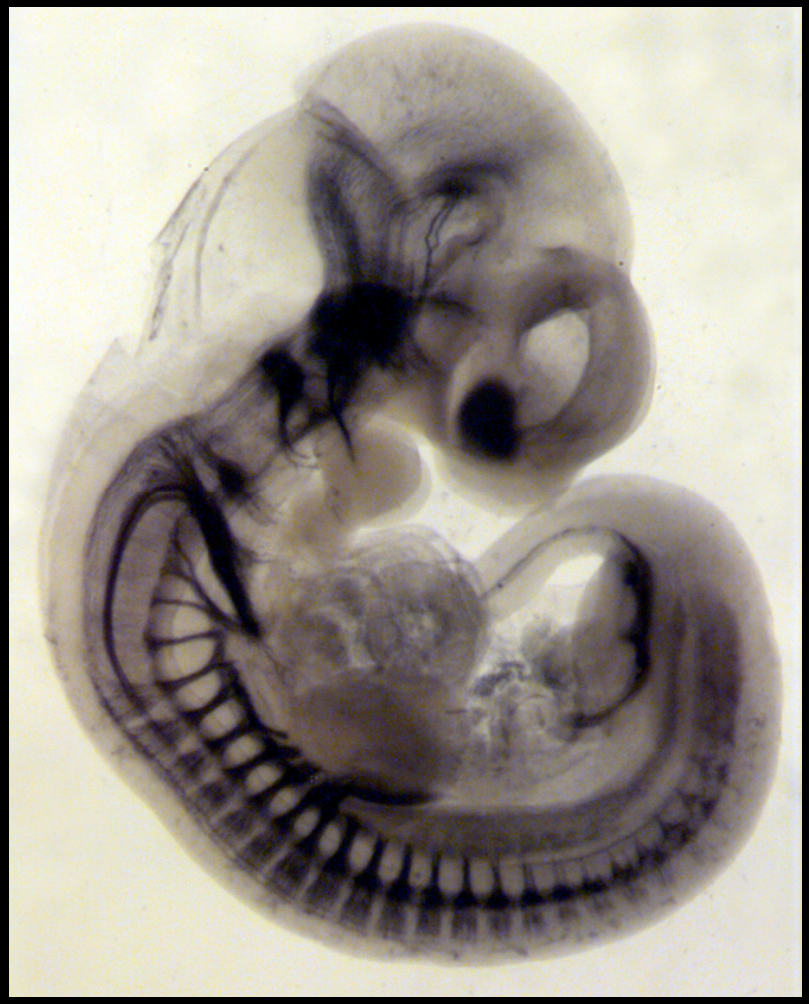
Development of the CNS

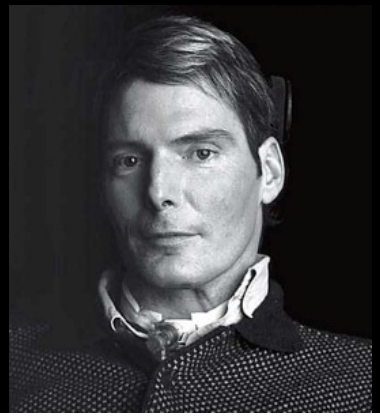


Lori Zeltser lz146@columbia.edu

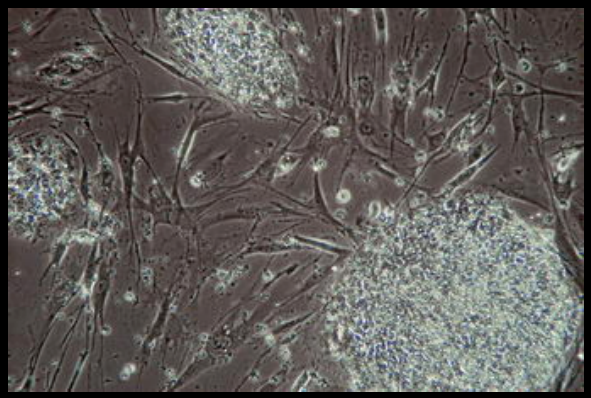
Why study CNS development?

To design better strategies to prevent/treat disorders of CNS development.

To serve as the foundation for efforts to treat neurological diseases/injury with stem cell-based therapies.

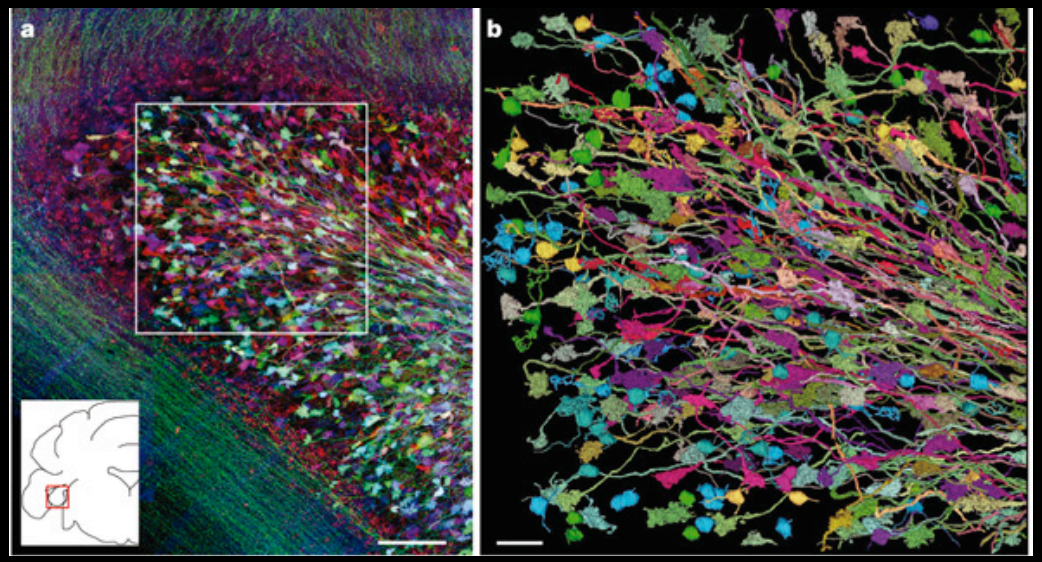


The Challenge



Miller

?



Livet, Lichtman

How to Make a Nervous System

- Neural induction
- Neural tube formation
- Acquisition of a positional identity
- Birth and migration of neurons and glia
- Specification of cell fates
- Axonal pathfinding and connectivity
- Binding of trophic factors for survival and differentiation
- Synapse formation, refinement and plasticity

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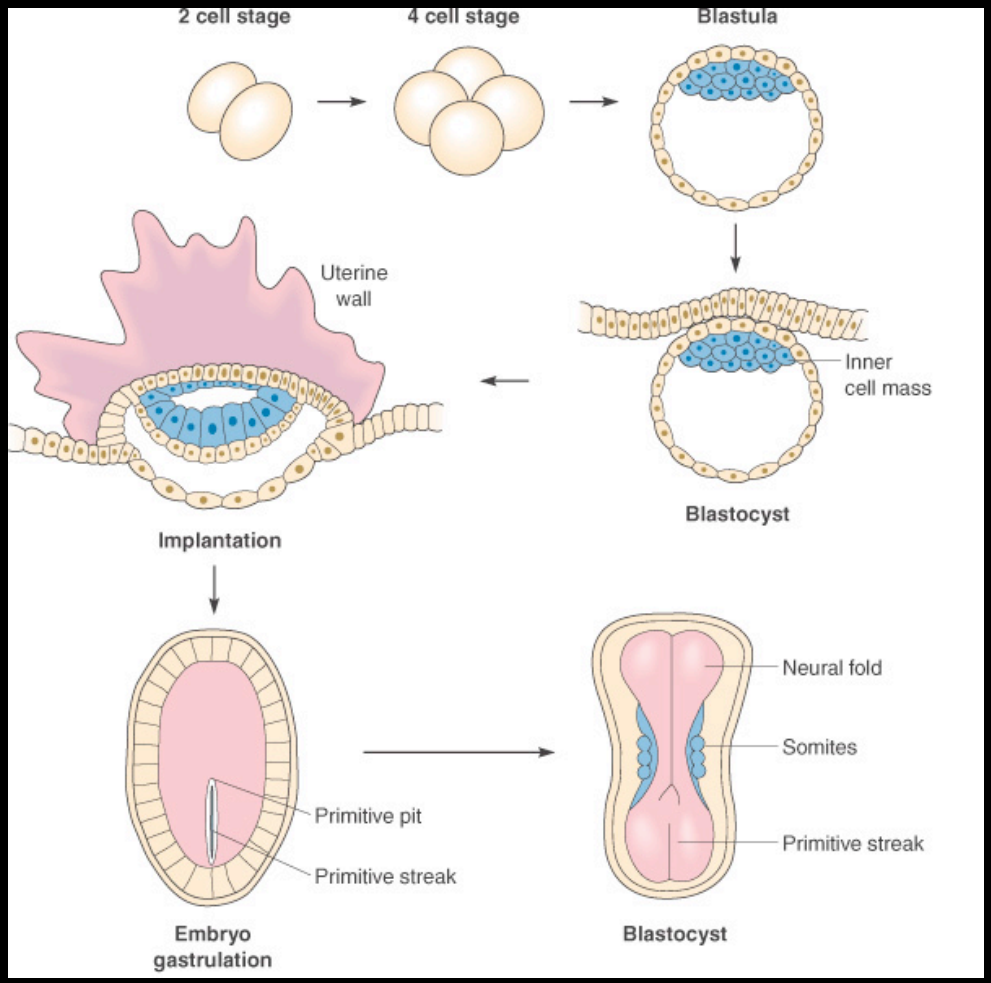
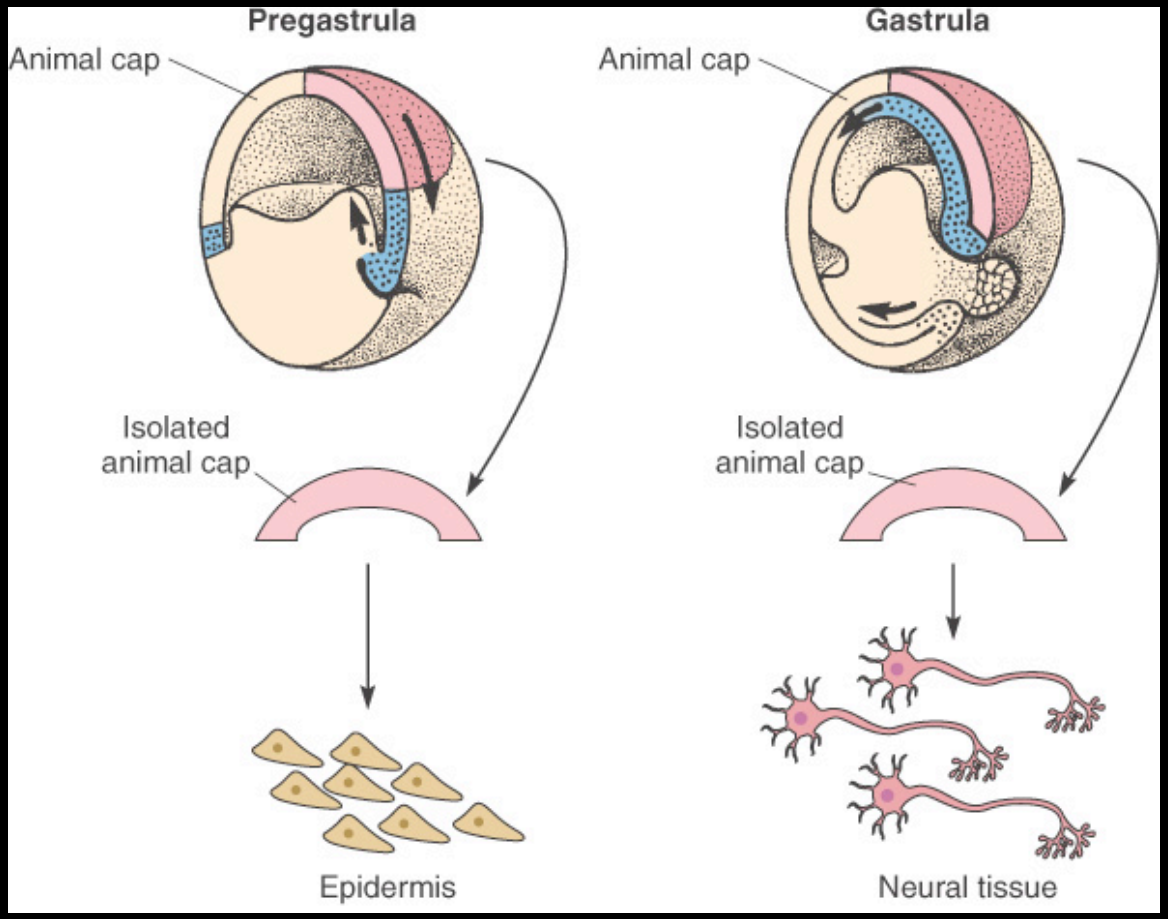
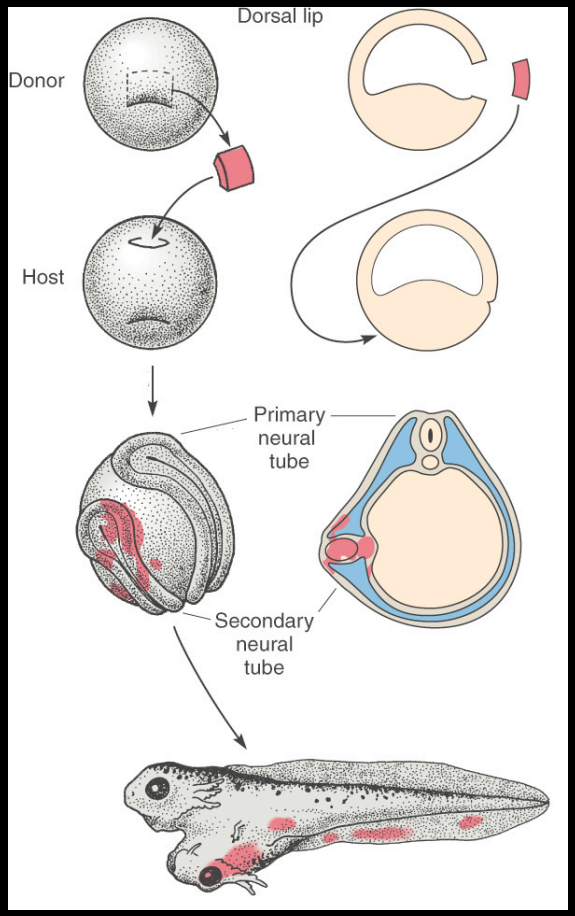
“The most important time in your life is not birth, marriage, or death, but gastrulation”

- Lewis Wolpert

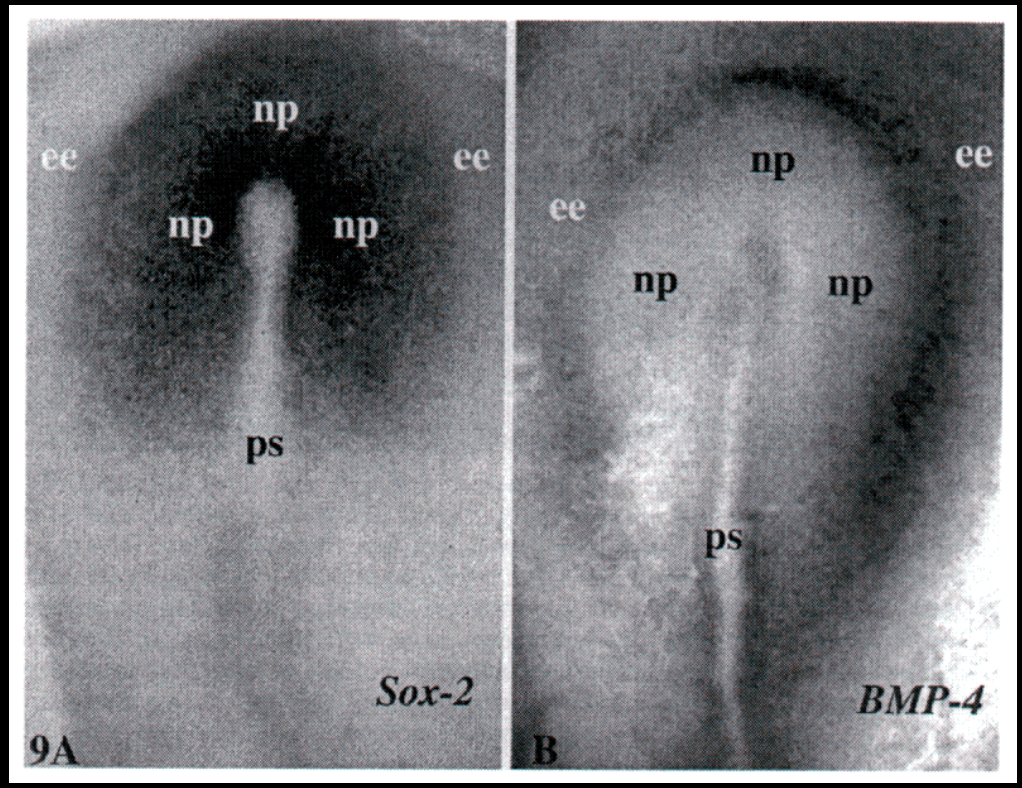


Gastrulation and Neural Induction





Neural Induction: a balance between neural and non-neural ectoderm



Streit, Stern

BMP signals must be repressed for neural tissue to form

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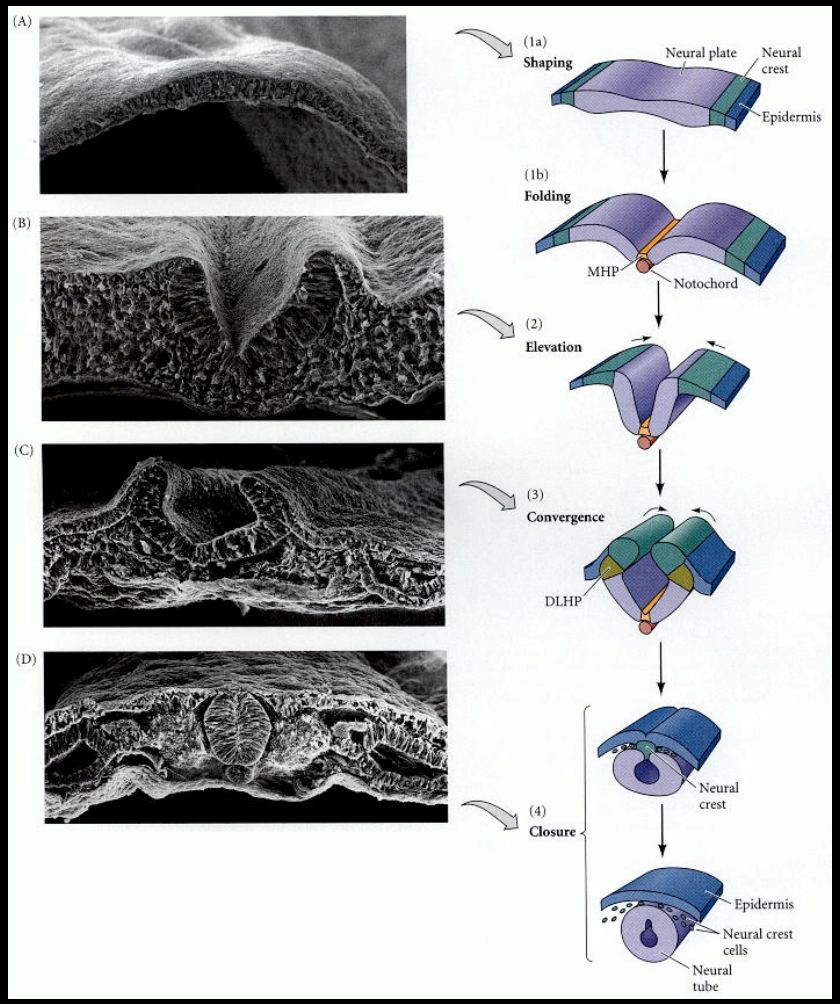
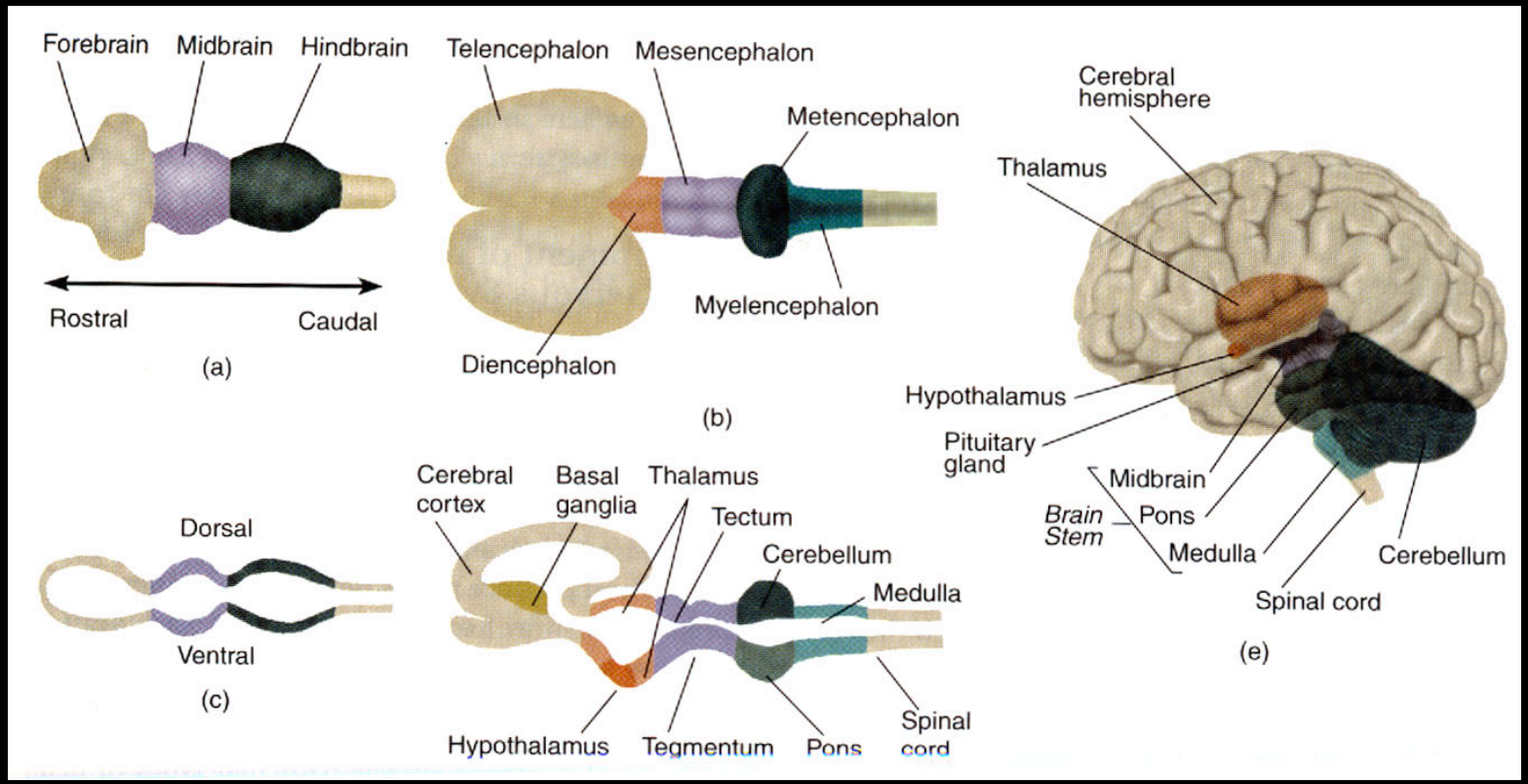
Neurulation- Neural tube formation



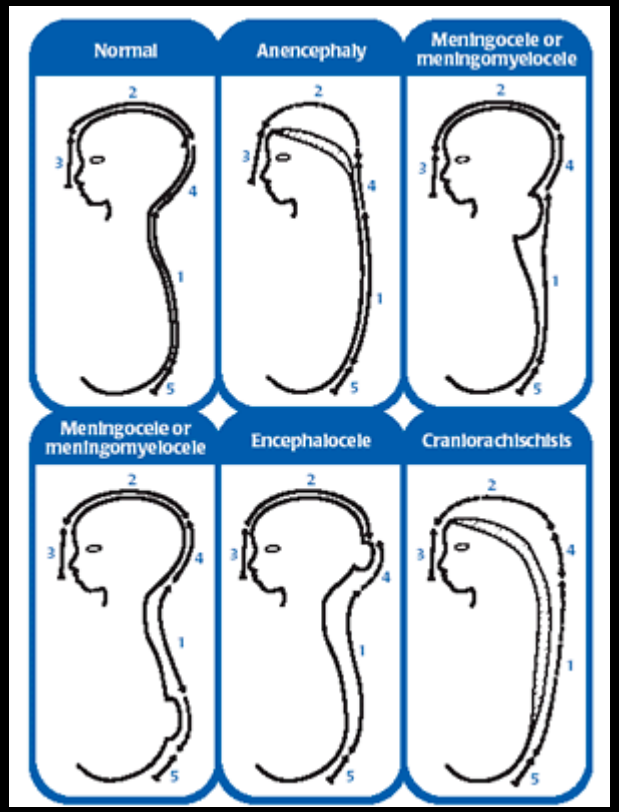
1. Formation of the neural plate
2. Shaping of the neural plate
3. Bending of the neural plate
4. Closure of the neural tube

Tosney, Schoenwolf

Differentiation of neural tube to form distinct vesicles



Neural Tube Defects



Van Allen, Kalousek

Anencephaly

Spina Bifida

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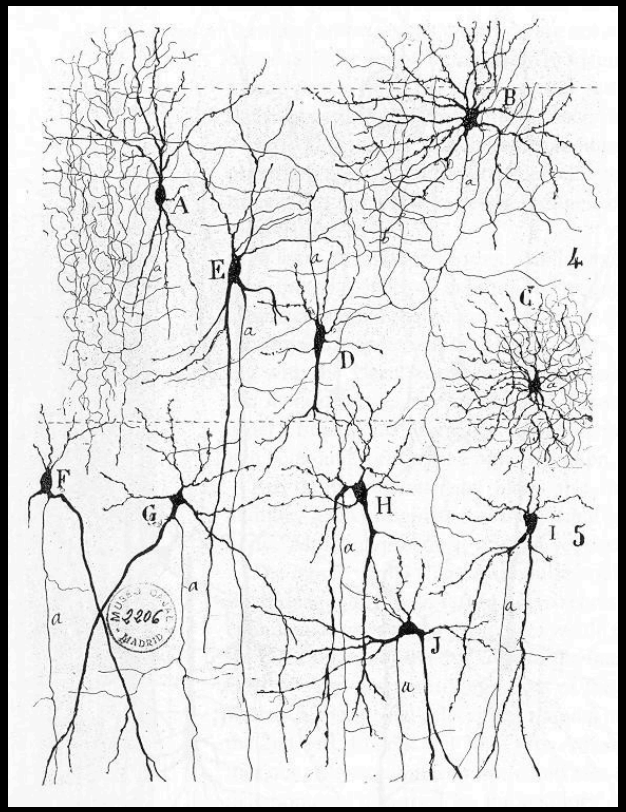
Generation of neuronal diversity



Ramon y Cajal

1. Patterning: acquisition of a positional identity
2. Differentiation: functionally distinct cell types

Patterning: acquisition of a positional identity

Dorsal

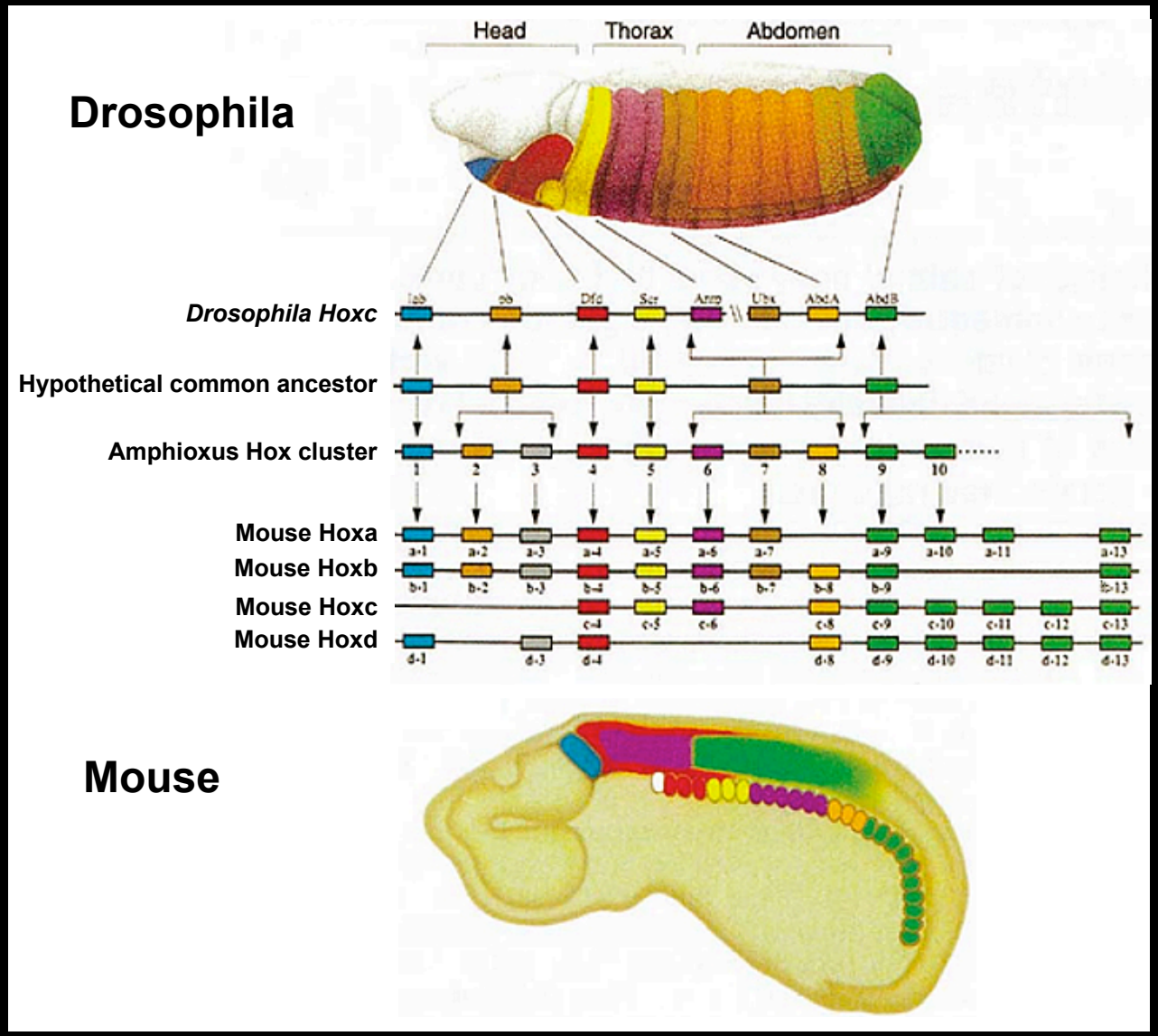
Rostral/Anterior

Caudal/Posterior

Ventral

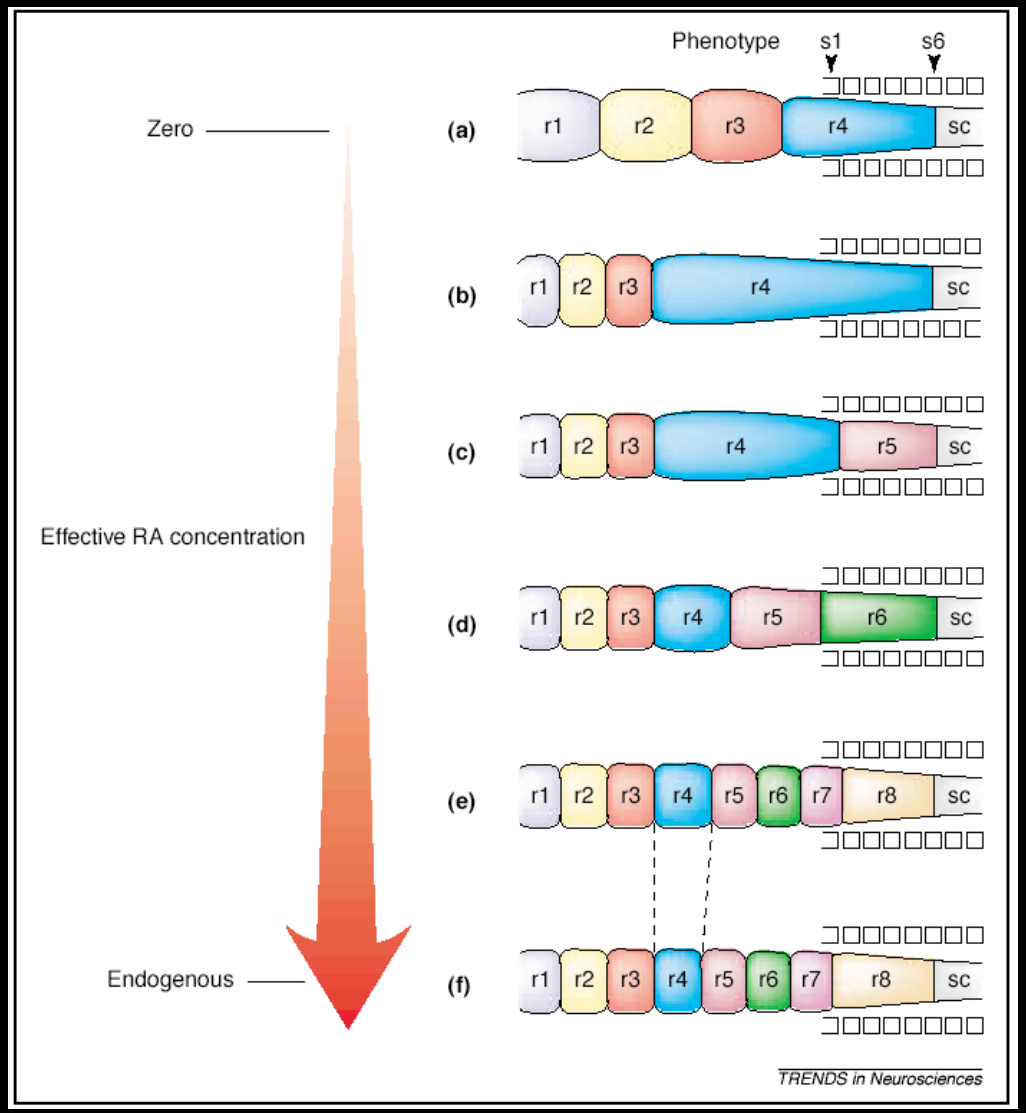
- Transcriptional regulation (cell autonomous)
- Secreted factors (non-cell autonomous)

Hox genes provide positional information along the A/P axis

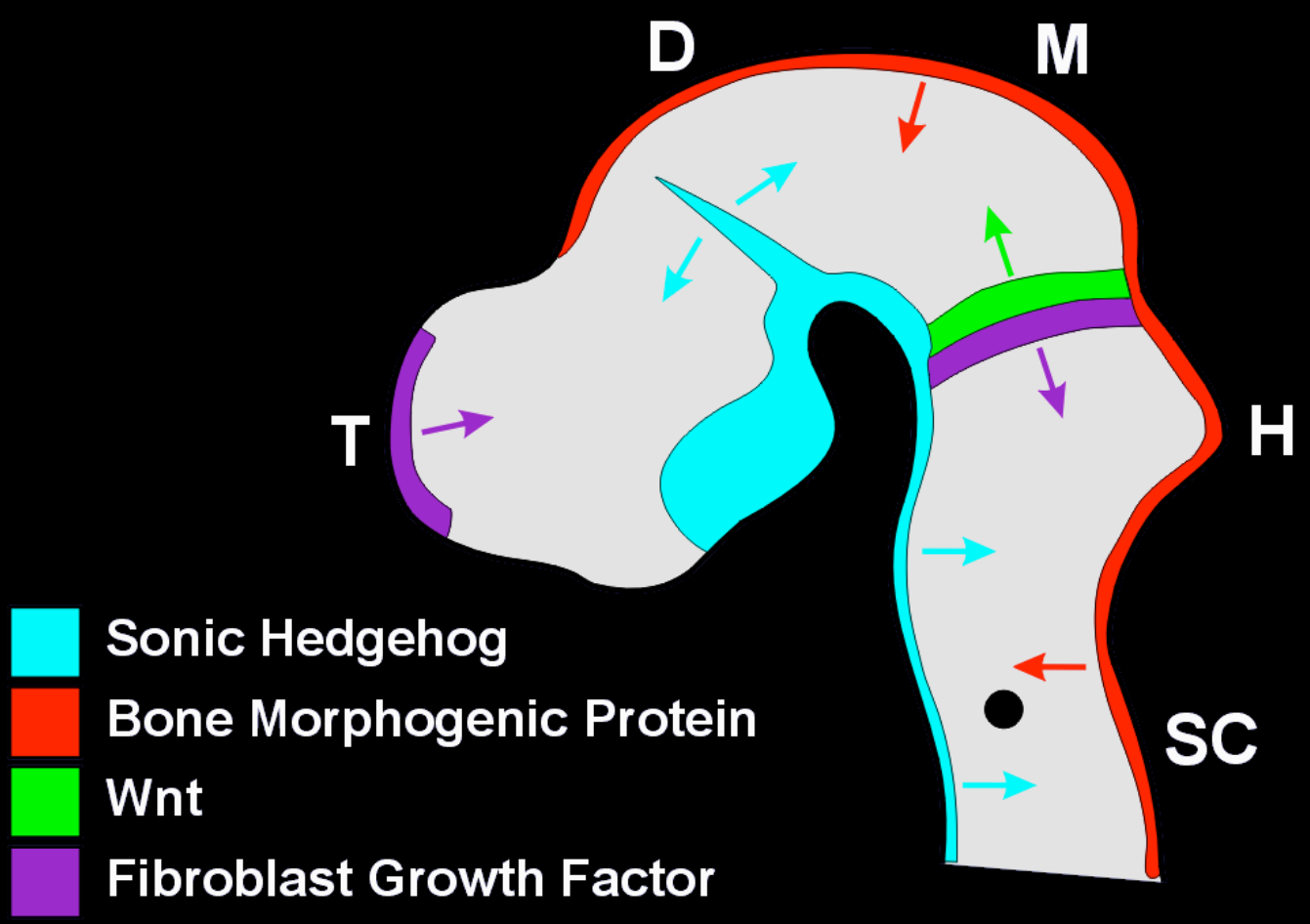


Carroll

A gradient of retinoic acid patterns posterior identities in the hindbrain



Secreted factors initiate neuronal diversity



Wnt1 is required for midbrain patterning

Wnt1

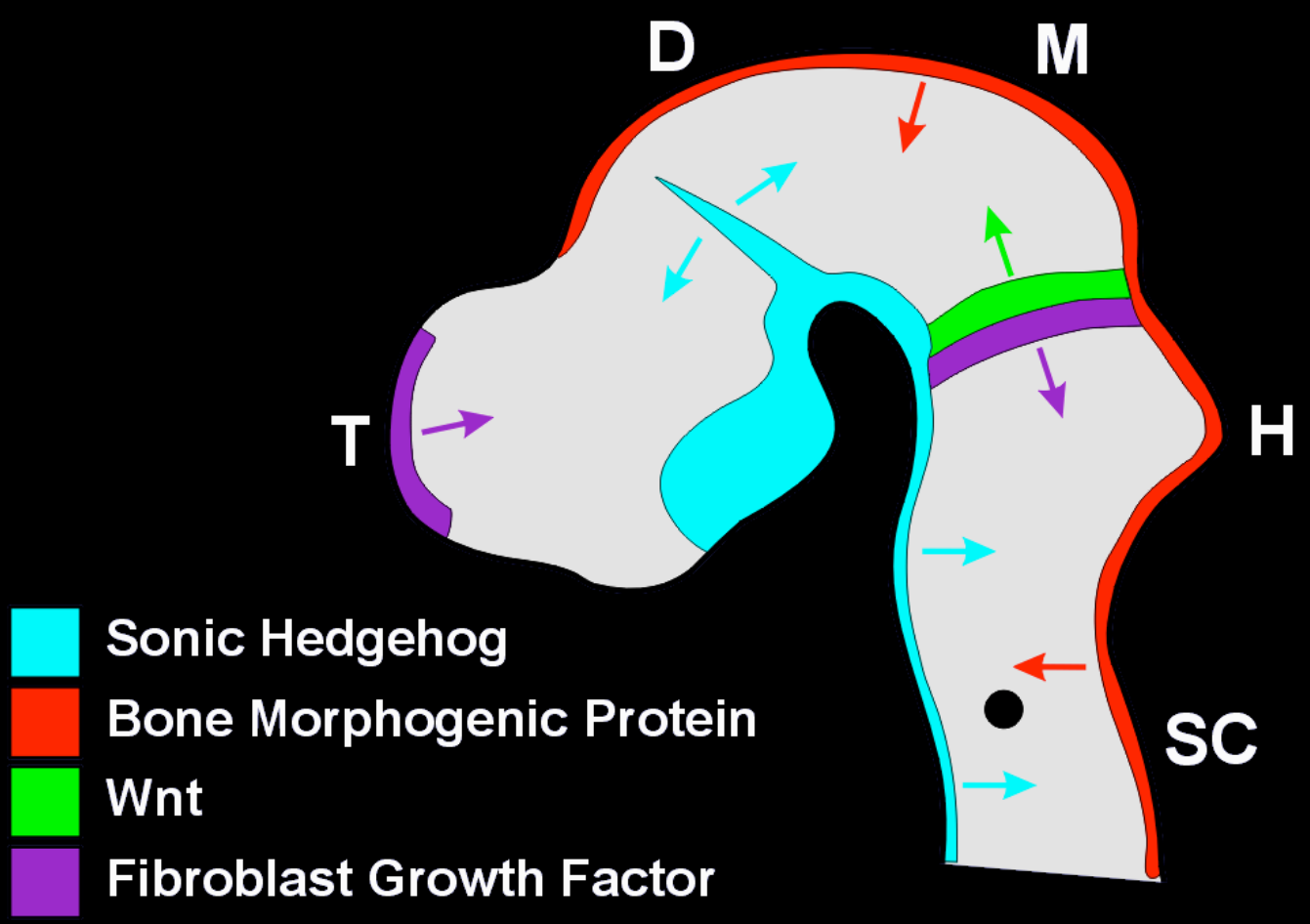
Crossley, Martin

wild type

Wnt1 -/-

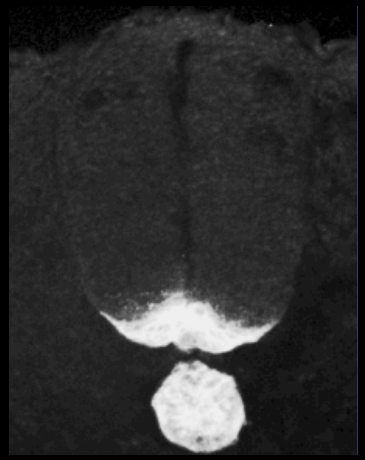
Thomas, Capecchi

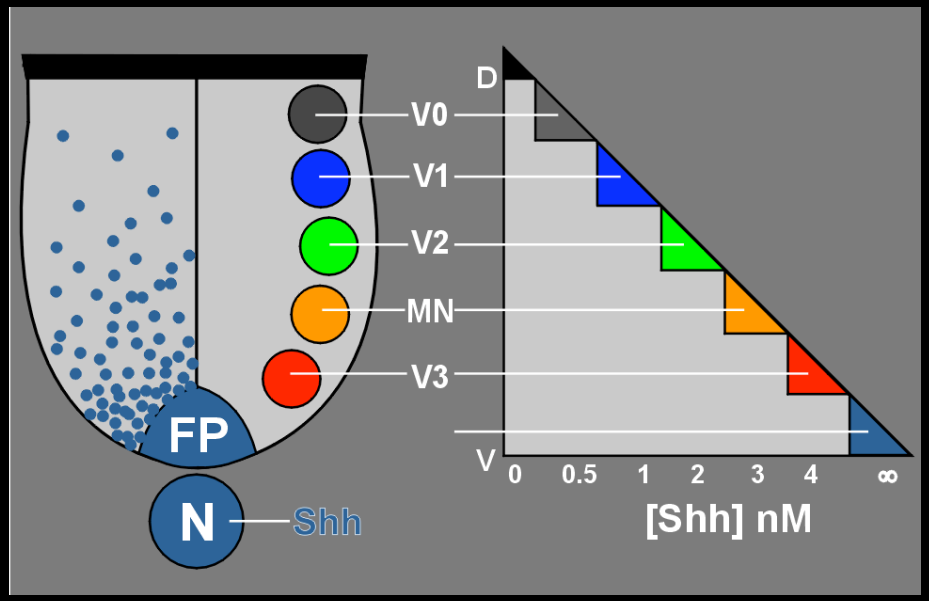
Secreted factors initiate neuronal diversity



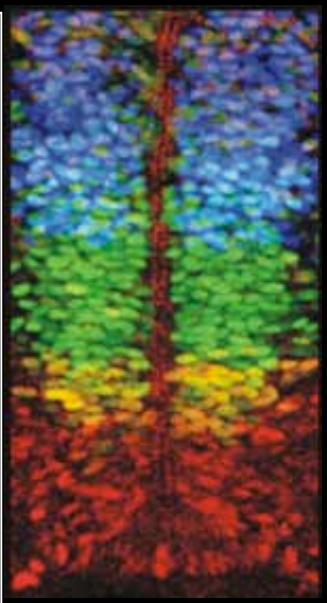
A gradient of Shh patterns ventral identities

Shh



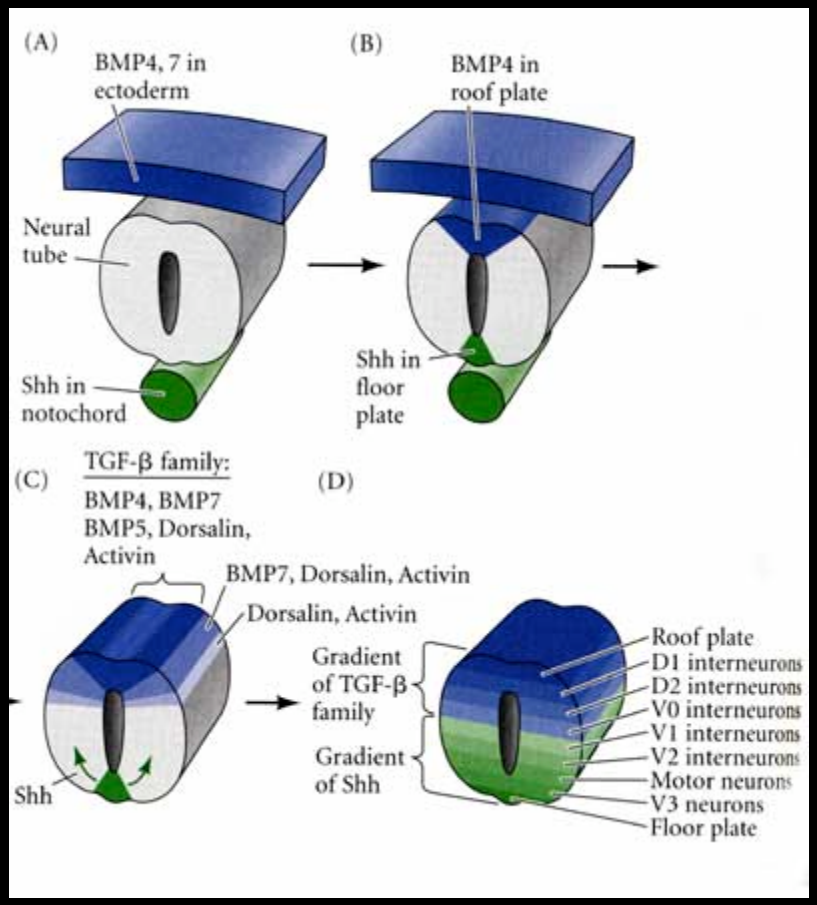


Nkx6.1 Pax6 Pax7



Roelink, Ericson, Briscoe, Jessell

Two Signaling Centers Specify Neural Cell Types along the DV axis

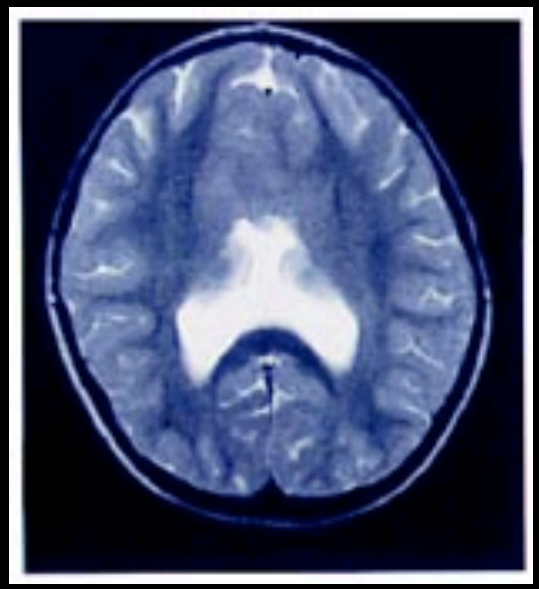


Jessell

Dorsal Signaling Center
Roof Plate
BMP/TGFβ

Ventral Signaling Center
Notochord and Floor Plate
SHH

Ventral patterning defect: Holoprosencephaly



Gripp, Elledge

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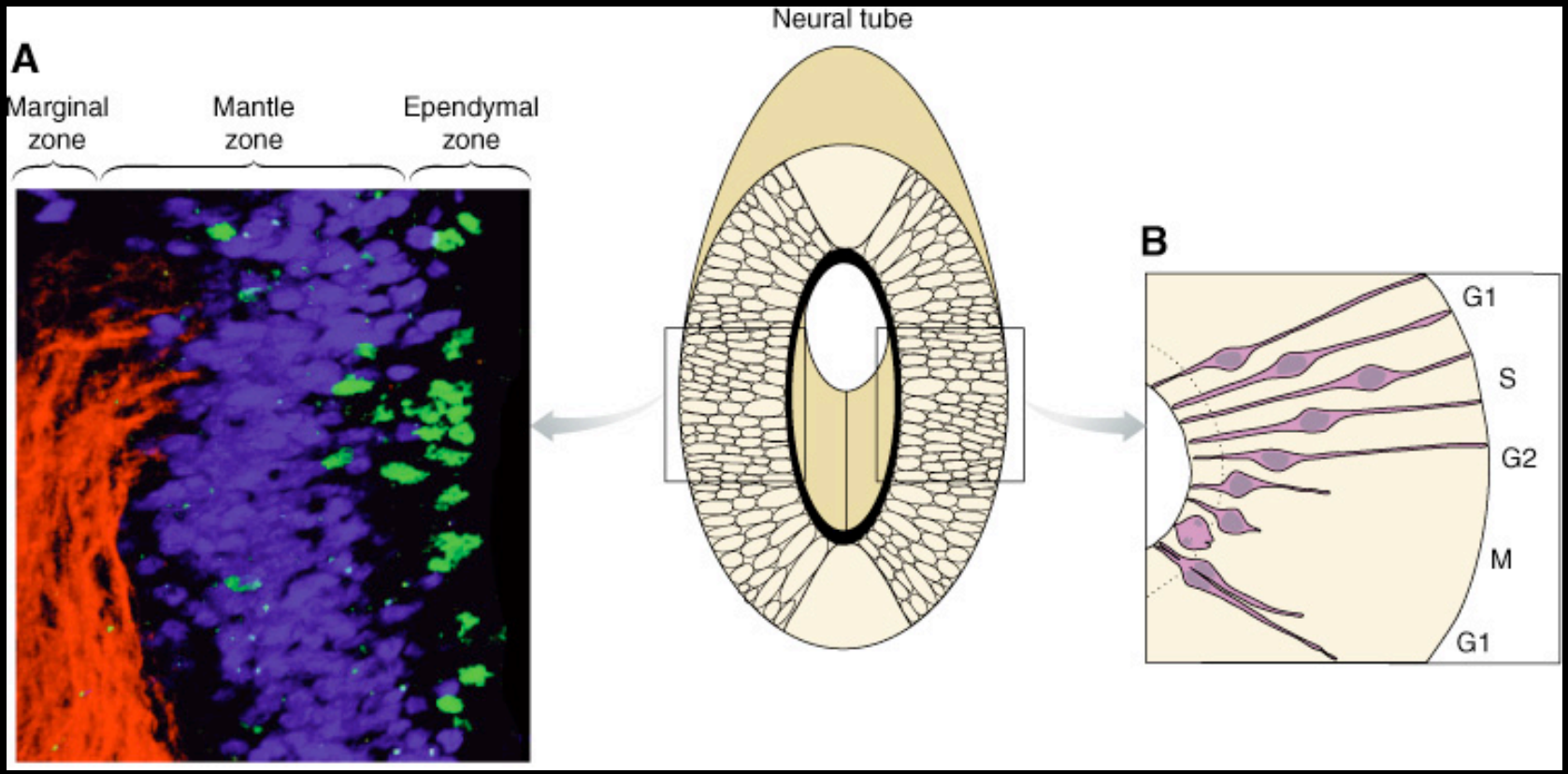
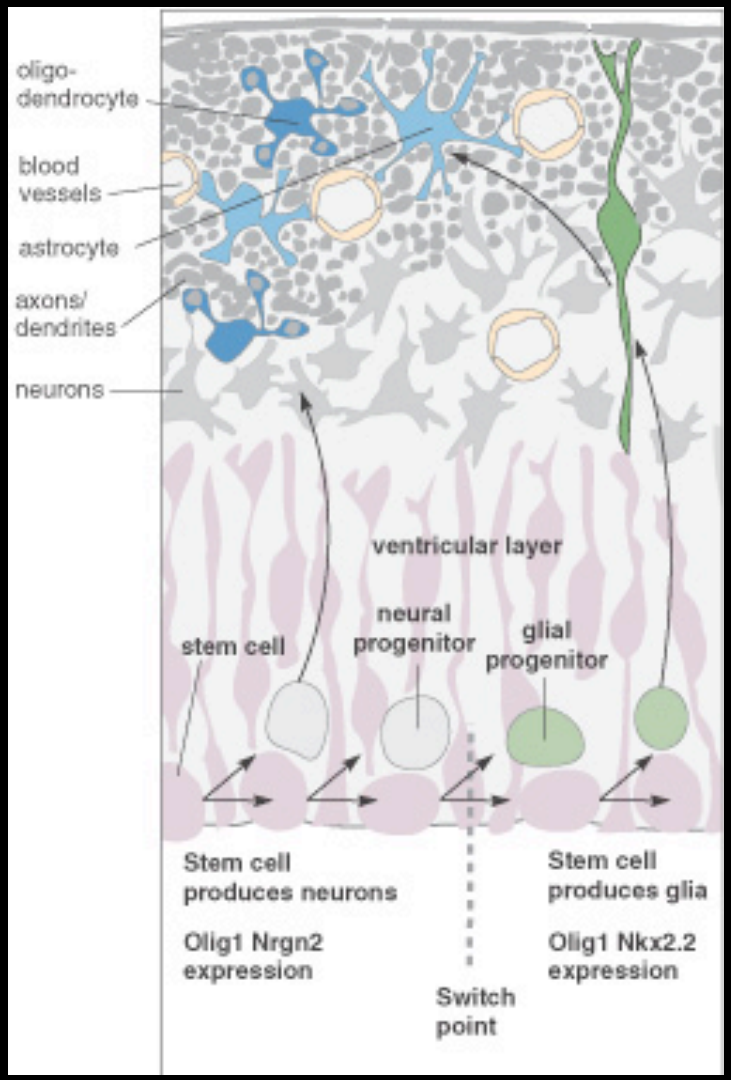
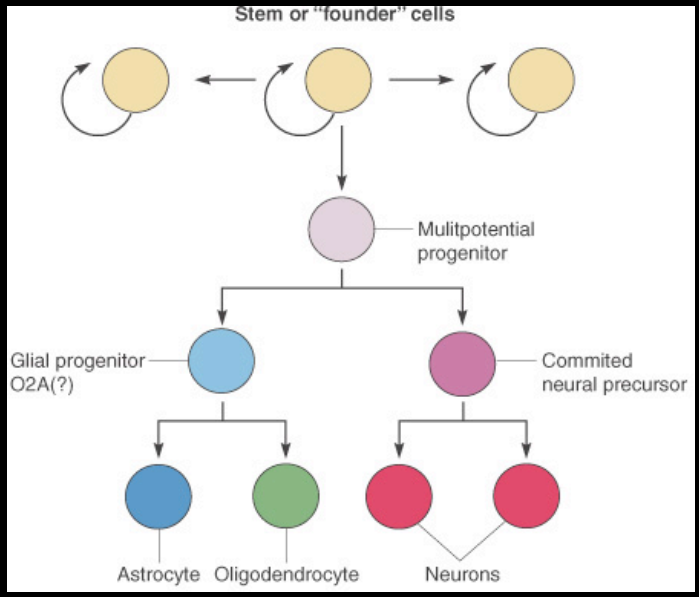
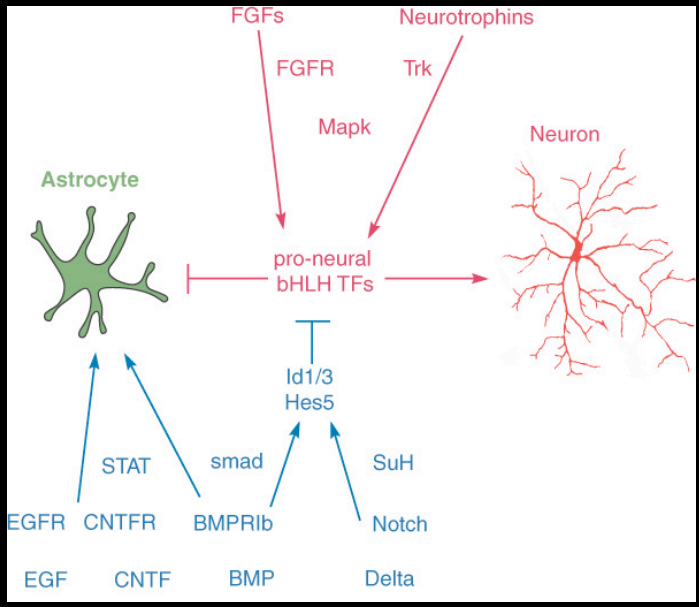
Differentiation of the walls of the neural tube



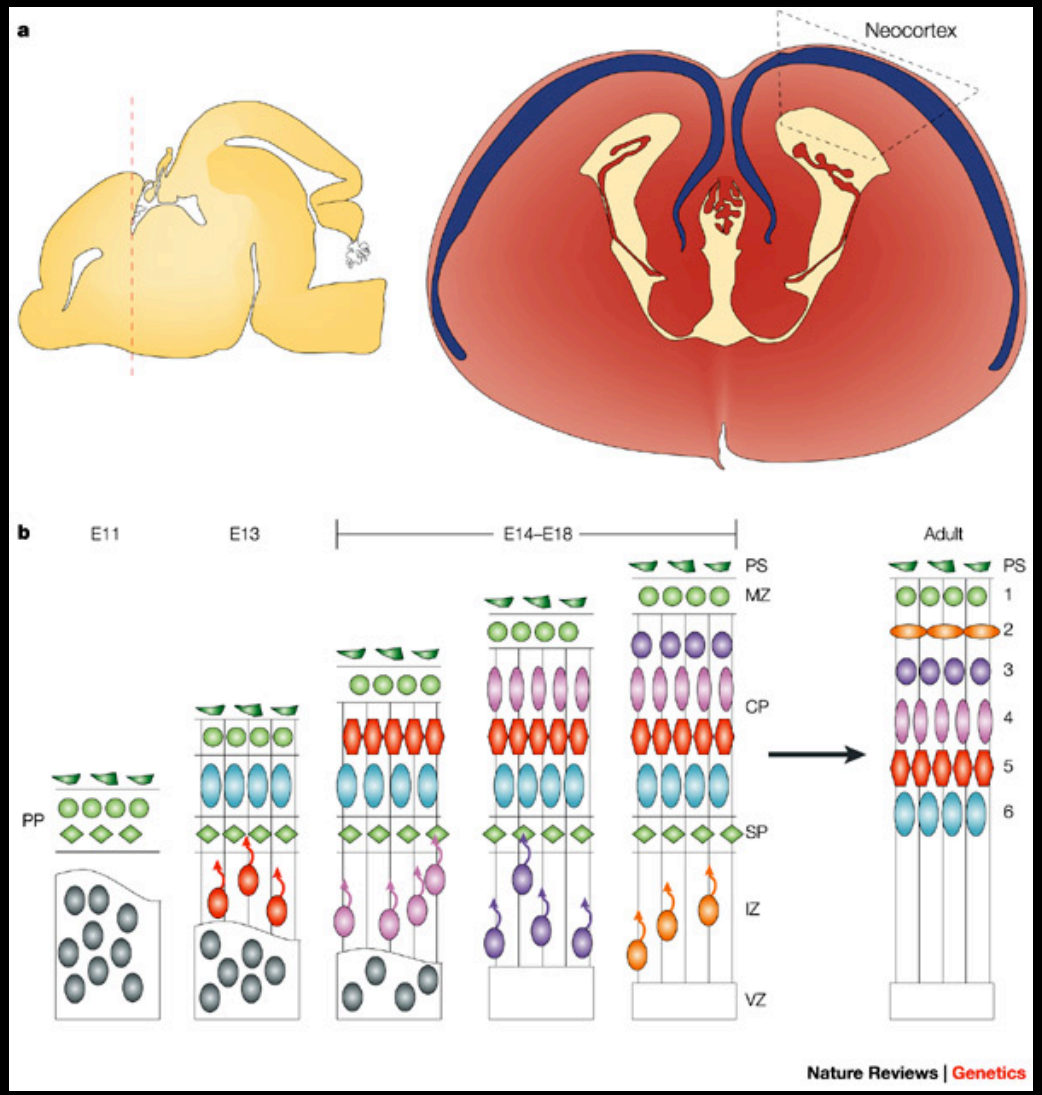
Stem cells produce neurons and glia



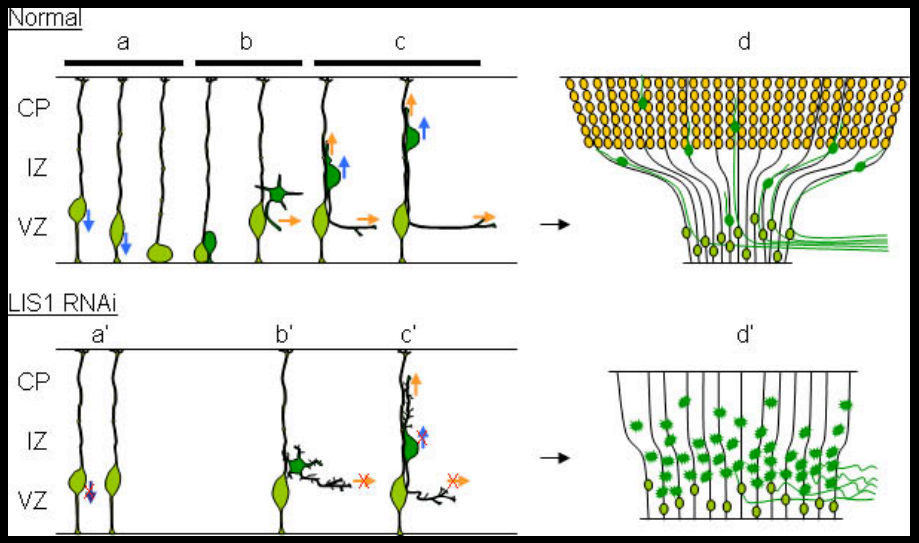


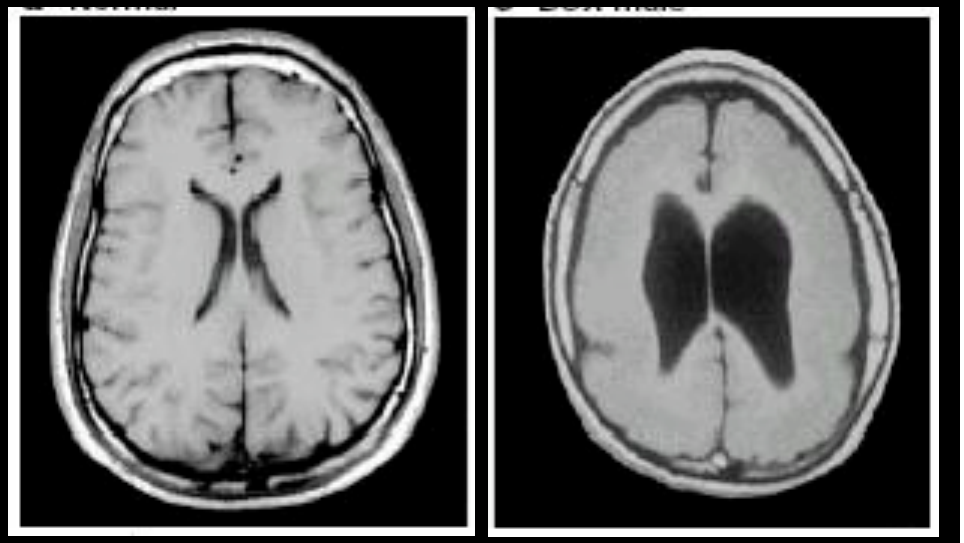


Inside-out pattern of cortical histogenesis



Neuronal Migration Defects: Lissencephaly

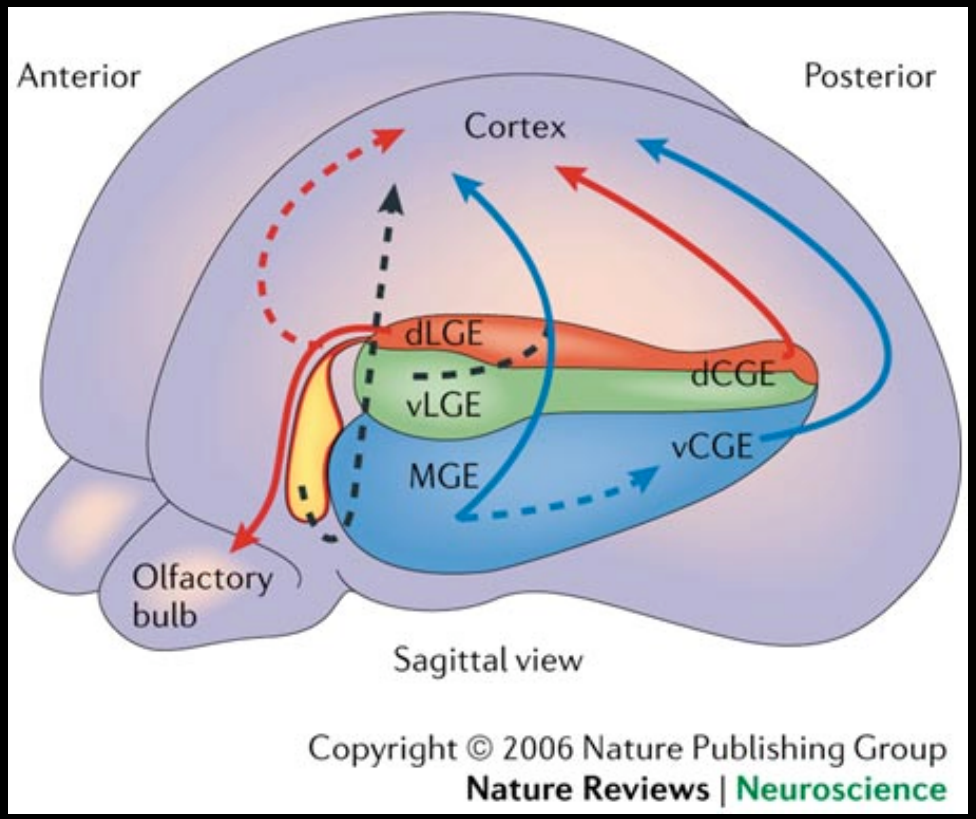


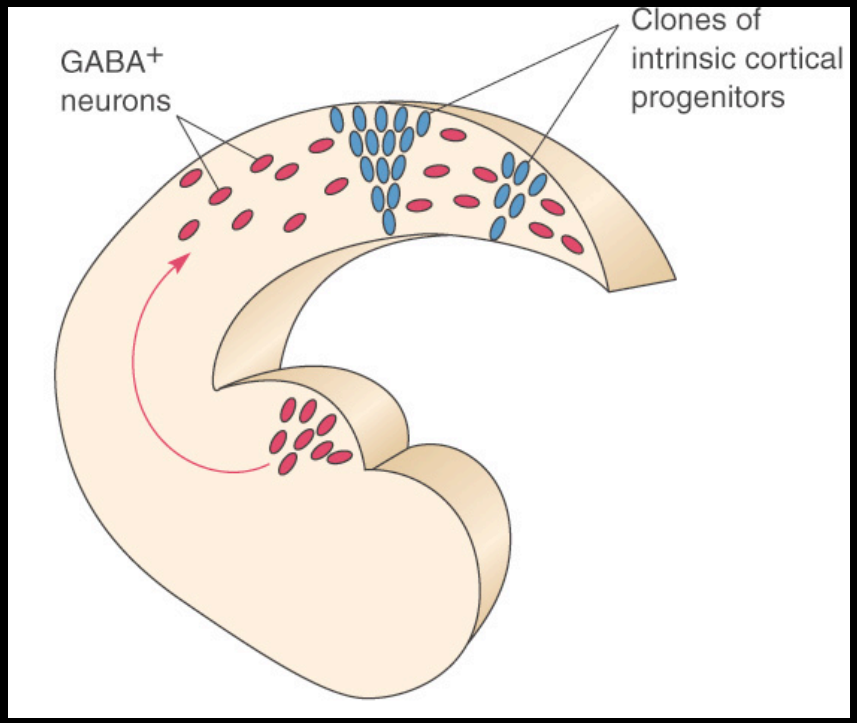


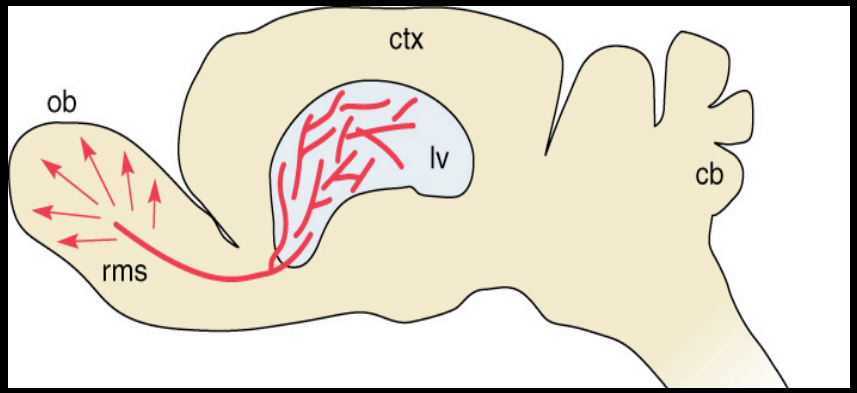
Tsai, Vallee

www.focosi.immunesig.org

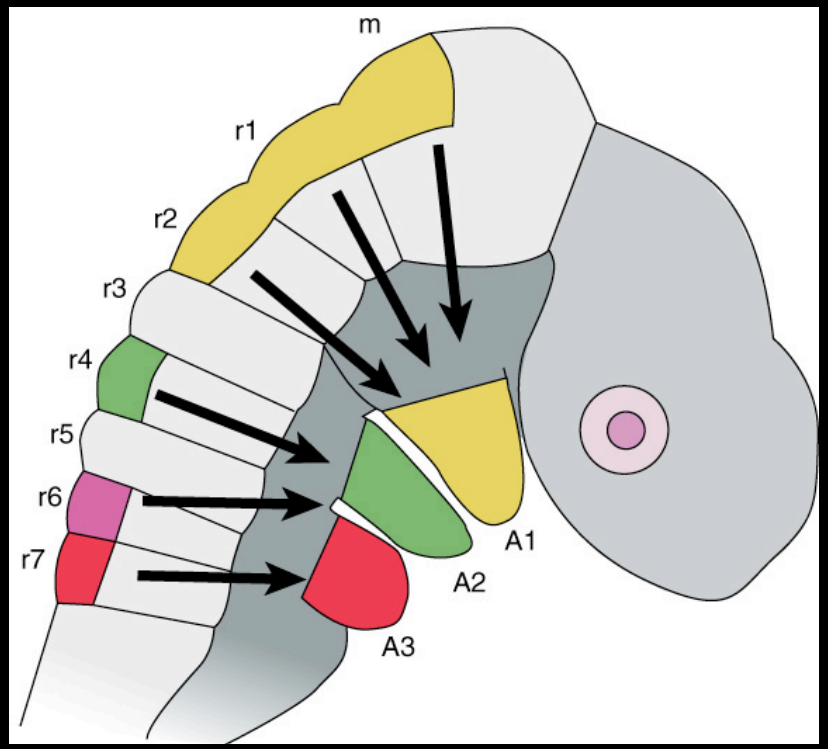
Some neurons migrate to their final destination

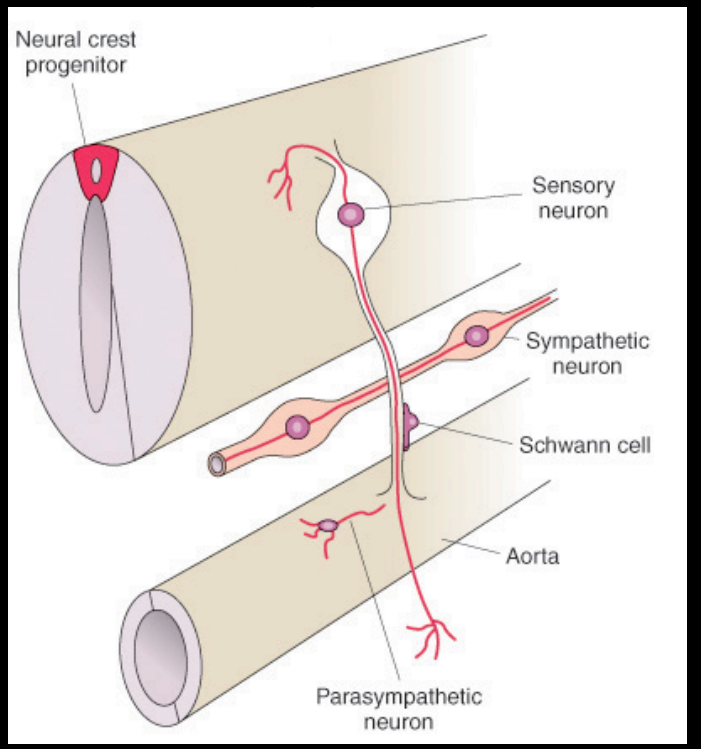






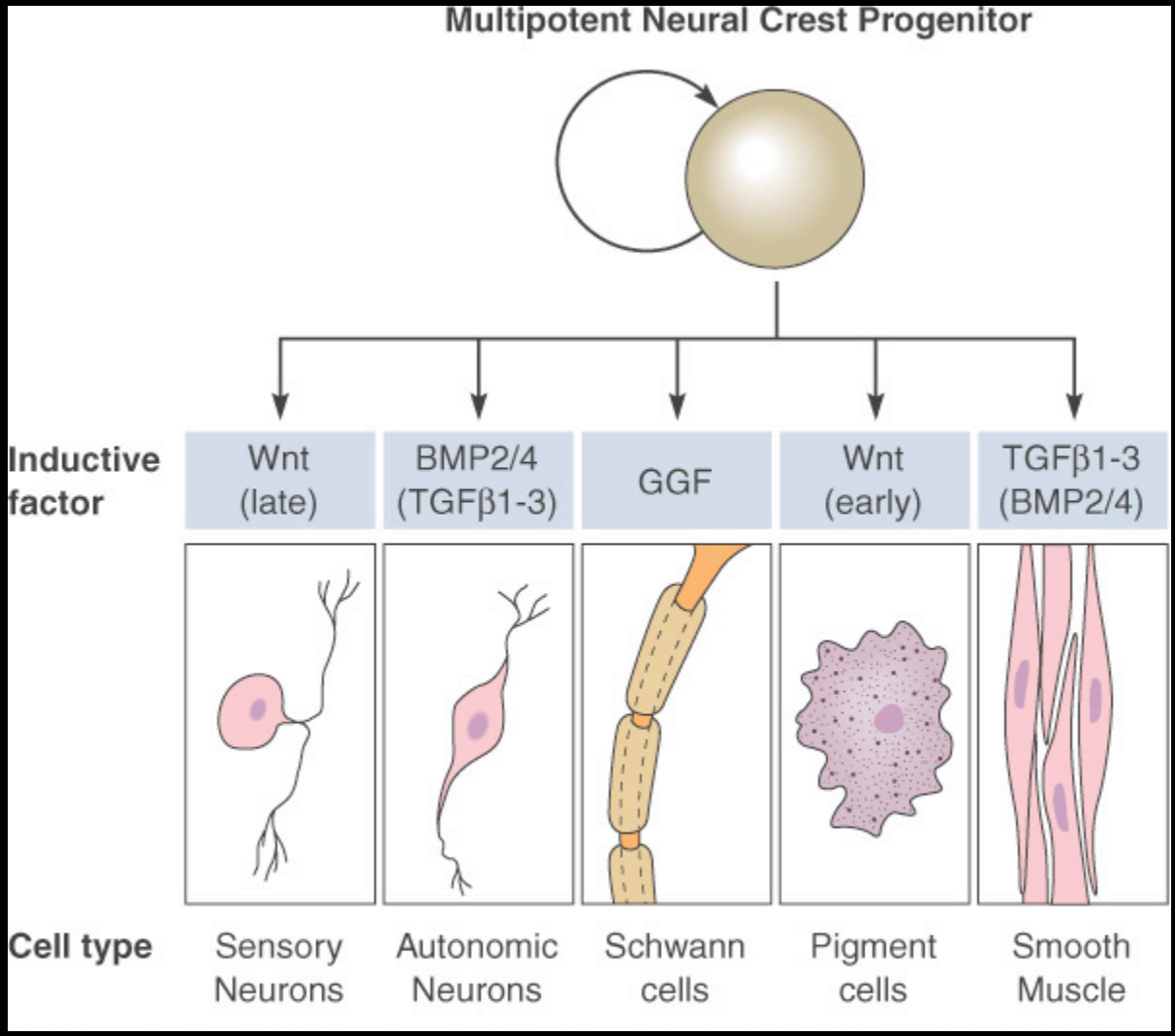
Neural crest cells migrate to form the peripheral nervous system





Bronner-Fraser, Fraser

Different neural crest fates are promoted by distinct target-derived signals



Dorsky

Defects in neural crest development

DiGeorge Syndrome

Waardenberg Syndrome

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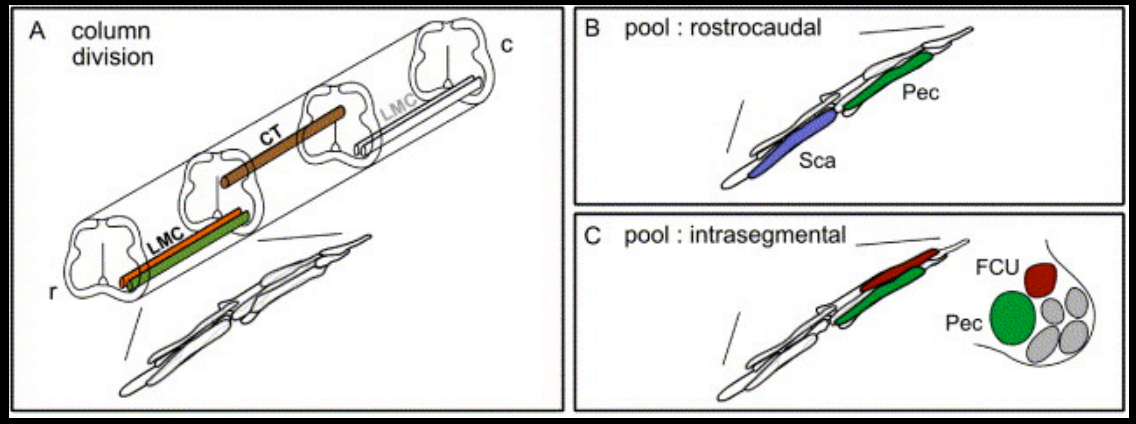
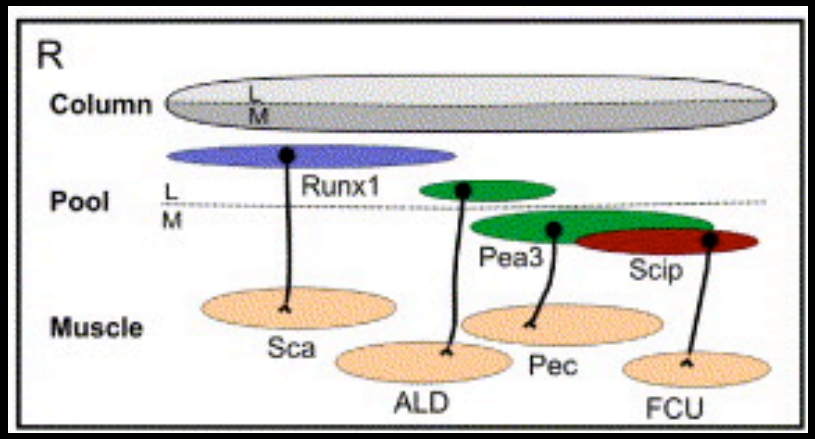
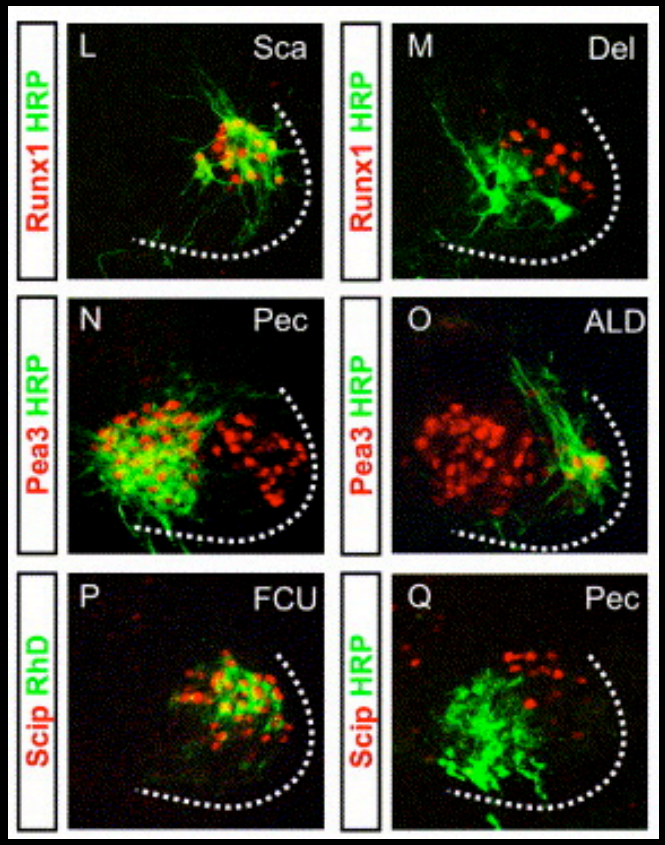
Specification of cell fates







Dasen, Jessell

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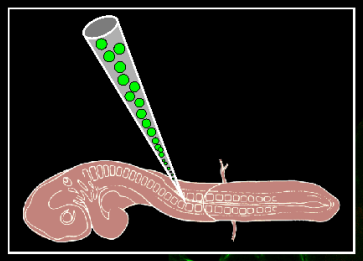
Specification of axonal connectivity

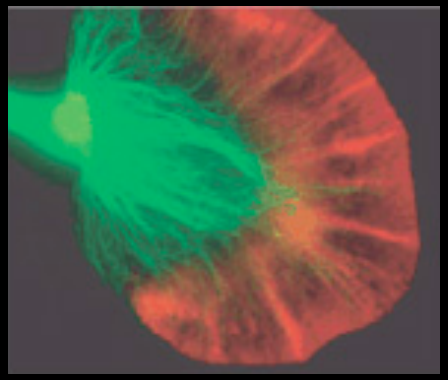


Wichterle, Lieberam, Jessell

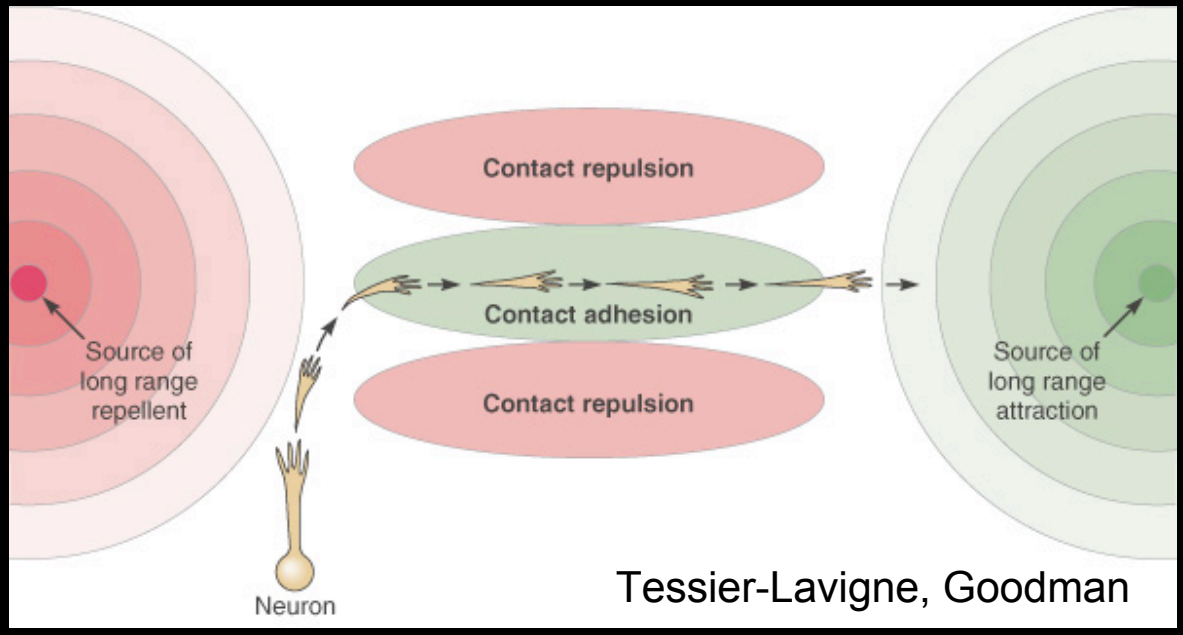
1. Pathway selection (route to target area)
2. Target selection (bind to appropriate target cells)
3. Address selection (refine/prune initial pattern)

Guidance by specific growth cone adhesion and repulsion

Microtubules
Actin



Forscher



Tessier-Lavigne, Goodman

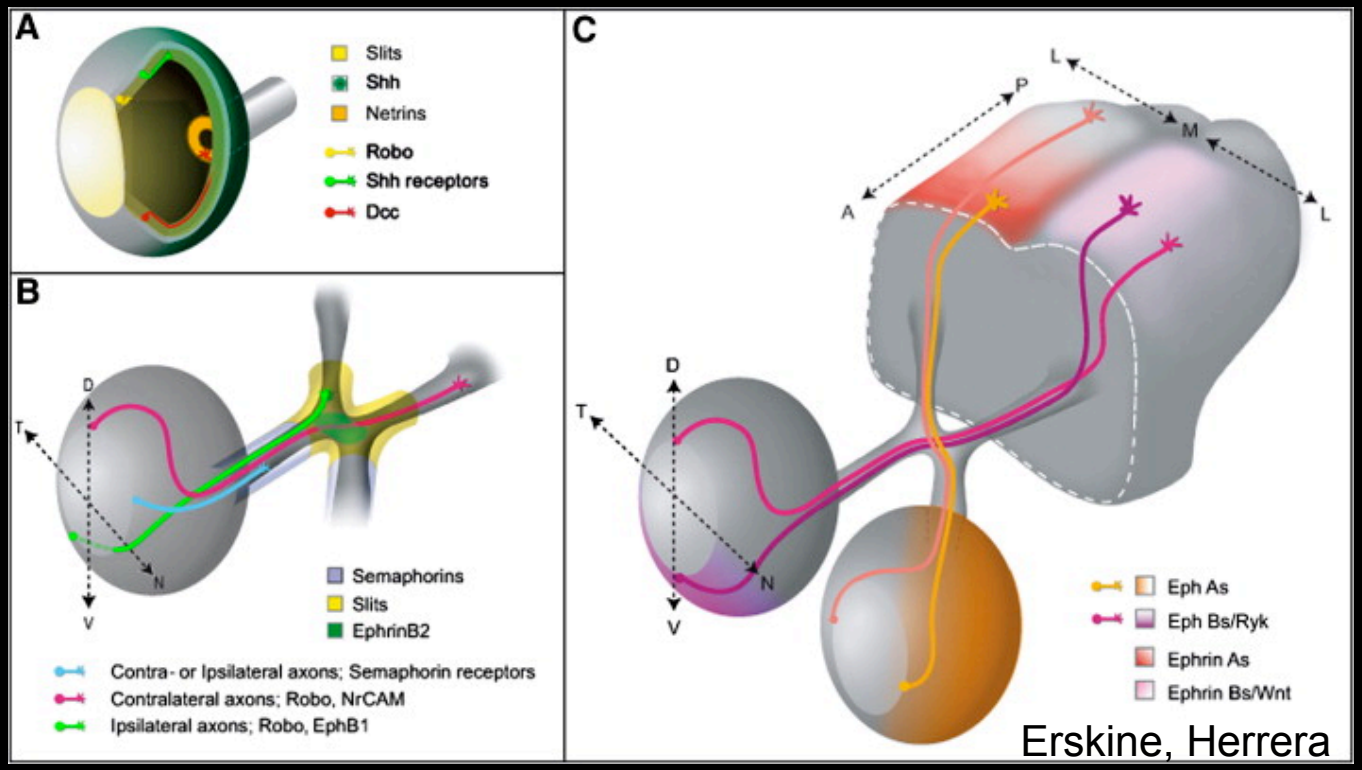
Permissive extracellular matrix protein: laminin

Repulsive cues: ephrins and semaphorins

Long range attractive cues: netrins

Secreted repulsive cues: slits

Guidance of Retinal Ganglion Axons

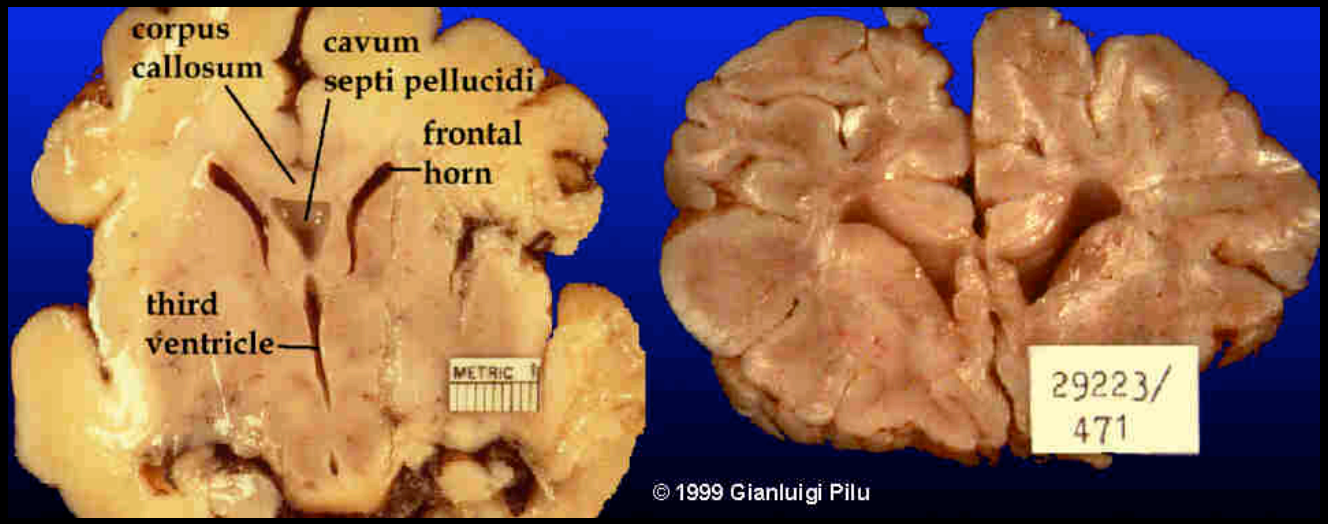


Retina: Slits, Shh and CAMs direct growth to optic disc; netrin guides axons out of the eye.

Optic chiasm: semaphorins, slits and Shh constrain axons to optic nerve; ephrins prevent ipsilateral axons from crossing; contralateral axons so not express receptor

Topographic mapping in the superior colliculus: gradients of Ephrins (ephrinA for A-P axis and ephrinB for M-L axis)

Axon guidance defects:
Agenesis of the corpus callosum



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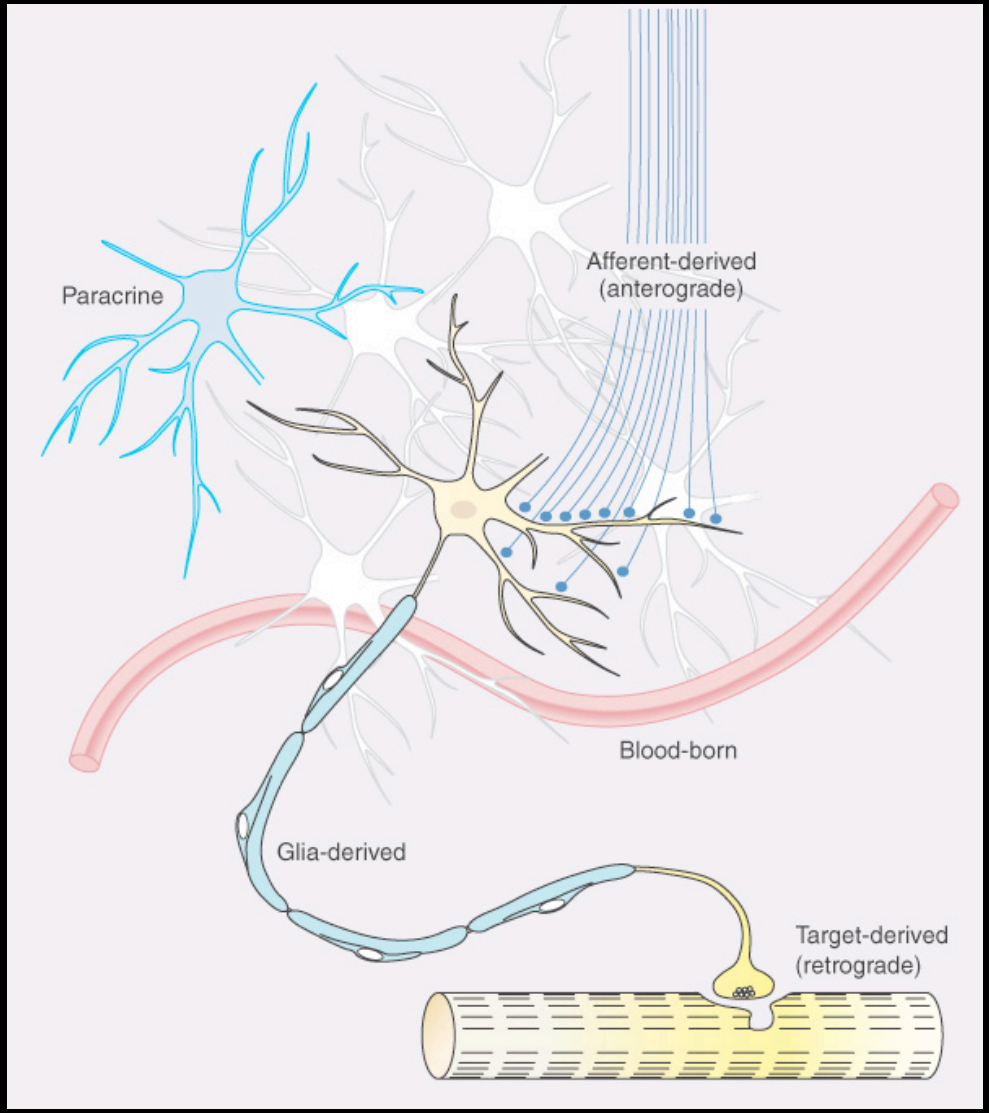
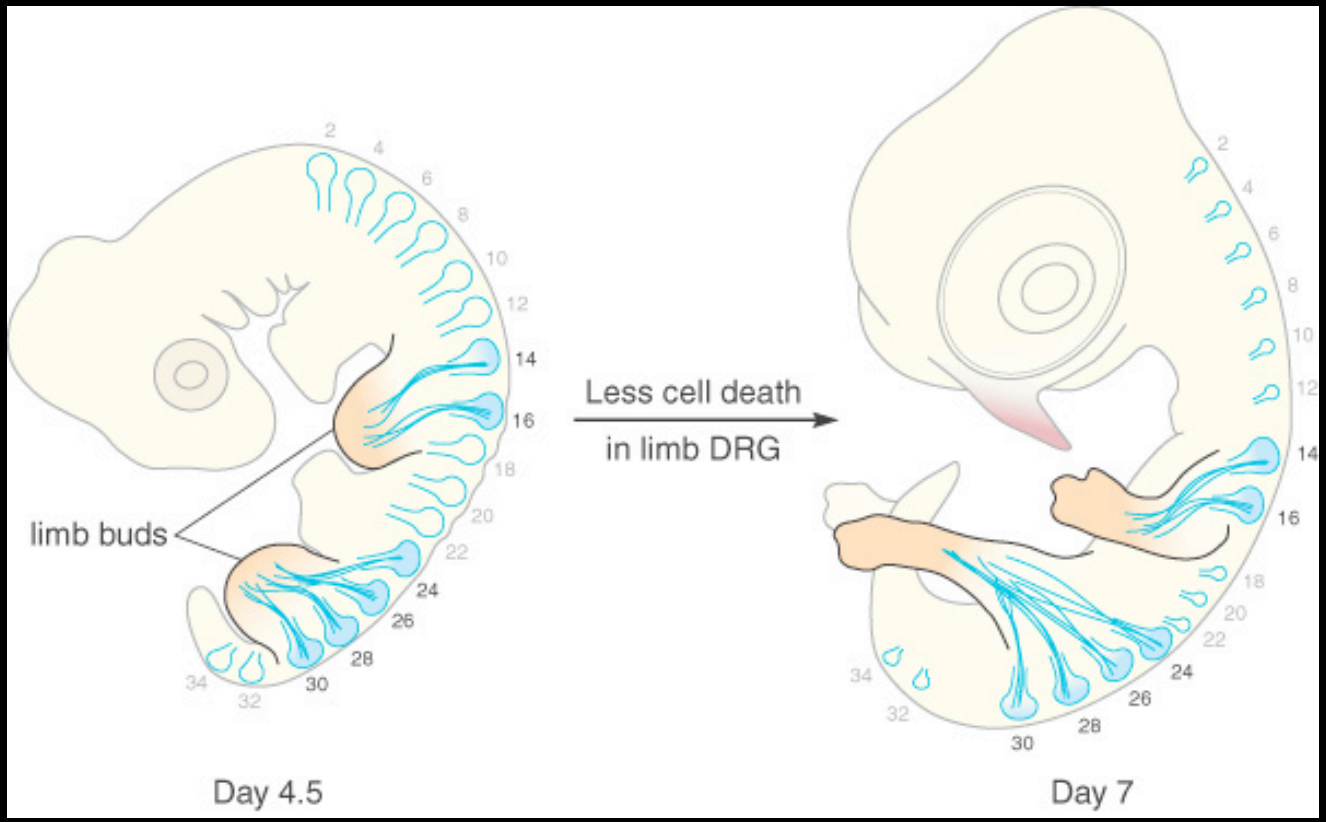
Factors influencing neuronal survival

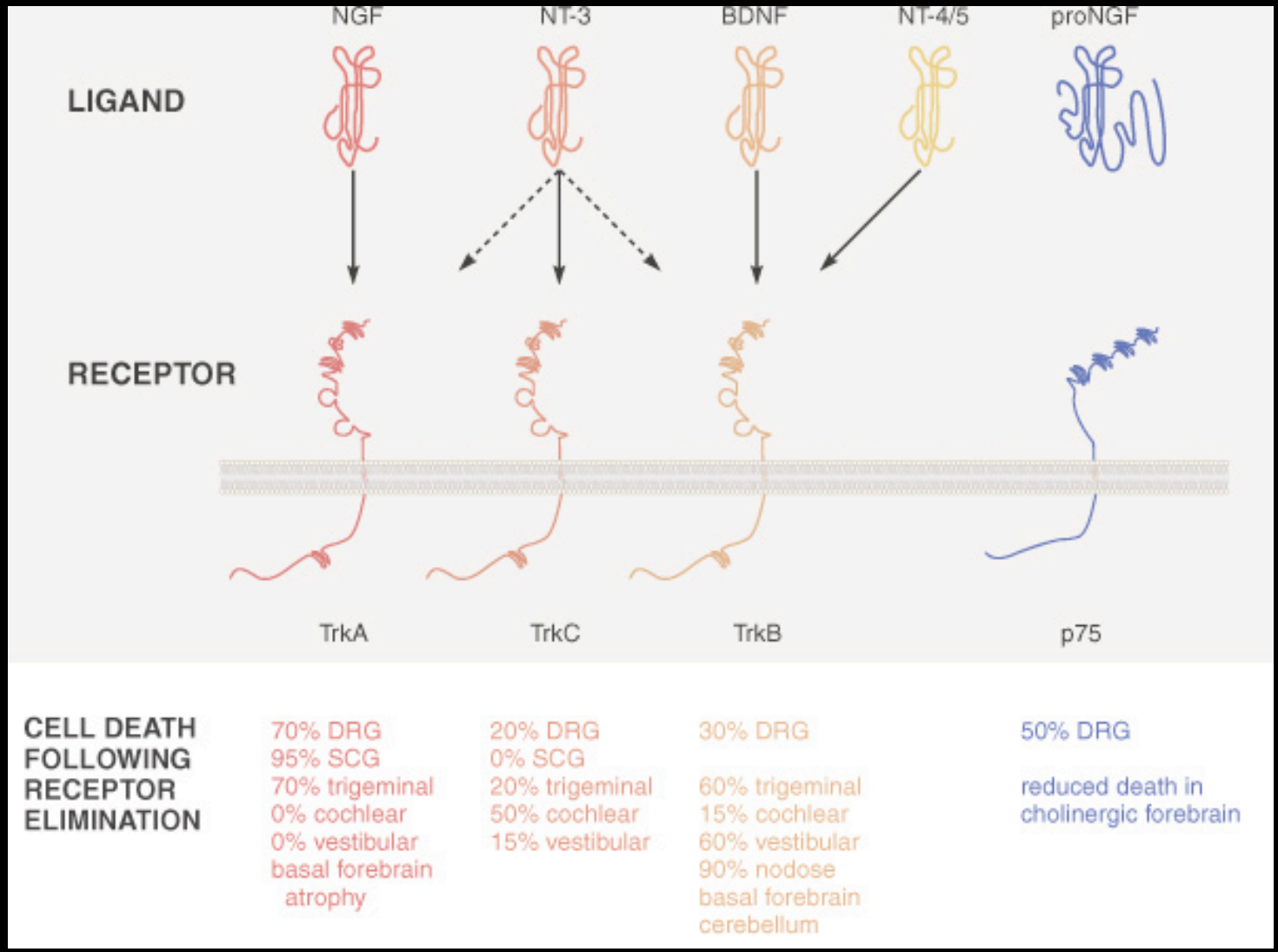


Neuronal survival correlates with innervation of target tissue

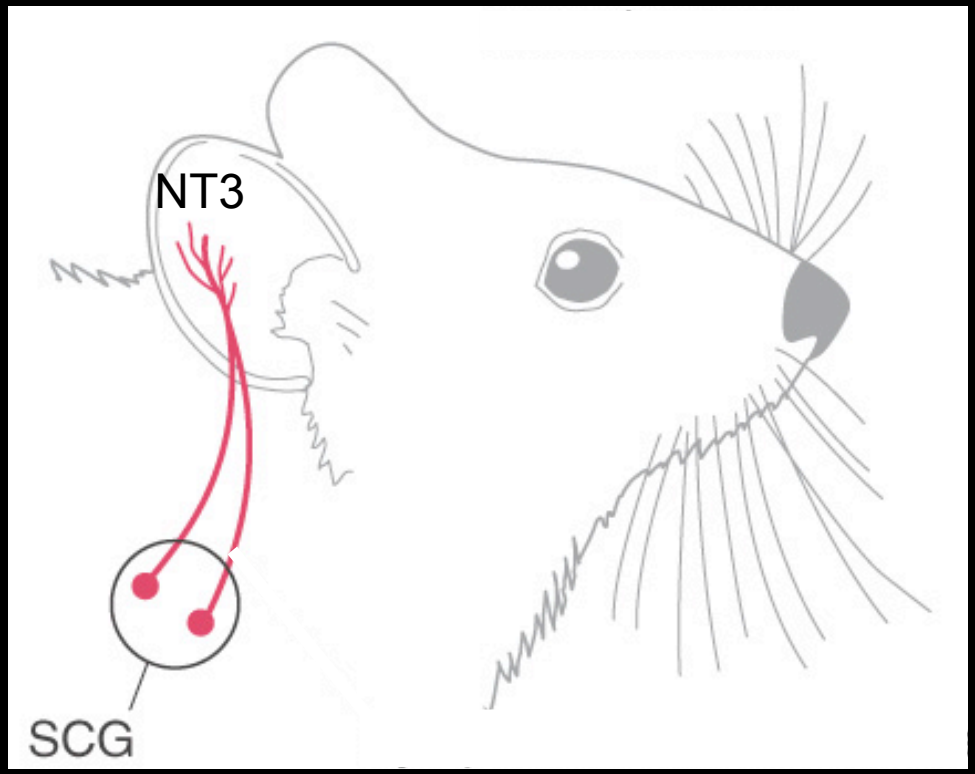


Hamburger, Levi-Motalcini

Differential requirements for neurotrophins



Neurotrophic factors influence target selection by promoting neuronal survival and differentiation



ElShamy

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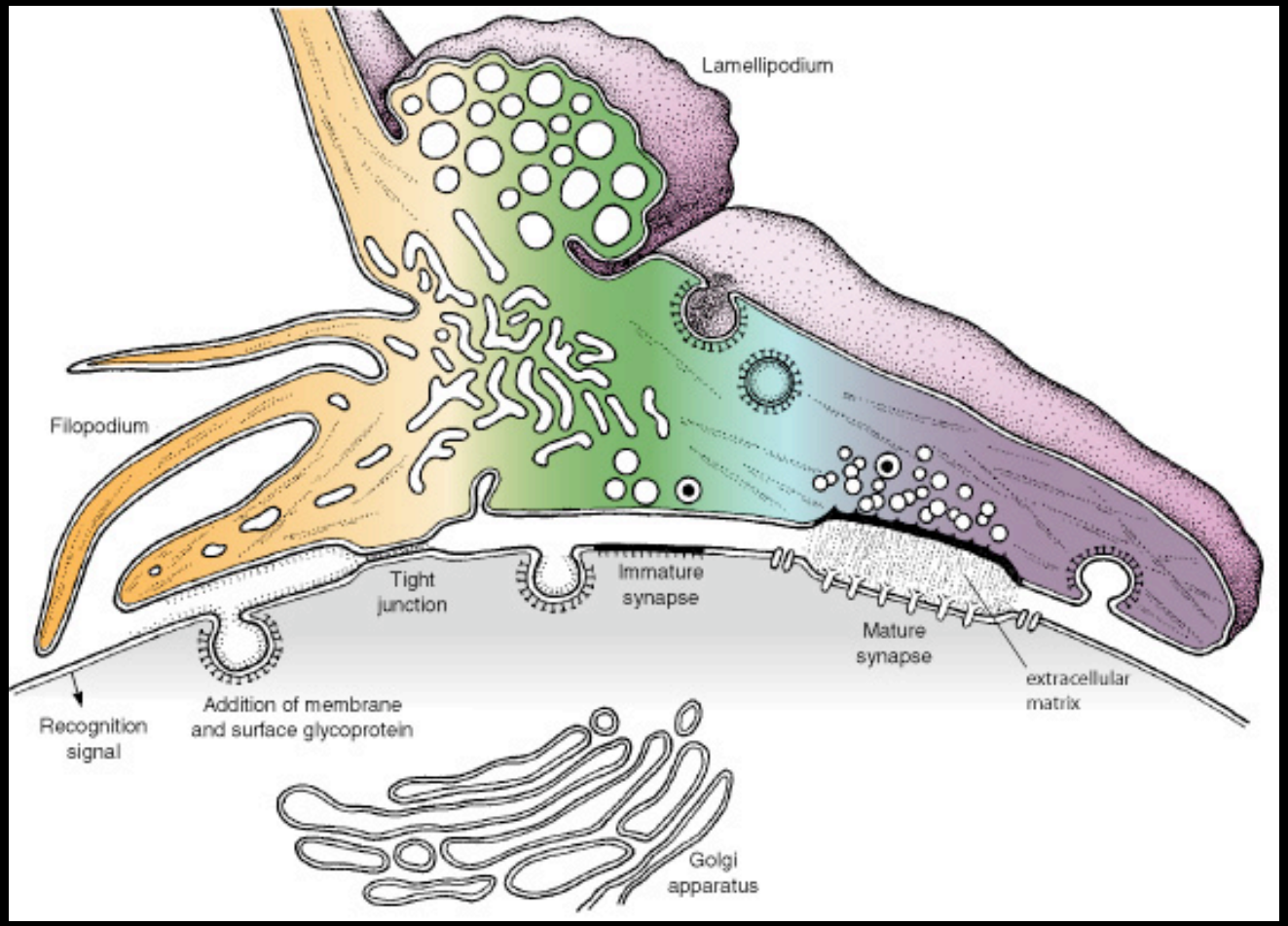
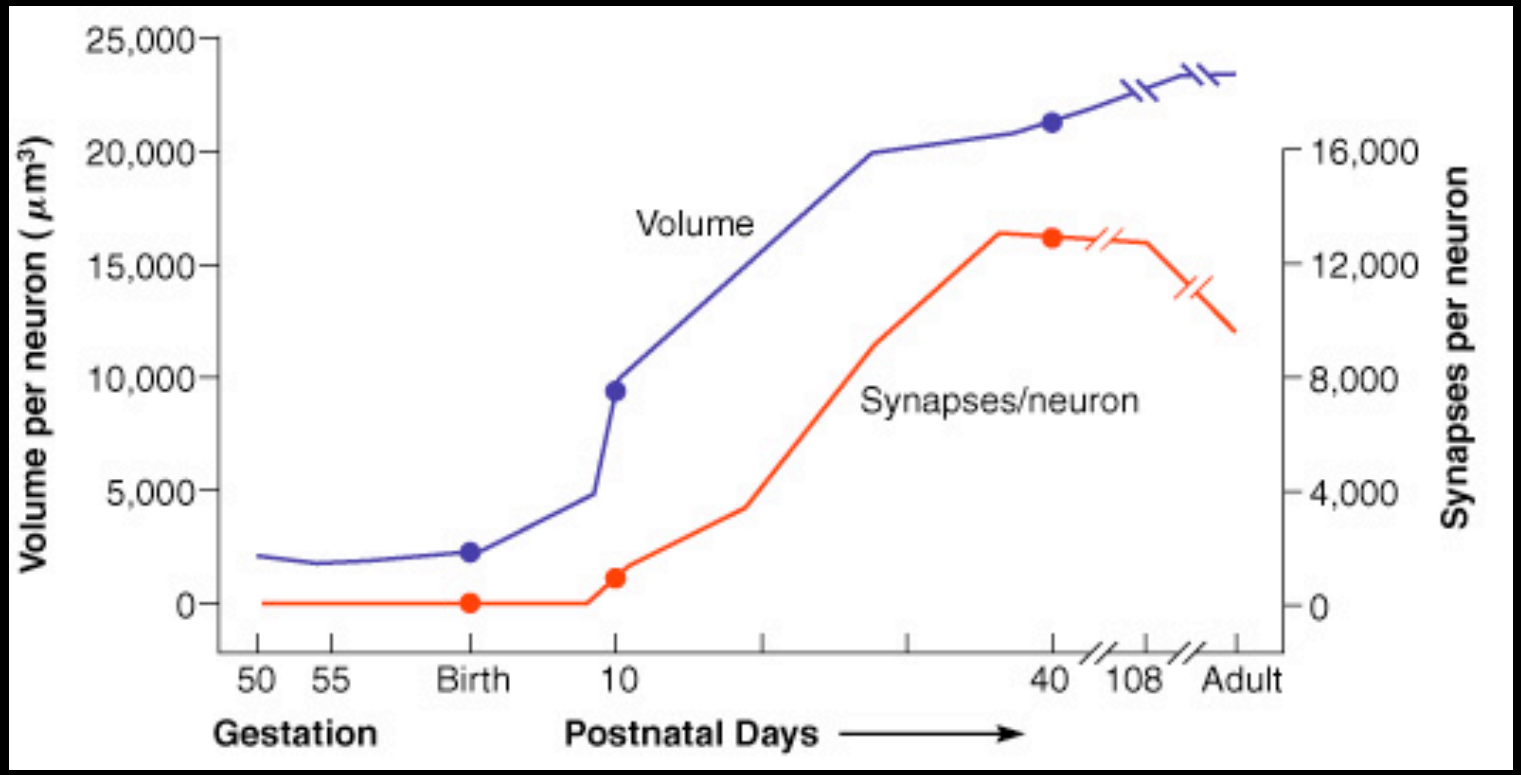
Synapse Formation



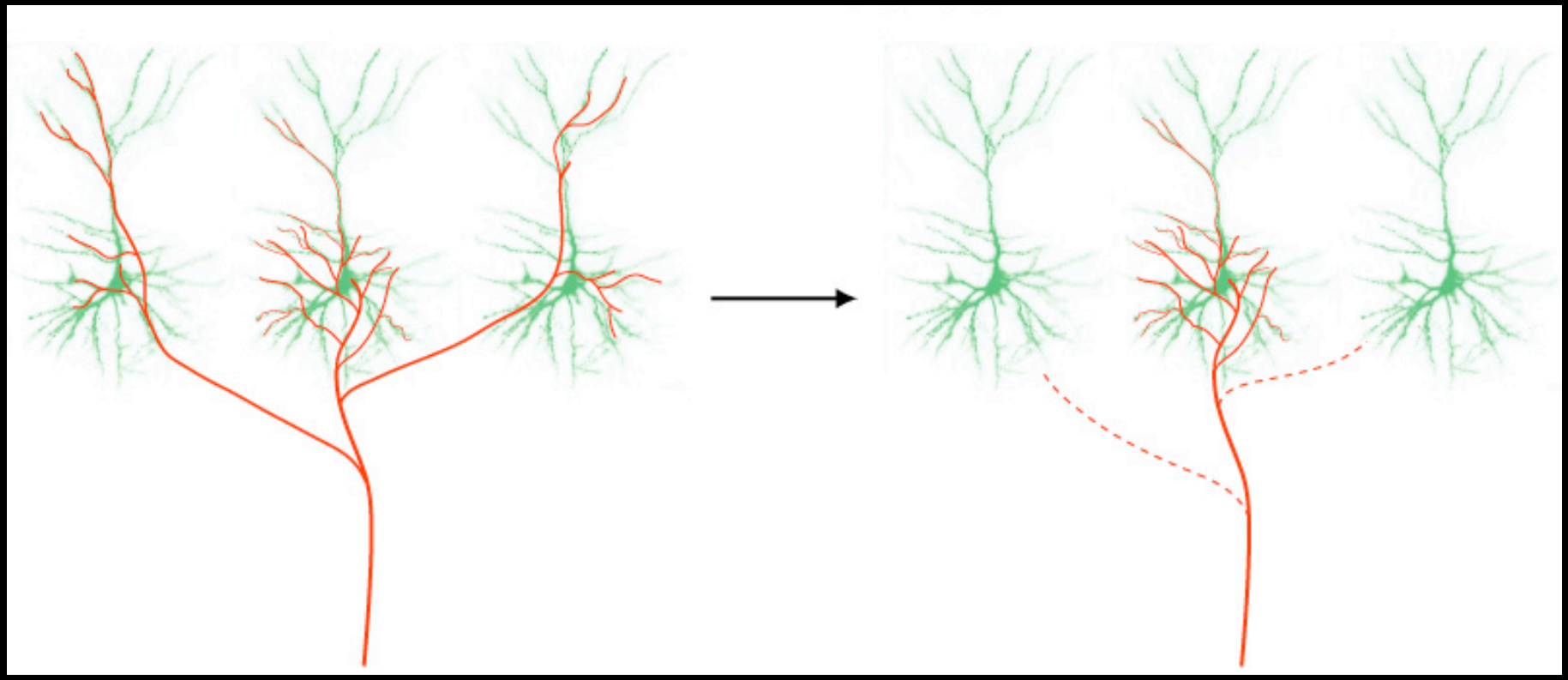
Rees

Growth and pruning of synaptic elements during development



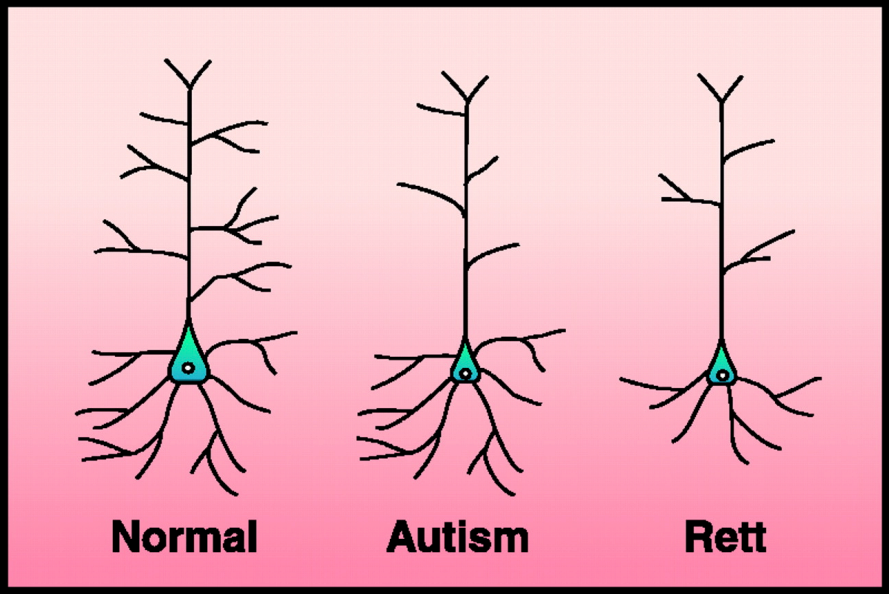
Cragg

Competition between axons and pruning of less active synapses drives “address selection”

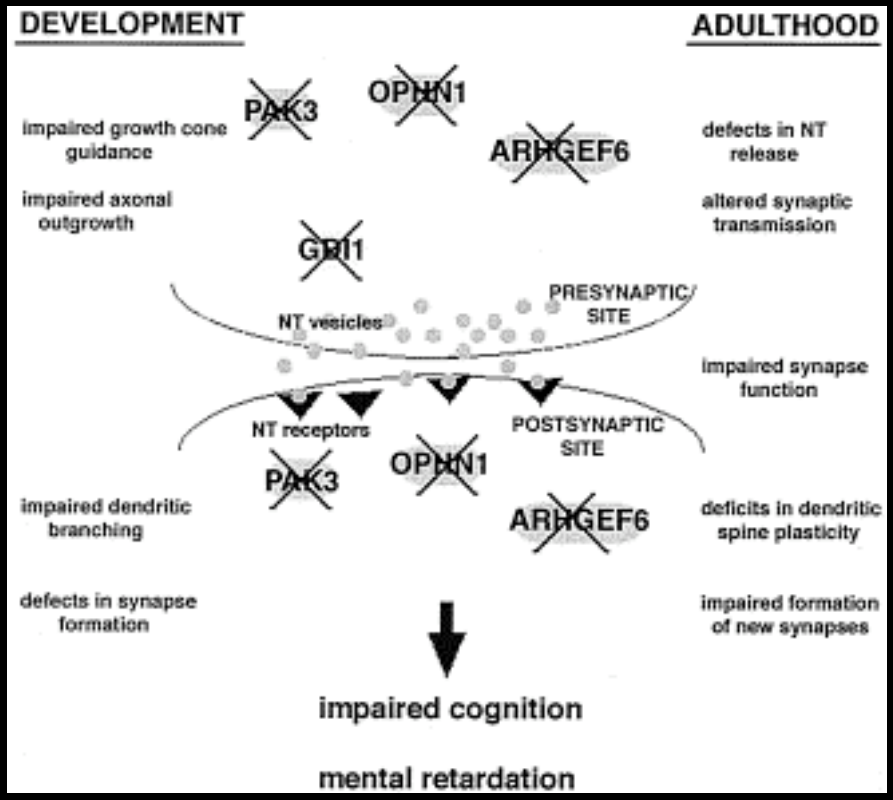


Impaired synapse formation and disease

Autism and Rett Syndrome

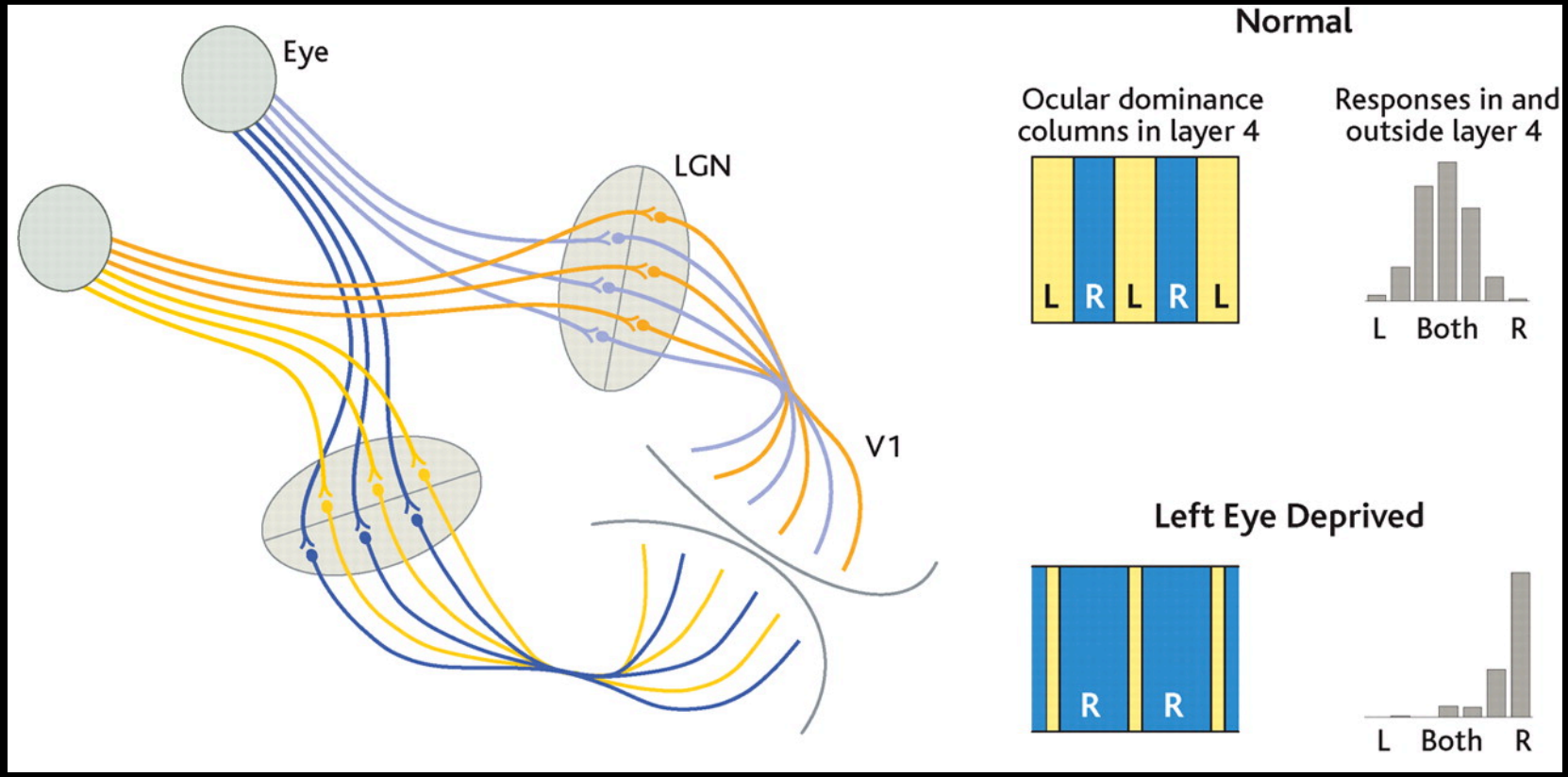


X-Linked Mental Retardation



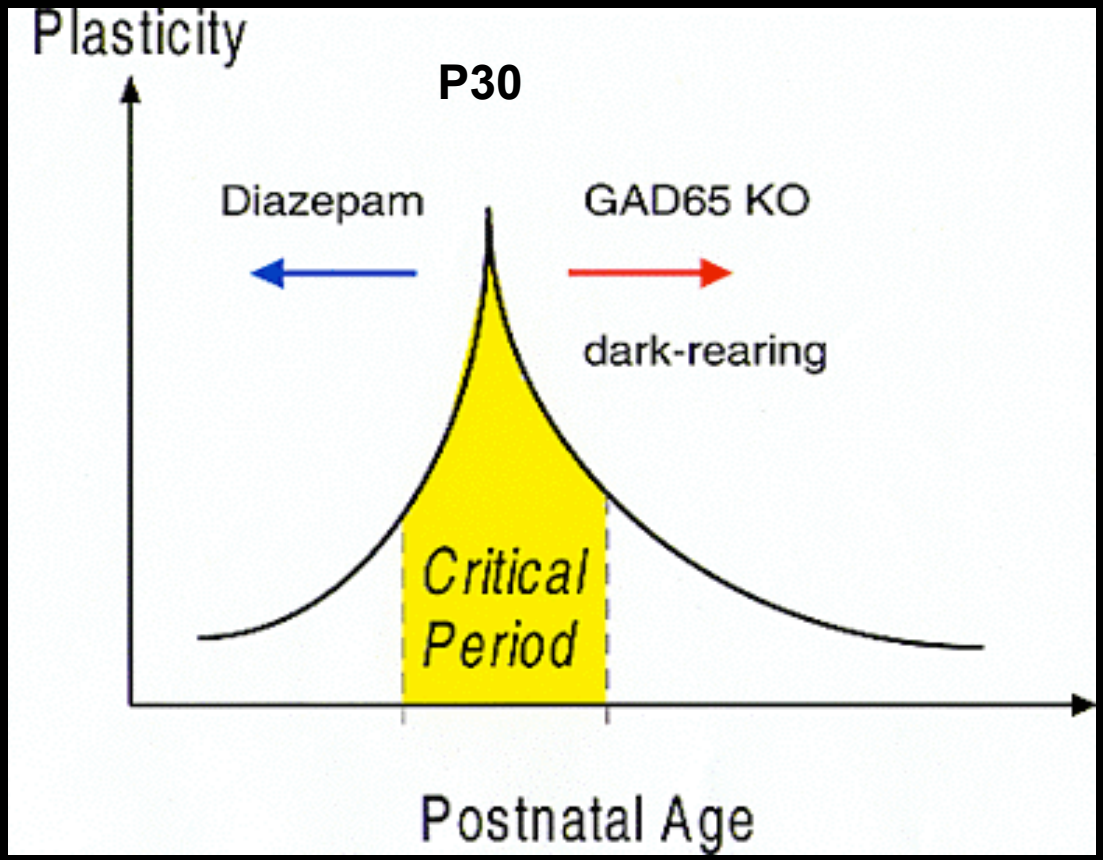
Chechlacz, Gleeson

Synaptic Plasticity



Huber, Wiesel

Critical period for synaptic plasticity



Hensch

Maternal imprinting of metabolic disease