



Neuroscience of Cannabis

Jodi Gilman, Ph.D.
Associate Professor
Center for Addiction Medicine
Massachusetts General Hospital
Harvard Medical School

Disclosures

- Jazz Pharmaceuticals is providing CBD (Epidiolex) for a clinical trial

Today's Talk

- Landscape of Cannabis Today: A Risky Profile
- The Endocannabinoid System and THC/CBD
- What is medical cannabis?
- Is cannabis harmful?
 - What are the risks, and who is most vulnerable?

In 2014, the NYT editorial board published a six-part series calling for the legalization of marijuana



- described marijuana addiction and dependence as “relatively minor problems”

More in this Series



PART 1
Let States Decide on Marijuana



PART 2
The Injustice of Marijuana Arrests



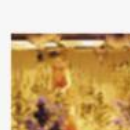
PART 3
The Federal Marijuana Ban Is Rooted in Myth and Xenophobia



PART 4
What Science Says About Marijuana



PART 5
The Great Colorado Weed Experiment



PART 6
Rules for the Marijuana Market

The tide is changing on cannabis use: 2026



- “it is now clear that many of these predictions **were wrong**,” the board says. “Legalization has led to **much more use**.” The ramp up in marijuana usage has also led to more **addiction** and **health problems among frequent users**. Because of this, the board argues, it’s time for better regulation.



The Evolution of Cannabis Legalization in the United States

From medical access to mainstream acceptance—transforming a generation's reality



Cannabis has shifted from an illicit drug to a widely available commercial product
within a single generation.

Sources: National Conference of State Legislatures (NCSL), Marijuana Policy Project, State government websites. | Data current as of May 2026.

What is the current landscape of cannabis use?

Cannabis use is at **an all-time high**

- 64.2 million Americans (22.3% of people age 12+) reported using cannabis in the past year in 2024.
- 44.3 million Americans (15.4%) reported past-month cannabis use in 2024.
- About 1 in 4 young adults (18–25 years) used cannabis in the past month.
- Cannabis use is becoming more frequent

Daily or near-daily cannabis use now **exceeds daily or near-daily alcohol use in the United States.**

- Approximately 17.7 million Americans reported daily or near-daily cannabis use in 2022, compared with 14.7 million daily or near-daily alcohol users.
- **Cannabis use disorder** is common
 - 20.6 million Americans met criteria for **clinically significant cannabis use disorder (CUD)** in 2024.
 - Among 18–25-year-olds, approximately 15.8% met criteria for CUD.



What is Cannabis?

- Dry, shredded mix of leaves, flowers, stems, and seeds, usually from *Cannabis sativa* or *Cannabis indica* plant
- Both are common subspecies of the hemp plant, which is common throughout the world
- Contains over 400 chemical compounds
 - THC is primarily responsible for intoxication
 - CBD is non-intoxicating and has very different pharmacology
- Products vary enormously in cannabinoid composition and potency

How is Cannabis Used?

SMOKED	VAPORIZED	EATEN/DRUNK
Smoked in a pipe, bowl, cigarette	Inhaled through machine that converts active compounds into inhalable form	Consumed as ingredient in baked goods, candies, sodas
Rapid effects	Rapid effects	Takes time to reach brain, so effects are delayed

*Oral THC also undergoes first-pass metabolism, producing **11-hydroxy-THC**, an active metabolite that contributes to the effects of edible cannabis*

Cannabis pre-legalization: THC 1-5%, flower-based products



Post-legalization (today): Novel forms of THC delivery are the new norm, yet use is difficult to detect



Cannabis is not “just a plant” anymore; derivatives contain up to 98% THC



Industry Tactics: The Commercialization of Cannabis Edibles



Borodovsky et al., 2016; Schauer, King et al., 2016; Wang et al., 2016; Weiss, 2015

Billboards

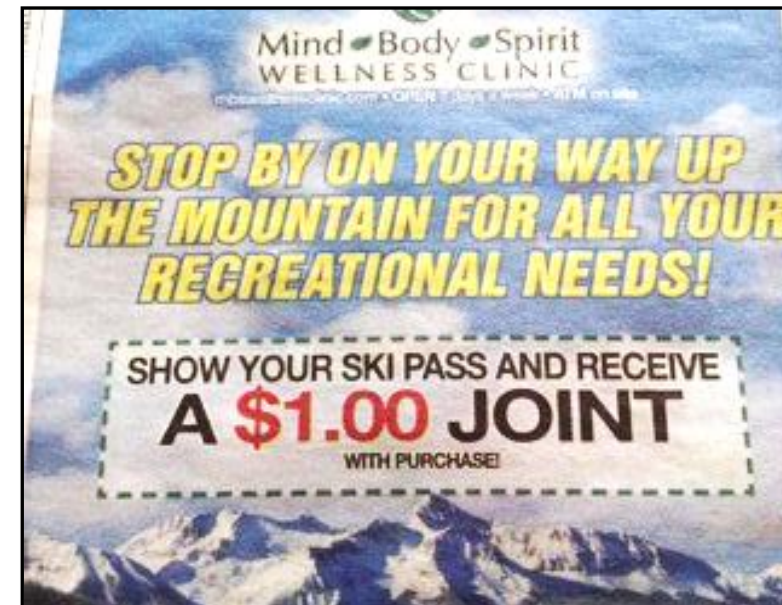


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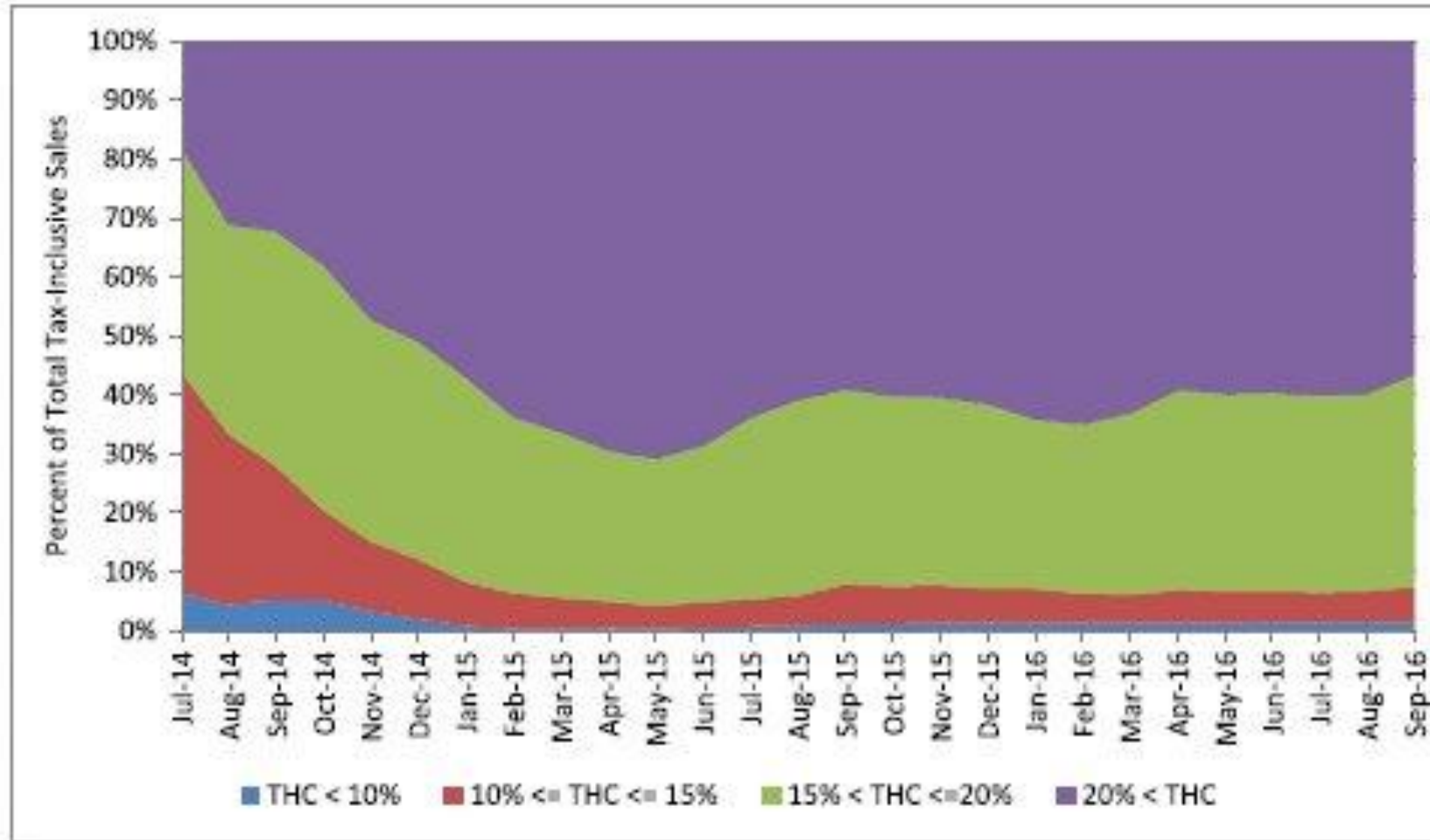
Coupons



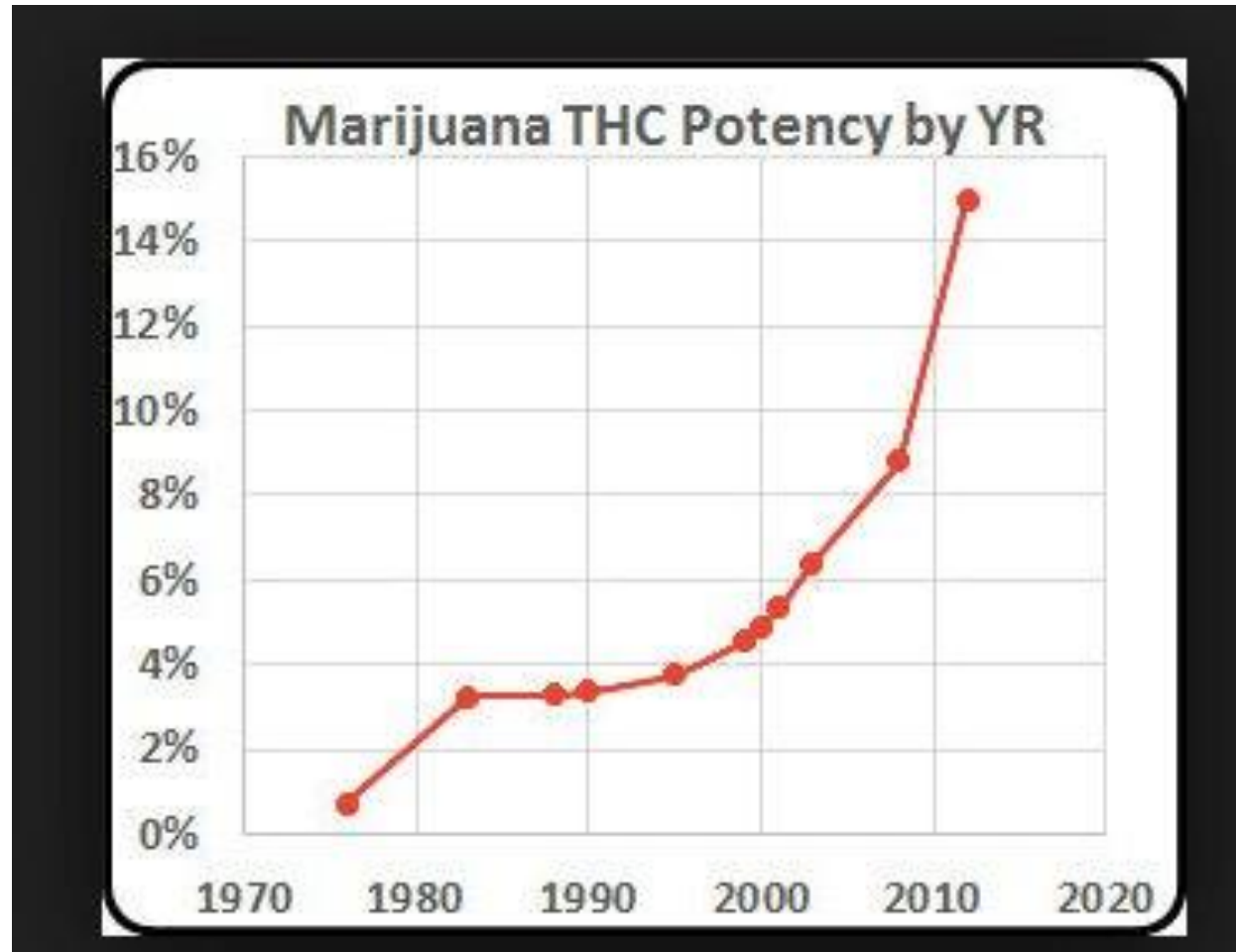
Cannabis Sodas



Even flower products are more potent than ever before



THC Potency has Increased Dramatically





How does cannabis affect the brain?

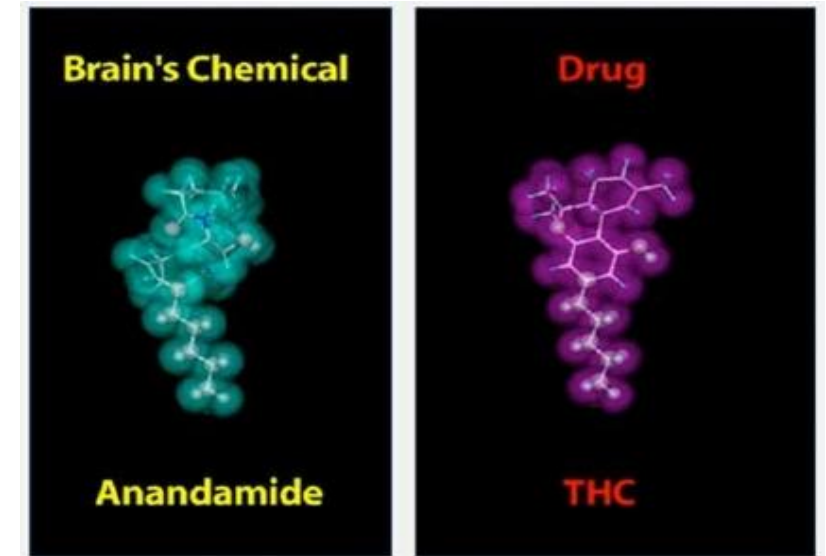
The Endocannabinoid System and THC/CBD

Cannabinoid receptors identified: CB1 and CB2

- The cannabinoid receptors were discovered in the late 1980s and early 1990s, and their discovery led directly to the identification of the endocannabinoid system.
- **1988: CB1 receptor was first identified through radioligand binding studies by Allyn Howlett and colleagues:**
 - Located primarily in the **central nervous system (CNS)**.
 - Found in the **brain (hippocampus, cerebellum, basal ganglia), spinal cord, and peripheral tissues**.
 - Involved in **mood, memory, motor function, and appetite**.
 - **Target of THC's psychoactive effects**.
- **1993: CB2 receptor was discovered and cloned by Sean Munro and colleagues:**
 - Mostly in the **immune system and peripheral organs**.
 - Found in the **spleen, tonsils, and immune cells**.
 - Modulates **inflammation and immune response**.
 - **Limited psychoactive effects**.

These discoveries prompted researchers to ask why the body would have receptors for a plant compound like THC?

- That question led to the discovery of **endogenous cannabinoid ligands**.
- THC acts on specific molecular targets on brain cells, called cannabinoid receptors.
- These receptors are ordinarily activated by chemicals similar to THC that naturally occur in the body (such as **anandamide**) and are part of a neural communication network called the endocannabinoid system.
 - This system plays an important role in normal brain development and function.



THC's chemical structure is similar to the brain chemical anandamide. Similarity in structure allows drugs to be recognized by the body and to alter normal brain communication

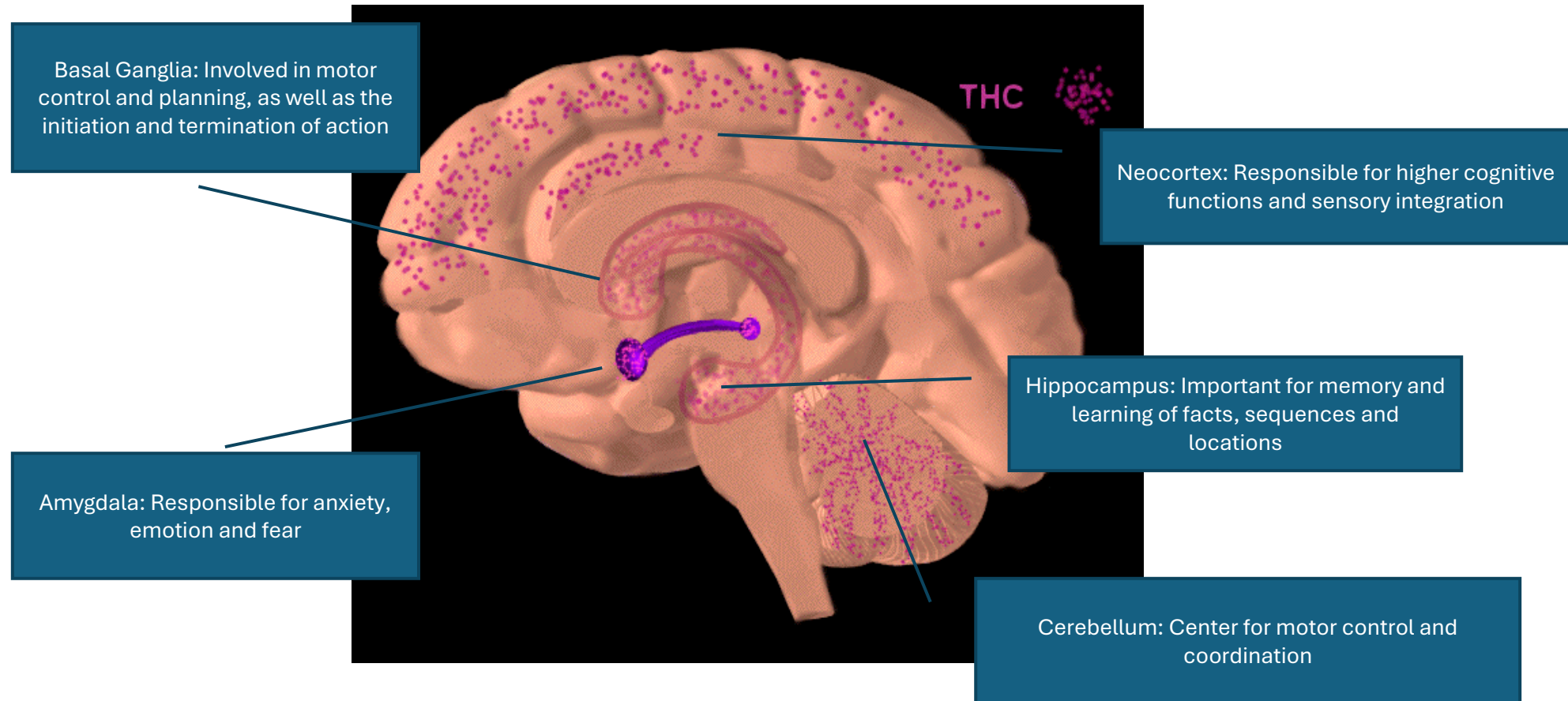
Two major phytocannabinoids: THC and CBD

- **Tetrahydrocannabinol (THC):**
 - **Partial agonist of CB1 and CB2 receptors.**
 - Produces **psychoactive effects** (euphoria, altered perception, relaxation).
 - Impacts **memory, coordination, and mood.**
 - Associated with **addictive potential and cognitive effects.**
- **Cannabidiol (CBD):**
 - The pharmacology of CBD is **complex**, as CBD is thought to be a weak inverse agonist of CB2 receptors, as well as an allosteric modulator of many other molecular targets.
 - **Indirect modulator of CB1 and CB2** (low binding affinity).
 - Acts on **serotonin, TRPV1, and adenosine receptors.**
 - **Does not cause a “high”.**
 - **Anti-inflammatory, neuroprotective, and anxiolytic properties?**

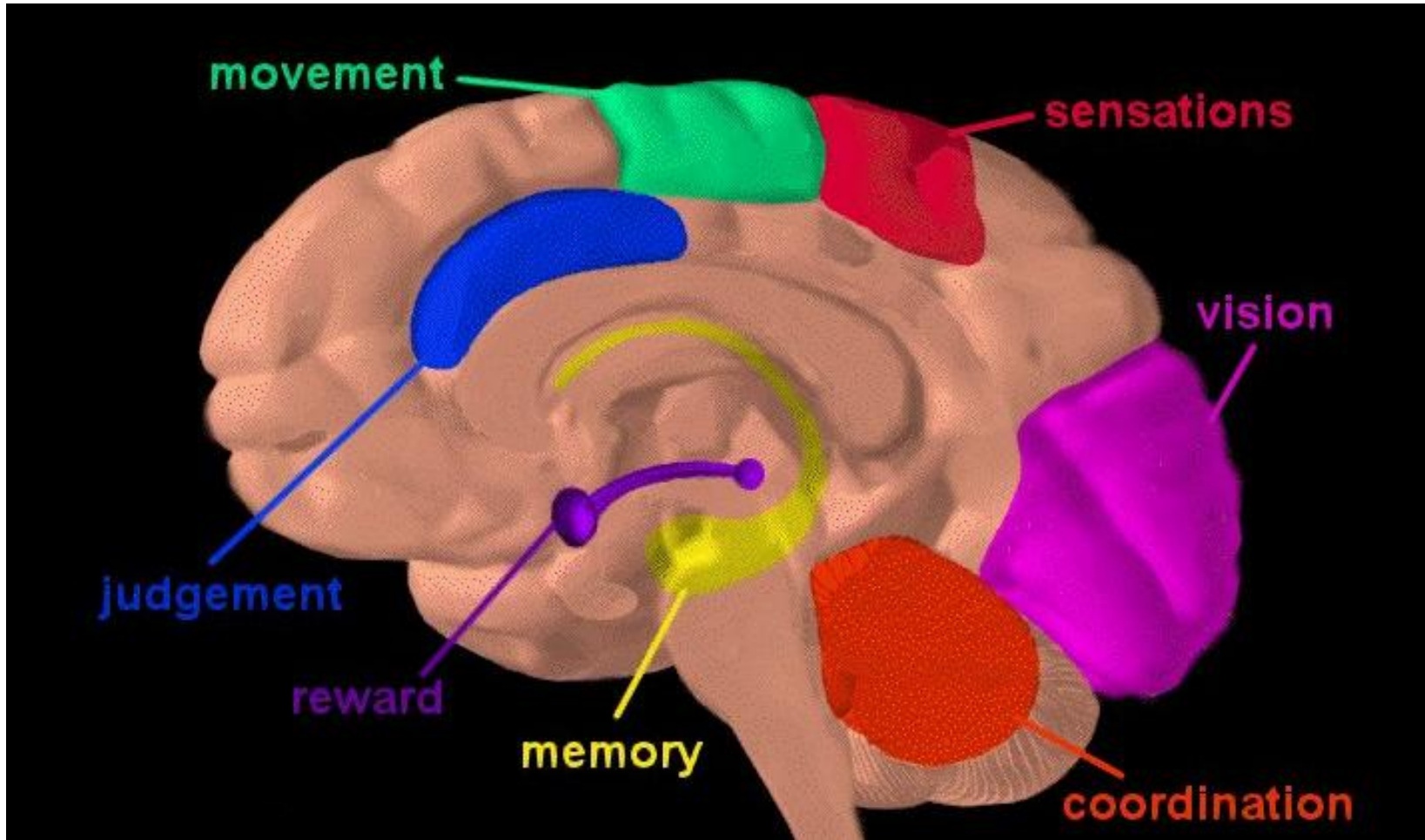
Endocannabinoid System

- Shapes brain development by...
 - guiding neurons to grow to the right places in the brain for correct function
 - controlling neuron activity, thereby affecting brain wiring (“neurons that fire together, wire together”)
 - supporting myelin growth on neurons
- THC and anandamide both dial down neuron activity to change neurotransmitter release
- THC has a MUCH STRONGER, LONGER effect than anandamide on brain cells
- THC can disrupt the normal timing and regulation of endocannabinoid signaling

Broad Distribution of THC Binding Sites



What domains are affected by THC?



Is cannabis harmful??? For whom, and under what conditions?

- FOR SOME, YES!
 - Can lead to Cannabis Use Disorder
 - Adolescents (Randi Schuster talk)
 - People with or at risk for psychosis (Eden Evins talk)
 - People with mental health co-morbidities (Gilman and Evins talk)
 - Harmful when smoked
 - Harmful during pregnancy

Cannabis: Potential for Addiction

- Repeated cannabis use can produce neuroadaptations associated with tolerance, withdrawal, craving, and compulsive use
- **Cannabis Use Disorder** is common among individuals with mental health disorders
- In 2024, an estimated 20.6 million Americans aged 12 or older met criteria for cannabis use disorder, making it the most common illicit drug use disorder in the United States
- Average adult entering treatment for cannabis use disorder has used daily for ten years, tried to quit six times

Cannabis Use Disorder Symptoms

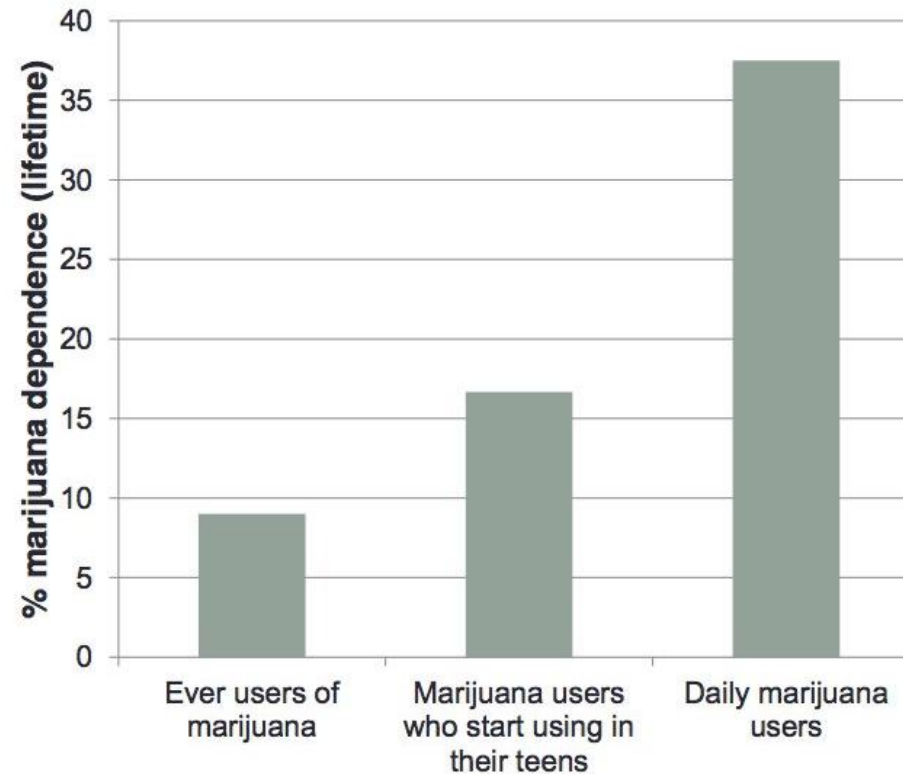
- Cannabis is often taken in larger amounts or over a longer period than intended.
- There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
- A great deal of time is spent obtaining, using, or recovering from cannabis.
- Craving, or a strong desire or urge to use cannabis.
- Recurrent cannabis use resulting in failure to fulfill major role obligations at work, school, or home.
- Continued cannabis use despite persistent or recurrent social or interpersonal problems caused or worsened by cannabis.
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
- Recurrent cannabis use in situations in which it is physically hazardous (e.g., driving while intoxicated).
- Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or worsened by cannabis.
- Tolerance, defined by either:
 - A need for markedly increased amounts of cannabis to achieve intoxication or the desired effect, or
 - A markedly diminished effect with continued use of the same amount.
- Withdrawal, manifested by either:
 - The characteristic cannabis withdrawal syndrome (e.g., irritability, anxiety, sleep difficulty, decreased appetite, restlessness, depressed mood, physical discomfort), or
 - Cannabis is used to relieve or avoid withdrawal symptoms.

Cannabis IS addictive

Addictiveness of marijuana

“Adolescents, especially troubled ones, and people with psychiatric disorders (including substance abuse) appear more likely than the general population to become dependent on marijuana... Some controlled substances that are approved medications produce dependence after long-term use; this, however, is a normal part of patient management and does not generally present undue risk to the patient”

-- Institute of Medicine



Anthony, J.; Warner, L.A.; and Kessler, R.C. *Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey*. Exp Clin Psychopharmacol 2:244–268, 1994;

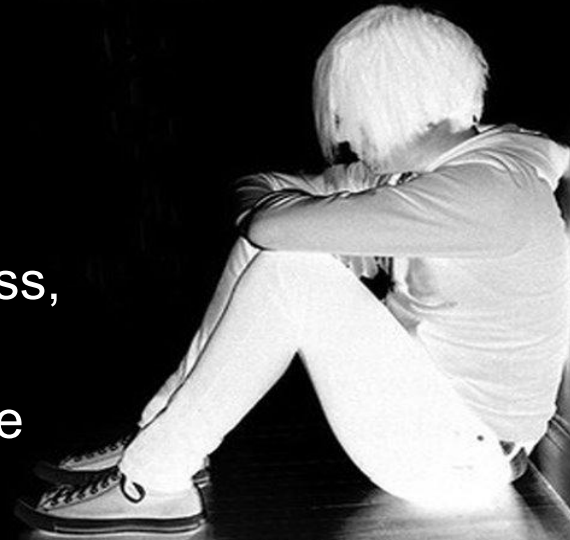
Hall, W.; and Degenhardt, L. *Adverse health effects of non-medical cannabis use*. Lancet 374:1383–1391, 2009;

Hall, W. *The adverse health effects of cannabis use: What are they, and what are their implications for policy?* Int J of Drug Policy 20:458–466, 2009

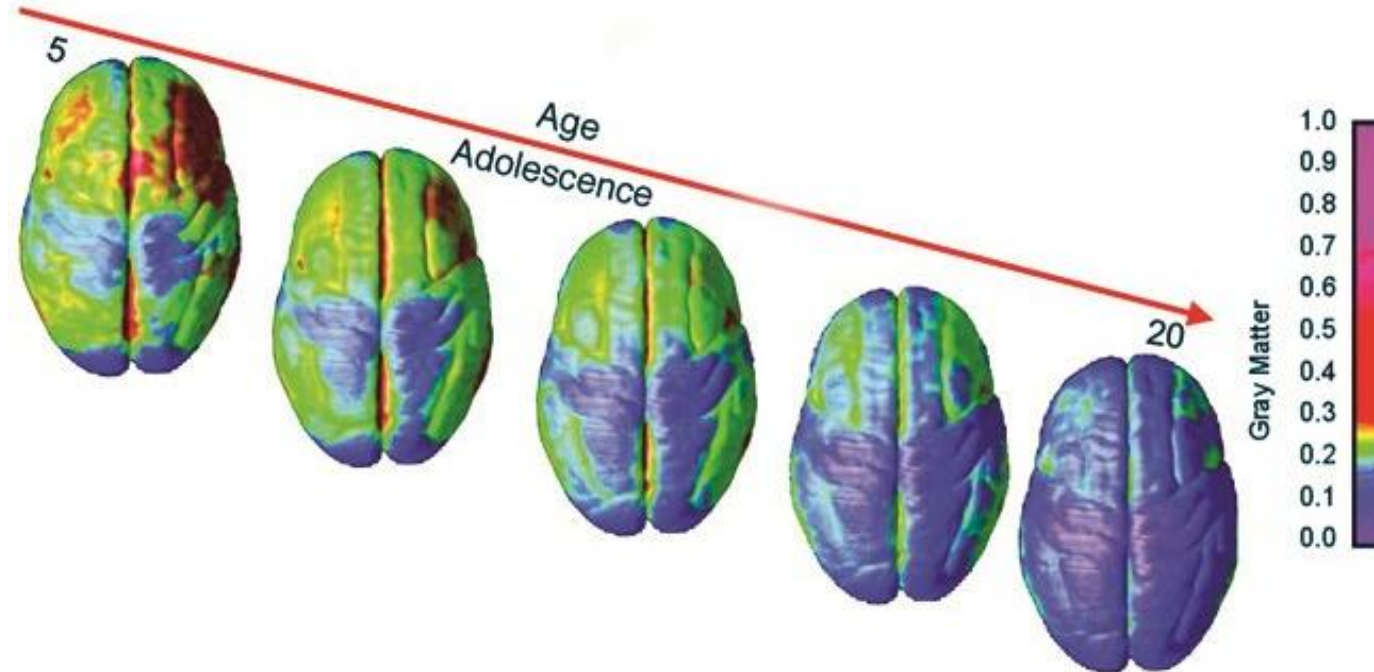
Cannabis addiction is also linked to a withdrawal syndrome that can make it hard to quit.

Symptoms include:

- Irritability
- Sleeping difficulties
- Craving
- Anxiety
- Increased aggression
- Physical symptoms:
 - Appetite change, Weight Loss, Chills, Fever, Headache, Shakiness, Stomach, Muscle Pain, Sweating, Tremors



Early age of initiation is especially problematic.



- Adolescence: a developmentally vulnerable period during which the brain is undergoing global cortical development
- Synaptic pruning of gray matter density occurs last in higher-order association areas such as the prefrontal cortex

Animal models demonstrate vulnerability with early exposure

- Rats exposed to THC during adolescence show neurobiological alterations
 - Blunted serotonergic/dopaminergic activity in the brainstem
 - Change in hippocampal morphology
- Also show neurocognitive abnormalities
 - Decreased reversal learning (e.g. cognitive flexibility) as adults
 - Decreased object recognition, impaired social interaction after 28 days as adults
 - Decreased inhibitory control in adulthood

Cannabis: Negative Effects When Smoked

Can lead to respiratory illness

- Exposes the lungs to many of the same combustion products found in tobacco smoke.
- Associated with cough, sputum production, wheezing, and chronic bronchitis symptoms

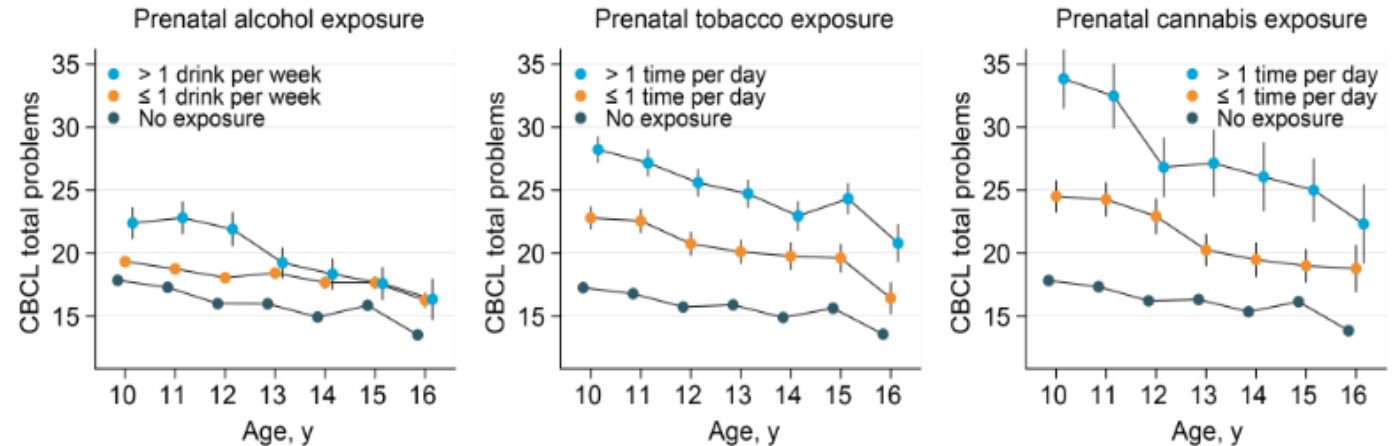
Can cause cardiovascular complications

- THC commonly increases heart rate
- Can alter blood pressure and cardiovascular demand
- Growing observational evidence links cannabis use with adverse cardiovascular outcomes, particularly in susceptible individuals

Cannabis: Negative Effects in Pregnancy

- THC crosses the placenta and reaches the developing fetus.
- The endocannabinoid system plays a critical role in fetal brain development.
- Prenatal cannabis exposure is associated with lower birth weight and increased risk of preterm birth.
- Studies suggest subtle but persistent effects on cognition, attention, and behavior.
- Neuroimaging studies reported differences in brain structure and functional connectivity in exposed offspring.

Dose-dependent effects of prenatal exposure



Take-home Points

- **The endocannabinoid system is a fundamental brain regulatory system**
 - Shapes synaptic signaling, plasticity, reward, memory, stress, and development
- **THC co-opts this normally tightly regulated system**
 - Endocannabinoids act locally, on demand, and transiently
 - THC produces broader and more prolonged CB1 receptor activation
- **Where and when THC acts matters**
 - CB1 receptors are widely distributed across brain systems
 - The developing brain may be particularly vulnerable to disruption of endocannabinoid signaling
- **Dose matters**
 - Today's high-potency products can produce very different brain exposures from traditional cannabis
- **Cannabis is not one drug**
 - THC and CBD have very different effects on the brain

Questions?