Leveraging Neuroscience to Slow the Cycle of Addiction

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What Is Addiction?

Addictio (Latin)

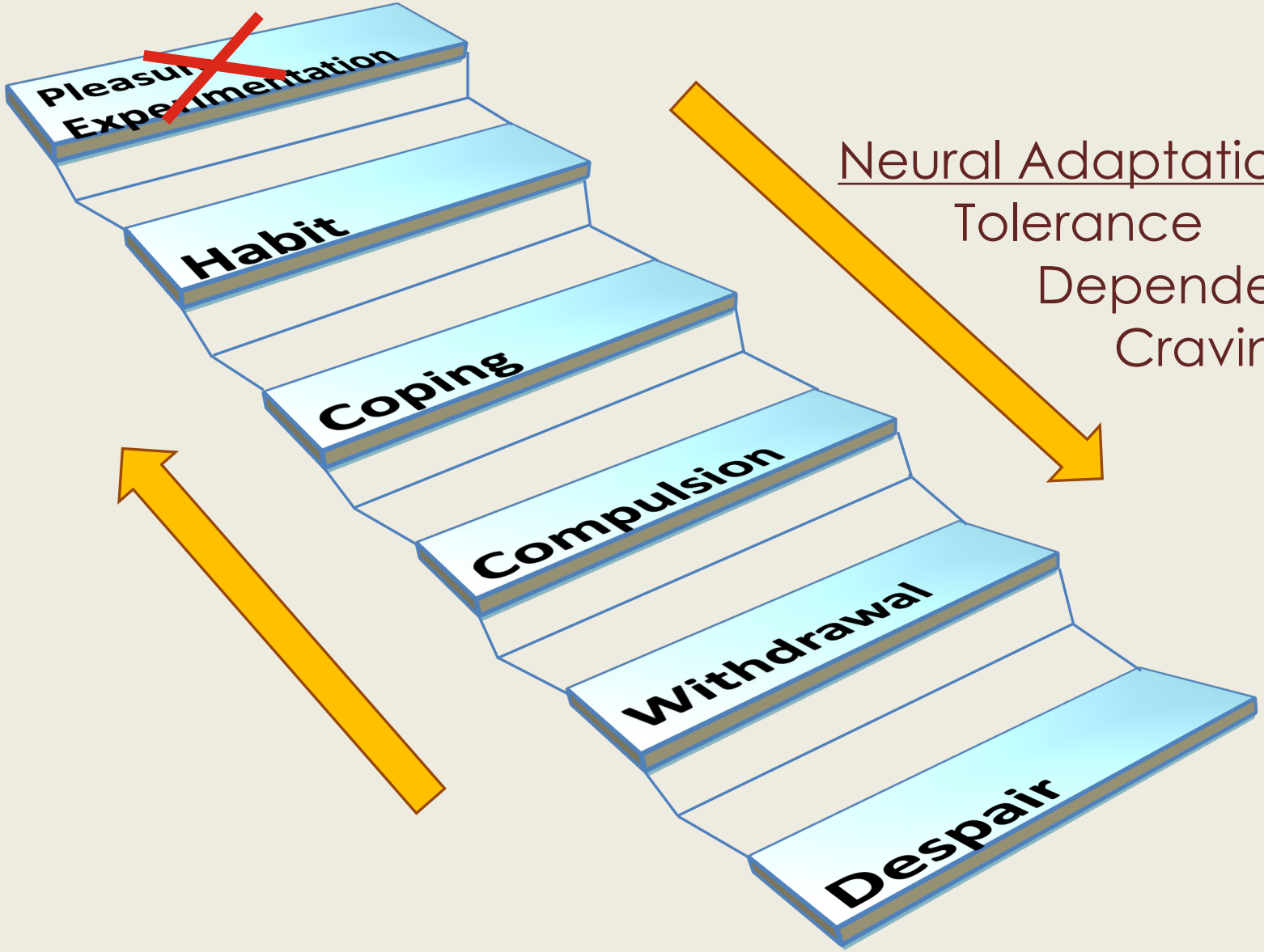
"to devote, sacrifice, or abandon"

Addiction:

When the debt from borrowing good feelings from the future comes due

(Schiavone, 2012)

Addiction is a Mental Illness

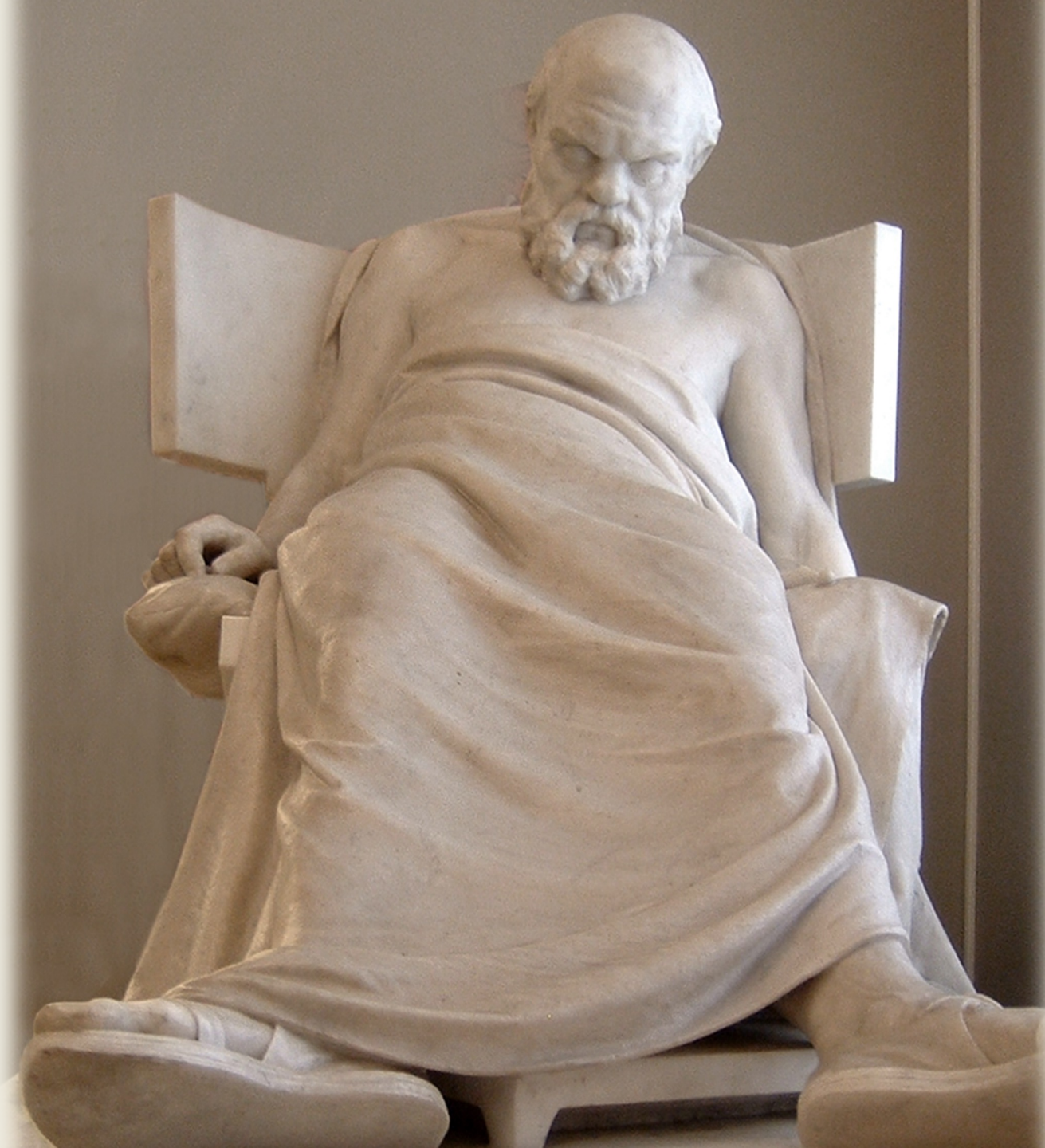


Neural Adaptation:
Tolerance
Dependence
Craving

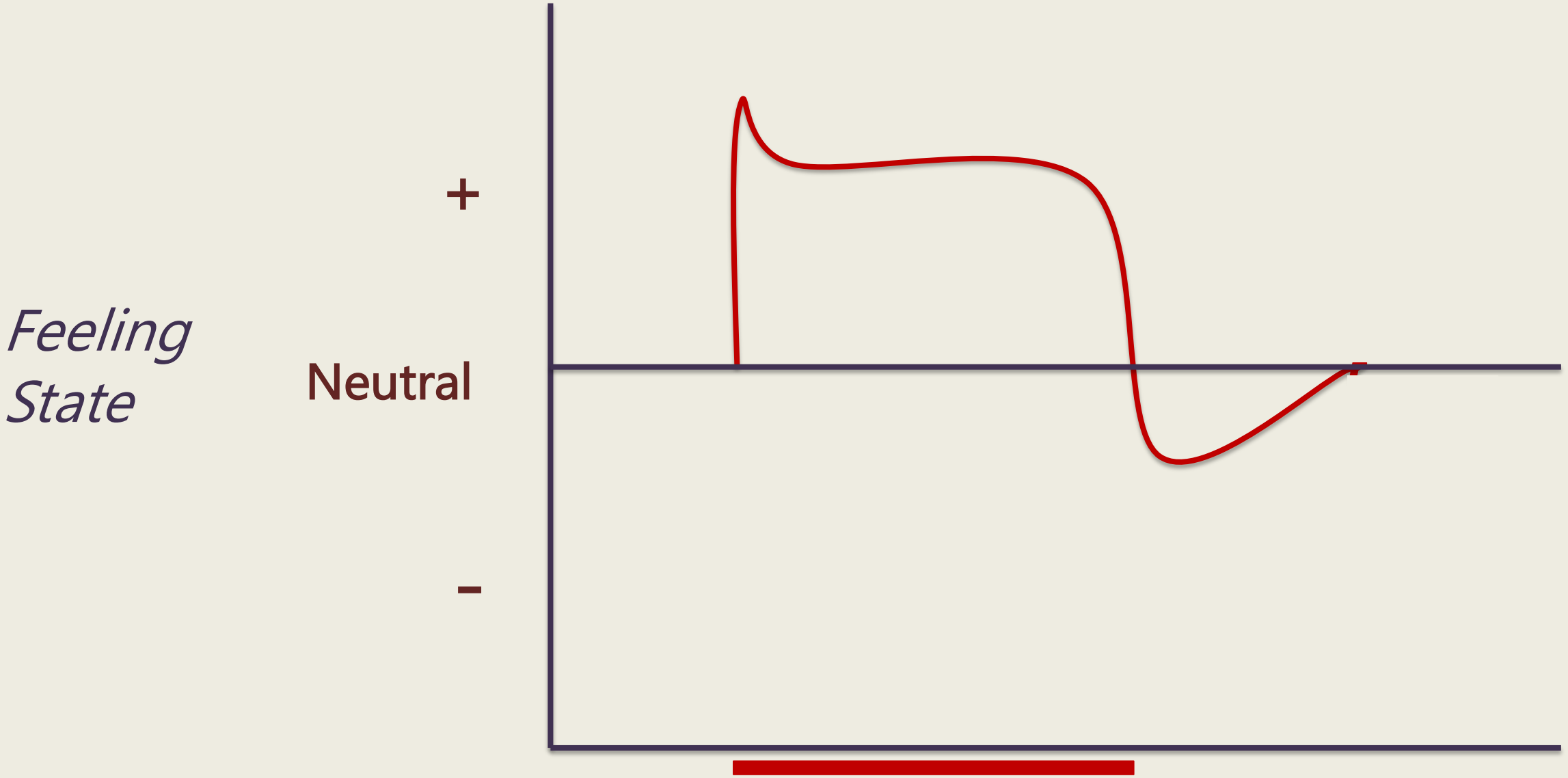
Socrates' Last Day

"How singular is the thing called pleasure, and how curiously related to pain, he (sic) who pursues either of them is generally compelled to take the other."

Recorded by Plato, about 350 B.C.E in *Phaedo*

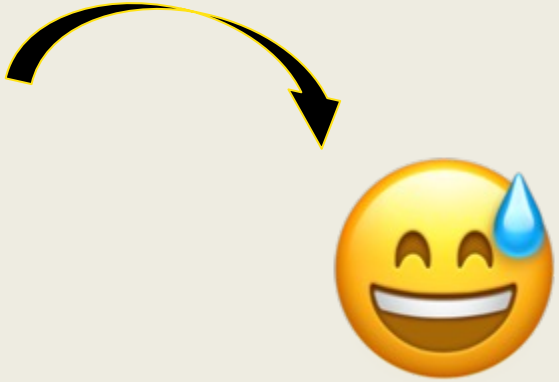


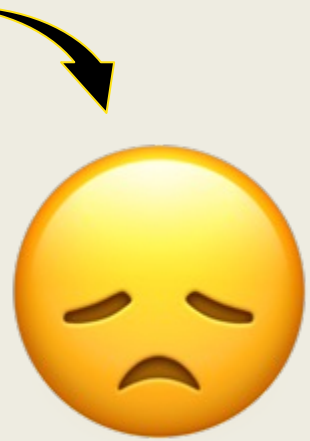
Effect of Any Addictive Drug



From Solomon & Corbit, 1974

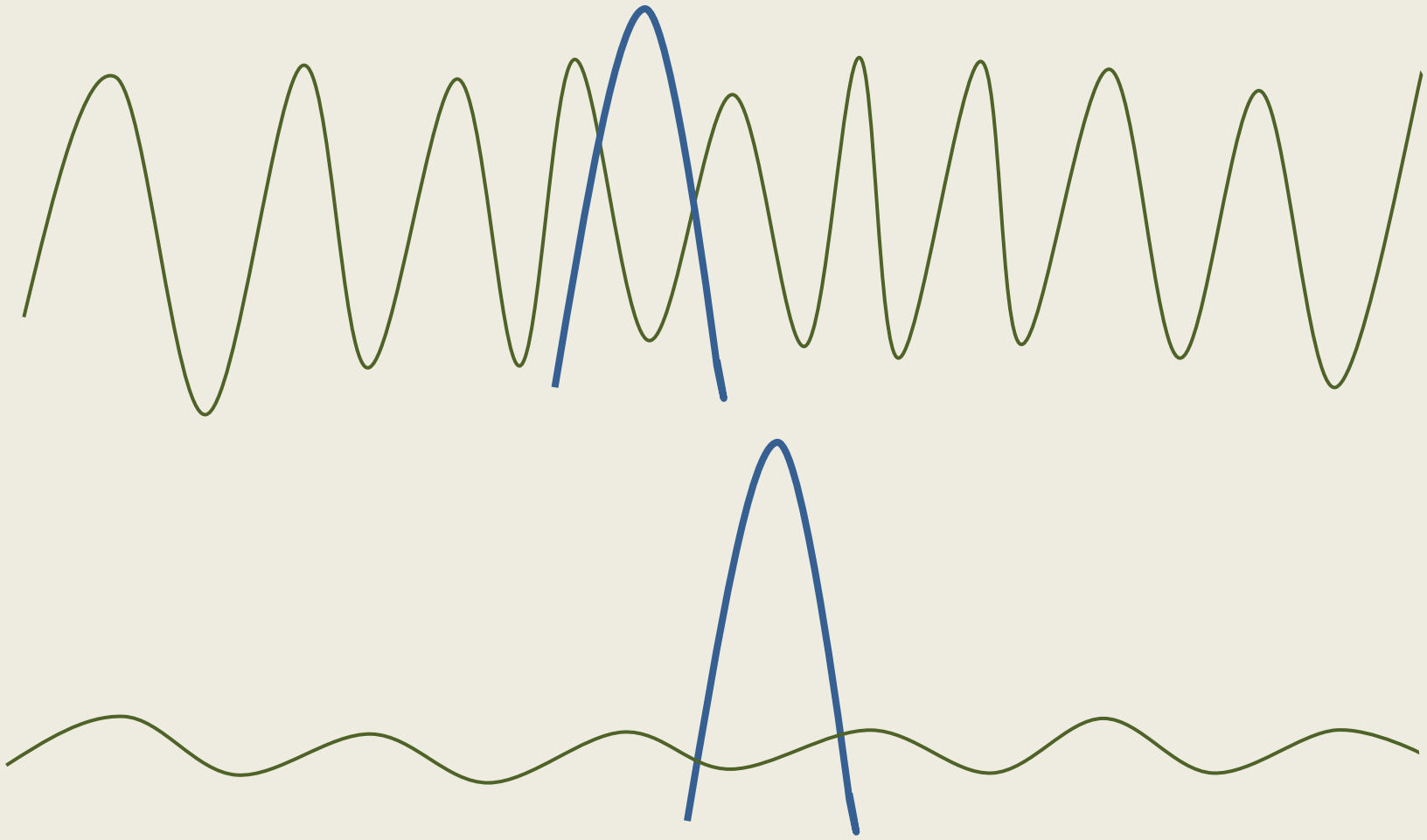
Happens all the time...





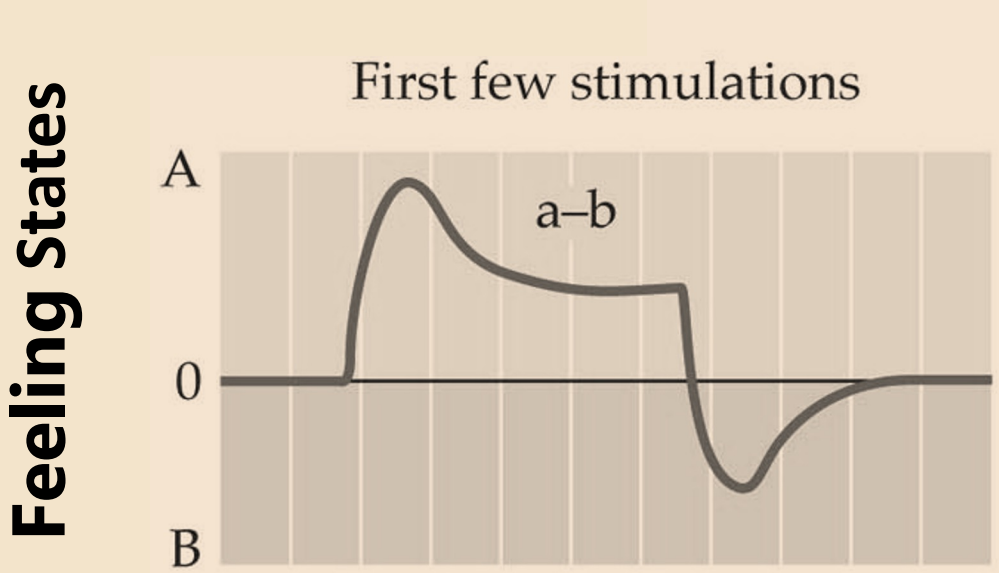
Happens all the time…

Why does the brain compensate for change?



Affective Homeostasis: Necessary for Detecting Meaningful Stimuli

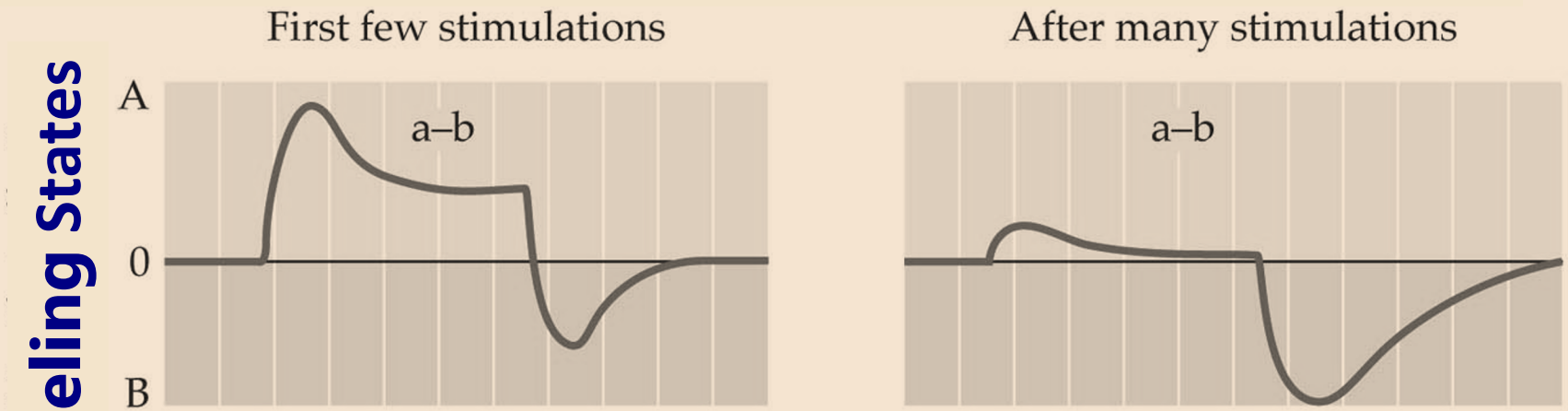
Two Process Underlie Drug Effects



From Solomon & Corbit, 1974

Drug-Induced Changes in Feeling States

Feeling States



Underlying Processes

"b process"adapts

- Earlier, larger, longer
- Learns to anticipate drug/"a process"

"Pop Quiz"

Predict the *b process (withdrawal state)* to:

Opiates ⟶

Methamphetamine ⟶

Alcohol ⟶

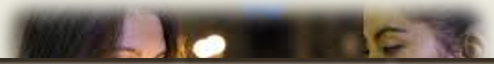
Ecstasy/MDMA ⟶

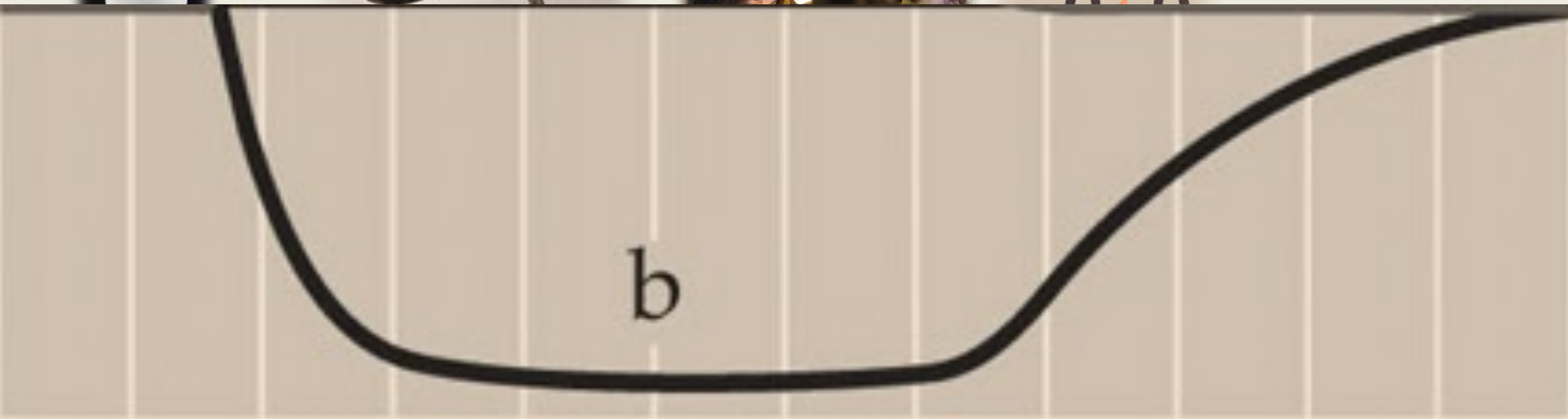
Benzodiazepines

(i.e., Xanax) ⟶

‘b process’ Learns

‘b process’ Learns





Causes of Relapse

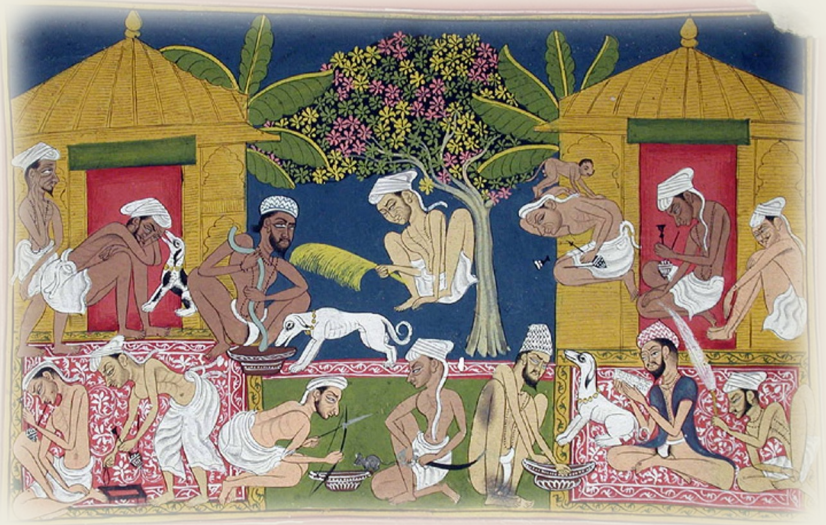
- ✓ Cues associated with drug *(b process)*
- ✓ "Taste" of drug *(b process)*
- ✓ Stress

Odds are Stacked High:
'Wired' to use mind-altering drugs

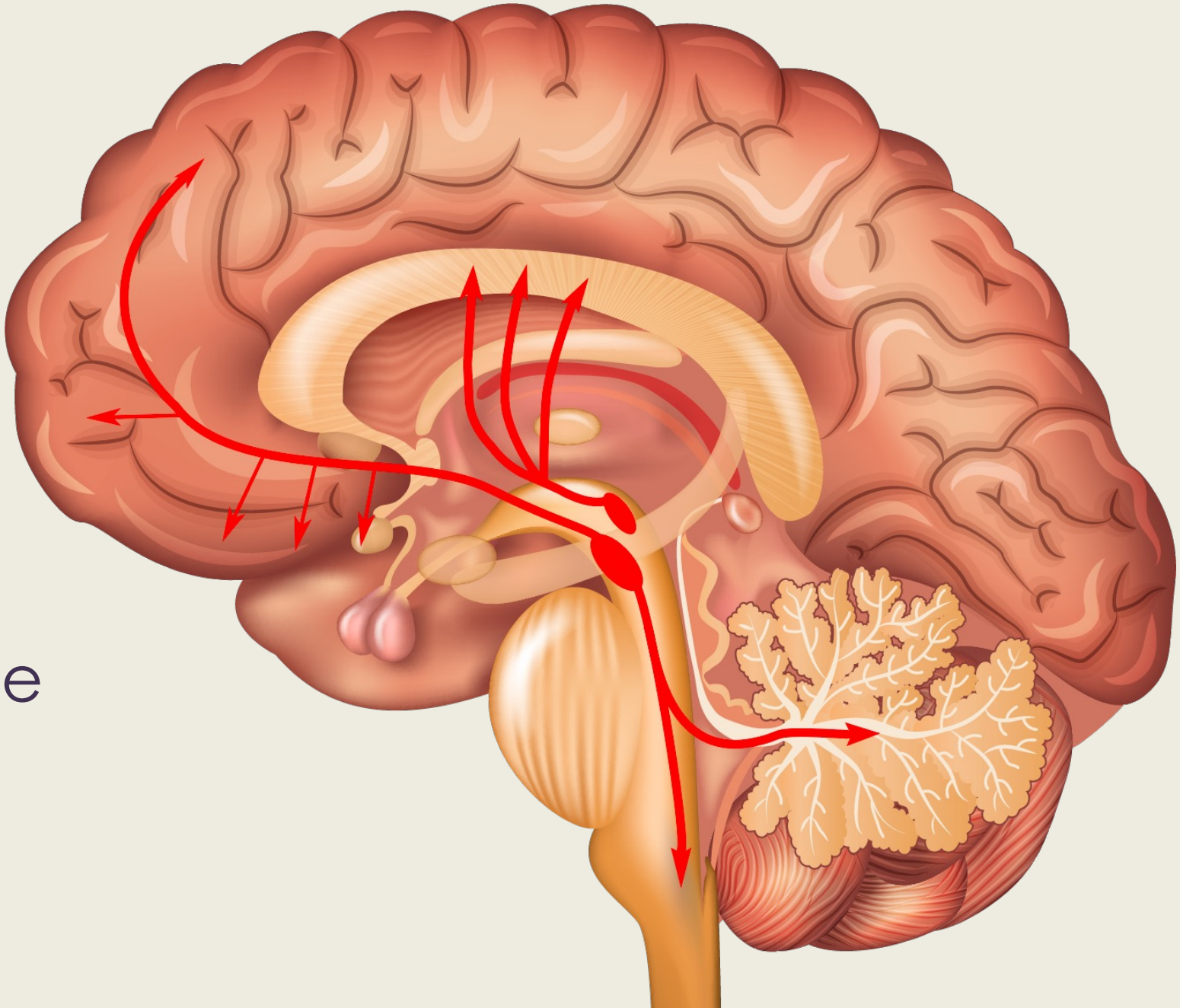
Since prehistoric times

Universal among humans

Ubiquitous in the animal kingdom

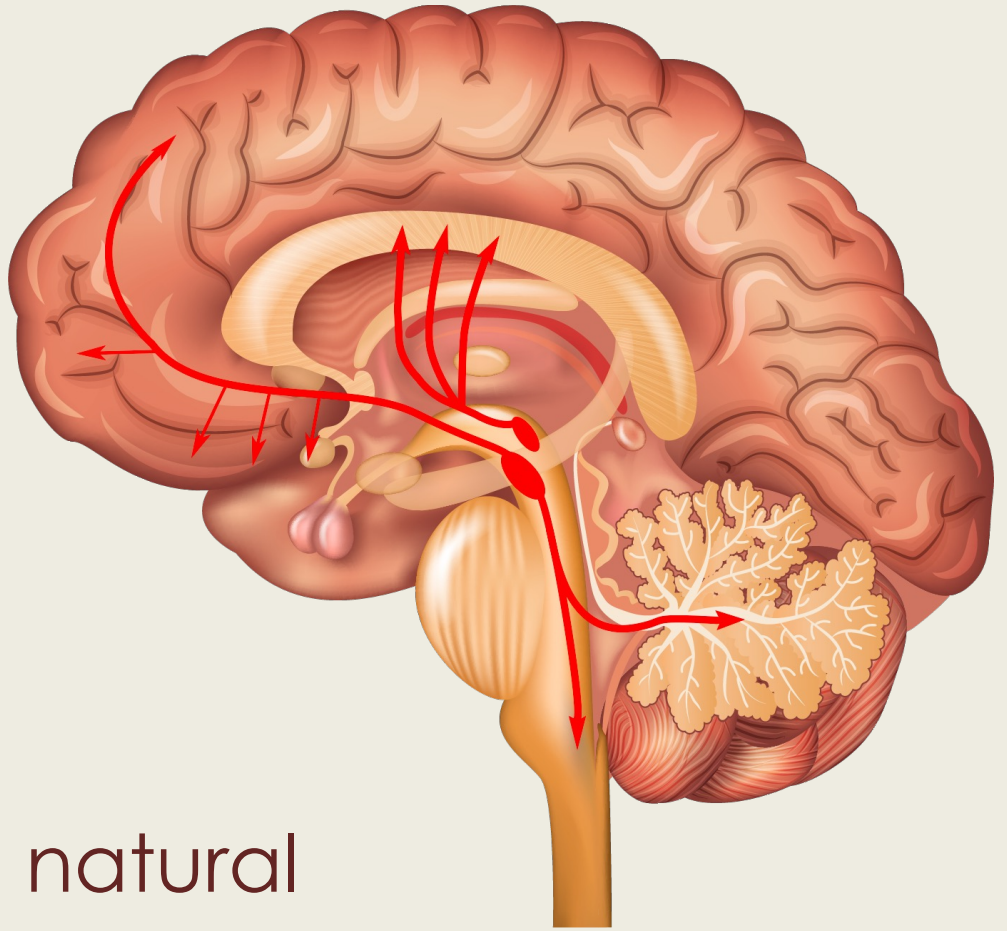


“Pleasure Pathway”



Mesolimbic Dopamine

Mesolimbic Pathway



- Evolved through natural selection
- Promotes eating and reproduction
- Co-opted by all drugs of abuse
  - Drugs are often more potent than natural stimuli
  - We control dose and delivery
- **Excess use dampens sensitivity**

Mesolimbic Dopamine Signals "News"

Surge

~~Antidepressant~~

Pleasure

Expectancy

Hunger

Excitement

Curiosity

Hope

Dip

~~Depression~~

Anhedonia

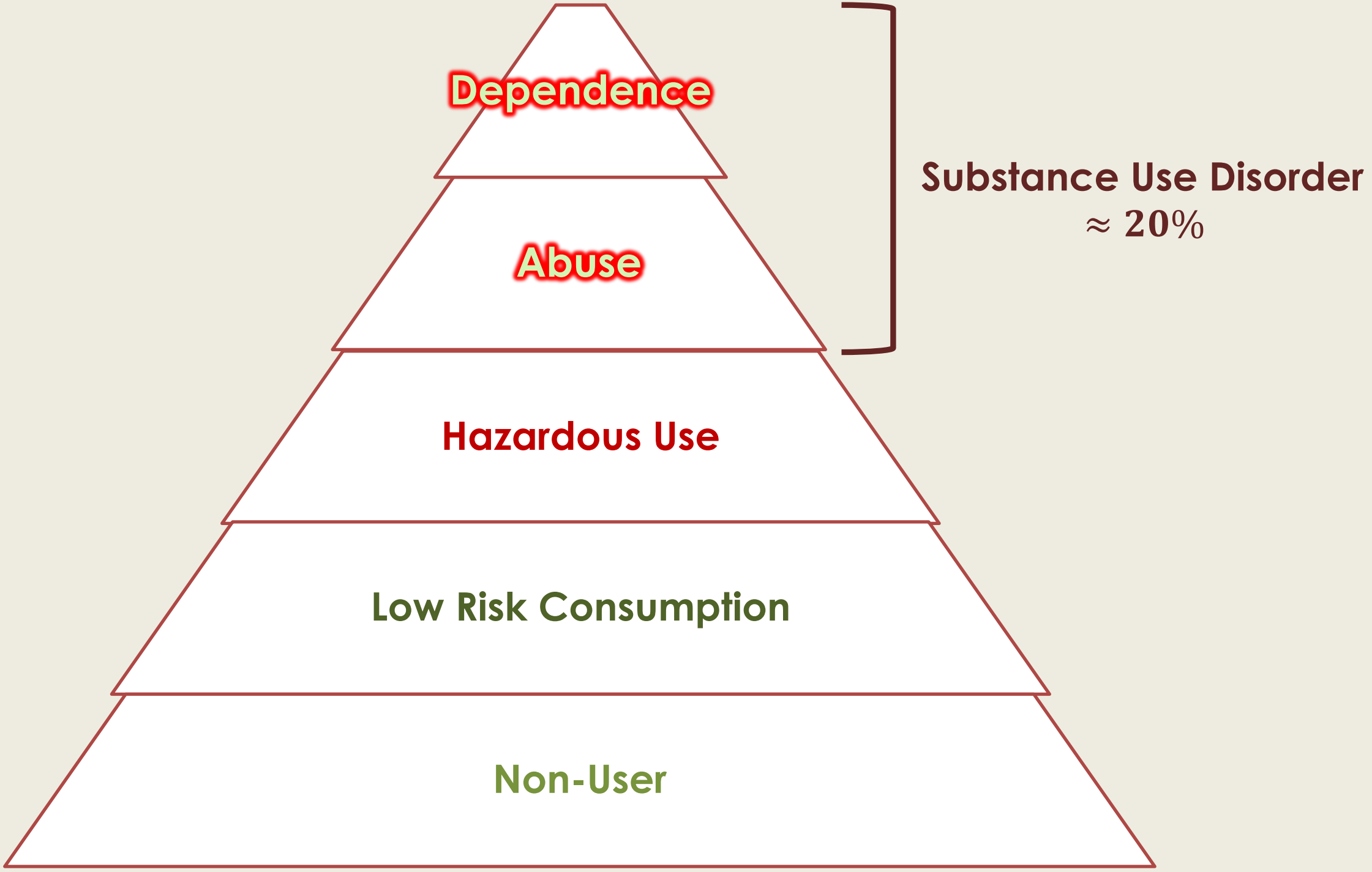
Disappointment

Indifference

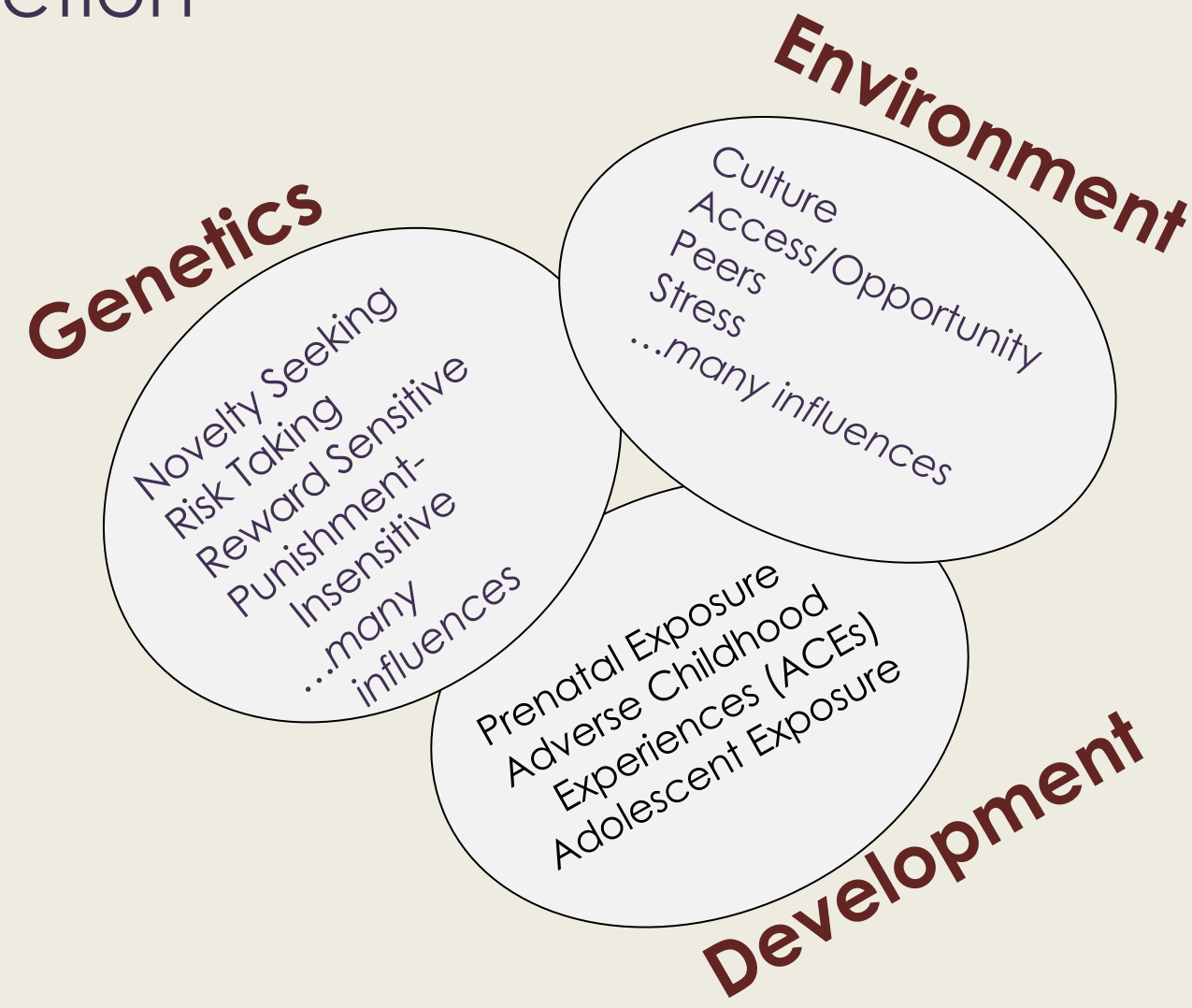
Boredom

Acedia

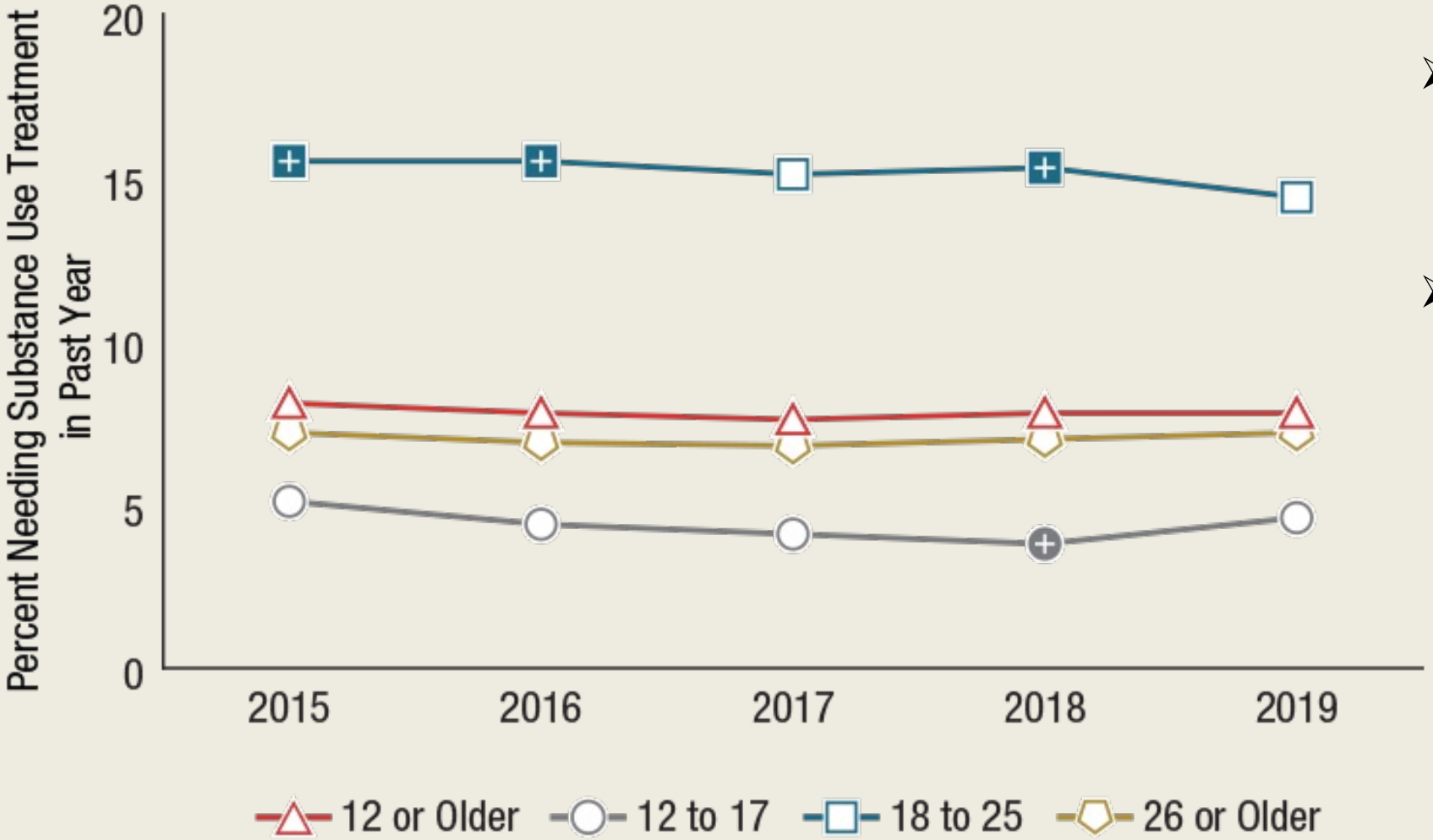
Despair


Dependence
Abuse
Substance Use Disorder
≈ 20%
Hazardous Use
Low Risk Consumption
Non-User

Causes of Addiction



Need for Substance Use Treatment in the Past Year among People Aged 12 or Older: 2015-2019



- Overdose deaths linked to synthetic opioids have risen dramatically: **six-fold from 2015-2020**
- In the past two years 3X among teenagers, and 5X for black teens

SAMSHA
Substance Abuse and Mental Health Services Administration

Brain Plasticity and Addiction

Adolescent substance use has been called the largest preventable and most expensive public health problem in the U.S.

At least 1-in-8 teenagers abused an illicit substance in the last year.

90 percent of Americans with a substance use disorder start using drugs before they are 18 years old.

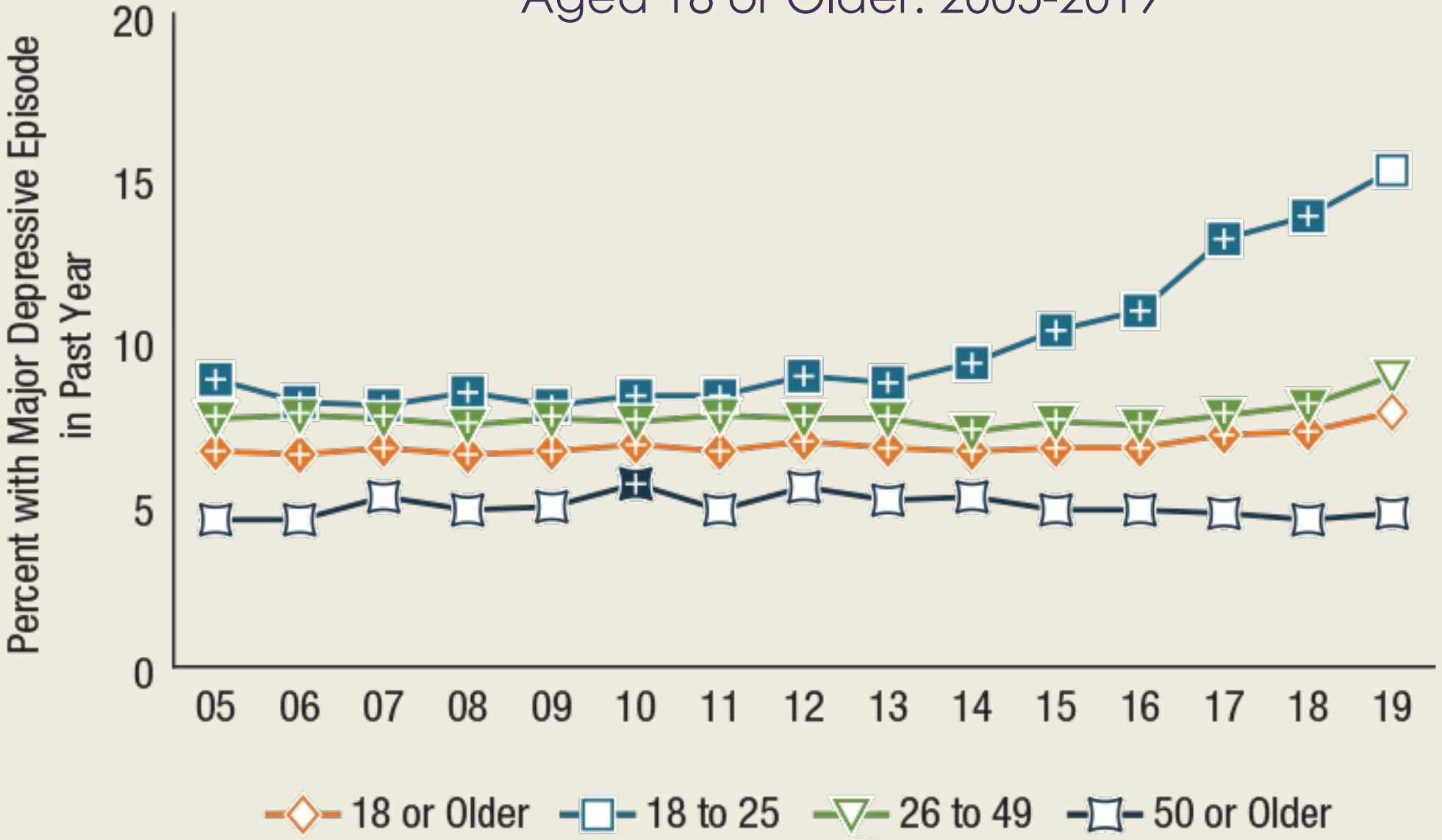
One-quarter who began using any addictive substance before age 18 are addicted, compared with one in 25 Americans who started using when they were 21 or older.

Center on Addiction and Substance Use, Report on Adolescent Substance Use, 2011

Why do kids use?

1. Escape suffering
   Negative Reinforcement
2. Experimentation / alleviate boredom
   Positive Reinforcement

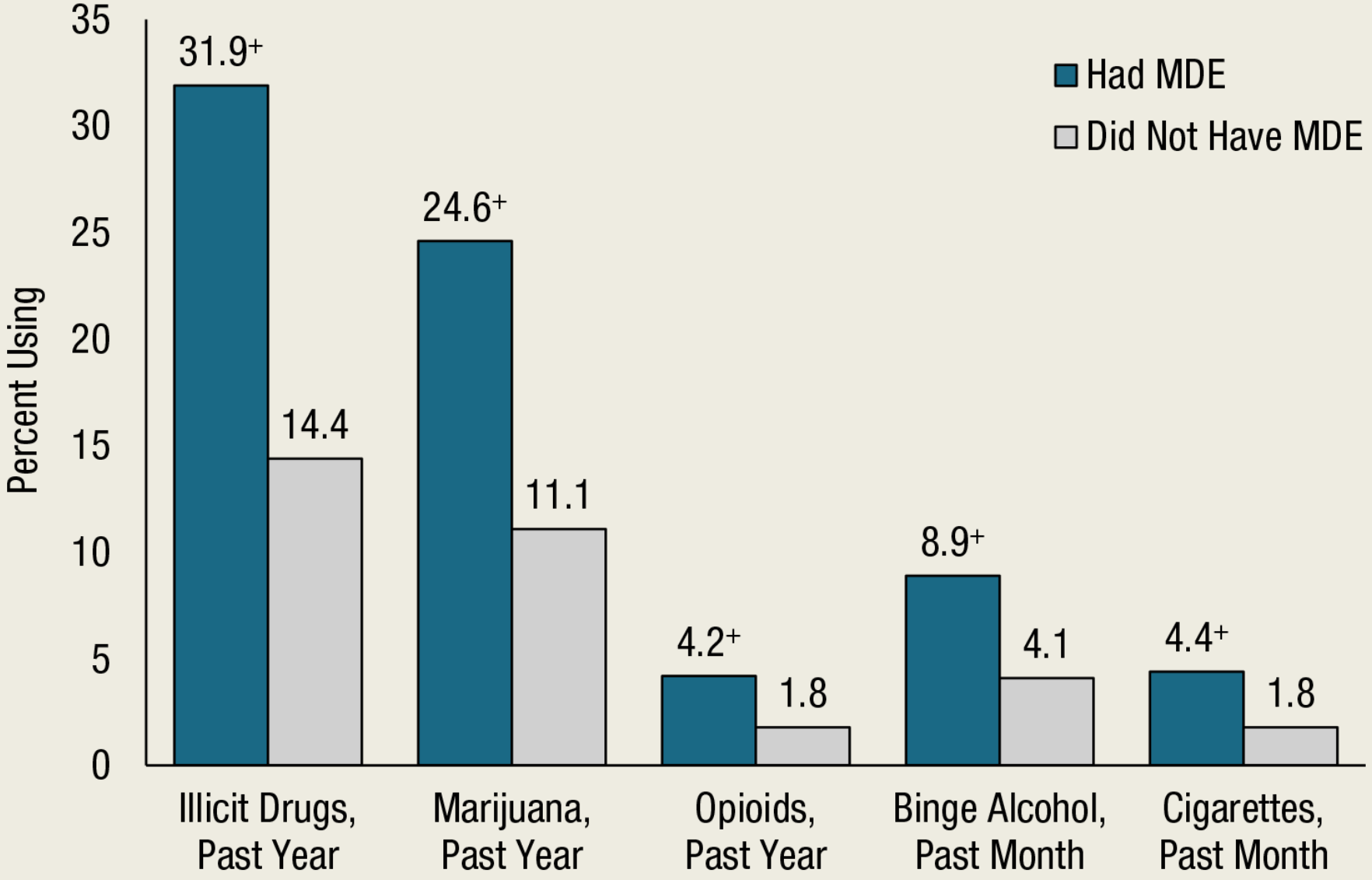
Major Depressive Episode in the Past Year among Adults Aged 18 or Older: 2005-2019



SAMSHA
Substance Abuse and Mental Health Services Administration

+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.

Substance Use among Youths Aged 12 to 17, by Past Year Major Depressive Episode (MDE) Status: 2019



SAMSHA
Substance Abuse and Mental Health Services Administration

+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.

Adverse Childhood Experiences

Adverse Childhood Experiences are Common

Household dysfunction

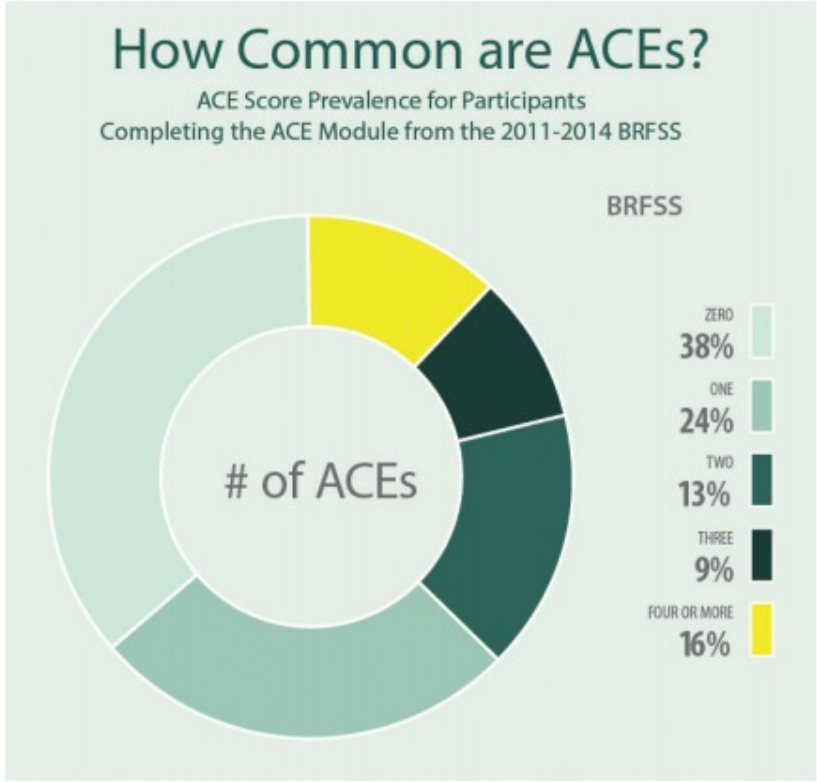
- **27% Substance Abuse**
- 23% Parental separation/divorce
- 17% Mental Illness
- 14% Violence toward mother
- 6% Criminal Behavior

Abuse

- 11% Emotional
- 28% Physical
- 21% Sexual

Neglect

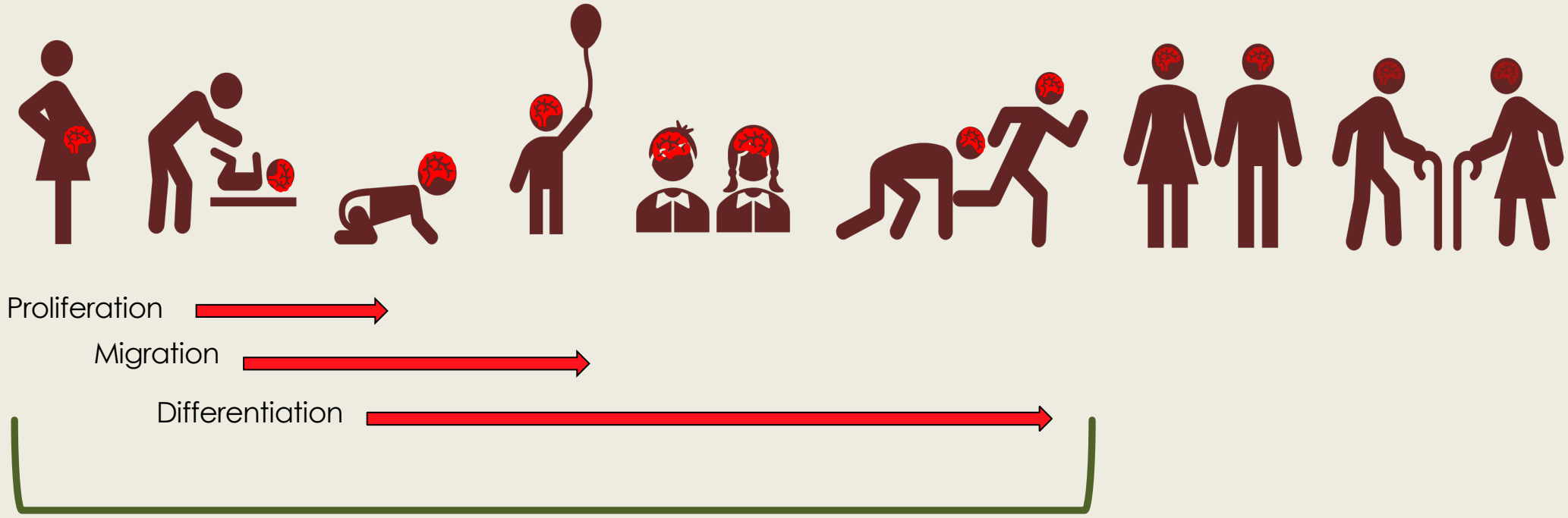
- 15% Emotional
- 10% Physical



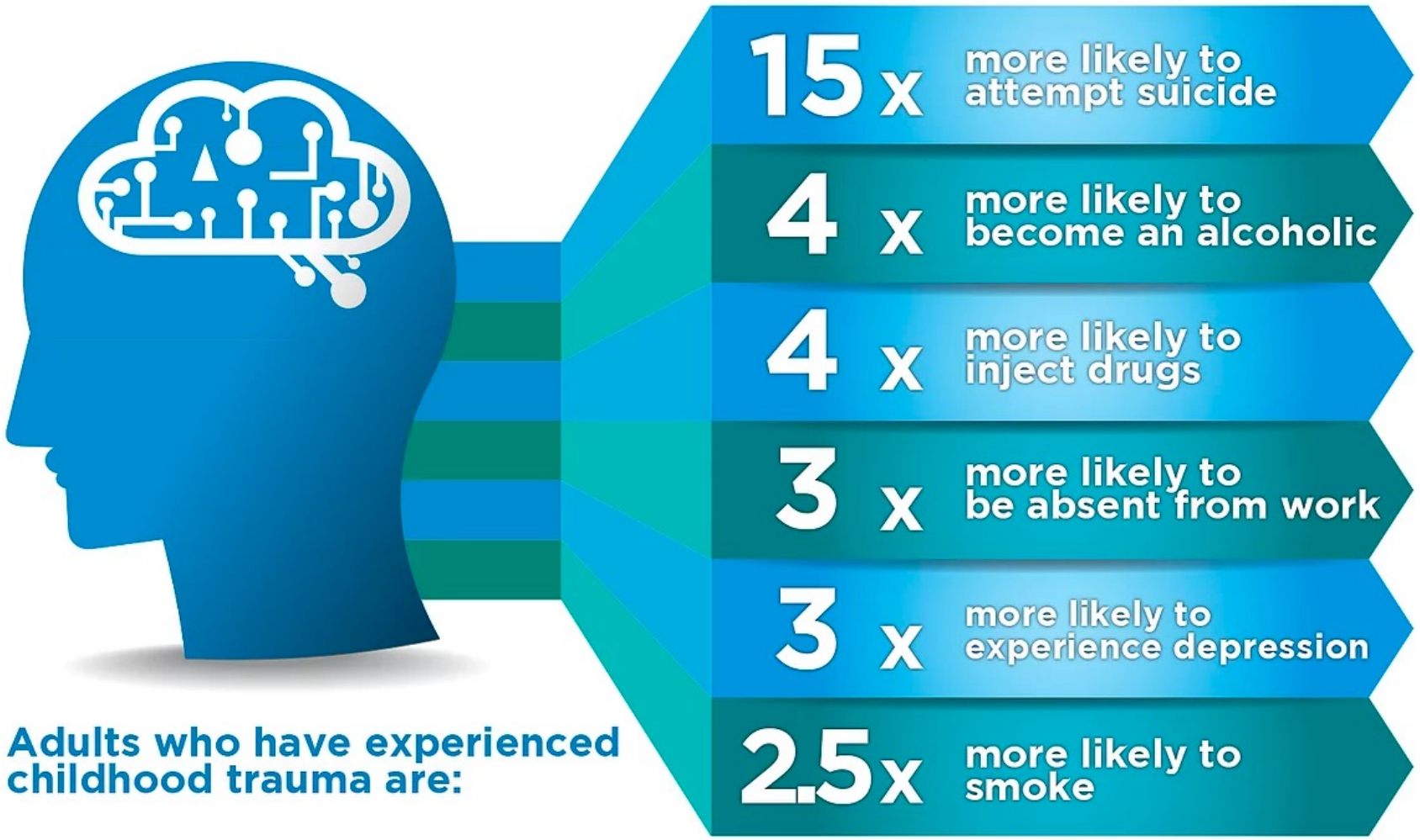
61%

of adults had at least one Adverse Childhood Experience

Developmental Plasticity → Lasting Impact



Adverse Childhood Experiences → Lasting Impact



For each adversity, risk for early initiation of substance abuse increases 2-4 X.

≥ 5 ACEs are seven to 10 times more likely to abuse drugs.

A boy with ≥ 4 ACEs is 46 times more likely to become an IV drug user in later life.

The majority of people with substance misuse have a trauma history.

Never Enough

The Neuroscience and Experience of Addiction

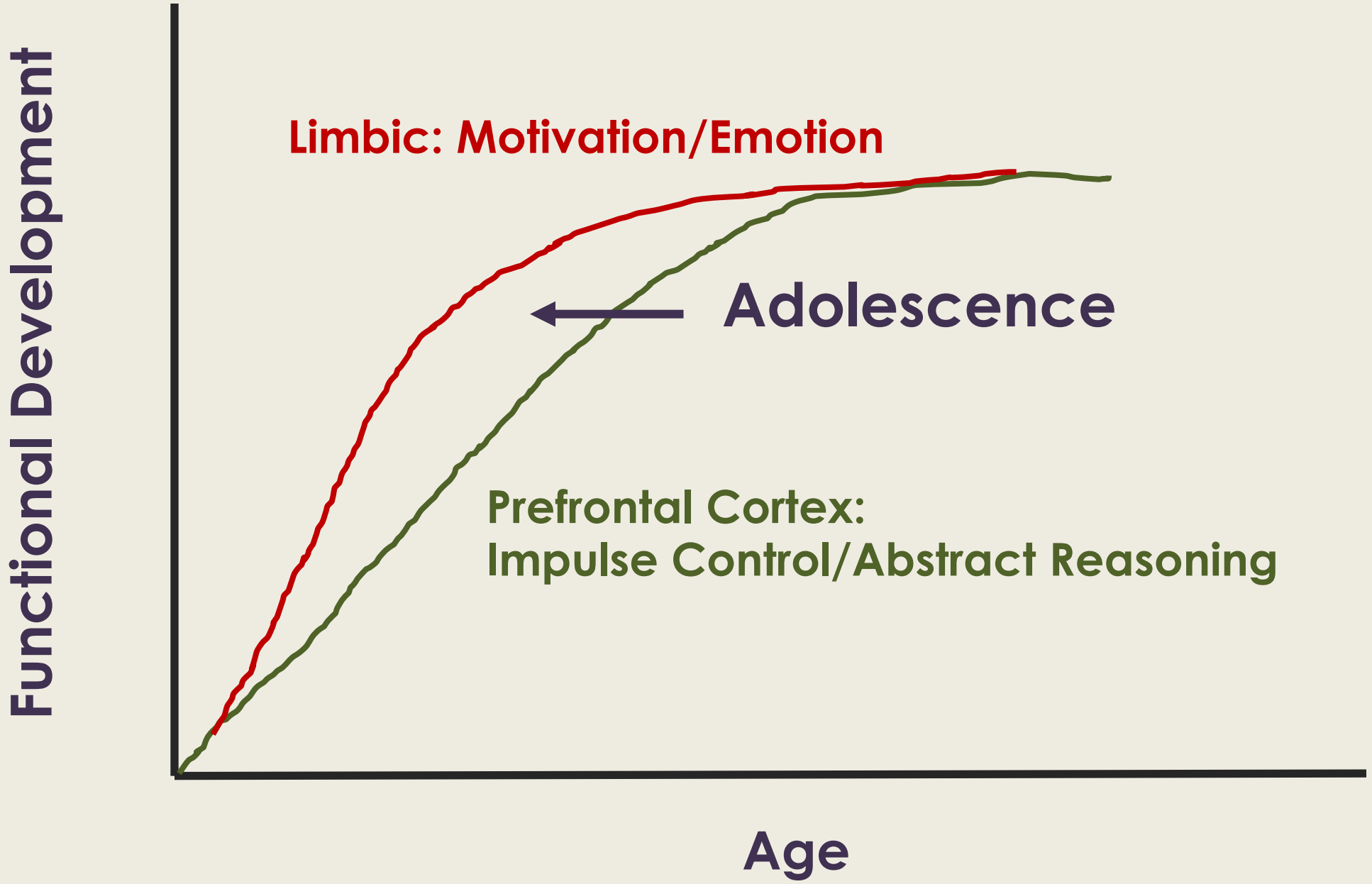
Judith Grisel

↑Novelty-Seeking

↑Risk-Taking

↓Impulse Control

↓Sensitivity to Punishment

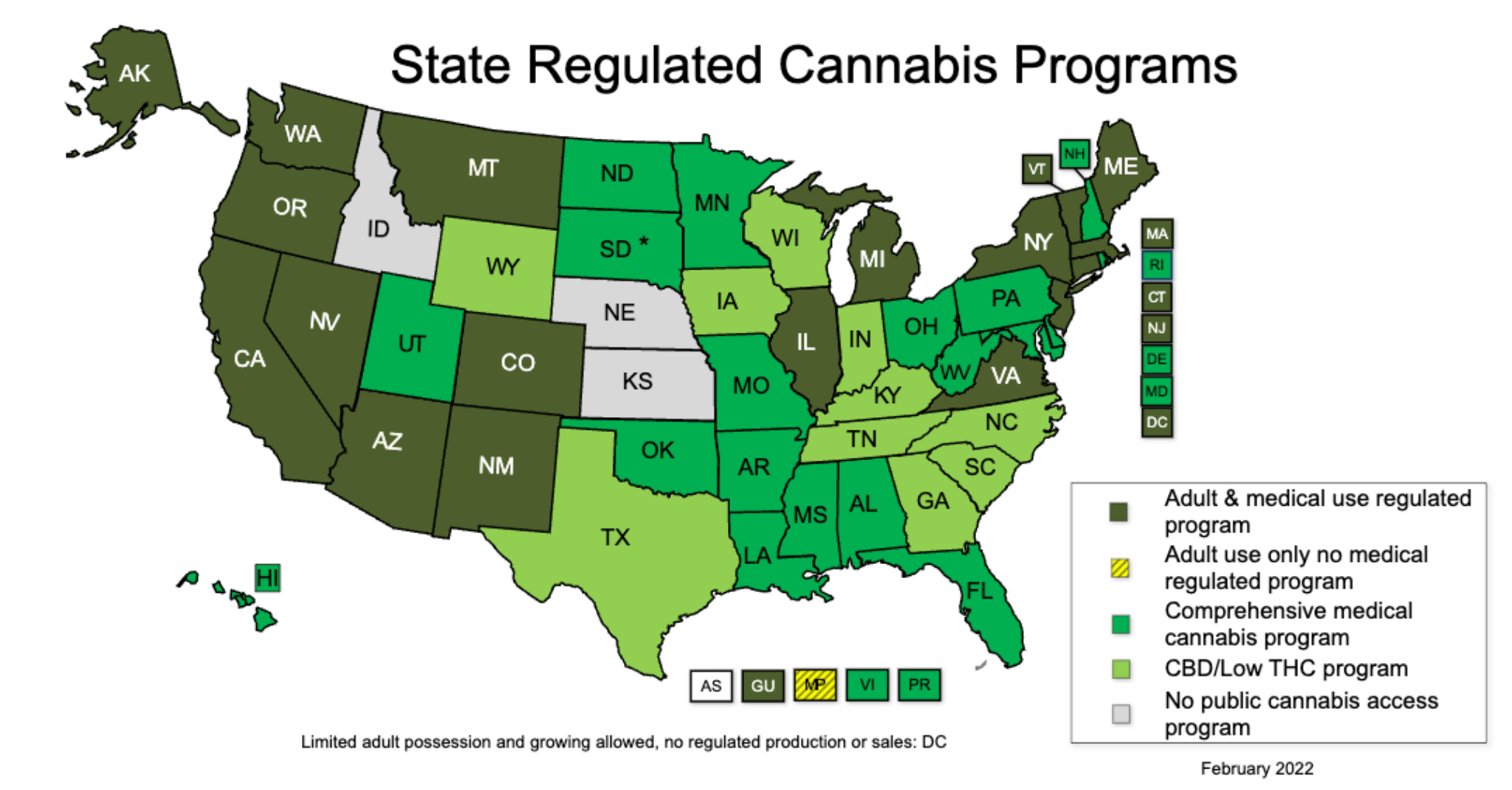

Functional Development
Limbic: Motivation/Emotion
Adolescence
Prefrontal Cortex:
Impulse Control/Abstract Reasoning
Age

How is adolescence a “sour spot” – catalyzing high addiction rates?

How might adolescence also be a “sweet spot” – for intervention?

Any muddy points about what addiction is or how it develops?

Today, 37 states, four territories and the District of Columbia allow the medical use of cannabis



Factors contributing to cannabis use disorder

- Early onset of use, progressing to daily use
- Genetic factors
- Positive reactions to cannabis during adolescence
- Use to cope with negative emotions
- Major life stressors
- Comorbid psychiatric disorder such as ADHD

Cannabinoids

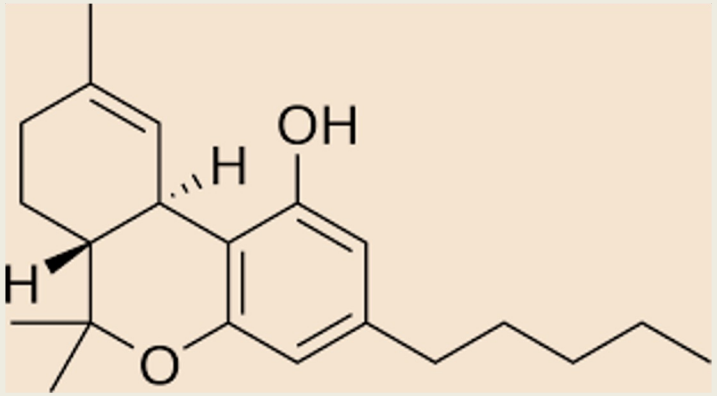
The marijuana plant produces well over 100 cannabinoids including:

No medical benefits
Significant risks

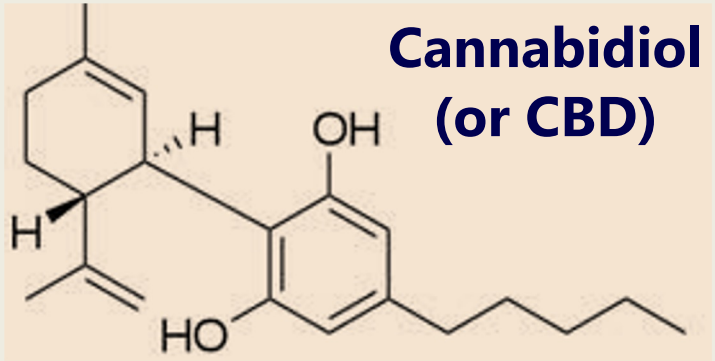
- Psychosis
- Reduced cognitive function
- Depression
- Cardiovascular Disease

Lancet Psychiatry, 2019; Gorinkel et al., 2020; Wei et al., 2022

Δ-9 Tetrahydrocannabinol (or THC)

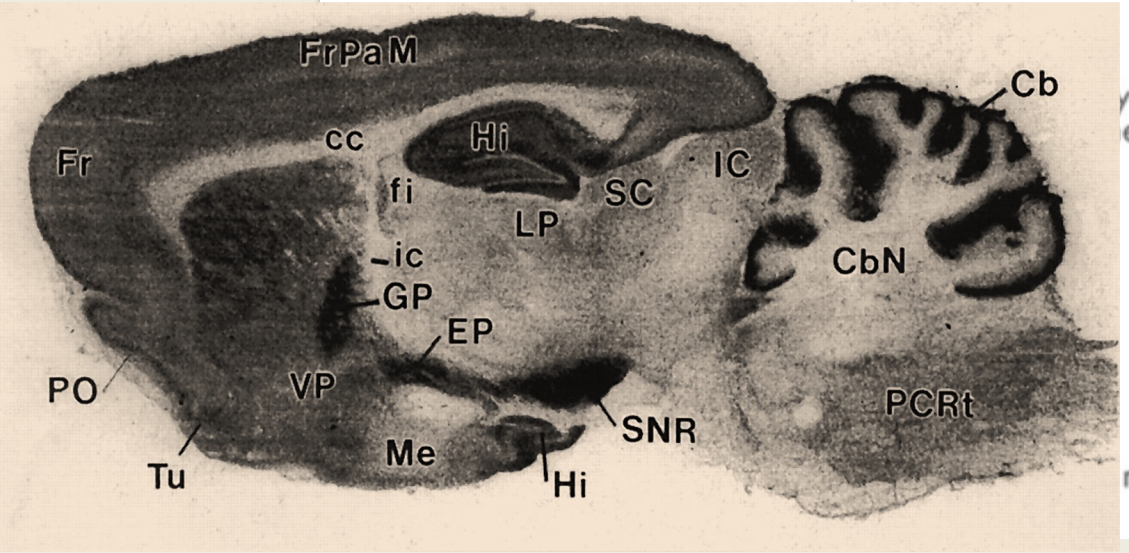


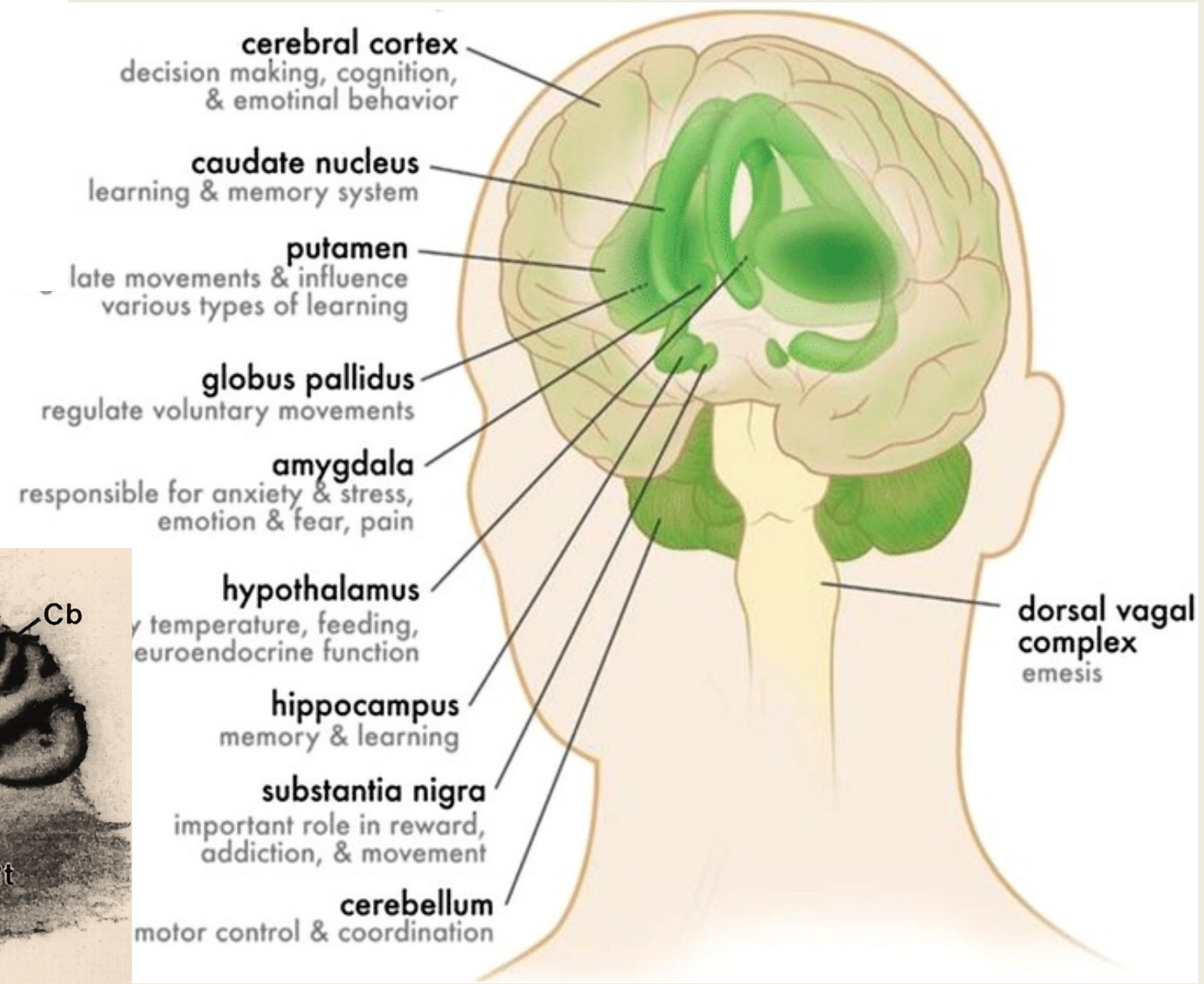
Cannabidiol (or CBD)



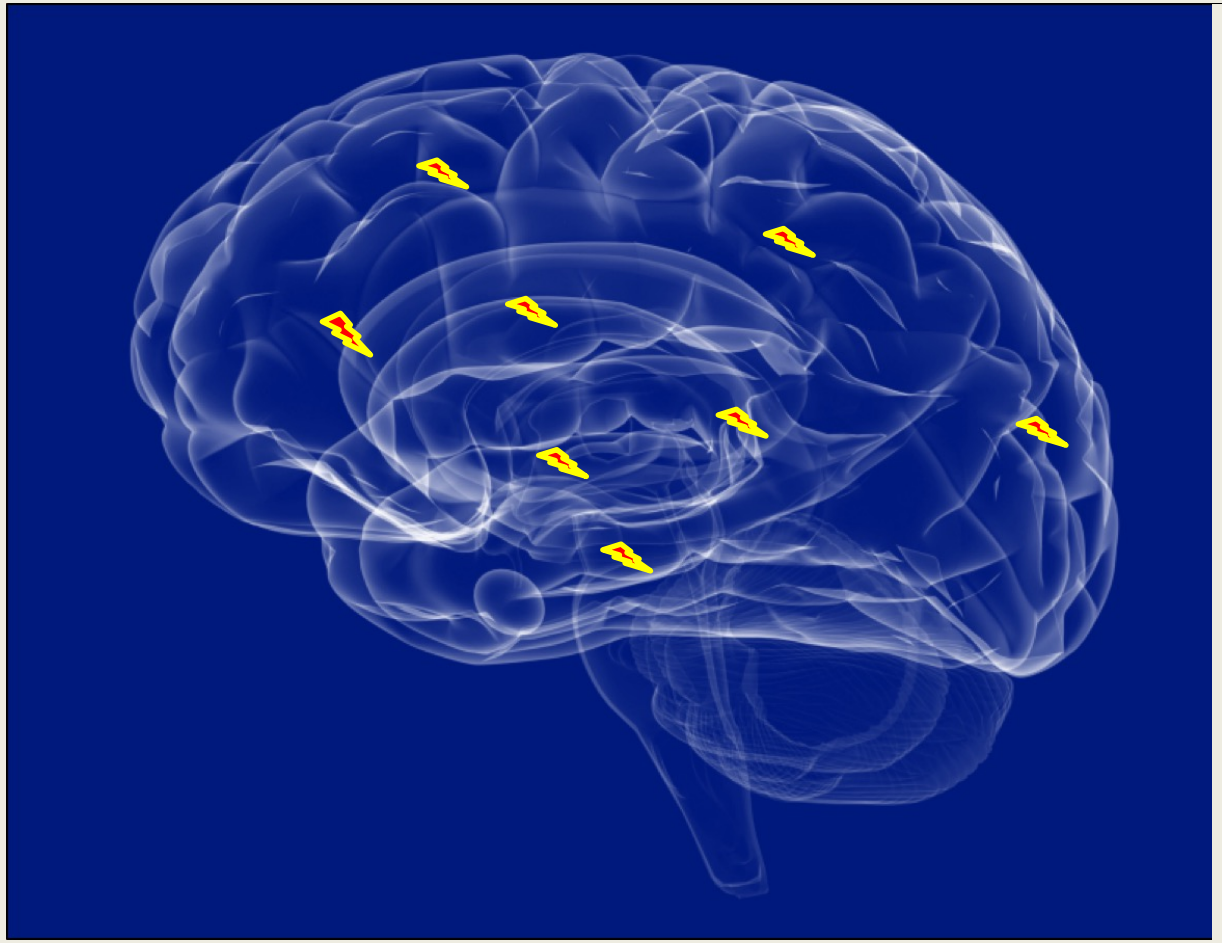
https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know

Endocannabinoids:
Anandamide and
2-Arachidonoylglycerol
(2-AG)





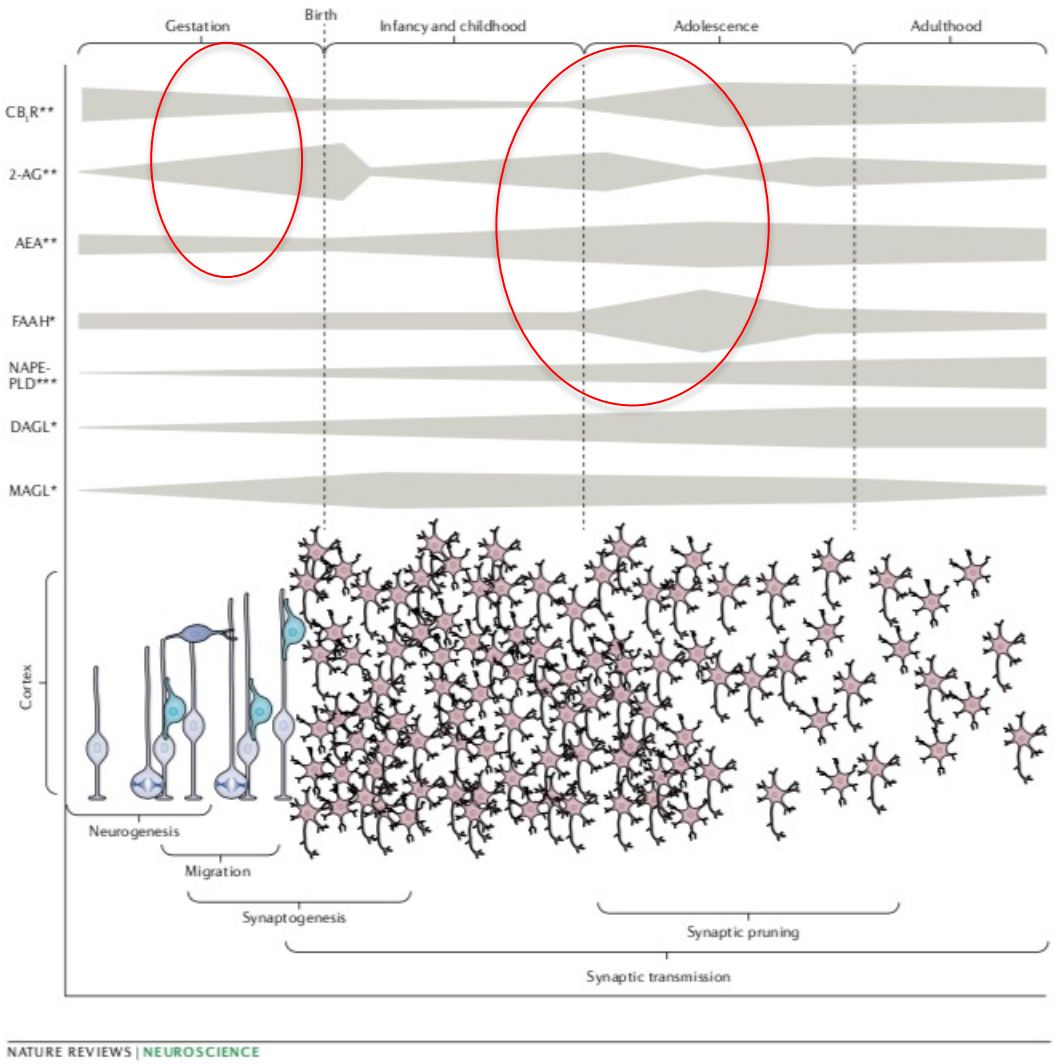
Anandamide and 2-AG

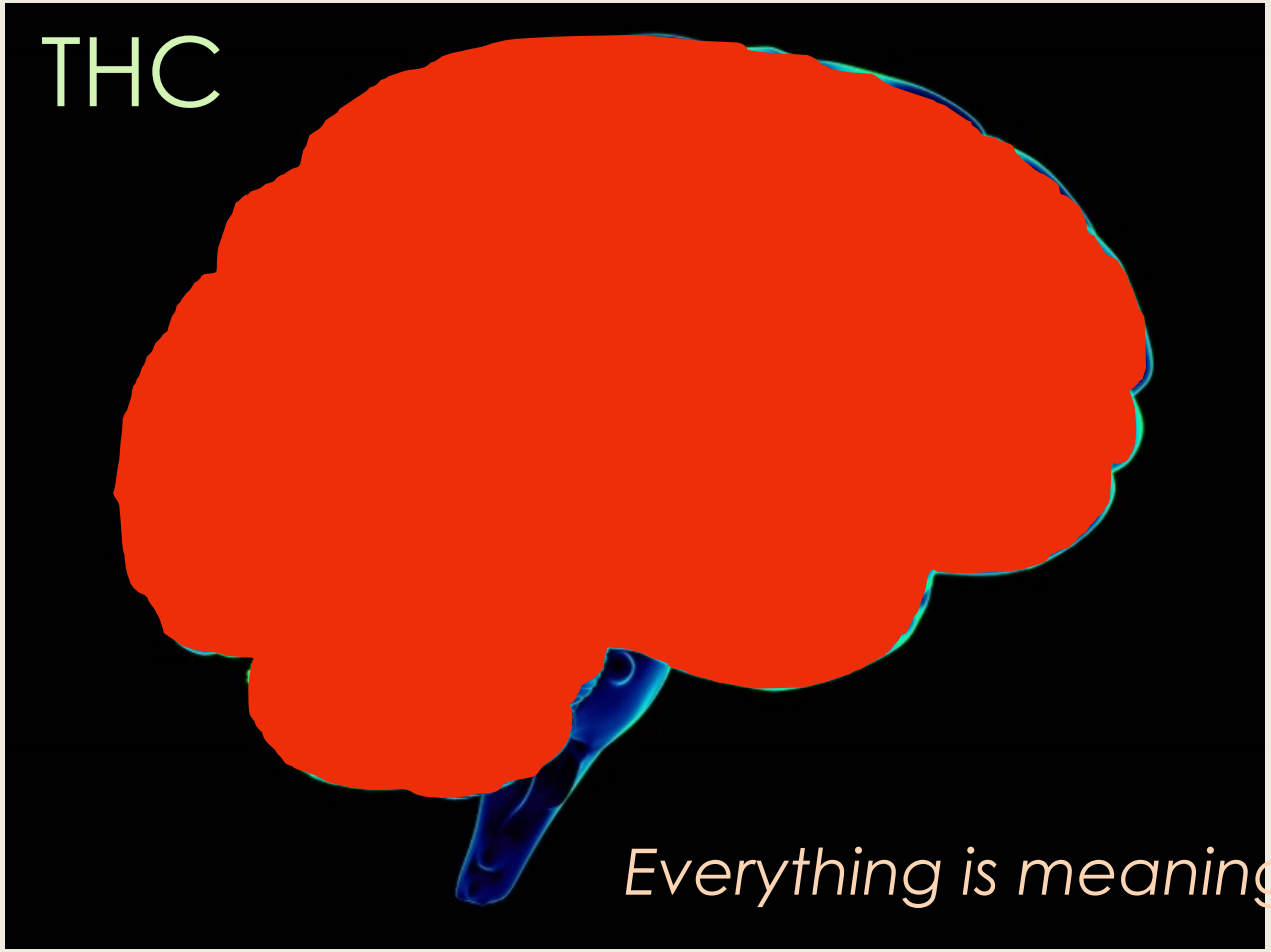


- Endocannabinoid modulate virtually all brain activity
- Play a critical role in neuroplasticity
- Like a **neurological highlighter** to mark meaning
- Help us sort important from unimportant stimuli

Abstract

Recent years have been transformational in regard to the perception of the health risks and benefits of cannabis with increased acceptance of use. This has unintended neurodevelopmental implications given the increased use of cannabis and the potent levels of Δ^9-tetrahydrocannabinol today being consumed by pregnant women, young mothers and teens. In this Review, we provide an overview of the neurobiological effects of cannabinoid exposure during prenatal/perinatal and adolescent periods, in which the endogenous cannabinoid system plays a fundamental role in neurodevelopmental processes. We highlight impaired synaptic plasticity as characteristic of developmental exposure and the important contribution of epigenetic reprogramming that maintains the long-term impact into adulthood and across generations. Such epigenetic influence by its very nature being highly responsive to the environment also provides the potential to diminish neural perturbations associated with developmental cannabis exposure.




THC
Everything is meaningful!?

Acute Effects of Marijuana

Causes pleasure, relaxation

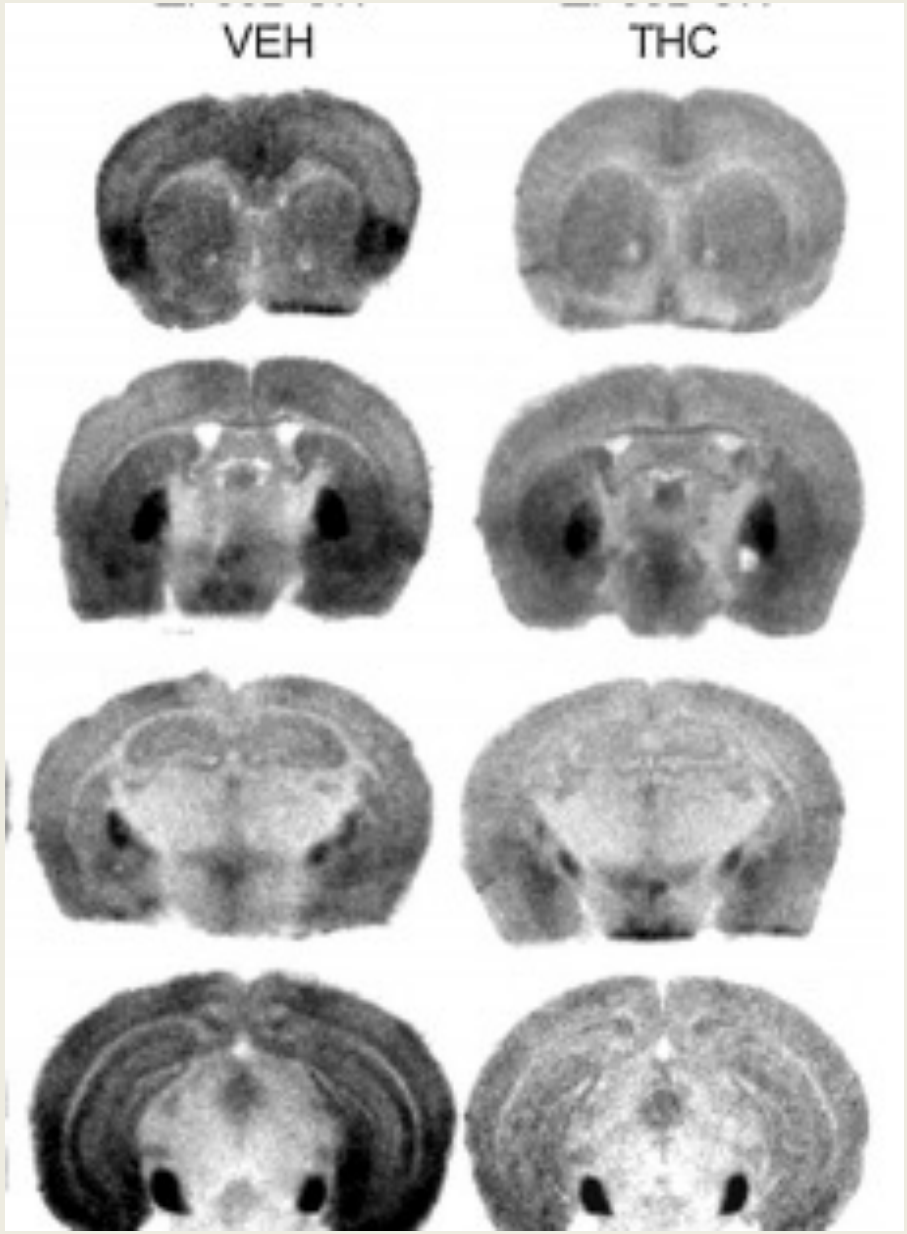
Stimuli are more rich and meaningful

- Impairs memory
- Slows response time
- Causes errors in critical tracking

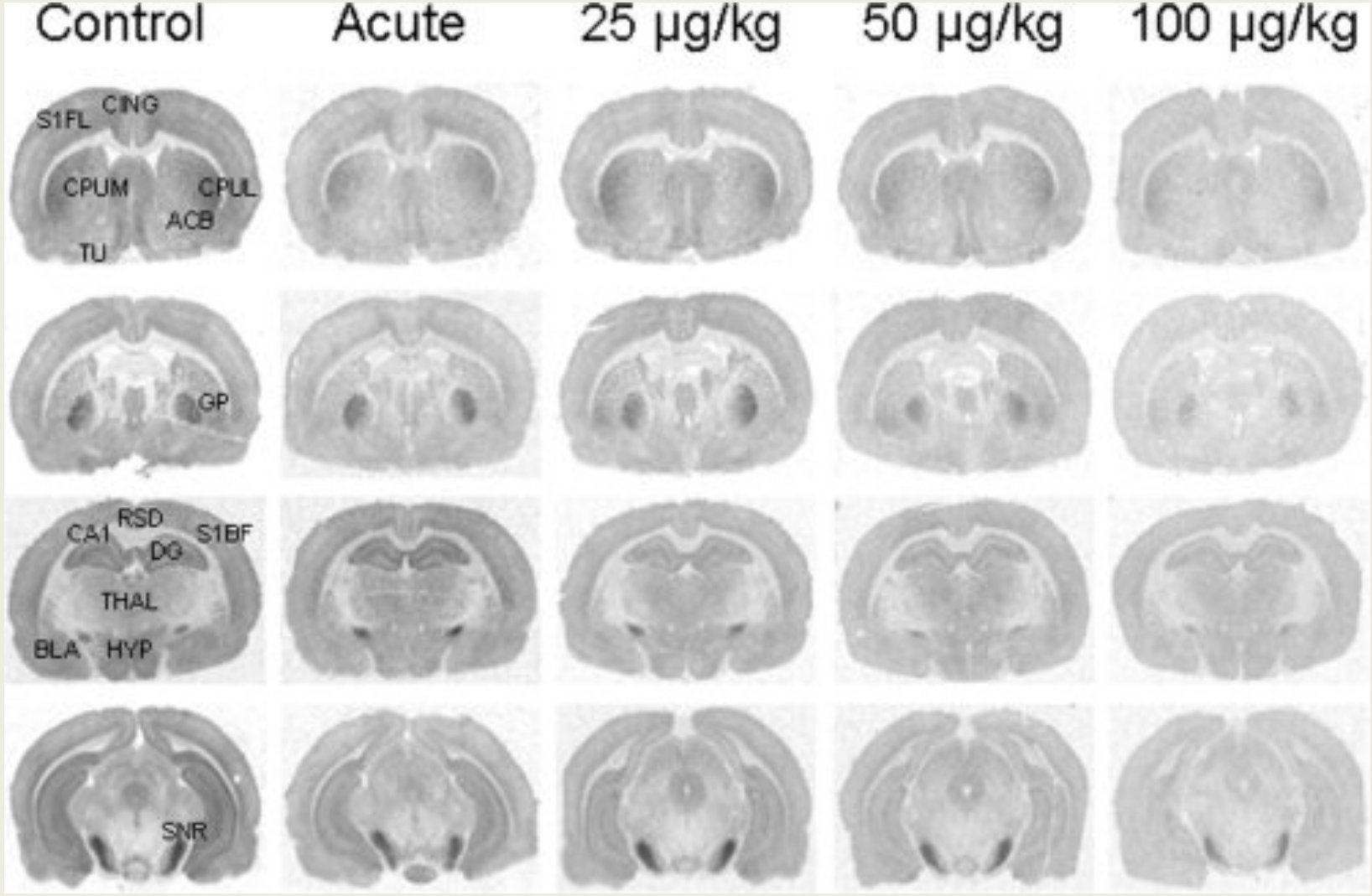
Not so bad… except for adaptive neural changes

Escalating doses for 6 days
Measure THC binding on day 7

Lazenka et al., 2014



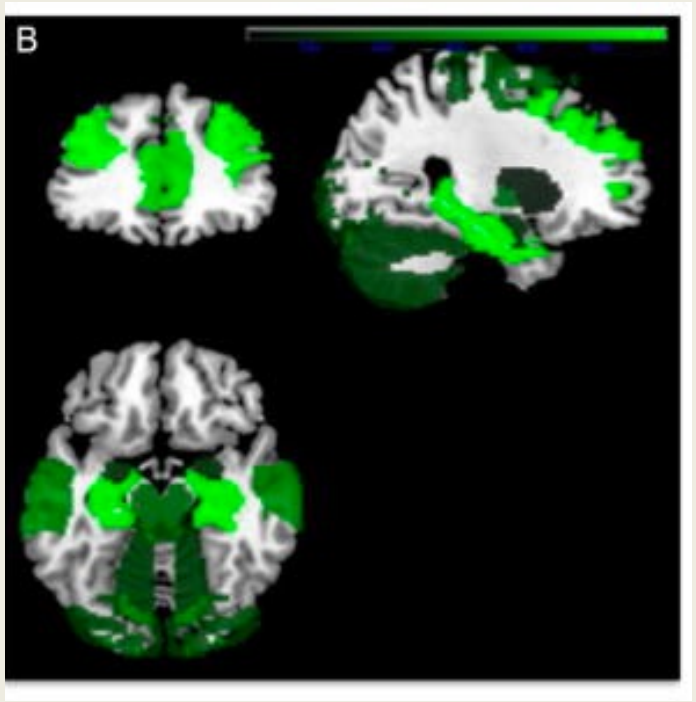
b-process: Downregulation of Endocannabinoid Signal



Dalton and Zavitasanou, Synapse, 64: 2010

Heavy-smoking teens

CB1 Downregulation



Jacobus et al., 2015, *Dev Cognitive Neuroscience*; Ganzer et al., 2016, *Neuropsychological Review;* Lorenzetti, V., Solowij, N., & Yücel, M. *2016, Biological Psychiatry*

Heavy-smoking teens

Reduced sensitivity to pleasure (Volkow et al., 2014, PNAS)

Enhanced heroin or alcohol self-administration as adults (Ellgren et al., 2007, Neuropsychopharmacology Panlilio & Justinova, 2018, Neuropsychopharm; Stopponi et al., 2014, Eur Neuropsychopharm)

Impulsivity (Aston et al., 2016; Ganzer et al., 2016)

Depression (Volkow et al., 2014; *Gorinkel et al., 2020*)

60% less likely to graduate high school (Daily smokers by 17, compared to non-smokers, Silins et al., 2014)

Risk of psychosis (Black et al., 2019; Hindley et al., 2020)

7X more likely to attempt suicide (Silins et al., 2014)

Epigenetics:
b-Process Across Generations

Offspring of adolescent users show

- Increased anxiety
- Increased risk of heroin addiction and alcoholism
- Increased depression
- Genetic, brain and behavioral changes in *their* offspring

Szutorisz & Hurd, 2018, Neuroscience & Biobehavioral Reviews;
Bara et al., 2021 Nature Neuroscience

JAMA Psychiatry | Original Investigation

Associations Between Prenatal Cannabis Exposure and Childhood Outcomes
Results From the ABCD Study

Paul et al., September, 2020

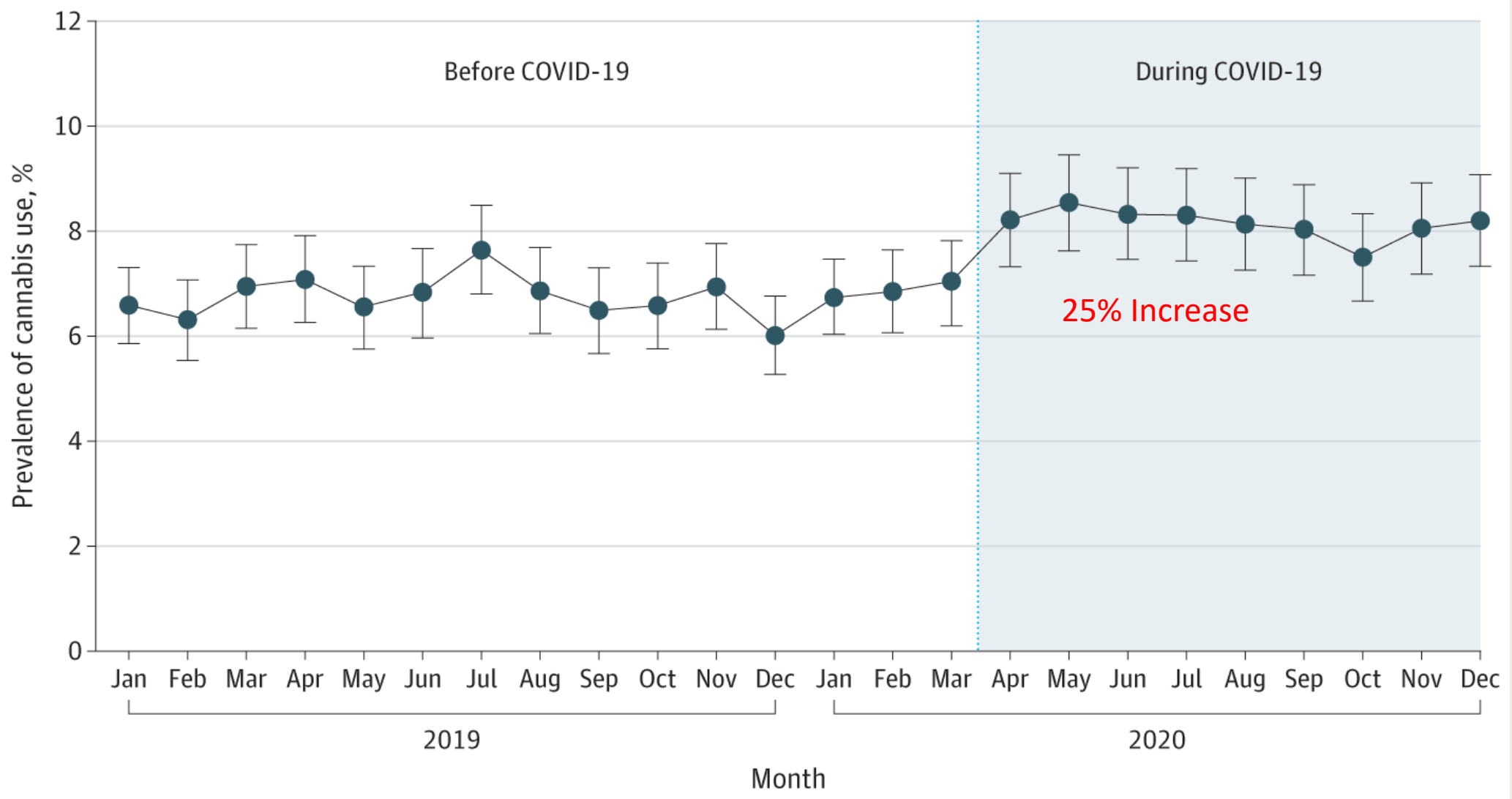
Past month cannabis use by pregnant women more than doubled 2002 → 2017, and continues to rise

2019 US Surgeon General issued advisory against use of marijuana during pregnancy

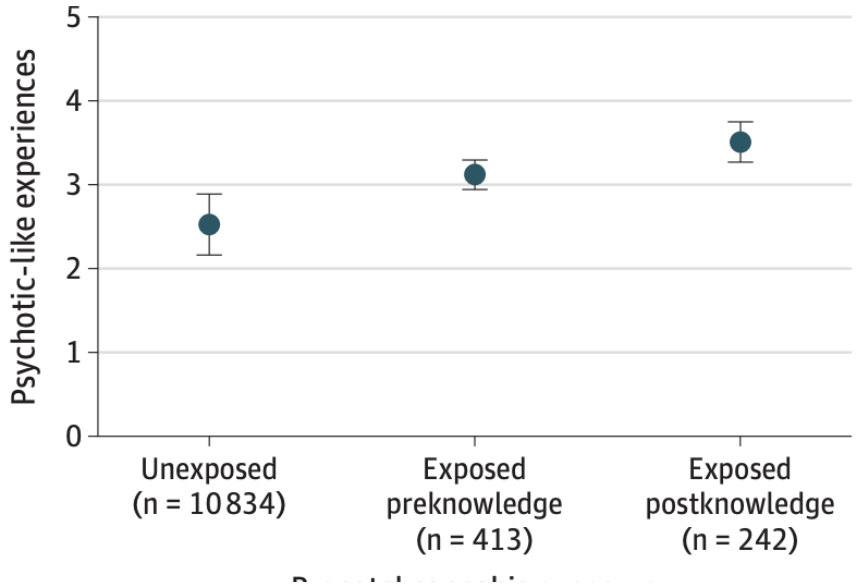
JAMA Network™

Rates of Prenatal Cannabis Use Among Pregnant Women Before and During the COVID-19 Pandemic

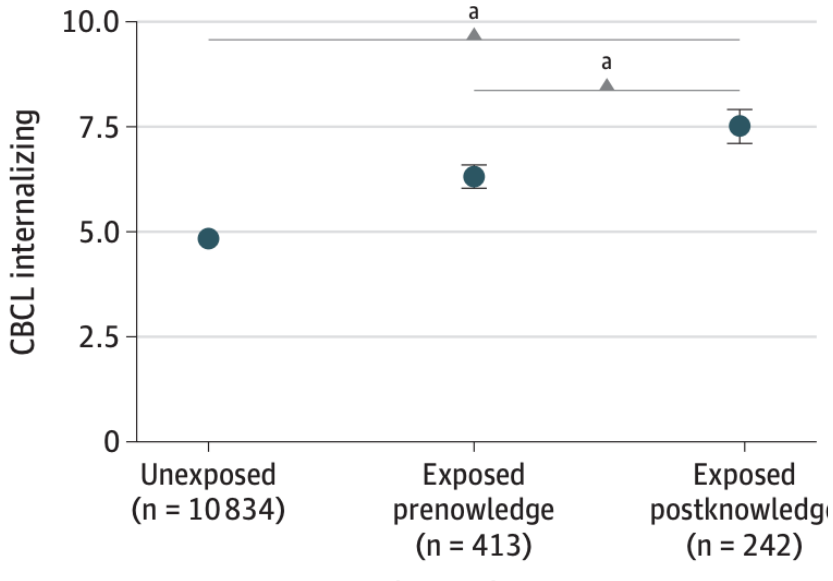
JAMA. Published online September 27, 2021. doi:10.1001/jama.2021.16328



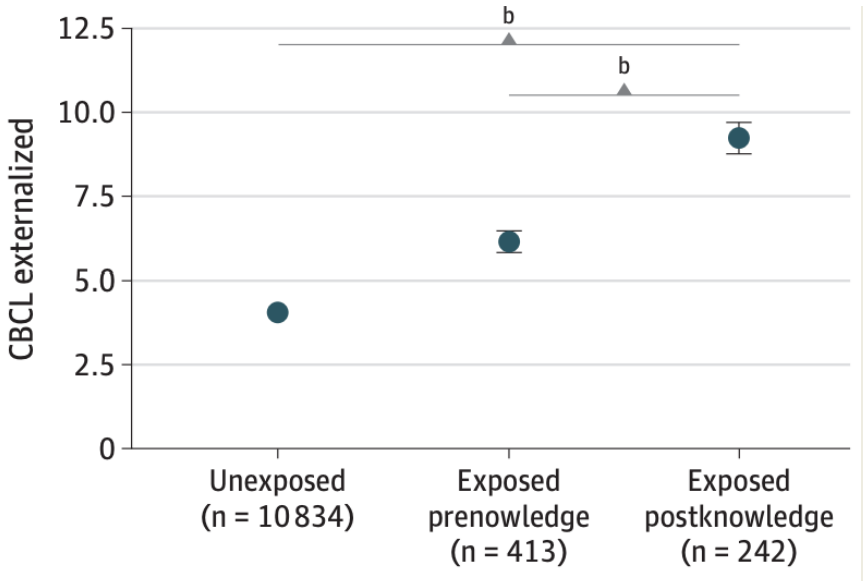
Psychotic-Like Experiences



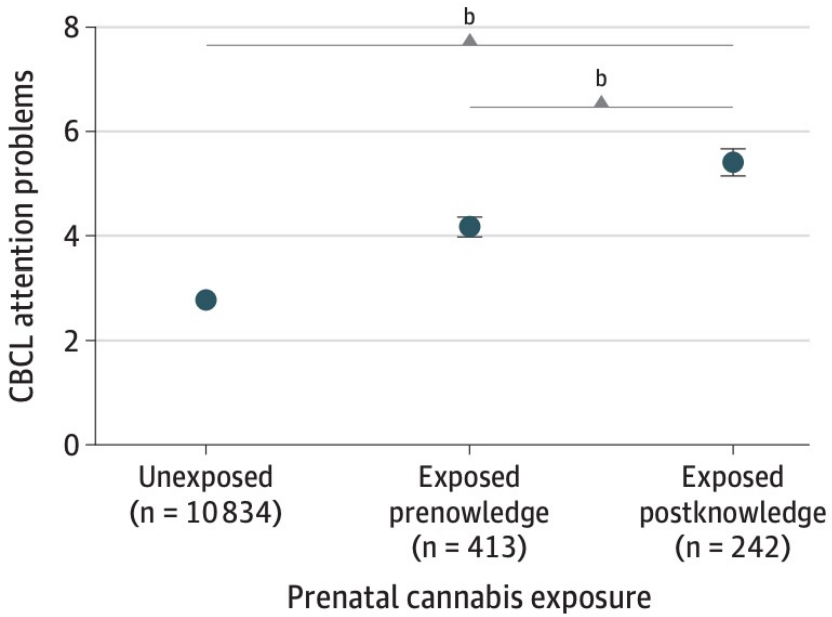
Internalizing Symptoms



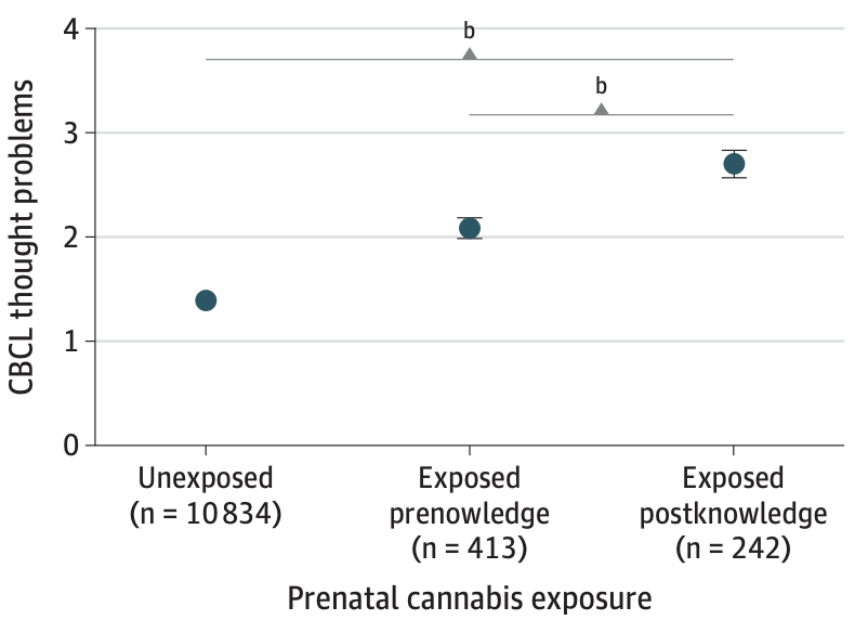
Externalizing Symptoms



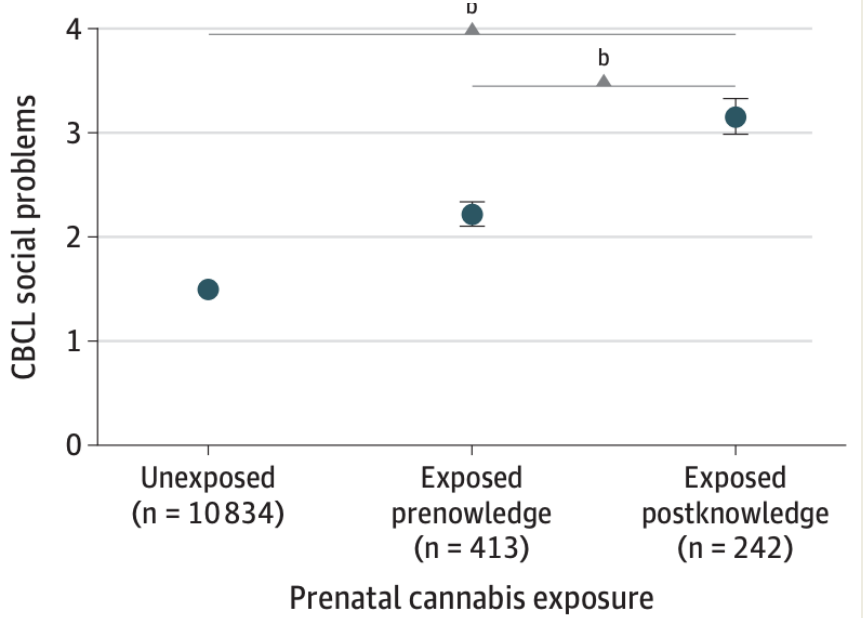
Attention Problems



Thought Problems

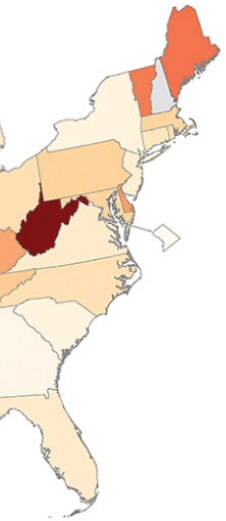


Social Problems

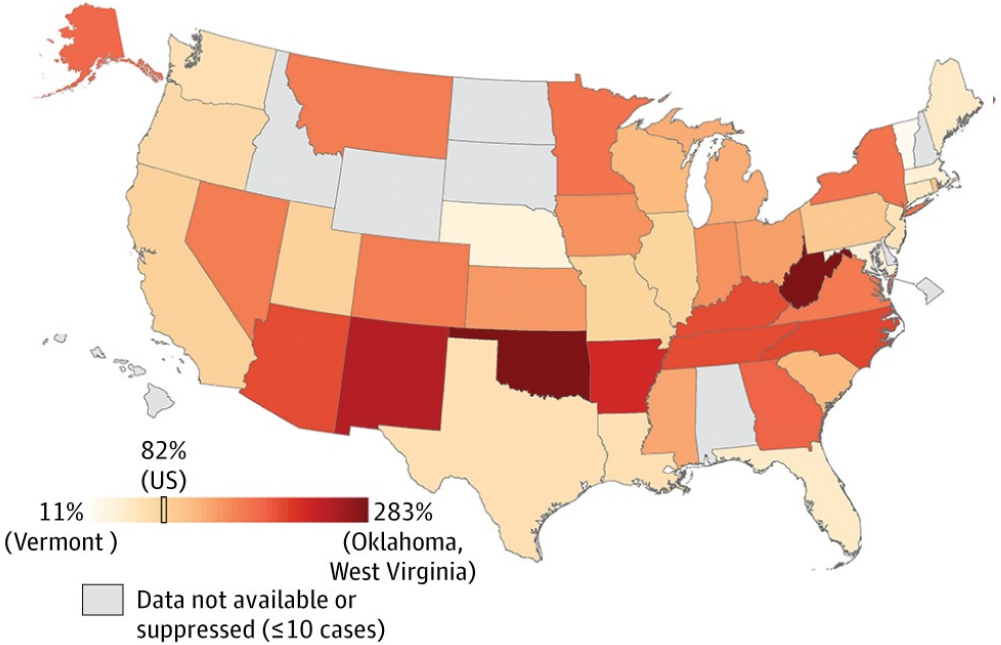


From: **Neonatal Abstinence Syndrome and Maternal Opioid-Related Diagnoses in the US, 2010-2017**

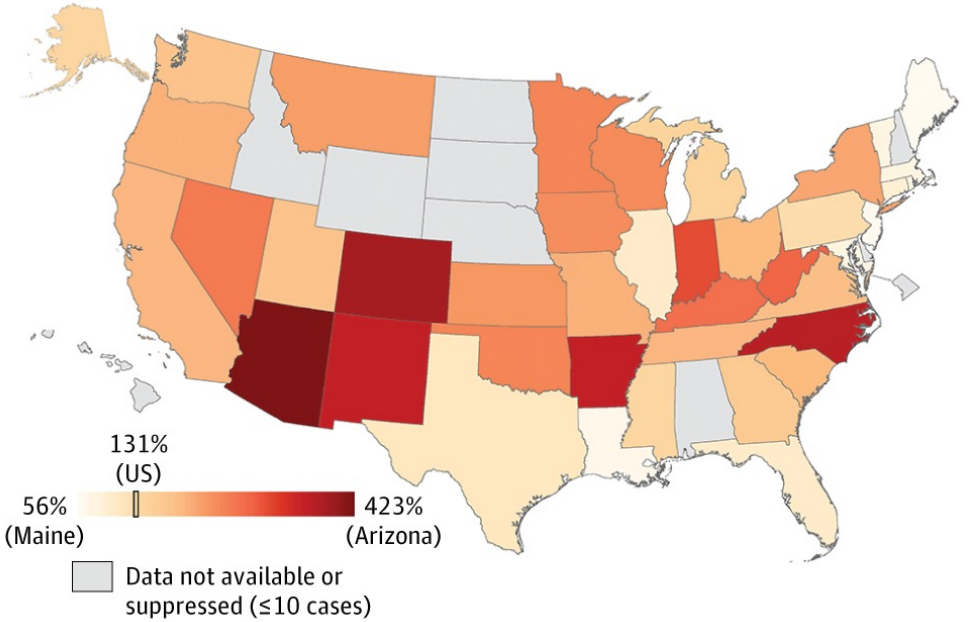
tions in 2017



B Percent change in neonatal abstinence syndrome rate per 1000 birth hospitalizations from 2010 to 2017



D Percent change in maternal opioid-related diagnoses rate per 1000 delivery hospitalizations from 2010 to 2017

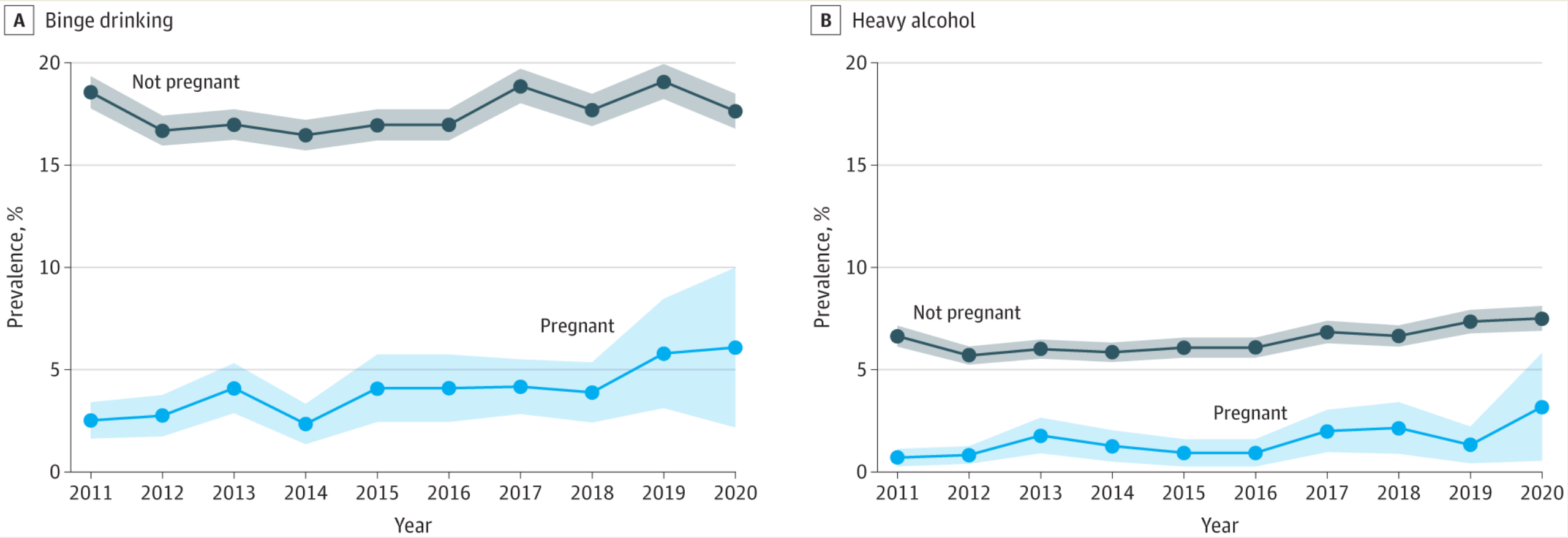


U.S. had 82% increase in NAS on average

U.S. had 131% increase in maternal OUD

From: **Trends in Binge Drinking and Heavy Alcohol Consumption Among Pregnant Women in the US, 2011 to 2020**

JAMA Netw Open. 2022;5(8):e2224846. doi:10.1001/jamanetworkopen.2022.24846

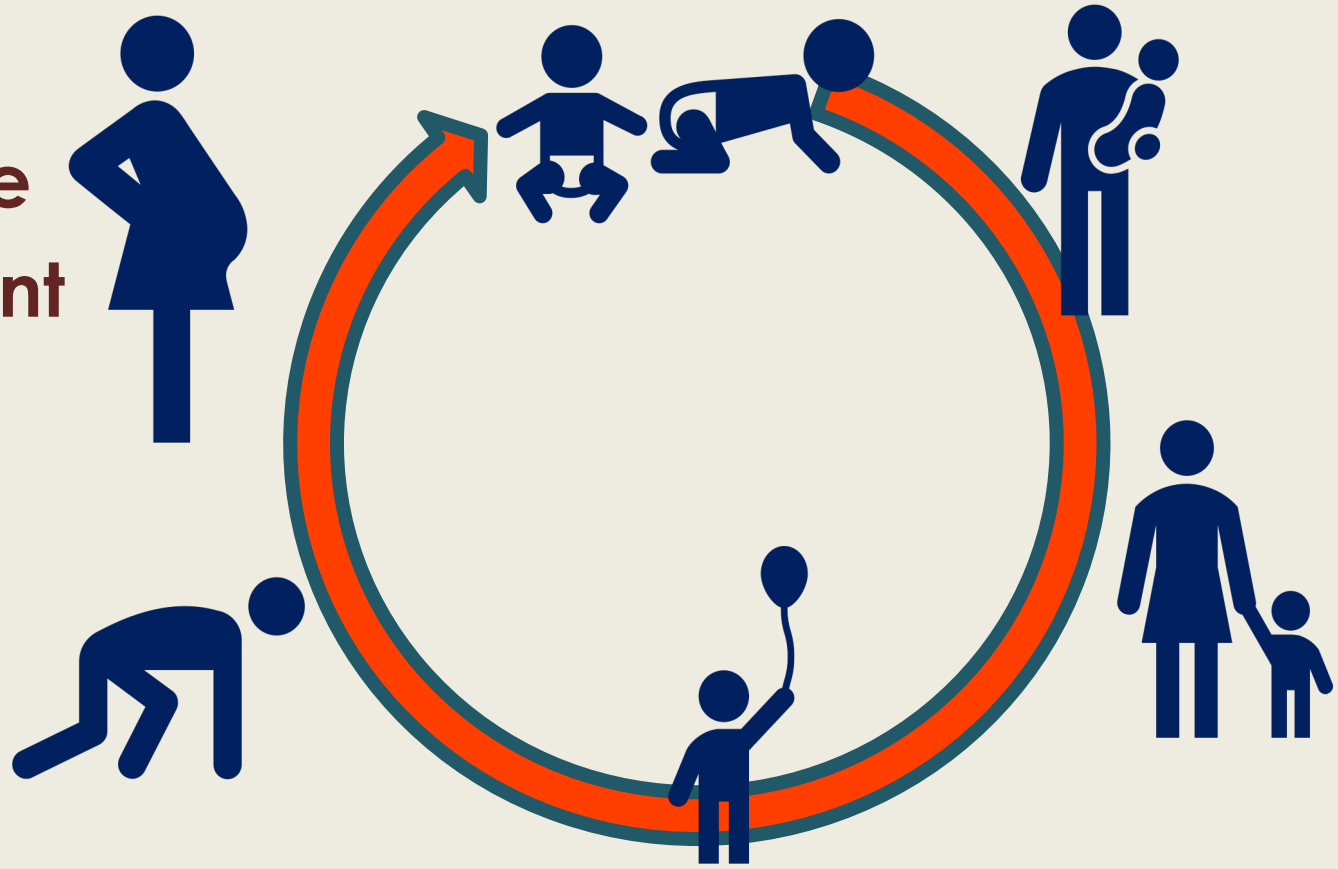


What is Addiction?

A change in state produced by the brain to counteract the reinforcing properties of drugs and maintain homeostasis.

A form of learning,

and like all learning, more robust during development



Dealing with Addiction

- War on drugs is futile
- Punishment doesn't really work
- Contingency management is better
- Oversight, support for long-term process
  - Requiring team effort, multi-pronged approach with physical, psychological, vocational, habitational, rehabilitation
  - Time
  - $
  - Our attention

Above all, the brain is adaptable and recovery is possible

Dopamine and Addiction

Addictive Drugs

Pleasure
Expectancy
Hunger
Excitement
Curiosity
Hope

Withdrawal/Abstinence

Anhedonia
Disappointment
Indifference
Boredom
Acedia
Despair

Alterative Drivers of Dopamine

Food
Sex
Drugs

Work
Family
Friends
Community
Nature

Tool-making
Hunting
Sports
Music
Dance

Innovation
Discovery
Experimentation
Art & Poetry
Purpose

Genetic and Developmental Factors

- Consequence of Natural Selection
- *BENEFICIAL (under the right circumstances)*
  - ✓ *Low/absent ACEs*
  - ✓ *Society/Culture that ensures and supports adolescents need to experience pleasure, expectancy, hunger, excitement, curiosity, and hope*

The brain adapts to every drug that alters its activity by producing the opposite state.

"The prisoner who lost faith in the future … was doomed. With his (sic) loss of belief in the future, he also lost his spiritual hold; he let himself decline and become subject to mental and physical decay."

Viktor Frankl – Man's Search For Meaning

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Thank you!