SEEDS Self-Care

John B. Arden, PhD, ABPP

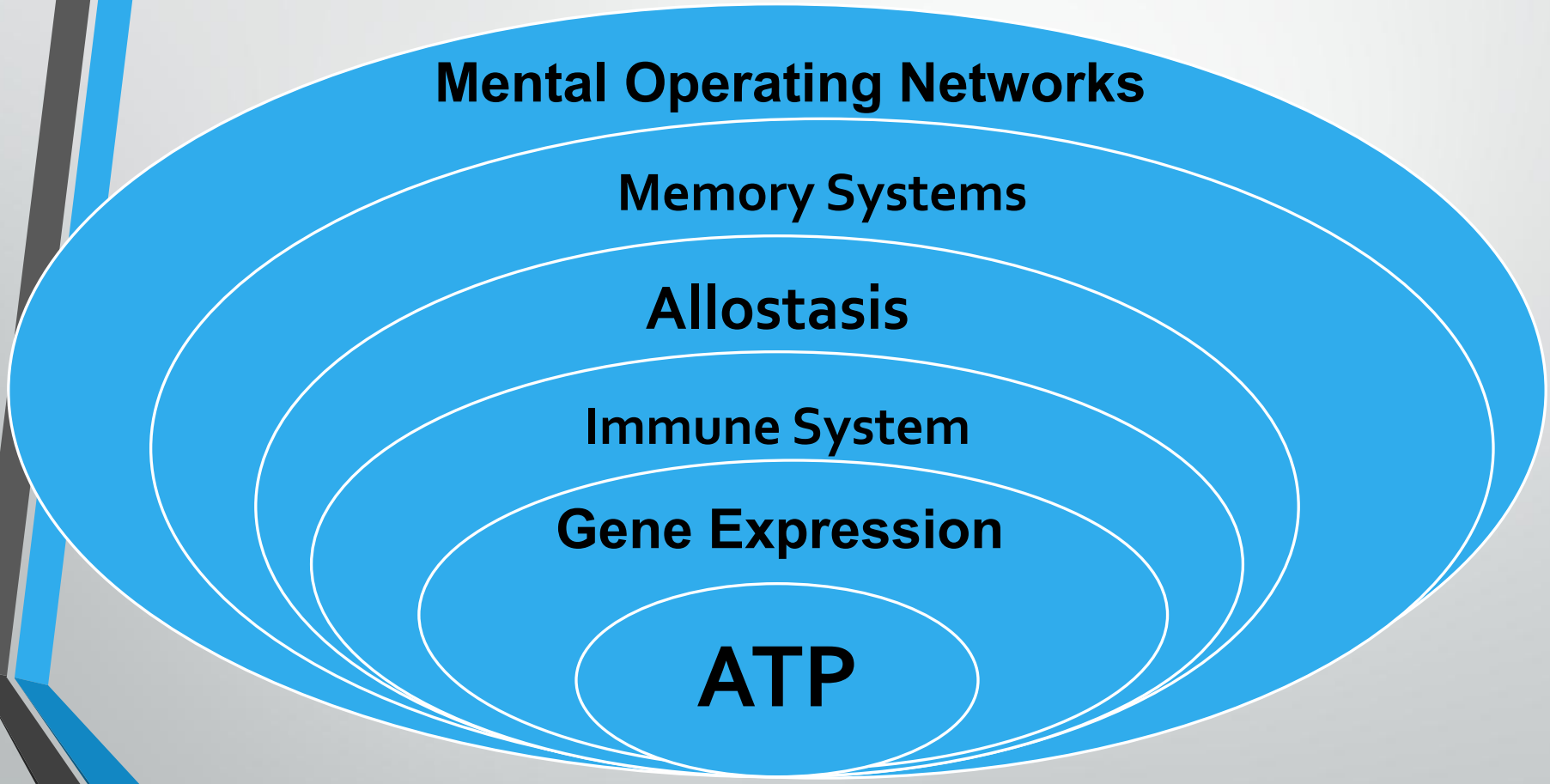
The Demise of the Medical Model

NIMH spent $20 billion of dollars, researchers have not found genetic risk for psychological disorders.

NIMH rejects DSM-5. The developers of DSM-IV also reject DSM-5 which was heavily funded by big Pharm.

"A system based on clusters of symptoms …not any objective, tested, reproducible, clinically actionable biomarkers for any psychiatric disorder."
(Insel, 2013)

“Self”-Organization



Free Energy Principle

- Minimize free energy
- Maximize energy

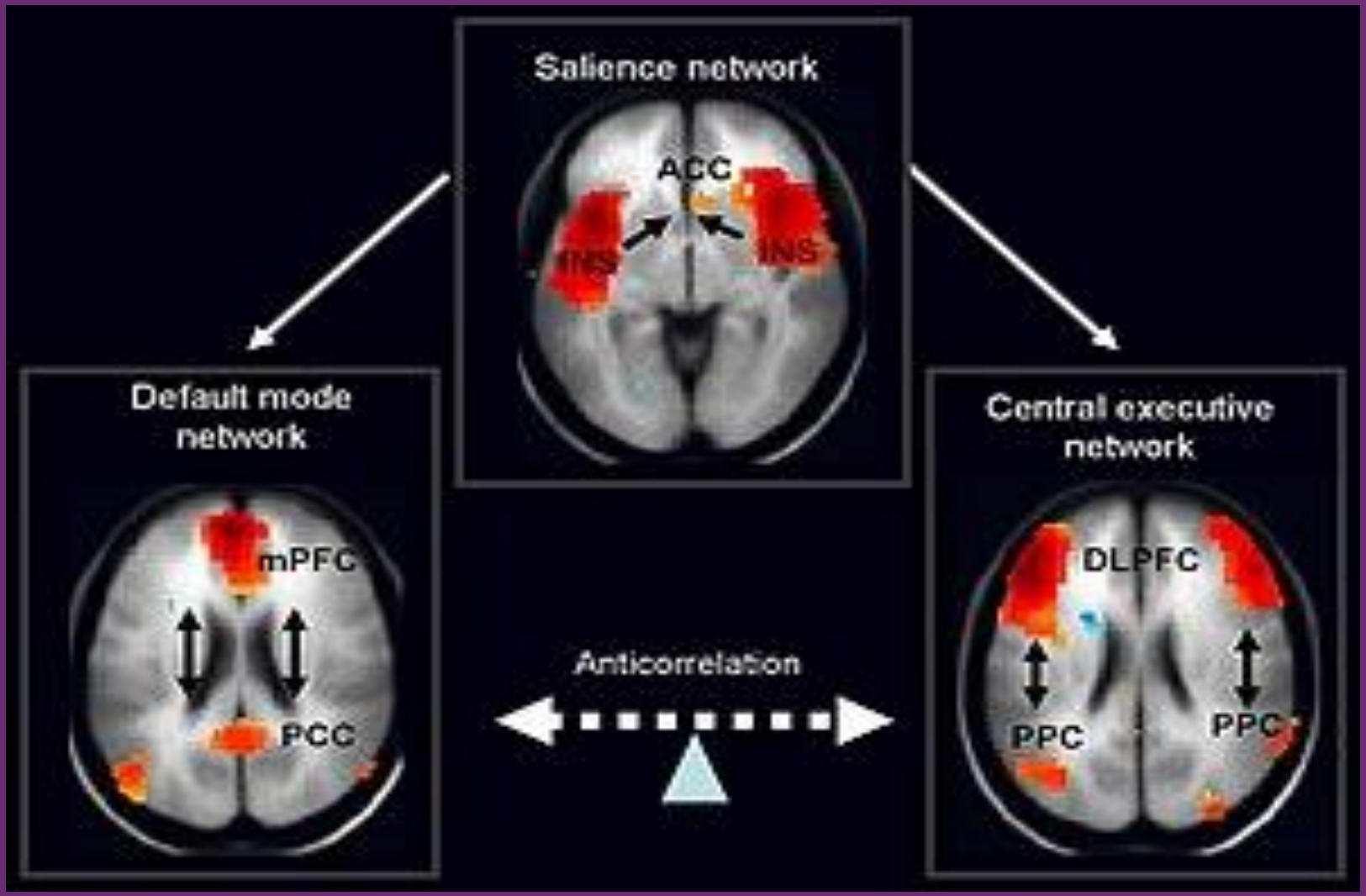
  efficiency
- Reduce uncertainty
- Prediction

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

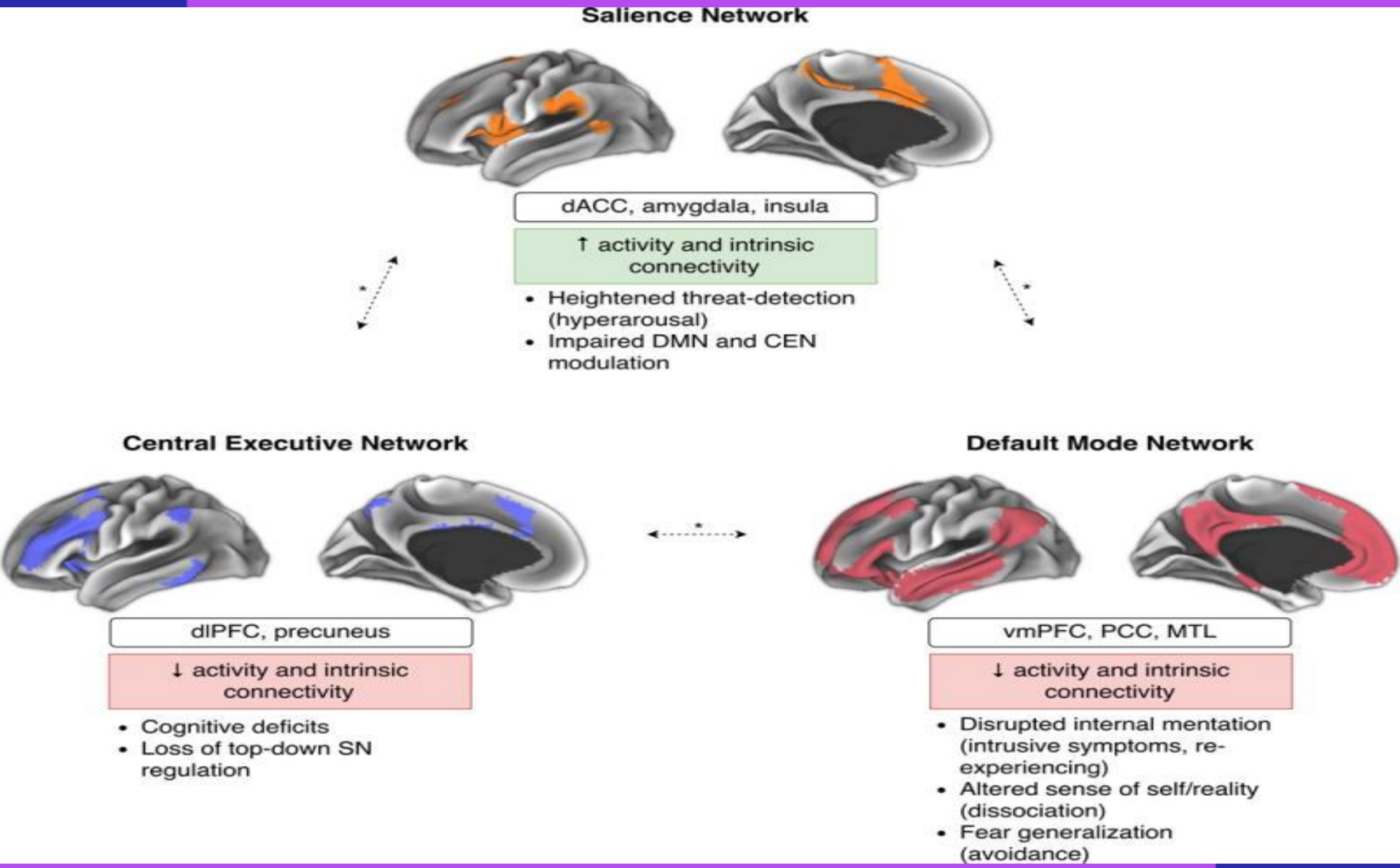
The Mental Networks



Life Satisfaction

- An indicator of brain flexibility and adaptability
- Self-construal (narrative) moderates the relationship
- Provides the infrastructure to minimize energy loss as we try to predict and adapt to new situations

States of mind in conflict



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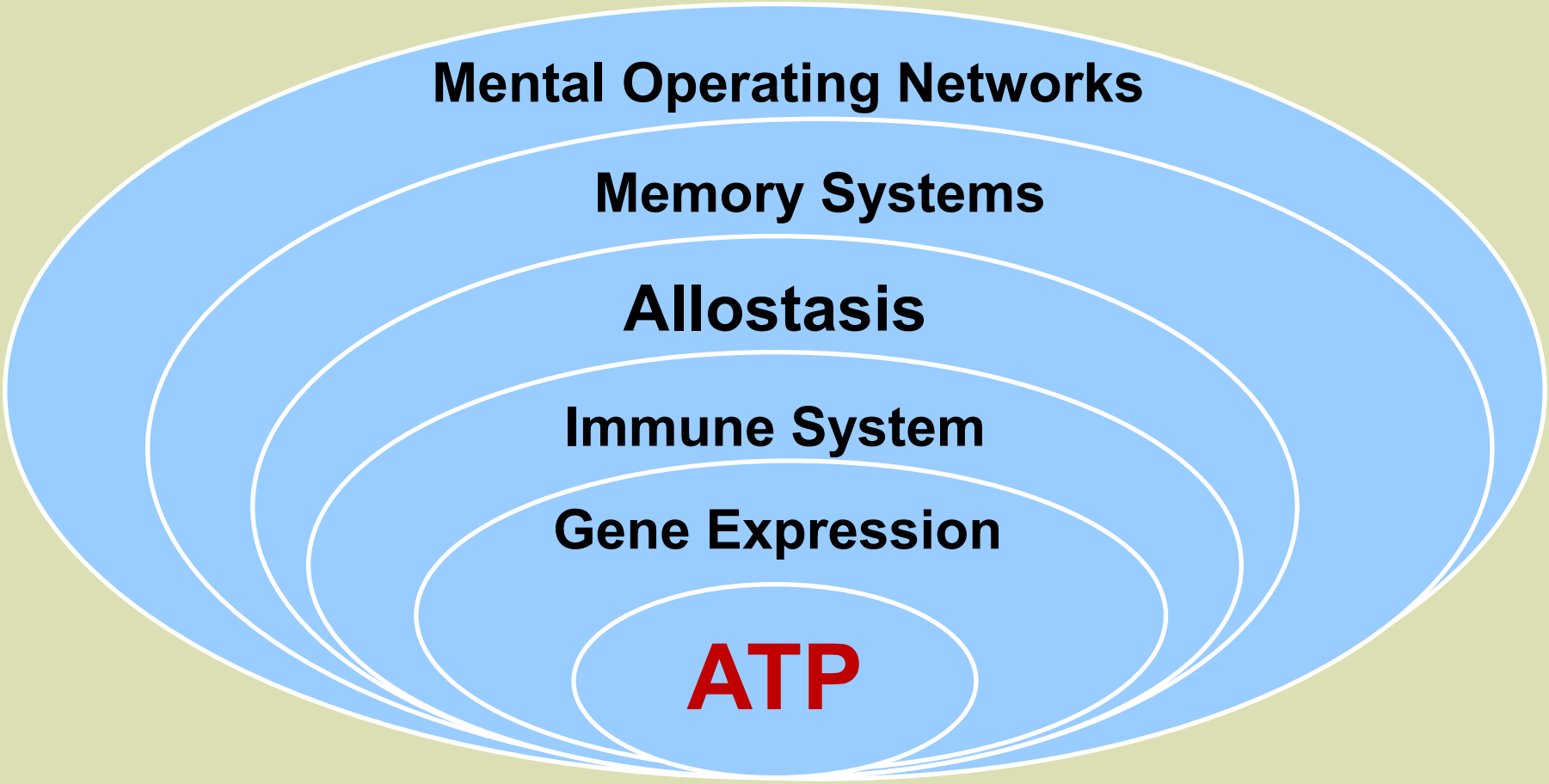
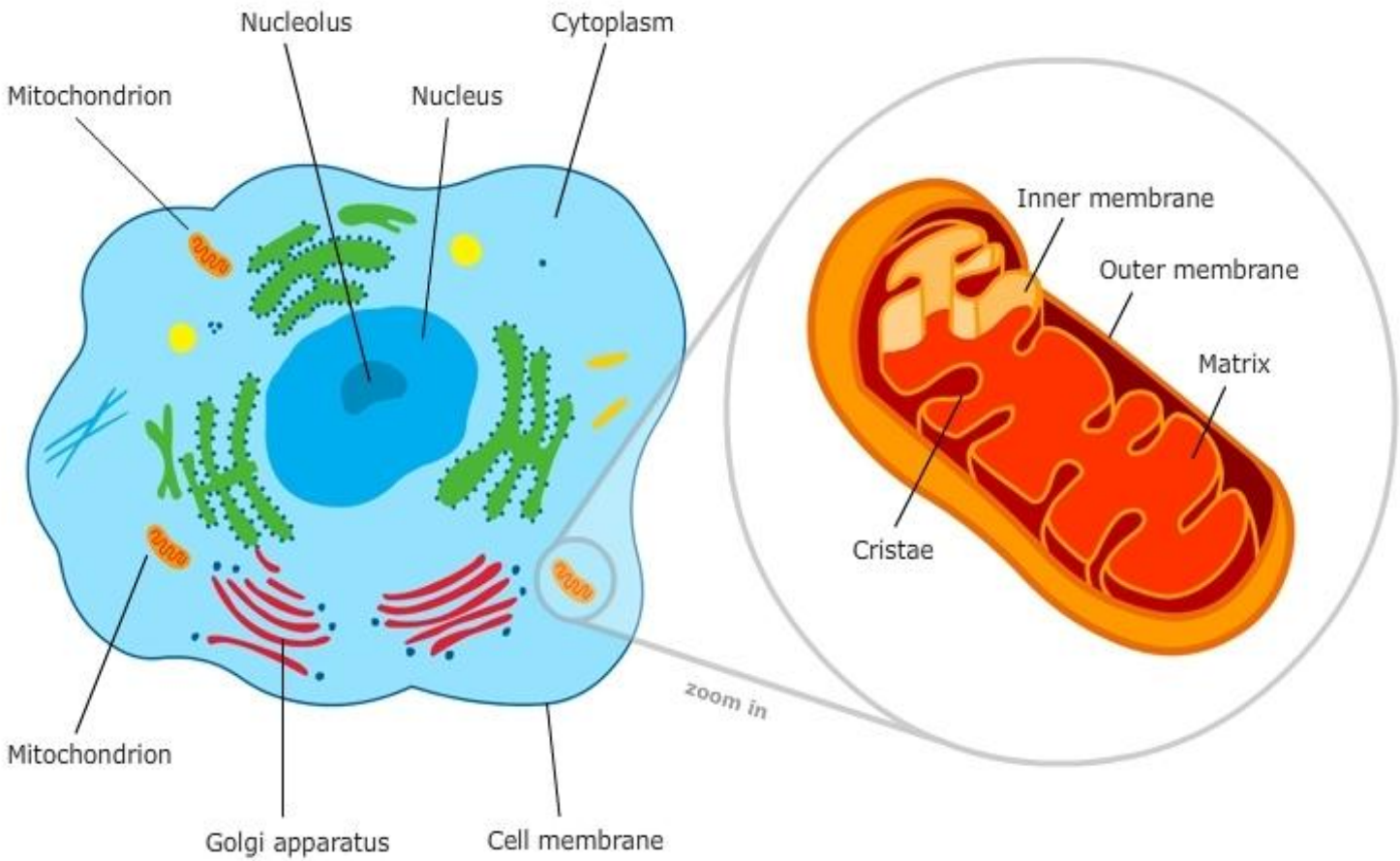
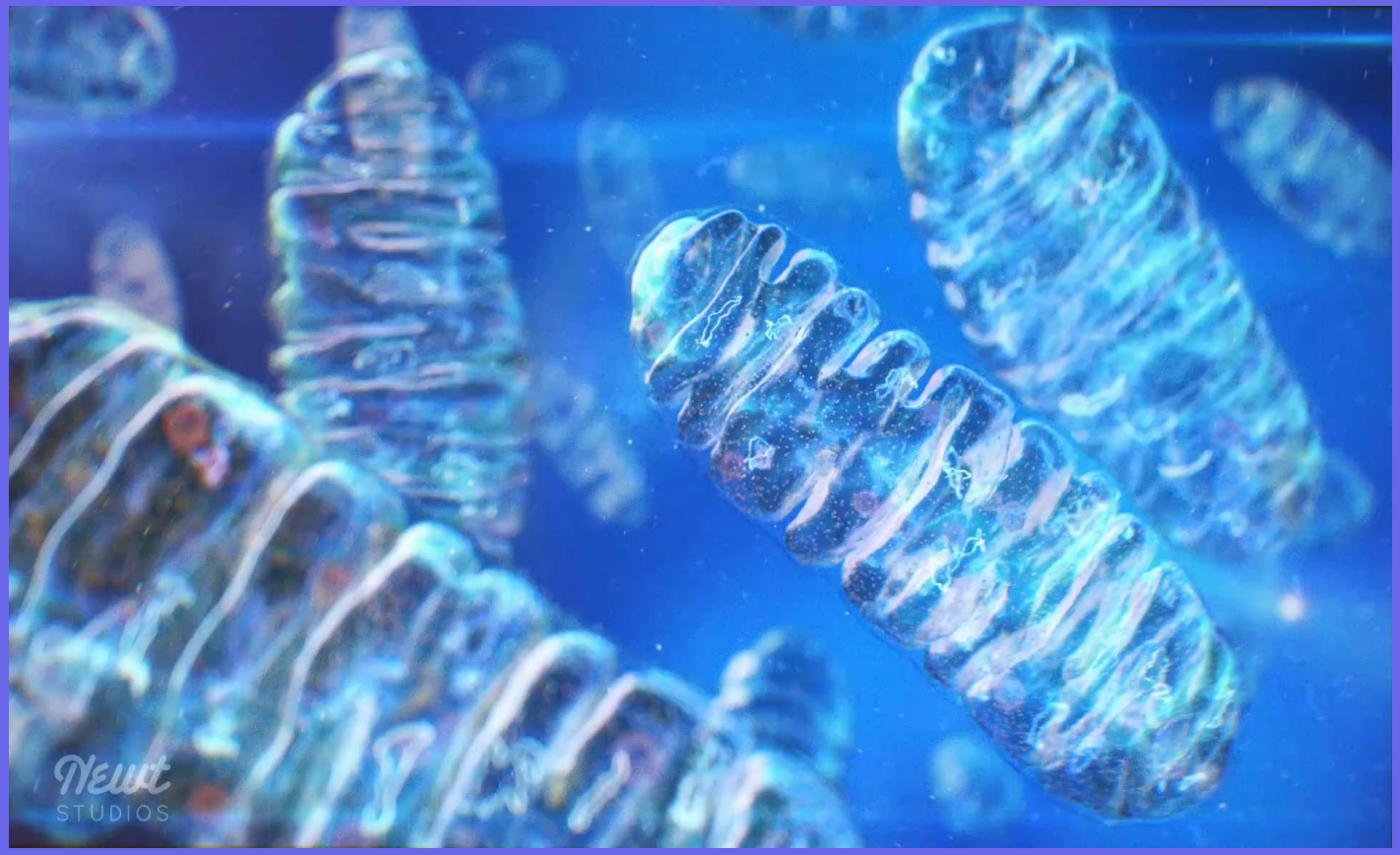


Cells and Their Energy Factories



Mitochondria: Our Energy Factories



Numbers of Mitochondria

- On average each of our cells host 500 mitos.
  - Roughly 10 percent of our total body weight.
- Energy needs: our heart and brain cells contain the greatest number of number of mitos.
  - There are approximately 10 million billion mitos in an adult human brain.

The Energy Generating Metaphor

Mitochondria, just like a dam, uses pressure in each step so that energy is released from electrons within the pump.

The biochemical reactions culminate with the final product, the synthesis of ***adenosine triphosphate*** *(ATP).*

Client Education

Because your energy generators are mighty: Call them ***Mitos***

They produce your principal energy: ATP for: ***All That Power***

Metabolic Energy = Life

- Energy production and use is called ***metabolism:***
  - Everyday a person's metabolism makes two hundred trillion trillion ATP molecules.
  - The rate at which the total number of ATPs are produced is a measure of your ***metabolic rate***.

Metabolic Rate

The metabolic rate is determined by how efficiently fuel is delivered to cells through our circulating system.

- Uses the right combination of oxygen, glucose, fatty acids, and sometimes amino acids to our mitochondria to produce ATP.

Energy Production

- ↑ food intake + Oxygen = ATP (energy)
  But with ↓ exercise --no demand for ATP
  And with regular oxygen ↑ free radicals

- When not enough antioxidants available:
  - Oxidation of lipids
  - Electron flow stops
  - More free radicals attack mtDNA
  - Cells fail to produce ATP and die

Cellular Reactive Oxygen Species (ROS)

- Like a flooding a dam endures the risk of leaks, so too can mitos excessively leak:
  - ROS, a type of free radical.
- When in excess, ROS can damage cells, including the mitos that produced it.
  - But, low levels of ROS can lead to gene expression of anti-oxidant enzymes which protect from cells damage.

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 (zombie cells)
  - –Cells are more vulnerable to disease
  - –DNA and mDNA more vulnerable to inaccurate gene expression

The Life Cycle of Mitochondria

- Mitos shelf life -- few days to a few weeks.
- They are recycled so that weak mitos are disposed of to insure quality of those that remain.
  - Removed by "***mitophagy***" ---killing off damaged mitos by mild ROS.
- Clears the way for mito ***"biogenesis."***

- **Poor self-care and ill health**
- **↑ flood of free radicals**

- Excessive fat cells ↑ ROS making all cells vulnerable to damage.
  - ROS and fat cells -- more likely with simple carbohydrates as fuel.
- The buildup of fat near mitos damages energy production.
  - Oxidative damage to the mitos spirals out of control.

Client Education

- Use it or lose it:
  - No exercise and overeating:
  - the dam leaks
  - ↑ flood of free radicals

Mobile Mitos

- Brain uses 20% of our body's energy, and our synapses use of 80% of that energy.
  - But, mitos at the synapses can only tolerate 25% drop in ATP before cognitive, emotional, and movement deficits.
- The energy fuels neuroplasticity by:
  - Mitos traveling on microtubules within our neurons to the synapses.

Mitochondria Burnout

- Mitos can burn out if the input and output is not balanced
  - Oxidative damage to:
    - Proteins
    - Lipids
    - mDNA
    - mito dysfunction.

Exercise and Biogenesis

- Aerobic exercise increases mitos in muscle cells by to 50% in 6 weeks.
  - ↑ ATP and ↓ ROS.
- ↑ biogenesis when ATP used up,
  - Number and size of healthy mitos increase to enhance energy production.

Diabetes of the Brain" - "Type 3 Diabetes."

- Insulin resistance and type 2 diabetes increase the risk of Alzheimer's and Parkinson's diseases.
  - "Insulin resistance in the brain leads to wide spectrum of neurogenerative impairments.
    - increases in free radicals, i.e superoxide,
    - low energy (ATP),
    - inflammation,
    - cell death,
    - neurotransmitter dysregulations.

Fat Cells and ROS

- Poor self-care and ill health leads to a flood of free radicals—a nonlinear tsunami.
  - Excessive fat cells, ↑ROS
    - makes all cells vulnerable.
  - Buildup of fat located near mitos causes damage to energy production.

Client Education

- Supply and demand is different for a athlete than it does for a couch potato.
  - Don’t assume that consuming more calories will give you energy
    - The reverse is true.
      - Overeating *decreases* energy.

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

Anaerobic Metabolism -- Shift

- Childhood-- for the growth our body.
- Adulthood – to no growth just but maintenance
    - Along with less aerobic capacity
    - We risk of building the wrong type of cells:
        - extra fat cells and less energy to burn it off.

Exercise & Biogenesis

- Using ATP up:
  - Prevents excessive free radicals.
  - Expands the number and size of healthy mitos
  - Increases biogenesis
    - All for more ATP!

Client Education

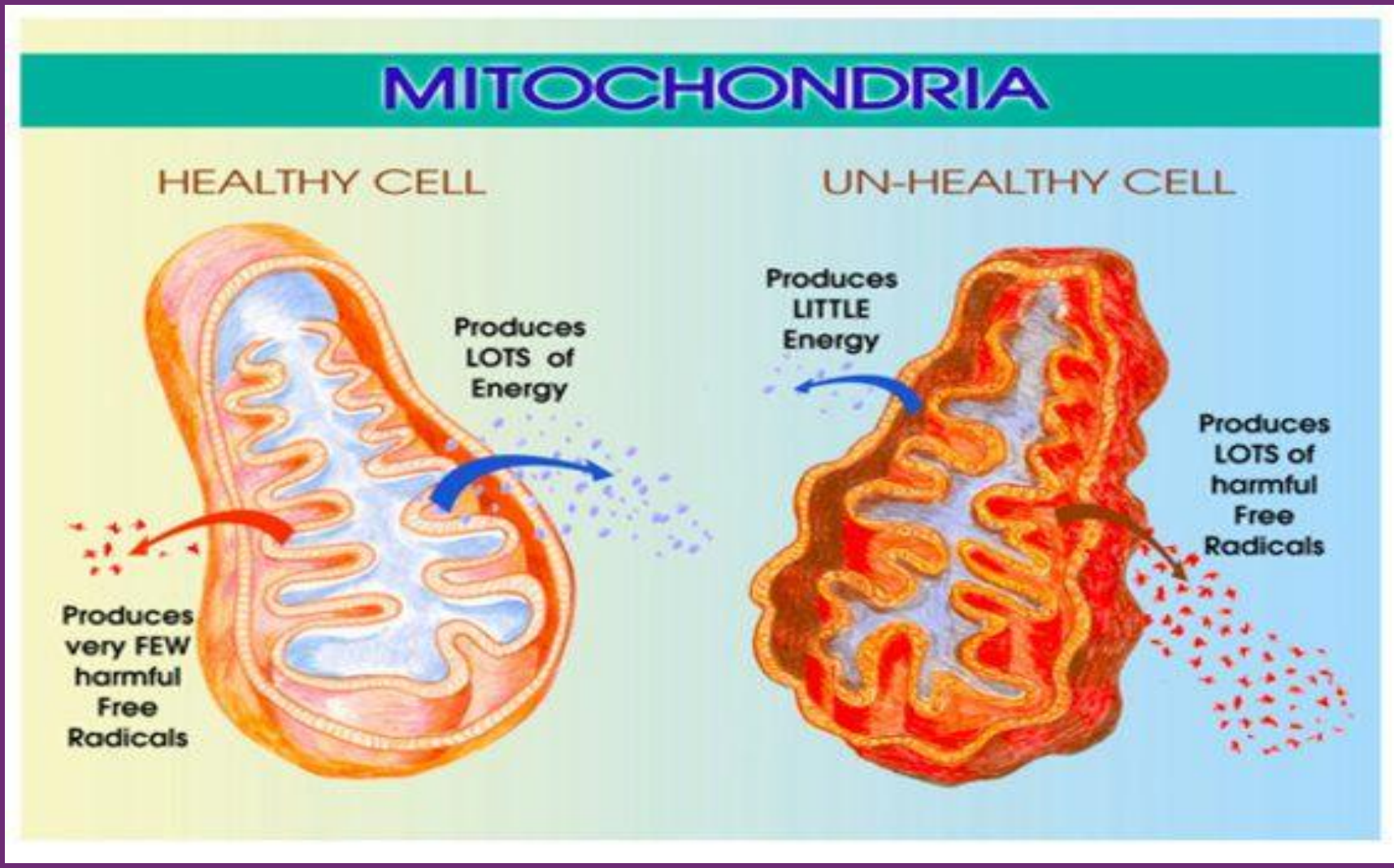
An Inflammatory Diet includes:

- Simple carbohydrates
- Saturated fats
- Trans fatty acids
- Processed foods

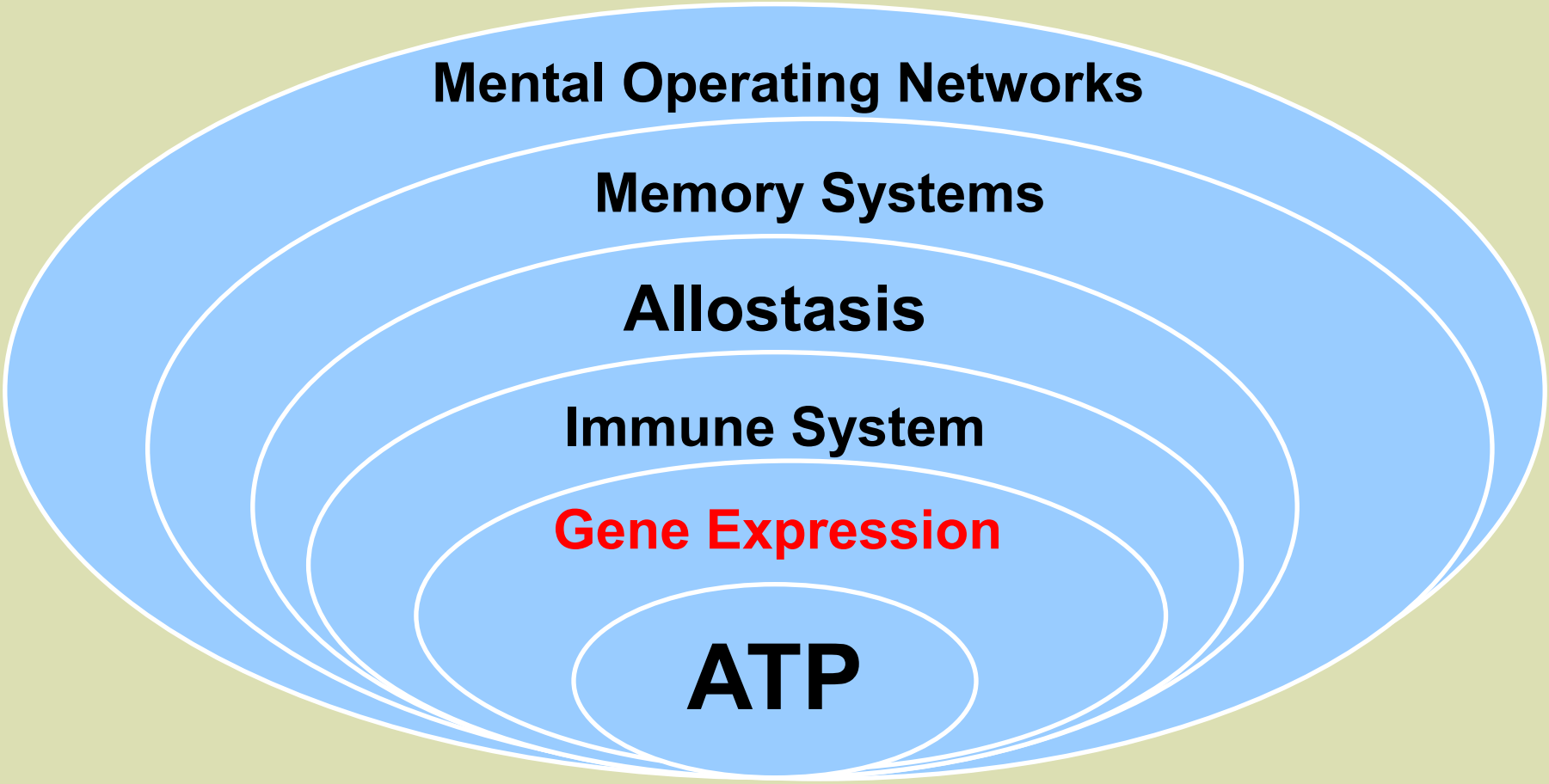
Resulting in a greater risk for:

- Metabolic syndrome
- Diabetes
- Dementia
- Cancer.

Free Radical Damage

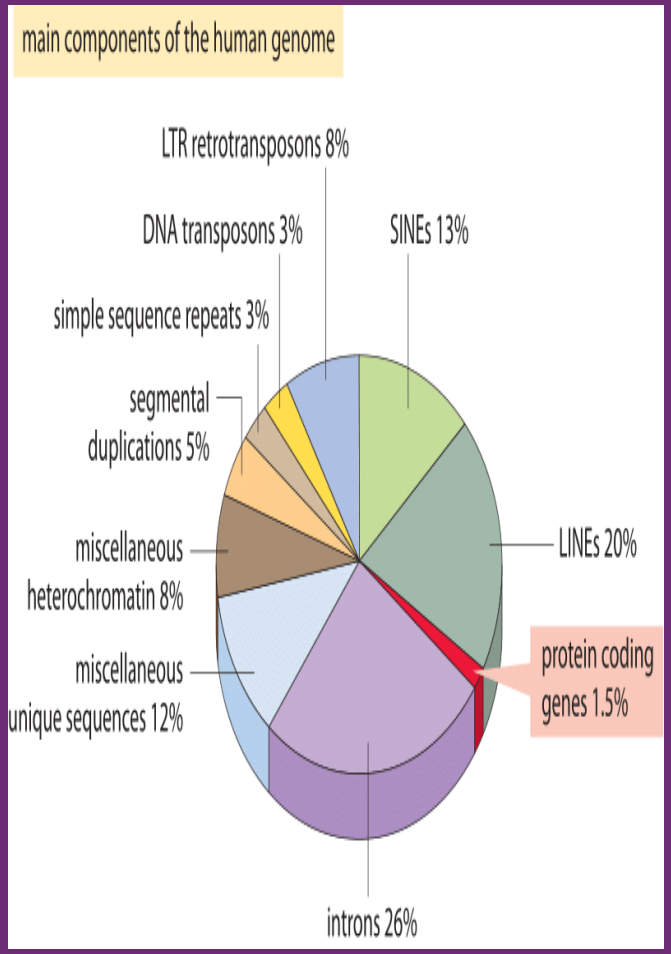


“Self”-Organization

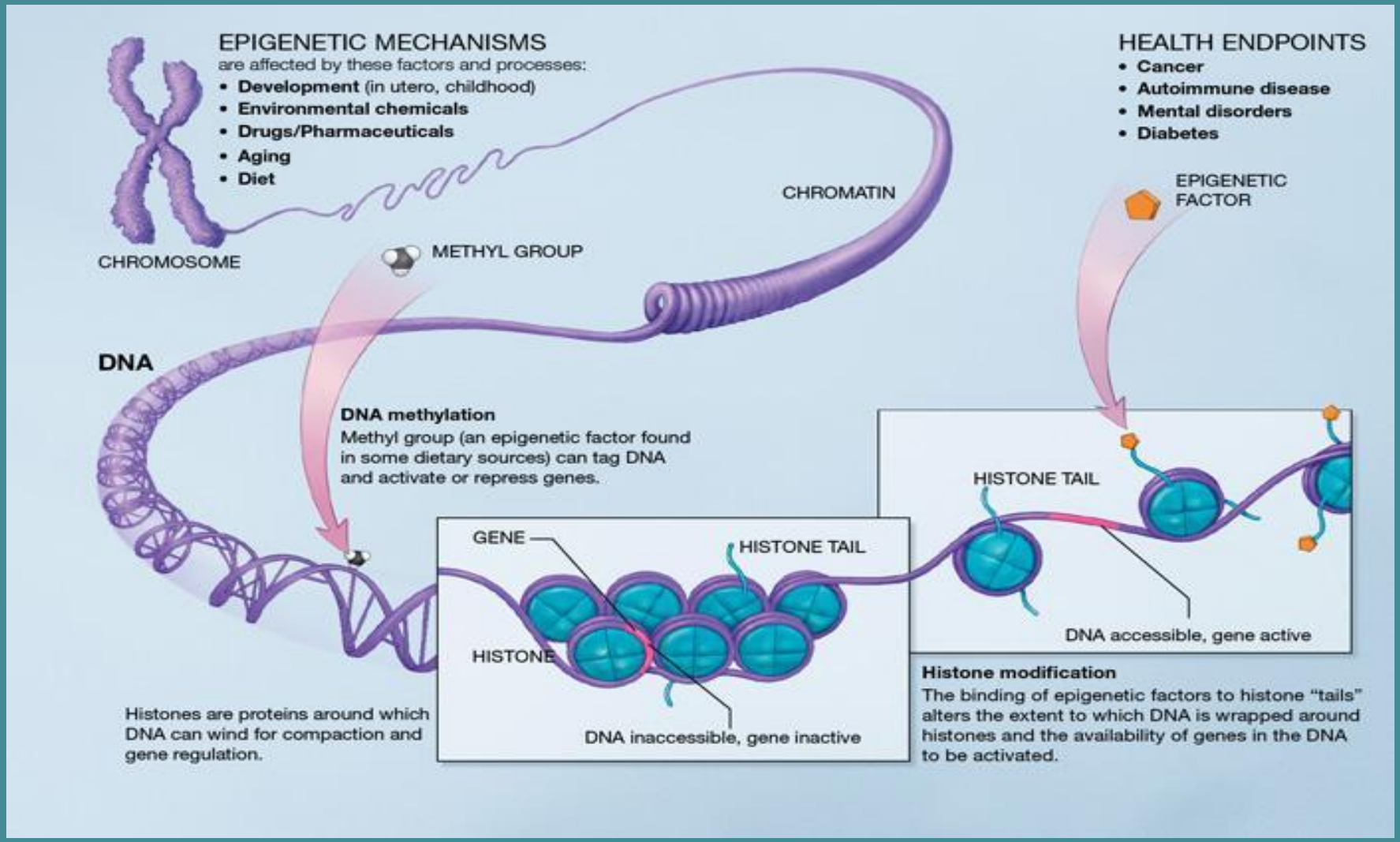


Epigenetics

- 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



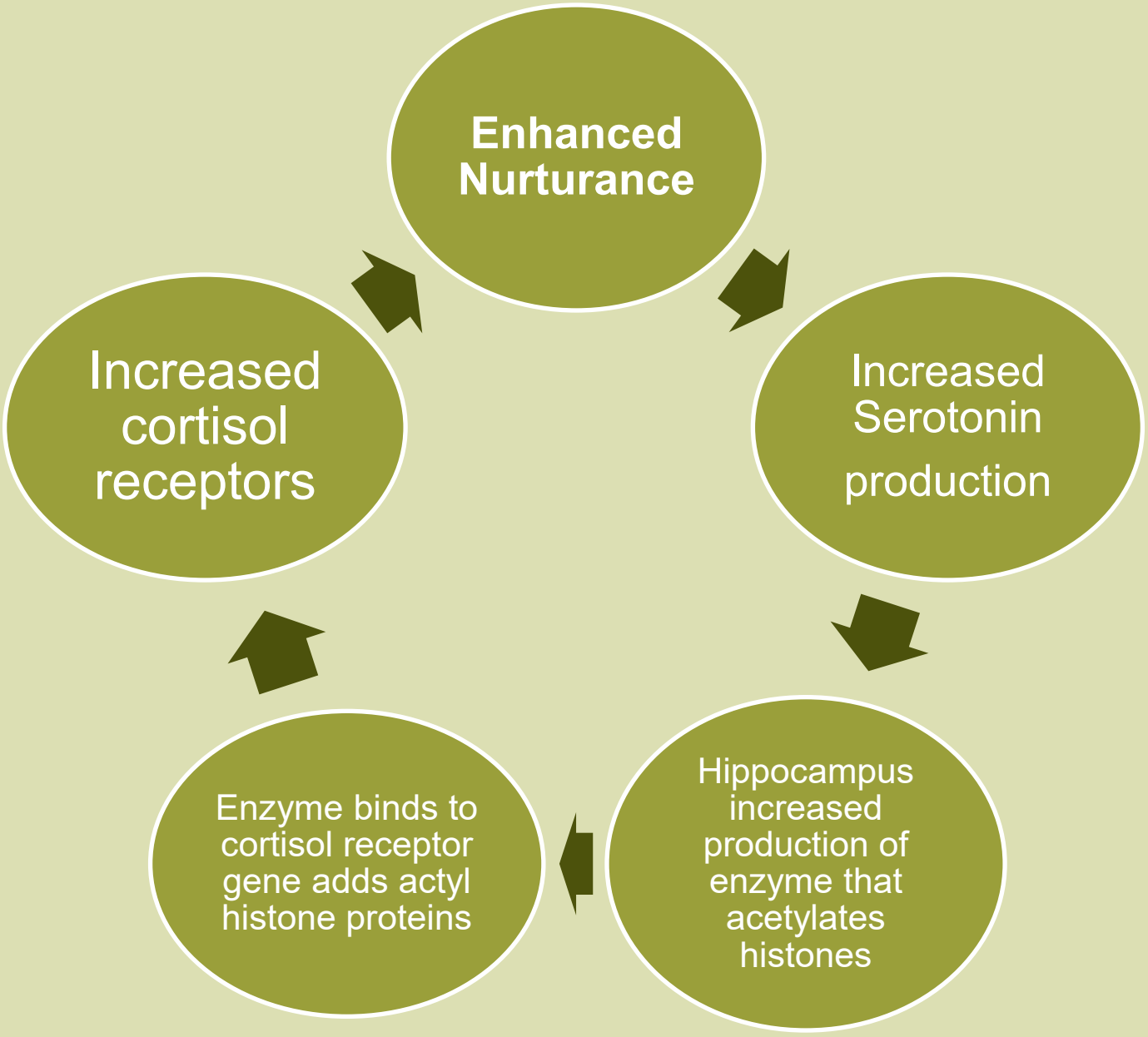
Epigenetics in Gene Expression

- 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

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



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

SEVERE NEGLECT:
Persistent Neurobiological Changes

- **Decreased serotonin**
  irritability; reduced emotional control
- **Increased CRF:** ↓ deep sleep; agitated depression; anxiety
- **Decreased Oxytocin:** attachment problems

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

- 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, predictive of mortality and genetic impairment (Epel, 2009, Current Directions)
- •Telomeres: non-coding sequences (AKA "junk DNA") 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)

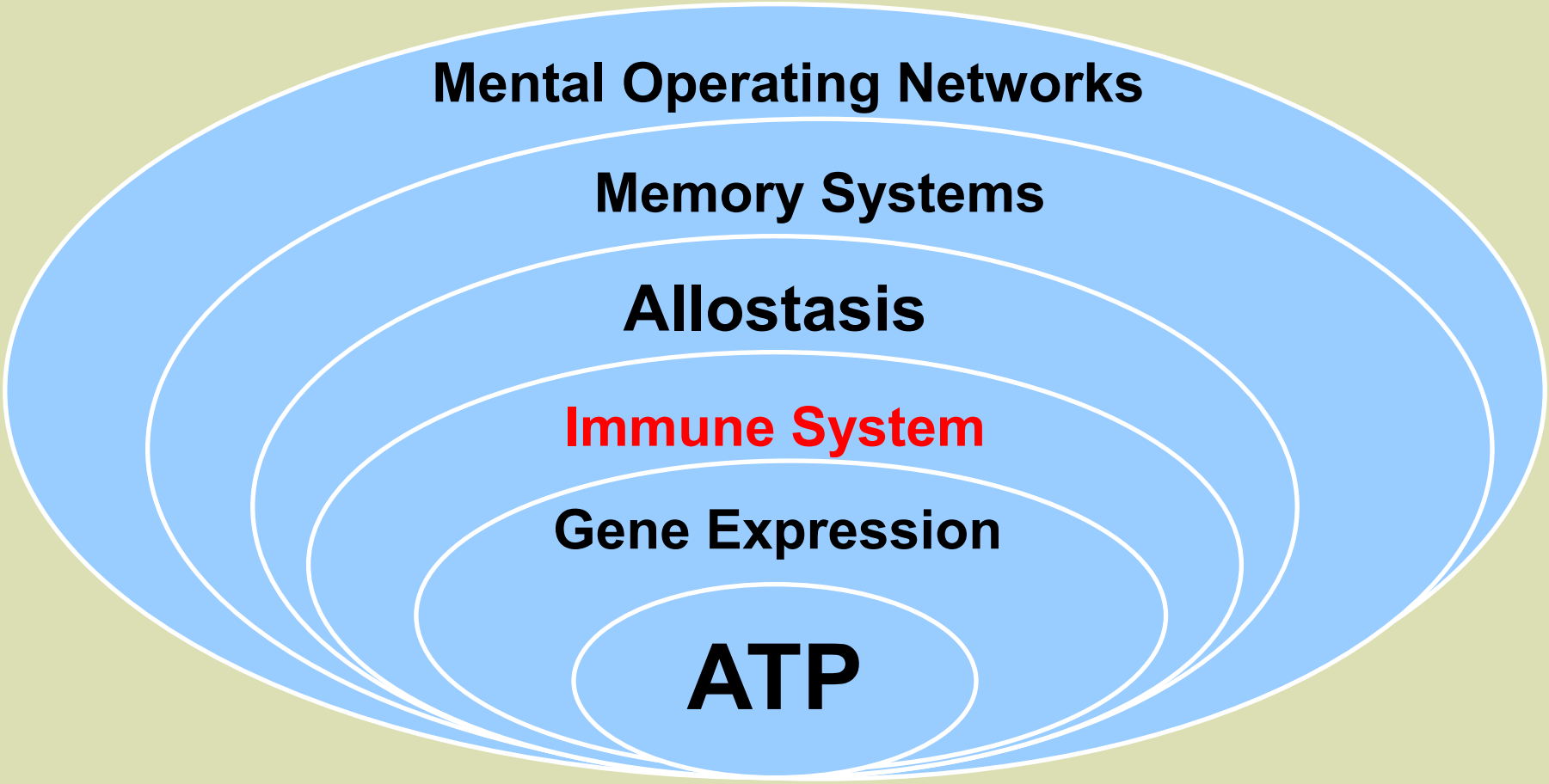
Factors that Impair DNA and Cells

- 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

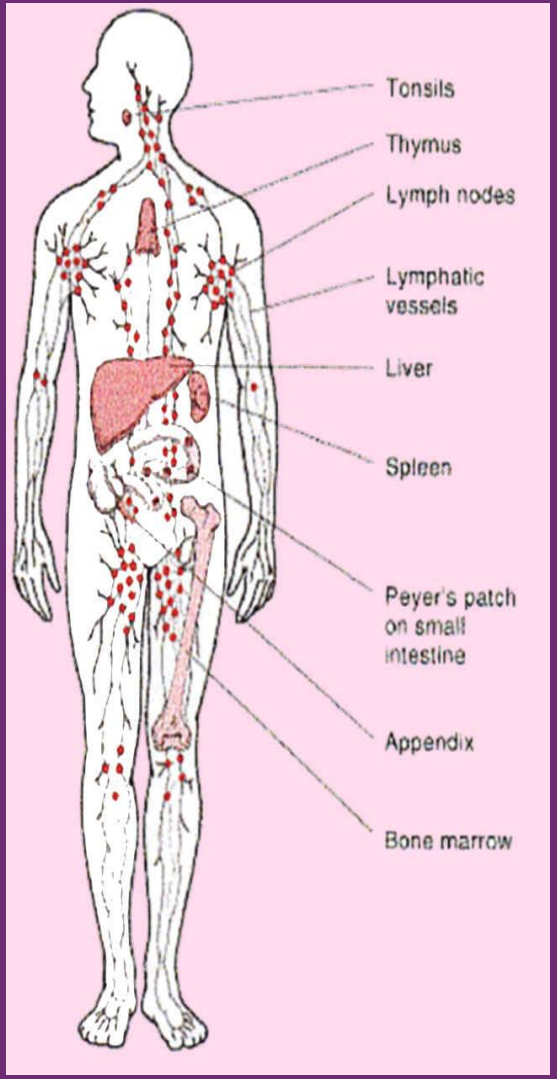
- Aging
- Cardiovascular disease
- Smoking
- Obesity (more than smoking!)
- Type 2 Diabetes
- Social isolation
- Poor diet
- No exercise
- Poor sleep
- Alcohol and other drugs
  - **All rendering DNA vulnerable to damage**

“Self”-Organization

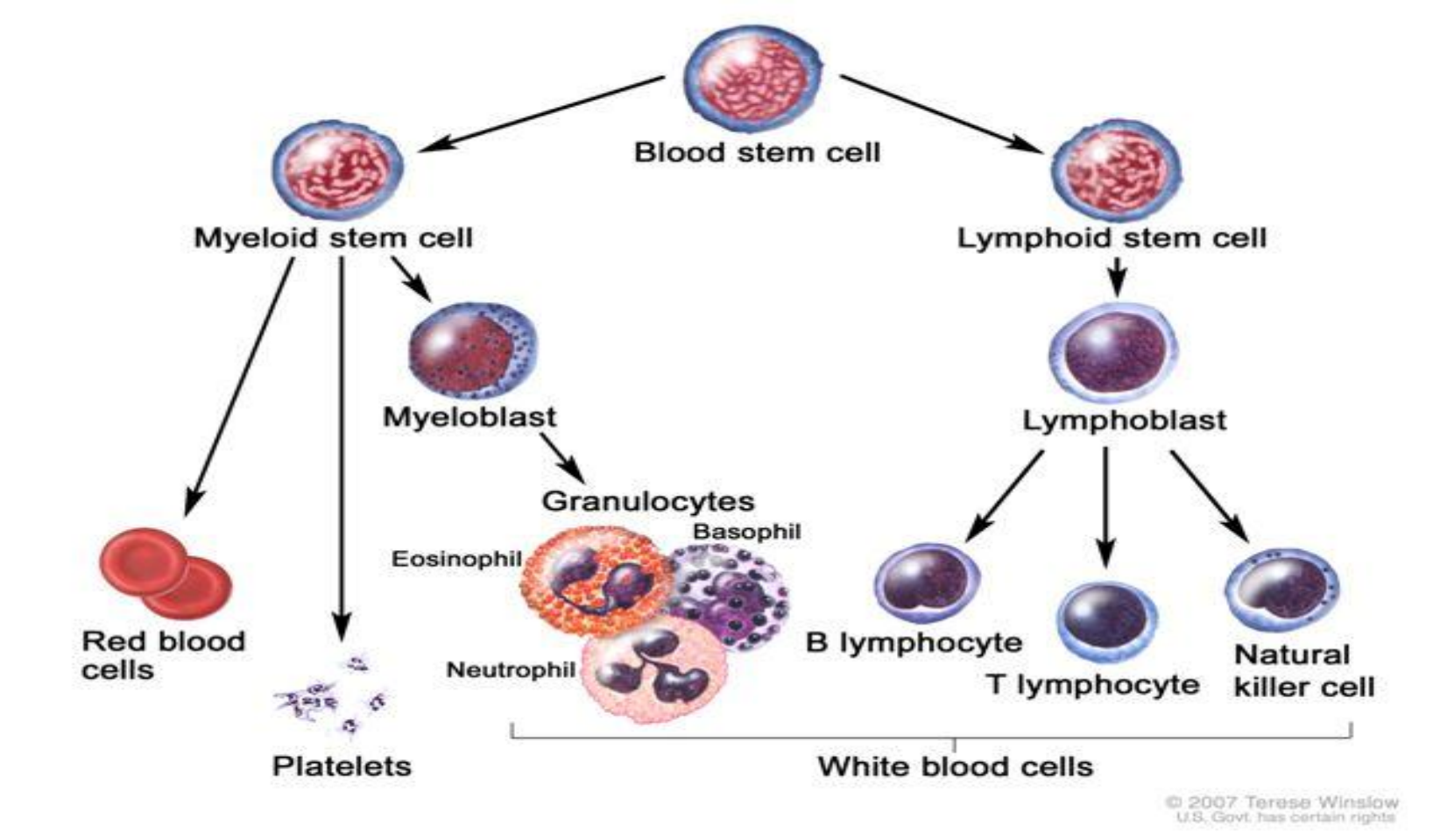


Components of the Immune System

- Lymph vessels and lymph nodes — filtering system for the lymph. WBCs lie in wait for foreign substance to destroy
- Bone marrow — origin of WBCs
- Thymus — where T cells differentiate into functioning cells from precursors
- Spleen — filtering system for the blood
- Other organs — gastrointestinal tract has Peyer's patches with high density of WBCs, respiratory tract has tonsils, skin, etc.



Me not Me Detection System



B and T “true” memory cells

Short Term Stress Can Suppress Immune System

Increased stress: (Kiecolt-Glaser/Glaser):

- Suppress T cell function
- Suppress natural killer cell function
- Suppress lymphocyte proliferation
- Reactivate latent viruses (herpes simplex virus; Epstein Barr virus)
- decreased ability of cell to repair broken DNA.
- Lower antibody response when vaccinated.

T cells attack a virus

*effects also seen in bereavement, divorce, and other stressors

Stress

Activation of corticotropin releasing hormone (CRH):

- Contributes to delayed gastric emptying
- Increased colonic activity
- Functional bowel disease (IBS)
- Increase in gut permeability
- Leaky gut – antigens leaking out
- Toxic liver overload
- Systemic disease

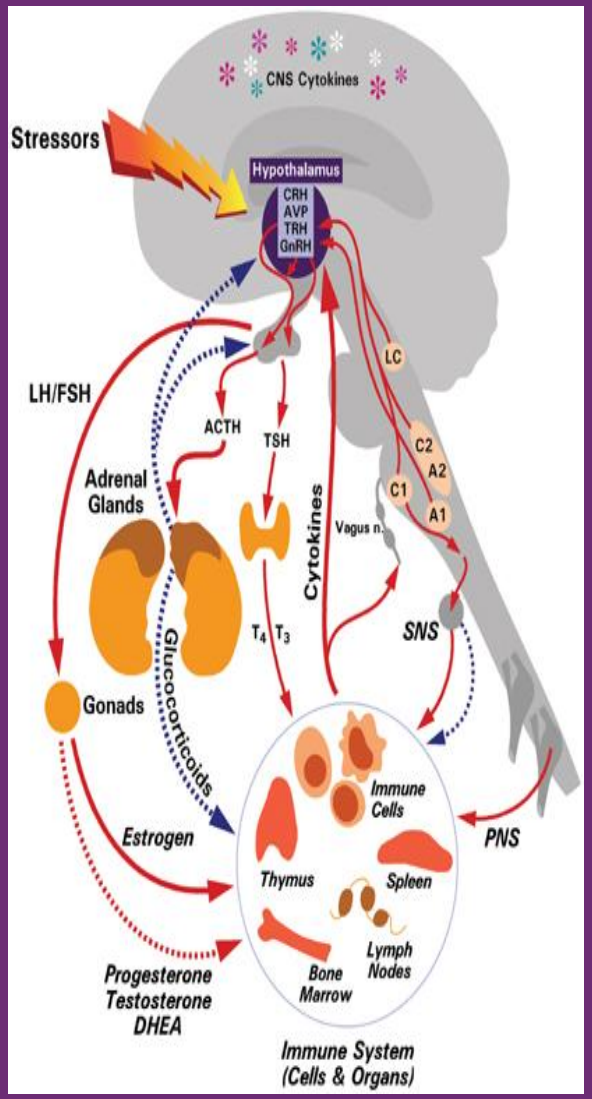
The Brain Controls the Stress Pathways

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



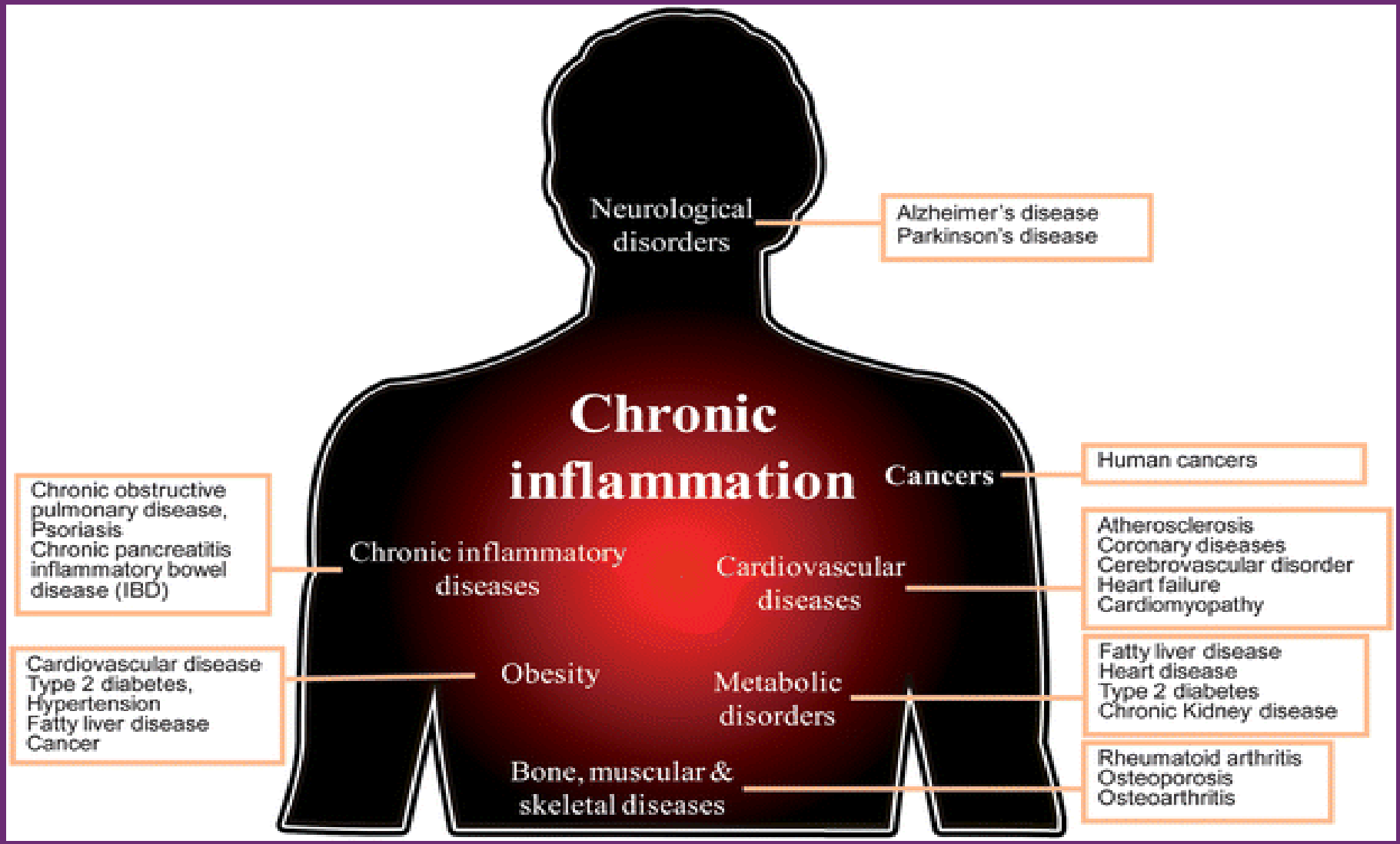
The Immune System Can Affect Your Emotions:

- 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)

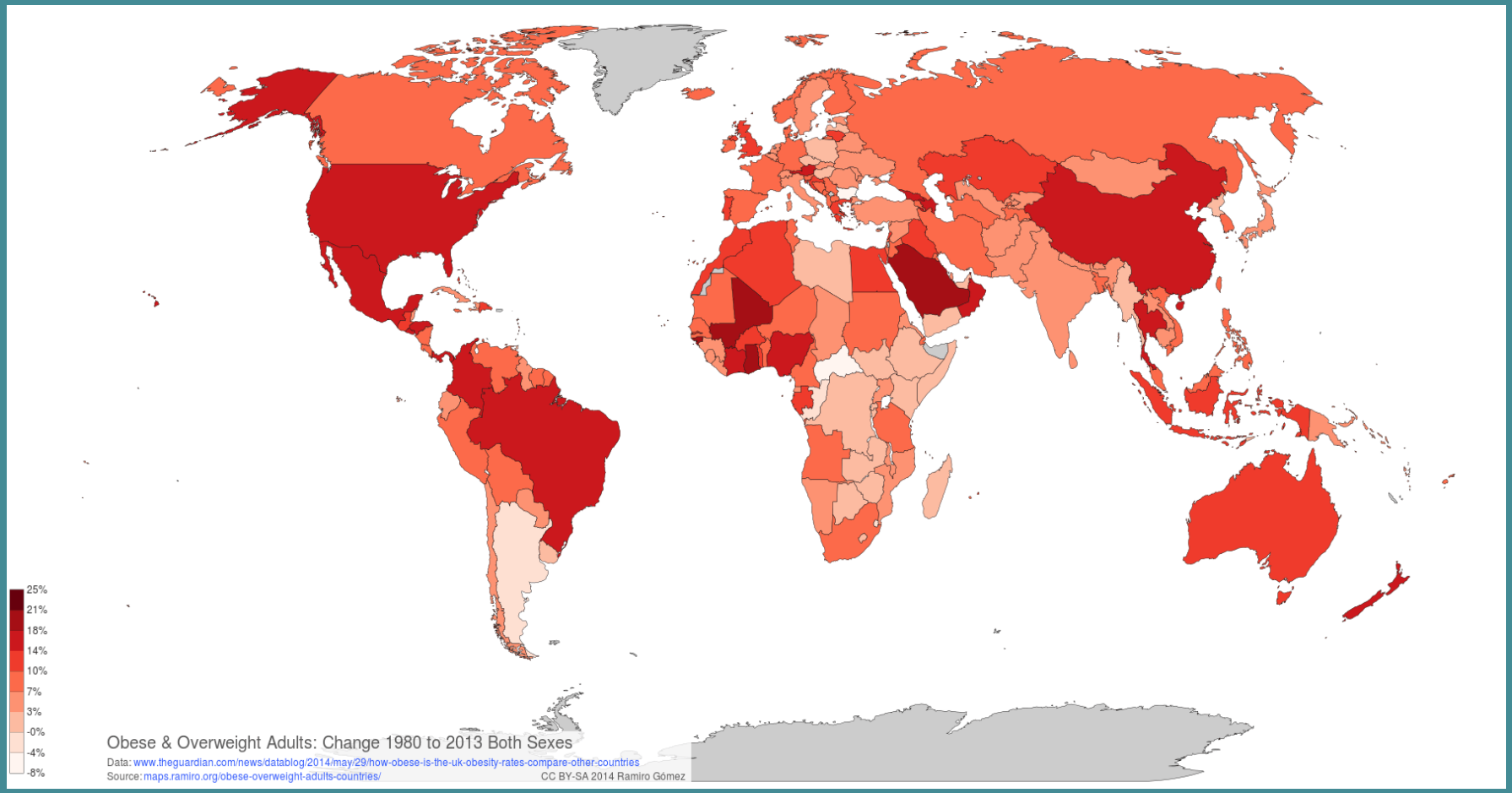
Pro-inflammatory Cytokines

- 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).

Inflammation in the Mainstream

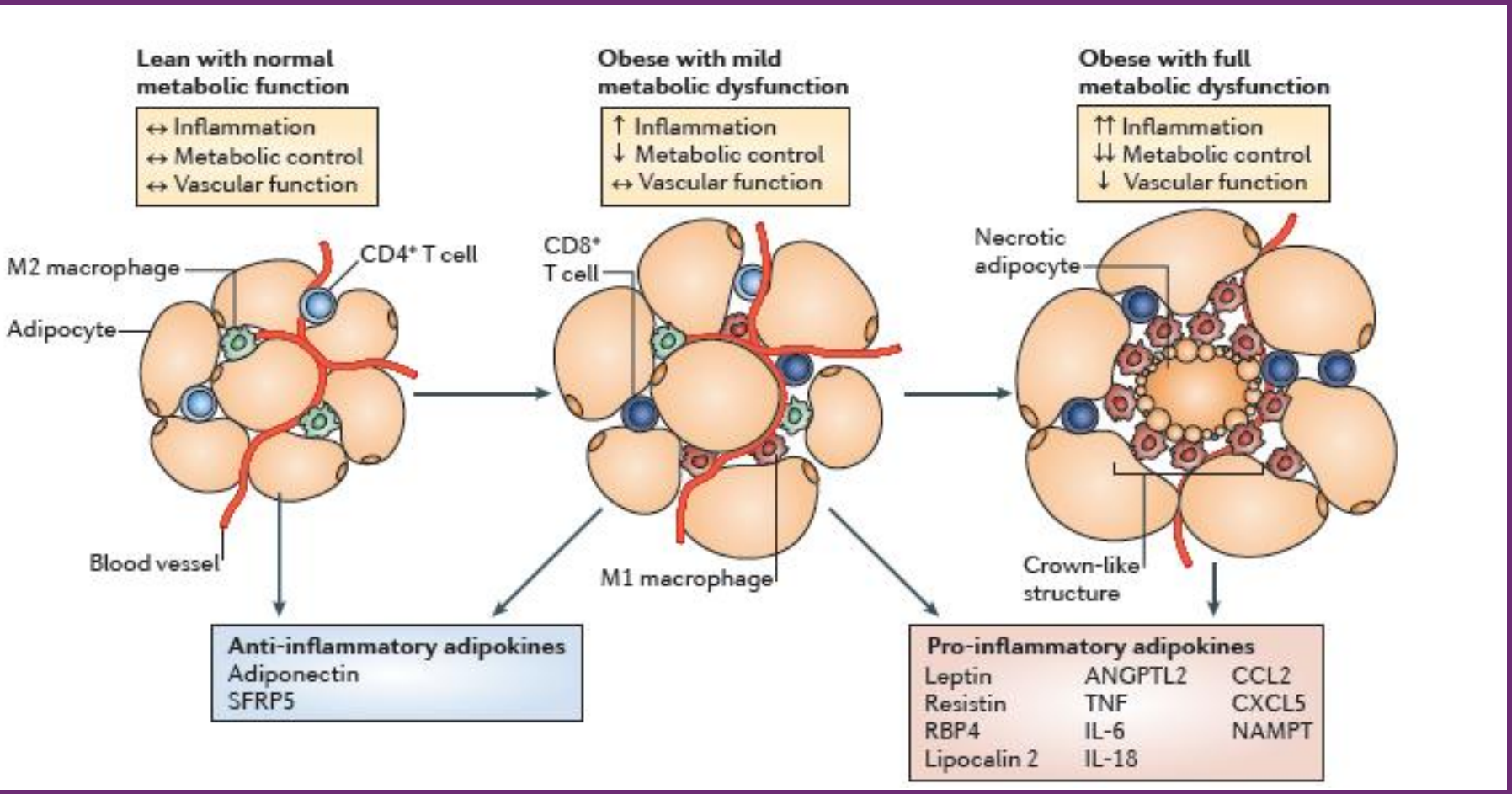

Neurological disorders
Alzheimer's disease
Parkinson's disease
Chronic inflammation
Cancers
Human cancers
Chronic obstructive pulmonary disease,
Psoriasis
Chronic pancreatitis
inflammatory bowel disease (IBD)
Chronic inflammatory diseases
Cardiovascular diseases
Atherosclerosis
Coronary diseases
Cerebrovascular disorder
Heart failure
Cardiomyopathy
Cardiovascular disease
Type 2 diabetes,
Hypertension
Fatty liver disease
Cancer
Obesity
Metabolic disorders
Fatty liver disease
Heart disease
Type 2 diabetes
Chronic Kidney disease
Bone, muscular & skeletal diseases
Rheumatoid arthritis
Osteoporosis
Osteoarthritis

The Pandemic



Obese people over 40 will die 6-7 years earlier

Obesity-Associated Adipose Tissue Inflammation

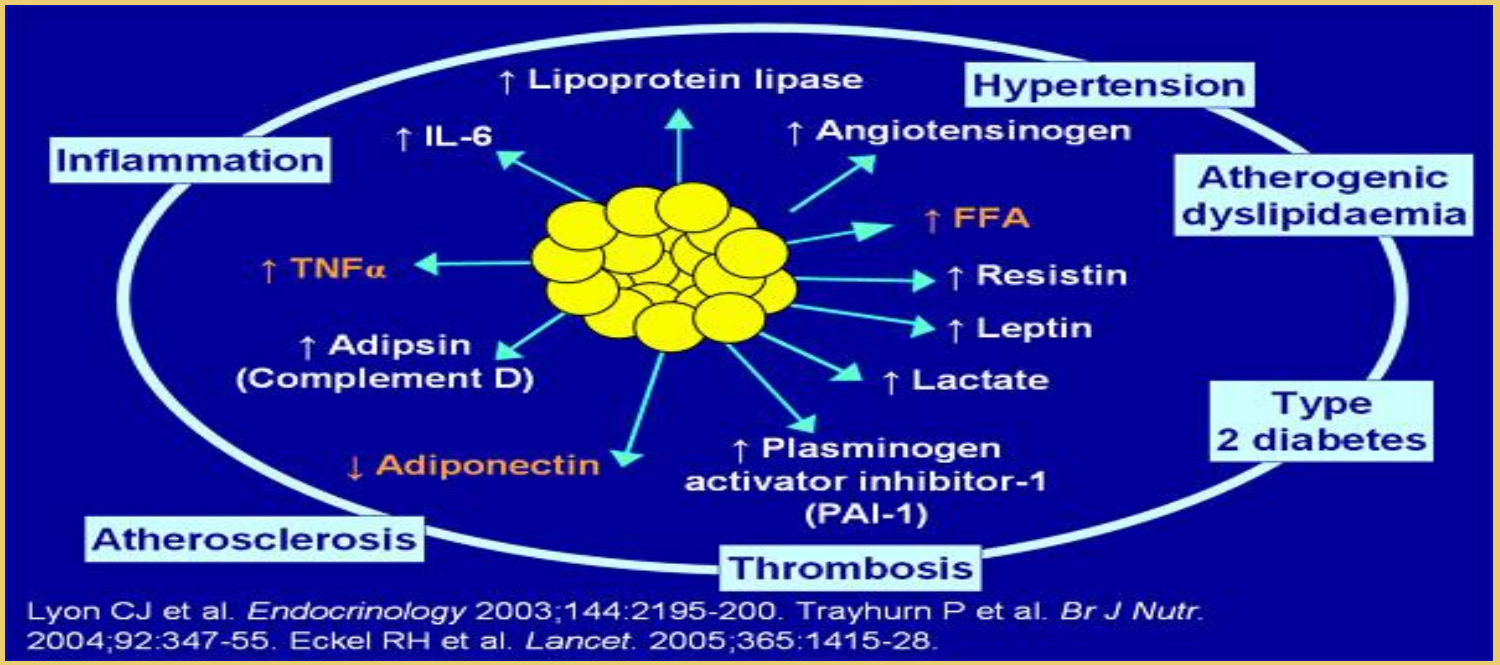


INFLAMMATION

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

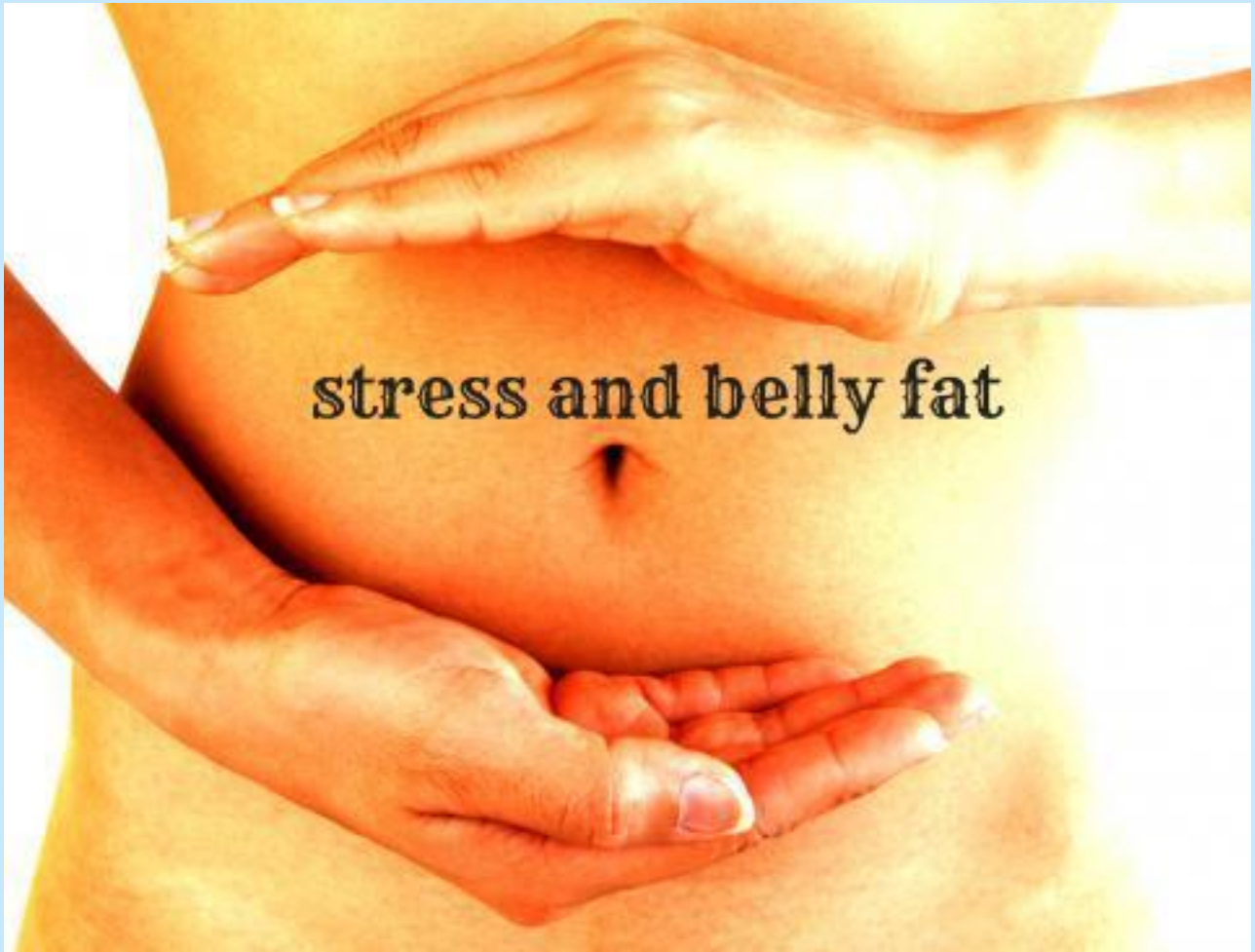
Belly fat generates inflammation by releasing proinflammatory cytokines

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

  to gain weight

  go for the pear not the apple shape

Increased health risks *and* Stores inflammatory cytokines



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.

WHO—World Population 7,505,257,673

- 4.7% with diabetes in 1980
- 8.5% with diabetes in 2014
- 10% forecast 2035

- Obesity Population: 774,000,000

Pre-diabetes

- Occurs when blood glucose levels higher than normal but not yet high enough for dx of diabetes
- According to the CDC-- 86 million
- Most develop type 2 diabetes in 10 years unless:
  - Lose 5 to 7 % of body weight
  - Make major changes to diet
  - Increase exercise diet

Diabetes and Psychological Disorders

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

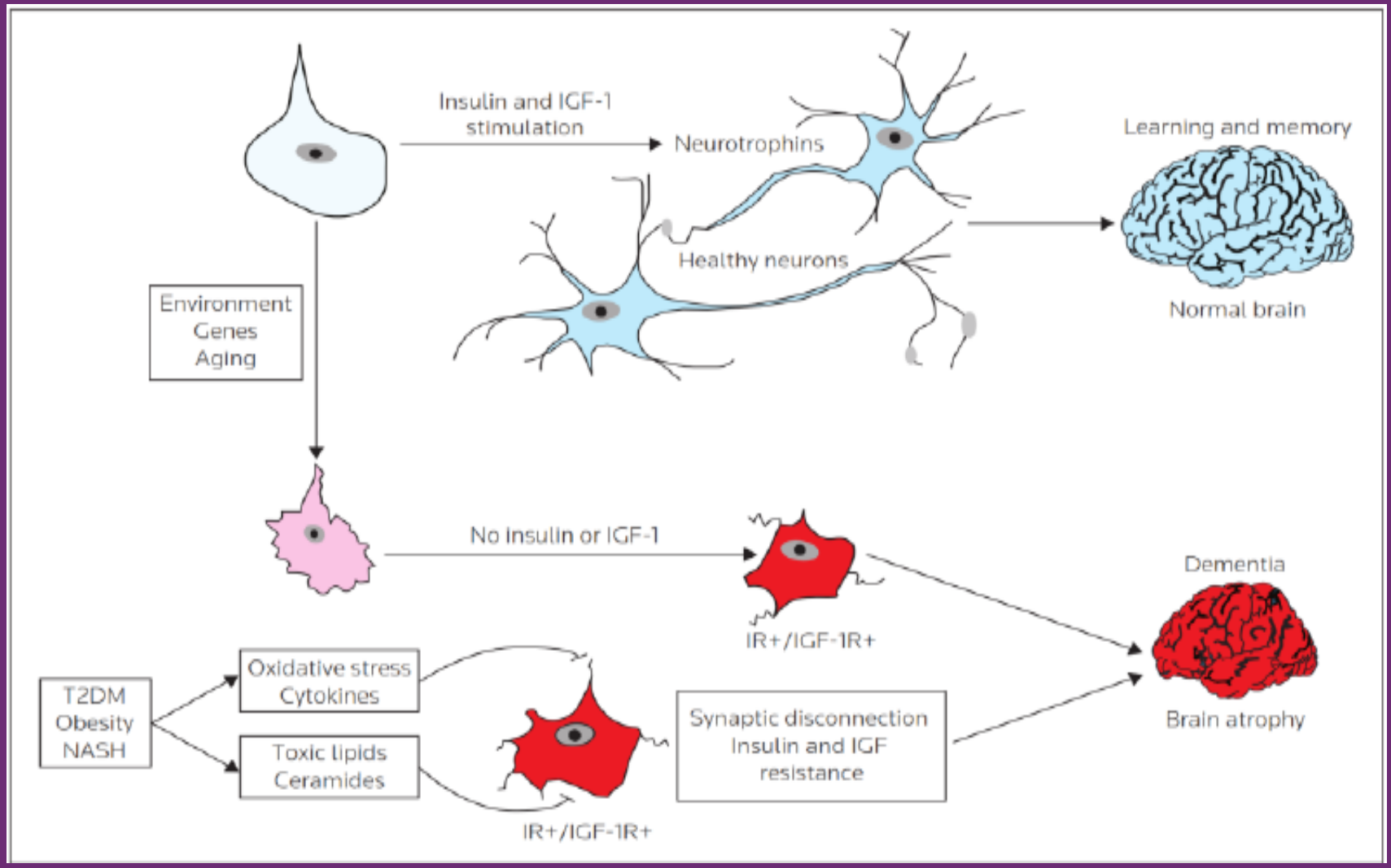
Stress and Diabetes

- Cells need glucose for fuel—This is insulin's principal job
- The body needs more fuel when stressed
- ↑ adrenaline and cortisol ↑ blood glucose
- ↑ cortisol triggers the breakdown of protein to glucose
- Excessive cortisol results in too much glucose floating around
- Thus, ↑ risk of insulin resistance –Diabetes II

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



Diet, inflammation and Pre-diabetes

- -increased markers of inflammation e.g. cytokines, CRP

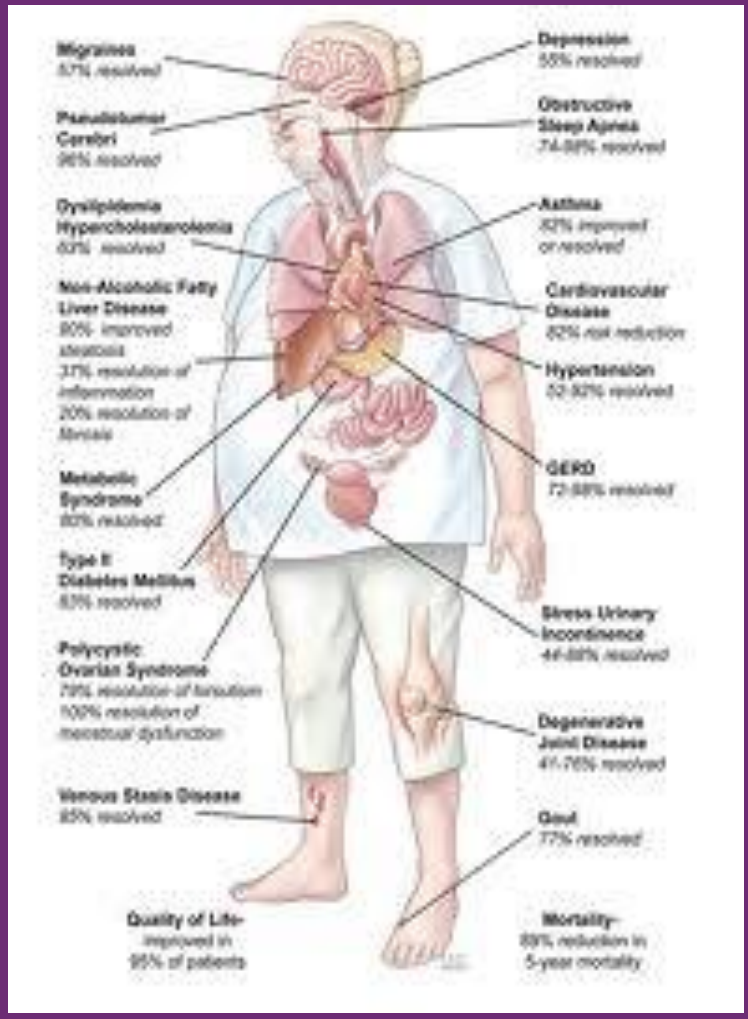
- -increased fasting blood glucose, elevated
- -weight loss improves inflammation and metabolic markers
- -dietary changes can help:
- Fruits and nuts, berries, fish, whole grains, omega-3 polyunsaturated fatty acids
- -avoiding trans-fat and saturated fats, sugary foods, red meat

Diabesity

- Increased leptin and insulin resistance
- Increased blood pressure
- Increased cardiovascular disease
- Increased depression
- Chronic inflammation
- Neurocognitive impairment

Cardo-Metabolic Syndrome

- Diabetes, cardiovascular disease, obesity
- Reduced microbial diversity
- Leptin resistance
- Mood disorders
- Inflammation



Metabolic Syndrome

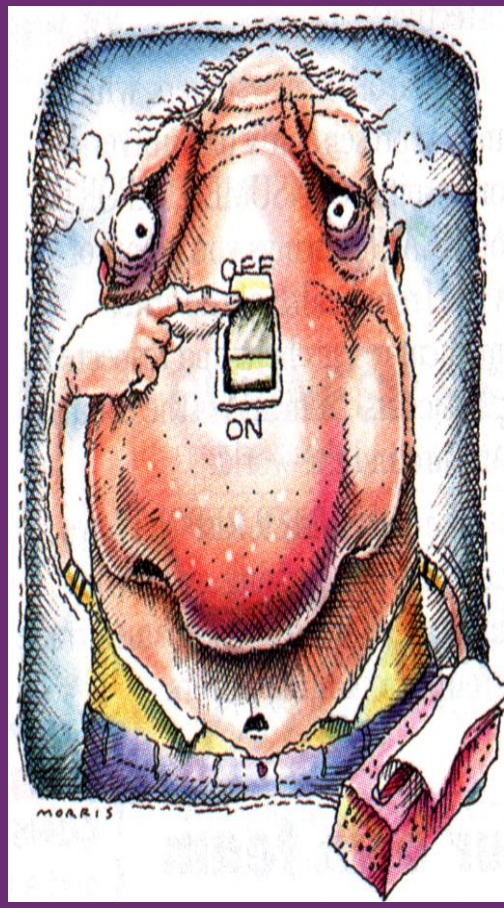
- **Increasing risk factors for:**
  - **Heart disease**
  - **Diabetes**
  - **Obesity**
  - **Low HDL, high LDL**
  - **High blood pressure**
- **All lead to depression**

➢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).

How does inflammation affect the brain: *Sickness behavior*

- *A symptom cluster also seen in chronic stress
  - Depressed and/or anxious mood
- * increased sensitivity to pain
- *loss of interest in food
- * social withdrawal
- * disordered sleep
- *fatigue, “cognitive fuzziness”

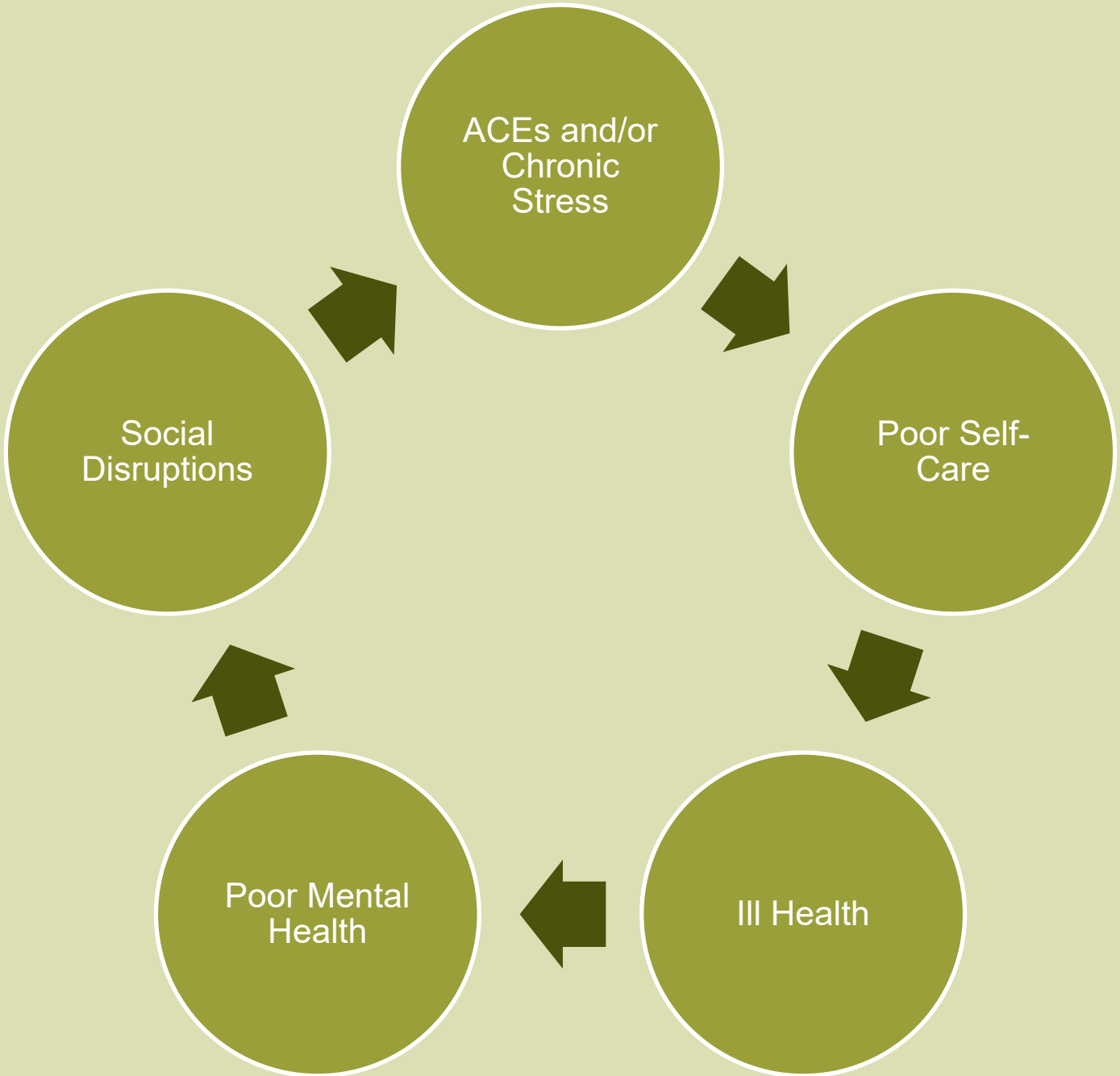


Depression and fatigue in illness

- Common symptoms of both acute and chronic illnesses
- Both caused by inflammation
- Involves suppression of brain arousal systems

Client Education

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

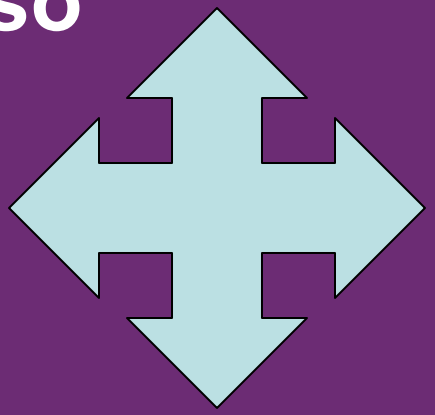

ACEs and/or Chronic Stress
Poor Self-Care
Ill Health
Poor Mental Health
Social Disruptions

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

Stress Can Enhance Inflammation

- Brief stresses can *increase* production of *pro-inflammatory cytokines*
  - *Study of tandem parachuters*
- Chronic stressors (i.e caregiving for a child with cancer) can also have this effect-prolonged
- Stressors with depression



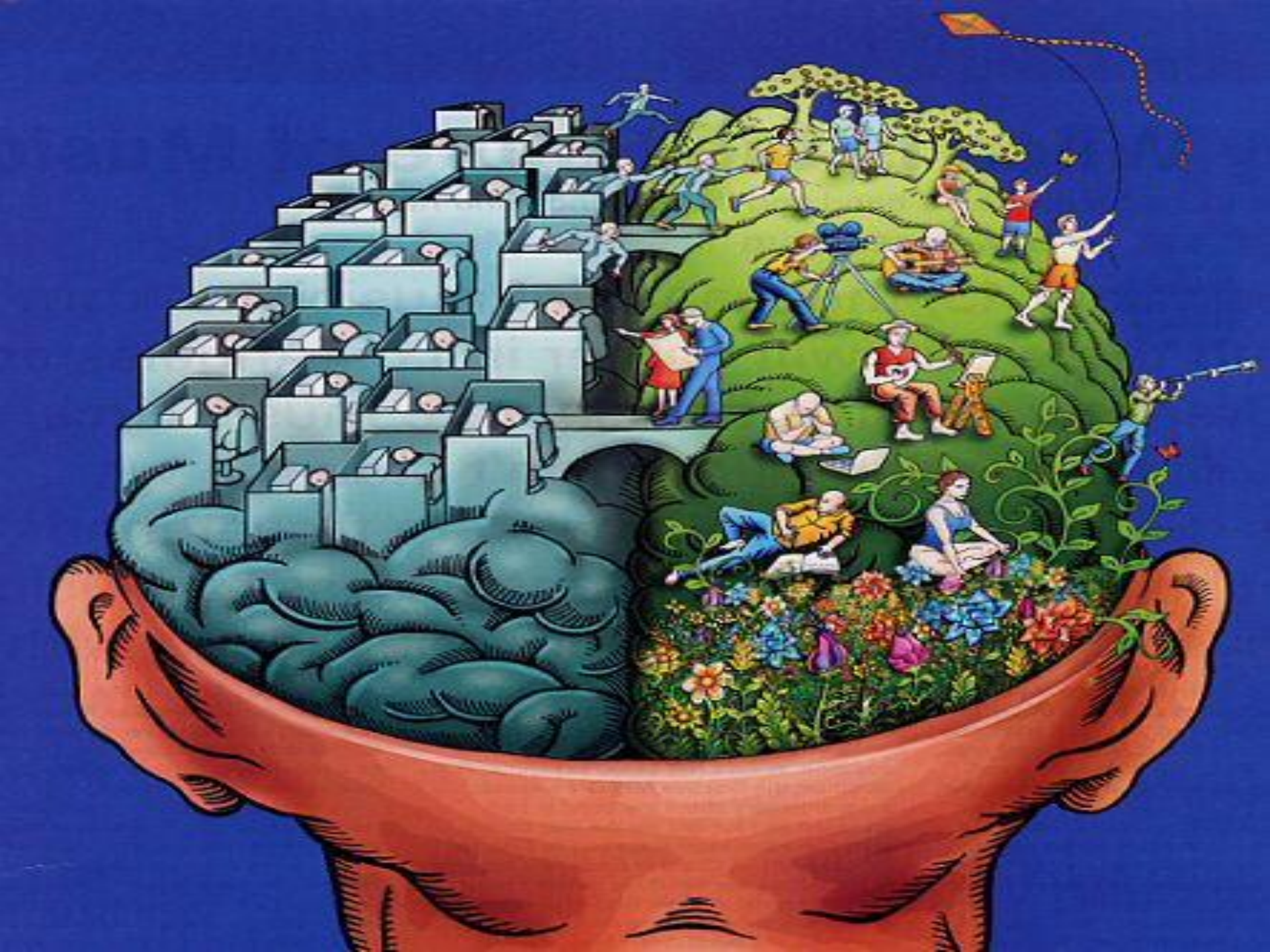
How does stress affect inflammation?

- Chronic stress- leads to increased inflammation (via cortisol resistance- immune cells –e.g. the microglia)
- Stress can disrupt balance within the immune system
- Chronic stress cause epigenetic changes in the expression of pro-inflammatory cytokine genes in immune cells
- -Peripheral inflammation induces neuroinflammation

Developmental Programming of stress responses

- Experiencing trauma or stress in infancy or childhood leads to impaired regulation of HPA axis
- Elevated inflammation, especially in gut
- Increased pain conditions including fibromyalgia & irritable bowel syndrome
- Epigenetic changes to genes involved in inflammation

A Brain User's Manual



Affect Asymmetry

Set points

Left Hemisphere

Positive emotions
Approach behaviors
Feeling engaged

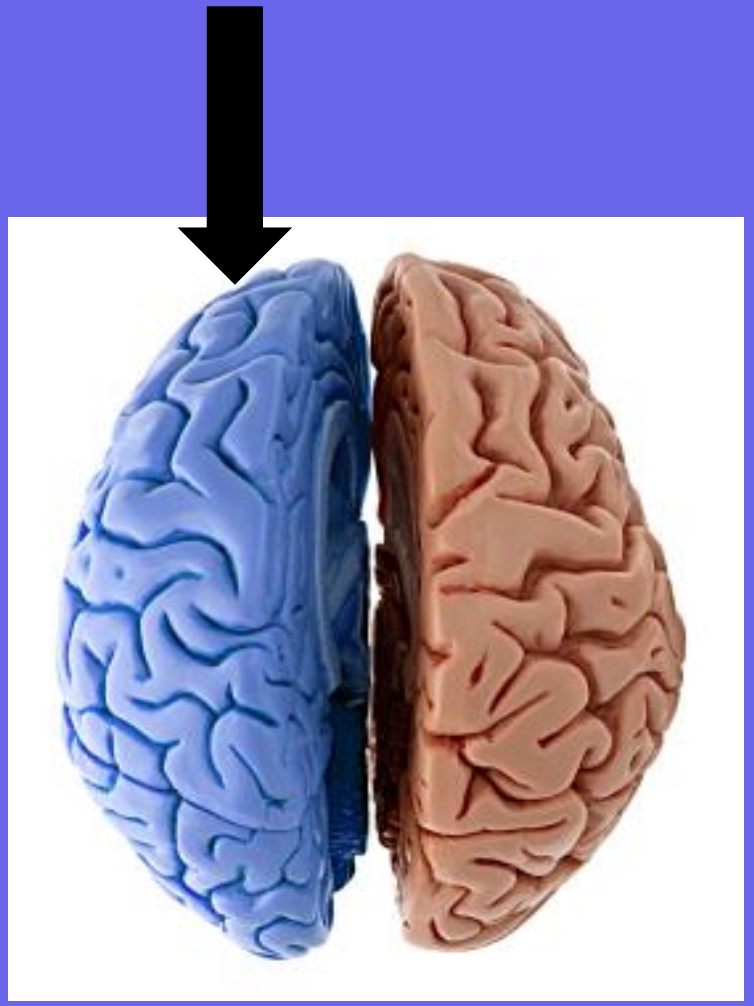
Right Hemisphere

Negative emotions
Withdrawal and Avoidance
Feeling overwhelmed

Left PFC:

Suppressing Sadness

Activating Positive Emotions



Client Education

- When you are overwhelmed with anxiety or depression it is best to shift from the big picture to the small, and do something that approaches a goal in a piecemeal and incremental manner.

Left PFC more DA:

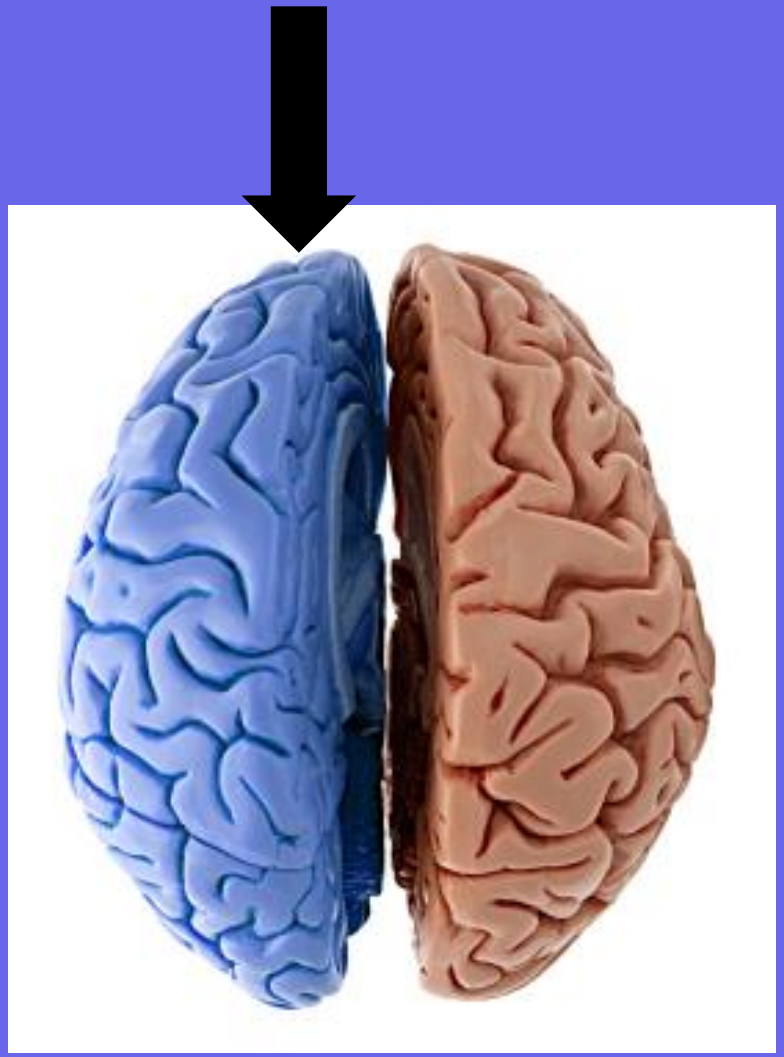
Activation

&

Approach

Behaviors

(curiosity; assertion)



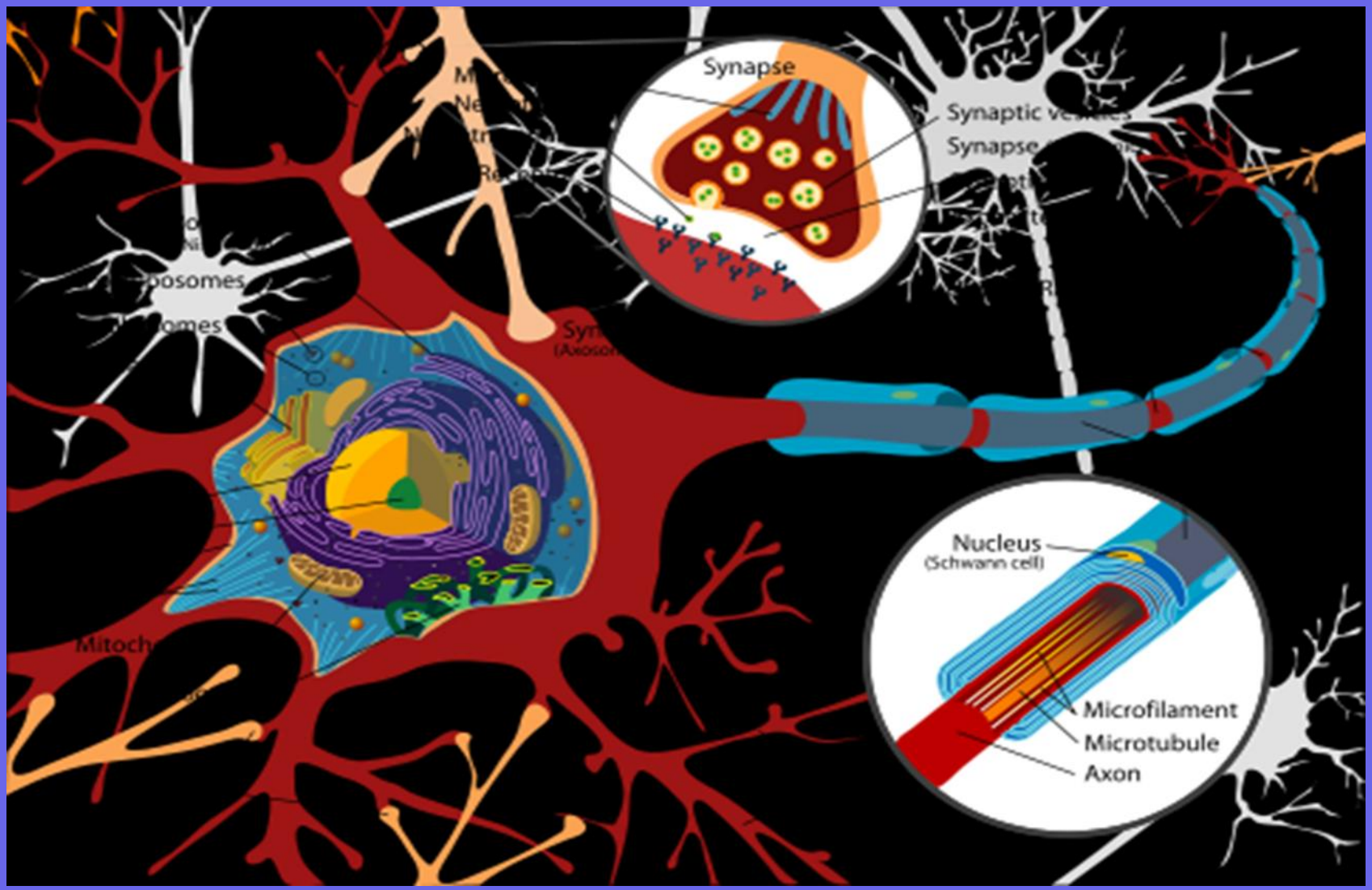
Right PFC more NE:

Activating
Behavioral
Inhibition

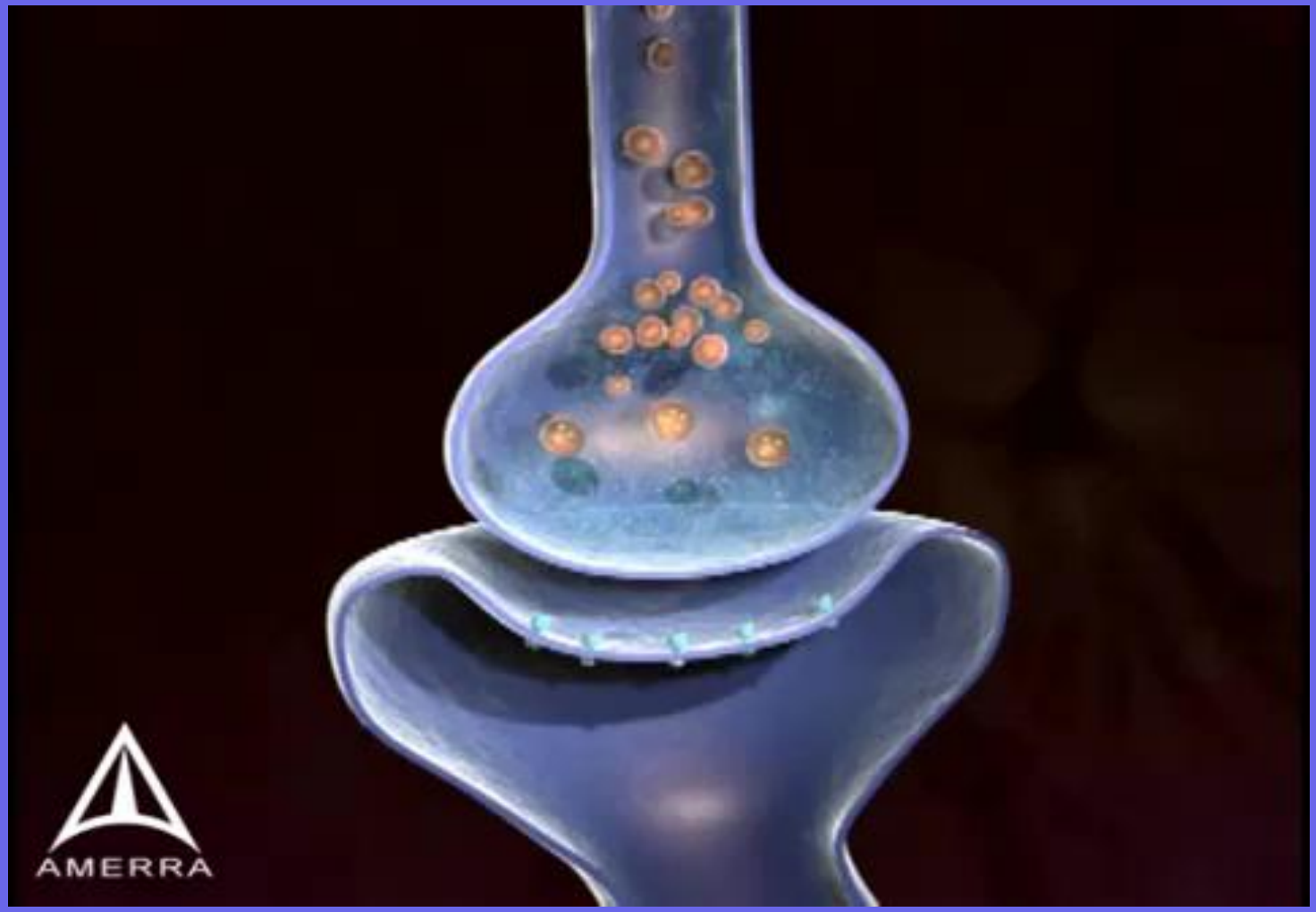
Associated
With negative
Emotions

87 Billion Neurons

Each with 10,000 synaptic connections

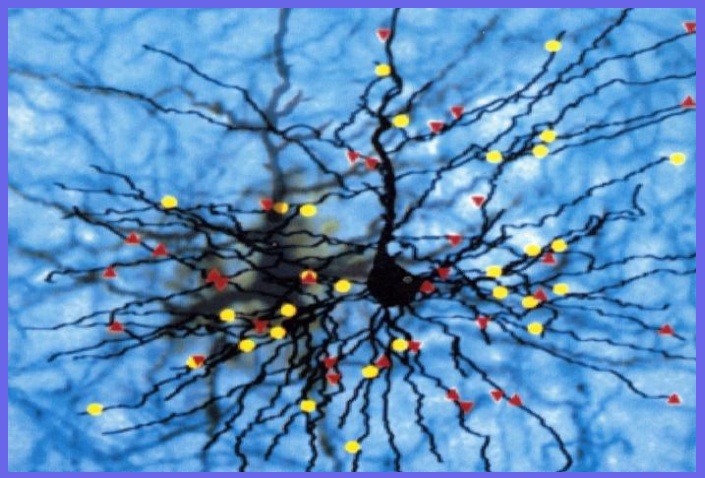


Synaptic Communication



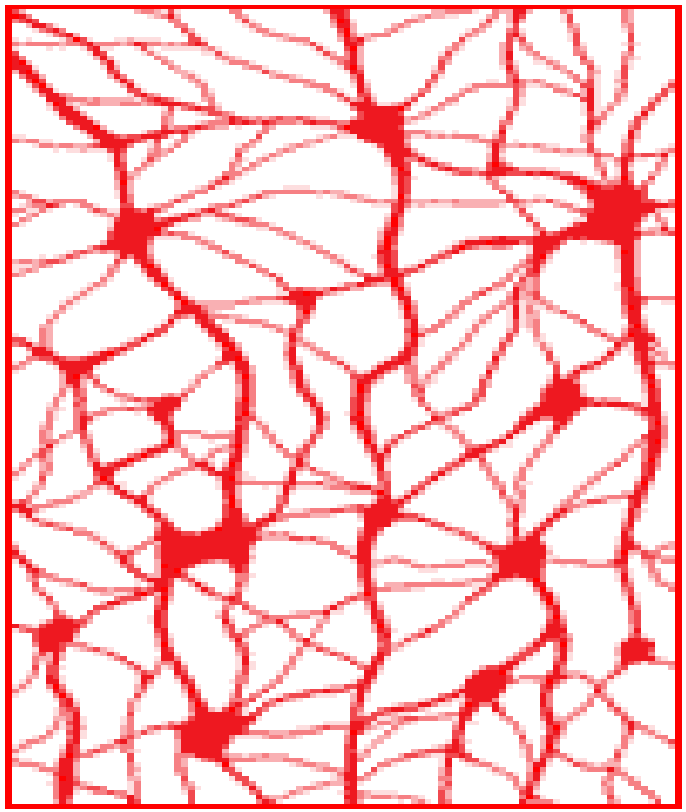
Neuroplasticity

- Increases in:
  - synaptic efficacy
  - receptor density

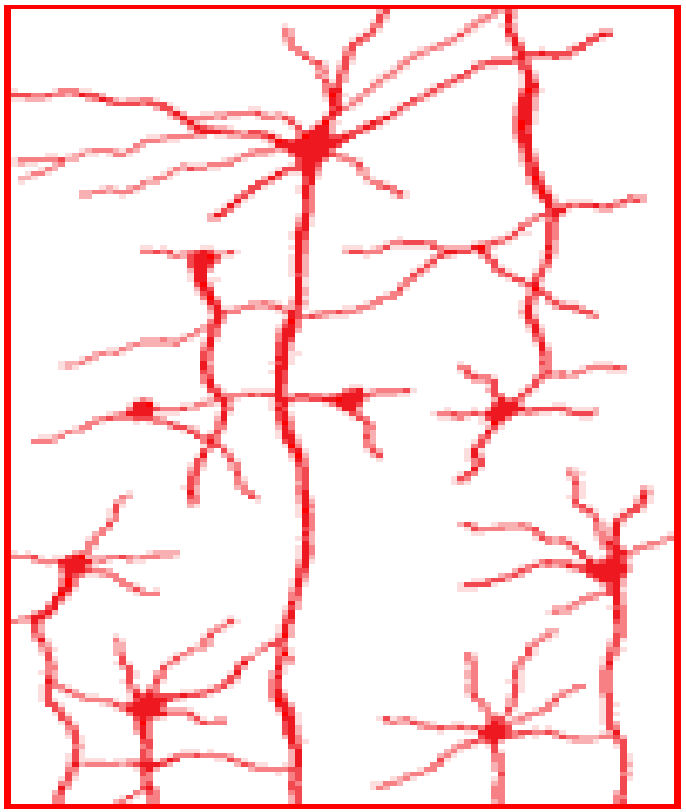


  - Up-regulating their activity
  - Glial cell availability
  - Changes in the shape and structure of synapses

Brain cell connections



section of a stimulated brain

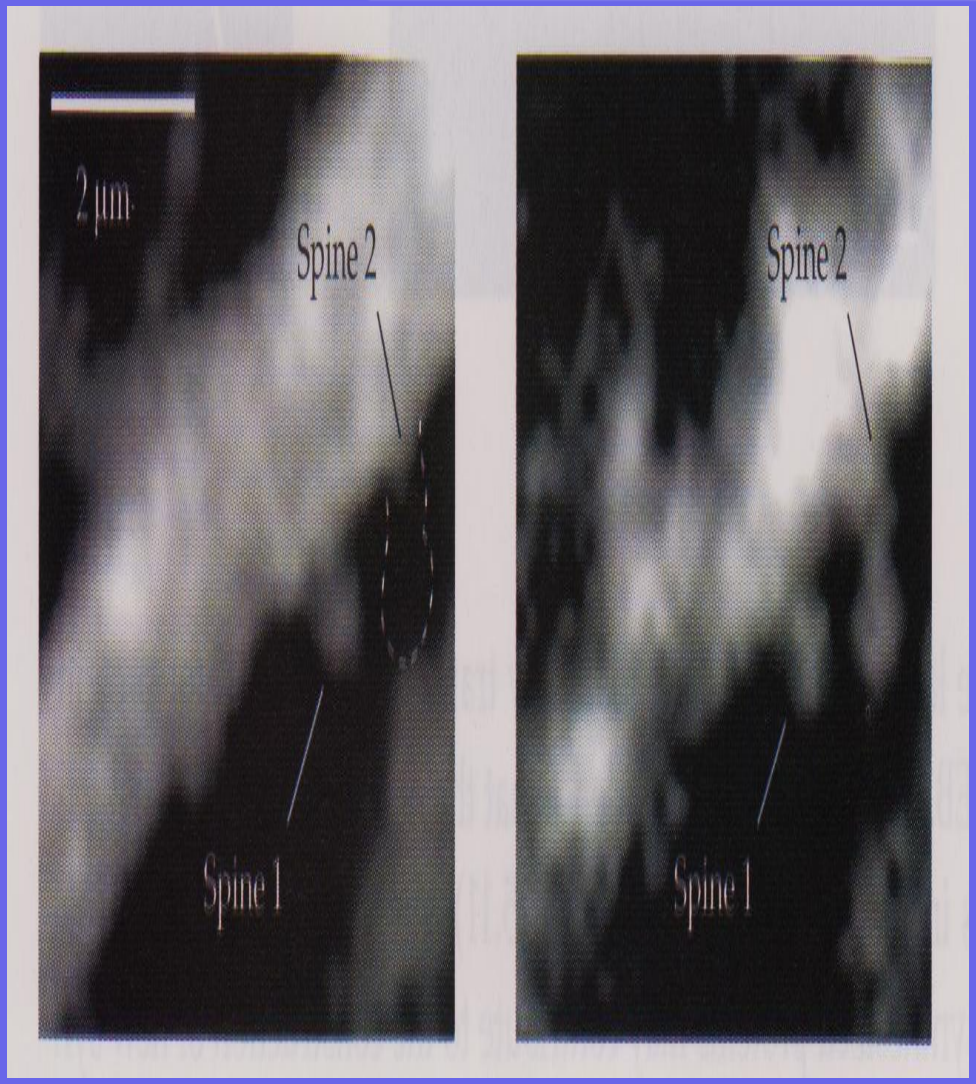


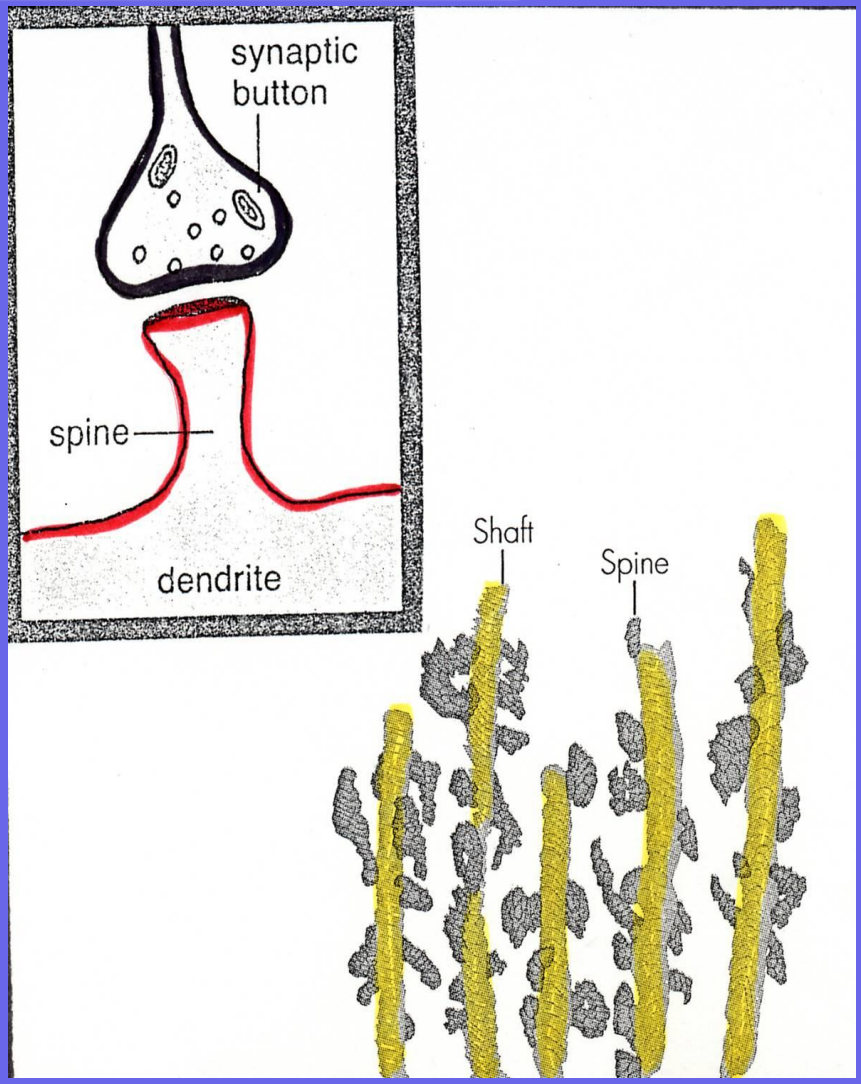
section of an unstimulated brain

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)**

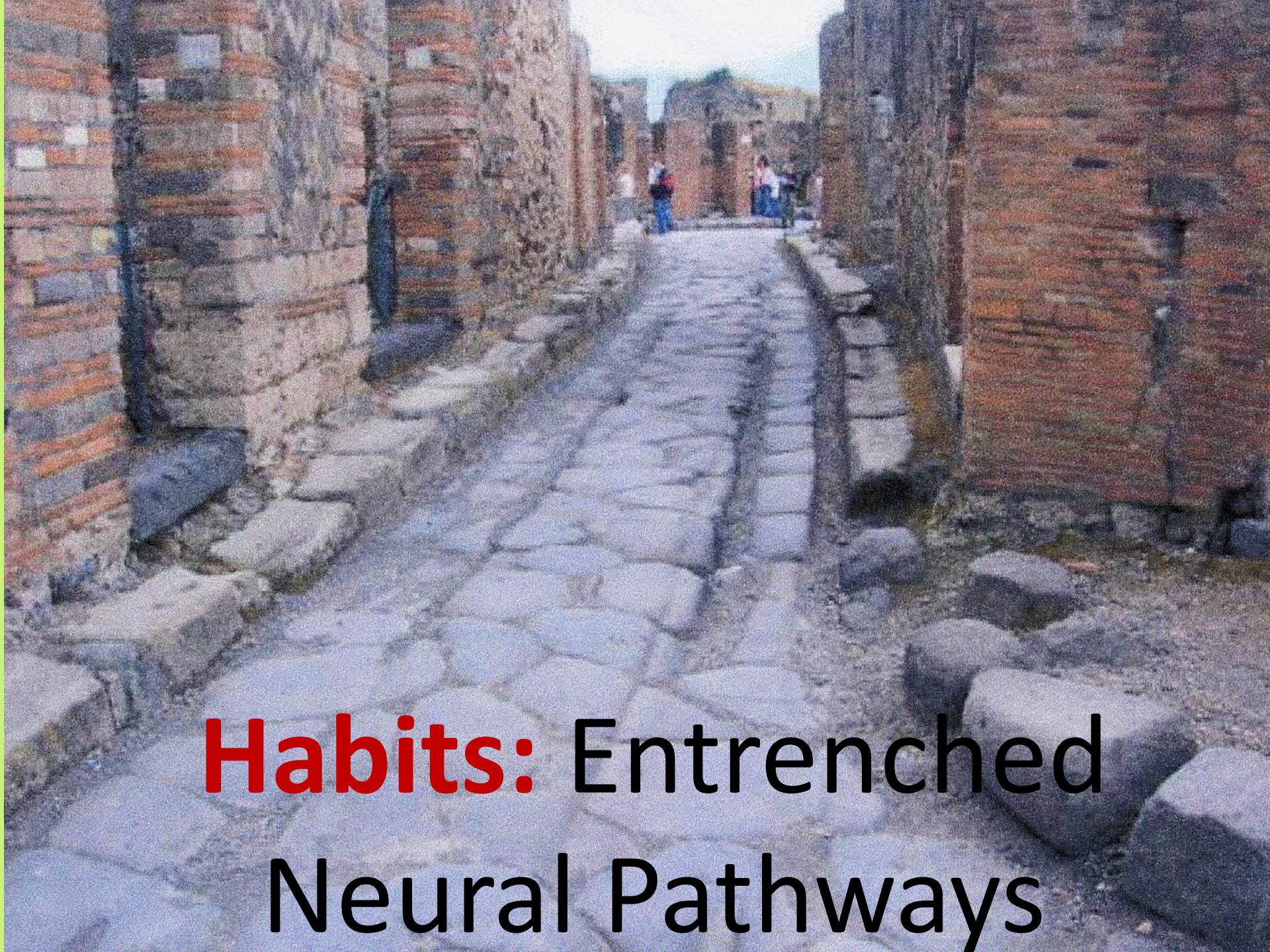
DENDRITE SPINES & SYNAPSES—one hour





Client Education

- Your brain is not hardwired but soft-wired.
- Our job together is to rewire your brain so that you no longer suffer from anxiety and depression.



Habits: Entrenched Neural Pathways

Bump the Needle!

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)

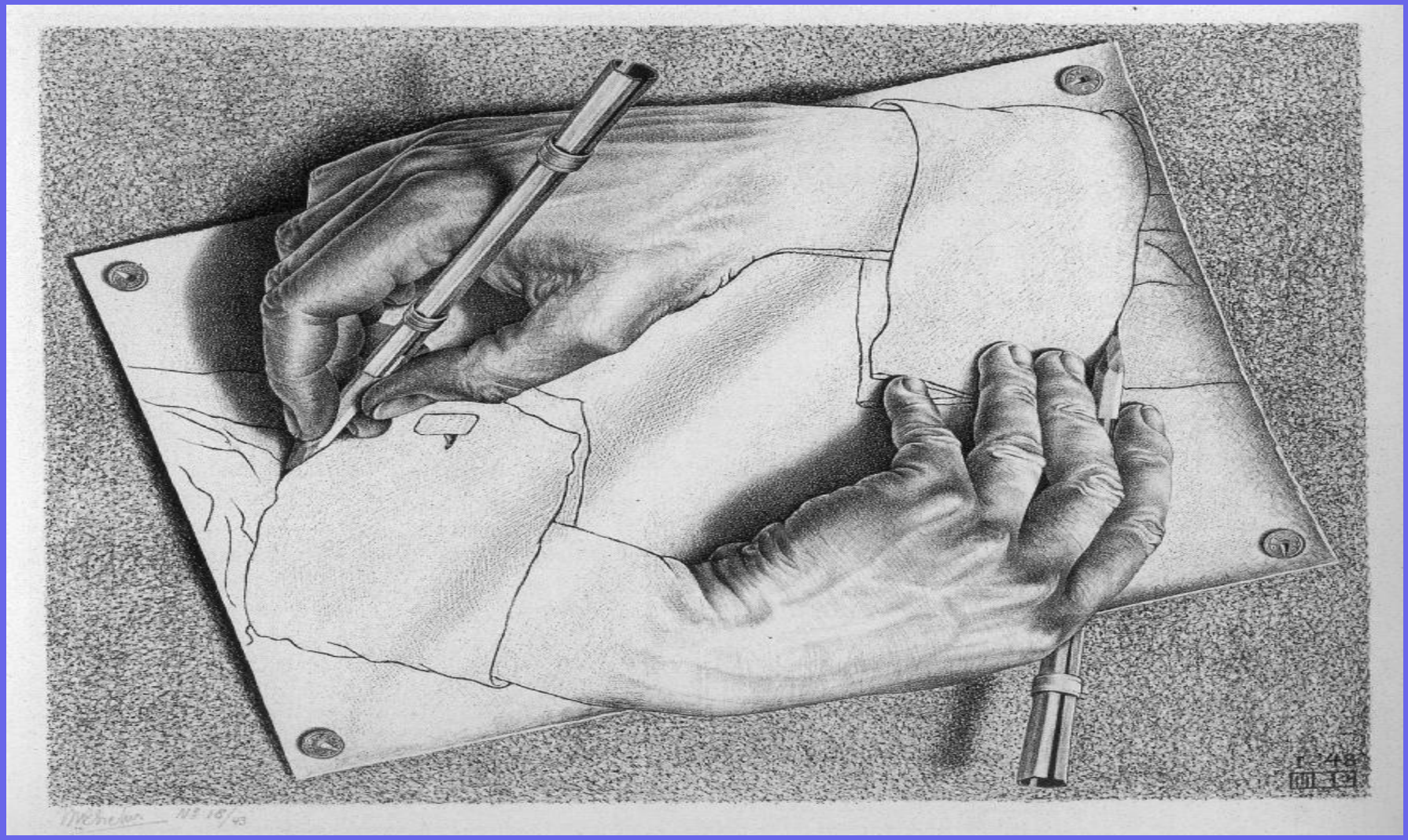
- Adults who juggled three balls for 3 months increased grey matter in the midtemporal area and left posterior intraparietal sulcus. - 3 months of little or no juggling, -- grey matter decreased and approached baseline values. (Draginski, et al, 2003)

Examples of Neuroplasticity

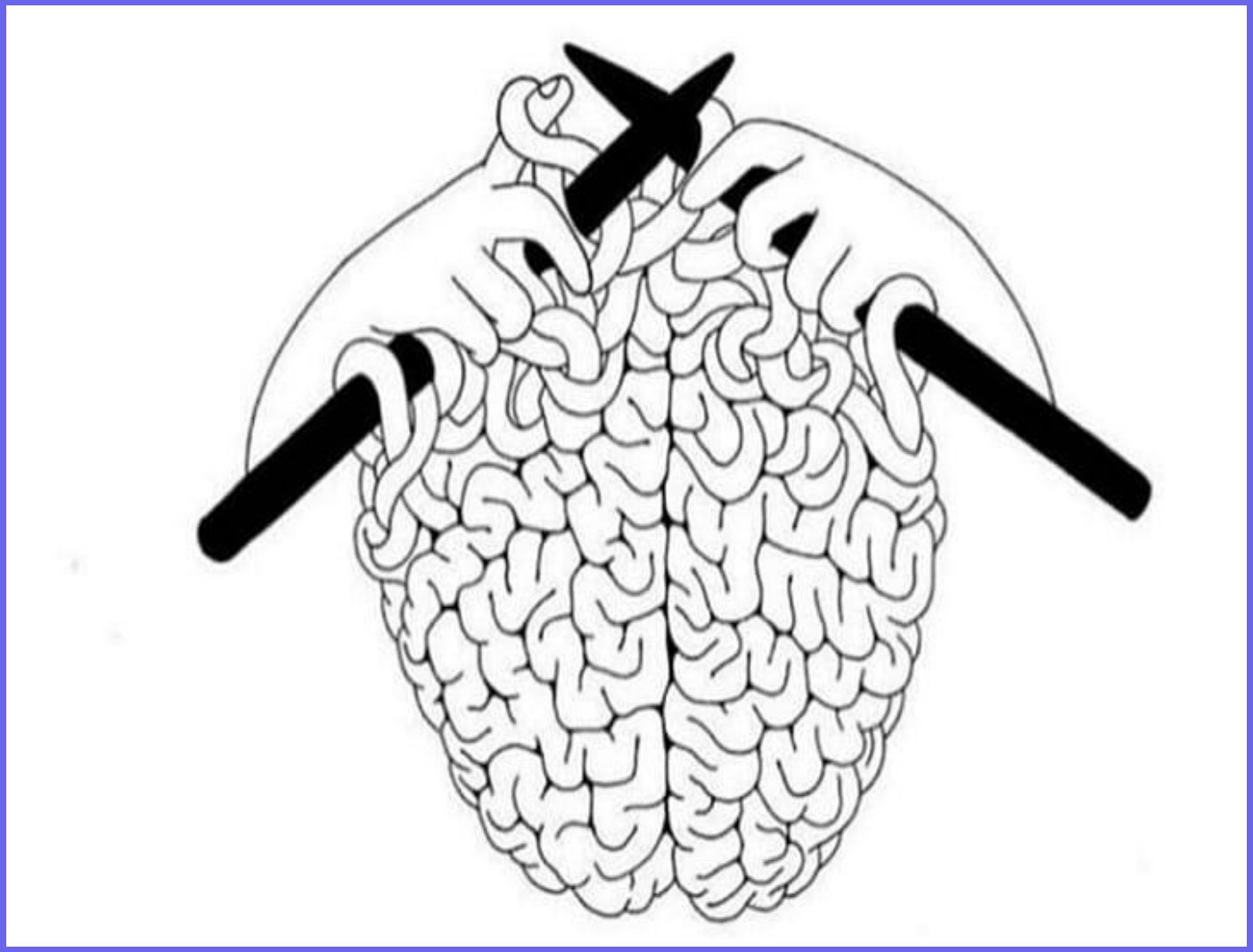
- Musicians using specific fingers to play their instruments showed enlarged areas of their somatosensory strips associated with those fingers. (Pantev, et al, 2001)

- Blind Braille readers showed enlarged cortical areas associated with their reading finger compared to blind non-Braille readers and to sighted people. (Pascul-Leone & Torres, 1993)

Mind/Brain Causality

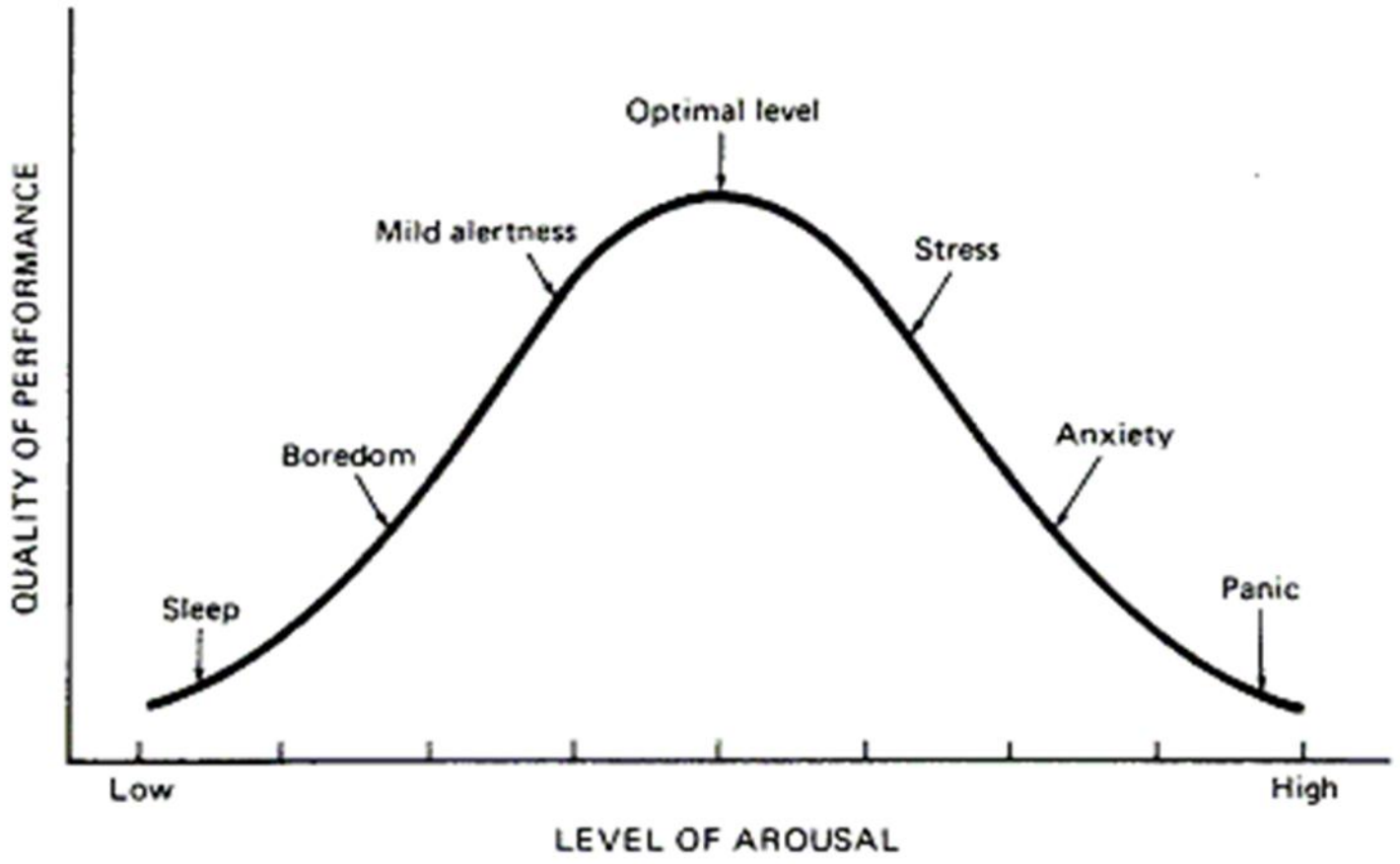


Mind/Brain Causality




WWZ 454

Yerkes Dodson arousal curve



Client Education

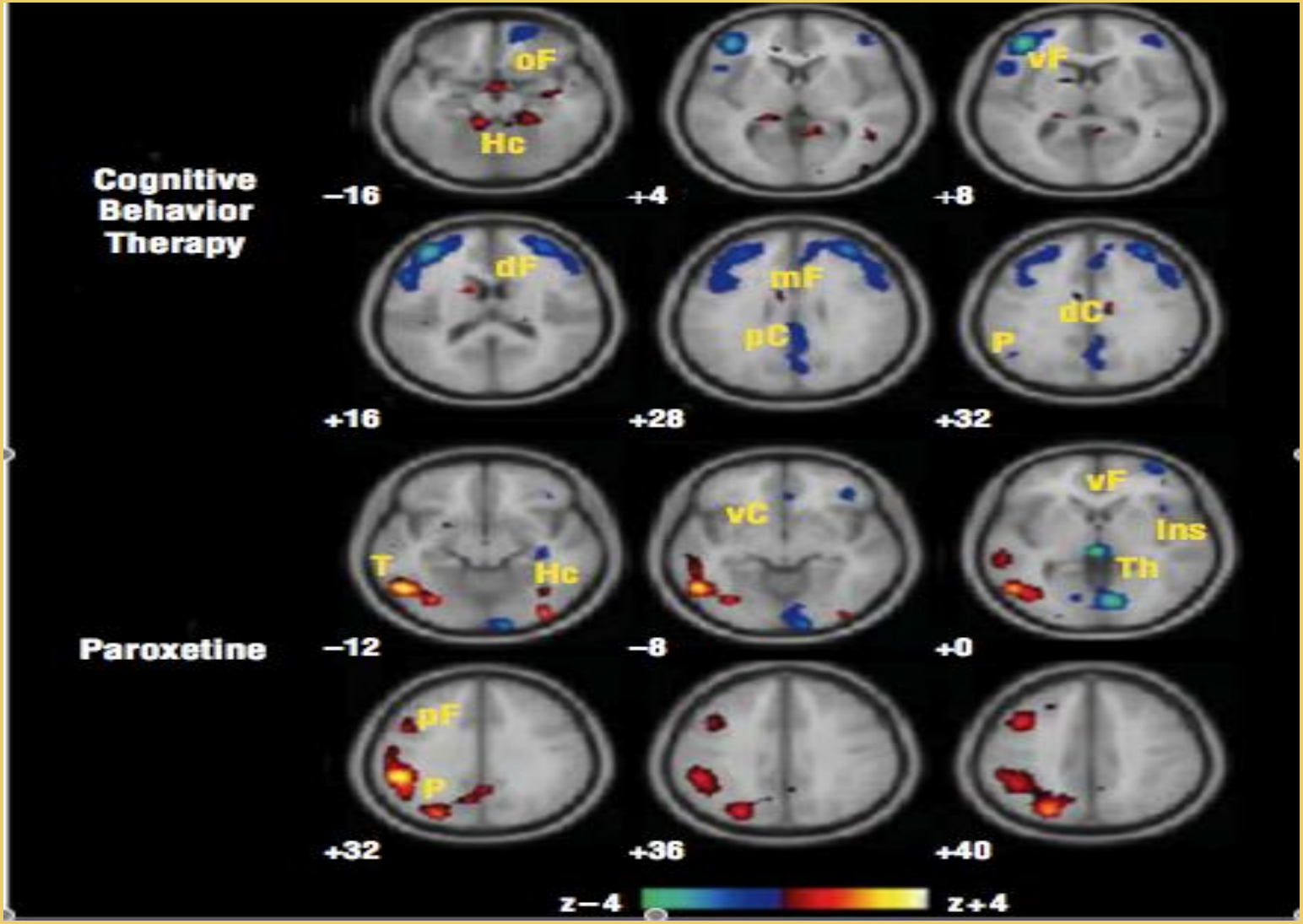
You have to do what you don’t feel like doing so that eventually you will feel like doing it.

Client Education

- Though you feel like you're not ready to take the first step, actually it is not feeling ready that provides the brain chemistry necessary to rewire your brain.

Don't wait to feel ready!

Brain Change: Two Perspectives



Psychotherapy and the Brain

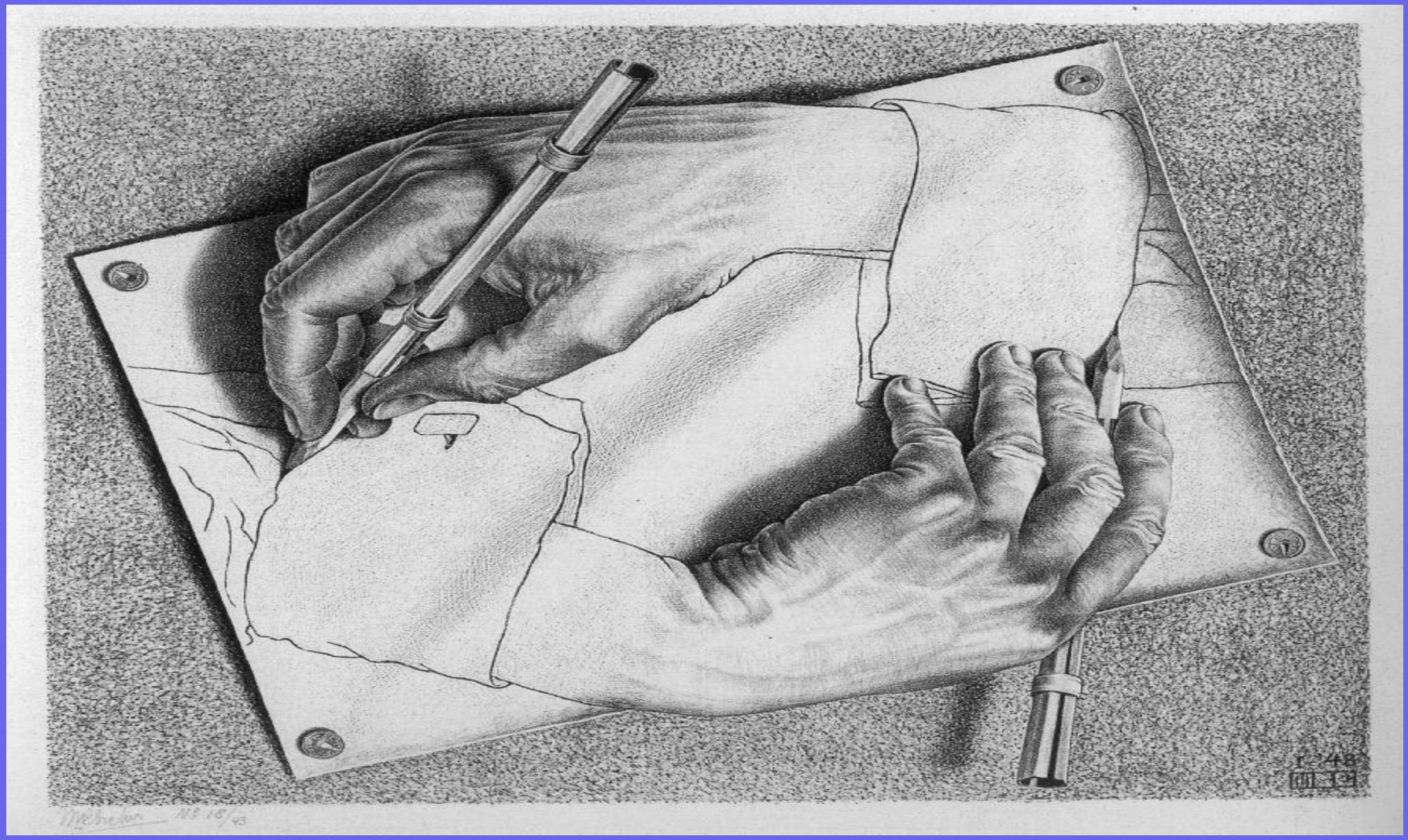
Direct, observable links between successful CBT/IPT and brain changes

- **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)

Brain-Based Therapy

- BBT changes how we think about the relationship and change:
  - Need a "Safe emergency."
  - Experience *creates* brain biology
  - Brain biology effects experience (e.g. depression)

Mind/Brain Causality

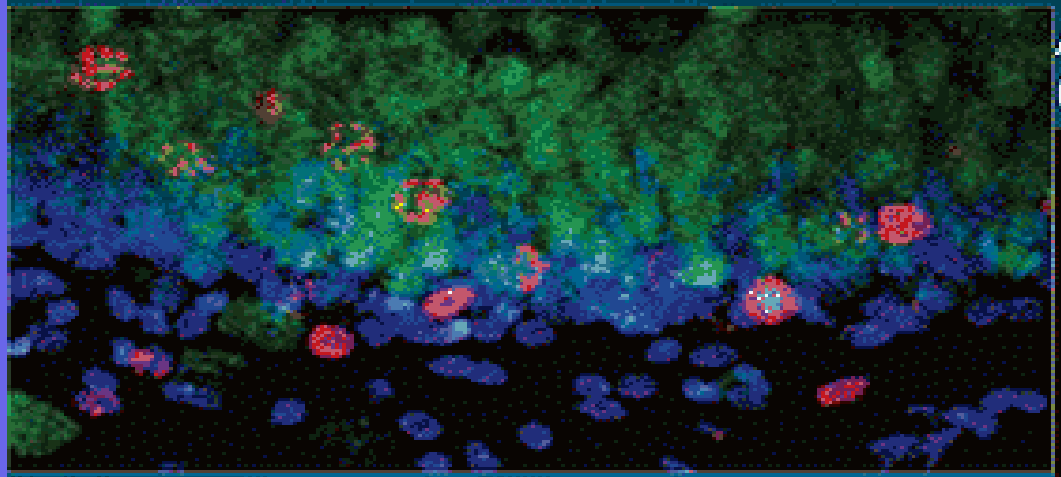


Brain Derived Neurotropic Factor

- 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

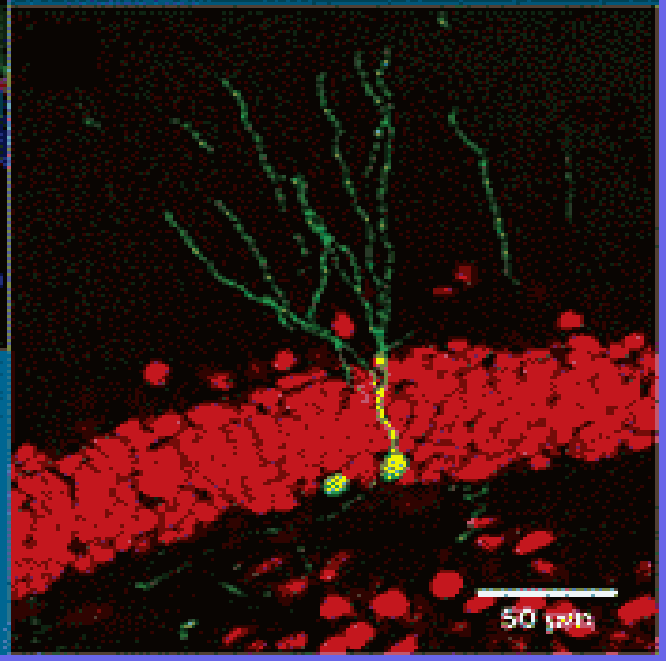
Neurogenesis

Neurogenesis in the Hippocampus

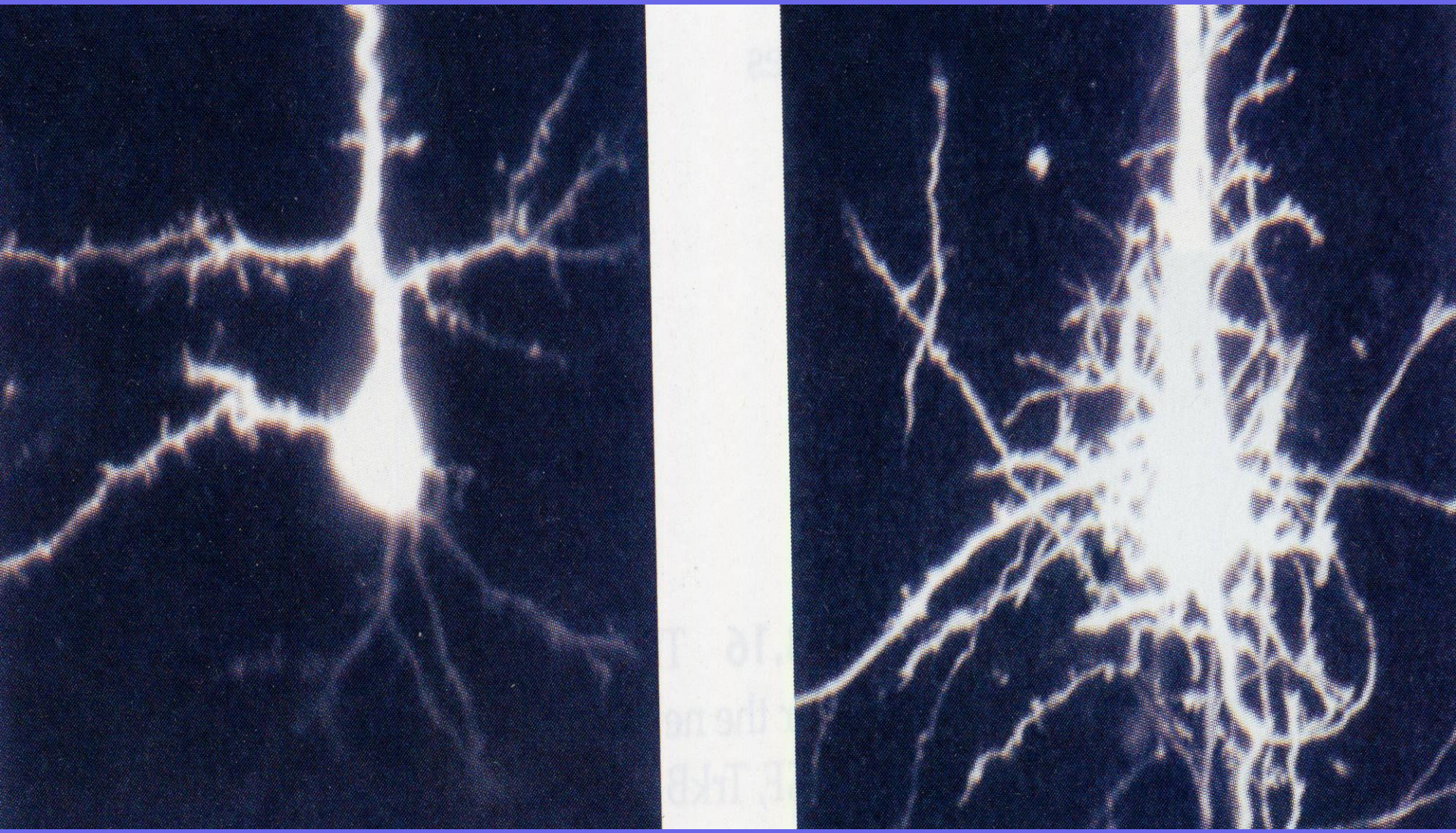


Adult rat brains spawn new cells (red) in the hippocampus

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

Client Education

You can grow new neurons in the area of your brain that gives you the capacity for memory. The first steps include maintaining a healthy diet, aerobic and cognitive exercise.

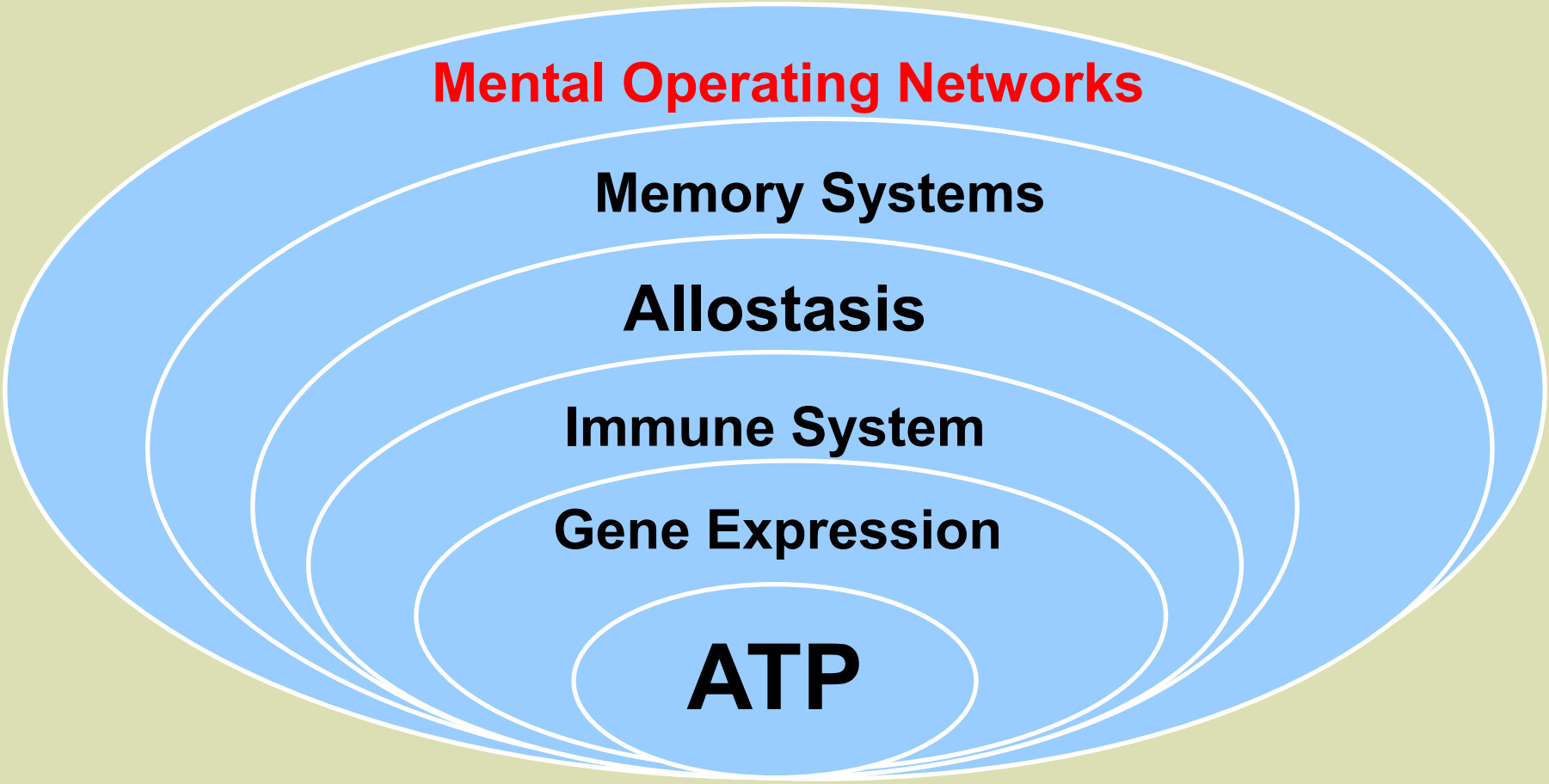
Neurotrophic Factors: "Brain Fertilizers"

- Insulin-like growth factor (IGF), is associated with energy utilization, brain growth, and maturation and can be epigenetically facilitated by prosocial circuits in the brain
- Nerve growth factor (NGF), promotes myelin and neuron differentiation
- Nurturing increases NGF which binds to the cortisol receptor gene to increase cortisol receptors:
  - However, when the cortisol receptor is suppressed, as occurs with neglect or child abuse, NGF does not bind well and fewer cortisol receptors are produced in the hippocampus

Neurotrophic Factors: Brain Fertilizers

- Decreased methylation of the glial cell-derived neurotrophic factor (GDNF) gene is associated with greater stress tolerance
- Increased methylation of the GDNF gene is associated with decreased stress tolerance. GDNF is essential for regulating dopamine release in the nucleus accumbens and for the survival of dopaminergic neurons.
- Chronic unpredictable stress alters dopaminergic functions, reshaping circuits in the prefrontal cortex, impairing decision making, and un-inhibiting maladaptive habits and working memory.

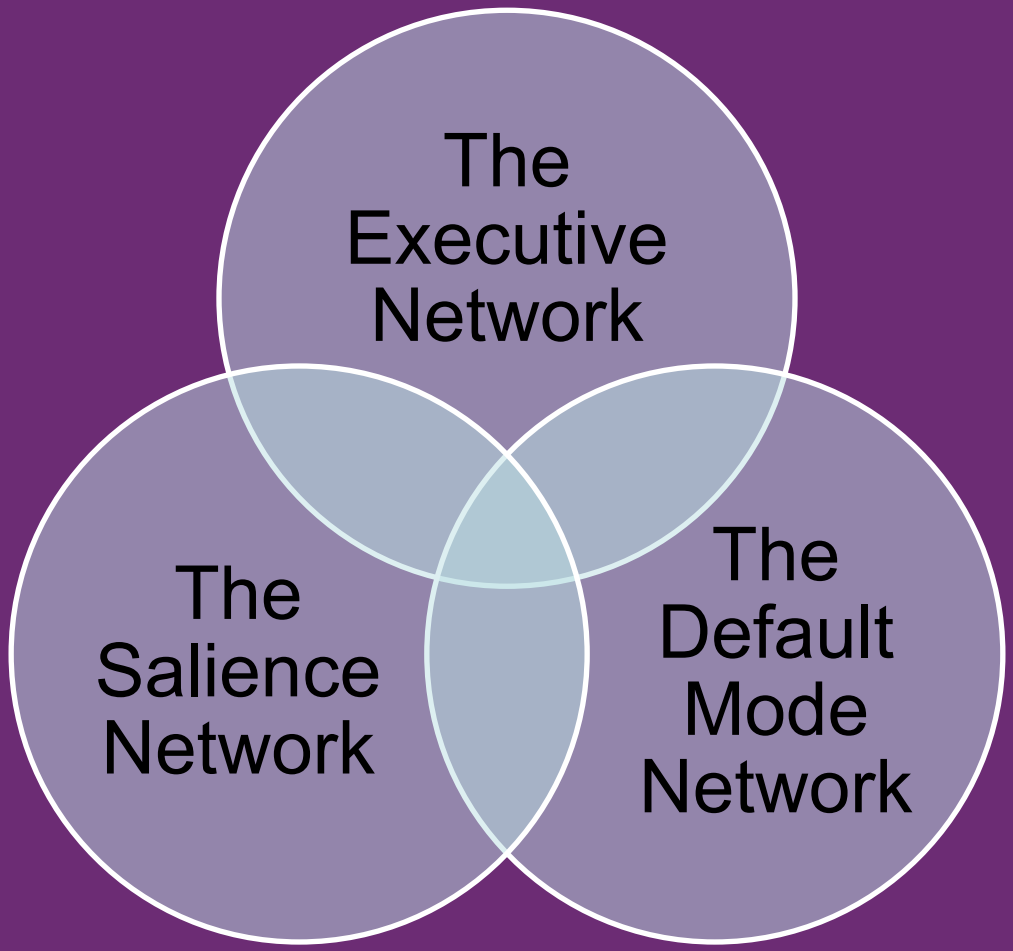
“Self”-Organization



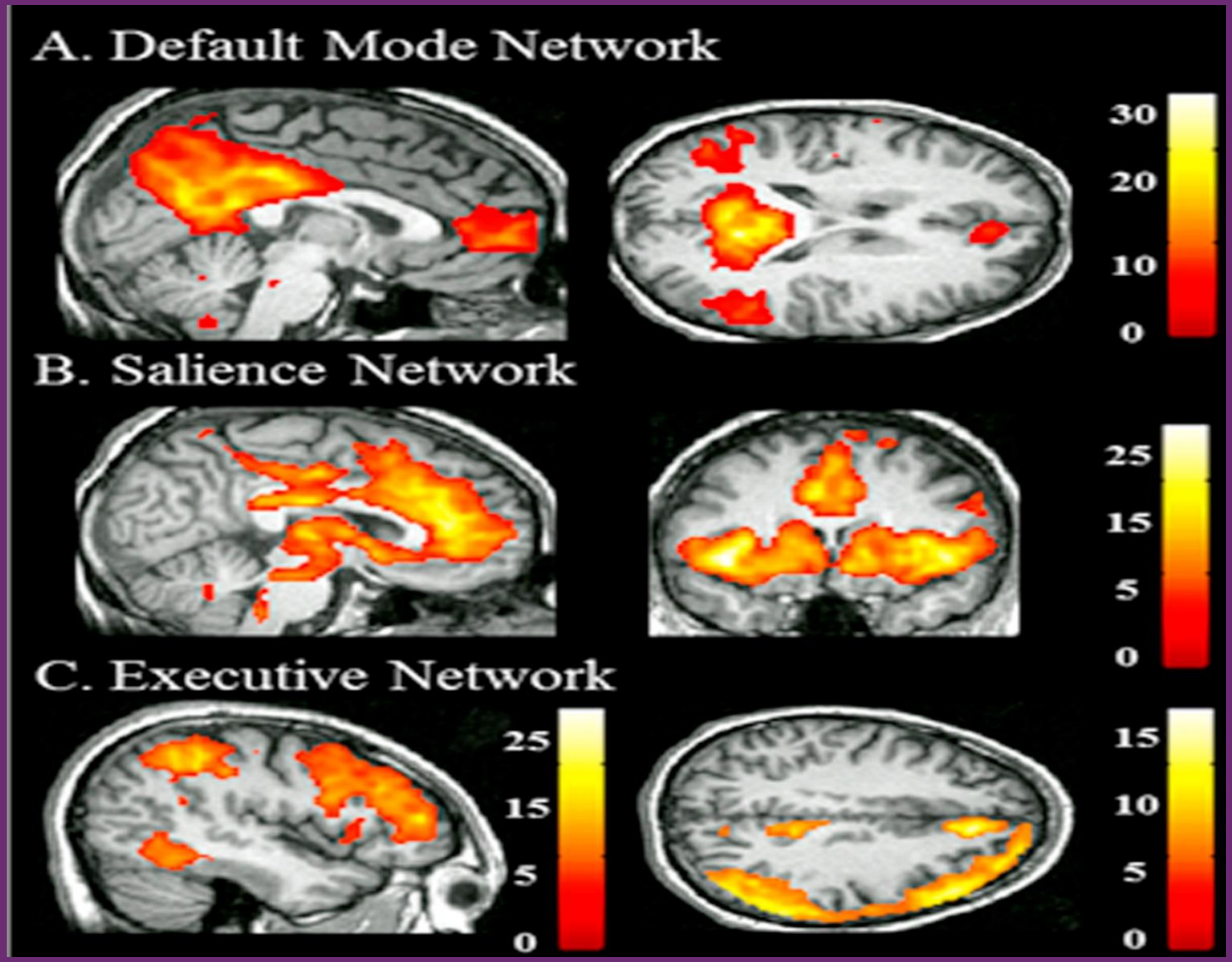
The Mind's Operating Networks:

- **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;

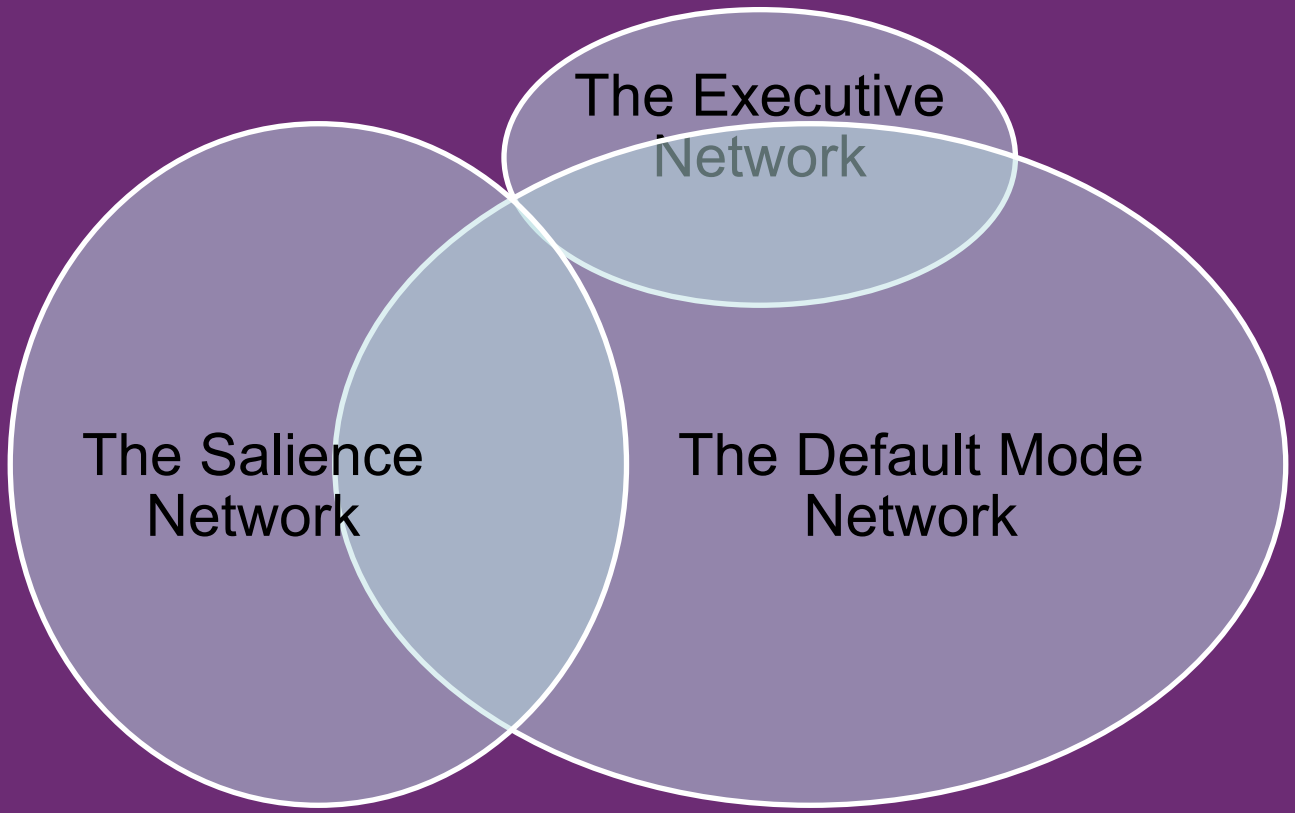
Balancing the Mental Networks



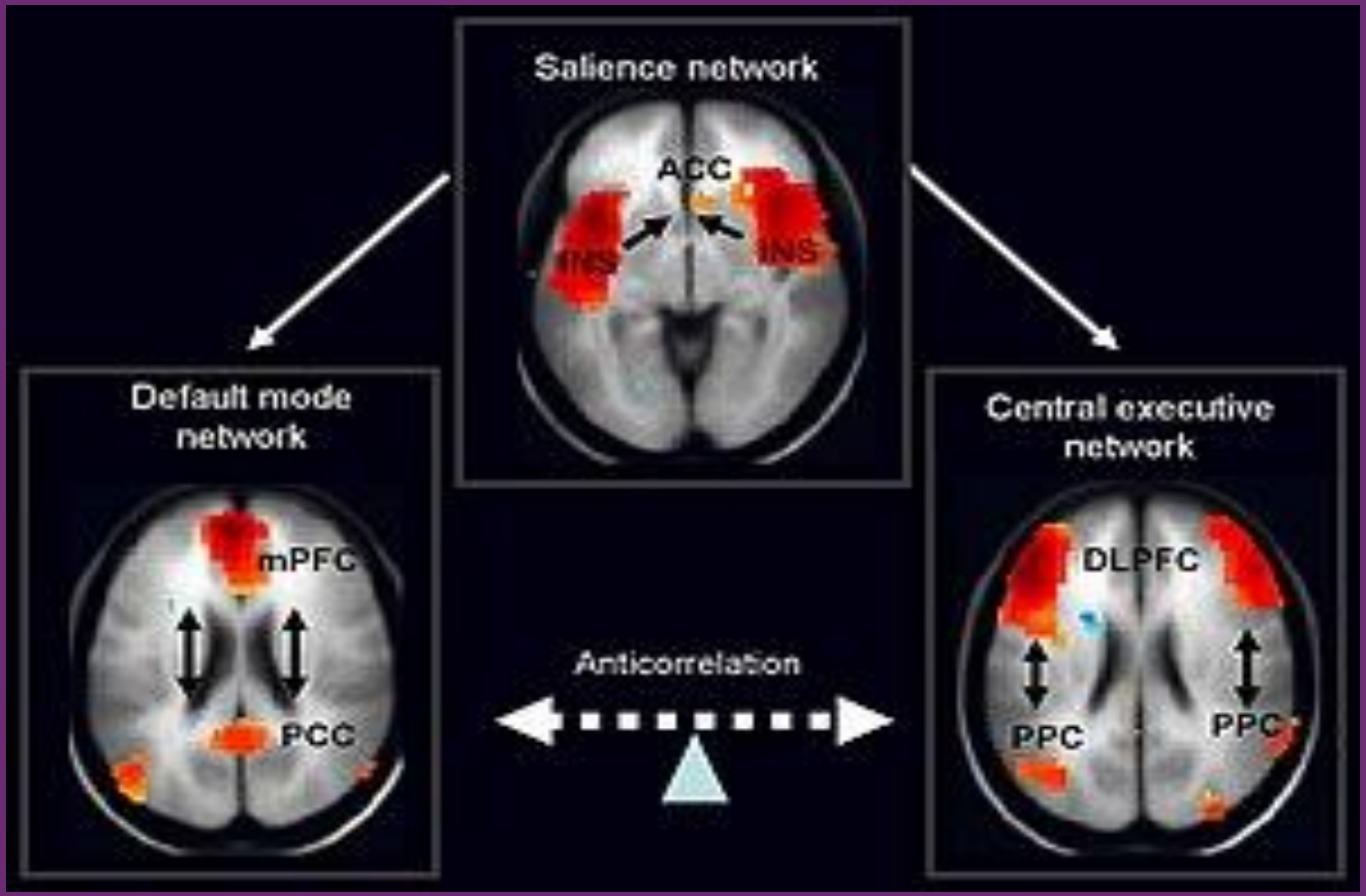
The Mental Networks



Imbalanced Mental Networks



The Mental Neworks

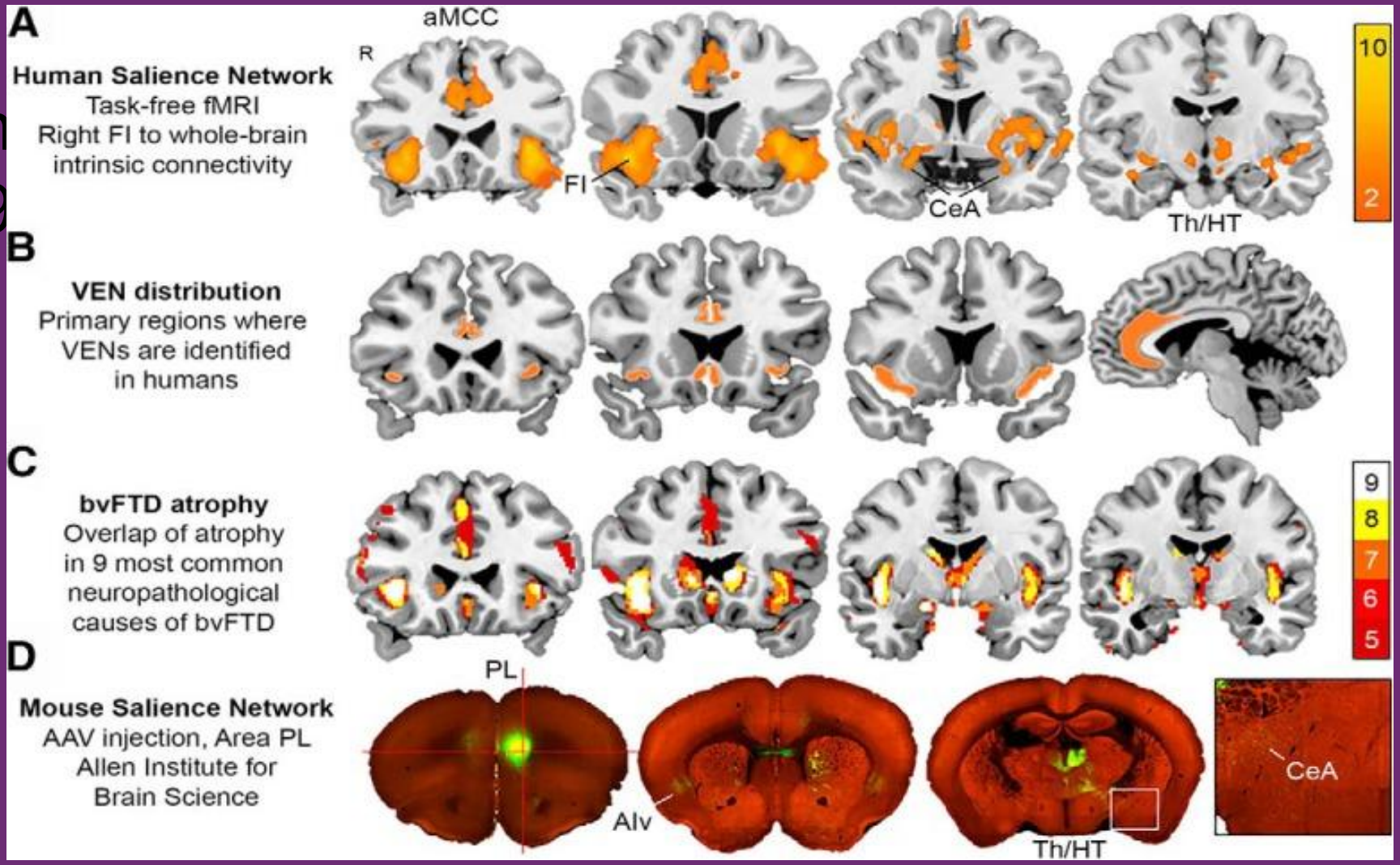


Salience Network:

- 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

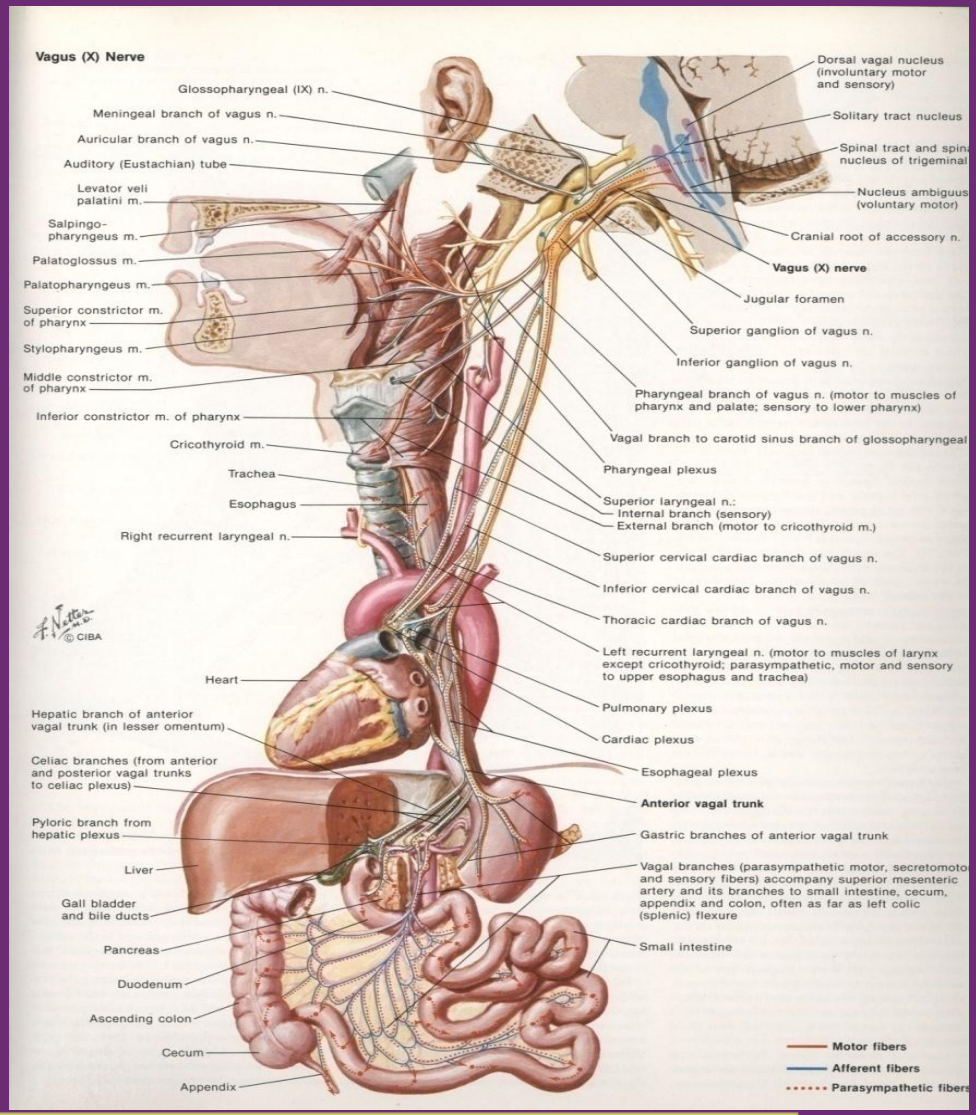
Salience Network and VENS

- h
  9



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.

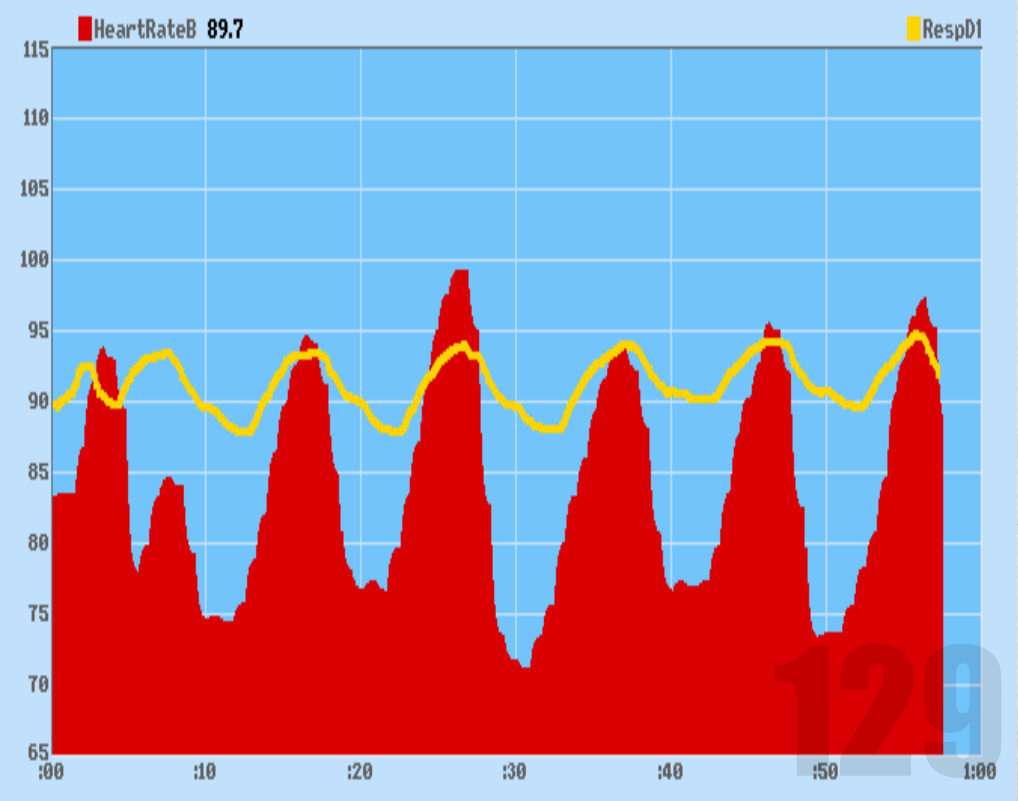


Variability is good

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.

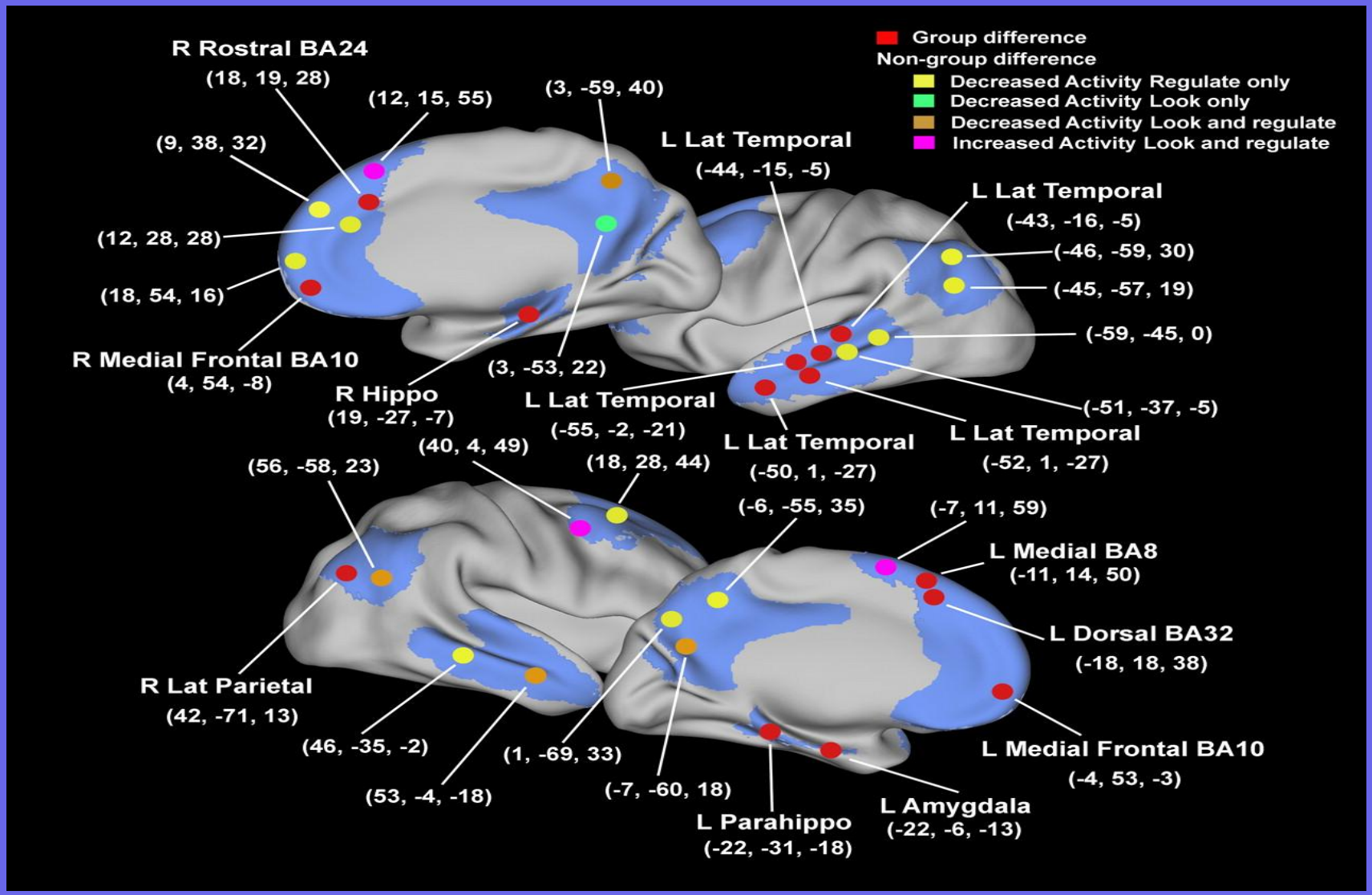


“Where is the Anxiety?” bumping the DMN

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 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

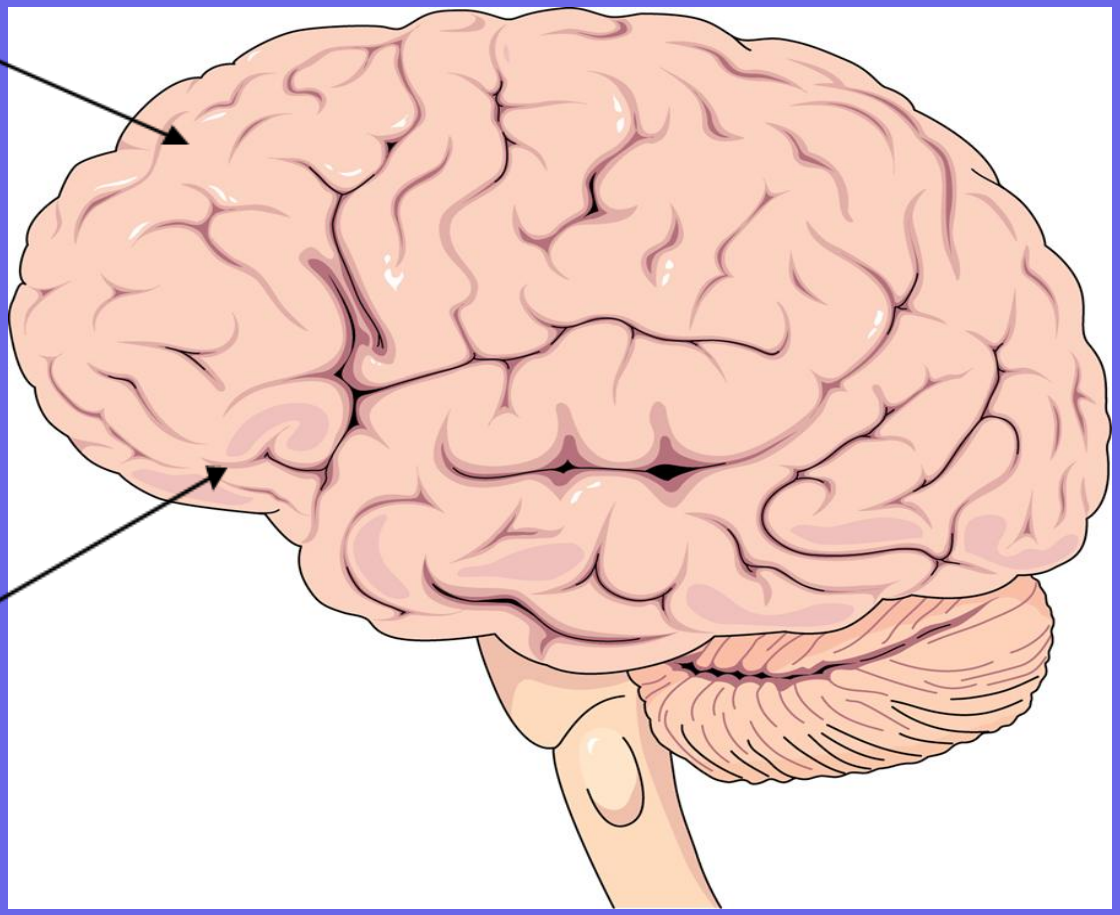
Central Executive Network:

- 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

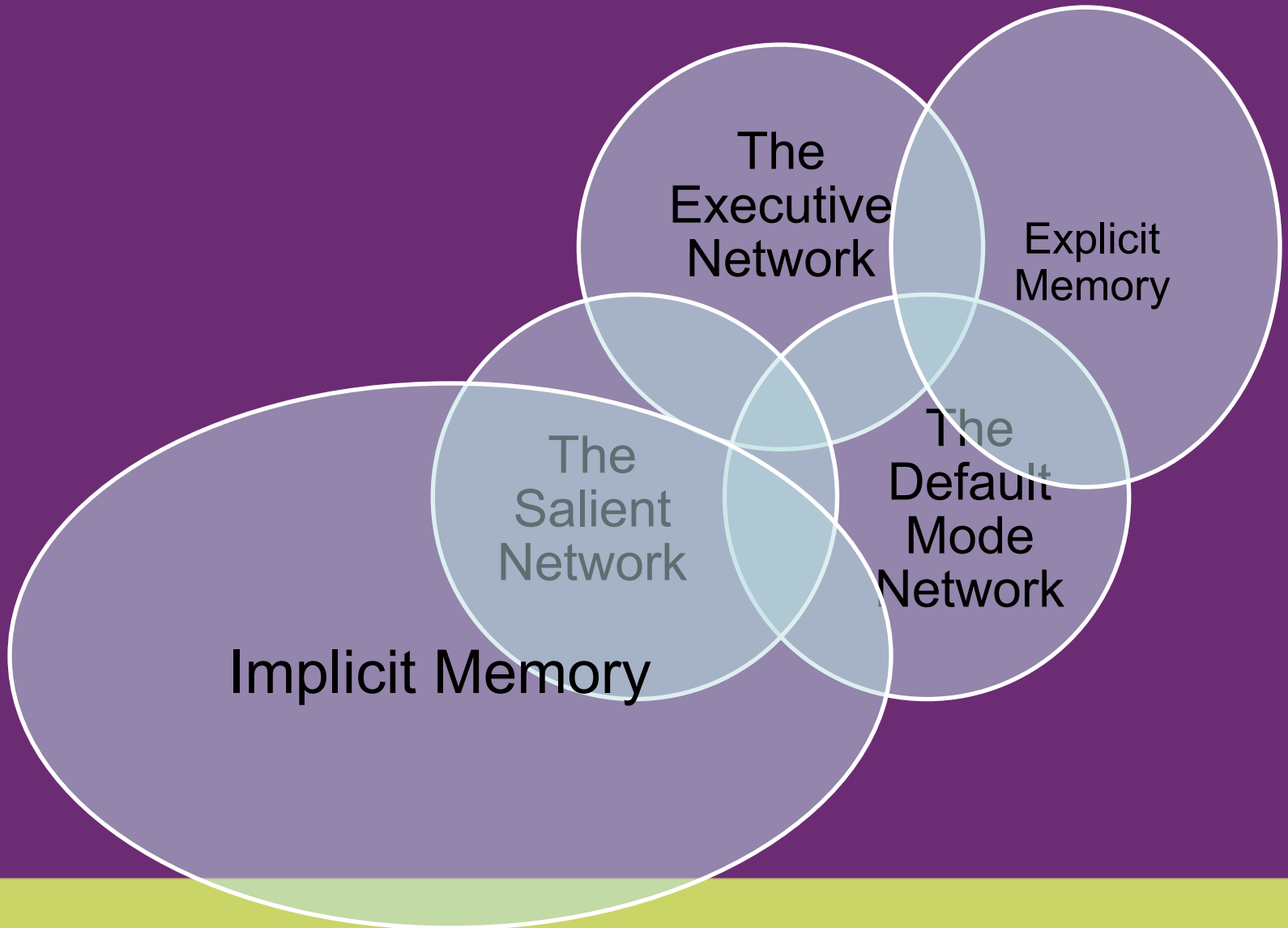
Underdevelopment and underactivity in the Executive Network can contribute to:

- Attentional disorders
- Paradoxical syndrome known as ”pseudo-depression,”
  - marked by a lack of spontaneity and affect, rather than negative affect. In other words, he looks depressed but denies depression when asked.

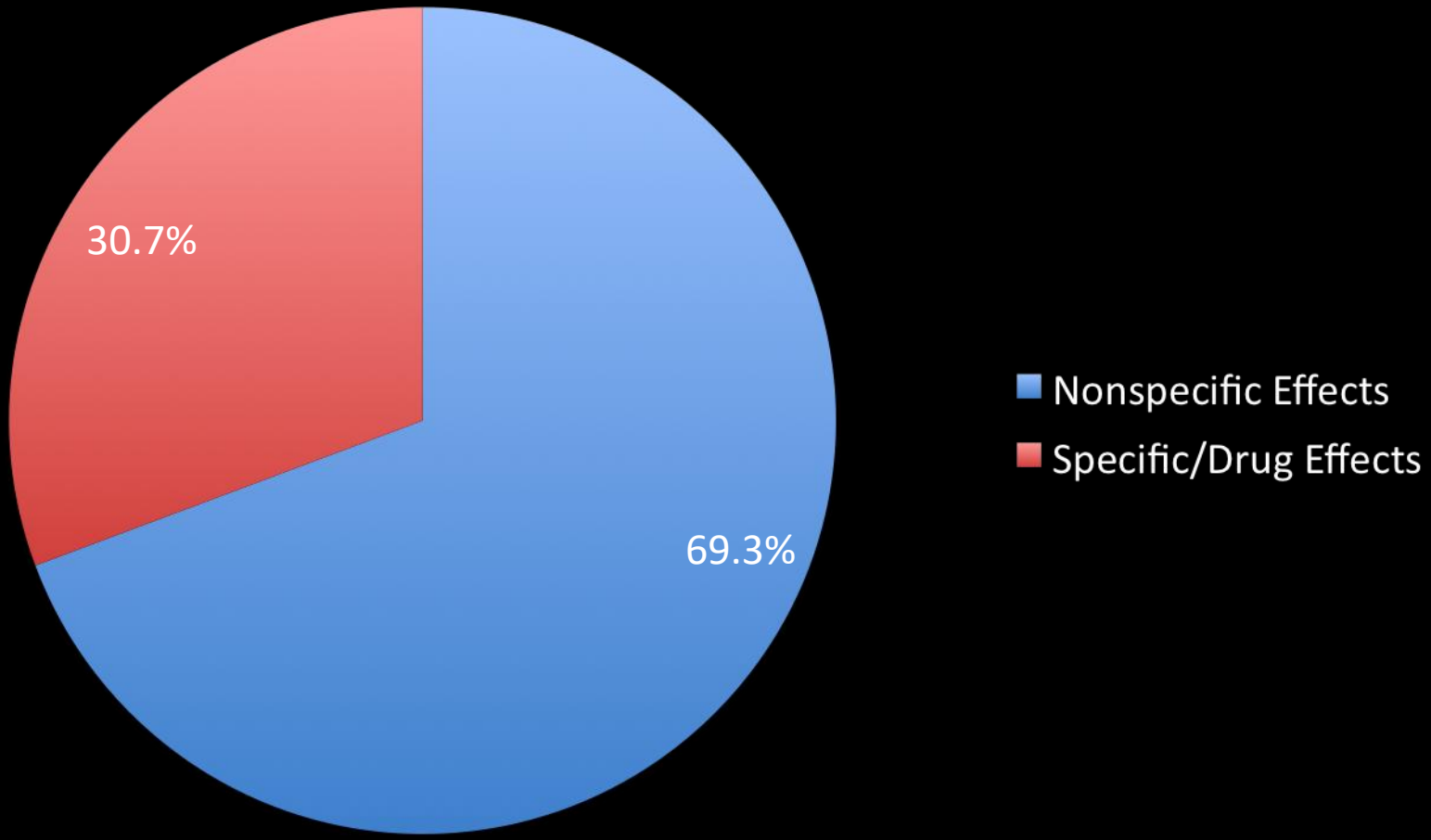
Symphony of Wellbeing

- mPFC involved in the representation and evaluation of self-referential information
- pCC involved in the integration of self-referential
- Together they support self-evaluation
- Increased connectivity within parts of the DMN

The Mental Neworks & the Long-Term Memory Systems



Placebo

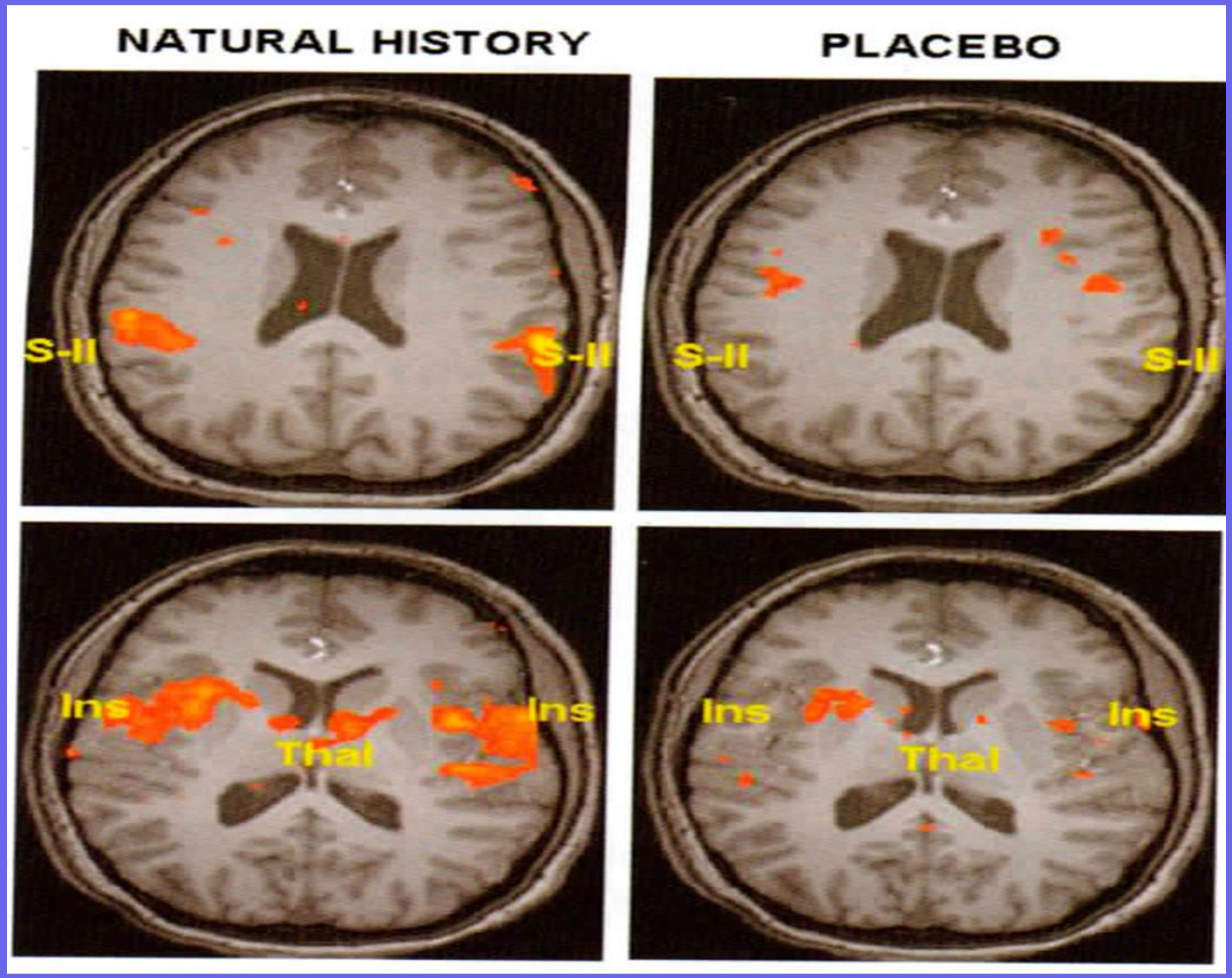


*Derived from pooled response rates for drug and placebo of 53.8% and 37.3%
Papakostas, *Eur Psychopharmacol*, 2009

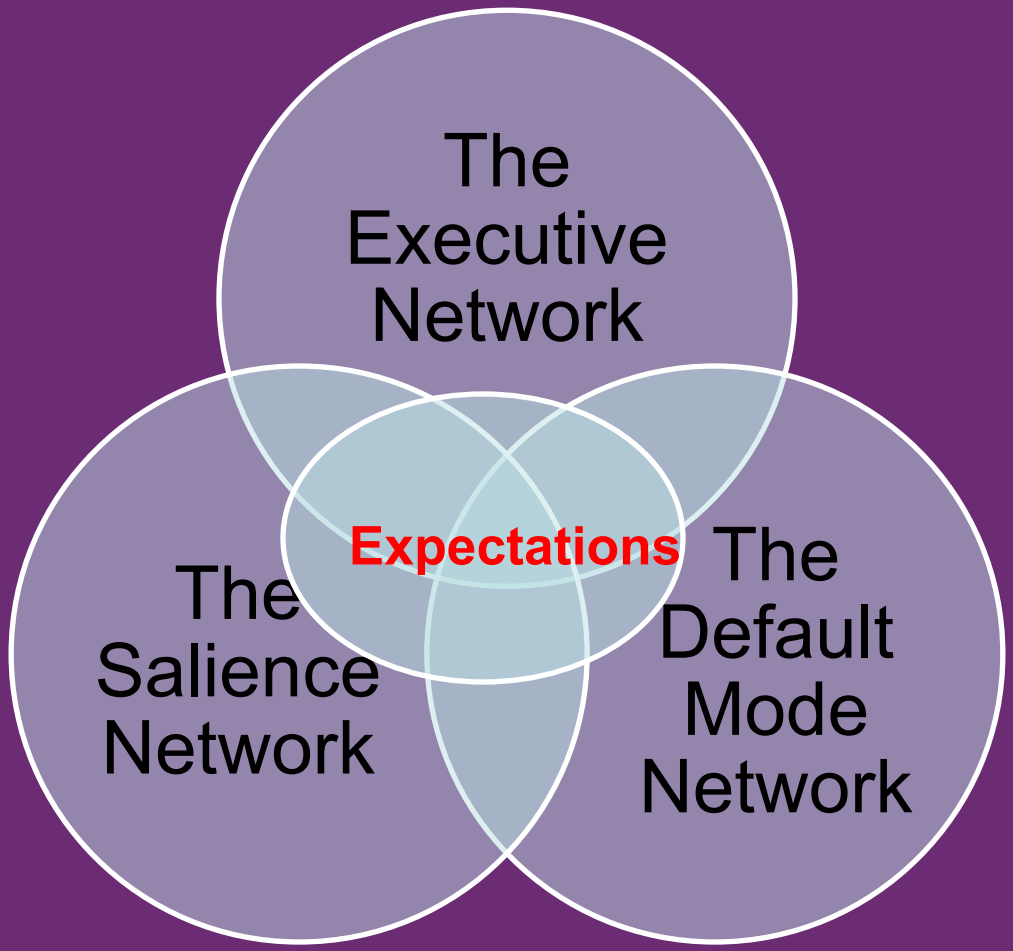
Incidence of Placebo Response

- 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



Balancing the Mental Networks



Beyond the alliance

Outcome Data

- 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

It is an evolutionary imperative to nurture our SEEDS (Heather Lowndes)





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…

Self-Care Behaviors

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

Hunter-gatherer Adaptation Boosted the Social Brain

Regulatory Networks of the Social Brain

- Bonding/Attachment
- Cognitive capacity
- Affect Regulation
- Safety
- Mental and physical health

Developmental Programming of stress responses

- Experiencing trauma or stress in infancy or childhood leads to:
  - Impaired regulation of HPA axis
  - Epigenetic changes to genes involved in inflammation
    - Elevated inflammation, especially in gut
    - Increased incidence of pain conditions including fibromyalgia & irritable bowel syndrome

The Effects of Social Medicine

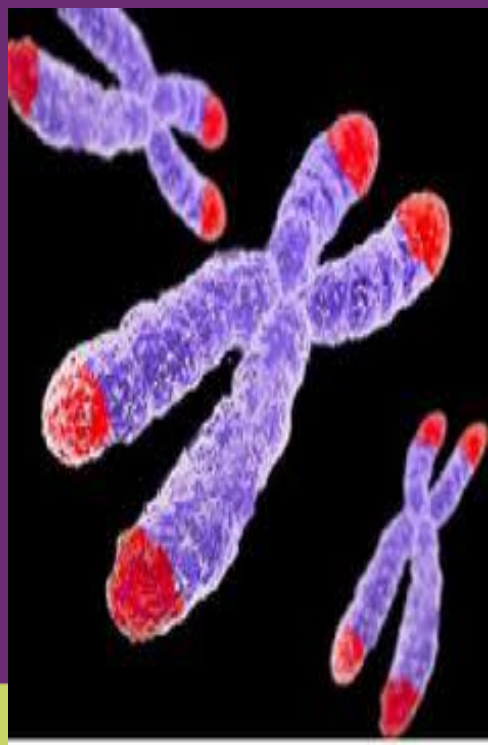
- ↓ Cardiovascular reactivity (Lepore, et al, 1993)
- ↓ Blood pressure (Spitzer, et al, 1992)
- ↓ Cortisol levels (Kiecolt-Glaser, et al, 1984)
- ↓ Serum cholesterol (Thomes, et al, 1985)
- ↓ Vulnerability to catching a cold (Cohen, et al, 2003)
- Depression (Russell & Cutrona, 1991)
- ↓ Anxiety (Cohen,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

Client Education

Your health will suffer without positive social connections

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.



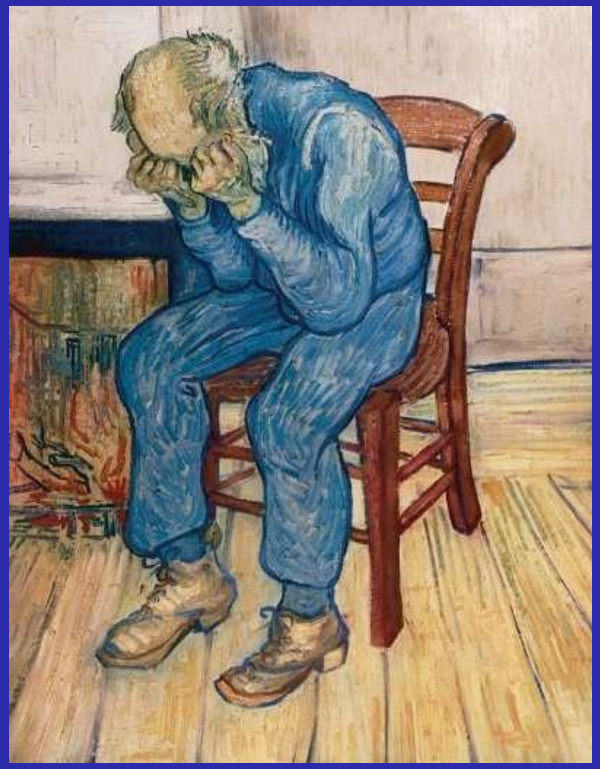
- Psychobiomarker": Linked to social status, perceived stress,
- depression, predictive of mortality (Epel, 2009, Current Directions)

Client Education

You will live longer with positive relationships

Loneliness

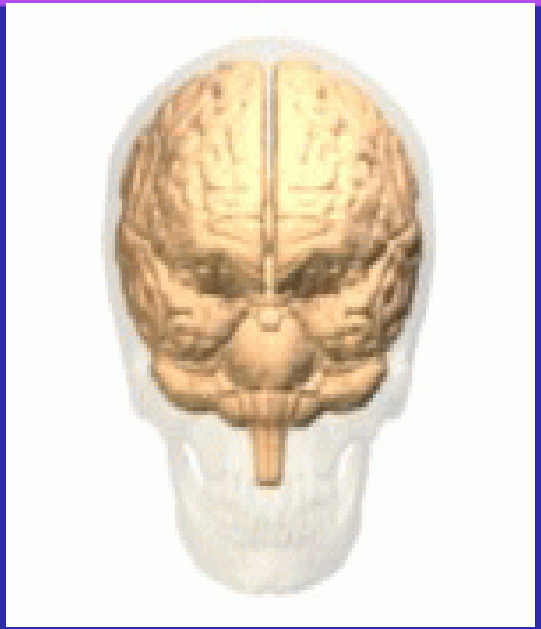
- In Portugal 1000 people 65> assessed:
  - Loneliness was the single most important predictor of depression (Paul, et al, 2006)
- In London 2600 people 65>
  - More than 15% were at risk for social isolation and depression (Illife et al., 2007)



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

The Cost of Loneliness



- As detrimental as smoking to longevity
- The temporal-parietal junction - cognitive empathy less activated and can atrophy
- Demished ventral tegmental area (VTA) and nucleus accumbuns
  - –Less of a sense of pleasure

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)

Client Education

You have brain networks that need social activity or they will shrink

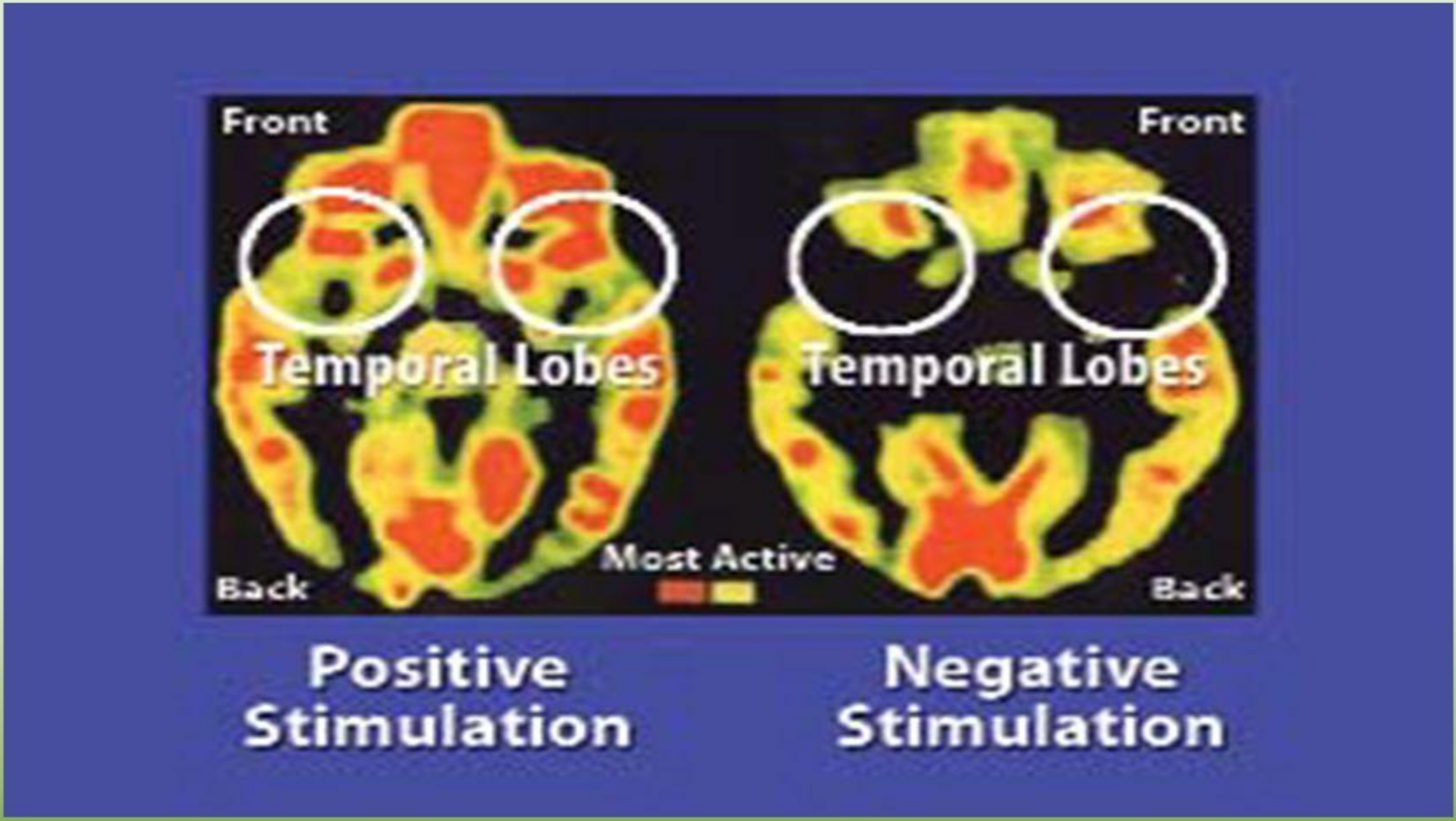
Deprived Social Brain Networks

- 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 Deprived

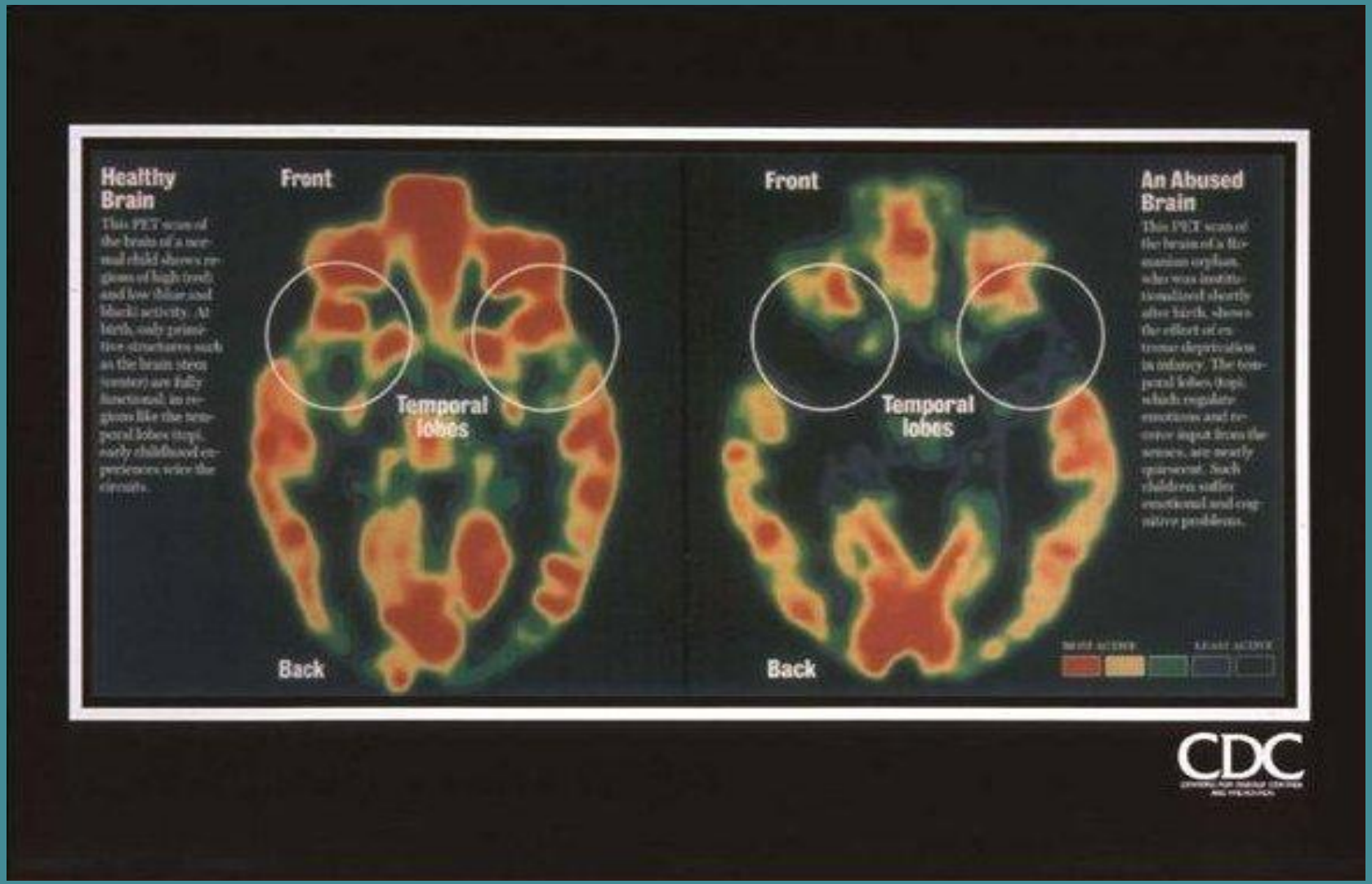


Brain activity of a normal five-year-old child (left)
and a five-year-old institutionalized orphan neglected in infancy (right).

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



Maternal separation leads to the following:

- ↓ development of inhibitory neurons and changes in the connections of serotonin and dopamine neurons in the mPFC
- Downregulation of gene expression for GABA receptors in the locus ceruleus, resulting in more norepinephrine
- Upregulation of gene regulating glutamate receptors, which contributes to anxiety and depression.
- Abnormally programmed gene expression in the amygdala, hippocampus, and PFC, priming the stress system
- Plasticity between the PFC and amygdala skewing toward the amygdala and the rest of the stress system

Epigenetic changes to the developing child's stress response system

Still Face and Visual Cliff

- **Visual Cliff paradigm** (Source, 1985)
  - Mother shows fear – child won't cross
  - Mother smiles 80% will cross
- **Still Face paradigm** (Tronick, Cohn, Field)
  - 9 months old no longer approach novel toys—imagination shuts down
  - s/he becomes agitated and distressed

Amygdala activation adults vs. children

- The amygdala involved in disambiguation of social situation—helps an individual disregard irrelevant information
- Fearful faces provoke more amygdala activity in adults than children
- Neutral faces (ie. Still Face Paradigm) provoke more amygdala activity in children than adults
(Tottenham, et. al., 2009 for review)
- With maturation: neutral faces and ambiguity are tolerated due to increased cortical processing
(Casey, et. al., 2005)

Gender Differences

- Boys more likely to likely to orient towards mothers' facial expression of joy, vocalizations, and gestures
- Girls more object oriented with sustained attention
  - Girls show more self-regulatory behaviors
  - Greater PFC—amygdala development
- The slower development of boys makes them more reliant on caregivers for help with their emotional regulation.
  - More at risk for suffering from abuse and neglect
  - More reactive to maternal emotions
  - More hostile attribution bias to ambiguous social situations

Infants of depressed mothers

- **Display more aversion and helplessness, and vocalize less**
- **Higher heart rates, decreased vagal tone, and more developmental delays at 12 months of age** (Field, 2005)
- **Maternal depression during the first two years of a child's life is the best predictor of cortisol production in children at age 7** (Ashman, et al., 2002)

Intergenerational Transmission

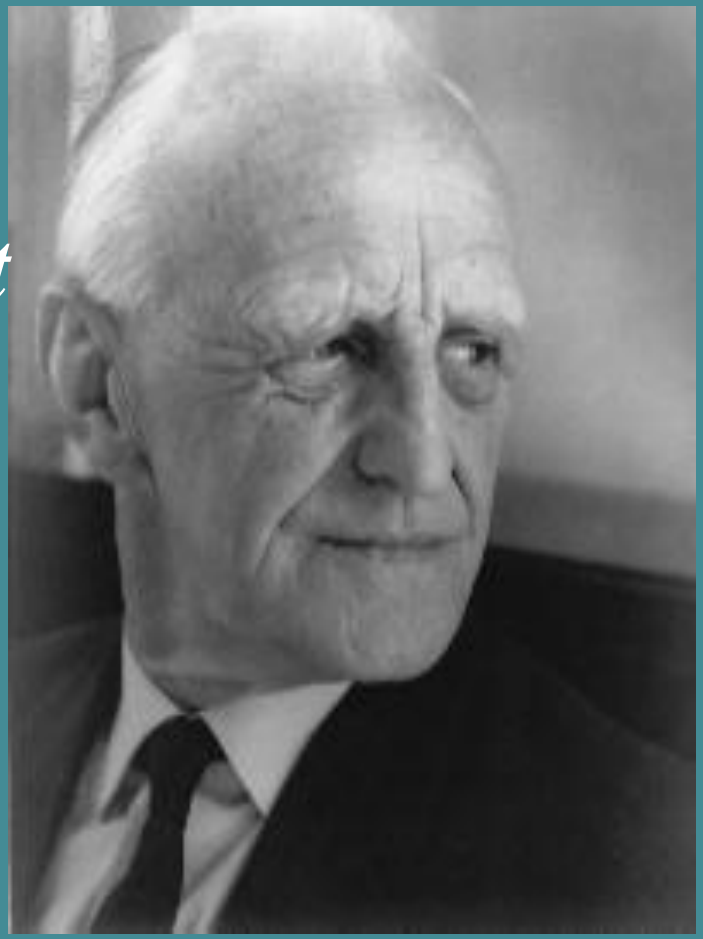
Infants of depressed mothers have:

- Over-active right frontal lobes
- Under-active left frontal lobes
- Lower levels of DA and 5-HT
- Higher levels of stress hormones (Field et al., 1998)

- Treating the mother's depression contributes to the child's improvement

D.W. Winnicott

- **Analysand of Melanie Klein**
- ***Good-enough parenting***
- **The *holding environment***
- ***Impingements mirroring***
- ***transitional object***



"Good Enough" Parents

- Perfect *isn't* good enough
- High levels of affective matching correlate with insecure attachment
- Low levels also correlate with insecurity
- Moderate matching is optimum

Good-enough parenting and frustration tolerance

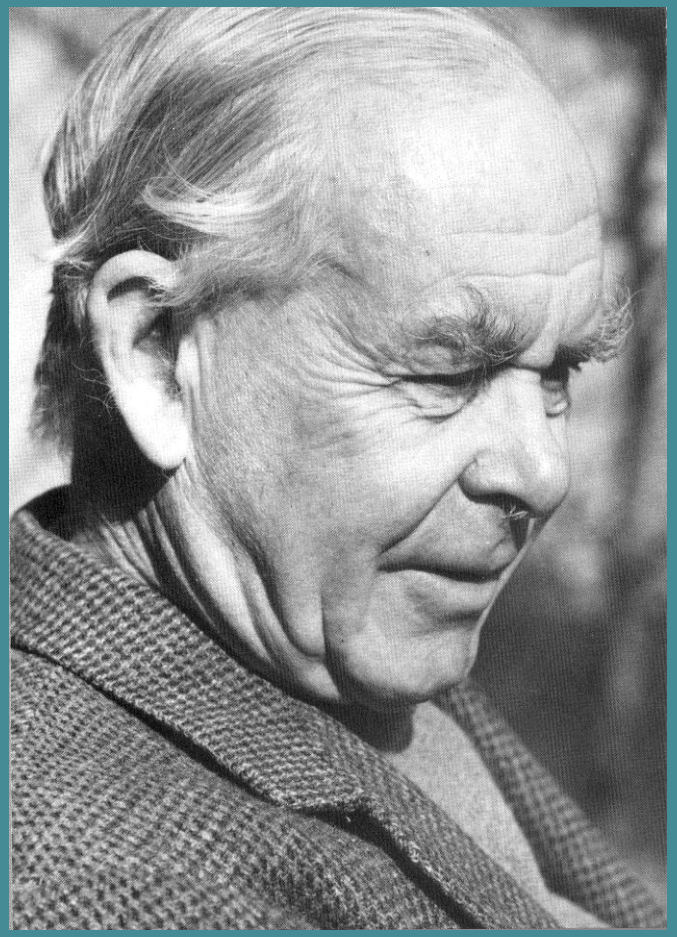
- If the baby is matched by instantaneous soothing s/he will not develop the PNS and the brakes to the SNS and HPA axis
- Good enough parenting factors in time before the baby is soothed
  - To anticipate being soothed and activate the parasympathetic nervous system
  - builds in frustration tolerance

John Bowlby (1907 – 1990)

- *Supervised by M. Klein*
- *Safe haven*
- *Attachment figures*
- *Proximity seeking*

  – **infants seek proximity to the attachment figure for safety.**

  "Like a thermostat"



ISS/ Maternal Behaviors

Child Categorization	*Maternal Behavior*
(Secure)	emotionally available, perceptive & effective
(Avoidant)	distant & rejecting
(Anxious/Ambivalent)	inconsistent availability
(Disorganized)	conflictual behavior

Boys Respond Differently

- Given that fathers excite and set limits, the research paradigm referred to as the Risky Situation (RS) serves as a measure of the father and boys activation relationship.
    - the father's caregiving behavior tends to focus on arousal and excitement as well limit setting (Paquette & Bigras, 2010).
- Rough- and-Tumble Play (RTP) paradigm, the father activates but also sets limits. When fathers do not exercise dominance in the RTP with preschoolers they are more likely five years later to have poor emotional control and high levels of physical aggression, especially boys (Flanders, et al, 2009).
    - **RTP trains the child's prefrontal cortex to learn to set limits on affect.**

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

Thermostat of Attachment

- Secure attachment limits elevations of cortisol in stressful situations because the parent perceives and responds to the inner state of the child (Fonagy & Target, 1997).
- Early positive maternal care protects the hippocampus from high levels of cortisol (Meaney et al., 1989).
- Insecurely attached toddlers in the face of stranger and separation situations show elevated cortisol levels (Nachmia, et al, 1996).

Insecure Attachment Longitudinally

- Anxious/ambivalent and avoidant attachment styles associated with the development of depression.
  - Avoidant style leads to depression based on a sense of alienation
  - Anxious /ambivalent style leads to depression based on an internalized sense of helplessness and self-doubt.

Client Education

- Though the stress thermostat function in your brain is not working, we will work together to rebuild it so that you will no longer react to normal situations as if they are dangerous.

Correspondence between Child & Adult Attachment Categories

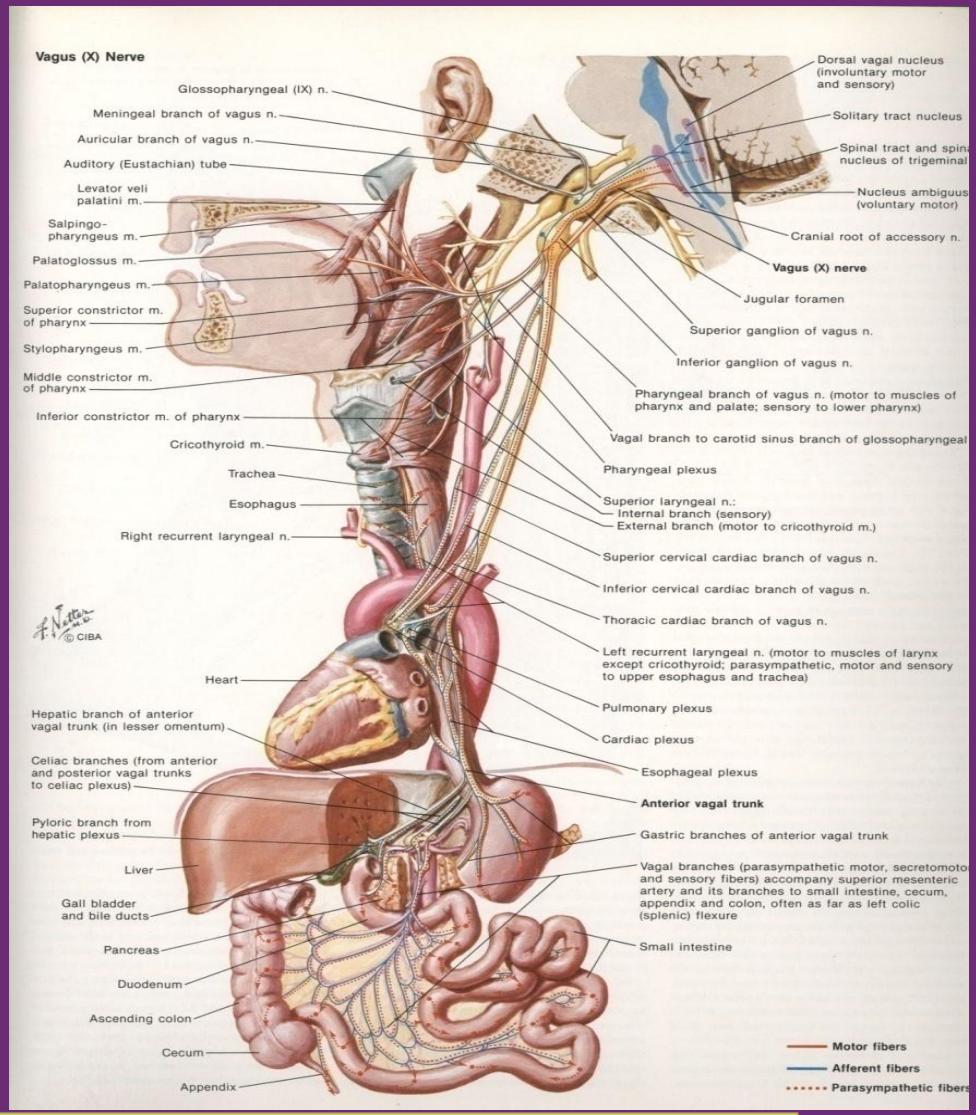
Child (ISS)	• *Adult (AAI)*
- secure	• - free/autonomous
- avoidant	• - dismissing
- ambivalent	• - preoccupied
- disorganized	• - unresolved

Social Brain and the PSN

- Neurochemistry includes:
  - Oxytocin
    - Turns down cortisol
- Central Parasympathetic Nerves
  - "Smart" Vagus Nerve

The Vagus Nerve System

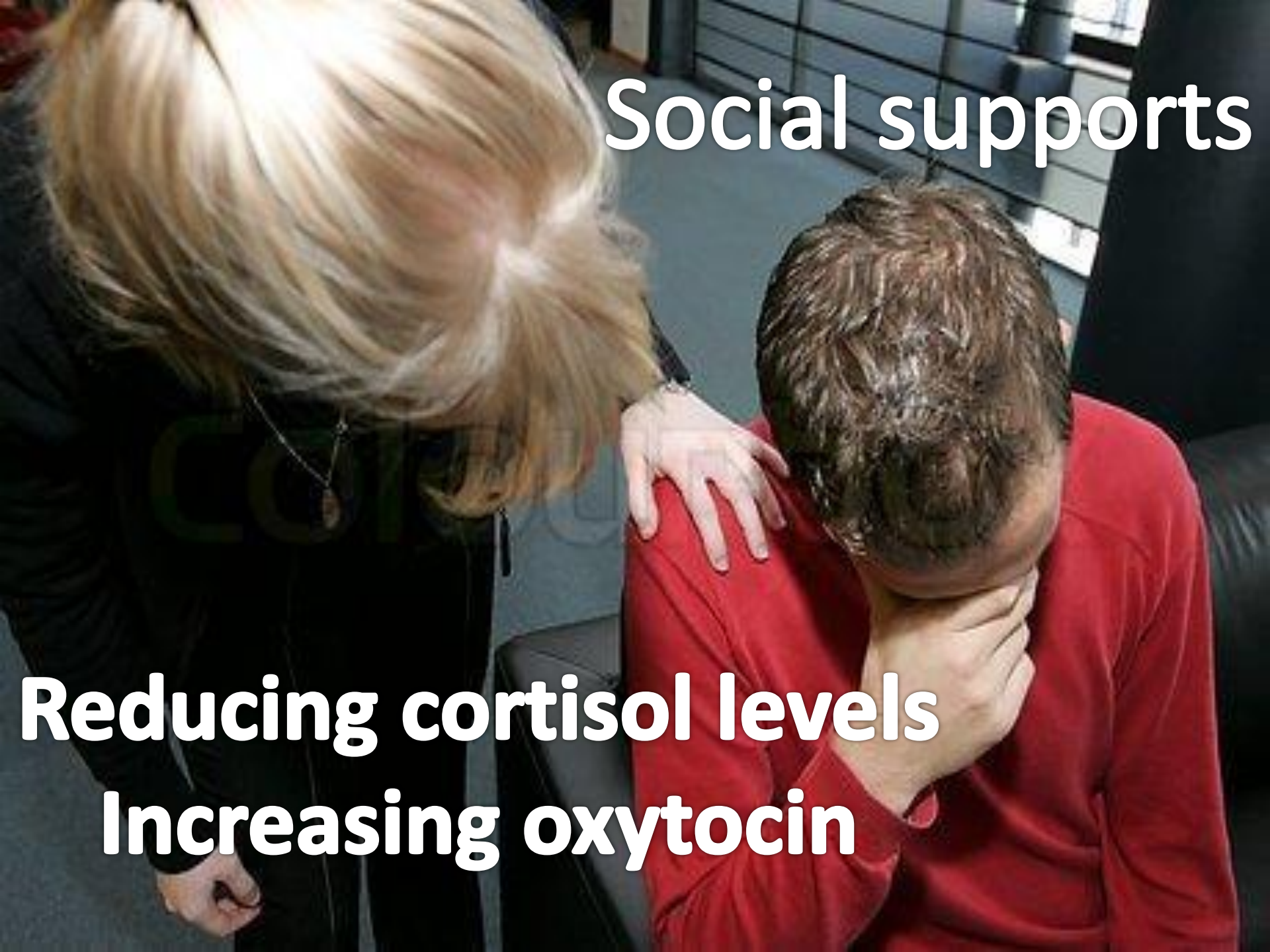
- Tenth Cranial Nerve --a complex of sensory and motor nerve fibers.
- *Vagal tone*- the ability to modulate target organs without sympathetic arousal
- allows attachment and sustained relationships.



Vagal Brake (Porges)

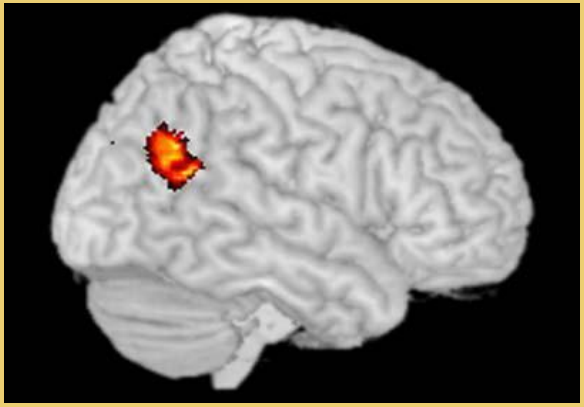
- *Higher vagal tone* correlates with:
  - Self-Soothing capacity
  - Quality of caretaking and attachment
  - More reliable autonomic responses
  - The range and control of emotional states
- *Lower vagal tone* correlates with:
  -- Anxiety
  - Impulse Control problems
  - Hyperactivity, Attention deficit and distractibility
  - Avoidant & Disorganized Attachment
  - Irritability

On the market


Social supports
Reducing cortisol levels
Increasing oxytocin

Theory of Mind

- Amygdala
- Insula
- Right TPJ
- Anterior cingulate (Siegal & Varley, 2002)

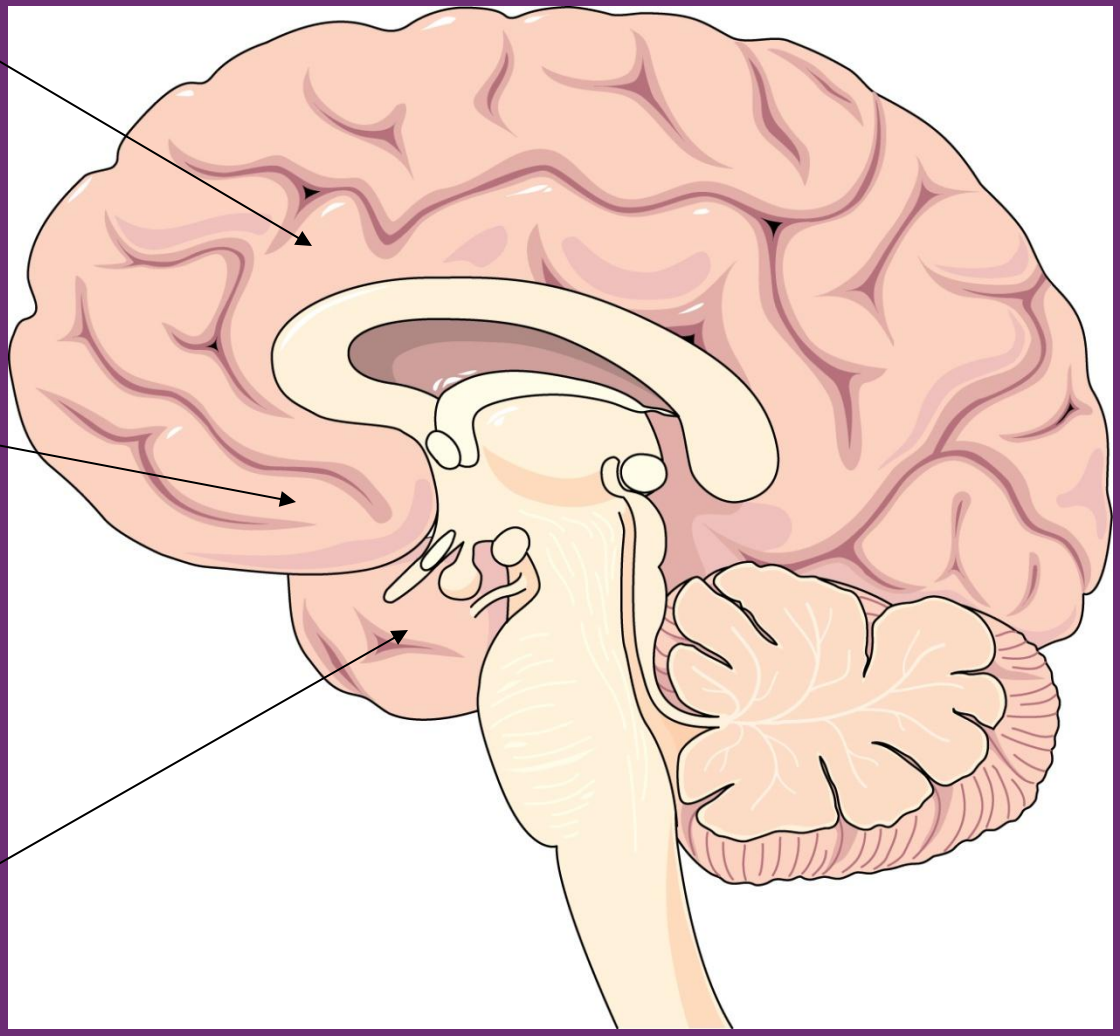


- The R-OFC -- decoding mental states
- The L-OFC -- reasoning about those states (Sabbagh, 2004).
- There may be major nodes:
  - the medial prefrontal cortex for self-related mental states;
  - the superior temporal sulcus for goals and outcomes

Cingulate Cortex

Orbital Frontal Cortex

Fusiform Gyrus

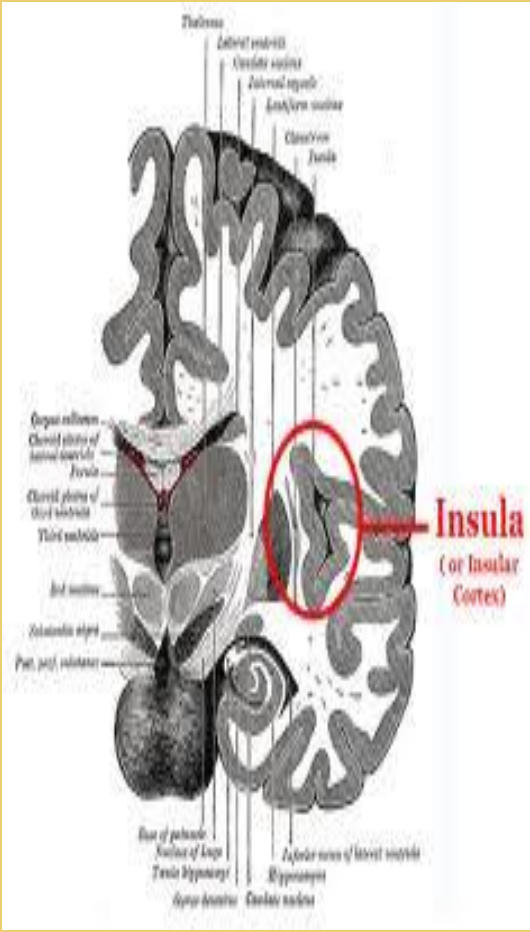


Anterior Cingulate Cortex

- ACC integrates cognitive and emotional information (Bush, et al, 2000)
- Active when detecting emotional signals from self and others (Critchley, et al., 2004)
  - The ACC is involved in both physical pain and social rejection (Eisenberger & Lieberman, 2005)
  - The dorsal ACC activates when fear of rejection occurs (Lieberman, 2005)
  - Activated when someone we love experiences pain or social ridicule (Botvinick, et al, 2005)
- Part of neural basis for cooperation (Pilling, et al, 2002)
- Damage results in reduced empathy and/or maternal behavior (Brothers, et al., 1996)

Insula and Empathy

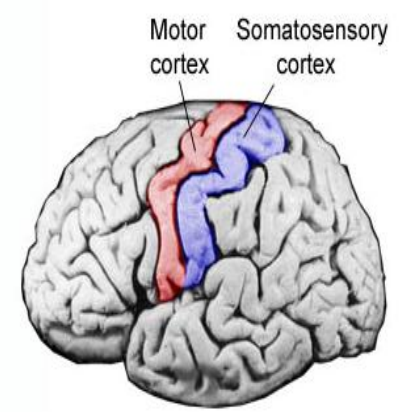
- Conduit between subcortical areas and cortex
- Draws on information from body areas, and input from amygdala and hippocampus
- Works with medial PFC to interpret and regulate emotional experiences
- Links mirror neuron systems with body states “Insula Hypothesis of empathy (Carr, et al, 2003)

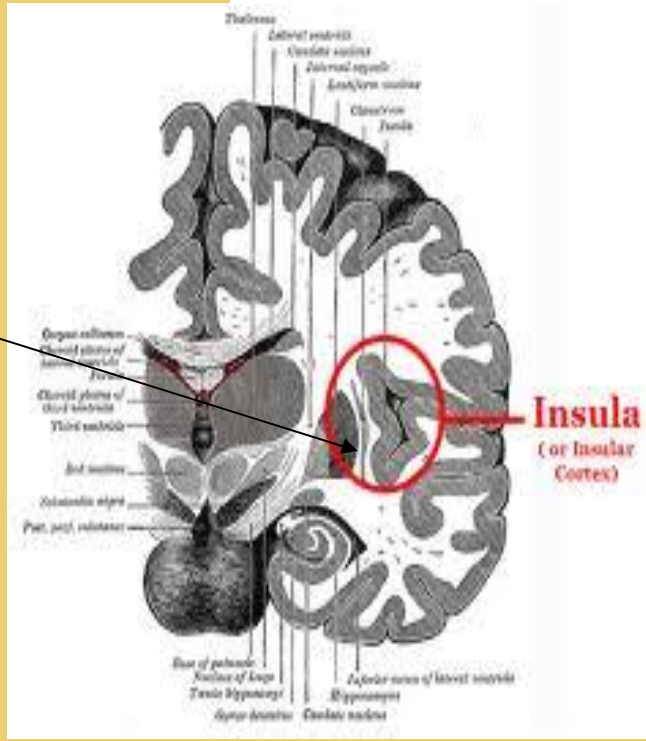


Insula and Touch

- Soft touch: C—Tactile fibers (CT)
  - Unmyelinated—thus slower, tracks to the:
    - **insula** (part of the Salience Network
    - Emotional touch
    - Oxytocin
    - Impaired in people struggling

with forming relationships





Spindle Cells

- Found in abundance in the OFC, AIC, and ACC---transmitting salience info
- Four times larger than other neurons, with a long extension
- At birth humans have approximately 28,000 spindle cells,
  - growing to 184,000 by age four,
  - 193,000 by adulthood.
- By comparison an adult ape has 7,000.

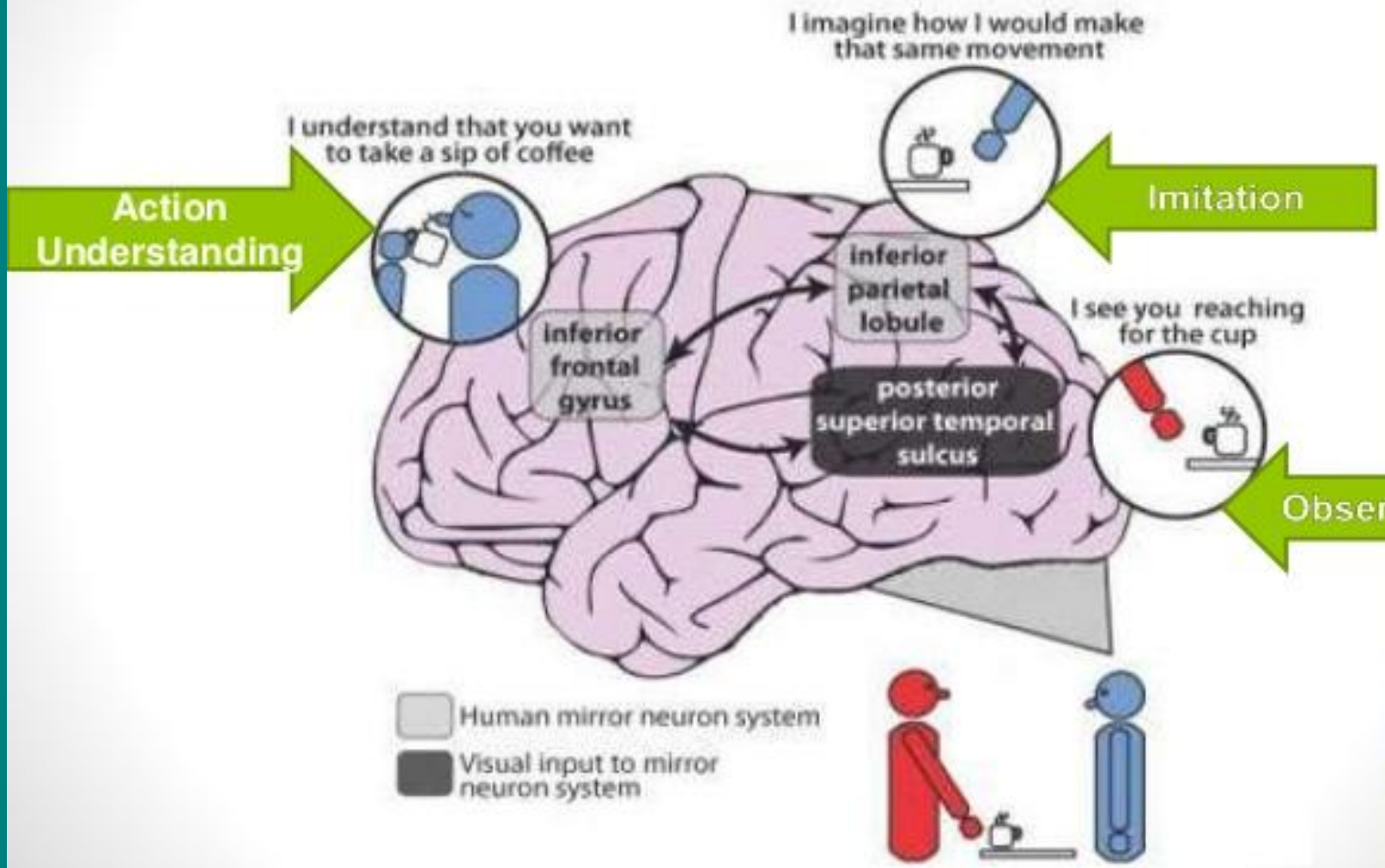
Spindle Cells

- Respond extremely quickly— “Behavioral Flexibility”
- Involved in making snap judgments, but also in solving complex problems in emotionally stirring situations
- Rich receptors of dopamine, serotonin, and vasopressin, important for generating mood and bonding
- Vulnerable to neglect, abuse, and trauma

Mirror Neurons

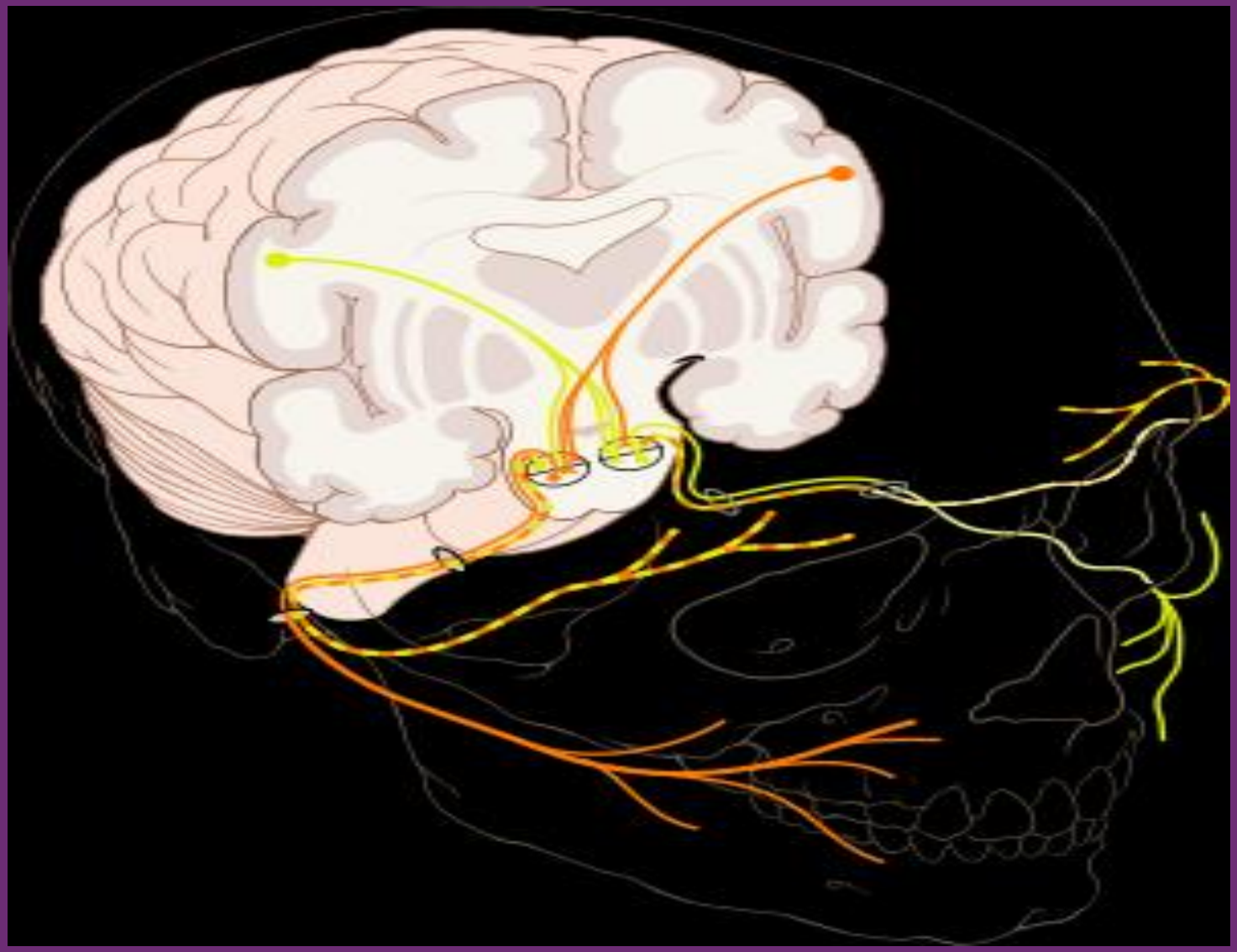
- Originally found in monkeys (Rizzolati & Arbib, 1998)
- Critical for evolutionary development of social skills
  - Associated with anticipating goal-directed behavior
- Associated with empathy (Iacobini; Miller, 2005)
- Found in PFC, posterior parietal lobe, superior temporal sulcus, insula, and cingulate cortex

Role of Mirror Neurons



Mirroring Human to chimp ?

Contralateral Facial Muscles and Nerves



Facial Expressions

Left Hemisphere

Controls expression on the lower right side of face

- Is NOT adept at reading facial emotion expression (e.g. alexithymics)

Right Hemisphere

Controls expression on the lower left side of face

- Is adept at reading facial emotion expression

Facial Expressions

- We view objects and faces with different systems
- Facial-reading systems --amygdala, fusiform gyrus, and supertemporal gyrus (Gauthier, et al, 2000)
- Reading of faces when faces are right-side up, but not when faces are upside-down (Kilts, et al, 2003)
- When we view faces upside-down, we view them as objects, unable to read their emotional content
- ASD patients read faces as if they were viewing objects

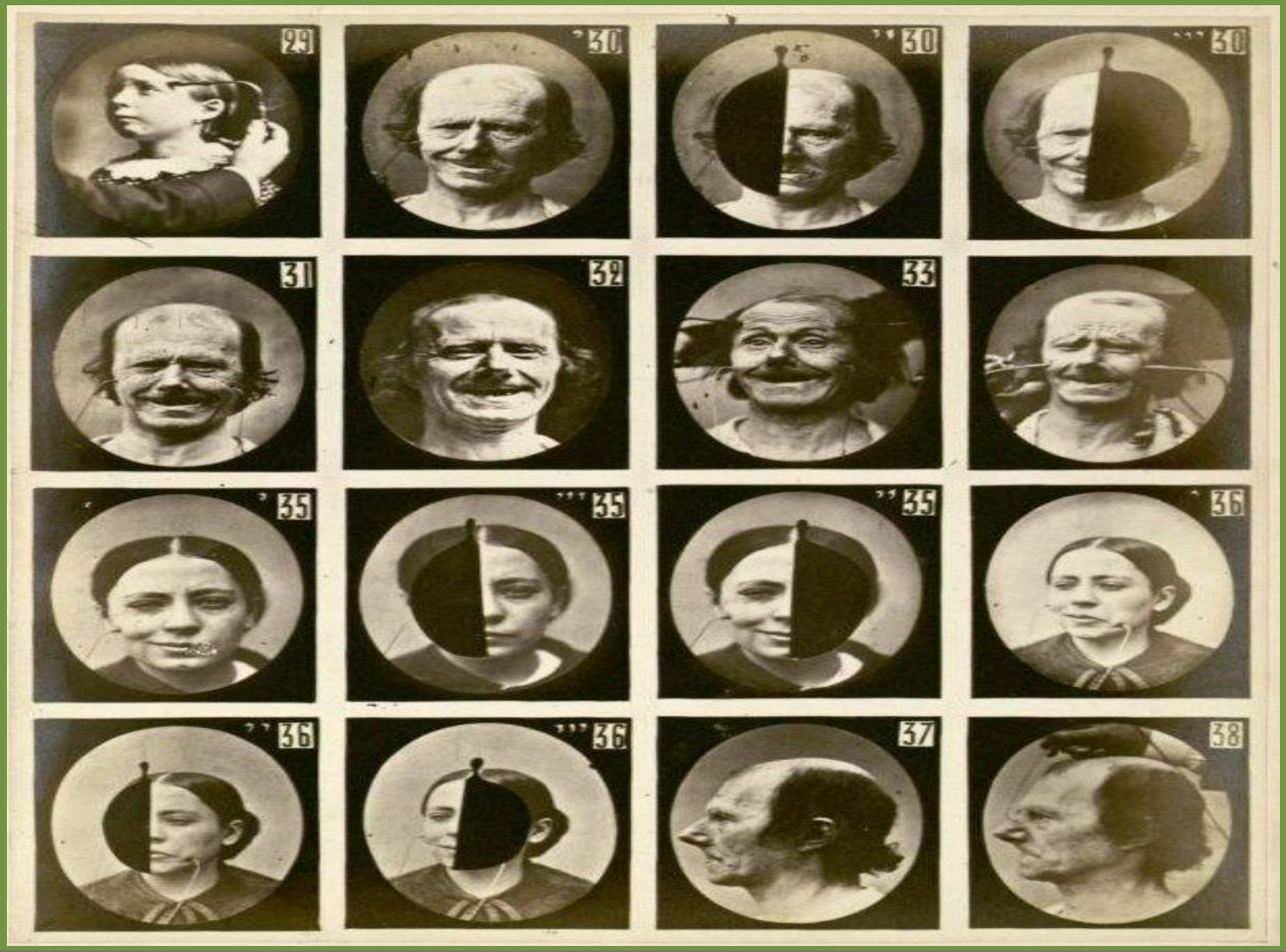
D Smiles

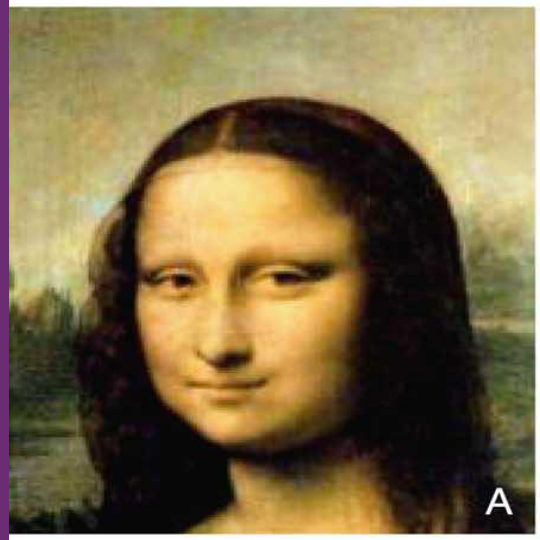
- Guillaume Duchenne (1806-1875) identified the orbicularis oculi muscles around the eyes
- Non-D smiles, possibly masking negative states and are more likely to be asymmetrical
- D smiles -- L-PFC activation
- Non-D smiles -- R-PFC activation (Ekman, et al, 1996)

Feedforward Expressions

- Therapists can model and influence the client's facial expressions and mood via feedforward and feedback:
  - Contracting muscles on the right side activates LH and positive emotions
  - Contracting muscles on the left side activates RH and negative bias--e.g., a "smirk" (Schiff, et al, 1992)

Duchenne 1862 Stimulating Facial Muscles

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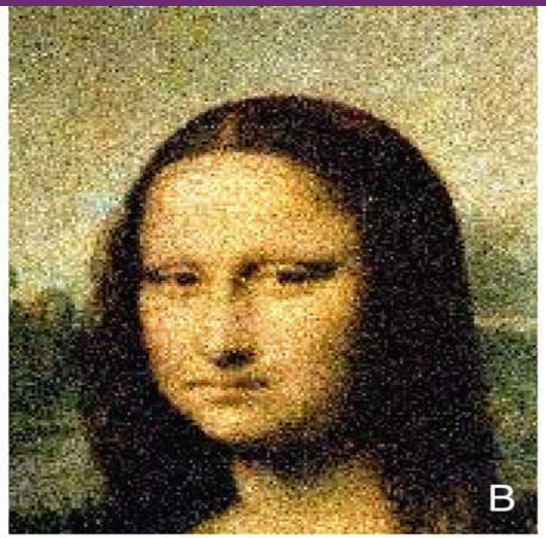
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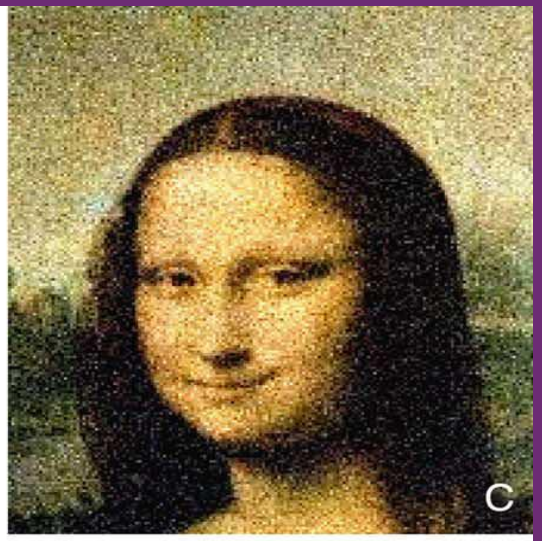
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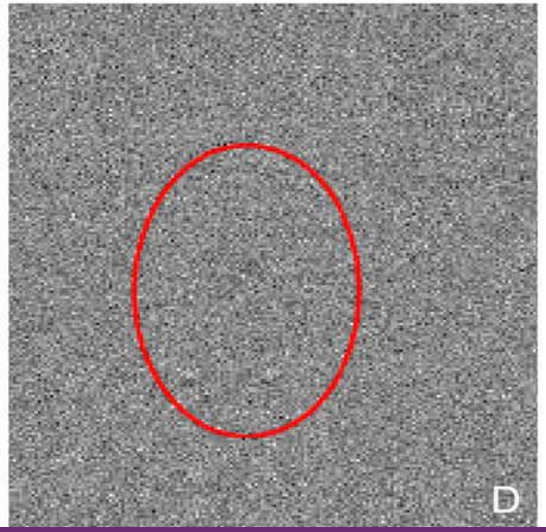
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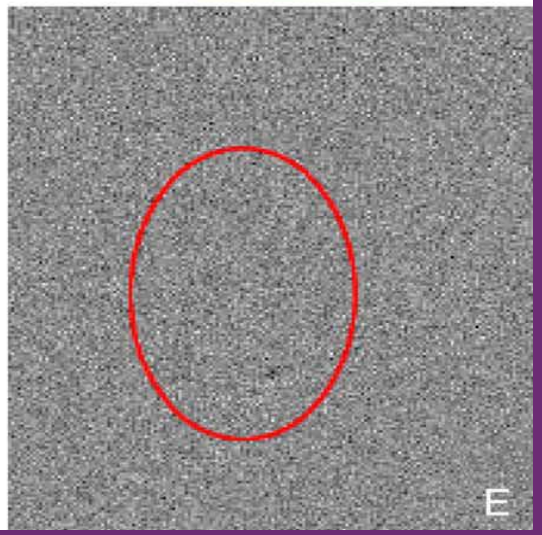
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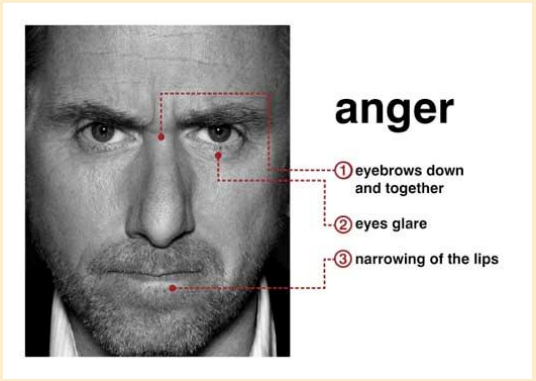
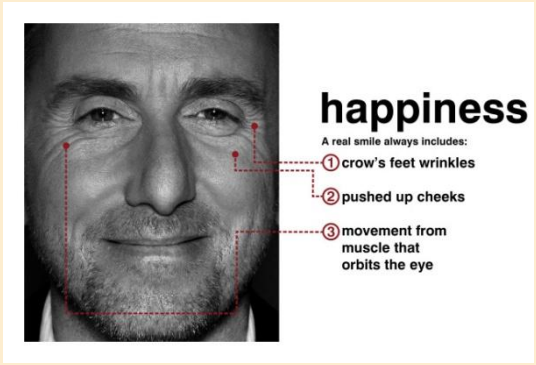
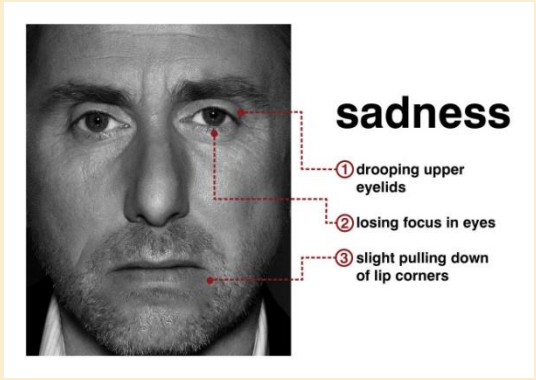
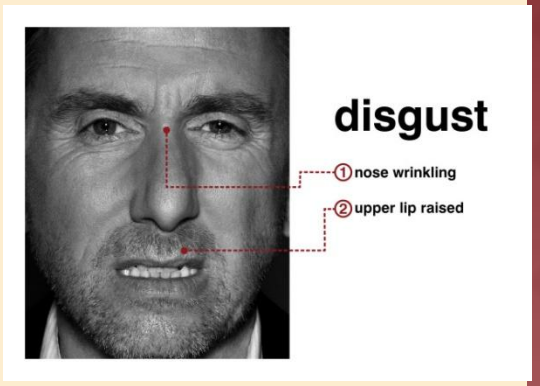
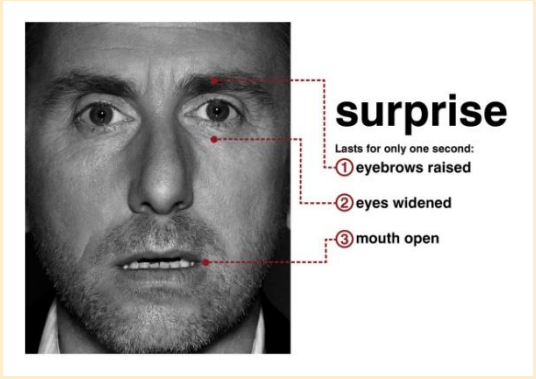
Micro-Expressions

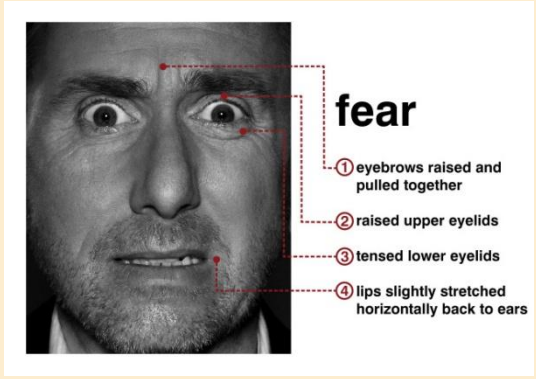


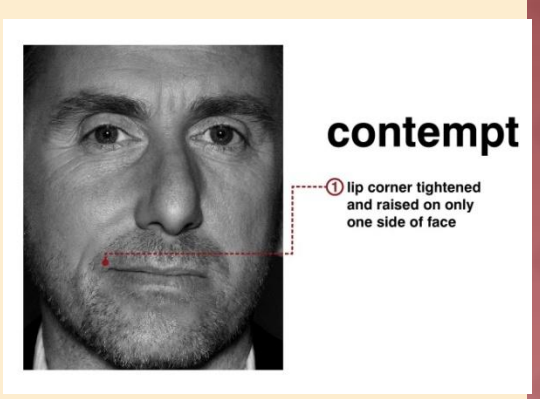




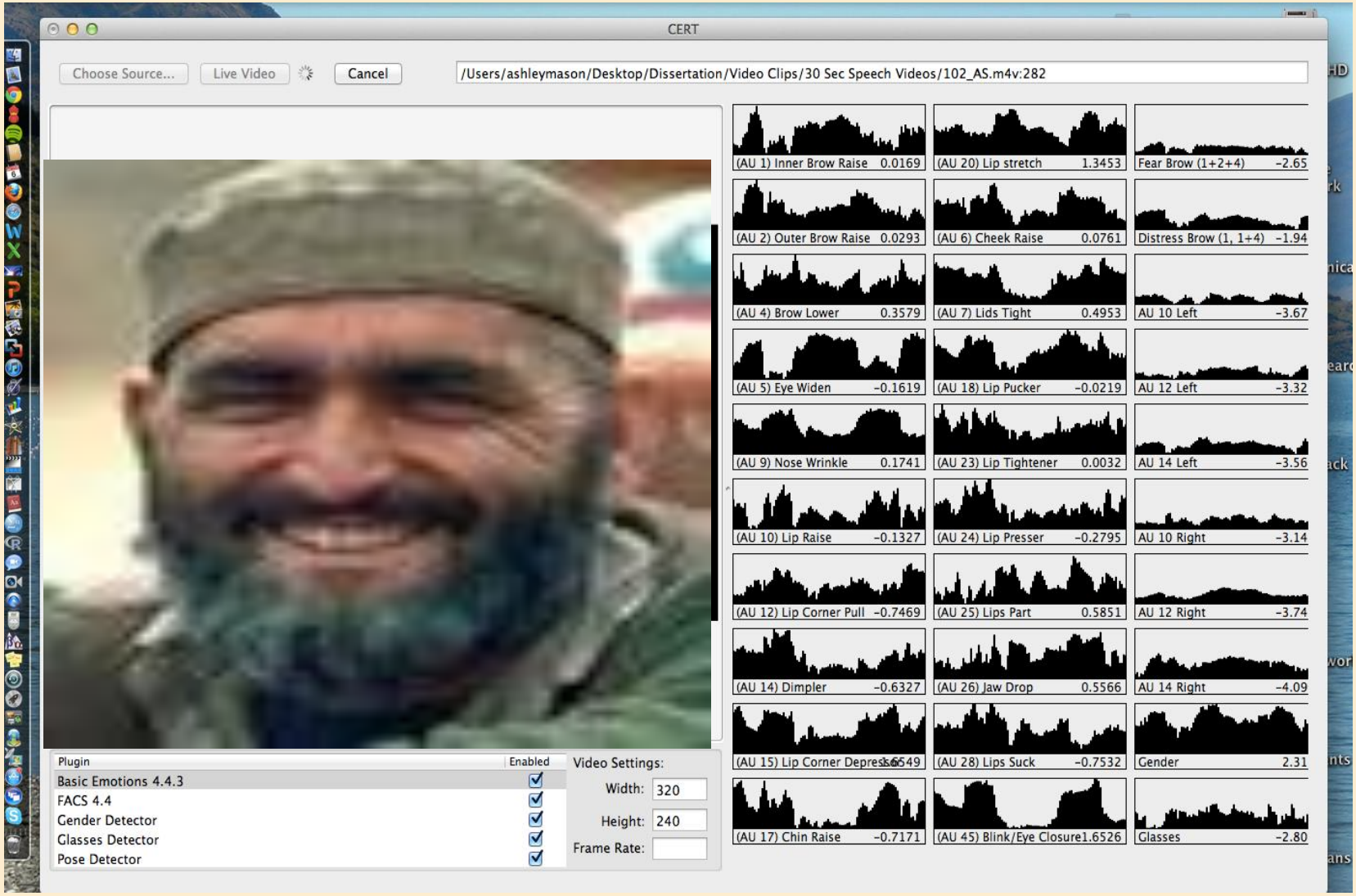








Facial Action Coding System--FACS



Smiling Kindles Positive Moods

- Perceiving the smiles of others triggers the release of DA (Depue & Morrone-Strupinsky)
- Presenting smiles for a fraction of a second followed by neutral stimulus increases the positive reaction to that stimulus (Dimburg & Ohman, 1996)
- Bilateral smiles ↑L-PFC positive moods
- Smiling during periods of stress ↓ cardiovascular arousal back to baseline

(Fredrickson & Levenson, 1998)

Psychological Boost of Humor

- ↓ Anxiety (Yovetich, et al, 1990)
- ↓ Stress (Wooten, 1996)
- ↓ Depression (Deaner & McConatha, 1993)
- ↑ Self esteem (Martin, etal, 1993)
- ↑ Energy and hope (Bellert, 1989)
- ↑ A sense of empowerment (Wooten, 1996)

Laughter is Good Medicine

- Improves cognitive functions (Fry, 1992)
- Exercises and relaxes the muscles (Kuhn, 1994)
- Increases heart rate and blood pressure (Pearce, 2004)
- Decreases cortisol levels (Berk, et al, 1988)
- Increases natural killer cell activity (Takahashi, et al, 2001)
- Altering gene expression (Hayashi, et al, 2006)
- Stimulates the dopamine reward system (Mobbs, et al, 2003)
- Increased longevity (Yoder & Haude, 1995)

Client Education

- The saying ‘laughter is good medicine’ is true.
- The more you practice laughing, the more likely you will feel good and feel like laughing.

Cultural Framing
Race -- Ethnicity

- An integrated constellation of practices, symbols, values, and ideals as well as humor
- Shared by a community
- Transmitted from one generation to the next
- Constantly renegotiated and subject to change
- Operating at the individual and societal level
    - Producing outcomes
        - Socialization
        - Identity
        - Healing

Maximizing the Placebo Effect

- Good listening skills
- Empathetic Attention
- Gaze Attunement
- Appropriate Touch
- Communication style (language and prosody)
- Welcoming physical appearance
- Physical Proximity
- Asymmetrical power dynamics between therapist/client (Kradin, 2008)

Therapeutic Frames of Reference

- The expectancy set
- Degrees on the wall
- Confidentiality explained
- Empathy—Compassion
- 50 minute hour
- Problem/symptom focus
- Solution focus

Social Summary

- Social brain networks need activation
- Health related costs without activation
- Neurochemistry of social connection
- Non conscious facial expressions
- The emotional and cognitive costs of loneliness
- Social medicine for stress reduction

Family Time?

Self-Care Behaviors

- 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.

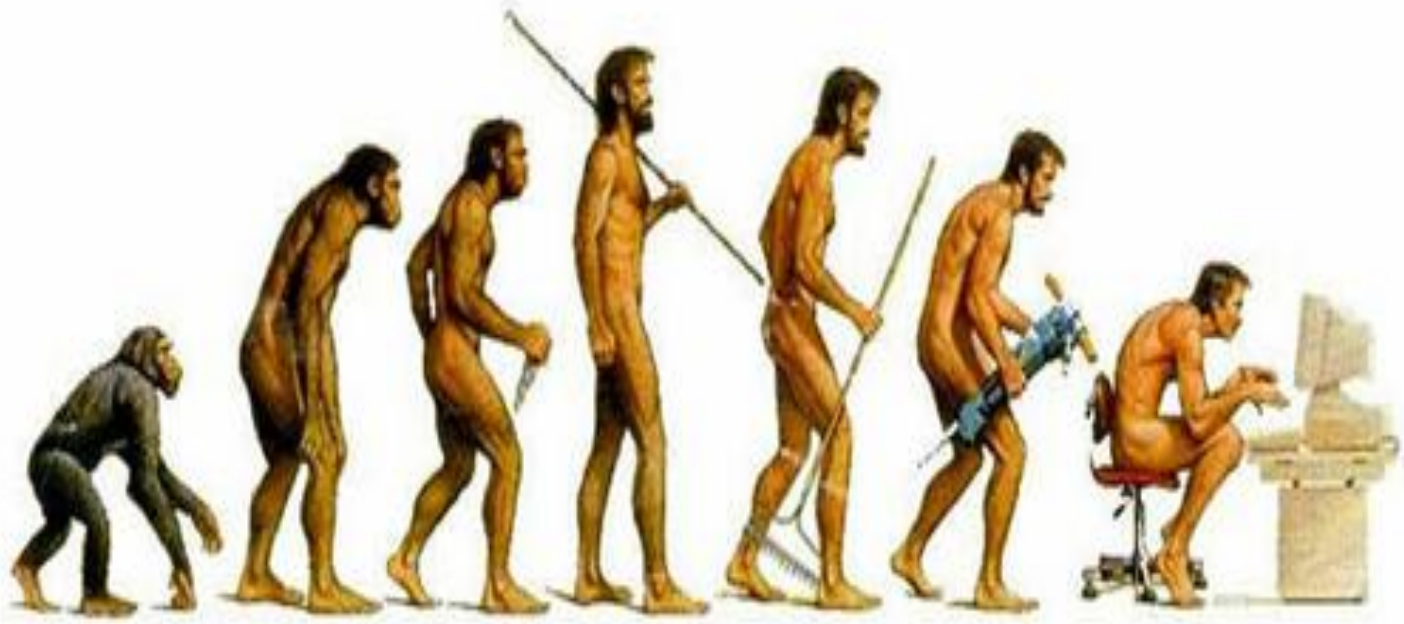
Resistance Training: Lifting, Throwing, and Carrying Objects

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



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

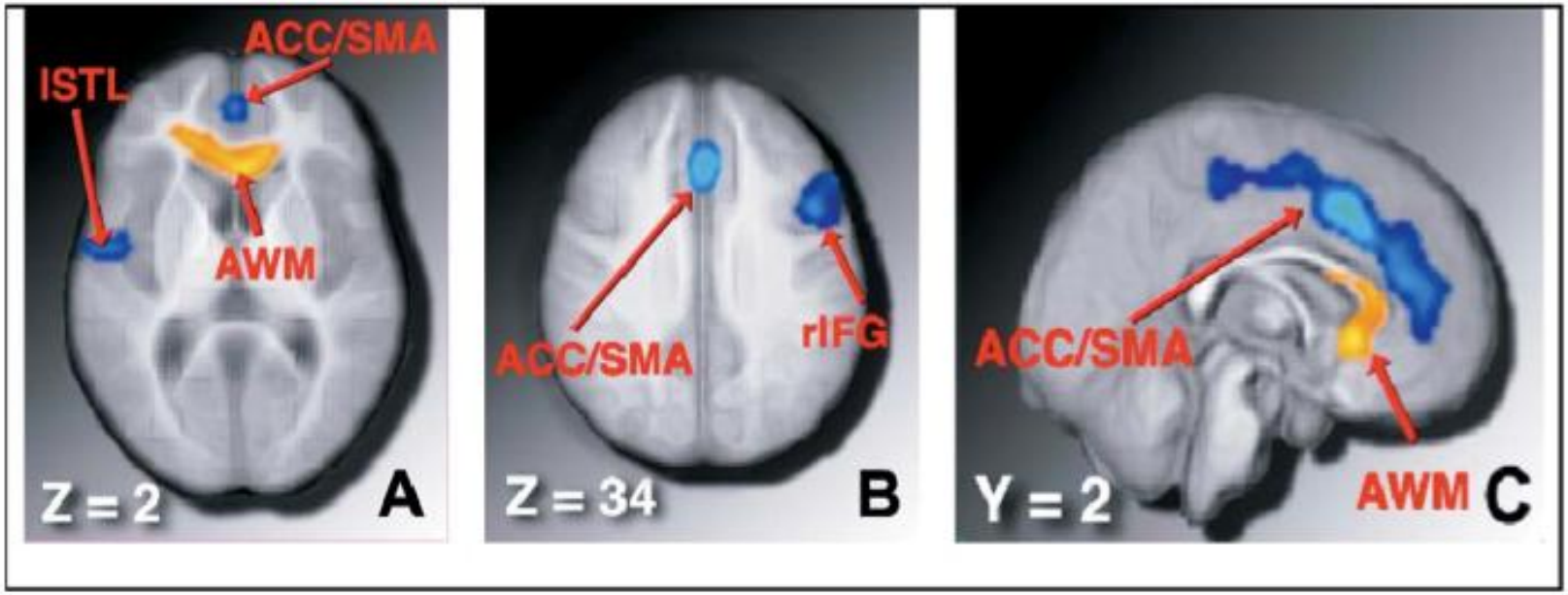
5-HT is modulated by exercise in specific brain regions and is also affected by intensity and duration of exercise.

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



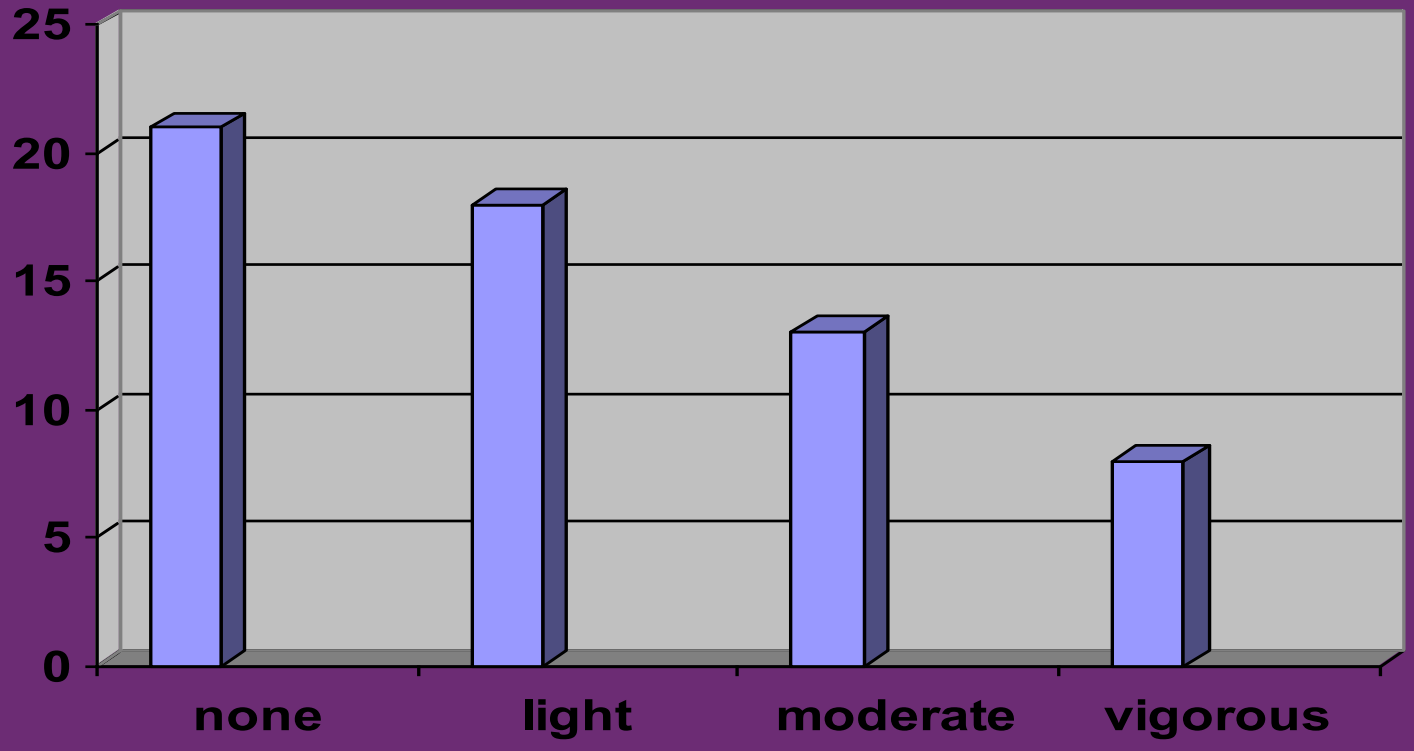
Blue regions: Gray matter volume was increased for aerobic exercisers

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 Improves Sleep

Exercise improves sleep quality and normalizes circadian rhythms.

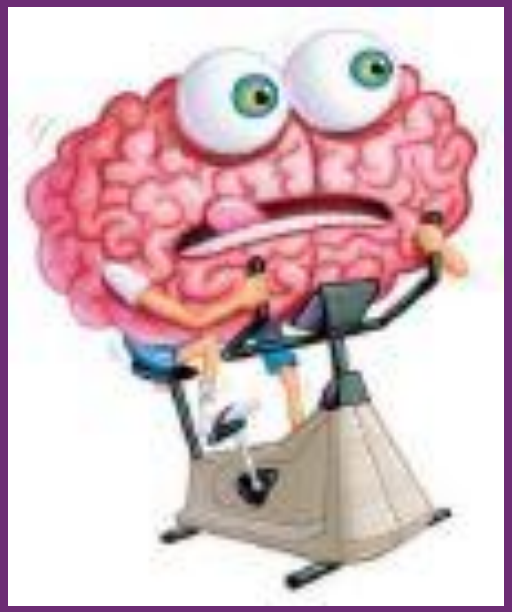
- increases slow wave sleep and total rest time
- decreases the amount of time to fall asleep
- decreases the amount of time spent in non-restorative sleep.

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



Exercise Optimizes

- Cognition
  - alertness
  - attention
  - motivation
  - cognitive flexibility

Telomerase

An enzyme that adds nucleotides to protects telomeres:

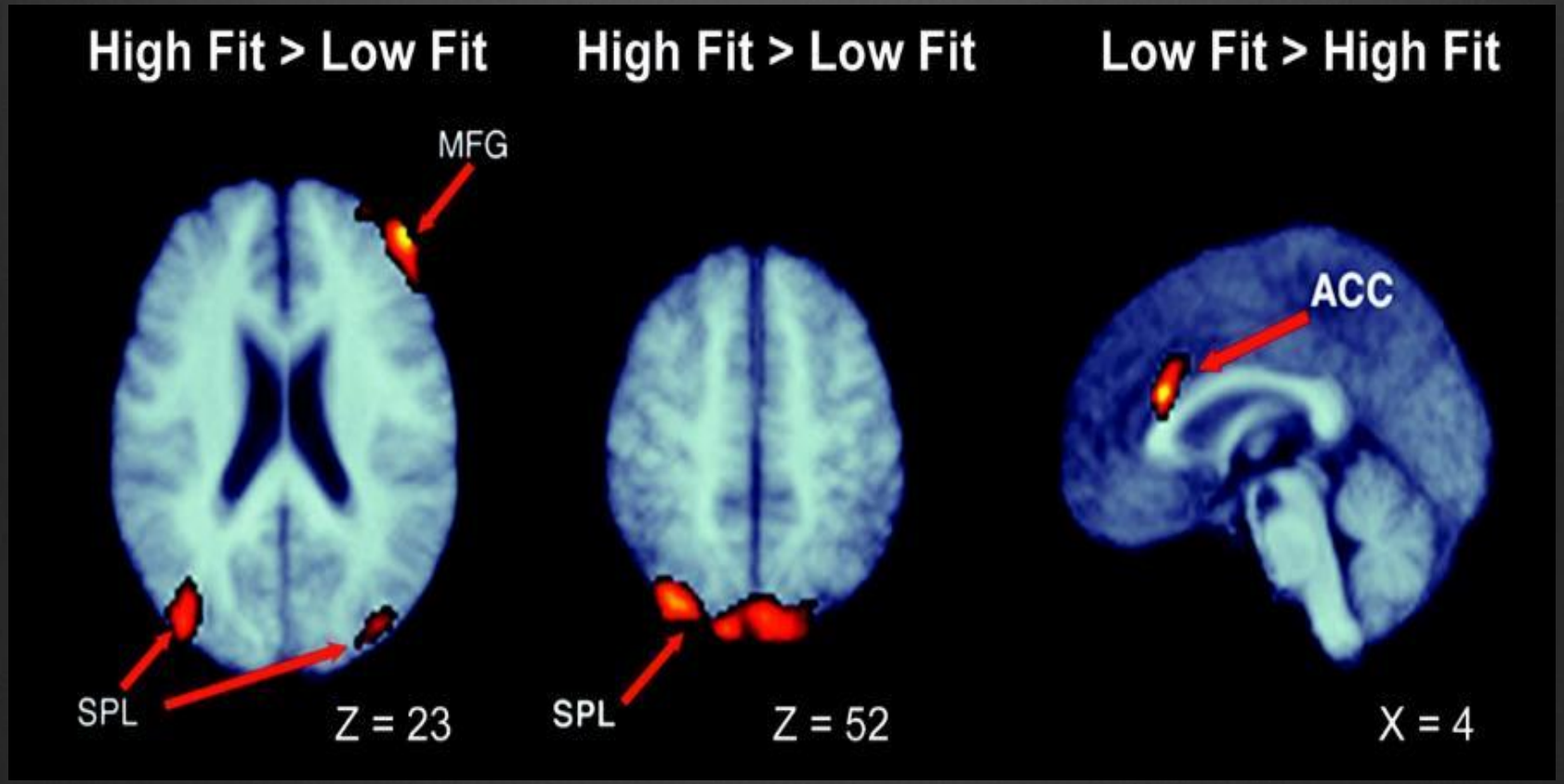
Insulin, IGF-1, VEGF, EGF upregulate telomerase activity.

All increased by aerobic exercise

Exercise and the Brain

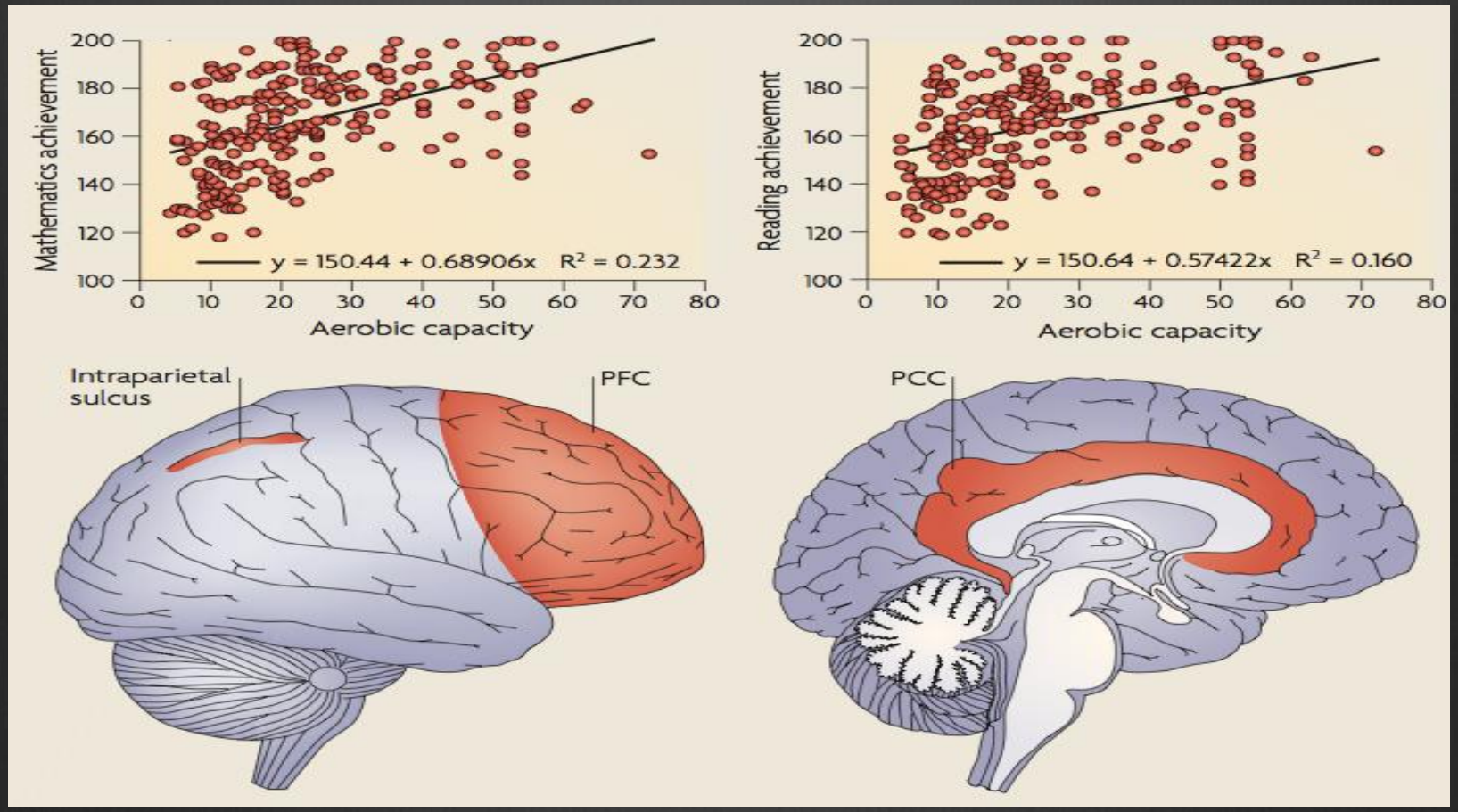
Mechanism	Impact
Gene Expression	Neuroplasticity (Cottman & Blanchard, 2002)
Brain Derived Neurotrophic Factor (BDNF)	Neurogenesis & Neuroplasticity (Adlard, et al, 2005)
Insulin-like Growth Factor (IGF-1)	Energy Utilization (Carro. et al 200)
Nerve Growth Factor	Enhanced Neuroplasticity (Neeper, et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

Cardiovascular Fitness and Cortical Plasticity in Aging Adults



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

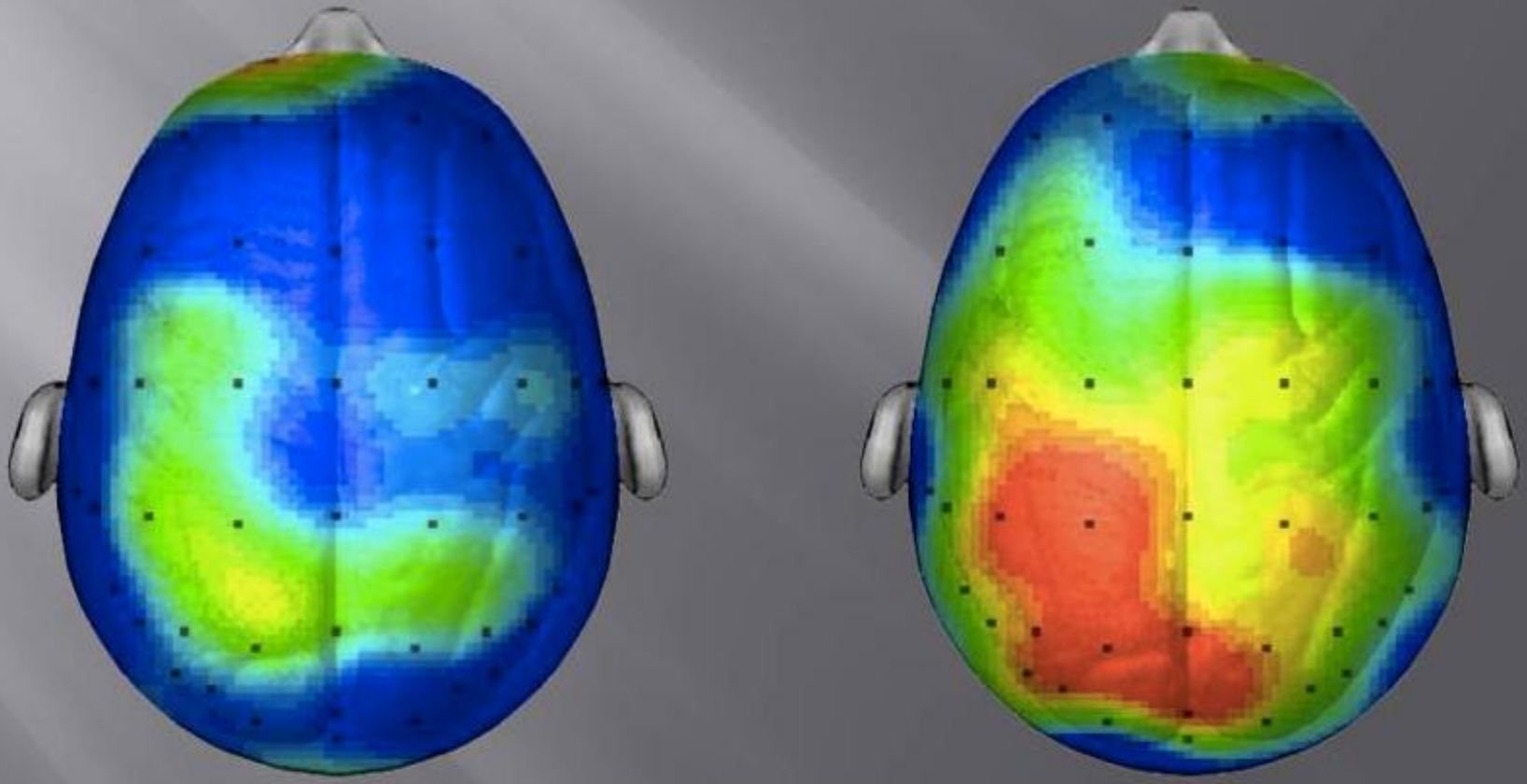
Fitness Correlates with Academic Achievement



Exercise to Clear the Mind

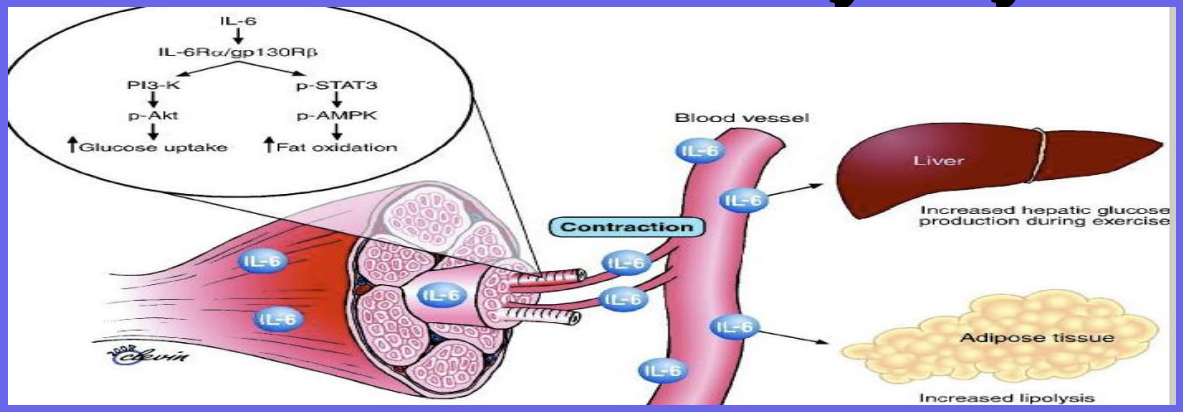
BRAIN AFTER SITTING QUIETLY

BRAIN AFTER 20 MINUTE WALK



Research/scan compliments of Dr. Chuck Hillman University of Illinois

Myokines:
Anti-inflammatory Cytokines



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

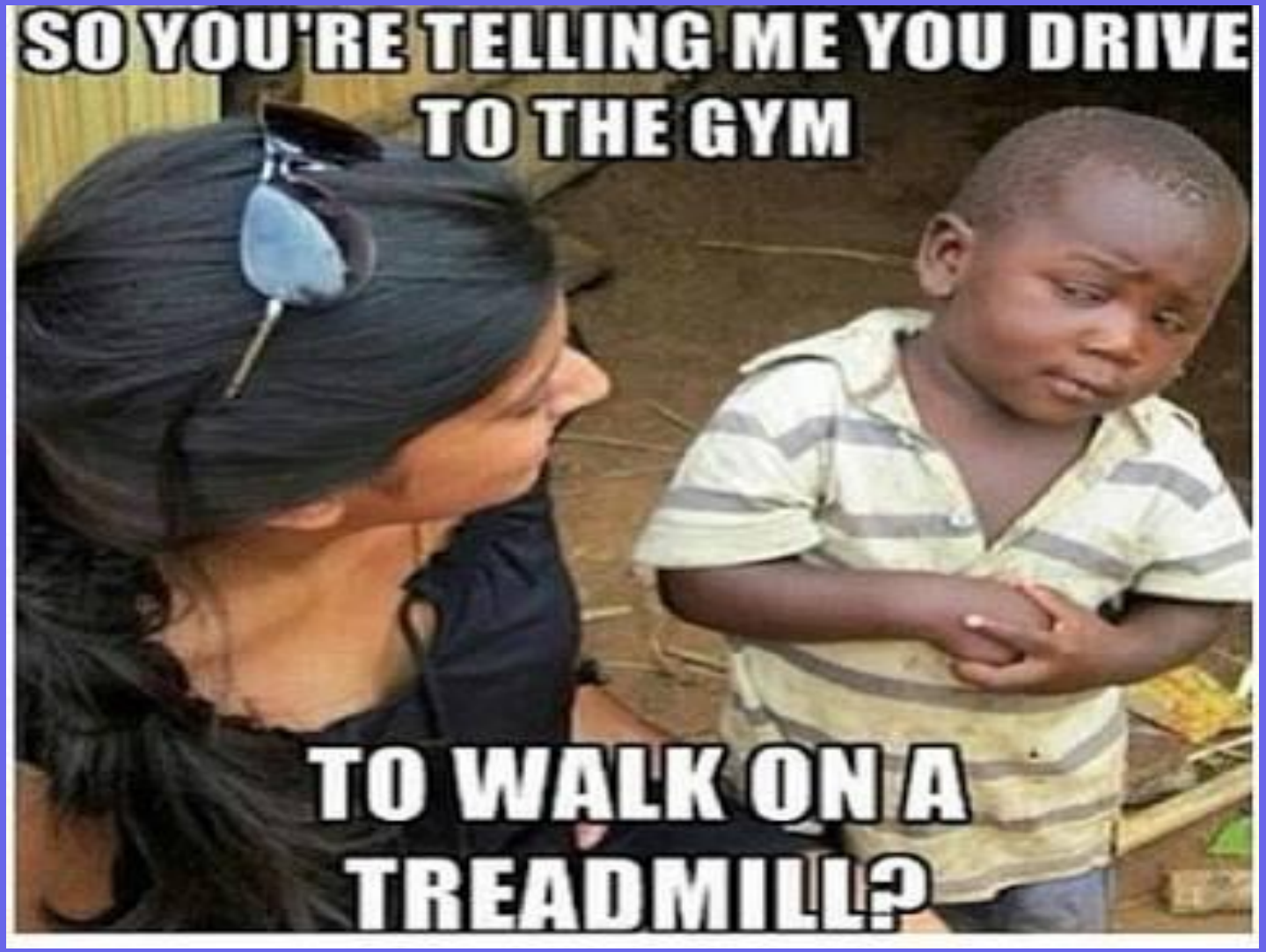
Exercise-induced myokines are involved in mediating anti-inflammatory effects

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

Self-Care Behaviors

- Social
- Exercise
- Education
- Diet
- Sleep

Working Memory

The Magic Number 7

+/- 2

- Telephone Number
- License Plate
- Days of the Week
- Colors of the Rainbow
- Deadly Sins
- 7 Dwarfs (Snow White)
- 7 wonders of the world
- Name Some Others….


ED
KSDFJ
3152946
BRVNQ
687134953
FTJSRCWX
53829631

Two LT Memory Systems

Implicit

Non-declarative

- Procedural
- Emotional
- Generalized
- Classical conditioning

Amygdala and BG-driven

Explicit

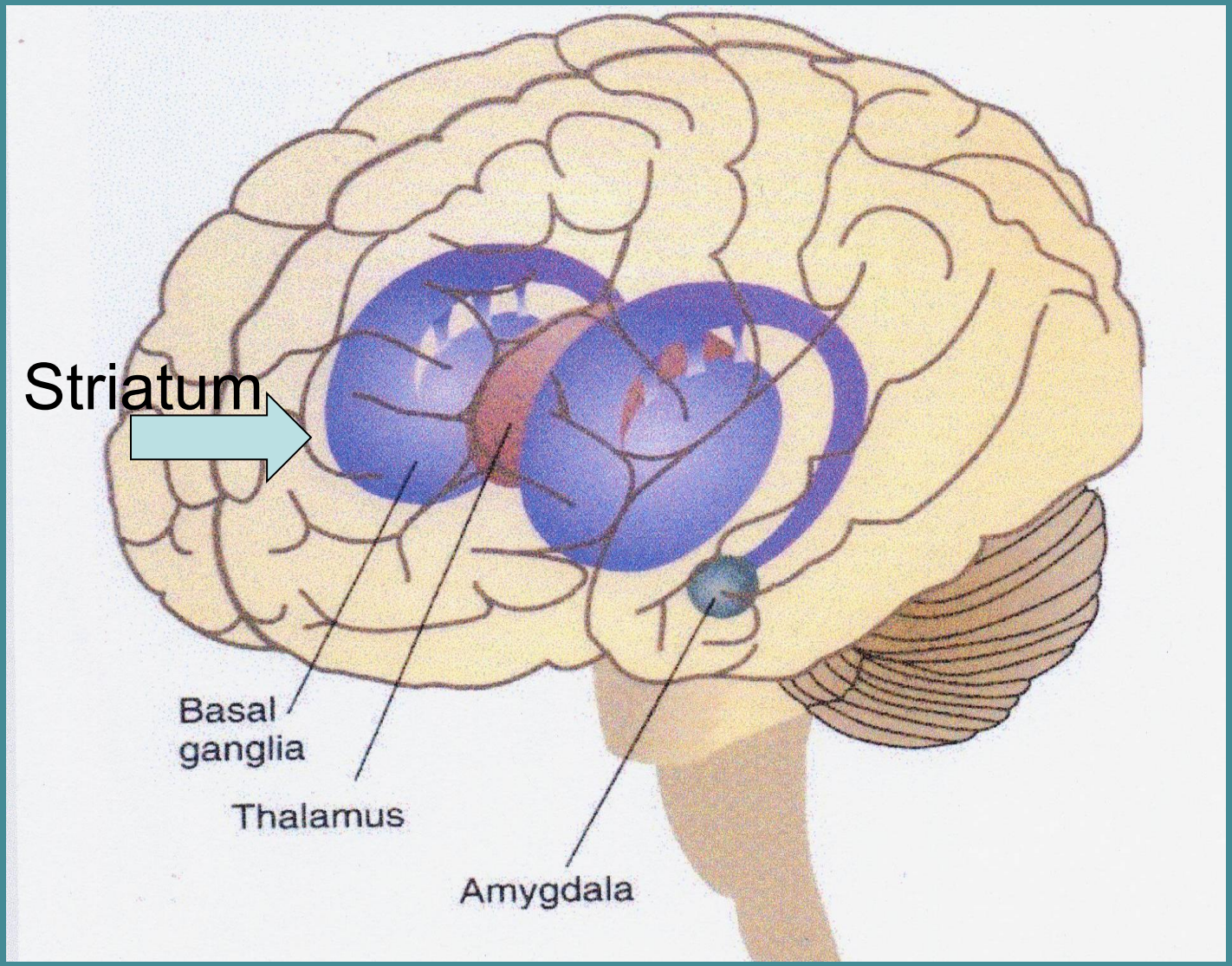
Declarative

- Episodic
- Autobiographical
- Semantic
- Context Specific

Hippocampus-driven

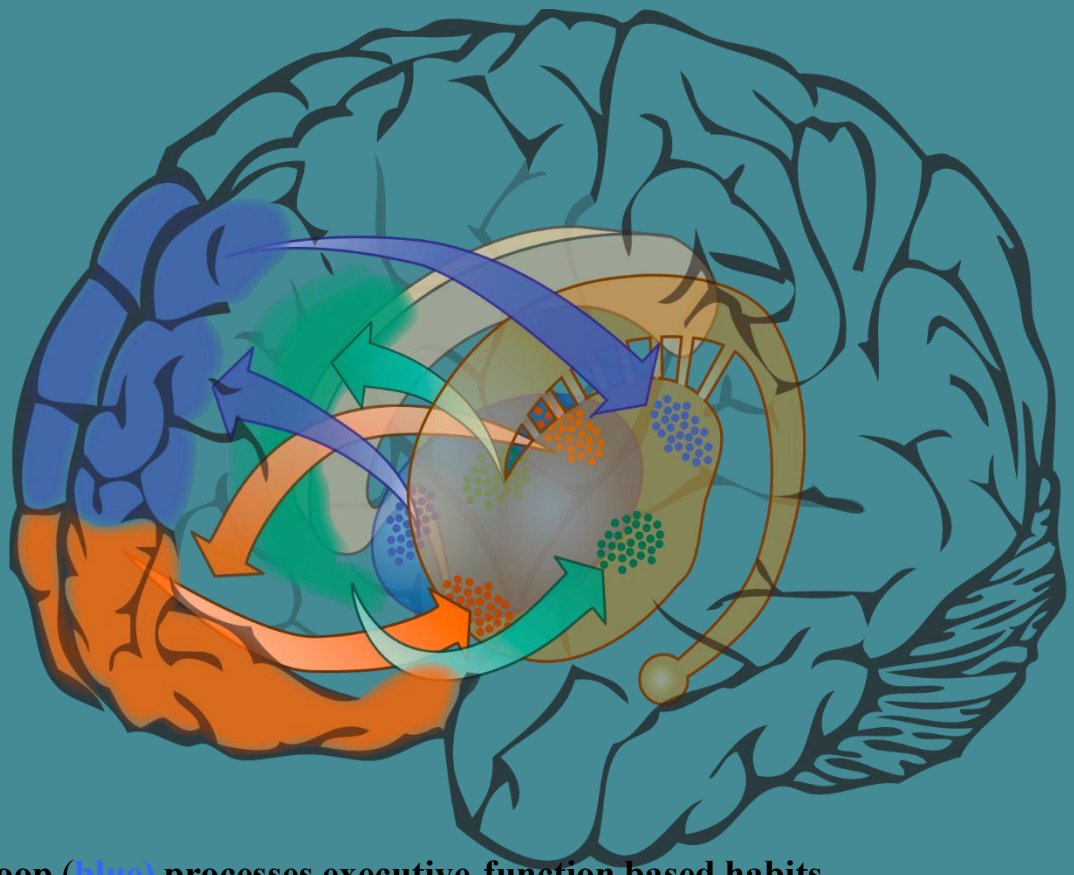

EXPLICIT DECLARATIVE KNOWLEDGE
IMPLICIT PROCEDURAL KNOWLEDGE

The Habit Circuits



Procedural Memory

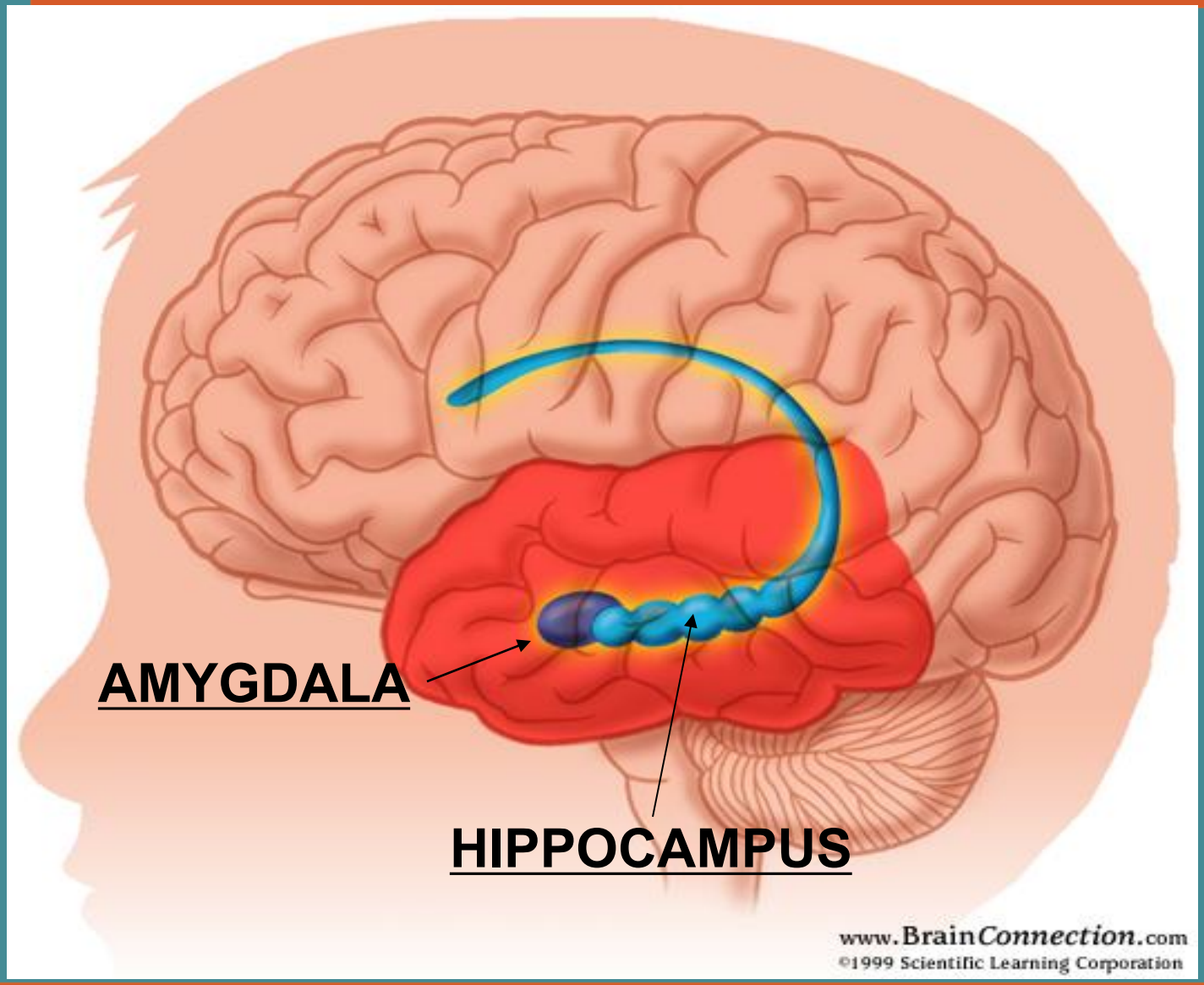
The Habit Circuits



The upper loop (blue) processes executive-function based habits.

The middle loop (green) processes attention-based habits.

The lower loop (orange) processes social-emotional and reward-based habits


AMYGDALA
HIPPOCAMPUS
www.BrainConnection.com
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AMYGDALA
Implicit Memory System

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

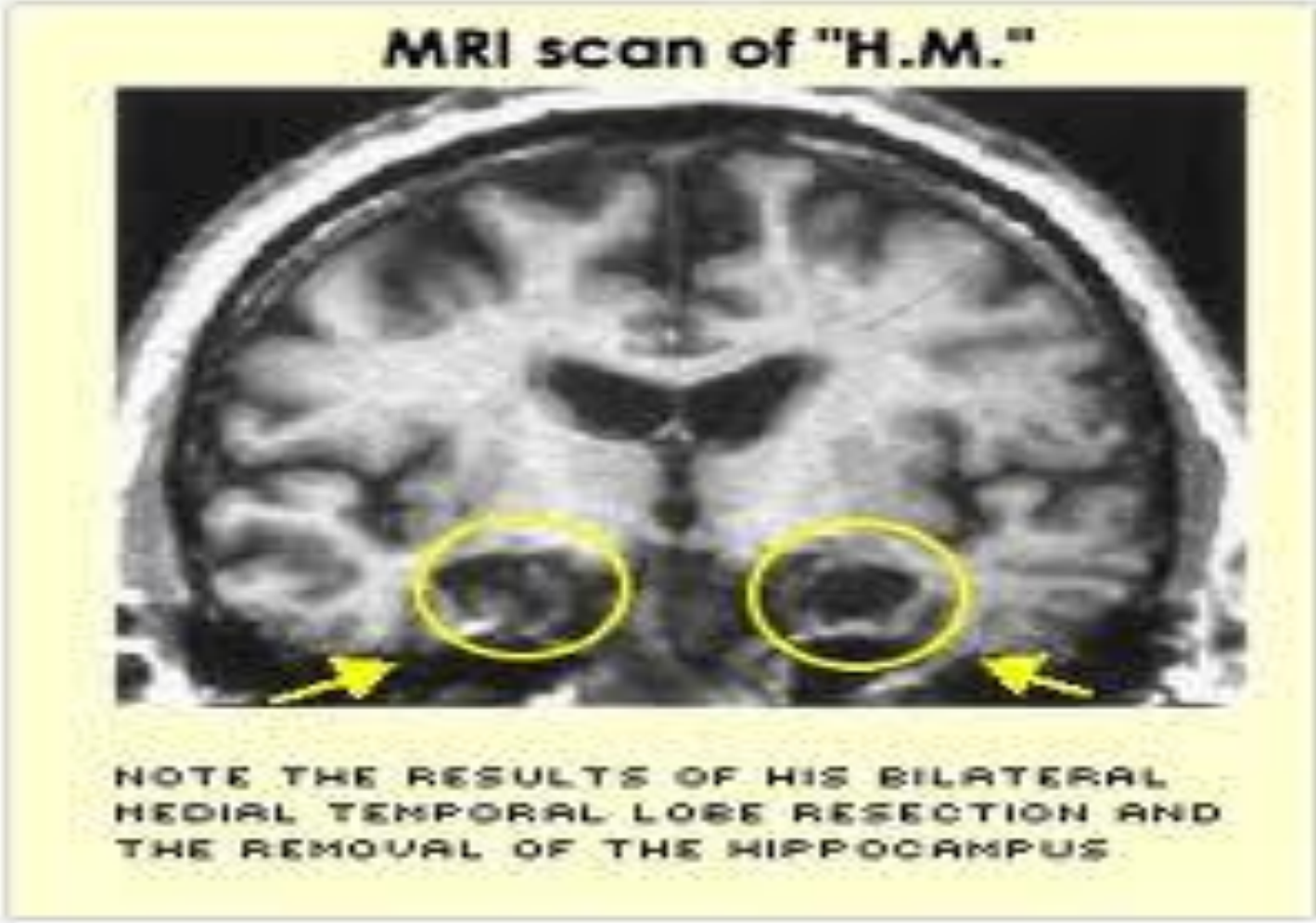
HIPPOCAMPUS
Explicit Memory System

- 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



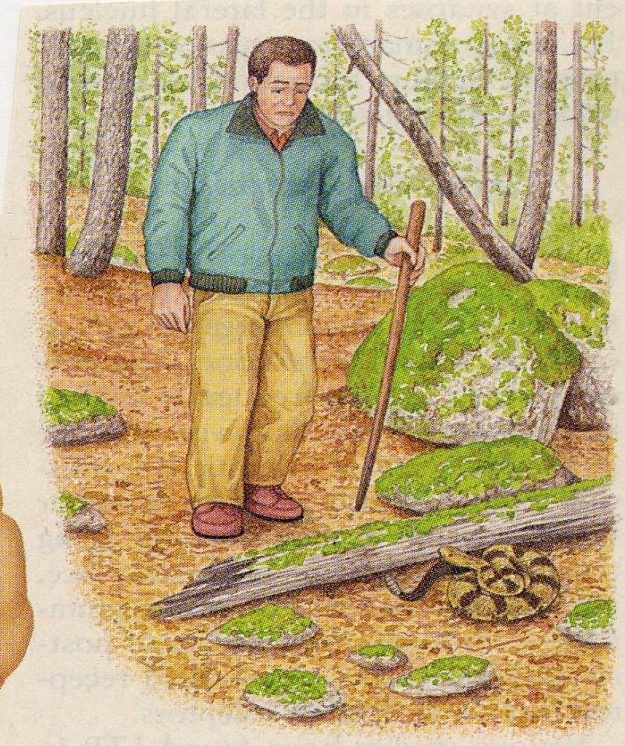
Amygdala and Hippocampus

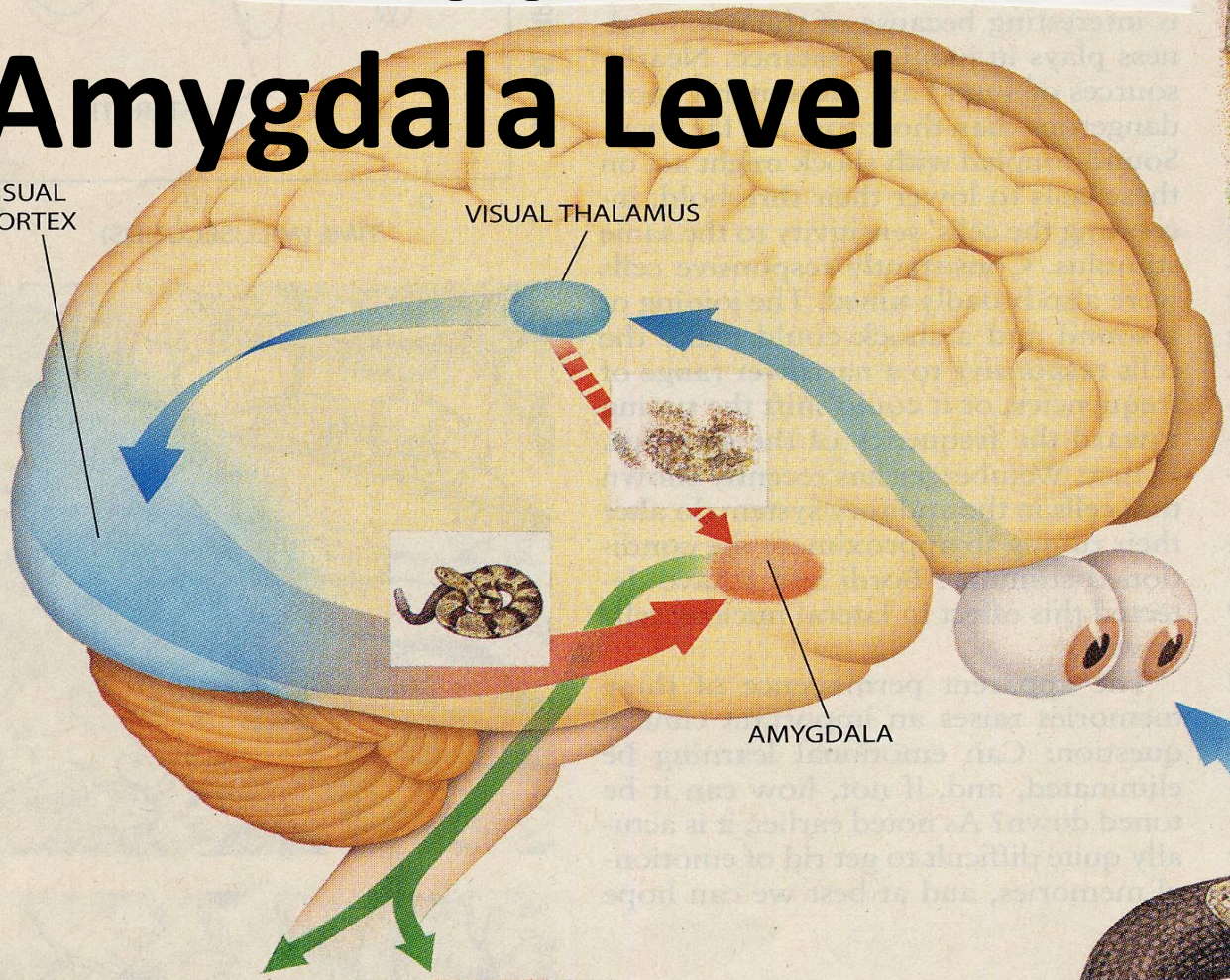
- Amygdala contributes to emotional amplification of explicit memories
- Explicit memories can be state-based (e.g., when we are depressed, we remember depressing events)
- When the amygdala and hippocampus are activated together memories are more robust and durable
  - Make what you want the client to remember emotionally relevant

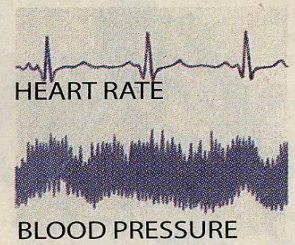
Hippocampal Coding

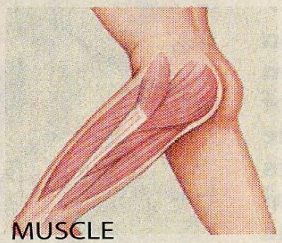
- Needed temporarily to bind together distributed sites in cortex that together represent a whole memory
  - Index to database of explicit memory
- Novelty detector: compares incoming info to stored knowledge; if difference, triggers dopamine increase
- Specialty is binding new to old information
  - Pattern completion (CA3)
  - Pattern separation—the ability to distinguish between similar experiences: (denate gyrus) ---**without it new safety memories cannot form and anxiety spreads**

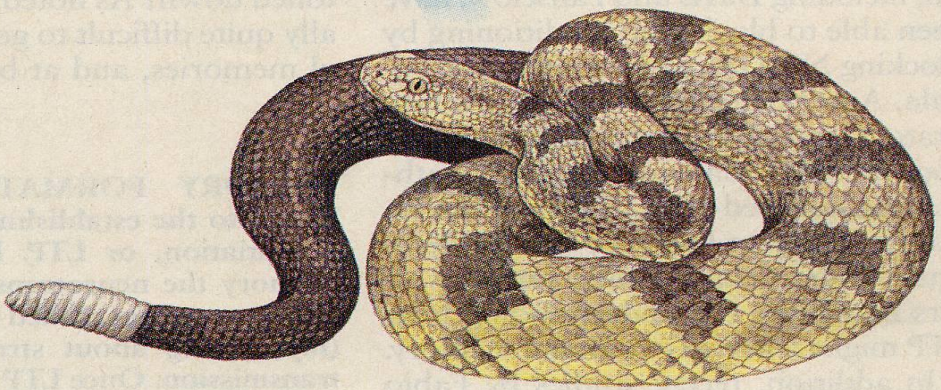
Threat Appraisal: Amygdala Level











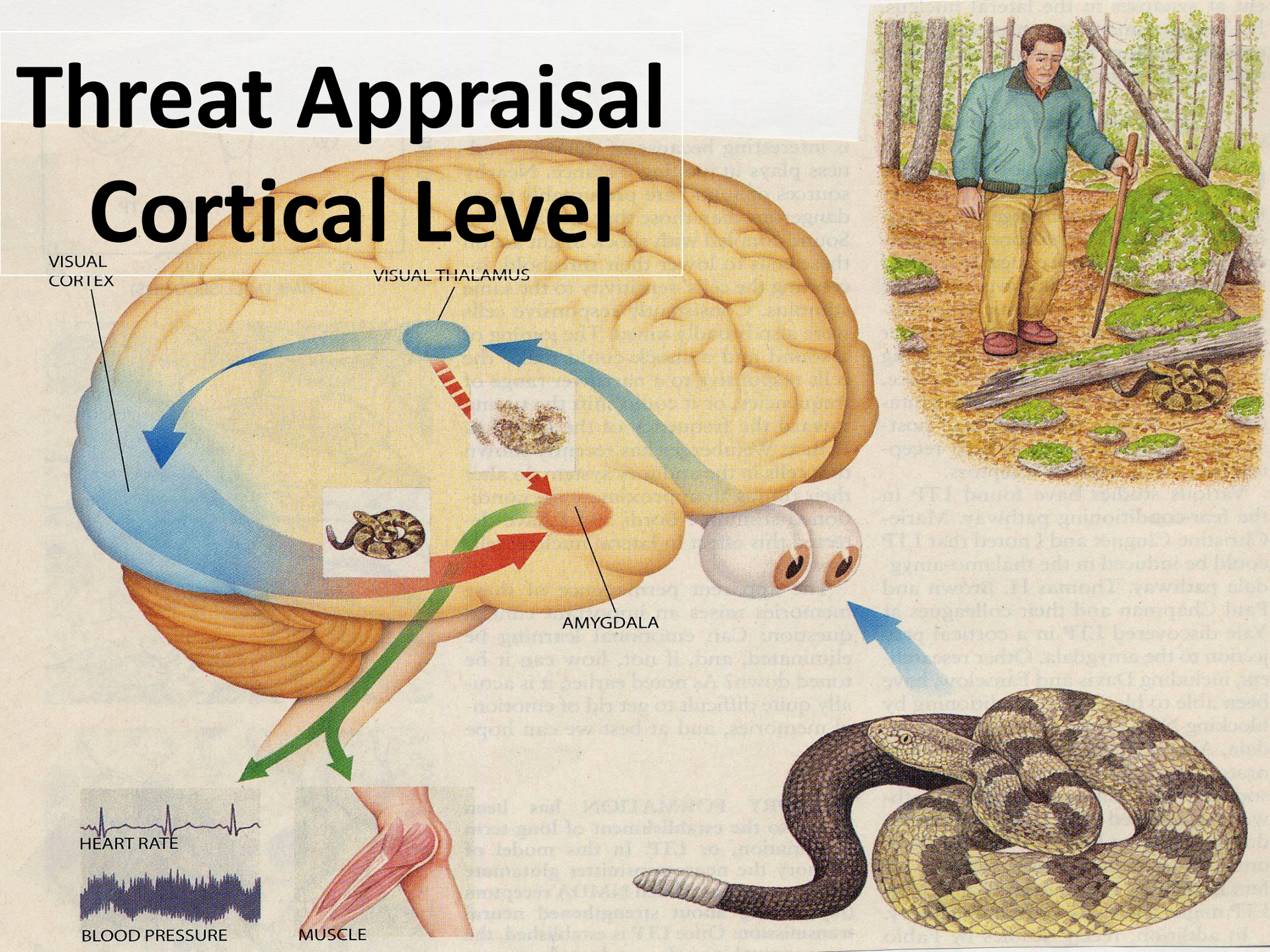
The Fast Circuit to the Amygdala

- 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

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:

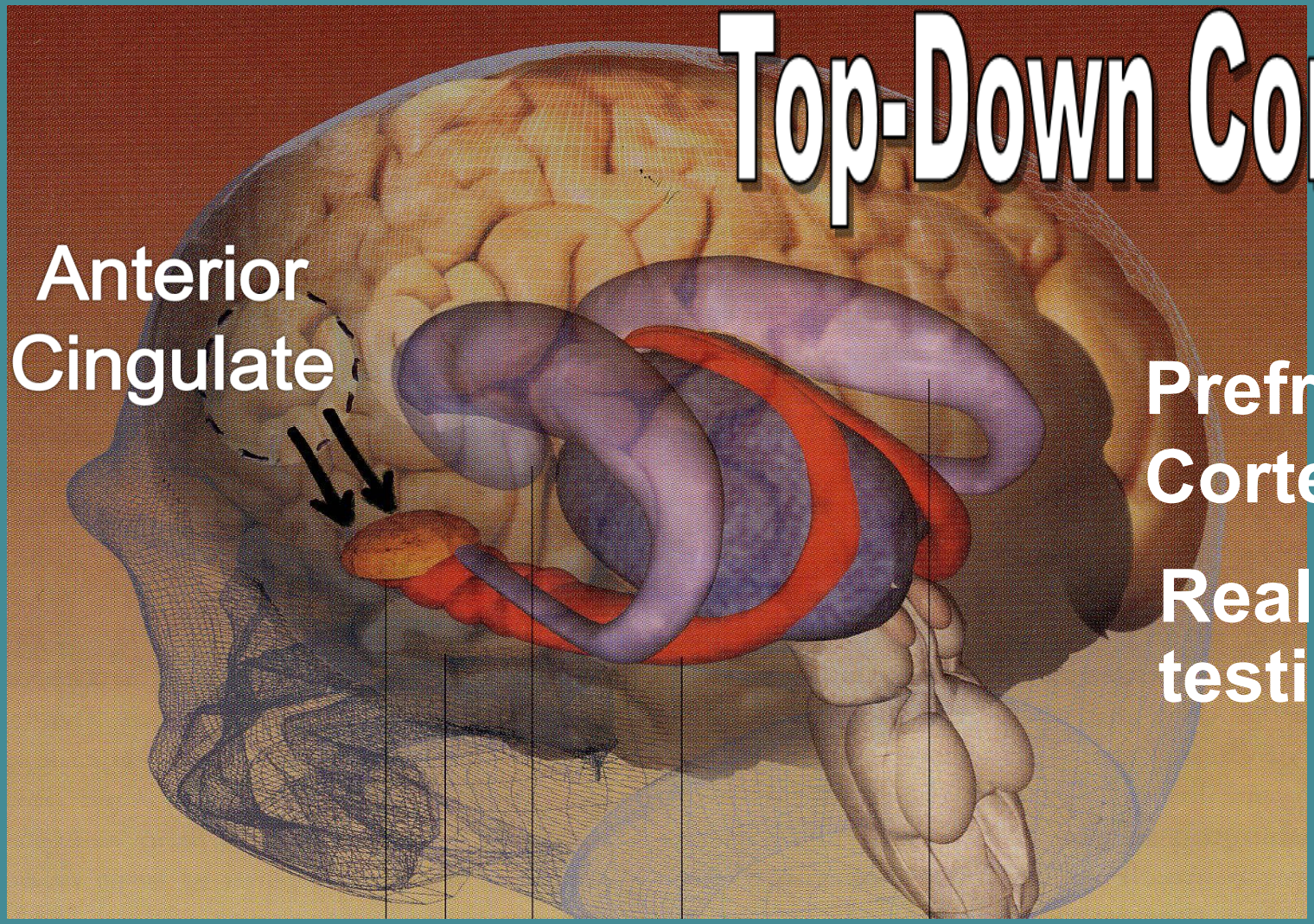
- **Worries and GAD**
- **Fears and Phobias**

Benefits:

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

"Top down"

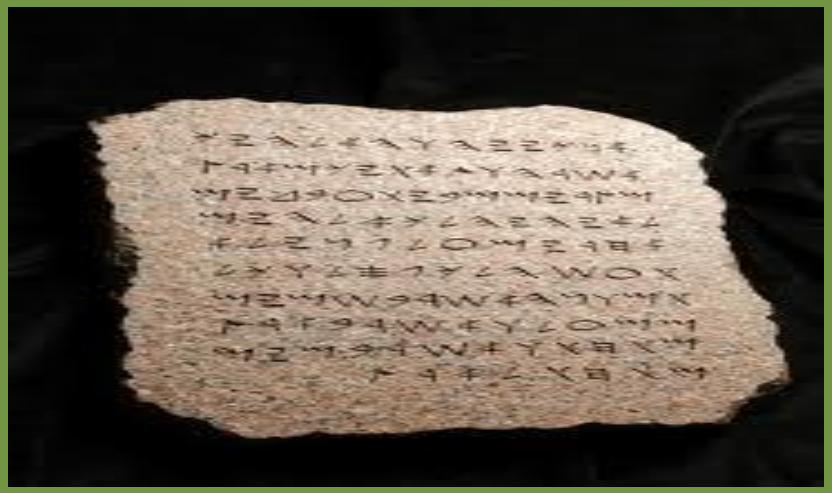
Cortical-level Appraisal



The Snake Temple—Top Down Control?

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")

Flashbulb Memories

- A particular type of explicit memory
- During emotional peaks, NE dramatically sensitizes synapses
  - Increasing the ability of receptors to be recruited to synapses
  - Primes neurons by increasing their sensitivity

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.)

Positive Emotion and Memory

- Positive emotion promotes wide frame
- During positive experience we may want to “take it all in”
- Recalling positive memories -- “reminiscence bump”
- with increased
- positive memories
- (Bertsen & Rubin, 2002)

Memory Giants

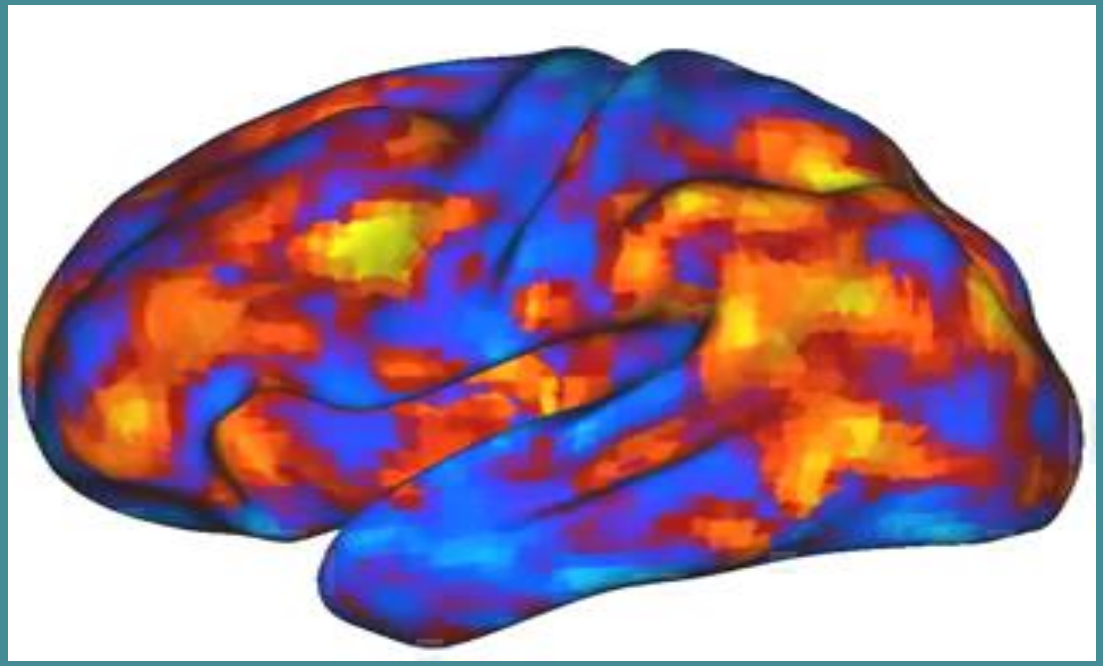
- Homeric Bards
- Talmudic Scholars
- Muslim Scholars
- West African griots: genealogies
- Thomas Aquinas: dictated the Summa Theologica (3100 pp) from memory
- Akira Haraguchi, age 60, recited Pi to 100,000 decimal places from memory in 16 hours in 2006

Phillip's Milk of Amnesia

for people who can't remember shit!

Memory and Brain Complexity

- Memory is not an exact copy—Not in one neuron or like a byte on a hard drive.
  - Distributed network located in multiple locations



Client Education

- Your brain is not like a computer, coding every program used or website visited.
- Your memories change in response to new experiences. That's what therapy does.

Memory (summary)

- Attention is critical to the coding of new memory
- The power of mnemonics
- The “Inverted U”: too little stimulation (e.g., boredom) or too much stimulation (e.g., trauma) conflict with the coding of new memory
- A moderate degree of anxiety works best to facilitate neuroplasticity and new memory

Self-Care Behaviors

- Social
- Exercise
- Education
- Diet
- Sleep


Brain food.
Swell snacks in yummy flavors!
NORMA FOX MAZER
Missing Pieces

Client Education

- A bad diet will deplete your brain chemistry, making your alarm system unnecessarily overactive.
- Just skipping breakfast will cause you to be depressed and have less energy and ability to deal with stress and anxiety.

Break a Fast

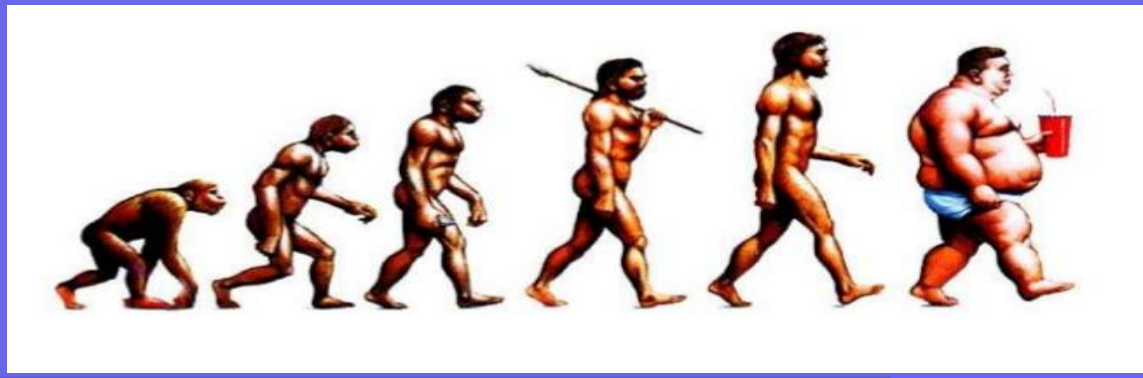
Skipping Breakfast contributes to:

↓ problem solving
↓ working memory
↓ attention
↓ concentration
↓ energy

↑ Mood swings
↑ depression
↑ stress reactivity
↑ anxiety

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




Aspartame
cola
MSG
Fish Filet
Fluoride
Springs
MSG
Burger
Prozac
Genetically
Altered
SPUDS

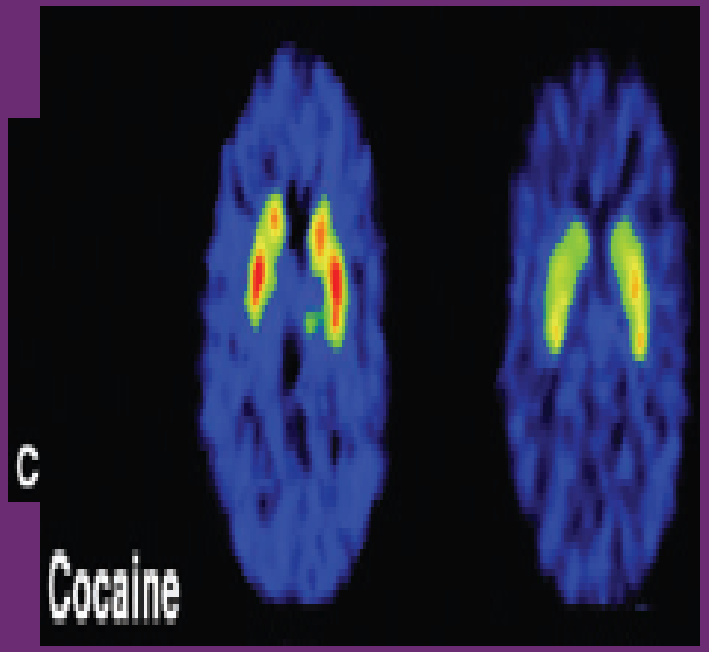
Client Education

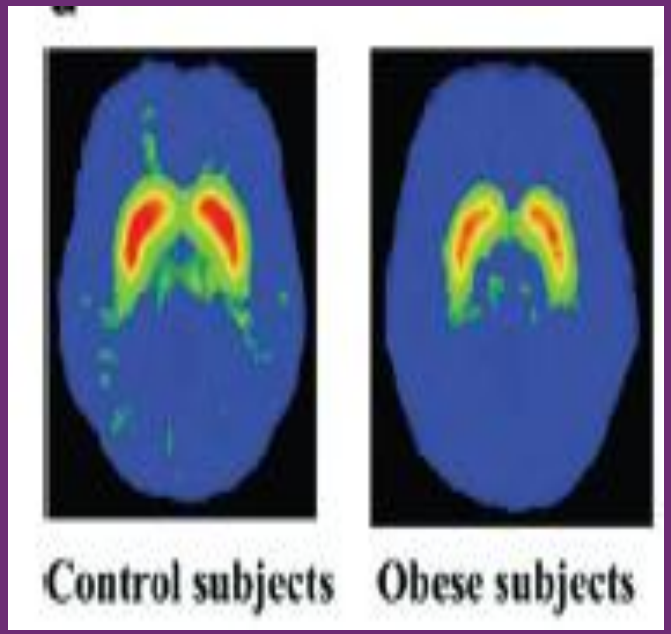
- A bad diet will deplete your brain chemistry, making your alarm system unnecessarily overactive.
- Just skipping breakfast will cause you to be depressed and have less energy and ability to deal with stress and anxiety.

Dopamine D2 Receptors in Drug Users And Comfort Food Addiction

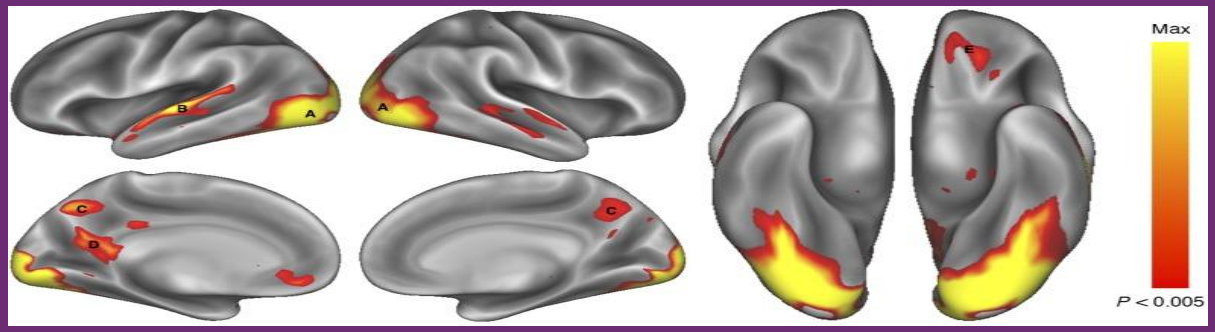
- Drug Addiction
- Obese

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





Priming Appetite and Obesity



Children can view 13 food ads per hour

The higher the BMI the greater the responsiveness to food commercials

Activity in the left OFC, Nacc, and right Insula

Priming Appetite for Bad Food

- Grey matter volume in two brain regions predicts selection of healthful food or tasty but unwholesome cuisine
- While the volume of grey matter in the DLPFC and the vmPFC predicts the choice of healthful food:
  - **Those people with less grey matter in these areas chose unhealthy foods**

Deficiencies of B Vitamins

Low B-1	Low B-2	Low B-6	Low B-12	Folic Acid
*Decreased Alertness *fatigue *Emotional Instability *Decreased reaction time	*Trembling *Sluggish *Tension *Depression *Eye problems *Stress	*Nervousness *Irritable *Depression *Muscle weakness *Headaches *Muscle Tingling	*Mental slowness *Confusion *Psychosis *Stammering *Limb weakness	*Memory problems *Irritable *Mental sluggishness

The OFC and Serotonin

- Large numbers of 5-HT receptors in the OFC
- ↓ 5-HT in OFC ↓ inhibition of the amygdala
- Tryptophan depletion impairs reverse learning tasks (Robbins & Everitt, 1995)
  - Ability to evaluate, integrate, and act on environmental cues
  - To stop responding to something when it becomes unhealthy and shift back to something healthier

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

Client Education

- Eating a lot of simple carbohydrates, especially sugar, causes your brain to become stiff, rigid, and make you less able to rewire your brain.
- This means that you effort to think clearly, feel calm in the face of anxiety and lift out of depression will falter.

Omega 3

20% of the brain is made up of essential fatty acids (EFAs)

One third of myelin is EFAs

International Recommendations: 650 mg

Current American average consumption: 130 mg

The imbalanced ratio between Omega-6 and Omega-3.

Increased triglycerides (vegetable oil and animal fat) is correlated with depression (Glueck, 1998)

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

Fructose

- Unlike other sugars, it produces uric acid and blunts the effect of leptin, the hormone that tells the brain to stop eating.
- It flips a switch in the body, causing it to hoard fat, raise blood sugar and blood pressure.
- Can increase LPS by 40%.
  - With Firmicutes, LPS increases gut permeability and so inflammation.
- Triggers free radical products of damaged fatty acids, called isoprostanes, rising 34% just ninety minutes after consumption (↑ with AD)

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

  Consuming 6000 calories a day doubles the risk of MCI

trans-fatty acids can:

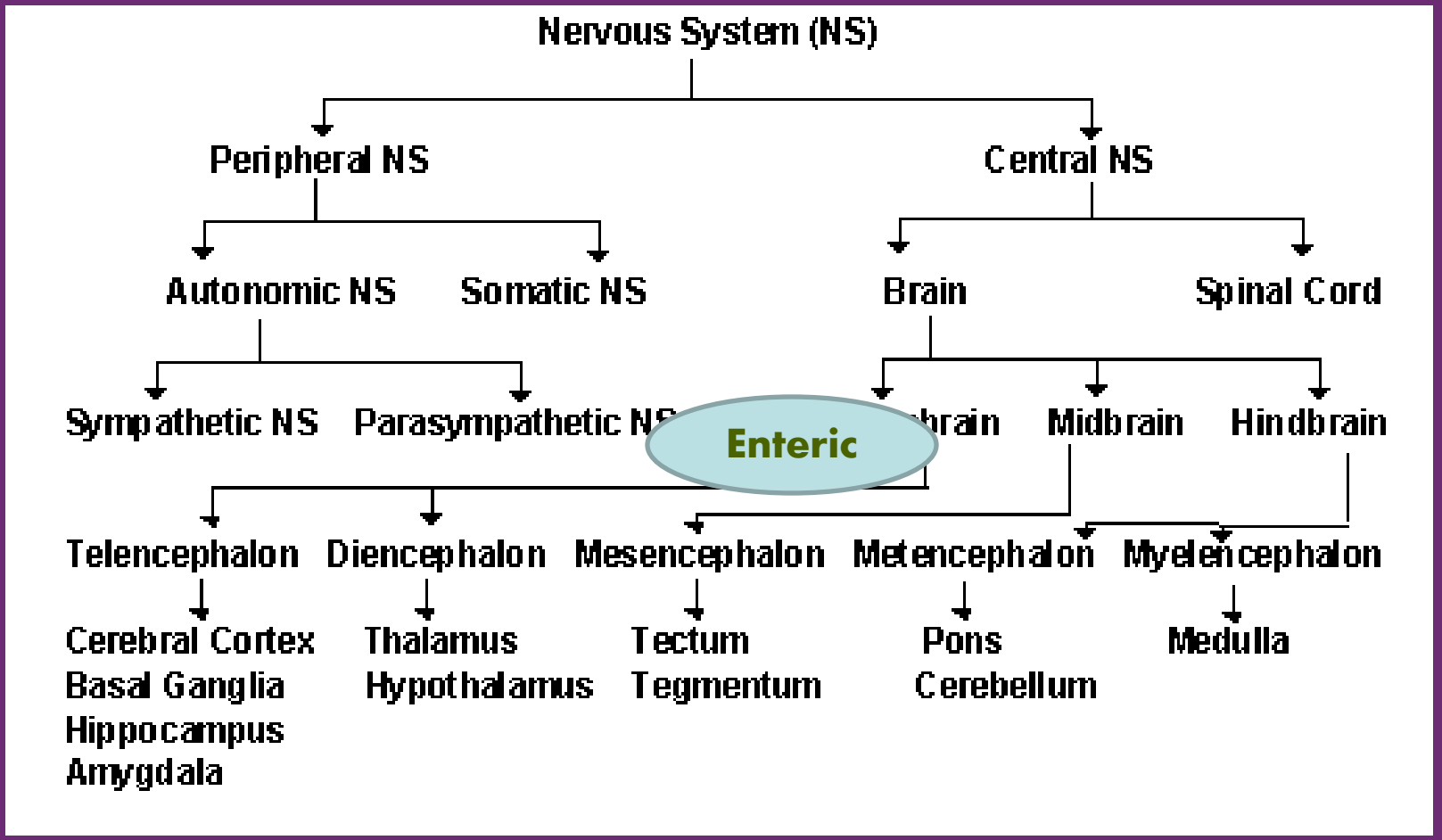
1. Be absorbed directly by the nerve membranes
2. Block the body's ability to make its own essential fatty acids
3. Alter the synthesis of neurotransmitters such as dopamine
4. Negatively effect the brain's blood supply
5. Increase bad (LDL) cholesterol while decreasing good (HDL) cholesterol

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

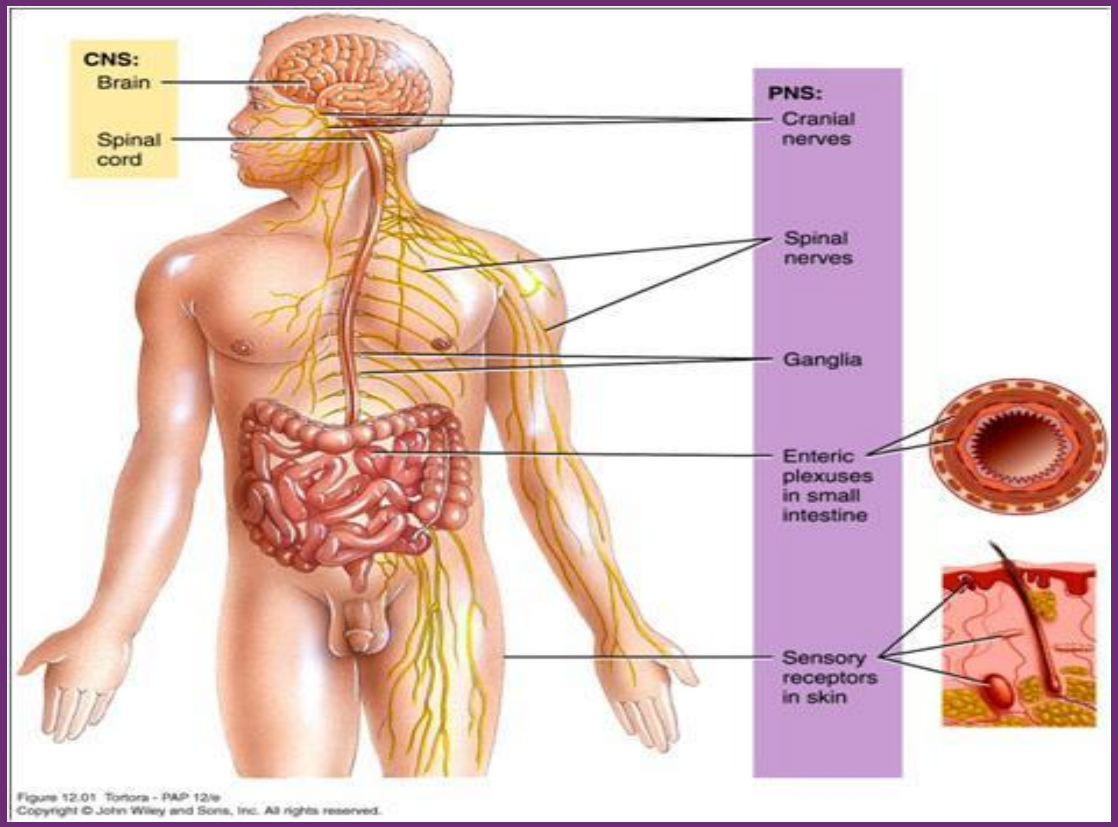
    i.e. pro-inflammatory cytokines

The Gut Brain



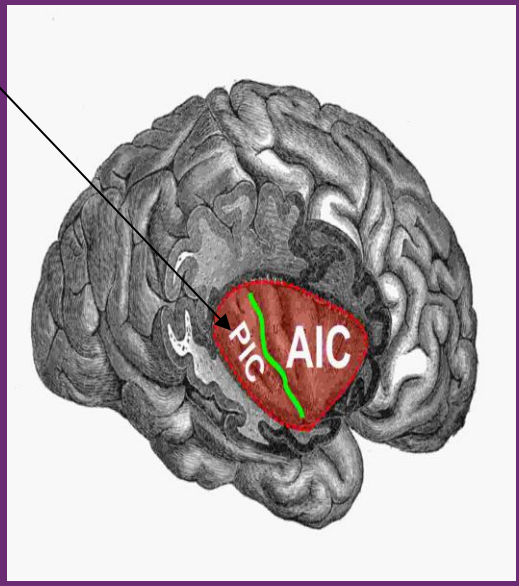
Enteric Nervous System

- ***Enteric*** **– meshwork of nerve fibers that innervate the viscera (gastrointestinal tract, pancreas, gall bladder)**



Language of Gut

- Visceral sensations include:
  nausea, bloating
- All arrive at Insular Cortex in brain
  - Part of the Salience Network
- Plays role in emotions & body homeostasis
- Regulates the immune system
- Conscious desires – food, drugs



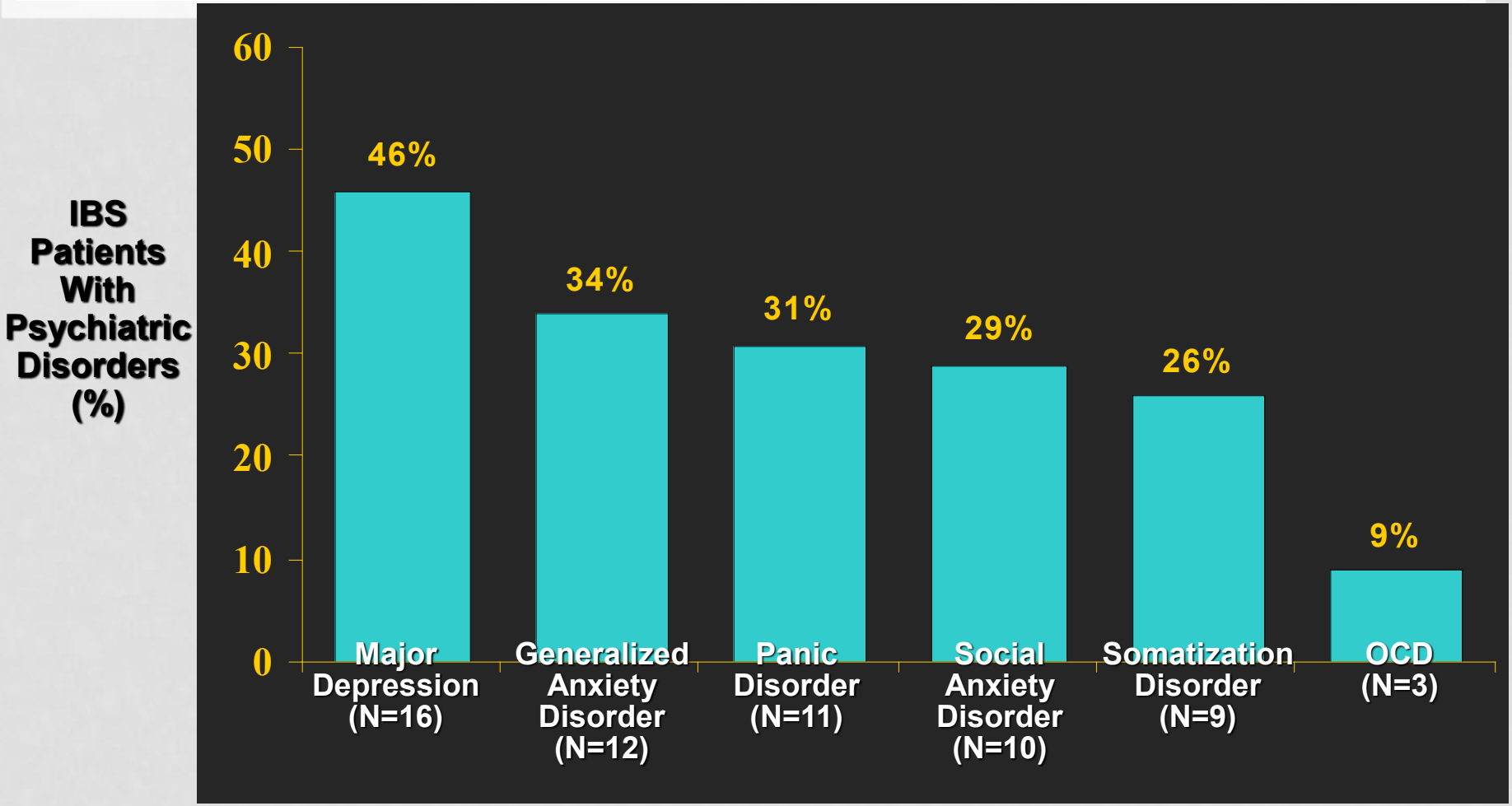
Gut bacteria

- Play a key role in nutrition
- Production of neurotransmitters
- Synthesize: vitamins such as thiamine (B_1), folic acid (B_9), pyridoxine (B_6), and vitamin K
- Produce digestive enzymes to absorption calcium, magnesium, and iron.

Gut Bacteria

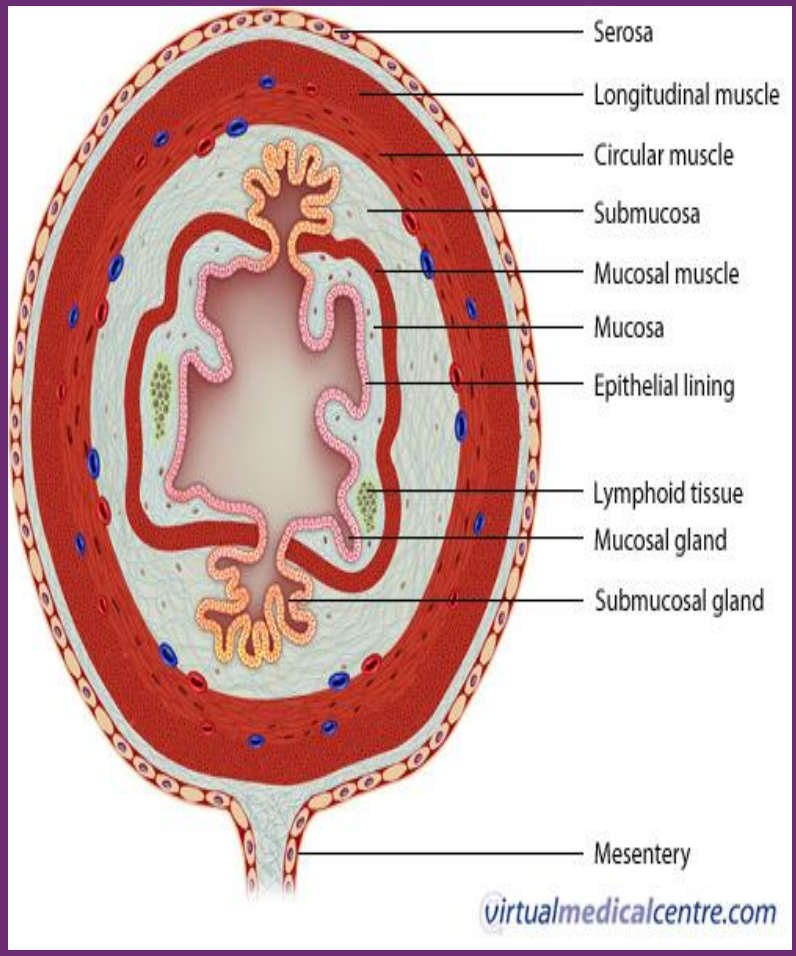
- 90% of bacteria in the colon F/B ratio:
- Firmicutes
  - Fat loving—increases fat absorption
  - Efficient at extracting calories from carbs
  - Turns on genes that increase the risk for obesity, diabetes, and CVD
- Bacteroidetes
  - More dominant in lean people

LIFETIME PSYCHIATRIC DISORDERS IN PATIENTS WITH IBS



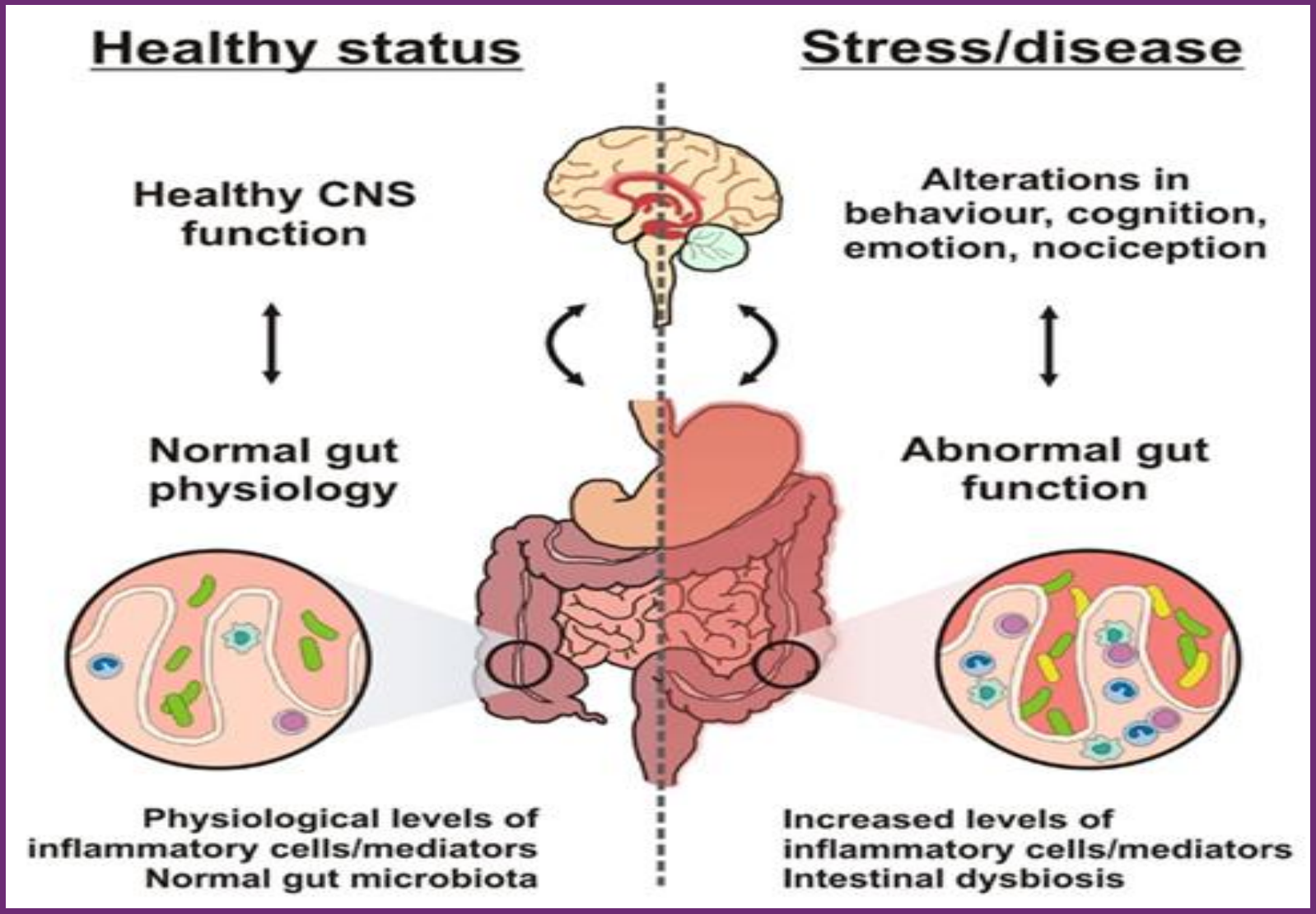
"Leaky gut": the consequences of stress and inflammation and link between diet and health

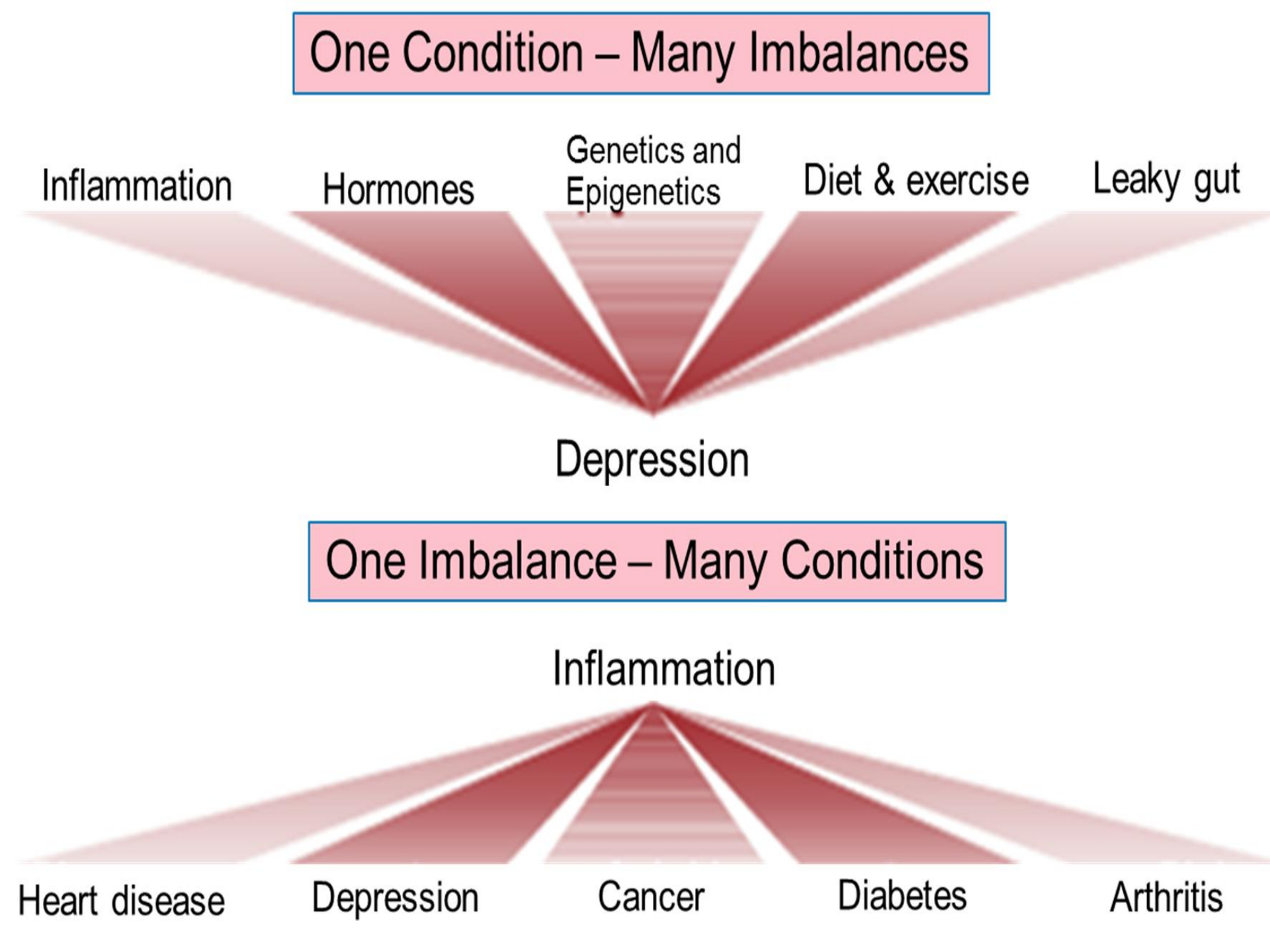
- **intestinal permeability**
- **Firmacutes + LPS**
- Lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, induces neuronal death, decreases neurogenesis, and impairs synaptic plasticity and memory,



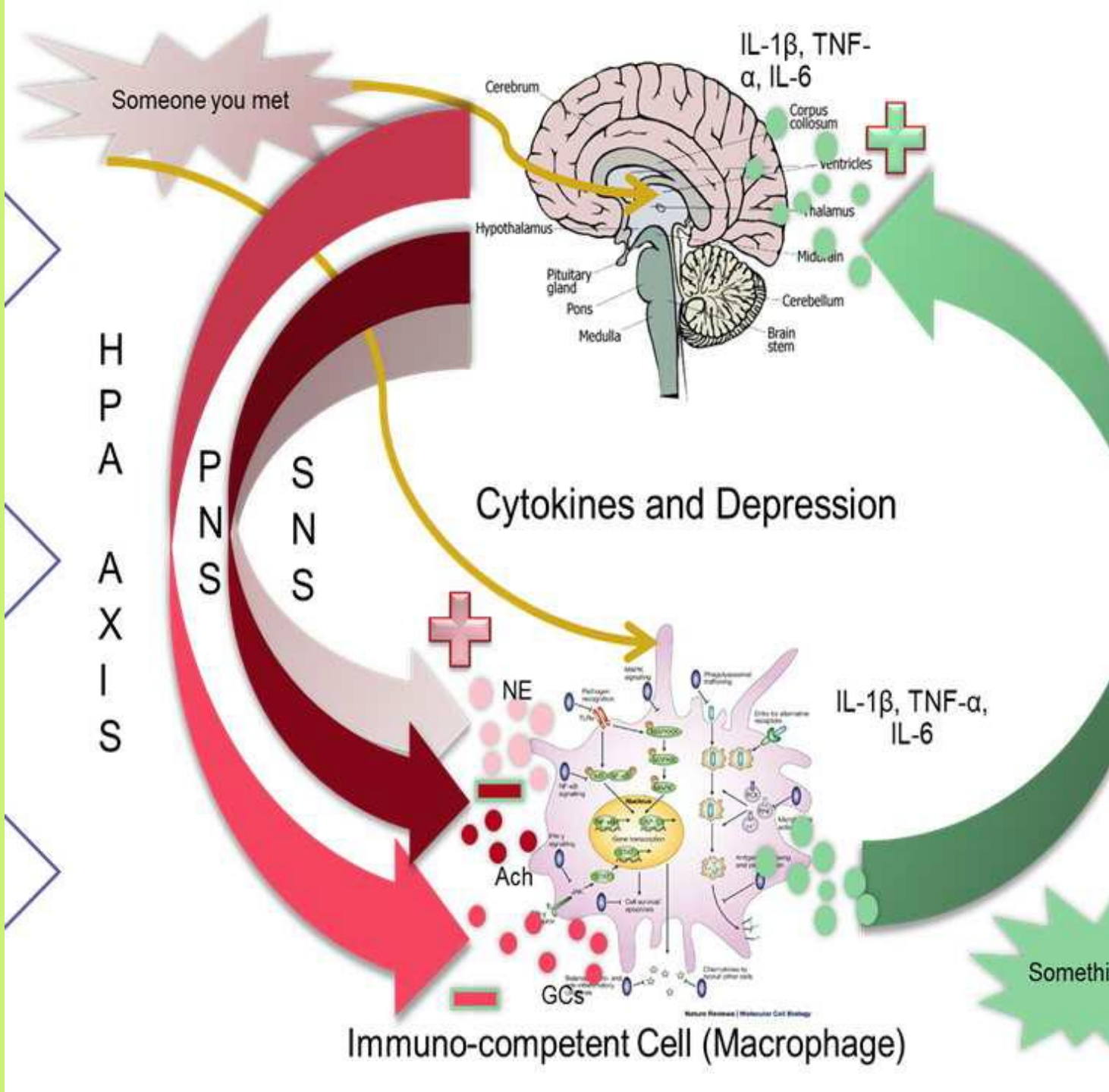
Dysbiosis and Microbial Diversity: the Importance of Balance

- Diversity is good- a hallmark of disease is reduced microbial diversity
- Low diversity is associated with DYSBIOSIS
- *Dysbiosis* is when there is an imbalance in microbes, leading to overgrowth of some species
- Dysbiosis with inflammation--↓5-HT


Healthy status
Stress/disease
Healthy CNS function
Alterations in behaviour, cognition, emotion, nociception
Normal gut physiology
Abnormal gut function
Physiological levels of inflammatory cells/mediators
Normal gut microbiota
Increased levels of inflammatory cells/mediators
Intestinal dysbiosis


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

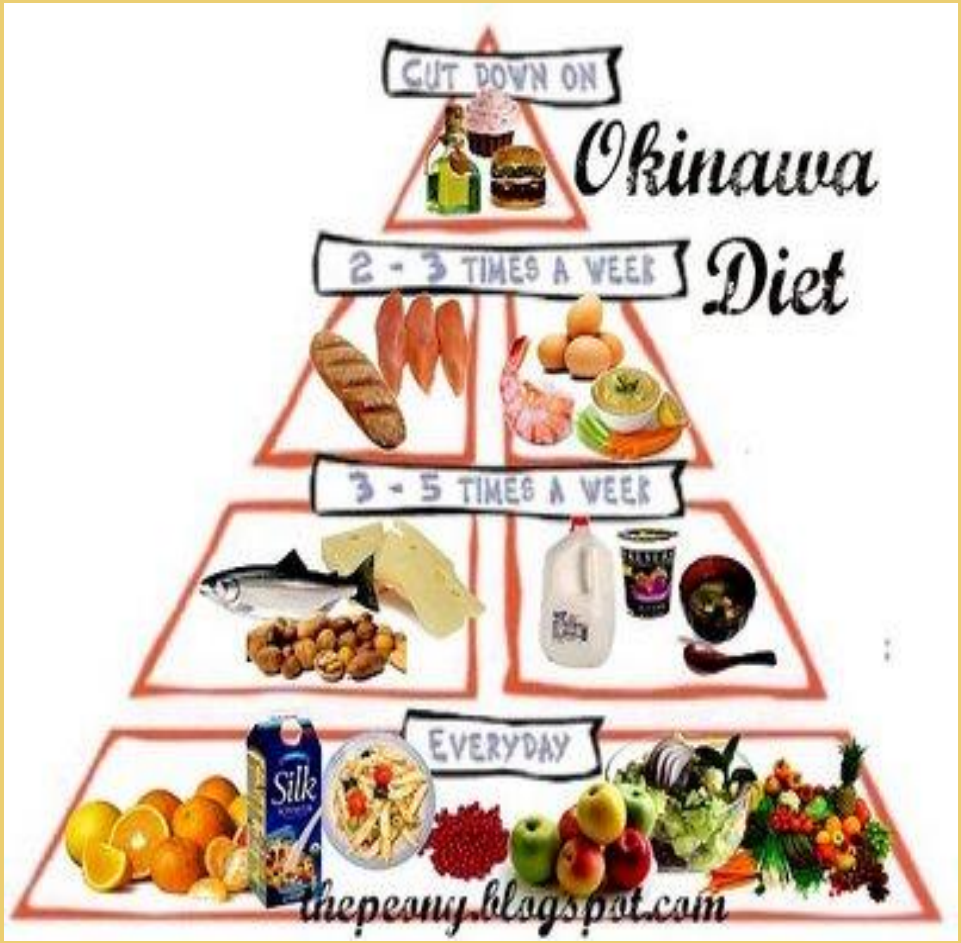
- Bad Diet
  - Simple carbs
  - Transfatty acids
  - Saturated fats
  - Food allergies
  - Bad oils
  - High dairy
  - High gluten
- No exercise
- Chronic illnesses
- Autoimmune disorders
- Chronic pain
- Chronic stress
- Being overweight
  - Apple shape
- Leaky gut



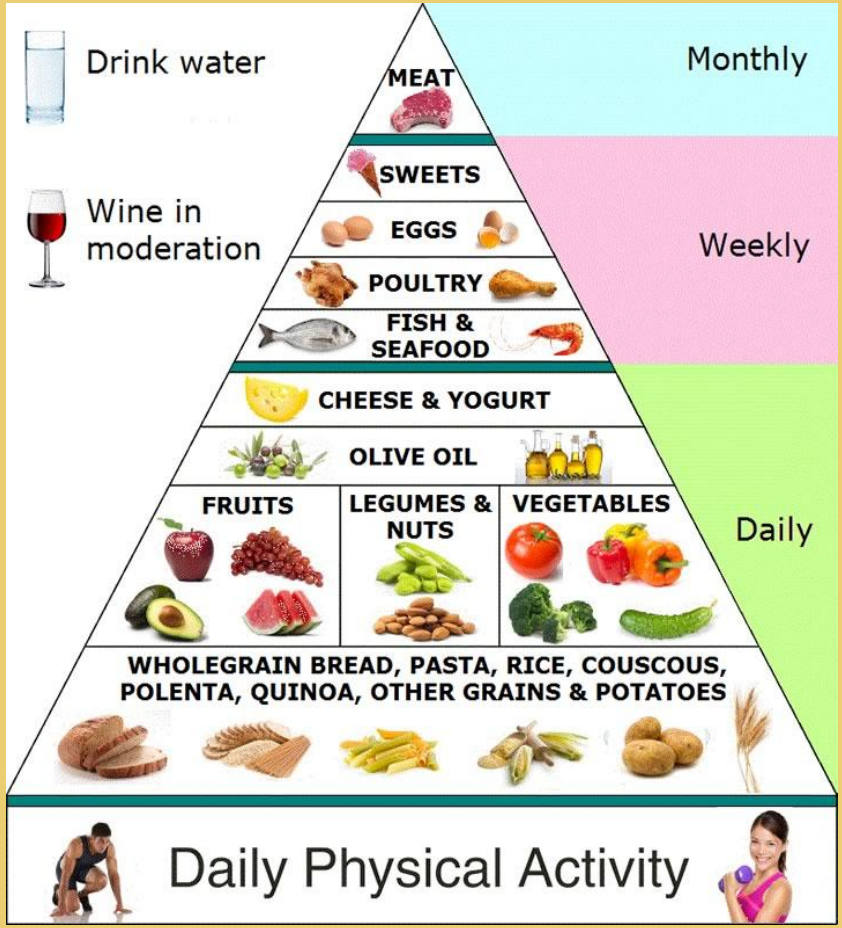
Protecting the Brain from Pre-Diabetes and Metabolic Syndrome

Diets styles for longevity:

Okinawan



Mediterranean



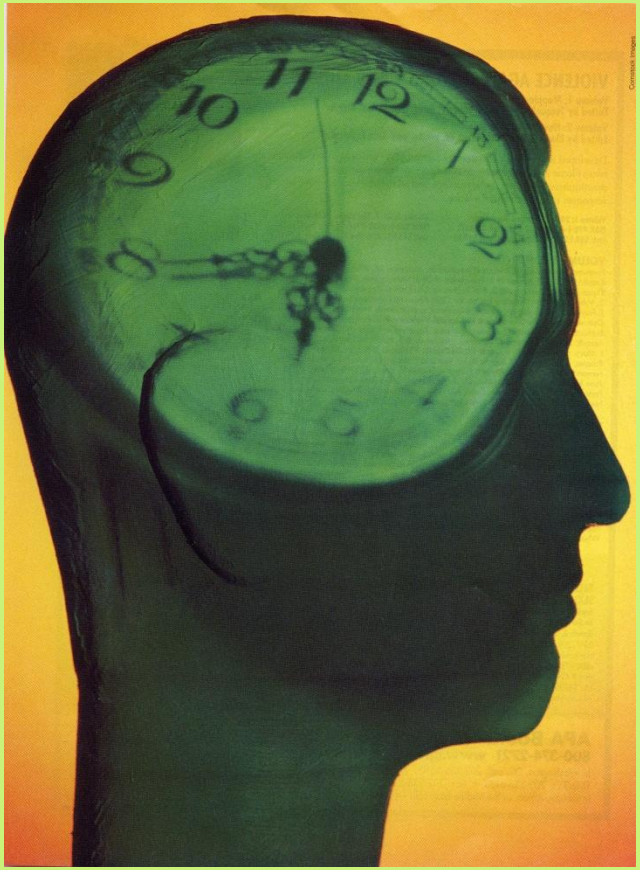
Diet Summary

- –The importance of breakfast
- –The perils of simple carbohydrates--↑ depression
- –Transfatty acids -↑ depression
- –Essential fatty acids
- –3-4 balanced meals
- –Vegetables 3xs per day
  - »↓ depression risk by 30%
    (Nurse's Health Study)

Self-Care Behaviors

- Social
- Exercise
- Education
- Diet
- Sleep

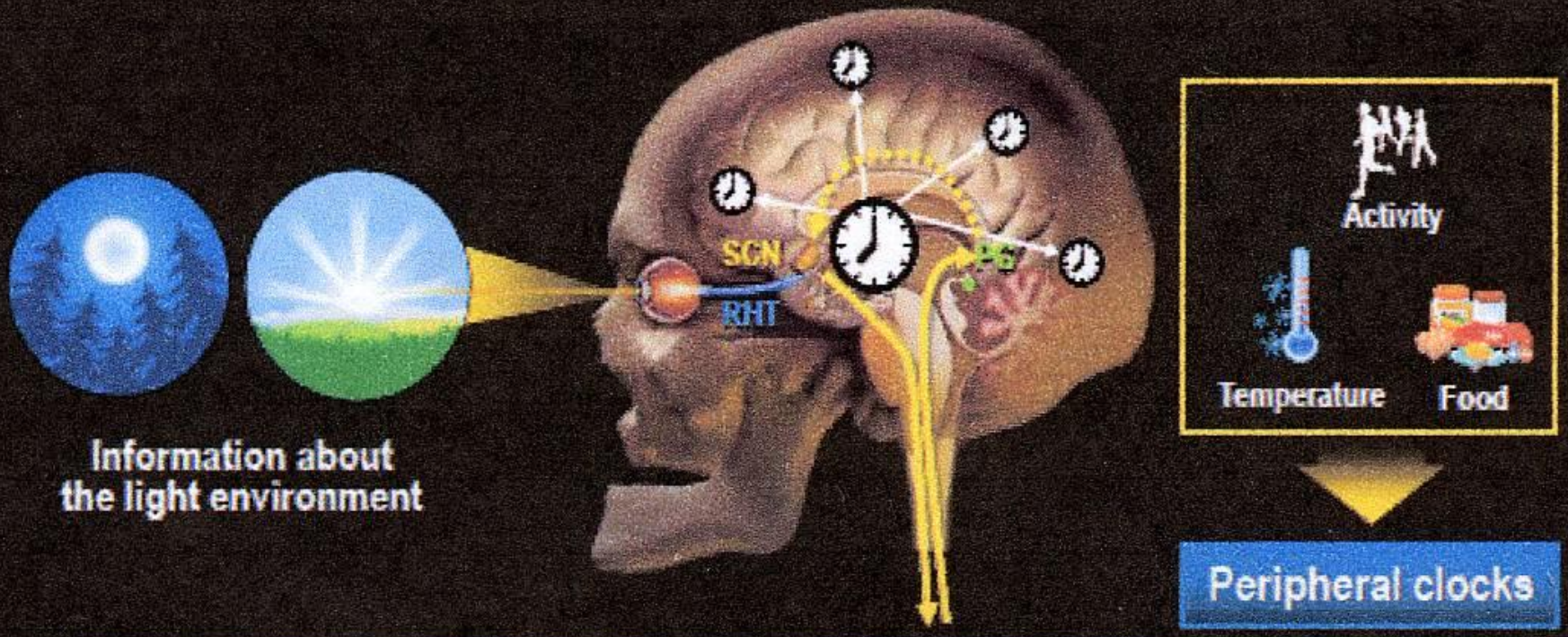
Circadian Rhythm



- **Wake and asleep times**
- **Body temperature**
- **Release of specific hormones**
- **Regulation of the immune system**
- **Recalibrating the brain**

Synchronizing Circadian Rhythms

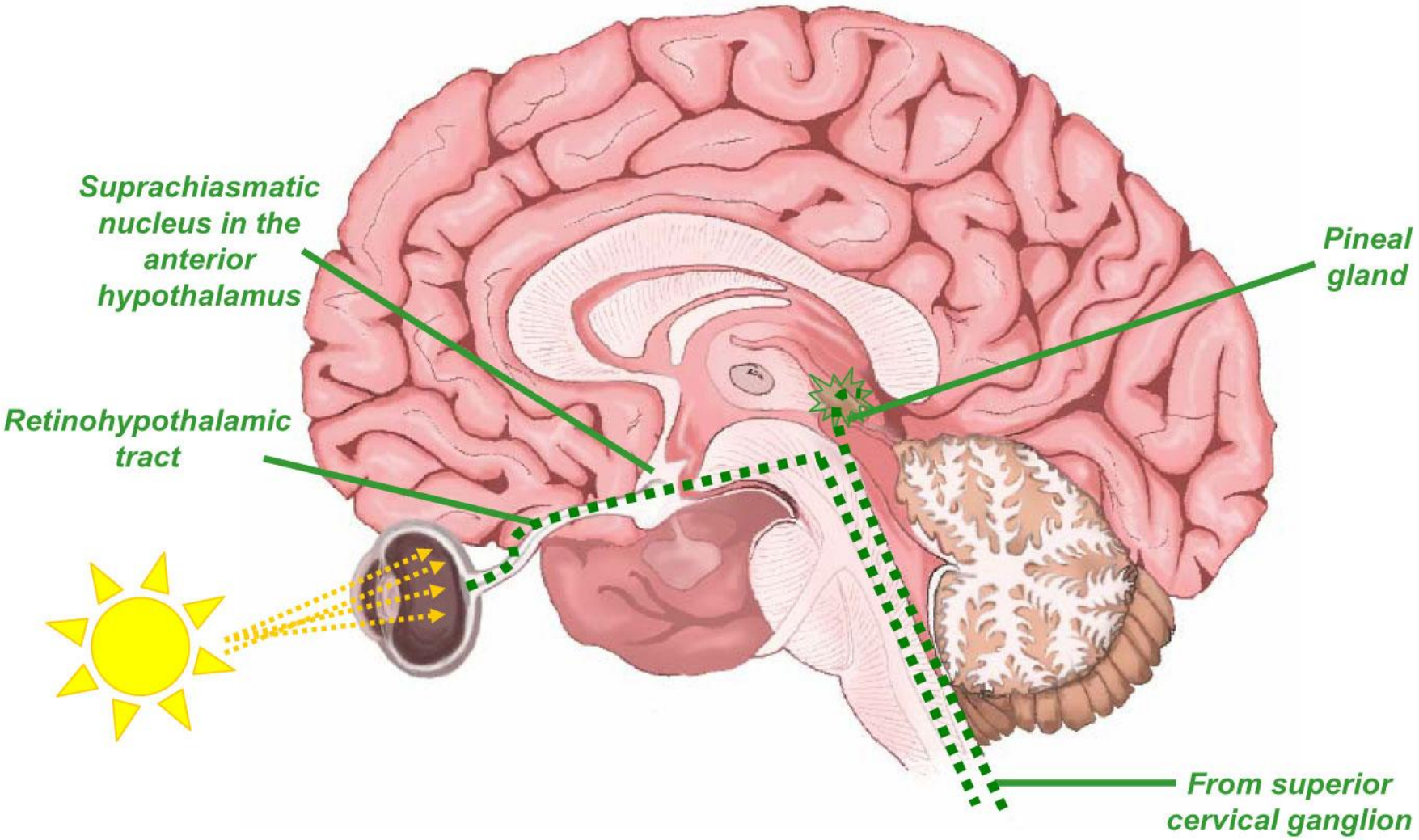
Entrainment of the SCN and Peripheral Clocks



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.

Circadian sleep drive is regulated by a "biological clock"



DLMO: Dim Light Melatonin Onset

Decreased blue light: cools the body

The Importance of Sleep for the Brain

- Protein synthesis (Ding, et al, 2004)
- Synthesis and transport of cholesterol (Cirelli, 2005)
- Expression of molecules associated with synaptic plasticity (Taishi, et al, 2005)
- Increase LTP (Cirelli, 2005)
- Gene expression (Cirelli, 2005)
- Memory consolidation

Medical Conditions - Insomnia

- Fibromyalgia
- Huntington's disease
- Kidney disease
- Hyperthyroidism
- Parkinson's disease
- Epilepsy
- Cancer
- Hypertension

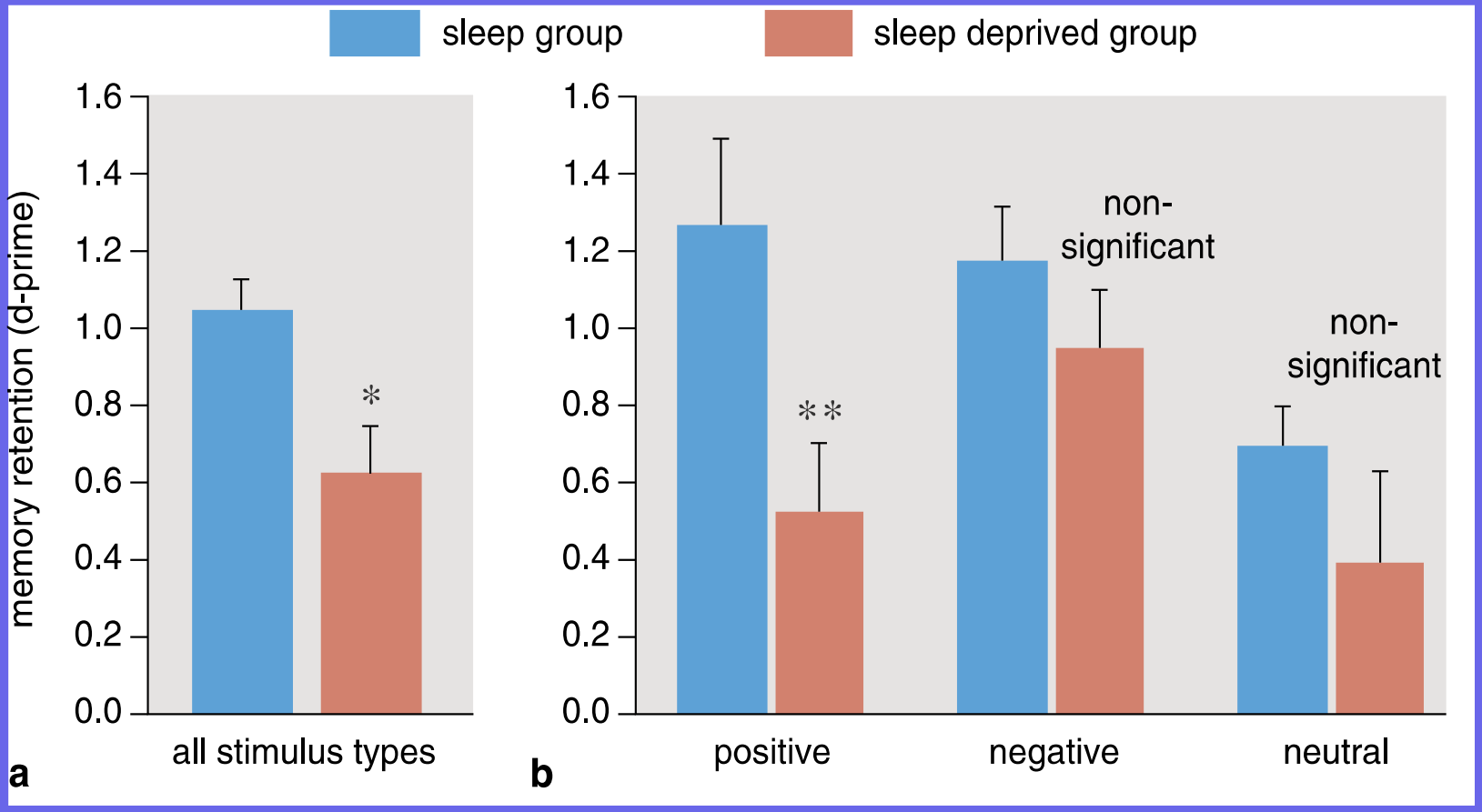
Poor Sleep Linked to Alzheimer's

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 deprivation impairs memory

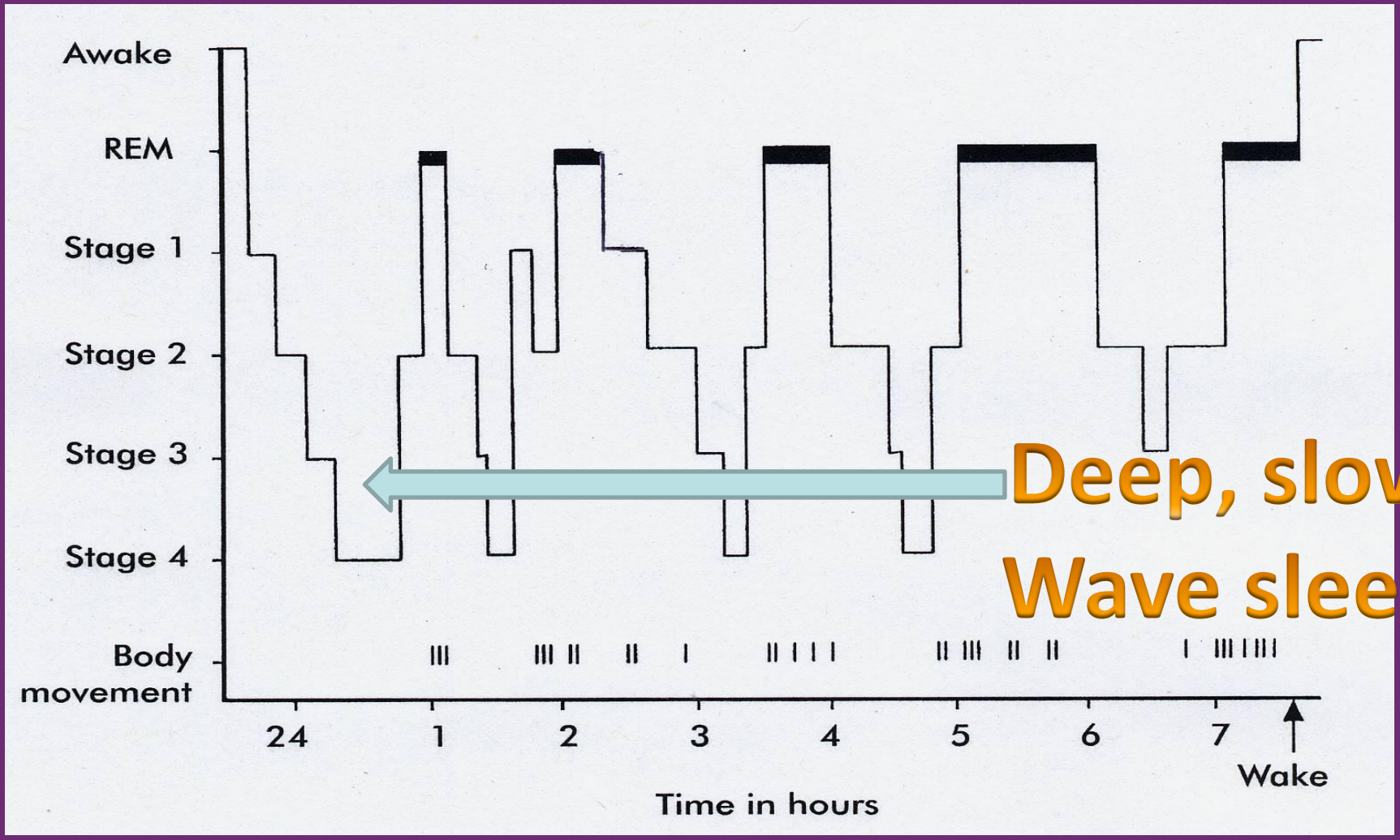


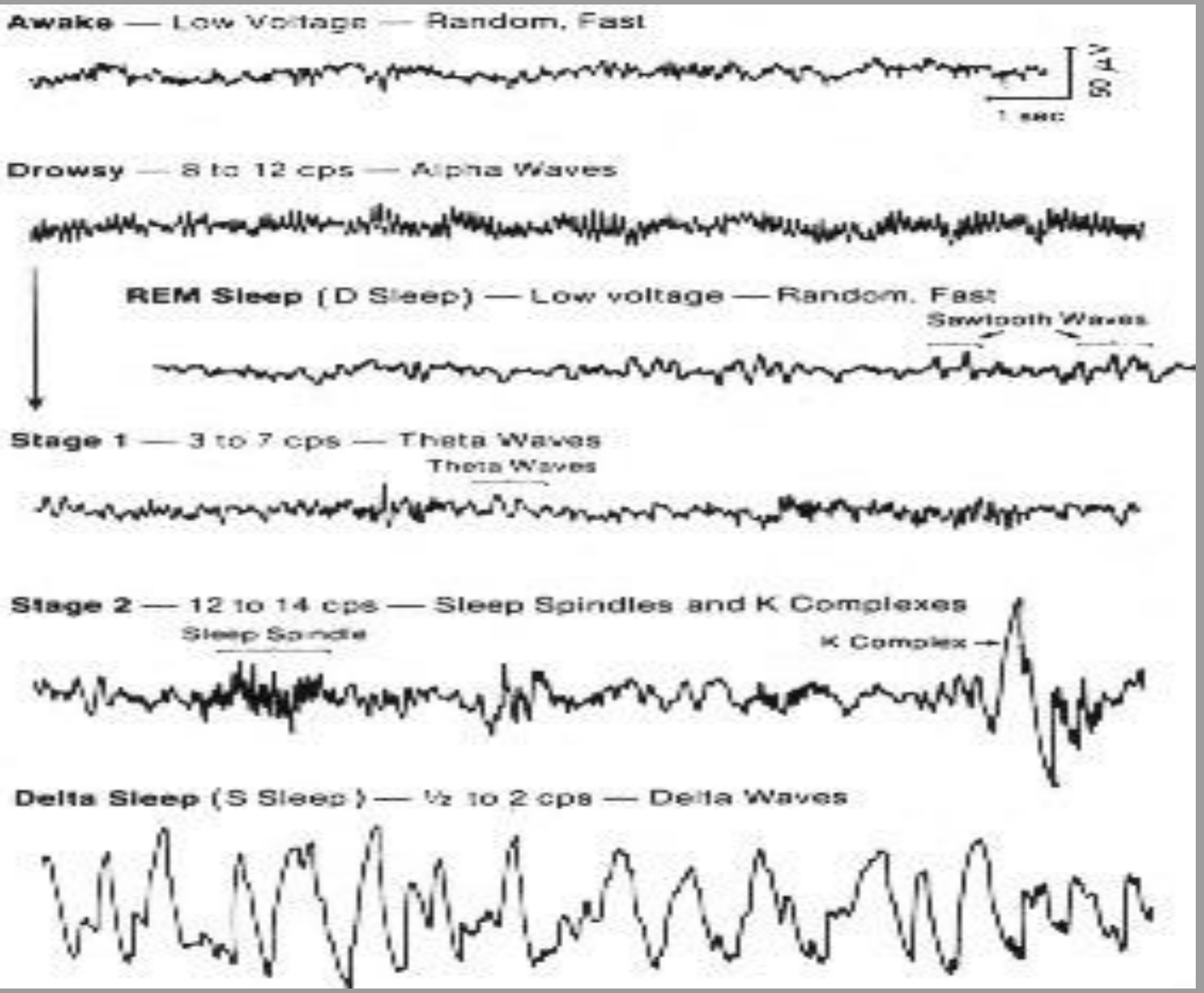
- 36 hours of sleep deprivation
- Word-pair test

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.

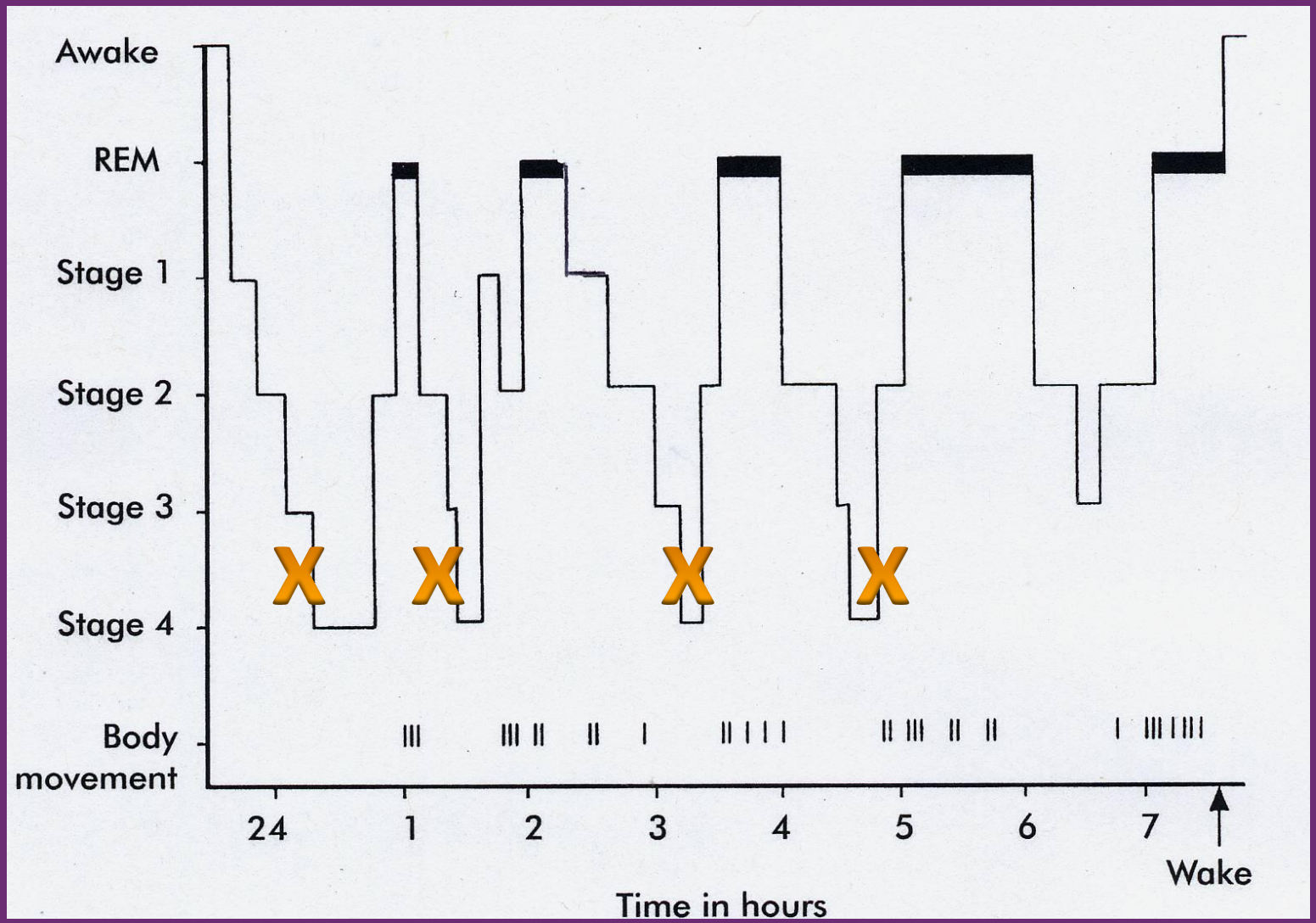
Normal Sleep Architecture




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**

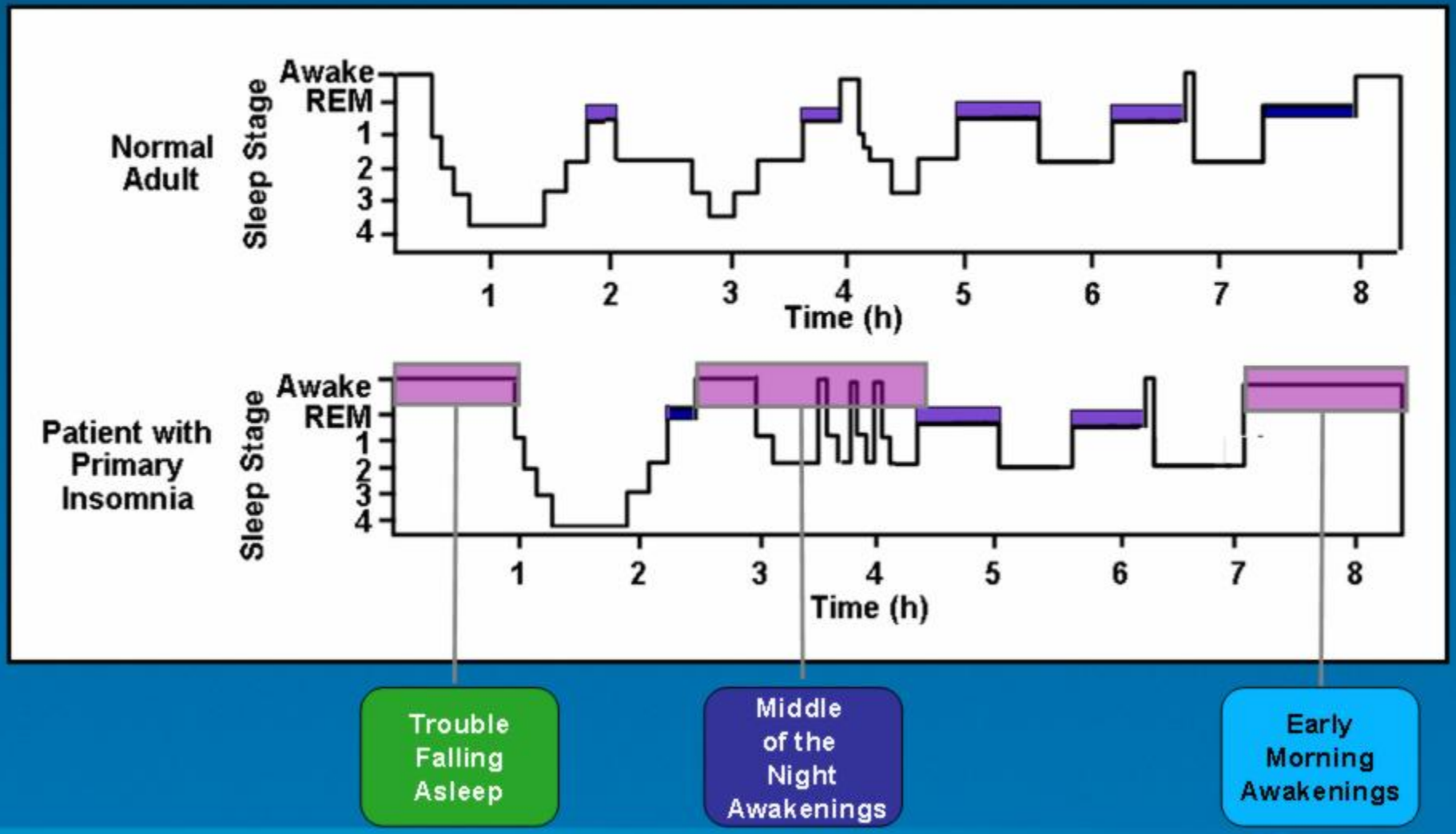
Increase in negative memories

–Increase in depression

Sleep deprivation

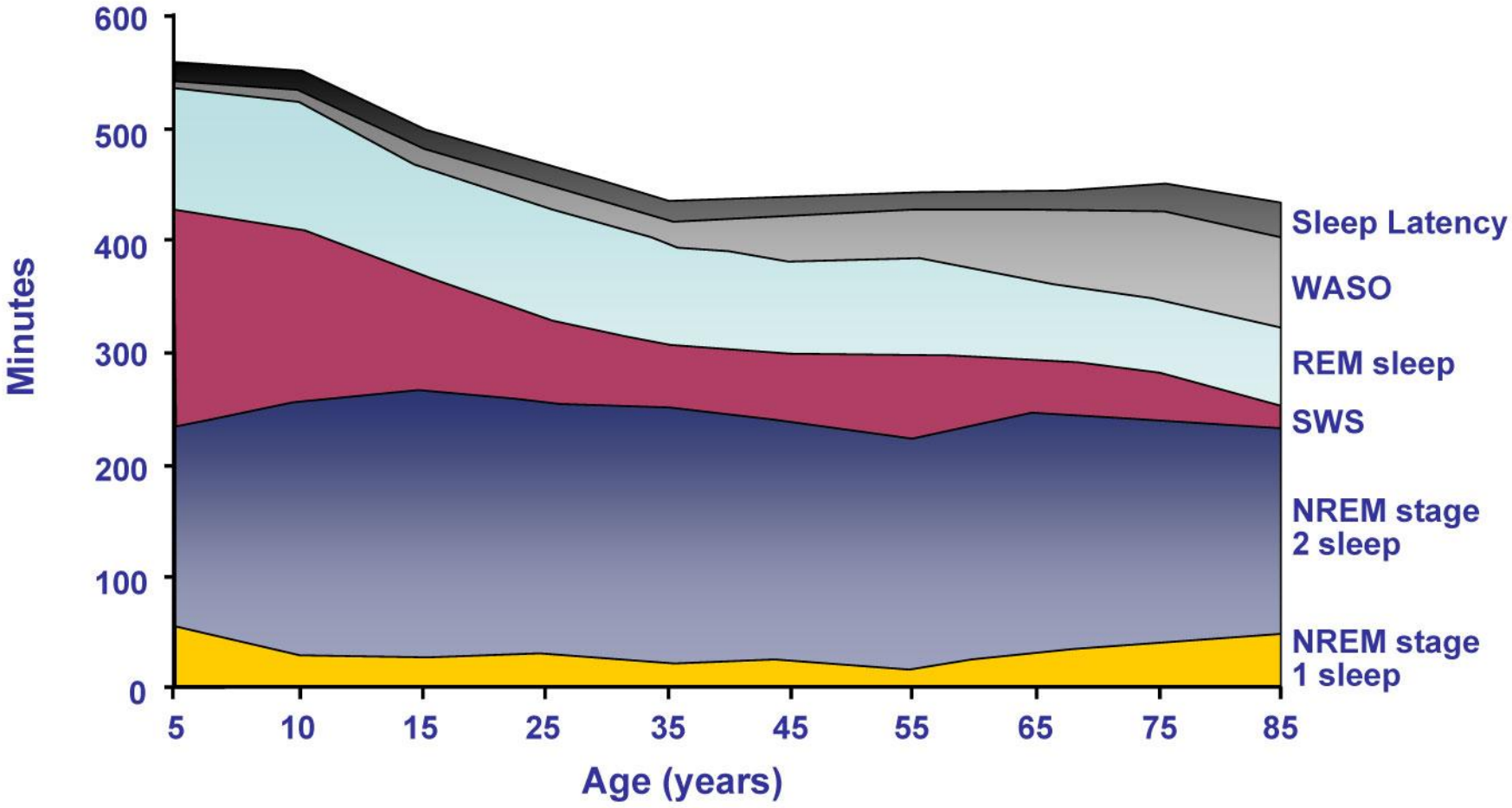
- ↓ ability to clear glucose
- ↓ in leptin (which normally would inhibit hunger)
- ↑ in ghrelin (increasing hunger)
- ↑ in weight
- ↑ vulnerability to type 2 diabetes

Sleep Hypnogram for a Normal Night's Sleep versus Insomnia



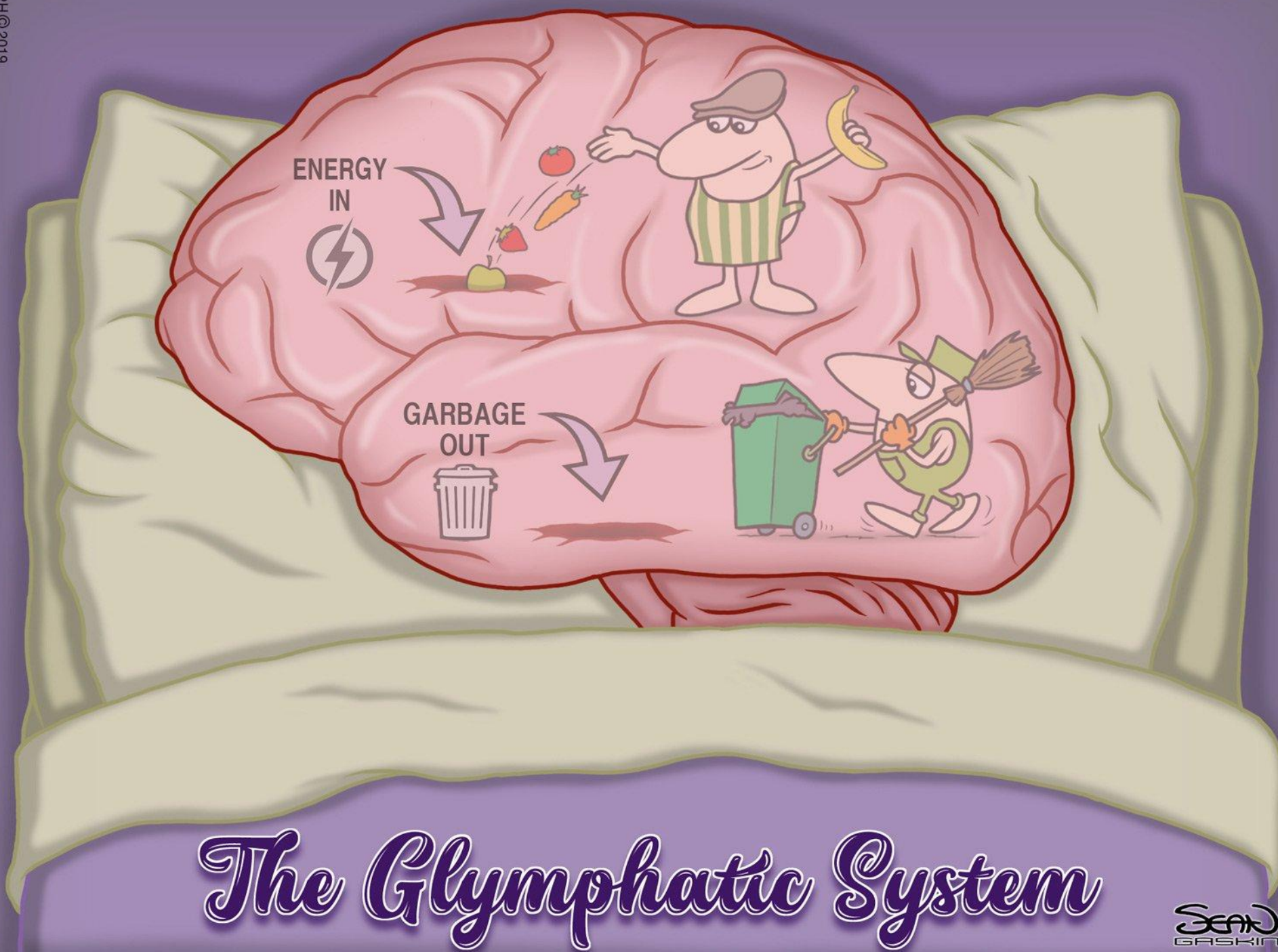
SEPRACOR

Sleep changes over the lifetime of an individual



WASO: wake after sleep onset
REM: rapid eye movement
SWS: slow wave sleep (stage 3-4 sleep)
NREM: non–rapid eye movement

Ohayon MM, et al. *Sleep*. 2004;27:1255-1273.

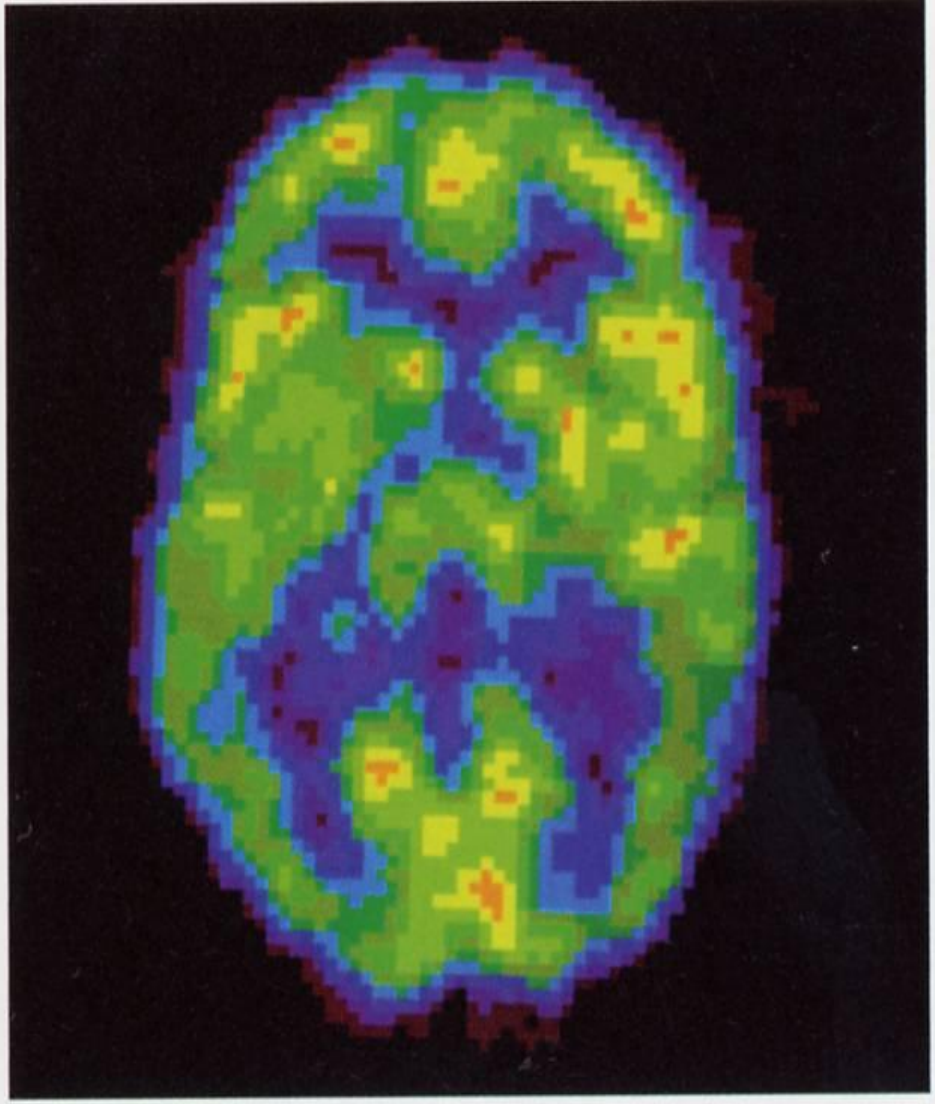


The Glymphatic System

SEAN GASKIN

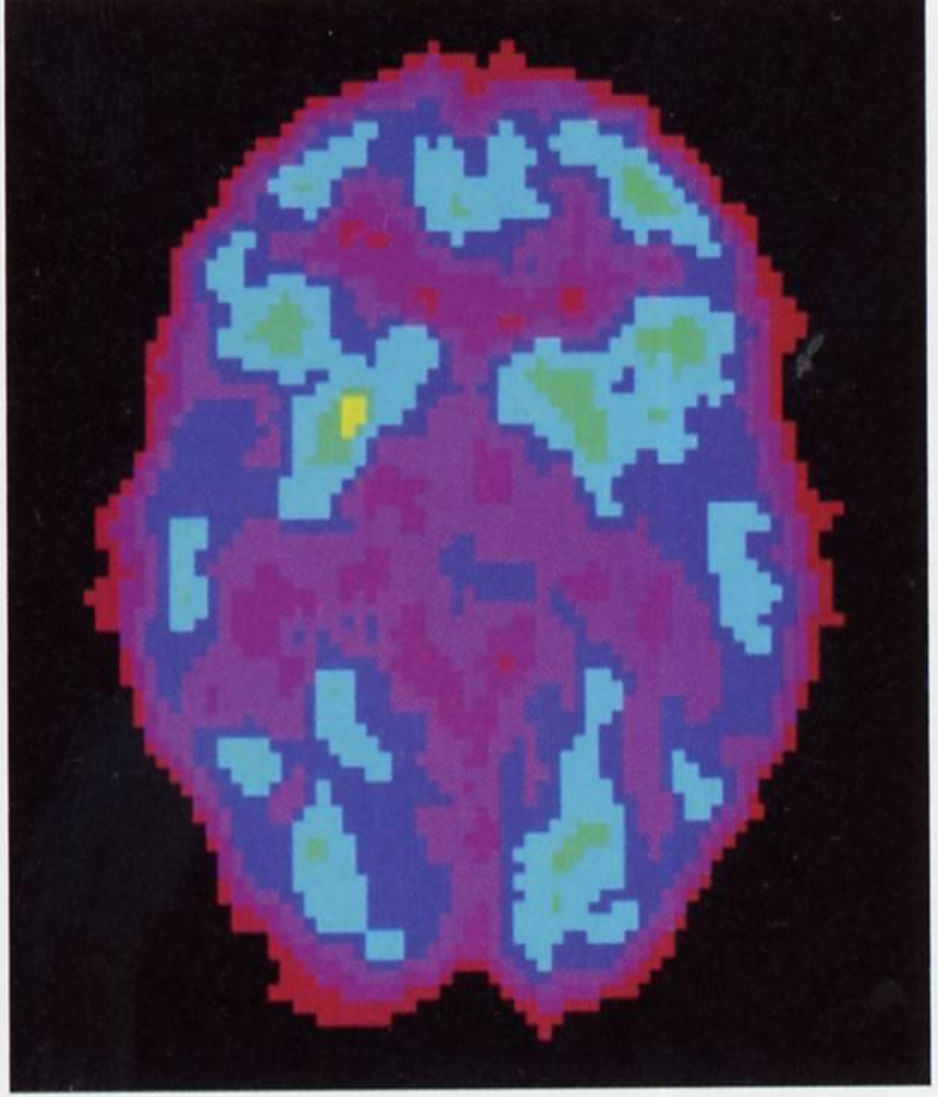
Brain Clearing

- “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.



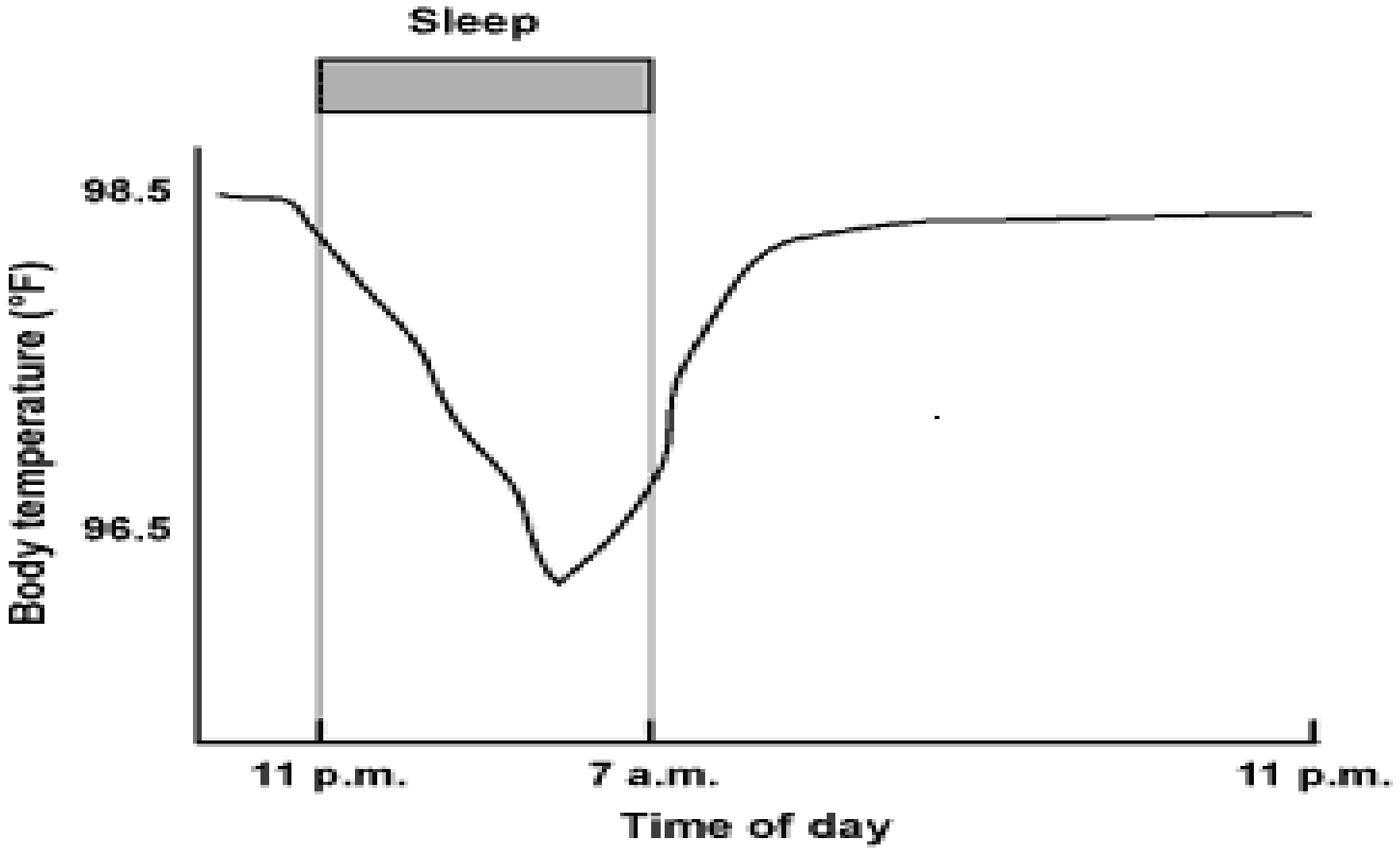
DRUGGED SLEEP

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

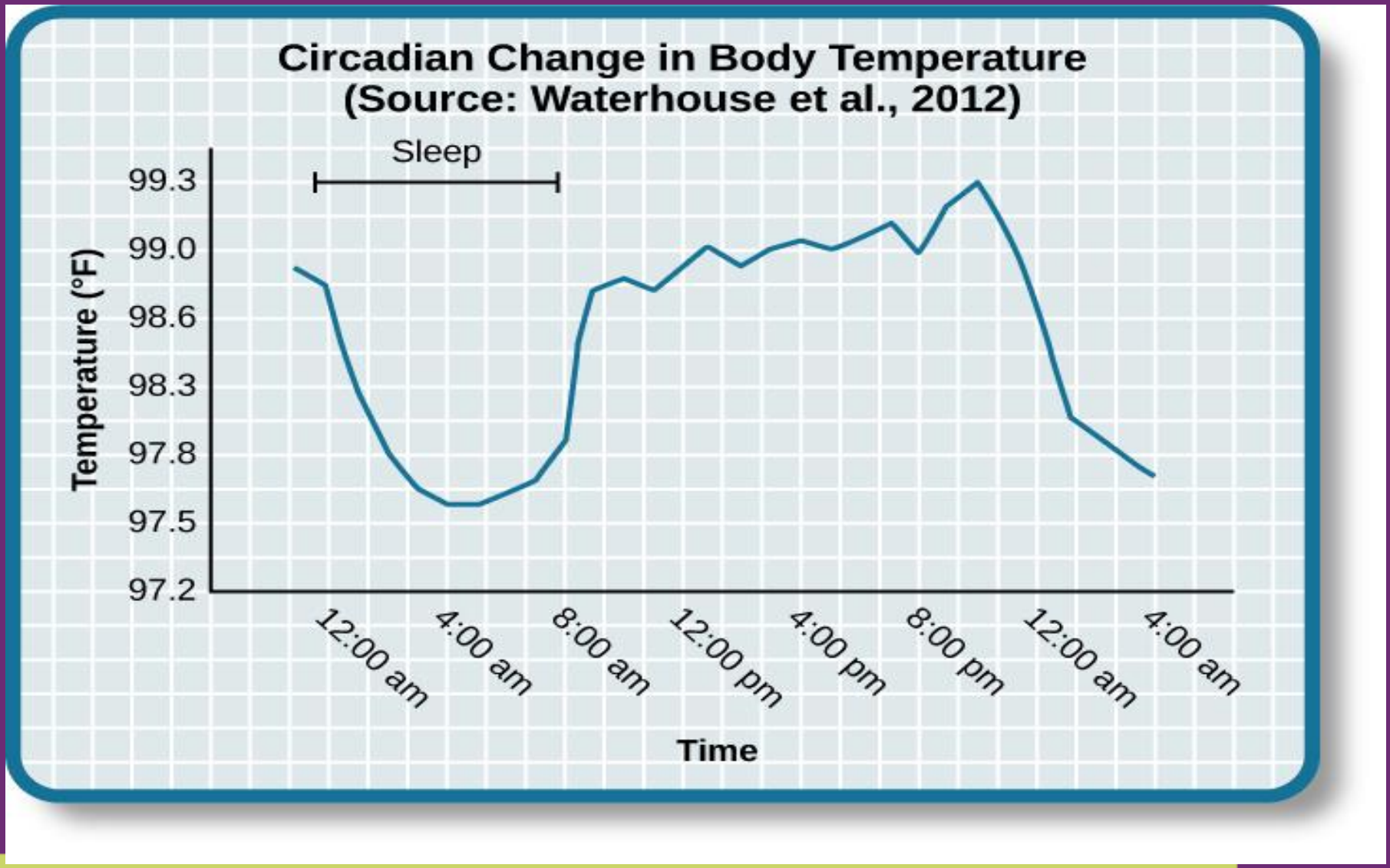
Glymphatic Pump

Brain Washing During Sleep

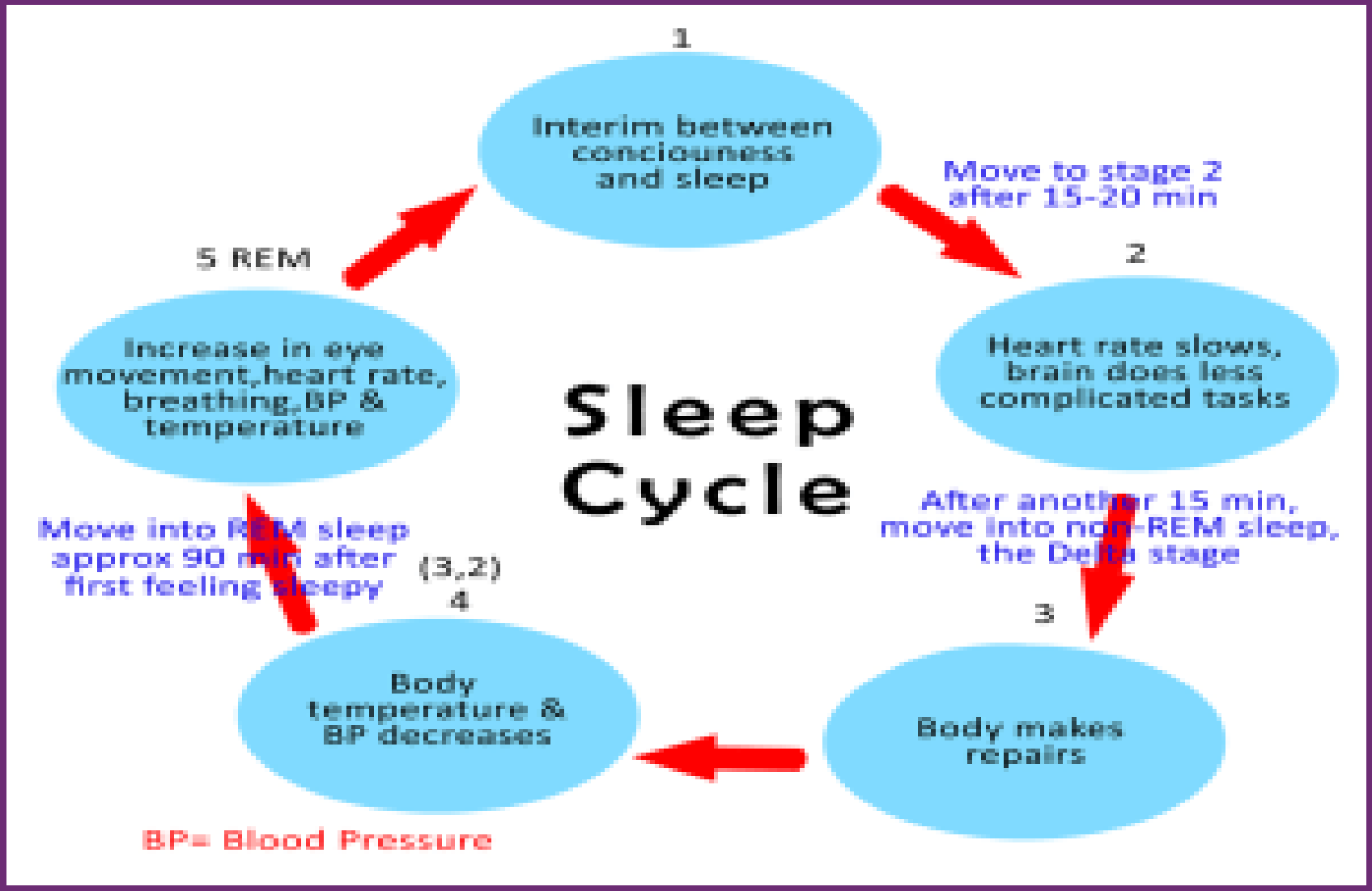
Body Temp and Sleep

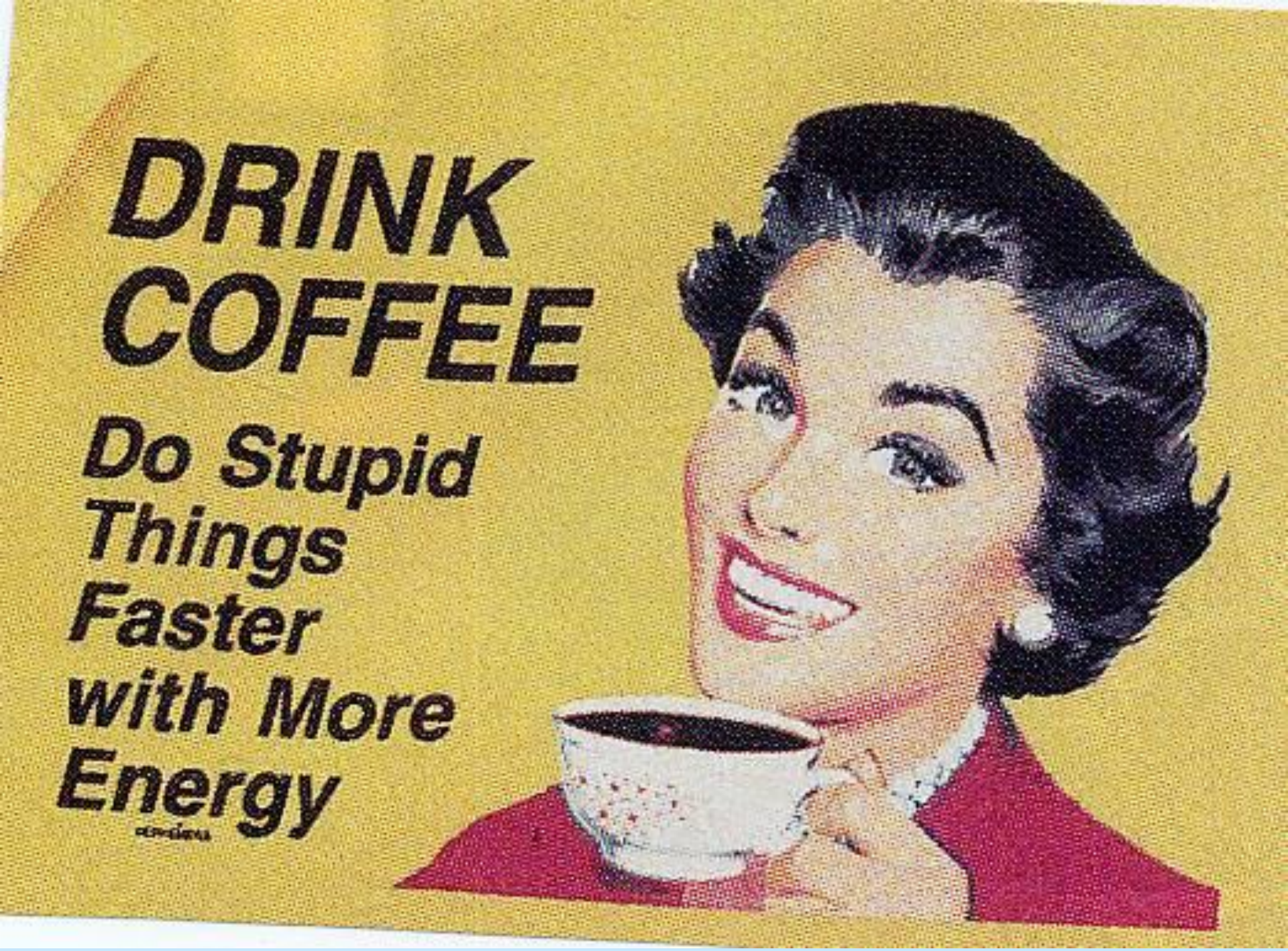


Body Temp per 24 Hours



Body Temp, Cortisol, and Melatonin



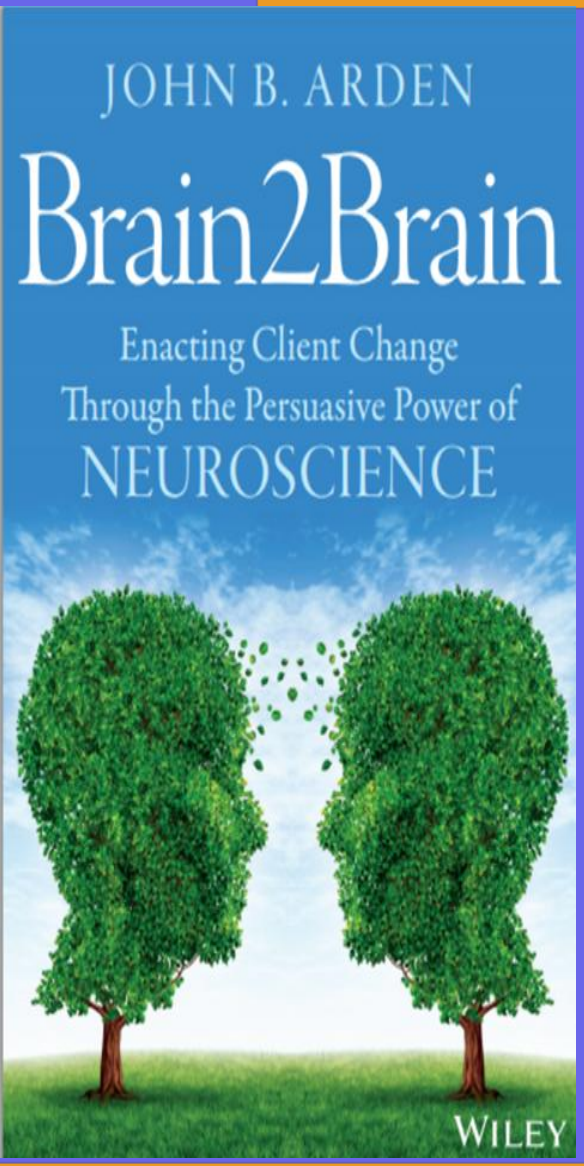

DRINK
COFFEE
Do Stupid
Things
Faster
with More
Energy

250 mg Before noon to maximize sleep

Sleep Summary

- Under 6 hours impairment
- Avoiding sleep depressors
- Negative sleep thoughts
- Body temperature
- Diet
- Exercise

References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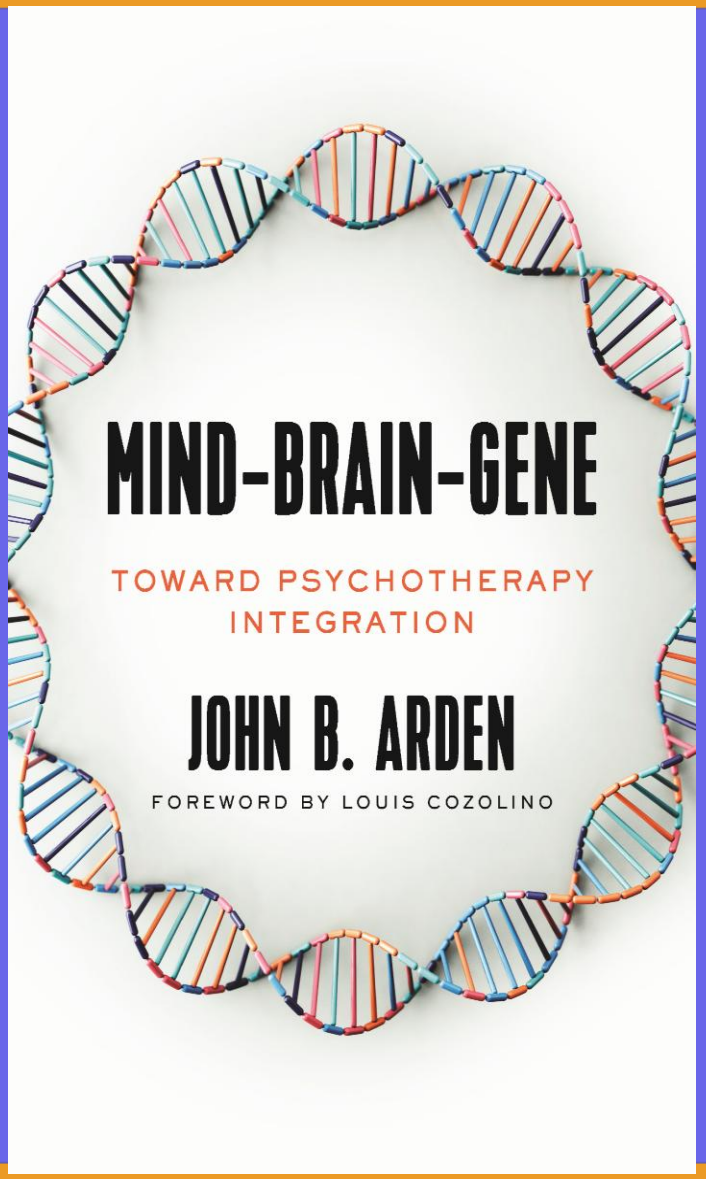
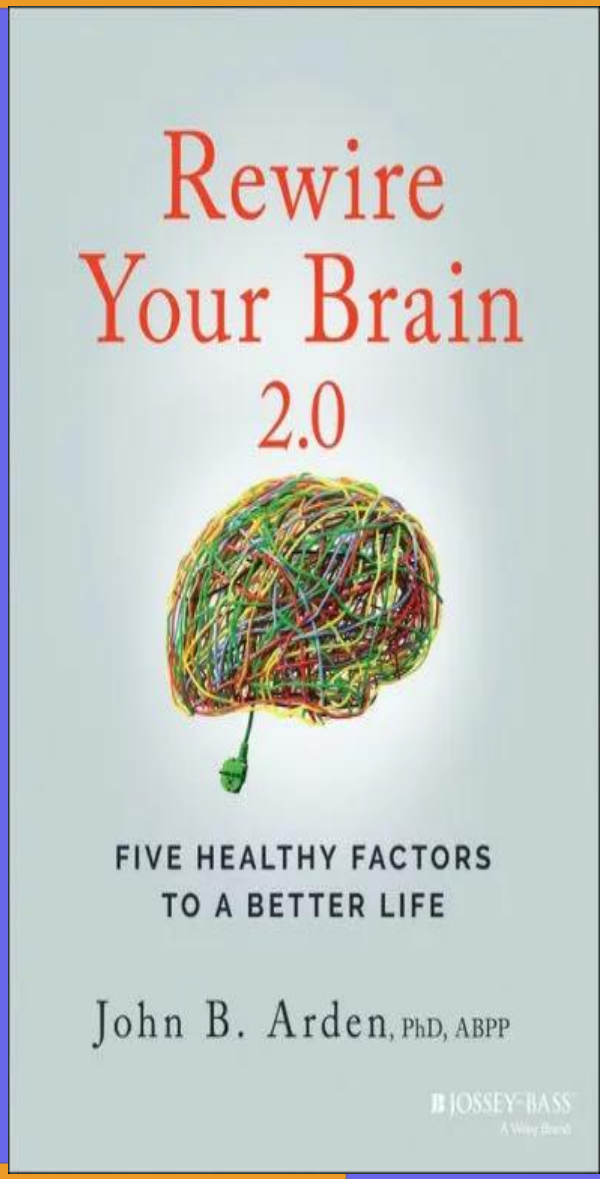
Brain2Brain
Enacting Client Change
Through the Persuasive Power of
NEUROSCIENCE
WILEY


MIND-BRAIN-GENE
TOWARD PSYCHOTHERAPY
INTEGRATION
JOHN B. ARDEN
FOREWORD BY LOUIS COZOLINO


Rewire
Your Brain
2.0
FIVE HEALTHY FACTORS
TO A BETTER LIFE
John B. Arden, PhD, ABPP
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