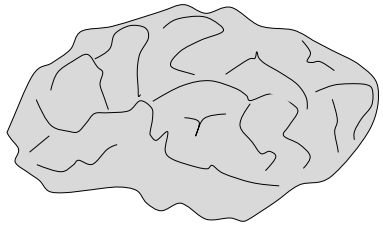
Densità lineare → n° di cellule/mm di perimetro corticale (strato II)

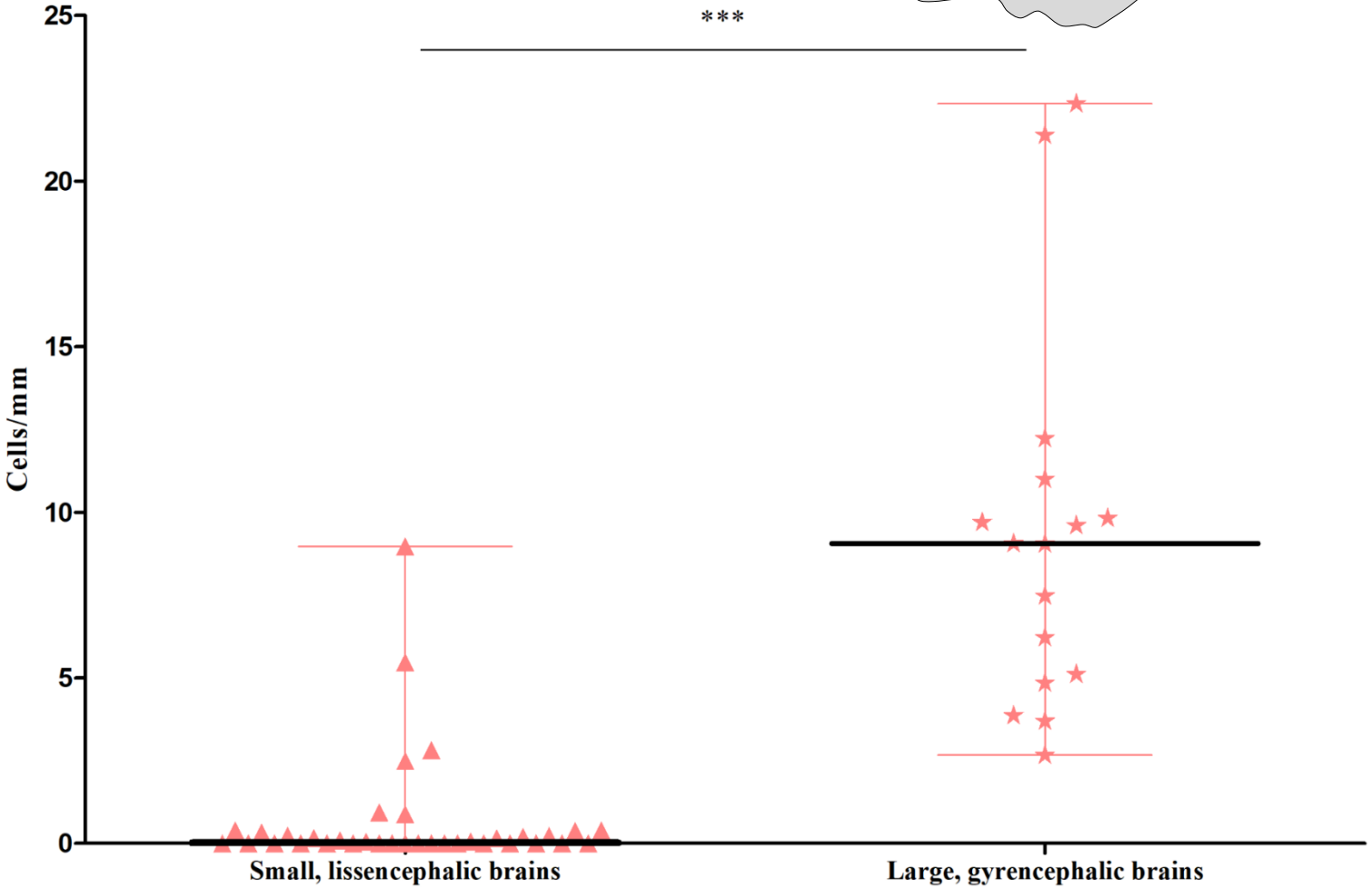


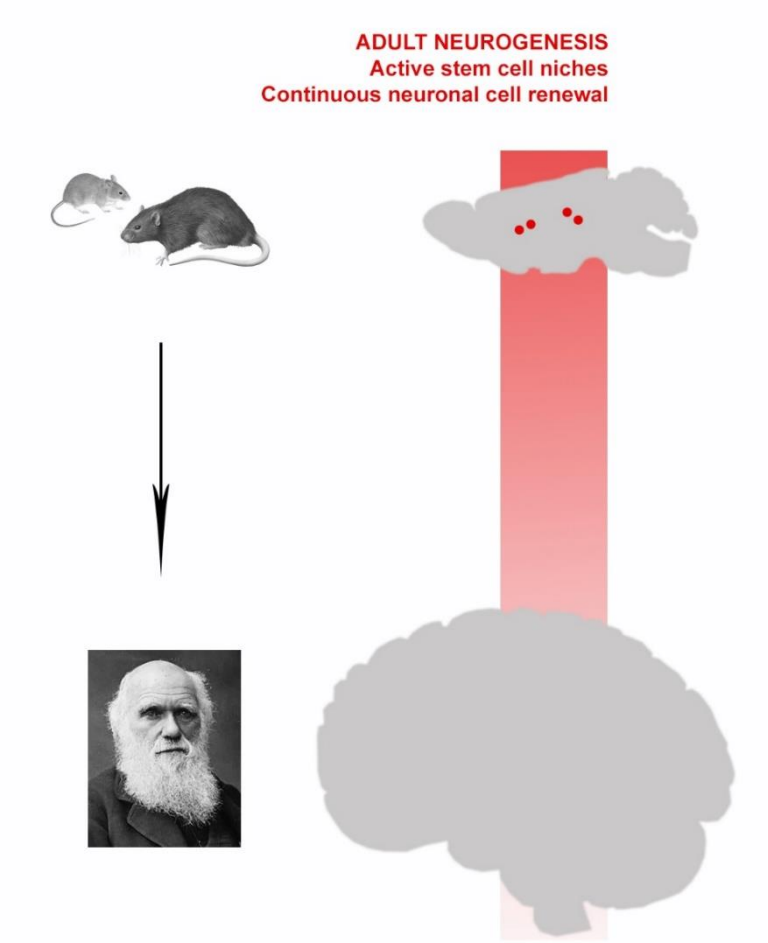
Densità lineare (quantità di neuroni immaturi) ed estensione della neocorteccia



small, lissencephalic brains vs. large, gyrencephalic brains







Ipotesi

I neuroni immaturi potrebbero «compensare» la perdita di neurogenesi nei cervelli con grande espansione della neocorteccia

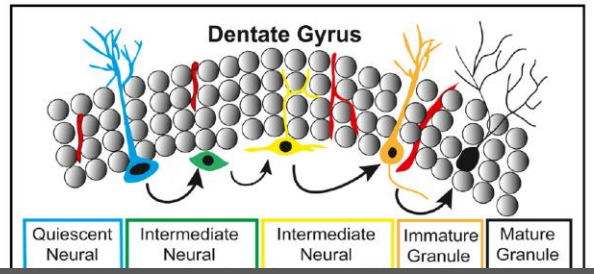
The claim for adult neurogenesis in humans

Short Article

Cell Stem Cell

Human Hippocampal Neurogenesis Persists throughout Aging

Graphical Abstract



Authors

Maura Boldrini, Camille A. Fulmore, Alexandria N. Tartt, ..., Andrew J. Dwork, René Hen, J. John Mann

Correspondence

mb928@cumc.columbia.edu

In Brief

Boldrini et al. find persistent adult

MENU

nature medicine

Letter | Published: 25 March 2019

Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease

Elena P. Moreno-Jiménez, Miguel Flor-García, Julia Terreros-Roncal, Alberto Rábano, Fabio Cafini, Noemí Pallas-Bazarra, Jesús Ávila & María Llorens-Martín

My vision:

None of these papers show substantial cell proliferation.

All these papers speak about «immature neurons» instead of «newly generated neurons»

The TITLE of these papers is wrong: they do not show «adult neurogenesis»

Human Hippocampal Neurogenesis Persists in Aged Adults and Alzheimer's Disease Patients

Matthew K. Tobin • Kianna Musaraca • Ahmed Disouky • ... David A. Bennett • Konstantinos Arfanakis • Orly Lazarov [7] • Show all authors • Show footnotes

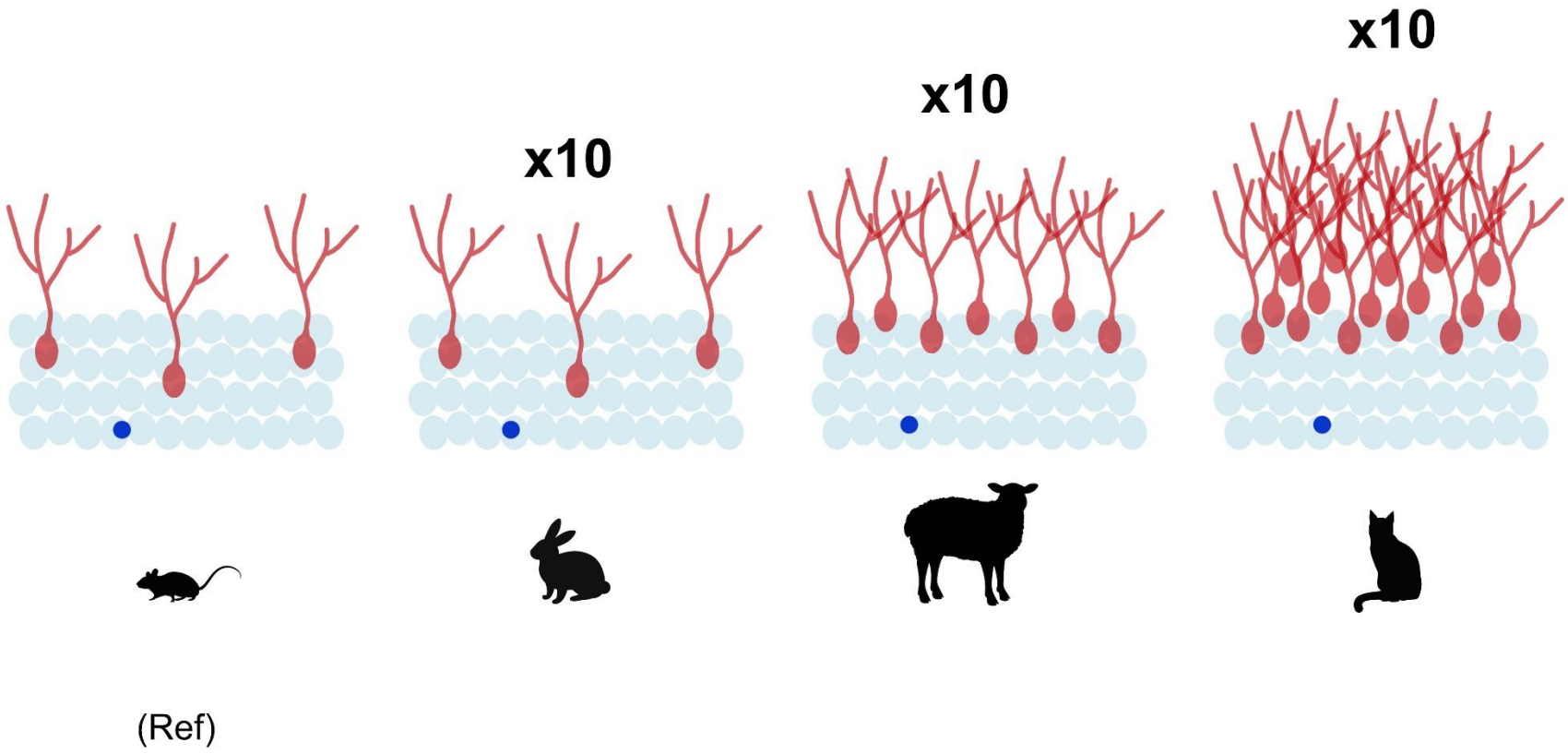
Published: May 23, 2019 • DOI: https://doi.org/10.1016/j.stem.2019.05.003

Hippocampal neurogenesis: a «flame» in a very hot topic

Dentate gyrus →

Preliminary results:

La Rosa, Olmeo, Ghibaudi, Amrein, Bonfanti



Neurons expressing markers of «immaturity» in the adult sheep hippocampus

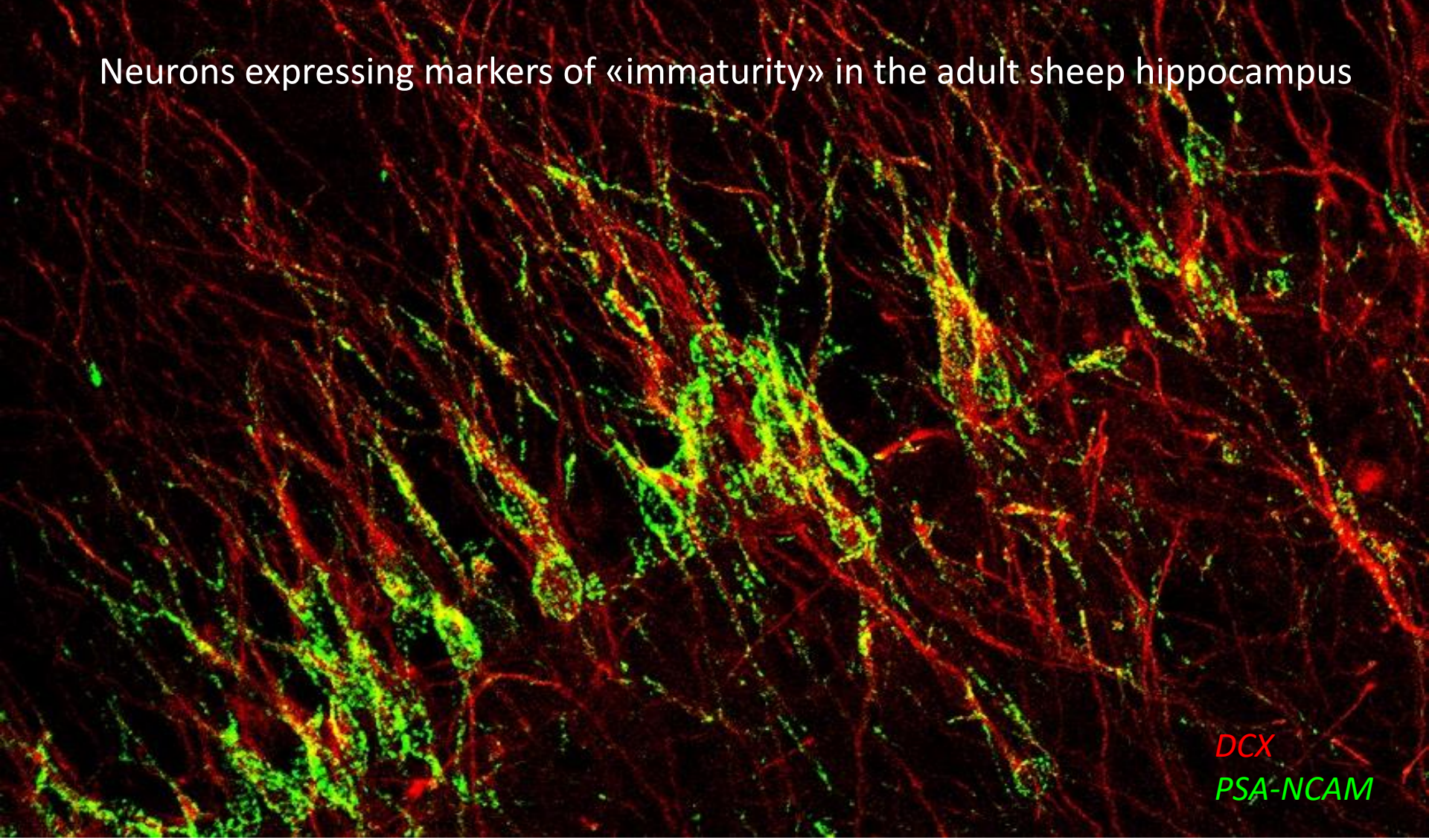


Foto: Ottavia Palazzo

Neuronal maturation:

Mouse: 3-4 weeks

Sheep: 3 months

Monkey: 6 months

Humans: ???

Published 3 days ago

NEUROSCIENCE

Adult neurogenesis in mammals

Neurogenesis in adulthood has implications for sense of self, memory, and disease

By **Fred H. Gage**

genetic markers (*4*). Moreover, adult neurogenesis was shown to occur in limited areas

genesis, including proliferation, maturation, migration, differentiation, survival, and inte-

Mammals?...


Now play with your neurons!