Development of the CNS

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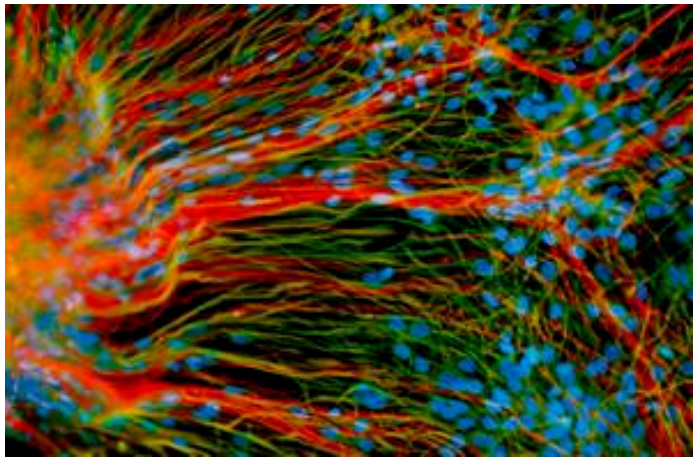
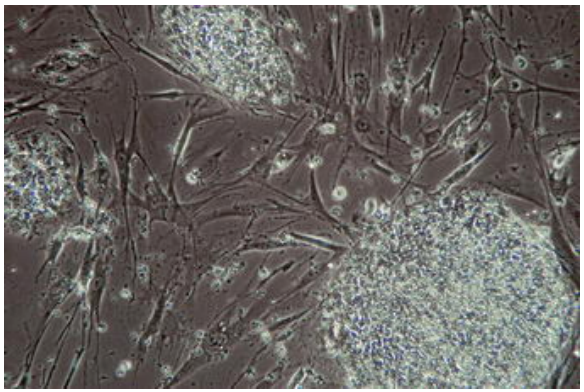
Why study CNS development?

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

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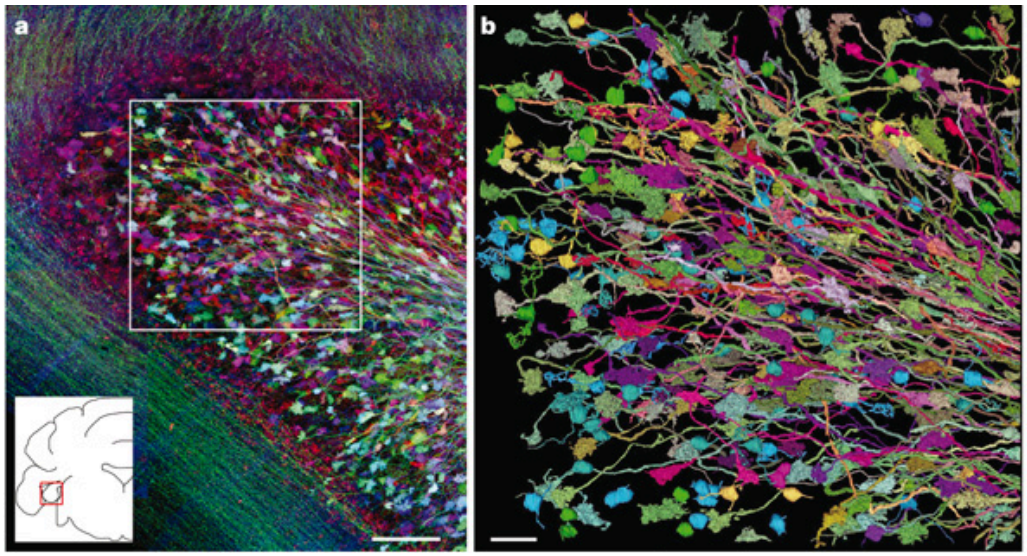

Livet, Lichtman

How to Make a Nervous System

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

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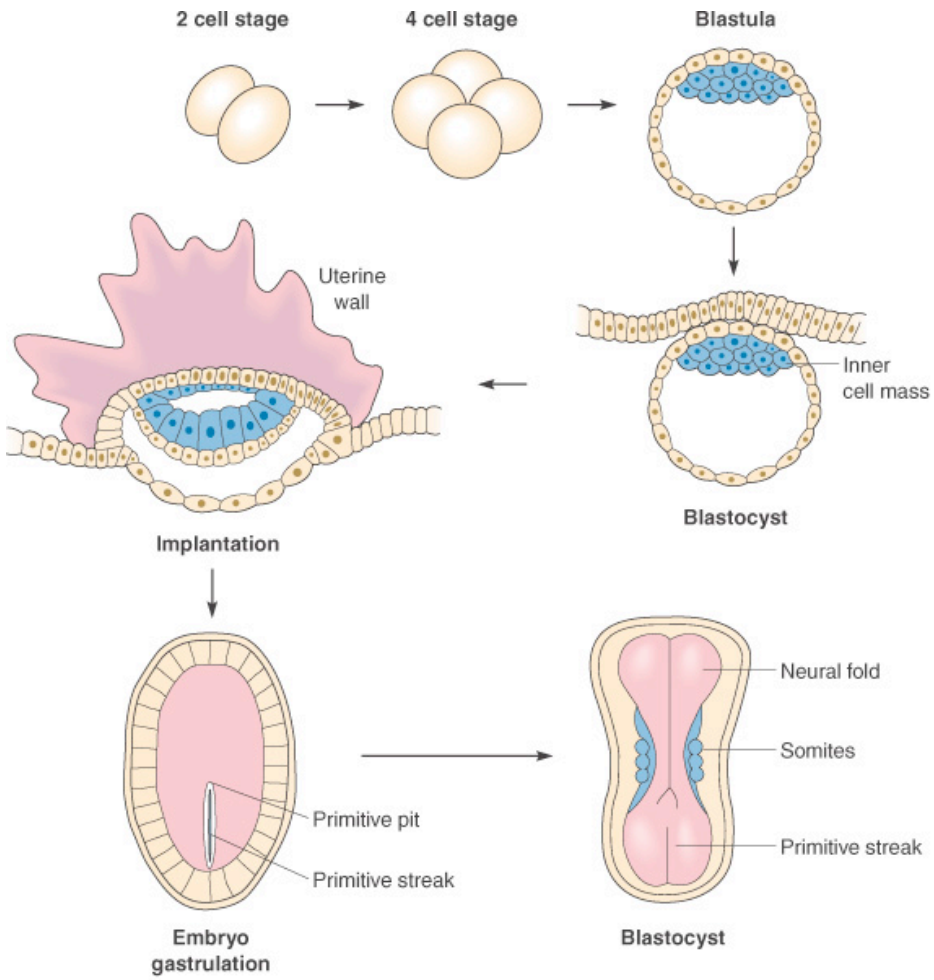
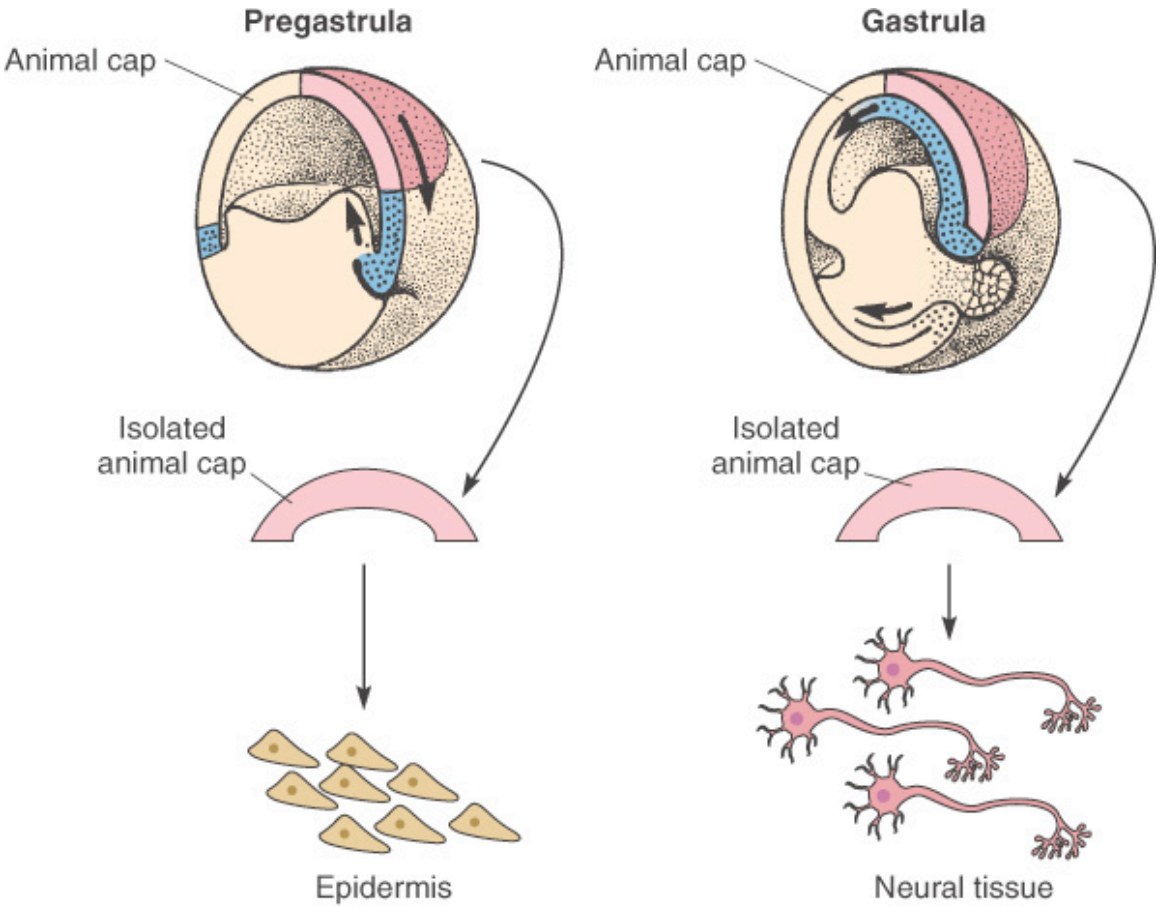
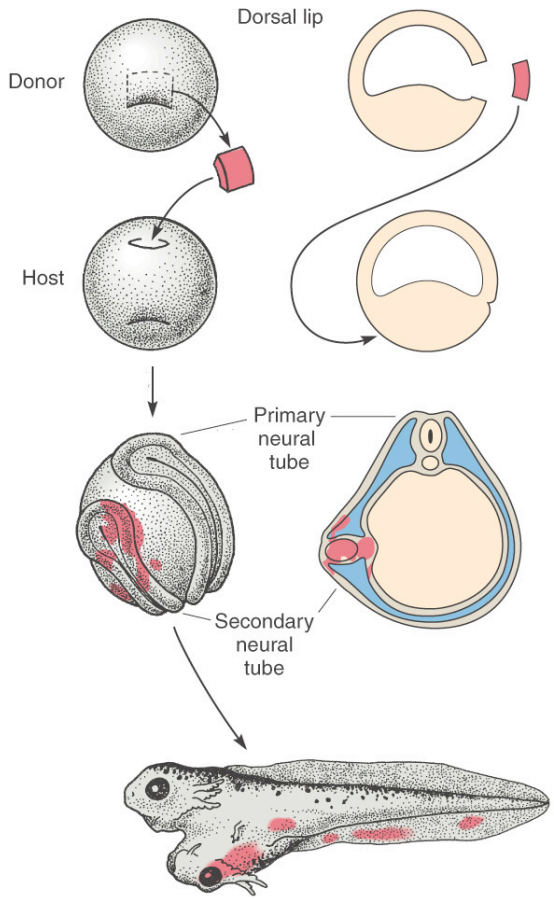
“The most important time in your life is not birth, marriage, or death, but gastrulation”

- Lewis Wolpert



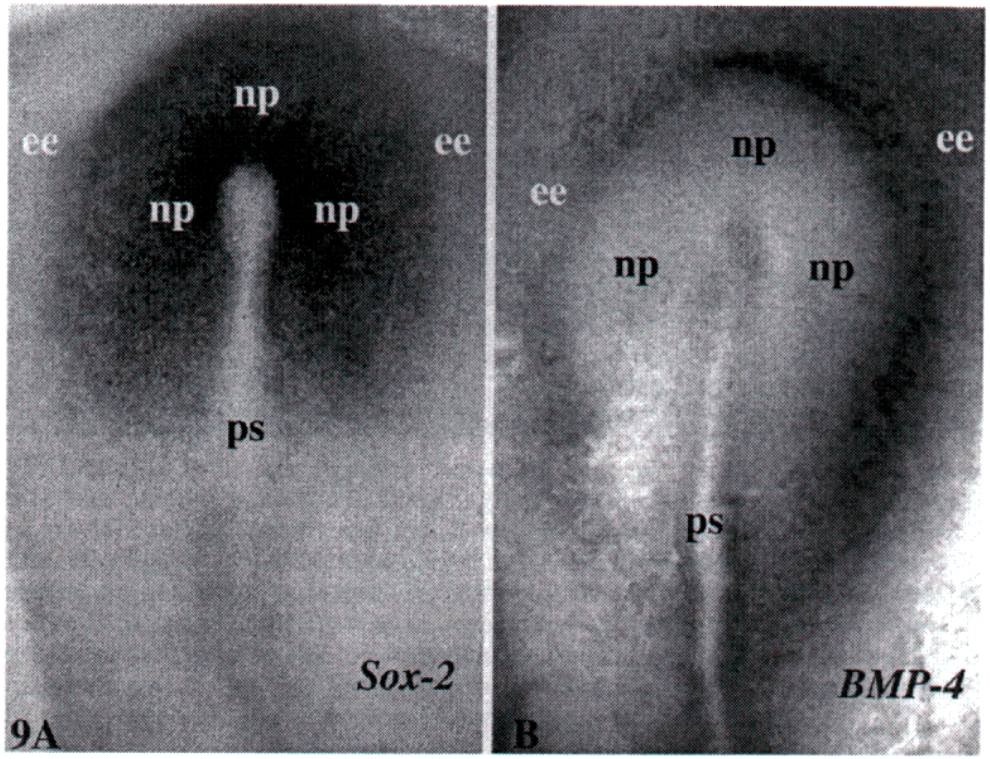
Gastrulation and Neural Induction





Spemann, Mangold

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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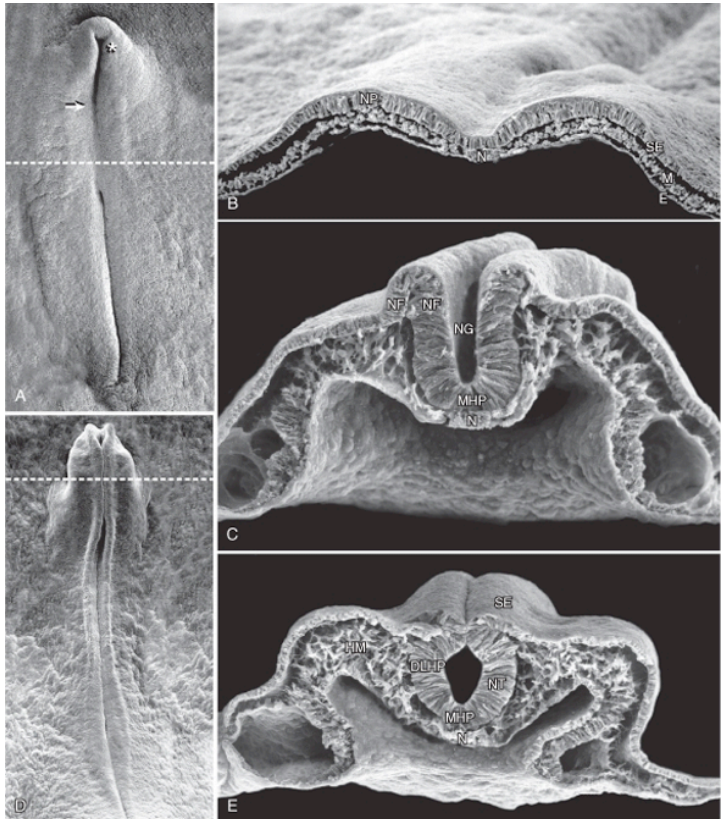
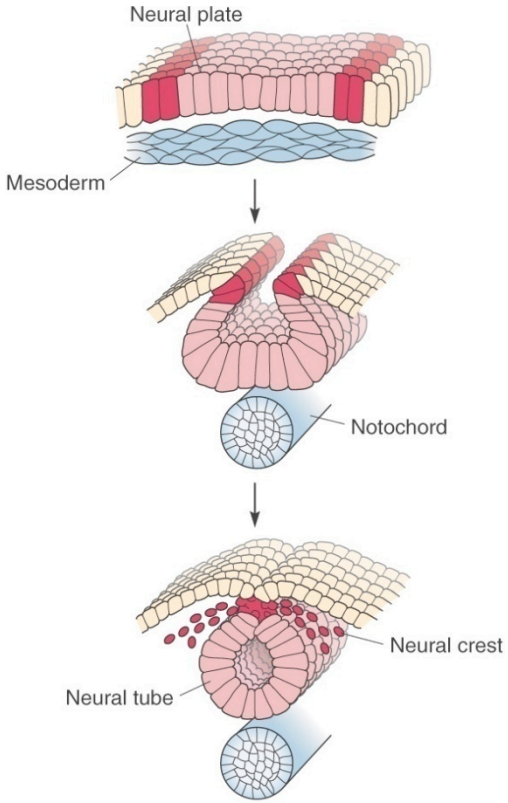
Neurulation- Neural tube formation





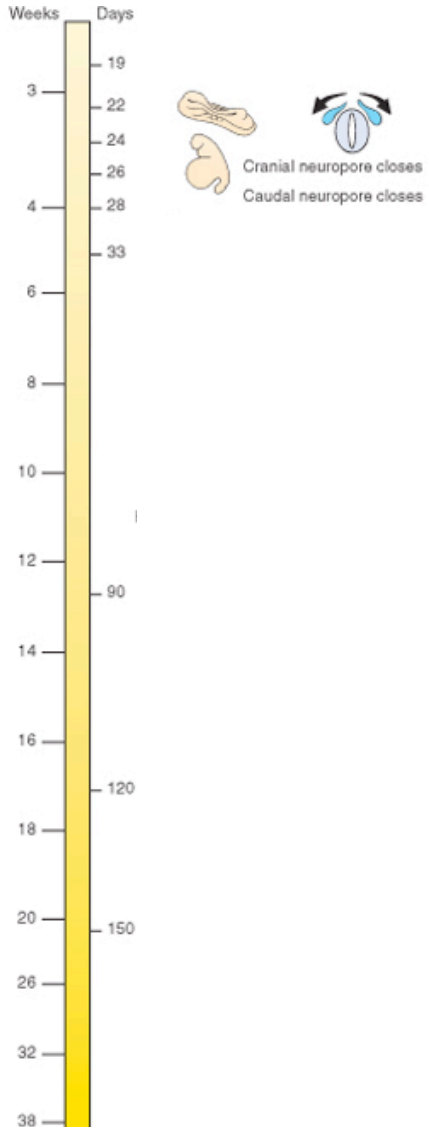
Formation
of the neural plate

Bending to form a
neural tube

Closure of the
neural tube

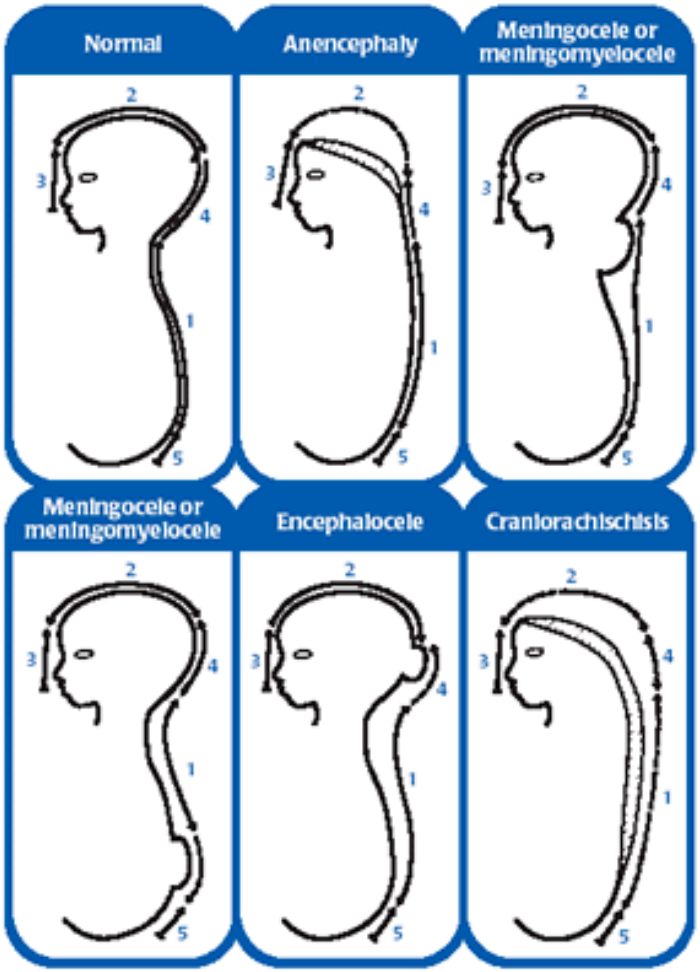
Tosney, Schoenwolf

Timing of neural tube closure in humans



Schoenwolf et al: Larsen's Human Embryology, 4th Edition

Neural Tube Defects

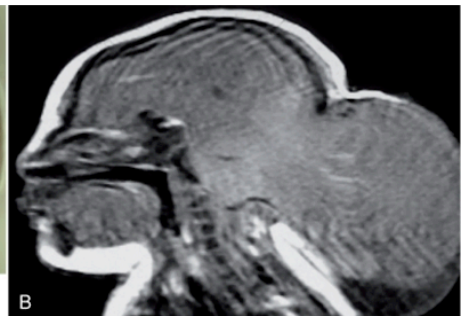


Van Allen, Kalousek

Anencephaly

Spina Bifida

Encephaly



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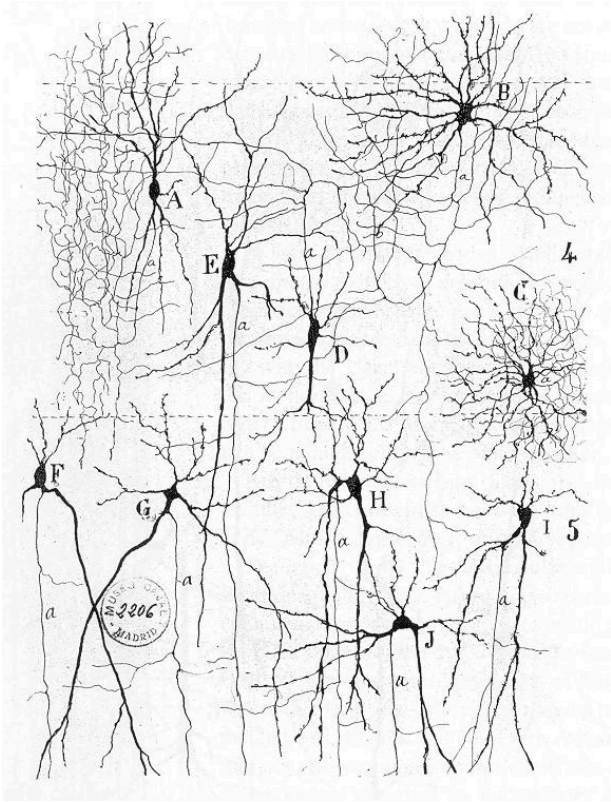
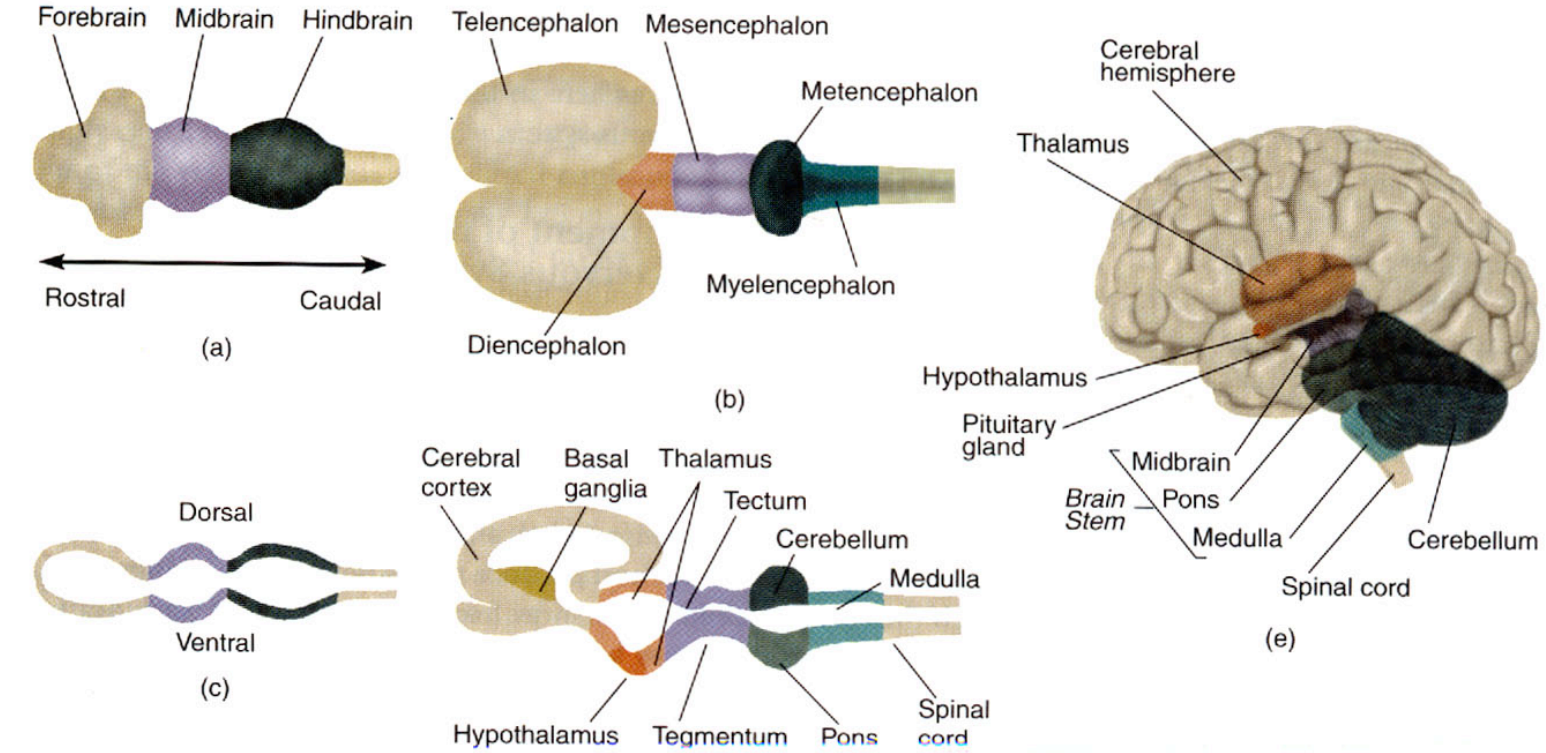
Generation of neuronal diversity



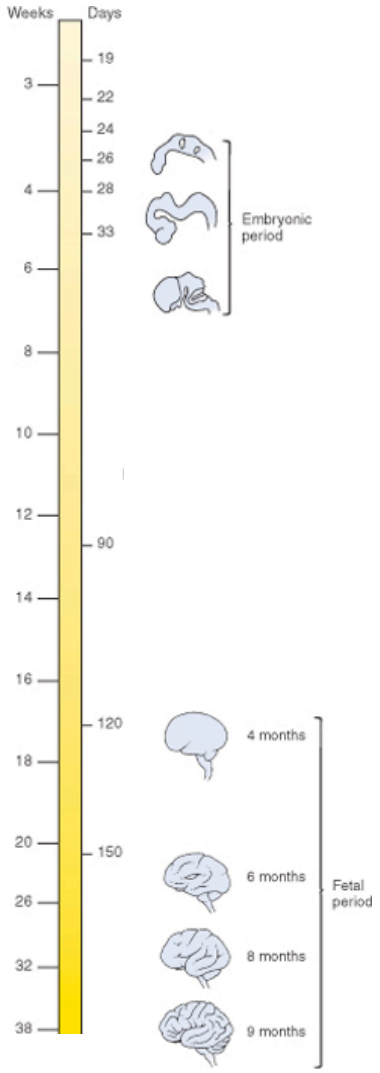
Ramon y Cajal

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

Differentiation of neural tube to form distinct vesicles



Timing of CNS development in humans

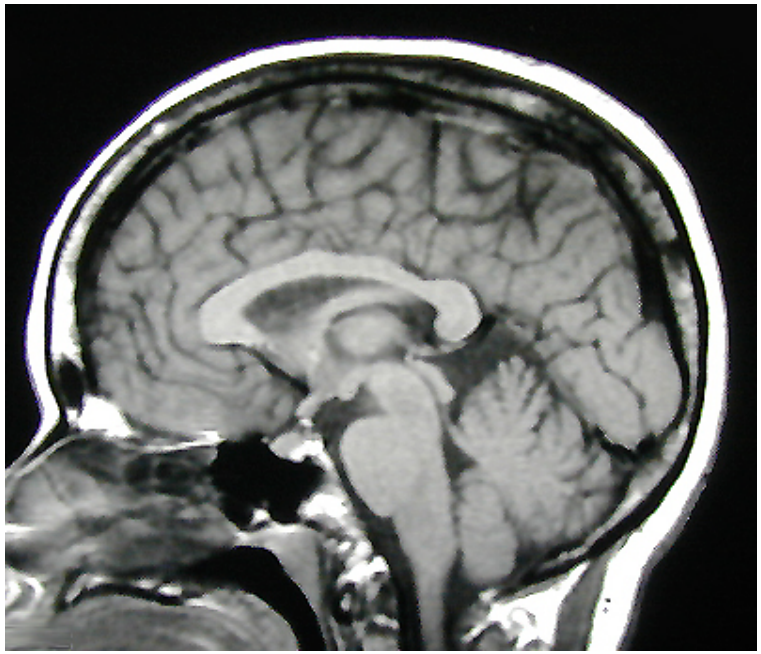


Schoenwolf et al: Larsen's Human Embryology, 4th Edition

Patterning: acquisition of a positional identity

Dorsal

Rostral/Anterior



Caudal/Posterior

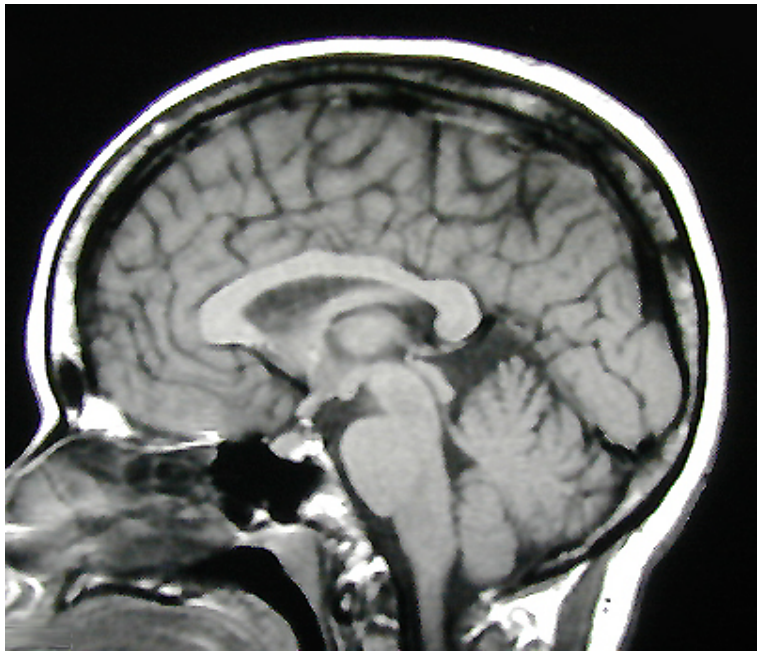
Ventral

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

Patterning: acquisition of a positional identity

Dorsal

Rostral/Anterior



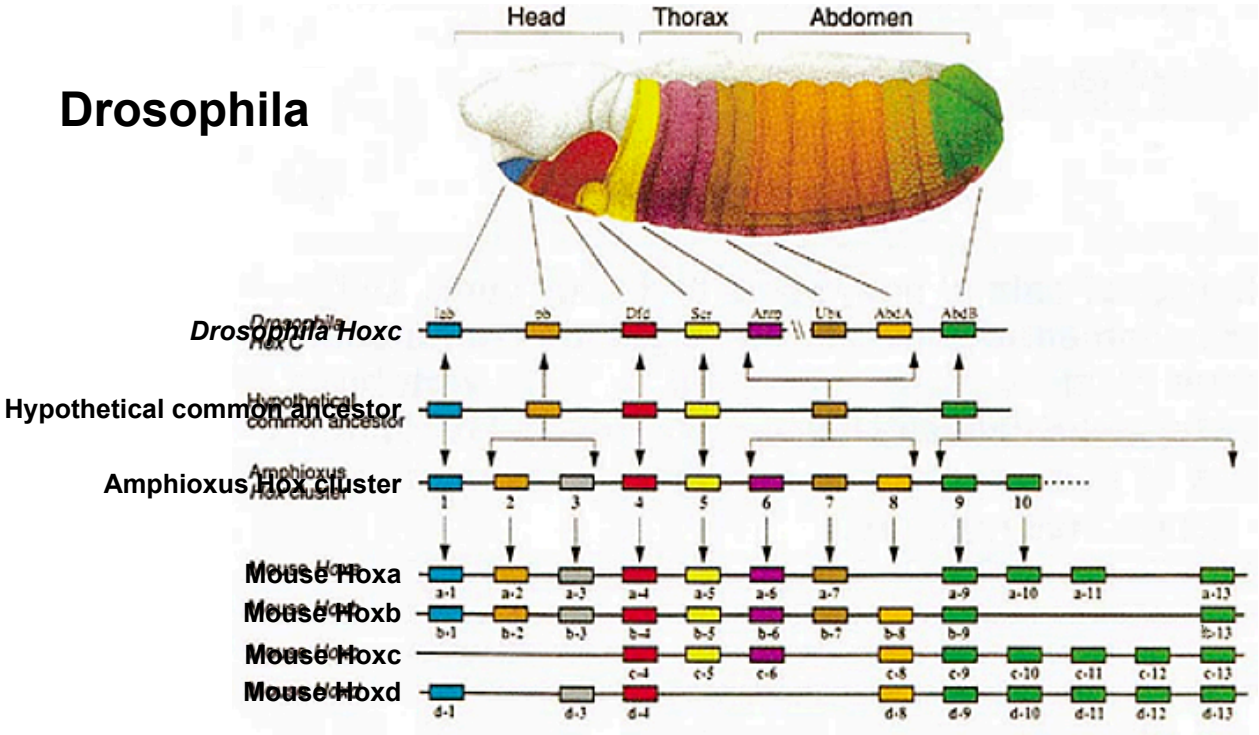
Caudal/Posterior

Ventral

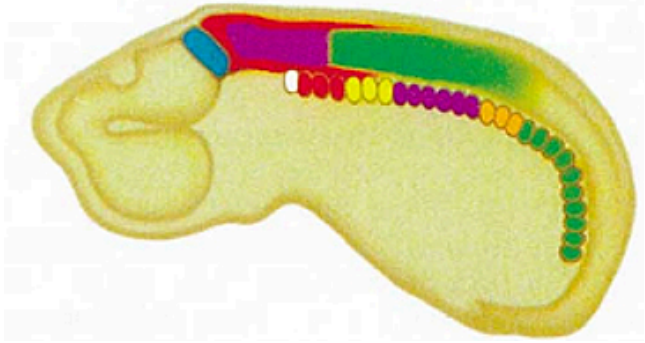
- Transcriptional regulation (cell autonomous)
- Secreted factors (non-cell autonomous)

Hox genes provide positional information along the A/P axis

Drosophila



Mouse

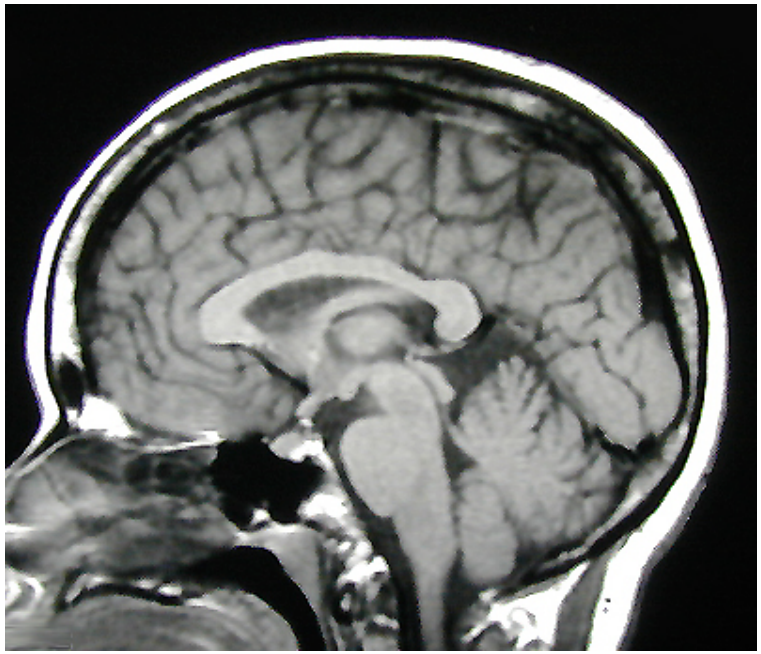


Carroll

Patterning: acquisition of a positional identity

Dorsal

Rostral/Anterior

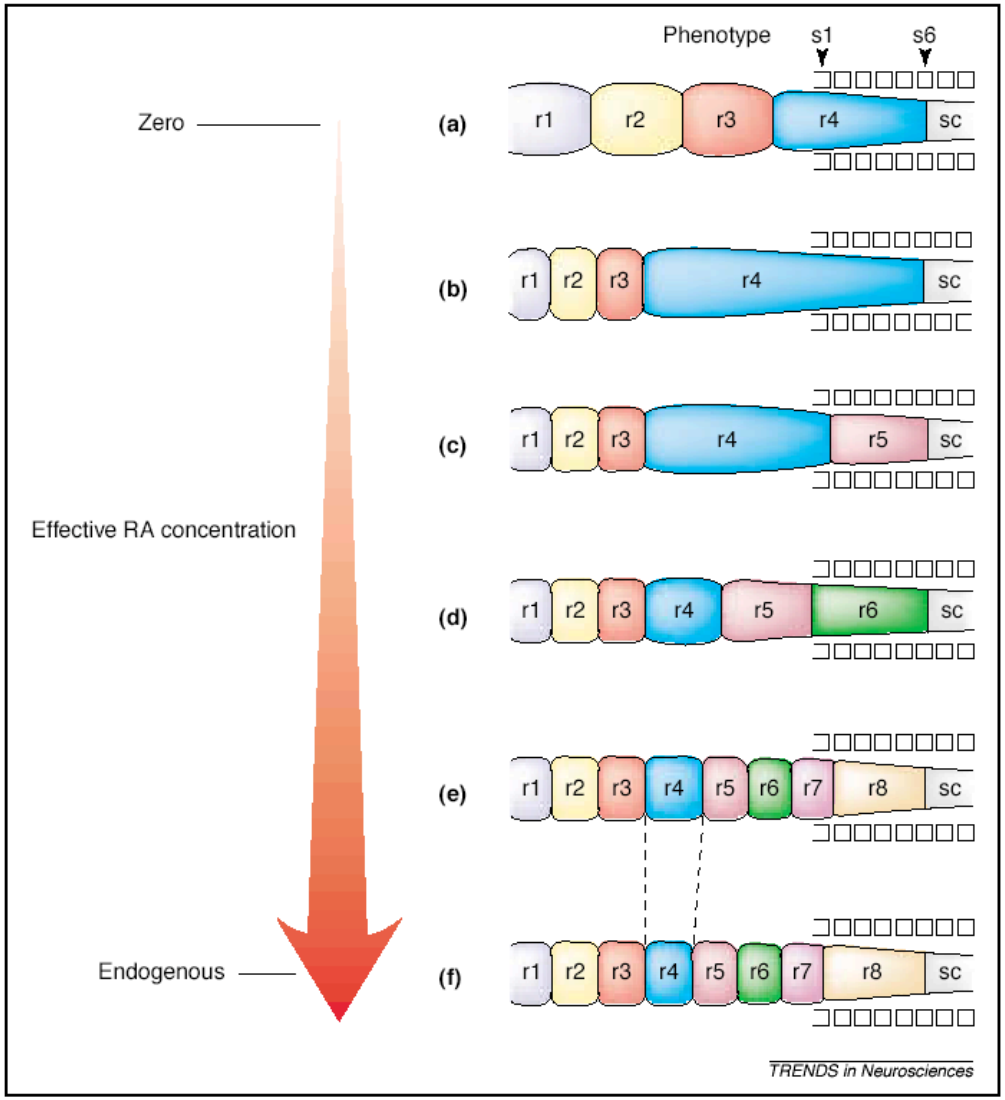


Caudal/Posterior

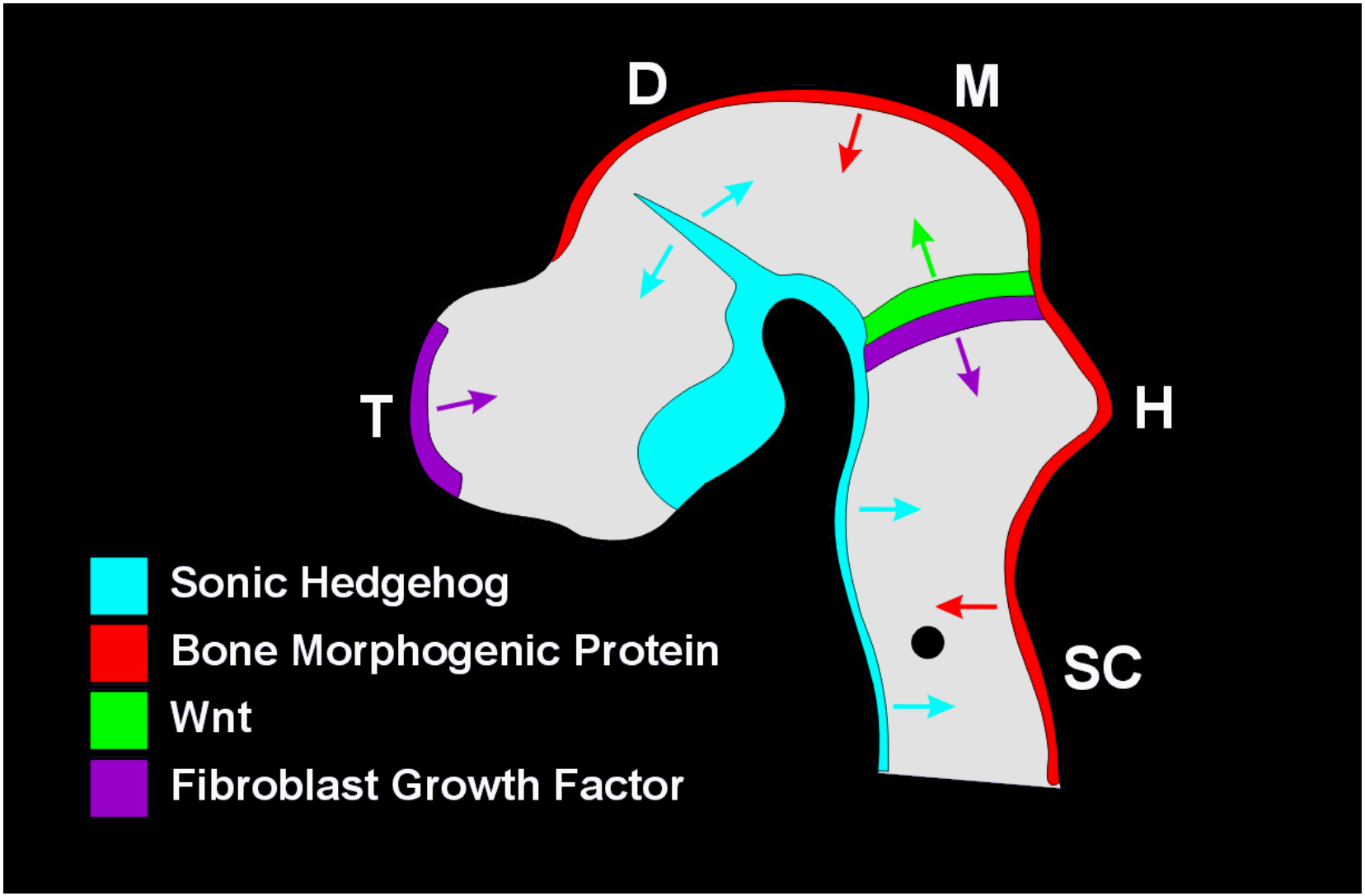
Ventral

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

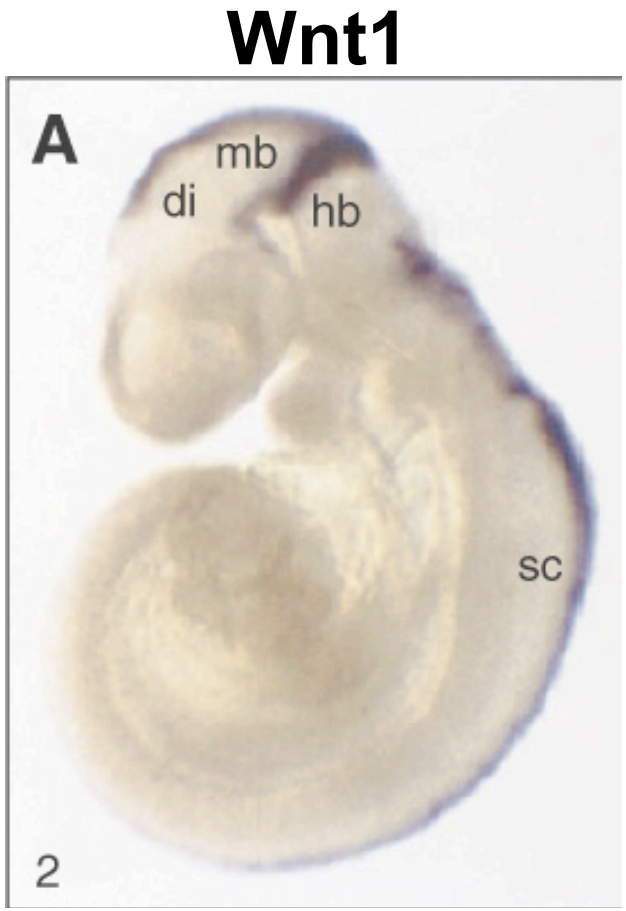
A gradient of retinoic acid patterns posterior identities in the hindbrain



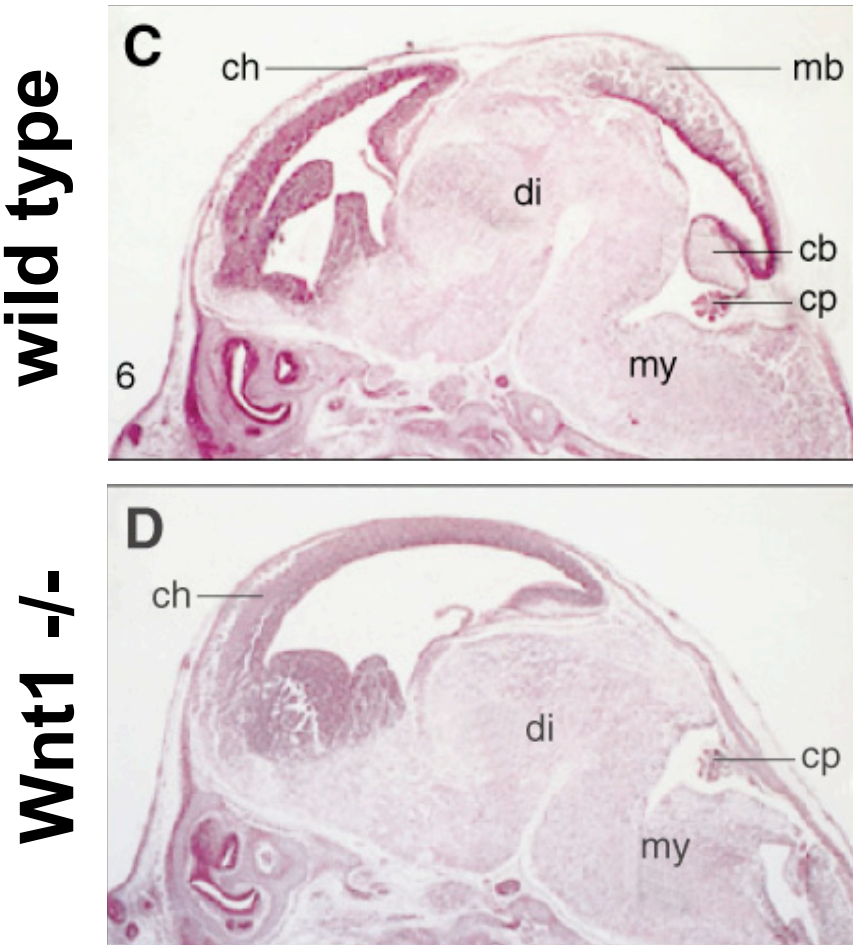
Secreted factors initiate neuronal diversity



Wnt1 is required for midbrain patterning



Crossley, Martin

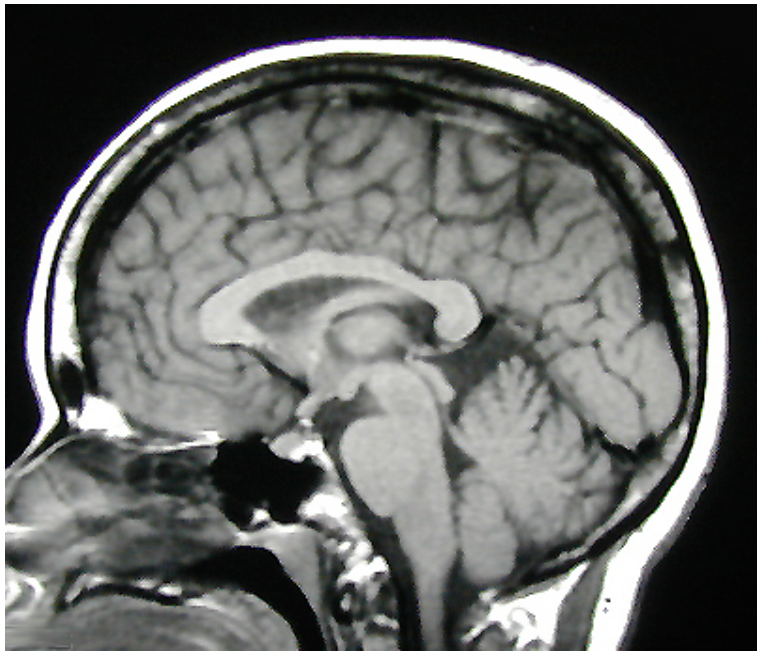


Thomas, Capecchi

Patterning: acquisition of a positional identity

Dorsal

Rostral/Anterior

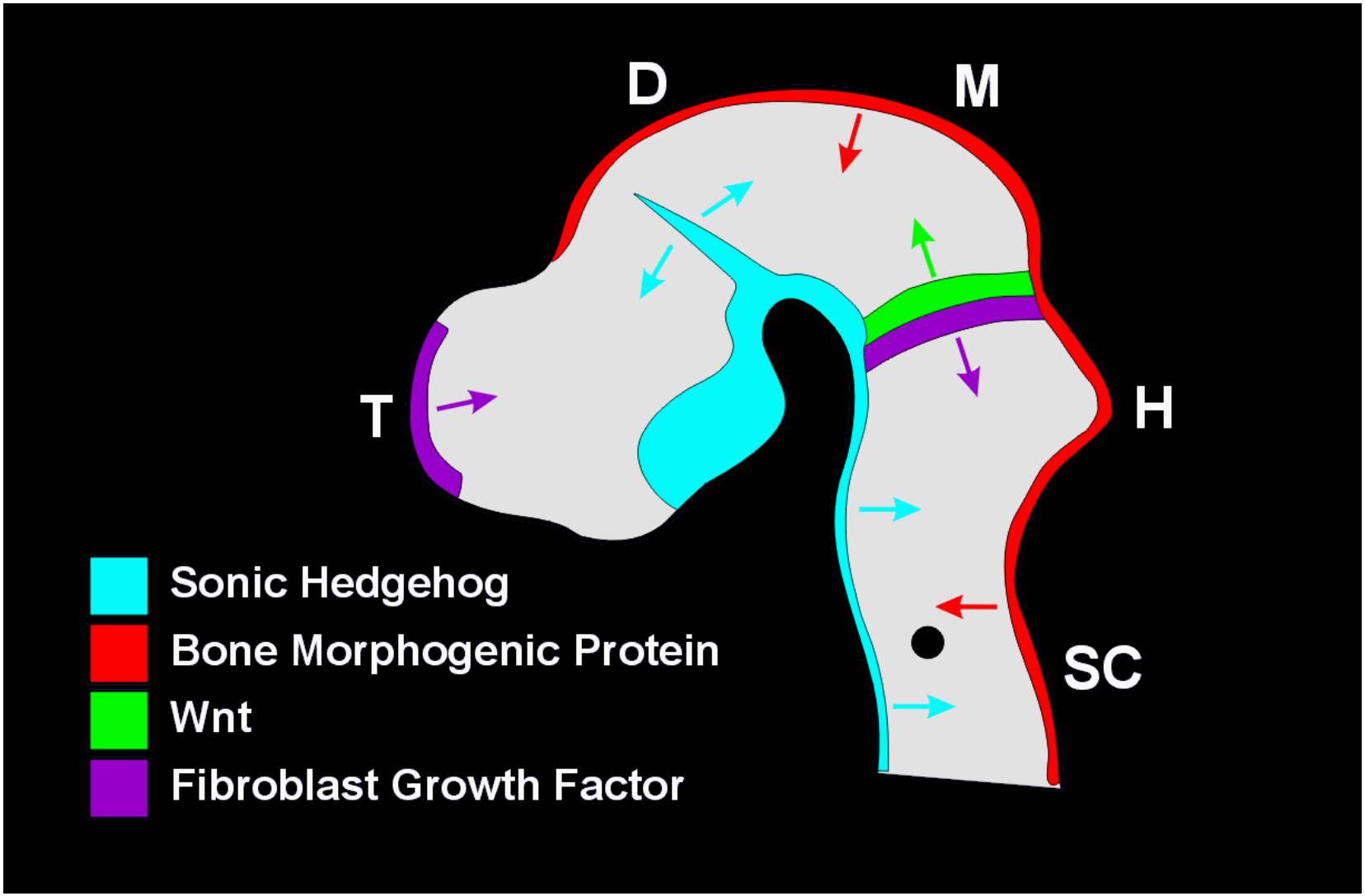


Caudal/Posterior

Ventral

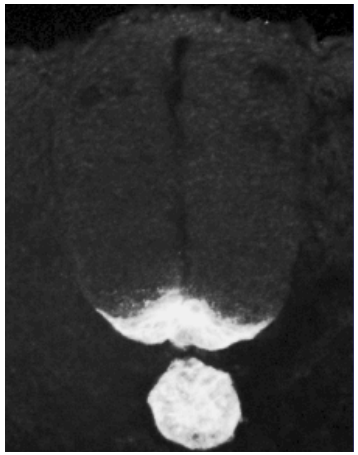
Secreted factors (non-cell autonomous)

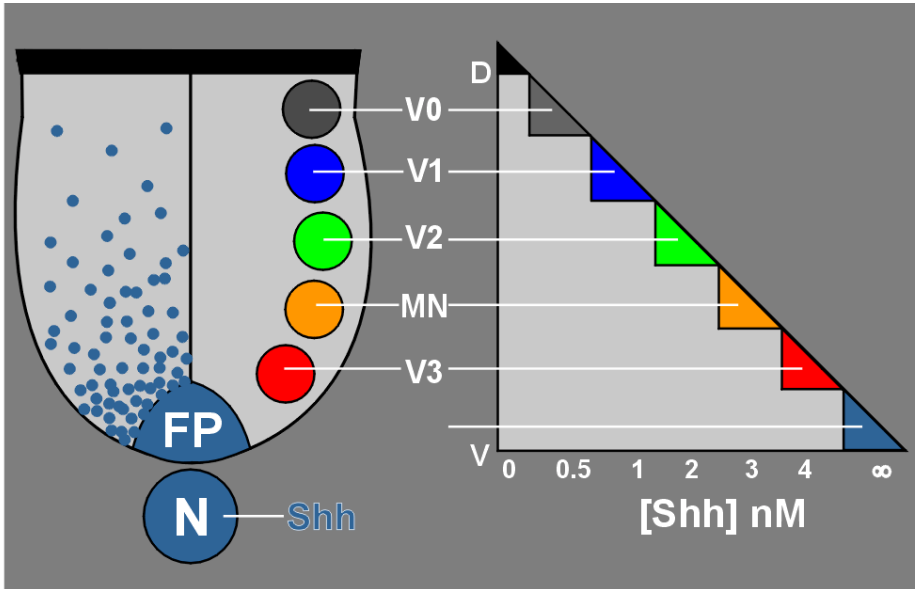
Secreted factors initiate neuronal diversity

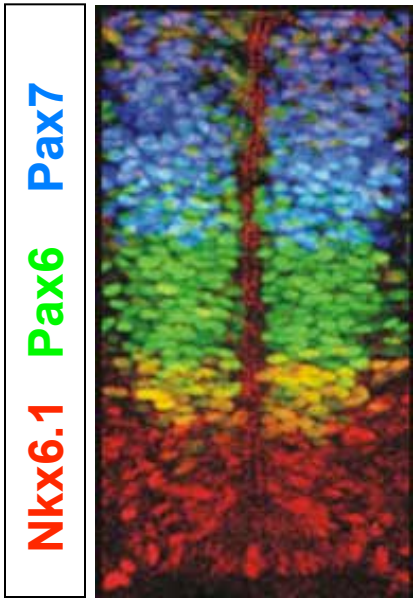


A gradient of Shh patterns ventral identities

Shh

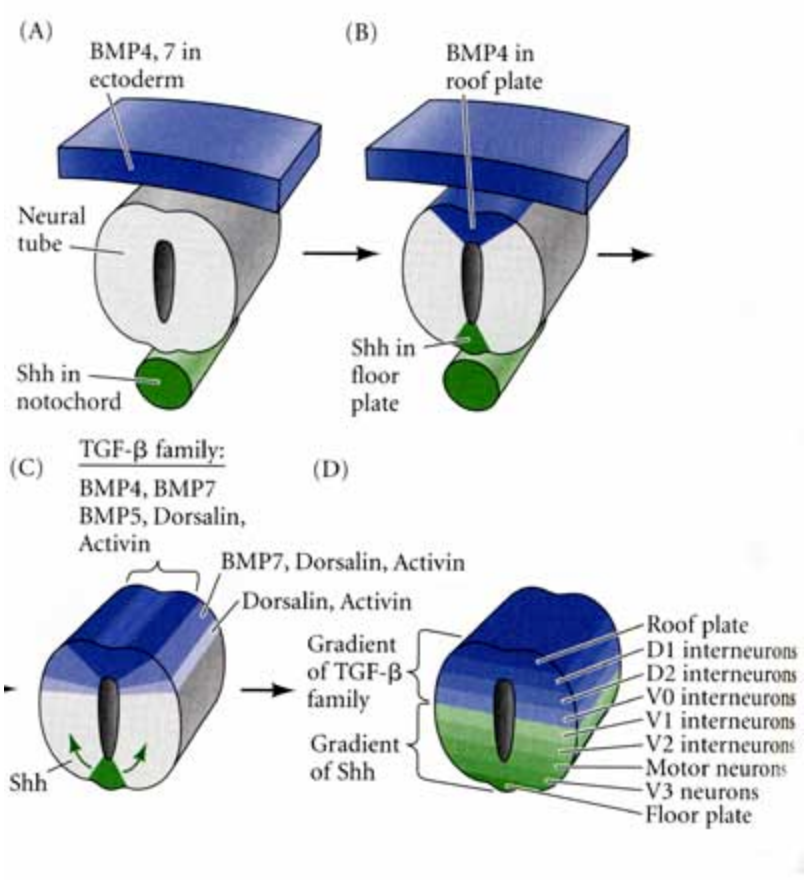






Roelink, Ericson, Briscoe, Jessell

Two Signaling Centers Specify Neural Cell Types along the DV axis

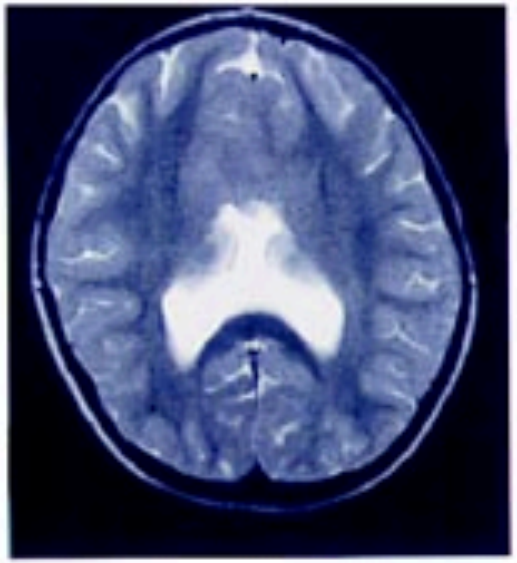


Dorsal Signaling Center
Roof Plate
BMP/TGFb

Ventral Signaling Center
Notochord and Floor Plate
SHH

Jessell

Ventral patterning defect: Holoprosencephaly



Gripp, Elledge

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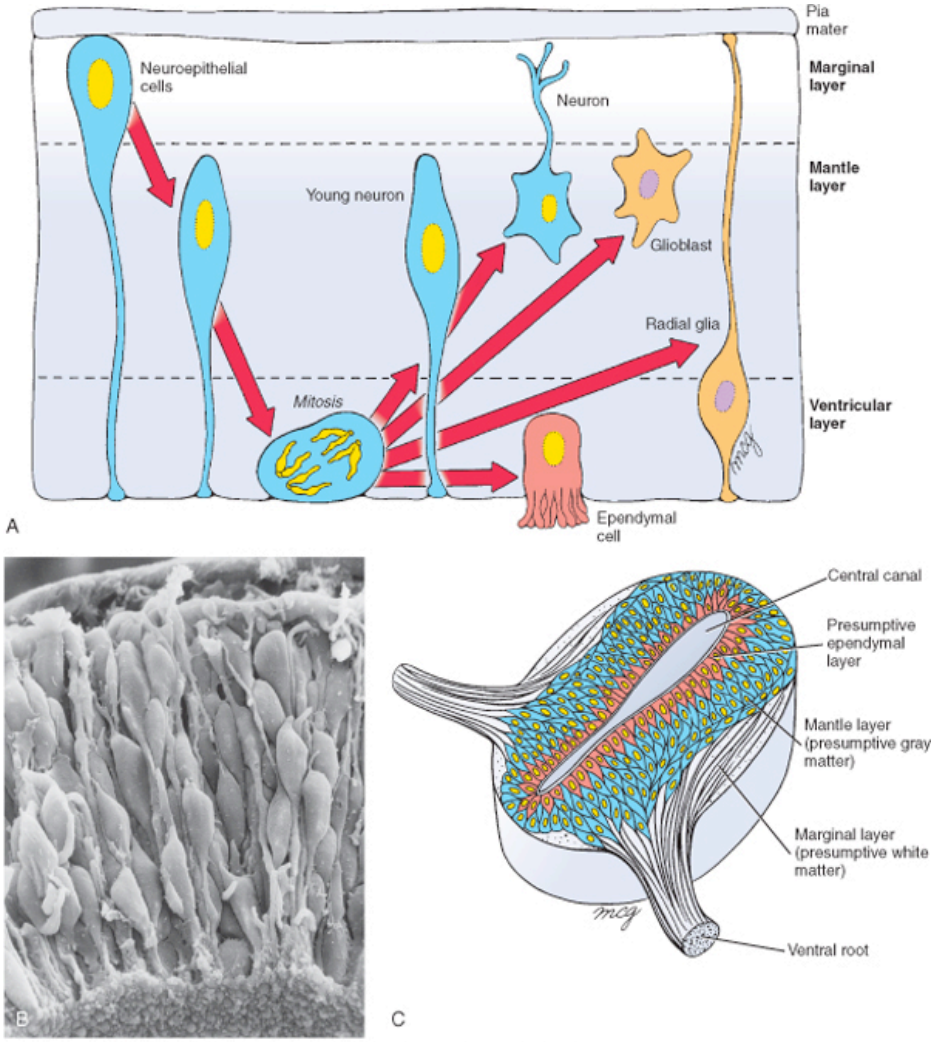
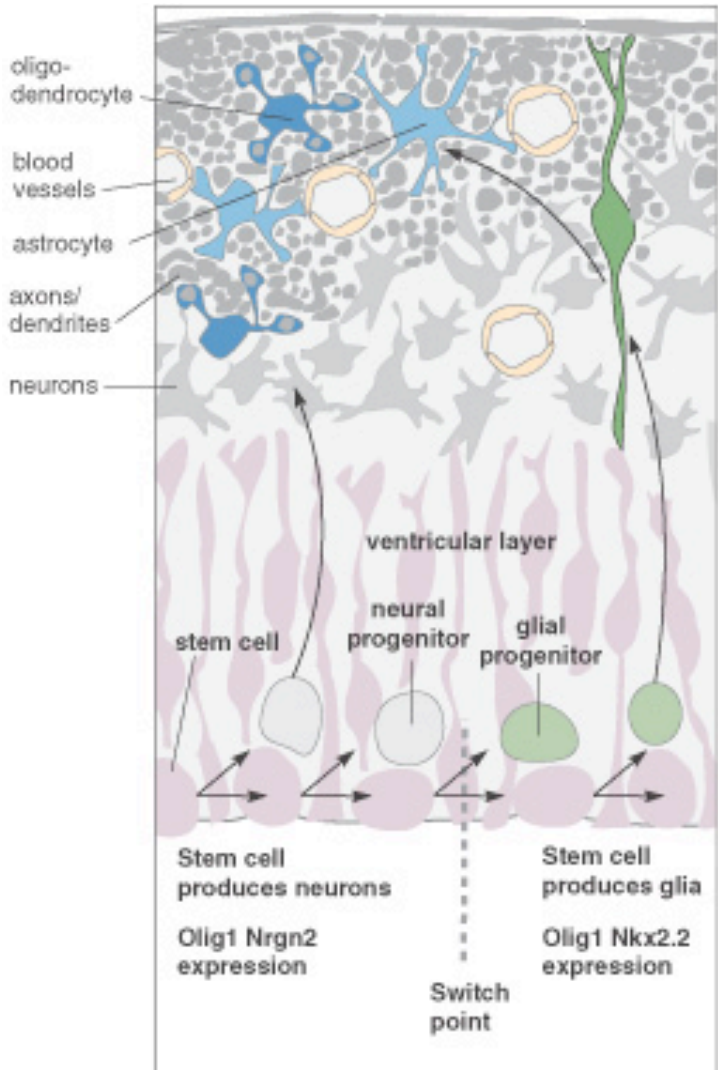
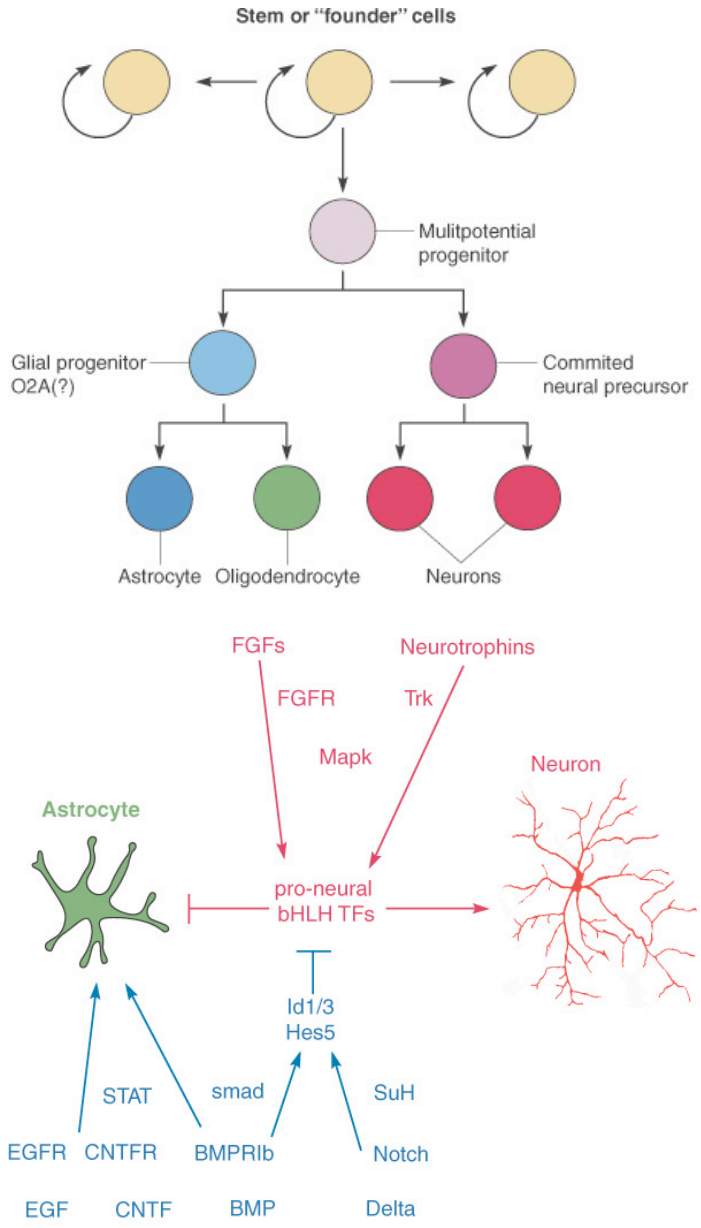
Differentiation of the walls of the neural tube

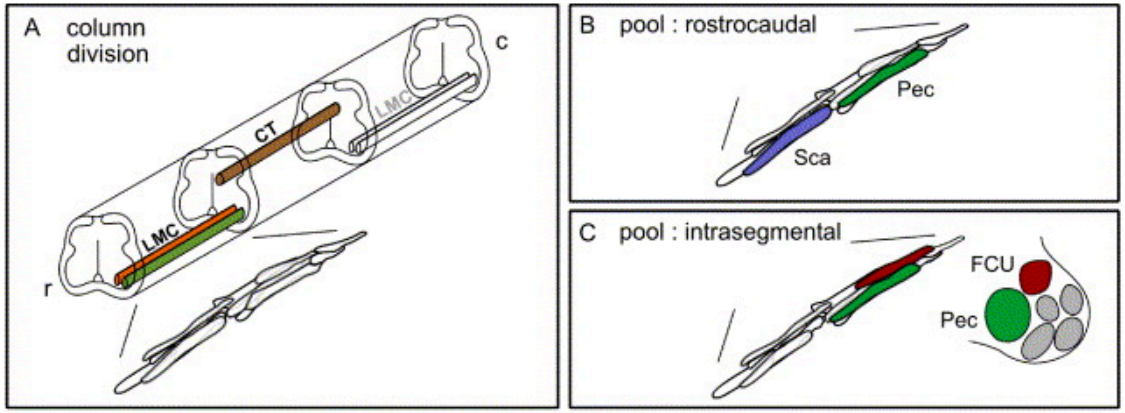


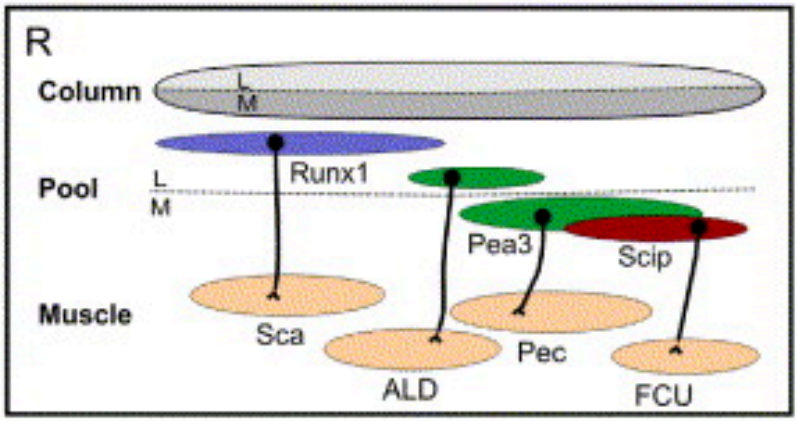
Stem cells produce neurons and glia

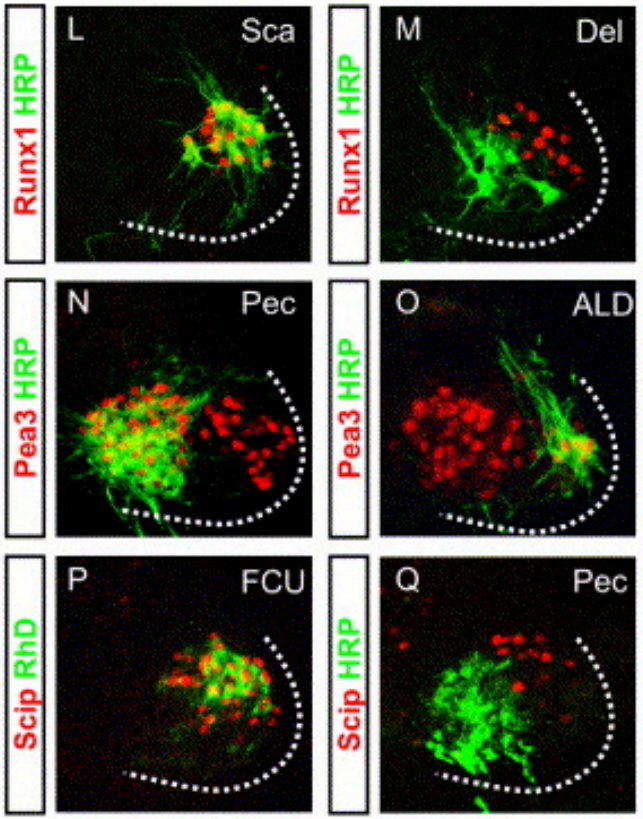




Specification of cell fates

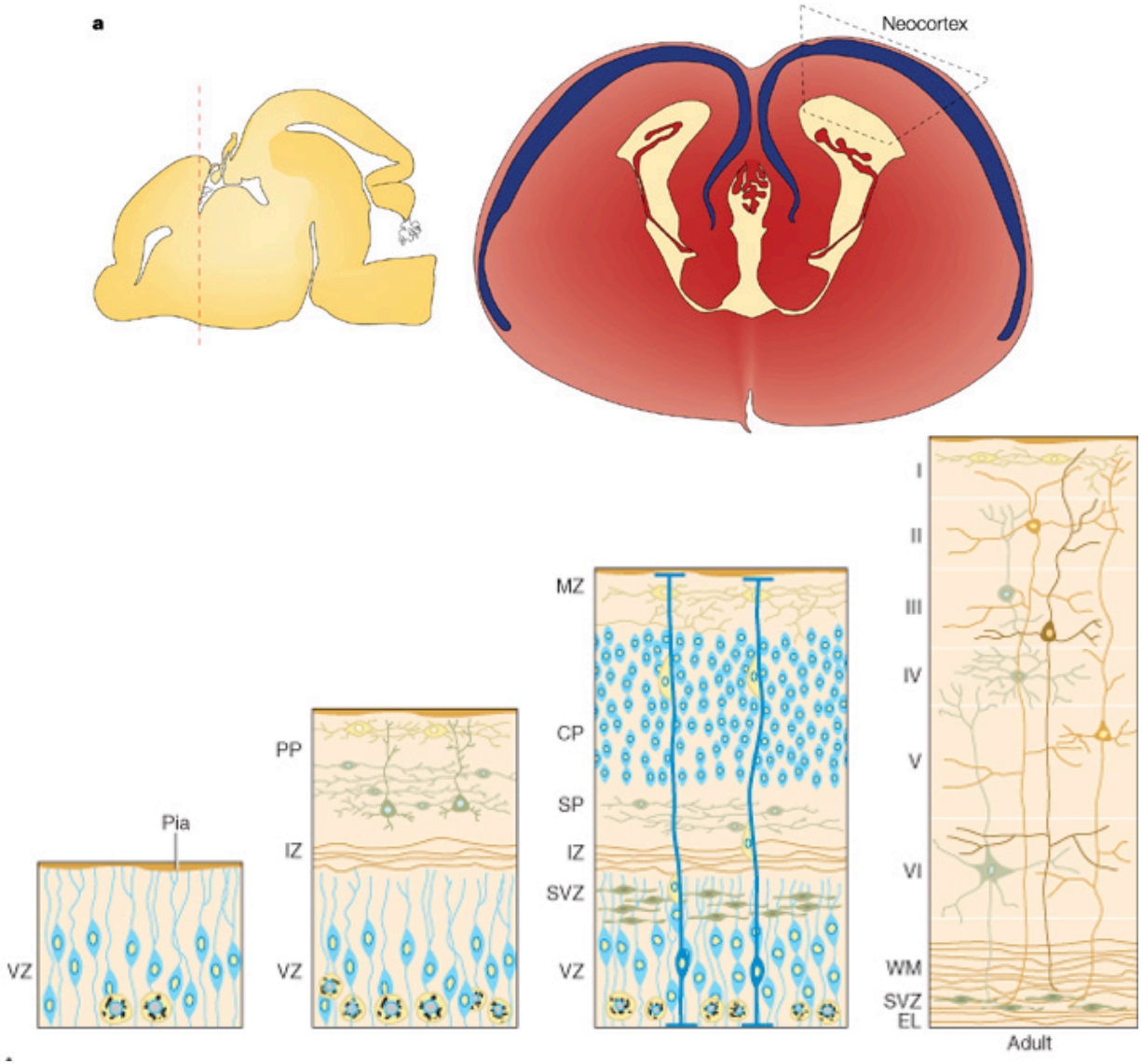




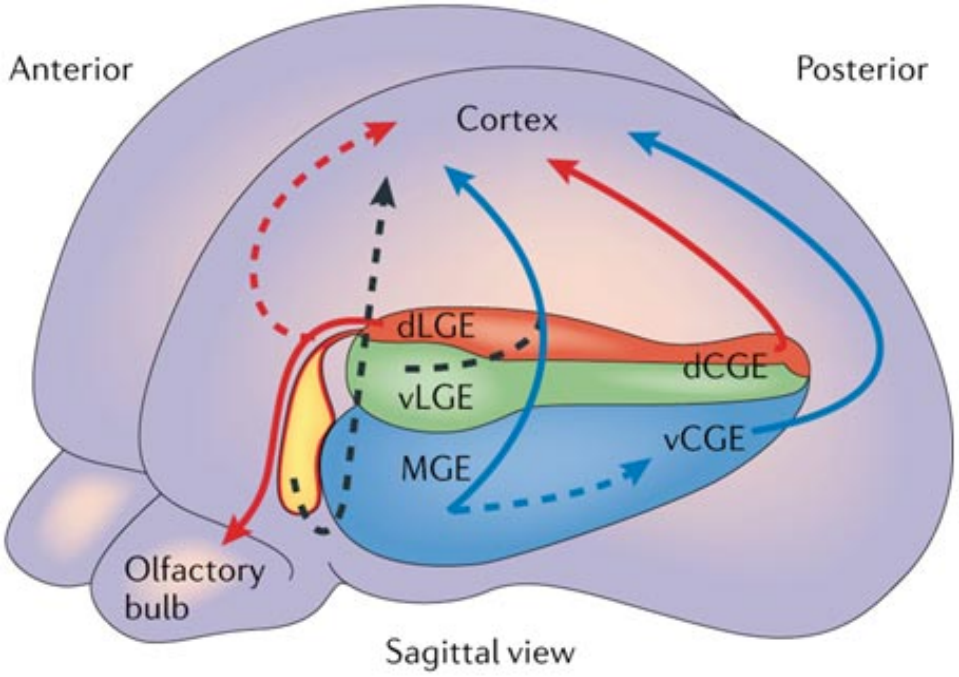


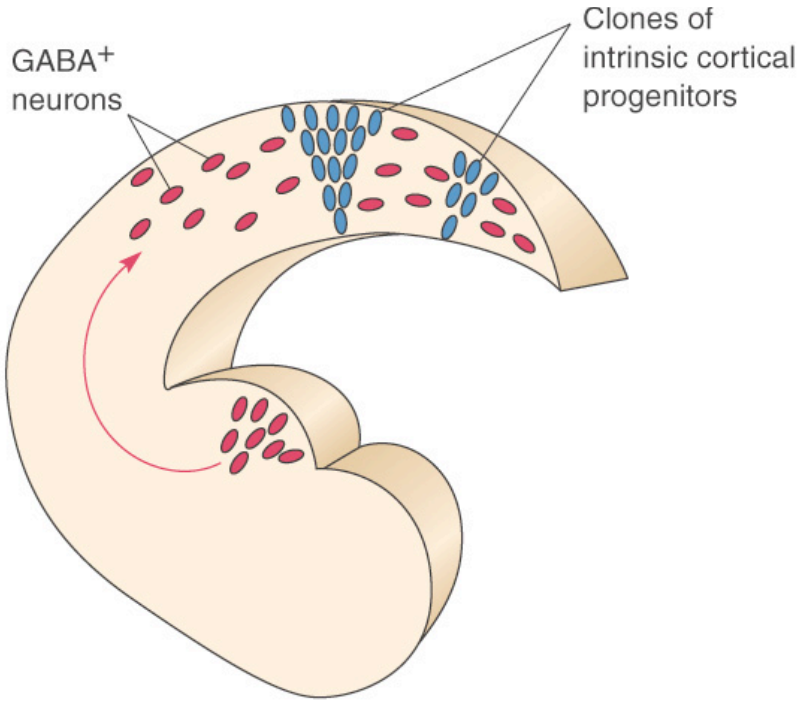
Dasen, Jessell

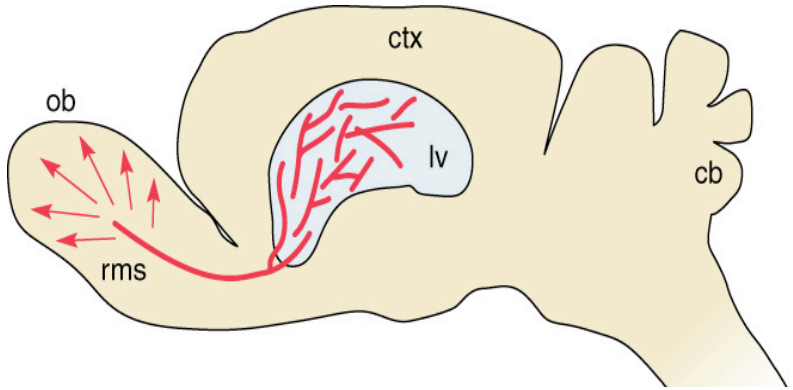
Inside-out pattern of cortical histogenesis



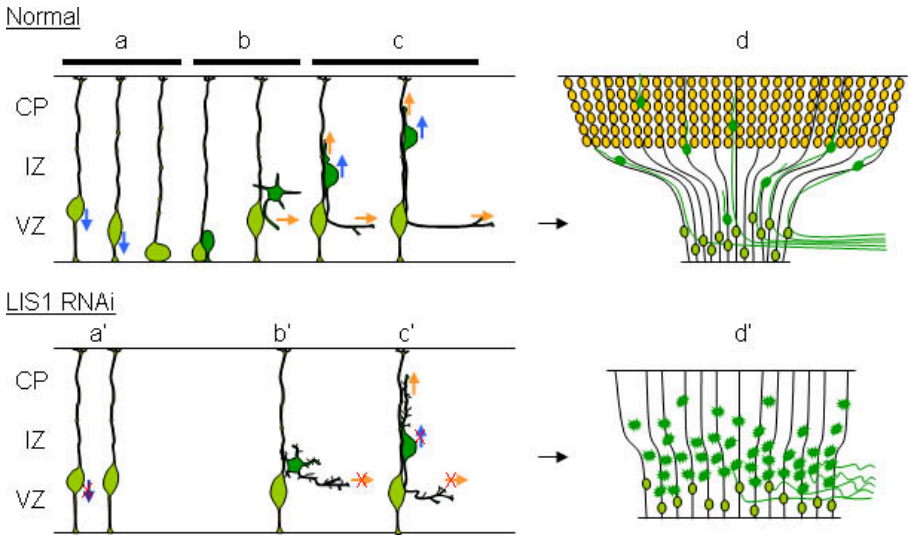
Some neurons migrate to their final destination

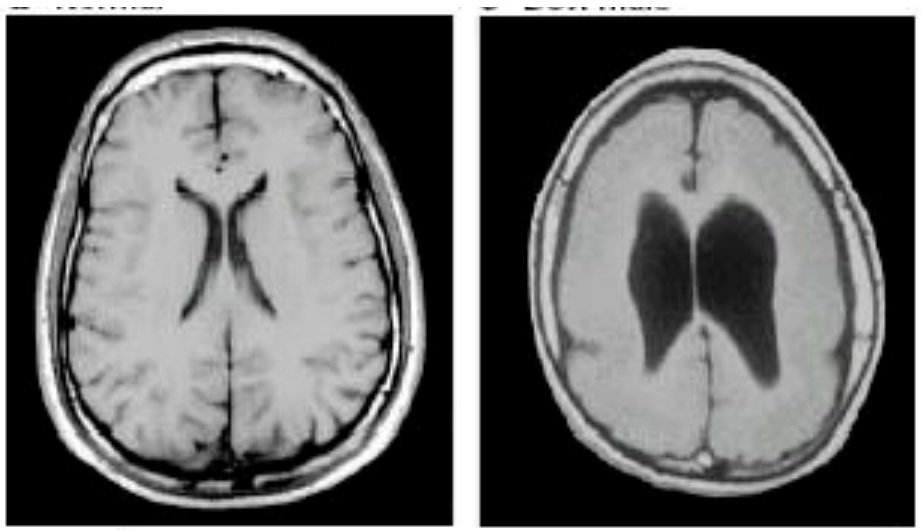






Neuronal Migration Defects: Lissencephaly

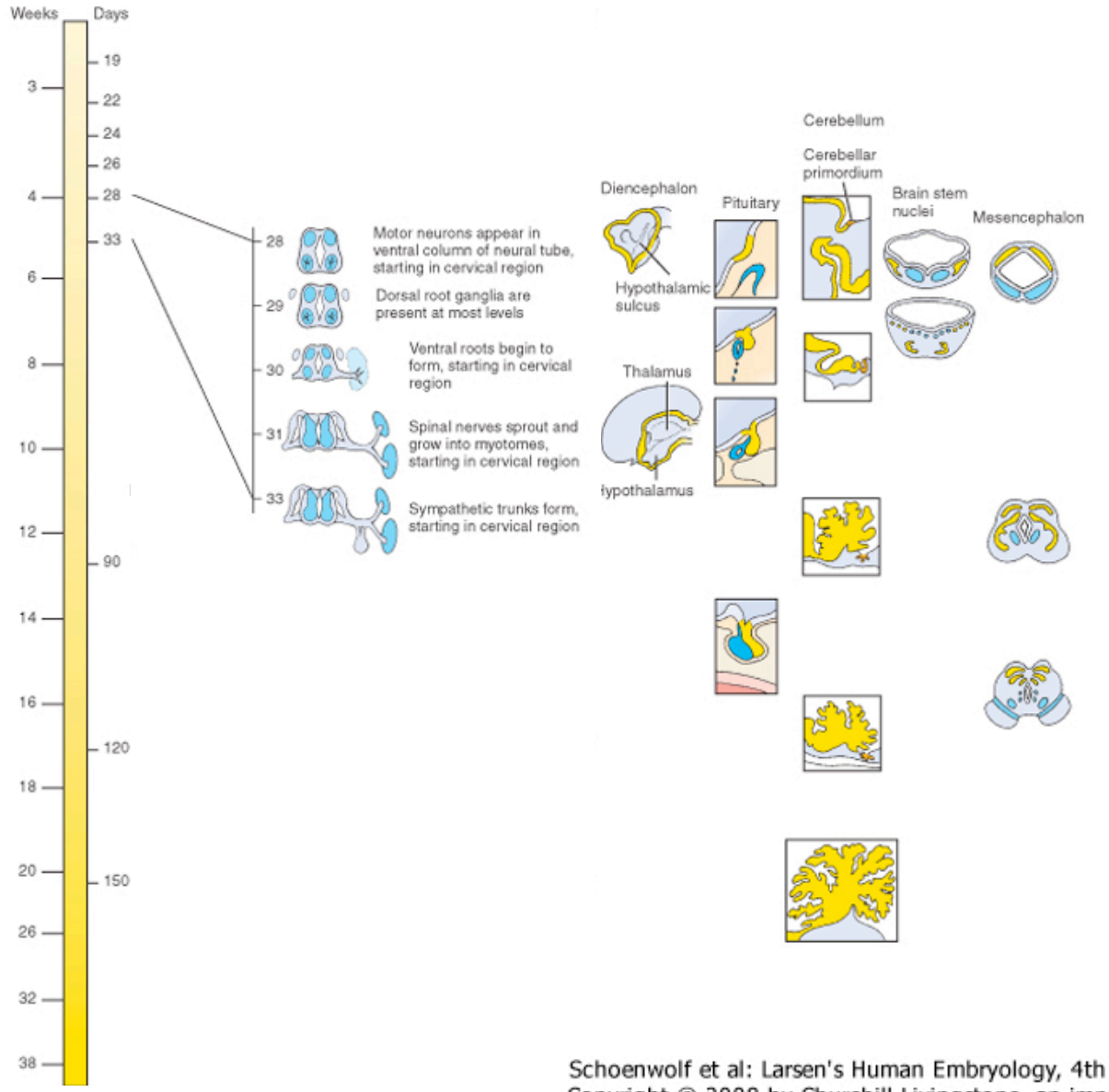




Tsai, Vallee

www.focosi.immunesig.org

Timing of CNS development in humans



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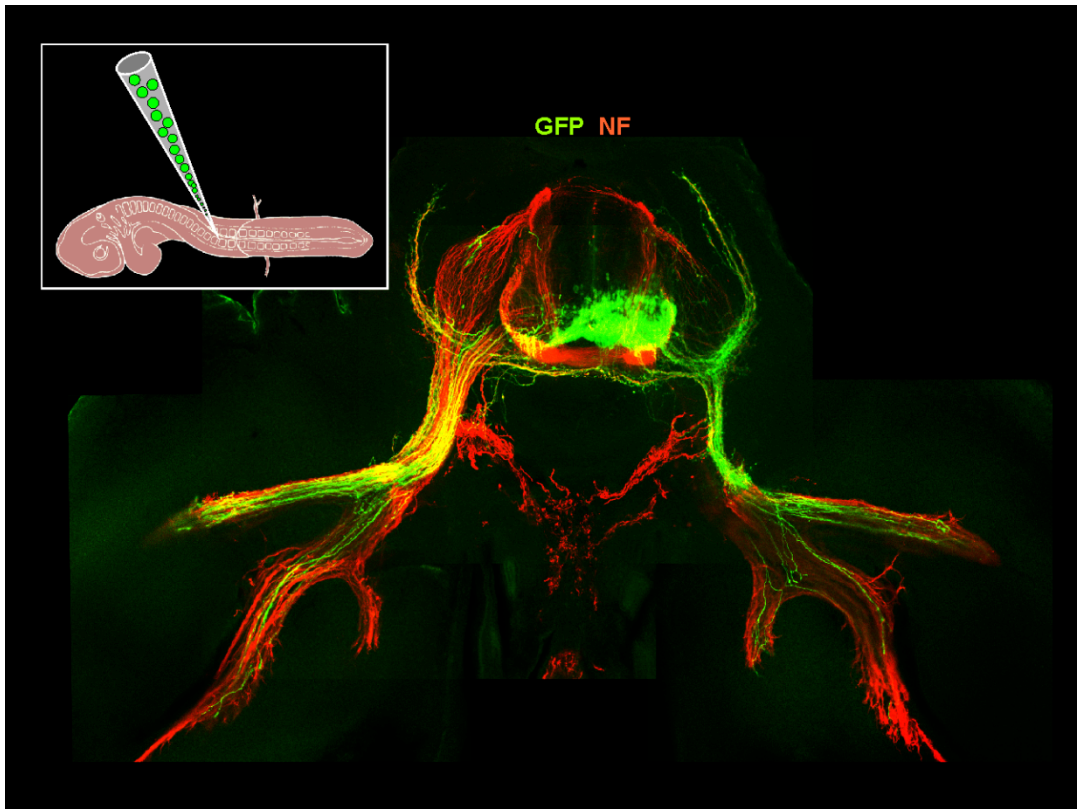
Specification of axonal connectivity

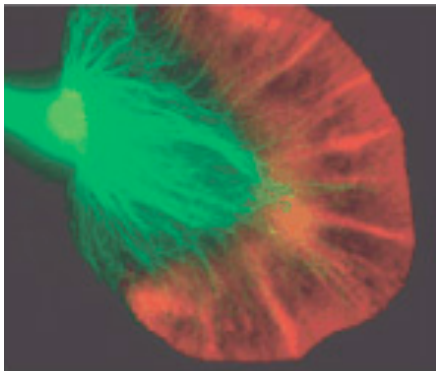


Wichterle, Lieberam, Jessell

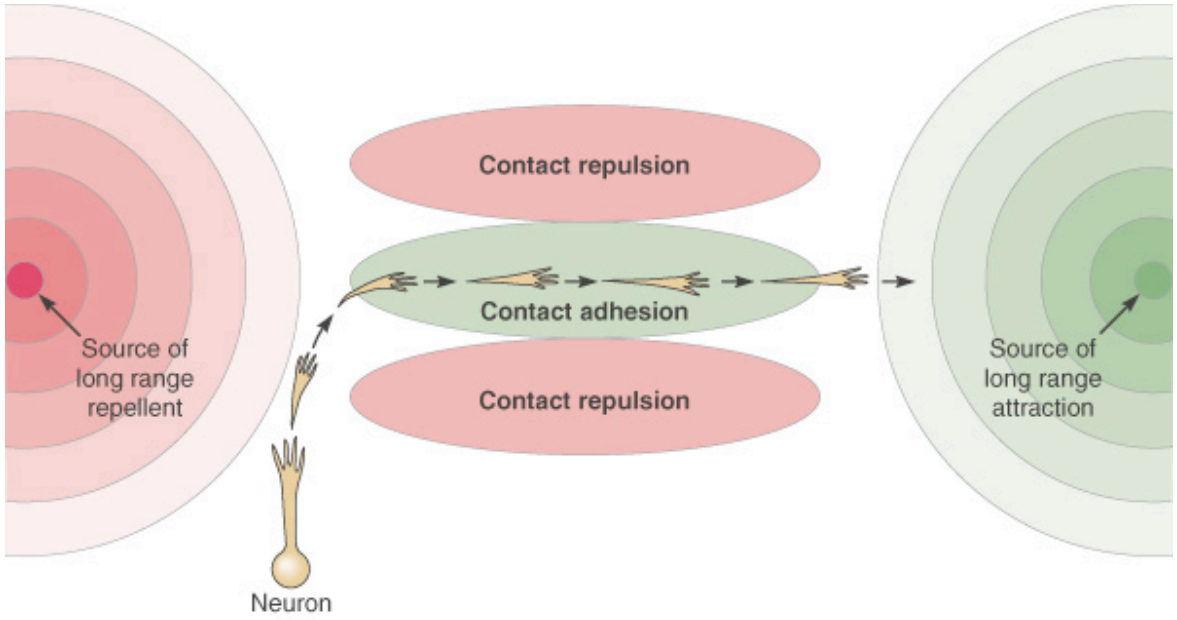
1. Pathway selection (route to target area)
2. Target selection (bind to appropriate target cells)
3. Address selection (refine/prune initial pattern)

Guidance by specific growth cone adhesion and repulsion

Microtubules
Actin



Forscher



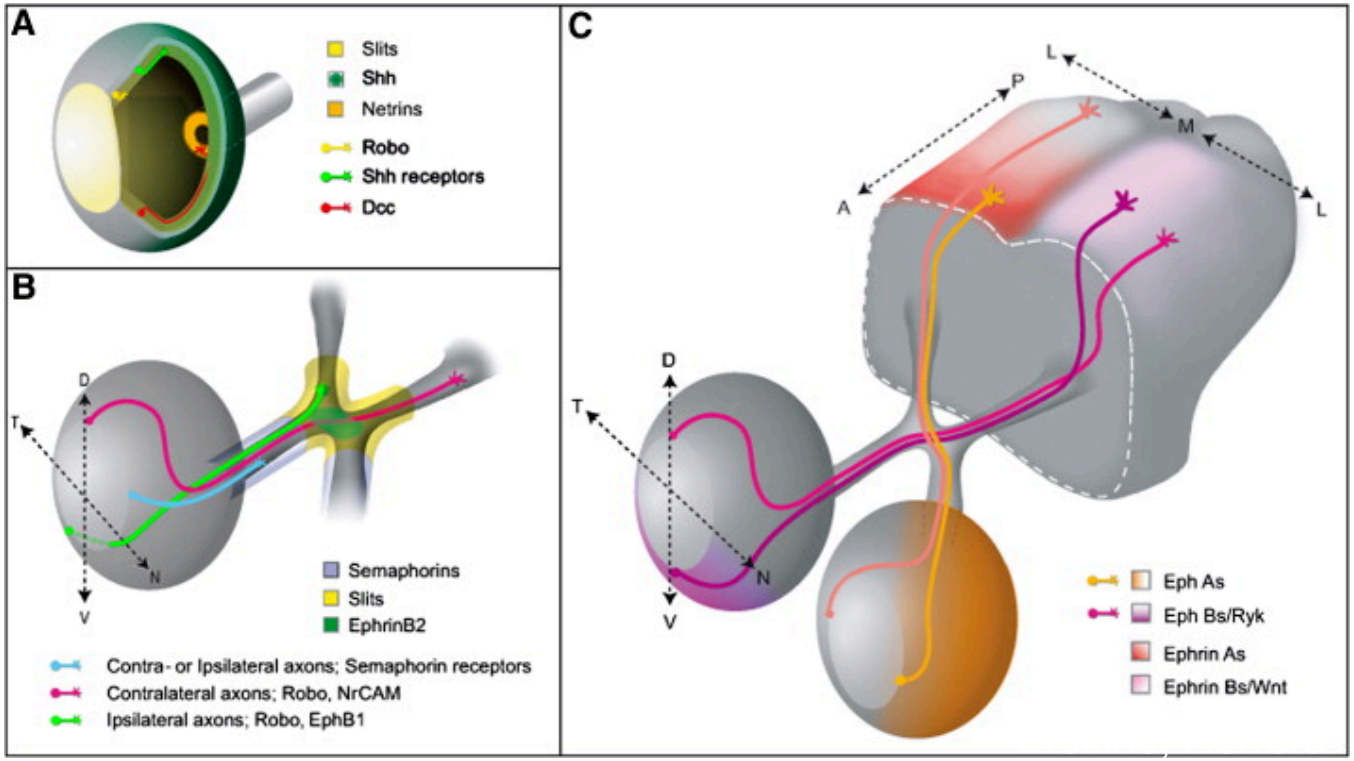
Permissive extracellular matrix protein: laminin

Repulsive cues: ephrins and semaphorins

Long range attractive cues: netrins

Secreted repulsive cues: slits

Guidance of Retinal Ganglion Axons

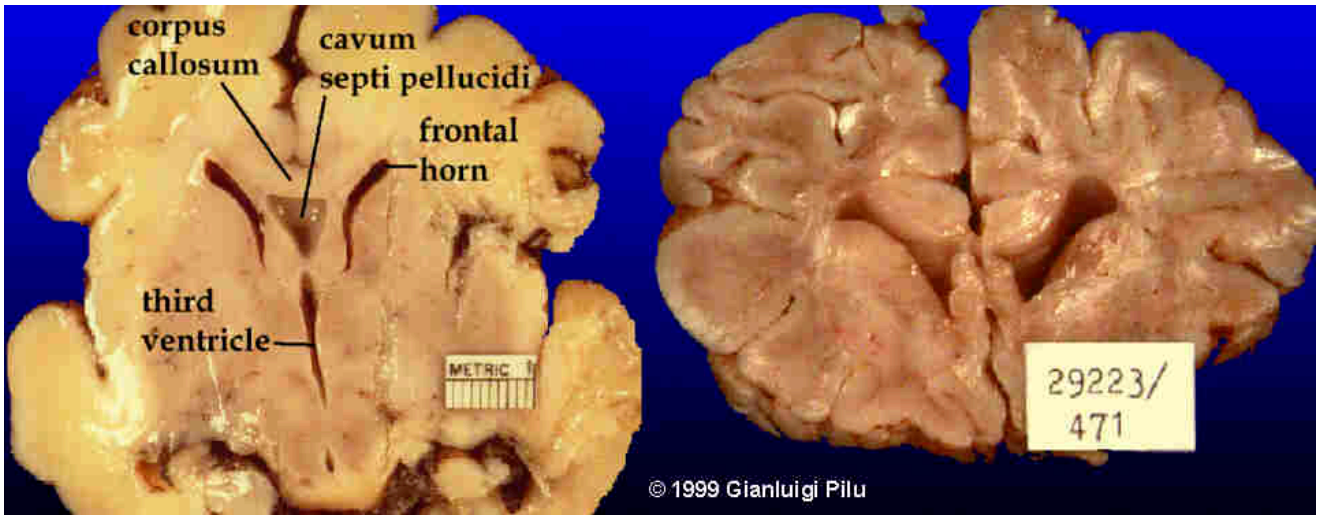


Retina: Slits, Shh and CAMs direct growth to optic disc; netrin guides axons out of the eye.

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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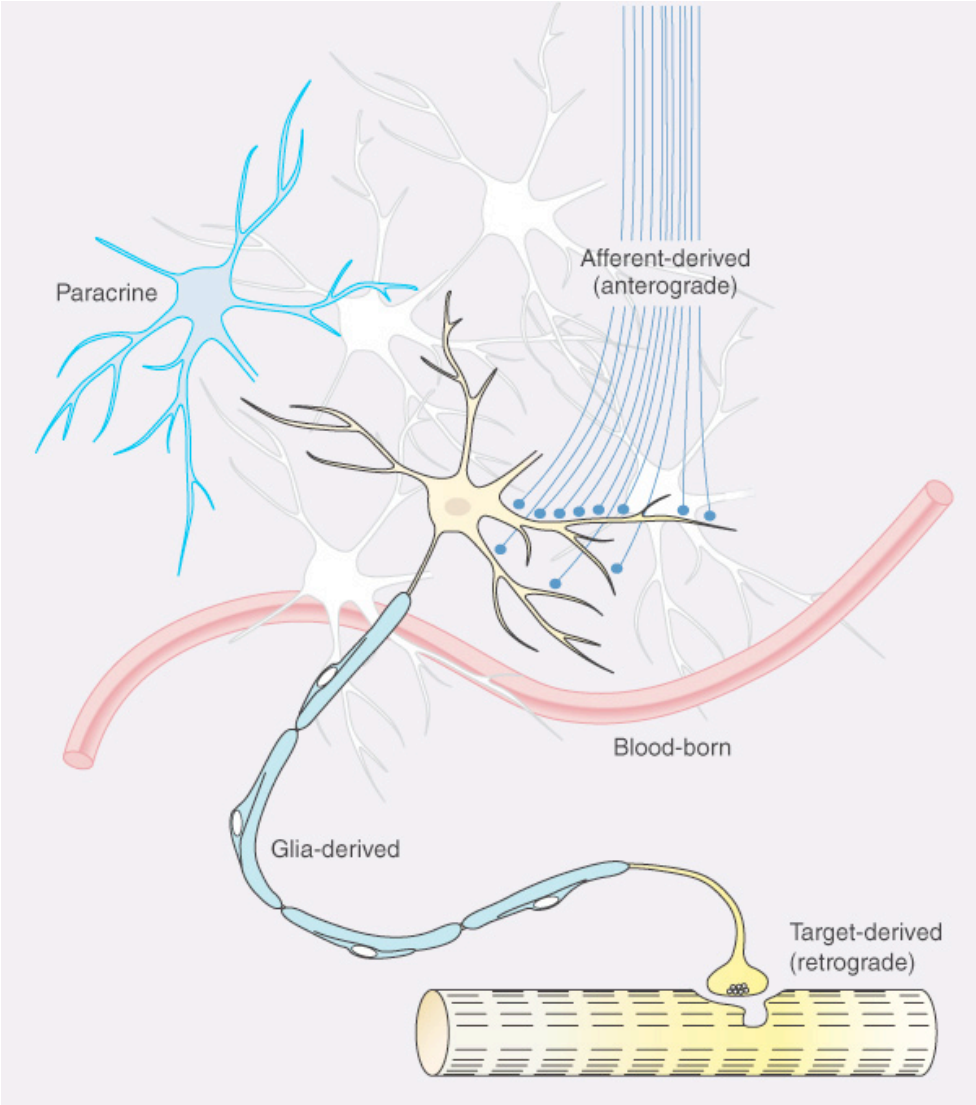
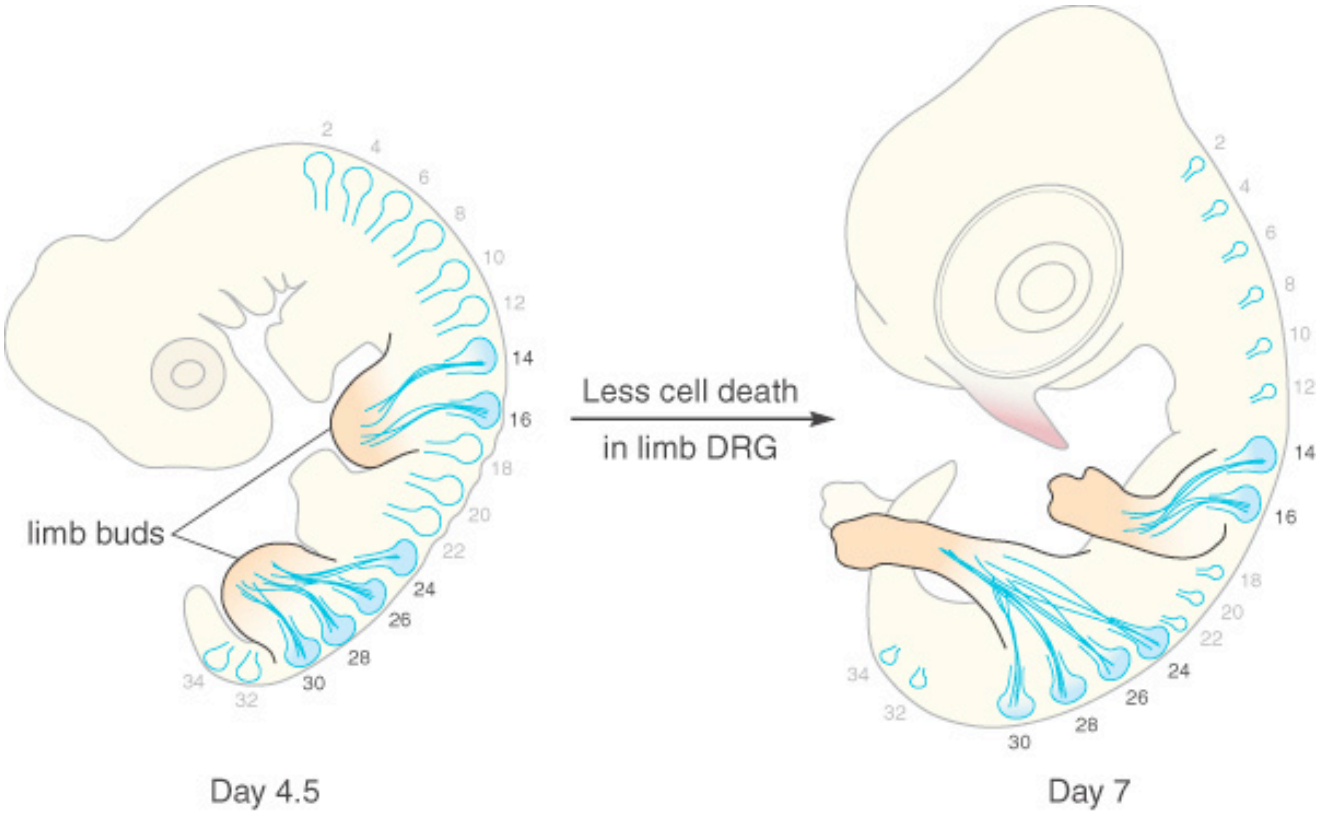
Factors influencing neuronal survival

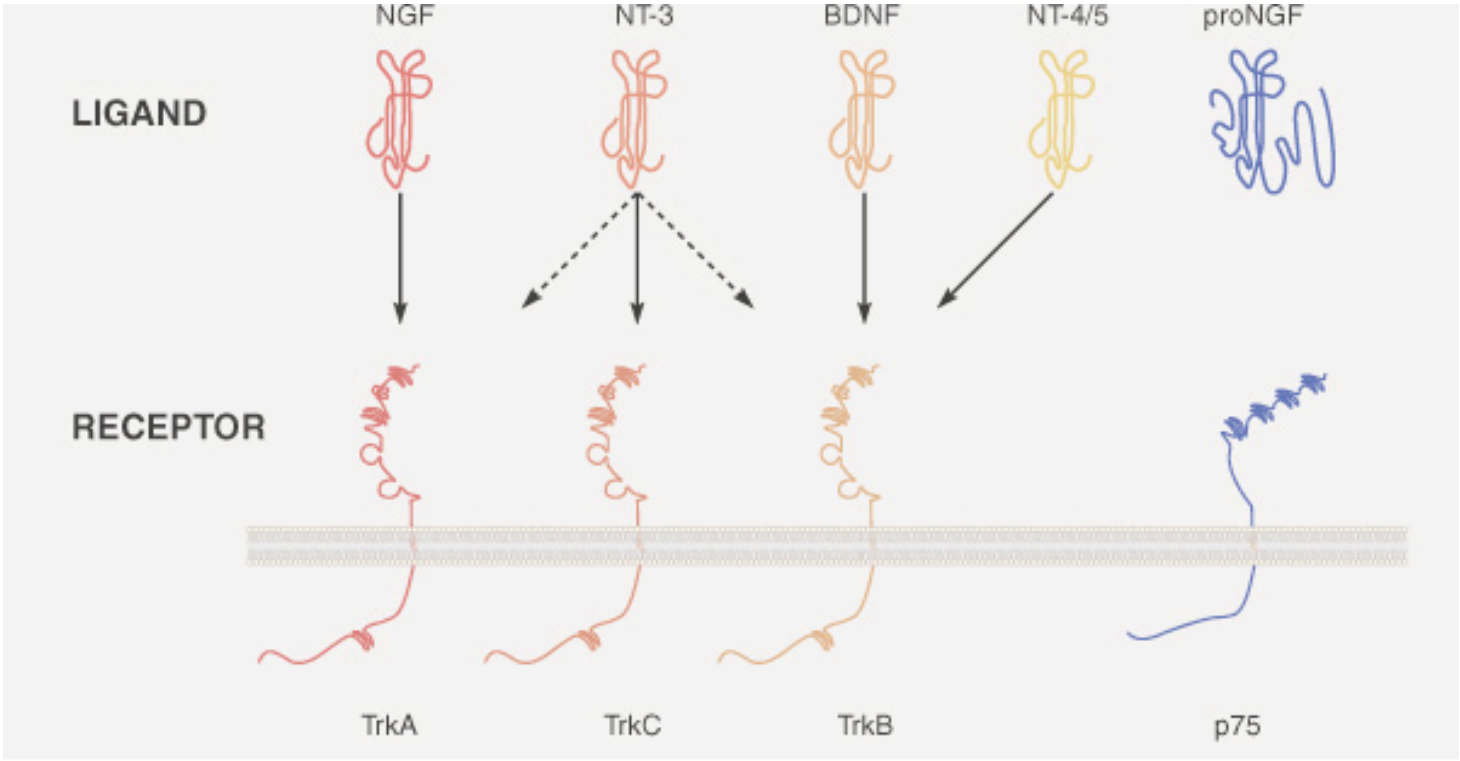


Neuronal survival correlates with innervation of target tissue



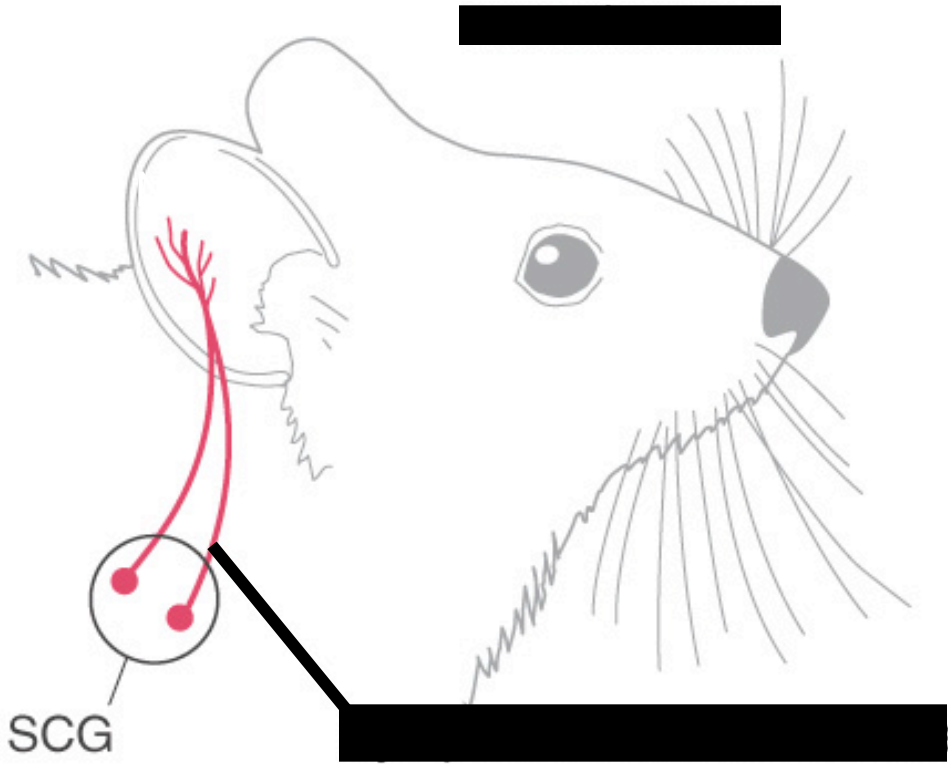
Hamburger, Levi-Montalcini

Differential requirements for neurotrophins



CELL DEATH FOLLOWING RECEPTOR ELIMINATION	70% DRG 95% SCG 70% trigeminal 0% cochlear 0% vestibular basal forebrain atrophy	20% DRG 0% SCG 20% trigeminal 50% cochlear 15% vestibular	30% DRG 60% trigeminal 15% cochlear 60% vestibular 90% nodose basal forebrain cerebellum	50% DRG reduced death in cholinergic forebrain

Neurotrophic factors influence target selection by promoting neuronal survival and differentiation

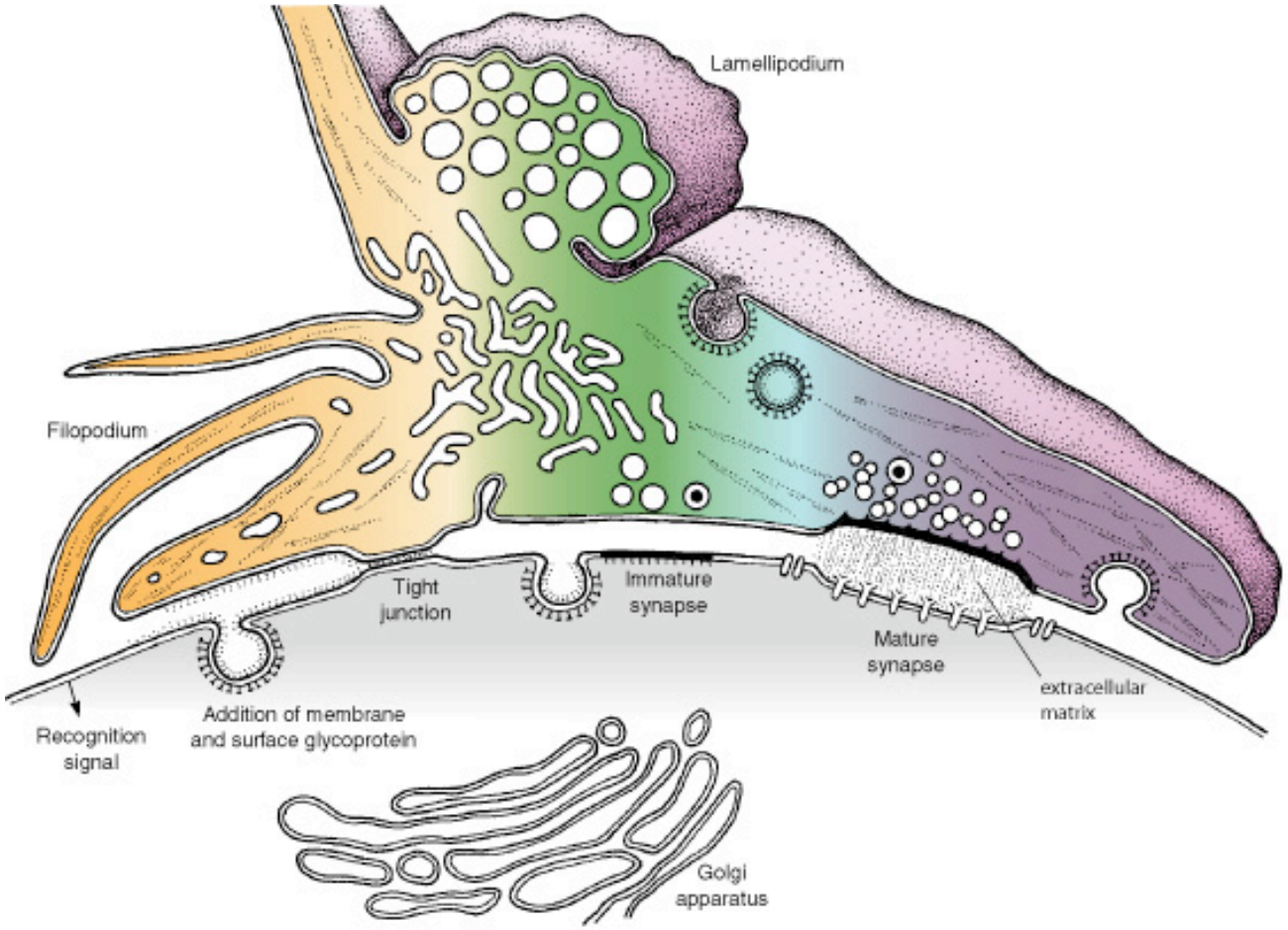


ElShamy

How to Make a Nervous System

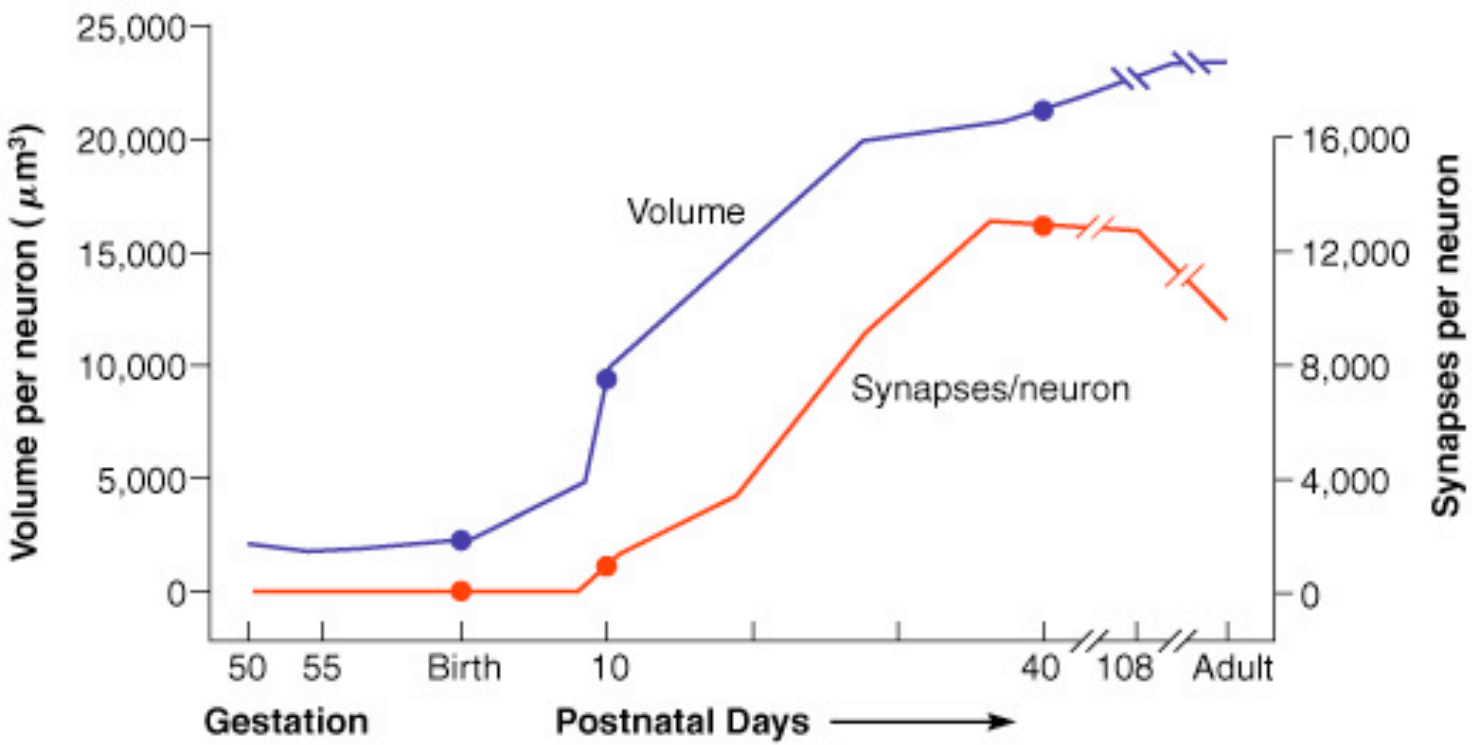
- Neural induction
- Neural tube formation
- Acquisition of a positional identity
- Birth, migration & differentiation of neurons and glia
- Axonal pathfinding and connectivity
- Binding of trophic factors for survival and differentiation
- Synapse formation, refinement and plasticity

Synapse Formation



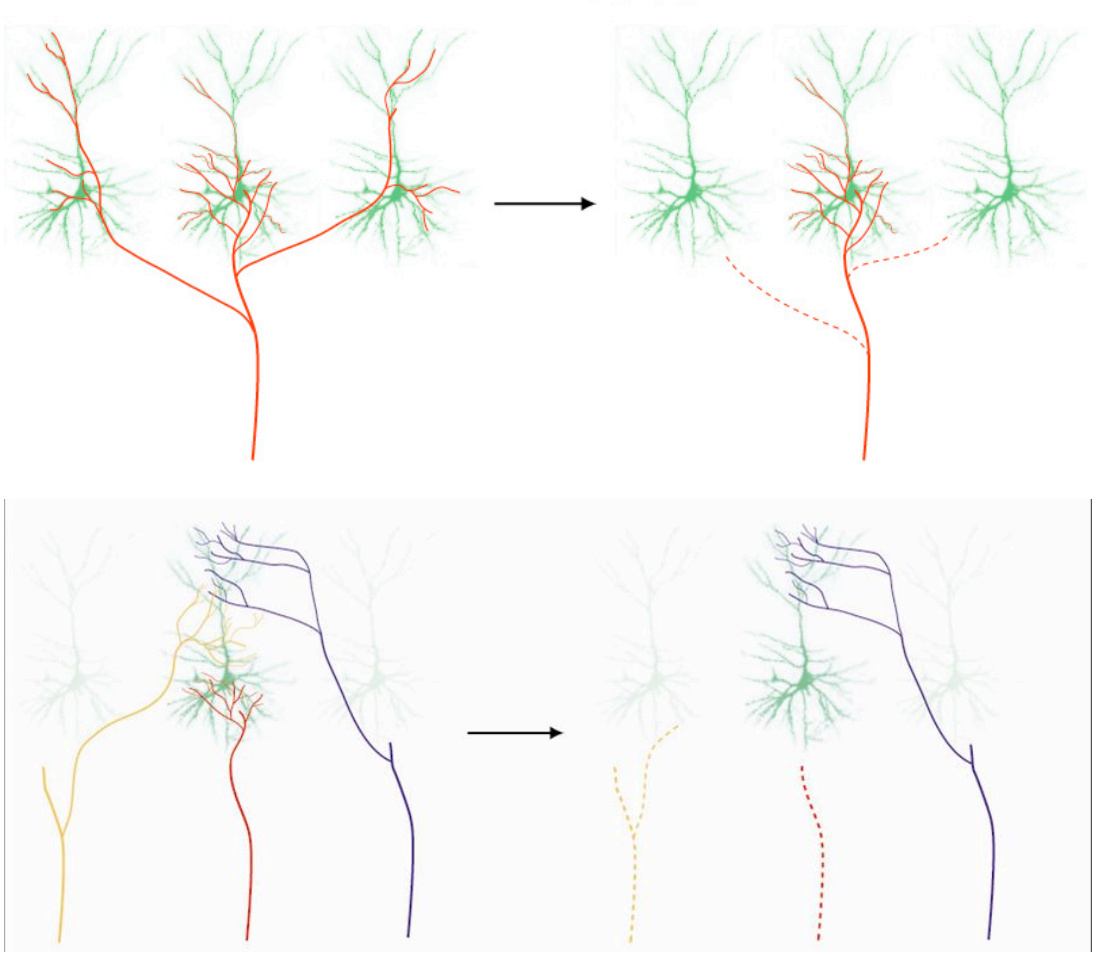
Rees

Growth and pruning of synaptic elements during development



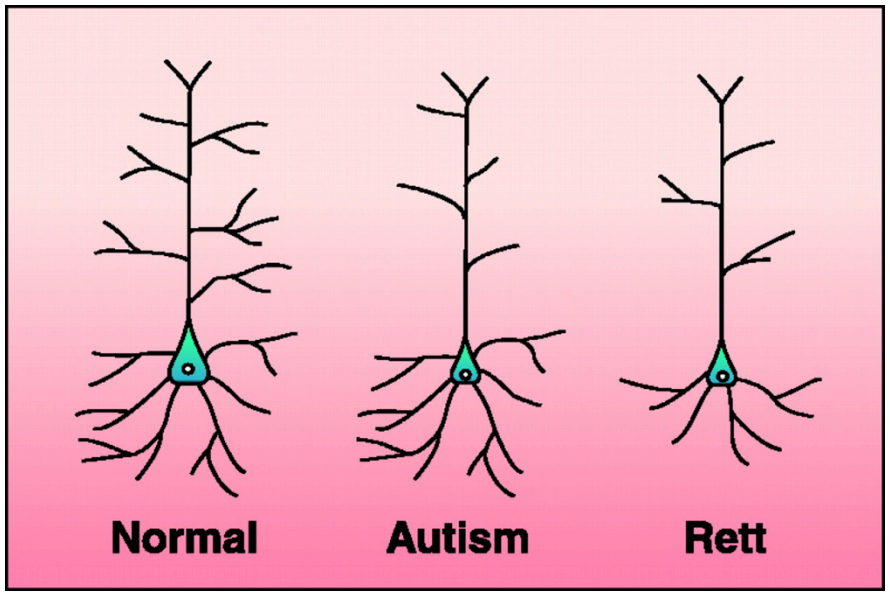
Cragg

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

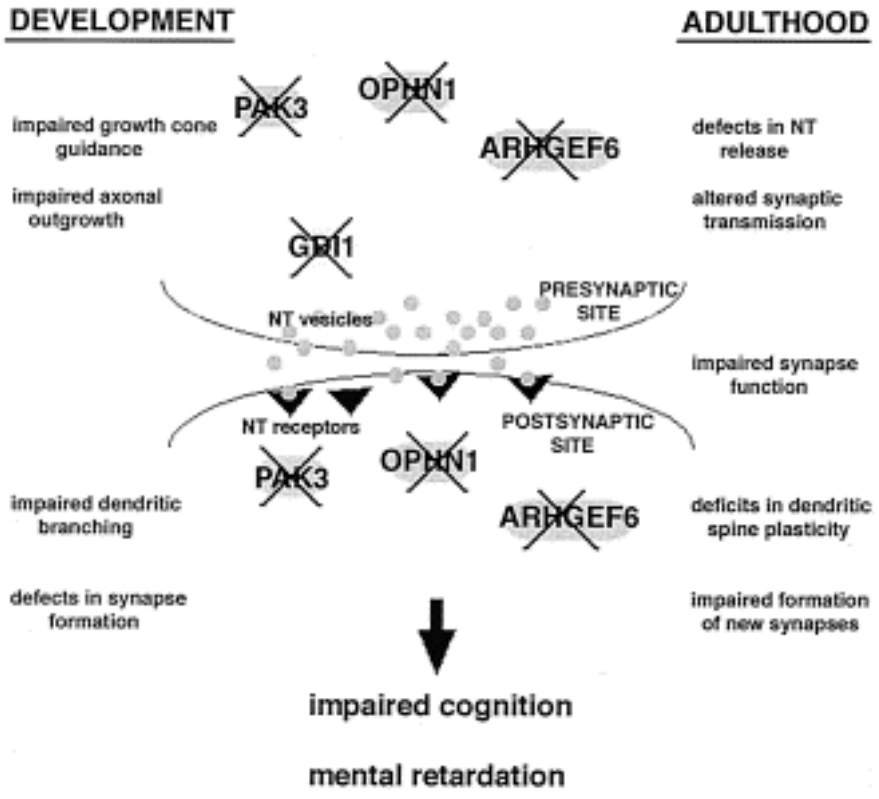


Impaired synapse formation and disease

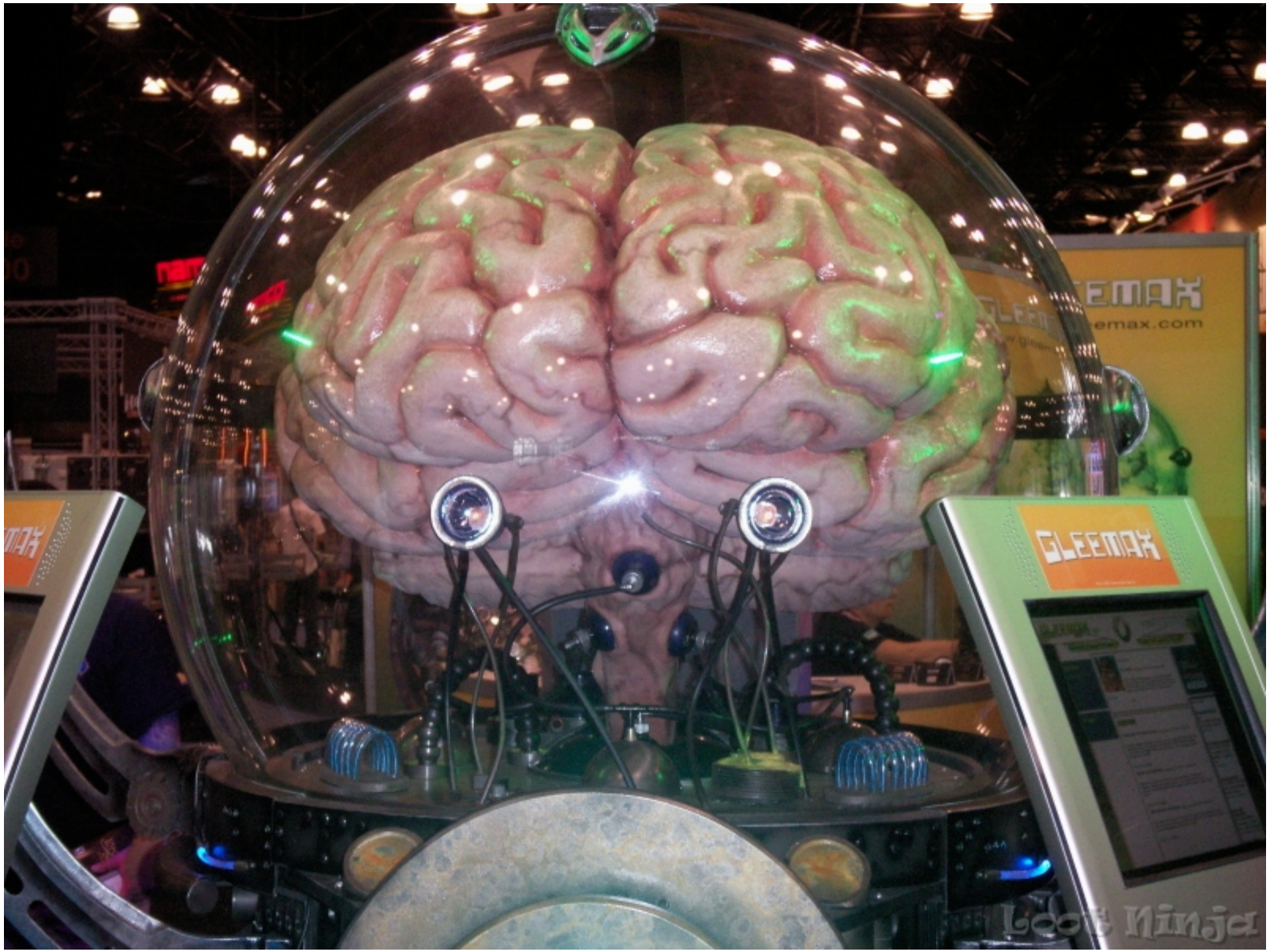
Autism and Rett Syndrome



X-Linked Mental Retardation



Chechlacz, Gleeson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