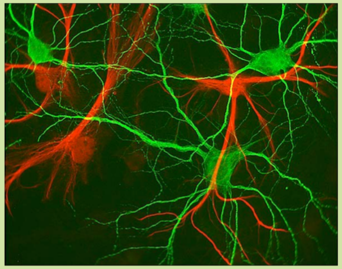
Nervous system development in Vertebrates

Caroline Borday

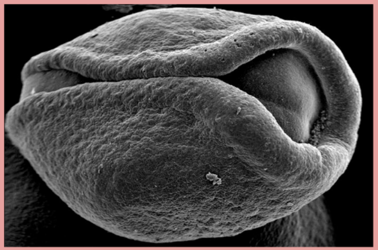
23th september 2024



- Nervous system description
- Nervous tissue

- Nervous system development

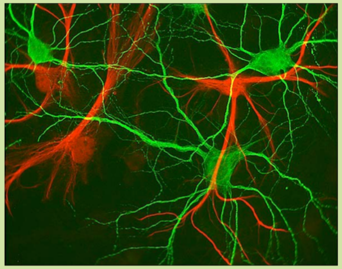
Neurulation



- Neural induction
- Anteroposterior regionalization

Rhombencephalon

- Dorsoventral regionalization
- Migration ans synaptogenesis



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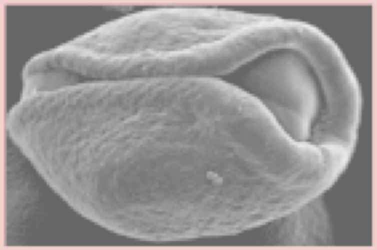

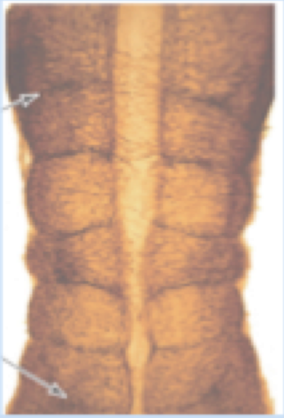

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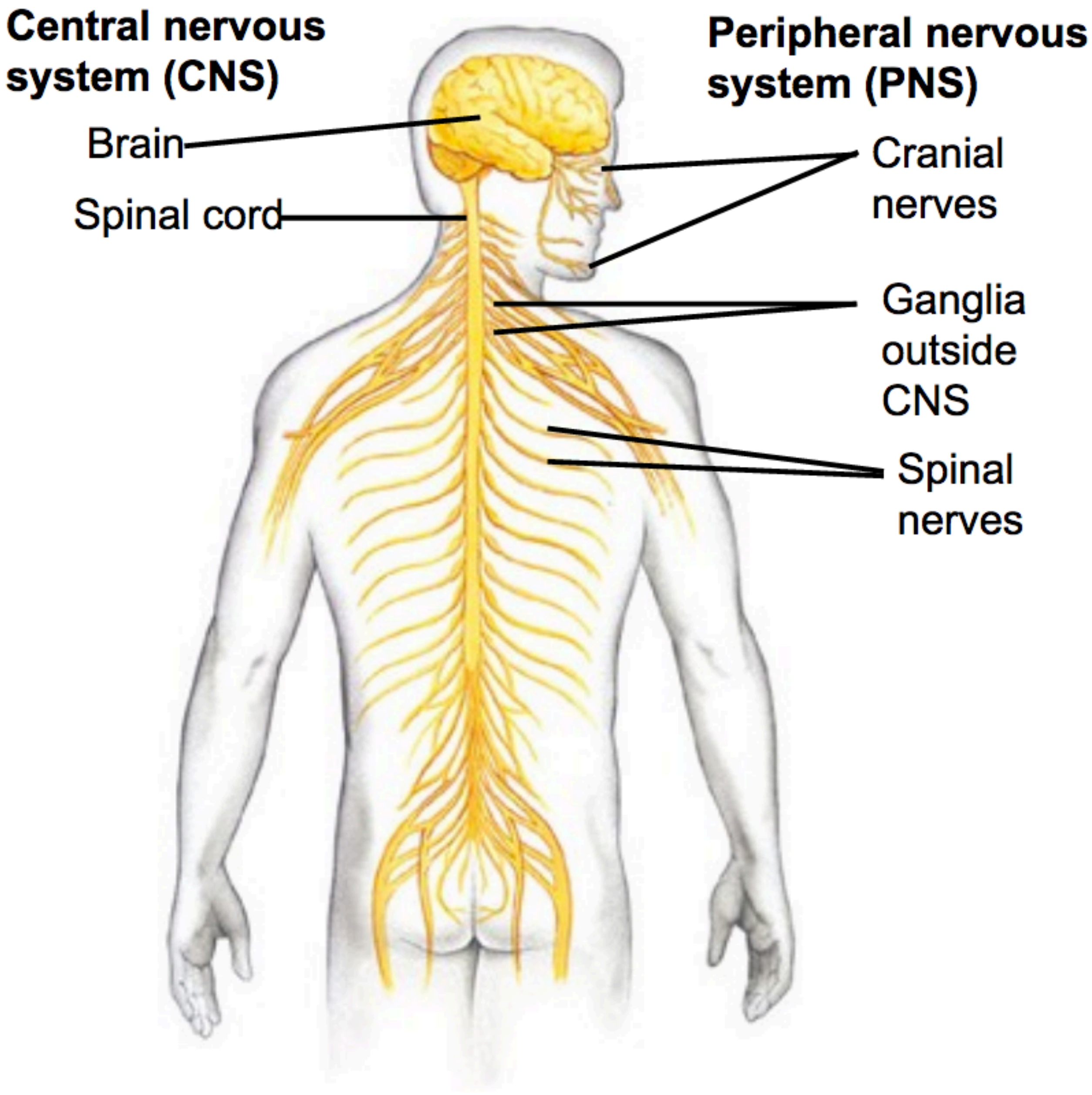
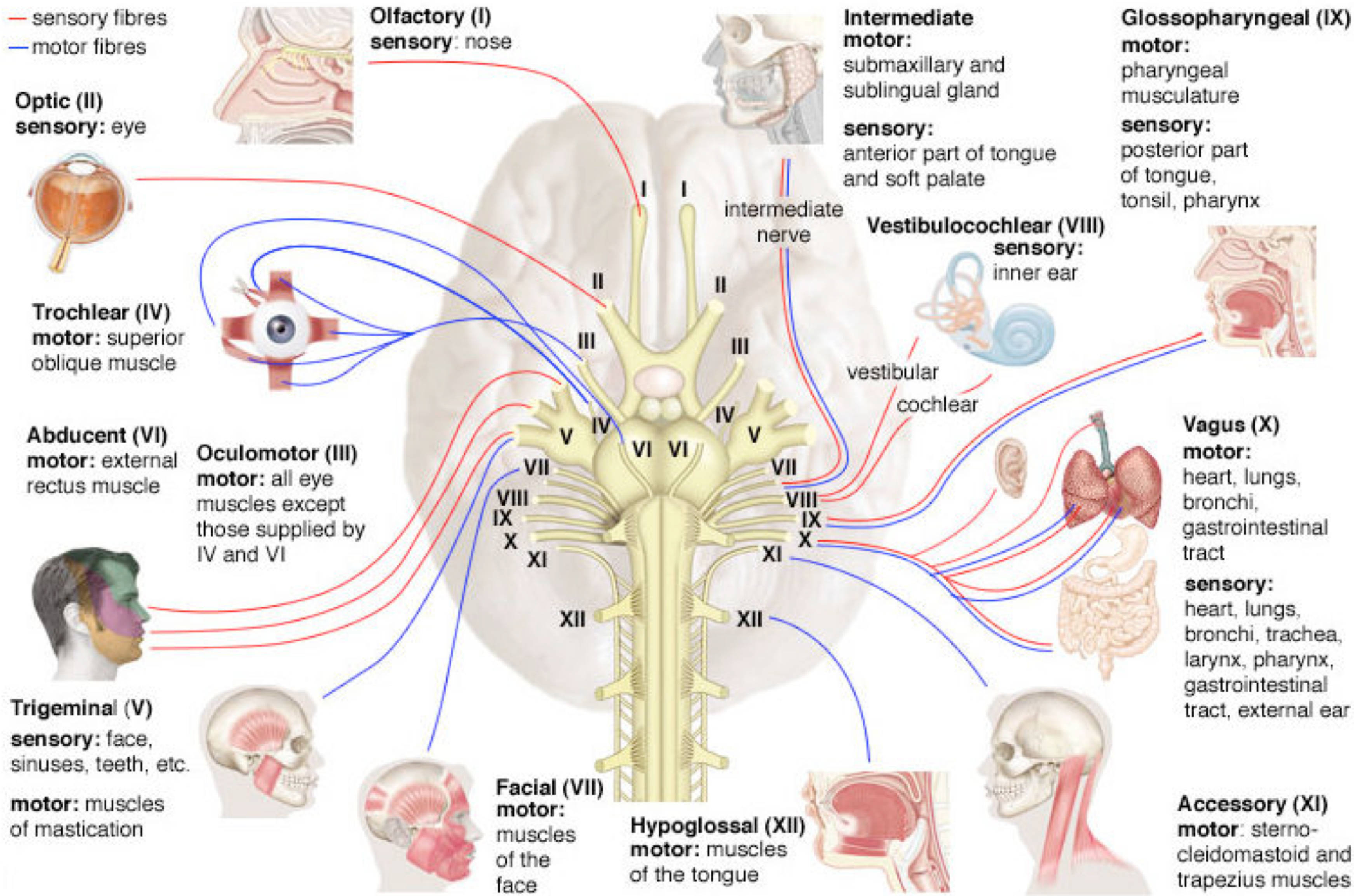
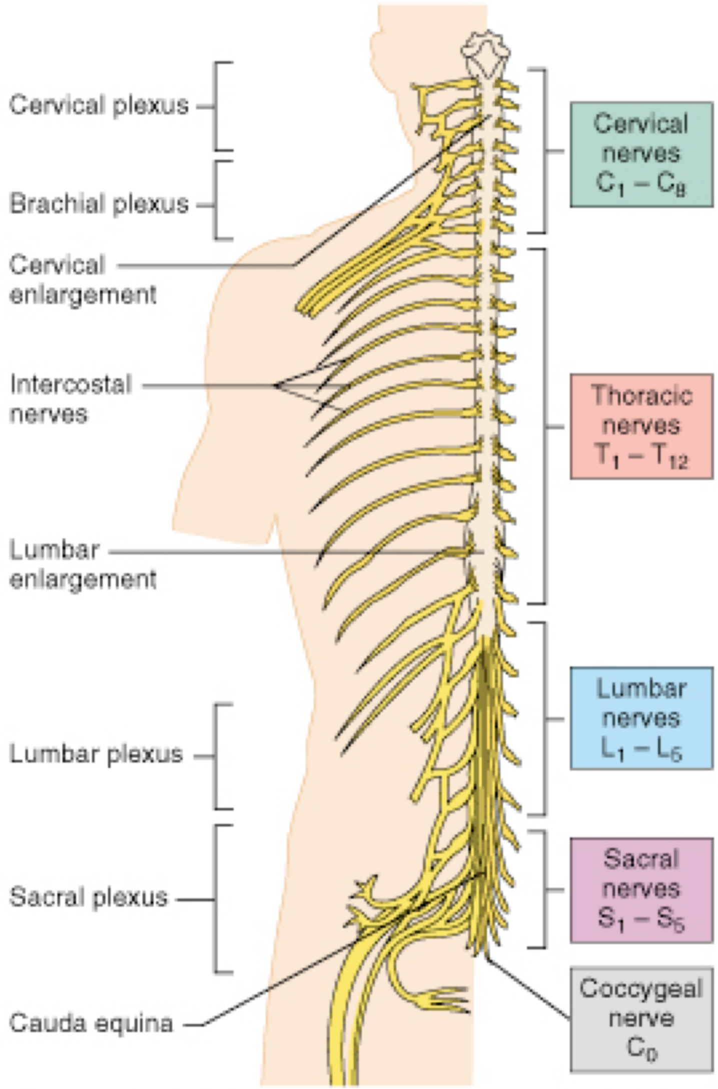
The nervous system: physiological point of view

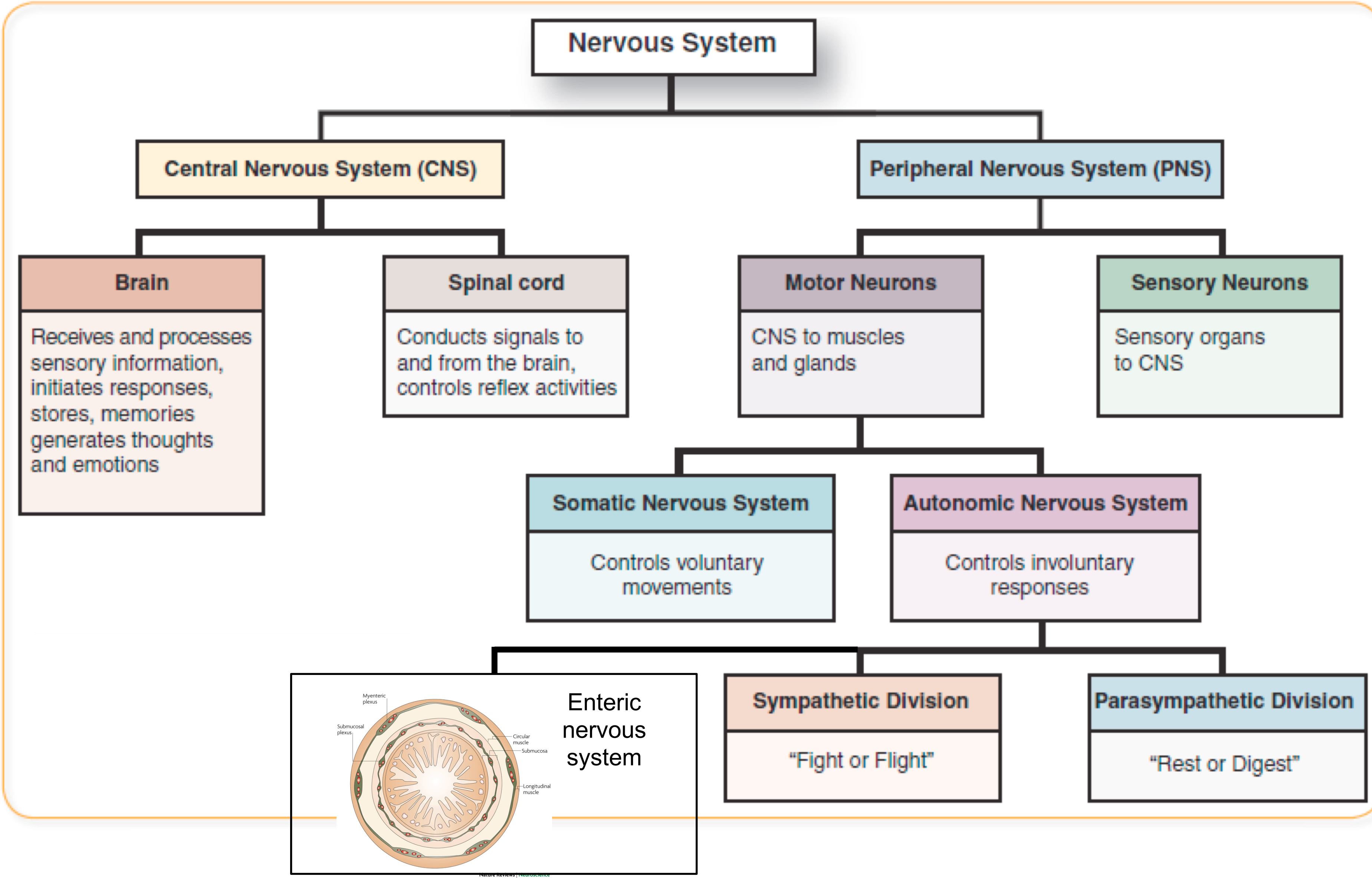


Cranial nerves



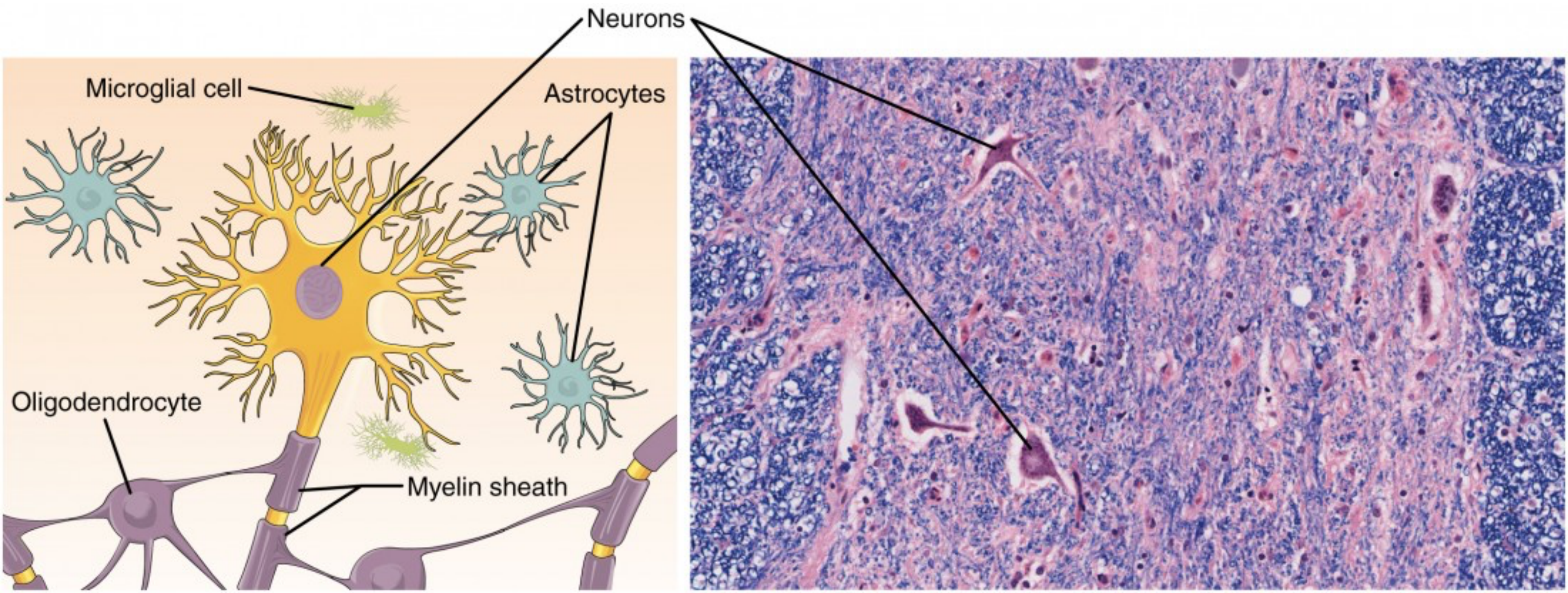
Spinal nerves



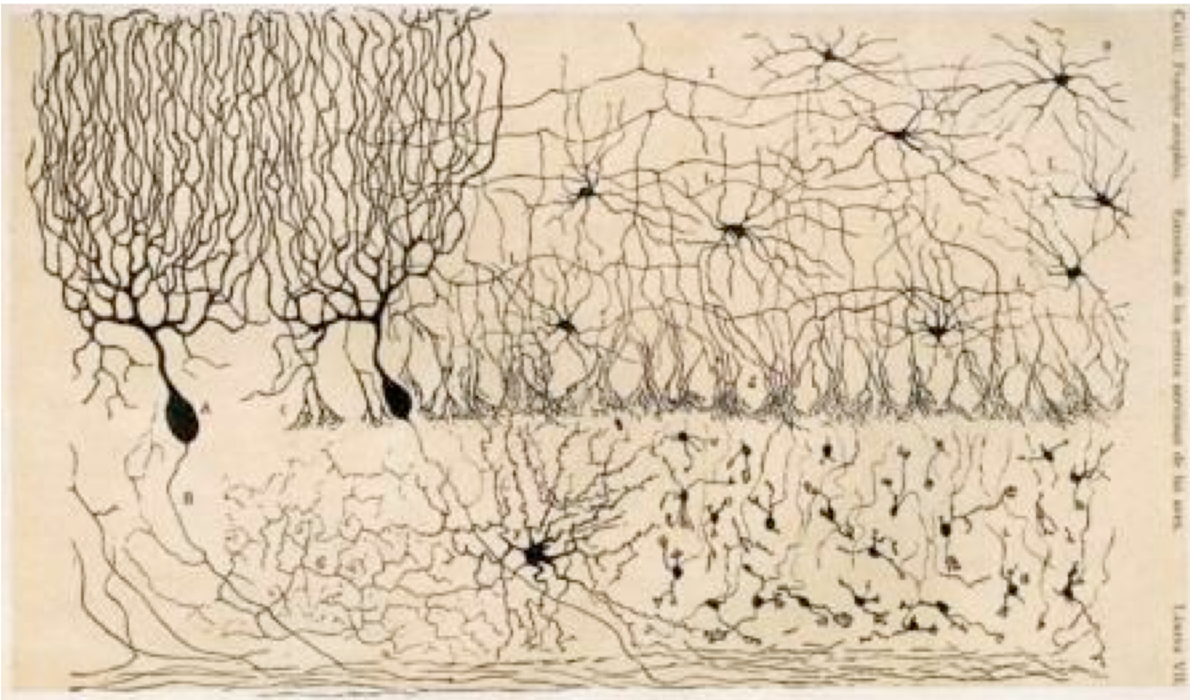


Nervous System
Central Nervous System (CNS)
Peripheral Nervous System (PNS)
Brain
Receives and processes sensory information, initiates responses, stores, memories generates thoughts and emotions
Spinal cord
Conducts signals to and from the brain, controls reflex activities
Motor Neurons
CNS to muscles and glands
Sensory Neurons
Sensory organs to CNS
Somatic Nervous System
Controls voluntary movements
Autonomic Nervous System
Controls involuntary responses
Enteric nervous system
Myenteric plexus
Submucosal plexus
Circular muscle
Submucosa
Longitudinal muscle
Sympathetic Division
"Fight or Flight"
Parasympathetic Division
"Rest or Digest"

Nervous tissue



Neuronal diversity

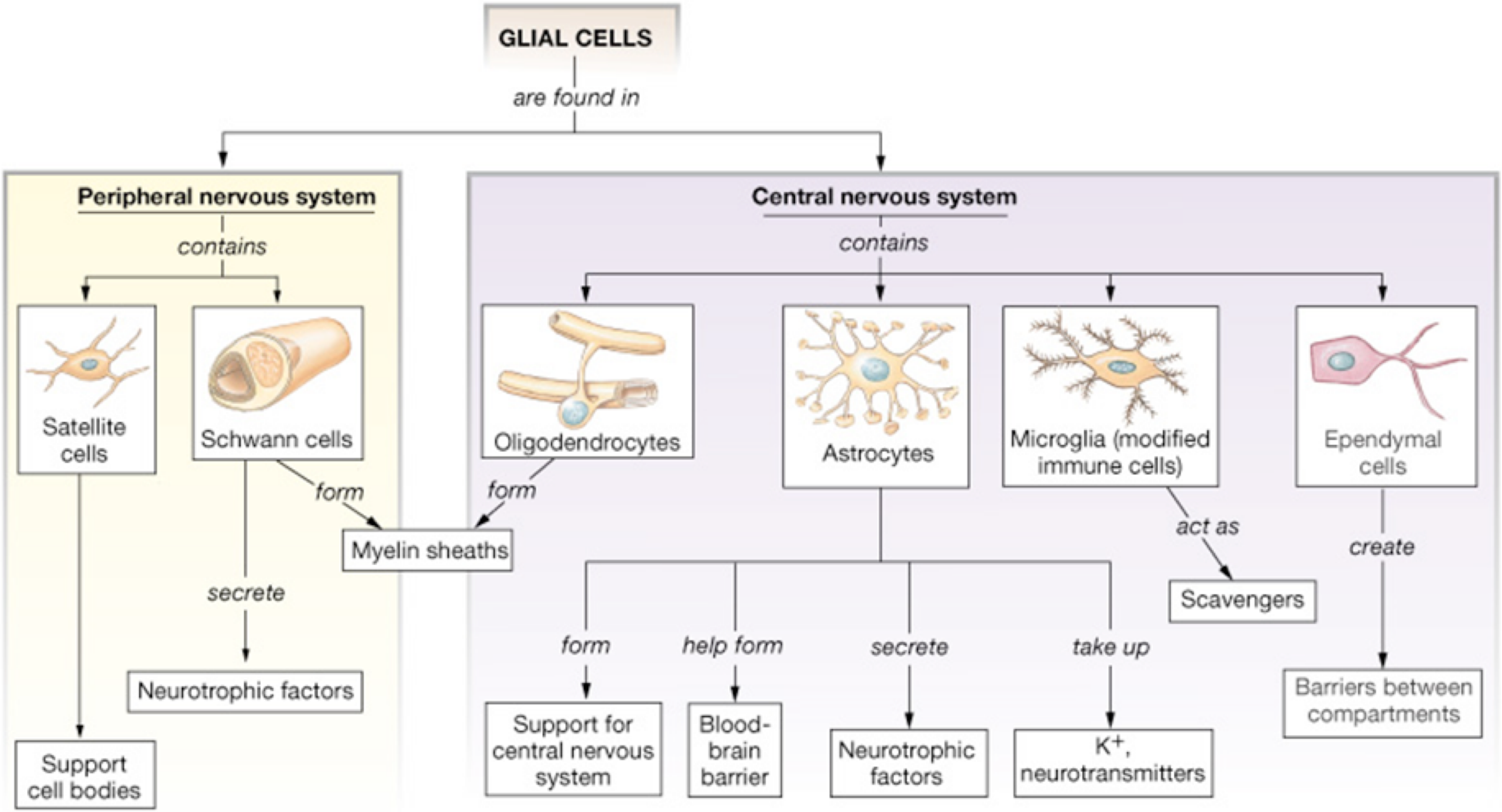


Ramon y Cajal, 1905

- Morphology
- Connectivity
- Electrical properties
- Neurotransmitter

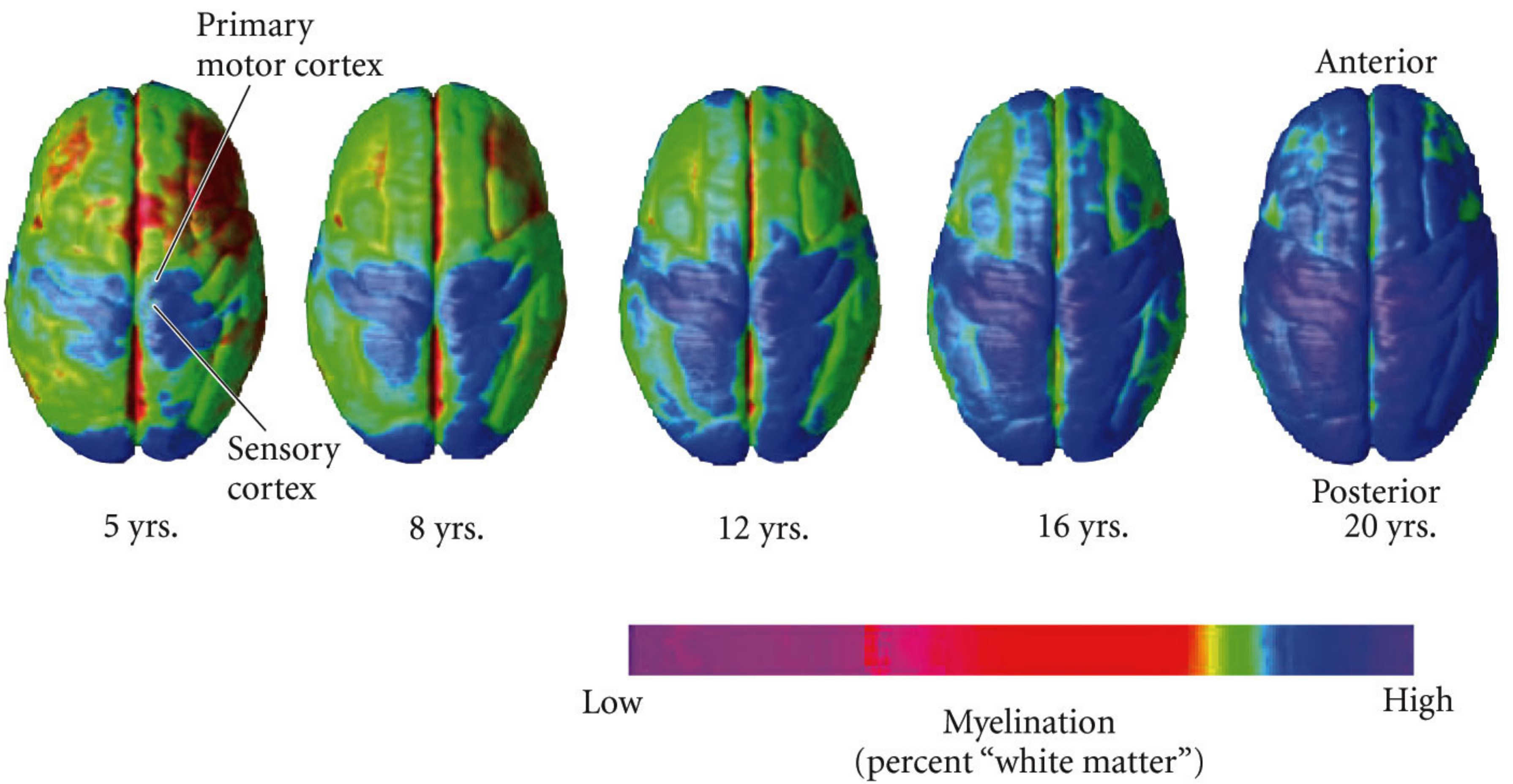
…

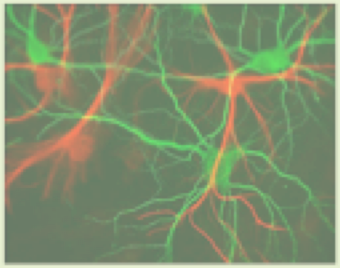
Glial cells and their functions



The myelination process

Dorsal view of the human brain showing the progression of myelination ("white matter") over the cortical surface during adolescence





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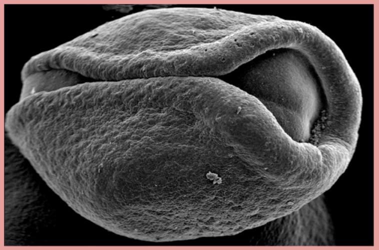

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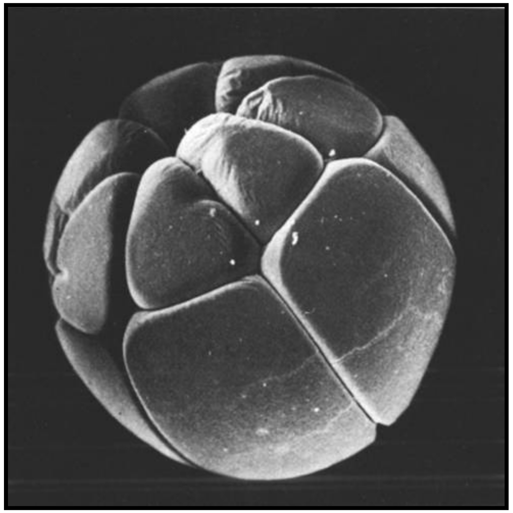
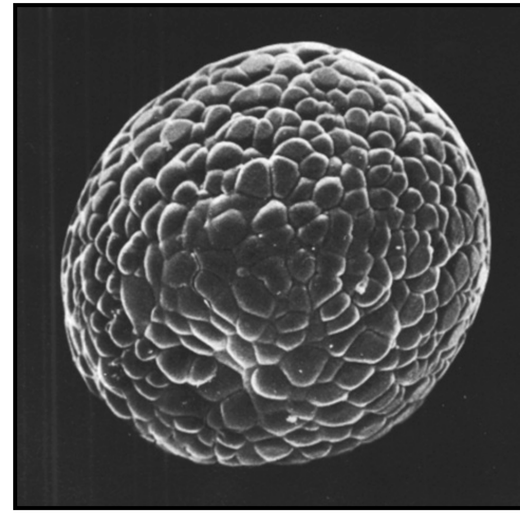
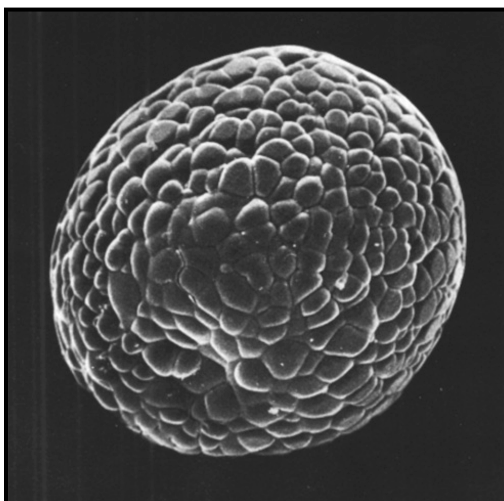
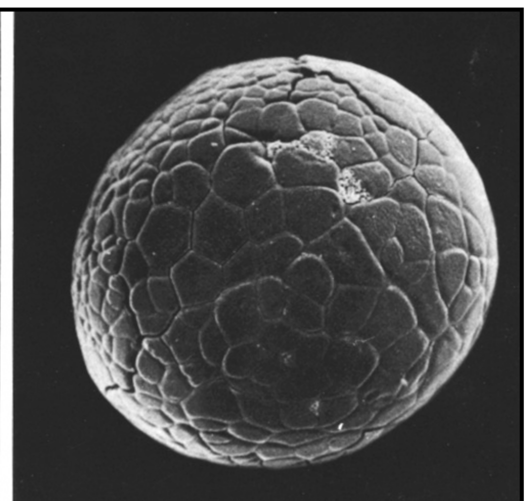
Cleavage (amphibian)



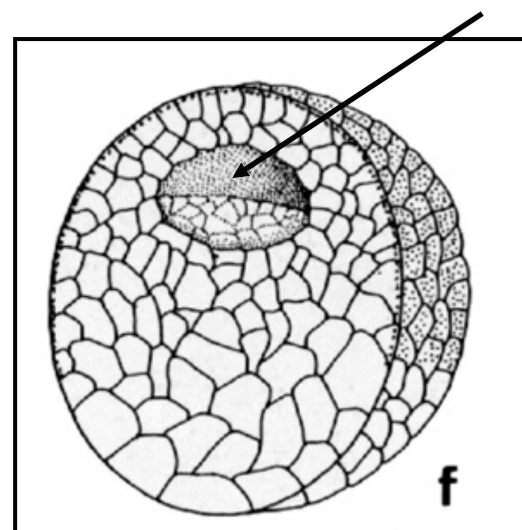




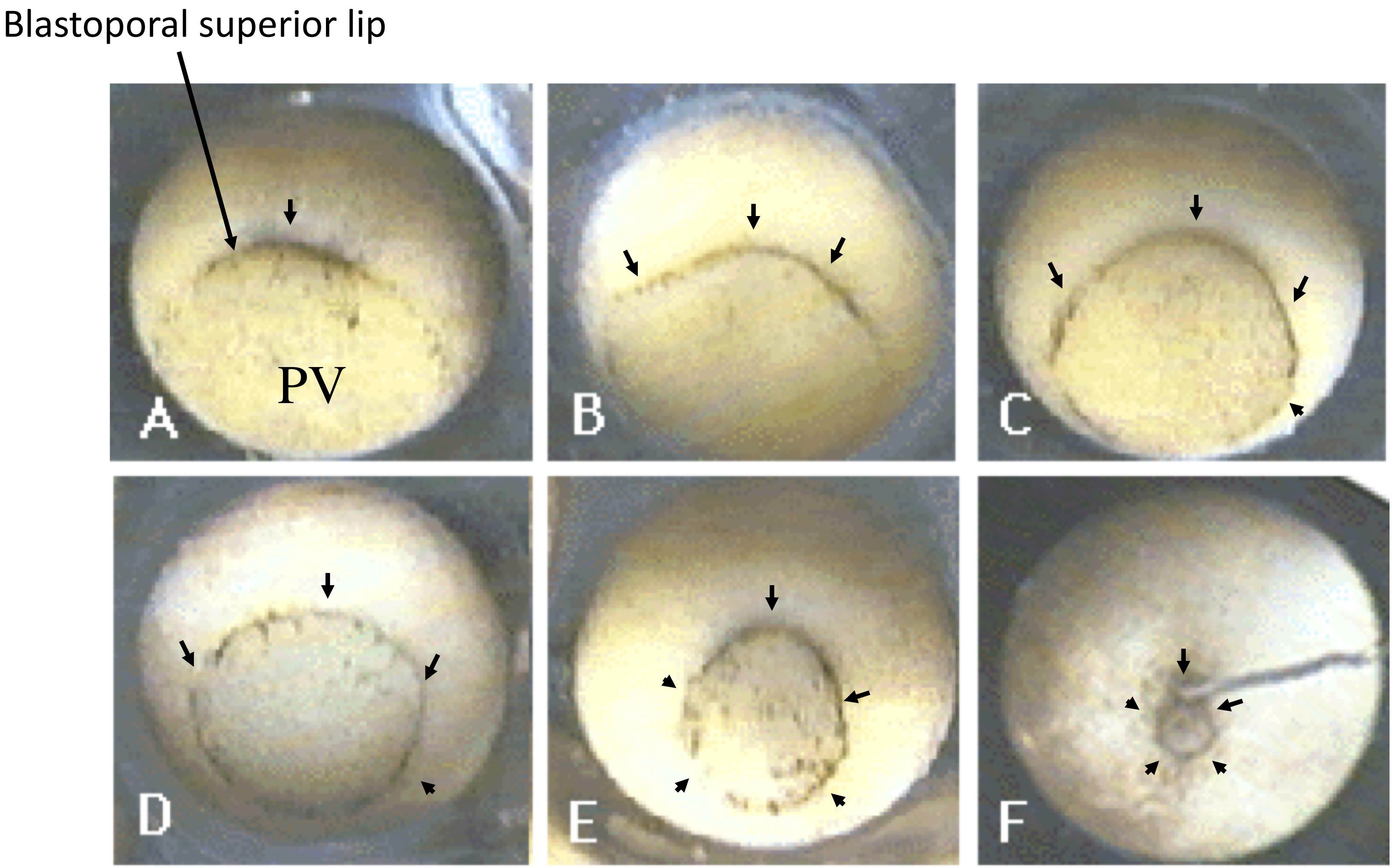
PA



PV



Gastrulation (amphibien)



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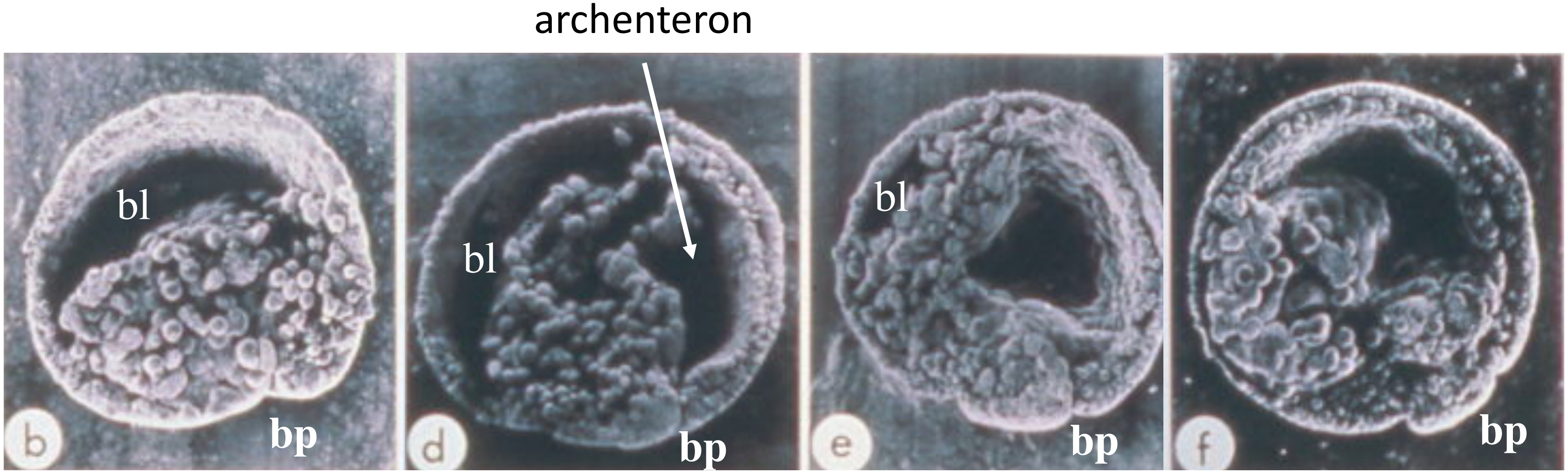
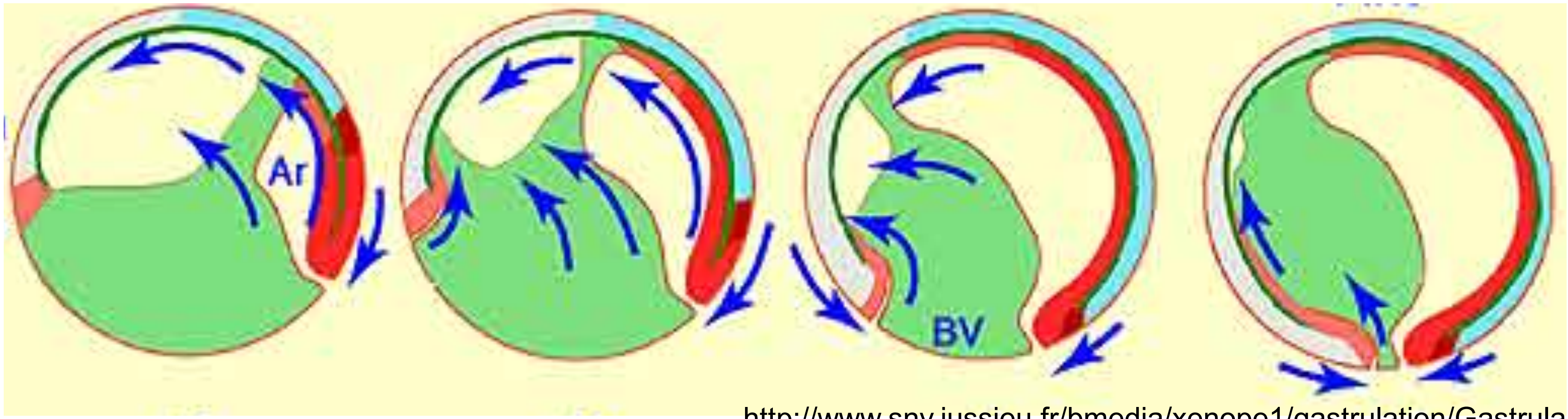
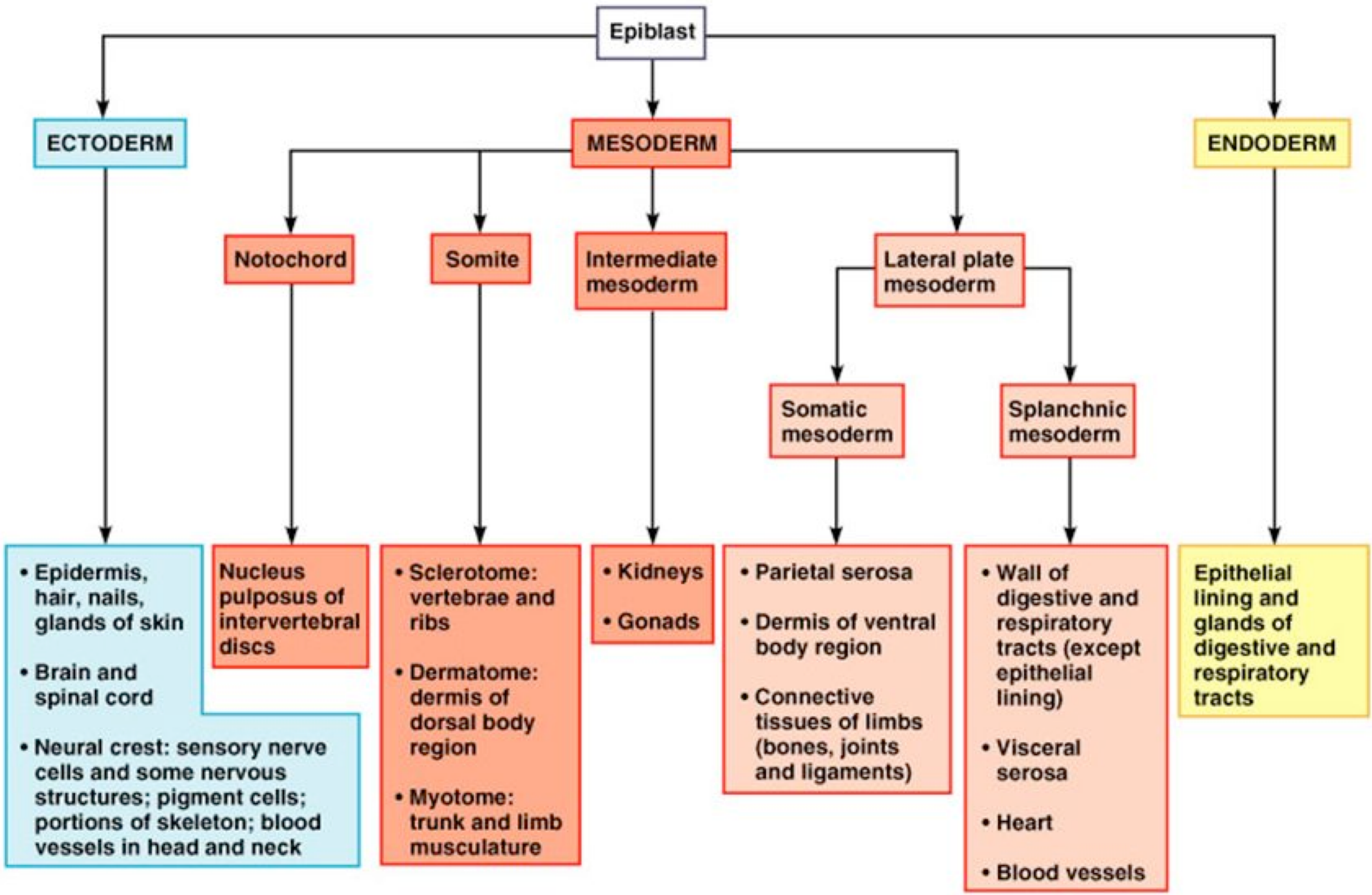




http://www.snv.jussieu.fr/bmedia/xenope1/gastrulation/Gastrula.html

Ectoderm
Mesoderm
Endoderm

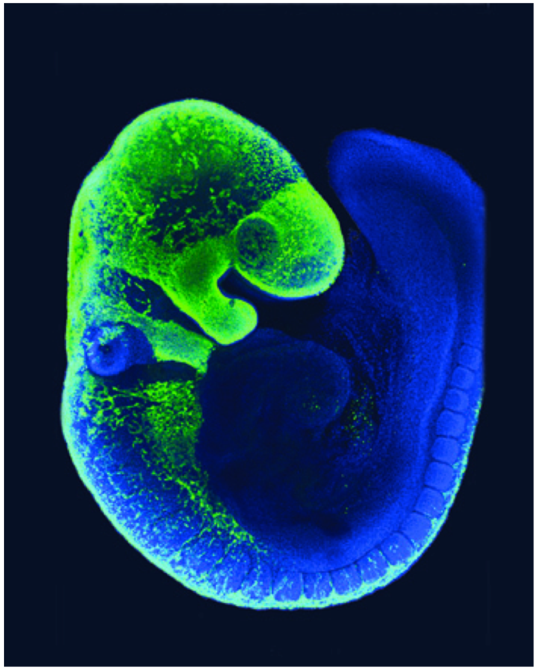
Many structures are derived from the three embryonic germ layers during organogenesis

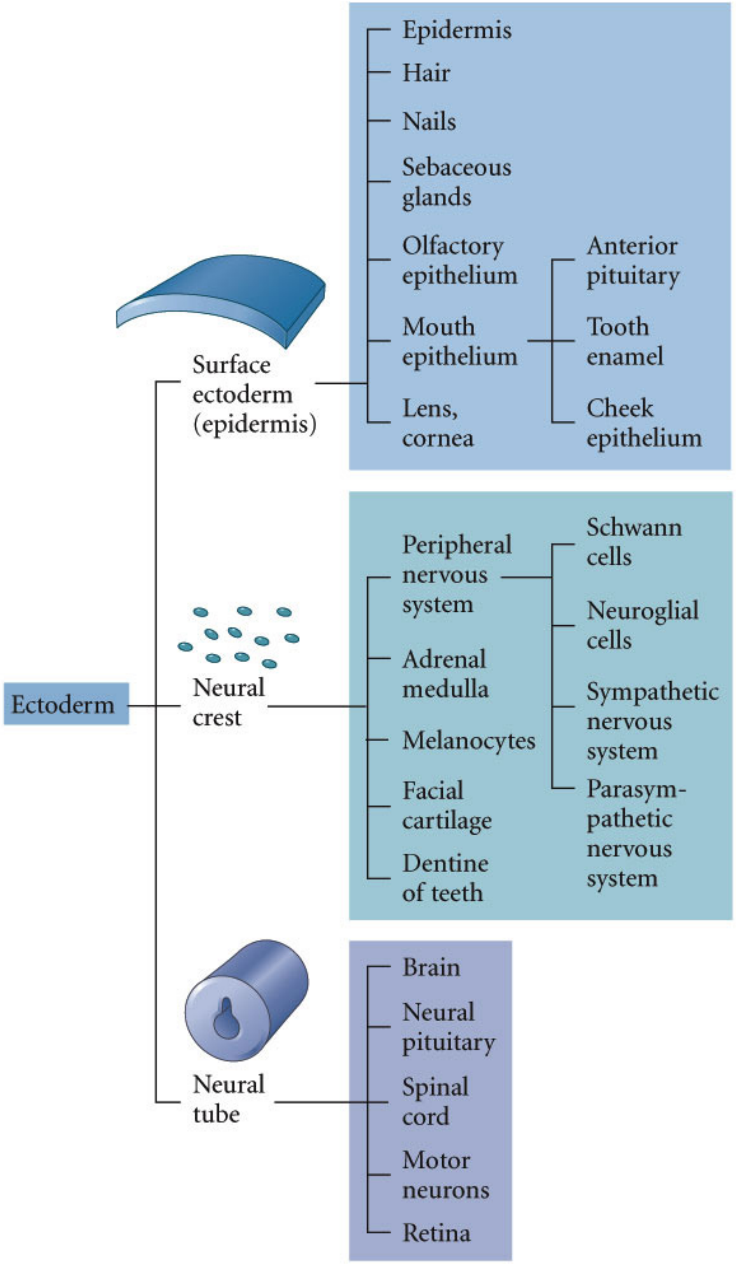


Major derivatives of the ectoderm

Three subdivisions of the ectoderm:

- Surface
- Neural Crest
- Neural Tube





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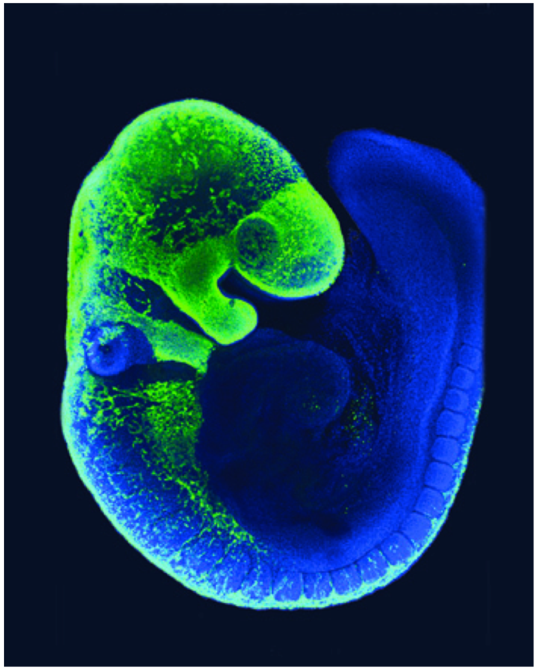
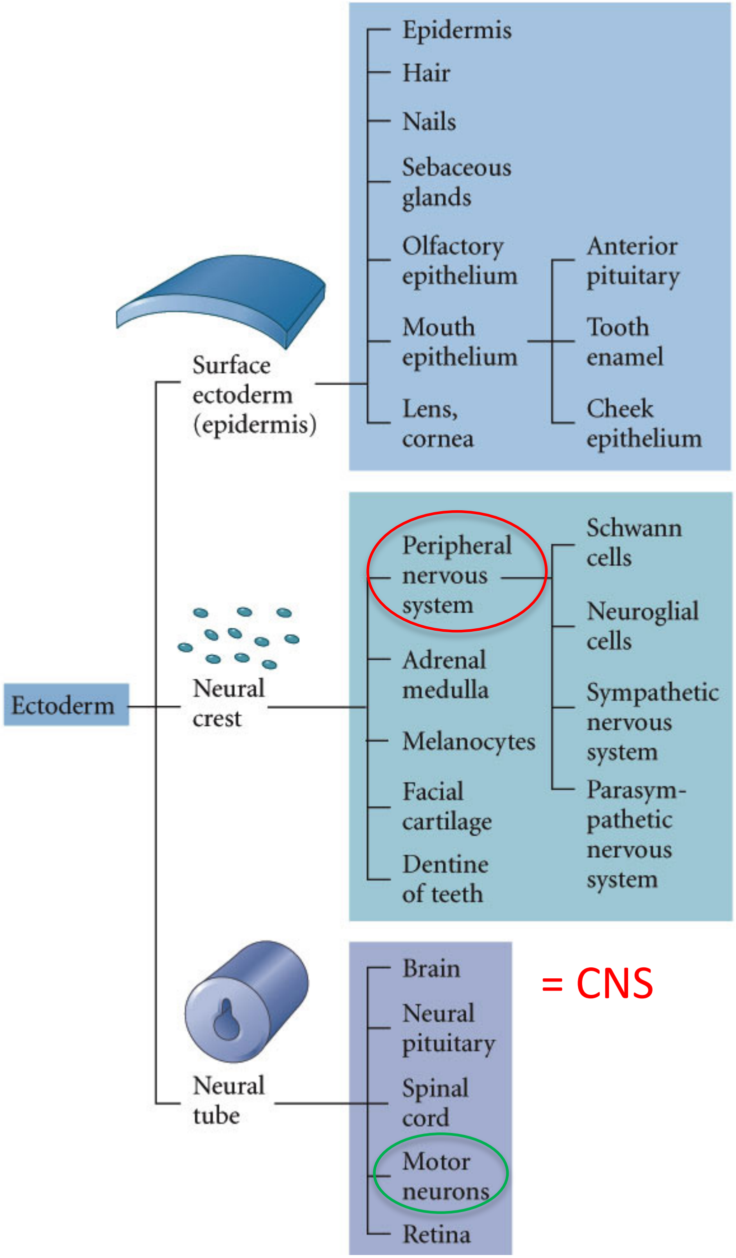
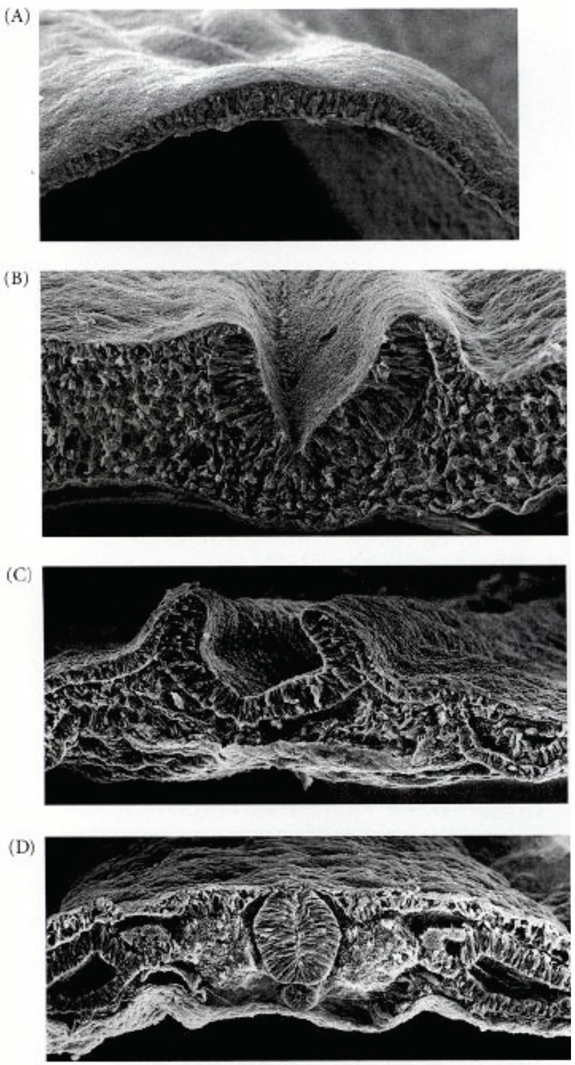
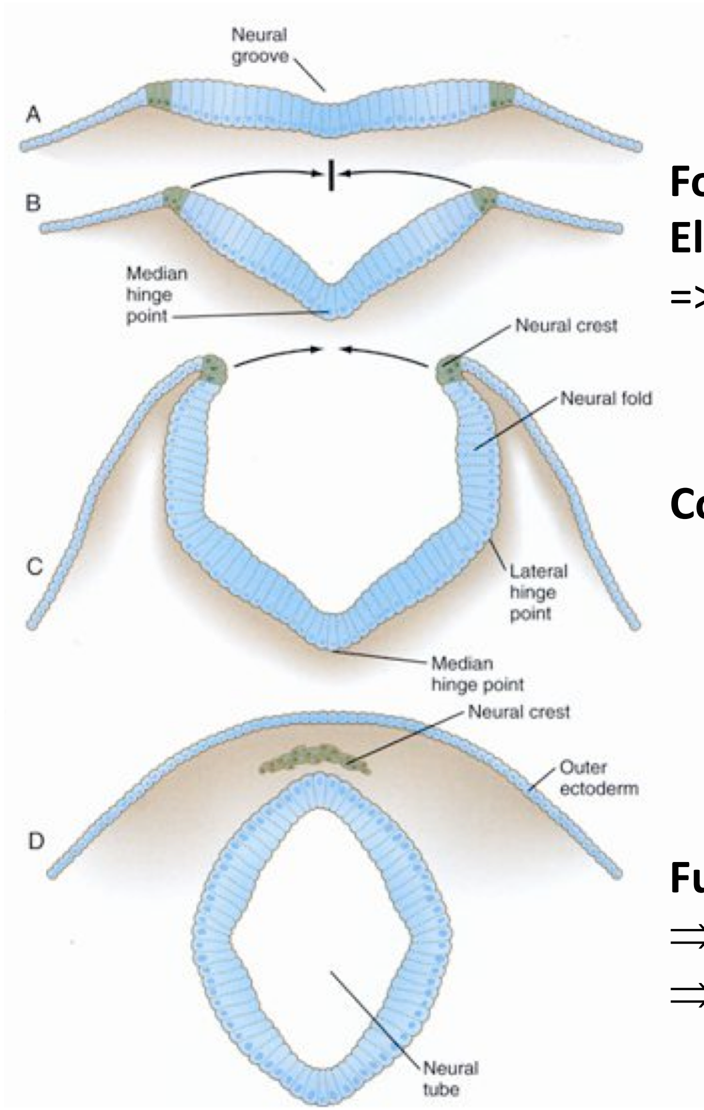




=> Embryological point of view of the nervous system subdivisions

Primary neurulation (chick)





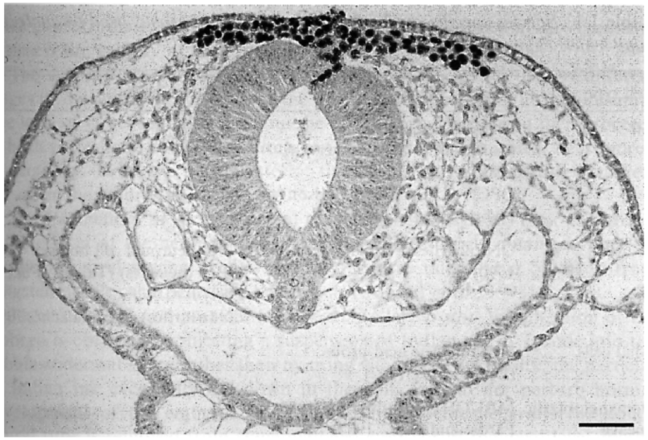
Folding
Elevation
=> Neural grove

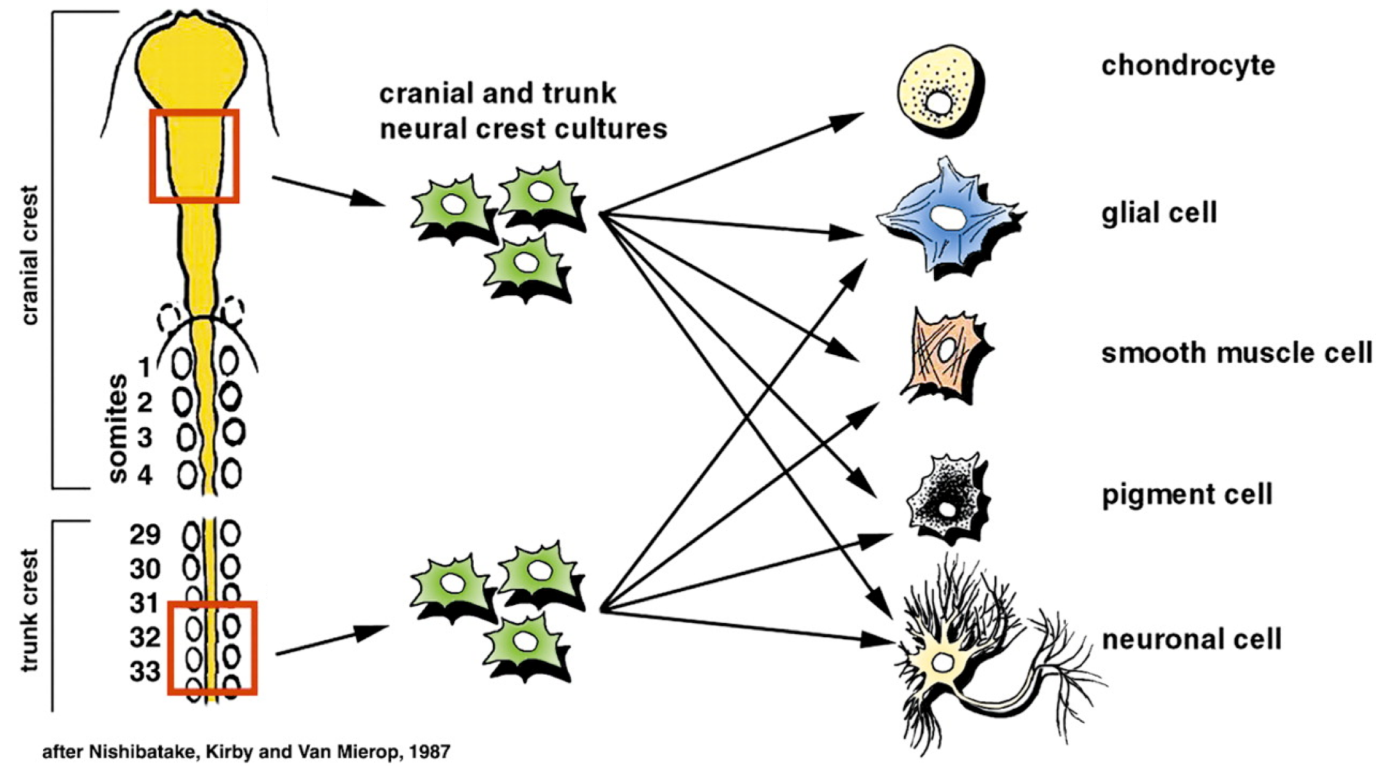
Convergence

Fusion
⇒ neural tube isolation
⇒ neural crest delamination

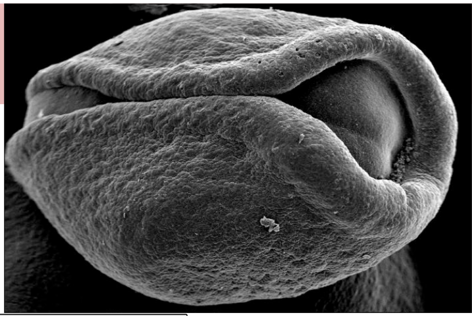
proliferation allowing growth in thickness

The neural crest cells

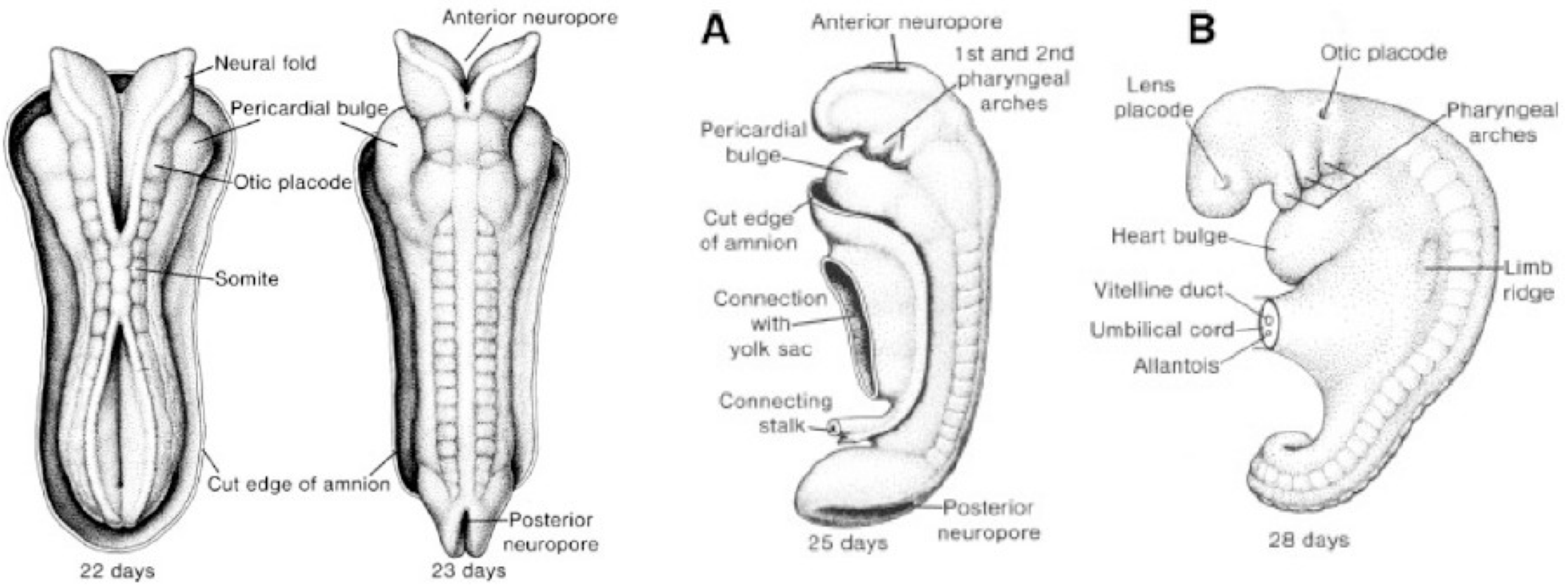




Neurulation in the *xenopus* embryo

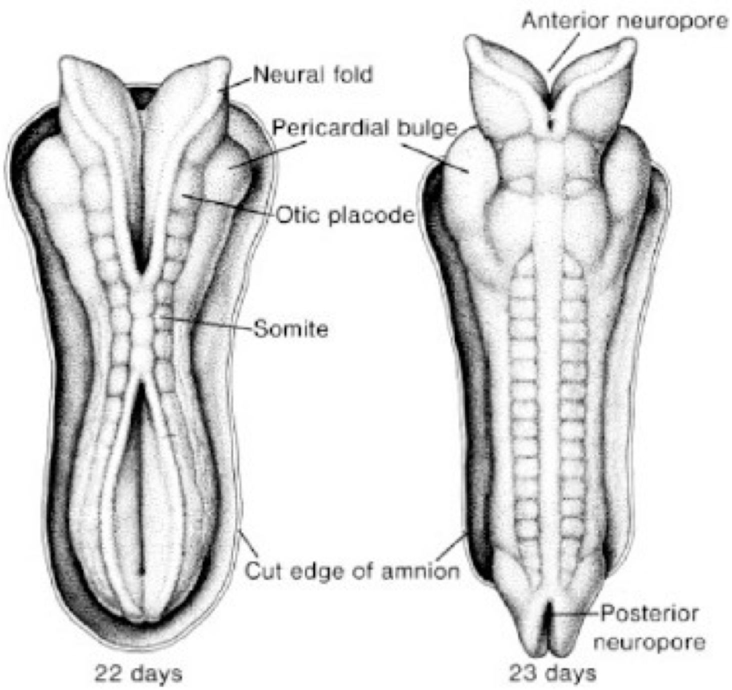


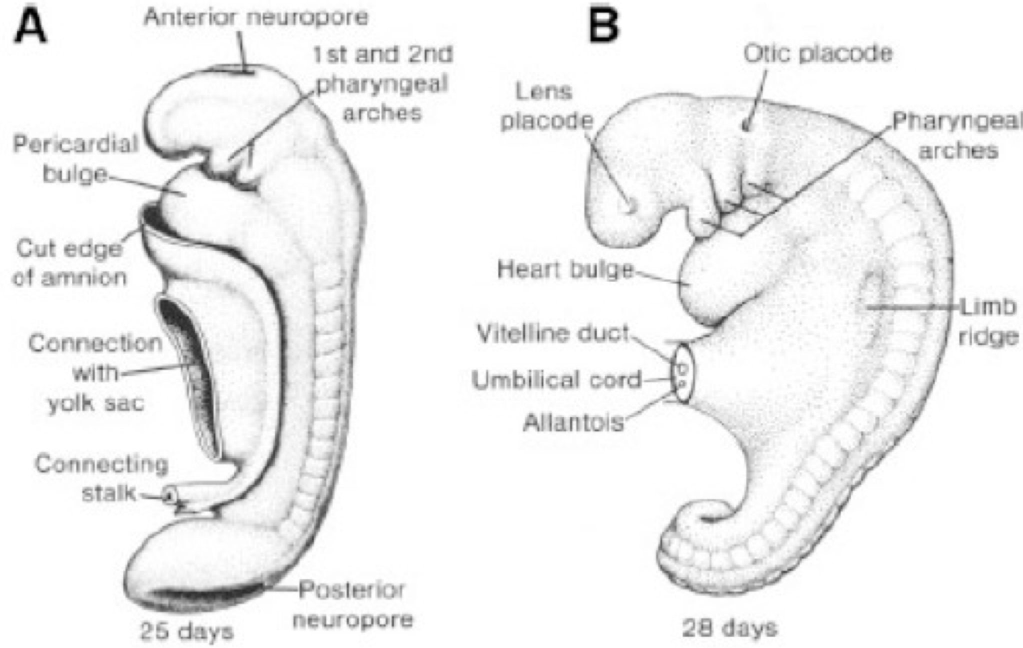
Neurulation in human

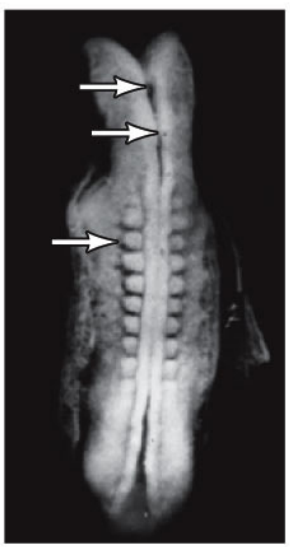


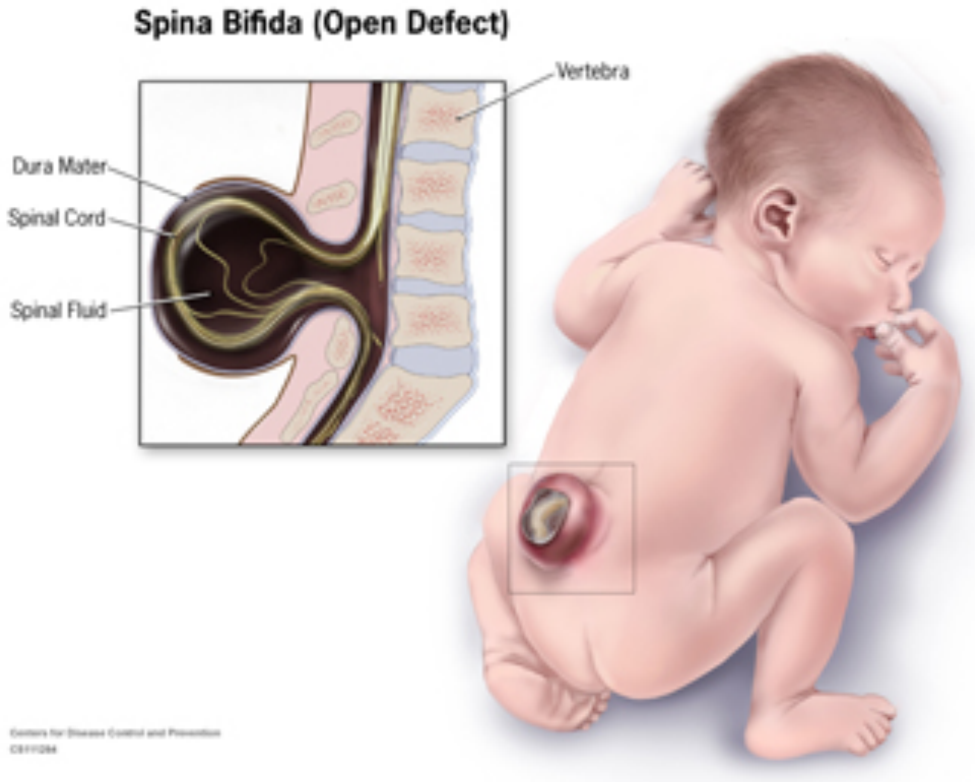
Anencephaly = absence of a major portion of the brain resulting from a neural tube defect occurring when the rostral end of the neural tube (anterior neuropore) fails to close.

Neurulation in human









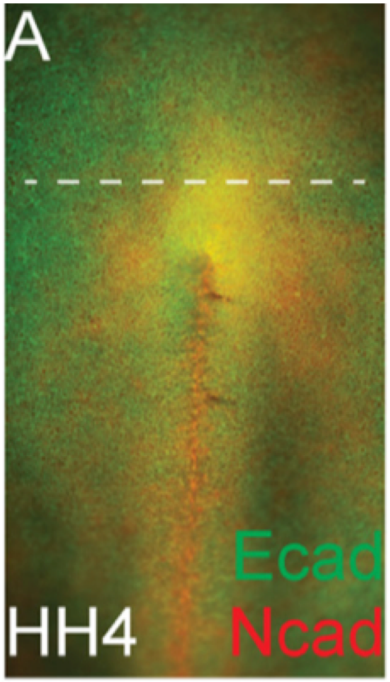
Spina Bifida = defect occurring at the posterior part of the neural tube. (prevalence: 1/2000)

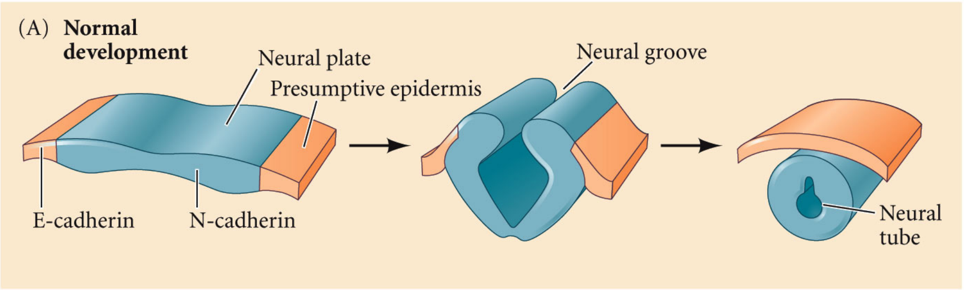
⇒ Surgery

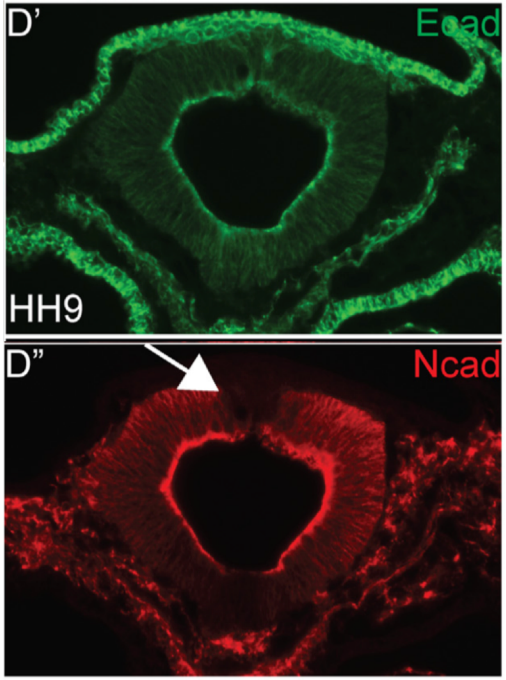
⇒ Often times, locomotor disorders

Lightest form: asymptomatic

Expression of N- and E-cadherin adhesion proteins during neurulation in *chick*







Rogers et al., 2018

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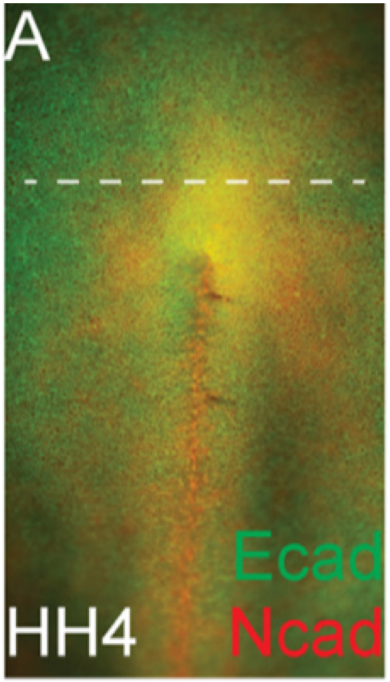
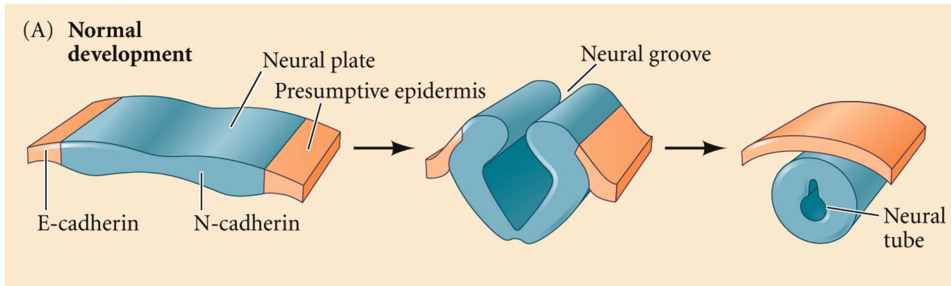
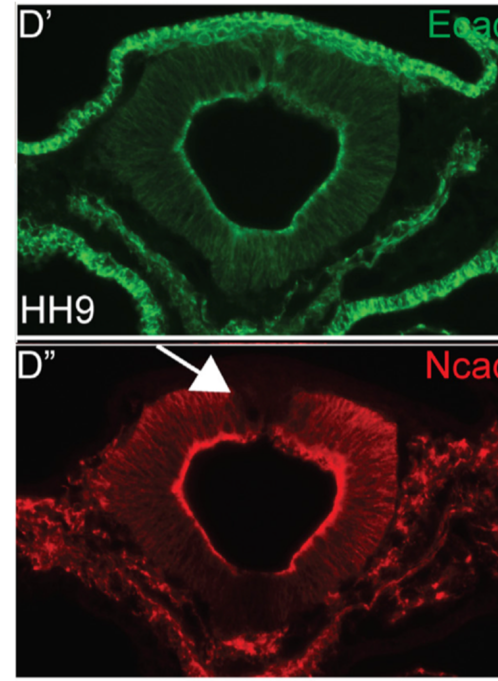
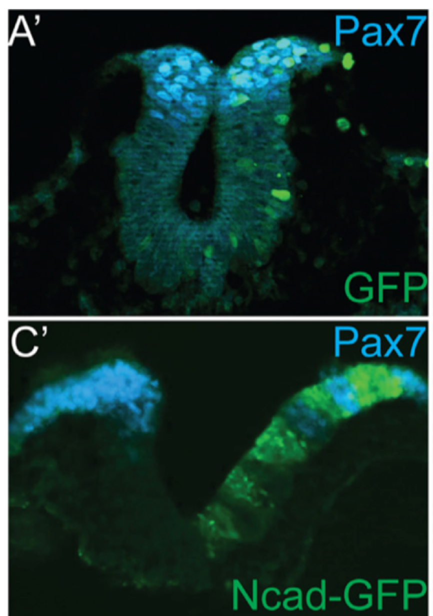


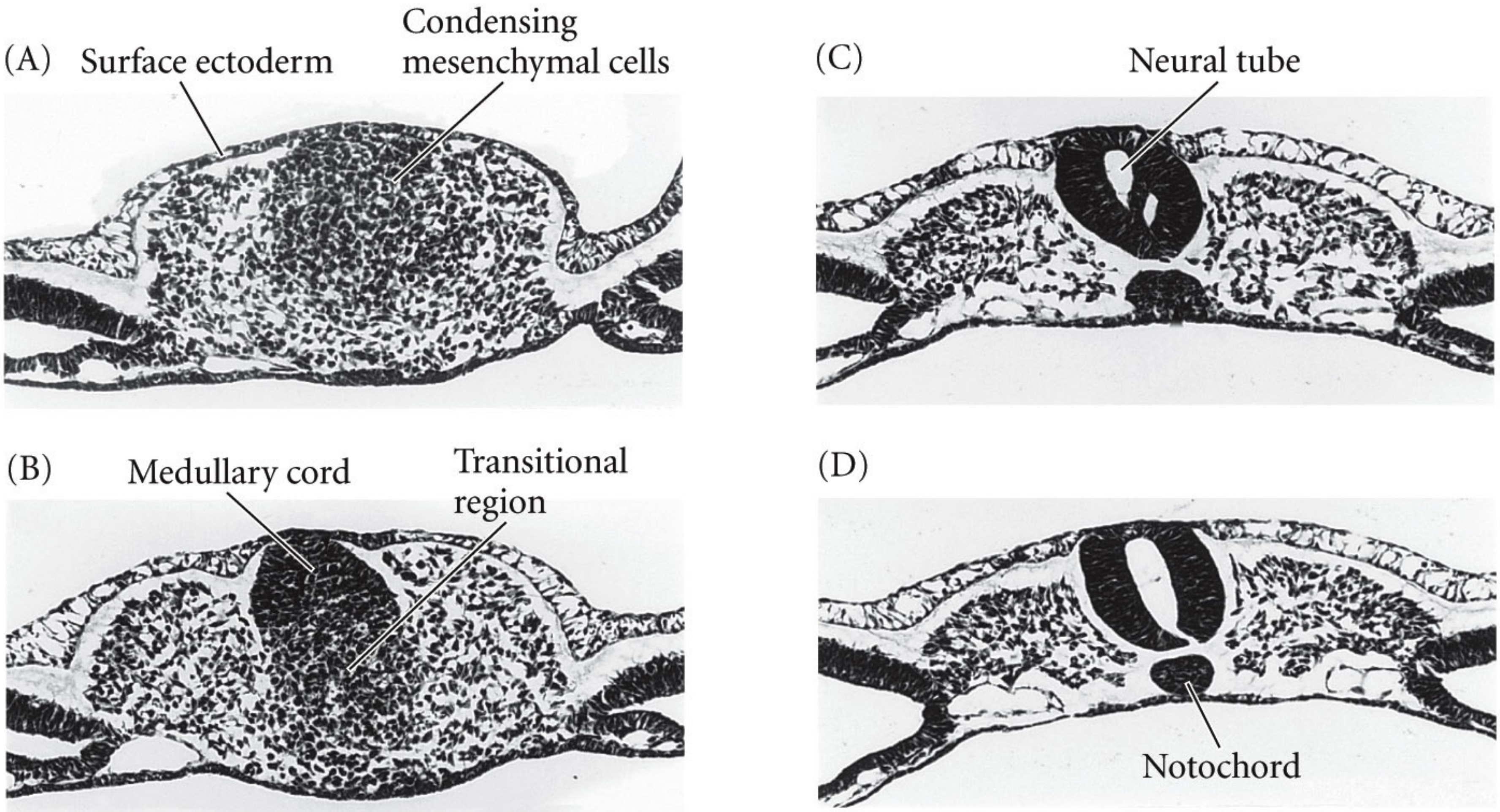




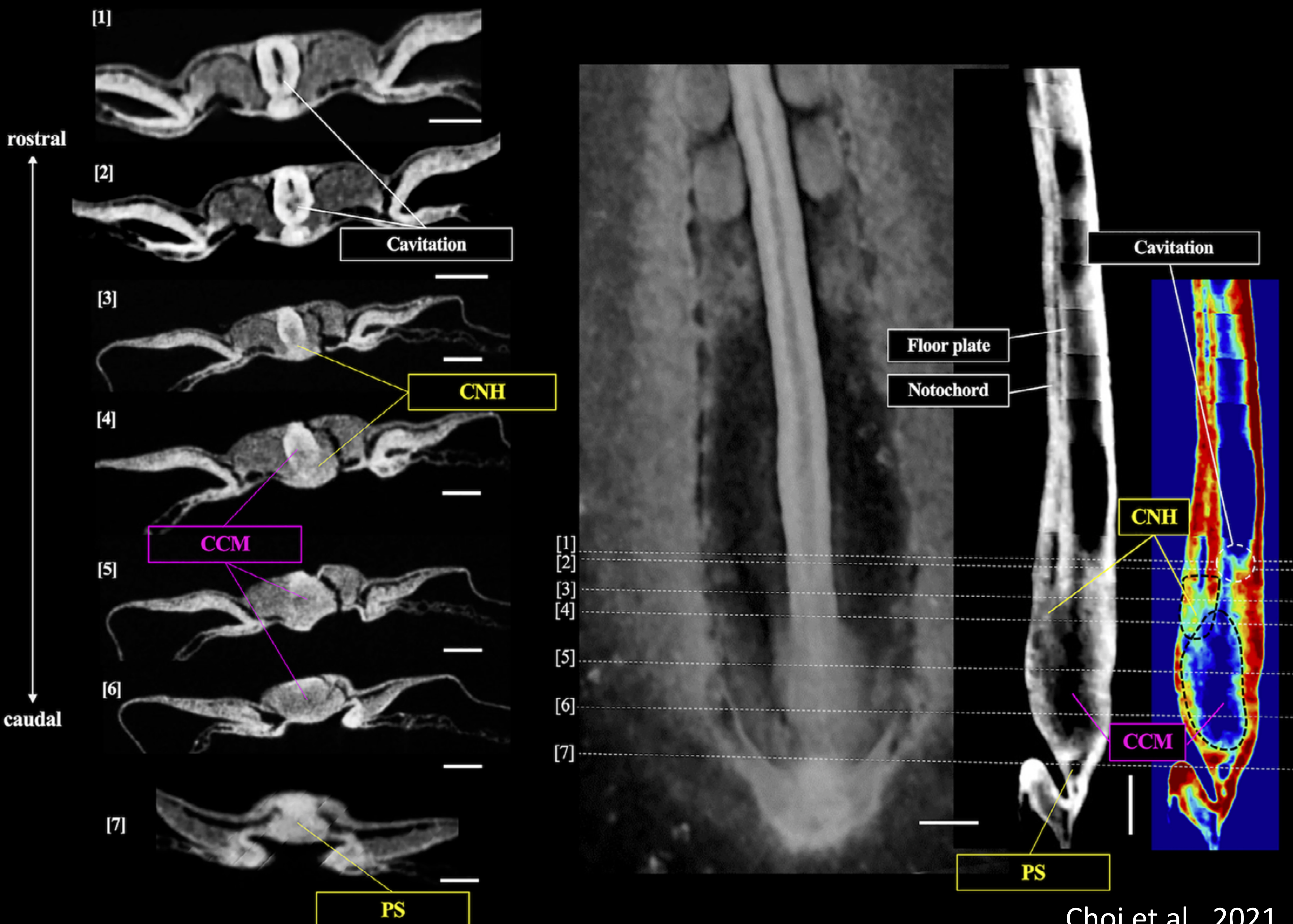


Rogers et al., 2018

Secondary neurulation: example in the caudal region of a 25-somite chick embryo

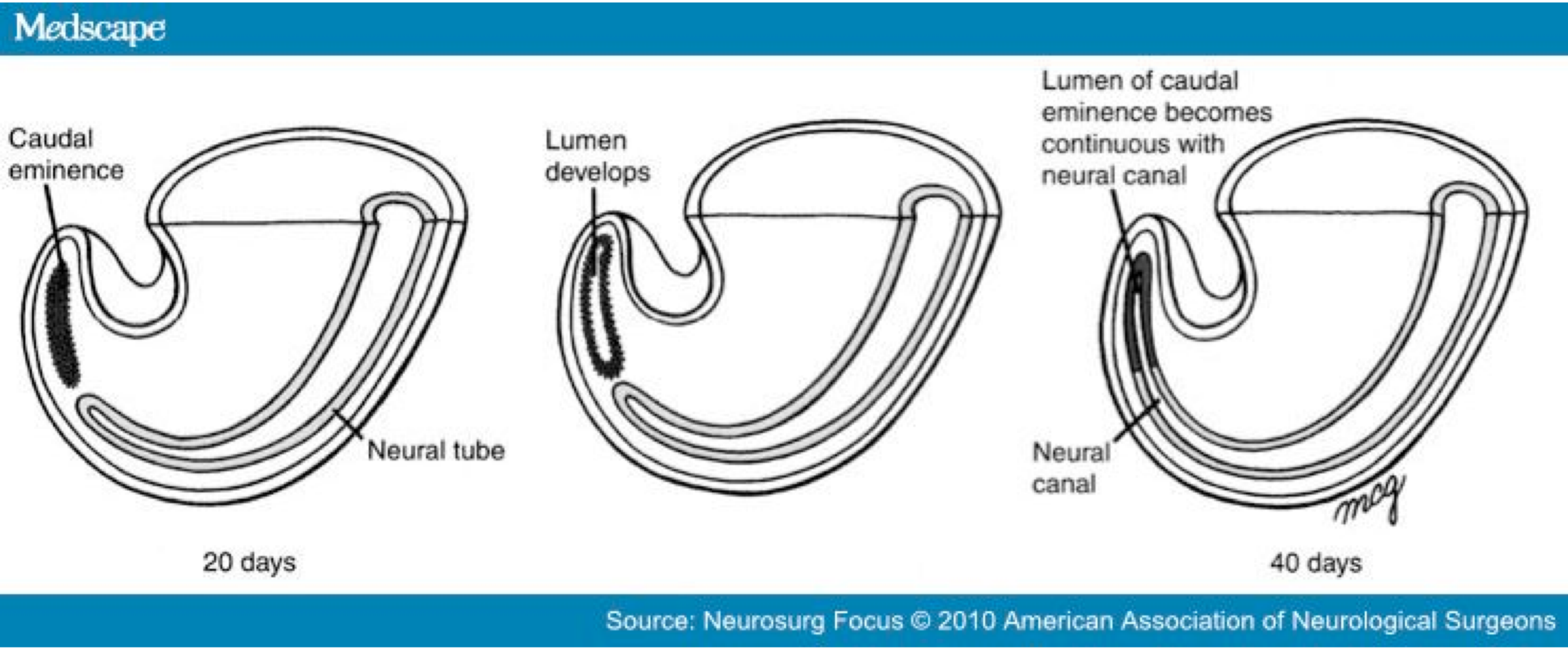


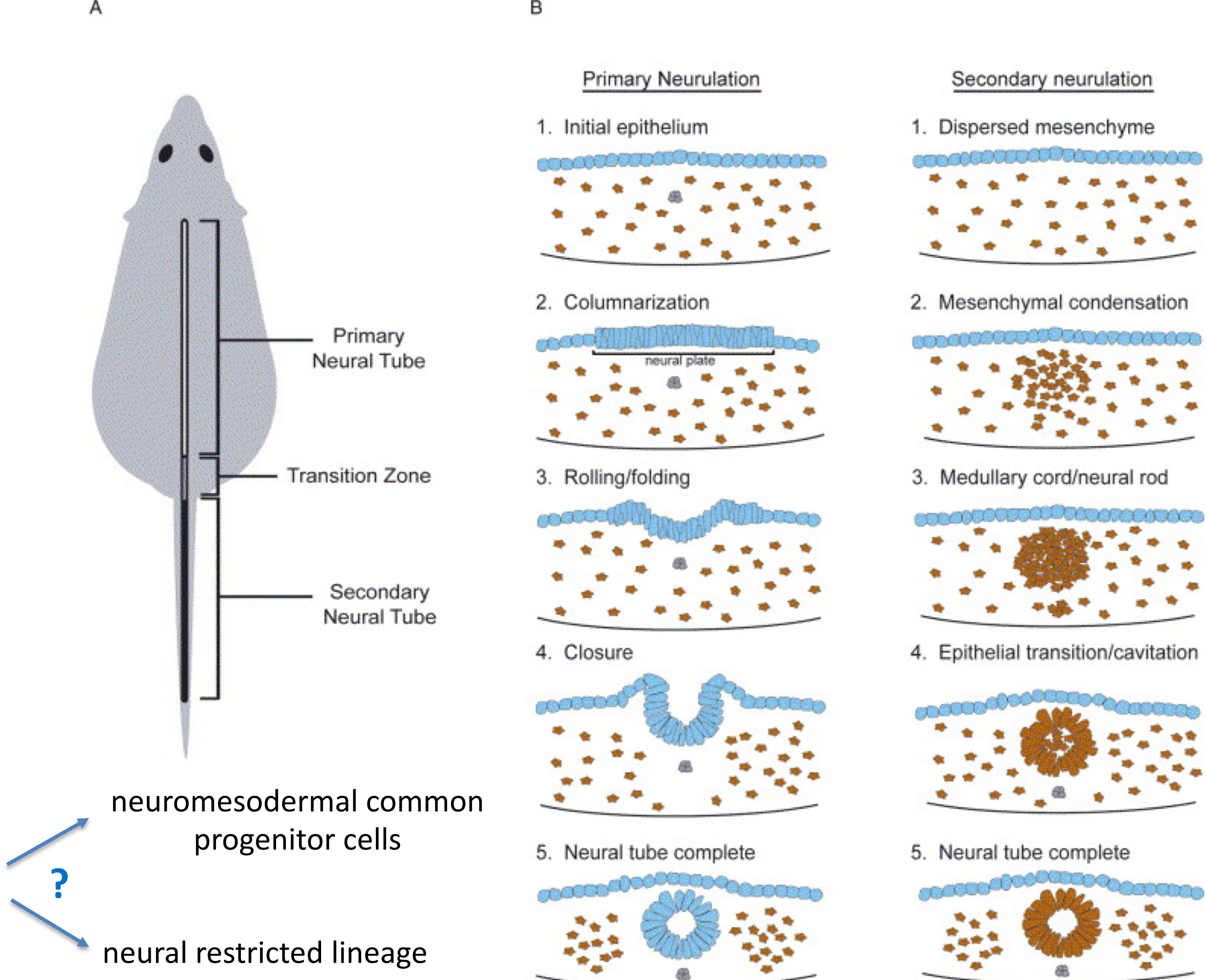
Shimokita and Takahashi., 2011



Choi et al., 2021

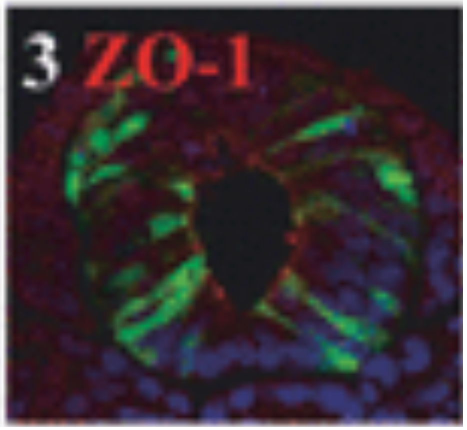
Secondary neurulation: in Human



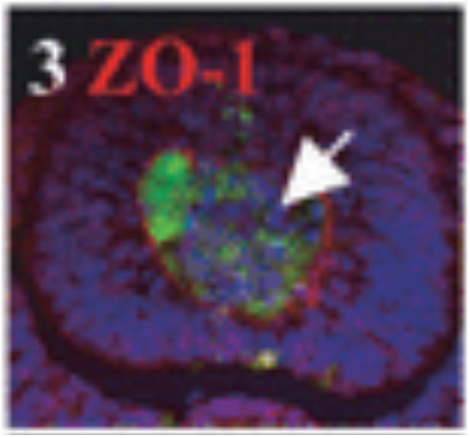

A
B
Primary Neural Tube
Transition Zone
Secondary Neural Tube
Primary Neurulation
Secondary neurulation
1. Initial epithelium
1. Dispersed mesenchyme
2. Columnarization
neural plate
2. Mesenchymal condensation
3. Rolling/folding
3. Medullary cord/neural rod
4. Closure
4. Epithelial transition/cavitation
5. Neural tube complete
5. Neural tube complete
neuromesodermal common progenitor cells
?
neural restricted lineage

Mesenchymal-epithelial transition during secondary neurulation is regulated by differential roles of Cdc42 and Rac1

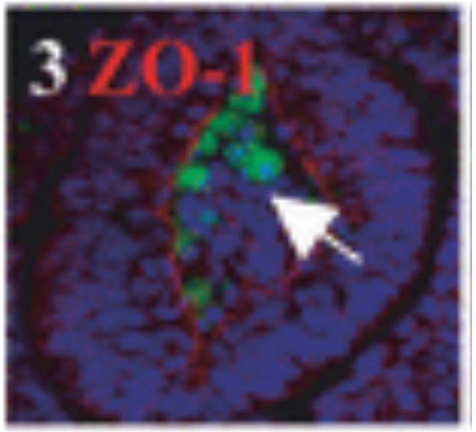
Control



CDC42 activation



Rac1 inhibition

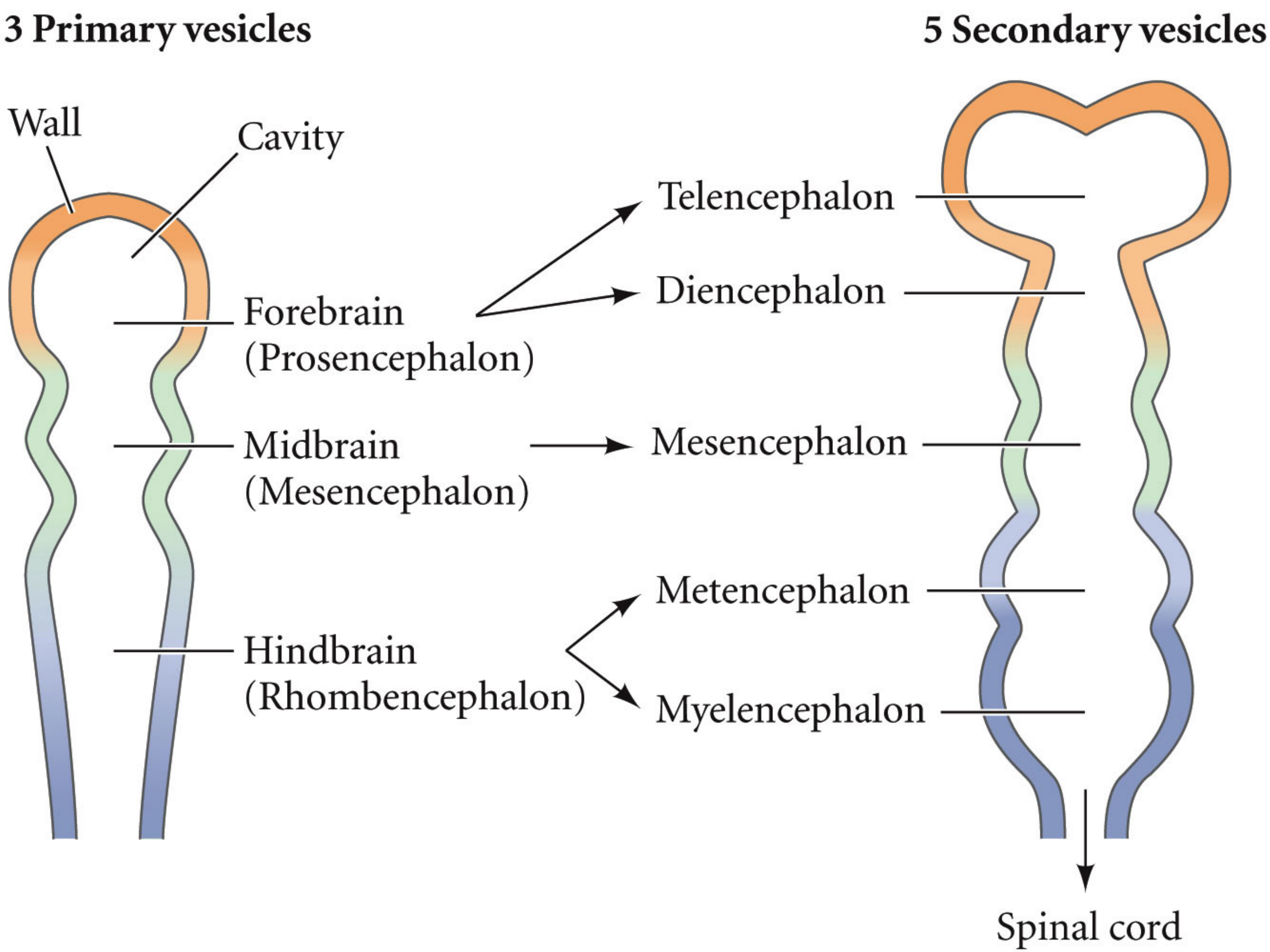


D'après Shimokita and Takahashi, 2011

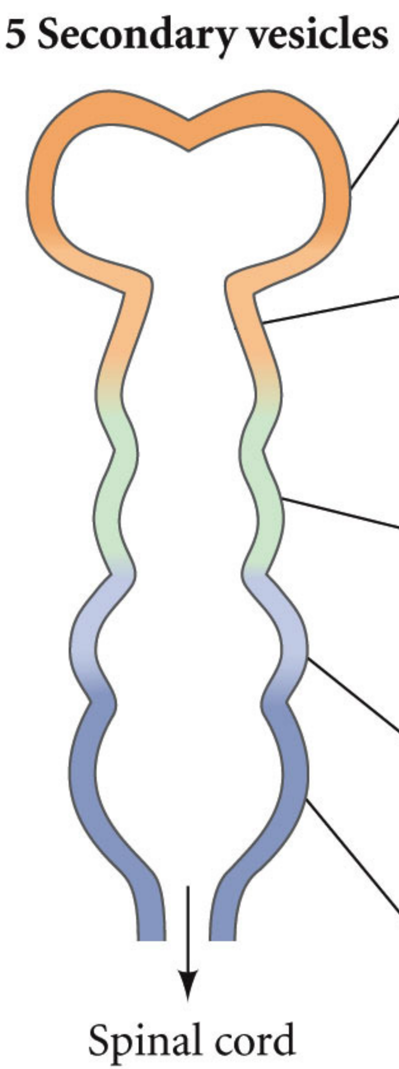
Electroporated cells

Early brain development

Proliferation to grow in thickness => Vesicule formation due to differential proliferation



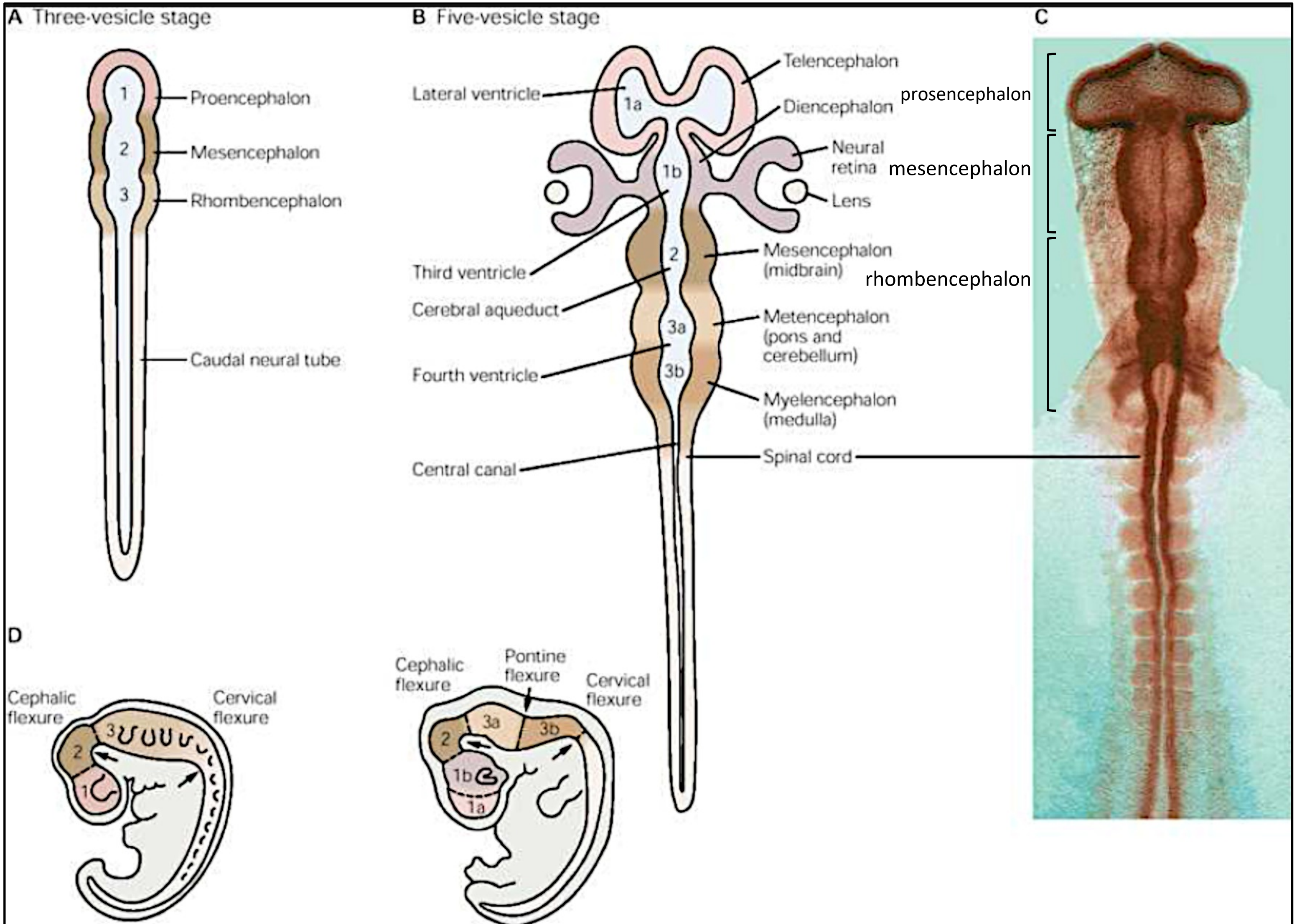
Early brain development

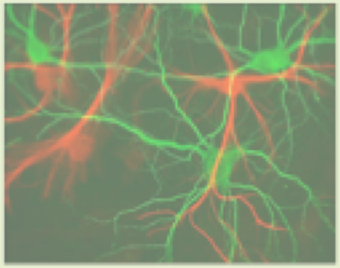


Adult derivatives

Structure	Function	Derived from
Olfactory lobes	– Smell	Telencephalon derived
Hippocampus	– Memory storage	Telencephalon derived
Cerebrum	– Association ("intelligence")	Telencephalon derived
Optic vesicle	– Vision (retina)	Diencephalon Derived
Epithalamus	– Pineal gland	Diencephalon Derived
Thalamus	– Relay center for optic and auditory neurons	Diencephalon Derived
Hypothalamus	– Temperature, sleep, and breathing regulation	Diencephalon Derived
Midbrain	– Fiber tracts between anterior and posterior brain, optic lobes, and tectum	Mesencephalon derived
Cerebellum	– Coordination of complex muscular movements	Metencephalon derived
Pons	– Fiber tracts between cerebrum and cerebellum (mammals only)	Metencephalon derived
Medulla	– Reflex center of involuntary activities	Myelencephalon derived

Curving of the neural tube





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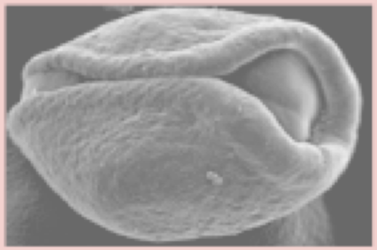
- Nervous system development

Neurulation



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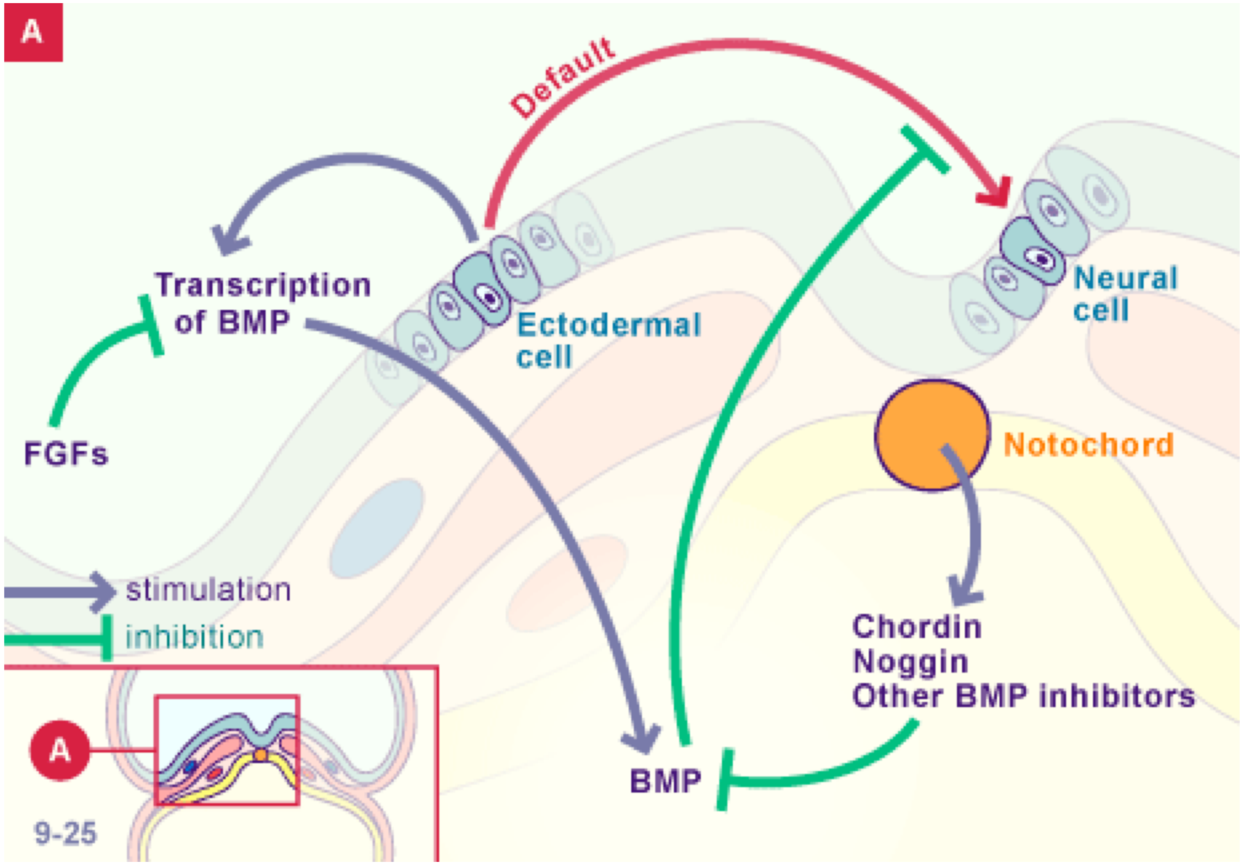
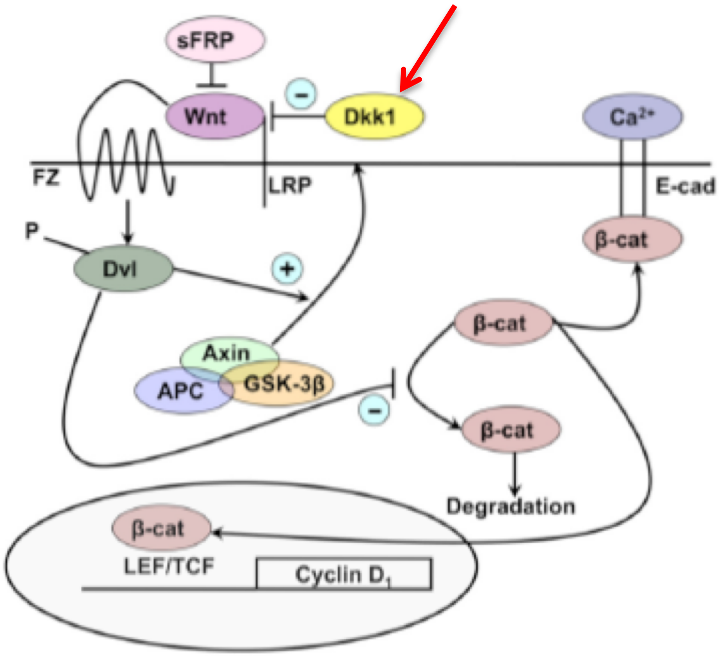
Neural induction



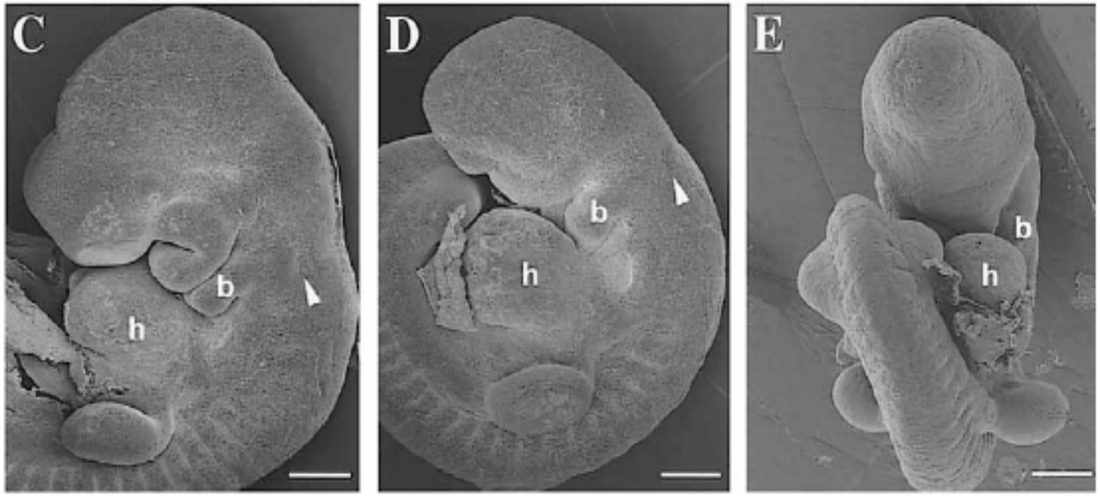
Wnt: posteriorization of the brain



Mouse embryo E9,5

WT

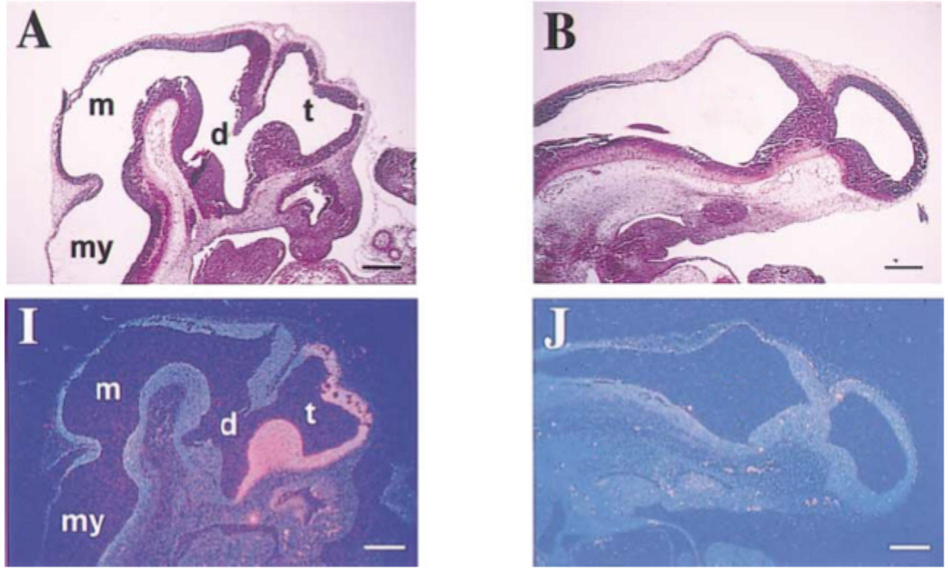
Dickkopf-1-/-



WT

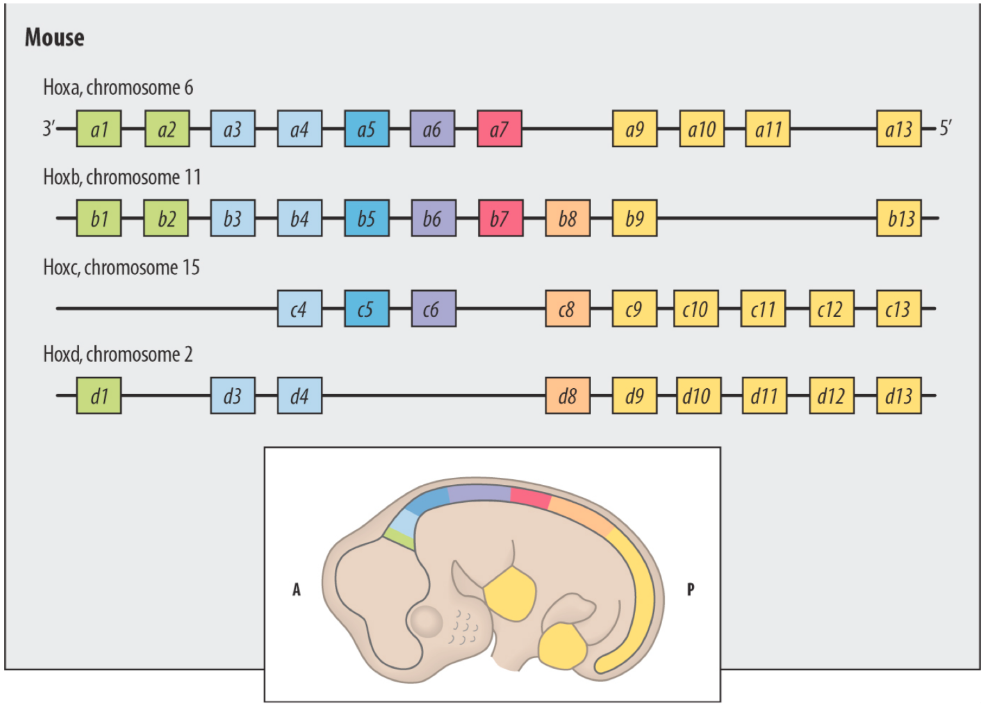
Dickkopf-1-/-

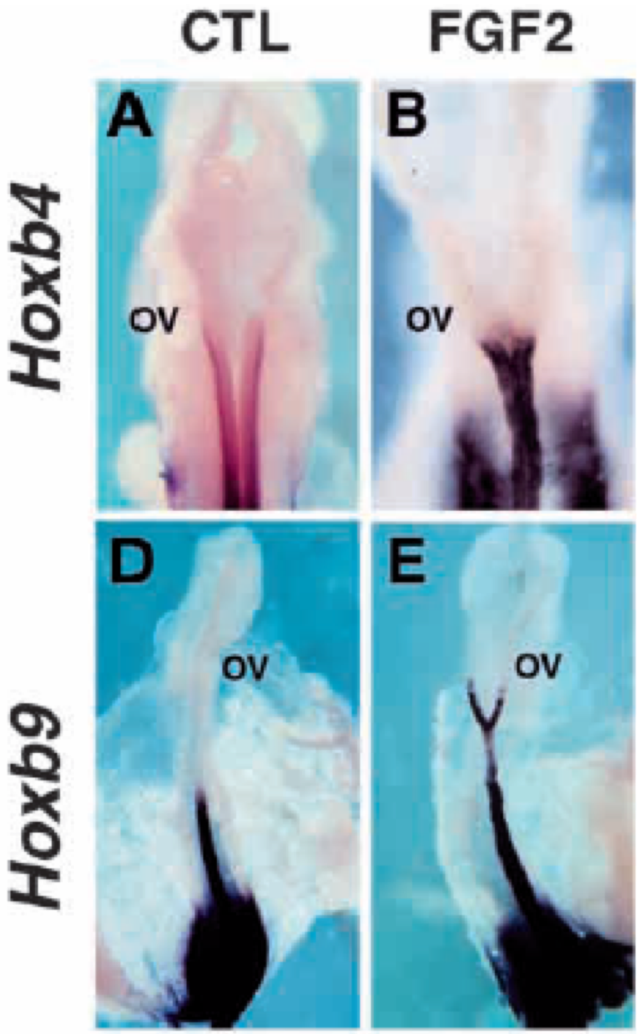
BF1



NB: Same results with other markers

Sensitivity of the neural tube to FGF





Bel-Vialar et al., 2002

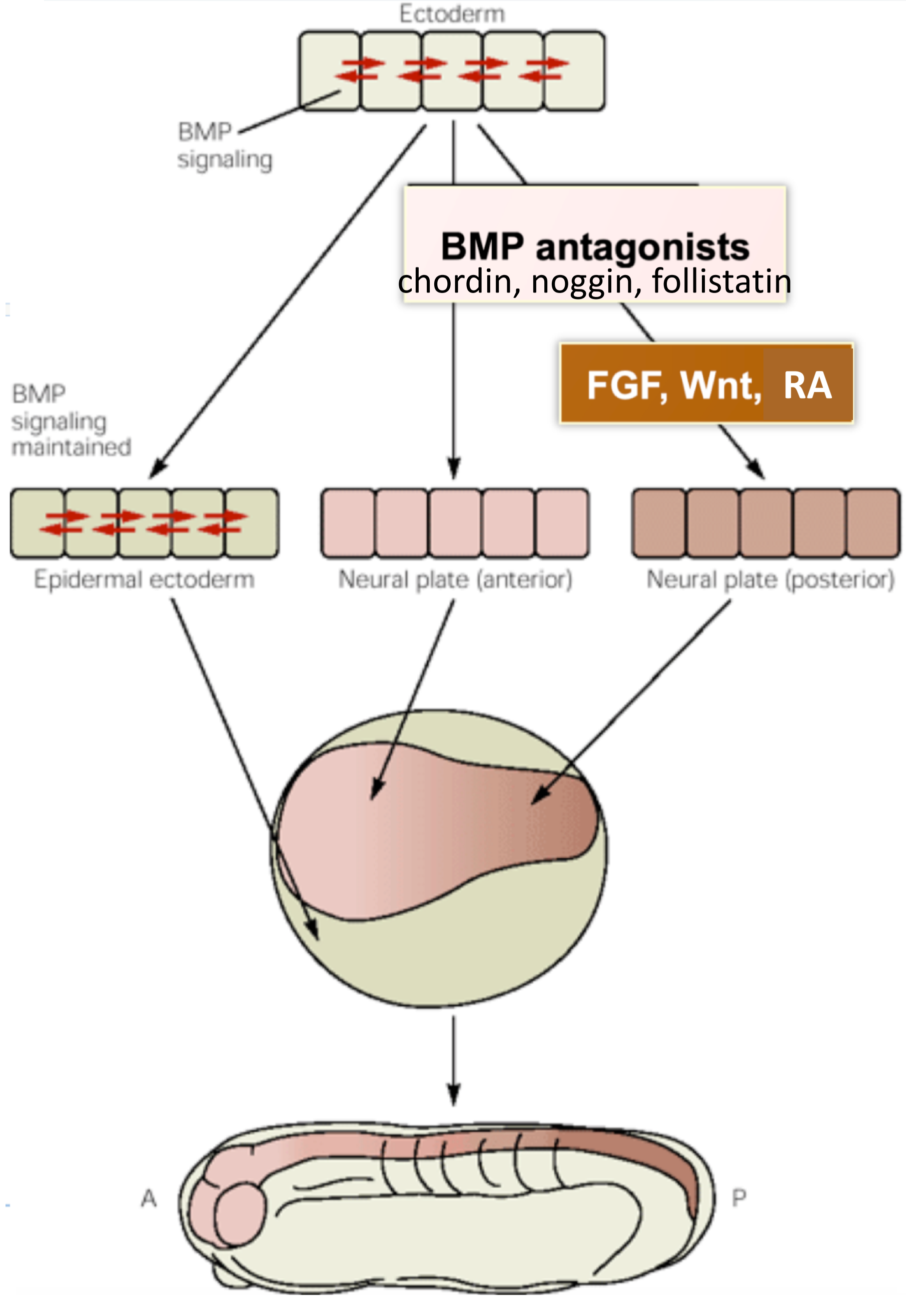
Regionalization defects

Example: Holoprosencephalias:

Anomalies during the subdivision of the prosencephalon to generate the telencephalon and the diencephalon. Moreover, the telencephalon does not divide totally into two hemispheres.

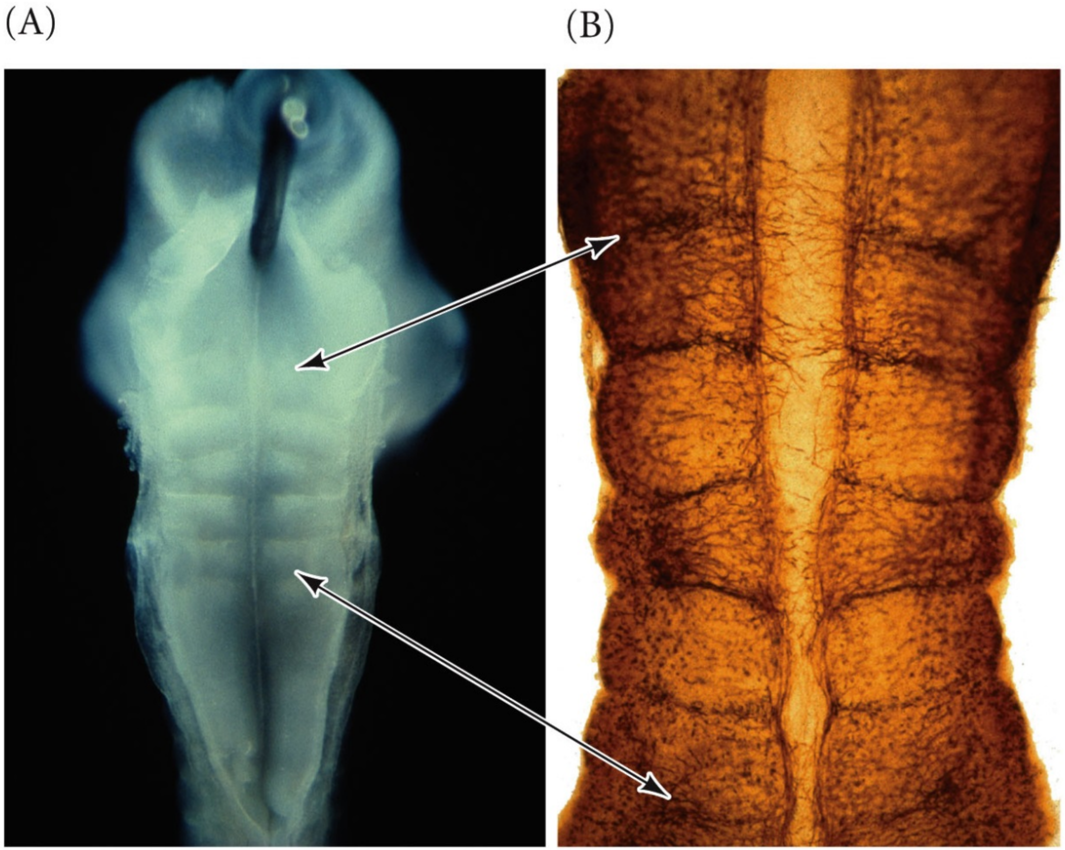
There are variable degrees of malformation.

To sum up

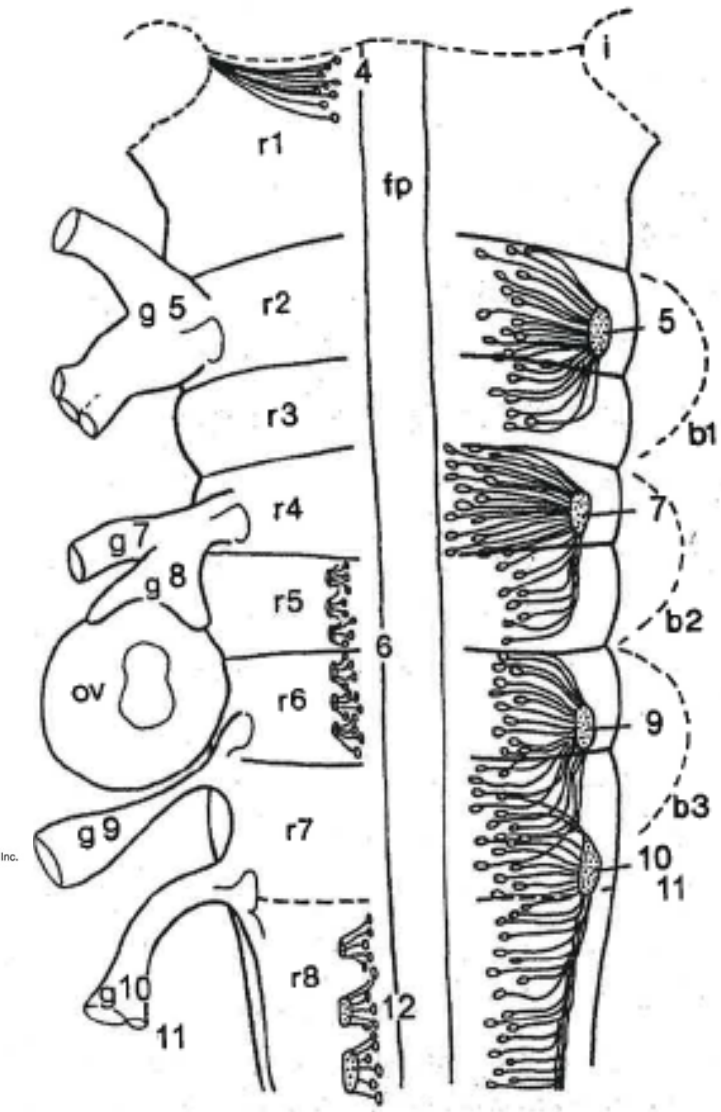


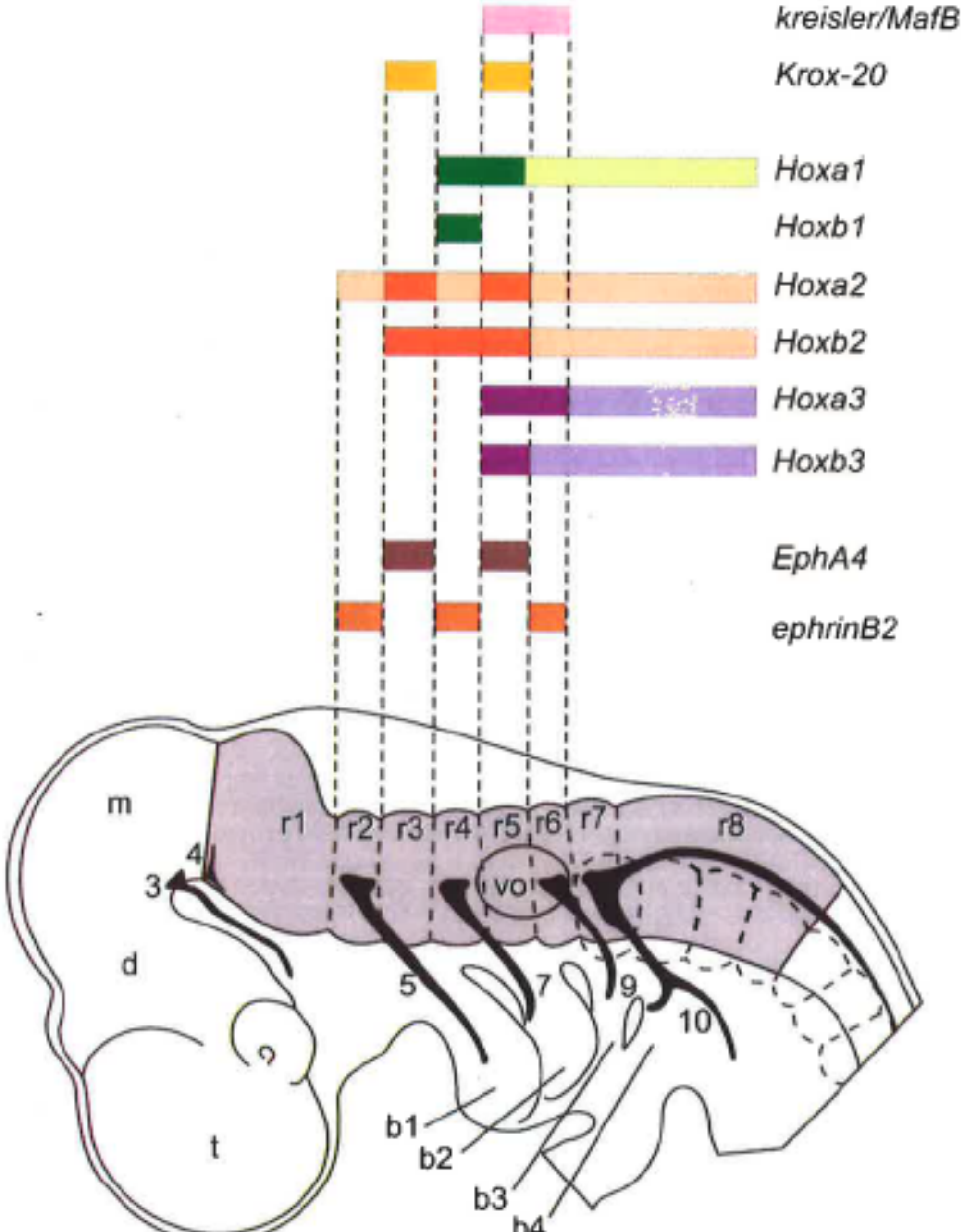
Ectoderm
BMP signaling
BMP antagonists
chordin, noggin, follistatin
FGF, Wnt, RA
BMP signaling maintained
Epidermal ectoderm
Neural plate (anterior)
Neural plate (posterior)
A
P

Hindbrain: an example of regionalisation



DEVELOPMENTAL BIOLOGY, 9e, Figure 9.10




kreisler/MafB
Krox-20
Hoxa1
Hoxb1
Hoxa2
Hoxb2
Hoxa3
Hoxb3
EphA4
ephrinB2
m
d
t
r1
r2
r3
r4
r5
r6
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r8
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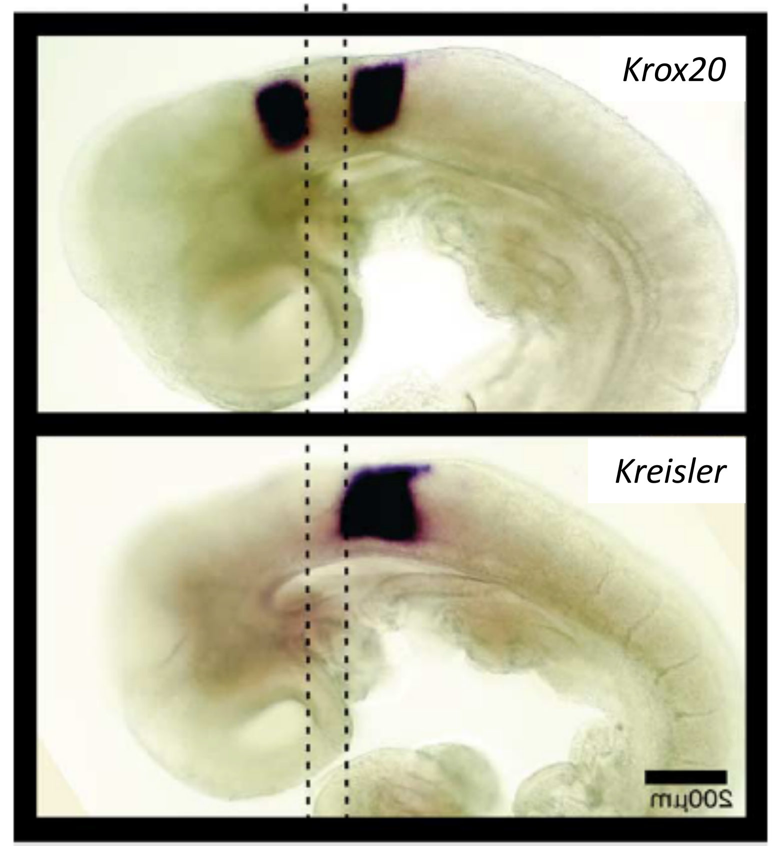
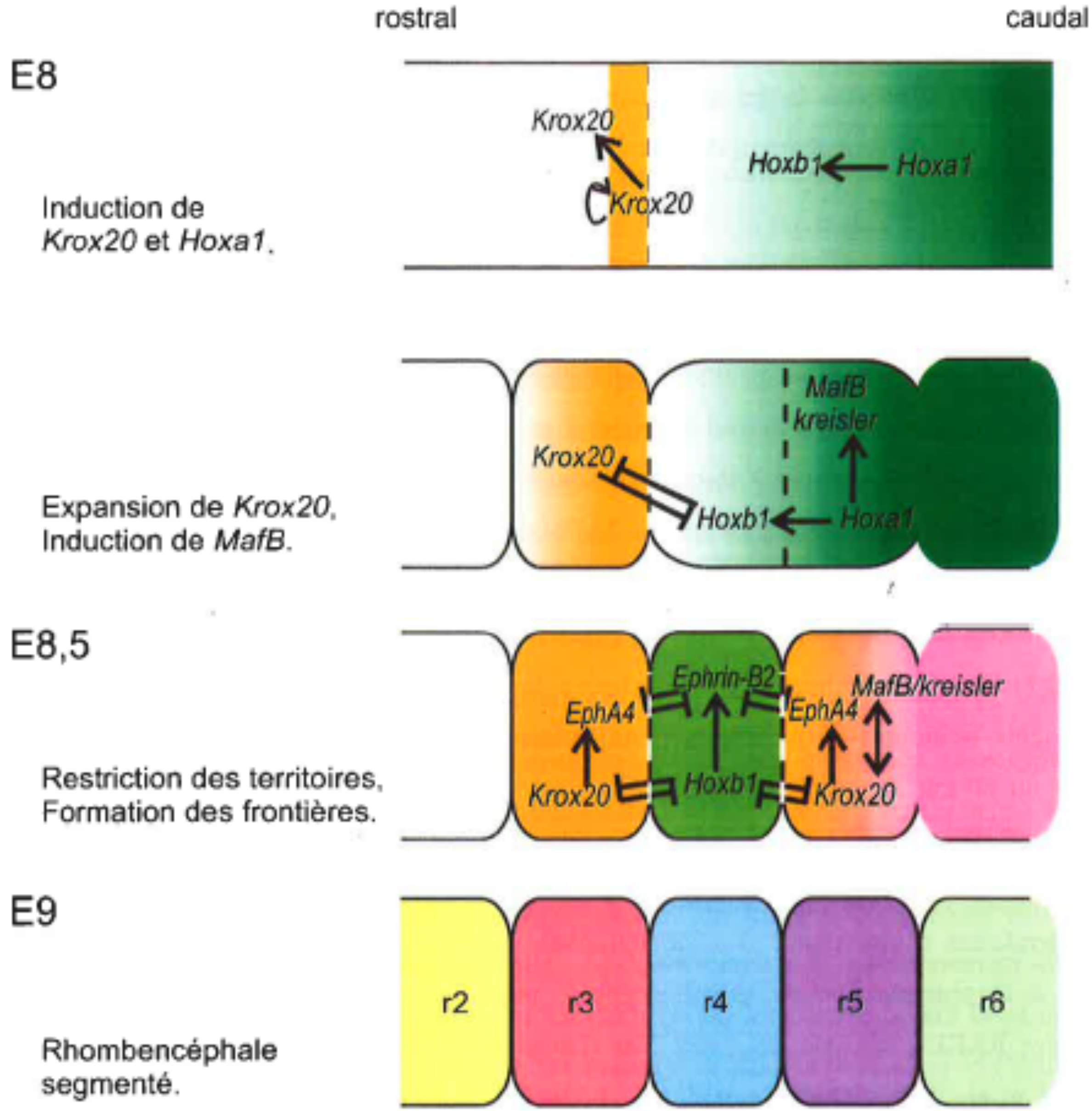
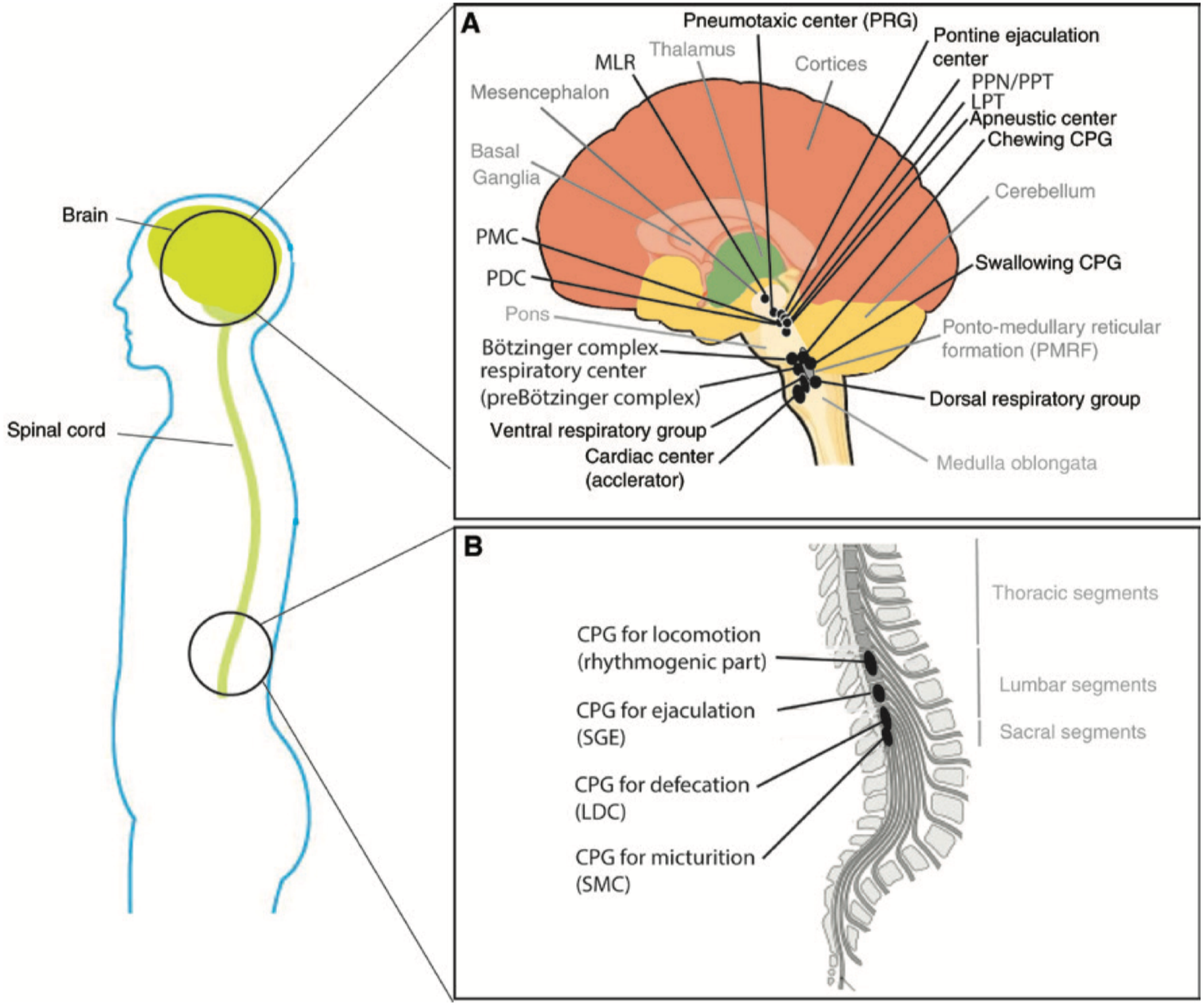
7
9
10
vo
b1
b2
b3
b4


Krox20
Kreisler



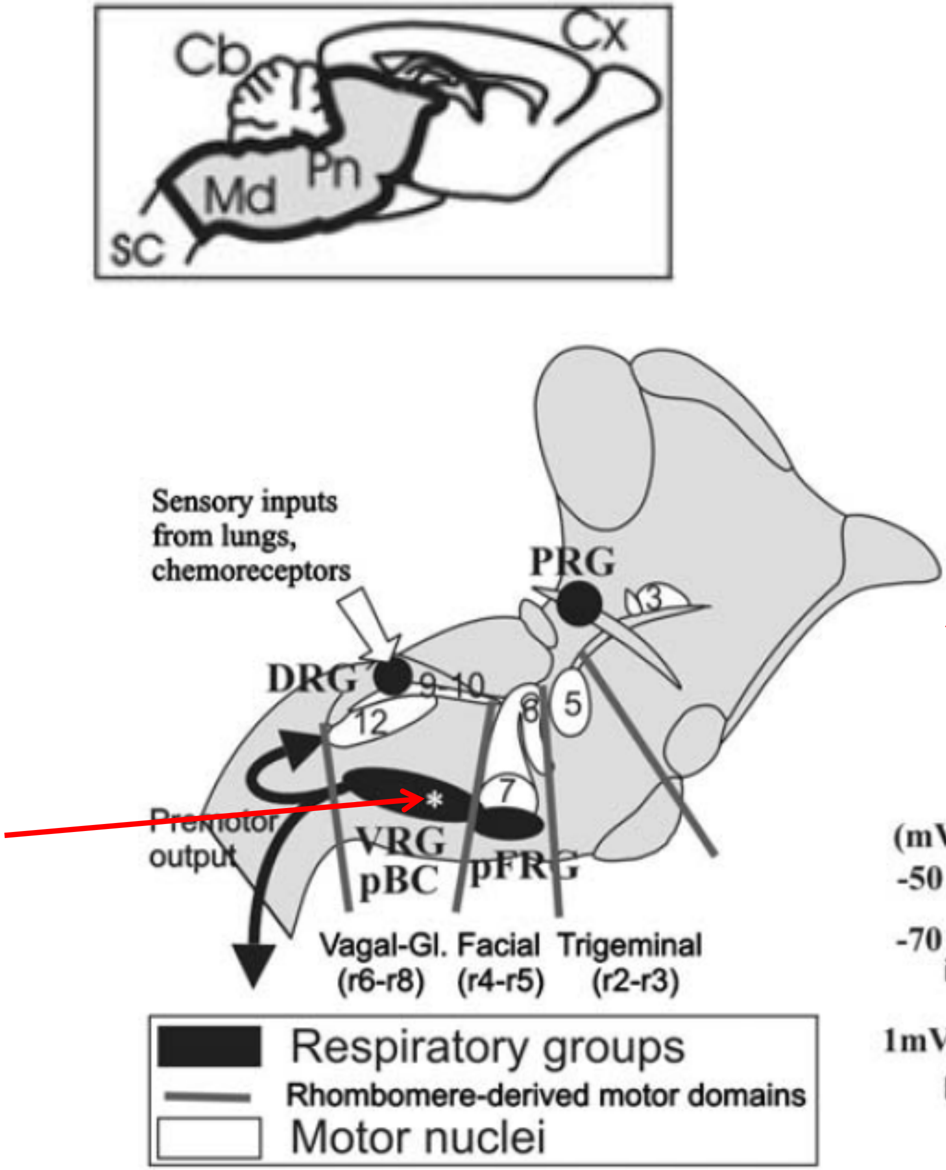
D'après Giudicelli et al., 2001

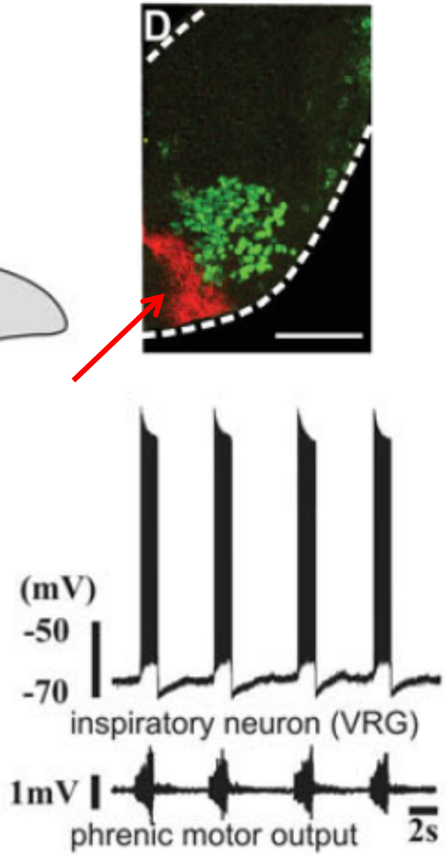
The main central pattern generators (CPGs) in the brainstem and the spinal cord



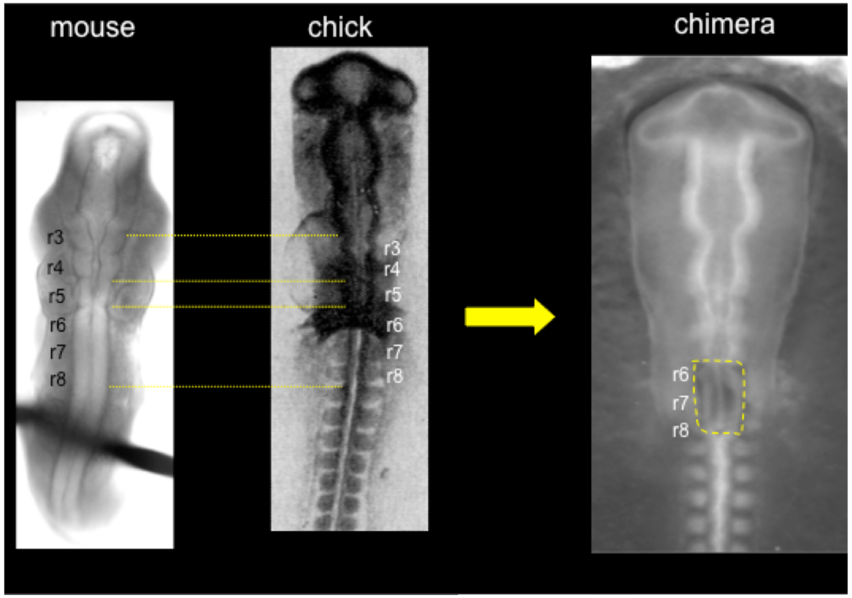
Steuer and Guertin, 2019

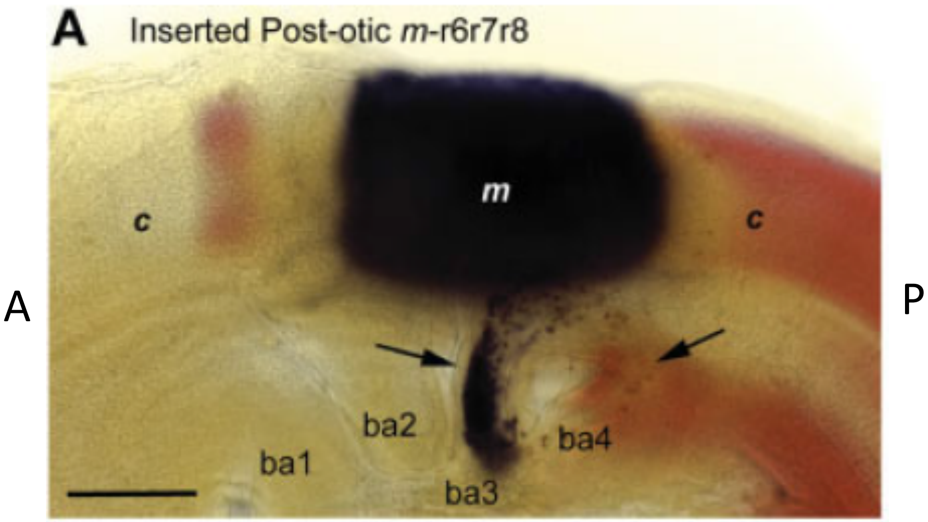
The PreBötzinger complex:
The respiratory central pattern generator



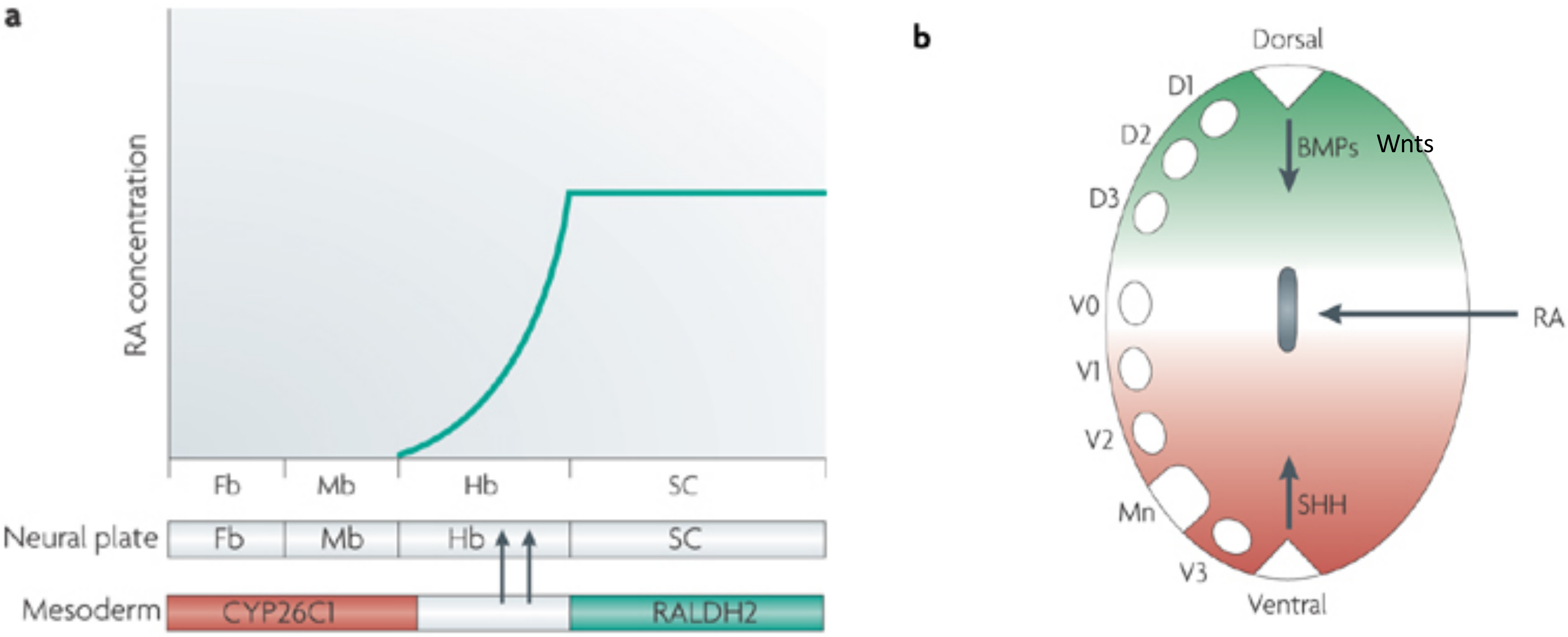


r6r7r8: Genetic program leading to the PreBötzinger complex



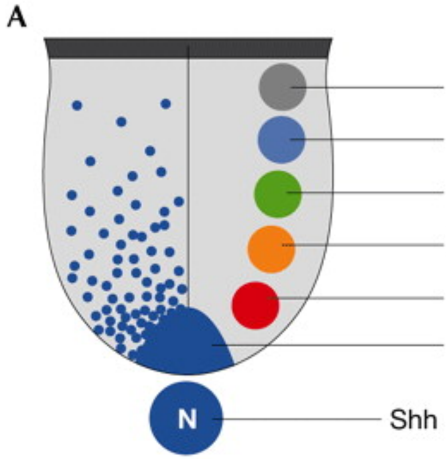


Control of the dorso-ventral patterning

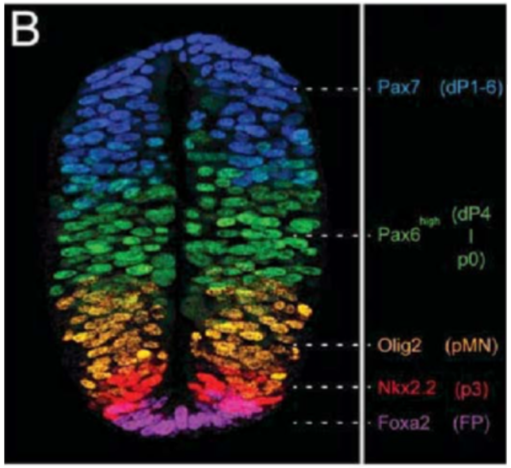


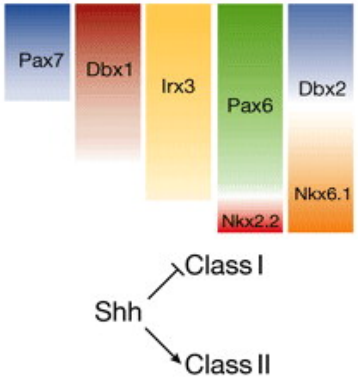
Modifié d'après Maden, 2007

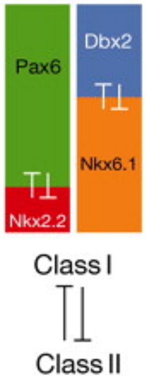
Cascade of inductions initiated by the notochord in the ventral neural tube



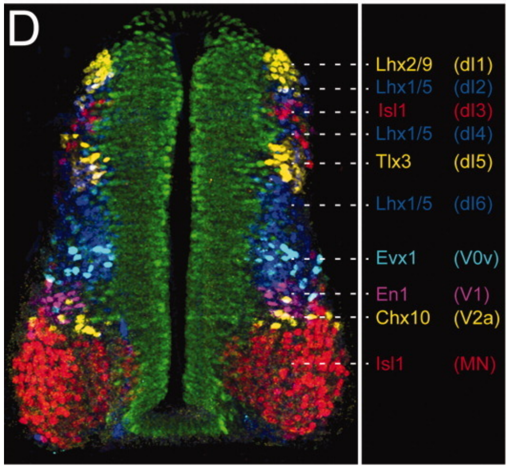
HH16 Determination



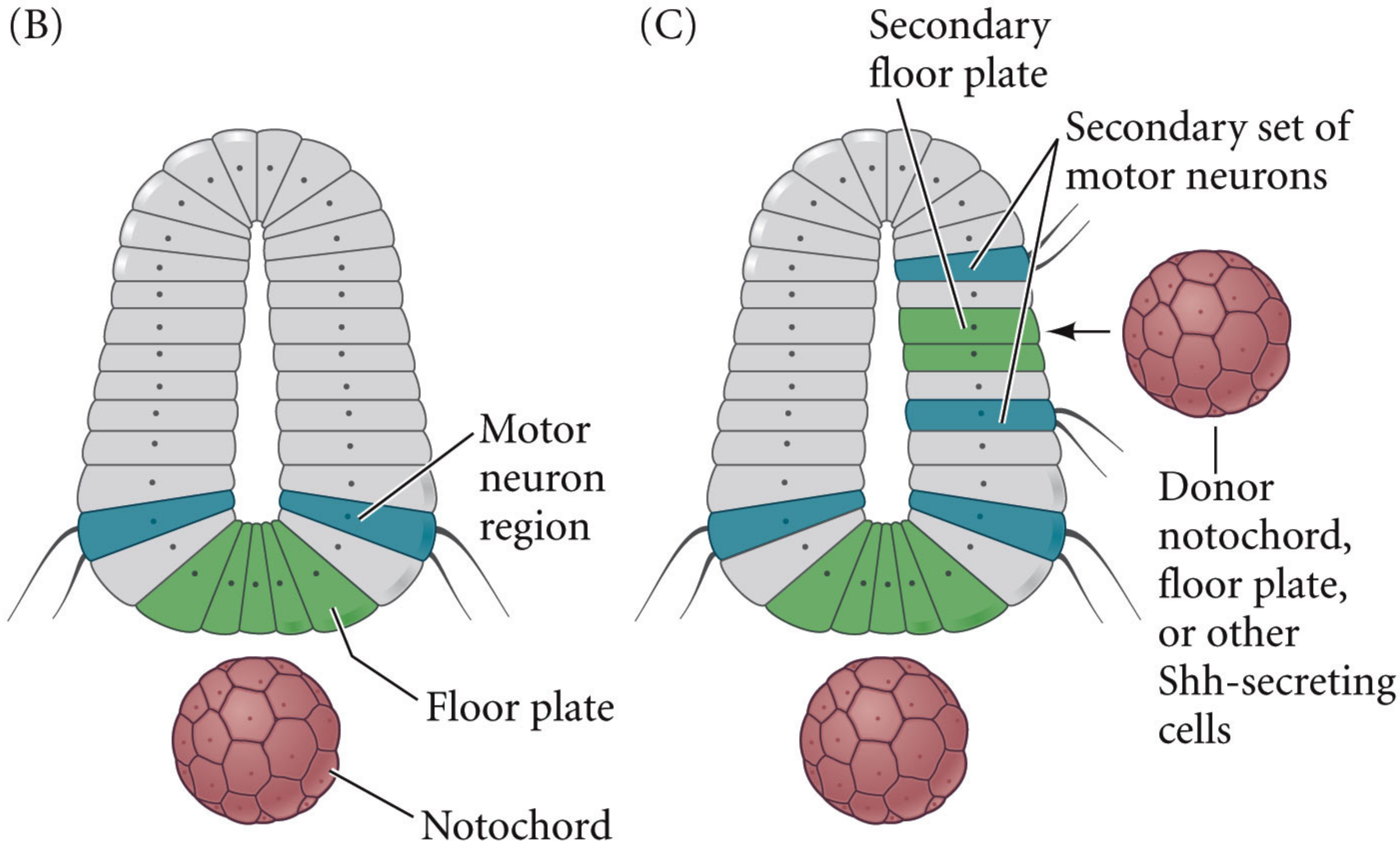




HH24 Differentiation

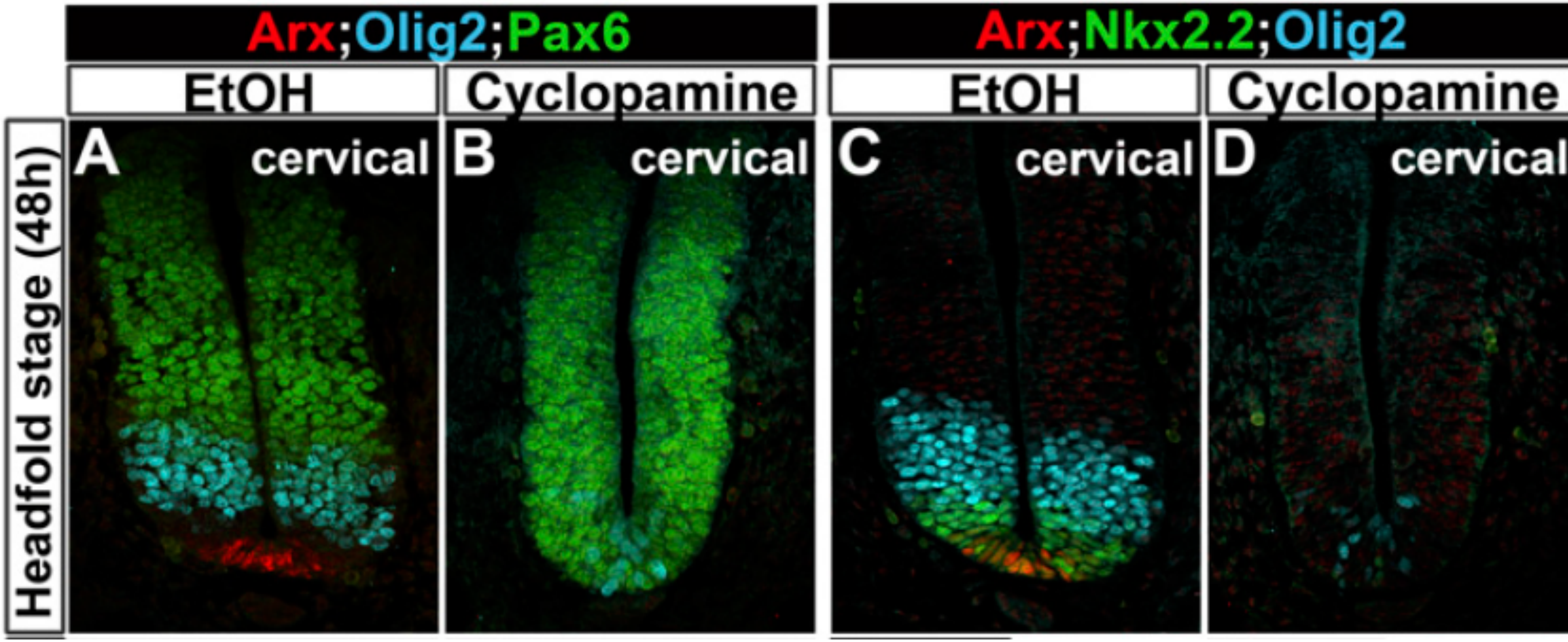


Jacob and Briscoe, 2003; Le Dréau and Marti, 2012



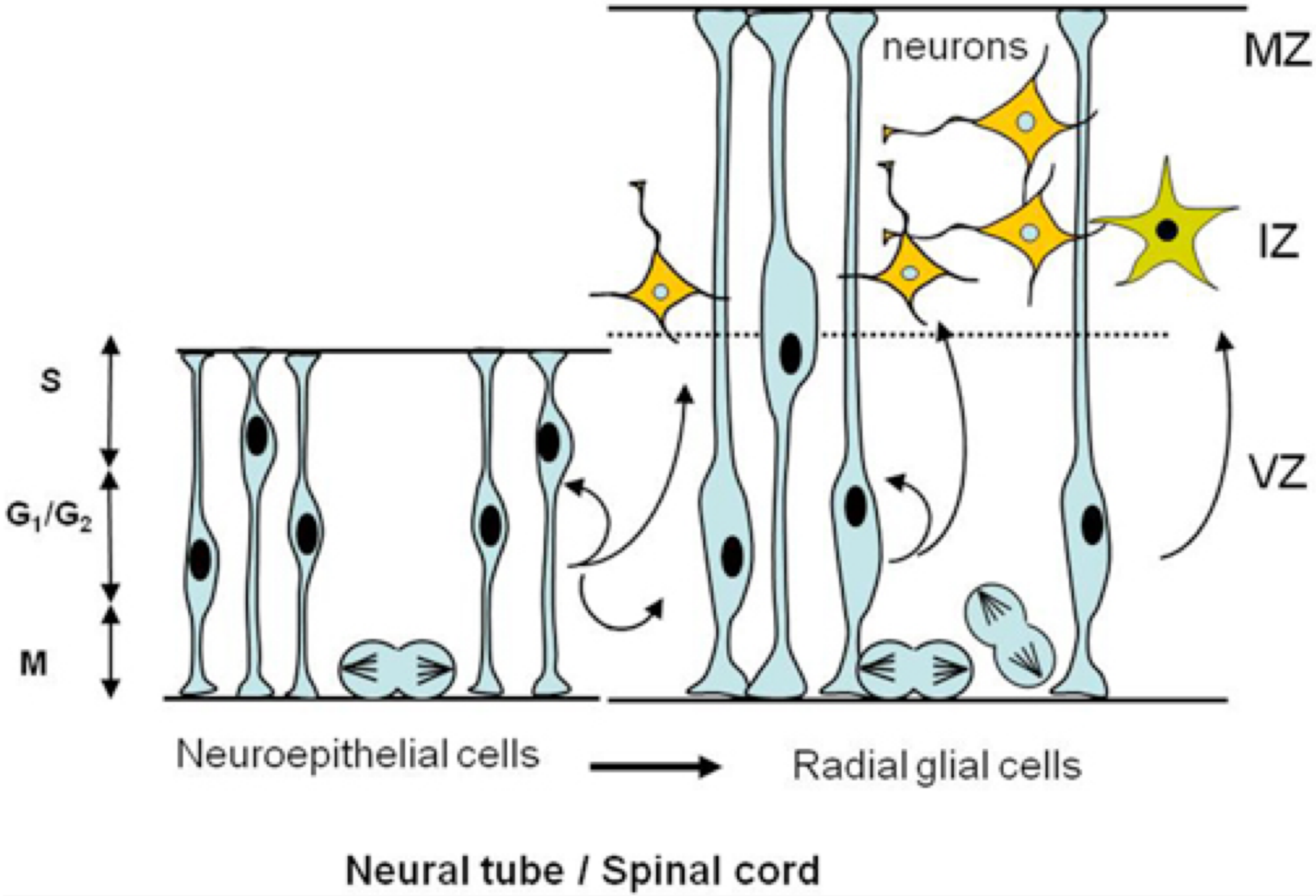
Placzek et al., 1990

Cyclopamine ⊣ Hh signaling



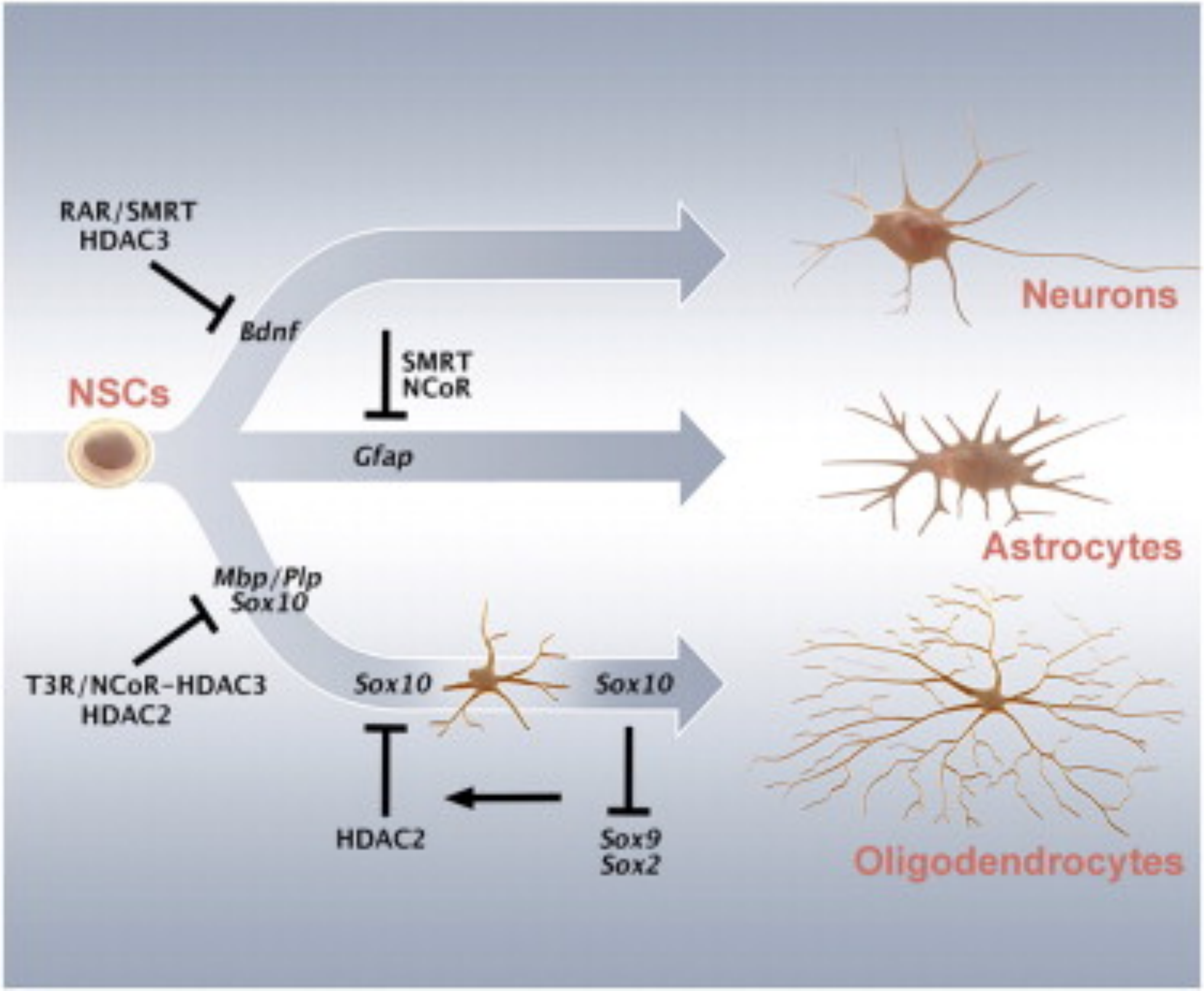
antagonizing Shh activity dorsally: a role for the Wnt canonical pathway signaling from the roof plate

Proliferation and differentiation



Leclerc et al., 2012

Proliferation and differentiation

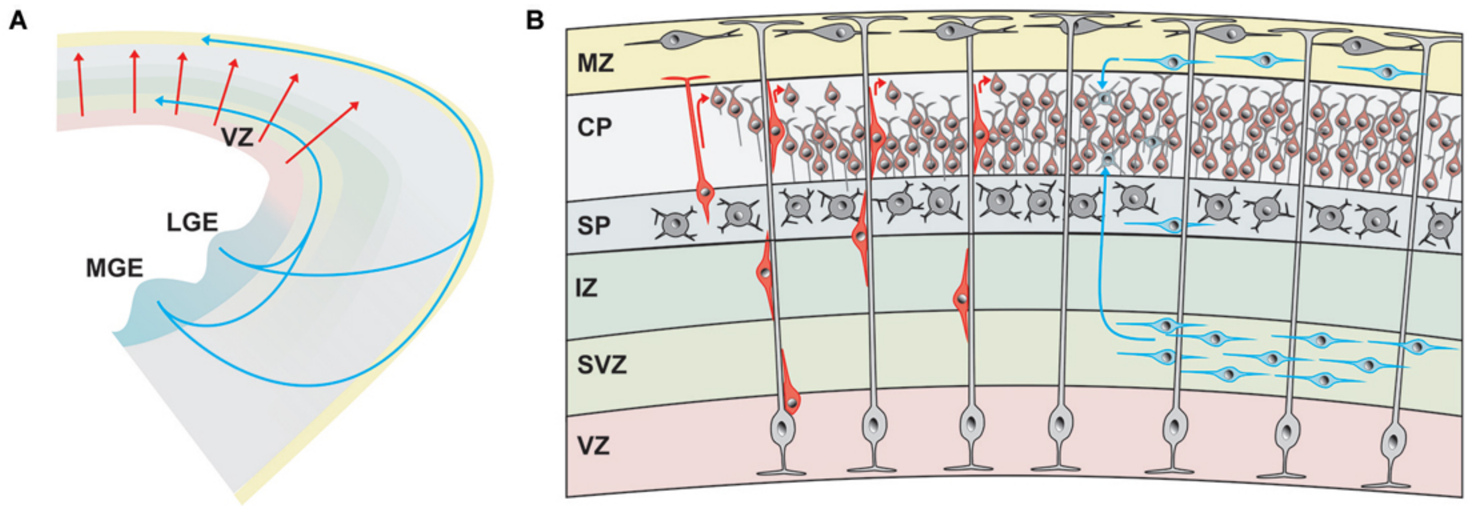


Neurogenesis defects

Disease	Description	Symptoms
Megalencephaly (macroencephaly)	Brain bigger than normality	The size of the head is increased
Hemimegalencephaly	One hemisphere bigger than normality	Intelectual disorders, epilepsy, paralysis on one side of the body
Microencephaly	Brain smaller than normality	Intelectual disorders

Neuronal migration

Example: migration of glutamatergic and GABAergic neurons in the telencephalon



- **Intrinsic cues:** Transcription factors
- **Chemical cues:** semaphorines and ephrins (attracting or repelling signals)
- **chemico-mechanical guiding structures:** vertical fibers of radial glial cells
- **extracellular matrix protein**

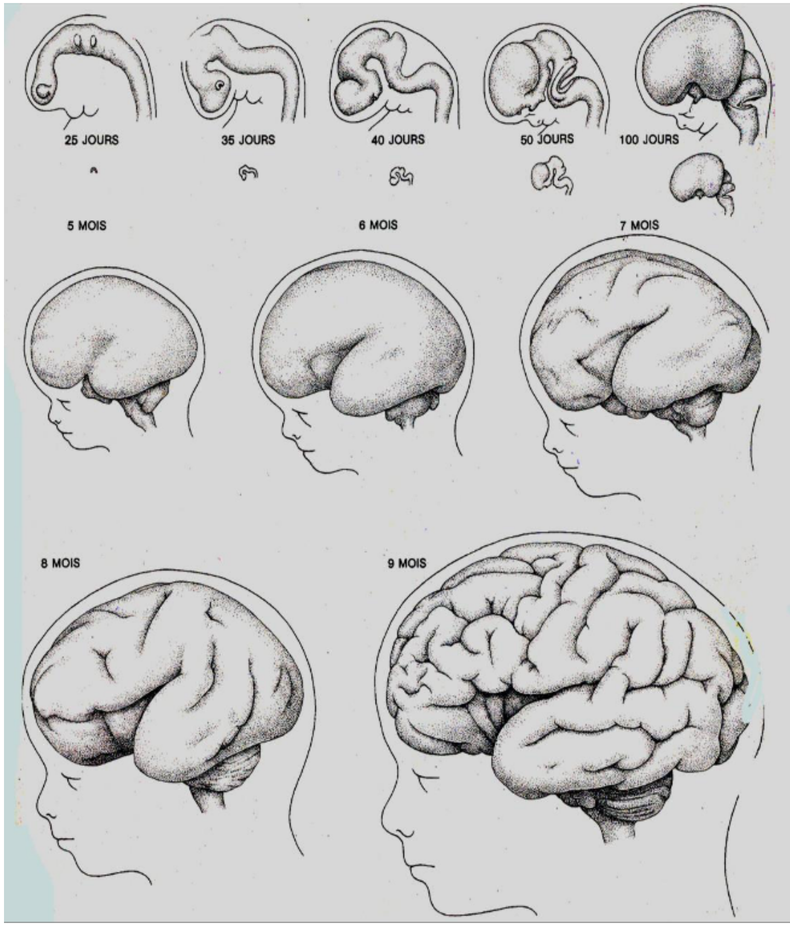
Luhmann et al., 2015

Migration and gyration defects

⟹ malformations of the cerebral cortex, which is not organized in six layers, as it should do.

Variable degrees: conserved organization in layers or architecture is totally disorganized

=> Gyrus are reduced compared to normal, or totally absent.

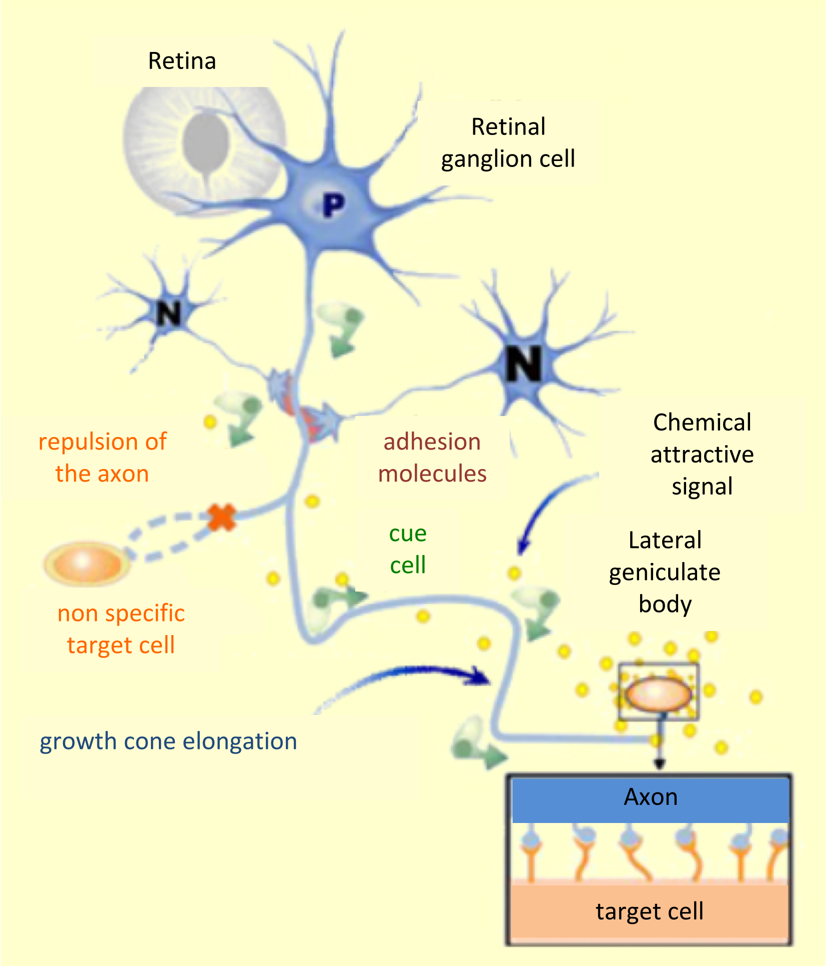


Schizencephaly, heterotopia, polymicrogyria, lyssencephaly

Synaptogenesis

- Selective recognition of the right way and the right targets by the axon growth cone

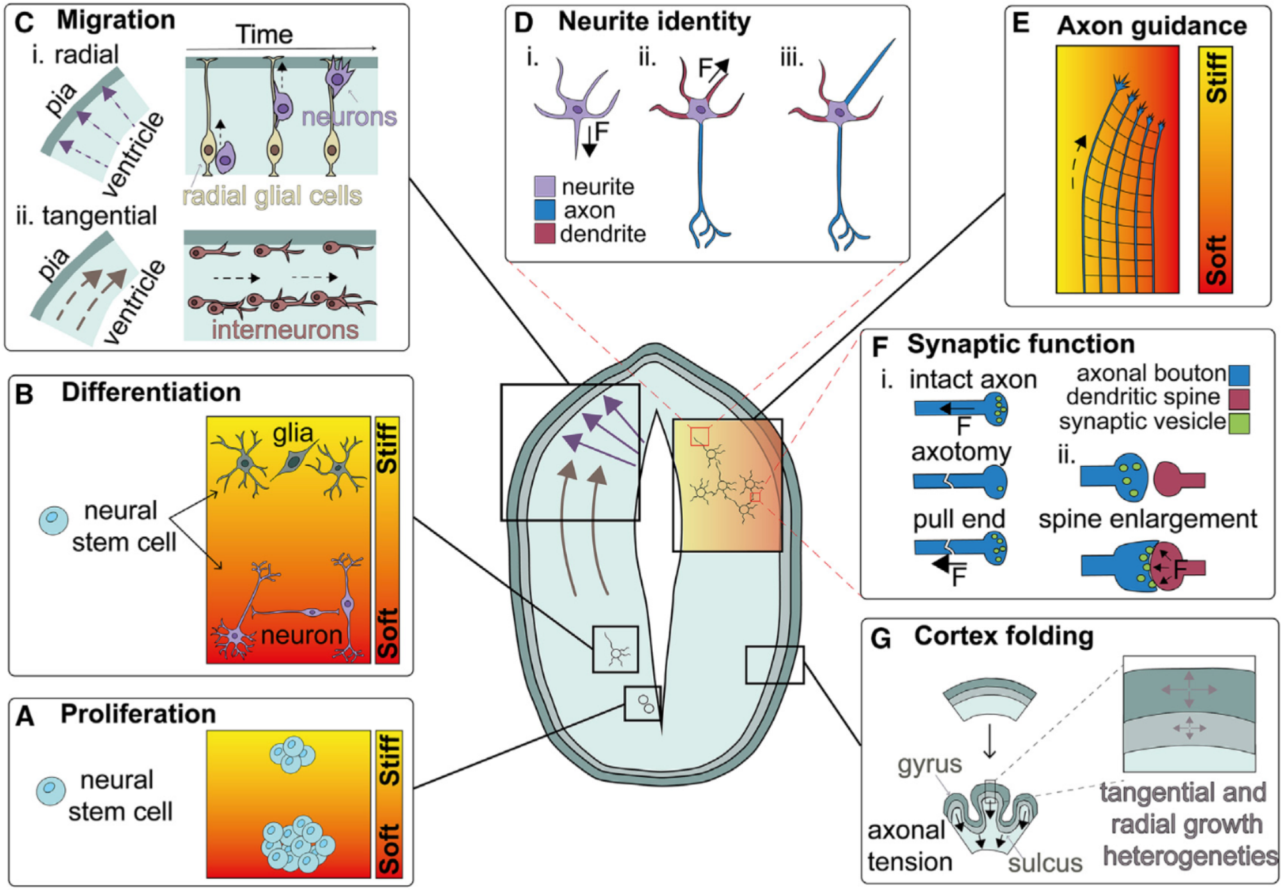
- Formation of the synapses



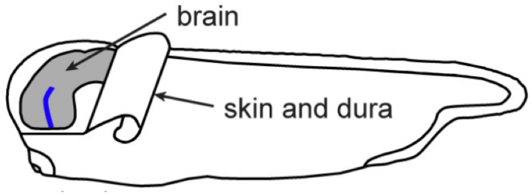
<u>Then adjustments:</u>

- <u>Neuronal apoptosis</u>
- <u>Synaptic pruning</u>: reduction in the number of synaptic connections => conservation of more efficient synaptic configurations

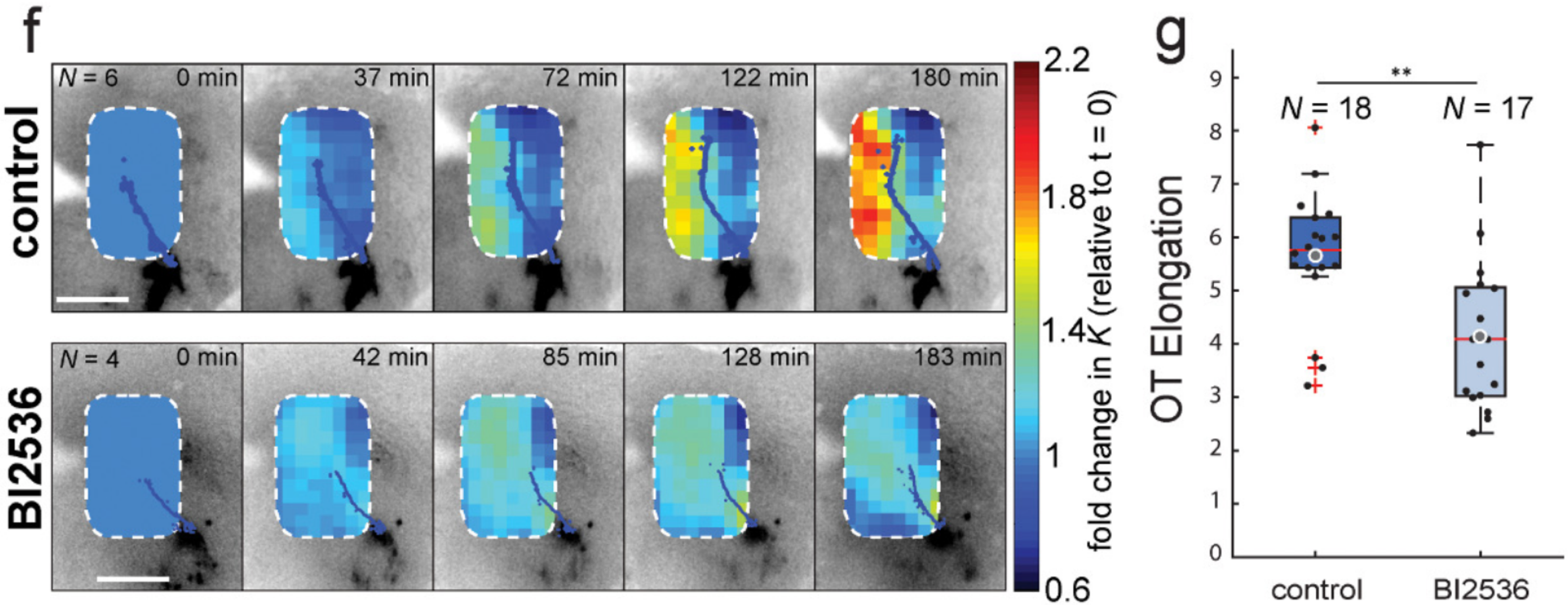
Mechanical regulation



Pillai and Franze et al., 2023



K = the apparent elastic modulus
⇔ a measure of tissue stiffness



BI2536: mitotic blocker

Development of a stiffness gradient in the Xenopus embryo brain

- precedes axon turning of ganglion cells
- is necessary for its correct elongation.

Thompson et al., 2019

Development and therapy

=> IPSc

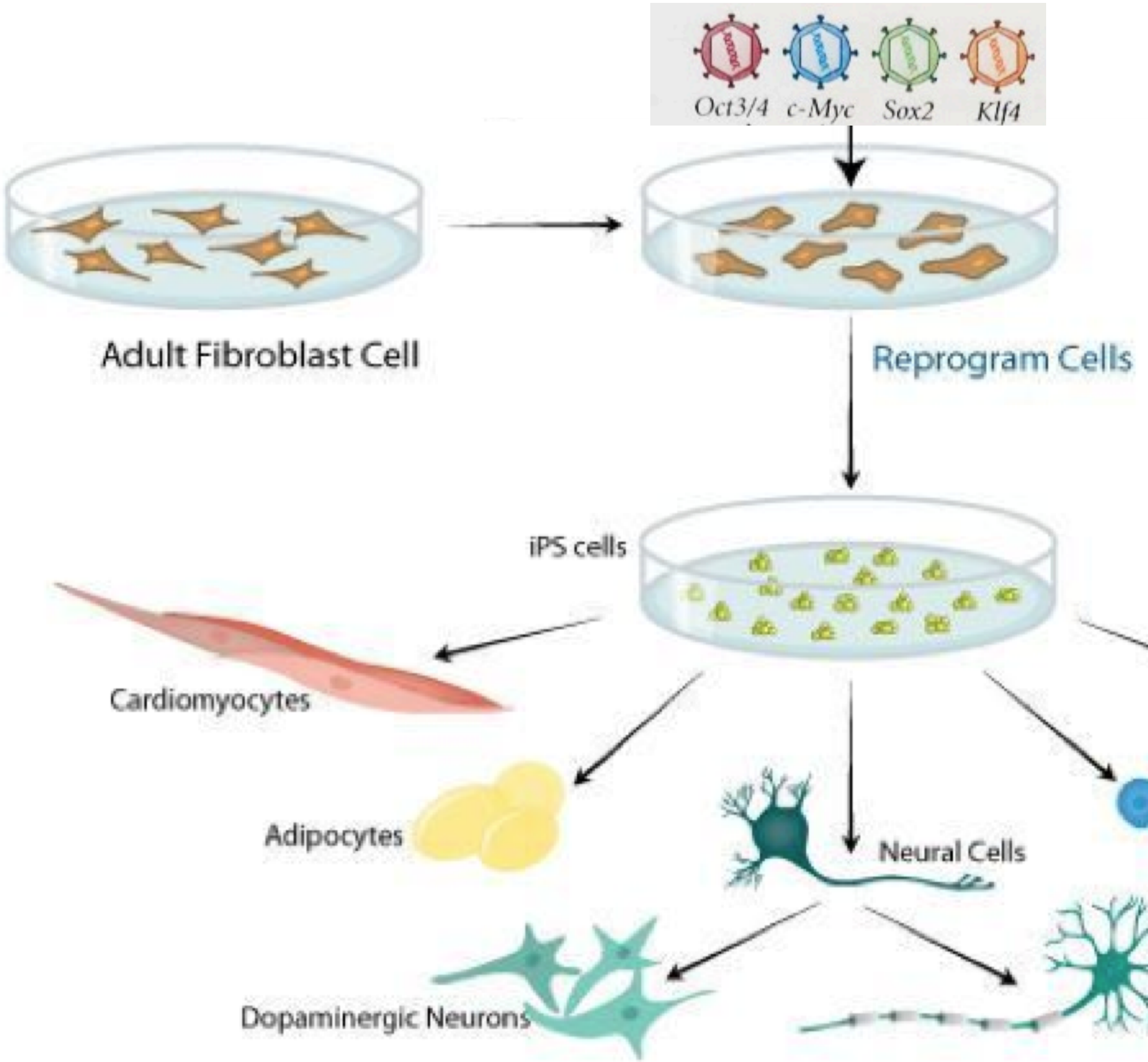
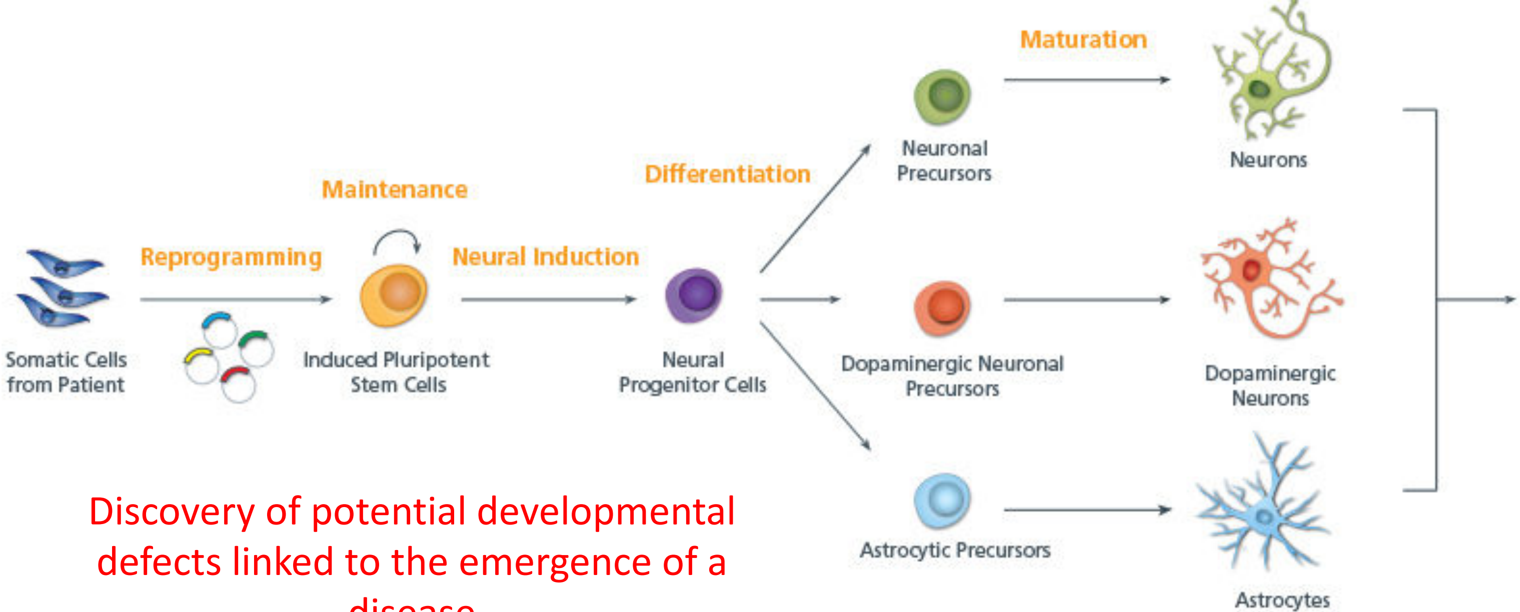


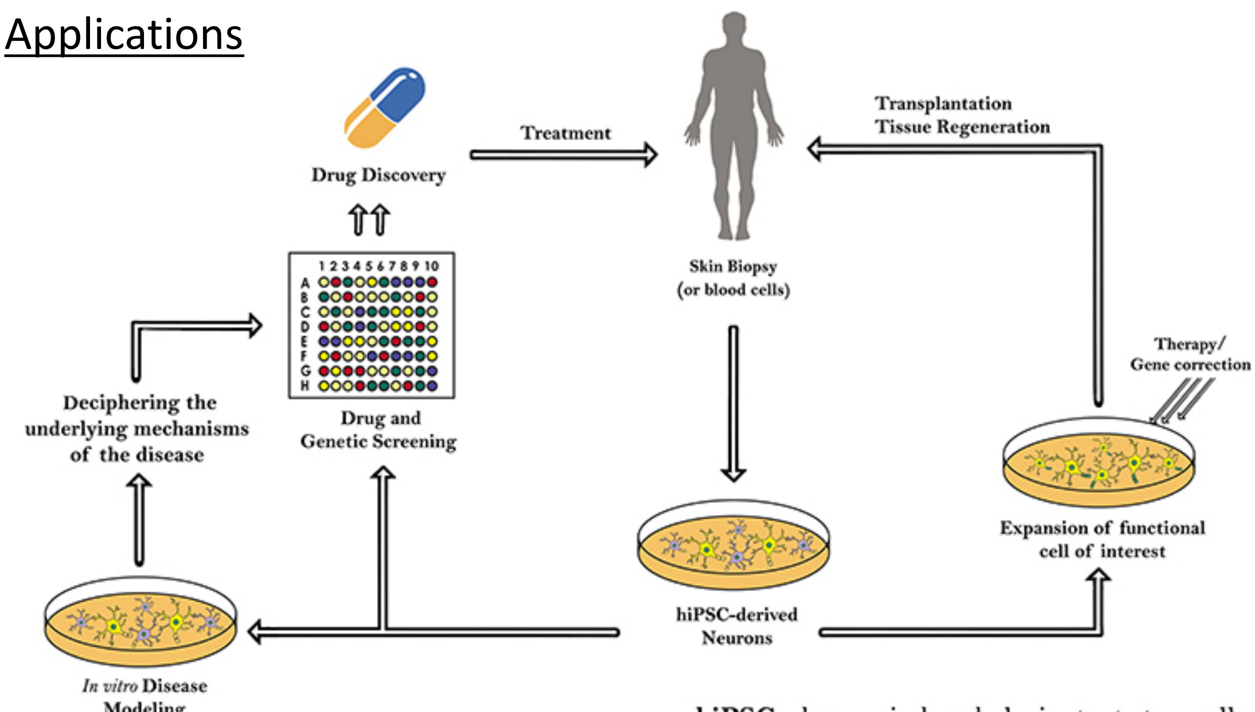
Photo: U. Montan

Shinya Yamanaka



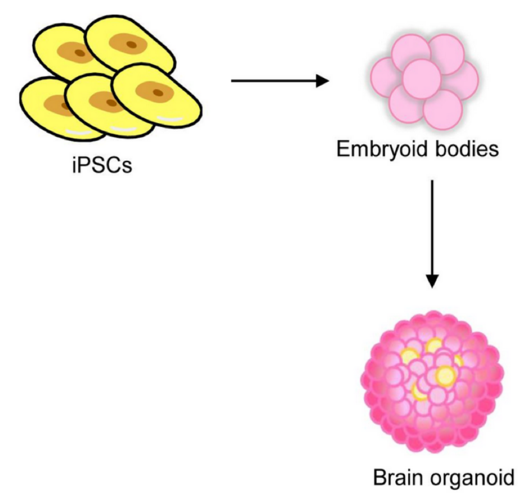
Discovery of potential developmental defects linked to the emergence of a disease

Applications

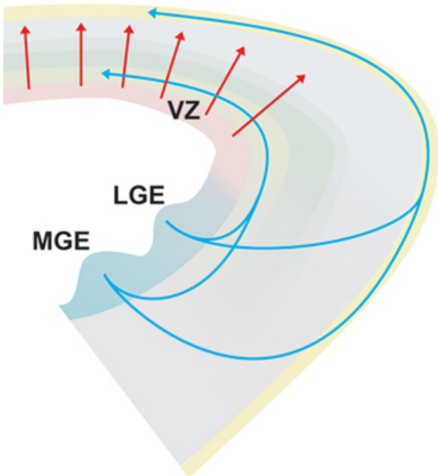


hiPSCs: human induced pluripotent stem cells

Organoids

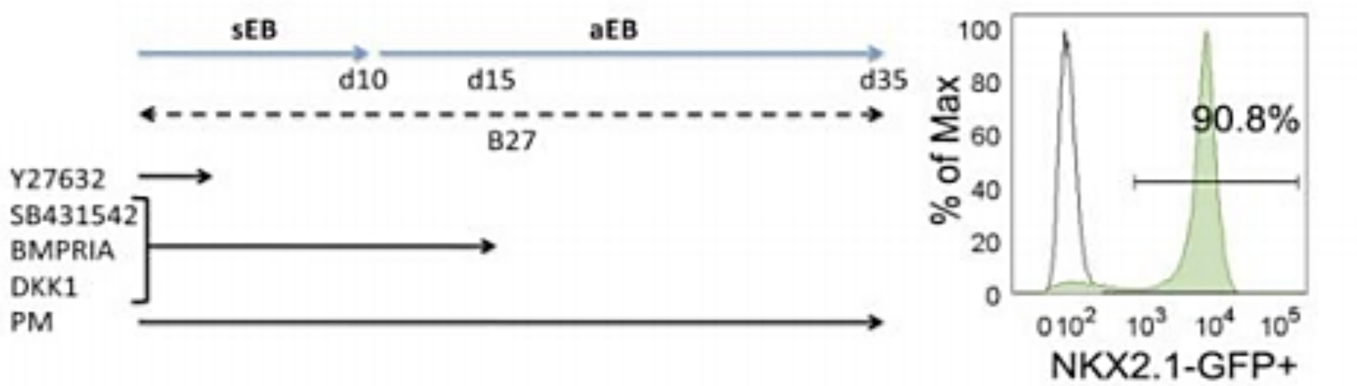


3D neuronal culture



Inhibitory GABAergiques neurons (Nkx2.1+) are involved in autism

⇒ generation of these neurons from IPSc



BMP inhibition: SB431542 et BMPRIA
Wnt inhibition: DKK-1 (Dickkopf-1)
Shh activation: PM (purmorphamine)
(Y-27632 for iPS survey)

Nicholas et al., 2013

Culotta and Penzes Molecular Autism (2020) 11:32
https://doi.org/10.1186/s13229-020-00339-0

Molecular Autism

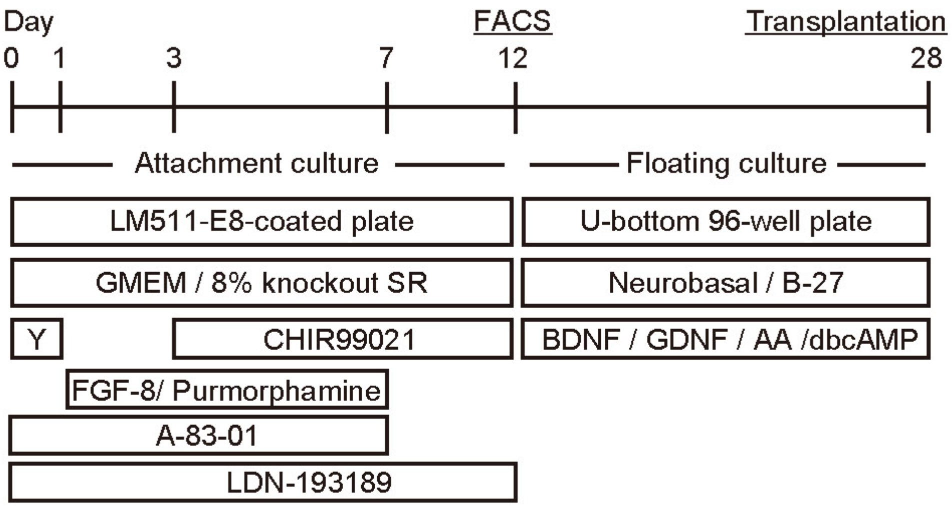
REVIEW Open Access

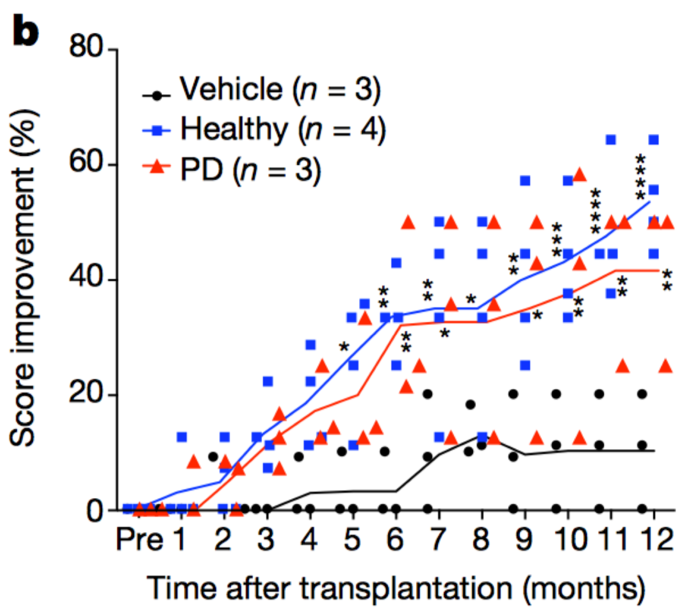
Exploring the mechanisms underlying excitation/inhibition imbalance in human iPSC-derived models of ASD

Lorenza Culotta[1,3] and Peter Penzes[1,2,3*]

Gene	Model type	Phenotype observed	Reference
ATRX, *AFF2*, *KCNQ2*, *SCN2A*, and *ASTN2*	Homozygous deletion	Reduced synaptic activity	[53]
CACNA1C	ASD-related mutations	Disrupted interneurons migration	[54]
CNTN5 and *EHMT2*+	Heterozygous deletion	Hyperexcitability.	[55]
CNTNAP2	Heterozygous deletion	Increased neuronal network activity	[56]
FMR1	Heterozygous deletion	Impaired retinoic acid (RA)-dependent homeostatic synaptic plasticity	[57]
MECP2	Heterozygous deletion or duplication	Altered synaptic density, altered calcium signaling; altered neuronal firing rate and synchronization; delayed GABA switch	[58,59,60,61]
NLGN4	Gene overexpression and ASD-related mutations	Increased excitatory synapse density, altered synaptic strength	[62, 63]
NRXN1α	Homozygous and heterozygous deletion, ASD-related mutations	Impaired synaptic strength, altered synaptic calcium signaling	[64,65,66]
SHANK2	Heterozygous deletion and ASD-related mutations	Hyperconnectivity, enhanced branching complexity, increased synapse density	[67]
SHANK3	Heterozygous deletion and ASD-related mutations	Hypoconnectivity, reduced synaptogenesis, and dendritic arborization; impaired neuronal excitability and excitatory synaptic transmission; impaired HCN channels	[68,69,70,71,72,73,74]
TSC1/2	Homozygous and heterozygous deletion	Altered neuronal excitability and activity, altered synchrony (cortical neurons); hypoexcitability (cerebellar Purkinje cells)	[75,76,77,78]
Other ASD models		Aberrant neuronal maturation, altered neuronal differentiation and synaptic formation	[79, 80]

Parkinson's disease: degeneration of midbrain dopaminergic neurons
⇒ Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model





Vehicle: monkeys that received control injection
Healthy: monkeys transplanted with cells derived from healthy individuals
PD: monkeys transplanted with cells derived from PD patients

Kikuchi et al., 2017