

**EARLY** BRAIN &  
BIOLOGICAL  
DEVELOPMENT  
A SCIENCE IN  
SOCIETY SYMPOSIUM

Dr. Charles Nelson – June 2010



Embryonic and Neural Development:  
Setting the stage for the lifespan



Where science meets real life

# Outline



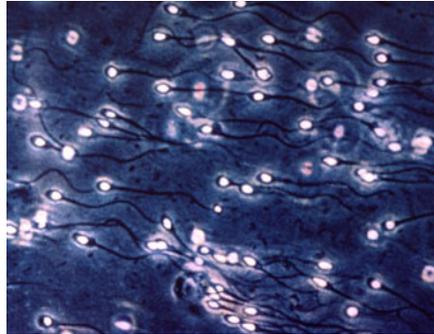
- I. Prenatal development
- II. A tutorial on brain development
- III. Précis to Neural Plasticity

# Developmental Milestones Across the Life Span

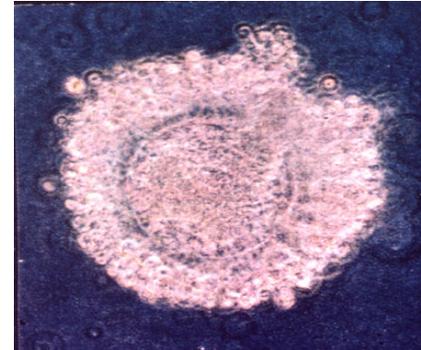


- At age 4 success is . . . not peeing in your pants.
- At age 12 success is . . . having friends.
- At age 16 success is . . . having a driver's license.
- At age 20 success is . . . having sex.
- At age 35 success is . . . having money.
- At age 50 success is . . . having money.
- At age 60 success is . . . having sex.
- At age 70 success is . . . having a driver's license
- At age 75 success is . . . having friends.
- At age 80 success is . . . not peeing in your pants.

# Prenatal Development



+



- Sperm + Egg = one cell containing 46 chromosomes (23 pairs); called *ZYGOTE*.
- **GERMINAL STAGE**
  - Cells multiply (*cleavage*) 12-16 cell stage called *MORULA*.
  - By 4<sup>th</sup> day after conception, morula has 16 to 64 cells. Each cell beginning to change shape and position, and now called *BLASTOCYST*.



- Dividing cells begin to pull away from center of mass and a cavity forms.
- Inner layer will form embryo (then infant), and outer layer forms support structures (placenta, amniotic sac, umbilical cord).
- 7-8 days after conception, *blastocyst* implants in uterus. NOTE: *where* implantation takes place one of determinants of pregnancy outcome, e.g., blood supply in various parts of uterus may be inadequate to support organism development, or may result in undernourished newborn.



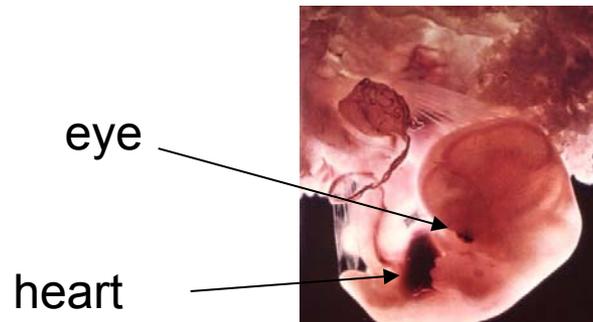
# Embryonic Stage



- Embryo forms 3 layers of cells:
- Inner layer of germ cells is precursor to the *ENDODERMAL* cells that eventually form lining of internal organs, such as digestive tract, respiratory system, bladder, etc.
- Outer layer of germ cells gives rise to 2 additional kinds of cells:
  - *ECTODERMAL* cells (outer), which develop in 2nd week post conception, and which become skin, sense receptors, nerve cells (and brain generally) mammary and pituitary glands, etc.
  - *MESODERMAL* cells (middle), which develop in 3rd week, and which become the muscles (including heart), connective tissue (bone and cartilage), circulatory system, and most of excretory and reproductive systems.

# Some landmarks of embryonic development

- 3rd week: neural tube (nervous system) develops (more elaboration shortly).
- 21 days: eyes form 24 days: heart (although just a tube) begins to flutter and beat. (By this time about 5mm long)



- 4th week: arm and leg buds appear, as does urogenital system. Heart develops into 4 chambers; blood vessels and cells begin to form
- (NOTE: FROM THIS POINT ON EMBRYO HAS OWN CIRCULATORY SYSTEM THAT IS SEPARATE FROM MOTHER'S).



- 5th week: cells inside arm and leg differentiate to become muscle cells, cartilage cells, and bone cells
- 6th week: arms and legs more differentiated and face begins to form (but is not recognizable); liver, gallbladder, and pancreas begin to form
- 7th week: facial structures fuse; errors here result in things like cleft nose, chin, and palate (which affect 1 in 500 births)
- By 8 weeks, embryo weighs 1/30 oz and is about 1 in long.



- During embryonic stage, 95% of body parts and structures form – process referred to as *ORGANOGENESIS*.
- Because so much forming, also thought of as critical period, and organogenesis most vulnerable to disruption.

# Fetal Stage



- What demarcates fetal from embryonic is that real bone cells begin to replace cartilage. Fetal period lasts 7 months and main event is substantial increase in size, along with elaboration and growth of body structures laid down during embryonic phase.



- 3rd month: About 3". Can make breathing and sucking movements (no lungs, though). Can kick, make fist, turn head; fingers and toes formed, fingernails and toenails growing.
- First reflexes appear (including facial reflexes, like squinting, frowning). Finally, sexual differentiation occurs.
- 4th month: By 4th month fetus grows more than any other time (6", 6oz). Head 1/3 length (previously 1/2). It is now mother feels "quickenings" (little flickers). Thumb sucking prevalent now; believed that this experience facilitates sucking reflex when born.





- 5th month: Fetus 12", 16oz. Has sleep/wake cycles, and has favorite sleep position. But, still poor breathing mechanism.
- 6th month: 14", 2 lbs. Eyelids finally open; skin red and wrinkled. Many taste buds on tongue and in mouth; good grasp reflex and some breathing movements; can perhaps do some crying. Is possible, but difficult, to keep such babies alive outside womb.



Hand-to-mouth activity

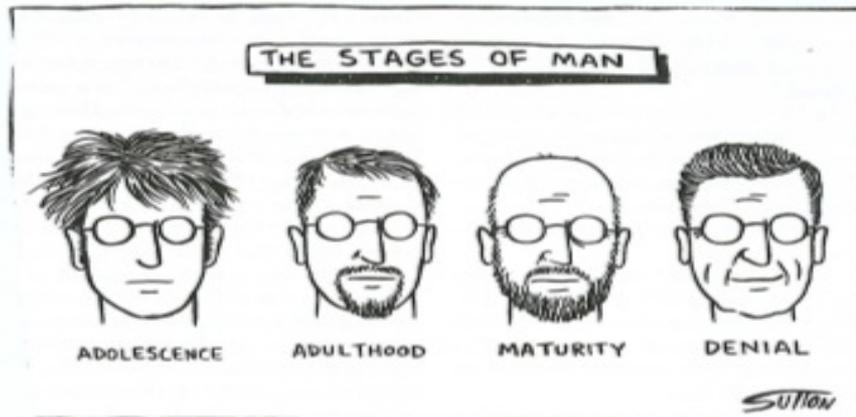


- 7th month: Growth slows down. Rough 23.5 to 25 weeks, fetus now considered VIABLE but needs protective environment.
- 8th and 9th month: Red, wrinkled skin fills out with fat (provides insulation). Gains 1/2 lb. per week. Startle reflex is present; responds to light and sound, lifts its head. 60 percent of adult head size present

# Summary of Prenatal Development



- Zygote forms after conception
- Blastocyst embeds in uterine wall
- Germinal stage gives rise to embryonic stage, which lasts about 8 weeks; during this time all organs, systems, etc. form
- Fetal stage lasts 7 months (in full term pregnancy) and is period of elaboration and growth
- Labor and delivery culmination of all this hard work – generally, 40 weeks post conception



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# Part II. Introduction to Brain Development



# An Accelerated View of Brain Development

15 1/2 wks



22 weeks



23 weeks



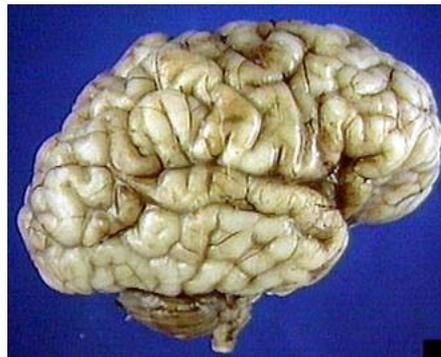
~25 weeks



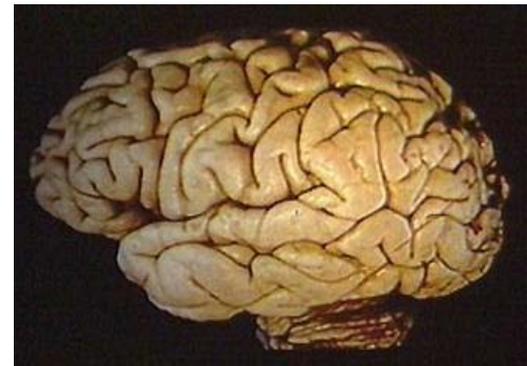
27 weeks



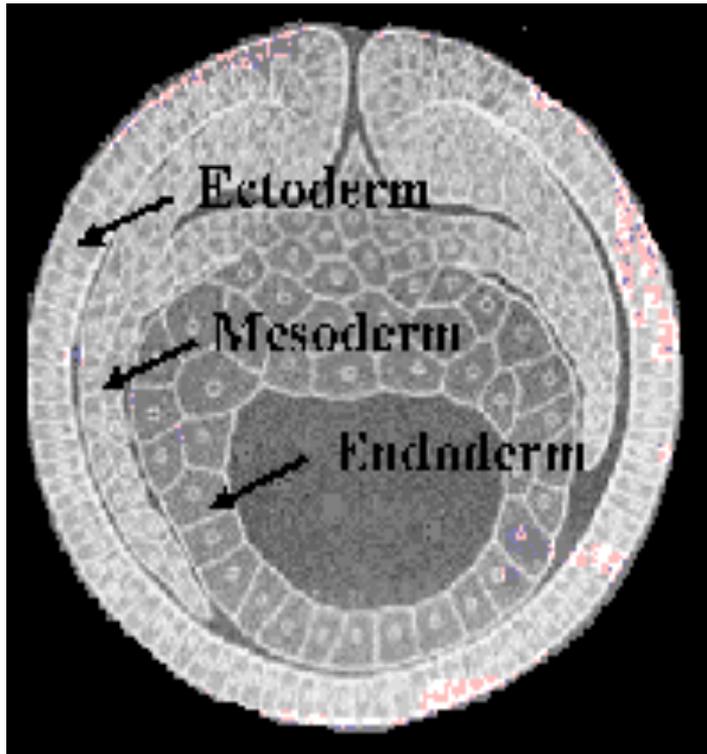
Full term brain



Adult

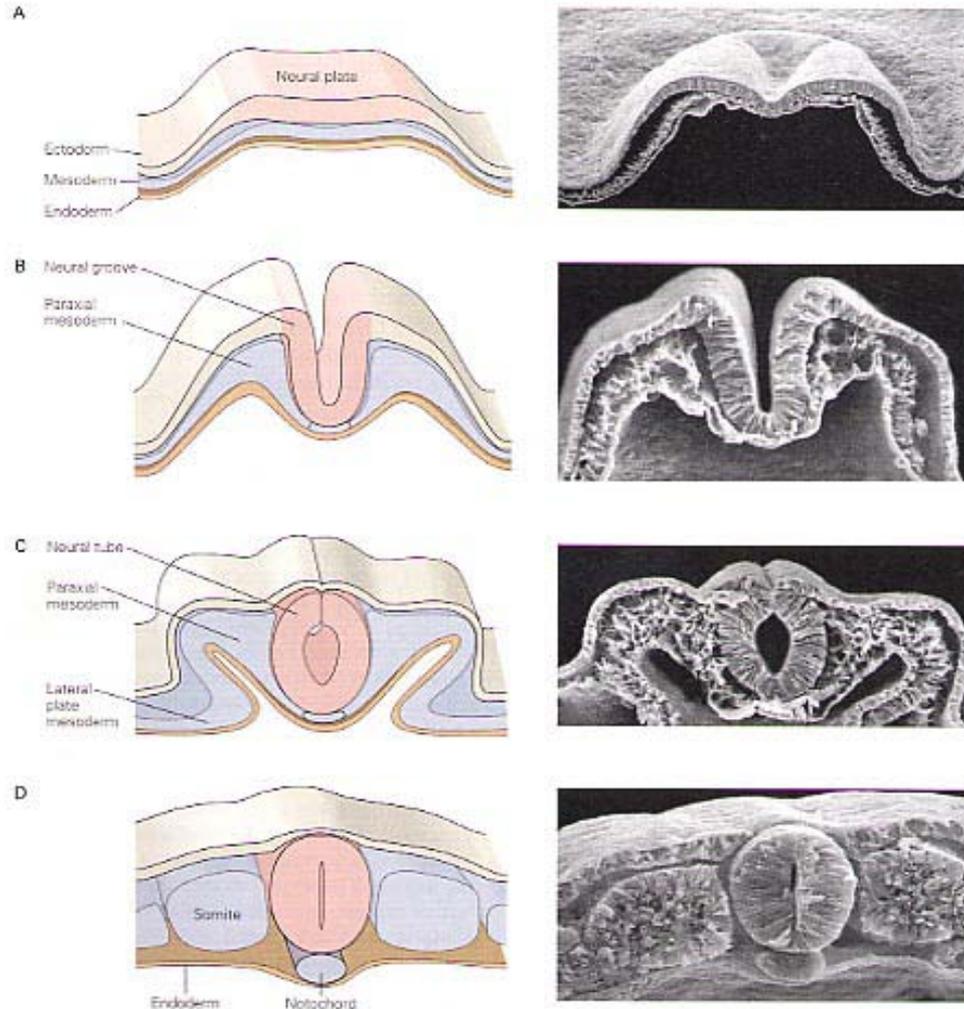


# Neuralation



- Days 18-24:
  - Dorsal (rear) region of ectoderm thickens and forms neural plate
  - neural plate forms a groove
  - neural tube forms
  - tube closes at rostral (top), then caudal (bottom) ends
  - cells trapped inside tube form Central Nervous System (CNS), those outside tube form Autonomic Nervous System (ANS)

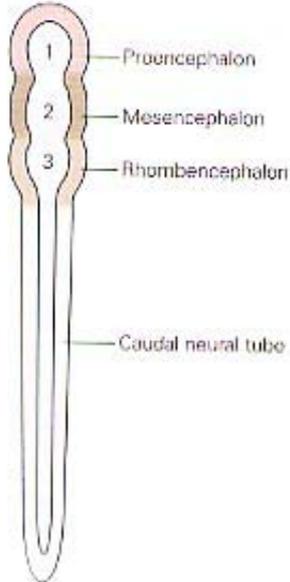
# Neural Tube Formation



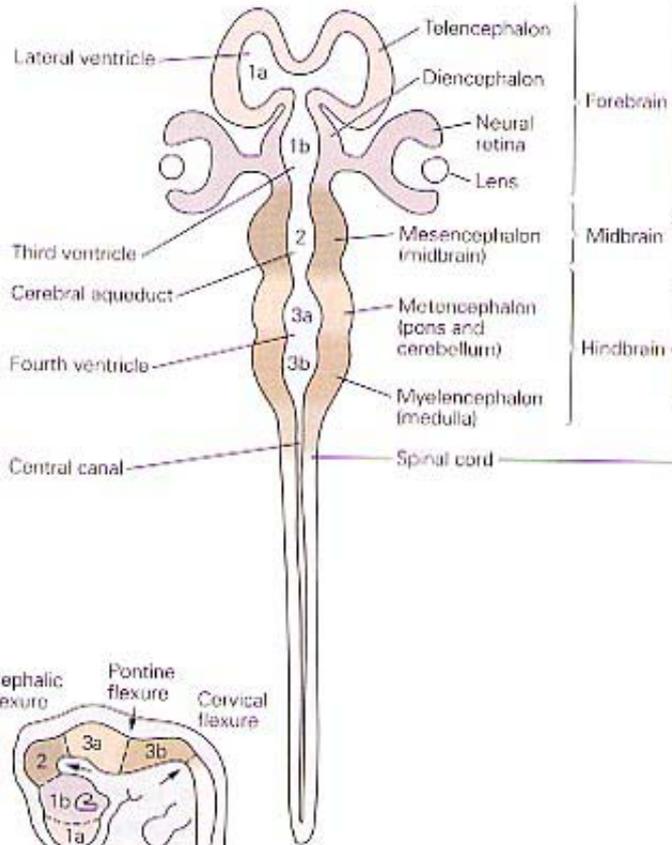
Source: From [The Induction and Patterning of the Nervous System](#), [by T. M. Jessell and J. R. Sanes, 2000](#), in E. R. Kandel, J. H. Schwartz, and T.M. Jessell (Eds.), [Principles of neuroscience \(4<sup>th</sup> ed., p. 1020, fig. 52-1\)](#), New York: McGraw Hill.



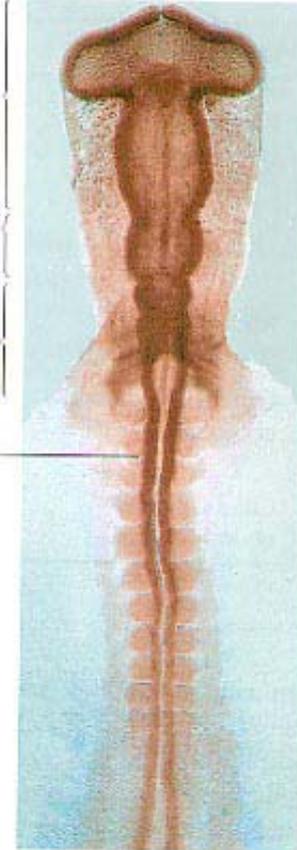
**A** Three-vesicle stage



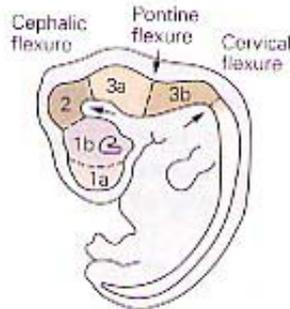
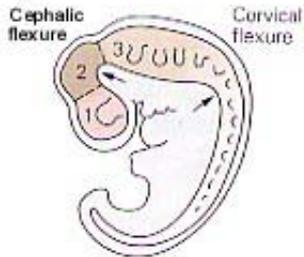
**B** Five-vesicle stage



**C**



**D**



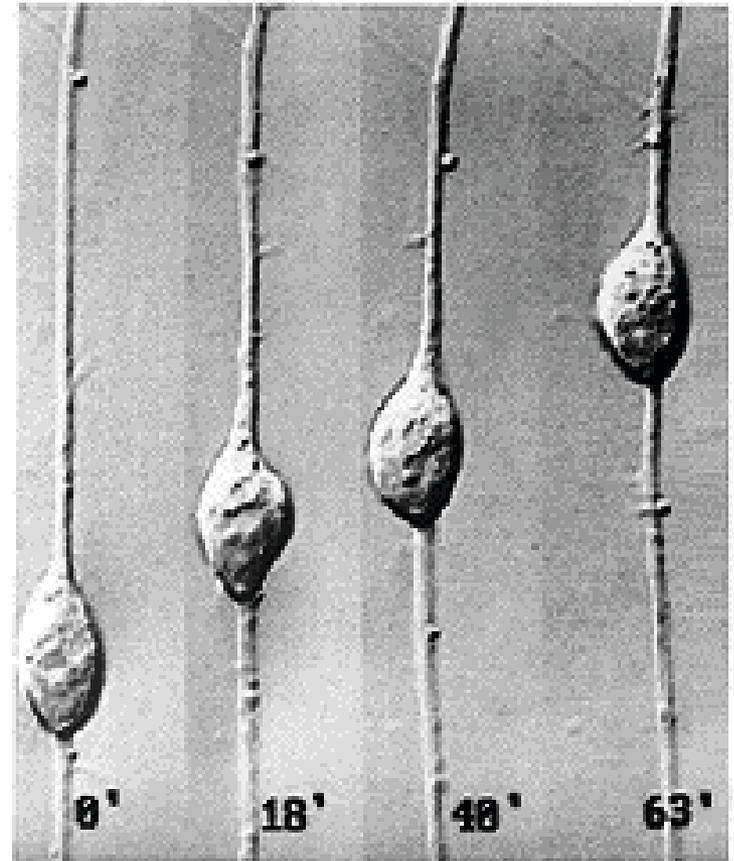
# Neurogenesis



- Precursors to neurons and supportive tissue (glia) form; this continues postnatally.
- Was previously believed most neurogenesis was complete at birth.
- We now know that there is postnatal neurogenesis in at least one area (hippocampus; involved in memory) through at least middle age
- Influenced by experience (learning, exercise ↑ new neurons, and negative/stress ↓ new neurons, notably in hippocampus).
- *Mystery*: what is the purpose of these cells?

# Cell Migration

- Following neural tube closure, there is proliferation of a single layer of epithelial cells that line the tube.
- Cells are connected to each other and in some cases, to radial glial fibers.
- Expansion occurs between layers
- Neuroblasts climb onto fibers and migrate radially or tangentially (see next slide).



Source:

[www.rockefeller.edu/pubinfo/astrotactin.nr.html](http://www.rockefeller.edu/pubinfo/astrotactin.nr.html)

(photo: Mary E. Hatten, Ph.D.)

# Cell migration in ferret

Courtesy of Susan McConnell, Ph.D

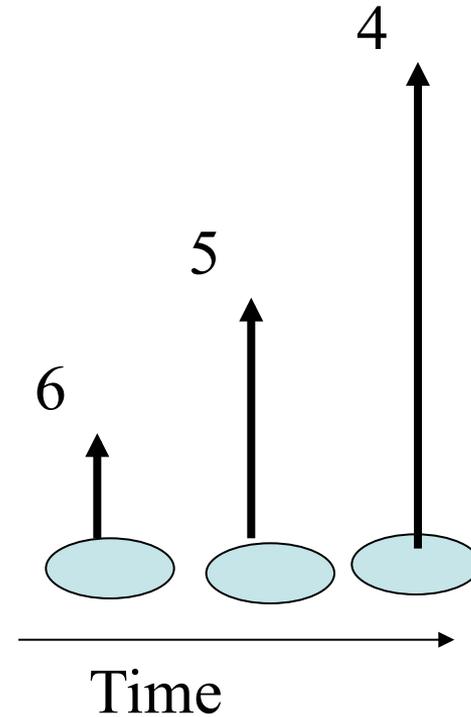


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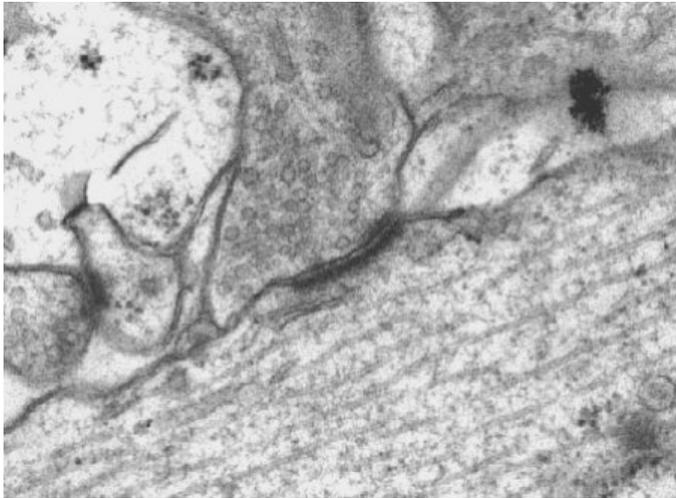
# Cell Migration



- The cerebral cortex forms in inside-out pattern.



# Differentiation and Synaptogenesis



- Differentiation refers to
  - growth of axons and dendrites
  - formation of synapses and
  - synthesis of neurotransmitters.
- Some dendrites and axons form as early as the 15<sup>th</sup> week; big increase seen after 25<sup>th</sup> week
- Both axons and dendrites continue to develop into second postnatal year; thus, is an initial overproduction of axons and dendrites followed by retraction
- Not all cells differentiate; there is massive programmed cell death (apoptosis), during which 40 - 60% of cells die.

# Synaptogenesis



- As with axons and dendrites, is an initial overproduction of synapses, such that newborn brain has many more synapses than adult brain.
- First synapses observed about 23<sup>rd</sup> prenatal week, with rapid proliferation that follows and continues postnatally (keep in mind that synapses can  $\square$  form until axons and dendrites have been born).
- This is followed by retraction to adult levels.
- In human, rate of retraction varies from brain area to brain area.

# Retraction of Synapses



- In visual and auditory cortices, adult levels of synapses are obtained in early childhood (2 - 6 years).
- In the middle frontal gyrus, adult levels are not reached until mid- to late adolescence (see next slide).

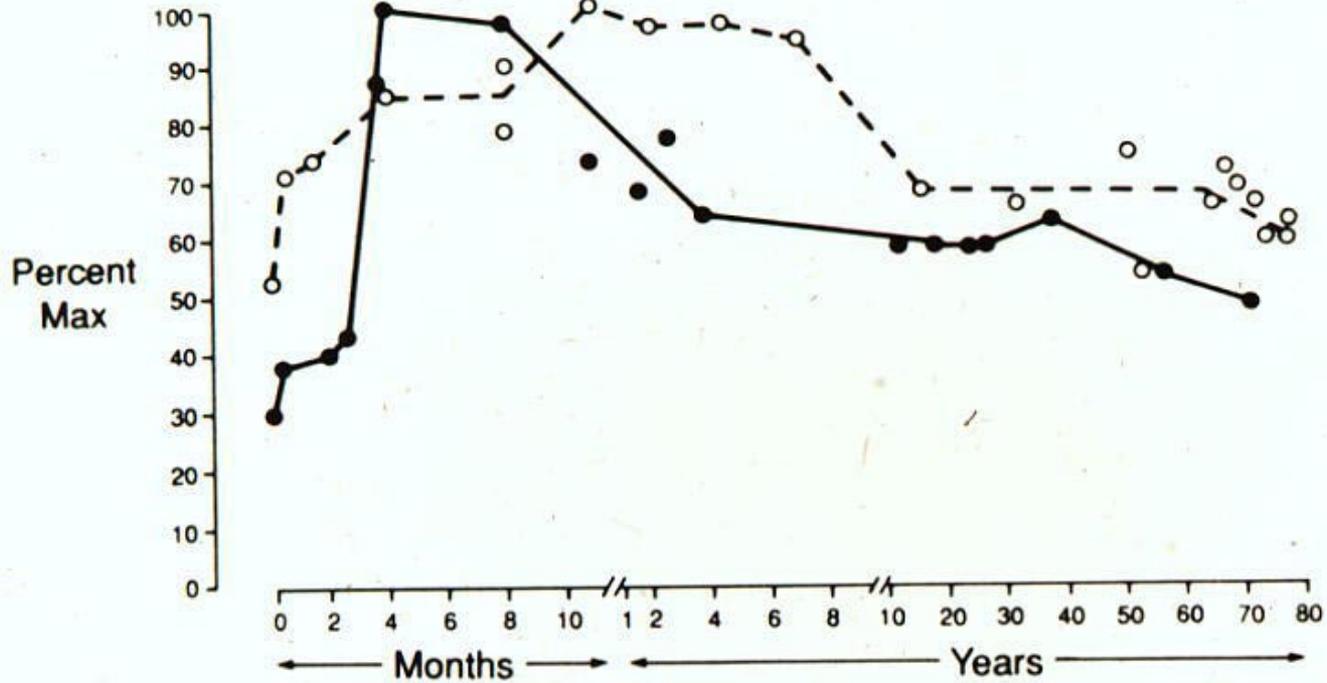


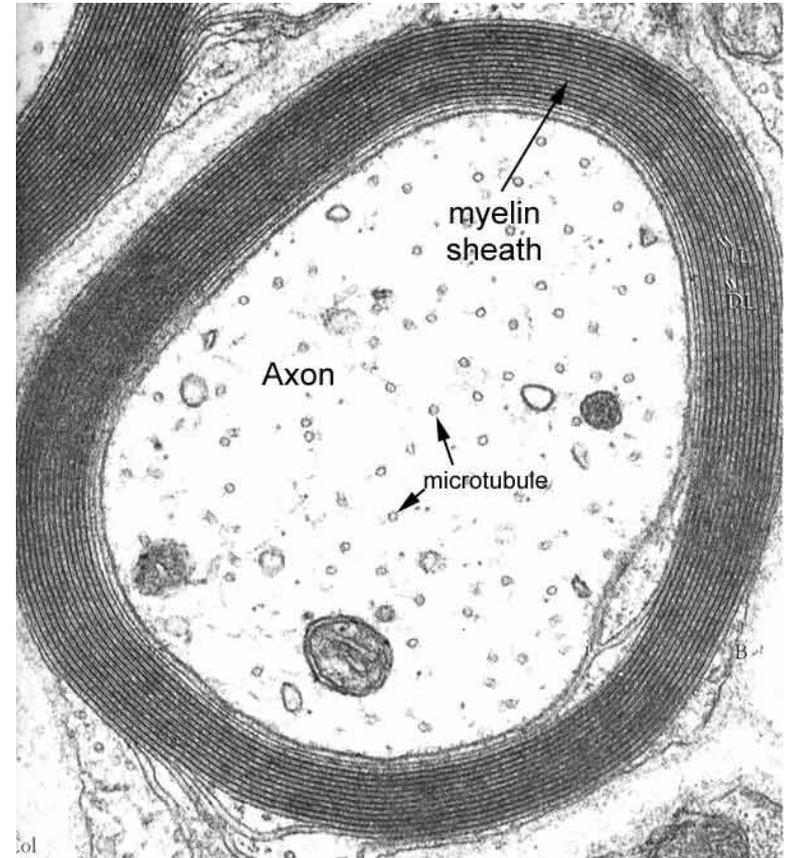
FIG. 2.1. Synaptic density as a function of age in two cortical regions. Solid line = visual cortex (Brodmann's area 17), dotted line = prefrontal cortex (middle frontal gyrus).

# Summary of Synaptogenesis

- Synapse overproduction occurs early in life, whereas synapses elimination occurs much later, and varies greatly by area.
  - e.g., 6 years for visual cortex, 15+ years for prefrontal cortex

# Myelination

- Myelin is lipid/protein substance produced by glia
- Myelin wraps itself around axon as form of insulation.
- Myelin speeds conduction velocity
- Myelination has implications for both serial and parallel processing (e.g., multitasking).



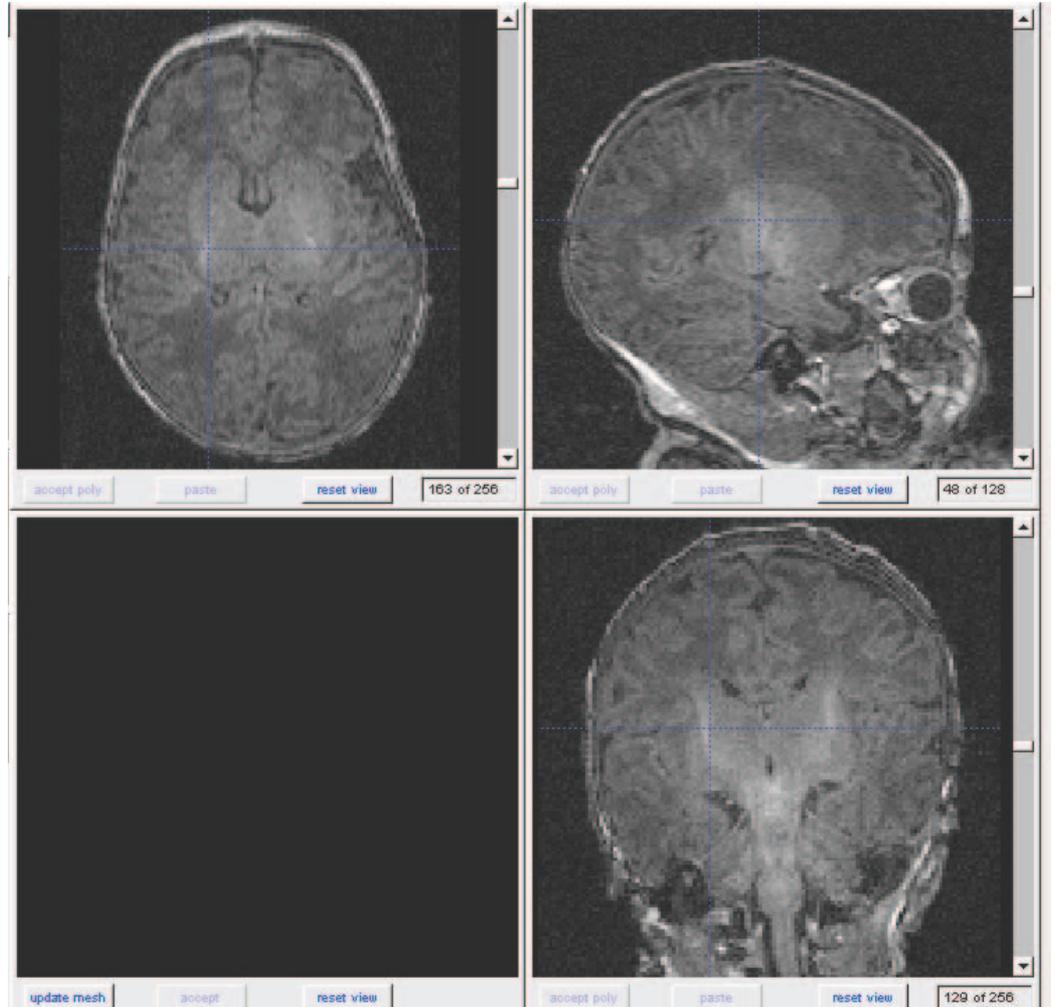
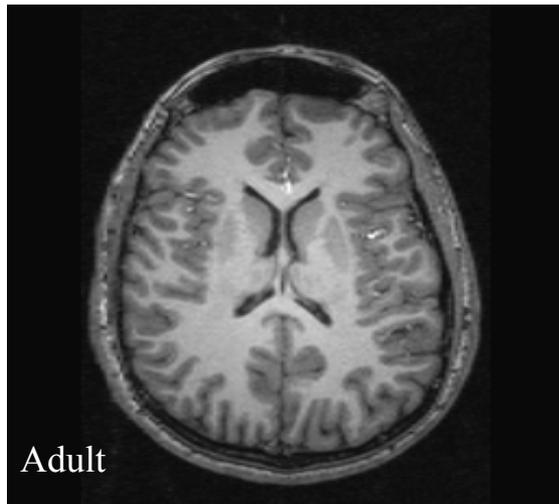
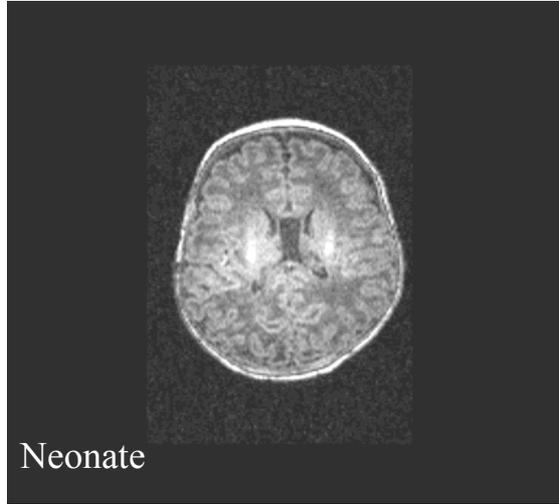
# Myelination



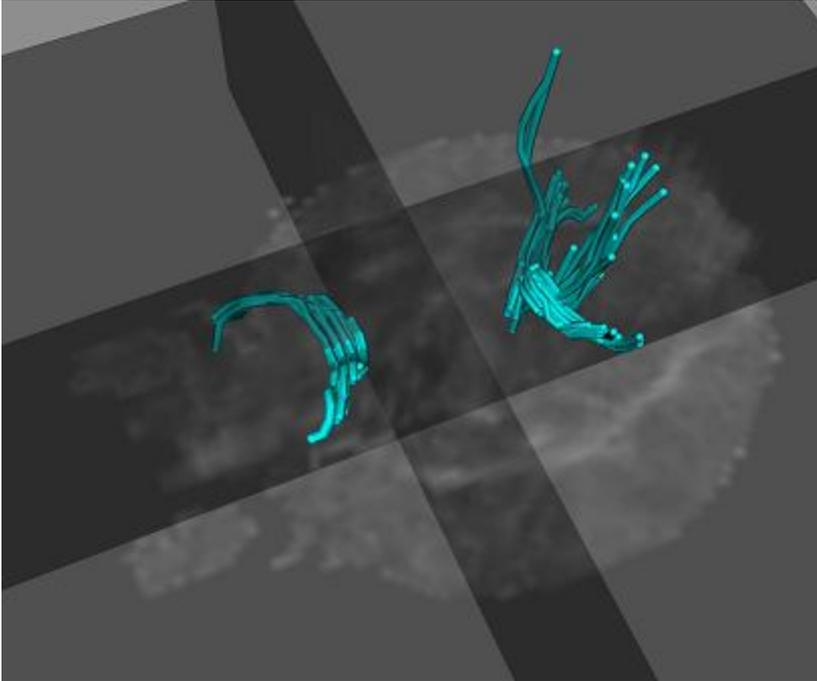
- Myelination occurs in waves beginning prenatally and ending in young adulthood (and in some regions, as late as middle age).
- Historically, researchers stained for myelin in postmortem tissue.
- We now use
  - Magnetic Resonance Imaging (MRI) (see next slides) to distinguish white (i.e., myelinated) from gray (unmyelinated; generally cell bodies) matter
  - Diffusion Tensor/Diffusion Weighted Imaging (DTI) to identify myelinated fiber and fiber tracts (see next slides)



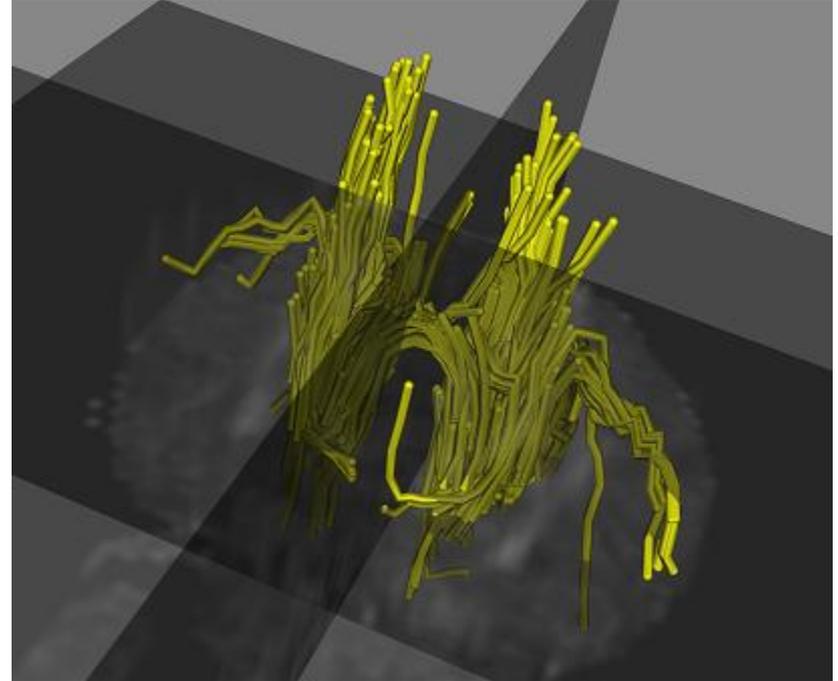
# The Challenge of Gray/White Matter Segmentation in Neonates



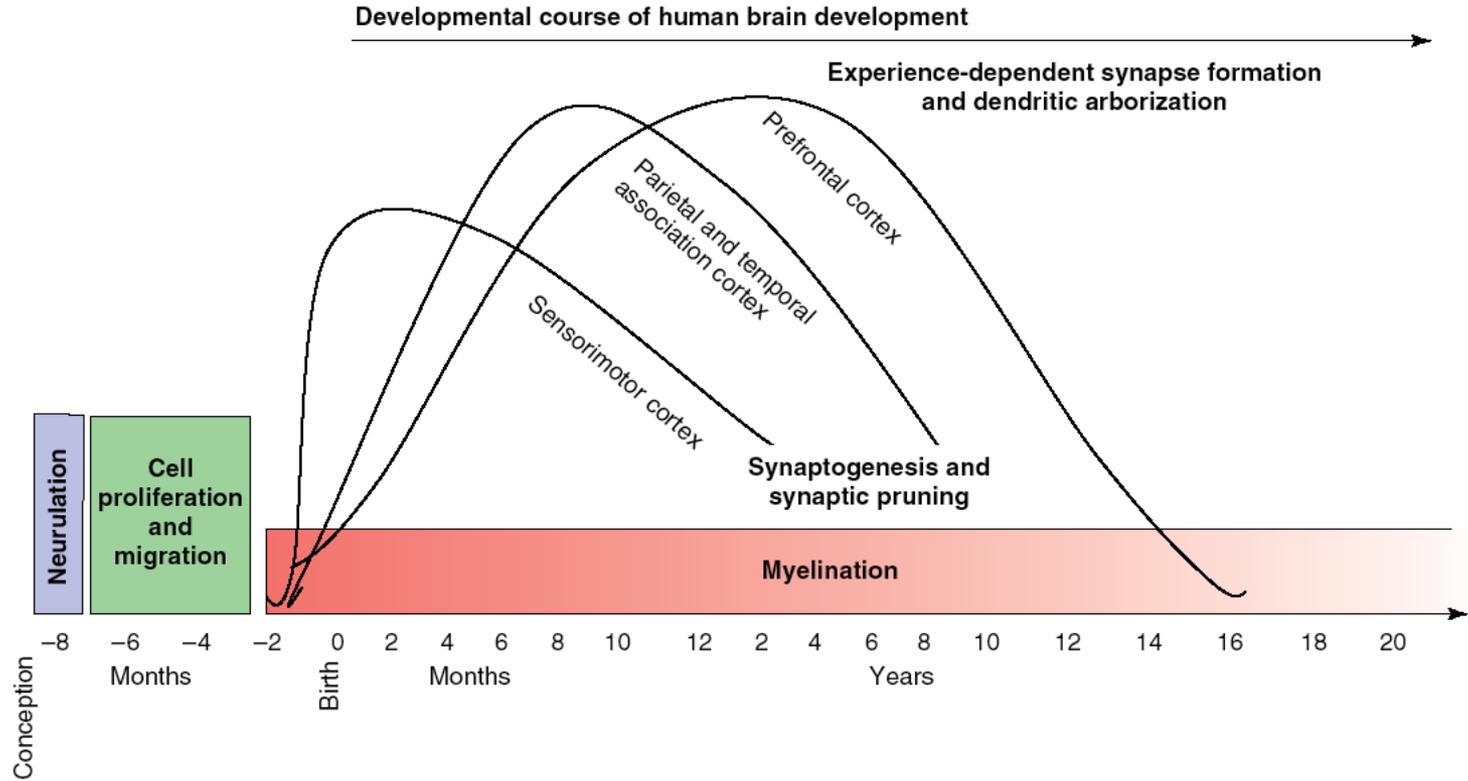
# Fiber Tracking



Genu and Splenium  
of Corpus Callosum



Internal Capsule/  
Auditory Tract



# Part III: Neural Plasticity

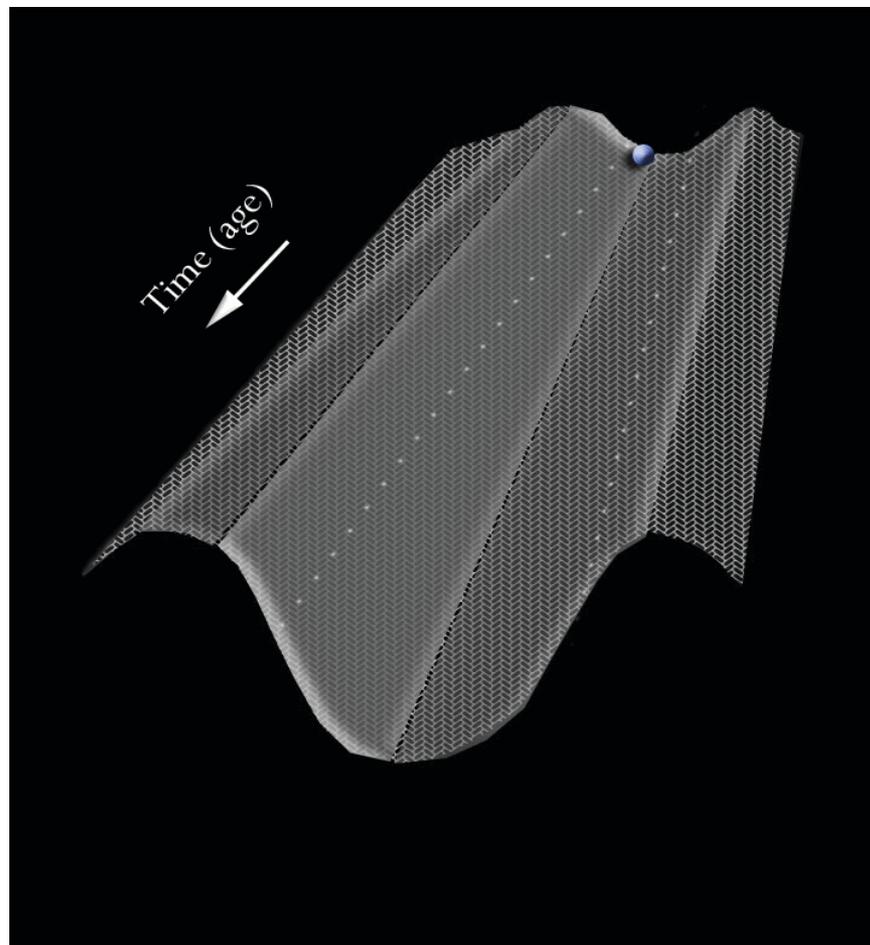


- Does the structure of experience work its way into the structure of the brain, and if so, how?

# Role of Experience (Cont.)

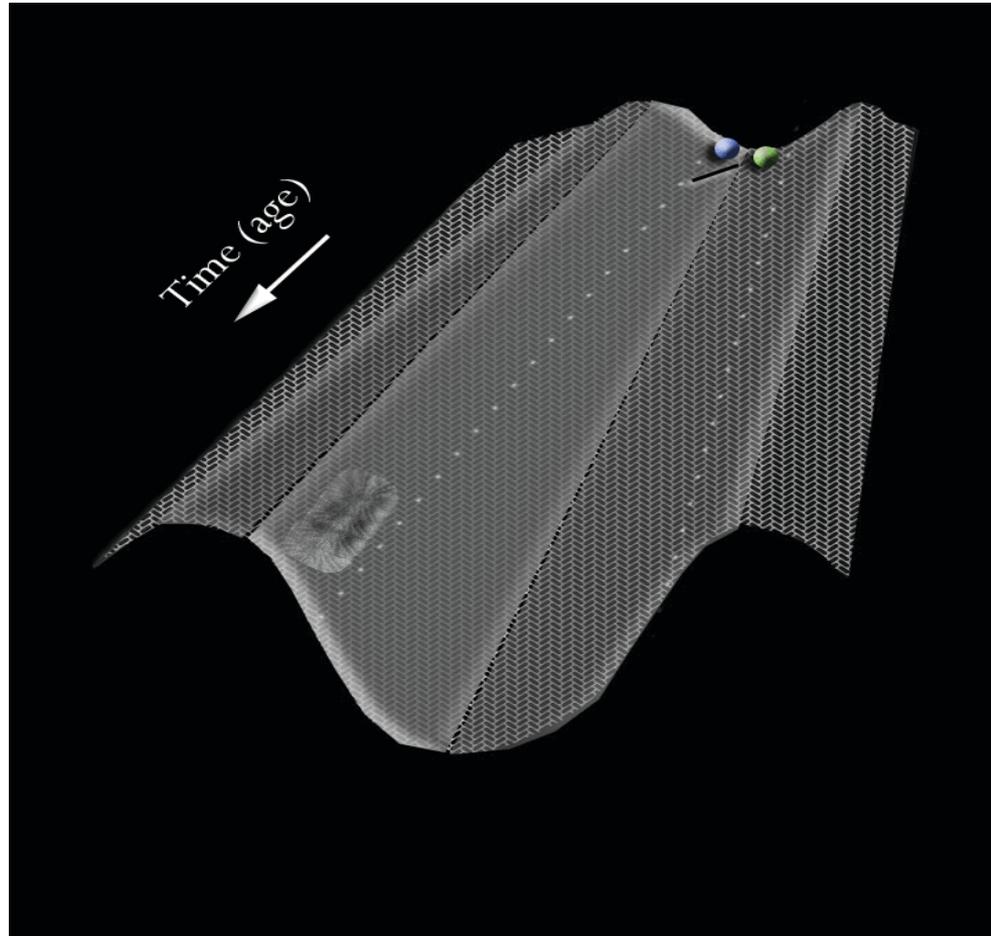
- The impact of experience on the brain is not constant throughout life
- Early experience often exerts a particularly strong influence in shaping the functional properties of the immature brain.
- Many neural connections pass through a period during development when the capacity for experience-driven modification is greater than it is in adulthood. Such phases are referred to as *sensitive* or *critical* periods.
- Language skills, emotional responses, and social behavior, as well as basic sensory and motor capacities, are shaped powerfully and permanently by such early experience.

# Typical Trajectory – a few “speed bumps” but basically development stays on course



Courtesy of William Greenough,  
modified by Eric Knudsen,  
“borrowed” by Charles A. Nelson III

# Effects of early (blue ball) vs. late (green ball) negative experience on brain development, both leading to atypical final outcome



Courtesy of William  
Greenough, modified by  
Eric Knudsen,  
borrowed by Charles  
A. Nelson III

# General Conclusions about Plasticity

- Dr. Kolb will talk at great length about plasticity. For now, assume
  - The likelihood of a given behavioral system exhibiting plasticity seems to depend on whether the system being challenged is one ...
    - that has had the right early experience to “set” it (e.g., access to a normal visual world)
    - In which function is somehow essential to the infant early in life
    - If so, will likely exhibit a sensitive period and will be less plastic with time;
    - if not, then no sensitive period and more plastic with time

# General Conclusions about Plasticity



- that depends on neural circuits whose elaboration require exposure to particular types of experience during a sensitive period of time, and finally
- that requires continual challenges and/or maintenance thereafter.

# Overall Conclusions

- The formation of the brain commences within weeks of the formation of the embryo
- Although the basic architecture of the brain is laid down by the third trimester of pregnancy, brain development continues through the first 2-3 years of postnatal life, when the brain looks (but doesn't function like) the adult brain

# Overall Conclusions (continued)

- But, in key regions (e.g., prefrontal cortex) and in key ways (e.g., myelination), brain development continues in earnest through adolescence/young adulthood.
- This prolonged process of development brings with it both a period of opportunity or vulnerability – what we refer to as neural plasticity
- We learn more about plasticity from Dr. Kolb.

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# THE END

