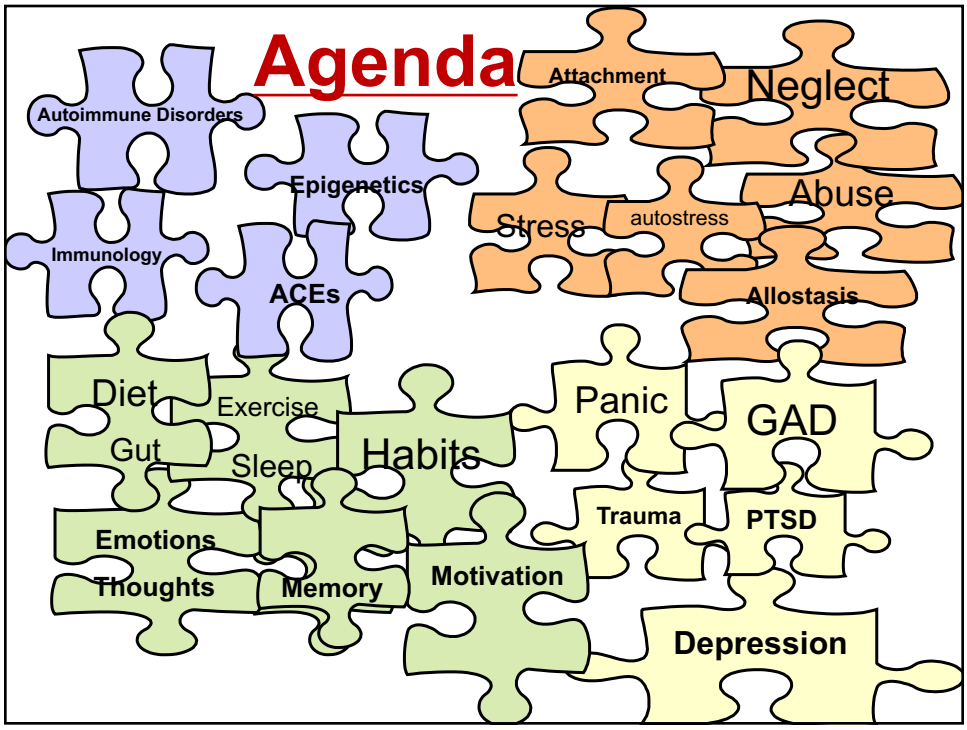
Mind-Brain-Gene:

Toward Psychotherapy Integration

John B. Arden, PhD, ABPP



Therapy might have been different

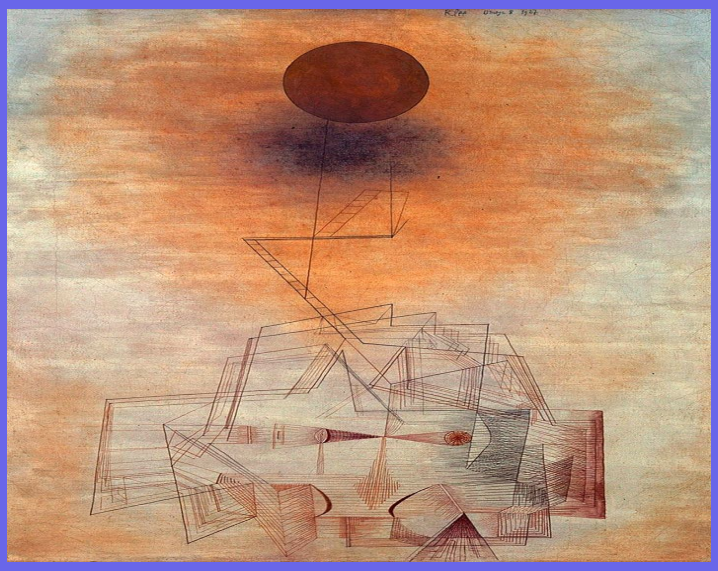
"We must recollect that all of our provisional ideas in psychology will presumably one day be based on an organic substructure."

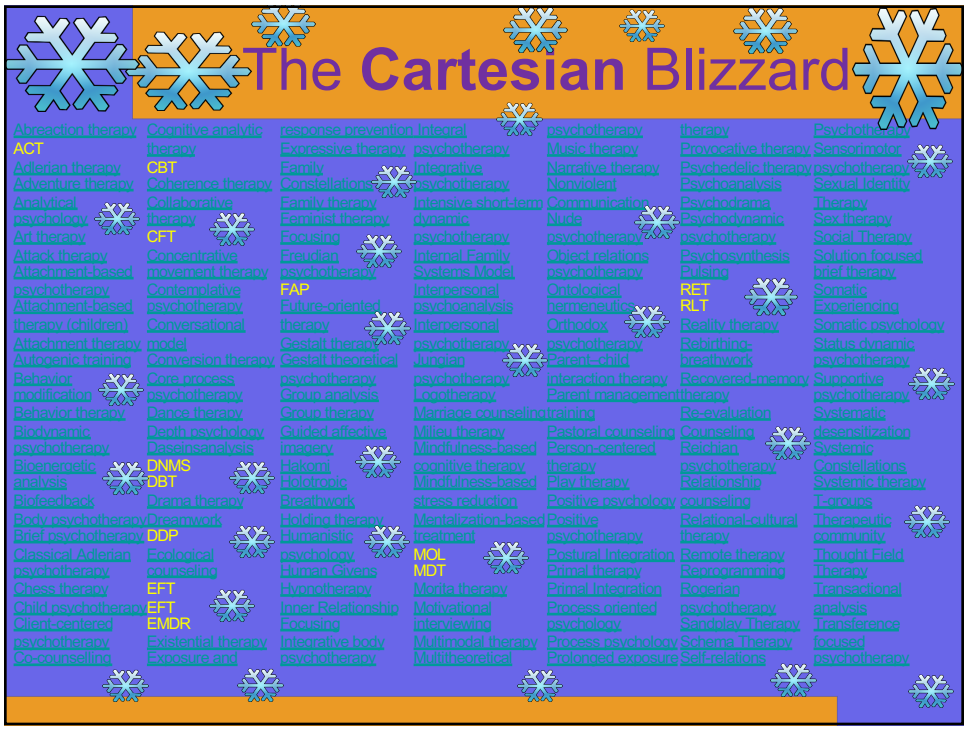
--Sigmund Freud

"The act of will activates neural circuits" **But……**

--William James

Limits of Understanding (Klee)





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

The "Pax Medica"

After the Cartesian area and Eysenck etc.

-brought us:

- **The DSMs**
- **SSRIs-NSRIs etc**
- **Evidenced-based psychotherapy**
- **The medicalization of psychotherapy**
- **Managed $**

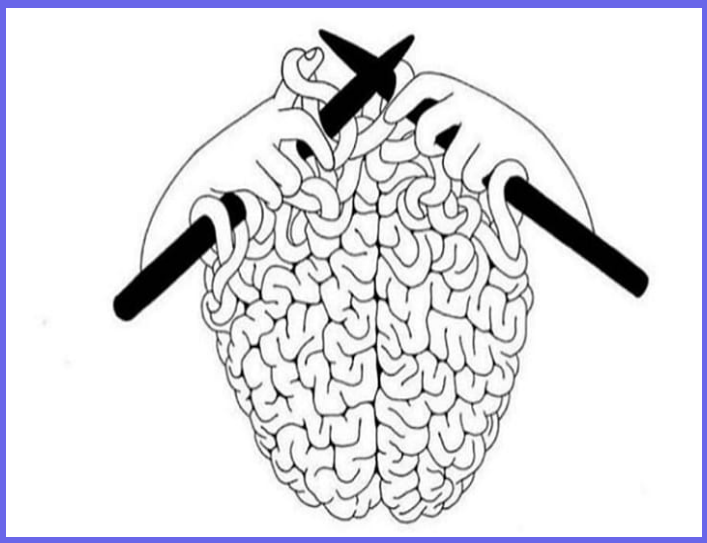
Pax Romana

The Science has Changed

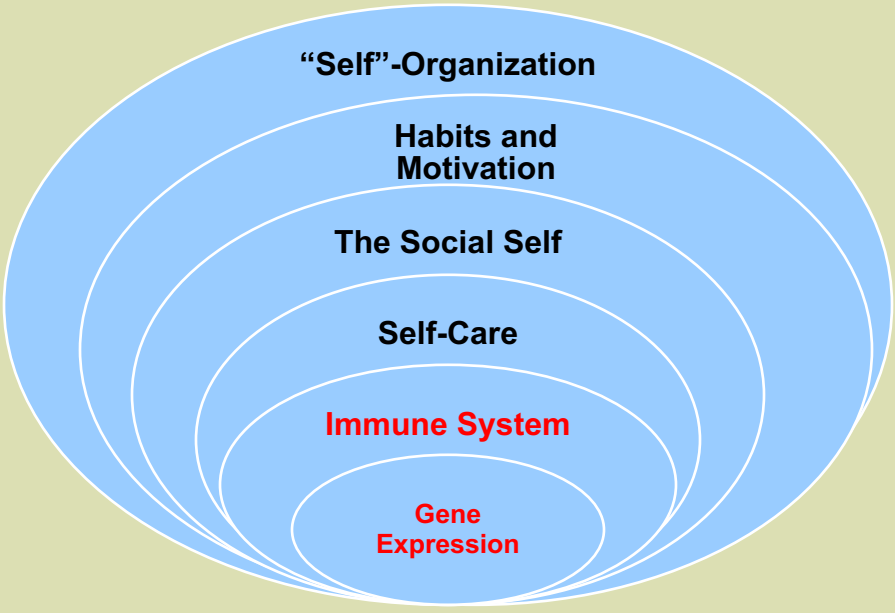
"Mental functions direct electrochemical traffic at the cellular level" Roger Sperry

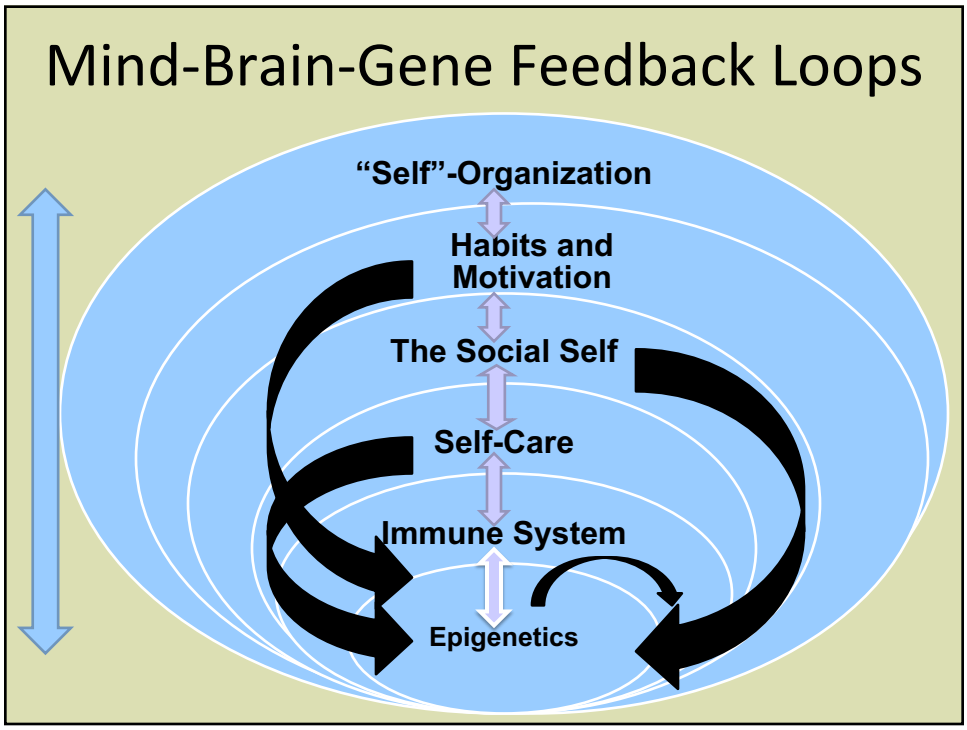
"Psychotherapy works by producing changes in gene expression that alter the strength of synaptic connections…" Eric Kandel

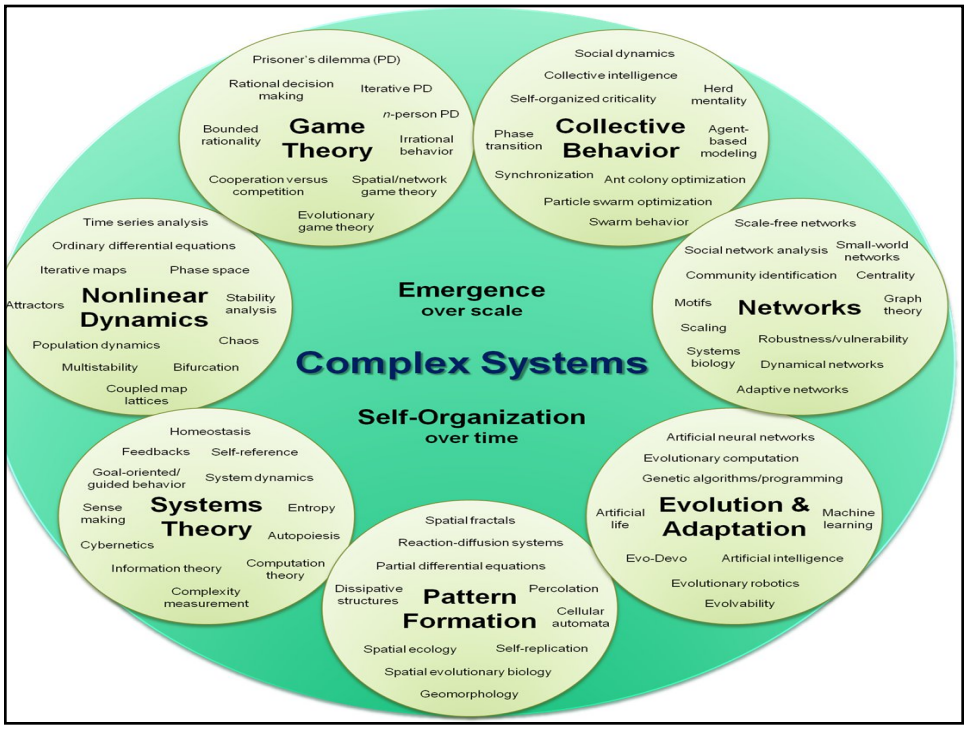
Mind/Brain Causality



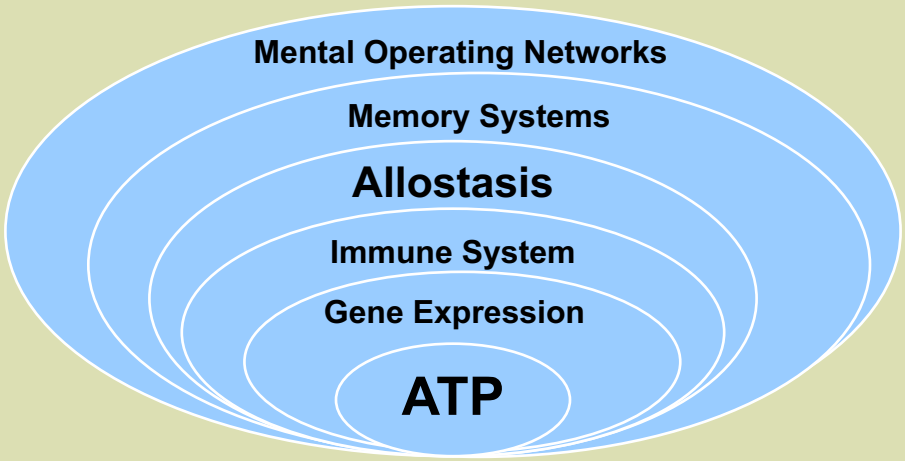
Mind-Brain-Gene Feedback Loops




Mind-Brain-Gene Feedback Loops
"Self"-Organization
Habits and Motivation
The Social Self
Self-Care
Immune System
Epigenetics


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

“Self”-Organization

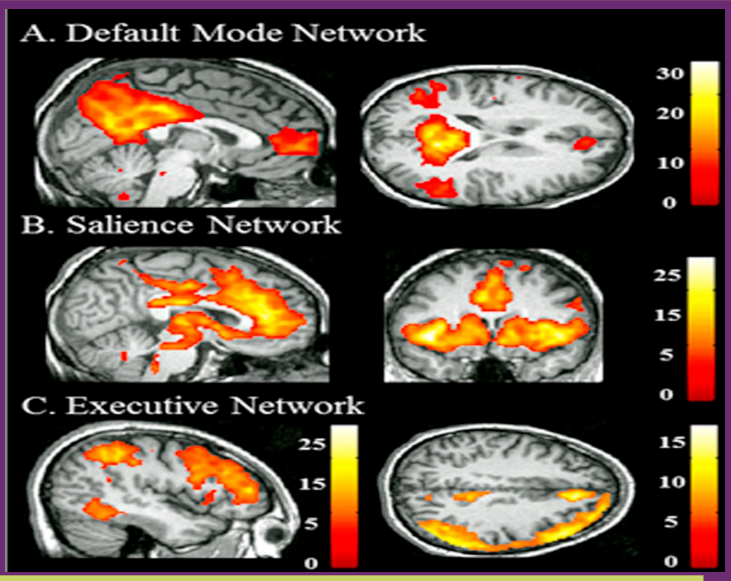


Mind-Brain-Gene Feedback Loops

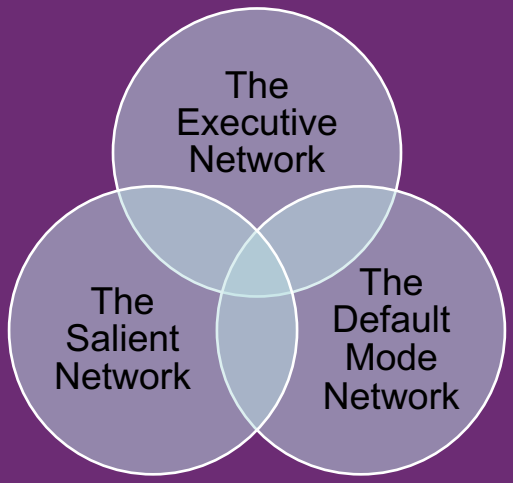
The Mind's Operating Networks:

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

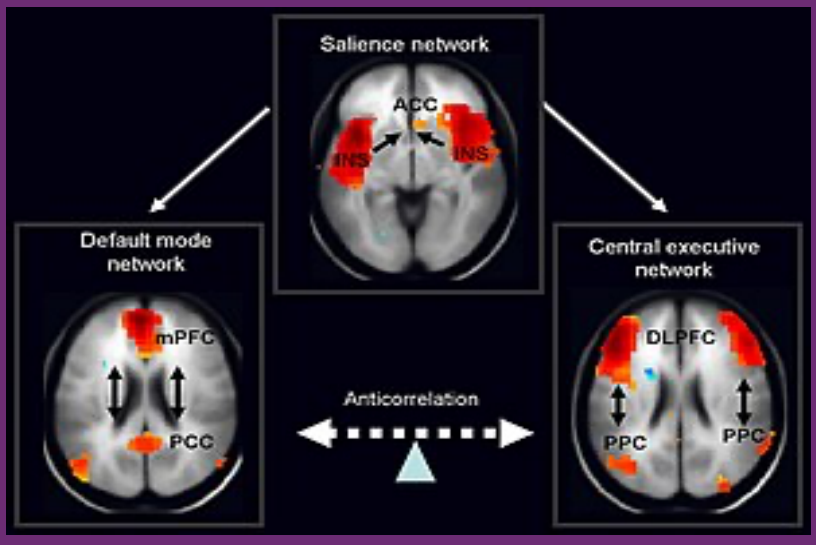
The Mental Networks



Balancing the Mental Networks



The Mental Neworks

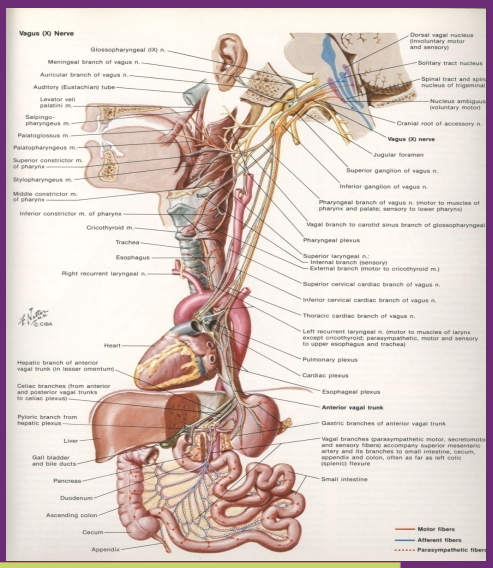


Salience Network:

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

The Vagus Nerve System

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

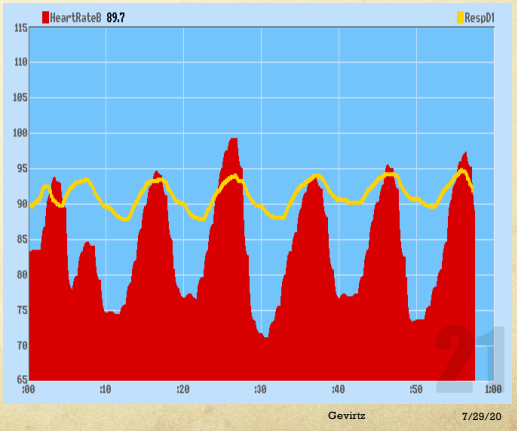


Variability is good

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

Heart rate increases with inhale.

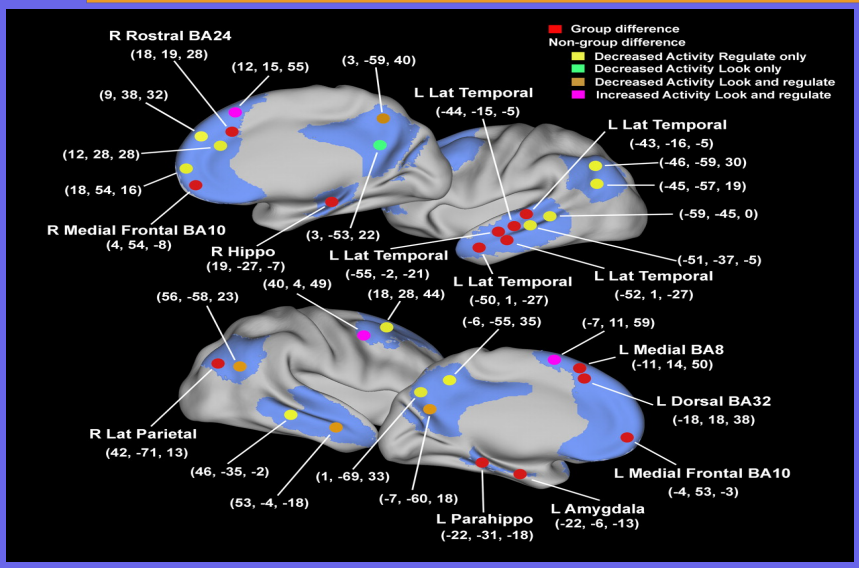
Heart rate decreases with exhale. This pattern shows high vagal tone (high PSNS activity) and a high amount of heart rate variability.



Default Mode Network:

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

Activity in the default mode network



Sheline Y I et al. (2009)

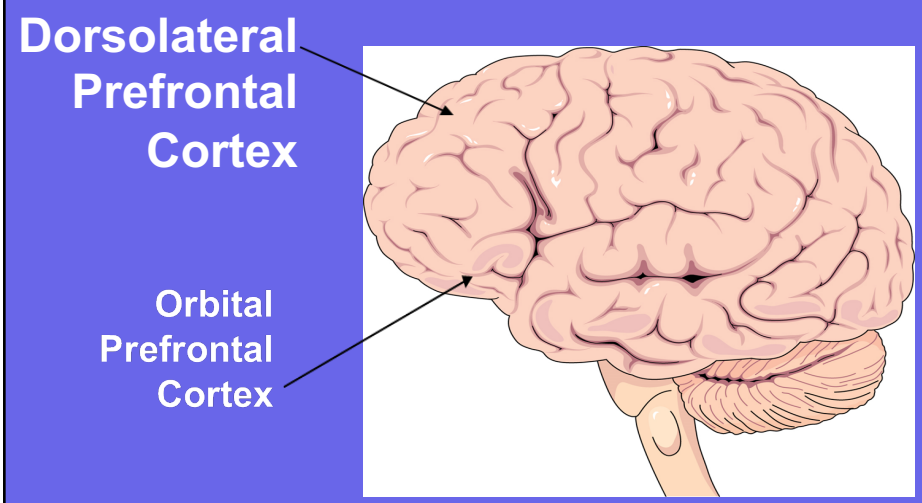
DMN Variations

- 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



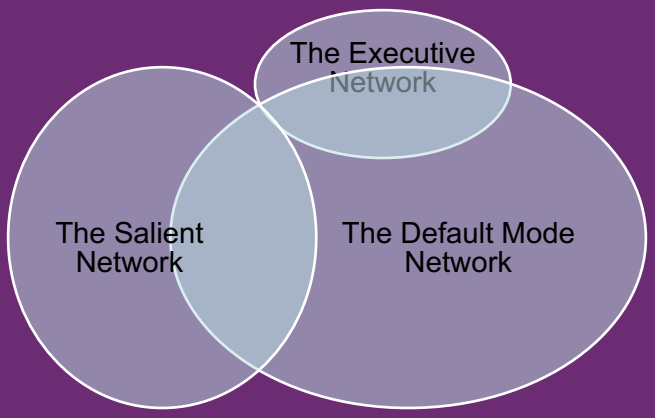
Pre-Frontal Cortex

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

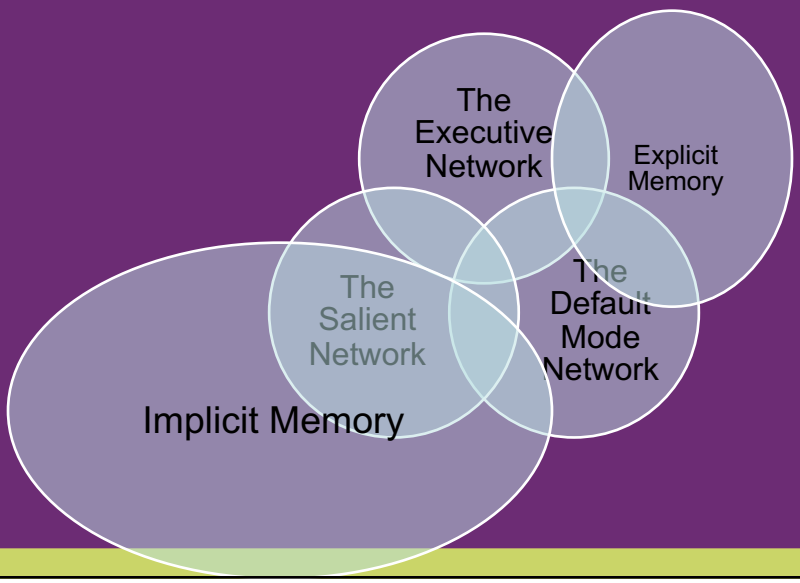
Anterior PFC
(the brain's brain)

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

Imbalanced Mental Networks



The Mental Neworks & the Long-Term Memory Systems

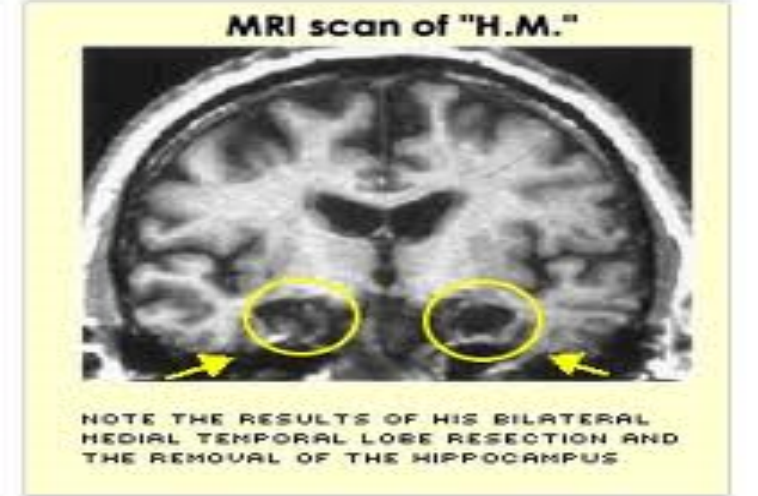


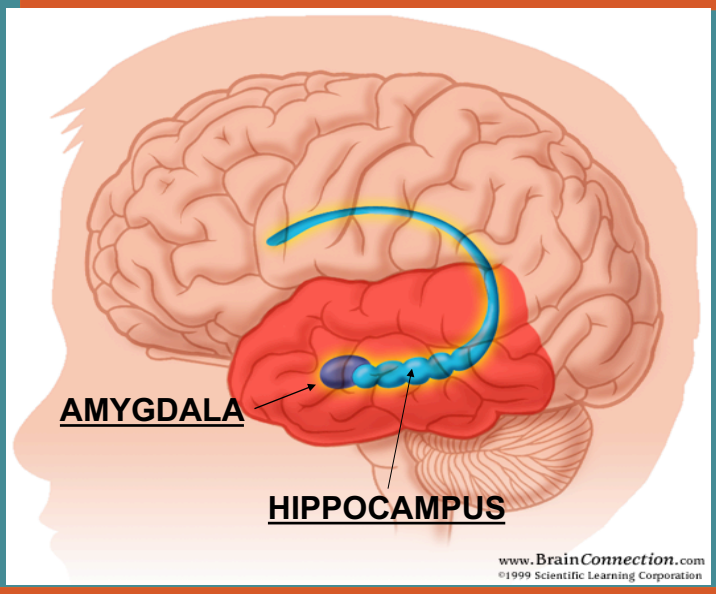
AMYGDALA *Implicit Memory System*	HIPPOCAMPUS *Explicit Memory System*
•Fear Conditioning •Emotional Valance •Generalized •Cortisol Heightened •Sensitivity • (Hypervigilence) •Matures Early •"Little Albert" •"LSMFT"	• Many Cortisol Receptors • Context Specific • Heightened Cortisol leads to atrophy • Matures Later • Vs. Infantile Amnesia • "H.M."

Henry Molaison

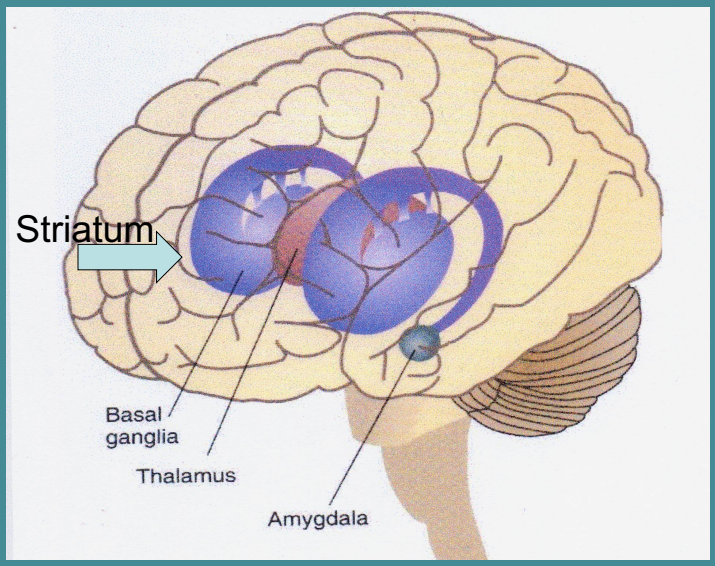
Dr. Brenda Milner

Henry's Brain





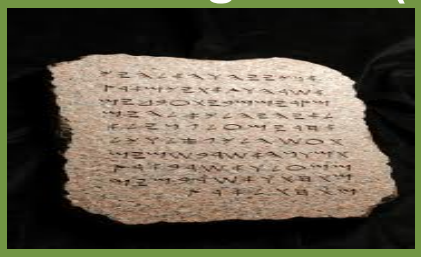
The Habit Circuits



Procedural Memory

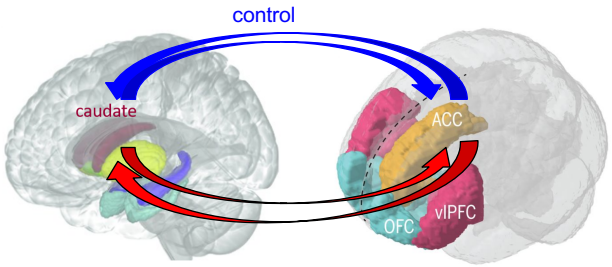
The Dynamics of Fear

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



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

Subcortical-Cortical Connectivity



ADHD/CD

Shannon, Sauder, Beauchaine et al., 2009

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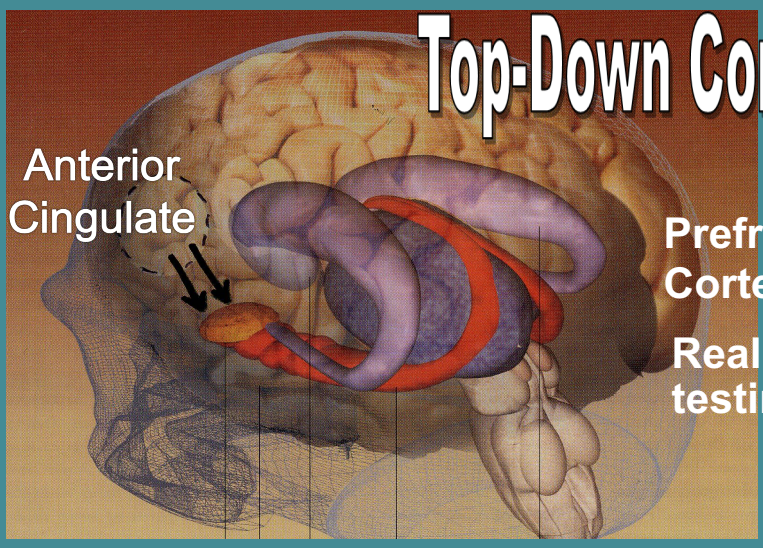
Cortical-level Appraisal



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.)

Therapeutic Frames of Reference

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

Affect Asymmetry

Set points

Left Hemisphere

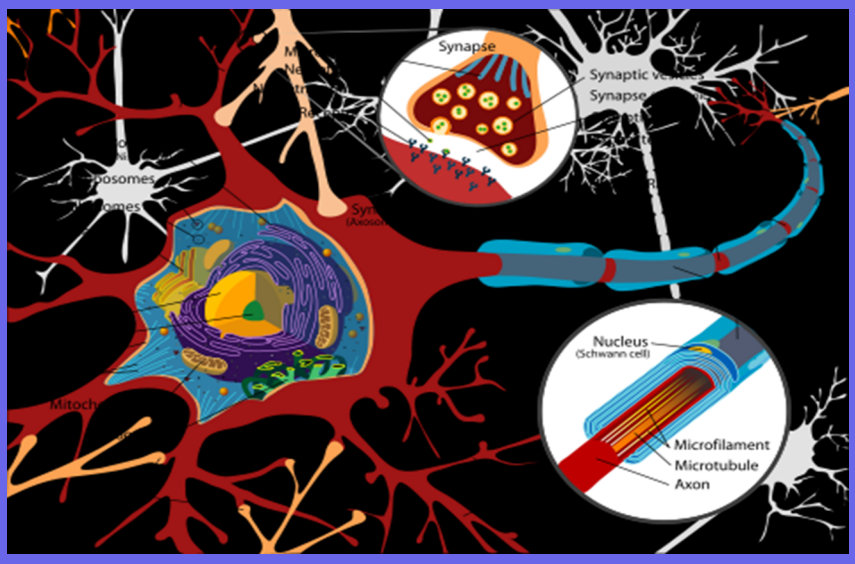
Positive emotions
Approach behaviors
Feeling engaged

Right Hemisphere

Negative emotions
Withdrawal and Avoidance
Feeling overwhelmed

100 Billion Neurons

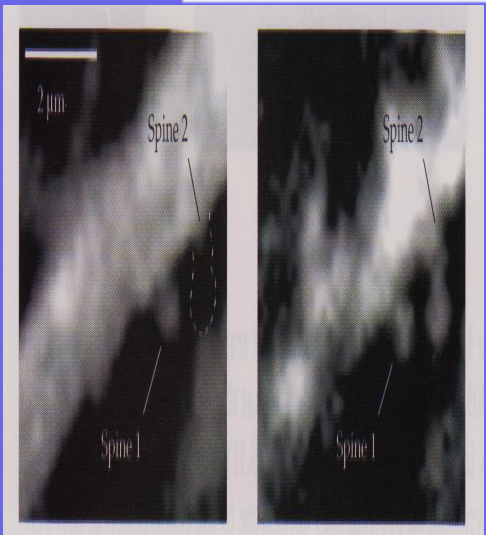
Each with 10,000 synaptic connections

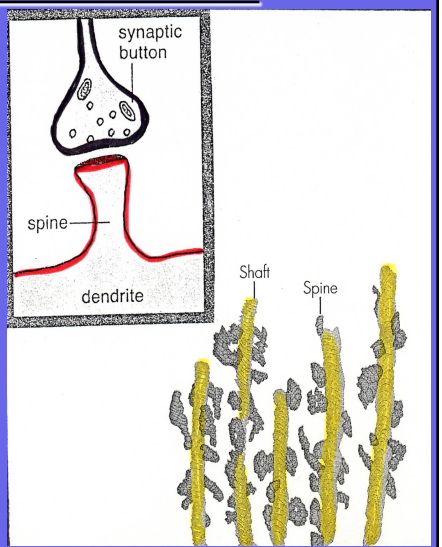


Neurons that fire together, wire together

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

DENDRITE SPINES & SYNAPSES—one hour



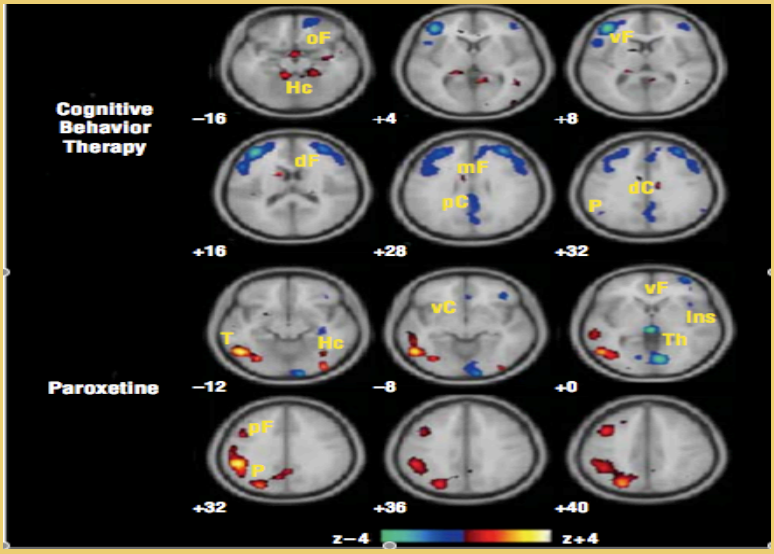


Examples of Neuroplasticity

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

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

Brain Change: Two Perspectives



Psychotherapy and the Brain

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

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

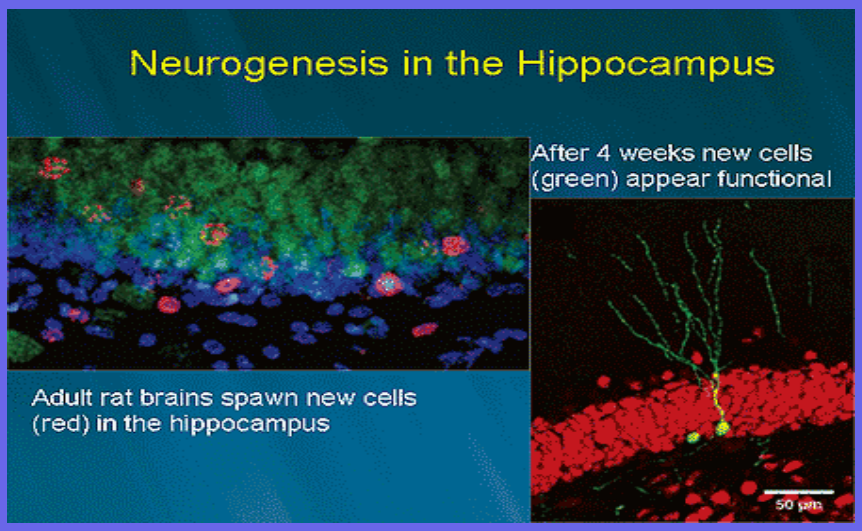
Between Session Neuroplasticity

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

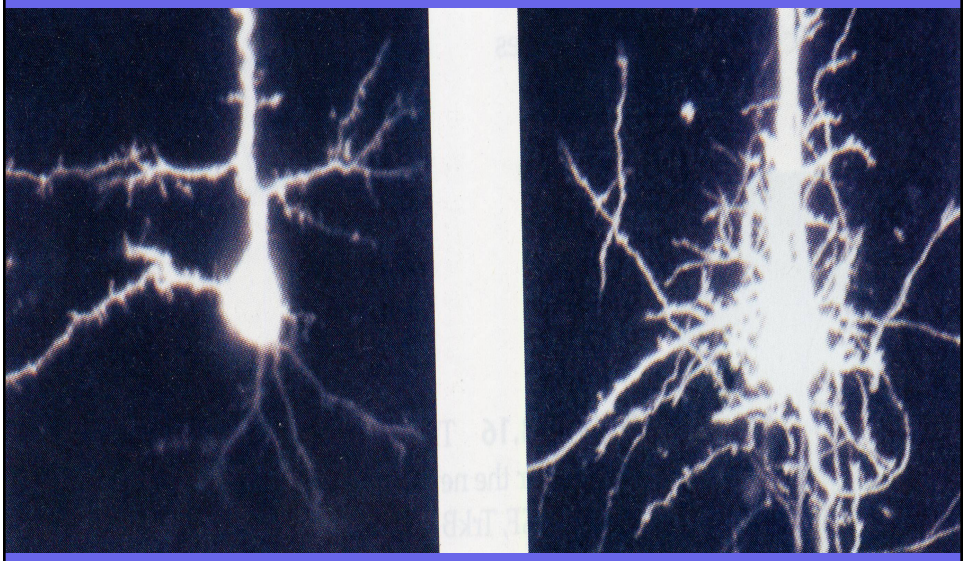
Brain Derived Neurotropic Factor

- 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



BDNF: Impact on Dendrite growth: 24 hours



Factors that Decrease Neurogenesis

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

Factors that Increase Neurogenesis

Exercise

- play induces BDNF gene expression

Fasting

Fewer calories consumed

Food content --(Omega—3)

Profound new experience---Ah!

Mind-Brain-Gene Feedback Loops

Hunter-gatherer Adaptation Boosted the Social Brain

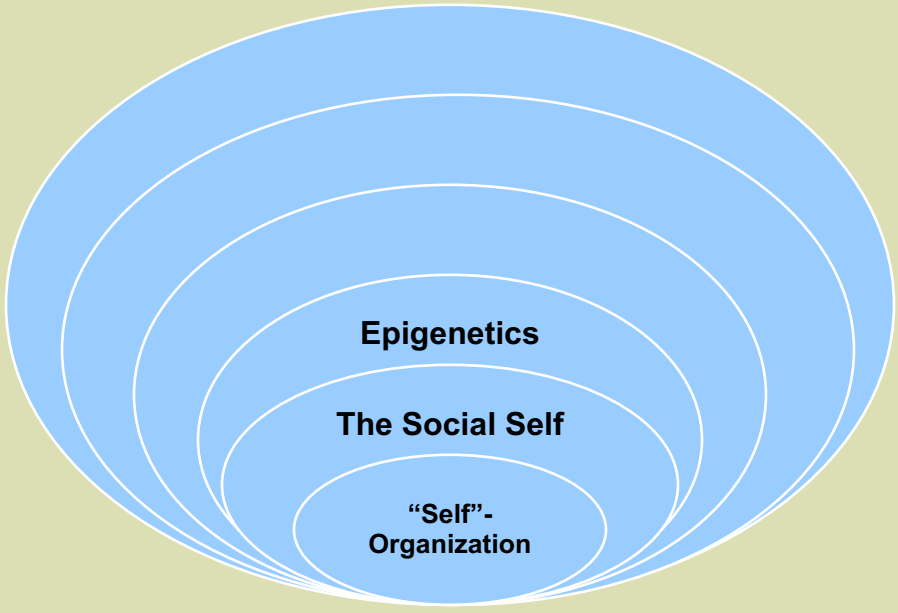
The Effects of Social Medicine

- ↓ 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)

The Neuroscience of Attachment

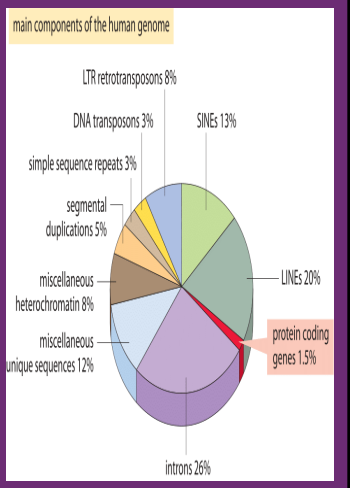
- Balance Between the two branches of the Autonomic Nervous System
- Endorphin & Benzodiazepine receptors
- Cortisol Regulation
- Positive Immunological Functioning
- Neural Growth and Plasticity

Mind-Brain-Gene Feedback Loops

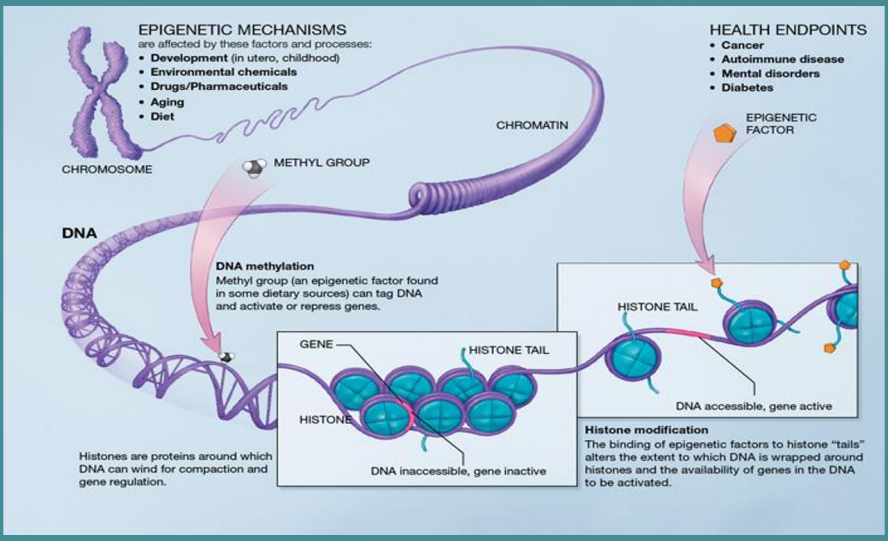


Epigenetics

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



Epigenetics



Epigenetics in Gene Expression

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

Someone Needs to Play (behave)

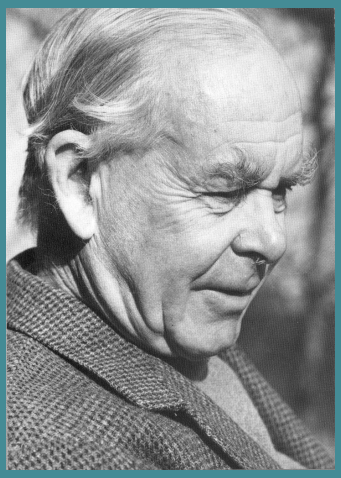
Epigentics and parenting

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

Cortisol level

John Bowlby (1907 – 1990)

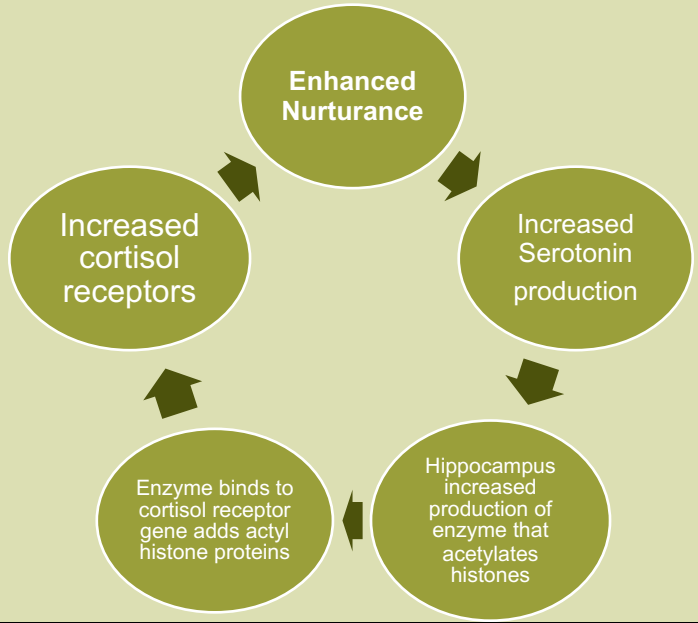
- *Supervised by M. Klein*
- *Safe haven*
- *Attachment figures*
- *Proximity seeking*
  – **infants seek proximity to the attachment figure for safety.**
  "Like a thermostat"



Epigenetics and Decreased Stress

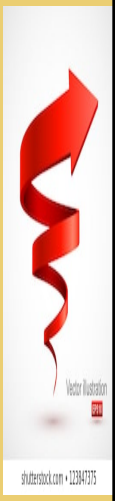
- Decreased methylation levels of cortisol receptor gene:
  - In offspring who had good nurturing produces more cortisol receptors on the hippocampus
    - Lower levels of CRH, ACTH, and cortisol
    - More 5-HT
    - Stress tolerance (Good thermostat)

Epigenetics of Stress Tolerance



Epigenetics and Increased Stress

- With methylation of the cortisol receptor gene, fewer cortisol receptors
  - it is difficult to turn off the stress response.
- Increased methylation levels of cortisol receptor gene:
  - In suicide victims with a family history of abuse and/or neglect
  - In preemies:



Epigenetics and Increased Stress

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

Loneliness and Epigenetics

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

Lisa M. Jaremka et al: 2012, 2013

Epigenetics: For Better or Worse

- Infants with a variant of the dopamine receptor gene (DRD4) have been linked to lower receptor efficiency and greater risk for disorganization and externalizing behaviors if exposed to maternal loss or trauma.
- Yet, when children with this supposed "vulnerability gene" were raised by mothers who had no unresolved loss they displayed significantly less disorganization. With nurturing mothers, they show the lowest levels of externalizing problem behavior.
- This variant of the DRD4 gene can afford the carrier to benefit disproportionally from supportive environments.

Epigenetics: For Better or Worse

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

Epigenetics: For Better or Worse

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

Variations of BDNF

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

Oxytocin Receptors (OXTR)

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

Glucocorticoid receptors (GR)

- GRs necessary for stress response regulation.
  - The FKBP5 gene associated with higher GR resistance and hence greater circulating cortisol levels –impaired negative feedback loop.
  - Traumatic stress -- leads to enhanced *FKBP5* gene expression and reduced GR sensitivity
  - FKBP5 may be a biomarker for PTSD—
    - Interactions between FKBP5 and early-life stress, could pose a significant risk factor for stress-associated disorders such as major depression and PTSD.
  - Maternal stress during pregnancy --methylation of FKBP5
    - A self-kindling cycle: parental trauma associated with subsequent trauma in their offspring (Yehuda, et al., 2001).

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

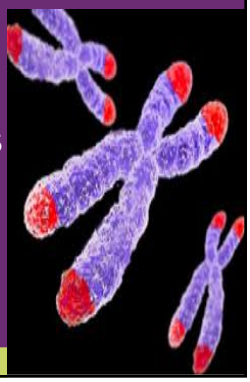
- 5-HTTLPR has been associated with later development of psychopathology (via ACEs),
  - MDD, suicide attempts, anxiety disorders, and ADHD.
- GAD responders showed an increase in 5-HTTLPR methylation, while nonresponders showed a significant decrease in methylation (Eley, et al., 2012)
- CBT with children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

MAO-A gene

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

Cell Aging: Telomeres Length

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



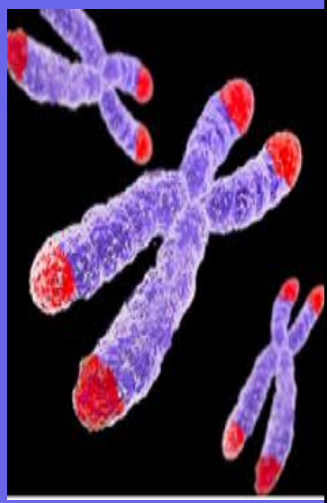
- Psychobiomarker": Linked to social status, perceived stress,
- depression, predictive of mortality (Epel, 2009, Current Directions)

Factors that Impair DNA and Cells

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

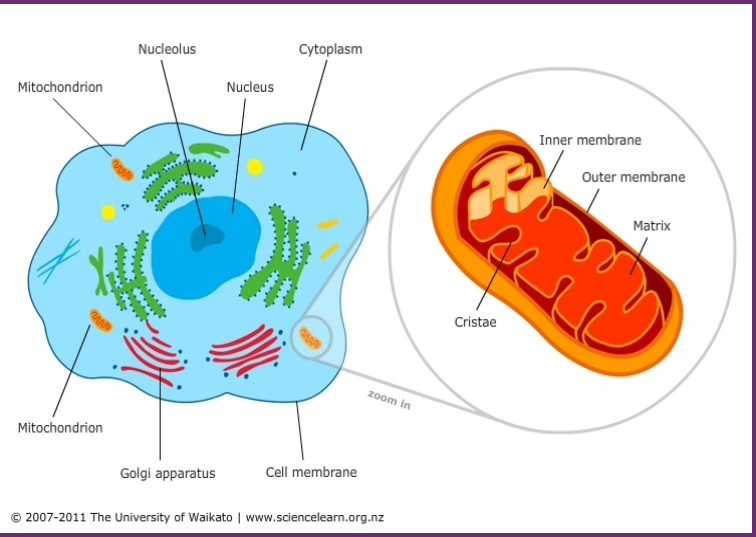
Factors that Shorten Telemeres

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



- **All rendering DNA vulnerable to damage**

Cells and Their Energy Factories

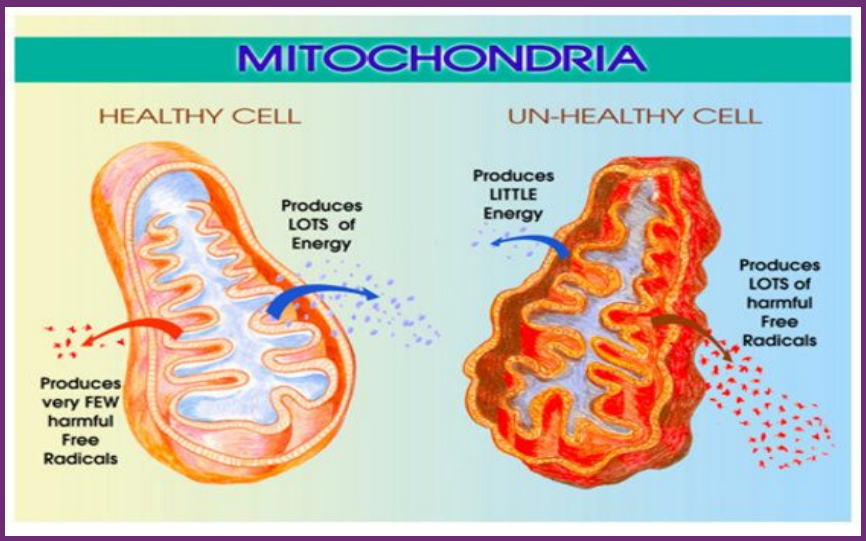


Free Radicals

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

Mitochondria Disfunction

Free Radical Damage



Mind-Brain-Gene Feedback Loops

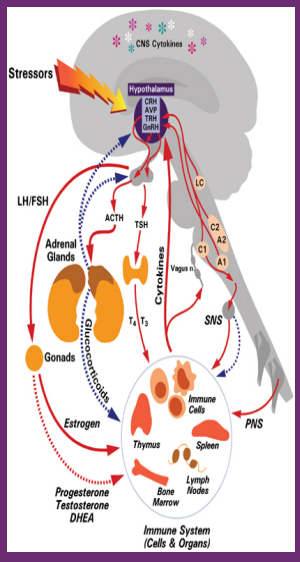
The Brain Controls the Stress Pathways

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

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

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

The hypothalamus also controls HPA stress response system



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

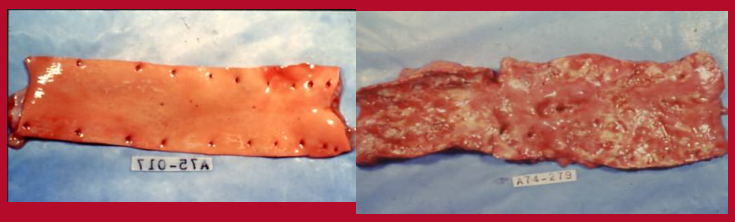
*effects also seen in bereavement, divorce, and other stressors

Hypocortisol vs. Hypercortisol Activity

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

Excessive Cortisol

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



The Immune System Can Affect Your Emotions:

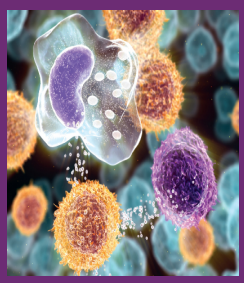
- **PICs contributes to depression as underlying inflammatory conditions**
- **Stressors may contribute to depression or exacerbate it via PICs**
- **Depression linked to medical conditions-- involves PICs**
- **Strong link between depression and vulnerability to medical diseases (CVD, autoimmune)**

Inflammatory pathways in the brain adversely affect memory and mood.

- PICs cause cognitive deficits that disturb synaptic strength.
  - High concentrations of receptors for PICs in the PFC and hippocampus, potentiating cognitive impairments,-- i.e. working memory, episodic memory, and executive functions
  - IL- 1 in the hippocampus impairs memory by interfering with BDNF, which is involved in neural plasticity, neurogenesis, memory, energy balance, and mood.

Communication in the immune system happens via chemicals

- *Cytokines:* Proteins released by immune cells that act on target cells to regulate immunity, and signal the brain
- *Proinflammatory cytokines:* coordinate inflammatory responses in the body; in response to microbes; mediates acute inflammation (e.g. IL-1, TNFa, IL-6)
- *Anti-inflammatory cytokines*: controls the pro-inflammatory response (e.g. IL-10)
- *Chemokines*: recruit cells to affected tissues
- *Prostaglandins:* recruit immune cells, and *signal the brain*

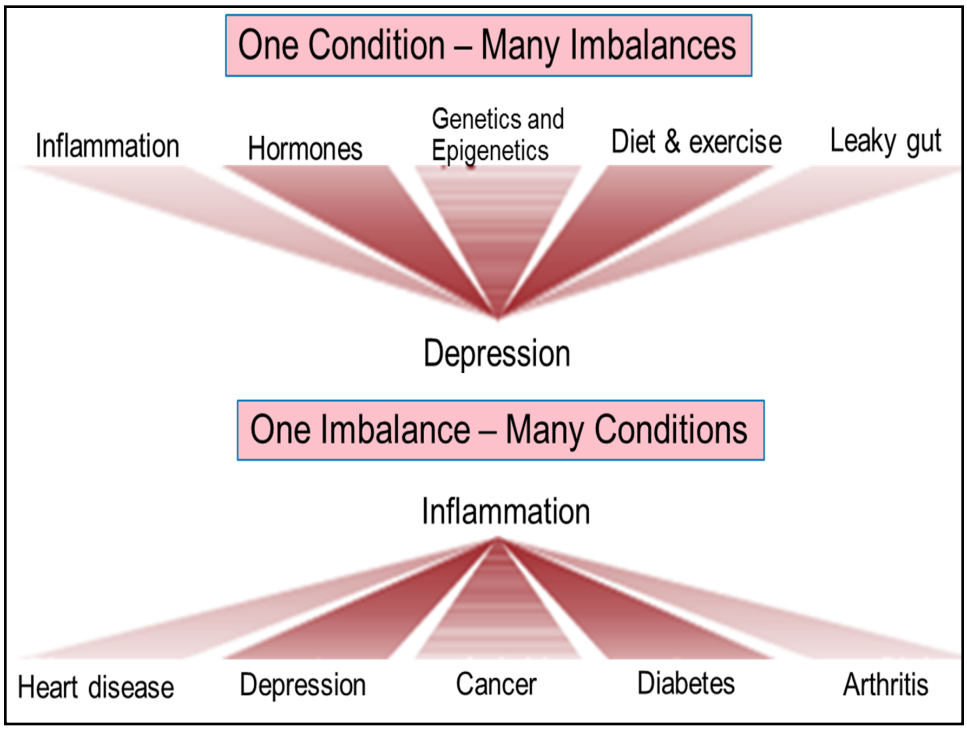


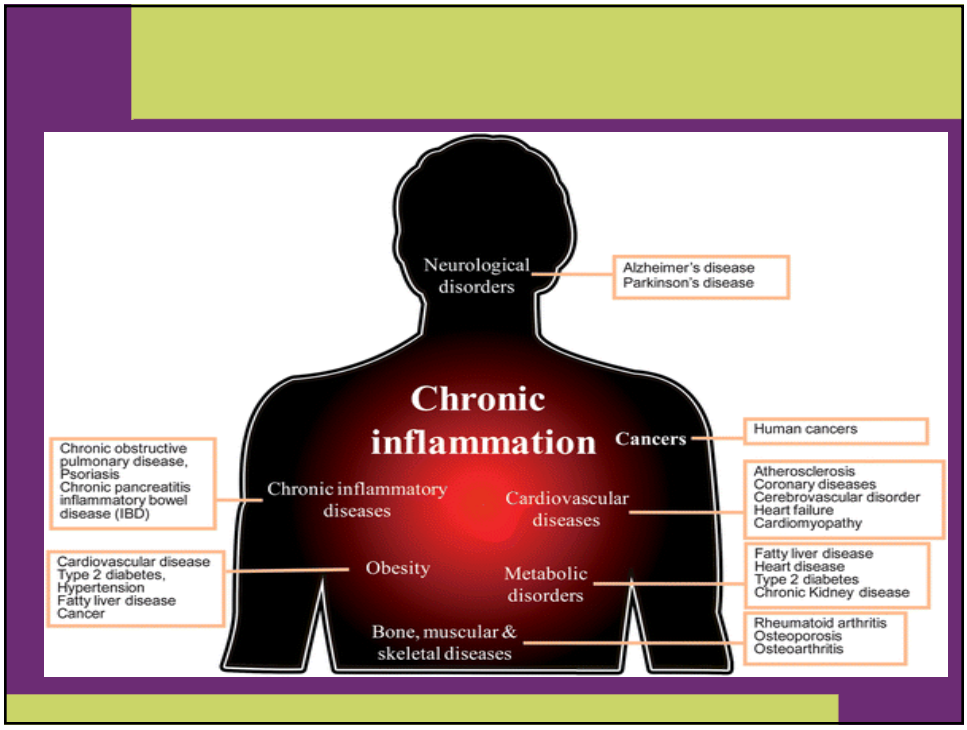
Stress

Activation of corticotropin releasing hormone (CRH):

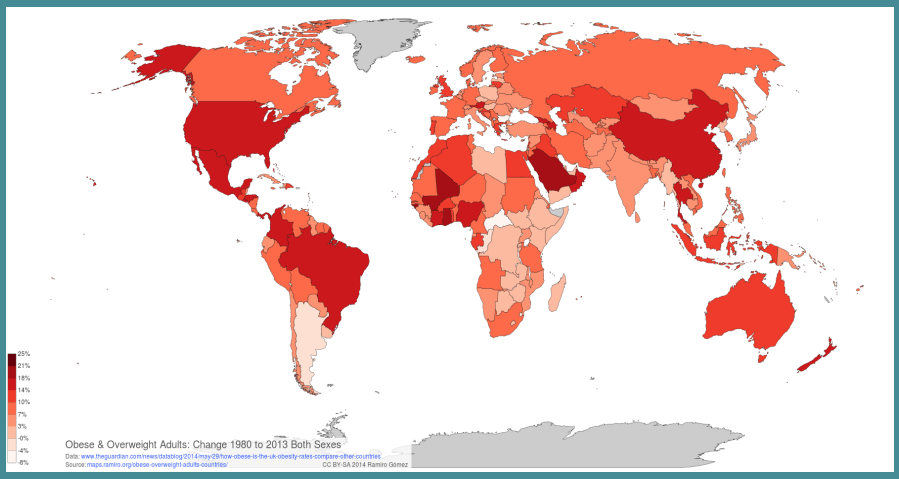
- Contributes to delayed gastric emptying
- Increased colonic activity
- Functional bowel disease (IBS)
- Increase in gut permeability
- Leaky gut – antigens leaking out
- Toxic liver overload
- Systemic disease

Inflammation in the Mainstream


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

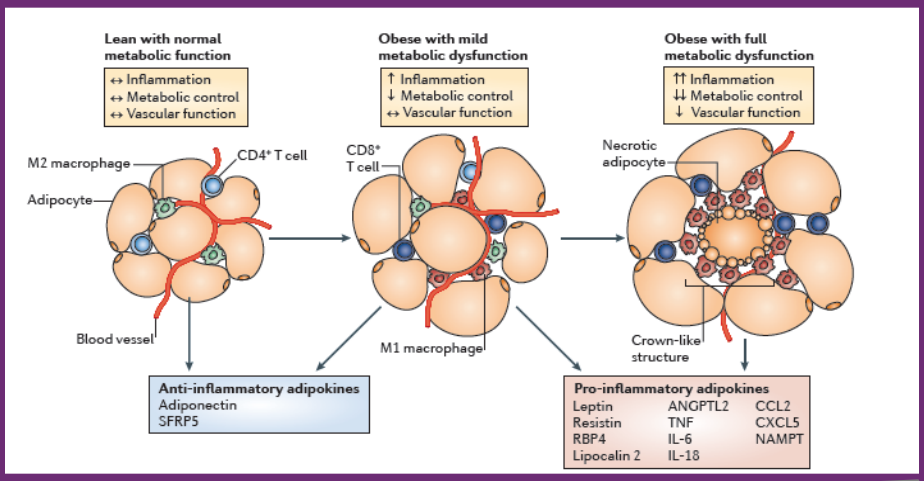

Neurological disorders
Alzheimer's disease
Parkinson's disease
Chronic inflammation
Cancers
Human cancers
Chronic obstructive pulmonary disease, Psoriasis
Chronic pancreatitis
inflammatory bowel disease (IBD)
Chronic inflammatory diseases
Cardiovascular diseases
Atherosclerosis
Coronary diseases
Cerebrovascular 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

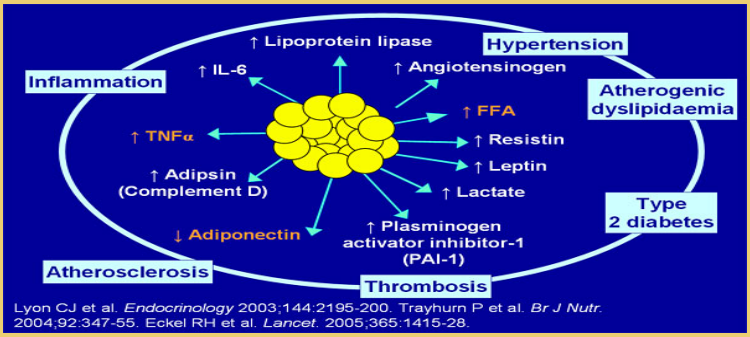


INFLAMMATION

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.

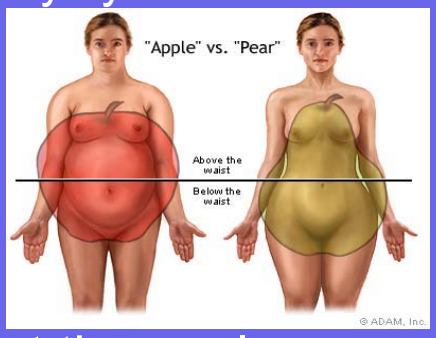
Belly fat

Belly fat generates inflammation by releasing proinflammatory cytokines

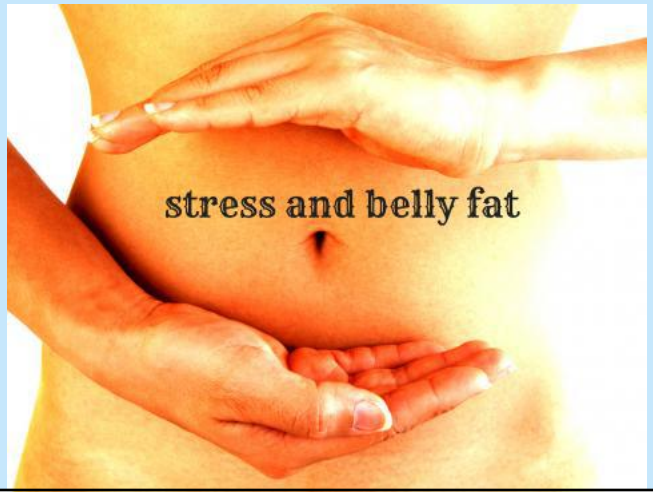
- Lowers BDNF
- ↑ risk of dementia
- If you're going

  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

Diabetes and Psychological Disorders

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

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

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**

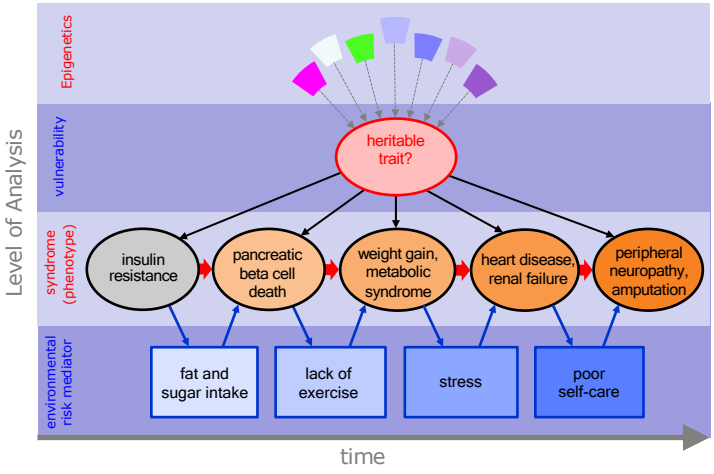
Diabetes, Superoxide, and DNA Damage

- As insulin fails there is more glucose flooding cells.
  - The mitochondria uses glucose as its raw fuel with oxygen and works overtime –eventually begins breaking down
  - Energy leaks—like cracks in a dam
  - Electrons get rerouted into a side channel and combines with free-floating oxygen molecules
    - One oxygen + electron = **superoxide**
      - Potential DNA damage
      - Harmful gene expressions
      - Speeded up DNA and cellular degeneration

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**

Ontogenesis of Type II Diabetes



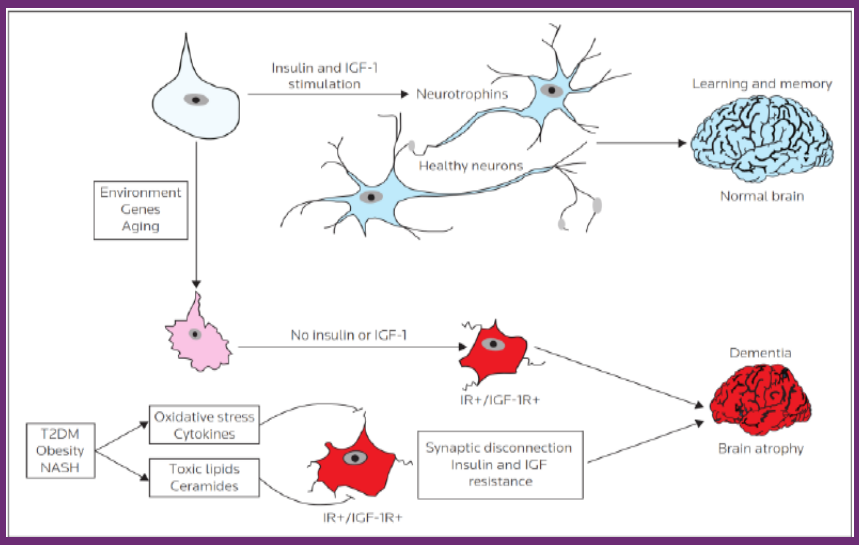
LaSalle et al., 2005

111

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



Diabesity

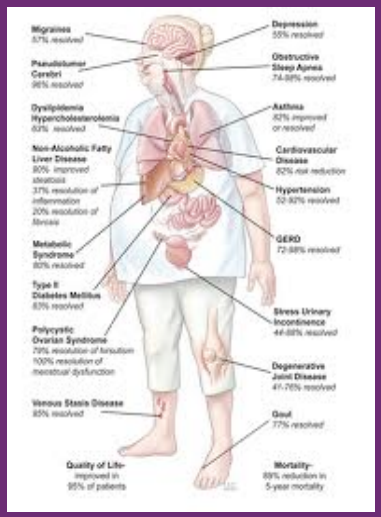
- Increased leptin and insulin resistance
- Increased blood pressure
- Increased cardiovascular disease
- Increased depression
- Chronic inflammation
- Neurocognitive impairment

Diabesity

Rank	Countries	Amount ▼
# 1	United States:	2,989 deaths
# 2	Mexico:	807 deaths
# 3	Brazil:	729 deaths
# 4	Germany:	654 deaths
# 5	Spain:	316 deaths
# 6	Austria:	219 deaths
# 7	Canada:	187 deaths
# 8	Australia:	115 deaths
# 9	South Africa:	114 deaths
# 10	Denmark:	104 deaths

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

What drives inflammation in cardio-metabolic syndrome?

- Obesity- fat releases pro-inflammatory immune cells
- Gut barrier dysfunction
- Dysbiosis
- Inflammatory diet (high intake of saturated fats, refined sugar, processed foods, additives, lack of anti-oxidants)
- Advanced Glycation End Products
- Pro-inflammatory cytokines

Depression Has a Relationship to Inflammation

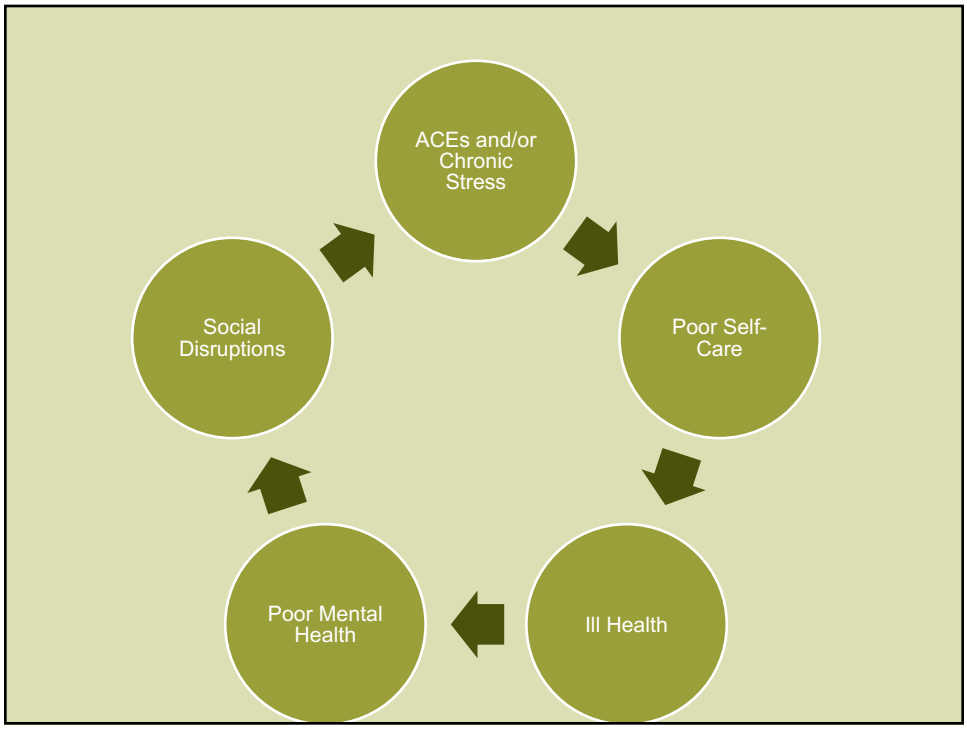
- Depressed patients -- increased levels of *proinflammatory cytokines* (PIC)—strong finding
- -Chronic inflammatory diseases are often associated with depressive symptoms
- --Depression is associated with inflammation in the brain
- So- does depression *cause* the increase in these cytokines or do these cytokines *cause* depression?
- Both: It is a nasty positive-feedback loop!

➢PICs cause a depression-like Sickness Behavior

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

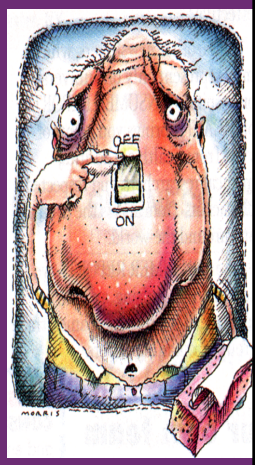
Client Education

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



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”

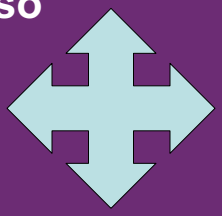


Depression and fatigue in illness

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

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

Immune Dysregulation and Hopelessness

- Ability to meet challenges is key- stress from not meeting them dysregulates immune system, increases inflammation and impairs brain function
- Acute or chronic: stress can impair immune responses
- Controllable vs. uncontrollable
- Social stress and loneliness

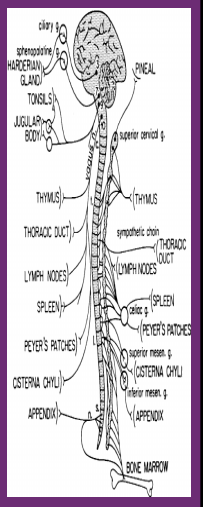
Inflammation and Dementia

- Dementia exacerbated by chronic inflammation.
- Obesity and diabetes as risk factors
- Small strokes may be caused by inflammation.
- Inflammation plays a role in deterioration of brain cells, formation of plaques.
  - Some of the protein in plaques are products of inflammation.
- Inflammatory mediators can cross into the brain and influence learning and memory.

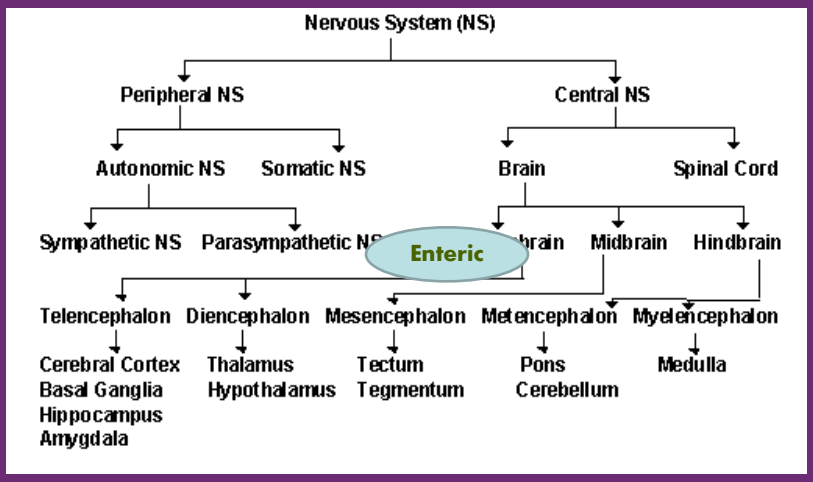
– Stress may influence the onset and course of dementia via these inflammatory pathways

Peripheral nerves are also involved in inflammation

- Bidirectional: nerves sense inflammation, contributing to it
- There are both pro-inflammatory and anti-inflammatory effects
- C-fibers modulate pain and inflammation
- Parasympathetic nerves reduce inflammation (especially vagus)

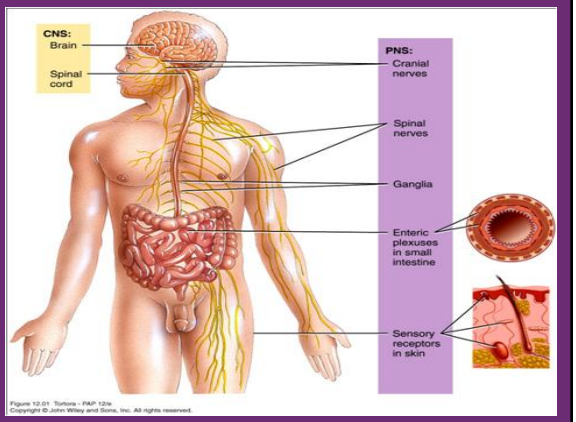


The Gut Brain



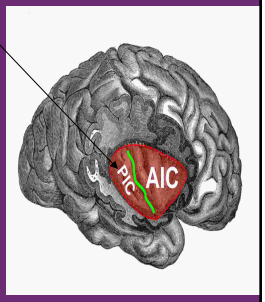
Enteric Nervous System

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

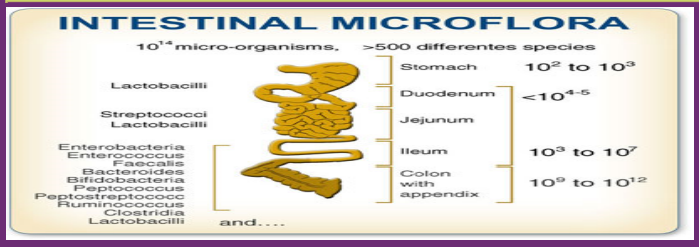


Language of Gut

- 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



Microbiome



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

Our microbes are like an organ

- Control each other's behavior
- Collaborate with our immune system in host defense
- Program phenotypes/activity states of immune cells
- Diet influence our microbial populations
- Link of inflammation and disease
- Influence brain development
- Influence our behavior

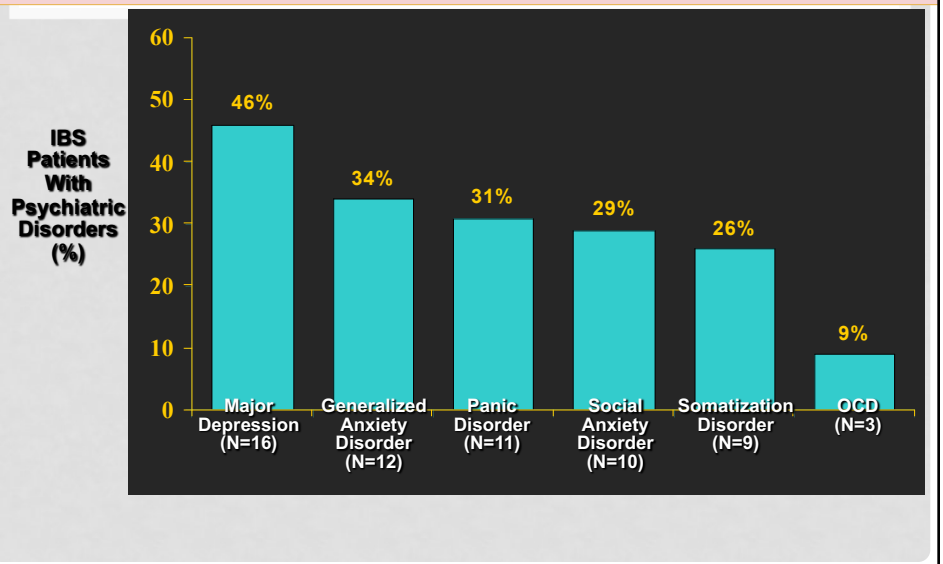
Gut bacteria

- 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

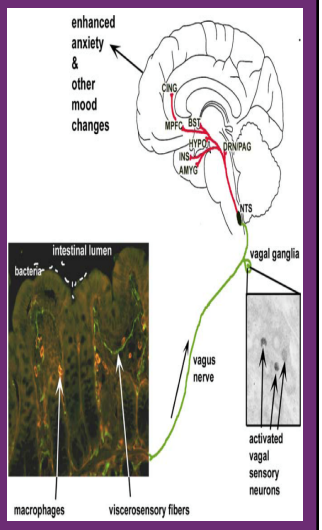


Stress/Depression and the Gut Microbiome

- Stress can induce increased permeability of the gut allowing bacteria to cross the epithelial barrier and activate a mucosal immune response, which alters the microbiome and leads to enhanced HPA activity.
- In irritable bowel syndrome (IBS; cramping, abdominal pain, bloating etc) and depression there can be an alteration of the HPA axis induced by increased gut permeability

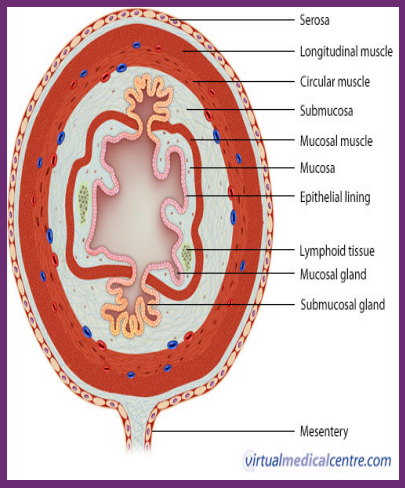
Inflammation, microbes and anxiety

- Anxiety is common in illness, and inflammatory signals from the body contribute, e.g. TNF, vagal activation
- A signal that something is not right
- Destructive role of dysbiosis (imbalance in microbes)



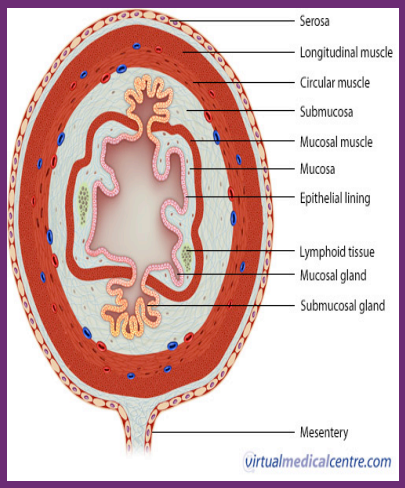
"Leaky gut": the consequences of stress and inflammation and link between diet and health

- AKA "increased intestinal permeability"
- Is associated with many disorders (diabetes, metabolic syndrome allergies, neurological etc.)
- Allows more absorption of toxins and lets fluid out e.g. during inflammation and infection (diarrhea)
- Many factor regulate this: immune cells and molecules, microbes, stress



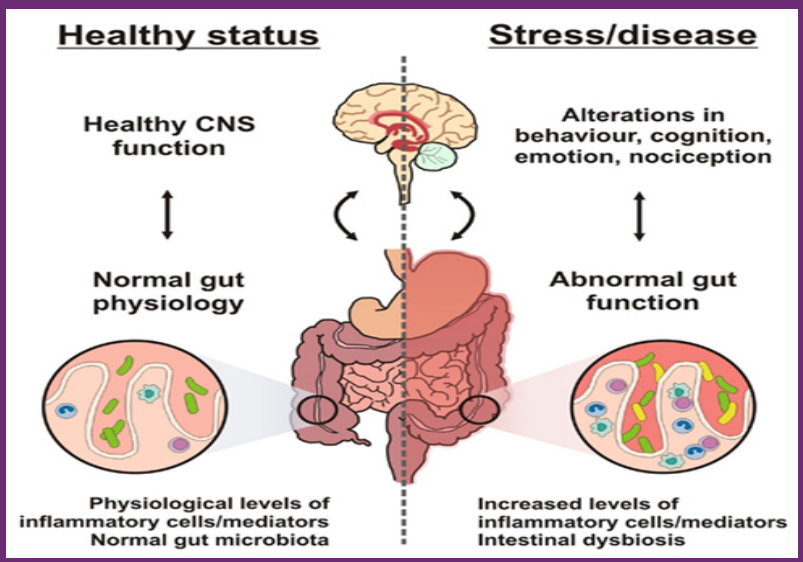
"Leaky gut": the consequences of stress and inflammation and link between diet and health

- 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,

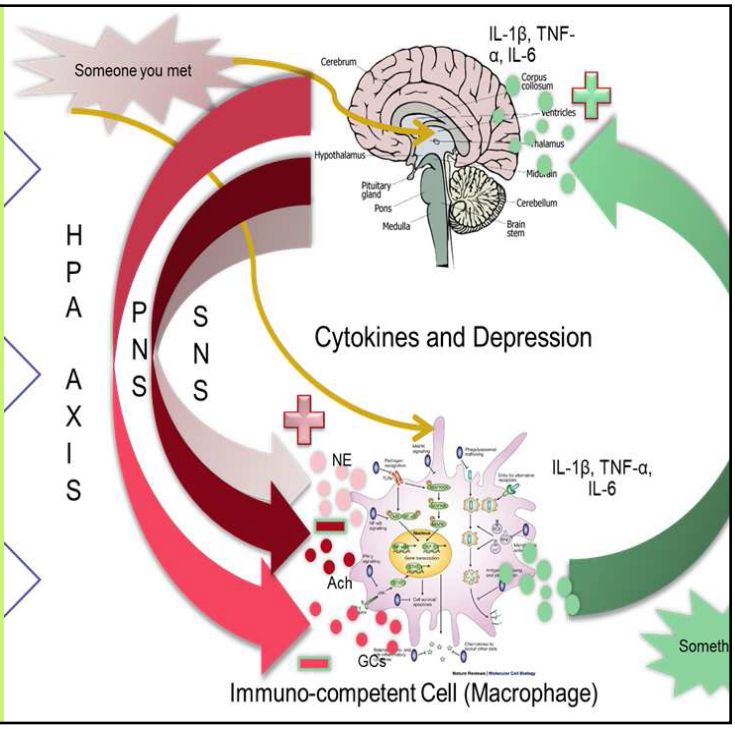


Dysbiosis and Microbial Diversity: the Importance of Balance

- 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



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

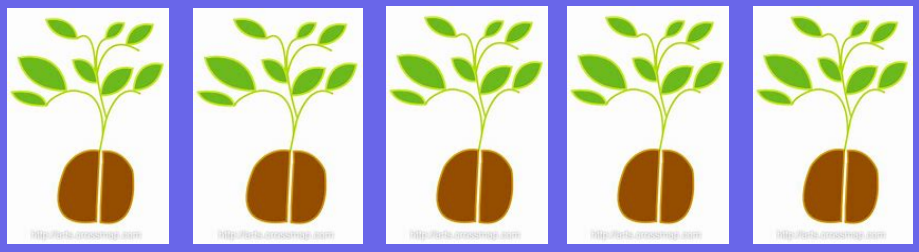


Mind-Brain-Gene Feedback Loops

Self-Regulation Factors

- Social
- Exercise
- Education
- Diet
- Sleep

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…

The Five Risiliency Factors

- Social
- Exercise
- Education
- Diet
- Sleep

SEEDS

Movement is an Evolutionary Imperative

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

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

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

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

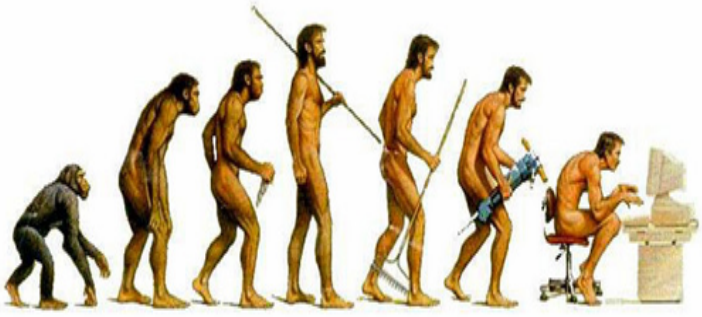
Resistance Training: Lifting, Throwing, and Carrying Objects

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

Interval Training: Periodic bursts of high-intensity activity

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

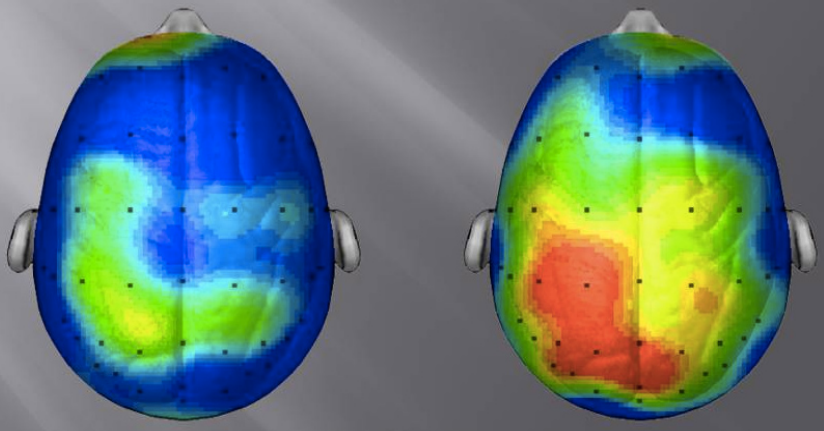
De-evolution



Exercise to Clear the Mind

BRAIN AFTER SITTING QUIETLY

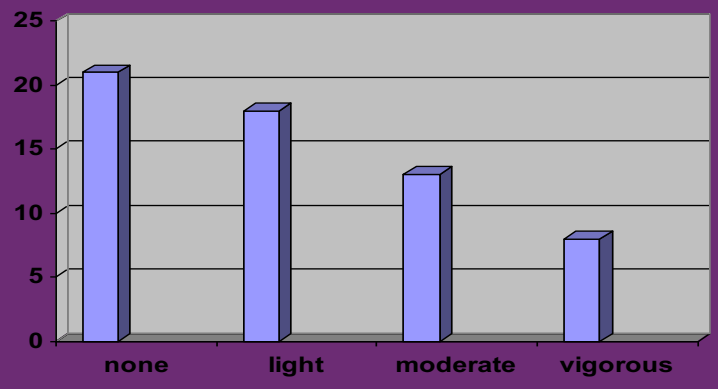
BRAIN AFTER 20 MINUTE WALK



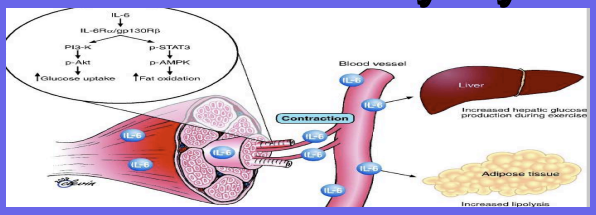
Research/scan compliments of Dr. Chuck Hillman University of Illinois

Effect on C-Reactive Protein

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



Myokines:
Anti-inflammatory Cytokines



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

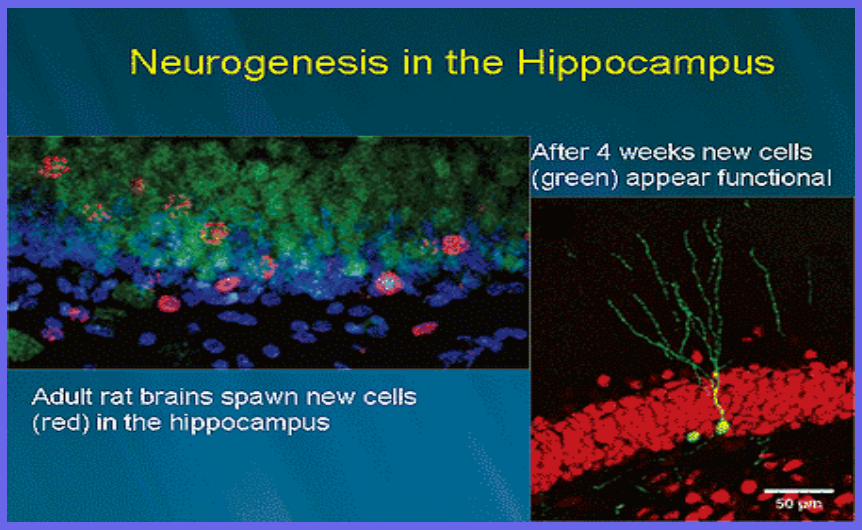
Exercise-induced myokines are involved in mediating anti-inflammatory effects

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

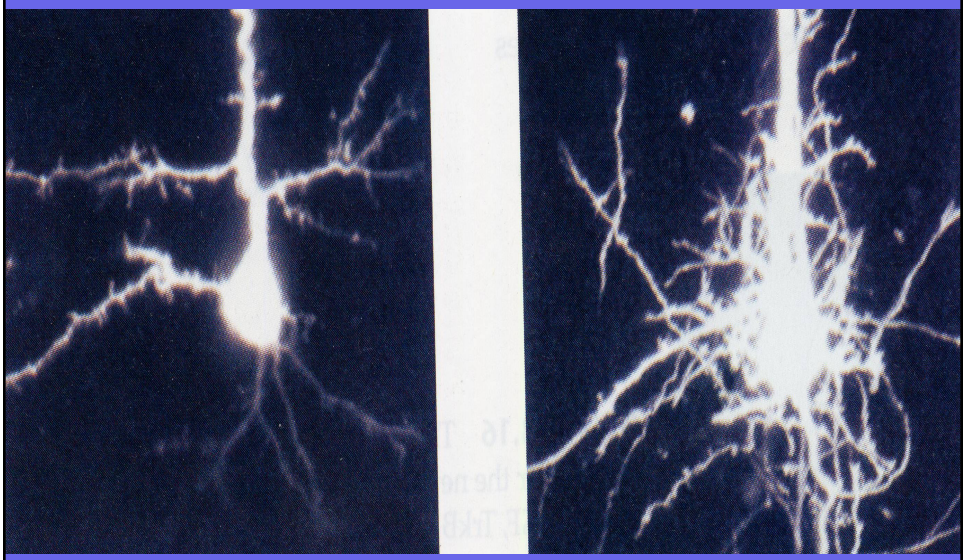
Brain Derived Neurotropic Factor

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

Neurogenesis



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

Exercise and the Brain

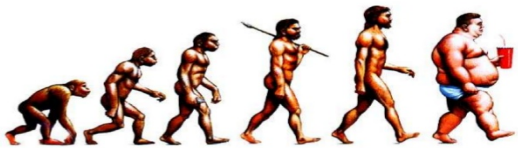
Mechanism	Impact
Gene Expression	Neuroplasticity (Cottman & Blanchard, 2002)
Brain Derived Neurotrophic Factor (BDNF)	Neurogenesis & Neuroplasticity (Adlard, et al, 2005)
Insulin-like Growth Factor (IGF-1)	Energy Utilization (Carro. et al 200)
Nerve Growth Factor	Enhanced Neuroplasticity (Neeper, et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

Self-Regulation Factors

- Social
- Exercise
- Education
- Diet
- Sleep

Perils of the Western Diet

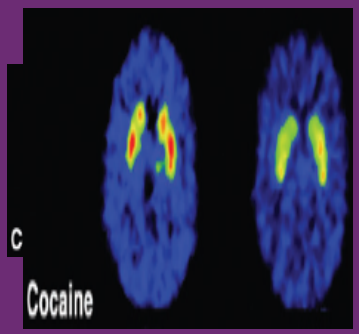
- Fructose blunts the effects of leptin which normally tells us we are "full"
  - Fructose produces uric acid
  - Increased cardiovascular disease
- Increasing risk of metabolic syndrome
- **Shrinks the left hippocampus**
- Increased blood pressure
- LDL cholesterol
- Increased stroke
- Type 2 Diabetes

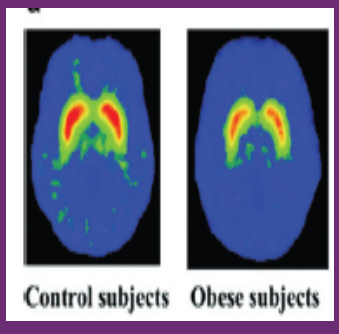


Dopamine D2 Receptors in Drug Users And Comfort Food Addiction

- Drug Addiction
- Obese

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





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

The higher the GL of a food:

the greater the adverse insulin effects

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

- Obesity
- Diabetes
- Inflammation
- Depression

Glycation (excess glucose)

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

Advanced glycation end products (AGEs)

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

trans-fatty acids can:

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

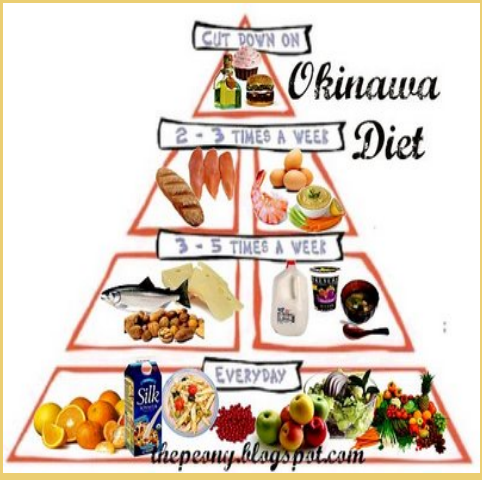
trans-fatty acids

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

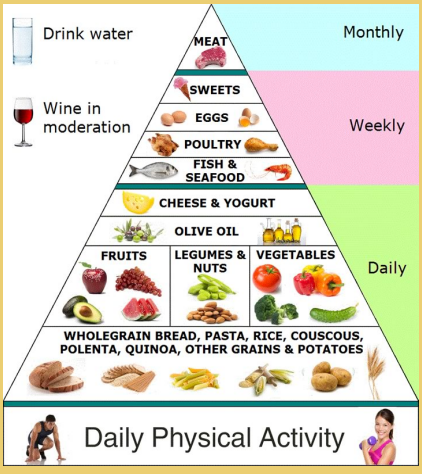
    i.e. pro-inflammatory cytokines

Diets styles for longevity:

Okinawan



Mediterranean



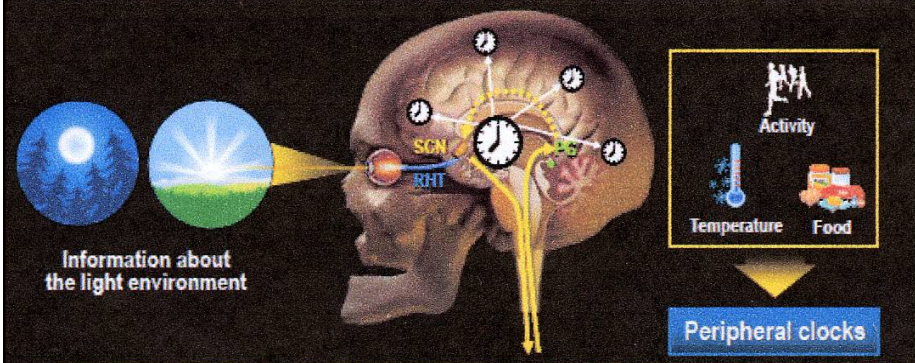
The Five Risiliency Factors

- Social
- Exercise
- Education
- Diet
- Sleep

SEEDS

Synchronizing Circadian Rhythms

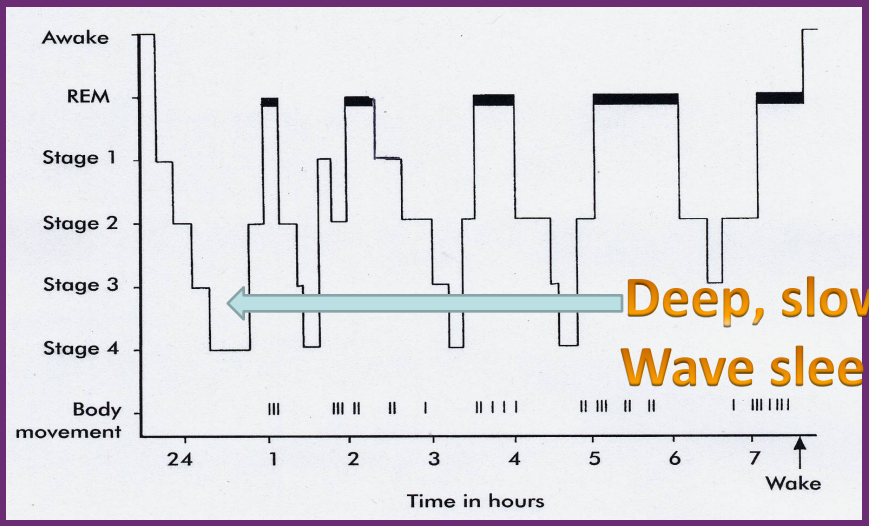
Entrainment of the SCN and Peripheral Clocks

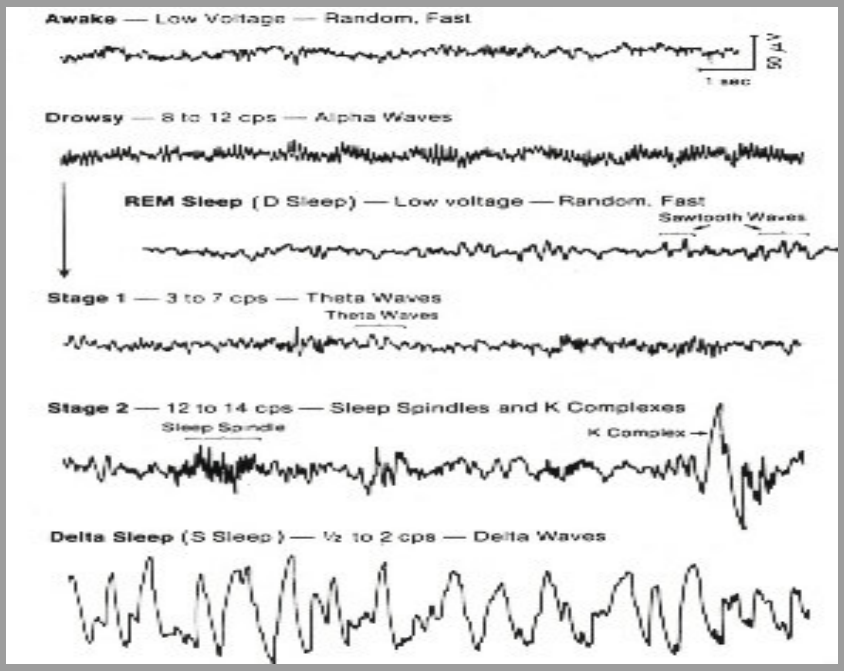


GI, gastrointestinal; PG, pineal gland; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; WBC, white blood cell.

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

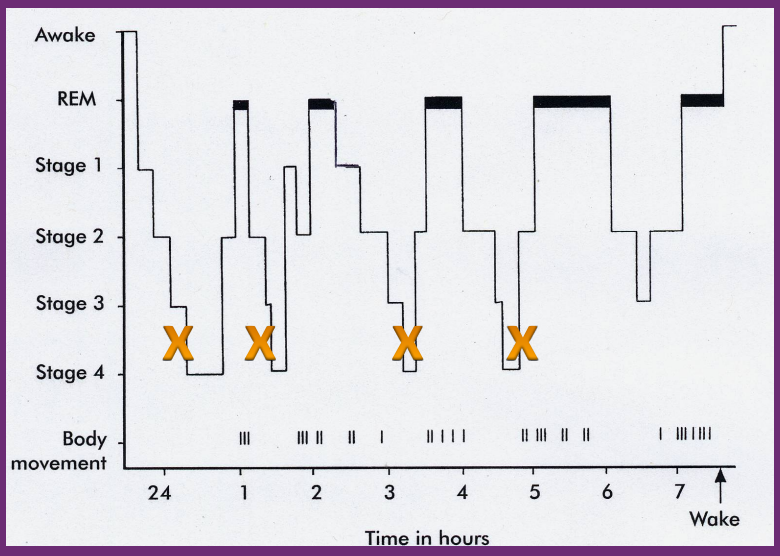
Normal Sleep Architecture





Pathologic Changes in Slow wave sleep

dep, anx, pain, apne, substance abuse



Slow wave sleep deprivation

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

Increase in negative memories

–Increase in depression

Sleep deprivation

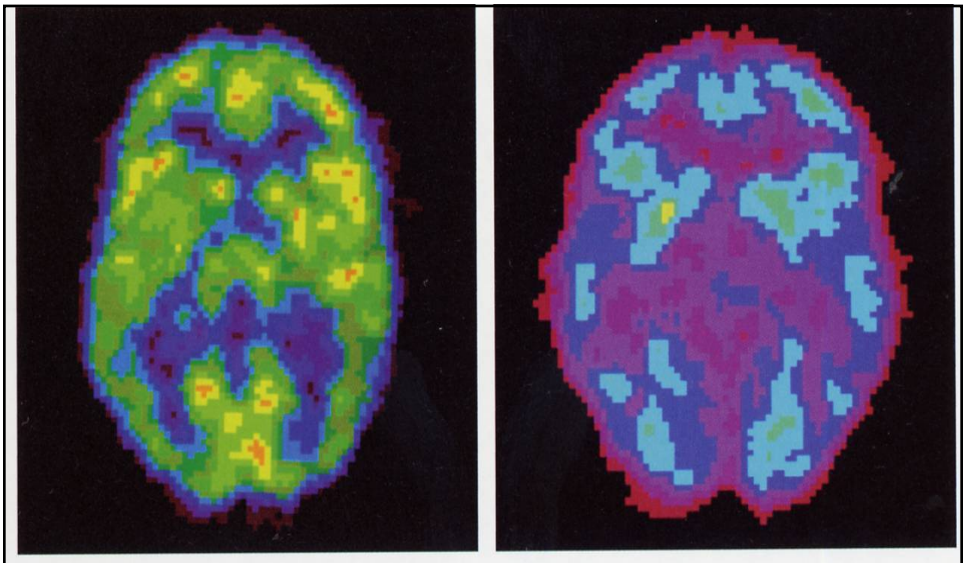
- ↓ ability to clear glucose
- ↓ in leptin (which normally would inhibit hunger)
- ↑ in ghrelin (increasing hunger)
- ↑ in weight
- ↑ vulnerability to type 2 diabetes

Memory and Sleep

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

Brain Clearing

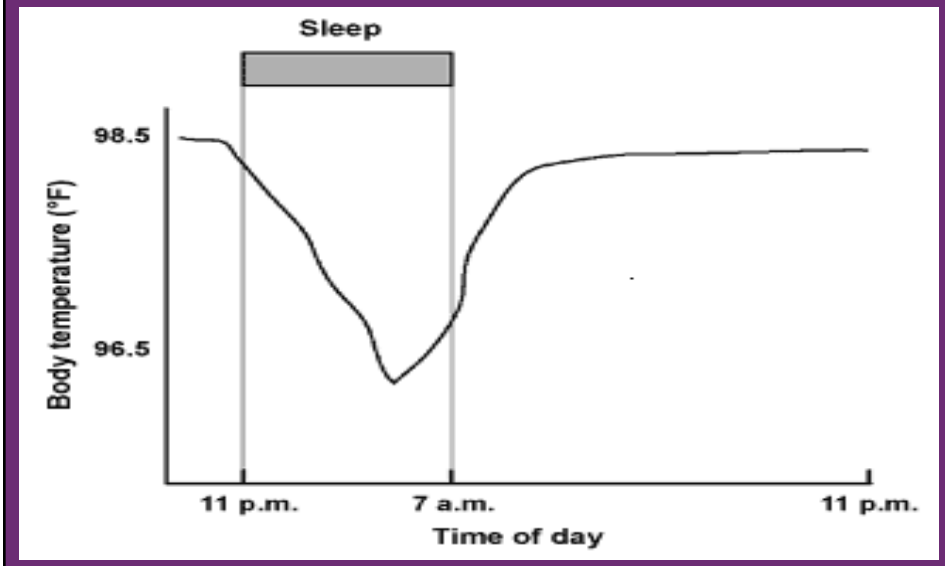
- "Glymphatic" system, a nod to both glial cells and its functional similarity to the lymphatic system
  - –Sleep as a dishwasher for your brain
- Sleep clears B-amyloid in the brain via increased CSF flow in interstitial space



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

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

Body Temp and Sleep



Poor Sleep Linked to Alzheimer's

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

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

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

Sleep Hygiene

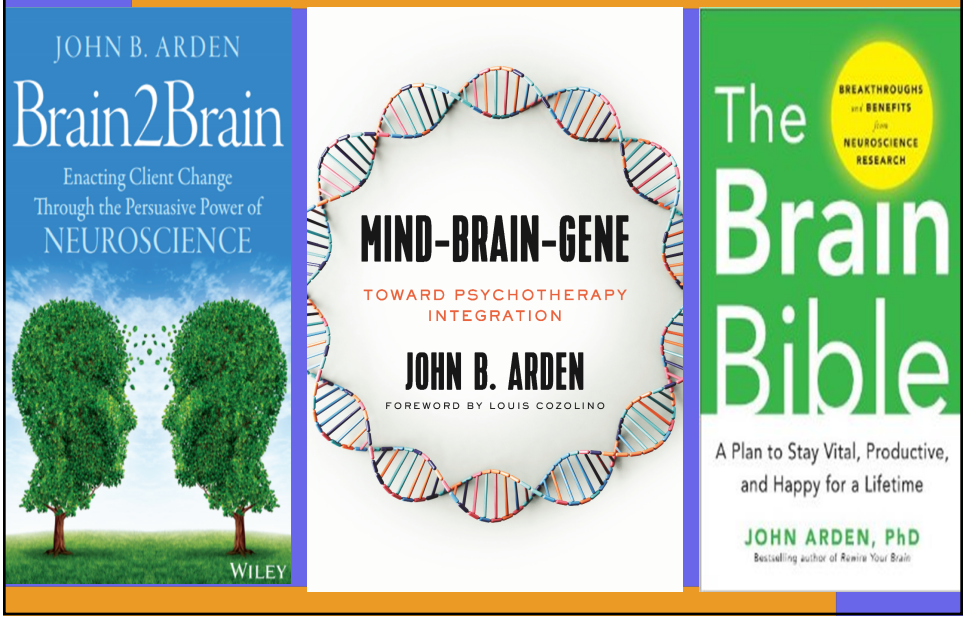
- **Don't do anything in your bed other than sleep (except for sex).**
  - **Do not watch television, balance your checkbook, discuss finances with your spouse, or argue in bed. Make your bed carry only one association—*sleep*.**
- **If you can't sleep and find yourself tossing and turning, get up and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

SEEDS Epigenetics

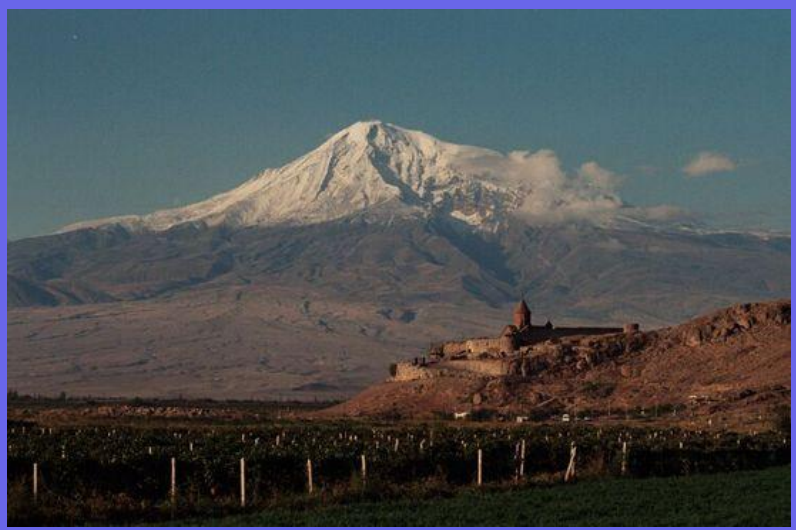
- Fruits, vegetables, --polyphenols found to epigenetically reduce stress and depression by modulating inflammatory responses and synaptic plasticity in the brains of those with depression.
- Epigenetic changes increase inflammation across tissues in response to sleep loss. --that the adipose tissue is attempting to increase its capacity to store fat following sleep loss
- Physical inactivity deactivates genes associated with inflammation and activates genes associated with lower inflammation
  - Muscle movement activates anti-inflammatory genes

Mind-Brain-Gene Loops

References



drjohnarden@gmail.com



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