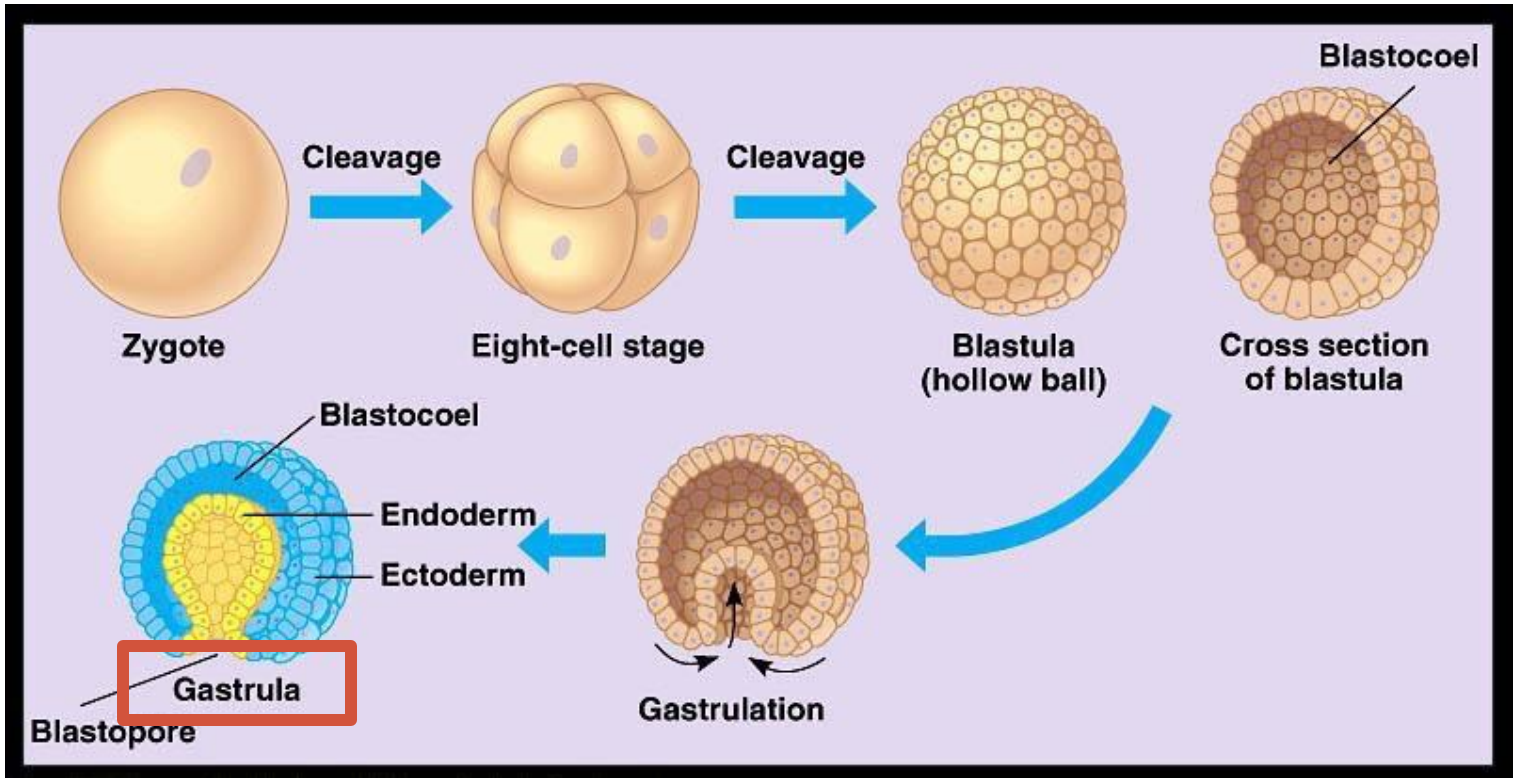
WEEK 2

BRAIN DEVELOPMENT AND ADULT NEUROGENESIS

Neurodevelopment

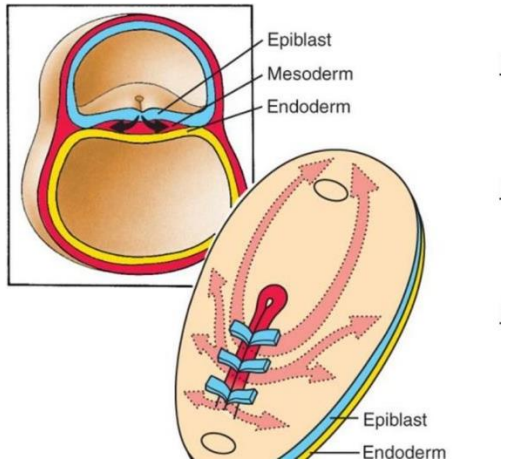
1) **Neurulation, cellular identity and patterning**
2) Stem cells and neurogenesis
3) Neuronal migration and axonogenesis

The first days in human embryonic development

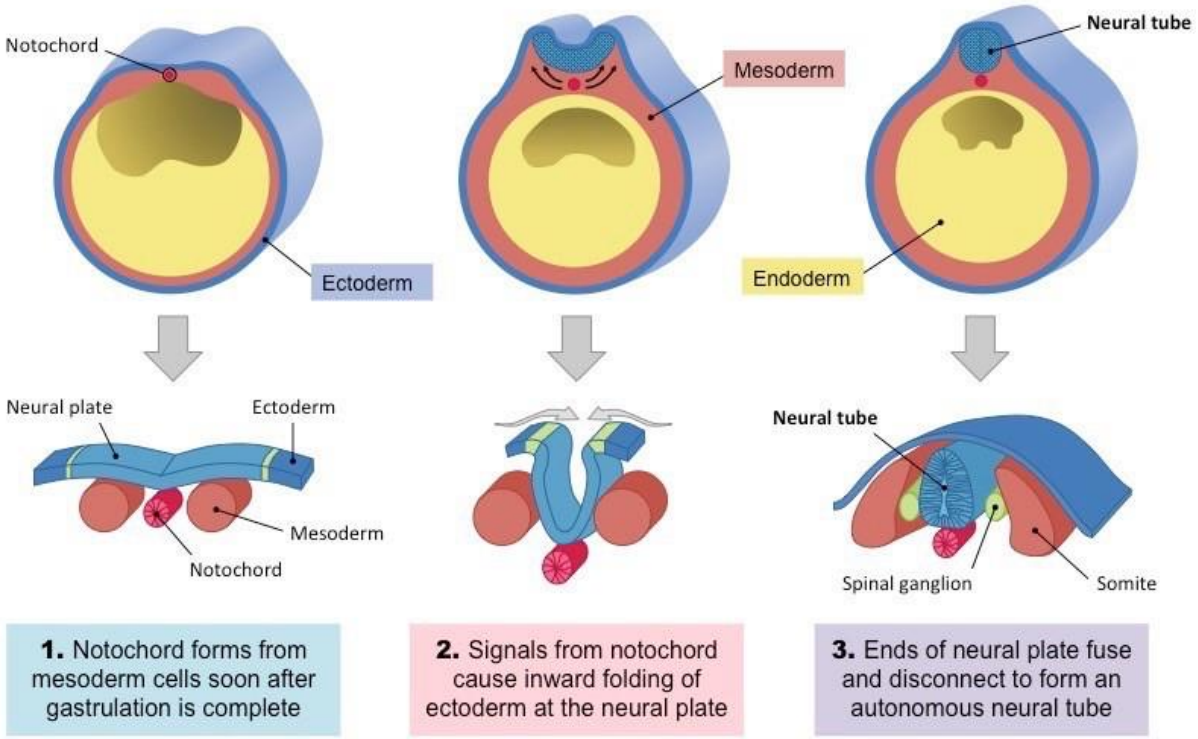


Nervous system derives from the ectoderm

- 3 germ layers
  - Ectoderm ➔ Nervous system, skin
  - Mesoderm ➔ Muscle, bone, connective tissue
  - Endoderm ➔ Viscera



- Neurulation: formation of the neural tube by folding of the neuroectoderm
  - 18 days after conception (humans)



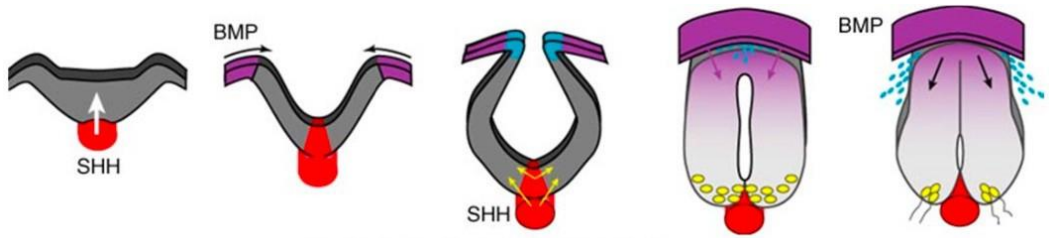
Morphogenes

- Diffused proteins that participate in the induction of the neural plate (neuroectoderm)

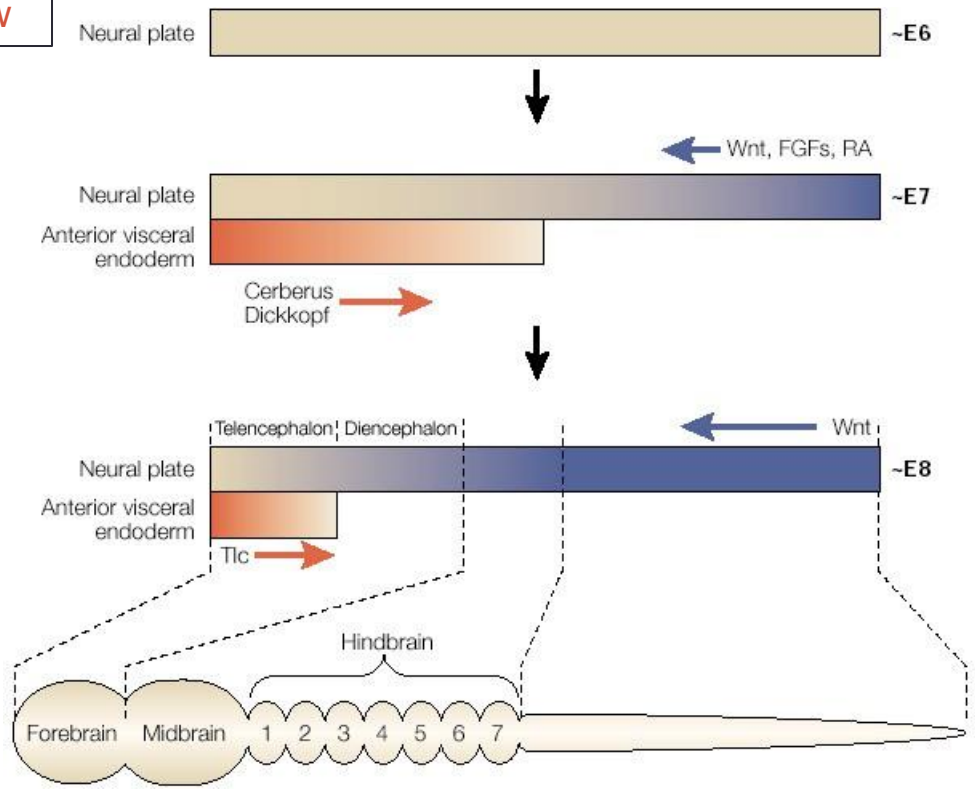
- Give positional information and induce the expression of specific transcription factors

  - Dorsal: **BMPs**
  - Ventral: **Shh**
  - Anterior: **Cerberus**
  - Posterior: **Wnt, FGFs, RA**

Cross-section

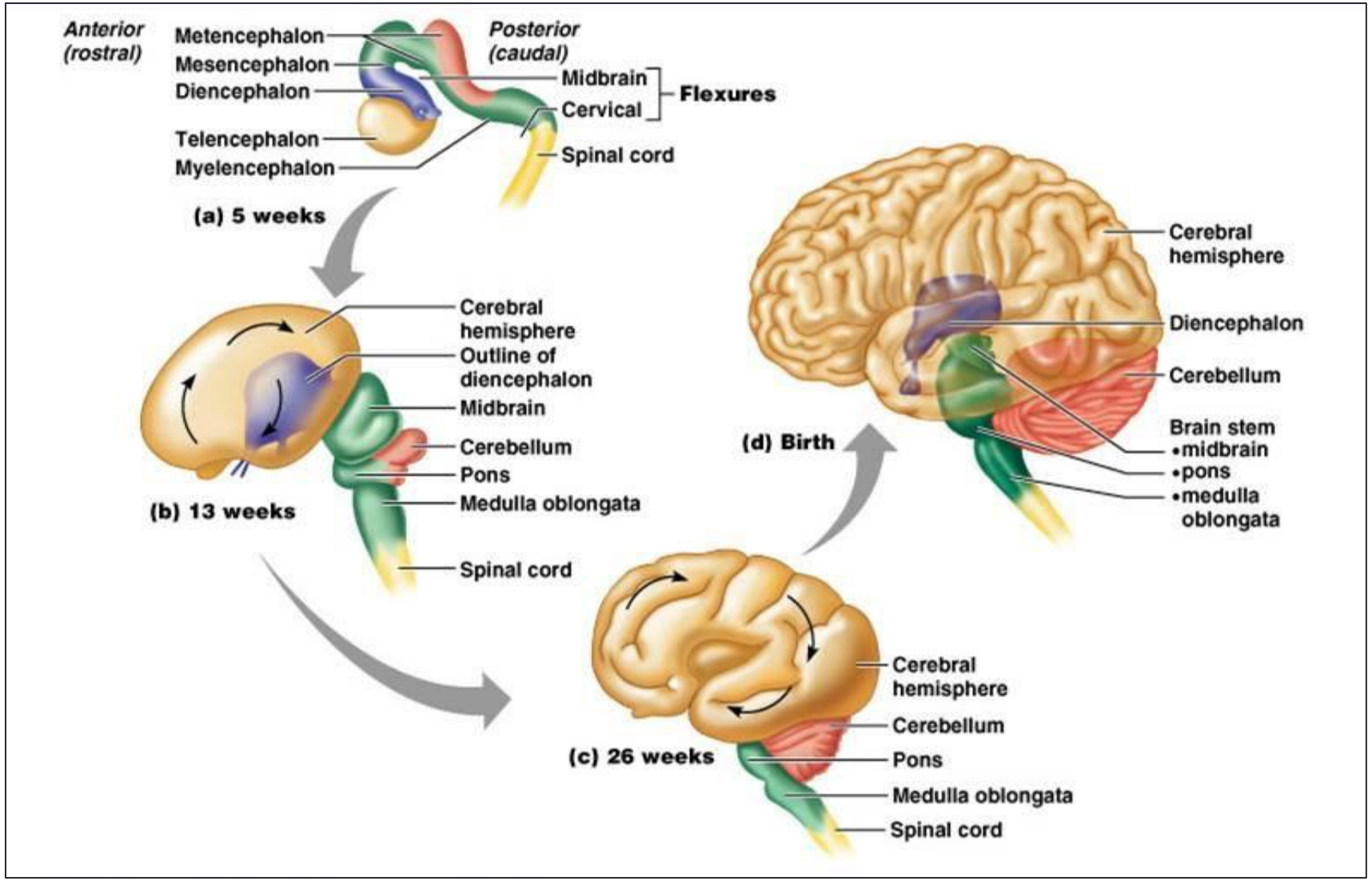


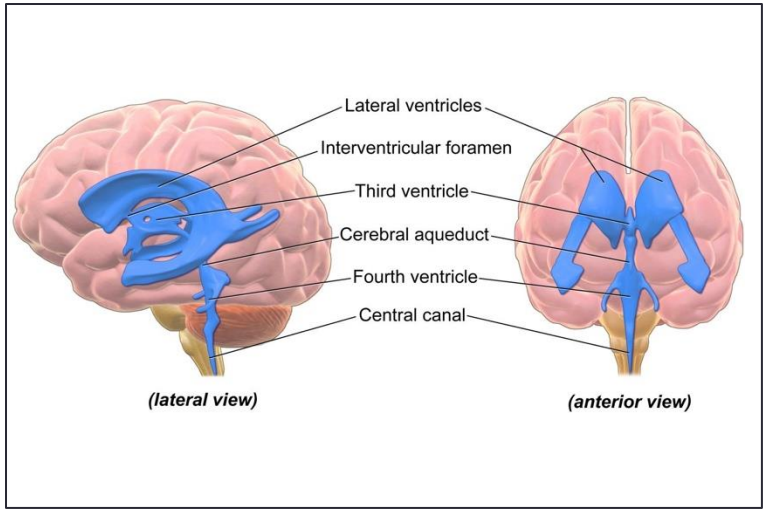
Dorsal view

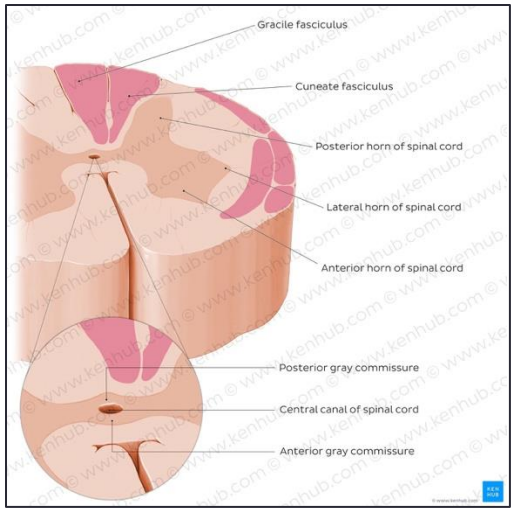


BMP=bone morphogenetic factor; Shh=sonic hedgehog; FGF=fibroblast growth factor; RA=retinoic acid

Formation of major brain subdivisions – timeline

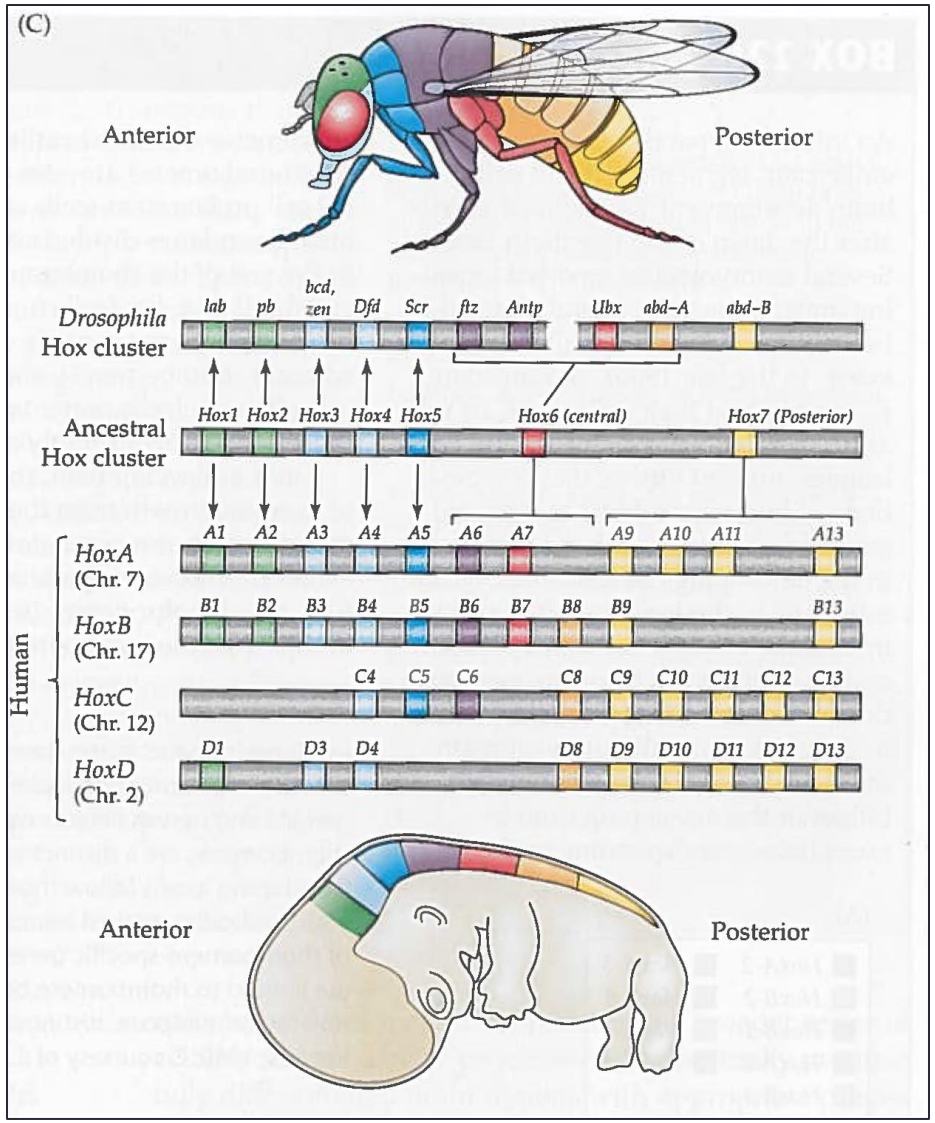






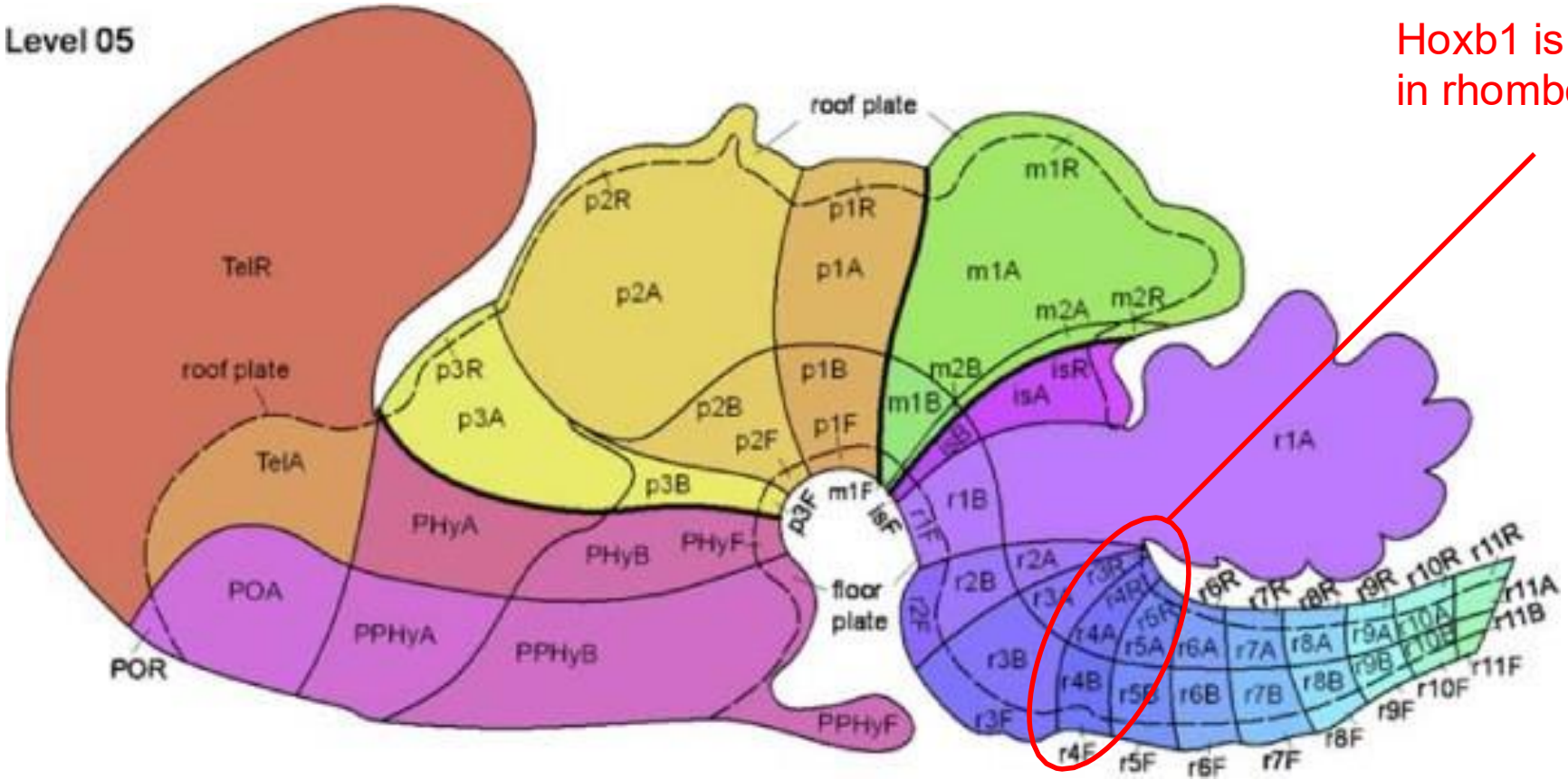
Formation of major brain subdivisions

- **How can a simple tube produce such a variety of brain structures?**
  - Neural tube is organized into repeat units called neuromeres
  - Each neuromere contains transcription factors that modulate the expression of specific sets of gene for each segment
  - Conserved segmentation in embryonic development between *Drosophila*, mice and humans



Establishment of cell identity

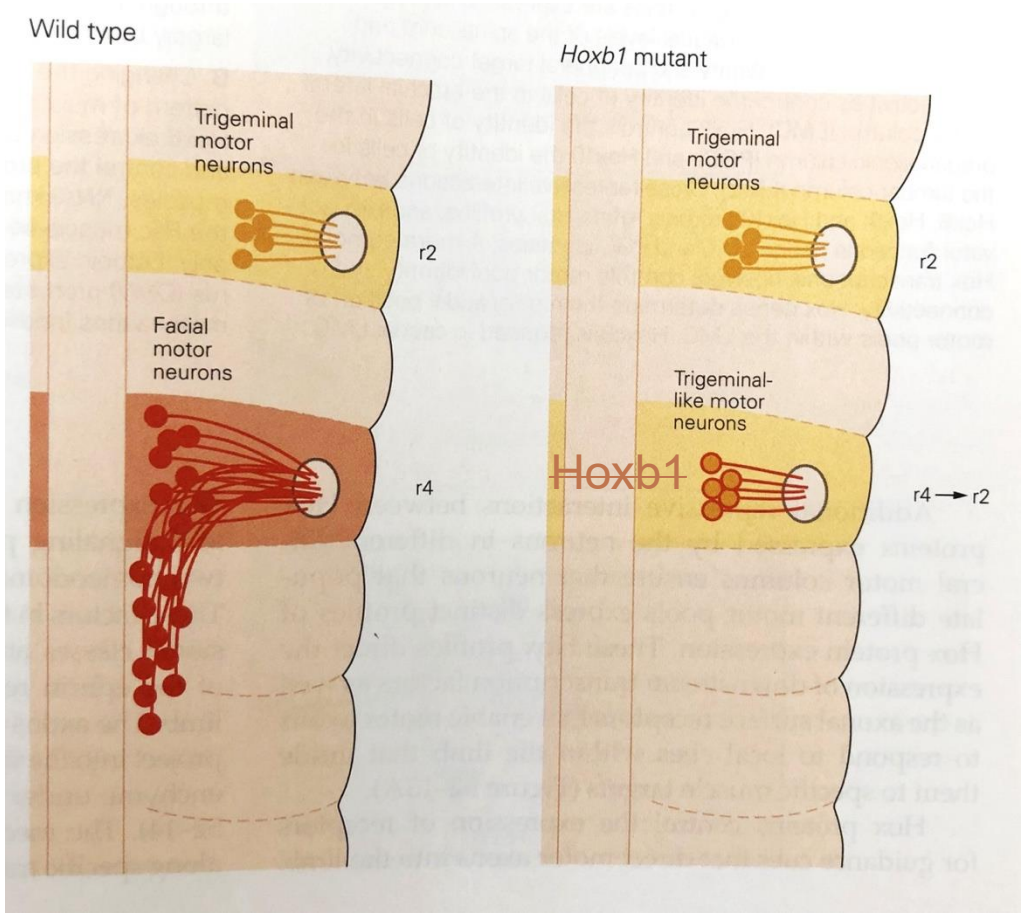
- The prosomeric model (Rubenstein et al., 1994)



Establishment of cell identity

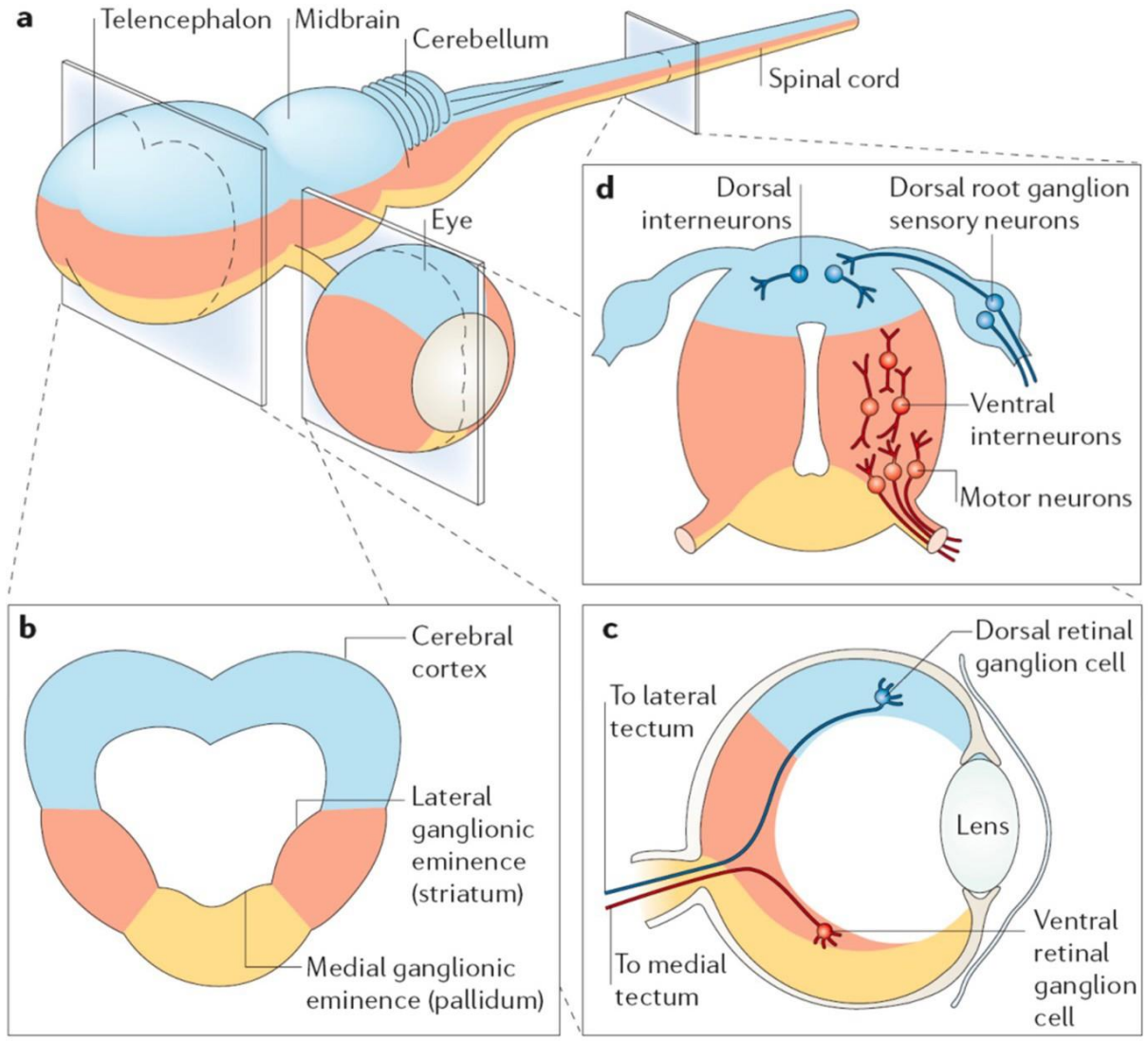
- Hoxb1 (rhombomere4) determines facial motor neuron identity

Hoxb1



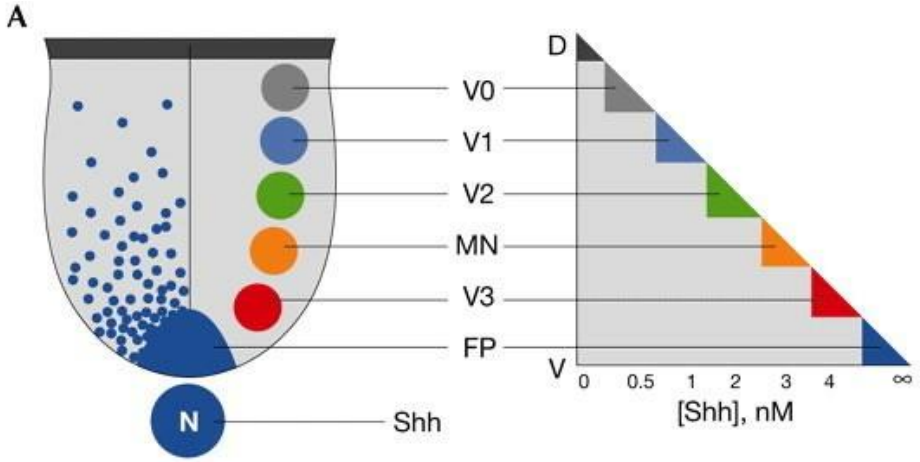
Establishment of cell identity

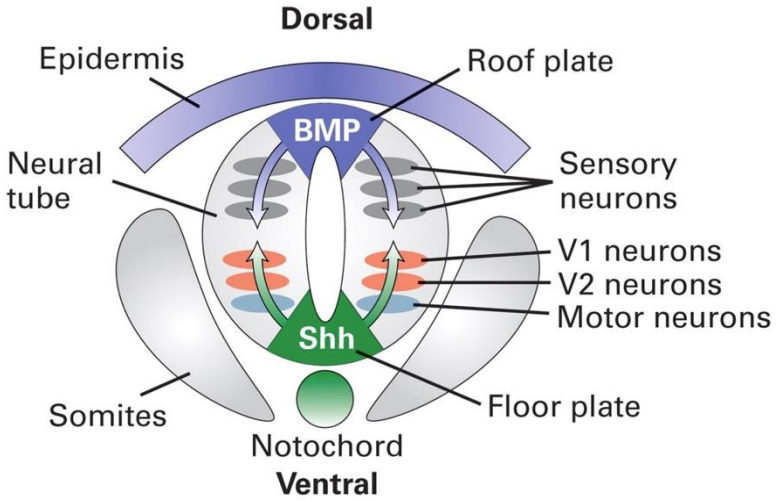
- Early positional information is induced by morphogenes in different parts of the neural tube
- Morphogenes regulate the expression of region-specific transcription factors
- Those transcription factors start unique developmental programs for each region



Establishment of cell identity

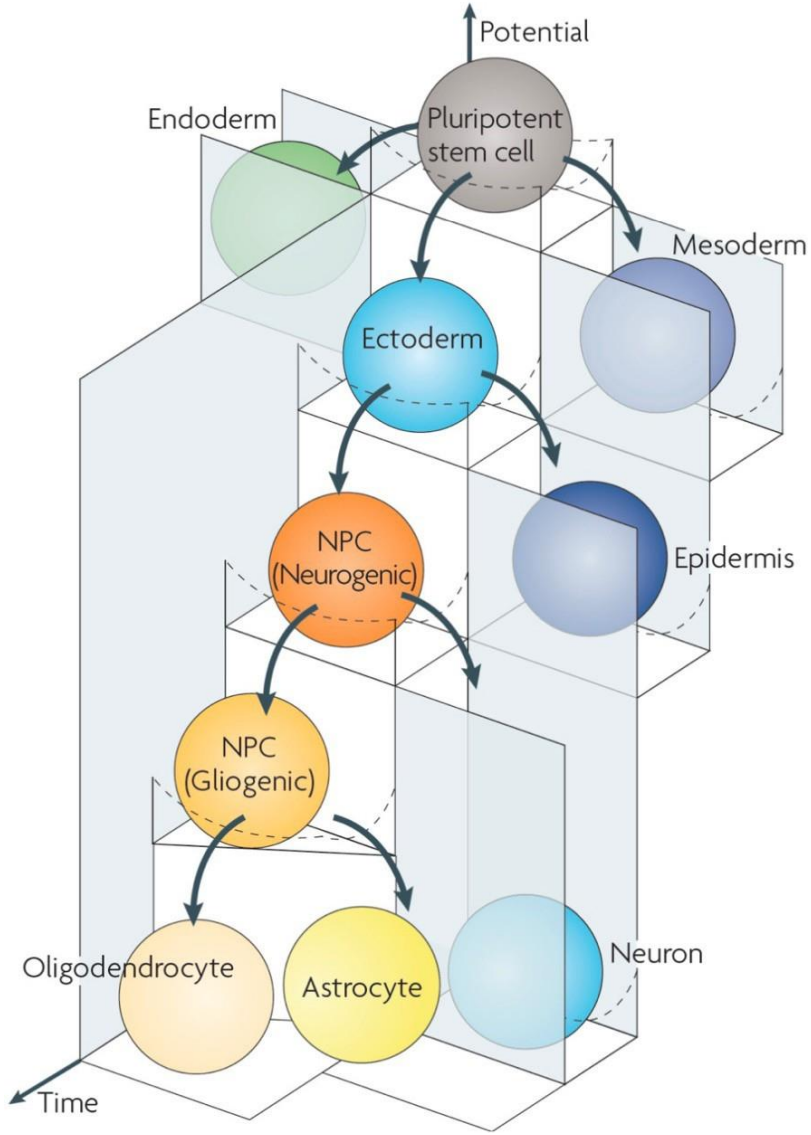
- **Spinal cord: different areas, different fates**
  - Dorso-ventral morphogenes…
  - …induce different identities in the spinal cord
  - Early transcription factors inhibit each other, establishing defined and separated cell identities





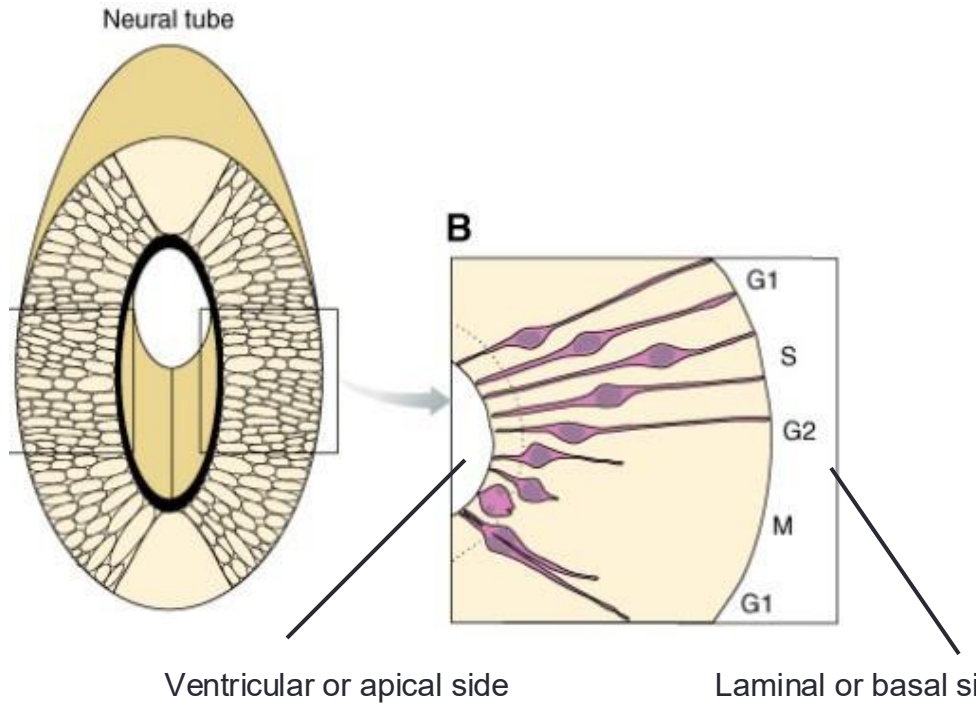
Neurodevelopment

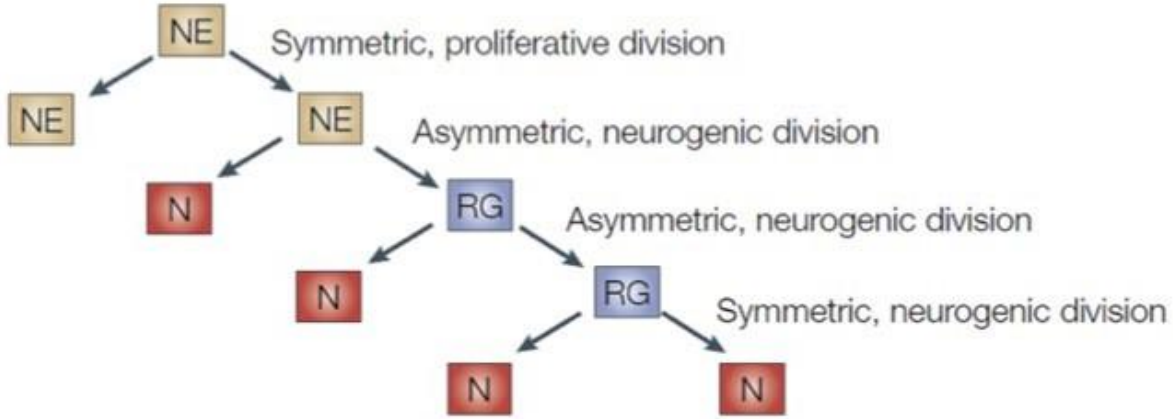
1) Neurulation, cellular identity and patterning
2) **Stem cells and neurogenesis**
3) Neuronal migration and axonogenesis



Neuroepithelium

- **Neural stem cells** (= neuroepithelia, NE) give rise to all neurons, astrocytes and oligodendrocytes in the CNS
- In the neural tube, NE form a pseudostratified epithelium
  - **Interkinetic nuclear migration:** periodic movement of cell nucleus in phase with cell-cycle progression
  - Apical mitosis
    - First, expansion of the pool of stem cells (symmetric division)
    - Later, formation of neurons (asymmetric, neurogenic division)



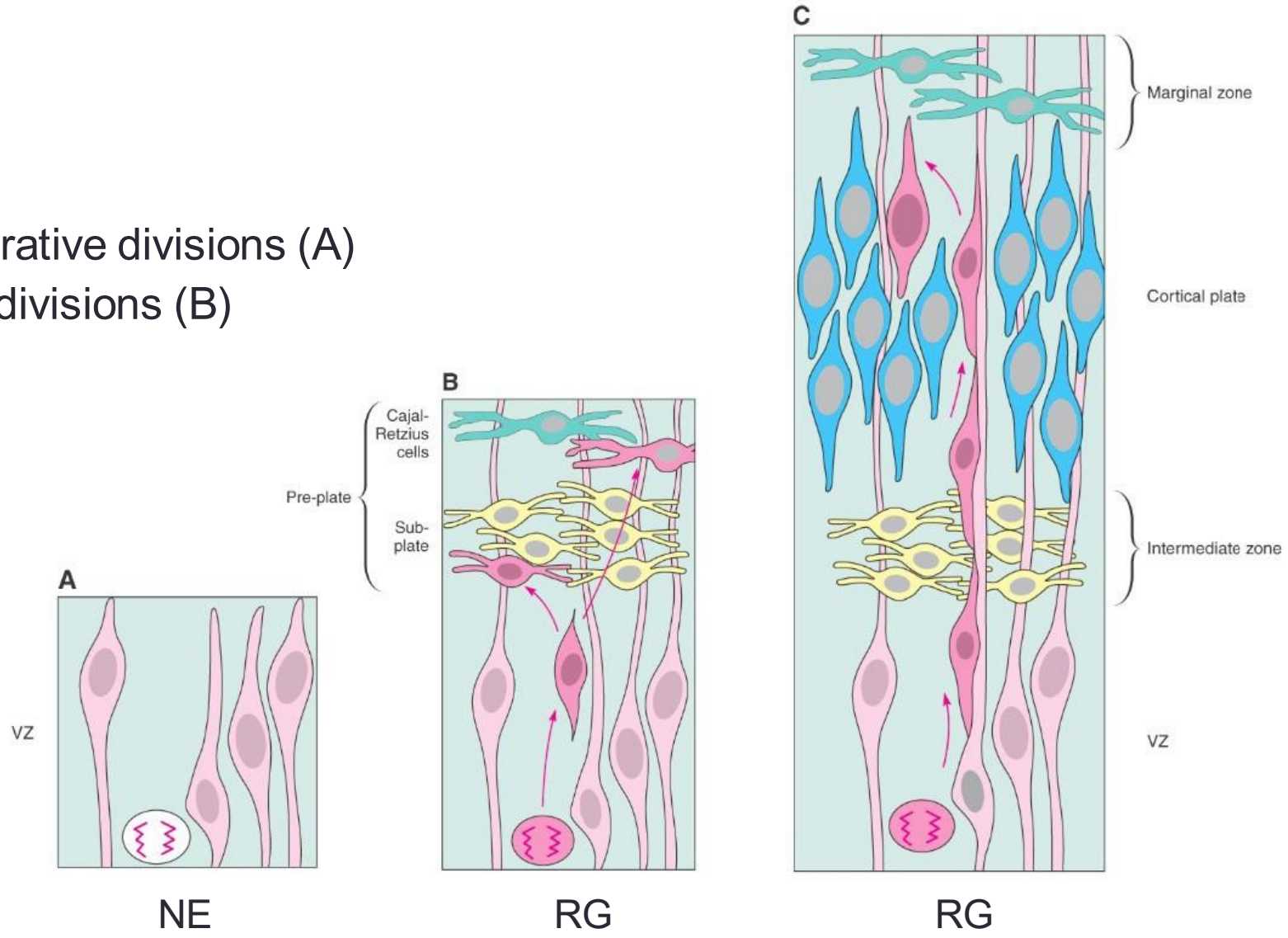


Corticogenesis

Formation of the cerebral cortex

- 1st, neuroepithelium with proliferative divisions (A)
- 2nd, radial glia with neurogenic divisions (B)
- 3rd, layer formation (C)

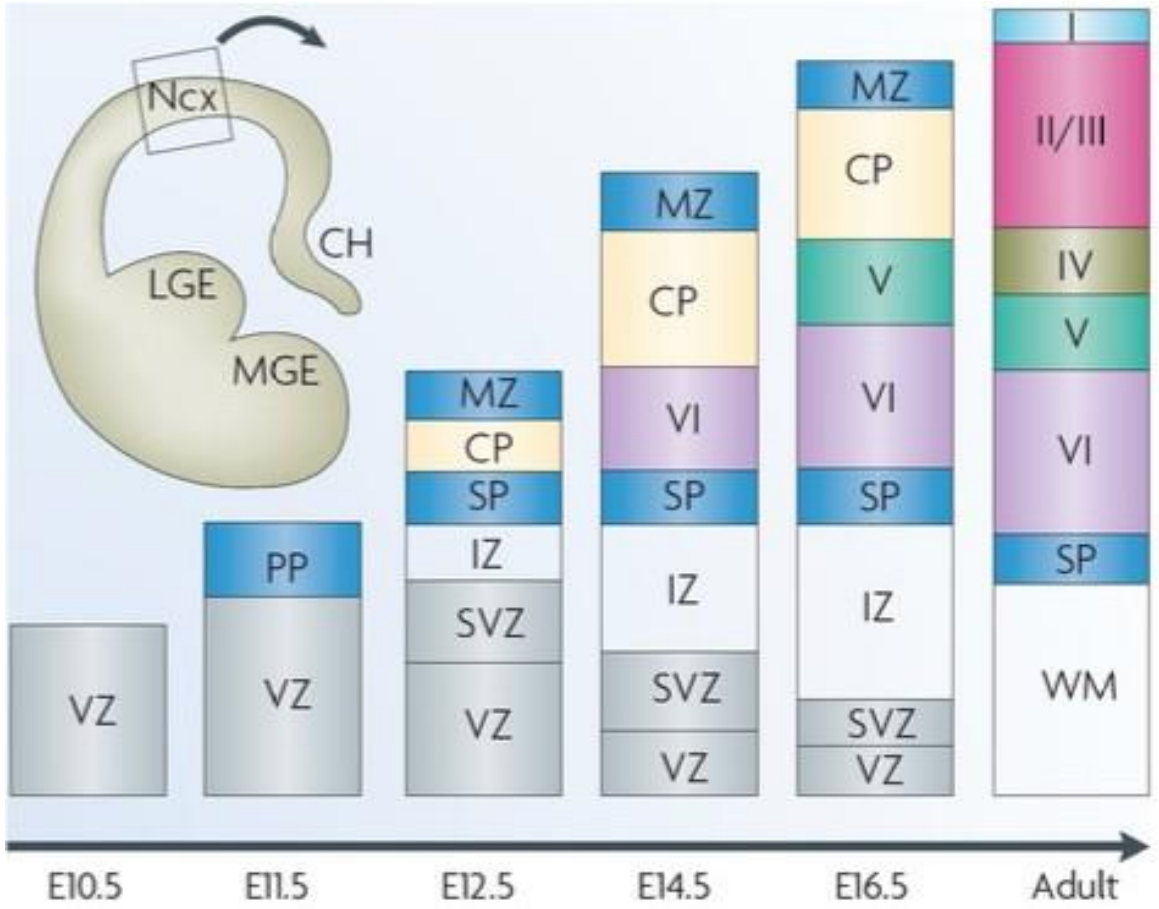
Neuroblasts migrate radially using the RG as a scaffold



Corticogenesis

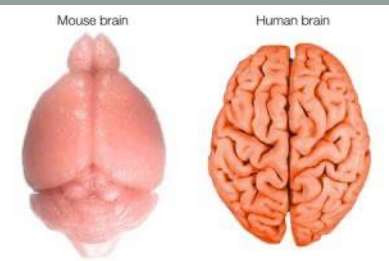
- Cajal-retzius neurons in the marginal zone (MZ) secrete reelin, that acts as chemoattractor for migrating neuroblasts

- Neurons generated early occupy more apical positions (lower layers). Later neurons occupy basal positions (upper layers)



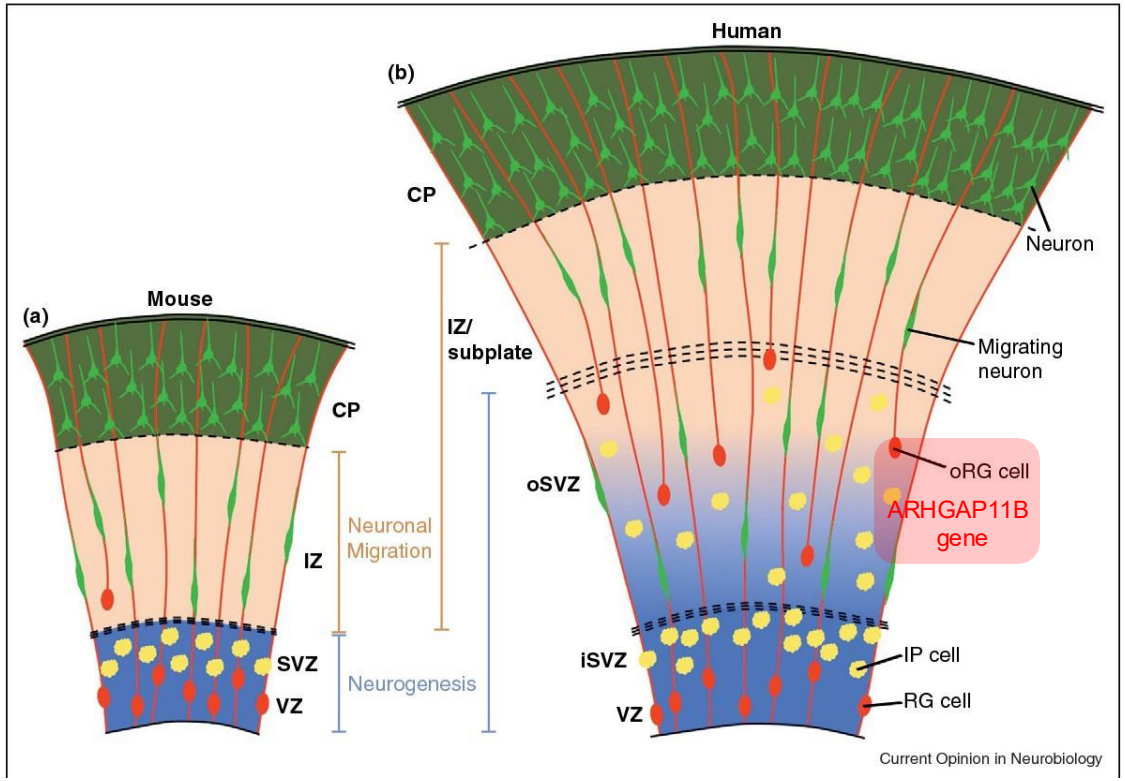
MZ – marginal zone
CP – cortical plate
IZ – intermediate zone
WM – white matter
PP – preplate
SVZ – subventricular zone
VZ – ventricular zone

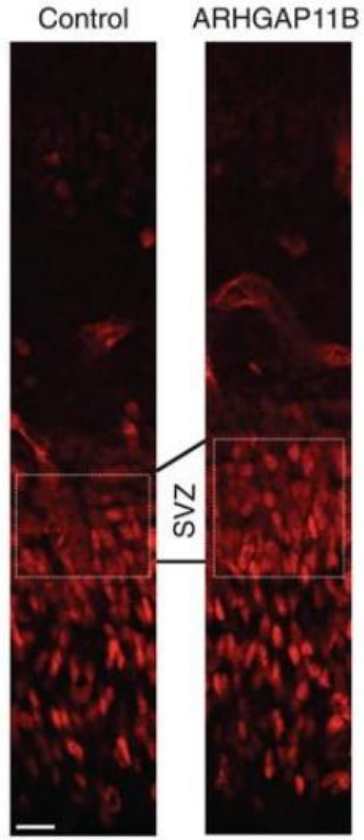
➔ **The cortex is formed in an inside-out manner**

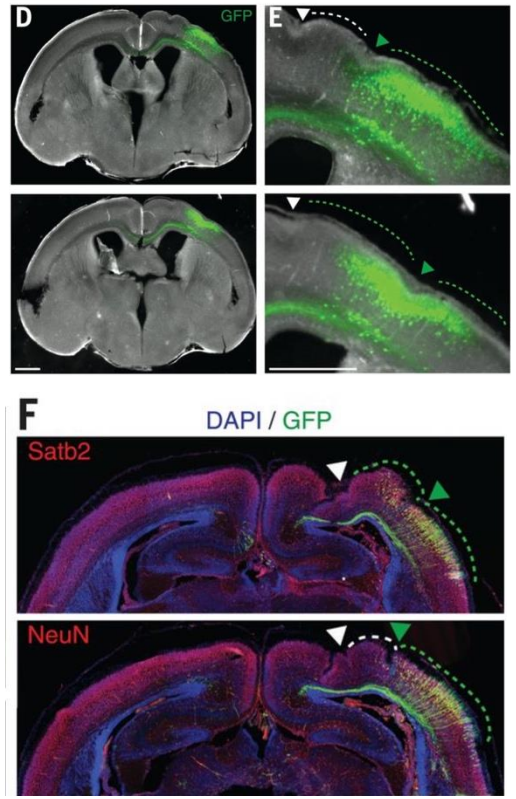


Cortical expansion in humans

- Outer subventricular zone with basal progenitors (oRG cells) contributes to greater cortical expansion in humans
- Expression of human-specific genes in the mouse developing embryo leads to gyrification (Florio et al., 2015)







Florio et al., 2015

Neurodevelopment

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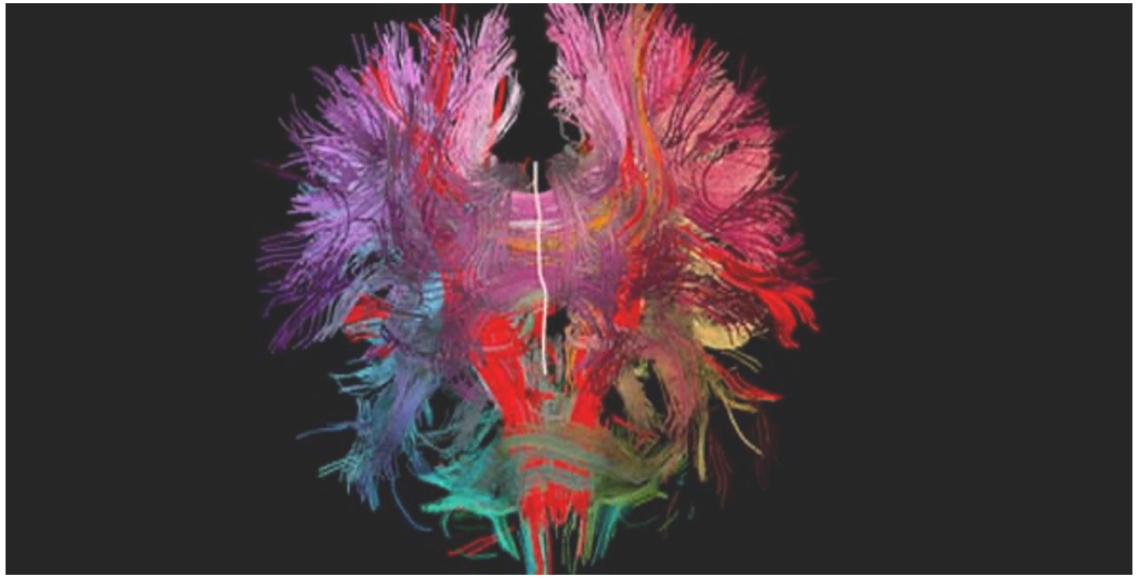
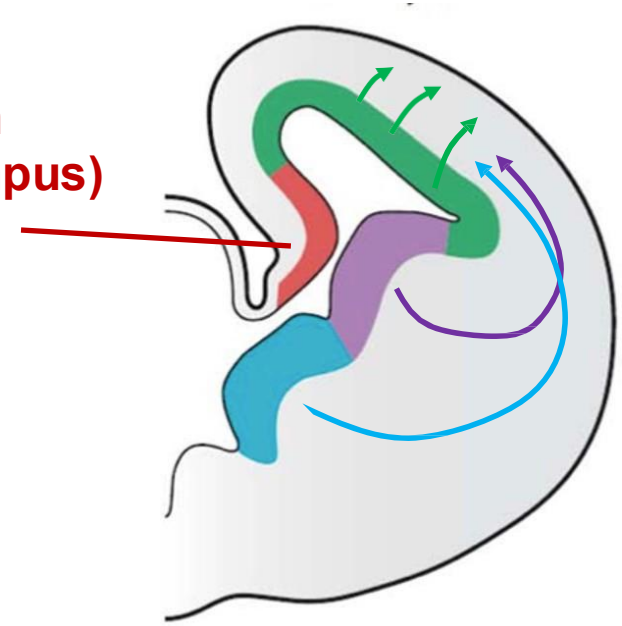
2) Stem cells and neurogenesis

3) **Neuronal migration and axonogenesis**

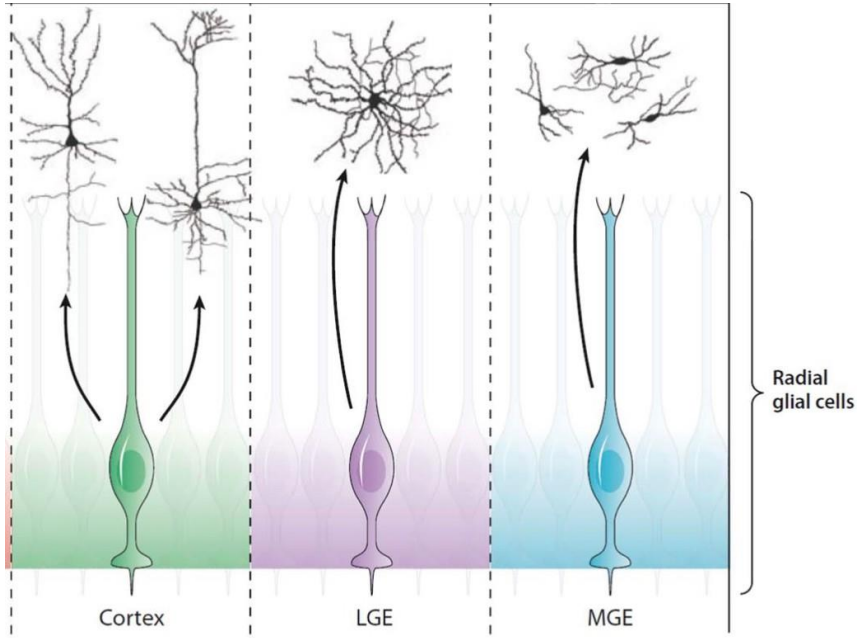


Neuronal migration



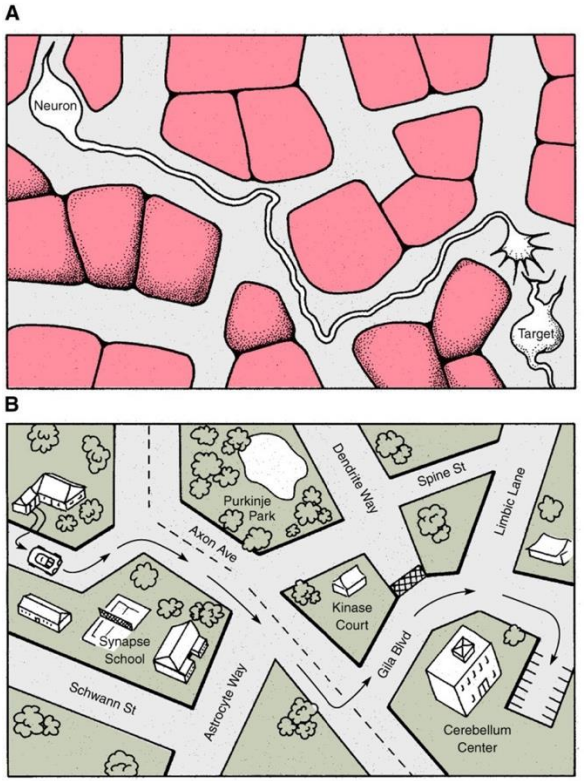
- **2 types**
  - Radial: cortex expansion; projection neurons (Glu)
  - Tangential: cortical interneurons (GABA); from ganglionic eminences (GE)

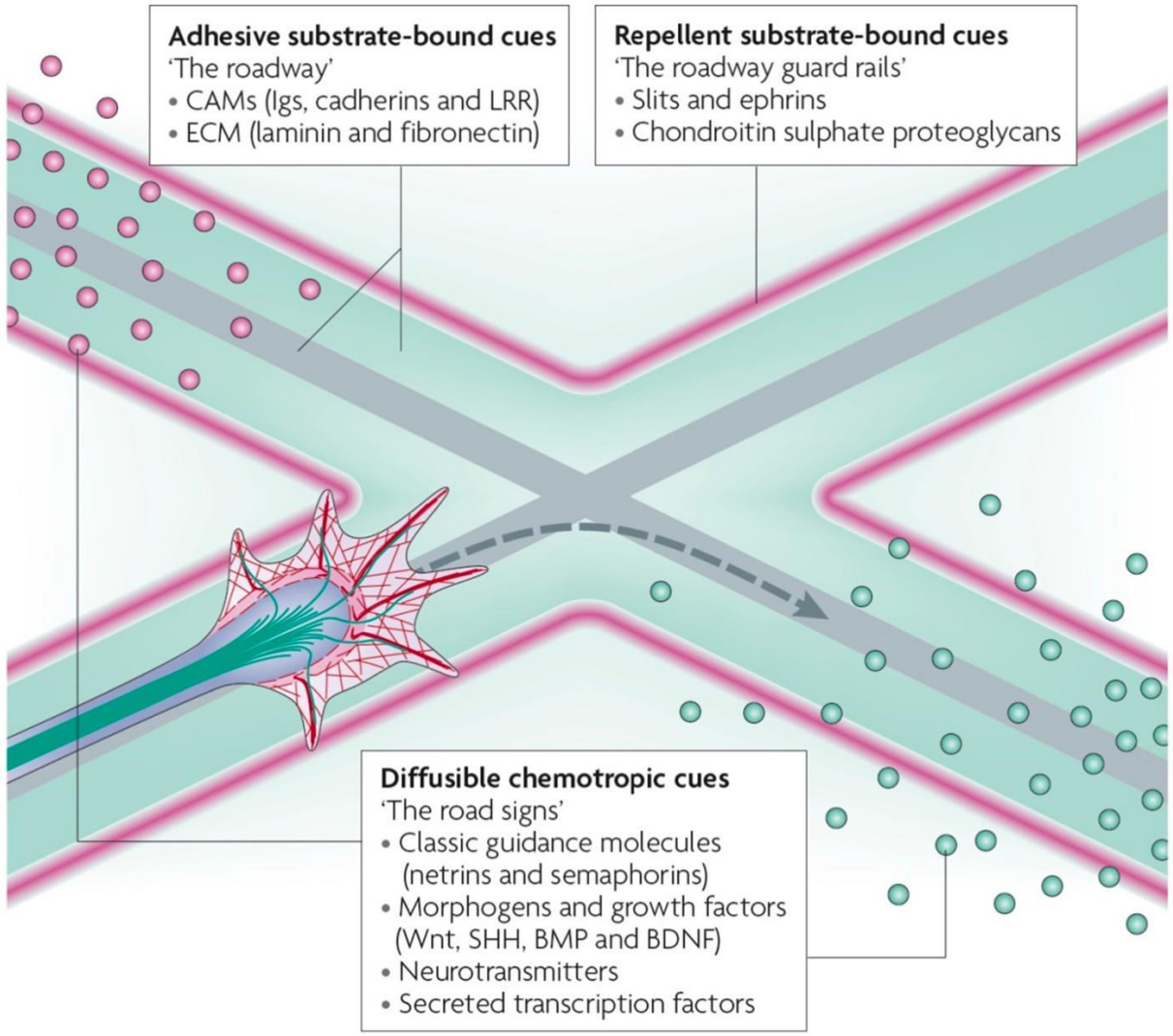
➔ Influenced by different signals



Axonogenesis (axon formation)

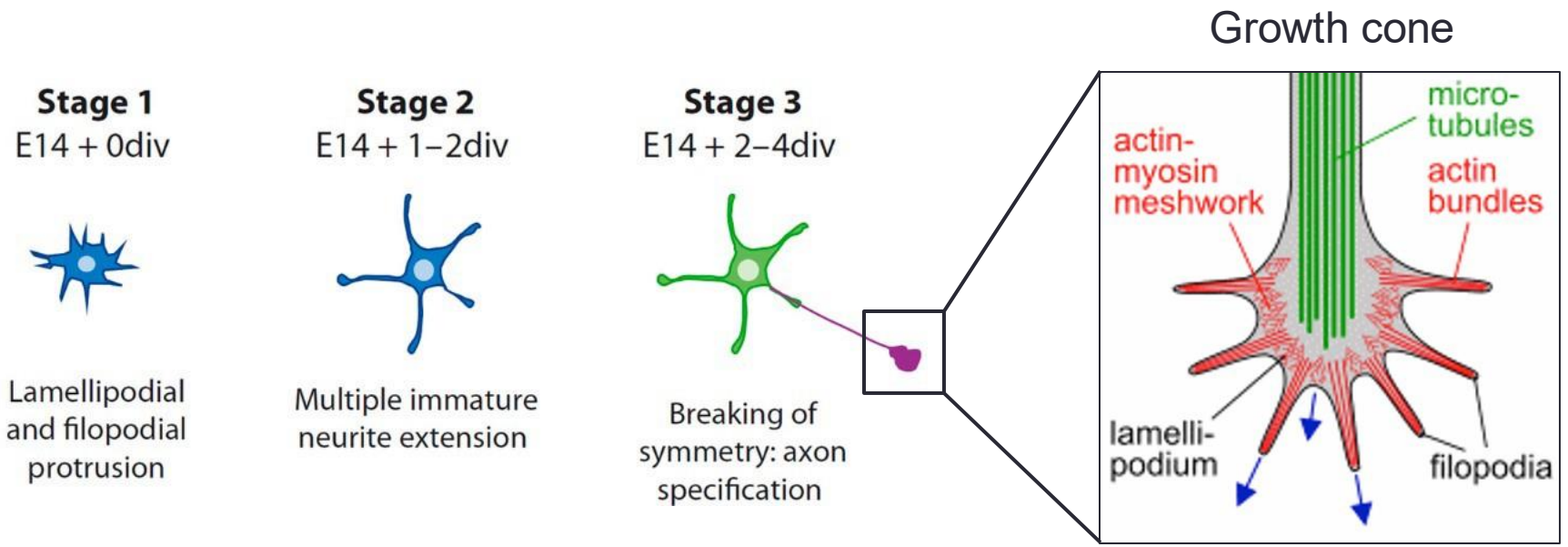
- **How do they find their specific targets?**

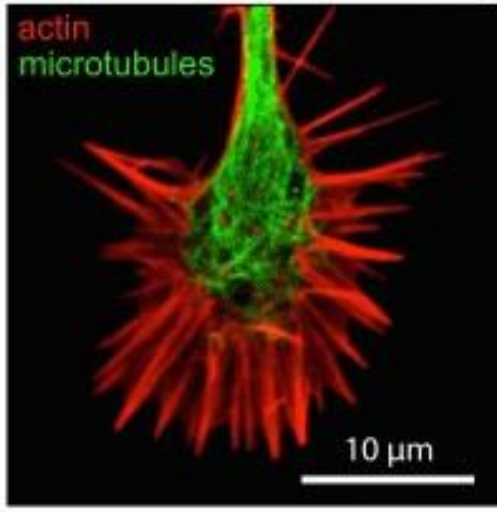




Axonogenesis

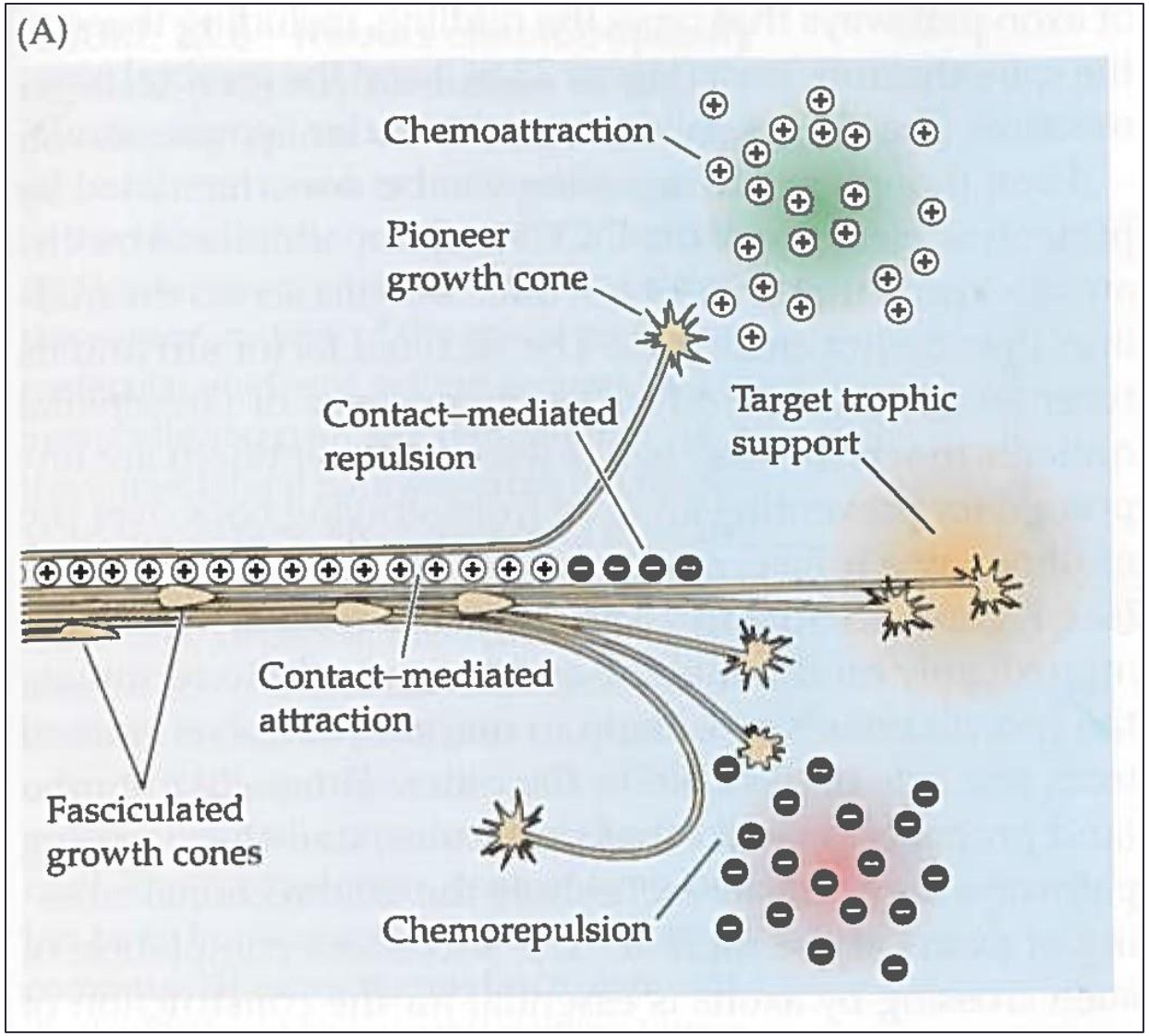
- **Establishment of the growth cone**





Axonogenesis

- **The growth cone "senses" the environment with finger-like structures (filopodia)**
- Chemoattraction (netrins)
- Chemorepulsion (semaphorines)

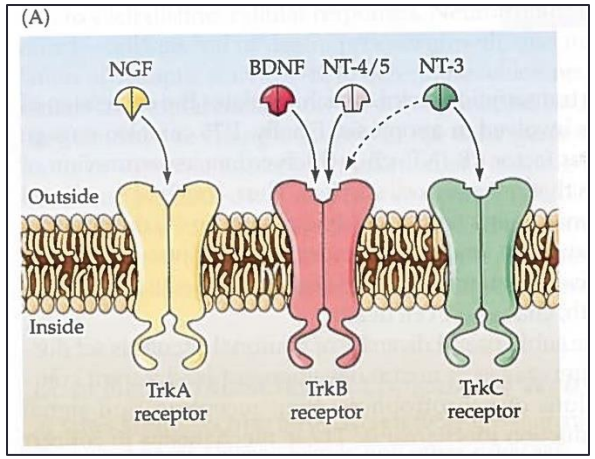


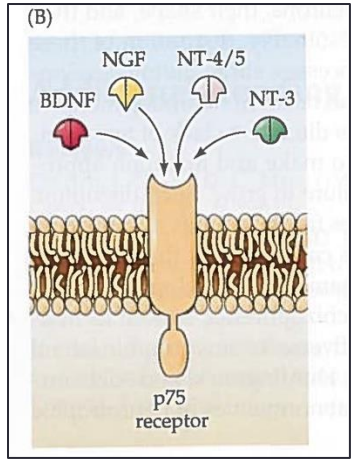
Axonogenesis – Synapse formation

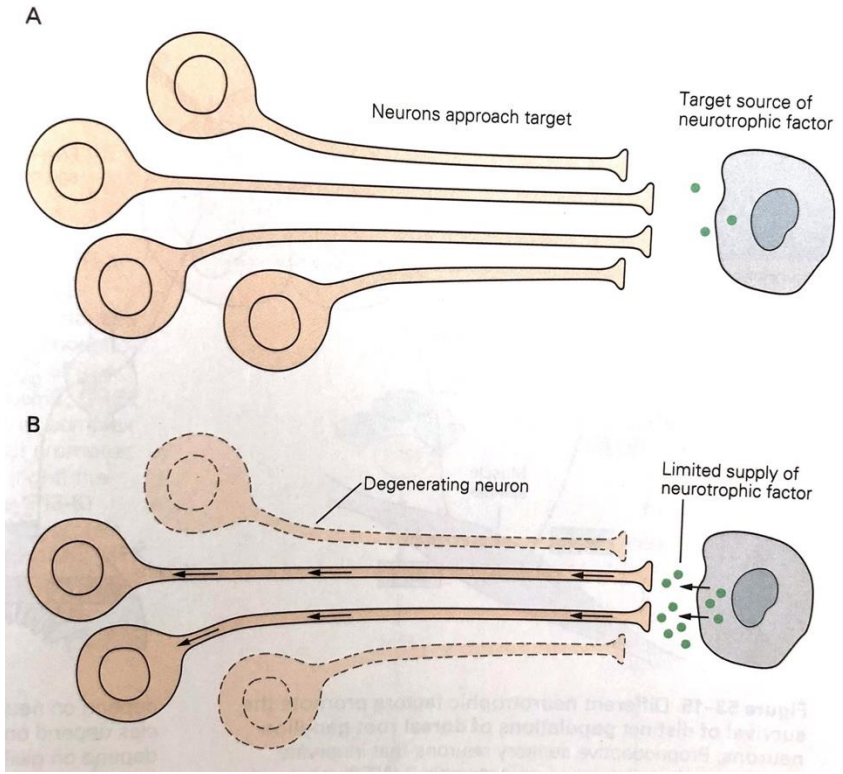
- Neurotrophic factors dictate neuronal/axonal survival

- Target-derived trophic factors
  - Neural growth factor (NGFs)
  - Brain derived growth factor (BDNF)
  - Neurotrofins (NTs)

- Absence of neurotrophic factors leads to apoptosis (controlled cell death)

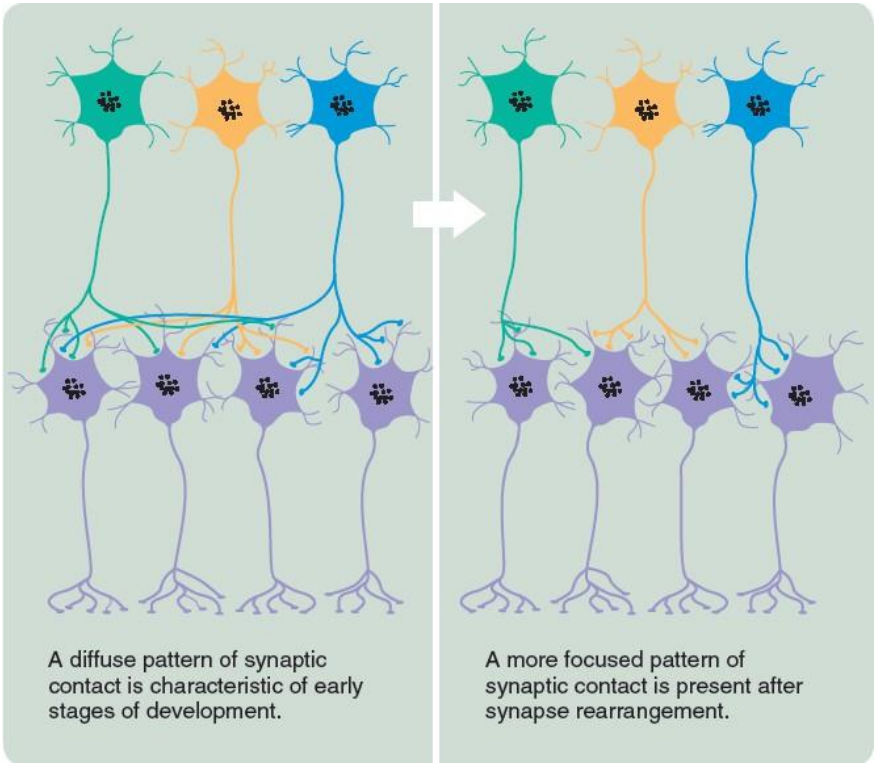


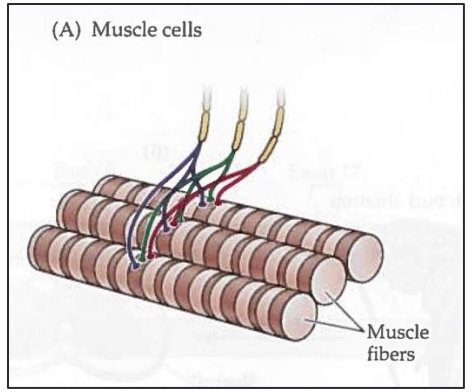


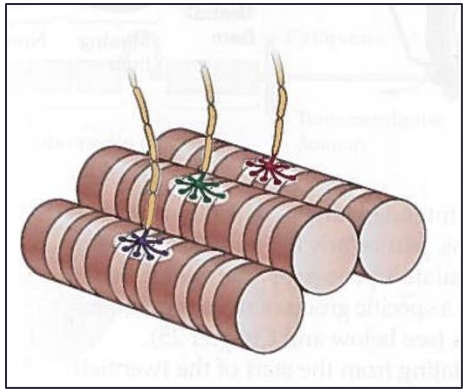


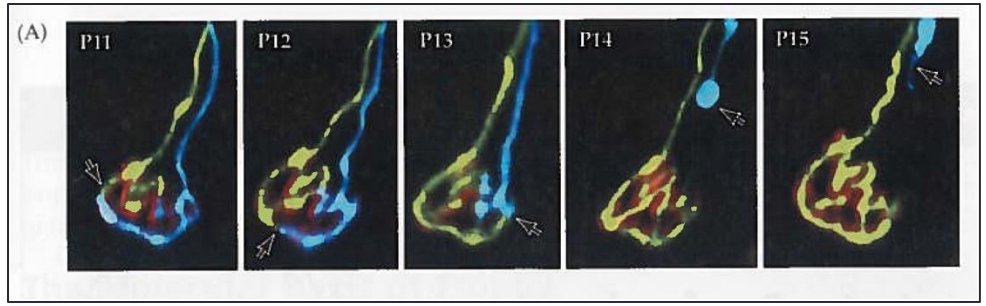
Axonogenesis – Synapse re-arrangement

- During development, connectivity gets rearranged towards more refined synaptic patterns
  - E.g., in early development muscle fibers are innervated by several motoneurons, but in the adult motor system, one muscle fiber is only innervated by one motoneuron







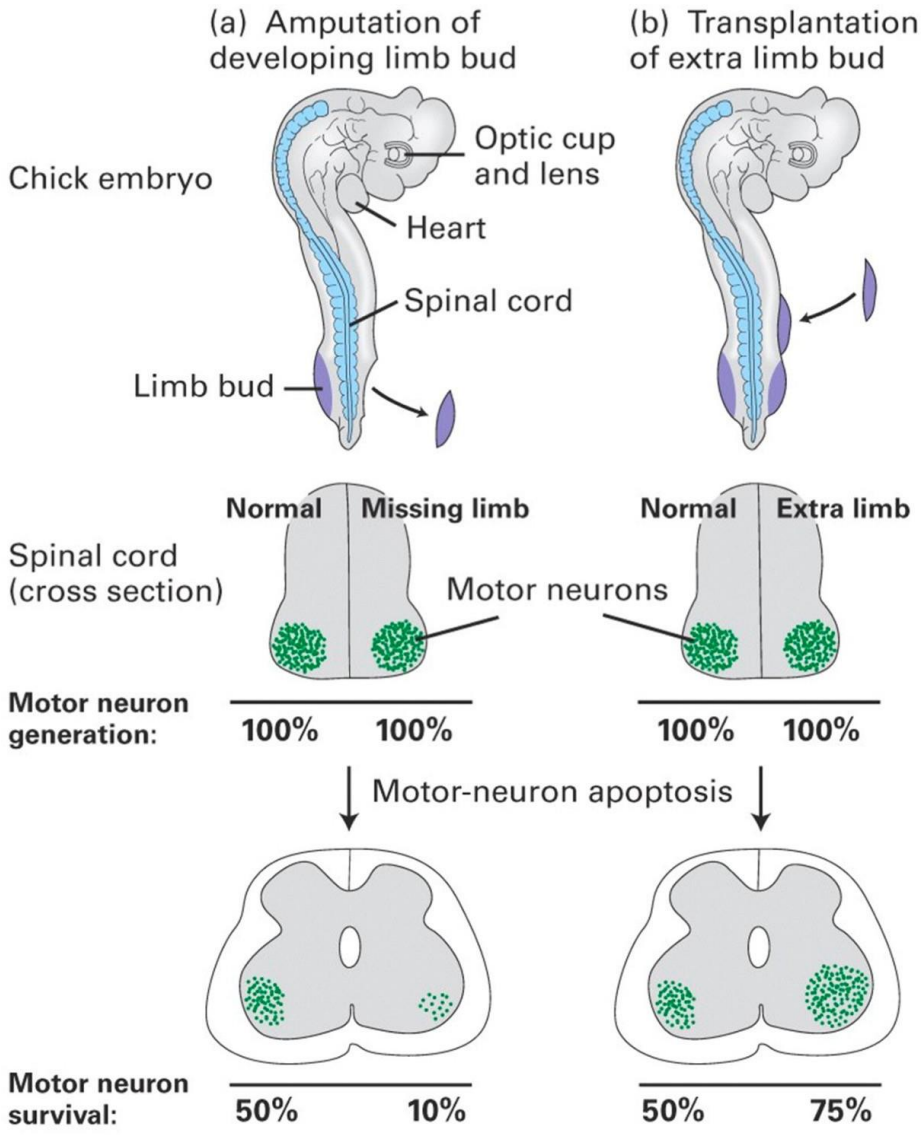


Axon A

Axon B

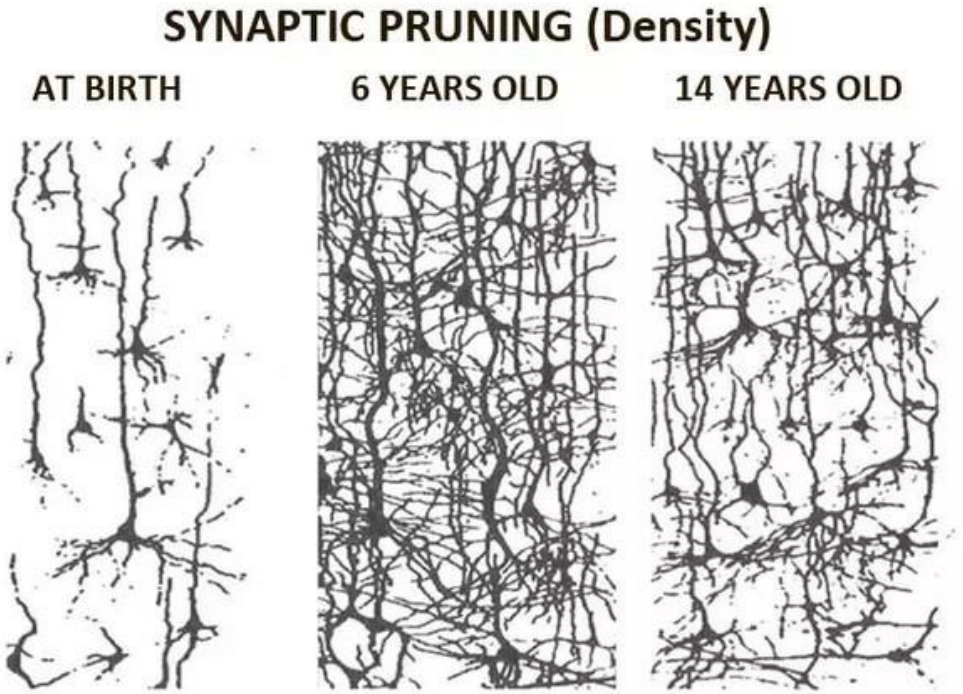
Axonogenesis – Synapse re-arrangement

- Neurons are created in excess during development
- Apoptosis adjusts number of nerve cells to size of targets



Axonogenesis – Synaptic pruning

- **Elimination of synapses when not used**
- mediated by microglia or astroglia



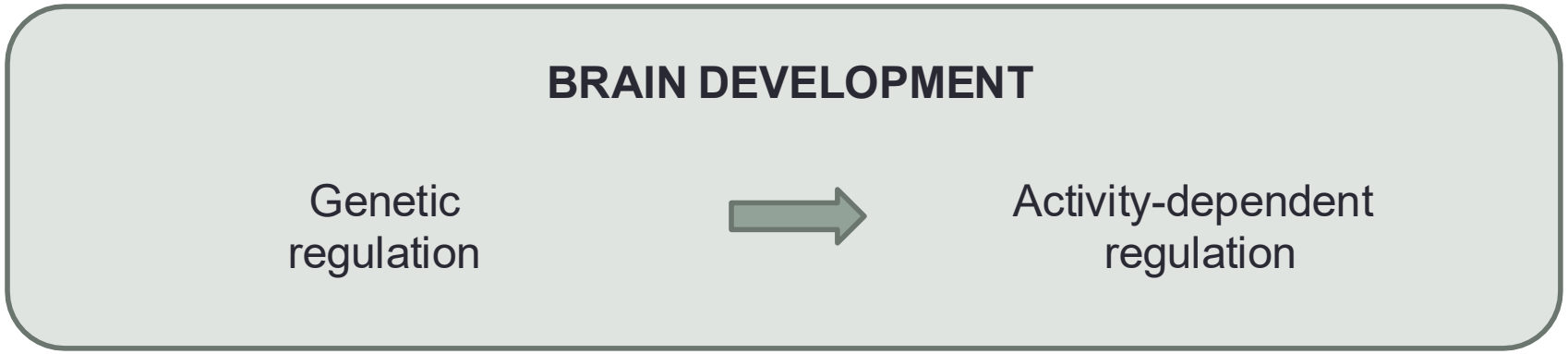
Synapses (neural connections) are created with astonishing speed towards 7 years old, the "synaptic growth spurts" become dense. By teenage years, pruning occurs to remove excess connections in order to make a more refined and efficient adult brain.

Neurodevelopment

1) Neurulation and establishment of cellular identity

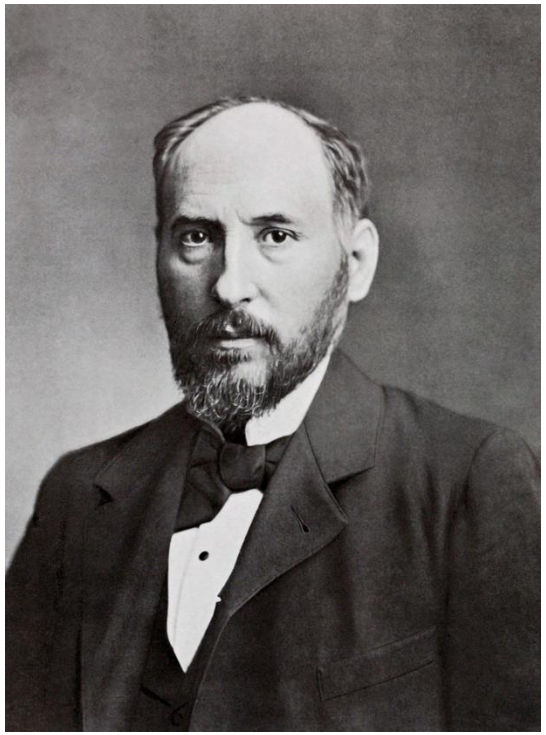
2) Stem cells and neurogenesis

3) Neuronal migration and axonogenesis



Adult neurogenesis

"*Once development was ended, the fonts of growth and regeneration of axons and dendrites dried up irrevocably. In the adult centers, the neural paths are something fixed and immutable: everything may die, nothing may be regenerated*"

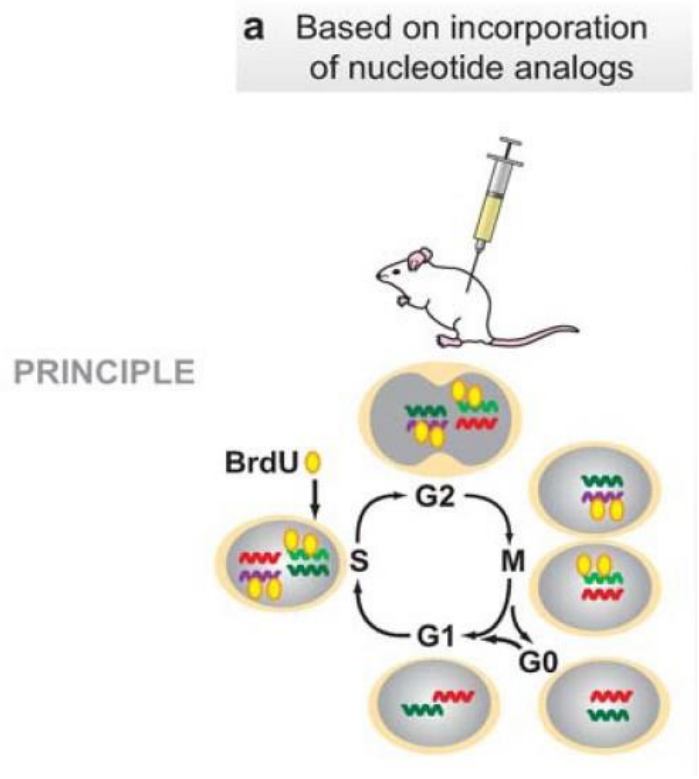


Ramón y Cajal

"…it is a duty for future generations find a way to overcome the intrinsic failure of adult brain to regenerate"

Early evidences of adult neurogenesis

- Joseph Altman, 1962-1967: adult rats injected with ^{3}H-thymidine to assess cell proliferation in response to cerebral lesions.
- Find labeled granule neurons in the dentate gyrus and olfactory bulb



Nucleotide analogs:
BrdU
EdU
CldU
IdU

➔ Indicate time of cell birth

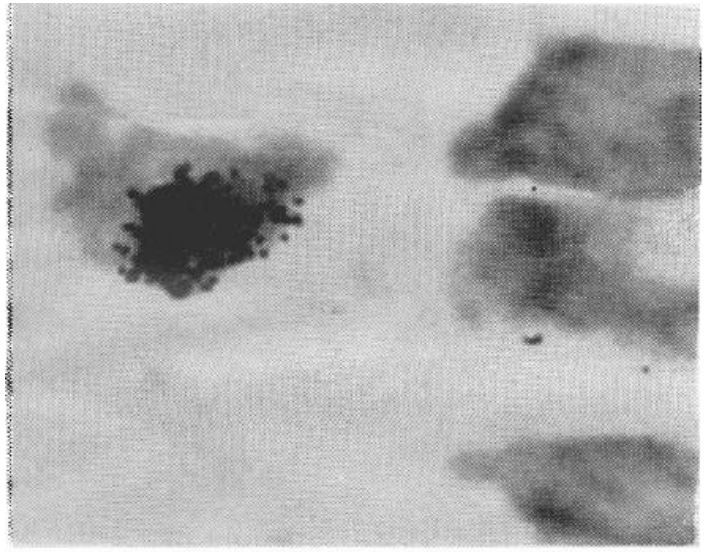
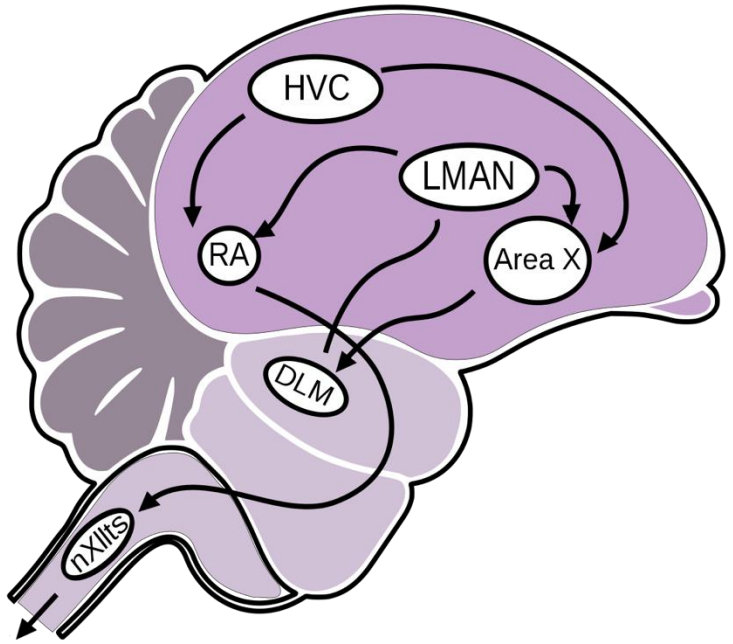


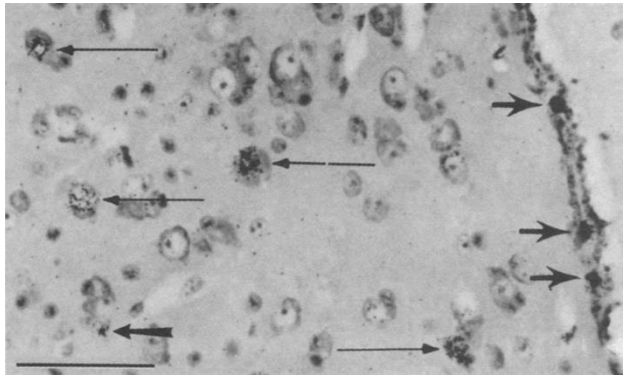
Fig. 2. Radioactive labeling of a neuron in the cerebral cortex of a rat which was sacrificed 1 month after the operation (about × 1170).

Early evidences of adult neurogenesis

- Nottebohm 1983: neurogenesis in the adult canary
- **HVC:** high vocal center, involved in song learning
- Sexual dimorphism:
  - Males sing many, complex songs, and have a big HVC whose size changes seasonaly
  - Females sing few simple songs, small HVC

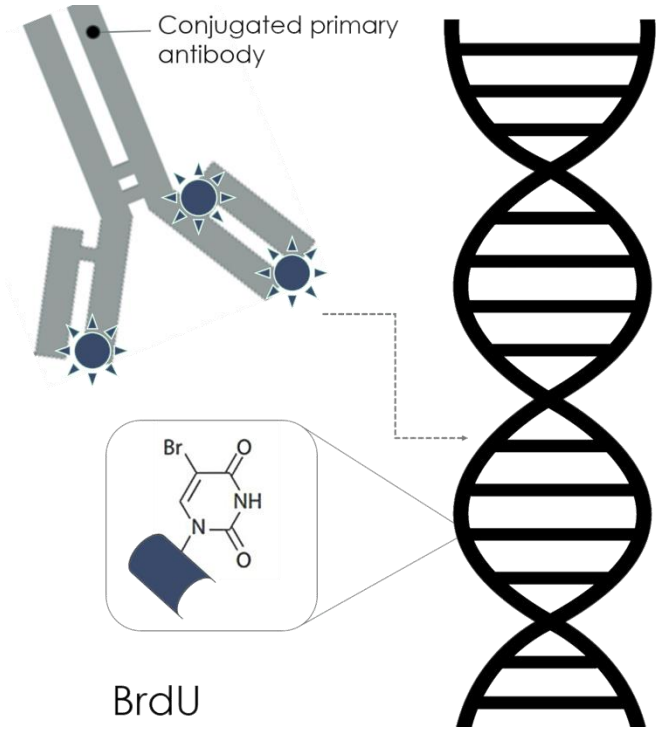


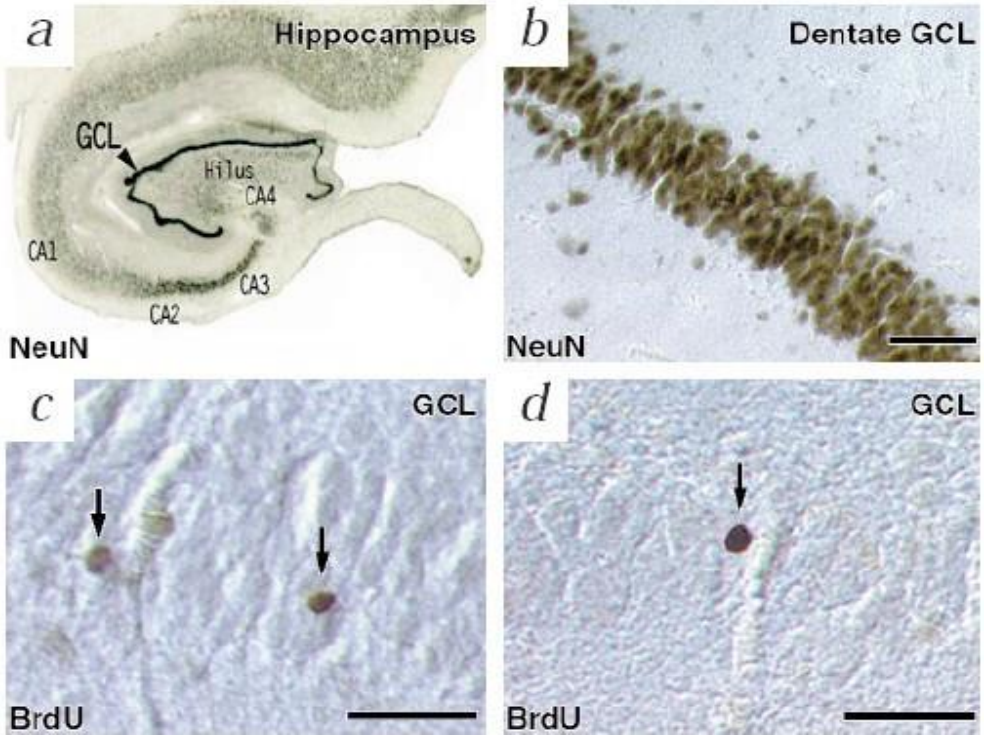
HVC
3H-Thym



Evidences of adult neurogenesis in humans

- Eriksson et al., 1998: postmortem brains of humans treated with BrdU

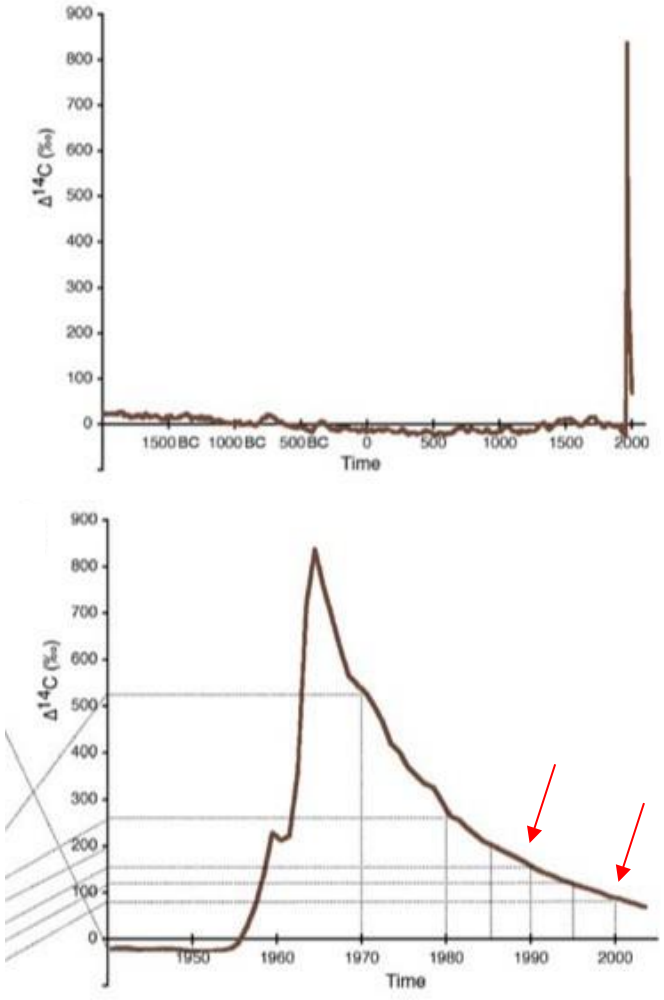


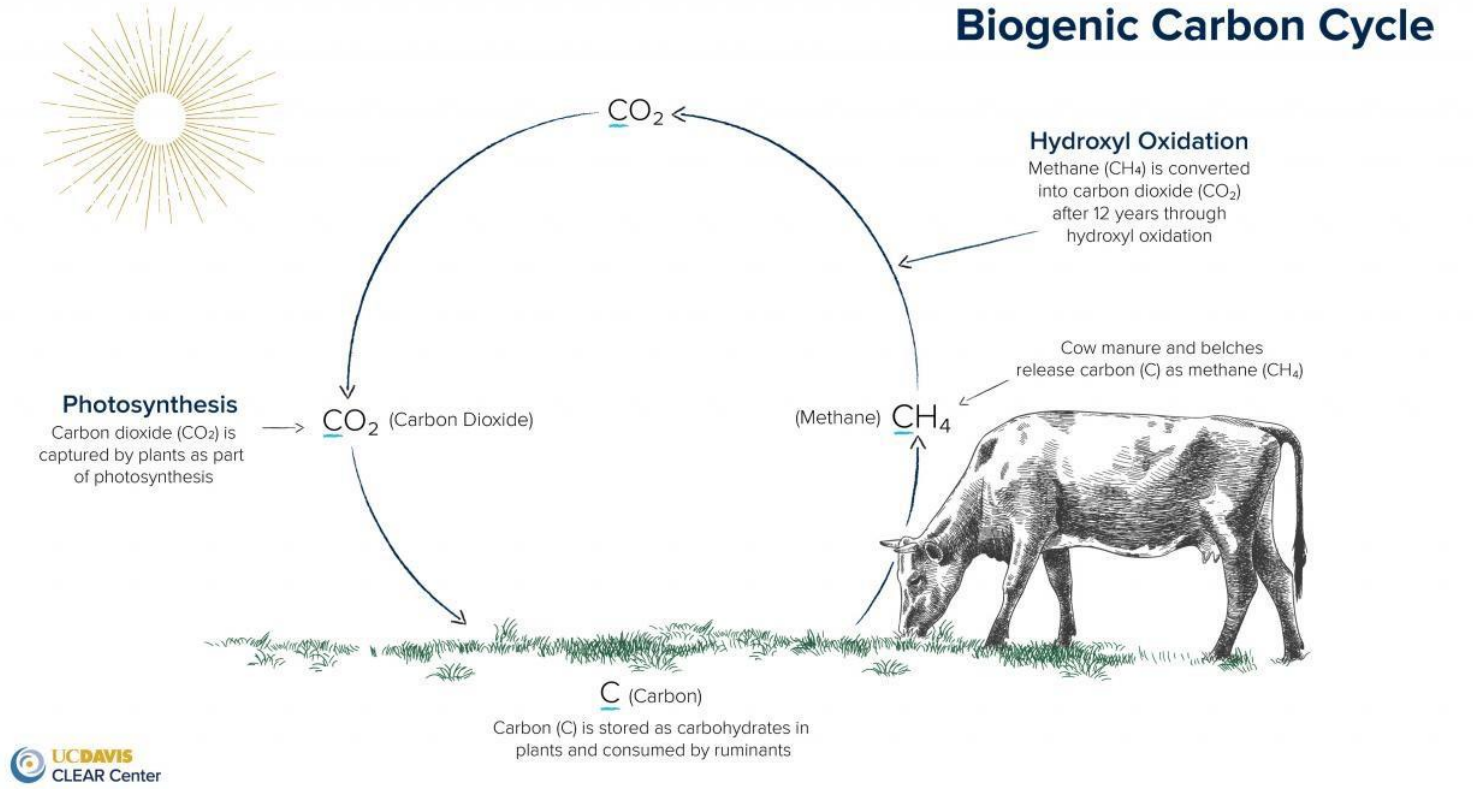


BrdU+, NeuN+ cells ➔ Neurons in the dentate gyrus

Evidences of adult neurogenesis in humans

- Spalding et al., 2013: ^{14}C approach



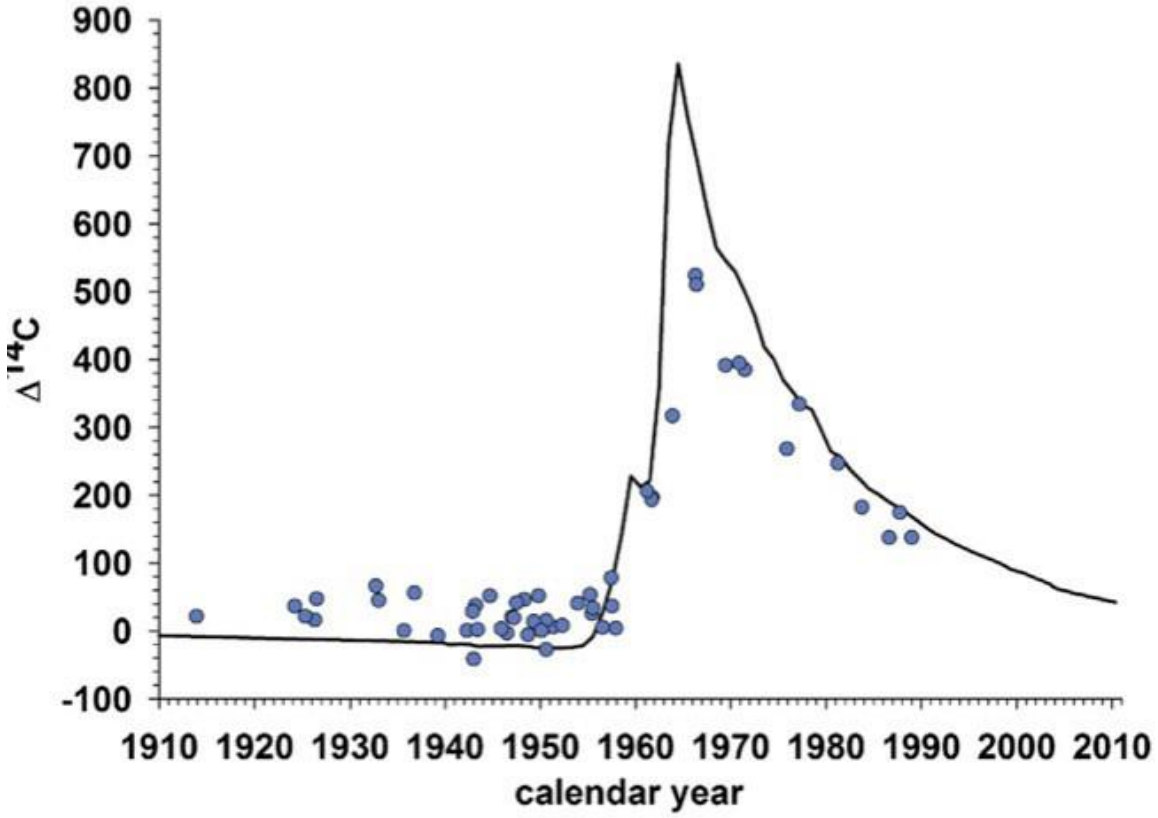


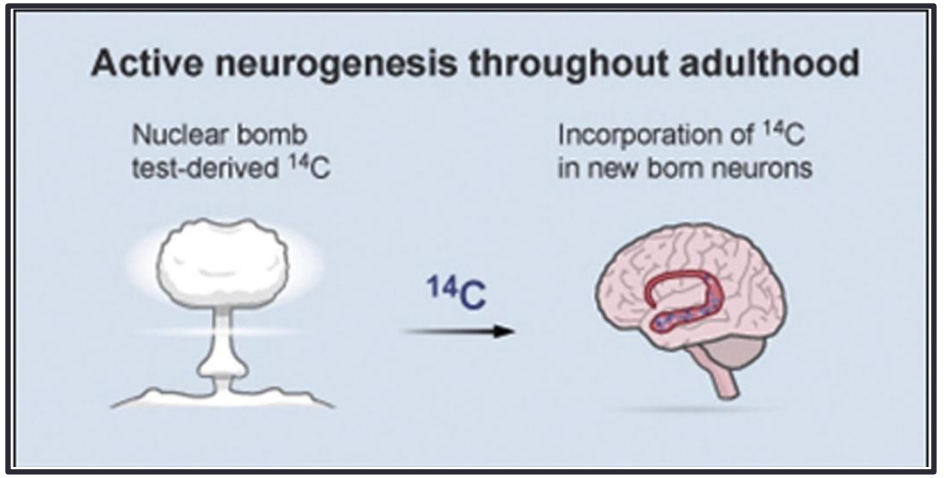
Tissues formed during development reflect the 14C signature of time of birth

Evidences of adult neurogenesis in humans

- Spalding et al., 2013: ^{14}C approach

Human hippocampus





The points represent the year of birth and 14C signature in hippocampus

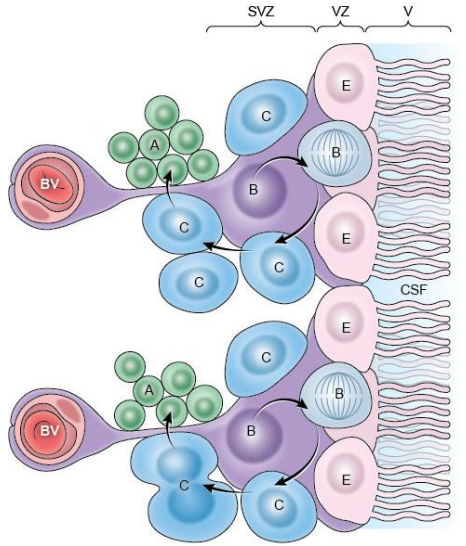
14C signature bigger than that of time of birth indicates generation of new neurons

Still, the presence of neurogenesis in humans is highly debated

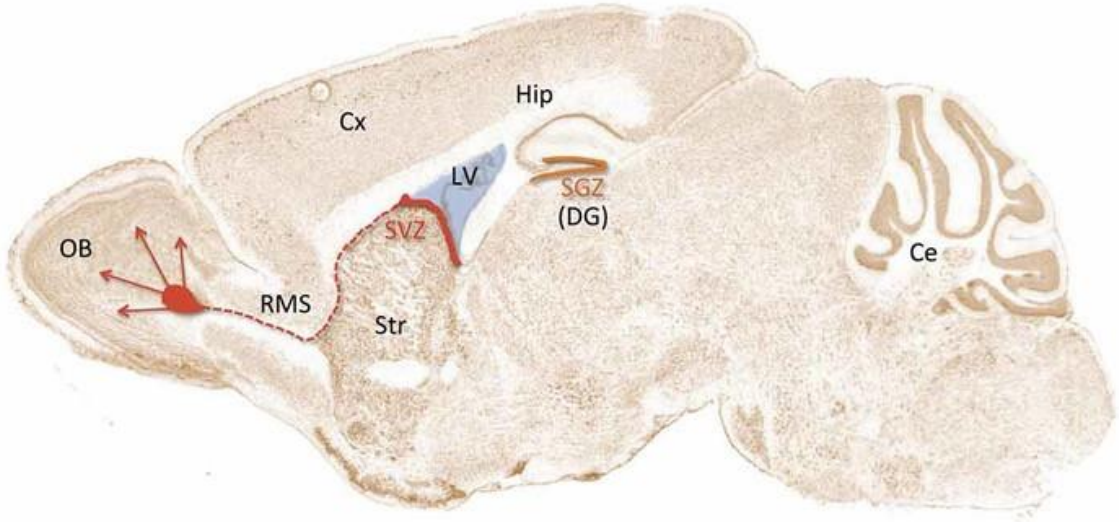
Adult neurogenic niches

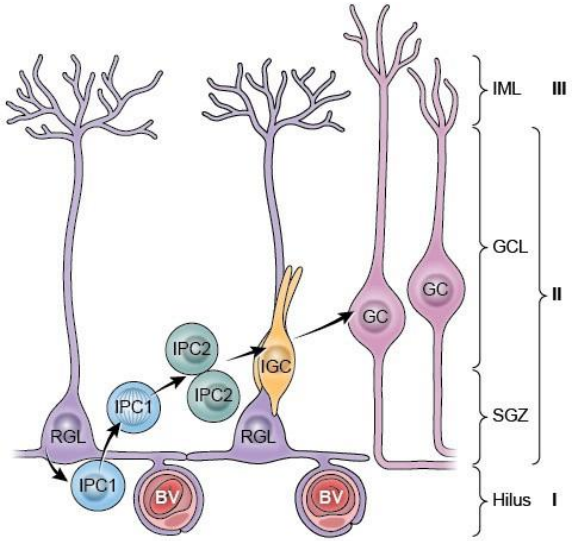
- **Neural stem cells** reside in the adult brain, surrounded by a special environment (niche, including blood vessels and glia)

- SVZ (subventricular zone) ➔ walls of the lateral ventricles
- SGZ (subgranular zone) ➔ hippocampal dentate gyrus



SVZ





SGZ

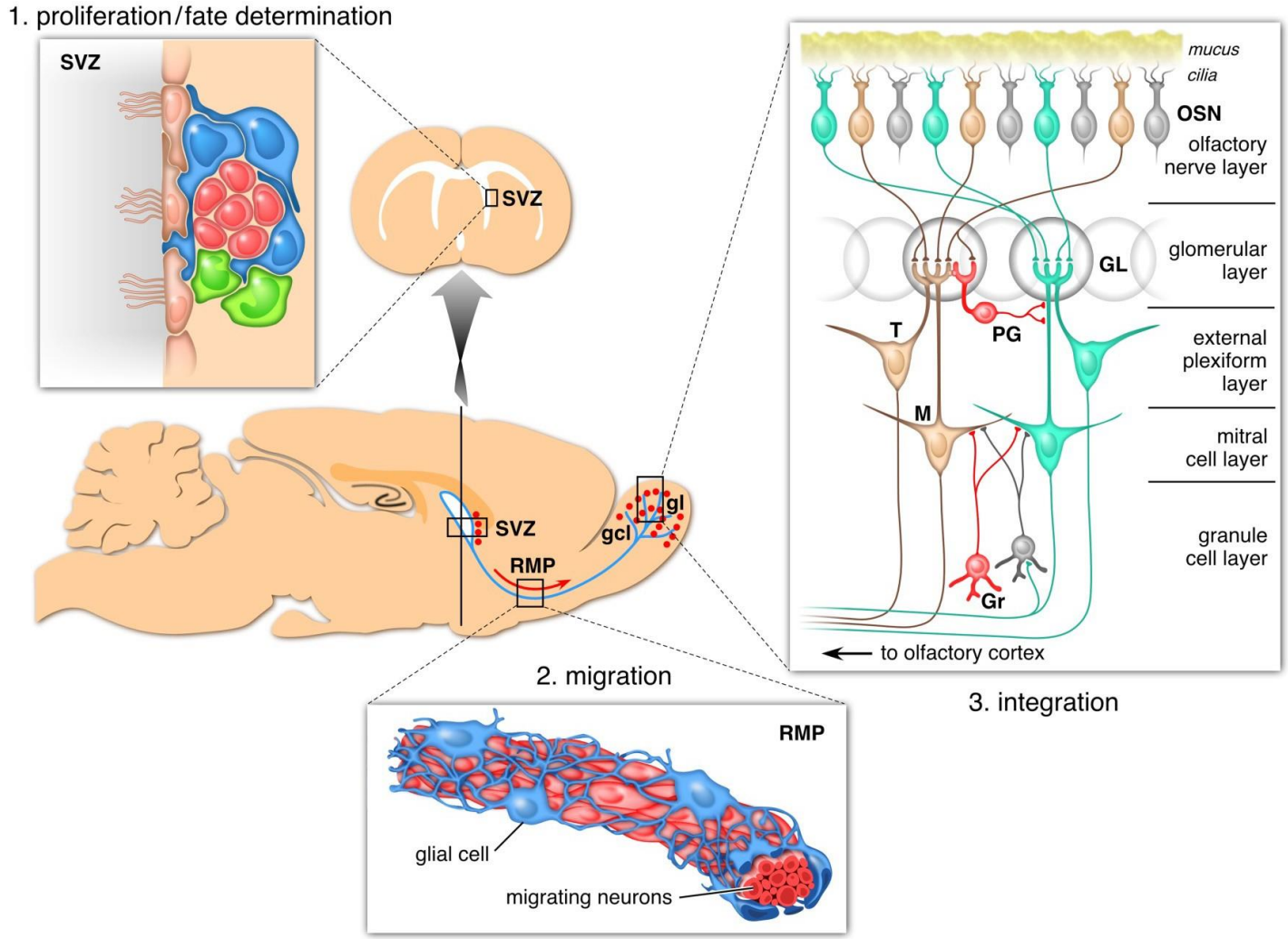
Adult neurogenic niches – SVZ

- B cells ➔ C cells ➔ A cells

NSC	Intermediate Progenitors	Neuroblasts
GFAP+	Dlx2+	DCX+

- Physiologically, neuroblasts migrate through the rostral migratory stream (RMS) to reach the olfactory bulb (OB)

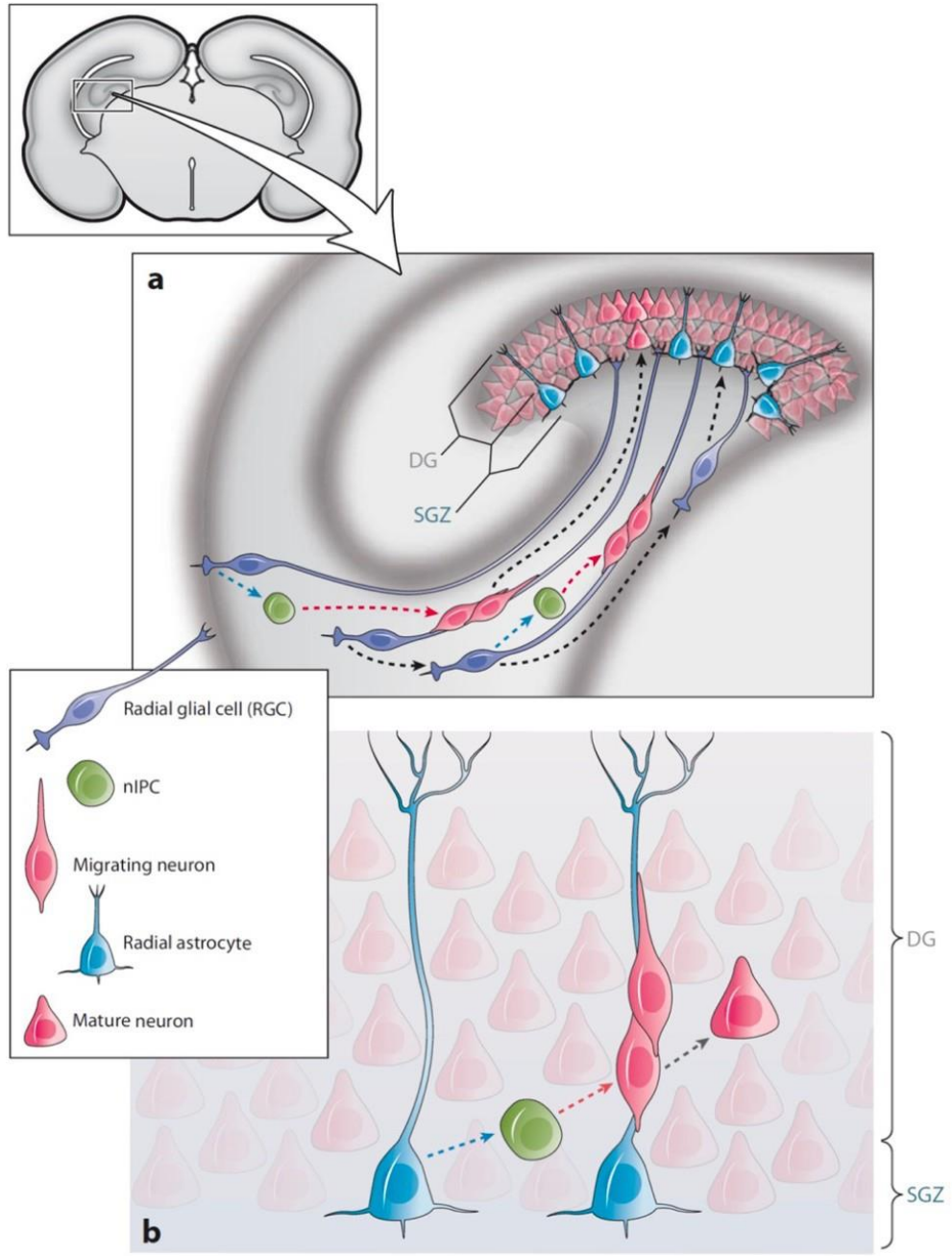
- In the OB, the differentiate into inhibitory interneurons important for odor discrimination



Adult neurogenic niches - SGZ

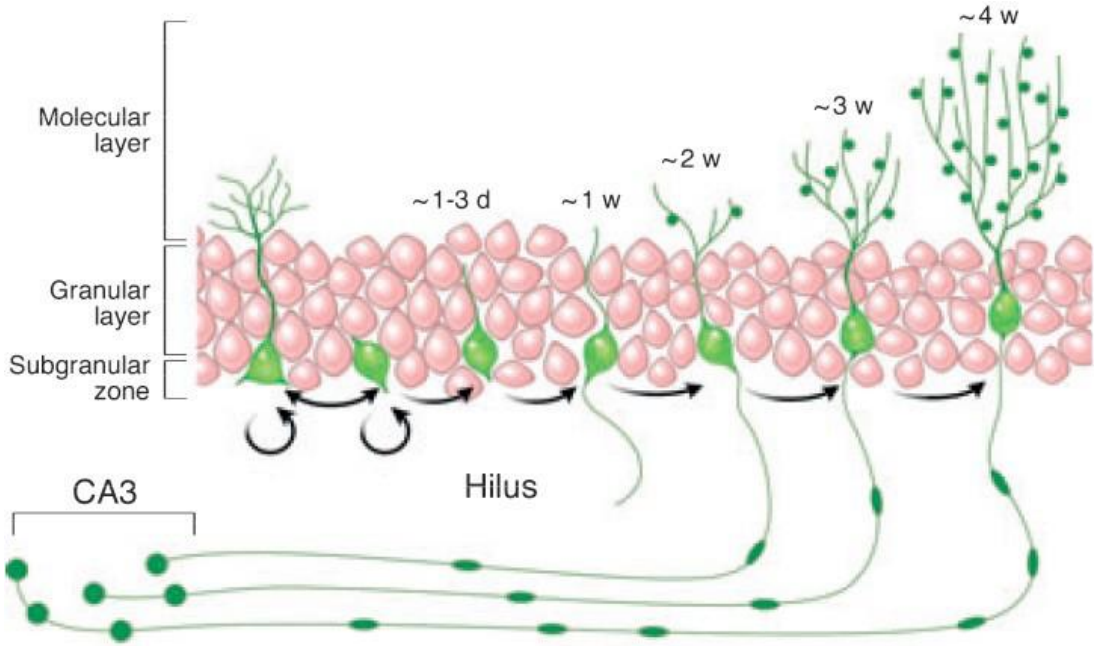
- The hippocampus derives from the cortical hem

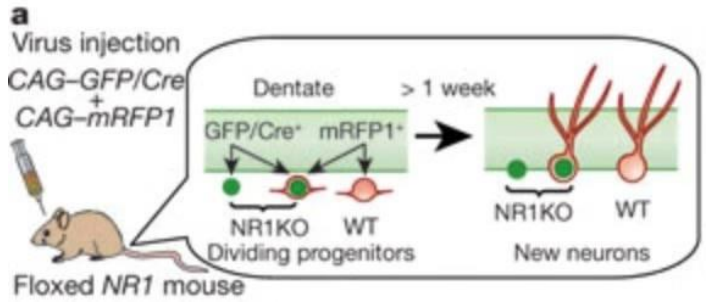
- Origin of adult hippocampal NSCs:
  - During development, radial glia cells delaminate and migrate towards the granule cell layer of the DG, forming the subgranular zone (SGZ)

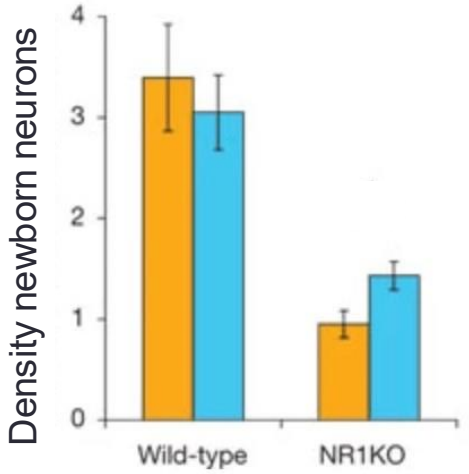


Adult neurogenic niches - SGZ

- Newborn neurons differentiate and integrate in the hippocampal memory circuits (around 4 weeks)
- Integration is an activity-dependent process





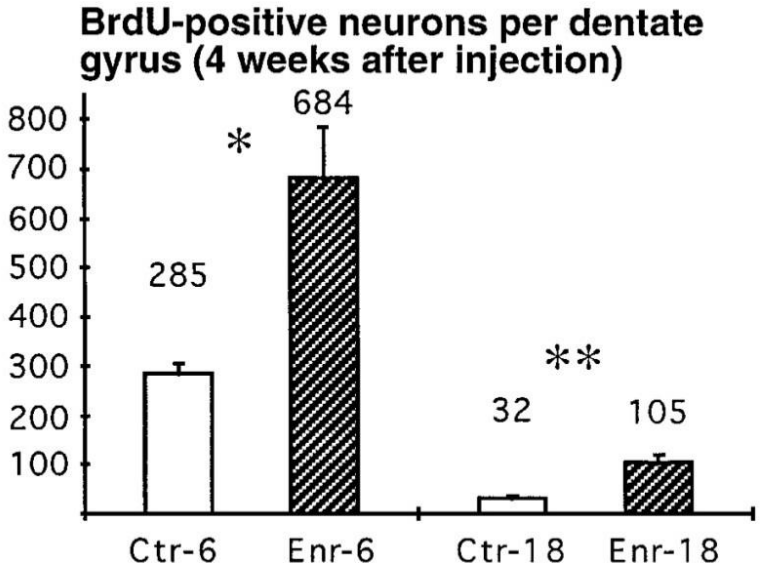


Retroviruses target exclusively dividing cells

➔ NMDA KO restricted to newborn neurons

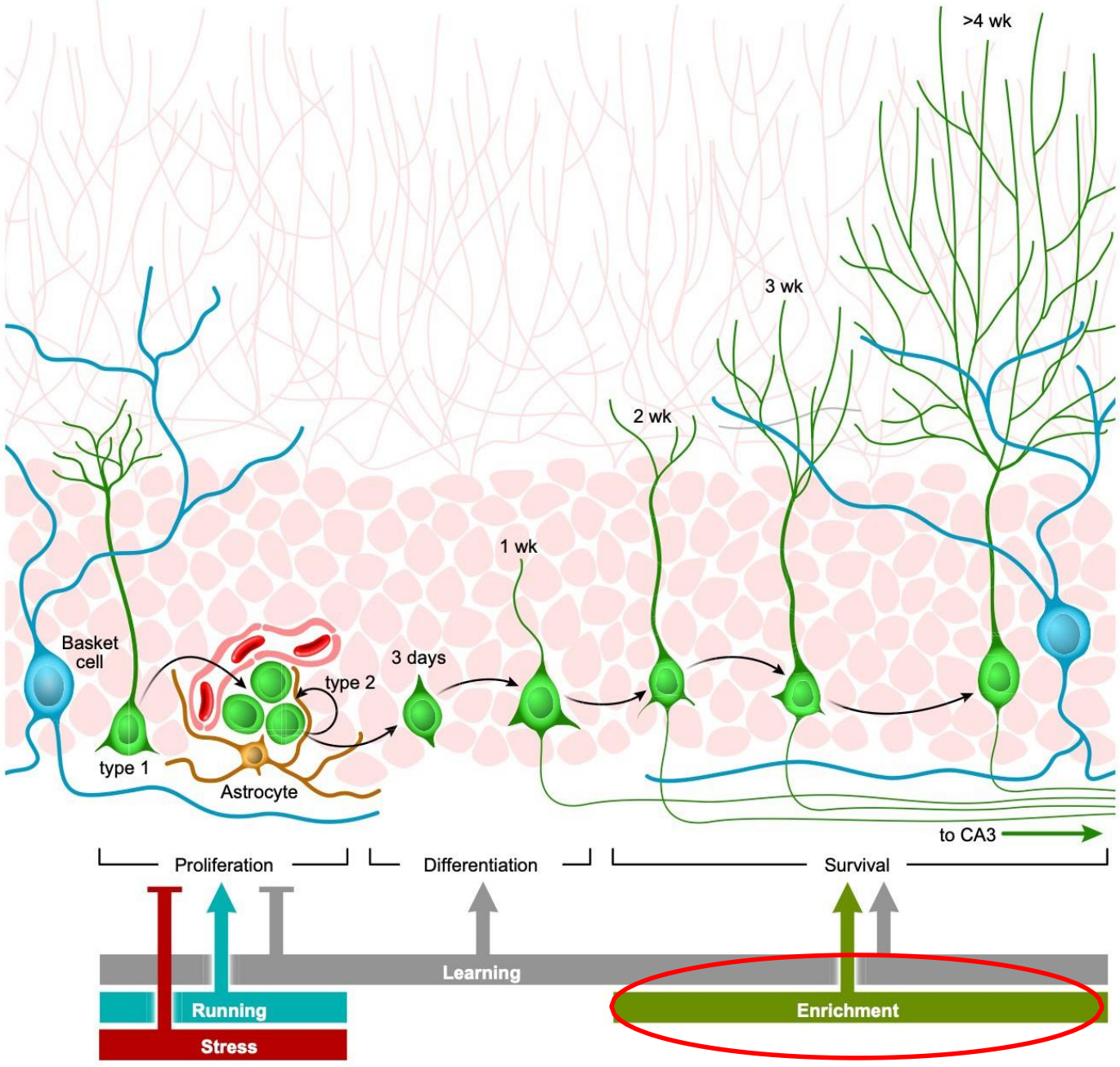
Adult neurogenic niches - SGZ

- Neurogenesis is influenced by many environmental factors



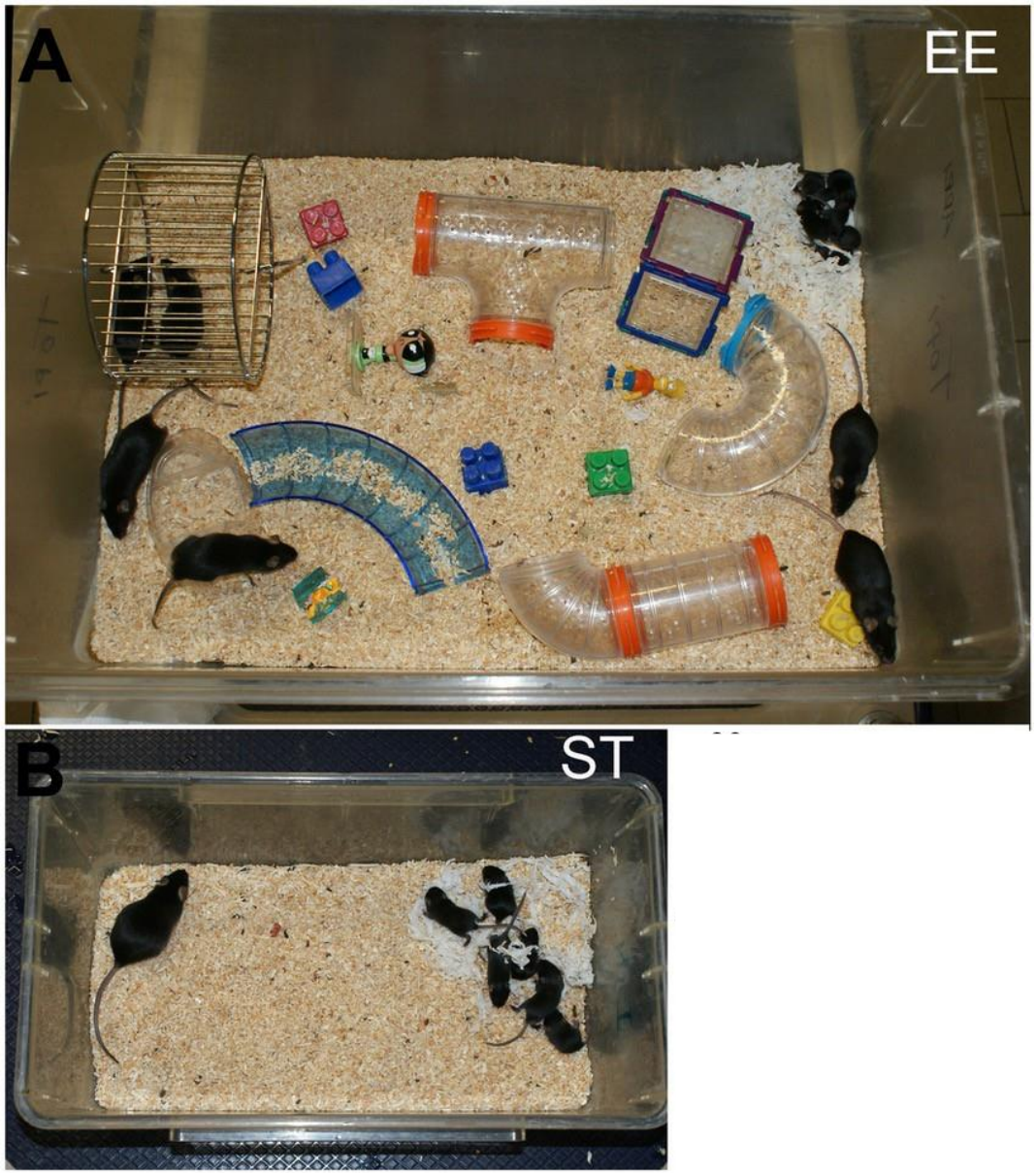
Environmental enrichment increases activity in hippocampus

Kempermann et al., 1998; Aimone et al., 2014



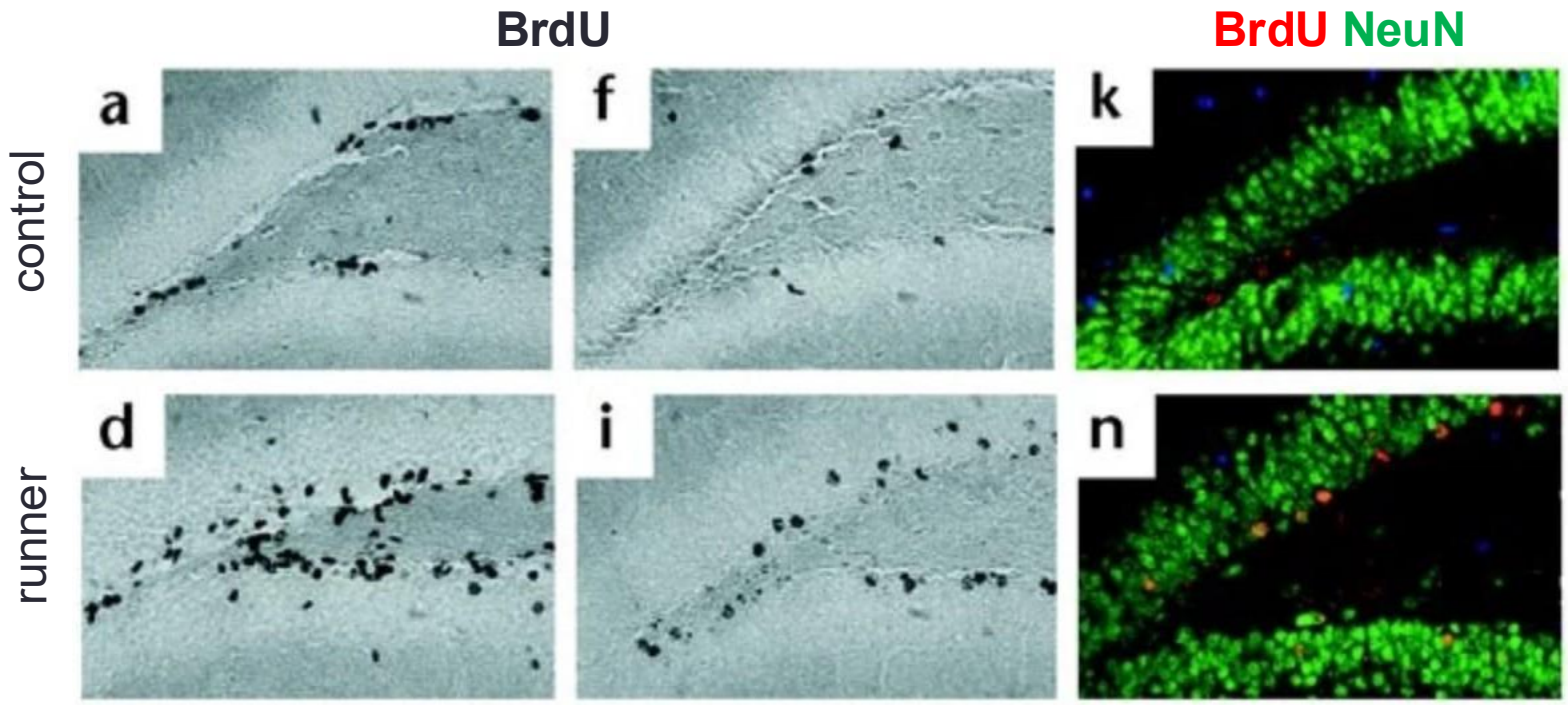
Adult neurogenic niches - SGZ

- Enrichment cage vs. standard cage

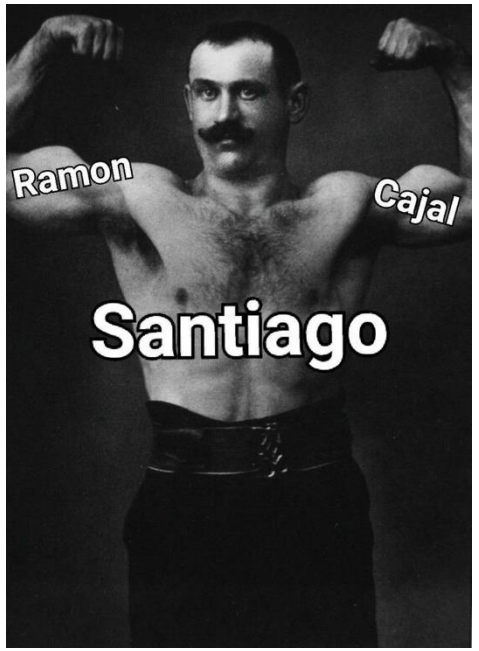


Adult neurogenic niches - SGZ

- Neurogenesis is influenced by running, physical exercise and learning itself
  - **Neurogenesis is a type of structural plasticity**



"Every man can, if he so desires, become the sculptor of his own brain"

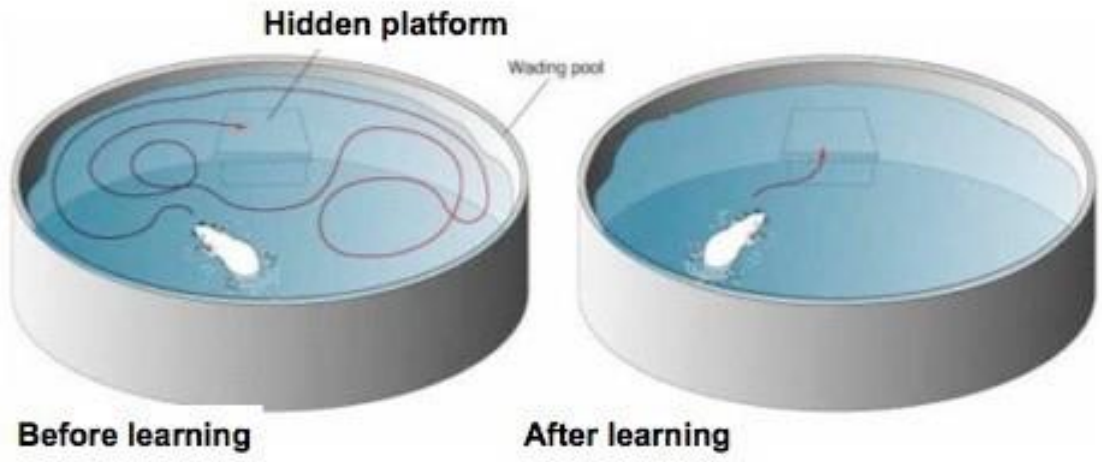


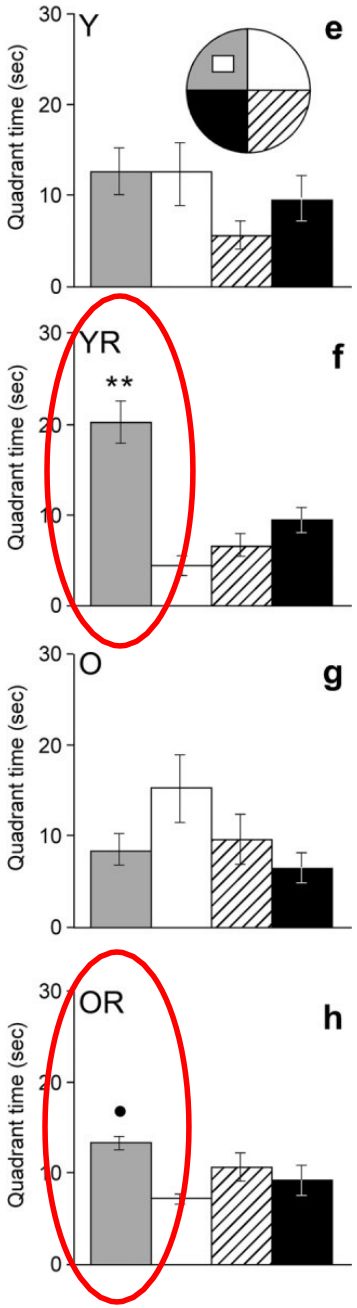
vanPraag et al., 1999

Adult neurogenic niches - SGZ

- In turn, exercise-induced neurogenesis improves hippocampal dependent behaviours

Morris water maze





vanPraag et al., 2005

New neurons in memory circuits

RESEARCH ARTICLE

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Adult-born neurons promote cognitive flexibility by improving memory precision and indexing

Gabriel Berdugo-Vega[1] | Chi-Chieh Lee[1] | Alexander Garthe[1,2] | Gerd Kempermann[1,2] | Federico Calegari[1]

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Increasing neurogenesis refines hippocampal activity rejuvenating navigational learning strategies and contextual memory throughout life

Gabriel Berdugo-Vega[1], Gonzalo Arias-Gil[2], Adrian López-Fernández[1], Benedetta Artegiani[1,4], Joanna M. Wasielewska[1], Chi-Chieh Lee[1], Michael T. Lippert[2], Gerd Kempermann[1,3], Kentaroh Takagaki[2] & Federico Calegari[1*]