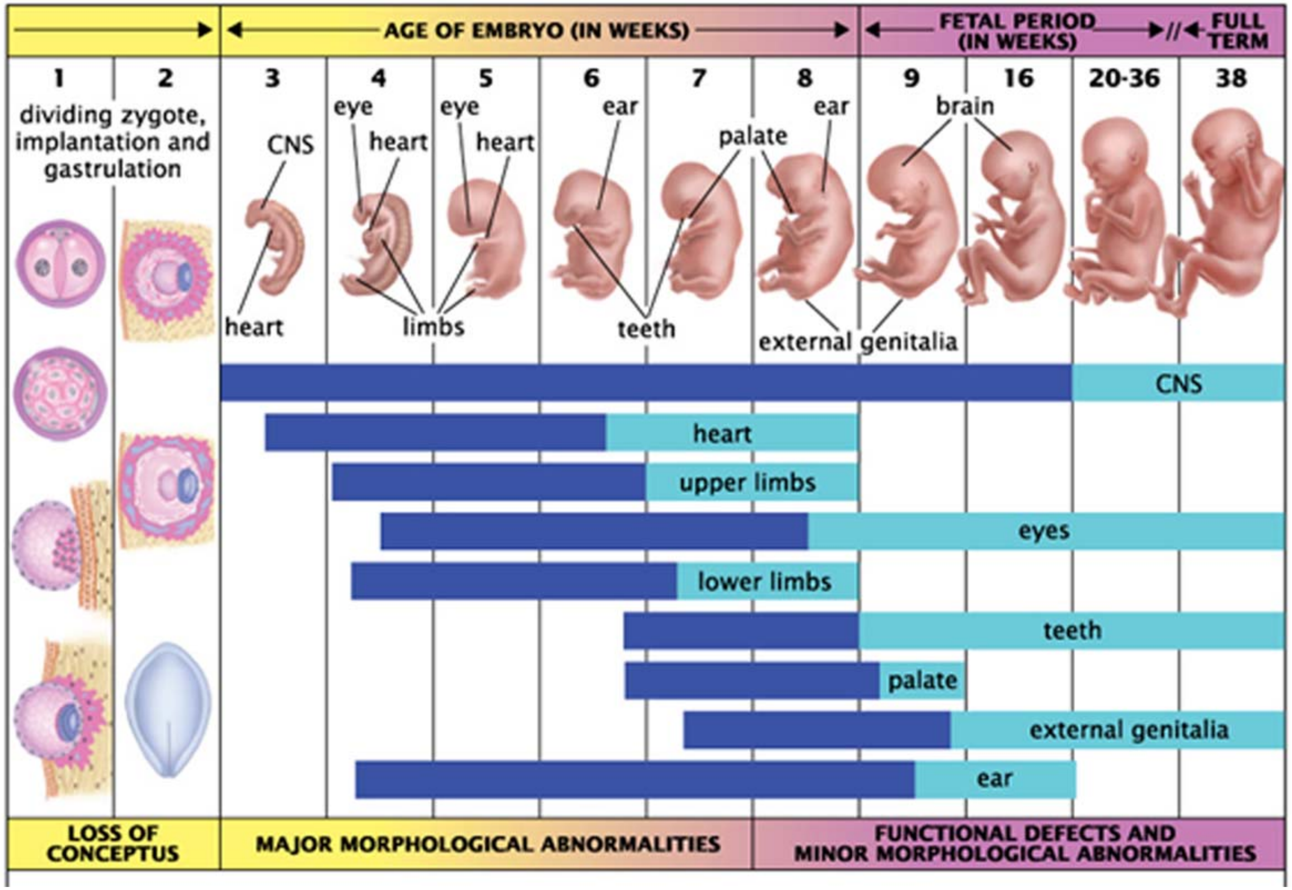
# Brain development: from an egg to a brain

## 3 phases of prenatal development

Germinal Period: period of the zygote

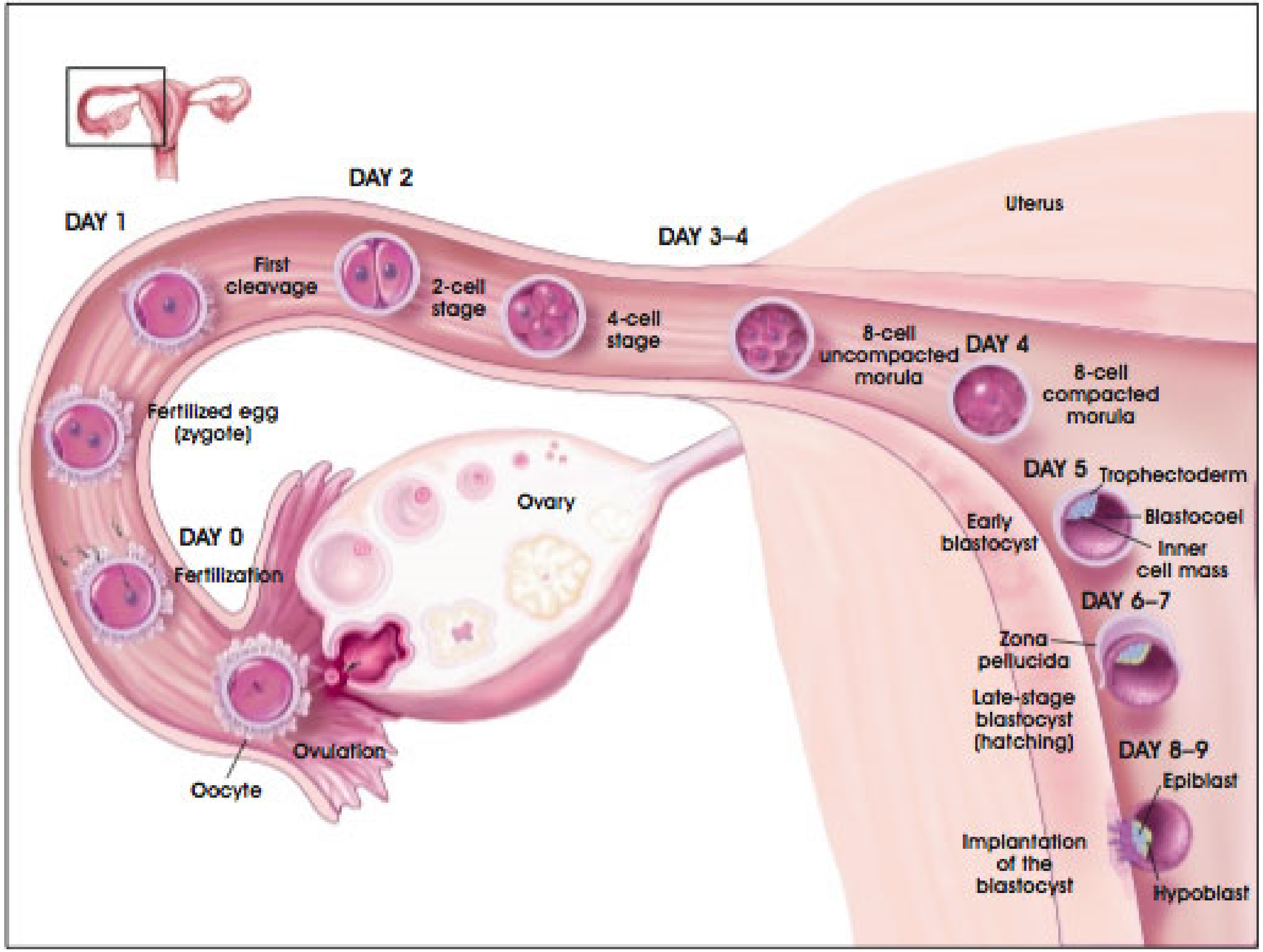
Embryo period: 3[rd] to 8[th] week

Fetus period: 9[th] week to birth



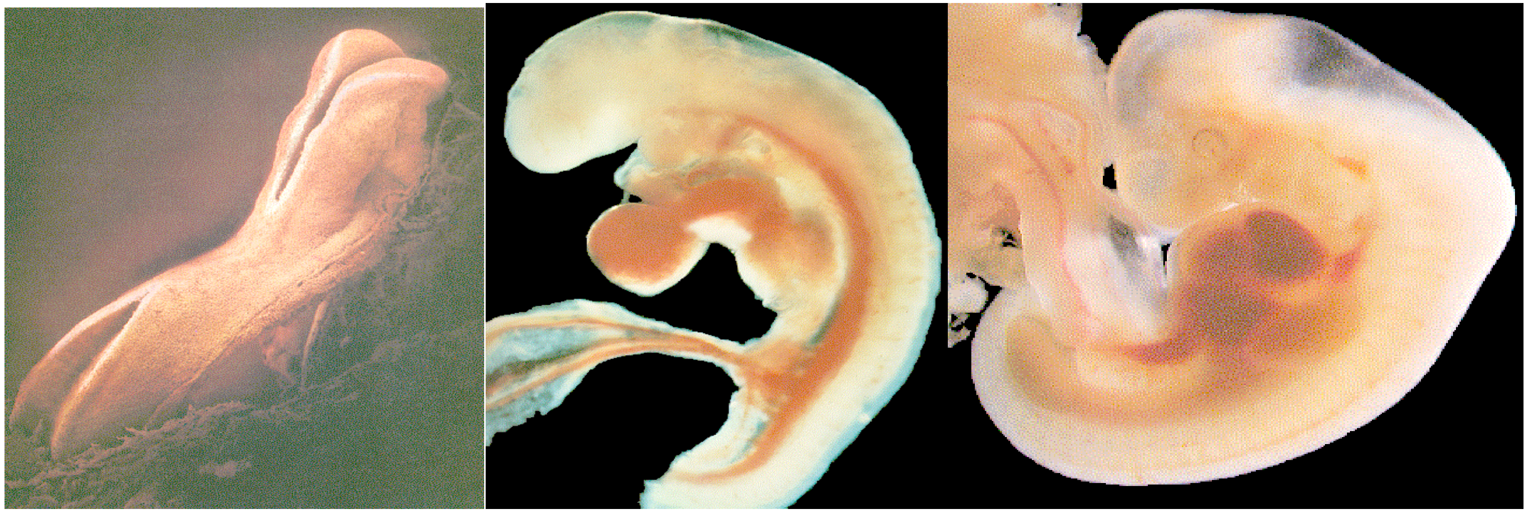

http://www.embryology.ch/genericpages/moduleembryoen.html

# Germinal period

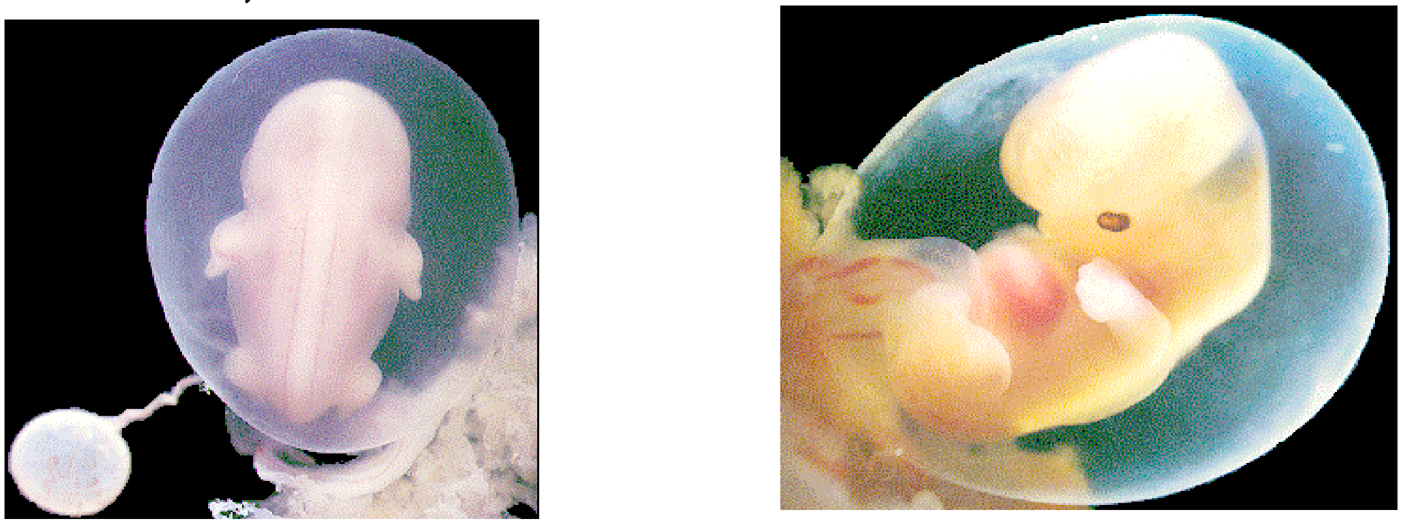


## The Embryo

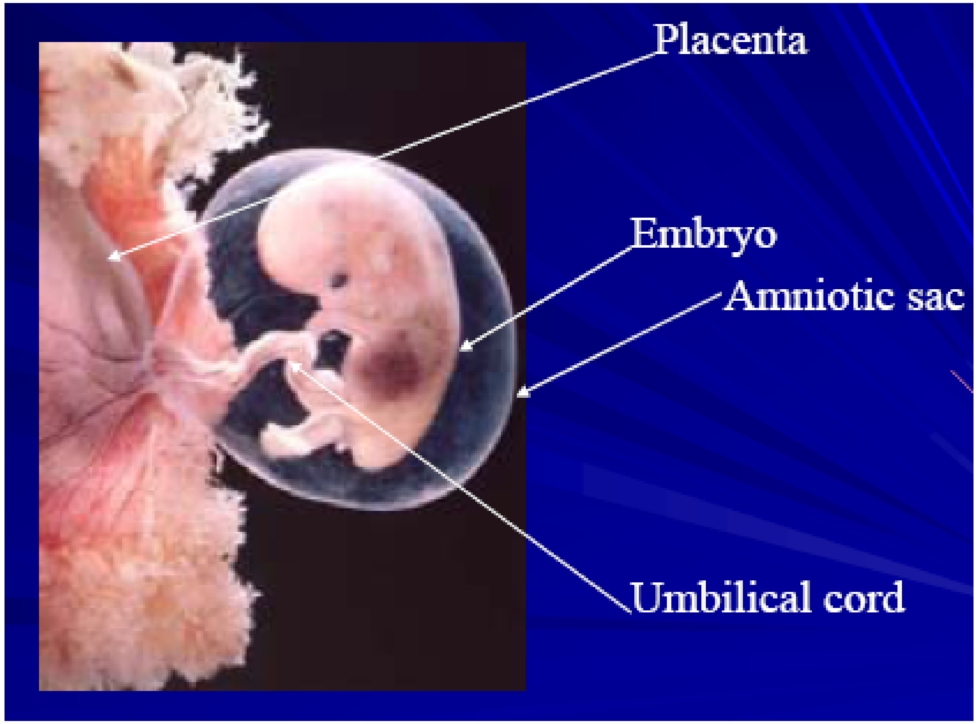
Week 3, 4, 5

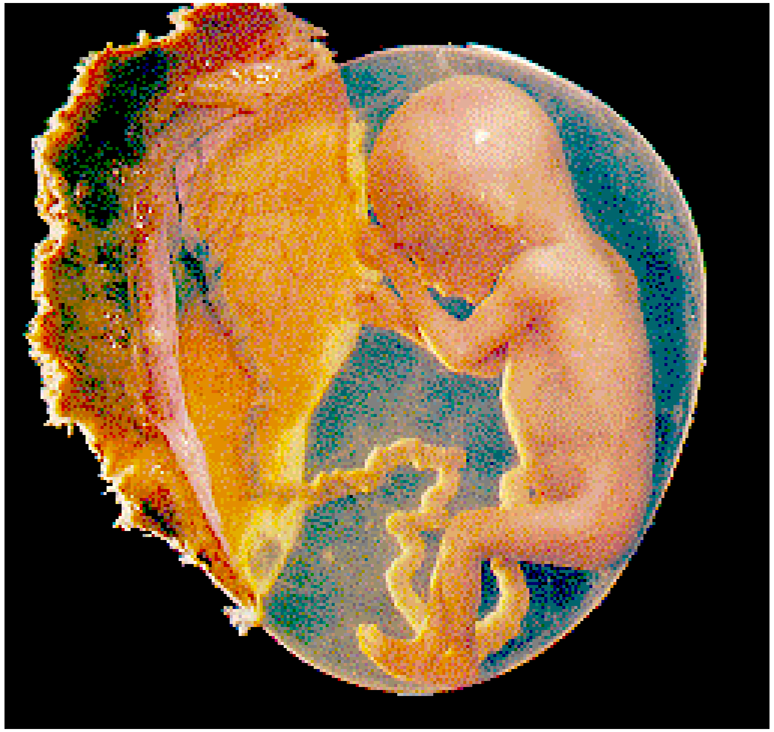


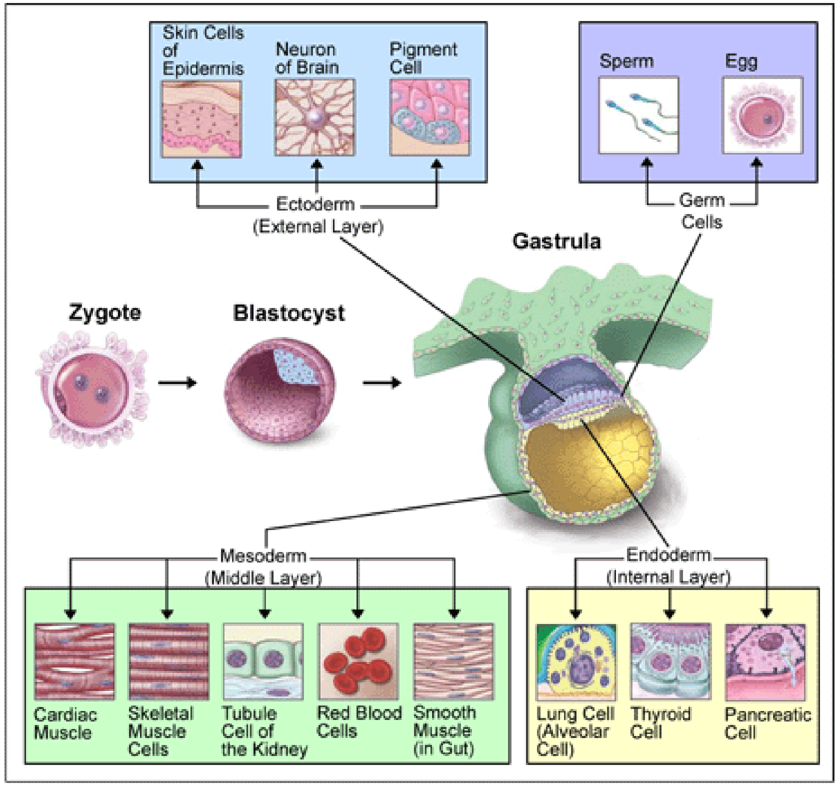
Week 6,8

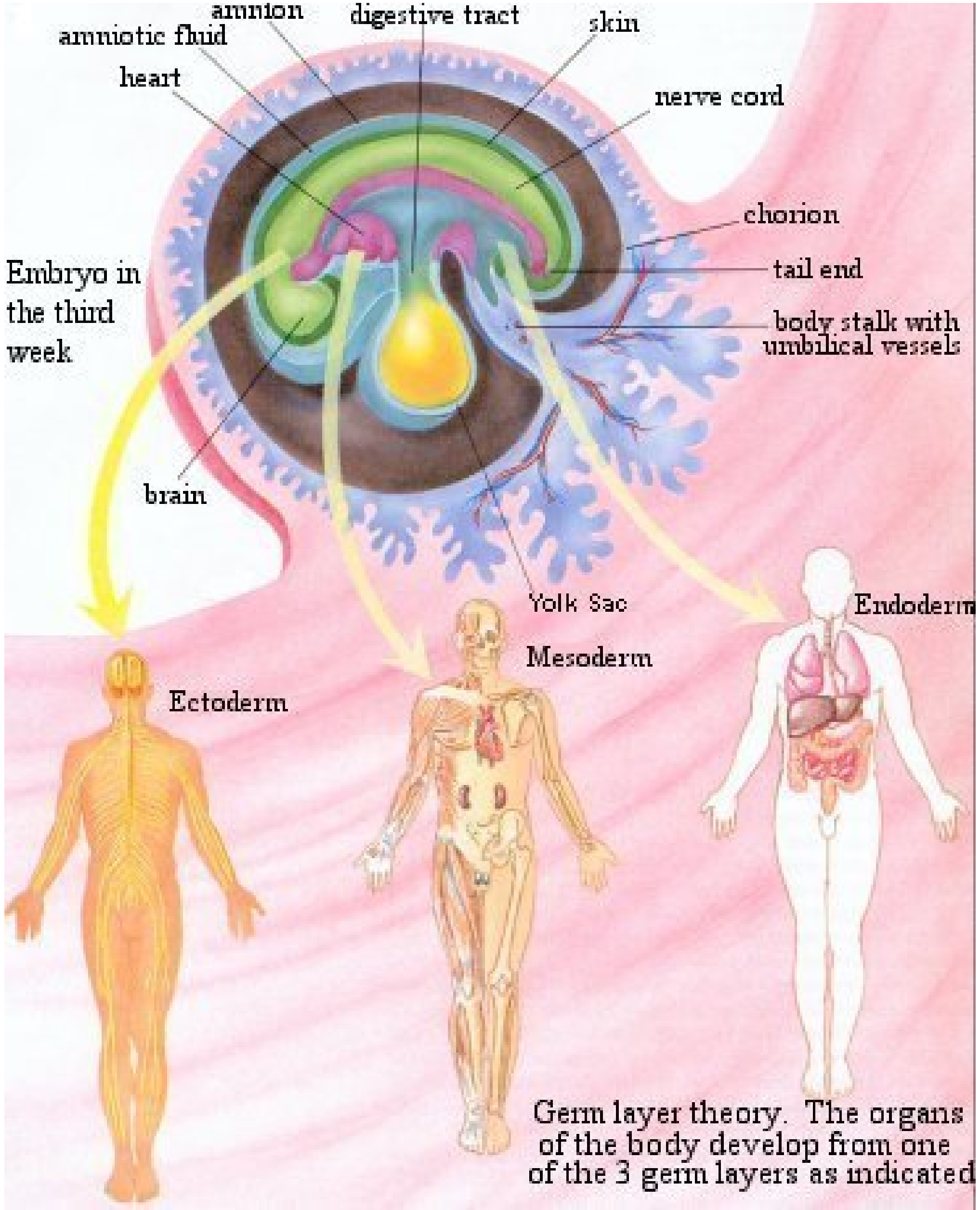


**The fetus:** week 16



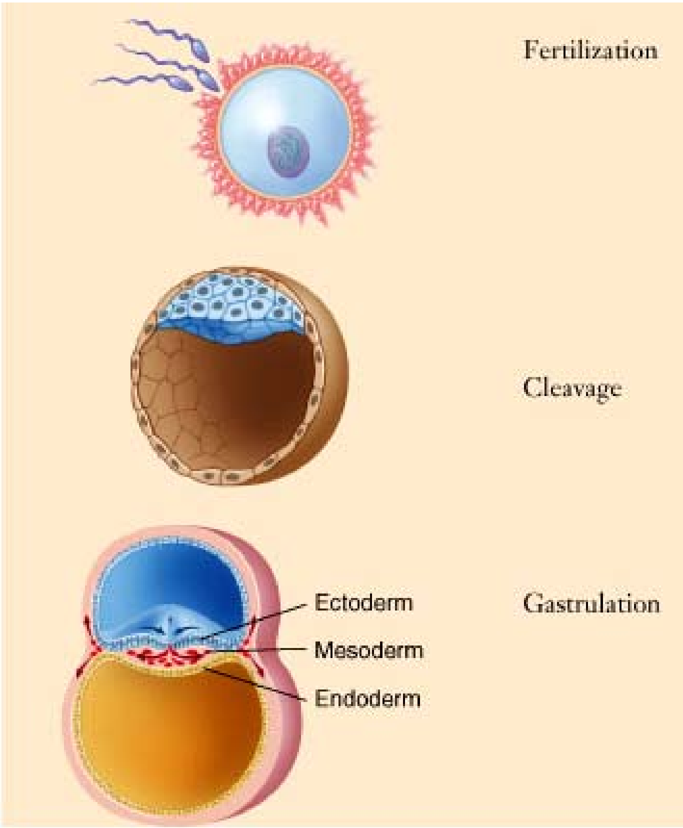



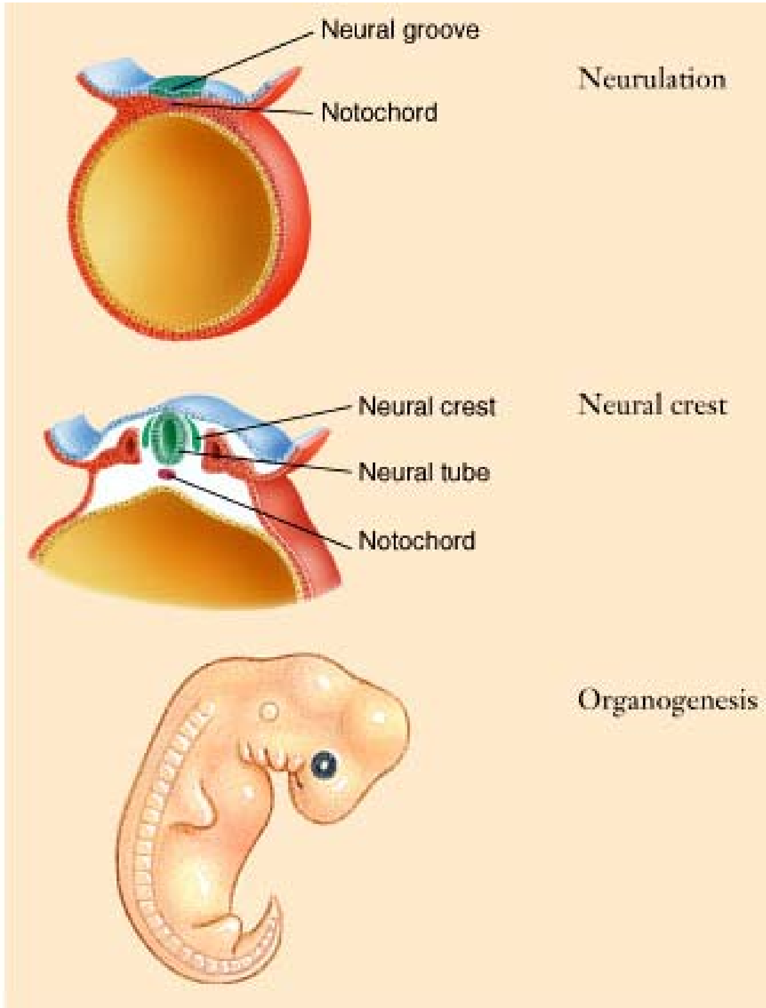

Skin Cells of Epidermis
Neuron of Brain
Pigment Cell
Sperm
Egg
Ectoderm (External Layer)
Germ Cells
Gastrula
Zygote
Blastocyst
Mesoderm (Middle Layer)
Endoderm (Internal Layer)
Cardiac Muscle
Skeletal Muscle Cells
Tubule Cell of the Kidney
Red Blood Cells
Smooth Muscle (in Gut)
Lung Cell (Alveolar Cell)
Thyroid Cell
Pancreatic Cell


amnion
amniotic fluid
digestive tract
skin
heart
nerve cord
chorion
tail end
body stalk with umbilical vessels
Embryo in the third week
brain
Yolk Sac
Endoderm
Mesoderm
Ectoderm
Germ layer theory. The organs of the body develop from one of the 3 germ layers as indicated

# Early development process

Fertilization
Cleavage
Blastrulation
Gastrulation
Neurulation
organogenesis



# Neurulation

The ectoderm layer (outermost layer) of the fertilized egg folds and fuses to form the neural tube surrounding a fluid-filled cavity.

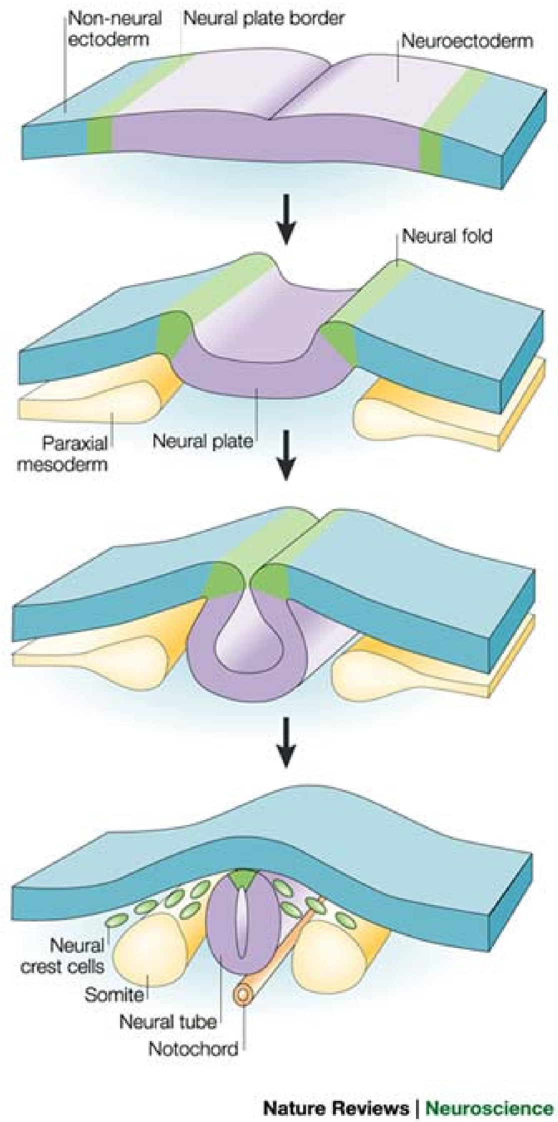
The open ends of the neural tube close around 25 days, with anterior regions giving rise to the brain, and posterior the spinal cord.

The cavity gives rise to the ventricular system, and the cells lining the cavity create the neurons and glia.

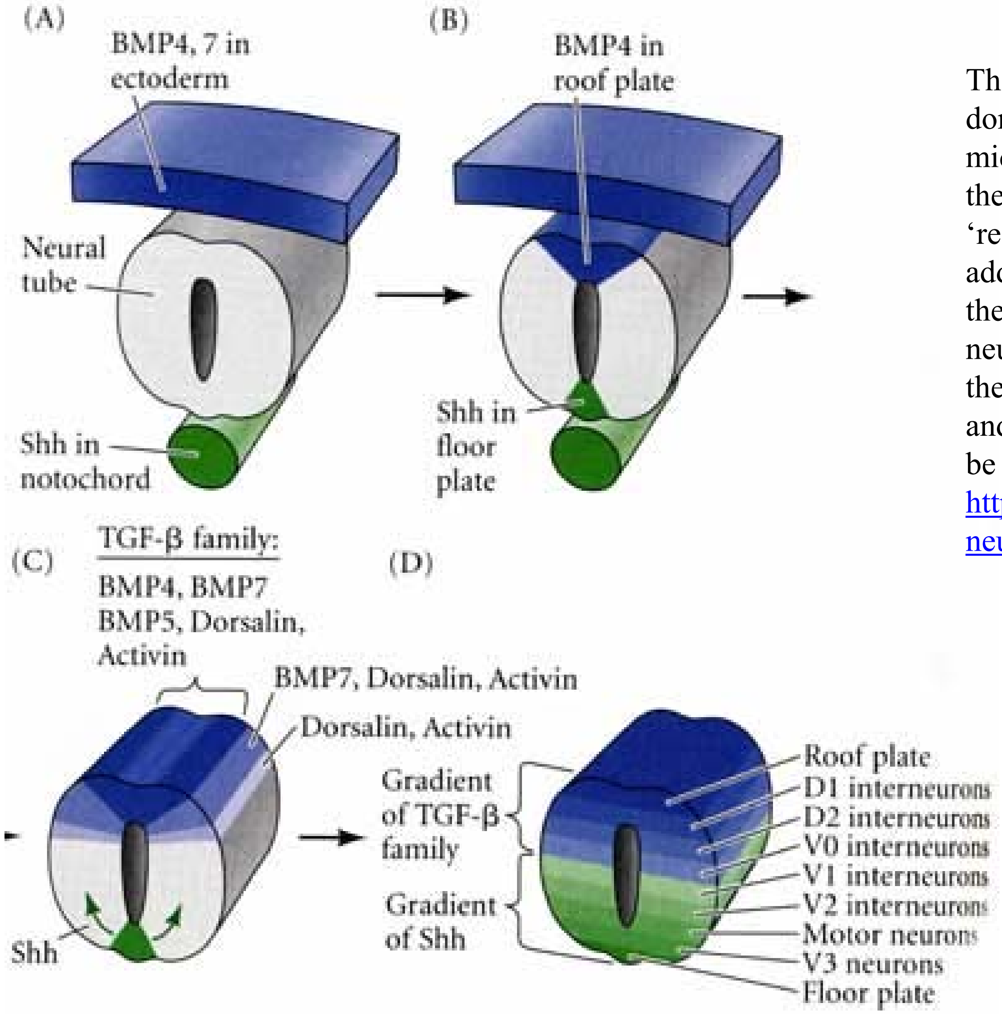
Neural crest becomes PNS

Neural tube becomes CNS

Somites become spinal vertebrae

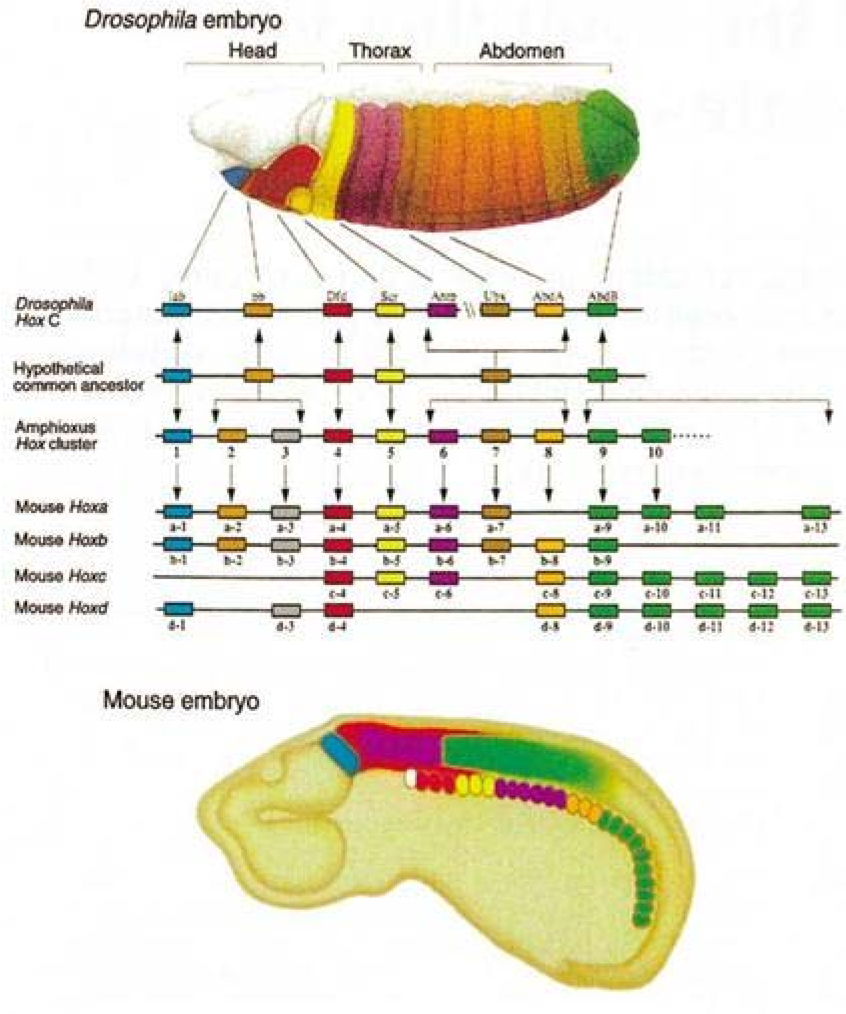



http://www.nature.com/nrn/journal/v4/n10/images/nrn1219-f1.jpg

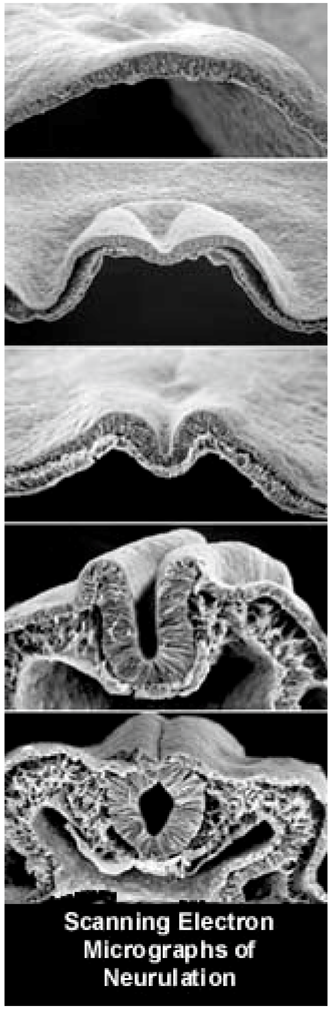


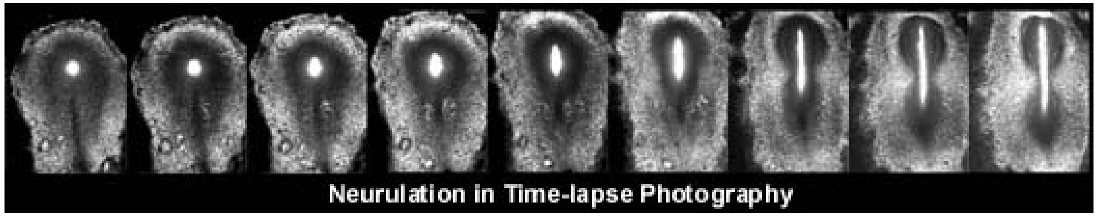

The double gradient — BMP4 spreading ventrally from the dorsal midline, Shh spreading dorsally from the ventral midline — sets up a pattern of regional specification, where the identity of neurons in the tube can be determined by just 'reading' the relative concentrations of the two factors. In addition, identity along the longitudinal axis is specified by the pattern of expression of the Hox genes. The process of neurulation sets aside a tube of tissue dedicated to forming the central nervous system, and establishes a dorsal-ventral and anterior-posterior coordinate system that allows cells to be parceled into unique fates.
http://scienceblogs.com/pharyngula/2007/03/22/basics-neurulation/

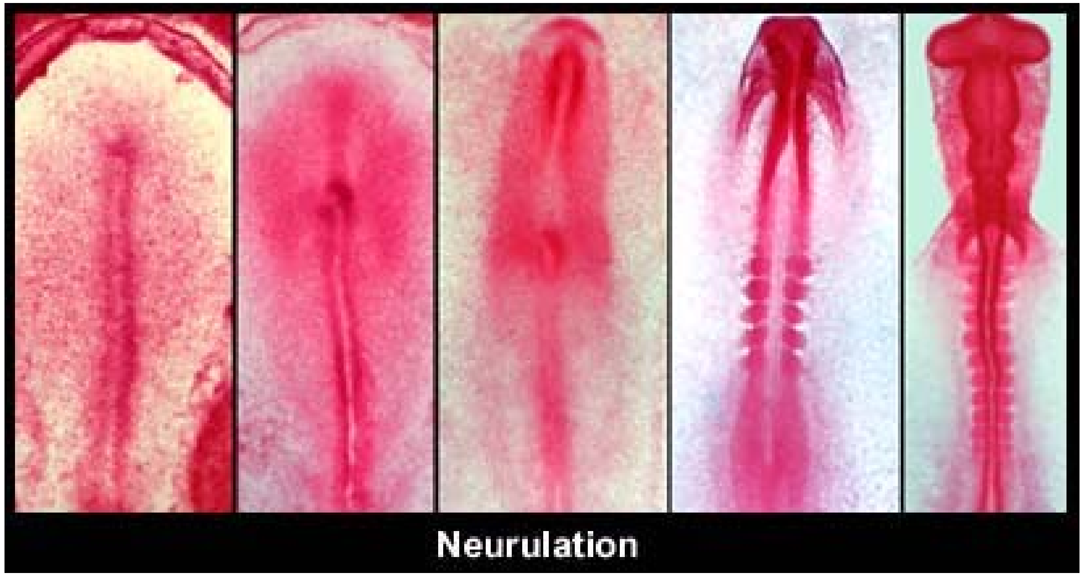
# Longitudinal axis specified by the pattern of expression of the Hox genes




**Homeobox** and **Homeodomain**: The homeobox is a 180-basepair sequence of DNA that has been found in many regulatory genes. The homeodomain is the 60-amino acid stretch that corresponds to the translated homeobox. This part of the protein is a DNA binding sequence; it forms three helices that nestle neatly into a groove formed by the DNA spiral, and the amino acids in these regions assign binding specificity to particular sequences in the DNA.


Scanning Electron Micrographs of Neurulation


Neurulation in Time-lapse Photography

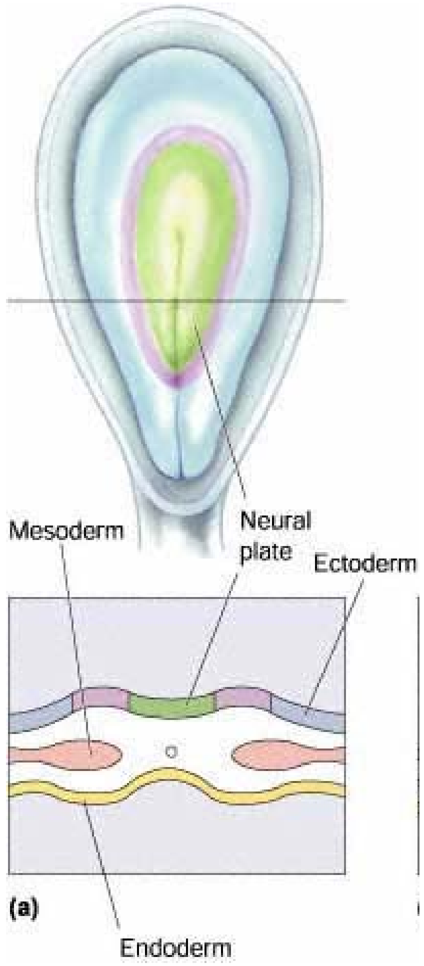

Neurulation

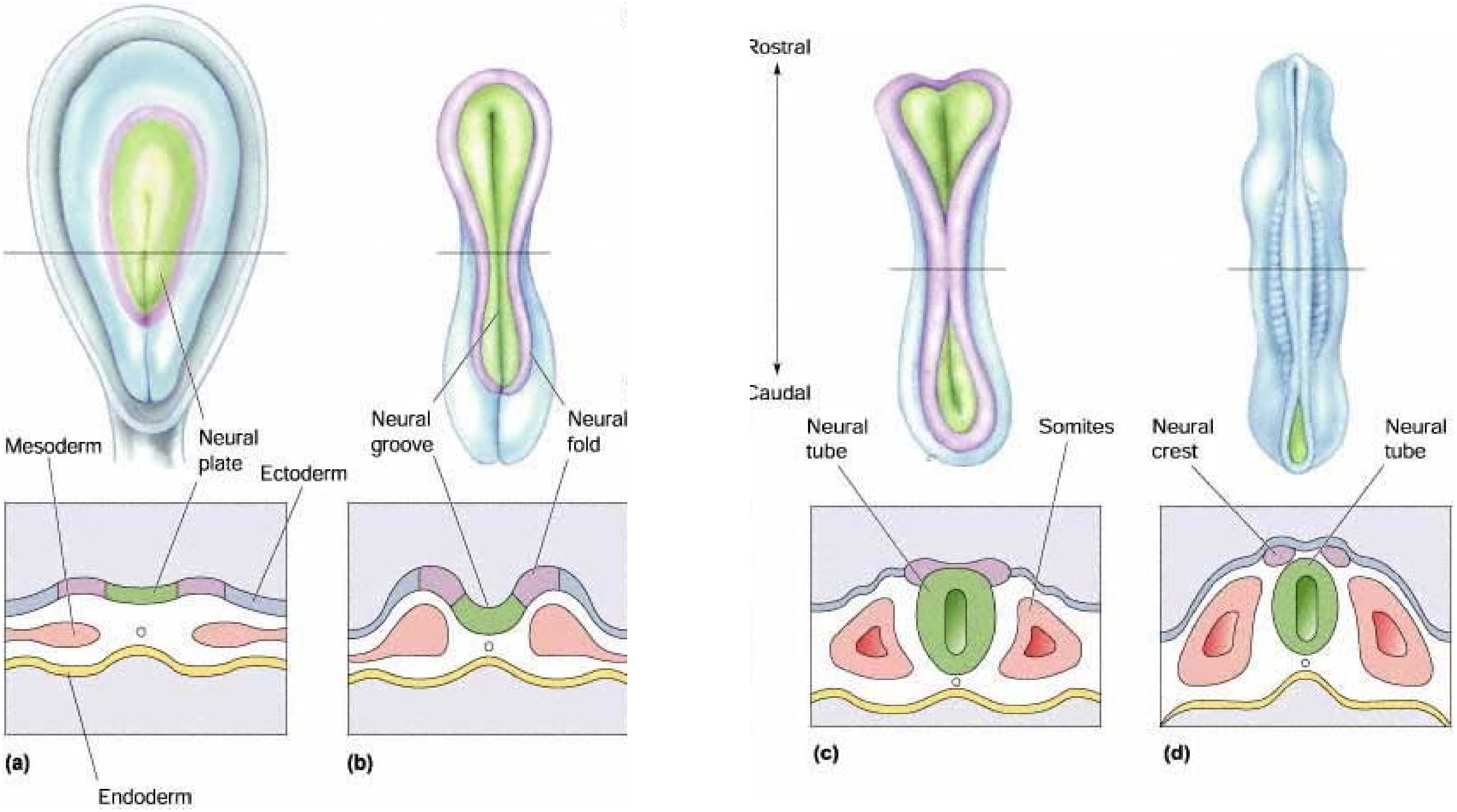
http://teratology.org/jfs/Schoenwolf.html

# Formation of Neural Tube

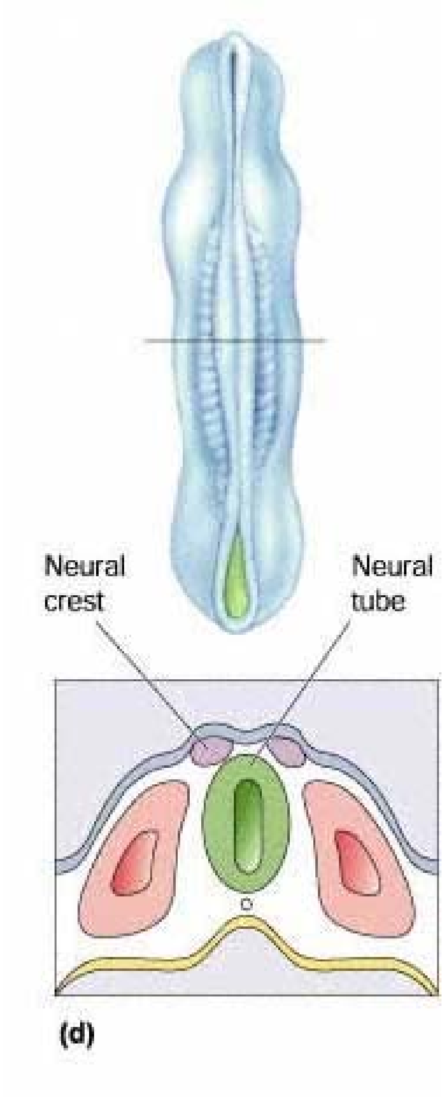
Three primordial tissues

- endoderm
- mesoderm
- Ectoderm: develop into nervous system



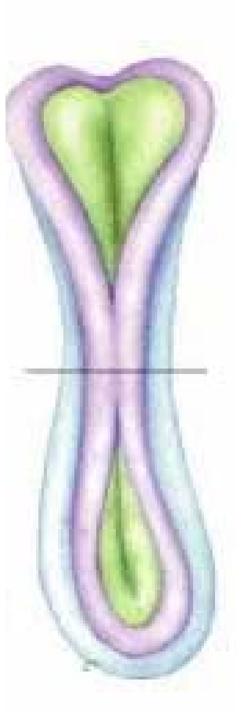


Mesoderm
Neural plate
Ectoderm
Endoderm
(a)
Neural groove
Neural fold
(b)
Rostral
Caudal
Neural tube
Somites
(c)
Neural crest
Neural tube
(d)



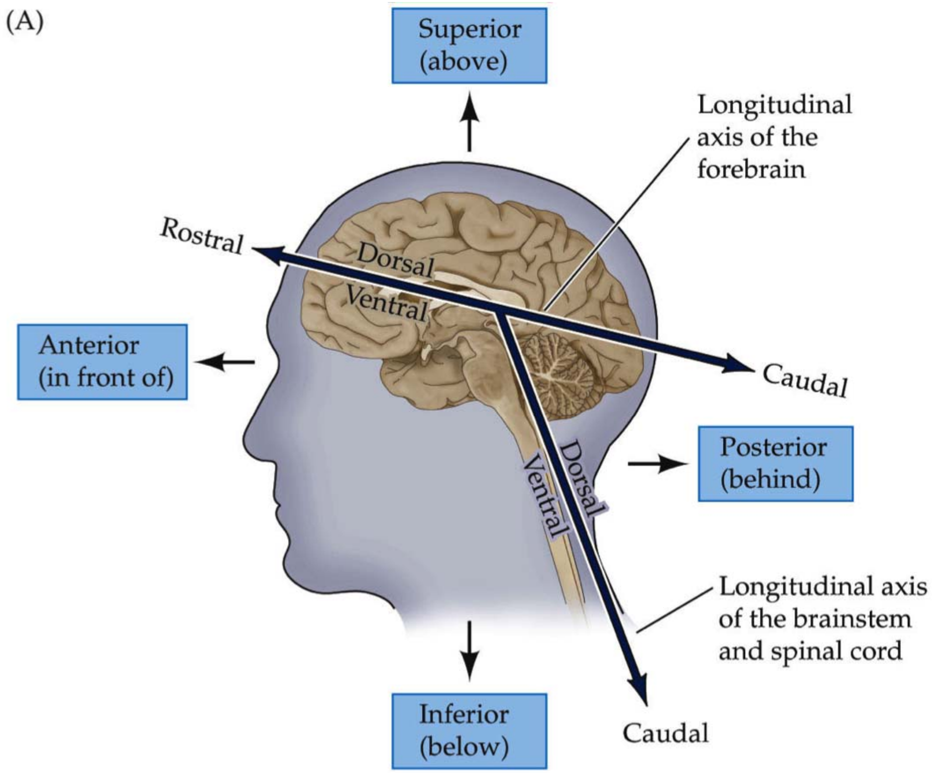

Neural crest becomes peripheral nervous system (PNS)
Neural tube becomes central nervous system (CNS)
Somites become spinal vertebrae.

Neural Tube Related Birth Defects

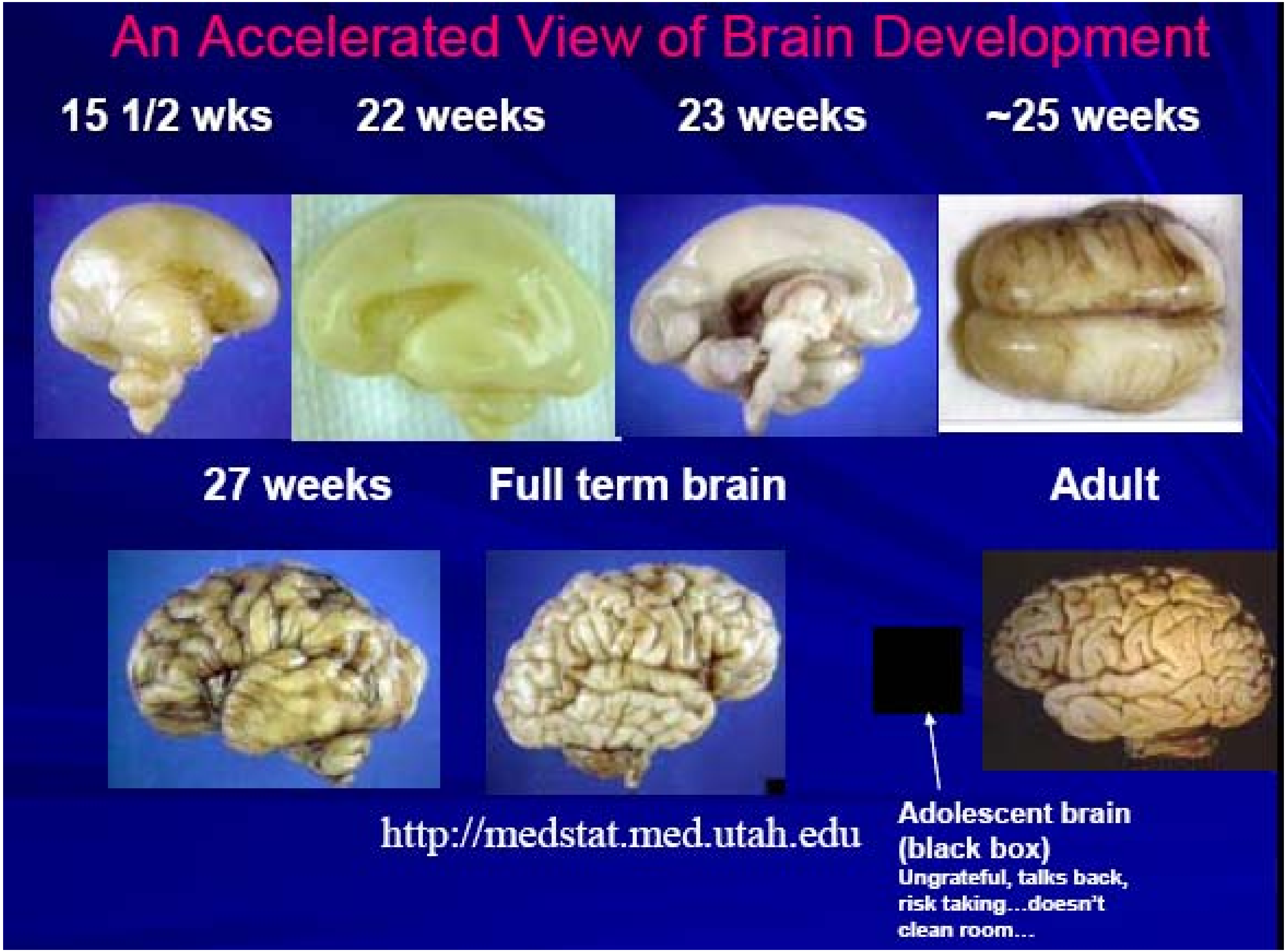


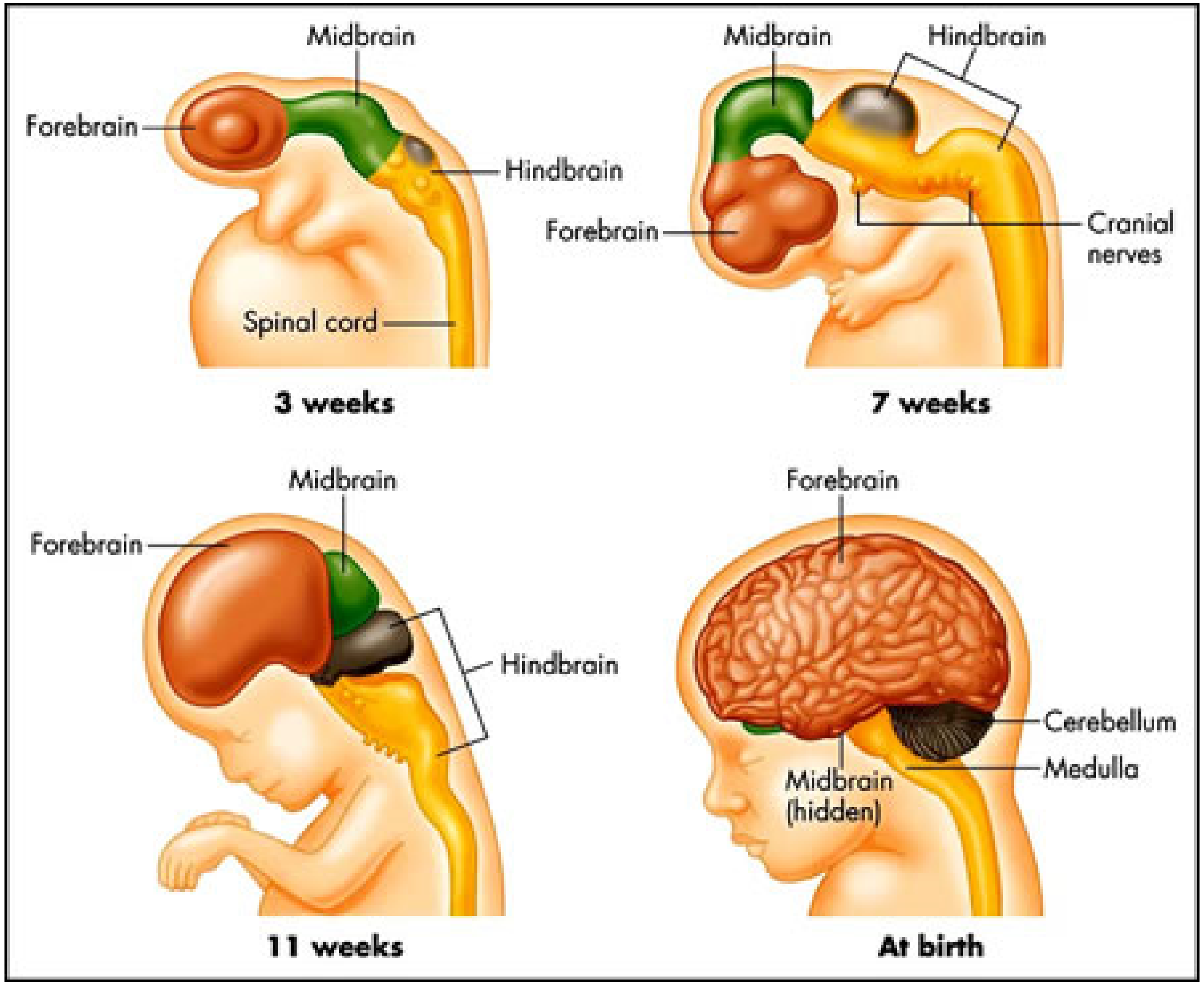
anterior neural pore

posterior neural pore

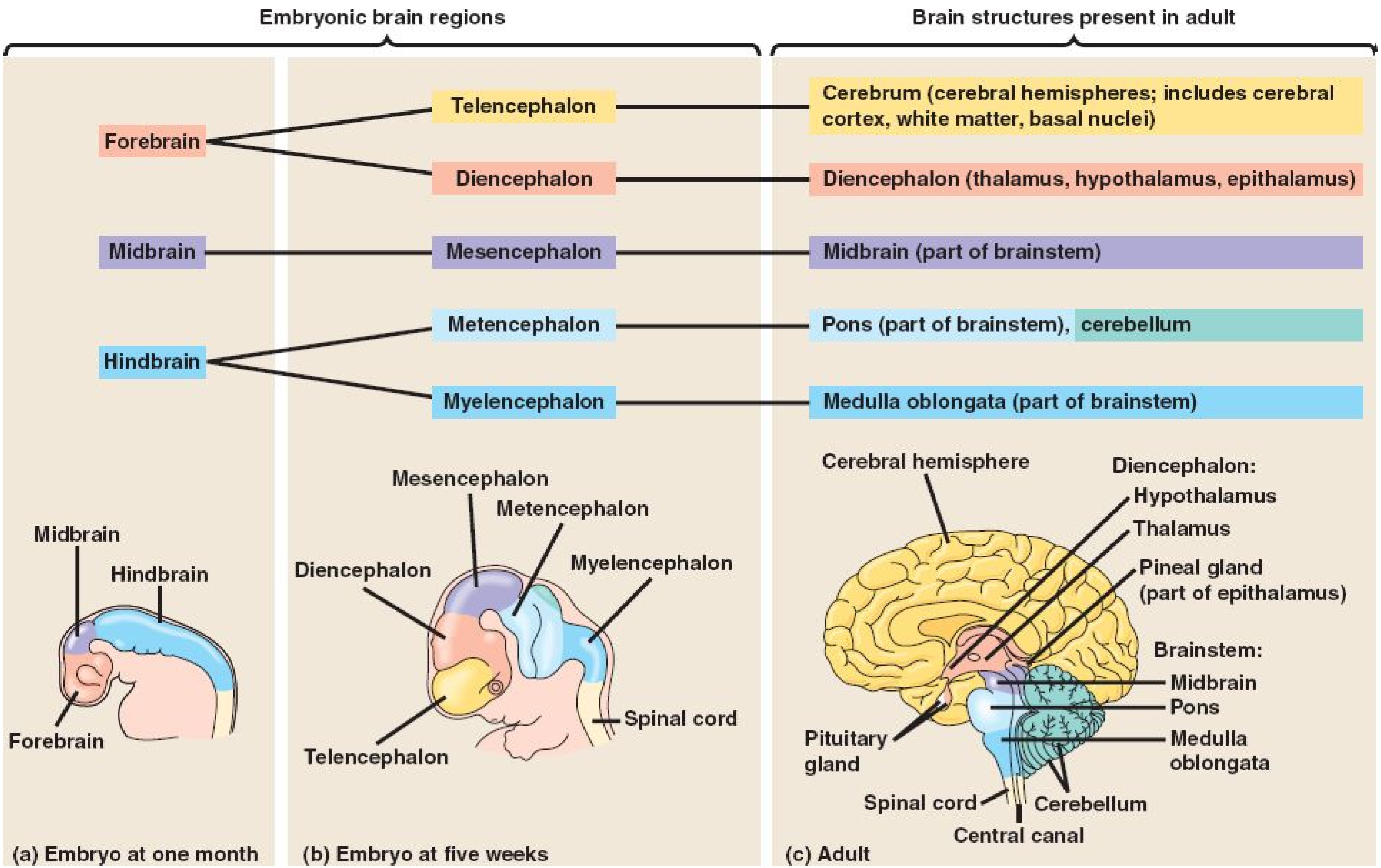




***NEUROSCIENCE*, *Fourth Edition*, Appendix, Figure A1 (Part 1)**


An Accelerated View of Brain Development
15 1/2 wks
22 weeks
23 weeks
~25 weeks
27 weeks
Full term brain
Adult
http://medstat.med.utah.edu
Adolescent brain
(black box)
Ungrateful, talks back,
risk taking…doesn't
clean room…




http://www.abieducation.com/binder/English/chap1.html


Embryonic brain regions
Brain structures present in adult
Forebrain
Telencephalon
Cerebrum (cerebral hemispheres; includes cerebral cortex, white matter, basal nuclei)
Diencephalon
Diencephalon (thalamus, hypothalamus, epithalamus)
Midbrain
Mesencephalon
Midbrain (part of brainstem)
Hindbrain
Metencephalon
Pons (part of brainstem), cerebellum
Myelencephalon
Medulla oblongata (part of brainstem)
Midbrain
Hindbrain
Forebrain
Mesencephalon
Metencephalon
Diencephalon
Myelencephalon
Spinal cord
Telencephalon
Cerebral hemisphere
Diencephalon:
Hypothalamus
Thalamus
Pineal gland
(part of epithalamus)
Brainstem:
Midbrain
Pons
Medulla
oblongata
Pituitary
gland
Spinal cord
Cerebellum
Central canal
(a) Embryo at one month
(b) Embryo at five weeks
(c) Adult

Human brain development reflects evolution?

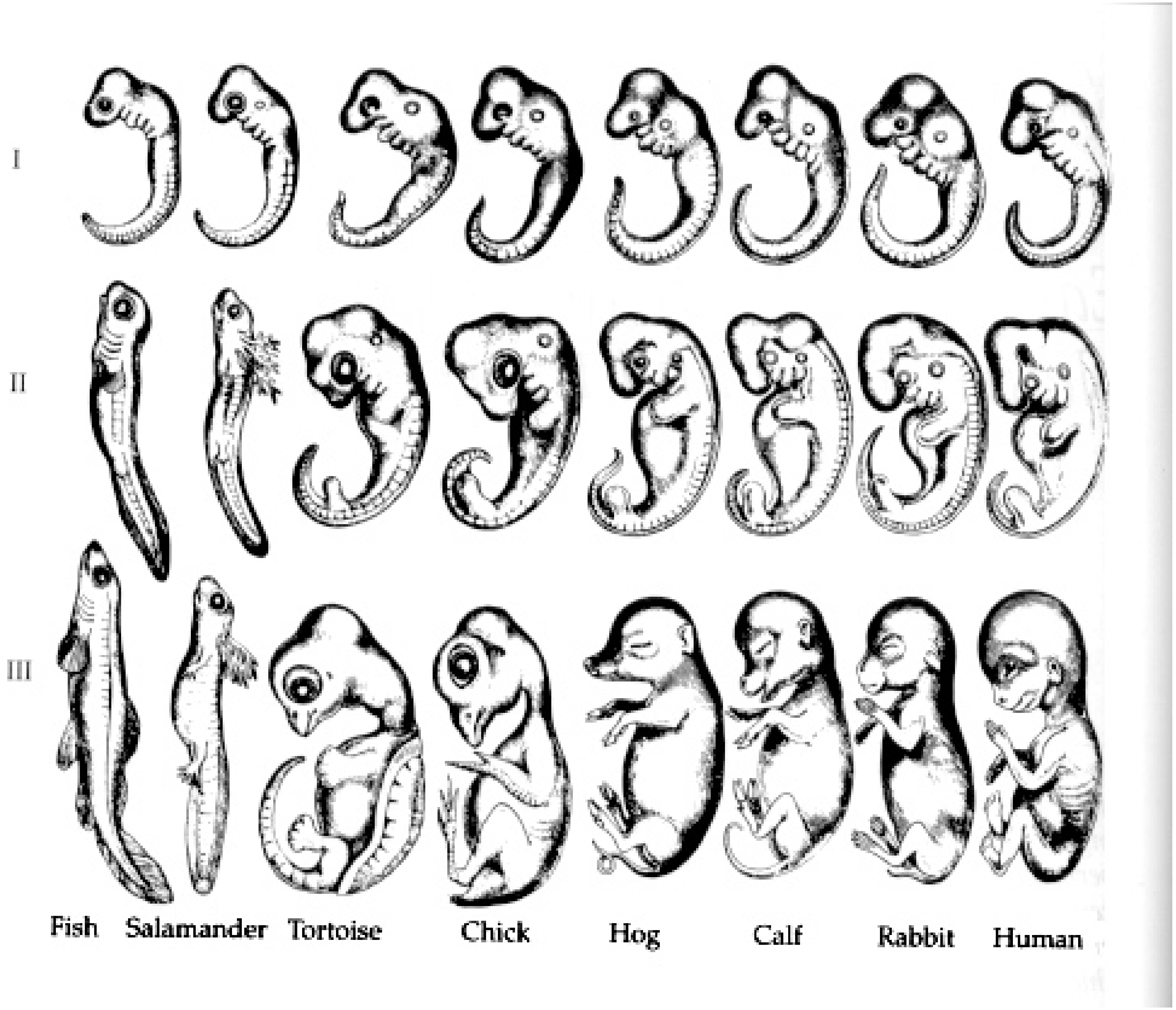
brains of reptile, fish, bird, rat, cat, higher animals,
primates, and finally human
(ontogeny reflects phylogeny)

immature cortex at different stages resemble
that of other species

development of a wrinkled cortex

are convolutions enough?
- dolphin has more convolutions but intelligent as dogs
- thinner than that of human
- less organized

# Ontogeny recapitulates phylogeny

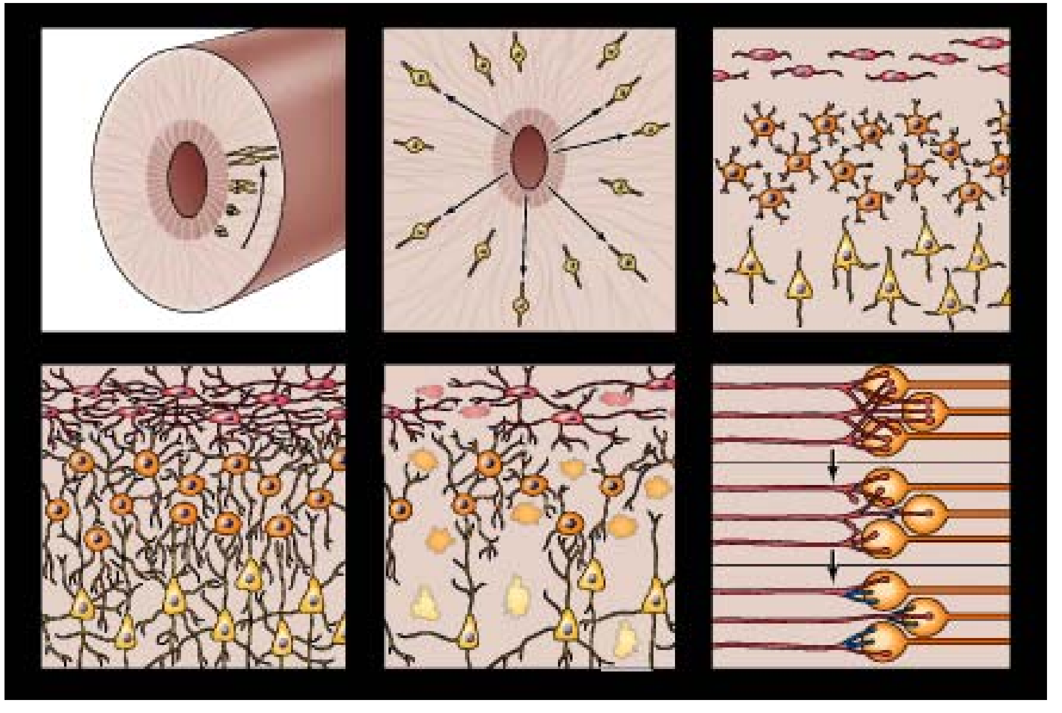


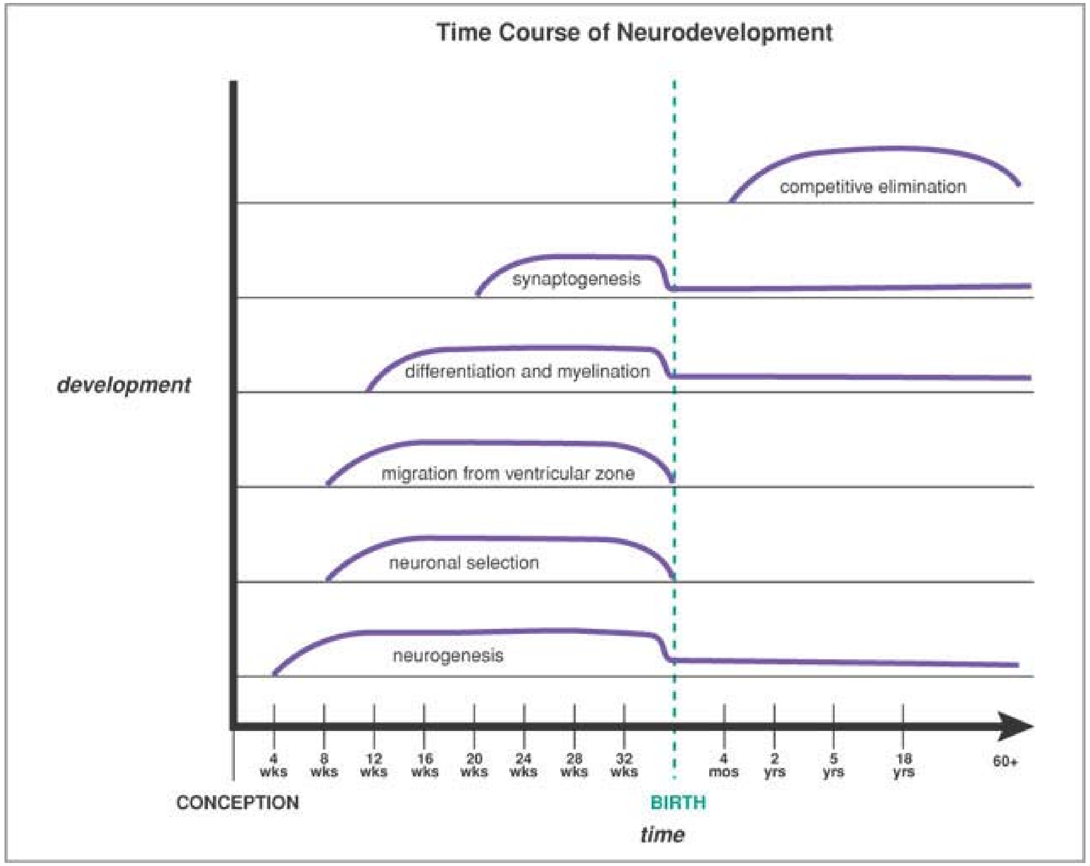
# Brain development at the cellular level (neuron)

# Early embryological events in the formation of the nervous system

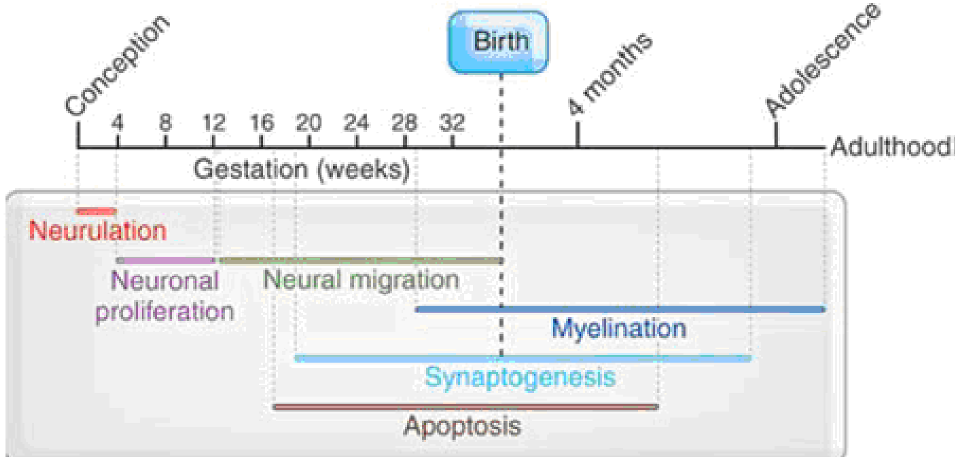
6 cellular processes (http://7e.biopsychology.com/vs/vs07/vs07.html)

(1) Neurogenesis: mitotic division of nonneuronal cells to produce neurons
(2) Cell migration: from site of origin to final location. development of distinct populations
(3) Cell differentiation: different neuron types
(4) Synaptogenesis: connection between cells by chemotatic guidance of axons
(5) Neuronal cell death: competition for targets and trophic factors (NGF)
(6) Synapse rearrangement: use it or loose it
(7) Myelination: (https://neurowiki2012.wikispaces.com/Synaptogenesis)






http://stahlonline.cambridge.org/content/ep/images/85702c02_fig1.jpg




https://neurowiki2012.wikispaces.com/Synaptogenesis

# Neurogenesis & Cellular Migration

The earliest stage of brain development involving the proliferation of neurons of the neural tube and the migration of these cells to predetermined locations.

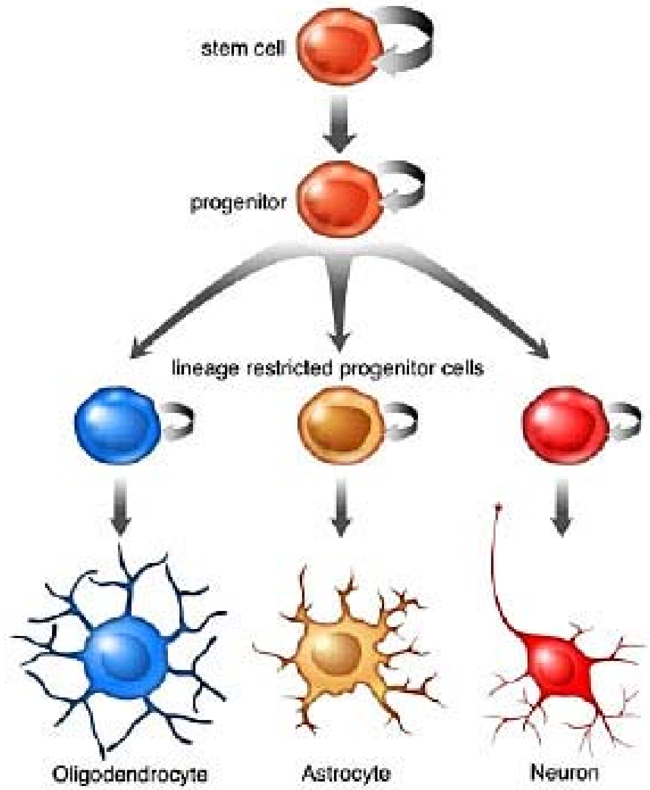
The CNS and PNS begin to develop approximately 18 days after conception.

Corticogenesis: the development of the cortex; begins at 6 weeks

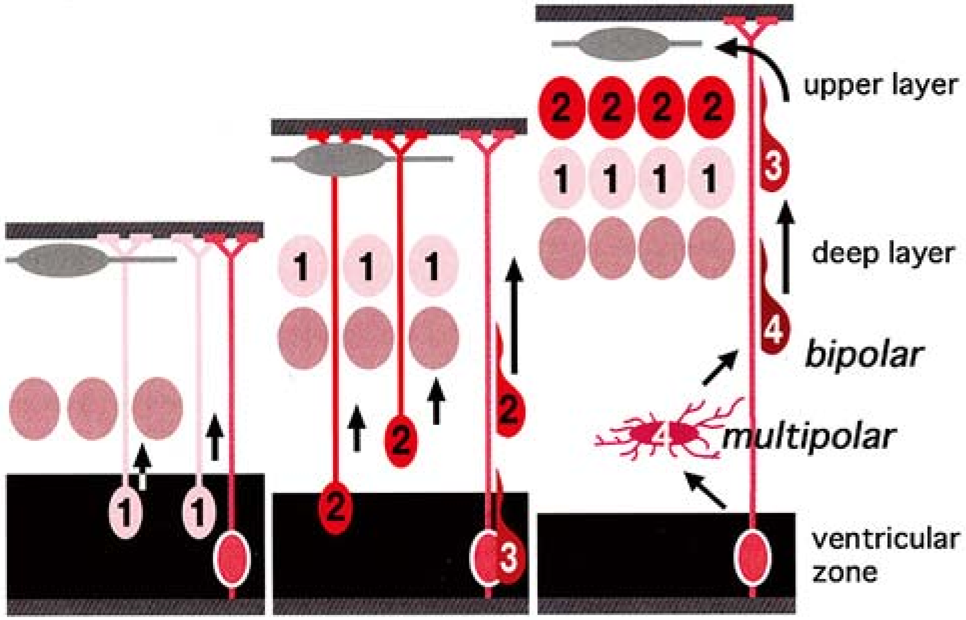
The rapidly proliferating cells along the wall of the neural tube migrate ("neural migration") outward at different predetermined times.

The neurons migrate in sheets, which ultimately create the 6 laminated layers of the cortex.

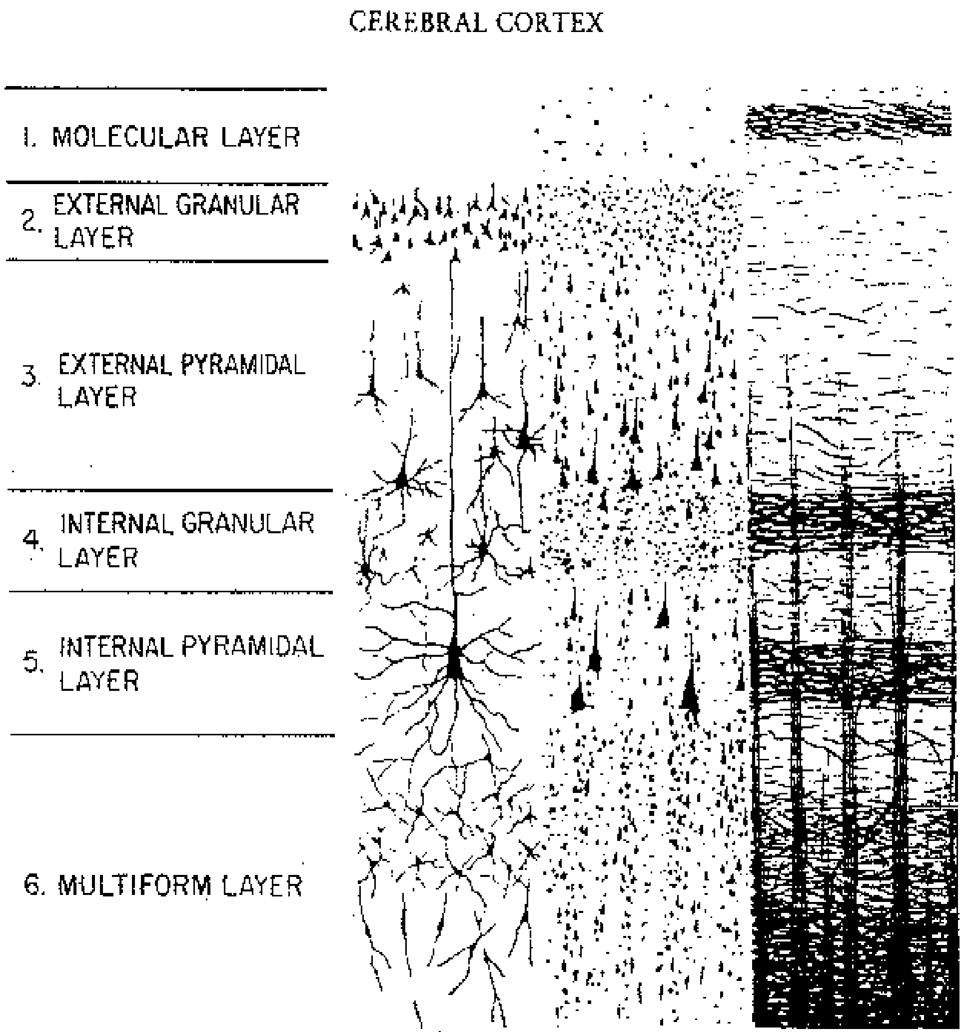
By week 18, nearly all cortical neurons have reached their designated locations.



# Radial Migration and Morphological Transition of Neurons




The pyramidal neurons constituting the cerebral cortex are neurons formed from the division of numerous neuronal precursors present in the cerebral ventricular zone of the embryonic cerebrum which then radially migrate toward the superficial layer. The cortex is formed through the radial migration of pyramidal cells adopting an “inside/out pattern” whereby the earliest neurons formed are placed in the deepest layers and later neurons occupy the more superficial layers. The numbers indicate the birth order. During the early part of initial migration there is a stage called “multi-polar” where many neurites are present; afterwards this change to “bipolar” where there are only two processes: one corresponding to a guide process and one to a future axon. After neurons adopt bipolar shape, they migrate in accordance with the structure known as the radial glia. http://www.brain.riken.jp/bsi-news/en/no40/research03.html




http://www.benbest.com/science/anatmind/anatmd5.html

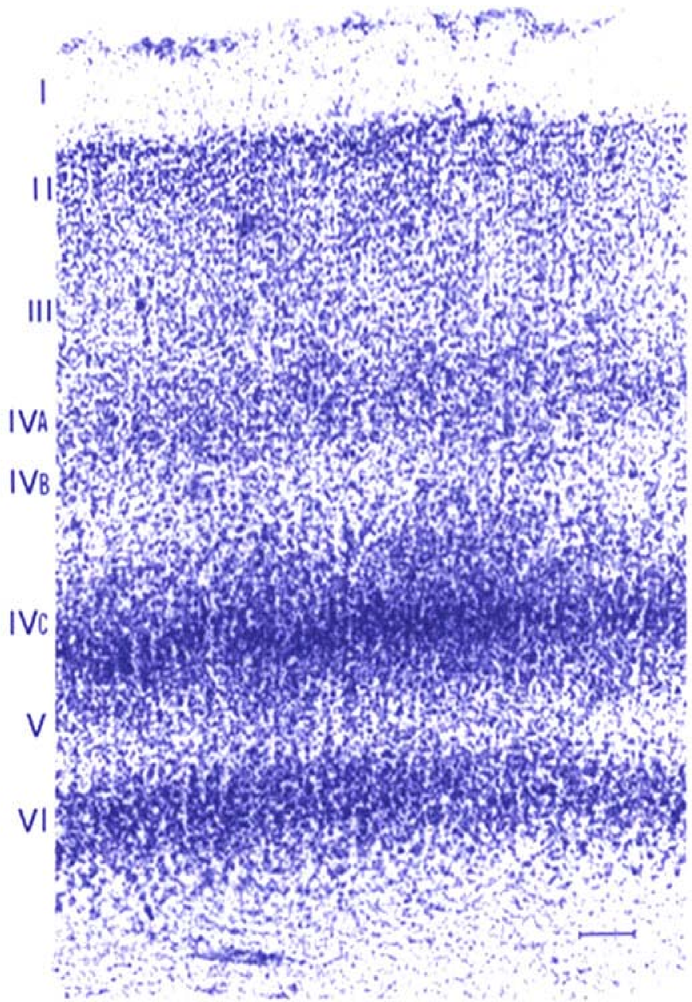
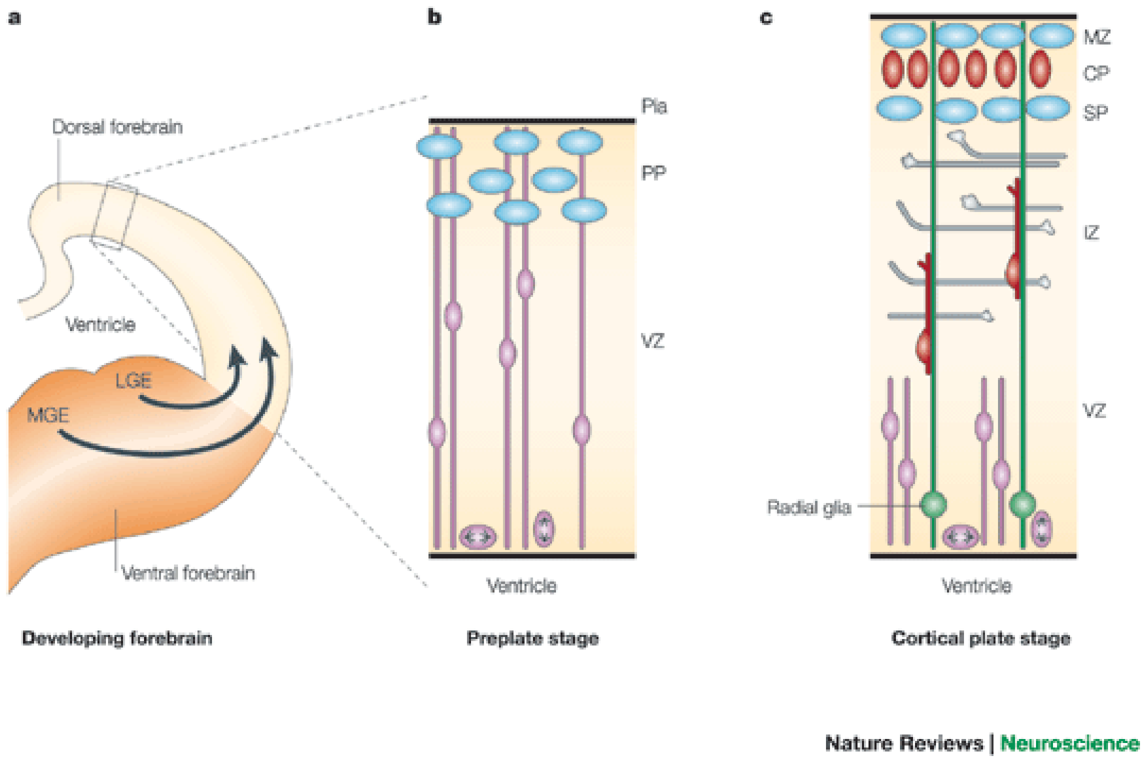


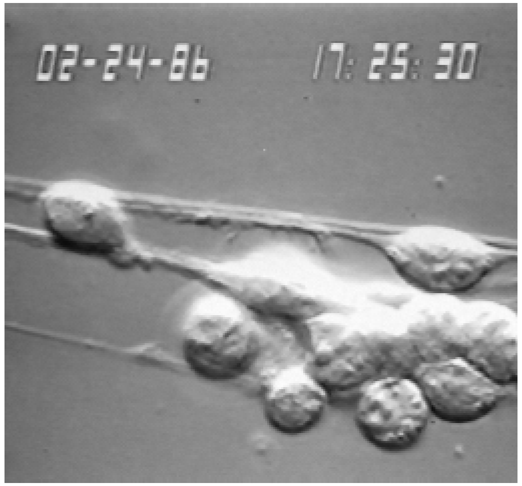

*Figure 13. Nissl stain of the visual cortex reveals the different layers I through VI quite clearly.*

# Neocortical development




**a** | Schematic diagram of a section through the developing rodent forebrain. **b**,**c** | Illustrations of the different stages of neocortical development. The dorsal forebrain gives rise to the cerebral cortex. The lateral ganglionic eminence (LGE) and medial ganglionic eminence (MGE) of the ventral forebrain generate the neurons of the basal ganglia and the cortical interneurons; the latter follow tangential migratory routes to the cortex (**a**; arrows). In the dorsal forebrain (**a**; boxed area), neuronal migration begins when the first cohort of postmitotic neurons moves out of the ventricular zone (VZ) to form the preplate (PP) (**b**). Subsequent cohorts of neurons (pyramidal cells) migrate, aided by radial glia, through the intermediate zone (IZ) to split the PP into the outer marginal zone (MZ) and inner subplate (SP) (**c**). CP, cortical plate

# Glial-Guided Neuronal Migration




http://www.rockefeller.edu/labheads/hatten/mechanism.html

# neural migration

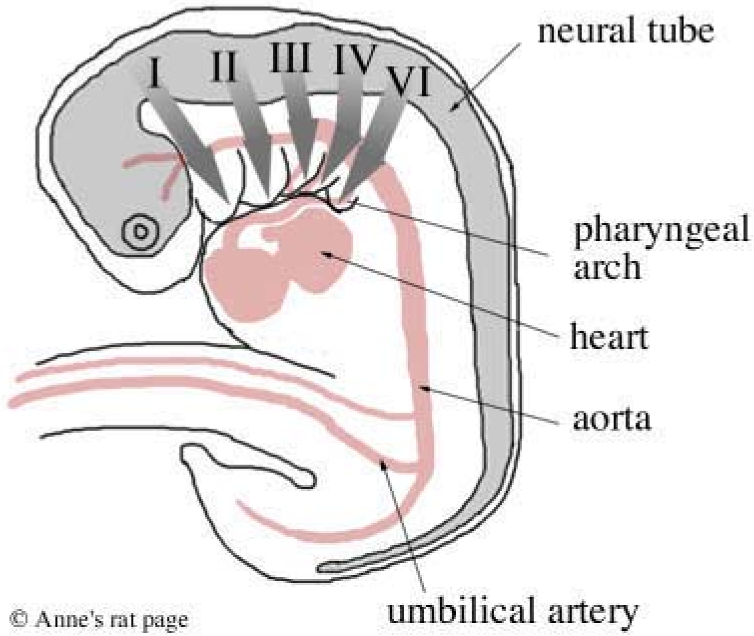



*Diagram of the migration of neural crest cells (thick grey arrows) from the neural crest to the five pharyngeal arches (I, II, III, IV, and VI. Arch V degenerates). (Adapted from Gilbert 1994, p. 284.)*
*http://www.ratbehavior.org/DumboRatMutation.htm*

# Axon & Dendrite Development

## Axons

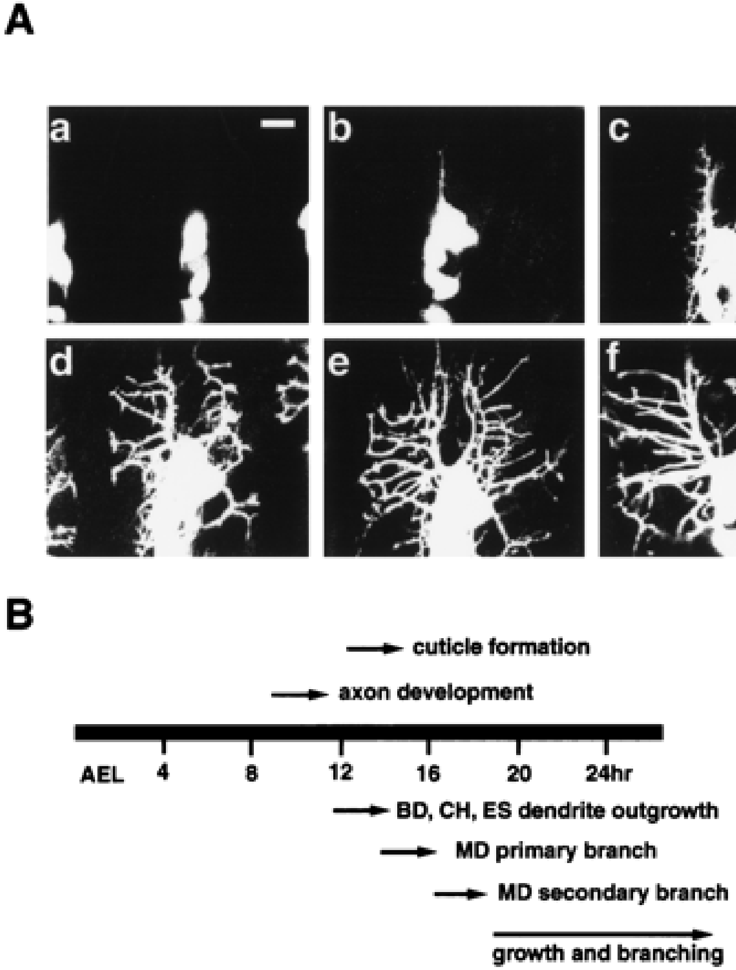
As the neurons migrate, axons form making cortical-cortical, cortical-subcortical, and interhemispheric connections.

## Dendrites

As the migrating neuronal cells reach their designated positions, dendrites being to sprout ("*arborization*").

Dendrites then form synapses for gathering information.

This begins prenatally, but the most intensive dendrite growth period is from birth to 18 months.




**Dendritic outgrowth, branching, and routing in *Drosophila***
Dorsal md neuron dendrites develop late in embryogenesis. (*A*) Pictures were taken from homozygous Gal4 109(2) 80-UAS–GFP embryos at different stages. (*a*) Dendrite budding begins at 12–13 hr AEL; (*b*) dorsal dendrites extend significantly by 14–15 hr AEL; (*c*) dorsal dendrite extension is almost complete at 16–17 hr AEL; (*d*) lateral dendrites continue extending and retracting at 18–19 hr AEL; (*e*) branching pattern is fixed by 20–21 hr AEL; (*f*) lateral branches cover the hemisegment before hatching (22–23 hr AEL). (*B*) The time line of dorsal cluster dendrite development. The tail of each arrow indicates the approximate time point at which a specific developmental process begins. Impermeable cuticle forms before dorsal branches fully extend. Bar, 10 µm. *Genes & Dev. 1999. 13: 2549-2561.*

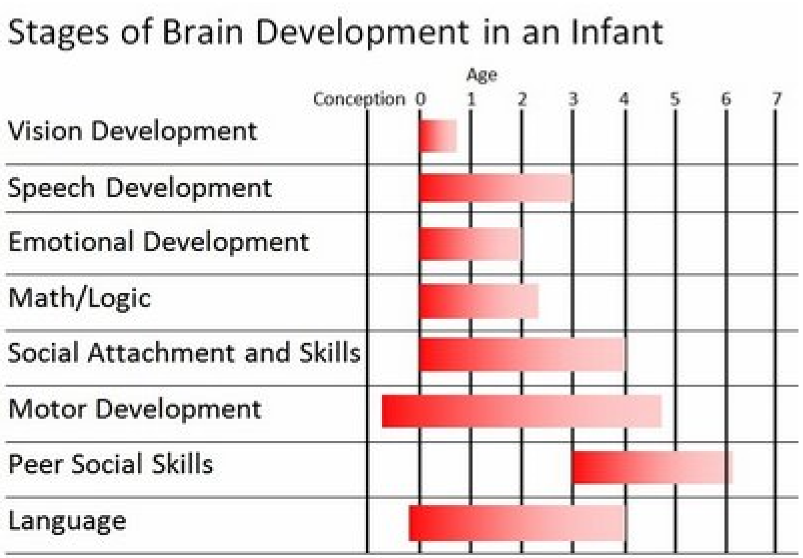
# Synaptogenesis

Synapses form as dendrites and axons grow.

Function emerges secondary to synaptic formation in specific regions.

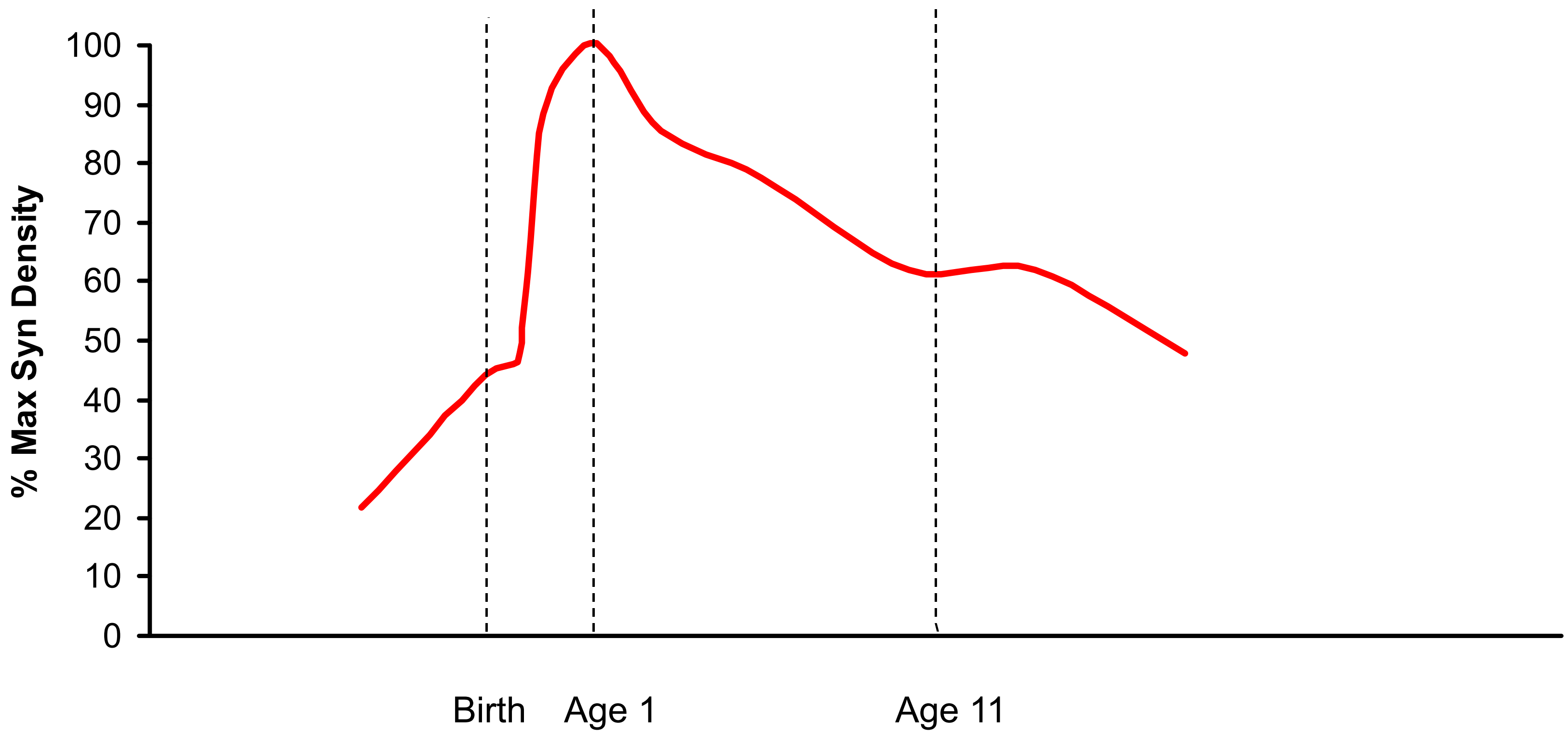
Synapses grow at different rates in different parts of the brain

- Occipital lobe – begins prenatally and achieves near adult-level synaptic density between ages of 2 to 4 years
- Prefrontal cortex – does not reach adult levels until late adolescence/adulthood

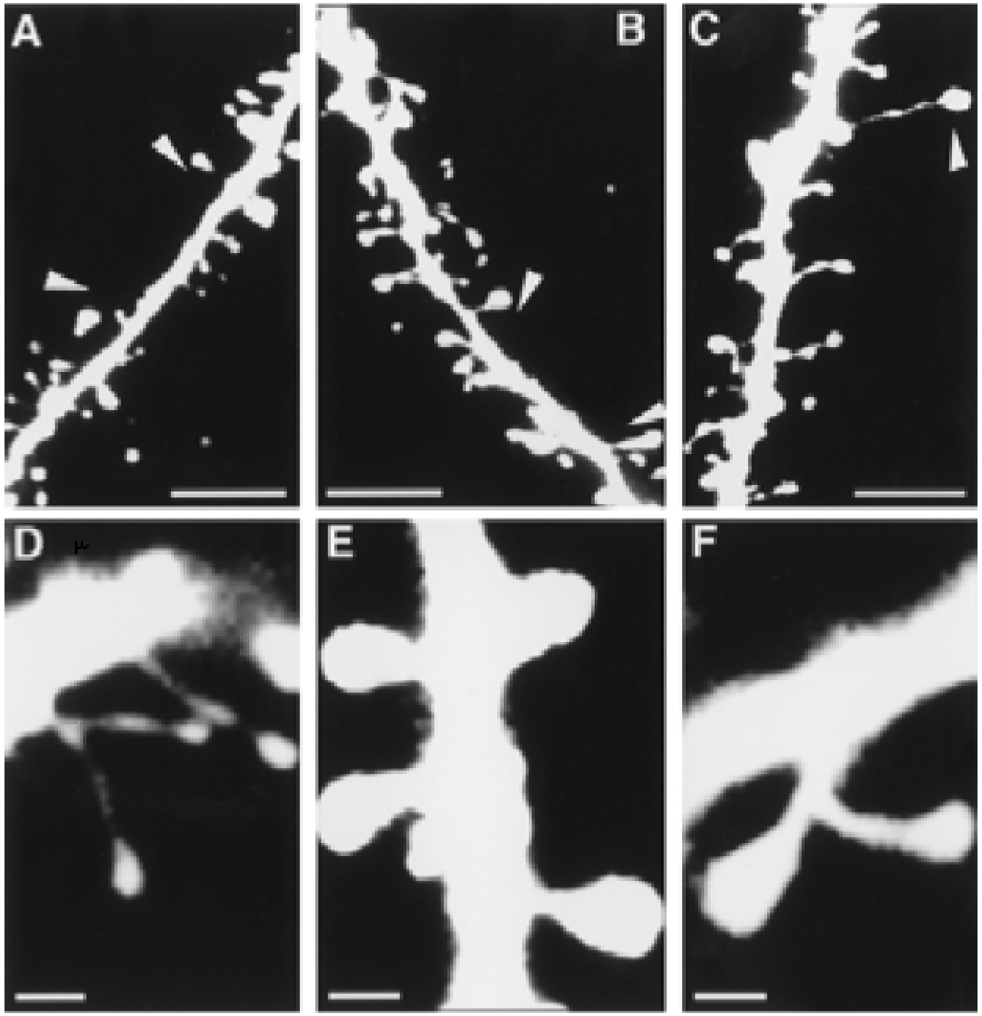


# Synaptic Density over the Lifespan

(human visual cortex)

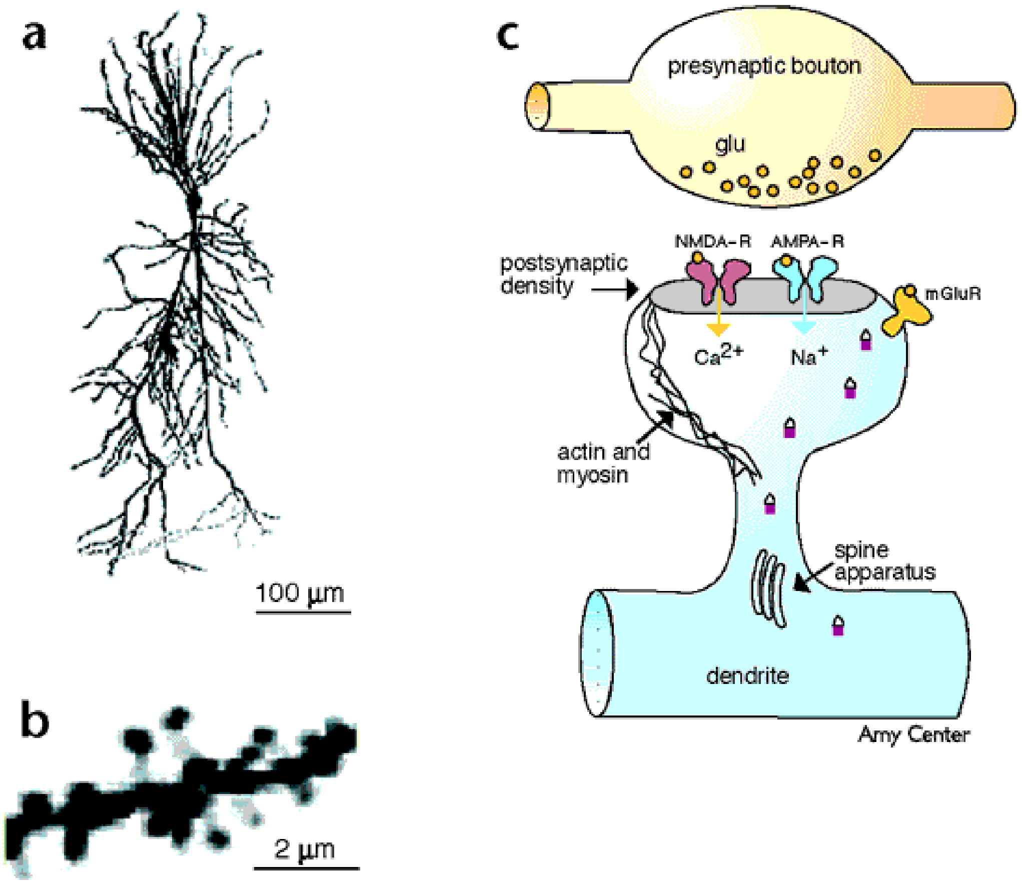


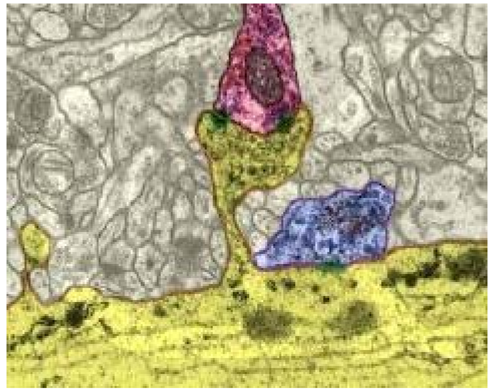
# Neuronal Plasticity and Dendritic Spines: Effect of Environmental Enrichment on Intact and Postischemic Rat Brain




Morphologic features of dendritic spines in the somatosensory cortex of adult rats housed in standard or enriched environments. "Naked" sections of dendrites (arrowheads) in rats housed in standard environment **(A** and **B)**.
Note the spine with a very long neck (arrowhead) in a rat housed in an enriched environment **(C)**.
"Inactive" thin spines on the oblique apical dendrite in standard-environment specimens **(D)**.
In enriched-environment specimens, many spines had big heads **(E)** or double heads **(F)**.
All illustrations are from pyramidal layer III except **A** (layer II). Scale bars = 5 m **(A–C)** or 1 m **(D–F)**.

http://www.nature.com/jcbfm/journal/v22/n1/full/9591196a.html

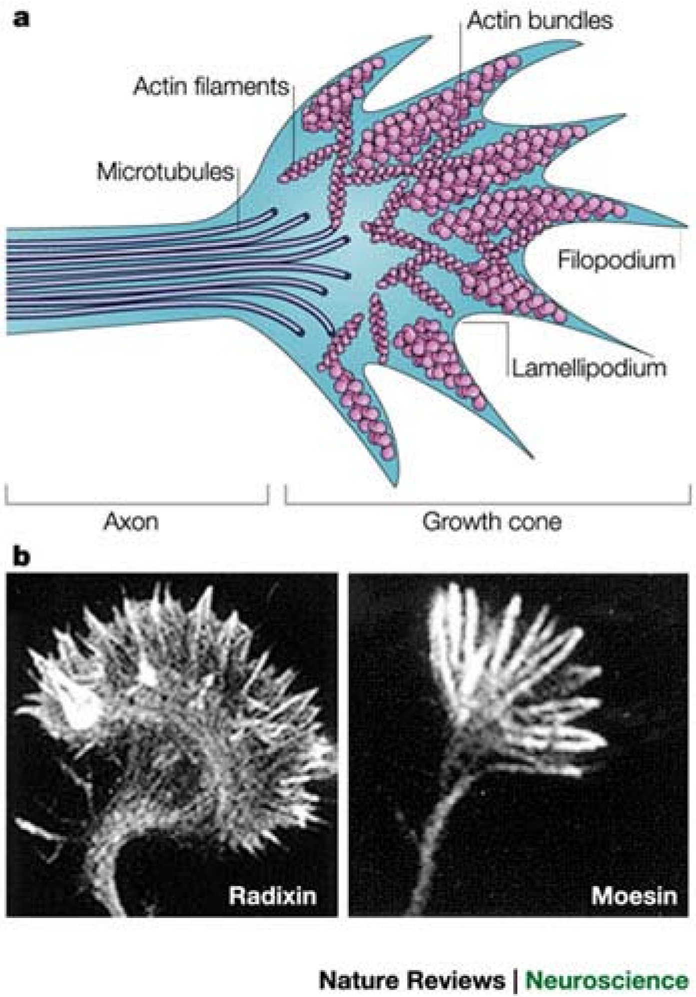


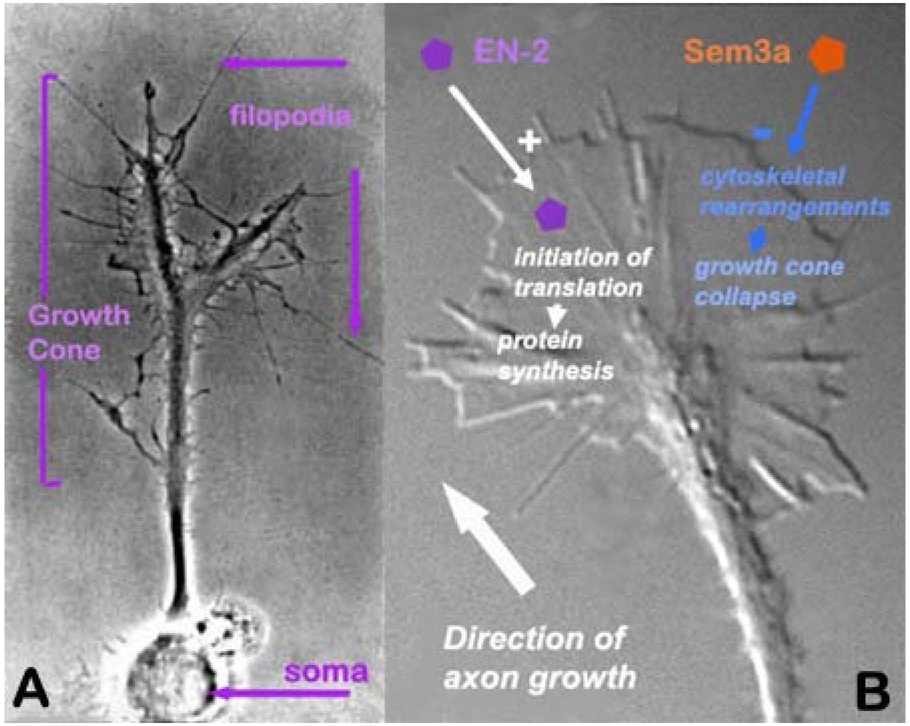
A CA1 pyramidal cell from a hippocampal slice
*Nature Neuroscience* **2**, 5 - 7 (1999)

# Growth cone

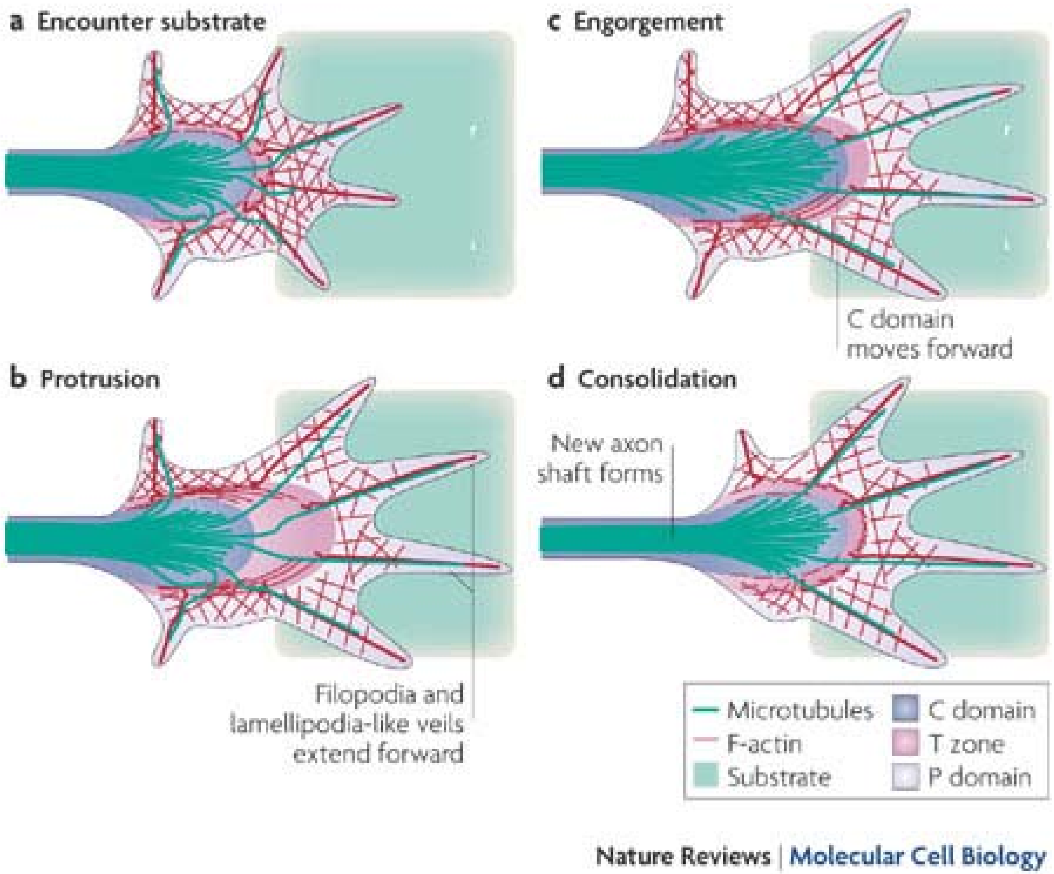
A dynamic, actin-supported extension of a developing axon seeking its synaptic target




*Nature Reviews Neuroscience* **5**, 462-470 (June 2004)

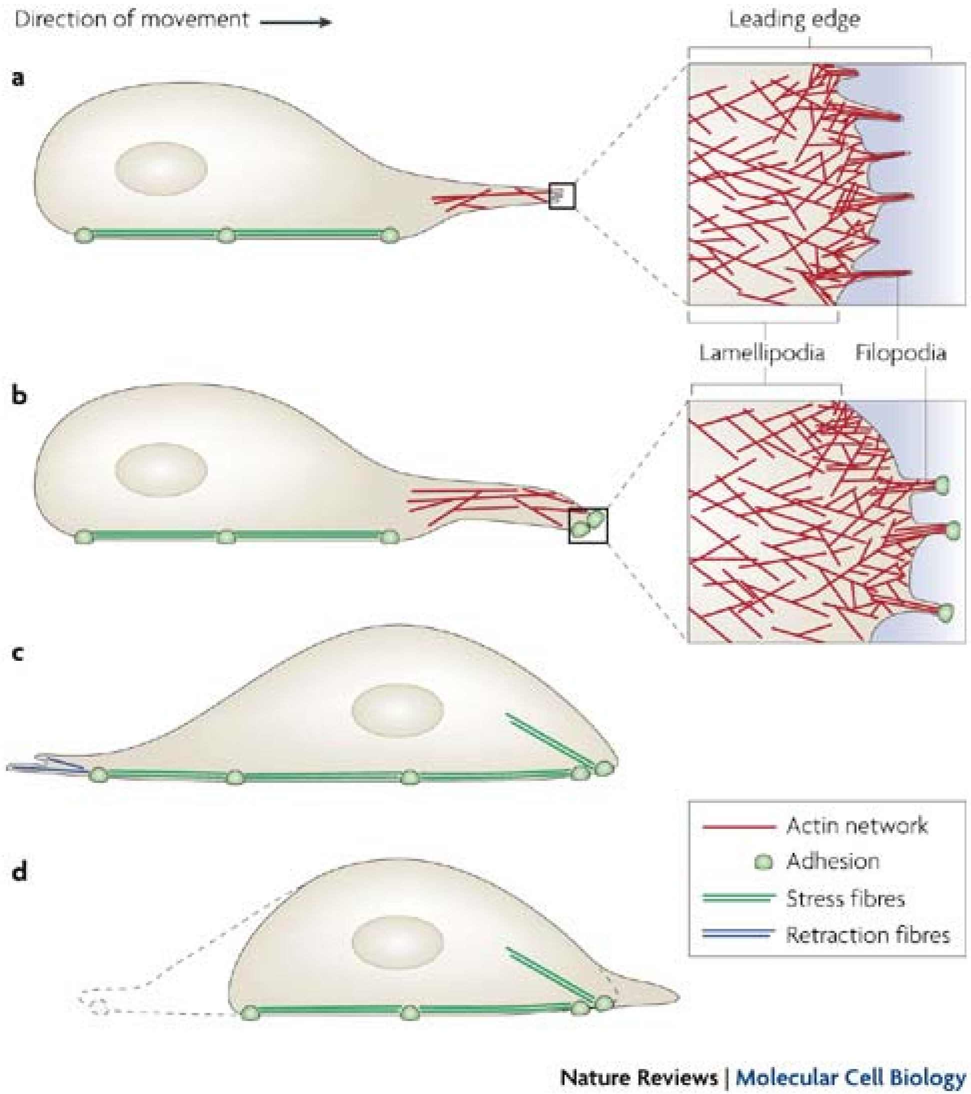



http://www.cellscience.com/reviews7/Protein_translation_axonal_dendritic_growth.html

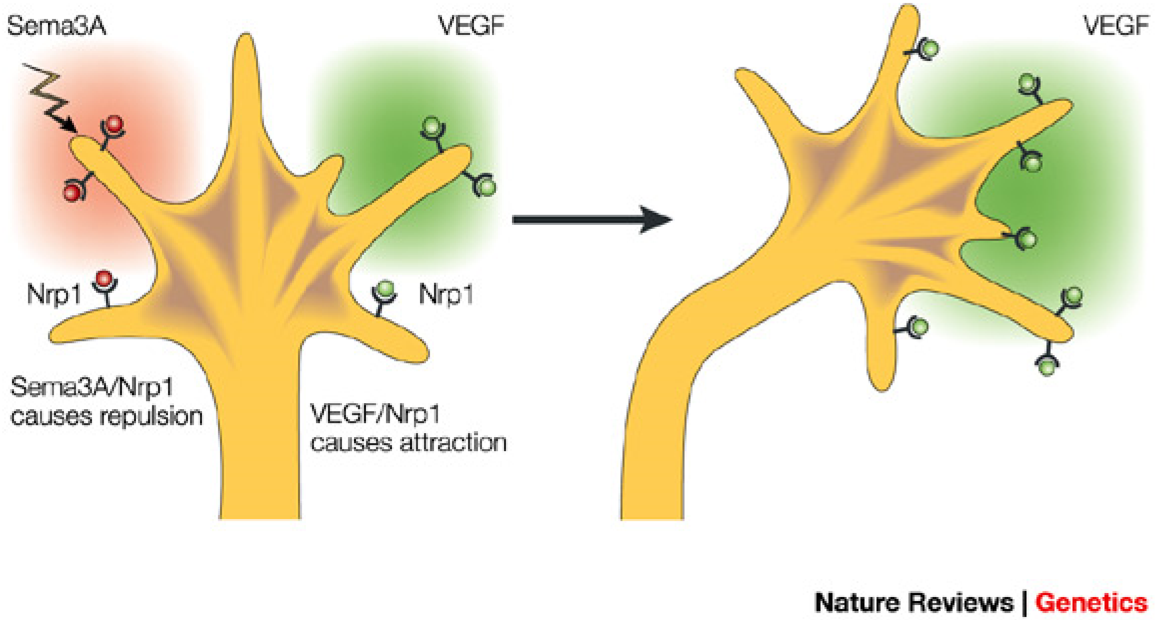



## Stages of axon outgrowth

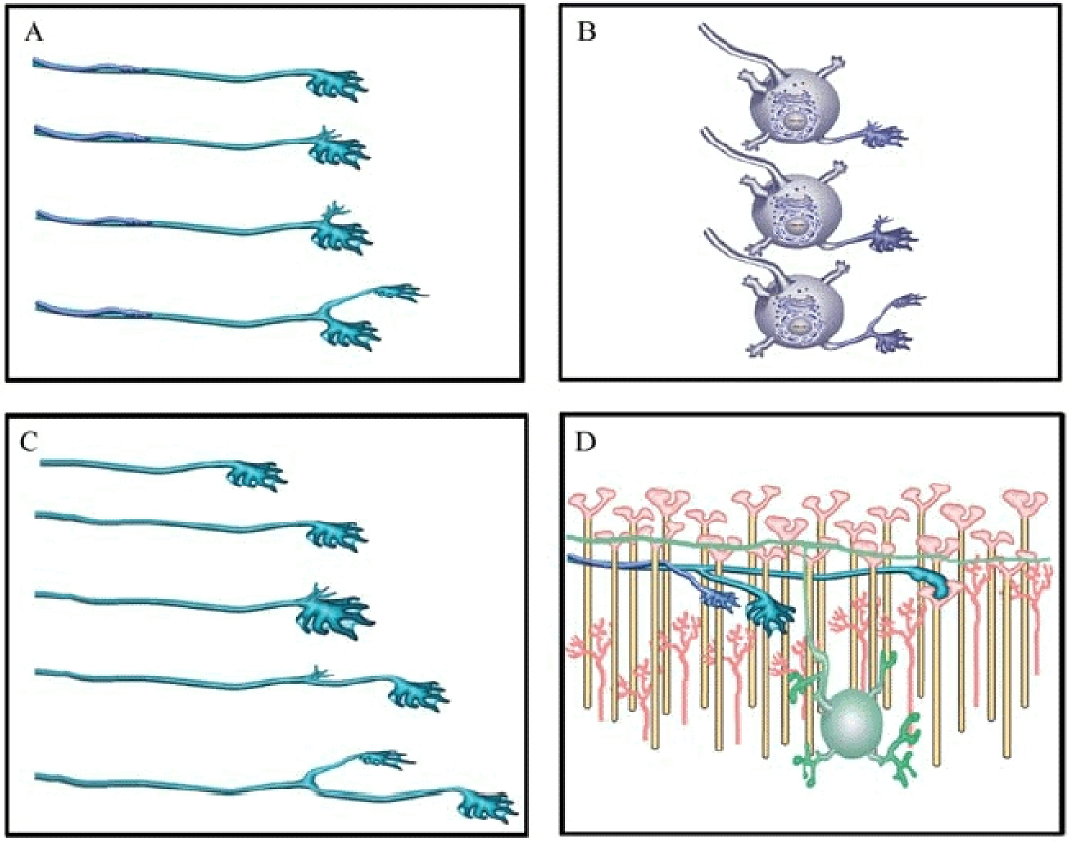
A traditional description of the axon outgrowth process separates it into three stages: protrusion, engorgement and consolidation[13, 14]. These occur upon encountering attractive, adhesive substrates. This sequence during growth cone progression provides a framework for understanding detailed molecular mechanisms, and we assume that some of the same mechanistic events are used in response to diffusible chemotropic cues. *Nature Reviews Molecular Cell Biology* **10**, 332-343 (May 2009)




**a** | Motility is initiated by an actin-dependent protrusion of the leading edge, which is composed of lamellipodia and filopodia. These protrusive structures contain actin filaments, with elongating barbed ends orientated towards the plasma membrane. **b** | During cellular extension, new adhesions with the substratum are formed under the leading edge. **c** | Next, the nucleus and the cell body are translocated forward through actomyosin-based contraction forces that might be mediated by focal adhesion-linked stress fibres, which also mediate the attachment to the substratum. **d** | Then, retraction fibres pull the rear of the cell forward, adhesions at the rear of the cell disassemble and the trailing edge retracts. *Nature Reviews Molecular Cell Biology* **9**, 446-454 (June 2008)




The filopodia of both endothelial cells (ECs) and axons express neuropilin-1 (Nrp1): the semaphorin Sema3A repels (jagged arrow) the filopodia, whereas vascular endothelial growth factor $VEGF^{164}$ attracts the filopodia, which drives the EC or axon to move in the direction of the VEGF gradient. The role of VEGF is best characterized for ECs. *Nature Reviews Genetics* **4**, 710-720 (September 2003)




Schematic illustration of mechanisms proposed to underlie neuronal branching morphogenesis. A) Axonal branching produced through simple growth cone bifurcation, in which local microenvironmental cues stimulate cytoskeletal reorganization culminating in the formation of a second active growth cone. B) Dendritic branching produced through simple growth cone bifurcation. C) Axonal branching produced through growth cone pausing followed by collateral branch outgrowth, or "delayed interstitial branching," in which a side shoot extends from the axon shaft well after the primary growth cone has continued to elongate. D) Axonal branching produced as repellent molecule exposure (green neuron and vertical pink cells) triggers primary growth cone collapse (turquoise axon) and the subsequent sprouting of lamellipodia and filopodia from the axon shaft (turquoise axon branch). In addition, defasciculation of bundled axons (blue axon) often accompanies this form of branch induction.
http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A46740

Growth cone guidance by an attractive surface

http://www.youtube.com/watch?v=Wj3C6cLqXzY

Chemotaxis of *Dictyostelium* cells

http://www.youtube.com/watch?v=Ql7i_TLUurM

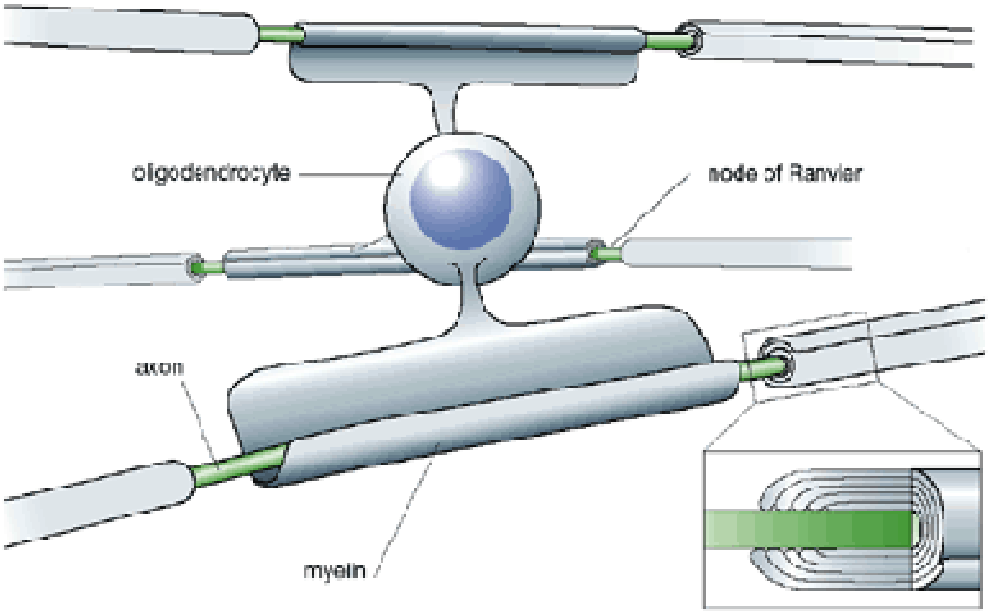
# Myelination

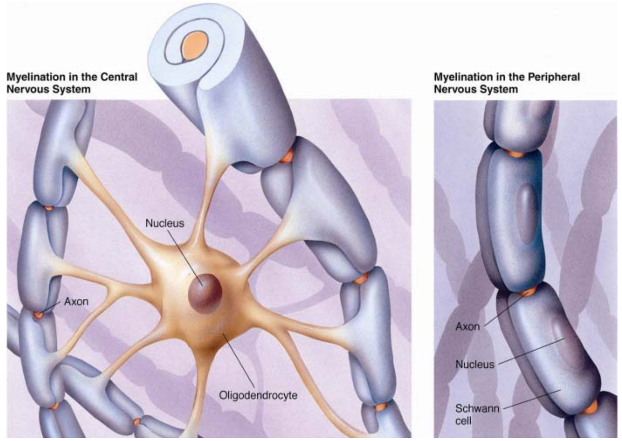
Near the end of neural migration, glial cells begin to encircle the axons, forming the myelin sheath.

Myelination begins with the spinal cord, then subcortical structures, then the cortex.

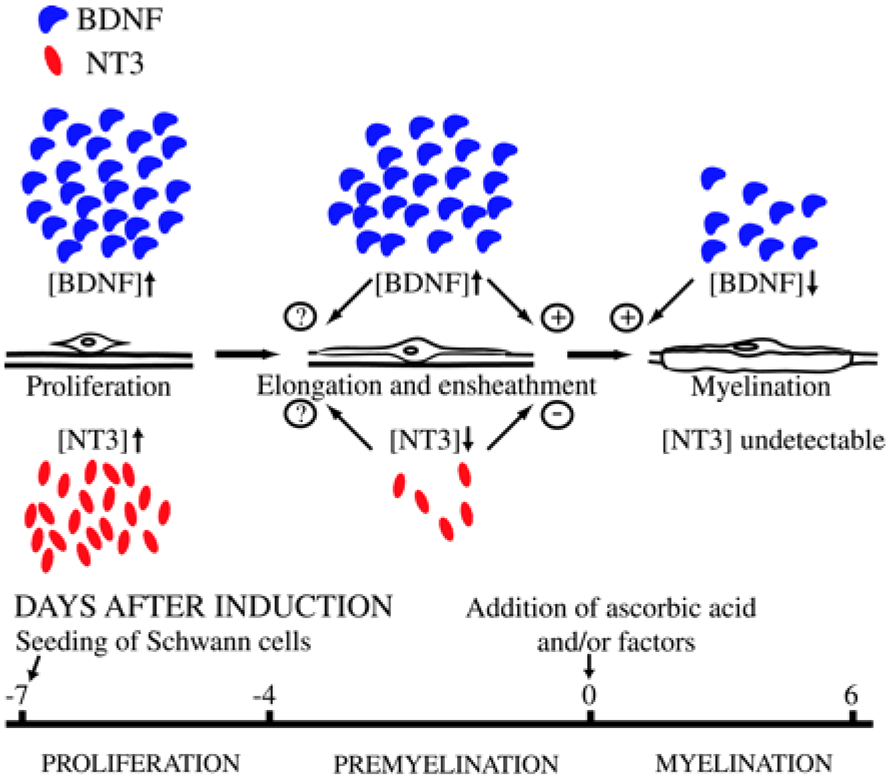
Within the cortex, myelination begins in posterior region and moves anteriorly, ending with the parietal and frontal lobes

<u>The significant increase in brain weight postnatally is primarily due to myelination.</u>




**Myelination by oligodendrocyte.** The figure schematically depicts an oligodendrocyte simultaneously wrapping multiple axons with a myelin sheath. Also shown are nodes of Ranvier, which are small unmyelinated regions where the voltage-gated sodium channels localize. The box shows a longitudinal section through a myelinated axon, illustrating its multilayered structure. *Nature Genetics* - **33**, 327 - 328 (2003)




**Myelin sheath in PNS**

Schematic model representing the modulation of the endogenous levels of neurotrophins and their possible roles during myelin formation. BDNF and NT3 are expressed at high levels during the initial phases of myelin development. Concomitant with the proliferation and premyelination phases, there is a marked decrease in NT3 levels, whereas BDNF remains constant. High levels of NT3 do not allow the myelination program to proceed further and keep the Schwann cell/axonal unit in an ensheathed premyelinated stage. When NT3 levels are diminished, the Schwann cell initiates the formation of a myelin internode surrounding the axon. On the contrary, high levels of BDNF are required for the myelination process to proceed and BDNF levels will decrease only after the myelination program has already been initiated. Elevated levels of BDNF during the early stages of myelination increase the speed and extent of the final process. An illustration of the timeline for the proliferation, premyelination, and myelination stages of Schwann cells in the coculture system appears below the model.

*PNAS December 4, 2001 vol. 98 no. 25 14661-14668*

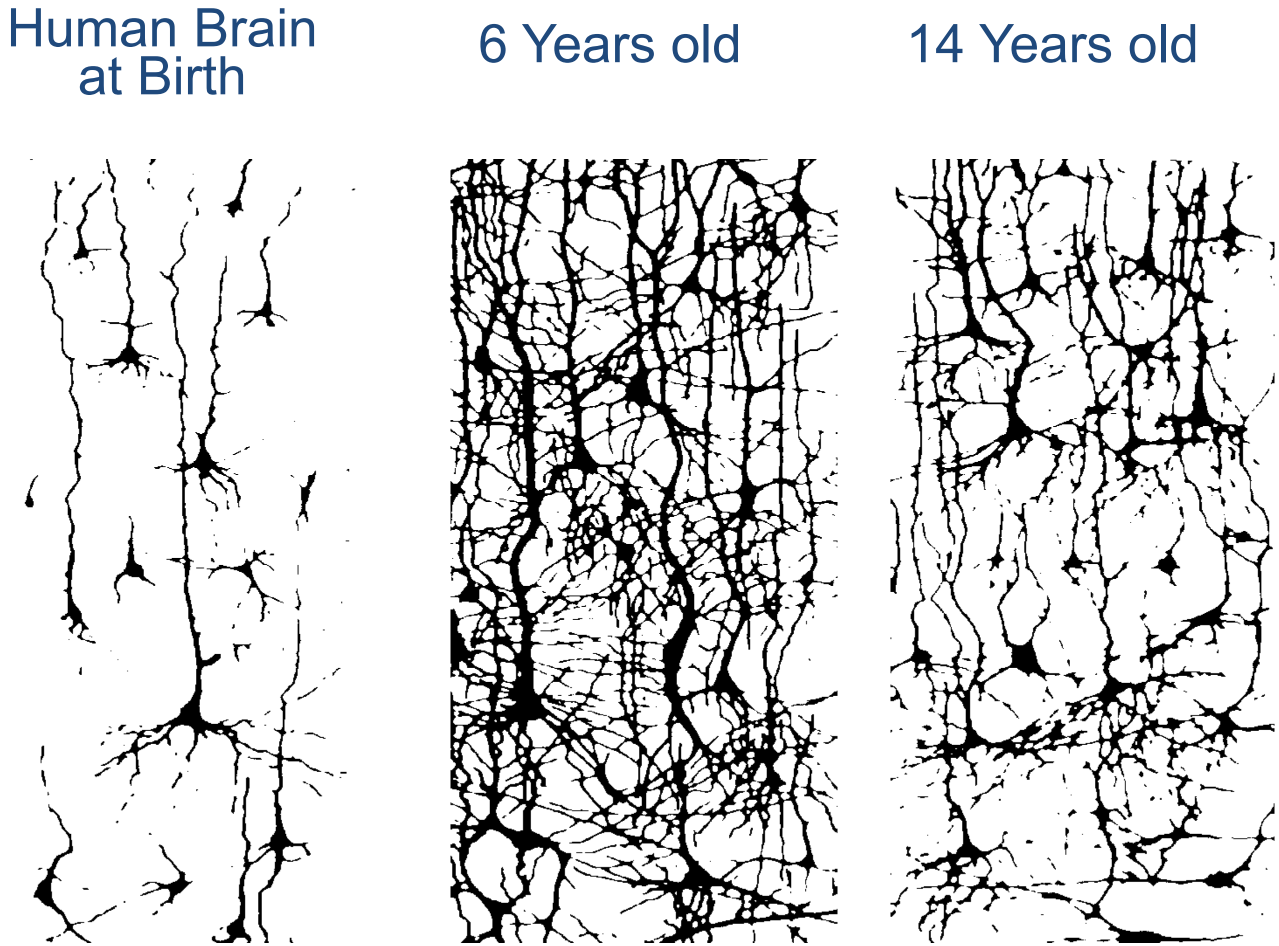
# Pruning

During early development, neurons and synapses are overproduced.

Early synapses are thought to be random, in part, thus resulting in some inappropriate connections.

Pruning is not random; it is the purposeful sculpting of the brain. Connections, which are used, are spared.

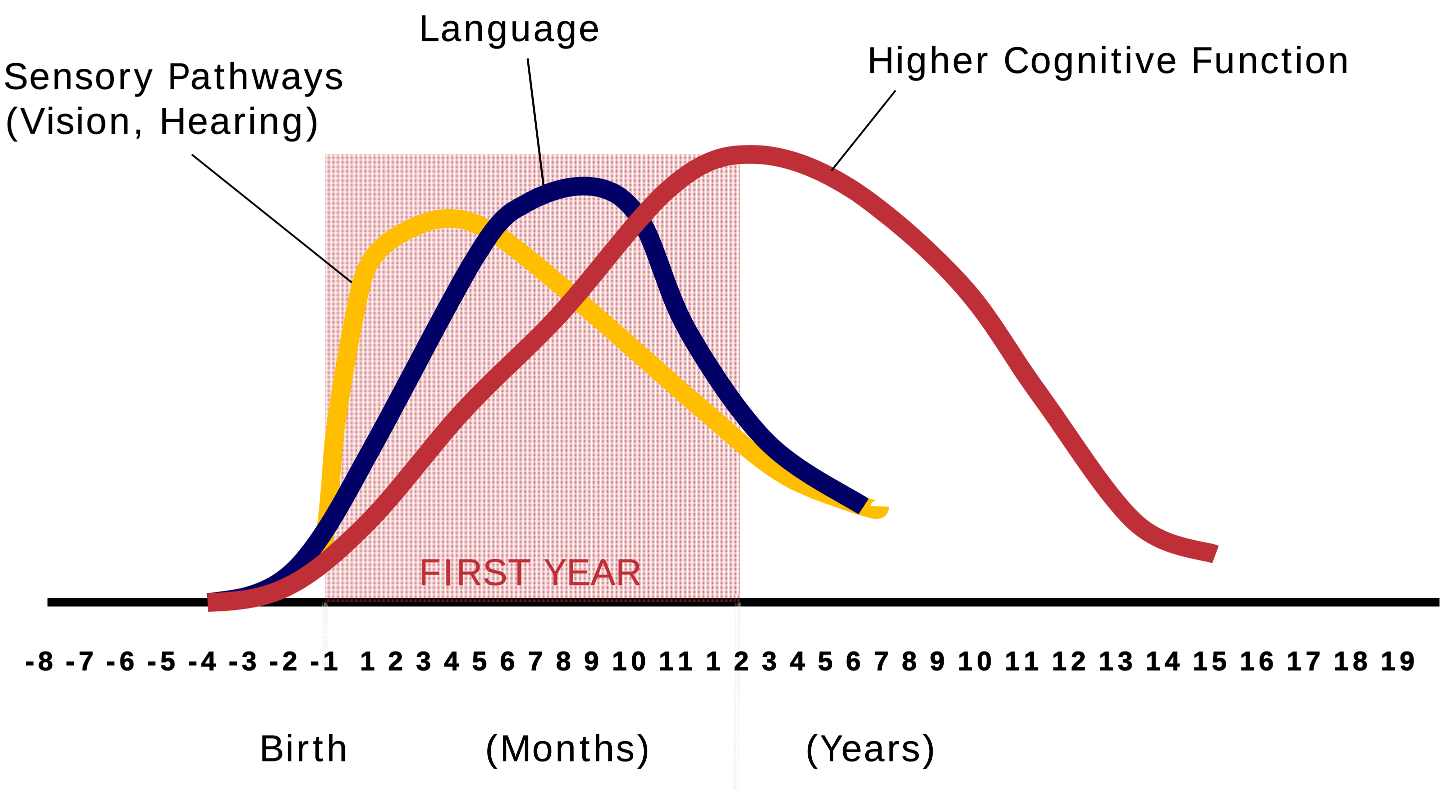
Pruning is primarily postnatal, eliminating 40% of the brain’s cortical neurons during childhood.


Human Brain
at Birth
6 Years old
14 Years old

Center on the Developing Child
HARVARD UNIVERSITY

# Human Brain Development

## Synapse Formation Dependent on Early Experiences




Source: C. Nelson (2000)

# Postnatal Development

At birth, the brain weighs ¼ of its final adult weight of approximately 1300 - 1500 g.

By age 2, it has achieved ¾ of its final weight.

During the first 2 years of life, the cortex doubles and reaches adult dimensions.

During this period, synapses, dendrites, and myelin form

Development of voluntary function: conscious control

Development of involuntary function: unconscious control

Development of consciousness

Connections: use it or lose it

Aging

Video of neuronal cells

http://www.ipmc.cnrs.fr/~duprat/neurophysiology/video.htm