Mind-Brain-Gene: Toward Psychotherapy Integration



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Therapy might have been different

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

"The act of will activates neural circuits" --William James

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

Cells and Their Energy Factories



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Use up cell's energy or suffer

- When energy demand is high, electrons flow down the ETC rapidly, the protons are pumped swiftly (the proton reservoir fills up)
 - The greater the reservoir the greater the pressure to form ATP
- However if there is no demand for ATP (but plenty of calories)
 - Proton gradient is too high (reservoir overfills)
 - The ETC backs up and electrons escape and form superoxide free radicals
 - Oxidize lipids and mitochondrial membranes, DNA damage
 - Necrotic cell death (necrosis)—cells swell and rupture
 - Organelles disintegrate and inflammation occurs
 - Consuming 2100—6000 calories per day doubles risk for MCI

Free Radicals

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

Free Radical Damage

MITOCHONDRIA



Epigenetics



Epigenetics

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



Epigenetics in Gene Expression

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

Epigenetics and Attachment

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





Cortisol level

Epigenetics and Decreased Stress

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

Epigenetics and Increased Stress

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



Epigenetics: For Better or Worse

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

Cell Aging: Telomeres Length

- "Psychobiomarker": Linked to social status, perceived stress, depression, loneliness: predictive of mortality (Epel, 2009, Current Directions)
- Telomeres: non-coding sequences capping ends, serving as a:

- "senescence clock" (Blackburn, 1978)

- Telomerase: enzyme that prevents telomere shortening, promotes cell resilience.
- Psychobiomarker": Linked to social status, perceived stress,
- depression, predictive of mortality (Epel, 2009, Current Directions)

Factors that 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

Components of the Immune System

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



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.

cells attack a virus

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



Excessive Cortisol

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



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

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



Proinflammatory Cytokines

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

COVID

- Patients with vascular risk factors such as obesity, hypertension, and diabetes have a more dire outcome as compared to healthy and fit individuals
- Sustained exposure to stress and high level of cytokines in these patients may contribute to a variety of neuropsychiatric and neurocognitive symptoms in the long term
- COVID increases the risk, severity, pace and progression of neurodegenerative diseases such as Alzheimer's and psychological disorders, including depression

Psych Disorders & COVID

- Study of 62,354 COVID cases in the USA:
 - COVID survivors have a significantly higher rate of psychiatric disorders, dementia, and insomnia.
 - Adults have an approximately doubled risk of being newly diagnosed with a psychiatric disorder after COVID diagnosis.
 - The two to three times increased risk of dementia

COVID and Long-COVID

- Dead tissue surrounding blocked blood vessels, found in the brain's gray matter.
 - A blood clot in a blood vessel, it completely obstructs blood flow. Without oxygen, the tissue dies.
- Swarms of immune cells converged around dead or dying neurons. They're actually attacking and eating the neurons
- Microglia are enlarged and signaling inflammation.
 - COVID results in an immune system on steroids!
- This hyper-reaction includes the <u>release of</u> <u>autoantibodies</u>, that end up harming a person's own cells or tissues.

Obesity-Associated Adipose Tissue Inflammation



INFLAMMATION

Obesity, Inflammation, and Diabetes

- Fat cells secrete IL-6
- IL-6 can induce insulin resistance
 Higher IL-6 may predict diabetes type 2



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



Diabetes and Neuropathology

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

Diabetes and Brain Shrinkage



PICs <u>cause</u> 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).

"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,



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

Diabetes and Psychological Disorders

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

 Memory impairment
 dementia



<u>AMYGDALA</u> Implicit Memory System

<u>HIPPOCAMPUS</u> 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."
The Mental Neworks & the Long-Term Memory Systems



The Habit Circuits



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AMYGDALA

HIPPOCAMPUS

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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"

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)

100 Billion Neurons Each with 10,000 synaptic connections



Affect Asymmetry Set points

Left Hemisphere Positive emotions Approach behaviors Feeling

engaged



Right Hemisphere Negative emotions Withdrawal and Avoidance Feeling overwhelmed

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;

Salience Network:

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

The Vagus Nerve System

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



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

DMN--Creativity

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

DMN Variations

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

Central Executive Network:

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

DLPFC and the OFC

Dorsolateral Prefrontal Cortex

Orbital Prefrontal Cortex



Pre-Frontal Cortex

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

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

Normal Sleep Architecture



Awake - Low Voltage - Random, Fast 1 880 Drowsy — 8 to 12 cps — Alpha Waves all an in the at an and the first of the second REM Sleep (D Sleep) - Low voltage - Random, Fast Sawlooth Waves Stage 1 - 3 to 7 cps - Theta Waves Theta Waves Jan Stage 2 — 12 to 14 cps — Sleep Spindles and K Complexes Sleep Sandle amplex -+ | Delta Sleep (S Sleep) - Vz to 2 cps - Delta Waves

Pathologic Changes in Slow wave sleep dep, anx, pain, apne, substance abuse



Brain Clearing

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



Body Temp and Sleep



Perils of the Western Diet

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



Glycemic load (GL) – a measure of rise in blood sugar The higher the GL of a food: the greater the adverse insulin effects Long-term consumption of foods with a high GL leads to a greater risk of: Obesity Diabetes Inflammation Depression

Glycation (excess glucose)

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

Advanced glycation end products (AGEs)

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

Diets styles for longevity:

Okinawan

Mediterranean



Exercise and Depression

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

Exercise Increases Neurotransmitters

NE increases abruptly at exercise

- NE turnover is increased in the frontal cortex and is helpful to alleviate symptoms of ADHD
- 5-HT is modulated by exercise in specific brain regions and is also affected by intensity and duration of exercise.

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

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

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

Effect on C-Reactive Protein

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



Myokines: Anti-inflammatory Cytokines



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

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

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

Brain Derived Neurotropic Factor

•BDNF plays a crucial role in reinforcing neuroplasticity and neurogenesis. It helps:

-Consolidate the connections between neurons.

-Promotes the growth of myelin to make neurons fire more efficiently

-Act on stem cells in the hippocampus and PFC to grow into new neurons

Factors that Decrease Neurogenesis

Aging

Chronically high cortisol

Chronic stress

Recurrent depression

Marijuana

Obesity

Factors that Increase Neurogenesis

Exercise

- play induces BDNF gene expression
- Fasting
- Fewer calories consumed
- Food content --(Omega—3)
- Profound new experience "Ah!"

Exercise and the Brain

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

- Brain development involves many forms:
 - the establishment of synaptic connections
 - the pruning of others
 - changes to the behavior of a single ion channel
 - dendritic outgrowth
 - changes to the shape and number of sprouting new axons
 - modifying their dendritic surfaces (Kolb & Gibb, 2001)

The Effects of Social Medicine

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

Deprived Social Brain Networks

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

Sustained impairment if over one year

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

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).

The Neuroscience of Attachment

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



Planting SEEDS Our Evolutionary Impetrative







Education

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

Diet

Calms nervous system

- ↑Brain chemistry
- ↑ Brain clarity
- ↑ Mood
- ↑ Sleep
- ↑ Energy
- ↑ Alertness
- \uparrow Concentration
- ↑ Ability to focus



Sleep

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

Socialise

Calms nervous system

- ↑ Oxytocin (feel good)
- \downarrow Cortisol (less stressed)
- \uparrow Sense of connection
- ↑ Problem solving
- ↑ Attention
- ↑ Humour and fun
- ↑ Energy

↑ Attention
↑ Chance to socialise

↑ Sleep

Exercise

个 GABA (calm)

↑ Energy levels

Calms nervous system

↑ Serotonin & Dopamine

↑ Growth new brain cells

↑ Alertness and thinking

- ↑ Cardiovascular strength
- \uparrow Physical strength
- ↑ Flexibility & endurance

...AND MUCH MORE...

Contemplative Experiences

Reorienting awareness with sustained attention

The Executive Network Mind Wandering The Default Mode Network

Moment of Awareness of Distraction

The Salience Network

References

JOHN B. ARDEN Brain2Brain

Enacting Client Change Through the Persuasive Power of NEUROSCIENCE



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

Rewire Your Brain 2.0

FIVE HEALTHY FACTORS TO A BETTER LIFE

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