

Adverse Effects of Marijuana: What We Know, What We Need to Know, and What Keeps Us Up at Night



THE TRIANGULUM: TOBACCO, MARIJUANA, AND E-CIGARETTES

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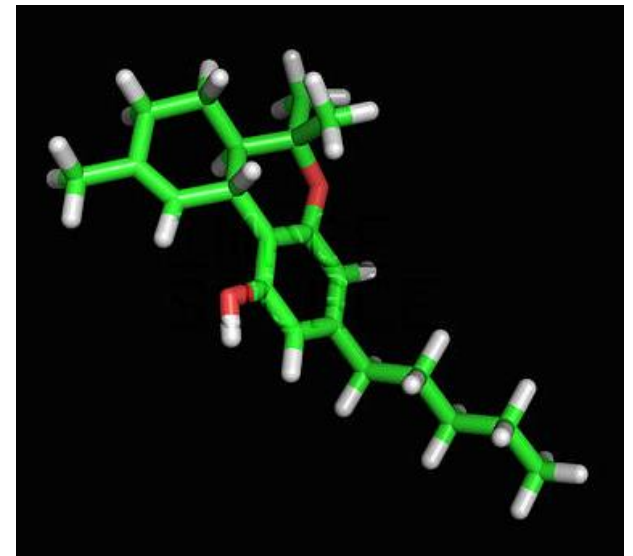
National Institute
on Drug Abuse



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



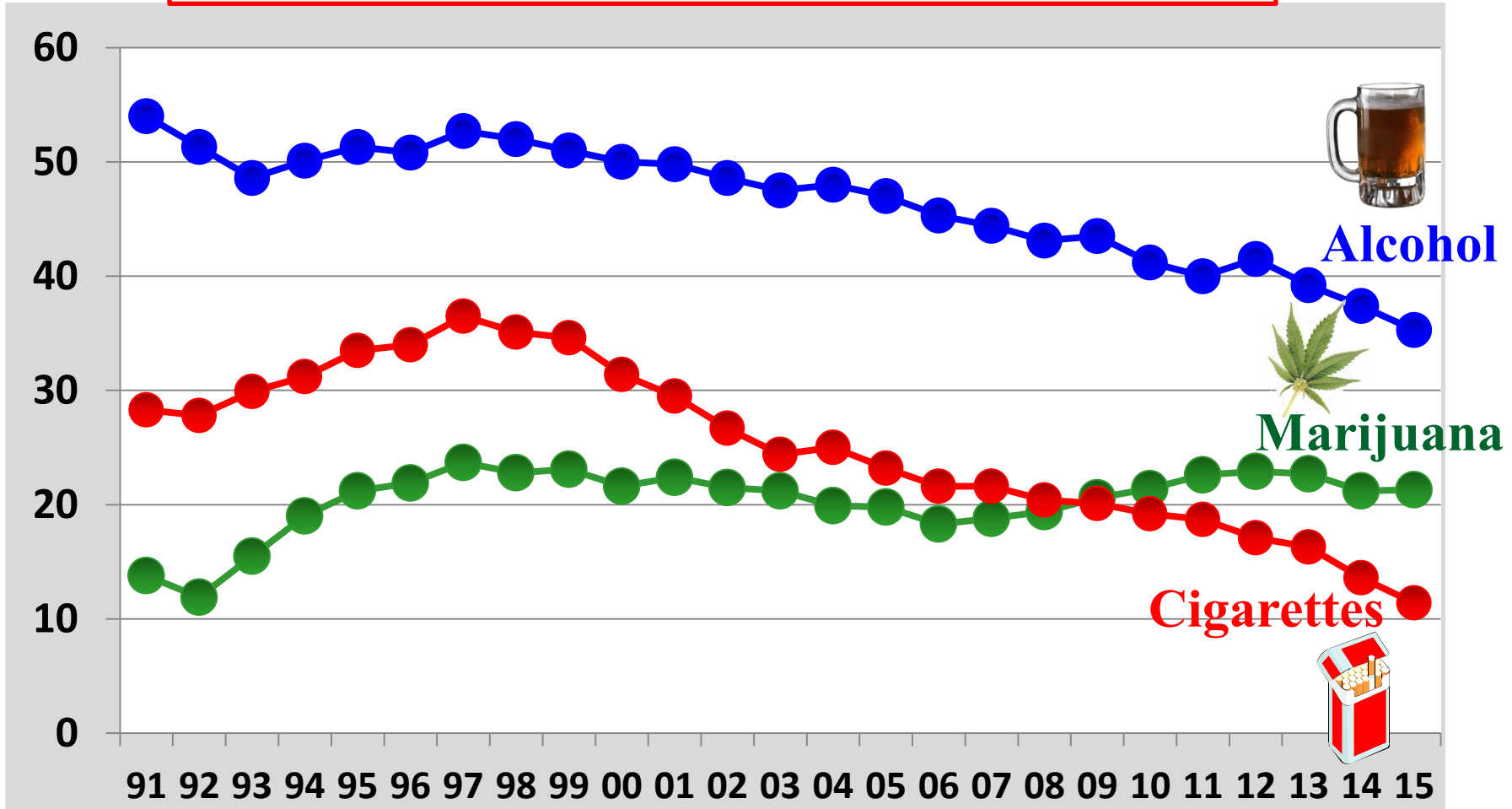
- Over **117 million** Americans 12 and older have tried it at least once; ~13% used it in the past year
- An estimated **2.6 million** Americans used it for the first time in 2014



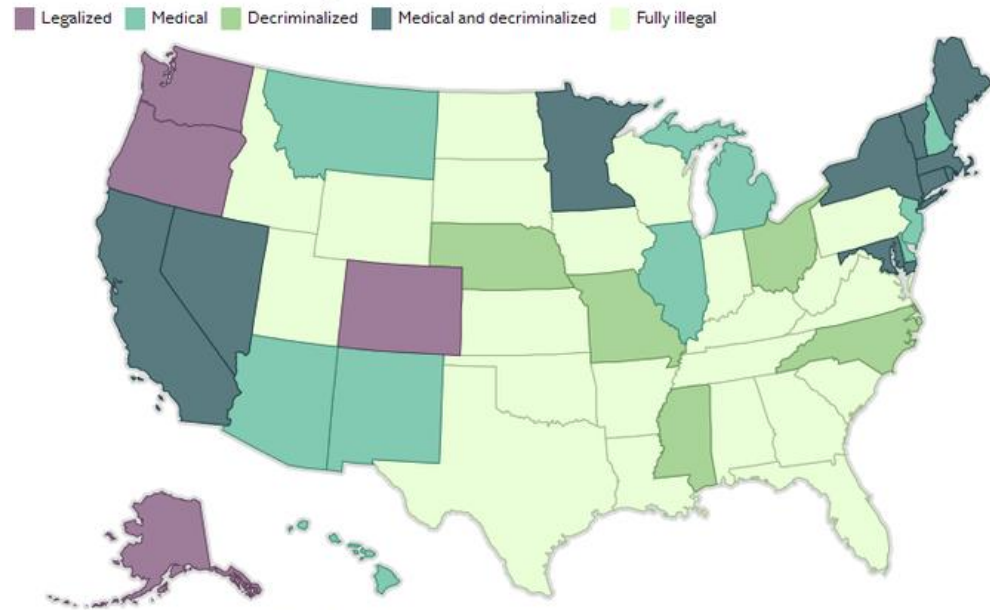
Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

Past Month Use of Cigarettes, Marijuana, and Alcohol in 12th Graders

Nearly 6% report daily use of marijuana



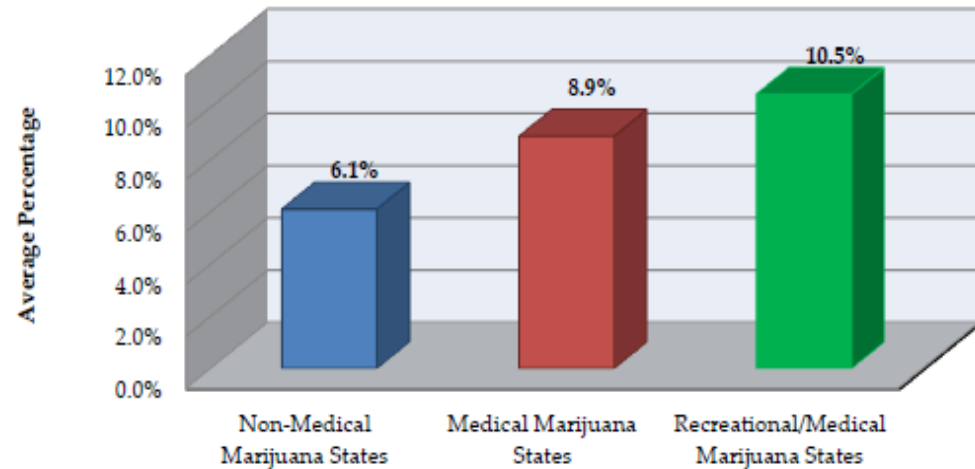
Changes in Marijuana Laws in the U.S.



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

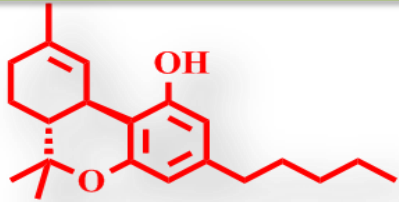
Adolescents Marijuana Use Higher in States Where it is Legal

Average Past Month Use by 12 to 17-Year-Olds, 2013

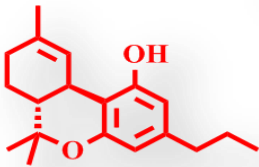


SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2012 and 2013

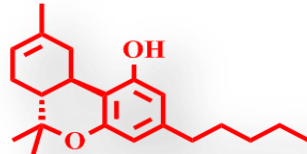
Marijuana contains ~100 cannabinoids plus other chemicals in varying concentrations



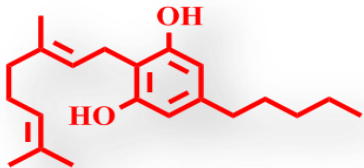
Δ^9 -THC
delta-9-tetrahydrocannabinol



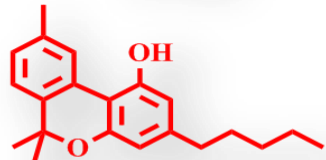
Δ^9 -THCV
delta-9-tetrahydrocannabivarin



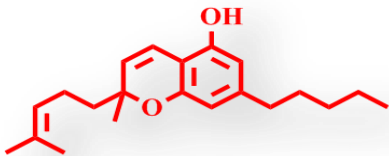
Δ^8 -THC
delta-8-tetrahydrocannabinol



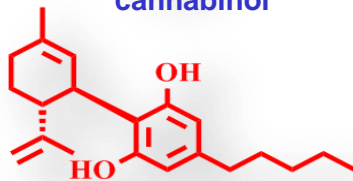
CBG
cannabigerol



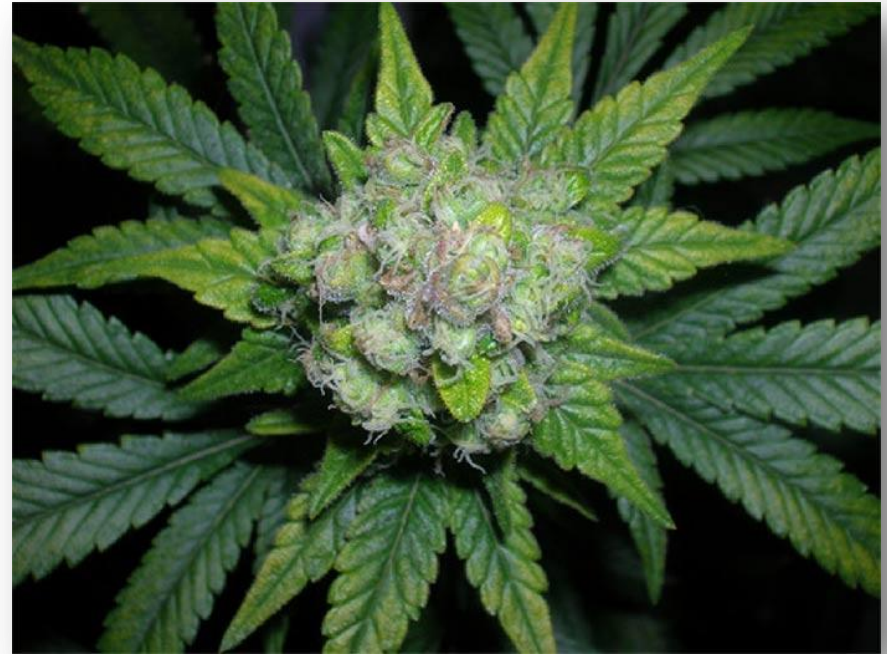
CBN
cannabinol



CBC
cannabichromene

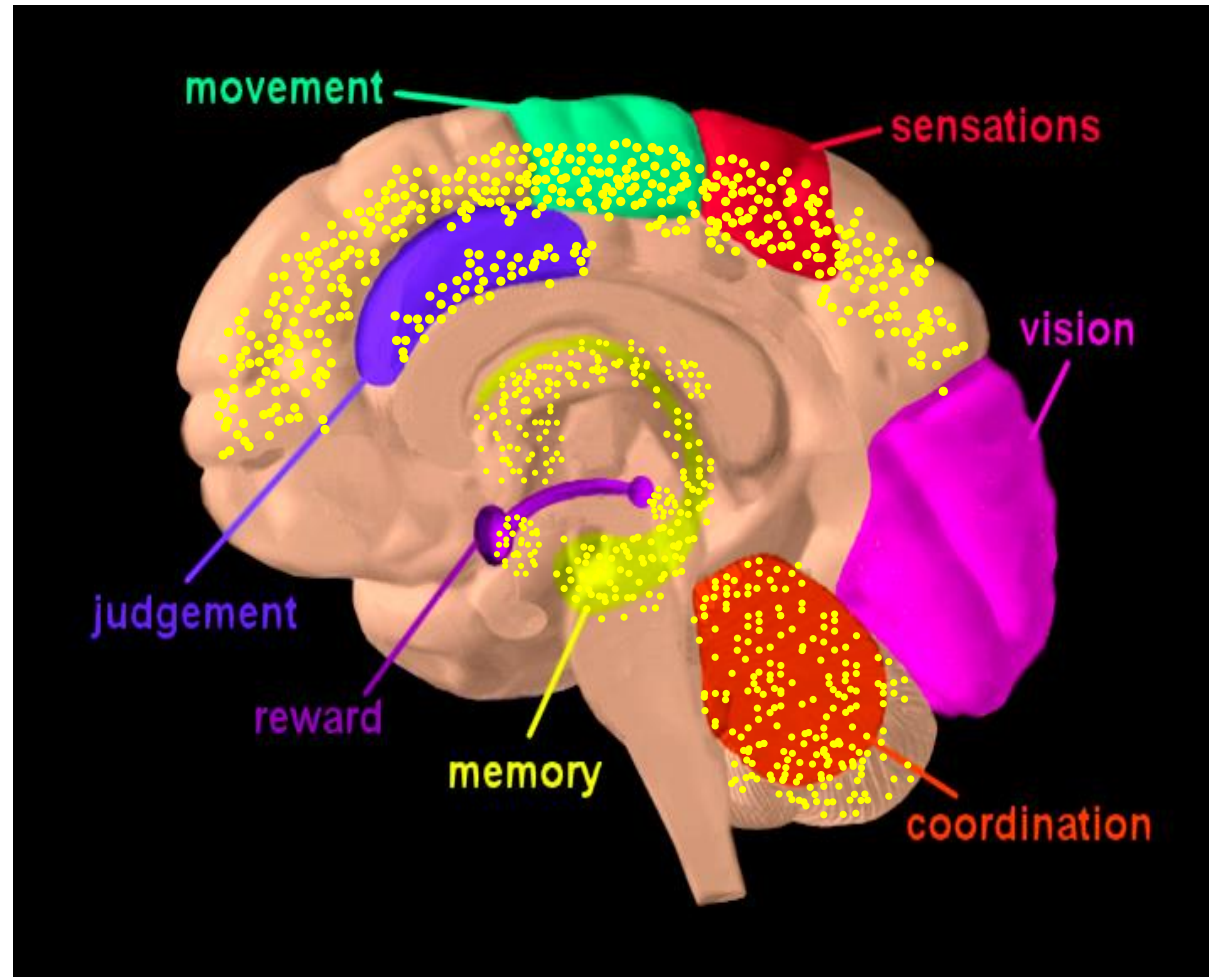


CBD
cannabidiol



Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory & Cognition
- Motivation & Reward
- Appetite
- Immune Function
- Reproduction
- Movement/Coordination
- Pain & Analgesia



Cannabis Effects on the Brain

Marijuana's *Acute* Effects

(Intoxication phase)

- Euphoria
- Calmness
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impairs coordination and balance
- Increased heart rate: 20 - 100%
 - Some evidence for increased risk of heart attack, may be exacerbated in vulnerable individuals (e.g., baby boomers?)
- Orthostatic (postural) hypotension
- Increased risk of accidents (~2 fold), higher when combined with alcohol



Marijuana's *Acute* Effects

(Intoxication phase)

- Cognition
 - Impaired short-term memory
 - Difficulty with complex tasks
 - Difficulty learning
- Executive Function
 - Impaired decision-making
 - Increased risky behavior – STDs, HIV?
- Mood (especially after high doses)
 - Anxiety – panic attacks
 - Psychosis – paranoia



Marijuana
Is it holding you back?

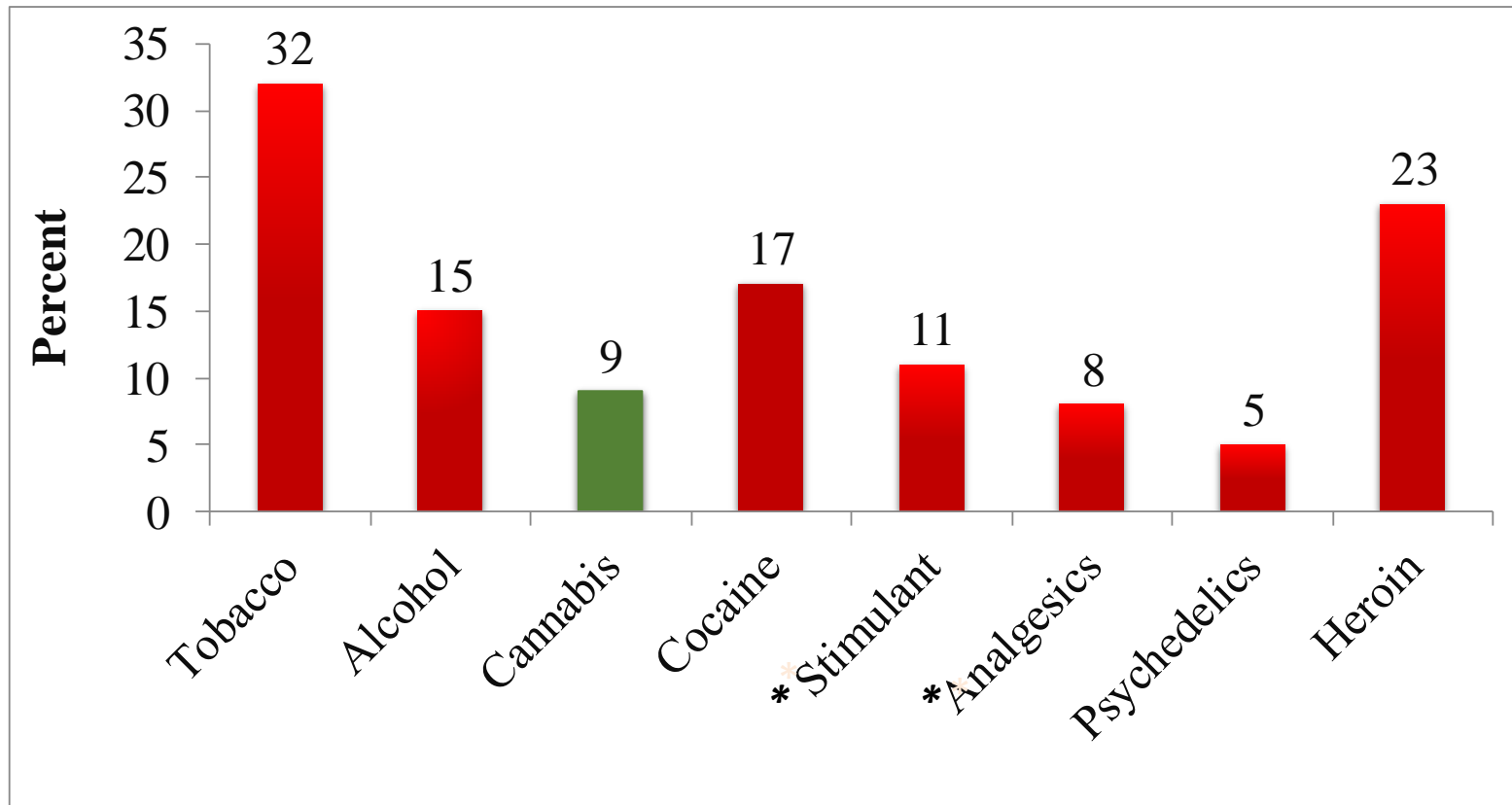
Long Term Outcomes:

We know less about the long term health impact following chronic marijuana use, particularly with respect to *causality*.

Long Term Effects of Marijuana

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

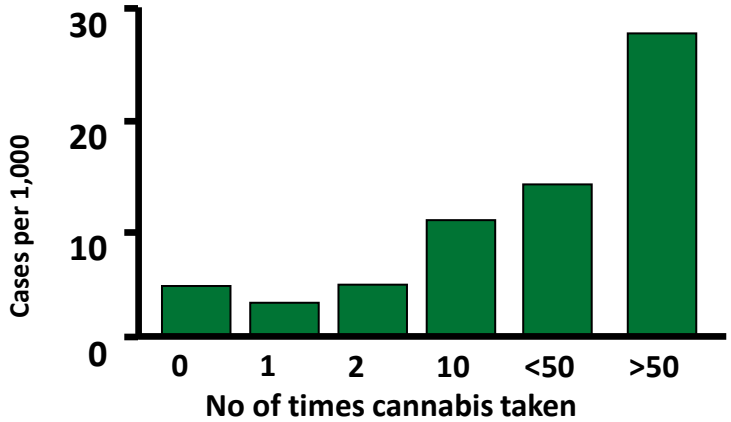
Estimated Prevalence of Dependence Among Users



* Nonmedical Use

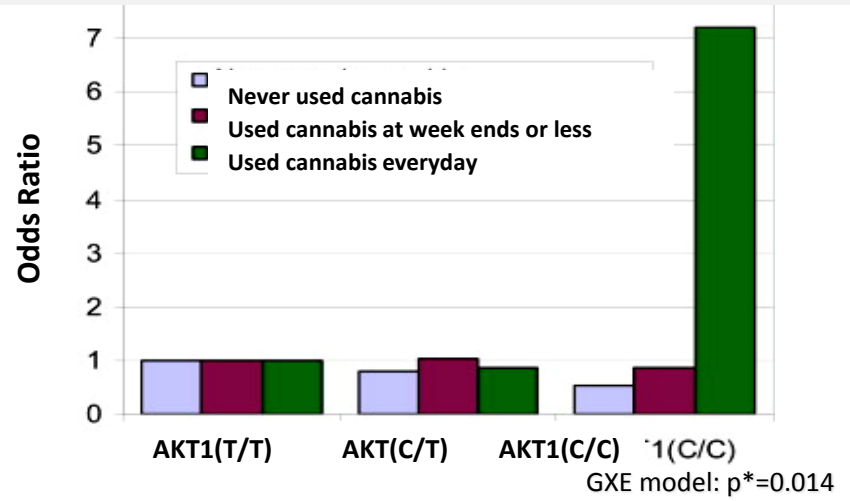
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)



Andréasson et al Lancet, 1987.

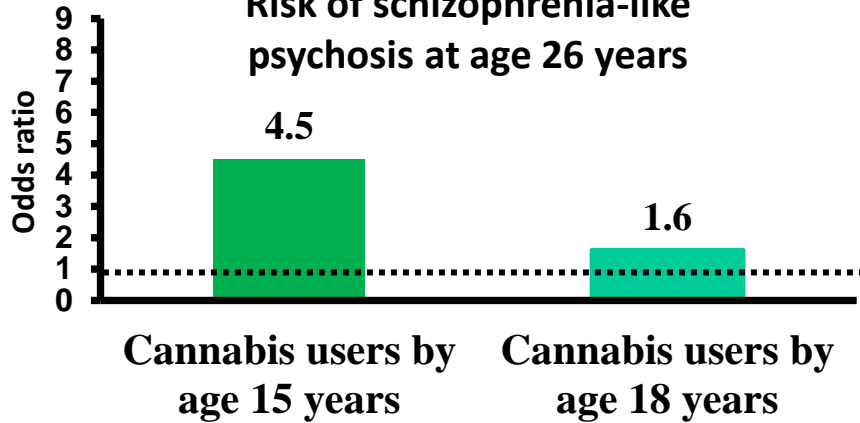
Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype



Di Forti et al., Biological Psychiatry, 2012.

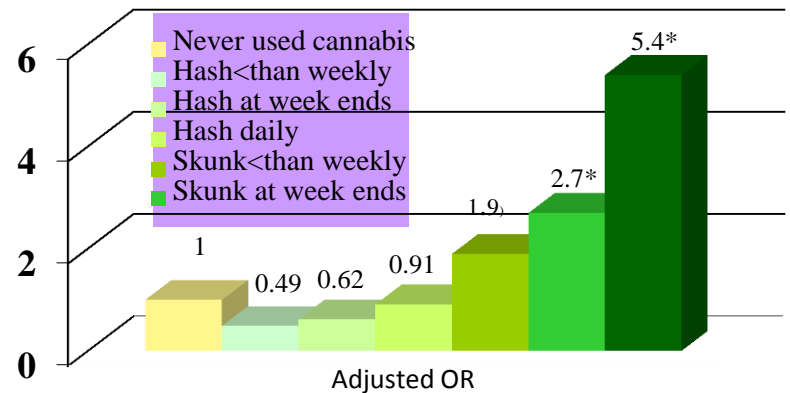
Prospective Dunedin study (n=1037)

Risk of schizophrenia-like psychosis at age 26 years



Arseneault et al BMJ 2002

Effect of High Potency Cannabis on Risk of Psychosis



Di Forti M et al., The Lancet published online February 18, 2015.

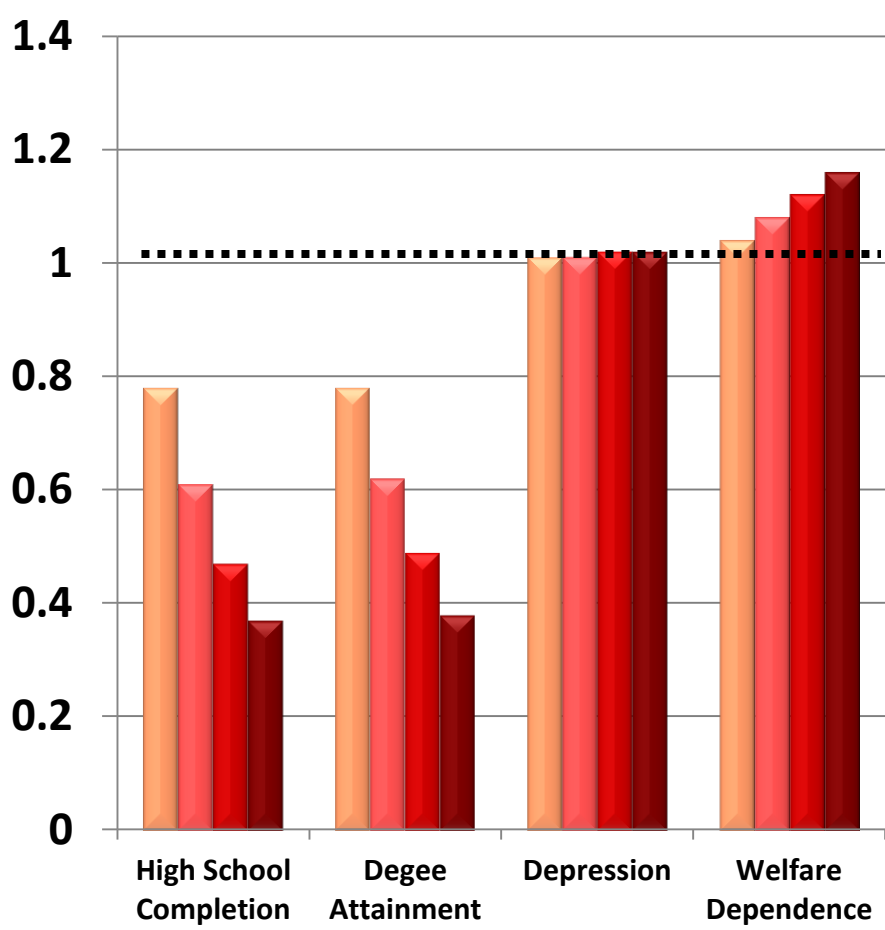
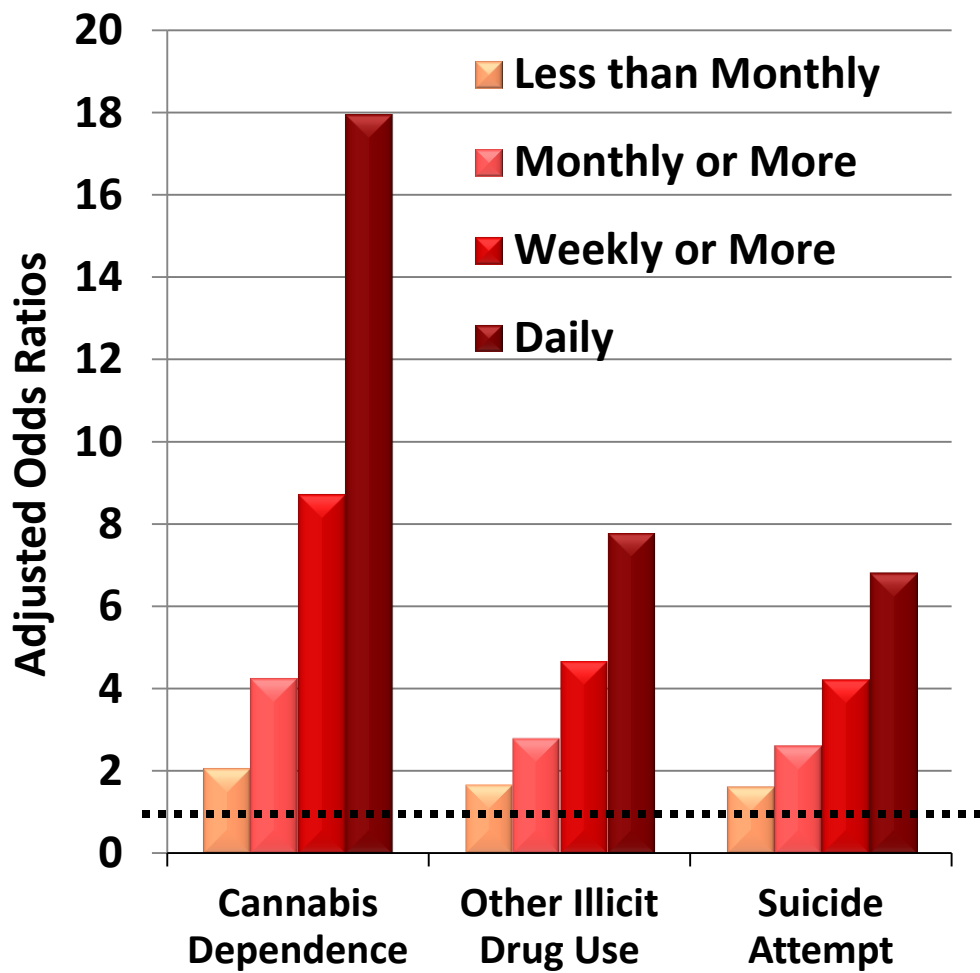
The Brain Continues to Mature into Early Adulthood.



Does **Marijuana** (and other substances) affect the developing brain and an individual's trajectory into adulthood?

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

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

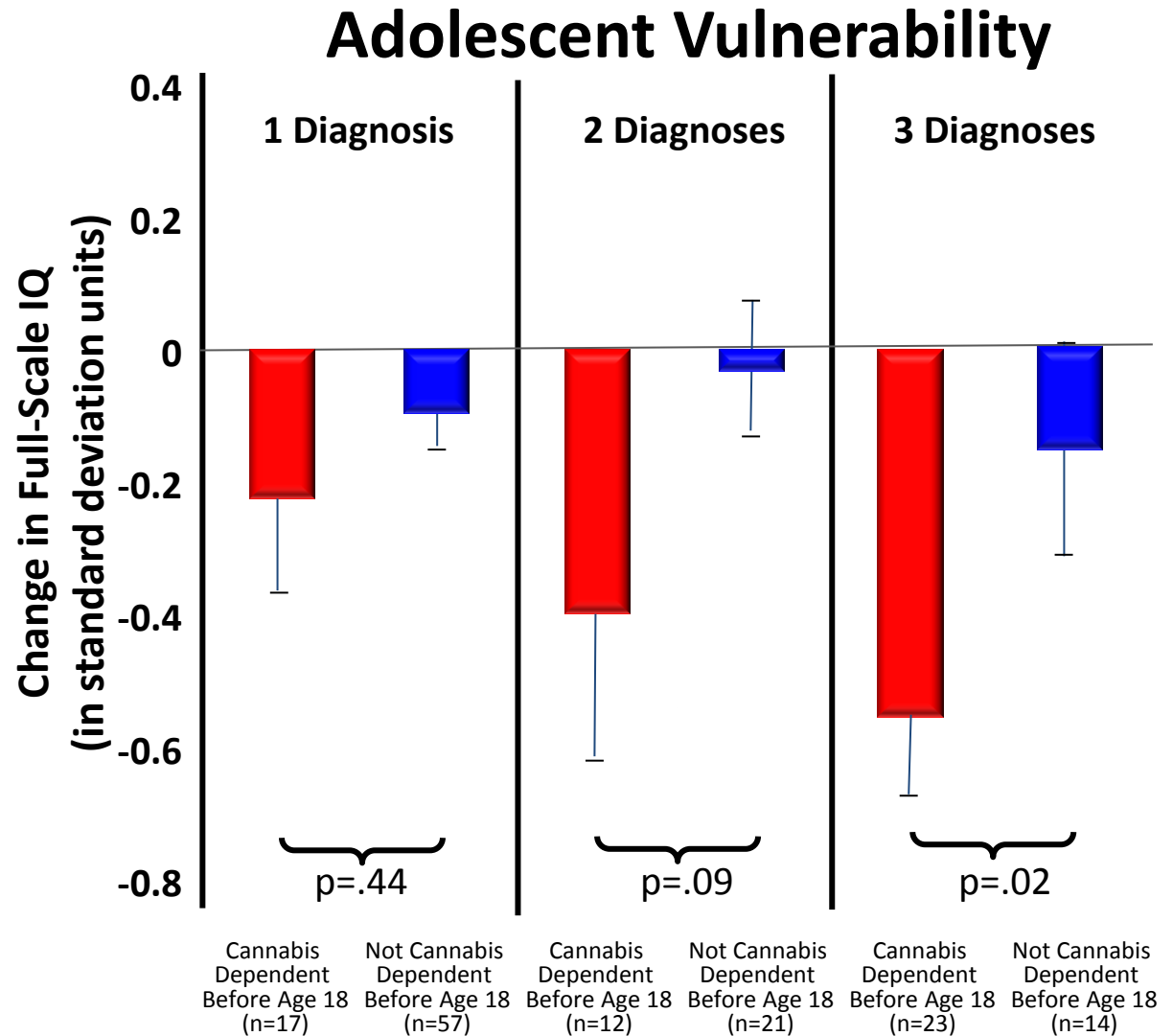


Persistent Cannabis Users Show Neuropsychological Decline from Childhood to Midlife

*Dunedin
prospective study
of 1037 Ss born
1972/73,*

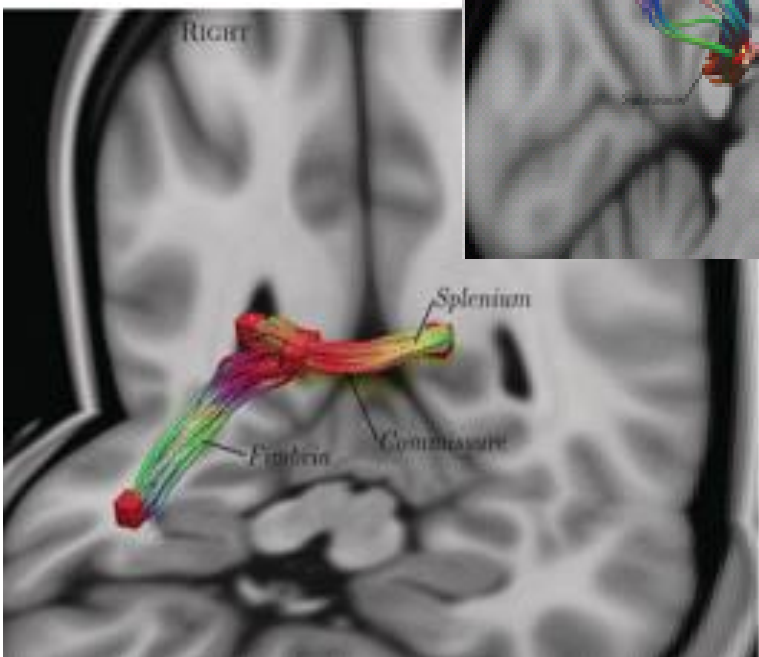
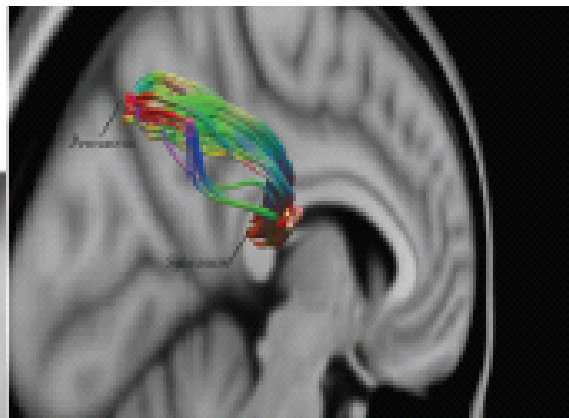
*Tested for IQ at age
13 and 38y.*

*Tested for cannabis
dependence ages
18, 21, 26, 32 and
38y*



Brain Structure: Early (<18y) Long-Term Cannabis Use Decreases Axonal Fiber Connectivity

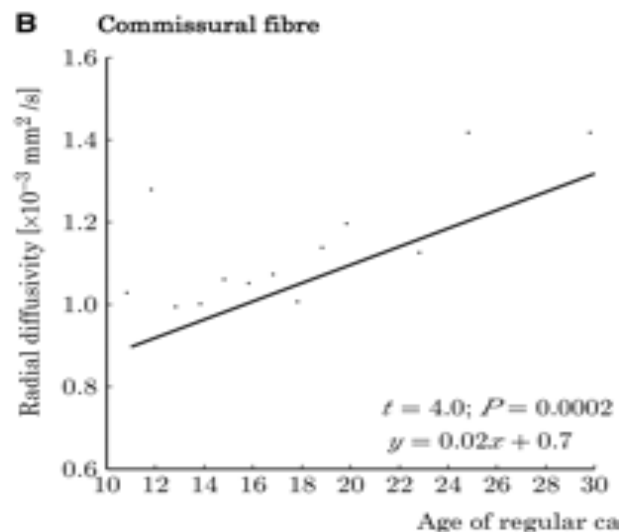
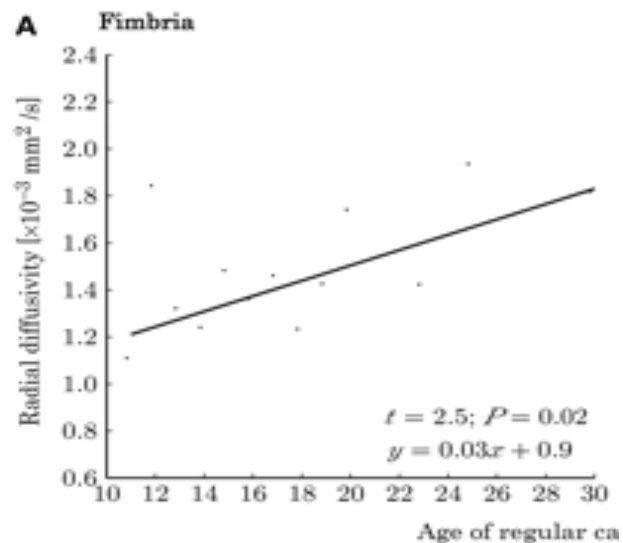
Precuneus to splenium



Fimbria of hippocampus, hippocampal Commissure, and splenium

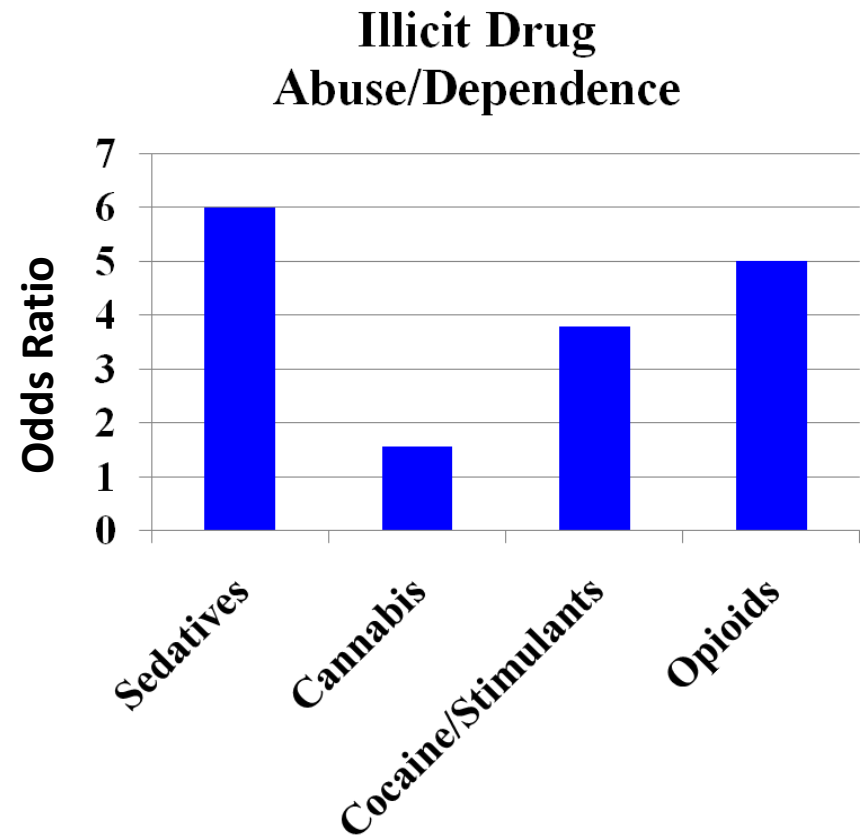
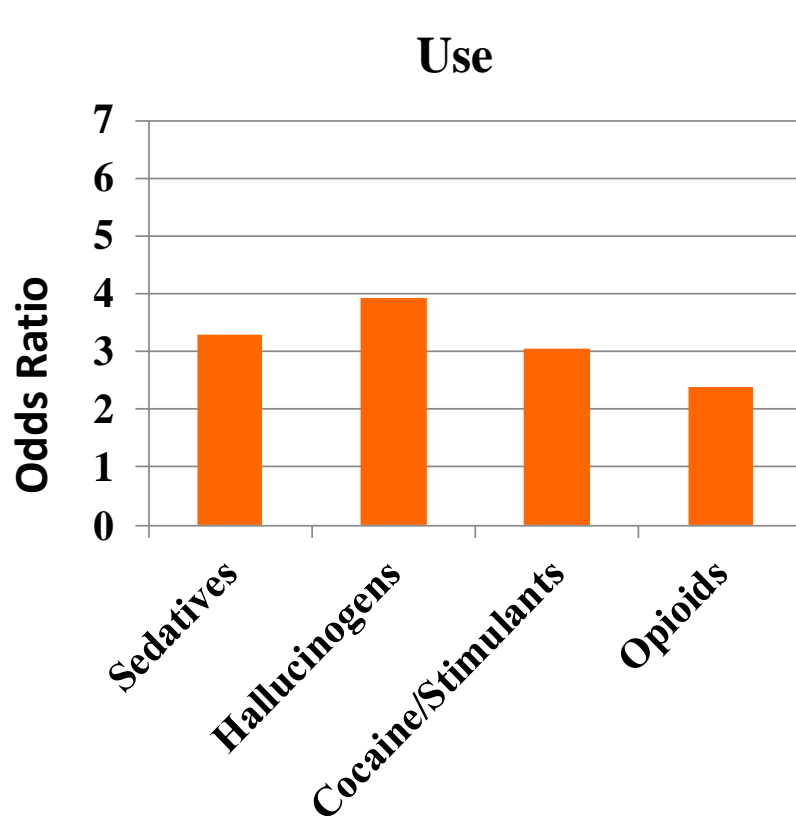
Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Zalesky et al Brain 2012.

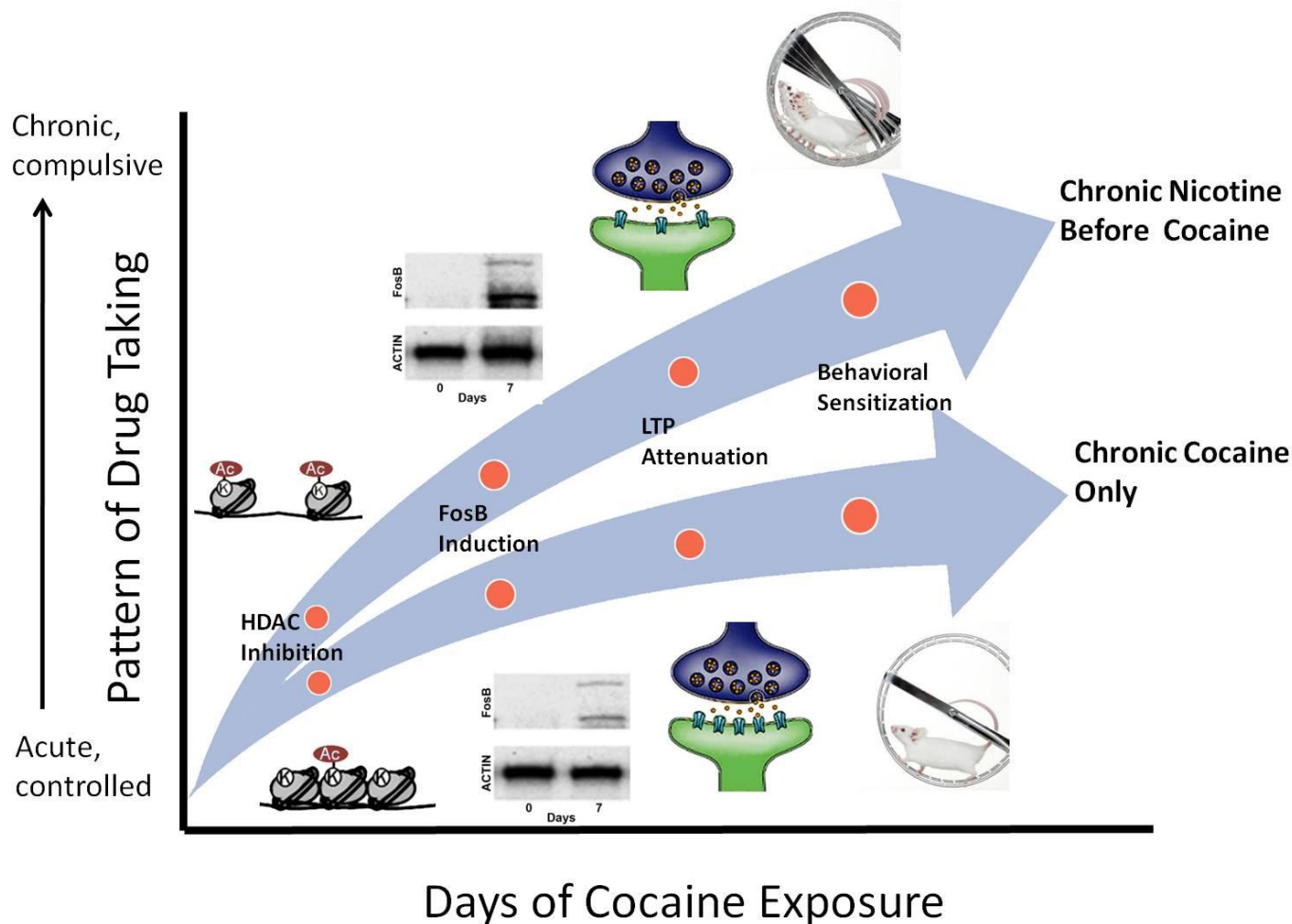


Gateway Effects

Drug Use Outcomes in Twin Pairs (n=234) Discordant for Cannabis Use Before Age 17



Gateway Effects: Nicotine Pre-exposure Enhances Cocaine Effects in Mice, but not Vice-Versa



What do we need to know about the Triangulum: cigarettes, e-cigarettes and cannabis?

- Substance Initiation: does using one substance increase the likelihood of using others?
 - Epidemiological evidence--Yes
 - Common genetic vulnerabilities--Yes
 - Common environmental vulnerabilities--Yes
 - Neurobiological evidence--Likely
- Cessation: does using one interfere with the ability to quit using another?
 - Data are mixed

What do we need to know about the Triangulum?

- Health Effects
 - Addiction
 - Are combined products more addictive than either alone?
 - Cancer
 - Can we disentangle cannabis vs. tobacco effects?
 - Heart Disease
 - Cognitive function, Affect, Motivation
 - Will cannabis and nicotine worsen or counter each other's effects?
- Let's not forget the Quadrangulum: ***Alcohol*** or even the Pentagulum (?) ***Mental Illness***