Cortical Development

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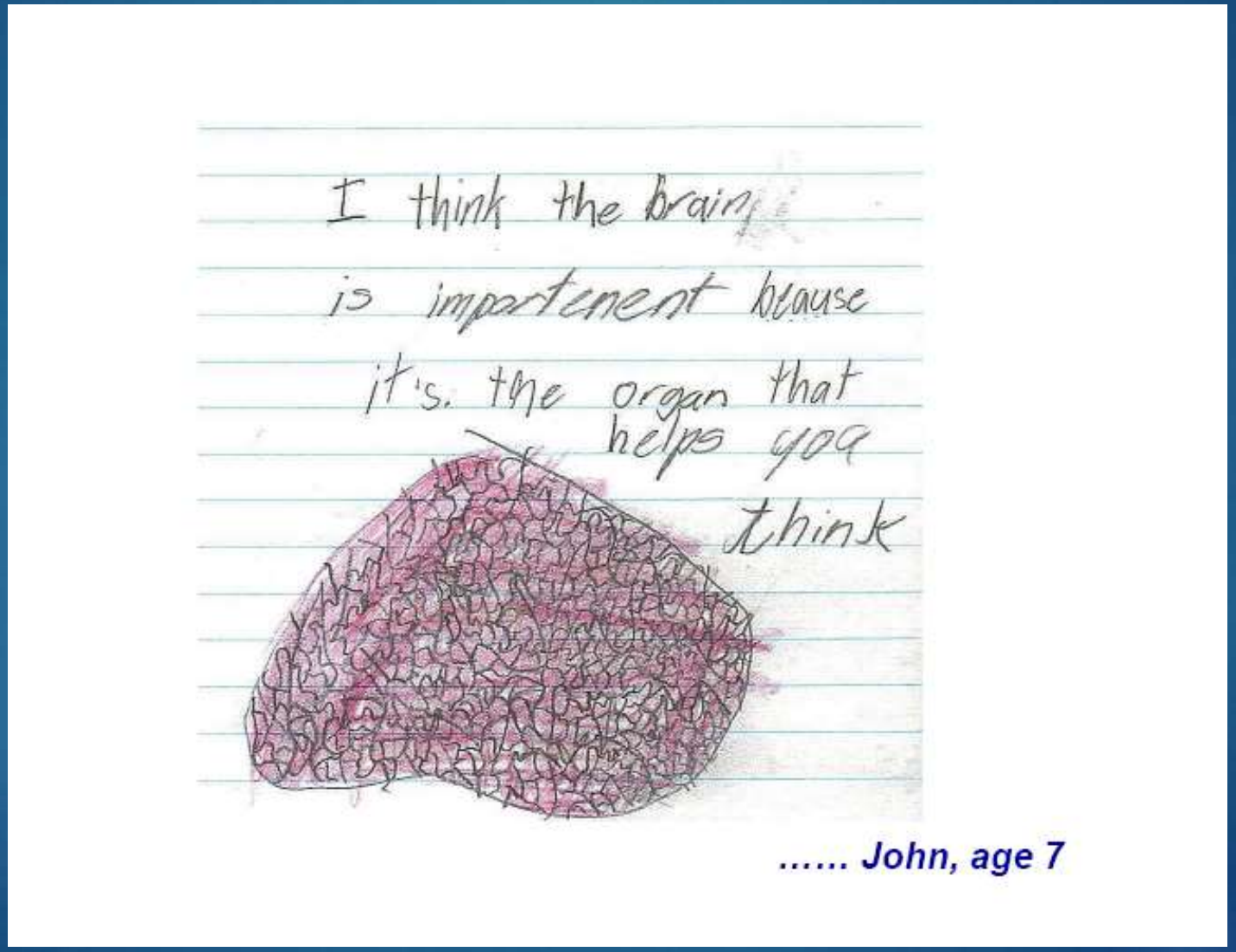
THANKS TO:

D. ROMER, E. WALKER, MARK BEIDELMAN, CHARLES NELSON

Early Musings



Humans & Primates

- 1.8 % Exon Difference: of 3 billion DNA letters, only 1.5 million are different
- Mostly in switches in junk DNA, not genes
- 50% of switches related to brain development genes
- Most change sequences: HAR1 (brain development), FOXP2 (speech), ASPM (brain size), HAR2 (hand and wrist development), AMY1 (digestion of starch), LC (digestion of milk)
- Chimpanzees: no Alzheimer's or CVA

Genes and the Brain

- ~6500 genes produce proteins in brain cells; abnormal proteins produce neurological disorders
- Life experiences effect gene expression through epigenetic effects
- Epigenetic effects produce changes in gene expression; produce ACEs
- Genes effect ability to produce cognition

170 Billion: Newest Official Count in 2009

- Adult male human brain contains on average 170 billion cells:
  - 86.1 ± 8.1 billion neurons
  - 84.6 ± 9.8 billion glial cells.

- Cerebral cortex: 77 billion cells:
  - 19% of all neurons
  - 82% of total brain mass.
  - 61 billion glia; 16 billion neurons = 3.8 to 1

- Cerebellum: 85 billion cells:
  - 81% of all neurons
  - 10% of brain mass
  - 69 billion neurons; 16 billion glial cells: 4 neurons to 1 glia

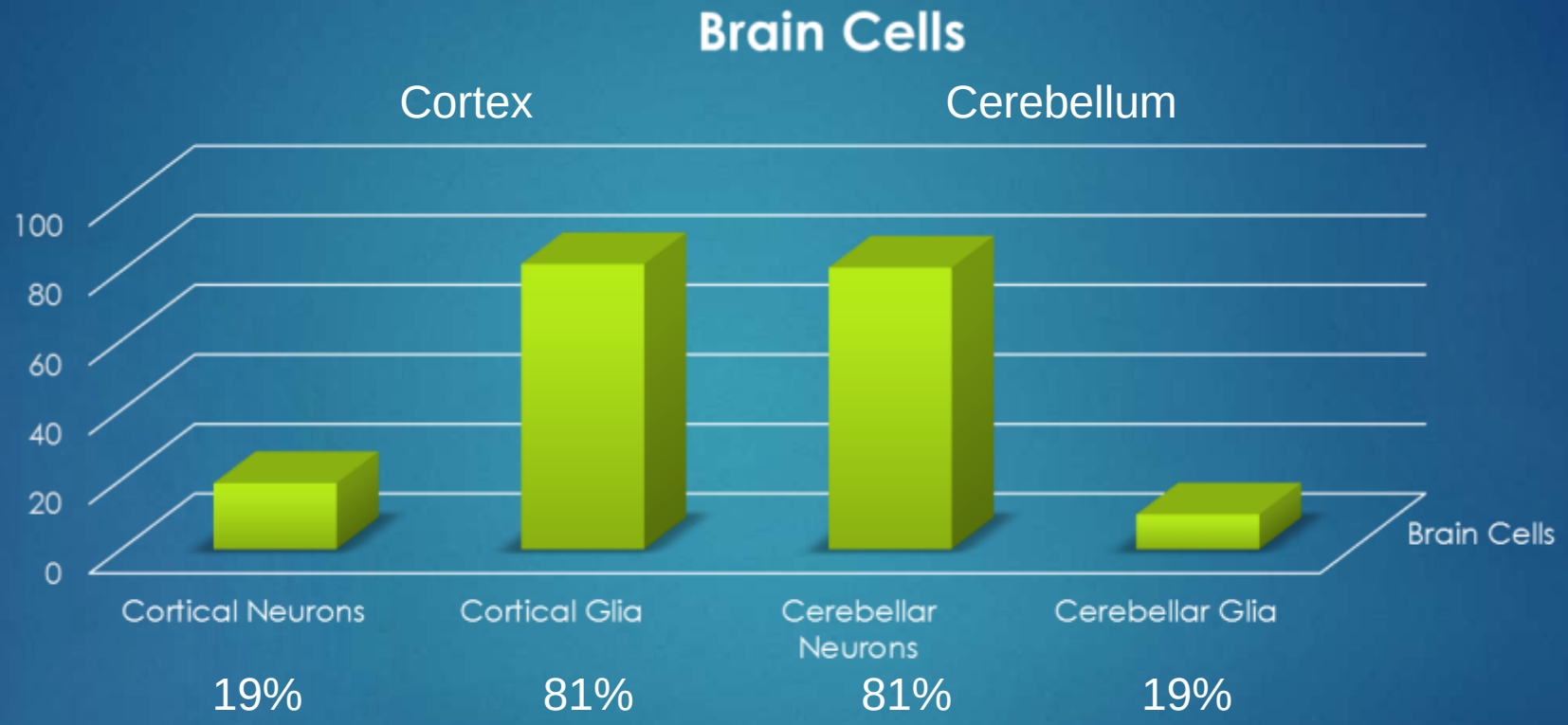
- Glial cells are 50% of all brain cells.

Gray: 6 billion neurons and 9 billion glia;

White: 1.3 billion neurons and 20 billion glia.

F. Azevedo et al., J. *Comp. Neurol*. 513:532–541, 2009

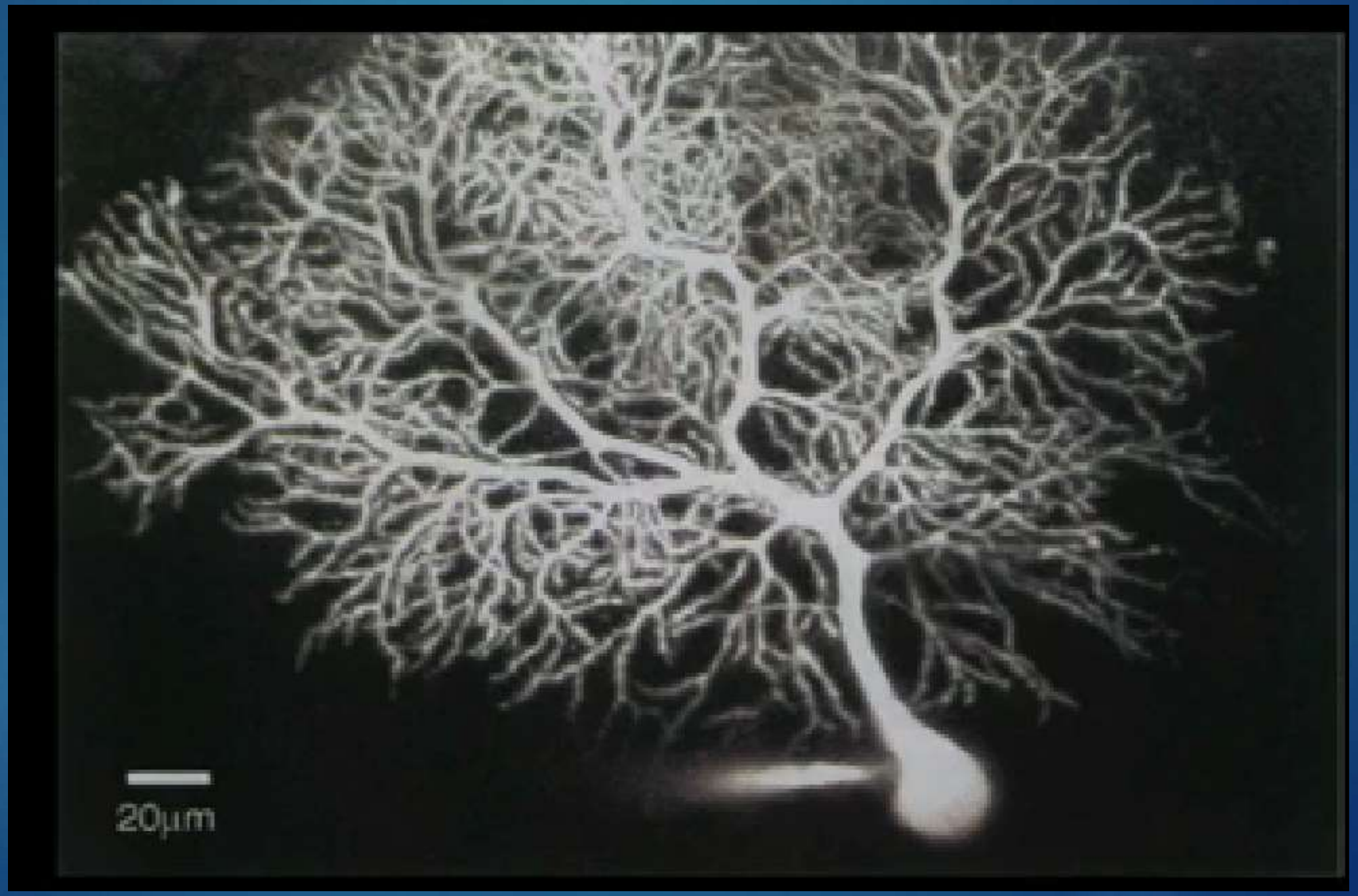
Cortical Brain Cells: 170 Billion



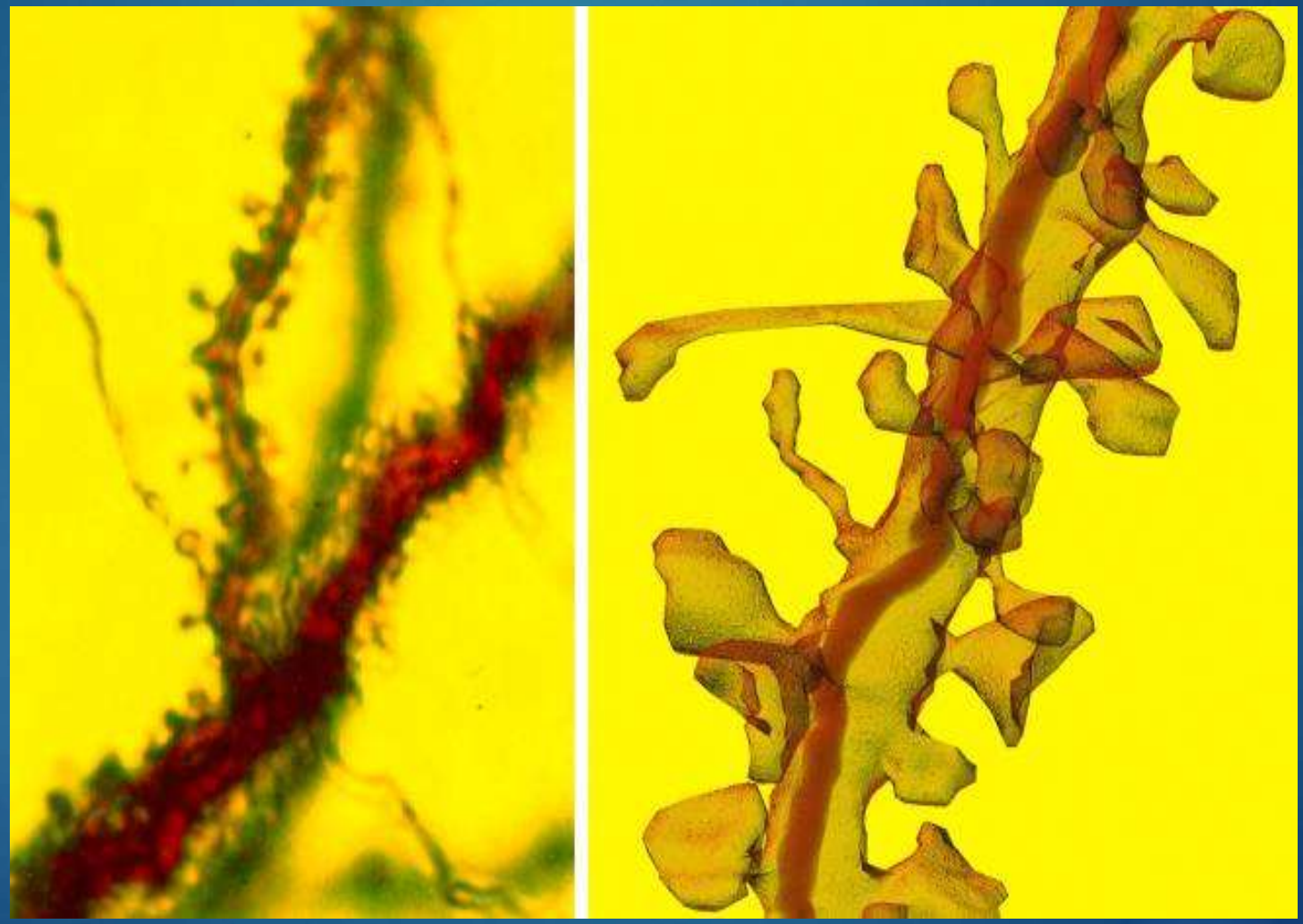
Adult male human brain contains on average:

- 86 ± 8 billion neurons
- 85 ± 10 billion glial cells.
- Cortex: 4 to 1 glia to neuron; Cerebellum: 4 to 1 neurons to glia

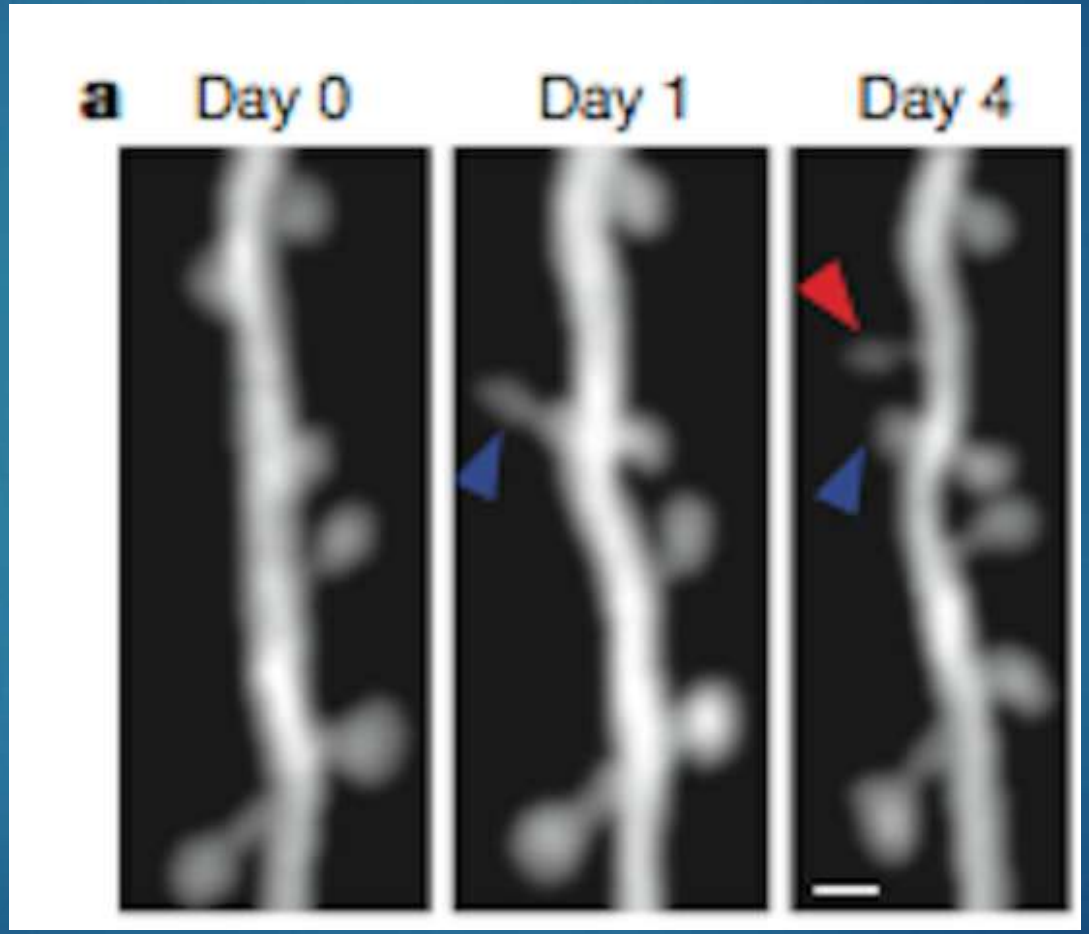
A Neuron



Dendrites: Electron Microscope

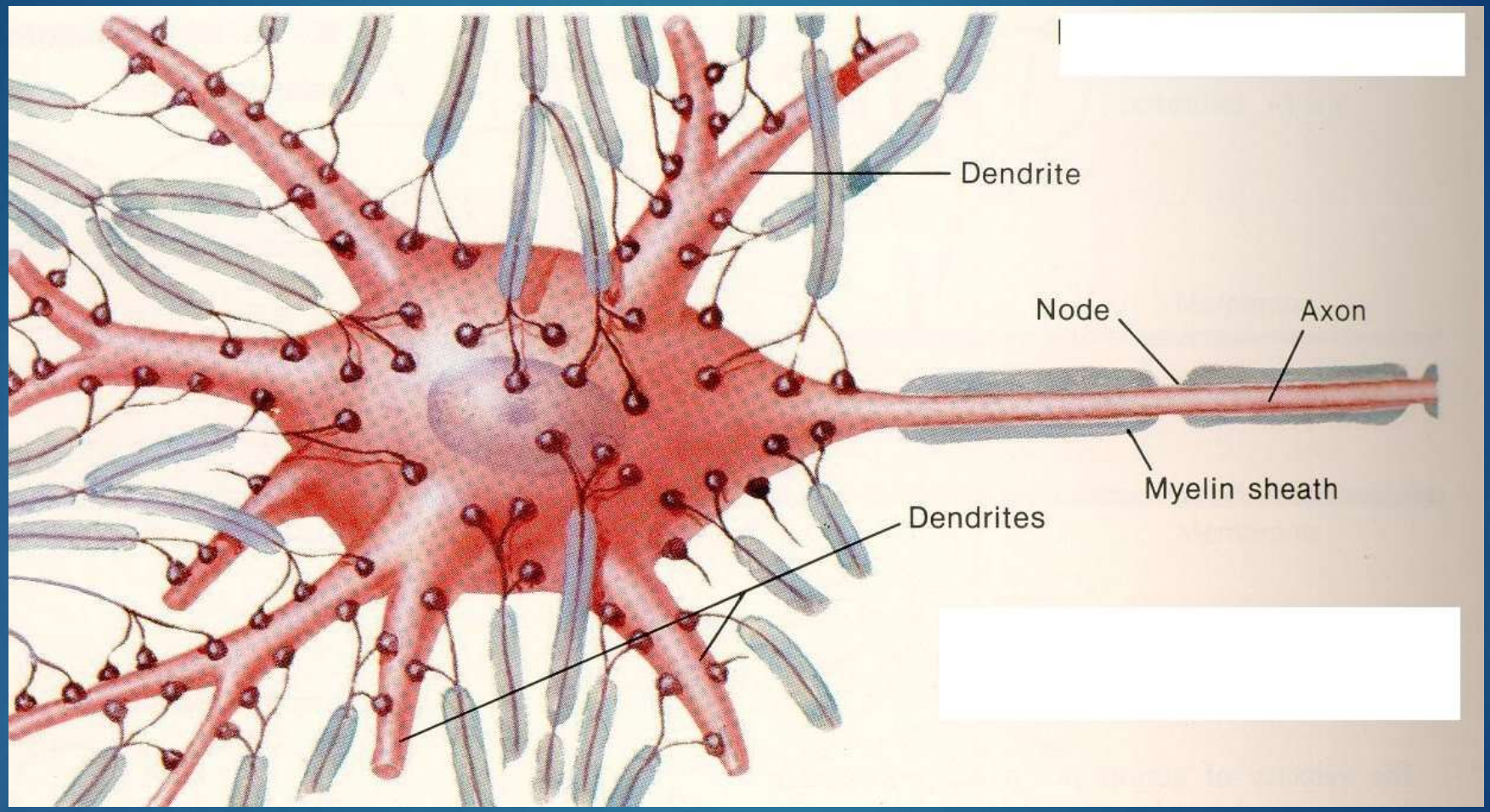


Physical basis of Neuroplasticity

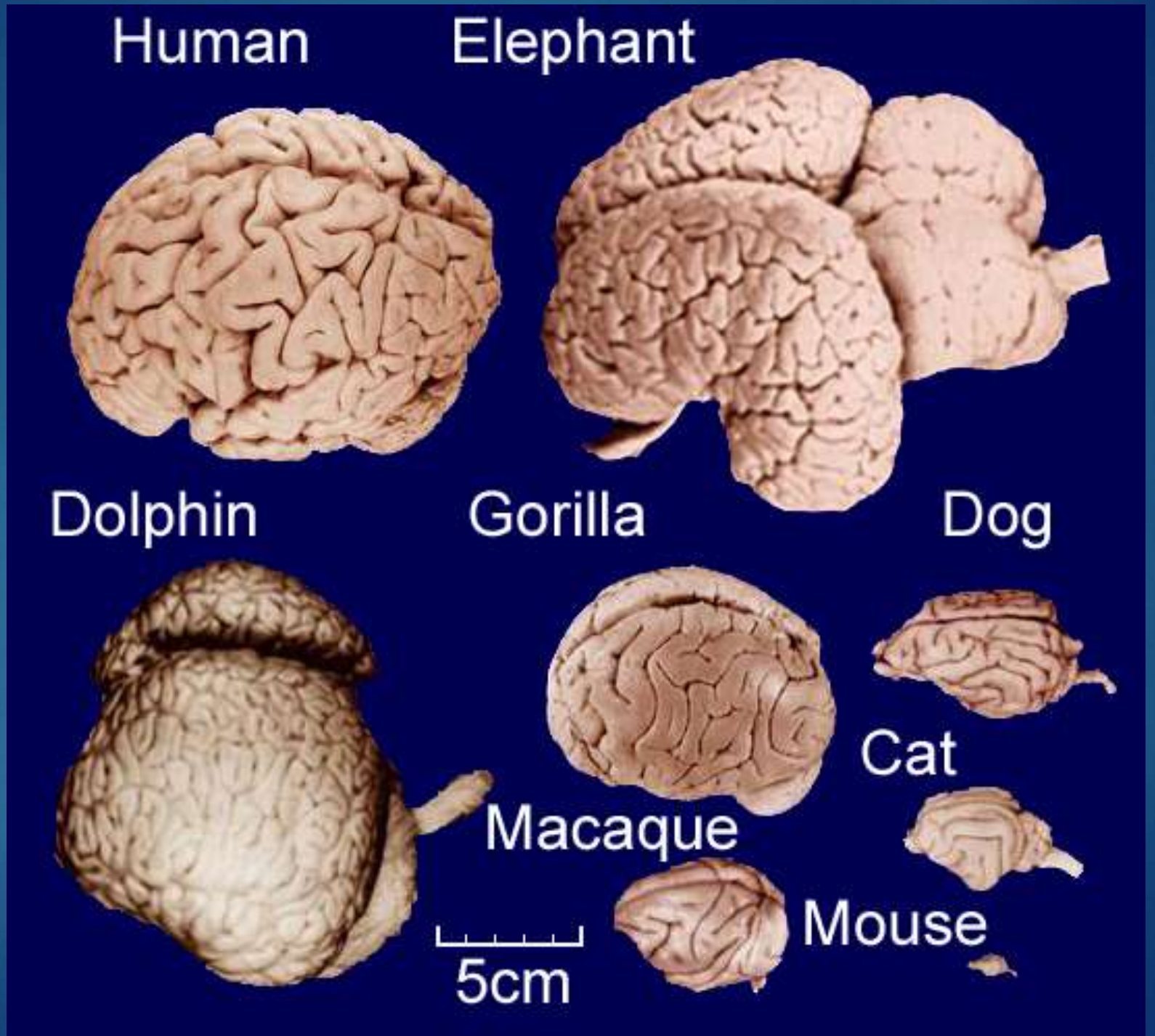


2 dendrites grow in a mouse after 4 days of reaching for a seed

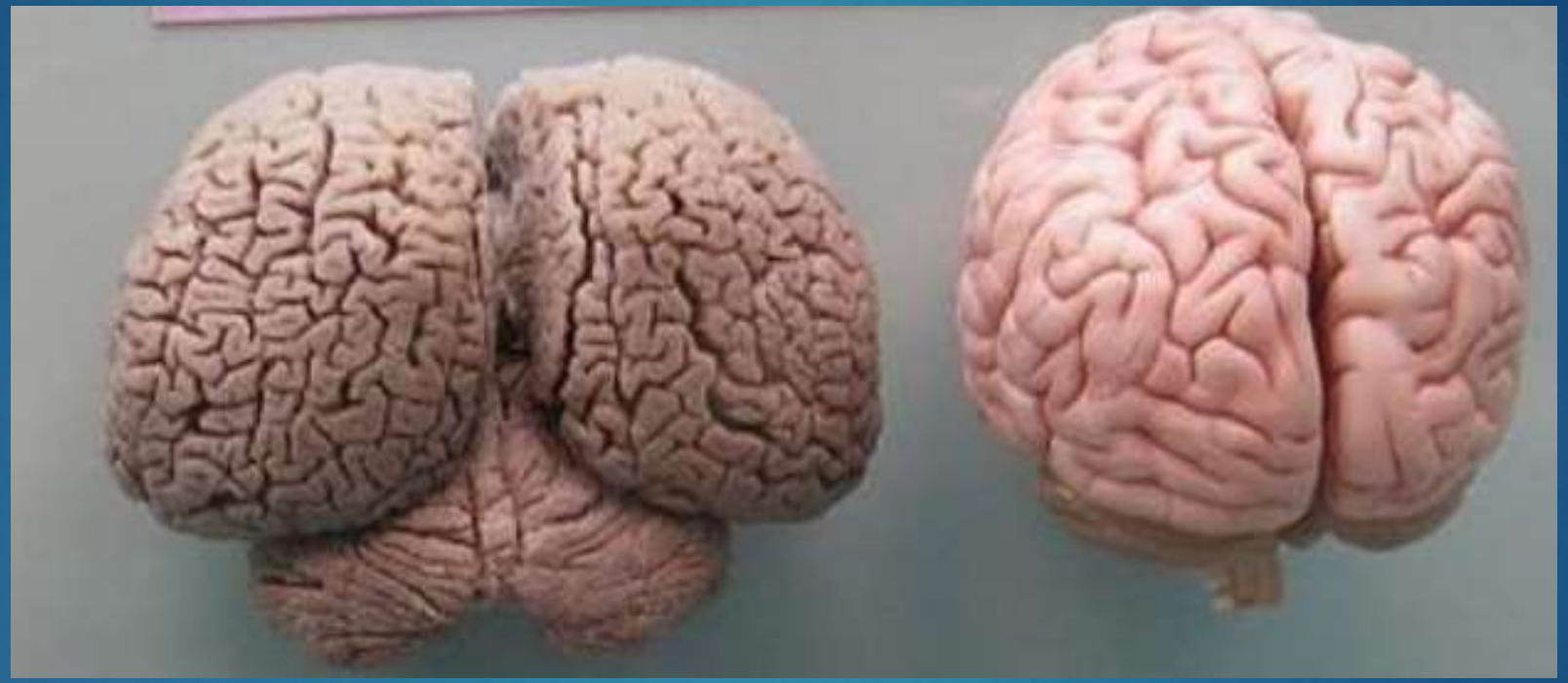
1000s of synapses per neuron



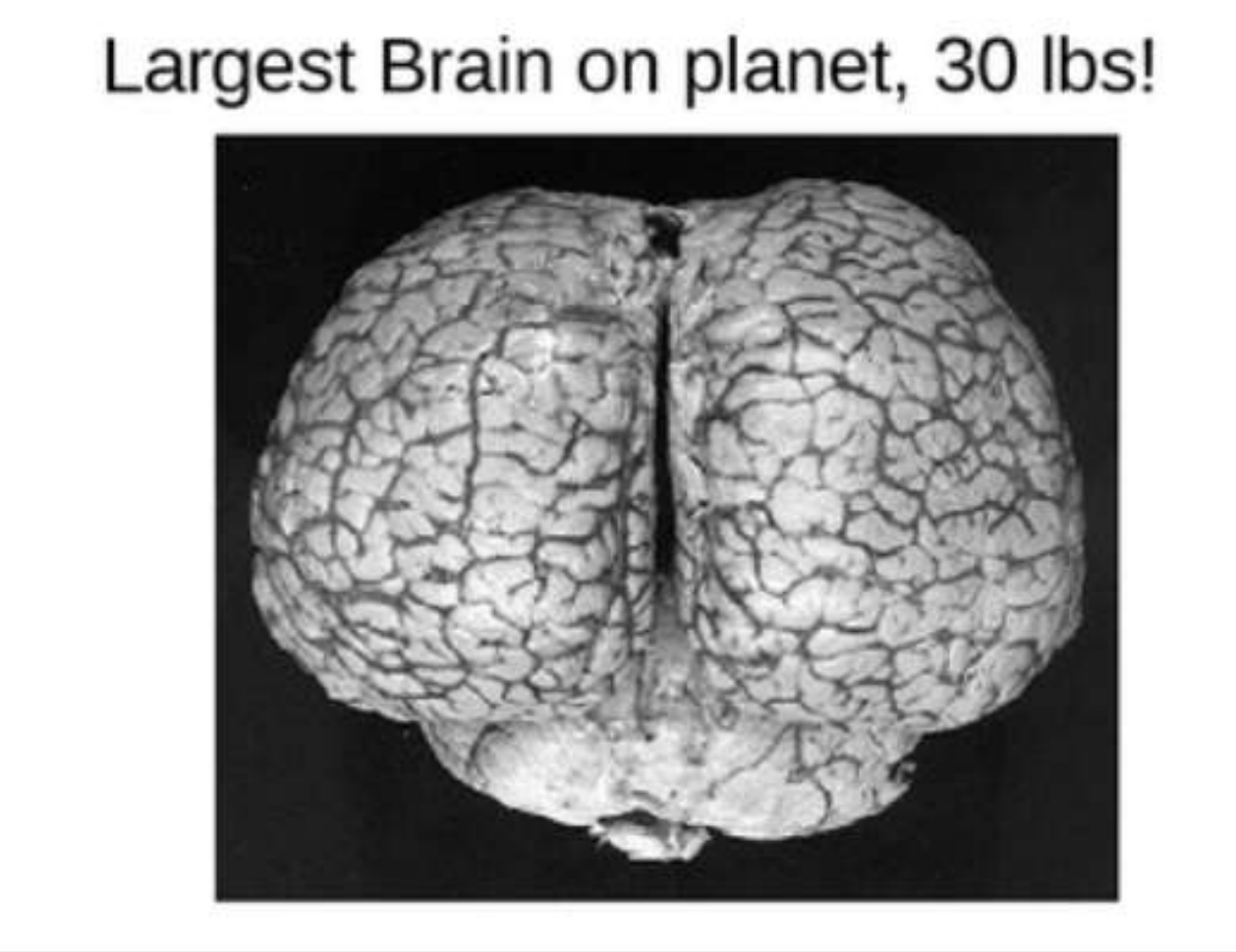
Data Estimate: 100-1000 terabytes of information


Human
Elephant
Dolphin
Gorilla
Dog
Cat
Macaque
Mouse
5cm

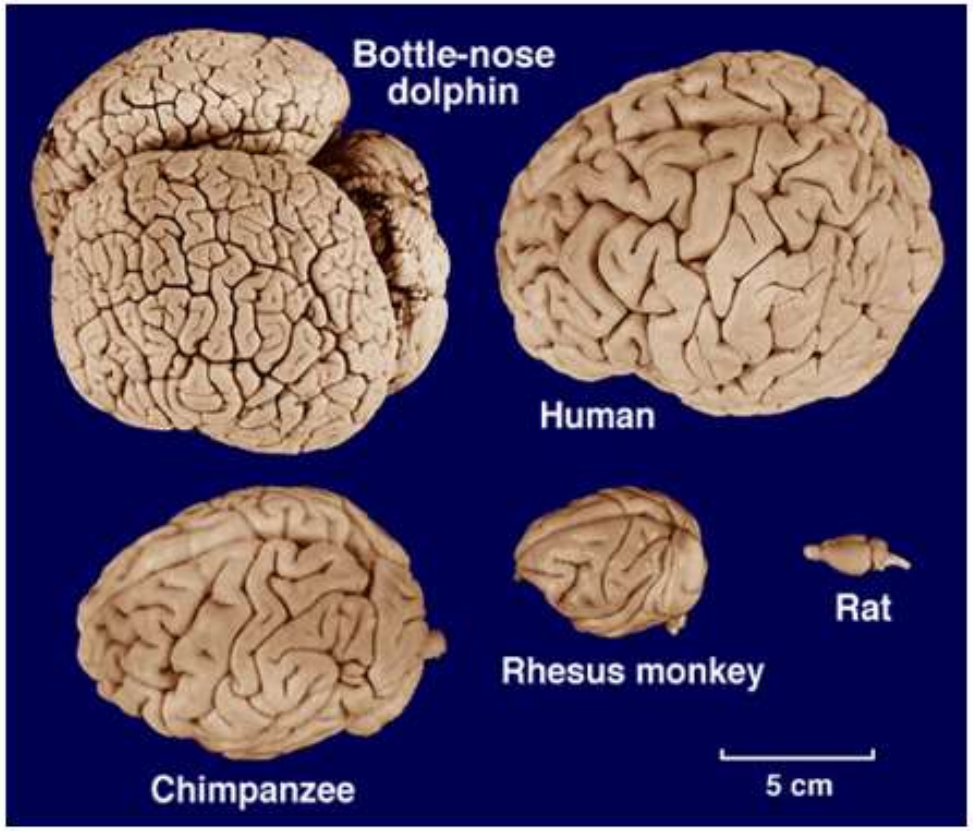
Dolphin & Human



Largest Brain on Planet: Sperm Whale



Brain Sizes



Species	Adult Brain Weight (grams)
Chimpanzee	450
Human	1,350
Bottlenosed dolphin	1,600
African elephant	6,075
Fin whale	7,200
Sperm Whale	9,200

Relative Brain Weight

Of all animals, man has the largest brain in proportion to his size" - Aristotle

Species	Brain to Body Weight
Human	2.1 %
Bottlenosed dolphin	1.2 %
Chimpanzee	0.70 %
African elephant	0.50 %
Killer whale	0.10 %
Cow	0.08 %
Sperm Whale	0.02 %

History of human brain evolution

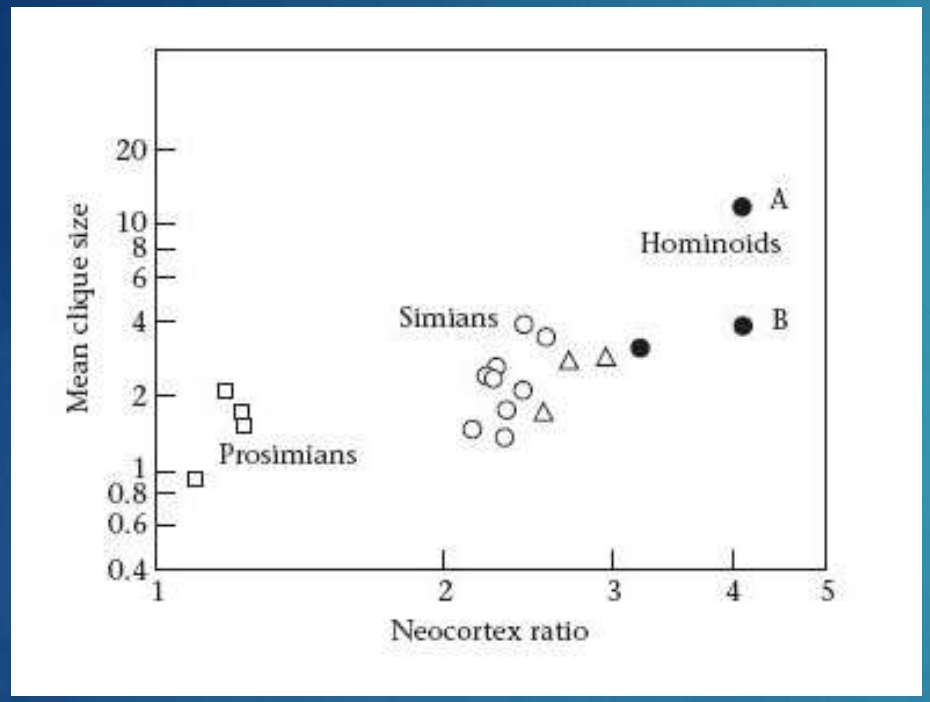
- About 4 MY, first hominids became bipedal with brains about 1/3rd of modern size (400 cc)
- No significant increase in brain size in next million years.
- From 3-2.5 MYA, small allometric (related to body size increase) growth (450-500 cc, A. afarensis to A. africanus)
- From 2.5-1.8 MYA, rapid major brain growth (750 cc, A. africanus to H. habilis); stone tools appear; meat & fish consumption

R. Holloway, 2009

History of human brain 2

- 1.8-.5 MYA, small allometric increase to 800-1000 cc (H. habilis to H. erectus); speculation about language development
- .5-.1 TYA, gradual and modest size increase to archaic H. sapiens, mostly nonallometric, 1200-1700 cc (H. erectus to H. neanderthal)
- .015 to present, small allometric reduction in brain size in modern H. sapiens

Social Brain Hypothesis: As social group size goes up, so does neocortical brain size



Mean clique size in primates

Average group size

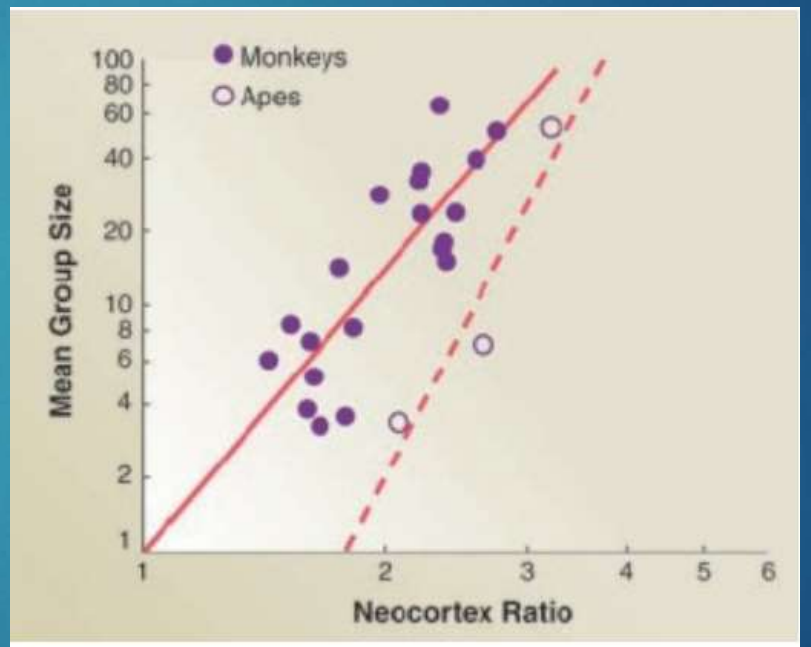


Figure 1. As average group size increases in monkeys and apes, so does neocortex ratio. Reproduced from Dunbar and Shultz (2007).

Social correlates of neocortical size: emphasis on complexity not quantity

- Social group size
- Average group size of free-ranging primates
- Mean number of females
- Frequency of tactical deception
- Length of the juvenile period (intensive social learning period)
- Grooming clique size
- Proportion of play that is social
- Capacity to exploit subtle mating strategies

R. Dunbar, 1998, 2011

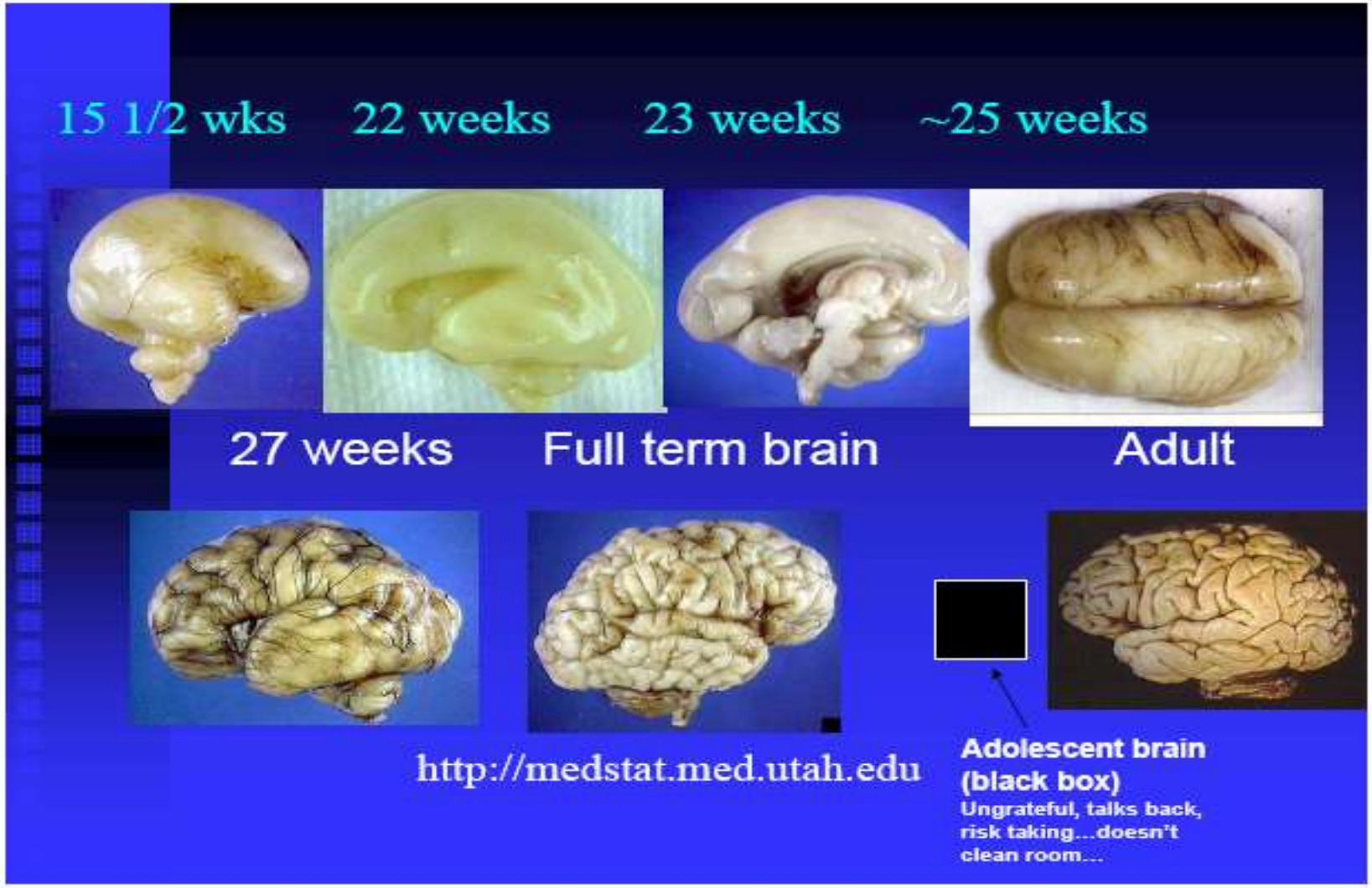
Sociality: Even if you are smart, it is important to have help

Larson

This little gesture encapsulates millions of years of primate brain evolution

Infants a few minutes old will stick out their tongues at adults doing the same thing. Hard wired for social imitation?

Brain Development



Experience

- Experience-expectant development = experiences that occur during narrow temporal window early in development have significant influence on subsequent development (all members of our species: i.e. access to light, faces, speech, caregiving)
- Experience-dependent development: changes that occur in brain throughout lifespan and are unique to individual (i.e. learning and memory)
- Timing of experience: sensitive periods (genes code for basics, but experience does fine-tuning) (i.e. language, attachment)
- Brain needs oxygen, glucose, experience & human attachment

Brain and Role of human relationships

- Early positive relationships (sensitive serve and return pattern) helps to build and strengthen brain architecture
- Michael Meaney: infant rates born to and cared for by mothers who do high degree of licking and grooming (= good maternal care) grow up to be less anxious, handle stress well, and possess greater cognitive abilities. Increases density of glucocorticoid receptor in hippocampus (& stress response). Female rats born to such mothers become high-lickers and groomers. This is an epigenetic phenomenon.

Human normal cortical development

- Normal cortical development involves
  - Proliferation of cells
  - migration,
  - arborization (circuit formation)
  - myelination
- First two processes occurring mostly during prenatal life and the latter two continuing through the first two post-natal decades.

Eight stages of prenatal cortical development

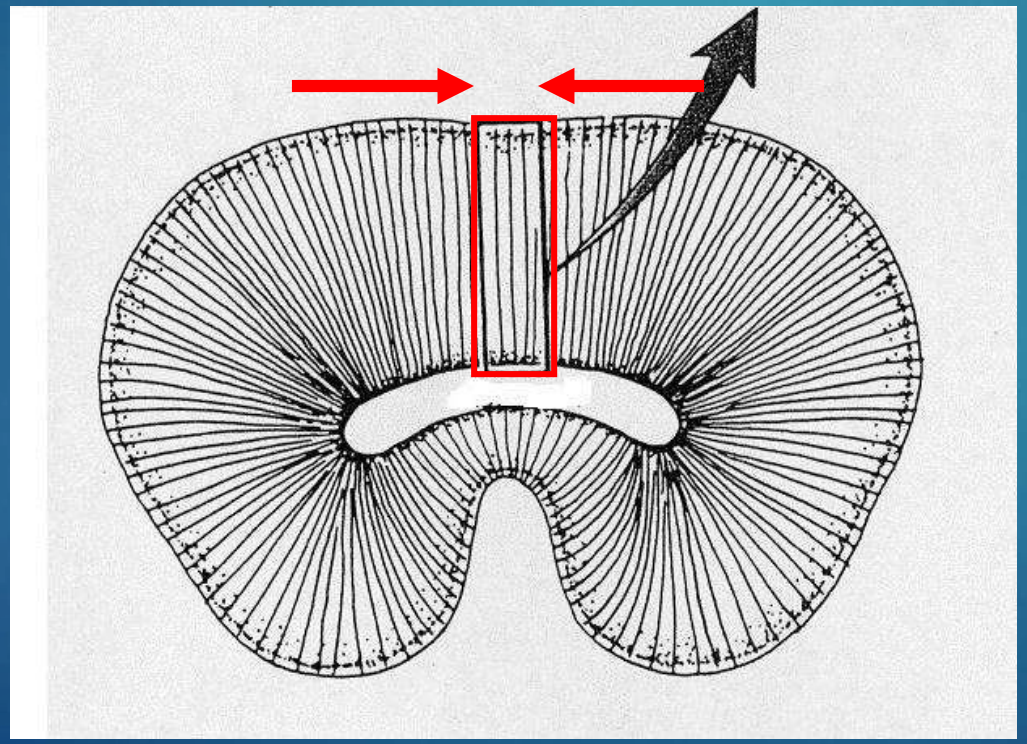
1. Neural proliferation
2. Neural migration
3. Neural differentiation
4. Axonal growth
5. Dendritic growth
6. Synaptogenesis
7. Myelination
8. Neuronal death

See **Normal Development of Brain Circuits by** Gregory Z Tau and Bradley S Peterson, *Neuropsychopharmacology*, 2010

Mark Beidelman presentation

1. Neural proliferation

- Begins with neural tube closure



3-4 Weeks

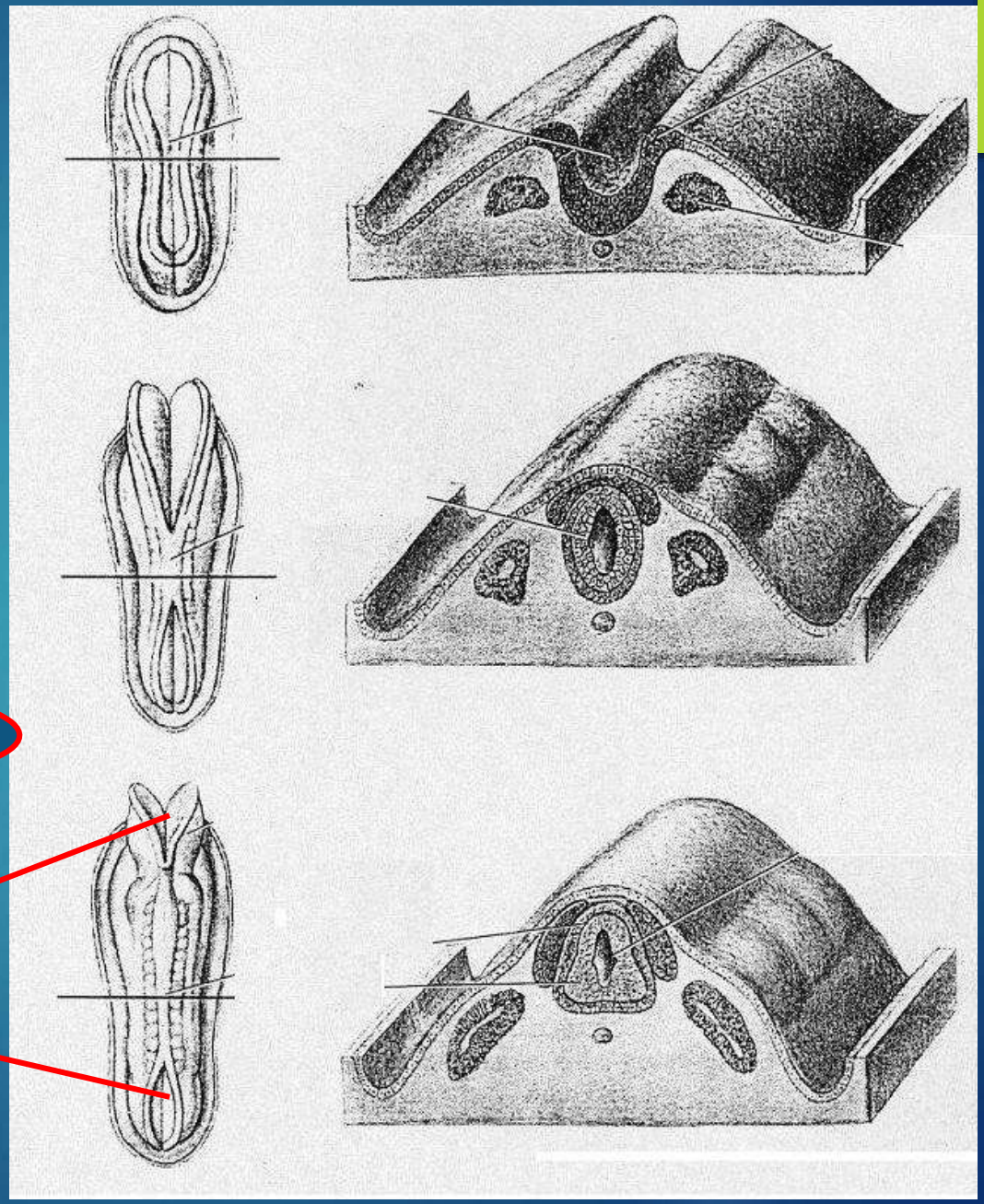
Neural Groove

Neural Tube

Neuroepithelium

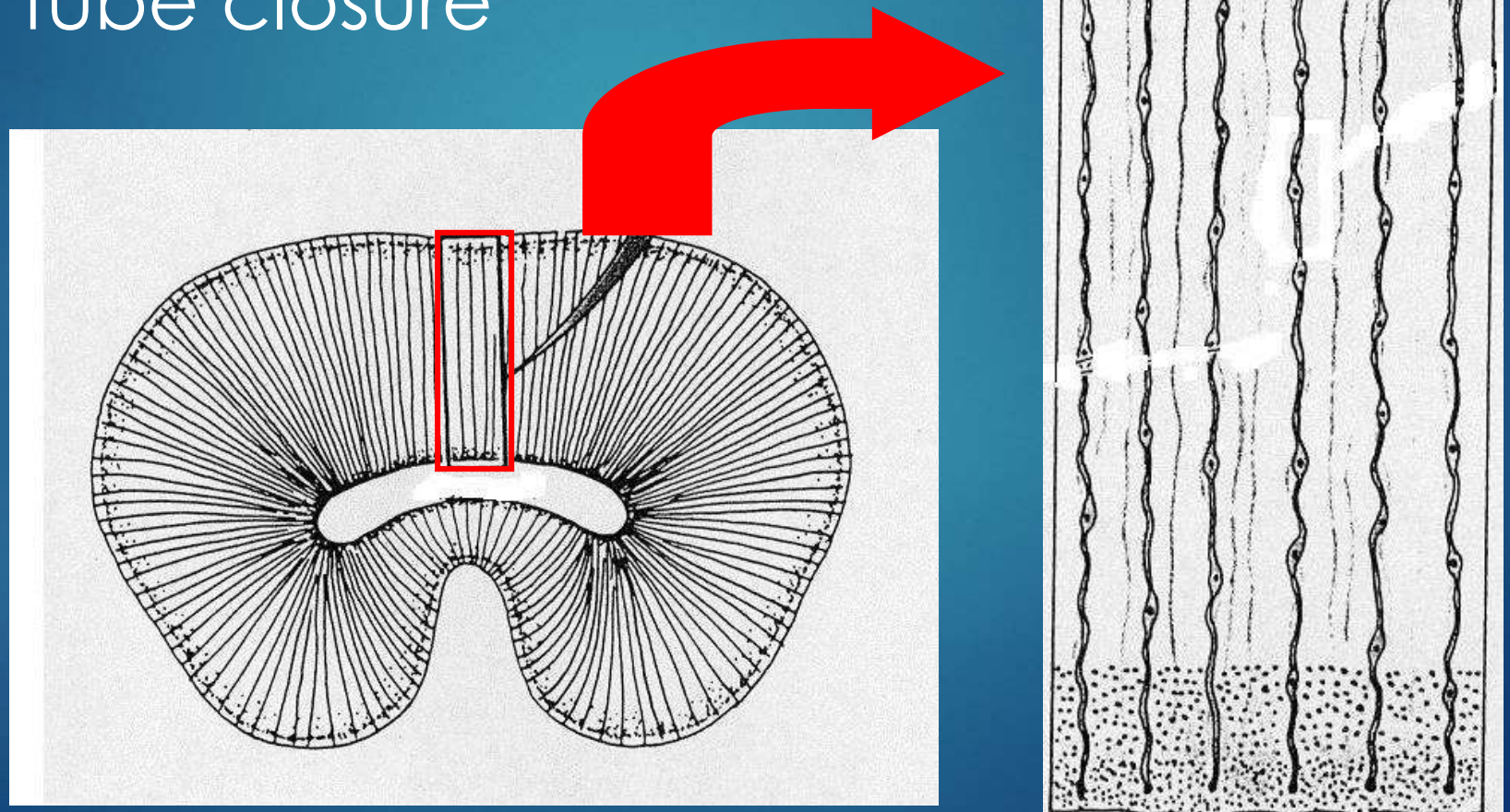
Brain

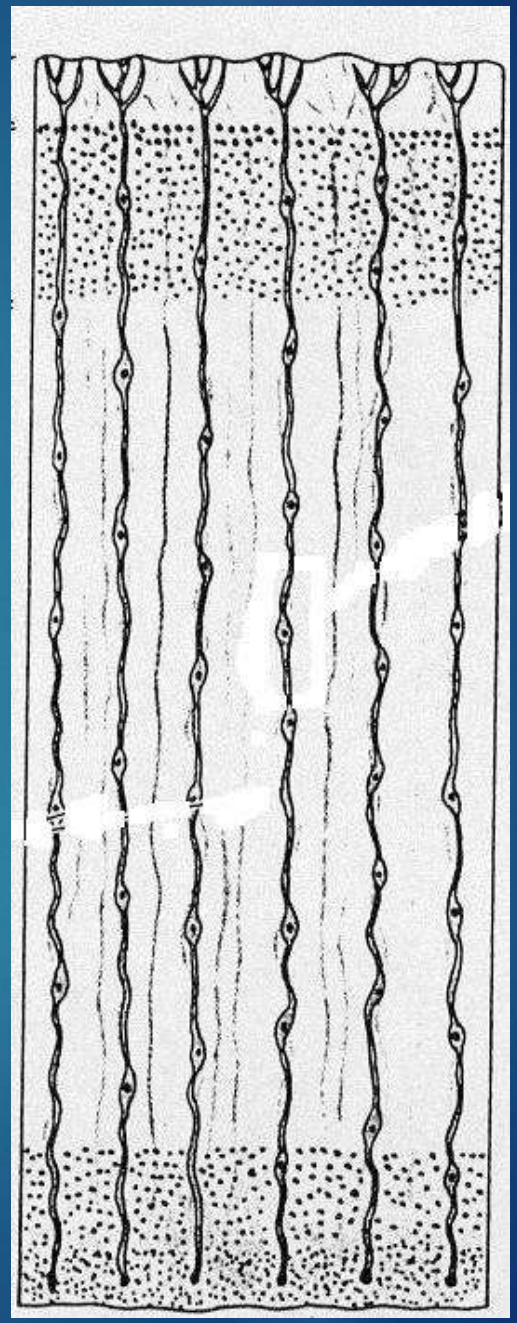
Spinal Chord



1. Neural proliferation

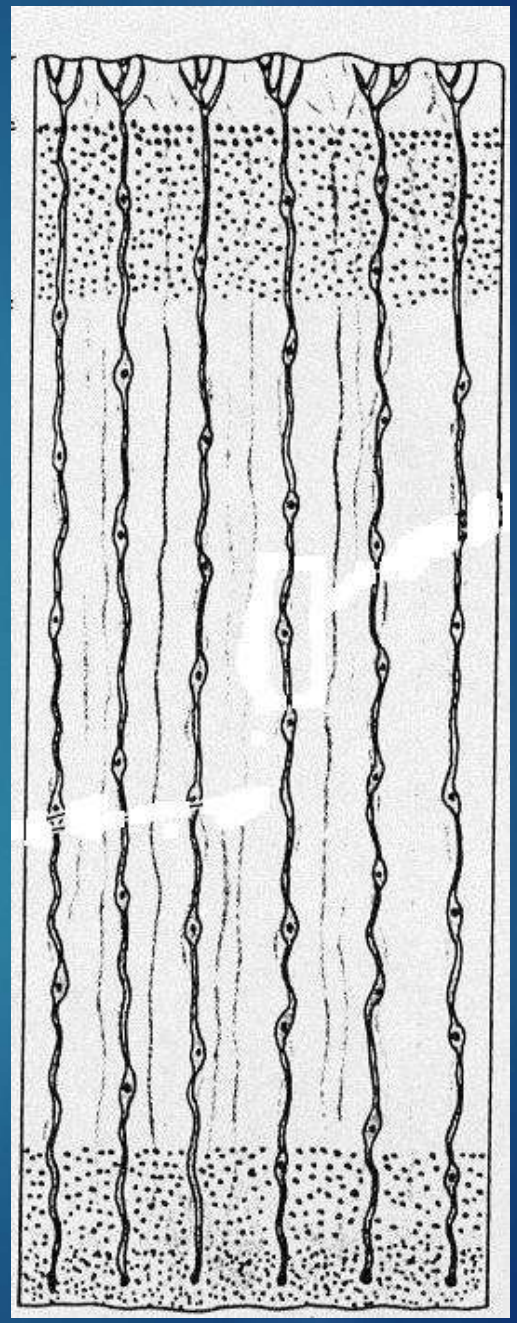
- Begins with neural tube closure





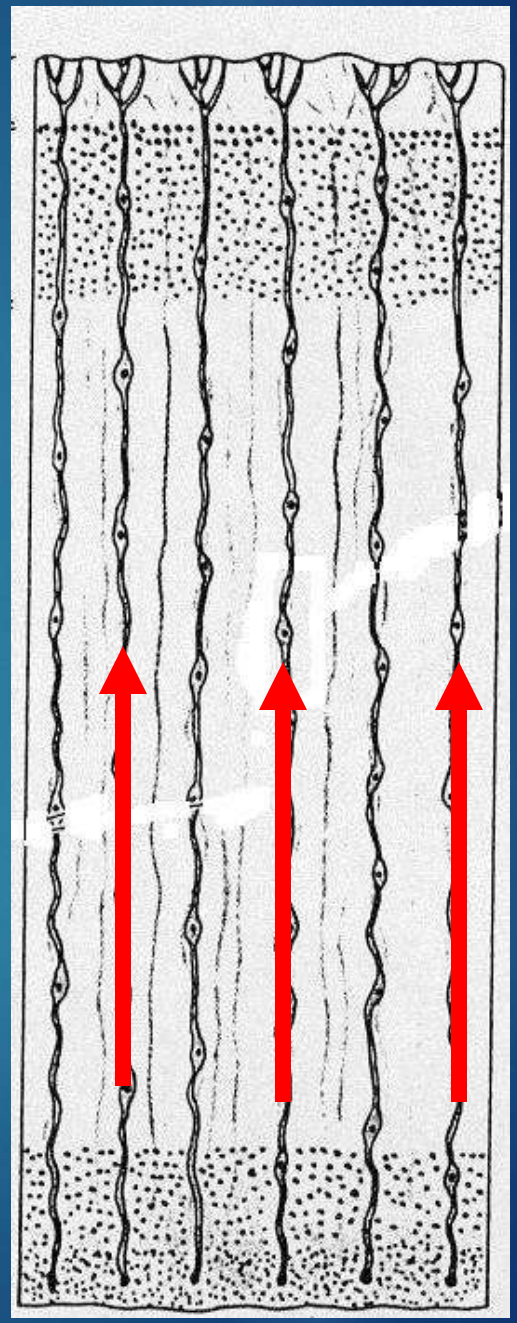
1. Neural proliferation

- New cells born in ventricular layer
- 1 mother cell produces ≈ 10,000 daughter cells
- All neurons (86 billion in total) are produced pre-natally
- Rate of proliferation extremely high; thousands/minute



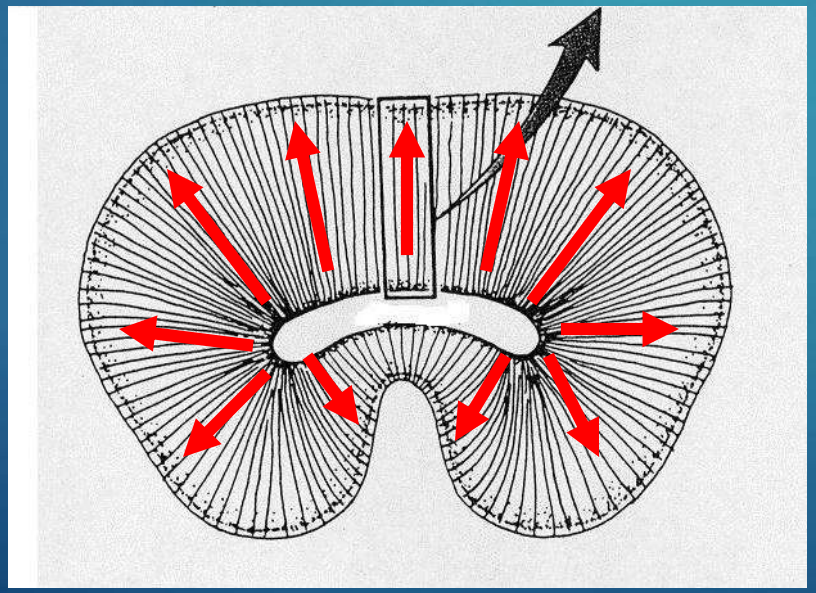
2: Cellular migration

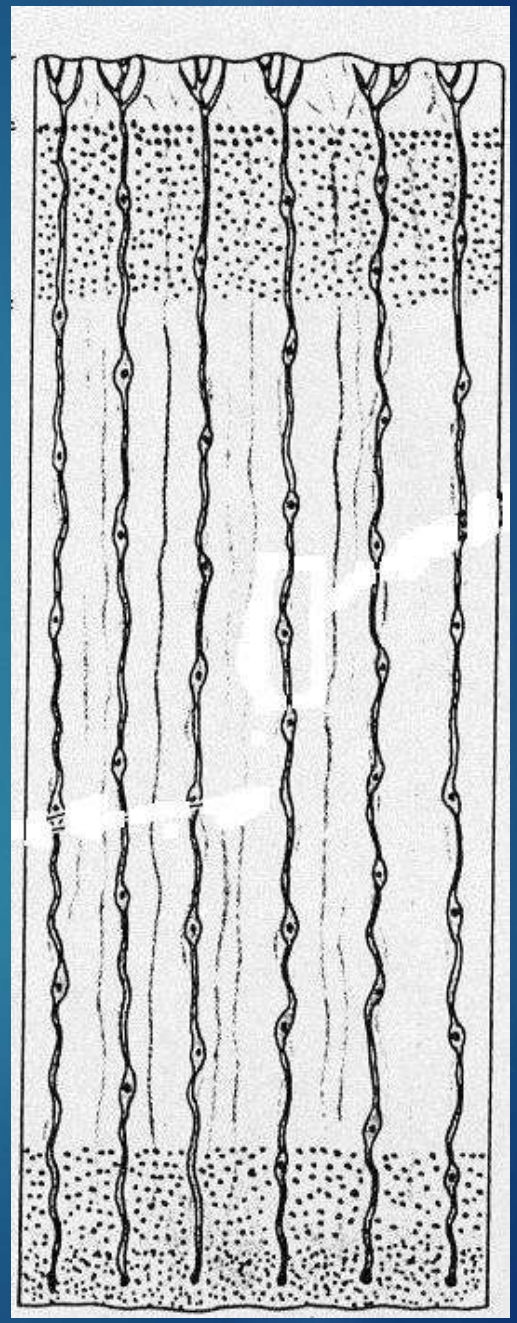
- Non-dividing cells migrate from ventricular layer



2: Cellular migration

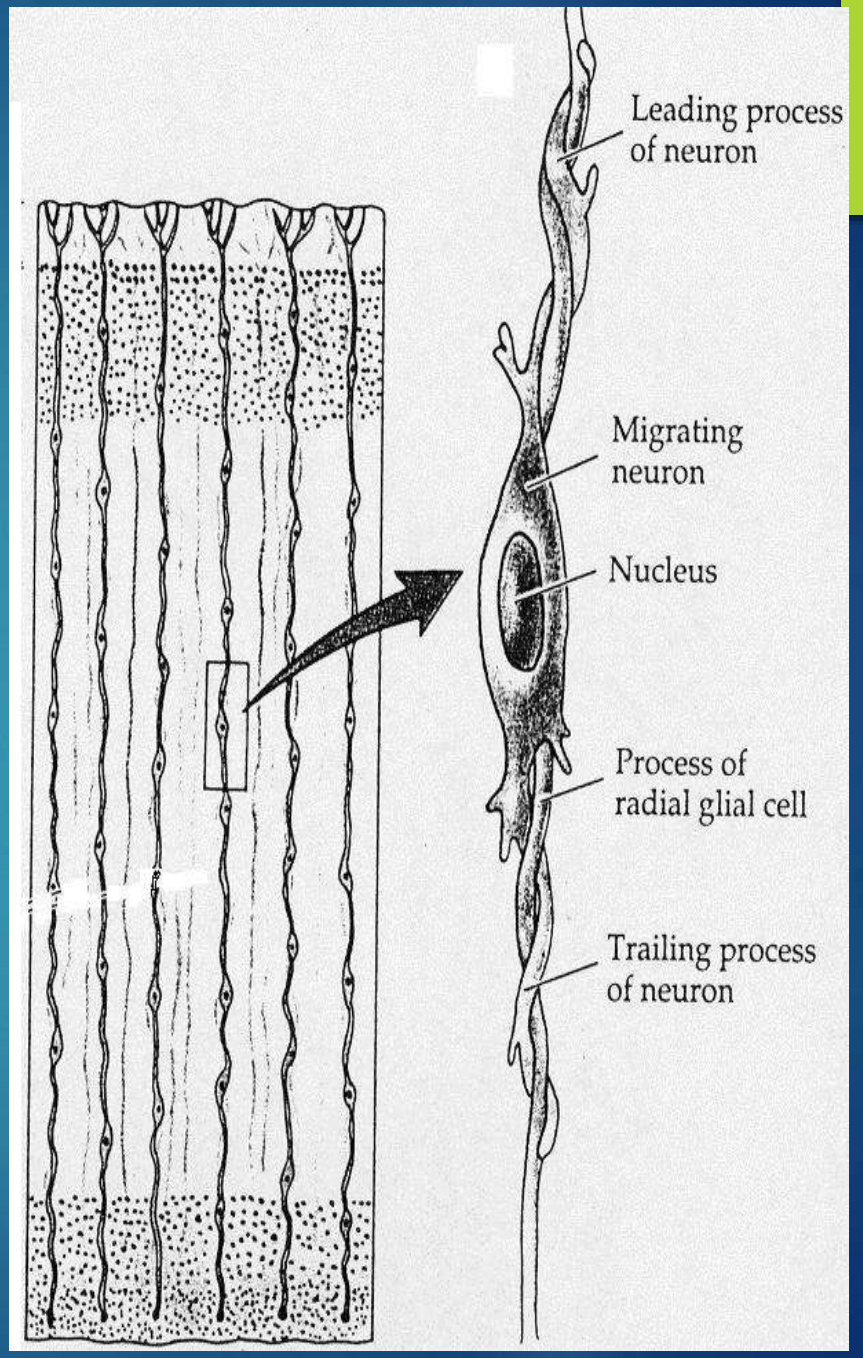
- Creates a radial inside-out pattern of development





2: Cellular migration

- Importance of radial glial cells



Glial Highway: Neurons use glial cells to guide placement in migration

By 24 weeks, all brain cells in place; builds 2 million connections per second via genetic blueprint for location of connections

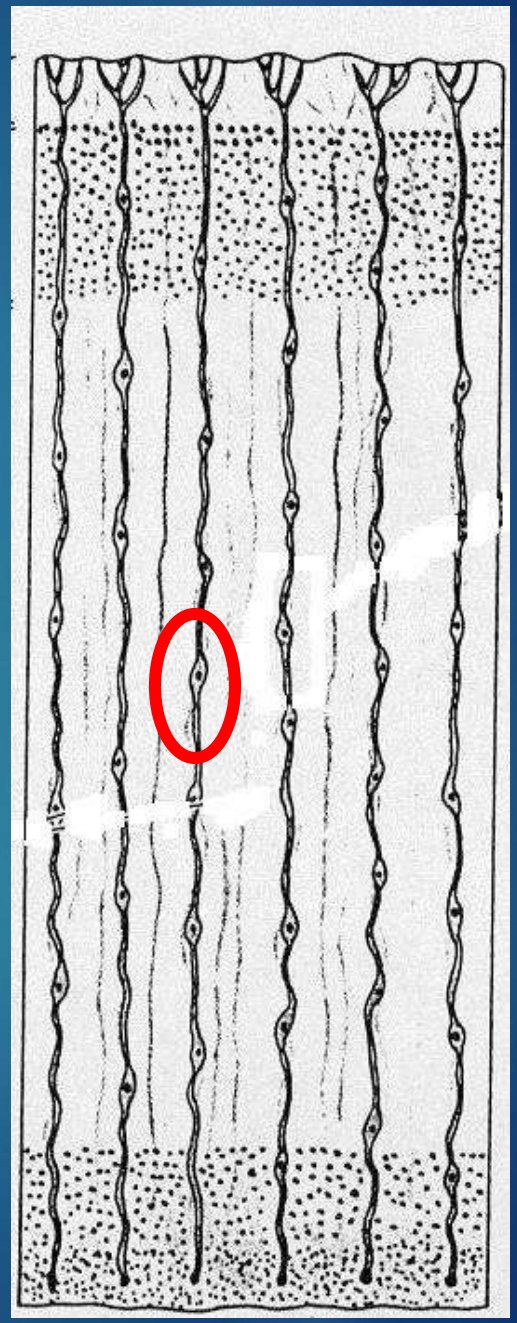
Neurons are genetically programmed for their destination, but unlike other cells do not get info from neighbors

Errors in Neuronal migration

- Errors in neuronal migration can have profound neurodevelopmental consequences.
- Lissencephaly, or ‘smooth brain,' for example, is a disorder of neuronal migration that disrupts the normal patterning of gyri and sulci.
- Its functional consequences range from mental retardation to death in infancy

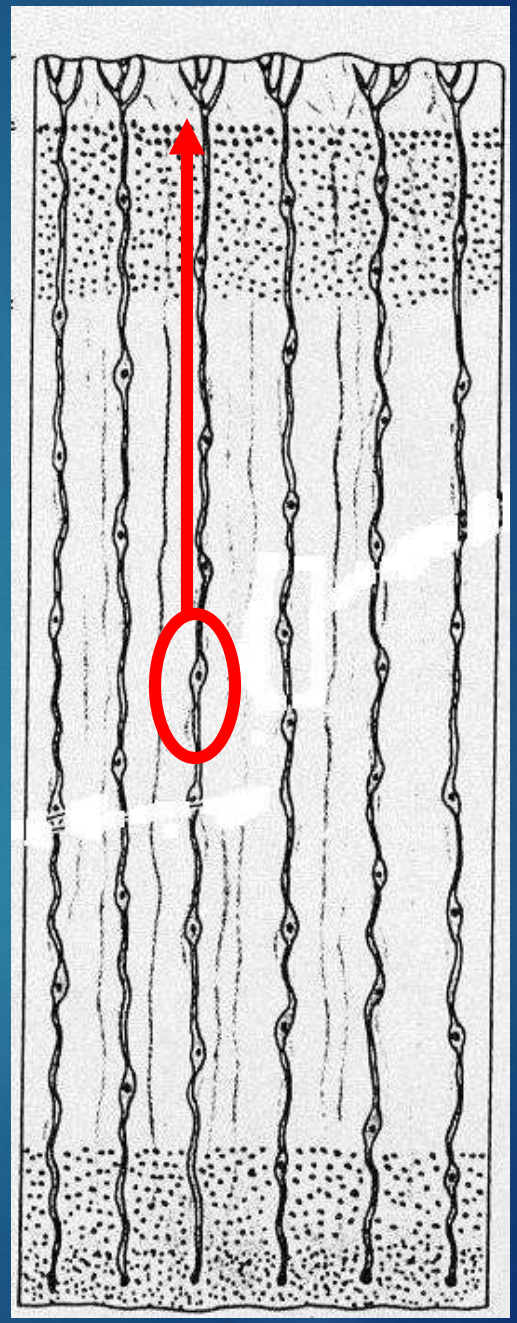
3. Cellular differentiation

- Migrating cells are structurally and functionally immature



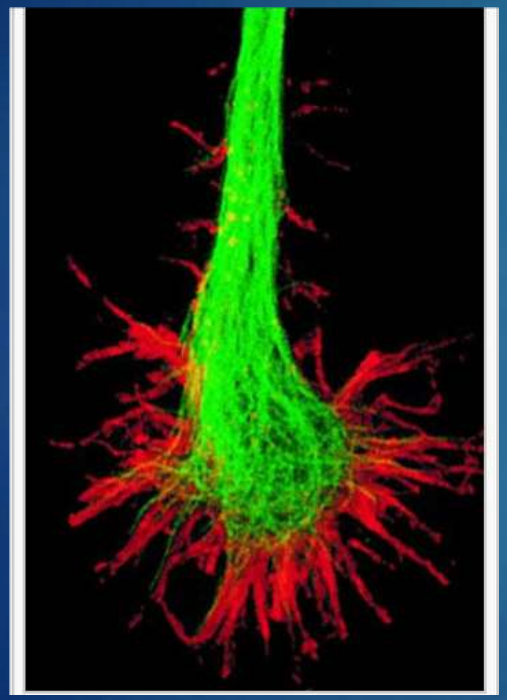
3. Cellular differentiation

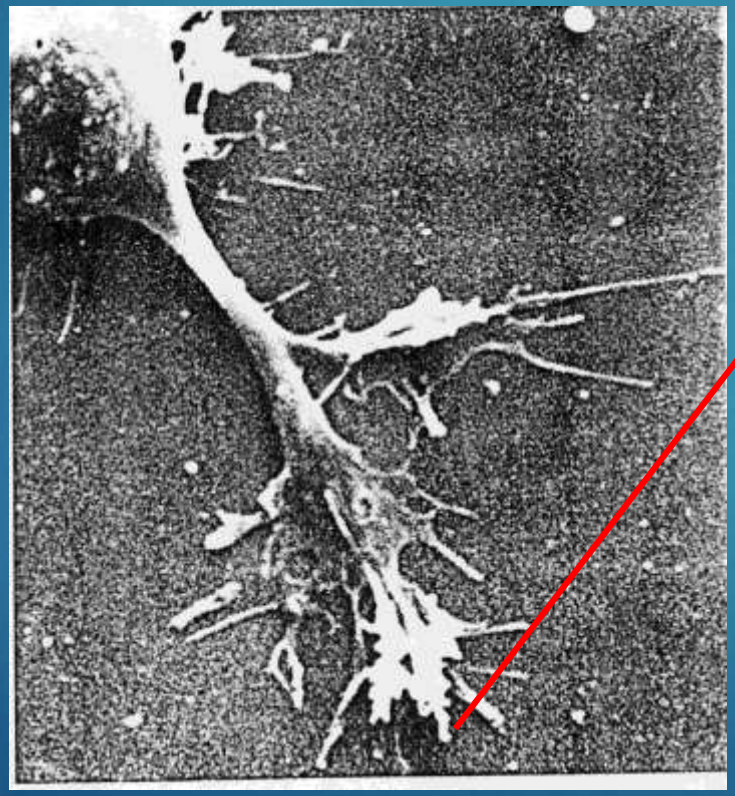
- Once new cells reach their destination, particular genes are turned on →growth of axons, dendrites, and synapses begins



4. Axonal growth

- Growth occurs at a growth cone





4. Axonal growth

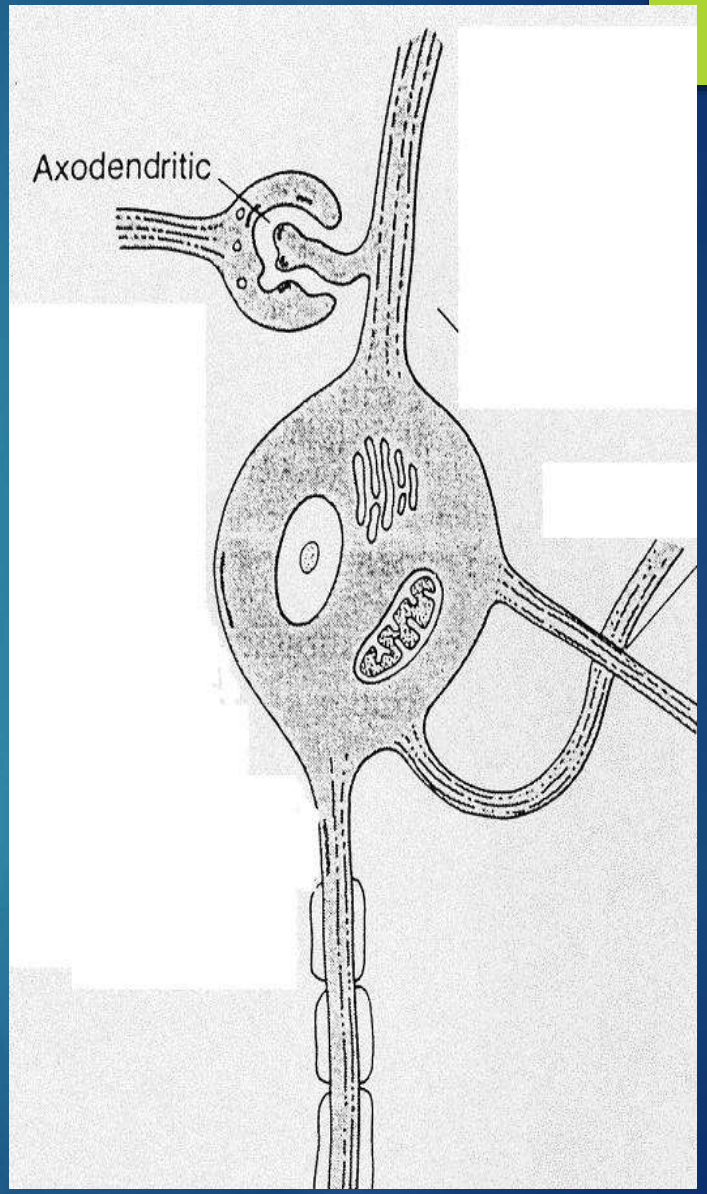
- Axons have specific targets
- Targets often enormous distances away
- Some axons extend a distance that is 40,000 times the width of the cell body to which it is attached
- Finding targets ? → chemical & electrical gradients, multiple branches

5. Dendritic growth

- Usually begins after migration
- Slow
- Occurs at a growth cone
- Begins prenatally, but continues postnatally
- Overproduction of branches in development and resultant pruning
- Remaining dendrites continue to branch and lengthen

6. Synaptogenesis: Exuberant Connectivity

- Takes place as dendrites and axons grow
- Involves the linking together of the billions of neurons of the brain
- 1 neuron makes up to 10000 synapses with other neurons
- Neurotransmitters and receptors also required



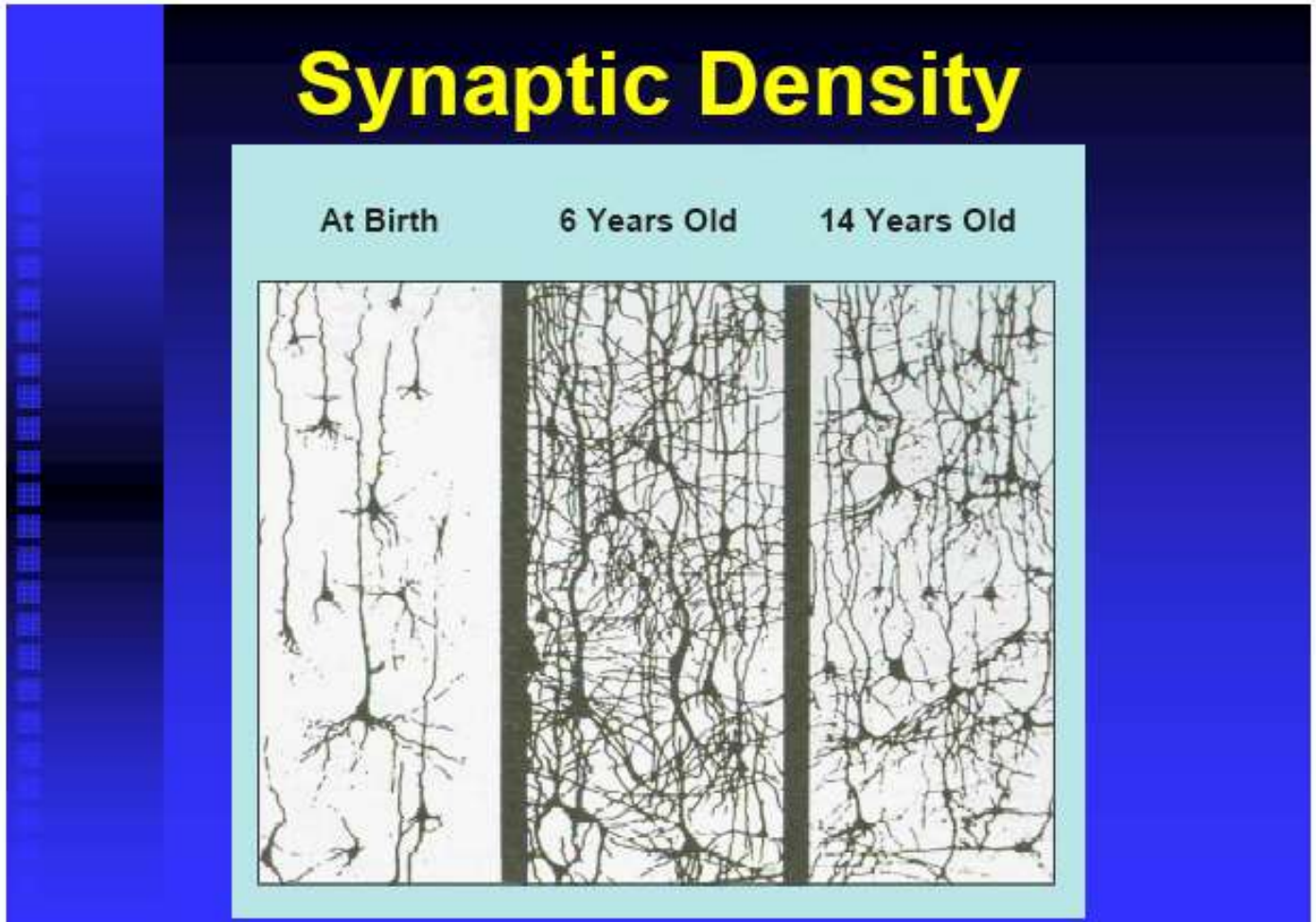
Synaptogenesis

- Synaptic density within the cortical plate grows at a rate of about 4% per week until approximately GA weeks 26–28, which is the time of peak transfer of afferent synaptic connections from the subplate to the cortical plate.
- Dendritic arborization and synaptogenesis accelerate in the third trimester to produce a thickening of the developing cortex, which coincides with the appearance of cortical gyri and sulci on fetal MRI scans.
- GA week 34 marks entry into the peak period of synaptogenesis, during which almost 40,000 new synapses are formed every second, a process that continues well into early postnatal life.

Timing of synaptogenesis

- The timing of synaptogenesis differs across cortical layers and across developing cortical regions. Following the inside–out sequencing of cortical lamination, synaptogenesis begins earlier in deeper layers than in more superficial ones.
- Synaptogenesis begins earlier in primary motor areas and later in anterior regions, such as the prefrontal cortex (PFC)
- The number of neurons in the human brain peaks at GA week 28.
- The reasons for the excess production of most neuronal types and glia are not fully understood.

Synaptic Density

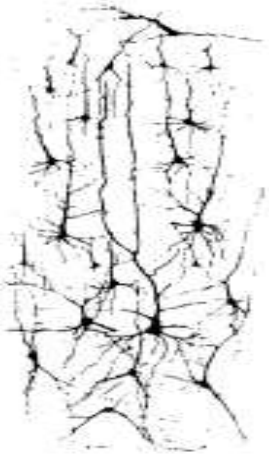


Neuronal formation

- During last 120 days of pregnancy, neurons form at a rate of around 580,000 per minute.

New born

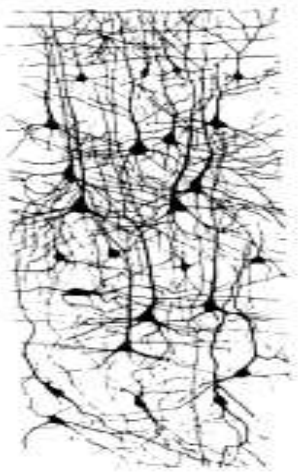
A



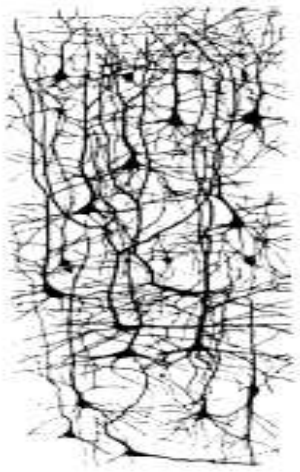
B

C

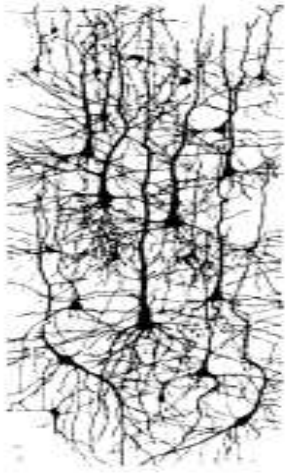
2 years



D



E



F

Apoptosis: Neuronal Hara-Kiri

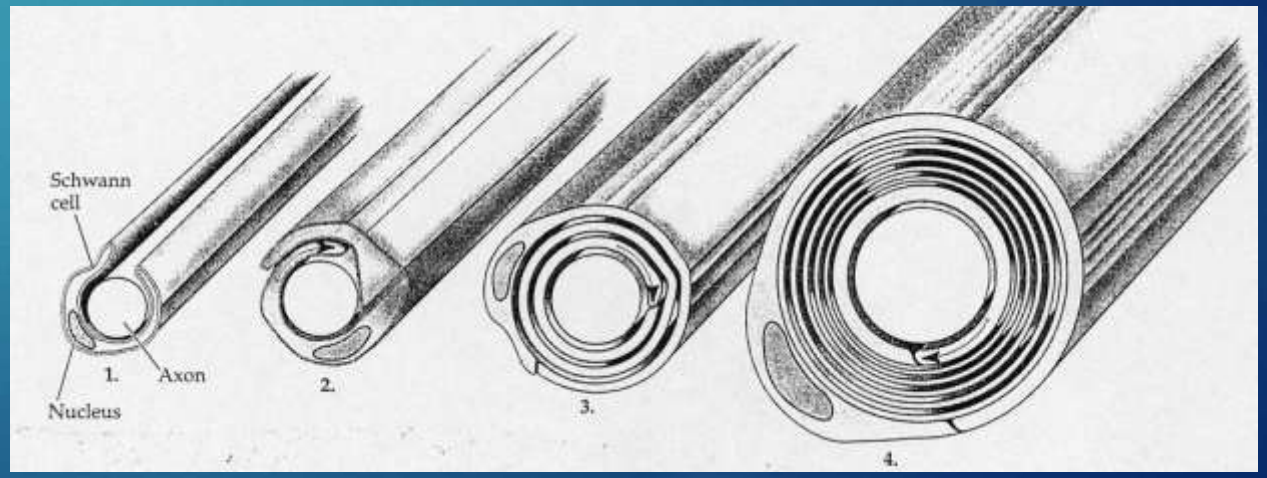
- The first wave of apoptosis involves primarily proliferating precursor cells and young postmitotic neuroblasts in the ventricular zone. It begins around GA week 7 and continues throughout the first trimester.
- The second wave of apoptosis peaks around GA weeks 19–23 and eliminates postmitotic neurons within the cortical plate.

Overproliferation and pruning

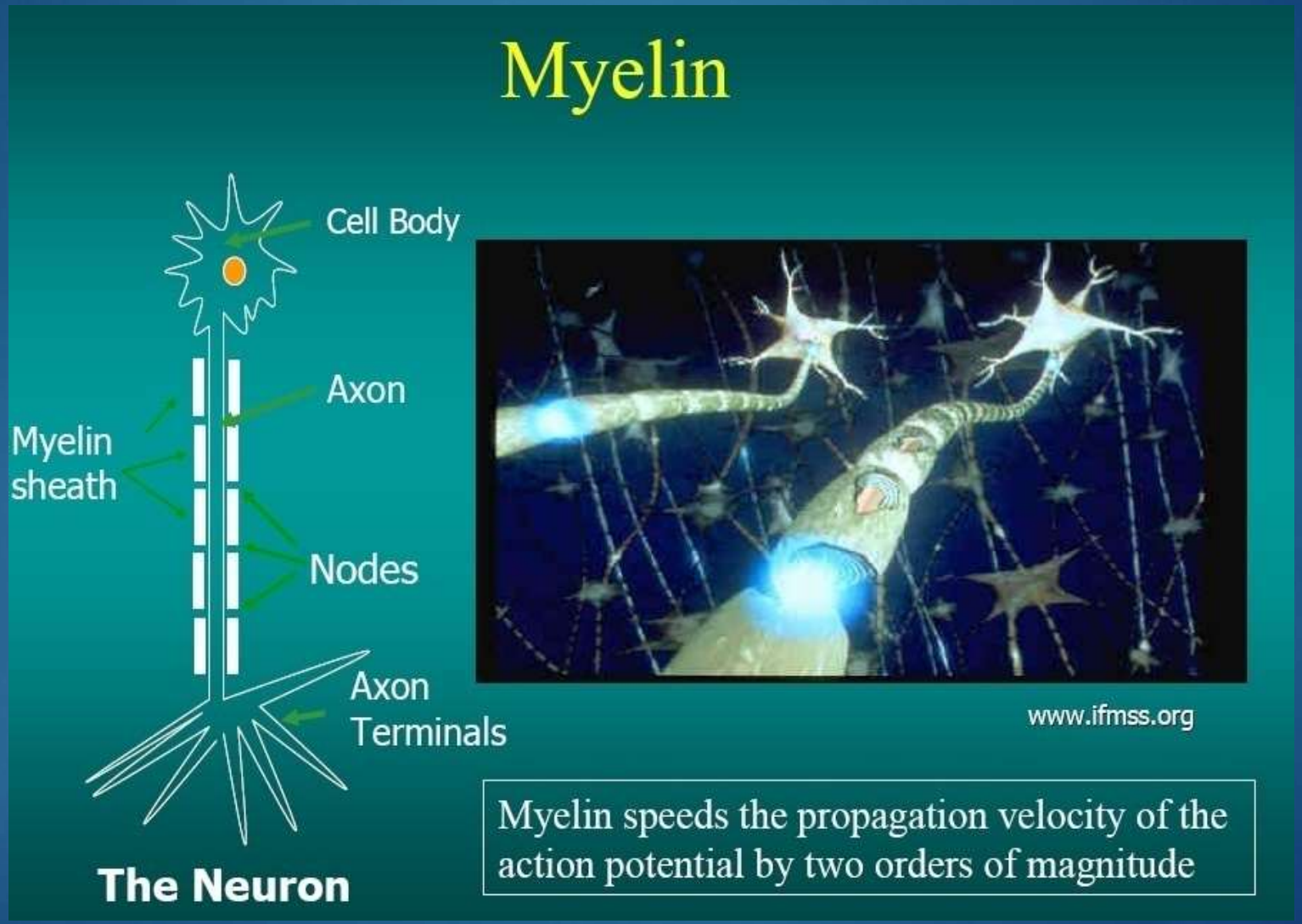
- The number of synapses reaches a maximum at about 2 years of age
- After this, serious pruning begins
- By 16-20, only 50% of the original synapses remain

7: Myelinization

- The process whereby glial cells wrap themselves around axons
- Increases the speed of conduction
- Begins before birth in primary motor and sensory areas
- Continues into adolescence in certain brain regions (e.g., frontal lobes)

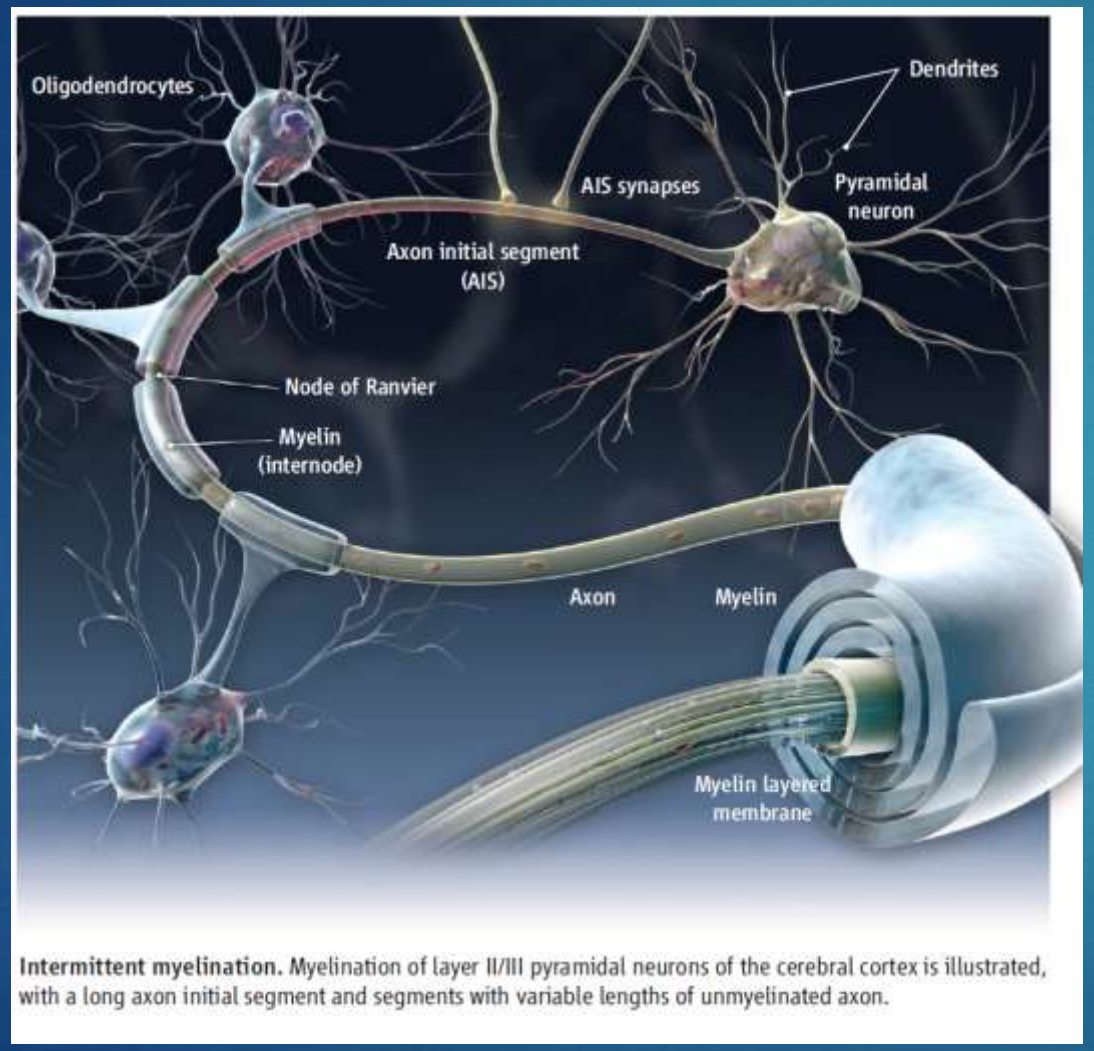


Myelin: 136,000 KM of Myelinated Axons

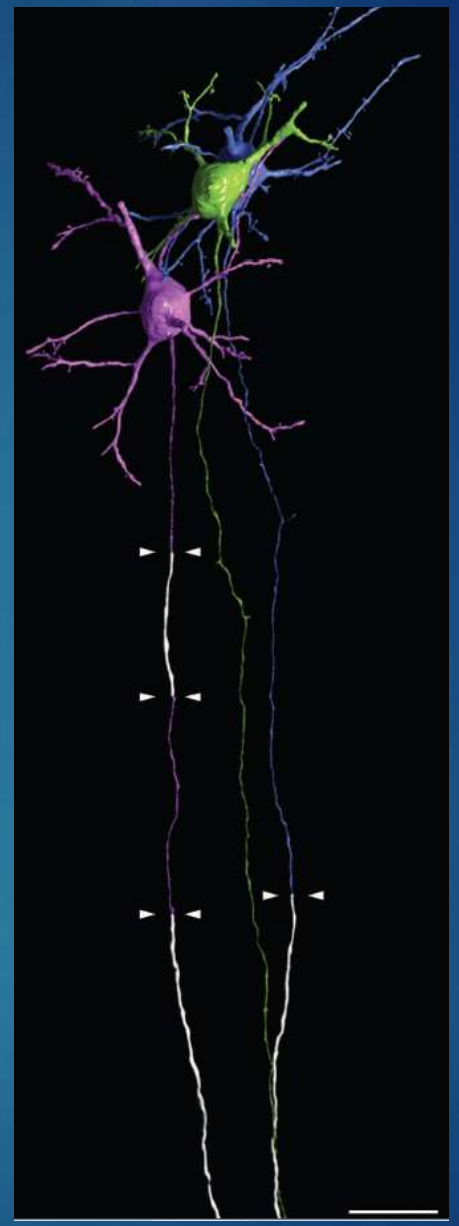


Mylenated speed: 100m/s; unmyelinated speed - less than 1m/s

Myelin: Oligodendrocytes



Intermittent myelination. Myelination of layer II/III pyramidal neurons of the cerebral cortex is illustrated, with a long axon initial segment and segments with variable lengths of unmyelinated axon.



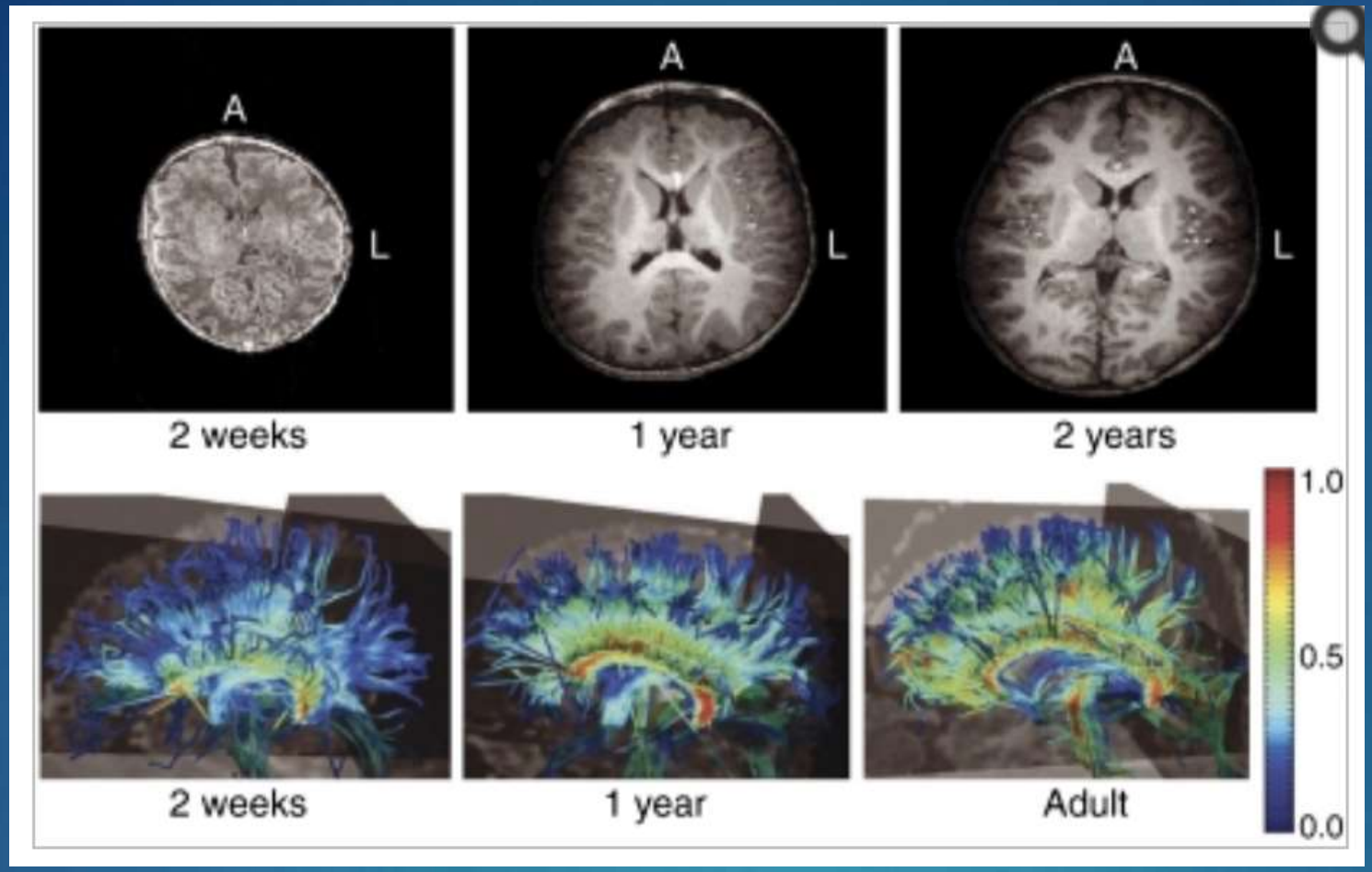
Not all Axons are mylenated

First WM

- On MRI, some myelinated white matter can be discerned in the brains of preterm infants by GA week 29, but the majority of white matter appears unmyelinated.
- Between GA weeks 36 and 40, the proportion of total brain volume that contains myelinated white matter increases from 1 to 5%.
- Premyelinating oligodendrocytes may be particularly sensitive to perinatal hypoxia or ischemia, which may disrupt white matter tracts in the frontal and temporal lobe to produce cerebral palsy or mental retardation

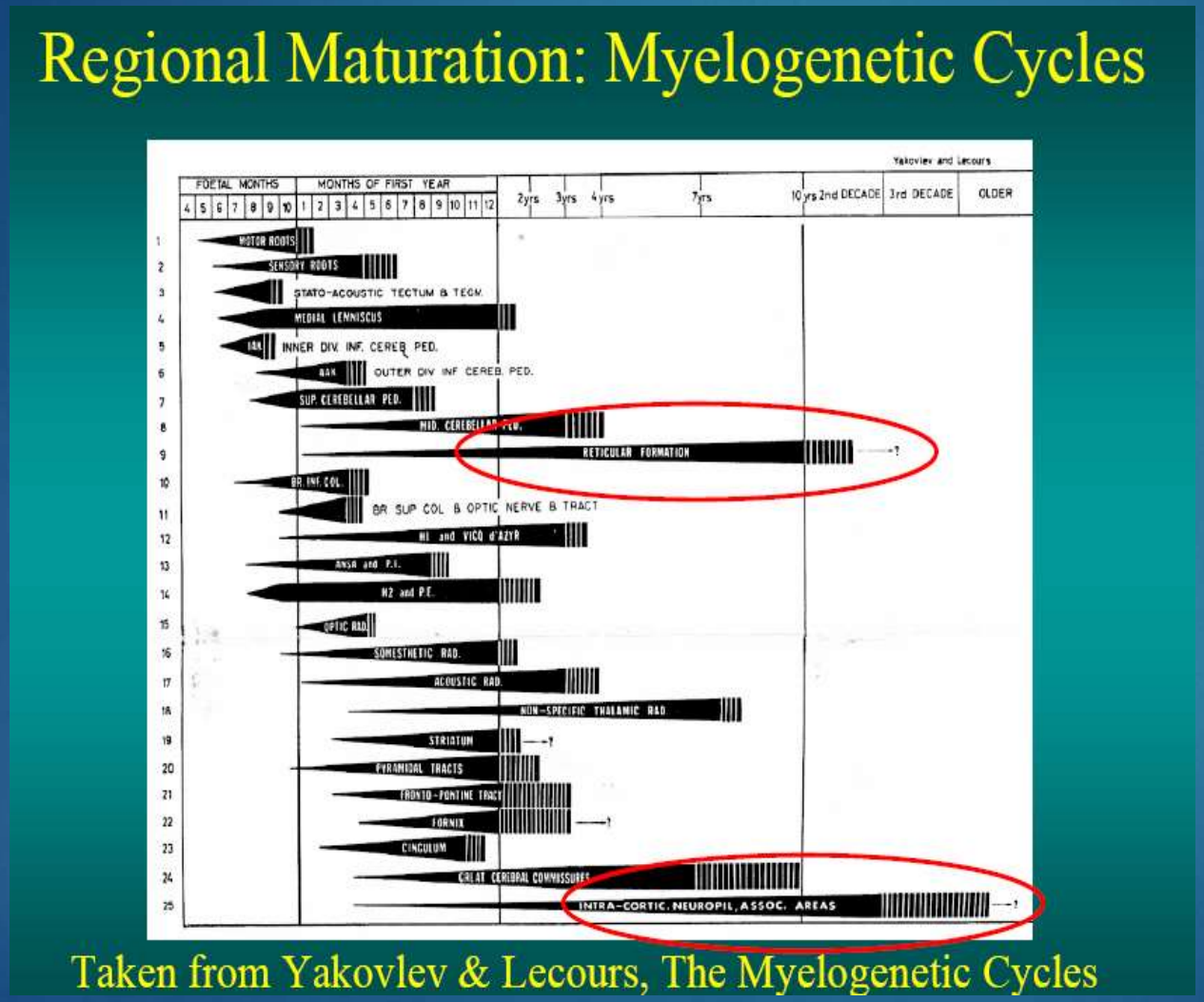
Myelination

- Myelination advances in a posterior-to-anterior direction, after the general pattern of maturation of neural circuits.
- Sensory pathways myelinate first, followed by motor pathways, and then association areas.
- Myelination reaches the furthest portions of the frontal lobes between 7 and 11 months of age.
- Within a given functional circuit, subcortical structures myelinate before cortical regions.



Top: T1-weighted axial MRI images acquired longitudinally from one child, showing age-related increase in brain size and white matter intensity. Bottoms: DTI images of white matter tractography in a cross-sectional comparison showing of age-related increase in the organization of corpus callosum white matter. Each panel represents one subject.

Myelin Sheets on Axons Mature Slowly in Frontal Lobes; may increase into 30+s.



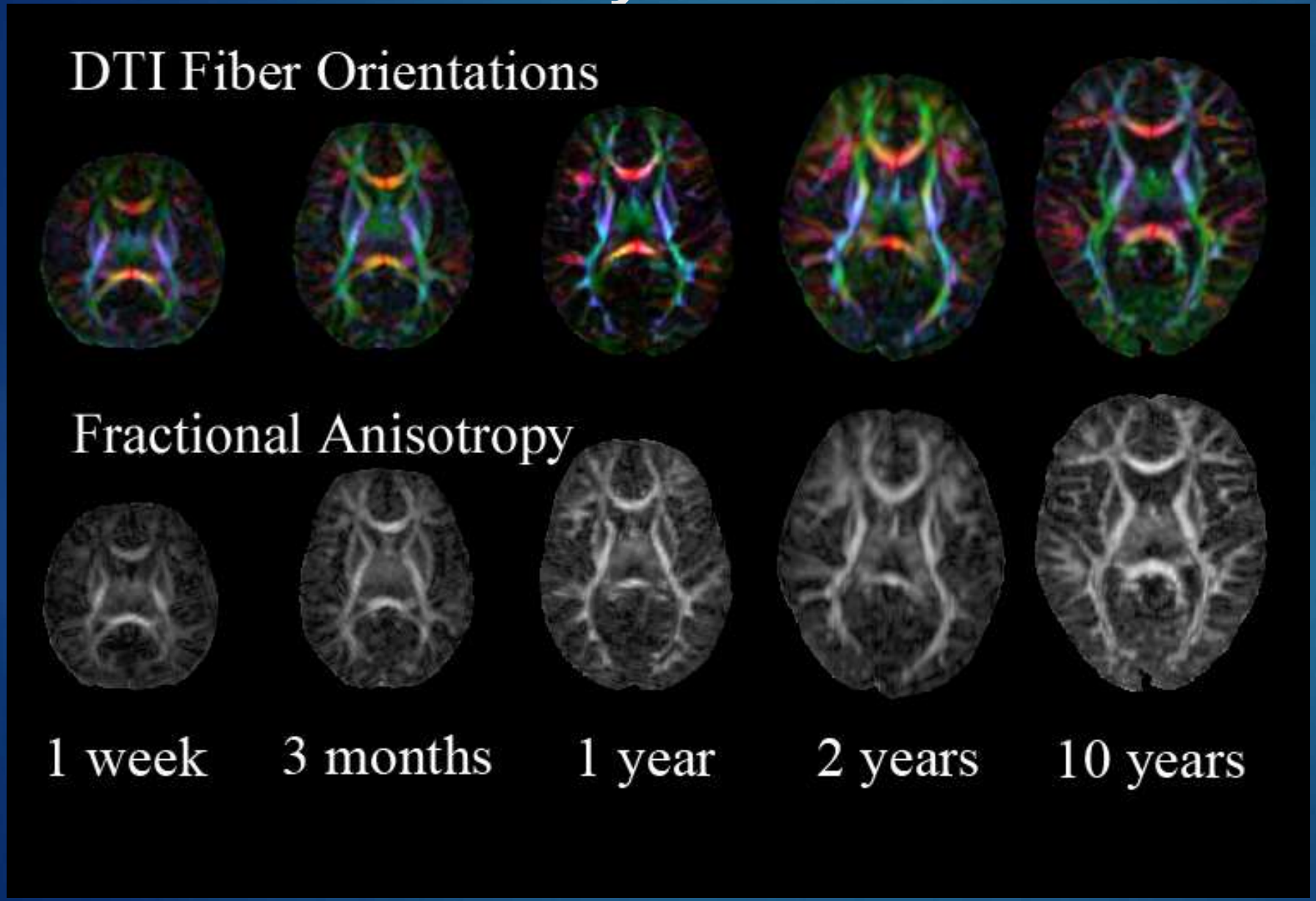
Yakovlev & Lecours 1967

Amount of white matter (axon interconnections) distinguishes us from primates, not amount of prefrontal lobes.

Creates “greater bandwidth” and processing speed.

Einstein had more white matter, not neurons.

Myelinization

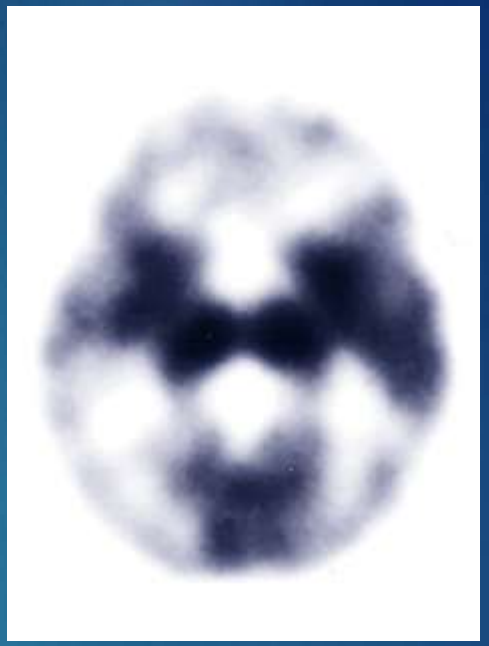


FA reflects fiber density, axonal diameter, and myelination in white matter

PET Scans: Metabolism

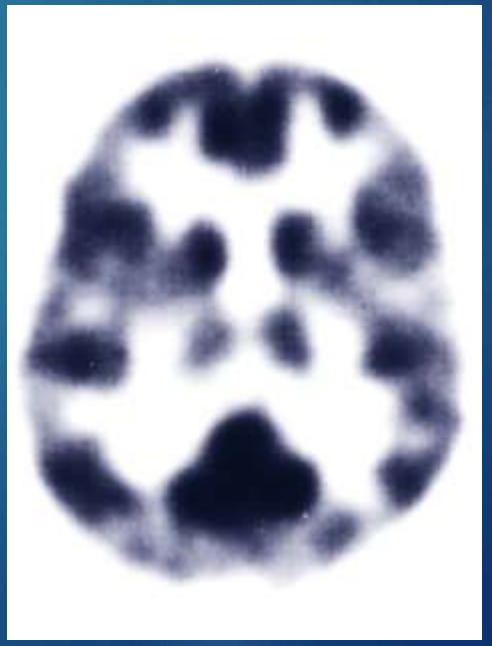
5 Days

2 Months

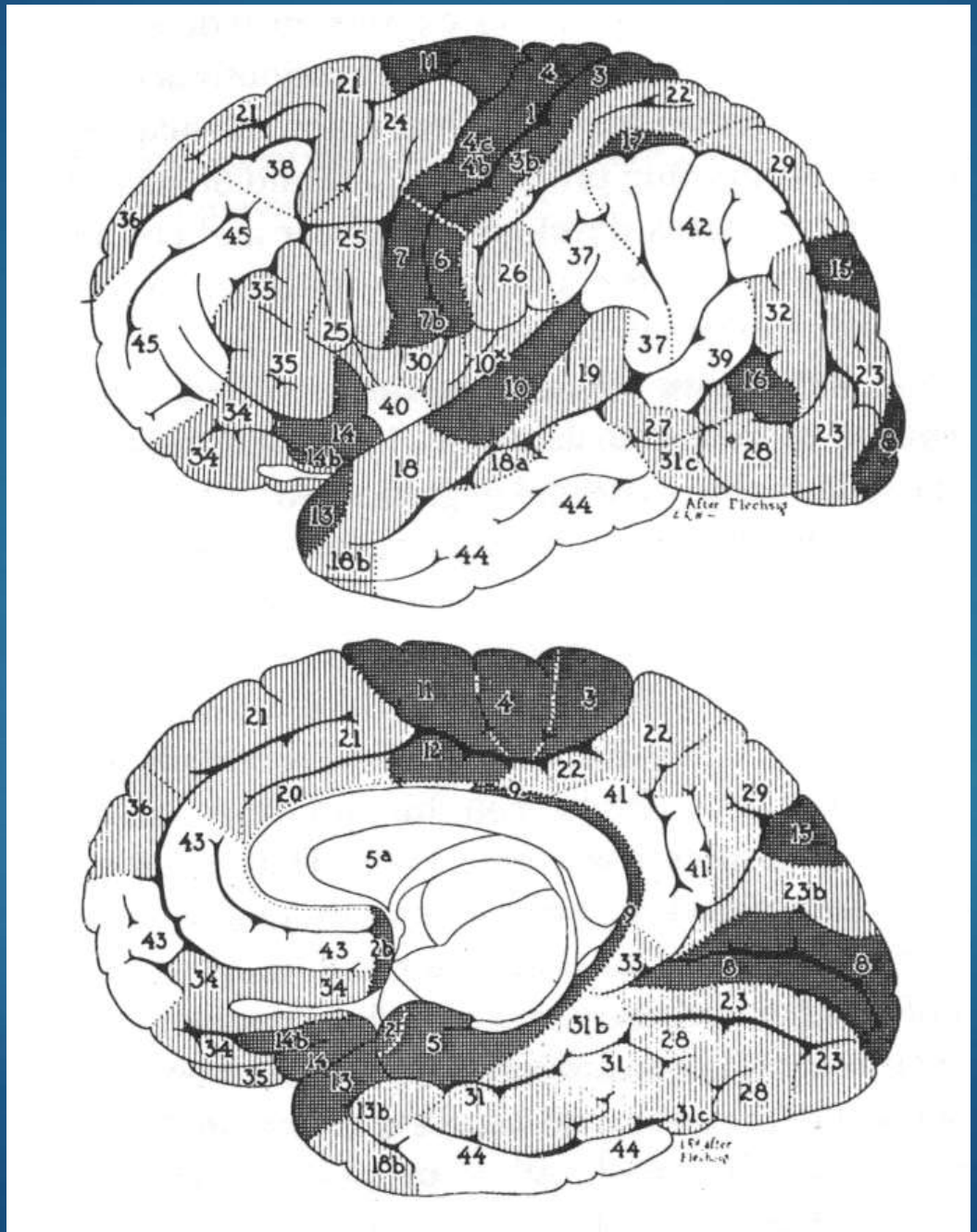


1 Year

28 Years



Order of myelination of the human cortex



based on

Flechsig P., 1920

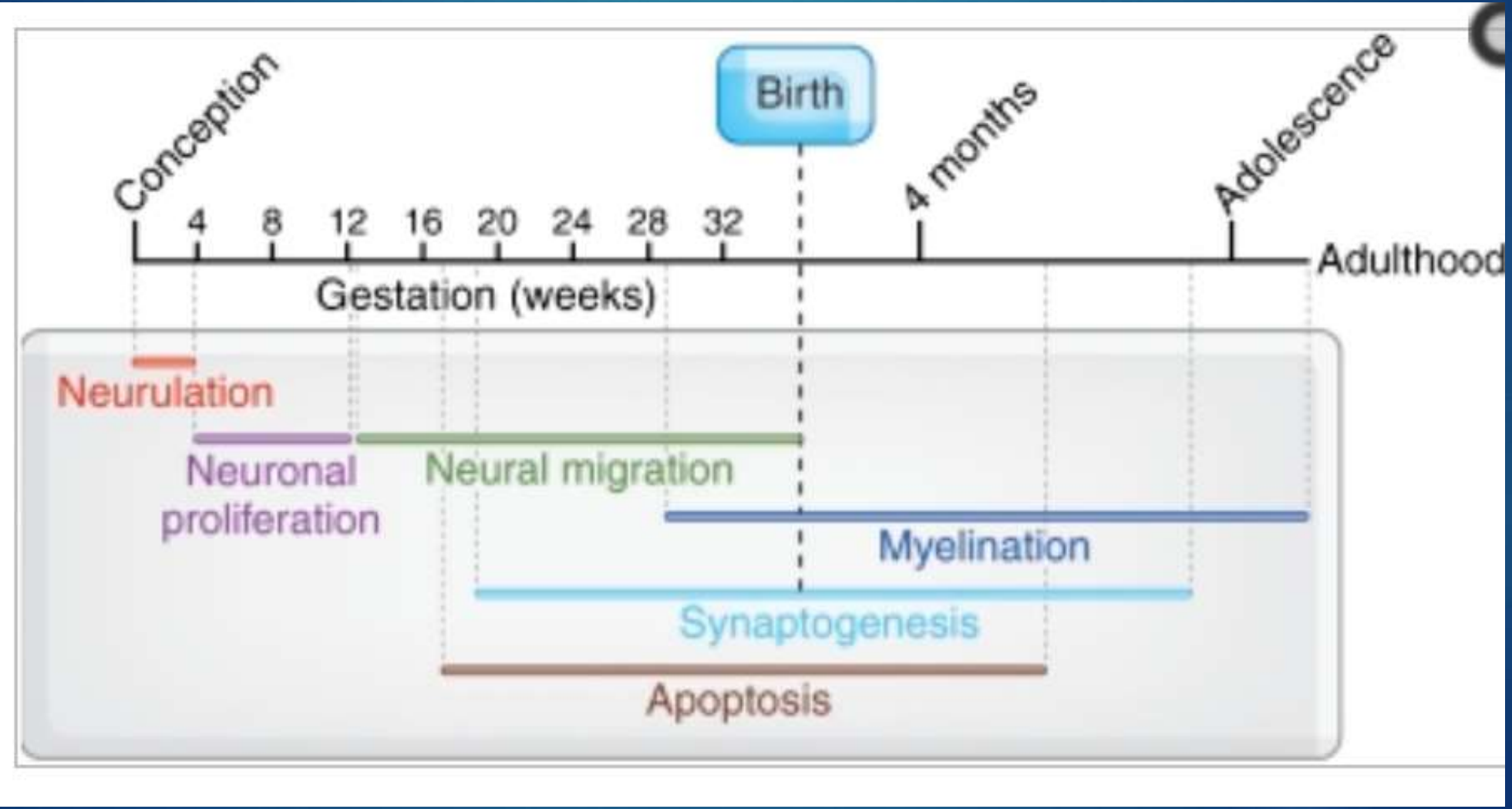
8. Apoptosis: Neuronal Hari-Kari

- Nearly 50% of all neurons and glial cells die in a form of programmed cell death (apoptosis) during the first 7 months of life

- Neurons that gain enough growth factor survive. Damaged cells die.

- Structure of the brain is a product of sculpting as much as growth

Timeline of major events in brain development.



The Brain: Nature versus nurture

- The adult brain consists of approximately 85 billion (surviving) neurons that make trillions of synaptic links
- It is functionally highly organized, supporting various perceptual, cognitive and behavioral processes
- Perhaps the most complex living system we know

Question

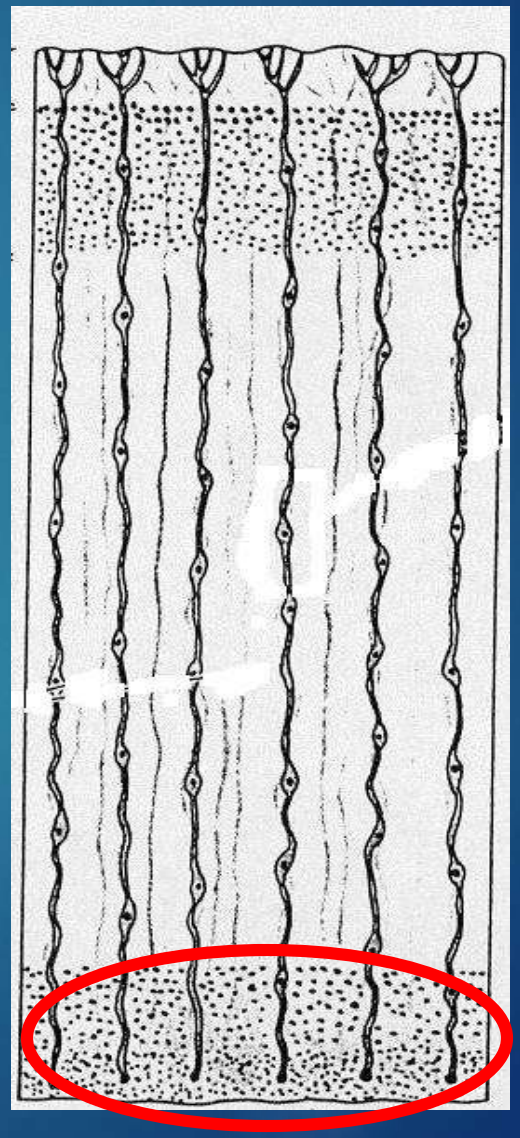
- Of all the information that is required to assemble a brain, how much is stored in the genes?
- Nature view: argues that most of the information is stored in the genes
- Nurture view: brain is structurally and functionally underspecified by the genes → emerges probabilistically over the course of development

Nature View

- (1) Not much is left to chance
- (2) Brain a collection of genetically-specified modules
- (3) Each module processes a specific kind of information & works independently of other modules
- (4) In evolution: modules get added to the "collection"
- (5) In development: genes that code for modules are expressed and modules develop according to these instructions

The nature view: Evidence

- Neurogenesis
- Neuroblasts give rise to a limited number of daughter cells
- Cells have a genetically mediated memory that allows them to remember how many times they have divided



The nature view: Evidence

- Cell death (apoptosis)
- Cells seem to possess death genes
- When expressed, enzymes are produced that effectively cut-up the DNA, and kill the cell
- Similar mechanism may control the timing of neuronal death

Nurture view

- (1) Brain organization is emergent and probabilistic *not* pre-determined
- (2) Genes provide only a broad outline of the ultimate structural and functional organization of the brain
- (3) Organization emerges in development through over-production of structure and competition for survival

- Gerald Edelman: Neural Darwinism: Overproliferation of structures + sensory experience produce Darwinian-like selection pressures in development; Structures that prove useful in development win the competition for survival; The rest are cast off

The “nurture” view: Evidence

- Does experience affect developing structures and functions?
- Is the pruning of brain structures systematic?
- Do developing brain regions interact competitively?

The “nurture” view: Evidence

Hubel & Weisel

- **Binocular deprivation**: Raised kittens but deprived them of visual stimulation to both eyes No abnormality in the retina or thalamus
- Gross abnormality in visual cortex
- Disrupted protein production caused fewer and shorter dendrites to develop, as well as 70% fewer synapses
- Effects only occur early in development, but persist into adulthood
- Example: Surgery on congenital cataracts in adult humans

The “nurture” view: Evidence

Hubel & Weisel

- Early monocular deprivation
- After restoring stimulation, vision in this eye is severely impaired
- One effect: Monocular deprivation disrupted the establishment of ocular dominance columns

The “nurture” view: Evidence

Hubel & Weisel

- Early monocular deprivation:
- After restoring stimulation, vision in this eye is severely impaired
- Sensory input competes for available cortex
- With input from one eye eliminated, no competition
- Therefore, input from uncovered eye assumes control of available visual cortex and disrupts the establishment of ocular dominance columns
- Findings point to the importance of stimulation from the *environment*

The “nurture” view: Evidence

Kratz, Spear, & Smith

- Early monocular deprivation
- After restoring stimulation, vision in this eye is severely impaired
- A second effect: Residual function of the deprived eye competitively inhibited by strong eye
- Deprived one of experience and then removed strong eye
- Prior to surgery, stimulation of deprived eye elicited activity in only 6% of cortical neurons: After surgery→ 31%
- Findings point to the importance of competitive interaction between developing brain regions

The “nurture” view: Evidence

Impoverished Environments

- Animal raised in impoverished environments have brains that are 10 to 20% smaller than animal raised in normal environments. Why?
- Decreased glial cell density
- Fewer dendritic spines
- Fewer synapses
- Smaller synapses

The “nurture” view: Evidence

Sur

- Cortical surgery
- Severed connection between optic nerve and the occipital cortex as well as the connection between auditory nerve and auditory cortex
- Reconnected optic nerve to auditory cortex
- Animals developed functionally adequate vision

The “nurture” view: Evidence

- Daphnia: A crustacean; easily cloned

- Simple nervous system consisting of several hundred neurons
- Connection patterns can be studied directly
- Genetically identical individuals show different patterns of neuronal connectivity

Summary: Nature vs Nurture

- Order in the brain is not completely specified by the genes
- Instead, structures and functions emerge probabilistically in development through the combined influence of initial over-production of structure, neural competition, and experience
- Genes are a critical source of guidance for brain development
- Nevertheless, there is abundant shaping and fine-tuning of brain structure and function with sensory-experience

Developmental Brain Processes in utero

- 1 Development of gray and white matter,
- 2 myelination,
- 3 synaptogenesis,
- 4 pruning,
- 5 synaptic modification
- These establish the fundamental anatomical organization for the initial functioning of neural circuits *in utero*.

Brain Development Conclusions

- (1) Brain changes throughout development both structurally and functionally

- (2) Developmental changes occur through and with interaction of genes and experience.

Premature brains

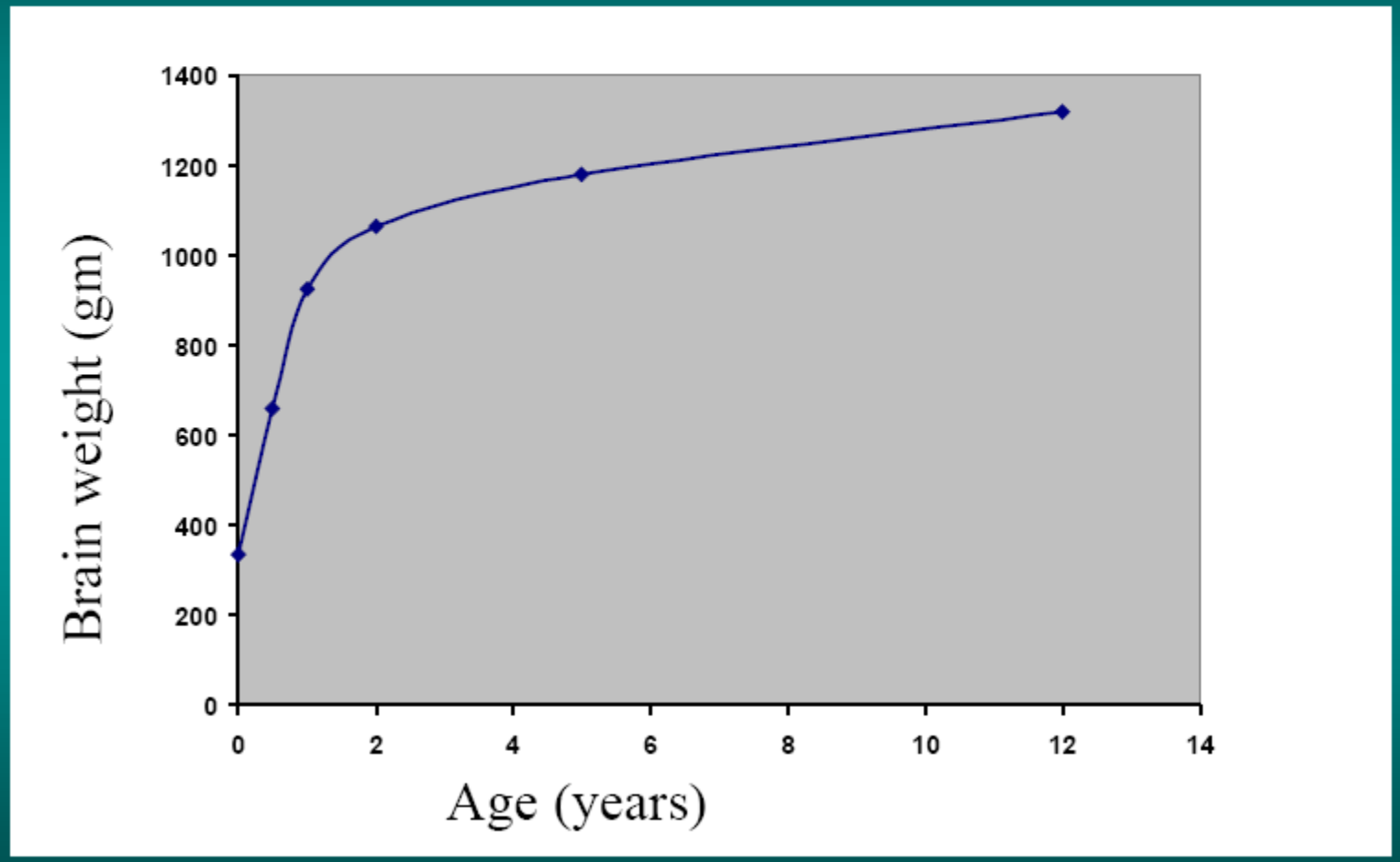
- 50% of premature (born before 27 months) babies will have attention, EF, and learning difficulties
- More hypersensitivity to stimuli
- ICU is part of problem: too much stimulation
- Better neonatal ICUs mimic the womb: skin to skin contact, darker, quieter

Heidelise Als of Harvard Medical School

Second phase of neuronal development: Use it or lose it

- Experience determines wiring
- For example, failure to correct congenital cataracts in infants by 6 months of age or strabismus by 7 years of age produces irreversible impairments in the visual system. Need patch on good eye post cataract surgery for 5 years post removal
- Certain epochs in the maturation of neural circuits for vision appear to constitute critical periods of developmental vulnerability, times when experiential input is necessary for the normal development of specific neural circuits and their functional capacities, and without which the potential for development of those functional capacities is lost forever

Brain weight from birth



Brain at Birth

- At birth the brain is almost fully developed –
  - Most of the brain's cells are formed before birth,
  - but most of the connections among cells are made during infancy and early childhood.
- 25% the size of the adult brain in weight and volume (less than 1 lb.)
- Nearly the same number of neurons as adult brain (170 billion)
- 10 trillion synapses
- Brain stem and lower brain well developed (reflexes), higher regions less developed

1st 2 years

- The brain grows to about 70% of its adult size by 1 year of age and to about 80% of adult size by age 2 years.

- This increase in brain volume during the first year of life is greatest in the cerebellum, followed by subcortical areas and then the cerebral cortex, which increases in volume by an impressive 88% in the first year, 15% in the second year, and then more modestly but steadily thereafter

Postnatal Brain Growth

- At birth, most neurons the brain will have are present
  - approx. 85 billion neurons
- By age 2 years, brain is 80% of adult size
- What keeps growing?
  - Other brain cells (glia)
  - New neuron connections
    - approx. 1000 trillion connections by age 3 yrs.

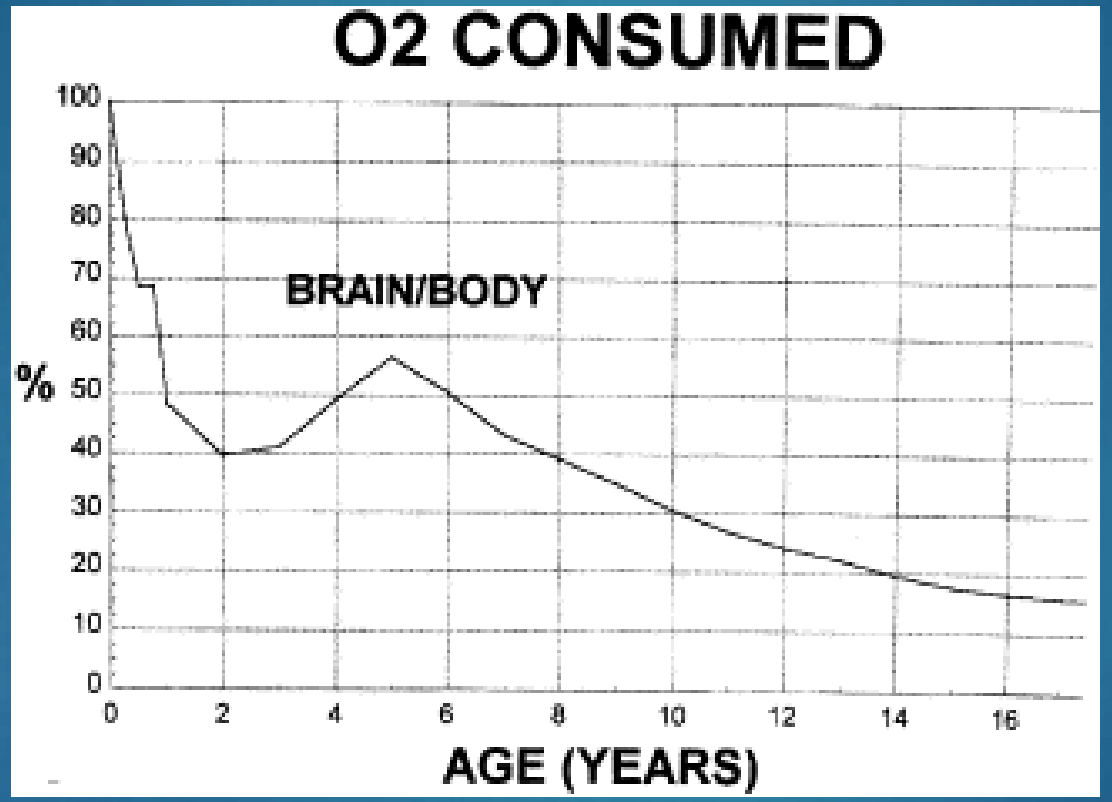
How Does the Developing Brain Become Aware, Learn, Think,?

- Overproduction of neurons and connections among neurons
- Selective reduction of neurons and connections among neurons
- Waves of intense branching and connecting followed by reduction in neurons
  - Before birth through 3-years-old
  - Again at 11- or 12-years-old

How Brain Areas are Developing

- Anatomical studies of brain development show
  - Occipital lobes show earliest pruning
  - Frontal and Temporal lobes show growth of neural connections longer than other areas of the brain…through 3 years old
  - Frontal and Temporal lobes show pruning of connections longer than other areas of the brain
    - Greatest change between 2 years and 5 years

Synaptic production and pruning correspond with overall brain metabolism



Young children's brains work harder and less efficiently than adults'

Gray Matter growth

- With time, experience has an increasingly more prominent function in the shaping of neural circuitry.
- The newborn brain at 2–4 weeks of age is approximately 36% the size of an adult brain
- MRI of preterm infants shows that total brain volume increases nearly three-fold between GA weeks 29 and 41. During this period, gray matter grows from 35 to 50% of total brain volume.
- MRI of term infants aged GA 39–48 weeks shows a robust increase in total gray matter volume.
- Infants born at term have more gray matter in sensorimotor and visual cortices, as well as in parieto-occipital regions, compared with preterm infants.
- Gray matter growth is pronounced in occipital and parietal cortices in the first weeks of life.

Frontal synaptic density peak

- Synaptic density peaked in the frontal area of the human brain at around 7 months of age.
- 7 months is the age is when human infants can first reliably succeed at delayed-response tasks.
- Thus, in both infant monkeys and human infants, representational memory abilities first appear when the number of synapses per unit of neuropil in the associated brain area reaches peak value.

Goldman-Rakic

End of synaptic formation: Conservative View

- According to Huttenlocher's data, the period of rapid synapse formation in the young human brain appears to end at around 3 years of age.
- The neuroscientific data suggest that environmental stimulation neither initiates this process nor causes more synapses to form.
- Neuroscientists have little idea how experience before puberty affects either the timing or the extent of synaptic pruning.
- Neuroscientists do not know, for monkeys or humans, whether early experience increases or decreases synaptic densities or synaptic numbers after puberty.

John Bruer: https://www.jsmf.org/about/j/neural_connections.htm

Development: Gray ↓, White ↑

- White matter volume and Corpus Callosum volume increase due to axonal growth and mylenization.
- Gray matter (neurons):
  - increase during preadolescence,
  - peaks in frontal cortex around age 12,
  - and then decreases
- Largest maturational changes occur between 12-16 and 23-30 in frontal lobes
- Reduction in gray matter reflects increased myelination (better cognitive processing)

Myelination & Glial growth

- Although cortical neurogenesis and neuronal migration continue through the postnatal period, it is more likely that the expansion of glia and myelination during this period makes a more significant contribution to the dramatic brain growth observed in newborns and toddlers

Abnormal brain size

- Abnormal brain size in early postnatal life often heralds the later onset of neurodevelopmental disorders.
- Malnutrition, for example, decreases brain size in infancy and produces a broad range of adverse effects on neural circuit development.
- Conversely, accelerated brain growth in infancy seems to be one early manifestation of a wide range of developmental delays of motor, language, and cognitive functions that includes autism.
- MRI findings in autistic individuals suggest expansion of both gray and white matter compartments.

- These findings may indicate the persistence of exuberant synapses and myelin or reduced apoptosis, and abnormal patterns of brain connectivity produce neurodevelopmental disorders.

Synaptogenesis

- The trajectory of expansion of gray matter has been shown with MRI and is consistent with postmortem studies showing that the elaboration of dendrites, spines, and synapses continues to accelerate at a near logarithmic pace through the first 350–400 postnatal days.
- The first 2 years of life see the arborization of both pyramidal cells and GABAergic inhibitory interneurons, as well as the relative expansion of cortical layers II and III, compared with other layers

Synaptic densities & pruning

- Huttenlocher, 1979: At birth infants have synaptic densities that are nearly the same as those found in adults.
- There is a rapid increase in synaptic densities between birth and age 1. Synaptic density peak in the frontal cortex at around 1 to 2 years of age, when it was 50% higher than average adult values.
- Between the ages of 2 and 16 years, densities declined to mature levels and remained there throughout adulthood.
- At age 7 years, the human brain has nearly reached adult volume, but synaptic density is still 36% higher than in adults.

Huttenlocher, 1979

Toddlers: Practice makes Permanent

- By eight months of age, the average infant, living in a stimulating, secure and loving environment, will have sparked 500 trillion of these connections.
- By the age of two, an infant has developed around 1000 trillion of these connections.
- Synaptic connections have reached their highest density (10,000 synapses per neuron) by age 3.
- A 3-year-old toddler's brain is twice as active as an adult's brain.
- Age 4 is most metabolically active period: use of 43% of metabolic output (adult = 20%)

Synaptic density follows inverted U pattern

- Synaptic densities follow an inverted-U pattern over our lifetimes.

- At birth, we have approximately the same synaptic densities in our cortex that we do as adults.
- Rapid synapse formation following birth leads to a plateau period during which synaptic densities exceed adult densities.
- Synapse elimination beginning at puberty reduces densities to adult levels.
- Synaptic loss is fundamental to normal brain development.

Metabolism also has Inverted U pattern

- Only 1 study: PET scans 29 epileptic children; synapses and dendrites account for most of the glucose the brain consumes.
- During the first year of life, glucose uptake in the infant cortex was between 65% and 85% of adult brains.
- In newborns, the area with the highest metabolic activity was the primary sensorimotor area.
- During the second and third months of development, there was a gradual increase in resting metabolic activity in other brain areas, such as those associated with hearing and vision.
- By age 8 months, metabolic activity began to increase in some frontal areas of the brain.

Chugani, et al., 1987

Metabolism 2

- At age I year, the anatomical distribution of glucose uptake in infants' brains had the same qualitative pattern as that found in adult brains; but quantitatively lower. After the first year, the maturational curves for all brain areas followed a similar pattern.
- In all the areas examined, metabolic levels reached adult values when children were approximately 2 years old and continued to increase, reaching rates twice the adult level by the age of 3 or 4. Highest at age 4, 43% of body metabolism (compared to adult 20%)
- Metabolic levels remained at this high plateau level until children were around 9 years old.
- At age 9, rates of brain glucose metabolism started to decline and stabilized at adult values by the end of the teenage years.

Learning after synaptic formation

- Patricia Goldman-Rakic: “While children's brains acquire a tremendous amount of information during the early years, most learning takes place after synaptic formation stabilizes. From the time a child enters first grade, through high school, college, and beyond, there is little change in the number of synapses.“
- It is during the time when no, or little, synapse formation occurs that most learning takes place.
- Early rapid synapse formation appears to be under genetic, not environmental, control.
- Latter learning based on reinforcement of existing synapses: If a pathway is not used, it’s eliminated based on the “use it or lose it” principle. Things you do a single time, either good or bad, are somewhat less likely to have an effect on brain development.

Synaptogenesis in different areas

- The time course of synaptogenesis differs across cortical regions. In the primary visual cortex, for example, after a burst of synapse formation between age 3 and 4 months, synaptic density reaches its peak at 140–150% of adult levels between the ages of 4 and 12 months, after which the mean number of synapses per neuron decline.
- Synaptogenesis in the PFC begins about the same time as in visual cortex, but it does not reach its peak period until age 8 months, continuing thereafter through the second year of life

Synaptic Plasticity and Neural Circuit Development in Postnatal Life

- Similar to pruning, the remodeling of existing synapses has a key function in the reorganization and fine-tuning of neural circuits.
- Synaptic plasticity refers to a set of mechanisms that mediate the activity-dependent strengthening or weakening of neuronal connections at the level of the synapse.
- The strength and pattern of activity at a given synapse produce transient or enduring depression or potentiation of communication between neurons.
- Thus, long-term potentiation and long-term depression are active processes that depend on electrical activity.

Synaptic density in different areas: short before long

- Synaptic density peaks first in primary sensory areas, followed by the association areas and then the PFC, cortices that subserve higher cognitive functions.
- Similarly, local cortical connections appear before more distant ones.
- Thickening of cortical layer II, which makes short range cortical connections with other cortical regions, precedes thickening of layer III, which makes longer-range connections with other cortical regions, between ages 15 and 72 months.

White Matter increase

- The rate of increase in white matter volumes is greatest during infancy.
- Growth in this compartment continues at a slower albeit steady rate through childhood, adolescence, and adulthood, and peaks in the middle of the fifth decade of life.
- DTI studies show that rates of increase in measures of white matter organization are greatest before age 10 years

(Matsuzawa *et al*, 2001; Paus *et al*, 2001)

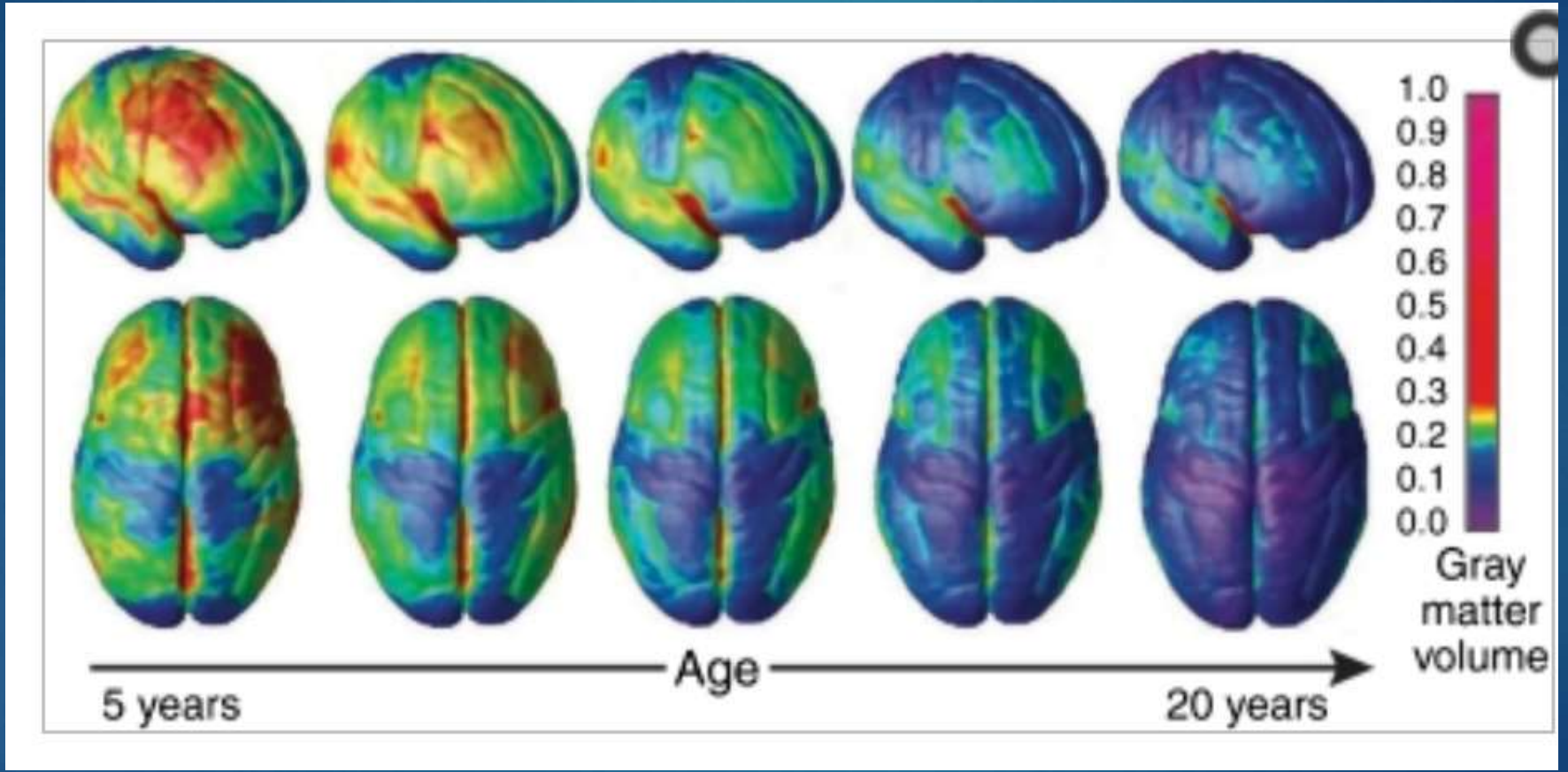
Pruning and Myelination

- Regressive (i.e., synaptic pruning) and progressive (i.e., myelination) cellular events are known to occur simultaneously in the brain during childhood, adolescence, and young adulthood, both of which could result in the appearance of gray matter density reduction or cortical thinning on MRI.

Cortical Gray Matter

- Volumes of cortical gray matter begin to decline in late childhood or adolescence
- Cortical thinning proceeds in a ‘back-to-front' direction,
- Occurs first in sensorimotor areas, followed by association areas, and lastly by higher-ordered association areas such as superior PFC and posterior parietal cortex
- Cortical thinning is viewed as a reliable marker of maturation

Cortical thinning of GM

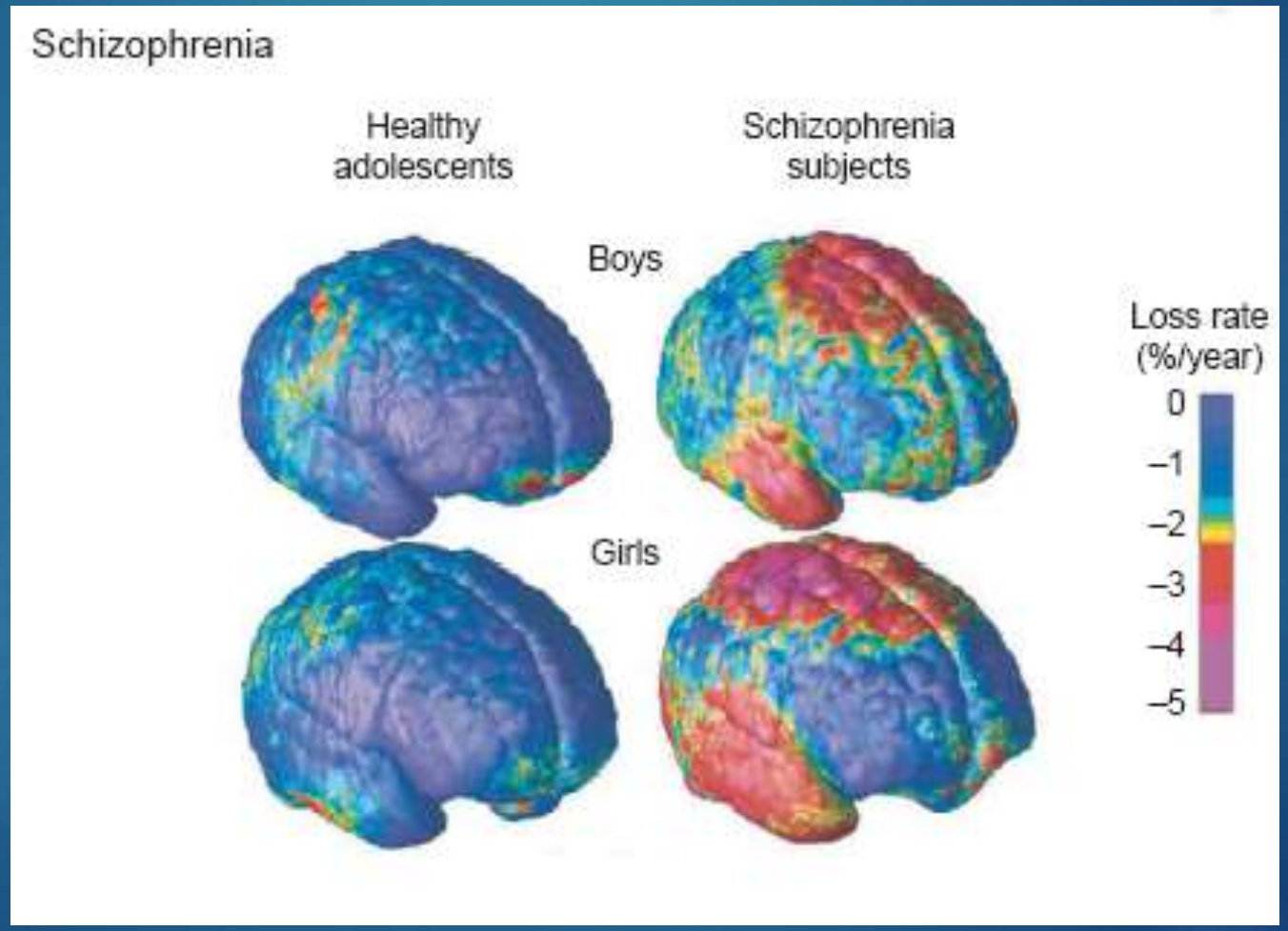


Influence of experience: Increase in inhibition

- Activity-dependent elimination of excitatory connections is mainly responsible for the 40% reduction of synapses during adolescence.
-
- In contrast, levels of local GABAergic inhibitory interneurons remain fairly stable from childhood through adulthood

(Huttenlocher, 1984; Rakic *et al*, 1994a)

Schizophrenia:
Loss Rate, Excessive Pruning?

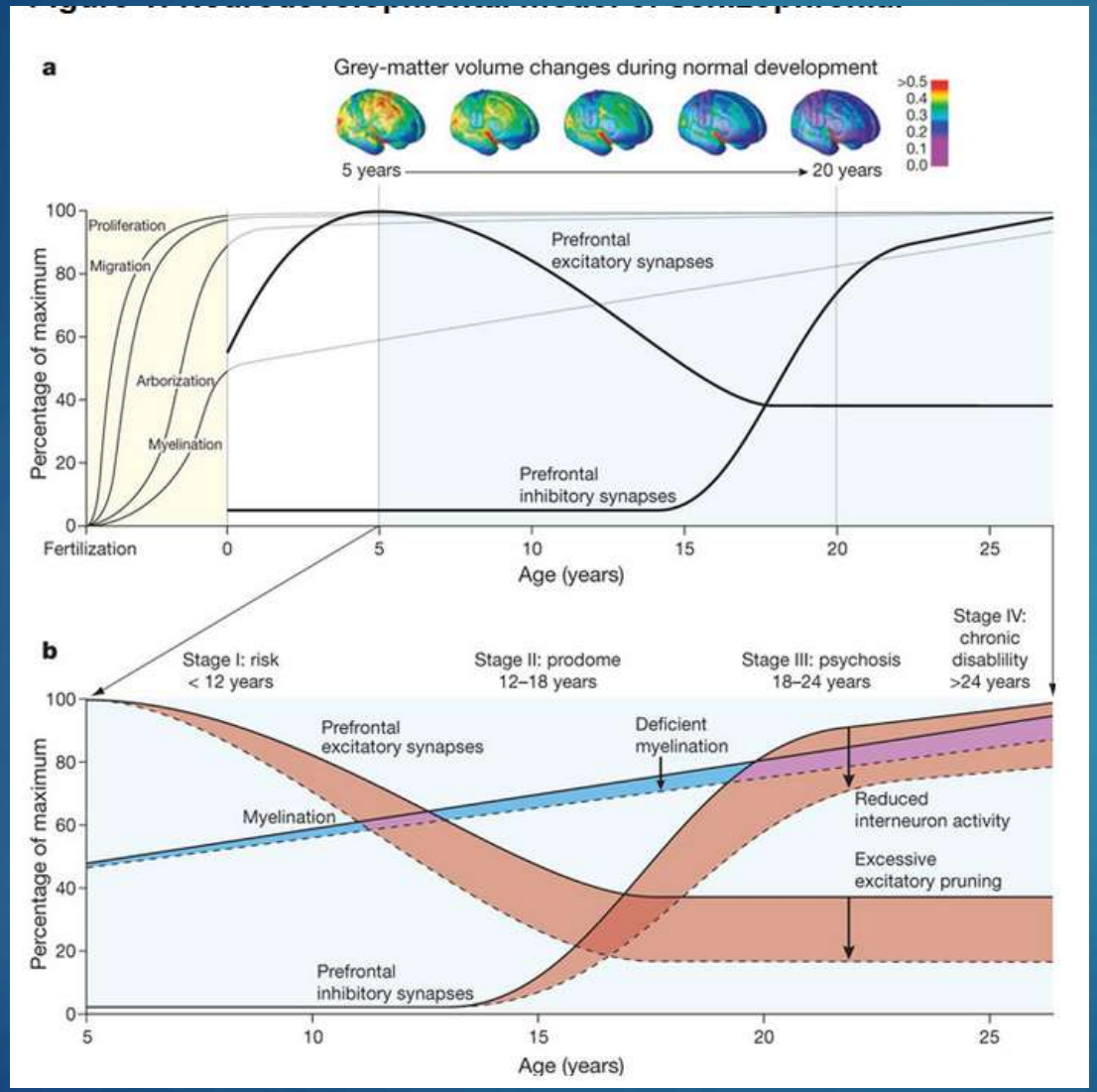


Schizophrenia: Excessive pruning

- In childhood-onset schizophrenia, cortical maturation follows a generally normal pattern of thinning, but it proceeds at a faster pace and is spatially more extensive than in typically developing youth.

- Excessive thinning is first detected in parietal cortices, which subserve visuospatial and associative processing, before spreading forward to temporal and prefrontal cortices.
- The extent of gray matter loss seems to correlate with the severity of psychotic symptoms. These decreases in cortical tissue are thought to involve decreased dendritic arborization and reduced numbers of cells, including glia and neurovasculature, but they are most commonly viewed as the consequence of excessive synaptic pruning or abnormality in synaptic plasticity

Neurodevelopmental model of schizophrenia



Normal:

Increase in inhibitory activity

Decrease excitatory activity

Schizophrenia:

Reduced Interneuron inhibitory activity

Excessive excitatory pruning

Deficient myelination

Thomas R. Insel

Neurodevelopmental model of schizophrenia 2

- **a**, The combined effects of pruning of the neuronal arbor and myelin deposition are thought to account for the normal progressive reduction of grey-matter volume observed with longitudinal neuroimaging.
- Data from human and non-human primate brain indicate increases in inhibitory and decreases in excitatory synaptic strength occurring in prefrontal cortex throughout adolescence and early adulthood, during the period of prodrome and emergence of psychosis.
- b, The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity.
- Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis.

Home Movies: Premorbid Behavioral abnormalities

- Elaine Walker and colleagues (1993, 1994) study of home movies
- Home movie identification: Pre-schizophrenia (0-5y)children can be reliably identified
- Pre-PWS children show less joy and more negative facial expressions of emotion when compared with healthy siblings
- Unusual movements and coordination problems in mid-childhood significantly associated with adult schizophrenia (Rosso, et al., 2000)
- More likely to have delayed milestones (Jones et al, 1994)

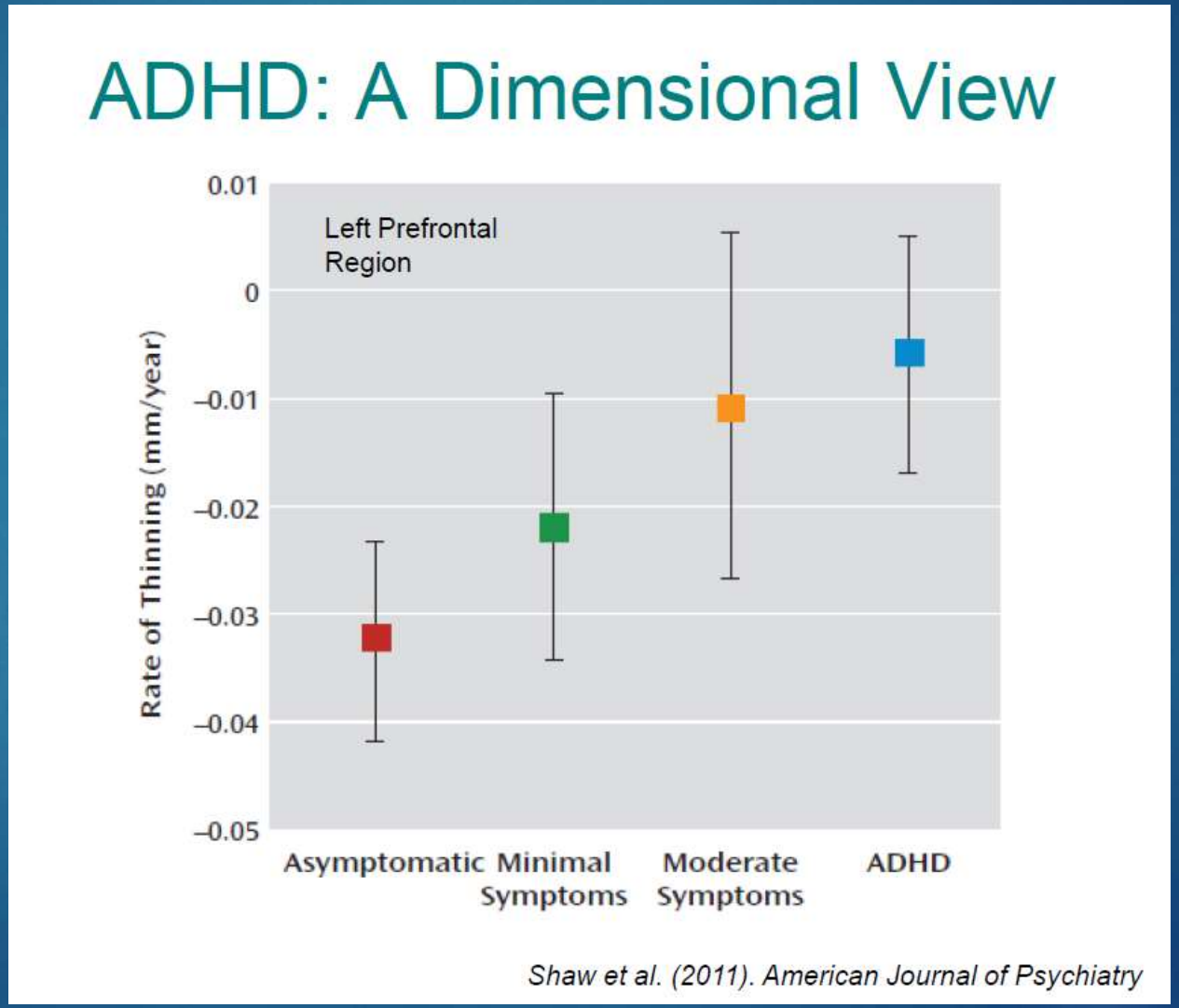
Home Movies:

1 – 1 handed; 2 –hyperextended fingers; 3 – asymmetric crawl

ADHD

- Longitudinal anatomical MRI findings in attention deficit/hyperactivity disorder (ADHD) reveal delays in the time course of cortical maturational, with peak cortical thickness attained later than in typically developing children, particularly in anterior temporal and prefrontal cortices

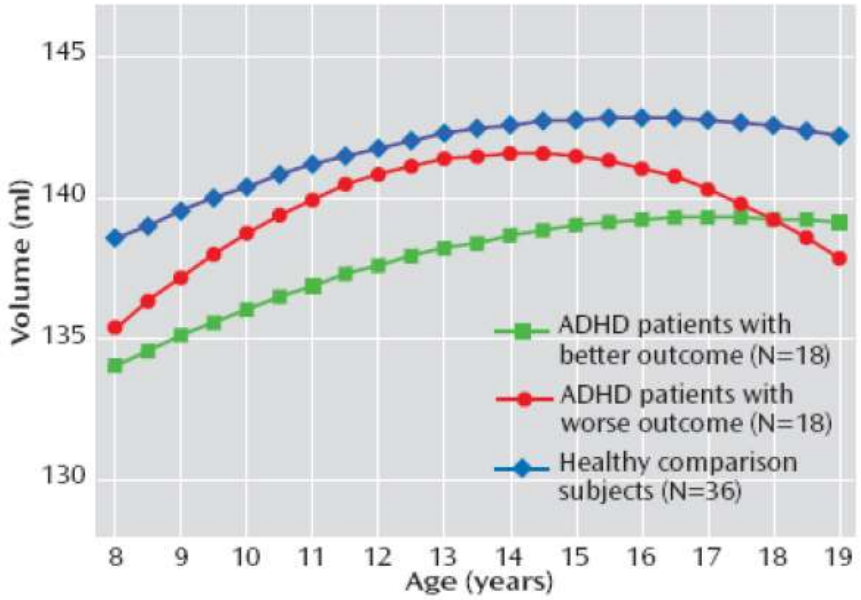
More Left PFC Pruning in ADHD 1



More Cerebellar Pruning in ADHD 2

Developmental Trajectory: ADHD

FIGURE 3. Developmental Trajectory of Whole Cerebellum in ADHD Patients With Better and Worse Outcomes and Healthy Comparison Subjects[a]



[a] Difference between better outcome group and worse outcome group, p=0.01; between worse outcome group and healthy comparison group, p=0.01; between better outcome group and healthy comparison group, n.s.

Mackie et al. (2007). Am. J. Psychiatry

Brain Connections Slower to Develop in Youth with ADHD

Researchers examined brain scans of 275 young people ages 7 to 21 with ADHD and 481 others without it to see how each group's brain networks communicate.

They found that one neural network in particular lagged behind when it came to children with ADHD.

This area, called the **default network**, is responsible for your stream of consciousness, or daydreaming. It turns on when you're not actively engaged in tasks and turns off when you're busy.

The default network is maturing very rapidly between youth and adulthood.

The inability to turn it on & off appropriately results in difficulties focusing on tasks or think further into the future. The daydreaming network interrupts the area of their brain working on tasks, causing a loss of attention.

ARTICLE SOURCE: http://www.washingtonpost.com/news/morning-mix/wp/2014/09/16/study-shows-brain-connections-slower-to-develop-in-youth-with-adhd/

Distributed & Parallel Processing Networks

- Ways brain is neuroanatomical organized into networks:
  - Extensive neuron to neuron connections
  - Neurotransmitter systems
  - Functional areas organized via heteromodal connections
  - White matter fiber tracts – short to distant
  - Multiple processing networks: i.e. semantic memory, language, attention, etc.
  - Hub regions, i.e. expressive, receptive
  - Connectivity networks

Dynamic networks model

- Brain isn't just modular. While certain regions are specialized to process certain types of information and are active during certain tasks, they are all part of distributed functional networks.

- The CNS is an integrated, wide, dynamic network made up of cortical functional epicenters connected by both short-local and large-scale white matter fibers.

- Brain function results from parallel streams of information dynamically modulated within an interactive, multimodal, and widely distributed circuit.

Broad Information Processing Network

- Specific brain regions belong to several intersecting networks based on their structural topology and functional connectivity.

- Impact of a brain region on behavior therefore depends on its structural and functional connectivity as a member of a broader information processing network.

Rich World Organization of Human Connectome

- Brain function is not solely attributable to individual regions and connections, but rather emerges from the topology of the network as a whole, the connectome of the brain.

- There are a number of highly connected and highly central neocortical hub regions, regions that play a key role in global information integration between different parts of the network.

Martijn P. van den Heuvel and Olaf Sporns, 2011

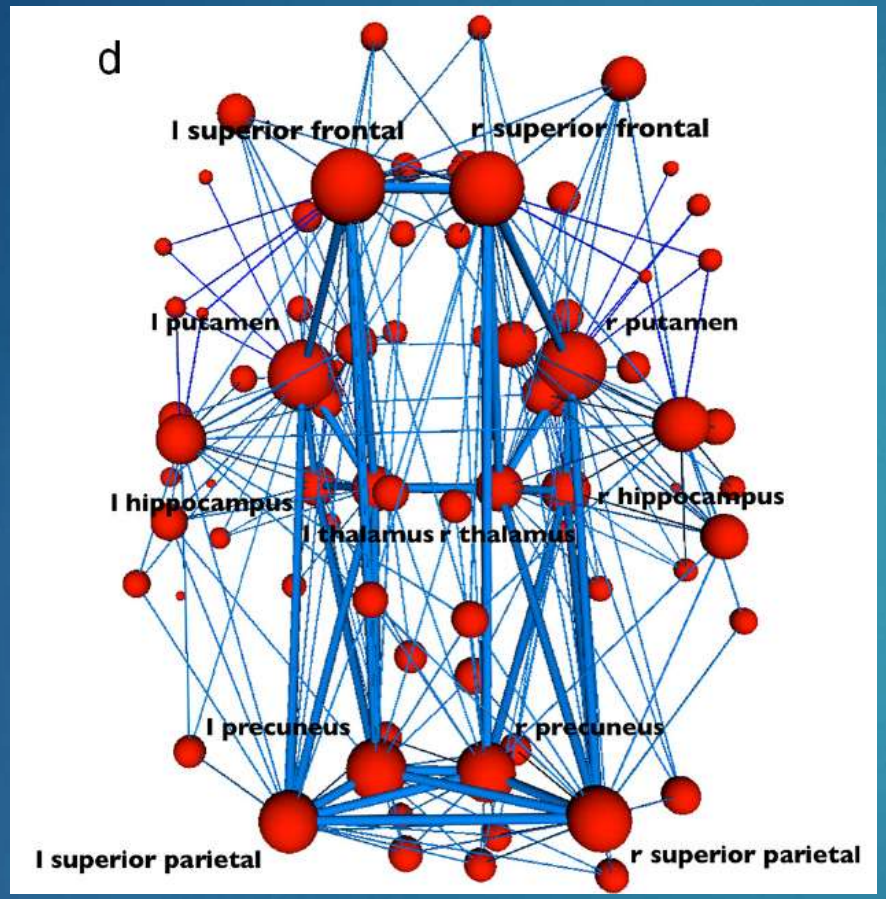
Rich World Organization 2

- Some regions have a high degree of connectivity, low clustering, short path length, high centrality and participation in multiple communities across the network, identifying them as "brain hubs"

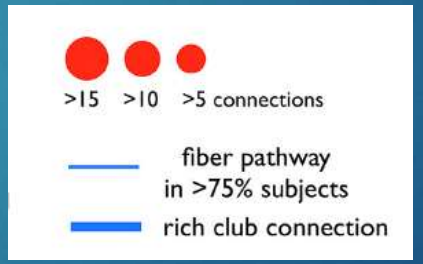
- Brain hubs form a "rich club," characterized by a tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree.

- There is a group of 12 strongly interconnected bihemispheric hub regions, comprising the precuneus, superior frontal, superior parietal cortex, subcortical hippocampus, putamen, and thalamus.

12 Rich World Hubs



Bilateral frontoparietal regions, including precuneus, superior frontal and parietal cortex, hippocampus, thalamus, and putamen are individually central & also densely interconnected, together forming a rich club.

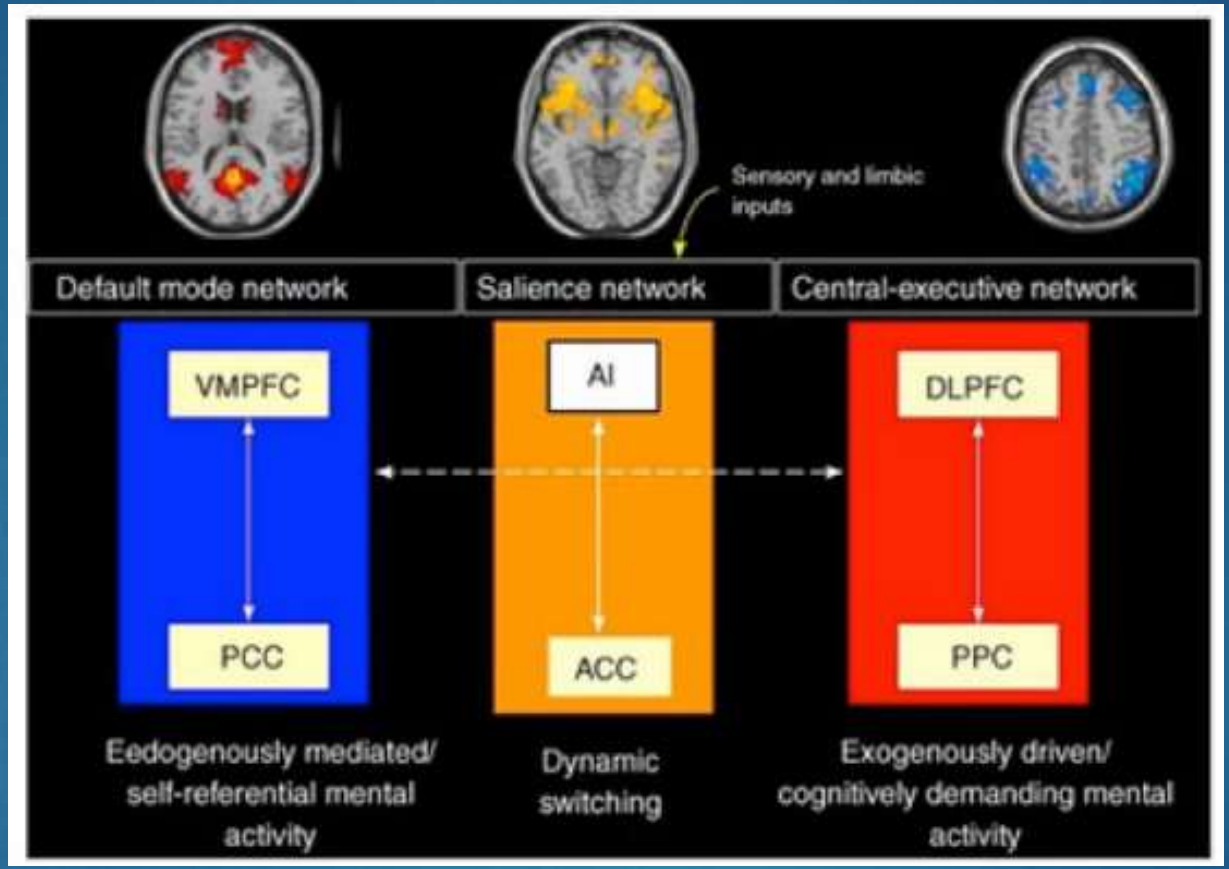


Connections between rich-club regions (dark blue) and connections from rich-club nodes to the other regions of the brain network (light blue). The figure shows that almost all regions of the brain have at least one link directly to the rich club.

Rich Club Hub Lesions are more damaging

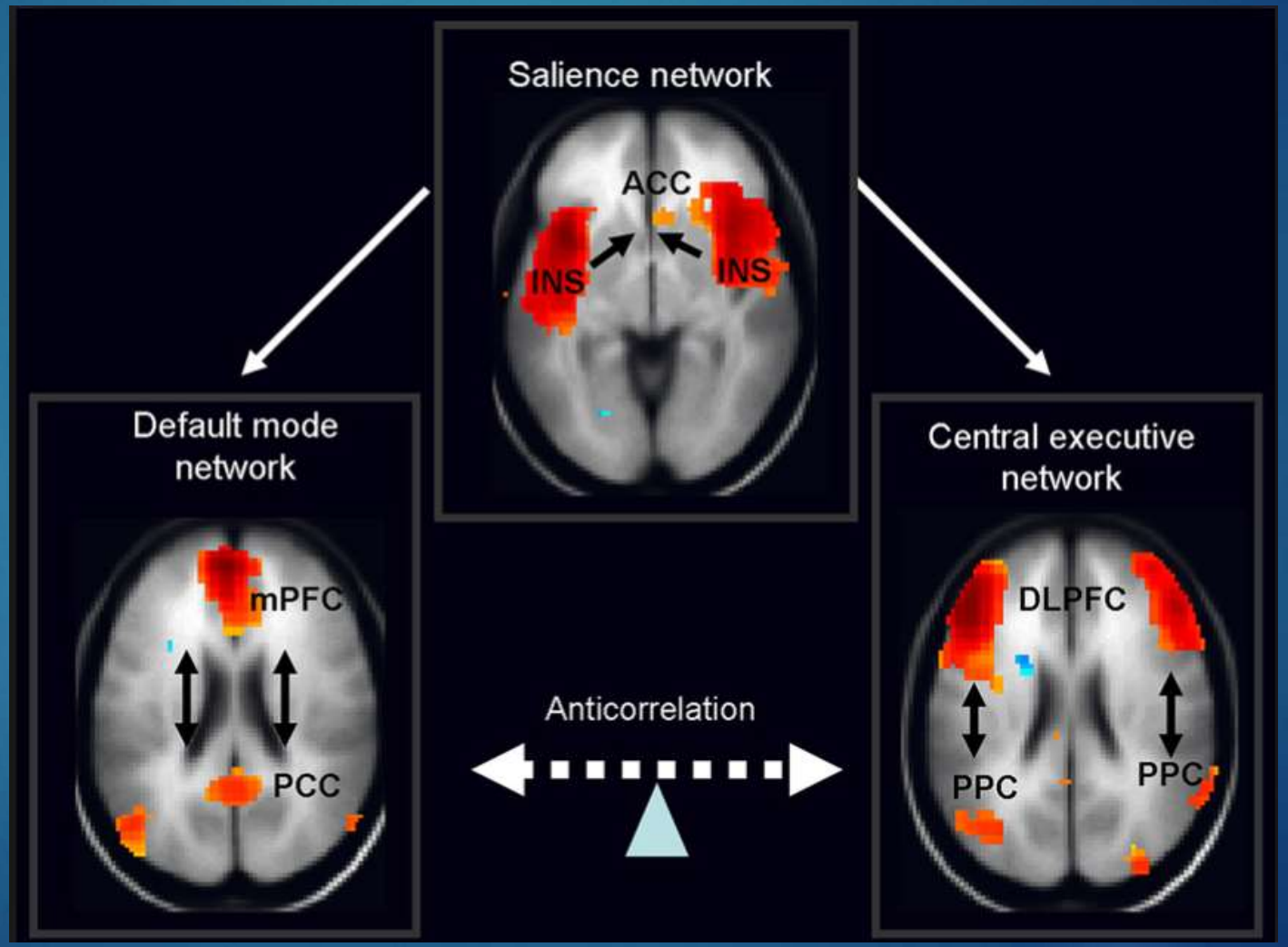
- Important role of functional hubs in optimizing global brain communication efficiency for healthy cognitive brain functioning
- Brain lesions that damage one of the rich club hubs will have more serious behavioral effects (3x more) than damage to non-hub area.

Major Connectivity Networks

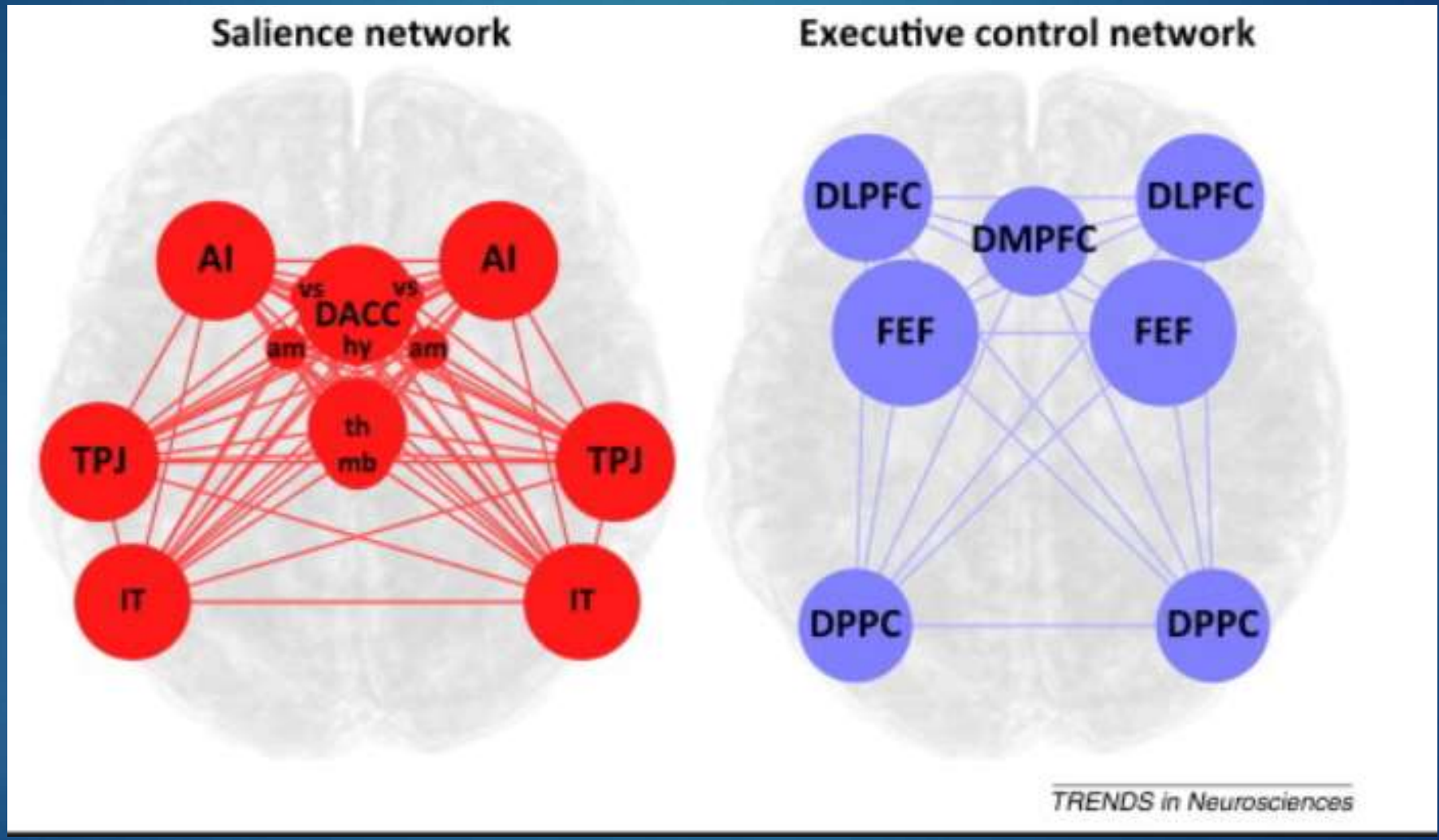


- Three major networks: Default, Salience, Executive; the central executive network "*is engaged in higher-order cognitive and attentional control*."

3 Major Networks



Salience & Executive Network regions



Intrinsic functional connectivity

Disease Conditions & Resting State Functional Connectivity

- Alzheimer's: decreased connectivity
- Autism: altered connectivity
- Depression: abnormal connectivity
- Schizophrenia: disrupted networks
- ADHD: Altered "small networks" and Thalamus changes
- Aging brain: disruption of brain systems and motor network
- Epilepsy: disruption and decrease/increase in connectivity
- Parkinson's disease: altered connectivity
- Obsessive Compulsive Disorder: increase/decrease in connectivity
- Pain Disorder: altered connectivity

Very early network development

- There are a number of distinct functional networks in neonates at GA 39–44 weeks of age, including visual, sensorimotor, and auditory processing networks, as well as a prefrontal network.
- In addition, functionally correlated medial and lateral parietal areas may represent a rudimentary default-mode network, a system that when mature consists of precuneus, midline prefrontal, and lateral parietal regions and that has been linked to abstract and autobiographical self-focused processing

Functional connectivity development

- Two types of age-related changes functional connectivity: decreases in local connectivity among anatomically adjacent but functionally distinct brain regions as they are integrated into their respective networks, and increases in long-range connectivity among nodes that comprise each network.

- They also support the other lines of evidence suggesting that neural circuits subserving attentional processes mature ahead of those supporting socioemotional functioning.

Executive Functioning: Sorting

- Age 3: can sort object by 1 criterion (red car), but not a 2nd criterion (yellow flower)
- Age 4: can do 2 categories

Working Memory development

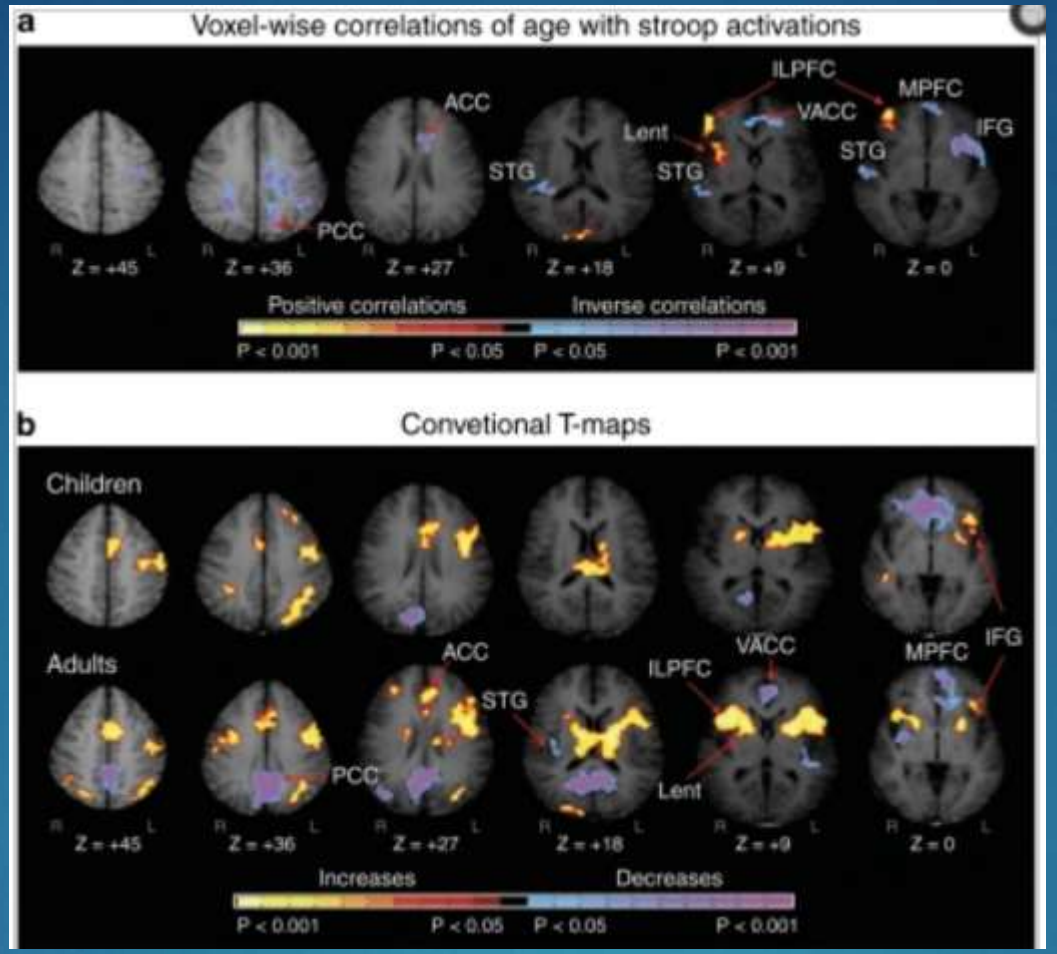
- By 9 months of age infants can perform delay tasks. The basic capacity for working memory is solidly in place by middle childhood, but distractors can overwhelm them.
- Older children activate frontoparietal regions. Compared with adolescents, children recruit ventromedial regions, such as caudate nucleus, and insula during performance of more complex working memory tasks
- Adolescents seem to recruit spatially more diffuse portions of frontal and parietal cortices when engaging working memory processes
- Working memory processes is, therefore, characterized by a fuller and more consistent recruitment of frontoparietal regions with increasing task difficulty between childhood and adolescence,

Cognitive Control

- There is an improving behavioral capacity for cognitive control with advancing age is associated with increasing activation of frontal and striatal circuits
  - conflict monitoring involves the anterior cingulate cortex,
  - regulation of attention involves DLPFC and parietal cortex,
  - suppression of interference involves VLPFC,
  - response inhibition involves parietal regions.
- In tasks of cognitive control, parietal activation continues to increase into adolescence, whereas prefrontal activation continues to increase into adulthood

Development of neural circuits for cognitive control.

Stroop task



Increases in signal during Incongruent relative to congruent are coded in yellow, and decreases are coded in purple or blue

(a) Correlations of age with Stroop activations.

(b) Right frontostriatal (ILPFC and Lent) increases in activity associated with incongruent stimuli came on line progressively with age.
Increasing activity in frontostriatal circuits with age supports the developmental improvements in cognitive control in healthy individuals.

Development of Executive Functions

- Performance on tasks of executive functioning improves along with DTI measures of maturation in frontostriatal and frontoparietal fiber tracts
- Developmental changes in the structure and function of frontoparietal and frontostriatal circuits may be related to remodeling of synaptic connections and greater connectivity between network nodes
- Impaired inhibitory control based within dorsal frontostriatal circuits: Torette's, OCD, ADHD

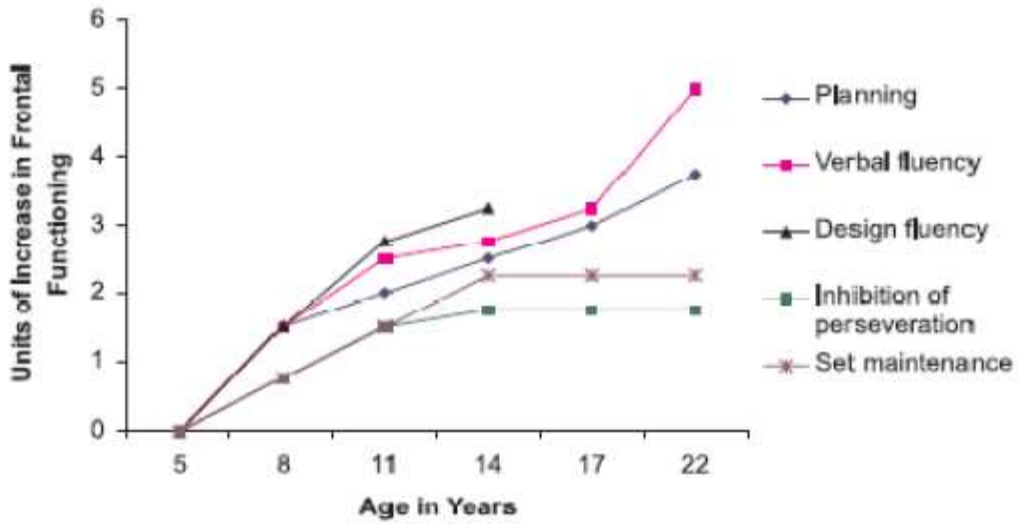


Figure 1. Developmental course of frontal functions based on average effect sizes of age-related change in performance on measures of frontal lobe functioning.

Developmental Trajectory of EF

C.B. Bromine & C. Reynolds "A model of the development of frontal lobe functioning: Findings from a meta-analysis." *Applied Neuropsychology 2005 12:4 190-201*

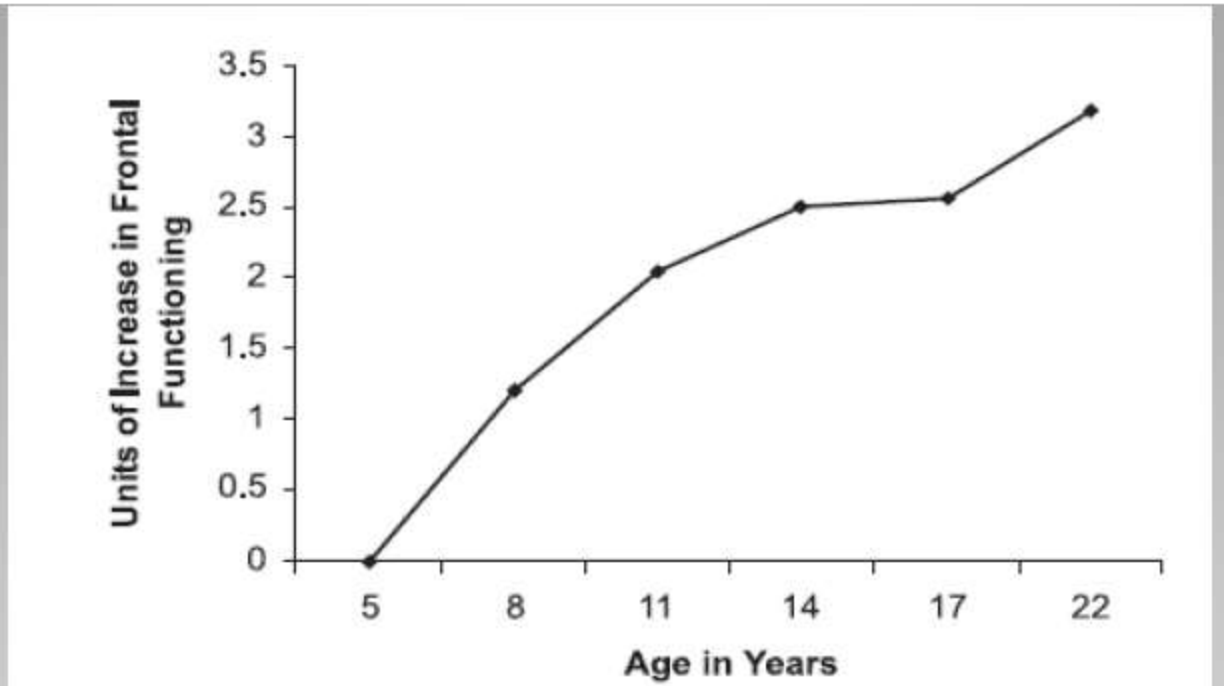
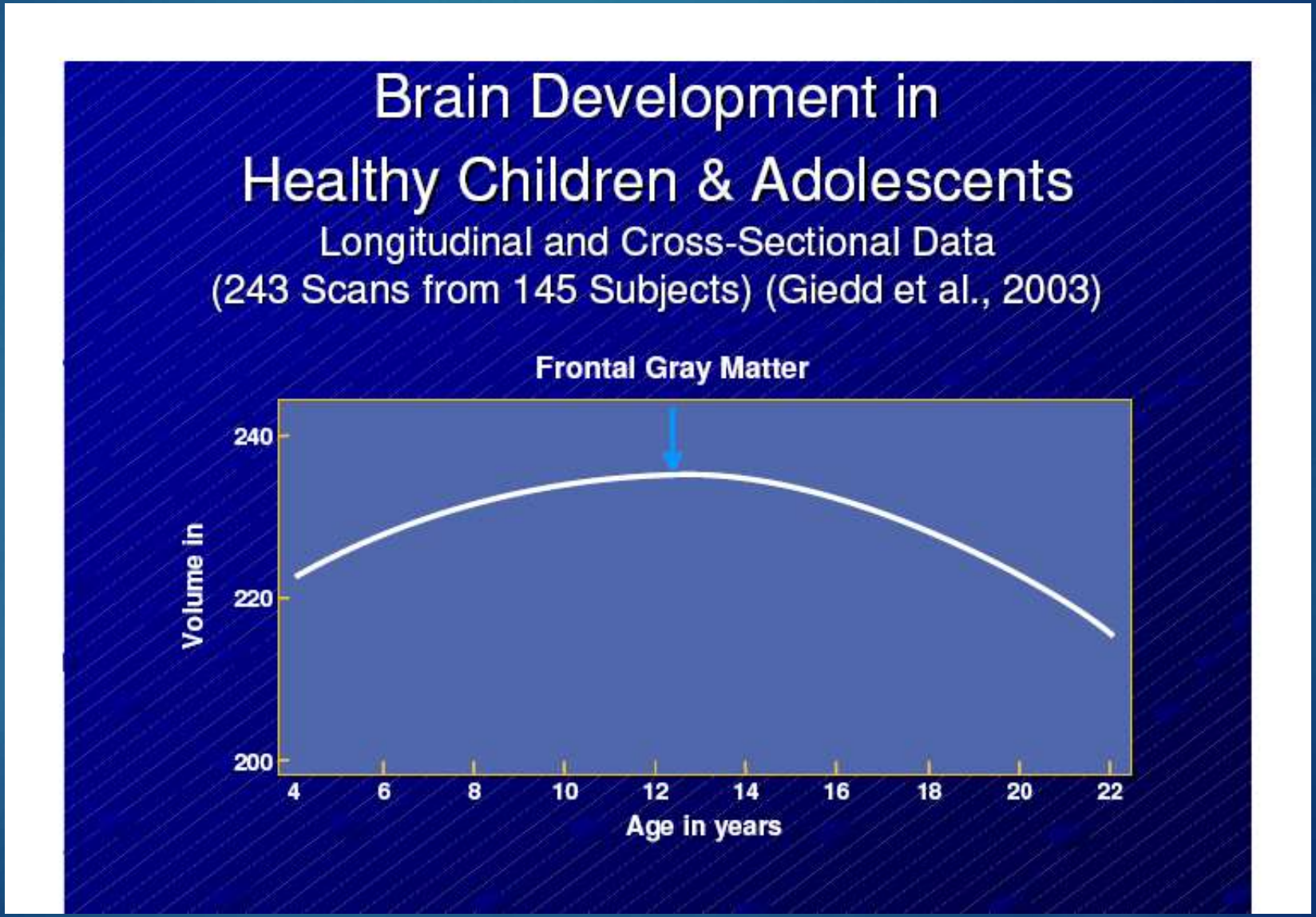


Figure 2. Developmental course of frontal functions based on average effect sizes across frontal functions.

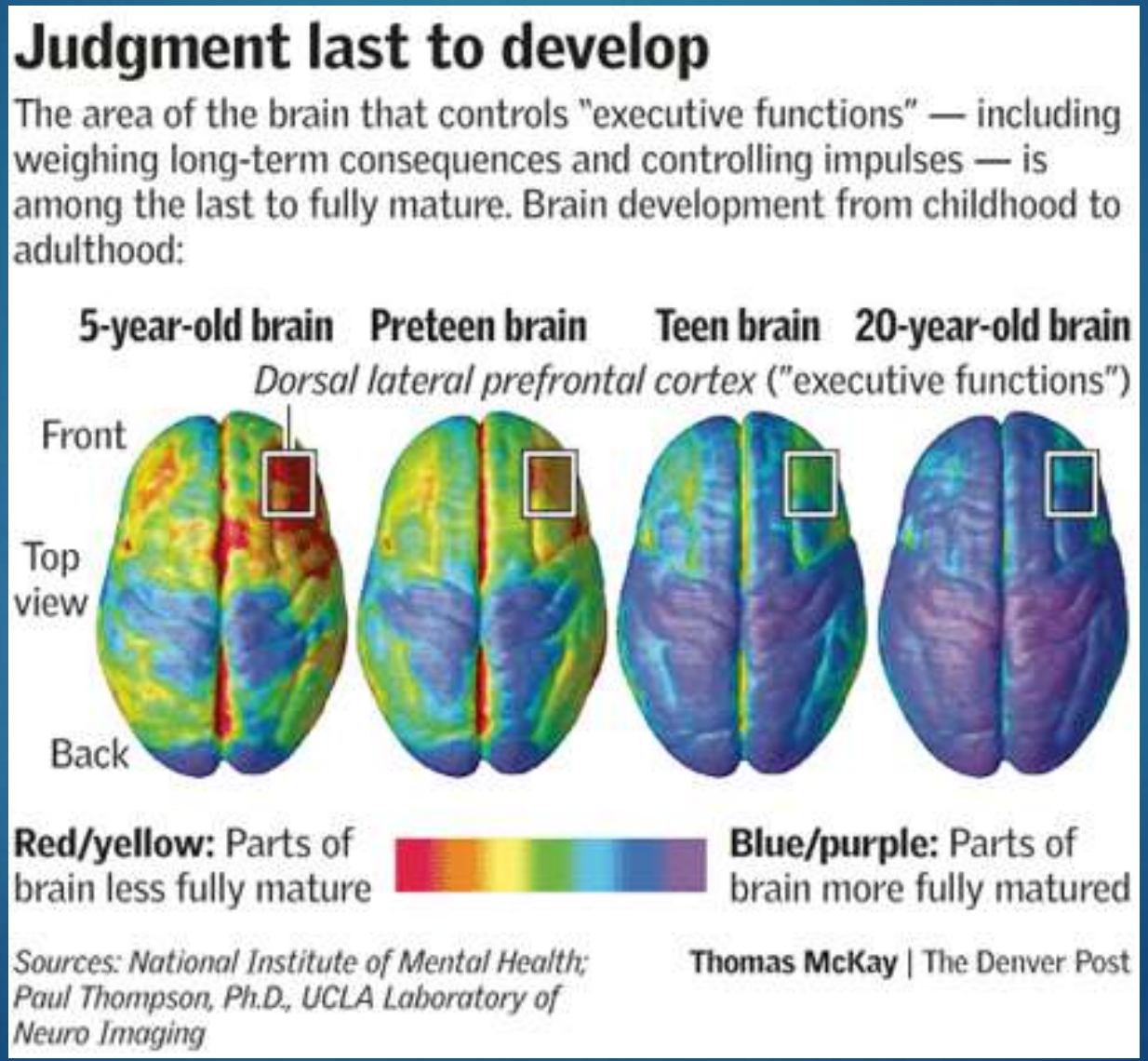
Developmental Trajectory of EF

C.B. Bromine & C. Reynolds "A model of the development of frontal lobe functioning: Findings from a meta-analysis." *Applied Neuropsychology 2005 12:4 190-201*

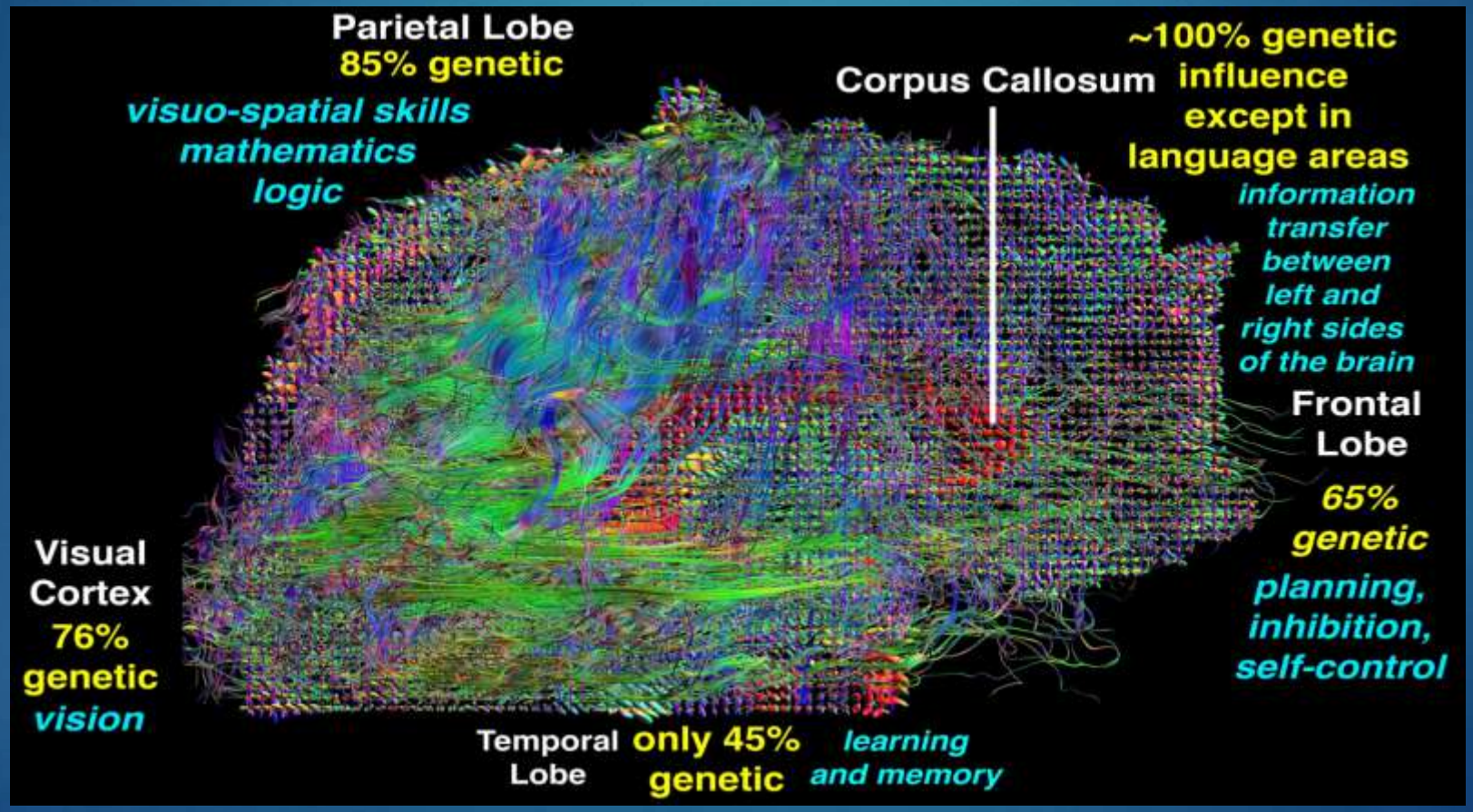
Gray Matter


Brain Development in
Healthy Children & Adolescents
Longitudinal and Cross-Sectional Data
(243 Scans from 145 Subjects) (Giedd et al., 2003)
Frontal Gray Matter
Volume in
240
220
200
4
6
8
10
12
14
16
18
20
22
Age in years

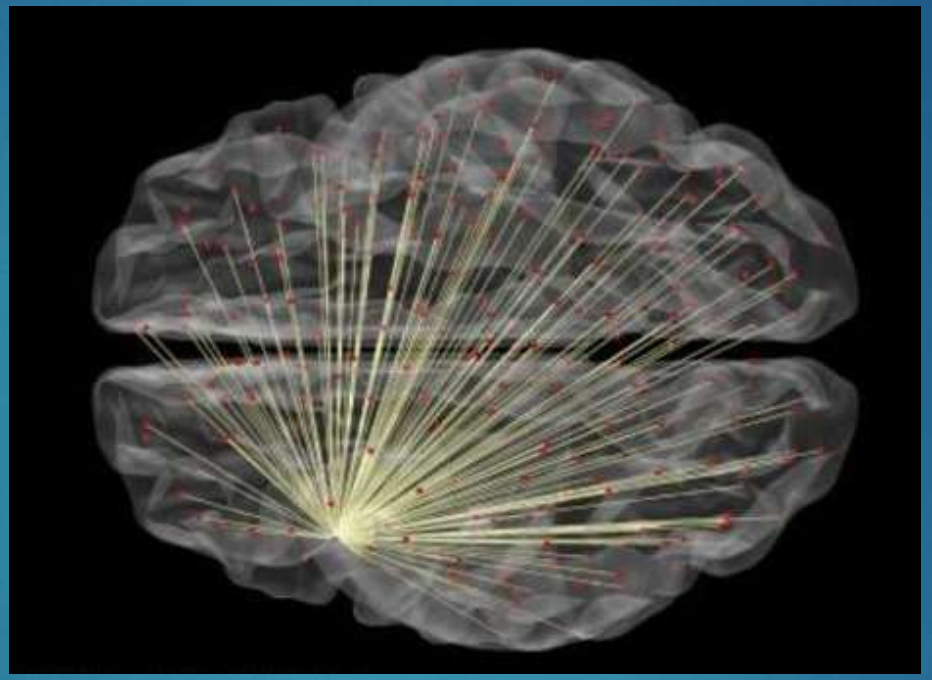
Executive Functioning



Genetics of IQ related to thicker white matter



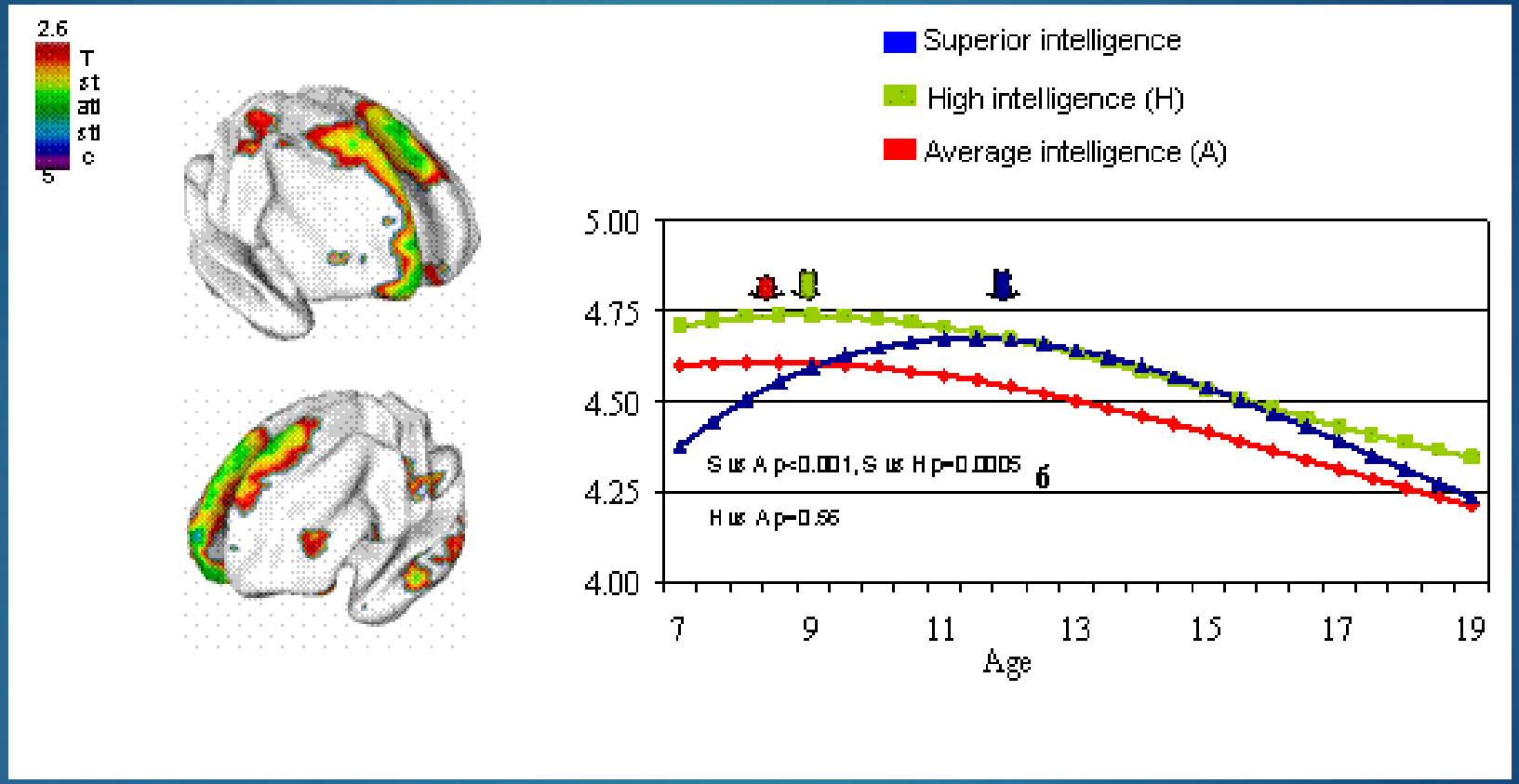
10% of Fluid IQ: Connectivity to Left DLPFC



10 per cent of individual differences in intelligence can be explained by the strength of neural pathways connecting the left lateral prefrontal cortex to the rest of the brain. **Goal monitor**. Strong predictor of both fluid intelligence and cognitive control abilities.

Michael W. Cole, et al., 2012

IQ and Brain Development: IQs of 100, 120, 140



Superior IQ peaks latest before pruning; those with superior IQ show more intense and prolonged cortical thickening, followed by more rapid thinning. shift in causal influences on IQ between childhood and adulthood—a shift away from environmental and toward genetic influences.

Self-Regulation

- Emotion Regulation
  - Capacity to identify feelings
  - Empathy
  - Management of strong emotions
- Behavioral Inhibition
  - Delay gratification
  - Control impulses

Marshmallow Test

Marshmallow at 4: Self control

- Walter Meschel, 1968, 4 year olds, get 2 marshmallows if wait 15 minutes; ring bell and get to eat, but no 2nds; 2 minute wait was average; 25% made it to 15 min; n = 653

- At age 4, ability to wait 15 minutes before eating a marshmallow predicts SAT scores 210 points higher at age 18.
- Children who rang the bell within a minute were much more likely to have later behavioral problems, both in school and at home. They struggled in stressful situations, often had trouble paying attention in class and had serious problems with their temper. Had a significantly higher BMI and are more likely to have had drug problems
- Ability to delay gratification is a far better predictor of academic performance than I.Q.

Marshmallows & Frontal Lobe

- They were better adjusted, were less likely to abuse drugs, had higher self-esteem, had better relationships, were better at handling stress, obtained higher degrees and earned more money.

- At age 45, delayers better at go/nogo task; increased activity in the inferior frontal gyrus and low ventral striatum activation.

- Practice or innate neural structures?

Key: Pay attention to something else

- Crucial skill was the "strategic allocation of attention". All wanted the marshmallow.
- "The key is to avoid thinking about it in the first place."
- Working memory and directed attention ability crucial
- Dorsolateral prefrontal cortex, the anterior prefrontal cortex, the anterior cingulate, and the right and left inferior frontal gyri.

Teaching Delay Ability

- Kids in marshmallow test that could not wait a minute where taught to pretend that the marshmallow is only a picture, surrounded by an imaginary frame—they dramatically improved their self-control.
- This technique allowed them to wait the 15 minutes.
- If you show a picture of the marshmallow and tell them to make believe it's real, they revert to 1 minute
- Can teach delay ability via imagination

Marshmallow Test 2012

- C. Kidd: Children lasted on ave. for 6 minutes
- New procedure: Half dealt with unreliable experimenter who failed to deliver on promises; rest had reliable experience
- Those with unreliable experience lasted 3 minutes (only 1 of 14 lasted 15 min.), others 12 minutes (9 of 12)
- Consistent with Mischel, 1961: 8 y old boys without fathers went for immediate reward

New Marshmallow Test: Multitasking while learning

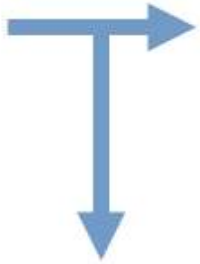
- When students multitask while doing schoolwork, their learning is far spottier and shallower than if the work had their full attention. They understand and remember less, and they have greater difficulty transferring their learning to new contexts.
- So detrimental is this practice that some researchers are proposing that a new prerequisite for academic and even professional success—the new marshmallow test of self-discipline—is the ability to resist a blinking inbox or a buzzing phone.
- 80 percent of college students admit to texting during class; 15 percent say they send 11 or more texts in a single class period.

Working Memory is key

- Working memory in children is linked strongly to reading and academic achievement; predicts success in all aspects of learning, regardless of IQ.
- Working memory develops through childhood and adolescence, and is key for successful performance at school and work.
- Research with young children has documented socioeconomic disparities in performance on tasks of working memory.
- Differences in working memory that exist at age 10 persist through the end of adolescence. Parents' education (related to SES) is related to children's performance on tasks of working memory, but neighborhood characteristics are not.
- An emphasis on executive functions in kindergarten may reduce poverty-linked deficits in school readiness.
- Tools of Mind program: focus on self-regulation & EF

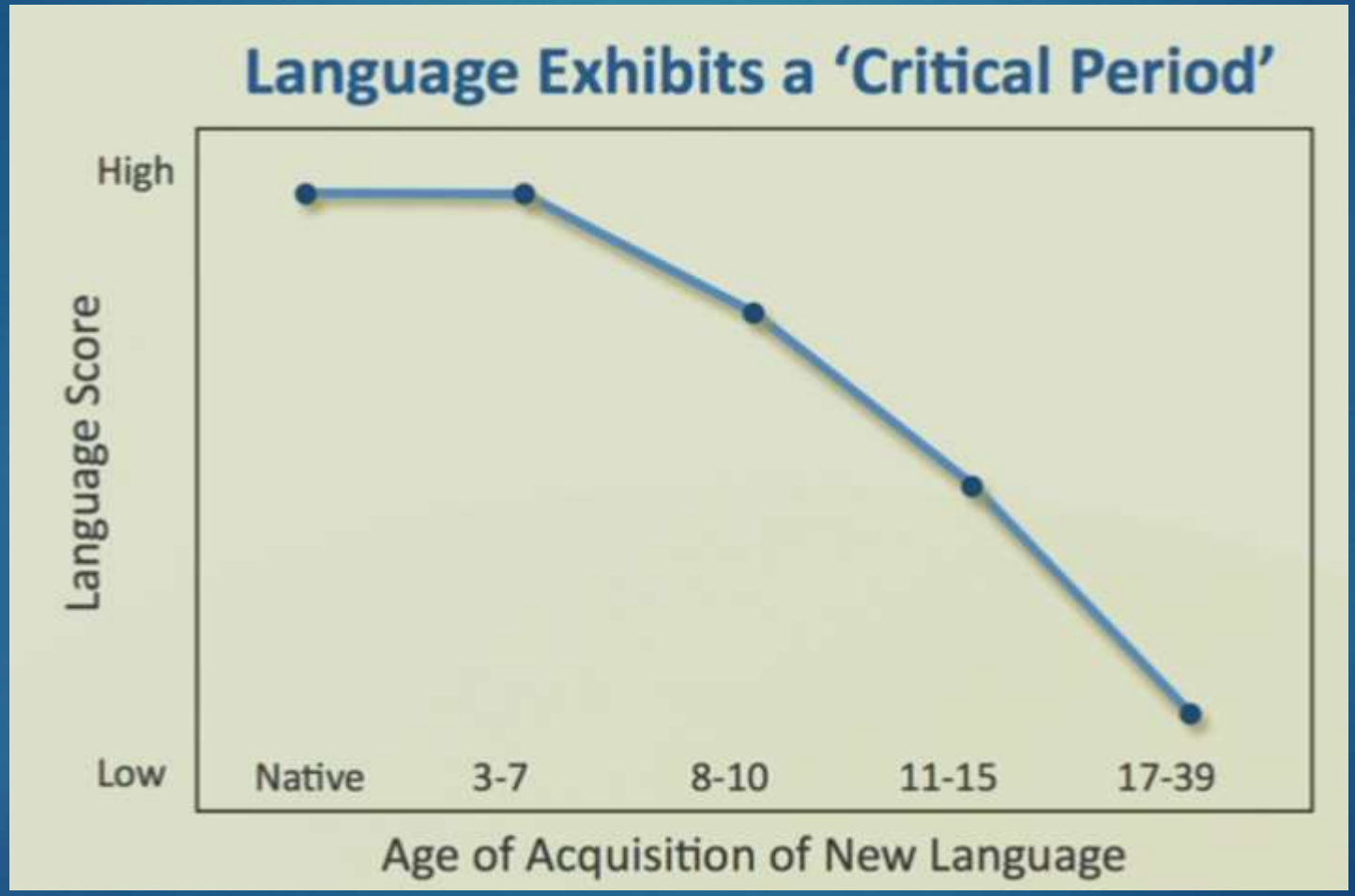
C. Blair & C. Raver, 2014

Early Experiences Influence Brain Architecture and Function

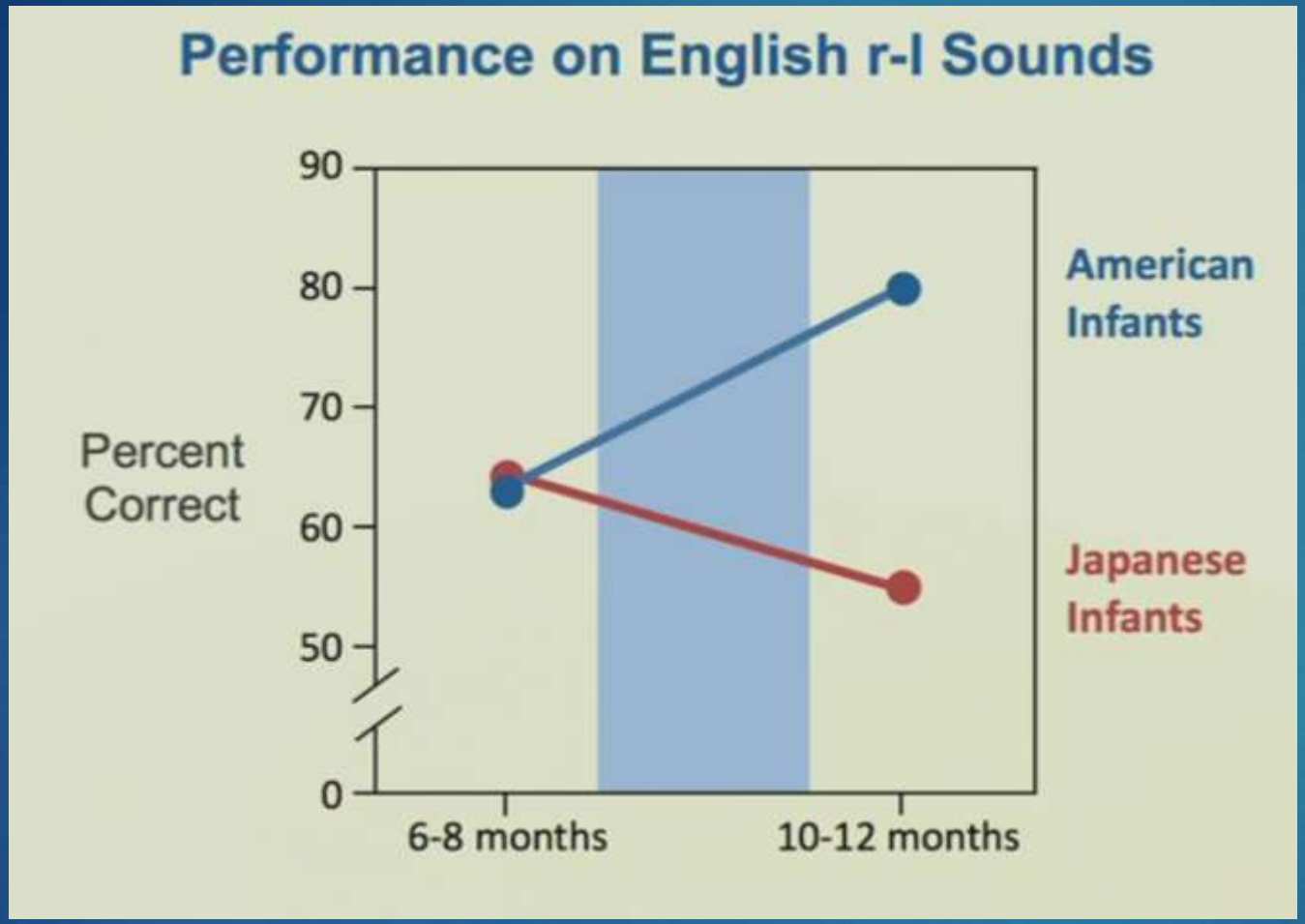


Initial Learned

Language as developmental process



Distinguishing the phonemes Ra vs La



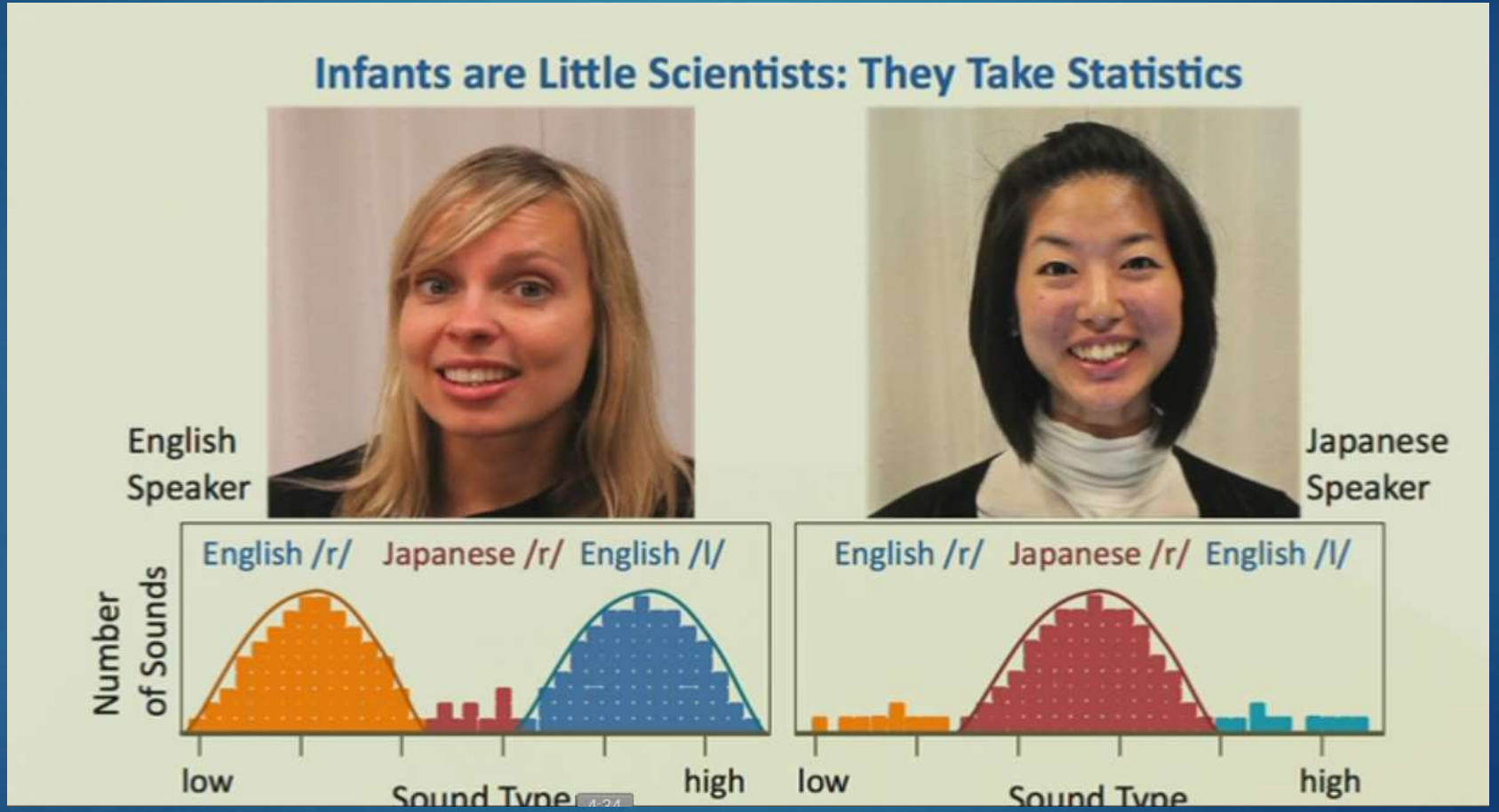
6-8 months is crucial for sound development

But only via live human being, not talking on TV or audio source

Before age 1, citizen of world; after age 1 our own culture language bound

Patricia Kuhl

Babies are linguistic statisticians



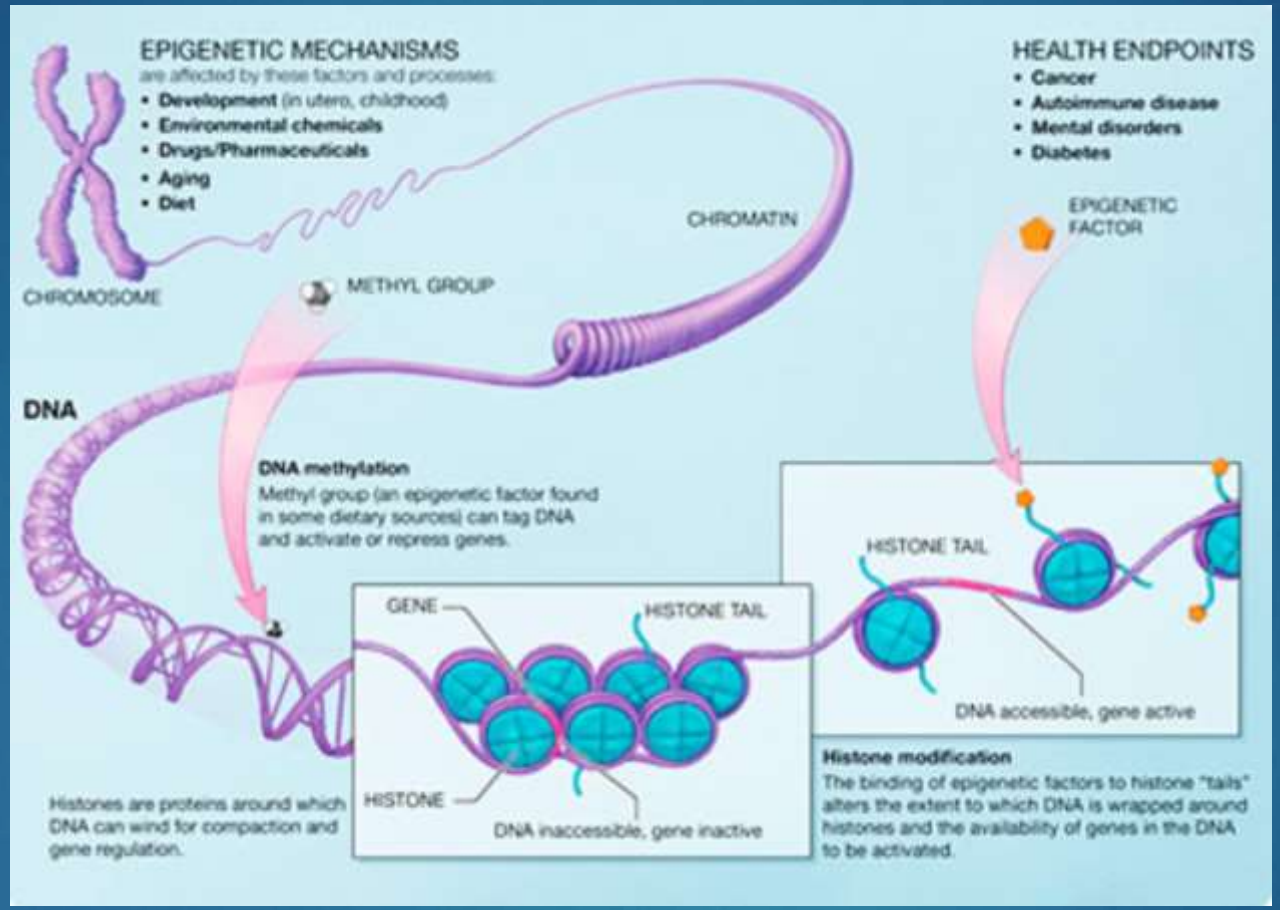
What is cause of adult outcome?

- Mother mouse and her son — sit on two bar stools, lapping gin from two thimbles.
- The mother mouse looks up and says, “Hey, geniuses, tell me how my son got into this sorry state.”
- “Bad inheritance,” says Darwin.
- “Bad mothering,” says Freud.
- But maybe its epigenetics! Experience can trump genetic expression.

Epigenetics

- The dynamic regulation of gene expression through epigenetic mechanisms is at the interface between environmental stimuli and long lasting molecular, cellular and complex behavioral phenotypes acquired during periods of developmental plasticity

Epigenetics: heritable changes in gene activity that are *not* caused by changes in DNA

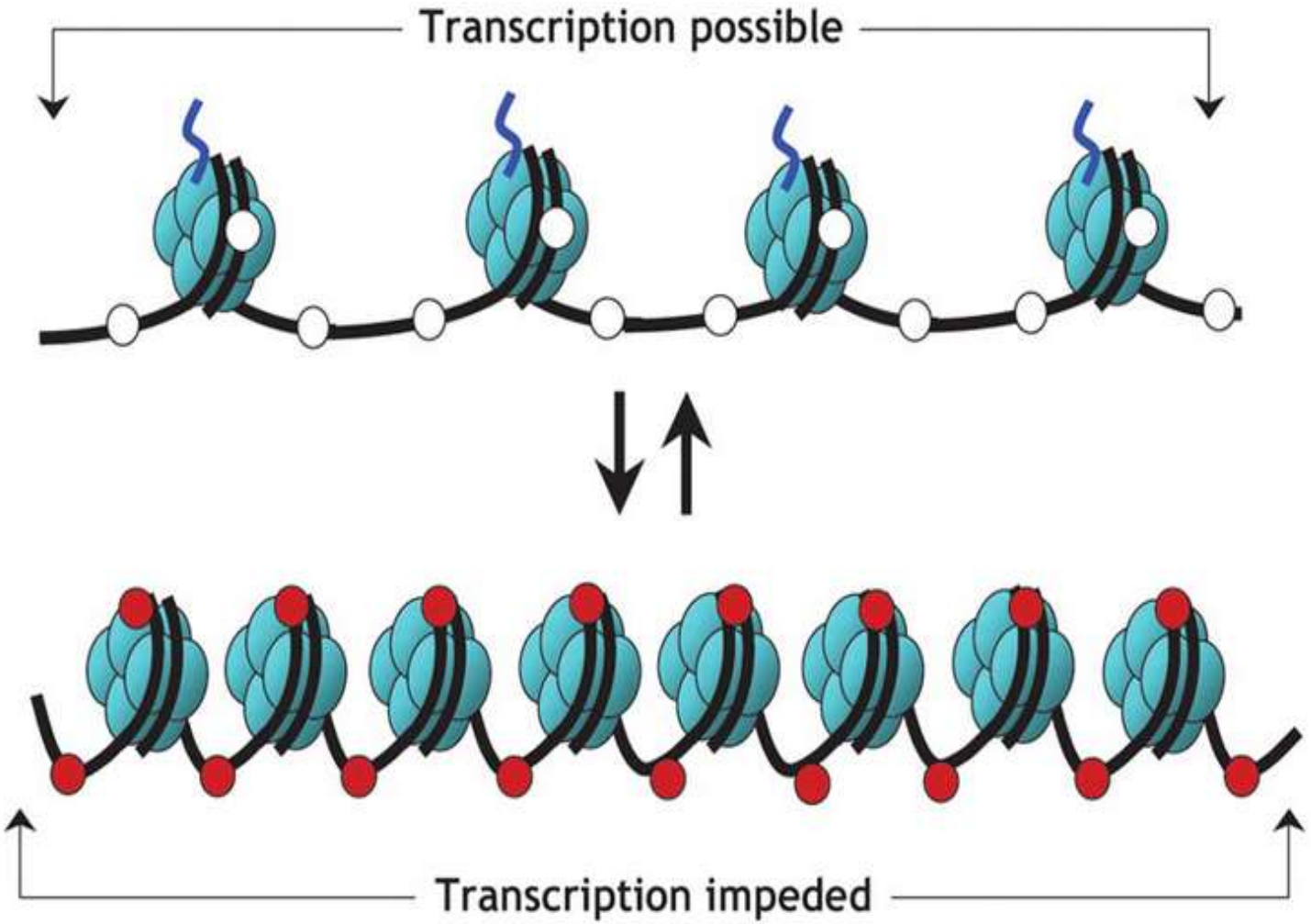


DNA wrapped around histones; histones can dial down gene activation; methyl group can activate or deactivate a gene expression; both determined by environment; can be generationally transmitted

Epigenetics: How your grandfather increases your risk for diabetes

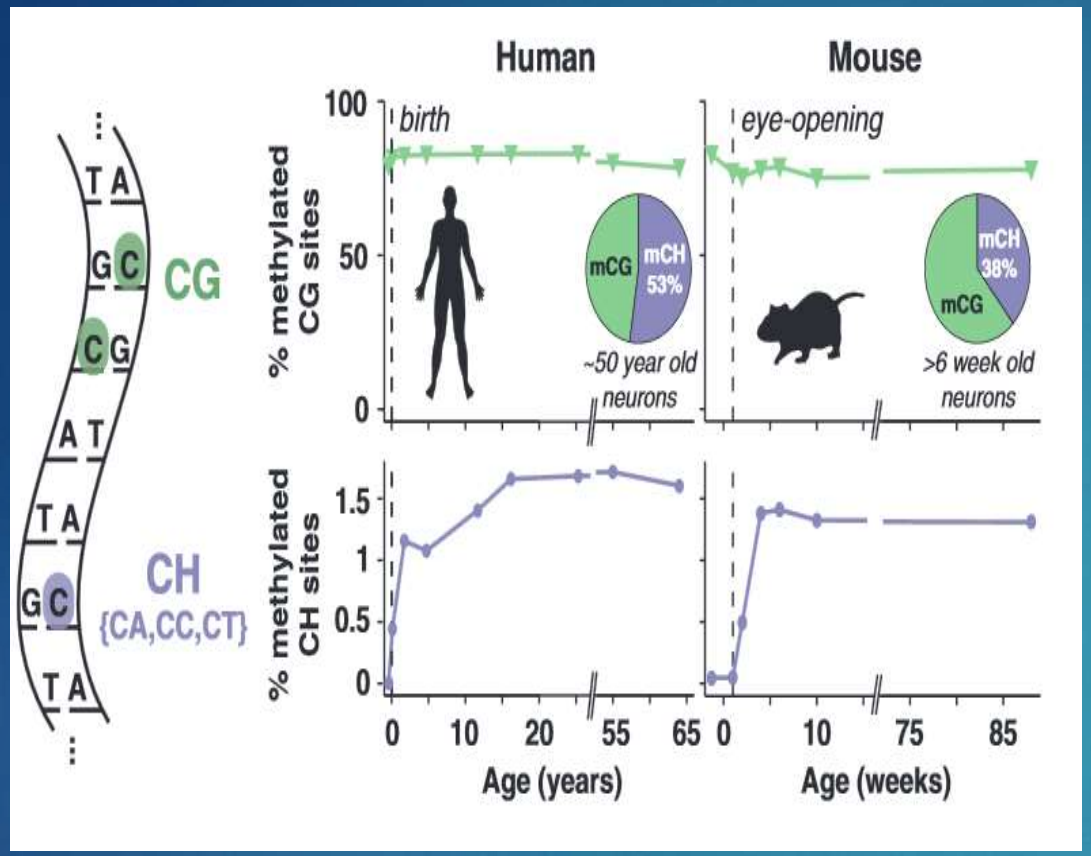
Gene "switched on"
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

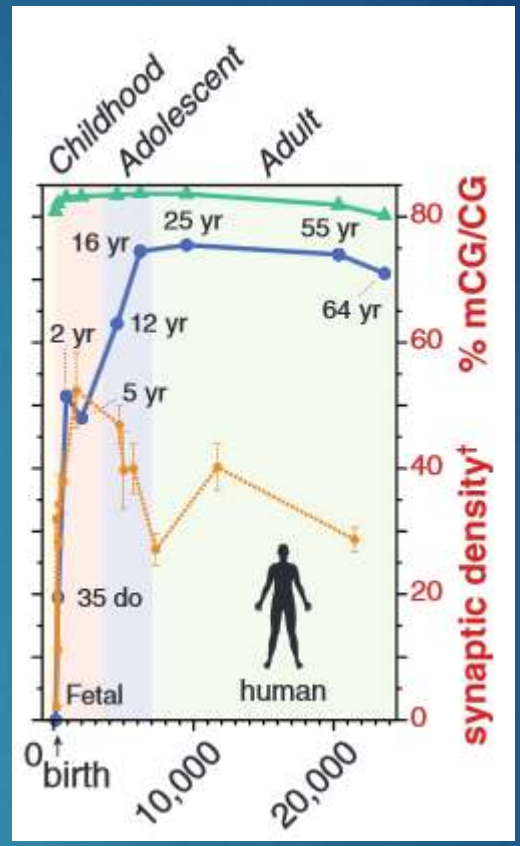
Gene "switched off"
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones



http://cnx.org/content/m26565/latest/graphics35.jpg

Epigenetics and synaptogenesis





- The DNA methylation landscape of human and mouse neurons is dynamically reconfigured through development.
- Neurons accumulate substantial mCH during the early years of life, coinciding with the period of synaptogenesis and brain maturation. (2nd = frontal lobe)

HPA & Epigenetics: Mother Nurturing

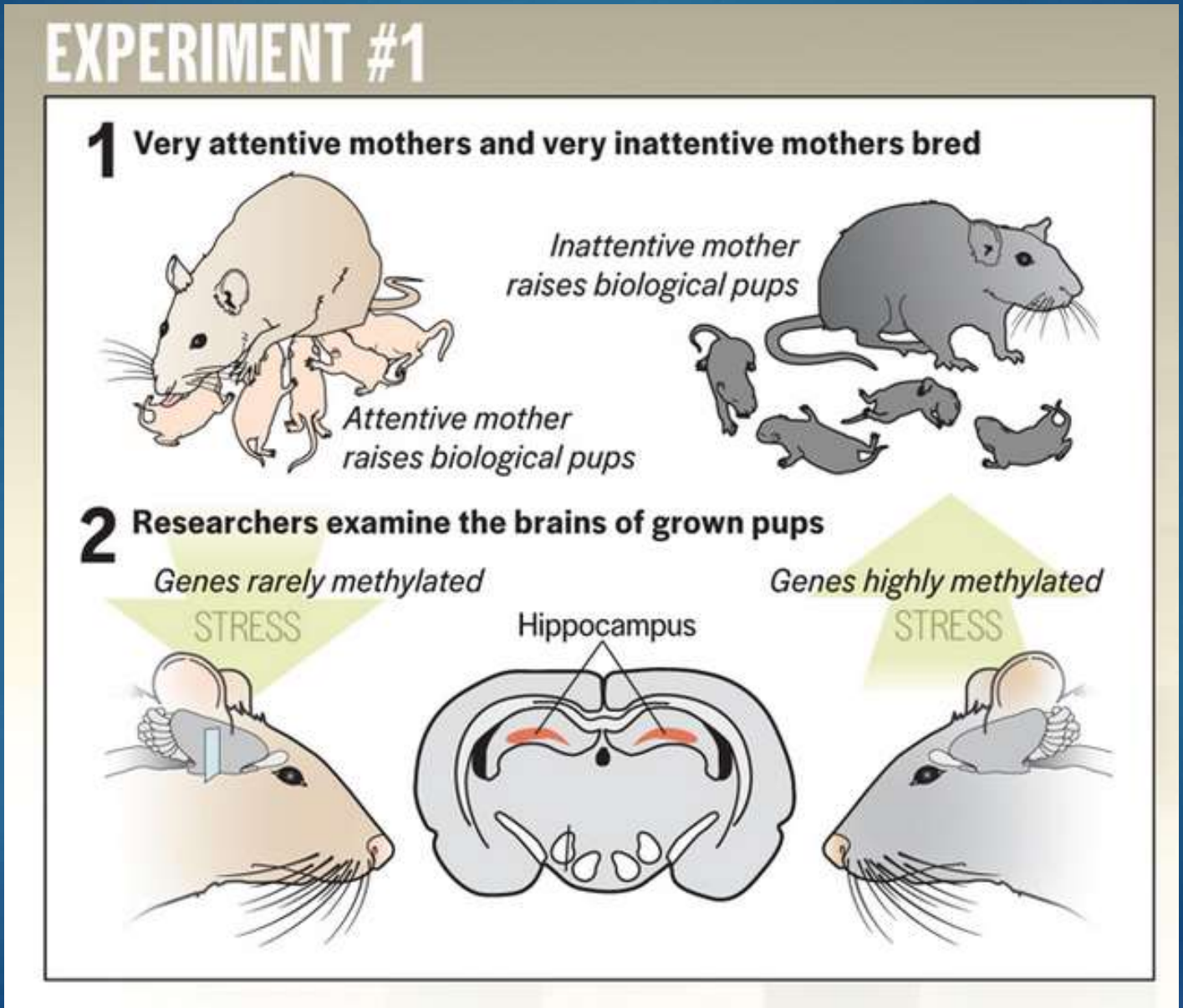
- HPA functions through epigenetic programming of glucocorticoid receptor expression:
- More stress, more methylation tags on genes
- Early adversity alters chemistry of DNA in the brain through methylation:
  - methylation disables stress hormone receptor genes, preventing the brain from properly regulating its response to stress.
  - Mouse mother licking pup; later calmer pup (genes for the glucocorticoid receptors rarely methylated; low levels of glucocorticoid receptors in their hippocampus)
- Variations in maternal care stably influence DNA methylation, gene expression, and neural function in the offspring.

Michael Meaney

Michael Meaney: Behavioral epigenetics

- Importance of maternal care in modifying the expression of genes that regulate behavioral and neuroendocrine responses to stress, as well as hippocampal synaptic development.
- Pups taken outside of their maternal environment to be handled for 15 minutes a day had lower hypothalamic-pituitary-adrenal (HPA) responses than pups separated from their mothers for 3 hours a day and pups with no handling whatsoever. He hypothesized that glucocorticoid receptor (GR) density was involved in the HPA feedback loop.
- Established a causational relationship between maternal care and behavioral epigenetic programing with cross fostering of pups by various mothers of differing maternal behaviors.
- Childhood abuse amongst suicide victims was associated with a distinct epigenetic mark on their DNA

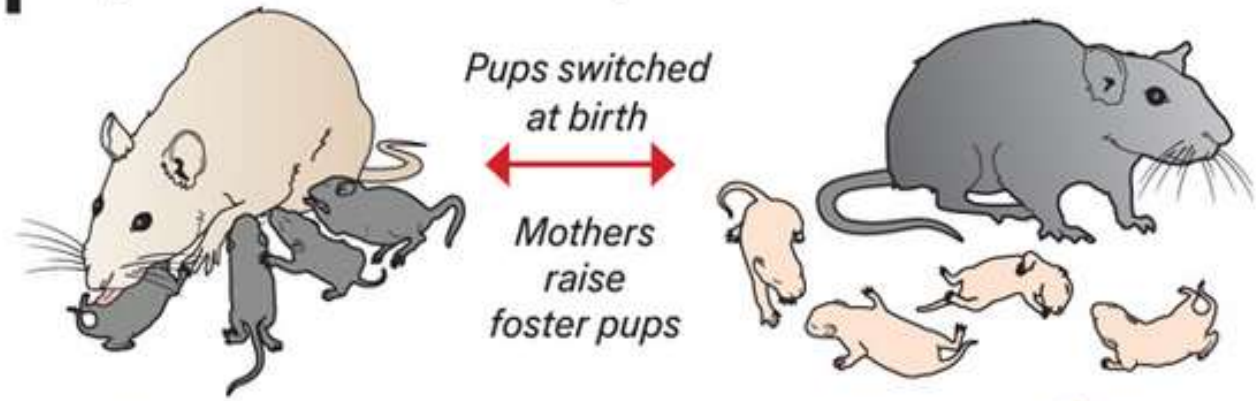
Epigenetic programming by maternal behavior



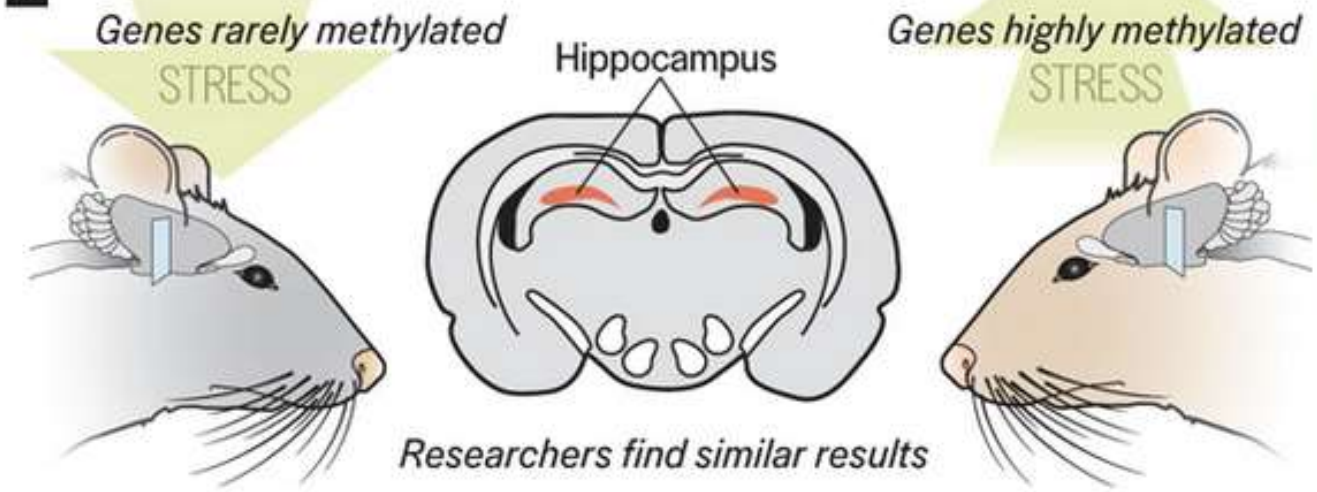
Meaney & Szyf, 1997

EXPERIMENT #2

1 **Very attentive mothers and very inattentive mothers bred**

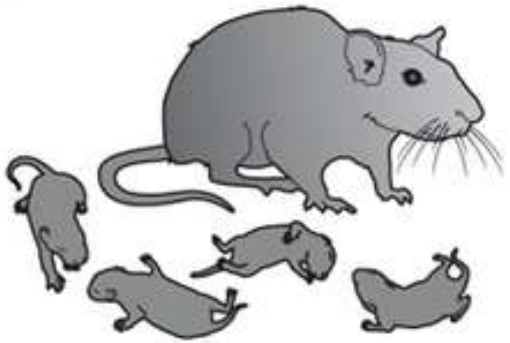


2 **Researchers examine the brains of grown foster pups**

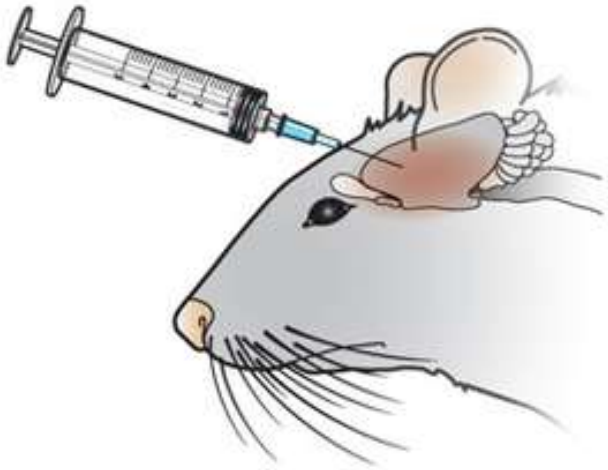


EXPERIMENT #3

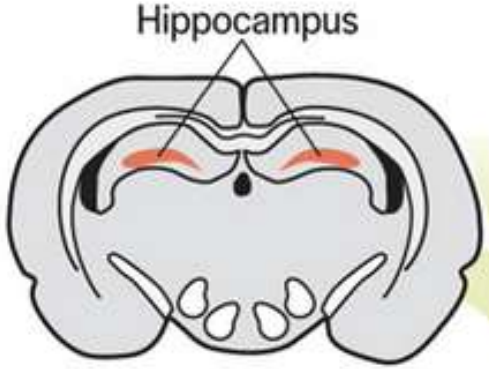
1 **Inattentive mothers bred**



Inattentive mother raises biological pups



2 **Brains of "damaged" pups treated with trichostatin A, a drug that removes methyl groups**

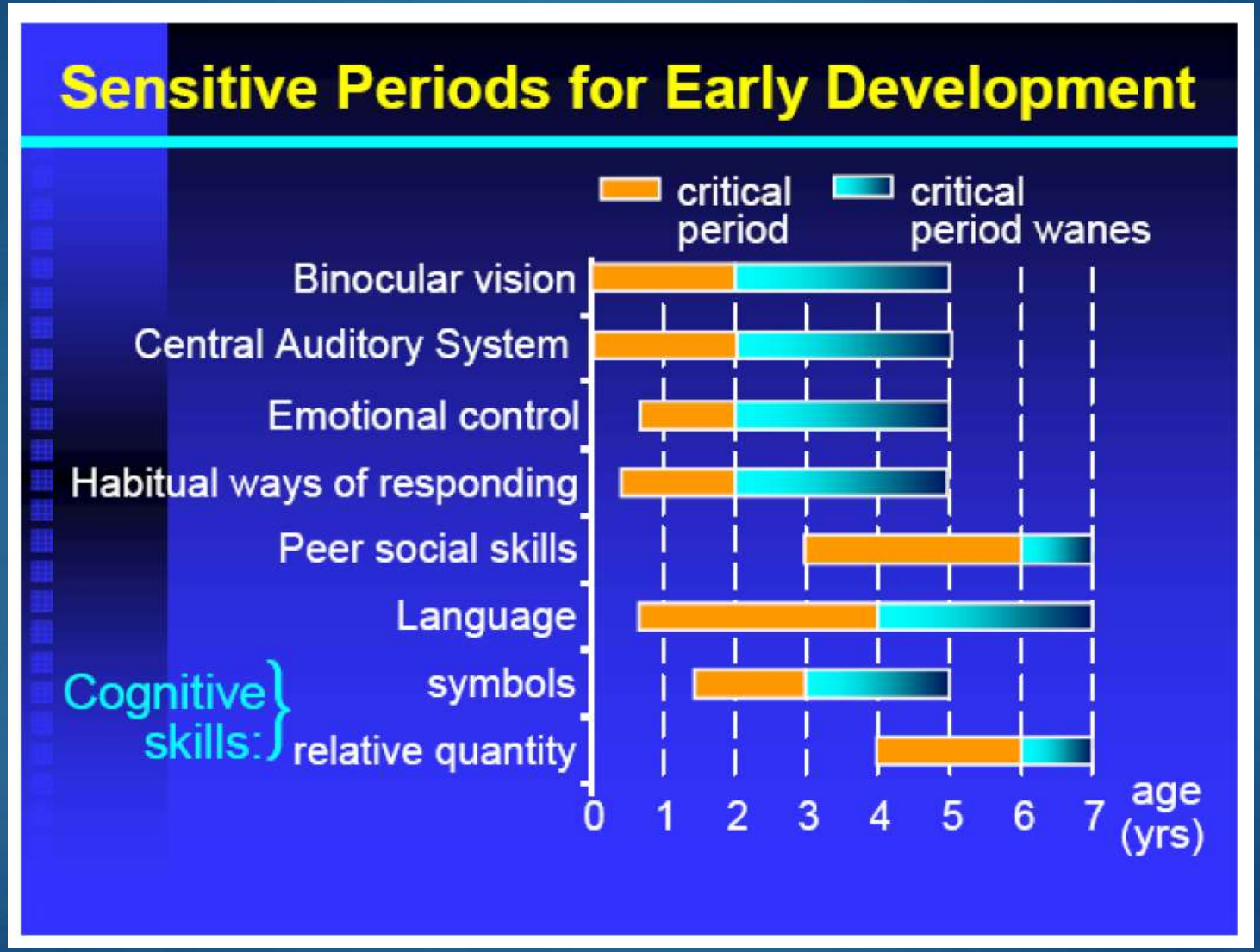


3 **Epigenetic changes disappear**

STRESS

Genes rarely methylated

Critical Periods



Brain Structure: Infancy/Early Childhood

- Rapid Growth
- Large Growth in

  number of Glial cells

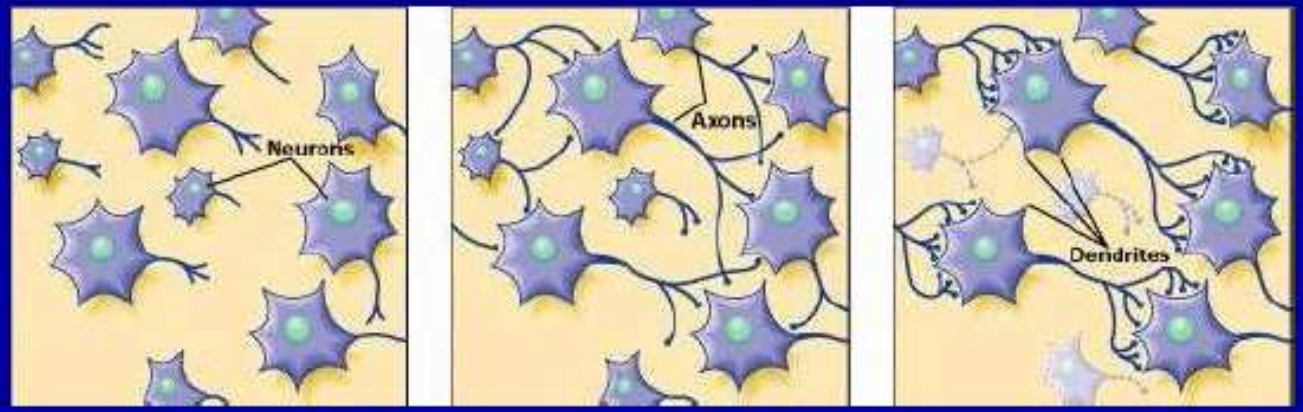
Age	18 m	2 y	5-6 yrs
Adult Brain Size	50%	80%	100%

- Huge increase in number of synapses

  -- First months of life: 50 Trillion → 1,000 Trillion (Carnegie, 1994)

- Synaptic Pruning begins

Synaptic Pruning



Birth

- Number of neurons are in place
- Few synaptic connections

0-1yr

- Number of synaptic connections increase

Childhood to Adolescence

- Unused connections are pruned
- Used synapses are strengthened

Cognitive Development: Piaget

Table 3-2. Cognition, Play, and Language

Piagetian Stage	Age	Object Permanence	Causality	Play	Receptive Language	Expressive Language
I	Birth-1 mo	Shifting images	Generalization of reflexes		Turns to voice	Range of cries (hunger, pain)
II	1-4 mo	Stares at spot from which object disappeared (looks at hand after yarn drops)	Primary circular reactions (thumb sucking)		Searches for speaker with eyes	Cooing; vocal contagion
III	4-8 mo	Visually follows dropped object through vertical trajectory (tracks dropped yarn to floor)	Secondary circular reactions (recreates accidentally discovered environmental effects, e.g., kicks mattress to shake mobile)	Same behavioral repertoire for all objects (bangs, shakes, puts in mouth, drops)	Responds to own name and to tones of voice	Babbling; four distinct syllables
IV	9-12 mo	Finds an object after watching it hidden	Coordination of secondary circular reactions	Visual motor inspection of objects; peek-a-boo	Listens selectively to familiar words; responds to "no" and other verbal requests	First real word; "jargoning"; symbolic gestures (shakes head "no")
V	12-18 mo	Recovers hidden object after multiple visible changes of position	Tertiary circular reactions (deliberately varies behavior to create novel effects)	Awareness of social function of objects; symbolic play centered on own body (drinks from toy cup)	Can bring familiar object from another room; points to parts of body	Many single words—uses words to express needs; acquires 10 words by 18 mo
VI	18 mo-2 yr	Recovers hidden object after invisible changes in position	Spontaneously uses nondirect causal mechanisms (uses key to move wind-up toy)	Symbolic play directed toward doll (gives doll a drink)	Follows series of two or three commands; points to picture when named	Telegraphic 2-word sentence

Brain Maturation

- The default network demonstrate little integration until after age nine.
- Longitudinal neuroimaging studies demonstrate changes in grey matter density until the mid-twenties with the prefrontal cortex being the last to mature.
- The cellular basis for the observed reduction in grey-matter density with MRI is not clear although classical anatomical post-mortem studies indicate that both synaptic elimination and increased myelination continue into early adulthood.

Brain Maturation 2

- Human post-mortem neuroanatomy literature of adolescence is scant, studies in non-human primate brain demonstrate that the refinement of circuits during early adulthood includes pruning of asymmetric (excitatory) synapses, proliferation of inhibitory circuits and the continued elaboration of pyramidal dendrites as targets of inhibitory input.

- Together these observations indicate that this late stage of brain maturation involves a careful calibration of excitatory–inhibitory balance in the cortex with the prefrontal cortex the last region to mature.

- As one potentially relevant modulator of this balance, dopamine innervation of the prefrontal cortex increases markedly during adolescence

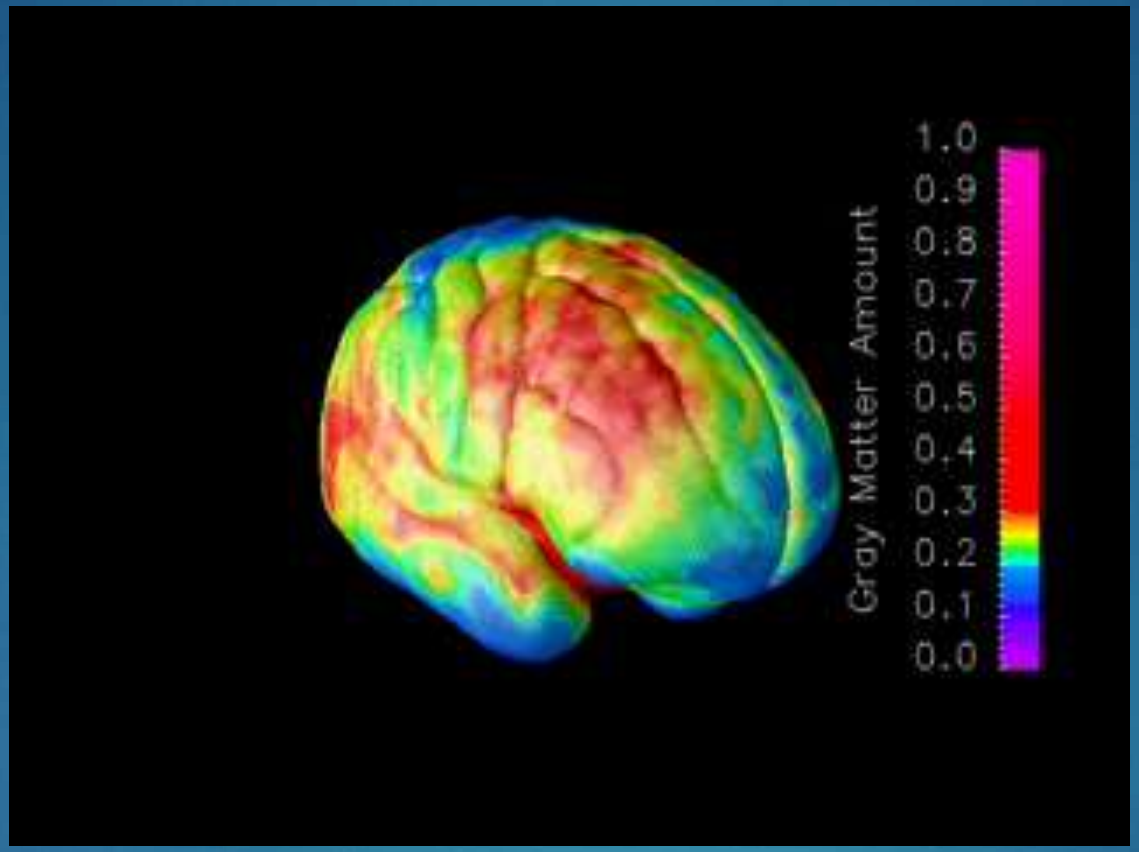
Synaptic Pruning

- During key periods, amount of gray matter in some areas doubles within 1 year, with corresponding loss of synapses in other areas
- A second wave of overproduction causes a thickening of gray matter, continues to increase, peaking around the time of puberty. With puberty, there is a second "pruning' of cells.
- This pruning process follows a "use it or loose it' principle – the cells and connections that are used are going to be the ones that survive; those that aren't will be the ones that perish.
- Teenagers determine how their brains are wired and sculpted.
- You need to lose connections in order to develop a fine-tuned system of brain networks, because if all parts of the brain talk to all parts of the brain, all you get is noise.

Brain Maturation ages 5-20

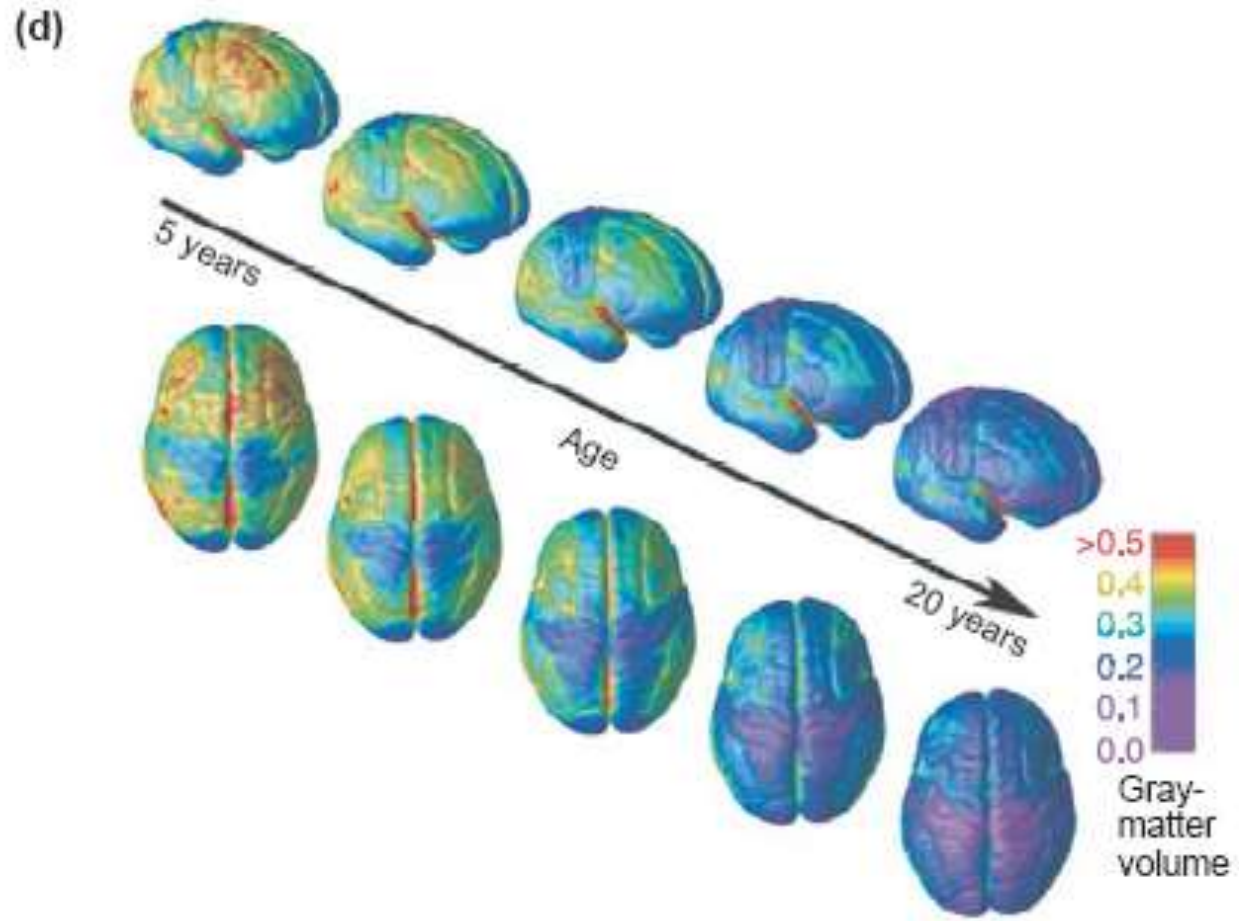
- Pruning away of synapses to neurons that are not used
- Increase in amount of white matter relative to grey neurons
- Increase in myelination of axons, which then can transfer information 1000s of times faster
- This improved connectivity of fewer more specialized neurons creates behavioral maturity
- Crucial decision making frontal lobes are the last to mature
- Females are 2 years ahead in this maturation process.
- High variability: can mature at 13 or 35

Teen Brain: age 5 to 21



Lose 50% of all synaptic connections. By the age of 18 the number of connections has been reduced to around 500 trillion –
the same number the young adult had as an 8-month old.

Density Decrease from 5 to 20: GM Thinning



Gogtay et al., 2004

Vision/Hearing, Language, Higher Cognitive

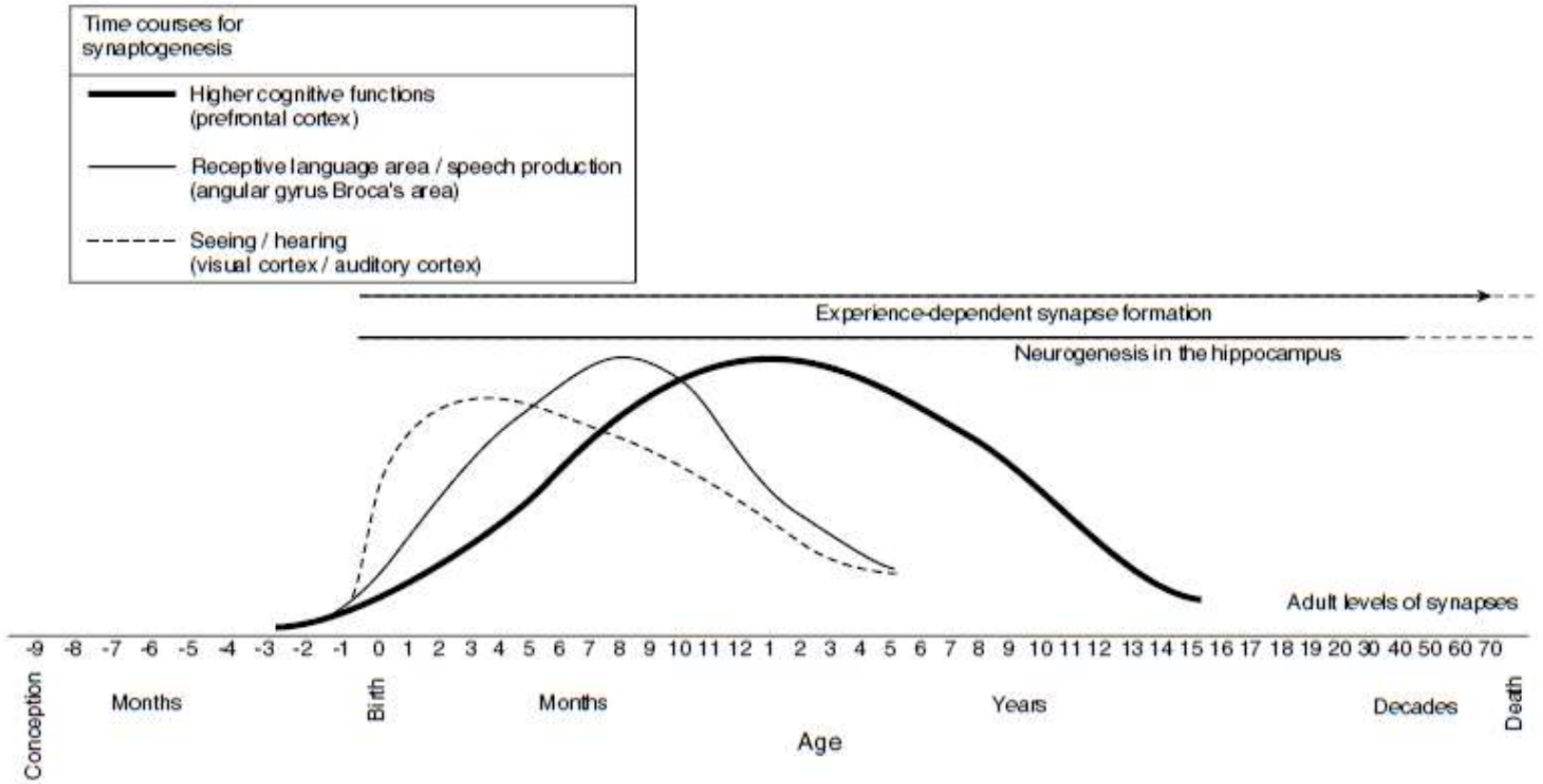
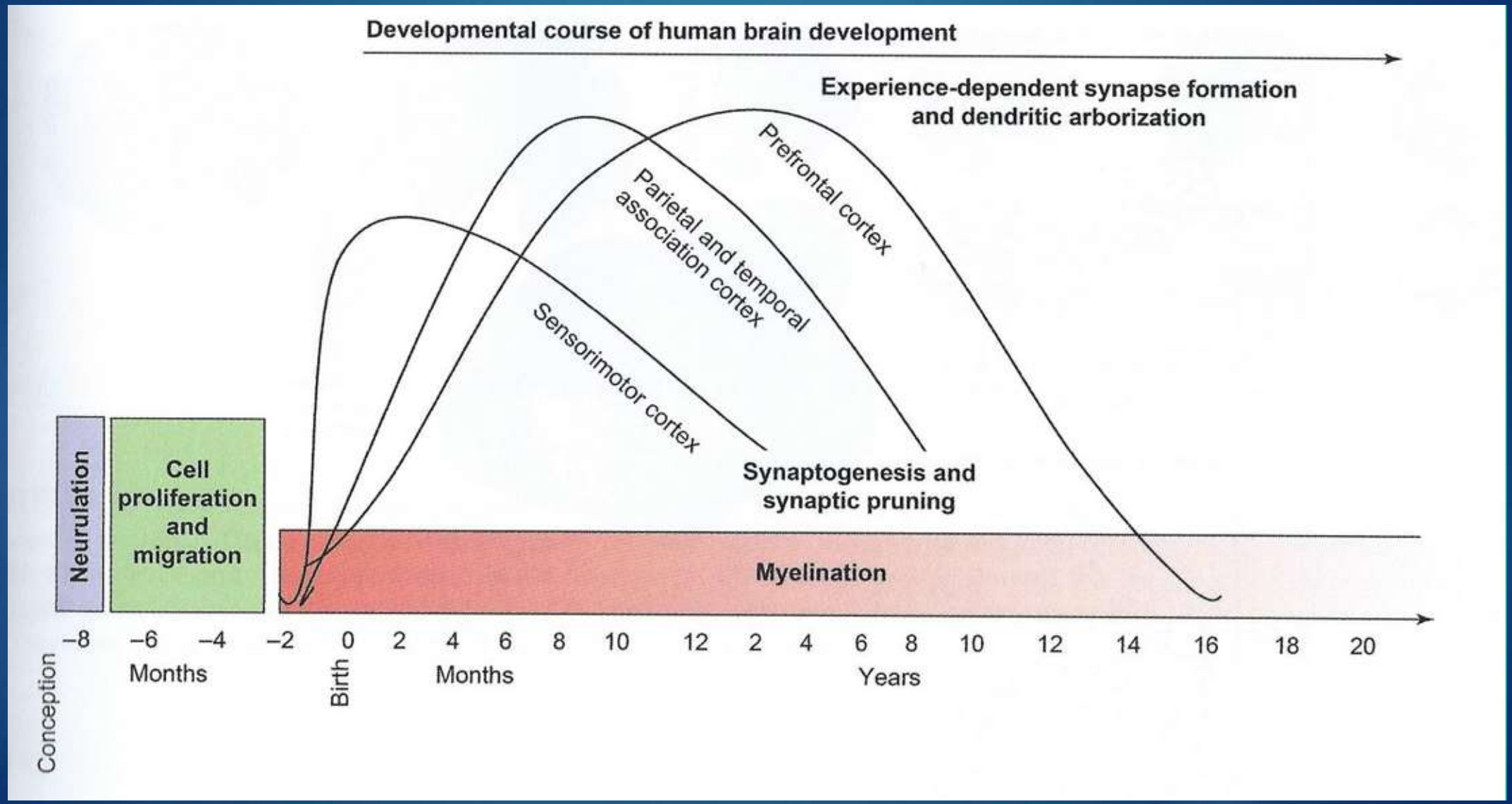
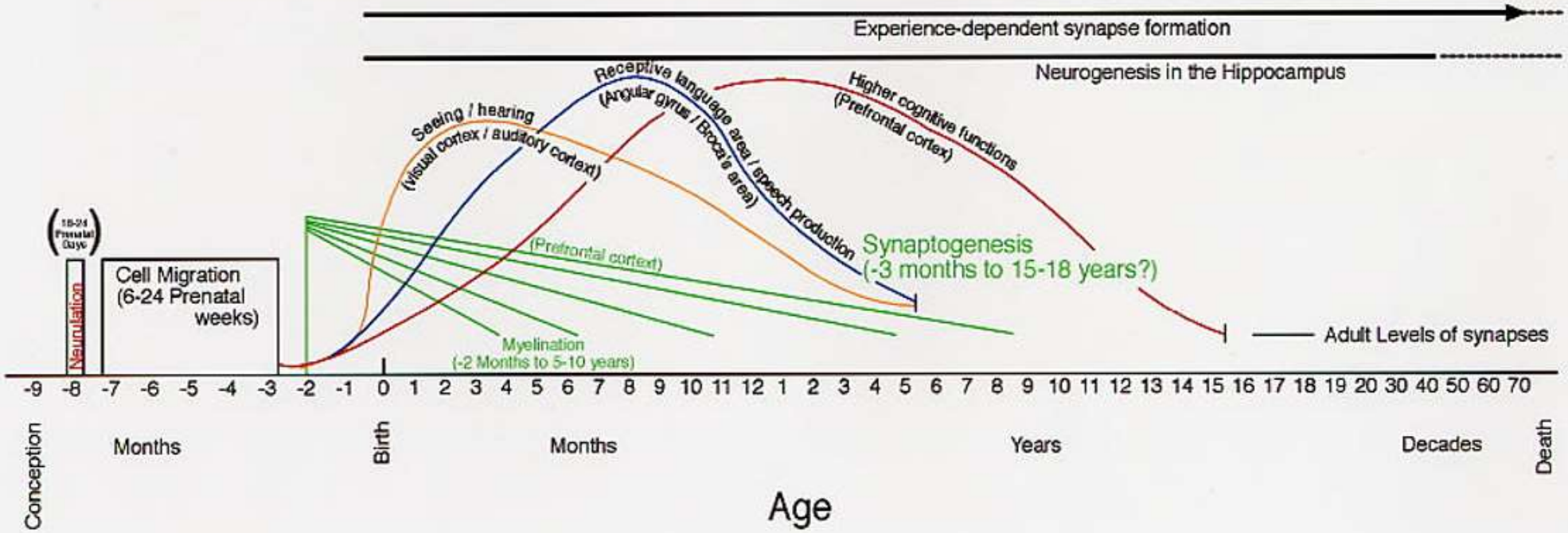


FIGURE 8-1 Human brain development. SOURCE: Charles A. Nelson, University of Minnesota. Reprinted with permission.

Experience-dependent synaptogenesis & pruning: A leaner brain is more efficient

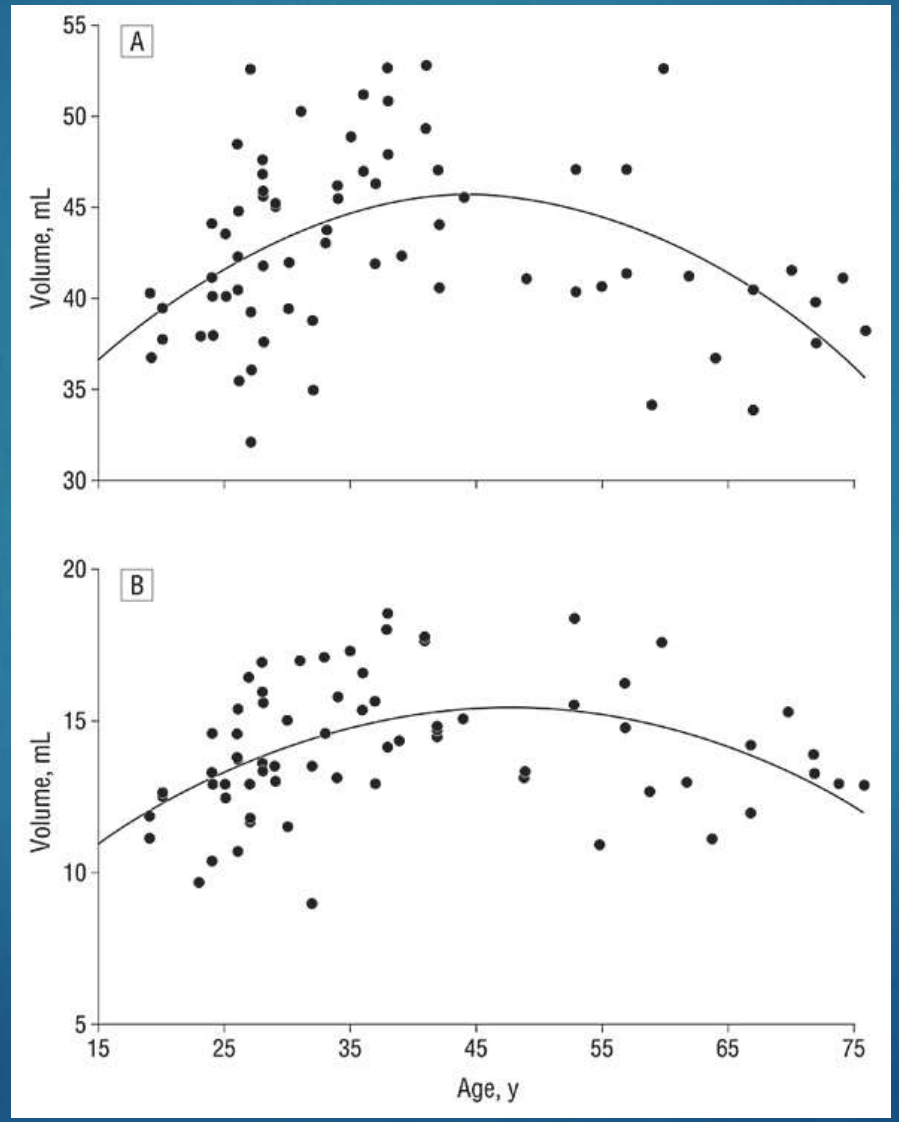


Human Brain Development



Thompson, R. A., & Nelson, C. A. (2001). Developmental science and the media: Early brain development. *American Psychologist, 56(1)*, 5-15.

White Matter Increases Ages 15 to 75



Prefrontal cortex

Temporal lobe

Bartzokis et al., 2001

What Changes?

- Gray matter first thickens then thins as neurons are weeded out and most-used connections are strengthened.
  - Development is sensory and motor first, then back-to-front with frontal areas last.
- White matter increases with myelination of axons providing interconnections.
  - This increases until age 50, then declines.
- Both curves are quadratic, not linear.

Tetris and Neuroplasticity

Richard Haier, 2009

Eleven 15 year old, non video gaming, girls, played Tetris 1.5 hrs. per week, vs controls

Results:
Grey cell increase and decrease in frontal and temporal areas

Parts of the brain showed less activity than three months earlier, when the girls were Tetris novices

Brain regions that got bigger over the three months of Tetris play were not the same regions that showed a drop in activity, ruling out the simple explanation that as brain regions get bigger, they become more efficient

Tissue Volume & Cognition in Adolescents

- Processing Speed: Gray -.50, White .52 ↑
- Verbal Ability: White .36 ↑, CSF -.42, Gray -.32
- Working Memory: CSF -.30

Cognition = matures as Gray ↓, White ↑

Yurgelun-Todd, ‘02:

Developmental Implications of Experience on Synaptic Development

- More environmental stimulation, the more synaptic development
- Genetics form the basis (nature), but environment and experience (nurture) drive the developmental process
- Adverse inputs (abuse, chemical exposure, malnutrition) have lasting effects

Growth Curve in networks

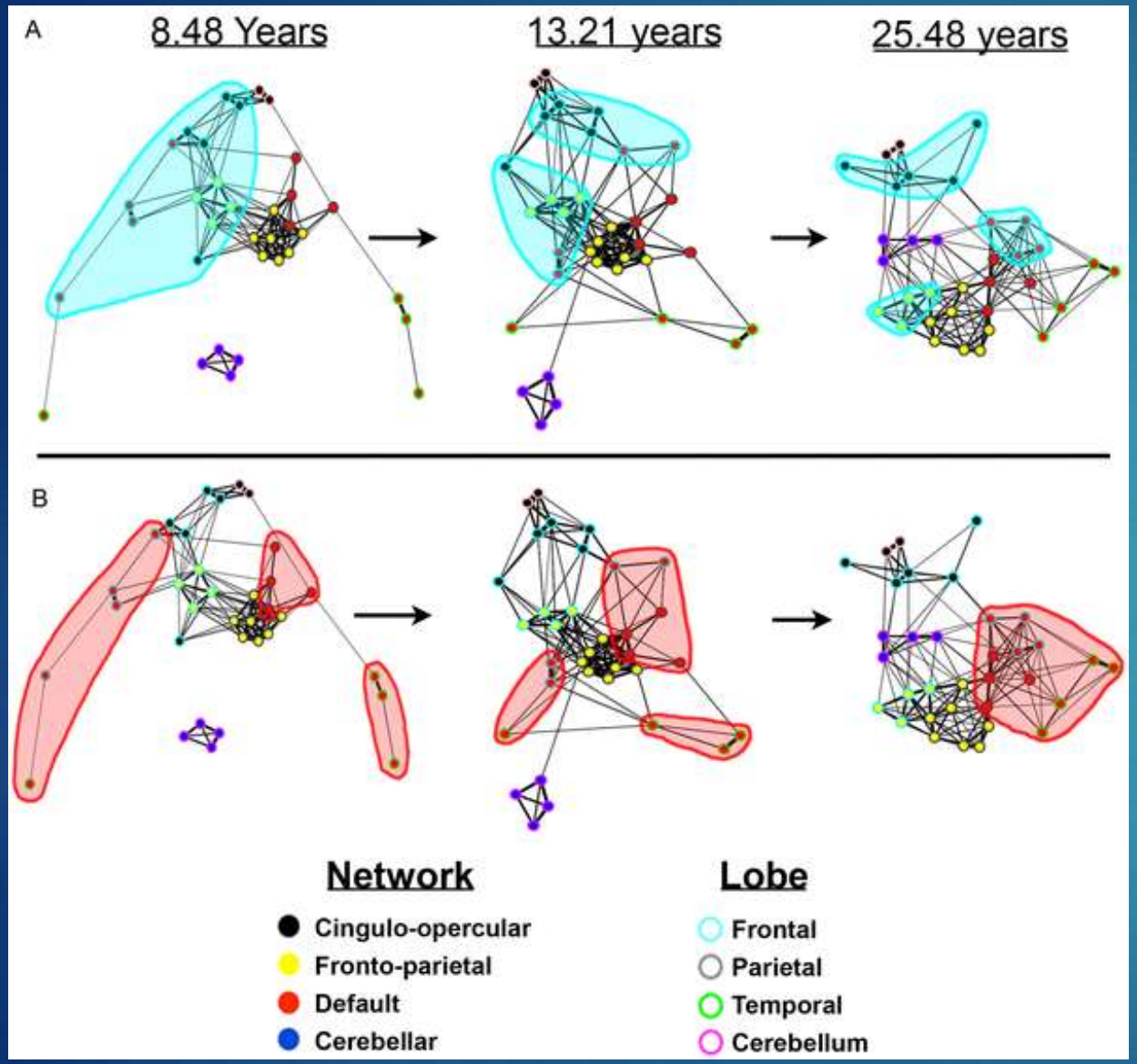
- Links between brain regions that are physically close to each other get weaker with age, while specific long-range connections tend to get stronger.
- The overall organization switches from
  - networks involving regions physically close to each other, which is the dominant motif in a child's brain,
  - to networks that connect distant regions, the primary organizational principal in adult brains.
- Connections involving two particular regions — the right anterior prefrontal cortex and the precuneus — were the best predictors for overall brain maturity

Development of connectivity

- Neuronal connectivity communities in children are predominantly arranged by anatomical proximity,
- Communities in adults predominantly reflect functional relationships, as defined from adult fMRI studies. In sum, over development, the organization of multiple functional networks shifts from a local anatomical emphasis in children to a more "distributed" architecture in young adults.
- In childhood, many regions were relatively isolated with few or no functional connections to other default mode regions. Over age, correlations within the default mode network increased and by adulthood it had matured into a fully integrated system. Interestingly, as opposed to the task-control and cerebellar networks, very few short-range functional connections involving the default mode network regions existed in children.

Damien A. Fair, et al., Plos, 2009

Over age the graph architecture matures from a “local” organization to a “distributed” organization.



A. In children regions are largely organized by their anatomical location, but over age anatomically clustered regions segregate. The cluster of frontal regions (highlighted in light blue) best demonstrates this *segregation*.
B. In children the more distributed adult functional networks are in many ways disconnected.
Over development the functional networks integrate. The isolated regions of the default mode network in childhood (highlighted in light red) that coalesce into a highly correlated network best illustrate this *integration*. Over age, node organization shifts from the “local” arrangement in children to the “distributed” organization commonly observed in adults.

Fair DA, Cohen AL, Power JD, Dosenbach NUF, et al. (2009) Functional Brain Networks Develop from a “Local to Distributed” Organization. PLoS Comput Biol 5(5): e1000381. doi:10.1371/journal.pcbi.1000381
http://www.ploscompbiol.org/article/info:doi/10.1371/journal.pcbi.1000381

Networks

- Dynamic process of over-connectivity followed by pruning, which rewires connectivity at the neuronal level, also operates at the systems level, reconfiguring and rebalancing subcortical and paralimbic connectivity in the developing brain
- Hierarchical networks are optimally connected to support top-down relationships between nodes and minimize wiring costs, but are vulnerable to attack on hubs
- Large-scale brain networks in children showed small-world properties (the presence of subnetworks of densely connected nodes, mostly connected by a short path) that were very similar to young-adults;
- Development is characterized by simultaneous reduction of short-range connectivity and strengthening of long-range connectivity

Kaustubh Supekar, et al., 2009

Childhood Networks

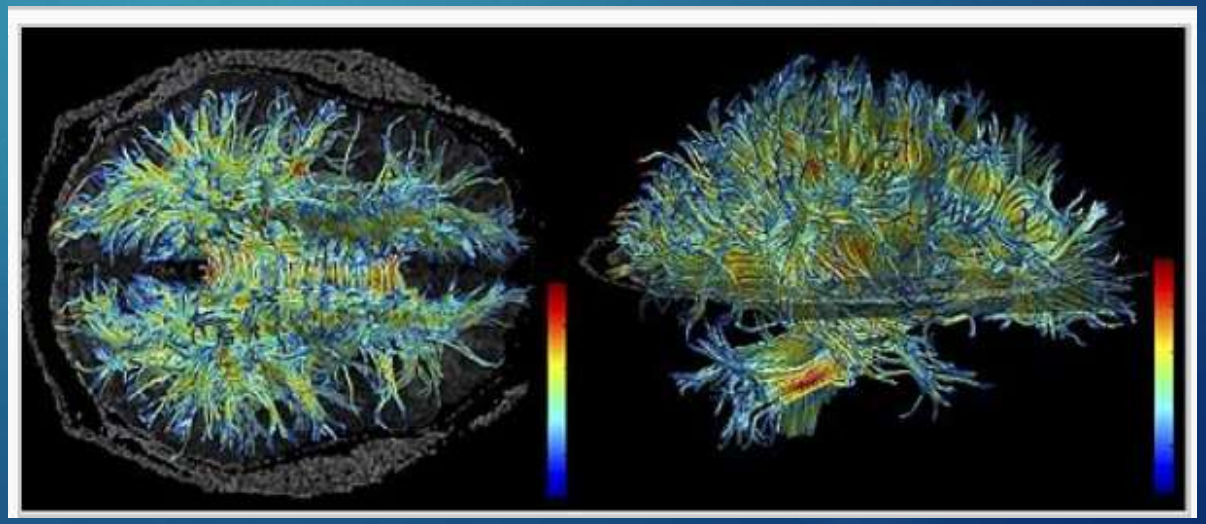
- (1) Large-scale brain networks in 7–9-y-old children showed similar small-world, functional organization at the global level, as young-adults;
- (2) Compared to young-adults, functional brain networks in children showed significantly lower levels of hierarchical organization;
- (3) children and young-adults have stronger subcortical-cortical and weaker cortico-cortical connectivity; and
- (4) the development of large-scale brain connectivity involves a shift from stronger short-range connections in children to stronger long-range connections in young-adults.

The name is the thing: Right to Left hemisphere

- Learning the name of a color changes the part of the brain that handles color perception.
- Infants perceive color in the right hemisphere of the brain, adults do the job in the brain's left hemisphere.
- Testing toddlers showed the change to the Left Hem. occurred when the youngsters learned the names to attach to particular colors.

White Matter

- Metaanalysis of non NCD WM disease (8 deficits in order of effect size):
  - thinking speed (greatest deficit)
  - immediate and delayed memory
  - executive functioning,
  - general functioning,
  - language,
  - working memory
  - visuo-spatial construction.



Conditions and Substances that Affect the Developing Brain

Needed for Normal Brain Development	Detrimental or Toxic
Oxygen	Alcohol
Adequate protein and energy	Lead
Micronutrients, such as iron and zinc	Tobacco
Adequate gestation	Prenatal infections
Iodine	Polychlorinated biphenyls (PCBs)
Thyroid hormone	Ionizing radiation
Folic acid	Cocaine
Essential fatty acids	Metabolic abnormalities (excess phenylalanine, ammonia)
Sensory stimulation	Aluminum
Activity	Methylmercury
Social interaction	Chronic stress

What is a neuronal commonality in social animals with large brains?

Von Economo Neurons

P. Hof: "They are like the 'express trains' of the nervous system" that bypass unnecessary connections, enabling us to instantly process and act on emotional cues during complex social interactions.

Elephants

Smithsonian.com

Cetaceans: Whales & Dolphins

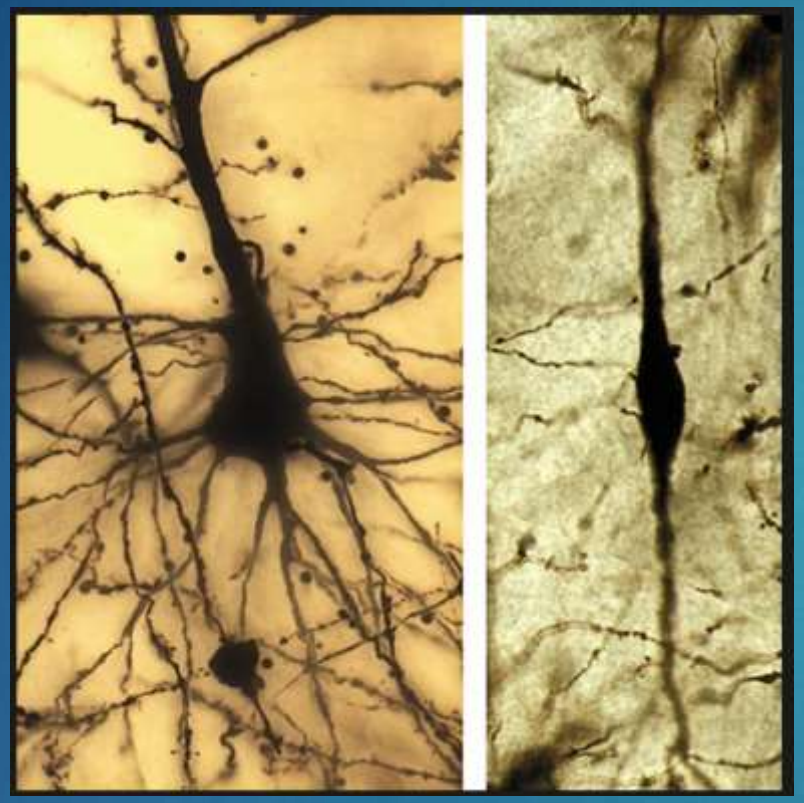
Primates

Constantin Freiherr von Economo, 1876 -1931

In 1925, his monumental work with Koskinas "Cytoarchitectonics of the Adult Human Cerebral Cortex“ was published.

The name “von Economo neurons” coined by Allman et al. (2005)

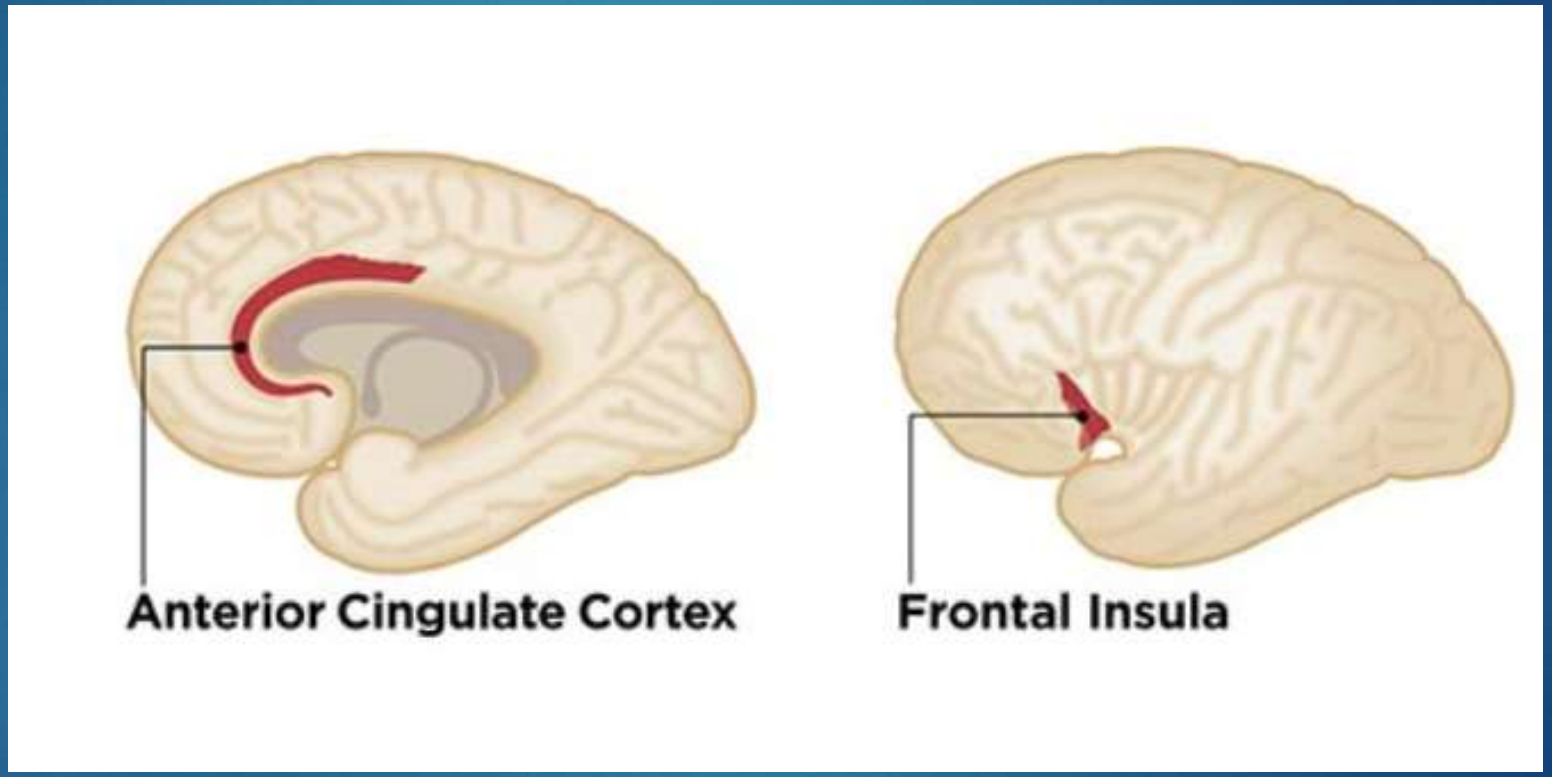
Brain Cells for Socializing?



A focal concentration of VENs in ACC and FI distinguishes large-brained, highly social mammals from other mammalian species.

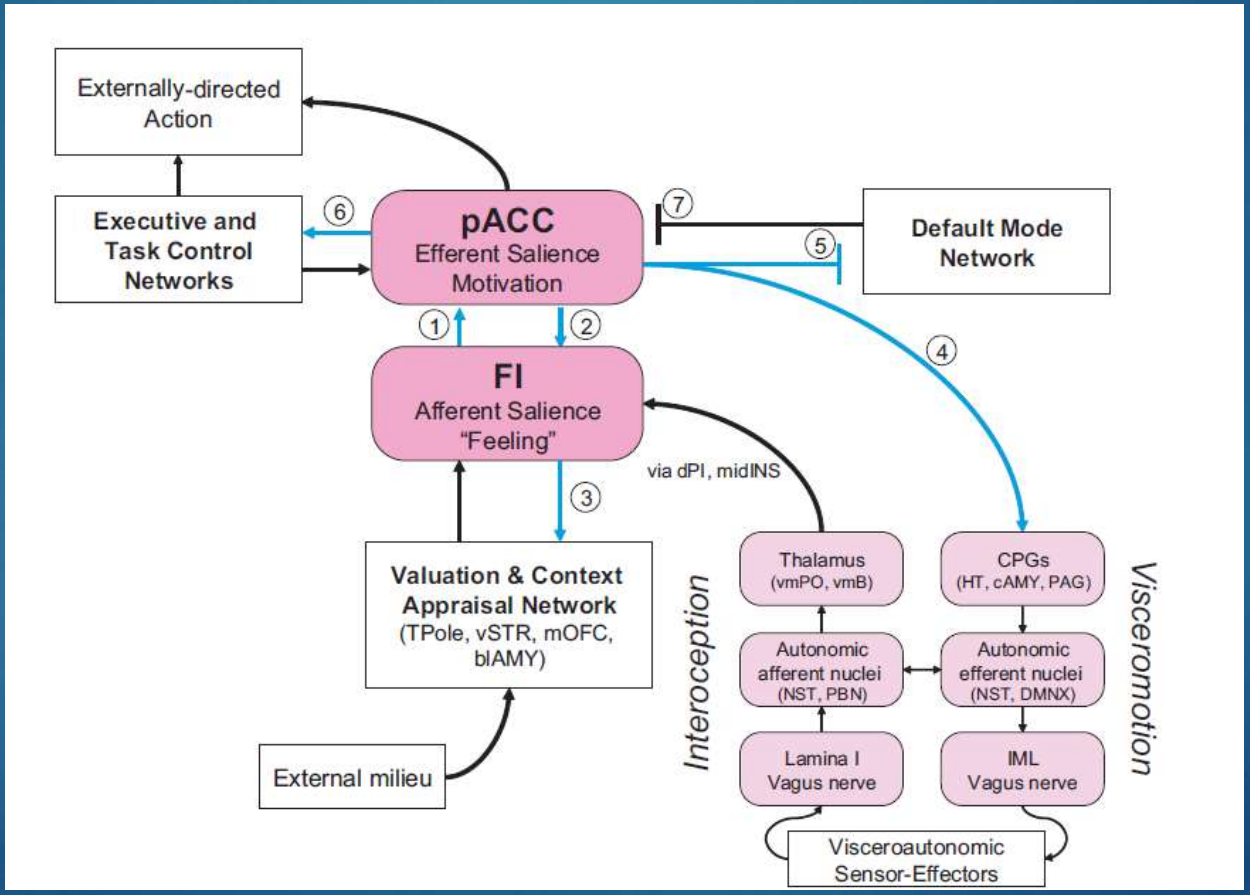
(Allman et al., 2010; Hakeem et al., 2009; Hof and Van der Gucht 2007; Nimchinsky et al., 1999; Rose 1928)

Location of VENS: ACC & FI



The FI features the other layer 5 neuron, the fork cell, which is scarcely seen in ACC.

Salience Network Central: pACC & FI, VENS



W. Seeley, et al., 2011

Von Economo Cells

- Von Economo neurons are fastest and largest neurons located primarily in the anterior cingulate and insula (layer Vb)
- Only 3 groups with significant VENs: primates/humans, certain cetacians, elephants
- Evolved to speed information around a big brain
- Recently discovered in Macaques insulas (but do not have the ability to recognize themselves in a mirror)

VENS: Von Economo Neurons

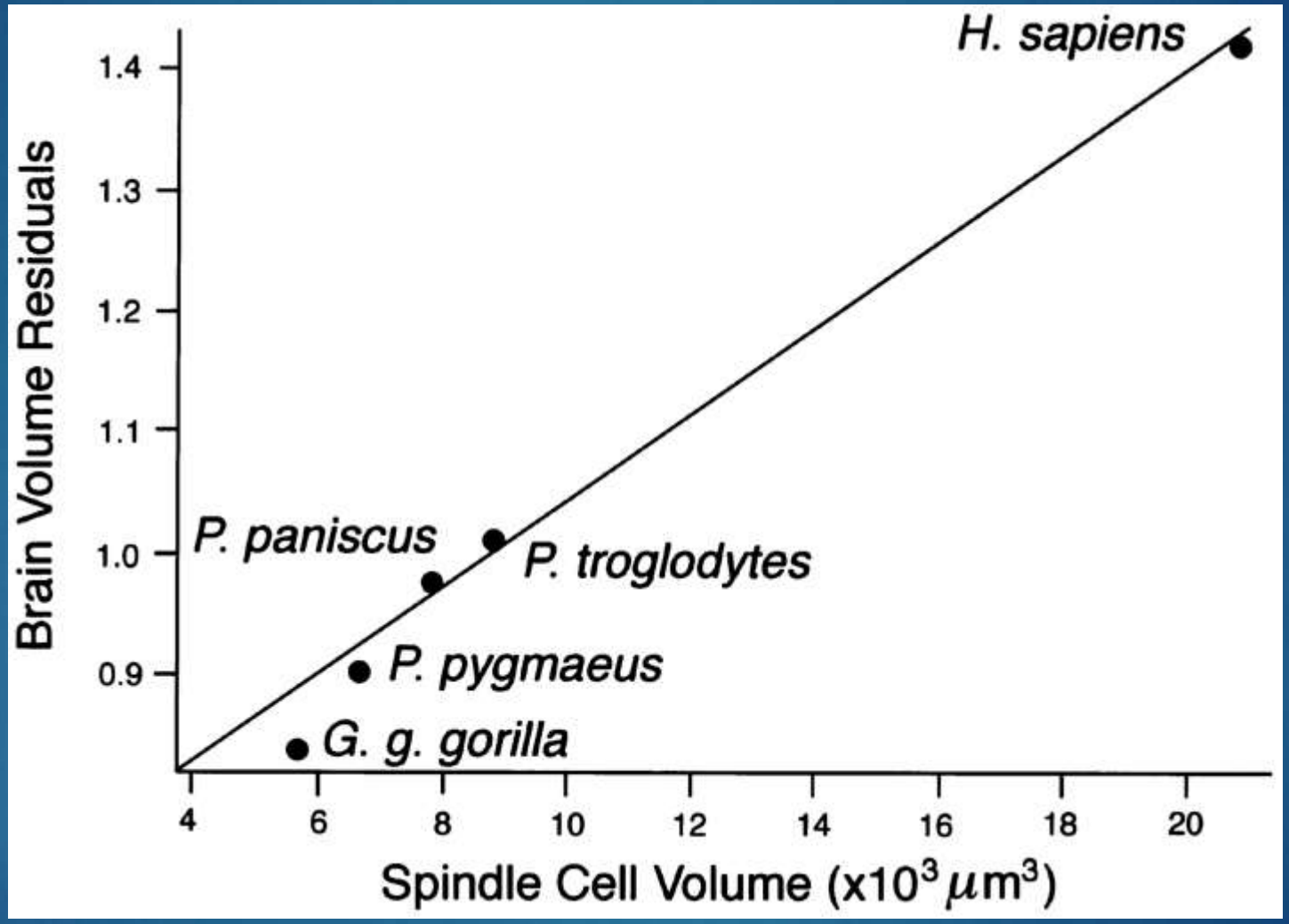
- Layer Vb neurons
- FI >>pACC; few in hippocampus & dlPFC
- R/L ~1.3 (30% more abundant in the right hemisphere)
- Emerge late in gestation, 34-38 weeks
- Peak # 8m to 4 y
- Pruned to adult status ~8 y
- Absent in monkeys and lesser apes
- Humans>>>chimps>gorillas>Orangs
- Correlated with increased encephalization
- Selectively destroyed in FTD

Nimchinsky et al., 1995, Allman et al., 2010, W. Seeley lecture, 2011

Possible functions of VENs

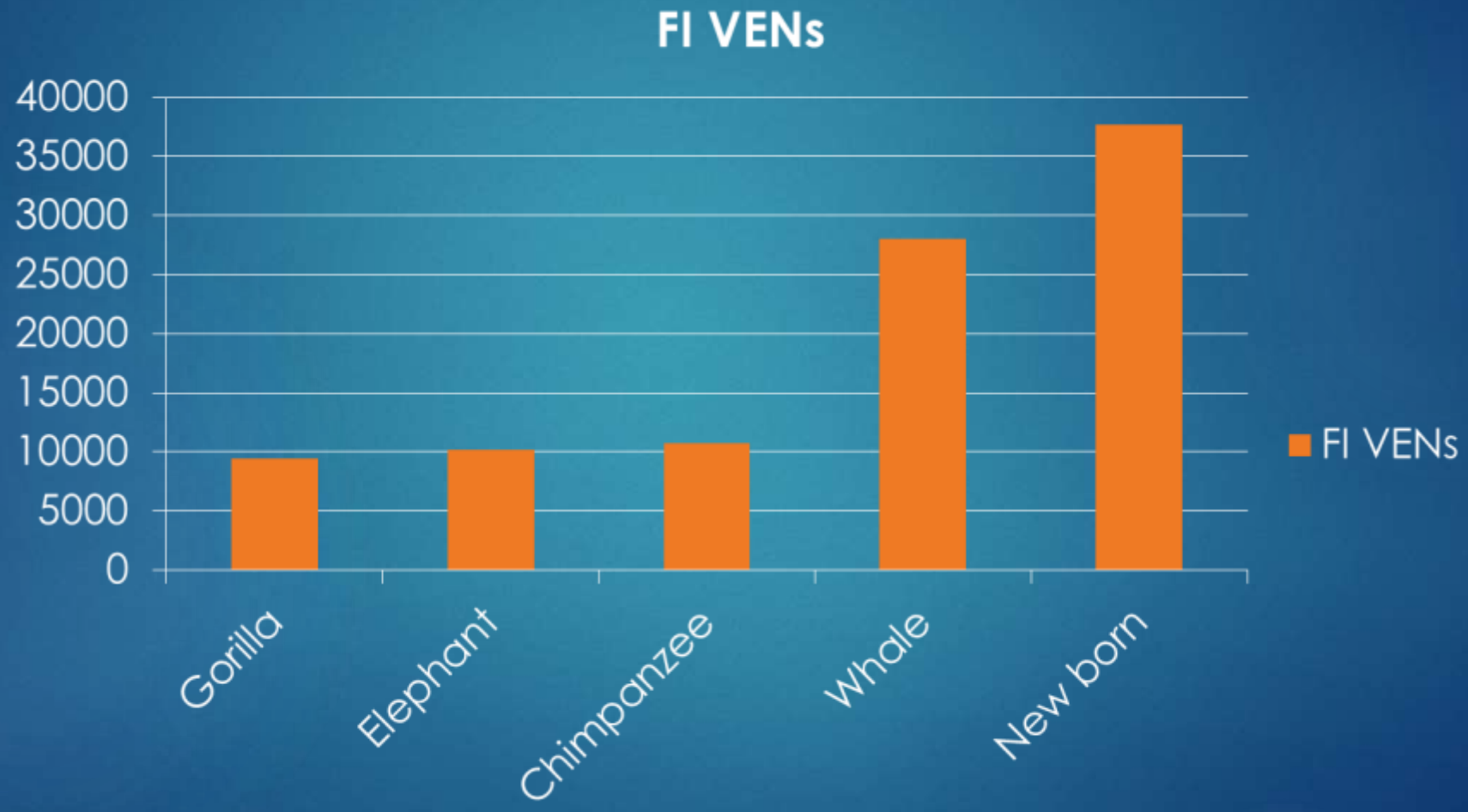
- Regulation of appetite and gastrointestinal function
- Gut feelings: conscious perception of bodily states and in its integration in conscious decisional processing
- Core of social salience network: social ability
- Possible neuronal basis of network switching
- Self awareness via insula

Comparison of VENs volume with relative brain volume



Nimchinsky E A et al. PNAS 1999;96:5268-5273

VENs in right anterior insula



(Allman et al., 2010, 2011; Butti et al., 2009; Hakeem et al., 2009; Hof and Van der Gucht, 2007; Nimchinsky et al., 1999).

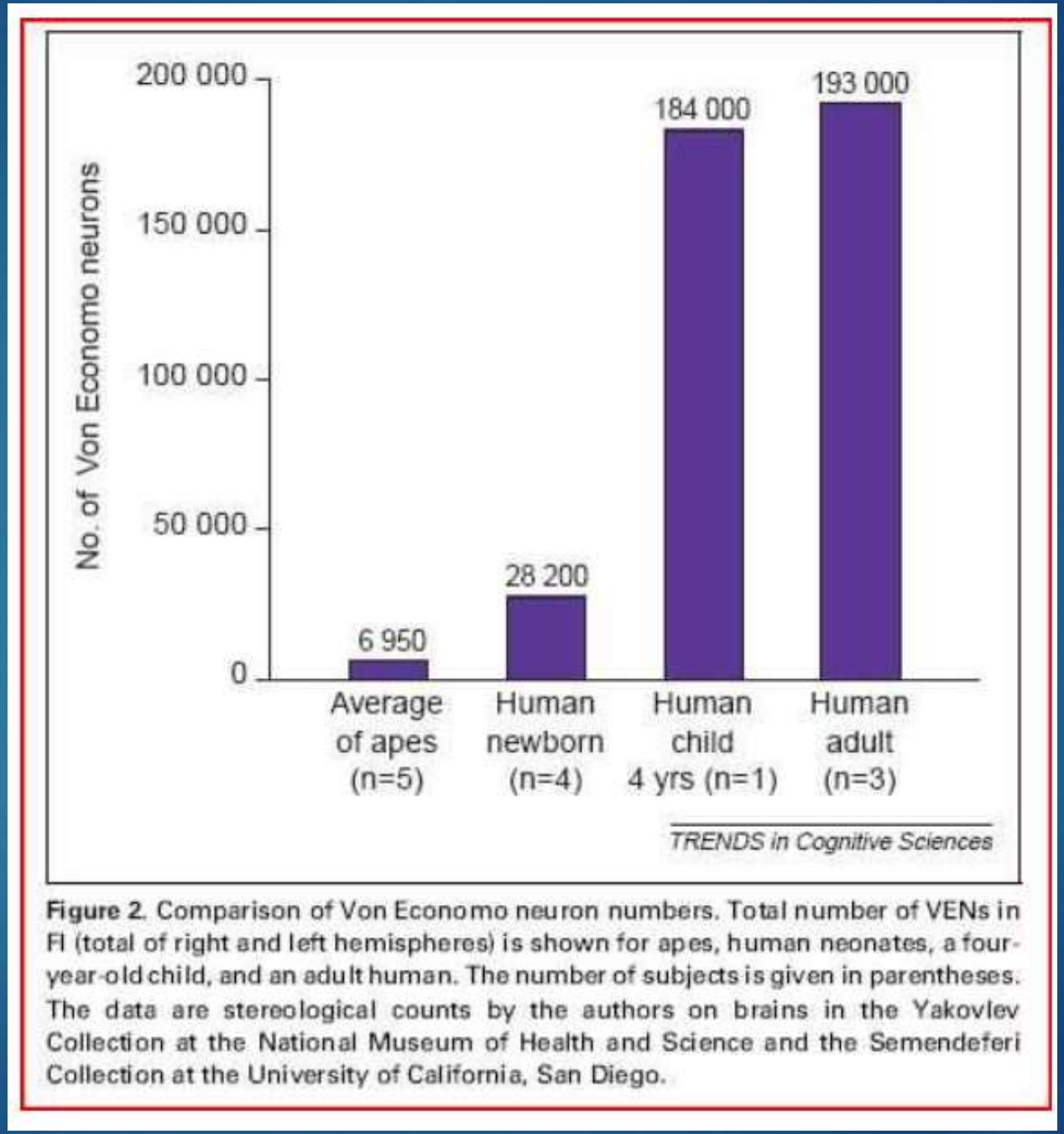


Figure 2. Comparison of Von Economo neuron numbers. Total number of VENs in FI (total of right and left hemispheres) is shown for apes, human neonates, a four-year-old child, and an adult human. The number of subjects is given in parentheses. The data are stereological counts by the authors on brains in the Yakovlev Collection at the National Museum of Health and Science and the Semendeferi Collection at the University of California, San Diego.

Salience Network: FI & pACC

- Salience Network: pACC, R insula (VENs), L inf OFC, R med PFC

- Activate in response to varied forms of social salience:
  - emotional dimensions of pain
  - empathy for pain
  - metabolic stress, hunger, or pleasurable touch
  - enjoyable "chills" to music
  - faces of loved ones or allies
  - social rejection
  - anxiety
- Damage: behave badly, fart humor

VENs: Involvement in neuropsychiatric disorders

- If you alter VENS, you produce deficits in social ability
- Frontal Temporal Dementia: destruction of Salience Network
  - 70% reduction VENs in ACC & FI; none in Alzheimer's
  - Correlates with behavioral severity of bvFTD

Seeley, Allman, and others 2007; Seeley and others 2006; Kim, et al. 2011

.

Toxic Stress

- Strong and prolonged activation of the body's stress management systems in the absence of the buffering protection of adult support.

- Precipitants include extreme poverty, physical or emotional abuse, chronic and serious neglect, enduring maternal depression, family violence.

- Disrupts brain architecture and leads to stress management systems that respond at relatively lower thresholds, thereby increasing the risk of stress-related physical and mental illness.

Social Basis of Early Brain Development

- Early experiences create brain neuron connections
- Parent-child interactions are key
- And when are they most effective?
- Neuroscience and other research says between birth and 3 to 4-years old

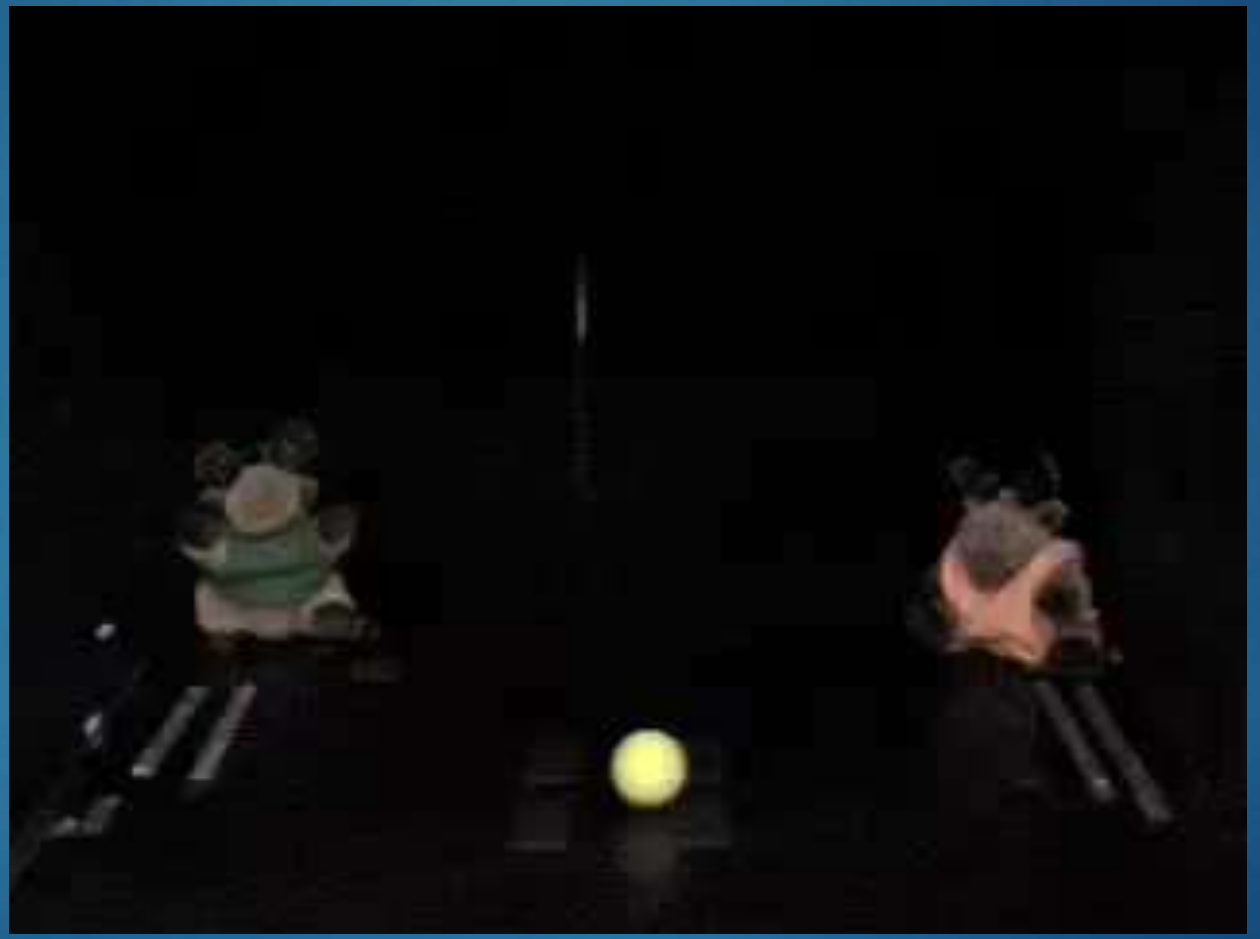
Neurobiology of Childhood Abuse

- Long term effects of early trauma/stress

- Effects Limbic circuits:
  - Amygdala = increased emotional reactivity (50 ms vs. 600ms for csness = 12 x faster),
  - Hippocampus = higher cortisol levels, stress sensitization, decreased neurogenesis

- Chronic Stress =
  - Smaller frontal regions
  - Smaller hippocampus,
  - More reactive amygdala (GABA↓= less inhibition)
  - Greater R Hemisphere activation

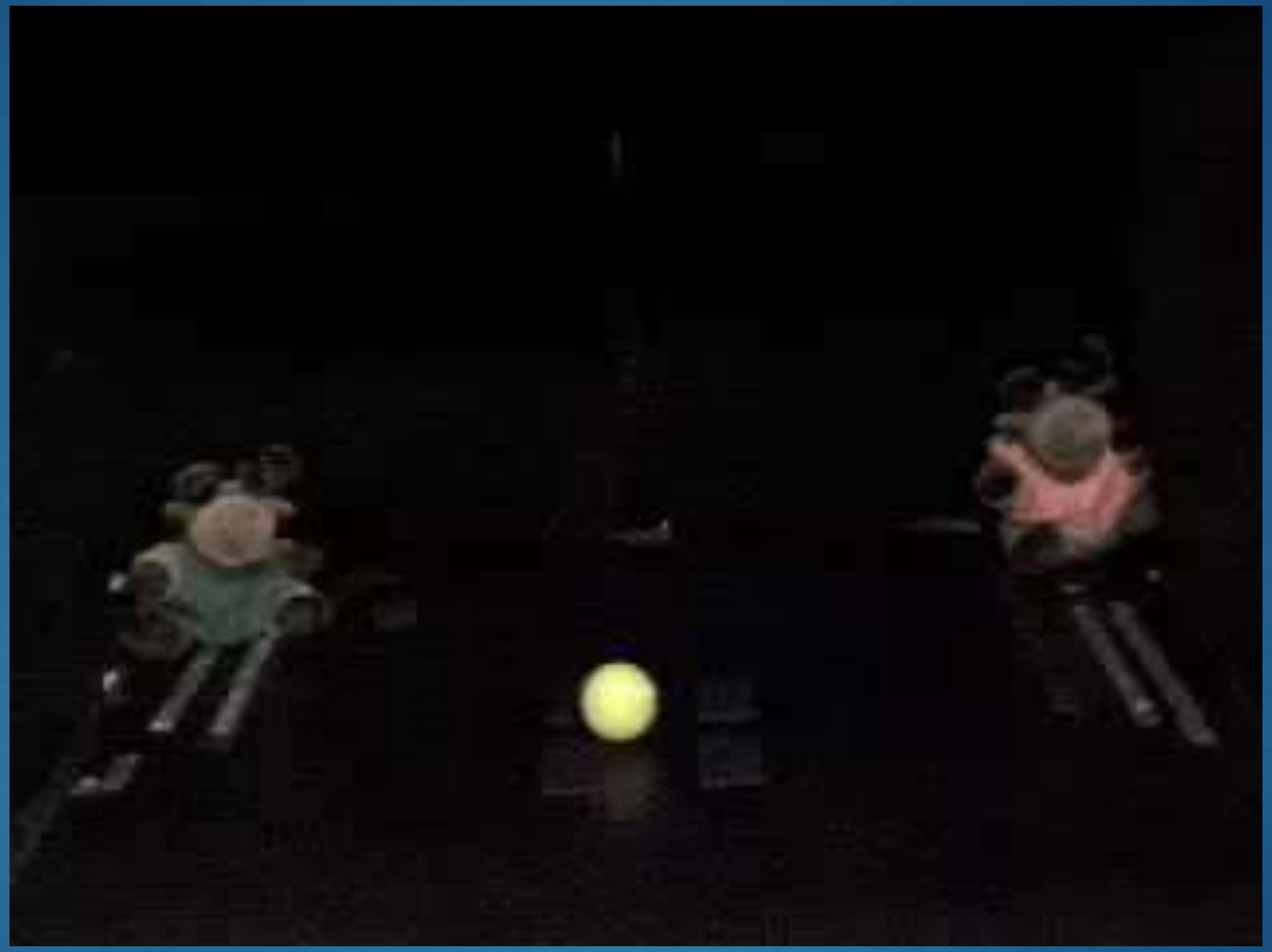
Giving



Notice colors of friendly Moose's shirts

Hamlin, J.K., & Wynn, K. (2011).

Taking



Notice Orange color of Taker

5 & 9 month old infants prefer prosocial to antisocial others

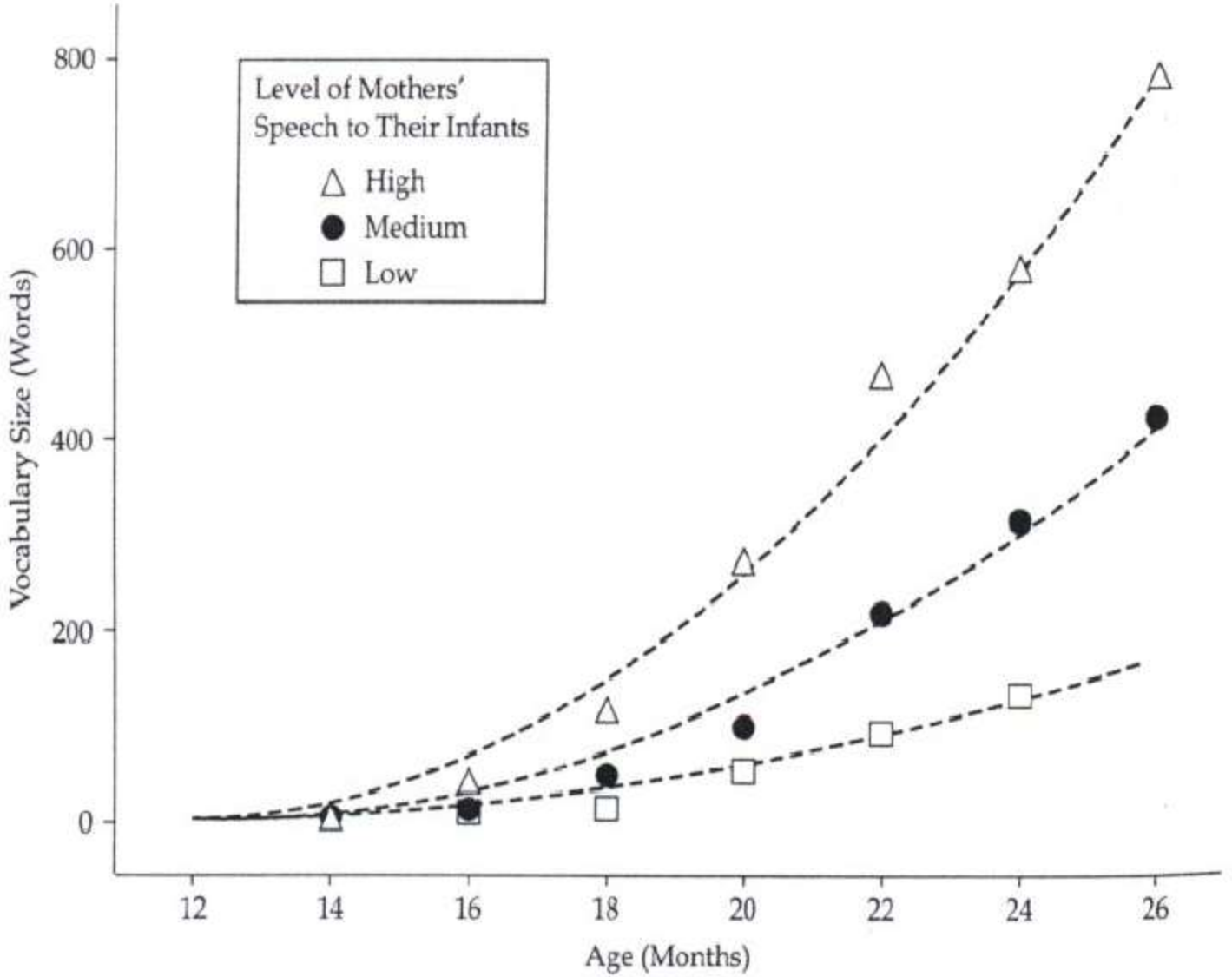
8 m old toddlers direct positive behaviors toward prosocial others & negative behaviors toward antisocial others.

Hamlin, J.K., & Wynn, K. (2011).

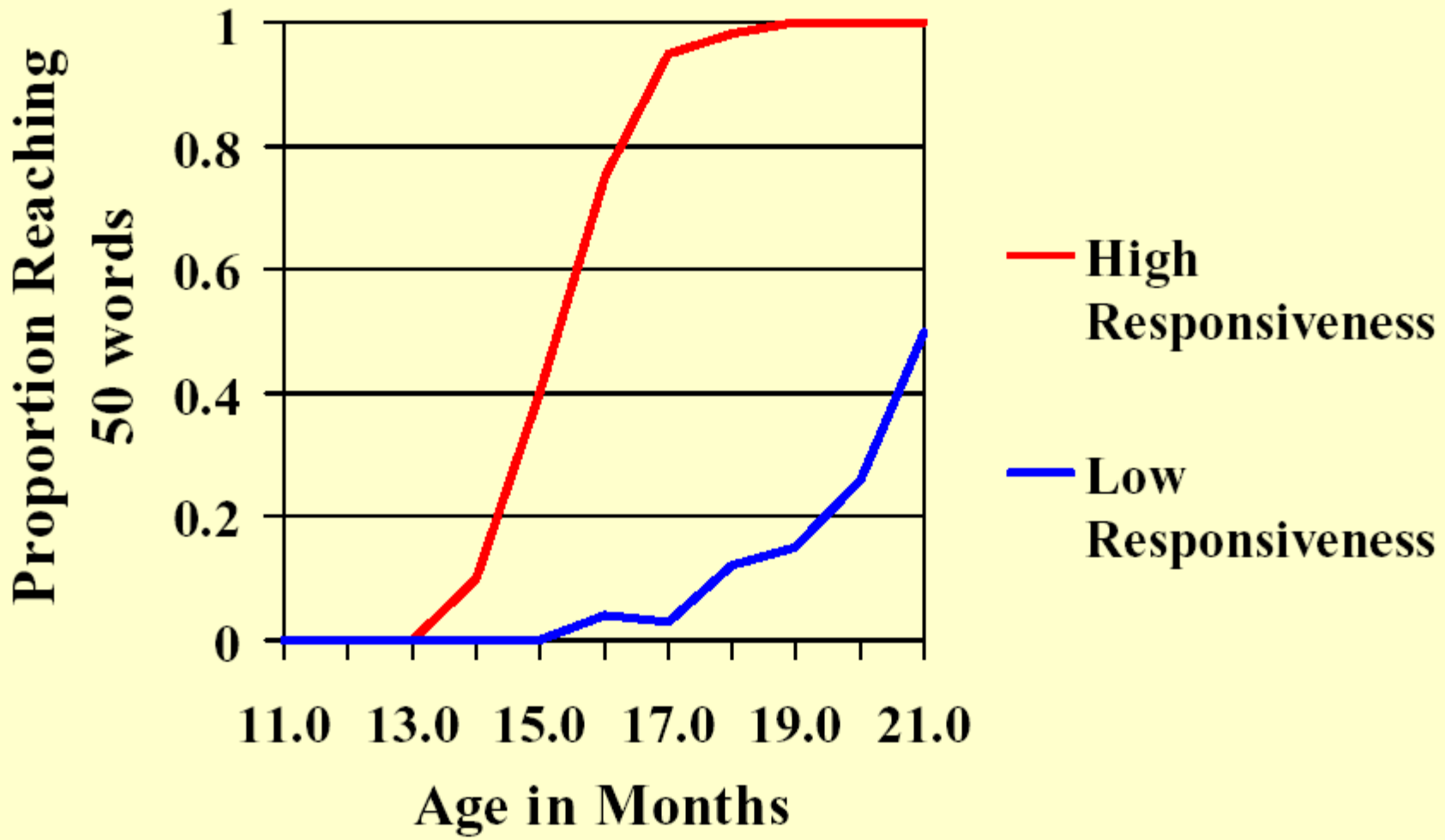
Babies…

- Scientists already know that babies expect some social graces:
- They expect people in a conversation to look at each other
- Talk to other people, not objects
- Are eager to see good guys rewarded and bad guys punished
- That they want to interact with nice people
- Before they have any friends themselves, young babies are already making predictions about how people get along: babies are also attuned to other people's relationships, even when those relationships have nothing to do with them.

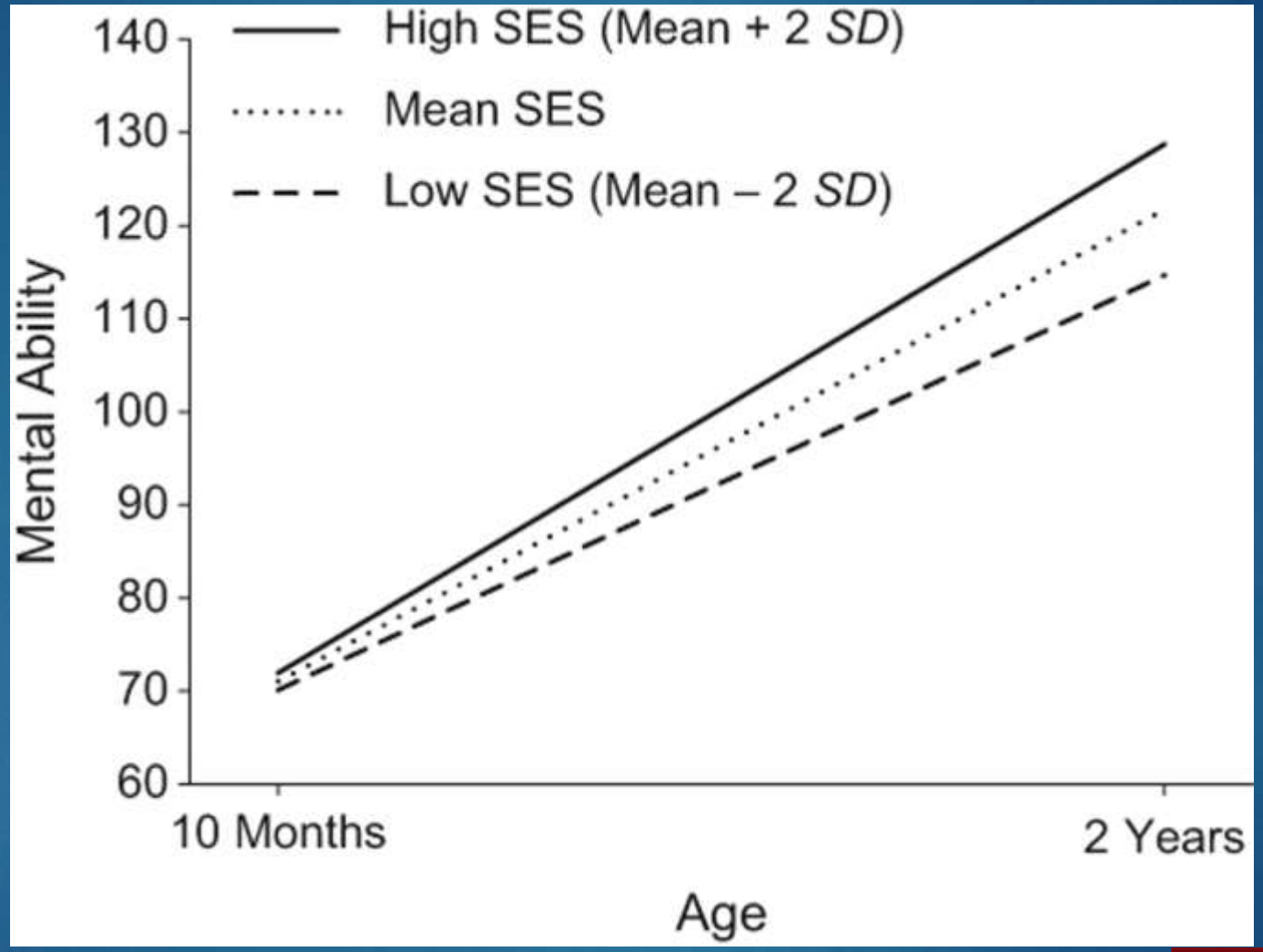
Effects of Mothers' Speech on Infant Vocabulary



Parenting and Word Acquisition



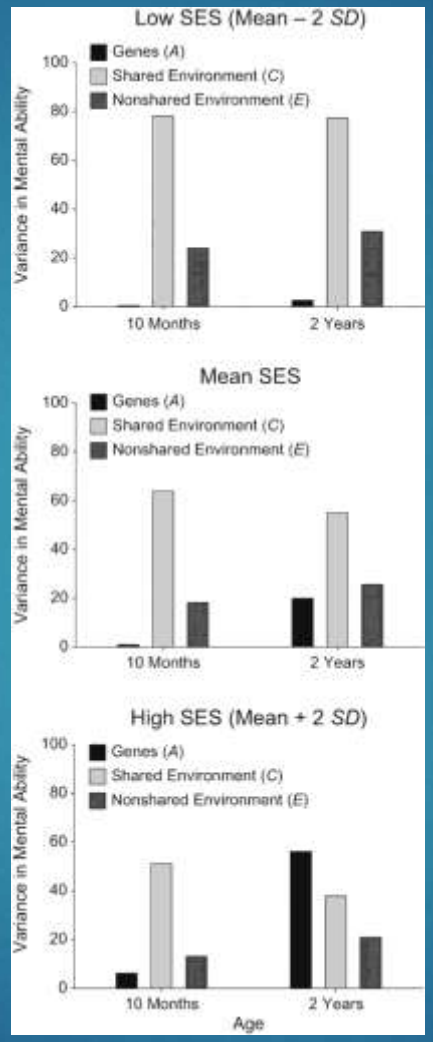
Mean longitudinal age trends in mental-ability scores for children being raised in homes with low, mean, and high levels of socioeconomic status (SES).



Tucker-Drob E M et al. Psychological Science 2010;0956797610392926

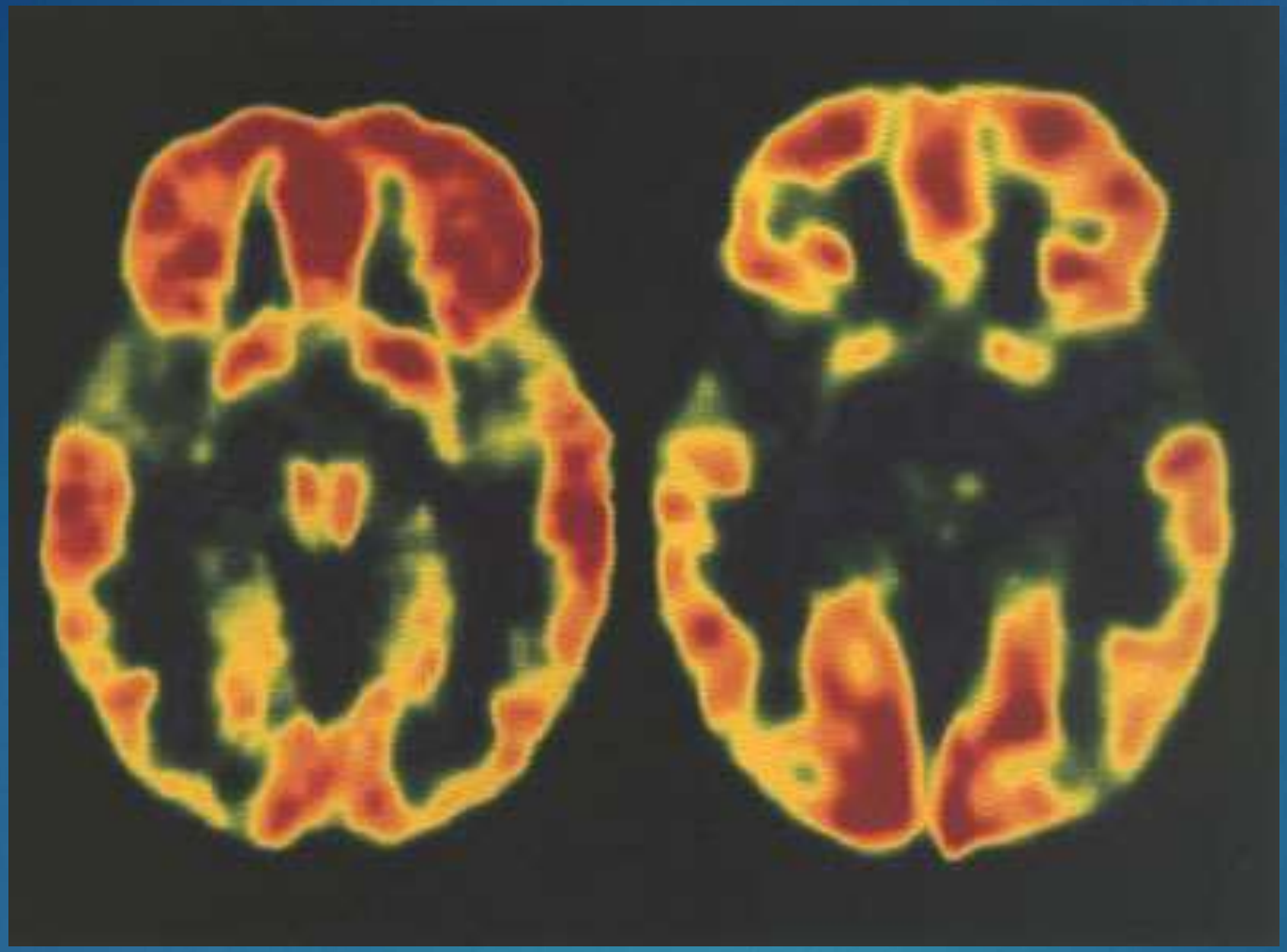
Psychological SCIENCE

Amounts of variance in mental-ability scores accounted for by genes (A), the shared environment (C), and the nonshared environment (E) at ages 10 months and 2 years.



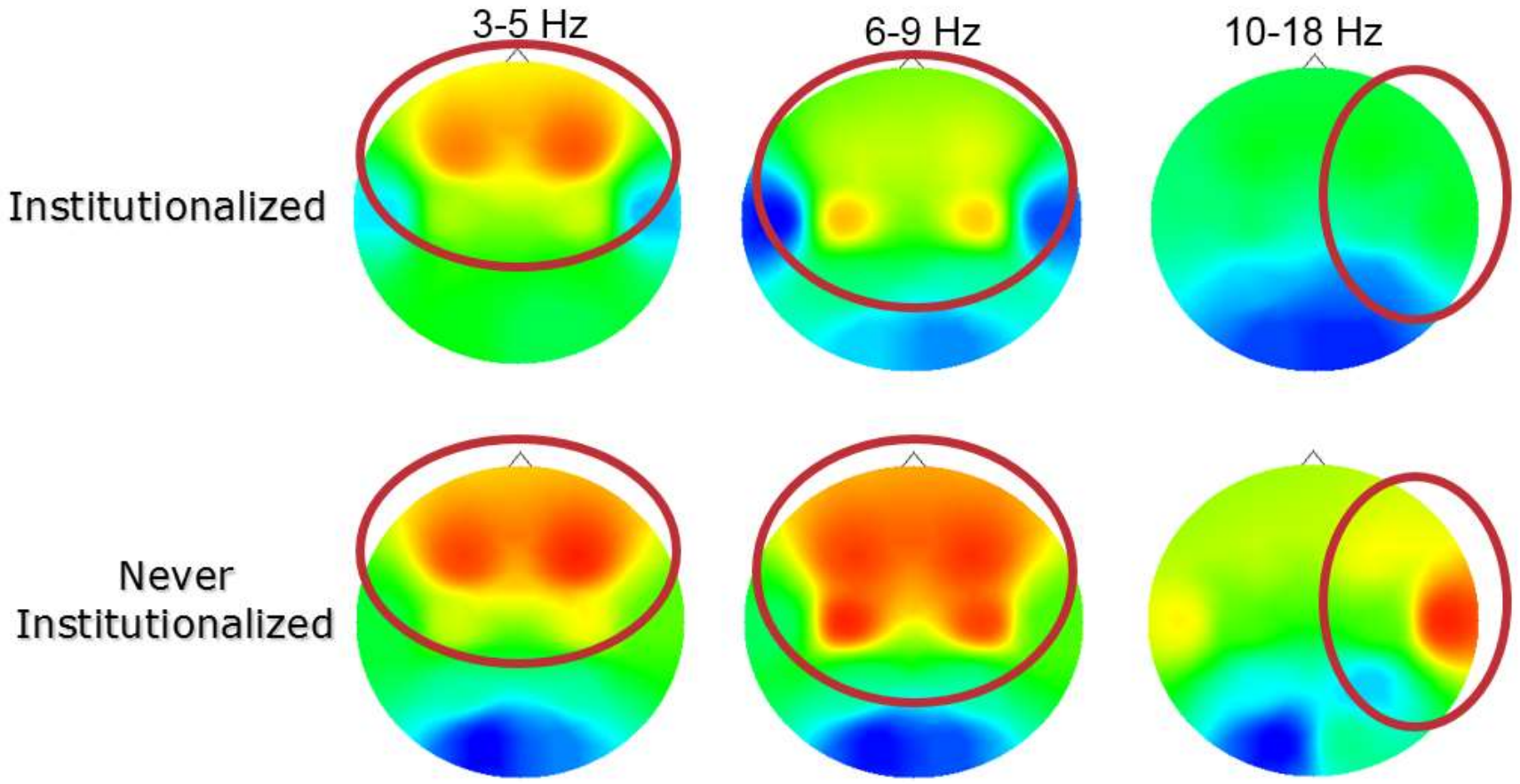
Tucker-Drob E M et al. Psychological Science 2010;0956797610392926

Psychological SCIENCE



Brain activity of a normal 5-year-old child (left) and a 5-year-old institutionalized Romanian orphan who was neglected in infancy (right).

Extreme Neglect Diminishes Brain Power



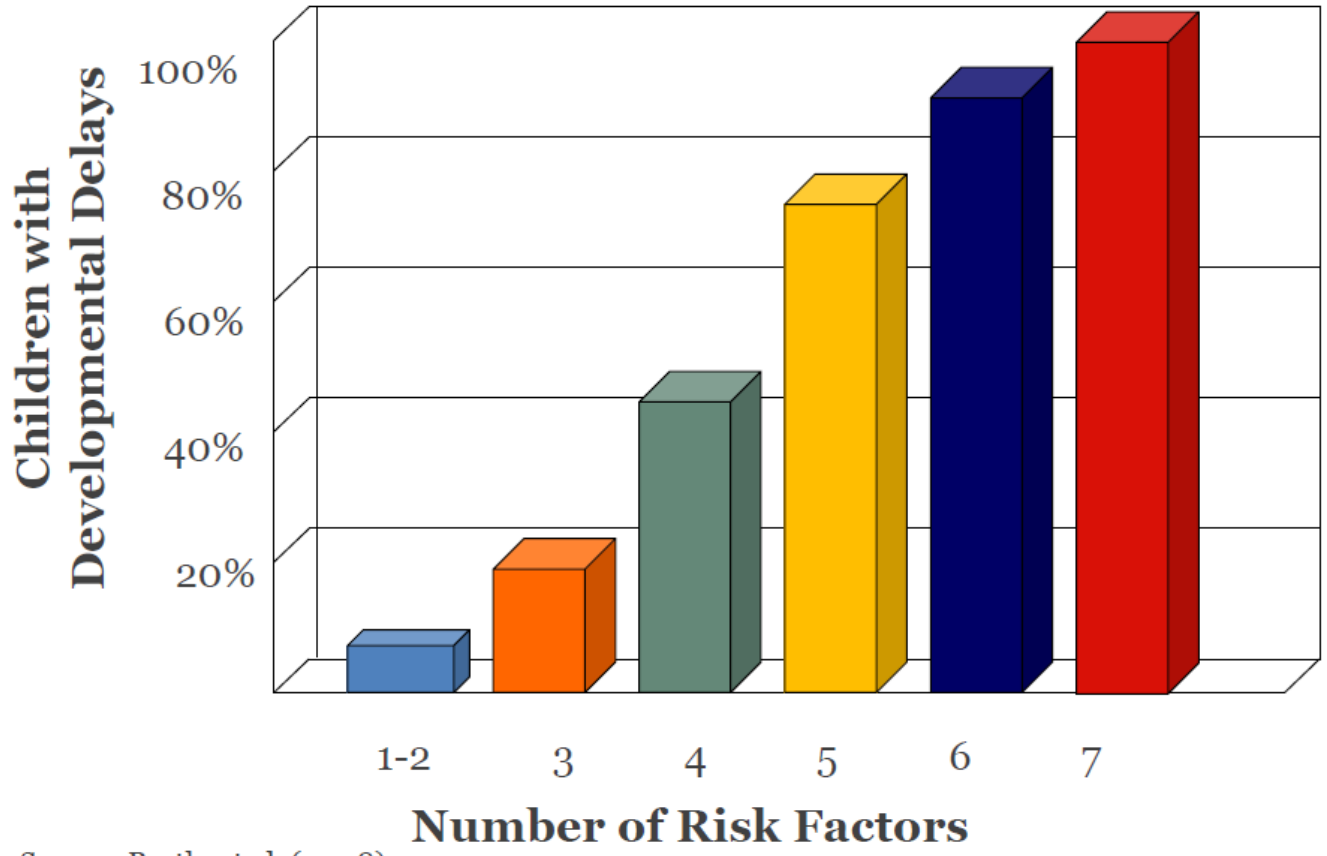
Source: C. Nelson (2008)

Long term effects of early experience

- "The Long Shadow": Baltimore Beginning School Study: only 4 % of disadvantaged children earned college degrees by age 28.
- Adverse Childhood Experience (ACEs) predict adult health and longevity
- Bucharest Early Intervention Project
- Felletti: ACEs are better predictors of adult medical status than most medical tests

http://acestudy.org/

Significant Adversity Impairs Development in the First Three Years



Data Source: Barth, et al. (2008)

Graph Courtesy: Center on the Developing Child at Harvard University

Read to your kids & grandkids!

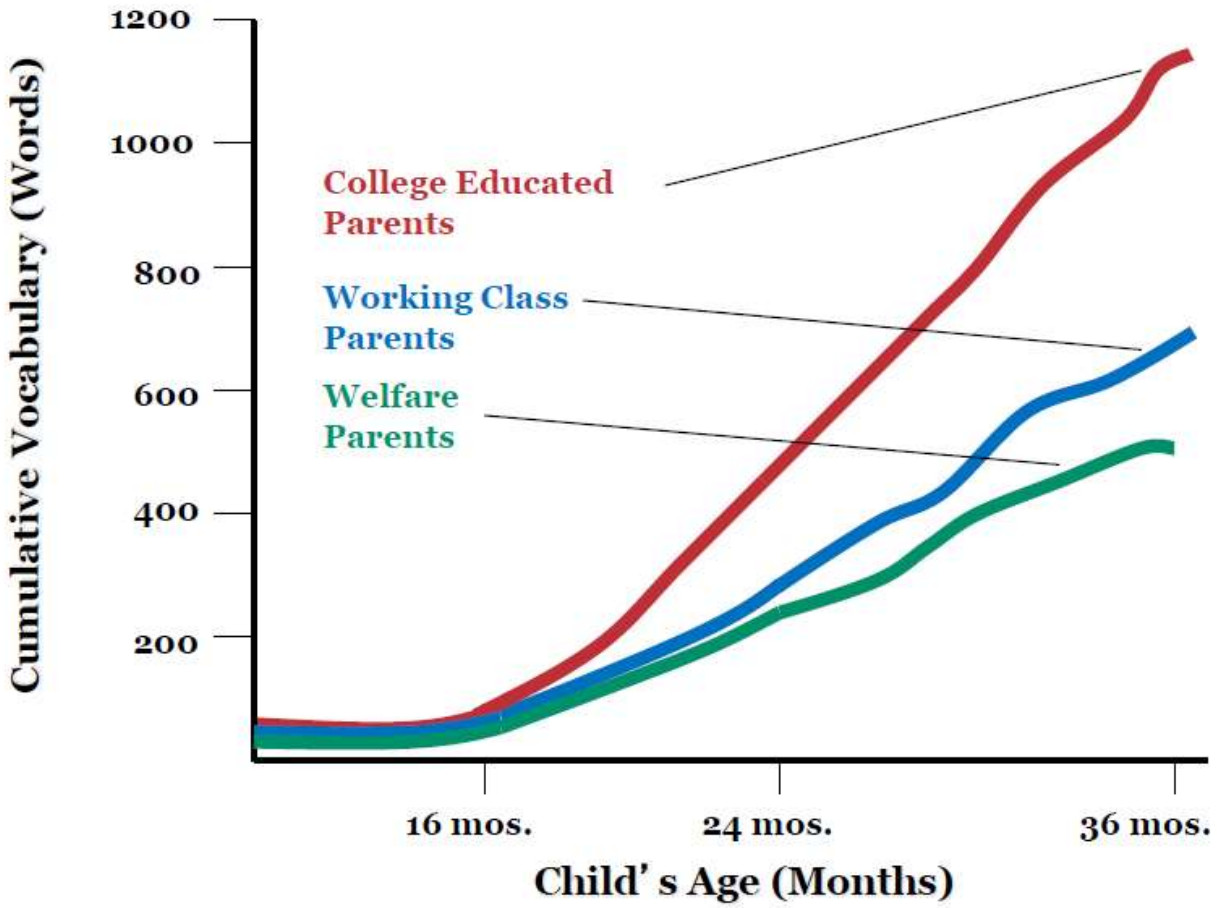
- Hart and Risley (1995) revealed that pre-4 aged children in high-income families are exposed to 30 million more words than children from families on welfare.

- Quantity: 2 1/2 years of observing 42 families for an hour each month
  - Low SES: 600 words spoken to child per day (5 affirmations vs 11 prohibitions: ratio of 1 to 2)
  - High SES: 2100 words spoken to child per day (32 affirmations vs 5 prohibitions: ratio of 6 to 1)

- Idea density depends on vocabulary & reading comprehension; best way to increase both is to read to your children starting early in life

Hart, B. & Risley, T.R. "The Early Catastrophe: The 30 Million Word Gap by Age 3" (2003, spring). *American Educator, pp.4-9.*.

Barriers to Educational Achievement Emerge at a Very Young Age



Data Source: Hart & Risley (1995)

Environmental impact on brain

- Lower maternal education is linked to poorer processing of auditory information, reading and working memory ability in the adolescent brain

- You are twice as likely to show epigenetic methylation changes based on family income during early childhood versus economic status as adults.

A Traumatized Child Grows Up:
Stress response becomes social culture

- How social interaction becomes neurological:

•A girl grows up in a household where there is domestic violence, which triggers her fight or flight stress response, which affects the way the hormone receptors in her brain develop, and her stress-regulation system goes off track.

- She tends to overreact to confrontation or she doesn't recognize risky situations and feels comfortable only around a lot of drama.

A Traumatized Child Grows Up 2

- She ends up with an abusive partner, who beats her kids.
- Her son goes to school where 10 of 30 kids come from same background, creating a classroom culture of fighting.
- When they are teenagers, they behave violently, and beat their kids.
- It becomes the cultural norm. The circle starts again

Traumagenic neurodevelopmental model

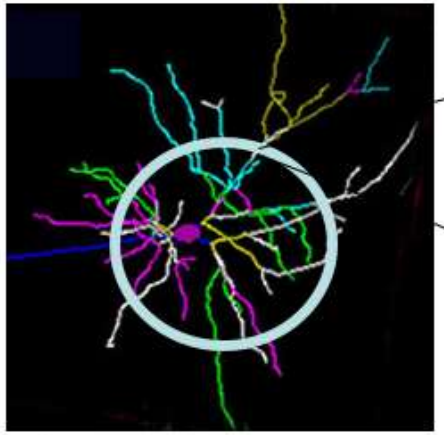
- Traumagenic neurodevelopmental model:
  - heightened sensitivity to stress, increases emotional reactivity to everyday experiences
  - originates in neurodevelopmental changes to the brain
  - caused by trauma in the early years.

- Childhood adversity plays a causal role in most mental health problems
  - in childhood (e.g., conduct disorder, ADHD and oppositional defiant disorder)

J. Read, et al., 2014

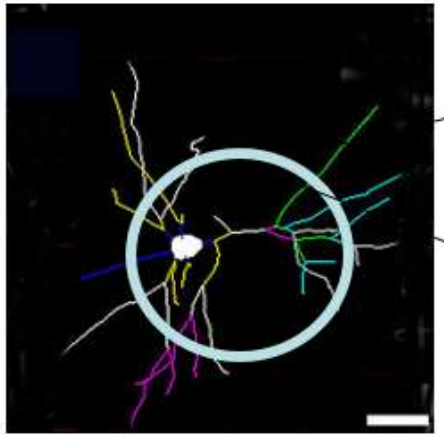
Persistent Stress Changes Brain Architecture

Normal



Typical - neuron with many connections

Chronic stress

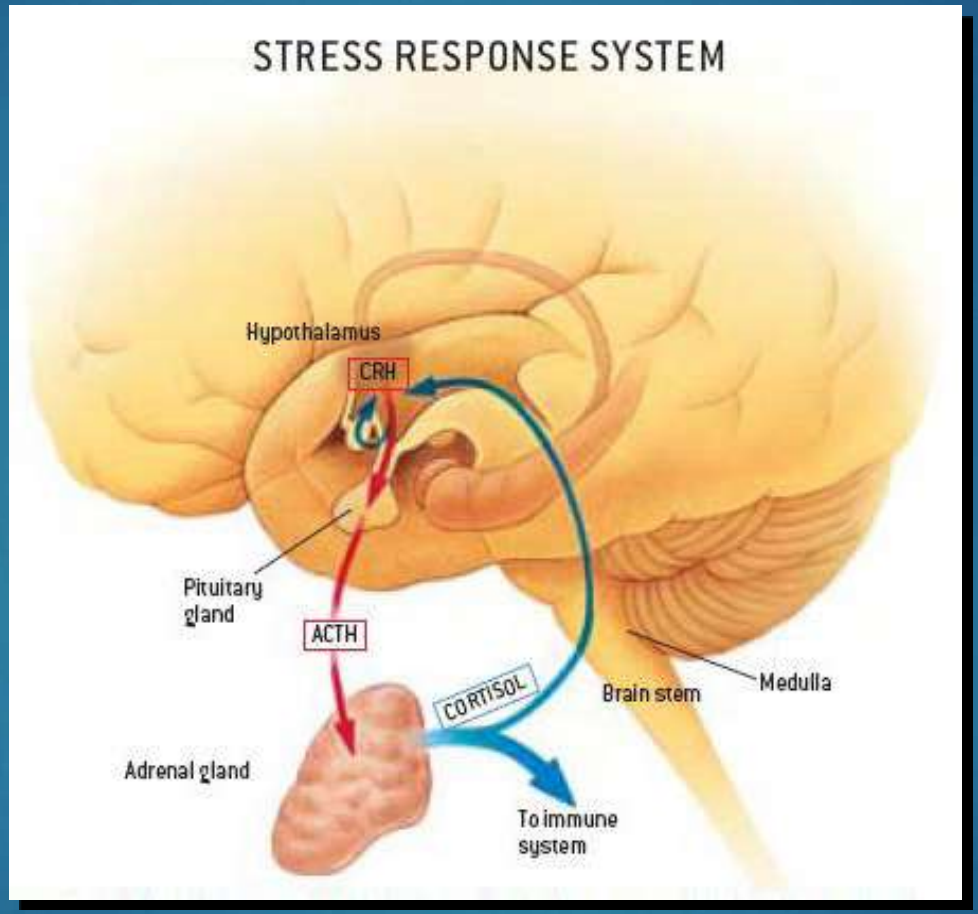


Neuron damaged by toxic stress – fewer connections

Prefrontal Cortex and Hippocampus

Source: C. Nelson (2008)
Bock et al Cer Cort 15:802 (2005)

Hypothalamo-Pituitary-Adrenocortical (HPA) Axis



HPA axis is a critical feature of the stress response. It is managed by a set of genes expressed in the hippocampus, including one that is epigenetically marked by the experience of childhood abuse.

HPA: Hypothalamus-Pituitary-Adrenal Axis

- HPA is a neuroendocrine control system for initiation, regulation, & termination of glucocorticoid secretions in response to stress.
- Glucocorticoid receptors influence metabolic & inflammatory processes.
- Involves Cortex, Hippocampus (inhibition), & amygdala (excitation), immune system
- Triggers release of CRH & vasopressin, which act on pituitary, which releases ACTH, which affects Adrenal cortex which releases cortisol
- Chronic stress = high cortisol levels (kills hippocampal cells, turns off neurogenesis)
- Affects depression, anxiety, and development of ACEs

Neurological Consequences of trauma

- HPA dysregulation: Severe early social adversity can induce a cascade of long-term disturbances in the HPA axis:
- **O**ver-activity of the hypothalamic–adrenal–pituitary (HPA) axis→→
- Causes dopamine, serotonin and norepinephrine abnormalities →→
- Creates structural differences such as hippocampal damage, cerebral atrophy, ventricular enlargements and reversed cerebral asymmetry.

Stress Decreases Frontal Lobe Volume

- Changes following severe stress:
  - dendritic retraction and debranching,
  - reduced volume in vmPFC and mPFC and ACC.

- Gray matter volume losses in the frontal lobes in adults exposed to child adversities/ACEs:
  - dorsolateral and medial prefrontal
  - orbitofrontal regions
  - anterior cingulate

Stress & BDNF

- Severe stress
  - reduces the expression of BDNF
  - excessive glucocorticoids interfere with BDNF signaling.

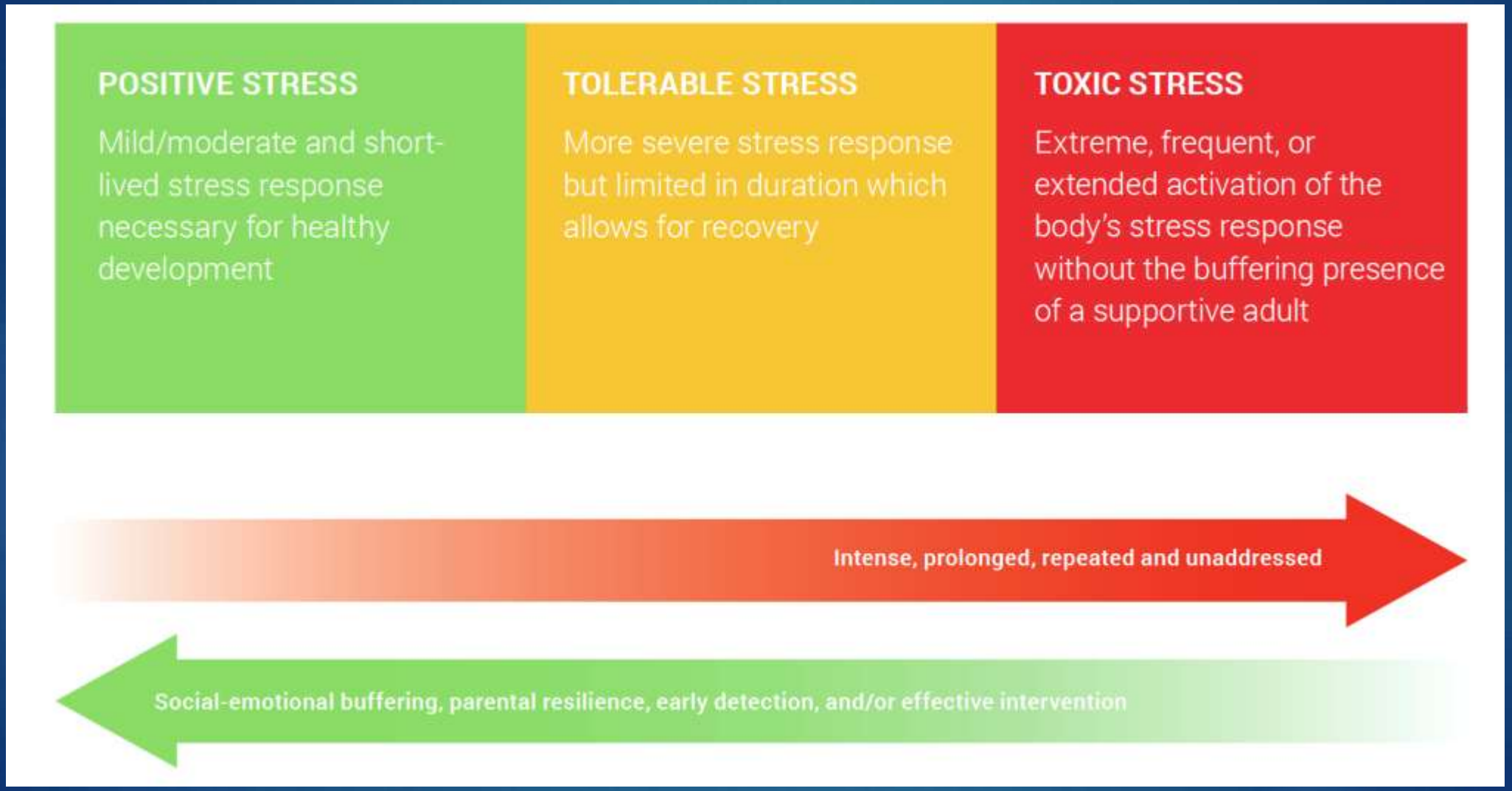
- Mechanism mediating early-life stress and BDNF reductions in rat studies includes:
  - reduced *BDNF* gene activity, observed in the prefrontal cortex, hippocampus and amygdala,
  - caused by changed epigenetic marking

Trauma and Brain Response

- If traumatic memory is evoked:
  - Right Hemisphere increased activation:
    - limbic
    - amygdala
    - visual centers
  - Decreased Left Broca's area (translating personal experiences into communicable language)

Rauch SL., van der Kolk BA., Fisler RE., et al., 1996

Stress


POSITIVE STRESS
Mild/moderate and short-lived stress response necessary for healthy development
TOLERABLE STRESS
More severe stress response but limited in duration which allows for recovery
TOXIC STRESS
Extreme, frequent, or extended activation of the body's stress response without the buffering presence of a supportive adult
Intense, prolonged, repeated and unaddressed
Social-emotional buffering, parental resilience, early detection, and/or effective intervention

Adverse Childhood Experiences: Felitti and Anda

Growing up (prior to age 18) in a household with:

- Recurrent physical abuse.
- Recurrent emotional abuse.
- Sexual abuse.
- An alcohol or drug abuser.
- An incarcerated household member.
- Someone who is chronically depressed, suicidal, institutionalized or mentally ill.
- Mother being treated violently.
- One or no parents.
- Emotional or physical neglect.

Robert F. Anda, MD, and Vincent J. Felitti, MD,

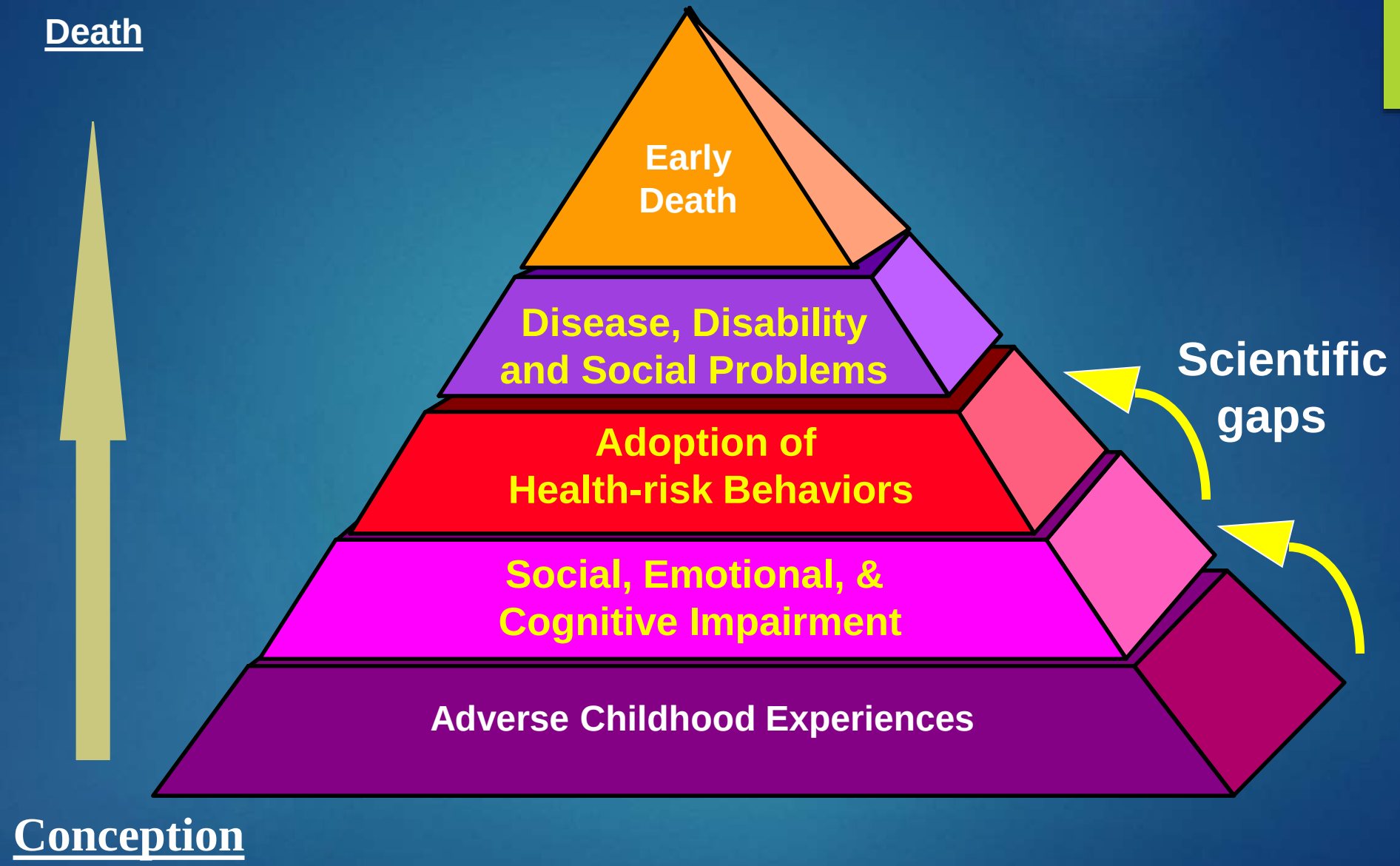
The three types of ACEs include

ABUSE	NEGLECT	HOUSEHOLD DYSFUNCTION
Physical	Physical	Mental Illness
Emotional	Emotional	Incarcerated Relative
Sexual		Mother treated violently
		Substance Abuse
		Divorce

Types of Adverse Childhood Experiences
Image courtesy of the Robert Wood Johnson Foundation

Adverse Childhood Experiences:

- Original study: 75 % Caucasian & college educated
- Estimate: 17% of all Caucasians, AA, Hispanic
- Nadine Burke Harris (Center for Youth Wellness): need to include:
  - Impoverished family
  - Experience of repeated discrimination
  - Experience of community violence
  - Being undocumented or deported
- Toxic Stress is known to alter
  - Brain structure and neurodevelopment
  - Epigenetics
  - Immune Response
- Need for routine pediatric screening (how many, not which; for mandatory reporting)


Death
Early Death
Disease, Disability and Social Problems
Adoption of Health-risk Behaviors
Social, Emotional, & Cognitive Impairment
Adverse Childhood Experiences
Scientific gaps
Conception

ACE Effects

Adverse Childhood Experiences Are Common

Household dysfunction:

Substance abuse	27%
Parental sep/divorce	23%
Mental illness	17%
Battered mother	13%
Criminal behavior	6%

Abuse:

Psychological	11%
Physical	28%
Sexual	21%

Neglect:

Emotional	15%
Physical	10%

Prevalence (%) of Early Trauma (ACEs)

Number of Adverse Childhood Experiences (ACE Score)	Women	Men	Total
0	34.5	38.0	36.1
1	24.5	27.9	26.0
2	15.5	16.4	15.9
3	10.3	8.6	9.5
4 or more	15.2	9.2	12.5

Felitti

N= 17,000: 87% had at least one ACE; -More than one third had 2 or more ACEs

15-20% of all of your patients will have a significant traumatic background

Hidden Crisis Report, 2014: a major public health crisis

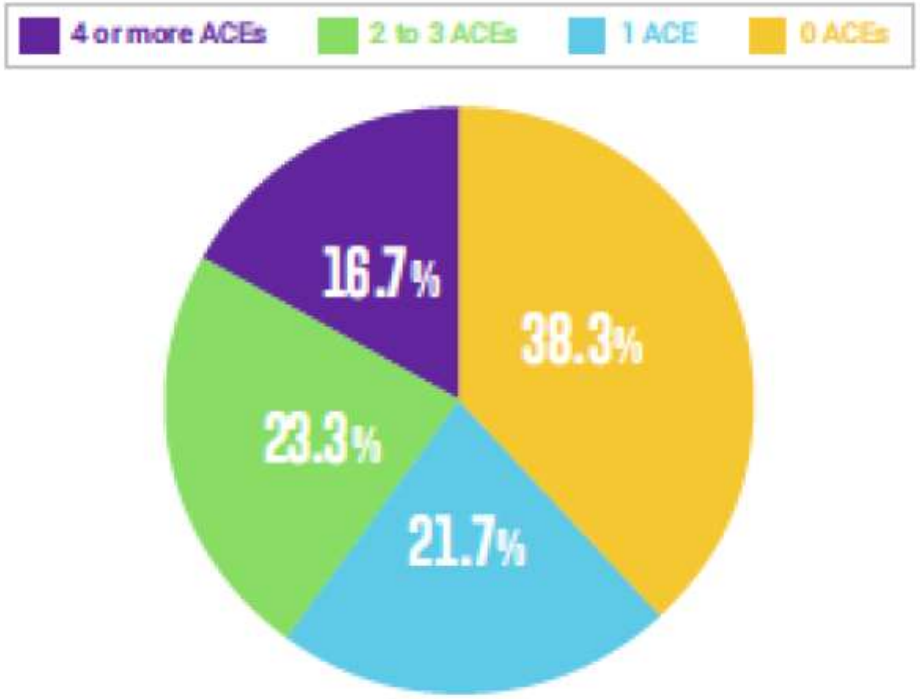
- California Behavioral Risk Factor Surveillance System: 27,745 adults conducted in 2008, 2009, 2011 and 2013 by the California Department of Public Health; county by county experience of ACES
- Long-term and far-reaching consequences of childhood exposure to trauma and chronic adversity
- Nearly 62 % of Californians have experienced at least one or more types of ACEs with 17% exposed to 4 or more ACES

ACES by California Counties

- In counties with the lowest prevalence of ACEs, 1 of 2 people has had at least 1 ACE in childhood.
- 4 or more ACEs:
  - Mendocino and Humboldt Counties combined (30.8 %)
  - Butte County (30.3 %)
  - Riverside County (19.5 %)
  - San Bernardino County (19.4 %)
  - San Diego County (14.5%)
  - Orange County (14.2 %)
  - Los Angeles County (13.5 %)
  - Santa Clara County (11%)
  - San Francisco County (9 %)

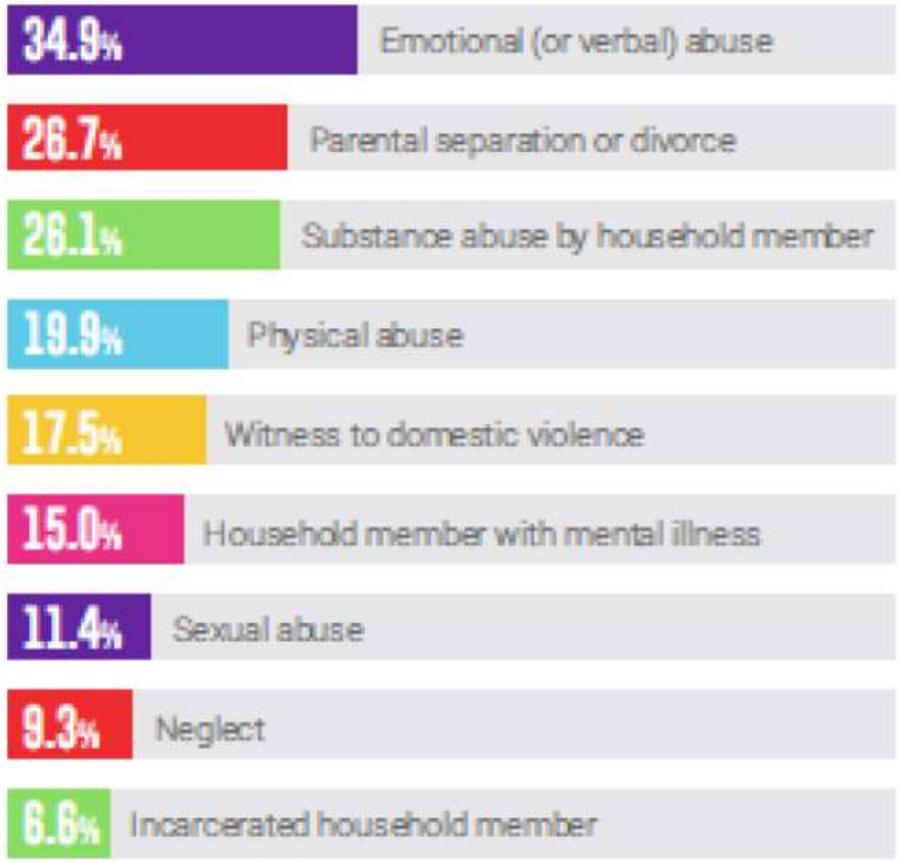
KEY FINDINGS

In California, **61.7%** of adults have experienced at least one ACE and **one in six**, or 16.7%, have experienced four or more ACEs. The most common ACE among California adults is emotional (or verbal) abuse.

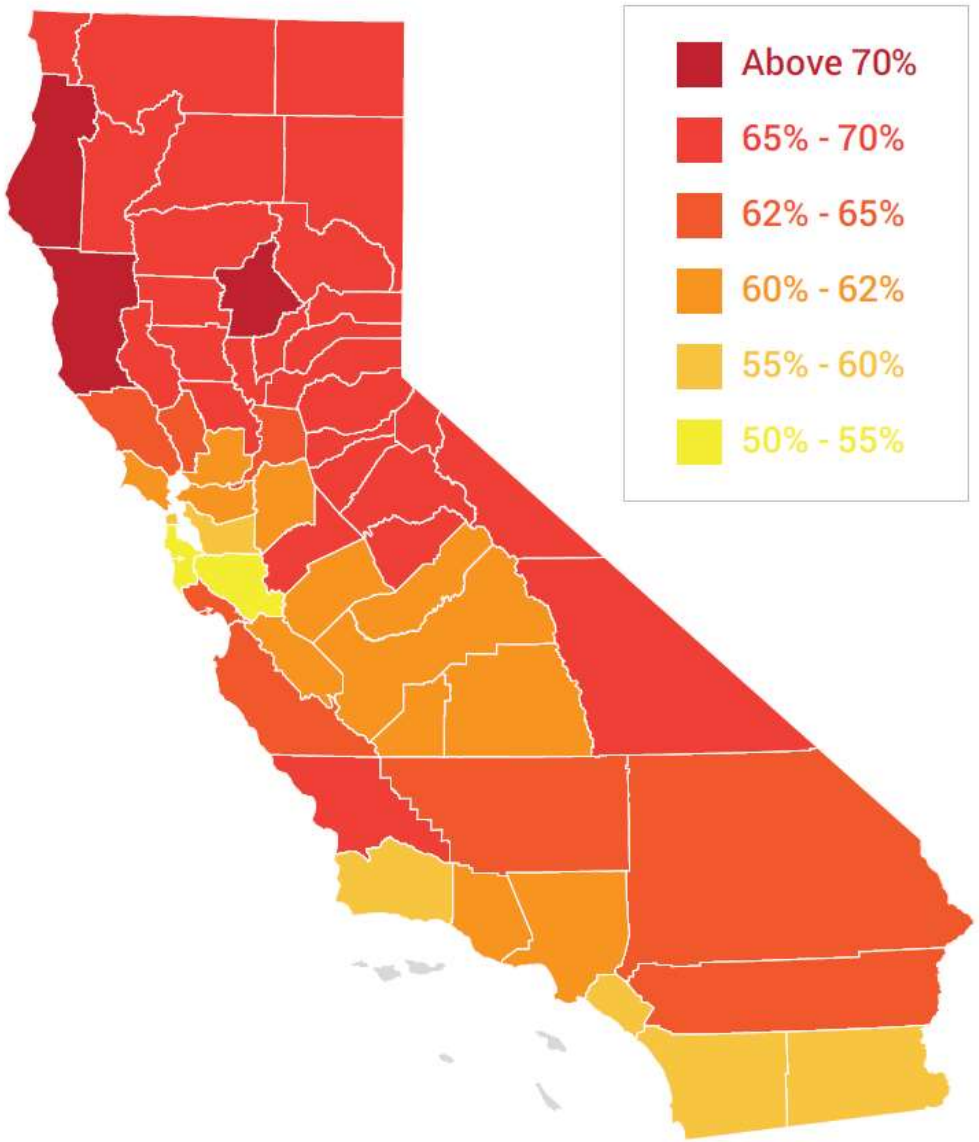


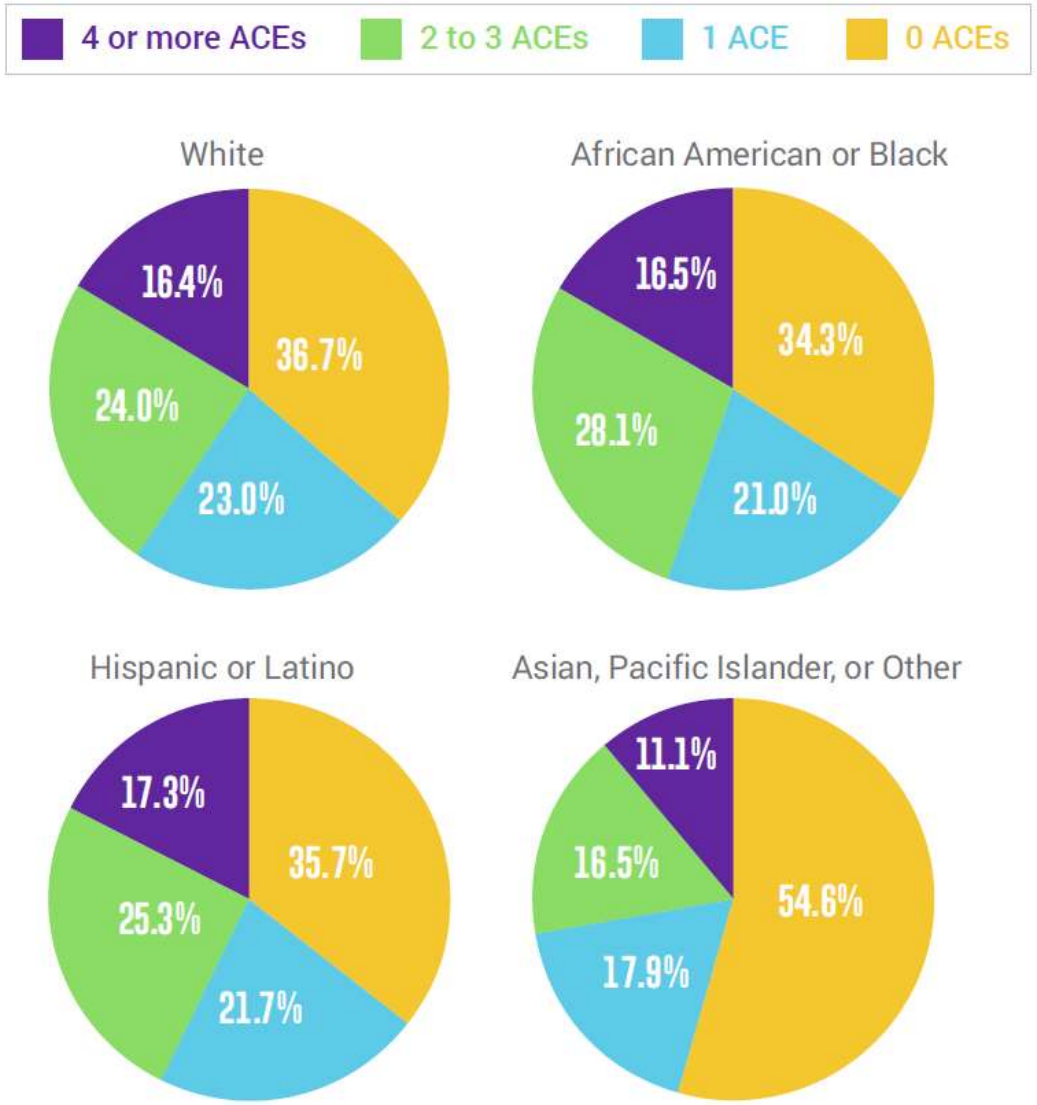
Prevalence of number of ACEs among California adults

Most common ACEs among California Adults



Most common ACEs among California adults


Above 70%
65% - 70%
62% - 65%
60% - 62%
55% - 60%
50% - 55%


4 or more ACEs
2 to 3 ACEs
1 ACE
0 ACEs
White
16.4%
24.0%
23.0%
36.7%
African American or Black
16.5%
28.1%
21.0%
34.3%
Hispanic or Latino
17.3%
25.3%
21.7%
35.7%
Asian, Pacific Islander, or Other
11.1%
16.5%
17.9%
54.6%

ACE Scores predict adult medical outcome

- 1 in 6 had 4 or more traumas
- High correlation between Ace score and negative adult medical outcome
- Linear dose-response model: the higher the ACE score, the worse the outcome on almost every medical illness

The ACE Study uses the ACE Score, which is a count of the total number of ACE respondents reported. The ACE Score is used to assess the total amount of stress during childhood and has demonstrated that as the number of ACE increase, the risk for the following health problems increases in a strong and graded fashion:

- Alcoholism and alcohol abuse
- Chronic obstructive pulmonary disease (COPD)
- Depression
- Fetal death
- Health-related quality of life
- Illicit drug use
- Ischemic heart disease (IHD)
- Liver disease
- Risk for intimate partner violence
- Multiple sexual partners
- Sexually transmitted diseases (STDs)
- Smoking
- Suicide attempts
- Unintended pregnancies
- Early initiation of smoking
- Early initiation of sexual activity
- Adolescent pregnancy

Linear dose-response increase

Adult Outcomes 2

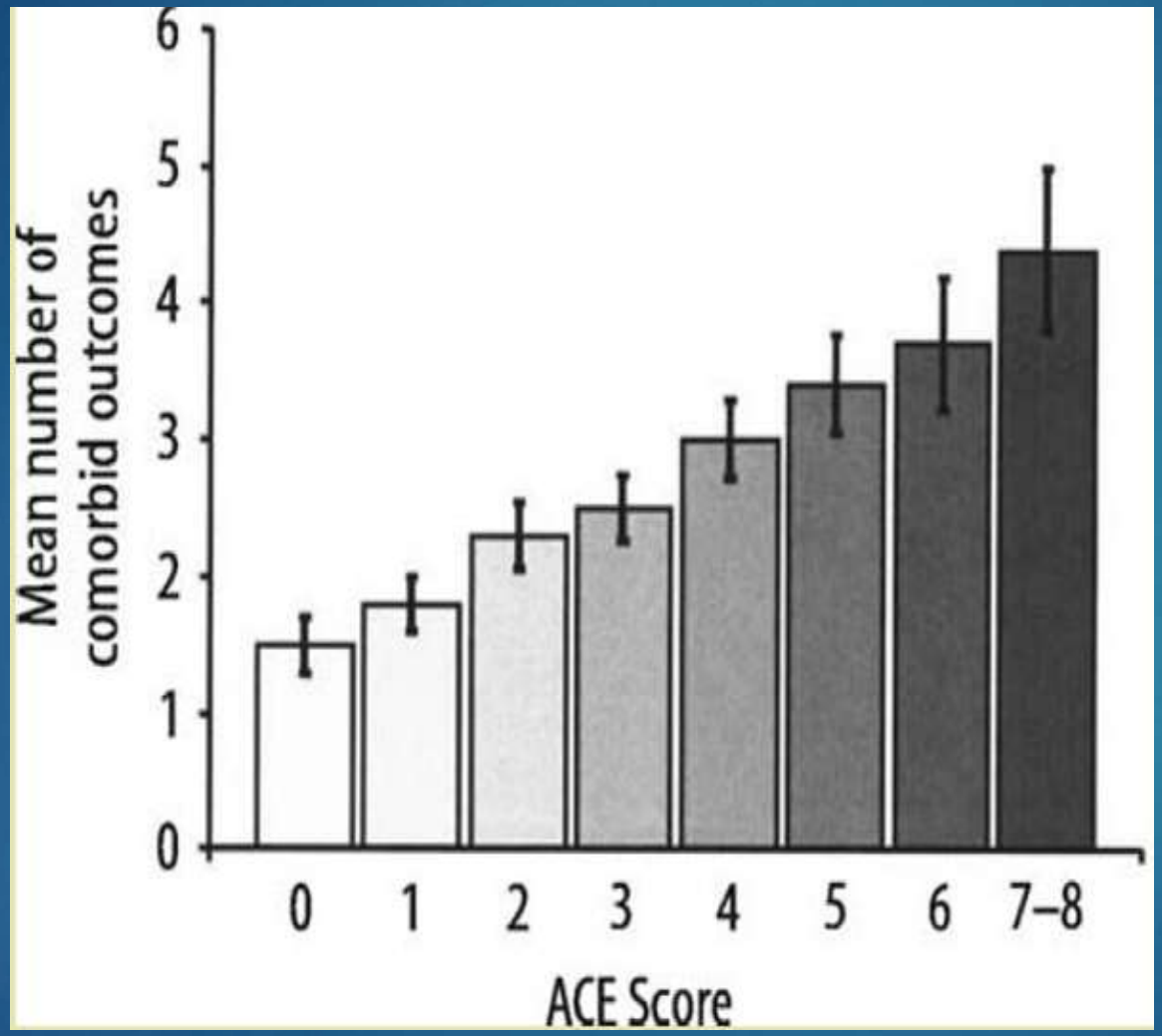
- Felitti's 1st theory: negative outcomes via "bad" behaviors,
  i.e. smoking, heavy drinking, overeating

- Data indicated ACEs had profound negative impact even when no "bad" behaviors were present:
  pts with 7+ who did not smoke, drink, or overeat, had ischemic heart disease 360x higher than 0 scorers

Dunedin, NZ Study: 30 years, n = 1000

- Incidence of early trauma among the Dunedin cohort is similar to that of the Kaiser respondents.
- The data in the Dunedin study, however, are prospective, not retrospective
- 40% of the children encountered one or more ACEs.
- Similar correlations between early trauma and later health problems: the children who were victims of maltreatment were almost three times as likely to experience major depression by their early thirties, and they were almost twice as likely to have an elevated risk of heart disease.
- Twice as likely to have elevated levels of an inflammatory protein in their blood—high-sensitivity C-reactive protein

Higher the Ace score, greater the negative outcome

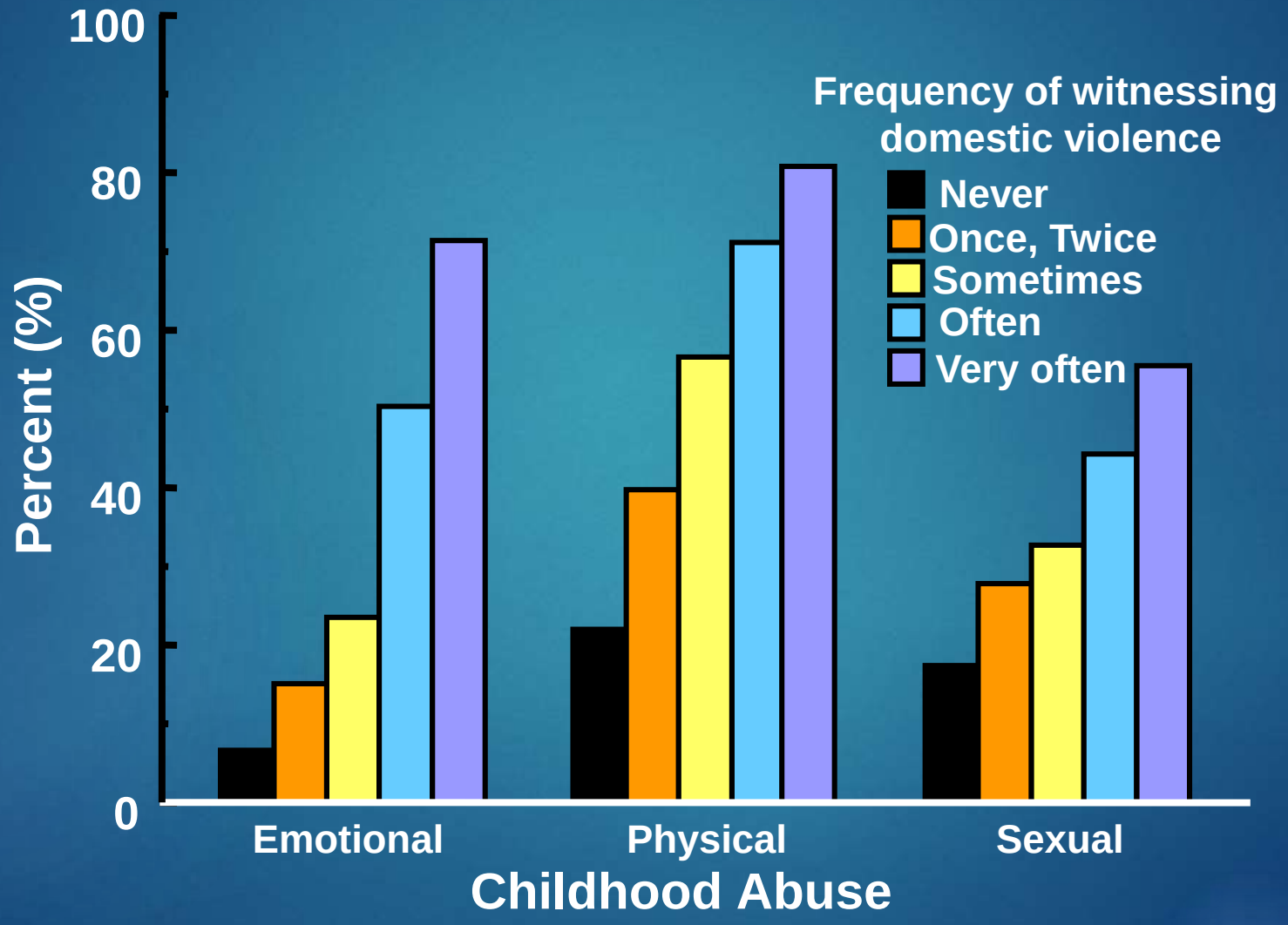


Adverse Childhood Experiences Rarely Occur in Isolation…

They come in groups.

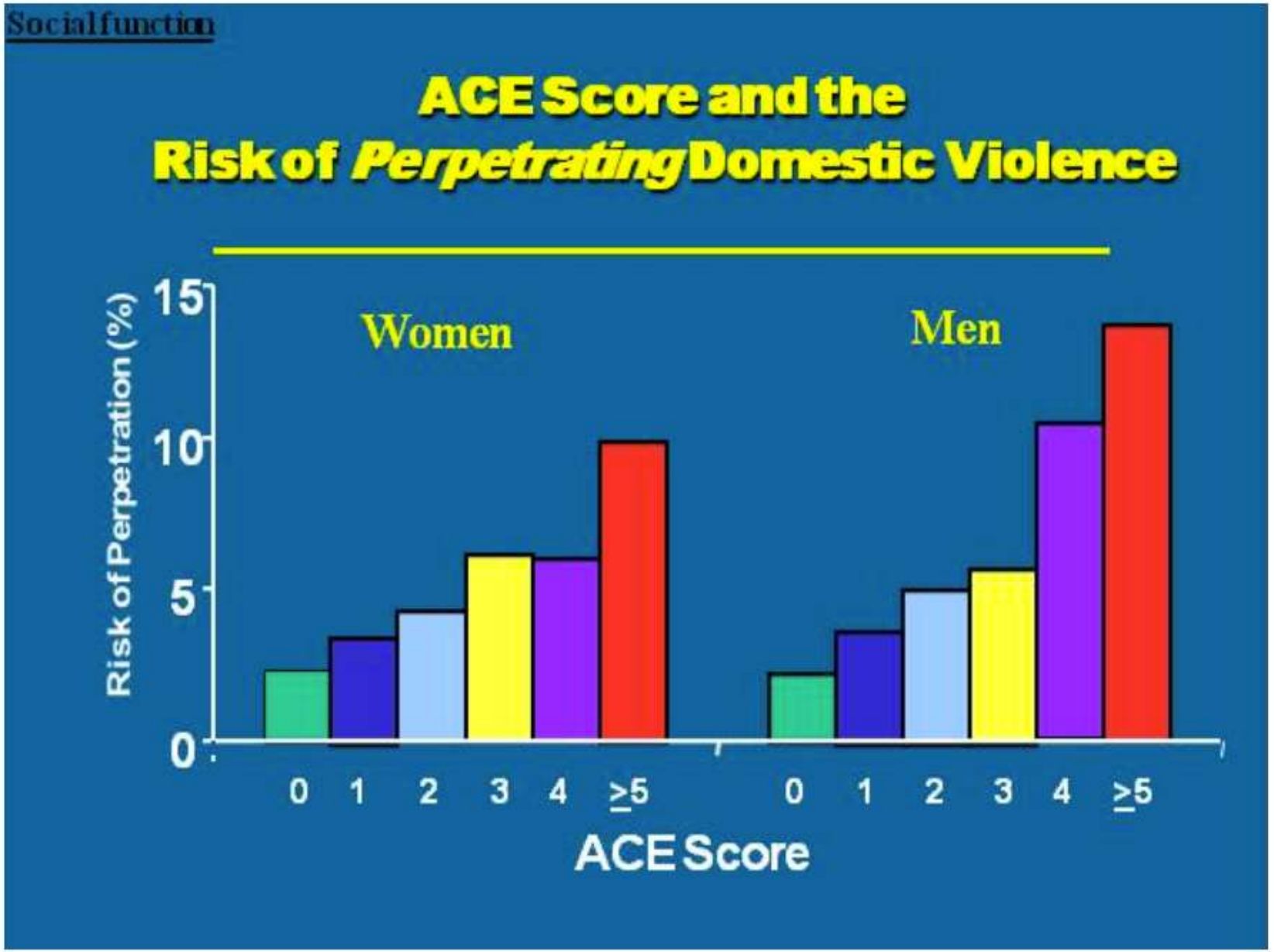
The Occurrence of One ACE Should Evoke a Search for Others

Prevalence of Childhood Abuse by Frequency of Witnessing Domestic Violence

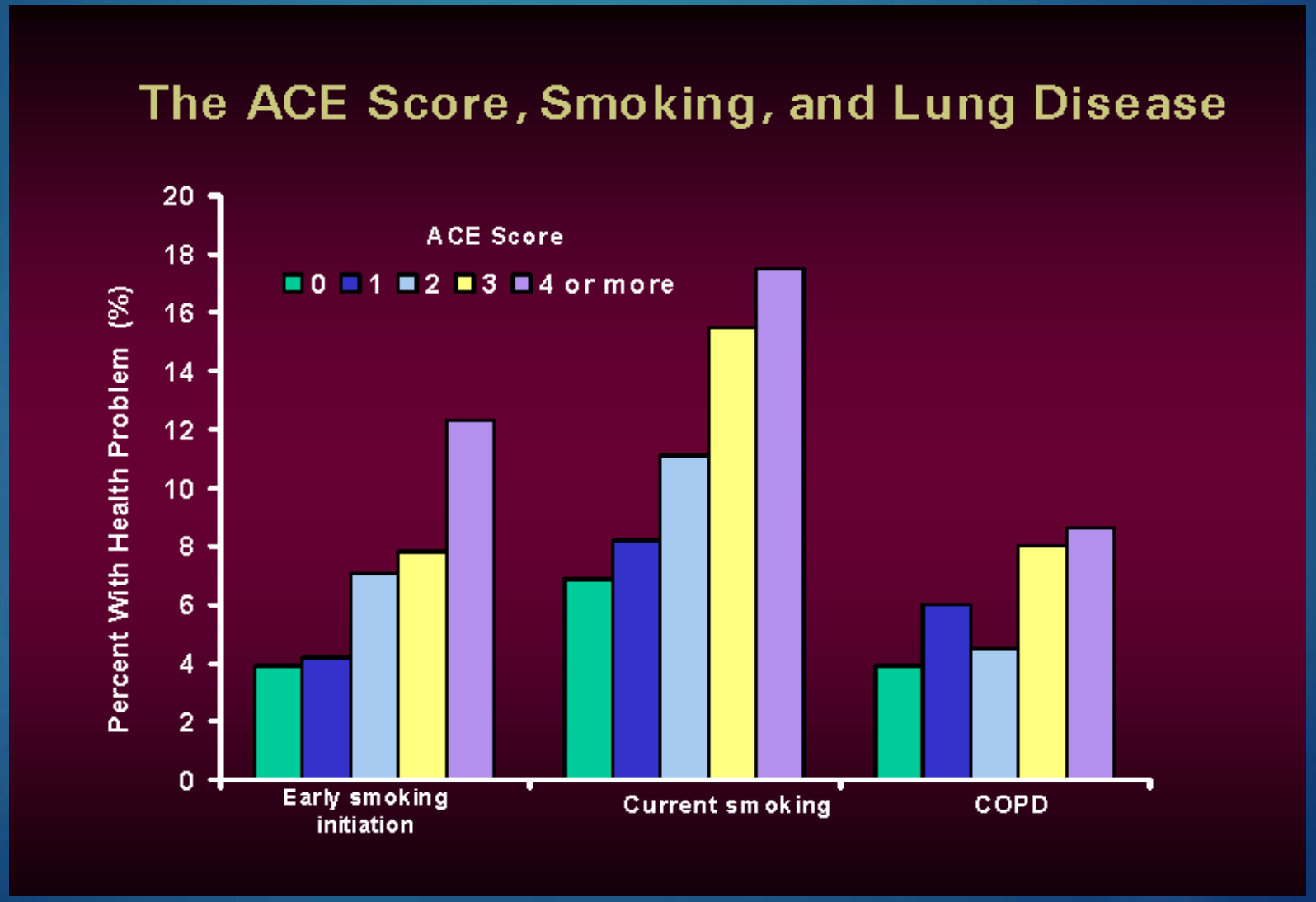


Domestic violence predicts child abuse

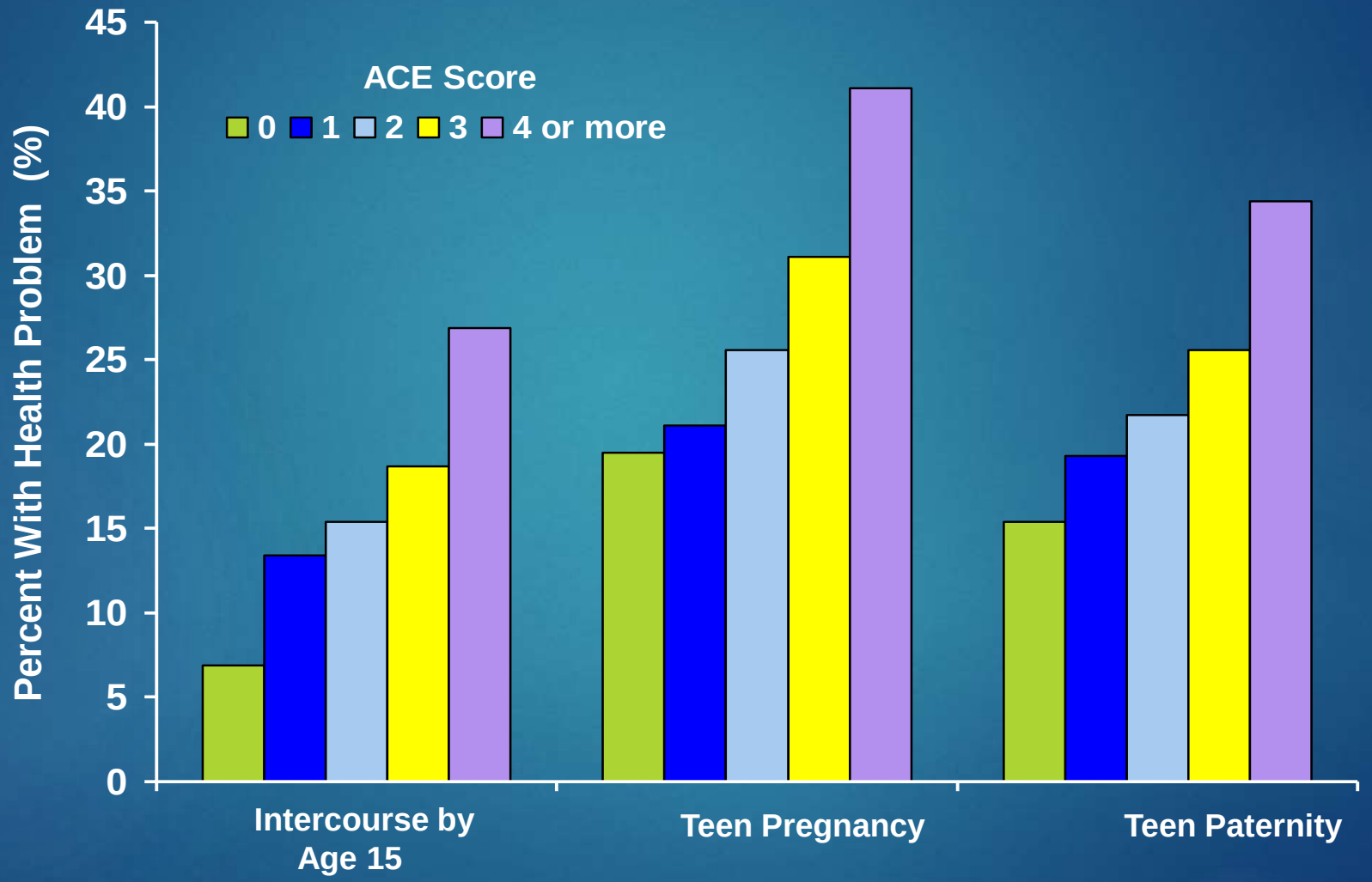
Social function



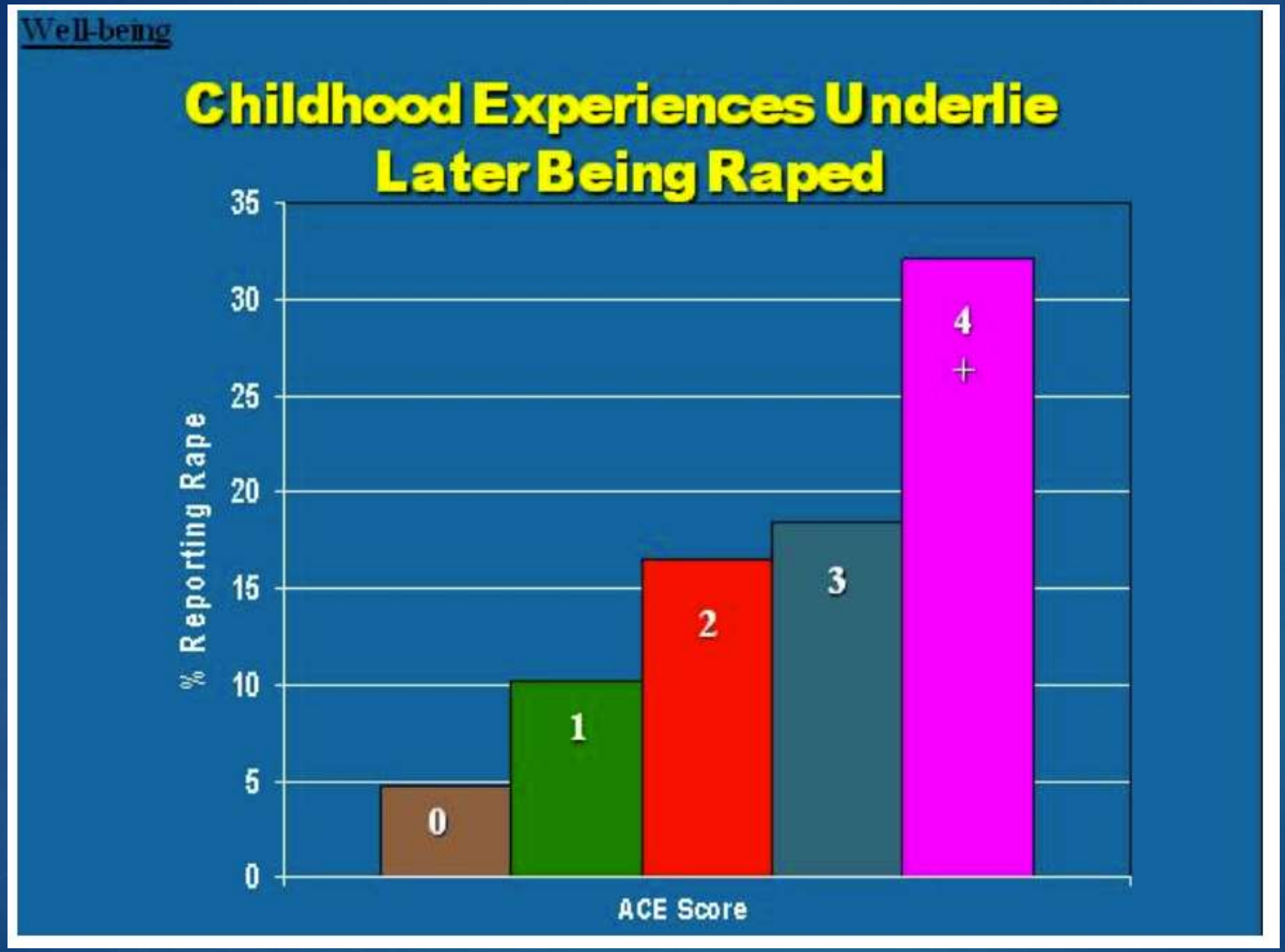
Smoking & COPD

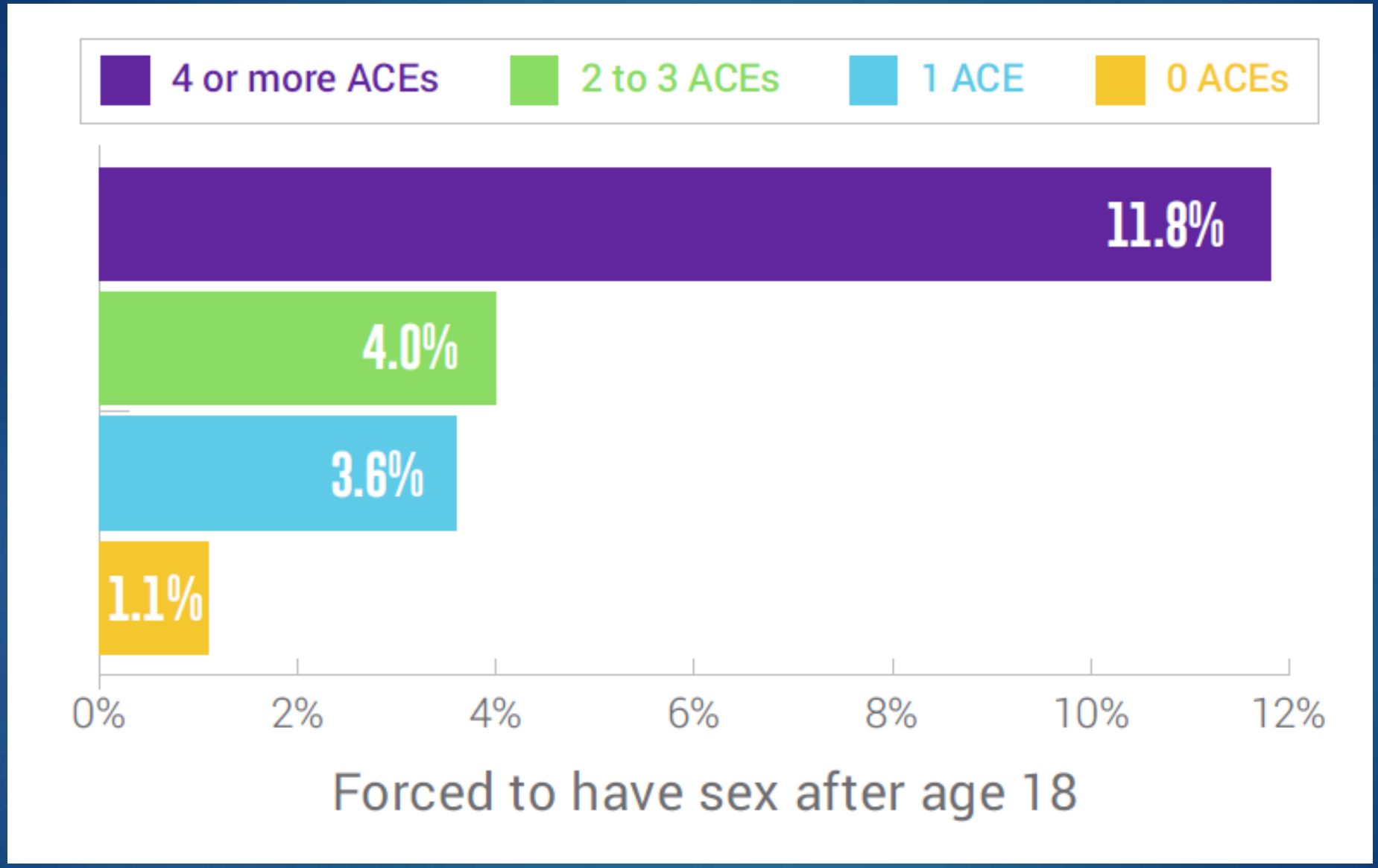


Teen Sexual Behaviors

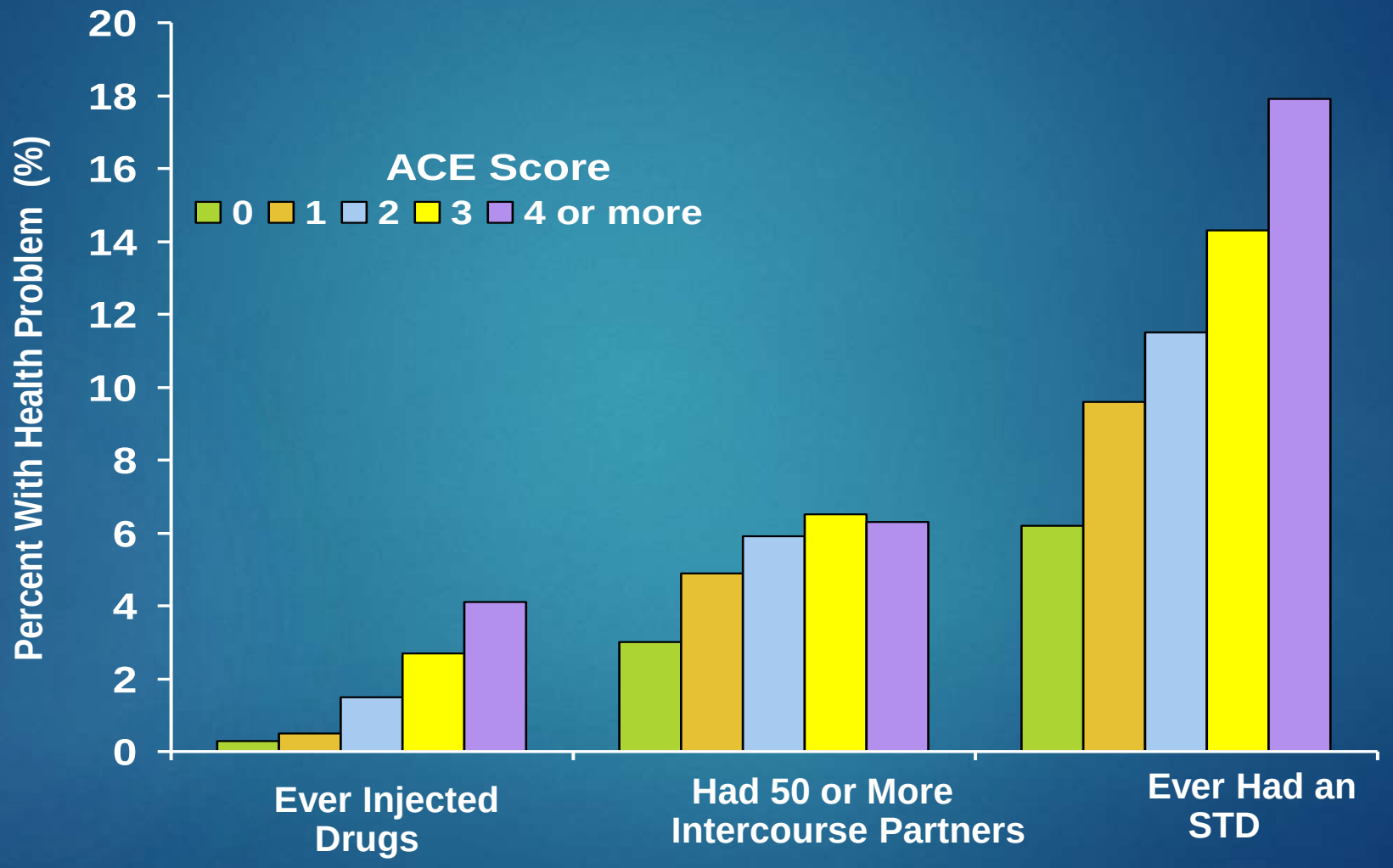


Well-being

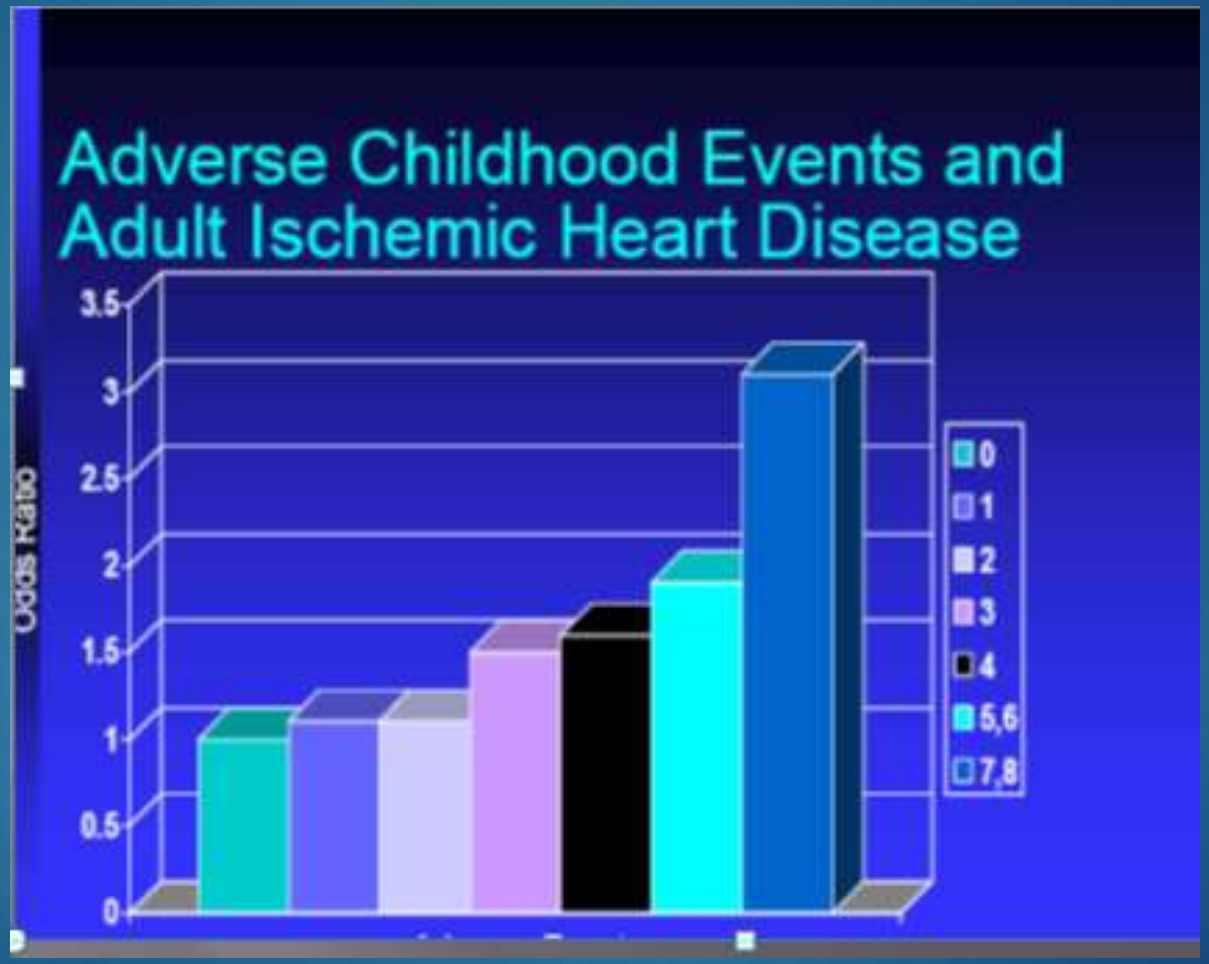

Childhood Experiences Underlie Later Being Raped
% Reporting Rape
35
30
25
20
15
10
5
0
0
1
2
3
4 +
ACE Score


4 or more ACEs
2 to 3 ACEs
1 ACE
0 ACEs
11.8%
4.0%
3.6%
1.1%
0%
2%
4%
6%
8%
10%
12%
Forced to have sex after age 18

Injected Drugs, Sex, STDs = HIV Risks

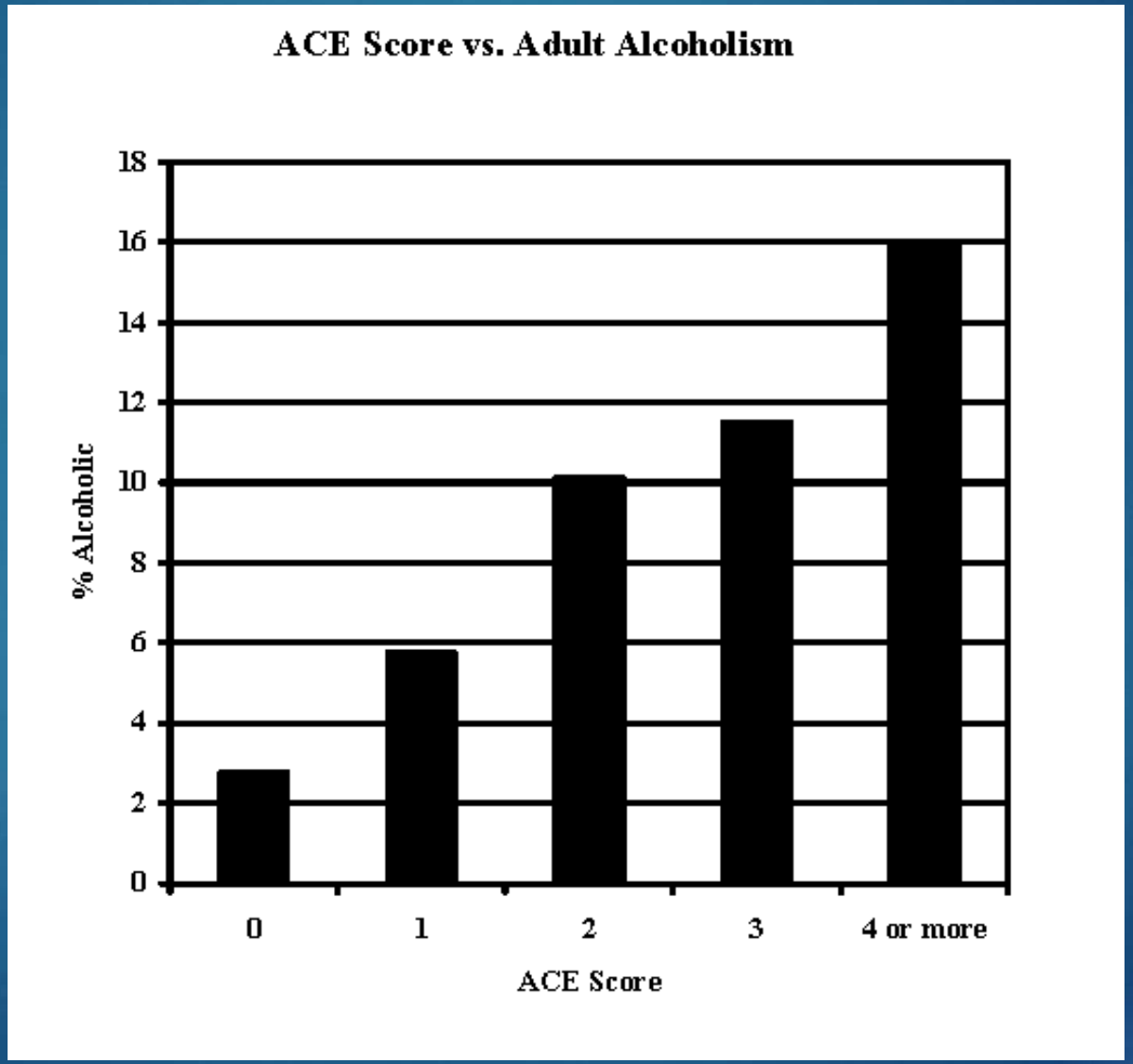


Adult Heart Disease

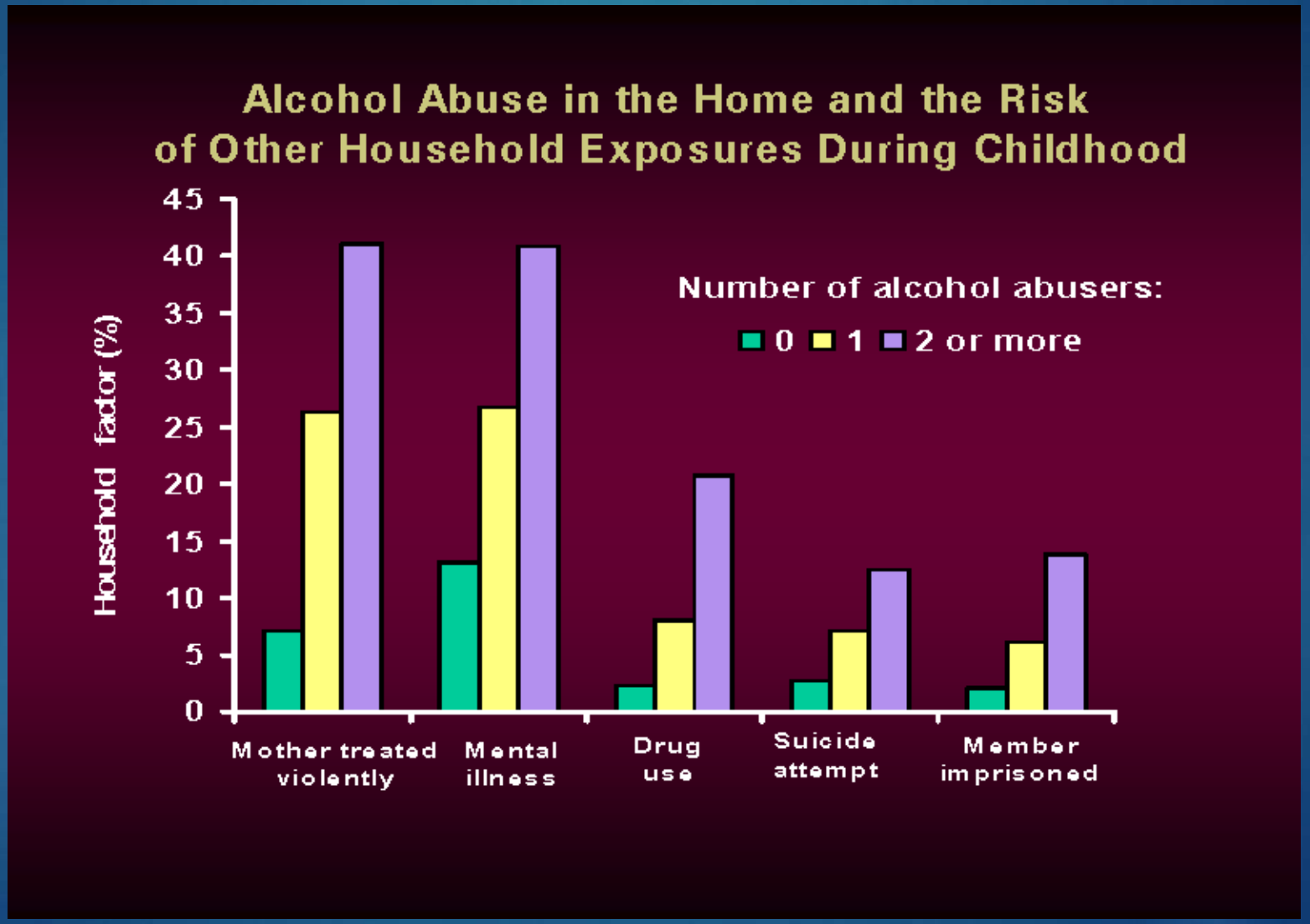


Having 6 or more ACES reduces life expectancy down to age 60.

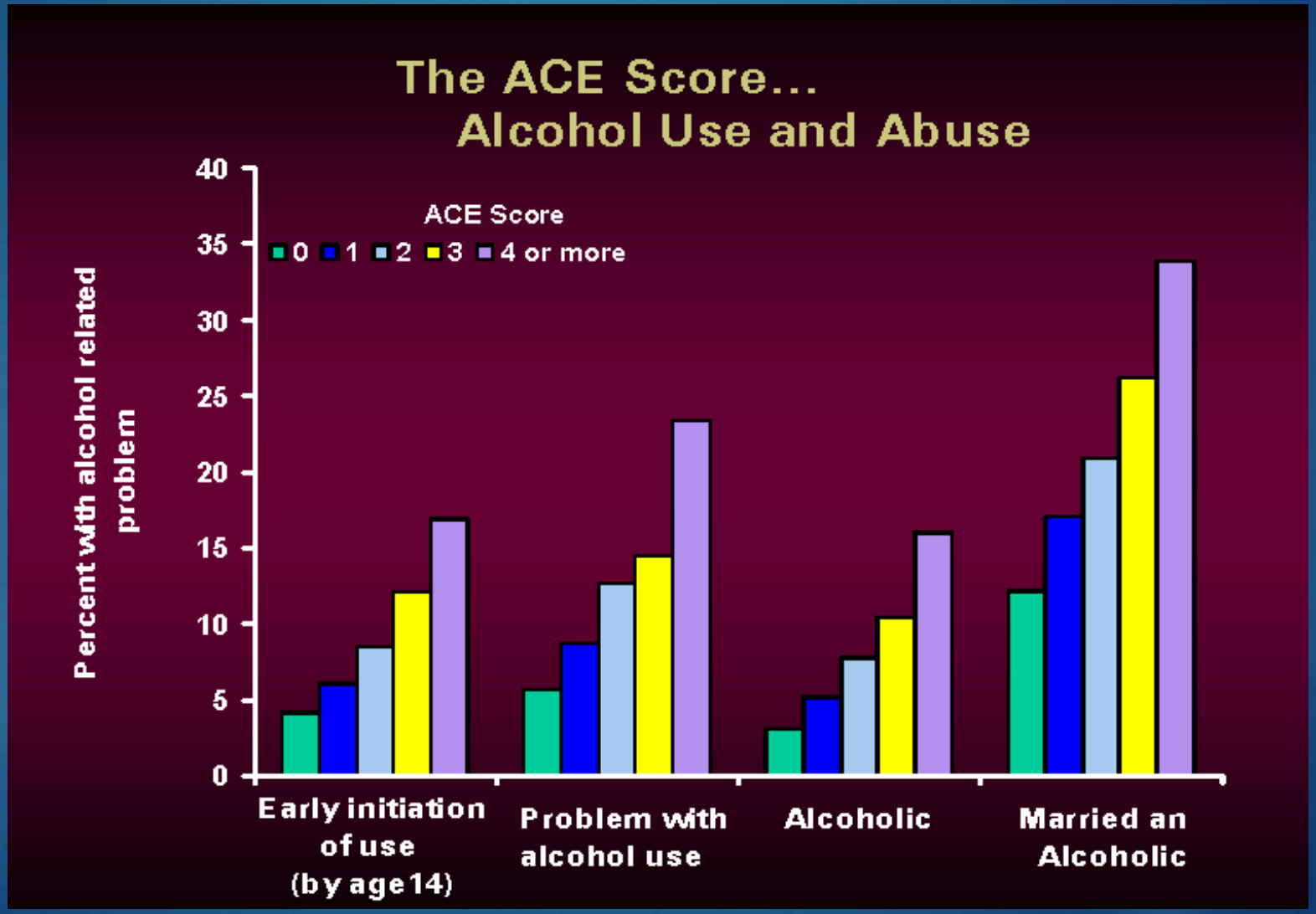
Alcoholism


ACE Score vs. Adult Alcoholism
% Alcoholic
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4 or more
ACE Score

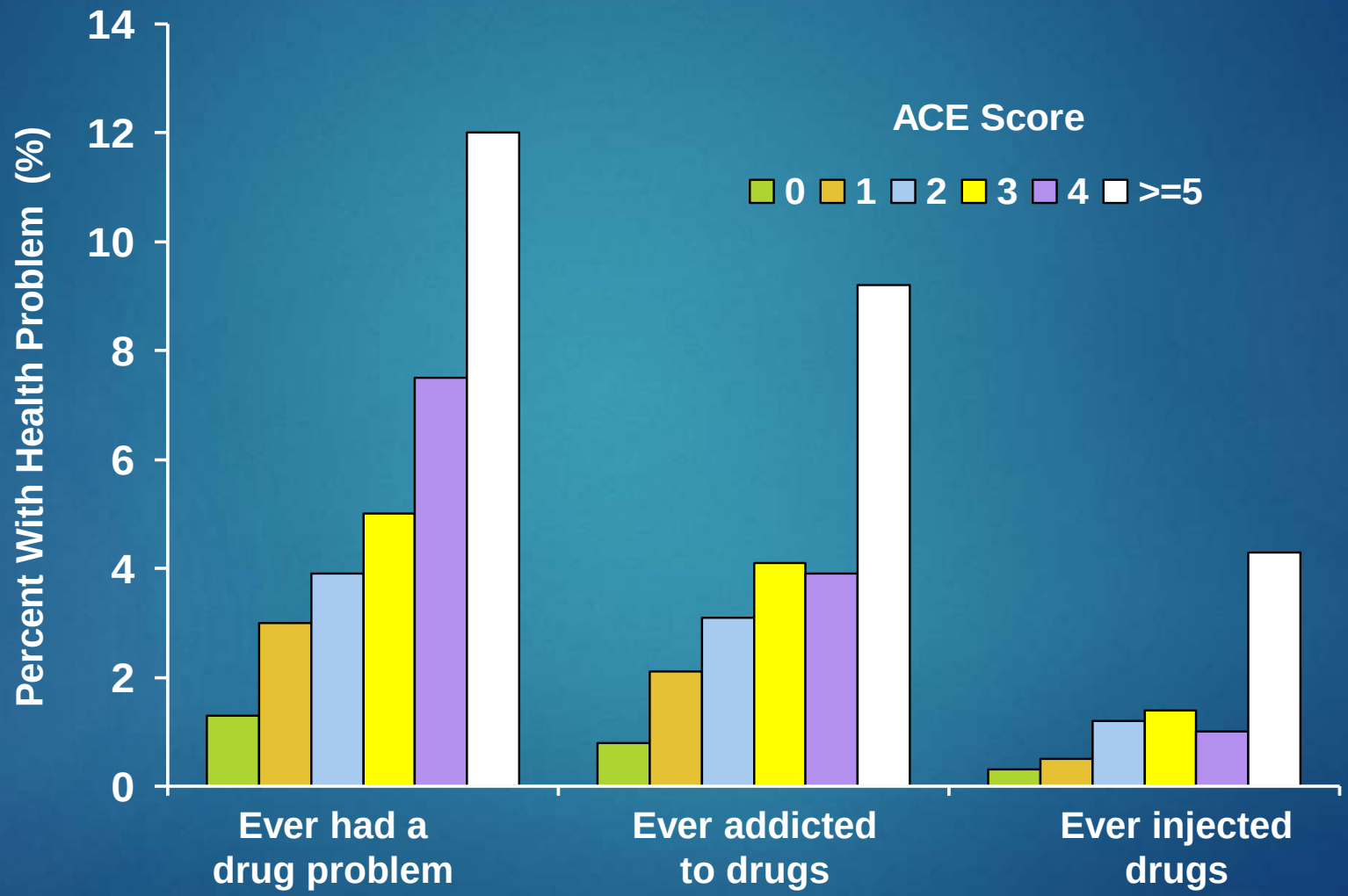
More alcoholism at home, the more abuse factors



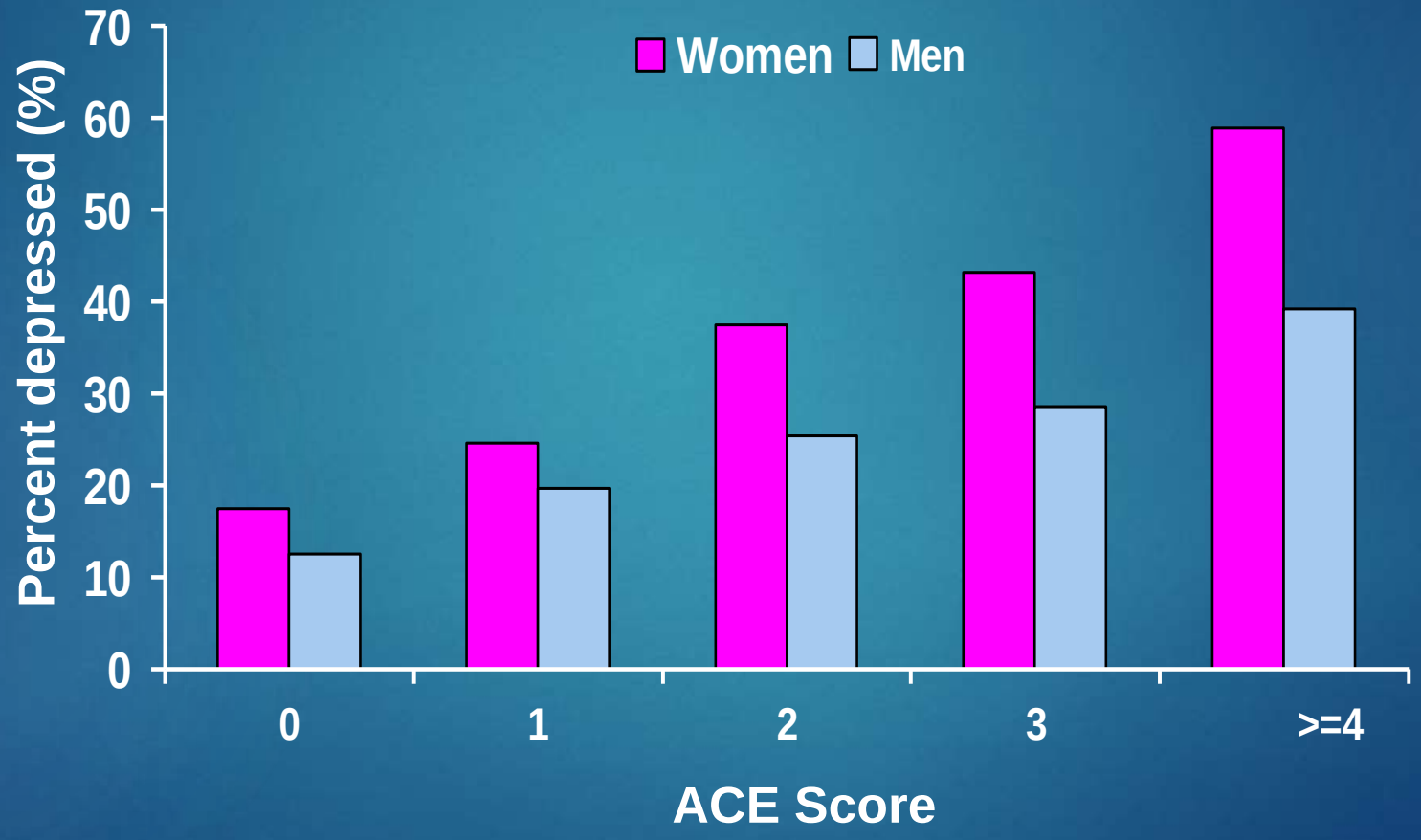
More alcoholism at home, more future alcohol problems



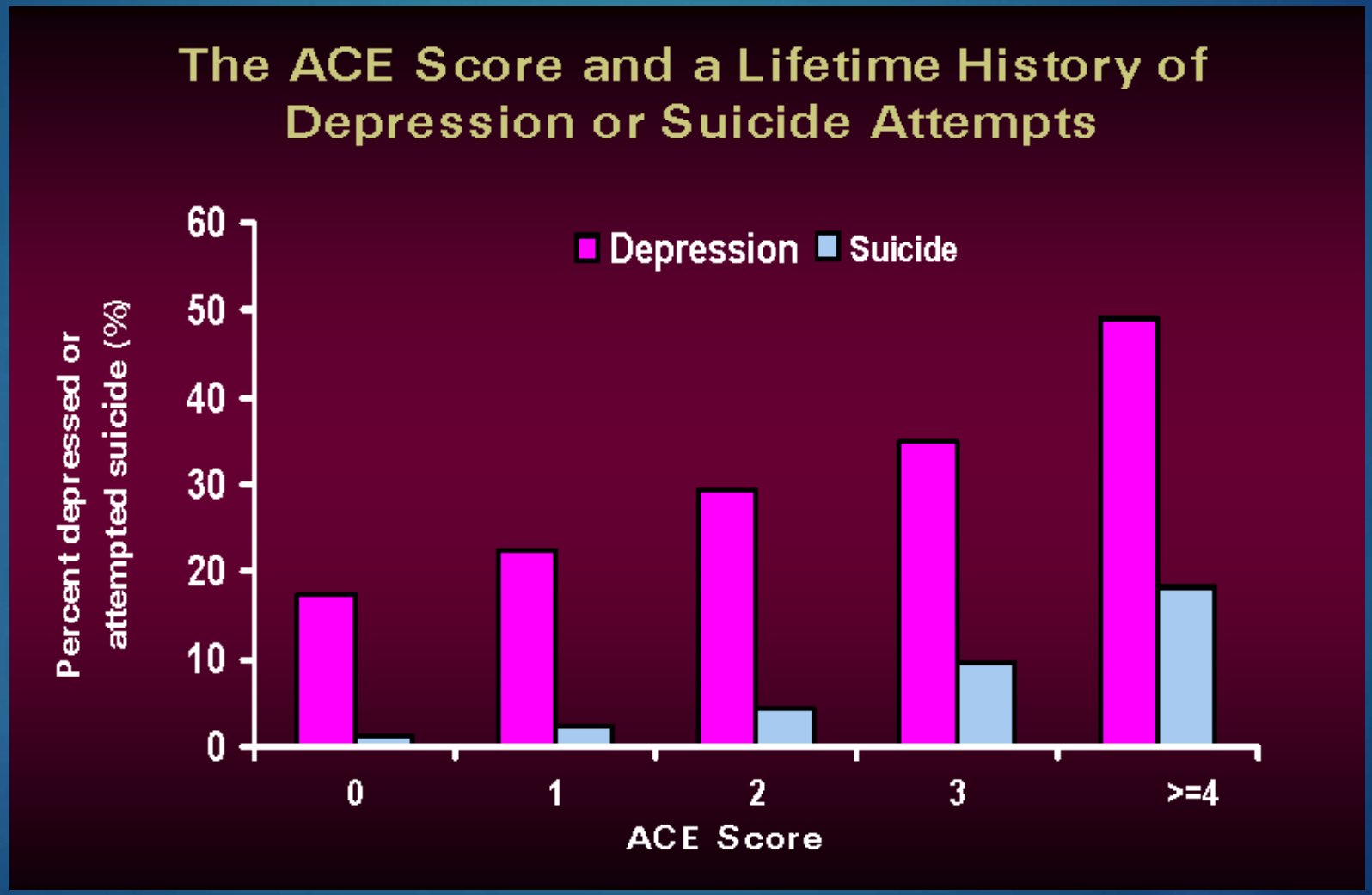
Drug Abuse


Percent With Health Problem (%)
14
12
10
8
6
4
2
0
ACE Score
0
1
2
3
4
>=5
Ever had a drug problem
Ever addicted to drugs
Ever injected drugs

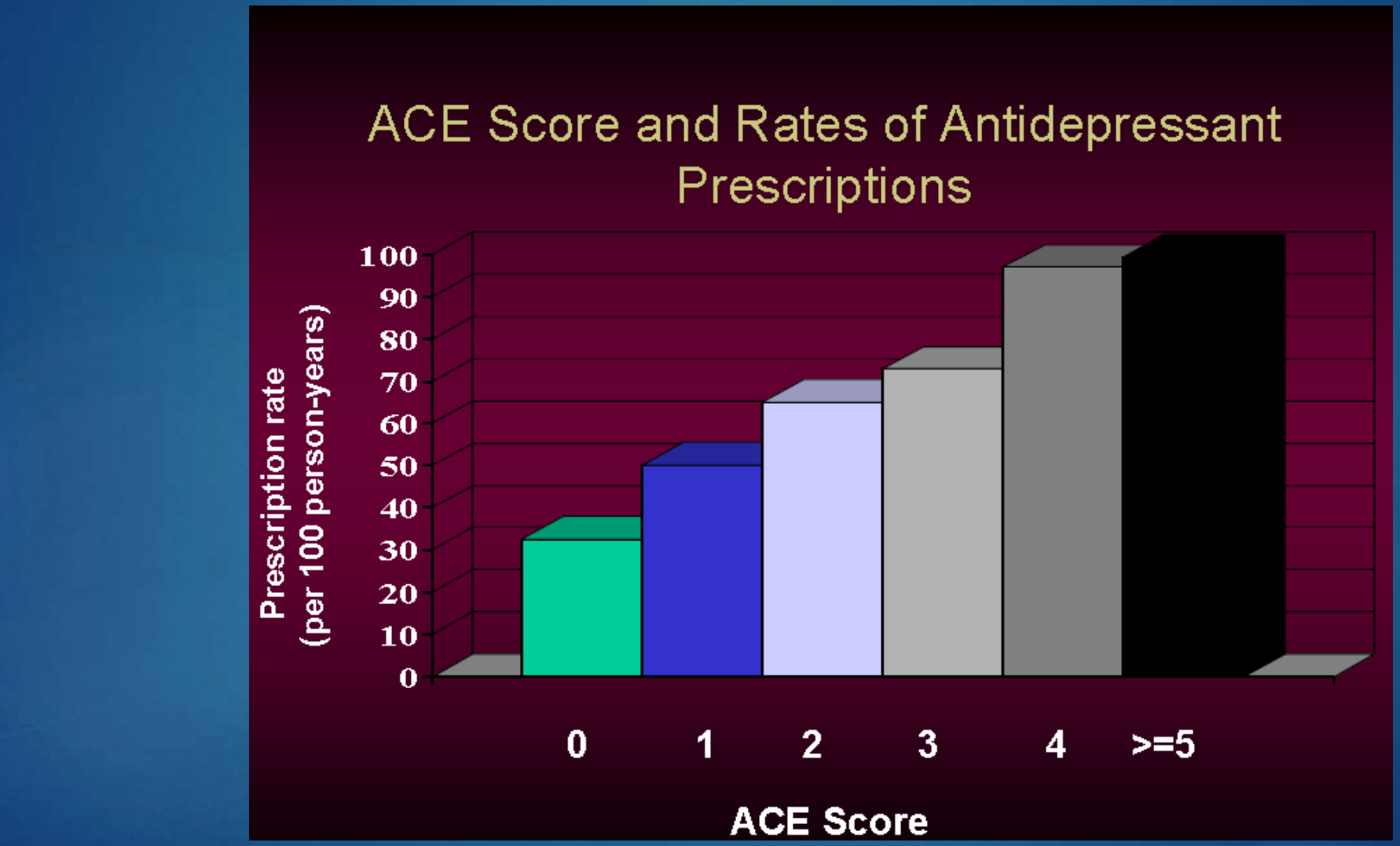
Lifetime History of Depression



Lifetime History of Depression & Suicide Attempts

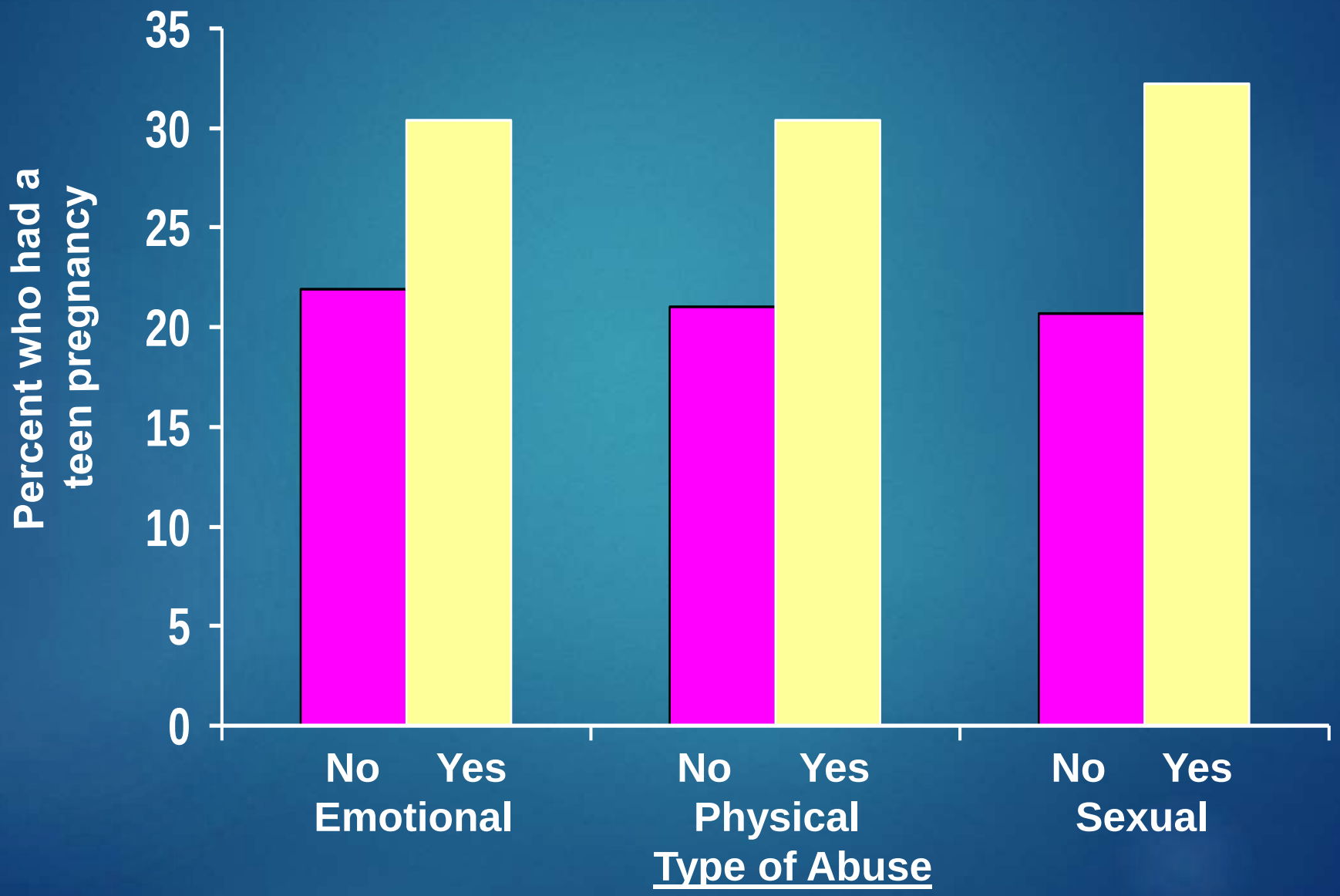


Antidepressant Prescriptions

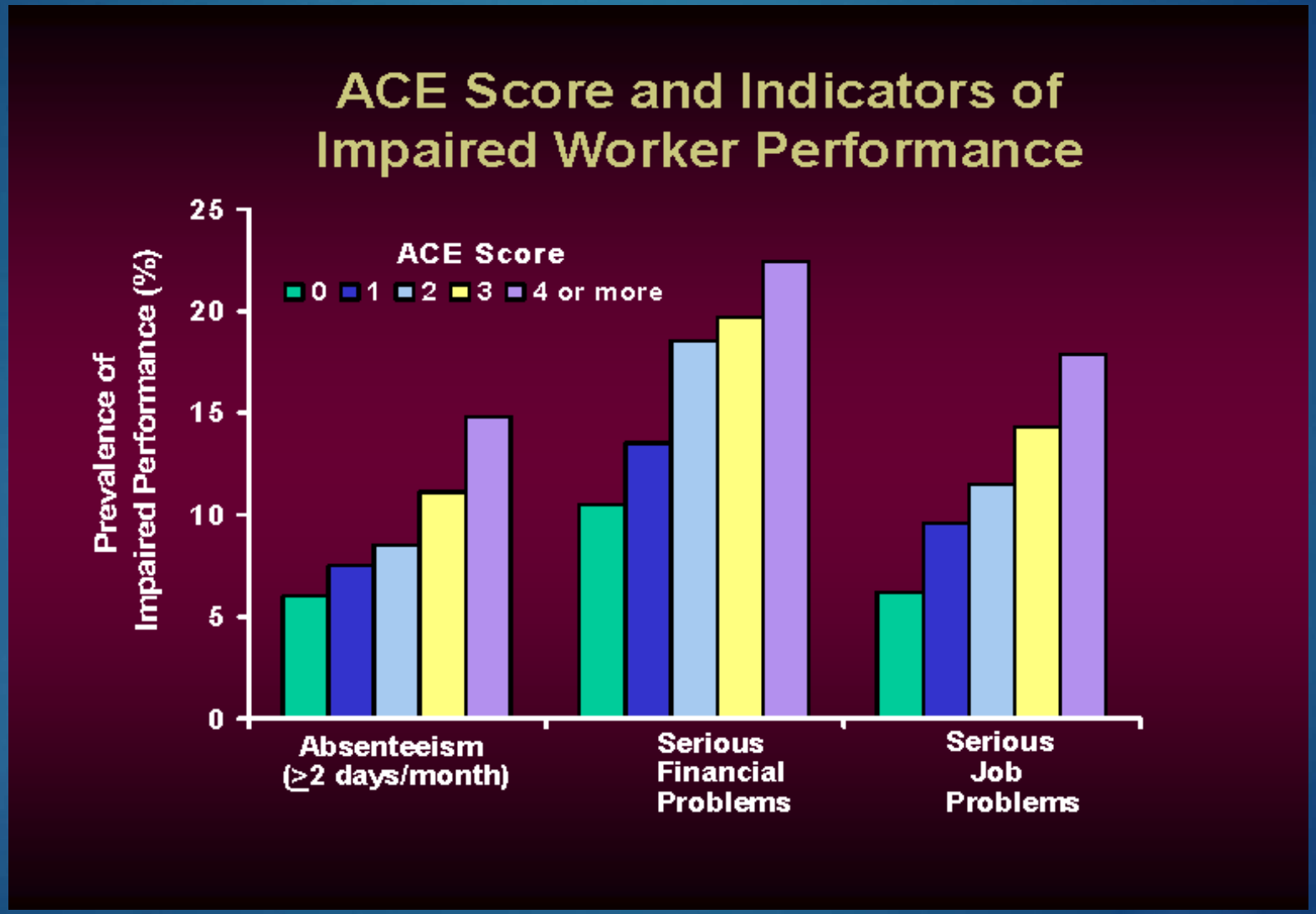


Impaired Memory of Childhood

Prevalence of Teen Pregnancy



History of Impaired Work Performance



Statistics of ACES: Adult outcomes

- 2.4 x more COPD
- 2 x asthma
- 2 x kidney disease
  2x diabetes
- 2 x have a stroke
- 5 x depression
- 4 x Alzheimer's or dementia.
- 3 x current smoking
- 2 x attempt suicide
- 3 x binge drinking

3 x risky sexual behavior.

12 x be the victim of sexual violence after the age of 18.

21% below 250 % of the Federal Poverty Level

27% lack a college degree

39% to be unemployed

50% lack health insurance

13 x removed from their home as children.

10 x inject drugs; 7 x alcoholic

2 x cancer

ACEs Predict Early Death

- Life expectancy of a person with six or more ACEs is 20 years shorter than a person with no ACEs
- Having 6 or more, reduces life expectancy to age 60.

Resilience: 14 items

1. My mother loved me when I was little.
2. My father loved me when I was little.
3. Other people helped my mother and father take care of me and they seemed to love me.
4. When I was an infant someone in my family enjoyed playing with me, and I enjoyed it, too.
5. Relatives in my family who made me feel better if I was sad or worried.
6. Neighbors or my friends' parents seemed to like me.
7. Teachers, coaches, youth leaders or ministers were there to help me.
8. Someone in my family cared about how I was doing in school.
9. My family, neighbors and friends talked often about making our lives better.
10. We had rules in our house and were expected to keep them.
11. When I felt really bad, I could almost always find someone I trusted to talk to.
12. As a youth, people noticed that I was capable and could get things done.
13. I was independent and a go-getter.
14. I believed that life is what you make it.

Autism: Too many synapses

David Sulzer, Neuron, 2014

- Autopsy study:
- Number of spines did not differ tremendously between the two groups of children, but adolescents with autism had significantly more than those without autism
- Normal 19-year-olds had 41 percent fewer synapses than toddlers, but those in their late teenage years with autism had only 16 percent fewer than young children with autism.
- One child with autism who was 3 when he died had more synapses than any of the typical children of any age
- Fact that young children in both groups had roughly the same number of synapses suggested a clearing problem in autism rather than an overproduction problem. Because the synapse difference comes on so late, it's too little pruning.
- Evidence of overconnectivity

Bucharest Early Intervention Project: foster care as intervention for institutionalization

- !989, Romania: 170,000 children in institutions; extreme neglect
- BEIP: Community, vs. Institutionalized (Foster Care vs. none; age 8 current assessment)
- Harry Harlow's famous maternally deprived monkeys: abnormal attachment behavior, unusual stereotypies (i.e. rocking), and poor intellectual functions.
- July Cameron & rhesus monkeys; timing of separation:
  - Mothers removed at 1 week: profound asociality
  - Mothers removed at 1 month: intense indiscriminate sociality, anxiety when alone

Romania's Abandoned Children, C. Nelson et al.

Prior Studies of Institutionalized children

- Head circumference = - 3 sd
- While early limited exposure does not have IQ effects, longer than 6 months lead to long term IQ decrease (ave 69)
- Executive functioning: with 6 months+, EF, theory of mind, ADHD deficits
- Language: delays, expressive deficits in 70%
- Attachment & Social/emotional: greatest deficits; externalizing or internalizing behaviors; often unable to attach
- MRI: more WM deficits, smaller GM & WM volumes, smaller left amygdala (greater activity)

Bucharest Early Intervention Project Results

- Institutionalized: lower IQ, delayed language, impaired EF & memory
- Those in foster care (7-33 months; ave age 22 m), had higher mean IQs (ave 81) and language than institutionalized, but lower than community; age of leaving institution was crucial; age of foster placement best predicted IQ
- 24 months was crucial; if placed after 24 months, worse IQ; if adopted before 6 months, normal
- *Ever*-institutionalized kids have variety of EF deficits, that are not resolved by placement
- Externalizing behavior did not respond to intervention

BEIP results 1

- Brain development: smaller brains (GM & WM) & head circumference, slower EEG; foster care – better EEG & WM, but not GM
- Telomeres: % of time in Institution at baseline predicted telomere length in females; at 54 months in males (epigenetic finding)
- Social/emotional: foster care – positive emotional response; once placed, remarkable recovery
- Psychopathology: strong relationship between institutional rearing & psychopathology; girls benefited significantly more than boys by foster care; effect of polymorphic genetic variants

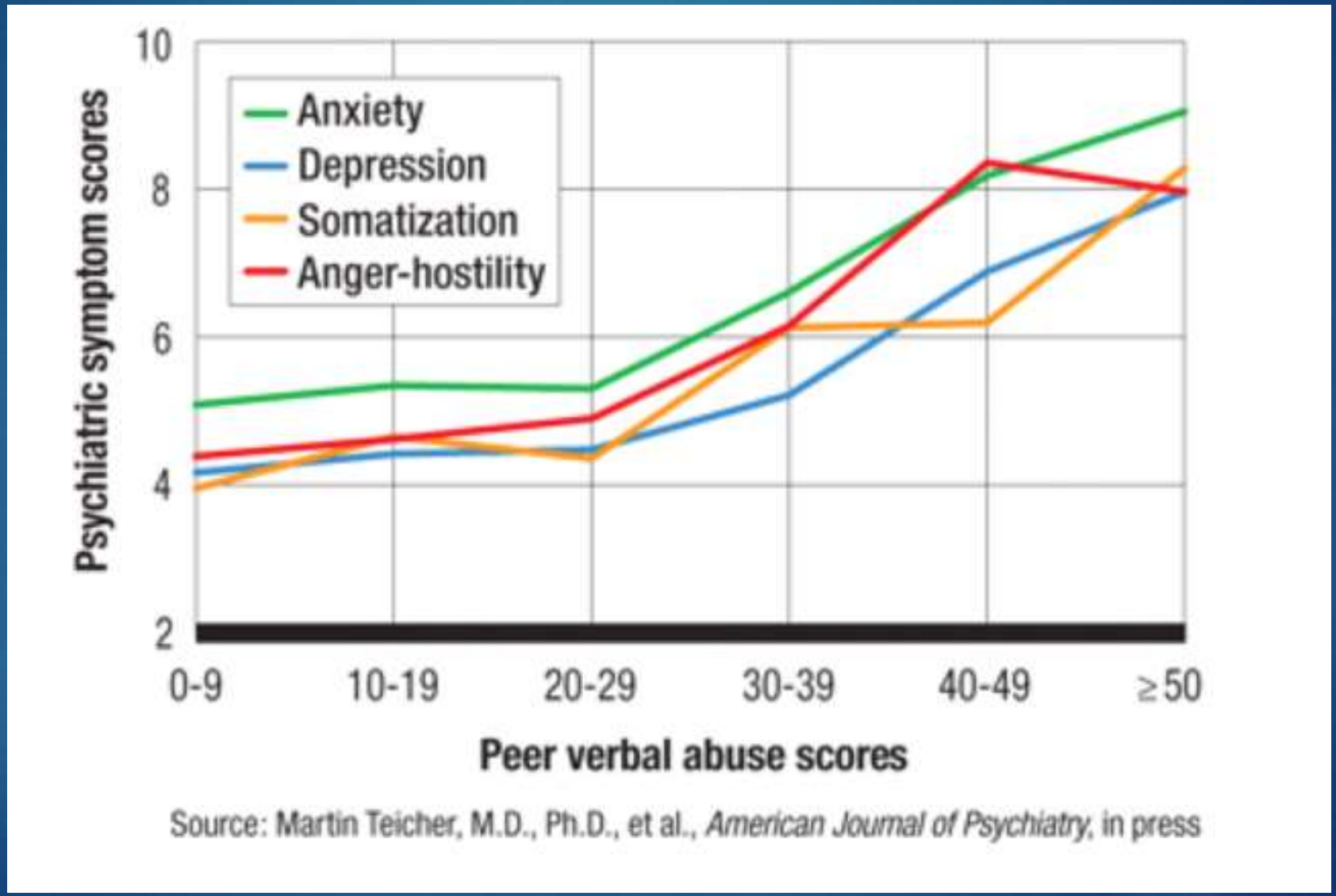
BEIP results 2

- Security of attachment was powerful mediator of reducing internalizing disorders; girls had more secure attachments
- EEG alpha & theta mediate effects on hyperactivity & impulsivity but not on inattention
- Institutional rearing associated with prolonged right frontal asymmetry, followed by blunted rebound in left frontal activation in middle childhood (normal is robust left frontal)

Hurtful Words

- Association of Exposure to Peer Verbal Abuse With Elevated Psychiatric Symptom Scores and Corpus Callosum Abnormalities.
- They have increased rates of depression, suicidal ideation, loneliness, and even psychosis; their grades are lower and their absentee rates higher; they are more likely to carry weapons to school and to engage in fights; they are likely to suffer more injuries, abuse over-the-counter medications, intentionally hurt animals and other people, and use weapons that could seriously harm others.

Peer Verbal Abuse



Source: Martin Teicher, M.D., Ph.D., et al., *American Journal of Psychiatry*, in press

Exposure to peer verbal abuse

- Reported by 9.2% of participants who had no exposure to childhood sexual abuse, witnessing of domestic violence, or parental physical or verbal abuse and by 17.9% of the entire community sample
- Associated with:
  - increased drug use and elevated psychiatric symptom ratings.
  - twofold increase in clinically significant ratings of depression,
  - a threefold to fourfold increase in anxiety and "limbic irritability,"
  - and 10-fold increase in dissociation.

Superior Temporal Gyrus Grey Matter Reduction

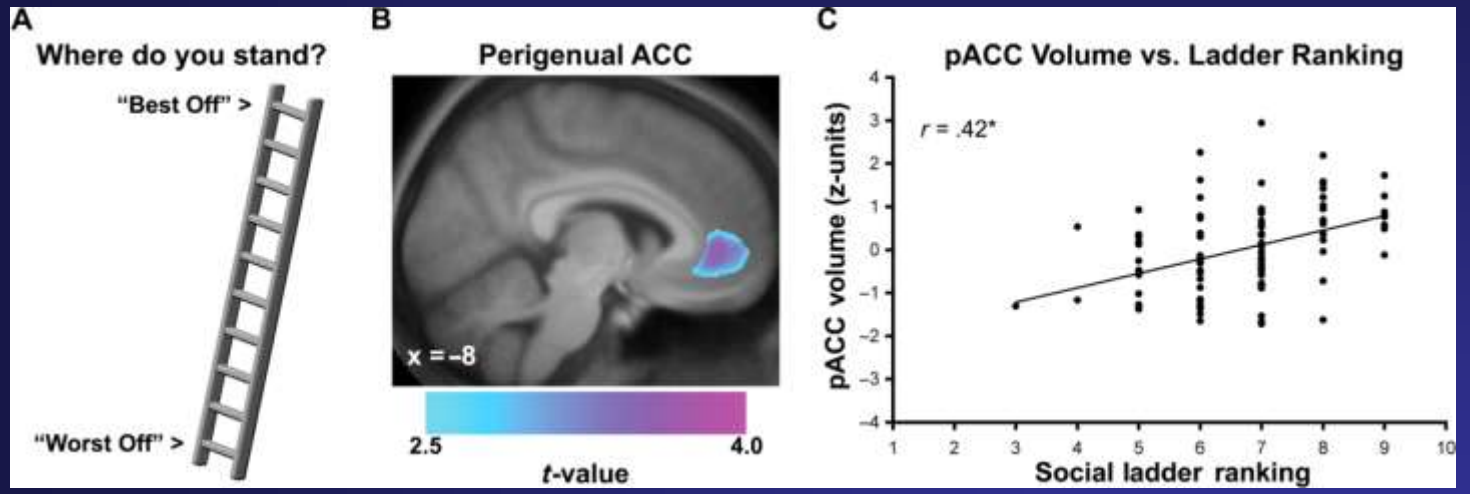
- Exposure to parental verbal abuse is associated with increased gray matter volume (GMV) in superior temporal gyrus
- GMV was increased by 14.1% in the left superior temporal gyrus

  Previous studies have demonstrated an increase in STG GMV in children with abuse histories, and found a reduction in fractional anisotropy in the arcuate fasciculus connecting Wernicke's and frontal areas in young adults exposed to PVA.
- Effect on auditory language processing.
- Also corpus callosum abnormalities

Martin Teicher, 2010

Social Status and the Brain: Effect of Stress

Lower subjective social status, as reflected by a lower self-reported ranking on a social ladder', was associated with reduced gray matter volume in the perigenual area of the anterior cingulate cortex (pACC)



Source: Gianaros et al. *Soc Cogn Affect Neurosci,* 2007 0:nsm013v1-13; doi:10.1093/scan/nsm013

Stereotypes

- A common stereotype is that boys develop more slowly than girls, putting them at a disadvantage in school where pressure to perform is starting ever younger.
- Another notion is that puberty is a time when boys' and girls' brains grow more dissimilar, accounting for some of the perceived disparities between the sexes.
- Brain differences are real but they are small.

Different Growth Patterns

- Although boys' and girls' brains show differences around age 10, during puberty key parts of their brains become more similar.
- And, rather than growing more slowly, boys' brains instead are simply developing differently.
- Young girls' brains tend to mature faster in the frontal region, which is responsible, among other things, for language learning and controlling aggression and impulsivity.
- For boys, the fastest development is in the back of the brain, which performs visual-spatial tasks at which males tend to excel such as geometry and puzzle-solving.

1100 Brain Scans

- Female brain has stronger neuronal connections than the male brain in certain areas, and vice versa. But in general, the study found that the male and female brains show more commonality than difference
- In about 10% of the young people studied, boys' and girls' brains were more similar to the brains of the opposite sex than to others' of the same sex.
- The way the cortex develops, and not its thickness, is more important in determining such factors as a person's level of intelligence.

Gender Brain Development

- At birth: Girls are a few weeks more mature neurologically and have more advanced hearing. Boys on average weigh half a pound more.
- First words: Girls typically utter their first word at 11 or 12 months, one month ahead of boys.
- Vocabulary: At 18 months, girls on average know 86.8 words, more than double boys' 41.8 words. By 30 months, boys' and girls' language skills have converged, at about 500 words.

Gender Development 2

- Walking: Caucasian girls and boys tend to walk around 12 months. African- Americans walk sooner, at nine to 10 months.
- Potty training: Girls are fully trained by 36 months, according to one study. Boys took a bit longer, training by 38 months.
- Onset of puberty: For girls, the process can start at age 9 to 10. For boys, it's closer to 11 to 12.

Next 4 slides: 2011 NIMH Development Study

- 1989-2011: 6000 scans from 2000 subjects, incl. normal, ADHD, ASD, SZ, and twins) from age 3 to 30
- Child Psychiatry Branch of NIMH

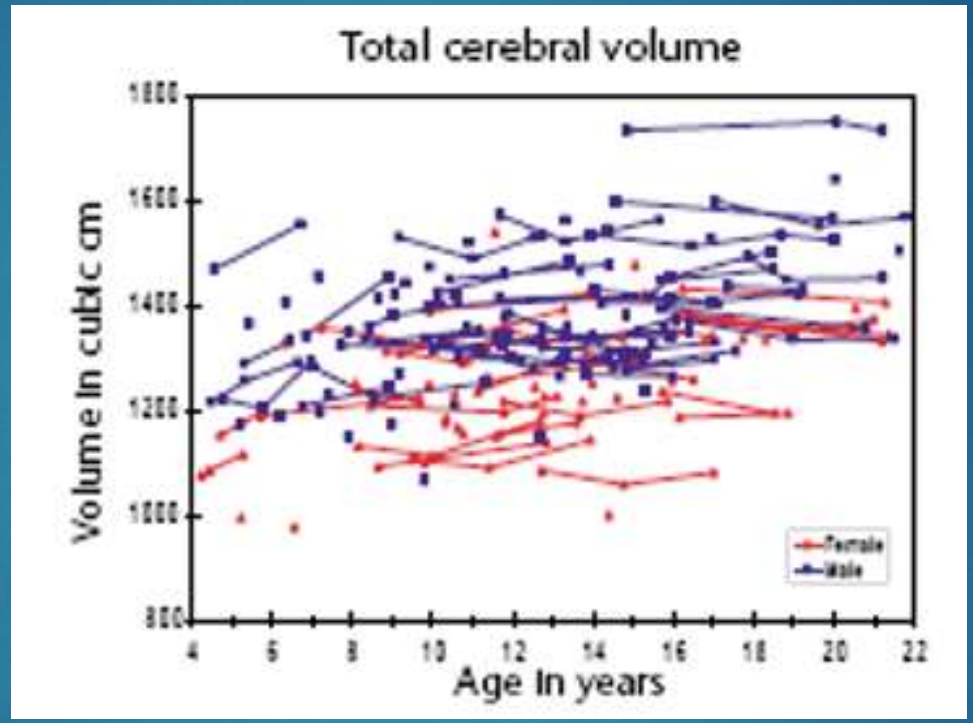
J. Giedd, et al., 2011

Total Cerebral Volume and Age

Inverted-U peak:
10.5 in girls
14.5 in boys

95% peak by age 6

High Variability:
2 10yo boys can be 2x different



Brain size not linked to body size:
Group ave size for males = 10% larger (in adults, on MRI & post mortem)

Boy's bodies not larger until after puberty; girls taller from 10-13

Variability range from 900 to 1500 cc

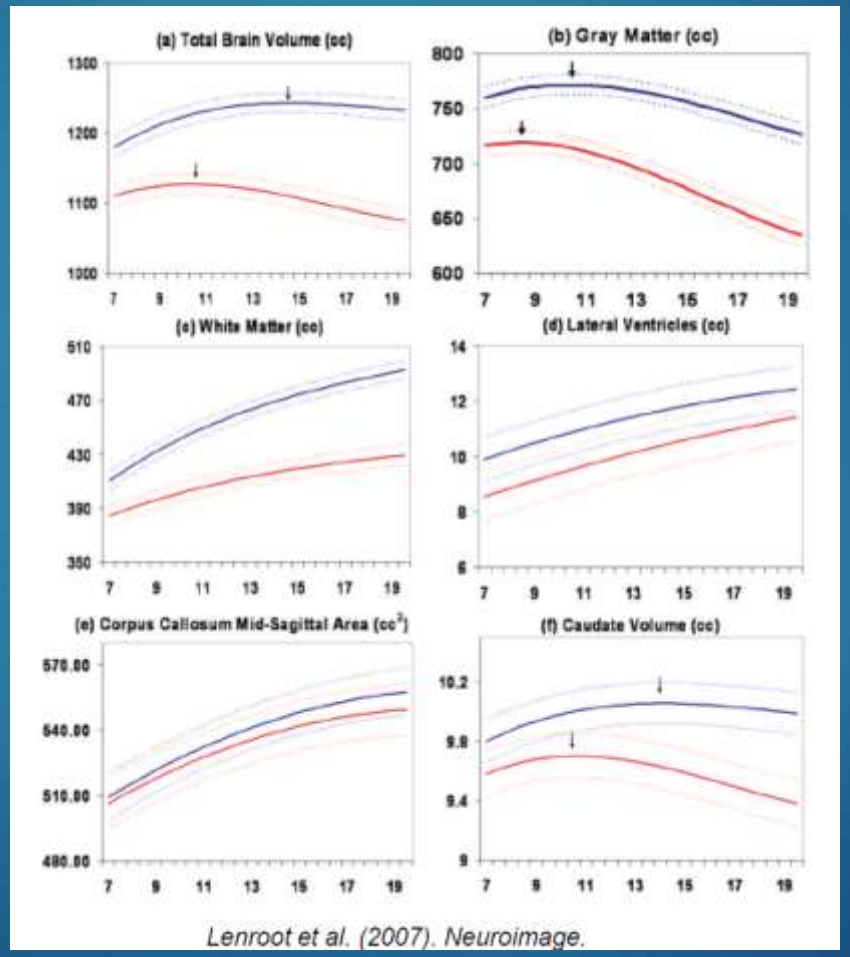
R. K. Lenroot, et al. 2007

Brain Component Development

Brain Volume

<u>White Matter & CC increase</u>:
<u>Increased processing speed</u> (3000-fold increase in info transmission per sec)

<u>Correlation with</u> improved language, reading, inhibition, & memory functions



Lenroot et al. (2007). Neuroimage.

<u>GM decrease</u>

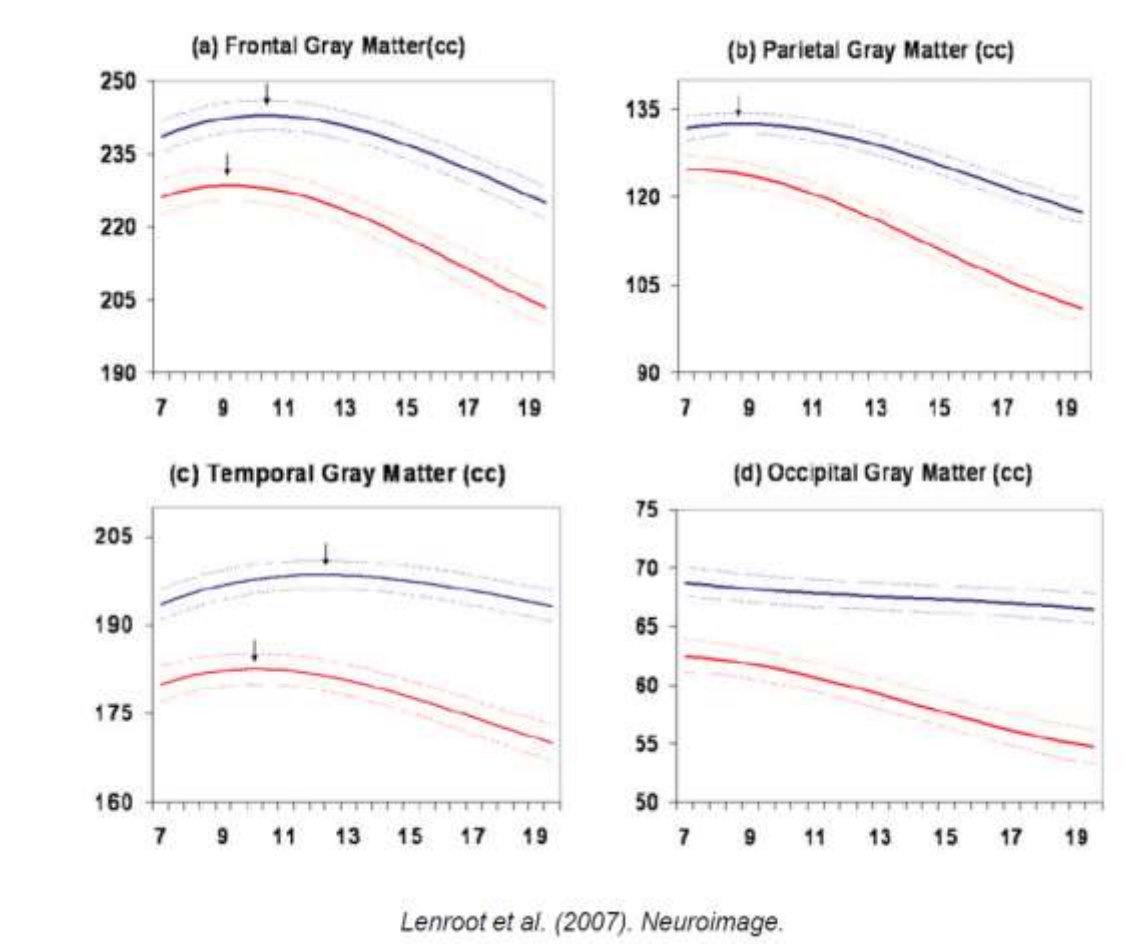
<u>Ventricle increase</u>

The Great Pruning: Inverted U: GM changes related to synaptic reduction

Frontal Peaks:
9.5 y in girls
10.5 in boys

<u>Prefrontal peaks latest</u>

Temporal Peaks:
10 in girls
11 in boys

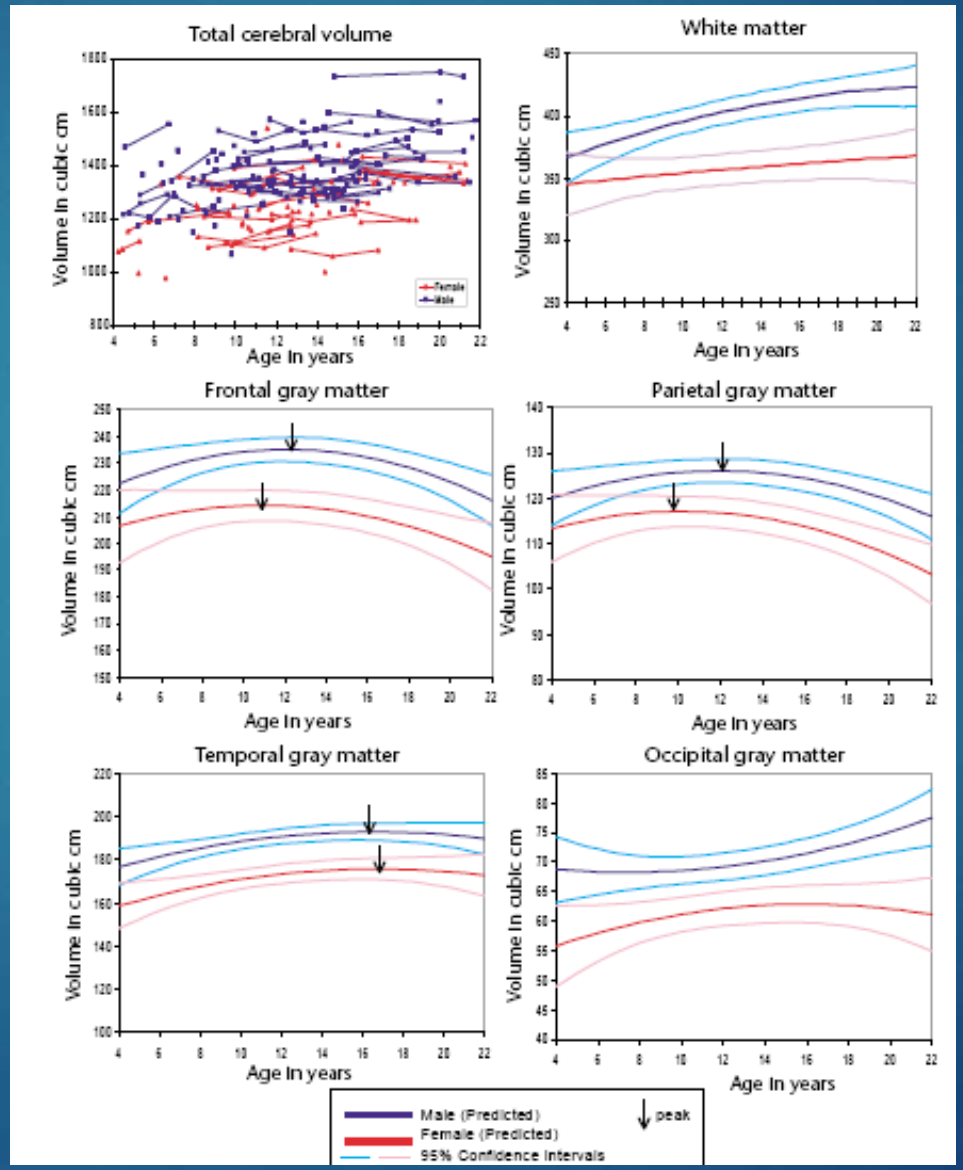


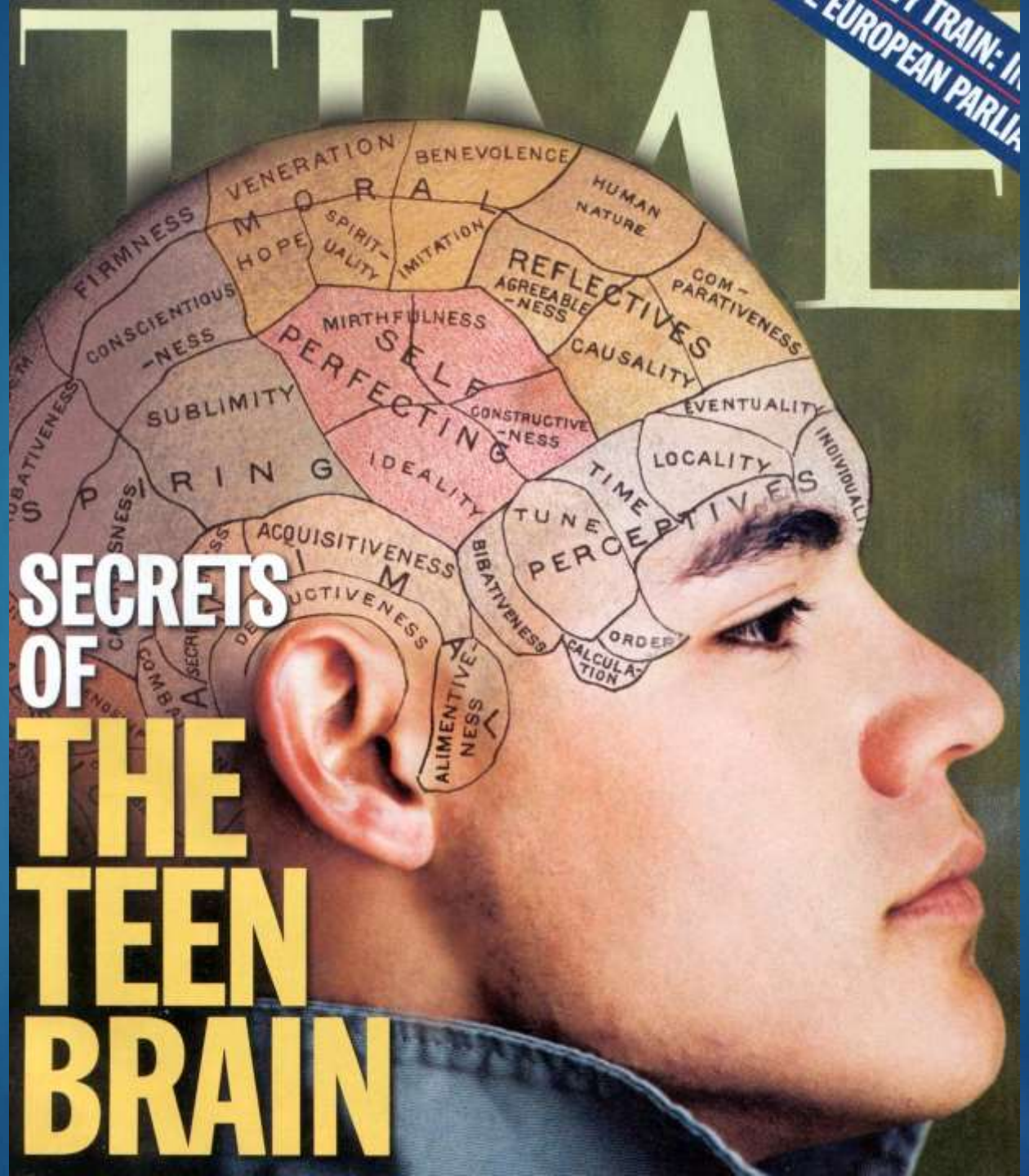
Parietal Peaks:
7.5 in girls
9 in boys

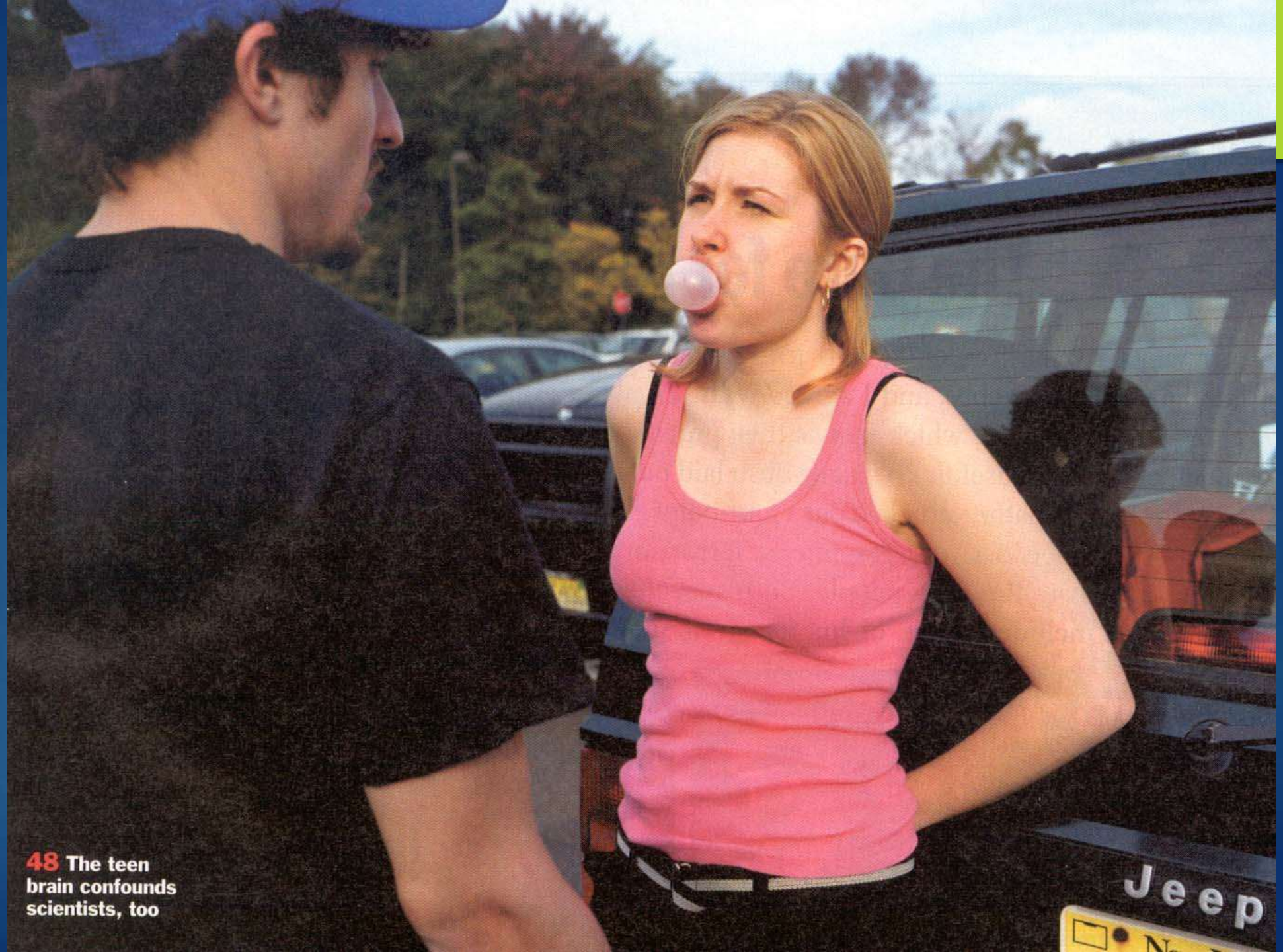
Caudate Peaks:
10.5 in girls
14 in boys

R. K. Lenroot, et al. 2007

Peak Volumes and Development: Gender Differences (Female red; Male purple)




TIME
SECRETS OF THE TEEN BRAIN



48 The teen brain confounds scientists, too

Adolescent Brain Sculpting

- Brain development during adolescence characterized by loss of connections rather than new connectivity, with 50% loss of synaptic connections between 7 and 16
- Mental Retardation has elevated # of synapses

Rakic et al., 1994

Adolescent sex differences in brain

- Robust sex differences in development, with females peaking earlier (related to puberty)
- Rate of cortical thinning more rapid in males; longer for maturity of frontal lobes (testosterone related)
- Amygdala volume increased only in males (higher androgen receptors in Amygdala)
- Hippocampus volume increased only in females (higher number of estrogen receptors in hippocampus)

J. Giedd, et al., 2011; Clark, MacLusky, & Goldman-Rakic, 1988; Morse, Scheff, & DeKosky, 1986

Major Adolescent Brain Changes

- Major synaptic pruning (loss of 50% of synaptic connections in the brain); but autistic brains have only 16% pruning (overactive mTOR gene = reduced autophagy, removal of damaged parts)

- Maturation of frontal and limbic regions

- Increased integration of brain circuitry

- Increase in mylenization, particularly in frontal region: increase in impulse control
  - In boys, self report of behavioral impulse control
  - In girls, increase in ability to inhibit incorrect answers
- Dopamine distribution changes (risk taking↑↑, reward seeking)

Adolescent Brain Changes 2

- Just before puberty, children lose up to 50 percent of their brain tissue in their deep motor nuclei. These systems control motor skills such as writing and sports.

- Language systems underwent a rapid growth spurt around the age of 11 to 15, and then drastically shut off in the early teen years (end of a period when we are thought to be most efficient at learning foreign languages)

- As abstract reasoning increases, so does social anxiety

Pruning = Sculpting

- Excitatory input to neocortex is particularly targeted
- More pronounced in prefrontal cortex rather than subcortical areas
- Involves circuitry within a region more than associational circuitry
- Conclusion:
  - pruning is not elimination of nonfunctional synapses
  - but sculpting brain into mature form, perhaps to match environmental demands

Energy Utilization

- Culling of excitatory cortical synapses, as reduction in brain effort
- Overall decline in brain energy utilization, with high rates of glucose metabolism, blood flow and oxygen utilization seen in childhood gradually declining
- Levels of O utilization is index of neural activation; decreases with maturation

Adolescent Brains Have a Missing Part

Why do most 16-year-olds drive like they're missing a part of their brain?

BECAUSE THEY ARE.

Even bright, mature teenagers sometimes do things that are "stupid."

But when that happens, it's not really their fault. It's because their brain hasn't finished developing. The underdeveloped area is called the dorsal lateral prefrontal cortex. It plays a critical role in decision making, problem solving and understanding future consequences of today's actions. Problem is, it won't be fully mature until they're into their 20s.

It's one reason 16-year-old drivers have crash rates three times higher than 17-year-olds and five times higher than 18-year-olds. Is there a way for teens to get their driving experience more safely — giving their brains time to mature as completely as their bodies? **Allstate thinks so.**

STRENGTHEN GRADUATED DRIVER LICENSING (GDL) LAWS.
GDL laws put limitations on teen driving so kids can gain experience safely. Since North Carolina implemented one of the most comprehensive GDL laws in the country, it has seen a 25% decline in crashes involving 16-year-olds.

HAVE THE DRIVING TALK.
75% of teens surveyed said their parents would be the best influence in getting them to drive more safely. The Allstate Parent-Teen Driving Contract can help start the conversation. **Contact an Allstate Agent to get a free copy or visit Allstate.com/teen for the interactive contract.**

Let's help our teenagers not miss out on tomorrow just because they have something missing today.

It's time to make the world a safer place to drive. That's Allstate's Stand.

Allstate. You're in good hands.
Auto Home Life Retirement

Adolescent Brain Changes

- Adolescents recruit PF areas less diffusely than children on WM task
- Increase in PF activation
- Increase in subcortical WM (axonal myelination: faster info processing)
- Declines in relative size of grey matter, esp. dorsal frontal and parietal areas
- Increases in grey matter in amygdala and hippocampus, and in posterior temporal cortex

Dopamine and Risk

- Teenagers tend to be more sensitive to rewards than either children or adult
- On money winning learning task, teenagers showed the highest spikes in prediction error signals, which likely means they had the largest dopamine response.
- Dopamine is known to be important for the motivation to seek rewards. It follows, then, that the greater prediction error signals in the adolescent brain could result in increased motivation to acquire more positive outcomes, and therefore greater risk-taking.
- Over activity in the mesolimbic dopamine system, a system which appears to be the final pathway to all addictions, in the adolescent brain

Not just hormones! PFC Changes

- Volumetric declines in PFC gray matter
- Pruning of glutaminergic excitatory input (decrease in number of glutamate NMDA receptors)
- Dopaminergic (DA) input to portions of PFC increases
- Decline in DA receptors in striatum (emergence of risk taking & novelty seeking)

Amygdala

- Emotional processing, modulating social behavior, affect attribution, establishing reward expectations = connect to orbital frontal region

- Increasing greater PFC modulation of emotional processing of amygdala

Cognitive and Behavioral Changes

- Improvement in executive functioning, response inhibition, attention and memory functions, and emotional self-control
- Increase in novelty seeking, stress sensitivity

Adolescence

- fMRI studies of reward processing suggested that adolescents differ from adults in the balance between top–down mechanisms of attention and cognitive control based primarily in the PFC and bottom–up motivational and emotional responses to situations of risk and reward based in the NAcc and amygdala
- Empirically supported view that compared with adults:
  - adolescents are more motivated by rewards,
  - are less averse to risks,
  - and are more easily influenced by peers

Ventral Striatum Reward in Adolescents

- Presence of adolescent friends activates VS reward center (attend to potential reward of risky choice, not the negative consequences)

- Most deadly drivers: Adolescents have more MVAs when they know friends are observing them (unlike adults); more teens in car, 3 x more accidents per mile driven; not from distraction which kills senior drivers

- Adolescents more likely to commit crimes in groups than alone

- Ventral Striatum (reward center) activates significantly in these scenario; overrides frontal inhibition

Adolescents: Give them rewards

- fMRI studies:
- Adolescent boys tend to disregard fear warnings.
- Adolescents tend to be insensitive to losses but hypersensitive to large gains

Neurobiology of Risk in Adolescence: A Tale of Two Systems

- Risk taking related to
  - a) earlier maturation of subcortical limbic region,
  - b) later maturation of top-down prefrontal control region,
  - c) context.
- Improved cognitive control with maturation of prefrontal cortex.
- Context of behavior increases in importance (presence of other teens, alcohol & drugs, sex, etc.)
- Larger dopamine release in adolescence leads to hypersensitivity to reward which leads to risker behavior

A. Galvan, 2011

Onset of Psychopathology: Growing into deficit

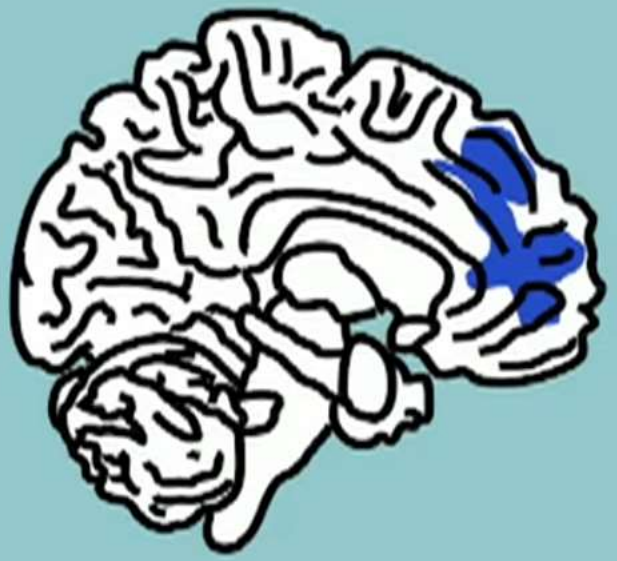
- Schizophrenia
- Bipolar
- Substance Abuse
- ADHD
- OCD

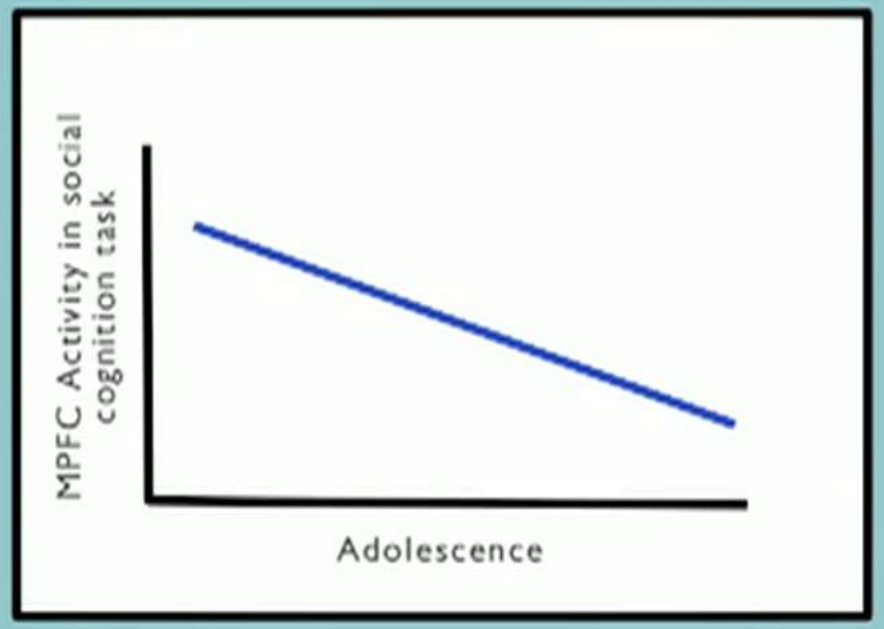
Taking the other's perspective: Increase in rTPJ

- With age, adolescents were increasingly sensitive to the perspective of the other player, as indicated by sharing more money with the partner, and this was associated with increased involvement of the left temporo-parietal junction, an area involved in social perspective-taking.
- In contrast, young adolescents showed more activity in the anterior medial prefrontal cortex, a region associated with self-oriented thought.
- These findings suggest that the asynchronous development of these neural systems may underlie the shift from thinking about the self to thinking about others.

Less medial prefrontal activation = improved social cognition

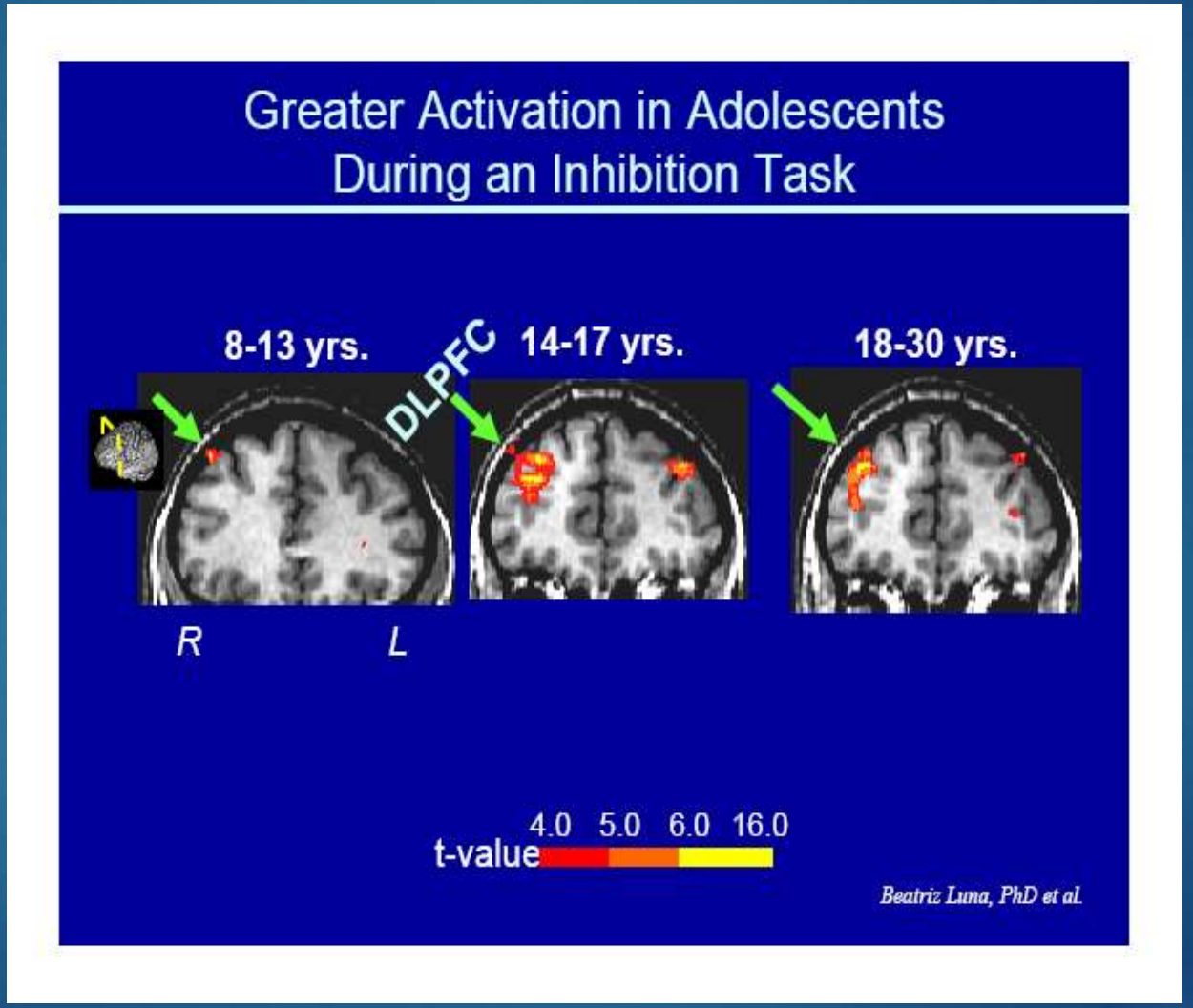
Medial prefrontal cortex activity in social cognition tasks decreases during adolescence in 9 developmental fMRI studies





Ability to take other people's perspective improves thru late adolescence

Inhibition Development: greater dlPFC activation



Development of Future Orientation

Rate of Change of Cortical Thickness: Ages 5 to 11

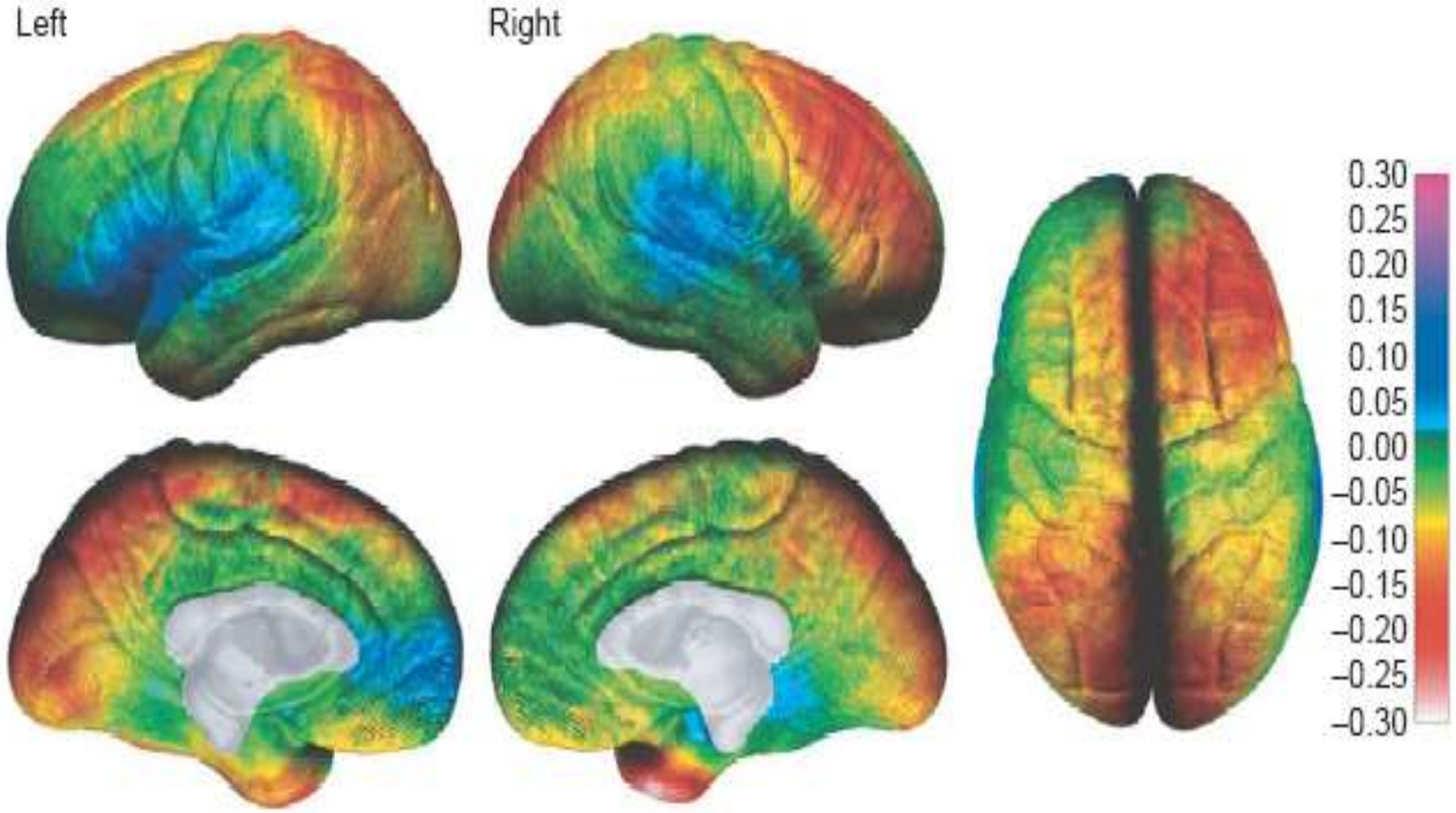


Figure 3. Annualized rate of change in cortical thickness. The average rate of change in cortical thickness is shown in millimeters according to the color bar on the right (maximum gray-matter loss is shown in shades of red and maximum gray-matter gain is shown in shades of blue). Forty-five children were studied twice (two-year scan interval) between 5 and 11 years of age. Reproduced, with permission, from [12].

Vocabulary and Cortical Thickness: Greater thinning = better vocab.

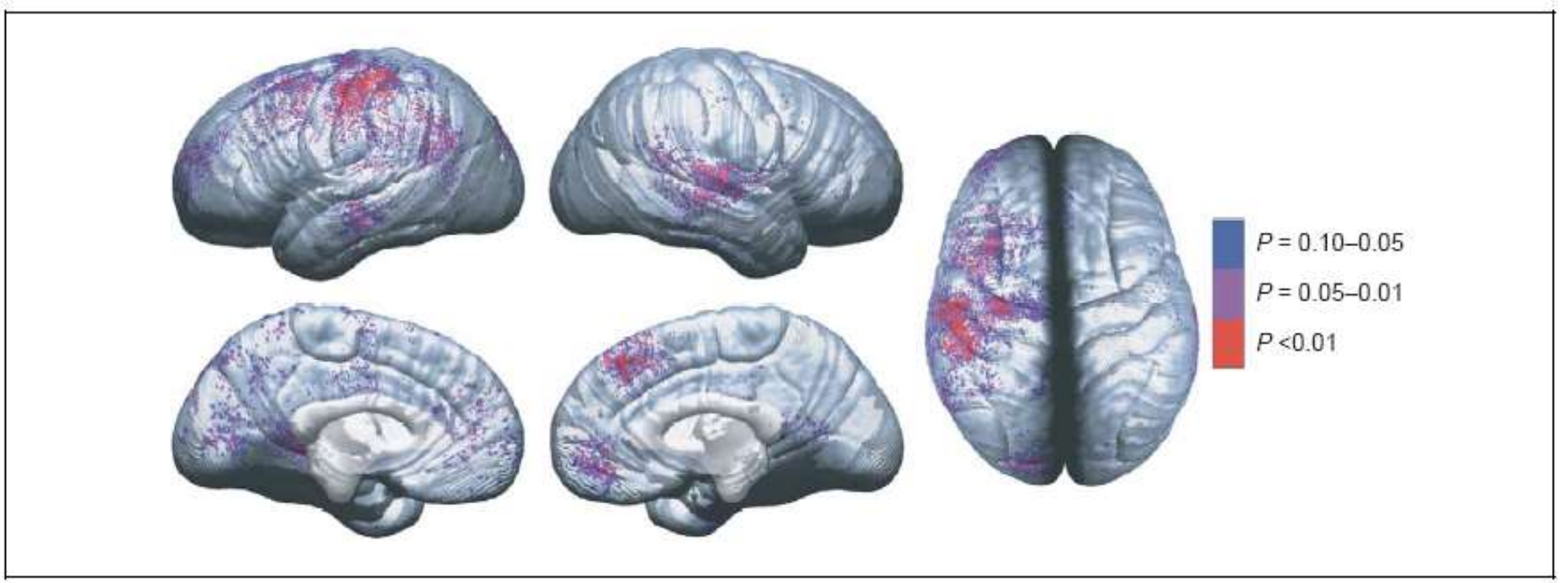


Figure 4. Brain-behavior maps for vocabulary and cortical thickness. *P* values are for negative correlations between change in cortical thickness (time 2 minus time 1, as shown in figure 2 of [12]) and change in vocabulary raw scores (time 2 minus time 1). Negative *P* values (i.e. regions where greater thinning was associated with greater vocabulary improvement) are color-coded, and regions in white showed no significant association. Positive correlations were not significant in the permutation analyses for any of the regions of interest, and are not shown here. Reproduced, with permission, from [12].

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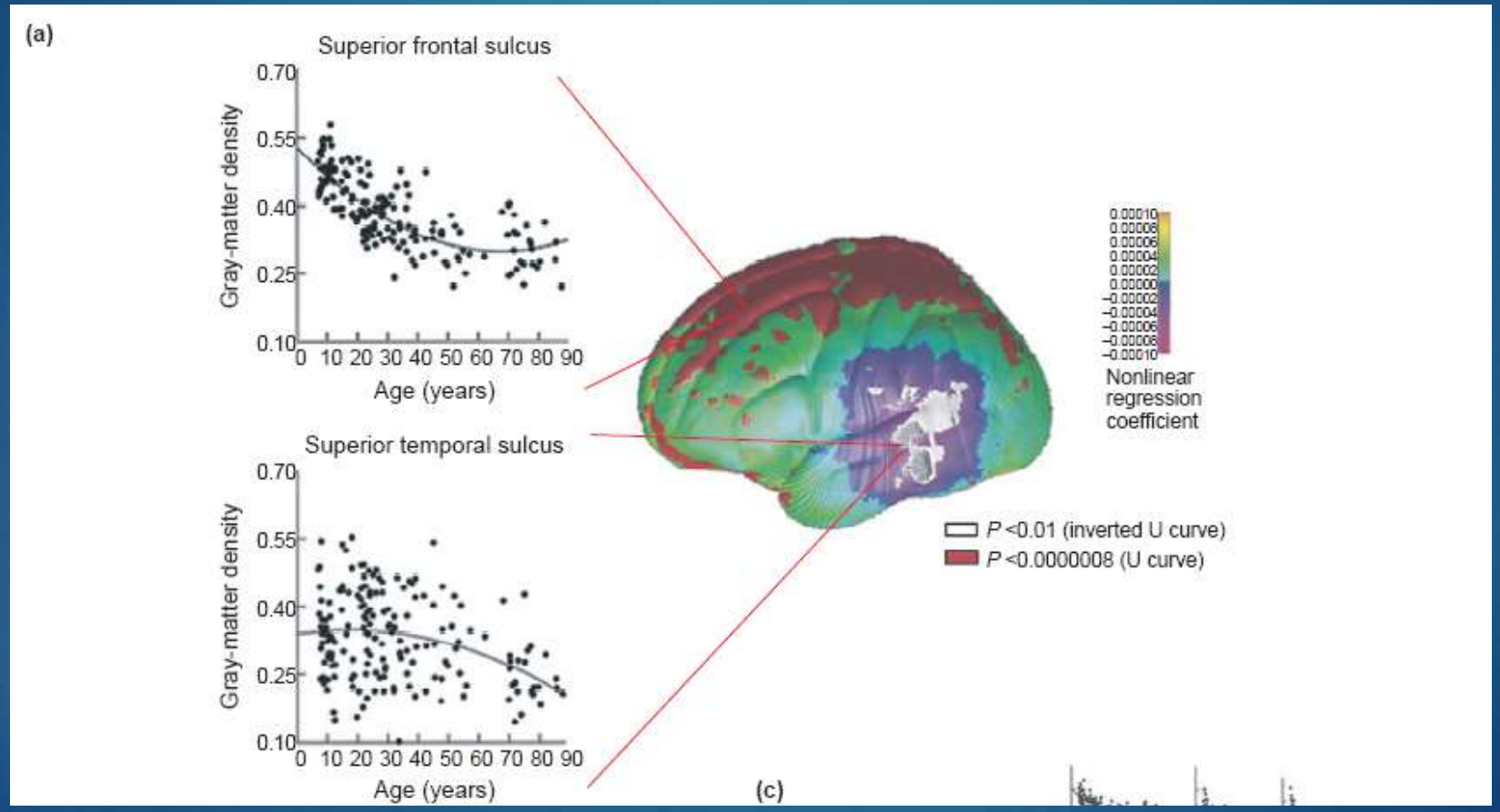
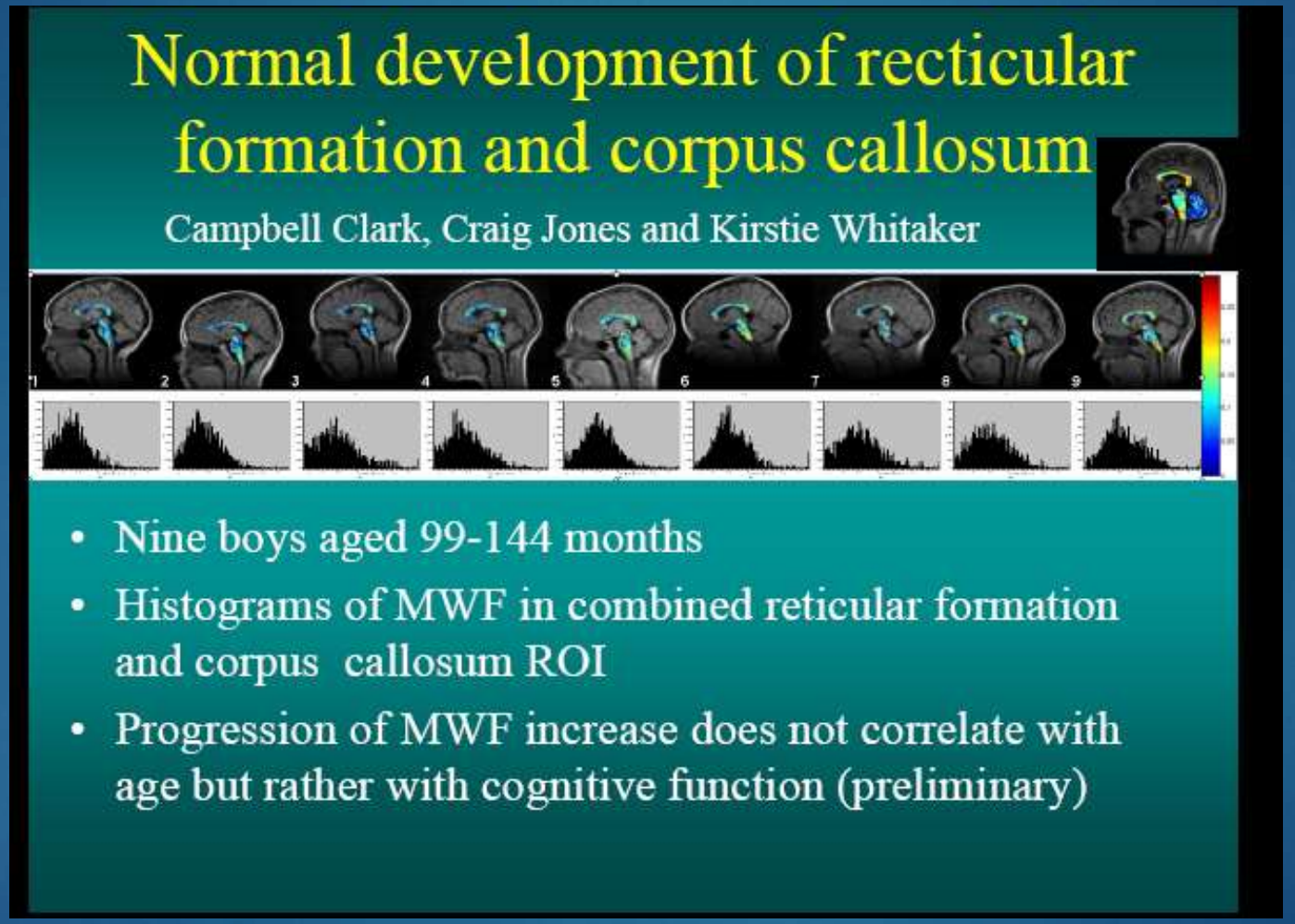
Grey matter density and age:
Rapid decrease in frontal grey in adolescence;
Steady decrease in temporal through lifespan



Myelin Water Fraction (MRI) and IQ

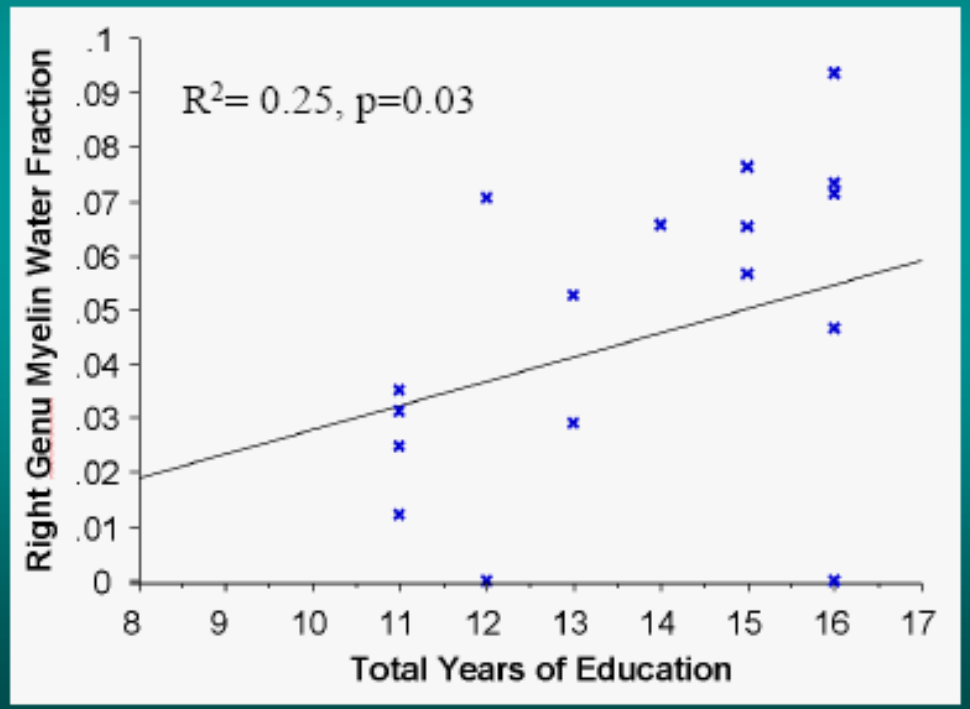


Higher IQ correlation with better myelinization

MWF and Education

MWF is correlated with education in normal volunteers

Donna Lang, in preparation



Gender Brain Size Differences: Males

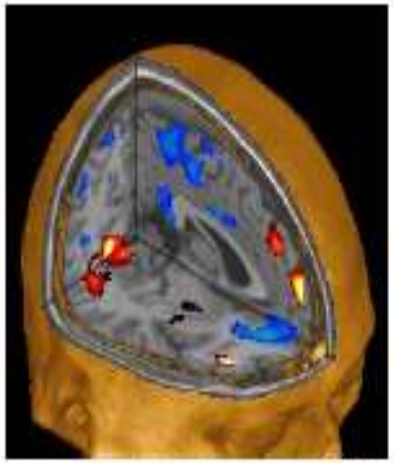
- Meta-analysis: 126 journal articles, 1990 and 2013; 18+ in age
- Males on average have larger total brain volumes than women (by 8-13%).
- Males had larger absolute volumes: in the intracranial space (12%), total brain (11%), cerebrum (10%), grey matter (9%), white matter (13%), regions filled with cerebrospinal fluid (12%), and cerebellum (9%).
- Males on average had larger volumes and higher tissue densities: in the left amygdala, hippocampus, insular cortex, putamen; higher densities in the right VI lobe of the cerebellum and in the left claustrum; in the bilateral anterior parahippocampal gyri, posterior cingulate gyri, precuneus, temporal poles, and cerebellum, areas in the left posterior and anterior cingulate gyri, and in the right amygdala, hippocampus, and putamen.

Amber Ruigrok, et al., 2014

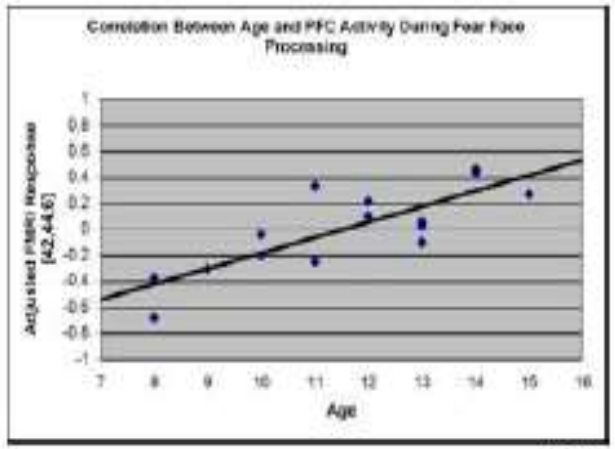
Gender Brain Differences: Females

- Females on average had higher density in: the left frontal pole, and larger volumes in the right frontal pole, inferior and middle frontal gyri, pars triangularis, planum temporale/parietal operculum, anterior cingulate gyrus, insular cortex, and Heschl's gyrus; bilateral thalami and precuneus; the left parahippocampal gyrus, and lateral occipital cortex.

Right DLPF & Fearful Affect: Development 7-16



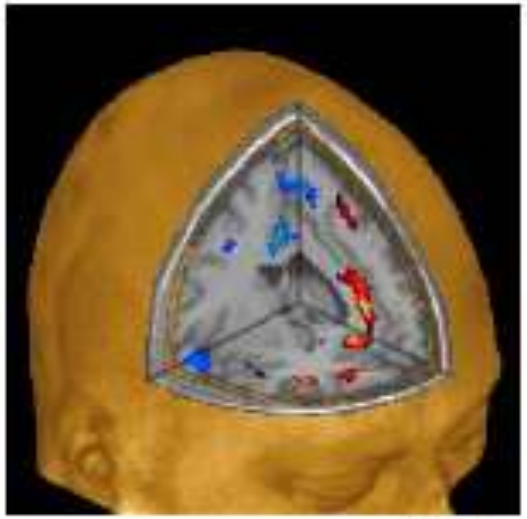
(A)



(B)

Figure 1. (A) Illustrates increased activation in the right dorsolateral prefrontal cortex during the perception of fearful affect. (B) Scatterplot demonstrates the significant age-correlated activation seen in the right dorsolateral prefrontal cortex during the perception of fearful affect.

Anterior Cingulate and happy affect perception: Development 7-16



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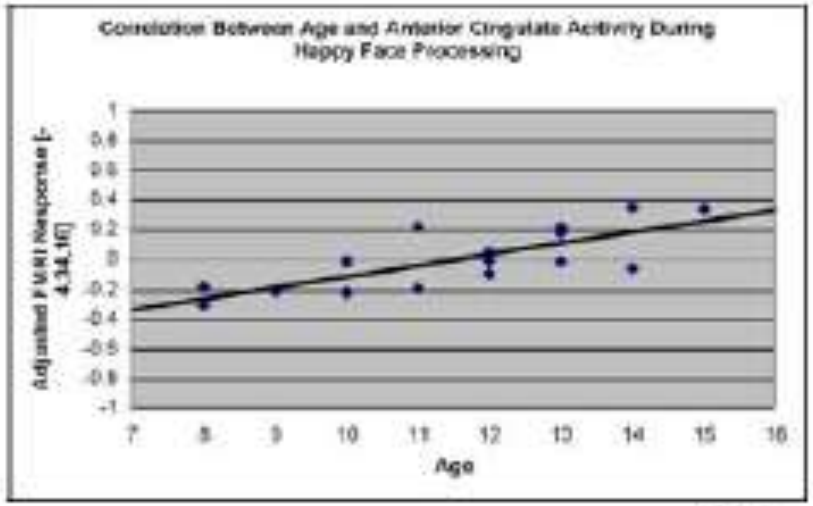

(B)

Figure 2. (A) Increased activation in the anterior cingulate during the perception of happy affect. (B) Scatterplot demonstrates the significant age-correlated activation in the anterior cingulate cortex during the perception of happy affect.

Adolescent Development: Cerebellar