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**SEMMELWEIS
UNIVERSITY**



Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.



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BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

Contributed by: Tamás Freund, Zsolt Liposits, Zoltán Nusser, László Acsády, Szabolcs Káli, József Haller, Zsófia Maglóczky, Nórbert Hájos, Emilia Madarász, György Karmos, Miklós Palkovits, Anita Kamondi, Lóránd Eröss, Róbert Gábrriel, Zoltán Kisvárday

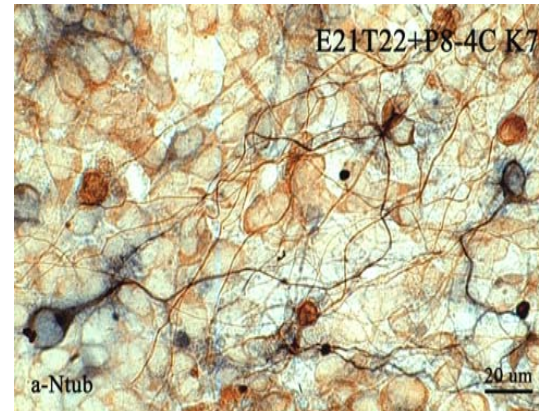
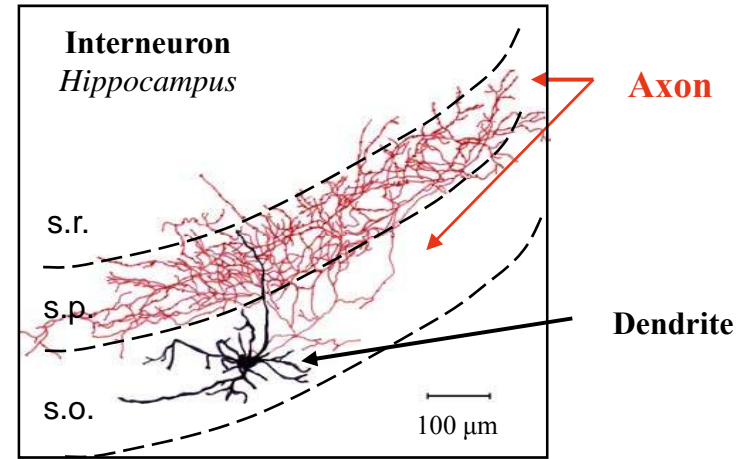
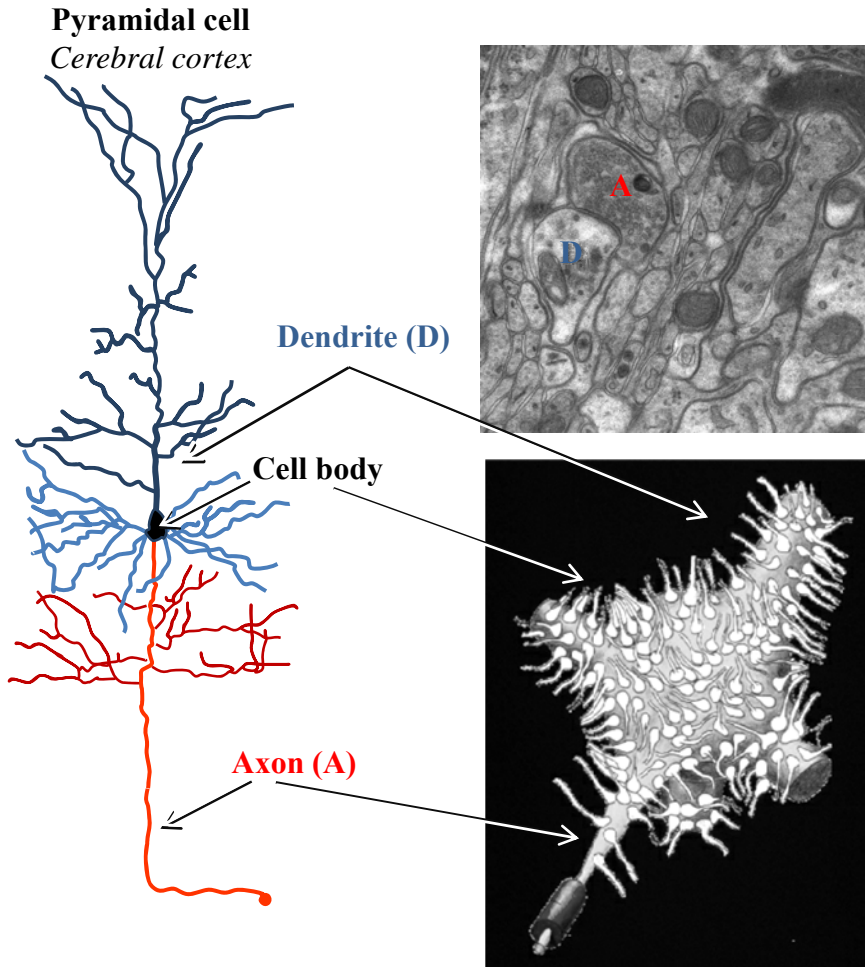
Stem cells and potential applications

Imre Kalló & Emilia Madarász

Pázmány Péter Catholic University, Faculty of Information Technology

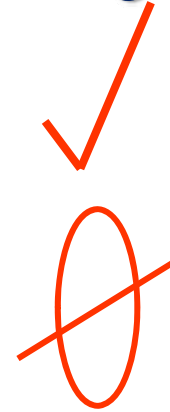
- I. Undifferentiated cells during embryogenesis and throughout life
- II. Proliferation versus differentiation
- III. Migration, axonal growth and synapse formation
- IV. Potential application of stem cells; from experiments to therapy

Neurons maintain a complex cellular morphology



Two dogma persisted about neurons for a long time

1. Mature neurons do not divide:
2. We have to manage our life with the set of neurons present at early postnatal period:



1984 Nottebohm: song-birds

1992 Reynolds és Weiss: rodents, human

Conclusion of these studies:

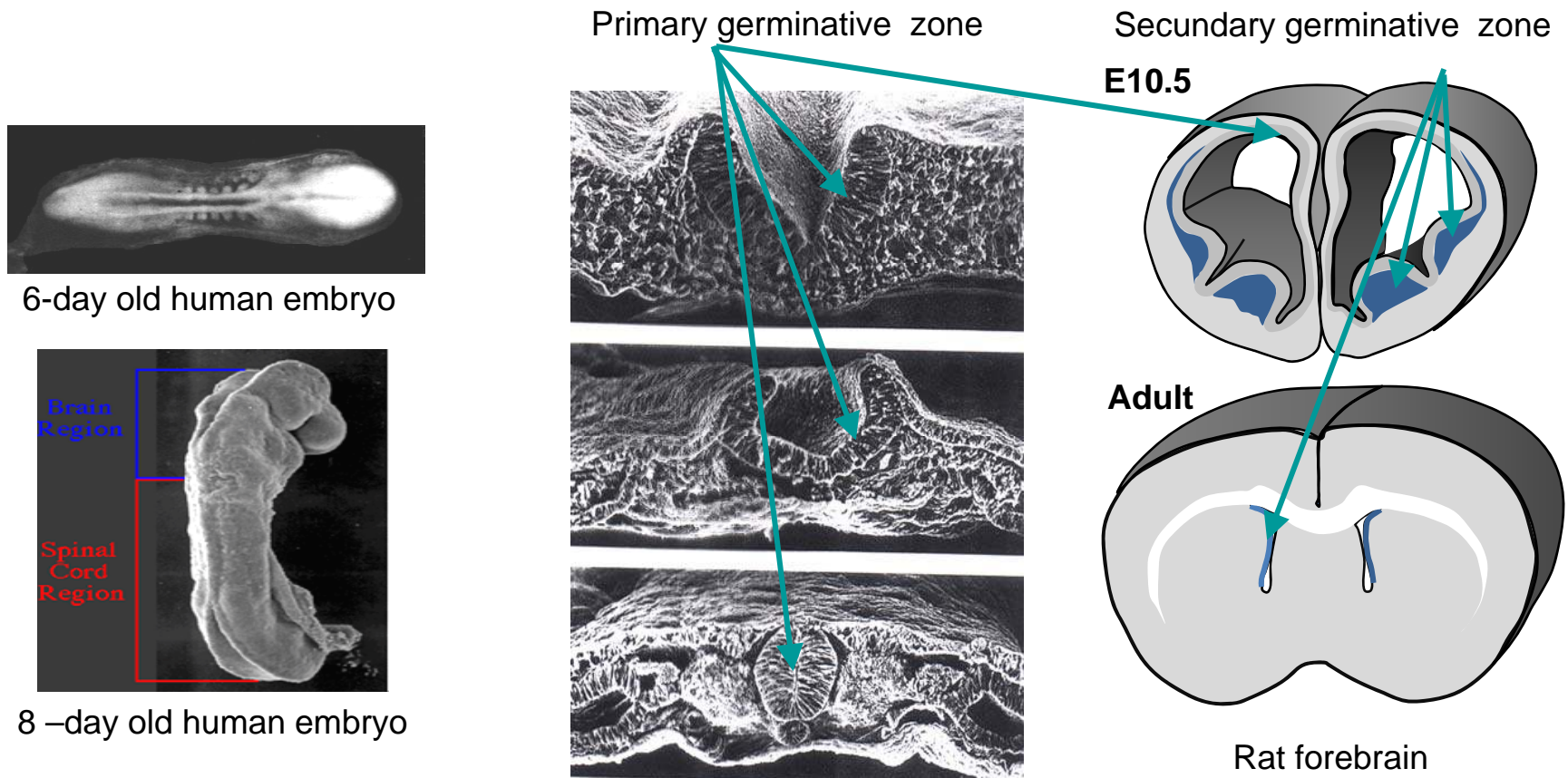
Nondifferentiated cells with the capability to produce new neurons are present throughout life.

Where are the neurogenic zones?

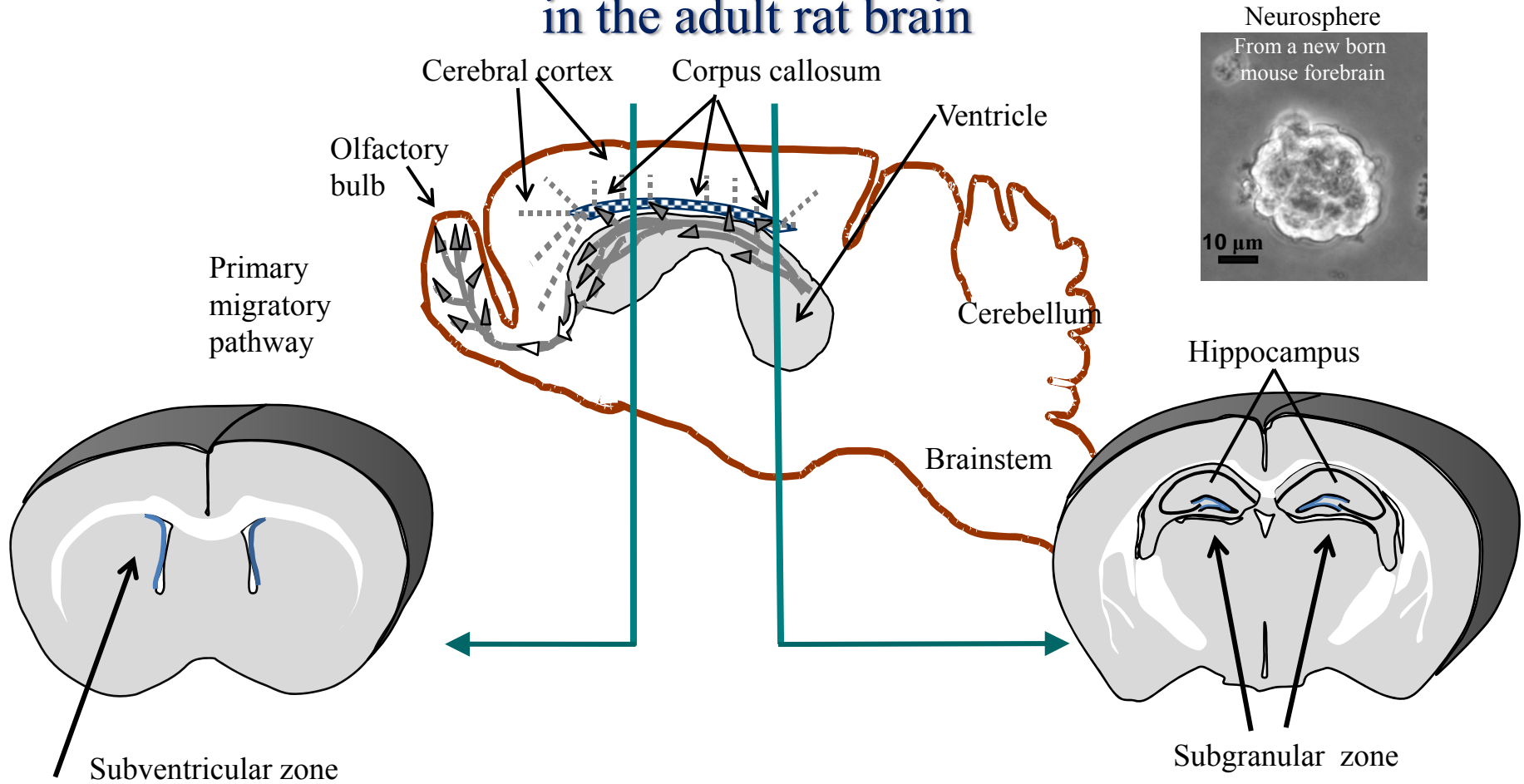
Location of proliferating cells (forming a germinative layer) in the neural primordium of human and rat embryos

The neural plate comprises the shoehorn-shaped dorsal thickening of the ectoderm at the rostral end of the early embryo. The neural plate forms the neural tube, which initially remains open at the caudal and rostral ends. The rostral part of the neural tube establishes the primordium of the brain. The neural tube is composed of a single layer of proliferating cells, the primary germinative layer. A second germinative layer appears in later stages of embryonic development under the ventricular wall through-out the entire neuraxis. In the ventral part of the forebrain the subventricular zone is the best explored residence of the stem cells during adulthood. Similar important adult neurogenic zone, the subgranular zone is located beneath the granule cell layer of the hippocampus.

Location of proliferating cells (forming a germinative layer) in the neural primordium of human and rat embryos

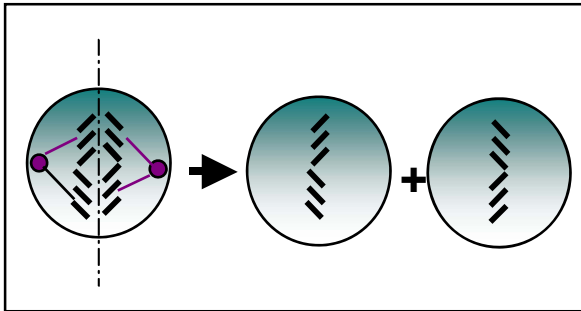


Location of stem cells (with the capability to proliferate) in the adult rat brain

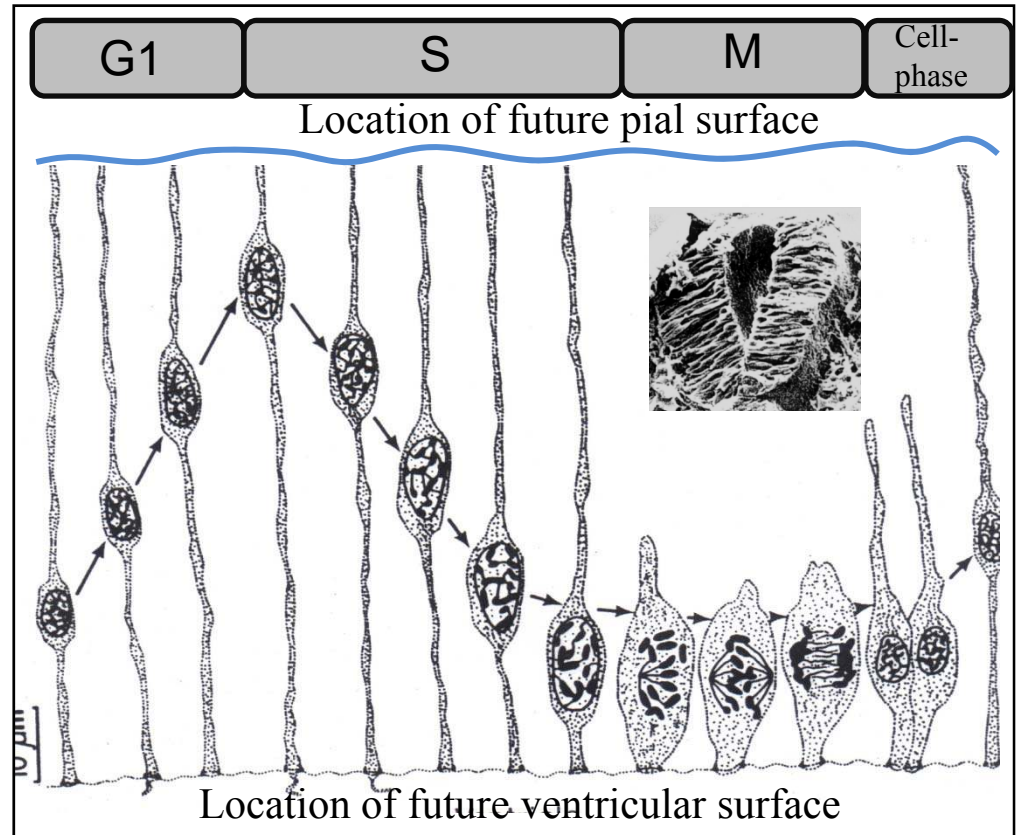
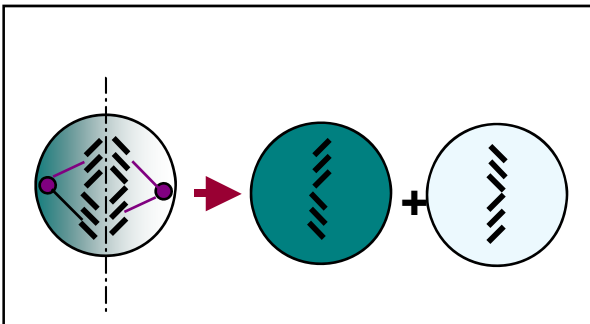


Cell proliferation and interkinetic migration of the cell nucleus in the primary ventricular zone

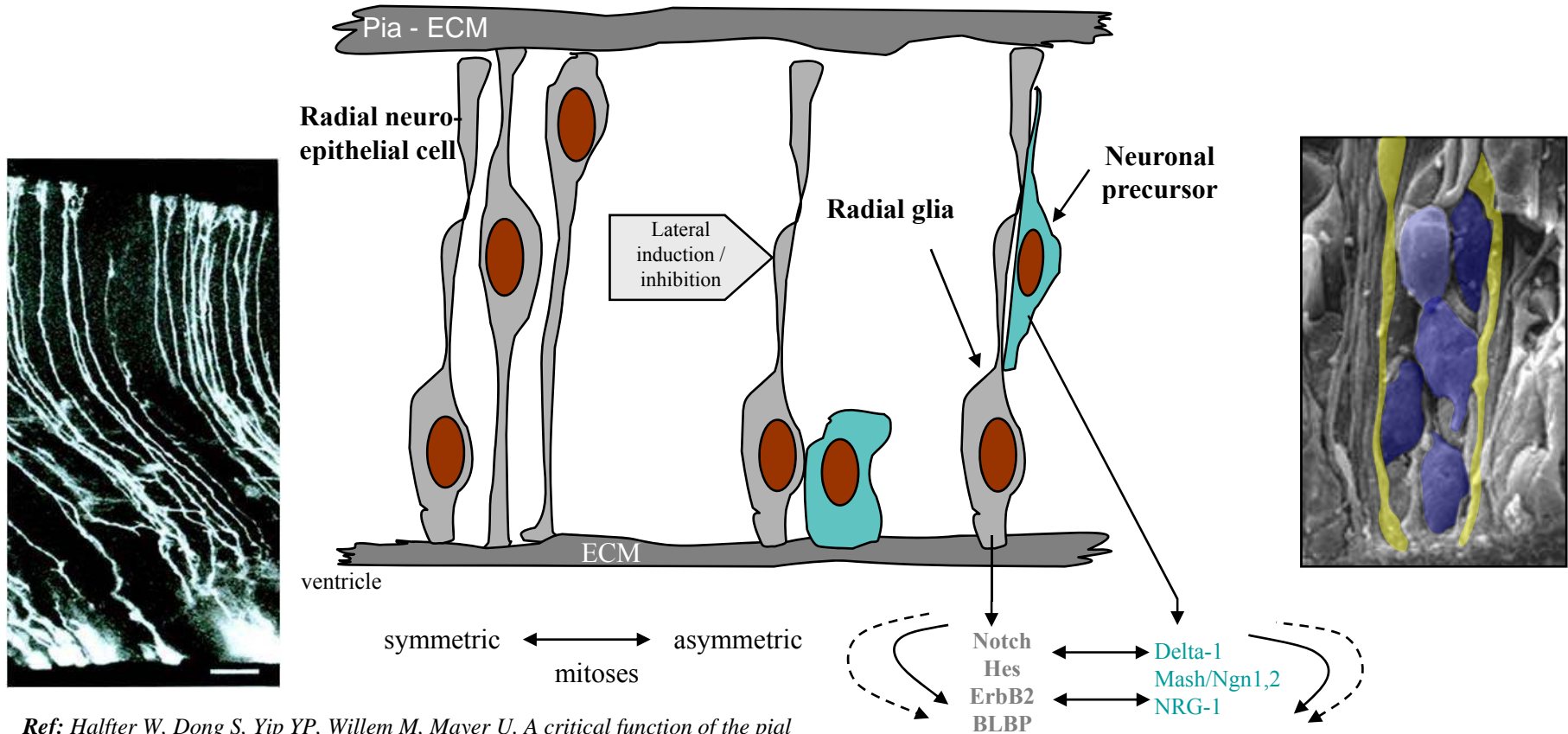
Symmetrical mitosis



Asymmetrical mitosis



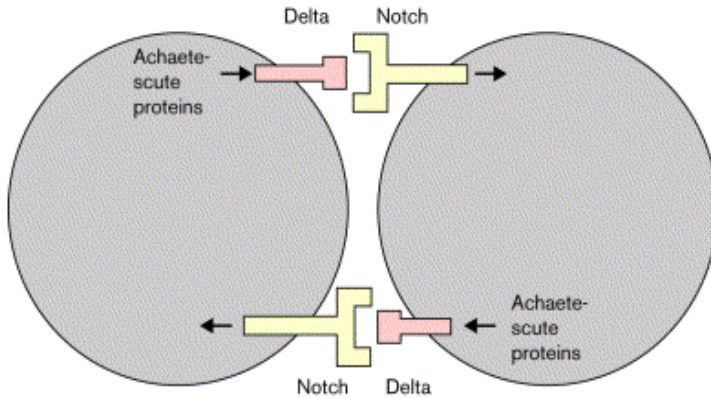
Cell proliferation and interkinetic migration of the cell nucleus in the primary ventricular zone



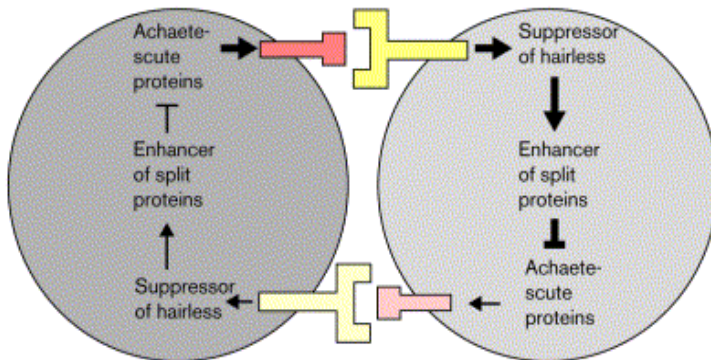
Ref: Halfter W, Dong S, Yip YP, Willem M, Mayer U. A critical function of the pial basement membrane in cortical histogenesis. *J Neurosci.* 2002 Jul 15;22(14):6029-40.

Notch/Delta system

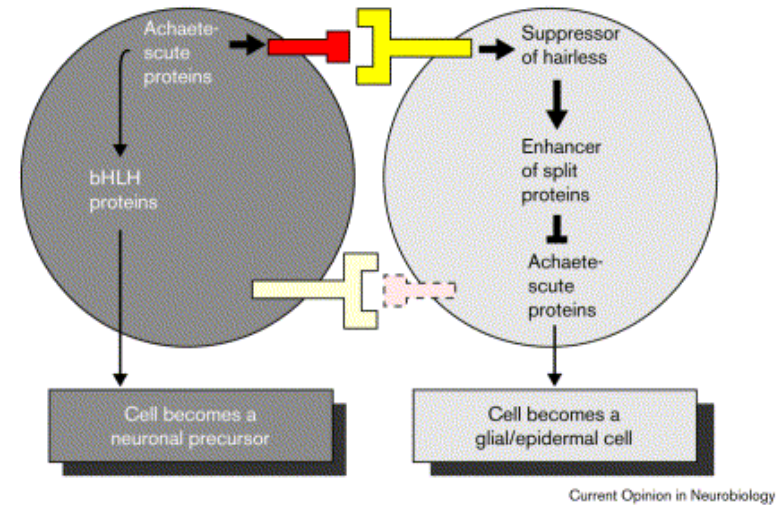
(a) Initially, Notch signaling between cells is balanced



(b) An imbalance in Notch signaling develops

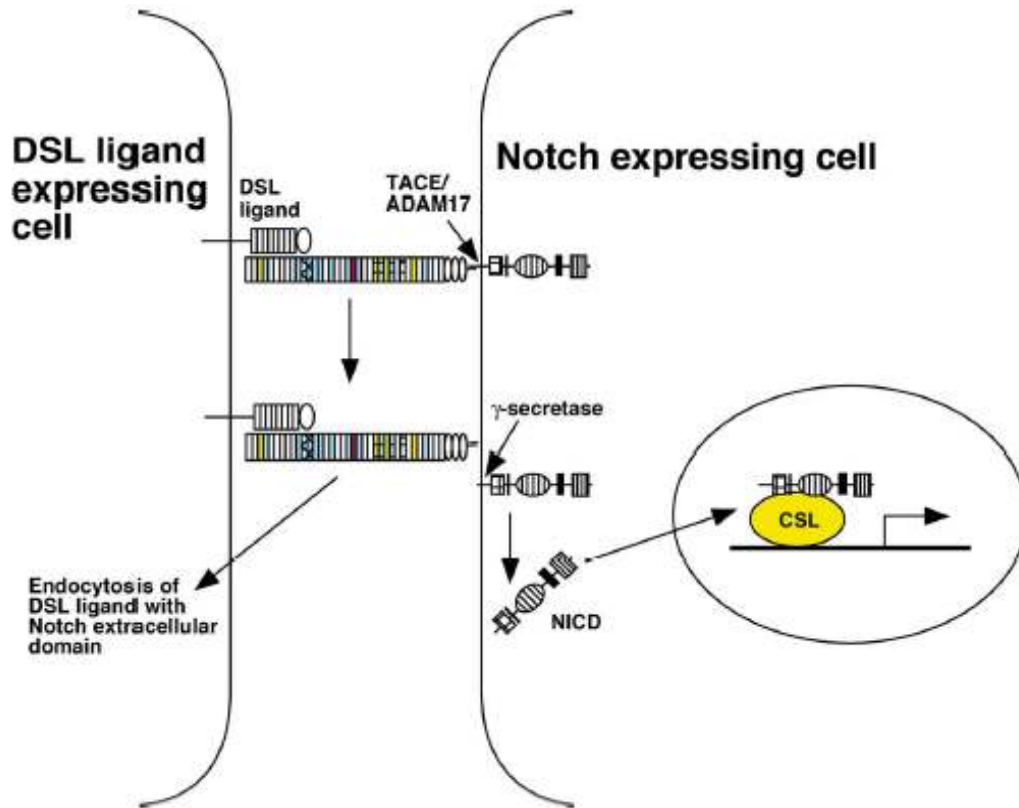


(c) The imbalance is quickly amplified, leading to development of a neuronal precursor



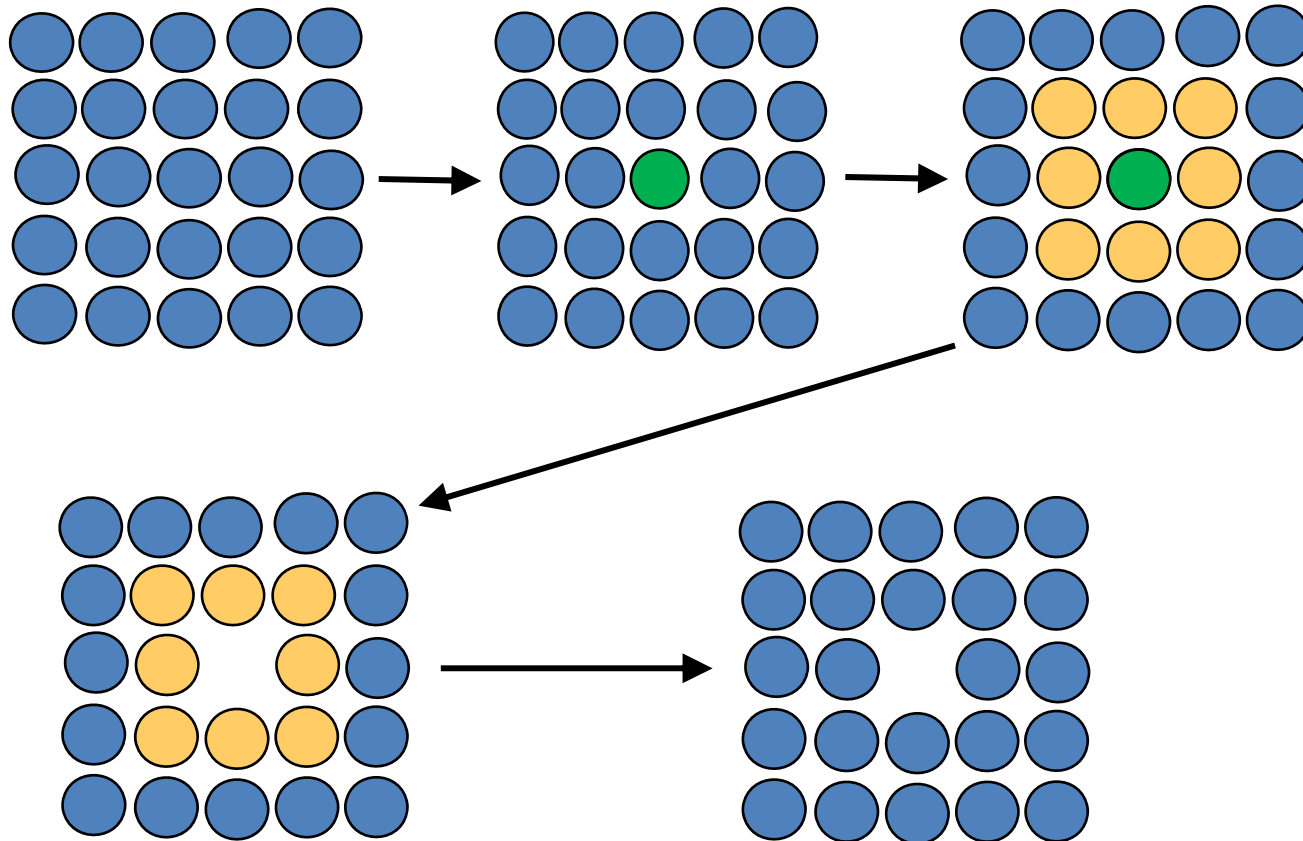
In general:
differentiating cell **undifferentiating cell**

Signalling pathways activated



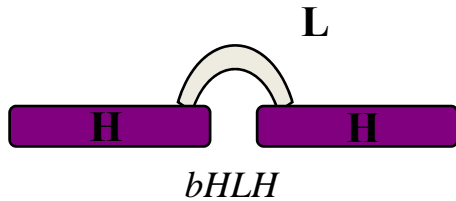
DSL – Delta, Serrate, Lag-2
 CSL – CBF1, Su(H), Lag-1
 NICD – Notch IntracelluIlar Domain
 TACE/ADAM17 – TNF α Converting Enzyme
A Disintegrin And Metalloprotease

Lateral inhibition (Drosophila proneuronal cluster)



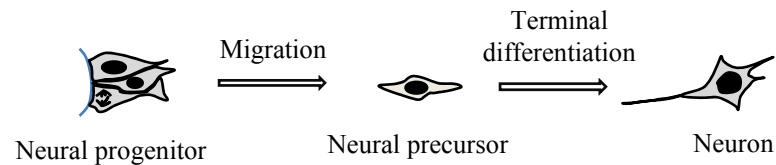
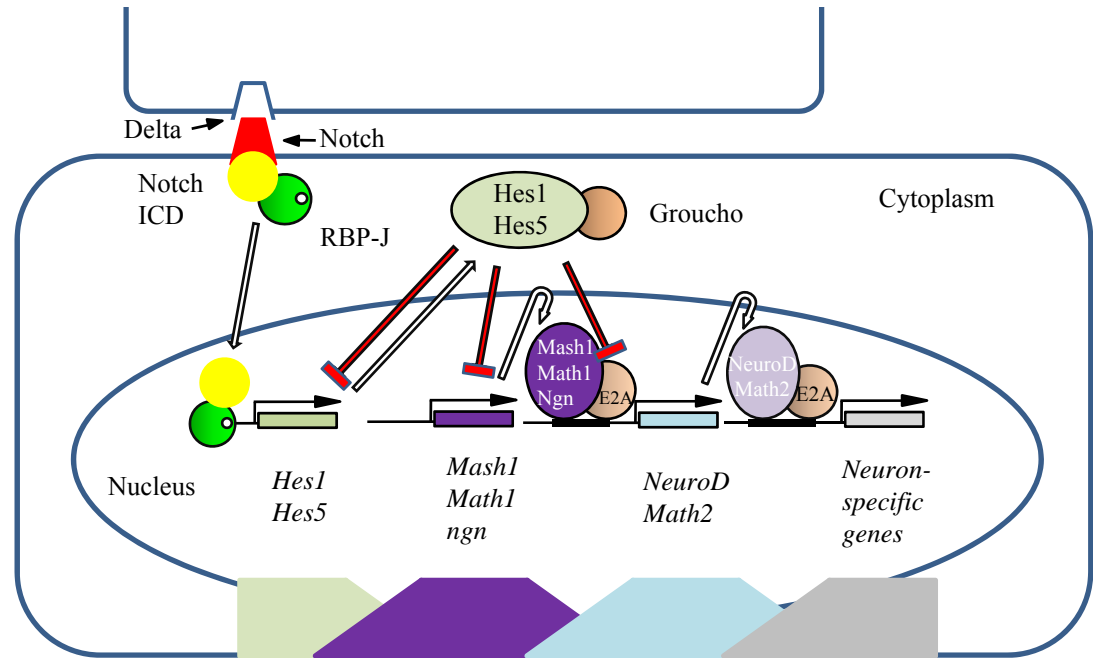
Role of bHLH transcription factors during differentiation

Basic helix-loop-helix transcriptional factors



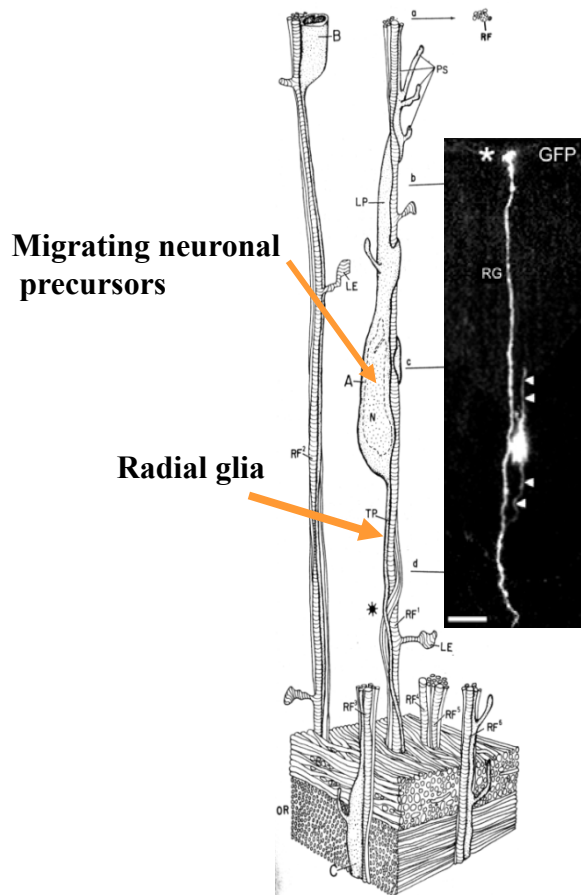
Pro-neural
Mash 1..., Ngn 1,2,
Math 1

Neural
Math 2, NeuroD

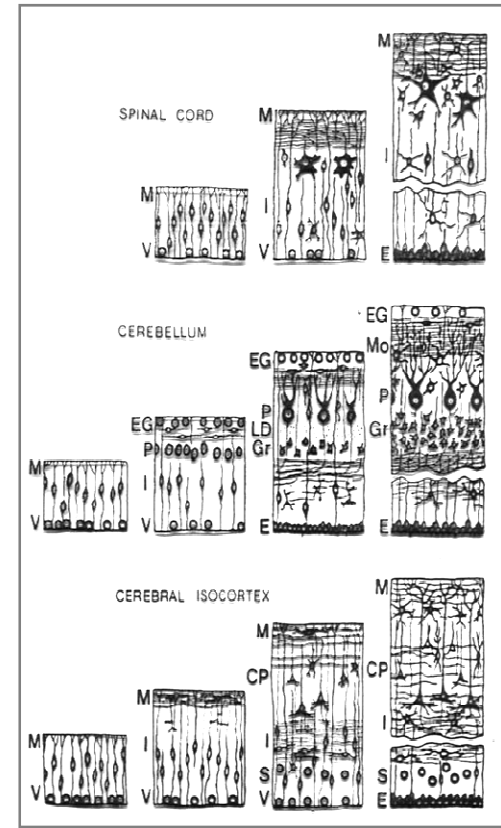
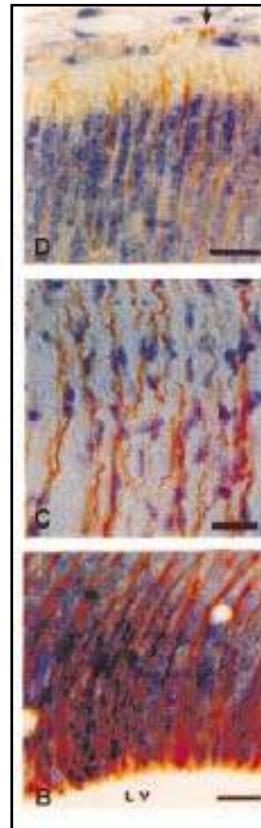


Ryoichiro Kageyama and Shigetada Nakanishi; Current Opinion in Genetics & Development 1997, 7:659-665

Migration of embryonic cells from the primary germinative zone

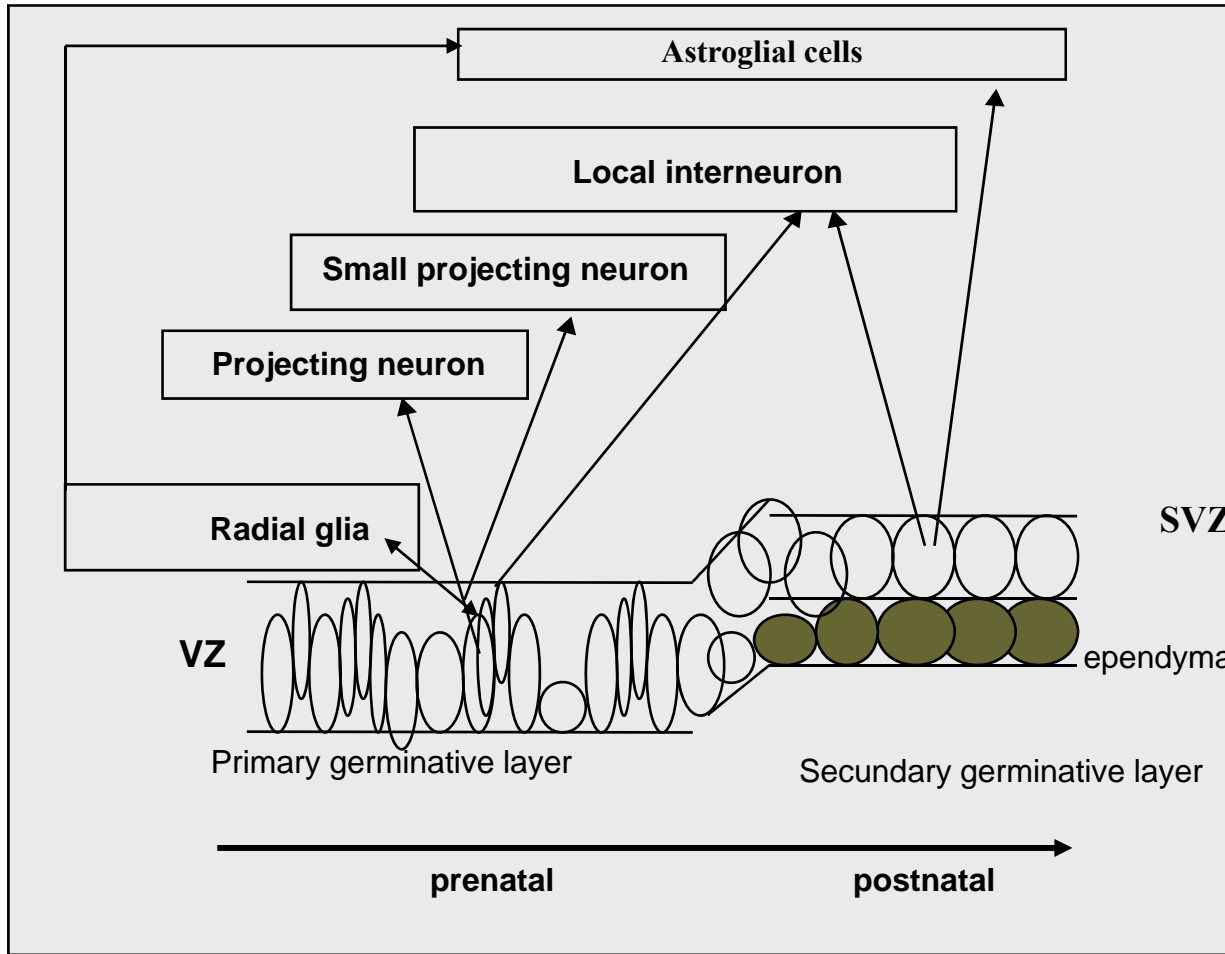


Rakic P. J. *Comp. Neurol.* 1972, 145: 61-84



Neuronal precursors deriving from the primary germinative zone migrate along the processes of radial glial cells

The secondary germinative zone derives from the primary one:

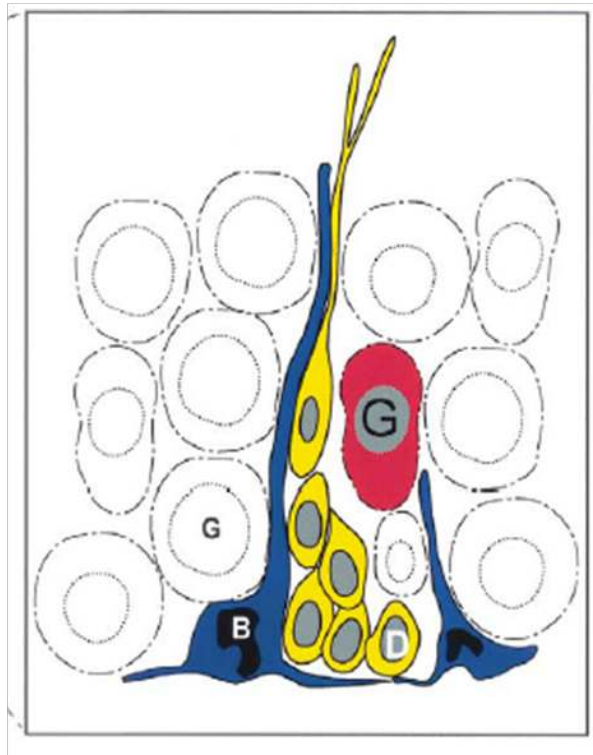


Projecting neurons are not produced

The neurogenic zones in adulthood are remnants of the SVZ
+ dentate gyrus subgranular zone (SGZ)

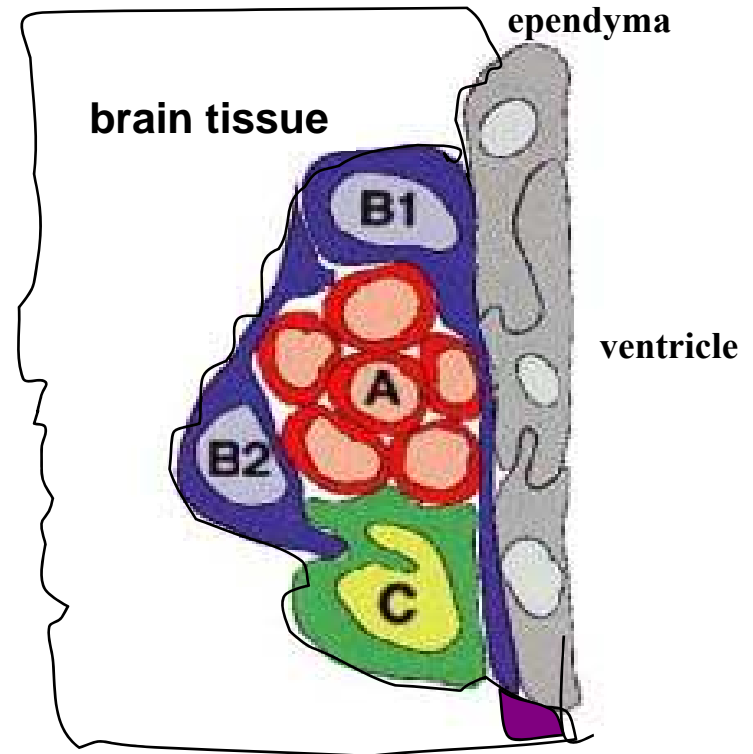
Migration of cells in adulthood

Subgranular zone



The neuronal precursors migrate among the already differentiated hippocampal neurons

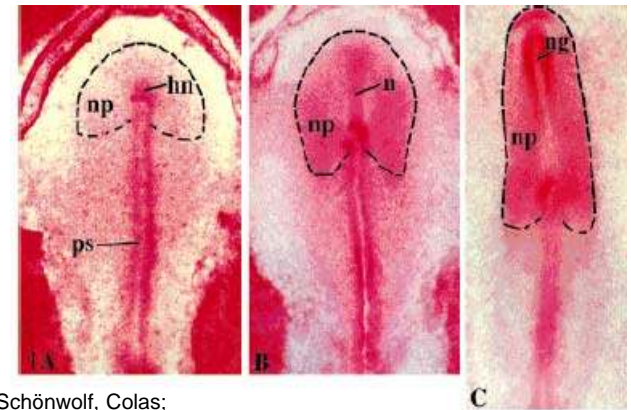
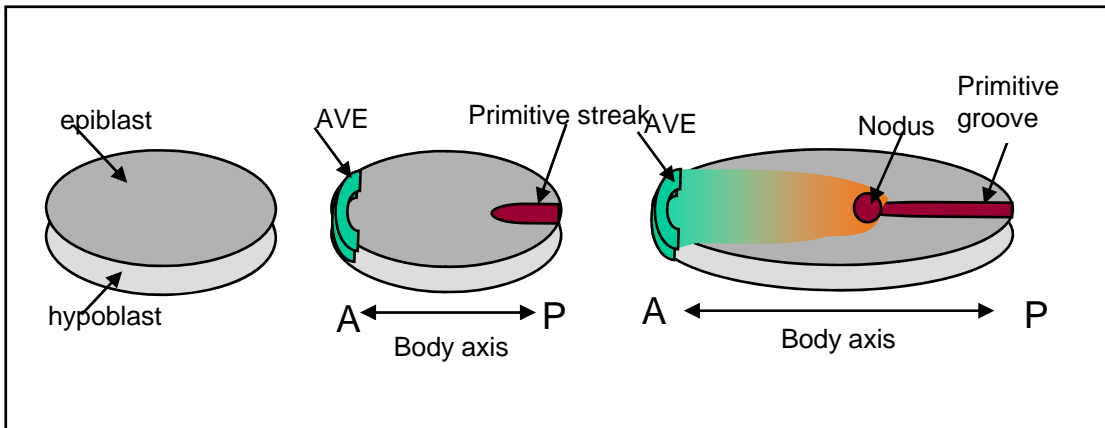
Subventricular zone



The neuronal precursors migrate separated from the already differentiated neurons

Doetsch F et al. J. Neurosci. 1997, 17(13): 5046 ; Sanai et al. Nature 2004, 427: 740

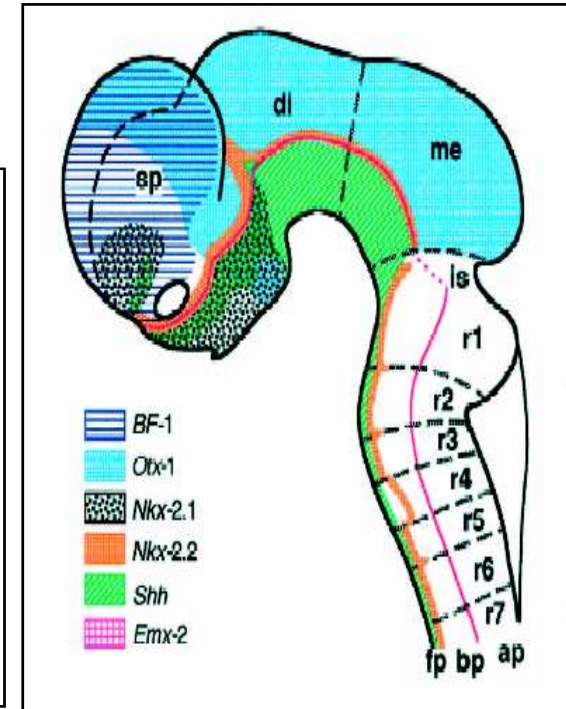
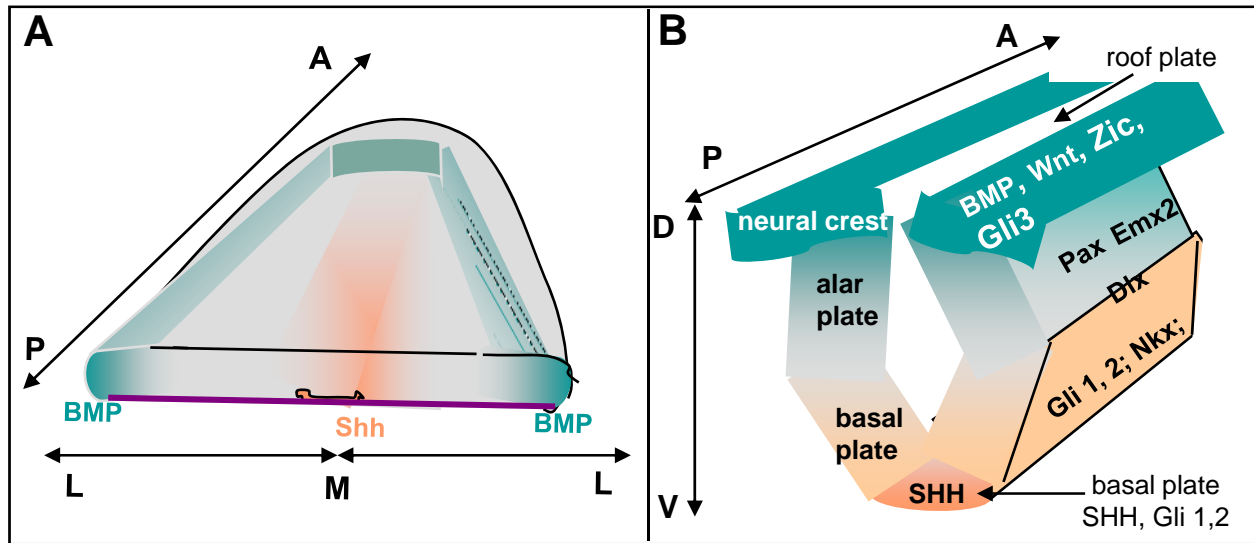
The antero-posterior axis is defined by the primitive streak and antero-visceral entoderm (AVE)



Schönwolf, Colas;
DEVELOPMENTAL DYNAMICS 221:117-145 (2001)

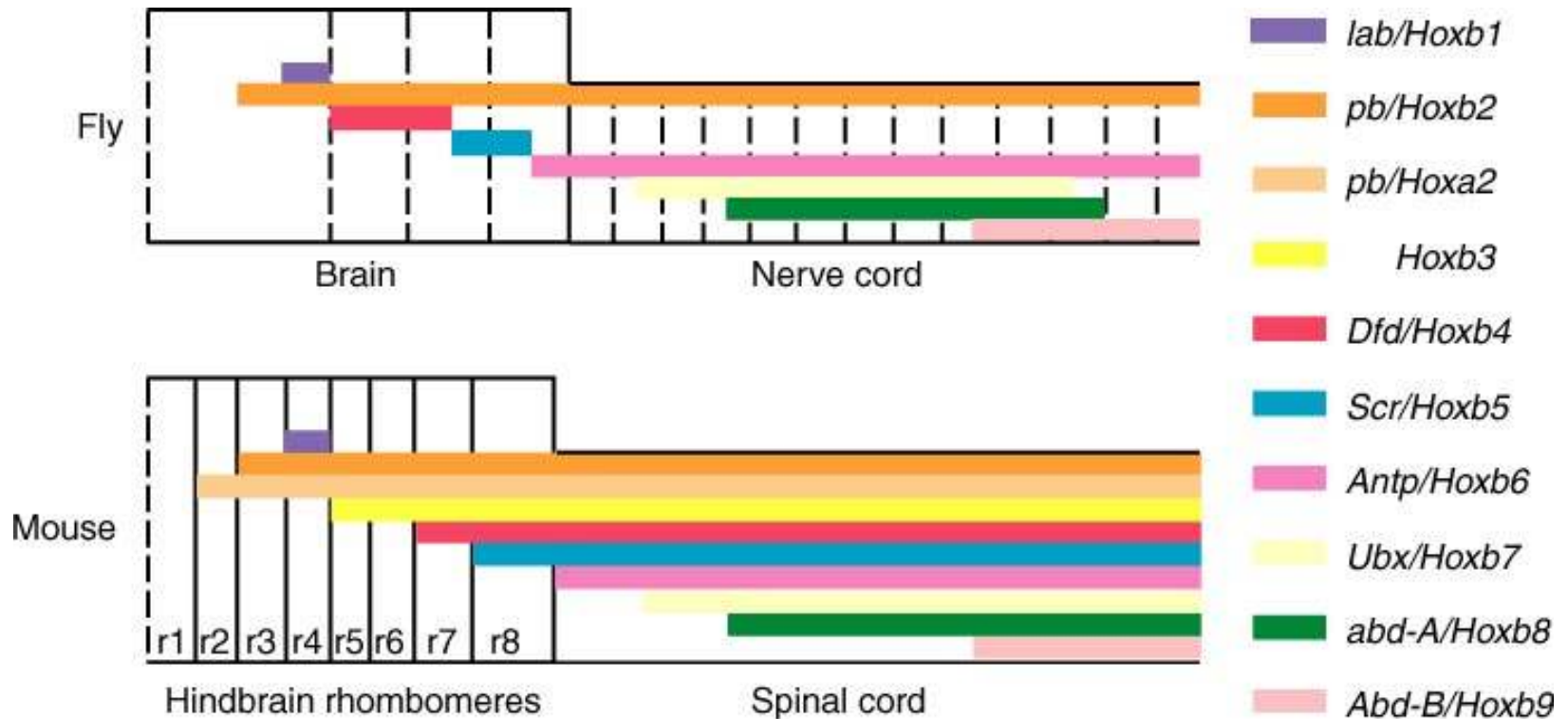
The antero-posterior axis is defined by the primitive streak and antero-visceral entoderma (AVE)

Dorso-ventral axis: Shh / Wnt



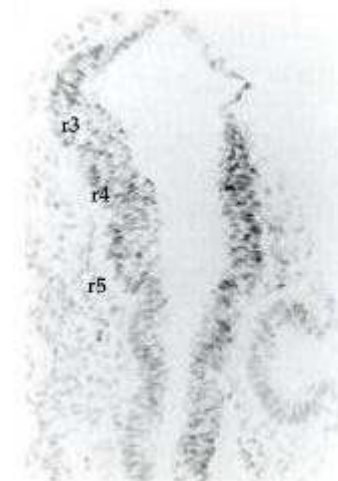
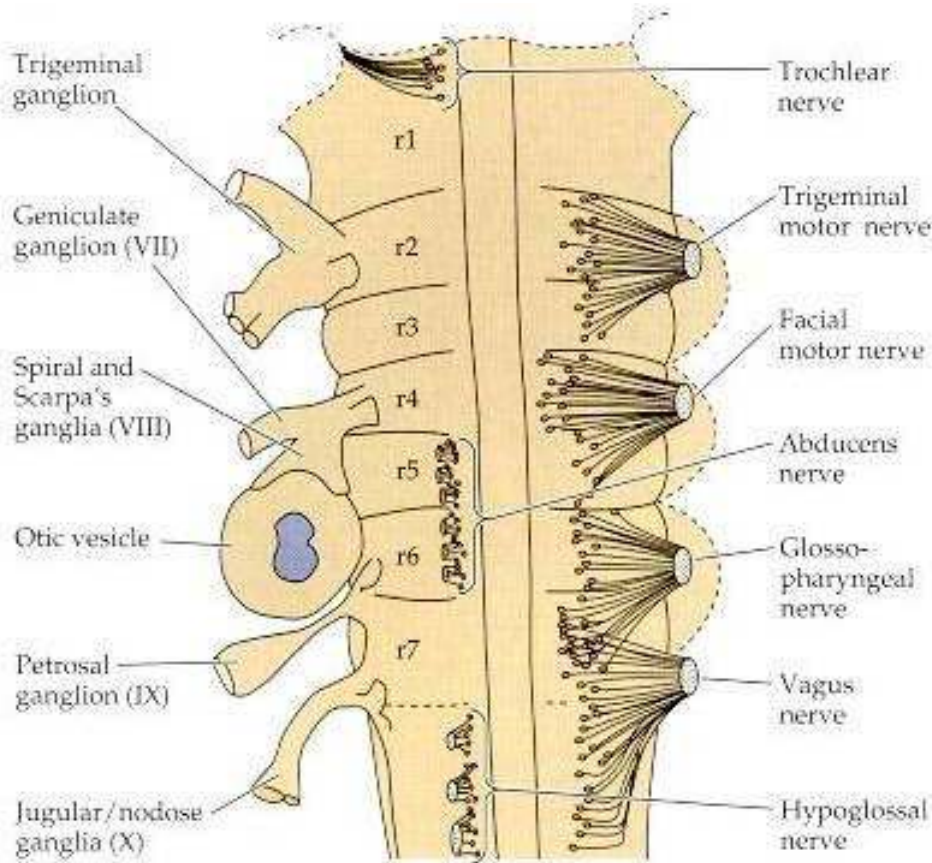
Shimamura, Rubenstein; 1995

Cranio-caudal expression pattern of homeobox genes

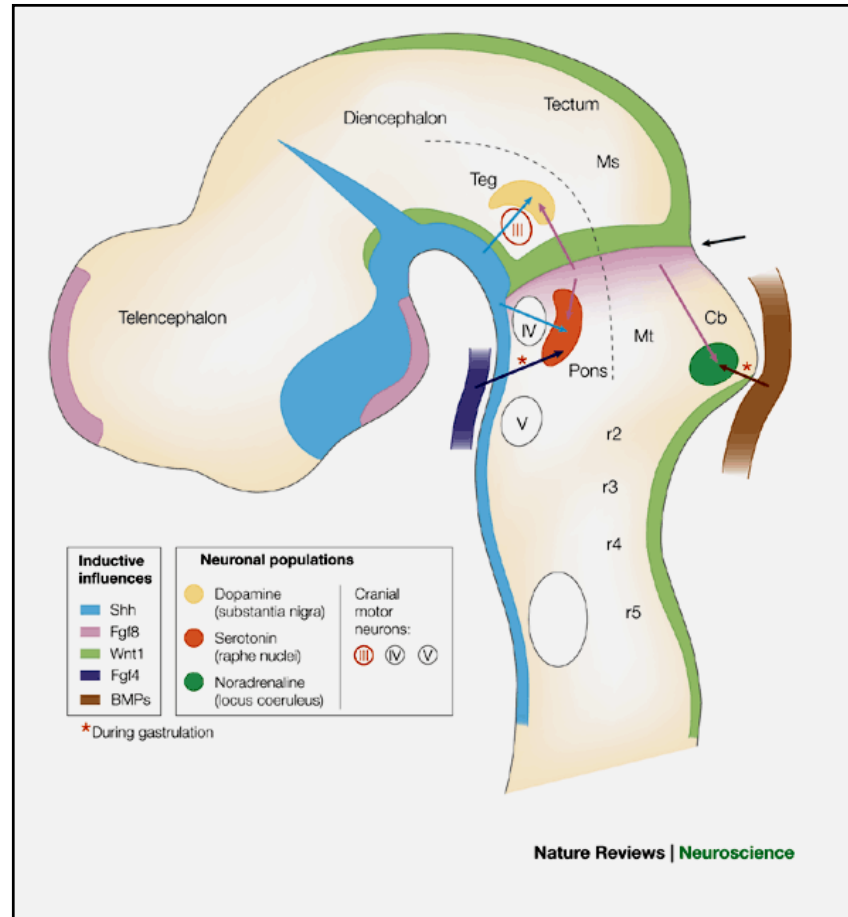


Hirth *et al.*, (1998).

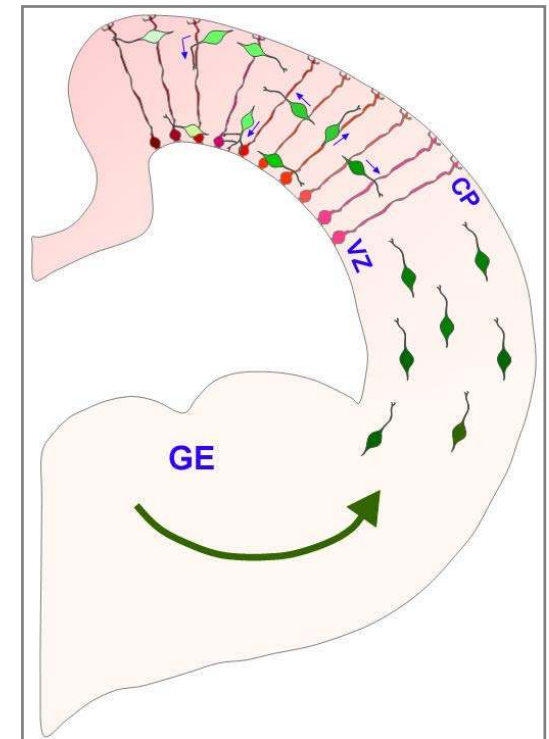
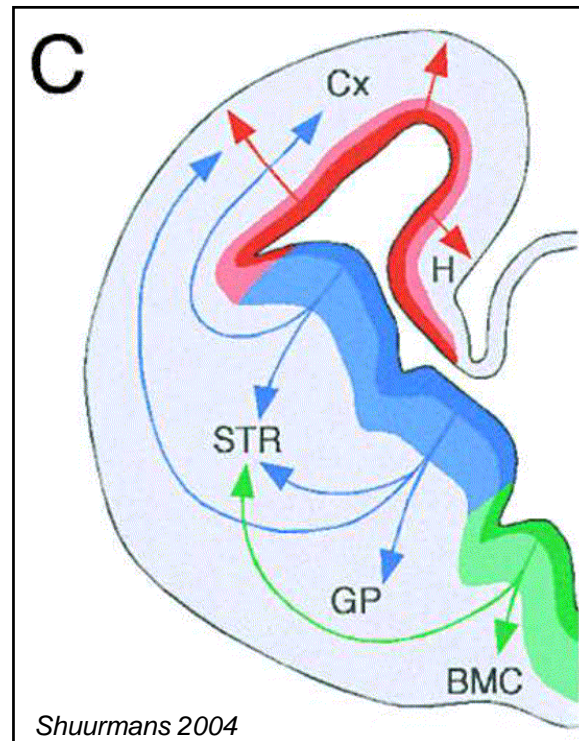
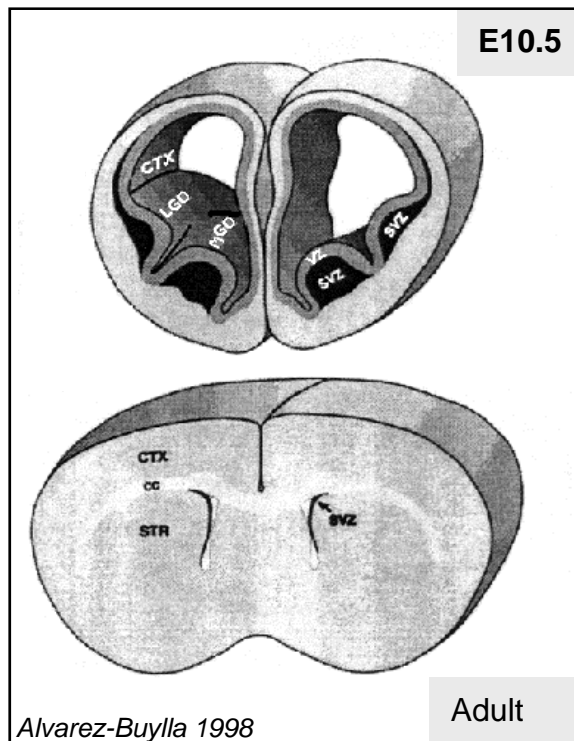
Differentiation of rhombomeres



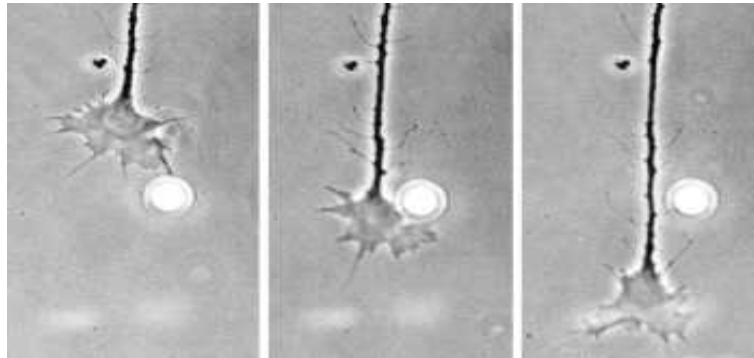
Differentiation of neuronal populations in the brain



The cerebral cortex is built up by cells deriving from different regions of both the primary and secondary germinative layers

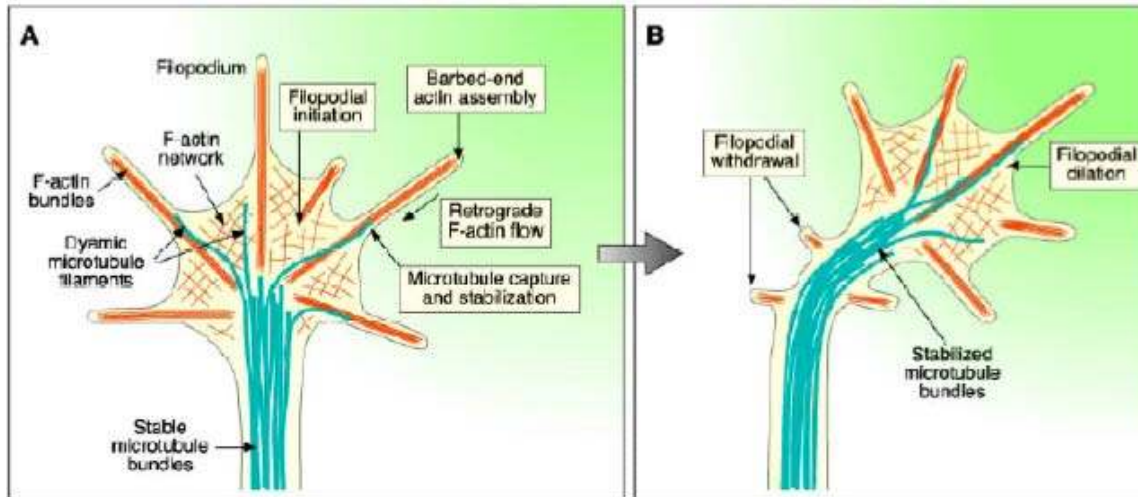
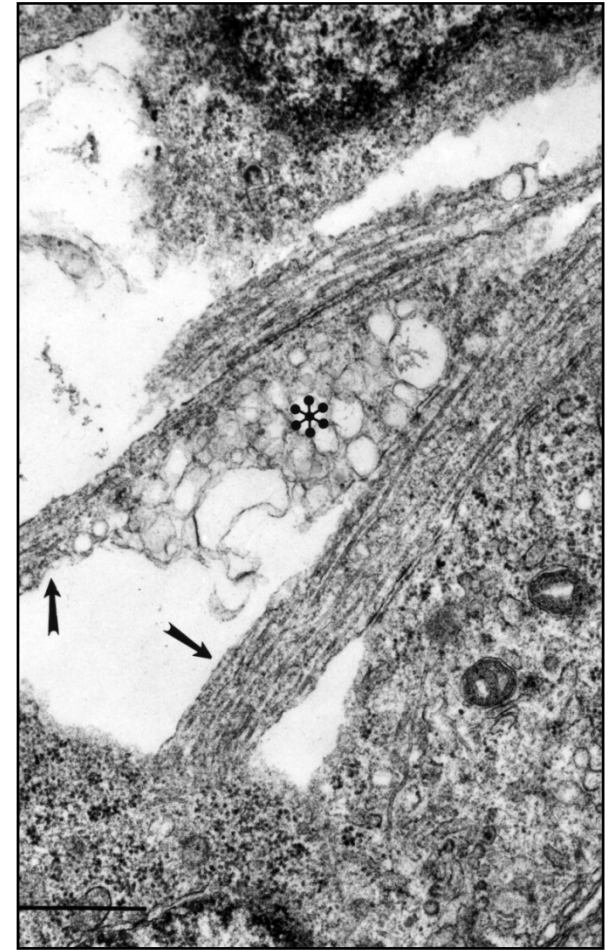


Developing of neuronal pathways: axonal growth and path finding

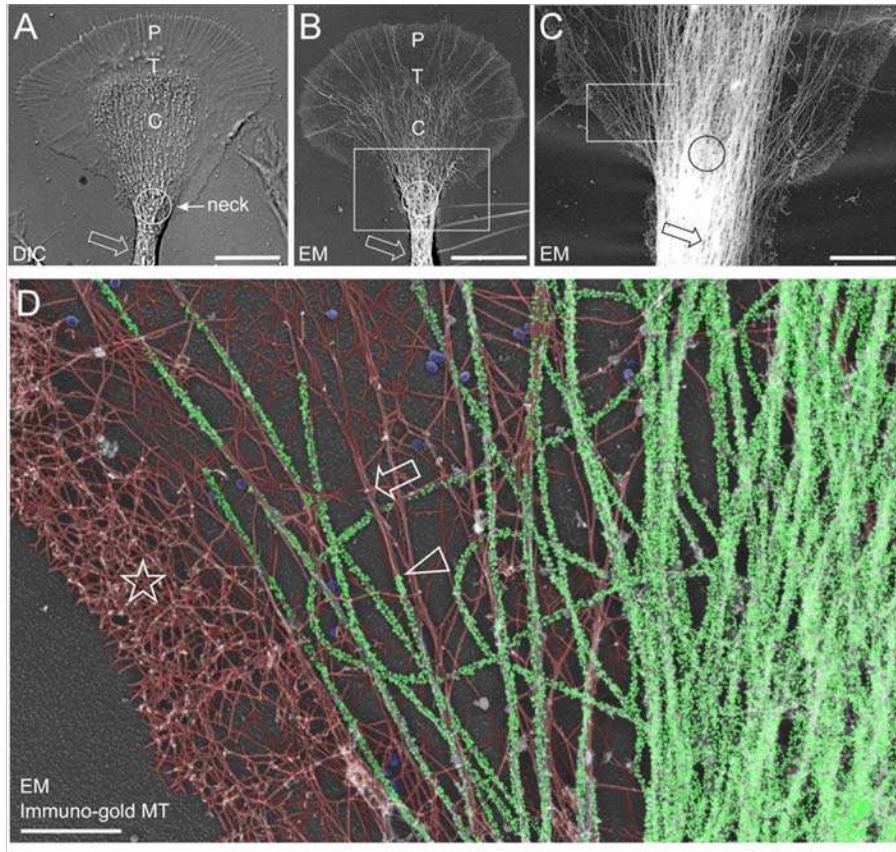


Phase-contrast image of growth cone

Electron microscopic image of growth cone

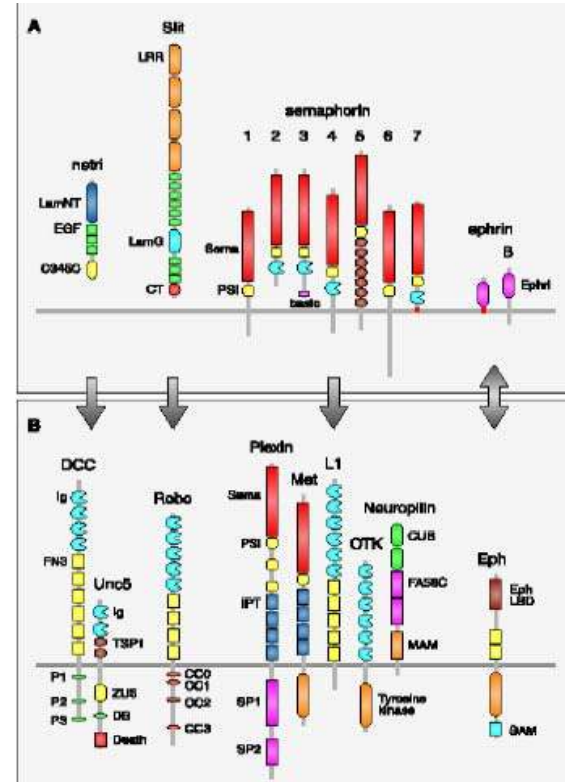
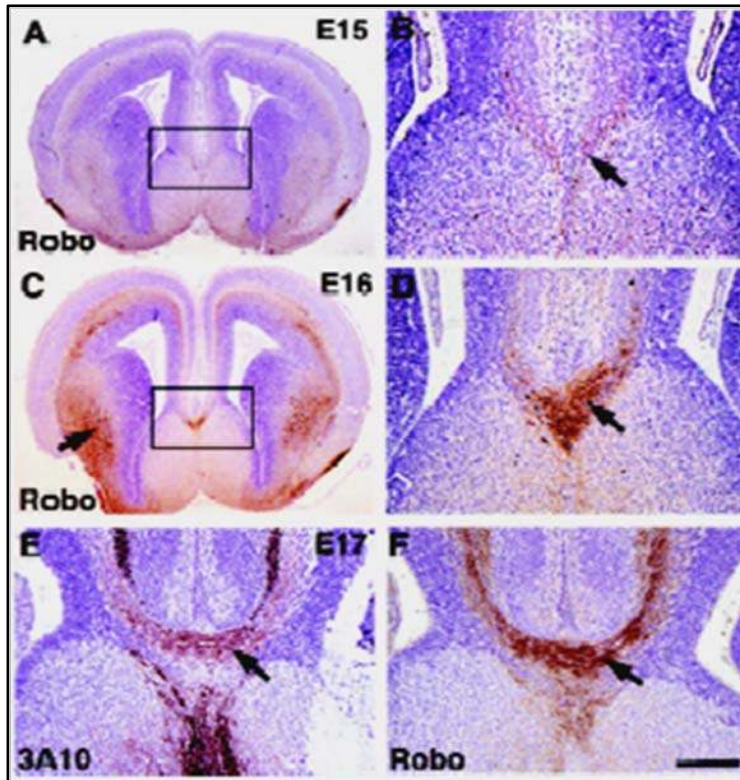


Developing of neuronal pathways: axonal growth and pathfinding



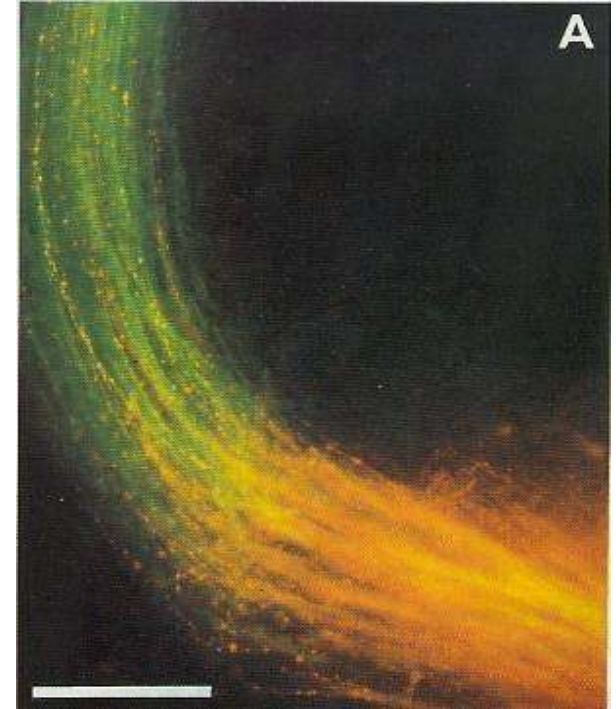
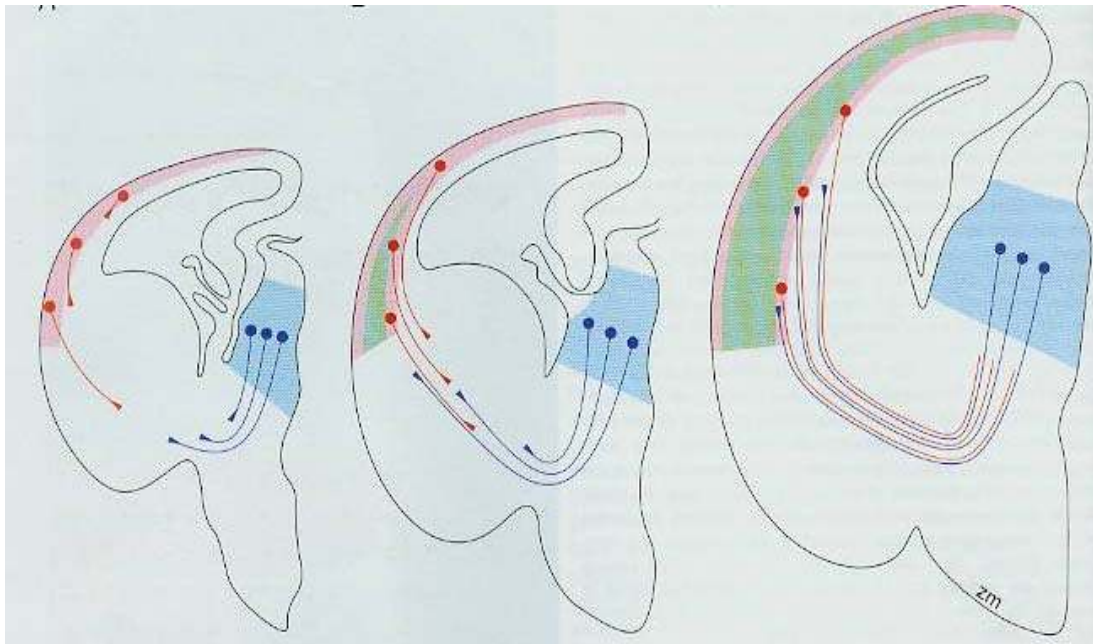
Burnette et al., 2008 Cell

„Pathfinder” processes: directed growth and „forbidden” directions



Timed appearance of guiding molecules and receptors!

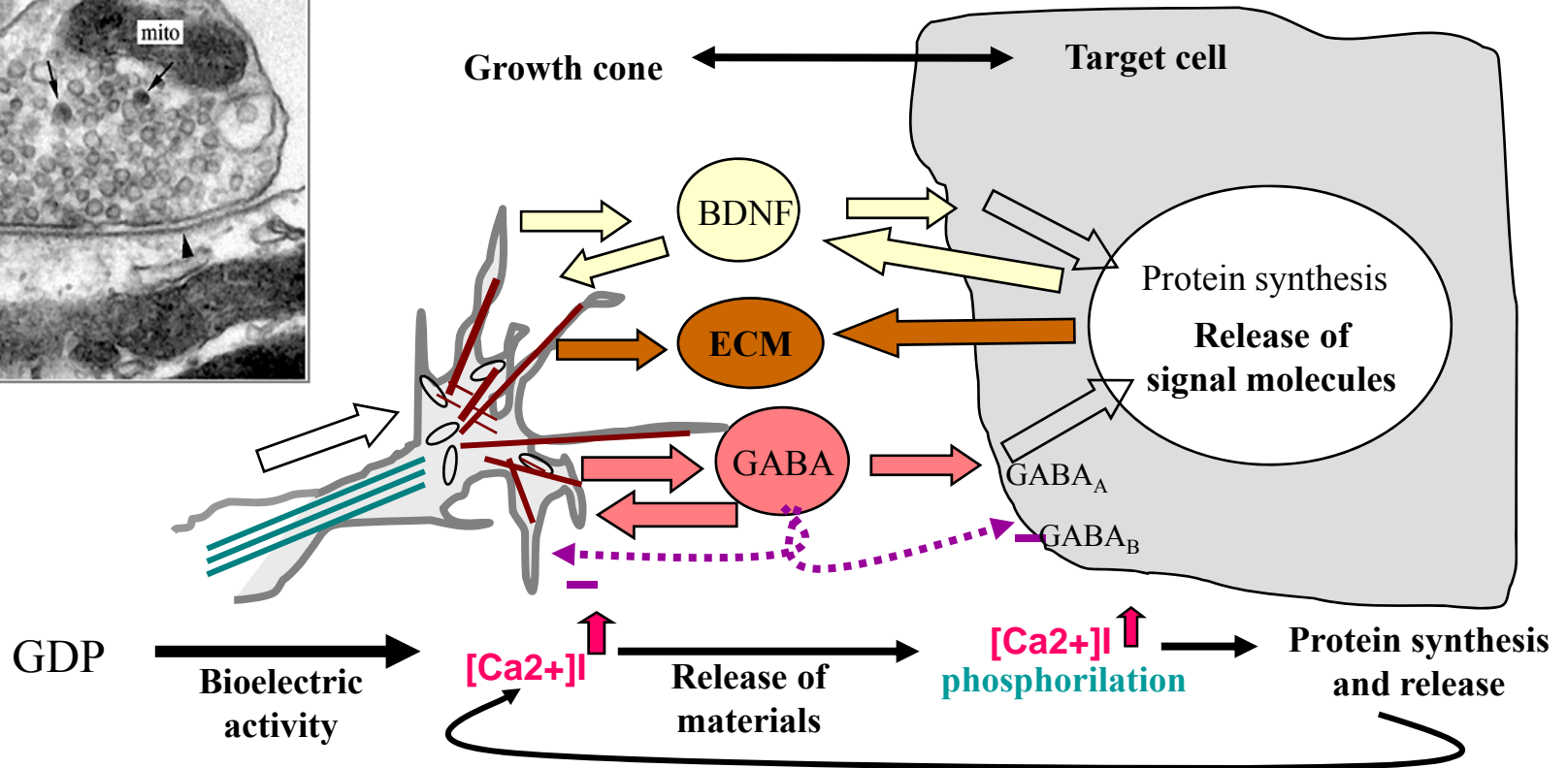
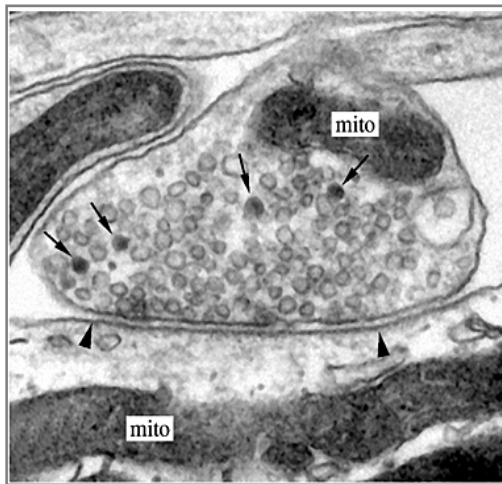
Ideal adherence of the growth cone to the surface of neighboring processes; they form bundles



Molnár Zoltán felvétele

Processes of cortical neurons „guide” the processes of thalamic neurons to the cortex

„Fire together – wire together”



Jelitai, Madarasz; *Int.Rev.Neurobiol.* 2006

Formation and subsistence of functional neuronal networks is the result of multiple selection

Production of cells: surviving cells are selected from a multitude of cells with great surplus

Migration of cells: cells are selected by permissive, attractive and repulsive adhesive signals

Axonal growth/withdrawal: the axonal sprouting is excessive; sustained axons „are being selected“ by the activity they show

Synapse formation/survival: it is possible only among mutually active partners

Selection by the ambience

For what purpose can the stem cells be used? Today „only” for scientific/clinical research

Stem cell therapy is still not sufficiently validated for neuronal diseases and currently is not a choice.....

But there are clinical studies with controls!
(Must be free of charge for the patients!!!)

Secernated factors inducing regeneration, and/or reducing inflammation?

Gene-therapy

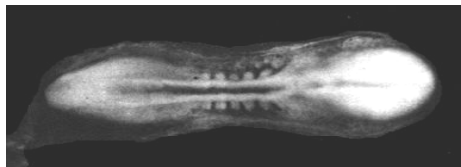
Clinical trials: LSDs (e.g. Batten-disease)

Future: Great possibilities in stem cell therapy

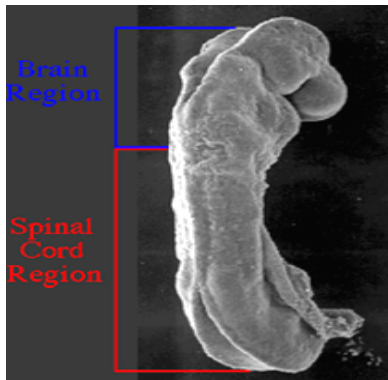
Location of proliferating cells (forming a germinative layer) in the neural primordium of human and rat embryos

Primary germinative zone

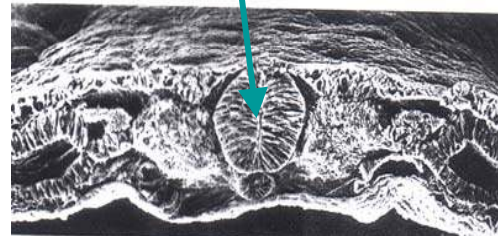
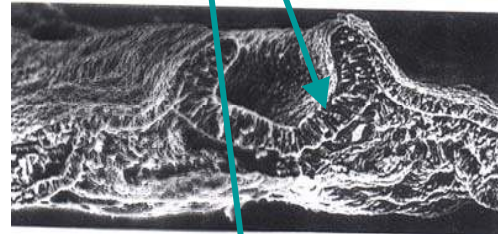
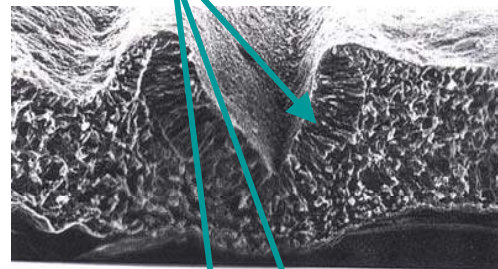
Secondary germinative zone



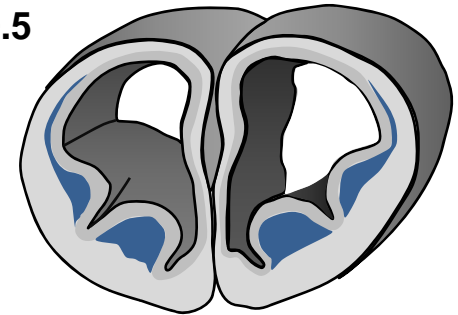
6-day old human embryo



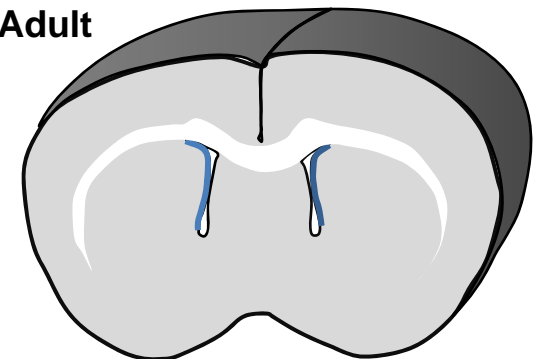
8-day old human embryo



E10.5



Adult



Rat forebrain