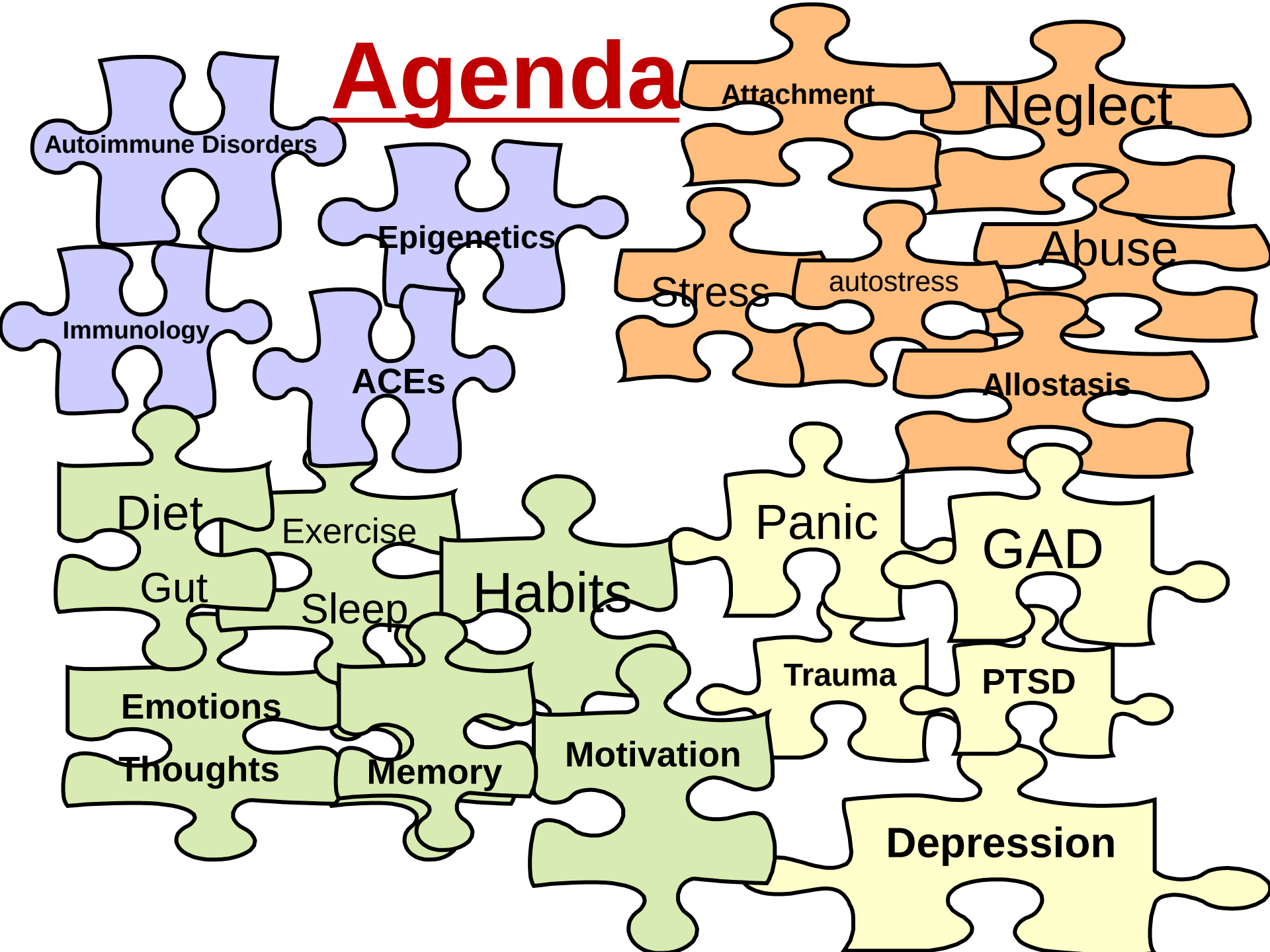
Mind-Brain-Gene:

Toward Psychotherapy Integration

John B. Arden, PhD, ABPP


Agenda
Attachment
Neglect
Autoimmune Disorders
Epigenetics
Abuse
Stress
autostress
Immunology
ACEs
Allostasis
Diet
Exercise
Panic
GAD
Gut
Sleep
Habits
Trauma
PTSD
Emotions
Motivation
Thoughts
Memory
Depression

Therapy might have been different

"We must recollect that all of our provisional ideas in psychology will presumably one day be based on an organic substructure."

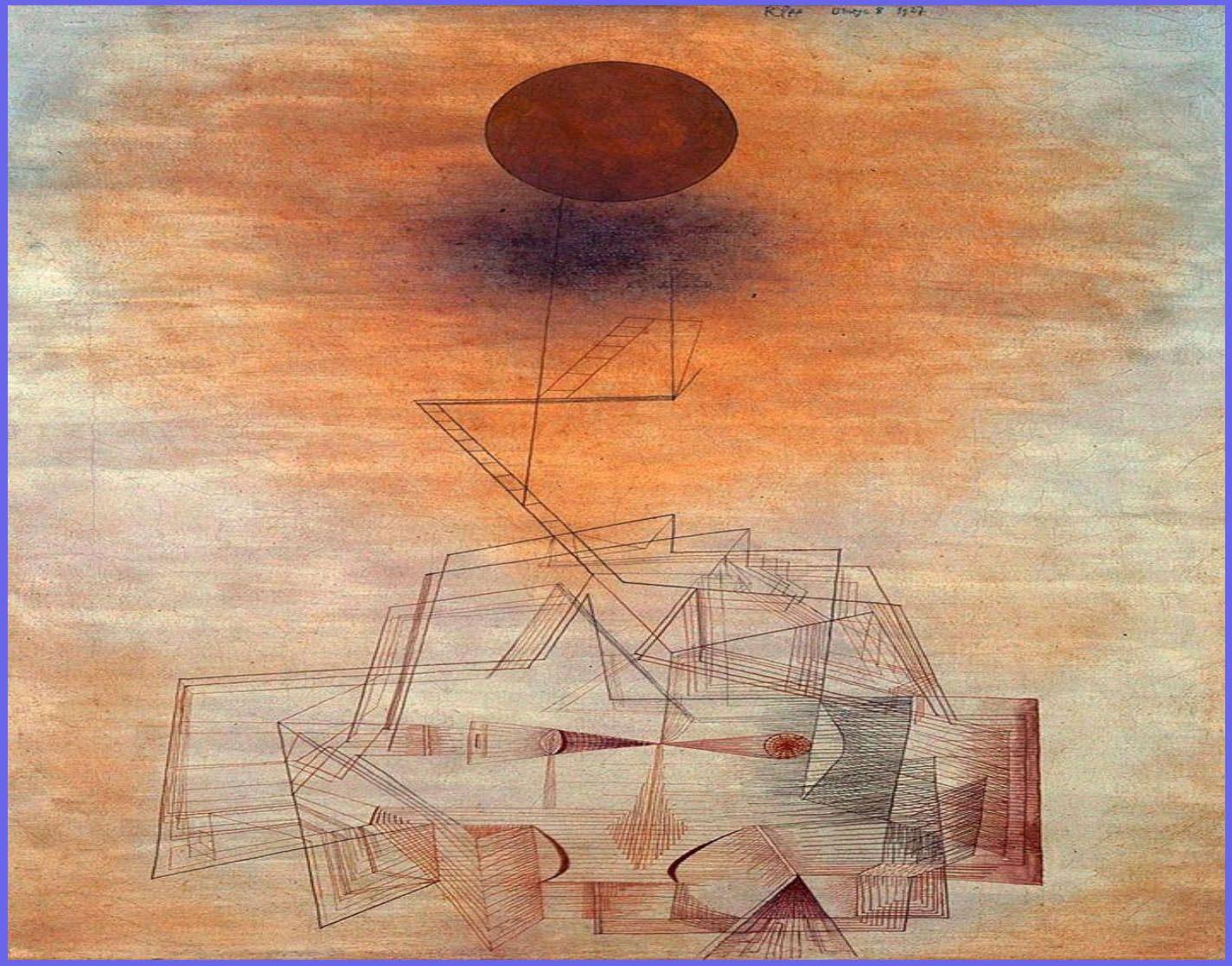
--Sigmund Freud

"The act of will activates neural circuits"

--William James

But……

Limits of Understanding (Klee)



The Cartesian Blizzard

Abreaction therapy
ACT
Adlerian therapy
Adventure therapy
Analytical psychology
Art therapy
Attack therapy
Attachment-based psychotherapy
Attachment-based therapy (children)
Attachment therapy
Autogenic training
Behavior modification
Behavior therapy
Biodynamic psychotherapy
Bioenergetic analysis
Biofeedback
Body psychotherapy
Brief psychotherapy
Classical Adlerian psychotherapy
Chess therapy
Child psychotherapy
Client-centered psychotherapy
Co-counselling
Cognitive analytic therapy
CBT
Coherence therapy
Collaborative therapy
CFT
Concentrative movement therapy
Contemplative psychotherapy
Conversational model
Conversion therapy
Core process psychotherapy
Dance therapy
Depth psychology
Daseinsanalysis
DNMS
DBT
Drama therapy
Dreamwork
DDP
Ecological counseling
EFT
EFT
EMDR
Existential therapy
Exposure and response prevention
Expressive therapy
Family Constellations
Family therapy
Feminist therapy
Focusing
Freudian psychotherapy
FAP
Future-oriented therapy
Gestalt therapy
Gestalt theoretical psychotherapy
Group analysis
Group therapy
Guided affective imagery
Hakomi
Holotropic Breathwork
Holding therapy
Humanistic psychology
Human Givens
Hypnotherapy
Inner Relationship Focusing
Integrative body psychotherapy
Integral psychotherapy
Integrative psychotherapy
Intensive short-term dynamic psychotherapy
Internal Family Systems Model
Interpersonal psychoanalysis
Interpersonal psychotherapy
Jungian psychotherapy
Logotherapy
Marriage counseling
Milieu therapy
Mindfulness-based cognitive therapy
Mindfulness-based stress reduction
Mentalization-based treatment
MOL
MDT
Morita therapy
Motivational interviewing
Multimodal therapy
Multitheoretical psychotherapy
Music therapy
Narrative therapy
Nonviolent Communication
Nude psychotherapy
Object relations psychotherapy
Ontological hermeneutics
Orthodox psychotherapy
Parent–child interaction therapy
Parent management training
Pastoral counseling
Person-centered therapy
Play therapy
Positive psychology
Positive psychotherapy
Postural Integration
Primal therapy
Primal Integration
Process oriented psychology
Process psychology
Prolonged exposure therapy
Provocative therapy
Psychedelic therapy
Psychoanalysis
Psychodrama
Psychodynamic psychotherapy
Psychosynthesis
Pulsing
RET
RLT
Reality therapy
Rebirthing-breathwork
Recovered-memory therapy
Re-evaluation Counseling
Reichian psychotherapy
Relationship counseling
Relational-cultural therapy
Remote therapy
Reprogramming
Rogerian psychotherapy
Sandplay Therapy
Schema Therapy
Self-relations Psychotherapy
Sensorimotor psychotherapy
Sexual Identity Therapy
Sex therapy
Social Therapy
Solution focused brief therapy
Somatic Experiencing
Somatic psychology
Status dynamic psychotherapy
Supportive psychotherapy
Systematic desensitization
Systemic Constellations
Systemic therapy
T-groups
Therapeutic community
Thought Field Therapy
Transactional analysis
Transference focused psychotherapy

Outcome Data (ie MPS)

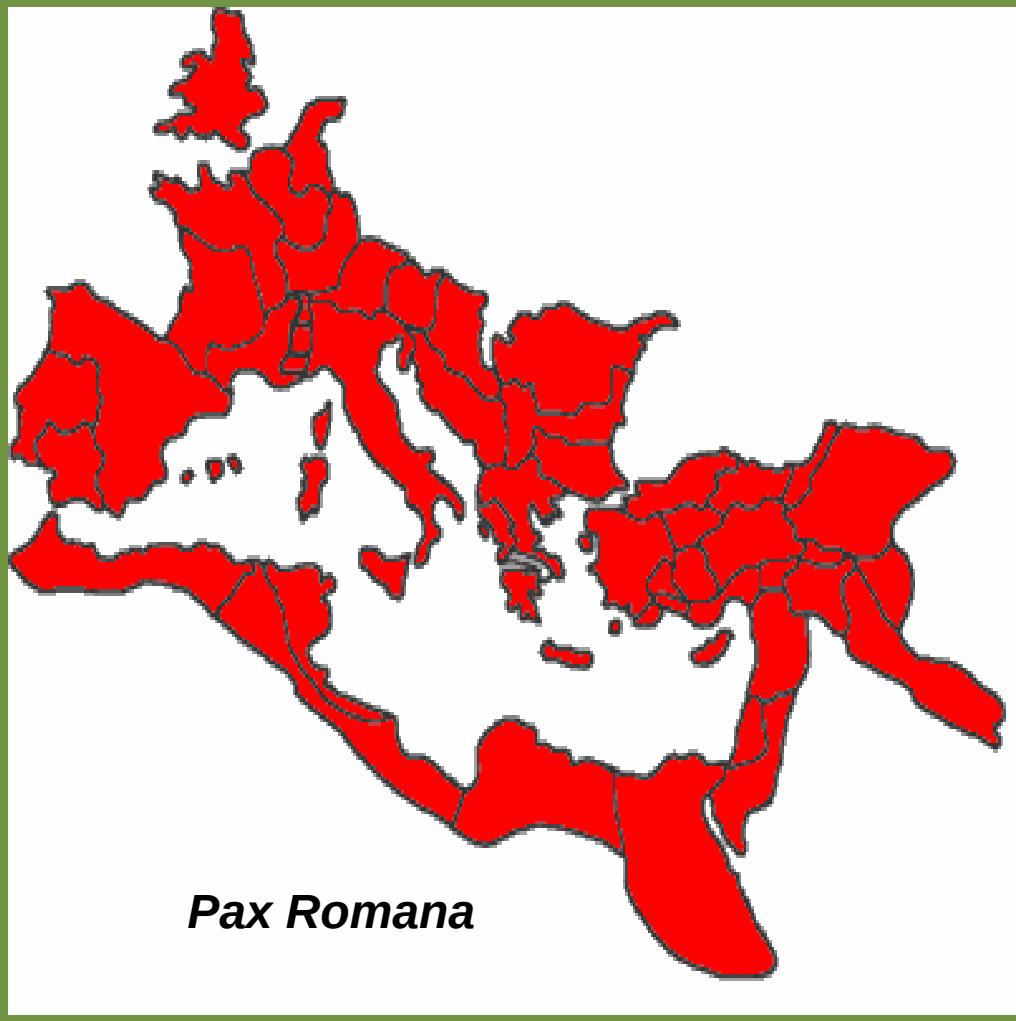
- 43% of patients recover without therapy
- Therapists are poor judges, not just of the outcome of a complete therapy, but even of a single session
- We overvalue our own competence and undervalue that of our colleagues:
  - 80% of the therapists consider themselves “better than the average” therapist
- Psychotherapy can produce enduring adverse effects

The “Pax Medica”

After the Cartesian area and Eysenck & Leary etc.

-brought us:

- **The DSMs**
- **SSRIs-NSRIs etc**
- **“Clinicians”**
- **The medicalization of psychotherapy**
- **Managed $**

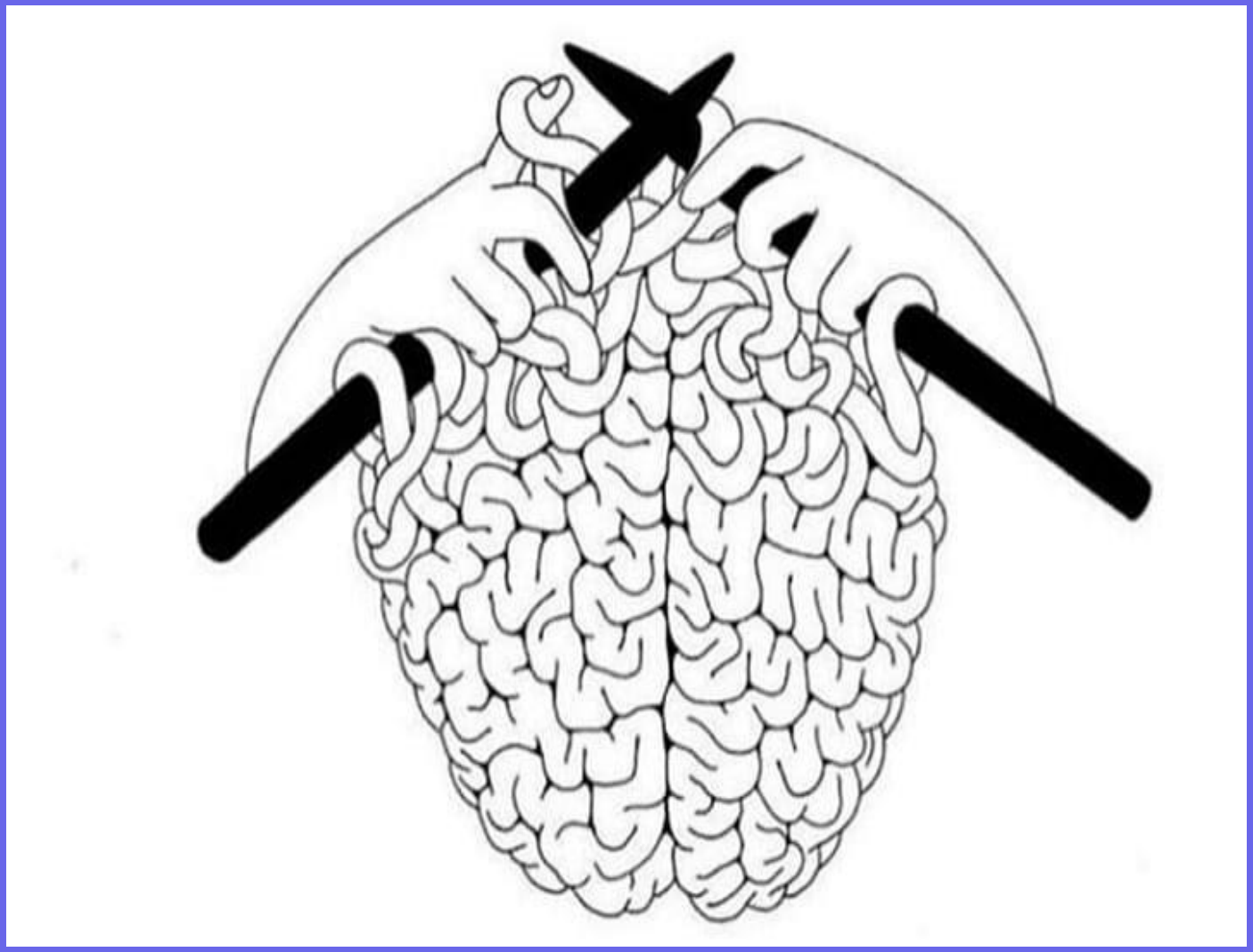


The Science has Changed

“Mental functions direct electrochemical traffic at the cellular level” Roger Sperry

“Psychotherapy works by producing changes in gene expression that alter the strength of synaptic connections…” Eric Kandel

Mind/Brain Causality

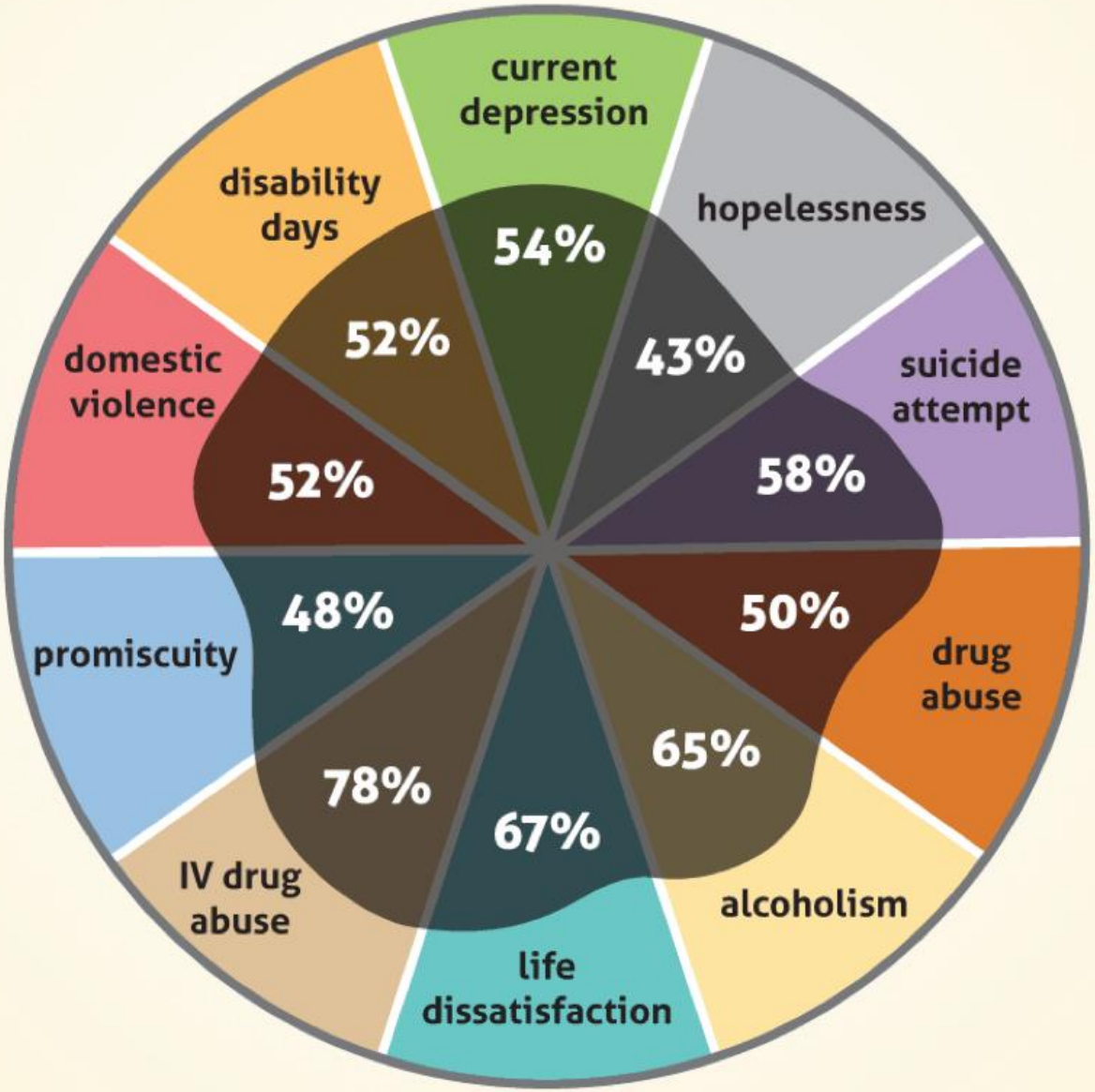


Mind-Brain-Gene Feedback Loops

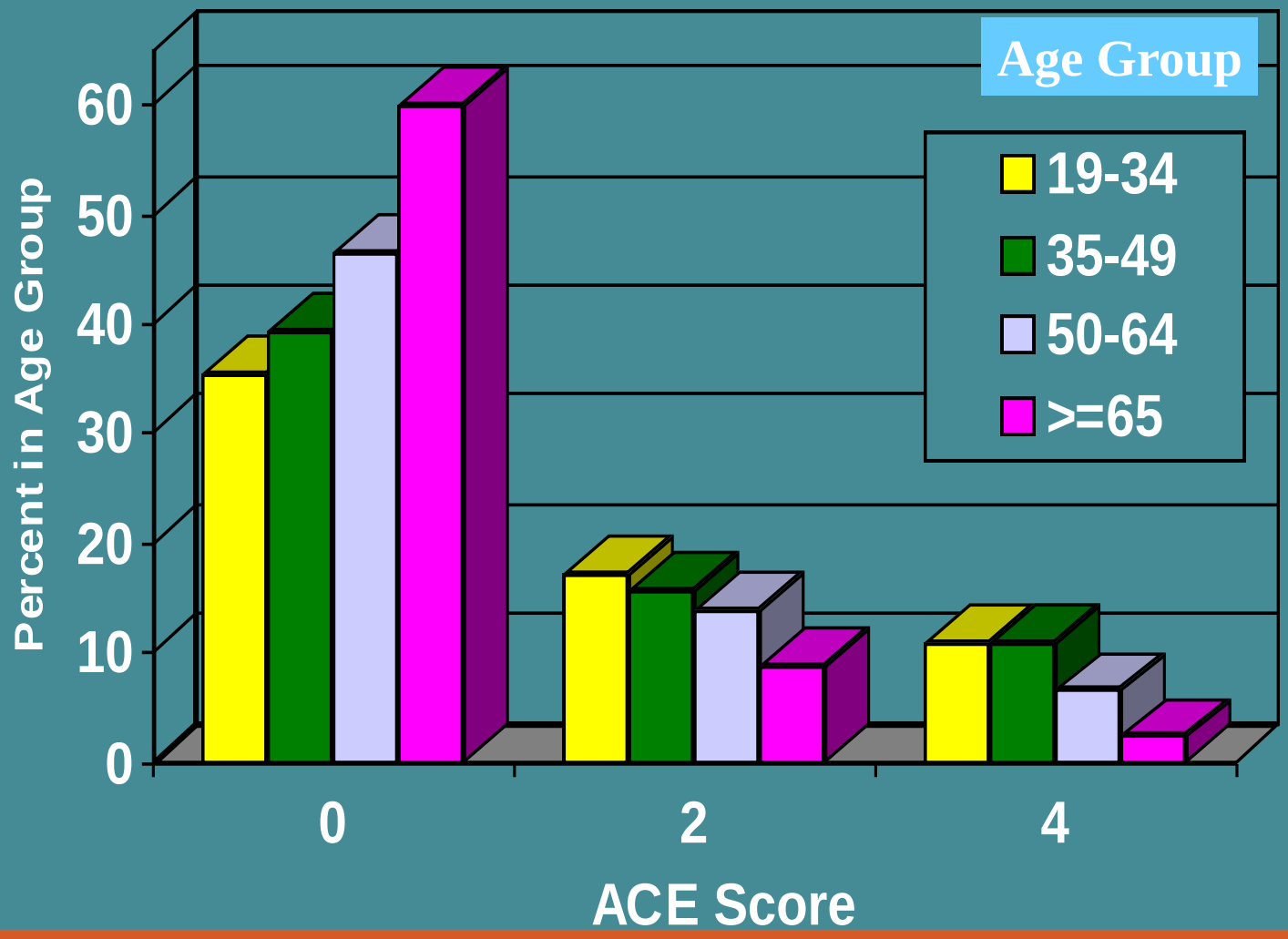
The ACE Study

- 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

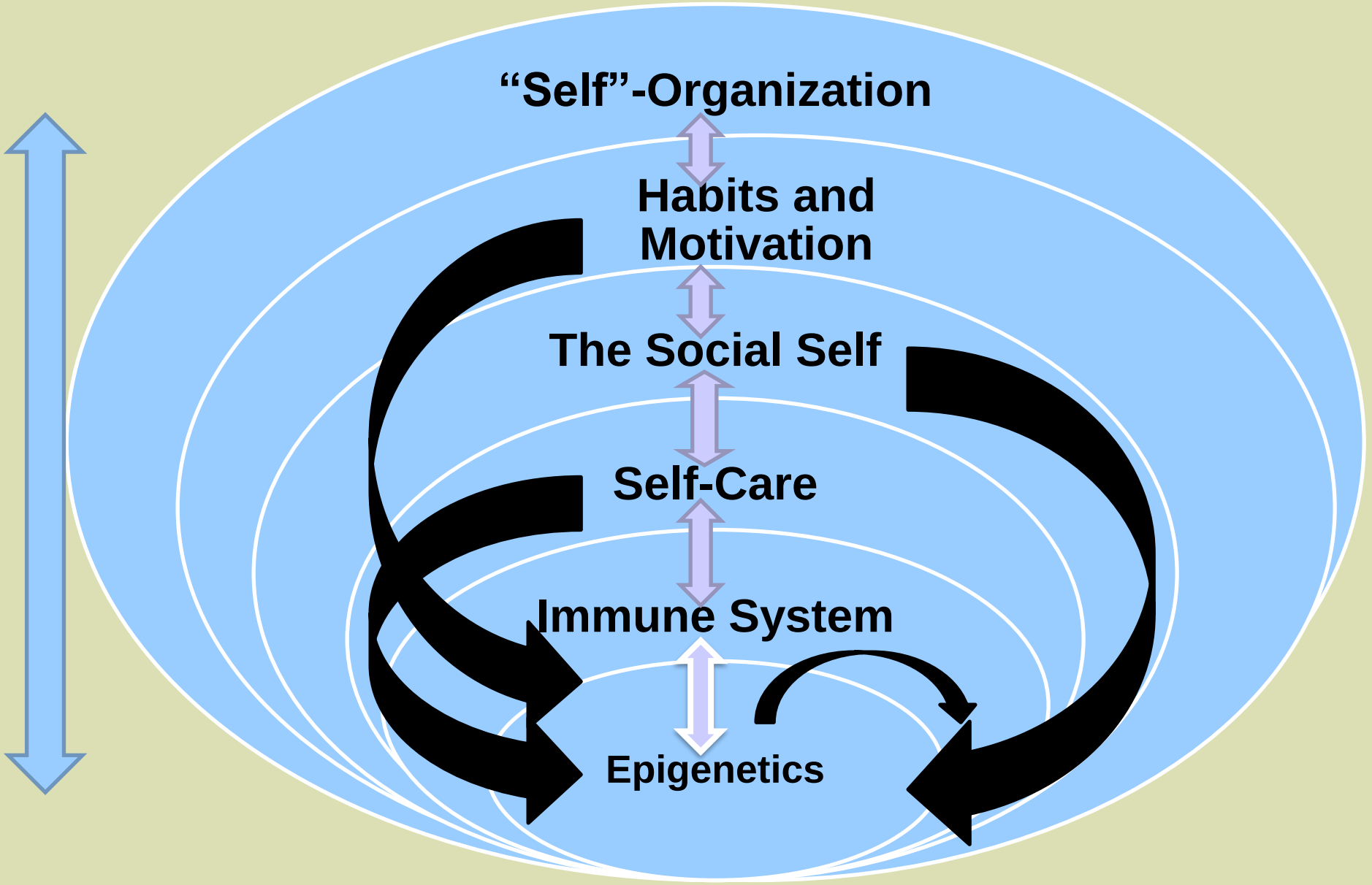
ACEs and Population Attributable Risks



Effect of ACEs on Death Rate

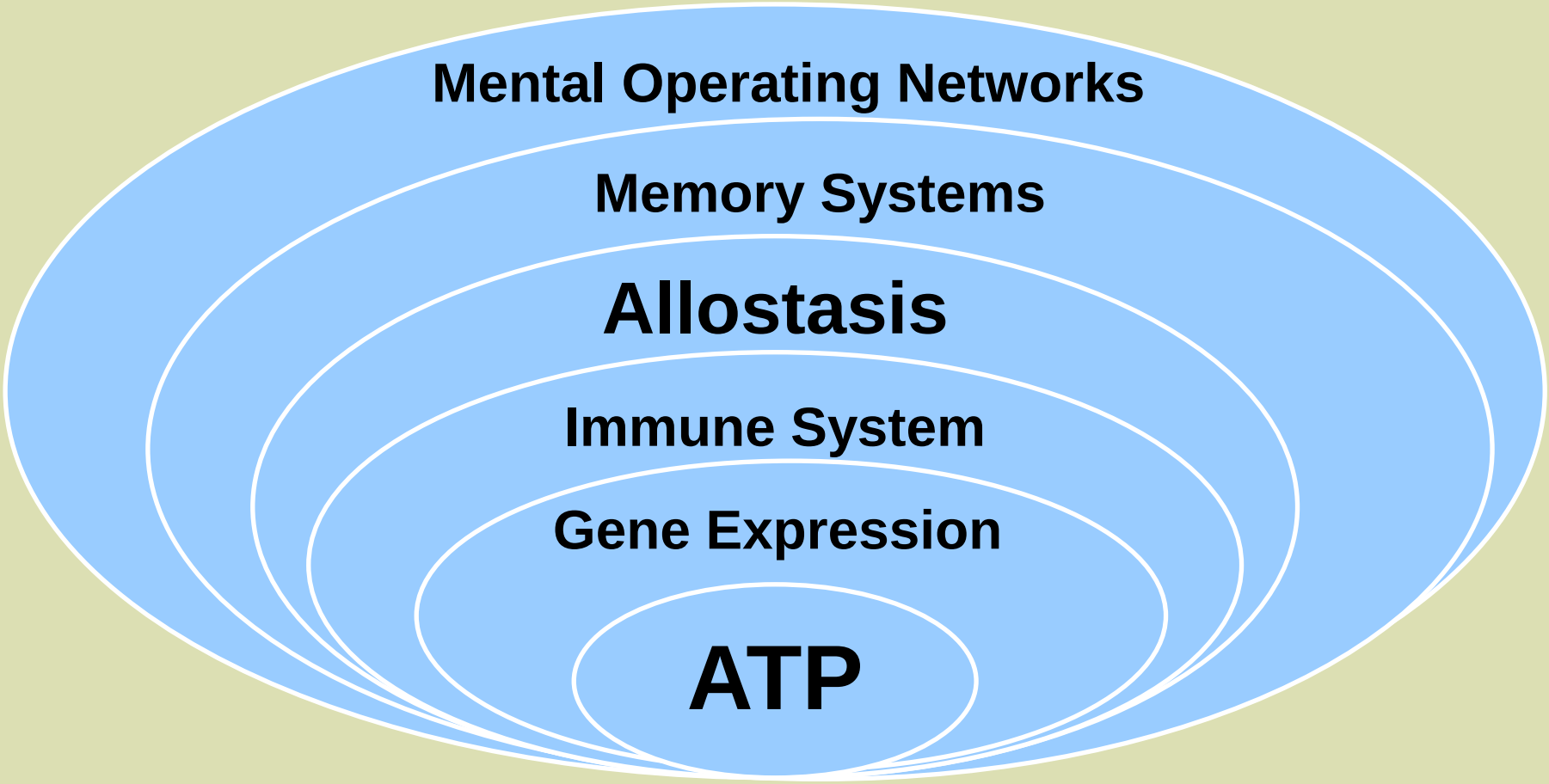


Mind-Brain-Gene Feedback Loops




Complex Systems
Emergence
over scale
Self-Organization
over time
Game Theory
Prisoner's dilemma (PD)
Rational decision making
Iterative PD
n-person PD
Bounded rationality
Irrational behavior
Cooperation versus competition
Spatial/network game theory
Evolutionary game theory
Collective Behavior
Social dynamics
Collective intelligence
Herd mentality
Self-organized criticality
Phase transition
Agent-based modeling
Synchronization
Ant colony optimization
Particle swarm optimization
Swarm behavior
Nonlinear Dynamics
Time series analysis
Ordinary differential equations
Iterative maps
Phase space
Attractors
Stability analysis
Chaos
Population dynamics
Multistability
Bifurcation
Coupled map lattices
Networks
Scale-free networks
Social network analysis
Small-world networks
Community identification
Centrality
Motifs
Graph theory
Scaling
Robustness/vulnerability
Systems biology
Dynamical networks
Adaptive networks
Systems Theory
Homeostasis
Feedbacks
Self-reference
Goal-oriented/ guided behavior
System dynamics
Sense making
Entropy
Autopoiesis
Cybernetics
Information theory
Computation theory
Complexity measurement
Evolution & Adaptation
Artificial neural networks
Evolutionary computation
Genetic algorithms/programming
Artificial life
Machine learning
Evo-Devo
Artificial intelligence
Evolutionary robotics
Evolvability
Pattern Formation
Spatial fractals
Reaction-diffusion systems
Partial differential equations
Dissipative structures
Percolation
Cellular automata
Spatial ecology
Self-replication
Spatial evolutionary biology
Geomorphology

“Self”-Organization



Planting SEEDS

Our Evolutionary Impetrative





Socialise

Calms nervous system
↑ Oxytocin (feel good)
↓ Cortisol (less stressed)
↑ Sense of connection
↑ Problem solving
↑ Attention
↑ Humour and fun
↑ Energy

Exercise

Calms nervous system
↑ Serotonin & Dopamine
↑ GABA (calm)
↑ Energy levels
↑ Growth new brain cells
↑ Sleep
↑ Alertness and thinking
↑ Attention
↑ Chance to socialise
↑ Cardiovascular strength
↑ Physical strength
↑ Flexibility & endurance

Education

↑ Brain power
↑ Serotonin & Dopamine
↑ Growth of new brain cells
↑ Thinking ability
↑ Working memory
↑ Challenge to learn
↑ Novelty – try new things
↑ Social connection
↑ Interest in life
↑ Ability to focus
↑ Sense of achievement

Diet

Calms nervous system
↑Brain chemistry
↑ Brain clarity
↑ Mood
↑ Sleep
↑ Energy
↑ Alertness
↑ Concentration
↑ Ability to focus

Sleep

↑ Hippocampus activity
↑ Memory
↑ Brain cell growth
↑ Serotonin
↑ Immune system
↑ Mood
↑ Energy
↑ Alertness
↑ Concentration

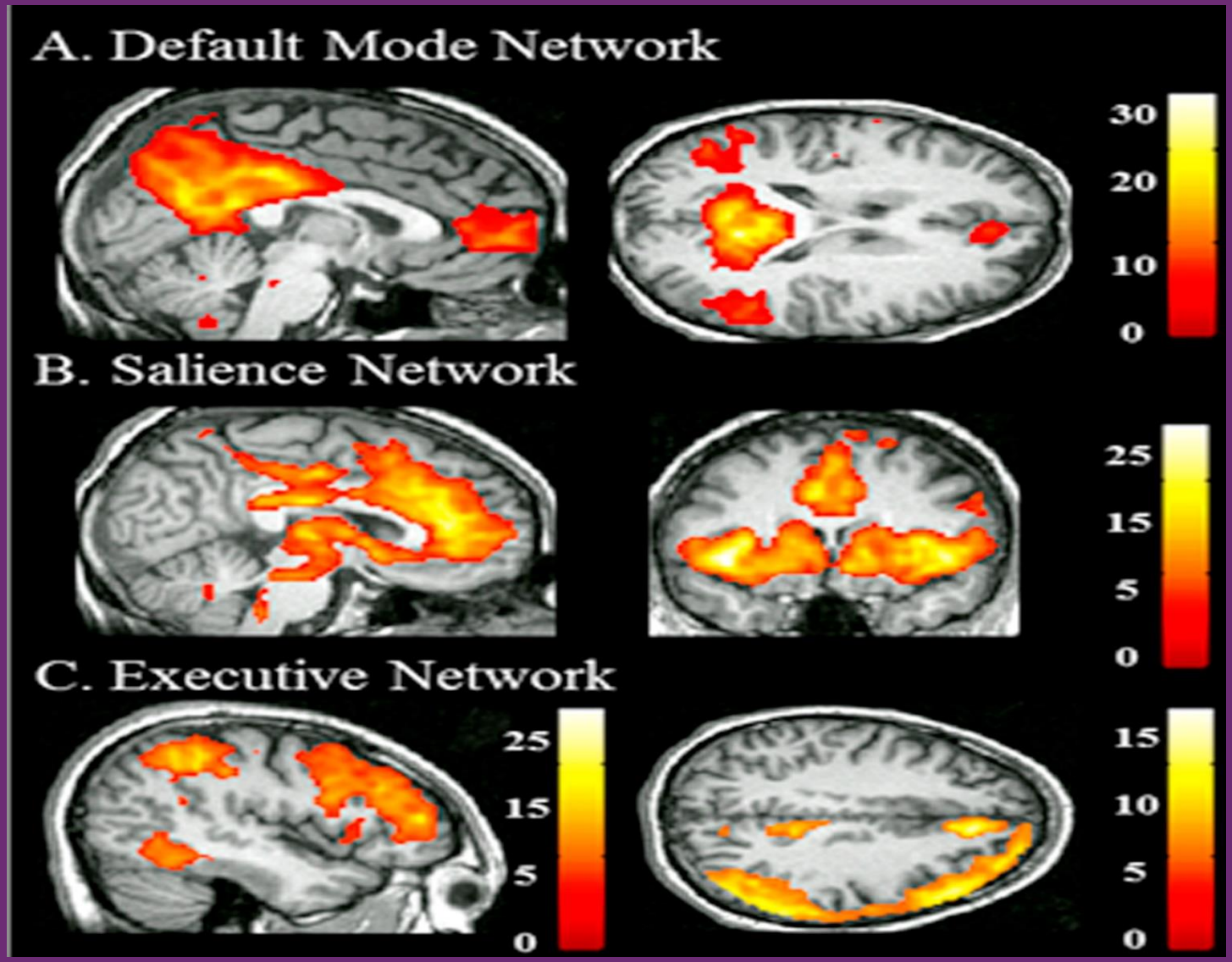
…AND MUCH MORE…

Mind-Brain-Gene Feedback Loops

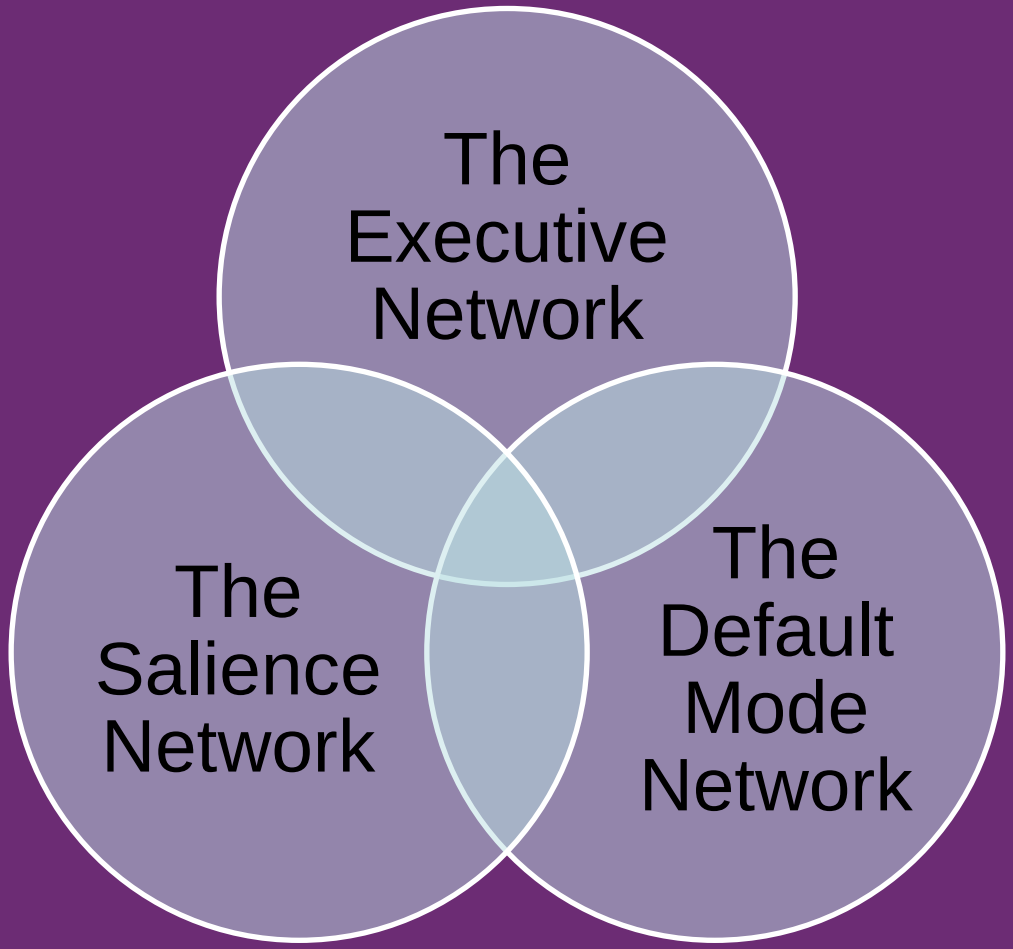
The Mind's Operating Networks:

- **Salience Network:**
- the material "me"
- emotional and reward saliency;
- **Default Mode Network:**
- mind-wandering; fantasying, ruminating
- mentalizing, projecting to the future or past;
- **Central Executive Network:**
- moment to moment monitoring of experience
- selection, planning, toward goals;

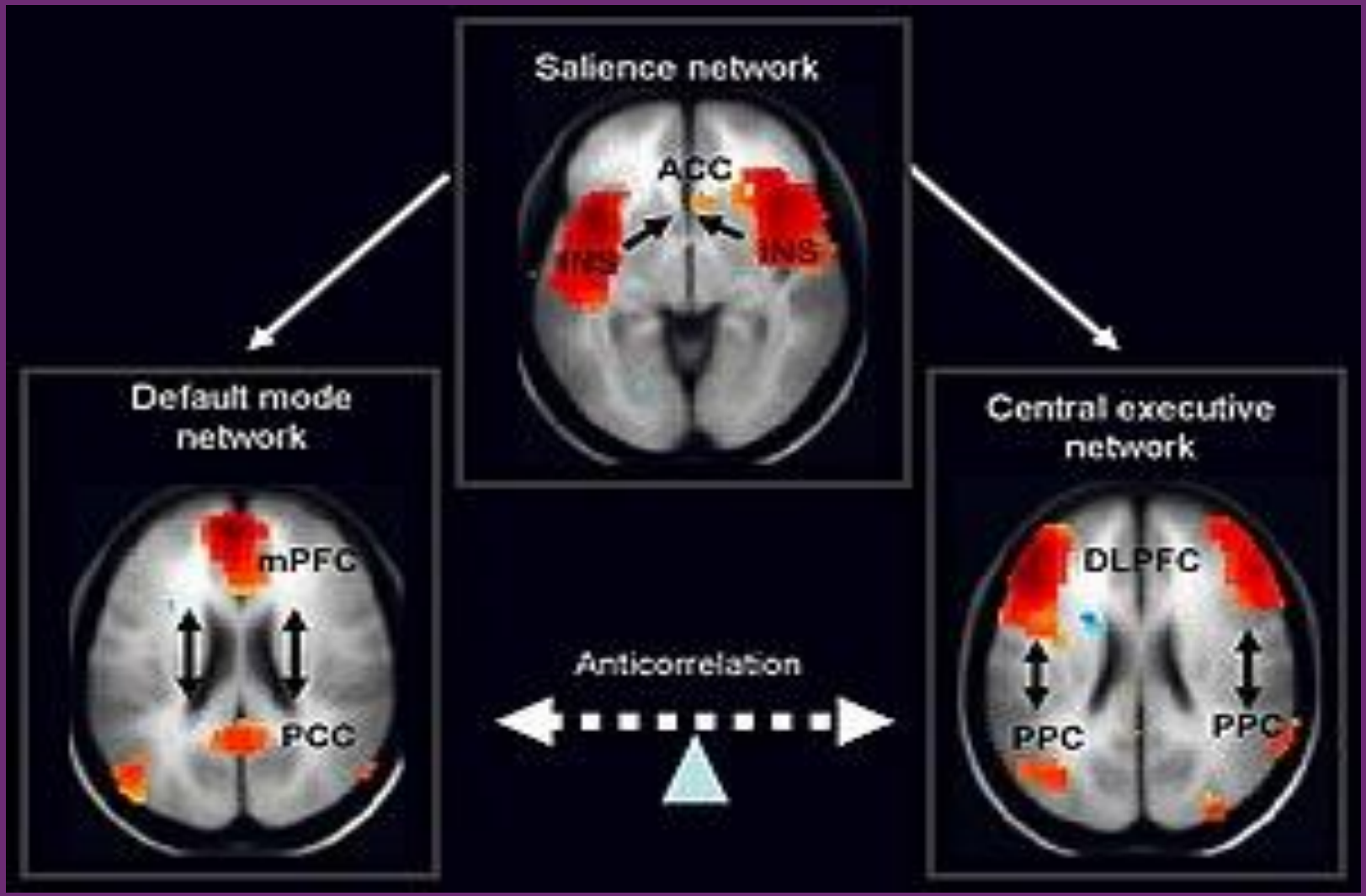
The Mental Networks



Balancing the Mental Networks



The Mental Neworks

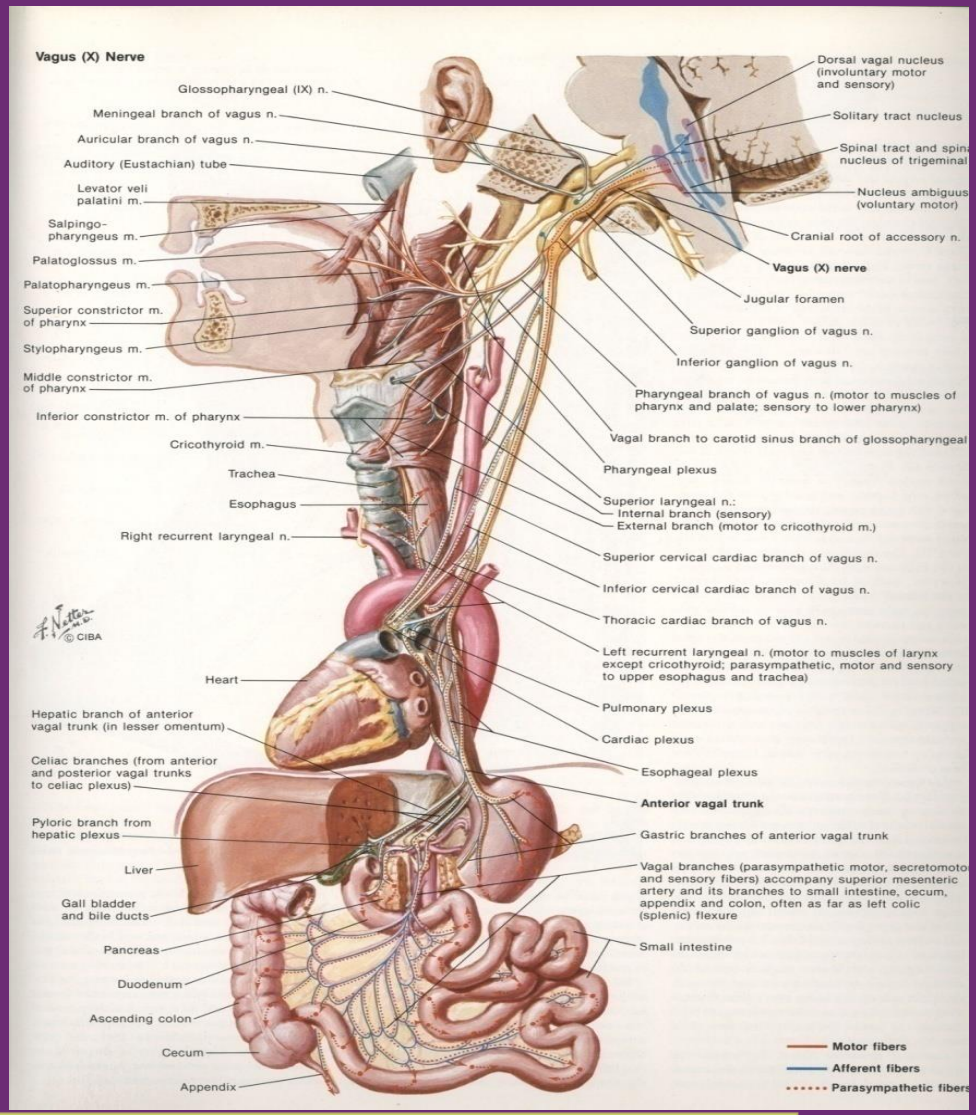


Salience Network:

- referred to as the ‘sentient self’ (the material “me”)
- detecting emotional and reward saliency;
- detecting and orienting toward external events in bottom-up fashion;
- bilateral anterior insula, dorsal anterior cingulate, amygdala

The Vagus Nerve System

- Tenth Cranial Nerve --a complex of sensory and motor nerve fibers.
- *Vagal tone*- the ability to modulate target organs without sympathetic arousal
- allows attachment and sustained relationships.



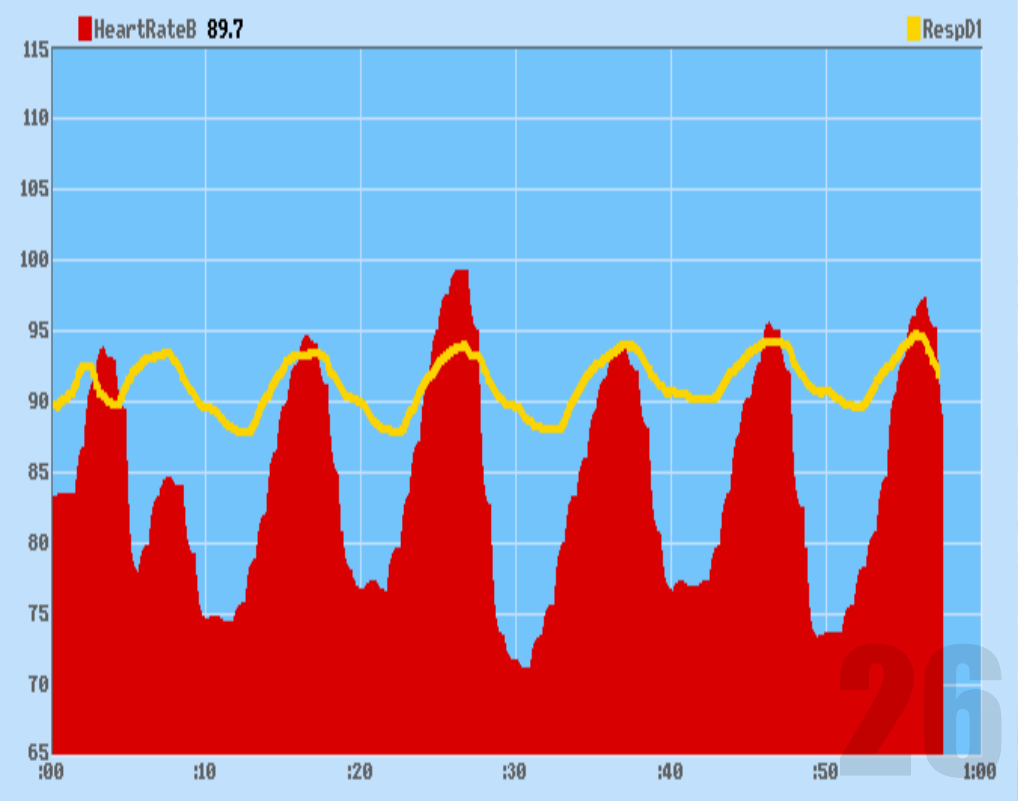
On the market

Variability is good

Peak/valley differences
= vagal tone ***when resp is in normal range***

Heart rate increases with inhale.

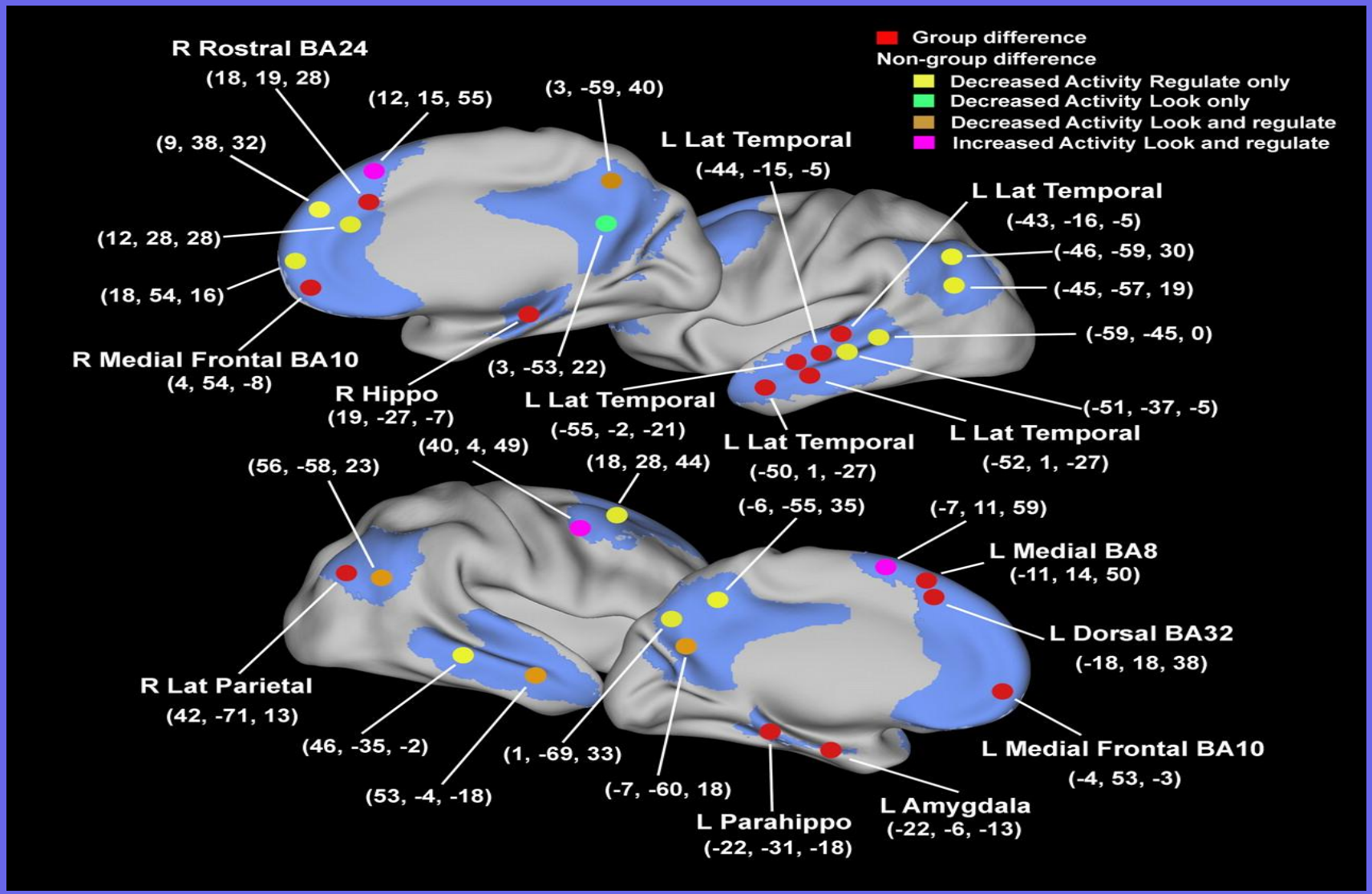
Heart rate decreases with exhale. This pattern shows high vagal tone (high PSNS activity) and a high amount of heart rate variability.



Default Mode Network:

- reflecting, spontaneous thoughts or mind-wandering;
- activated during tasks of mentalizing, projecting oneself into the future or past;
- activation when reflecting on social relationships;
- anterior and posterior midline and cingulate cortex

Activity in the default mode network



Sheline Y I et al. (2009)

DMN--Creativity

- “When I examine myself and my methods of thought, I came to the conclusion that the gift of fantasy has meant more to me than my talent for absorbing positive knowledge.”
- ---Albert Einstein

DMN Variations

- Increases when DLPFC is not engaged:
  - Stressed, bored, no novelty, or tired
- Social and self-referential –needed for sense of self
- Malfunctions in the DMN:
  - Schizophrenia—impaired self reflection—not sure where thoughts come from
  - Depression—negative ruminations

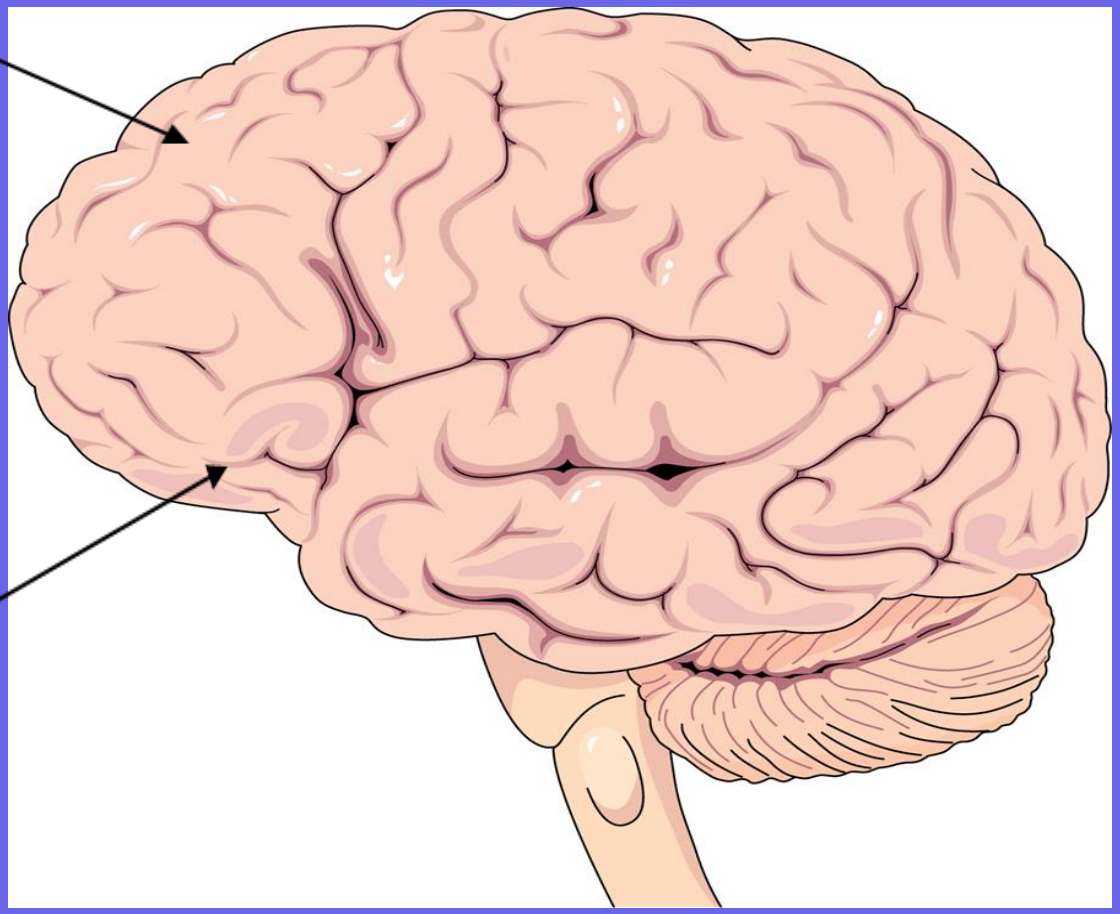
Central Executive Network:

- moment to moment monitoring of experience (meta-cognition)
- responsible for selection, planning, and decision-making toward goals;
- working memory that helps select, orient, and maintain an object in the mind;
- bilateral dorsolateral prefrontal cortex

DLPFC and the OFC

Dorsolateral Prefrontal Cortex

Orbital Prefrontal Cortex



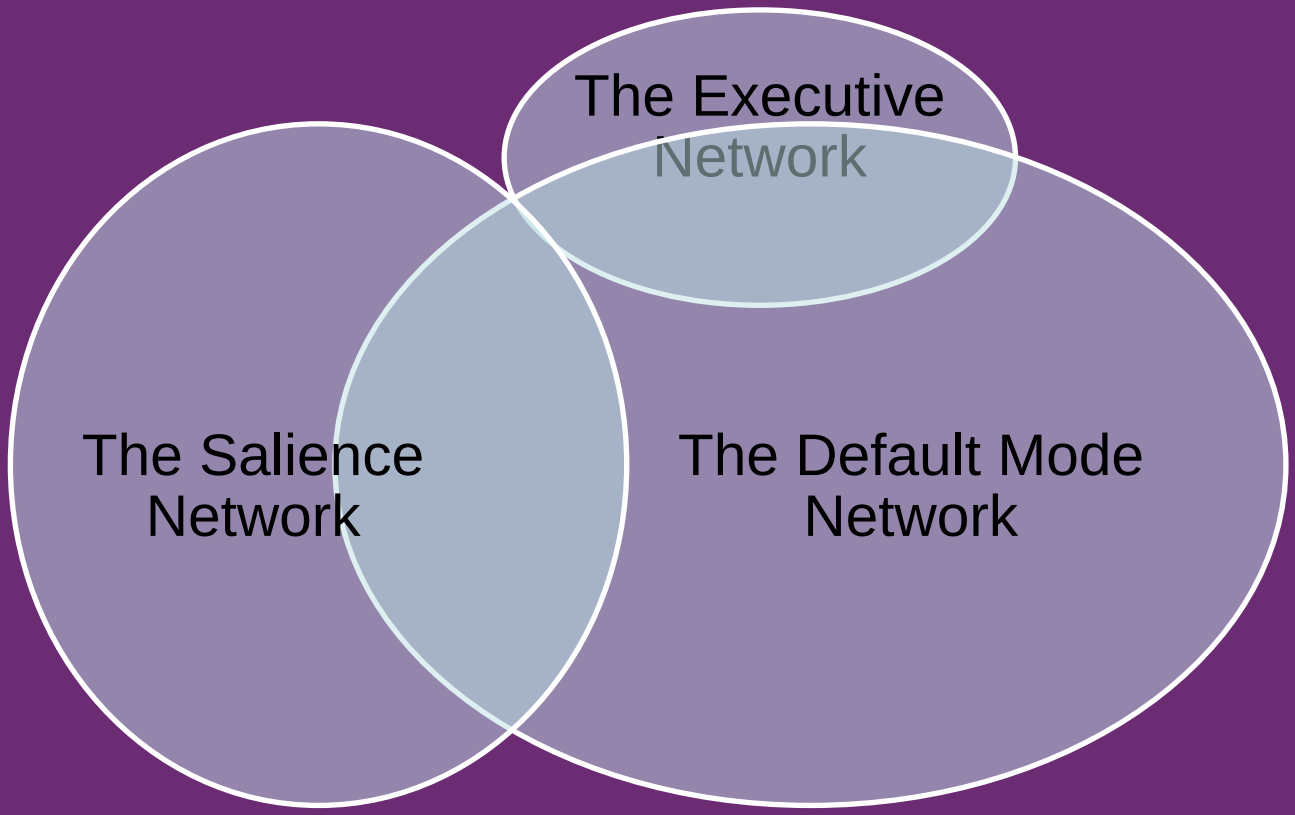
Pre-Frontal Cortex

- Dorsolateral pre-frontal cortex (DLPFC)---working memory: 7, plus or minus 2, …….or 20-30 seconds of information
- Orbital frontal cortex (OFC)
  - Social brain
  - Affect regulator
  - Empathy
  - Attachment, warmth, and love
  - Connections with limbic area, i.e., amygdala
  - Phineas Gage

Anterior PFC
(the brain's brain)

- Critical for juggling more than one concurrent behavioral task or mental plans (Knoechlin & Hyafil, 2007)
- Has more dendritic spines per cell and spine density
  - Making it more adept at very broad integration of inputs (Ramnani & Owen, 2004)
- Bidirectionally interconnected with the hetermodal association regions of the posterior cortex, but not modality specific regions
  - Making it adept at integrating outcomes of several cognitive operations in the context of a superordinate goal

Imbalanced Mental Networks



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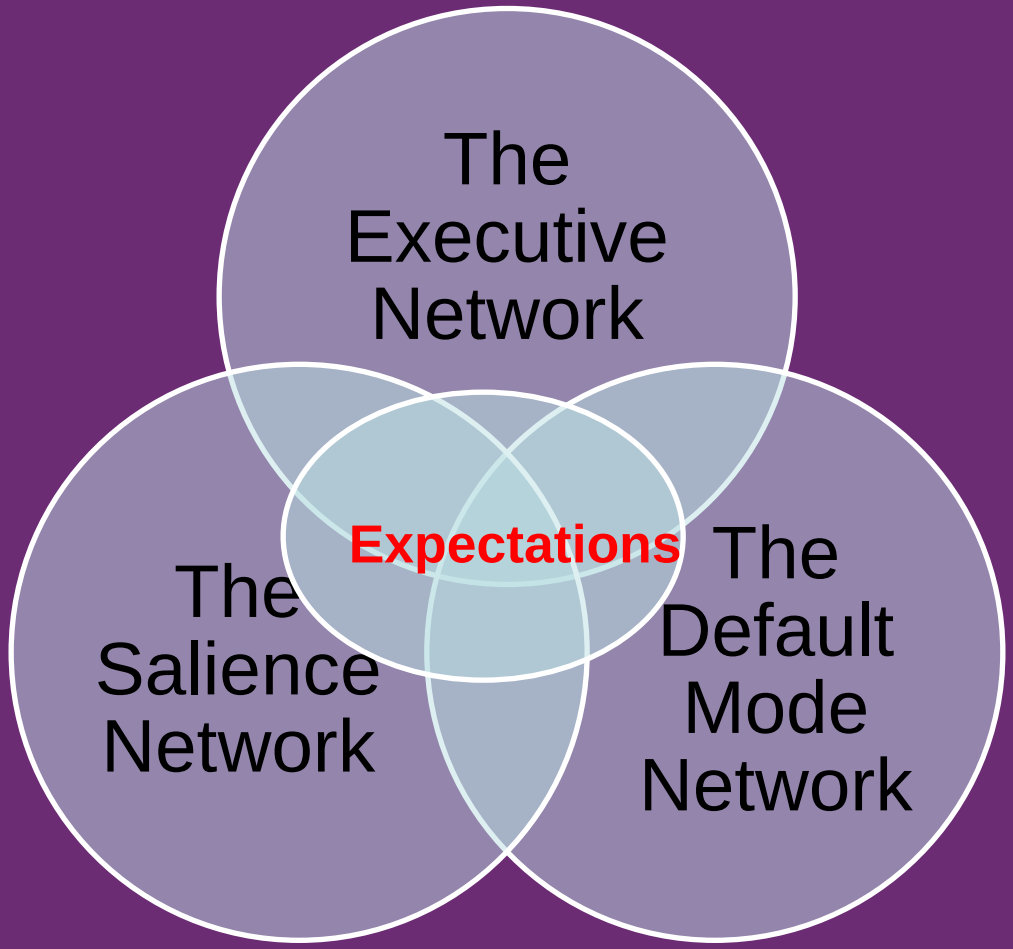
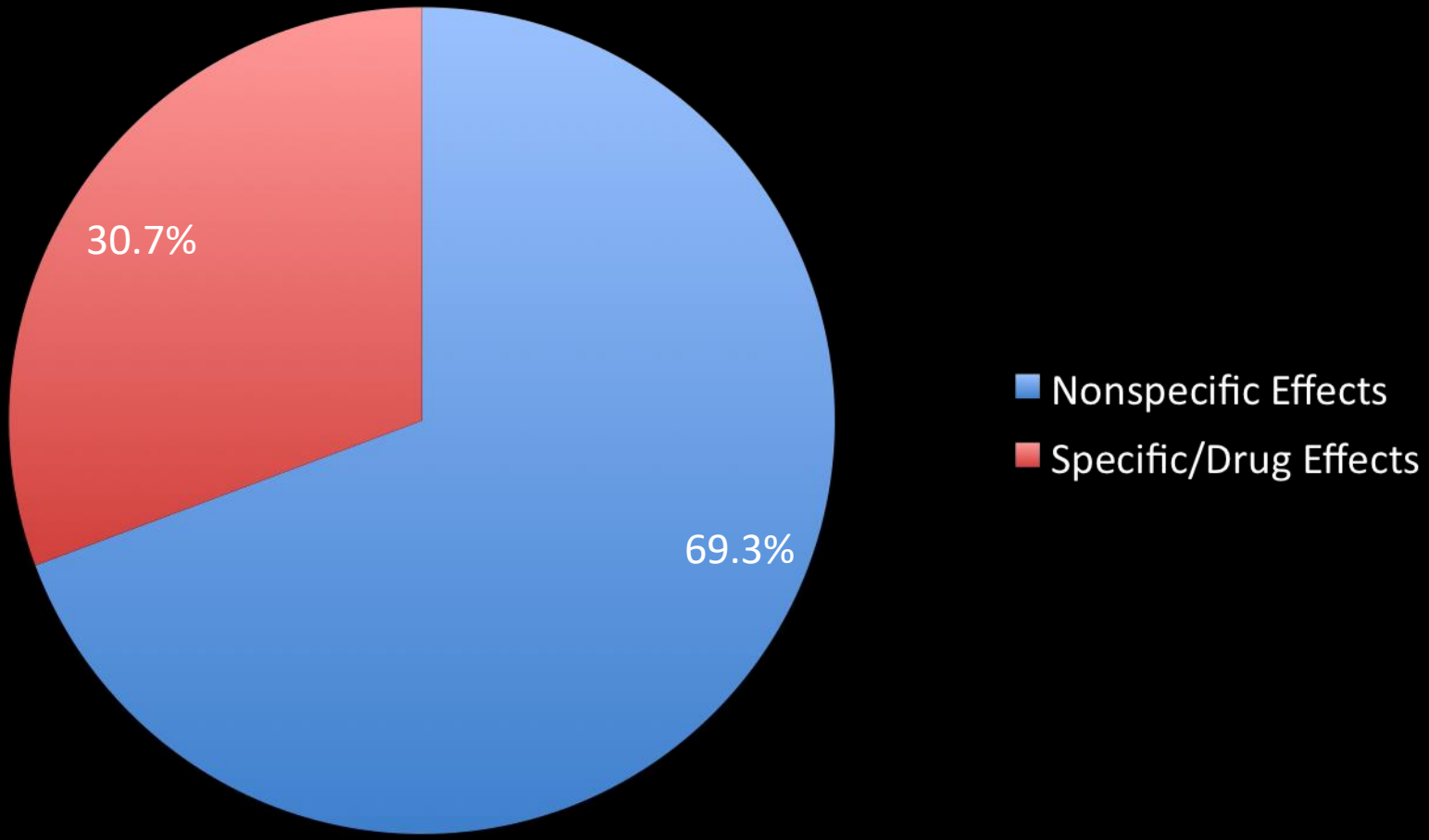


Placebo or Nocebo

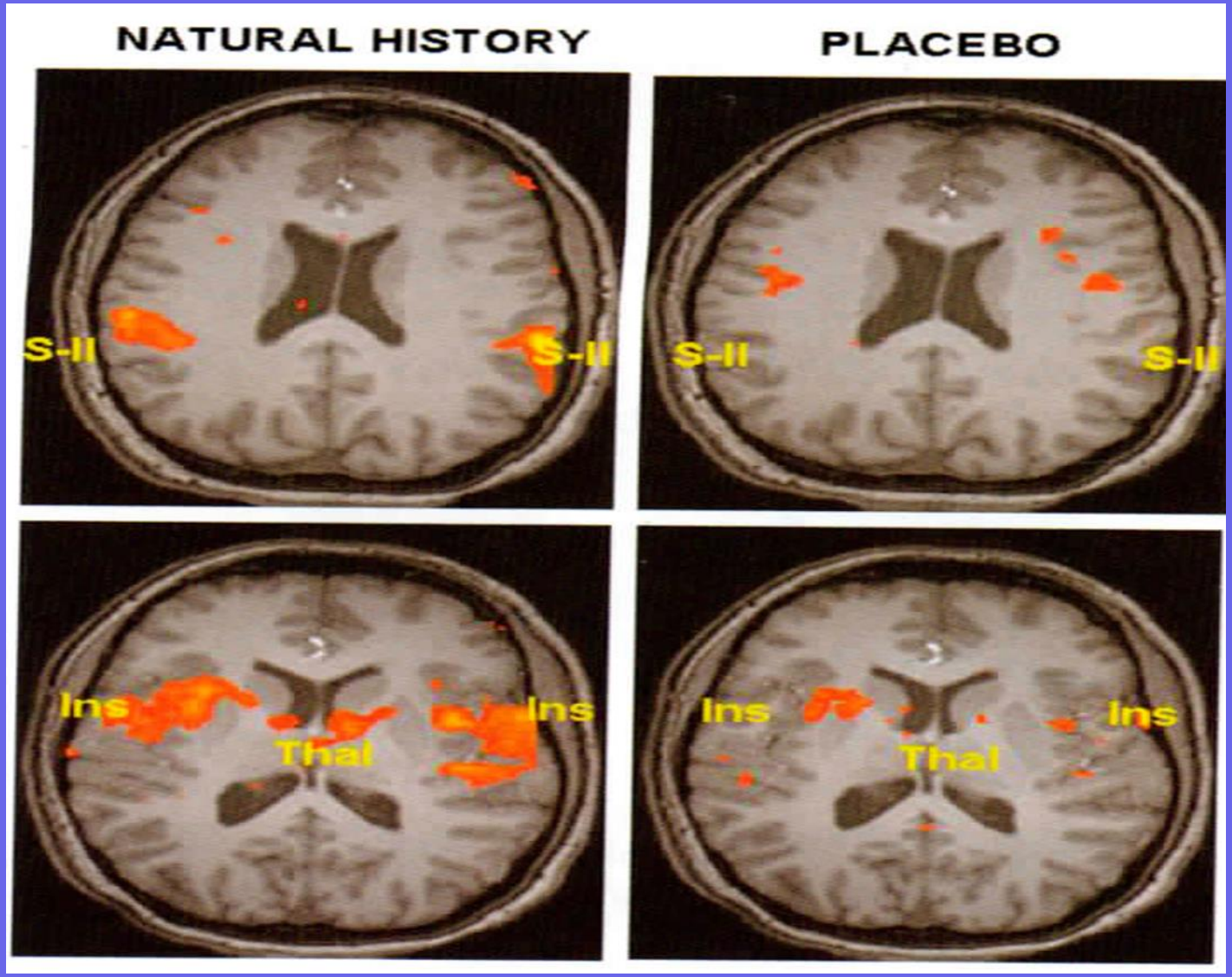


*Derived from pooled response rates for drug and placebo of 53.8% and 37.3%
Papakostas, *Eur Psychopharmacol*, 2009

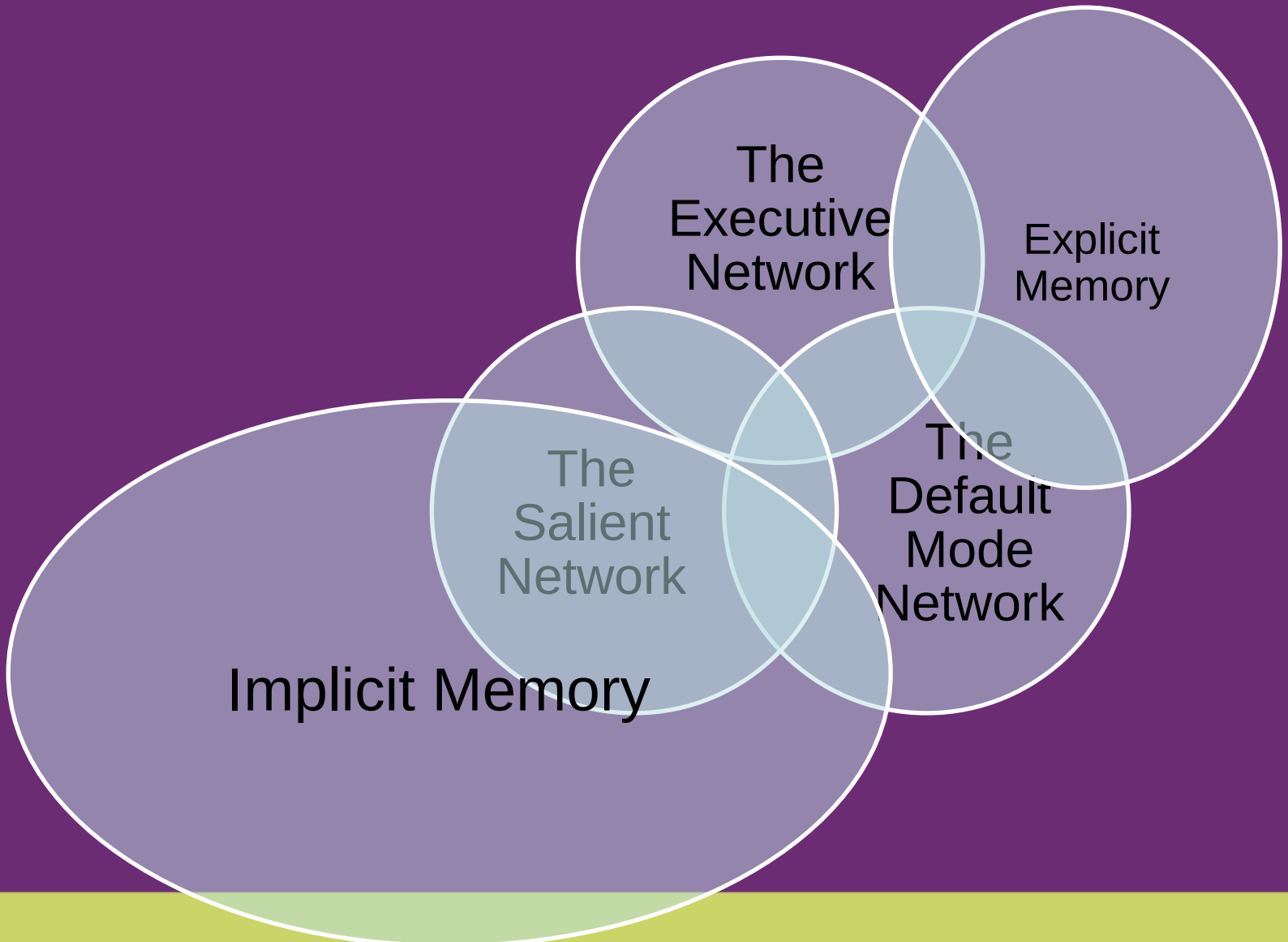
Incidence of Placebo Response

- 10% to 70%
- Average 35% across studies and diseases as well as psych disorders
- Works best for subjective outcomes like pain and psychological disorders
- Half as effective as morphine
- Quite effective with depression and anxiety

IBS and Pain vs. Placebo



The Mental Neworks & the Long-Term Memory Systems



AMYGDALA
Implicit Memory System

- Fear Conditioning
- Emotional Valance
- Generalized
- Cortisol Heightened
- Sensitivity
- (Hypervigilence)
- Matures Early
- "Little Albert"
- "LSMFT"

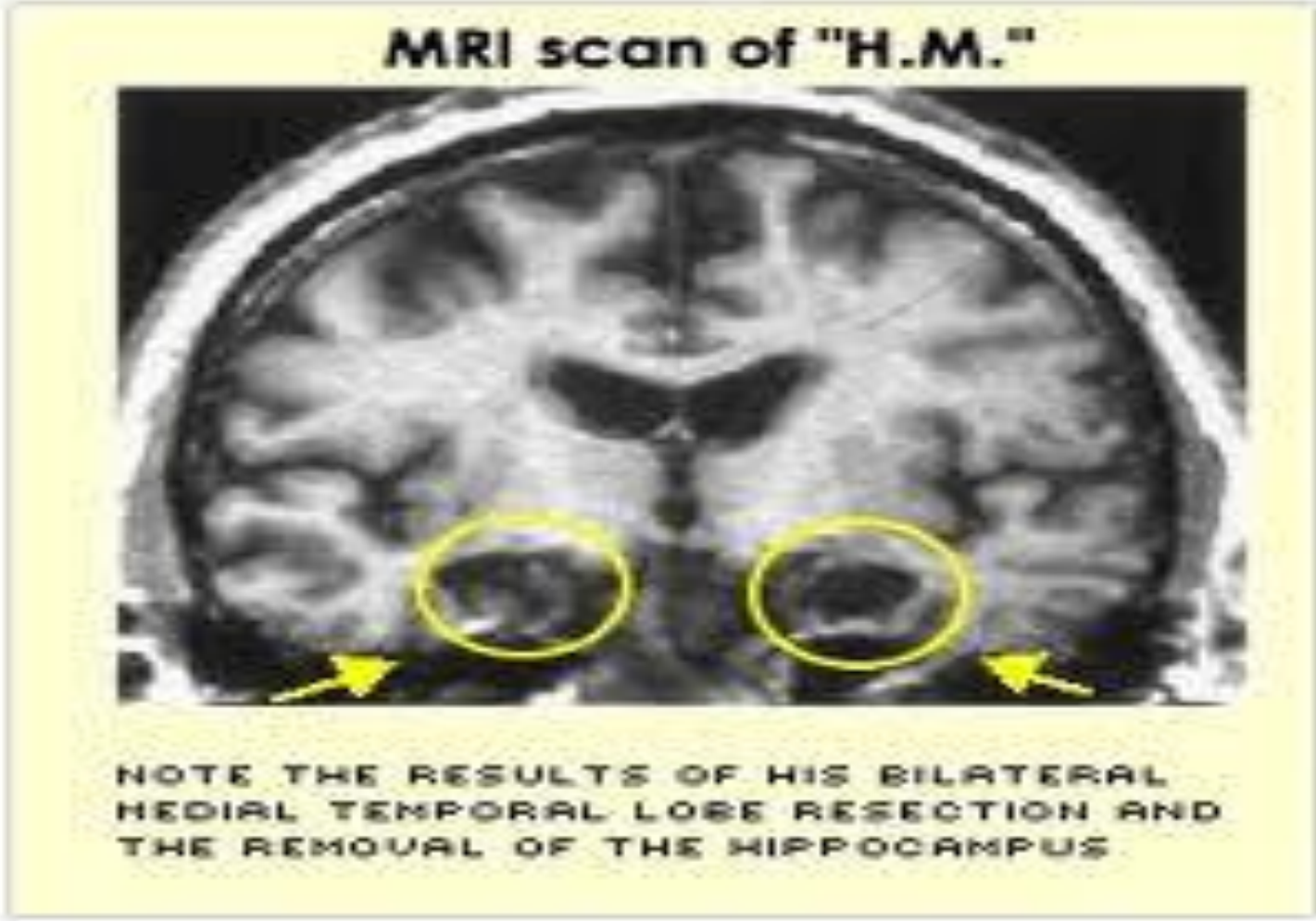
HIPPOCAMPUS
Explicit Memory System

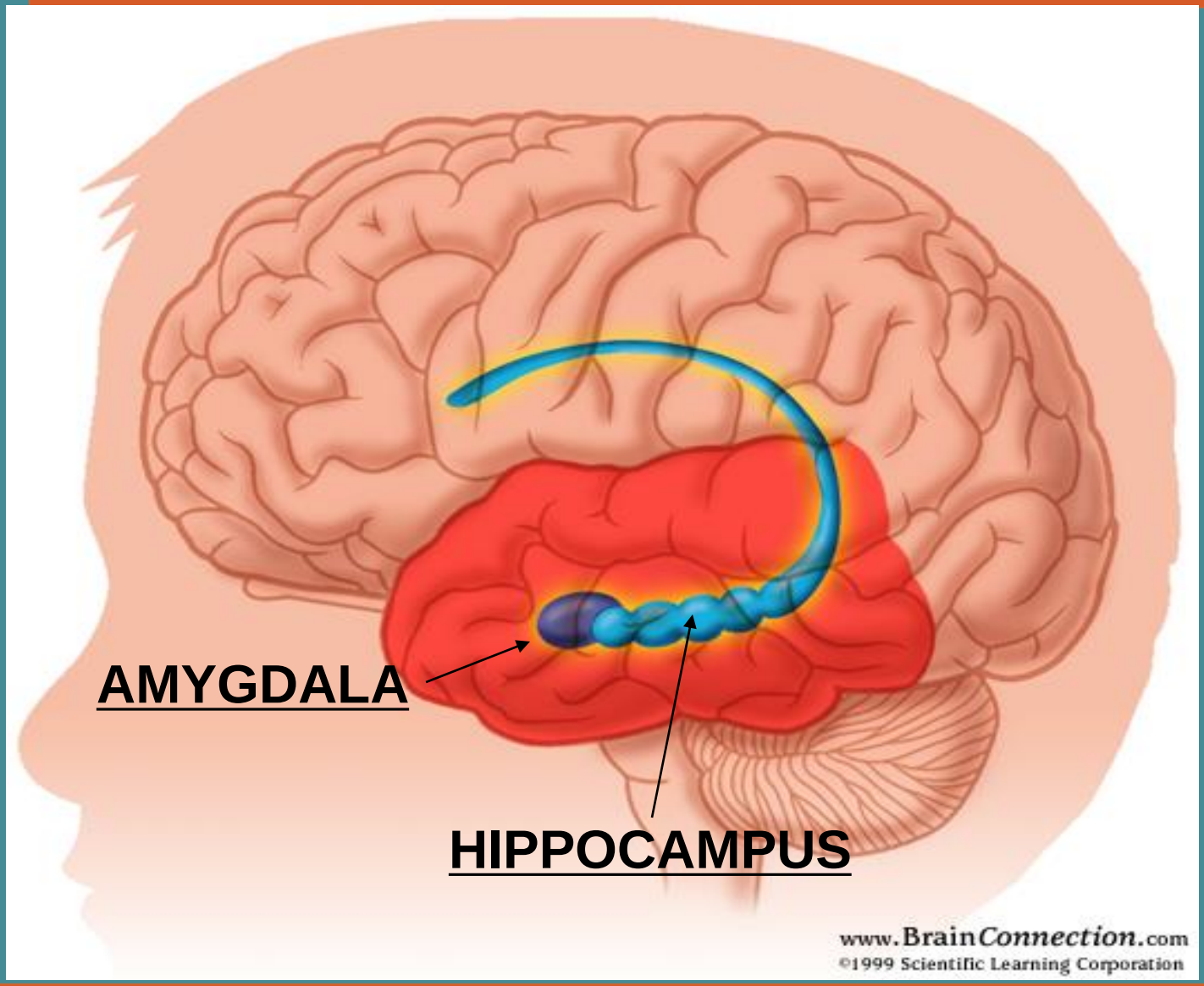
- Many Cortisol Receptors
- Context Specific
- Heightened Cortisol leads to atrophy
- Matures Later
  - Vs. Infantile Amnesia
- "H.M."

Henry Molaison

Dr. Brenda Milner

Henry's Brain




AMYGDALA
HIPPOCAMPUS
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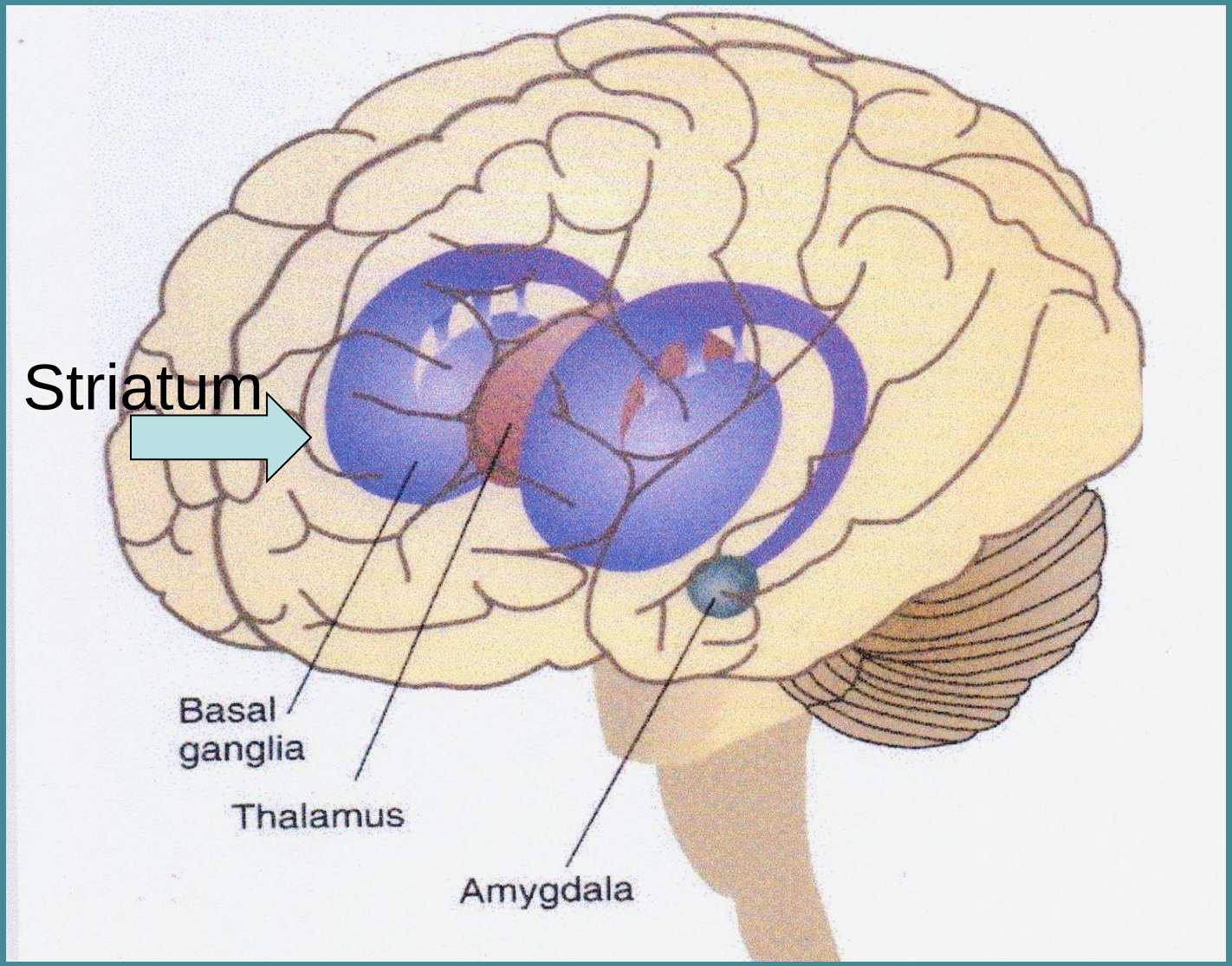
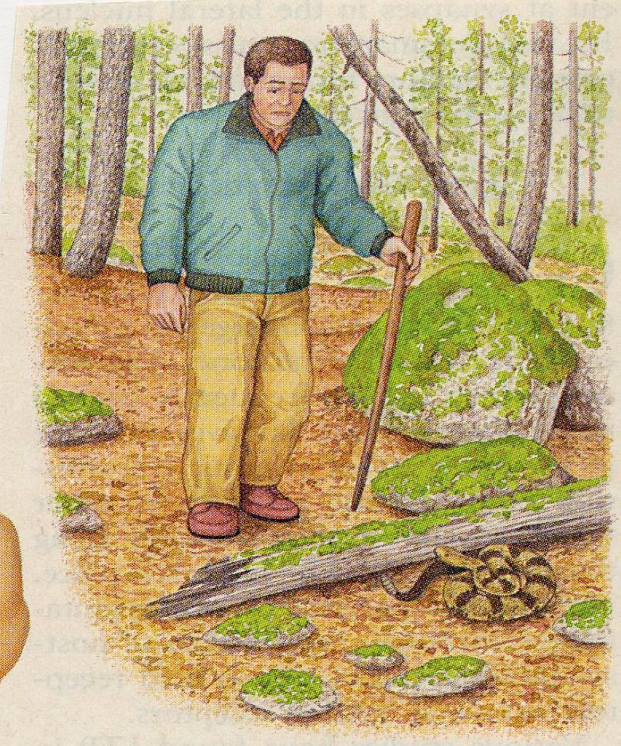
EXPLICIT DECLARATIVE KNOWLEDGE
IMPLICIT PROCEDURAL KNOWLEDGE

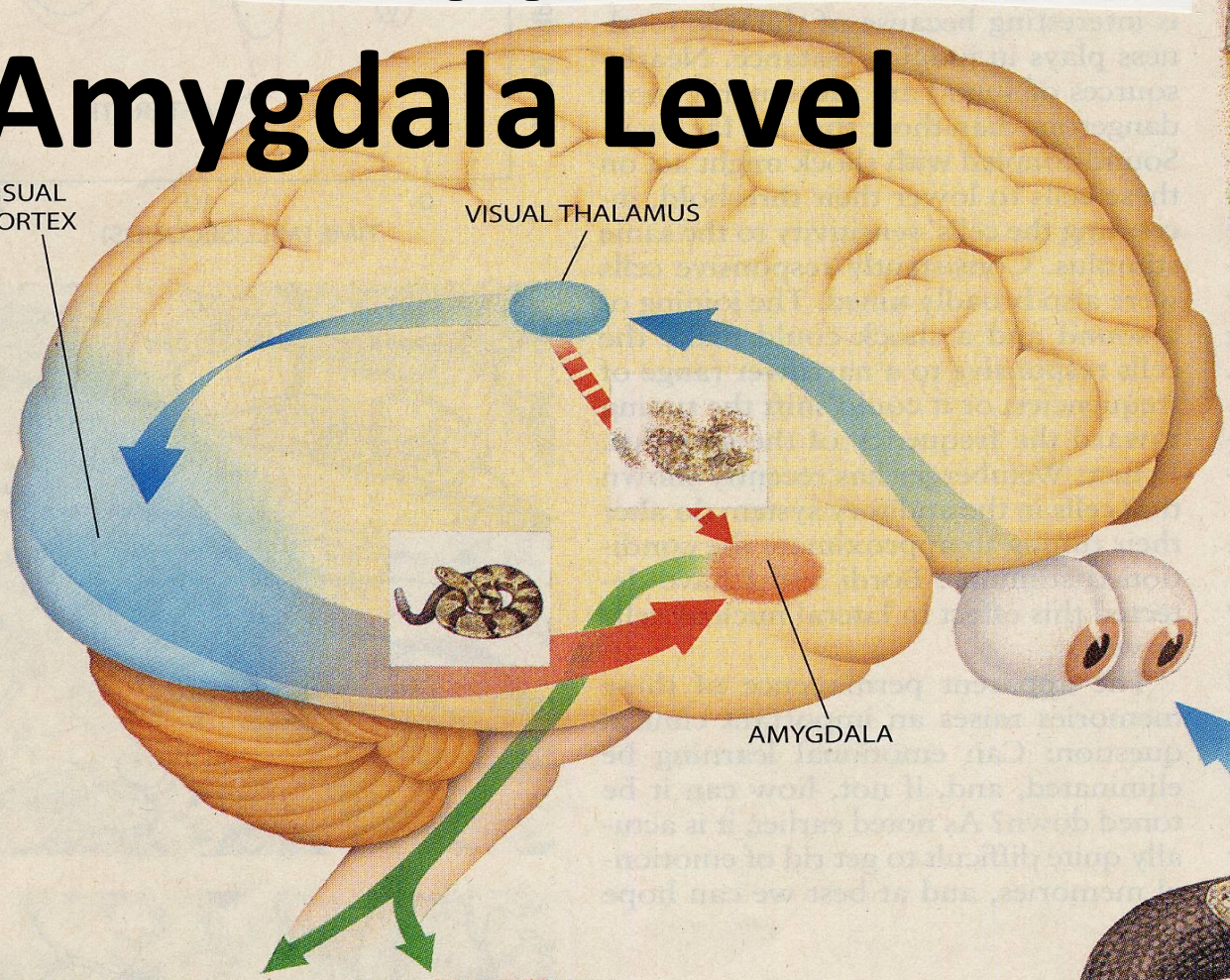
The Habit Circuits

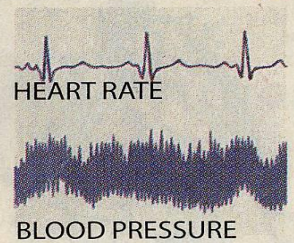


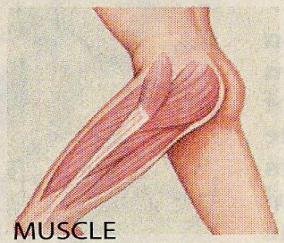
Procedural Memory

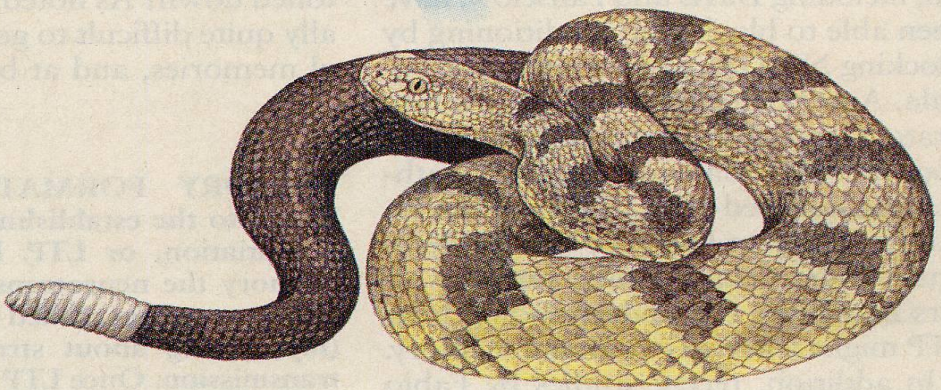
Threat Appraisal: Amygdala Level











The Fast Circuit to the Amygdala

- Sensory info goes to the Thalamus then directly to the Amygdala:
- Fight or Flight: SNS and HPA activation
- Emotional Learning
- Fear Conditioning
- PTSD, panic, etc.
- Flashbacks
- “Bottom up”

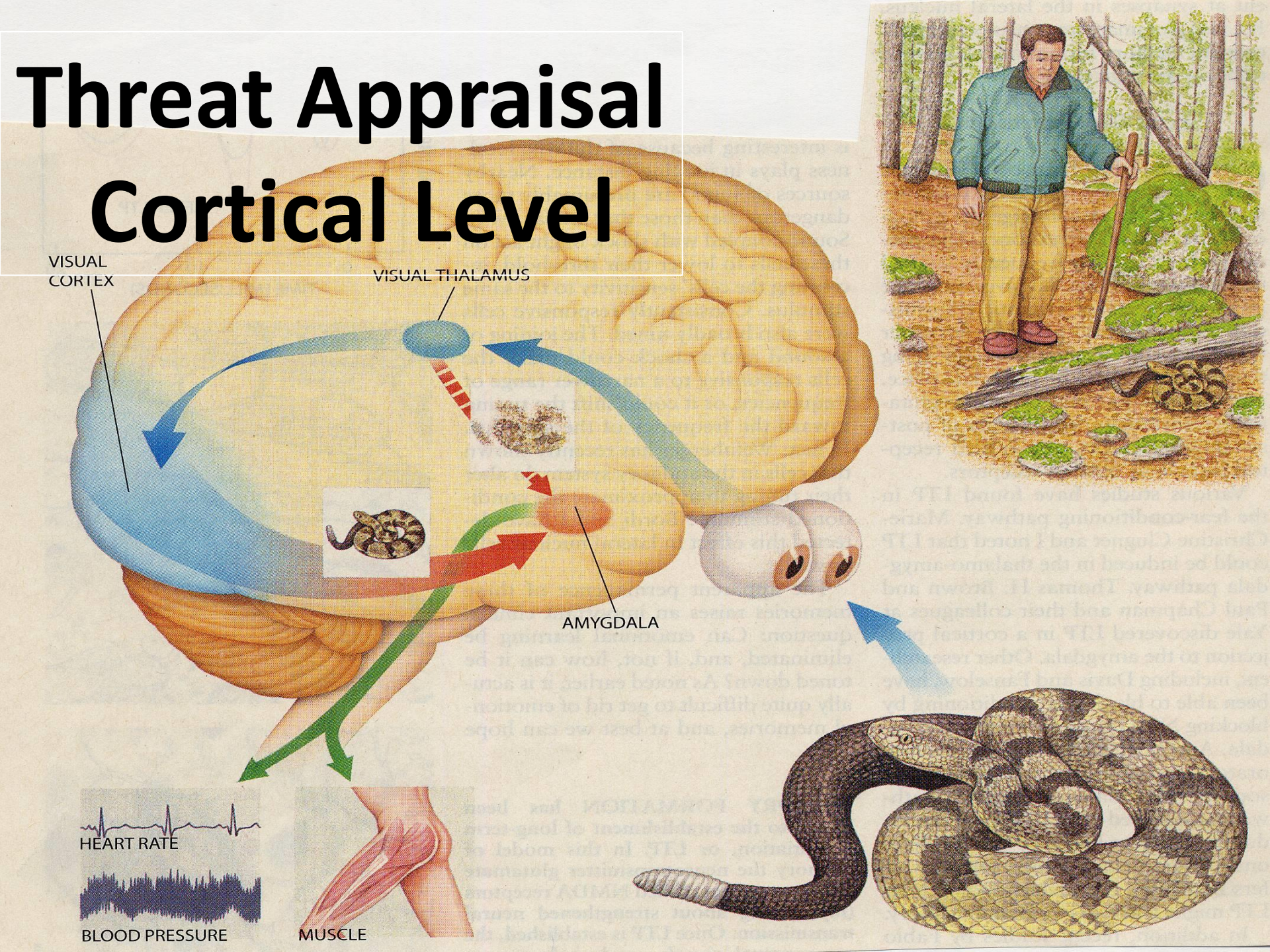
The Fast Track to Survival

- Rapid, crude, adaptive, and immediate
- Cannot reality test
- Prone to false alarms

The Fast Track to Survival

- Rapid, crude, adaptive, and immediate

Threat Appraisal
Cortical Level



The Slow Circuit to the Amygdala

Sensory info goes to the Thalamus through the Cortex and Hippocampus to the Amygdala

Complications:

- **Worries and GAD**
- **Fears and Phobias**

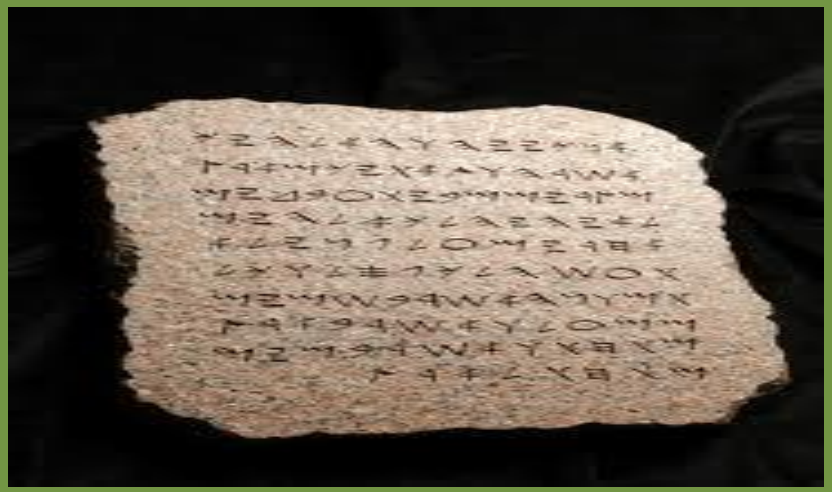
Benefits:

- **Tames the Amygdala**
- **With exposure, New Thinking (cortex)**

"Top down"

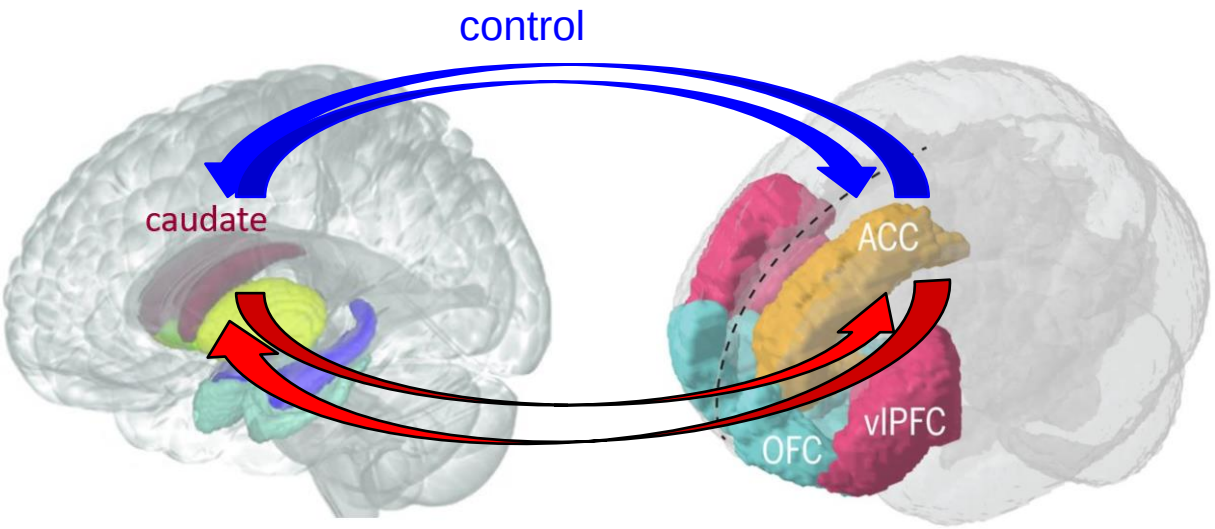
The Dynamics of Fear

- Amygdala memories are hard to forget ("Stone tablet")



- Hippocampal circuits tell us what to fear and in what context ("Etch-a-Sketch")

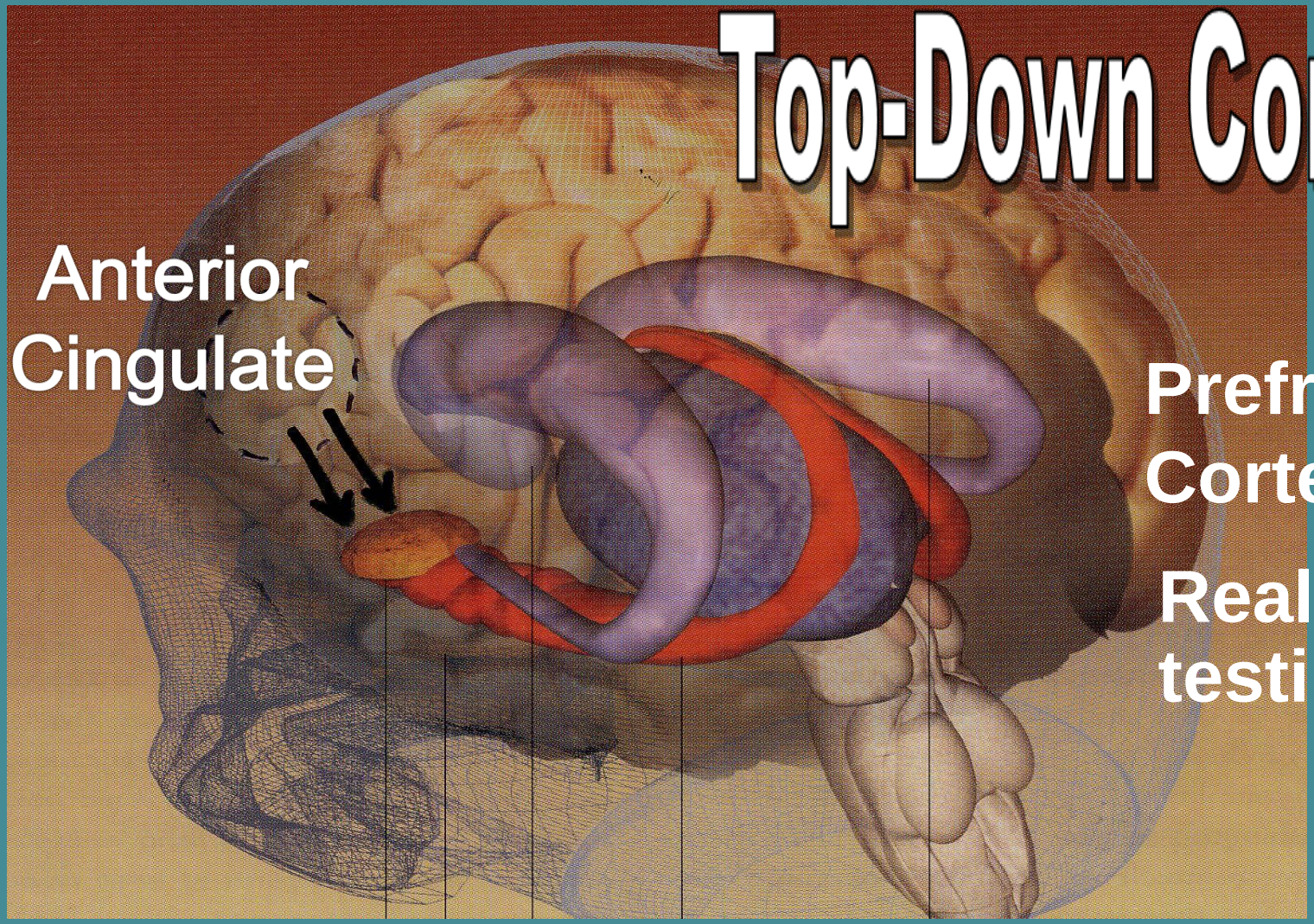
Subcortical-Cortical Connectivity



Immediate

Shannon, Sauder, Beauchaine et al., 2009

Cortical-level Appraisal



The Snake Temple—Top Down Control?

Negative Memories

- Fear and negative emotion narrows attention to threat:
  - **–"weapons focus"**
- Thus, less accuracy for peripheral memory of stimuli (i.e. color of the car or person's hair) more to the object of threat (gun, knife, etc.)

Phillip's Milk of Amnesia

for people who can't remember shit!

Memory Giants

Affect Asymmetry

Set points

Left Hemisphere

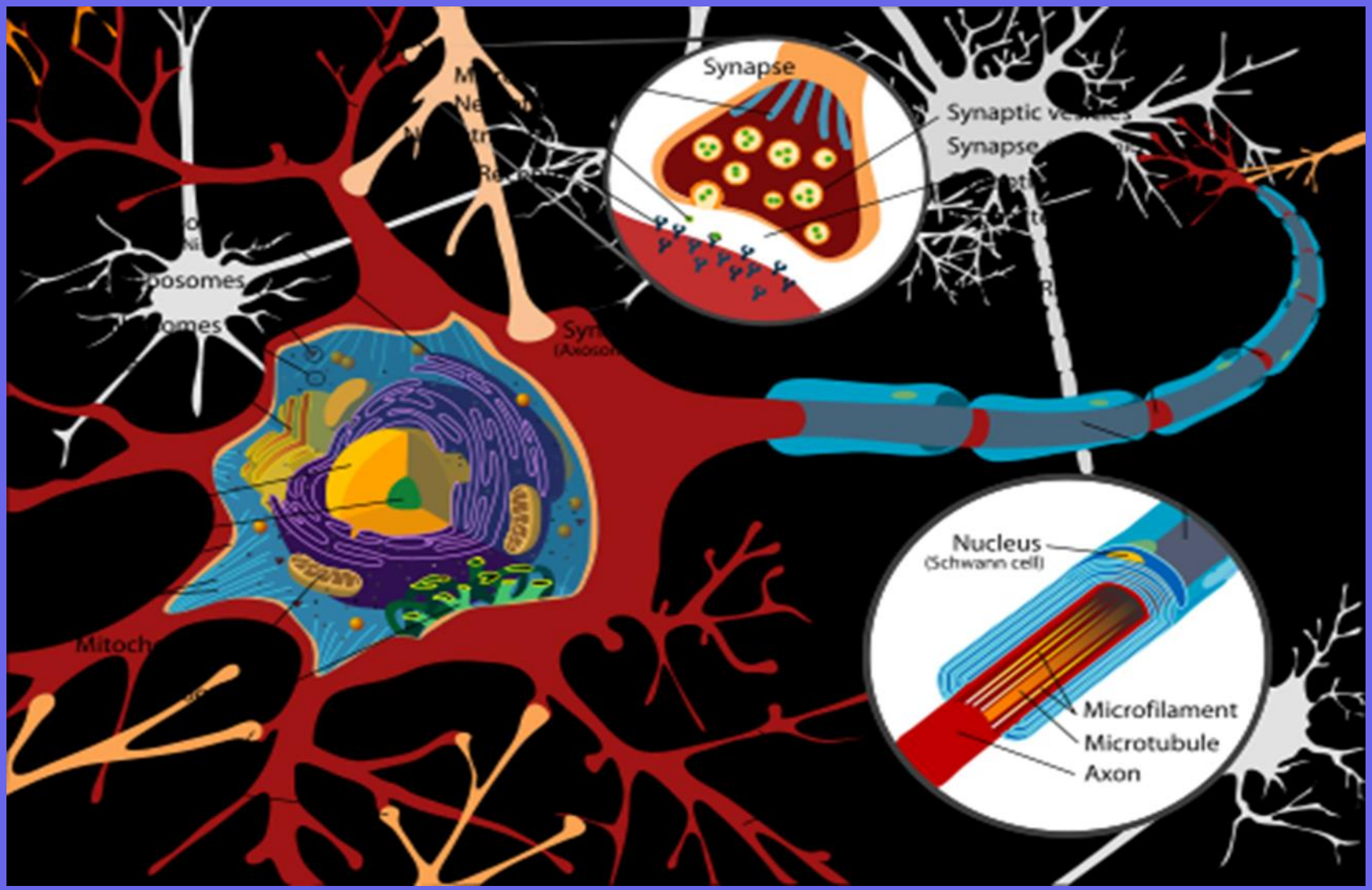
Positive emotions
Approach behaviors
Feeling engaged

Right Hemisphere

Negative emotions
Withdrawal and Avoidance
Feeling overwhelmed

100 Billion Neurons

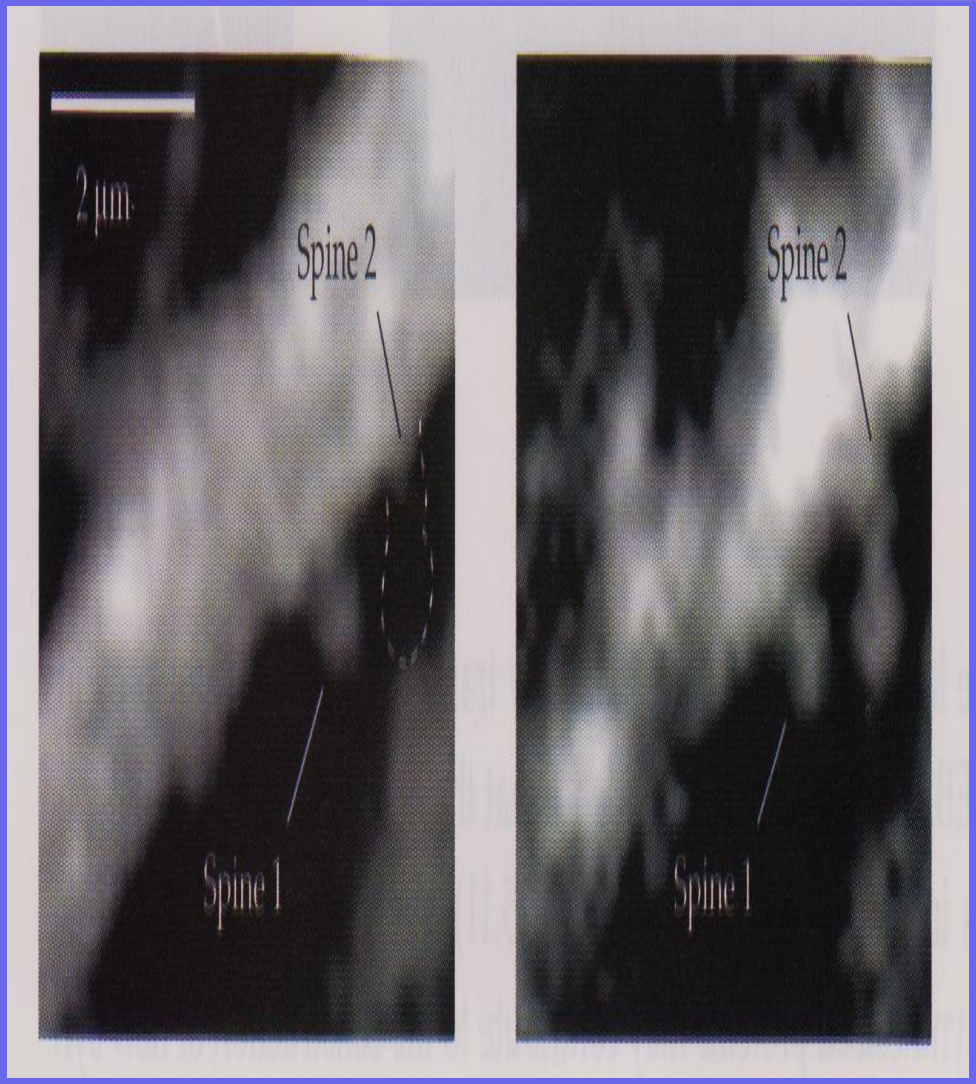
Each with 10,000 synaptic connections

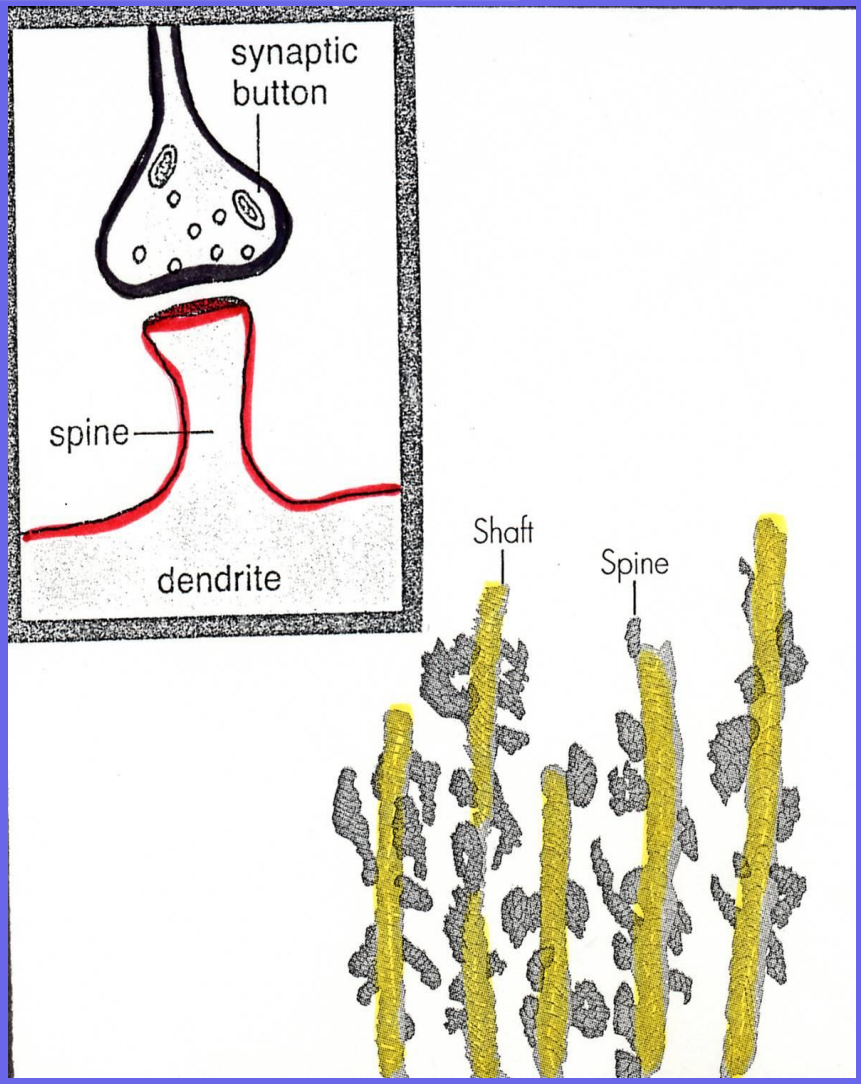


Neurons that fire together, wire together

- ***Neuroplasticity*** **is a general term that describes changes in the brain as you experience and learn** (Buonomano & Merzenich, 1998)
- **Neuroplasticity involves many changes to the brain including:**
  - **New synaptic connections**
  - **Strengthening of connections through LTP**
  - **The growth of new dendrites (dendritogenesis)**
  - **Neurogenesis (the growth of new neurons)**

DENDRITE SPINES & SYNAPSES—one hour



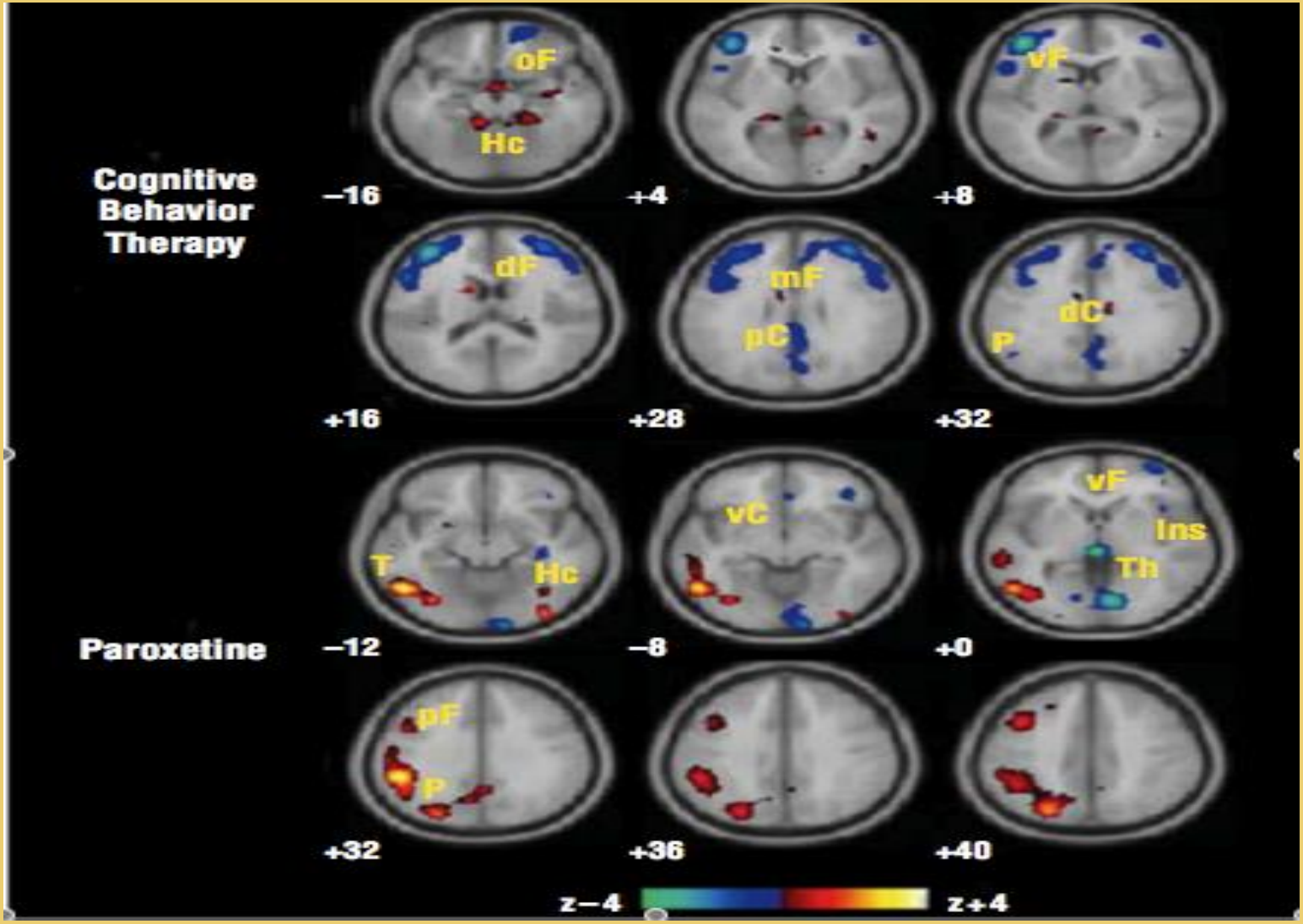


Examples of Neuroplasticity

- London cabdrivers - larger right posterior hippocampus. The longer they were on the job, the larger the size of their hippocampus. (Maguire, et al, 2000)

- Adults who juggled three balls for 3 months increased grey matter in the midtemporal area and left posterior intraparietal sulcus. - 3 months of little or no juggling, -- grey matter decreased and approached baseline values. (Draginski, et al, 2003)

Brain Change: Two Perspectives



Psychotherapy and the Brain

Direct, observable links between successful CBT/IPT and brain changes

- **Reduced amygdalar activity in:**
  - **phobics** (Straube, *et al.,* 2006),
  - **panickers** (Prasko *et al.,* 2004),
  - **social phobics** (Furmark *et.al,* 2002)
- **Increased ACC activation in PTSD** clients (Felmingham *et al.,* 2007)
- **Increased hippocampal activity in depressives** (Goldapple *et al.,* 2004)
- **Decreased caudate activity in OCD** (Baxter, *et al.,* 1992)

Self-Regulation Factors

- **Social**
- **Exercise**
- **Education**
- **Diet**
- **Sleep**

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.

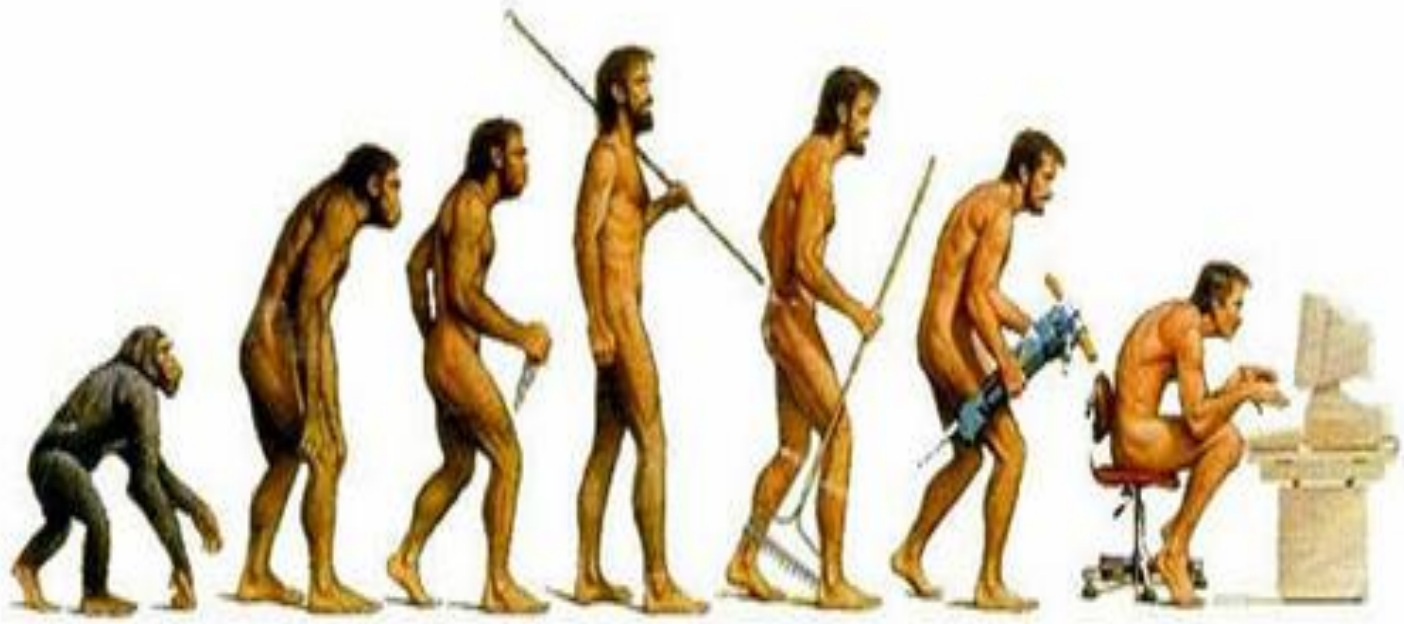
Resistance Training: Lifting, Throwing, and Carrying Objects

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

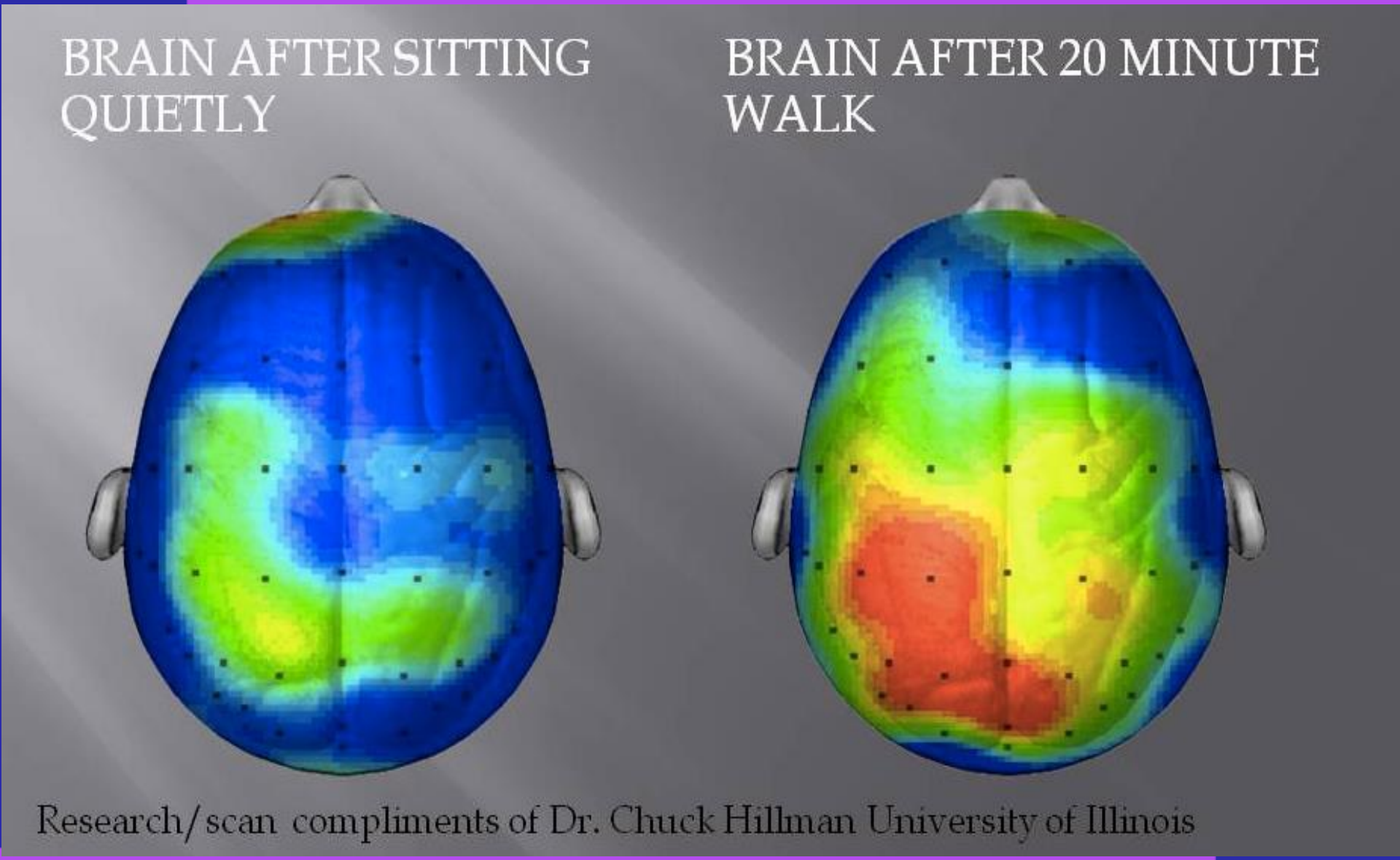
Interval Training: Periodic bursts of high-intensity activity

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

De-evolution



Exercise to Clear the Mind



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 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.

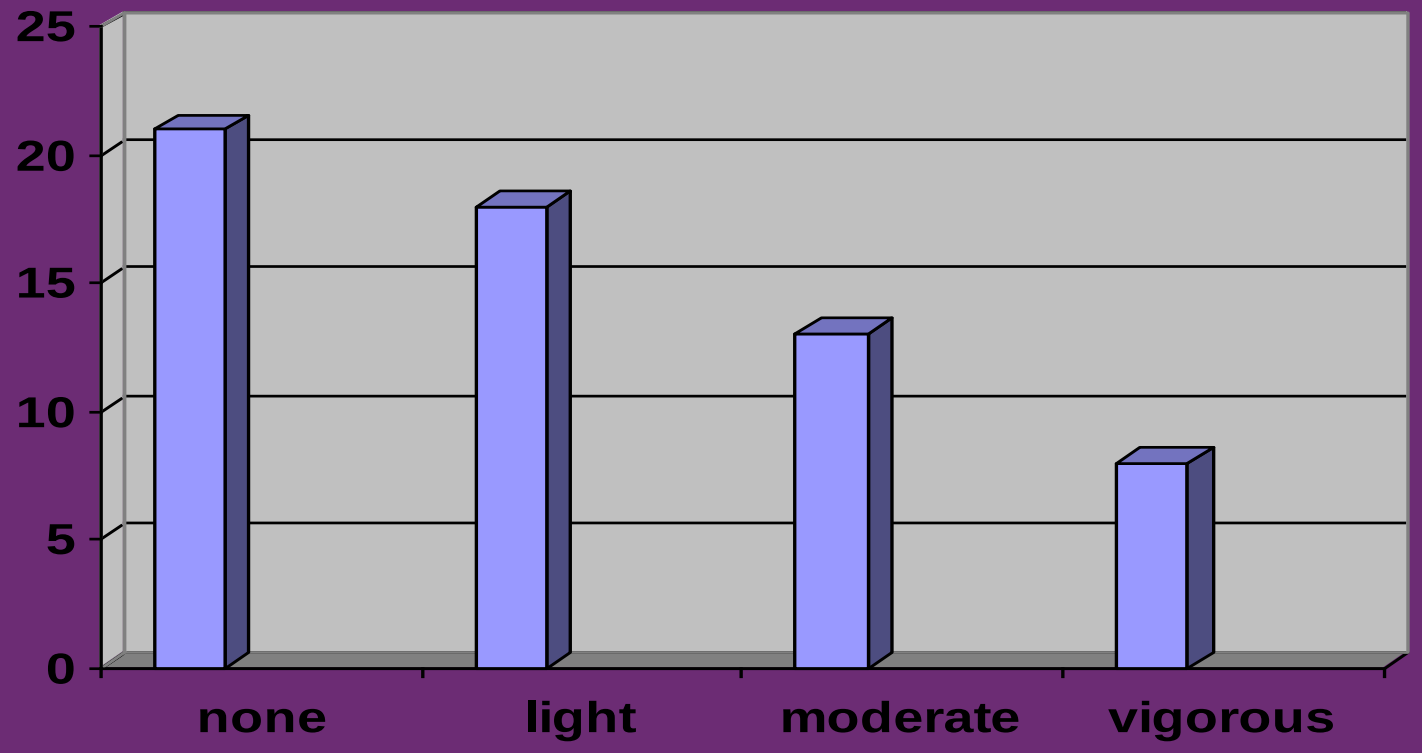
5-HT synthesis in the hippocampus via interaction with BDNF.

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

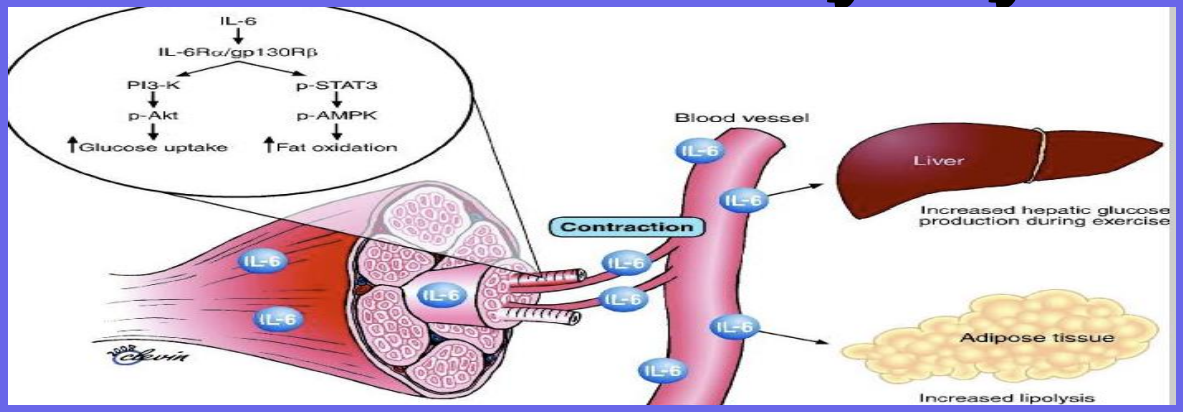
Higher levels of moderate to vigorous activities lowers the risk of developing Parkinson disease

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)**



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

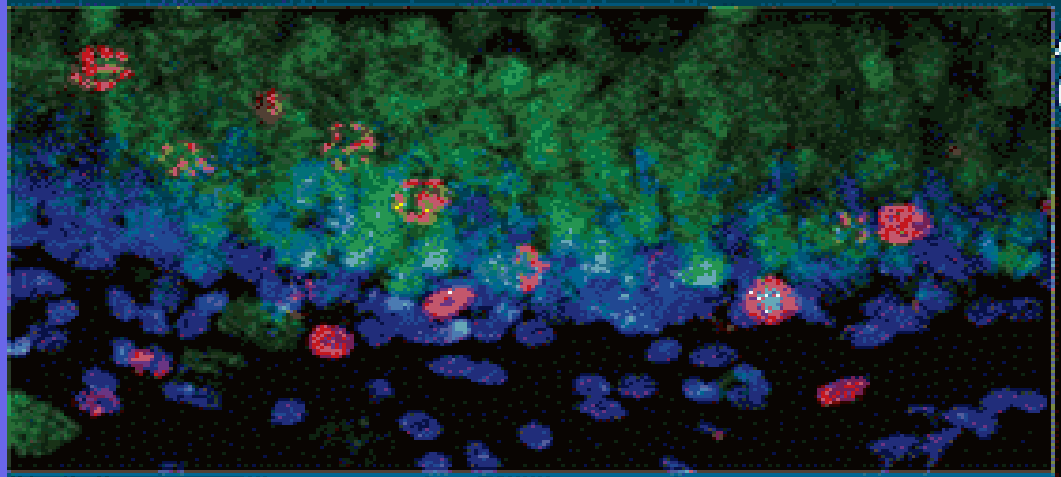
Pedersen BK. The disease of physical inactivity - and the role of myokines in muscle-fat cross talk. The *Journal of Physiology*. 2009;587(23):5559–5568. doi:10.1113/jphysiol.2009.179515.

Brain Derived Neurotropic Factor

- BDNF plays a crucial role in reinforcing neuroplasticity and neurogenesis. It helps:
  - Consolidate the connections between neurons.
  - Promotes the growth of myelin to make neurons fire more efficiently
  - Act on stem cells in the hippocampus and PFC to grow into new neurons

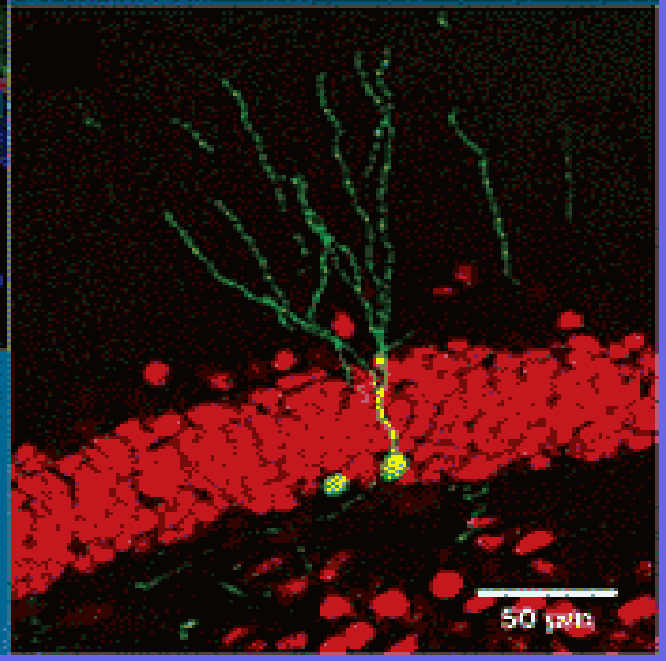
Neurogenesis

Neurogenesis in the Hippocampus

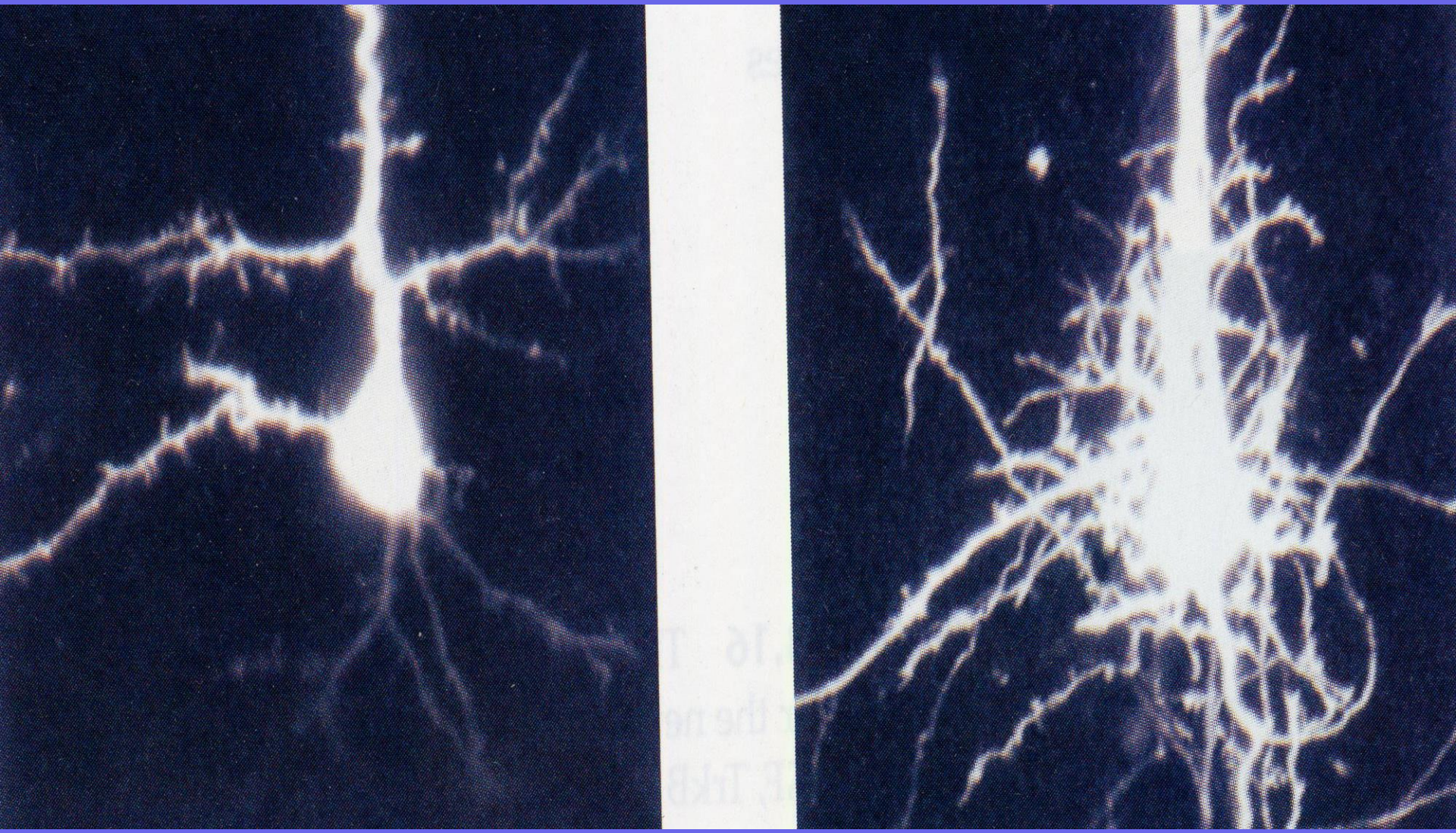


Adult rat brains spawn new cells (red) in the hippocampus

After 4 weeks new cells (green) appear functional



BDNF: Impact on Dendrite growth: 24 hours



Factors that Decrease Neurogenesis

- **Aging**
- **Chronically high cortisol**
  - **Chronic stress**
  - **Recurrent depression**
- **Marijuana**
- **Obesity**

Factors that Increase Neurogenesis

Exercise

- play induces BDNF gene expression

Fasting

Fewer calories consumed

Food content --(Omega—3)

Profound new experience “Ah!”

Exercise and the Brain

Mechanism	Impact
Gene Expression	Neuroplasticity (Cottman & Blanchard, 2002)
Brain Derived Neurotrophic Factor (BDNF)	Neurogenesis & Neuroplasticity (Adlard, et al, 2005)
Insulin-like Growth Factor (IGF-1)	Energy Utilization (Carro. et al 200)
Nerve Growth Factor	Enhanced Neuroplasticity (Neeper, et al, 1996)
Vascular Endothelial Growth factor (VEGF)	Capillary Health (Fabel, et al, 2003)

Mind-Brain-Gene Feedback Loops

Self-Regulation Factors

- **Social**
- **Exercise**
- **Education**
- **Diet**
- **Sleep**

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 Effects of Social Medicine

- ↓ Cardiovascular reactivity (Lepore, et al, 1993)
- ↓ Blood pressure (Spitzer, et al, 1992)
- ↓ Cortisol levels (Kiecolt-Glaser, et al, 1984)
- ↓ Serum cholesterol (Thomes, et al, 1985)
- ↓ Vulnerability to catching a cold (Cohen, et al, 2003)
- Depression (Russell & Cutrona, 1991)
- ↓ Anxiety (Cohen, 2004)
- ↓ Natural killer cells (Kiecolt-Glaser, et al, 1984)
- ↑ Slows cognitive decline (Bassuk, et al 1999)
- Improves sleep (Cohen, 2004)

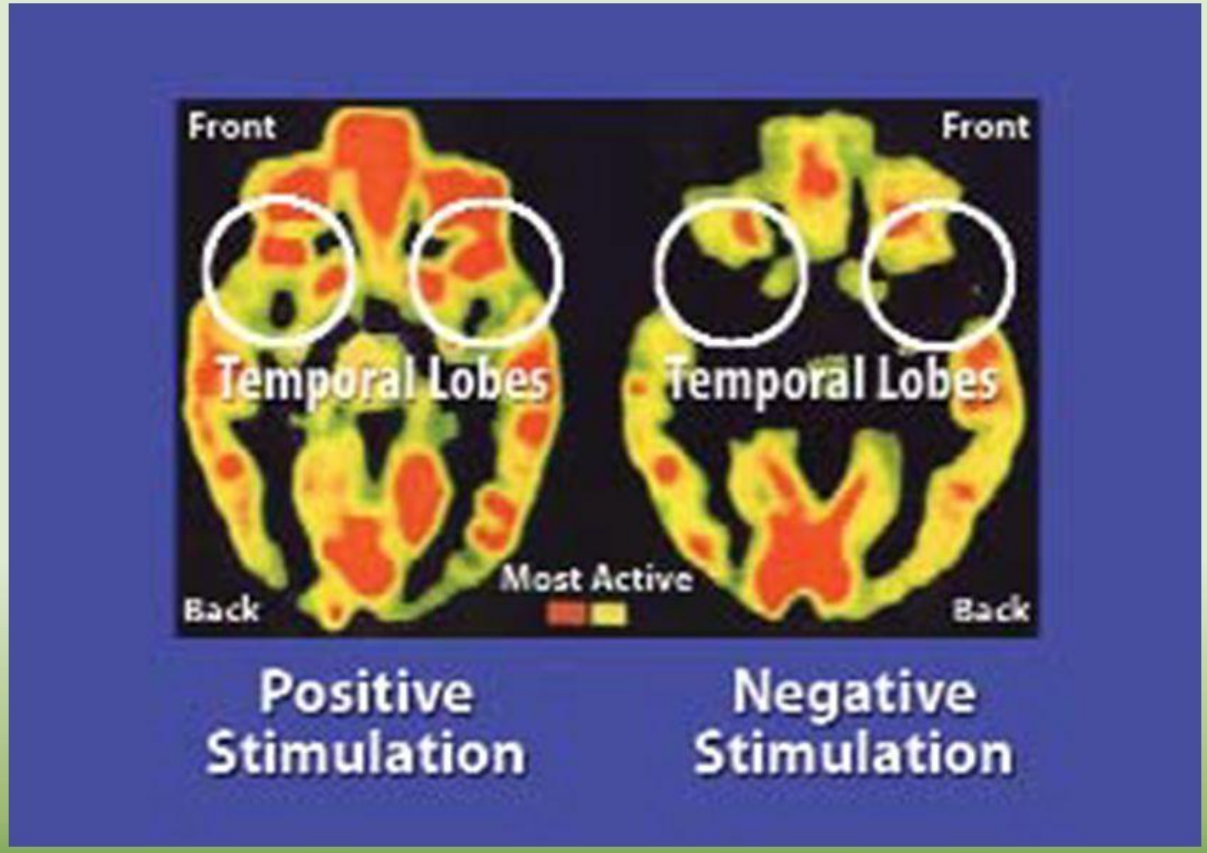
Deprived Social Brain Networks

- 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

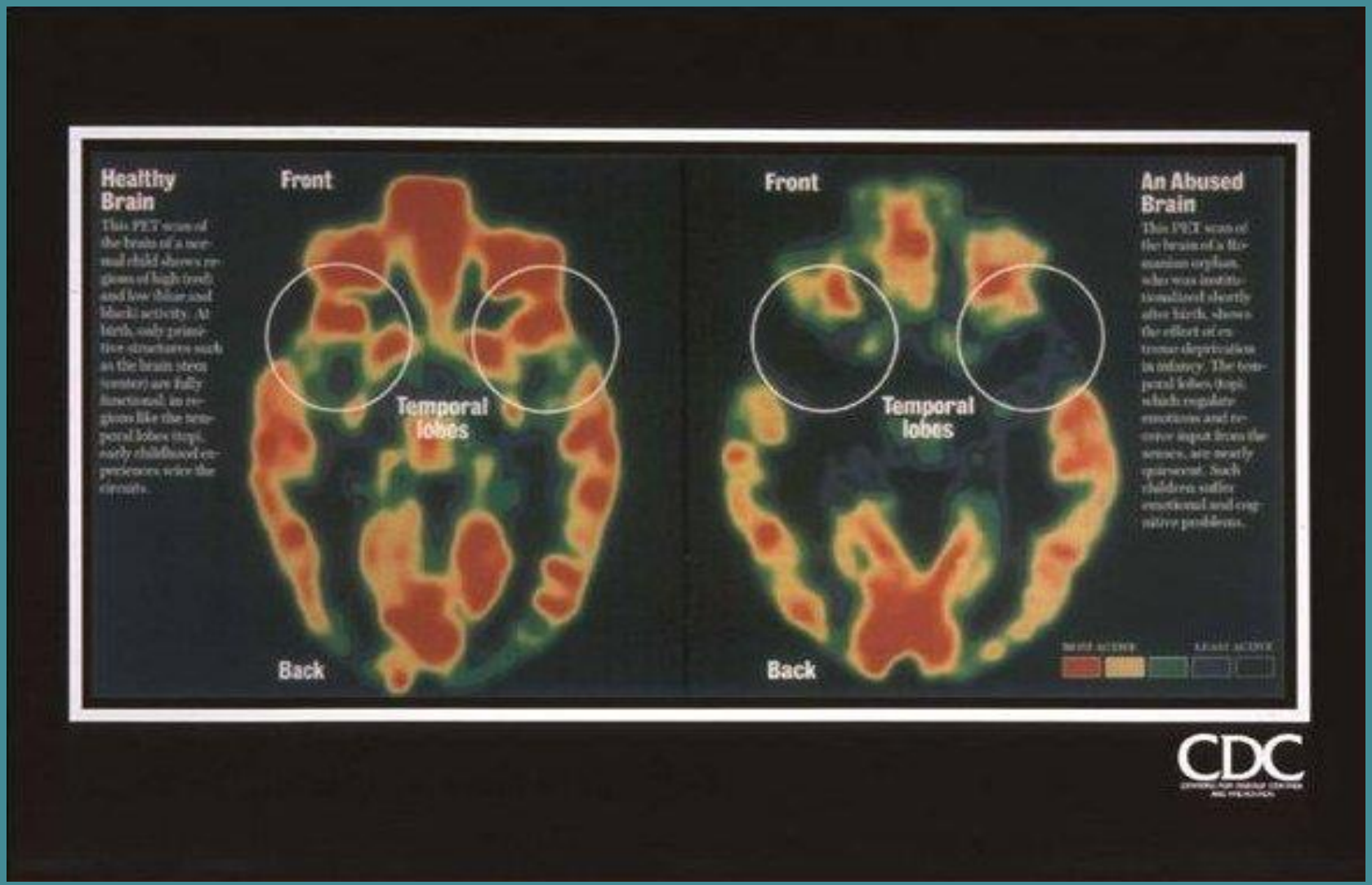


Brain activity of a normal five-year-old child (left)
and a five-year-old institutionalized orphan neglected in infancy (right).

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

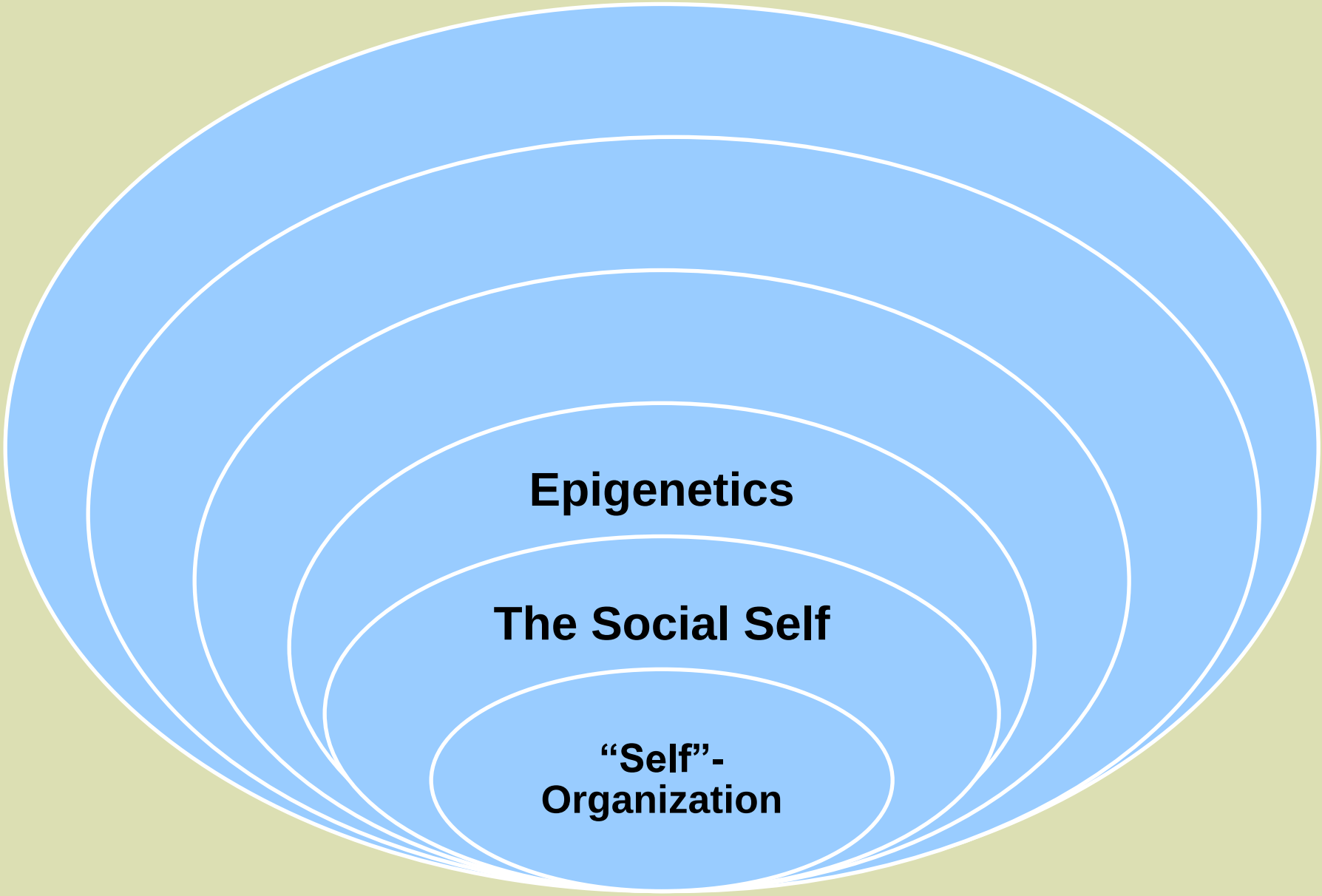
- Balance Between the two branches of the Autonomic Nervous System
- Endorphin & Benzodiazepine receptors
- Cortisol Regulation
- Positive Immunological Functioning
- Neural Growth and Plasticity

Mirror Neurons

Modeling

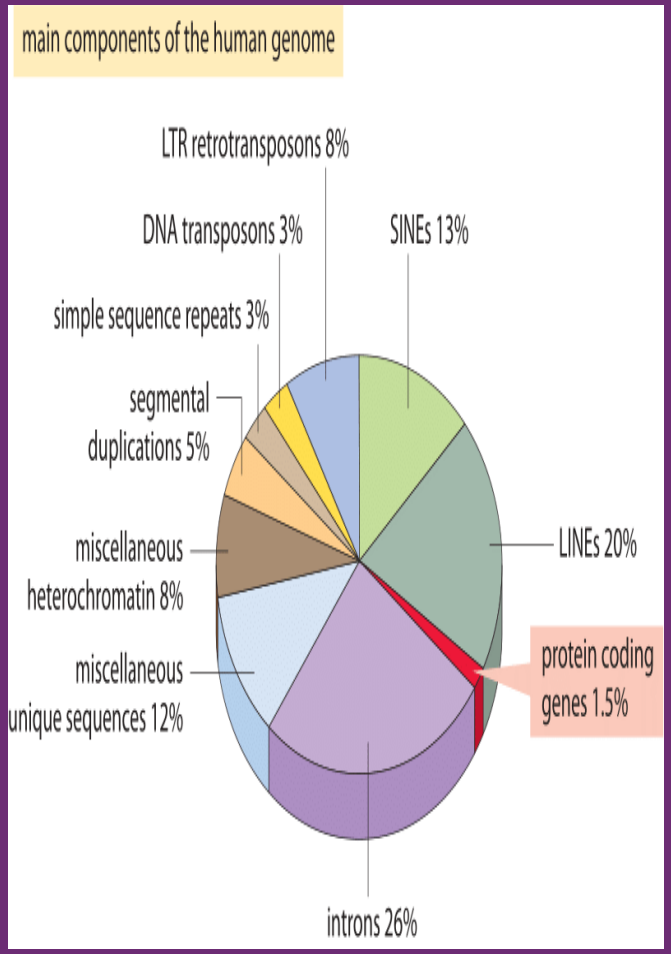
Family Time?

Mind-Brain-Gene Feedback Loops

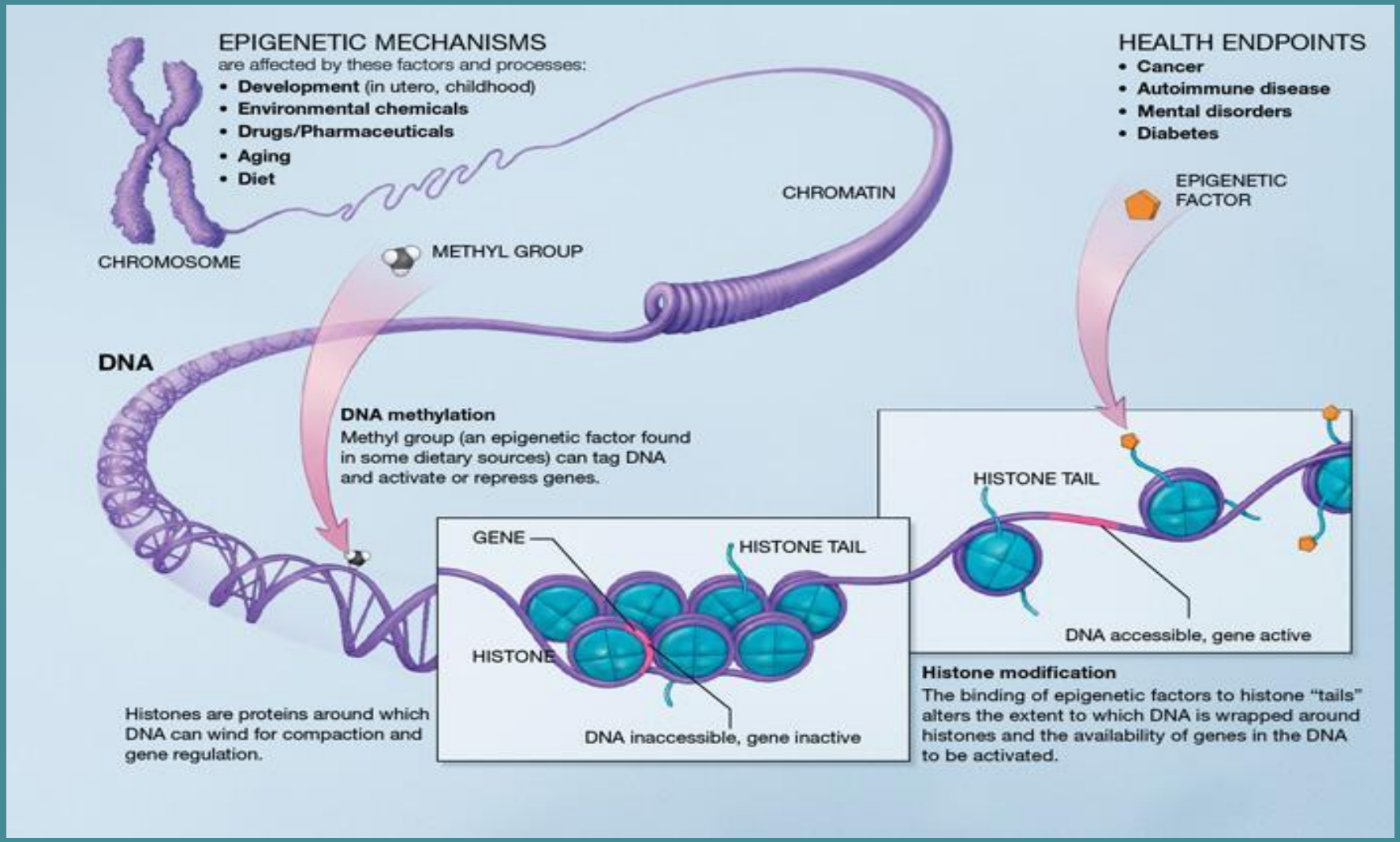


Epigenetics

- 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

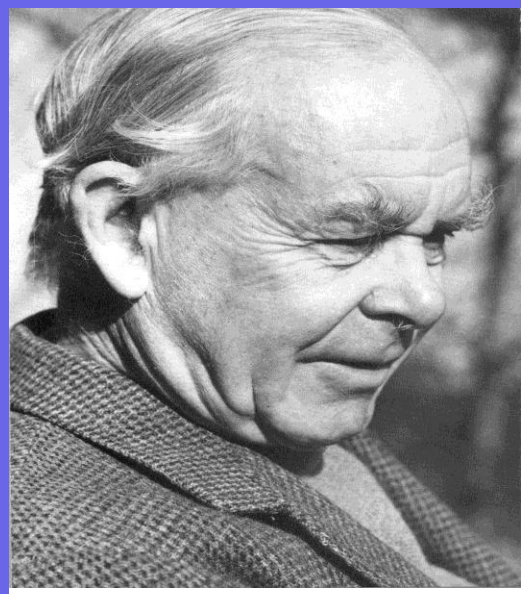
- Histones are proteins wrapped tightly into ball like shapes with floppy tails
- Acetylation of histones allows transcription—unwrapping genes for expression
- Methylation of histones keeps them in place—suppressing gene expression

Someone Needs to Play (behave)

Epigenetics and Attachment

- 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

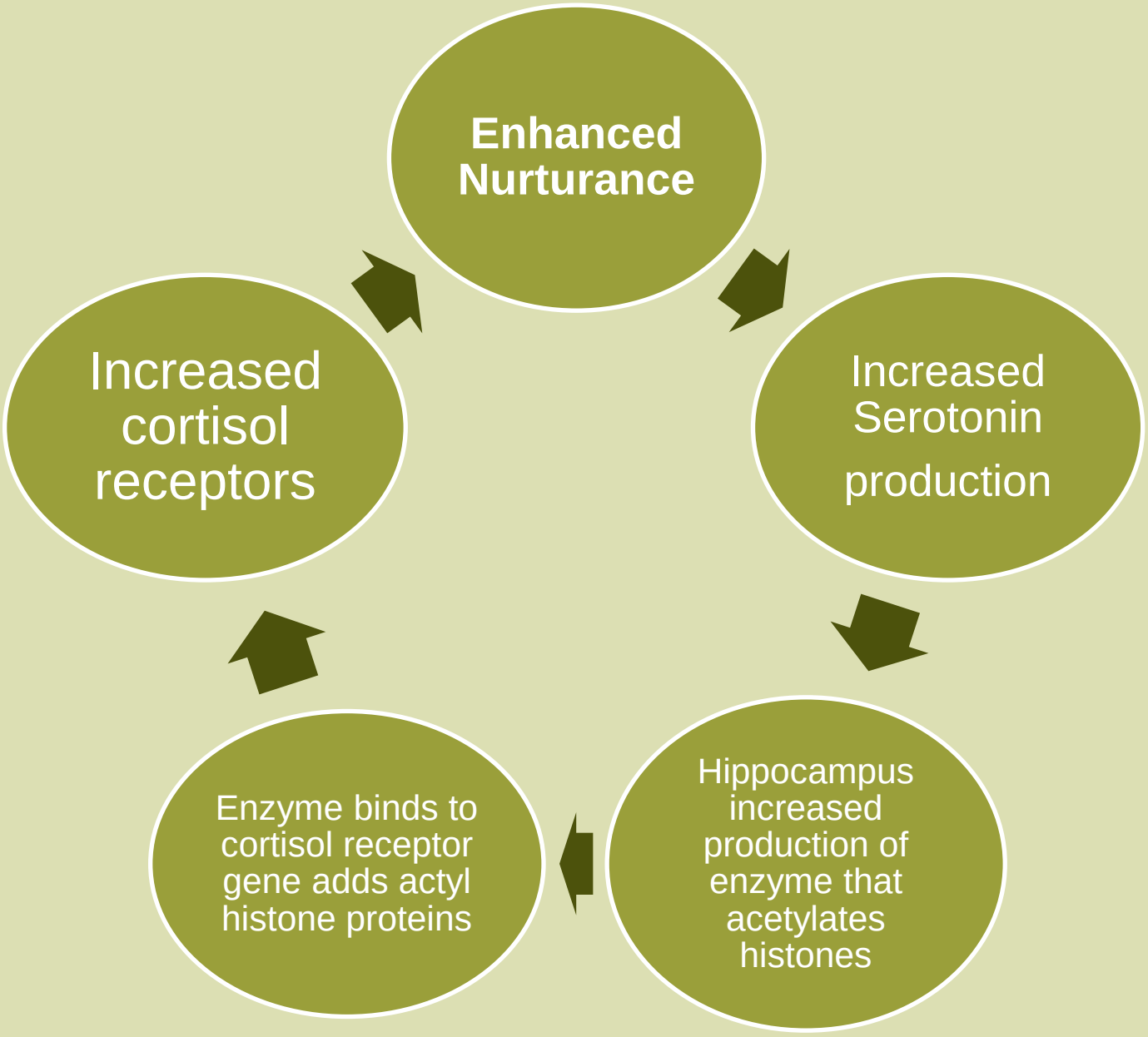


Cortisol level

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: 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.

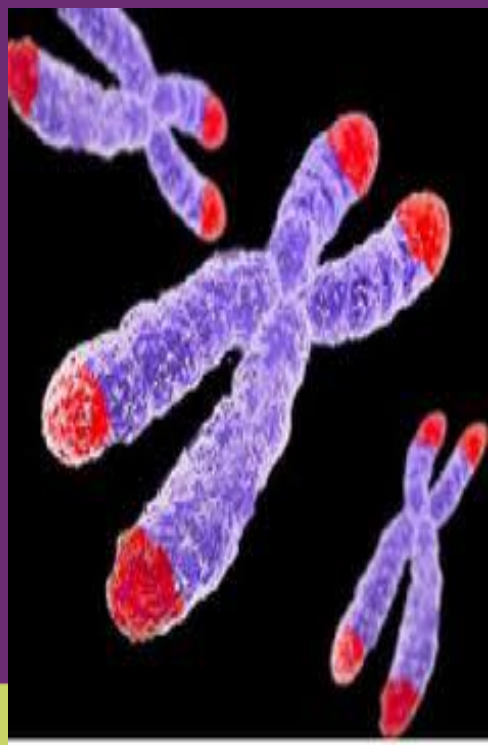
- This variant of the DRD4 gene can afford the carrier to benefit disproportionally from supportive environments.

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.

Cell Aging: Telomeres Length

- "Psychobiomarker": Linked to social status, perceived stress, depression, loneliness: predictive of mortality (Epel, 2009, Current Directions)
- •Telomeres: non-coding sequences capping ends, serving as a:
  - "senescence clock" (Blackburn, 1978)
- •Telomerase: enzyme that prevents telomere shortening, promotes cell resilience.



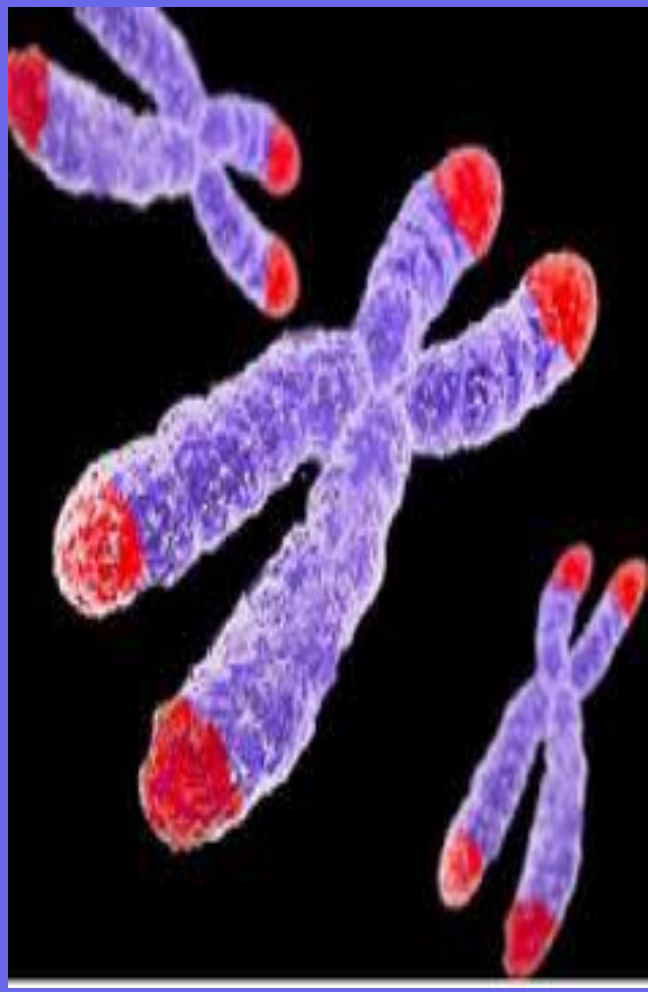
- Psychobiomarker": Linked to social status, perceived stress,
- depression, predictive of mortality (Epel, 2009, Current Directions)

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

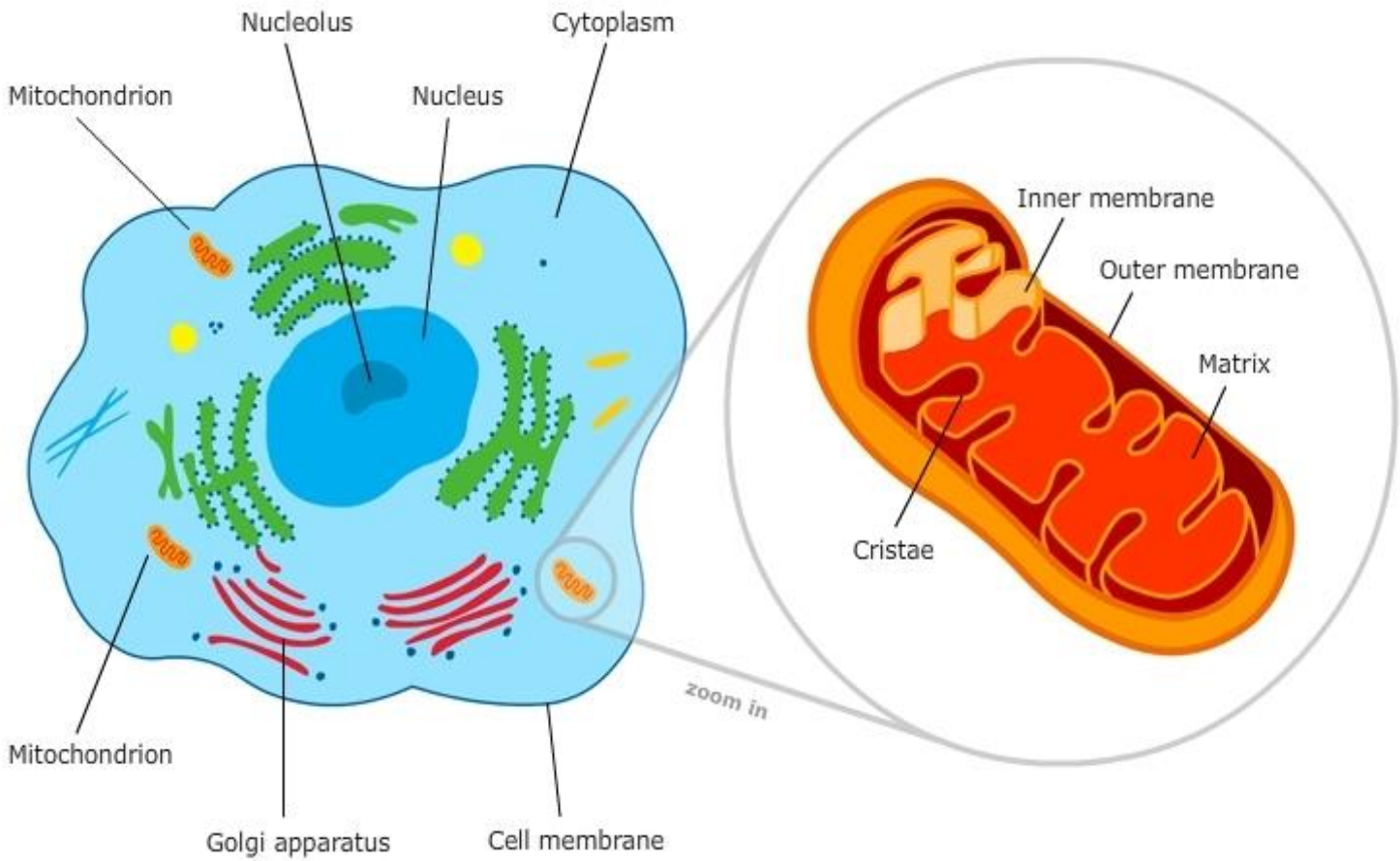
Factors that Shorten Telemeres

- 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 Demands

- They comprise roughly 10 percent of our total body weight.
  - Everyday the average person makes two hundred trillion trillion ATP molecules.
- Because of their relative energy needs our heart and brain cells contain the greatest number of number of mitochondria.
  - There are approximately 10 million billion mitochondria in an adult human 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

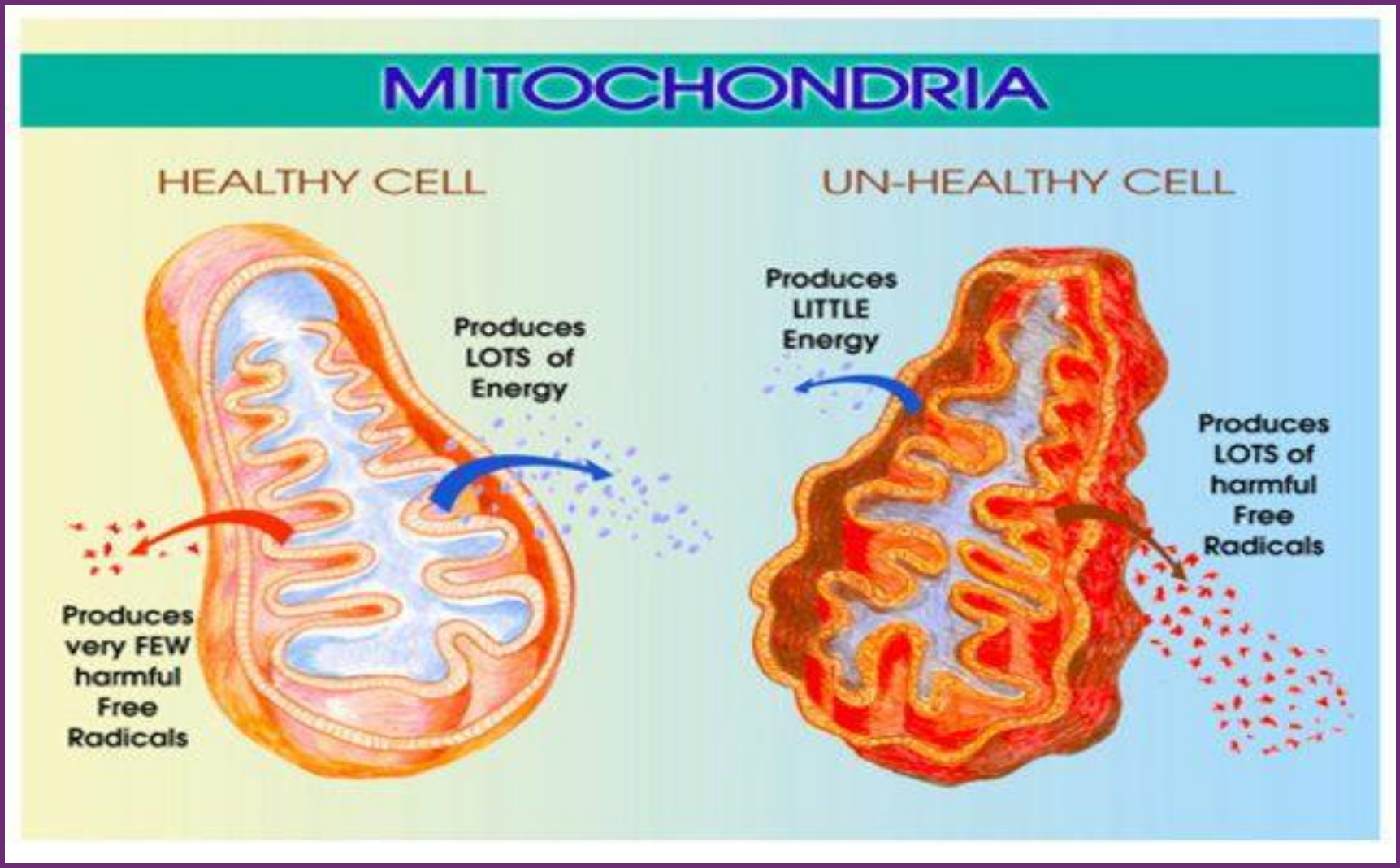
Consuming 2100—6000 calories per day **doubles risk for MCI**

Free Radicals

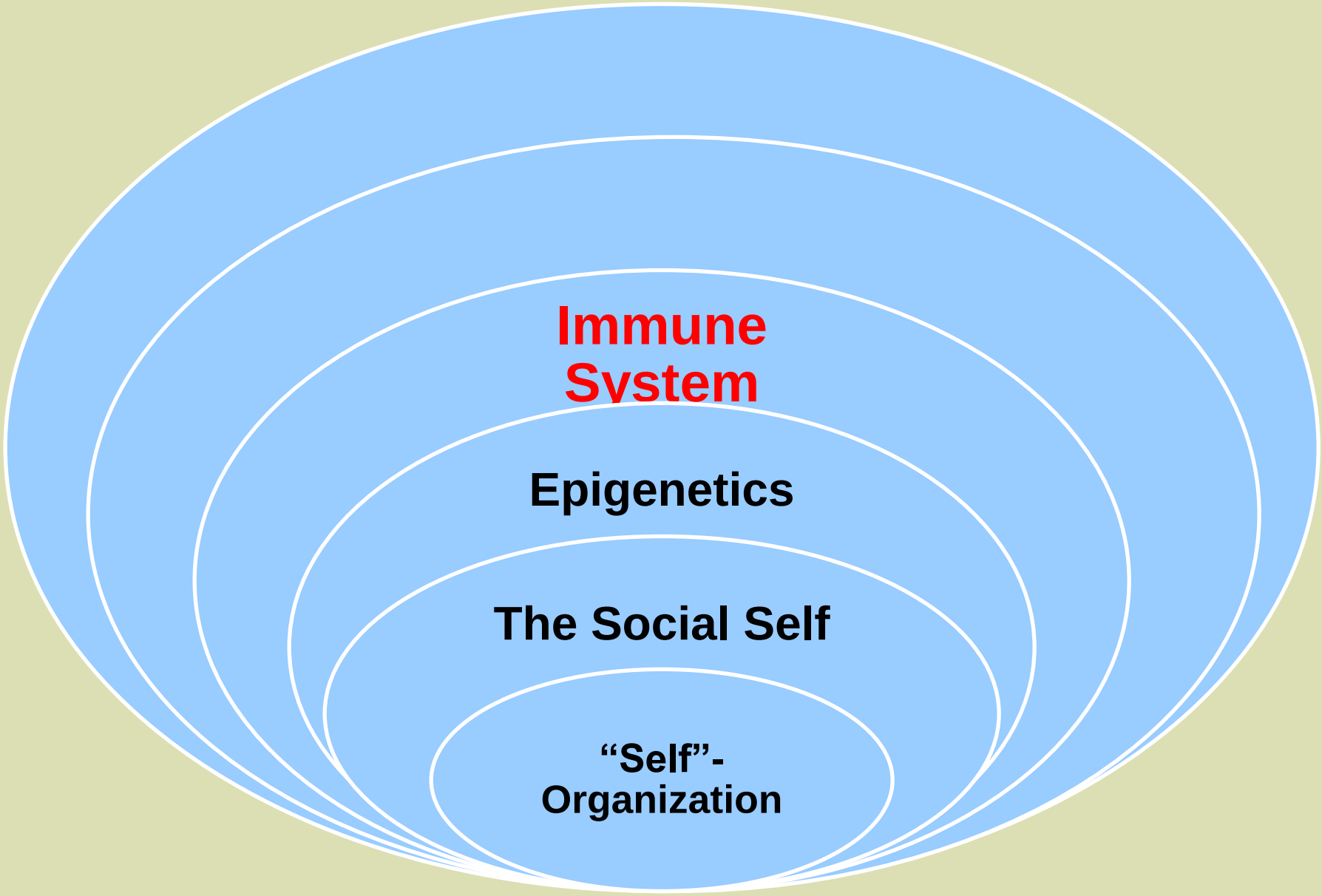
- Highly reactive molecules that contribute to oxidative stress
- They lost an electron and are on the prowl to steal one from neighboring molecules.
  - Cells malfunction
  - Cells age
  - Cells are more vulnerable to disease
  - DNA more vulnerable to inaccurate gene expression

Mitochondria Disfunction

Free Radical Damage



Mind-Brain-Gene Feedback Loops



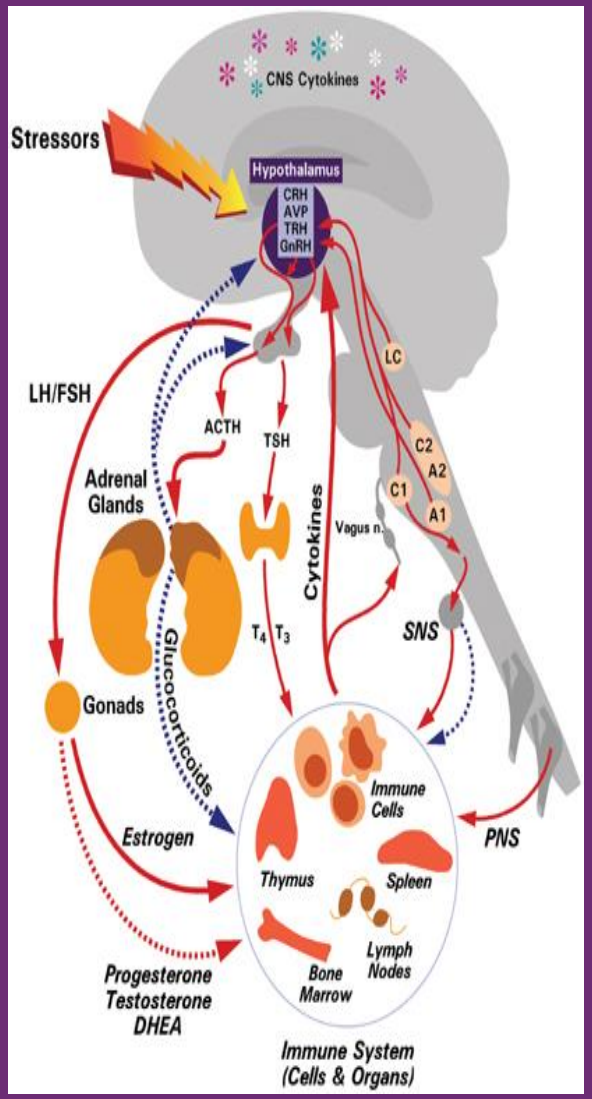
The Brain Controls the Stress Pathways

Distress, via the cortex and amygdala signal to the hypothalamus.

The hippocampus (memory) also has inputs to the hypothalamus.

The hypothalamus maintains homeostasis by regulating visceral activities: heart rate, blood pressure, body temperature, thirst, hunger, weight, sleep/wakefulness.

The hypothalamus also controls HPA stress response system



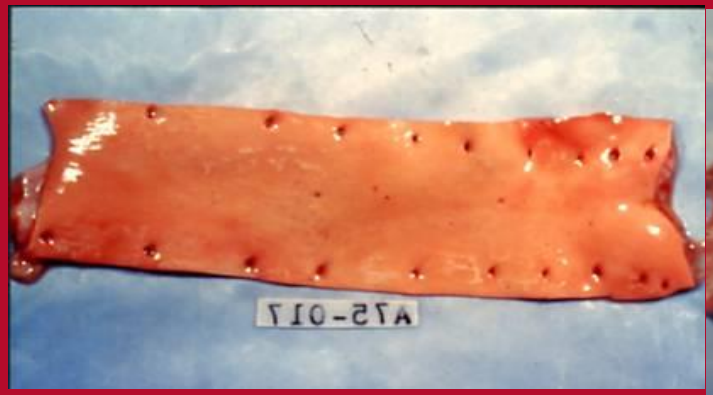
Hypocortisol vs. Hypercortisol Activity

- Chronic stress (especially uncontrollable) alters the cortisol system
- Early on there can be *higher* cortisol
  - Can lead to agitated depression
  - Kills white blood cells
  - Metabolic syndrome
- More distant traumas may result in an inadequate cortisol response
  - Autoimmune disease
  - Inflammation
  - depression

Excessive Cortisol

- **Causes: Extremely severe, prolonged, and inescapable stress. (perceived lack of control)**

Hypercortisolemia and damage to arteries

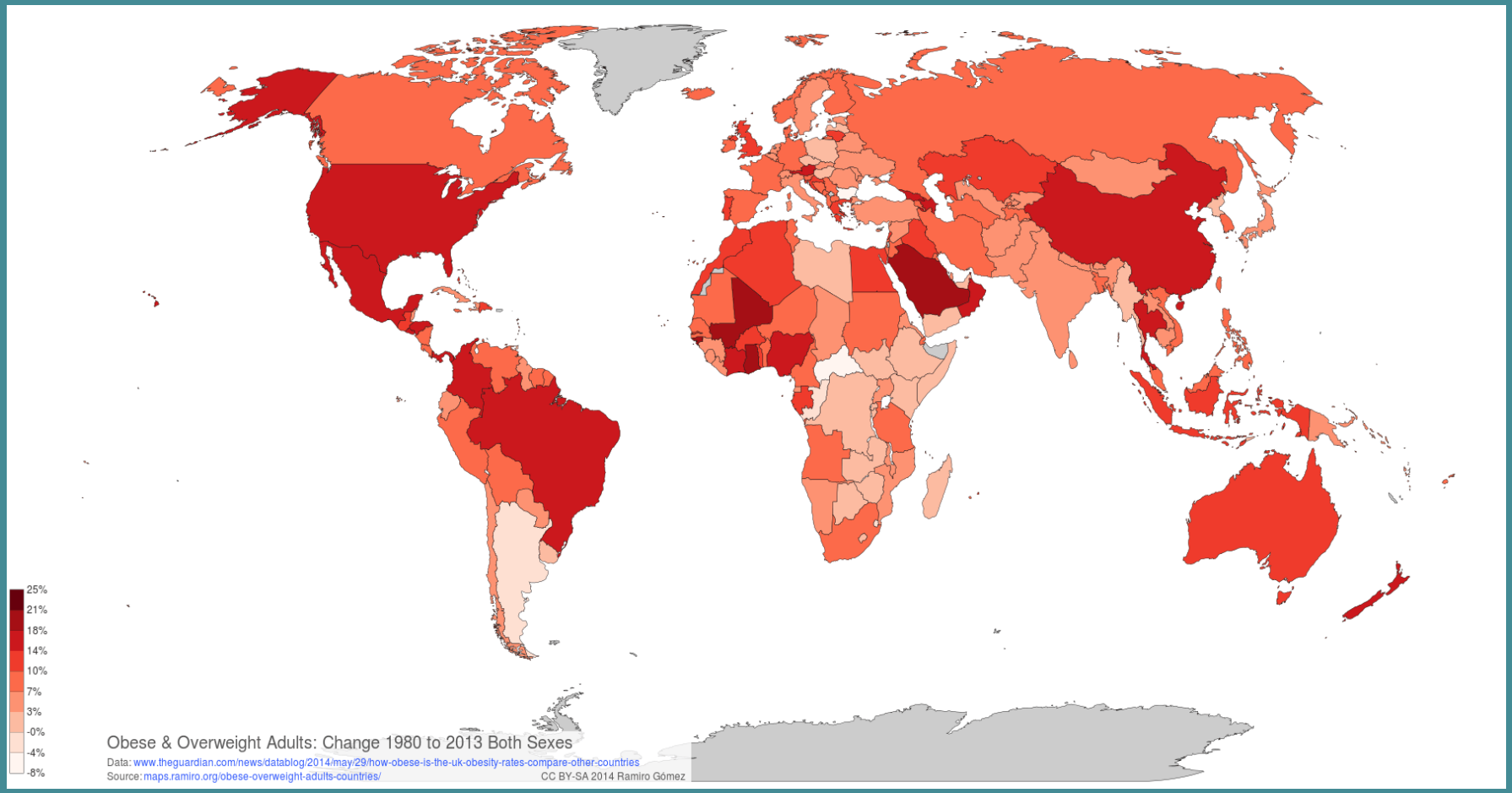


Hippocampal atrophy

Proinflammatory Cytokines

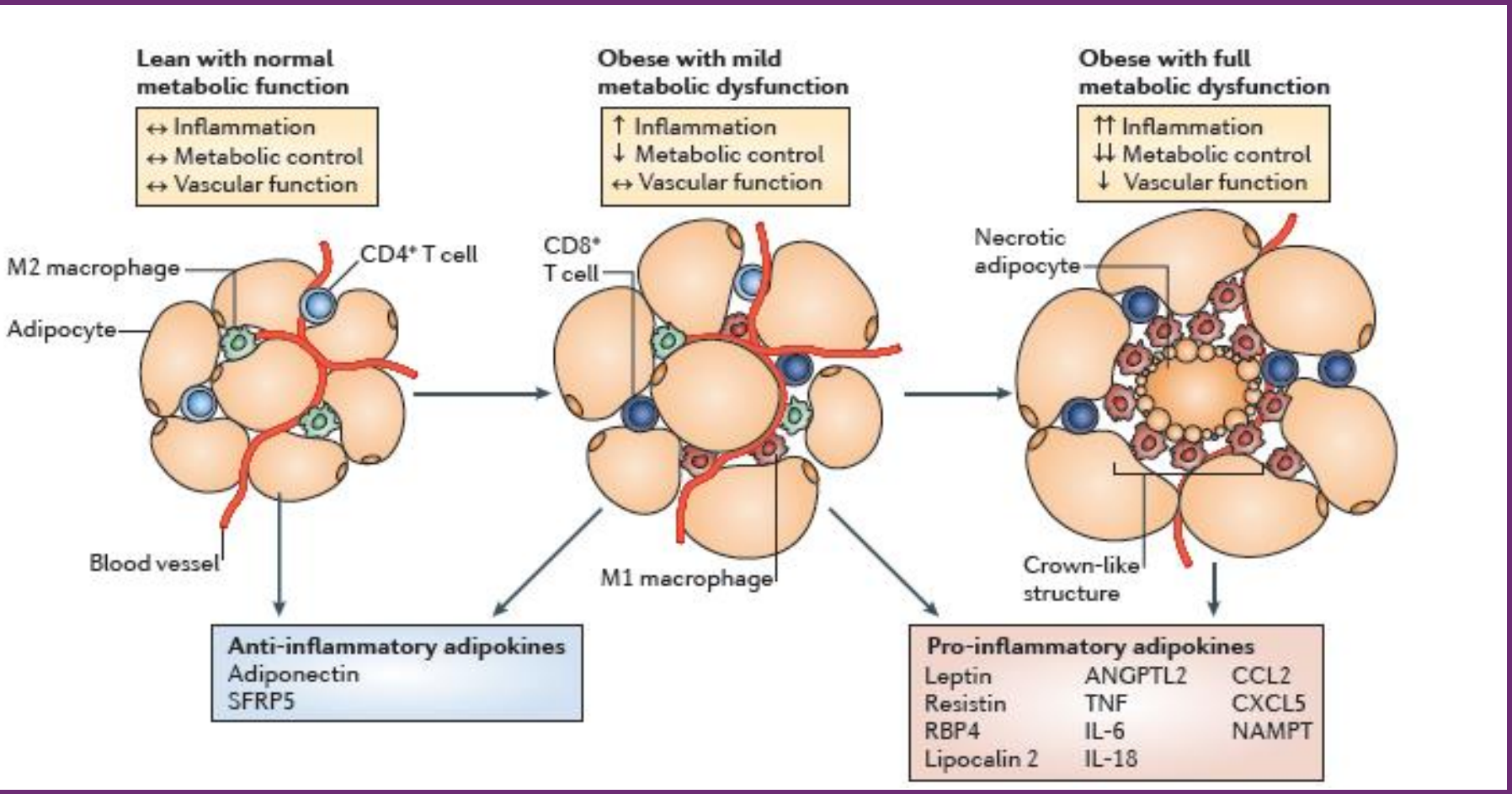
- PICs contributes to depression as underlying inflammatory conditions
- Stressors may contribute to depression or exacerbate it via PICs
- Depression linked to medical conditions-- involves PICs
- Strong link between depression and vulnerability to medical diseases (CVD, autoimmune)

The Pandemic



Obese people over 40 will die 6-7 years earlier

Obesity-Associated Adipose Tissue Inflammation

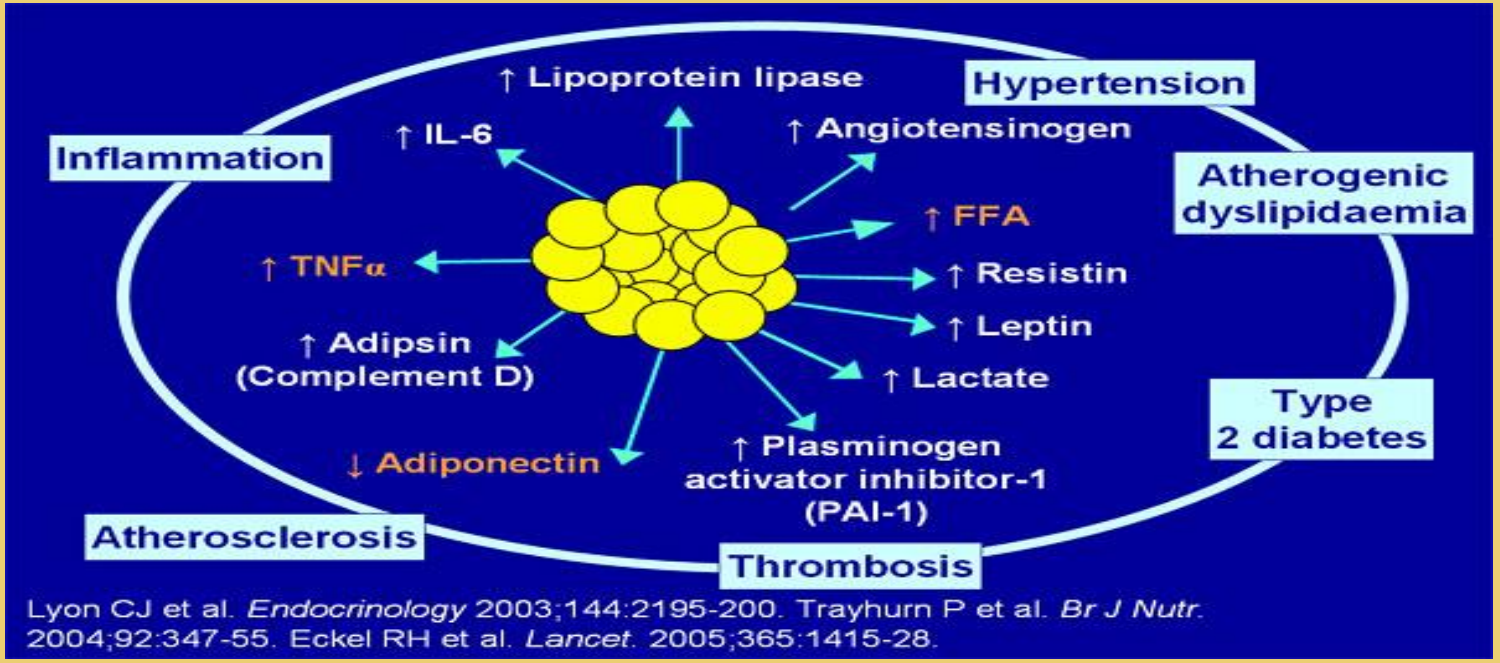


INFLAMMATION

Obesity, Inflammation, and Diabetes

- Fat cells secrete IL-6
- IL-6 can induce insulin resistance

Higher IL-6 may predict diabetes type 2



Lyon CJ et al. *Endocrinology* 2003;144:2195-200. Trayhurn P et al. *Br J Nutr.* 2004;92:347-55. Eckel RH et al. *Lancet*. 2005;365:1415-28.

Belly fat

Belly fat generates inflammation by releasing proinflammatory cytokines

- Lowers BDNF
- ↑ risk of dementia
- If you're going

  to gain weight

  go for the pear not the apple shape

Client Education

If you have extra weight, hope for the pear not the apple shape. Better yet, lose the body fat for the sake of your brain.

Fat cells leak out toxins that go to the brain causing inflammation, clouding thinking, and increasing depression.

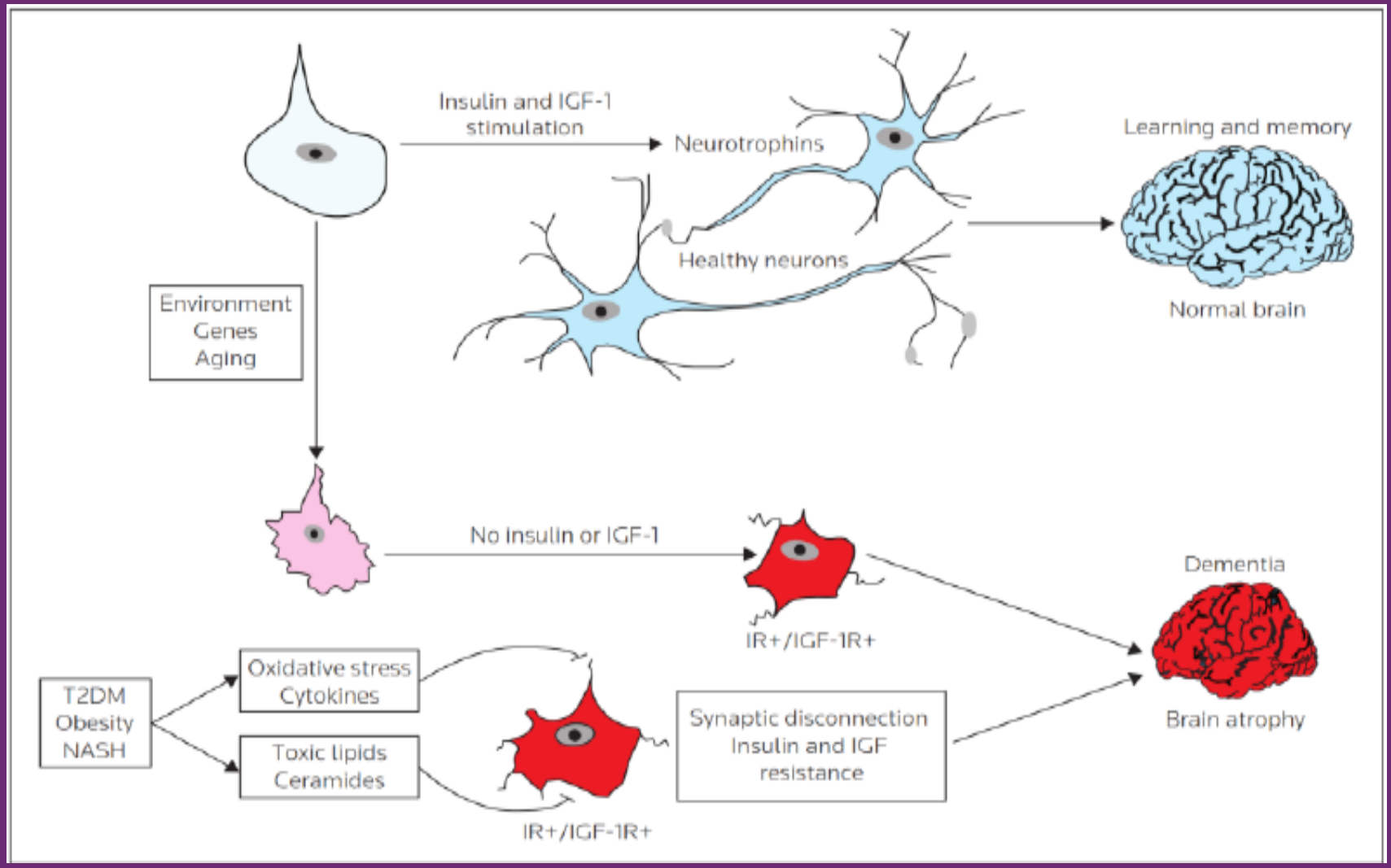
Diabetes and Psychological Disorders

- Depression 38%
- Anxiety 20%
- PTSD predicts the onset of type 2 diabetes
- Increases of cognitive impairment
  - Memory impairment
  - dementia

Diabetes and Neuropathology

- Grey matter volume reduction in multiple brain regions (i.e. frontal temporal)
- Microstructral changes in white matter
  - ↓ connectivity and lesions
- Microvascular complications
- Metabolic impairment
  - ↓ insulin receptors

Diabetes and Brain Shrinkage



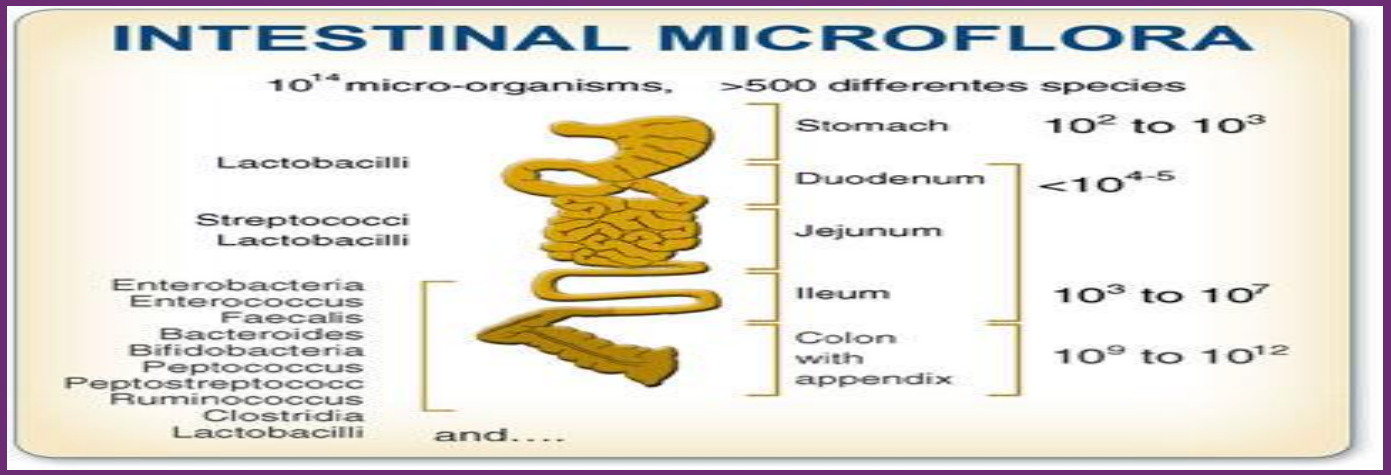
➢PICs cause a depression-like Sickness Behavior

- Stress can increase PICs levels
- High PICs can lower the concentration of serotonin and DA
  - –Cognitive dysfunction, anxiety, fearfulness, depression, thoughts about suicide
- "Sickness behavior"---fatigue, social withdrawal, and immobility--depression (Hickie and Lloyd 1995).

Client Education

- Feeling ill makes you act ill and if you do, the feelings of depression will increase.

Microbiome

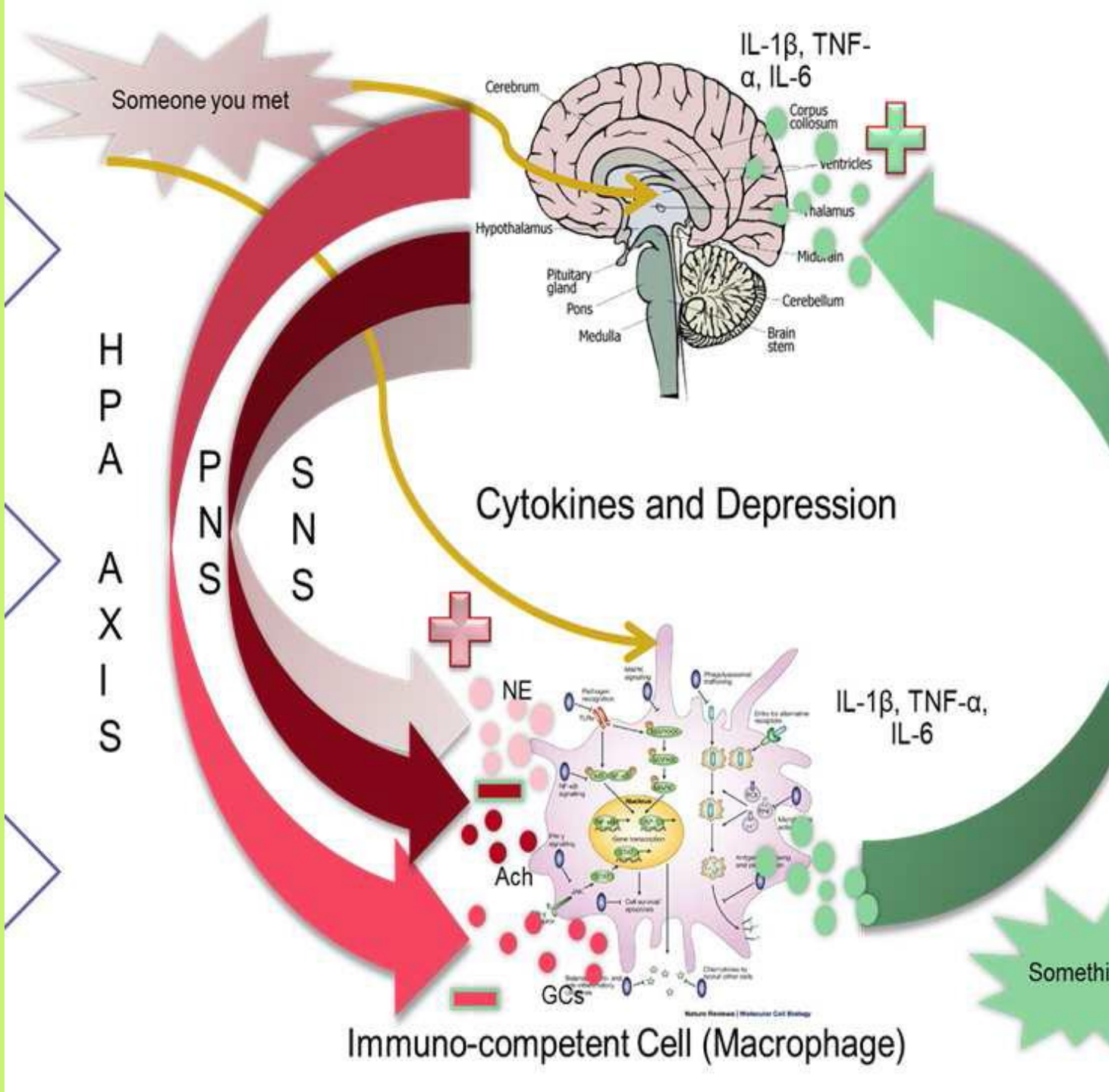


- **The GOOD: helps digest certain foods the stomach/small intestine doesn't, can combat invading microorganisms. Microbes generally do not cause disease unless they grow abnormally; they exist in harmony with us.**
- **The BAD: may have a role in auto-immune diseases (e.g., diabetes, rheumatoid arthritis, multiple sclerosis, fibromyalgia) and possibly some cancers. A poor mix of microbes in the gut may also aggravate obesity.**

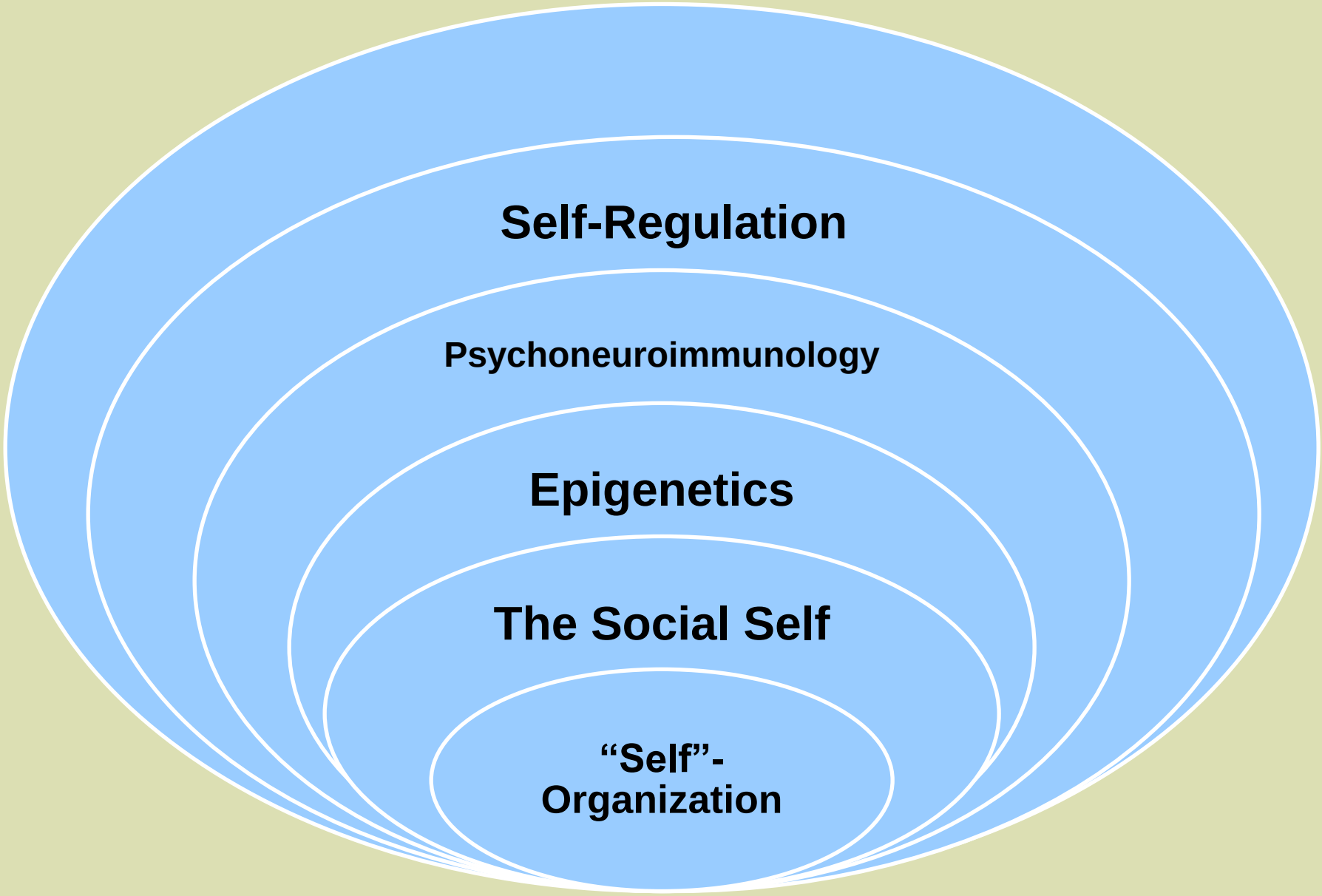
Gut Bacteria

- 90% of bacteria in the colon F/B ratio:
- Firmicutes
  - Fat loving—increases fat absorption
  - Efficient at extracting calories from carbs
  - Turns on genes that increase the risk for obesity, diabetes, and CVD
- Bacteroidetes
  - More dominant in lean people

- Bad Diet
  - Simple carbs
  - Transfatty acids
  - Saturated fats
  - Food allergies
  - Bad oils
  - High dairy
  - High gluten
- No exercise
- Chronic illnesses
- Autoimmune disorders
- Chronic pain
- Chronic stress
- Being overweight
  - Apple shape
- Leaky gut



Mind-Brain-Gene Feedback Loops

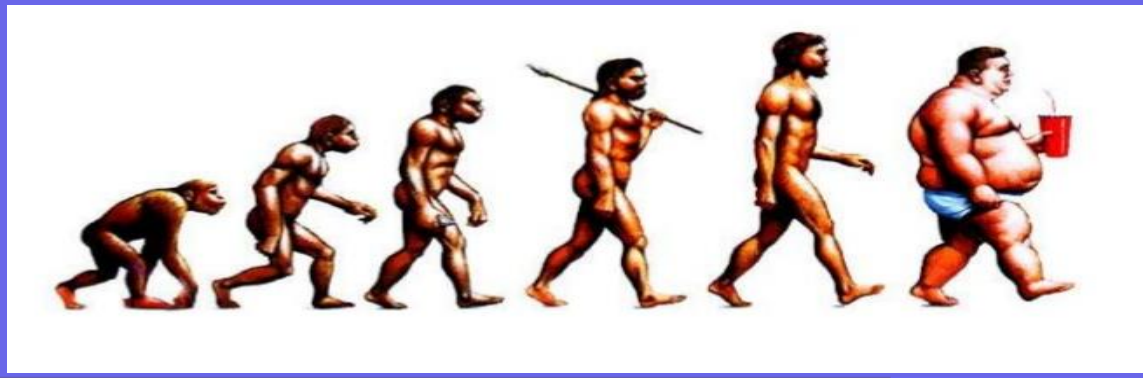


Self-Regulation Factors

- **Social**
- **Exercise**
- **Education**
- **Diet**
- **Sleep**

Perils of the Western Diet

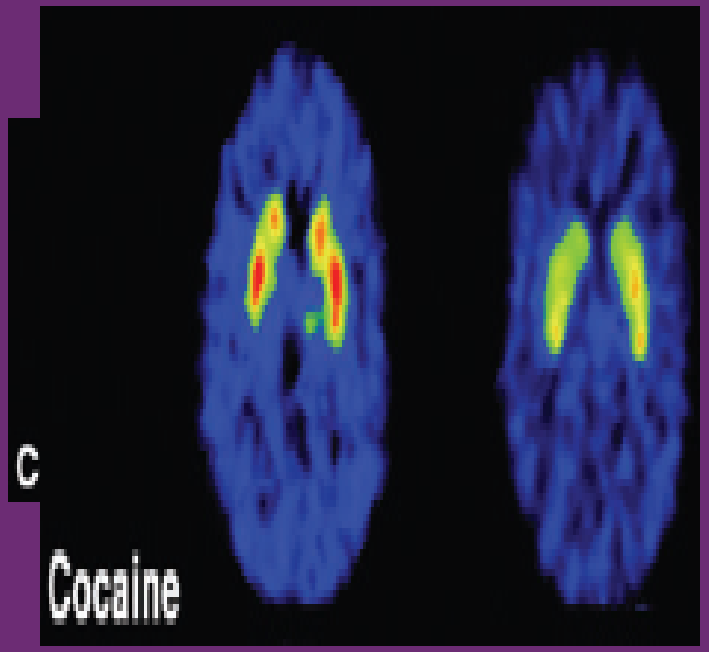
- Fructose blunts the effects of leptin which normally tells us we are “full”
  - Fructose produces uric acid
  - Increased cardiovascular disease
- Increasing risk of metabolic syndrome
- **Shrinks the left hippocampus**
- Increased blood pressure
- LDL cholesterol
- Increased stroke
- Type 2 Diabetes

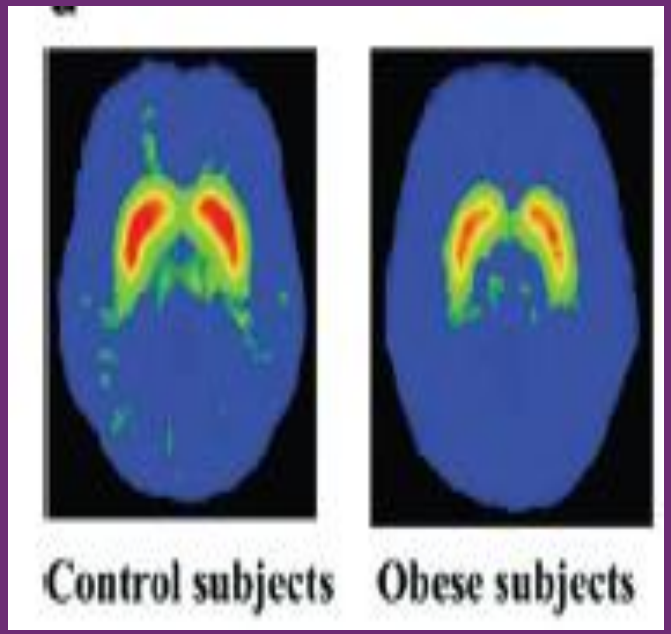


Dopamine D2 Receptors in Drug Users And Comfort Food Addiction

- Drug Addiction
- Obese

  - DA D2 (Dopamine Receptors)
  - In the brains of controls, drug abusers, and obese subjects





Glycemic load (GL) – a measure of rise in blood sugar

The higher the GL of a food:

the greater the adverse insulin effects

Long-term consumption of foods with a high GL leads to a greater risk of:

- Obesity
- Diabetes
- Inflammation
- Depression

Glycation (excess glucose)

- The body's membranes become "gunked up"--slowing down neural communication
- Blocks protein from moving freely
- Interferes with synaptic transmission
- Causes structural damage to the mitochondria (the cells' energy factories)
- Lead to free radicals
- Causes inflammation.

Advanced glycation end products (AGEs)

- Acts as chemical glue that attaches molecules to one another
  - Causes *cross-linking*, (like overcooked meat)
- Associated with the formation of plaque, inflammation, atherosclerosis, particularly in diabetes

trans-fatty acids can:

1. Be absorbed directly by the nerve membranes
2. Block the body's ability to make its own essential fatty acids
3. Alter the synthesis of neurotransmitters such as dopamine
4. Negatively effect the brain's blood supply
5. Increase bad (LDL) cholesterol while decreasing good (HDL) cholesterol

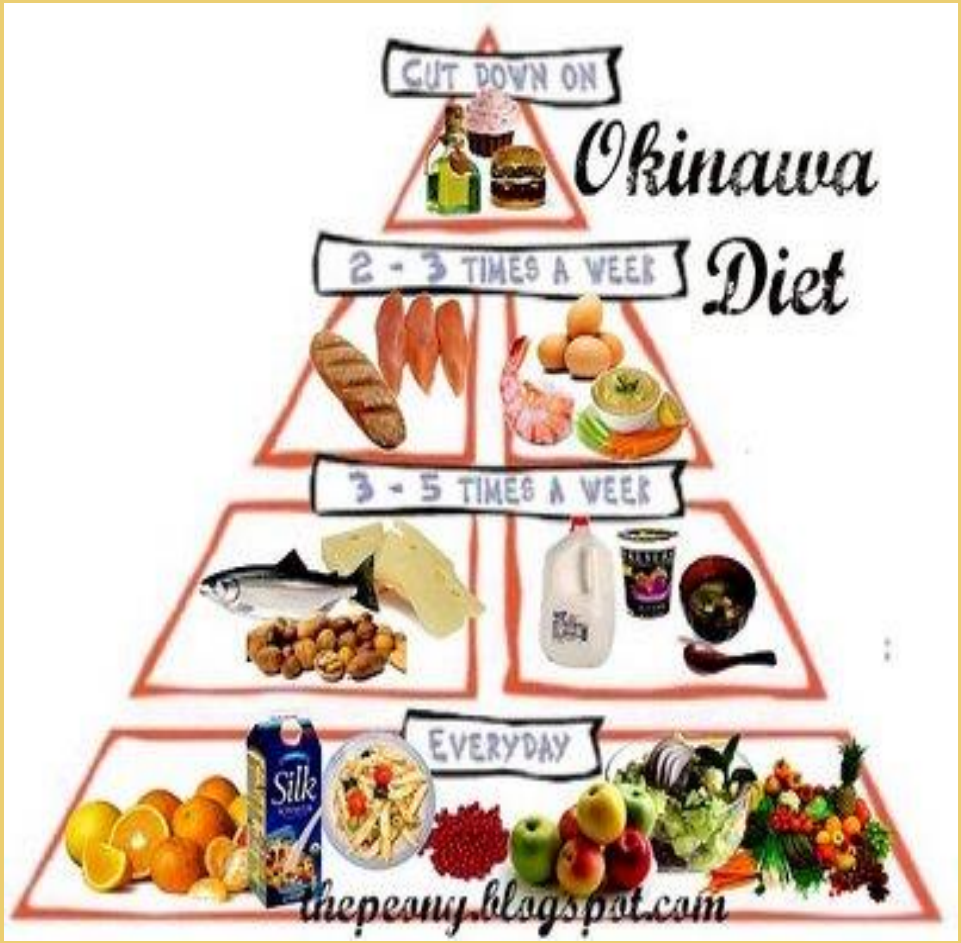
trans-fatty acids

6. Increase plaque in the blood vessels
7. Increase blood clots
8. Increase triglycerides, which cause the blood to be sluggish and reduces the amount of oxygen to the brain
9. Cause excess body fat, which can have a destructive effective on the brain

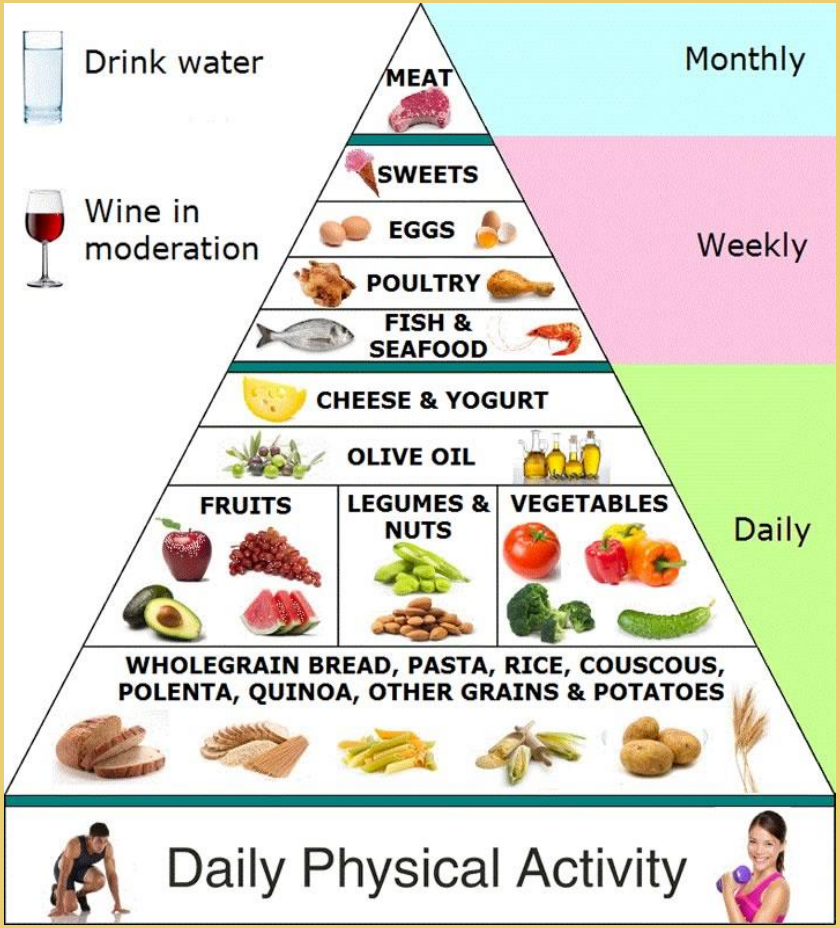
    i.e. pro-inflammatory cytokines

Diets styles for longevity:

Okinawan



Mediterranean

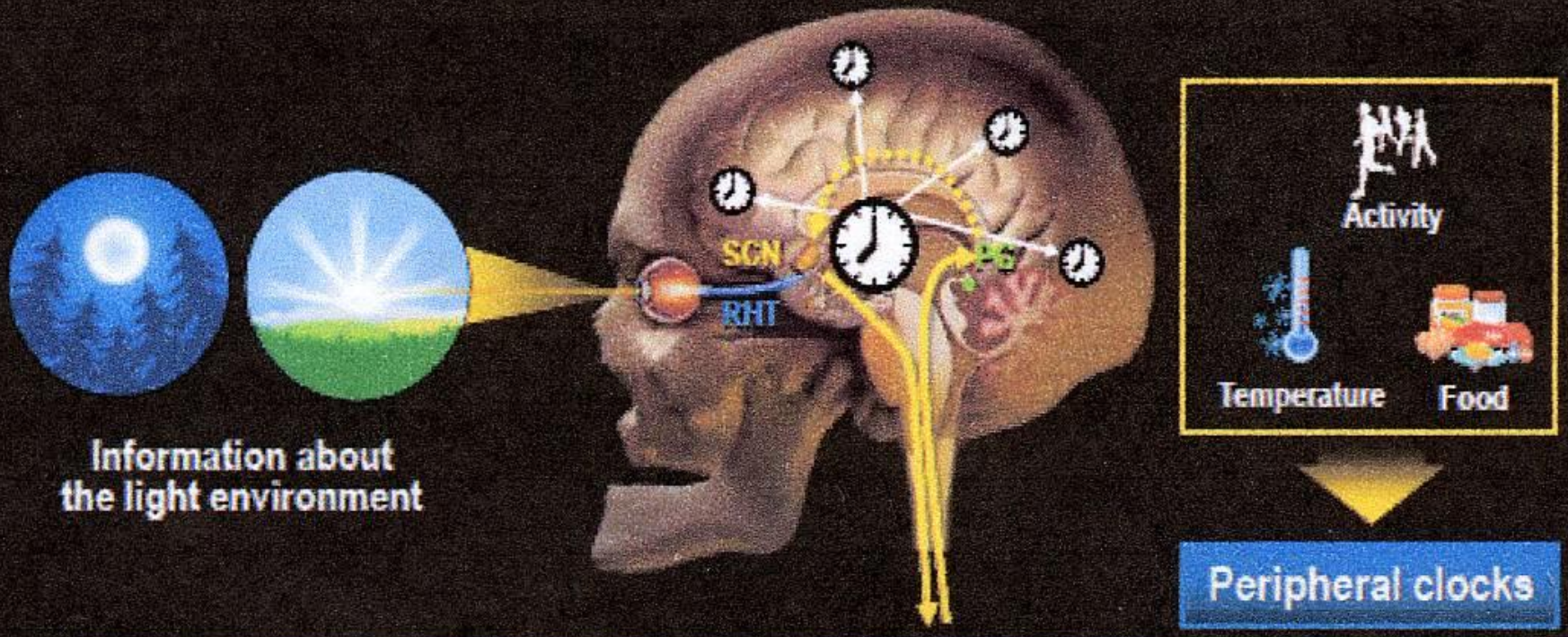


The Five Risiliency Factors

- **Social**
- **Exercise**
- **Education**
- **Diet**
- **Sleep**

Synchronizing Circadian Rhythms

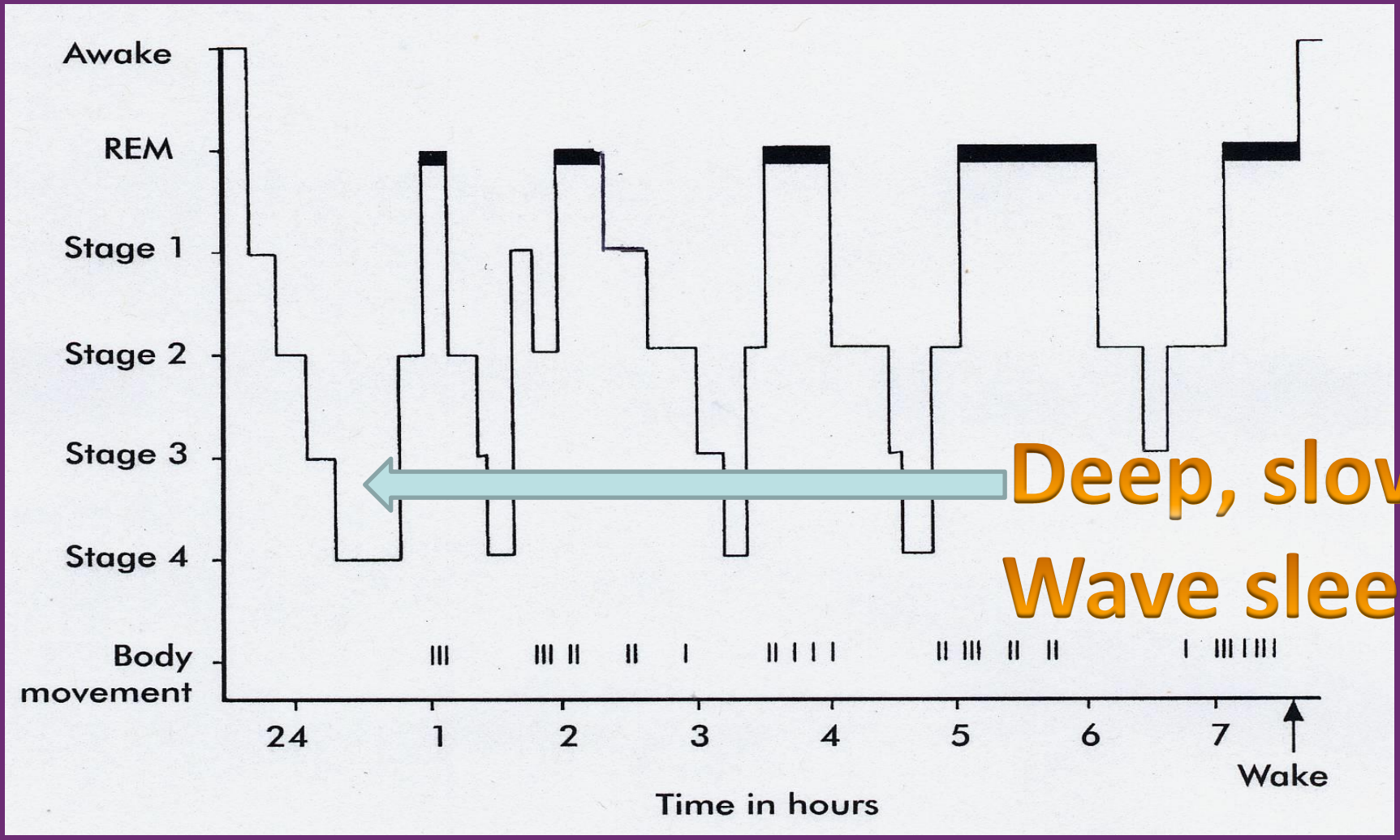
Entrainment of the SCN and Peripheral Clocks

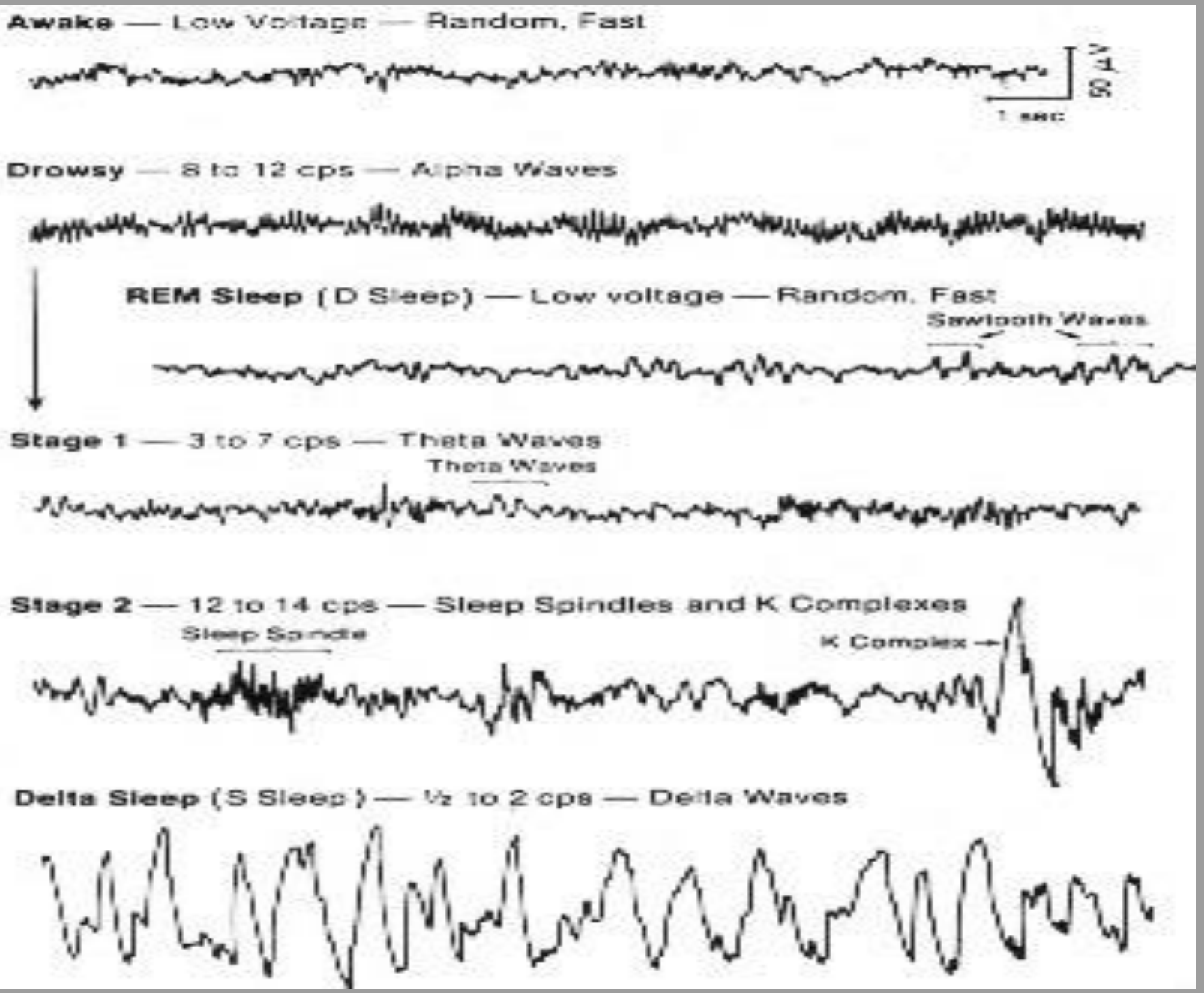


GI, gastrointestinal; PG, pineal gland; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; WBC, white blood cell.

Beckett M, Roden LC. *S Afr J Sci*. 2009;105(11-12):415-420; Dibner C, et al. *Annu Rev Physiol*. 2010;72:517-549; Young M, et al. *Sleep Med*. 2007;8(6):656-667.

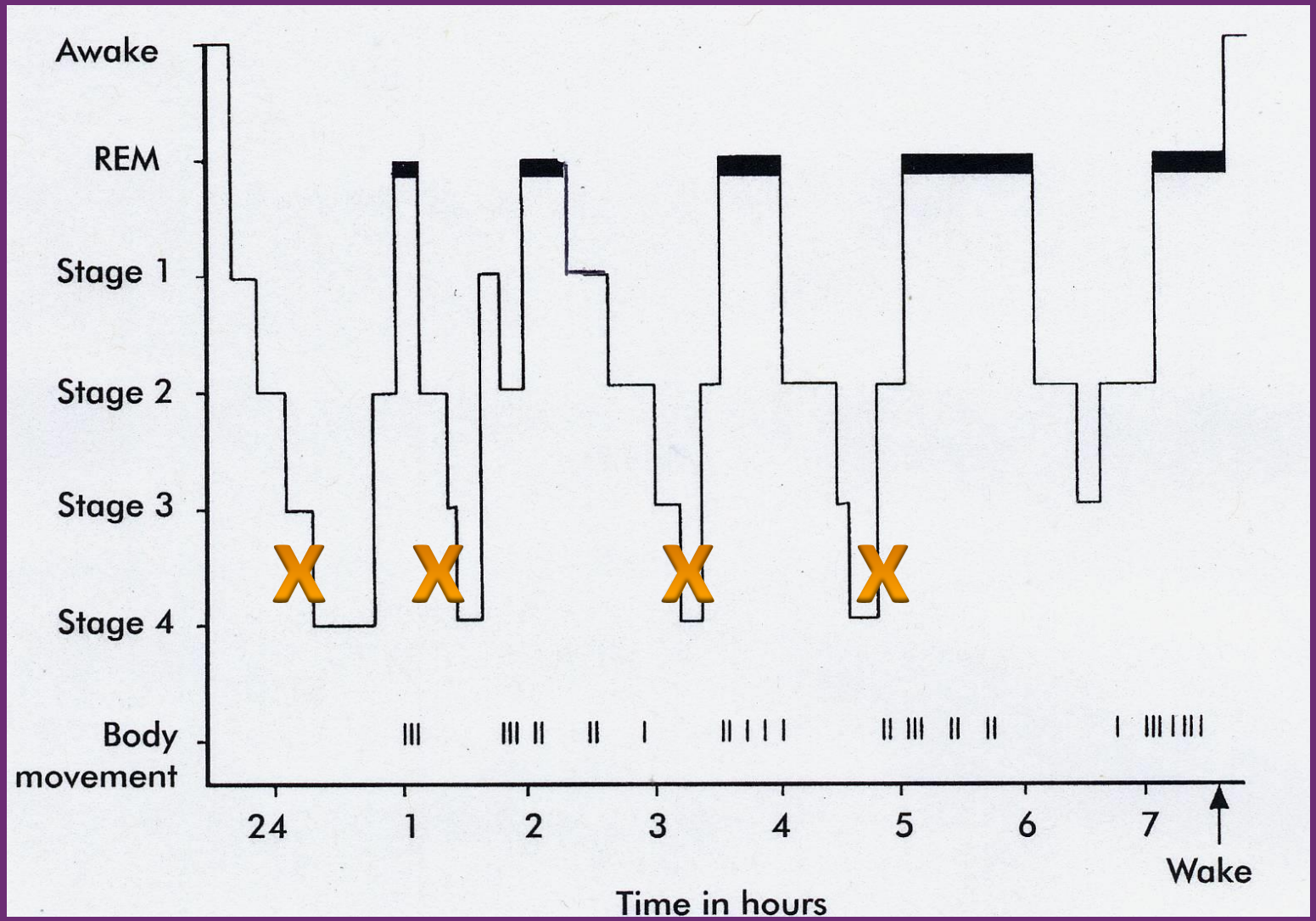
Normal Sleep Architecture




Awake — Low Voltage — Random, Fast
50 μV
1 sec
Drowsy — 8 to 12 cps — Alpha Waves
REM Sleep (D Sleep) — Low voltage — Random, Fast
Sawtooth Waves
Stage 1 — 3 to 7 cps — Theta Waves
Theta Waves
Stage 2 — 12 to 14 cps — Sleep Spindles and K Complexes
Sleep Spindle
K Complex
Delta Sleep (S Sleep) — ½ to 2 cps — Delta Waves

Pathologic Changes in Slow wave sleep

dep, anx, pain, apne, substance abuse



Slow wave sleep deprivation

- **> Fatigue**
- > Increases in cortisol
- **> Inflammation**
  - **> Trouble concentrating**
  - **> Impaired emotion regulation**

Increase in negative memories

–Increase in depression

Sleep deprivation

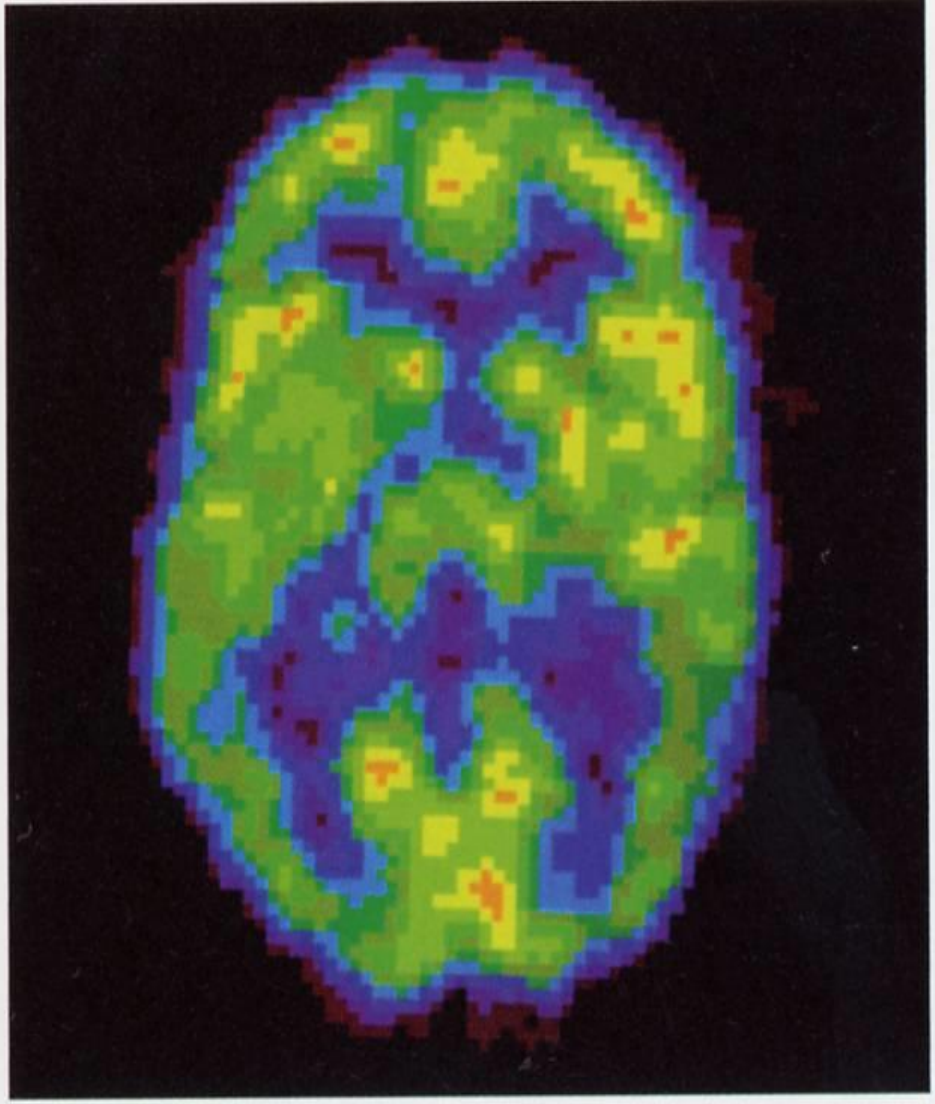
- ↓ ability to clear glucose
- ↓ in leptin (which normally would inhibit hunger)
- ↑ in ghrelin (increasing hunger)
- ↑ in weight
- ↑ vulnerability to type 2 diabetes

Memory and Sleep

- REM improves implicit (procedural) learning
- Non-REM improves explicit (declarative)
- Sleeping during a retention interval leads to better memory than wakefulness: i. e. consolidation
- A single night of sleep deprivation produces a significant deficit in hippocampal activity during episodic memory encoding, resulting worse subsequent retention

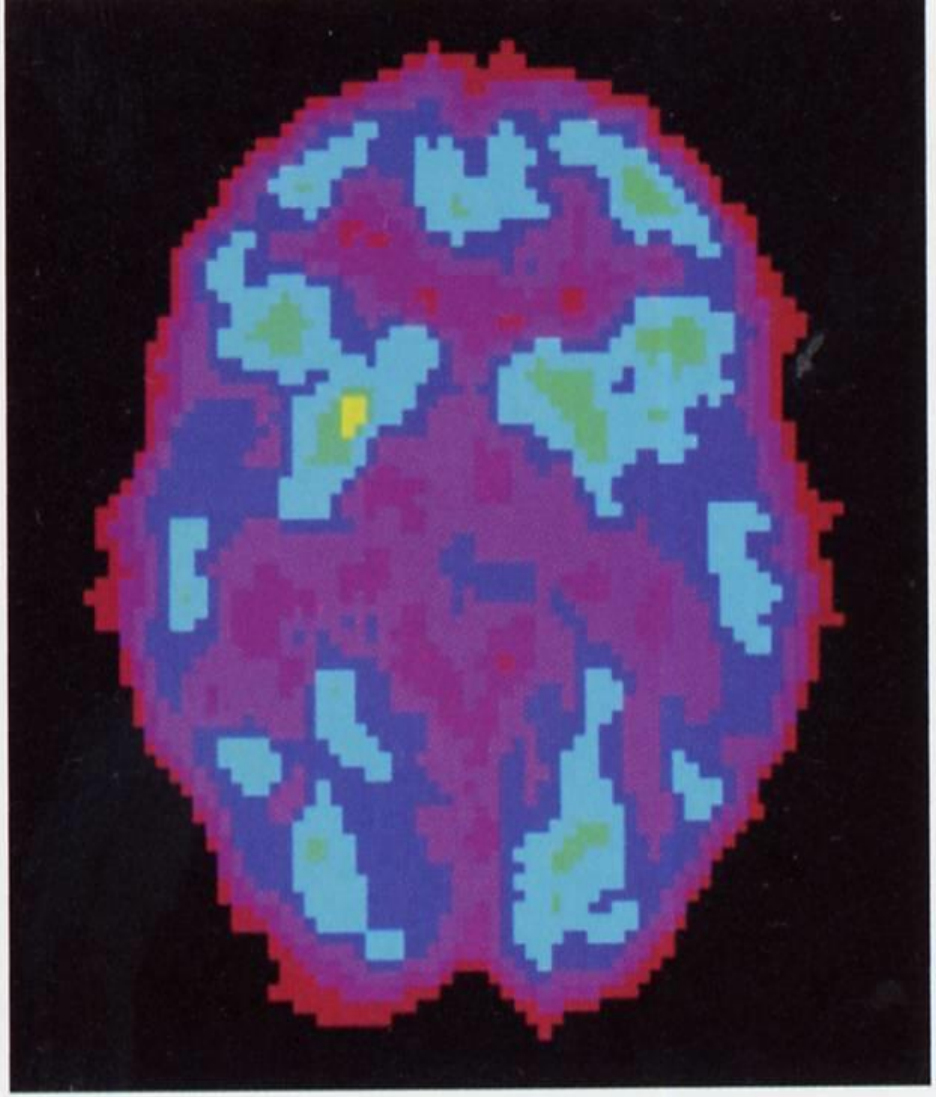
Brain Clearing

- “Glymphatic" system, a nod to both glial cells and its functional similarity to the lymphatic system
  - –Sleep as a dishwasher for your brain
- Sleep clears B-amyloid in the brain via increased CSF flow in interstitial space



DEEP SLEEP

This PET scan shows that activity quiets down in many areas of the brain during deep sleep. The purple areas are the least active.

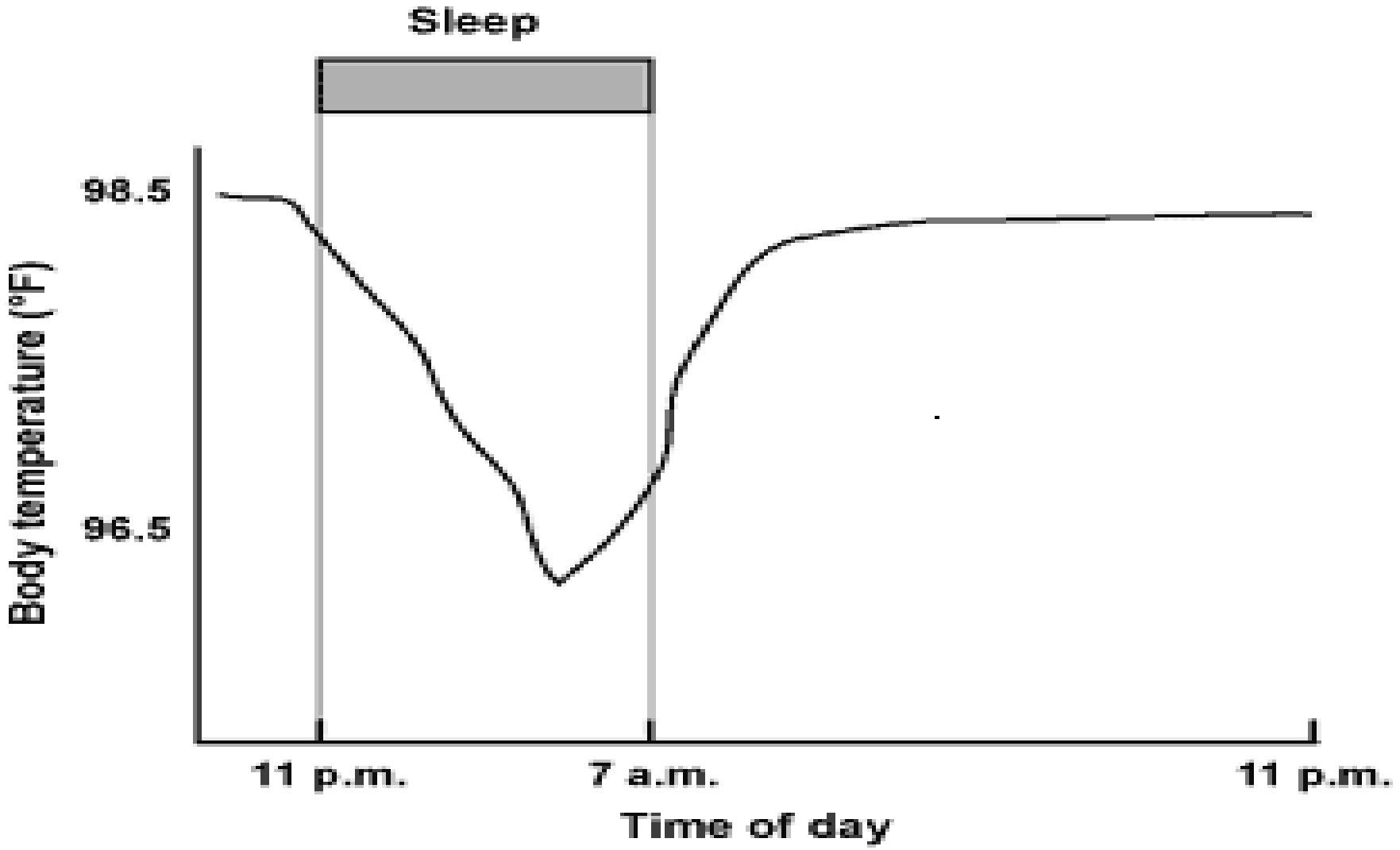


DRUGGED SLEEP

Most sleeping drugs induce a deeper sleep than normal. The purple areas on this PET scan show that much of the brain is inactive.


Laura Lewis, N. Fultz et al/Science 2019
SN

Body Temp and Sleep



Poor Sleep Linked to Alzheimer's

Lack of sleep or waking up several times may increase the risk of Alzheimer's disease

Getting less sleep or sleeping poorly is tied to an increase in brain levels of beta-amyloid

Older adults, (average age 76); those who said they got under five hours a night, or who slept fitfully had higher levels of beta-amyloid in the brain than those who slept over seven hours a night

Sleep Hygiene

- Don’t do anything in your bed other than sleep (except for sex).
  - –Do not watch television, balance your checkbook, discuss finances with your spouse, or argue in bed. Make your bed carry only one association—*sleep*.
- If you can’t sleep and find yourself tossing and turning, get up and go to another room.

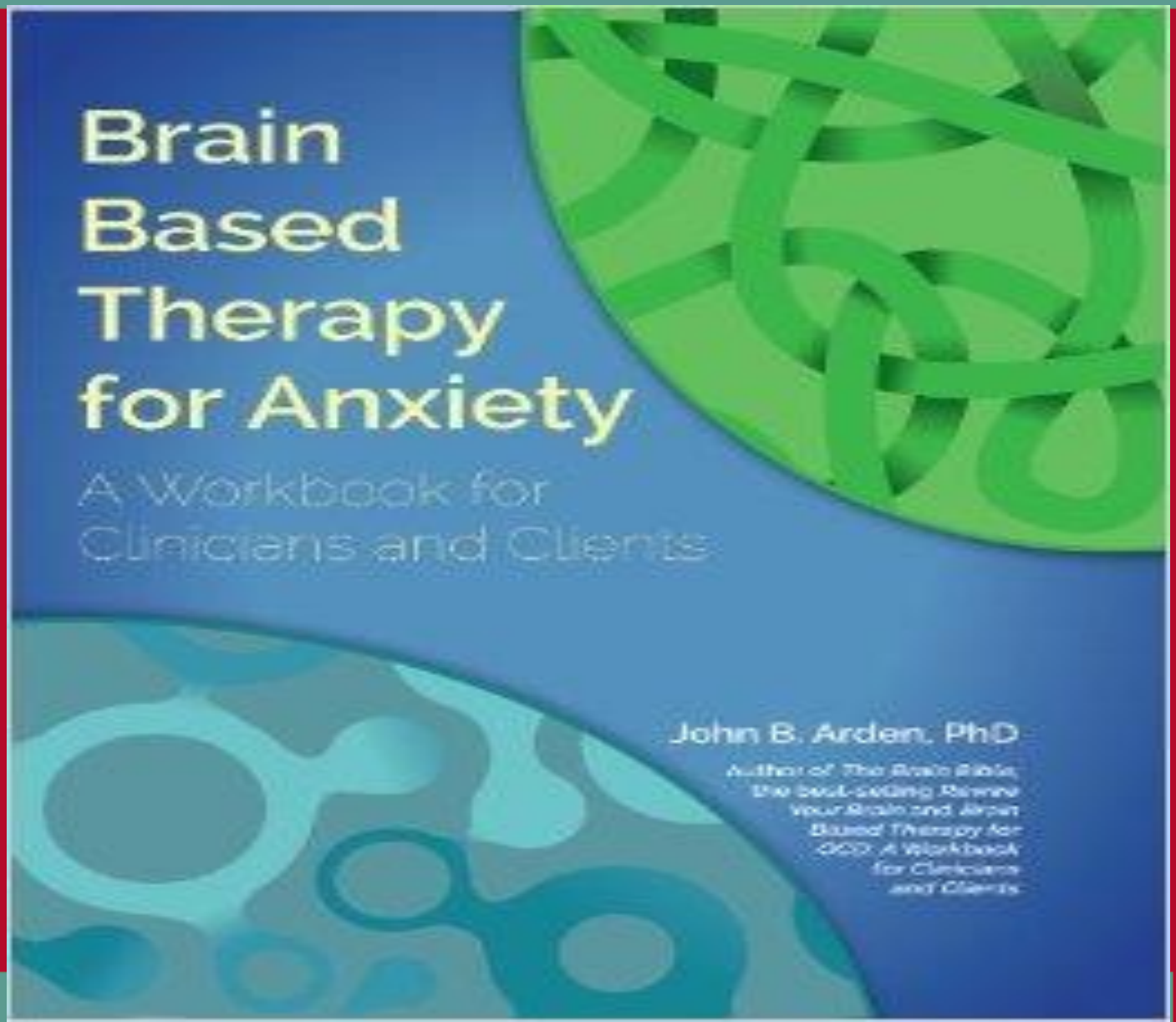
Mind-Brain-Gene Loops

Allostasis

&

Allostatic Load

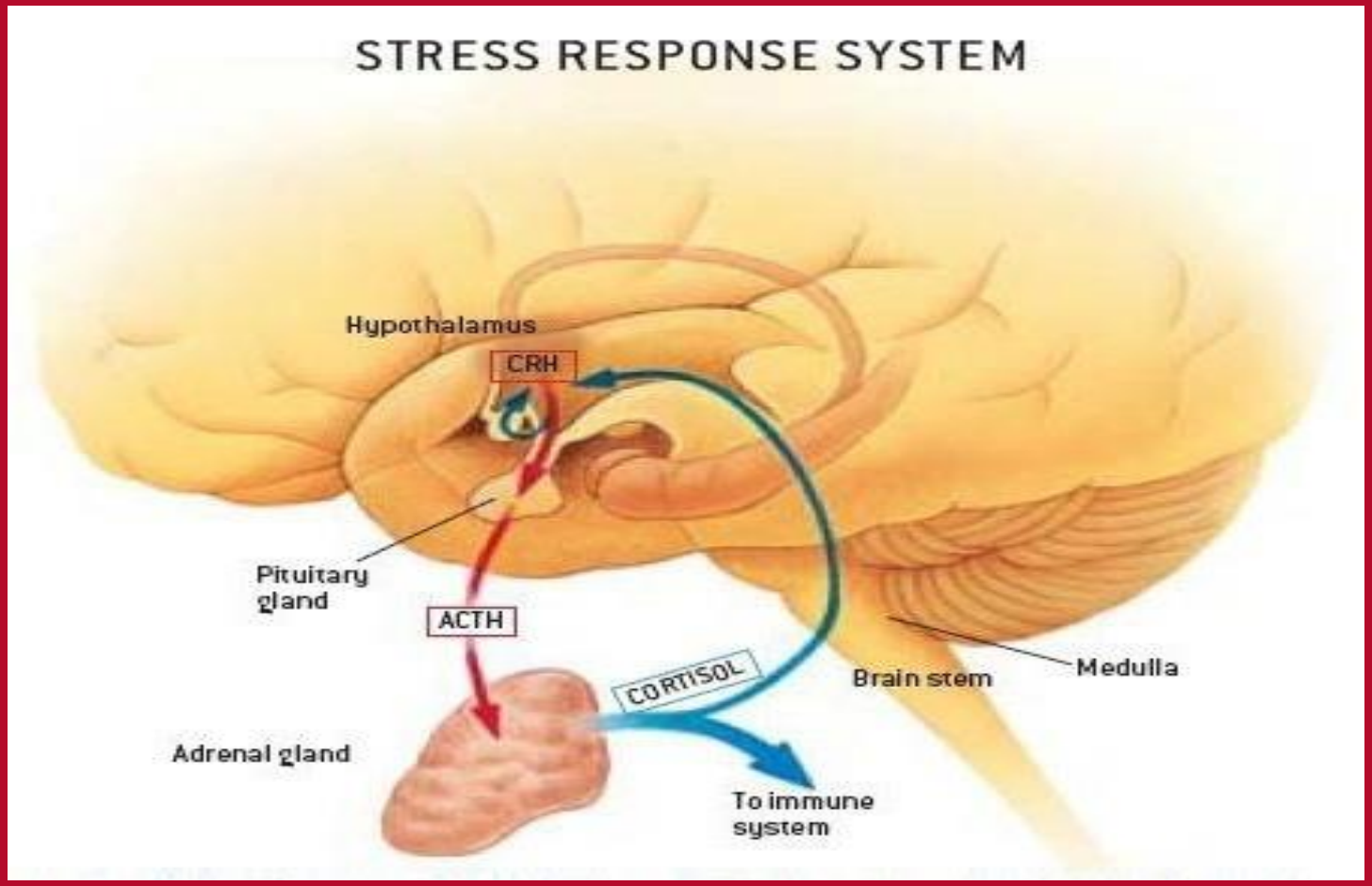
Anxiety


Brain
Based
Therapy
for Anxiety
A Workbook for
Clinicians and Clients
John B. Arden, PhD

Allostasis

- Allostatic adjustments are adaptive over the short term with moderate and fluctuating levels of cortisol to help orchestrate adjustments by:
  - enhancing or inhibiting gene transcription
  - regulation of BDNF
  - up regulates amygdala activity
  - targets prefrontal systems involved in stress and the emotion (Sullivan & Gratton, 2002).
  - maintaining stability through a change (McEwen, 1998).
- *Allostatic load* --When demands exceed the balance of energy and regulatory gains from rest and recuperation. (McEwen and Wingfield, 2003).

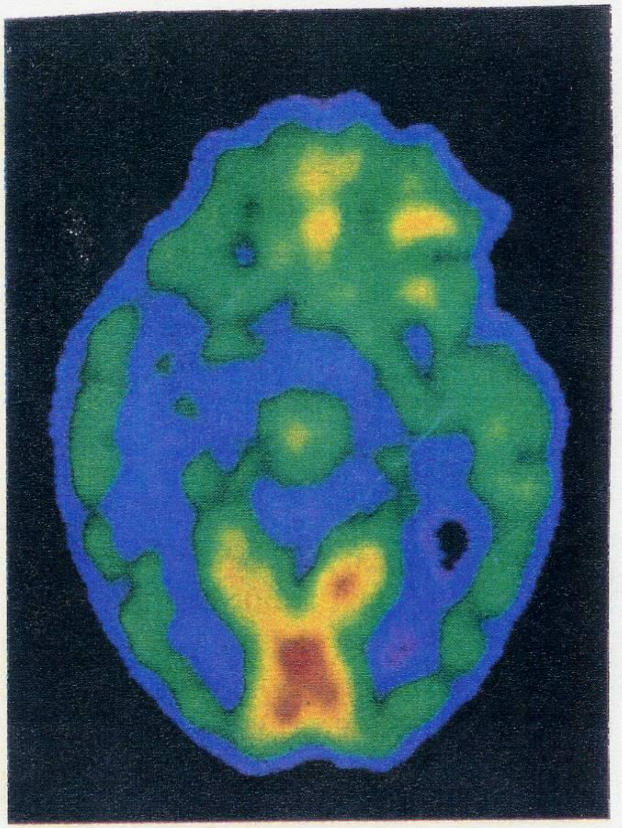
Sympathetic ANS and Neuroendocrine Systems



Locus Coeruleus (LC) source of NE which has extensive projections throughout the brain and can trigger the HPA axis (Aston-Jones, et al., 1994).

Neurodynamics of Anxiety

- Two routes to the amygdala, the fast and slow
- Right frontal bias in general for anxiety disorders
- Under-activation of the left frontal lobes and in Broca's area explains why some people feel "speechless" when they're scared (Rauch et al., 1997).



The Jamesian Fast Track and MI

CBT vs. Metacognitive Models

(ACT, DBT, MBCBT, etc.)

CBT

Rationale=control

Cognitive restructuring

Breathing retraining

Interoceptive exposure to lessen fear & avoidance

Situational exposure to lessen fear fear and avoidance

MC Models

Rationale=relinquish control

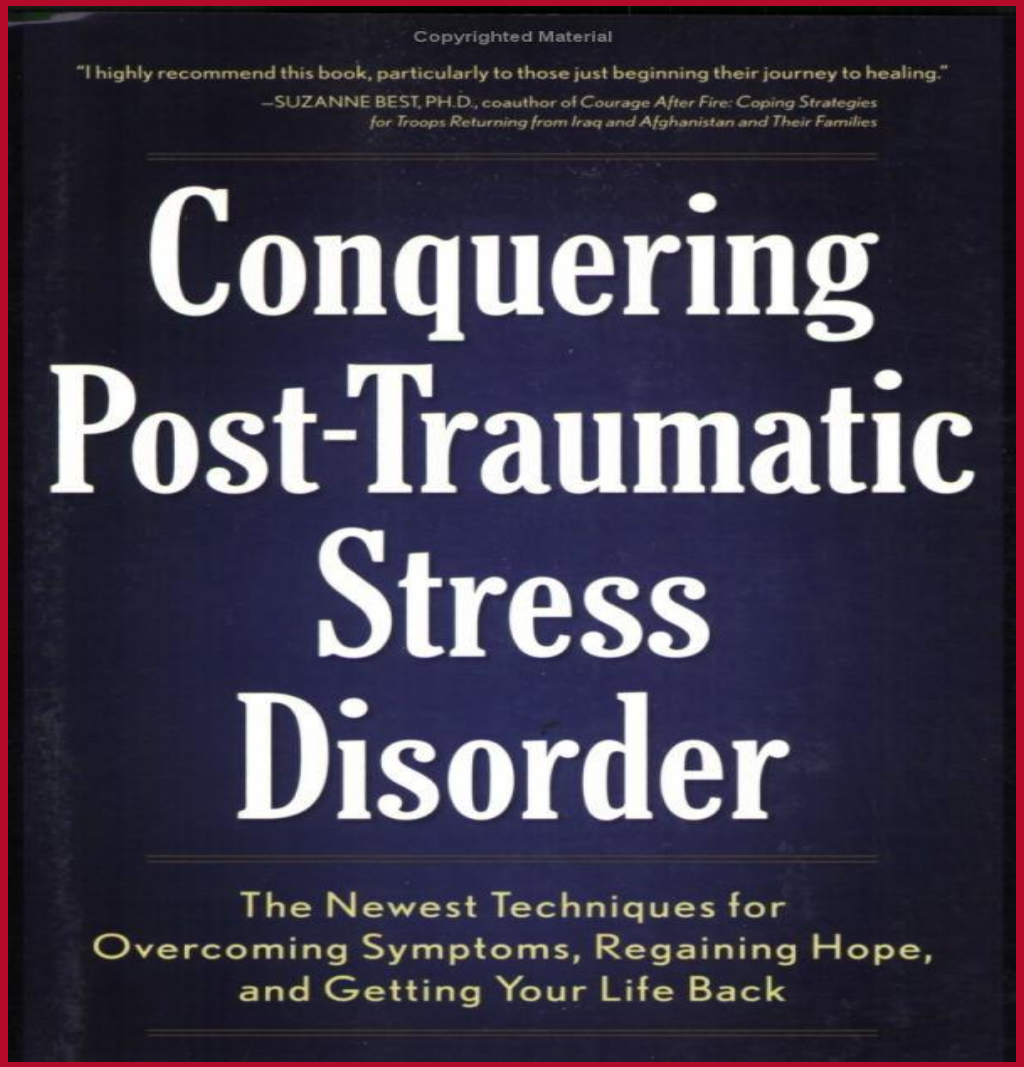
Thought Diffusion

Observe & accept

Interoceptive exposure with acceptance of internal cues

Situational exposure to achieve life values and goals

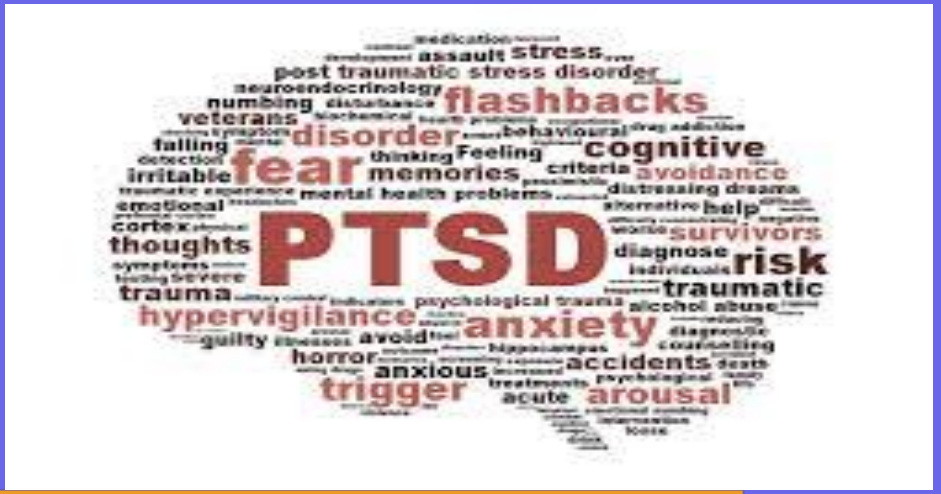
Post Traumatic Stress Disorder



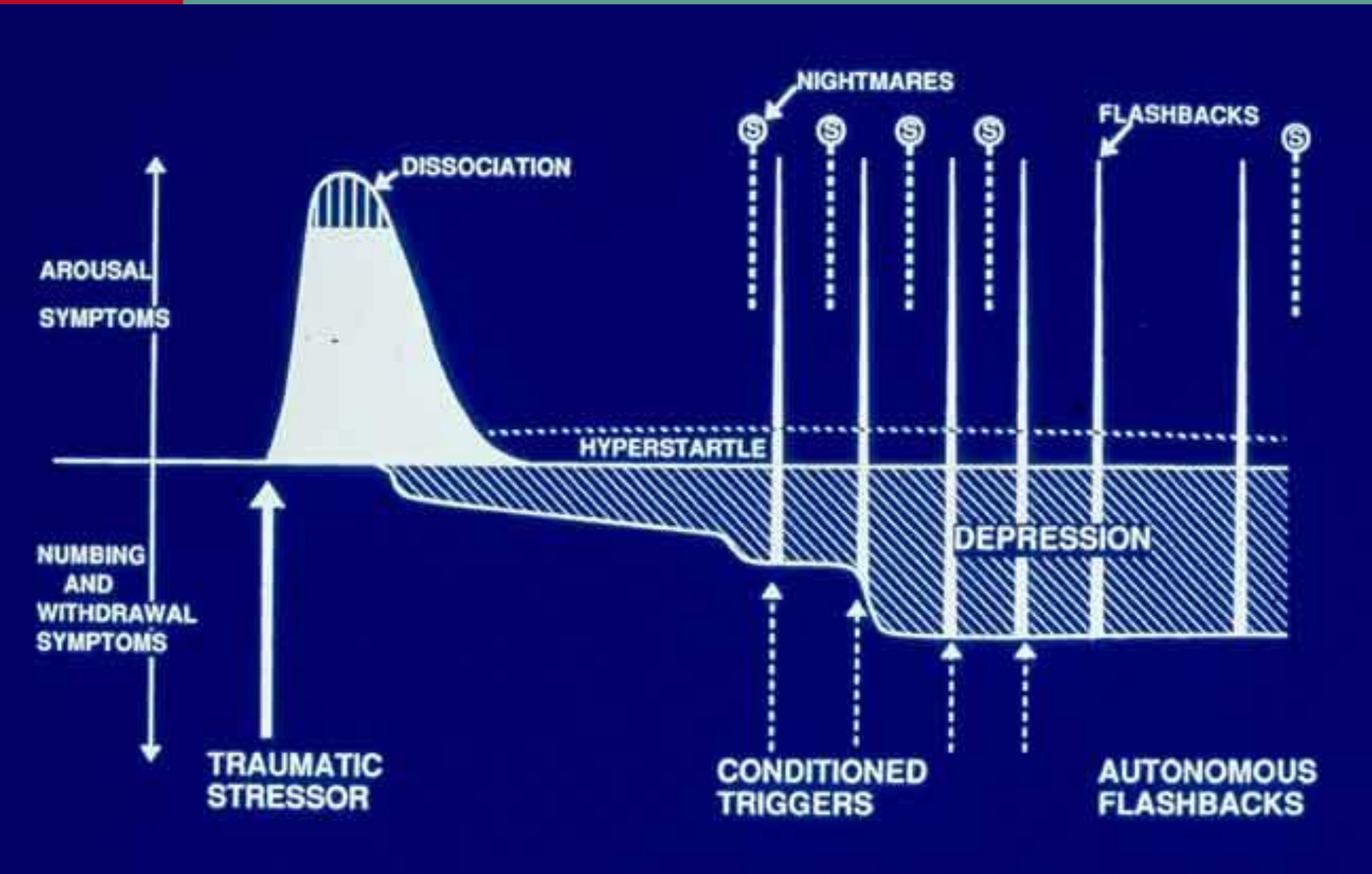
Refugee Crisis

Re-traumatization caused by:

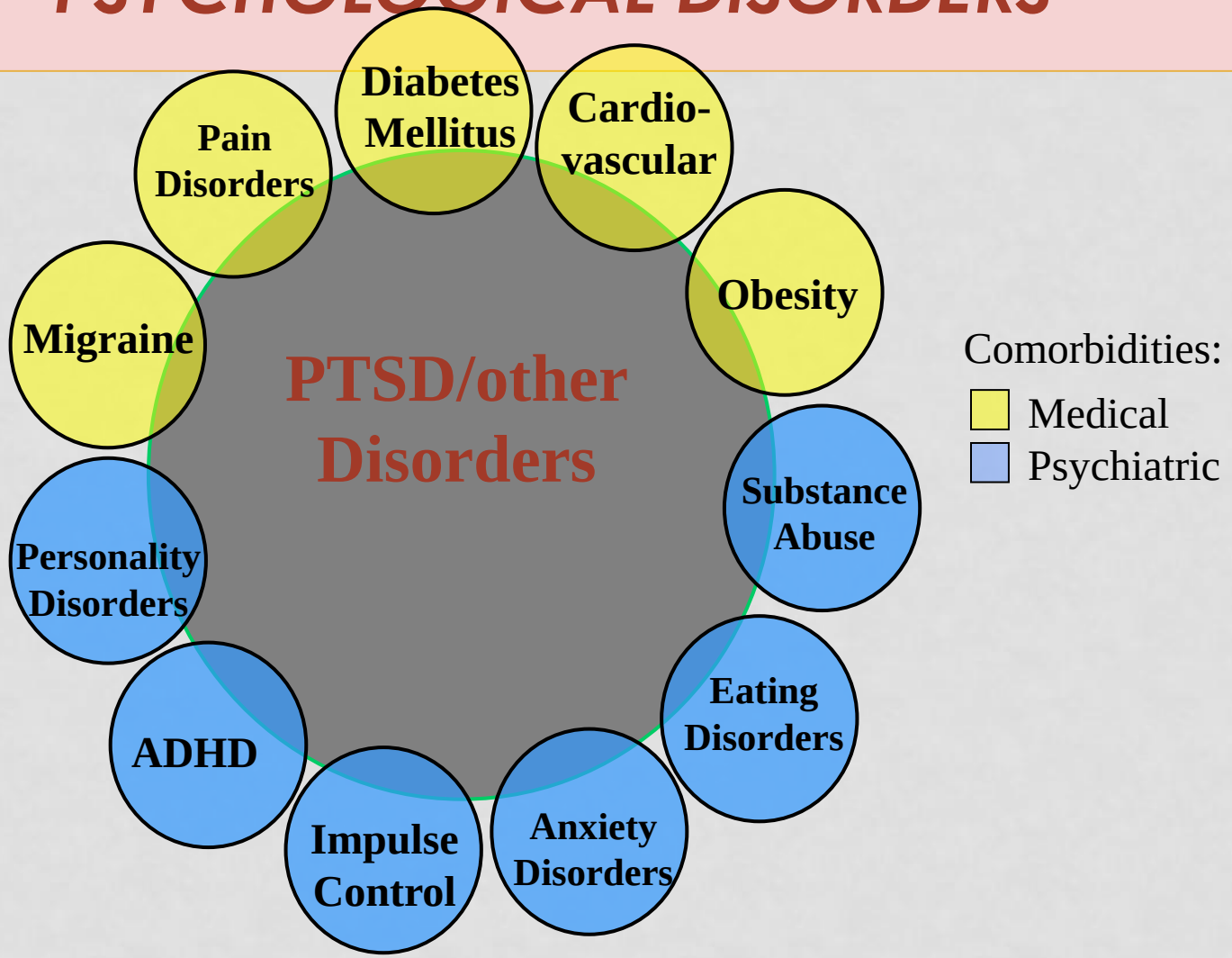
- relentless war in the region
- growing level of violence
- traumatic experiences
- extreme deprivation in daily life



Time Sequence

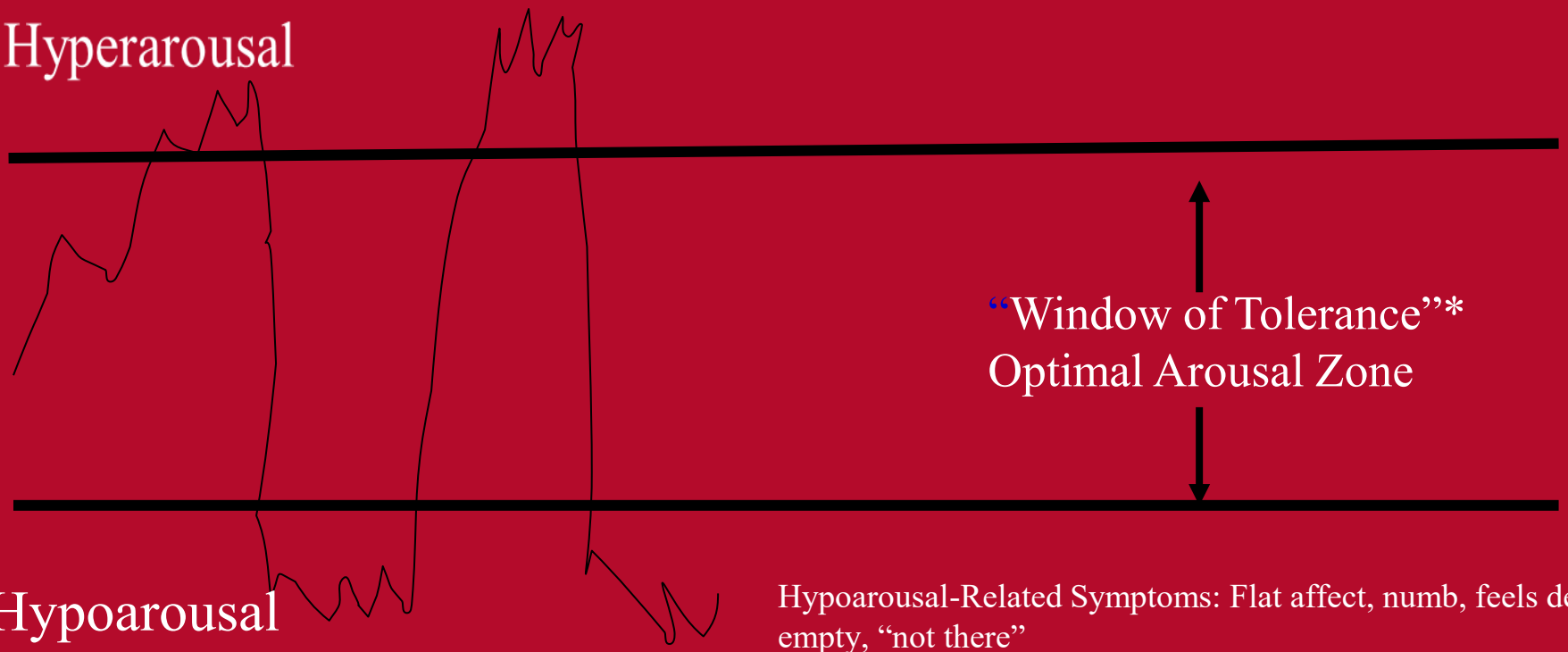


THE RULE NOT THE EXCEPTION
THE MULTIDIMENSIONALITY OF NEURO-PSYCHOLOGICAL DISORDERS



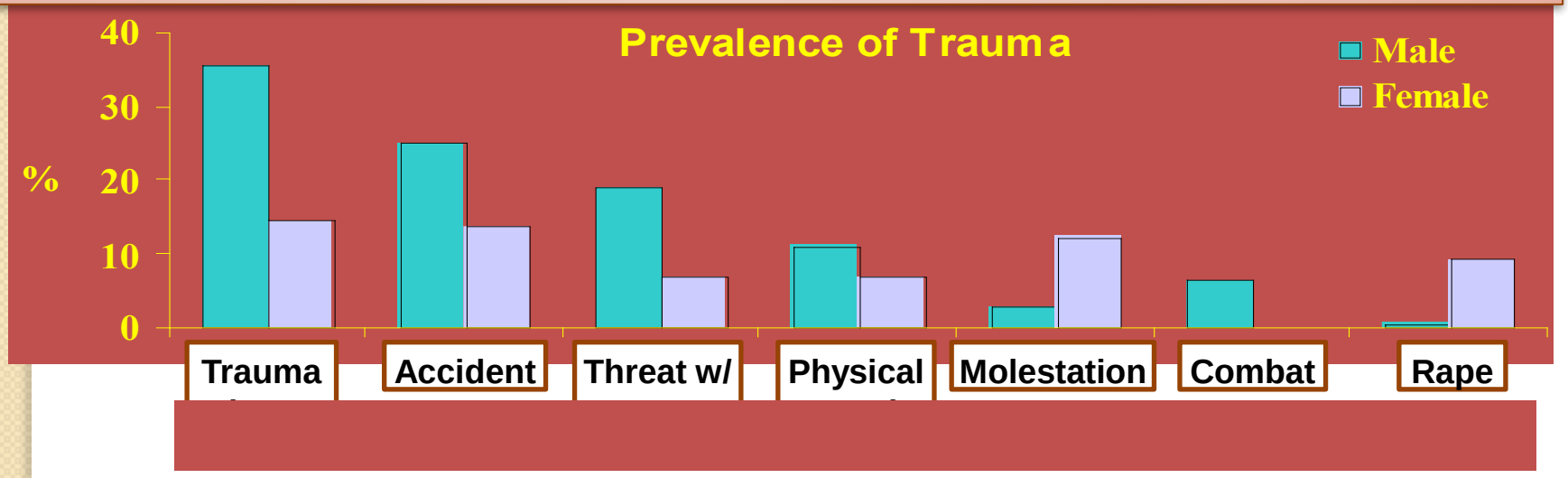
Trauma Responses are Autonomically Driven

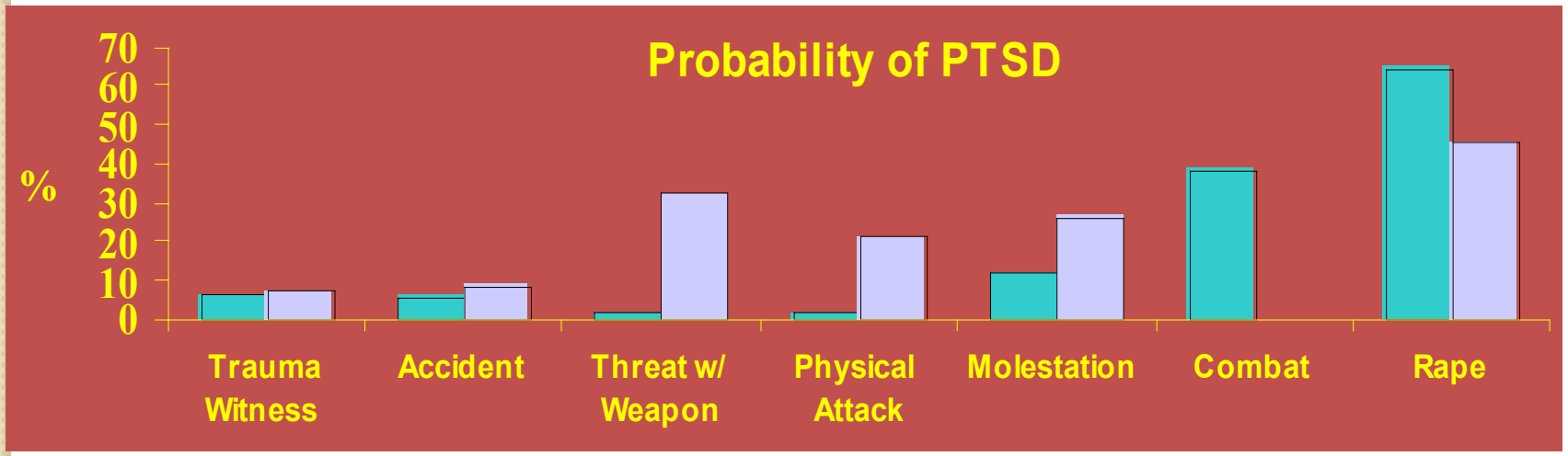
Hyperarousal-Related Symptoms:
High activation resulting in impulsivity, risk-taking, poor judgment
Chronic hypervigilance, post-traumatic paranoia, chronic dread
Intrusive emotions and images, flashbacks, nightmares, racing thoughts
Obsessive thoughts and behavior, cognitive schemas focused on worthlessness and dread



Hypoarousal-Related Symptoms: Flat affect, numb, feels dead or empty, "not there"
Cognitively dissociated, slowed thinking process
Cognitive schemas focused on hopelessness

Prevalence of Trauma and Probability of PTSD



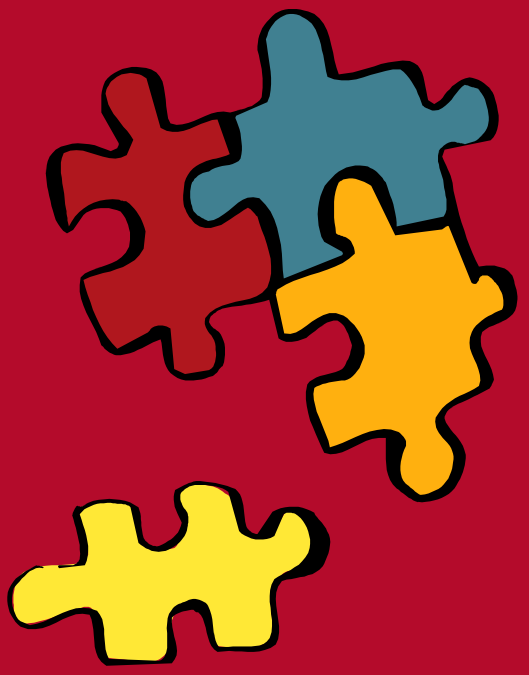


Kessler. *J Clin Psychiatry*. 2000;61(suppl 5):4.
Kessler et al. *Arch Gen Psychiatry*. 1995;52:1048.

Impaired Information Processing in Post-Traumatic Stress Disorder

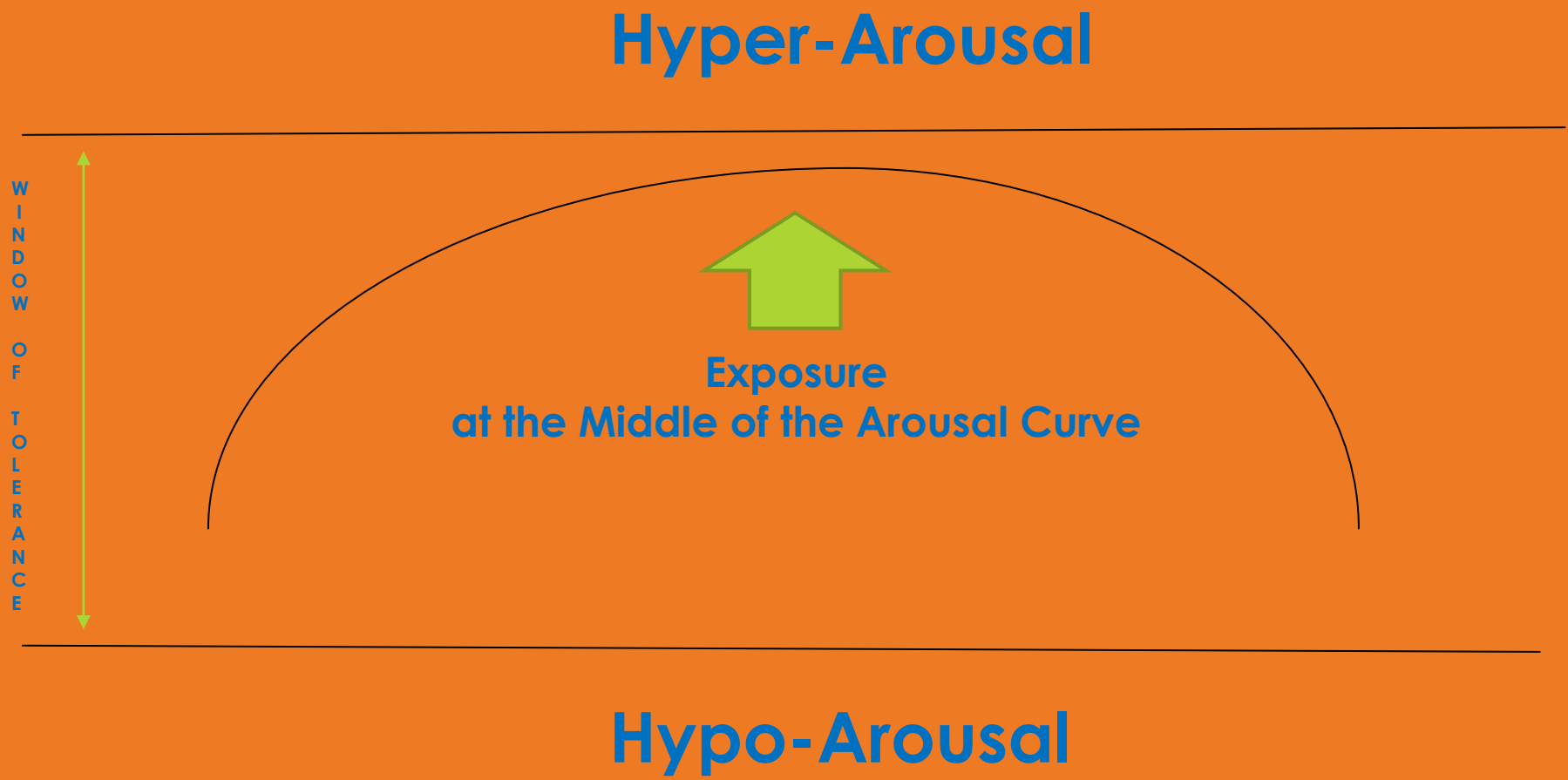
Dissociation at time of trauma (encoding)
Fragmented, "jigsaw" memories

images, emotions, bodily sensations, cognitions……..
dis-integrated



Dual Processing Theory

- **Limitations of the "fear network" theory – doesn't account for implicit memory:**
  - **Verbally accessible memories (VAMs) on the conscious memory level. VAMs can be accessed in therapy through deliberate recall.**
  - **Situationally accessible memories (SAMs) non-conscious. SAMs are only accessible through exposure cues that activate the non-conscious network** (Brewin, Dalgleish, and Joseph, 1996).


Hyper-Arousal
WINDOW OF TOLERANCE
Exposure
at the Middle of the Arousal Curve
Hypo-Arousal

Orienting Response, REM, and Memory

- Somatic stimulation of the orienting response (i.e. via EMDR, EFT, acupressure etc.) involve:
  - *Shto takoe?* (Что такое? or *What is it?)*
  - Reorienting of attention -- triggered automatically when a sudden movement grabs attention or intentionally when you chose to look at an object
  - The reorienting of attention requires you to release your focus on one location so that it can shift to a new location
- The shift in attention involves:
  - The orienting response (Sokolov, 1990)
  - Induces REM like state
- Both facilitate cortical integration of memories (Stickgold, 2002)

Shifts in attention and asymmetry

- **Why activate the RH when it is already overactive? How about tapping the right hand and/or foot?**
- **The right limb tapping method still includes:**
  - **reorientation response**
  - **attentional shift**
  - **grounding**
- **This method is portable—the client can practice on his own (neuroplasticity)**

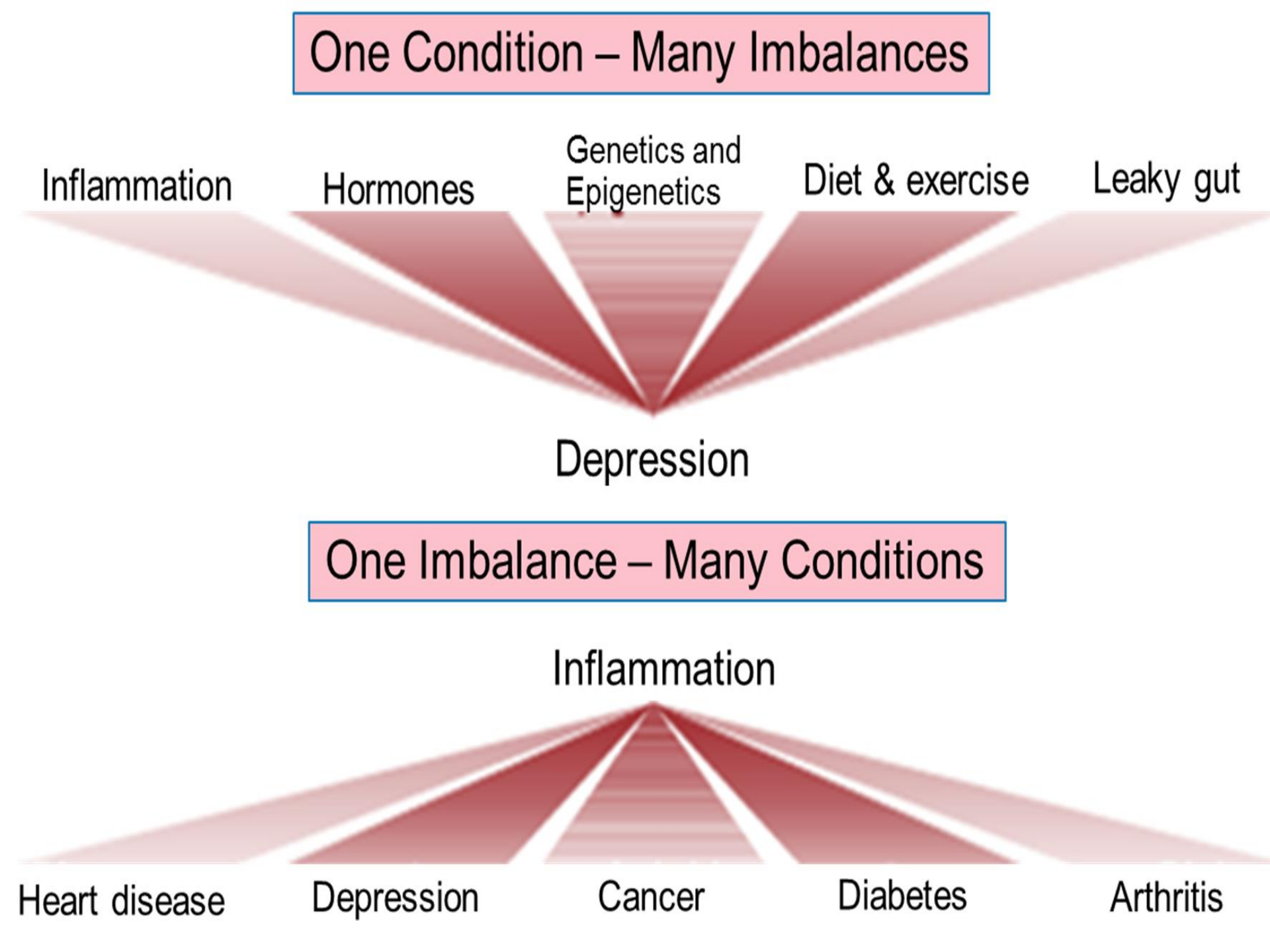
Orienting and Recoding

- A stimulus that prompts a person to notice what happens next primes PFC activity.
- Coding in novelty, an unexpected somatic sensation, integrates PFC, anterior cingular cortex, hippocampus, and basal ganglia circuits by moderate bursts of dopamine,
  - orienting serves as a sort of a kickstart to the connectivity between the executive and the salience networks

BBT and PTSD

- Phase 1: Psychological first aid—stabilizing ASD and preventing PTSD
- Phase 2: Integration of implicit and explicit memory systems:
  - Explicit memories (VAMs) –The conscious memory level, which can be accessed in therapy through deliberate recall.
  - Implicit memories (SAMs) –The nonconscious, which are only accessible through cues that activate the network.
  - Aided by somatic reorienting method
  - Phase 3: Posttraumatic growth—developing meaning and direction (Constructivism)

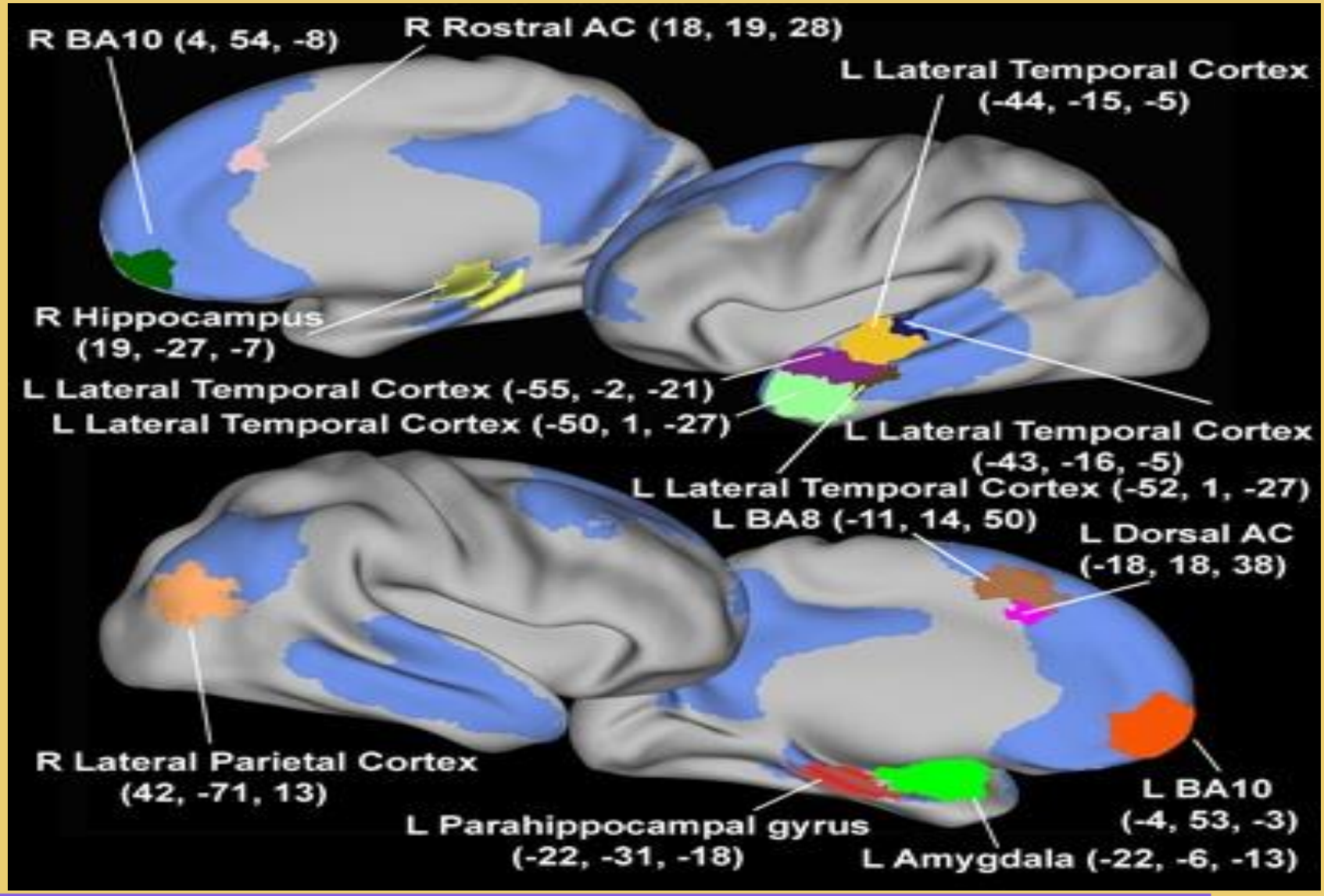
Depression


One Condition – Many Imbalances
Inflammation
Hormones
Genetics and Epigenetics
Diet & exercise
Leaky gut
Depression
One Imbalance – Many Conditions
Inflammation
Heart disease
Depression
Cancer
Diabetes
Arthritis

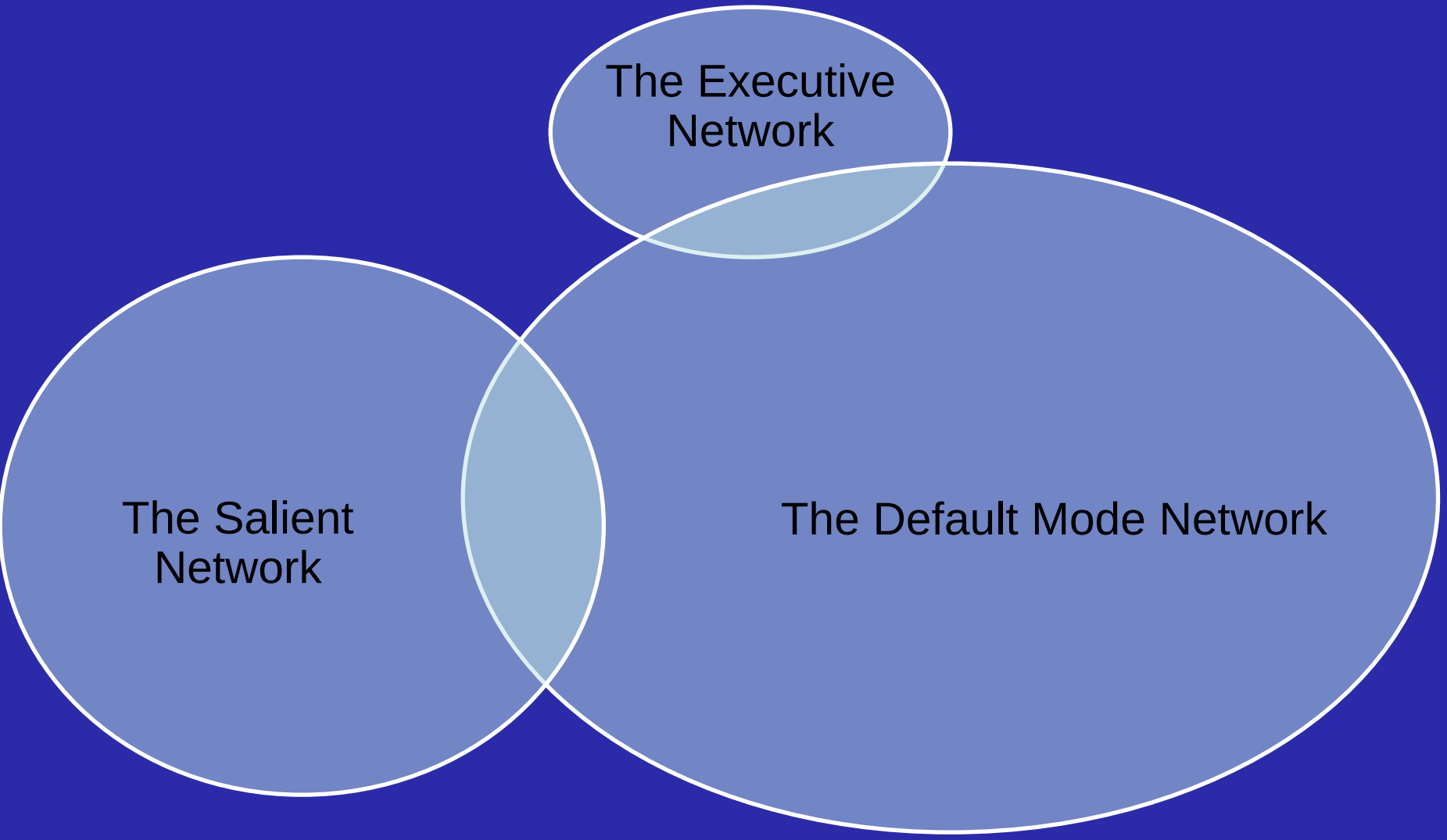
Pro-inflammatory Cytokines

- Stress can increase PICs levels
- High PICs can lower the concentration of serotonin and DA
  - –Cognitive dysfunction, anxiety, fearfulness, depression, thoughts about suicide
- “Sickness behavior”---fatigue, social withdrawal, and immobility--depression (Hickie and Lloyd 1995).

DMN (in blue). All of the other colors are overactive in people with depression.



Dysregulated Mental Networks



DMN and Depression

- The DMN increases when DLPFC (EN) is not engaged:
  - Stressed, bored, no novelty, or tired
  - Obsessive ruminations over negative experiences

Ruminations fade with:

- Goal directed behaviors
- Exercise
- Social activities
- mindfulness

Therapy: Mind-Brain-Gene Feedback Loops

Up regulate

- **The Social Brain Networks**
  - Individual psychotherapy
  - Groups
  - Expanding social supports
- **Activity Reward Circuit**
  - **Behavioral activation**
- **Hippocampus**
  - Exercise
  - Rebuilding a positive explicit memory system
- **Prefrontal Cortex**
  - Mindfulness
  - Goal planning and follow-through
  - Meta-awareness

Therapy: Working the Mind-Brain-Gene Feedback Loops

Down regulate

- **Right hemi withdrawal tendency by:**
  - Social engagement
  - Active behavior
  - Challenging negative generalizations
  - **Humor**
  - Labeling moods
- **The amygdala and the HPA axis by:**
  - Exposure
  - Exercise
  - Goal directed behavior
- **The ACC by:**
  - Challenging self-criticism

Therapy: Working the Mind-Brain-Gene Feedback Loops

Interventions that bolster under-active areas of the brain

- **Metabolism**
  - **Exercise**
  - **Sleep hygiene**
  - **Diet, including Omega 3**
- **Hippocampus**
  - **Counter mood-congruent bias with inquiry**
- **Rebalance left PFC**
  - **Details**
  - **Active**
  - **Goal directed behavior**
- **Activity Reward Circuit**
- **Mindfulness**
  - **Quieting ruminations and monotony**

Client Education

- Because many factors can contribute to your depression you'll need to do all the things we talk about doing simultaneously to climb out of depression.

TEAM for Depression

T is for thinking to defuse negativistic thinking associated with depression.

E is for effort, to activate the approach circuits of the L-PFC and the effort driven reward circuit.

A is for accepting that the world is not perfect and the things that happen are not always good.

M is for mindfulness to focus on the present moment and novelty of each experience, gratitude, and forgiveness (Meta-awareness)

Mind-Brain-Gene Feedback Loops

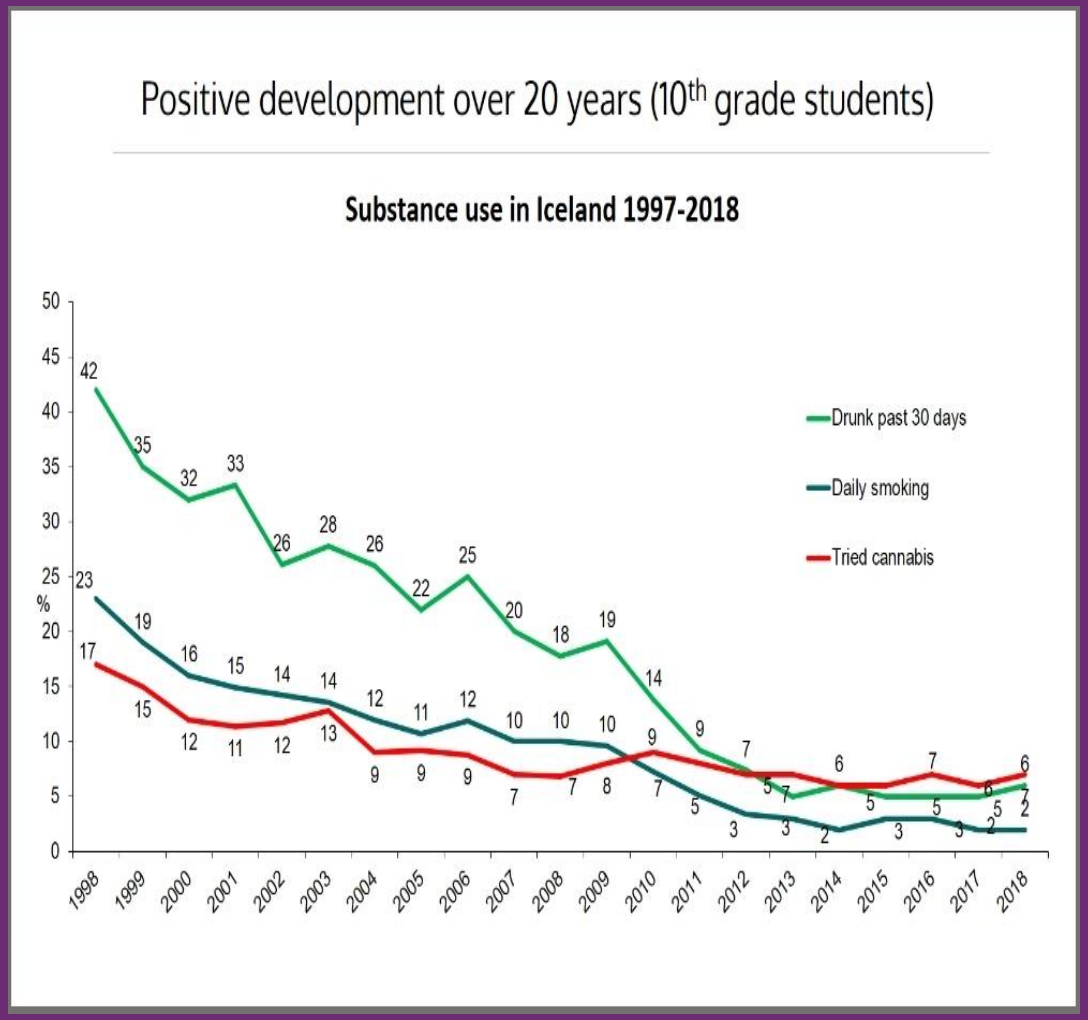
Wanting vs. Liking

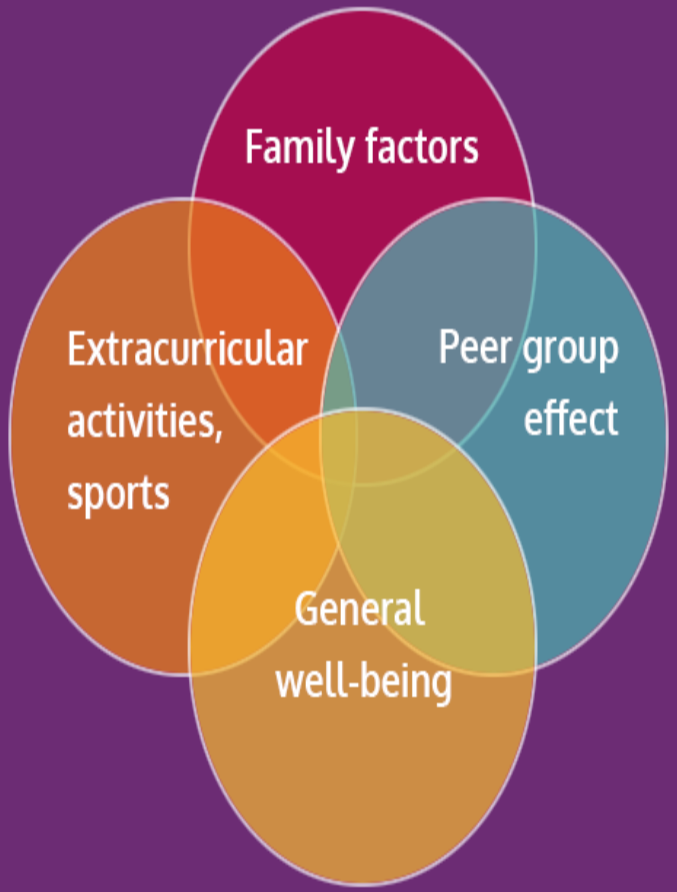
- Wanting—dopamine
- Liking—opioids
  - Sometimes you get wanting without liking
- Dopamine firing like a Geiger counter approaching a radiation source
- D1 receptors direct to the BG –mindless habit
- D2 receptors indirect—grow with a wide variety of positive experiences

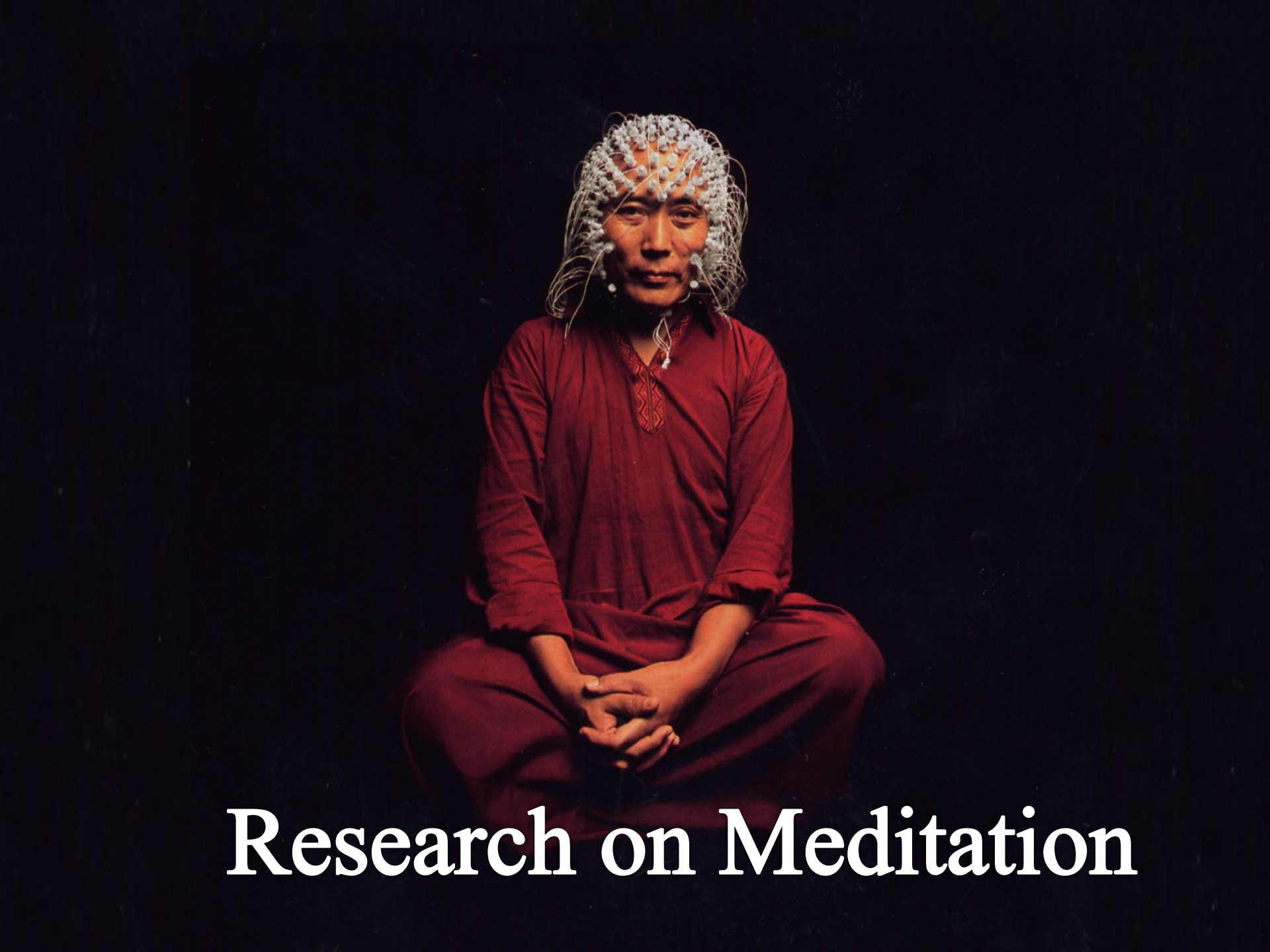
The Middle Path

- Normally, when dopamine binds to D2 dopamine receptors, the receptors change shape and cannot send another signal until they go through a recycling process.
  - The receptor is taken inside the neuron and chemically treated so that it can return to a functional state. This recycling process is messy, with the loss of some receptors in the process. If loss of receptors outpaces the rate at which the neuron makes new ones, D2 dopamine receptor levels will decline.
  - Moderate- size rewards stimulate moderate dopamine release, and a relatively small portion of the receptors go through this recycling process, leaving a large population of D2 dopamine receptors available to put on the indirect pathway brakes.
  - In contrast, drug use surges dopamine release to the extreme; with overwhelming dopamine release the D2 dopamine receptor population becomes depleted. The person becomes less able to put the brakes on habits. In recovery those receptors come back over a period of weeks and month

The Iceland Project






Research on Meditation

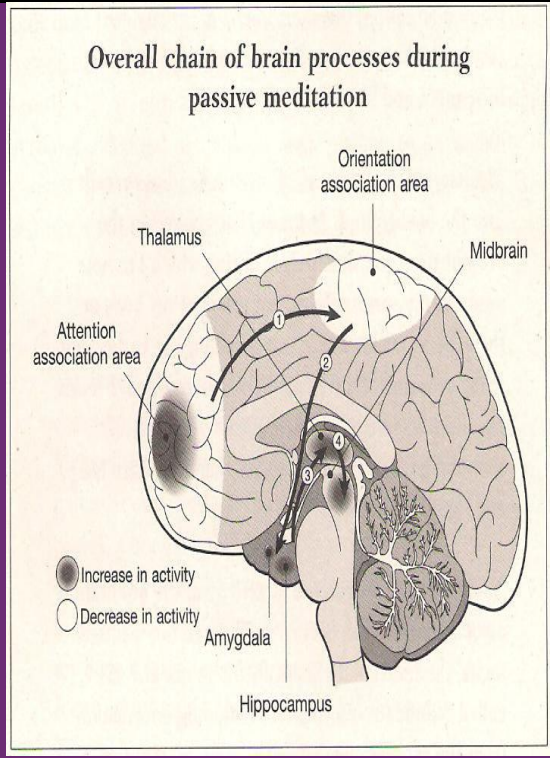
Mindfulness and the Brain

- **Long-term meditators show increased thickness of the medial prefrontal cortex and also enlargement of the right insula** (Lazar, et al, 2005).

- **The process of verbal labeling of affective states reduces anxiety and negative affect** (Leiberman, et al, 2004)

- **The middle prefrontal cortex has been associated with self observation and mindfulness meditation** (Cahn and Polich, 2006).

- **A shift to the left PFC which puts a positive spin on the experience** (Davidson, et al., 2003).



7 Principles Common to prayer, meditation, relaxation exercises, and hypnosis.

- 1) Breathing Rhythmically—deep, deliberate, and focused breathing allows you to slow your heart beat.
- 2) Focused attention—to the present moment can transform each experience into a rich and calm experience by turning on your brain's brain.

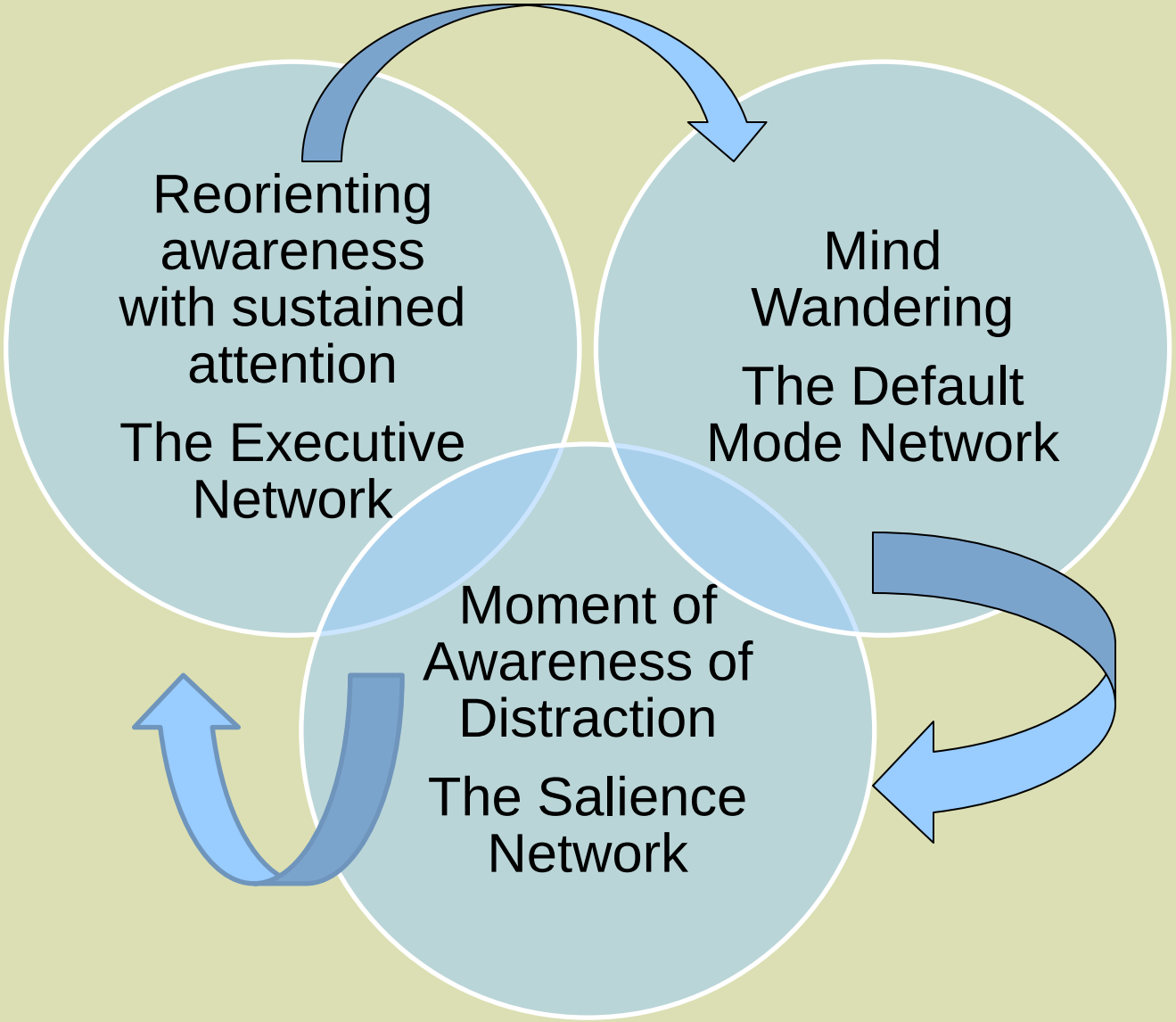
7 Principles of Relaxation

- 3) An accepting and a nonjudgmental attitude shift away from rigid expectations that helps you appreciate reality as it is, rather than what you fear it could be.
- 4) Observation—This allows you to detach from bad feelings by not denying their existence.

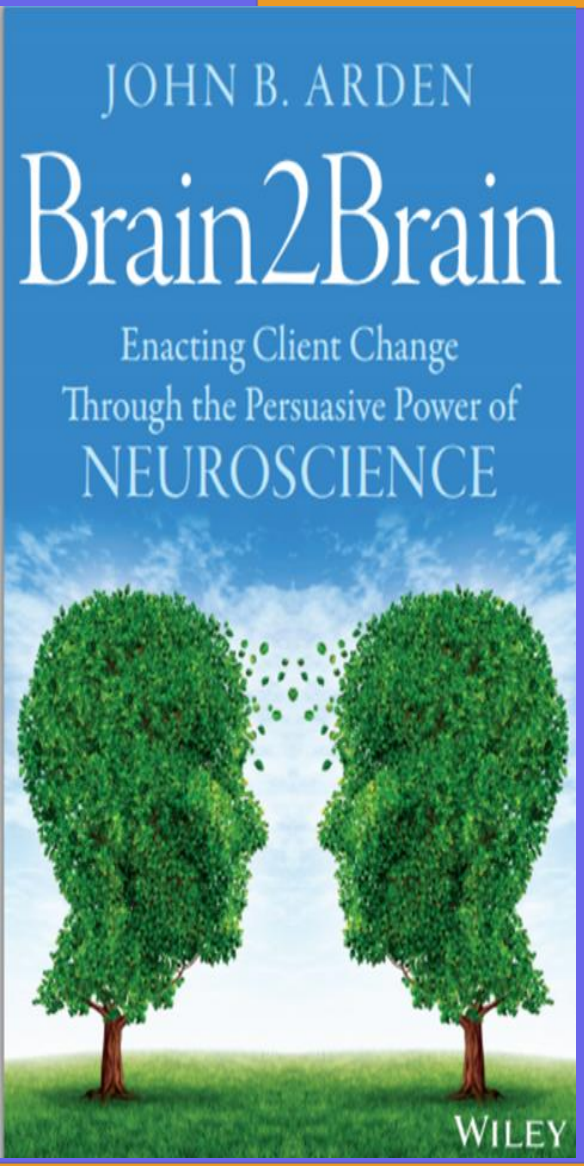
7 Principles of Relaxation

- 5) Labeling what you experience can calm your amygdala.
- 6) A quiet environment—This will give you an opportunity to learn how quiet your mind without distractions.
- 7) A relaxed posture—This can reduce tension include sitting in a relaxed posture or stretching (e.g. hybrid yoga)

Contemplative Experiences



References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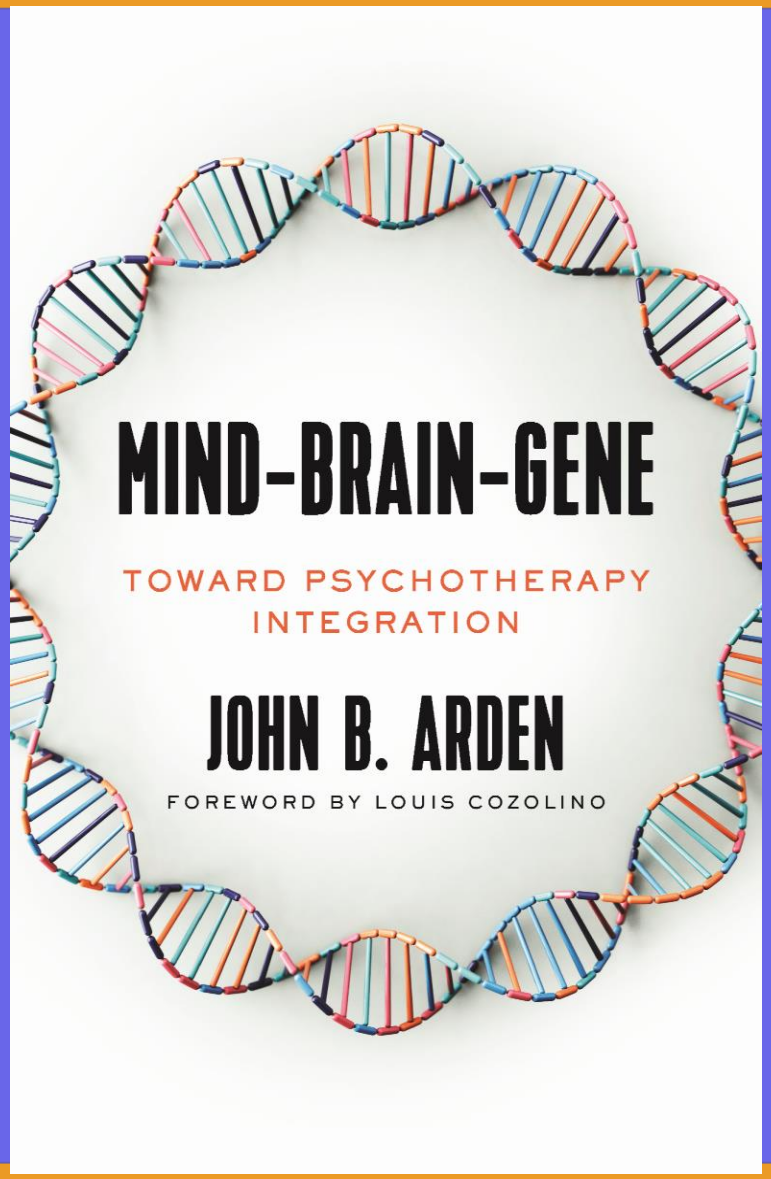
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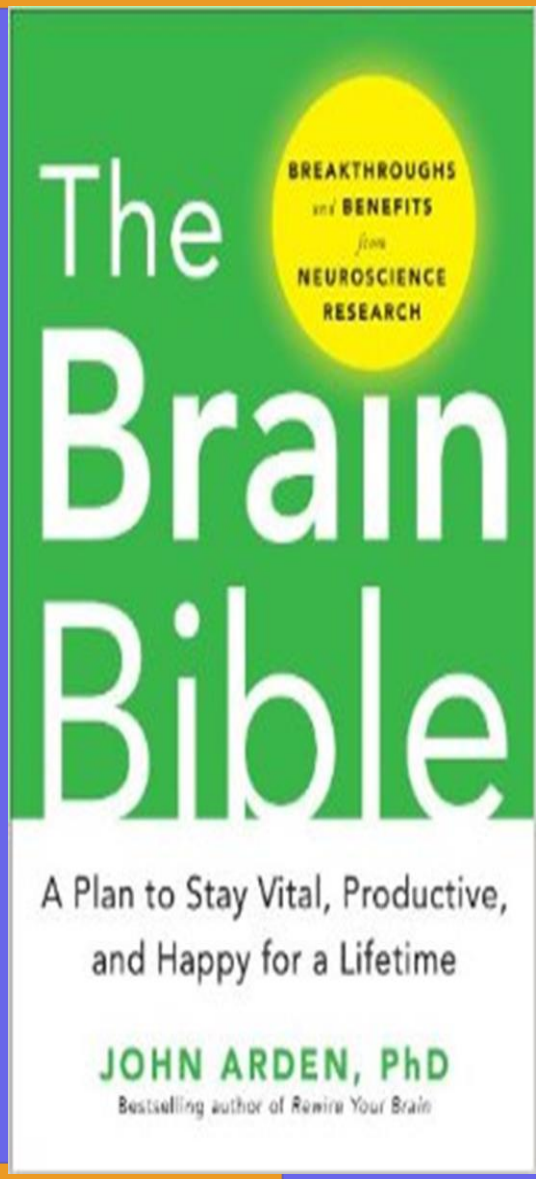
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