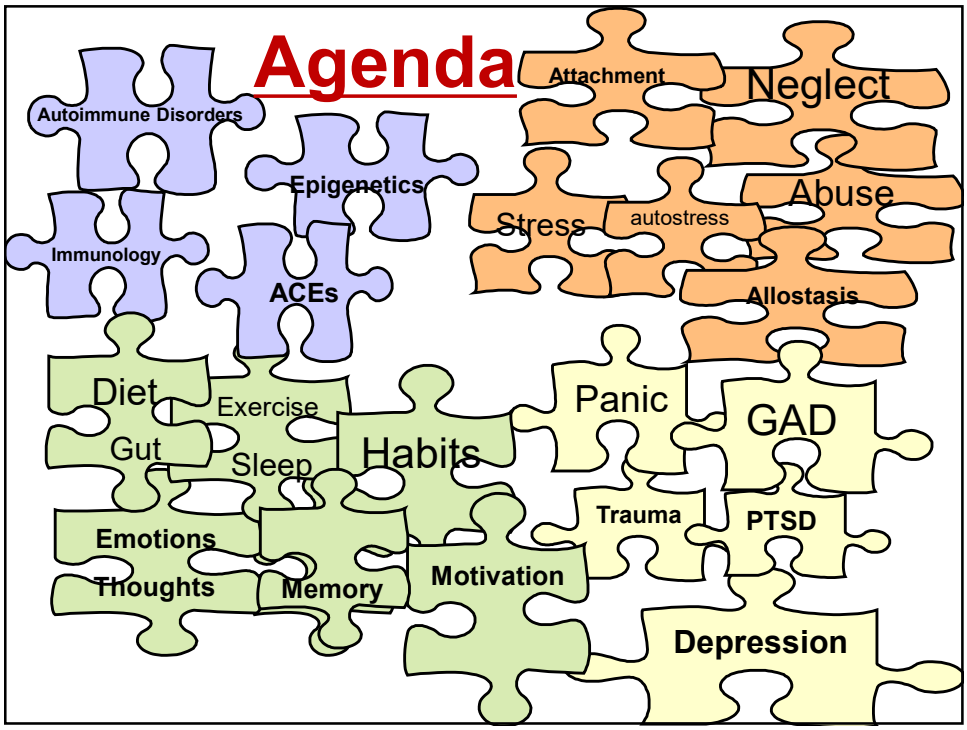
Mind-Brain-Gene:

The Integration of Psychotherapy

John B. Arden, PhD, ABPP

1

Agenda



2

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

3

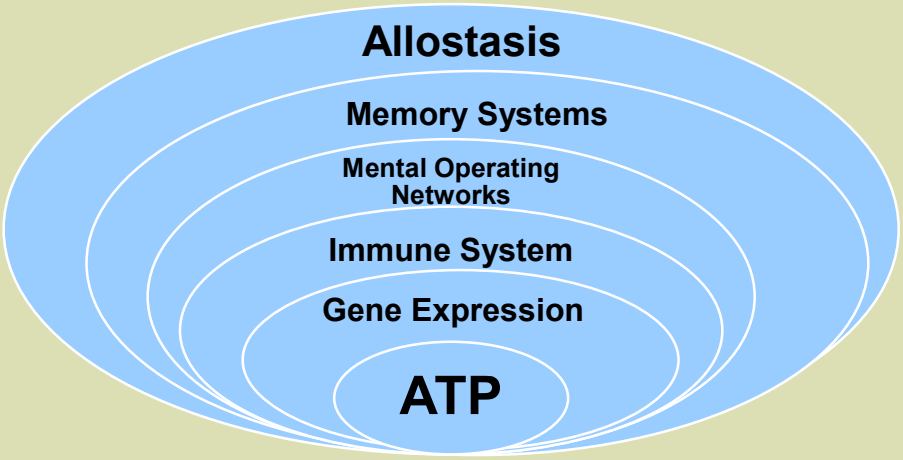
The Science has Changed

"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

4

"Self"-Organization



5

The ACE Study

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

6

ACEs score percentages

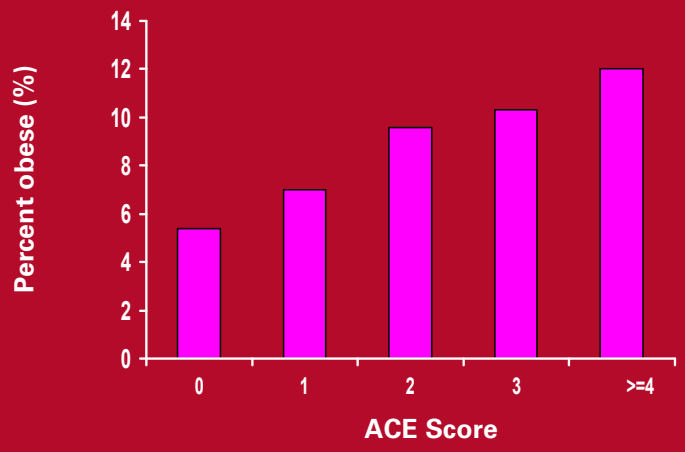
Number of categories of childhood experiences are summed

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

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

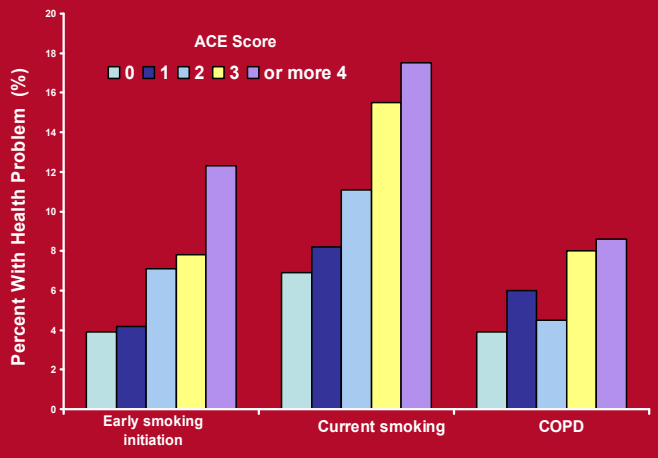
7

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



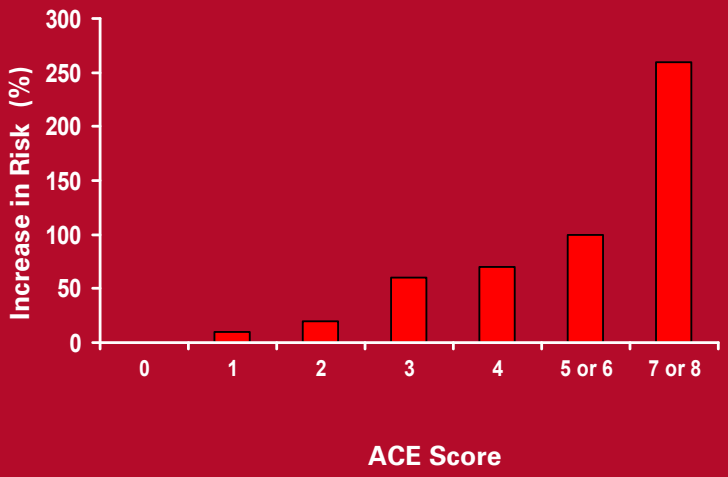
8

ACE's Smoking and Lung Disease

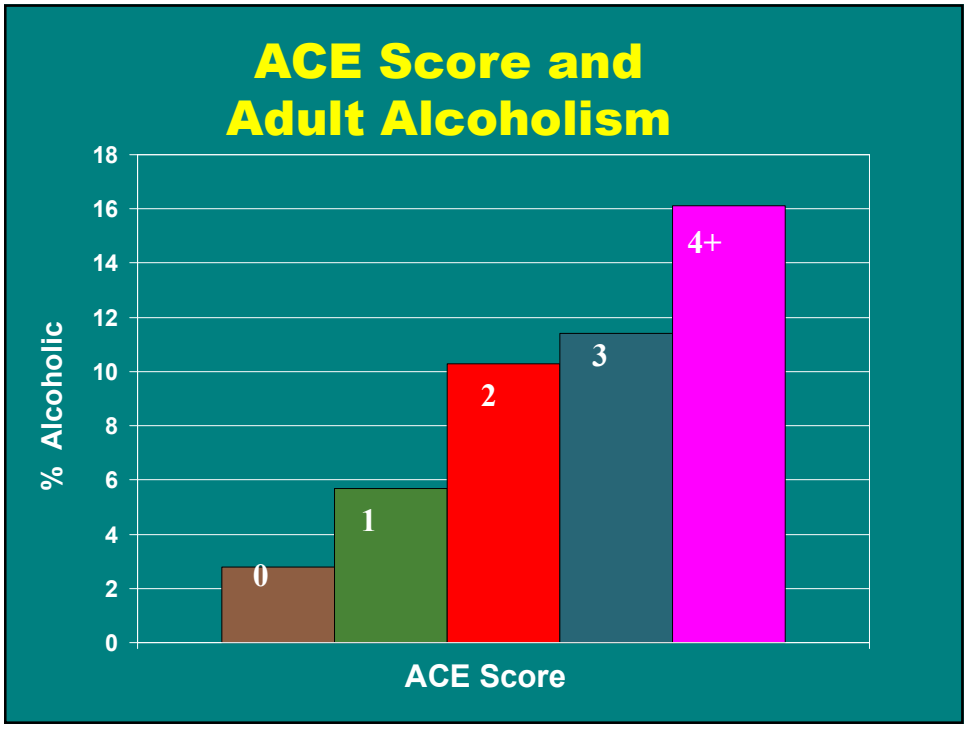


9

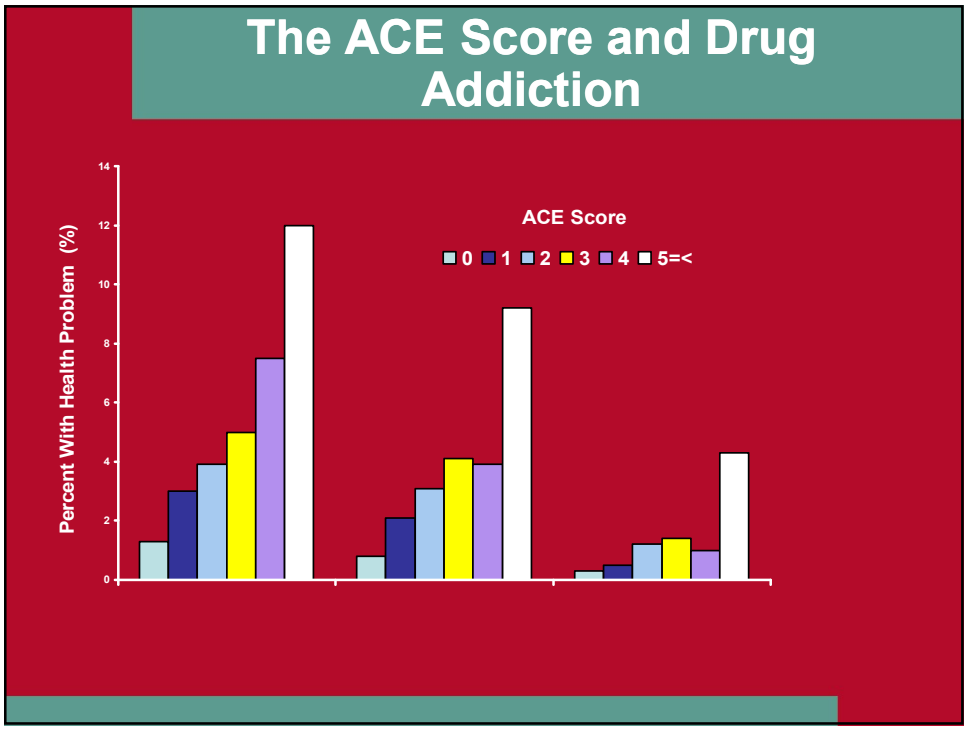
The ACE Score and the Risk of Coronary Heart Disease



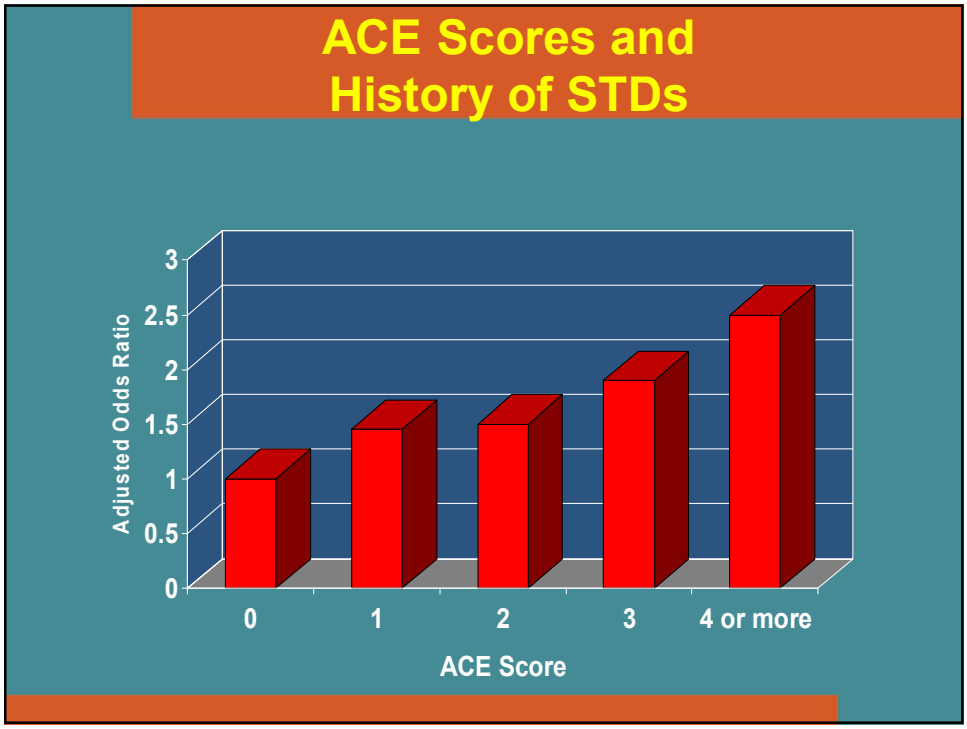
10


ACE Score and
Adult Alcoholism
% Alcoholic
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4+
ACE Score

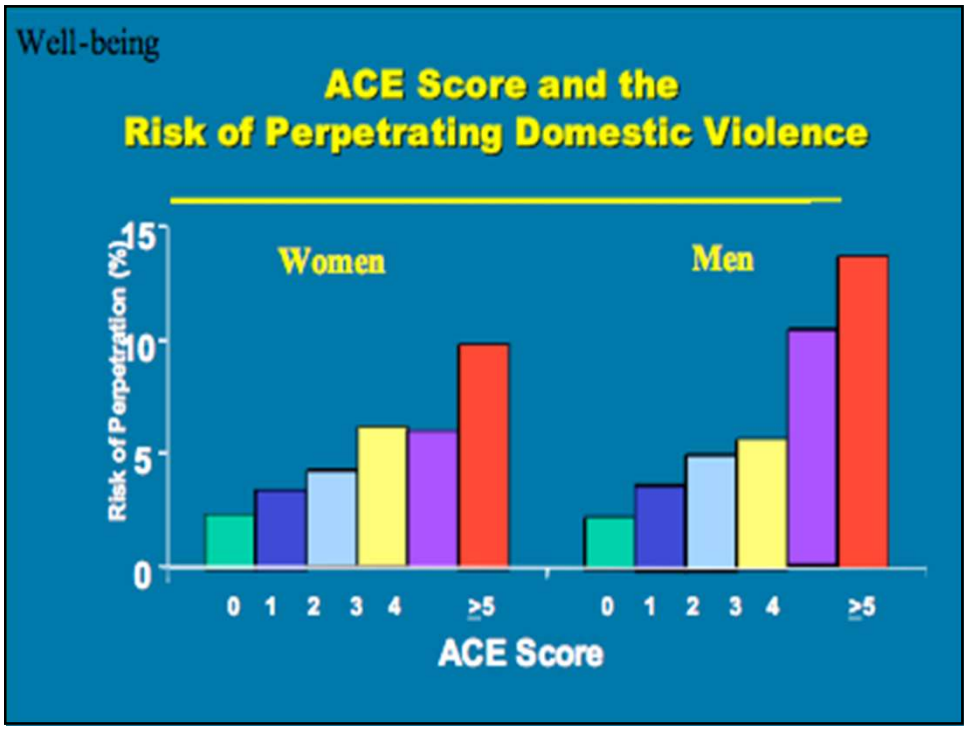
11


The ACE Score and Drug Addiction
Percent With Health Problem (%)
14
12
10
8
6
4
2
0
ACE Score
0 1 2 3 4 5=<

12


ACE Scores and History of STDs
Adjusted Odds Ratio
3
2.5
2
1.5
1
0.5
0
0
1
2
3
4 or more
ACE Score

13


Well-being
ACE Score and the Risk of Perpetrating Domestic Violence
Women
Men
Risk of Perpetration (%)
15
10
5
0
0 1 2 3 4 ≥5
0 1 2 3 4 ≥5
ACE Score

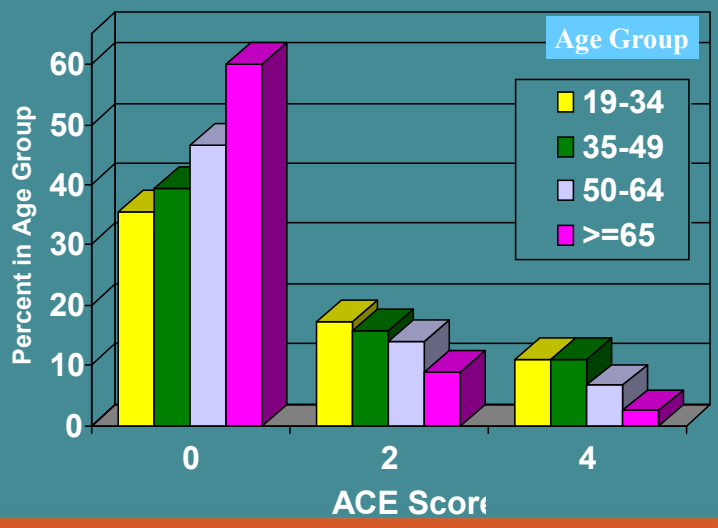
14

A Connection with Homelessness

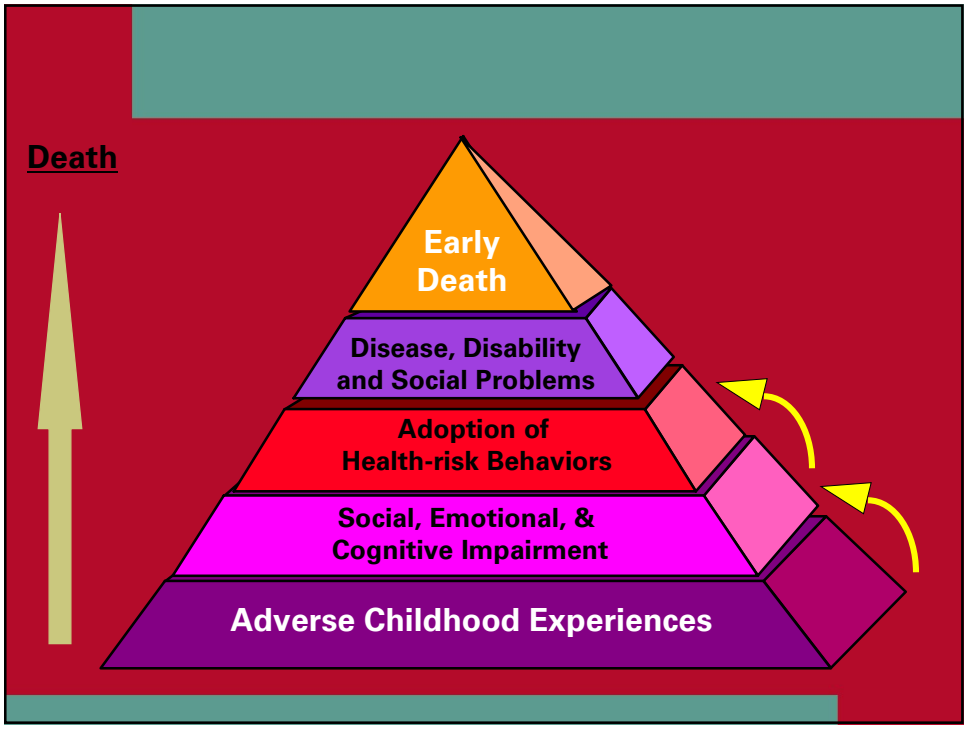
- Psychological disorders and substance abuse are more common among homeless people
- ACEs connection to substance abuse and psychological disorders
- Over 50% of homeless with ACE Score of 4 or higher

15

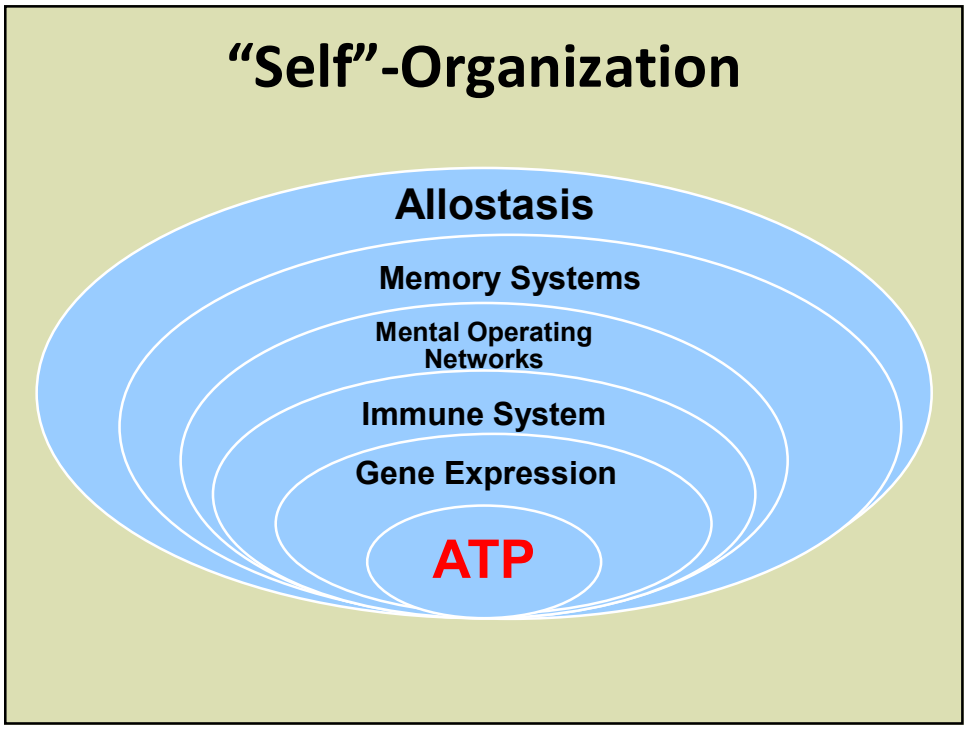
Effect of ACEs on Death Rate



16

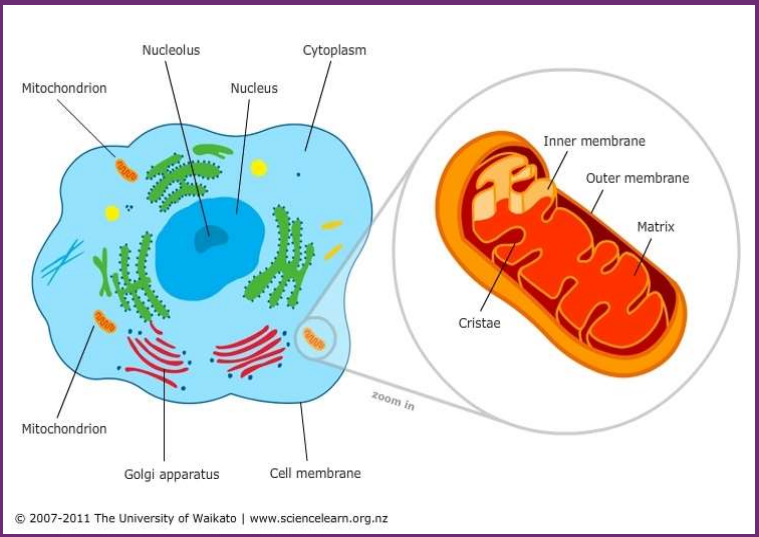

Death
Early Death
Disease, Disability and Social Problems
Adoption of Health-risk Behaviors
Social, Emotional, & Cognitive Impairment
Adverse Childhood Experiences

17


"Self"-Organization
Allostasis
Memory Systems
Mental Operating Networks
Immune System
Gene Expression
ATP

18

Cells and Their Energy Factories



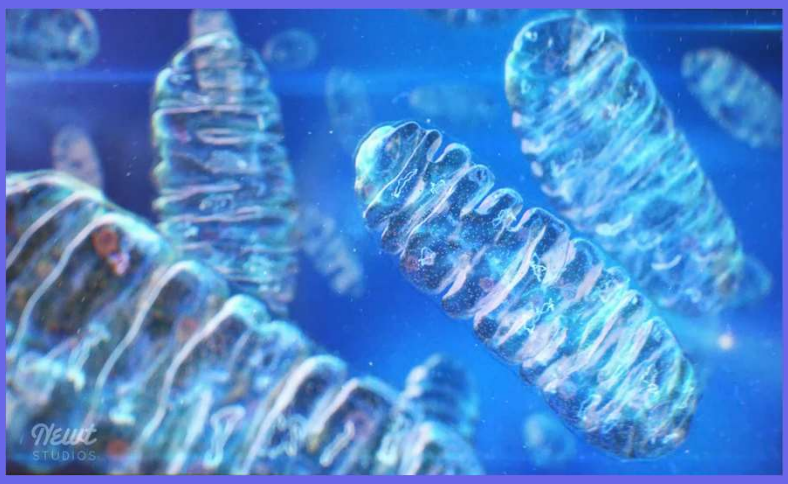
19

Mitochondrial Demands

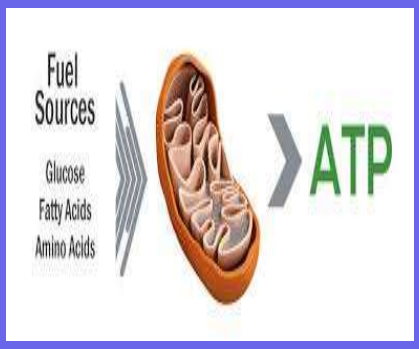
- They comprise roughly 10 percent of our total body weight.
  - Everyday the average person makes two hundred trillion trillion ATP molecules.
- Because of their relative energy needs our heart and brain cells contain the greatest number of number of mitochondria.
  - There are approximately 10 million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

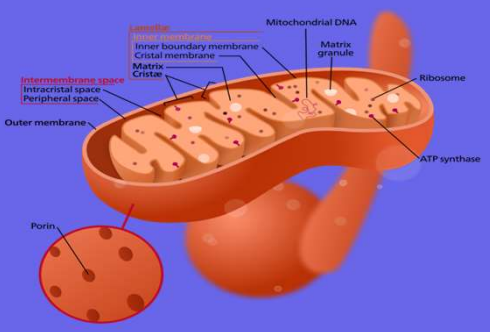
20

Mitochondria: Our Energy Factories



21





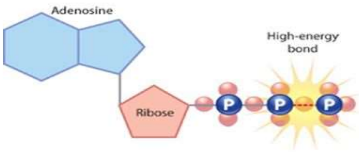
22

What is "Energy" in Biology???

Adenosine Triphosphate = ATP

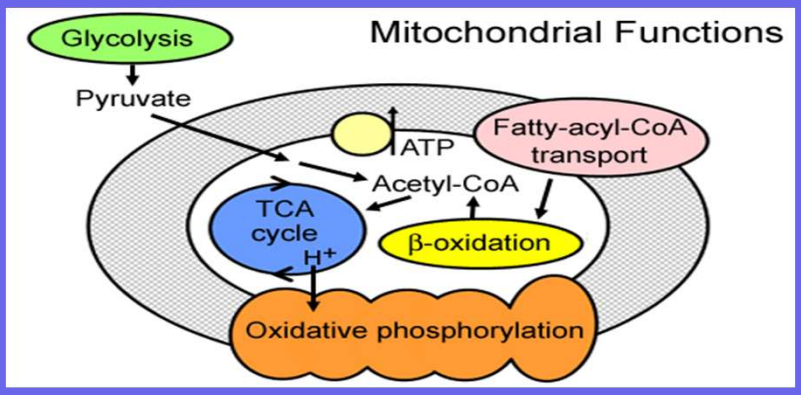
ATP is a high energy molecule produced in the Mitochondria (cell organelle)

It is made in a process called cellular respiration



What ATP is and How it Works - BioVid Episode 3 - YouTube

23



24

Mitochondrial Recycling

- The mitochondria recycling loop disposes of those that are unhealthy so that those that are can dominate.
- Reactive oxygen species (ROS) trigger both mitophagy (killing off damaged mitochondria) and mitochondrial biogenesis (the generation of new mitochondria).

25

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

26

Free Radicals

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

27

Use up cell's energy or suffer

When energy demand is high, electrons flow down the ETC rapidly, the protons are pumped swiftly (the proton reservoir fills up)

- The greater the reservoir the greater the pressure to form ATP

However if there is no demand for ATP (but plenty of calories)

- Proton gradient is too high (reservoir overfills)
- The ETC backs up and electrons escape and form superoxide free radicals
- Oxidize lipids and mitochondrial membranes, DNA damage
- Necrotic cell death (necrosis)—cells swell and rupture
- Organelles disintegrate and inflammation occurs

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

28

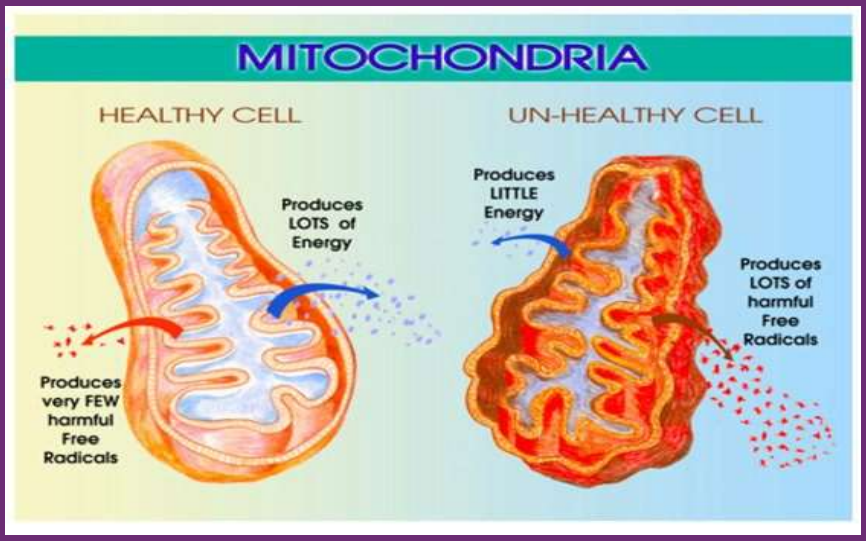
Hyperglycemia

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

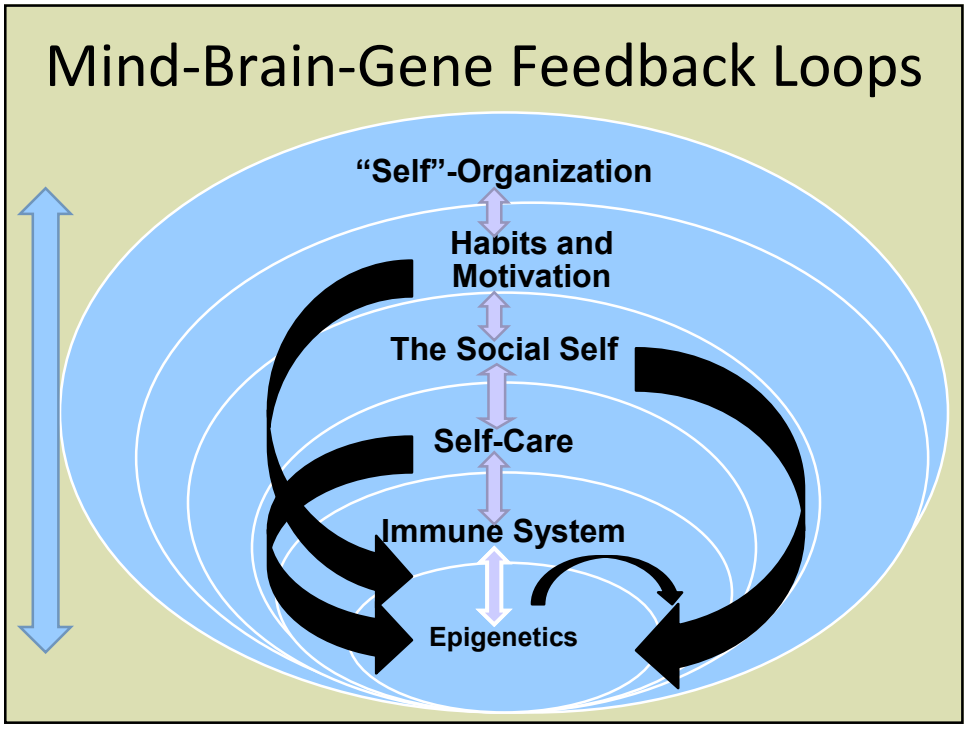
  Eating 2100-6000 calories a day doubles the risk of MCI

29

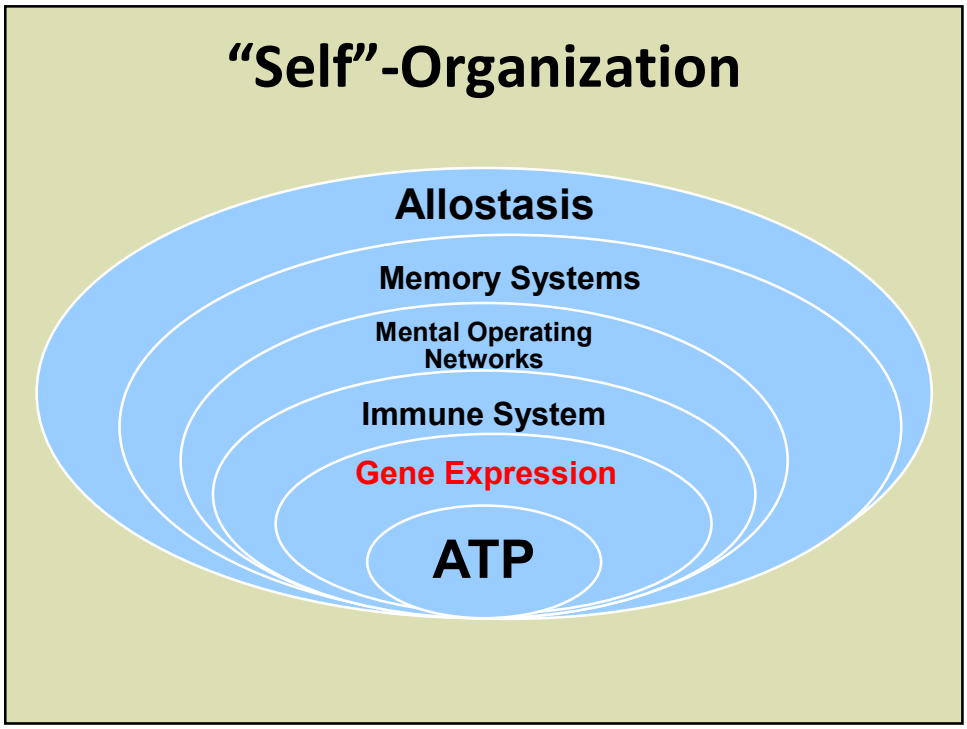
Free Radical Damage



30


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

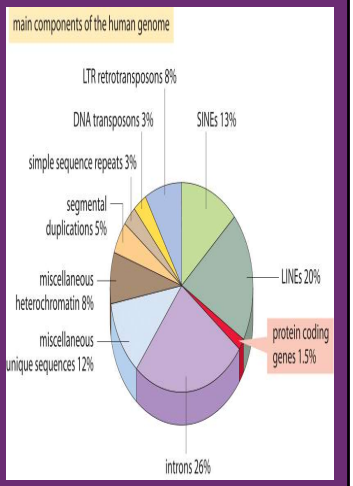
31


"Self"-Organization
Allostasis
Memory Systems
Mental Operating Networks
Immune System
Gene Expression
ATP

32

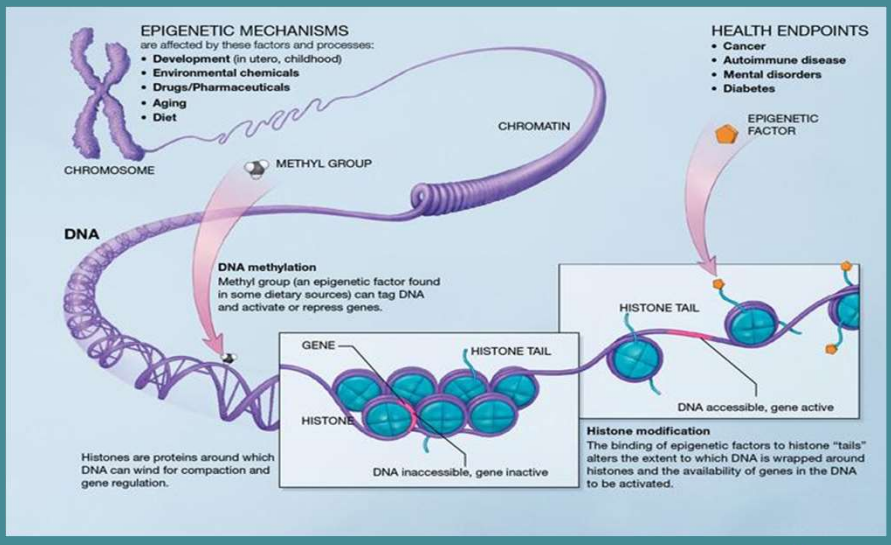
Epigenetics

- 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"



33

Epigenetics



34

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

35

Epigentics and parenting

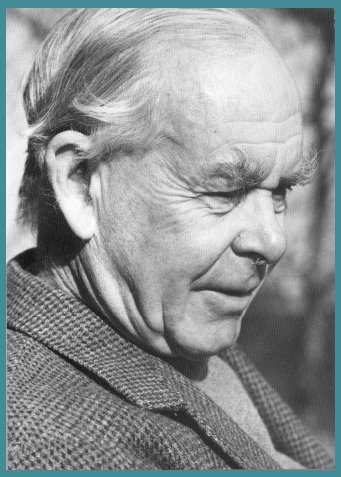
- Good parenting produces kids with less methylation of the cortisol receptor gene
- The kids have a better thermostat for cortisol and can turn of the stress response system more easily

Cortisol level

36

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"



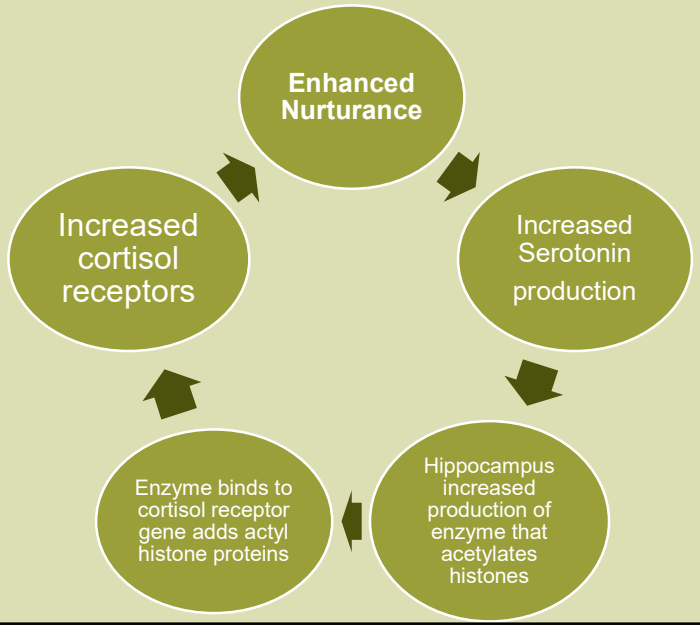
37

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)

38

Epigenetics of Stress Tolerance



39

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:

40

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.

41

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

42

"Differential susceptibility"

CNS systems	Genes related to resilience	Influences of polymorphisms on resilience	References
NPYergic	Neuropeptide Y gene (NPY)	Increased susceptibility to anxiety disorders after childhood adversity.	Donner et al., 2012
HPA Axis	CRH receptor 1 gene (CRHR1)	Affected the likelihood of developing adult depressive symptoms from child abuse.	Bradley et al., 2008
	FK506-binding protein 5 gene (FKBP5)	Predicted severity of adult PTSD symptoms and onset of depression in individuals with childhood trauma.	Binder et al., 2008; Zimmermann et al., 2011
Noradrenergic and Dopaminergic	Catechol-O-Methyltransferase gene (COMT)	Influenced the risks of developing PTSD and deficits in stress response and emotional resilience.	Heinz and Smolka, 2006; Skelton et al., 2012
Dopaminergic	Dopamine transporter gene (DAT1)	Contributed to susceptibility to PTSD with a history of trauma.	Segman et al., 2002
	Dopamine receptor genes (e.g., DRD2, DRD4)	Induced differential emotional processing and variability in brain responses to emotional stimuli; Influenced vulnerability to stress and trauma and risk of developing PTSD.	Blasi et al., 2009; Ptacek et al., 2011
Serotonergic	Promoter region of serotonin transporter gene (5-HTTLPR)	Short allele strongly associated with increased stress sensitivity and risk for depression upon stress exposure, especially early life stress.	Karg et al., 2011
	Serotonin receptor genes (e.g., HTR1A, HTR3A, HTR2C)	Interacted with environment to mediate stress response and to predict susceptibility to depression.	Gatt et al., 2010; Kim et al., 2011a; Brummett et al., 2012
BDNF	Brain-derived neurotrophic factor gene (BDNF)	Interacted with early life stress to predict syndromal depression and anxiety; no clear evidence of association between the $Val^{66}Met$ polymorphism and anxiety disorders.	Frustaci et al., 2008; Gatt et al., 2009

43

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.

44

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.

45

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.

46

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

47

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).

48

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).

49

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%.

50

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

51

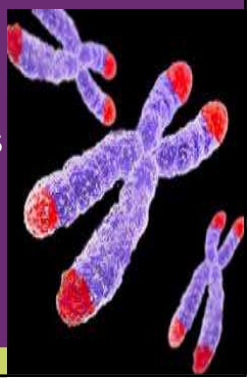
Between Session Neuroplasticity

- 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)

52

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.

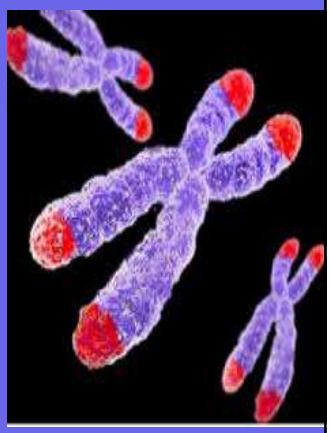


- Psychobiomarker": Linked to social status, perceived stress,
- depression, predictive of mortality (Epel, 2009, Current Directions)

53

Factors that Impair DNA and Cells

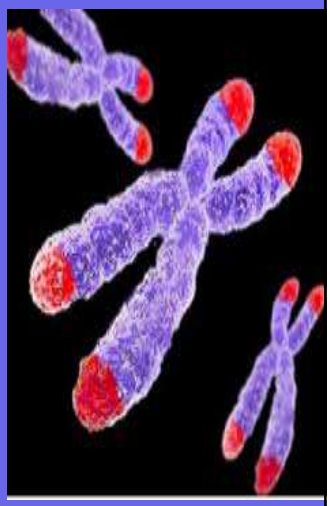
- When cells divide
- Telemeres shorten
- Gene expression changes
- Impairs cellular repair
- Recycling of cells slows
- Errors accumulate
- Cells fail
- Cells die



54

Factors that Shorten Telemeres

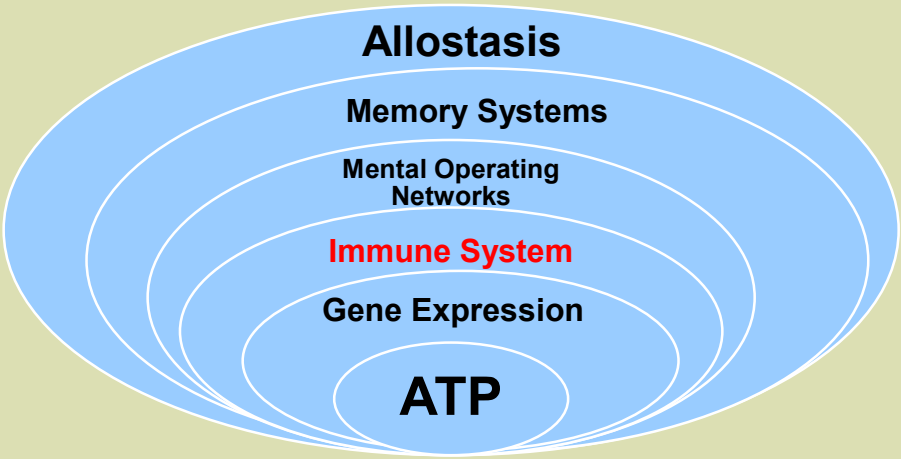
- Smoking
- Obesity (more than smoking!)
- Type 2 Diabetes
- Social isolation
- Poor diet
- No exercise
- Poor sleep
- Alcohol and other drugs



- **All rendering DNA vulnerable to damage**

55

"Self"-Organization



56

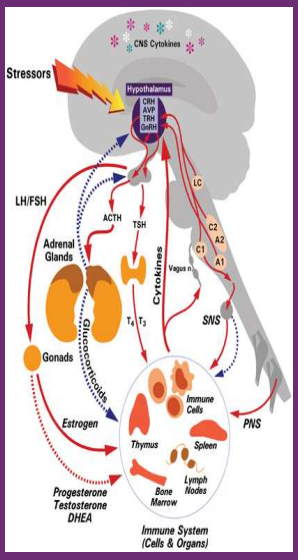
The Brain Controls the Stress Pathways

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



57

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

58

Hypocortisol vs. Hypercortisol Activity

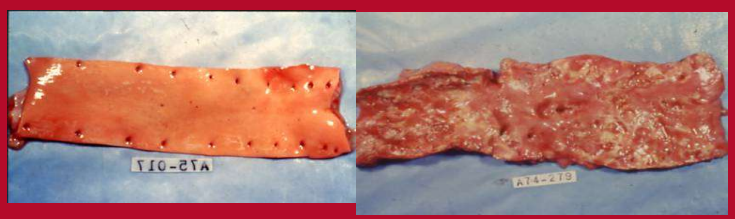
- Chronic stress (especially uncontrollable) alters the cortisol system
- Early on there can be *higher* cortisol
  - Can lead to agitated depression
  - Kills white blood cells
  - Metabolic syndrome
- More distant traumas may result in an inadequate cortisol response
  - Autoimmune disease
  - Inflammation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

59

Excessive Cortisol

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

Hypercortisolemia and damage to arteries



60

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)

61

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.

62

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*

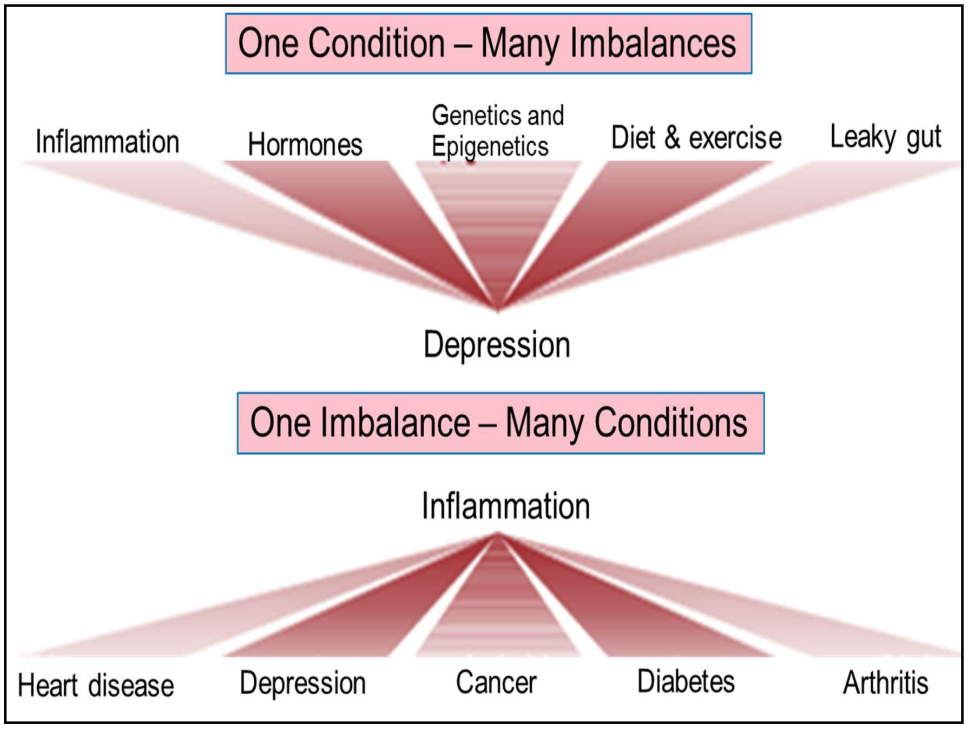
63

Stress

Activation of corticotropin releasing hormone (CRH):

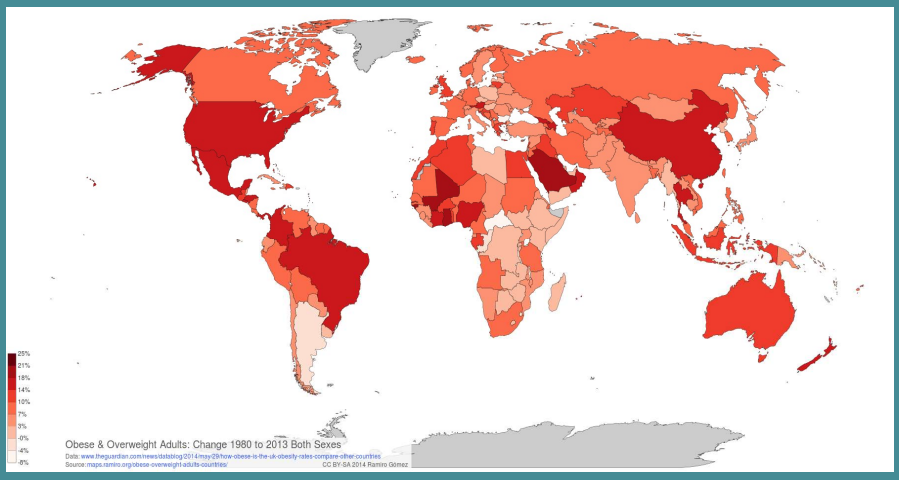
- **Contributes to delayed gastric emptying**
- **Increased colonic activity**
- **Functional bowel disease (IBS)**
- **Increase in gut permeability**
- **Leaky gut – antigens leaking out**
- **Toxic liver overload**
- **Systemic disease**

64



65

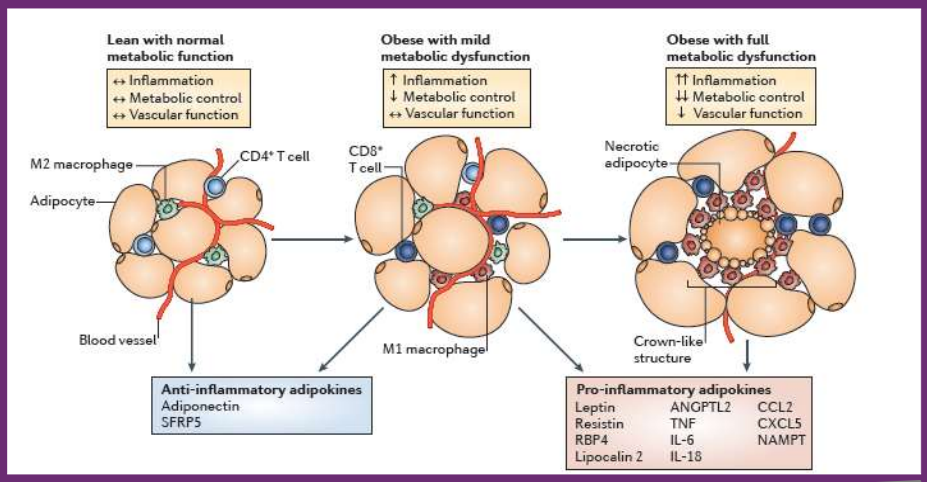
The Pandemic



Obese people over 40 will die 6-7 years earlier

66

Obesity-Associated Adipose Tissue Inflammation



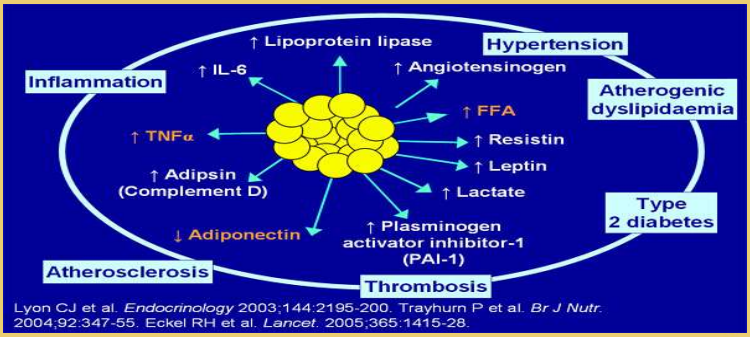
INFLAMMATION

67

Obesity, Inflammation, and Diabetes

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

Higher IL-6 may predict diabetes type 2



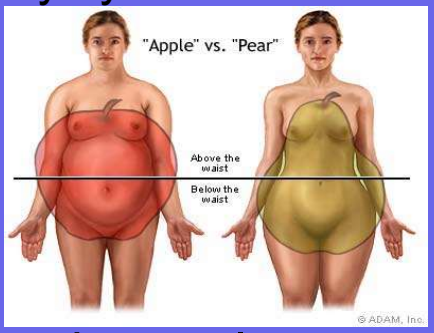
Lyon CJ et al. *Endocrinology* 2003;144:2195-200. Trayhurn P et al. *Br J Nutr.* 2004;92:347-55. Eckel RH et al. *Lancet.* 2005;365:1415-28.

68

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



69

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.

70

WHO—World Population
7,505,257,673

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

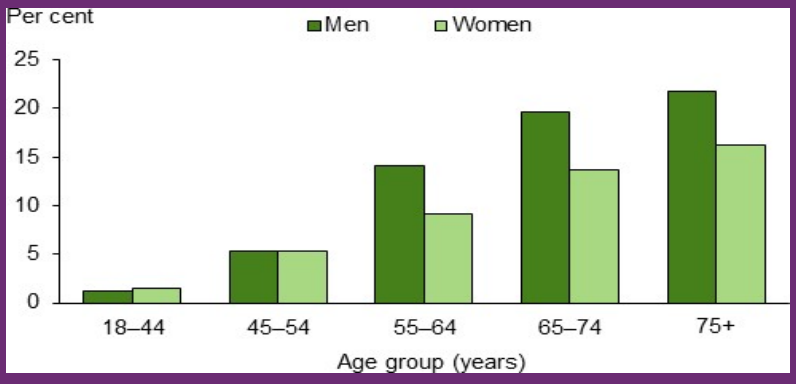
- Obesity Population: 774,000,000

71

Diabesity in Australia

63.4 percent of **Australian** adults were overweight or **obese**

Diabetes -



72

Diabetes and Psychological Disorders

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

73

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

74

Progression to Diabetes

- High glucose
- Mitochondrial damage and lipid accumulation
- Insulin resistance
- Beta cells increase metabolism to create more insulin
- Beta cells accumulate damage due to high metabolism
- Beta cells begin to die, with a corresponding drop in insulin
- Spikes of glucose

75

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**

76

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

77

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**

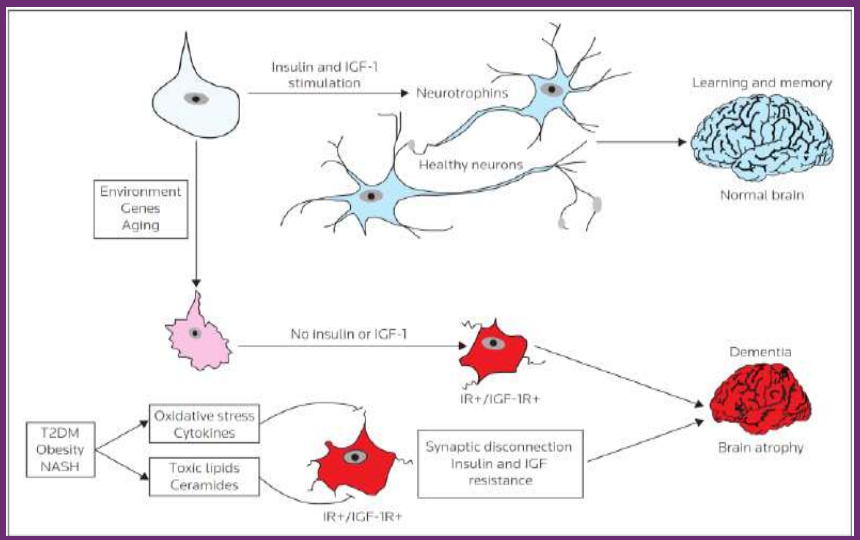
78

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

79

Diabetes and Brain Shrinkage



80

Diabesity

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

81

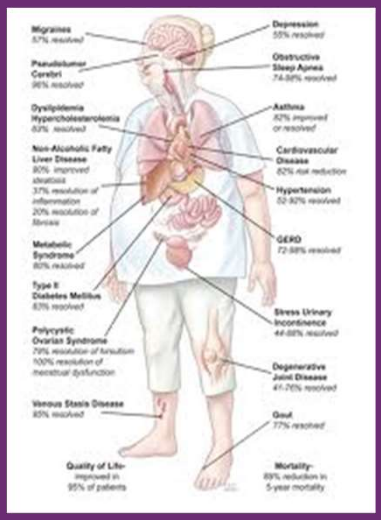
Diabesity

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

82

Cardo-Metabolic Syndrome

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



83

Metabolic Syndrome

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

84

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

85

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!

86

➢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).

87

Client Education

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

88

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”

89

Depression and fatigue in illness

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

90

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

91

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

92

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

93

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

94

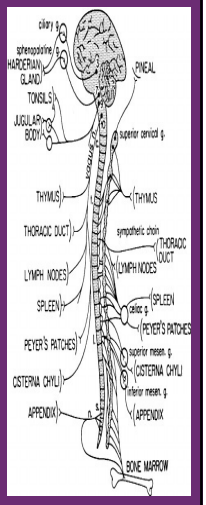
Inflammation and Dementia

- 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

95

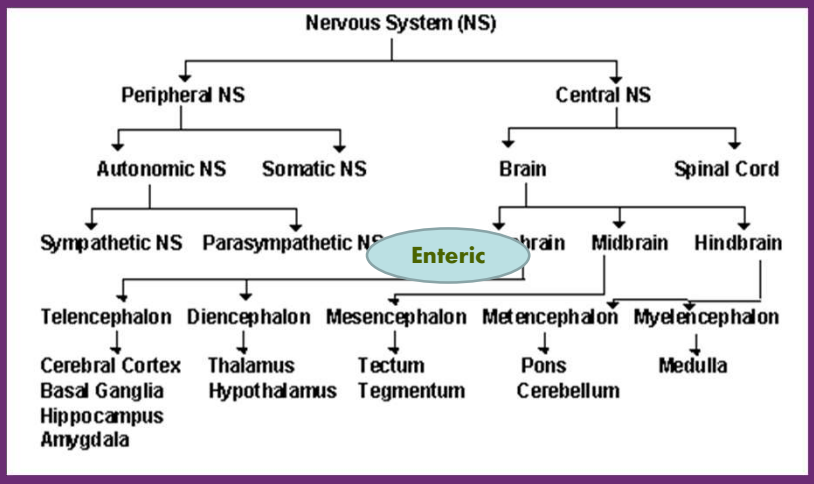
Peripheral nerves are also involved in inflammation

- 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)



96

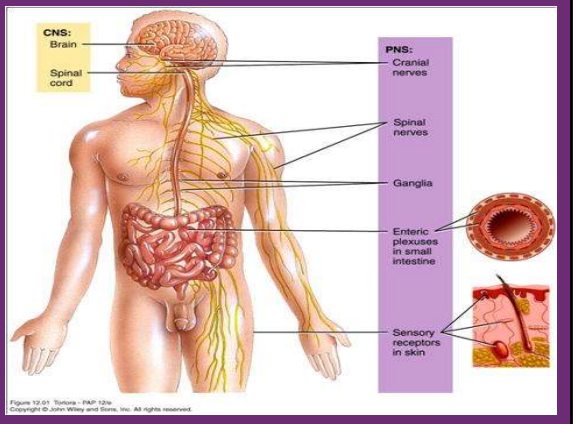
The Gut Brain



97

Enteric Nervous System

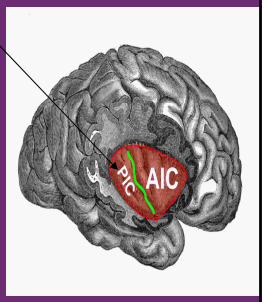
- ***Enteric*** – meshwork of nerve fibers that innervate the viscera (gastrointestinal tract, pancreas, gall bladder)



98

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**



99

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.**

100

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

101

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.

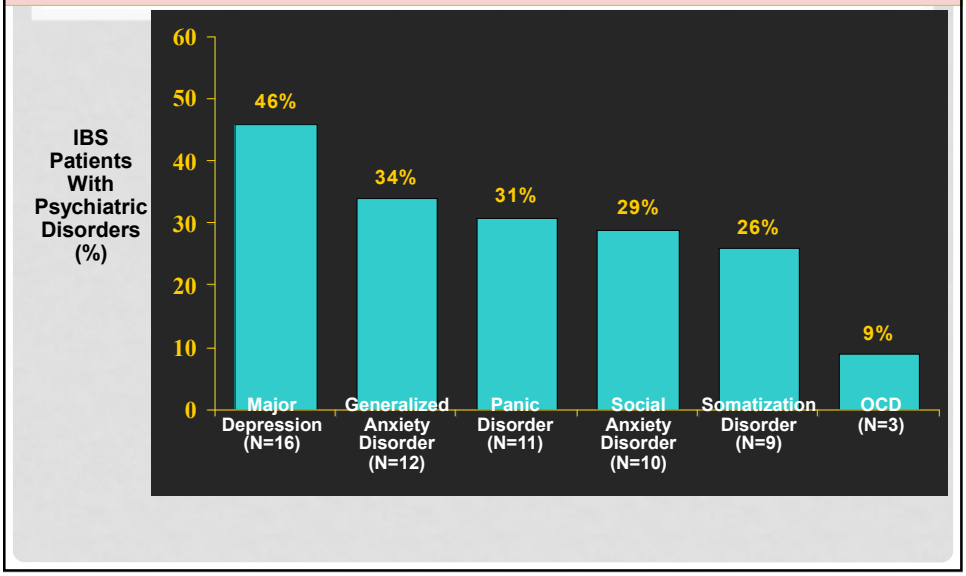
102

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

103

LIFETIME PSYCHIATRIC DISORDERS IN PATIENTS WITH IBS



104

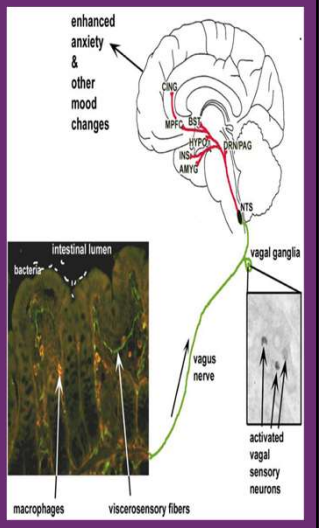
Stress/Depression and the Gut Microbiome

- 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

105

Inflammation, microbes and anxiety

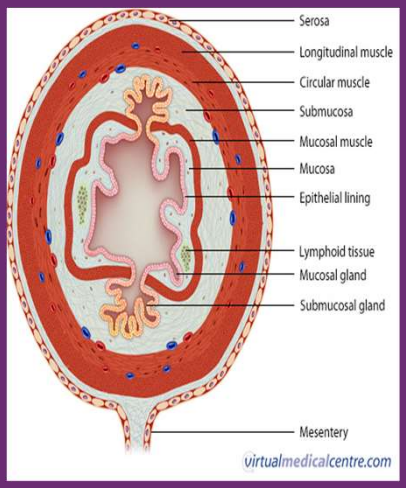
- Anxiety is common in illness, and inflammatory signals from the body contribute, e.g. TNF, vagal activation
- A signal that something is not right
- Destructive role of dysbiosis (imbalance in microbes)



106

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

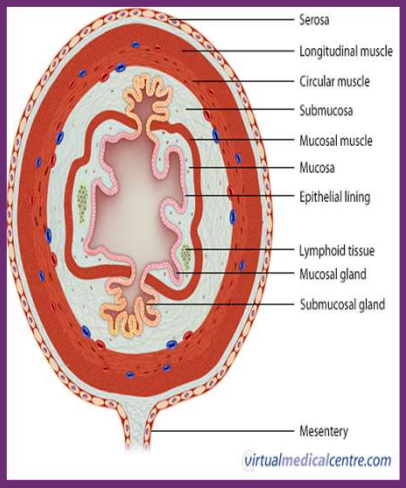
- **AKA "increased intestinal permeability"**
- **Is associated with many disorders (diabetes, metabolic syndrome allergies, neurological etc.)**
- **Allows more absorption of toxins and lets fluid out e.g. during inflammation and infection (diarrhea)**
- **Many factor regulate this: immune cells and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



107

"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,

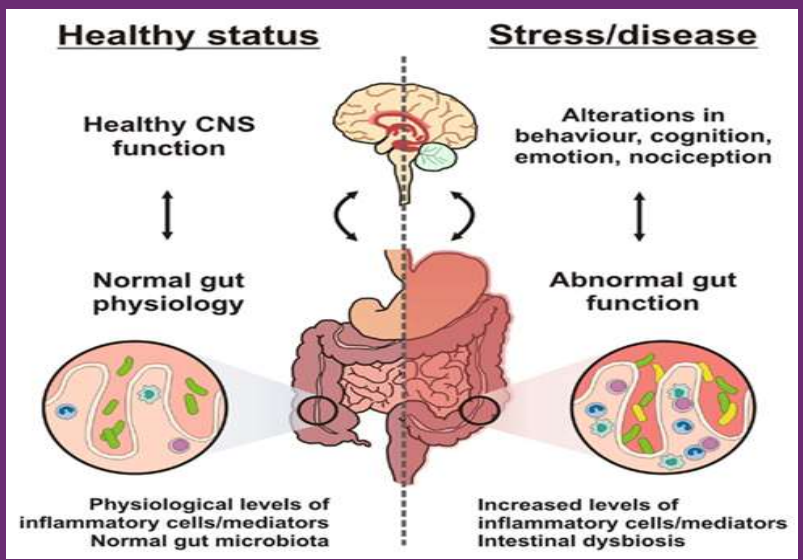


108

Dysbiosis and Microbial Diversity: the Importance of Balance

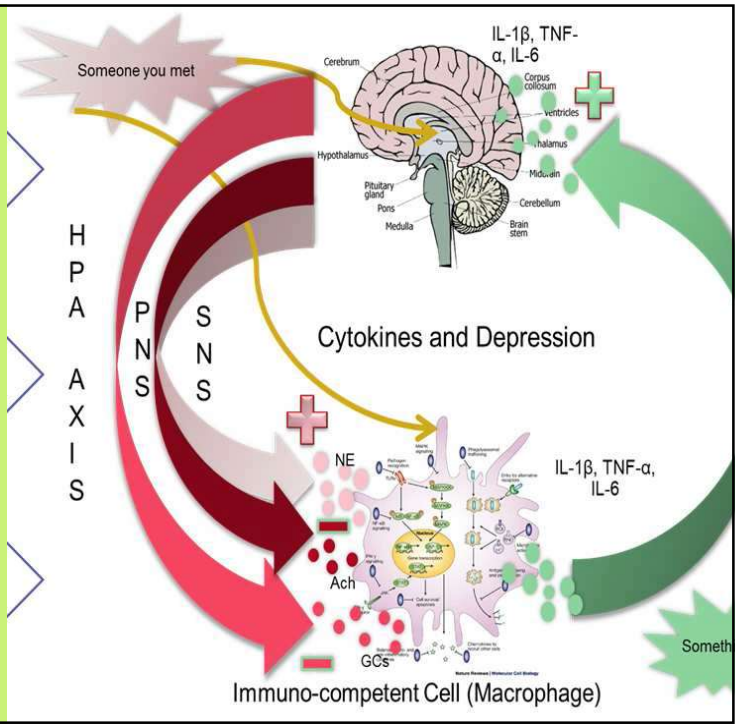
- Diversity is good- a hallmark of disease is reduced microbial diversity
- Low diversity is associated with DYSBIOSIS
- *Dysbiosis* is when there is an imbalance in microbes, leading to overgrowth of some species
- Dysbiosis with inflammation--↓5-HT

109



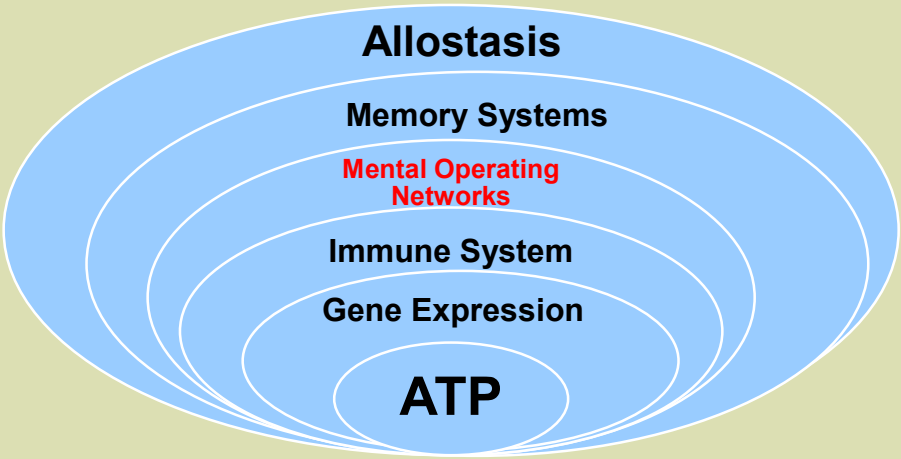
110

- 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



111

"Self"-Organization



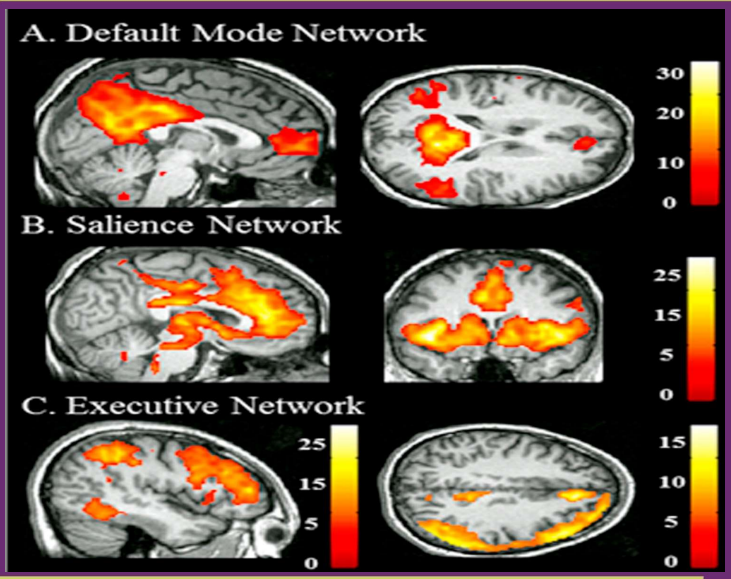
112

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;

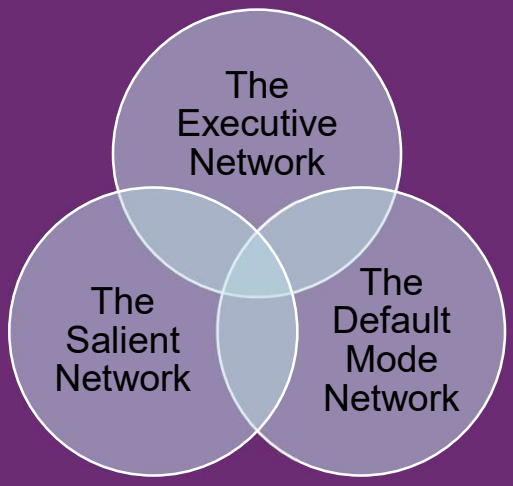
113

The Mental Networks



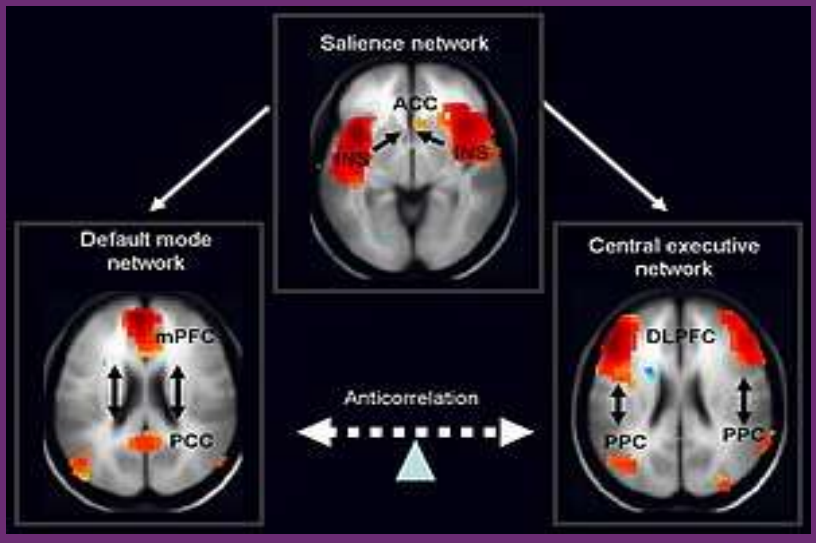
114

Balancing the Mental Networks



115

The Mental Neworks



116

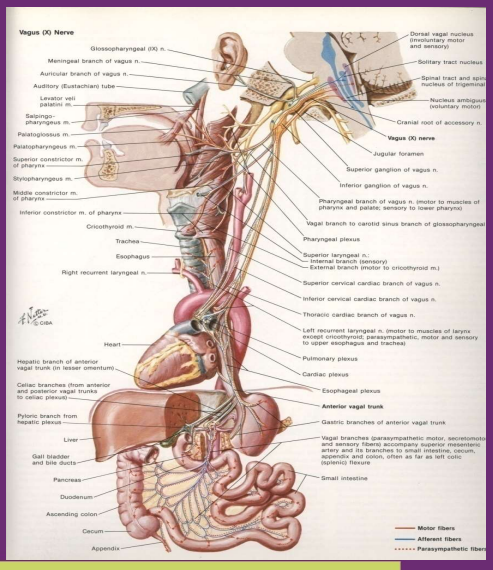
Salience Network:

- 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

117

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.



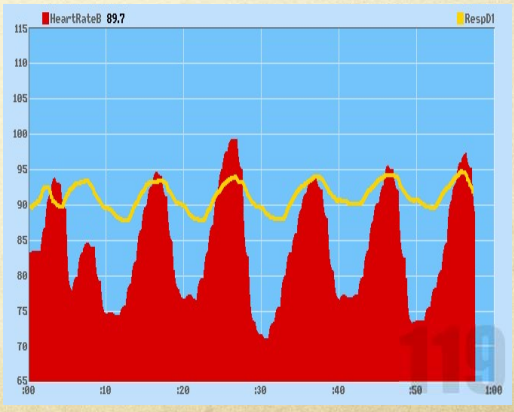
118

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.



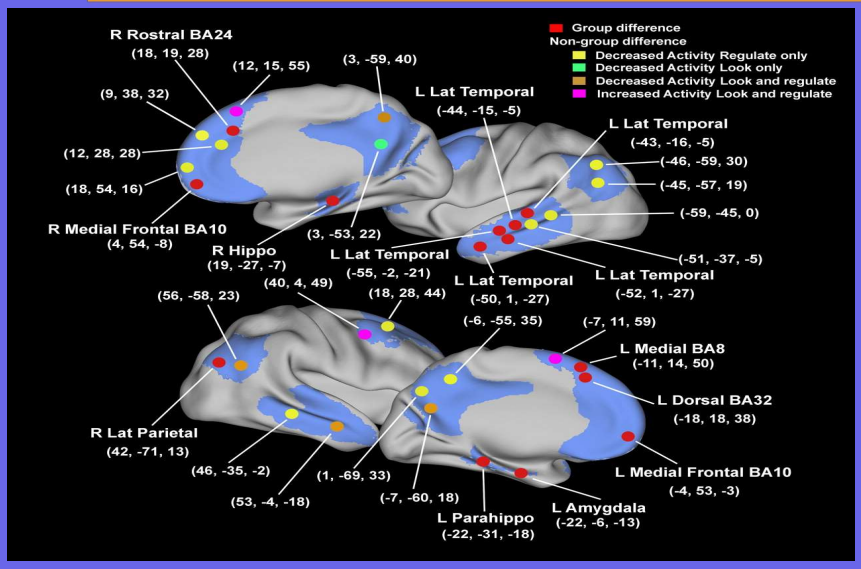
119

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

120

Activity in the default mode network



Sheline Y I et al. (2009)

121

DMN

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

122

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

123

Central Executive Network:

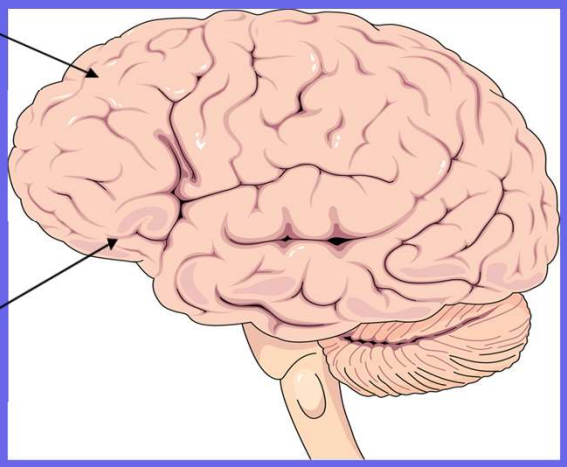
- moment to moment monitoring of experience (meta-cognition)
- responsible for selection, planning, and decision-making toward goals;
- working memory that helps select, orient, and maintain an object in the mind;
- bilateral dorsolateral prefrontal cortex

124

DLPFC and the OFC

Dorsolateral Prefrontal Cortex

Orbital Prefrontal Cortex



125

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

126

Marshmallow Experiment

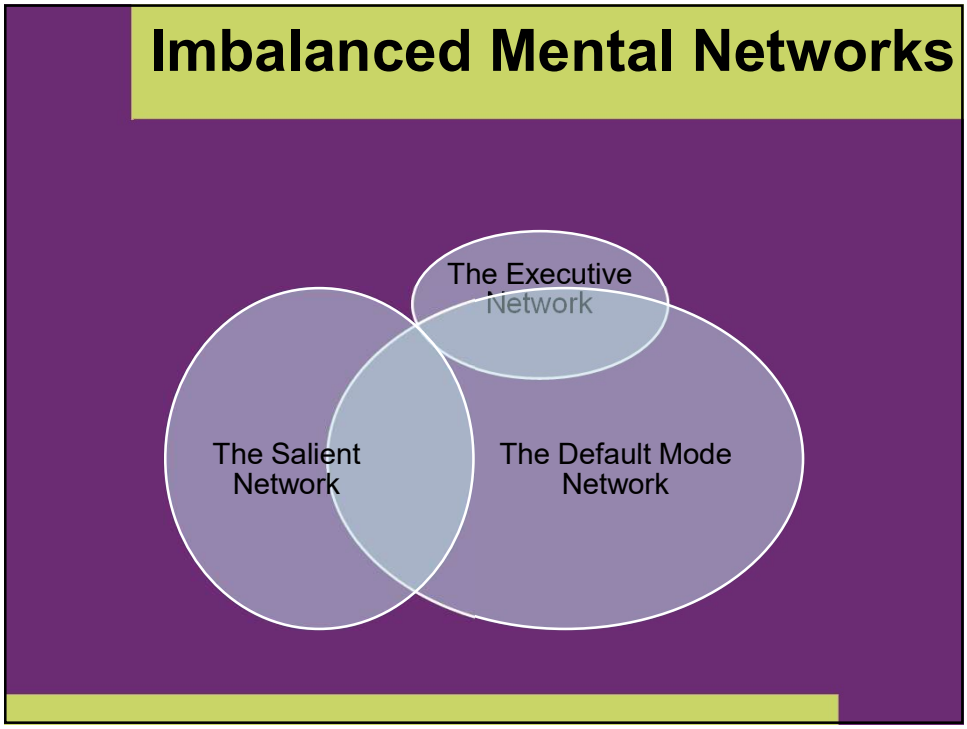
- Kids that were able to resist eating the first marshmallow for the promise of the second more successful later
- Greater PFC development
- What if the kids were trained by parents that they would get another anyway?
- No reason to inhibit—less PFC development

127

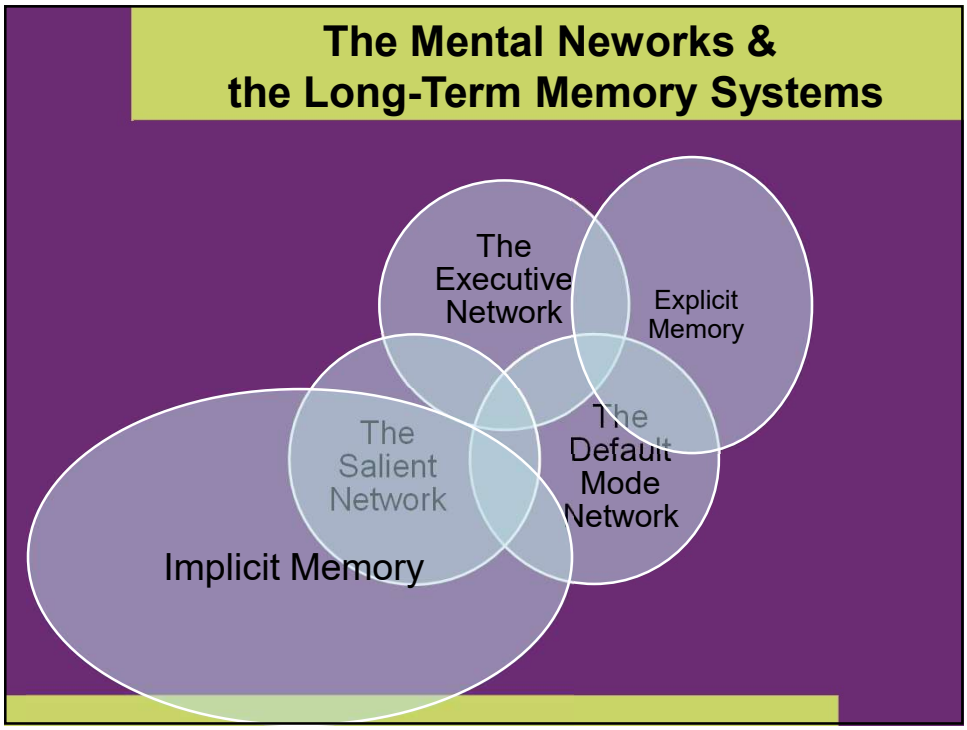
Anterior PFC
(the brain's brain)

- 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

128


Imbalanced Mental Networks
The Executive Network
The Salient Network
The Default Mode Network

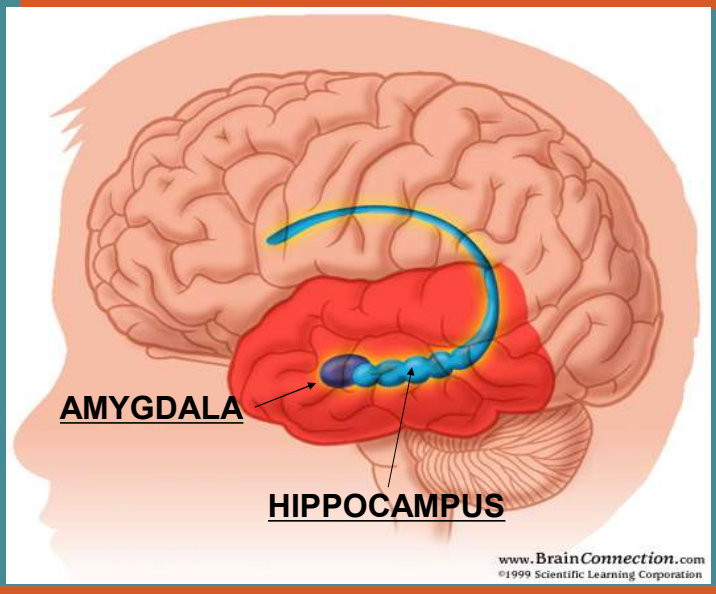
129


The Mental Neworks &
the Long-Term Memory Systems
The Executive Network
Explicit Memory
The Salient Network
The Default Mode Network
Implicit Memory

130

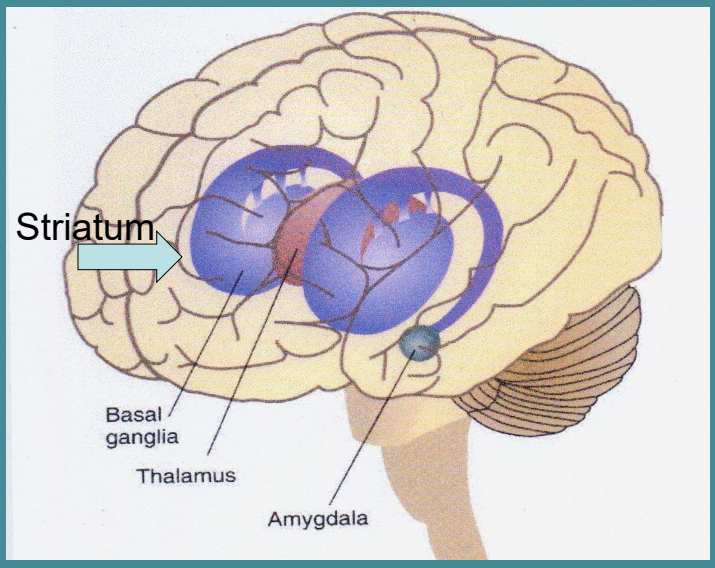
AMYGDALA *Implicit Memory System*	HIPPOCAMPUS *Explicit Memory System*
•Fear Conditioning •Emotional Valance •Generalized •Cortisol Heightened •Sensitivity • (Hypervigilence) •Matures Early •"Little Albert" •"LSMFT"	• Many Cortisol Receptors • Context Specific • Heightened Cortisol leads to atrophy •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

131



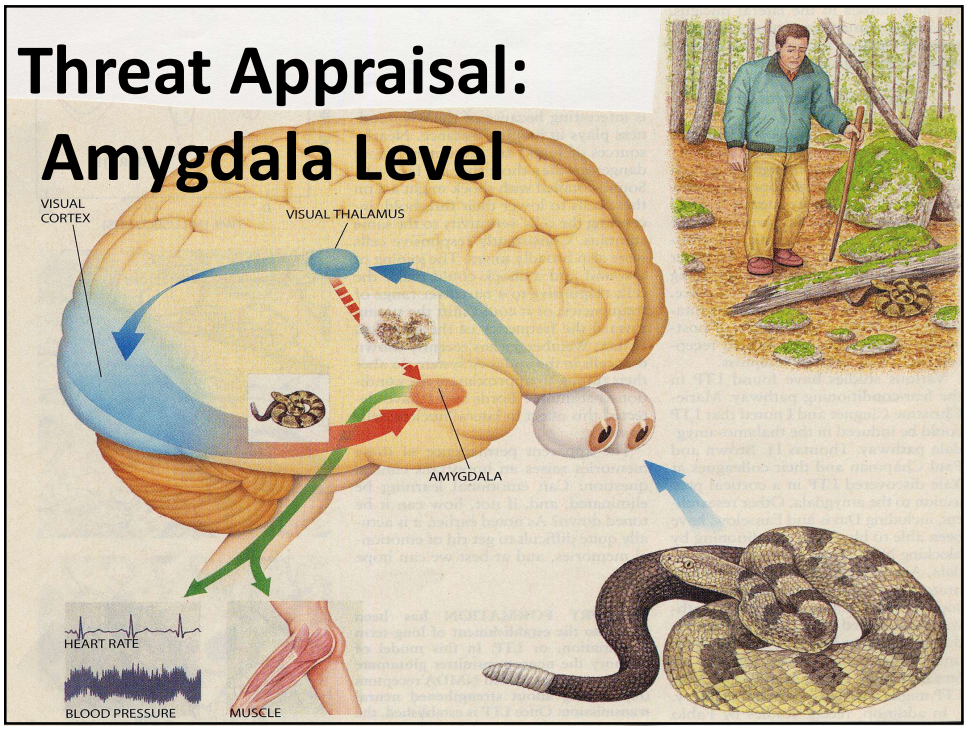
132

The Habit Circuits



133

Threat Appraisal: Amygdala Level

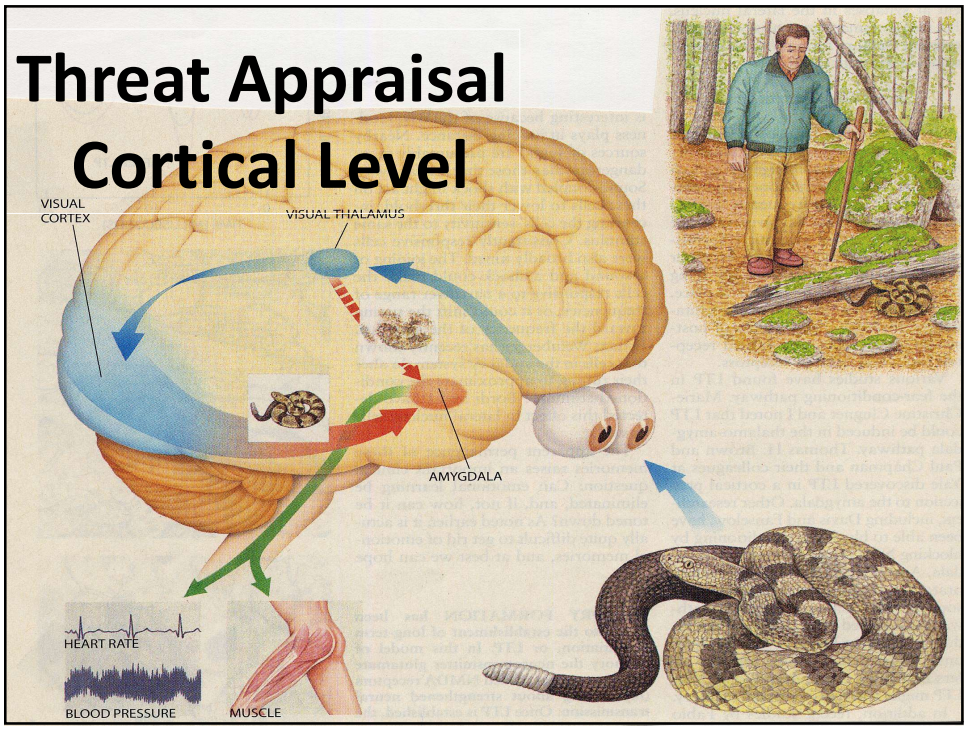


134

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"

135



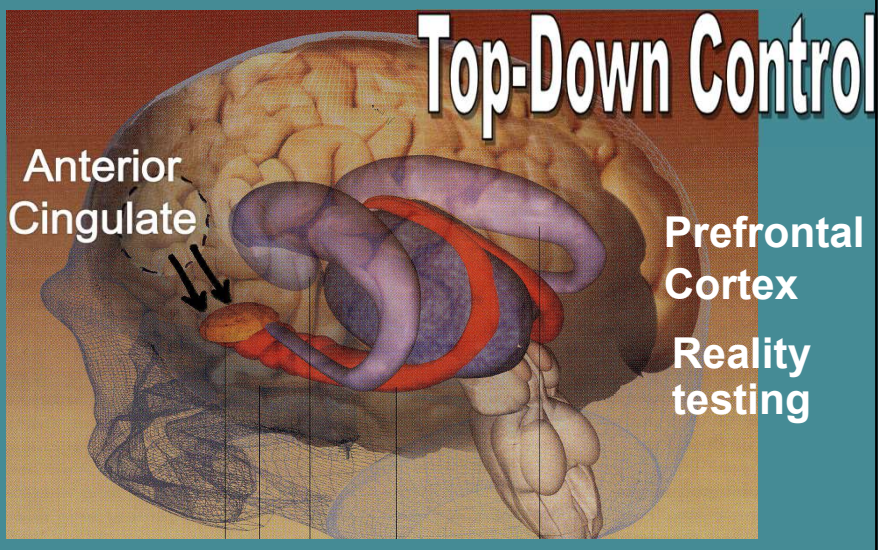
136

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"

137

Cortical-level Appraisal

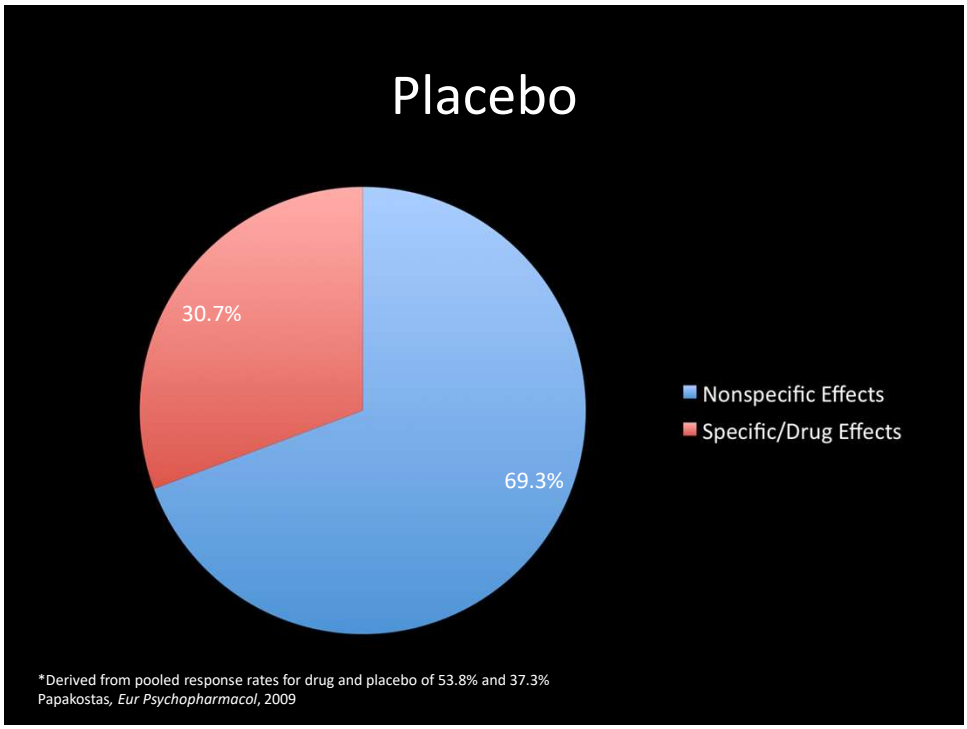


138

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.)

139



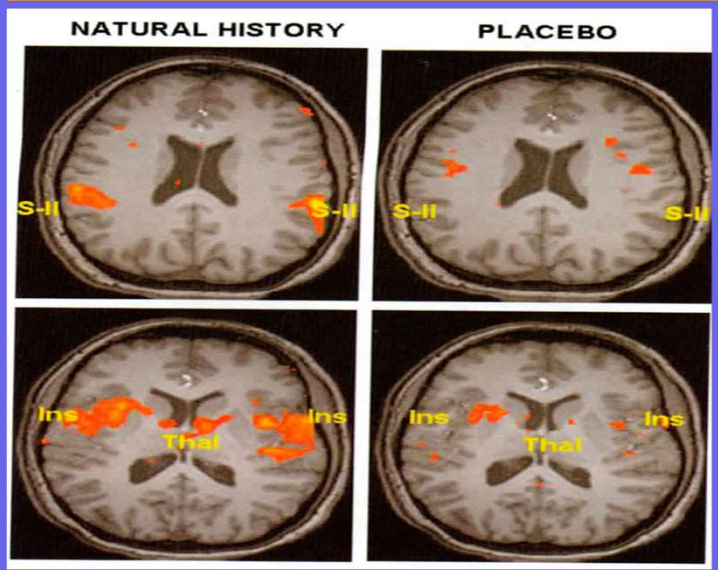
140

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

141

IBS and Pain vs. Placebo



142

Affect Asymmetry

Set points

Left Hemisphere

Positive emotions
Approach behaviors
Feeling engaged

Right Hemisphere

Negative emotions
Withdrawal and Avoidance
Feeling overwhelmed

143

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)**

144

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)

145

Mind-Brain-Gene Feedback Loops

146

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

147

Deprived Social Brain Networks

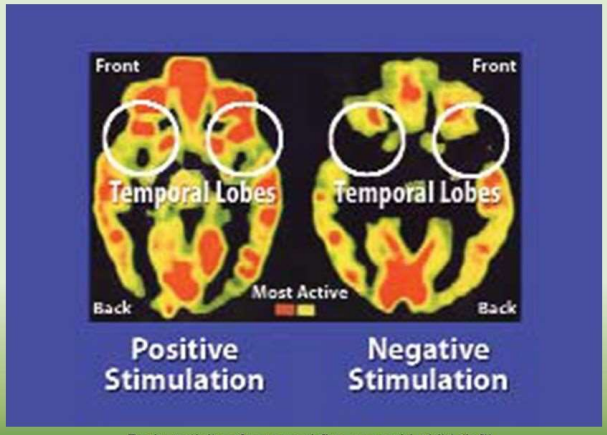
- **150,000 children found languishing in Romanian orphanages. They were emotionally neglected.**
- **They missed human contact during critical periods** (Kuhn & Schanberg, 1998).

Sustained impairment if over one year

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

148

"Normal" vs Romanian Brains



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

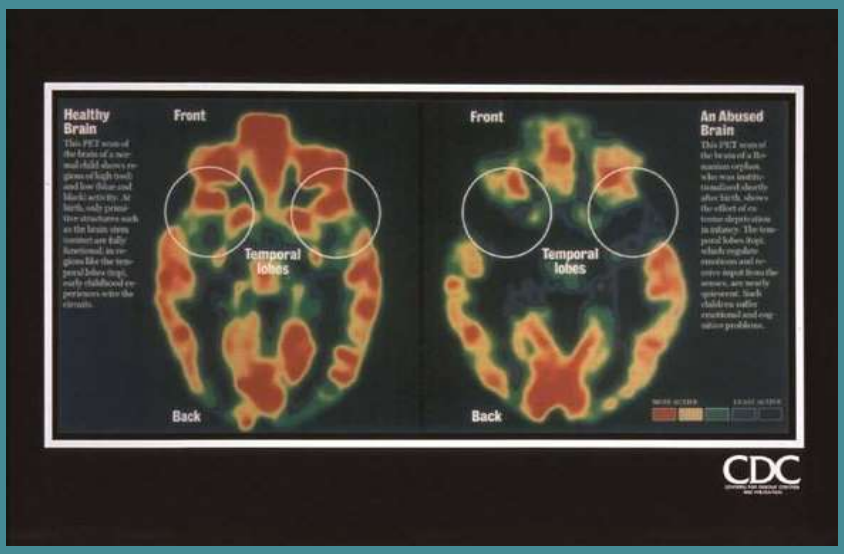
149

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).

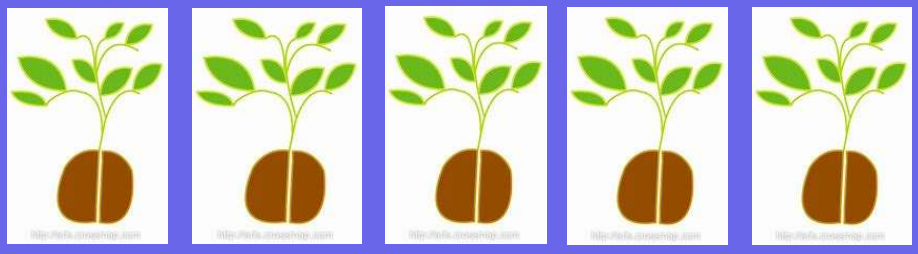
150

"Normal" vs Abused Brains



151

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...

152

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

153

Mind-Brain-Gene Spectrum

154

Wanting vs. Liking

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

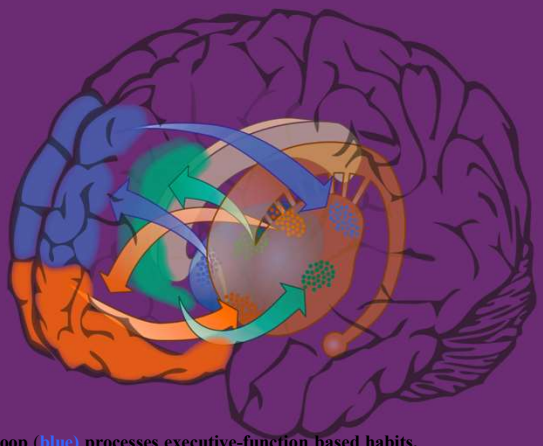
155

The Middle Path

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

156

The Habit Circuits



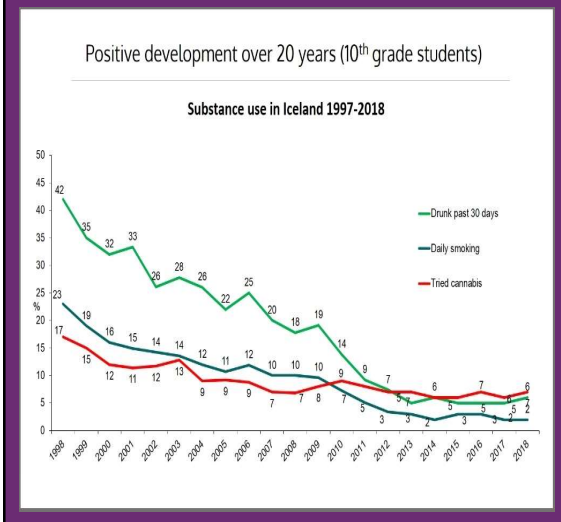
The upper loop (blue) processes executive-function based habits.

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

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

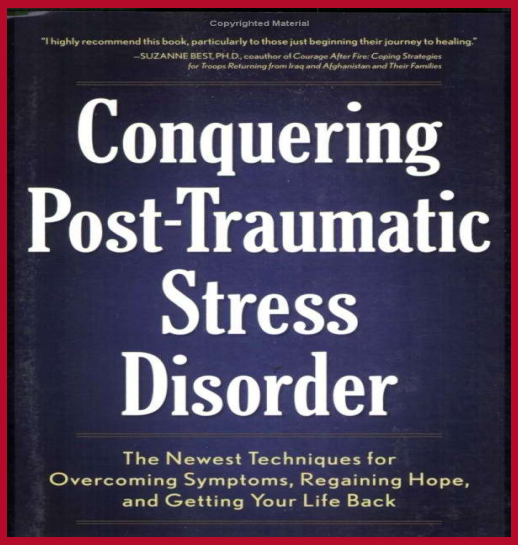
157

The Iceland Project



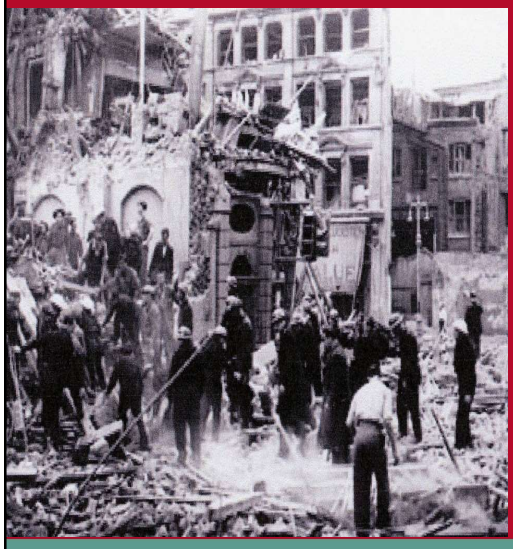
158

Post Traumatic Stress Disorder



159

Chronic, severe, inescapable



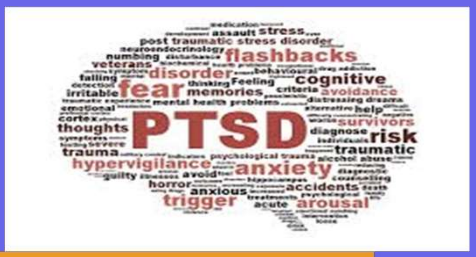
- War Zones
- Rape
- Child abuse
- Elder abuse
- Domestic violence
- POWs and refugees

160

Refugee Crisis

Re-traumatization caused by:

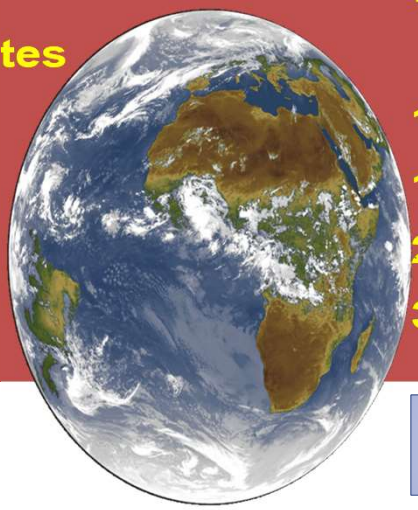
- relentless war in the region
- growing level of violence
- traumatic experiences
- extreme deprivation in daily life



161

PTSD as a Worldwide Problem

Germany	2.2%*
United States	7.8%
Ethiopia	15.8%
Gaza	17.8%
Cambodia	28.4%
Algeria	37.4%



Iraq, Syria, Afghanistan?

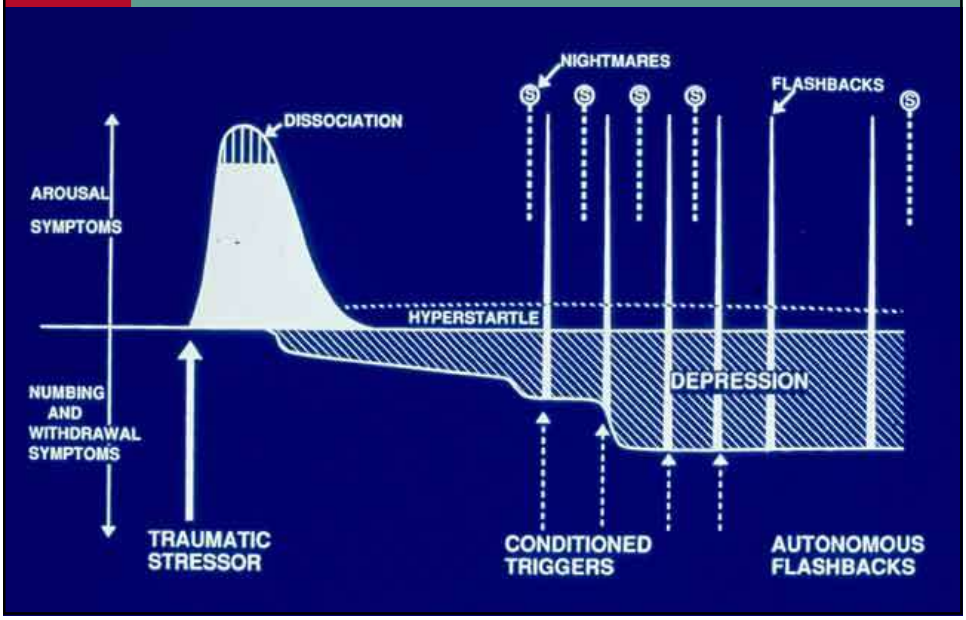
162

Risk Factors for PTSD

- Greater distress before/after the trauma
- Poverty and low socioeconomic status
- Previous or current psychological disorder and poor affect regulation
- Family discord and/or insecure attachment
- Cognitive disengagement at the time of the trauma and dissociation involving depersonalization and de-realization
  - Especially with early and repeated trauma

163

Time Sequence



164

Phylogenetic Responses to Stress

- 1) Trigger the social engagement system—the myelinated vagus
- 2) Fight or flight—SNS and HPA axis arousal
- 3) Immobilization—freeze, collapse, and feigned death:
  - 2 stages
    - Freezing in terror
    - Paralyzed—shut down—total submission, trancelike, dissociation

165

PTSD Neurodynamic Aspects

- ↑ amygdala—general false positives for threat
- ↓ mPFC especially the ACC (reduced neurointegration and cortical volumes) (De Bellis, et. al., 2000) (inadequate top down inhibition of the amygdala)
- ↓ hippocampus (cortisol, excitotoxity, blocking of neurogenesis)

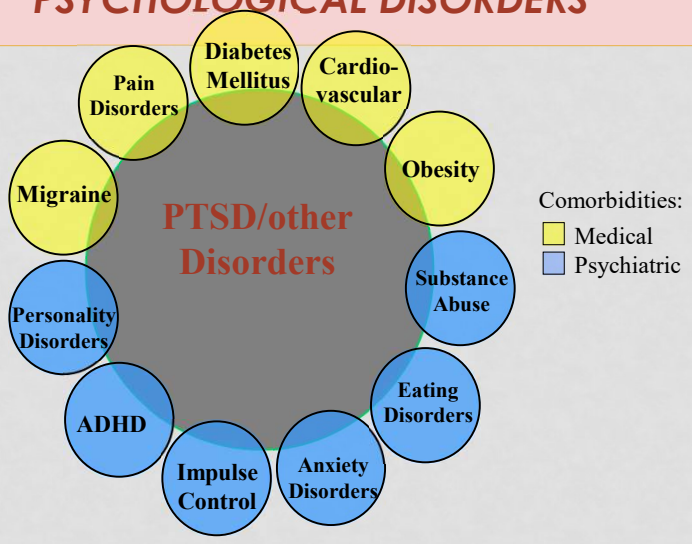
166

Most Common Acute Post-Traumatic Stress Response

- Depression
- Anxiety Disorders
- Substance use / abuse
- Acute Stress (ASD) only later PTSD
- Adjustment disorders
- Persistent complex bereavement

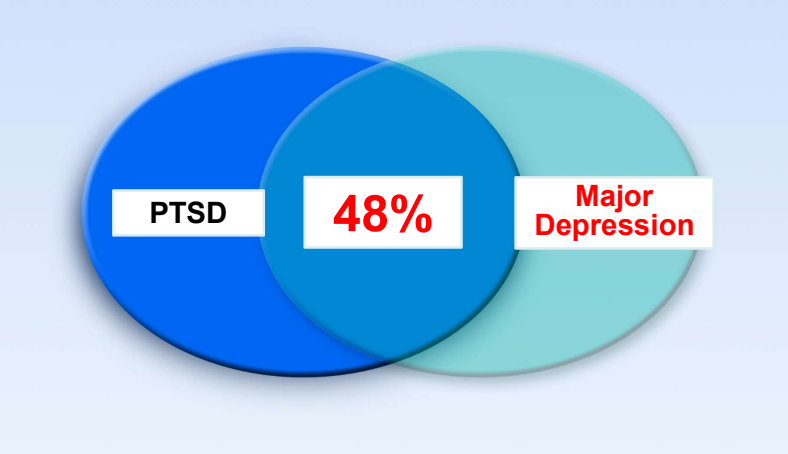
167

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



168

Common Occurrence of PTSD and Depression



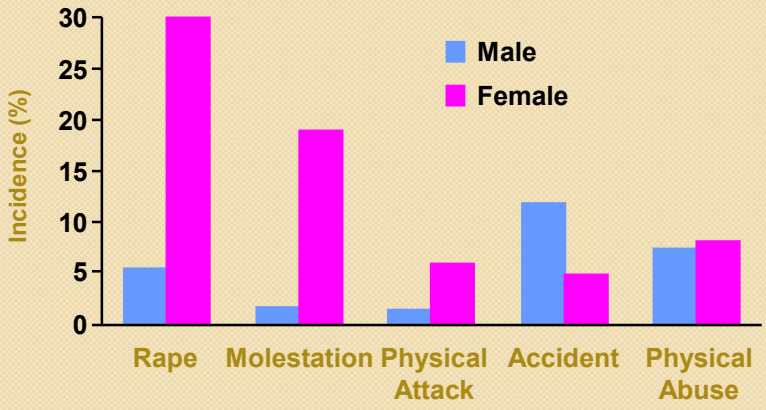
169

A Big Problem: Reluctance to tell or seek out help

- **Sexual assaults**
- **Bullying** (kids and adults)
- **Work-place violence**
- **Domestic violence**

170

Non-Combat-Related Trauma Associated with PTSD

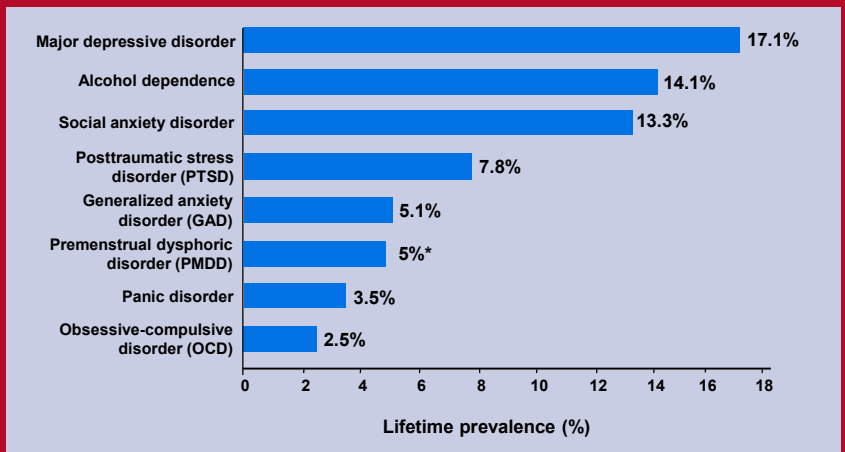


Kessler et al. Arch Gen Psychiatry. 1995;52:1048

Courtesy of: David V. Sheehan, M.D., M.B.A.

171

Lifetime Prevalence of Common Psychological Disorders



172

Predicting PTSD

Dissociation or amnesia at the time of traumatic event

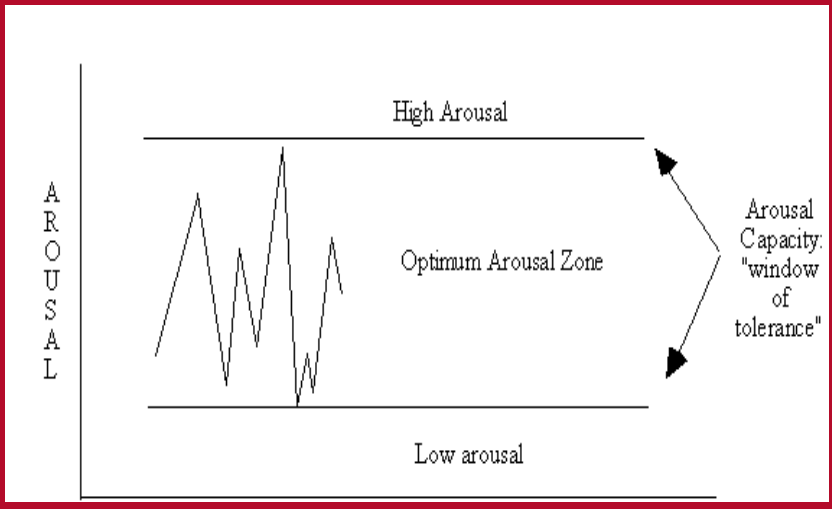
Panic attack: first 24 hours

70% greater risk

The Severity of the Traumatic Event is <u>not</u> predictive of outcome

173

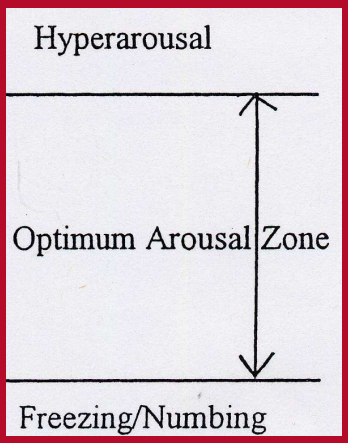
Window of Tolerance



174

Working the "Therapeutic Window"

Over-Shoot

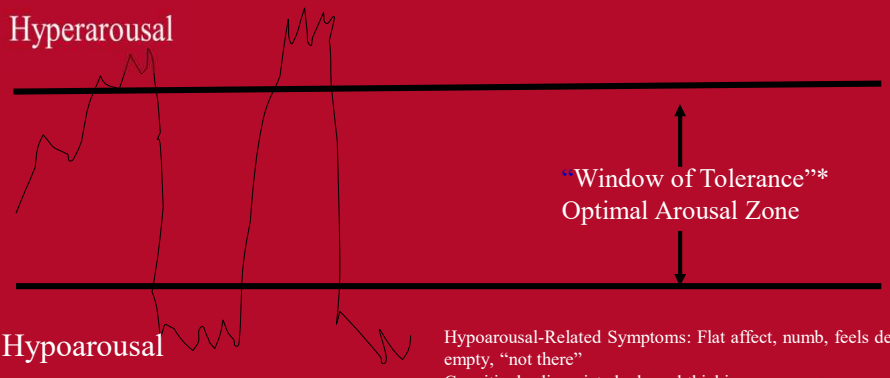


Under-Shoot

175

Trauma Responses are Autonomically Driven

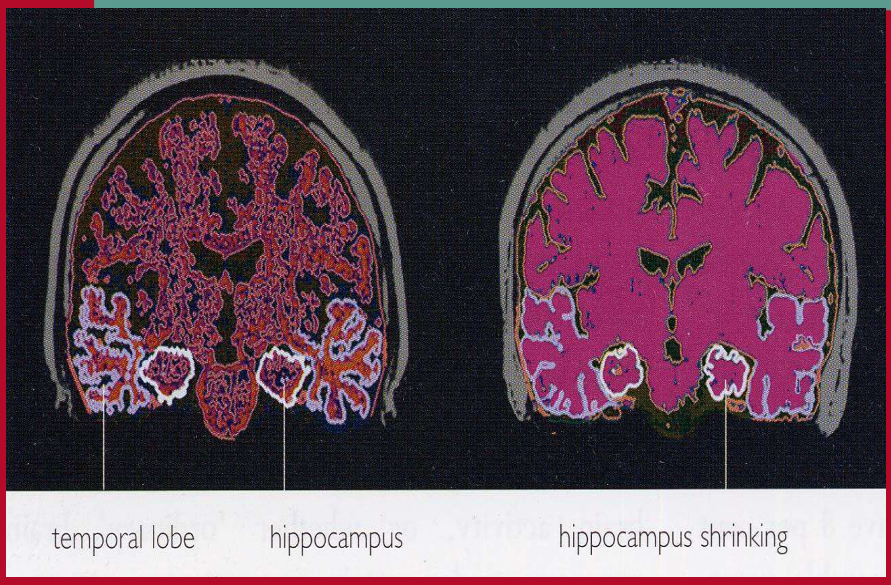
Hyperarousal-Related Symptoms:
High activation resulting in impulsivity, risk-taking, poor judgment
Chronic hypervigilance, post-traumatic paranoia, chronic dread
Intrusive emotions and images, flashbacks, nightmares, racing thoughts
Obsessive thoughts and behavior, cognitive schemas focused on worthlessness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



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

176

Hippocampal atrophy



177

Client Education

- Though your memory may be temporarily impaired, you can revitalize these areas of your brain by aerobic exercise followed by learning and goal oriented behaviors.

178

Possible Neurochemical Vulnerability of PTSD

- ↑ NE post trauma may predict PTSD (Yehuda, et. al., 1998)
- ↑ cortisol in the evening not in the morning
- ↑ proinflammatory cytokines post trauma
  - The secretion of IL-6 inflammatory cytokines can be triggered by B-adrenergic receptors with ↑ NE
  - Inflammation can occur post trauma via CRH/substance P-histamine axis with ↑ cortisol and IL-6 (Elenkov, et. al., 2005)

179

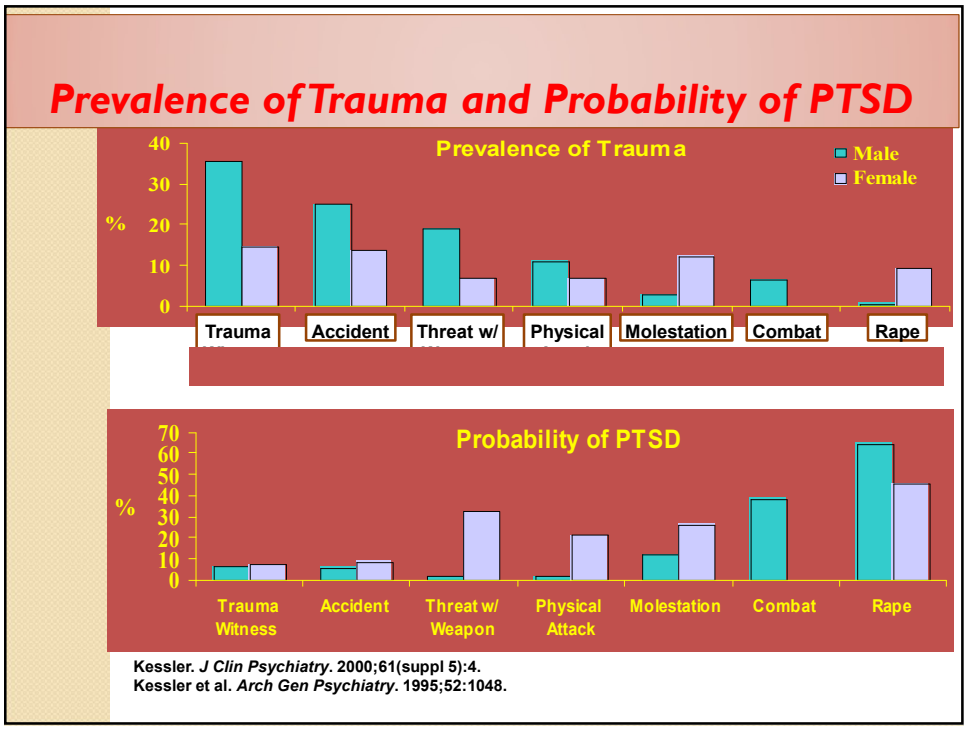
Client Education

- It's common to feel like being alone after a traumatic event. But, isolating now will make you worse and feel even more alone.
- Parts of your brain activate when you are with people which helps you buffer anxiety and lift depression.

180


Disordered Fear Regulation in PTSD
Disordered fear regulation
Appropriate fear regulation
Development of PTSD
Resilience / Recovery
Stress sensitivity
Over-consolidation of fear
Generalization of fear cues
Impaired extinction of fear memories
Stress resistance
Recovery from fear
Discrimination of fear cues
Normal extinction of fear memories
From: Mahan AL, Ressler KJ. Trends Neurosci, 2012, 35:24-35.

181


Prevalence of Trauma and Probability of PTSD
Prevalence of Trauma
Male
Female
%
40
30
20
10
0
Trauma
Accident
Threat w/
Physical
Molestation
Combat
Rape
Probability of PTSD
%
70
60
50
40
30
20
10
0
Trauma Witness
Accident
Threat w/ Weapon
Physical Attack
Molestation
Combat
Rape
Kessler. J Clin Psychiatry. 2000;61(suppl 5):4.
Kessler et al. Arch Gen Psychiatry. 1995;52:1048.

182

Avoidance

The major factor in perpetuating PTSD and contributing to a more chronic course

Avoiding specific trauma triggers; Reminders:

- **People**
- **Situations**
- **Conversations**
- **Media**
- **Medical Treatment**

183

Avoidance

The major factor in perpetuating PTSD and contributing to a more chronic course

Avoiding specific trauma triggers; Reminders:

- **People**
- **Situations**
- **Conversations**
- **Media**
- **Medical Treatment**

184

Amygdala-Level Processing

Rapid, Crude, Generalized
Many false alarms
Non-Responsive to
new "Data"
Outside awareness & Automatic
Beneath the radar of consciousness

185

Watch for Implicit Memory of Trauma

- Notice that….
- Wow! What just happened
- Did you feel the change in….
- Noting somatic communication
  - "The body knows the score"
- Gentle exposure to changing somatic
  - sensory motor experience

186

Research on PTSD Treatments

- Institute of Medicine (IOM) 2007 Review
  - Thorough review of psychotherapy research for PTSD (requested by the VA)
- Treatments not found to have clear empirical support:
  - EMDR, group therapy, hypnotherapy, eclectic, CBT alone….
- Exceptions: review found strong efficacy of exposure:
  - Prolonged Exposure (PE)
  - Cognitive Processing Therapy (CPT)

187

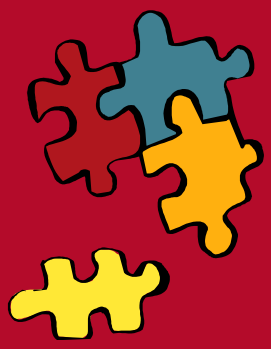
Exposure

- Imaginal exposure (trauma memory)
  - Exposes client to memory of the trauma in structured, controlled way
  - Trauma exposure helps client in two ways:
    - Helps reduce anxiety associated with trauma memory (via extinction of conditioned fear)
    - Helps client organize memory into coherent narrative (calms overactive amygdala)
  - Generally need minimum of 12 sessions (CBT, PE, CPT)
    - CBT approach starts with psychoeducation, anxiety management, and coping skills
    - Minimum 4-6 imaginal exposure sessions (temp. increase of anxiety and re-experiencing symptoms)
    - Cognitive processing of trauma memory & associated meaning (beliefs)
- Situational exposure (CBT & PE)
  - targets avoidance of trauma-related situations (and agoraphobic avoidance)
- Interoceptive exposure
  - Targets “fear of fear” or somatic phobia (treatment for panic disorder)

188

Impaired Information Processing in Post-Traumatic Stress Disorder

Dissociation at time of trauma (encoding)
Fragmented, "jigsaw" memories
images, emotions, bodily sensations, cognitions……
dis-integrated



189

Watch for Implicit Memory of Trauma

- Muscle tension
- Motor impulses
- Heart rate
- Facial expression
- Trembling
- Breathing rate
- Mood changes

190

Dual Processing Theory

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

191

The Explicit system

- Verbally accessible memory (VAM) system—the narrative—autobiographic
  - Can be deliberately retrieved (Brewin, 2005)
  - Cortex and hippocampus
  - Past, present, and future
  - Available to verbally communicate
  - Restricted by attention and arousal
- Traumatized people use the VAM system to evaluate the trauma
  - They ask themselves "could it have been prevented?"
  - "What are the consequences….the meaning?"

192

The Explicit system

- VAM system memories are accompanied by "secondary emotions" (not experienced at the time of the trauma)
  - Directed at the past—i.e. regret or anger about the risks taken
  - Often involves guilt or shame over perceived failure or not preventing the event
  - Thoughts about the future—i.e. sadness at the loss of cherished plans or hopeless at the thought of not finding fulfillment

193

The Implicit System

- Lower level perceptual processing—too briefly apprehended to be bounded together in consciousness memory required for VAMs
  - Sights
  - Sounds
  - Physiological sensations including changes in heart rates, temp, or pain

194

The Implicit System

- Primary emotions—fear, horror, helplessness
- Accounts for flashbacks that can be triggered involuntary by cues related to the trauma (sight/sounds etc.)
- Not structured by verbally coded memories—therefore more extensive
- The more drawn out the trauma, the greater the tendency to experience a range of sensations and emotion
- Difficult to access in therapy

195

Client Education

- Every time you go through this exposure exercise it will get easier.
- The higher parts of your brain, will rewire to put the brakes on the alarm button in the lower part of your brain.

196

Converting traumatic memories into meaning

- Traumatic memories are fragmented and disorganized into “hotspots” which can spur flashbacks
- Hotspots occur where there is maximal functioning separation between SAMs and VAMs (i.e. less integration) (Brewin, 2005)
- They need to be integrated and converted into a coherent and an organized form to reduce the risk intrusions into flashbacks (Ehlers & Clark, 2000; Conway & Playdell-Pearch, 2000)

197

Client Education

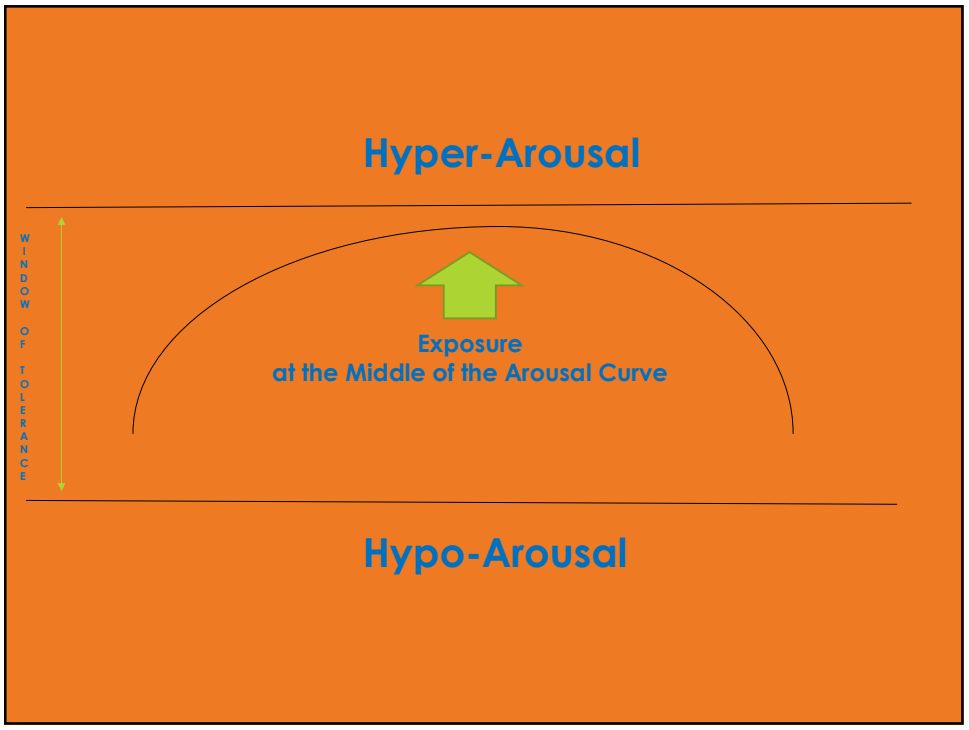
- Step-by-step. I am going to help you expose yourself to the cues that trigger the flashbacks so that you can bring them under control.

198

Explicit and Implicit Integration

- The process needs to be repeated for:
  - Neuroplasticity—the inverted "U"
  - To neutralize the traumatizing quality of the SAM system
  - So that VAMs can compete with SAMs and integrate them
    - The new VAM system puts the SAM system in perspective

199



200

Client Education

- By getting your memory systems in sync, what had triggered flashbacks will fade away.
- Those flashbacks will lose their ever presence and be placed where they belong, in the past as you develop a meaningful future.

201

Continuum of Detachment

- **Traumatized people can experience:**
  - **Mild detachment or absorption: involving a breakdown in the ability to notice outside events and extending to an altered sense of self.**
  - **Moderate detachment: involving feelings of depersonalization and derealization. The person sees himself as if from afar as an observer.**
  - **Extreme detachment: involving a state of unresponsiveness. The person can act catatonic and have no sense of self or time.** (Allen, 2001)

202

Affective Regulation of Condition Emotional Response (CERS)

- The skill of perceiving, labeling, and accepting emotion
- Identifying and modifying thoughts that exacerbate emotions
- Practical action—act in concert with values
- Insight into why/how the emotions are coming up
- Titrate the exposure within the window of tolerance in the middle of the inverse "U"
  - Highest affect in the middle of the session then calm at the intensity curve at the end

203

Exposure

- An activity that provokes or triggers memories of the traumatic event:
  - Repeated or extended (prolonged) to objectively harmless but feared stimulus
  - For at least 20 minutes allows enough time to habituate and enough time to recoup with sufficient support
  - Also allows for the release of BE release
  - Start low—go slow

204

Exposure

Goal—for traumatic memories to lose their power

– a disparity between what a client is feeling (i.e. fear) and the objective reality that there is nothing to fear in the current environment

– Counterconditioning—the presence of positive phenomena that are antithetical to physical or psychological danger. "Cells that fire out of link lose their link." LTD

205

Client Education

- Delay tension reduction behaviors
  - "Urge surfing"-ride it out, they are only temporary
  - Hold off long enough to defuse the power
  - The upsetting feeling will eventually become tolerable
  - Don't try to change the feeling but change your relationship to it.

206

Activation

- Conditioned Emotional Responses (CERs e.g. fear, sadness, or horror)
- CERs are critical to trauma processing to extinguish emotional-cognitive associations to a given trauma memory must be:
  - Activated
  - Not reinforced
  - Counter-conditioned

207

Dissociative Disorders

- Depersonalization/Derealization disorders + persistent or reoccurring experiences of unreality from mind, self, body, and/or surroundings
- Dissociative amnesia – psychogenic inability to recall autobiographical info. Specifier—dissociative
- Dissociative identity disorder (DID)—2 or more personalities with reoccurring memory "gaps" (episodes of amnesia can include possession)

208

Dissociative Dynamics

- Because the development of a coherent and durable sense of self thrives on safety and positive attachment:
  - When interpersonal environment is dangerous hypervigilance and attention is drawn outward away from the development of a coherent self-system
  - Attention inward could be punished
  - Internal representations could be fragmented

209

"Identity Training" from Dissociation

- Therapy entails helping the client build a coherent and positive model of the self by facilitating self-exploration and self-reference
  - Helping the client identify, label, accept feelings, and needs
  - Development of a coherent internal life (DMN) and self-determination (EN)

210

"Identity training" from Dissociation

- Because relational schemas (internal working model—attachment styles) are framed before explicit memory, their implicit nature are "triggered" by situations & feelings states that need reconditioning—activation—reconsolidation
  - Emergent "relational feedback" do not contain the contextual representation of the past (i.e. abuse)
  - "corrective emotional experience" (psychodynamic)

211

PTSD Treatment

- Increased size and activity of DLPFC
- Increased size and activity of the hippocampus
- Decreased activity of the amygdala
- SNS activity within the window of tolerence
- Decreased PICs
- Recalibrated HPA

212

Orienting Response, REM, and Memory

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

213

Orienting and Recoding

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

214

Shifts in attention and asymmetry

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

215

Client Education

- I'm going to ask you to direct your attention to the specific movement while at the same time you describe the traumatic event.
- This will help you reset your brain so that it will no longer be stuck in the past and you can move ahead to a positive future.

216

BBT and PTSD

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

217

SAFE from PTSD

"S" is for stabilizing. To establish a healthy foundation for recovery.

"A" is for acceptance of what happened.

"F" is for future. To visualize a hopeful future--posttraumatic growth.

"E" is for exposure. To confront the feelings and sensations that trigger flashbacks.

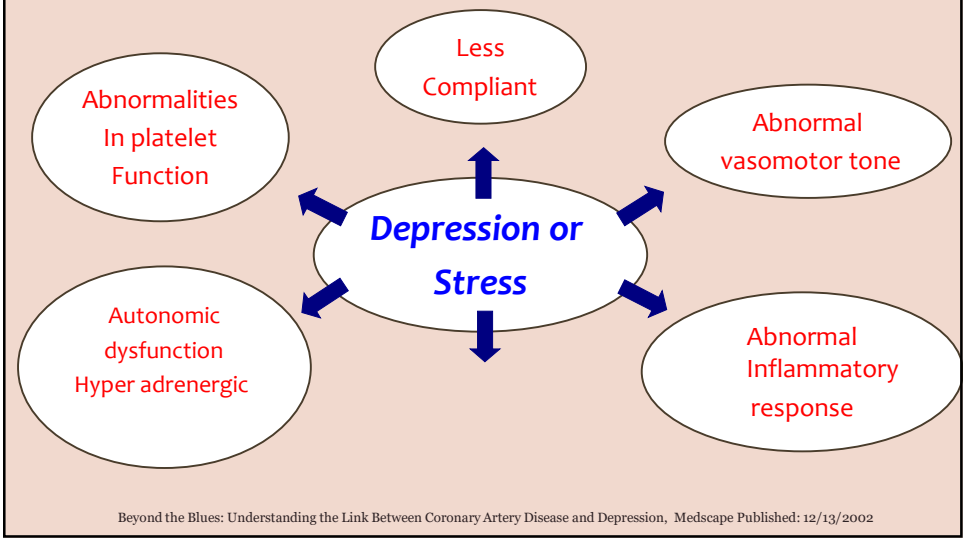
218

Illness and Depression

- Anemia
- Mono
- Asthma
- Diabetes
- Hepatitis
- Congestive Heart Failure
- Hypothyroidism
- MS
- Obesity
- inflammation
- Medications, drugs, and alcohol

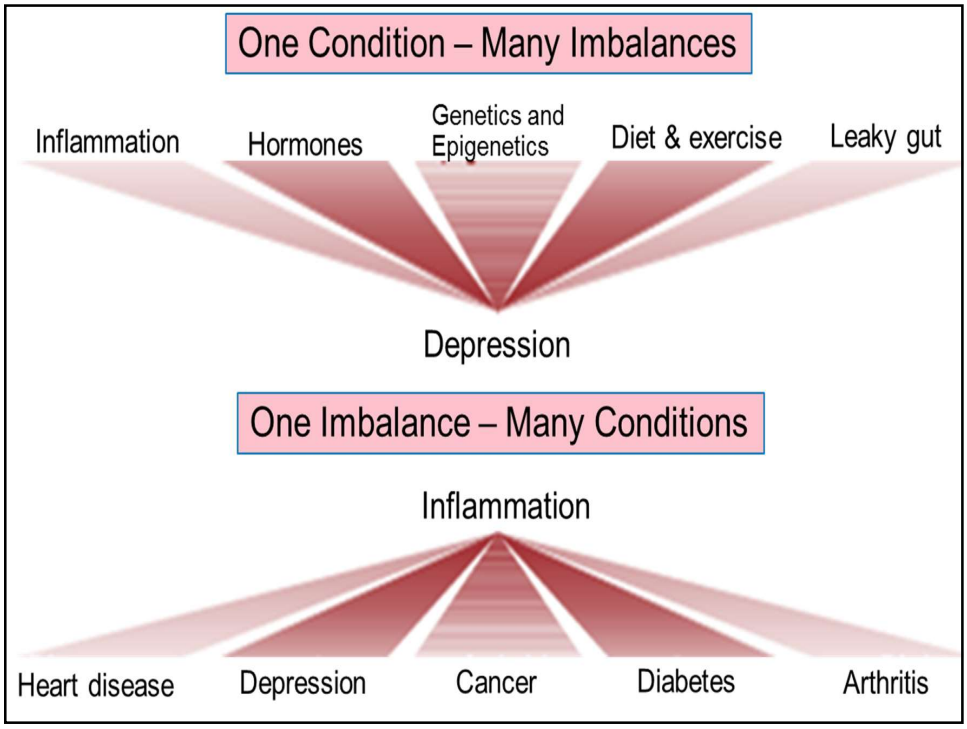
219

Biologically plausible mechanisms linking depression with CHD



Beyond the Blues: Understanding the Link Between Coronary Artery Disease and Depression, Medscape Published: 12/13/2002

220



221

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).

222

- PICs increase the enzyme IDO, which depletes tryptophan
  - Thus, IDO indirectly lowers serotonin.
  - IDO also catabolizes tryptophan into kynurenine and its metabolite, quinolinic acid.
  - IDO and quinolinic acid have been associated with increased suicidality.
- Inflammation- induced quinolinic acid can spur excitotoxicity through direct activation of NMDA receptors.
- Loss of neurons and glia cells in mood- relevant brain areas such as the subgenual ACC has emerged as one of the hallmarks of depression.
- Compromised integrity of the amygdala- ACC circuitry,
  - reduced ACC, amygdala, and hippocampal volumes, are associated with greater risk for depression

223

Symptoms of Sickness Behavior

- Anhedonia
- Feelings of helplessness
- Depressed mood
- Cognitive deficits
- Loss of social interest
- Fatigue
- Low libido
- Poor appetite
- Somnolence
- Pain sensitivity
- Anxiety
- Anhedonia

224

Client Education

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

225

Bidirectional Systems of Depression

- **Mood changes (dysphoria, hopelessness, suicidality, anhedonia, anxiety)**
- **Circadian dysregulations (low drive, energy, appetite, sleep, libido)**
- **Motor deficits (slow movement, restlessness, agitation)**
- **Cognitive impairments (poor attention, working memory, executive functions, ruminations)**

226

Gender Differences and Depression

- **2:1 women > men--** Only Post pubescence
- **Male symptoms –anger, irritability, recklessness**
- **Female symptoms—sadness**
- **4:1—men from suicide**

"Women seek help, men die"

227

Stress Induced Depression

- **↓ DA, NE, and 5-HT as much as 90 minutes post stress** (Irwin, 2000)
- **↓ DA is associated with psychomotor retardation**
- **Psychomotor retardation is associated with ↓ blood flow to the PFC**
- **L-PFC can inhibit negative affect ↓ amygdala activation** (Davidson & Sutton, 1995)

228

Re-balancing Hemispheric Asymmetry

- Instead of putting details into context, depressed patients are overwhelmed by a global negative perspective.
- Creating a constructive and goal oriented narrative generates positive, optimistic emotions which are all products of robust left hemispheric functioning
- Behavioral activation (left PFC) is one of the principal EBPs for depression

229

Effort-Driven Reward Circuit (Lambert, 2008)

- Nucleus accumbens-striatal PFC network
  - ↓ accumbens—loss of pleasure
  - ↓ striatum—sluggishness and slow motor responses
  - ↓ PFC—poor concentration

230

Client Education

- When depressed, if you do what you feel like doing, which is not much, you will become more depressed.
- Inactivity will fuel your depression.

231

Effort-Driven Reward Circuit (Lambert, 2008)

- **PFC activates when you plan an activity**
- **Striatum activates as you do it**
- **Accumbens activates when you feel the pleasure of doing it**
- **All the above increases the sense of self control**

232

Effort-Driven Reward Circuit (Lambert, 2008)

- Kindling this circuit by activities (Behavioral Activation)
  - ↑ DA and 5-HT
  - ↑ positive feelings
  - Reap rewards of problem solving

233

Impaired Hippocampus and Over-generalizing

- The denate gyrus facilitates "orthogonalization" of information, ensuring that new patterns do not interfere with old
- The CA3 region has many connections with other regions
- Impairment in the denate and CA3 results in black-and-white generalizations (Viamentes & Beitman, 2006)

234

Exercise and Depression

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

235

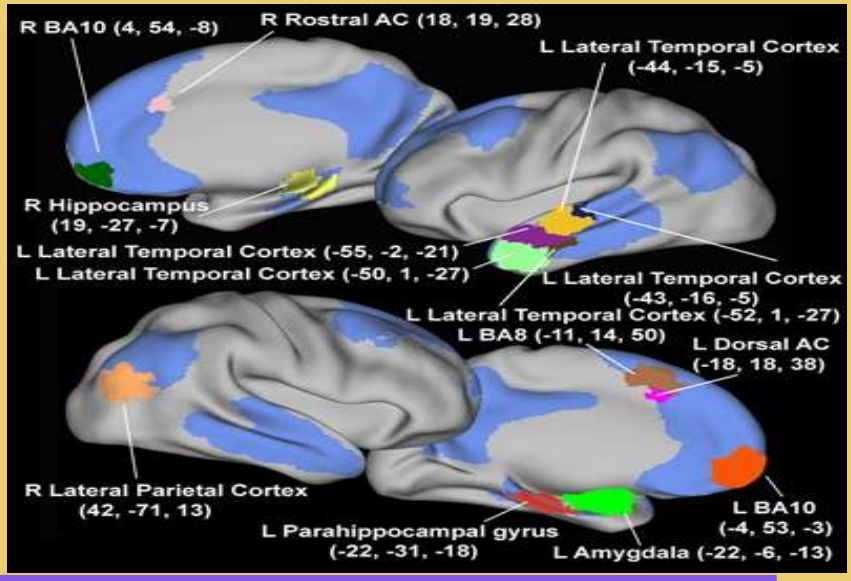
Exercise and Depression

- 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.

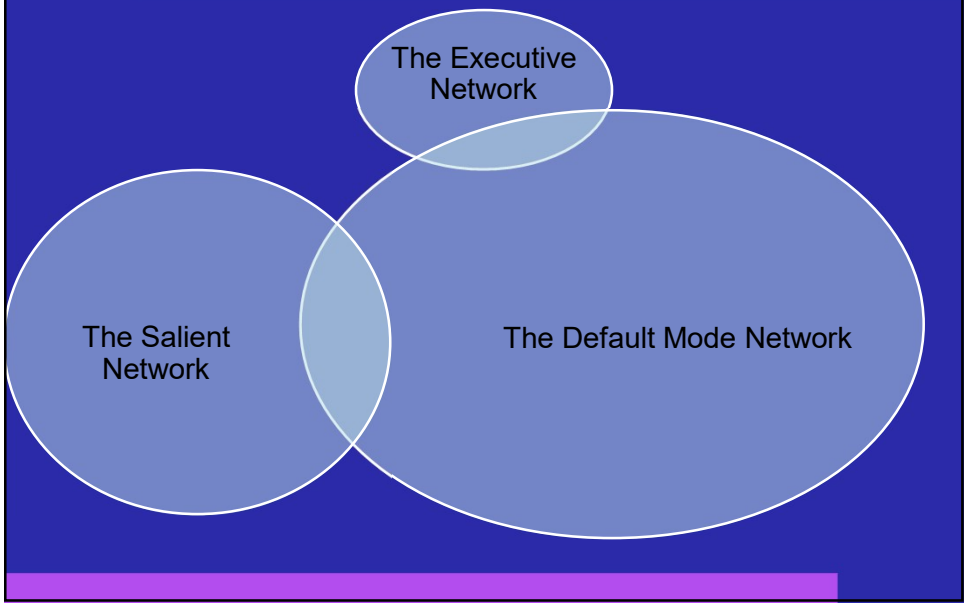
236

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



237

Dysregulated Mental Networks



238

DMN and Depression

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

Ruminations fade with:

- Goal directed behaviors
- Exercise
- Social activities
- mindfulness

239

Client Education

- When you find yourself drifting into ruminations bring yourself back to the present moment.
- Pulling out of the rumination stew and into the now will help you climb out of the black hole of depression.

240

Mindfulness and Depression

Targets depression by neutralizing:

- **Monotony: via attention to novelty and cultivation of curiosity**
- **Ruminations: via wide spectrum thought and detachment**
- **Thinking errors: via affective labeling**
- **Fixations on imperfections: via acceptance**

241

Client Education

- When you have a depressing thought, call it just that, a depressing thought.
- This will help you put distance between the thought and the feeling.

242

Meta-awareness: General Concepts

- **Decentering – thoughts and feelings are events—not realities**
  - Meta-Cognitive Awareness: Change your relationship to the thought.
- **Intentionality – breaking out of automatic thoughts and behaviors**
- **Reducing Avoidance -- facing difficulties**
- **Anti-ruminative – here and now focus not the past or future**

243

Therapy: Mind-Brain-Gene Feedback Loops

Up regulate

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

244

Therapy: Working the Mind-Brain-Gene Feedback Loops

Down regulate

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

245

Therapy: Working the Mind-Brain-Gene Feedback Loops

Interventions that bolster under-active areas of the brain

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

246

Client Education

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

247

TEAM for Depression

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

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

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

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

248

Mindfulness and the Brain

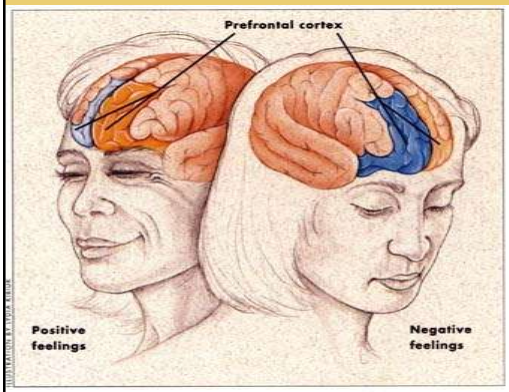
- Long-term meditators show increased thickness of the medial prefrontal cortex and also enlargement of the right insula (Lazar, et al, 2005).
- The process of verbal labeling of affective states reduces anxiety and negative affect (Leiberman, et al, 2004)
- The middle prefrontal cortex has been associated with self observation and mindfulness meditation (Cahn and Polich, 2006).
- A shift to the left PFC which puts a positive spin on the experience (Davidson, et al., 2003).

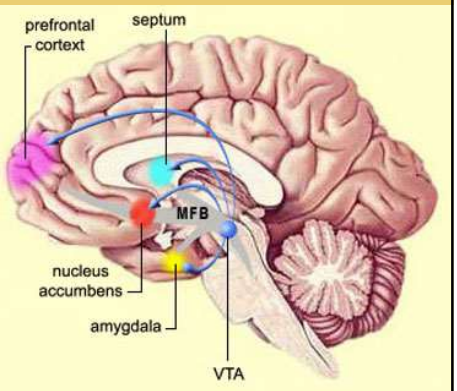
249

Mindfulness: Brain Changes

(Sara Lazar: Harvard, Davidson and Kabat-Zinn, 2003)

- Shifting attention activates prefrontal circuits
- Increase left PFC activation (better affect regulation)





250

Mindfulness for Various Groups

- Borderline via Dialectic Behavior Therapy-DBT (Linehan, 1993)
- OCD (Baxter, et al., 1992)
- Depression (Teasdale, Sigal)
- General medical problems such as chronic pain (Kabit-Zinn, 1990).

251

Mindfulness and Open Focus

- Increases in Gama waves with meditation
- Neurofeedback
  - –Global coherence
  - –Open focus—widened

252

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

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

253

7 Principles of Relaxation

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

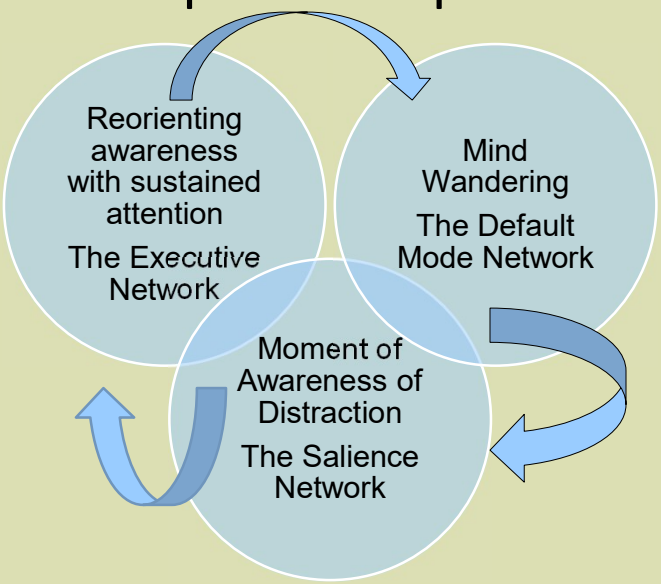
254

7 Principles of Relaxation

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

255

Contemplative Experiences



256

Balancing the Mental Operating Networks

- The forest and trees together—not one or the other
  - A symphony—all pieces in synch
- Not passivity—instead of mindless action -- move with purpose with time
  - Mindful action—Zen is not like chopping wood. Zen *is* chopping wood.

257

Sustaining Positive Habits

- **Pleasure…often fleeting**
- **Positive habits --associated with sustained levels of well being**
  - **But during stressful times: having fun, self-nurturing and humor are the first to go**
- **Ongoing work toward a valued goal**
- **Daily contact with nature**
-

258

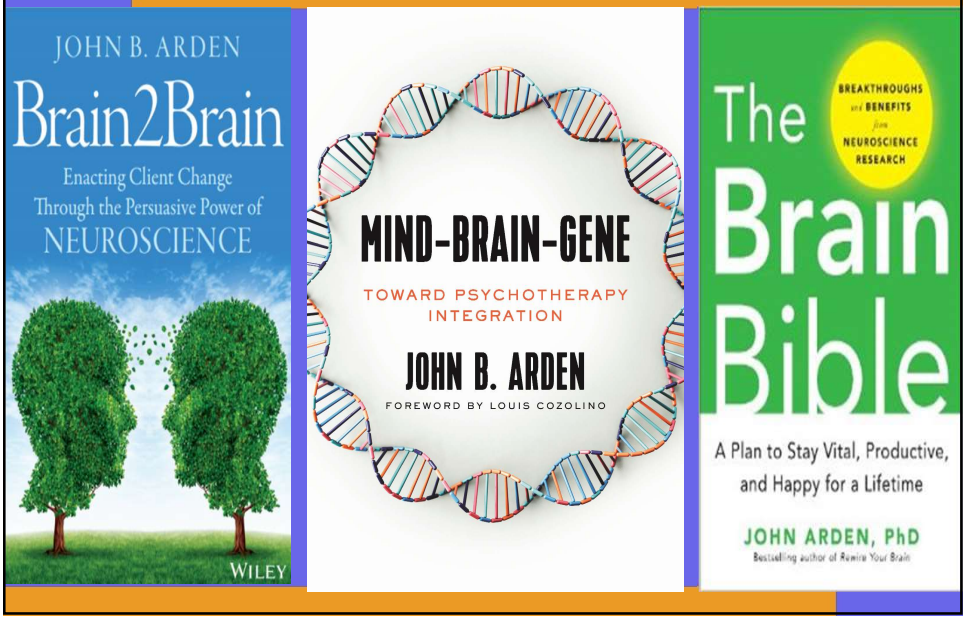
Transcendent Awareness

- Contemplative Attention
- Mindfulness
- Acceptance
- Forgiveness
- Gratitude
- Compassion

»The 9th!

259

References



260

261