Stress, the Evolution of Mood and Clinical Depression

For UC Berkeley IB 139, Fall 2022

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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?*

Pivot point in our talks…

- From mood's **normal function**...

  ...to **mood dysfunctions,** diseases, disorders

  (from Behavioral Ecology to Psychiatry)

- From considering **Adaptation** and **Phylogeny...**

  ...to considering biological **Mechanisms**

- From all-new material...

  ...to adding some **review** of material you've covered already (but fitting it into new contexts)

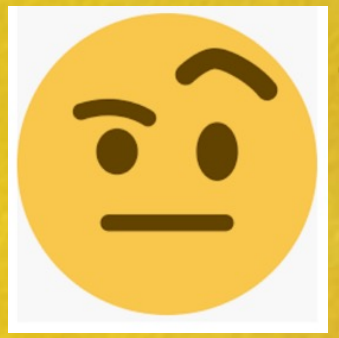
Ending with: What about you all?

- The Penthouse:

Human Mood and its Disorders (Psychiatric stuff)

We must simplify human mood and its disorders!



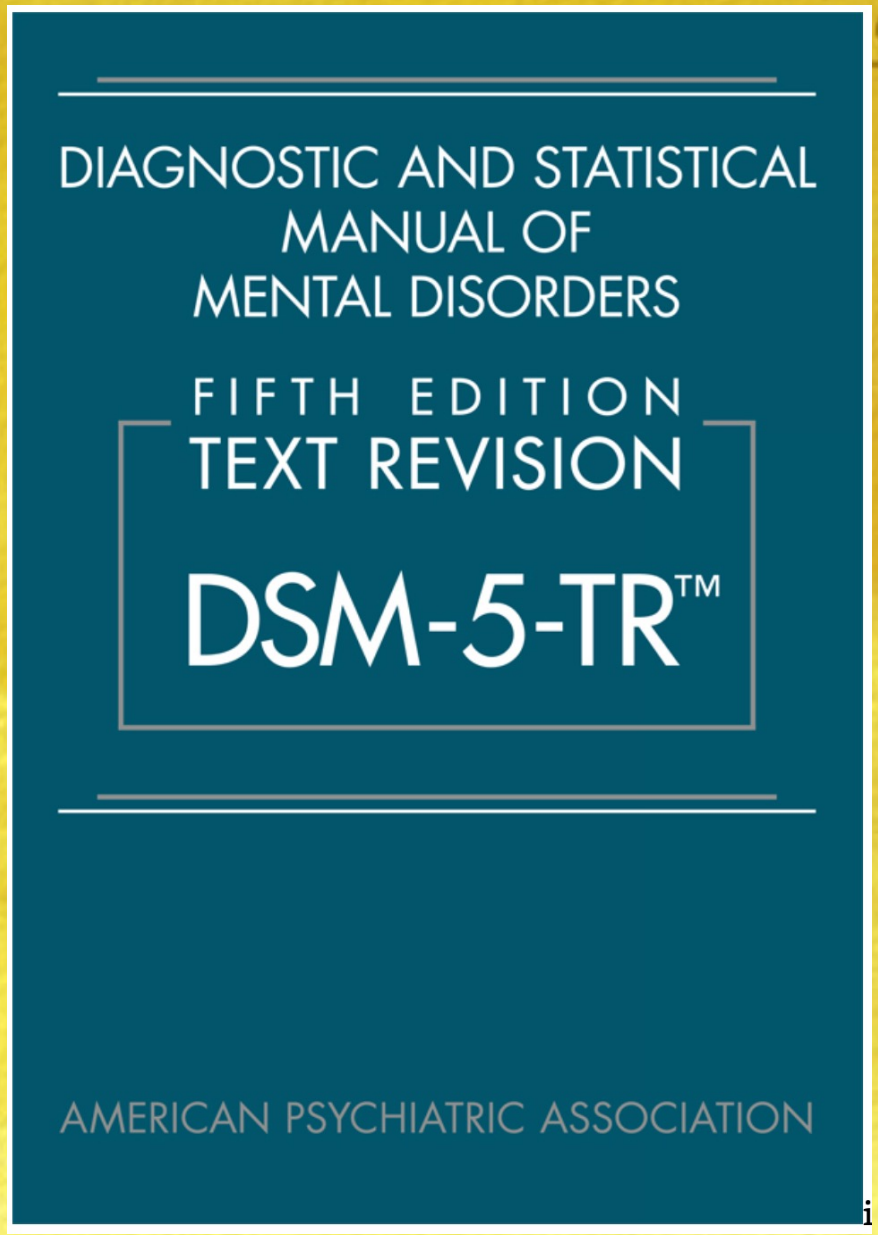







"Official Definitions" of Disorders

- The workhorse; psychiatry's "bible": DSM-5-TR
- A *conventional* agreement to classify emotional/behavioral distress/dysfunctions.
- Only claims to tell apart "*disorders*", not "*diseases*".
- Disorders are defined by clusters of symptoms that often "go together". (Are merely syndromes)
- Re-written periodically (motivated by science? profit?)
- Mildly useful when selecting treatments, but less useful in research (discovering genetic associations, figuring out disease mechanisms, etc..)



DSM 5 categories of disorders **in relation to stress:**
In **large bold type**: Informally known to be precipitated by stress; in *large italic type, defined* as precipitated by stress:

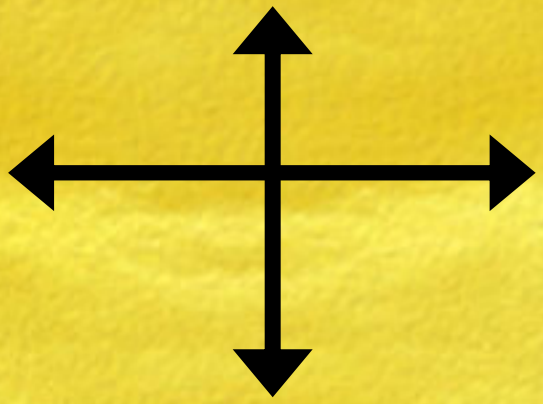
- Neurodevelopmental
- Schizophrenia spectrum and other psychotic
- Bipolar and related
- **Depressive**
- **Anxiety**
- Obsessive-compulsive and related
- *Trauma and stressor related*
- Dissociative
- Somatic symptom and related
- Feeding and eating
- Elimination
- Sleep-wake
- Sexual dysfunctions
- Disruptive, impulse-control, and conduct
- Substance-related and addictive
- Neurocognitive
- Personality
- Paraphilic

Wait...what's missing from this list? What overarching category of emotional disorders?

DSM 5 TR Quirks: *No Mood Disorders category!*

In "The Foundation of Mood" we elegantly considered mood a single "natural kind" whose variation could be mapped on two dimensions, But DSM 5 TR ...

Dysfunctionally elevated:
Mania (Bipolar Disorders)



Dysfunctionally anxious:
Anxiety Disorders

Dysfunctionally calm:
No *recognized* disorders!

Dysfunctionally depressed:
Depressive Disorders

Y axis: Threshold to detect reward
X axis: Threshold to detect punishment

Still, professional lingo includes the category of Mood Disorders, whose prototypes are Mania and Depression
We will concentrate on the dysfunctional extreme of low mood,
The most *pain-like* mood disorder.

A normal **Defense**? An abnormal **Defect**? Who makes the call?

- We discussed depressed mood as a *normal*, *adaptive* modulation of behavior (a “Defense”). But now, we are introducing “dysfunctional” low mood - “Major Depressive Disorder (a “Defect”).
- The difference is *somewhat* arbitrary... conventional... cultural...defined by a committee... (DSM)
- But...there is no mental disorder with a longer tradition of being recognized as illness than depression - back to Hippocrates.
- Pragmatically, at least with severe depression, the impairment and suffering leave no question in most everyone’s mind.
- For any given case, what would you consider when evaluating a patient?

Imagine: You are the psychiatrist…
For a given patient, how would you tell *Defect* from *Defense*?

Your call: "This patient is *sick*- their depression is a defect."

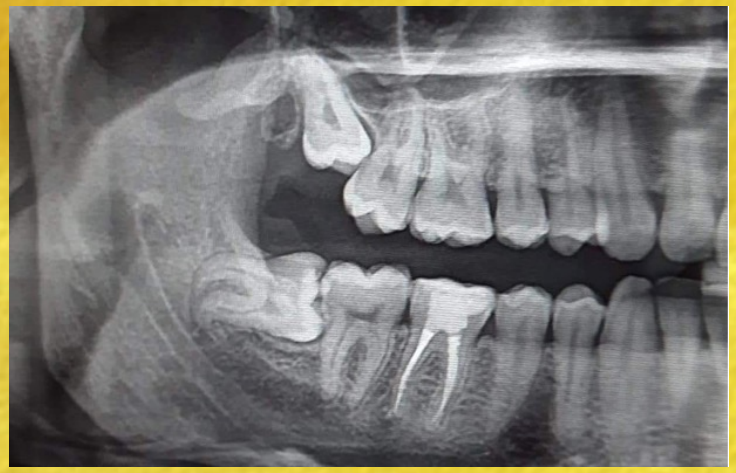
- Only mild (or no) depressogenic precipitants
- Symptoms are severe, incapacitating, dangerous
- History of recurrences, of very early onset, of family history
- Failure to recover spontaneously even with improving life events
- Concurrent substance use disorder, medical conditions

Your call: "This patient is normal- their depression is a defense."

- Evident depressogenic precipitants
- Symptoms mild to moderate
- No history of recurrences, no family history
- *Course is self-limiting* – patient improves with promising life events (ex. a new relationship, support from therapist or friends, improved health, etc)

What if your patient has a condition that's **highly prevalent**, especially so in otherwise **healthy young people**? It's more likely a normal **Defense**, right?

1) Well... Many of you have had this one:



2) Many of you also have this mystery one. You can tell Dr. Ozores has it (he was afflicted in his early twenties) by just looking at him.

?

Two **disorders – <u>Defects</u> -** highly prevalent in young people, due to ***<u>mismatch</u>***.

A fuzzy view of clinical depression: Before the technical definition, what do we mean by the term?

- A persistent mood state characterized by frequent *sadness, loss of interest or pleasure, ruminating on guilt low self-worth or inadequacy, disturbed sleep or appetite, tiredness, poor concentration, indecisiveness, and thoughts of death or suicide.*
  - Of life-threatening gravity: At its most severe, it *can* lead to suicide. (Note: Depression is not the only mental state or disorder that can lead to suicide.)

The DSM 5 TR Criteria for an *Episode* of Major Depressive Episode: Five (or more) out of nine…must include one from column one

- **1) Depressed mood** most of the day, nearly every day (by subjective report or observation of others – i.e. appears tearful)
- **2) Loss of interest or pleasure** in nearly all activities most of the day, nearly every day (by subjective report or observation)
- 3) Weight loss or weight or decrease or increase in **appetite**
- 4) **Insomnia** or hypersomnia
- 5) Psychomotor agitation or **retardation**
- 6) **Fatigue** or loss of energy
- 7) Feelings of **worthlessness** or inappropriate guilt ***("Assessment of the Self")***
- 8) Diminished ability to think or **concentrate**, or indecisiveness
- 9) Recurrent **thoughts of death or suicidal ideation**, plans, or attempts.

You are the psychiatrist:
Depressed mood states and *even Major Depressive* *Episodes*
occur in *several* *disorders* proper…
You MUST make sure to not mis-diagnose Major Depressive Disorder when it's Bipolar Disorder

Depressive Disorders "Proper" (Unipolar):

Major Depressive Disorder
Persistent Depressive Disorder
Premenstrual Dysphoric Disorder
Disruptive Mood Dysregulation Disorder (A childhood diagnosis)
Depressive Disorder Due to Another Medical Condition
Substance/Medication-Induced Depressive Disorder
Other Specified Depressive Disorder
Unspecified Depressive Disorder

Bipolar Disorders:

Bipolar I Disorder
Bipolar II Disorder
Cyclothymic Disorder
Substance/Medication-Induced Bipolar Disorder
Bipolar Disorder *Due to Another Medical Condition*
Other Specified Bipolar Disorder
Unspecified Bipolar Disorder

You are the psychiatrist:

Sometimes specifying further features of a Major Depressive Episode makes a difference in treatment

Depressive Disorders "Proper" (Unipolar)

- **Major Depressive Disorder**
  - **Specifiers**... *with* ***anxious distress****, with* ***melancholic*** *features, with* ***psychotic*** *features, with atypical features, with* ***peripartum*** *onset, with* ***seasonal*** *pattern, with* ***mixed features****, etc...*

Persistent Depressive Disorder (Dysthymia)

Premenstrual Dysphoric Disorder

Disruptive Mood Dysregulation Disorder (A new, childhood diagnosis)

Depressive Disorder Due to Another Medical Condition (Note causal inference in definition)

Substance/Medication-Induced Depressive Disorder (Note causal inference in definition)

Other Specified Depressive Disorder

Unspecified Depressive Disorder

Bipolar Disorders

Bipolar I Disorder

Bipolar II Disorder

Cyclothymic Disorder

Substance/Medication-Induced Bipolar Disorder (Note causal inference in definition)

Bipolar Disorder *Due to Another Medical Condition* (Note causal inference in definition)

Other Specified Bipolar Disorder

Unspecified Bipolar Disorder

Back to the plain, common "prototype depressive disorder", a **MDE**.

Let's critique the DSM: Part 1

(Think of "The Foundation of Mood", The SCH and The SRH)

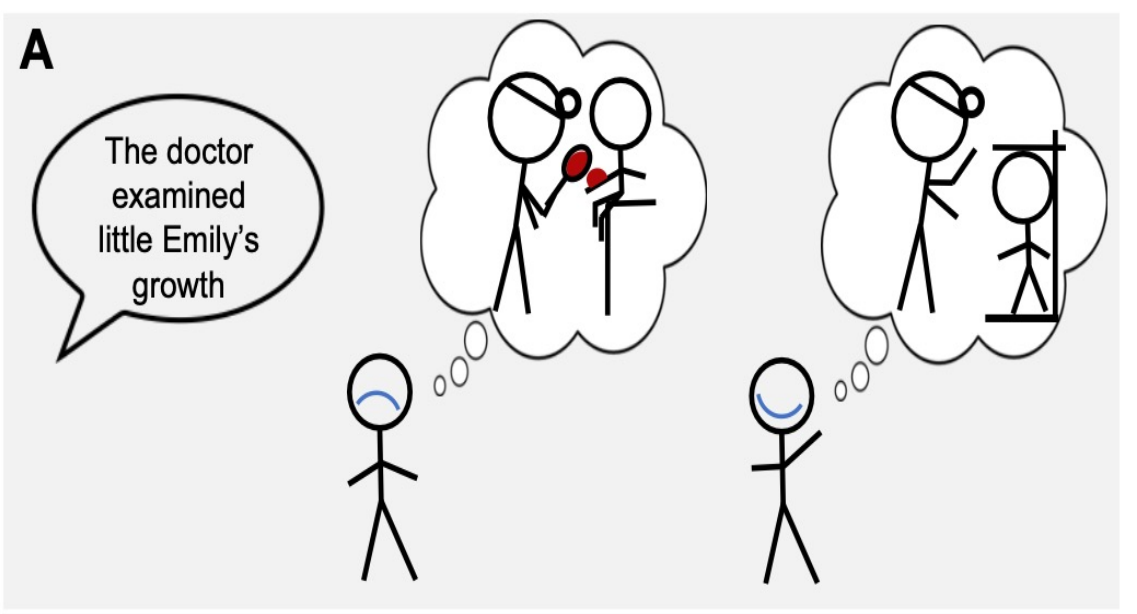
1) **Depressed mood**
2) **Diminished interest or pleasure**
3) ***Appetite changes***
4) ***Insomnia/sleep changes***
5) **Psychomotor changes**
6) ***Fatigue***
7) ***Poor concentration***
8) ***Worthlessness...guilt***
   ("Assessment of the Self")
9) ***Thoughts of death or suicide***

- What symptoms are *species specific* to humans? What symptoms might occur in another mammal?
- What criterion is missing that might separate normal depressed mood ("defense") from disordered depressed mood ("defect")?
- What symptom is **glaringly** missing, given we've seen it in a *scientific* definition of depressed mood
  - (Hint: It's key for Cognitive Behavioral Therapy, and ...we saw stressed bees have it)

(Consider also glitches in the DSM definition: Why is it *Major* Depressive Disorder? Where's the *Minor*??)

Continuing our DSM critique: Part 2:

Missing symptoms



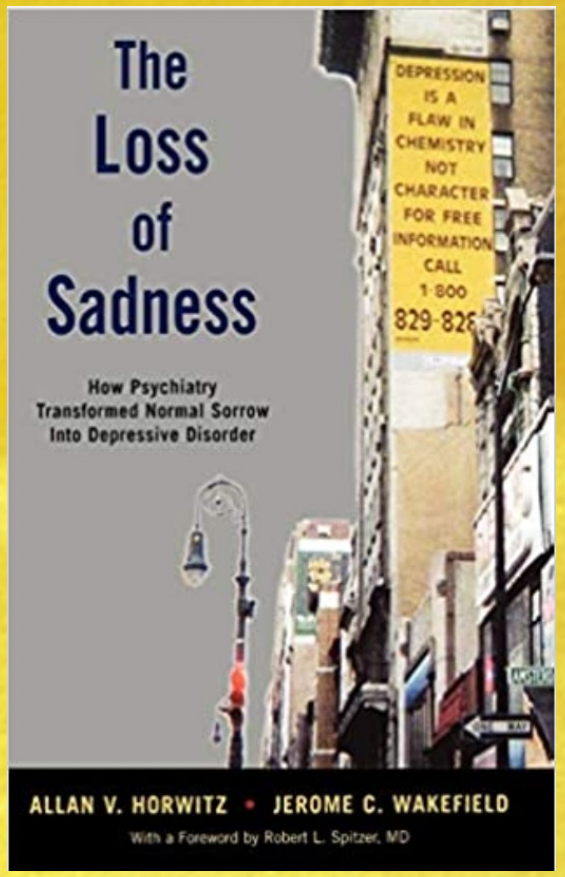
(This cartoon is from a study with *anxious* patients, showing their judgment bias towards *threat.* Eysenck et al, 1991

- *Cognitive distortions* ("judgment bias") missing from the criteria. Yet they are the **key feature** of depression that Cognitive Behavioral Therapy (CBT) addresses!
- Other generally recognized symptoms that are missing: *Social withdrawal, hypersensitivity/vigilance rumination over negative social feedback, rumination on inadequacy in social comparison...*

Continuing our DSM critique: Part 3:

No life context

- The "check the boxes" diagnosing that DSM inadvertently promotes does not account for life context (neither **precipitating** nor **perpetuating** stressors), conflating normal low mood with disordered low mood.
- A classic regarding this debate: *The Loss of Sadness* (2007)
  - "...while depressive disorder certainly exists and can be a devastating condition warranting medical attention, the apparent epidemic in fact reflects the way the psychiatric profession has understood and reclassified normal human sadness as largely an abnormal experience. This system is fundamentally flawed, the authors maintain, because it fails to take into account the **context** in which the symptoms occur." (From the publisher's review)

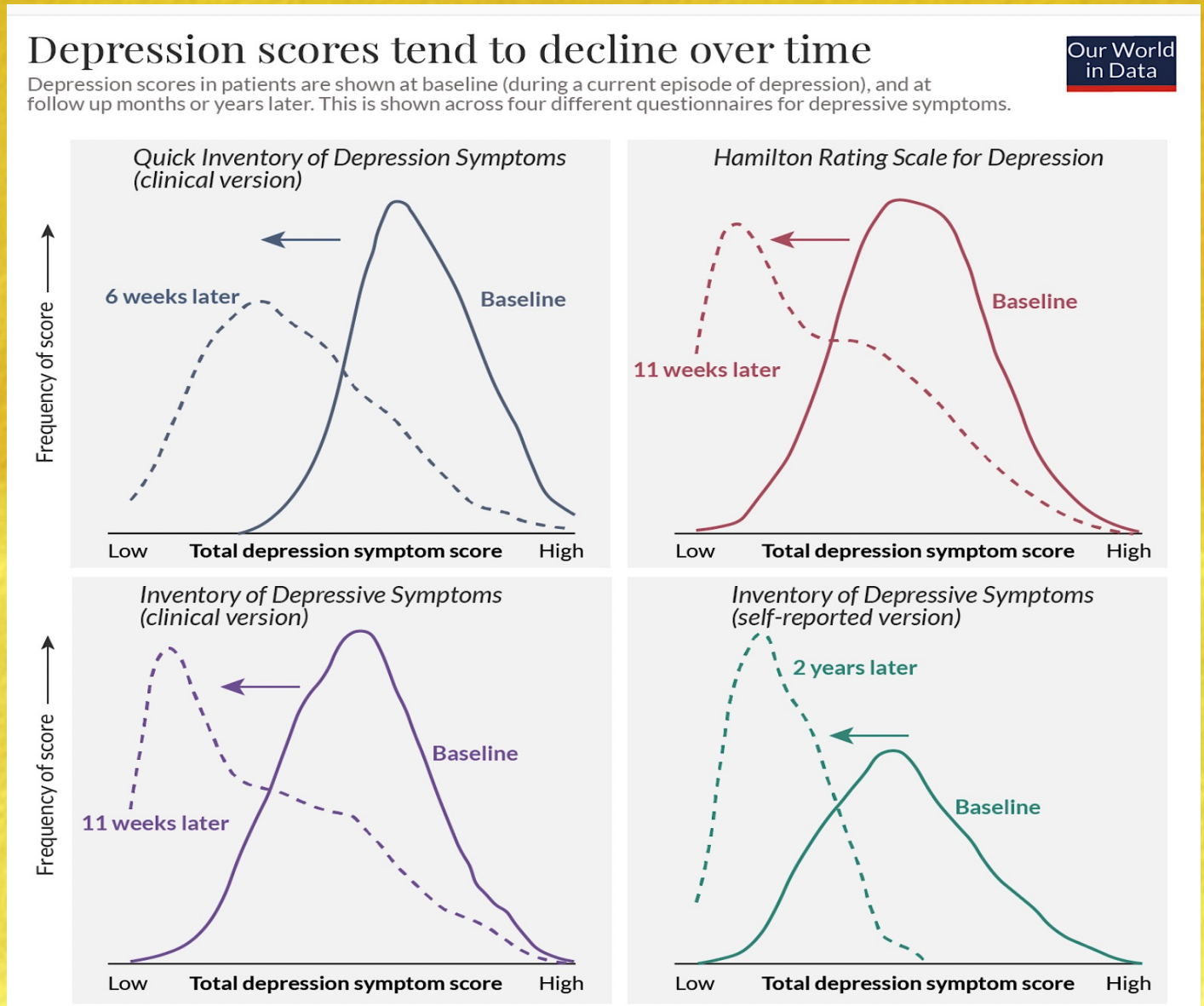


Prevalence

- Very common (highly prevalent):
  - A world-wide take from **The World Health Organization**: "Globally, it is estimated that 5% of adults suffer from the disorder" ..." a common illness worldwided...3.8% affected..."... "At least 350 million people live with depression and it is the leading cause of disability worldwide."
  - The **lifetime risk** for MDD has been estimated to be from 10 to 25% for women and 5 to12% for men.
- Average **age of onset** in *early to mid-twenties.*
- Along with anxiety disorders, treating depression is the "bread and butter" of mental health clinicians.

Natural History: Symptoms tend to get better

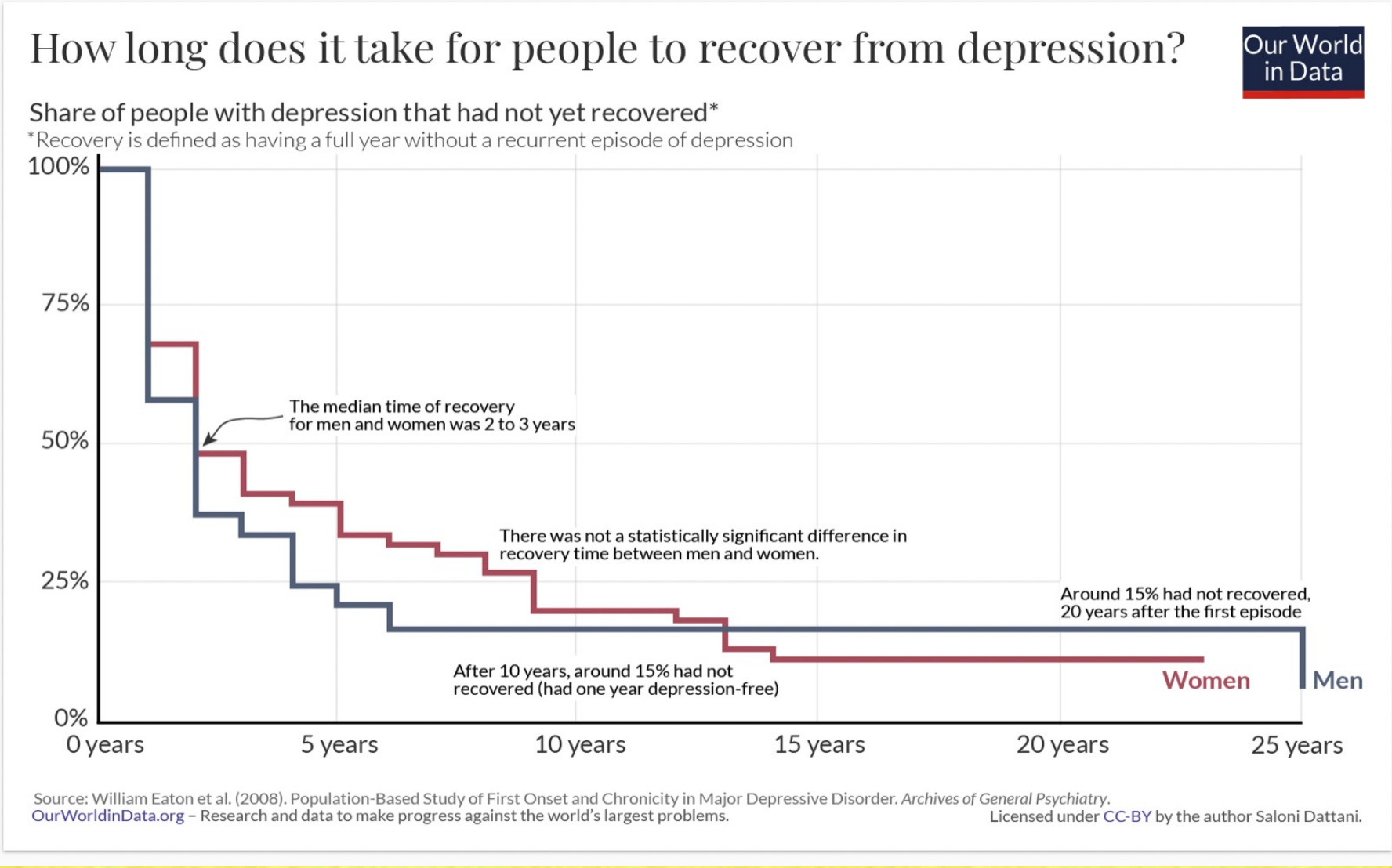
Four different questionnaires show baseline (solid line) "shift to the left" (dotted line)



Source: Fried et al. (2016). Measuring depression over time [..] Lack of unidimensionality and longitudinal measurement invariance in four common rating scales of depression.
OurWorldinData.org – Research and data to make progress against the world's largest problems.
Licensed under CC-BY by the author Saloni Dattani.

Natural history:
Recovery (achieving a full year of wellness) can take a while for many

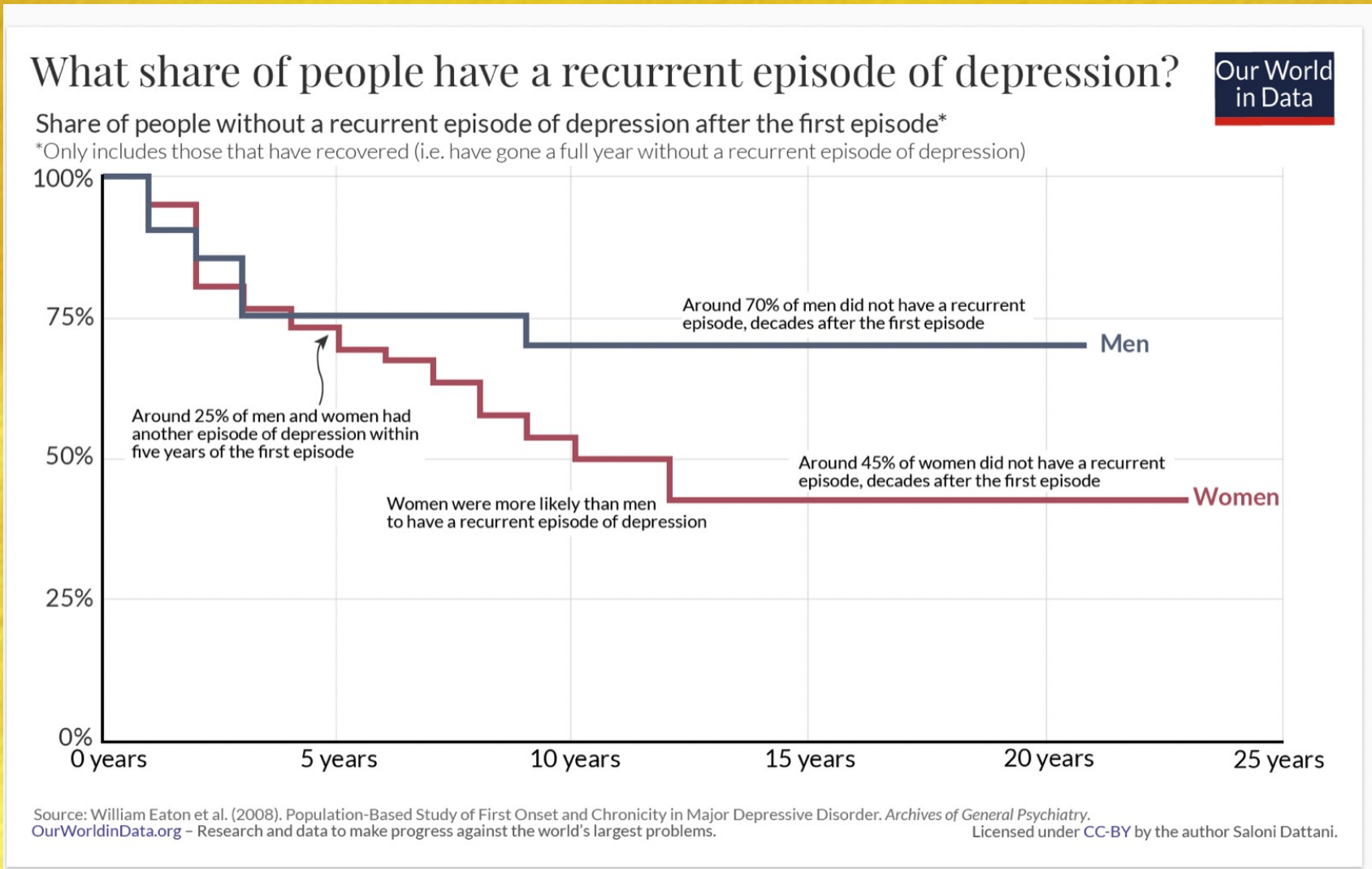
(Graph of a *population based* study)



Natural history: It may recur..

50-60% of individuals with a Major Depressive Episode can be expected to have a second episode; after two episodes a 70% chance of having a third, and three episodes a 90% chance of having a fourth.

(From the same *population based* study)



You are the psychiatrist…
Based on the natural history of depression (also known as the course of illness) how would you answer your patients when they ask:

- Will I **get better** without treatment?
- When will I **recover** fully without treatment?
- Will it **come back**?

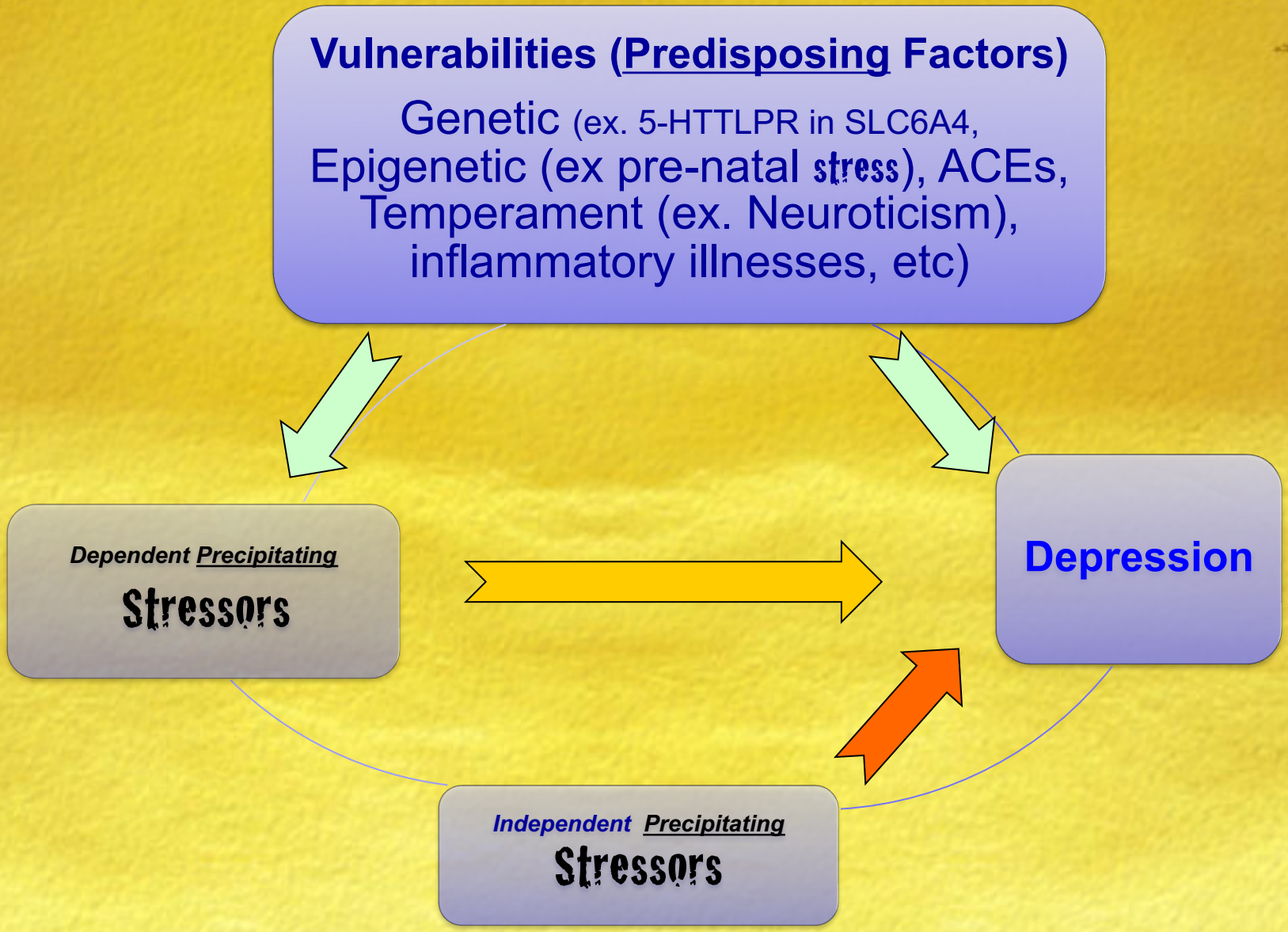
Heritability

- *Somewhat* heritable... how much so depends:
  - **Persistent** depression has a stronger association with *early life* stress, and is less heritable; [2] **highly recurrent** depression is more heritable.
- If it's heritable, what about susceptibility genes?
  - Despite many reports in recent years, a recent analysis concluded: No single genes, nor small group of genes have been discovered that confer susceptibility... [1]
  - So...It *is* heritable, but (genetic) susceptibility likely conferred by many, many variants, each with a tiny effect.

Precipitating factors: Stress and onset of depressive episodes

- How "stress linked"? Really two questions in one:
  - Does *early life* stress **predispose**?
  - Does *proximate life* stress **precipitate**? (That is, are *onsets* of episodes of depression *causally* linked to current environmental stressors ?
- If proximate life stress precipitates, is it stress of *a special kind,* or any old kind of stress*?*
- Are the *precipitating* causes of major depressive episodes ("clinical depression") the same as the causes of periods of non-disordered depressed mood?

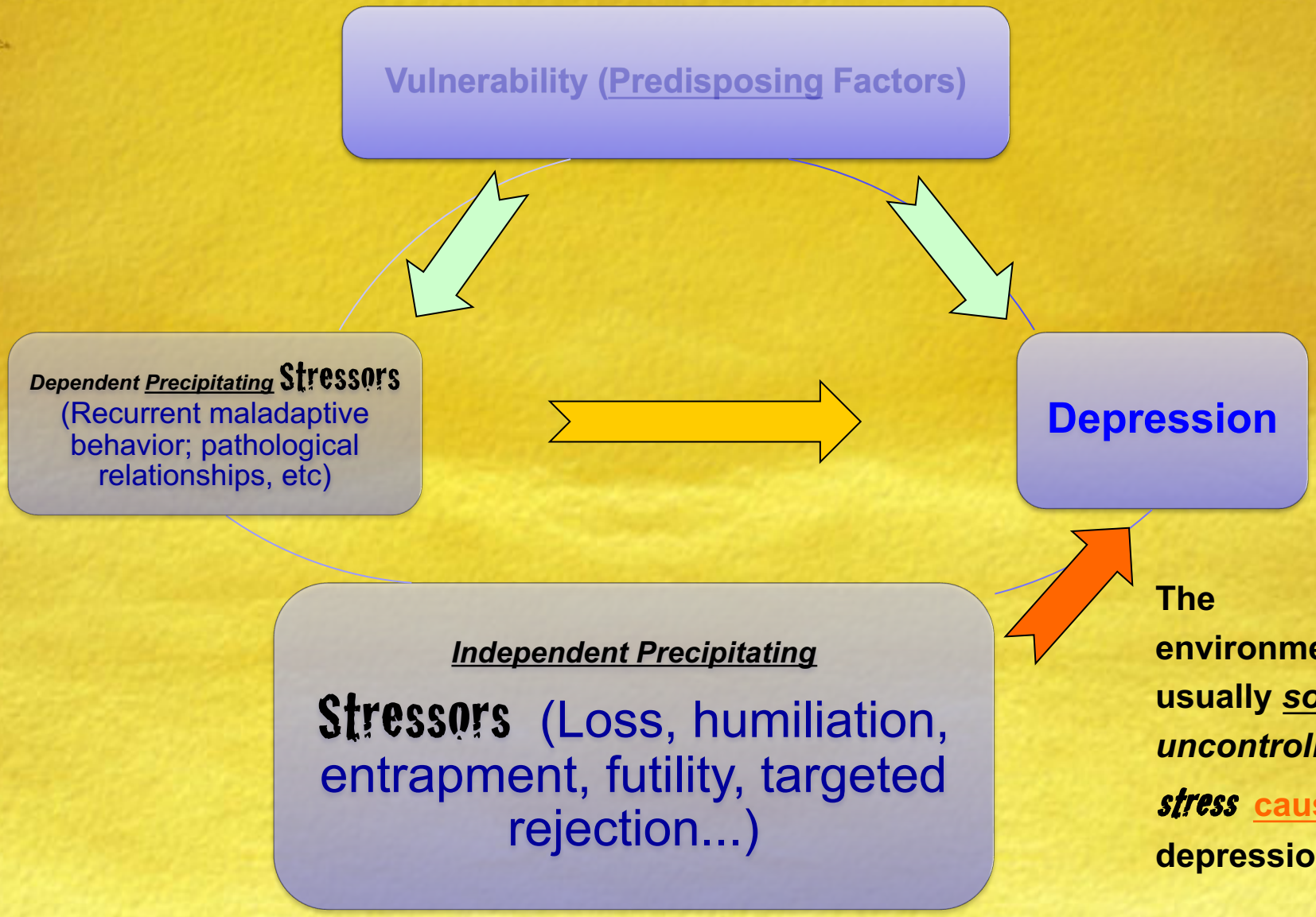
Vulnerabilities and depression:
Predisposing Factors – stress related and other



Comment on two kinds of Vulnerabilities (Predisposing Factors)

- Adverse Childhood Experiences (ACE)
  - A straightforward **tally** of different types of adversity - abuse, neglect, and other hallmarks of a rough childhood.
- ACE items relate to:
  - Physical, sexual or emotional abuse
  - Neglect
  - Household dysfunction (witnessing violence in home or community)
- Neuroticism
  - NOT a disorder; only a personality trait that is defined “in purely descriptive psychometric terms” (not a “Freudian” term)
  - Persons high in Neuroticism are often self-critical, sensitive to the criticism of others, and feel personally inadequate.

Life events and depression: Stressors as Precipitating Factors



The environmental usually *social*, *uncontrollable* *stress* cause of depressions

Two classic studies of Precipitating Factors:

- **Gene-by-Environment Interaction (GxE)**

  The 2003 Caspi/Dunedin study:

  Precipitating **stressors** *interact* with predisposing genes (polymorphisms of the serotonin transporter gene)

  Link to list of Dunedin studies published in 2003, including the famous Caspi study:

  https://dunedinstudy.otago.ac.nz/publications?keyword=&year=2003

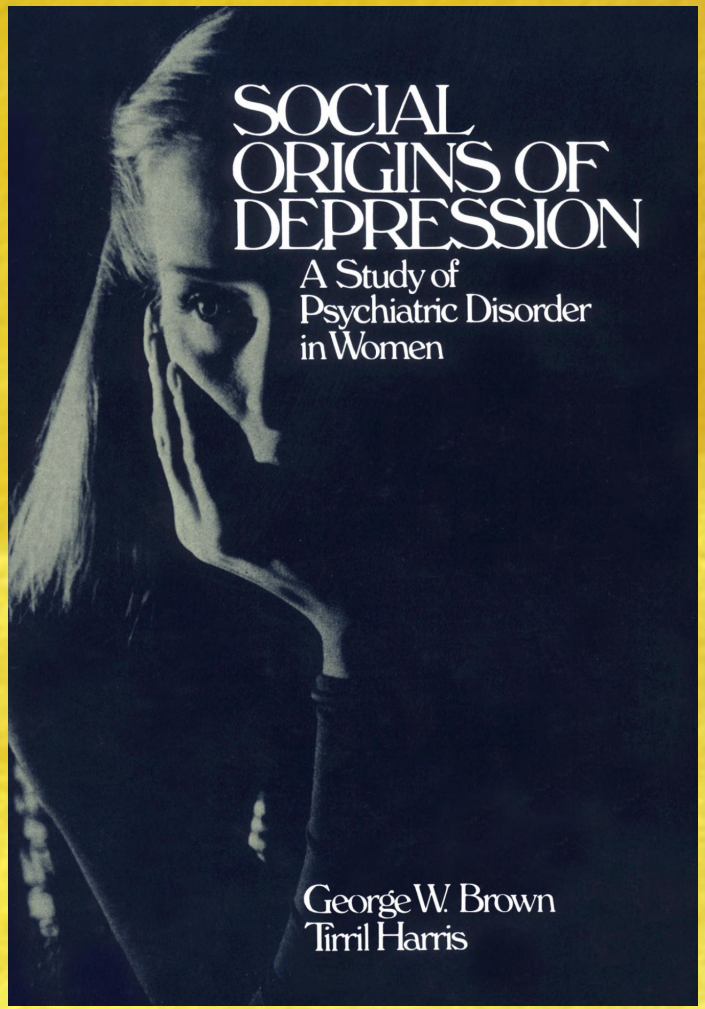
- **Plain old environment...**

  The 1978 classic "The Social Origin of Depression" by Brown and Harris

  A classic sociological study that teased out how the *meaning* of life events (**stressors**) is what matters.

- Link to The Social Origin of Depression abstracts:

  https://www.taylorfrancis.com/books/mono/10.4324/9780203714911/social-origins-depression-george-brown-tirril-harris?refId=06979e85-2588-471a-ad81-c2108ccf446f&context=ubx



Pathophysiological hypotheses of Major Depressive Disorder

Four blind men examining an elephant?...

i. **Neurotransmitter "imbalance" (monoamines)**
ii. **Neural network and neuroendocrine**
iii. **Inflammation**
iv. **Neurogenesis related**

So...which is the right one?

MDD episodes may **be different** (different symptom clusters).

Some mechanisms could apply to one kind, some to the other.

Non-disordered low mood mechanisms may be different from disordered depression

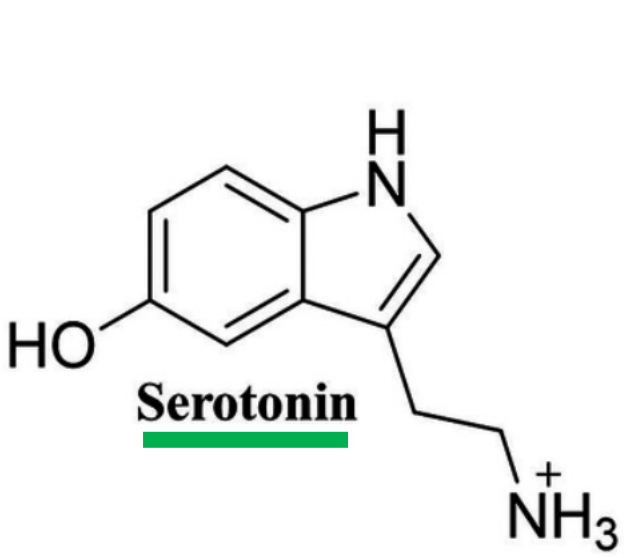
Even for those MDD episodes that **look the same symptomatically,** underlying ***endophenotypes*** could be different (a common endpoint).

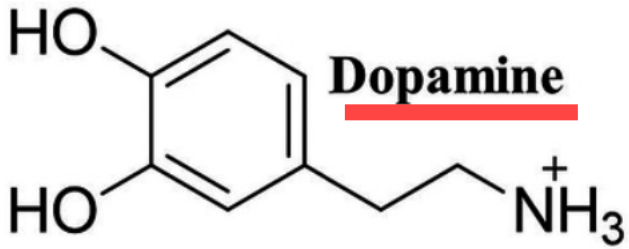
Mechanisms may **interact** as "nodes in a matrix".

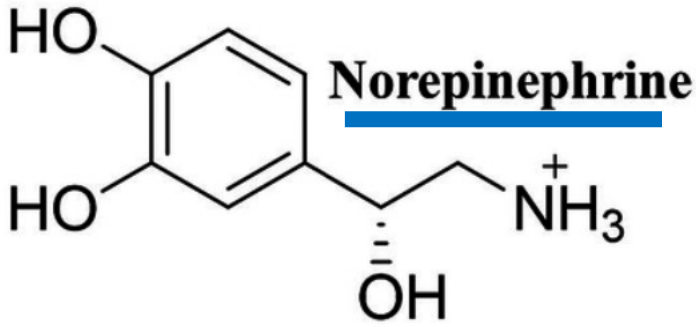
Pathophysiological hypotheses of Major Depressive Disorder I

i. **Neurotransmitter "imbalance" (monoamines)**
ii. Neural network and neuroendocrine
iii. Inflammation
iv. Neurogenesis related

The monoamine neurotransmitters







Monoamine Hypothesis

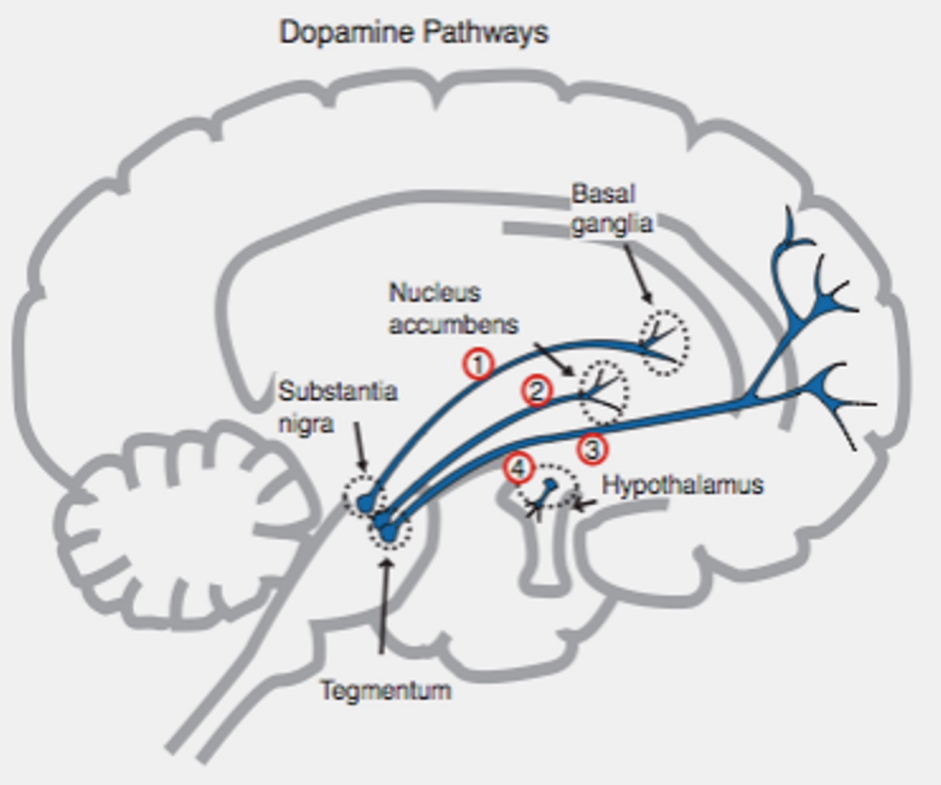
- It *was* said: Depression must be caused by a deficit of *some* "monoamine function" in the brain. Why look! serotonin, dopamine and norepinephrine pathways are involved in widespread modulation of emotion-related areas (limbic – frontal cortex).

- How the hypothesis got rolling:
  - Iproniazid – a drug against tuberculosis that *just happened* to be an *irreversible, nonselective monoamine oxidase inhibitor* ("MAOI") serendipitously improved depression in tuberculosis patients (1958).
  - Later came the "tricyclic antidepressants"; all blocked monoamine reuptake pumps.
  - Drugs (ex. reserpine) that depleted monoamine *worsened* depression.

- Later antidepressants, lo and behold, also affected monoamine transmission either by inhibiting neuronal reuptake of a monoamine (ex. SSRIs) or their degradation (ex. MAOIs).

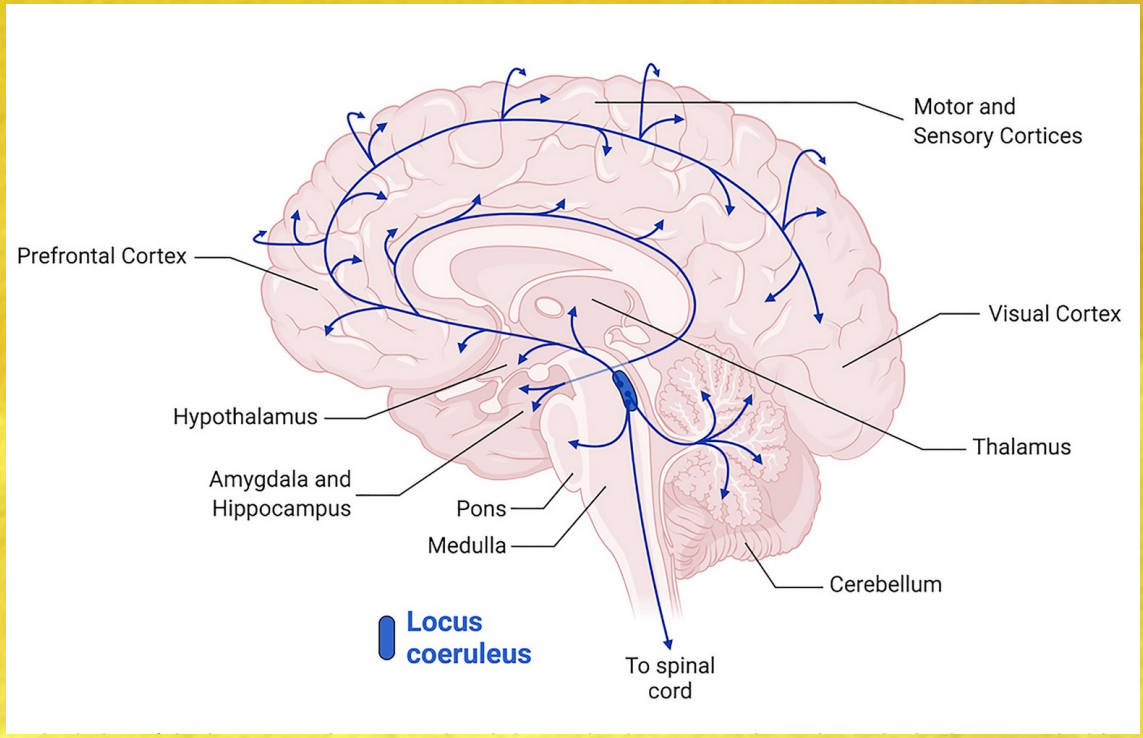
The Dopamine Pathways

- Four pathways ("cables") run from the midbrain to specific, distant regions:
  - 1. Nigrostriatal (MOTOR fine-tuning)
  - 2. **Mesolimbic (VTA-NAc)**
  - 3. Mesocortical
  - 4. Tuberoinfundibular
- The key pathway related to mood is #2, the **mesolimbic dopamine pathway,** fron dopaminergic neurons in the midbrain's **ventral tegmental area (VTA)** that project to the **nucleus accumbens (NAc)** in the limbic system.
- Involved in motivation, in seeking **reward**, in initiation of consumption, and *also* in aversion. Also hypothesized to be involved in the perception of social status (Insel 2004) (Recall the Social Competition Hypothesis' RHP ?)



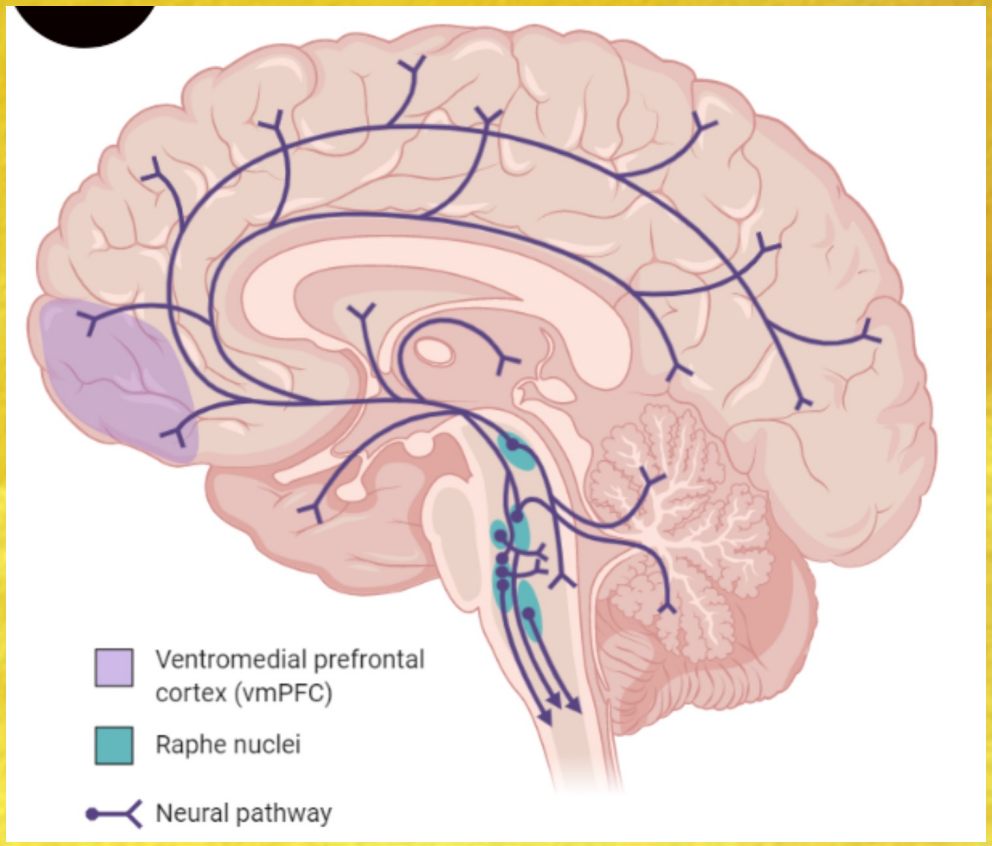
The Norepinephrine Pathways

- Originate in the midbrain's locus coeruleus ("blue spot") and project *widely* thru the brain and spinal cord.
- It's like "the adrenal gland of the brain", spritzing norepinephrine to keep you awake...
- Has a major role in the control of attention, in arousal, in the startle response and in the stress response.



The Serotonin Pathways

- Originate in the midbrain's raphe nucleii and project widely to the brain and spinal cord. Especially relevant to **mood** are the projections to the nucleus accumbens, frontal cortex and hippocampus
- Involved in modulation of mood, in sleep, memory processing.
- Serotonin: The main false culprit in the "chemical imbalance" popularization (propaganda?)

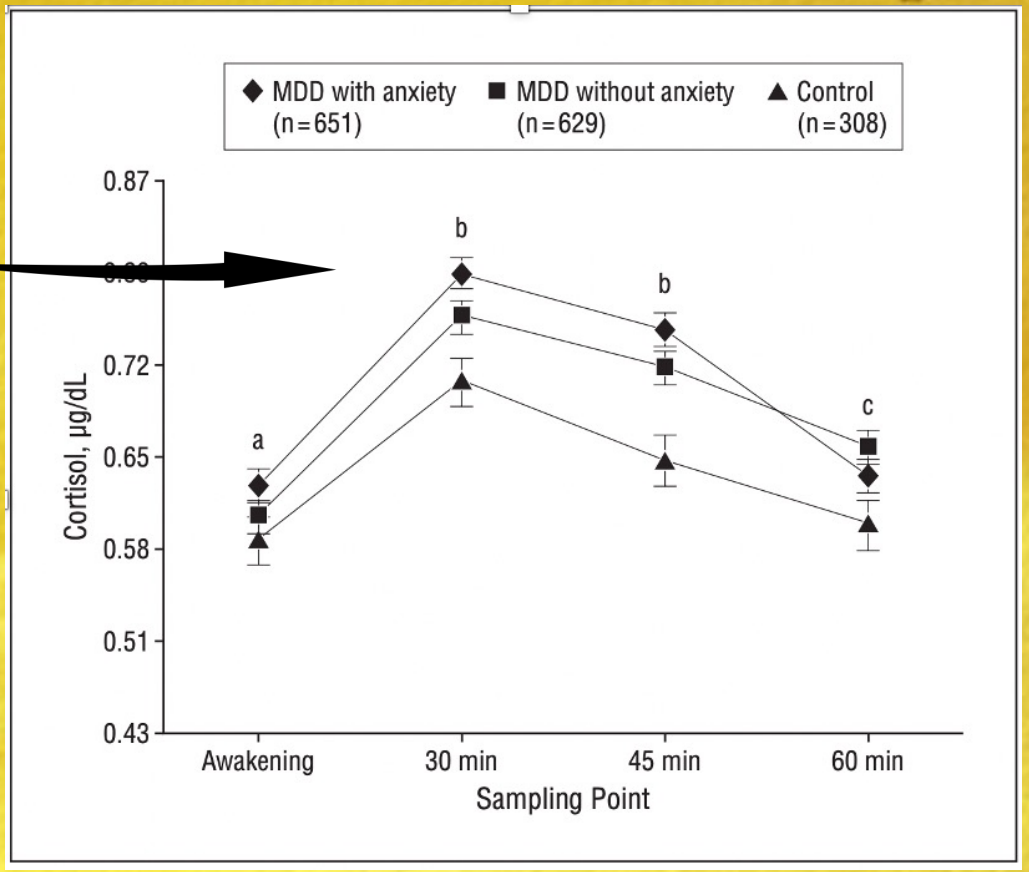


Pathophysiological hypotheses of Major Depressive Disorder II

i. Neurotransmitter “imbalance” (monoamines)
ii. **Neural network and neuroendocrine**
iii. Inflammation
iv. Neurogenesis related

Neuroendocrine: **Two ways** the HPA axis seems dysfunctional in MDD

- *Generally*, a hyper-activation of the HPA axis: Elevated **cortisol** – and **corticotropin-releasing hormone (CRH);** consequent hippocampal volume reduction.
- *Specifically*, a failure of the negative feedback response. How can you tell? Probe the HPA axis with the **Dexamethasone Suppression Test (DST)**
  Administer the corticosteroid **dexamethasone** in the evening. Collect blood for cortisol the next day. NORMAL: Cortisol release is SUPRESSED. ABNORMAL: Cortisol does not decrease enough ("DST NON SUPRESSION")
- BUT... ***the DST is not clinically useful***... It has very low sensitivity, especially with outpatients.



Mean awakening salivary **cortisol** in controls, MDD patients with and without comorbid anxiety

Vreeburg SA, Hoogendijk WJG, van Pelt J, et al. Major Depressive Disorder and Hypothalamic-Pituitary-Adrenal Axis Activity: Results From a Large Cohort Study. *Arch Gen Psychiatry*. 2009;66(6):617–626. doi:10.1001/archgenpsychiatry.2009.50

Circuit level changes in MDD

The effects of stress/glucocorticoids

- Review from an earlier IB 139 lecture:

  *"The same neurochemical events that **impair prefrontal function** .. **strengthen the emotional operations of the amygdala.** Thus, uncontrollable **stress** switches control of behavior from the "thoughtful" PFC to the more "primitive, conditioned responses" of the amygdala.*

- Glucocorticoids cause alterations in emotional circuits that *shift an organism away from ... learning and exploration...*

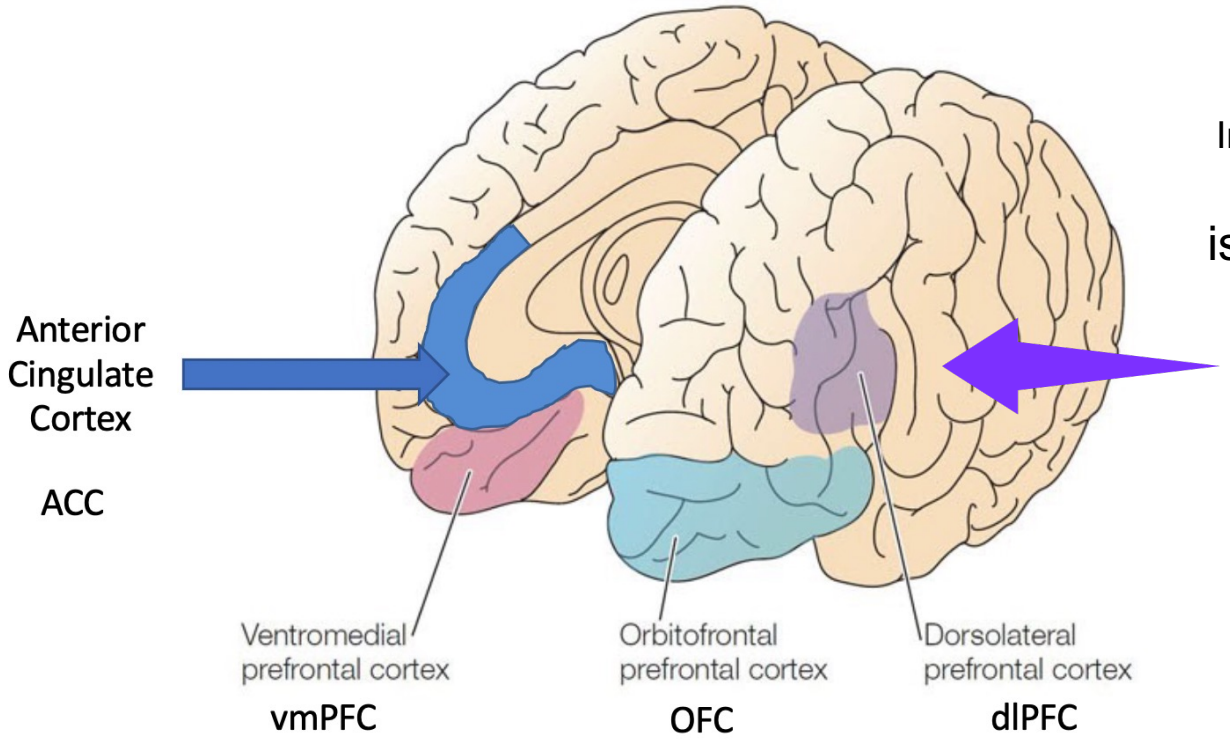
  - **An adaptarionist rationale**: In health, this makes sense, skewing behavior to AVOID exploration during chronic **stress** and rely on habit.
  - But if this dysfunctions, it leads to "disinterest in the external world, internal focus, and depression symptoms".

Circuit level changes in MDD: mPFC

- More specifically: Glucocorticoids /chronic stress shown to alter at cellular level:
  - the **medial prefrontal cortex** (**mPFC**) (involved in executive functioning and cognitive processing of emotion generated by subcortical regions like the amygdala)
  - the **hippocampus** (involved in memory) Chronic stress causes reduced plasticity – impaired learning/adaptation
  - the **amygdala** (processing of emotion) (increased excitability in response to later stress)
- The medial prefrontal cortex is part of the **Default Mode Network** implicated in **self-referential functions -** perhaps its dysfunction in turn implicates the obsessive self-absorbed rumination of severe depression.

A nice diagram (review from earlier IB 139 lecture) illustrating where the famous, mood-related PFC areas are.

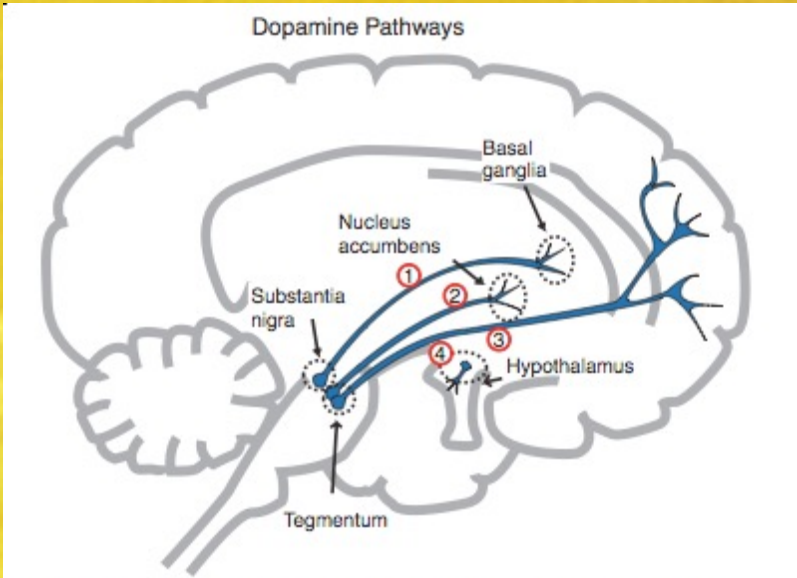
Prefrontal cortex (PFC) anatomy



Incidentally...
TMS is aimed at the dlPFC

Other implicated circuitry: The mesolimbic dopamine reward circuit

- Recall the **mesolimbic dopamine pathway -** from the midbrain's **ventral tegmental area (VTA)** projecting to the **nucleus accumbens** (#2)
- Remember, this pathway is associated with the rewarding effects of food, sex, and drugs of abuse.
- A modulation of its function may contribute to the *anhedonia*, *reduced motivation* and *low energy* in depression.



[a]Reprinted with permission from Stahl.[4] The pathways are (1) the nigrostriatal pathway, (2) the mesolimbic pathway, (3) the mesocortical pathway, and (4) the tuberoinfundibular pathway.

Hand-wavingly, let's say...

- Depression is associated with changes functional connectivity in the neural circuits involved in affect regulation – the circuits between...
  - **..."lower" limbic centers -** amygdala, hippocampus, basal ganglia, nucleus accumbens - that mediate raw emotion "bottom-up", and...
  - ..."higher" cortical areas of the prefrontal cortex (PFC) - subgenual PFC, **medial prefrontal (mPFC)**, **dorsolateral (dlPFC)** as well as cingulate cortex - that mediate ***inhibition/modulation*** "top-down".

- *So, imagine "two possible imbalances": 1) Too much negative emotion "bottom-up" 2)Too little emotion regulation/reappraisal "top-down"*

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

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, activity and feeding. (Sounds like a **Defense** – adaptive "low mood" behavior.)
- But also, laboratory model stressors not only cause "depression-like behavior" – they 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.
- Social stressors like *targeted rejection* **up-regulate** pro-inflammatory immune response genes! (while down-regulating antiviral immune response genes).
  - Hypothesized: This is 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.

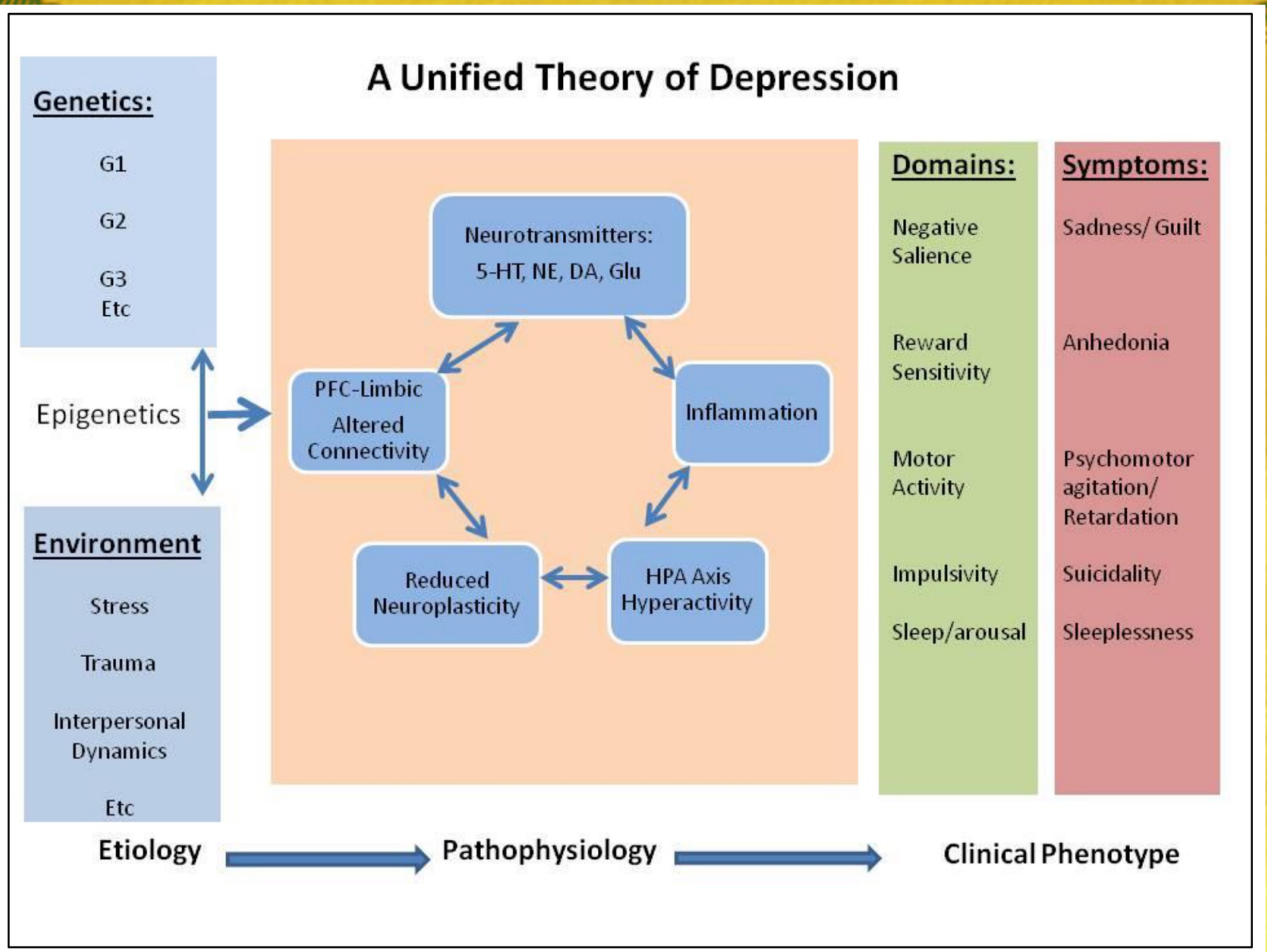
Pathophysiological hypotheses of Major Depressive Disorder IV

- Neurotransmitter “imbalance” (monoamines)
- Neural network and neuroendocrine
- Inflammation
- **Neurogenesis related**

Clues that neurogenesis is involved in the pathophysiology of (and *recovery* from) MDD

- *Decreased* neurogenesis found in *post-mortem* human brains, and in animal models of depression.
- All antidepressant therapies *increase* adult hippocampal neurogenesis (SSRIs, MAOIs, TCAs, Li, ECT, physical exercise...) – and blocking this hippocampal adult neurogenesis nullifies the antidepressant effects.
  - The **lag** between starting the frequently used antidepressant medications and response may be due to the time needed for gene expression involved in neurogenesis.
- New clues from burgeoning psychedelic studies!
  - Psychedelics such as "... psilocybin...show ... potential to treat **depression**, anxiety, and addiction. Importantly, clinical improvements can **last** for months or years after treatment. 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

Takeaways


A Unified Theory of Depression
Genetics:
G1
G2
G3
Etc
Epigenetics
Environment
Stress
Trauma
Interpersonal Dynamics
Etc
Neurotransmitters: 5-HT, NE, DA, Glu
PFC-Limbic Altered Connectivity
Inflammation
Reduced Neuroplasticity
HPA Axis Hyperactivity
Domains:
Negative Salience
Reward Sensitivity
Motor Activity
Impulsivity
Sleep/arousal
Symptoms:
Sadness/ Guilt
Anhedonia
Psychomotor agitation/ Retardation
Suicidality
Sleeplessness
Etiology
Pathophysiology
Clinical Phenotype

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)**