Pathophysiological hypotheses of Major Depressive Disorder III

i. Neurotransmitter “imbalance” (monoamines)
ii. Neural network and neuroendocrine
iii. Inflammation ***Rubor,Tumor, Calor, Dolor, Functio Laesa***
iv. Neurogenesis related

Linking together disparate pathophysiologies: Inflammation in depression

- Inflammation is *another* ancient **defense** – the first-line, ready-to-go response to pathogen attack. (Innate immunity)
- Why might **mechanisms** be shared between **depressed mood** and inflammation?
  - We must go "way down" to "*The Foundation of Mood*": The *condition of the organism was* also predicted, theoretically, to affect mood .
- Mechanisms for coping with **social** attack (low status, rejection, shunning) may be "rigged together" with mechanisms for coping with **pathogen** attack.
- Being depressed is like being sick...

Clues that link inflammation to depression From animal models:

- Injecting bacterial endotoxin ("LPS") elicits a defensive inflammatory response that includes "sickness behavior": Decreased self-care, decreased social interaction, lethargy, and anorexia. (Sounds like a **Defense** – a kind of adaptive "low mood" behavior...)
- Laboratory model stressors that cause "depression-like behavior" **also** affect inflammatory cytokines.

Go figure... yet another negative effect of social defeat stress is a *leaky blood–brain barrier* ("neurovascular pathology"). This "leak" allows inflammatory factors to *penetrate the brain*, especially around the nucleus accumbens (NAc) - an area central to *motivation*. (Sounds like a **Defect**...)

Clues that link inflammation to depression From human, medical observations:

- There is a high comorbidity of depression and inflammatory diseases.
- There are elevated inflammatory blood markers in *(many cases of...)* depression. Markers such as tumor necrosis factor (TNF), interleukins (IL) 1 and 6 and the acute phase protein C-reactive protein (CR)
- Pro-inflammatory *treatments* (such as interferon for hepatitis C) often precipitate depression.

If (normal low mood) is an adaptations to **social** trouble. why do we see causal links between inflammation and depression?

- Some theories say there **is** an adaptationist logic: **The Social Transduction Theory of Depressed Mood** notes that social stressors such as *targeted rejection* **up-regulate** pro-inflammatory immune response genes (while down-regulating antiviral immune response genes).
  - This would be a **Defense -** a re-deployment of immune system "soldiers" to prepare for ostracism, attack, wounding, and bacterial infection.
  - Inflammatory cytokines affect the brain and elicit sickness behavior – a behavioral program very similar to depression.

Neuroscience & Biobehavioral Reviews, 35(1), 39-45.Slavich, G. M., O'Donovan, A., Epel, E. S., & Kemeny, M. E. (2010). Black sheep get the blues: A psychobiological model of social rejection and depression. Neuroscience & Biobehavioral Reviews, 35(1), 39-45.

The YES adaptationist logic camp:

The Social Transduction Theory of Depressed Mood, in

Psychological Bulletin
2014, Vol. 140, No. 3, 774–815

0033-2909/14/$12.00 DOI: 10.1037/a0035302

From Stress to Inflammation and Major Depressive Disorder: A Social Signal Transduction Theory of Depression

George M. Slavich and Michael R. Irwin
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Major life stressors, especially those involving interpersonal stress and social rejection, are among the strongest proximal risk factors for depression. In this review, we propose a biologically plausible, multilevel theory that describes neural, physiologic, molecular, and genomic mechanisms that link experiences of social-environmental stress with internal biological processes that drive depression pathogenesis. Central to this *social signal transduction theory of depression* is the hypothesis that experiences of social threat and adversity up-regulate components of the immune system involved in inflammation. The key mediators of this response, called *proinflammatory cytokines*, can in turn elicit profound changes in behavior, which include the initiation of depressive symptoms such as sad mood, anhedonia, fatigue, psychomotor retardation, and social-behavioral withdrawal. This highly conserved biological response to adversity is critical for survival during times of actual physical threat or injury. However, this response can also be activated by modern-day social, symbolic, or imagined threats, leading to an increasingly proinflammatory phenotype that may be a key phenomenon driving depression pathogenesis and recurrence, as well as the overlap of depression with several somatic conditions including asthma, rheumatoid arthritis, chronic pain, metabolic syndrome, cardiovascular disease, obesity, and neurodegeneration. Insights from this theory may thus shed light on several important questions including how depression develops, why it frequently recurs, why it is strongly predicted by early life stress, and why it often co-occurs with symptoms of anxiety and with certain physical disease conditions. This work may also suggest new opportunities for preventing and treating depression by targeting inflammation.

Keywords: early life stress, social threat, cytokines, mechanisms, disease

Depression is among the most common and costly of all psychiatric disorders. Nearly one in four women and one in six men experience depression during their lifetime (Kessler et al., 2010), and up to 65% of individuals have recurrent episodes of the disorder (Eaton et al., 2008; Monroe & Harkness, 2011; Yiend et al., 2009). Compounding the issue is the fact that many people with depression never receive diagnosis or treatment, and only about 30%–35% of adults achieve remission using current therapeutic approaches, leaving over two thirds of the disease burden intact (Alexopoulos, 2005; Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004; Chisholm, Sanderson, Ayuso-Mateos, & Saxena, 2004; Roose & Schatzberg, 2005). These features contribute to substantial social and economic burden (Greenberg et al., 2003; Vos et al., 2004). In fact, depression has been estimated to be the fourth leading cause of overall disease burden and the leading cause of nonfatal disease burden worldwide (Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Identifying biobehavioral factors that can be targeted for preventing and treating depression is thus of paramount public importance.

Central to most contemporary theories of depression is the notion that stress can initiate cognitive and possibly biological processes that increase risk for the disorder (Beck, 1967; Blatt, 2004; Brown & Harris, 1978). Consistent with these theories, major stressful life events are one of the best predictors of an impending onset of depression (Kendler, Karkowski, & Prescott, 1999; Kessler, 1997). Indeed, certain life events, such as those involving social rejection, confer a 21.6% increase in risk for onset of major depressive disorder (MDD; Kendler, Hettema, Butera, Gardner, & Prescott, 2003). Whereas an abundance of research has examined cognitive processes that may mediate the link between stress and depression (Gotlib & Joormann, 2010; Kircanski, Joormann, & Gotlib, 2012), though, relatively little is known about the biological processes that are influenced by stress and that, in concert with cognitive and affective processes, may lead to depression.

The development of tools for assessing neural activity, peripheral biology, genetic variation, and gene expression has been

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If (normal low mood) is an adaptations to **social** trouble. why do we see causal links between inflammation and depression?

- Some theories say there is **NO adaptationist logic,** reminding us that...

  *"...when diseases have been common in human populations for many generations and still have a substantial negative impact on fitness, they are likely to have **infectious causes**... "* Infectious Causation of Disease: An Evolutionary Perspective; Gregory M. Cochran, Paul W. Ewald, and Kyle D. Cochran, 202

- **The Pathogen-Host Defense Theory of Depression (PATHOS-D)** claims...
  - , "... the genes that subserve (depression), evolved to help us manage... **pathogens** ...Across evolutionary time, inflammatory responses and depressive symptoms were part of **an integrated adaptive response to pathogens"** A., Raison, C. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* **16**, 22–34 (2016). https://doi.org/10.1038/nri.2015.5

The NO adaptationist logic camp, in:

The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D)

Open

Molecular Psychiatry (2013) 18, 15–37

www.nature.com/mp

HYPOTHESIS

The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D)

CL Raison[1,2] and AH Miller[3]

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Given the manifold ways that depression impairs Darwinian fitness, the persistence in the human genome of risk alleles for the disorder remains a much debated mystery. Evolutionary theories that view depressive symptoms as adaptive fail to provide parsimonious explanations for why even mild depressive symptoms impair fitness-relevant social functioning, whereas theories that suggest that depression is maladaptive fail to account for the high prevalence of depression risk alleles in human populations. These limitations warrant novel explanations for the origin and persistence of depression risk alleles. Accordingly, studies on risk alleles for depression were identified using PubMed and Ovid MEDLINE to examine data supporting the hypothesis that risk alleles for depression originated and have been retained in the human genome because these alleles promote pathogen host defense, which includes an integrated suite of immunological and behavioral responses to infection. Depression risk alleles identified by both candidate gene and genome-wide association study (GWAS) methodologies were found to be regularly associated with immune responses to infection that were likely to enhance survival in the ancestral environment. Moreover, data support the role of specific depressive symptoms in pathogen host defense including hyperthermia, reduced bodily iron stores, conservation/withdrawal behavior, hypervigilance and anorexia. By shifting the adaptive context of depression risk alleles from relations with conspecifics to relations with the microbial world, the Pathogen Host Defense (PATHOS-D) hypothesis provides a novel explanation for how depression can be nonadaptive in the social realm, whereas its risk alleles are nonetheless represented at prevalence rates that bespeak an adaptive function.
Molecular Psychiatry (2013) **18,** 15–37; doi:10.1038/mp.2012.2; published online 31 January 2012

Keywords: major depression; evolution; immune; inflammation; infection; genetic

Introduction

Major depression is so detrimental to survival and reproduction that it is hard to understand why allelic variants that promote the disorder have not been culled from the human genome, why in fact—far from being culled—genes that promote depression are so common and numerous and appear to have actually increased in prevalence during recent human evolution.[1] To address this issue, we have developed a novel theoretical framework positing that risk alleles for depression originated and have been largely retained in the human genome because these alleles encode for an integrated suite of immunological and behavioral responses that promote host defense against pathogens. This enhanced pathogen defense is accomplished primarily via heightened innate immune system activation, which results in reduced death from infectious causes,[2–5] especially in infancy when selection pressure from infection is strongest,[6] and the adaptive immune system is not yet fully operational.[6–9] A vast literature has associated depressive symptoms and/or major depressive disorder (MDD) with increased innate immune inflammatory responses,[10] with meta-analyses reporting the most consistent findings for increased plasma concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein and haptoglobin.[11–13] Recent longitudinal studies extend these cross-sectional observations by reporting that increased inflammatory markers in nondepressed individuals predict the later development of depression.[14–16] Because infection has been the primary cause of early mortality and hence reproductive failure across human evolution,[9,17–21] it would be expected that if depressive symptoms were an integral part of a heightened immunological response, allelic variants that support this response would have undergone strong positive selection pressure and thus would be both numerous and prevalent, as they appear to be. However, because

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Takeaways

Just like normal **stress responses** and normal inflammation are **Defense** systems that can go awry and become diseases (**Defects)...**

...so too is *non-disordered depressed mood* a **Defense** that can become depressive disorder (**Defect)**

Stress, the Evolution of Mood and Clinical Depression

For UC Berkeley IB 139, Fall 2022

Julio Ozores, M.D.

Four Days, Six Questions

- Day One: *Why do animals have moods?*
- Day Two: *How did animals evolve depressed mood as an adaptive response to social stressors?*
- Day Three: *Why and how does mood regulation go awry in the human depressive mood disorders?*
- Day Four: *How is disordered depressed mood treated? Why is there an increasing prevalence of depression in "Gen Z"? What to do about it?*

Treatments for depressive disorders
Standard, "Approved", Professional…

- **Psychotherapy**
  - Cognitive Behavioral (CBT), Interpersonal (IPT), Behavioral Activation (BAT), Psychodynamic
- **Antidepressant Medications**
  - For their "bottom-up" pharmacological effect on neurobiology.
  - For their "top-down" **placebo** effect on psychology
- **A <u>combination</u> of psychotherapy and antidepressant medications ✓**

- Brain Stimulation Therapies:
  - **Electroconvulsive (ECT)**
  - **Transcranial Brain Stimulation (TMS)**
  - Deep Brain Stimulation (DBS) (not FDA approved *for depression*)
- Botulinum toxin ("Botox") (not FDA approved *for depression*)

*We'll be discussing **Psychotherapy**, **Antidepressant Medications**, **ECT** and **TMS***

Treatments for depressive disorders that either have 1) "Do-it-yourself" appeal, or 2) Alternative treatments *sometimes* worth trying

- **Social Support**
- **Exercise**
- **Self-Help**:
  - Books, web sites, apps
- Nutritional and Herbal
  - Nutritional: Omega-3- fatty acids, SAMe
  - Herbal: St. John's Wort, saffron
- Light therapy
- Sobriety

*We'll be discussing **Social Support, Exercise**, and **Self-Help** as <u>prevention</u>.*

Everyone says "therapy" – but what kind? 1) "Psychodynamic" ?

- "**Your average therapy**" in the community, often dubbed "psychodynamic", is likely to include...
  - ...a *blend* of therapeutic strategies: Support, advice, confrontation, interpretations to enhance insight into repetitive maladaptive behavior patterns, clarification of interpersonal conflicts, guidance in role transitions.
    - Well-rounded therapists will *add* special interventions for special issues – trauma, self-harm, substance use, eating disorders, panic, autism spectrum social deficits, etc.

Plus and Minus

The "*Psychodynamic Plus*": Idiographic attention to *your* life-jam, *your* quirks, *your* depressogenic precipitants. May foster insight and personal growth.

The "*Psychodynamic Minus*" : Can meander endlessly and passively. No targeting of depression symptoms *per se*, nor cognitive patterns that perpetuate depression. Less evidence base for depression.

Everyone says "therapy" – but what kind?
2) Cognitive Behavioral Therapy (CBT)

- **A structured therapy** that *does* target depressive cognitive distortions and behavioral patterns that *perpetuate* depressive states.
- **CBT** promotes *learning skills* to "step aside" and evaluate your "automatic thoughts". Usually involves homework that "keeps the fire going" between sessions.
- Well-rounded CBT therapists do go beyond "the cookbook" and modify techniques to account for your idiosyncratic life-jam and quirks – but less so than psychodynamic therapists.

Plus and Minus

The "*CBT Plus*": A defined course of psychological learning targeted to relieve depression. More active. Considered "the gold standard"

The "*CBT Minus*": Less emphasis on your idiosyncratic life stressors and conflicts , on solving real-life dilemmas, and on predisposing factors.

Obstacles that often come up in any therapy

- Depressive symptoms *cause each other*, snagging the patient in vicious circles.
  - Example: Low *self-esteem* and guilty rumination result in the patient feeling he/she ***doesn't deserve*** to get better.
  - Example: Low energy, anhedonia make exercise or rewarding activities feel impossible.
- Socioeconomic obstacles:
  - Example: Unemployment and unstable housing are associated with worse outcomes *regardless of kind of treatment.* (Socioeconomic Indicators of Treatment Prognosis for Adults With Depression: A Systematic Review and Individual Patient Data Meta-analysis. JAMA Psychiatry.2022)

Try doing CBT at a ZSFGH...

- Other obstacles:
  - The patient is socially isolated.
  - The psychiatrist (or other clinician) fails to instill hope, trust, allyship:

"***Meanings***, such as the ***relationship*** with the prescribing psychiatrist, have ***more effect on the variance in depression improvement*** than the choice of medication" (Psychiatrist effects in the psychopharmacological treatment of depression J Affect Disorders, 2006)

Medications: The better-known antidepressants in historical order

Notice: All work modifying the action of the "monoamines"

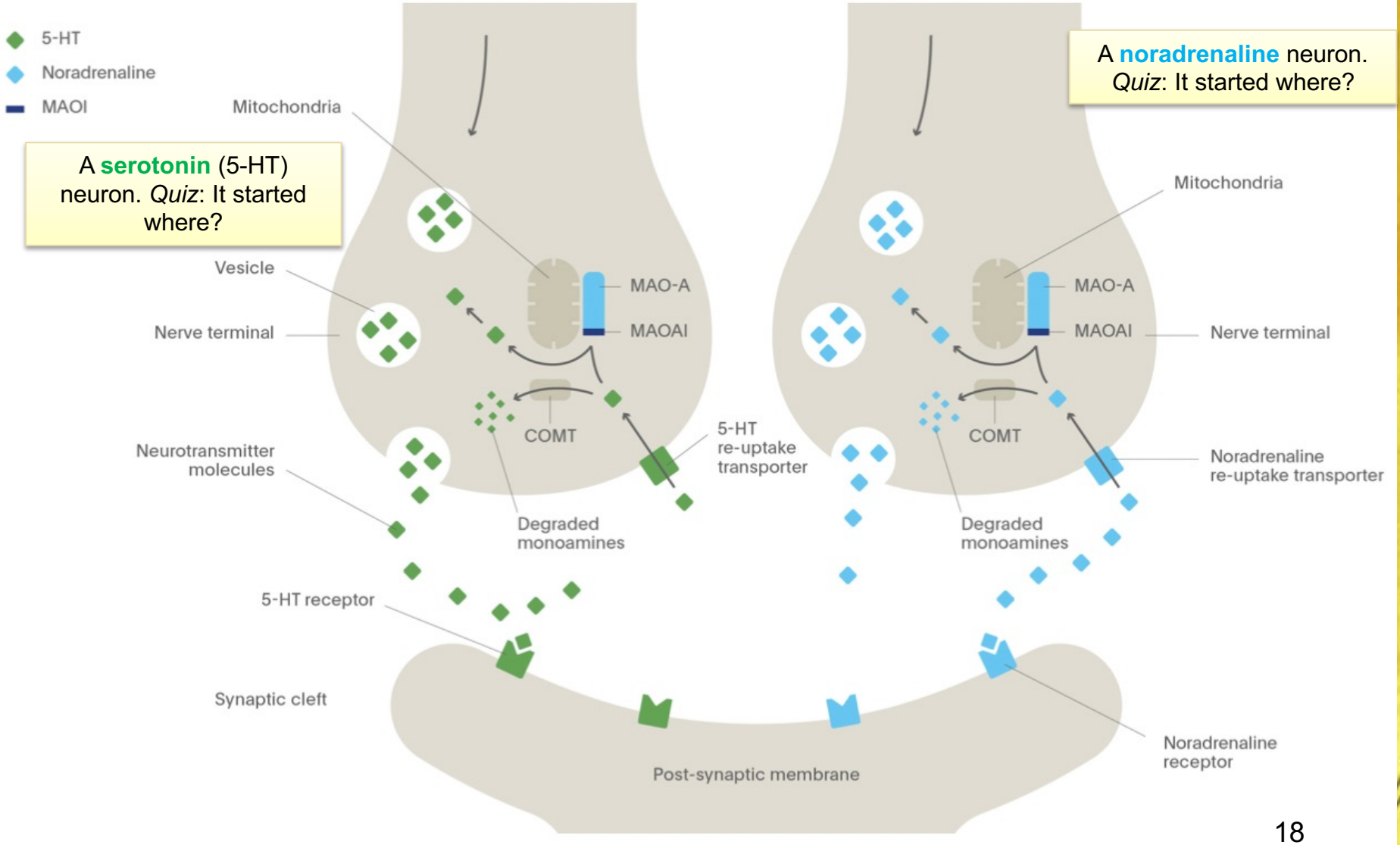
- **Old (1958-1987)** (A live history: Dr. O's birth-to-end-of-residency period...)
  - **Tricyclics** (imipramine, desipramine...) Reuptake inhibtion of serotonin and norepinephrine
  - **Monoamine Oxidase Inhibitors (**Nardil, Emsam..) Block degradation of serotonin, norepinephrine and dopamine
  - **Wellbutrin** Norepinephrine and dopamine Reuptake Inhibitor *Best known as*:.
  - **Trazodone** Selective Serotonin Reuptake Inhibitor and Serotonin-2 *Receptor Antagonist*.
- **Middle aged (1987- 2010's)**
  - **Prozac**, **Zoloft**, **Celexa**, **Lexapro... (SSRIs**)*:* Selective Serotonin Reuptake Inhibitors
  - **Effexor, Cymbalta...** (**SNRIs**) Serotonin and Norepinephrine Reuptake Inhibitors
  - **Remeron -** Noradrenergic Alpha-2 *Receptor Antagonist* and Serotonin 2 and 3 *Receptor Antagonist*
- **Young (2010's – 2020)**
  - **Viibryd** Selective Serotonin Reuptake Inhibitor and Serotonin-1A *Receptor Partial Agonist:*
  - **Trintellix** Selective Serotonin Reuptake Inhibitor, Serotonin 5-HT3 *Receptor Antagonist* and Serotonin 5-HT1A *Receptor Agonist*

The effectiveness of all is about equal – from young to 65 year-old drugs!

Modifying the action of the monoamines

Inhibit enzyme...block reuptake pump... tickle receptors... block receptors

(These modifications do NOT mean a "correction of a chemical imbalance")



Very young antidepressants
Not monoamine based

- Neuroactive steroids that modify GABA receptors
  - brexanolone (**Zulresso**) for post-partum depression (IV)
  - zuranolone (Not approved yet. Oral: If it is, it would be the first non-monoamine acting, **new** drug, take-at-home "*pill*")
- NMDA receptor antagonists that modify glutamate receptors
  - **ketamine** (IV)
  - esketamine (**Spravato**) (Intranasal – but at doctor's office...)
  - dextromethorphan/bupropion combination (**Auvelity**) **Not** a new drug... Marketing : Costs $500+ for a monthly supply. (Note: 45mg dextromethorphan (3 15mg capsules) and 100mg bupropion purchased separately cost $20)

- Notice these new drugs modify the receptors for GABA and glutamate: The primary **excitatory** and **inhibitory** neurotransmitters

Drugs for special kinds of depression (bipolar) and as "add-on" ("augmentation drugs") for MDD

- "Atypical antipsychotics" (work on dopamine and serotonin neurotransmission)
  - aripiprazole (**Abilify**)
  - lurasidone (**Latuda**)
  - quetiapine (**Seroquel**)
  - lumateperone (**Caplyta**)
  - cariprazine **(Vraylar)**
  - brexpiprazole **(Rexulti)**
- Anticonvulsants
  - lamotrigine (**Lamictal**)

Antidepressant problems, Part 1:
The **frequent**, but usually **transient** and (usually) **manageable** ones

(Side effects of the most frequently prescribed drugs - SSRI and SNRIs)

- *Early,* very common side effects:
  - Nausea, headache, restlessness, anxiety/insomnia
- *Late*, common side effects:
  - Sexual dysfunction (decreased libido, delayed orgasm or anorgasmia)
  - A syndrome of amotivation, and blunted emotions

- Discontinuation side effects may be severe with some medications (but *usually* avoidable or tolerable)

Antidepressant problems, Part 2

The **infrequent**, but very **serious** ones

- *Increased risk of suicidal thinking and behavior*, mostly in adolescents younger than 18, perhaps in young adults up to age 24-25.
  - Why does this occur in this age group? *A hypothesis:* Antidepressants may precipitate a mixed/manic episode in an "undeclared" bipolar young person.
  - A rare and unpredictable effect.
  - A "between a rock and a hard place" dilemma for clinicians: The suicide-related risk of antidepressant treatment is dwarfed by the suicide risk of untreated depression.
- Risk of "switching" to **mania** for anyone, of any age, with a propensity ("undeclared bipolar")

- Highly controversial: *Could conventional antidepressants worsen the **long-term course** of illness? Or the converse – do episodes of depression "kindle" later episodes, thus making long-term maintenance the wiser bet?*

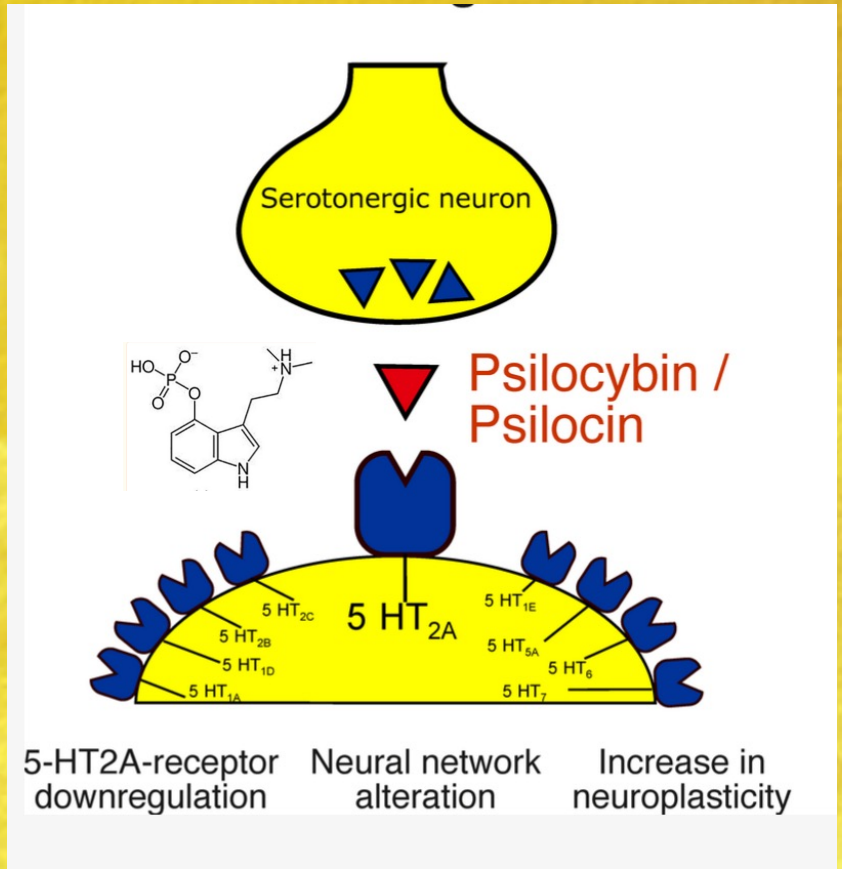
Can Long-Term Treatment With Antidepressant Drugs Worsen the Course of Depression?
Giovanni A. Fava, MD; The Journal of Clinical Psychiatry; February 15, 2003 https://www.psychiatrist.com/jcp/depression/long-term-treatment-antidepressant-drugs-worsen-course/

Stressful Life Events and Previous Episodes in the Etiology of Major Depression in Women: An Evaluation of the "Kindling" Hypothesis
Kendler et al Am Journal of Psychiatry Aug 2020
https://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.157.8.1243

Very young, potential future "antidepressants"
(Really, a come-back of very old..)
Back to monoamines..? But in new ways

- Psilocybin (and other psychedelics) (partial agonist at serotonin 2A receptors)
  - For treatment resistant depression and *end-of-life depression*, the benefits are large, fast, and **long-lasting**. *(Caveat: The evidence still skimpy.)*
  - "It has been *theorized* that these **long-term** improvements arise because psychedelics rapidly and lastingly stimulate neuroplasticity (including **neurogenesis,** synaptogenesis, and expression of plasticity-related genes)"

    Calder, A.E., Hasler, G. Towards an understanding of psychedelic-induced neuroplasticity. *Neuropsychopharmacol.* (2022). https://doi.org/10.1038/s41386-022-01389-z

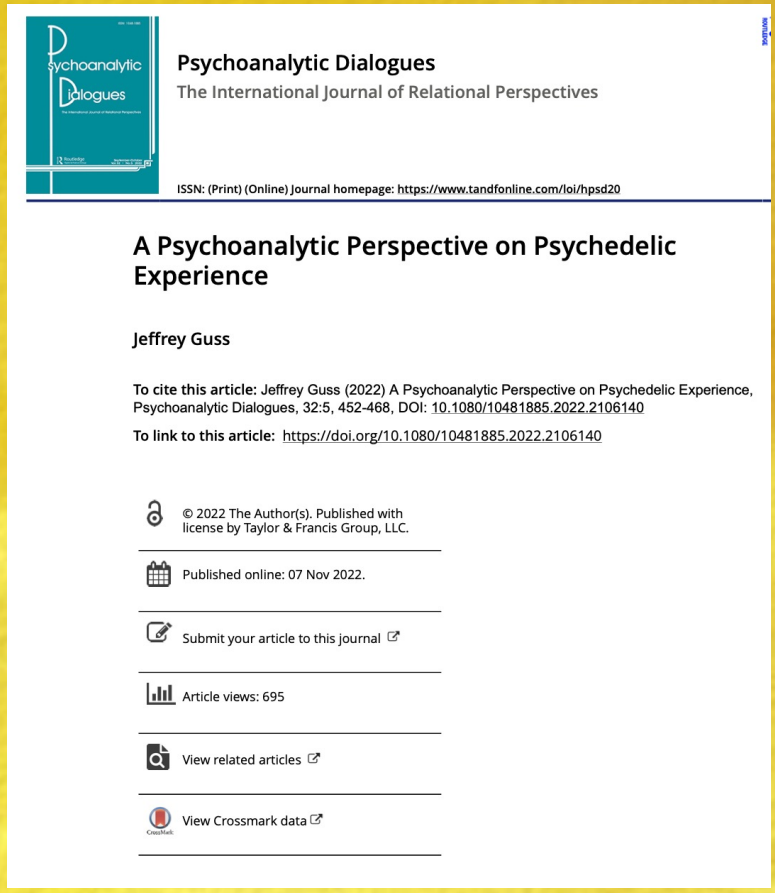


Zeiss, R.; Gahr, M.; Graf, H. Rediscovering Psilocybin as an Antidepressive Treatment Strategy. *Pharmaceuticals* **2021**, *14*, 985. https://doi.org/10.3390/ph14100985

Therapy or "tripping"?

- Therapeutic effects of psychedelics depend on "Set and Setting" which affects not only the acute experience, but the long-term outcome.
- Being studied either in conjunction with **psychotherapy** or otherwise administered in **intentional** therapeutic setting.
  - Even **psychoanalysts** are becoming interested! In...

"...psychedelics' capacity to evoke egolysis, or ego dissolution, and mystical states... their capacity to support hyperassociative states, free association, and emergence of unconscious material" (Nov 2022 Psychoanalytic Dialogues)



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A Psychoanalytic Perspective on Psychedelic Experience

Jeffrey Guss

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PSYCHOANALYTIC DIALOGUES 2022, VOL. 32, NO. 5, 452–468
https://doi.org/10.1080/10481885.2022.2106140

Back to *conventional* antidepressants, a personal view

- **Dr. O. as prescriber: "C**onventional antidepressants *do* work" - but his perspective is structurally biased:
  - Any prescriber's perspective brings a **close-up view** and **"a large n"** – good! But also a "too-close-up" view ("can't see forest for the trees").
  - Any prescriber's impression of "how well conventional antidepressants work" is biased by:
    - **Their *broad spectrum*** of benefits: Ex. SSRIs are "the aspirins of psychiatry" – helping conditions often co-morbid with depression: Anxiety disorders, post-traumatic disorders, eating disorders obsessive-compulsive disorder, premenstrual dysphoria.
    - **The summation** of drug and other healing effects: "Direct effects" plus placebo effect, plus regression-to-the-mean, plus the reassurance of a **treatment alliance**
  - Any prescriber's impression of adverse long-term effects is biased by: Short follow-up of clinic patients, and, for patients seen in long-term practices, a lack of comparison groups.
- **Dr. O. as a patient**...

Prozac for dogs…yet another perspective

From the ad:

"Reconcile *achieves a calmer frame of mind in dogs… ..reduces stress for both the pet and the owner…*"

Electroconvulsive Therapy (ECT)

Effective, but scary

- The gold standard for *Treatment Resistant Depression.* *A 2022 meta-analysis concluded: It still beats ketamine.*
- The procedure: 1) Anesthesia 2) Induction of brief paralysis (no shaking) 2) An electrical pulse is applied to the scalp.

- The effect requires **a seizure**. The pulse excites brain cells causing them to fire **in unison** and producing a **seizure**.
- A course of ECT runs from six to twelve treatments.
- Modulates prefrontal functional connectivity and enhances hippocampal neurogenesis.
- Main adverse effects: Memory impairment
  "A temporary deficit in the cognitive processes of information encoding, consolidation, and retrieval"
- Underused due to stigma, scariness, shortage of providers (ECT-trained psychiatrists + aesthesiologists).
- Case anecdotes...

Transcranial Magnetic Stimulation (TMS)

Less scary, but less effective

- Usually reserved for *Treatment Resistant Depression.*
- The procedure: Patient sits in ”like a dental chair”; remains awake.
- Repeated pulses of magnetic fields are focused on limbic-related cortex (left DLPFC)
- Promising 2022 upgrade: “Stanford Accelerated Intelligent Neuromodulation Therapy” ((SAINT)
  - A high-dose, fast-paced TMS that uses MRI for precision targeting of the left dorsolateral prefrontal cortex (DLPFC) “most functionally anticorrelated to subgenual anterior cingulate cortex."

Some future directions
(Other than psychedelic therapy…)

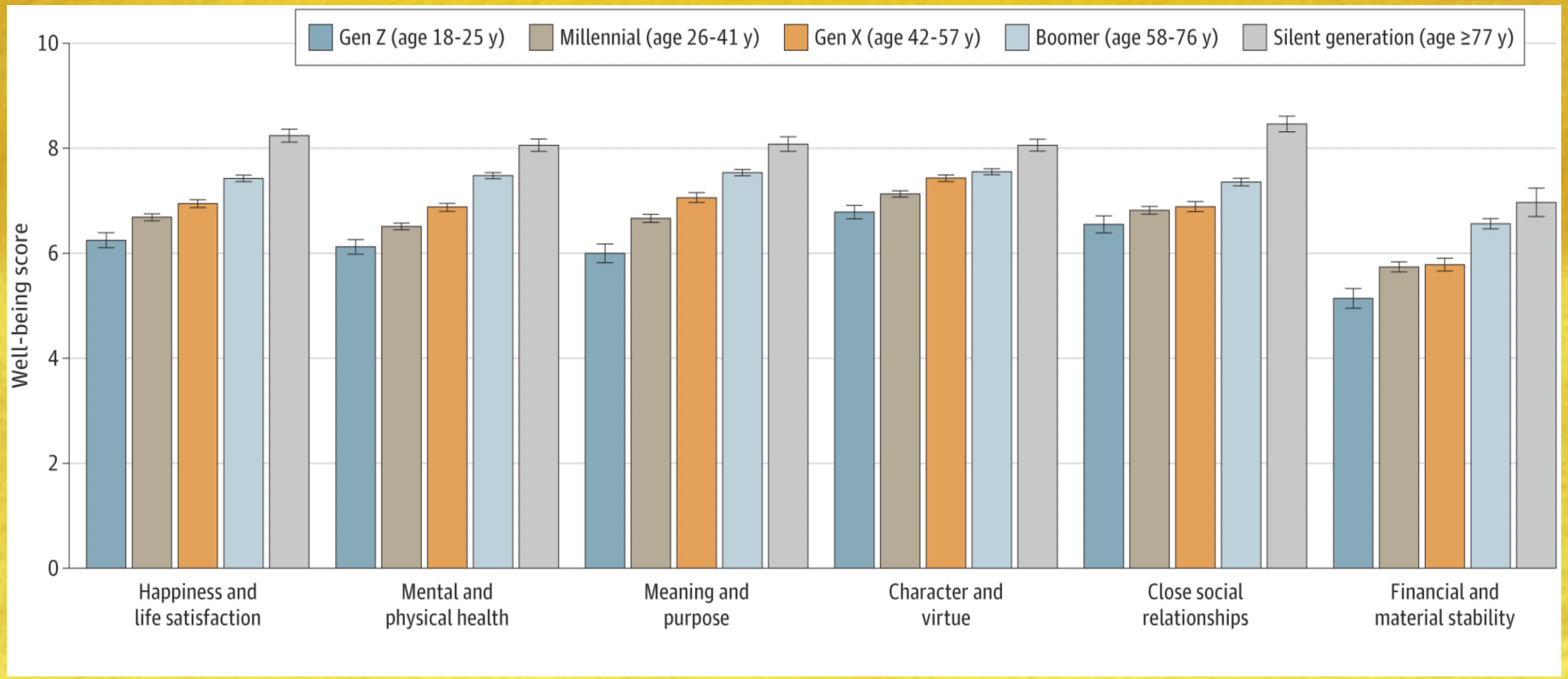
- **"Precision Medicine" to *individualize* treatment**
  - **Blood biomarkers** could match patient's "omics" (genomic, epigenomic, transcriptomic, proteomic, metabolomic, microbiomic...) or inflammation profiles to treatments.
    - Example: **The Promise and Limitations of Anti-Inflammatory Agents for the Treatment of Major Depressive Disorder** https://link.springer.com/chapter/10.1007/7854_2016_26
  - **Neuroimaging**: Structural scans, fMRI could discern connectivity /circuit level functional changes and distinguish depression "biotypes".
    - Example using fMRI: **Resting-state connectivity biomarkers define neurophysiological subtypes of depression** https://www.nature.com/articles/nm.4246?TB_iframe=true&width=921.6&height=921.6 - citeas
  - **Evolutionary theory-inspired sub-typing?**
    - Examples: **Loss-precipitated depression? Defeat/humiliation precipitated depression? Chronic low-rank perpetuated depression? Inflammatory/sickness behavior-linked depression?**
- **Digital access to therapy (for convenience and for *equity*)**
  - Example**: Mindstrong** https://mindstrong.com/ (Commercial startup)
  - Example**: MoodText Project** https://dheal.berkeley.edu/current-projects/moodtext-project (Research project at UC Berkeley Digital Health and Equity Lab)

WHAT ABOUT YOU ALL?

Worrisome data regarding "Gen Z" #1:
Age Gradients in Well-being Among US Adults

From JAMA Psychiatry, 2022

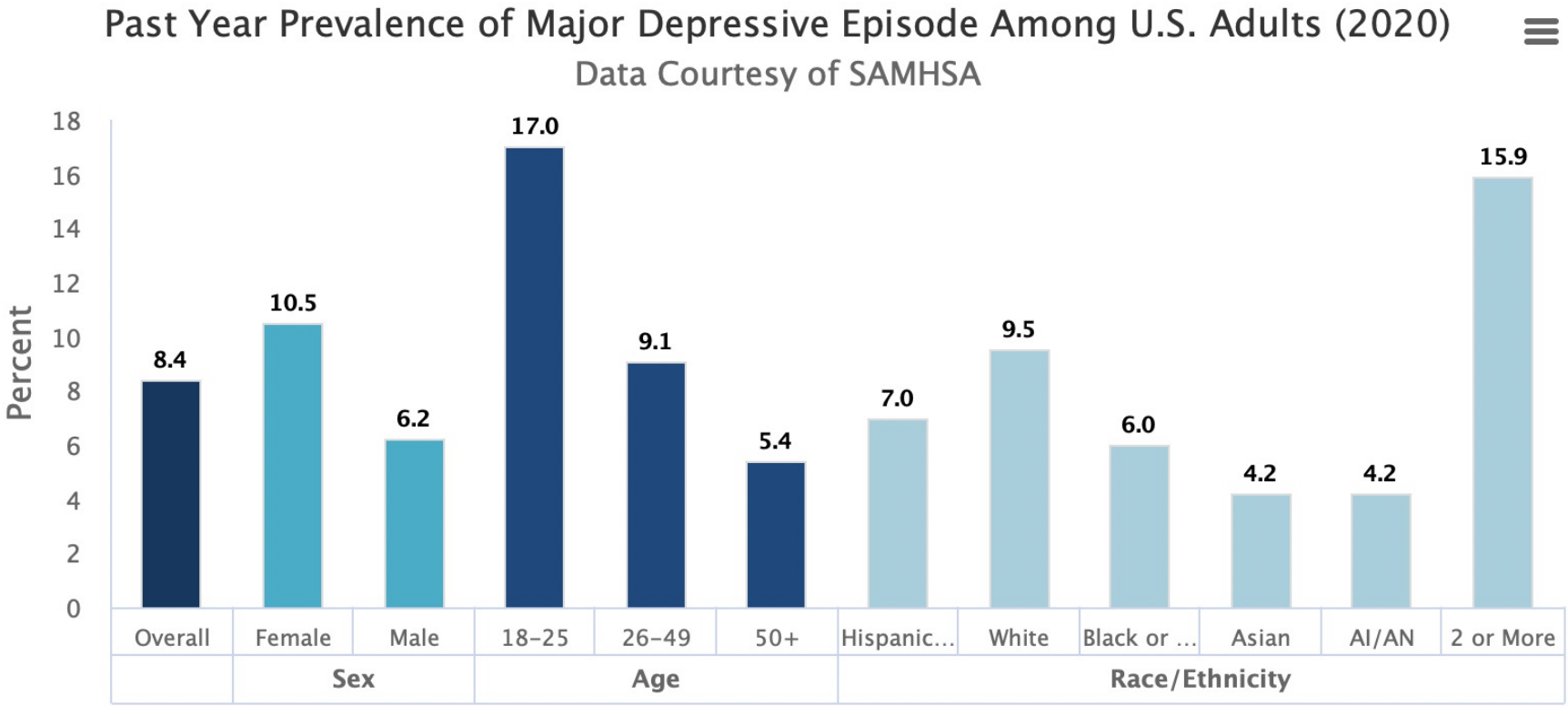
*"These findings suggest that **the well-being of young people has declined** compared with older age groups. Protecting the mental health of young people is regarded as a national emergency; this study suggests that other facets of their well-being also need attention."*



Worrisome data regarding "Gen Z" #2:
Past Year Prevalence of Major Depressive Episode

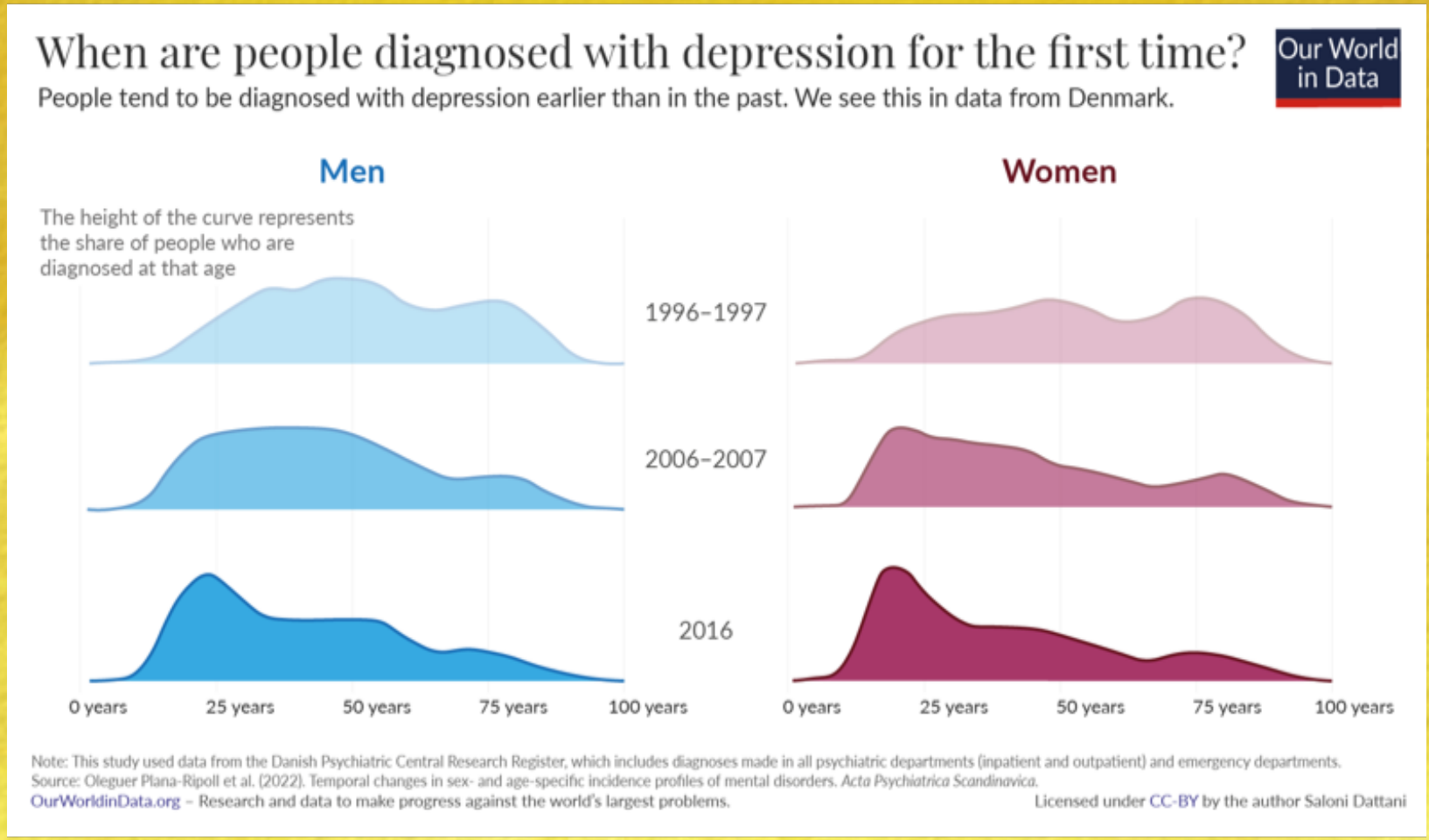
From National Institute of Mental Health (NIMH) (2020)

"Generation Z" (born 1996-2010) are facing challenges unlike previous generations, having grown up in an age of pandemic and increased stress, mental illness, and digital distractions"



Worrisome data regarding "Gen Z" #3:
The "diagnosis bump" scrunches up to younger than age 25

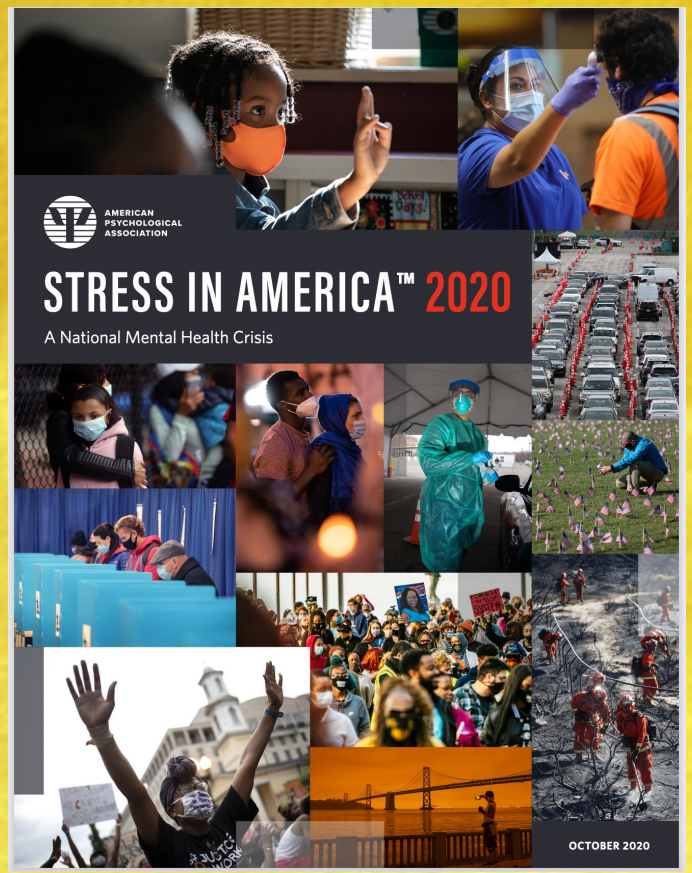
From Our World in Data

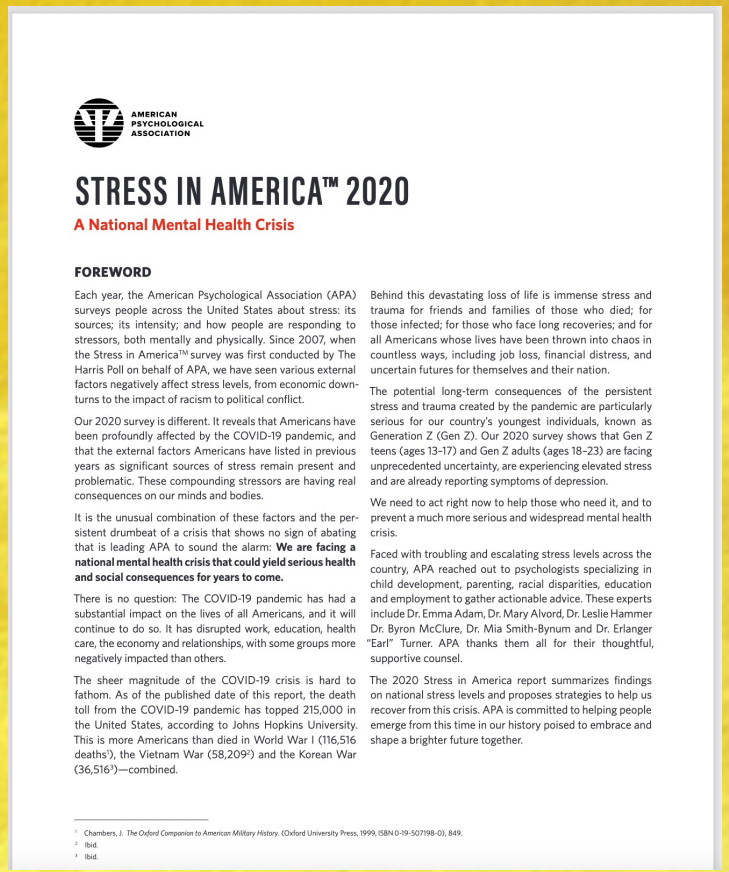


Worries from the American Psychological Association:

From Stress in America 2020 Survey

*"...reported **stress** levels among Gen Z adults have been increasing slightly over the past two years...to **(a) high recorded in 2020**....a decline in social interaction due to the pandemic may be a contributing factor. "*





AMERICAN PSYCHOLOGICAL ASSOCIATION

STRESS IN AMERICA™ 2020

A National Mental Health Crisis

FOREWORD

Each year, the American Psychological Association (APA) surveys people across the United States about stress: its sources; its intensity; and how people are responding to stressors, both mentally and physically. Since 2007, when the Stress in America™ survey was first conducted by The Harris Poll on behalf of APA, we have seen various external factors negatively affect stress levels, from economic downturns to the impact of racism to political conflict.

Our 2020 survey is different. It reveals that Americans have been profoundly affected by the COVID-19 pandemic, and that the external factors Americans have listed in previous years as significant sources of stress remain present and problematic. These compounding stressors are having real consequences on our minds and bodies.

It is the unusual combination of these factors and the persistent drumbeat of a crisis that shows no sign of abating that is leading APA to sound the alarm: **We are facing a national mental health crisis that could yield serious health and social consequences for years to come.**

There is no question: The COVID-19 pandemic has had a substantial impact on the lives of all Americans, and it will continue to do so. It has disrupted work, education, health care, the economy and relationships, with some groups more negatively impacted than others.

The sheer magnitude of the COVID-19 crisis is hard to fathom. As of the published date of this report, the death toll from the COVID-19 pandemic has topped 215,000 in the United States, according to Johns Hopkins University. This is more Americans than died in World War I (116,516 deaths[1]), the Vietnam War (58,209[2]) and the Korean War (36,516[3])—combined.

Behind this devastating loss of life is immense stress and trauma for friends and families of those who died; for those infected; for those who face long recoveries; and for all Americans whose lives have been thrown into chaos in countless ways, including job loss, financial distress, and uncertain futures for themselves and their nation.

The potential long-term consequences of the persistent stress and trauma created by the pandemic are particularly serious for our country's youngest individuals, known as Generation Z (Gen Z). Our 2020 survey shows that Gen Z teens (ages 13–17) and Gen Z adults (ages 18–23) are facing unprecedented uncertainty, are experiencing elevated stress and are already reporting symptoms of depression.

We need to act right now to help those who need it, and to prevent a much more serious and widespread mental health crisis.

Faced with troubling and escalating stress levels across the country, APA reached out to psychologists specializing in child development, parenting, racial disparities, education and employment to gather actionable advice. These experts include Dr. Emma Adam, Dr. Mary Alvord, Dr. Leslie Hammer Dr. Byron McClure, Dr. Mia Smith-Bynum and Dr. Erlanger "Earl" Turner. APA thanks them all for their thoughtful, supportive counsel.

The 2020 Stress in America report summarizes findings on national stress levels and proposes strategies to help us recover from this crisis. APA is committed to helping people emerge from this time in our history poised to embrace and shape a brighter future together.

1 Chambers, J. *The Oxford Companion to American Military History.* (Oxford University Press, 1999, ISBN 0-19-507198-0), 849.
2 Ibid.
3 Ibid.

Worries from headlines

- ***"Generation Z is stressed, depressed and exam-obsessed"***
  Feb 2019 The Economist
- ***"The future of Gen Z's mental health: How to fix the 'unhappiest generation ever"*** August 2020 The Telegraph
- ***"Mental health issues increased significantly in young adults over last decade"*** March 2019 ScienceDaily
- ***"Is young people's mental health getting worse? "*** Feb 2019 BBC NEWS

What is going on? Speculations…

Who is qualified to answer? Medical doctors? Psychiatrists? Psychologists? Sociologists? You *all* or "experts"?...

- "**Quarterlife Crisis**"? (Doesn't explain the sudden rise)
- **Lessened stigma leading to more self-disclosure**? (May contribute – but unlikely to explain rise in severity)
- **Covid-19 pandemic?** (Surely contributes – but the alarming trends *predate* 2019)
- **World becoming scarily unpredictable?** (Political polarization, climate crisis, inequality, racism, pandemic...)
- **Increased loneliness?** (Reported – but, why now?) ".. **younger generations** are experiencing more loneliness" AMA public policy statement, June 2022
- **Social media?** *Hmm...*

Dr. Ozores' *social media* when he was in college: A rotary dial phone hanging from a kitchen wall.

Exploring one possibility: Social media as an evolutionary **mismatch** for the *development* of the social brain

- As is the case for *impacted wisdom teeth* and *myopia*, could the high prevalence of depression in Gen Z be due to **mismatch?**
  - The **mismatch** would be between our social world and the **developmental needs** of our mood regulation needs between adolescence and adulthood.

- Deprivation of play? (Remember the kittens...)

*"Tech companies **destroy**...**play** and replace it with **device addiction**, a simulacrum and a false promise of connection that does none of the **developmental work** of the real thing".*

From a review of *Who's Raising the Kids*, by Susan Linn; NY Times Book Review, November 13, 2022

Exploring one possibility: Social media as an evolutionary **mismatch** in **flooding** of social comparison and toxic interaction

- *Designed* to be an **addictive mismatch** to our reward system.
  - (Other mismatches bad for humanity: Distilled spirits, gambling casinos, fentanyl, highly palatable cheap processed food...etc..)
- Exposes the user to 24/7 risk of being bullied, of invidious social comparison

"Meta's own internal research showed Instagram to be a source of lower self-esteem in girls and suicidal thoughts in teens in America and the U.K" (ibi

From a review of *Who's Raising the Kids*, by Susan Linn; NY Times Book Review, November 13, 2022

- Makes **sadistic gossiping** *cost-free* for the aggressor.
- Plays on our need-to-belong and protect reputation (remember Social Investment Potential)

Indictment:

*"...there is **no alternative hypothesis** that can explain the suddenness, enormity and international similarity (of the spike in mental health disorders)."* Jonathan Haidt

What to do?

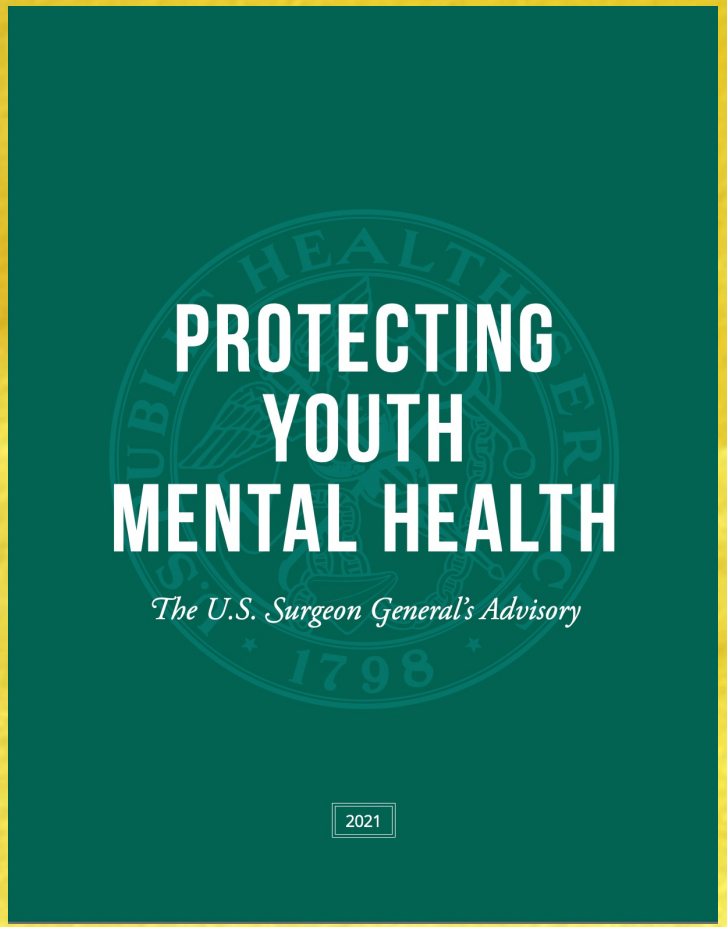
- The ”indictment” is a *social origins of depression* hypothesis... how to test it?
  - Remember, research on *the social origins* of depression has been done (Brown and Harris 1972; others...).
- A **societal** response is needed. In the mean time... what can individuals do?
- First let’s consider ***generic*** **suggestions** for prevention and resilience.
  - **Preventive self-help is like vaccination.** Self-help may ”inocculate” you against cognitive distortions and mental habits that *entrap* one in dysfunctional depressed mood.
- Then we’ll discuss suggestions **based on the evolutionary hypotheses we discussed.**

A societal response?

The Surgeon General's effort (aimed at a younger cohort– but still worth reading)..

Protecting Youth Mental Health: The U.S. Surgeon General's Advisor

https://www.hhs.gov/sites/default/files/surgeon-general-youth-mental-health-advisory.pdf



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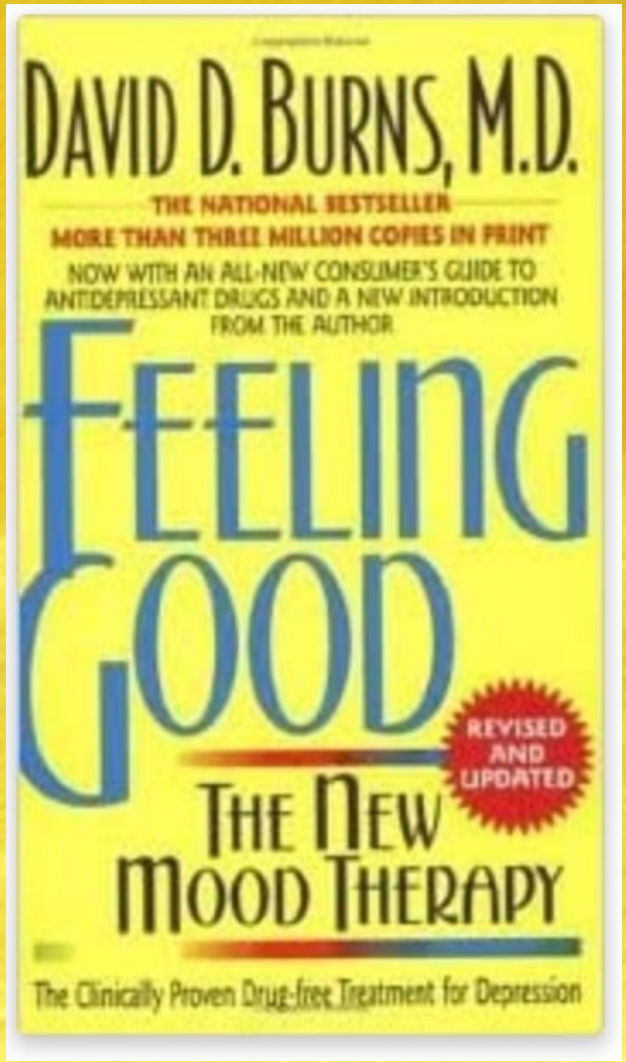
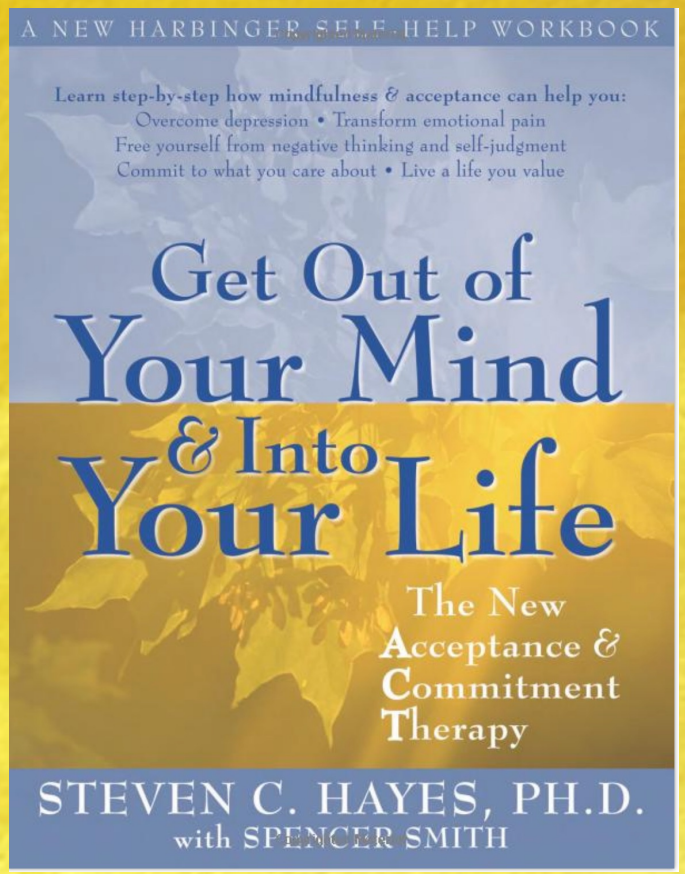
Generic prevention suggestion #1: Learn about Cognitive Behavioral Therapy (CBT)

- CBT teaches you how to recognize and counter automatic "cognitive distortions" that precipitate and perpetuate depression.
  - Read the classic "do-it-yourself" CBT book "*Feeling Good*" by David Burns https://feelinggood.com/
- Pros and cons of CBT:
  - *Pro*: Easy to learn
  - *Pro*: Has the most research support; is "the gold standard" https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5797481/
  - *Con*: Can overemphasize "inner causes" and invalidate realistic adversities or trauma. Does not focus on adaptive problem solving of realistic life situations.



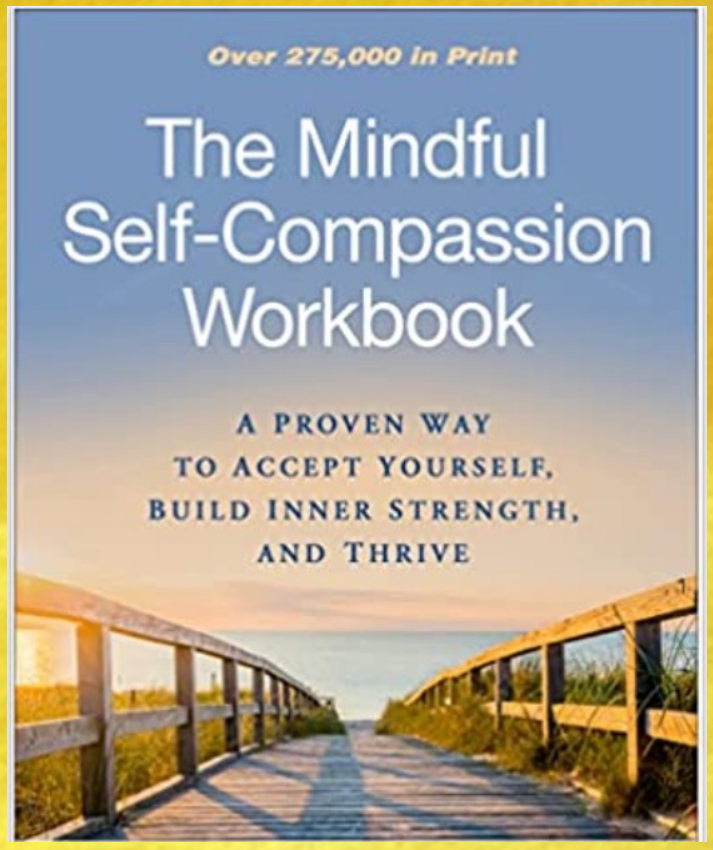
Generic prevention suggestion #2: Learn about Acceptance and Committment Therapy (ACT)

- ACT teaches you how to *de-fuse* from unhelpful mental thoughts/experiences (not fighting them), assess the *workable value* of your thoughts and emotions, and choose *actions* . Mindfulness is part of the process
  - Read "Get Out of Your Mind and Into Your Life" by Steven C. Hayes, PhD
- Pros and cons
  - *Pro*: No "debating with cognitions" needed. Thoughts and feelings assessed for their *usefulness.*
  - *Pro*: Foundation in the "Perennial Wisdom" and mindfulness.
  - *Con*: Also overemphasizes "inner attitudes" (v.s. problem solving of "outer causes", such as trauma, role transitions, societal, etc.)



Generic prevention suggestion #3: Learn about Self-Compassion

- **Inoculate yourself** against toxic self-criticism:
- Learn about Self-Compassion (Suggestions: Kristin Neff's book, and website: https://self-compassion.org)
- Pros and cons:
  - Pro: Foundation in the "Perennial Wisdom"
  - Con: Narrow focus on depression cased by perfectionism and self-abasement



Prevention inspired by evolutionary hypotheses

- Modern environments are **mismatched** to our evolved emotion-regulating system and arouse *useless* bad feelings:
  - *Fear*
  - *Envy*
  - *Dissatisfaction* with ability, physique, intelligence, etc...etc... Images and narratives of hyper beauty, hyper physique, talent, prowess, power, success... (From presentation by Randolph Nesse, MD)
- *Don't believe the hype...*

  View the titillations of the media ironically. Or, stop up your ears with wax.. like the sailors in *The Odyssey*

Prevention inspired by evolutionary hypotheses
What to do about social media?

- Having bad-mouthed it as toxic, we know it brings benefits as well...

- Social media is like a giant wave. You can't fight it -- you gotta get wet – but *learn to surf the wave.* Skillfully watch it, time it, get in and out when you choose.

Prevention inspired by evolutionary hypotheses

1) By The Social Competition Hypothesis

- Recognize when low mood was triggered by losing in competitive situations. Spot if the feeling lingers too long– “can’t let it go”.

- **Win** if you can! Butt...you can’t win all the time. If you can’t win,go for **compromise**; if you can’t compromise, **substitute strategic, canny voluntary yielding** for involuntary, morose, ruminative yielding that risks becoming a stuck depression.

- **Exercise** to increase your ***Resource Holding Potential***. *Any* exercise will do, but the best kinds “*tells your brain that you are strong*” and offer:
  - *Autonomy*: The ability to exert oneself independently and have control over one’s actions,
  - *Mastery*: A clear and ongoing path of progress that can be traced back to one’s efforts,
  - *Belonging*: Being part of a community, lineage or tradition that is working toward similar goals.

Prevention inspired by evolutionary hypotheses

2) By The Social Risk Hypothesis

- Increase your ***Social Investment Potential***. Buffer against rejection precipitants of low mood by cultivating varied contexts where you get feedback of *Social Value:*

  - **Diversify** your areas of competence and collaboration, especially in arenas *where you are of service to others*.

  - **Keep up the care and feeding** that maintains social networks alive.
  - Join **affiliation** groups. Church, sports teams, affinity groups, volunteer groups, arts/music/performance groups, Meetups, etc

  - Find occasions to join activities that involve ***synchrony*** **with others: Dancing, singing (ex. church), playing music (bands, orchestras)** - or just eating dinner together.

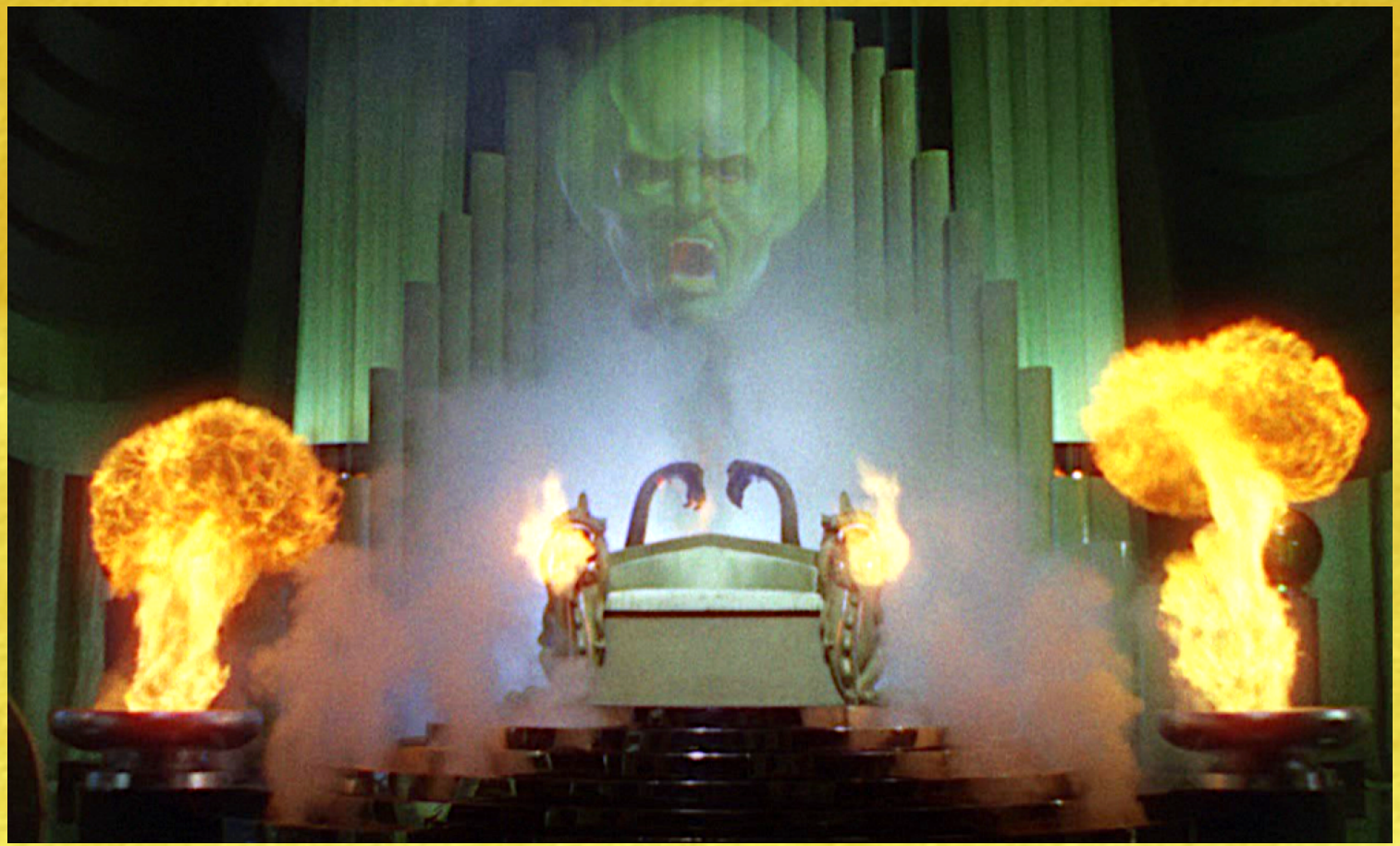
Prevention inspired by evolutionary hypotheses

Recall how the SCH and SRH theorized *self-esteem* as mindless, automatic:

Won ? Yeah !! Lost? Boo !!

Accepted ? Yeah !! Shunned ? Boo !!

Confront your automaton *Self-Esteem* **Wizard**…



Look behind his curtain and
Disenthrall yourself from The Wizard.

Instead, anchor your *self-esteem* on *self-approbation*, the *human component* of *self-esteem* that is not dependent on whether you win or lose, are loved or shunned – but on doing the right thing.

Prevention inspired by evolutionary hypotheses

- Low moods are a **normal feature** of our human – indeed our animal - psychology**.**
- When depressogenic stressors come your way, greet your ensuing mood: *"Everything is working as it should".*
- **Accept** a measure of low mood as *informative* and as an occasion to "hibernate", reduce engagement for a while and reflect on your predicament.
- But! ➔➔➔➔➔➔➔➔➔➔➔➔➔➔➔

Get professional help if you need it!

- All suggestions up to now had to do with promoting *resilience* and *prevention,* assuming professional help is not needed...
- Get help if you need it!

Mental health resources *for UC Berkeley Students*

- **Counseling and Psychological Services (CAPS)**
  - To schedule an appointment, call CAPS (510) 642-9494, visit the eTang patient portal, or stop by CAPS.
- **CAPS Satellite Offices** all over campus
  - Informal consultation with counselors (*Let's Talk* program) -no appointments or paperwork needed—uhs.berkeley.edu/counseling/satellite
- **Berkeley Recalibrate** Wellness Resources
  - https://recalibrate.berkeley.edu
- **Urgent Concerns access**
  - Crisis drop-in at the Tang Center is available Monday-Friday 10am–5pm
  - For consultation when CAPS is closed, call the **After Hours Line** (855) 817-5667

Mental health resources for anyone

- Mental Health America Screener Resource
  - https://screening.mhanational.org/screening-tools/
- The Patient Health Questionnaire-2 (PHQ-2): A two-question screener:
  - https://www.hiv.uw.edu/page/mental-health-screening/phq-2
- National Suicide Prevention Line
  - ***Call 988*** (Formerly 1-800-273-8255)
- Protecting Youth Mental Health; *The U.S. Surgeon General's Advisory*
  - *https://www.hhs.gov/sites/default/files/surgeon-general-youth-mental-health-advisory.pdf*
- The Jed Foundation
  - https://jedfoundation.org/
- Canadian Network for Mood and Anxiety Treatments website
  - https://www.canmat.org/
  - CANMAT's "The Choice-D Patient and Family Guide to Depression Treatment" . Free download: https://www.canmat.org/wp-content/uploads/2019/07/Choice-D-Guide-Public.pdf

"Philosophical prevention" inspired by "Big Picture Thinkers"
Read Spinoza

- Spinoza says in *The Ethics* that our affects (love, anger, hate, envy, pride, jealousy) (we may add, **moods)**,

"...*follow from the same necessity and force of nature as... other ..things"...(thus) "...we shall bear calmly those things that happen to us contrary to what ...our advantage demands, if we are conscious that we have done our duty, that the power we have could not have extended itself to the point where we could have avoided those things, and that* ***we are a part of the whole of nature, whose order we follow"***

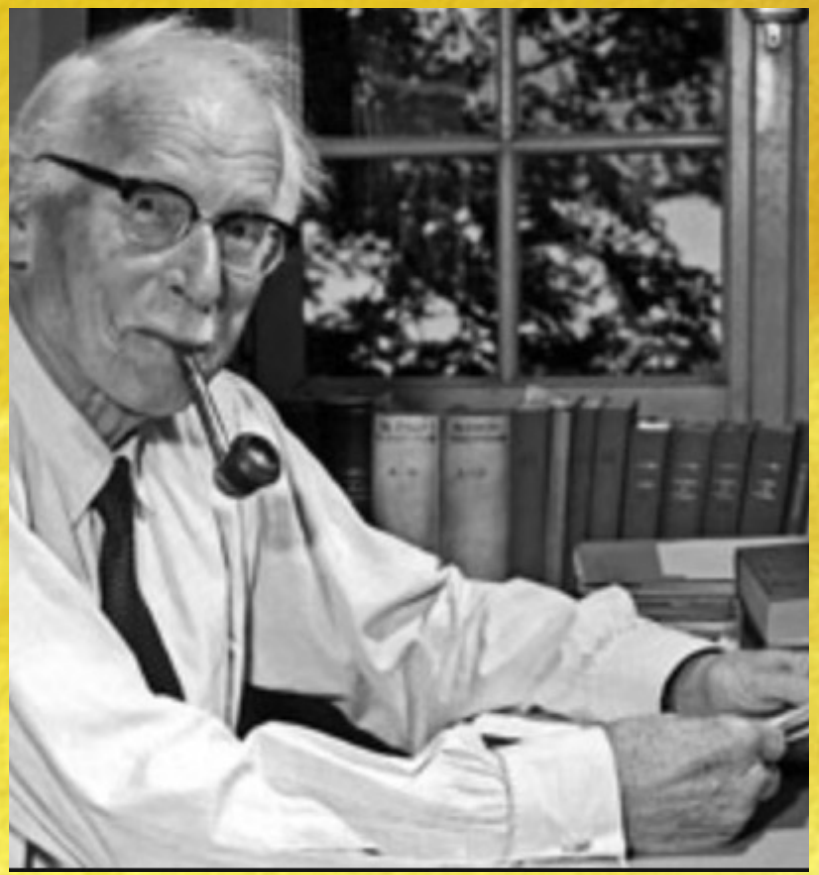
The view "*sub specie aeternitatis*" – the view from eternity.

"Philosophical prevention" inspired by "Big Picture Thinkers"

Psychiatrist Carl Jung on the evolutionary foundation of human psychology

"If the unconscious is anything at all, it must consist of earlier evolutionary stages of our psyche... It is time this obvious fact were grasped at last. Just as the body has an anatomical prehistory of millions of years, so also does the psychic system. And just as the human body today represents in each of its parts the result of that evolution, and everywhere still shows traces of its earlier stages - so the same may be said of the psyche."

Carl Jung, *Memories, Dreams, Reflections* (1961)



"Philosophical prevention" inspired by "Big Picture Thinkers"
The Buddha

The play of forces in the world makes for **stress** for entities like us that *care about their homeostasis.*

We animals don't just care about our homeostasis, we are *sentient* and suffer.

Moods are part of the *dukkha* दुःख of being a sentient being.

To see ourselves in kinship with all sentient beings is a "liberating insight".

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