ASHI691:

Why We Fall Apart: The Neuroscience and Neurophysiology of Aging

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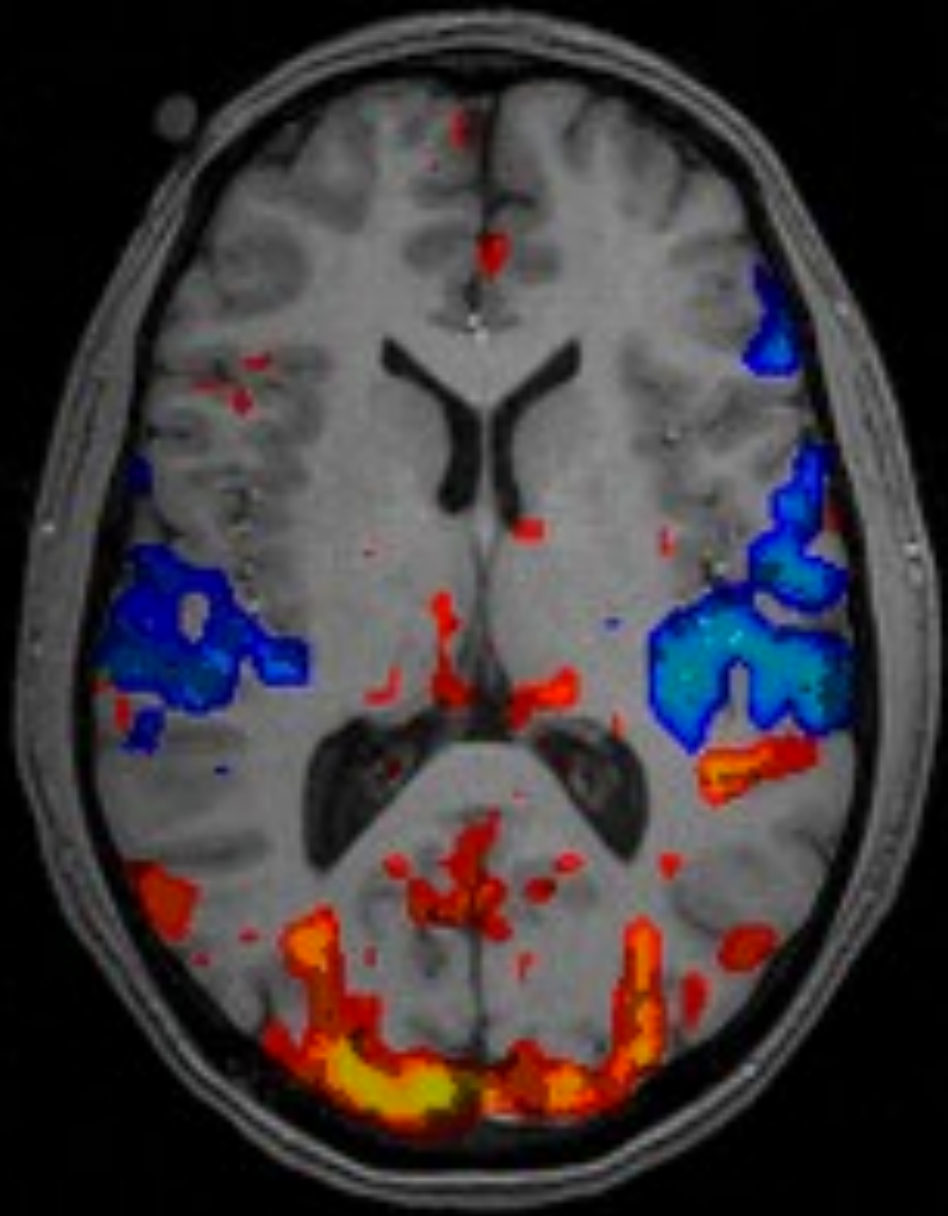
LECTURE 1:
NEURAL DEVELOPMENT

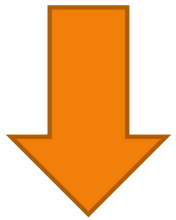


Development of the Central Nervous System

- an ongoing process, through adolescence and maybe even adult hood ?
  - the nervous system is "**plastic**"
- Experience plays a key role
- Dire consequences when something goes wrong
  - "teratogens"
    - Drugs of abuse, industrial chemicals, caffeine?, household chemicals

Stages of Development

Phase	Approximate Age	Highlight
Prenatal	Conception - birth	Rapid physical growth
Infancy	Birth - 2 yrs	Motor development
Childhood	2 - 12 yrs	Abstract reasoning
Adolescence	13 - 20 yrs	Identity creation, "Judgement"

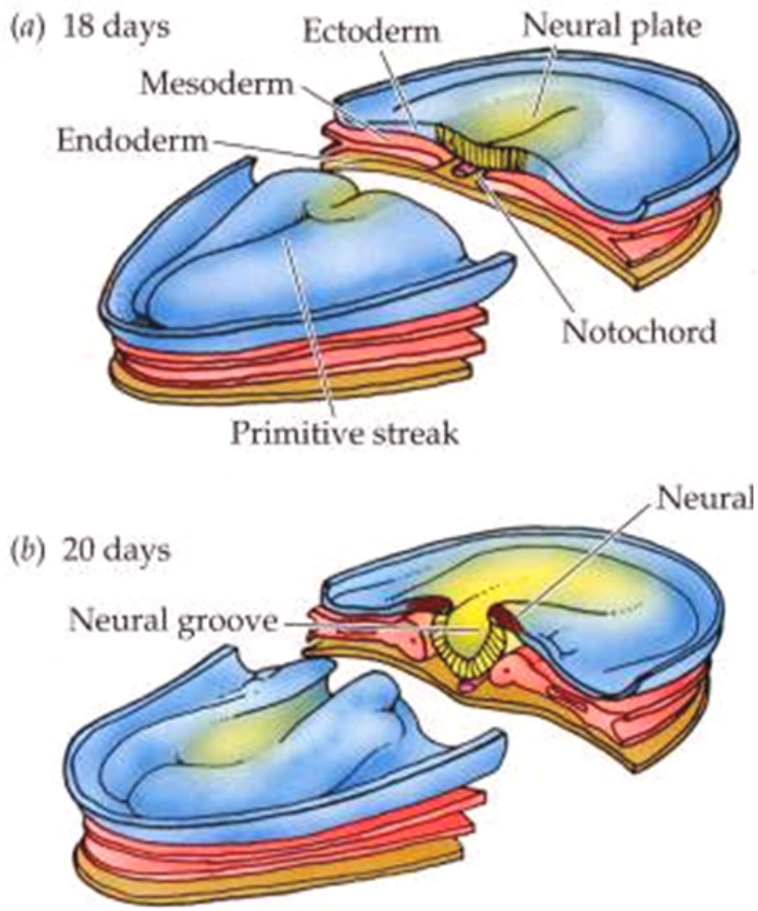


Directly related to maturation of the "Prefrontal Cortex"

Phases of Prenatal Development

- Ovum + sperm
  - zygote
- Once zygote implants in uterus
  - embryo
- Week 8 until birth
  - fetus

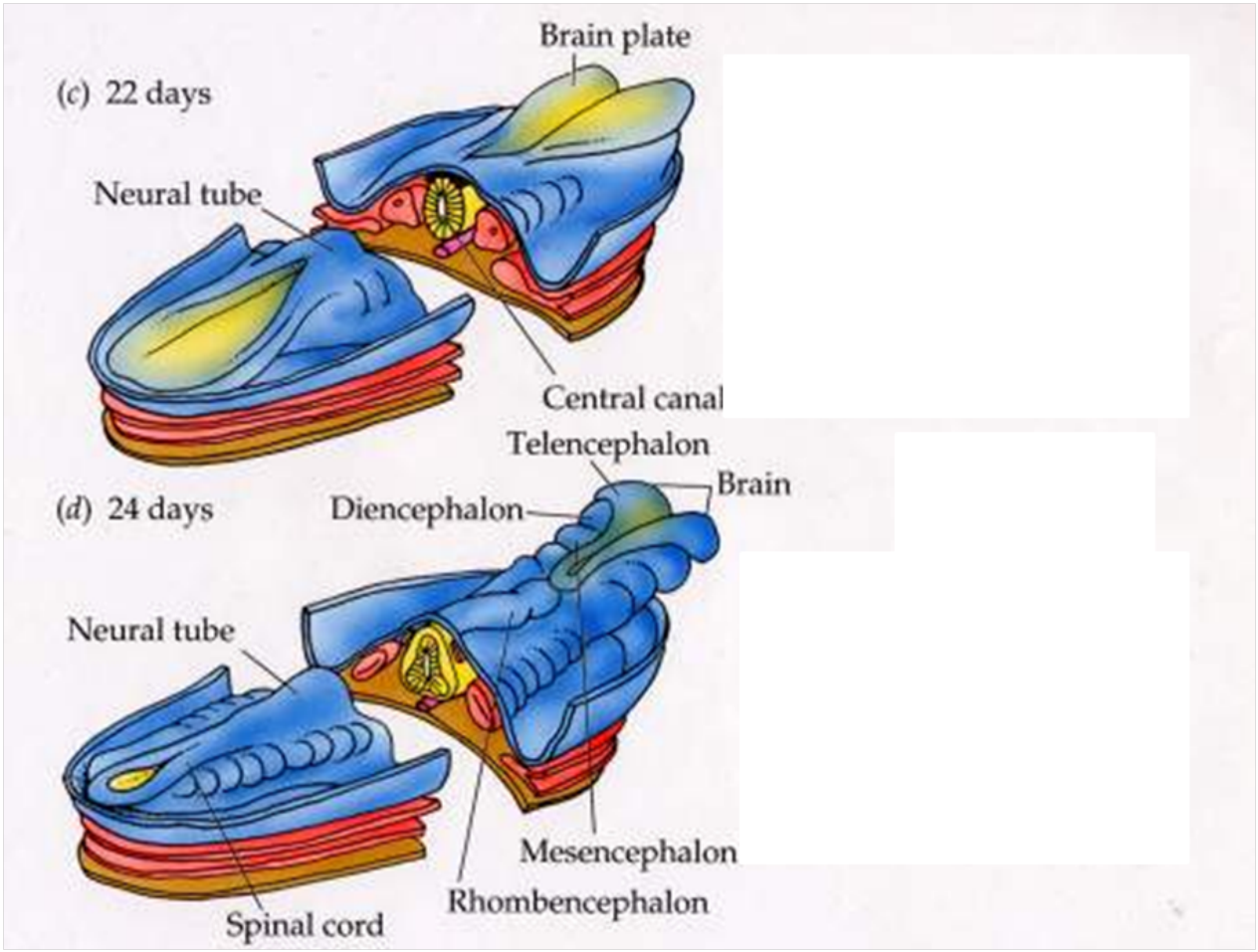
At about 18 days after conception the embryo begins to implant in the uterine wall.



a. Consists of 3 layers of cells: endoderm, mesoderm, and ectoderm.

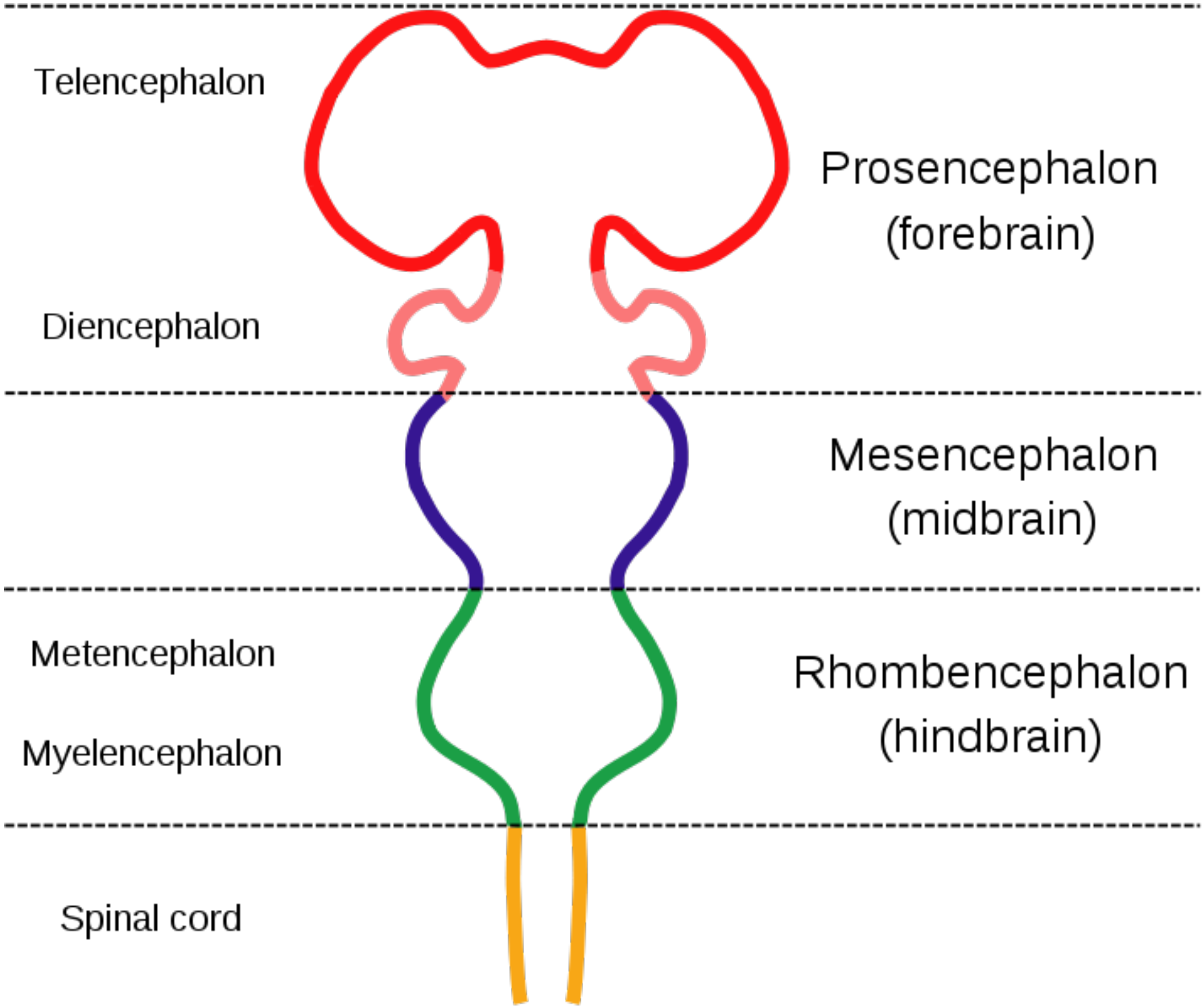
Thickening of the ectoderm leads to the development of the neural plate

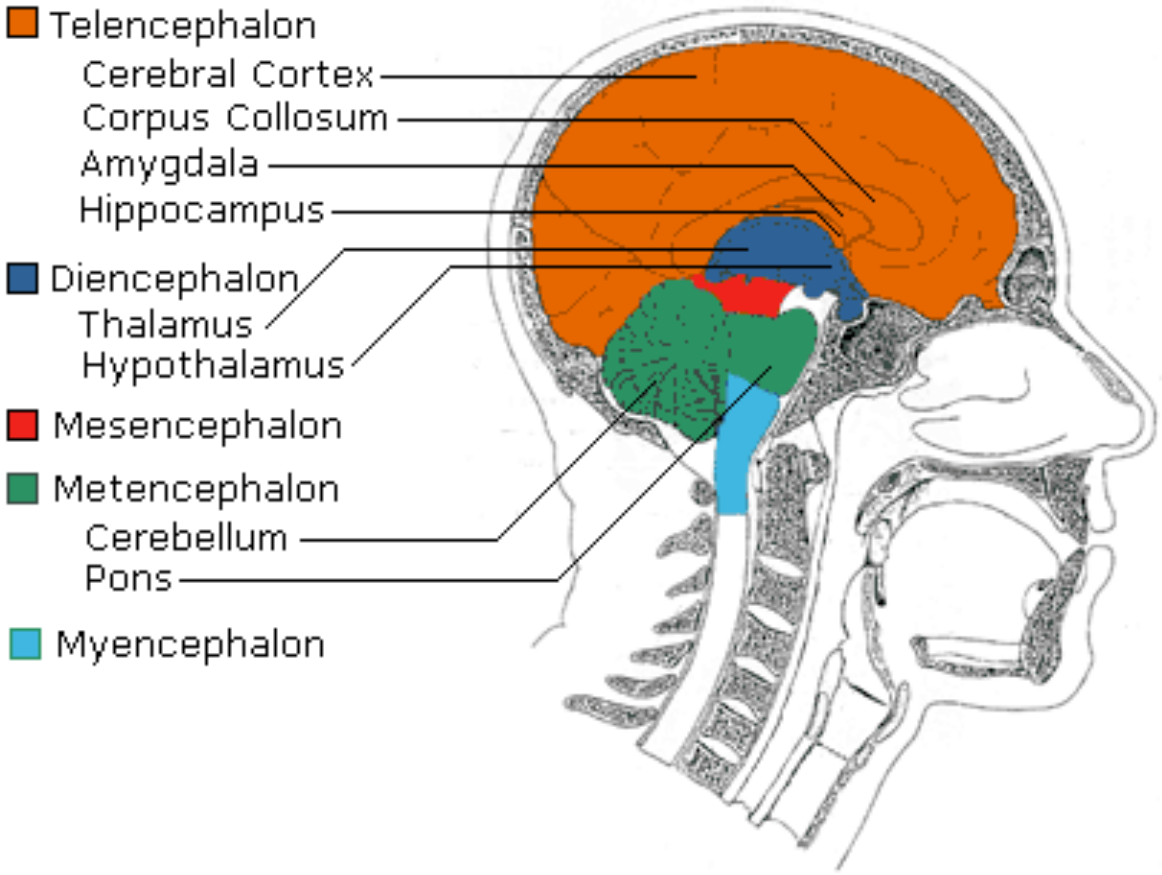
b. The neural groove begins to develop at 20 days.



c. At 22 days the neural groove closes along the length of the embryo making the neural tube.

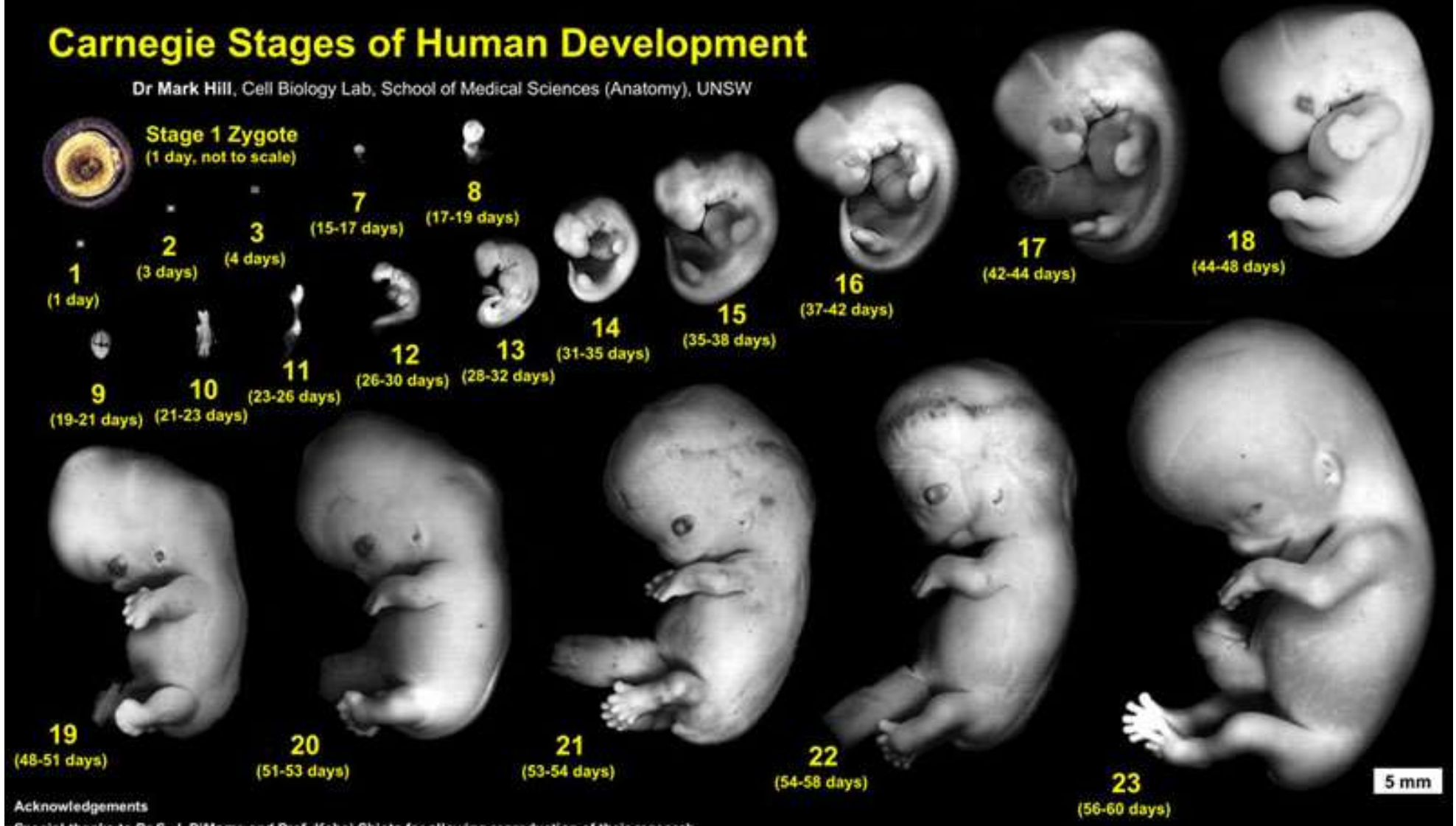
d. A few days later 4 major divisions of the brain are observable – the telencephalon, diencephalon, mesencephalon, and rhombencephalon.


Telencephalon
Diencephalon
Prosencephalon
(forebrain)
Mesencephalon
(midbrain)
Metencephalon
Myelencephalon
Rhombencephalon
(hindbrain)
Spinal cord


Telencephalon
Cerebral Cortex
Corpus Collosum
Amygdala
Hippocampus
Diencephalon
Thalamus
Hypothalamus
Mesencephalon
Metencephalon
Cerebellum
Pons
Myencephalon

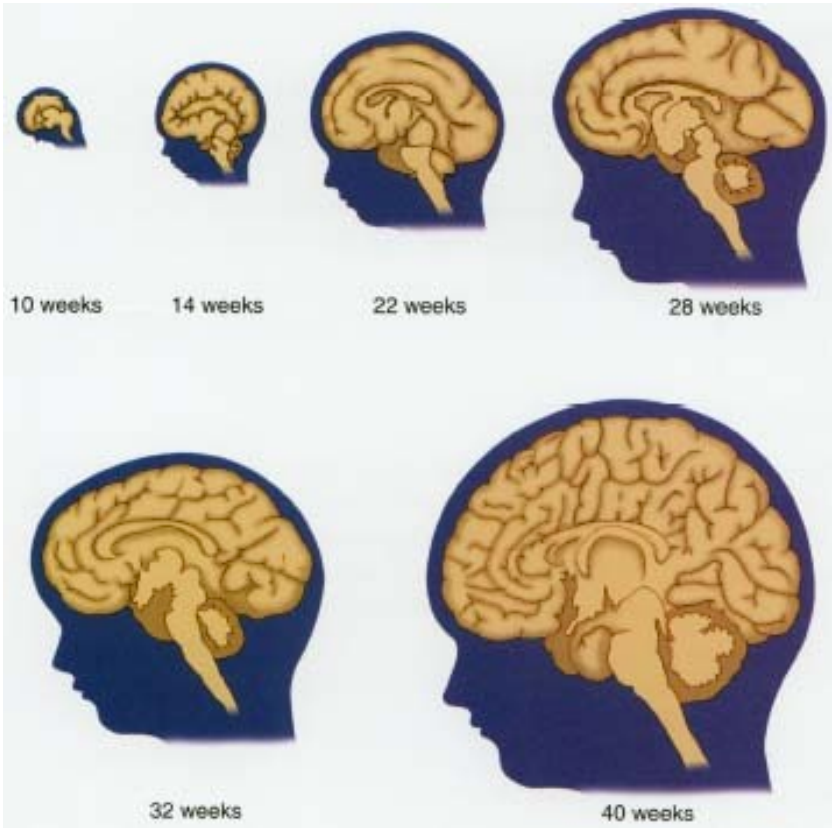
Carnegie Stages of Human Development

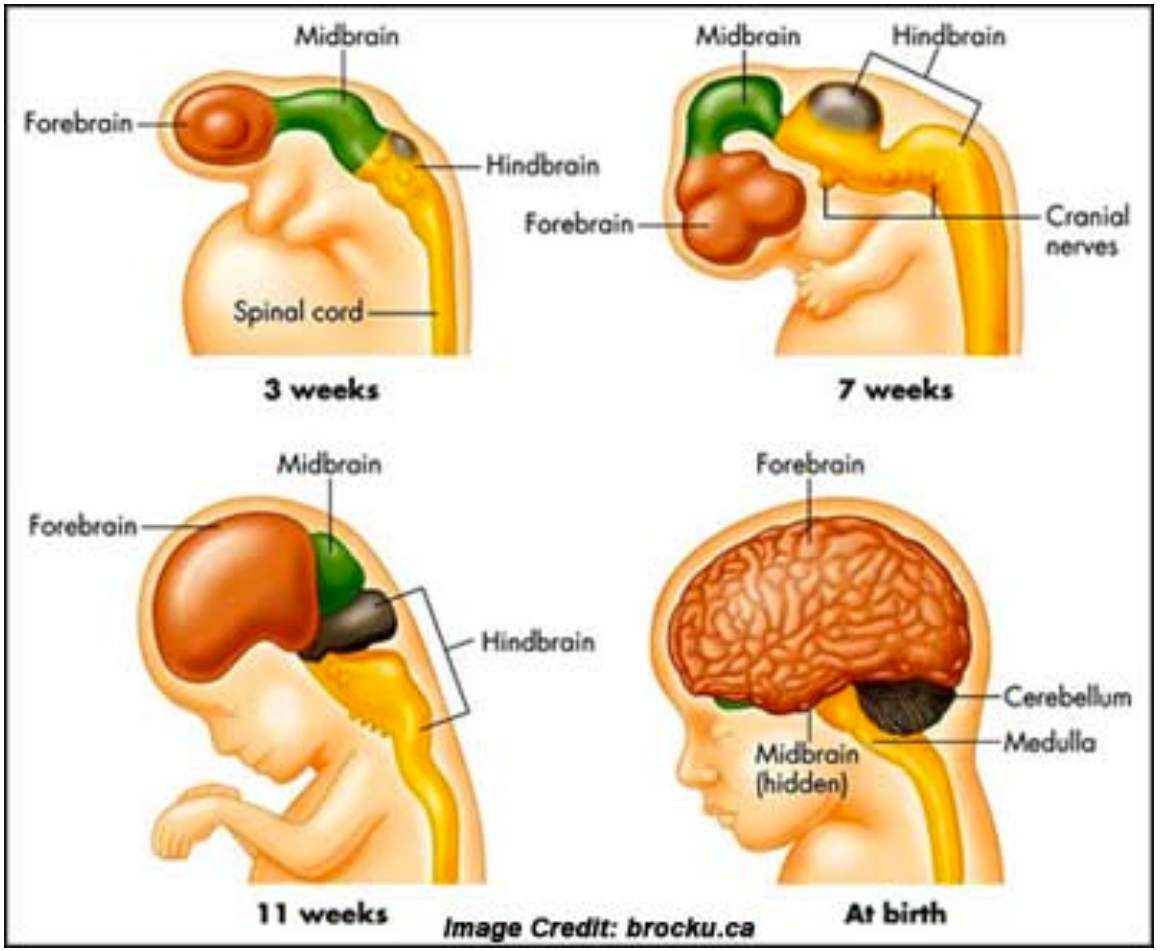
Dr Mark Hill, Cell Biology Lab, School of Medical Sciences (Anatomy), UNSW

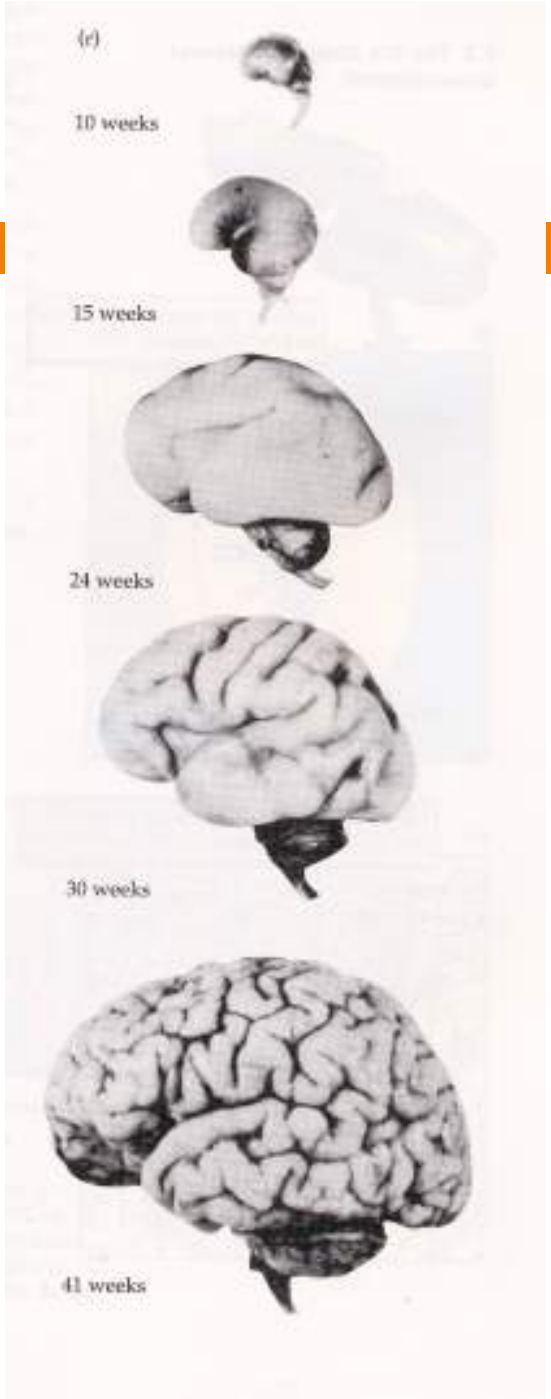


Acknowledgements

Special thanks to Dr S. J. DiMarzo and Prof. Kohei Shiota for allowing reproduction of their research images and material from the Kyoto Collection and Ms B. Hill for image preparation.


10 weeks
14 weeks
22 weeks
28 weeks
32 weeks
40 weeks


Midbrain
Forebrain
Hindbrain
Spinal cord
3 weeks
Midbrain
Hindbrain
Forebrain
Cranial nerves
7 weeks
Midbrain
Forebrain
Hindbrain
11 weeks
Forebrain
Cerebellum
Medulla
Midbrain (hidden)
At birth
Image Credit: brocku.ca



Photographs of Human Fetal Brain Development

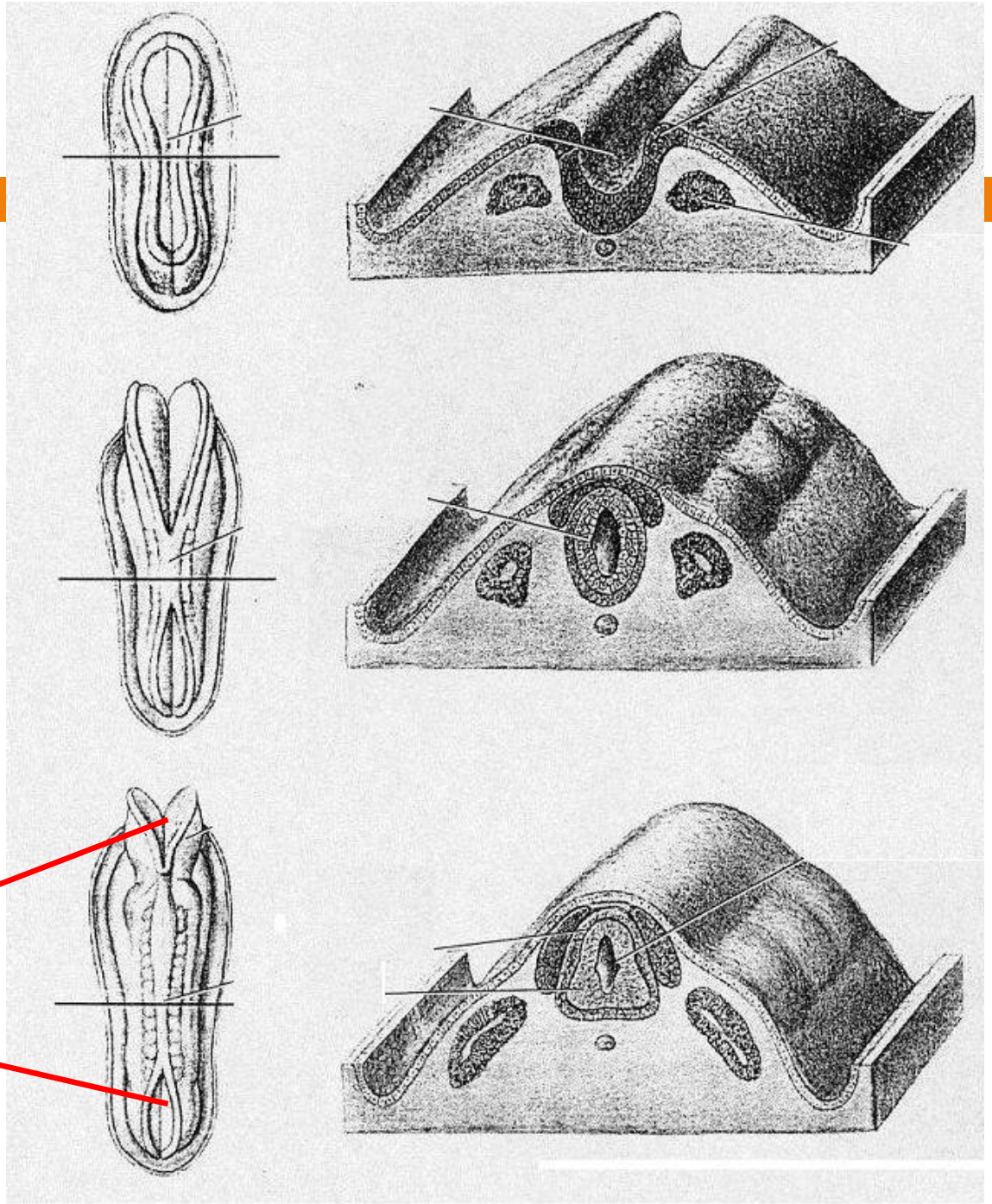
Lateral view of the human brain shown at one-third size at several stages of fetal development. Note the gradual emergence of gyri and sulci.

Neural Groove

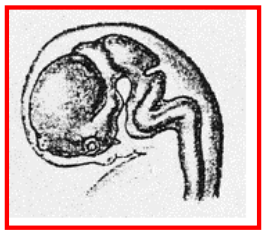
Neural Tube

Brain

Spinal Chord

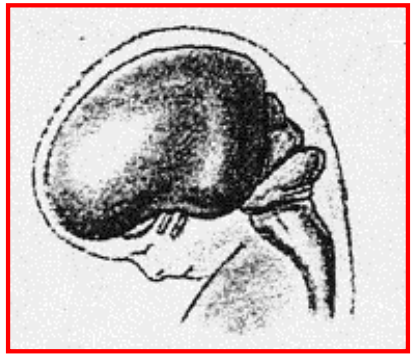


•Neurons forming rapidly
•1000's per minute

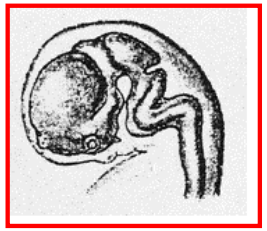


7 Weeks

Division of the halves of the brain visible



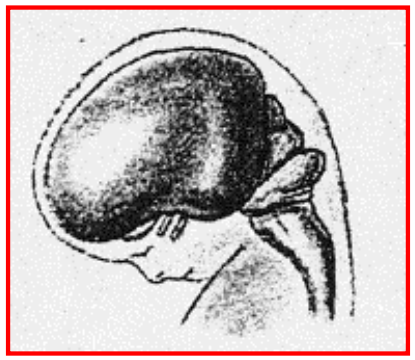
14 Weeks



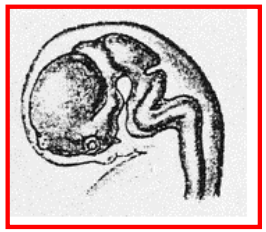
7 Weeks

•Nerve cell generation complete
•Cortex beginning to wrinkle
•Myelinization

6 Months

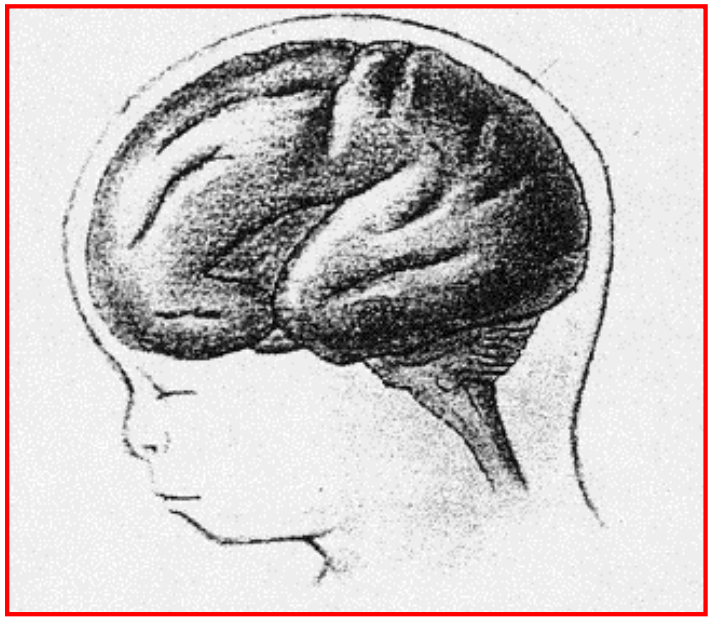


14 Weeks

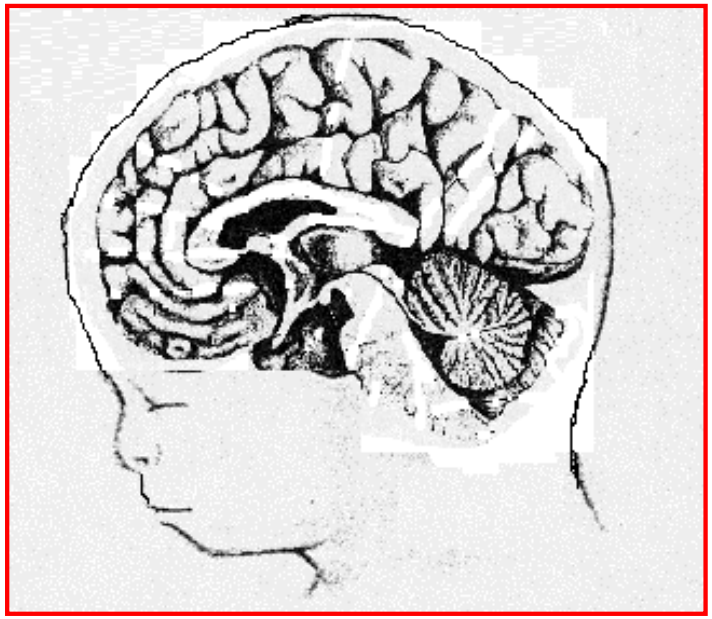


7 Weeks

9 Months



9 Months



Before Birth

- Tremendous development occurs in utero. Nutrition, maternal emotions, etc. all affect brain development.
- There is no significant growth in the number of brain cells (neurons) following birth.
- What **does** grow after birth are the connections (synapses) between neurons.

Development of the Cortex

- 2 types of cells:
- Neurons
- Glial cells

Development of the Cortex

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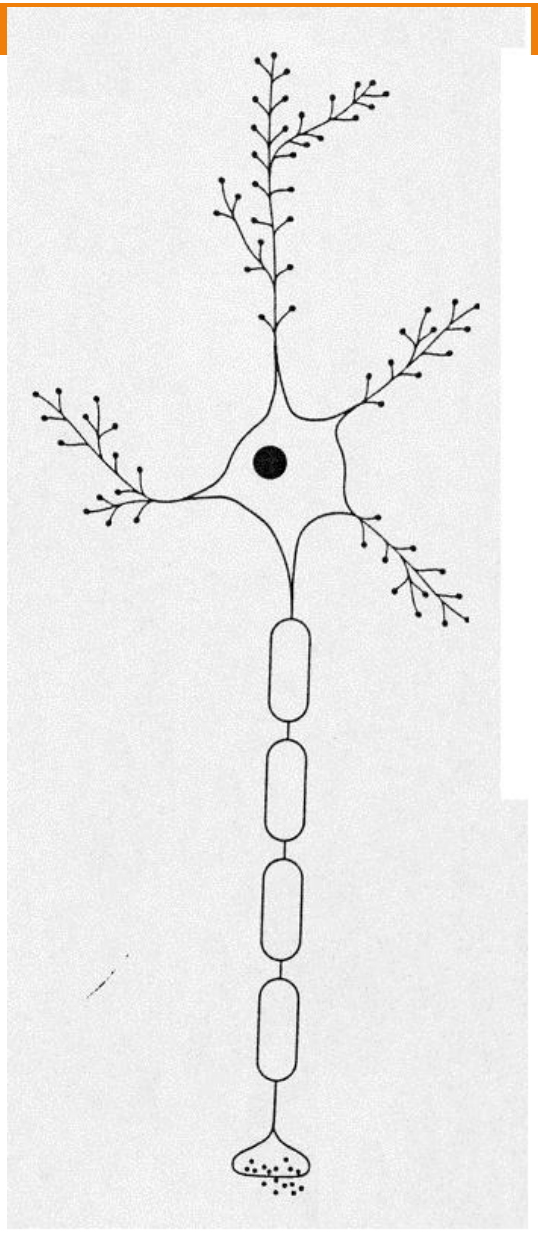

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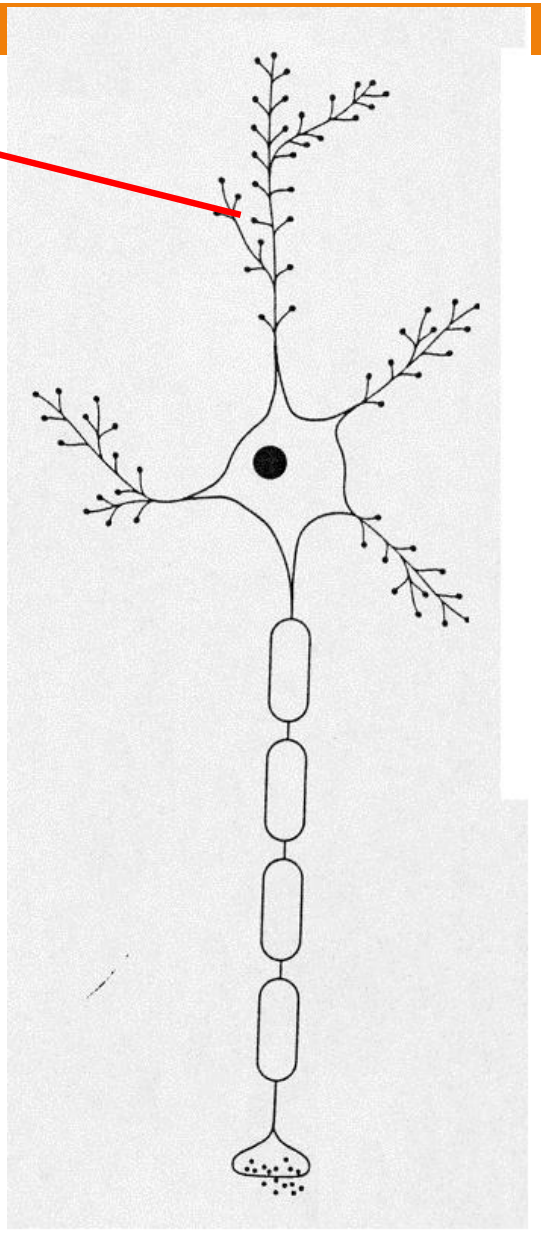

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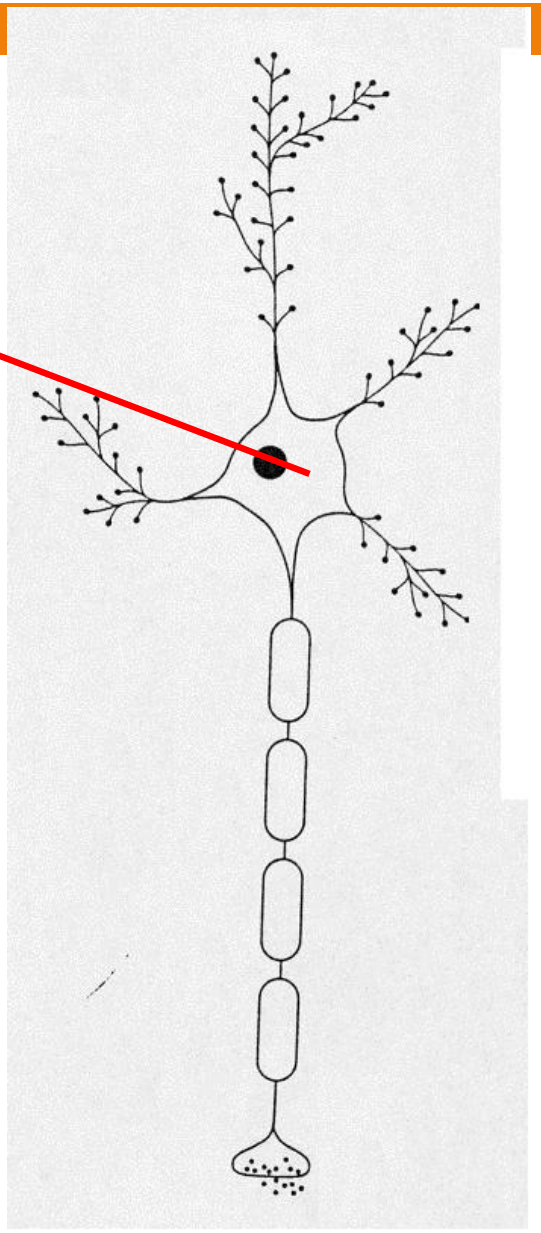

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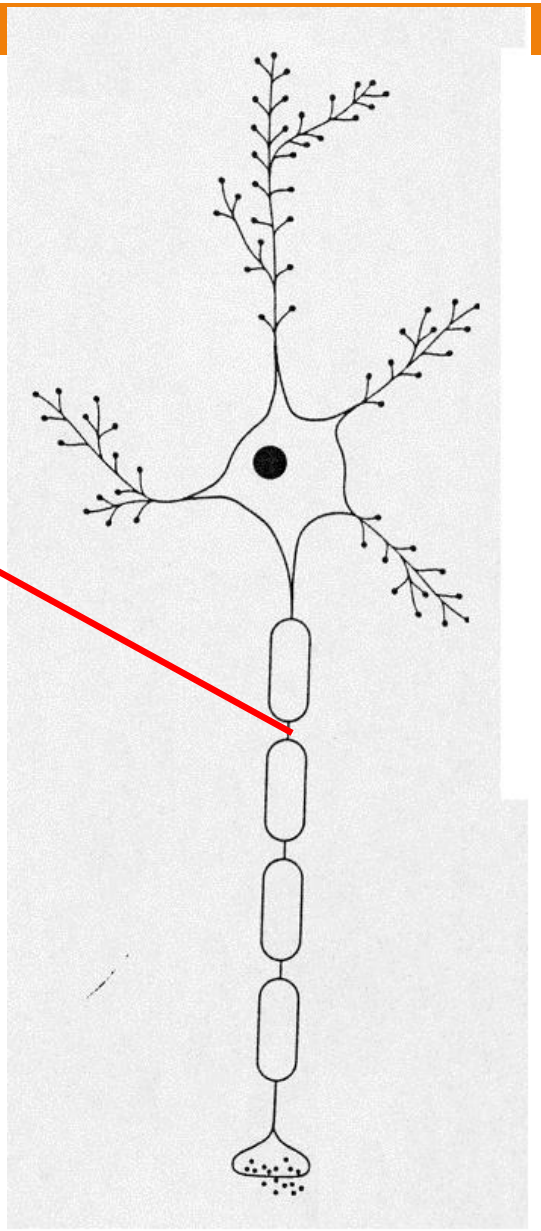

Development of the Cortex

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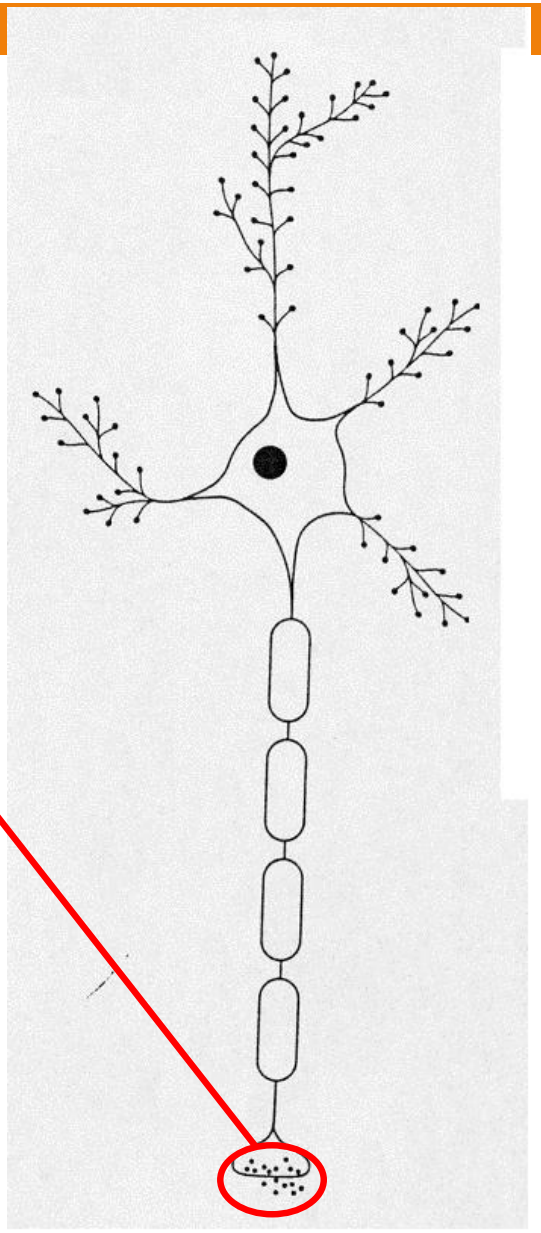


Development of the Cortex

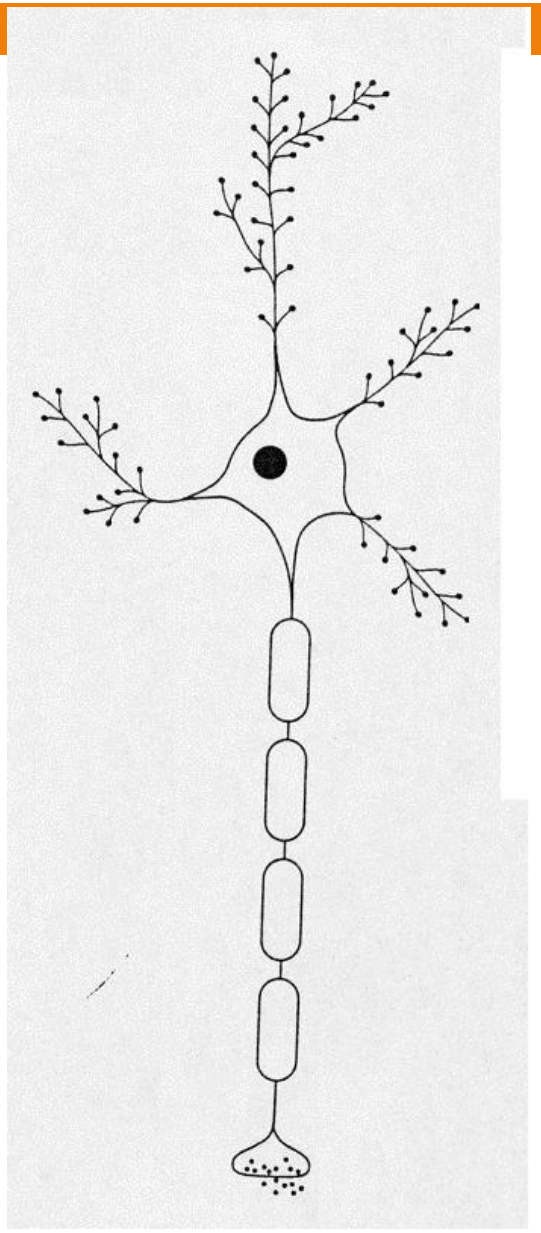
- 2 types of cel
- Neurons
- Glial cells

Dendrite

Cell body

Axon

Synapse



Transmit information through the brain

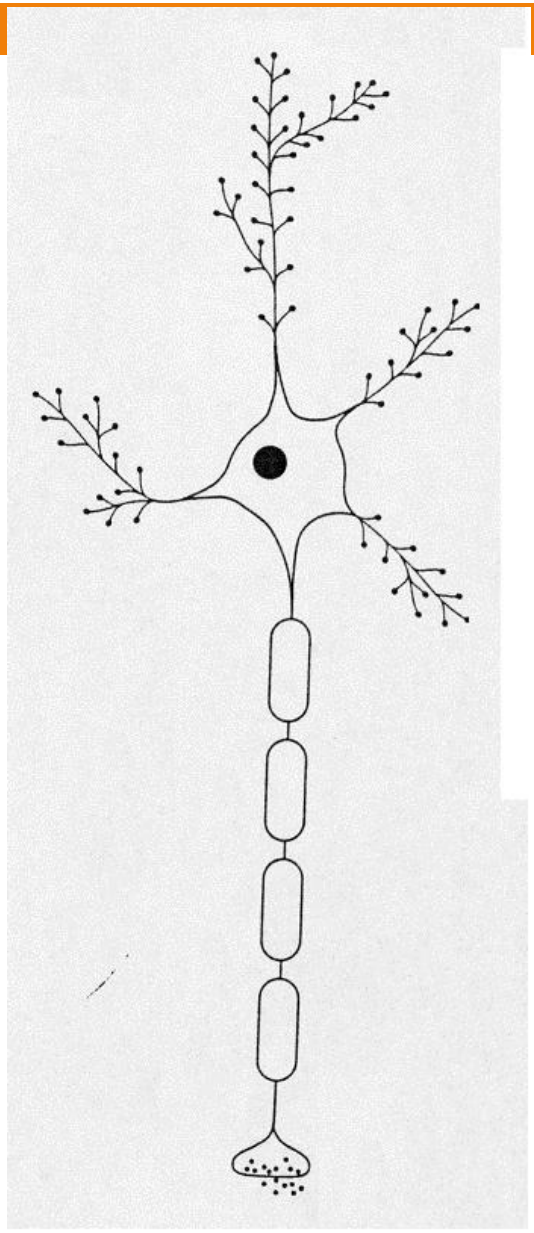
Development of the Cortex

- 2 types of cells:
- Neurons
- Glial cells

Outnumber neurons 10:1

Nourish, repair, & mylenate neurons

Crucial for development



Phases of brain development

- Neural plate induction
- Neural proliferation
- Migration & Aggregation
- Axon growth & Synapse formation
- Cell death & Synapse rearrangement

Induction of the Neural Plate

- 2-3 weeks after conception
- A patch of tissue on the dorsal surface of the embryo that will become the nervous system
- Development induced by chemical signals

"growth factors": several chemicals produced in developing and mature brain that stimulate neuron development and help neurons respond to injury

Neural Plate

- **Totipotent (zygote)** –
  - Fertilized ovum has ability to divide and produce all cells of the body (brain, kidney, liver, skin, bone etc.)
    - Can produce a whole animal

- **Pluripotent:** 5 days after fertilization = blastocyst forms, some of these cells are embryonic"stem cells". Can be taken and differentiated into any organ ?

- With the development of the neural tube, cells become **multipotent** –
  - able to develop into any type of mature nervous system cell

Phases of brain development

- Neural plate induction
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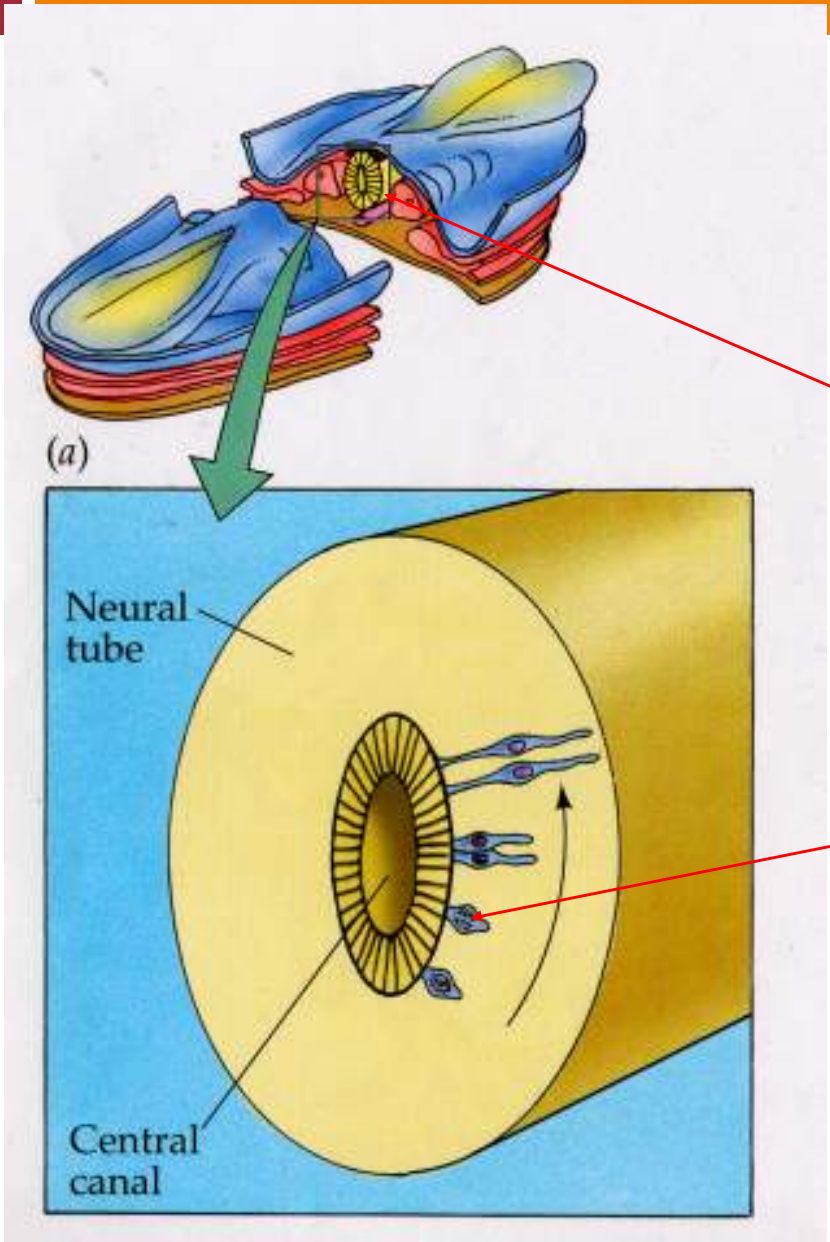
- Cell death & Synapse rearrangement

2. Mitosis/Proliferation



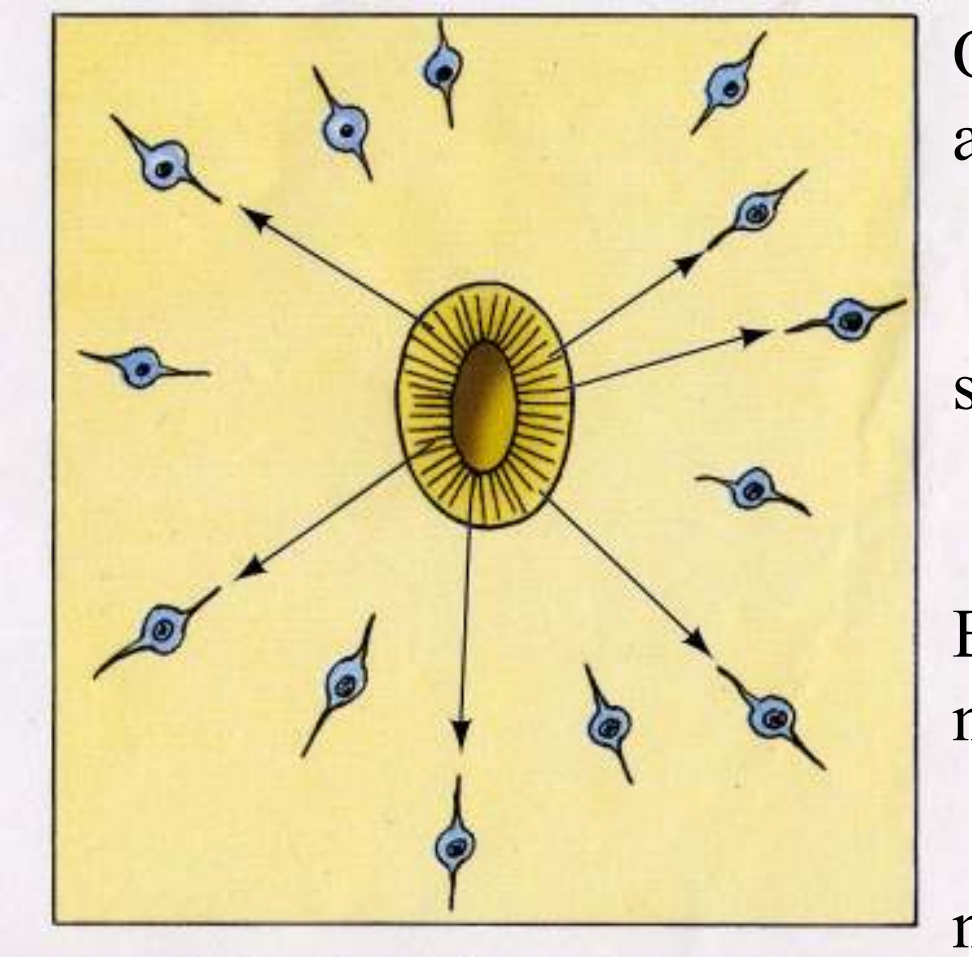
- **Proliferation** –
  - Generation of new cells
- 3 swellings at the anterior end in humans will become the forebrain, midbrain, and hindbrain

•Occurs in ventricular zone

•Rate can be 250,000/min

•After mitosis "daughter" cells become "fixed" post mitotic

3. Migration: slow movement to the "right place"



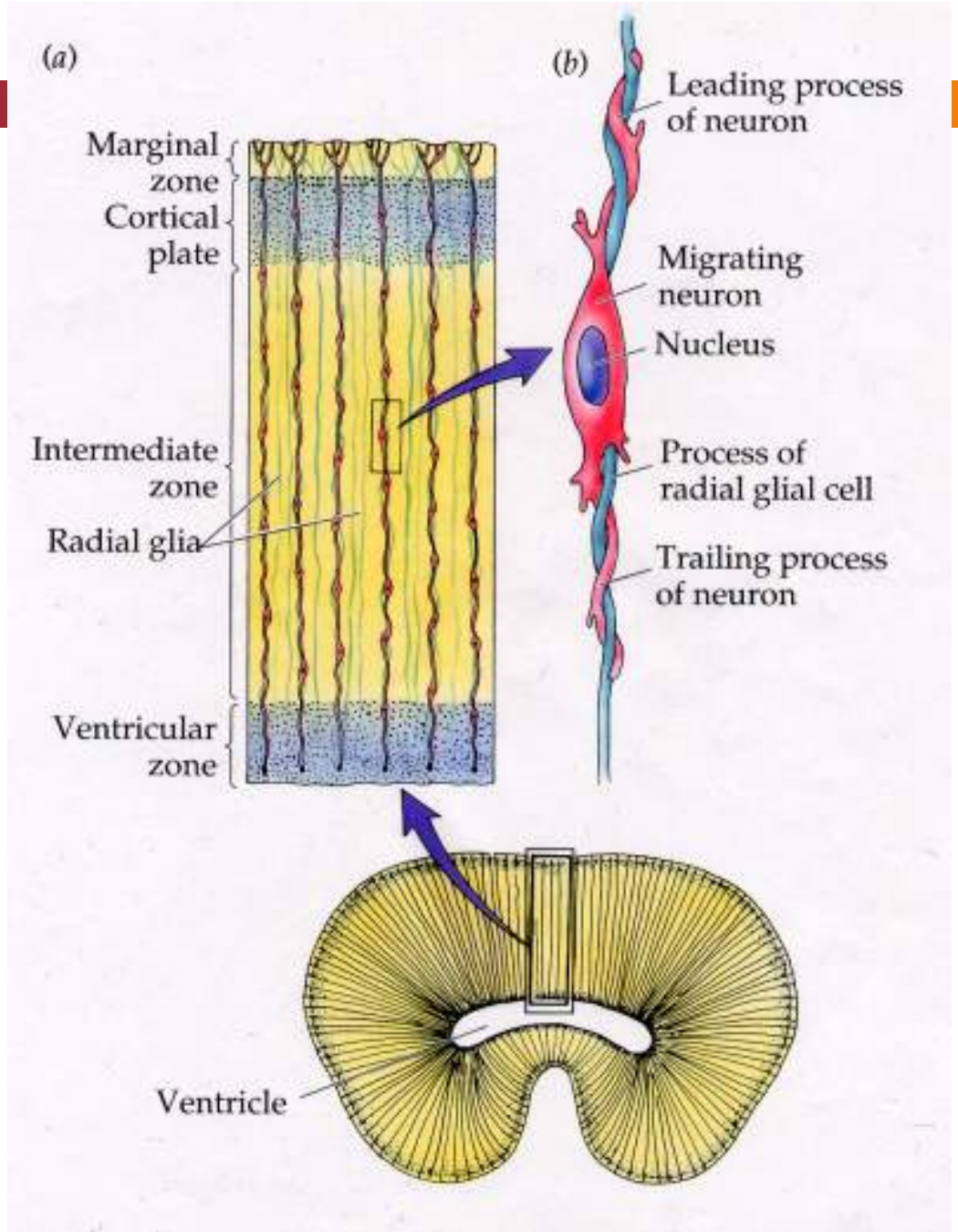
Only a soma and immature axon at this point

-undifferentiated at start of migration.

But, differentiation begins as neurons migrate.

They develop neurotransmitter making ability, action potential

3. Migration



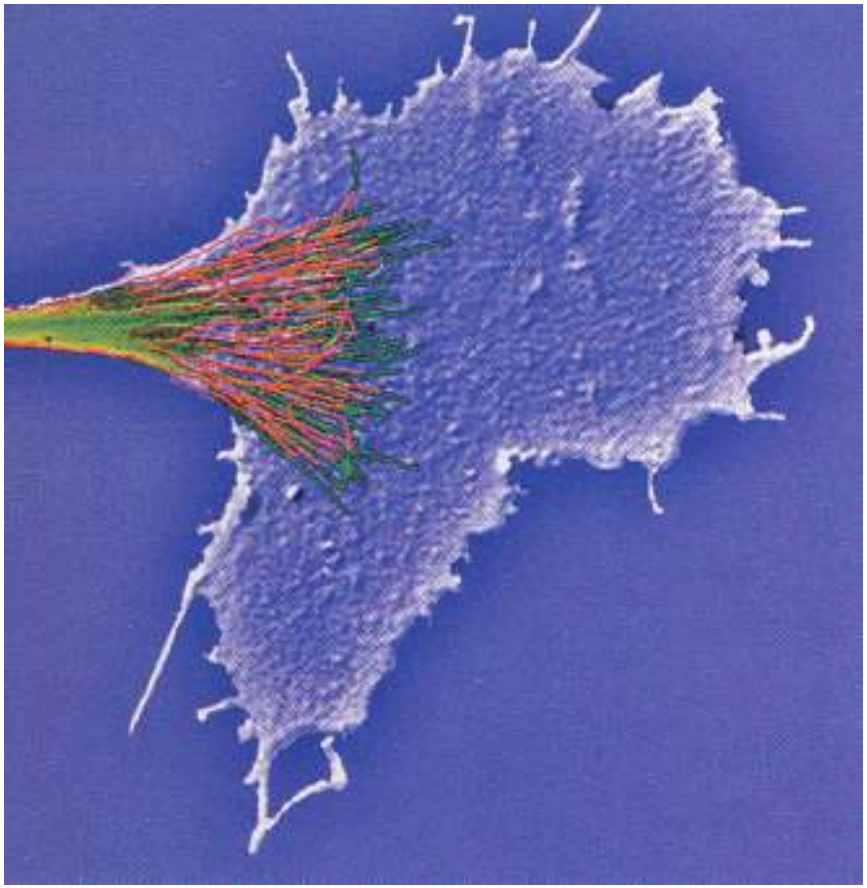
Radial Glia

Radial glial cells act as guide wires for the migration of neurons

Migrating cells are immature, lacking dendrites

Cells that are done migrating align themselves with others cells and form structures (Aggregation)

Growth Cones: tips of axons on migrating, immature neurons



Growth cones crawl forward as they elaborate the axons training behind them. Their extension is controlled by chemical cues in their outside environment that ultimately direct them toward their appropriate targets.

Chemoattractants

Vs

Chemorepellants

5 Phases of Neurodevelopment

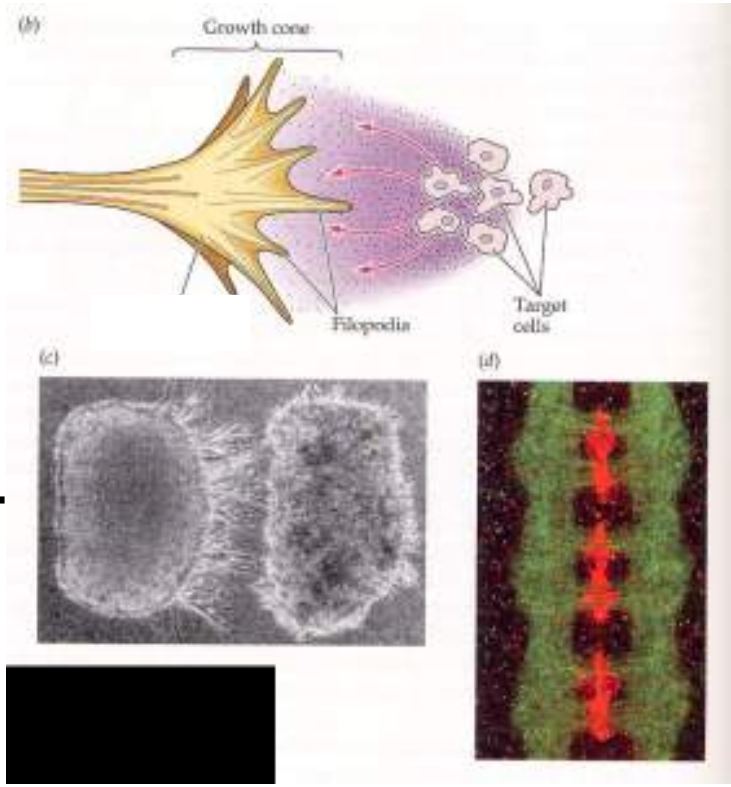
- Neural plate induction
- Neural proliferation
- Migration & Aggregation
- Axon growth & Synapse formation
- Cell death & Synapse rearrangement

4. Axon Growth/Synaptogenesis

- Once migration is complete and structures have formed (aggregation), axons and dendrites begin to grow to their "mature" size/shape.

- Axons (with growth cones on end) and dendrites form a synapse with other neurons or tissue (e.g. muscle)

Growth cones and chemo-attractant are critical for this.



Synaptogenesis

- Formation of new synapses
- Depends on the presence of glial cells – especially astrocytes
- Chemical signal exchange between pre- and postsynaptic neurons is needed

5 Phases of Neurodevelopment

- Neural plate induction
- Neural proliferation
- Migration & Aggregation
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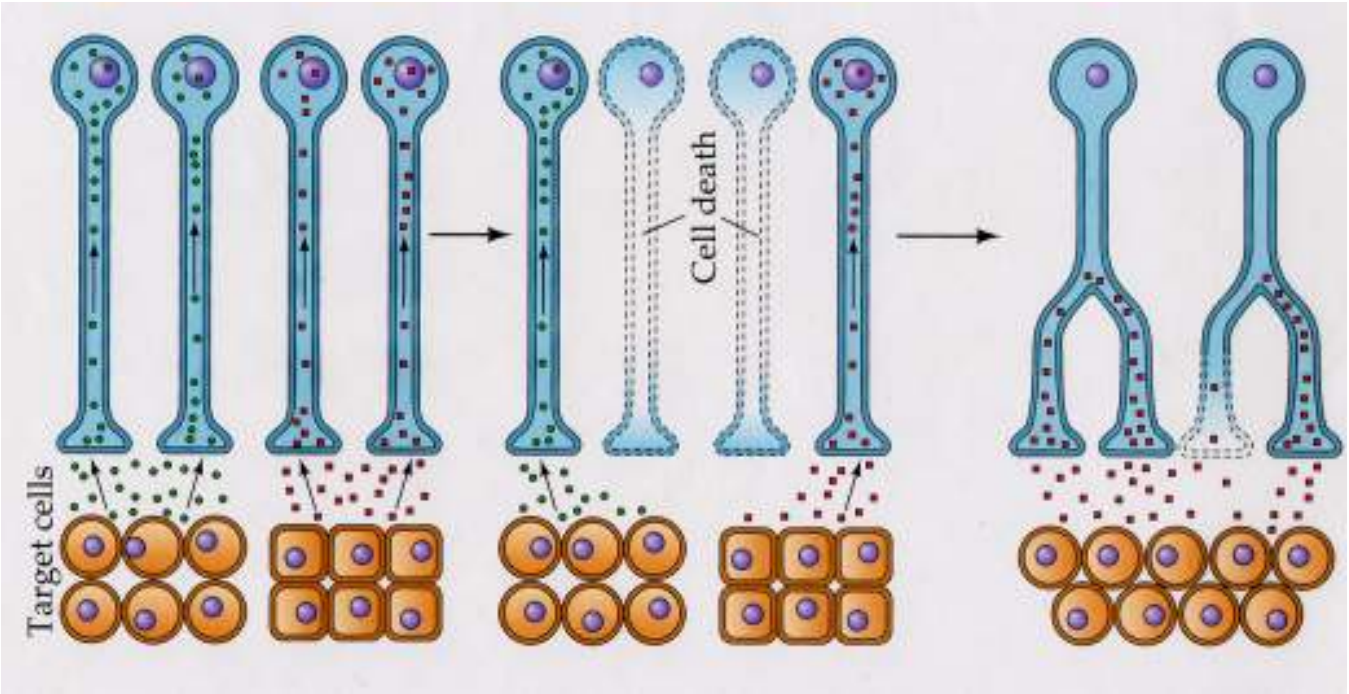
5. Neuronal Death

- Between 40-75% neurons made, will die after migration – death is normal and necessary !!
- Neurons die due to failure to compete for chemicals provided by targets
- Neurotrophins –
  - promote growth and survival
  - guide axons
  - stimulate synaptogenesis

Synaptic rearrangment

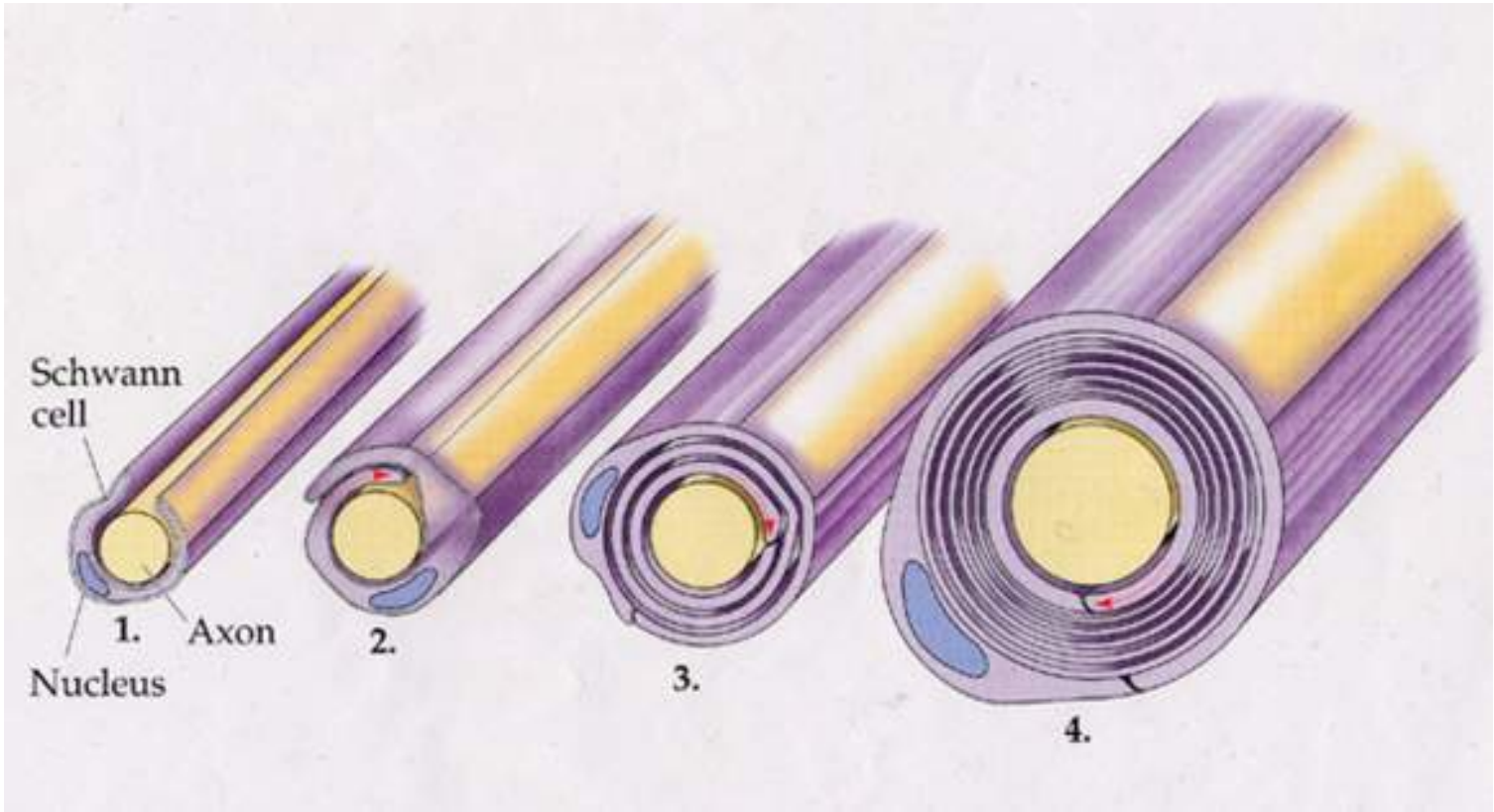


Release and uptake of neurotrophic factors

Neurons receiving insufficient neurotropic factor die

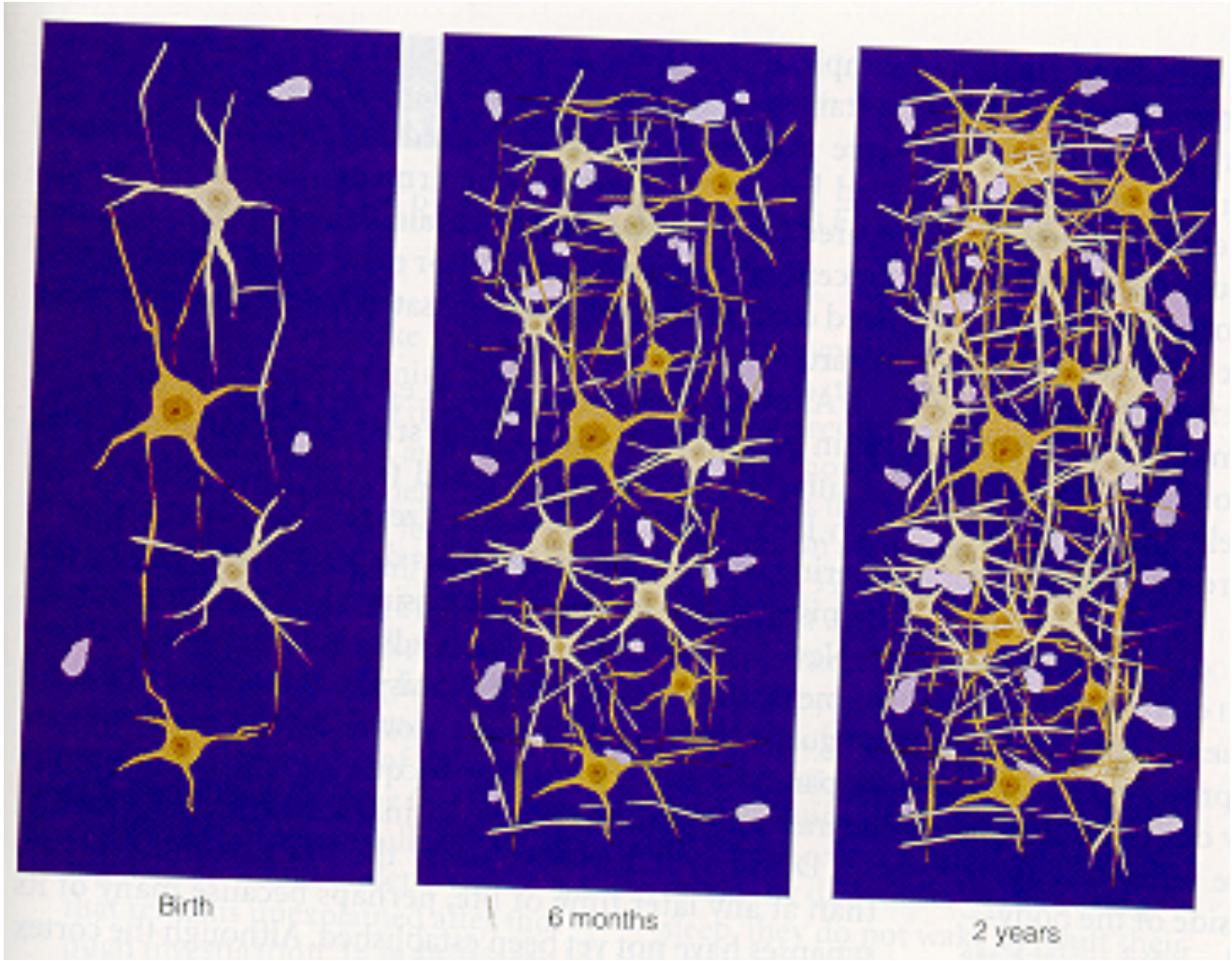
Axonal processes complete for limited neurotrophic factor

Synaptic rearrangment, cont'd: Myelination



Time after synaptogenesis

After birth - development is refinement of neuronal connections, maturity of the neurons, and increasing complexity of dendrite interconnections.



Each cell can form up to 15,000 connections.

Use it or lose it – Natural Selection of Brain Wiring

- Neurons and synapses must get hooked together properly to develop specific skills and abilities in humans
- How the "right" connections are made is still being researched
- During infancy and early childhood the cerebral cortex overproduces synapses (2X as needed)

Use it or lose it – Natural Selection of Brain Wiring

- The overproduction leads to a competition for survival of the fittest synapses
- Experience shapes and solidifies these synapses

Synaptogenesis & Pruning

- In cortex, synapses begin to form after neuronal migration, 23 weeks prenatal
- However, most synapses form after birth
- Many form randomly (as axons and dendrites meet)
- Flourish, then selectively prune
- Up to 100,000 synapses pruned per second (Kolb, 1999)

Pruning

- During childhood, pruning causes a loss of up to 10% of volume of gray matter in the cortex (with 607% shrinkage in frontal lobes between 13 and 18 years of age). Weight of human brain is maintained, however, due to increased myelination (Huttenlocher, 1999)

2 Types of Synapse Development

1. Experience-expectant development
   - Overproduce synapses, prune with experience
   - "Experience leads to *less*"
   - Tied to critical/sensitive periods
   - Organizes brain to process information, behaviors *expected* for all humans
     - Sensory processes
     - Parental attachment
     - Eye-hand coordination
     - Language capacity

Greenough & Black, 1999

2 Types of Synapse Development

2. Experience-dependent development
   - New synapses formed, maybe some pruning
   - "Experience leads to *more*"
   - Continues throughout life
   - Codes experiences/learning that is person-specific
     - -A particular language
     - Specific knowledge, memories, skills
       - Greenough & Black, 1999

Development of the Brain

- Some theorists refer to the idea of the selection process of neural connections as neural Darwinism.
- In this competition amongst synaptic connections, we initially form more connections than we need.
- The most successful axon connections and combinations survive while the others fail to sustain active synapses.

Development of the Brain

- Nerve growth factor (NGF) is a type of neurotrophin released by muscles that promotes the survival and growth of axons.
- The brain's system of overproducing neurons and then applying apoptosis enables the exact matching of the number of incoming axons to the number of receiving cells.

Development of the Brain

- A neurotropin is a chemical that promotes the survival and activity of neurons.
- Axons that are not exposed to neurotropins after making connections undergo apoptosis, a preprogrammed mechanism of cell death.
- Therefore, the healthy adult nervous system contains no neurons that failed to make appropriate connections.

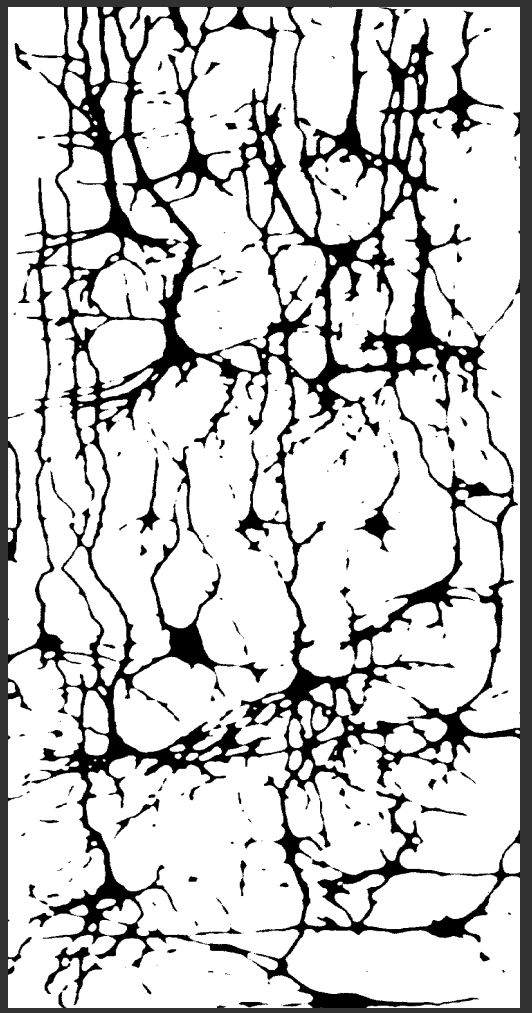
Development of the Brain

- The elimination and period of massive cell death is part of normal development and maturation.
- After maturity, the apoptotic mechanisms become dormant.
- Neurons no longer need neurotrophins for survivals, but neurotrophins increase the branching on axons and dendrites throughout life.

Human Brain at Birth

6 Years Old

14 Years Old



Postnatal Cerebral Development Human Infants

- **Post**natal growth is a consequence of
  - Synaptogenesis
  - Increased dendritic branches
  - Myelination (prefrontal cortex continues into adolescence)

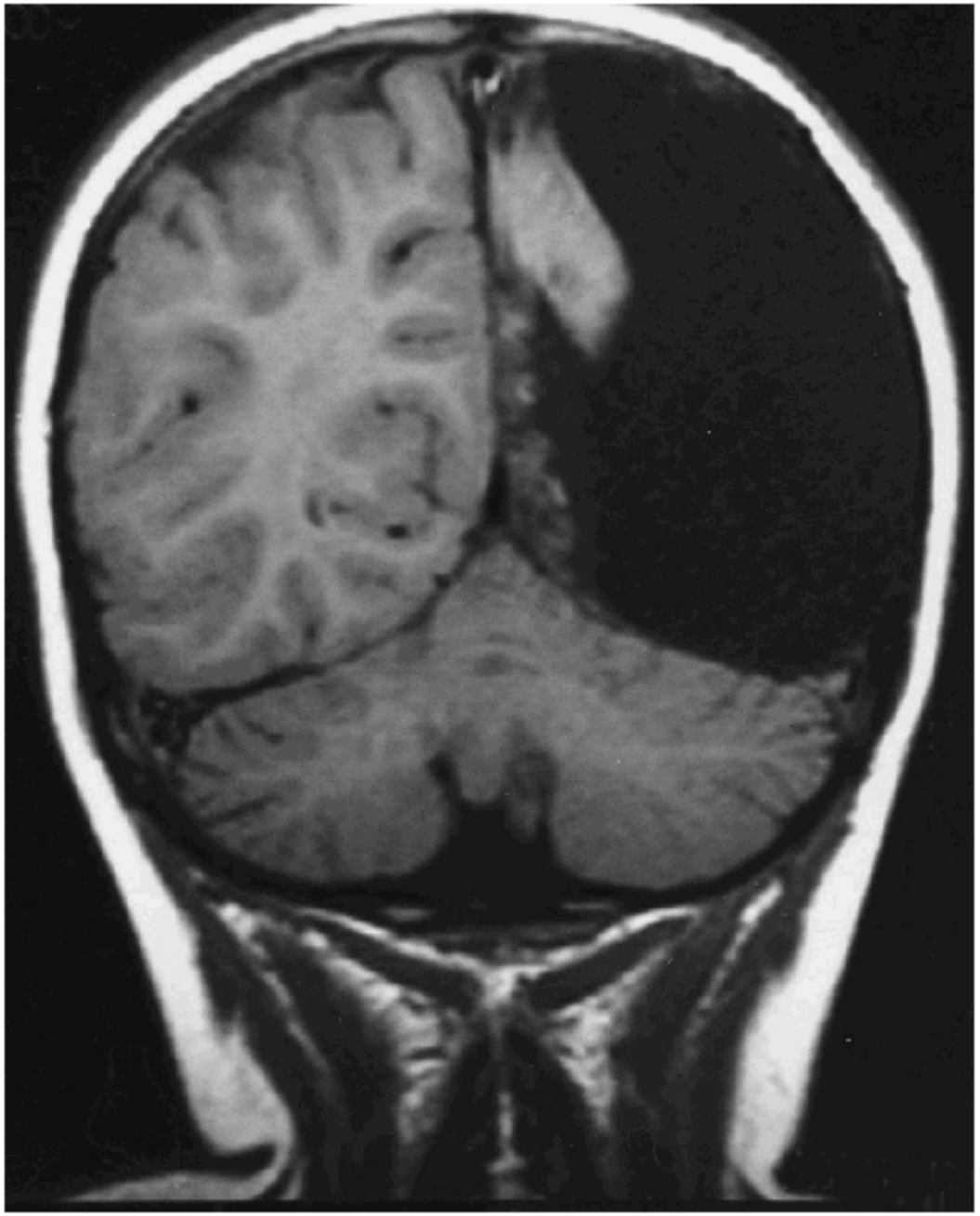
- Overproduction of synapses may underlie the greater "plasticity" of the young brain
  - Young brain more able to recover function after injury, as compared to older brain

Clinical picture

The Lancet, 359, Feburary 6, 2002

Half a brain

Johannes Borgstein,
Caroline Grootendorst



This 7-year-old girl had a hemispherectomy at the age of 3 for Rasmussen syndrome (chronic focal encephalitis). Intractable epilepsy had already led to right-sided hemiplegia and severe regression of language skills. Though the dominant hemisphere was removed, with its language centres and the motor control for the left side of her body, the child is fully bilingual in Turkish and Dutch, while even her hemiplegia has partially recovered and is only noticeable by a slight spasticity of her left arm and leg. She leads an otherwise normal life.

University Hospital Rotterdam, 3015 GJ Rotterdam, Netherlands (J Borgstein MD, C Grootendorst MD)

Early Studies of Experience and Brain Development

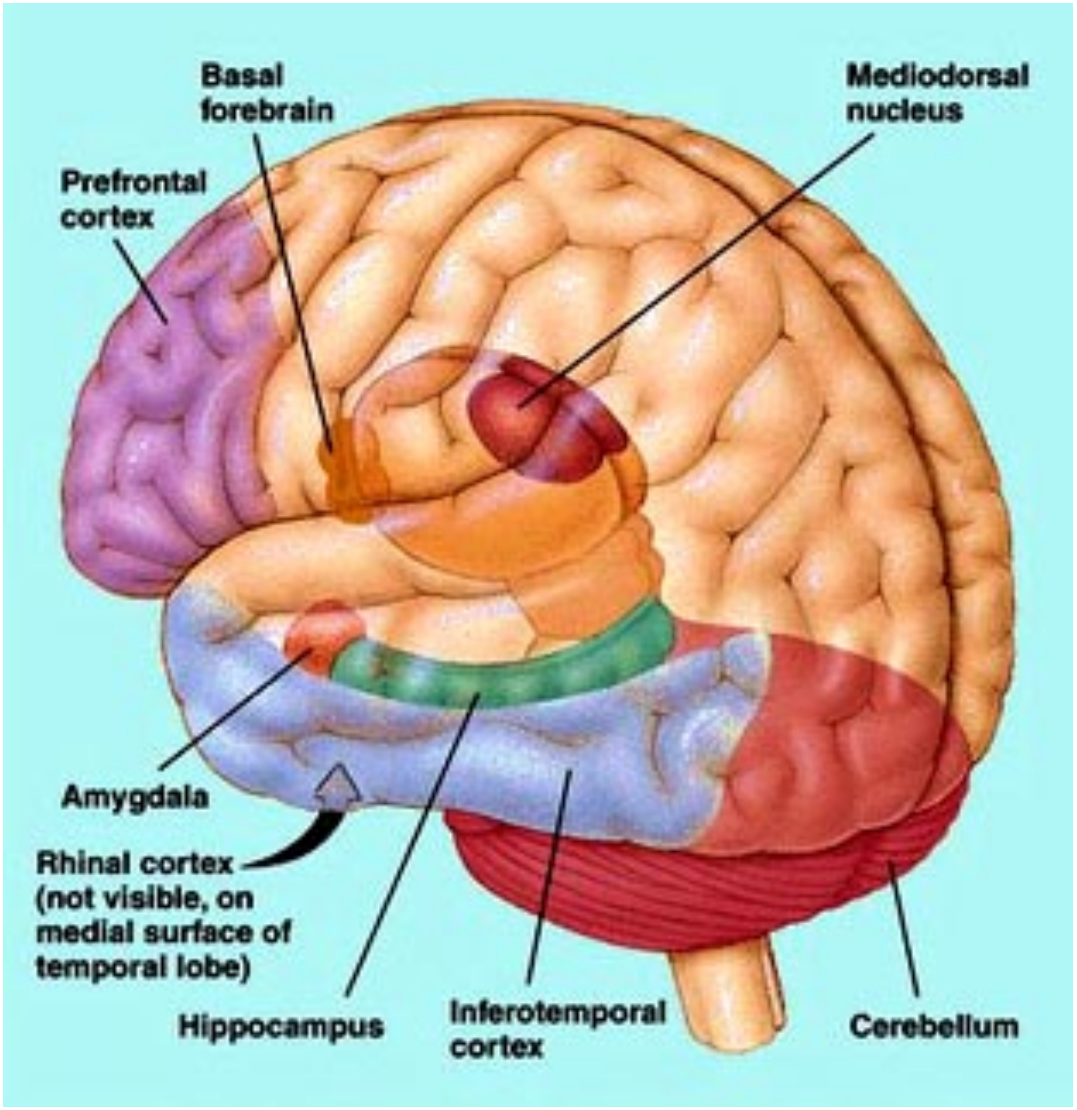
- Early visual deprivation →
  - fewer synapses and dendritic spines in visual cortex
  - deficits in depth and pattern vision

- "Enriched" environment →
  - thicker cortices
  - greater dendritic development
  - more synapses per neuron

Development of the Prefrontal Cortex

- Believed to underlie age-related changes in cognitive function, judgement, decision-making
- No single theory explains the function of this area
- Prefrontal cortex plays a role in working memory, planning and carrying out sequences of actions, and inhibiting inappropriate responses

Where is your Prefrontal Cortex ?



The last part of your brain to fully develop

Neuroplasticity in Adults ?

Originally believed that no new neurons were formed after early development. But…

1. Stem cells are undifferentiated cells found in the interior of the brain that generate "daughter cells" which can transform into glia or neurons.

2. New olfactory receptors also continually replace dying ones. Neuronal growth also seen in the hippocampus (memory?)

Neuroplasticity in Adults ?

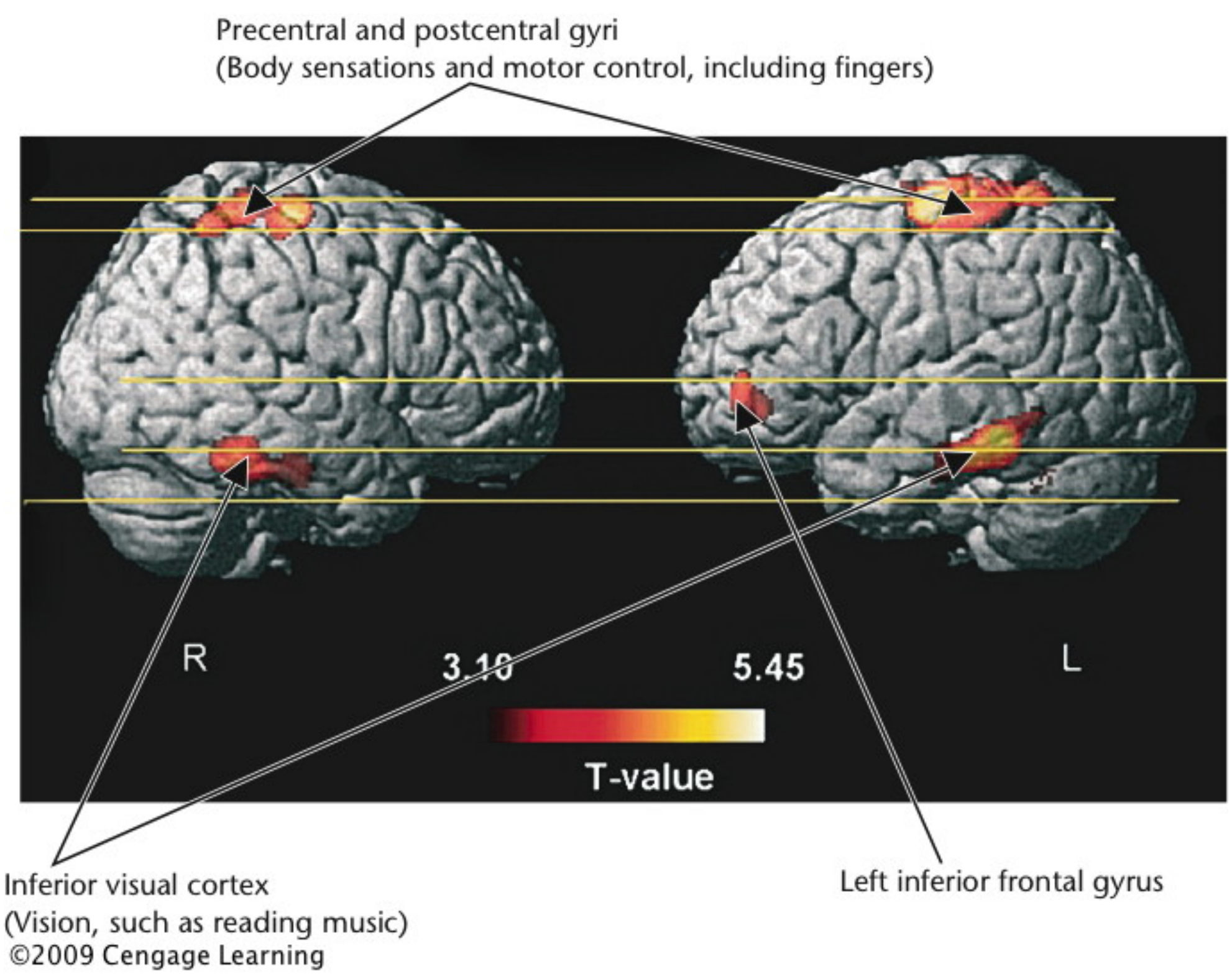
Mature brain changes and adapts. But does it keep growing?

Effects of Experience on the Reorganization of the Adult Cortex

- Skill training leads to reorganization of motor cortex
- Adult musicians who play instruments have an enlarged representation of the hand in somatosensory cortex
- Reorganization is synaptogenesis or pruning of unused synapses…

Development of the Brain

- Extensive practice of a skill changes the brain in a way that improves the ability for that skill.
- For example, MRI studies reveal following:
  - the temporal lobe of professional musicians in the right hemisphere is 30% larger than non-musicians.
  - thicker gray matter in the part of the brain responsible for hand control and vision of professional keyboard players



Neurodevelopmental Disorders

- Autism Spectrum Disorders
  - 1/91 live births in U.S.)
- Fetal Alcohol Spectrum Disorders
  - (1/100 live births in North America ?)

Autism

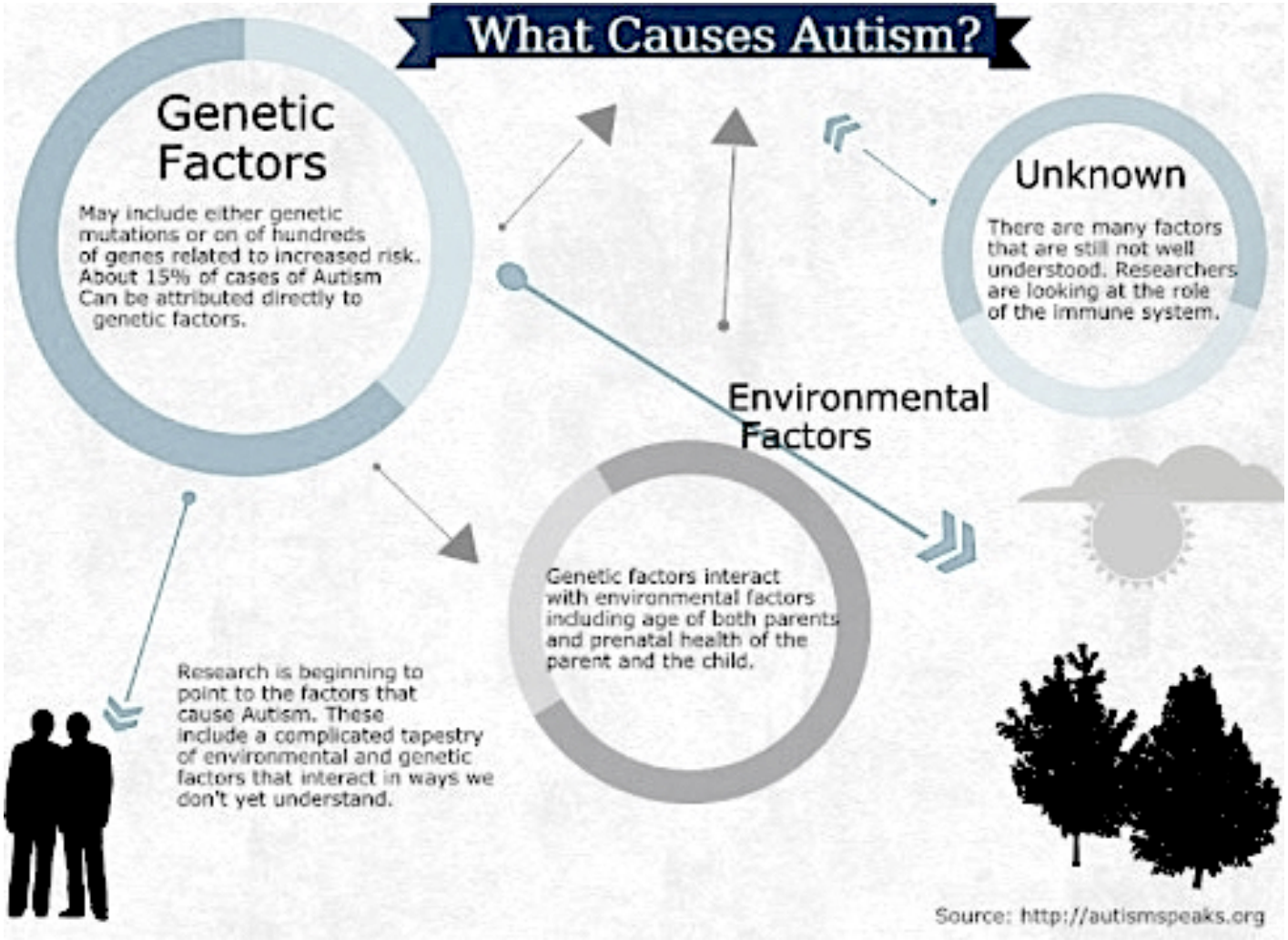
- 3 core symptoms:
  - Reduced ability to communicate
  - Reduced capacity for social interaction
  - Preoccupation with a single subject or activity
- Heterogenous – level of brain damage and dysfunction varies (Autism Spectrum Disorder)
  - Probably no single cause

Autism

- Most have some abilities preserved

- Savants – intellectually handicapped individuals who display specific cognitive or artistic abilities
  - ~1/10 autistic individuals display savant abilities

Neural Basis of Autism



Fetal Alcohol Spectrum Disorders

50+% of women who could become pregnant are drinking

2% of women drink significantly during pregnancy, 10% drink some

Glass of wine, bottle of beer, shot of liquor are equal approximately 0.5 oz absolute alcohol

Fetal brain damage occurs at regular doses of 1-2 oz/day (2-4 drinks)

Symptoms of FASD

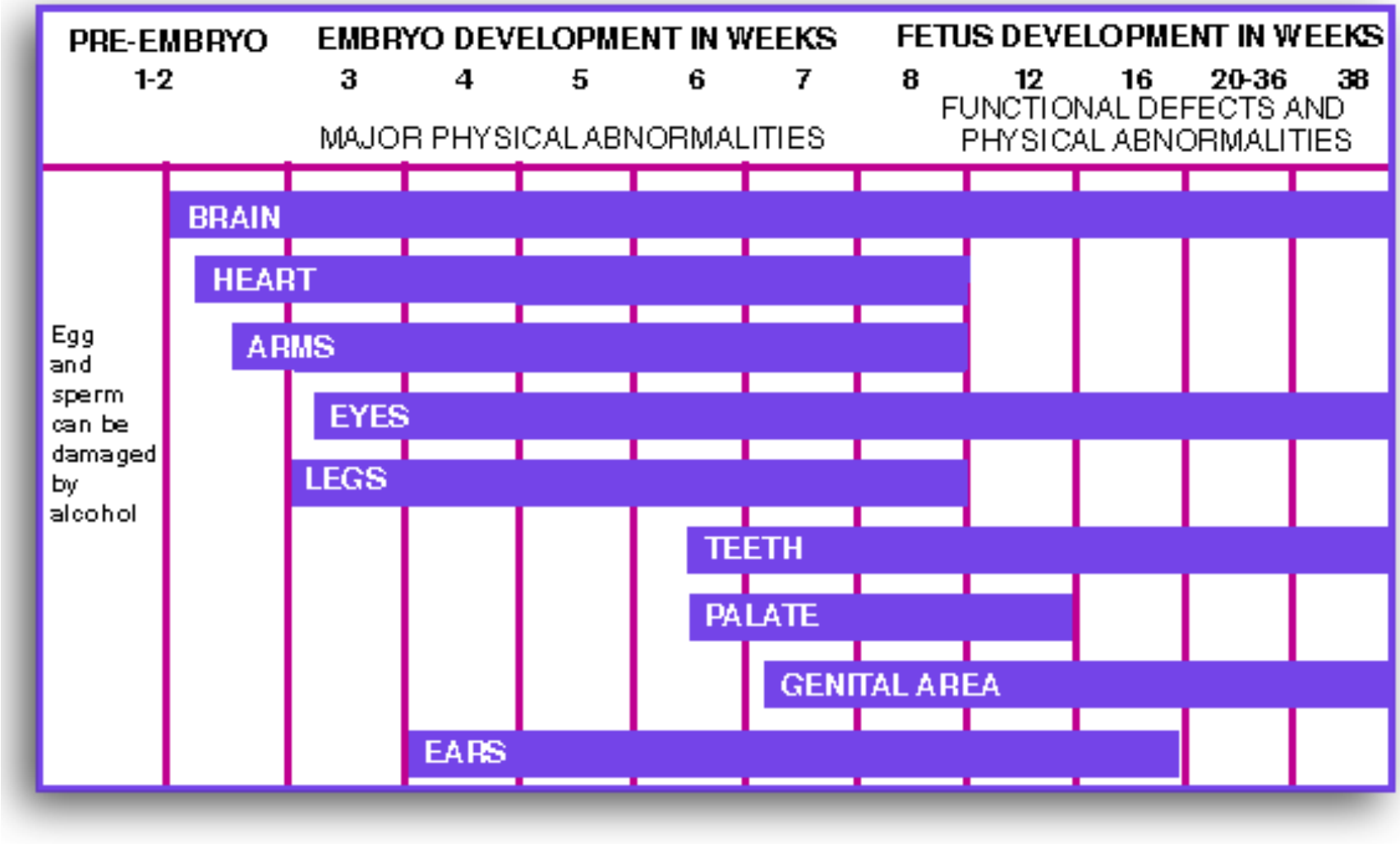
Infant: Problems with sleep, feeding, milestones, muscle tone, sensory information processing

Child: Hyperactive, poorly coordinated, learning delays

Adolescent/Adult: poor judgment, attention, problems with arithmetic, memory, abstraction, frustration/anger

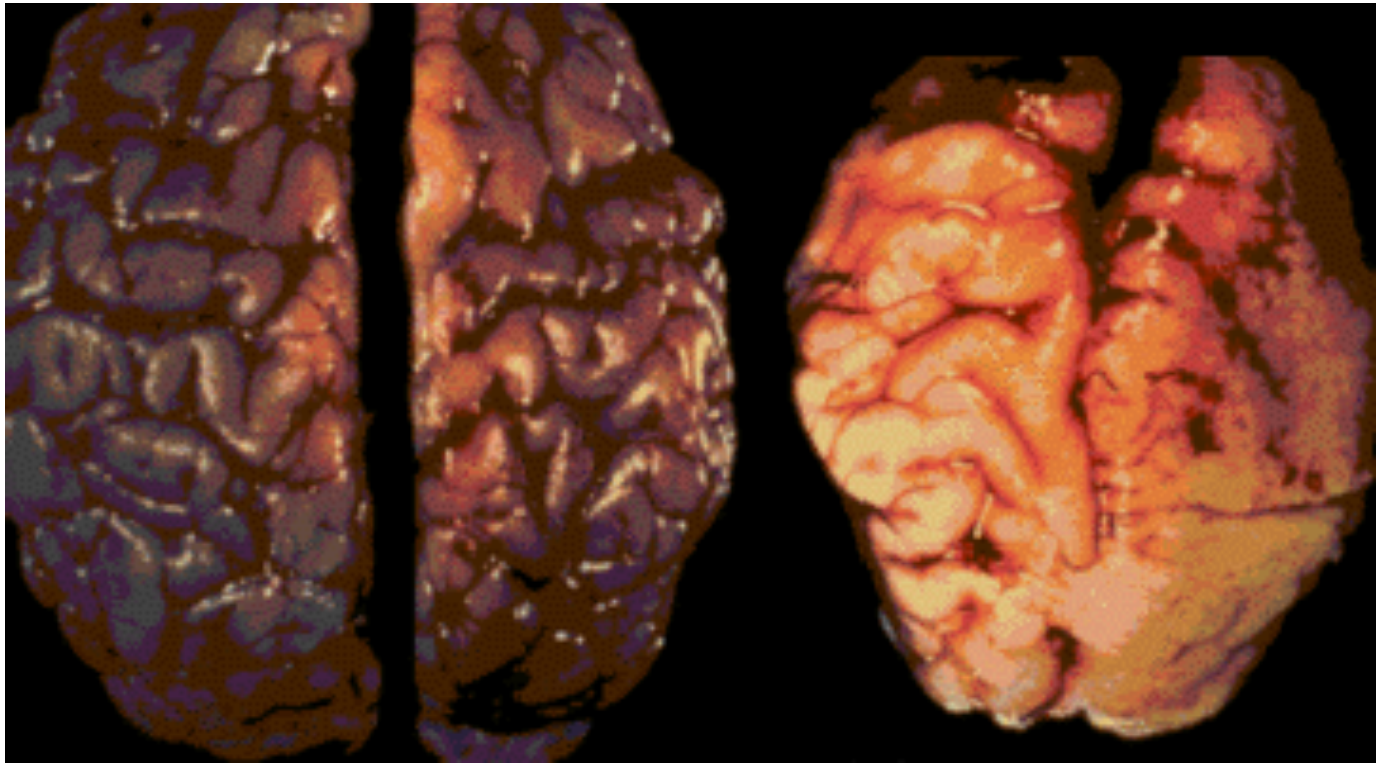
Neural Basis of Fetal Alcohol Spectrum Disorders

When is alcohol exposure most dangerous ???



Neural Basis of Fetal Alcohol Spectrum Disorders

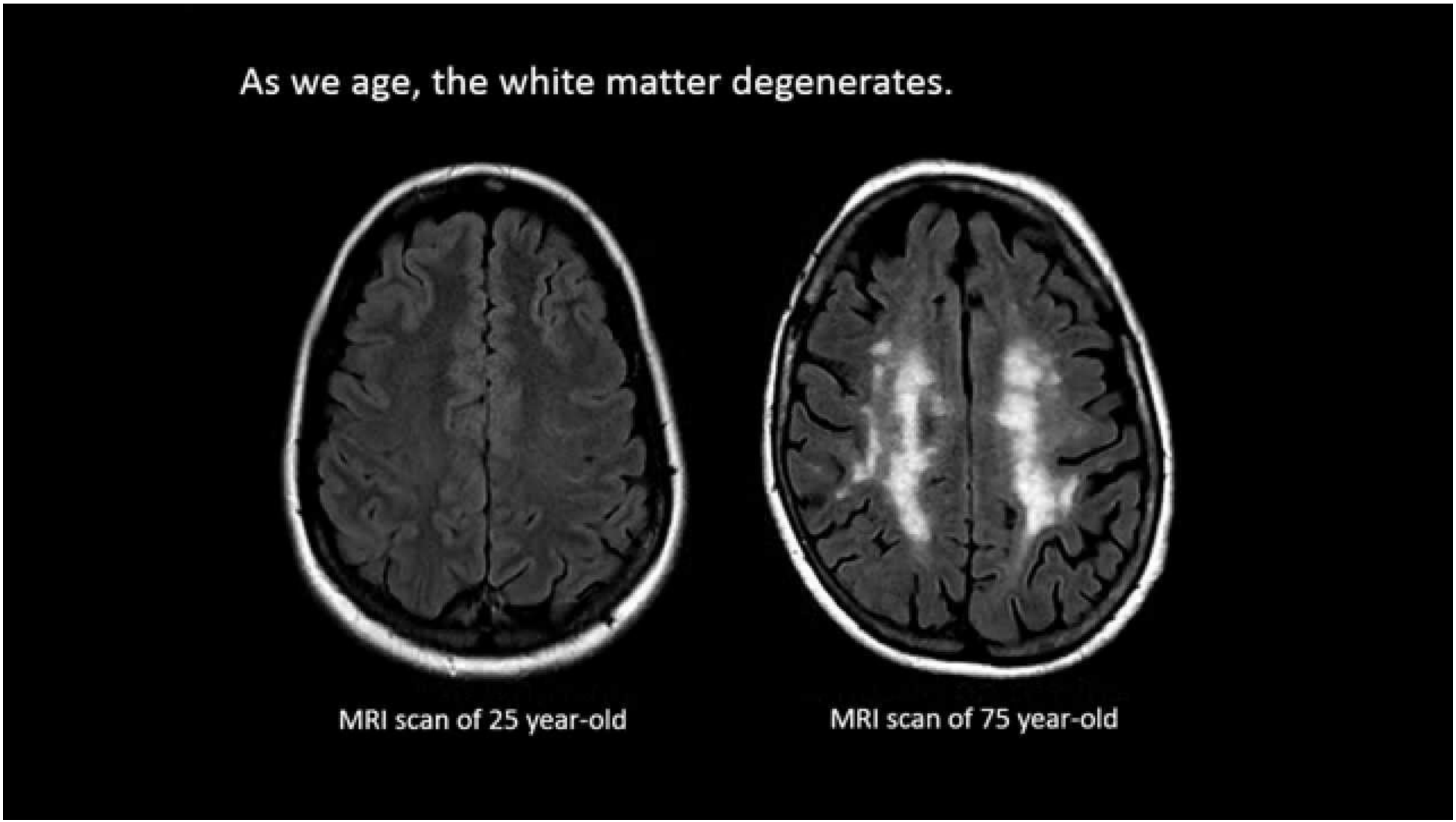
Alcohol inhibits all stages of brain development, except neuronal death, which it promotes.



The Positives?

Early intervention with rich environments

Next Week


As we age, the white matter degenerates.
MRI scan of 25 year-old
MRI scan of 75 year-old