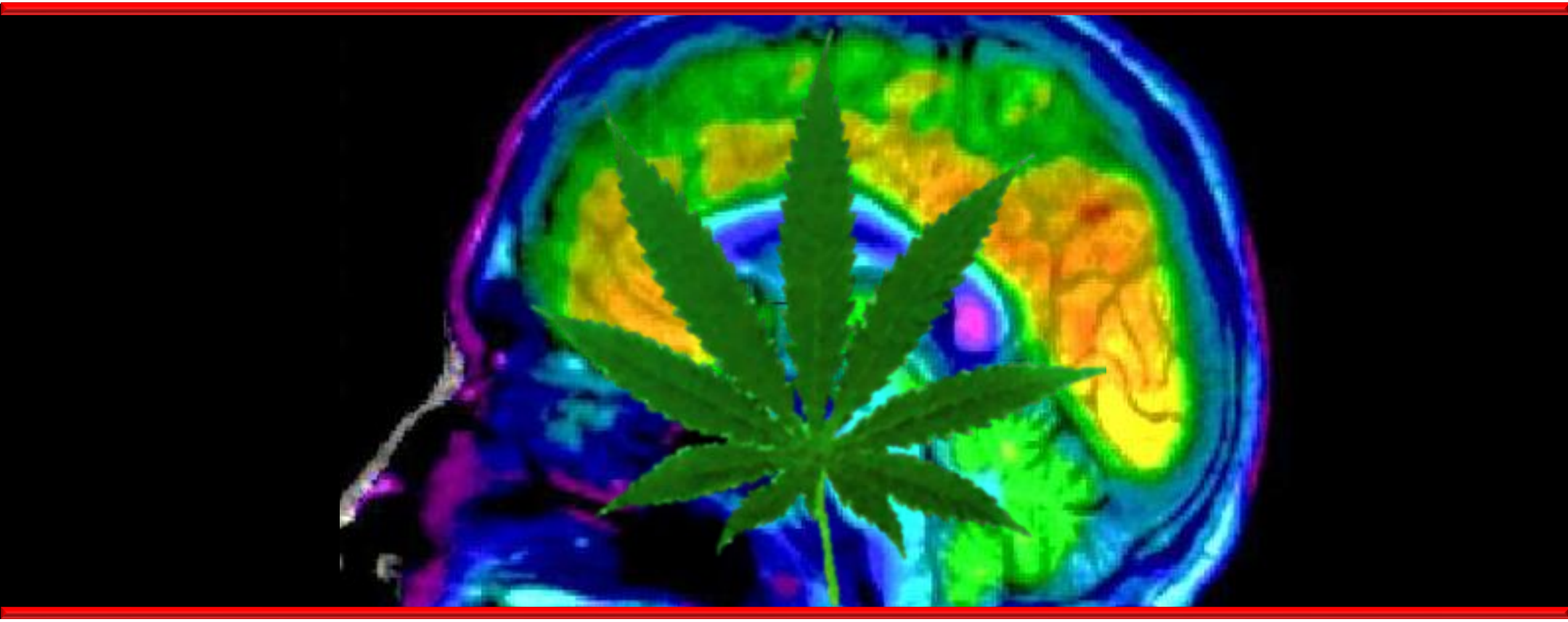
MARIJUANA

What Does the Science Tell Us?



Ruben Baler, PhD

NIH National Institute on Drug Abuse

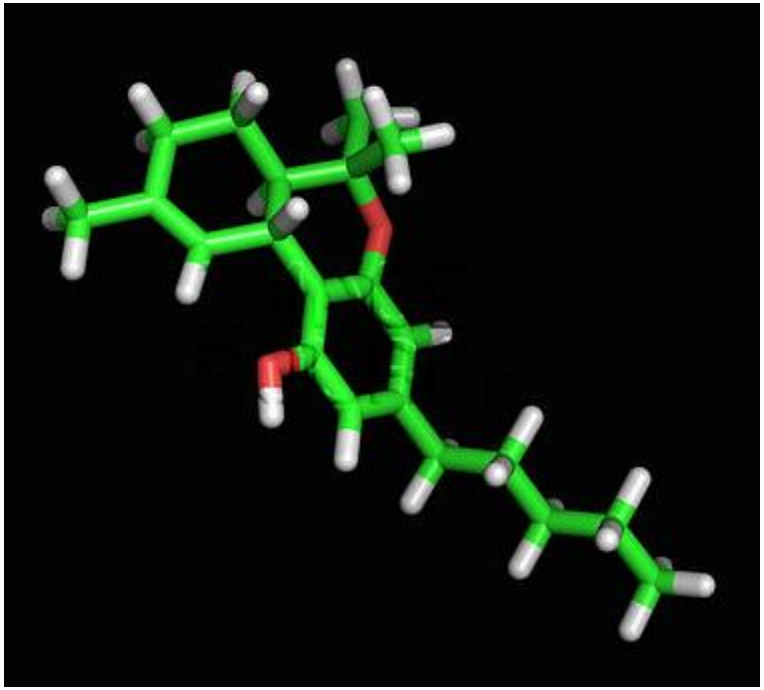
- Marijuana use
- Marijuana effects
- Marijuana as medicine

- Marijuana use

Marijuana is the Most Commonly Used Illicit Drug In the U.S.

- Over 114 million Americans have tried it at least once

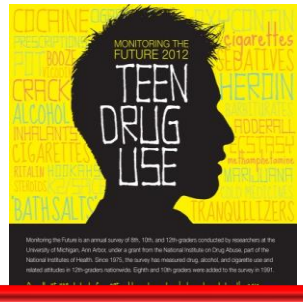
- An estimated 2.4 million Americans used it for the first time in 2013

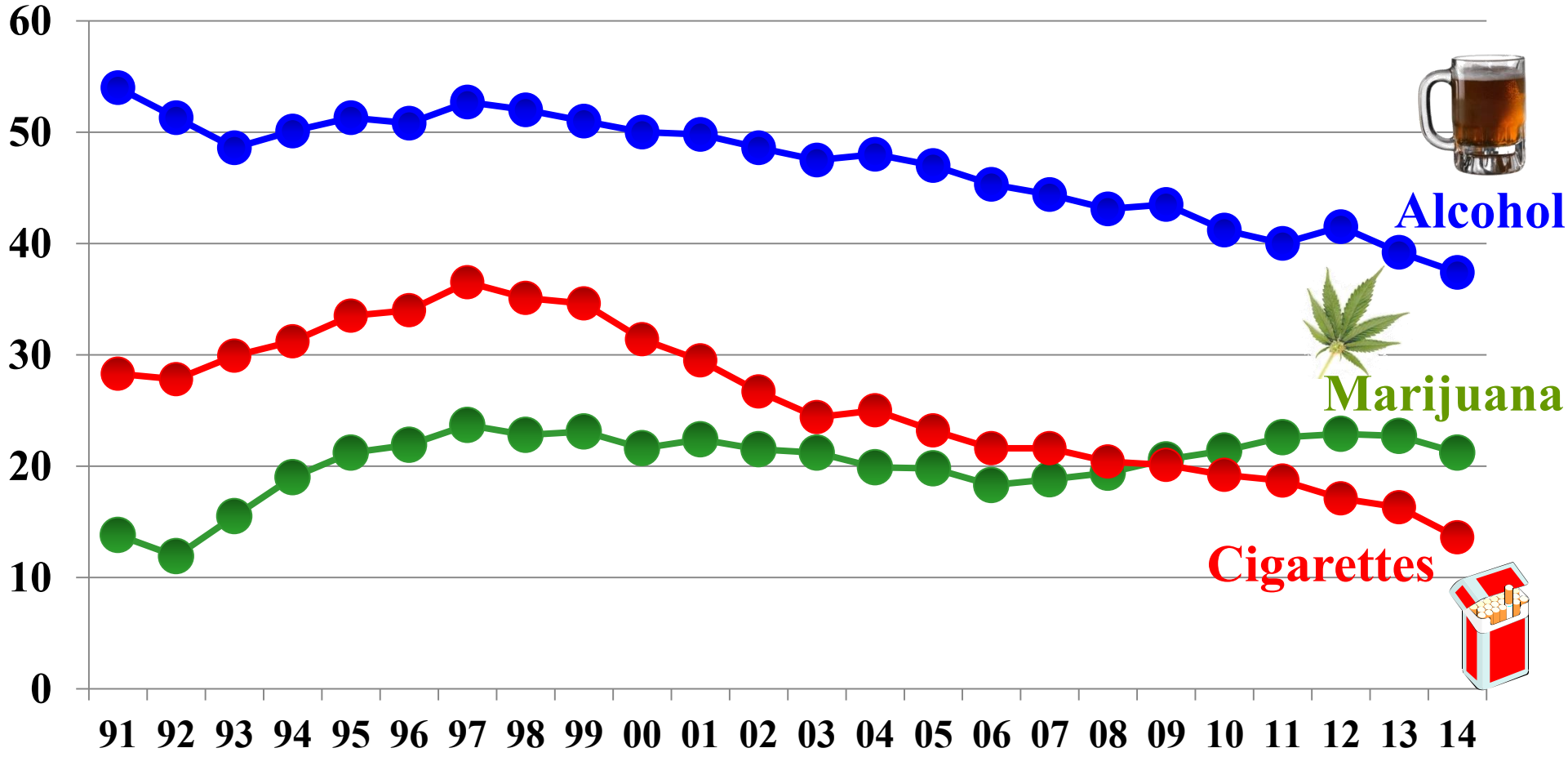


Tetrahydrocannabinol (THC)
Active Ingredient in Marijuana

2013 National Survey on Drug Use and Health, SAMHSA, 2014.

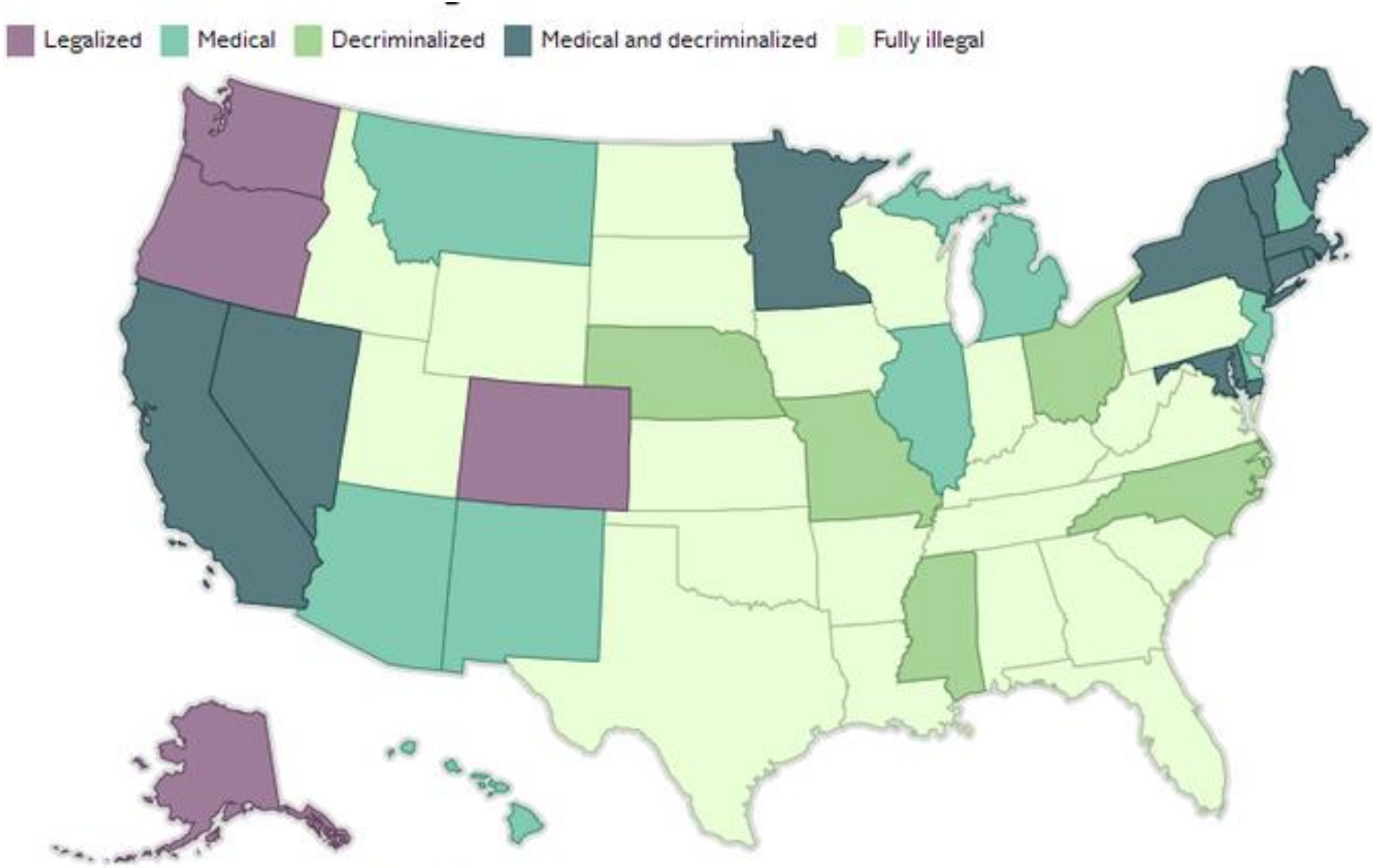
Percentage of U.S. 12th Grade Students Reporting Past Month Use of Cigarettes, Marijuana and Alcohol





SOURCE: University of Michigan, 2014 Monitoring the Future Study.

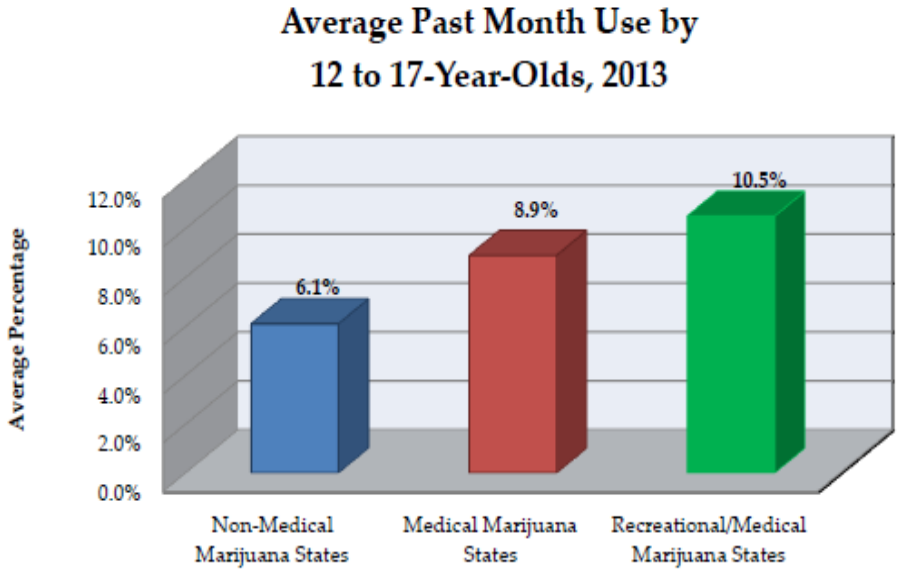
Status of Marijuana Laws in the United States



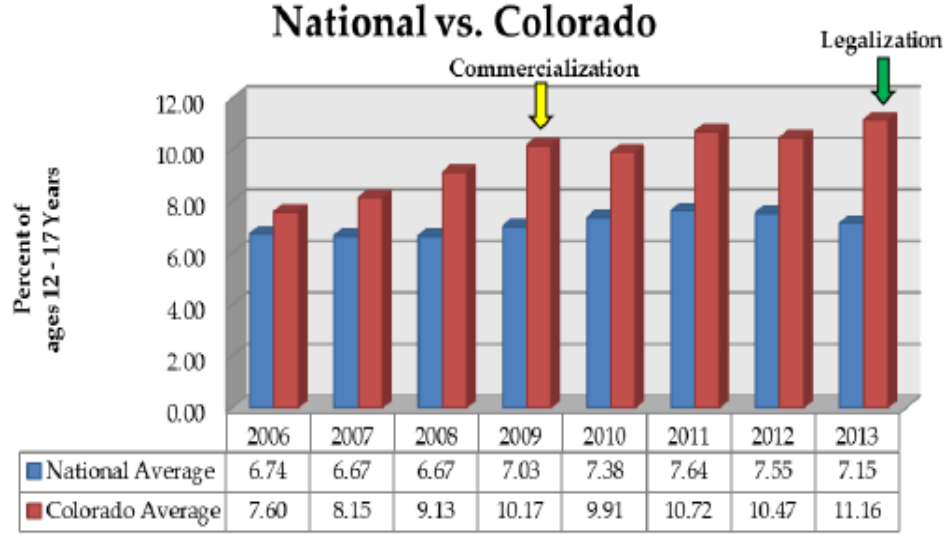
Source: NORML, Drug Policy Alliance, and the Marijuana Policy Project

MARIJUANA LAWS IN USA

Prevalence of Marijuana use in Teenagers

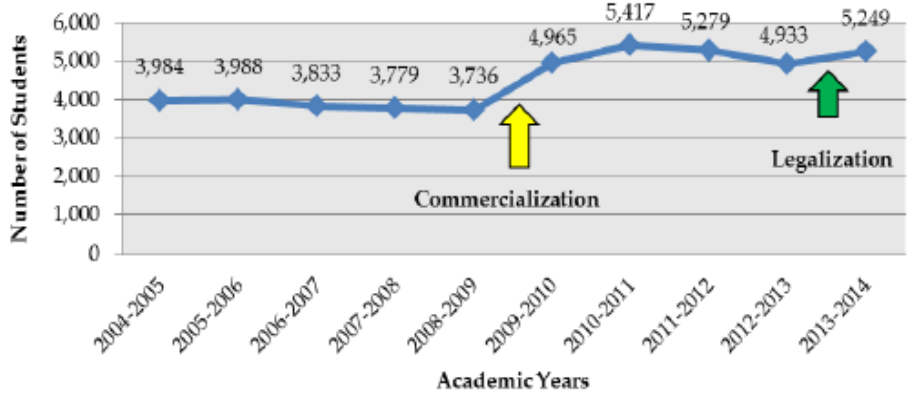


URCE: SAMHSA.gov, National Survey on Drug Use and Health 2012 and 2013



	2006	2007	2008	2009	2010	2011	2012	2013
National Average	6.74	6.67	6.67	7.03	7.38	7.64	7.55	7.15
Colorado Average	7.60	8.15	9.13	10.17	9.91	10.72	10.47	11.16

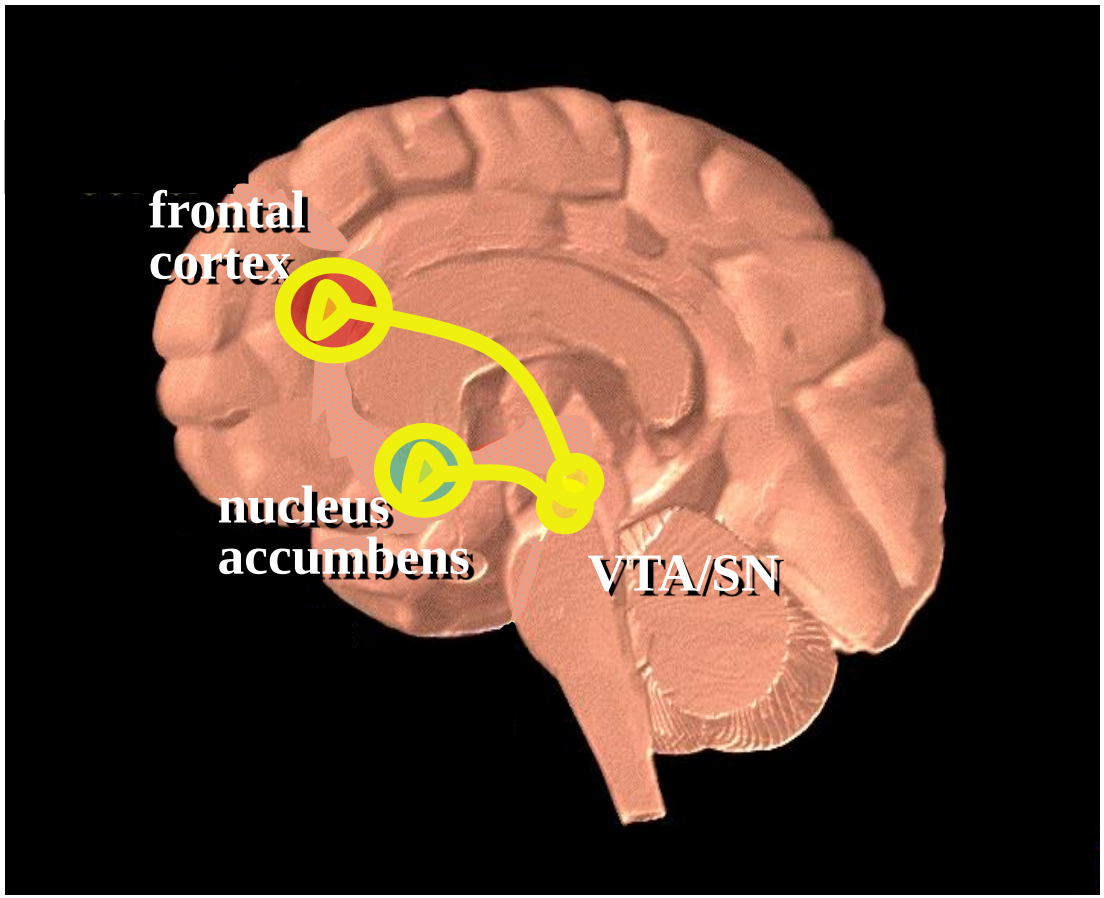
Marijuana-Related School Suspensions in Colorado



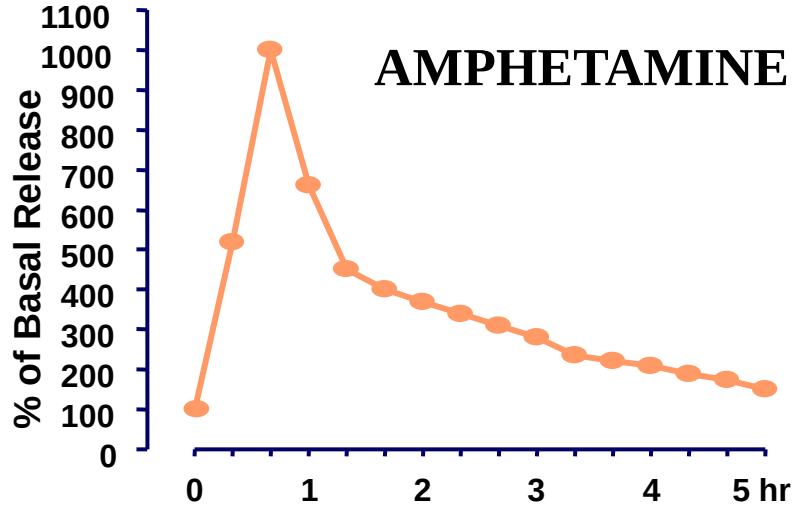
Colorado Department of Education, 10-Year Trend Data: State Suspension and Expulsion Incident Rates and Reasons

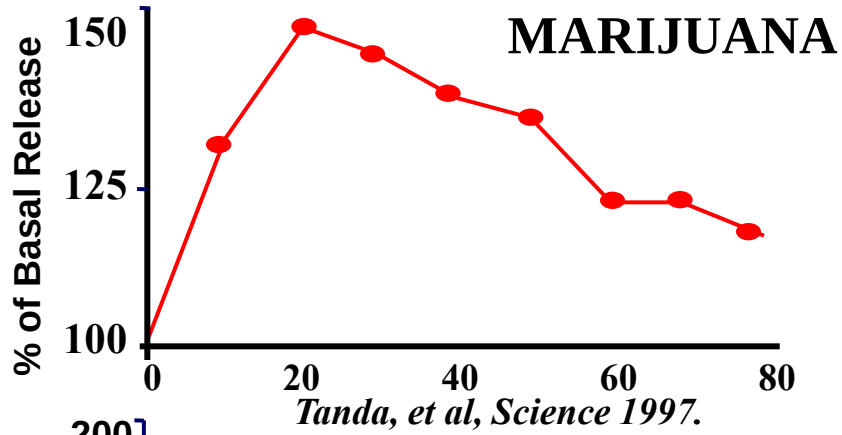
- Marijuana effects

Natural and Drug Reinforcers Increase Dopamine in NAc

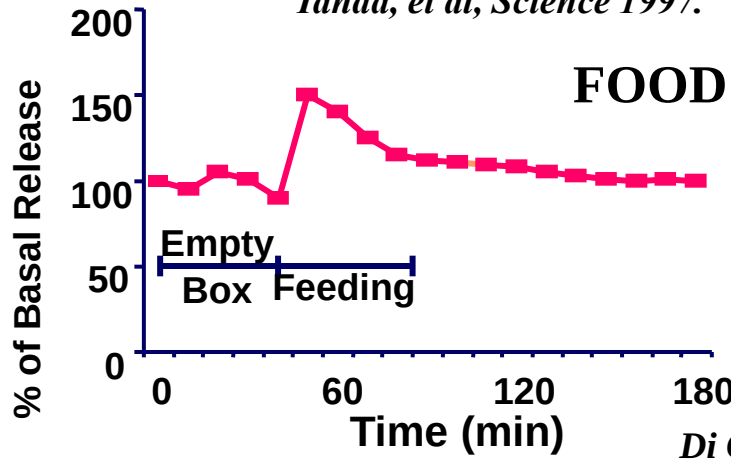


Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptions that result in addiction





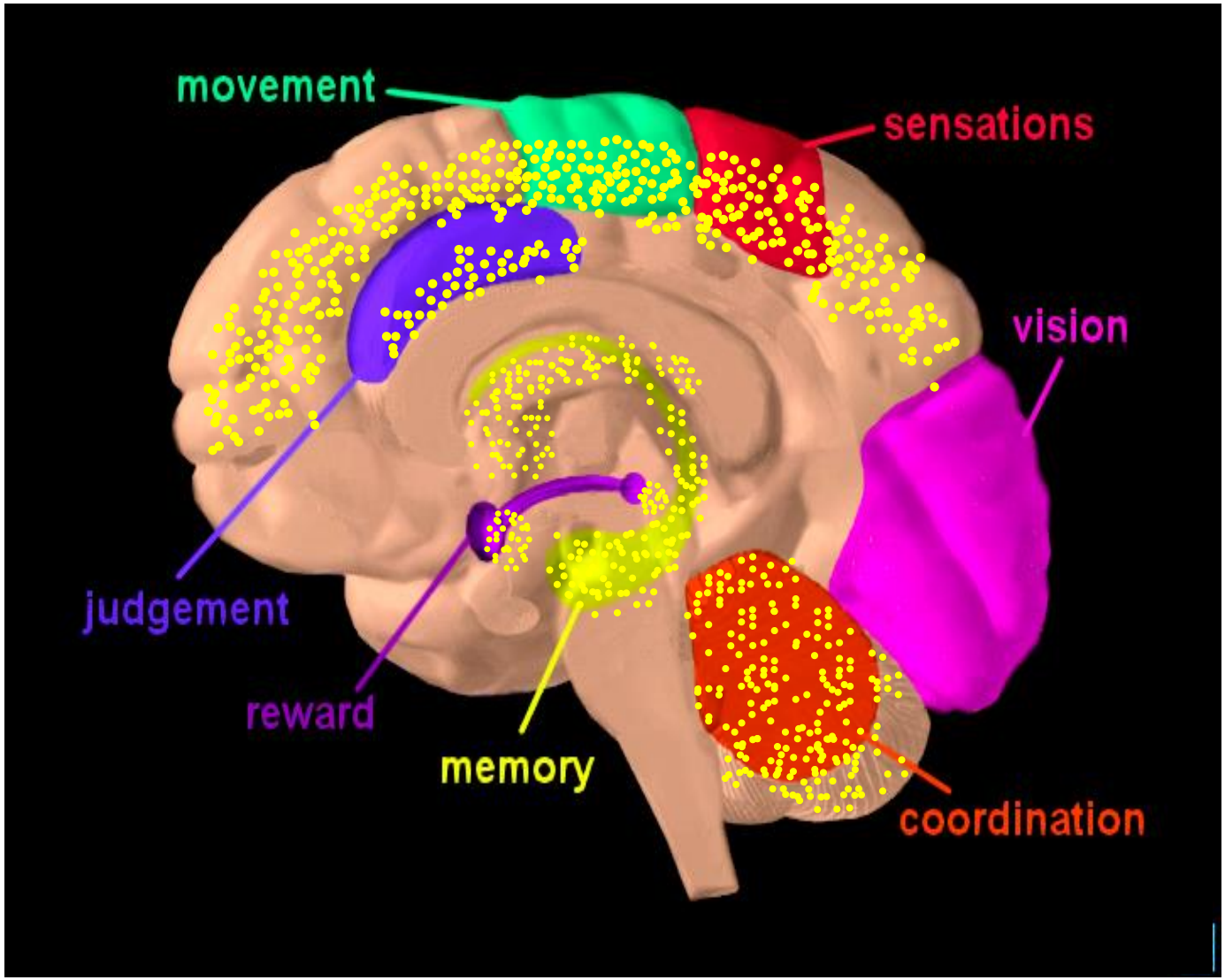
Tanda, et al, Science 1997.



Di Chiara et al.

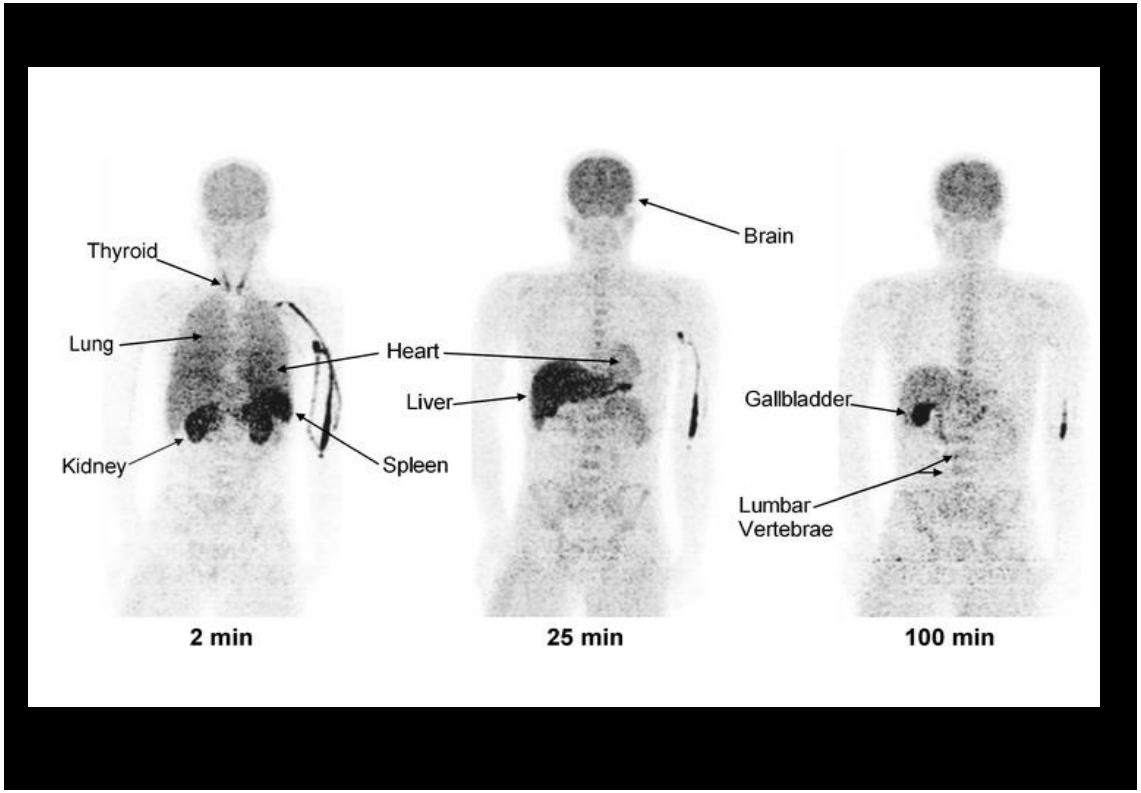
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory & Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia



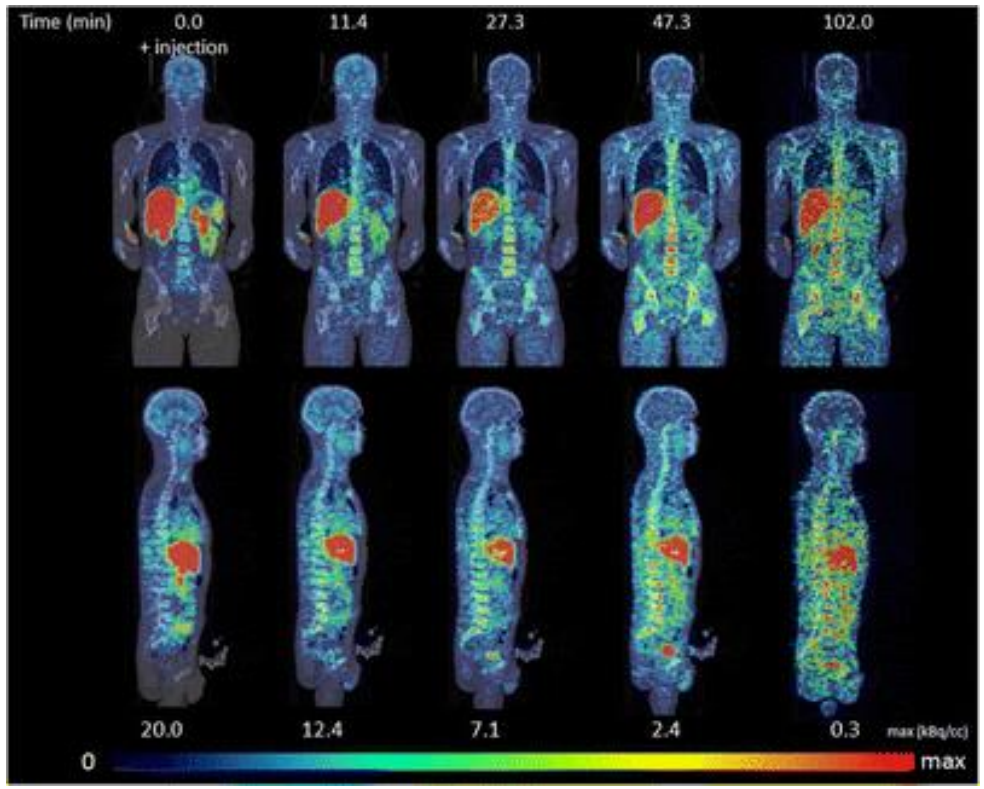
Cannabinoid Receptors Are Also Located Throughout the Body

Whole Body Distribution of CB1 Receptors (2, 25, and 100 min after injection of 11C-MePPEP)



Terry et al., Eur J Nucl Med Mol Imaging. 2010

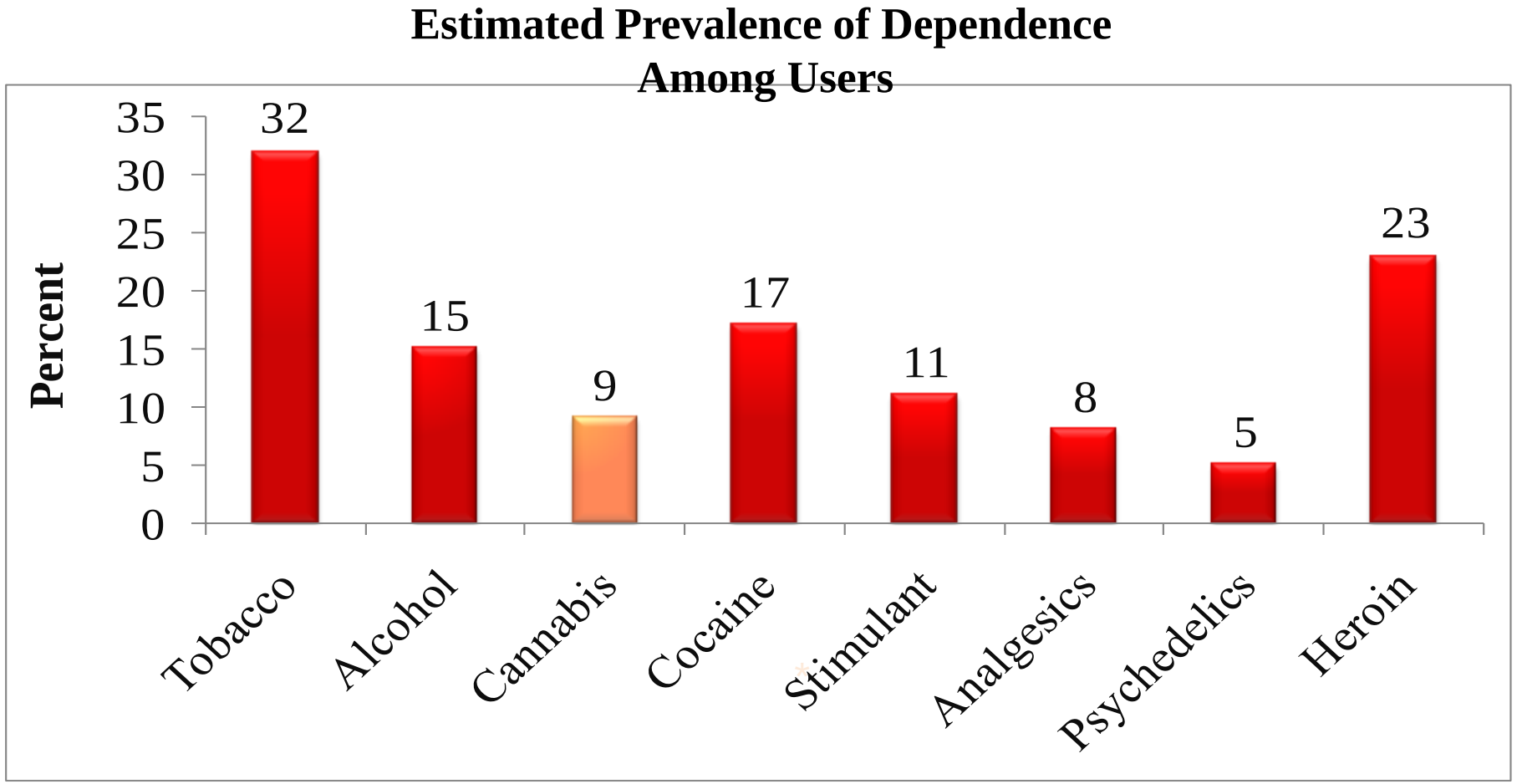
PET images of [11C]-NE40 (CB2R radioligand)



Ahmad et al., Mol Imaging Biol. 2013 A

Long Term Effects of Marijuana: Addiction:

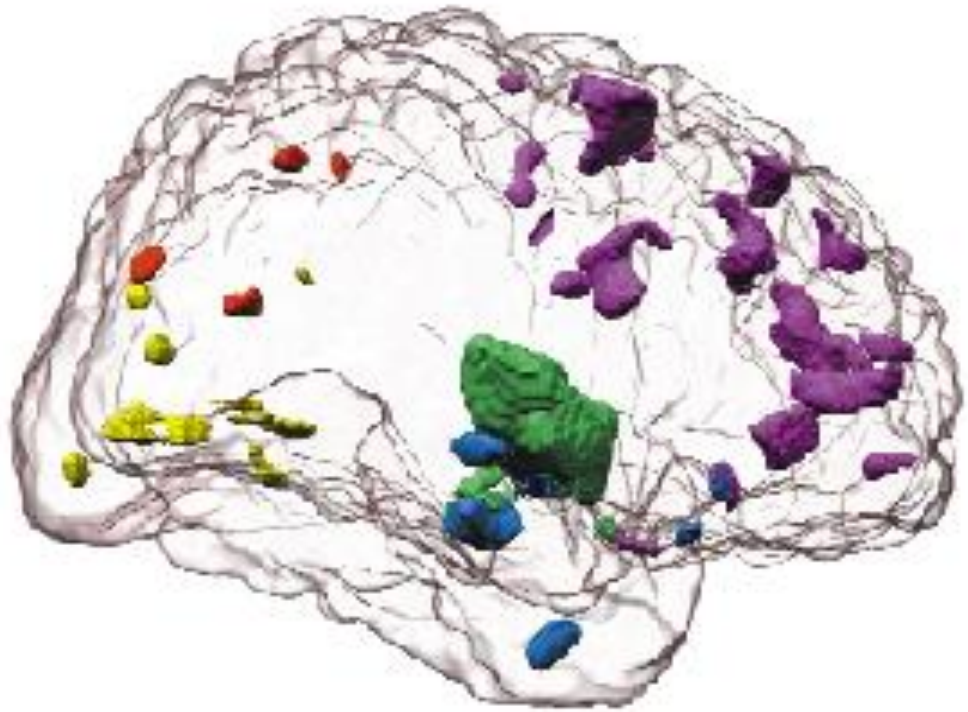
About 9% of users may become dependent,
1 in 6 who start use in adolescence,
25-50% of daily users



**** Nonmedical Use***

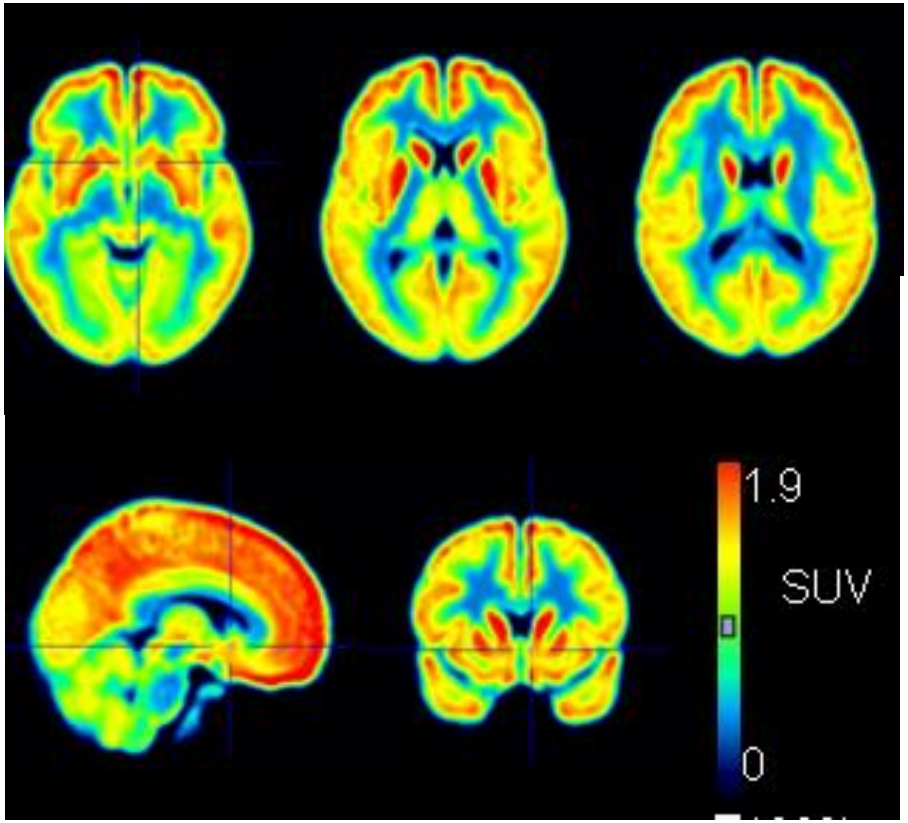
Source: Anthony JC et al., 1994

Does Marijuana Use negatively affect the developing brain and an individual's personal trajectory into adulthood?

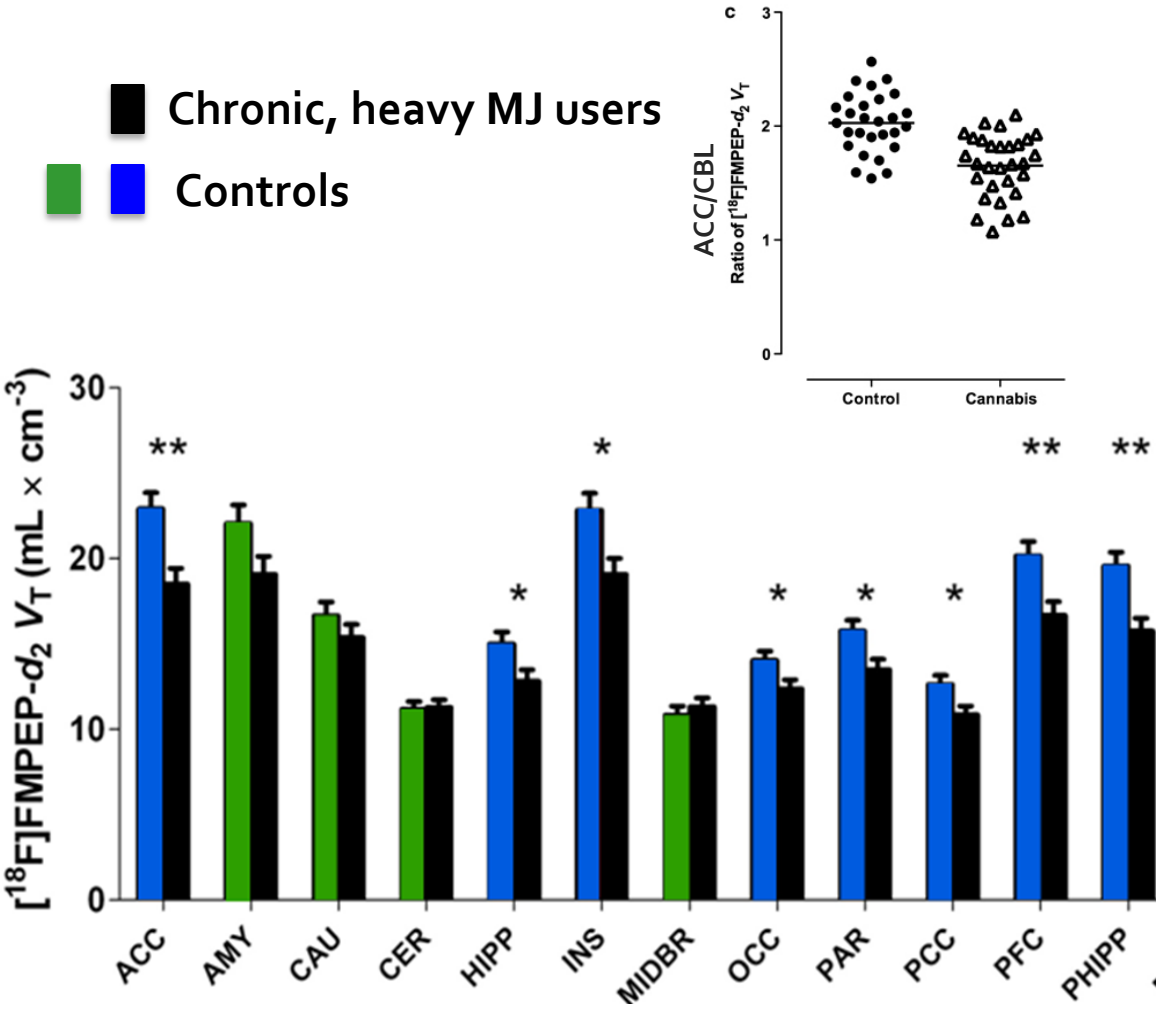


Lower CB1R in Heavy MJ Users

(partially reversible after 4 weeks of abstinence)

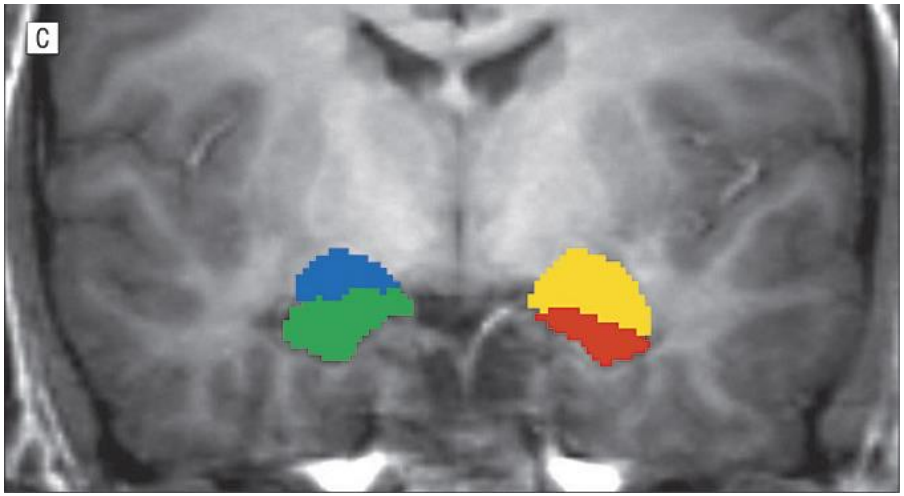


Selective inverse CB1R agonist [^{18}F]MK-9470
Van Laere et al., 2007.



Hirvonen et al., Mol Psychiatry 2013

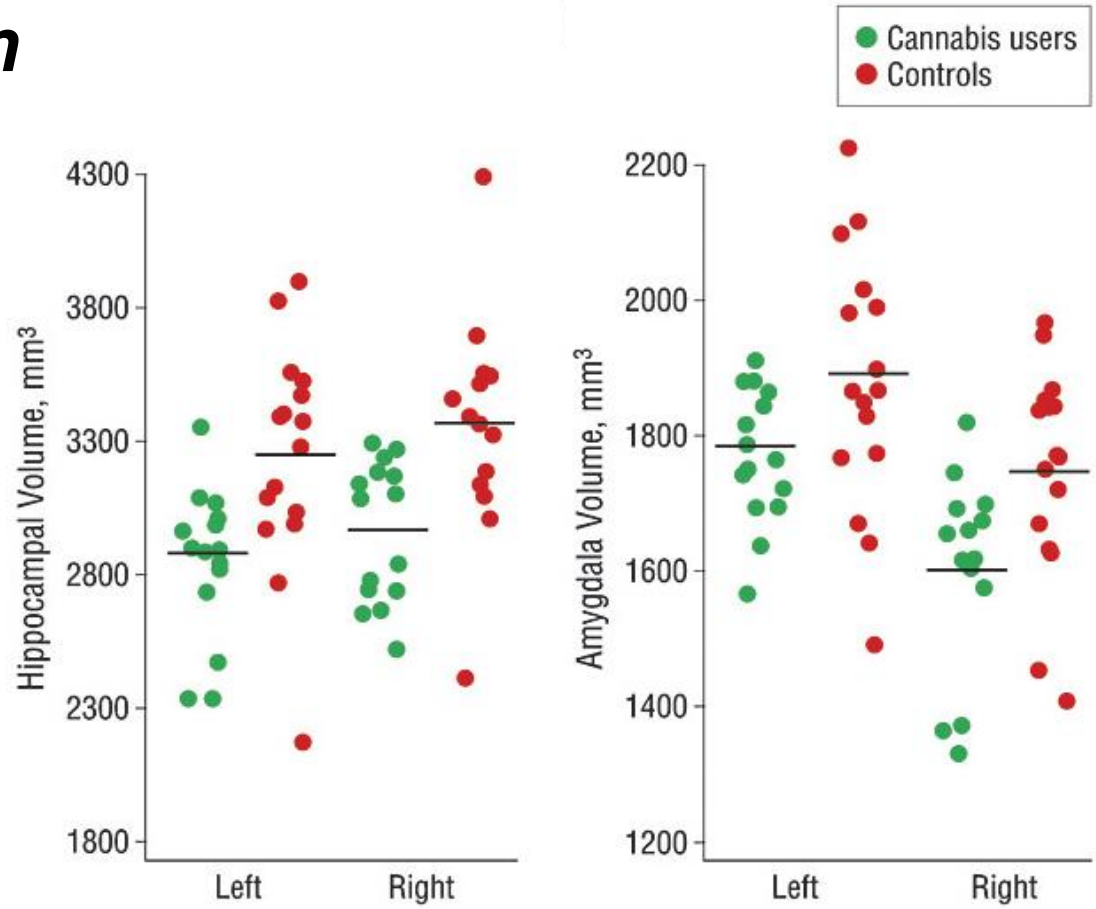
Smaller brain regions associated with long-term heavy marijuana use



L (yellow) and R (blue) amygdala
L(red) and R(green) hippocampus

Dysfunction of the hippocampus has been linked to reduced memory performance in heavy cannabis users.

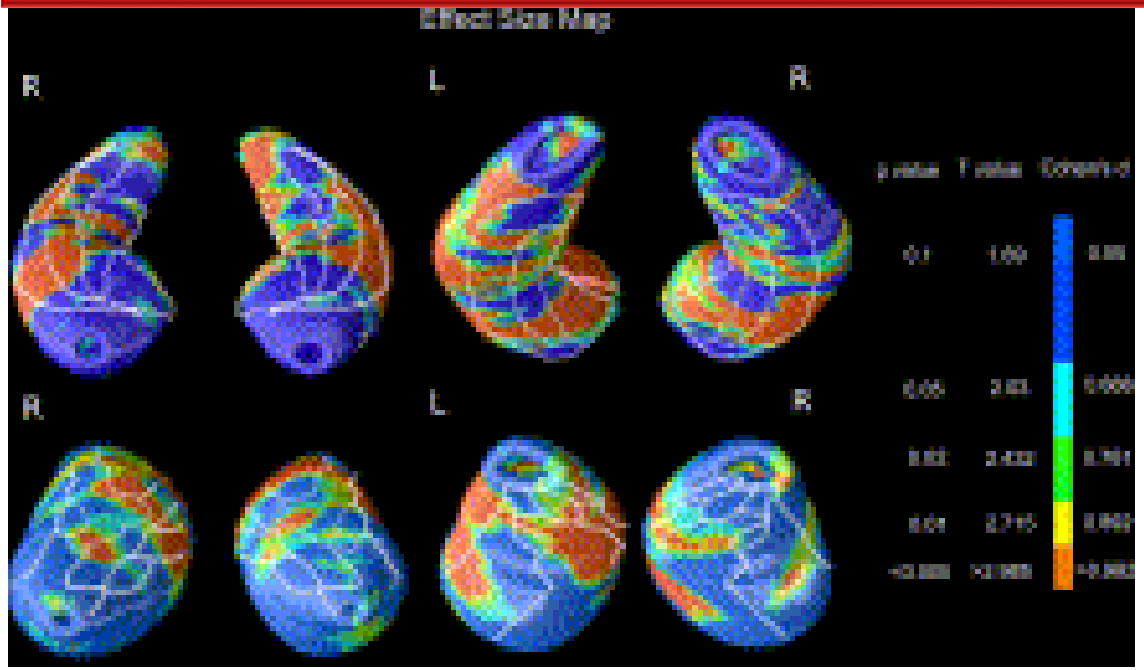
Hippocampus ***Amygdala***



Hippocampal and amygdalar volumes are smaller in heavy MJ users

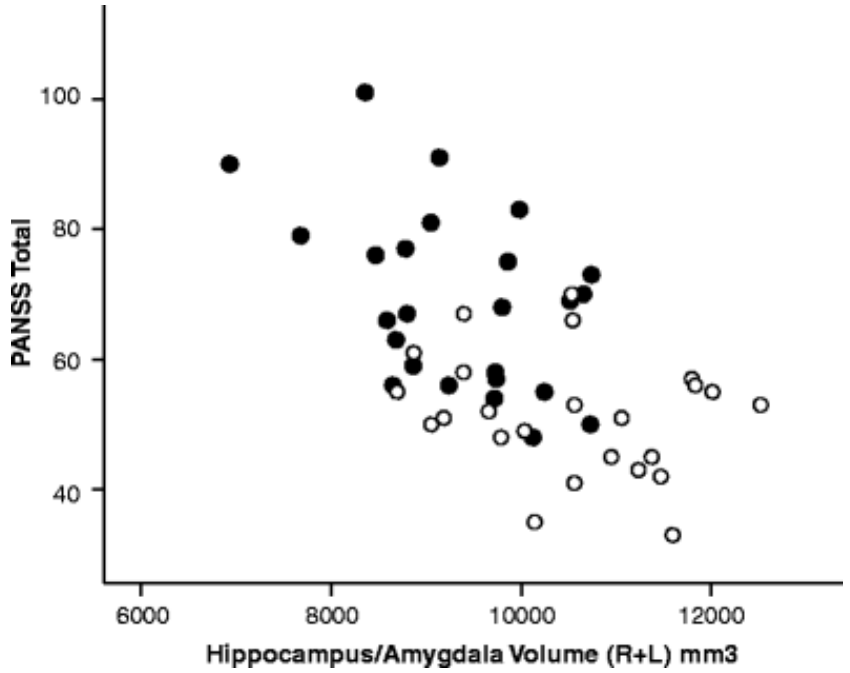
Yucel et al., Arch Gen Psychiatry. 2008 Jun;65(6):694-701.

Schizophrenics have Smaller Hippocampus and Amygdala



Areas in Hippocampus and Amygdala where volumes were smaller in schizophrenics than controls

Prestia et al., Am J Geriatr Psychiatry 2015.

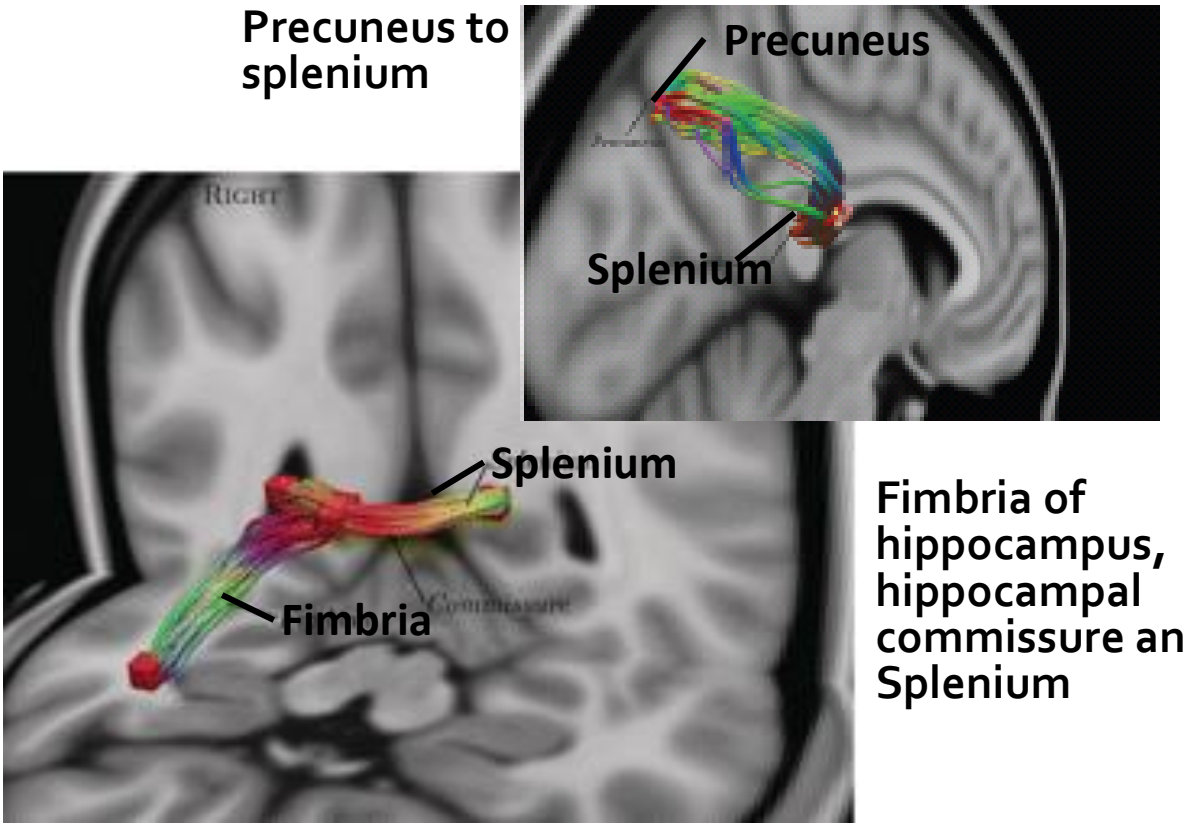


Hippocampus/Amygdala volumes correlated with psychosis in schizophrenics (closed) and bipolar patients (open)

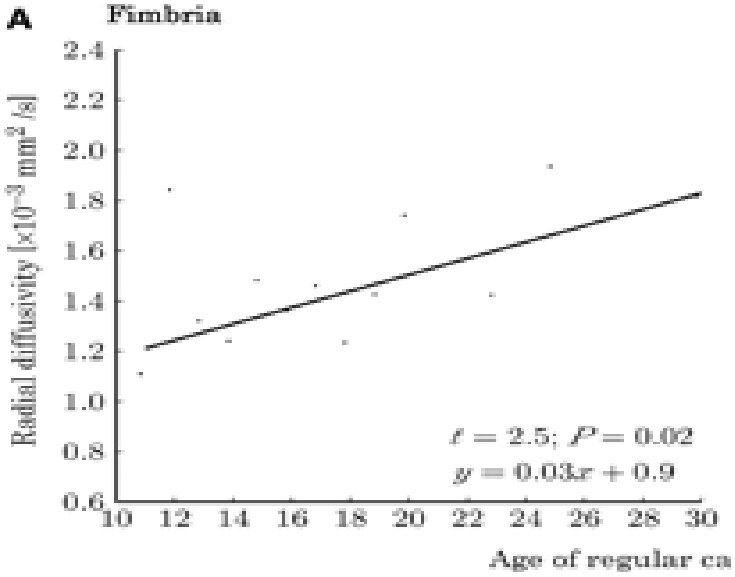
Watson et al., Brain Imaging Behav. 2012.

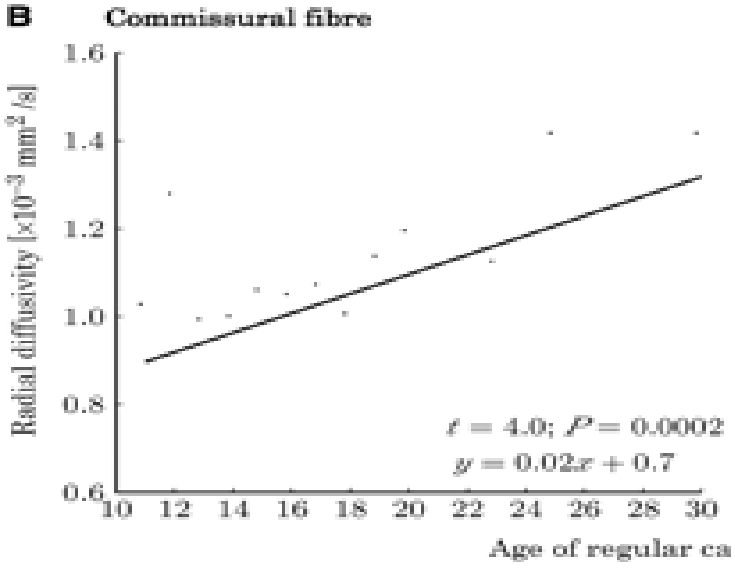
Early (<18y) Long-Term Cannabis Use Linked to Decreased Axonal Fiber Connectivity (no alcohol)

Precuneus to splenium



Fimbria of hippocampus, hippocampal commissure and Splenium





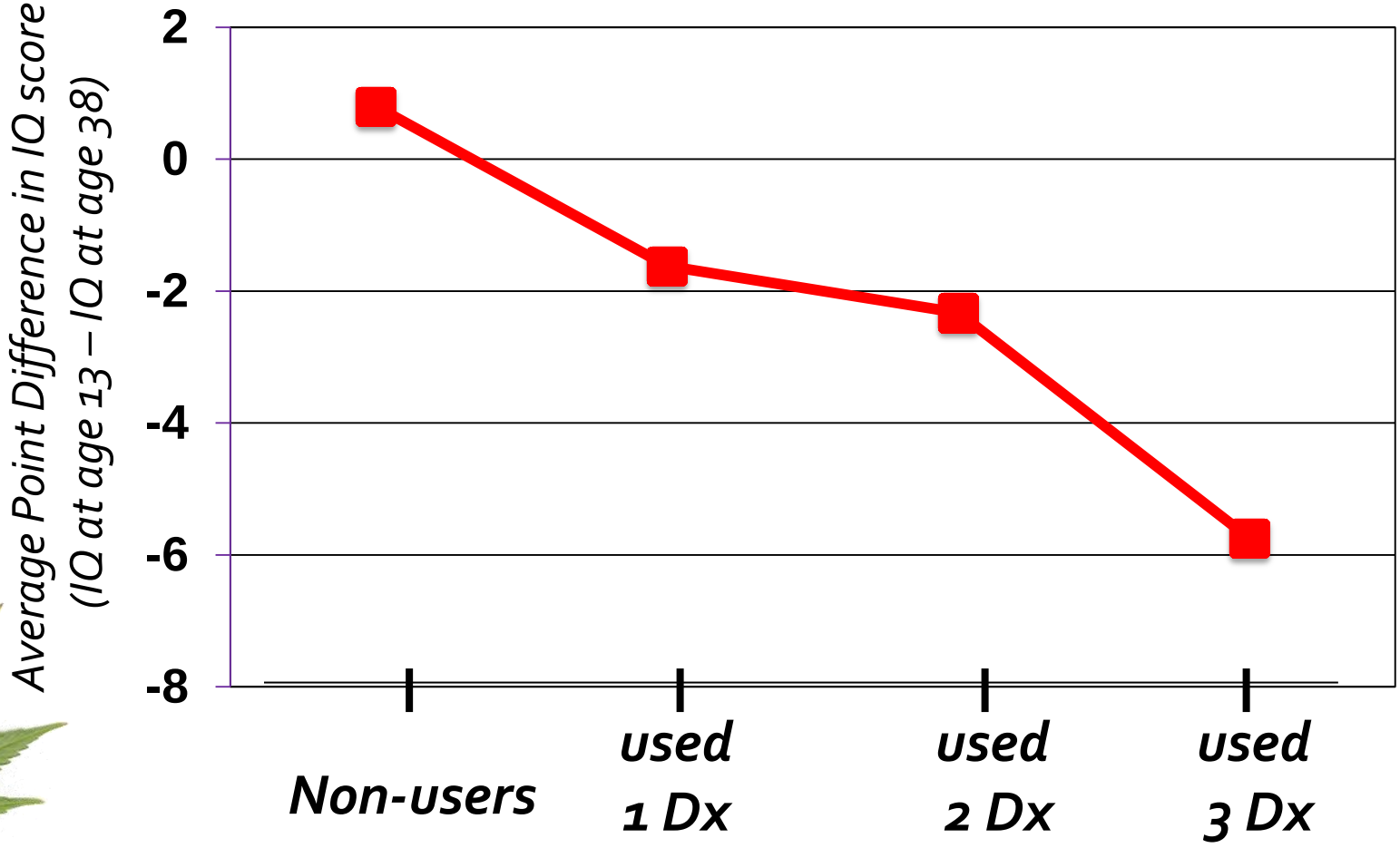
Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33). *Zalesky et al Brain 2012.*

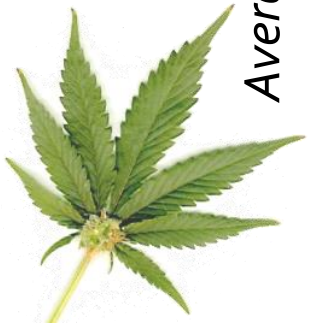
Early, chronic and heavy MJ use

- Down-regulation of CB1 receptors
- Smaller Amygdala and Hippocampus
- Decreased Connectivity

Persistent Marijuana Users Show A Significant IQ Drop between Childhood and Midlife

Followed 1,037 individuals from birth to age 38. Tested marijuana use at 18, 21, 26, 32 and 38. Tested for IQ at ages 13 and 38

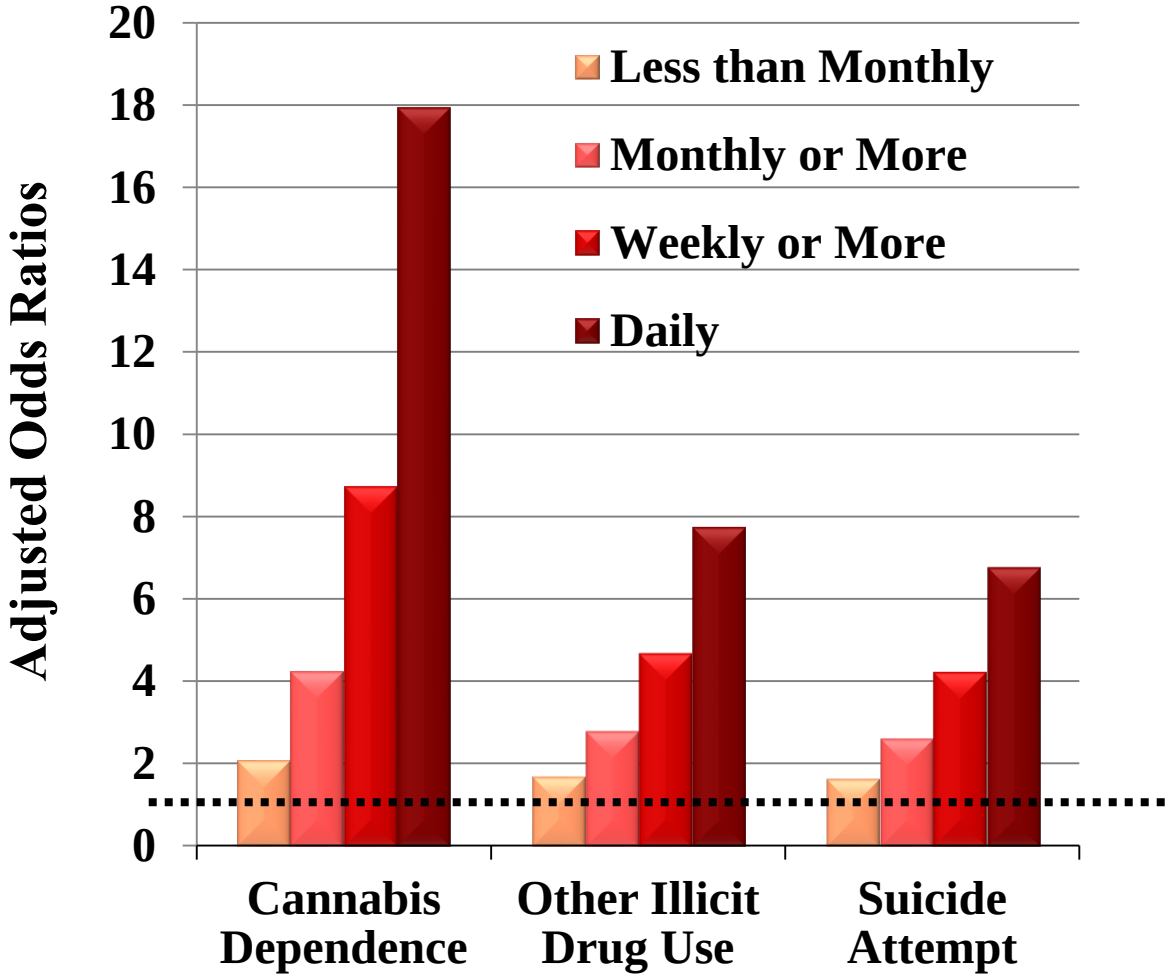


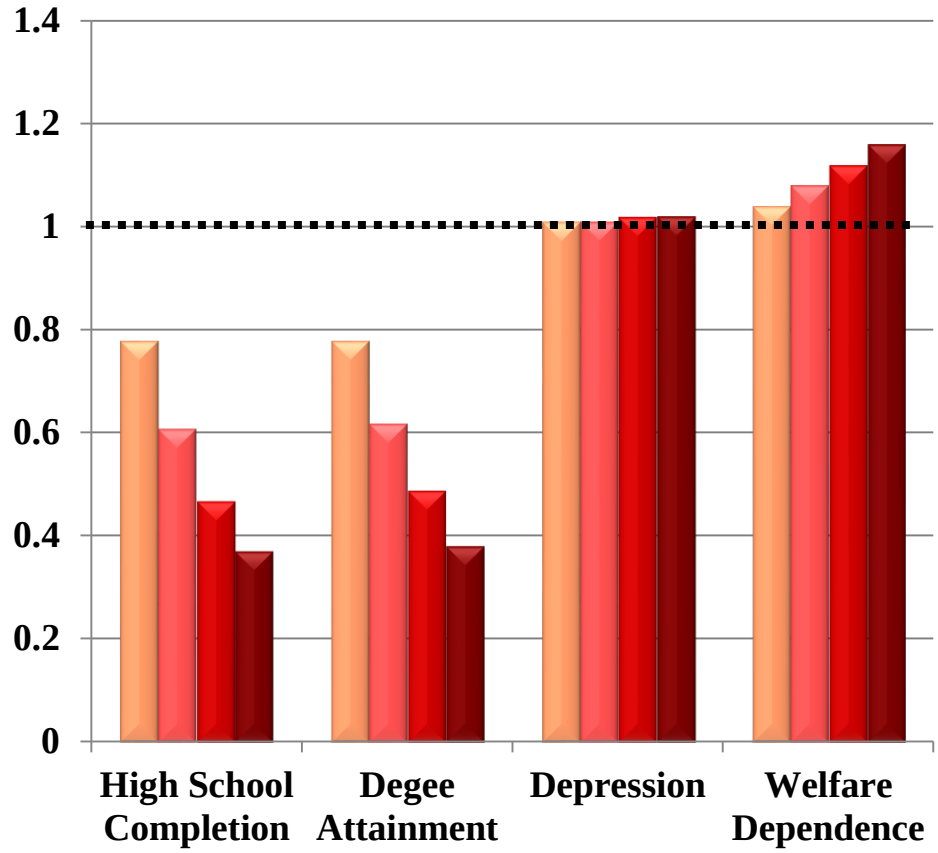


Source: Meier MH et al., PNAS Early Edition 2012

Frequency Of Cannabis Use Before Age 17 Years and Adverse Outcome (30years age) (n=2500-3700)

Consistent and dose-response association were found between frequency of adolescent cannabis use and adverse outcomes





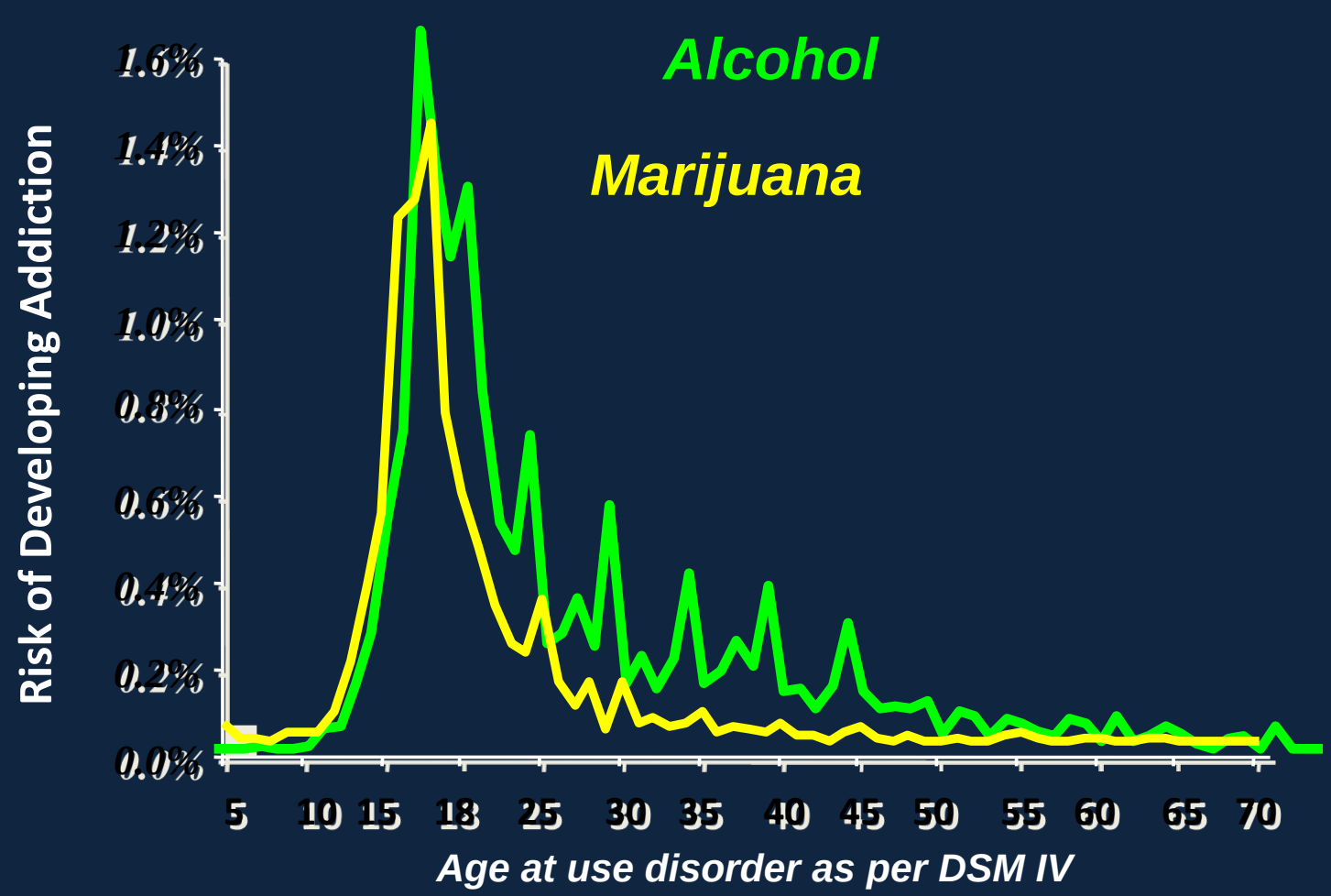
Silins E et al., The Lancet September 2014.

Adolescent Brain Cognitive Development
National Longitudinal Study

NIDA, NIAAA, NCI, NICHD, NIMH, NINDS, NIMHD, OBSSR, ORWH

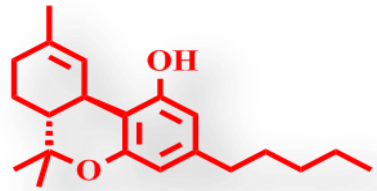
Ten year longitudinal study of 10,000 children from age 10 to 20 years to assess effects of drugs on individual brain development trajectories

ADDICTION IS A DEVELOPMENTAL DISEASE
It starts in adolescence and even childhood



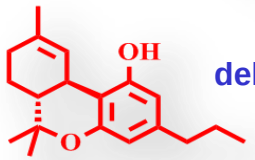
NIAAA national Epidemiologic Survey on Alcohol and related Conditions 2003

Constituents of MJ and the Cannabinoid System



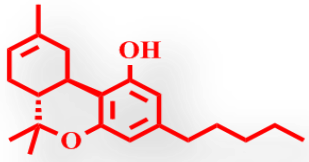
Δ^9-THC

delta-9-tetrahydrocannabinol



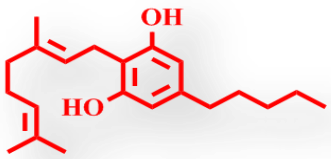
Δ^9-THCV

delta-9-tetrahydrocannabivarin



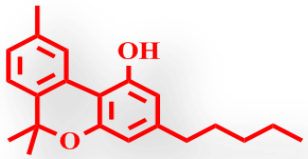
Δ^8-THC

delta-8-tetrahydrocannabinol



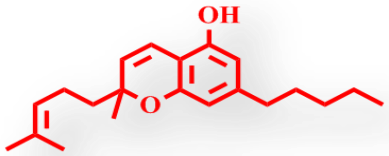
CBG

cannabigerol



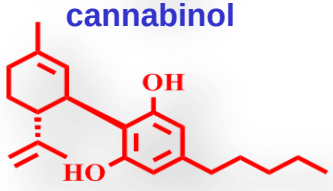
CBN

cannabinol



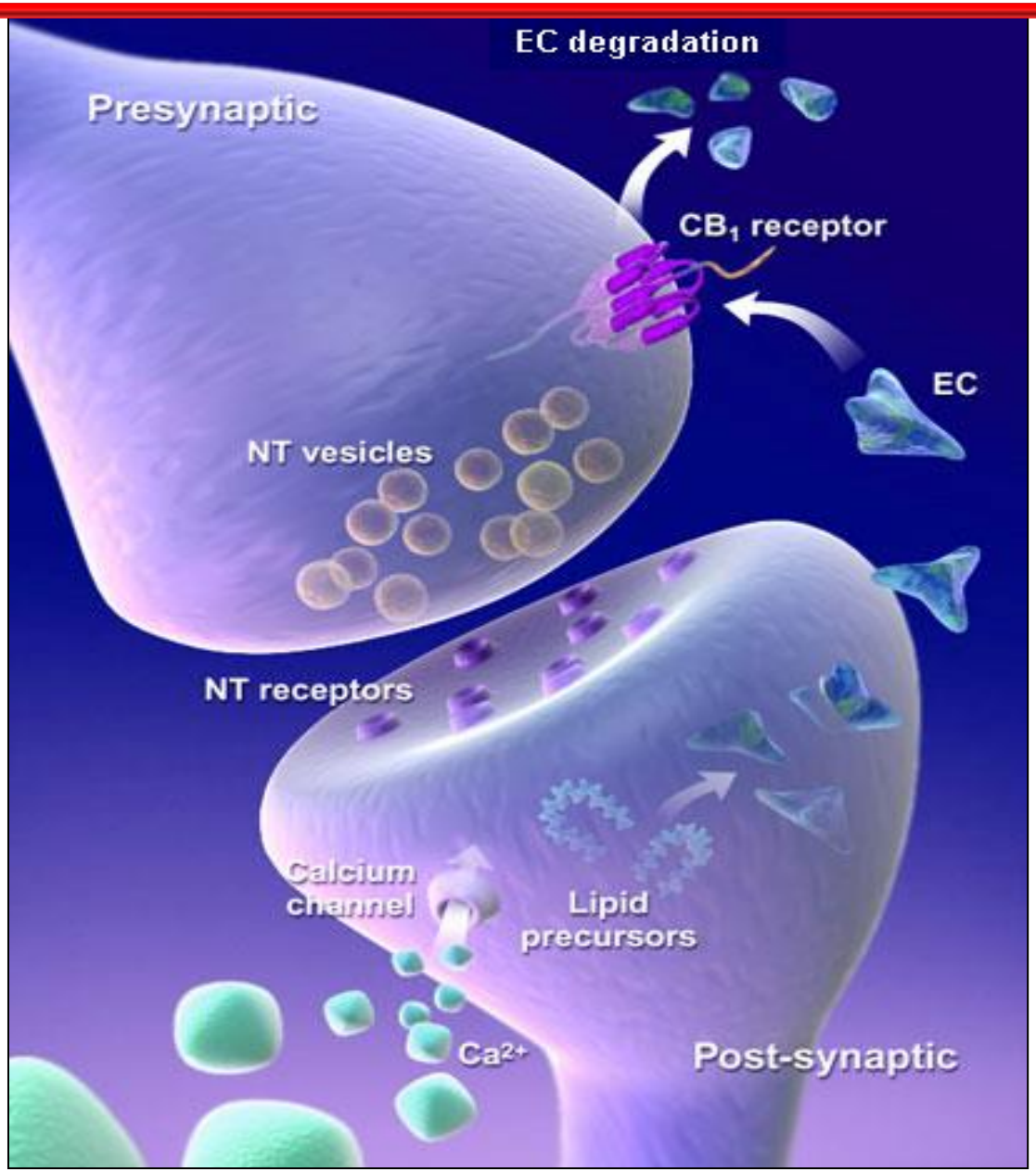
CBC

cannabichromene

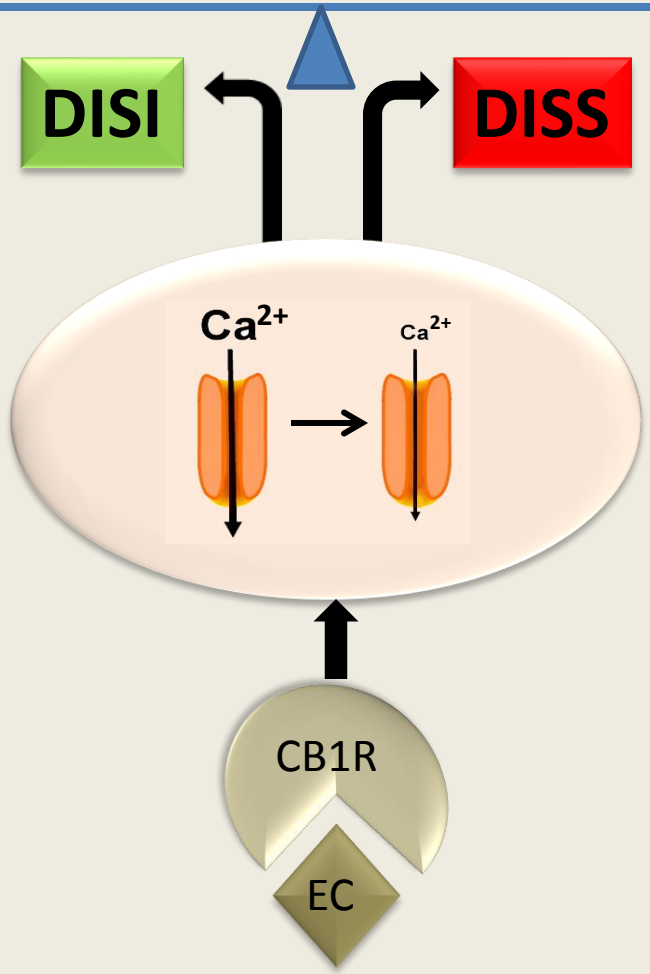


CBD

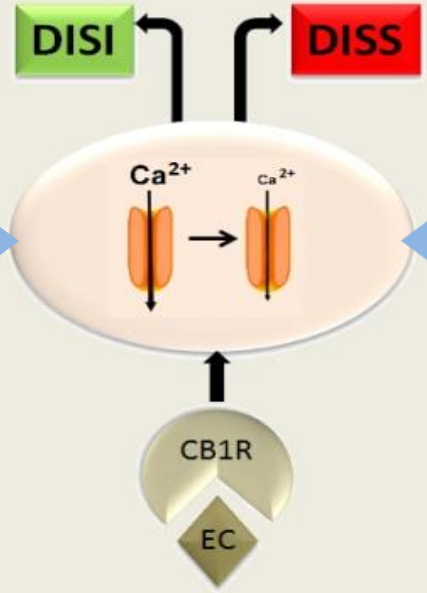
cannabidiol



Inhibition Excitation



Genetics
DA, 5HT, others
Development
Drug exposure
Parental style
Early life stress
Social milieu
Obesity



Cognition
Motivation
Schizotipy
Motor coordination
Sensory perception
Nociception
Depression
Attention
Learning
Memory
Appetite
Mood
Sleep
SUD


Microsoft
Esc
F1
F2
F3
F4
F5
F6
F7
F8
F9
F10
F11
F12
Backspace
Del
Ins
Tab
Caps Lock
Enter
PgUp
Home
PgDn
End
Shift
Ctrl
Alt
Fn

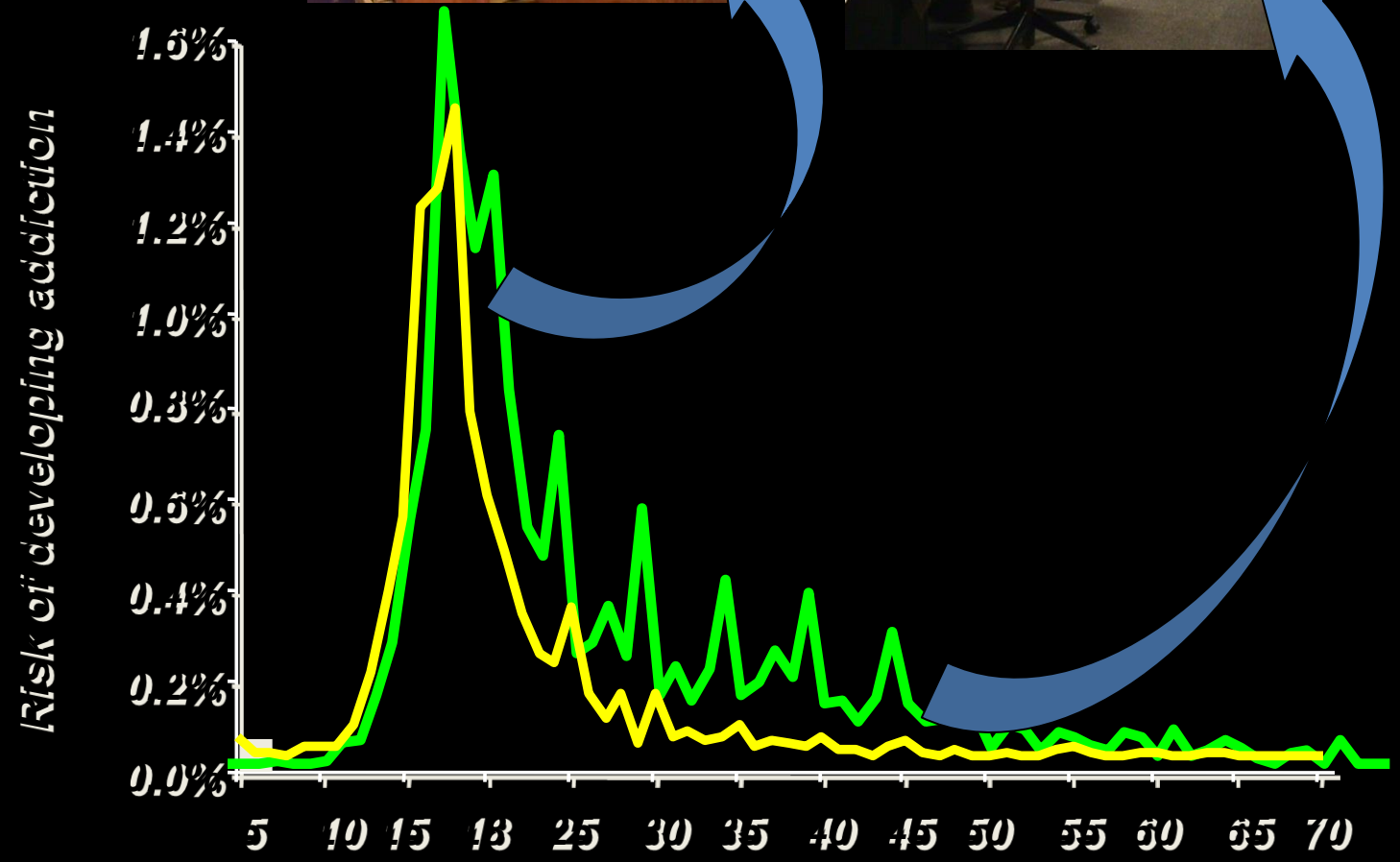
The Effects of Keyboard Scrambling are Time-Dependent

After the Programming

Temporary Difficulties Running a Program

During the Programming

Persistent Glitches in the Program


Risk of developing addiction
1.6%
1.4%
1.2%
1.0%
0.8%
0.6%
0.4%
0.2%
0.0%
5
10
15
18
25
30
35
40
45
50
55
60
65
70

- Marijuana as medicine

Three scientific questions

What medical conditions, if any, can **benefit** from marijuana use?

What are the **risks** associated with its medicinal use?

What can marijuana **teach us** that may lead to the better therapies?

31

We need evidence-based answers

We may have **personal** answers to those questions, but are they based on **evidence**?

What do we **really** know?

32

What medical conditions, if any, can benefit from marijuana use?

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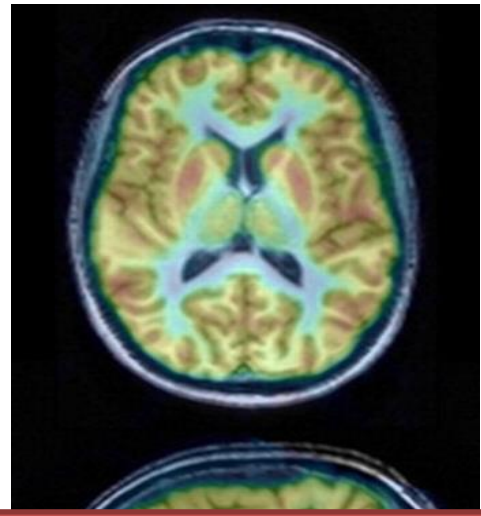
33

Cannabinoid receptors



eating

emotion

In what medical conditions can THC in marijuana be beneficial?

Fact: THC is already approved by the FDA to reduce nausea and stimulate eating in cancer and HIV patients

Δ^9-tetrahydrocannabinol (Δ^9-THC)

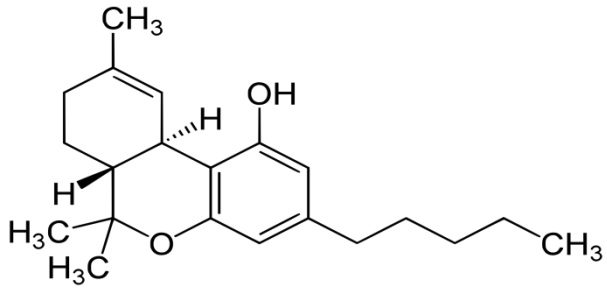
memory

Garth *et al.*, 2010

Chronic neuropathic pain

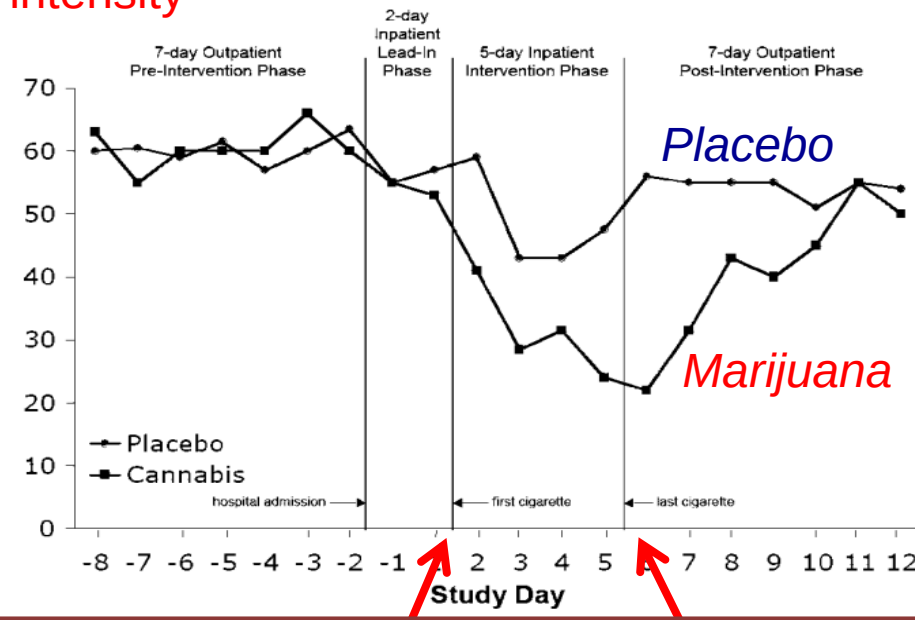
1 in 10 Americans experience at least once in their life

long-lasting excruciating pain caused by nerve damage



Δ^9-THC

Pain intensity



Pure THC also appears to be moderately effective in neuropathic pain, but with more side effects

Than smoked marijuana

Abrams *et al.*, *Neurology*, 2007

Other potential indications

Inflammatory bowel disease (marijuana)

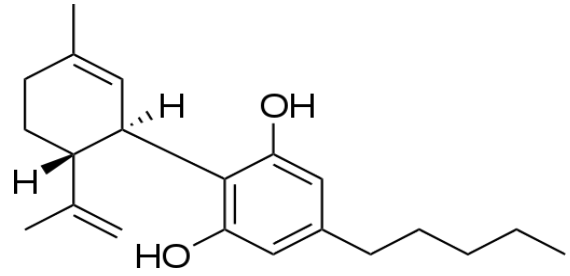
Multiple sclerosis (Sativex® = marijuana extract)

Anx

These results are preliminary
Additional clinical studies are needed

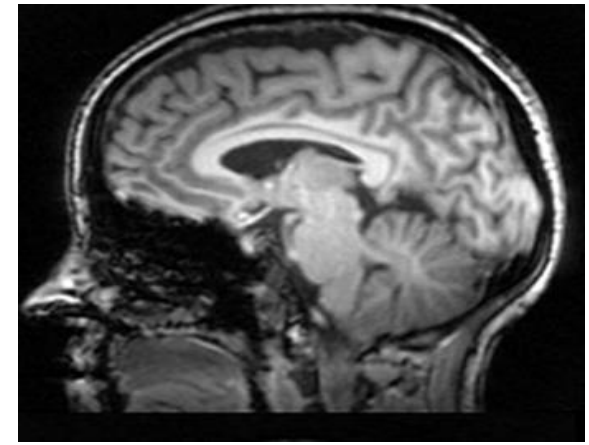
Tourette syndrome (Marinol®)

Cannabis use disorder (Marinol®)



Cannabidiol (CBD)

?

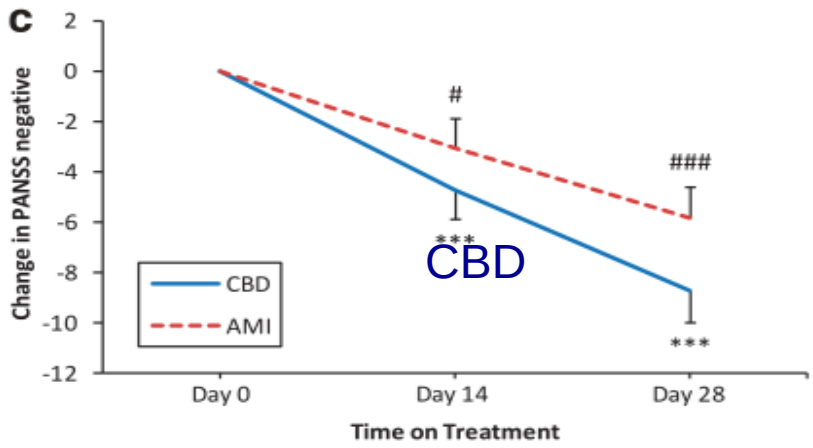


Schizophrenia

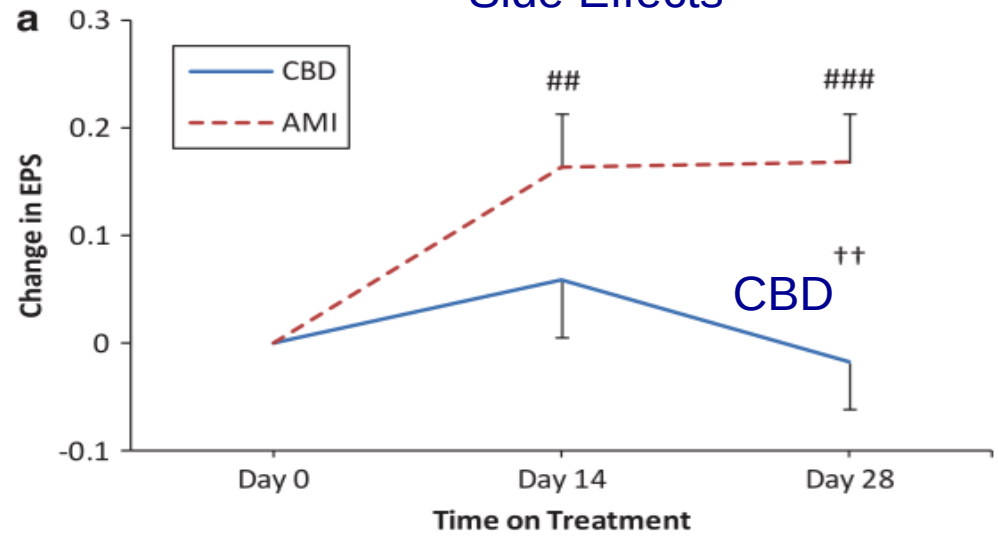
1 in 100 people suffer from this debilitating mental disorder

42 acutely exacerbated schizophrenic patients who had met the DSM-IV criteria

Disease Symptoms



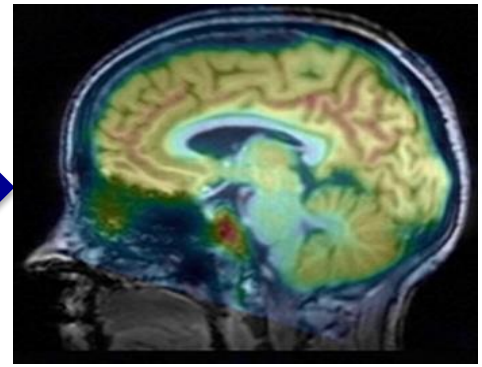
Side Effects

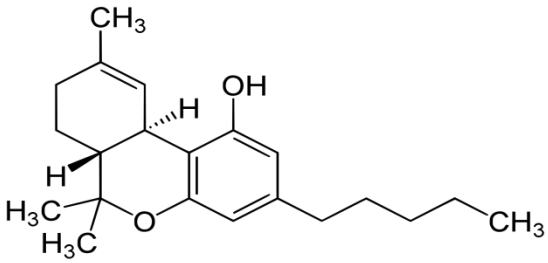


Leweke *et al.*, *Transl.Psychiatry* 2012

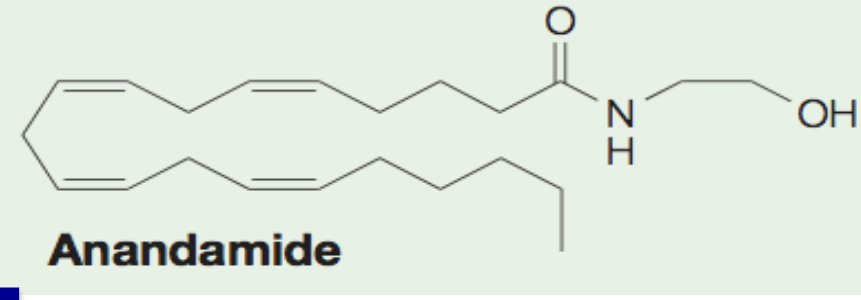
What did marijuana teach us?
The brain's own marijuana

Cannabinoid receptors





Δ^9-THC



Anandamide

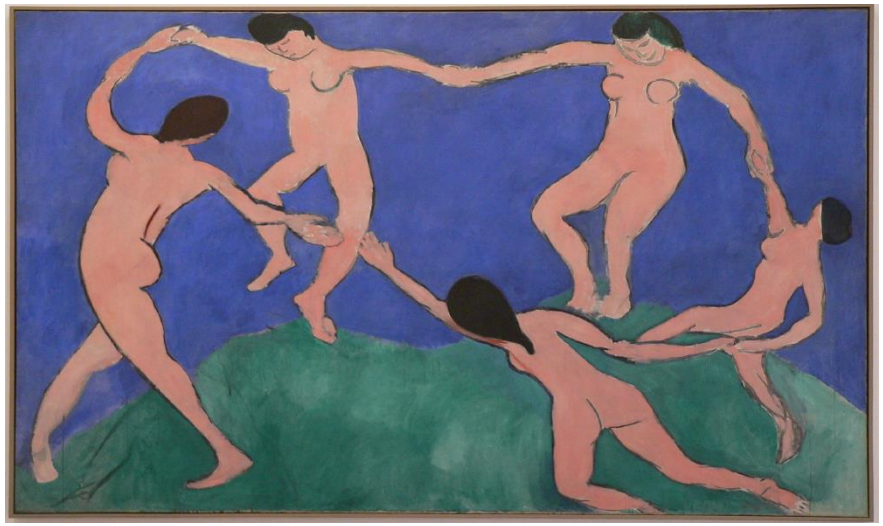
2-Arachidonoylglycerol

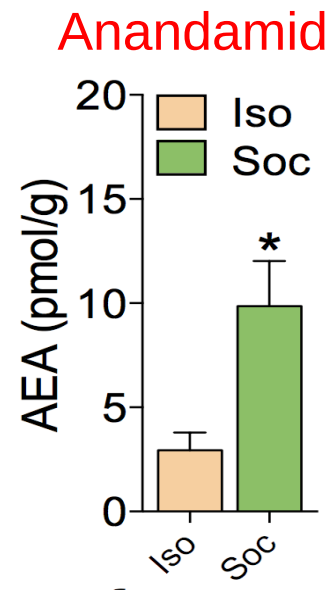
emotion

memory

Can the endocannabinoid system be exploited to discover better medicines?

Endocannabinoids and social behavior





Socialize

Isolate all

Block

Boost

The endocannabinoid anandamide plays an essential role in social behavior

Drugs that boost the pro-social effects of anandamide may be used in disorders in which our social nature is undermined (autism, schizophrenia)

What do we need to do next?

- Abandon the notion that smoked marijuana offers medical benefits
- Assess indications, effectiveness, and risks of CB used for medical purposes
- Leverage our growing knowledge of the endocannabinoid system to create better medicines for pain, autism and schizophrenia
- Ensure that guidelines and regulations are evidence-based and prioritize the protection of vulnerable populations.