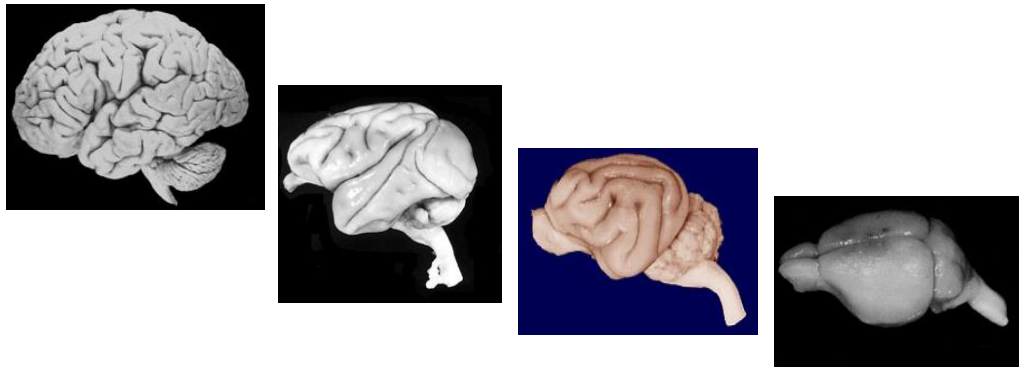

General concepts of brain development

Grazia M.S. Mancini
klinical geneticist
ErasmusMC University Medical Center, Rotterdam, The Netherlands

MaNaMa Day Neurogenetics, February 7th , 2023.
Campus VUB, Jette, Brussels

Outline

Normal brain development

Examples of abnormal development

Global overview of disease mechanism

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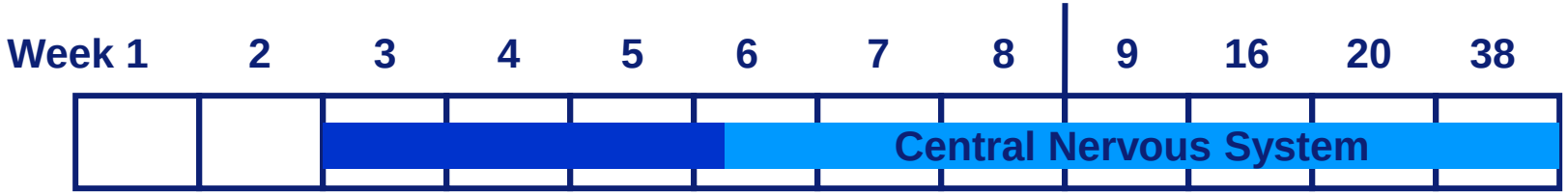
Stages of CNS development during the pregnancy



Processes	Time
- Separation of three layers	2 w.
- Dorsal Induction	3-7 w.
- Ventral Induction	5-6 w.
- Neuronal/Glia Proliferation	8-16 w.
- Migration	12-20 w.
- Organization	>24 w.
- Myelination	>24w/2 yr.

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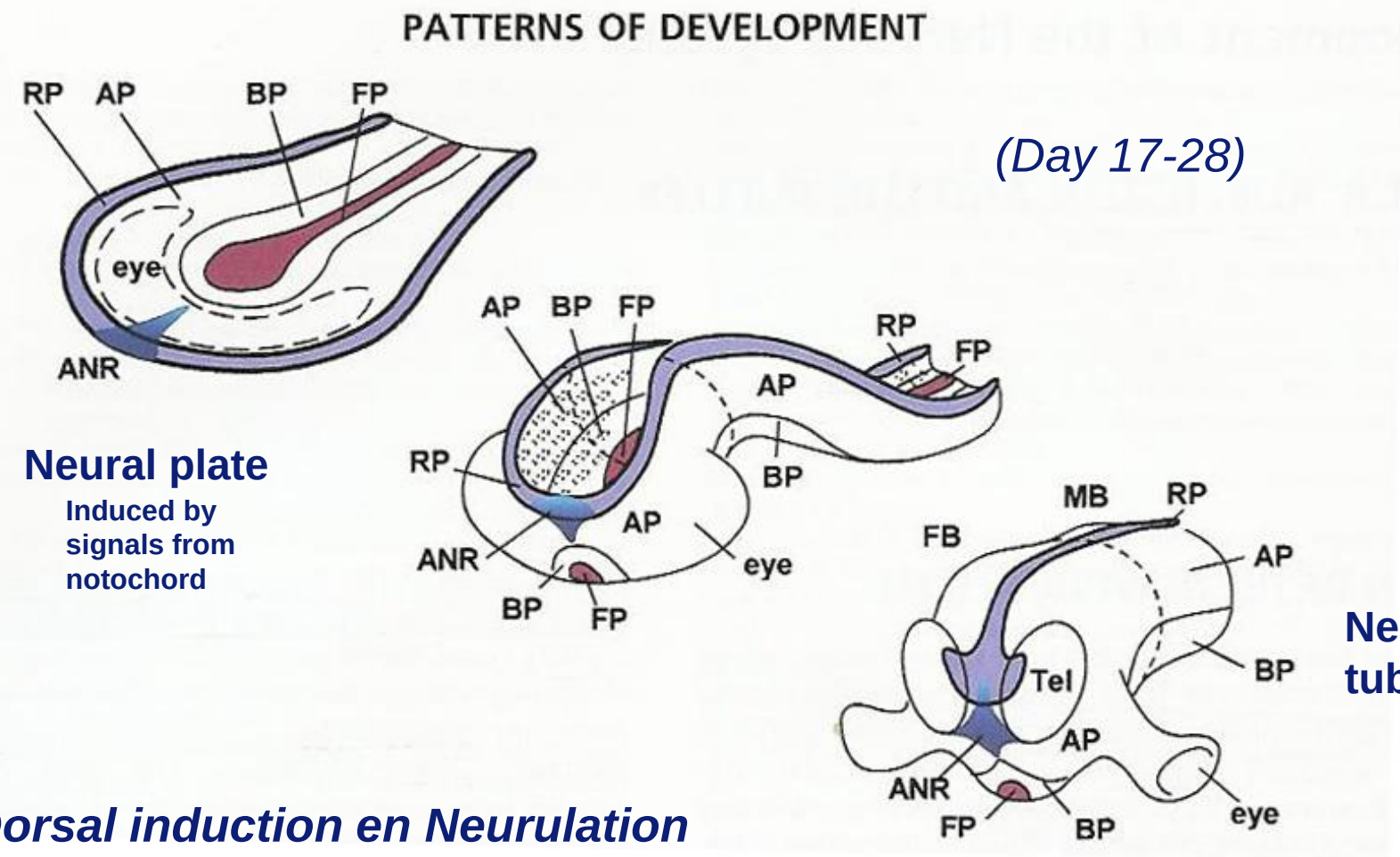
Epstein et al. Inborn errors of development 2004



Dorsal induction en Neurulation

(formation and closure of neural tube)

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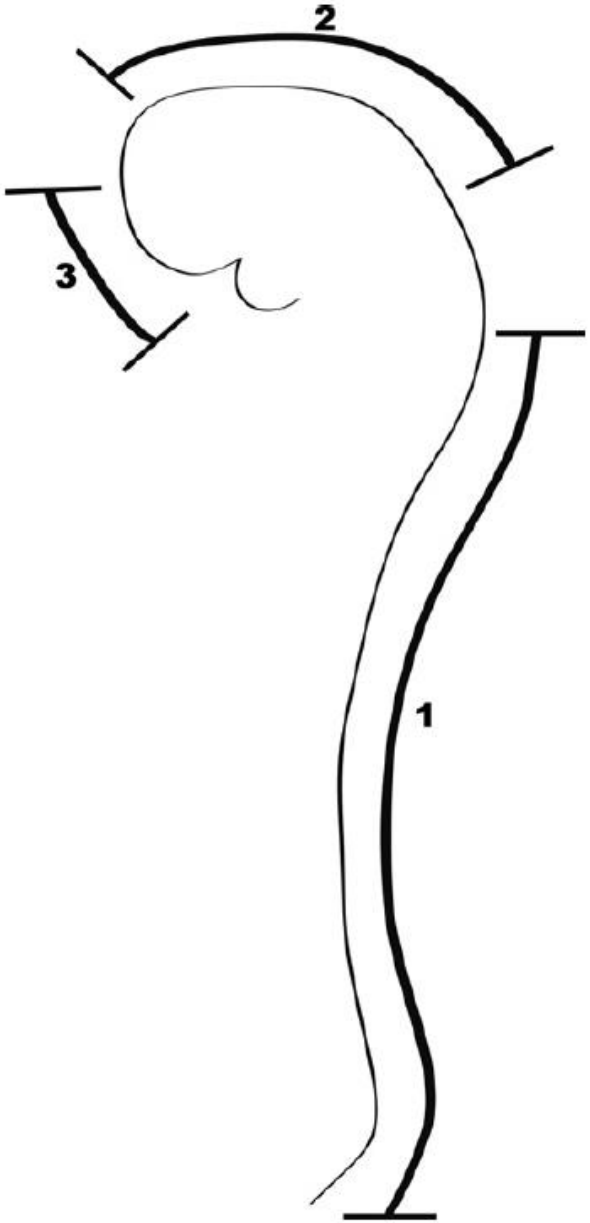

Neurulation timeline

1. Cervical-thoraco-lumbal region
2. Mesencephalon-rhombencephalon border
3. Rostral prosencephalon

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1. Dorsal induction: Neural Tube Defects

Early

Lumbal myelomeningocele

Thoracic myelomeningocele

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Neural Tube Defects

late

Encephalocele

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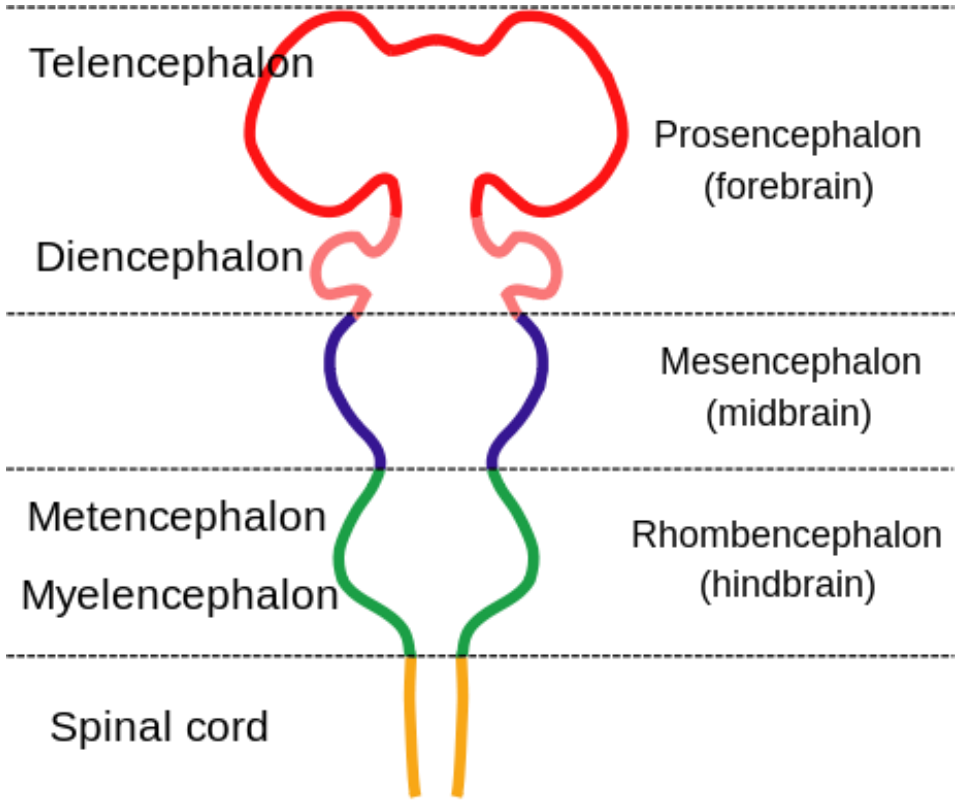
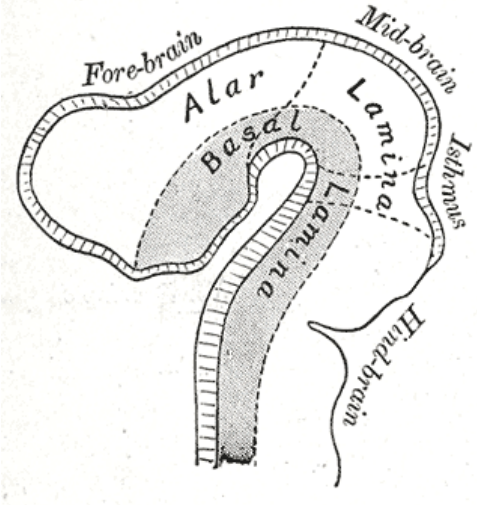
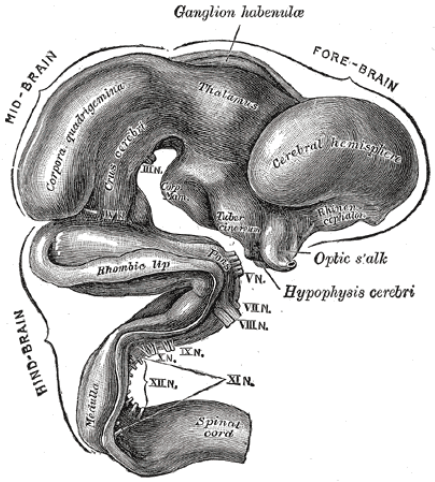
2. Ventral induction

Ventral induction (5-10 w)

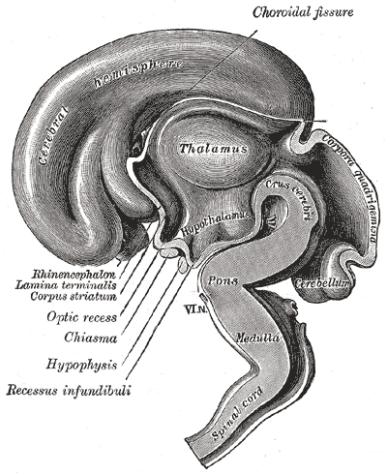




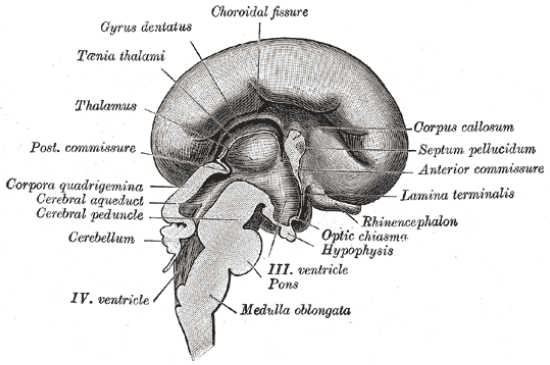
Brain development



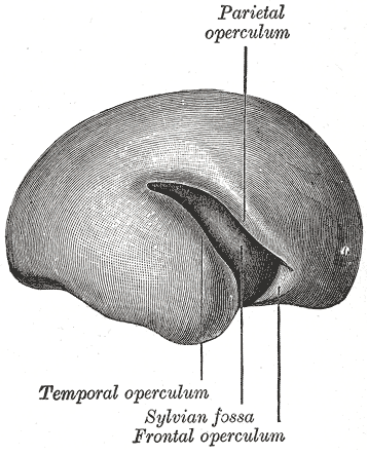
5 wks



3 mo



4 mo



5 mo

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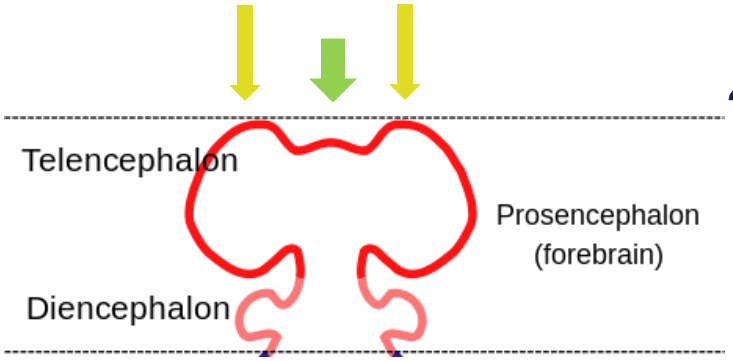
2. Ventral induction: Prosencephalon



- Cerebral hemispheres

- Corpus callosum
- Basal ganglia
- Hypothalamus
- Pituitary gland
- Thalamus
- Pinealis g.

2a. Prosencephalon layout

Aprosencephaly (no tel-, no dien-)

Atelencephaly (brain stem preserved)

2b. Prosencephalon longitudinal separation

(yellow arrow)

Holoprosencephaly

2c. Midline prosencephalon development

(green arrow)

Aplasia bulbus olfactorius

Agenesis corpus callosum

Agenesis septum pellucidum

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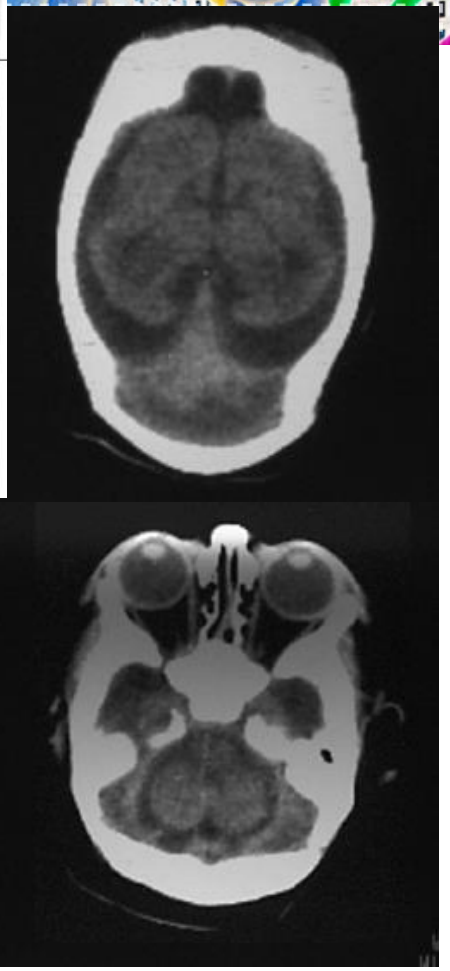
2. Ventral induction: prosencephalon development



2a. Prosencefalon vorming

Atelencefalie

2b. Prosencefalon longitudinale scheiding

Holoprosencefalie/holotelencefalie

2c. Middelijn prosencefalon ontwikkeling

Aplasie bulbus olfactorius

Agenesie van het corpus callosum

Agenesie van het septum pellucidum

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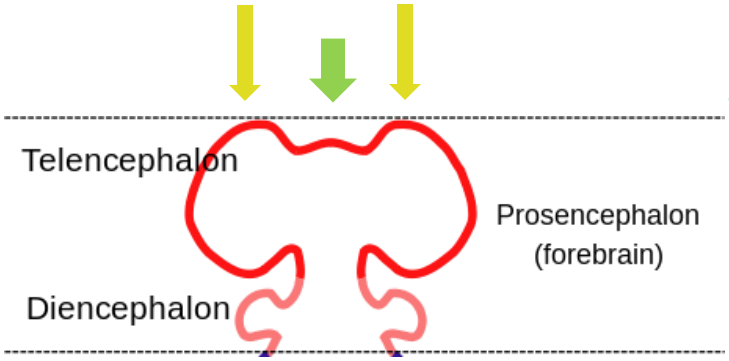
2. Ventral induction: prosencephalon development



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2a. Prosencephalon layout

Aprosencephaly (no tel-, no dien-)

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Holoprosencephaly

2c. Midline prosencephalon development *(green arrow)*

Aplasia bulbus olfactorius

Agenesis corpus callosum

Agenesis septum pellucidum

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Holoprosencephaly morphological variants

life

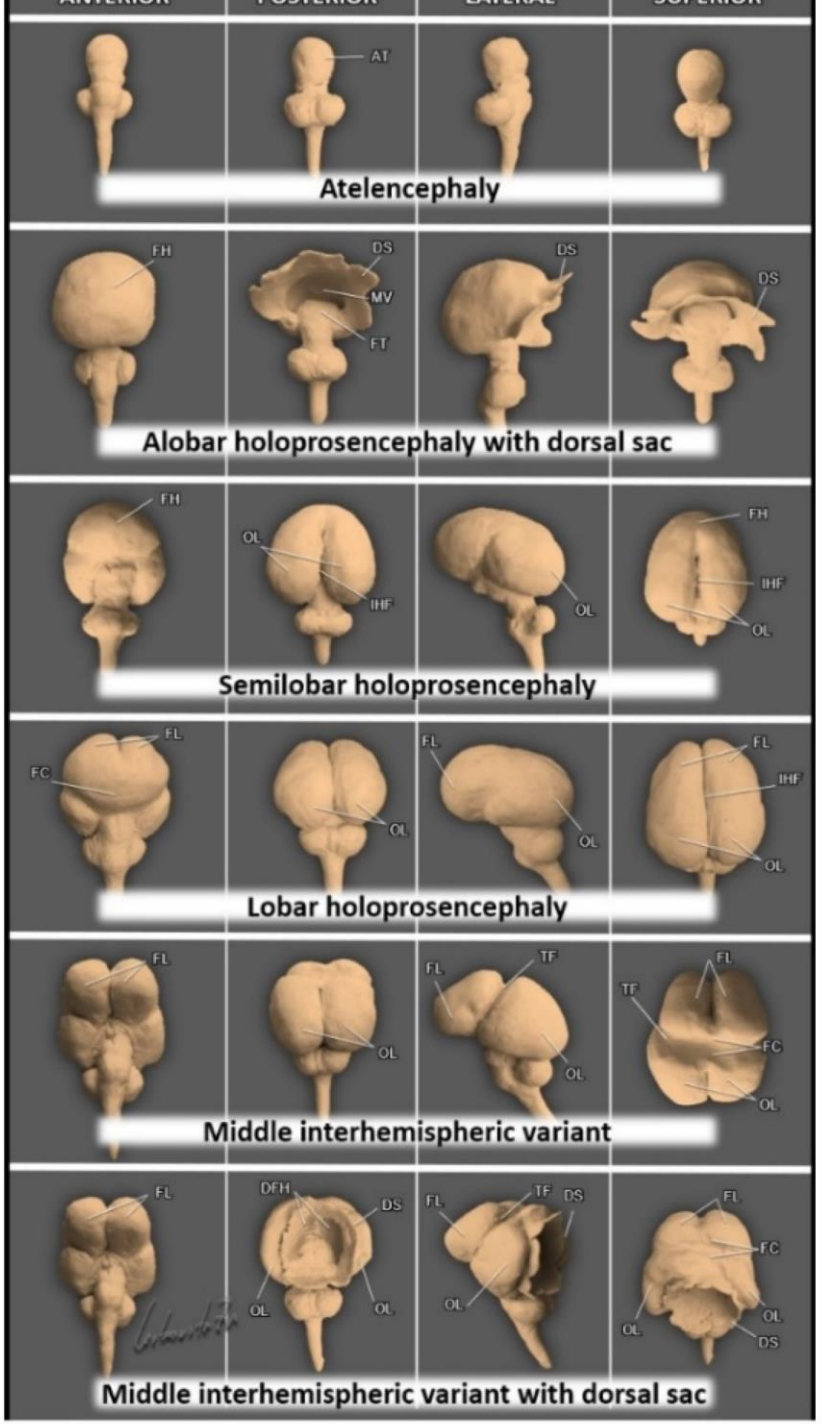
MDPI

Review

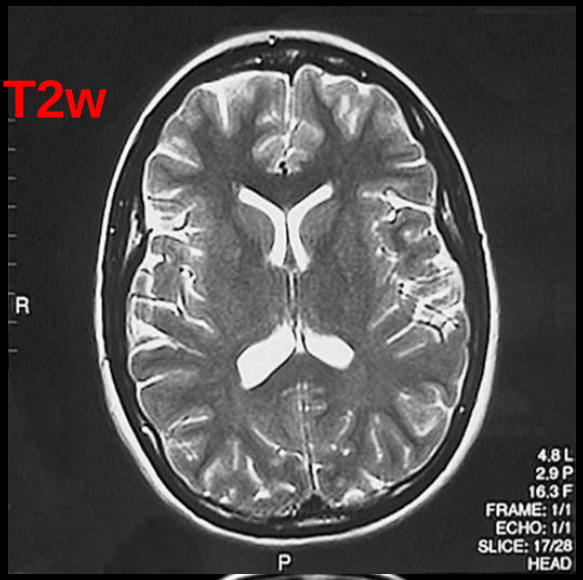
Fetal Brain Development: Regulating Processes and Related Malformations

Zvi Leibovitz [1,2,*], Tally Lerman-Sagie [1,3] and Leila Haddad [2]

2022



Normal MRI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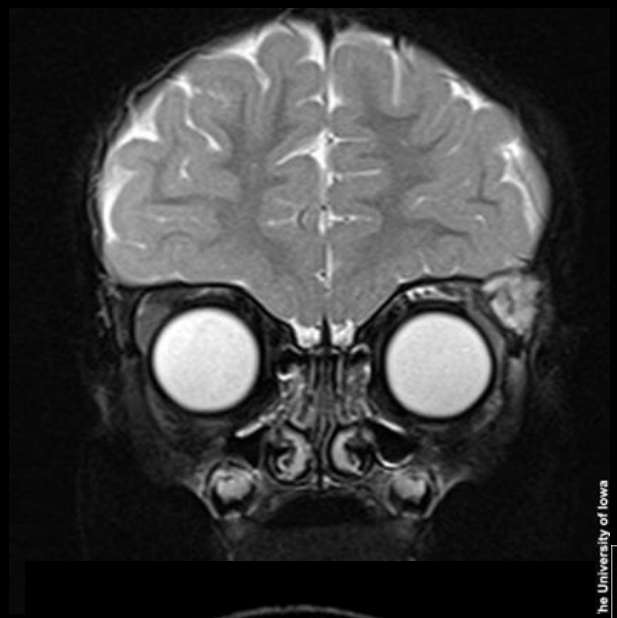
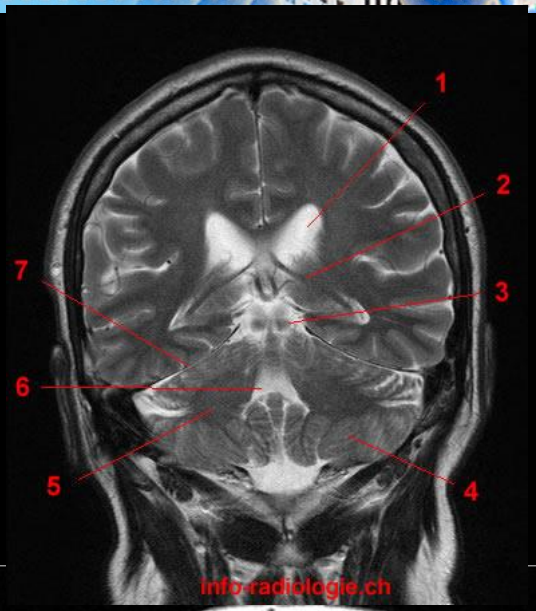
R
P
4.8 L
2.9 P
16.3 F
FRAME: 1/1
ECHO: 1/1
SLICE: 17/28
HEAD

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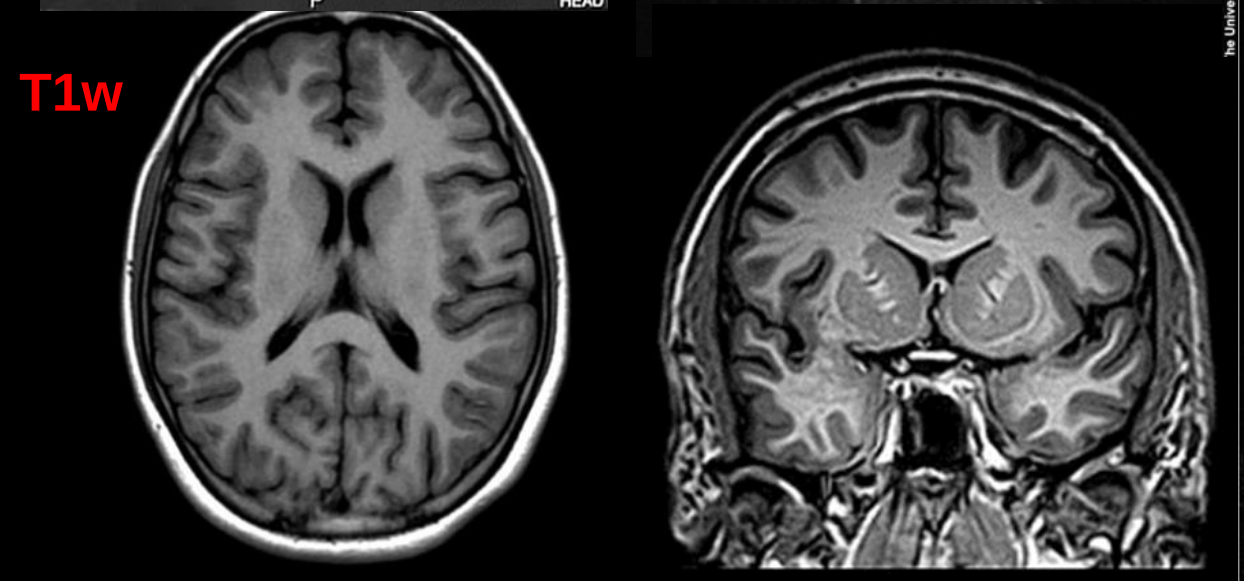
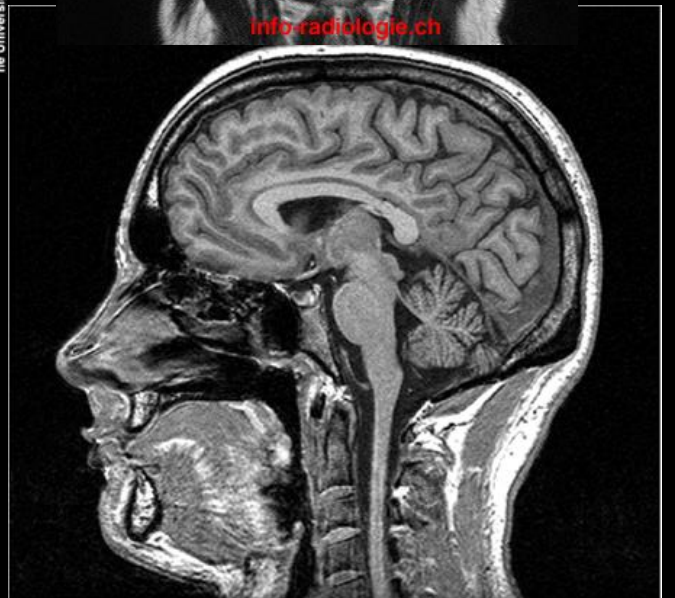
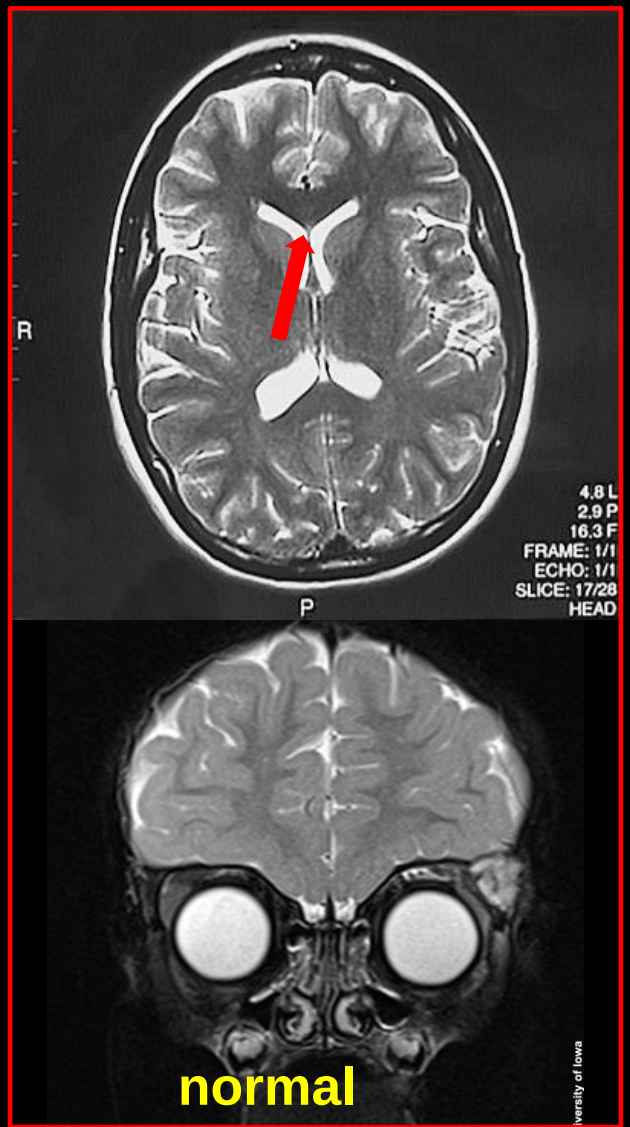
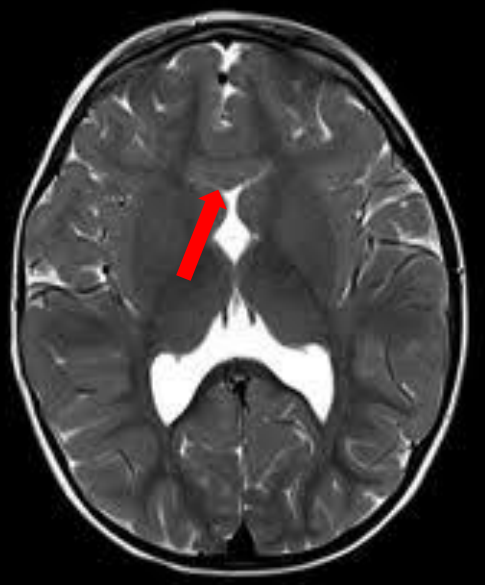
info-radiologie.ch

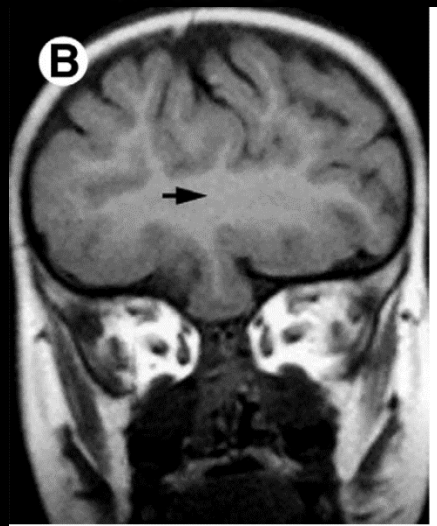

T1w

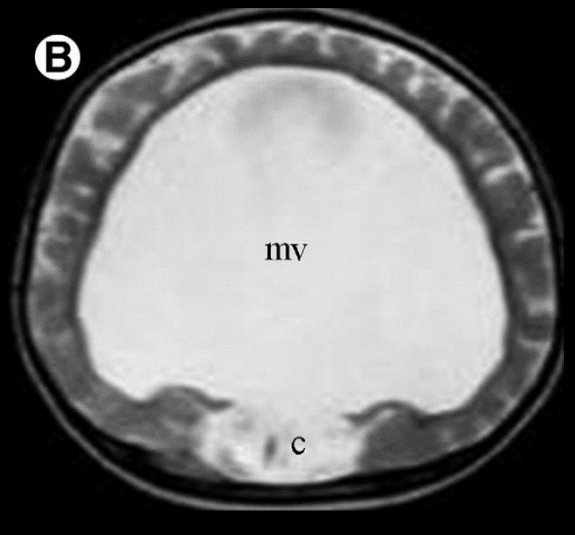

The University of Iowa

2b. Holoprosencefaly: insufficient longitudinal separation

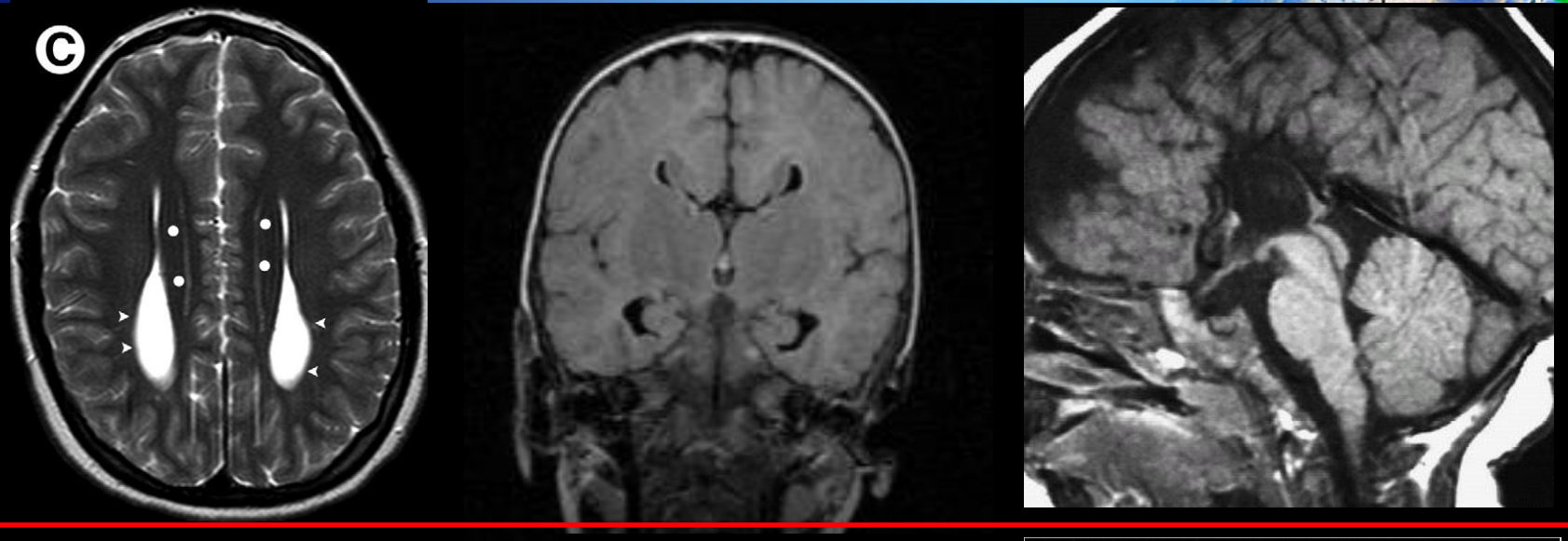




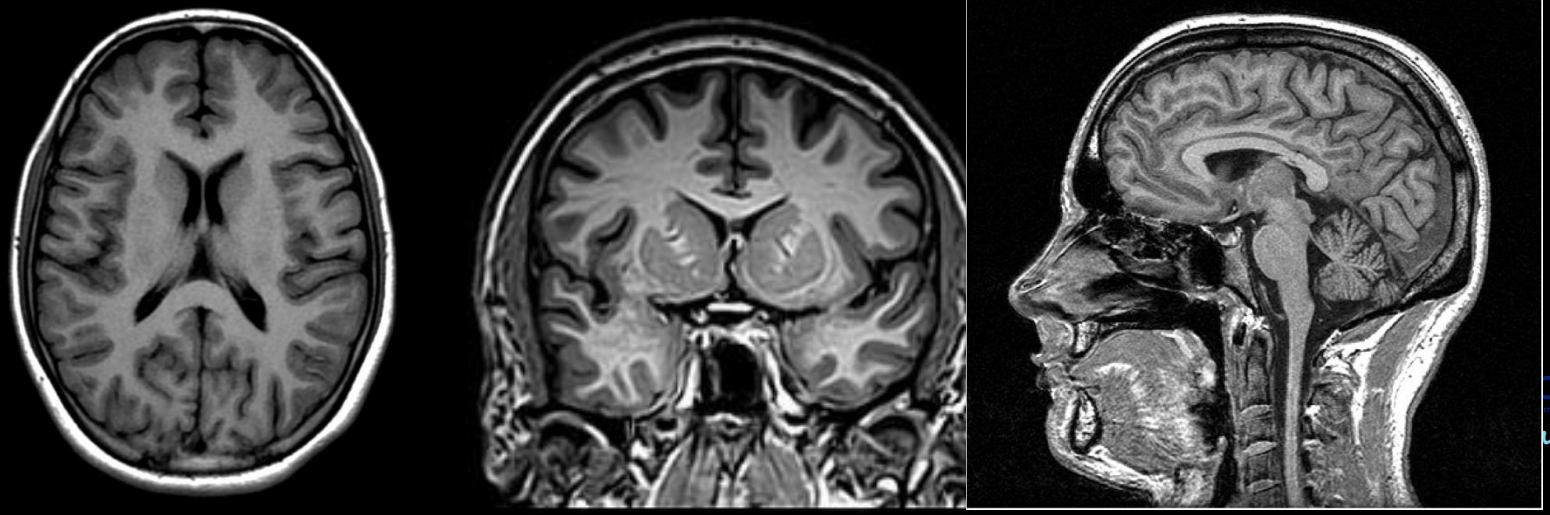




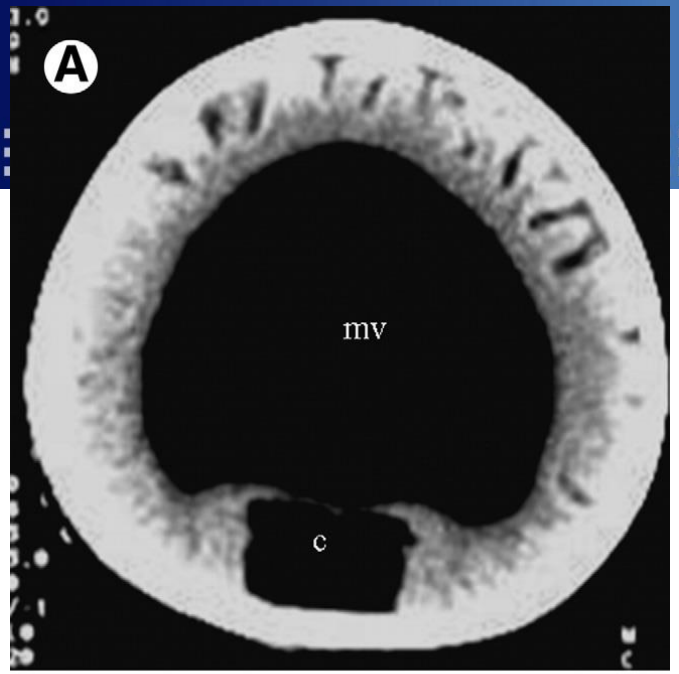
2c. Agenesis of the corpus callosum: insufficient midline development



normal



Holoprosencephaly: ventral induction occurs in parallel with face development



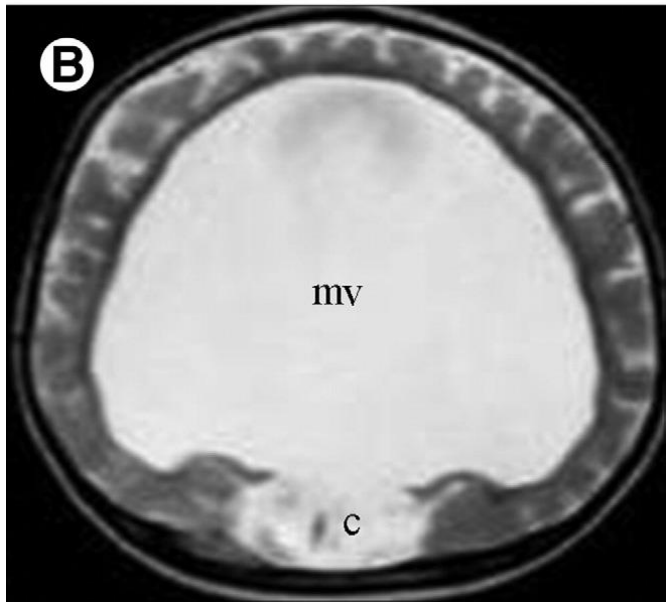
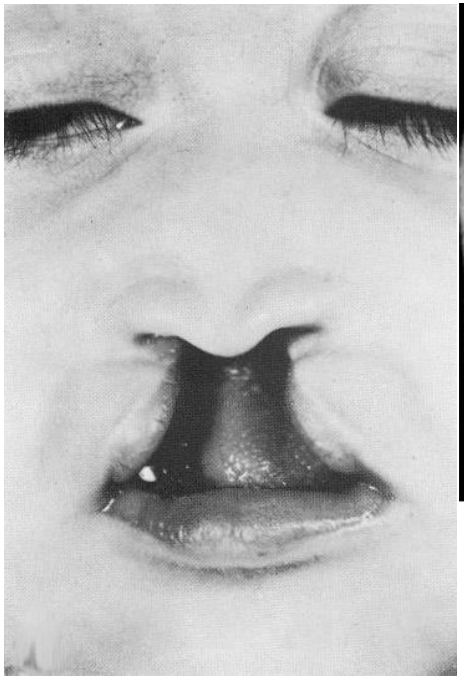
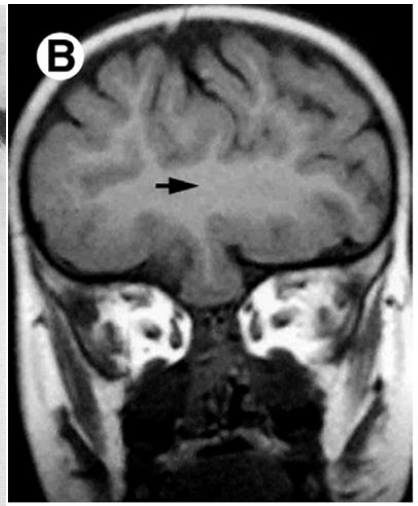
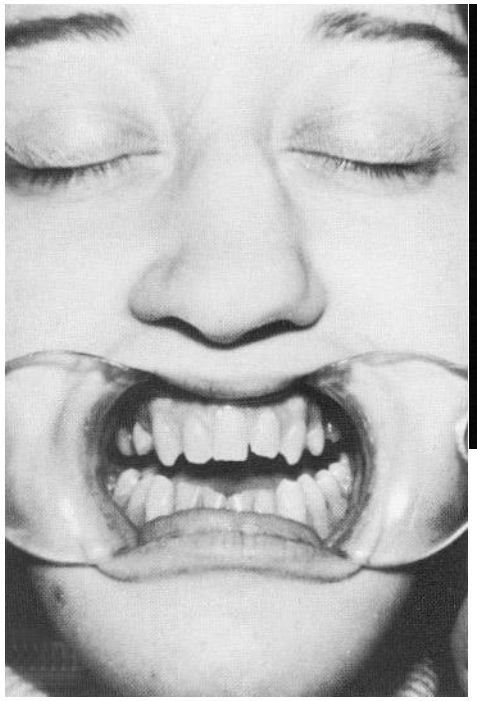


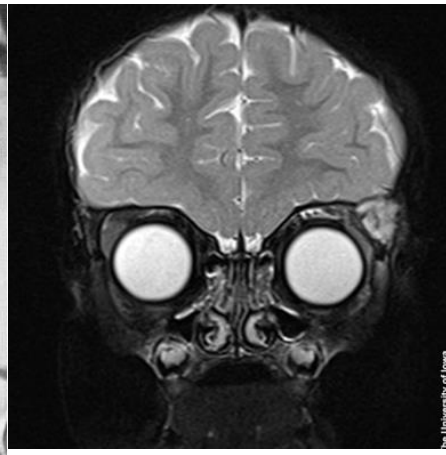
Figure 7. Spectrum of facial anomalies associated with varying degrees of holoprosencephaly. **A:** Cyclopia without proboscis. Note the single central eye. **B:** Cyclopia with proboscis. **C:** Ethmocephaly. **D:** Cebocephaly. Ocular hypotelorism with a single-nostril nose. **E:** Median cleft lip, flat nose, and ocular hypotelorism. **F:** Ocular hypotelorism and surgically repaired cleft lip. A–D, F from Cohen et al. [1971a] and Cohen [1989b]. E from DeMyer and Zeman [1963].

Holoprosencephaly: ventral induction of brain and face goes wrong





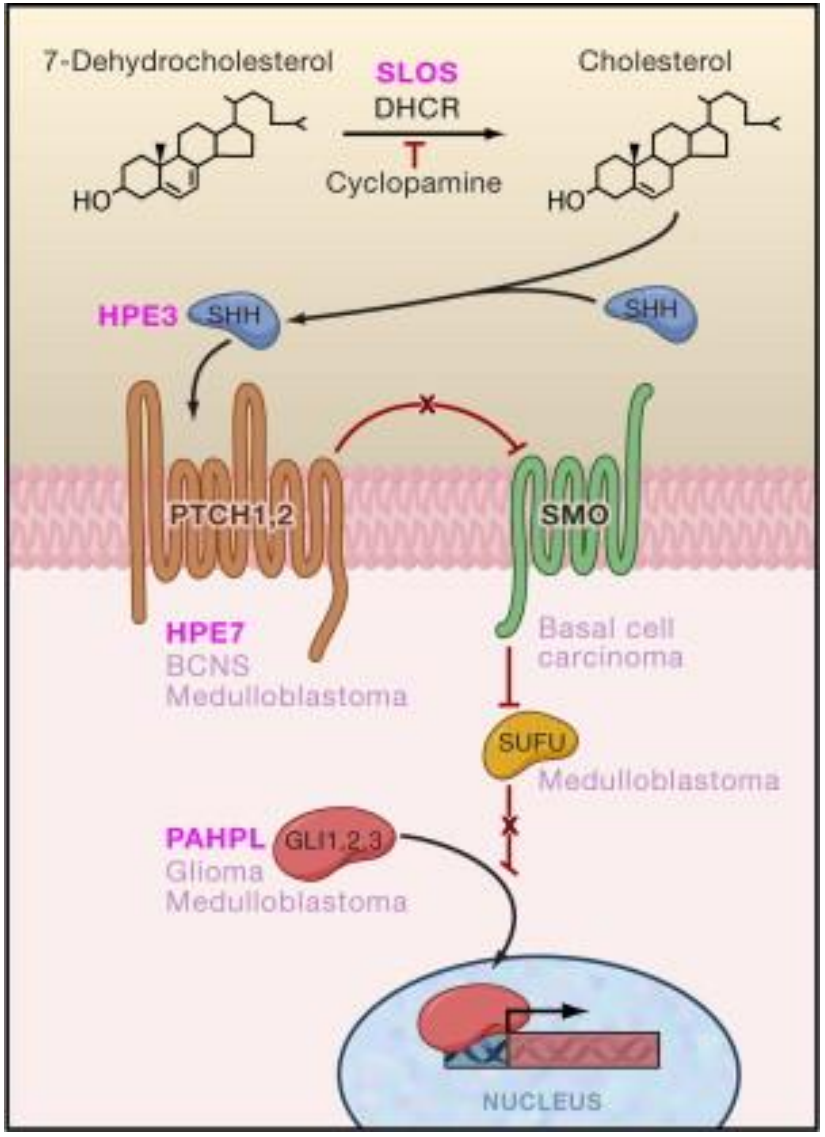




SHH, Sonic HedgeHog gene involved in midline development

>> Familial *SHH* mutation with reduced penetrance

SHH is produced by the notochord and is activated by cholesterol



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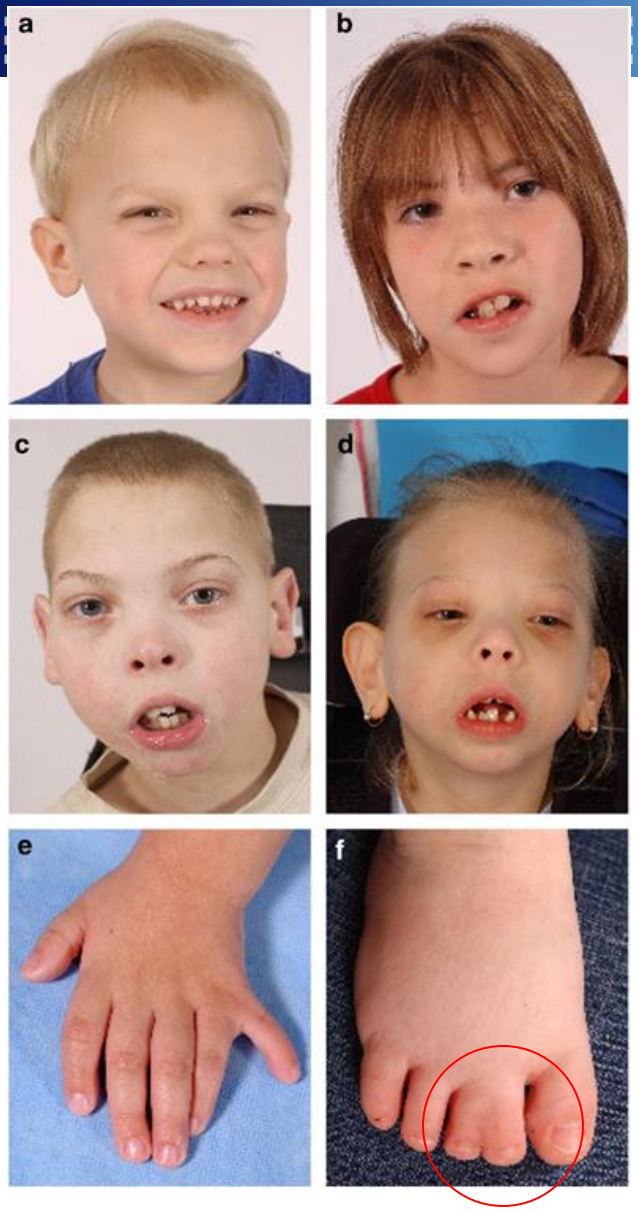
Agenesis of the corpus callosum (ACC)



Smith-Lemli-Opitz syndroom (SLOS)

Defect in cholesterol biosynthesis

Accumulation of cholesterol precursors (7-dehydro-cholesterol)

- Microcephay, **ACC**, ptosis, renal cysts and genital abnormalities, syndactyly 2-3 and polydactyly

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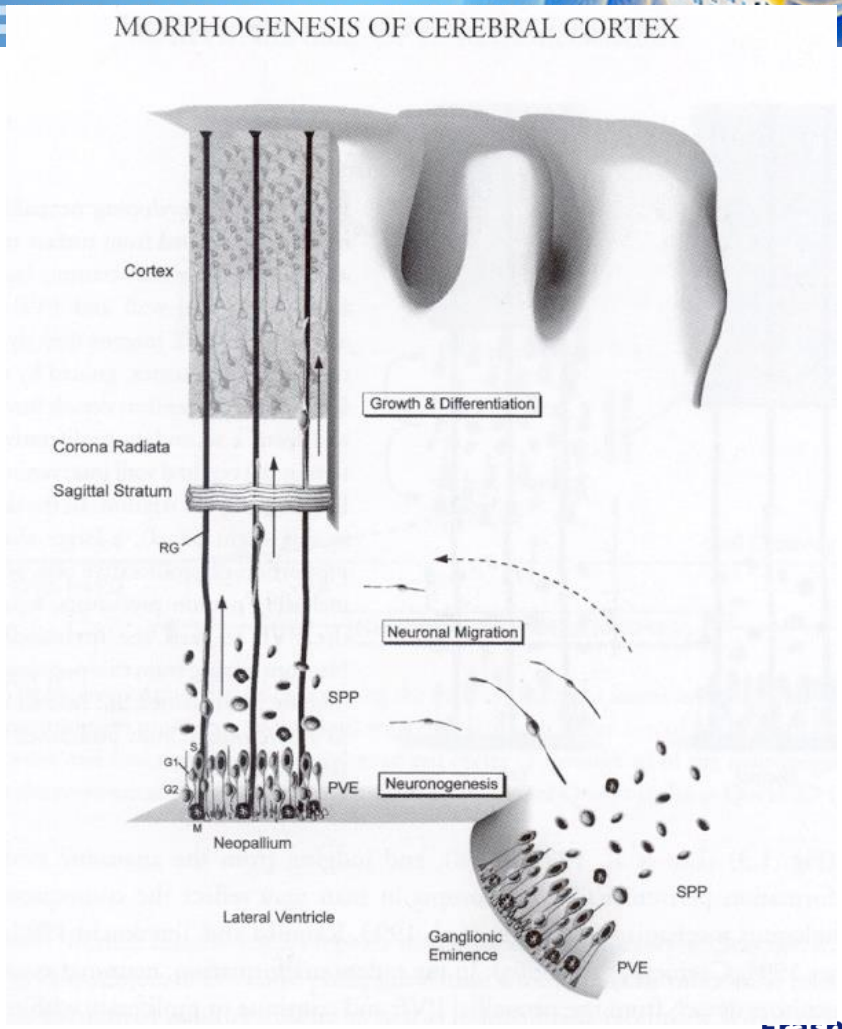
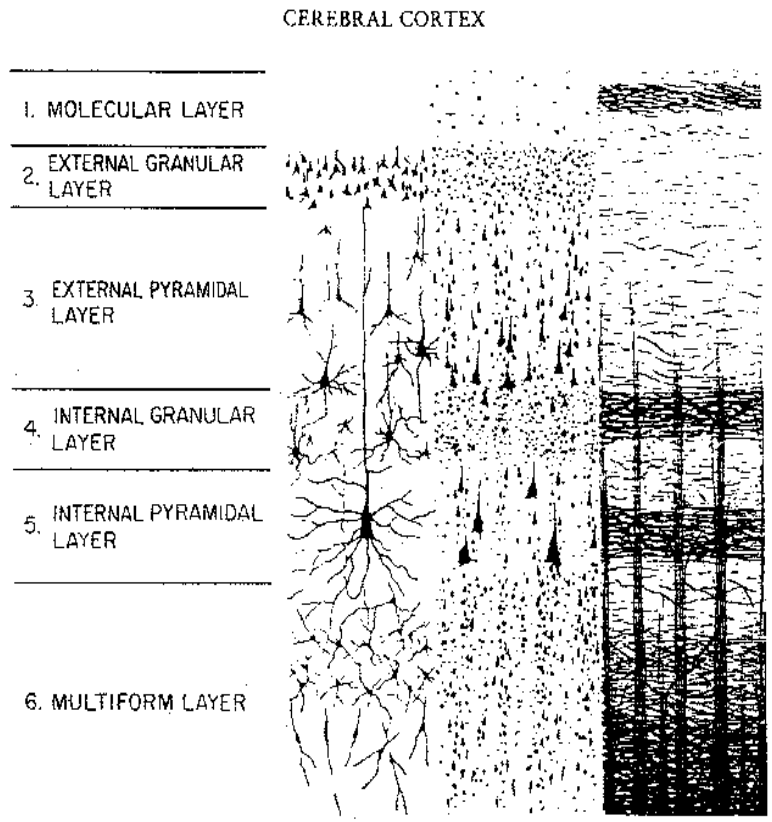
Development of the cerebral cortex

https://boneclones.com/product/human-brain-multiple-coronal-sections-KO-515



P.G. Barth, “Disorders of Neuronal Migration”, ICNA series, 2003

Developmenat of the cerebral cortex



1. Dorsal Induction	3-7 w.
2. Ventral Induction	5-6 w.
3. Neuronal/Glia Proliferation	8-16 w.
4. Migration	12-20 w.
5. Organization	>24 w.
6. Myelination	>24w/2 yr.

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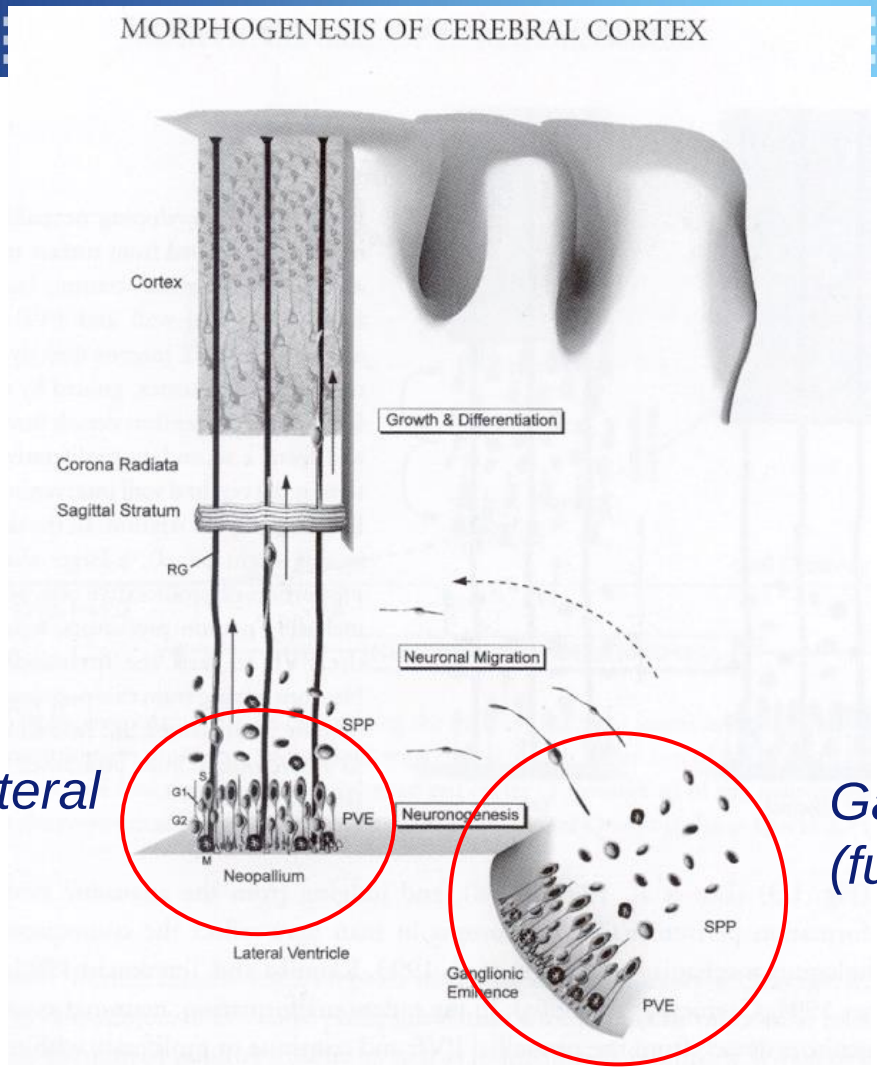
3. Neuronal and glia proliferation/ Neurogenesis

Neopallium (border of the lateral ventricles)



Ganglionic eminences (future basal ganglia)

Barth, “Disorders of Neuronal Migration”, ICNA series, 2003

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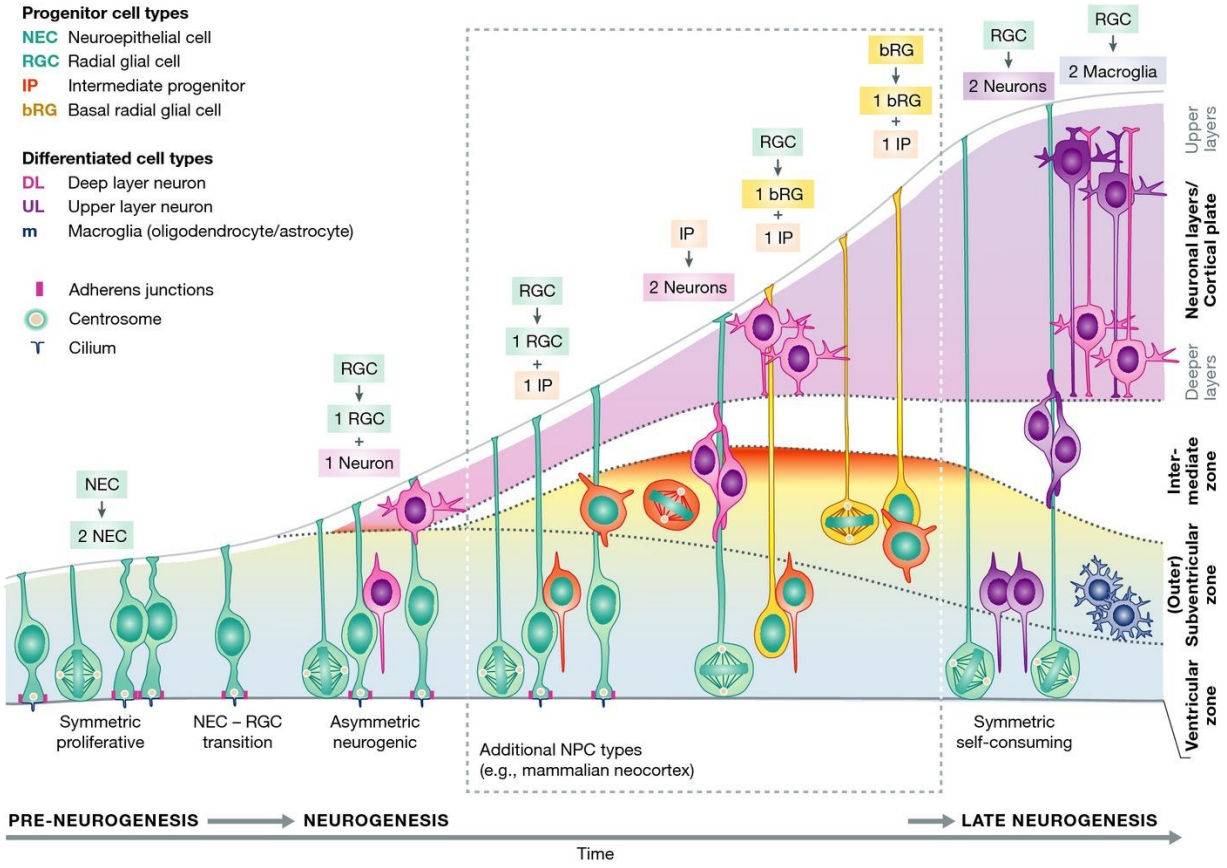
Neurogenesis: Many NPC progenies occur and persist during different periods



EMBO Rep, Volume: 15, Issue: 4, Pages: 351-364, First published: 17 March 2014, DOI: (10.1002/embr.201438447)

The principal types of NPCs with the progeny they produce are indicated by different colors. Additional NPC types that are typically found in mammalian neocortex are indicated in the box

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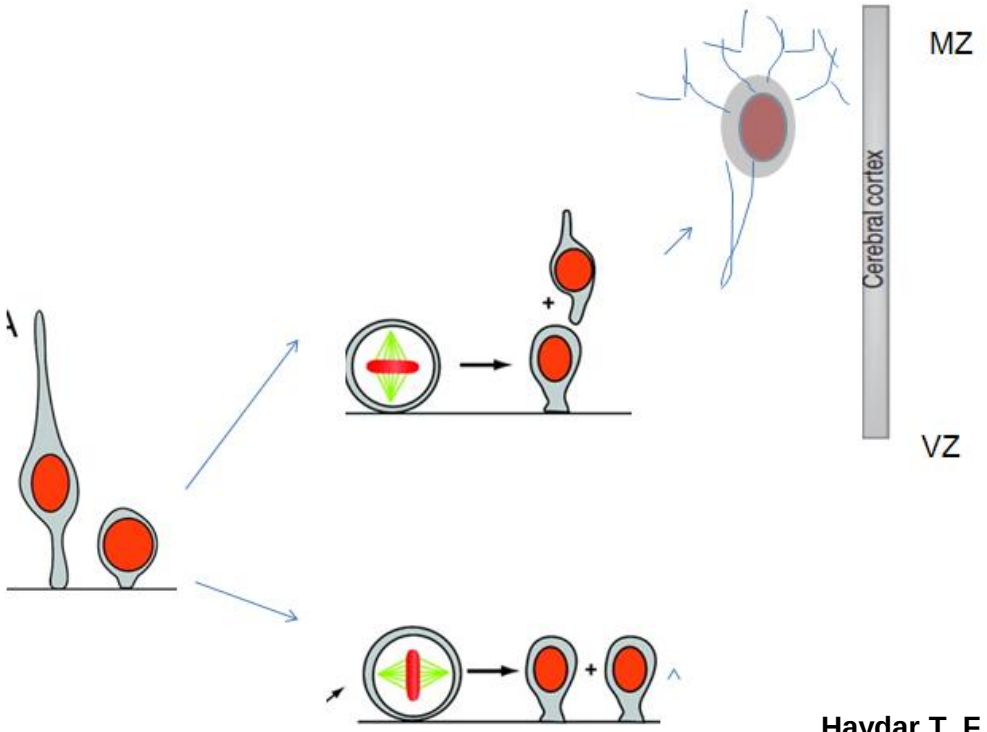
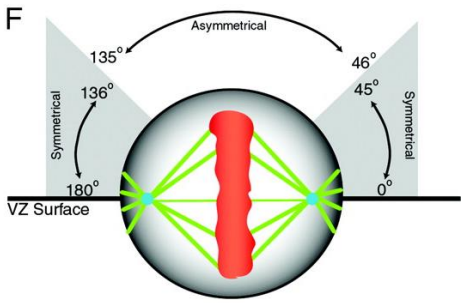
NPC proliferation and differentiation regulated by balance between "symmetric" and "asymmetric" mitosis





Haydar T. F. et.al. PNAS 2003;100:2890-2895

Change of mitotic "cleavage plane" determines the switch from proliferation to differentiation and migration (change in cell fate)

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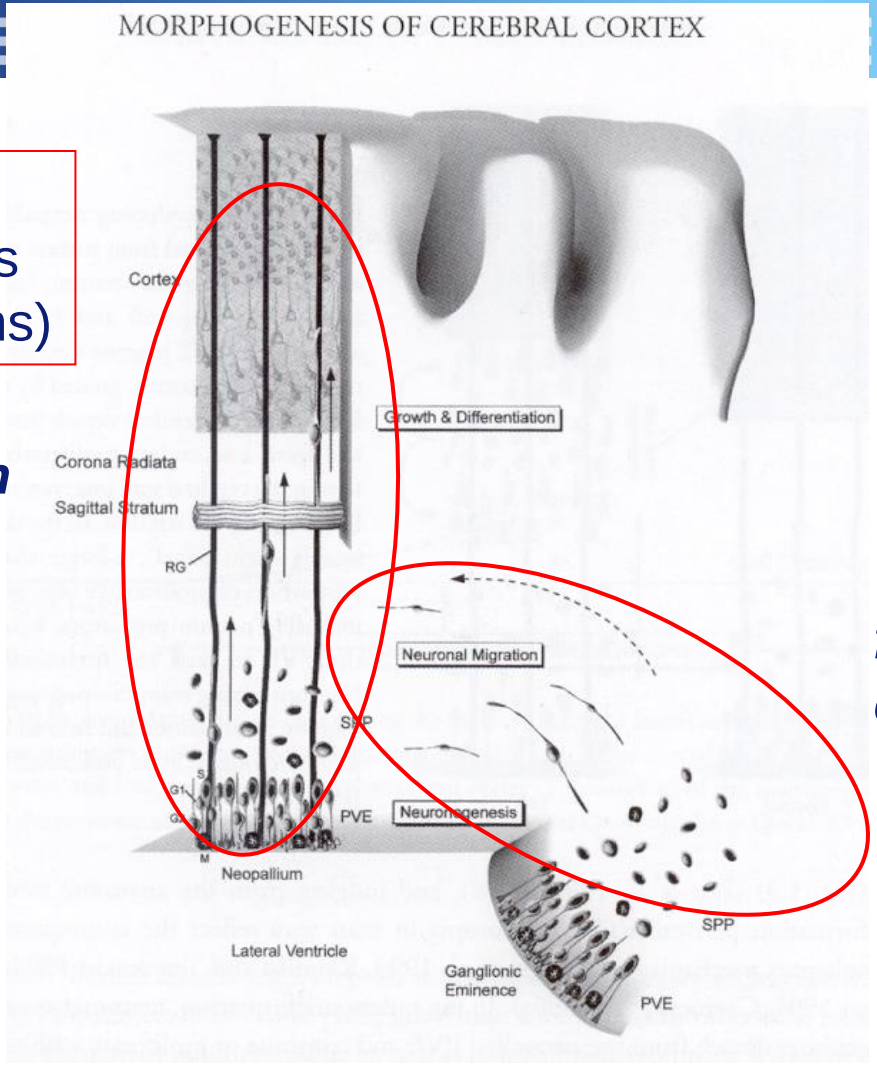
4. Neuronal migration

Glutamatergic
Excitatory neurons
(pyramidal neurons)

Radial migration
from the Neopallium

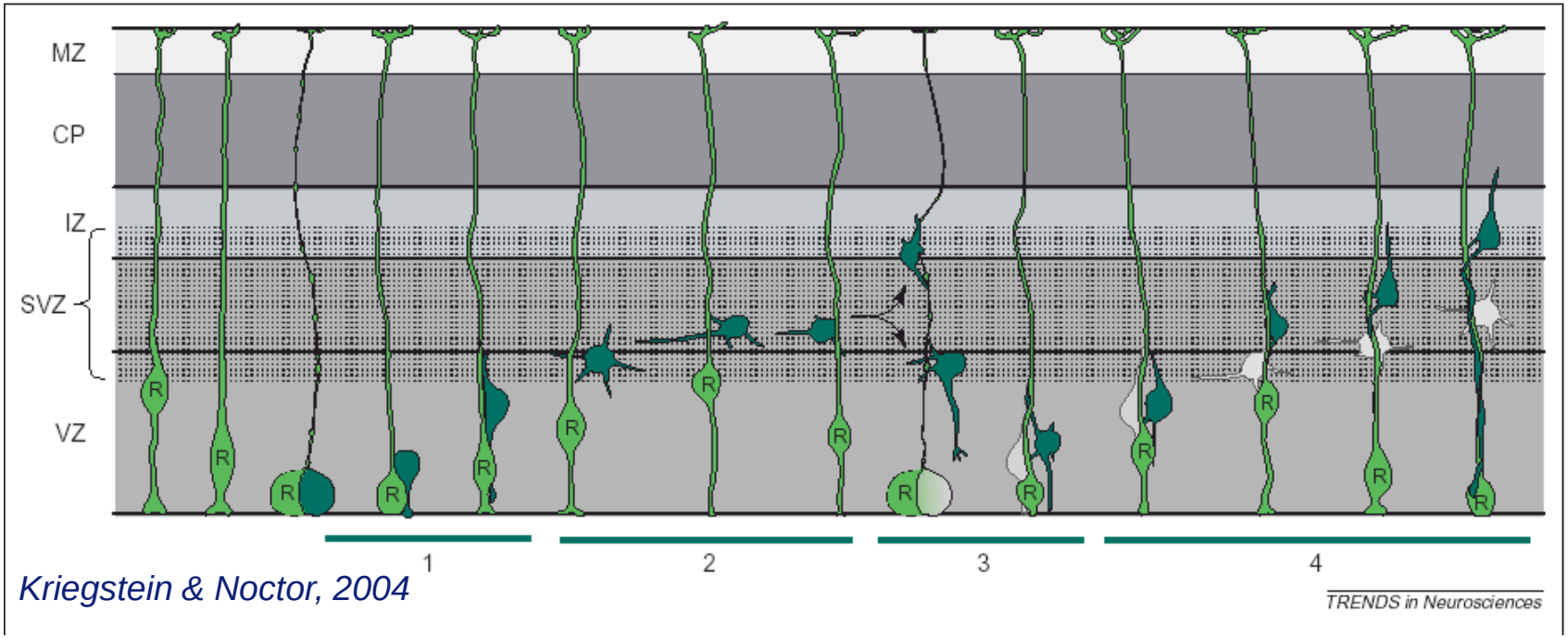


Tangential migration
from the Ganglionic eminences

GABAergic
Inhibitory neurons
(interneurons)

Barth, “Disorders of Neuronal Migration”, ICNA series, 2003

Radial migration (pyramidal neurons)



Kriegstein & Noctor, 2004

Radial glial cells:

Common progenitors for neurons and (oligodendro)glia

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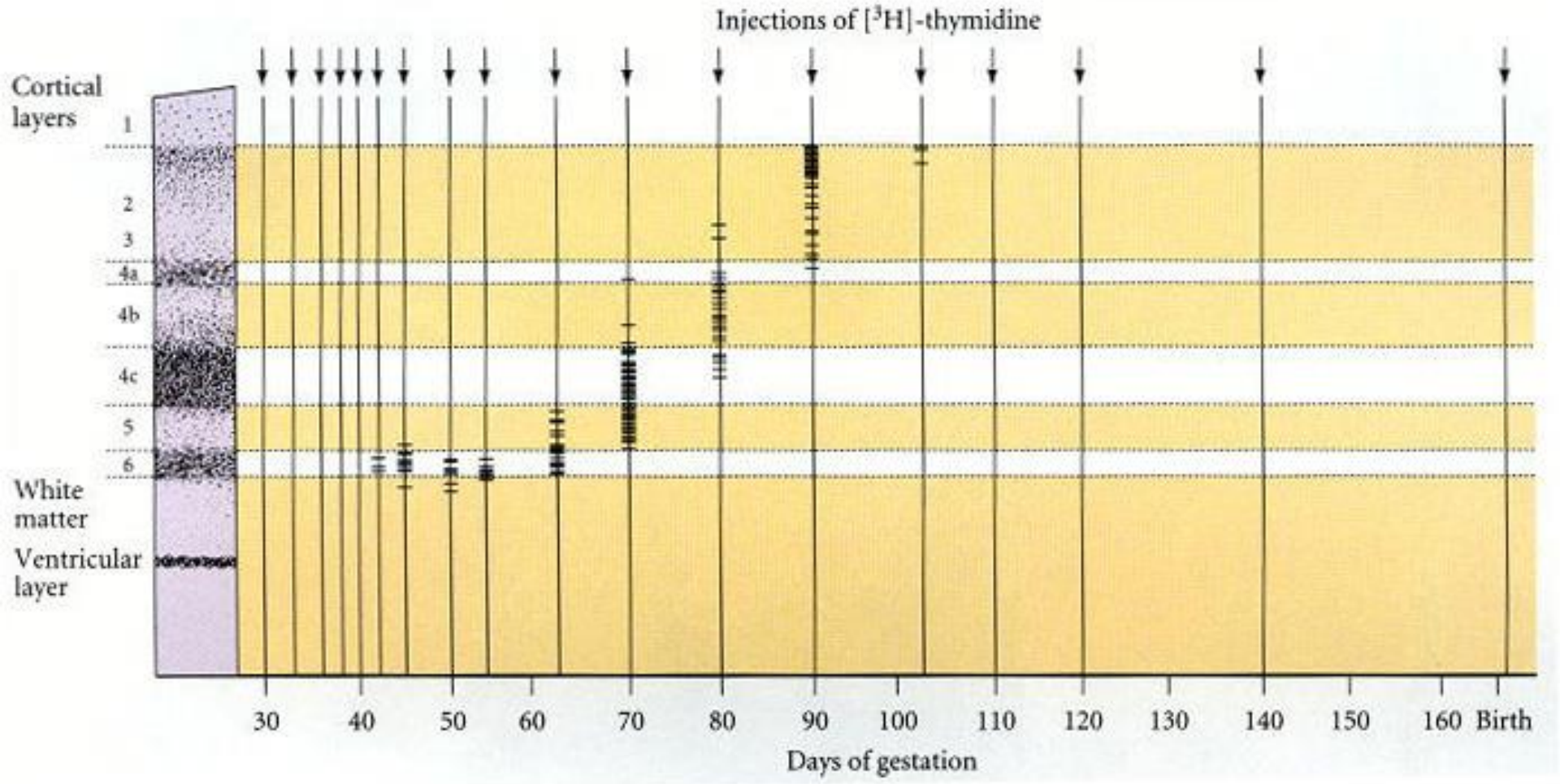

Cortical neurons migrate inside-out (later-born neurons migrate past early-born neurons to occupy superficial layers)

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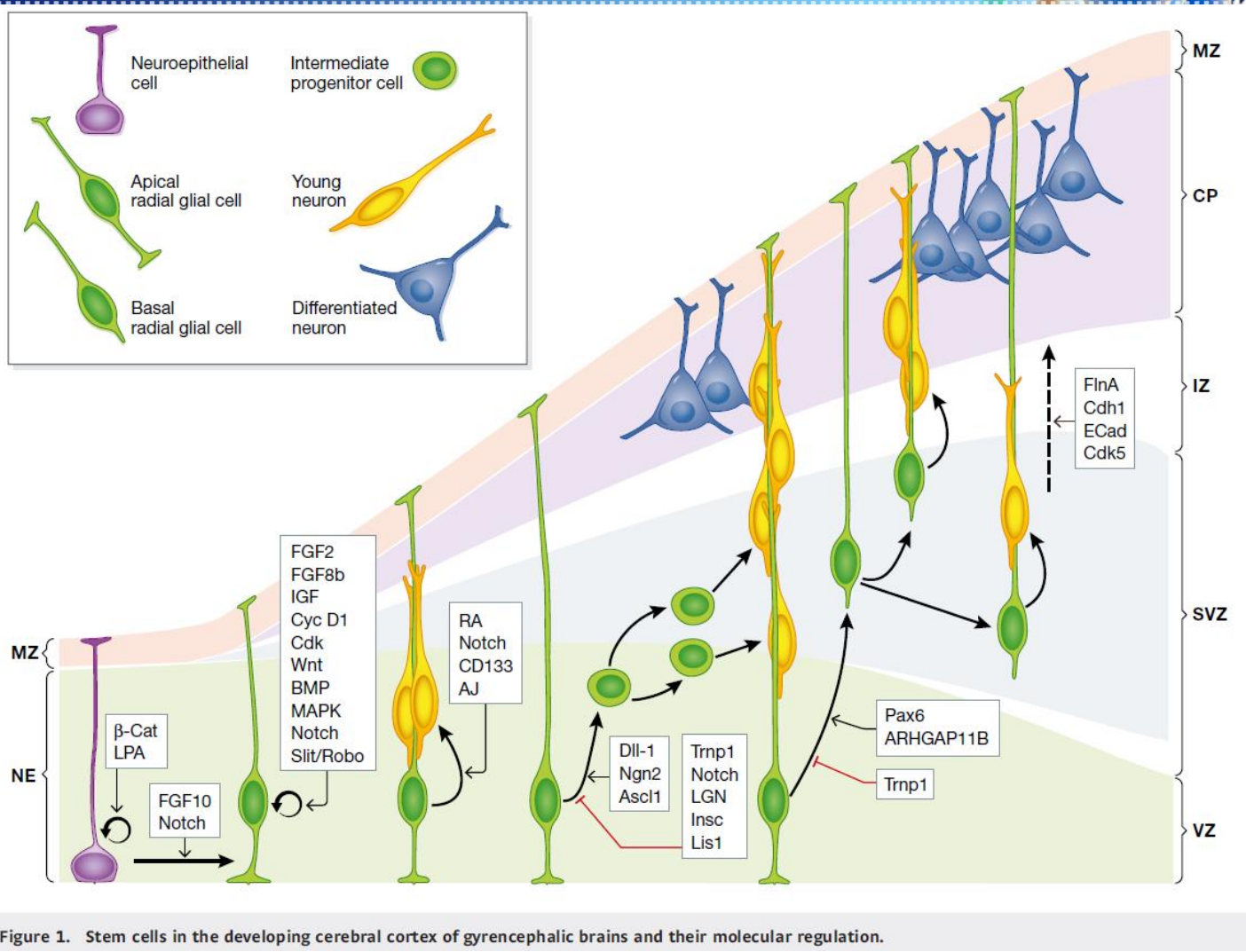

Figure 1. Stem cells in the developing cerebral cortex of gyrencephalic brains and their molecular regulation.

Published online: April 7, 2016

Review

THE EMBO JOURNAL

Cerebral cortex expansion and folding: what have we learned?

Virginia Fernández*, Cristina Llinares-Benadero† & Víctor Borrell*

Cellular determinants of cortical development:

- *Mitotic rate*
- *Differentiation*
- *Interactions through axons, dendrites, synapses*

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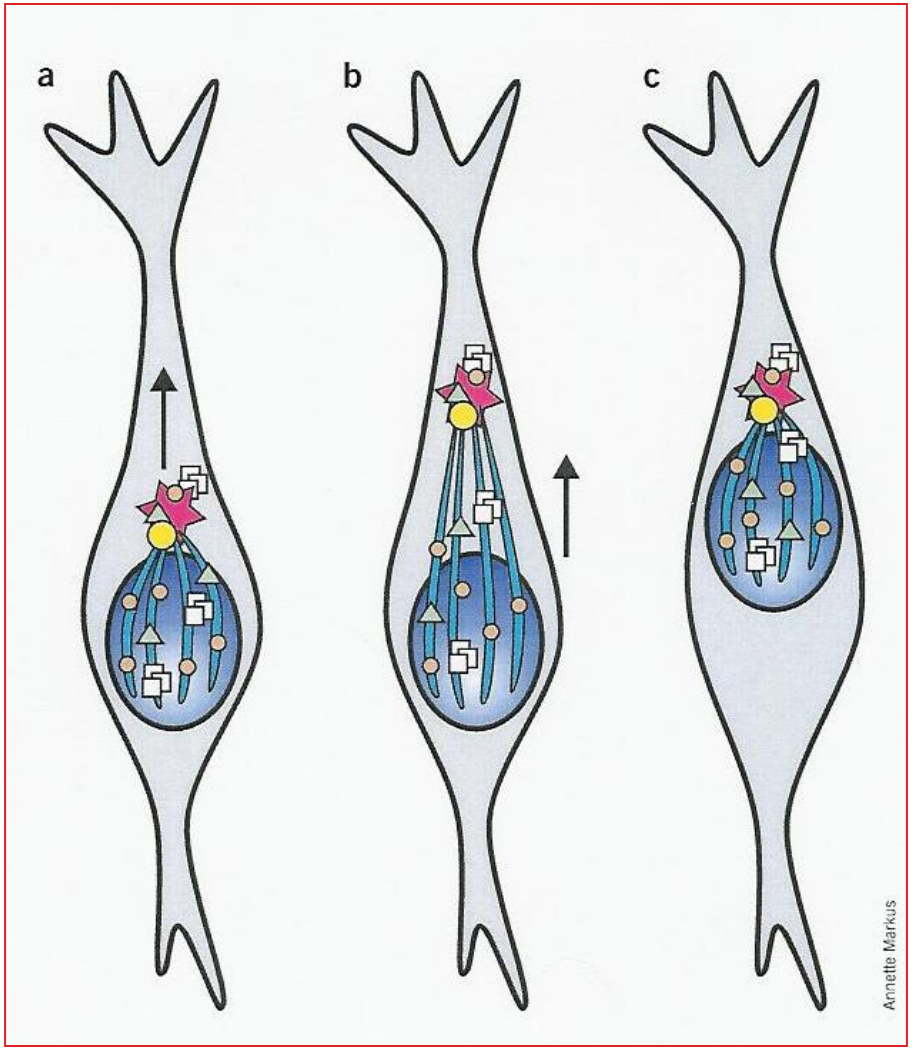
Neuronal migration is mediated by extension of leading process and saltatory nucleokinesis (somal translocation)



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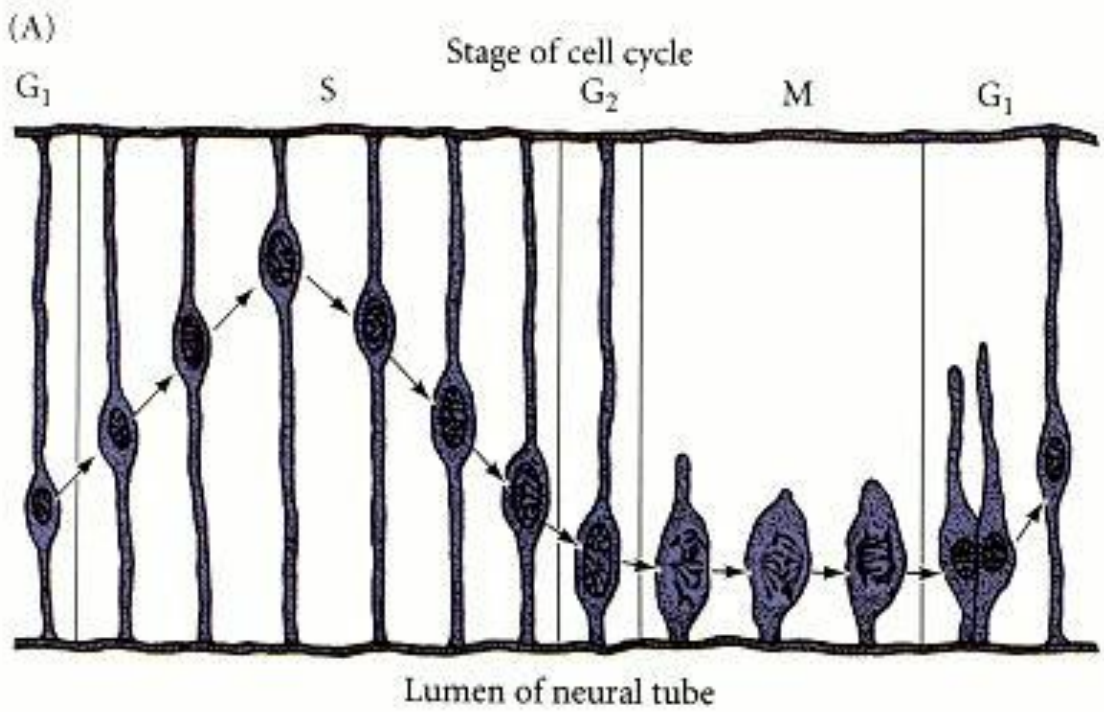
Neuronal migration is cell cycle- dependent



Only neurons in S phase undergo nucleokinesis

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Outer Radial Glia (oRG) undergo pre-Mitotic Soma Translocation (MST) and mitosis has horizontal cleavage plane

Available online at www.sciencedirect.com
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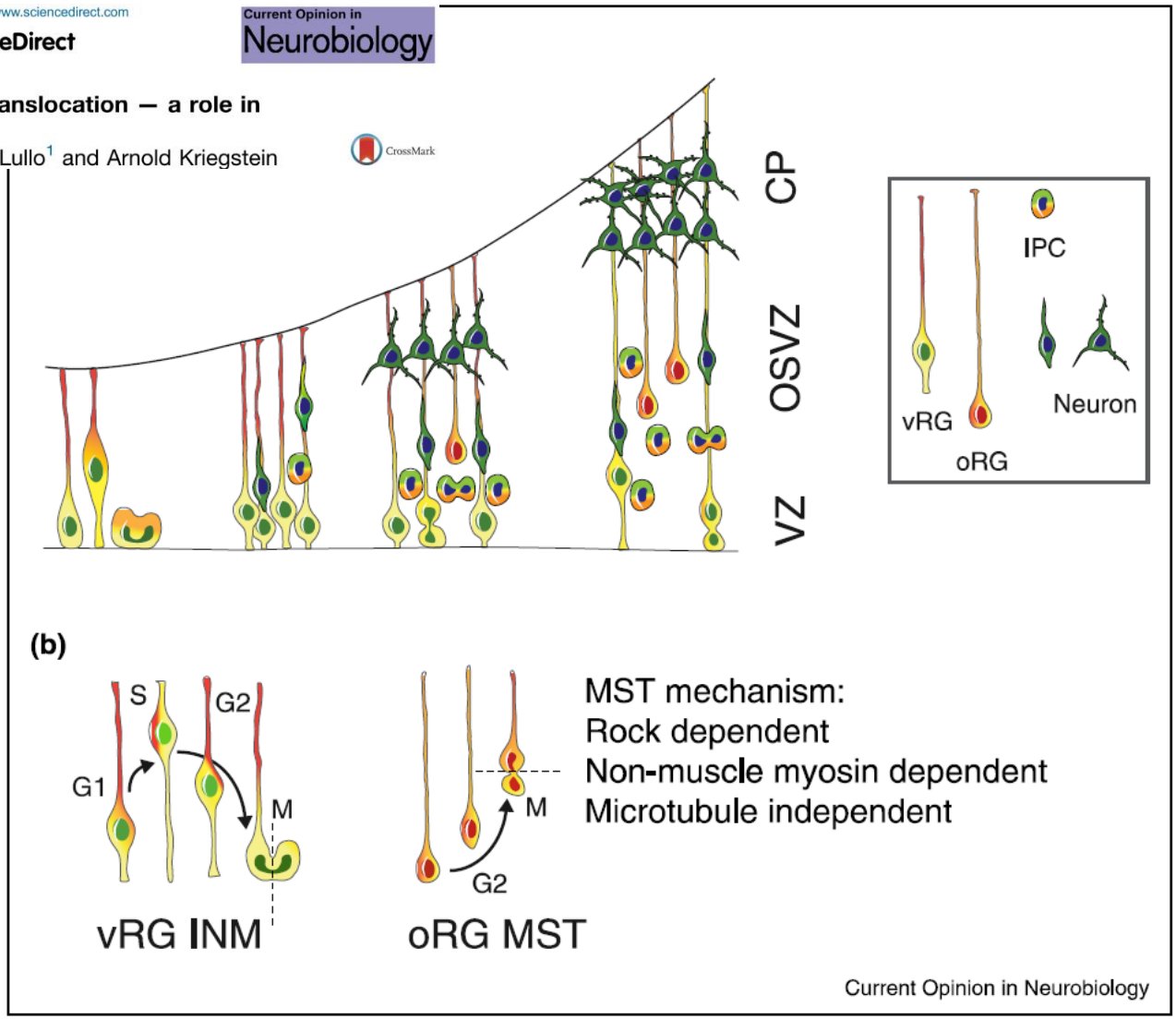
Current Opinion in Neurobiology

oRGs and mitotic somal translocation — a role in development and disease

Bridget Ostrem[1], Elizabeth Di Lullo[1] and Arnold Kriegstein



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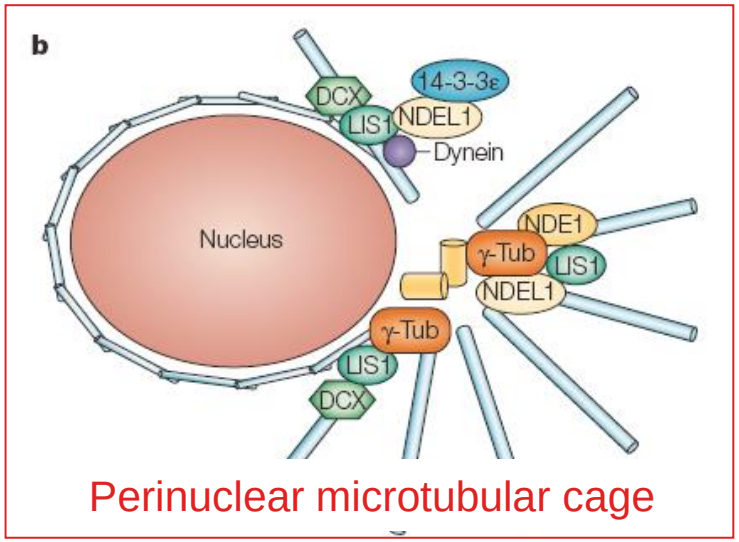
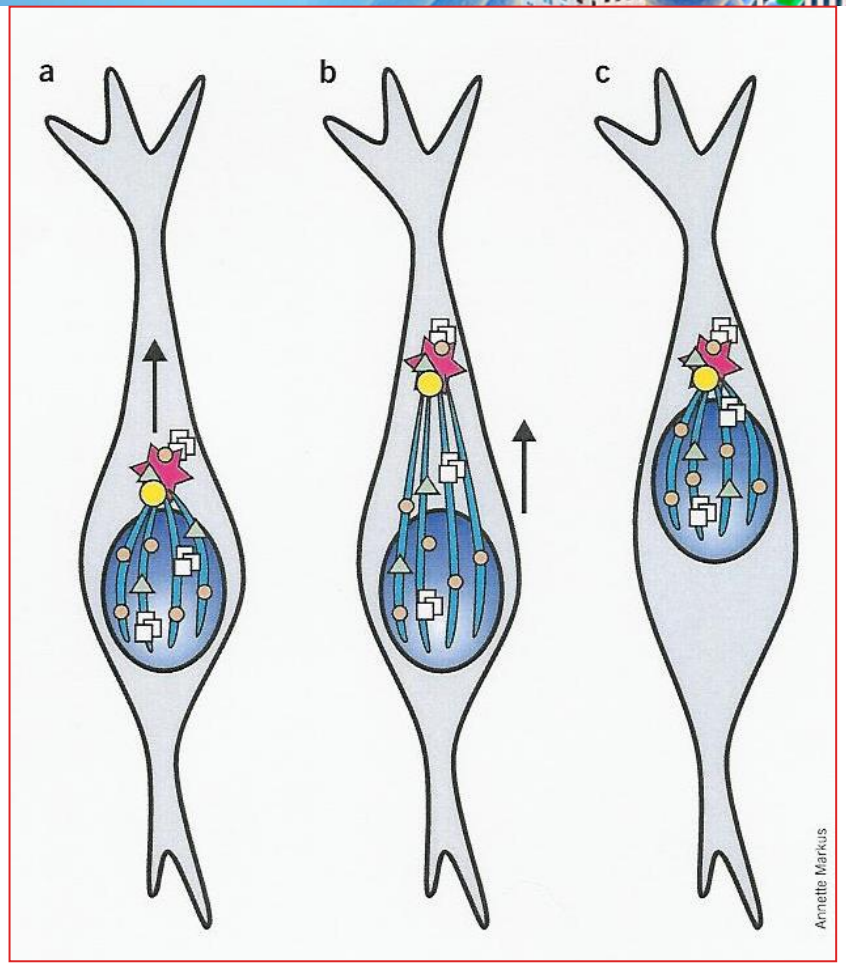
Cellular components regulating neuronal migration

- Microtubule Organizing Center (=centrosome)
- Cytoskeleton
- Golgi
- RER
- Mitochondria
- Endosomal vesicles



Perinuclear microtubular cage



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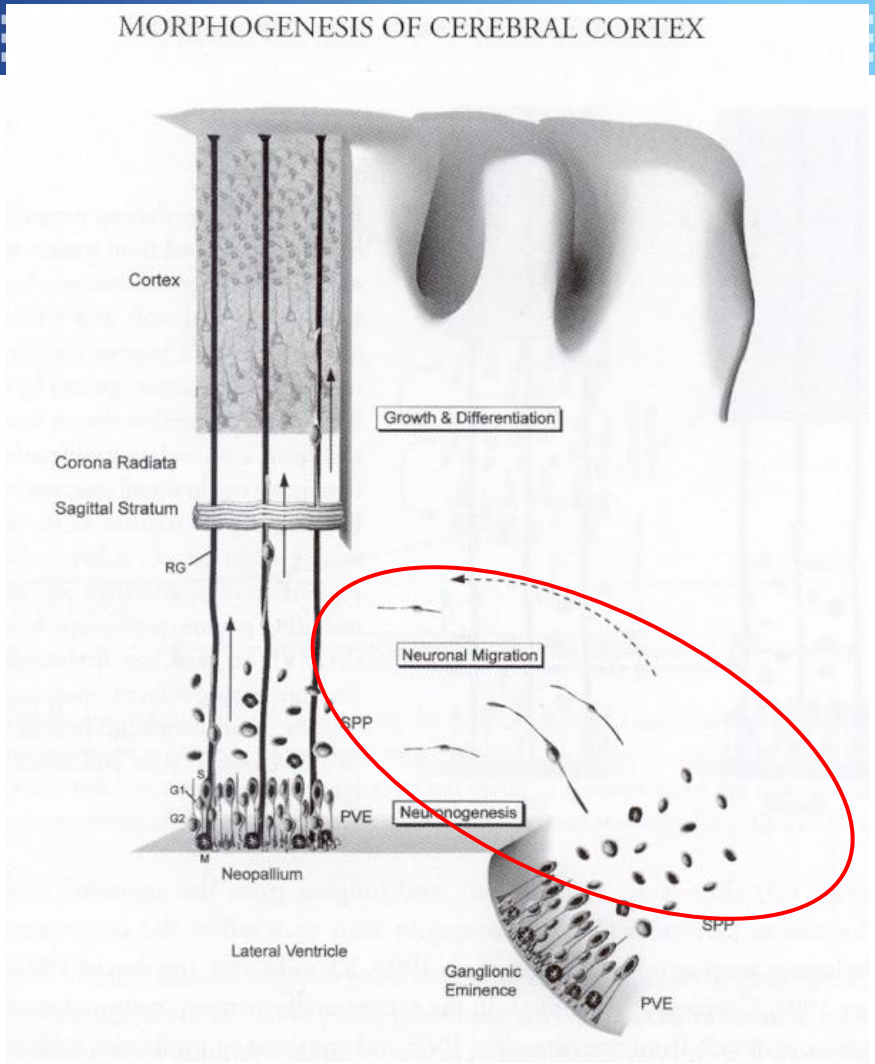
4. Neuronal migration



Tangential migration

from the Ganglionic Eminences and the "Cortical hem"

Barth, "Disorders of Neuronal Migration", ICNA series, 2003

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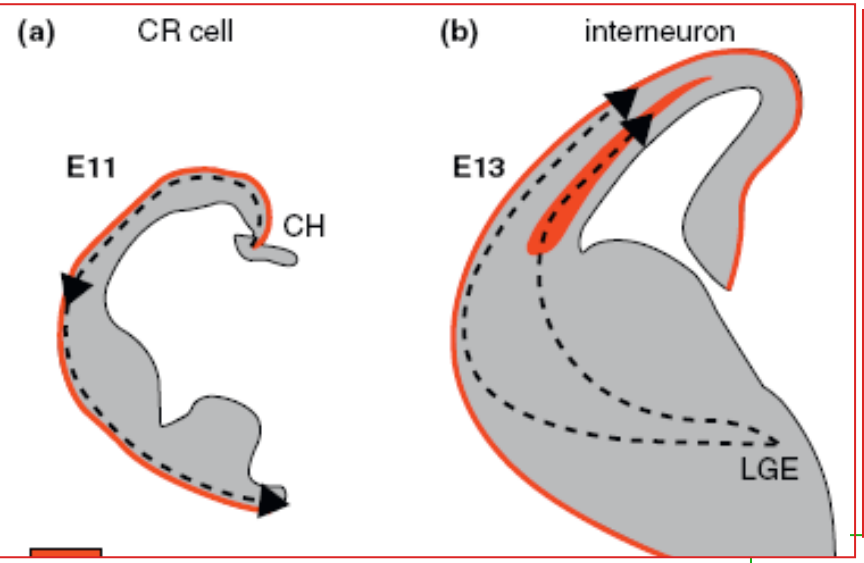
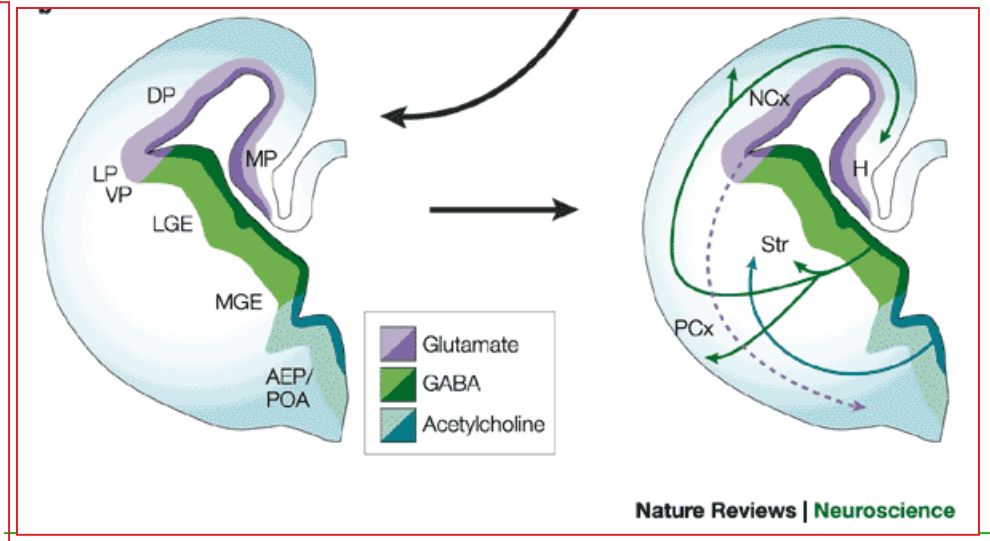
Tangential migration

mouse E11: from the Cortical Hem (Cajal-Retzius, glutamatergic)
mouse E13: from the ganglionic heminences (GABA-ergic)

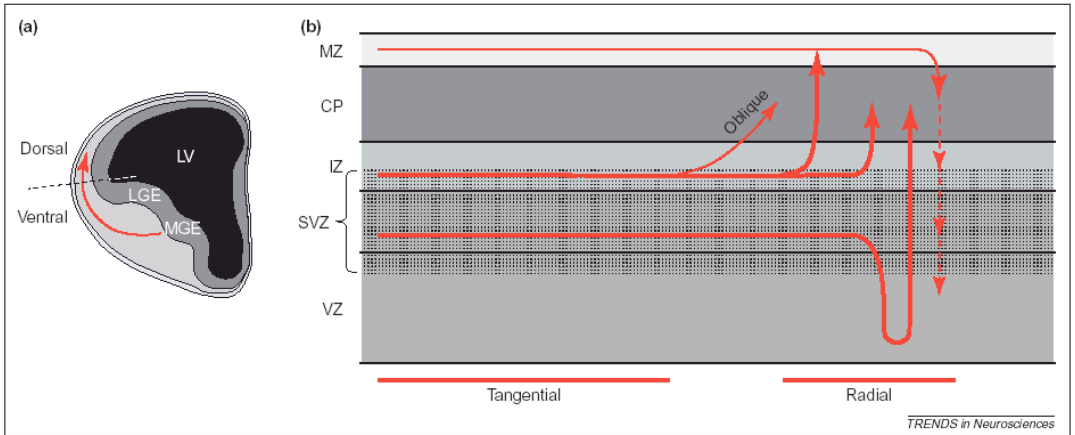




CH= cortical hem

LGE= lateral ganglionic eminence

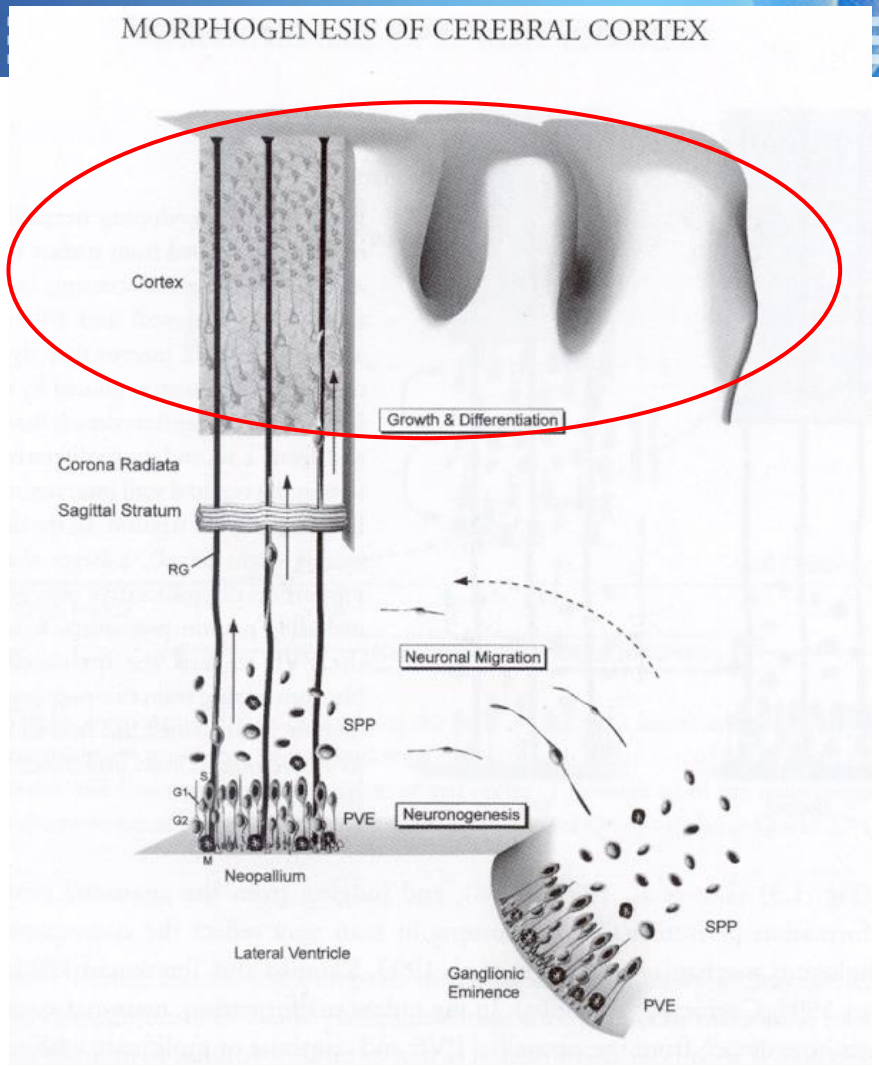
MGE= medial ganglionic eminence



5. Organization of the cerebral cortex

Organization of the gyri after neuronal migration

Dendritogenesis and synaps formation



Barth, “Disorders of Neuronal Migration”, ICNA series, 2003

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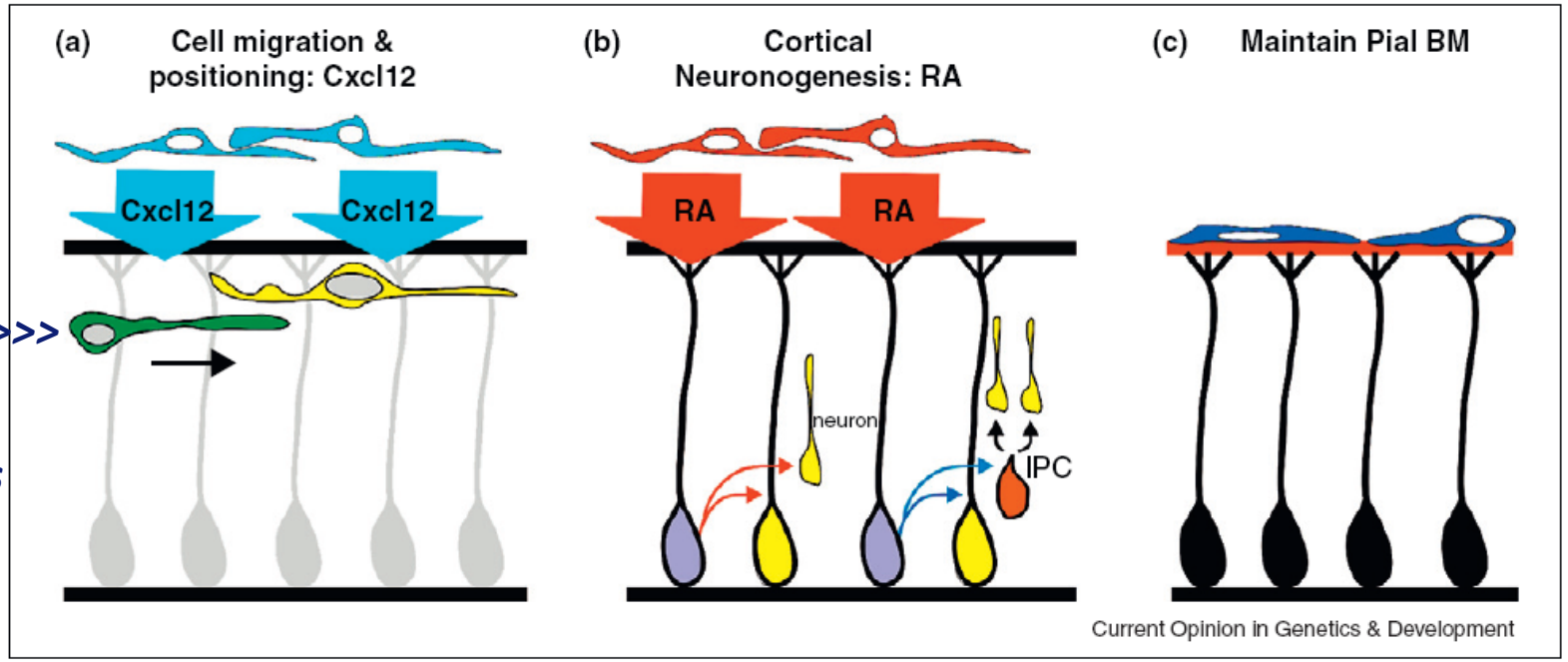
Cortical organization is controlled by the Cajal-Retzius neurons, the radial glia and the meninges via Retinoic Acid (Vit A).

Cajal-Retzius >>>

secrete reelin, that regulates neuron positioning



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We have got you 'covered': how the meninges control brain development

Julie A Siegenthaler and Samuel J Pleasure

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When does gyration start?

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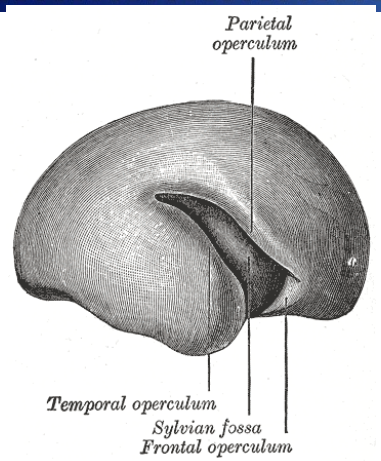
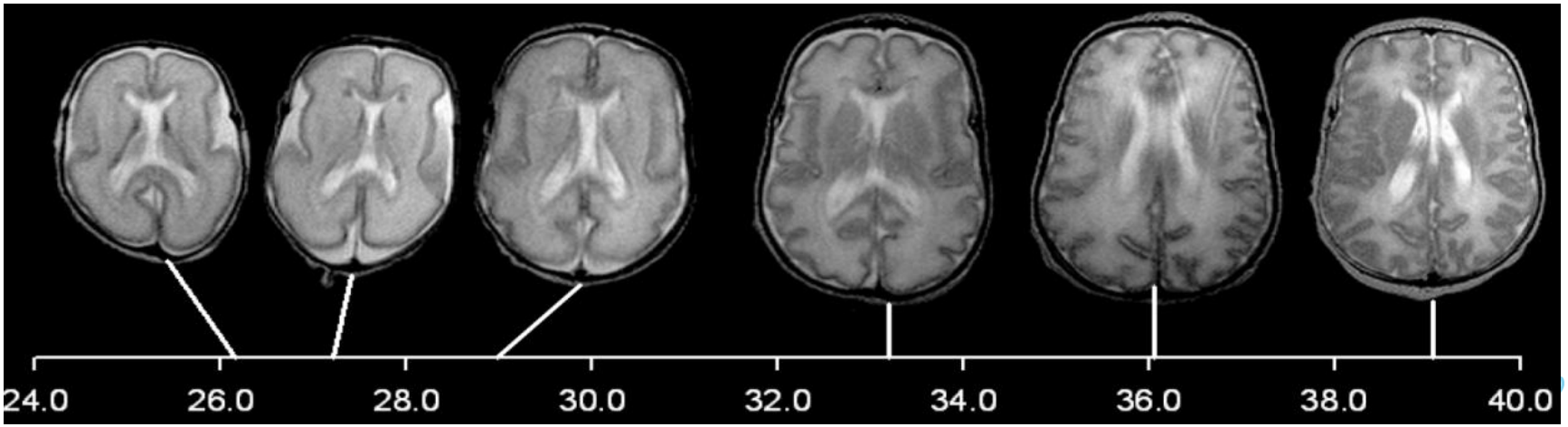
Gyration occurs in the 3rd trimester (> 24w)



GW 20

Prenatal brain MRI



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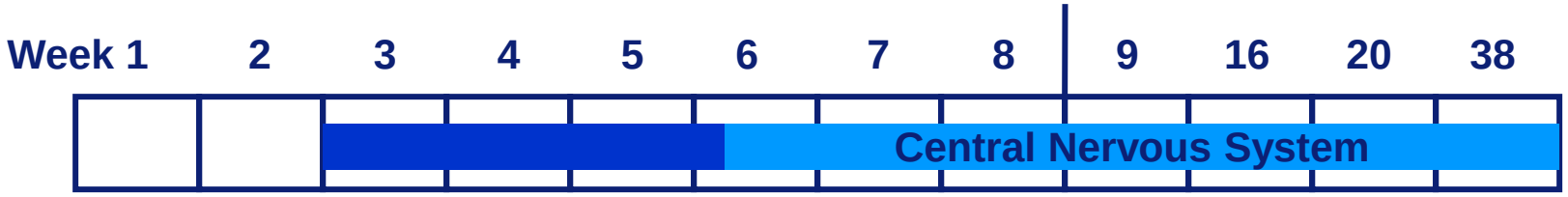

Malformations of Cortical Development

Process	Abnormality	Time of gestation
1.Dorsal Induction	Neural Tube defects	3-7 w.
2.Ventral Induction	Holoprosencephaly	5-6 w.
3.Neuronal/Glial Proliferation	Micro/Megalencephaly	8-16 w.
4.Migration	Lissencephaly/Heterotopia	12-20 w.
5.Organization	Polymicrogyria, cort.dysplasia	>24 w.
6.Myelination	Hypo/dysmyelination	>24w.-2 yr.

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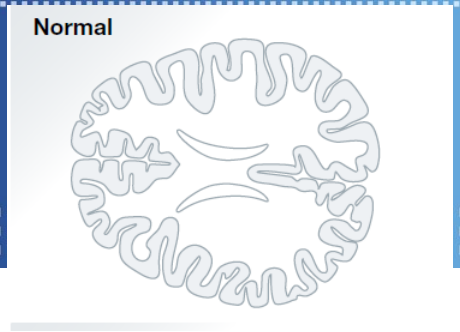
Malformations



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Review

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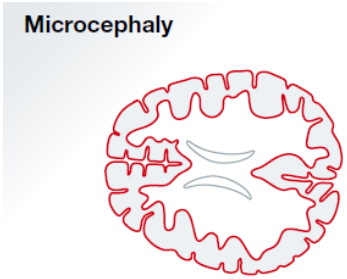
THE EMBO JOURNAL

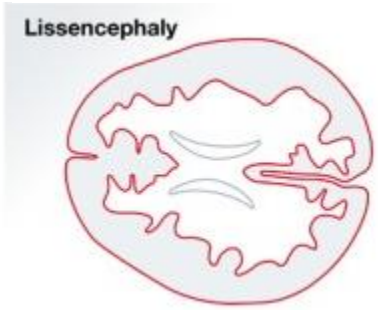
Cerebral cortex expansion and folding: what have we learned?

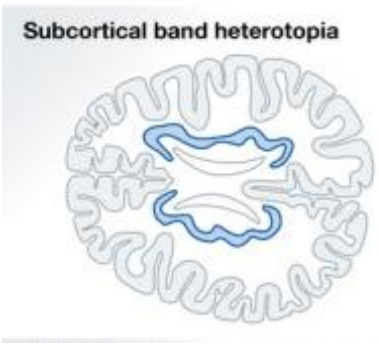
Virginia Fernández†, Cristina Llinares-Benadero† & Víctor Borrell*

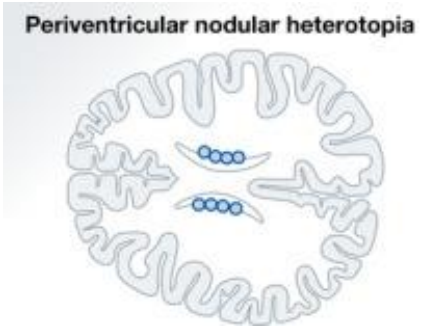
Proliferation



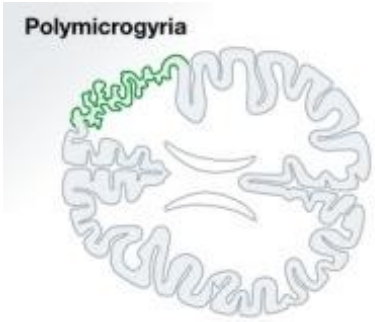
Migration







Organization



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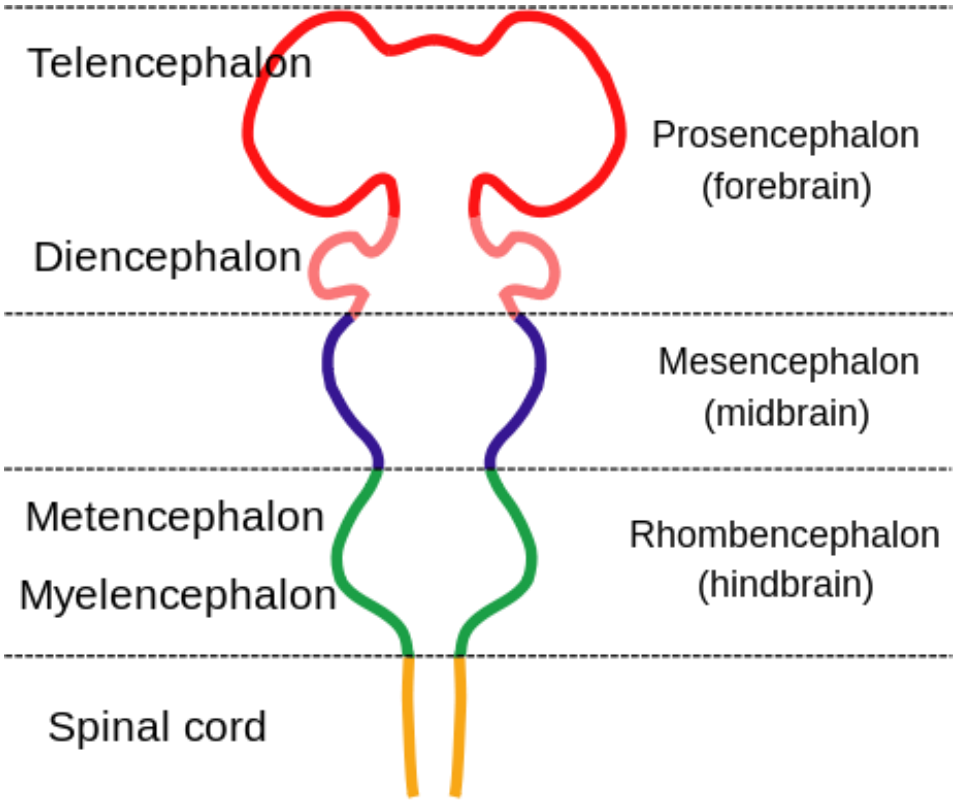
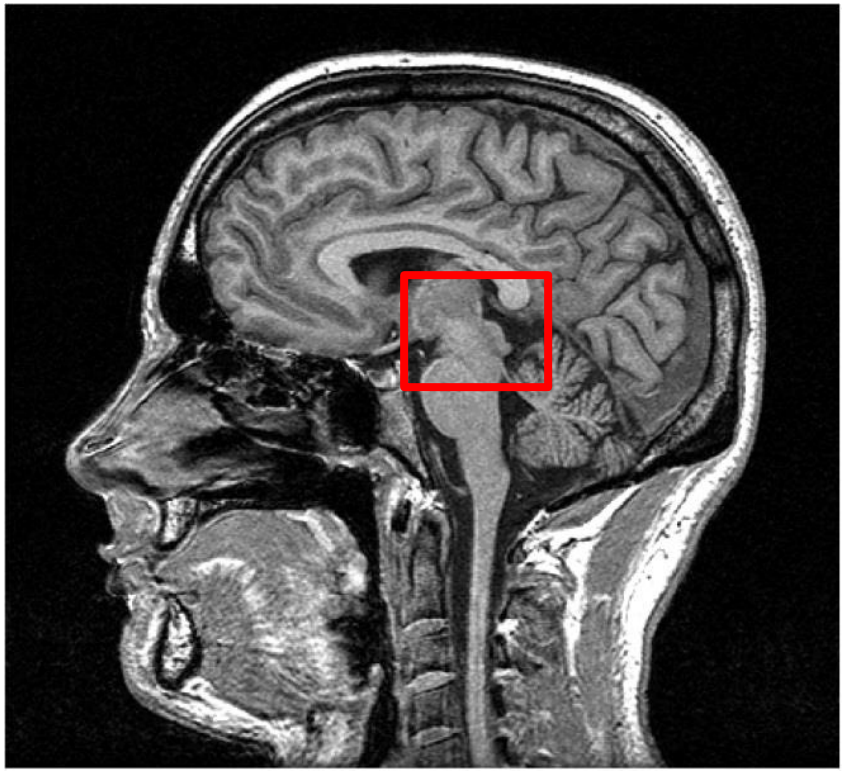
Mesencephalon





From the mesencephalon derive: cerebral peduncles, substantia nigra, aqueduct of Sylvius, tectum (lamina quadrigemina), CN III and IV…

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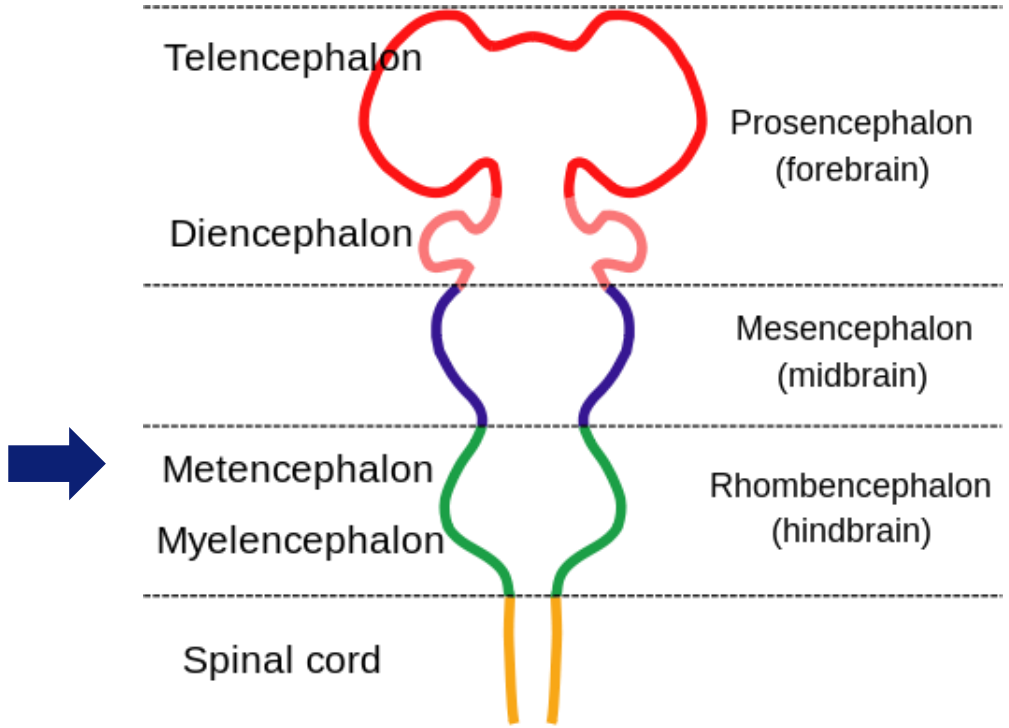
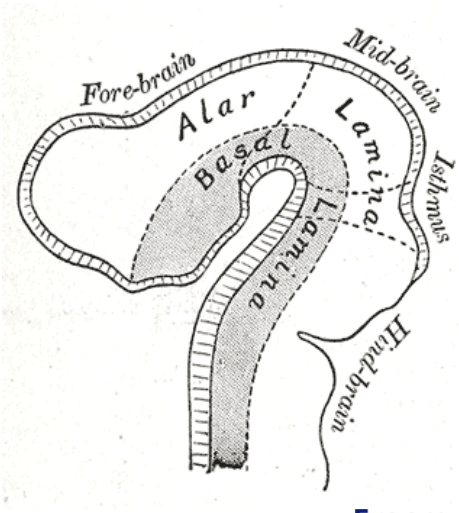
Cerebellum development

- Metencephalon: pons and cerebellum

- Time span: 4w post-conception > 2 yr

- Extensive proliferation: 10% of total brain volume, contains >50% of neurons





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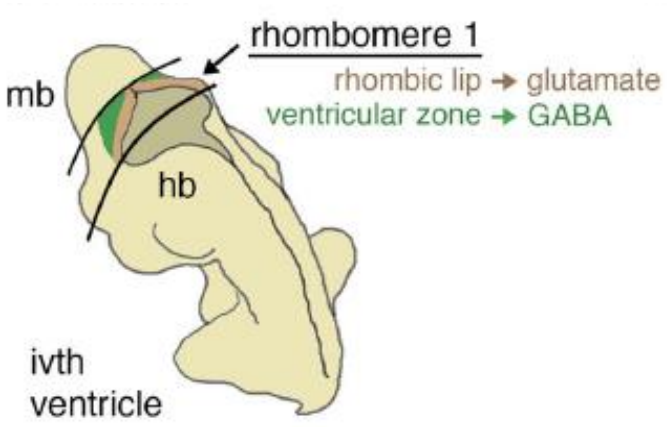
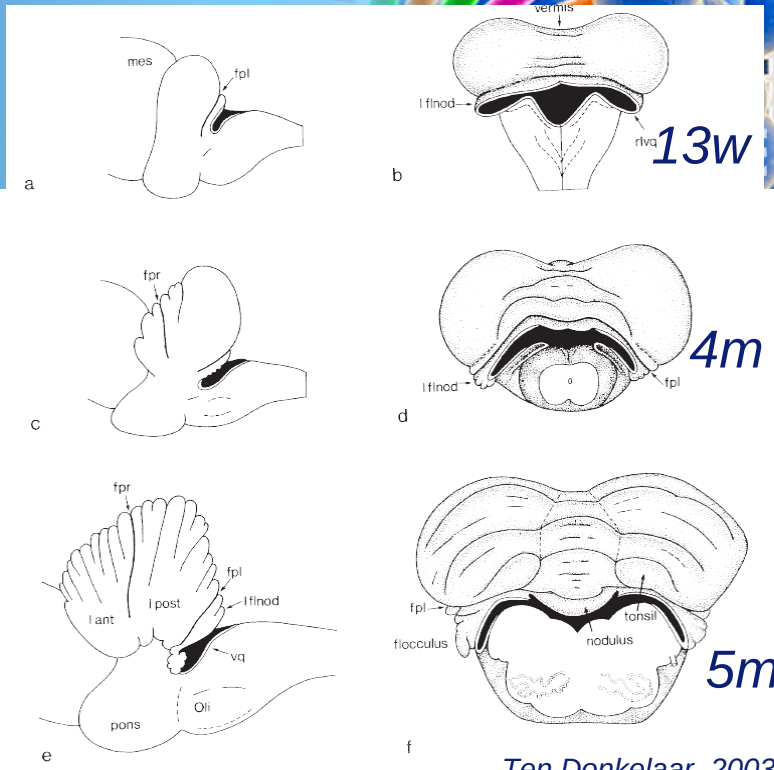
Cerebellum development





Ten Donkelaar, 2003

Basic steps:

1. Characterization of the territory at midbrain-hindbrain boundary (**IsO**)
2. Formation of two compartments for cell proliferation: **VZ** and **uRL**
3. Inward migration of granule cells: **EGL** > **IGL**
4. Cerebellar circuitry formation and differentiation

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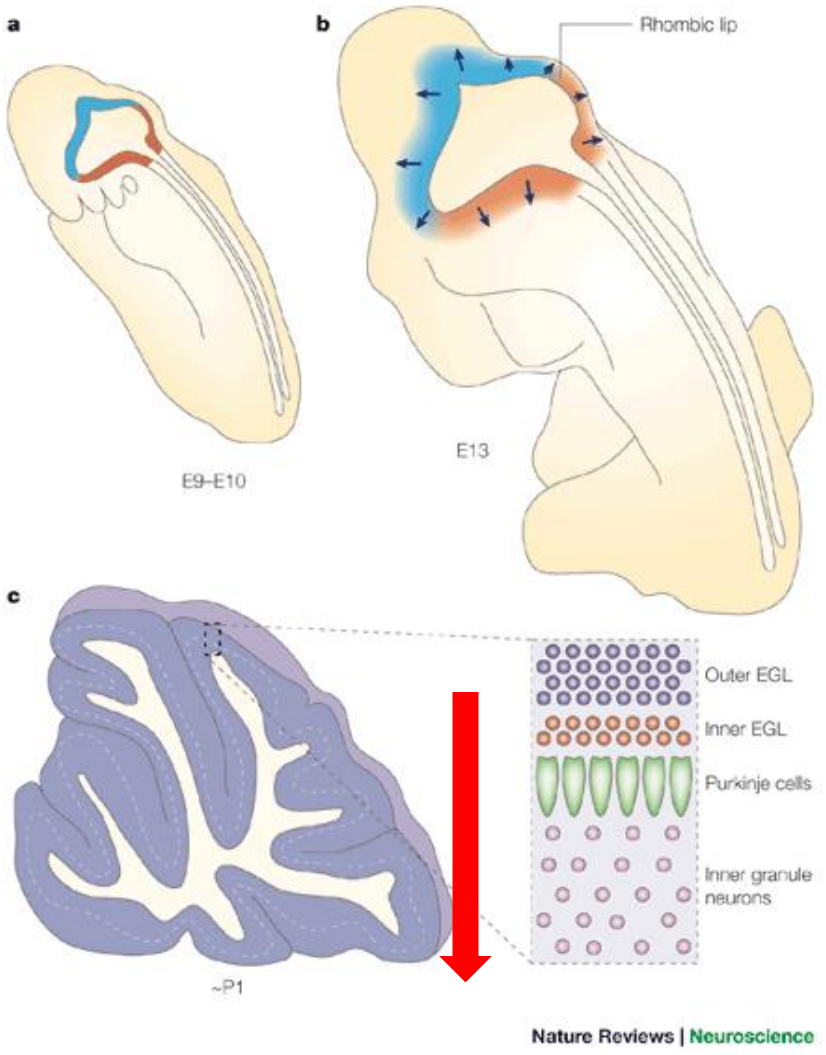
Cerebellum: neuronal migration is outside-in

Two germinal matrices:

-**Ventricular zone** > **GABA**-ergic Purkinje c., Golgi n., stellate and basket cells

-**Rhombic lip** > **Glutamatergic** granule neurons

-**EGL glutamatergic** neurons produce **reelin** and organize the outside-in migration



Wang V & Zoghbi H, 2001

Cerebellar cortex: three layers

frontiers in Systems Neuroscience

A Focus on the Cerebellum: From Embryogenesis to an Age-Related Clinical Perspective

Greta Amore[1], Giulia Spoto[1], Antonio Ieni[2], Luigi Vetri[3], Giuseppe Quatrosi[3], Gabriella Di Rosa[1†] and Antonio Gennaro Nicotera[1*†]

Neuronal types

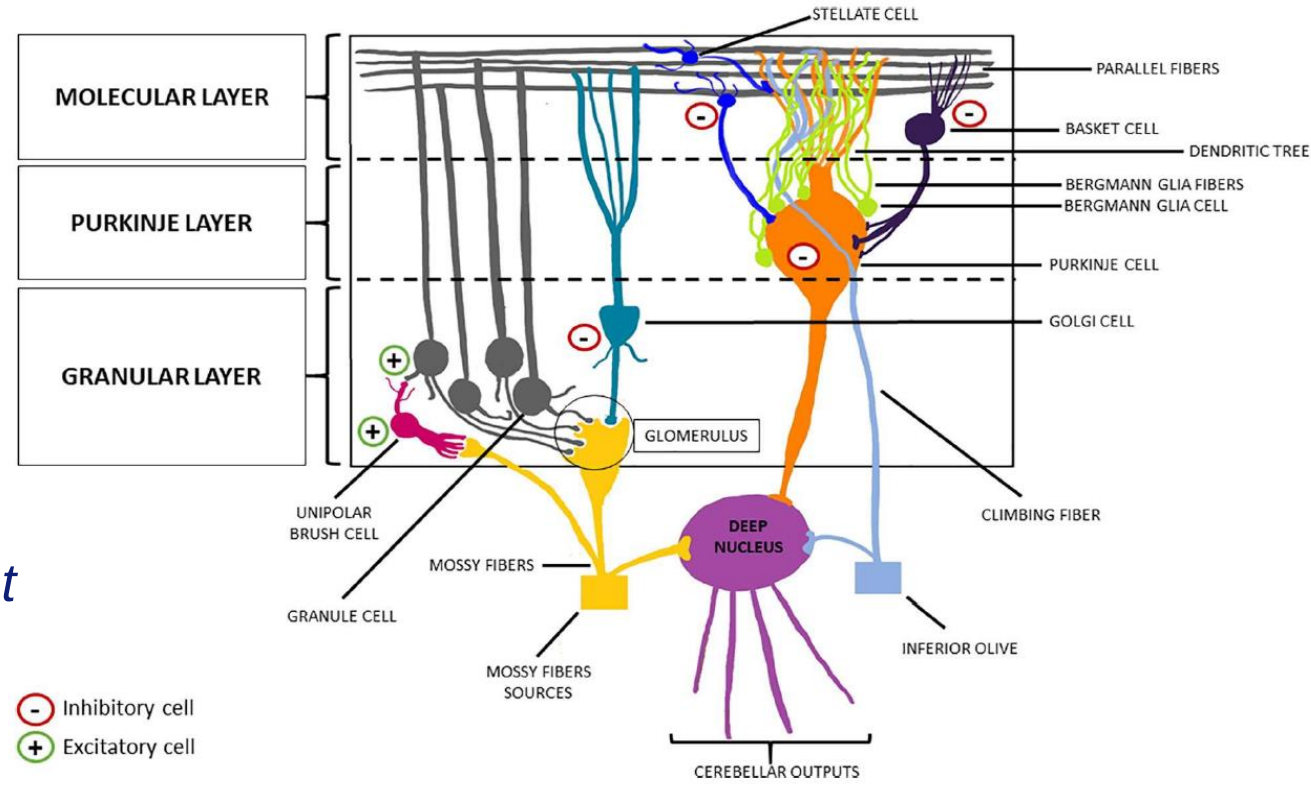
1-Glutamatergic

- *Granule cells*
- *Unipolar brush cells*
- *Deep cerebellar nuclear neurons*

2-GABAergic

- *Purkinje cells*
- *Interneurons, basket cells*
- *Golgi cells*
- *Deep cerebellar nuclear neurons*

3-Glia



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Cerebellum

1. Cerebellar hemispheres

Diffuse/focal hypoplasia
Polymicrogyria
Rhombencefalosynapsis

2. Vermis

Vermis hypoplasia (Molar tooth)
Dysplasia
Dandy Walker malformation

3. Pons

Pontocerebellar hypoplasia
Tegmental cap dysplasia
Hindbrain disconnection
Commissural / decussation defects

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