

Neurobiology of Depression And Drug Free Treatments

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Could It Be This Simple? A Biblical Model for Healing the Mind

*The God-Shaped Brain: How Changing Your View of God
Transforms Your Life*

The Journal of the Watcher

The Remedy NT Expanded Paraphrase

*The God-Shaped Heart: How Correctly Understanding God's Love
Transforms Us*

*The Aging Brain: Proven Steps to Prevent Dementia and Sharpen
Your Mind*

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Resource

THE
AGING
BRAIN

PROVEN STEPS TO PREVENT DEMENTIA
AND SHARPEN YOUR MIND

TIMOTHY R. JENNINGS, MD

Major Depressive Disorder

What is it?



Depression

Complex Brain/Body Disease

**Changes in Brain
Circuits**
Functionally and
Structurally

**Neuroendocrine &
Immune changes**

**Changes to Brain
Cells
& Gene Expression**



Factors in Depression

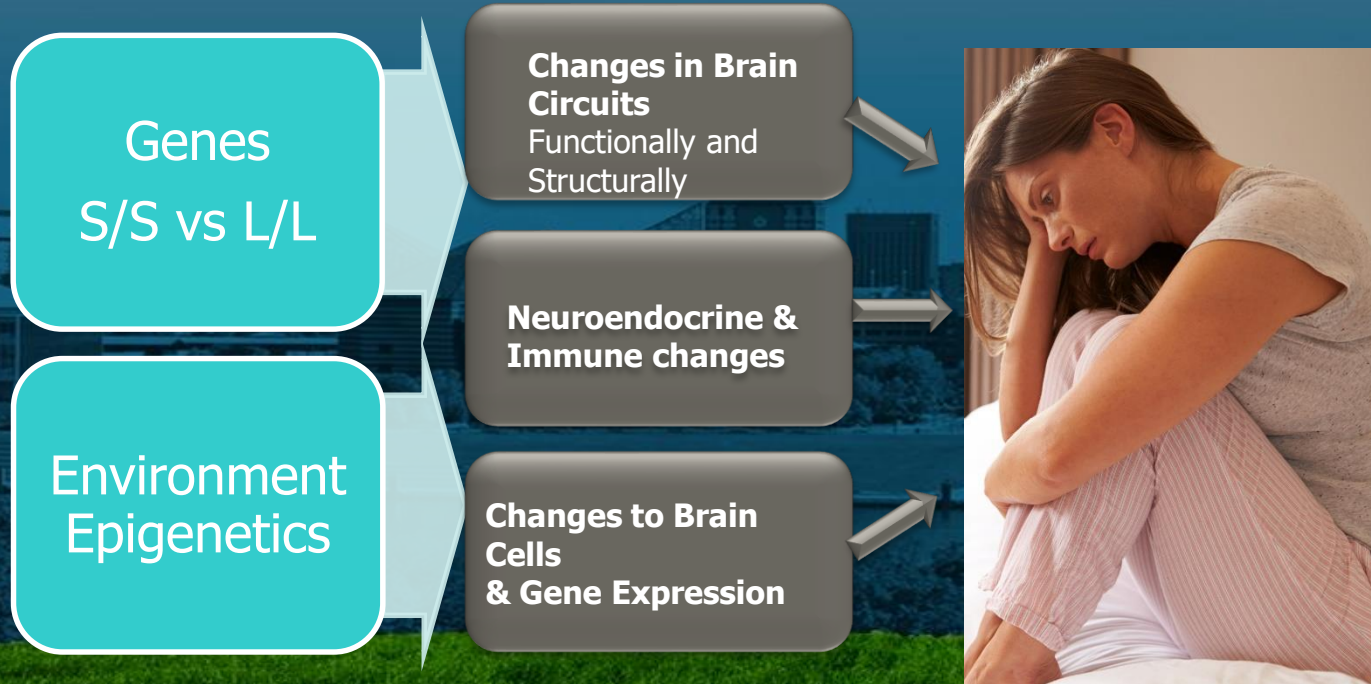
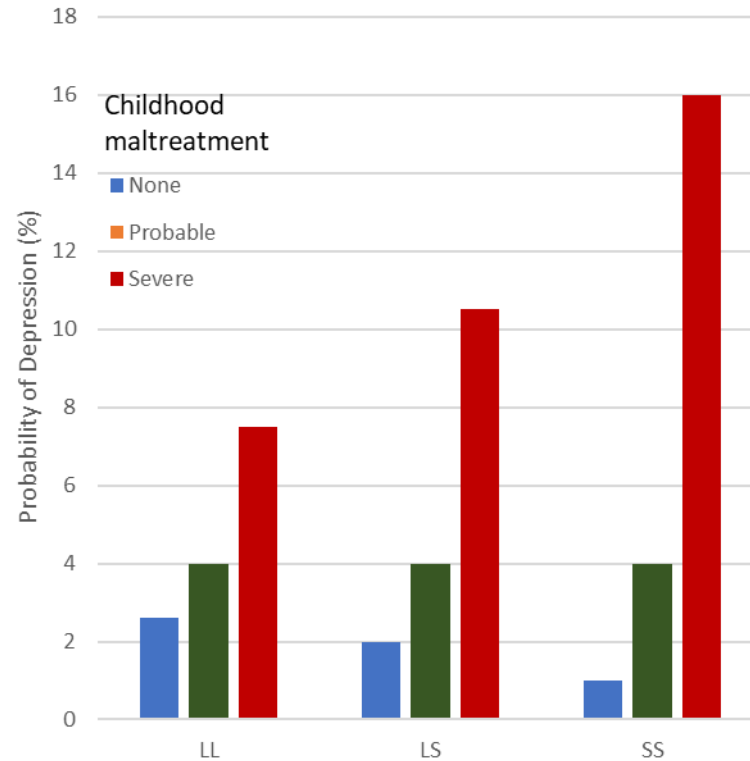
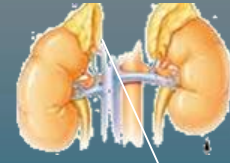


FIGURE 1. Probability of a diagnosis of a Depressive Episode at Age 18/19 for Each Childhood Maltreatment Exposure Group, by 5-HTTLPR Genotype. Adjusted for Gender



Brain Circuits



**Adrenal
Glands**
Emergency
responders

DLPFC
Administrator

Hypothalamus
911 Operator

Pituitary

Amygdala
Alarm

Hippocampus
Fire Chief

Illustration by Simon Harrison

Alterations in Depression

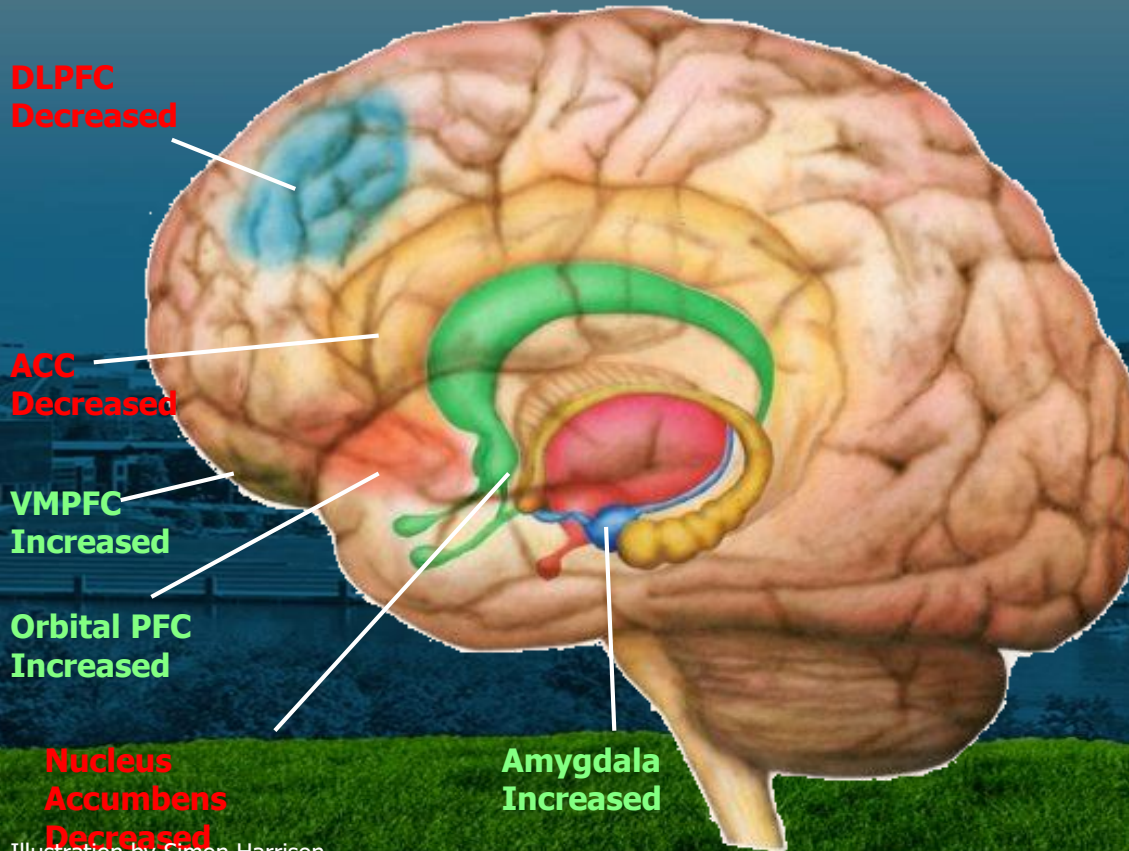


Illustration by Simon Harrison

Anything that Imbalances Brain Circuits Contributes to Depression

- Intrauterine environment – high stress mother vs. low stress mother¹

What if Mother is Stressed While Pregnant?

- Mother's stress hormones cross the placenta
- Interferes with the stress response "braking system"
- This occurs through epigenetic modification
- Children are more stress prone, irritable, moody, and greater vulnerability to depression

Mother's Thinking While Pregnant

- Study of over 4000 mothers and their children
- Followed for over 18 years
- Mothers with negative, pessimistic, depressive thinking patterns when pregnant increased the risk of their child being depressed 18 years later.
- This association remained after accounting for maternal and offspring depression.
- The thought patterns of the mother accounted for 21% of the association between maternal and child depression.

Anything that Imbalances Brain Circuits Contributes to Depression

- Intrauterine environment – high stress mother vs. low stress mother¹
- Stressful childhood environment vs. nurturing environment^{2,3}

1. Medina, J. *Psychiatric Times*, April 2010, p. 16
2. Danese A, et al. *Arch Pediatr Adolesc Med*. 2009;163(12):1135-1143
3. [Nat Neurosci. 2004 Aug;7\(8\):791-2.](#)

The 25-year study, funded by the National Institute of Mental Health

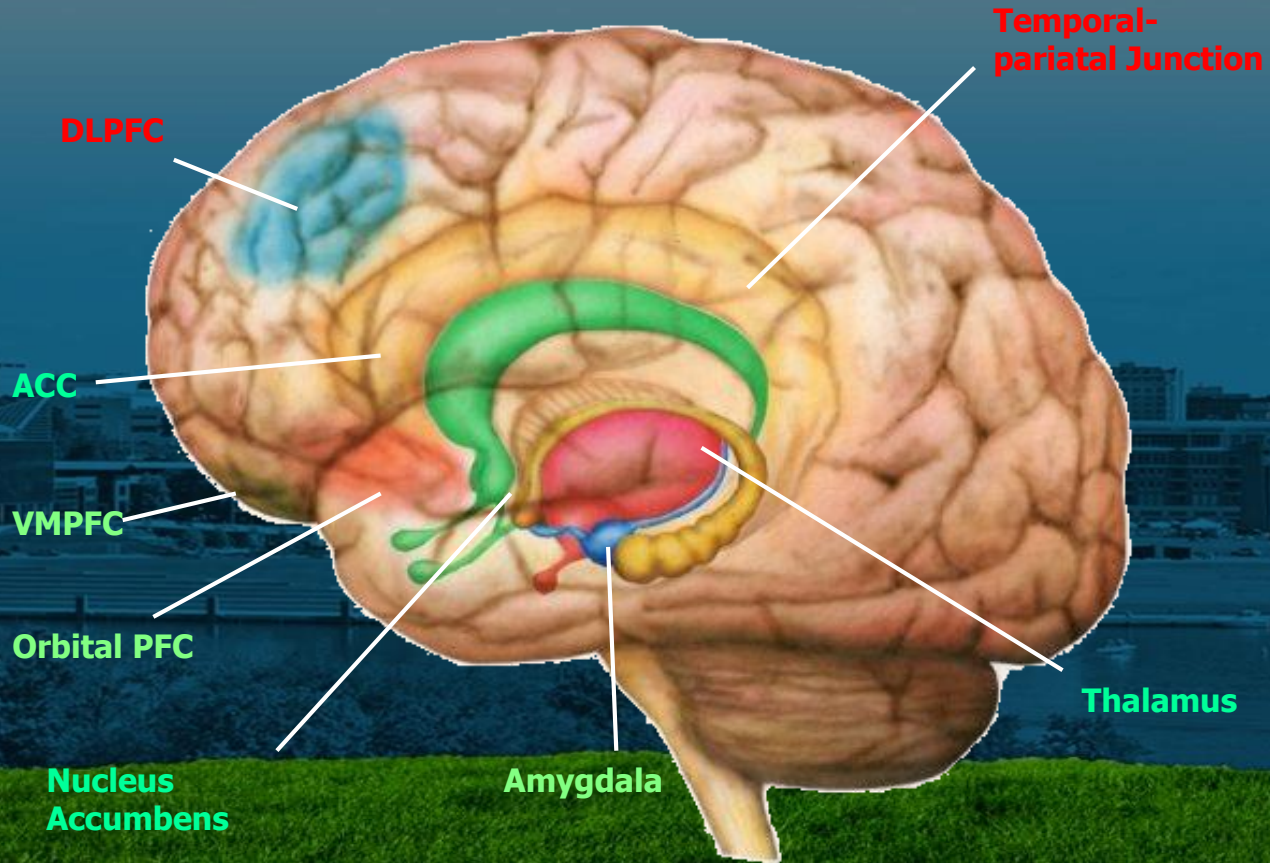
- Family conflict and violence
 - The youths appeared to be more affected by conflict in the home than by marital disruption, divorce or separation.
- Adolescents exposed to family conflict and violence
 - Increased suicidal thoughts
 - Depression
 - Emotional and behavioral problems
 - Drug dependence
 - Have post traumatic stress disorder.

Anything that Imbalances Brain Circuits Contributes to Depression

- Intrauterine environment – high stress mother vs. low stress mother¹
- Stressful childhood environment vs. nurturing environment^{2,3}
- Unresolved guilt, unforgiveness, denial

1. Medina, J. *Psychiatric Times*, April 2010, p. 16
2. Danese A, et al. *Arch Pediatr Adolesc Med*. 2009;163(12):1135-1143
3. [Nat Neurosci. 2004 Aug;7\(8\):791-2.](#)

Salience Network



What Disrupts Salience Network?

- Denial, refusing truth, lies believed
- Exploiting others – guilt and refusing to repent
- Grudge holding and resentment

What if Amygdala doesn't Calm?

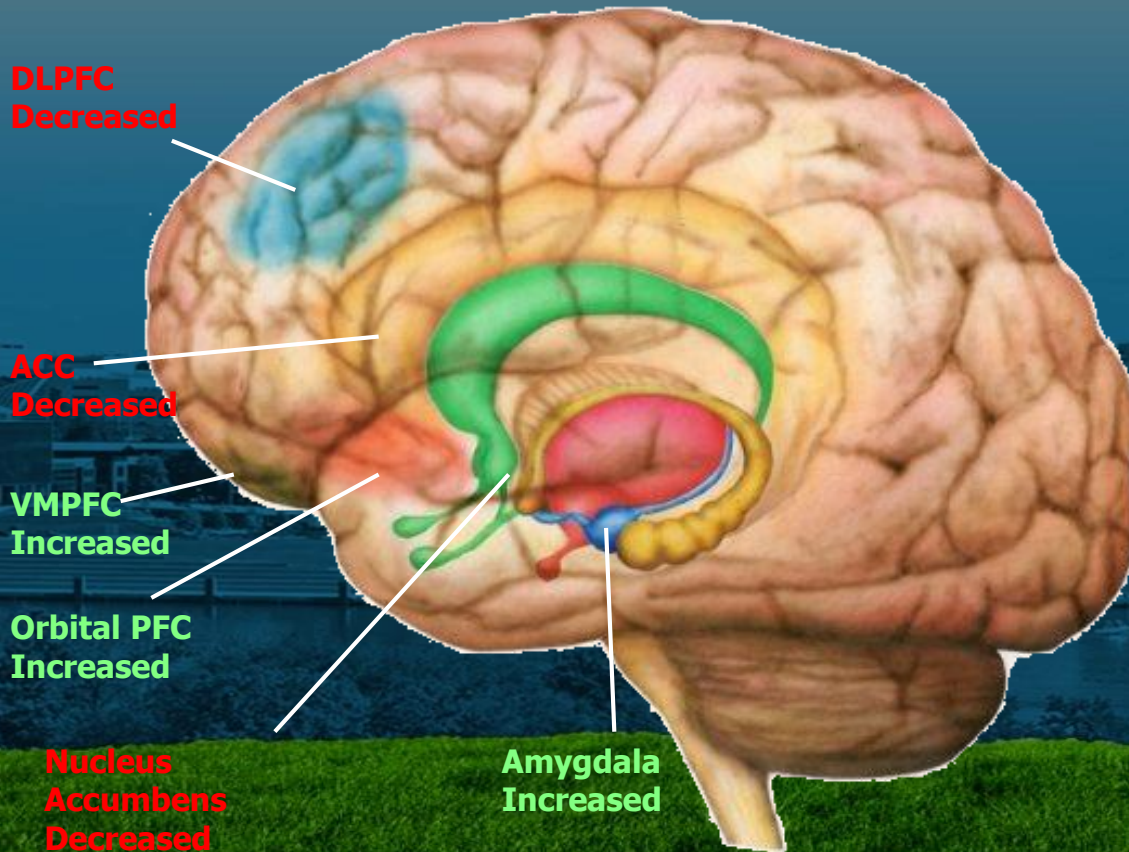


Illustration by Simon Harrison

Over active Amygdala

- Activates sympathetic nervous system
- Which activates macrophages –
 - Why?
- Which release cytokines – IL1, IL6, TNF
- Which damage:
 - Insulin receptors, glucocorticoid receptors, interfere with NE, 5HT, DA signaling
- Resulting in:
 - Increased DM, obesity, high cholesterol, MI, Stroke, autoimmune problems and bone density loss

The Tripartite Synapse: The Role of Astroglia in Signaling

Pictures showed:

Astrocytes make contact with synapses in several regions of the brain in a structure that has been defined as the tripartite synapse, where the astrocytic process is associated with the presynaptic and postsynaptic elements of the synapse

Panel (a) depicts an electron micrograph showing a presynaptic (Pre) and postsynaptic (Post) terminal enwrapped by the astrocytic process (green) forming the tripartite synapse

Panel (b) demonstrates that the close association of the astrocytic process with the presynaptic and postsynaptic terminals exerts crucial roles in clearing K^+ ions that accumulate following neuronal activity and in the uptake of the synaptic transmitter glutamate by the activity of plasma-membrane glutamate transporters

Glia-Neuron Interaction May Influence Neurotrophic Factors

This theoretical model illustrates the effects of the CNS inflammatory cascade on neural plasticity; these effects include

- Diminished neurotrophic support
- Decreased neurogenesis
- Increased glutamatergic activation
- Oxidative stress

Induction of apoptosis in relevant cell types such as astrocytes and oligodendrocytes
Dysregulation of glial-neuronal interactions and cognitive function

Excessive and/or prolonged activation of cytokine networks in the CNS, which can adversely affect neural plasticity, are thought to be relevant to the pathophysiology of depression

Brain Changes during Depression

- Inflammatory factors damage glia
- Glia stop providing support and instead release oxidative factors
- Impaired neurogenesis
- Altered DNA expression
- Loss of neurotrophic factors
- Impaired PFC function
- Thinning of PFC and hippocampal regions

PET Scan

Two pictures showing
the difference between
a depressed and a not depressed brain

Why Do Imbalanced Brain Circuits Lead to Depression?

- Increases inflammation



Anything that increases inflammation increases depression

- Study of 9000 adults examining amount of fast food and junk food consumed (pizza, hamburgers, doughnuts, croissants, candy, cakes etc)
- Those who ate junk food 40% higher rate of depression than those who did not
- Any amt increased risk, dose dependent curve.

Anything that increases inflammation increases depression

- Smoking¹
- Alcohol abuse²
- Drug Abuse³
- DM type 2 increases risk 24%⁴
- Chronic pain⁵

1. Nicotine & Tobacco Research, Volume 19, Issue 1, 1 January 2017, Pages 3–13
2. Volume 106, Issue 5, May 2011, Pages 906–914
3. Arch Gen Psychiatry. 2002;59(11):1039-1044.
4. Diabetologia, December 2010, Volume 53, Issue 12, pp 2480–2486
5. Arch Intern Med. 2003;163(20):2433-2445

If Someone Has Depression Does that Mean...



If Someone Has Depression Does that Mean...

**Depression is Sin?
They are in Sin?
They don't have enough
Faith?**

Interventions

- What is the number one treatment for depression – the most common intervention?
 - Antidepressants
 - How Effective?

STAR*D Study Results

Patients treated in STAR*D were either first episode patients, or treatment-responsive patients. To get into the study, the patient could not have previously been treated with and failed to benefit from any of the options offered in either Level 1 or 2. Patients were recruited from both primary care and specialty psychiatric treatment settings in the United States. About 4,000 patients entered into this study.

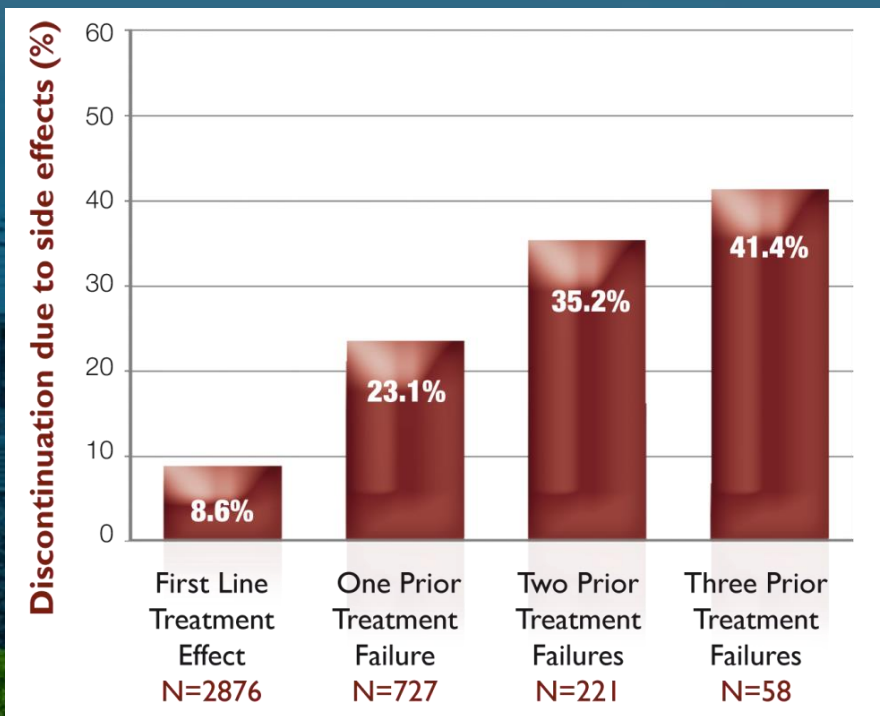
The first Level results showed that in response to an adequate course of treatment with an SSRI (in this study, **citalopram** was the option used) only about 28% of patients were able to achieve remission as measured using the 17 Item Hamilton Depression Rating Scale.

At Level 2, the results are shown for those patients who were offered a switch to another antidepressant of the same or a different class (these options included **sertraline, bupropion SR, or venlafaxine SR**). You can already observe the drop in likelihood of remission, here at about 21% after failure of only one prior adequate antidepressant treatment.

At Level 3, the switch options offered were **either mirtazapine or nortriptyline**, and again the remission likelihood degrades further.

Finally, at Level 4, the switch option offered was the MAOI **tranylcypromine**. Here the likelihood of remission after failure of three prior adequate treatments was 6.9%.

Likelihood of discontinuing treatment increases with each new medication attempt



Systemic Drug Side Effects

- Weight Gain
- Constipation
- Diarrhea
- Nausea
- Drowsiness
- Insomnia
- Decreased Libido
- Nervous Anxiety
- Increased Appetite
- Fatigue
- Headache/Migraine
- Abnormal Ejaculation
- Impotence
- Sweating
- Tremor
- Treatment Discontinuation Side Effects
- Weakness
- Dry Mouth
- Dizziness

Medications



- Circulate throughout body
- Effect multiple receptors and organs causing side effects
- Impact fetus
 - SSRI alter language development¹
 - Paroxetine cardiac defects
 - No increased Autism^{2 3}
- Secreted breast milk

1. *Proc Natl Acad Sci*. Published online October 8, 2012

2. Brown HK, *JAMA* 2017;317(15):1544-1552

3. Sujan AC, *JAMA* 2017;317(15):1553-1562

How Antidepressants Work



Bildet er tatt av Ciker-
Free-Vector-Images by
Pixabay

Medicines ultimately increase BDNF

- Here was a picture of a serotonin receptor and norepinephrine receptor on the cell membrane. Serotonin and norepinephrine bind to these receptors, which are linked to G proteins and an array of second messenger signal transduction systems, which ultimately change gene transcription at the level of DNA.
- The ultimate, targeted increase in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may lead to increased cell survival through synaptogenesis, neuroplasticity, and neurogenesis.
- This is just the opposite of what happens in depression.
- Serotonin and norepinephrine may be gateways to neurogenesis in areas of the brain known to be involved in depression.

PKA = protein kinase A

CaMK = calcium-calmodulin-dependent kinase

CREB = cAMP response element binding protein

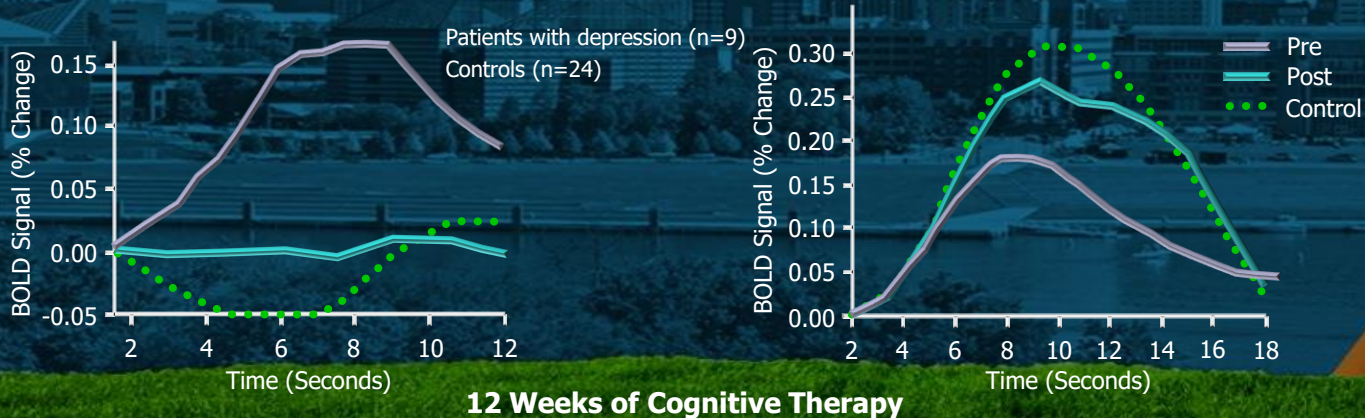
BDNF = brain-derived neurotrophic factor

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear) reconnects the salience network



Impact of Cognitive Therapy on Amygdala and Prefrontal (Dorsolateral PFC) Activity in MDD



12 Weeks of Cognitive Therapy

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social



Loneliness and Gene Expression

- Gene expression in WBC of six lonely people were compared to eight socially connected individuals
- 209 gene differences were identified
- Genes associated with inflammation were upregulated whereas genes that have antiviral roles were down regulated
- Lonely people may be at greater risk for inflammatory and viral diseases¹
- These findings confirmed in separate study of 93 individuals²

1. *Genome Biology* 2007, **8**:R189

2. PNAS vol. 108 no. 7; Cole, 3080–3085, doi: 10.1073/pnas.1014218108

Healthy Relationships Are Protective (NIH Study)

- Family member confidant
 - significantly reduced the risk of overall behavioral and emotional problems by age 18.
 - Females at age 18 who had a family member confidant
 - higher self-esteem and reduced risks of major mental disorders, suicidal thoughts, depression, drug disorders, and overall behavioral problems
 - Males with advice-giving families
 - had better school performance, lower school dropout rates, less depression, behavioral or emotional problems
- Family cohesion
 - males and females had higher grades, greater likelihood in receiving school and community honors, and a reduced risk of numerous problems and some mental disorders. Family cohesion appeared to be especially important for young women in reducing risk of serious mental disorders.

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social



Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
 - Exercise

Exercise

- Increases insulin sensitivity
- Turns on BDNF, Vascular GF, Nerve GF
- Increases endorphins, enkephalins, DA
- 2017 AJP Article 33,908 followed for 11 years
- 1 hour per week of leisure time exercise
- Reduced Depression occurrence by 12%¹

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
 - Exercise
 - Lifestyle changes
 - Nutrition (L-methyl folate, omega 3 Fas, Vit D, NAC)

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
 - Exercise
 - Lifestyle changes
 - Nutrition (L-methyl folate, omega 3 Fas, Vit D, NAC)
 - Avoid junk food and eat a healthy diet

Plant Based Diet Reduces Depression

- 41 studies, 20 longitudinal. Evaluated various diets, Mediterranean diet, the Healthy Eating Index, the Alternative Healthy Eating Index, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Dietary Inflammatory Index.
- Four studies involving 36,556 adults, adherence to a Mediterranean diet, had a 33% decreased risk of depression.
- At the other end of the spectrum, eating a pro-inflammatory diet high in fat, sugar, and processed food was linked with higher depression risk, according to data from 5 longitudinal studies involving 32,908 adults.

Lassale C, Batty GD, Baghdadli A, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Molecular Psychiatry*. 2018 September 26;[Epub ahead of print].

Why Does a Plant Based Diet Reduce Depression?

- Anything that increases inflammation increases depression—so what about decreasing inflammation?
- Anti-inflammatory foods rich in plant fiber, vitamins, minerals, and polyphenols— reduce depression
- At the other end of the spectrum, eating a pro-inflammatory diet high in fat, sugar, and processed food was linked with higher depression risk, according to data from 5 longitudinal studies involving 32,908 adults.

Lassale C, Batty GD, Baghdadli A, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Molecular Psychiatry*. 2018 September 26;[Epub ahead of print].

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
 - Exercise
 - Lifestyle changes
 - Nutrition (L-methyl folate, omega 3 Fas, Vit D, NAC)
 - Avoid junk food and eat a healthy diet
 - Sleep

Sleep

- OSA – Cognitive impairments, mood disorders and loss of gray matter which reversed with treatment¹
- Sleep disorders double the risk of depression²
- During sleep the brain cells contract expelling metabolic waste and increasing clearance from brain, including beta amyloid³

1. American Journal of Respiratory and Critical Care Medicine, Vol. 183, No. 10 (2011), pp. 1419-1426. doi: [10.1164/rccm.201105-0693OC](https://doi.org/10.1164/rccm.201105-0693OC)
2. *Archives of Internal Medicine*, vol 16, p 1709
3. Science 18 October 2013: Vol. 342 no. 6156 pp. 373-377 DOI: 10.1126/science.1241224

Low Level Light At Night

- Elderly who sleep with low light; higher rate depression than those in darkness
- How much light? – 5 lux
- Family room lights 50 lux
- Streetlights 20-50 lux
- Full moon 0.5 – 1.0 lux

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
 - Exercise
 - Lifestyle changes
 - Nutrition (L-methyl folate, omega 3 Fas, Vit D, NAC)
 - Avoid junk food and eat a healthy diet
 - Sleep
 - Eliminate toxins (alcohol, drugs)

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
 - Exercise
 - Lifestyle changes
 - Botox
 - TMS

Neurostar TMS by Neuronetics FDA Cleared since 2008



Transcranial Magnetic Stimulation (TMS)

This slide showed a schematic example of the targeted action of a TMS coil.

At a practical level, a TMS coil generates strong, MRI-strength, rapidly pulsed magnetic fields. The magnetic field remains sufficiently strong to a depth of about 2-3 centimeters into the brain as it extends away from the face of the TMS magnetic coil. This rapid magnetic pulsing in turn induces an electrical current in an adjacent electrical conductor.

- The treatment coil produces MRI-strength magnetic field pulses.
- Magnetic field pulses pass unimpeded through the cranium for 2-3 cm. and induce a small electric current.
- Induced electric currents stimulate the firing of nearby neurons, causing the release of neurotransmitters and clinical effects.

Targeted Effects on Mood Circuits in Brain

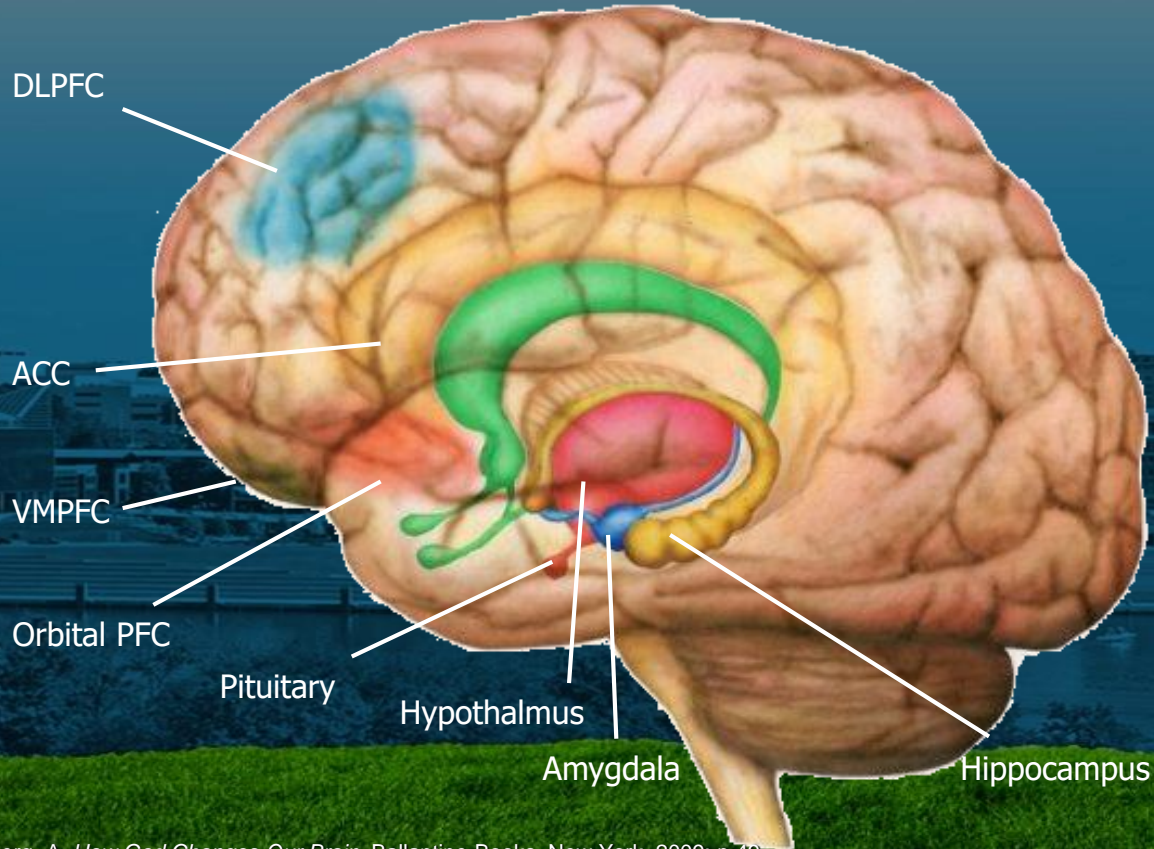
This slide showed all of these scientific principles in action in a group of patients (N=12 males) with major depression who have received a course of TMS to their left prefrontal cortex. These pictures represent images from a SPECT (single photon emission computed tomography) scan of the aggregate results in these patients, looking at the areas of the brain that showed changes in cerebral blood flow that correlated with improvement in symptom ratings, as measured by the Hamilton Depression Rating Scale.

Activation of fronto-cingulate brain circuit following a course of TMS applied to the left dorsolateral prefrontal cortex in patients with Major Depression

Non Drug Interventions

- Think – what are the Contributing Factors
- Psychotherapy which activates PFC teaching people to reason, think, problem solve and discern (bring truth to bear)
- Social
- Somatic
- Spiritual

God Construct Changes Brain



Altruism

- Adults who volunteer (after accounting for variables such as education, baseline health, smoking, etc.)
 - Live longer, have less illness, less disability, less depression, less dementia and live independently longer than those who did not.¹

1. Post, S. *Altruism and Health Perspectives from Empirical Research*, Oxford University Press, New York, 2007: p. 22, 26).

How Healthy Spirituality Helps Slow Aging

- Activates PFC and ACC, calms amygdala, lowers inflammatory response resulting in improved mental and physical health
- Altruistic activities result in better mental and physical health
- Reduced anxiety and worry
- Healthier lifestyle so reduced oxidative stressors
- Healthier relationships lower stress

Summary

- Depression is a debilitating illness, with damaging changes to brain and body
- Antidepressants alone are often inadequate to effectively treat depression
- There are various non-drug treatments available for treating depression
- Treatment should be individualized

QUESTIONS

