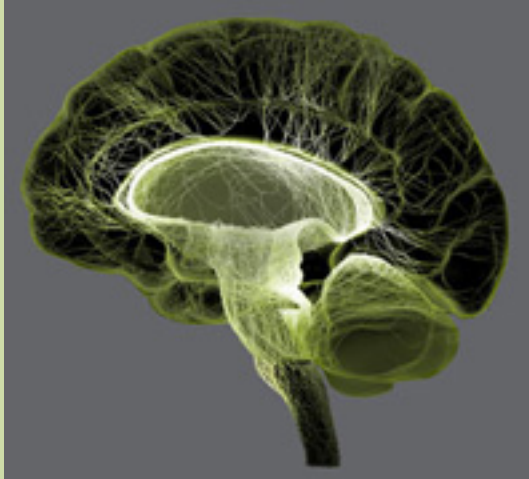
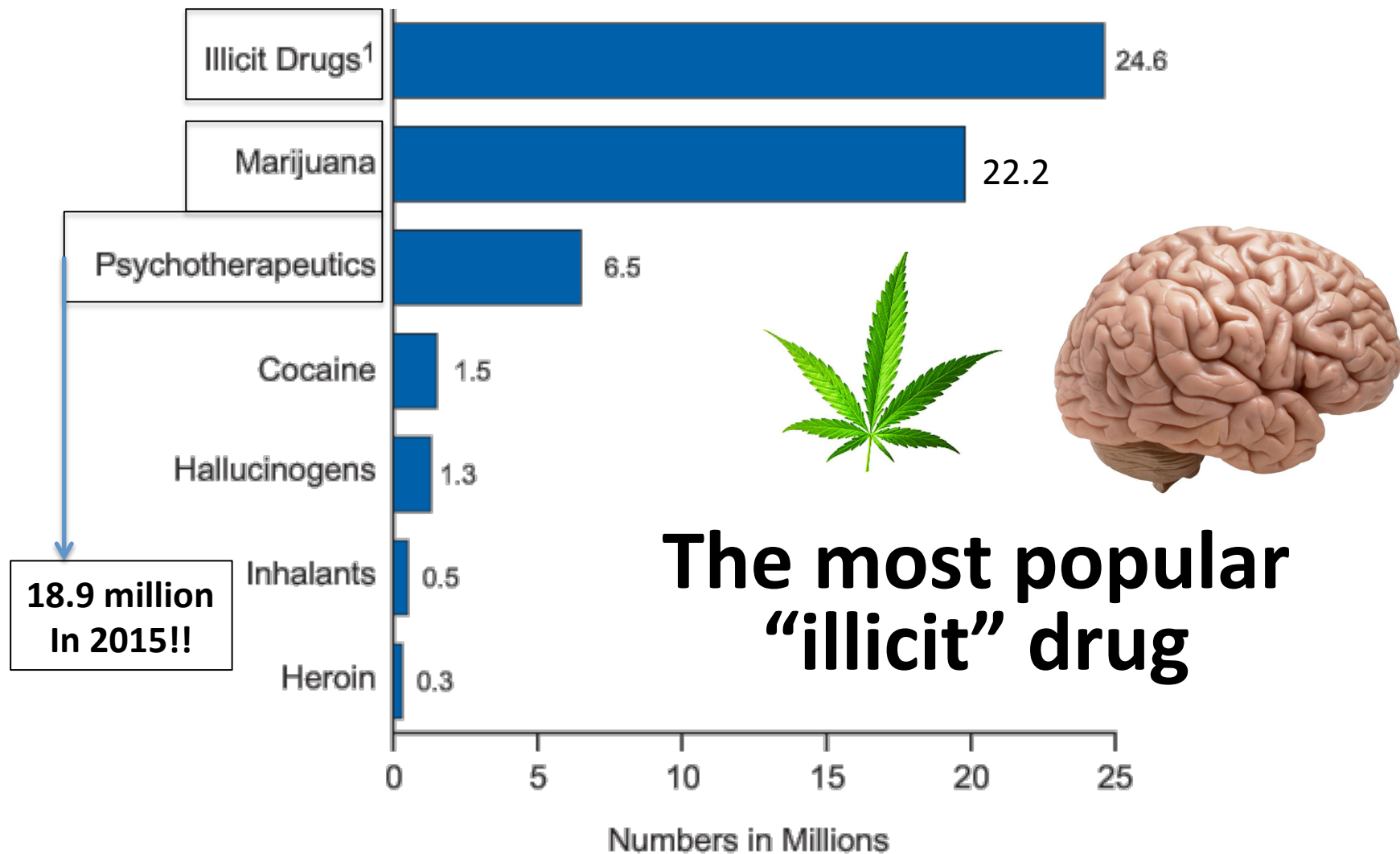


# Art, Pain & Cannabinoids



- **Bill Griesar, Ph.D.**
  - Neuroscience, WSU Vancouver
  - Psychology, Portland State University
  - Behavioral Neuroscience, OHSU
  - NW Noggin
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  - Neuroscience, WSU Vancouver
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- **Ram Kandasamy**
  - Neuroscience, WSU Vancouver
  - NW Noggin
- **Cole Taylor Dawson**
  - Neuroscience, WSU Vancouver
  - NW Noggin

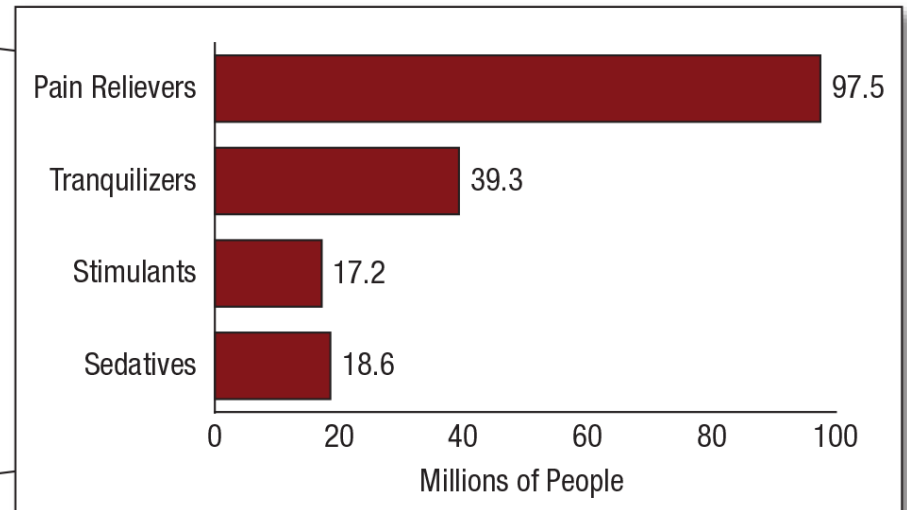
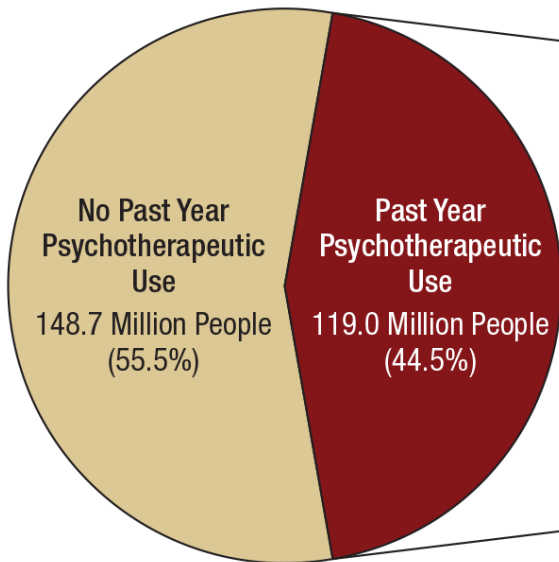
# Past Month Illicit Drug Use among Persons 12 or Older: 2014



SOURCE: Substance Abuse and Mental Health Services Administration, Health & Human Services (2015)  
<http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.htm>

# NSDUH Report on Prescription Psychotherapeutics 2015

In 2015, **119.0 million Americans** aged 12 or older *used* prescription psychotherapeutic drugs in the past year, representing **44.5 percent** of the population. (SAMHSA)

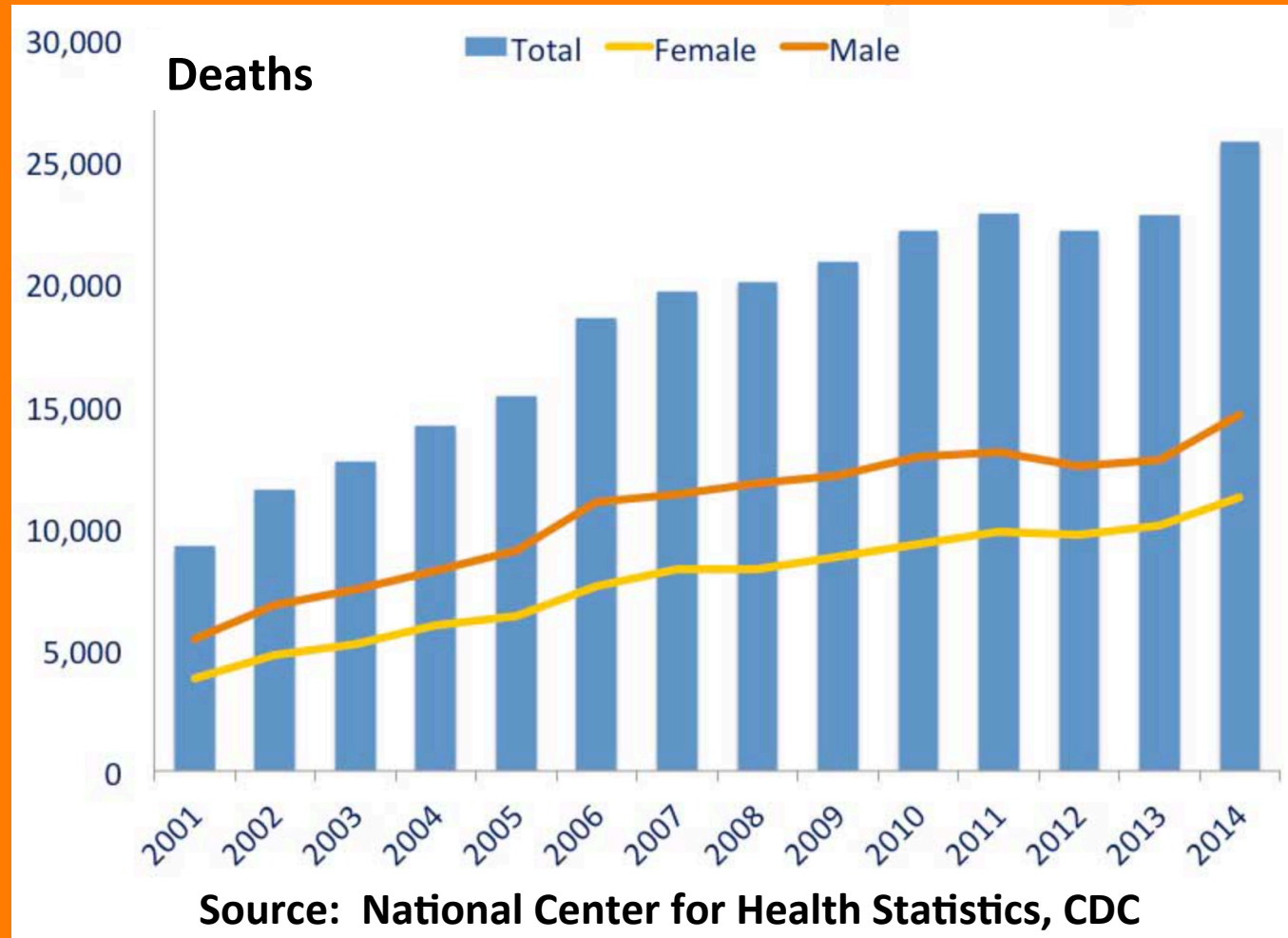


Report issued in September, 2016

# Opioids are addictive, and kill

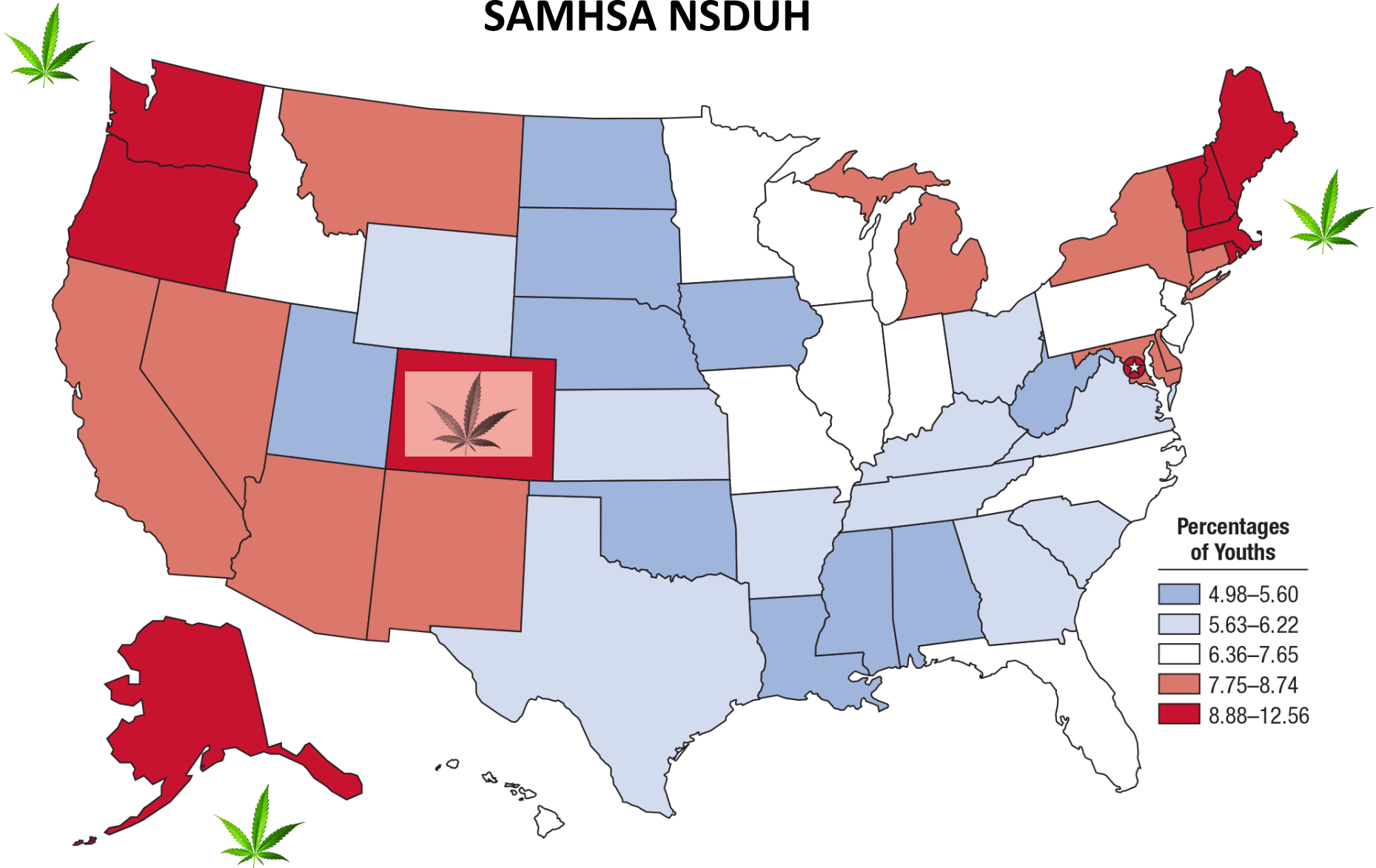
“In 2014, more than 28,000 people died from opioid overdose, and at least half of those deaths involved a prescription opioid. Many more became addicted to prescription and illegal opioids.”

- NIH

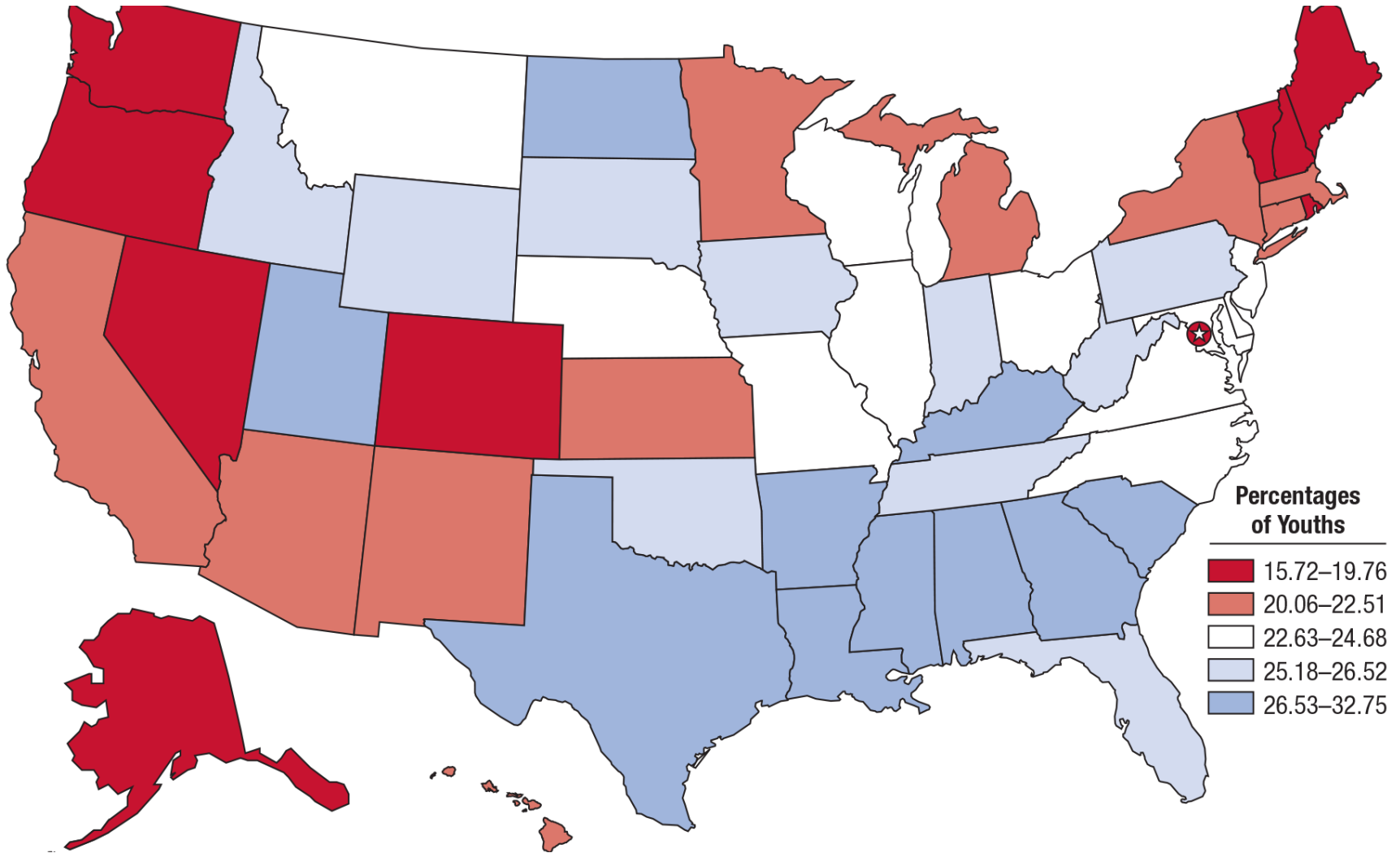


SOURCE: <https://medlineplus.gov/magazine/issues/fall16/articles/fall16pg12-14.html>

# Marijuana use in the past month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014; SAMHSA NSDUH



# Perceptions of great risk of harm from smoking marijuana once a month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014; SAMHSA NSDUH



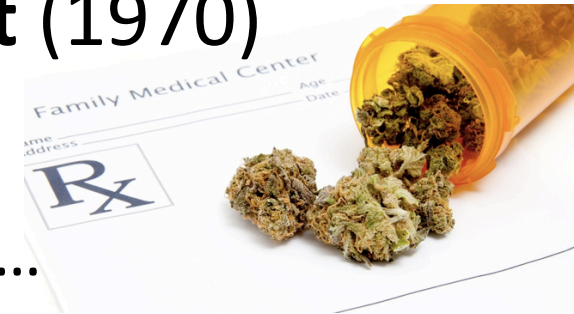


- Harry Anslinger, first Commissioner of Narcotics, Bureau of Narcotics
- *“Those who are habitually accustomed to use of the drug are said to develop a delirious rage after its administration, during which they are temporarily, at least, irresponsible and liable to commit violent crimes.”*



## A history of demonization

# Controlled Substances Act (1970)



- The drug or other substance...
  1. ...has a high potential for abuse
  2. ...has no currently accepted medical use
- There is a lack of accepted safety for use of the drug...under medical supervision...

**Marijuana is *still* a  
Schedule I substance**



# DEA Rejects Attempt To Loosen Federal Restrictions On Marijuana

SOURCE: National Public Radio, August 10, 2016

“We had them smoke it in the lab, then studied their mood and cognition,” recalls Dr. Hutchinson\*... “And what they told me was ‘that was disgusting, what are you giving me? I would never, ever smoke that stuff.’”

Low-Quality Cannabis



High-Quality Cannabis



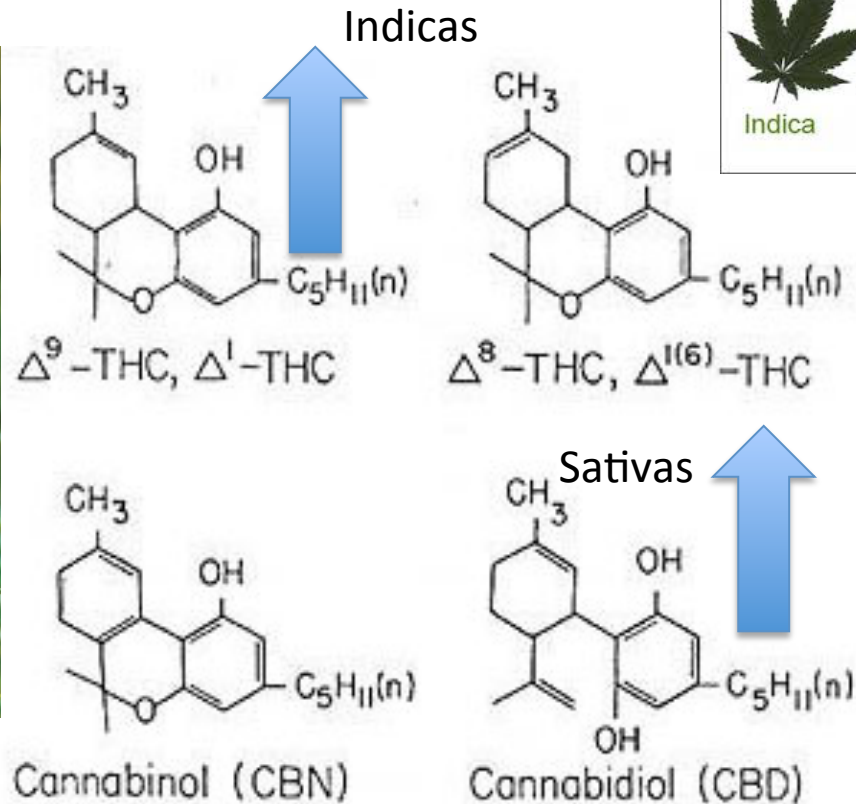
\*<http://www.colorado.edu/changelab/dr-kent-hutchison>

-Scientists Frustrated with Low Quality Weed from the Government,  
<https://massroots.com/blog/scientists-frustrated-with-low-quality-weed-from-government-want-dispensary-pot>


- From August 2016: *more sources now permitted for research...* Up until now, the DEA only certified ONE supplier, the University of Mississippi, known for shipping freeze-dried, re-hydrated samples...

# Cannabis contains cannabinoids

SOURCE: Cannabis, a complex plant: different compounds and different effects on individuals, Atakan (2012)



- More than 100!
- Concentrated in resin
- *Lots of variability*, depending on strain, other factors...

TEXT-FIGURE 1.—Structures of the four major cannabinoids. 

# Method of drug administration matters



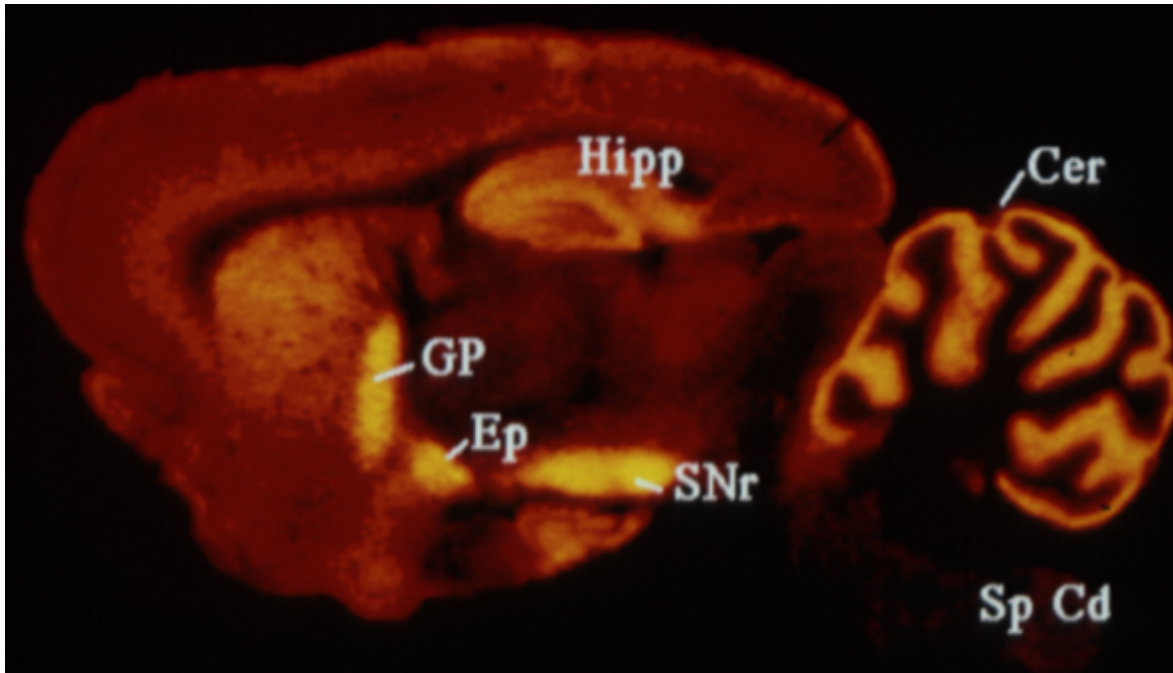
Burning vaporizes cannabinoids, which reach the brain in seconds. Oral administration delivers less THC, CBD, CBN, etc. more slowly...

## Marijuana is smoked...and eaten

*"I strained to remember where I was or even what I was wearing, touching my green corduroy jeans and staring at the exposed-brick wall. As my paranoia deepened, I became convinced that I had died and no one was telling me..." New York Times, 6/3/13*



# Cannabinoids act at cannabinoid receptors: CB1 and CB2



SOURCE: *Herkenham et al. (1991) J. Neurosci. 11: 563*

## CB1 Receptors

*Abundant!*

Cerebellum

Basal ganglia

Hippocampus

Brainstem

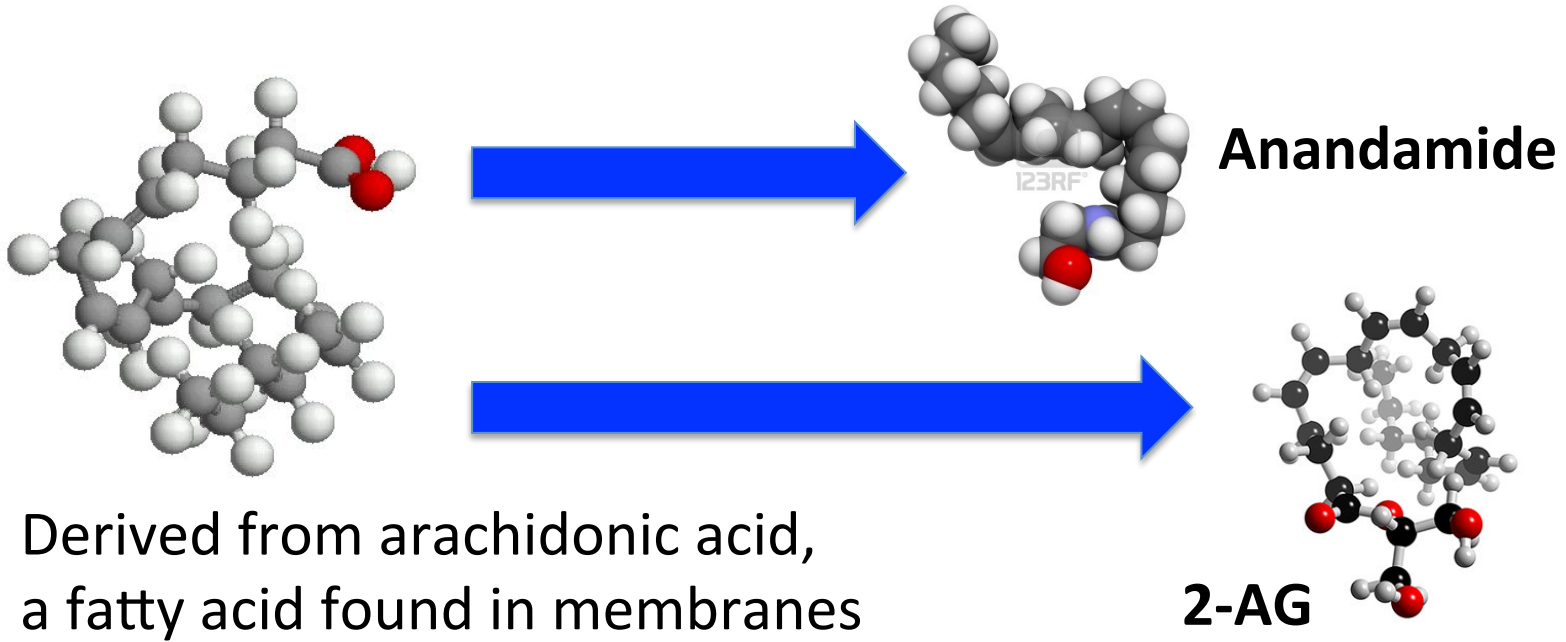
Spinal cord

Neocortex

CNS expression in areas important for motor coordination, memory, nausea, decision making, pain...

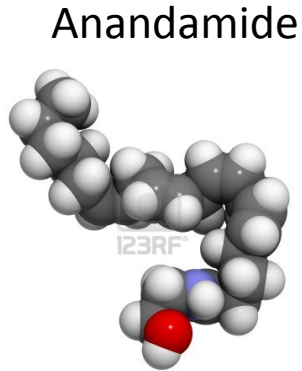
# Endogenous cannabinoid neurotransmitters

*If we have receptors for cannabinoids like THC, why are they there? What neurotransmitters act at these endogenous receptors..?*



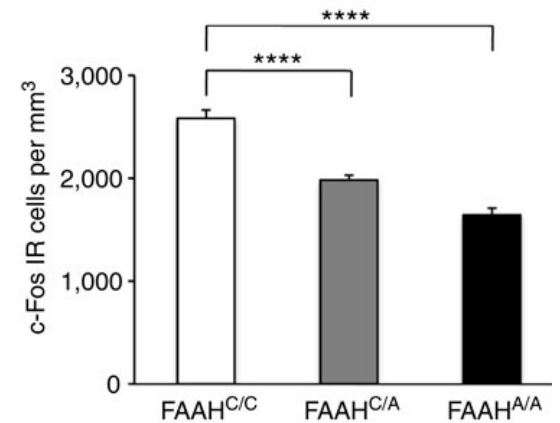
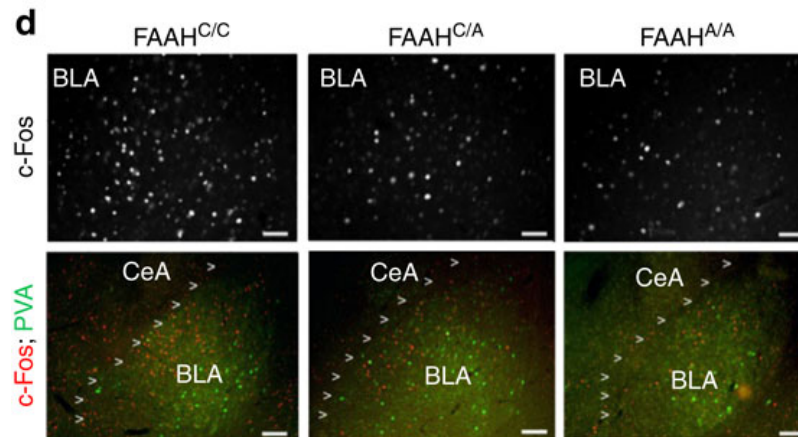
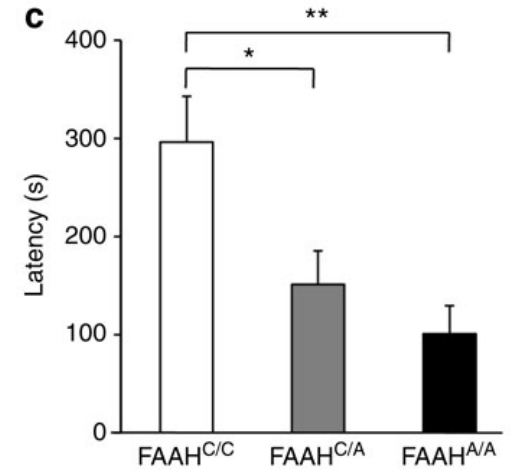
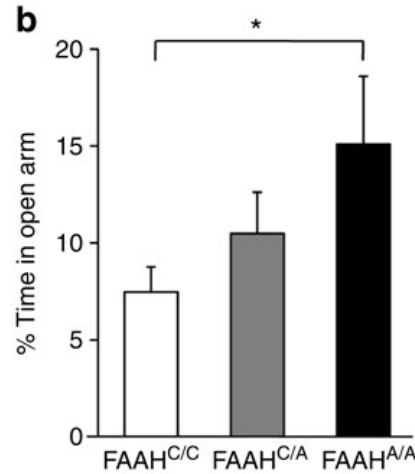
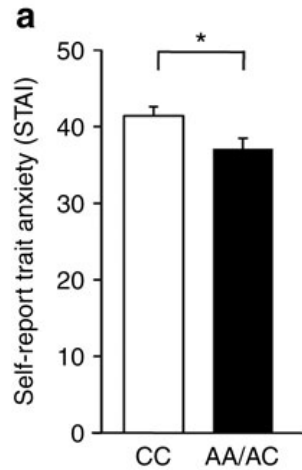
# Anxiety: Genetic protection?

Decreased anxiety in humans and mice with FAAH C385A



Breakdown by  
FAAH; several  
Forms (A, C)

A less common;  
Less effective at  
breakdown



FAAH genetic variation enhances fronto-amygdala function in mouse and human, Nature Communications, Iva Dincheva et al (2015)

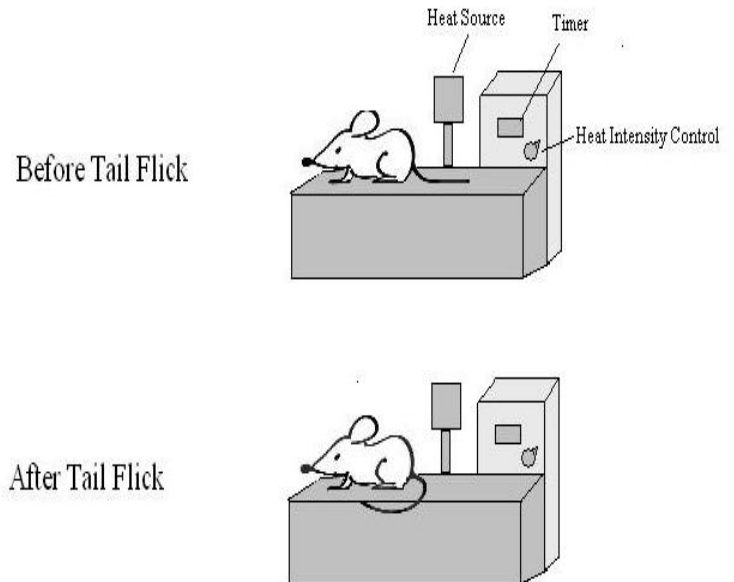
# Cannabinoids reduce pain

A large body of literature indicates that cannabinoids suppress behavioral responses to acute and persistent noxious stimulation...

(Walker JM, Hohmann AG, 2005)

**Co-administration of cannabinoids and opioids allows for pain relief with a lower opioid dose!**

(e.g., Wilson AR, Maher L, Morgan MM, 2008)



# More therapeutic effects



- **Appetite stimulation**  
(e.g., Foltin, 1988; Grotenhermen, 2012)  
*Why is this therapeutic?*
- **Nausea relief**  
(e.g., Parker et al (2011); “The anti-emetic effect of cannabinoids has been shown across a wide variety of animals that are capable of vomiting in response to a toxic challenge.” Also studies referenced by the National Cancer Institute at [cancer.gov](http://cancer.gov); though chronic use linked to hyperemesis syndrome; Soriano-Co M, 2010)





# STILL MORE therapeutic effects



- Multiple sclerosis
  - E.g., “Current status of cannabis treatment of multiple sclerosis,” Deutsch et al (2008)
- Epilepsy
  - E.g., “The case for medical marijuana in epilepsy,” Maa (2014)
- Cancer
  - E.g., “The combination of cannabidiol and  $\Delta 9$ -THC enhances the anticancer effects of radiation in an orthotopic murine glioma model,” Scott et al (2014)

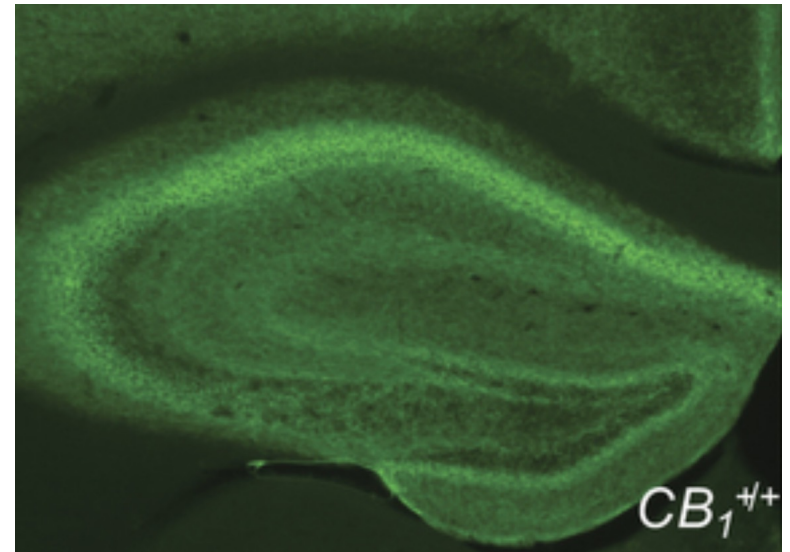
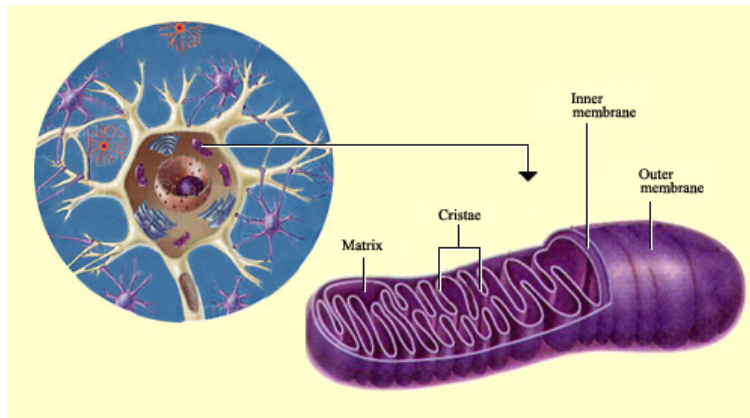
# Marijuana impairs cognition, memory, motor coordination

- Deficits in acute verbal and spatial memory (e.g., Curran et al, 2002)
- Deficits in working/short-term memory (Schoeler 2013)
- Cannabis and alcohol both impair skills critical for driving (Sewell RA et al, 2009)
- Differential effects on socialization (Atakan, 2012)



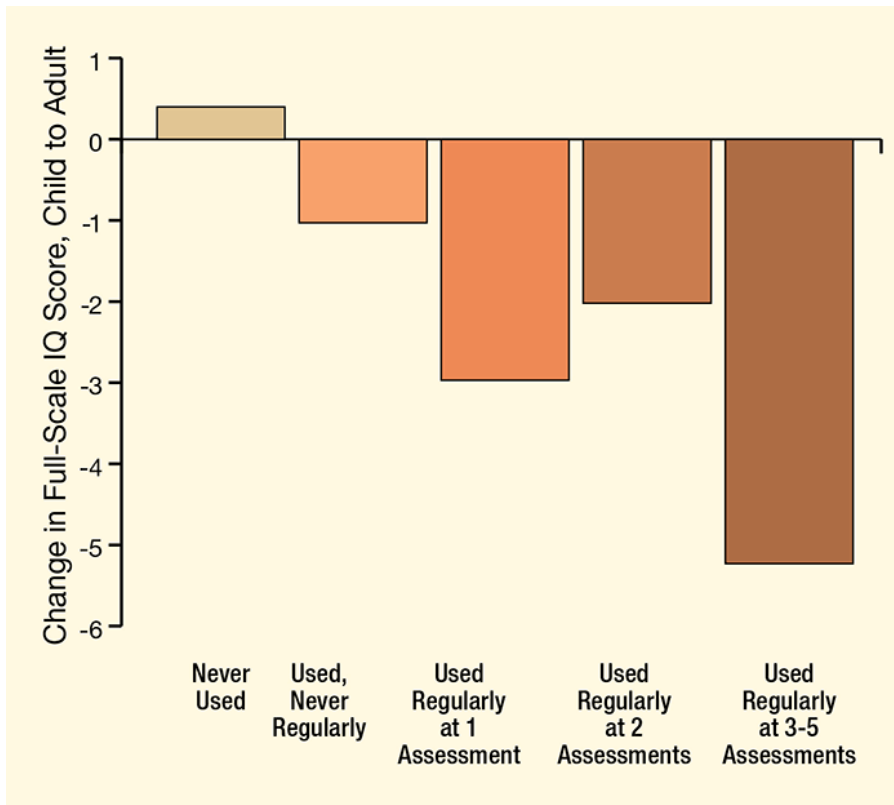
# A cannabinoid link between mitochondria and memory

Etienne Hebert-Chatelain, et al  
Nature (2016)



Cellular activity depends on mitochondria  
Mitochondria site of cellular respiration (ATP)  
Mitochondria have many CB1 receptors (mtCB1)  
Cannabinoid action at mtCB1 inhibits respiration  
Hippocampus starved of energy (less ATP)  
*A mechanism for amnesia..?*

# Early chronic marijuana exposure linked to decline in IQ



Regular cannabis use that starts in adolescence strips away IQ, a NIDA-supported 25-year study of 1,000 individuals suggests. Study participants who initiated weekly cannabis use before age 18 dropped IQ points in proportion to how long they persisted in using the drug, while nonusers gained a fraction of a point.

Meier, M.H. et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *PNAS* 109(40):E2657–E2664, 2012.

# Risks of chronic adolescent use

Volkow et al (2014), NEJM

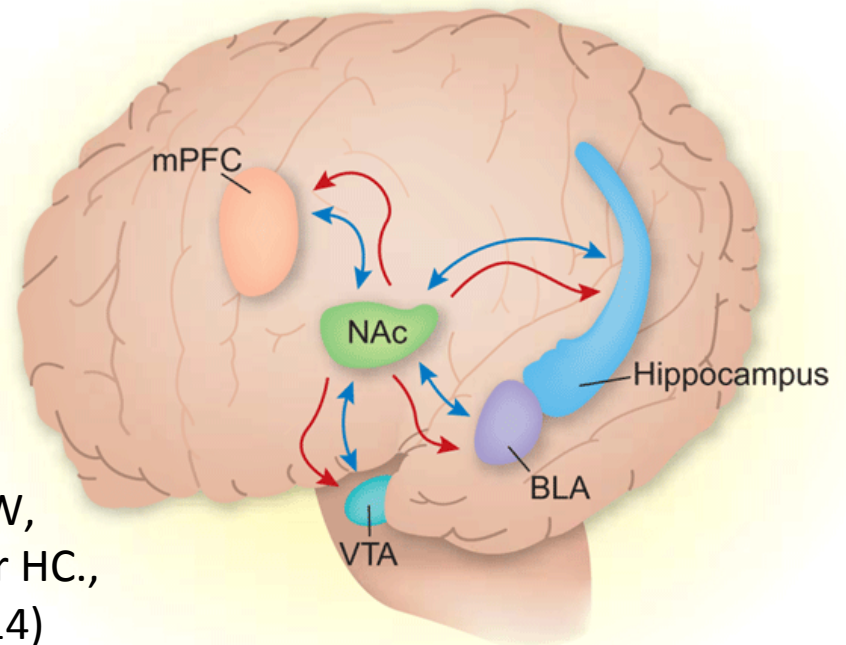
- **Cognitive impairment:** IQ drop
- **Risk of dependence:** 9% of those who experiment; 1 in 6 of those who start using in adolescence, and 25 – 50% of those who smoke daily...
- **Changes in functional connectivity**
- **Increased risk of anxiety and depression, and schizophrenia/psychosis** in those with a preexisting genetic vulnerability (**But from Volkow article:** *“It is inherently difficult to establish causality in these types of studies because factors other than marijuana use may be directly associated with the risk of mental illness...”*)
- **School performance:** “Early marijuana use is associated with impaired school performance...*although reports of shared environmental factors... suggest that the relationship may be more complex...*”

# However...we're still learning

- Cannabis use *is quantitatively associated* with nucleus accumbens and amygdala abnormalities in young adult recreational users.

Nucleus accumbens, amygdala are part of motivational networks (what you seek, what you avoid...)

Gilman JM1, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, van der Kouwe A, Blood AJ, Breiter HC., J Neurosci. 2014 Apr 16;34(16):5529-38 (2014)



# But wait - *which is it..?*

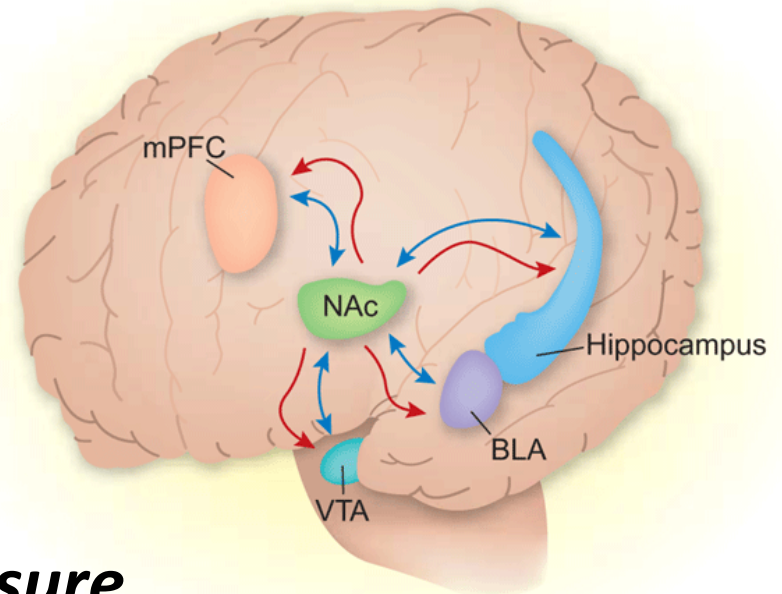
- **Daily Marijuana Use *Is Not Associated* with Brain Morphometric Measures in Adolescents or Adults**

Barbara J. Weiland, Rachel Thayer,  
Brendan E. Depue, Amithrupa Sabbineni,  
Angela Bryan, Kent E. Hutchison, *The Journal*  
of Neuroscience, 28 January 2015

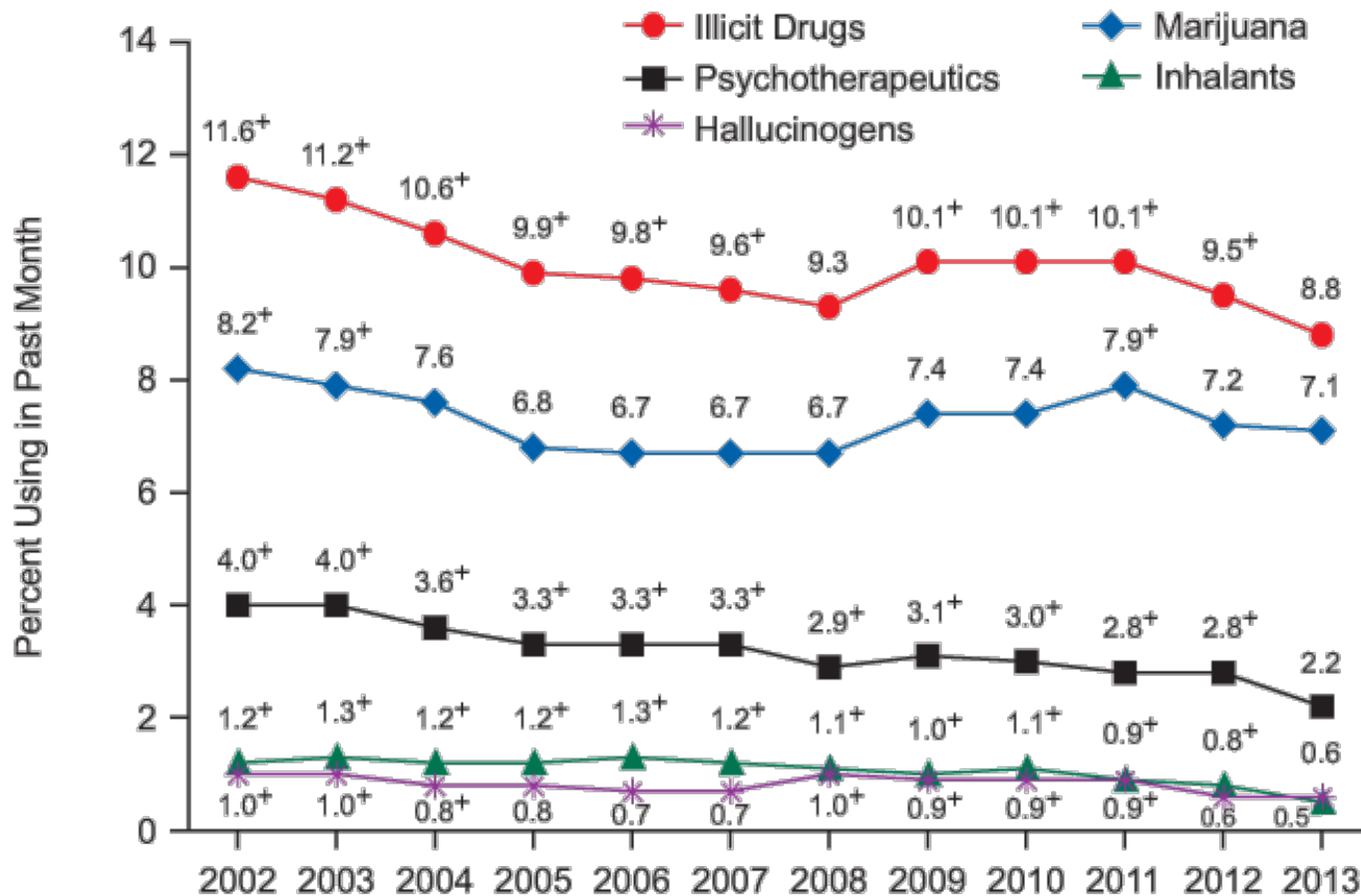
Same journal

Different research group

\* ***Controlled for alcohol exposure...***



# Past Month Illicit Drug Use

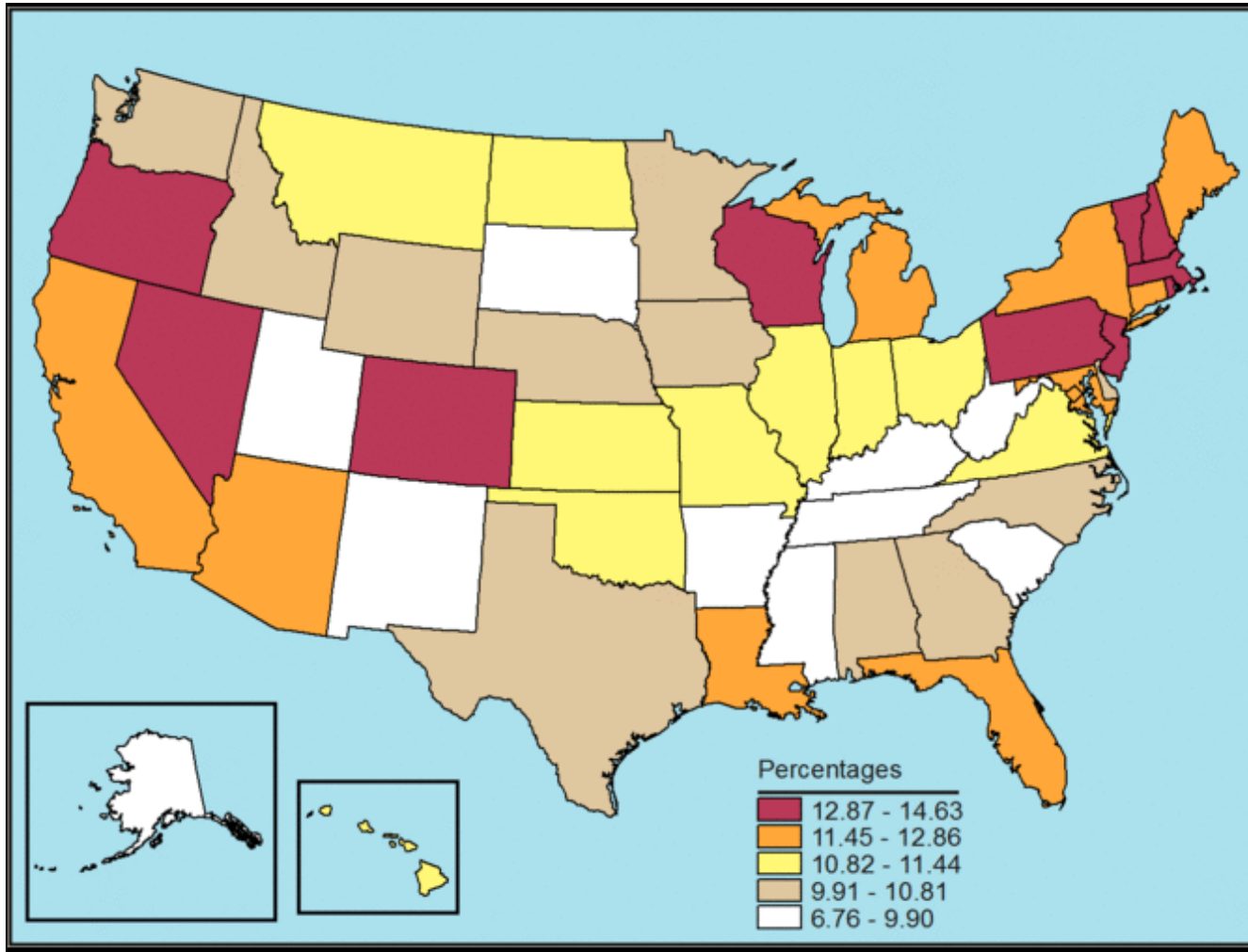


## Youths Aged 12 to 17: 2002-2013

Substance Abuse and Mental Health Services Administration  
National Survey on Drug Use and Health, 2013



# ***Alcohol Use in the Past Month among Youths Aged 12 to 17, by State; SAMHSA NSDUH***



**Percentages, Annual Averages Based on 2013 and 2014 NSDUHs**