ACES and Epigentics

John B. Arden, PhD, ABPP

Mind-Brain-Gene Feedback Loops

The ACE Study

- Examined the health effects of ACE's throughout the lifespan among 17, 421 members of Kaiser Permanente in San Diego county
- What are Adverse Childhood Experience?
  - Childhood abuse and neglect
  - Growing up with domestic violence, substance abuse, parental discord, crime, or mental illness in the home

Categories of Adverse Childhood Experiences

Abuse, by Category	**Category Prevalence (%)**
• Psychological (by parents)	11%
• Physical (by parents)	11%
• Sexual (anyone)	22%
Household Dysfunction, by Category	
• Substance Abuse in family	26%
• Mental Illness in family	19%
• Domestic Violence	13%
• Imprisoned Household Member	3%
• Loss of parent	23%

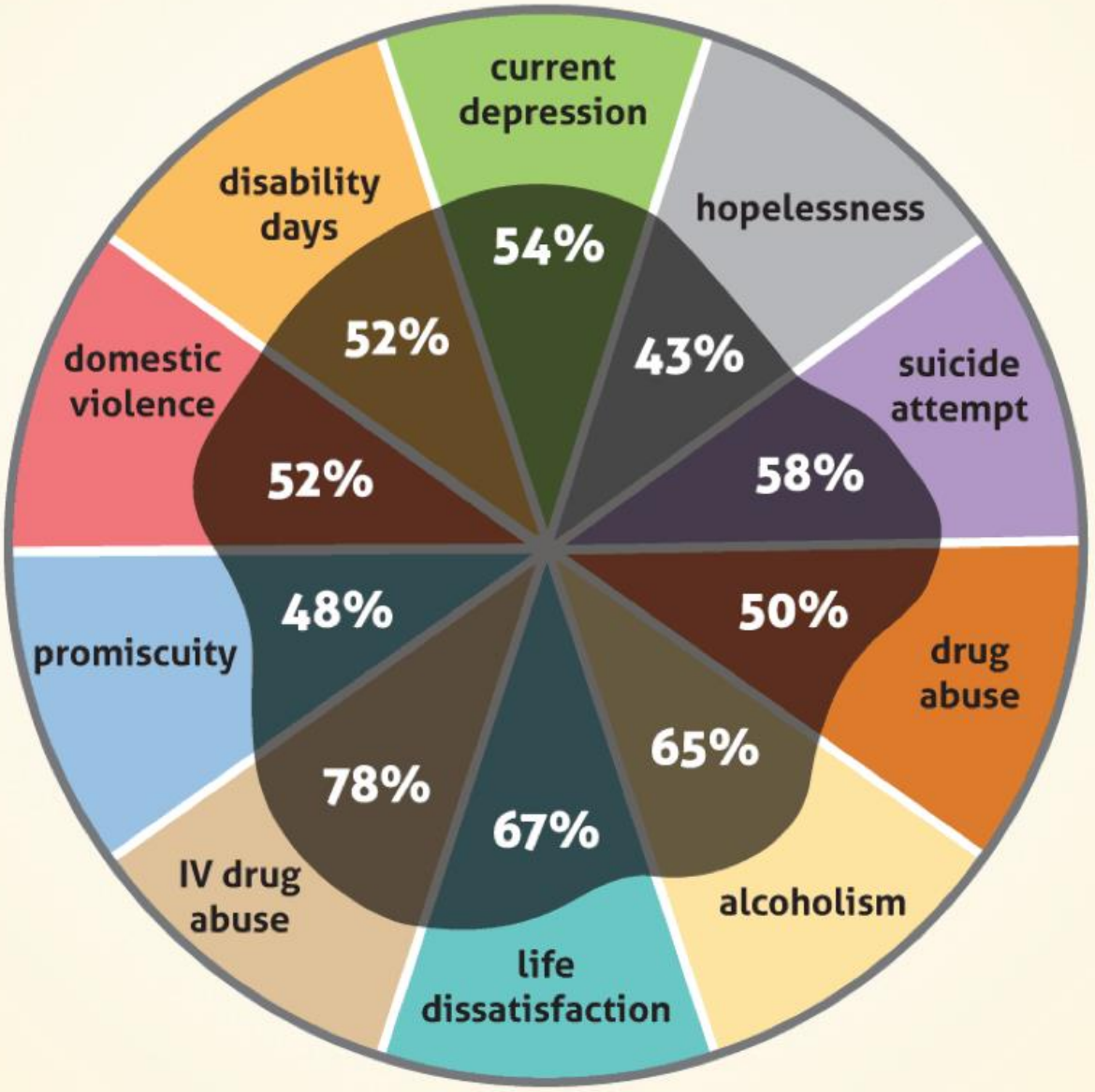
ACEs score percentages

Number of categories of childhood experiences are summed

ACE Score	*Prevalence*
0	48%
1	25%
2	13%
3	7%
4	7%

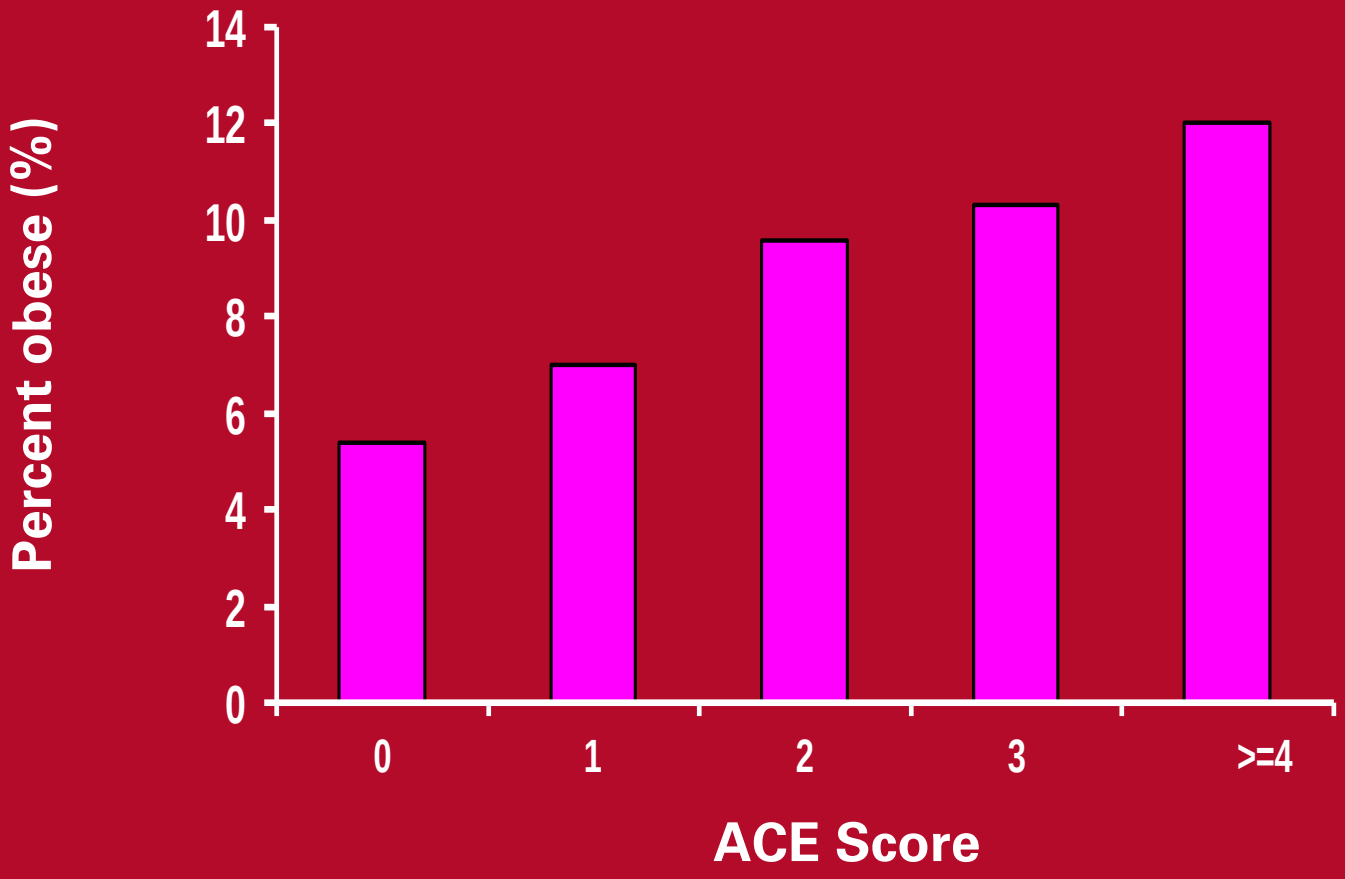
- More than *half have at least one ACE*
- Slightly more than one quarter have experienced 2 – 4 ACE categories

ACEs and Population Attributable Risks

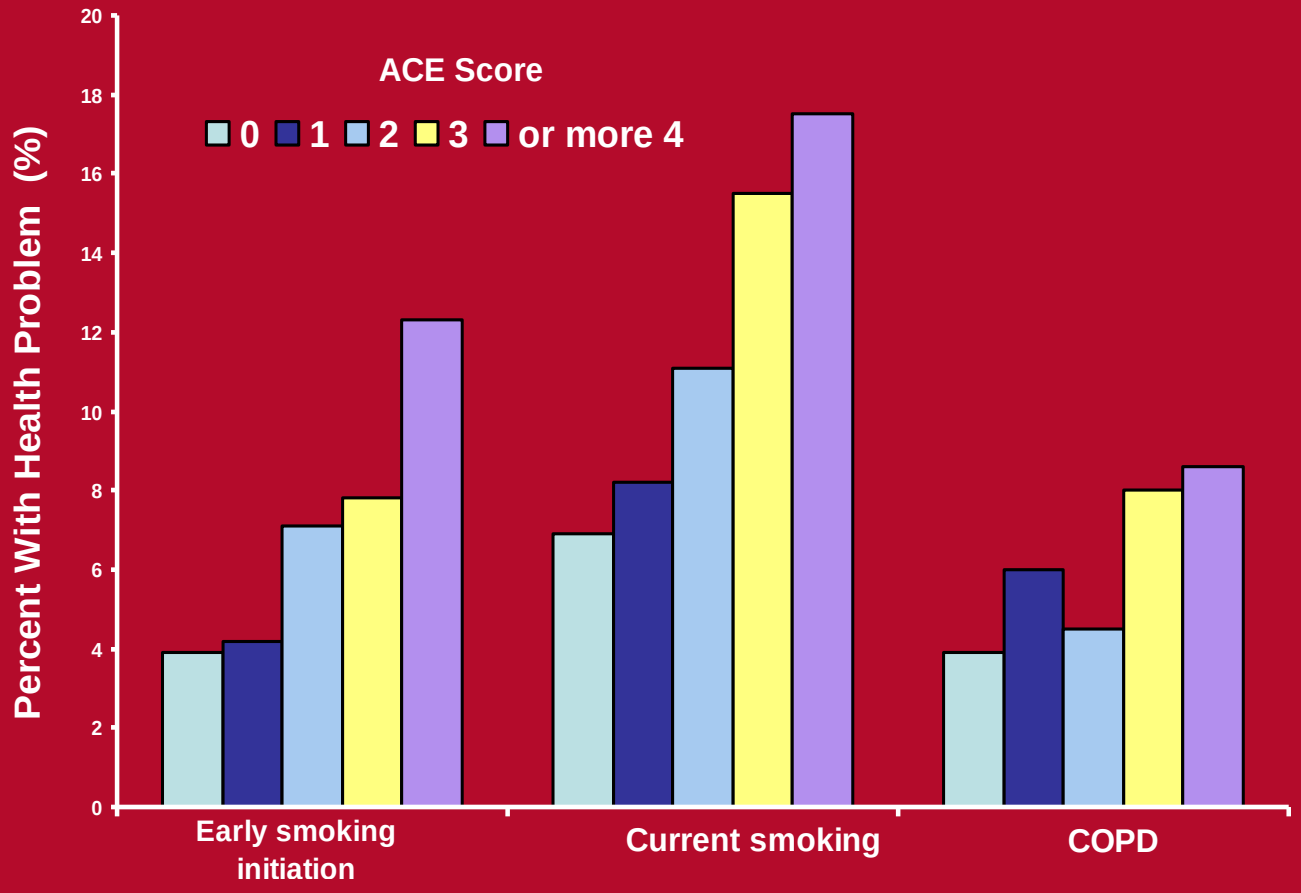


ACE Interface © 2013

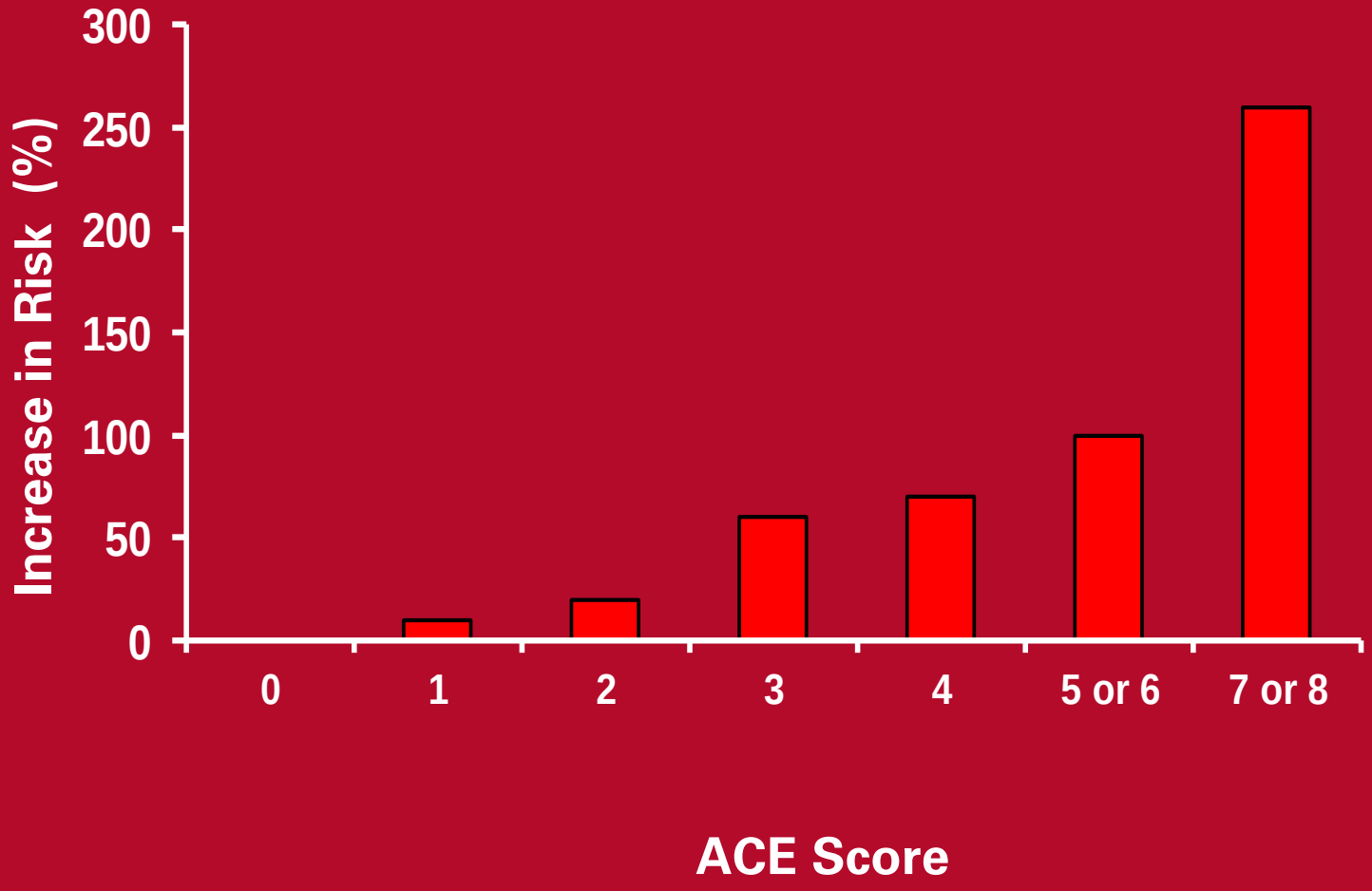
The ACE Score and the Prevalence of Severe Obesity (BMI>35)



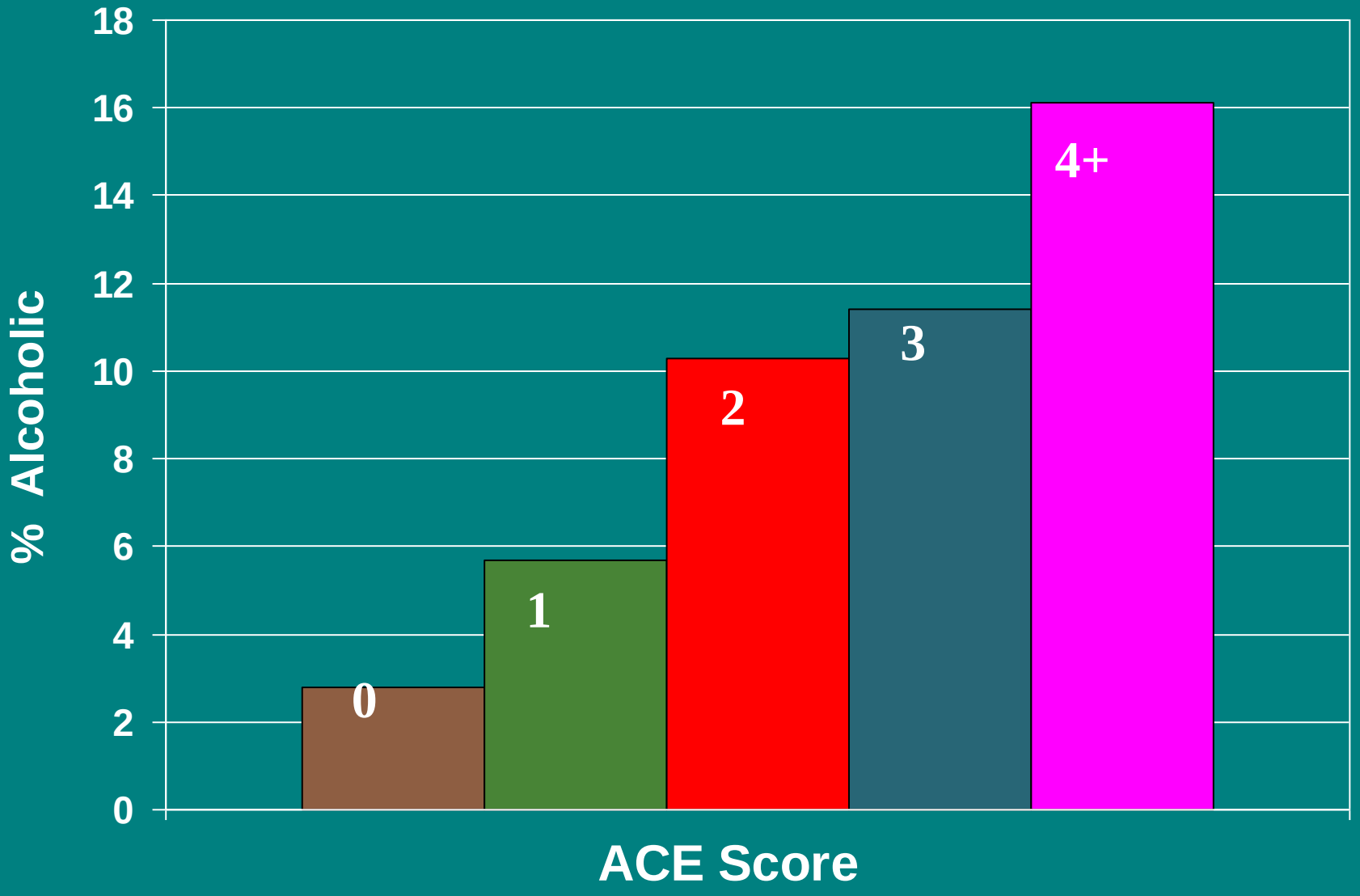
ACE's Smoking and Lung Disease



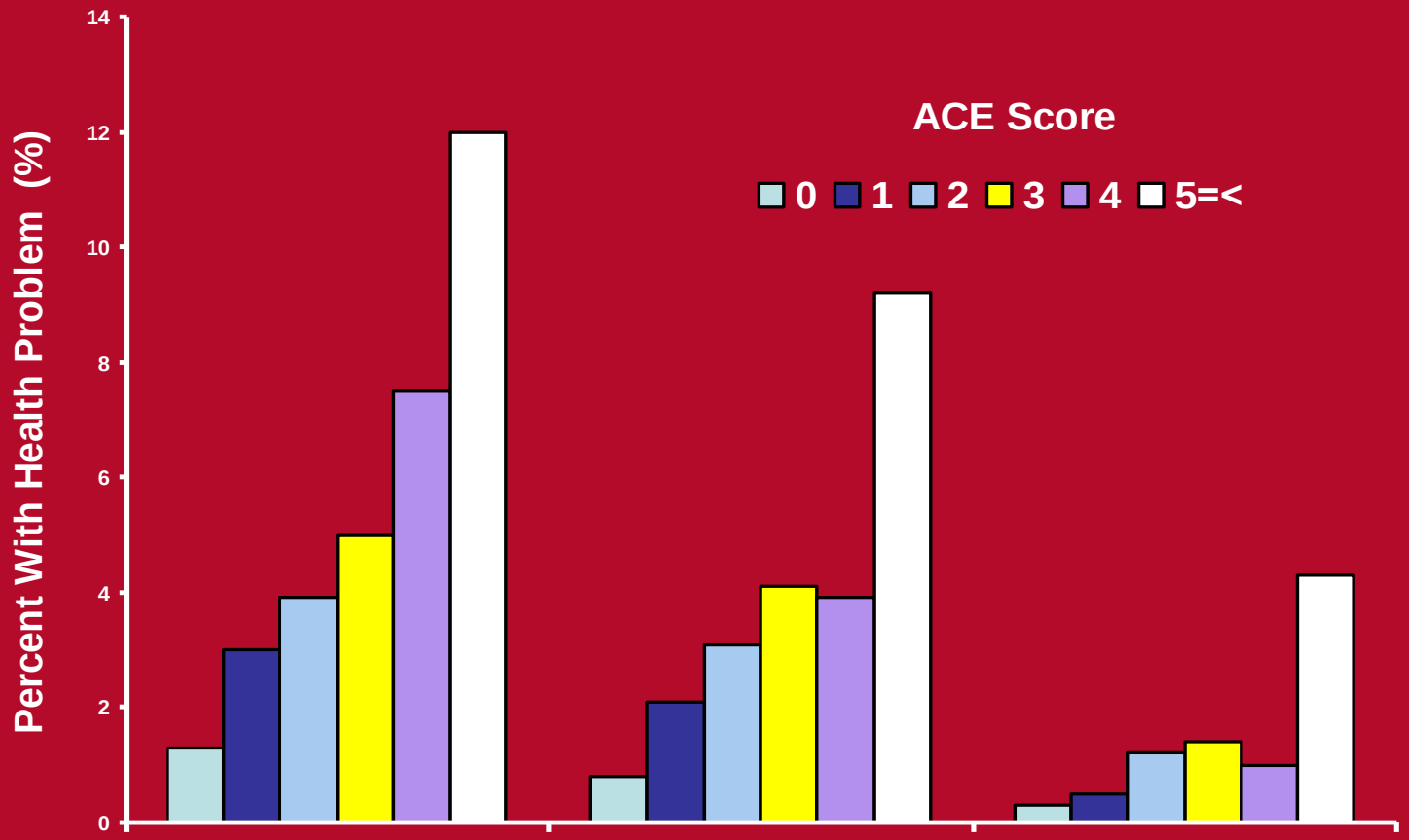
The ACE Score and the Risk of Coronary Heart Disease



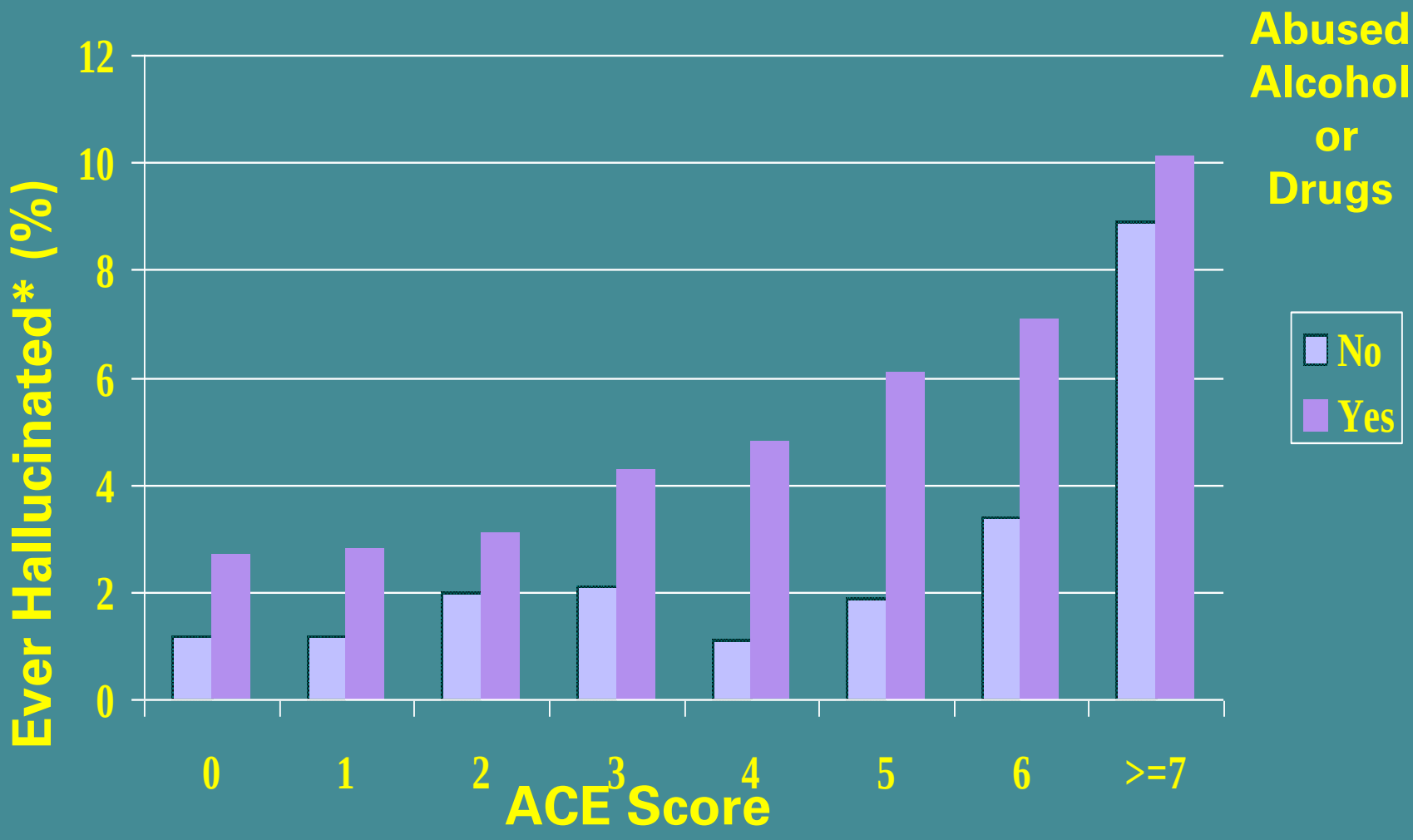
ACE Score and Adult Alcoholism



The ACE Score and Drug Addiction

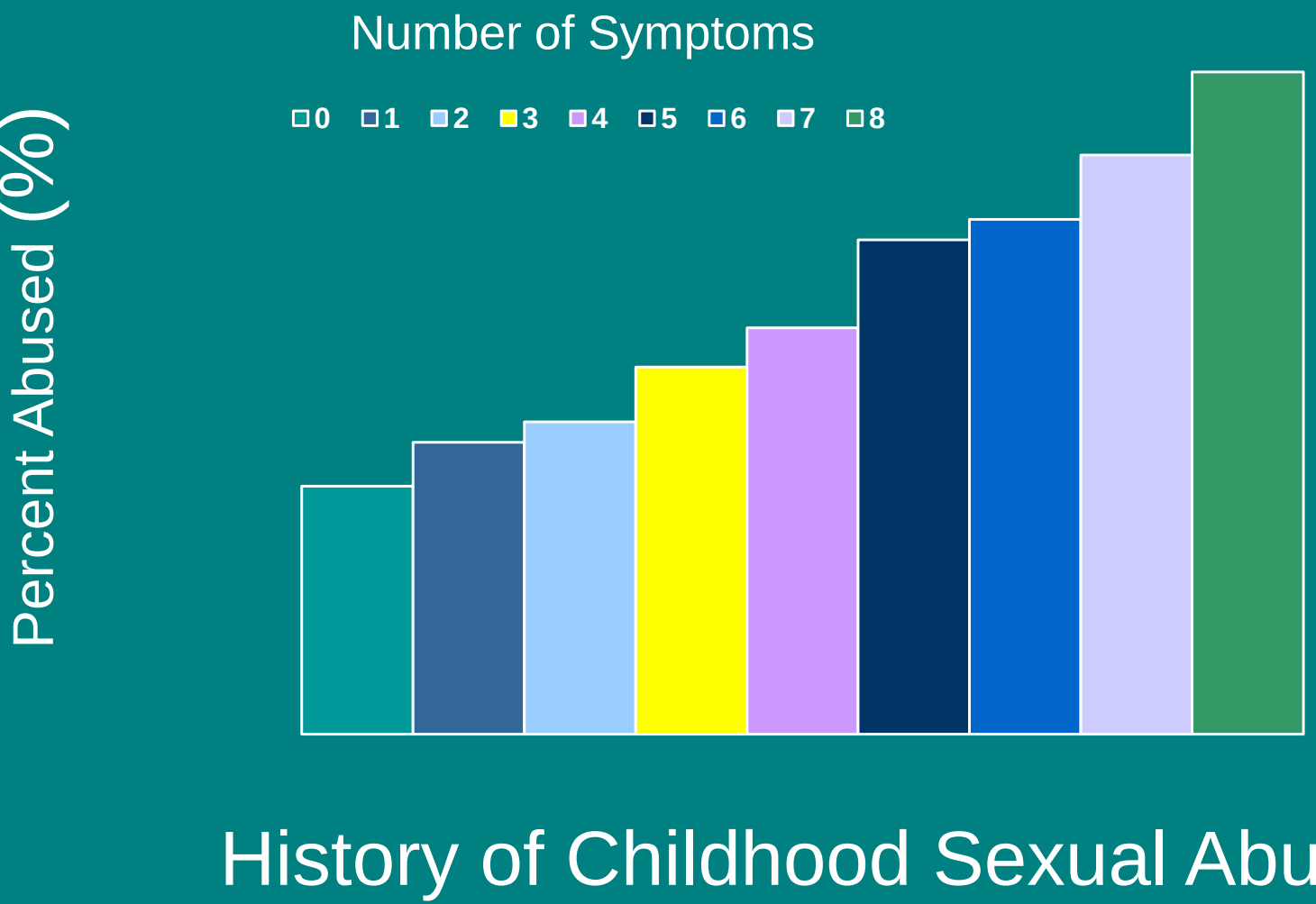


ACE Score and Hallucinations

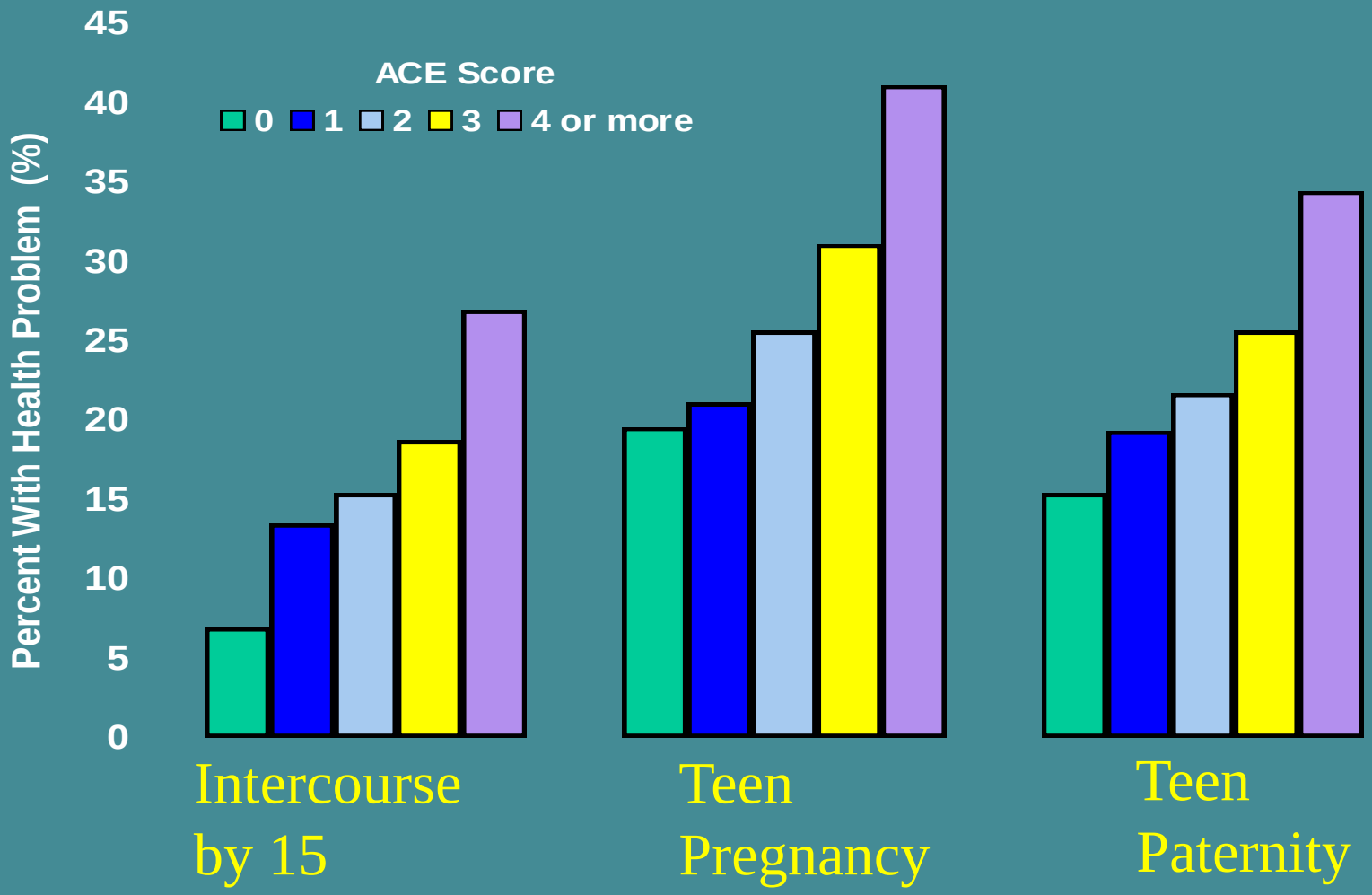


*Adjusted for age, sex, race, and education.

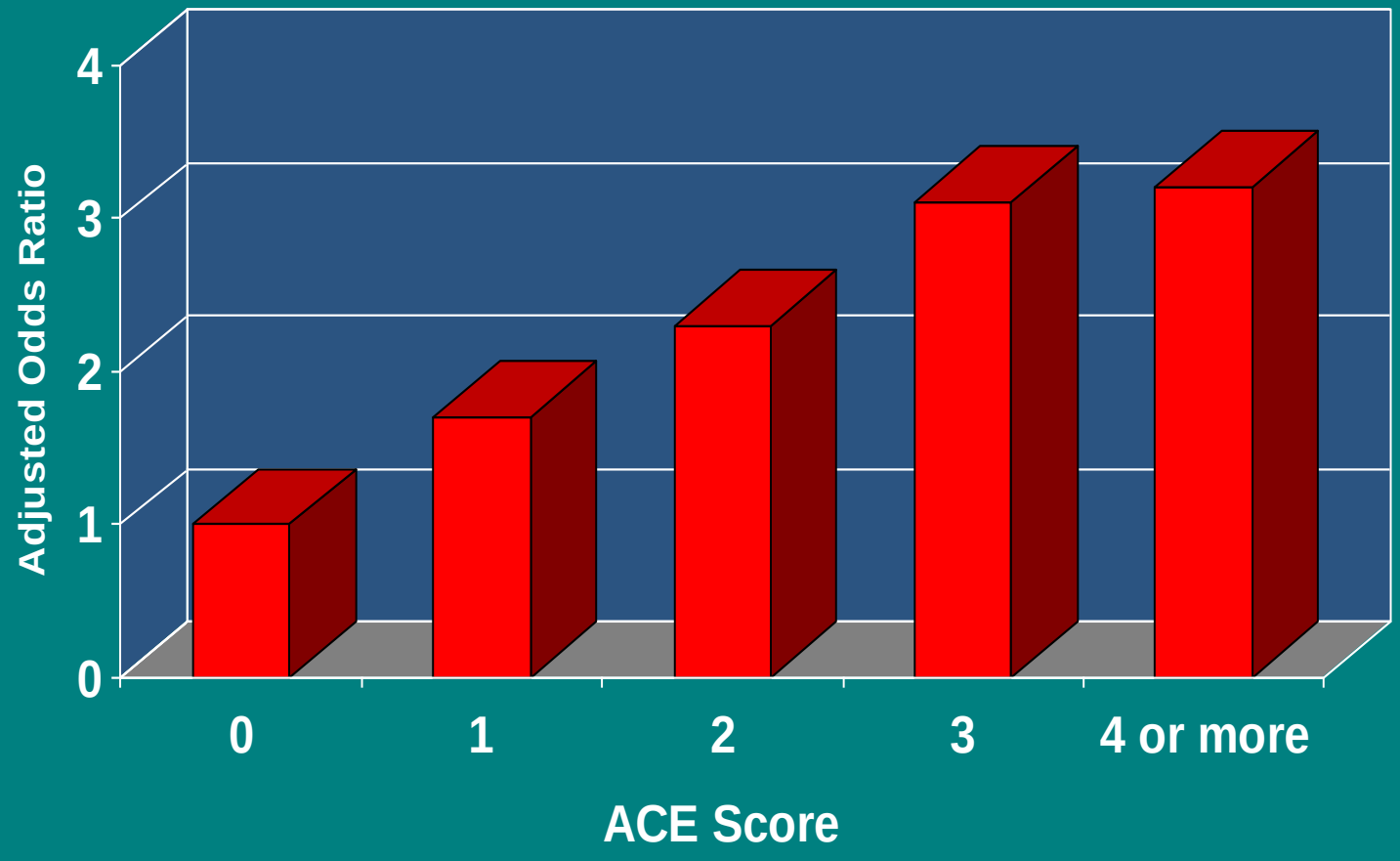
Childhood Sexual Abuse and the Number of Unexplained Symptoms



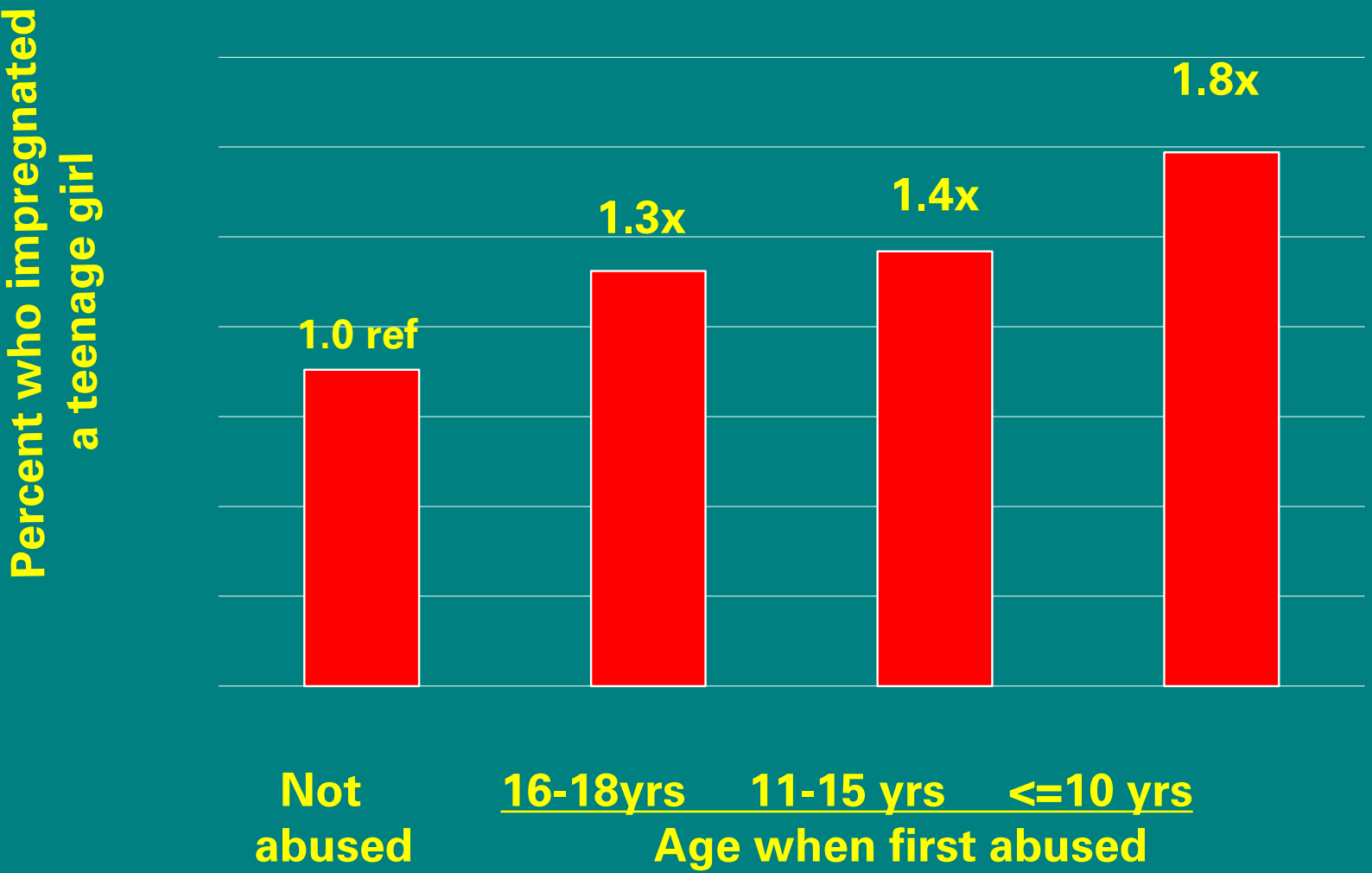
ACE Score and Teen Sexual Behaviors



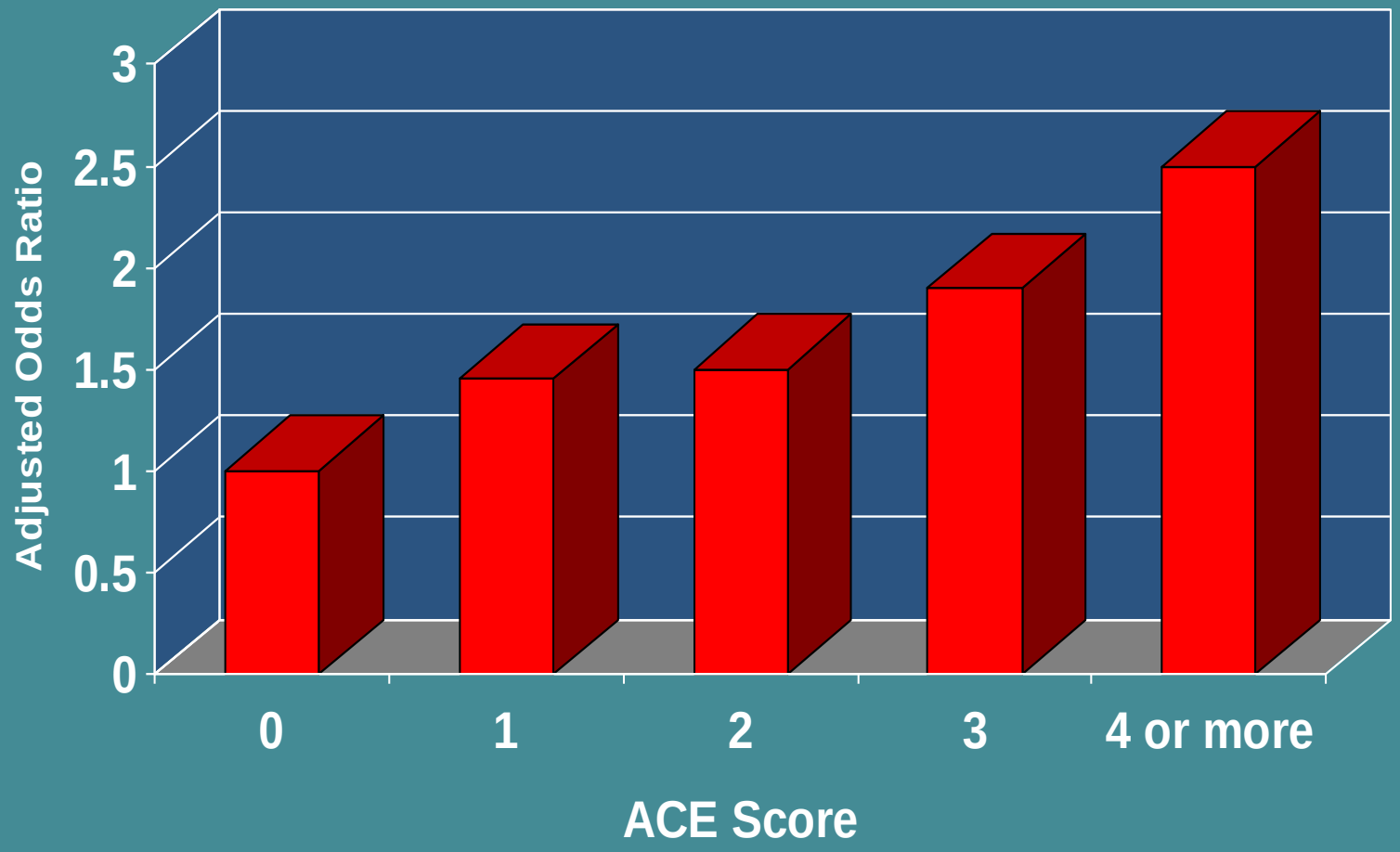
ACE Scores and Likelihood of > 50 Sexual Partners



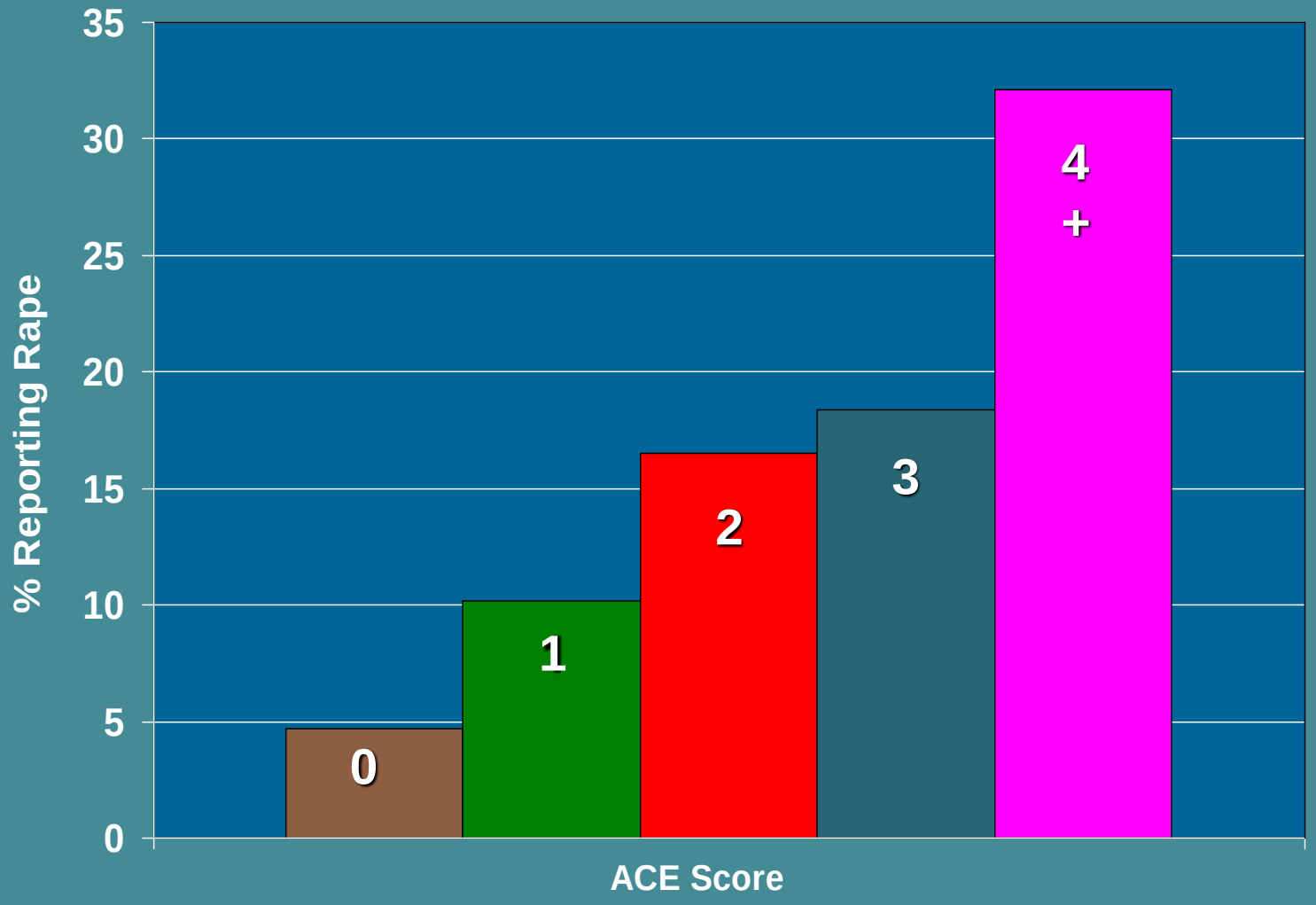
Sexual Abuse of Male Children and Their Likelihood of Impregnating a Teenage Girl



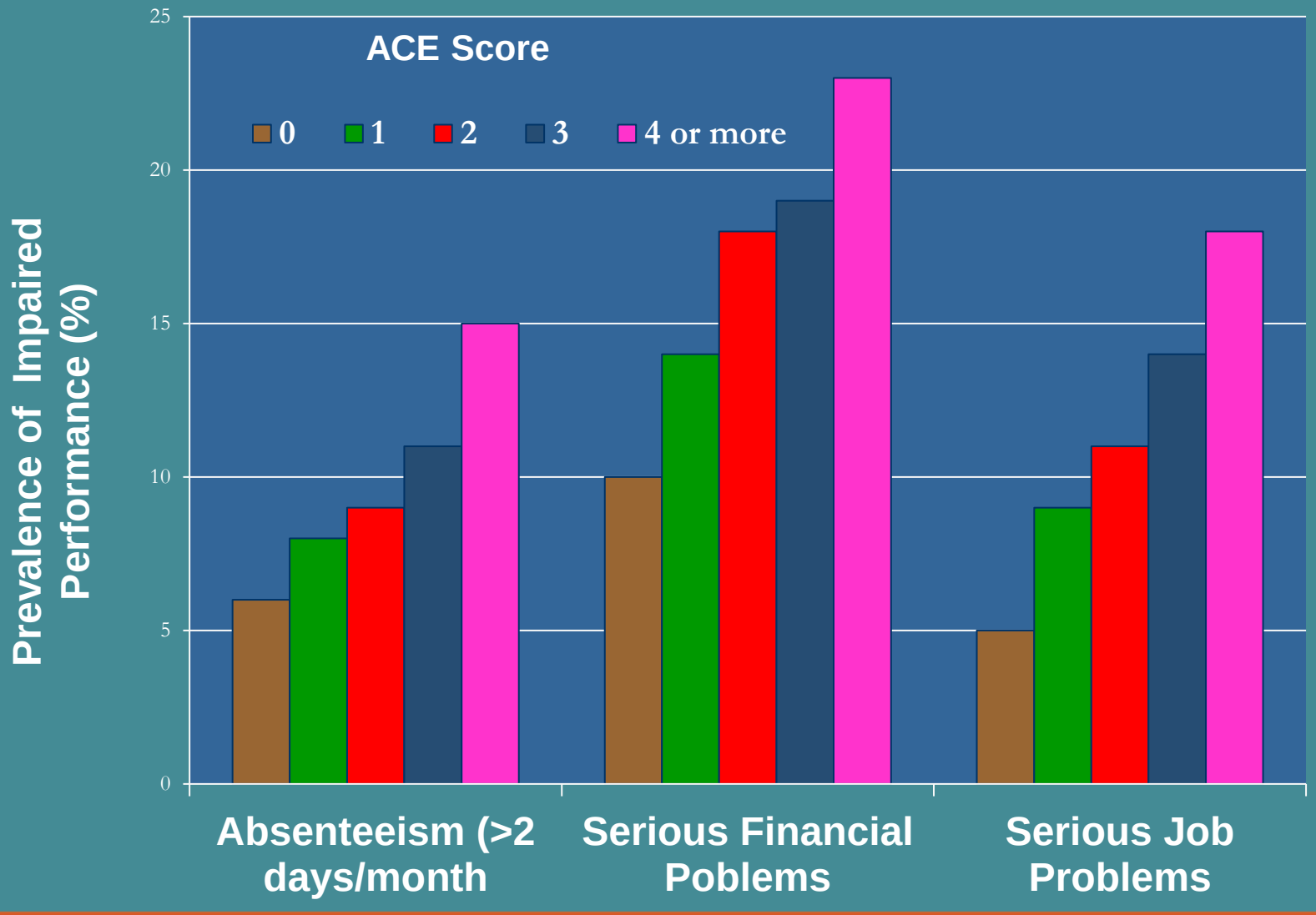
ACE Scores and History of STDs



Childhood Experiences Underlie Later Being Raped

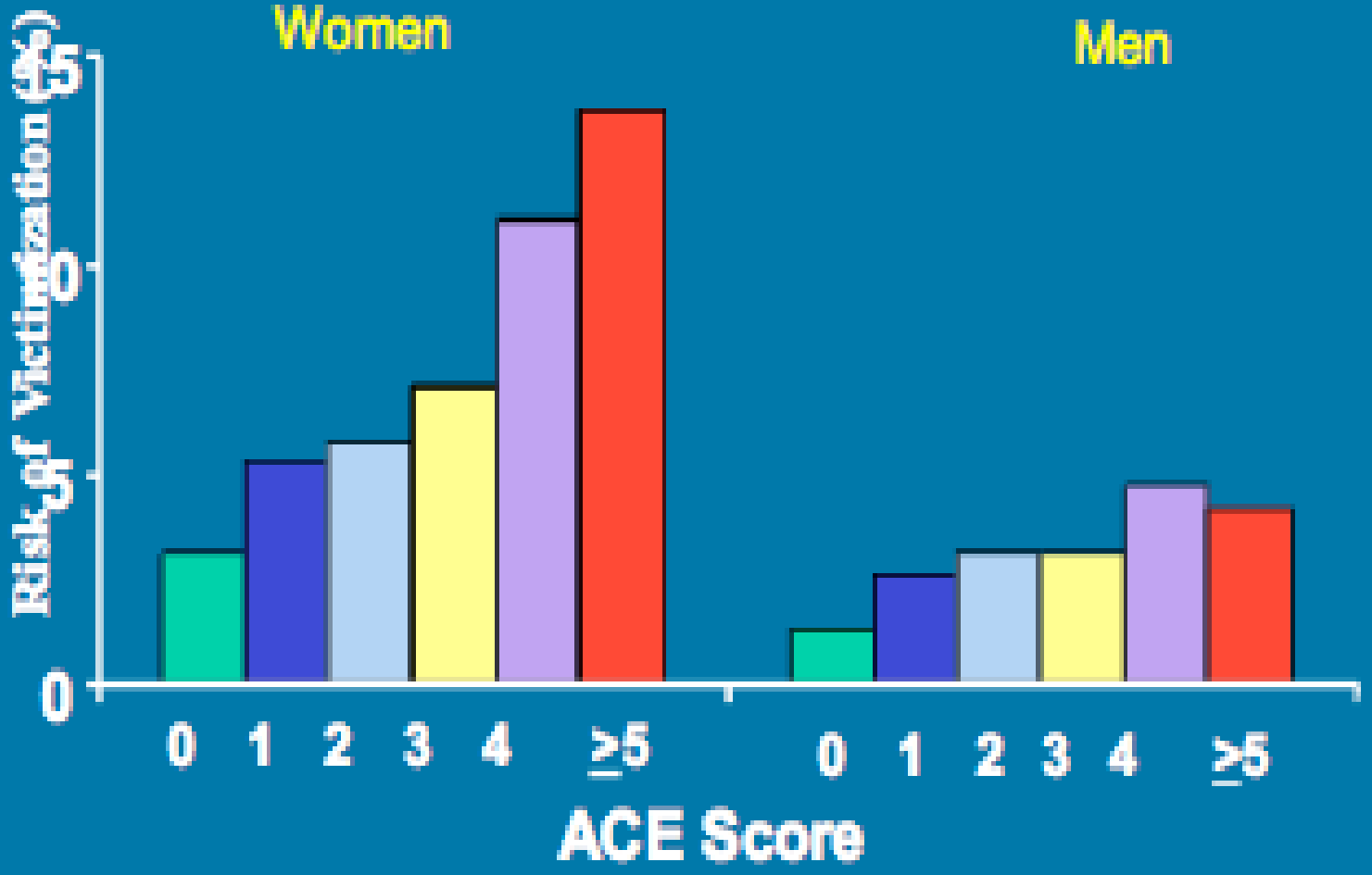


ACE Score and Indicators of Impaired Worker Performance

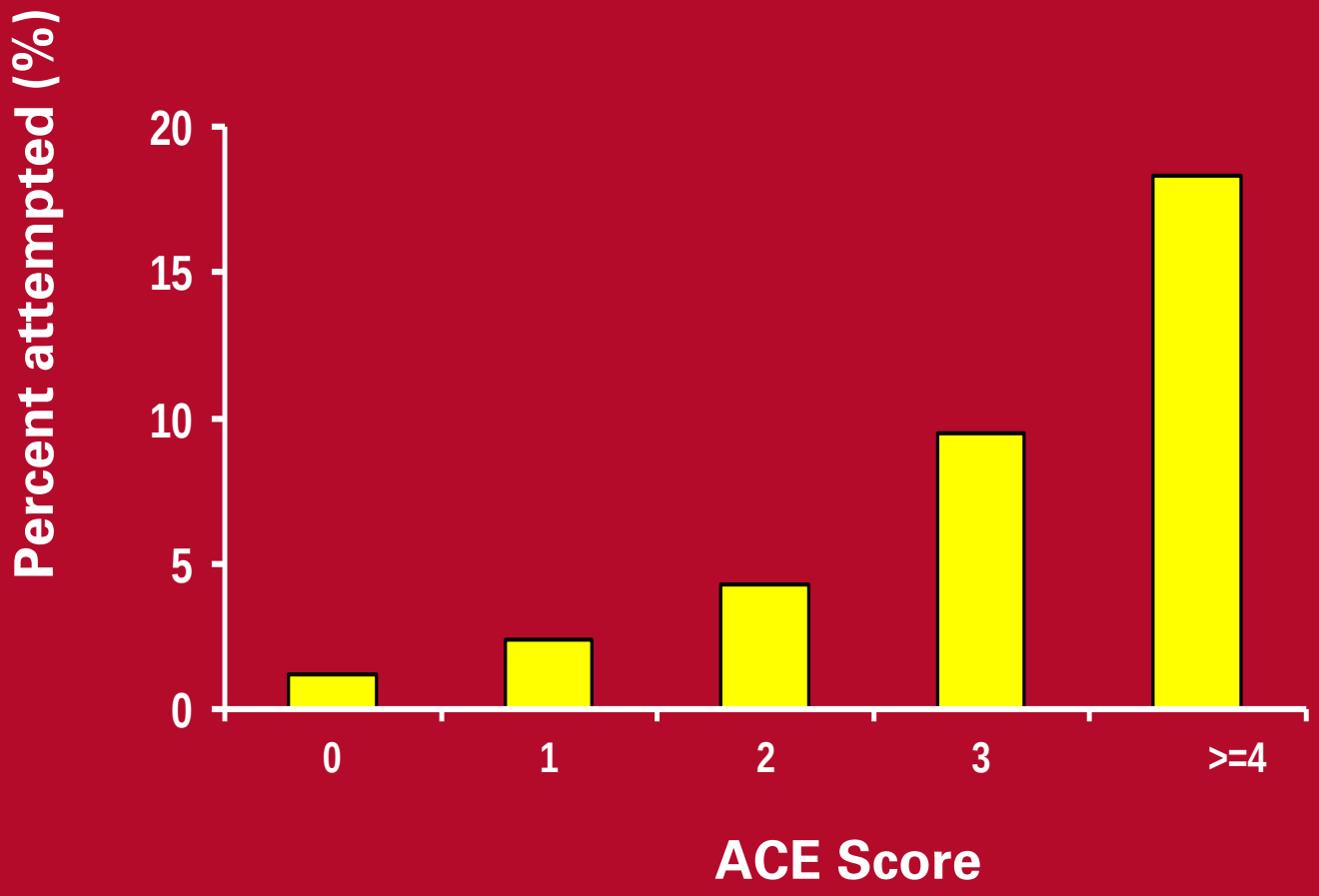


Well-being

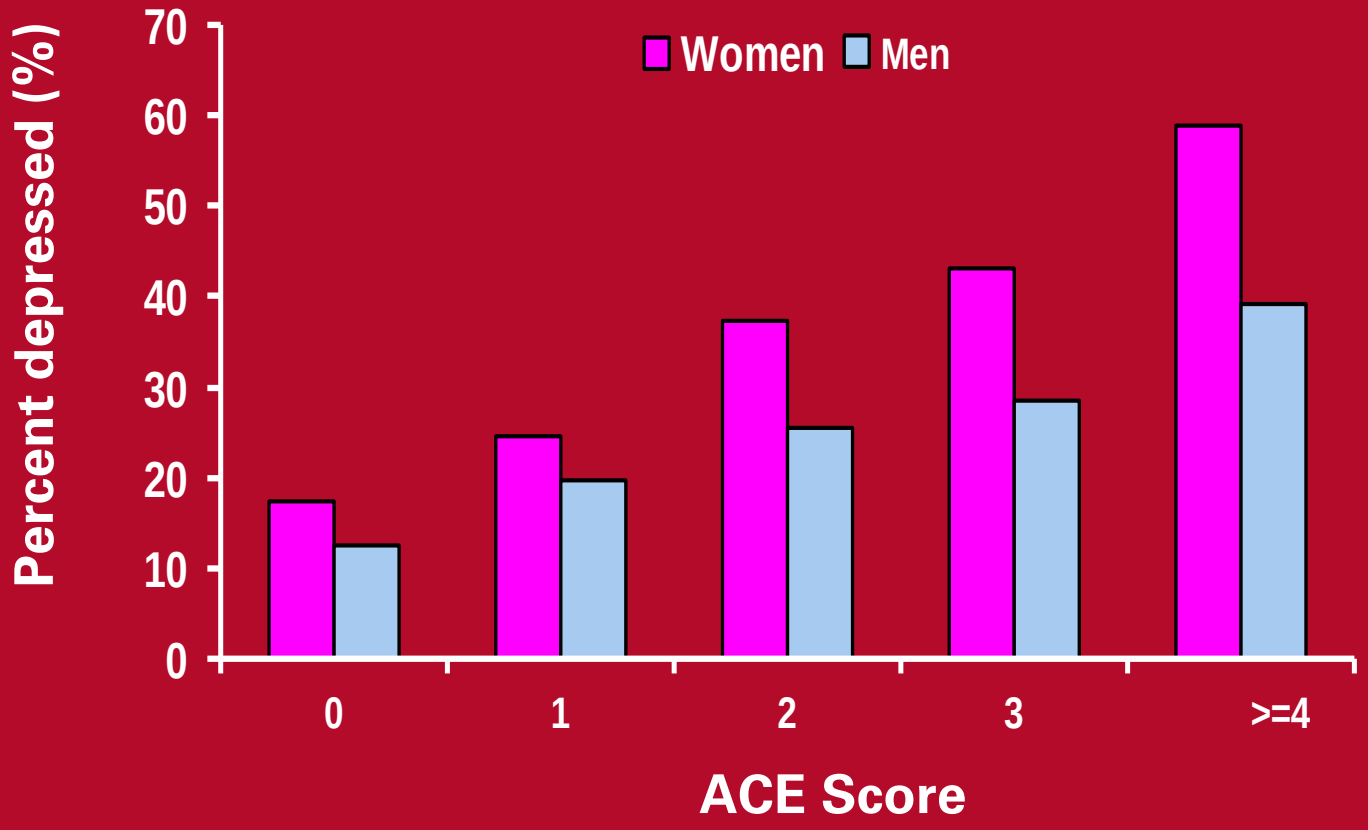
ACE Score and the Risk of Being a Victim of Domestic Violence



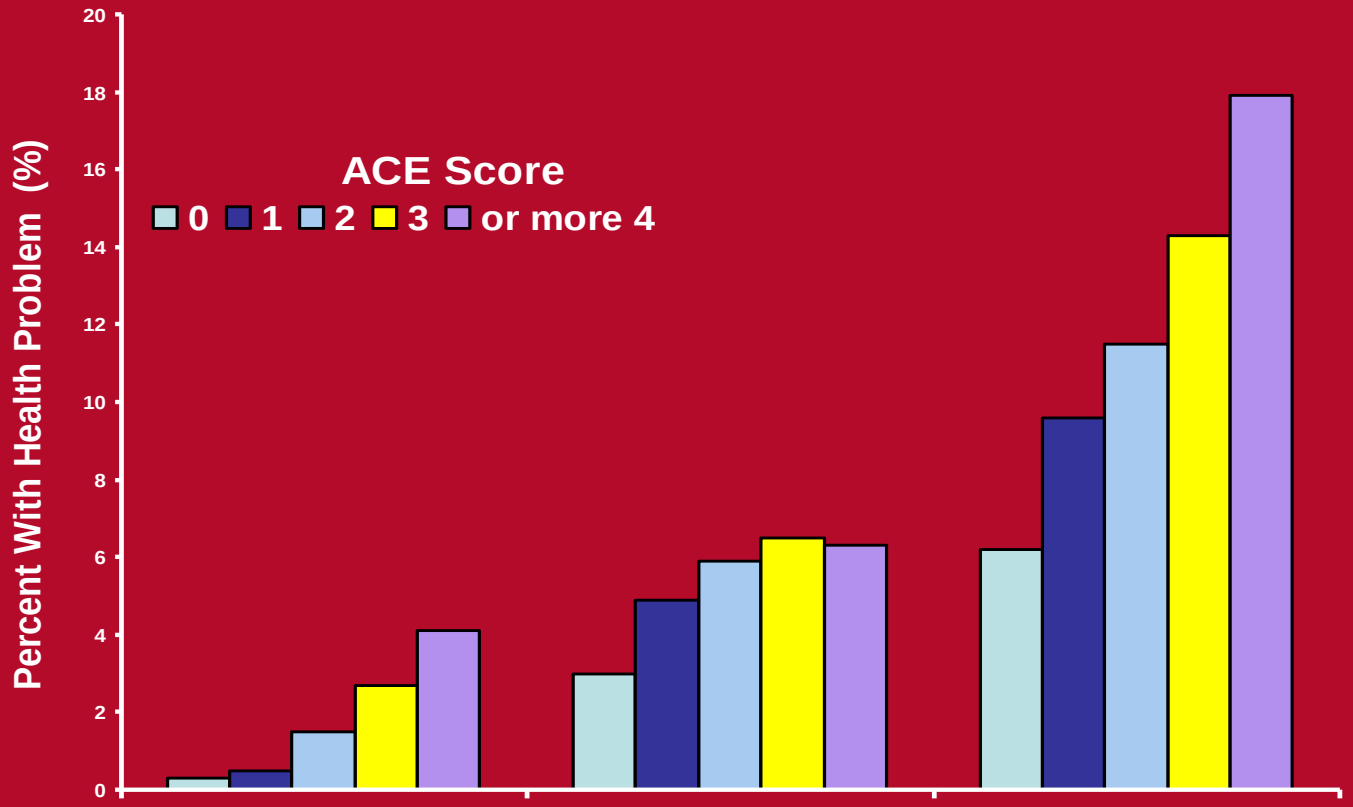
The ACE Score and the Prevalence of Attempted Suicide



The ACE Score and a History of Lifetime Depression

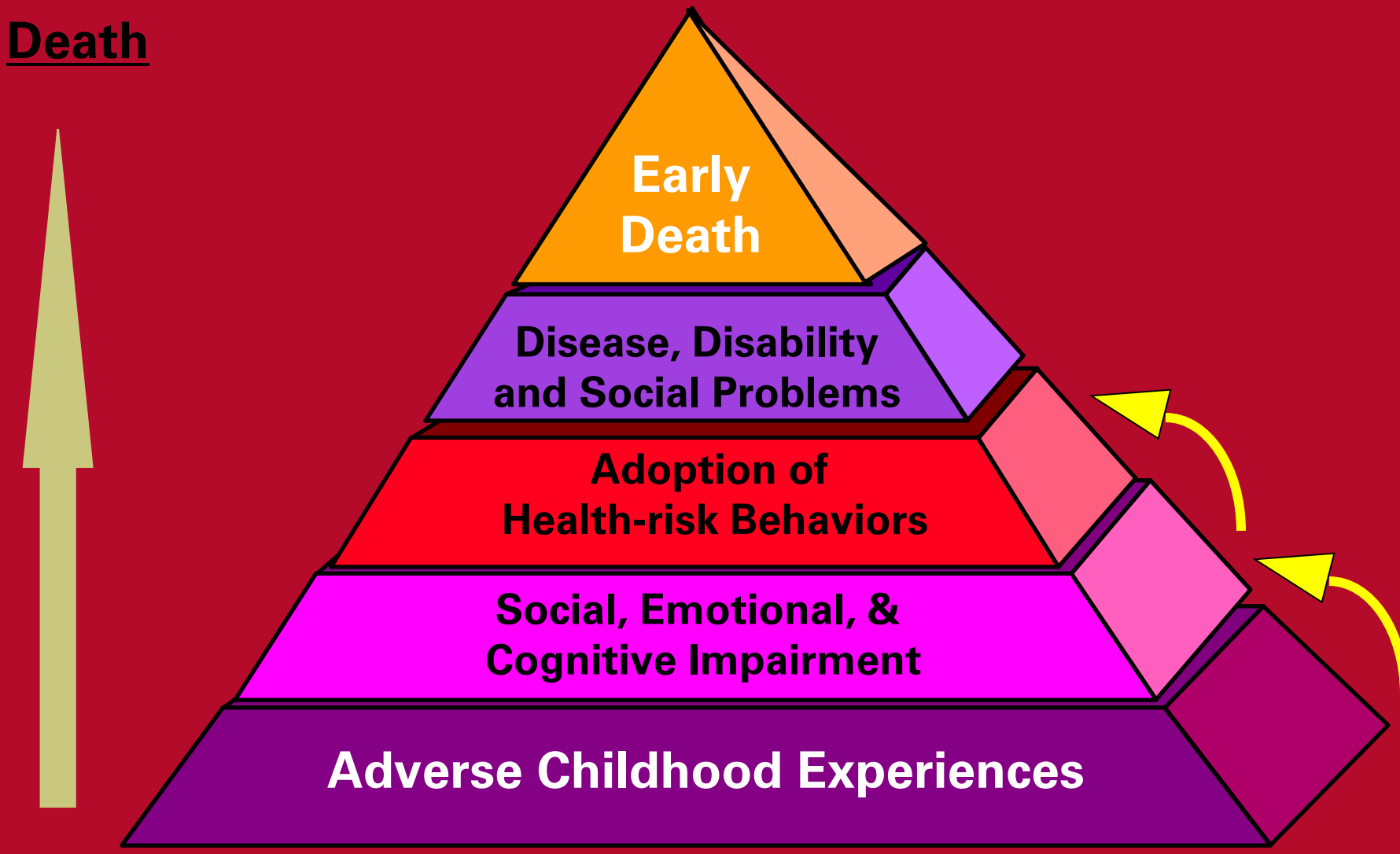


ACE Score and HIV Risks



A Connection with Homelessness

- Psychological disorders and substance abuse are more common among homeless people
- ACEs connection to substance abuse and psychological disorders
- Over 50% of homeless with ACE Score of 4 or higher


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

Hunter-gatherer Adaptation Boosted the Social Brain

Hungry Social Networks

- Brain development involves many forms:
  - the establishment of synaptic connections
  - the pruning of others
  - changes to the behavior of a single ion channel
  - dendritic outgrowth
  - changes to the shape and number of sprouting new axons
  - modifying their dendritic surfaces

(Kolb & Gibb, 2001)

The Cost of Loneliness

- In the long-run as detrimental as smoking to longevity (Cacippo & Hawley, 2009)
- The temporal-parietal junction (TPJ)—associated with cognitive empathy is much less activated and can atrophy
  - Creates a downward spiral → less successful → less successful
- Less activity of the ventral tegmental area (VTA) and the nucleus accumbuns
  - Less of a sense of pleasure

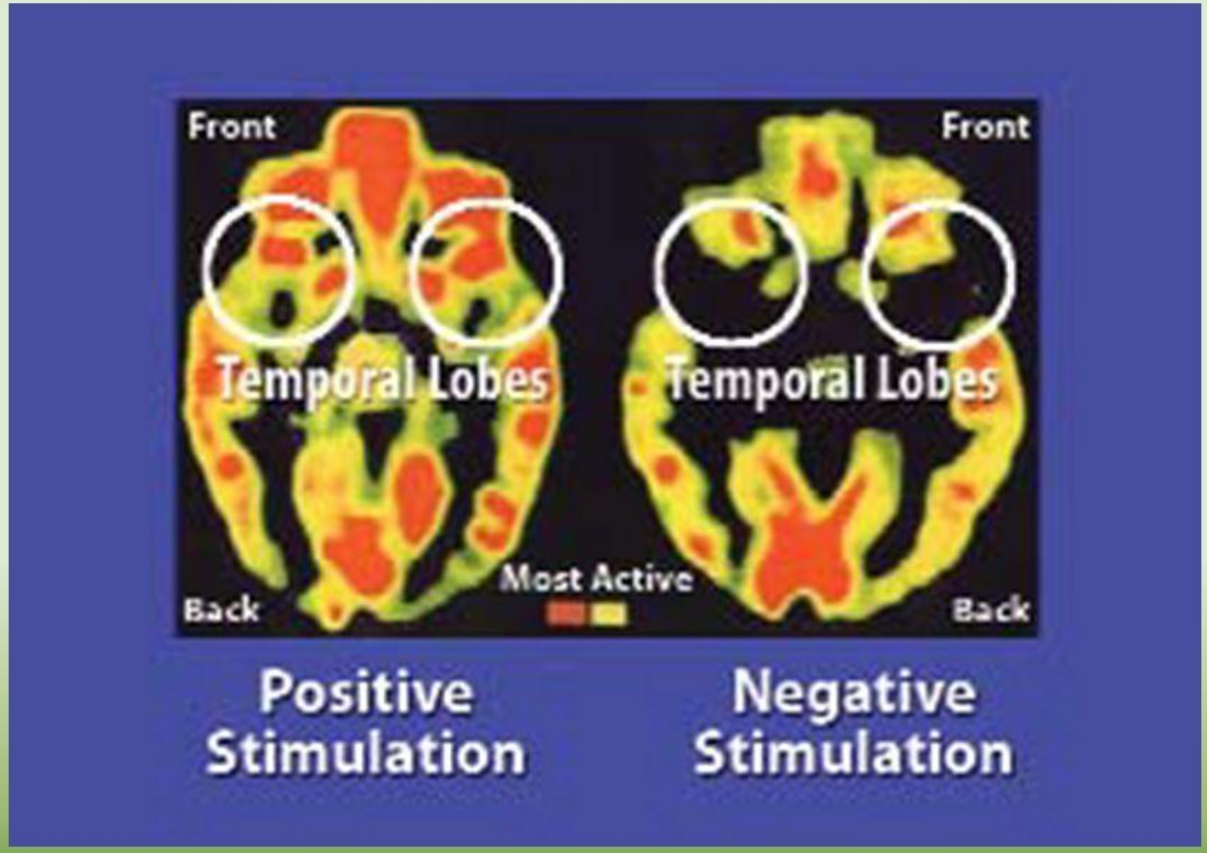
Deprived Social Brain Networks

- 150,000 children found languishing in Romanian orphanages. They were emotionally neglected.
- They missed human contact during critical periods (Kuhn & Schanberg, 1998).

Sustained impairment if over one year

  - Increased Cortisol
  - Impaired OFC
  - Cognitive impairments (i.e. ADD)
  - Shorter Telemeres

“Normal” vs Romanian Brains

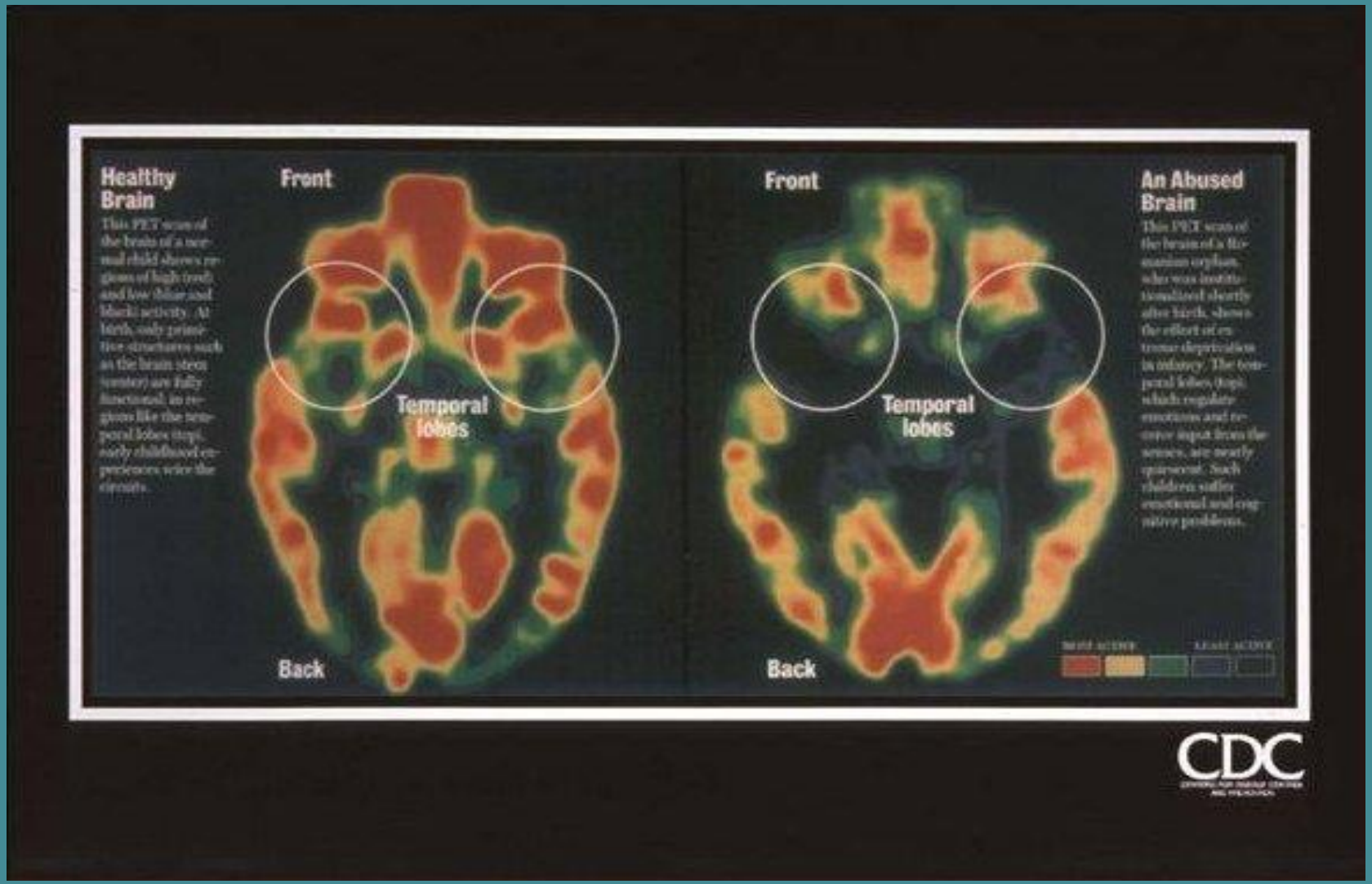


Brain activity of a normal five-year-old child (left)
and a five-year-old institutionalized orphan neglected in infancy (right).

Child Abuse and Neuropathology

- **Diminished left hemisphere and left hippocampal volume** (Bremner et al., 1997).
- **Accelerated loss of neurons** (Simantov, et. al., 1996)
- **Delays myelination** (Dunlap, et. al., 1997)
- **Abnormalities in developmentally appropriate pruning** (Todd, 1992)
- **Inhibition of neurogenesis** (Gould, et. al., 1997)
- **Adults who were physically or sexually abused as children – high IL-6 & CRP**
  - **diminished left hippocampal development** (Howe, Roth, & Cicchetti, 2006).

“Normal” vs Abused Brains



The Neuroscience of Attachment

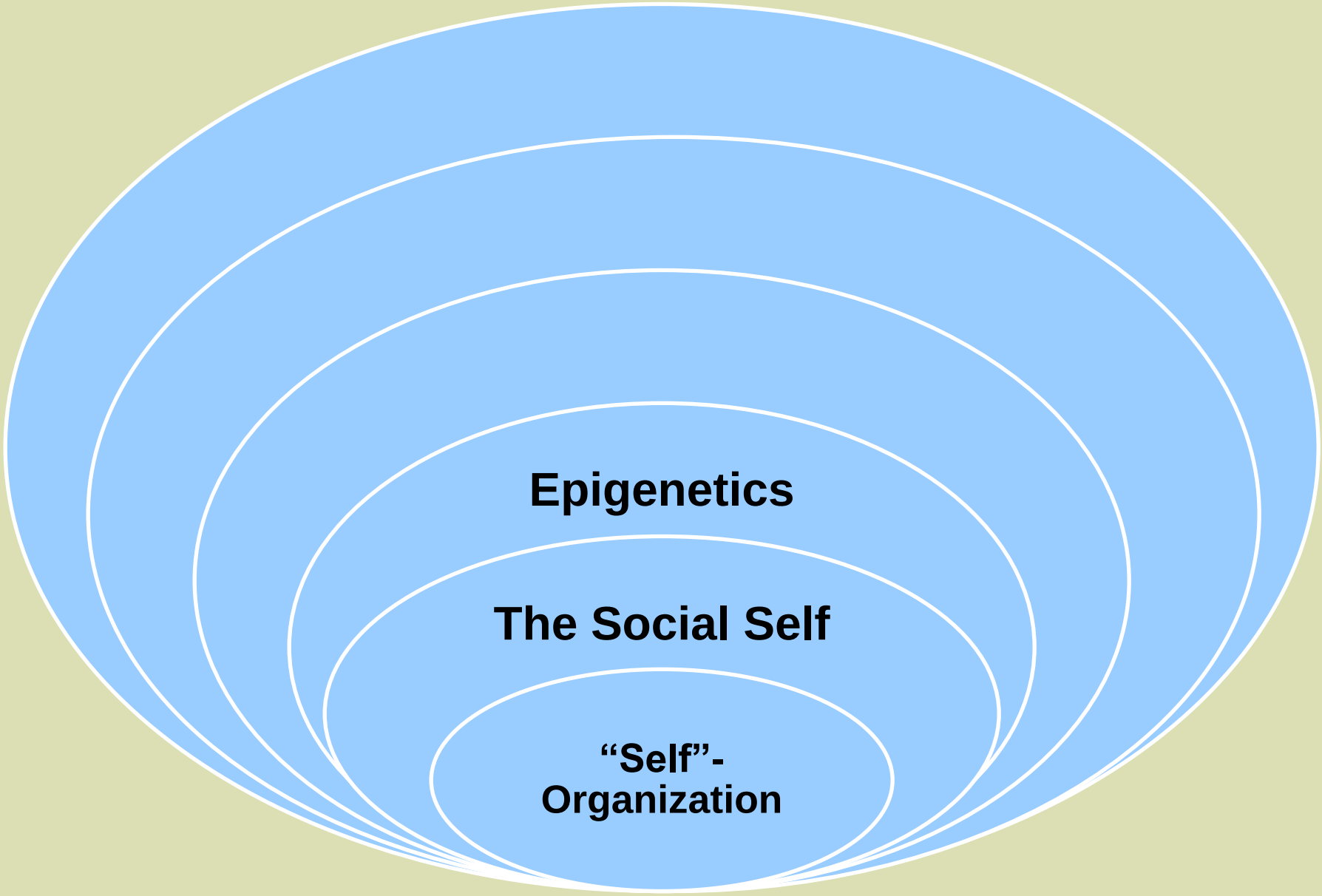
- Balance Between the two branches of the Autonomic Nervous System
- Endorphin & Benzodiazepine receptors
- Cortisol Regulation
- Positive Immunological Functioning
- Neural Growth and Plasticity

Good-enough parenting and frustration tolerance

- **If the baby is matched by instantaneous soothing s/he will not develop the PNS and the brakes to the SNS and HPA axis**
- **Good enough parenting factors in time before the baby is soothed**
  - **To anticipate being soothed and activate the parasympathetic nervous system**
  - **builds in frustration tolerance**

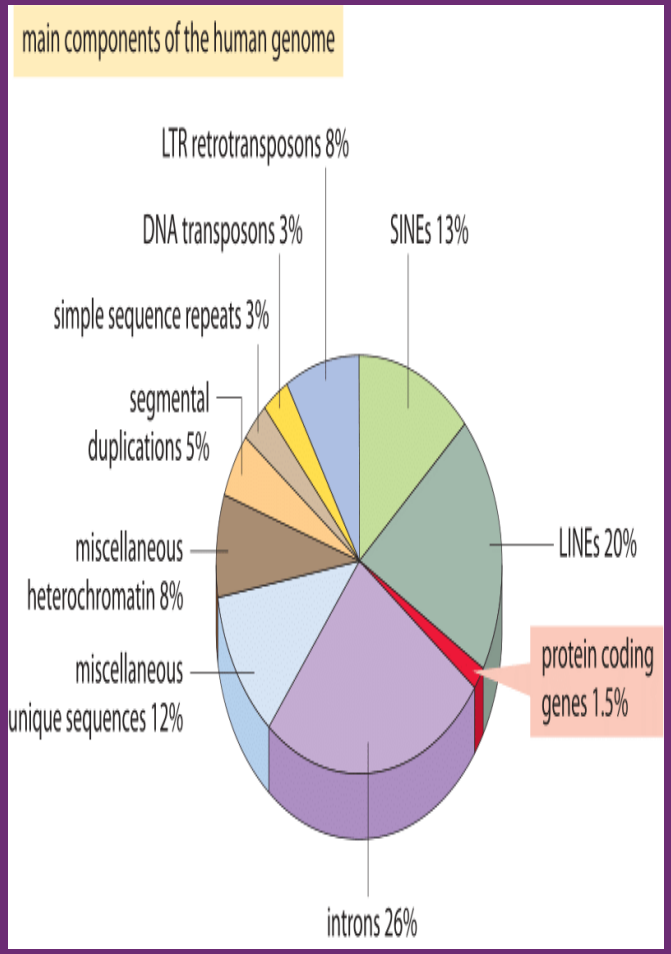
Family Time?

Mind-Brain-Gene Feedback Loops

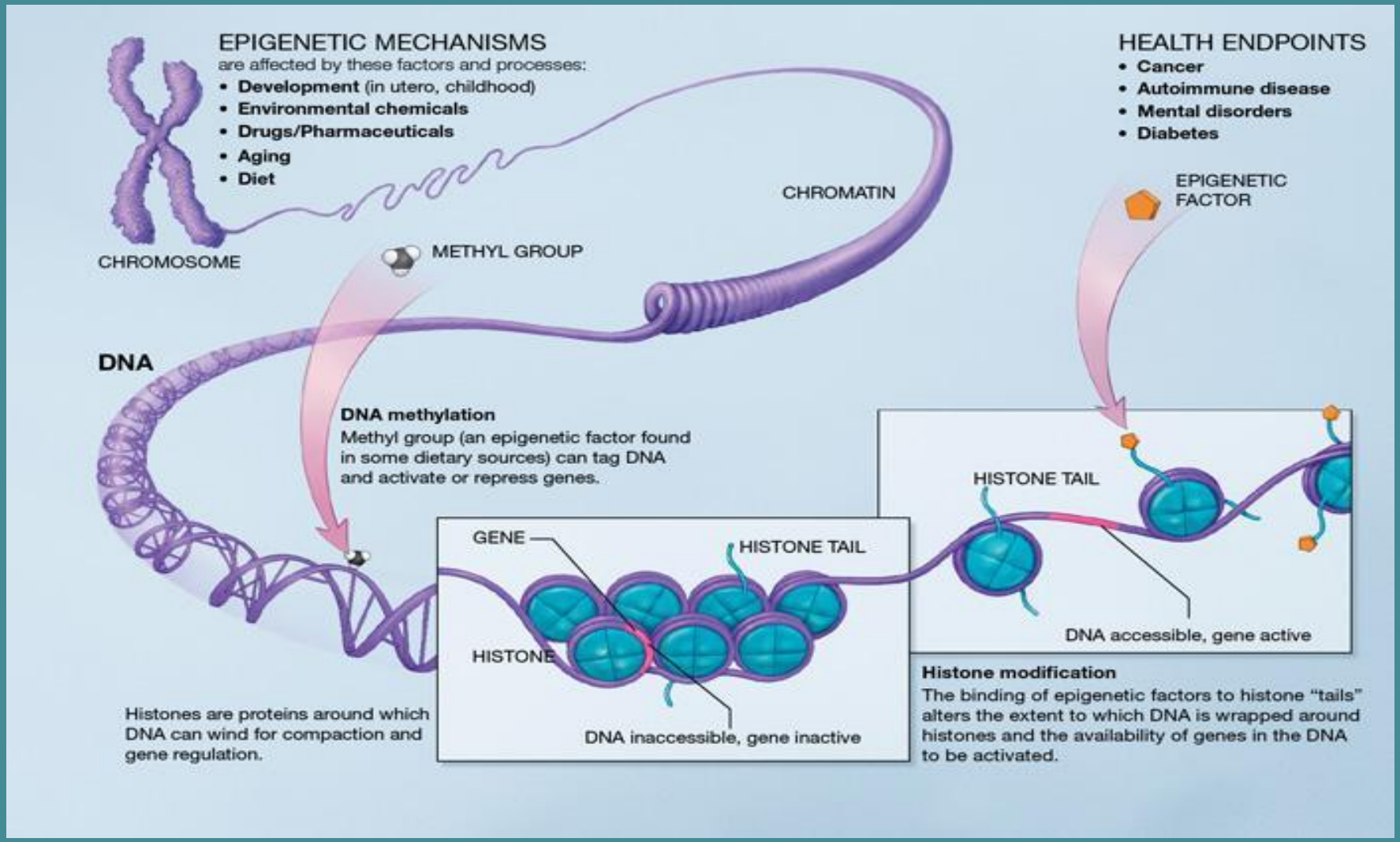


Epigenetics

- 24,00 genes (that code for protein)
  - Worm and human
- 2% (the rest—”junk DNA”)
- As the complexity of the species increases so does the amount of “junk DNA”



Epigenetics



Epigenetics in Gene Expression

- Histones are proteins wrapped tightly into ball like shapes with floppy tails
- Acetylation of histones allows transcription—unwrapping genes for expression
- Methylation of histones keeps them in place—suppressing gene expression

Someone Needs to Play (behave)

Epigentics and parenting

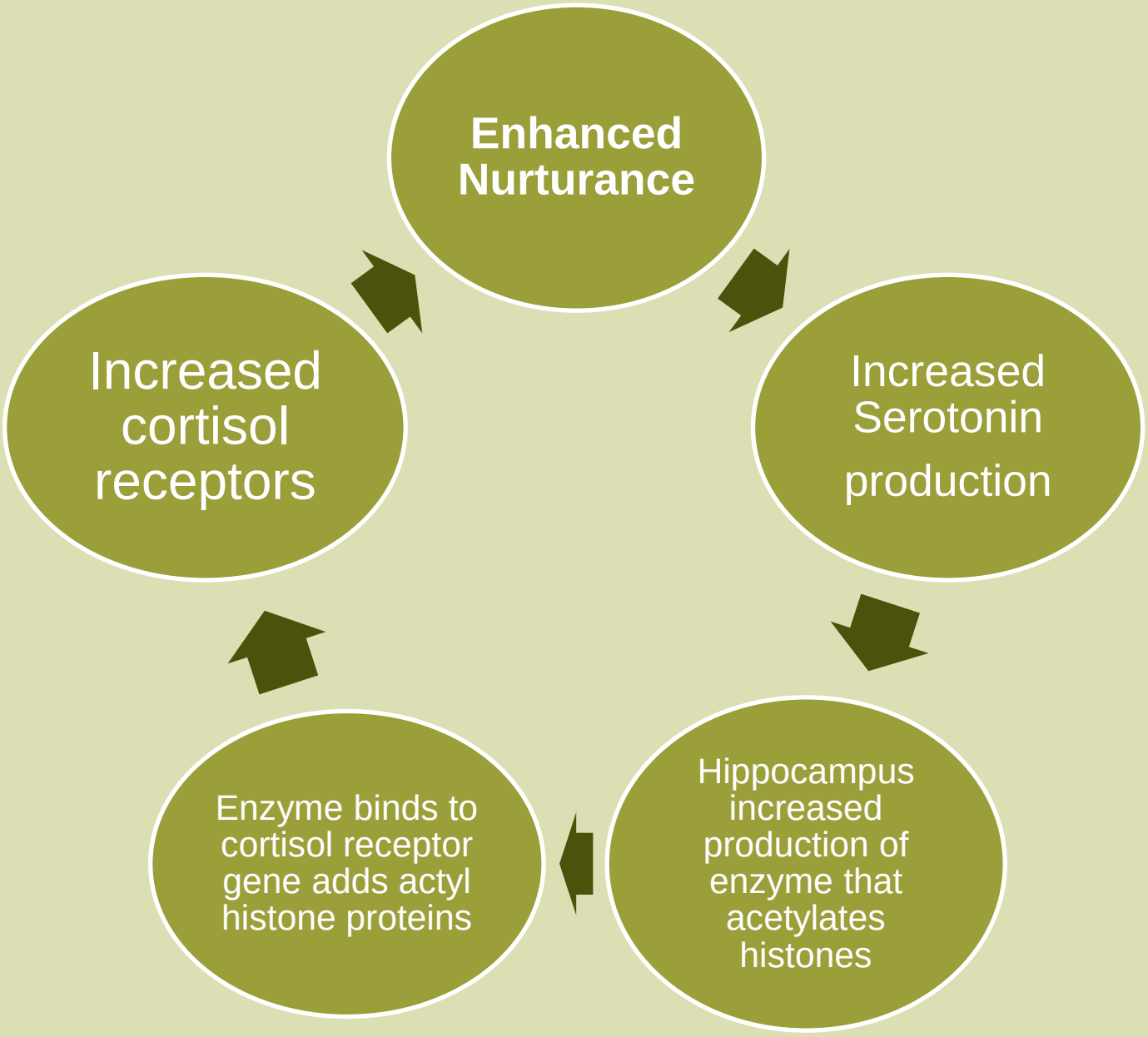
- Good parenting produces kids with less methylation of the cortisol receptor gene
- The kids have a better thermostat for cortisol and can turn of the stress response system more easily

Cortisol level

Epigenetics and Decreased Stress

- Decreased methylation levels of cortisol receptor gene:
  - In offspring who had good nurturing produces more cortisol receptors on the hippocampus
    - Lower levels of CRH, ACTH, and cortisol
    - More 5-HT
    - Stress tolerance (Good thermostat)

Epigenetics of Stress Tolerance



Epigenetics and Increased Stress

- With methylation of the cortisol receptor gene, fewer cortisol receptors
  - it is difficult to turn off the stress response.

- Increased methylation levels of cortisol receptor gene:
  - In suicide victims with a family history of abuse and/or neglect
  - In preemies:

Epigenetics and Increased Stress

- Maternal separation;
  - leads to decreased DNA methylation of the arginine vaseopressin and CRH genes.
  - This results in the increased production of arginine vaseopressin and CRH, which stimulates the HPA axis— the stress response system.

Epigenetics: For Better or Worse

- Infants with a variant of the dopamine receptor gene (DRD4) have been linked to lower receptor efficiency and greater risk for disorganization and externalizing behaviors if exposed to maternal loss or trauma.

- Yet, when children with this supposed “vulnerability gene” were raised by mothers who had no unresolved loss they displayed significantly less disorganization. With nurturing mothers, they show the lowest levels of externalizing problem behavior.

- This variant of the DRD4 gene can afford the carrier to benefit disproportionally from supportive environments.

Epigenetics: For Better or Worse

- The serotonin- transporter gene differentiates those people with the “short version” from the “long version” (eg S/S, L/S, or L/L).
  - Short version - mistaken for the “depression gene.”
  - Yes, carriers of the short version may become depressed if they experienced ACEs, **but** those with supportive early environment and positive experiences can have the fewest symptoms.
- The genetic polymorphism BDNF alone does not operate as a plasticity factor, but the environment and multigene interactions together do.

Epigenetics: For Better or Worse

- Carriers of a specific mutation of the catechol-O-methyltransferase (COMT) gene, --who use of cannabis during adolescence -- more likely to develop psychotic symptoms
- The COMT gene protein is of particular importance in regions such as the PFC, which is typically dysregulated in schizophrenia.
- The COMT gene is NOT a “schizophrenia gene” but is an enzyme that breaks down dopamine, norepinephrine, and epinephrine.

Variations of BDNF

- BDNF Val(66)Met carriers show an environmentally informed change in circulating BDNF levels, with lower concentrations found in individuals who suffered childhood abuse (Elzinga, et al., 2011).
  - Methylation of the BDNF gene associated with BPD, given this disorder's high rate of childhood abuse (Thaler, et al. 2014).
  - BDNF gene methylation associated with completed suicides (Keller, et al., 2010).
- BDNF gene plasticity through demethylation or creating new neurons is not an inexorably positive change, -- the concept of “differential susceptibility” is key
  - ACEs are associated with an increase in BDNF in the BLA, more resistant to modification later in life (Vyas, et al, 2004).
- DBT non-responders show an increase in methylation of the BDNF gene, while responders showed a decrease in methylation

Oxytocin Receptors (OXTR)

- Early life stress may lead to low levels of oxytocin in the cerebrospinal fluid of women - potentially impairing the bonding process with her infant
- Decreased in OXTR in the brain when exposed to conditions of suboptimal nurturing (Francis, et al., 2000).
- Optimal levels of oxytocin - instrumental in mitigating amygdala and brainstem hyperactivity in the fear response (Kirsch, 2005).
- Higher expression of OXTRs may increase an individual's capacity for empathy (Rodrigues, et al, 2009)
  - But may also predispose to greater sensitivity to negative environmental effects, with, for instance, higher risk for separation anxiety and disorganized attachment (Bradley, et al., 2011).

The short (s) allele of the serotonin transporter- (5-HTTLPR)

- 5-HTTLPR has been associated with later development of psychopathology (via ACEs),
  - MDD, suicide attempts, anxiety disorders, and ADHD.
- GAD responders showed an increase in 5-HTTLPR methylation, while nonresponders showed a significant decrease in methylation (Eley, et al., 2012)
- CBT with children with anxiety disorders responders increased in methylation, whereas nonresponders showed a decrease in DNA methylation (Roberts, et al, 2014)
- maternal sensitivity may allay some of the negative emotionality in children showing the 5-HTTLPR, demonstrating the interplay with the environment
- The prevalence in the general population of the 5-HTTLPR is around 43% and that of a hypofunctioning MAO-A allele is approximately 29%.

MAO-A gene

- MAO-A -- the key role in the catabolism of serotonin, norepinephrine, and dopamine. The “warrior gene”--Adverse outcomes later in life, conduct disorder, antisocial personality disorder, violence, and incarceration.
- Pronounced when immersed in a threatening and unpredictable environment.
    - Panic disorder -- greater expression of the MAO-A gene, heightened autonomic response characteristic of panic attacks, such as the dorsal PAG
  - No maltreatment, found to be *less* than the group with the normally functioning alleles.
    - Increased levels of noradrenaline and dopamine can also be associated, (given nurturing environment), with prosocial and egalitarian behaviors, as well as with cognitive flexibility (Sáez, et al., 2015).
  - Also a hypoactive MAO-A –more adaptive in optimal settings.
    - CBT responders -- increased methylation of the MAO-A gene—to decrease the activation of areas of the brain involved in the avoidance and fear responses

Between Session Neuroplasticity

- New hippocampal neurons require at least a two-weeks to mature before being able to contribute to cognitive functioning (Fischer, 2014).
- There is a “labile period” during which the continued input of the environment will inform whether an adaptive or maladaptive memory reconsolidation will occur
  - extra glutamate type effects (i.e. DCS) can increase NMDA plasticity and accelerate responses to treatment;
  - however, this can facilitate extinction or *enhance* consolidation of fear memories, depending on the success of the treatment and what the person experiences after session
- The patient can clinically worsen as a result of post-treatment settings (Litz, et al., 2012)

Loneliness and Epigenetics

- Pro-inflammatory genes are overexpressed
- Anti-inflammatory genes are under-expressed
- Elevated herpesvirus antibody titers reflect poor cellular immune system control over the latent virus.

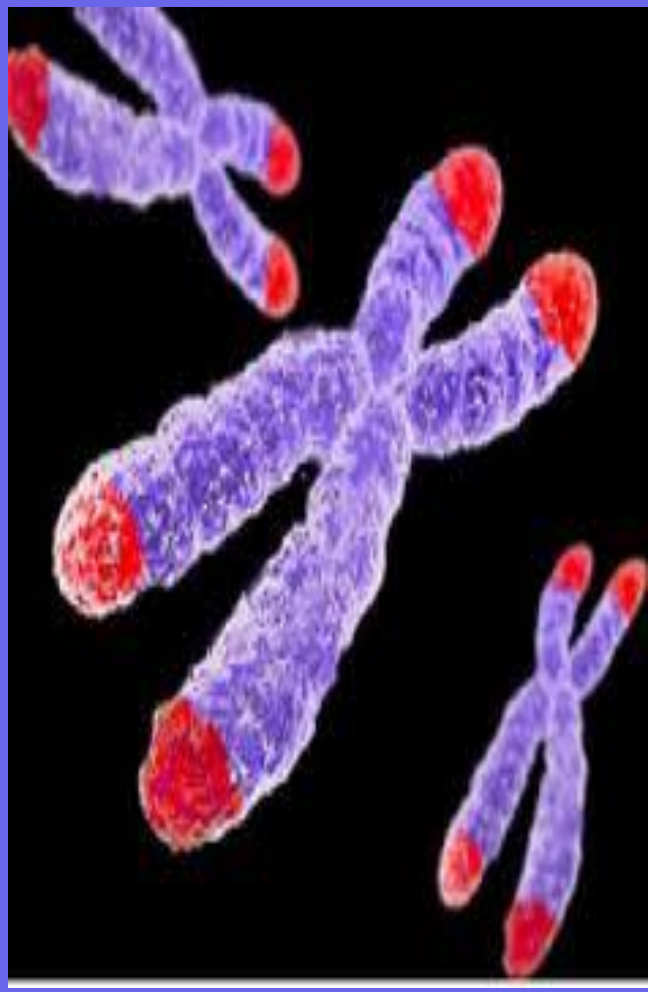
Lisa M. Jaremka et al: 2012, 2013

Factors that Impair DNA and Cells

- When cells divide
- Telemeres shorten
- Gene expression changes
- Impairs cellular repair
- Recycling of cells slows
- Errors accumulate
- Cells fail
- Cells die

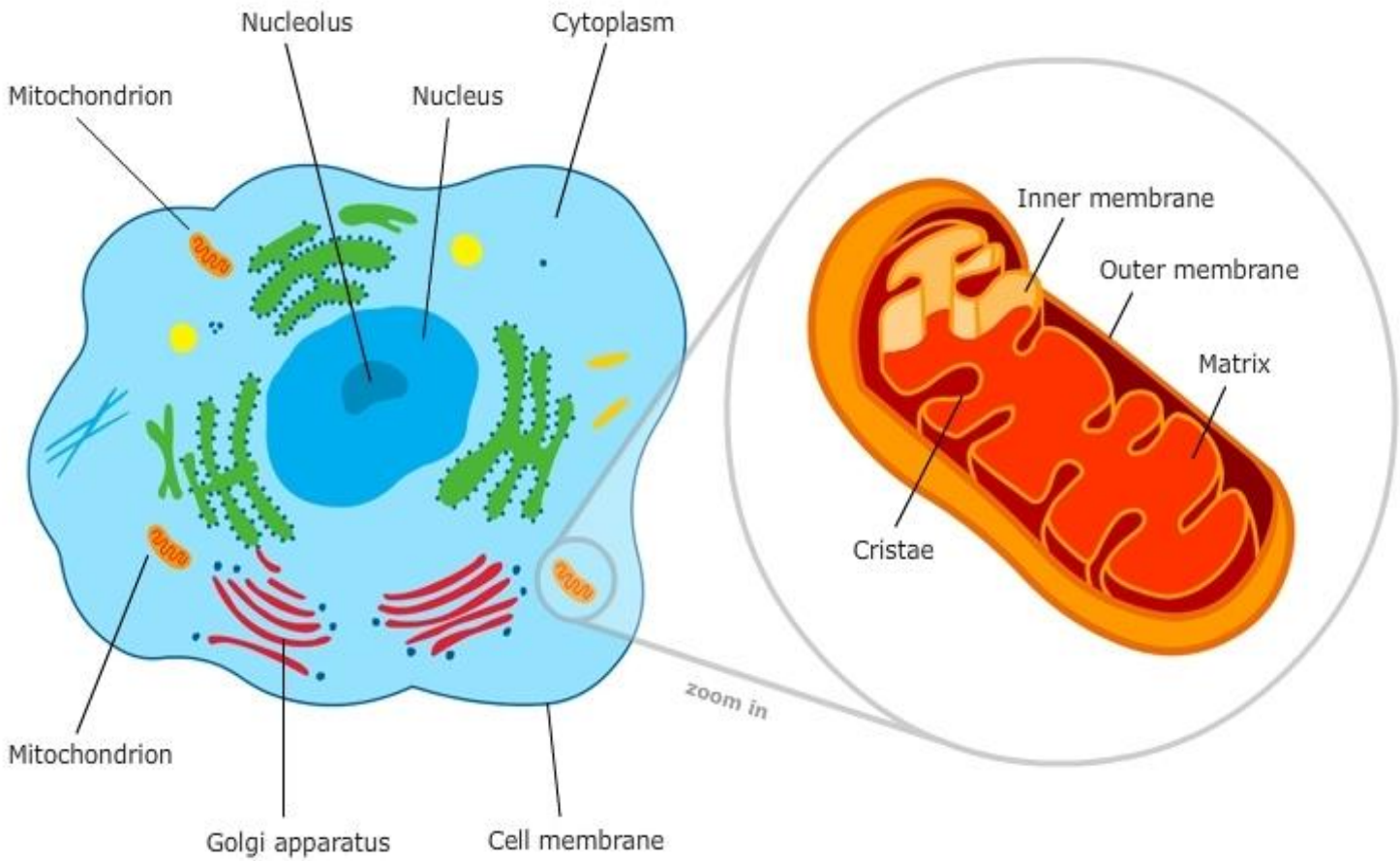
Factors that Shorten Telemeres

- Smoking
- Obesity (more than smoking!)
- Type 2 Diabetes
- Social isolation
- Poor diet
- No exercise
- Poor sleep
- Alcohol and other drugs



- **All rendering DNA vulnerable to damage**

Cells and Their Energy Factories



Mitochondrial Dysfunction

- Energy deficiency to astrocytes—which supply lactate to rapidly firing neurons
- Less also to oligodendrocytes where lactate is used for myelin synthesis
- Lactate uptake glucose from blood, stored as glycogen, conversion to lactate
- Since neural activity triggers the astrocytes to uptake glucose from blood and breakdown stored glycogen into glucose
  - Both get metabolized into lactate—which shuttles to neurons
  - Neurons take the lactate into the TCA cycle to produce ATP

Free Radicals

- Highly reactive molecules that contribute to oxidative stress
- They lost an electron and are on the prowl to steal one from neighboring molecules.
  - Cells malfunction
  - Cells age
  - Cells are more vulnerable to disease
  - DNA more vulnerable to inaccurate gene expression

Free Radicals

- Generally we produce antioxidant enzymes and DNA repair mechanisms
- But when damage accumulates faster than repairs, damage to the mitochondria themselves occur, especially to the mDNA
- As cells lose their ability to produce energy, they die.
- The organs of those cells falter, including the brain.

Use up cell's energy or suffer

- When energy demand is high, electrons flow down the ETC rapidly, the protons are pumped swiftly (the proton reservoir fills up)
  - The greater the reservoir the greater the pressure to form ATP
- However if there is no demand for ATP (but plenty of calories)
  - Proton gradient is too high (reservoir overfills)
  - The ETC backs up and electrons escape and form superoxide free radicals
  - Oxidize lipids and mitochondrial membranes, DNA damage
  - Necrotic cell death (necrosis)—cells swell and rupture
  - Organelles disintegrate and inflammation occurs

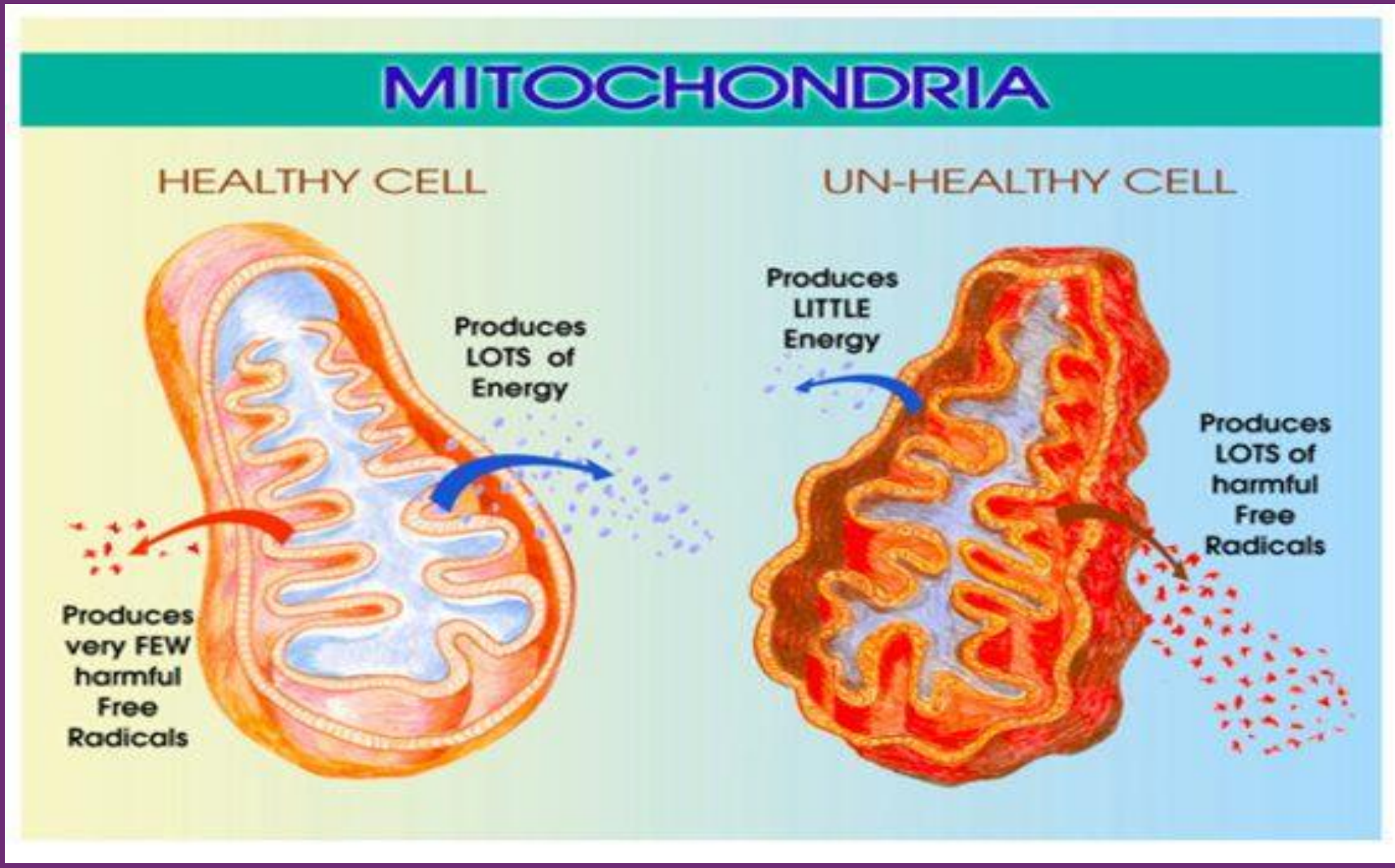
Consuming 2100—6000 calories per day **doubles risk for MCI**

Hyperglycemia

- Induces mitochondrial superoxide production in the cells that line the blood vessels
  - Atherosclerosis
  - Hypertension
  - Heart failure
  - Accelerated Aging
  - Type 2 diabetes (who have smaller mitochondrial)
  - AGE bind to mitochondria and complicate the functioning

  Eating 2100-6000 calories a day doubles the risk of MCI

Free Radicals



Movement is an Evolutionary Imperative

- 5 million years as Hunter-gathers
  - Activity level
- Walking 10 miles a day

Typical Activities of Hunter-Gatherer: Correlates in modern day forms of exercise

Slow Cardio: 5-10 miles/day of low intensity walking

- Hunter gatherers cover 5-15 miles per days. Persistence hunters cover in excess of 30 miles/day.

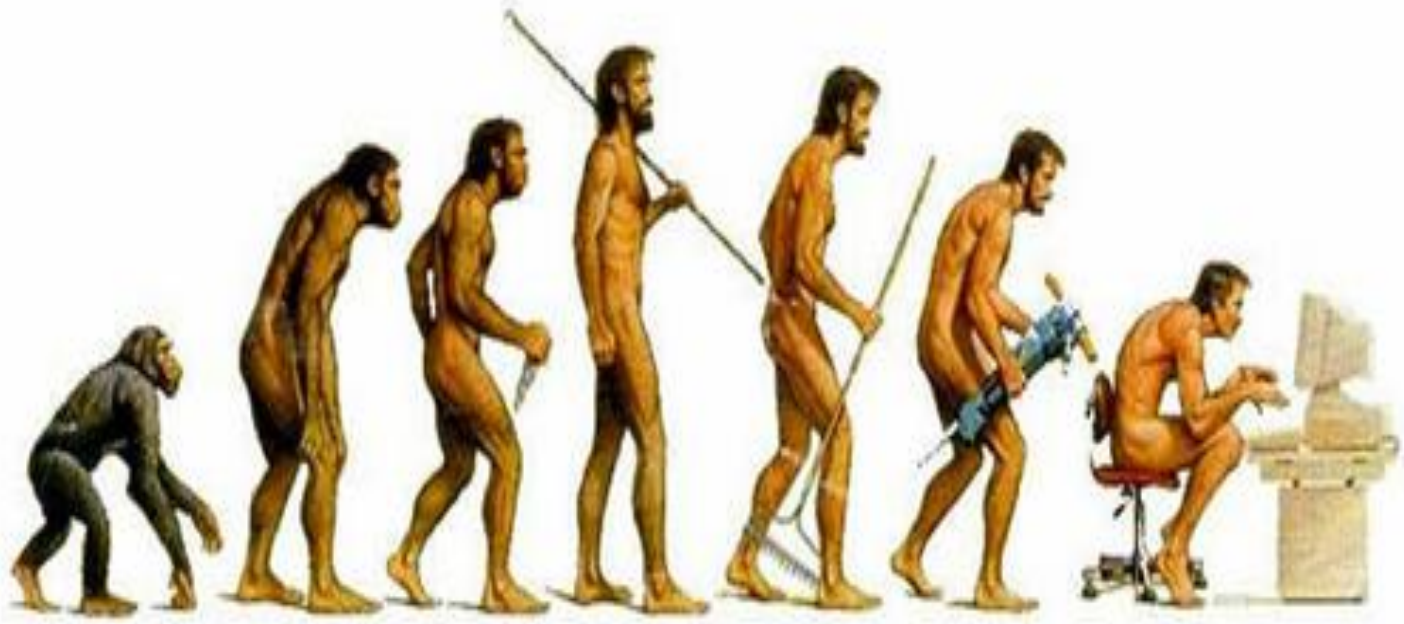
Resistance Training: Lifting, Throwing, and Carrying Objects

- Encompass functional movements such as pushing, pulling, sprinting, and jumping

Interval Training: Periodic bursts of high-intensity activity

- Brief bouts of sprinting alternating with walking or jogging in pursuit of prey

De-evolution



Beta-Endorphin and the High

Exercise, a form of voluntary stress, activates the hypothalamic-pituitary-adrenal axis

- Beta-endorphin is released from anterior pituitary

Subjective feelings of euphoria are mediated by rising levels of beta-endorphin

- Beta-endorphin increases in prefrontal and limbic regions of the brain after 2 hours of endurance running and levels correlate with euphoria

Exercise Increases Neurotransmitters

NE increases abruptly at exercise

- NE turnover is increased in the frontal cortex and is helpful to alleviate symptoms of ADHD

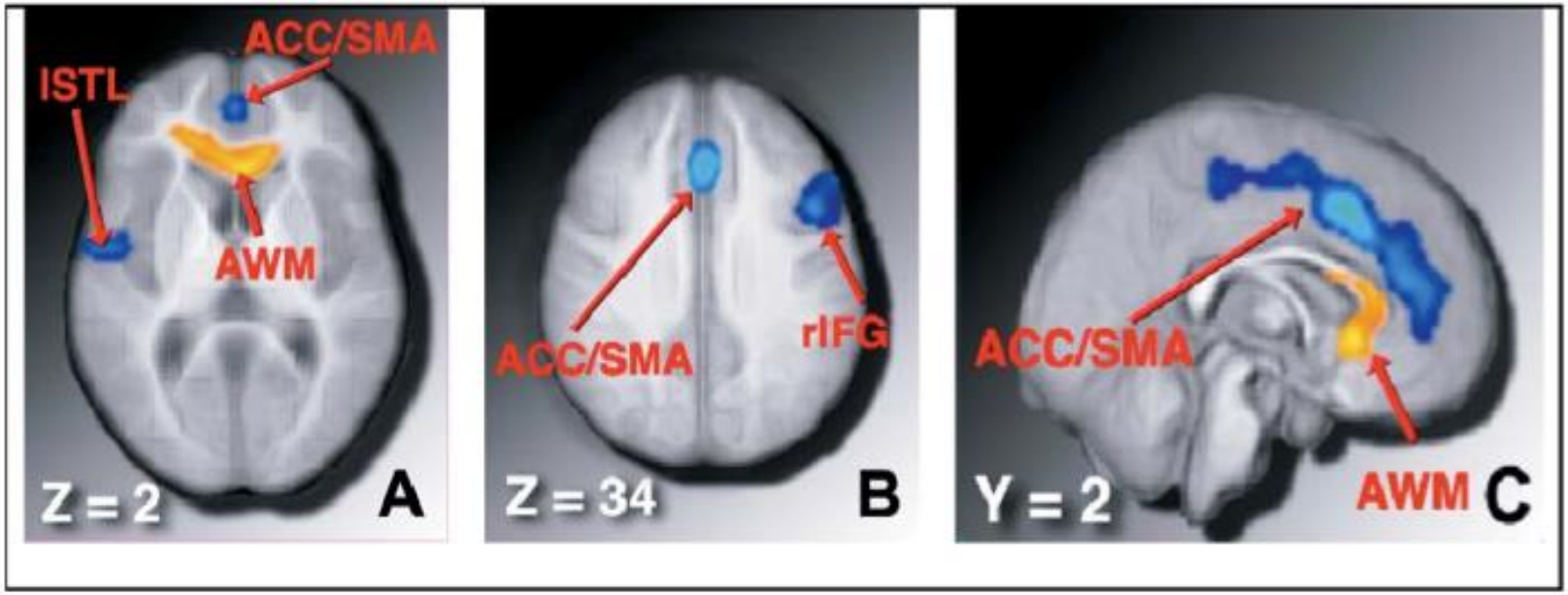
5-HT is modulated by exercise in specific brain regions and is also affected by intensity and duration of exercise.

High-intensity interval training increases 5-HT synthesis in the hippocampus via interaction with BDNF.

DA is also increased in pathways involved in regulation and control of movement

Higher levels of moderate to vigorous activities lowers the risk of developing Parkinson disease

Aerobic Exercise Training Increases Brain Volume in Aging Adults



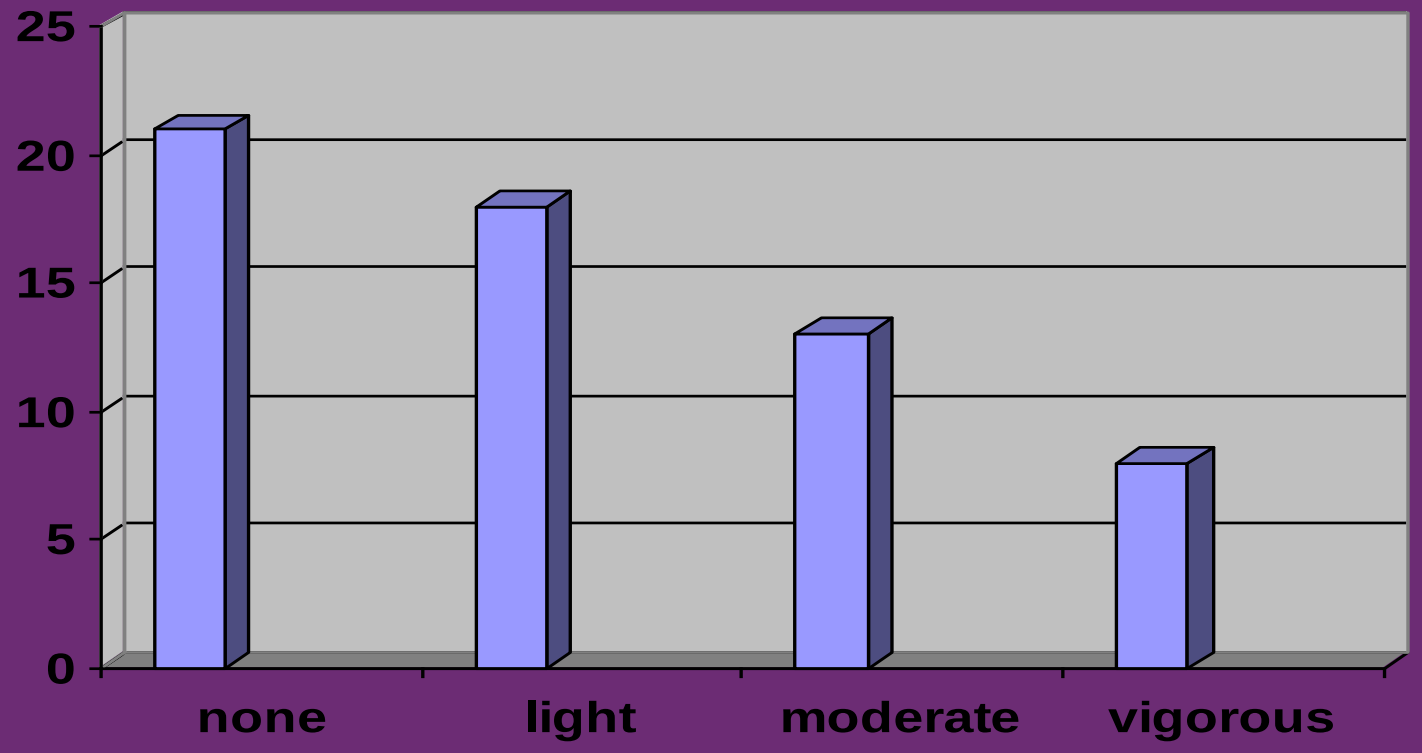
Blue regions: Gray matter volume was increased for aerobic exercisers

Yellow regions: White matter was increased for aerobic exercisers

Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2006;61(11):1166–1170.

Effect on C-Reactive Protein

- The effect of exercise on C-Reactive Protein (inflammation chemical). Degree of physical activity by level of C-Reactive Protein Based on study of 13,748 people (Ford, 2002)



Exercise and Depression

- Ohio State study---45 minutes of walking per day/ 5 days per week (heart rate at 60% to 70% of their maximum) lowered BDI mean scores from 14.81 to 3.27 compared to no change for controls (depressed non-walkers)
- Univ. of Wisconsin – exercise (jogging) as effective as psychotherapy for moderate depression
  - After one year 90% of exercise group were no longer depressed. 50% of psychotherapy group
- Duke Univ. – found that exercise was as effective as Zoloft
  - At 6 month follow-up exercise was 50% more effective in preventing relapse
  - Combining exercise and Zoloft added no benefit re: relapse (Babyak, et. al. 2000)
- NIMH panel concluded that long-term exercise reduces moderate depression.

Exercise and Depression

- Alameda County study of 8,023 tracked for 26 years
  - Those that didn't exercise were 1.5 times more likely to be depressed
- Finnish study of 3.403
  - those that exercised 2 to 3 times per week were less depressed, angry, stressed and cynical
- Dutch study of 19,288 twins and their families –
  - those that exercised were less anxious, depressed, neurotic and more socially outgoing
- Columbia University study of 8,098
  - same inverse relationship between exercise and depression (Ratey, 2008)

Exercise Improves Sleep

Exercise improves sleep quality and normalizes circadian rhythms.

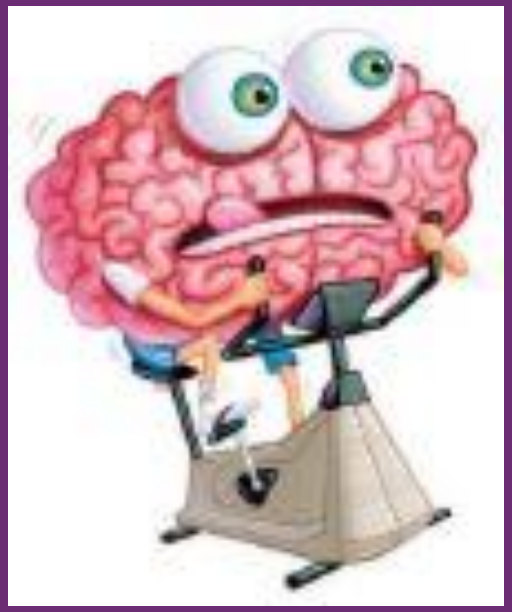
- increases slow wave sleep and total rest time
- decreases the amount of time to fall asleep
- decreases the amount of time spent in non-restorative sleep.

Lack of restorative sleep increases PICs and is associated with chronic disease

A single night of sleep deprivation results in higher levels of PICs

Exercise Optimizes

- Mood
  - –↑ neurotransmitters
    - »Serotonin
    - »Dopamine
    - »norepinephrine
  - –physical health



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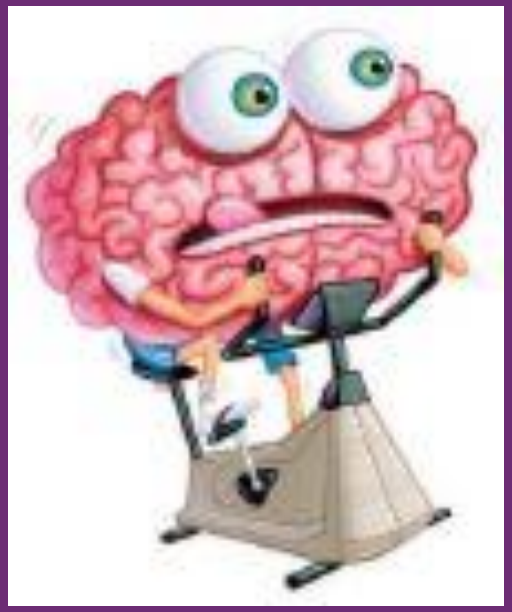
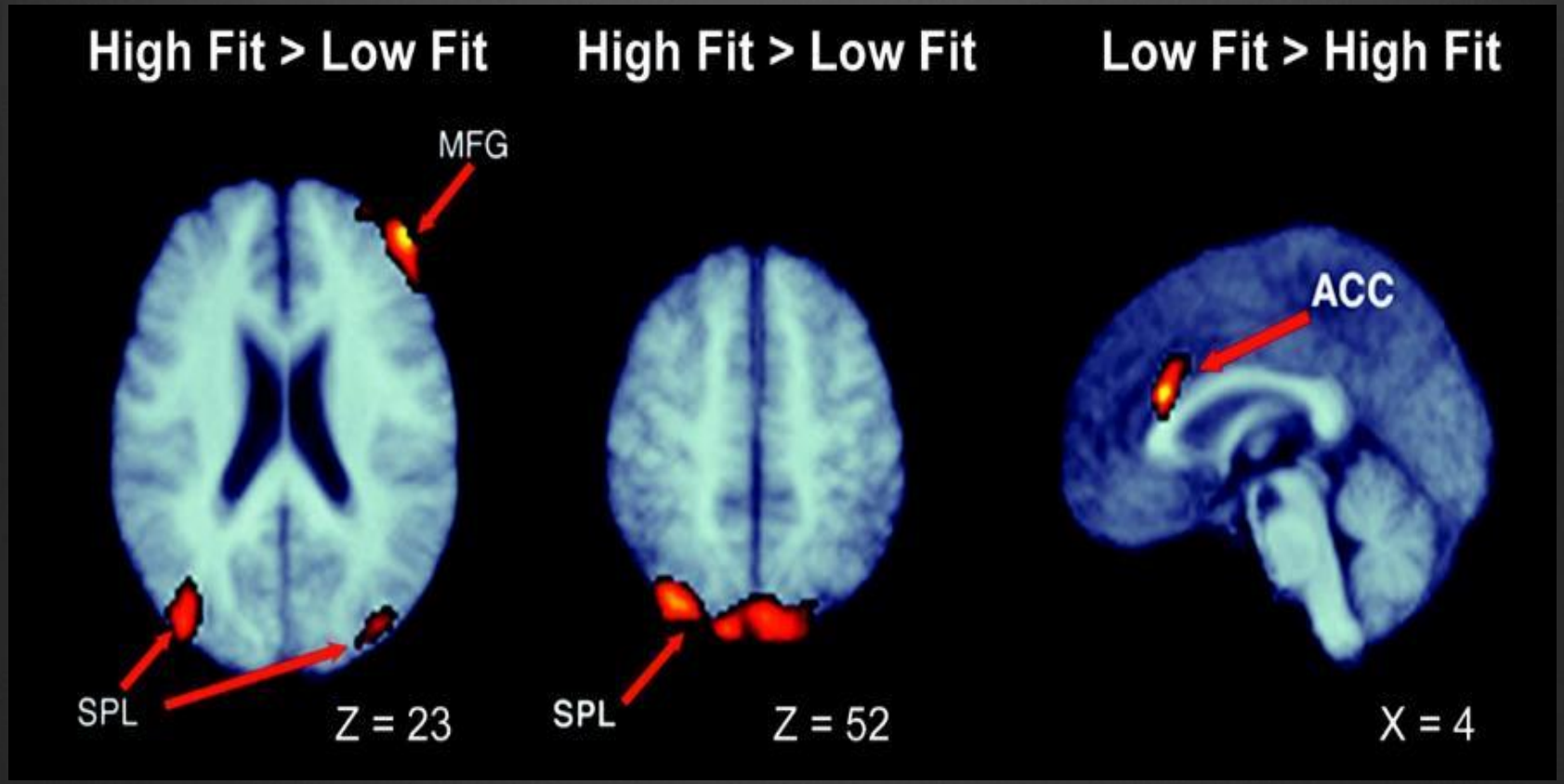


Exercise Optimizes

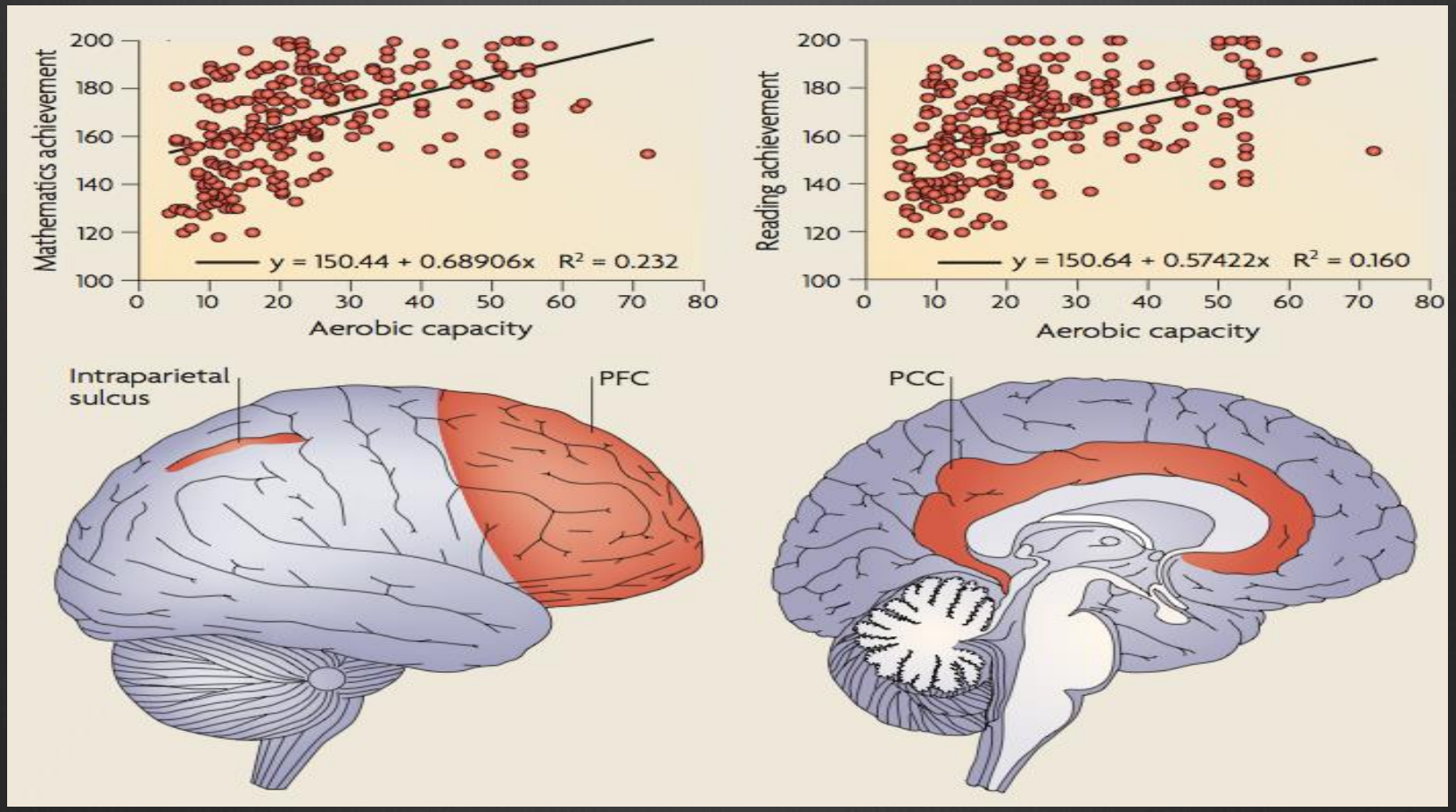
- Cognition
  - alertness
  - attention
  - motivation
  - cognitive flexibility

Cardiovascular Fitness and Cortical Plasticity in Aging Adults

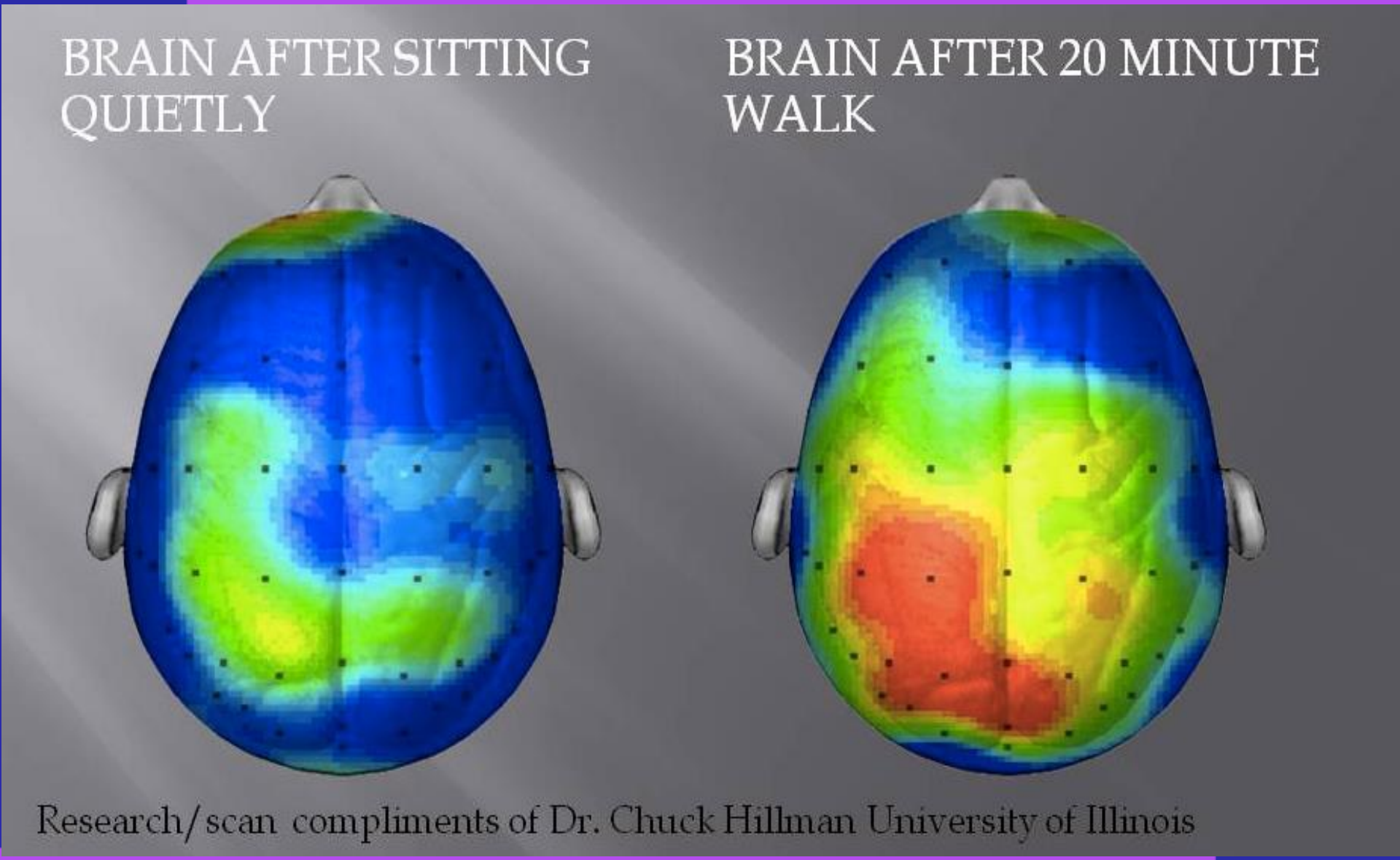


Colcombe SJ. Cardiovascular fitness, cortical plasticity, and aging. *PNAS*. 2004;101(9):3316–3321

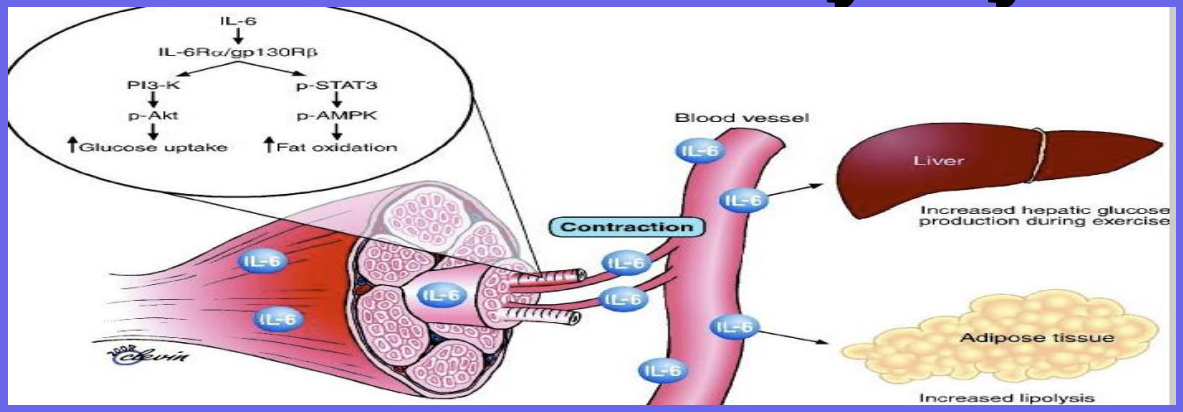
Fitness Correlates with Academic Achievement



Exercise to Clear the Mind



Myokines:
Anti-inflammatory Cytokines



While inactive muscle could contribute to pathologies, myokines are candidates for treating metabolic diseases

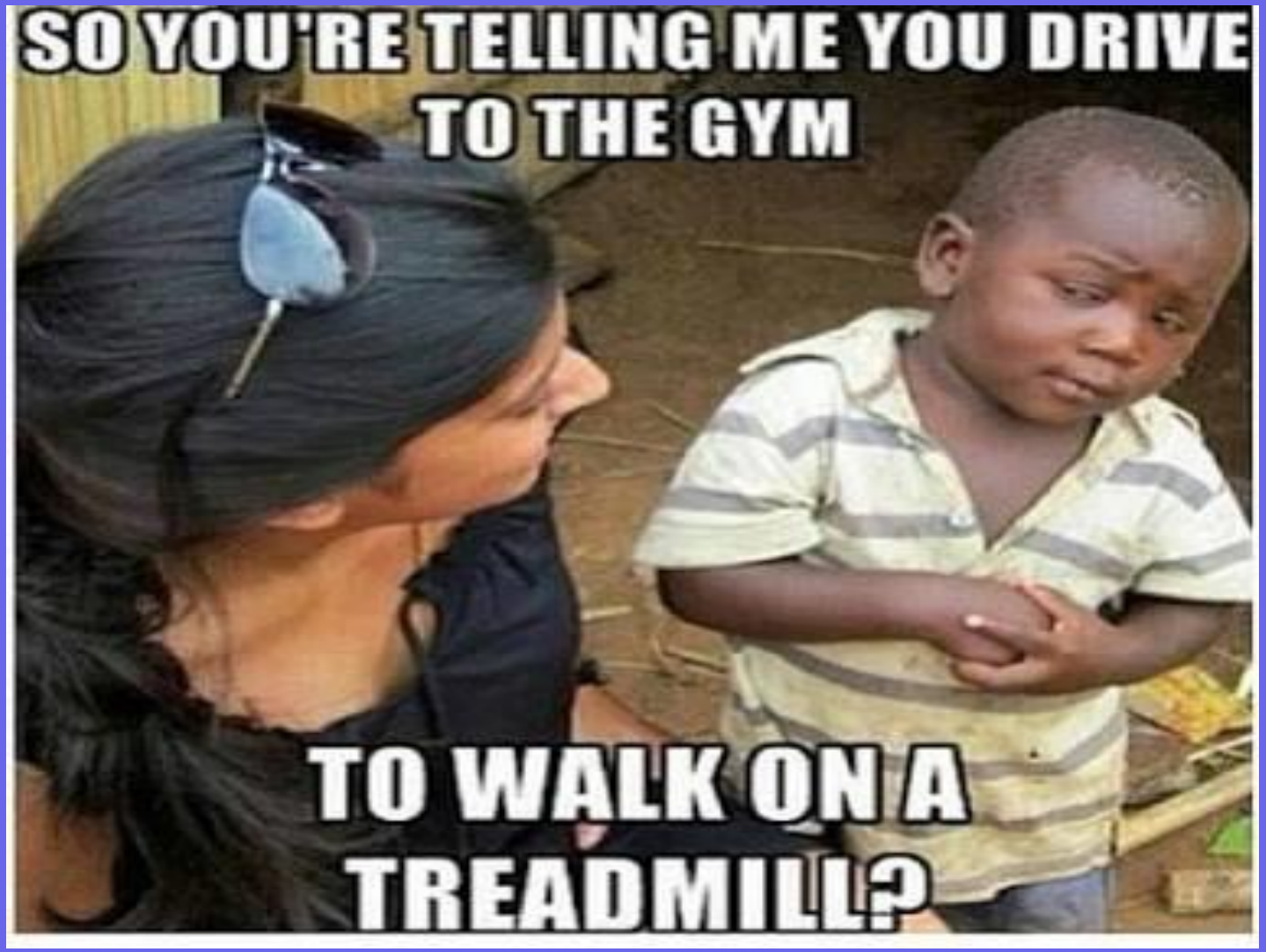
Exercise-induced myokines are involved in mediating anti-inflammatory effects

Pedersen BK. The disease of physical inactivity - and the role of myokines in muscle-fat cross talk. The *Journal of Physiology*. 2009;587(23):5559–5568. doi:10.1113/jphysiol.2009.179515.

Mood Regulation Exercise:

- Must be aerobic
- Intensity in keeping with level of fitness
- 30 minutes 3-4 times a week

Or three 10 minute periods of exercise every day


SO YOU'RE TELLING ME YOU DRIVE TO THE GYM
TO WALK ON A TREADMILL?

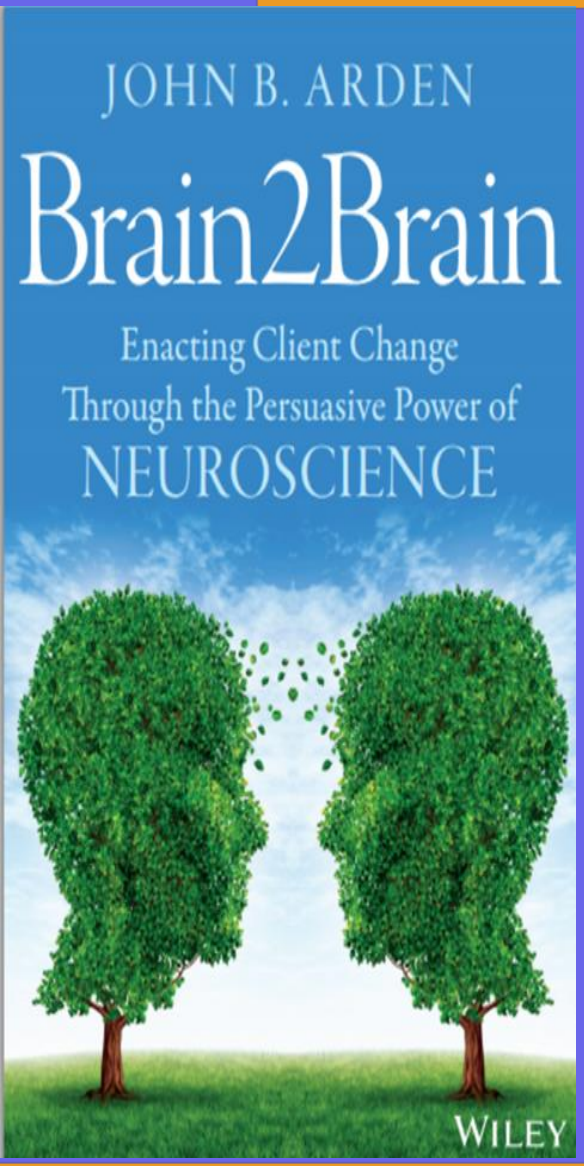
Exercise Doses

- **10,000 steps per day (5 miles)**
- **Average: 6000**
- **10 minute brisk walk: ↑ energy 60-120 minutes**
- **Mood: feel better than during any otherpart of the day** (Gauvin, et al.., 2000)

Exercise Summary

- Evolutionary imperative
- Not exercising is worst than "Smokadiabesity"
  - –WHO study of 200K—not exercising worse than smoking
- Exercise boosts mood
- Exercise boost cognition
- New neurons—neurogenesis

References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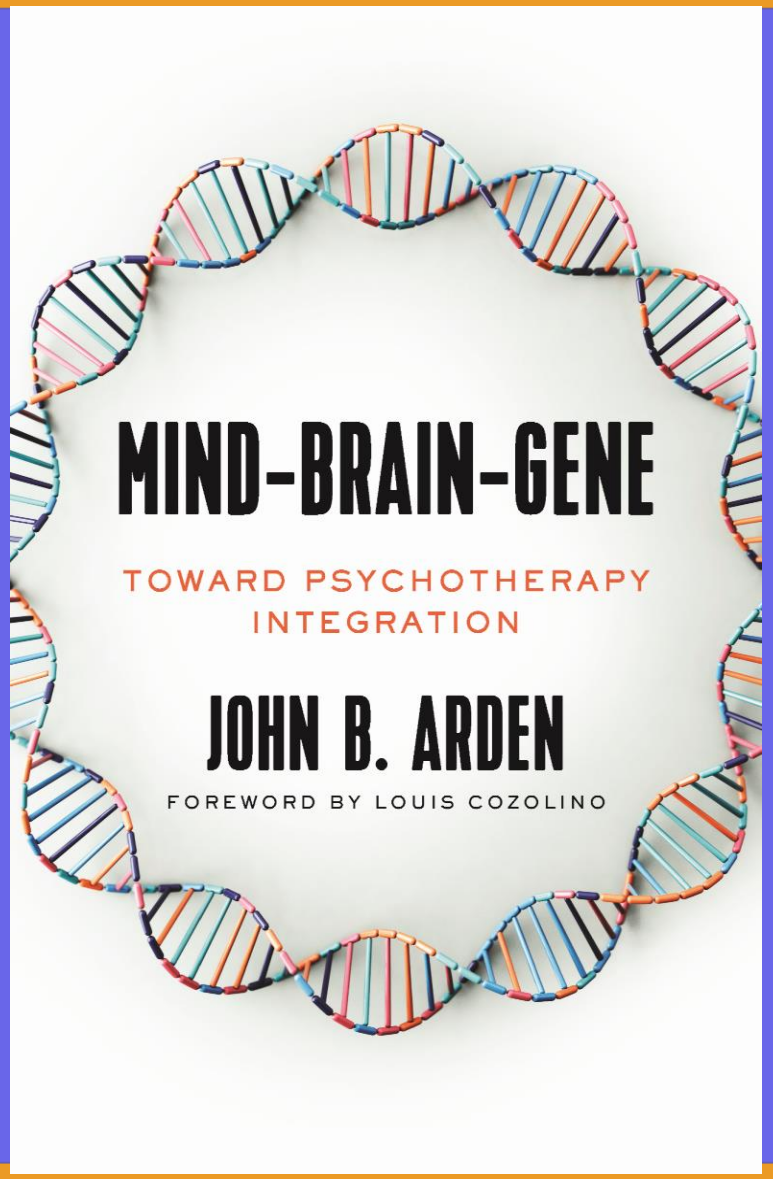
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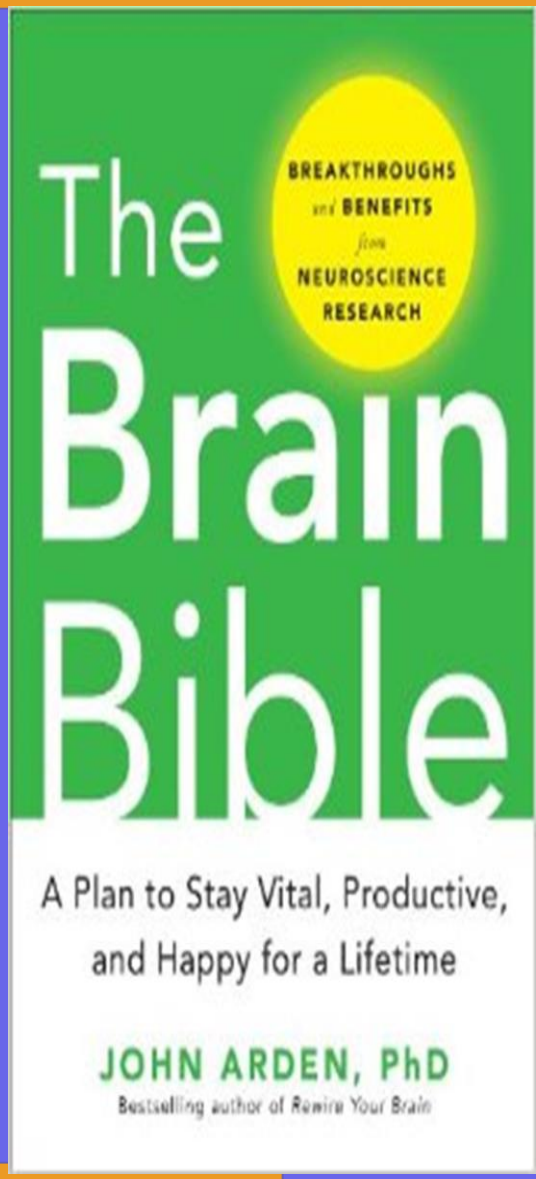
TOWARD PSYCHOTHERAPY
INTEGRATION
JOHN B. ARDEN
FOREWORD BY LOUIS COZOLINO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