Marijuana and the Adolescent Brain

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THANKS TO:

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  - Go to Neuropsych Seminar (Login: Kaiser; Password: Kaiser)
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Neuropsychological Bias

- All behavioral experiences lead to physiological change of brain, not just psychological change
- Substance abuse leads to physiological changes in brain functioning, cognitive, behavioral, and emotional ability
- Ignore these facts at the risk of not truly understanding your patient & failure as a therapist

Today: California Proposition 64

- Proposition 64 would legalize the recreational use of marijuana for adults aged 21 years or older.
- Smoking MJ would be permitted in a private home or at a business licensed for on-site marijuana consumption.
- It would remain illegal while driving a vehicle, anywhere smoking tobacco is illegal, and in all public places.
- Possession on the grounds of a school, day care center, or youth center while children are present would remain illegal

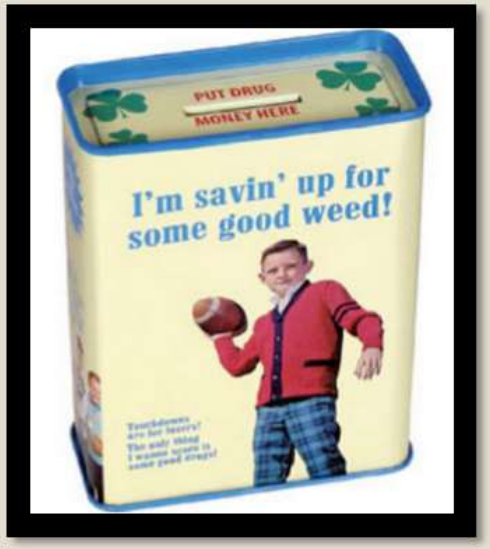


IMAGE SOURCES: http://www.perpetualkid.com/savin-for-good-weed.html & http://theracketreport.com/wp-content/uploads/2015/05/Girl-Scout-Cookies-Weed-Conspiracy-Theory.jpg & https://s-media-cache-ak0.pinimg.com/236x/47/5d/27/475d27e93dea8550d52b033f589e0661.jpg & http://www.coachingbysubjectexperts.com/marijuana-is-legal-in-colorado-so-what-are-my-rights/

Current concerns about MJ

- Legalization of marijuana in variety of states:
  - 50% favor MJ legalization
  - 25 states & District of Columbia currently have laws legalizing marijuana for medical use (epilepsy, pain, appetite stimulation)
  - AL, OR, CO, WA & DC have legalized marijuana for recreational use.
  - 5 states vote today: CA, MA, ME, AZ, NV (bringing it to 25% of states)
  - MJ is still federally illegal (MJ is still cash only business)

- Where legalization for recreational use occurs:
  - increased use/abuse by adolescents
  - increased # of babies born with detectable THC
  - high concentration (7x greater) of THC in breast milk

Current concerns about MJ

- Ever increasing potency of marijuana
- Decreased perception of harm of MJ: if used medically, must be safe
- Increasing knowledge about brain effects of marijuana, esp. impact on developing brain of adolescents
- Reality of MJ addiction: Currently the #1 reason adolescents enter drug treatment programs

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

- Over 104 million Americans have tried it at least once
- An estimated 2.4 million Americans used it for the first time in 2009

Tetrahydrocannabinol (THC)
Active Ingredient in Marijuana

National Survey on Drug Use and Health, SAMHSA, 2010.

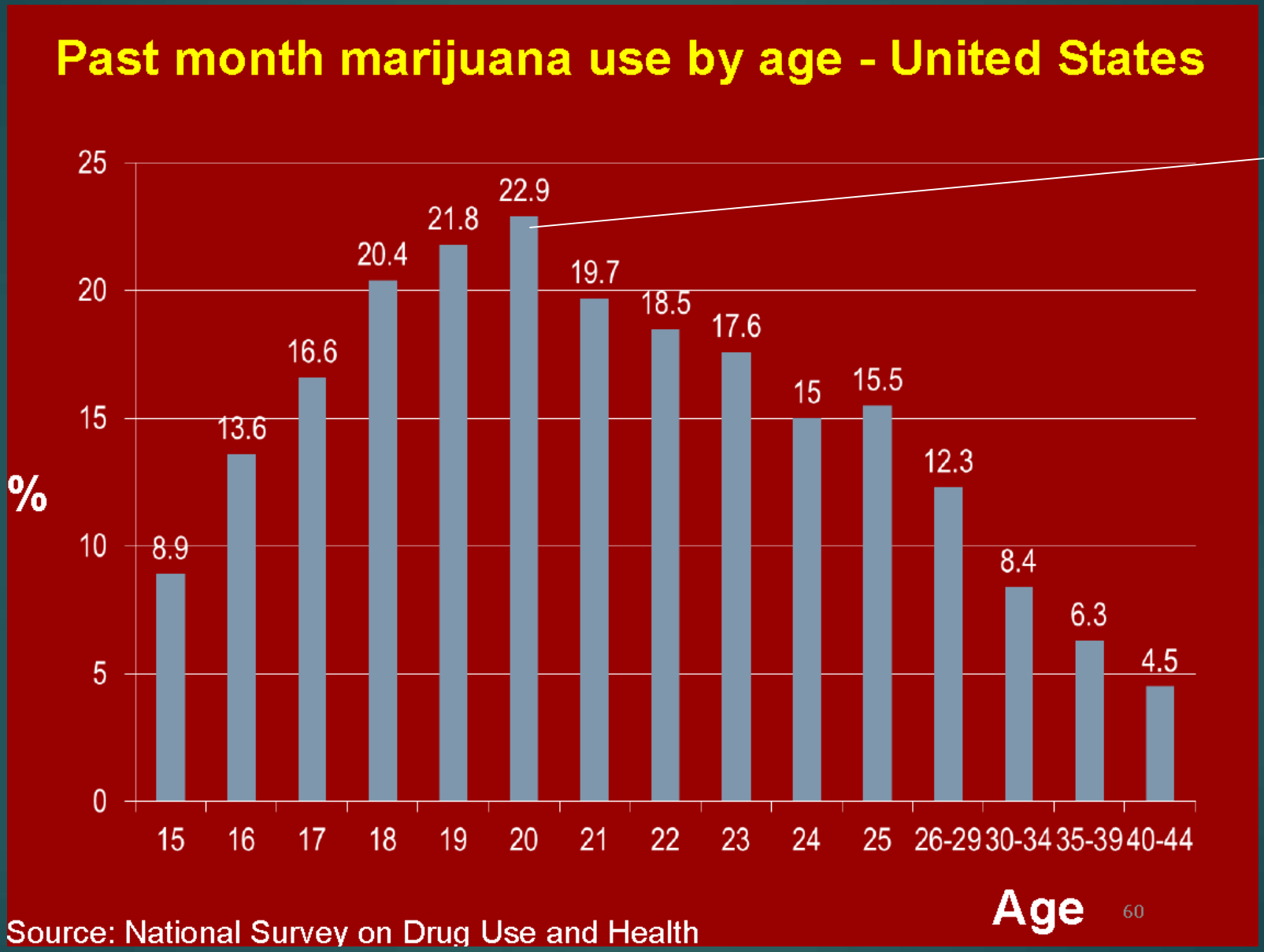
Epidemiology

- More than 34% (75 million) of Americans 12 years or older have tried it at least once & almost 19 million have used it in the past year

- Average age of 1st use has been declining:
  - 12-17 year olds – 14 years
  - 18-25 year olds – 16 years

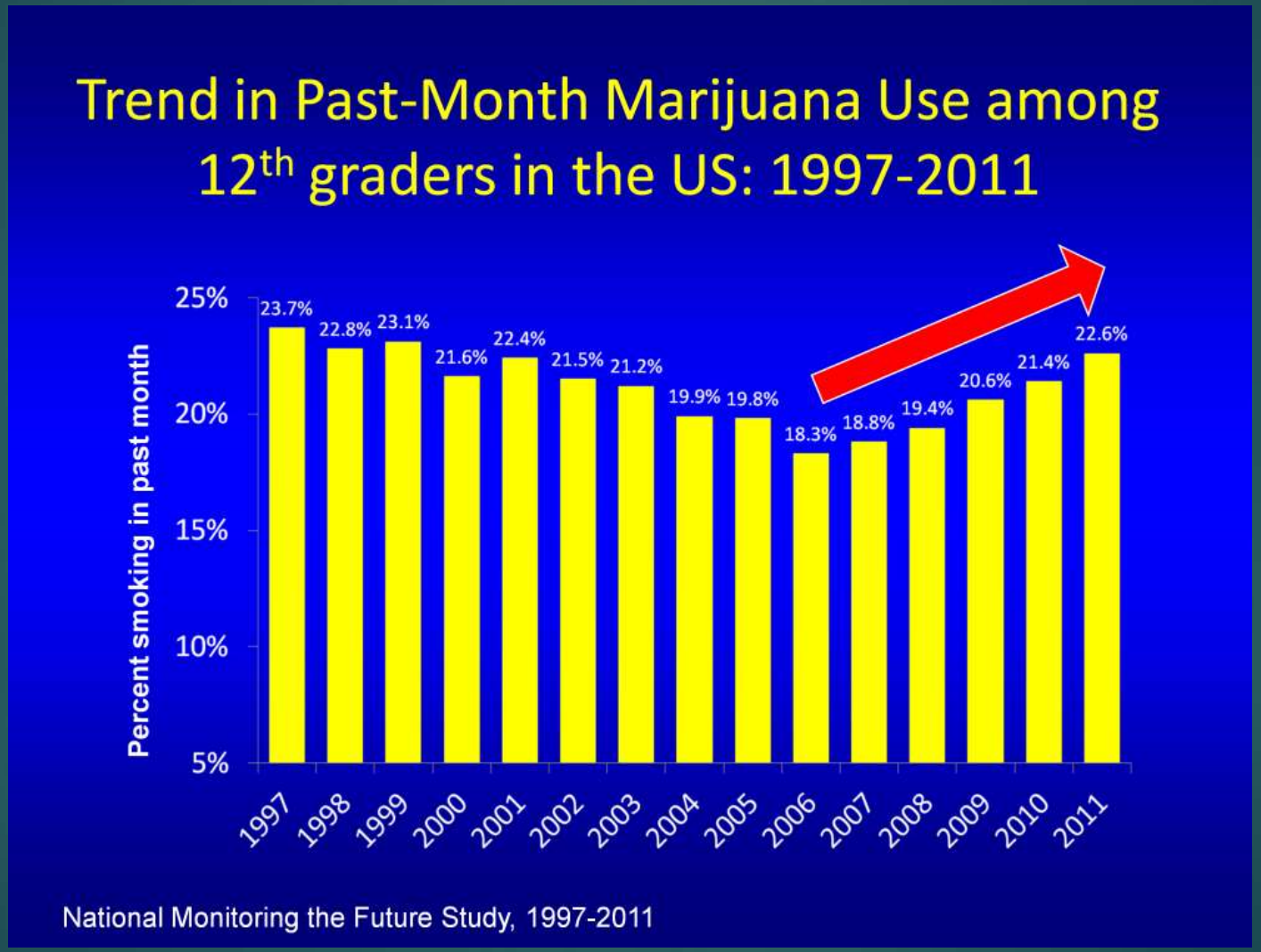
- Most discontinue marijuana by their mid-20's

- Subset maintain daily, long-term use


Past month marijuana use by age - United States
%
25
20
15
10
5
0
8.9
13.6
16.6
20.4
21.8
22.9
19.7
18.5
17.6
15
15.5
12.3
8.4
6.3
4.5
15
16
17
18
19
20
21
22
23
24
25
26-29
30-34
35-39
40-44
Age
Source: National Survey on Drug Use and Health

Peak:
Age 20

MJ use has started to increase again



Adolescent use of MJ

- Cannabis is the second most used drug after legal alcohol, with 23 % of high-school seniors and 20 % of college students using in the past month
- 36 percent of high-school seniors have used cannabis in the past year.
- 7 % smoked cannabis daily, up from 2 % in 1993;
- 1 in every 15 seniors report using daily

Lisdahl, et al., 2014

Incidence & Perspective

- 12 -18 yo: 39% tried, 20% current, 3% daily
- 18 -25 yo: 48% tried, 5-7% daily use of pot
- Other Drugs by US high school seniors:
  Alcohol: 88% tried, 5% heavy use
  Nicotine: 27% tried, 17% daily use
  Methamphetamine/cocaine: ~8% tried, <1%
  Ecstasy (MDMA): 10% tried, < 0.1 daily use

(Johnson Monitoring the Future; DAWN; PATS, NSDUH et al.)

Types of Marijuana

- Three Species:
  - Cannabis sativa
  - Cannabis indica
  - Cannabis ruderalis
- Sinsemilla (seedless, high potency) and growth manipulations
- Infinite varieties/hybrids/strains
- MJ contains some 480 chemicals
- 66 are cannabinoids, 80-100 of which are psychoactive
- Δ9THC (delta-9-tetrahydrocannabinol): THC is considered to be responsible for most of physiological effects

SLANG FOR MARIJUANA

HTTP://WWW.THEWEEDBLOG.COM/LIST-OF-MARIJUANA-SLANG-TERMS/

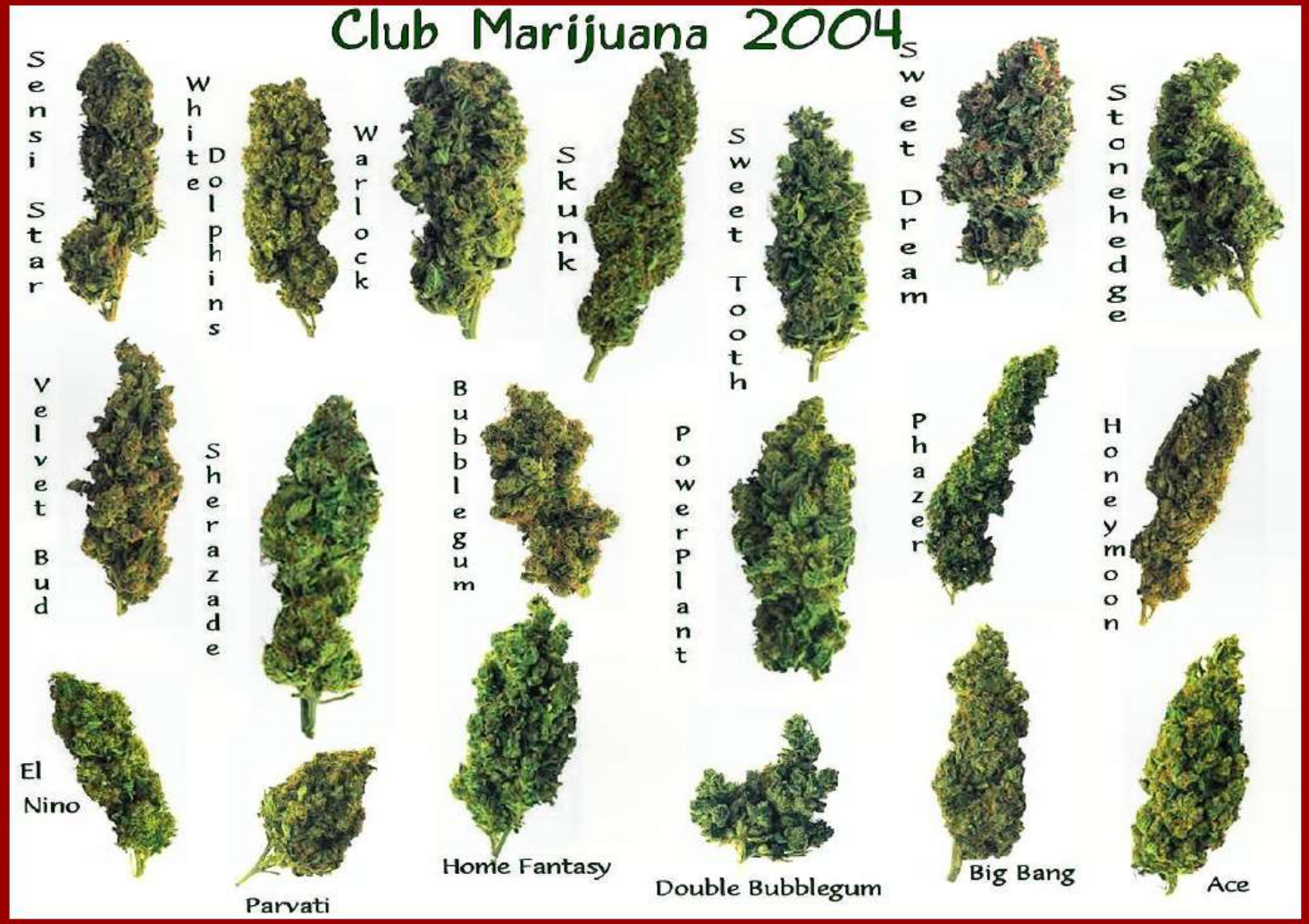
420 – bammer – BC bud – blunt – bomb – bone – boo – boo-yah – bubonic chronic – bud – buddha – burger – candle – cheeba – chiba – chief – chiefs – chino – choke – chronic – cigga-weed – cigweed – clickem – colitas – combustible herbage – crippy – cronick – dank – dirt weed – ditch weed – doja – dolja – doob – doobie – dope – drat – draw – dro – dub – dube – Dutchie – endo – erve – fatty – fatty boom blatty – gange – ganja – ganje – giggle stick – gonj – grass – green – green bud – heim – herb – herbal refreshment – hippie lettuce – hog leg – hooter – hydro – indica – indo – j – jay – jib – joint – keef – kief – kill – kind bud – la la – left-handed cigarette – limbo – loud – Mary Jane – Mexican dirt weed – mighty mez – MJ – mota – Mr. J – nib – nugget – onion – paca lolo – pakaloco – pakalolo – pato – pot – purp – reefer – reggie – reggs – roach – schwag – shake – shwag – skater – skunk weed – smoke – spliff – spliffy – sticky icky icky – sweet – tea – Thai stick – tical – toke – treats – trees – tweed – wacky tobaccy – weed – whifty – woolies – zombie

Why the term "420"?

It was a designated meeting time for teens in San Rafael, CA in 1971.

For more information:
https://en.wikipedia.org/wiki/420_(cannabis_culture)

IMAGE SOURCE: http://onlineslangdictionary.com/thesaurus/words+meaning+marijuana.html



3 species but infinite number of strains & hybrids

Available legally over the counter in Colorado

Medicinal Marijuana Websites

- **1. Harborside Health Center (Oakland, CA)**
  - This site offers free delivery to residents in the San Francisco Bay Area but only accepts cash, money orders and cashier's checks. Drivers only accept exact amounts of money.
- **2. Speed Weed (Los Angeles, CA)**
- **3. Crown Collective (Forestville, CA)**
- **4. Weed Store USA (Atlanta, GA)**
  - Claiming to be the "world's largest herbal smoke shop," this site sells 100 percent natural buds online along with vaporizers and other cannabis products. Strains include Big Bud, Mr. Nice, Blackberry Kush, Super Lemon Haze, Hawaiian Indica, Girl Scout Cookies and Jack Herer. Rush delivery orders are available within the United States.
- **5. Real Scientific Hemp Oil (Poway, CA)**

SMOKABLES

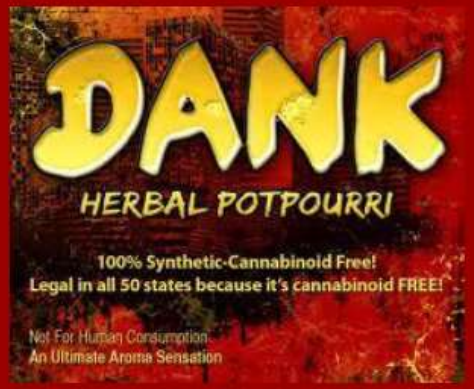
EDIBLES

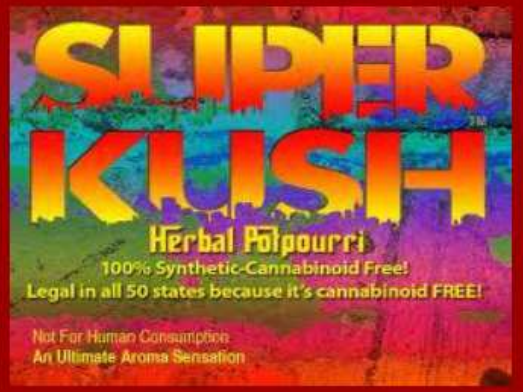
So, Now Legal Potpourri

Synthetic MJ (K2) Street Names

- Bliss
- Black Mamba
- Bombay Blue
- Fake Weed
- Genie
- Spice

- Cannabis also comes in synthetic cannabinoids ("Spice" or "K2")
  - 30 X greater rate of seeking emergency services
  - 60% of overdoses of synthetic cannabinoids are in people under age 25
  - More likely to cause psychosis in susceptible individuals than cannabis


DANK
HERBAL POTPOURRI
100% Synthetic-Cannabinoid Free!
Legal in all 50 states because it's cannabinoid FREE!
Not For Human Consumption
An Ultimate Aroma Sensation


SUPER
KUSH
Herbal Potpourri
100% Synthetic-Cannabinoid Free!
Legal in all 50 states because it's cannabinoid FREE!
Not For Human Consumption
An Ultimate Aroma Sensation


• Full Aroma Strength
• Relieves Unwanted State of Mind
NOT FOR HUMAN CONSUMPTION.
RELAXINOL
POTPOURRI
Relaxation For any State You're In.
Net Wt 1.0g (.035oz)


Red Leaf
HERBAL POTPOURRI
One of Our Premium Potpourri Blends
Made From Some of the Rarest Herbs & Ingredients
It is ONE POWERFUL Potpourri!
100% Synthetic-Cannabinoid Free!
Legal in all 50 states because it's cannabinoid FREE!


USA LAB CERTIFIED LEGAL
DEMON
RITUAL SPICY BOTANICAL
POTPOURRI
NOT FOR THE MEEK OR WEAK


SENSE
JOKER


RED
PLANET
HERBAL POTPOURRI
100% Synthetic-Cannabinoid Free!
Legal in all 50 states because it's cannabinoid FREE!
Not For Human Consumption
Releases a Rich Aroma When Burned

Also new oral pot street products Marijuana Gel Caps: Pot + Olive Oil Blended and Capsulized

“Dabbing” butane hash oil (BHO) aka “wax, shatter, honey oil” et al.

Alleged to result in a waxy product containing 70-90% THC!

THE NEW FORMS OF CANNABIS

Also Commercial Products (e.g. PureGold) via Tetralabs CA. et al. sold as medical marijuana

Sold as liquid, gel cap, gel Ampoule and solution for E-Cigarette Use

Alleged 95% cannabinoid with 75% Δ_9 THC

Use of E-cigarette devices to "vape" cannabis products: produces odorless vapor


GRAPE APE
SODA
MEDICINAL USE ONLY
JONES'N
JONES'N
JONES'N
JONES'N
JONES'N
JONES'N
JONES'N
DEA


Munchy Way
Reese's
KeefKat
Buddahfinger
OEO
Tri-Chrome
CRUNCH
DEA

MJ Candy

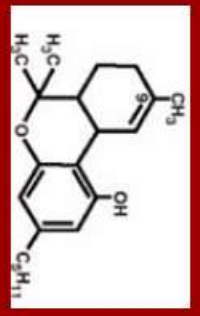

EdiPure
Raspberry Jellies
EdiPure
Fruit Jellies
EdiPure
Gourmet Tropical Fruit
EdiPure
Mixed Nut Clusters
EdiPure
Fruit Jellies
EdiPure
Cherry Cola Bottles

Hemp Oils Alleged Cancer Cure Used in Baking, Butter, Salads, Marinades, et al.

Legal Federal Research MJ

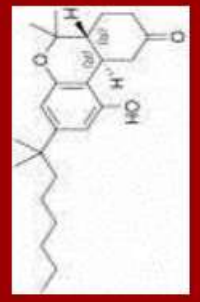
FDA-Regulated Cannabinod-Based Medicines: Chemicals, Extracts, Botanicals

Dronabinol (Marinol™)



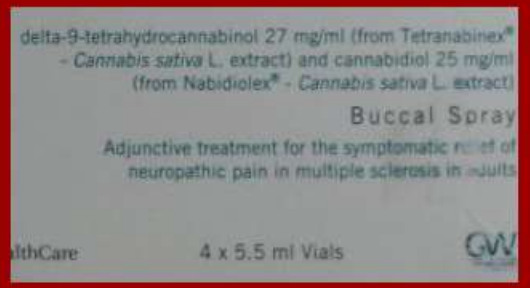
1985

Nabilone (Cesamet™)



1985

Cannabis Sativa Extract (Sativaex™)



2006

Cannabis Sativa L. Cigarettes

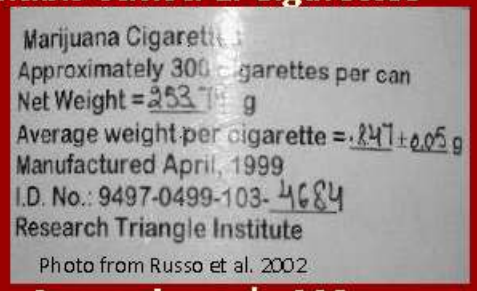


Photo from Russo et al. 2002

Approximately 460 chemical constituents, >100 phytocannabinoids

1976

Why people use MJ: Acute Intoxication Effects

- alteration of conscious perception
- euphoria,
- feelings of well-being,
- relaxation or stress reduction,
- increased appreciation of the arts, including humor and music
- joviality
- introspection
- enhanced recollection
- increased sensuality & libido
- increased awareness of sensation

- Anxiety is the most commonly reported negative side effect of smoking marijuana; 20- 30 percent of recreational users experience intense anxiety and/or panic attacks after smoking cannabis

CANNABIS- ACUTE NEGATIVE EFFECTS

SOURCE: THE ACUTE EFFECTS OF CANNABINOIDS ON MEMORY IN HUMANS: A REVIEW., RANGANATHAN, ET. AL., PSYCHOPHARMACOLOGY (BERL) 2006 NOV;188(4):425-44.

- ↑Anxiety
- ↑ Paranoia
- ↑ Disorientation
- ↑ Delusions
- ↑ Hallucinations
- ↑ Disordered thinking
- ↑ Psychomotor agitation
- ↑ Emotional lability
- ↑Irritability
- ↓ Judgment
- ↓ Coordination and balance
- ↓ Spatial perception
- ↓ Attention
- ↓ Awareness of passage of time
- ↓ Memory (encoding, consolidation, & retrieval)
- ↓ Short-term memory
- Depersonalization
- Derealization

Main Phytocannabinoids (480 chemicals in pot, ~66 are psychoactive)

- Cannabinoids that occur naturally in the cannabis plant.
- Three most considered in medical pot:

- THC (Delta-9-tetrahydrocannabinol): Main psychoactive chemical, anti-emetic, appetite stimulant, analgesia; neuroprotective antioxidant

- CBD (cannabidiol): much less psychoactive, anti-seizure, -spasmodic, -emetic, -inflammatory, analgesia, sedating, neuroprotective

- CBN (cannabinol): anti-seizure, -inflammatory, sedative effects

Important Brain Locations

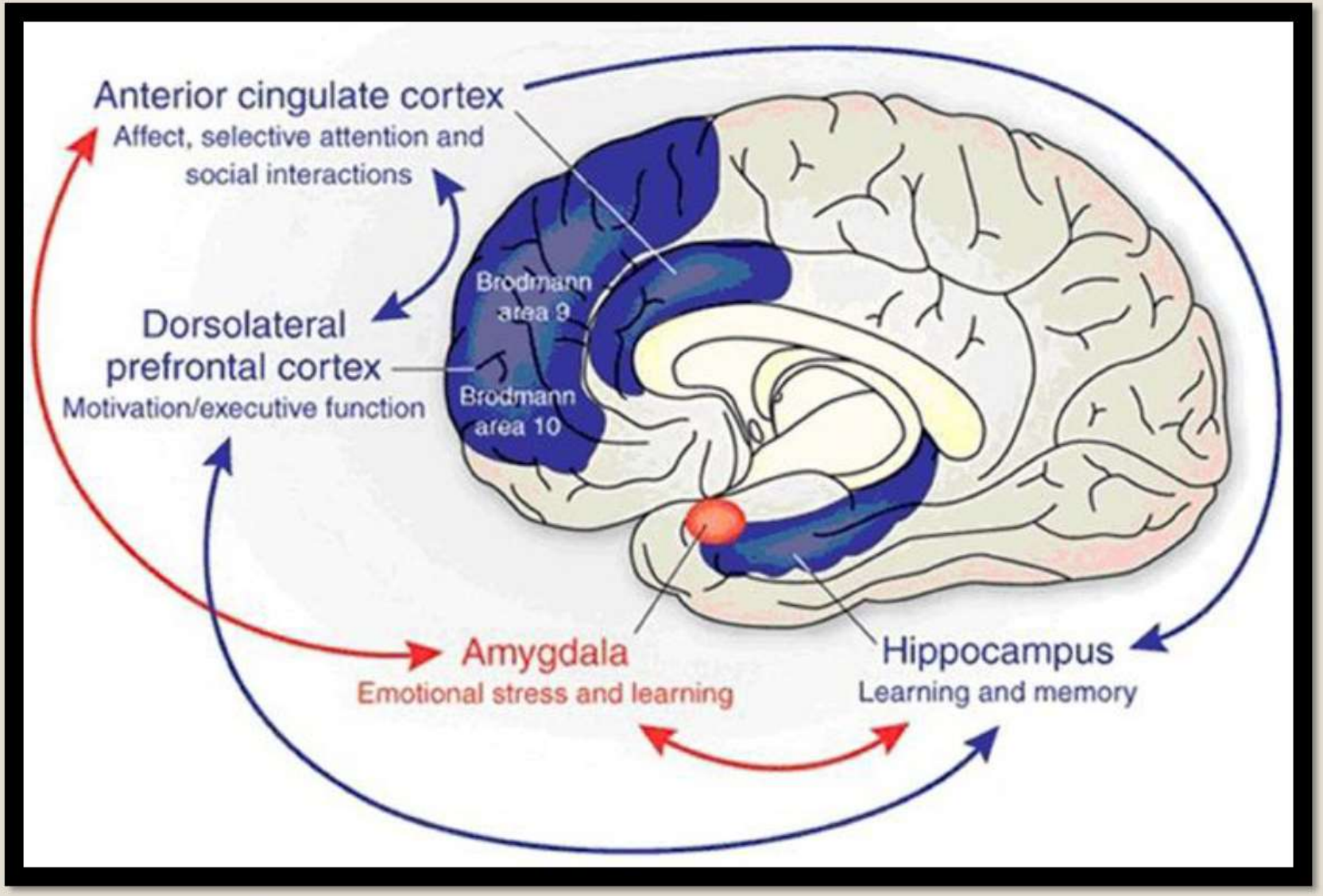


IMAGE SOURCE: http://www.frontiersin.org/files/Articles/25631/fnint-06-00036-HTML/image_m/fnint-06-0

Screen Clipping

THC & CBD have opposing effects in different brain location

DISTINCT EFFECTS OF 9-TETRAHYDROCANNABINOL (THC) AND CANNABIDIOL (CBD) ON NEURAL ACTIVATION DURING EMOTIONAL PROCESSING (FUSAR-POLI, P., ET AL., *ARCH GEN PSYCHIATRY. 2009;66(1):95-105)*

Cannabis use can both increase and reduce anxiety in humans. The neurophysiological substrates of these effects are unknown.

RESULTS of this study (n=15) revealed:

CBD and 9-THC had distinct and *opposite* modulatory effects on the regional neural response to fearful faces.

9-THC modulated activation in frontal and parietal areas and was associated with an **anxiogenic** effect.

CBD attenuated the neurofunctional engagement of the amygdala and cingulate cortex and was associated with an **anxiolytic** effect.

THC AREAS **CBD AREAS**

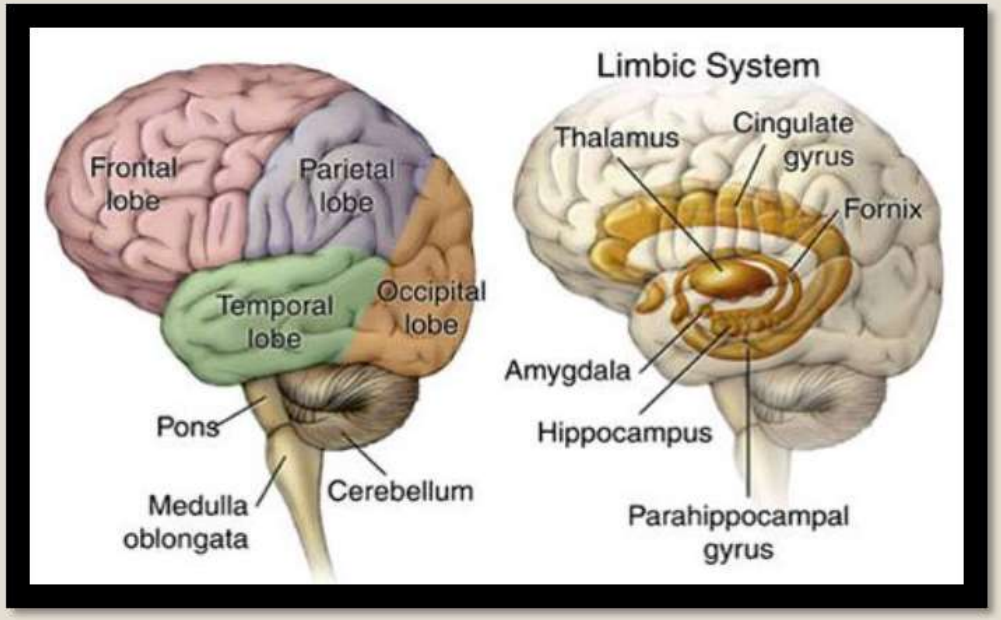


IMAGE SOURCE: http://www.sadclinic.com/uploads/brain_anatomy.jpg

Physical reaction to MJ

- Fast, good absorption if smoked or vaporized

- The psychoactive effects of cannabis are experienced immediately after smoking, with peak levels of intoxication within 30 minutes and lasting several hours

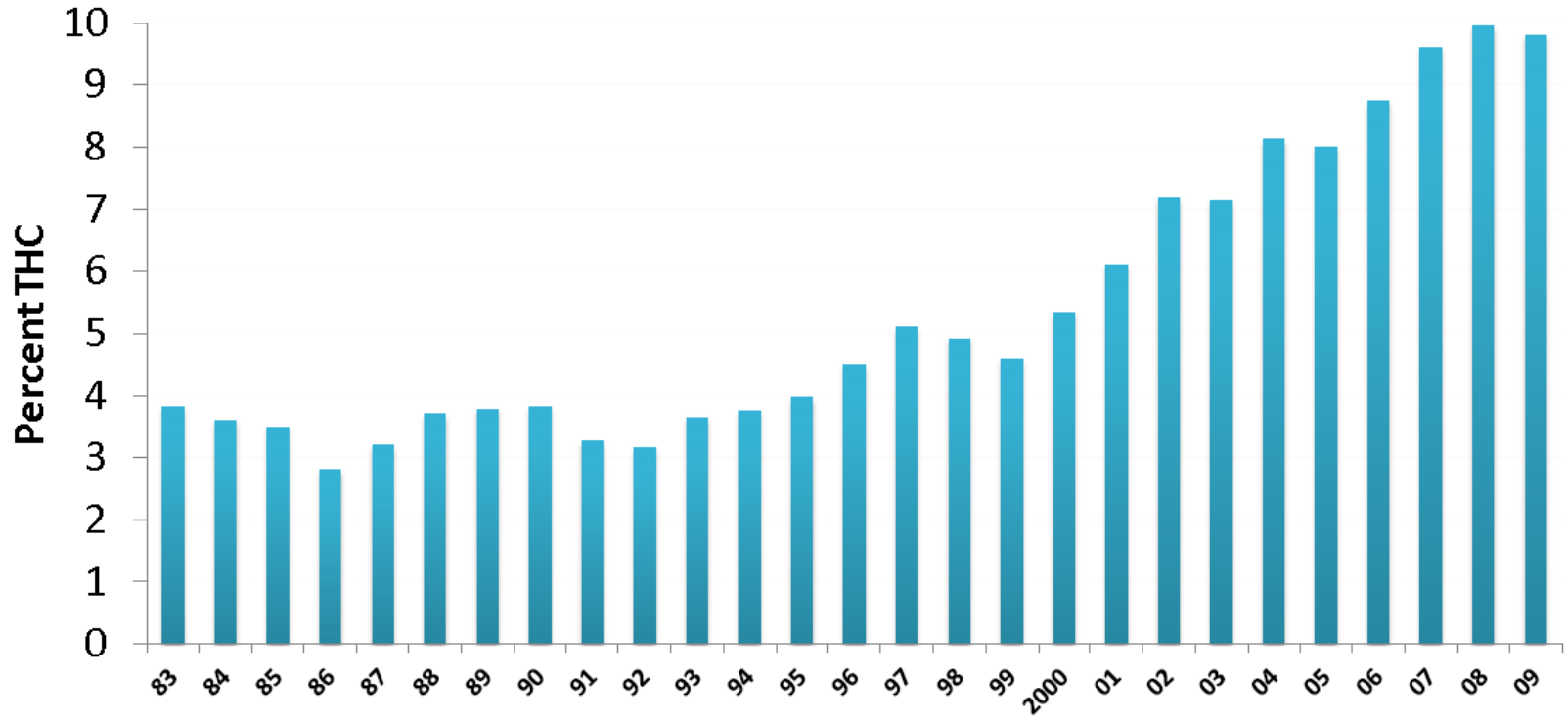
- Slower effect if orally ingested: ingested MJ takes longer to activate within the body (sometimes as long as two hours), but produce a longer-lasting effect (up to eight hours)

Clinical Pharmacology of Cannabis

- THC is fat soluble (esp. adipose fat) and, therefore, easily stored and released into the bloodstream.
- Because it is fat soluble, THC has a long half-life and can be detected in urine anywhere from one to ten days. long-term users can produce positive tests for two to three months after ceasing cannabis use
- Elimination is slow: days to weeks, 20-35% found in urine; 65-80% found in feces
- Can be detected in breast milk

THC Potency

Potency: Increased THC Content in Seized Marijuana, 1983-2009



Sources: The University of Mississippi Potency Monitoring Project

More Potent Pot

Marijuana Potency Monitoring Project University of Mississippi

Average Potency of US street marijuana

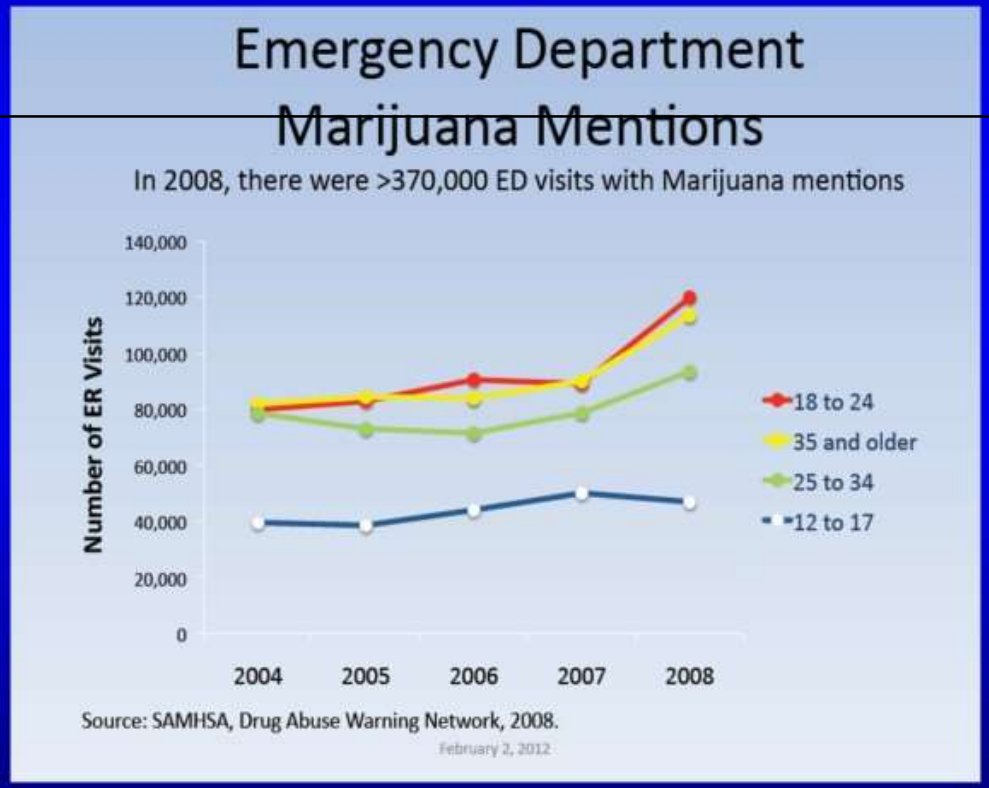
- 1976 – 2% THC
- 1983 – 4% THC
- 2005 – 5.2% THC
- 2007 – 7.3% THC
- 2008 – 10.1% THC
- 2013 - *15% THC *unpublished

THC Dosing <7mg=low dose, 7-18mg=Medium, >18mg.=High Dose but more than 80 cannabinoids plus 400 phyto and 2,000 combustion bioactive molecules

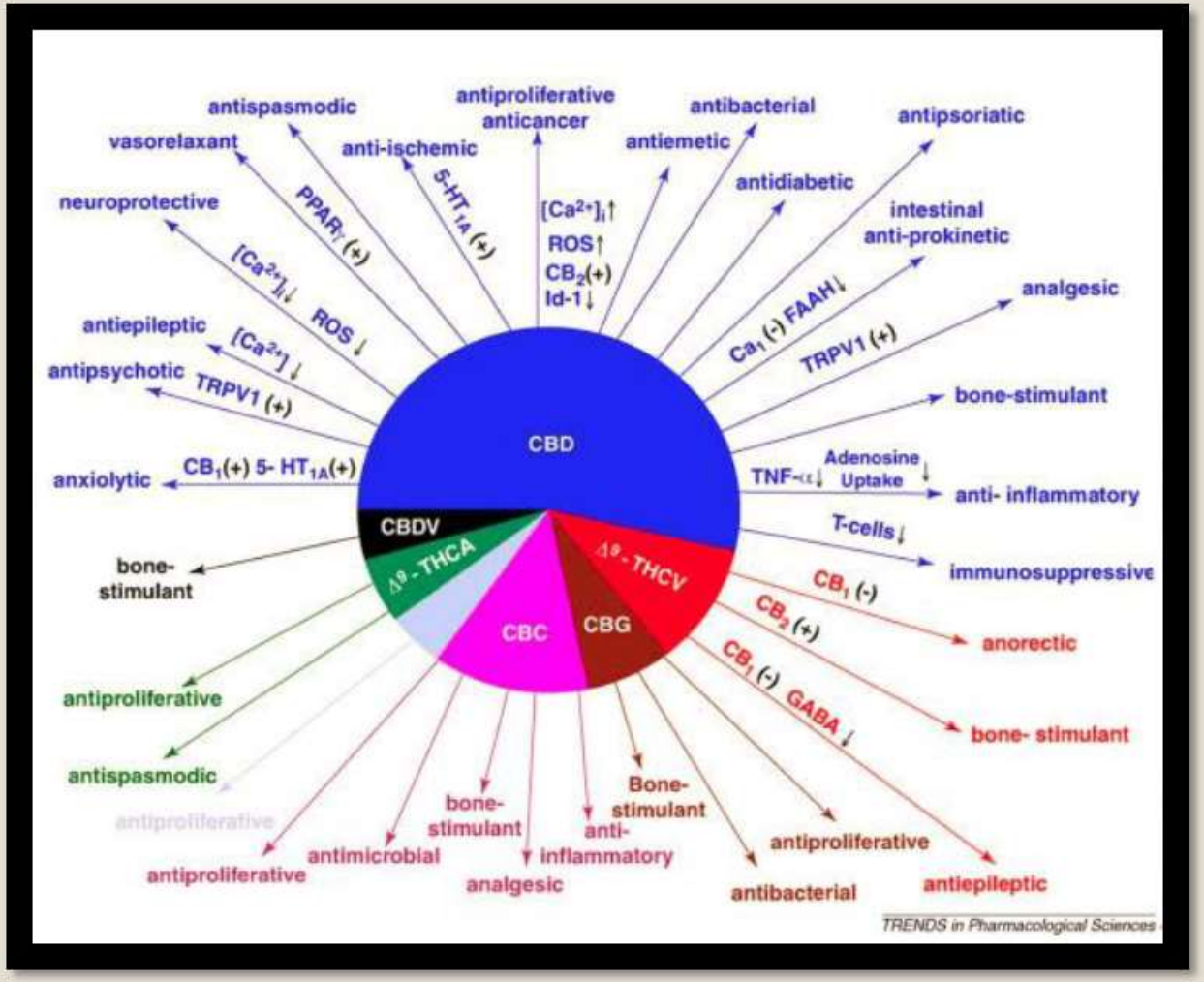
Highest tested sample ever tested between 1975 and 2009 had 37% THC

As THC content increases, we see more adverse effects:

- Paranoia
- Anxiety and panic
- Hallucinations
- Erratic mood swings
- Aggressive behavior



Cannabinoids:
483 Known Chemical Compounds Found in The Cannabis Plant



Endocannabinoid System:
Regulates Activity in a Wide Variety of Systems

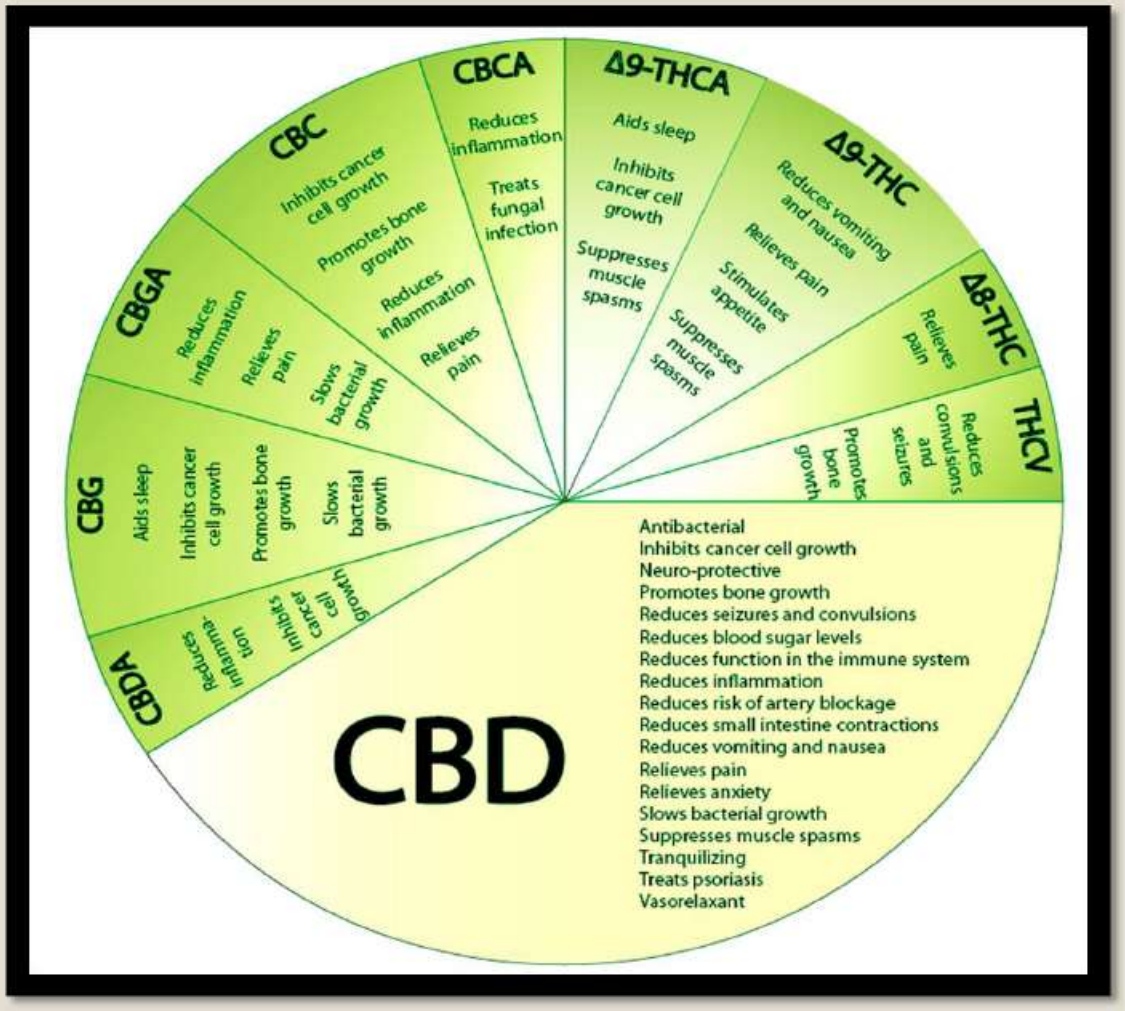
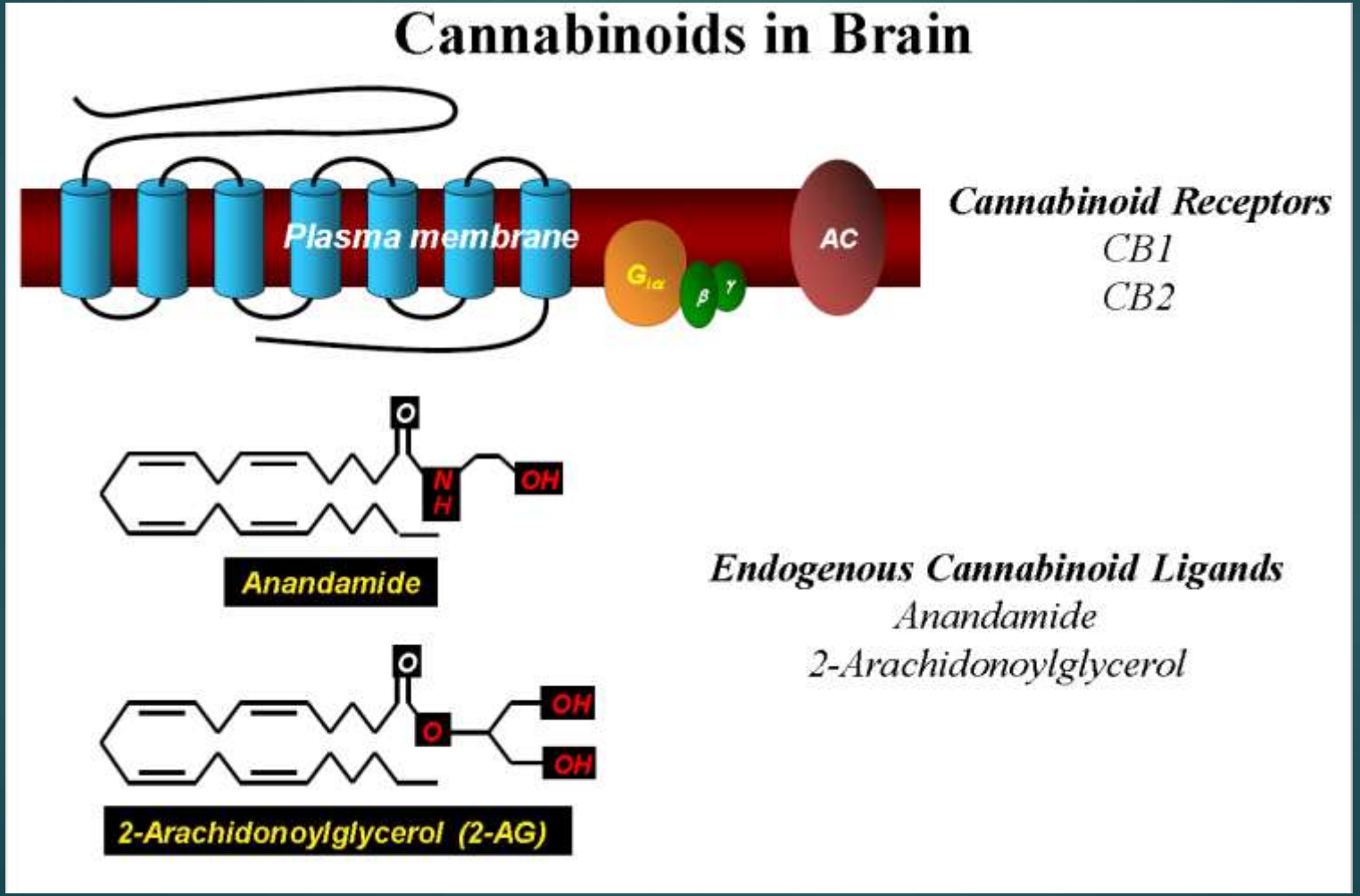


IMAGE SOURCES: http://idrasilrx.com/doctor-information/human-receptor-information/ & http://idrasilrx.com/doctor-information/human-receptor-information/

Endocannabinoid System: Why MJ works in the human brain

Human brain and body have Cannabinoid receptors & neurotransmitters



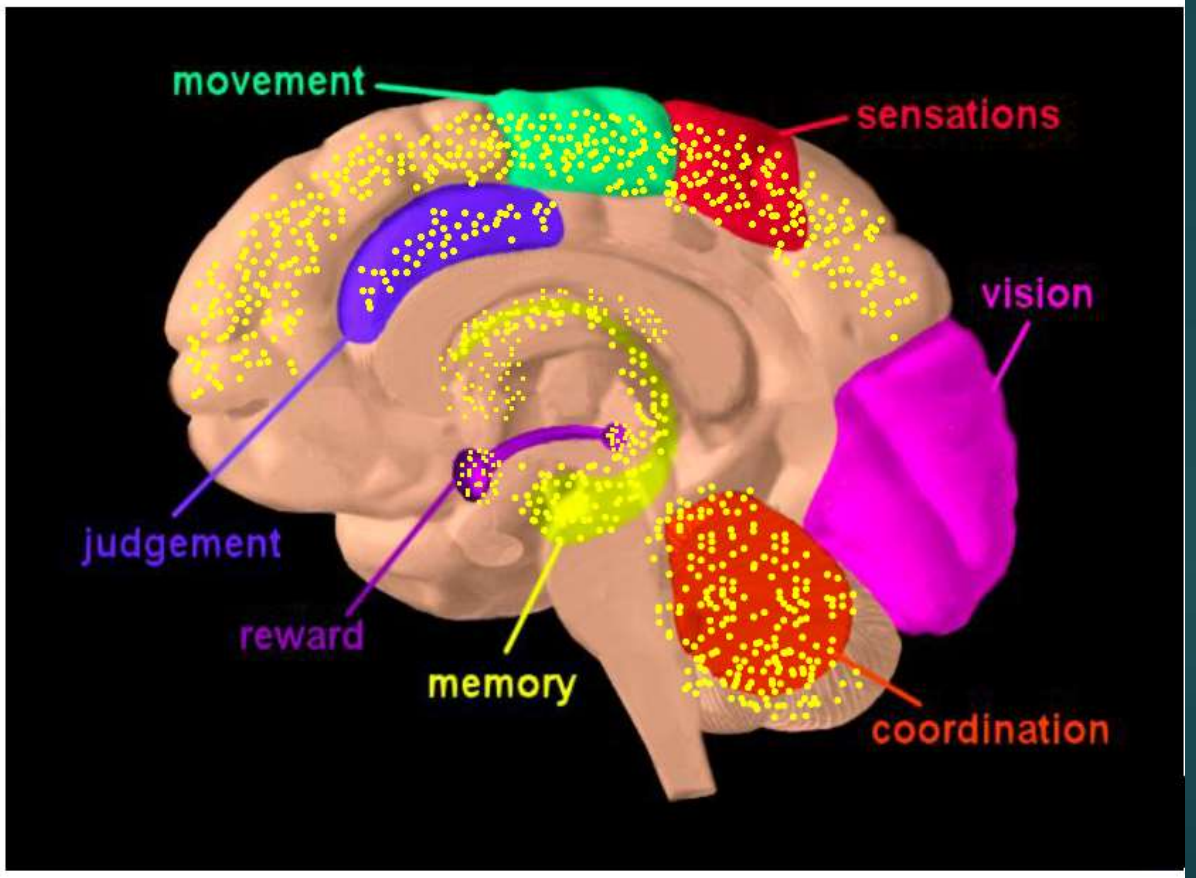
Anandamide: neurotransmitter involved in:
feeding behavior,
reward, motivation,
& pleasure.

Why do we have Cannabanoid receptors in our brains?

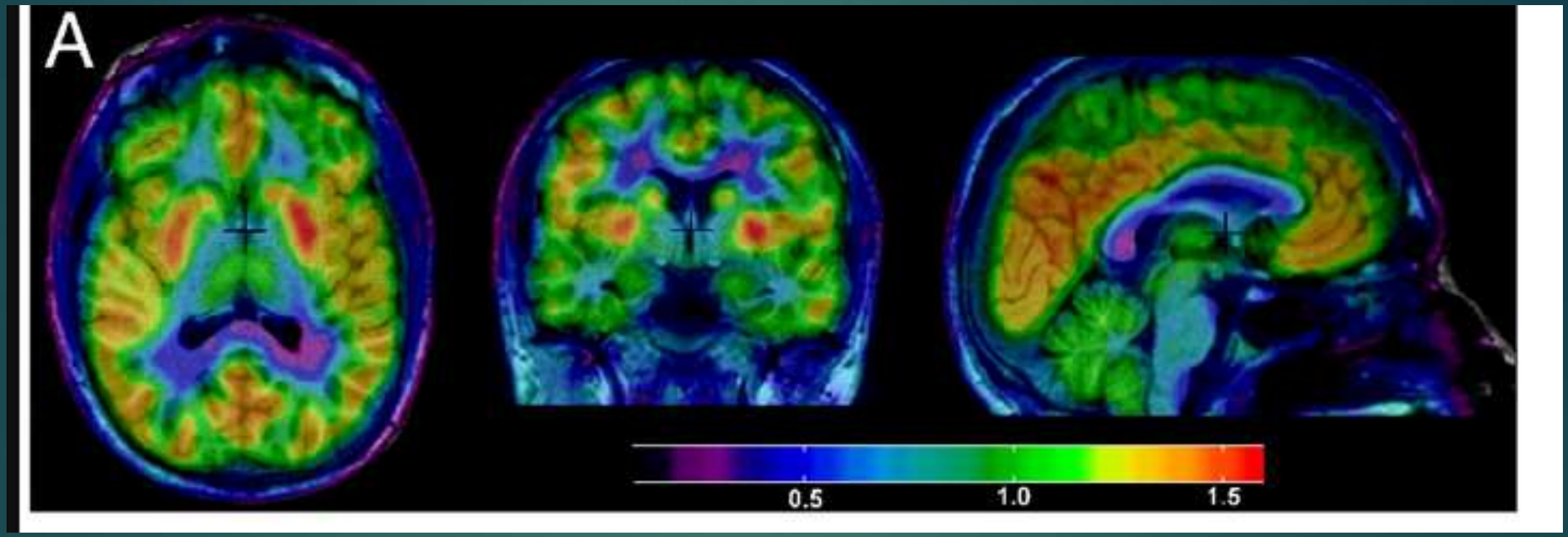
- The human brain is sensitive to marijuana because we are all born with "cannabinoid" receptors on our brain cells to which THC binds.
- Cannabinoid receptors are one of the most common types of receptors in the brain. Two main types of cannabinoid receptors:
  - CB1 receptors are located primarily in the brain, but they also are found in blood vessels and heart cells
  - CB2 receptors are primarily located outside of the brain, in the peripheral nervous system and glands; esp. in immune system
- Marijuana can have a widespread effect on the brain, heart, cardiovascular system, nervous system, reproductive system, and immune system.

Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

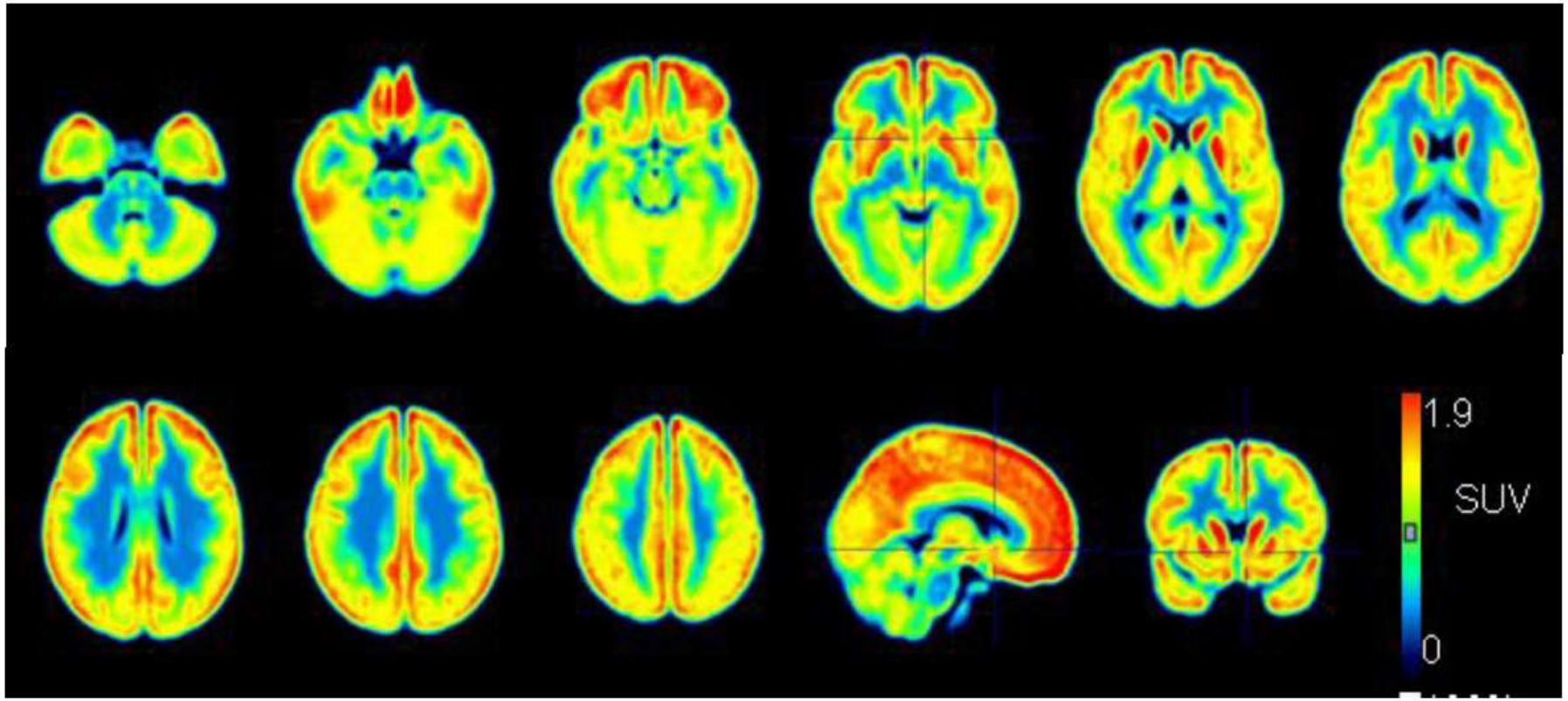
- Brain Development
- Memory and Cognition
- Motivational Systems
- & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation
- & Analgesia



Endocannabinoid Receptors in the Brain



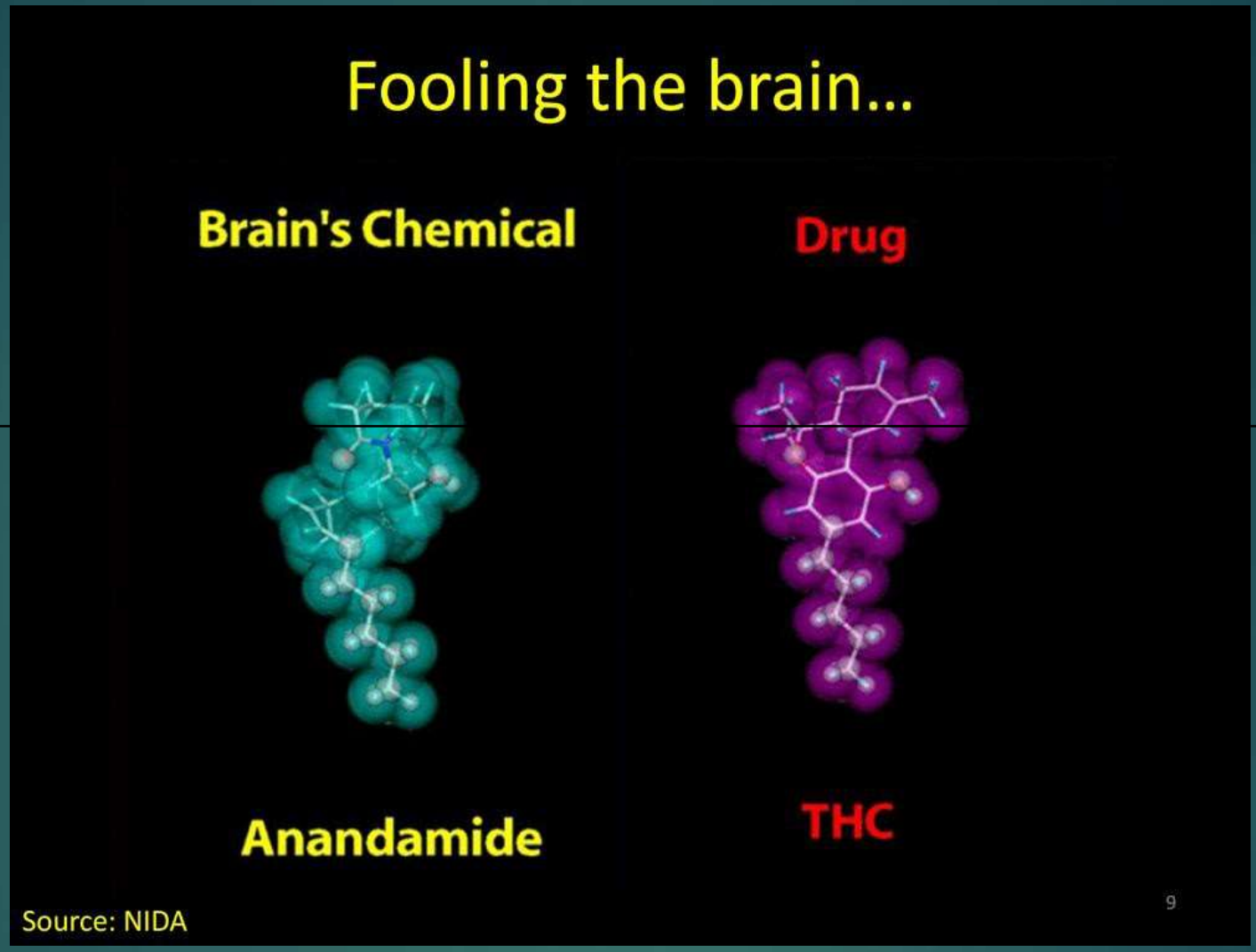
Cannabinoid Receptors in Human Brain



Van Loere et al., 2007.

Brain's Endocannabinoid System

- The endocannabinoid system acts like the brain cell's volume control dial. If the volume or signal coming from one neuron gets too loud, the receiving neuron sends anandamide backwards through the synapse to turn the volume down on overactive neuron.
  - regulates (monitor and control) how active neurons are
  - controls how much neurotransmitter gets released, including neurotransmitters that affect pleasure, mood, pain, appetite, motivation, memory, muscle activity, etc. (e.g., dopamine, serotonin, endorphins).
  - helps to keep brain cell activity in BALANCE, not underactive (like in depression or ADHD) or overactive (like in epilepsy or post-traumatic stress disorder).



Trojan Horse: THC can substitute for neurotransmitter Anandamide in Cannabanoid receptors (but sledgehammer effect not surgeon’s knife)

THC vs. Anandamide

- Both THC and anandamide dial down neuron activity, thereby changing the amount of neurotransmitters released.

- When THC binds to our cannabinoid receptors, it has a much stronger and longer effect on brain cell activity than anandamide.

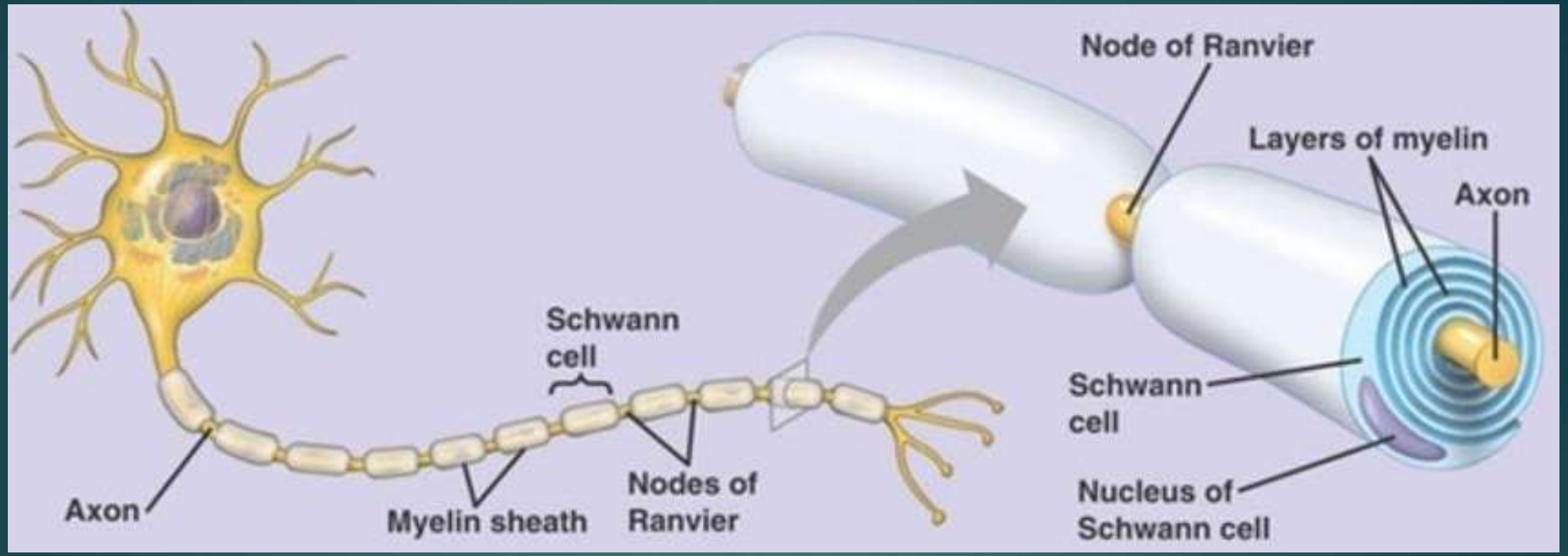
- By occupying those cannabinoid receptors, THC interferes with anandamide's ability to naturally protect and balance cell activity.

Brain's Endocannabinoid System 2

- This system helps shape brain development.
  - Helps guide neuron growth in the fetus
  - Because it helps to control neuron activity, it plays a major role in brain wiring – that is, how brain cells grow new synapses and connections to other neurons.
  - Plays a role in the myelinization of axons.
  - Proper endocannabinoid system function is important for neuron growth, activity, and connectivity

Galve-Roperh, L. et al., 2009

Myelin: speed of processing in the brain



Neuron communicates 3000x faster once myelinated

Continued THC exposure

- With repeated THC exposure, brain cells start to adapt.

- Brain cells that get overstimulated by the effects of THC start to compensate by scaling back the number of receptors (this is why you get "tolerance" after repeated use of a substance, and this happens with all types of substance use).

- Repeated THC exposure continually dampens down the activity of many brain cells, causing there to be over inhibition.

- Eventually chronic neuronal inhibition has a negative rebound causing increased excitation of neurons to compensate.

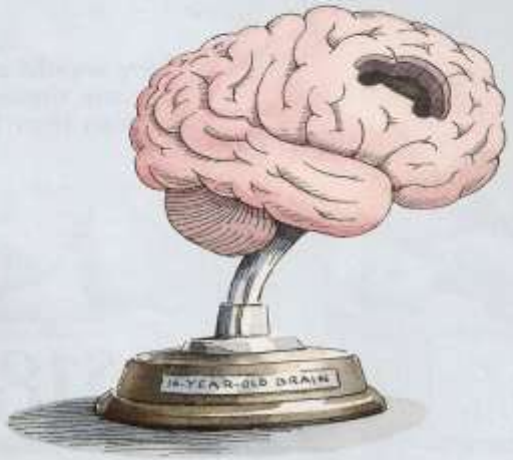
Brain still under construction

“It’s sort of unfair to expect (teens) to have adult levels of organizational skills or decision making before their brains are finished being built.

-- Jay Giedd, MD, NIH, 2002

Why do most 16-year-olds drive like they're missing a part of their brain?

BECAUSE THEY ARE.



Even bright, mature teenagers sometimes do things that are "stupid."

But when that happens, it's not really their fault. It's because their brain hasn't finished developing. The underdeveloped area is called the dorsal lateral prefrontal cortex. It plays a critical role in decision making, problem solving and understanding future consequences of today's actions. Problem is, it won't be fully mature until they're into their 20s.

It's one reason 16-year-old drivers have crash rates three times higher than 17-year-olds and five times higher than 18-year-olds. Is there a way for teens to get their driving experience more safely — giving their brains time to mature as completely as their bodies? **Allstate thinks so.**

STRENGTHEN GRADUATED DRIVER LICENSING (GDL) LAWS.
GDL laws put limitations on teen driving so kids can gain experience safely. Since North Carolina implemented one of the most comprehensive GDL laws in the country, it has seen a 25% decline in crashes involving 16-year-olds.

HAVE THE DRIVING TALK.
75% of teens surveyed said their parents would be the best influence in getting them to drive more safely. The Allstate Parent-Teen Driving Contract can help start the conversation. **Contact an Allstate Agent to get a free copy or visit Allstate.com/teen for the interactive contract.**

Let's help our teenagers not miss out on tomorrow just because they have something missing today.

It's time to make the world a safer place to drive. That's Allstate's Stand.

Allstate. You're in good hands.

Normal sculpting the adolescent brain

- Cortical gray matter volume follows an inverted U- shaped development in adolescence, with cortical volume peaking around ages 12-14.

- Cortical gray matter reduction related to synaptic pruning, beginning in dorsal parietal cortices, then the sensorimotor areas, then frontal cortex, then posterior brain. There are volume declines in medial parietal, temporal, frontal and cerebellar areas.

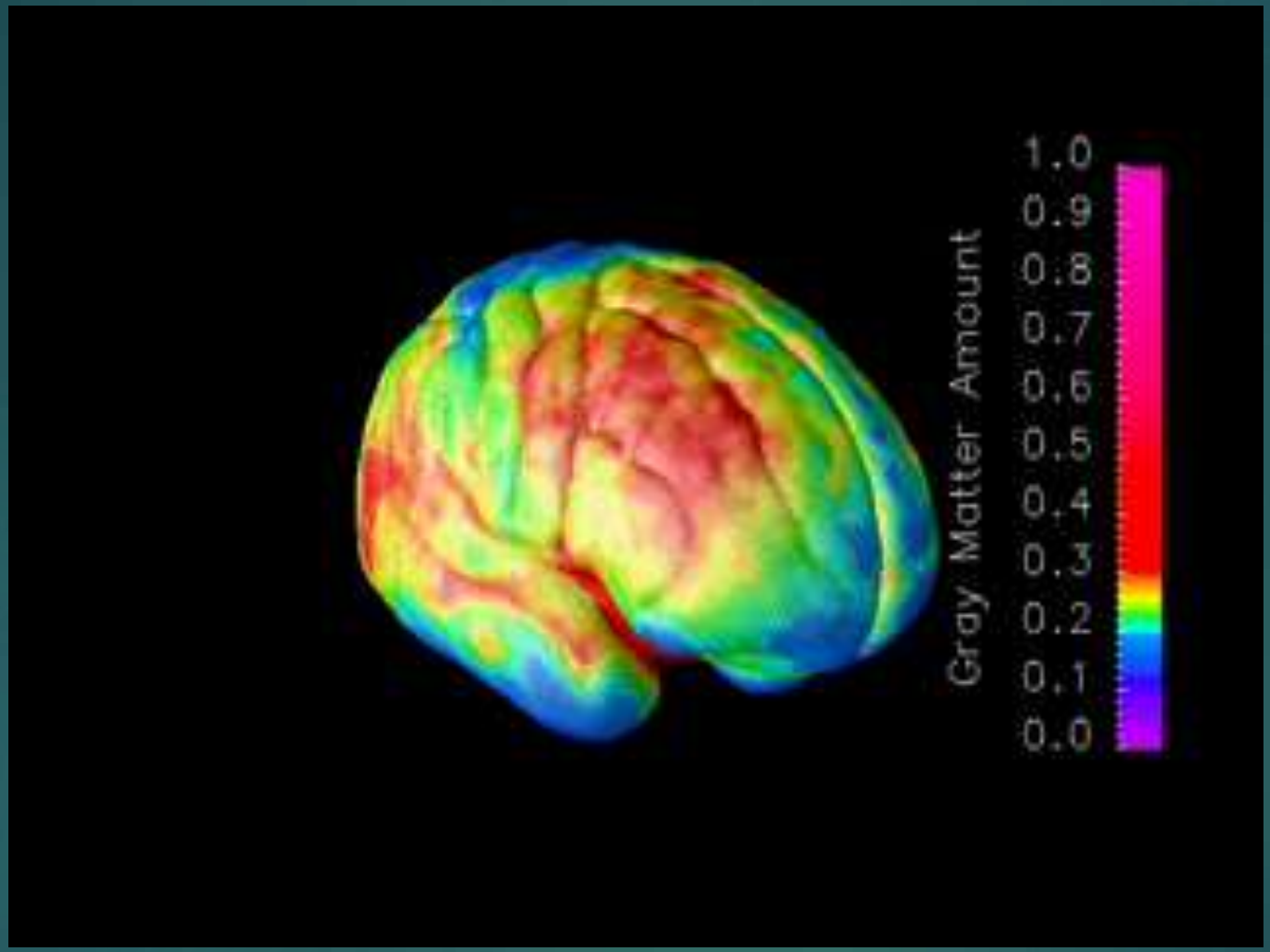
- White matter characterized by volume increases, esp. in frontal & corpus callosum (resulting in greater connectivity and speed of processing).

Normal sculpting the adolescent brain

- Adolescence is a critical neurodevelopmental period and therefore vulnerable to any neurotoxins.

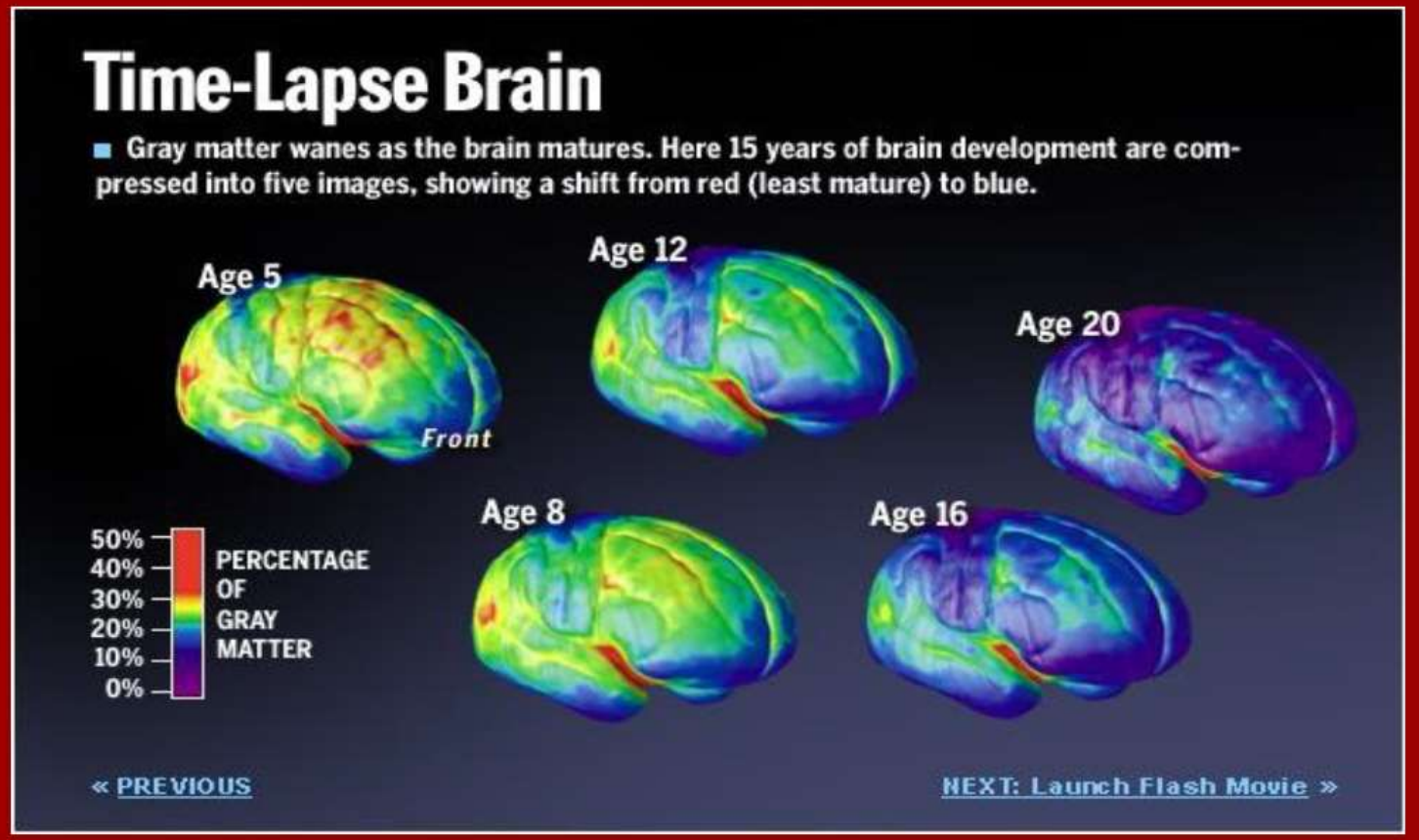
- During the period of adolescent neurodevelopment (12-18), the brain is thought to be particularly sensitive to damage from drug exposure, esp. the frontal cortex.

Teen Brain: age 5 to 21



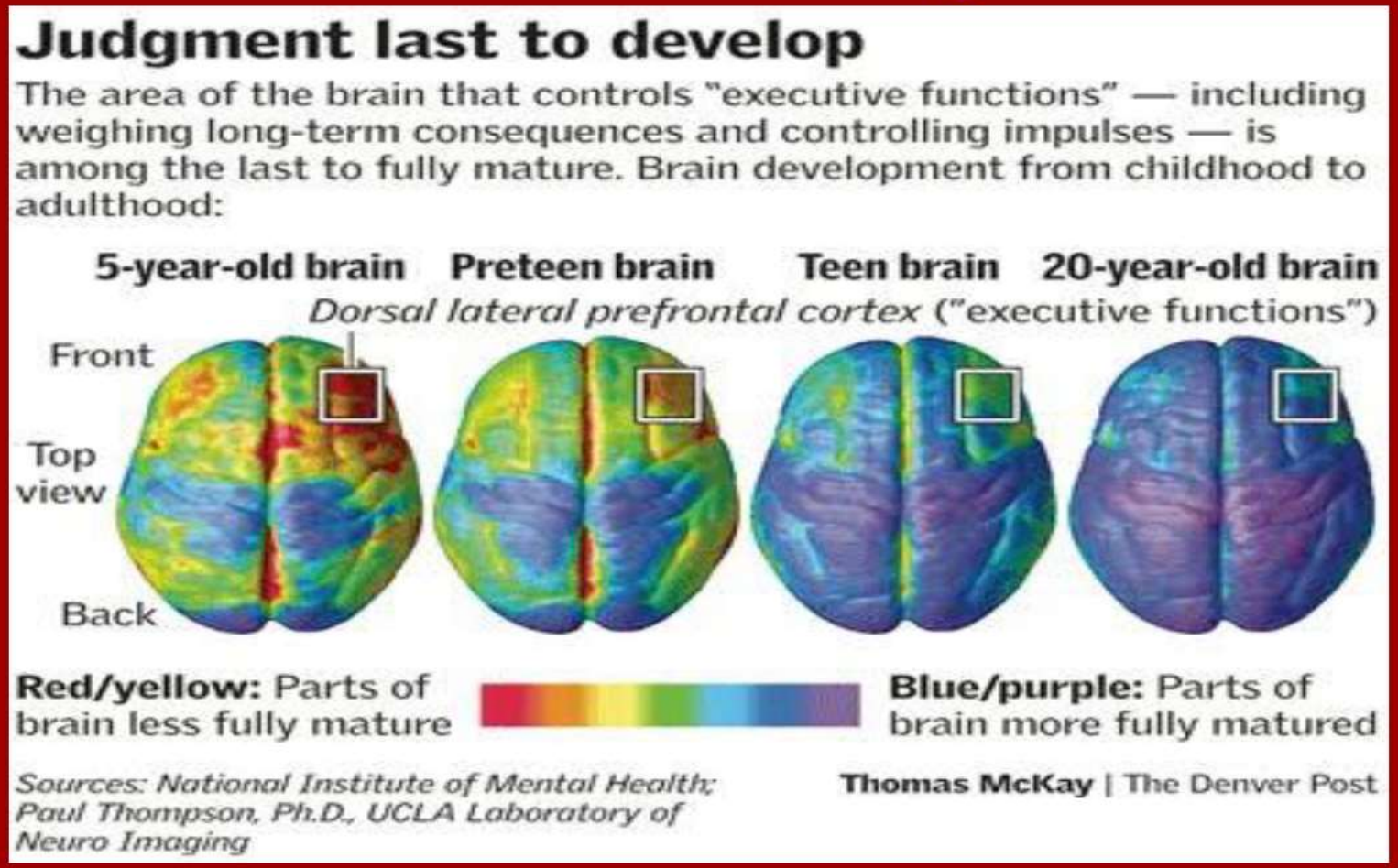
Lose 50% of all synaptic connections;
Motor areas first, frontal last to develop

Brain loss of gray matter and increase in white matter from age 5 to age 20

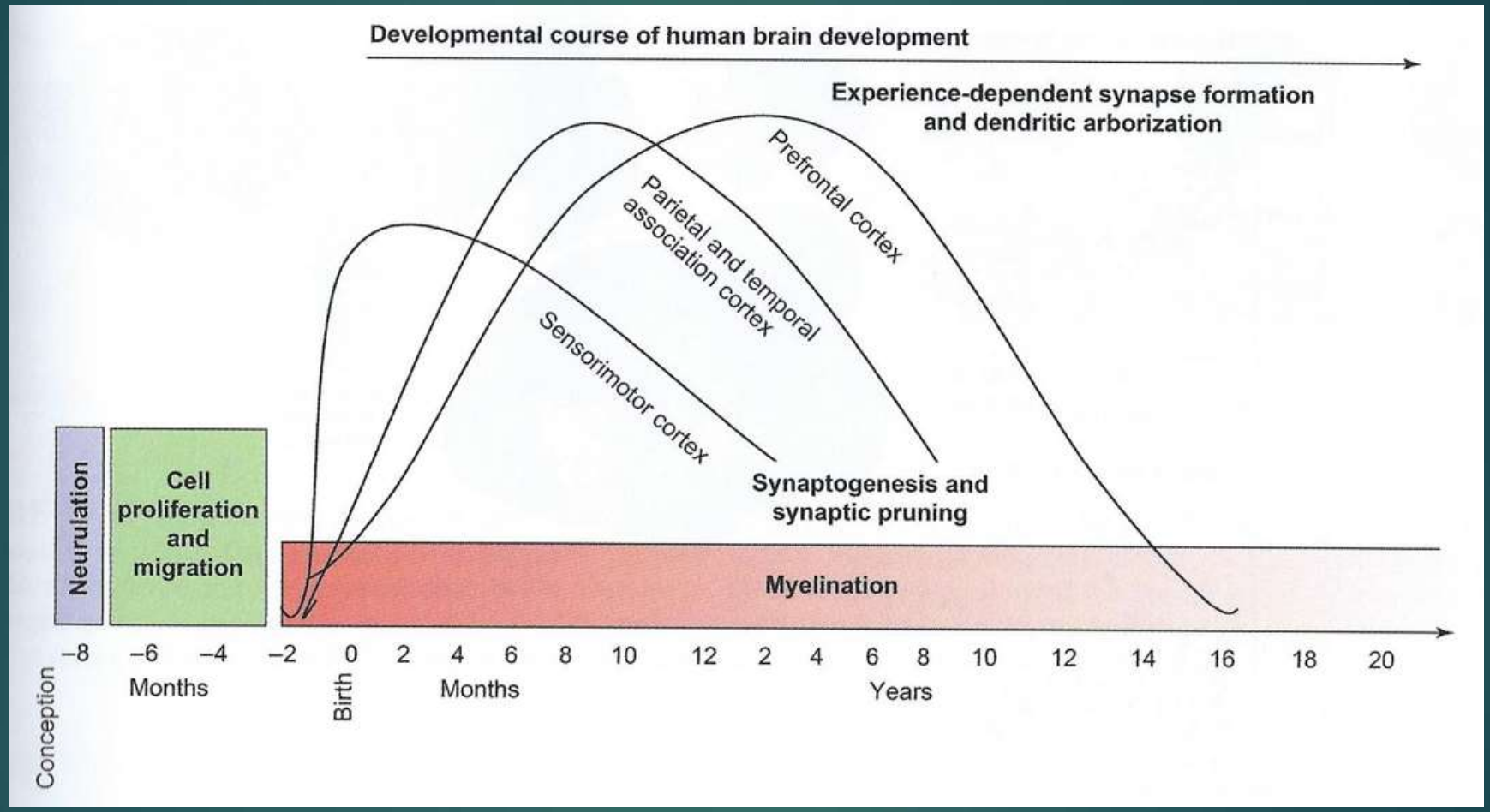


Prefrontal based Executive Functioning (judgment and planning)

Why we all make such "great" decisions before age 25



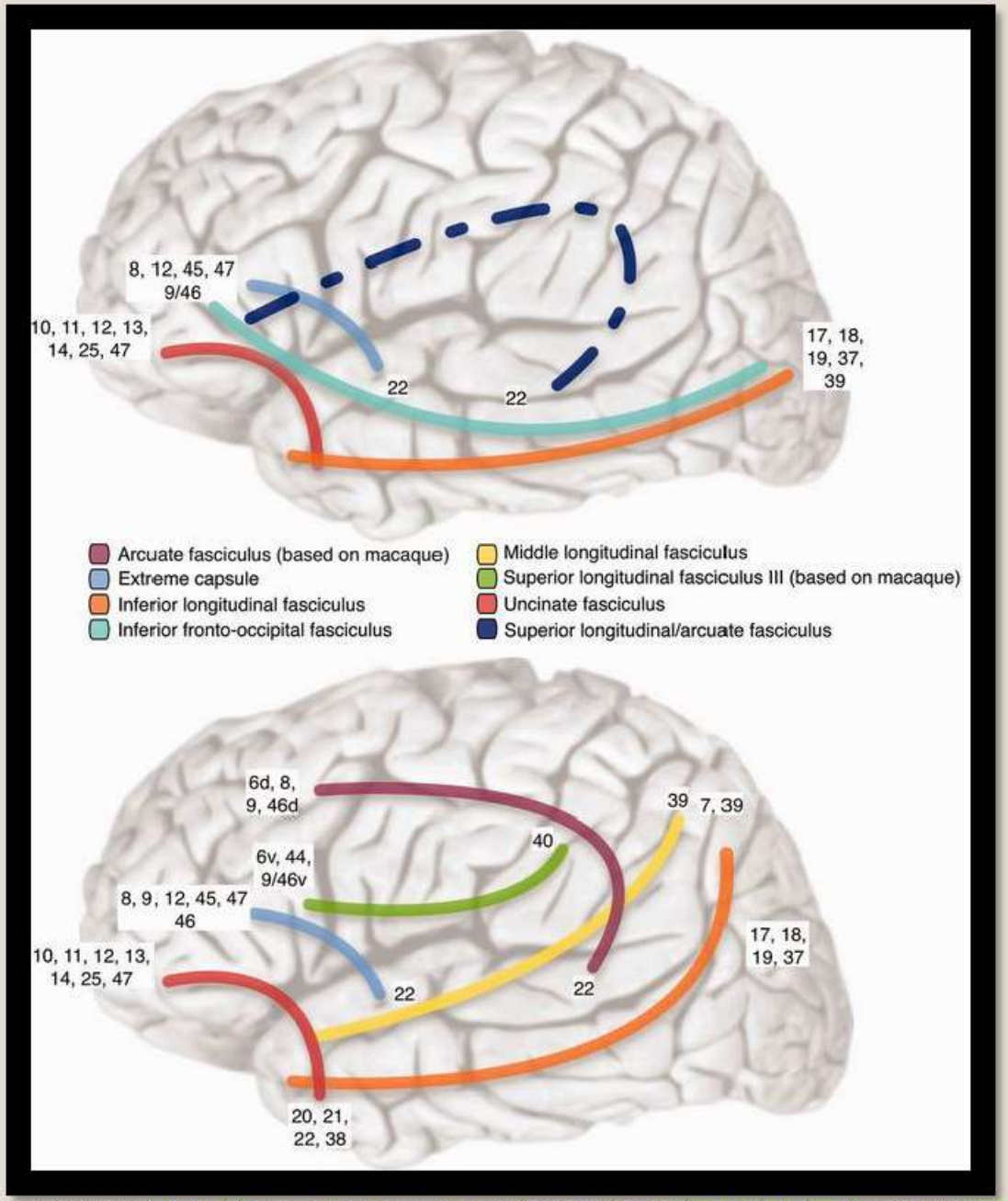
The Great Pruning: A leaner brain is a better brain

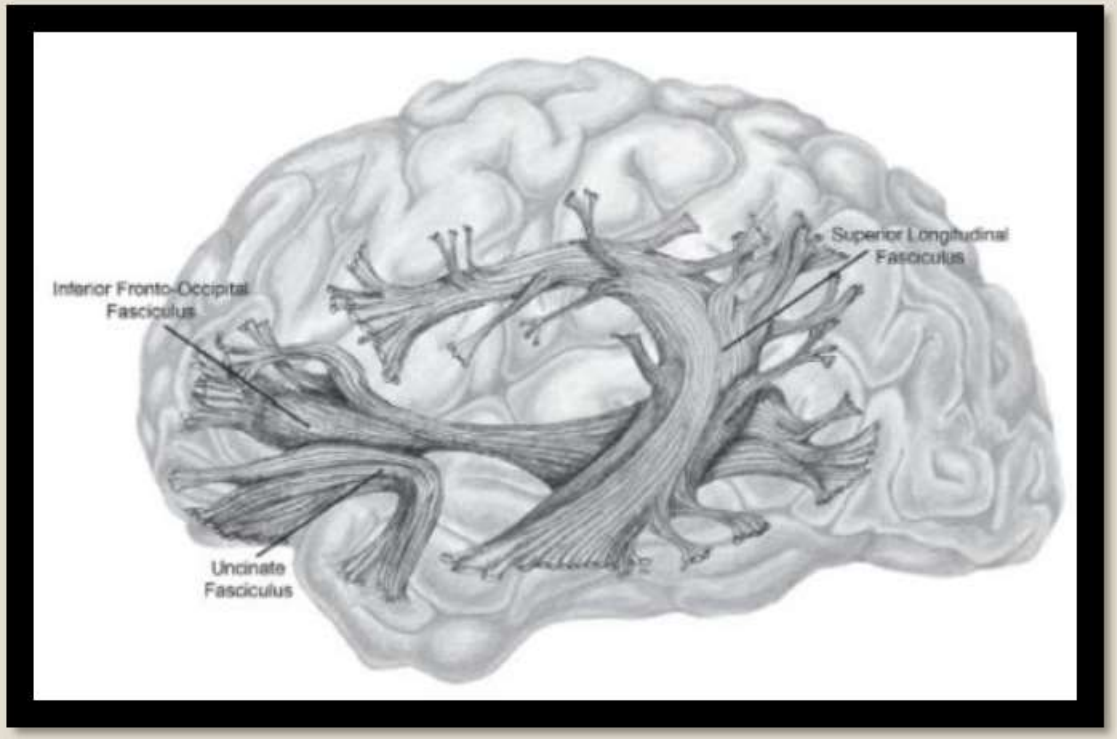


Intellectually challenged have significantly more synaptic connections than gifted do; as do autistic; but schizophrenia, ADHD = too much pruning

Adolescence Brain

- More vulnerable to neurotoxic events because brain is in last major developmental period
- Arrested Development: Substance use can impair normal brain development
- Period of maturation of frontal and limbic regions
- Increase in myelinization (15x faster), particularly in frontal region: increase in impulse control
- Dopamine distribution changes (risk taking↑↑, reward seeking); adolescents are hypersensitive to reward, which leads to risker behavior

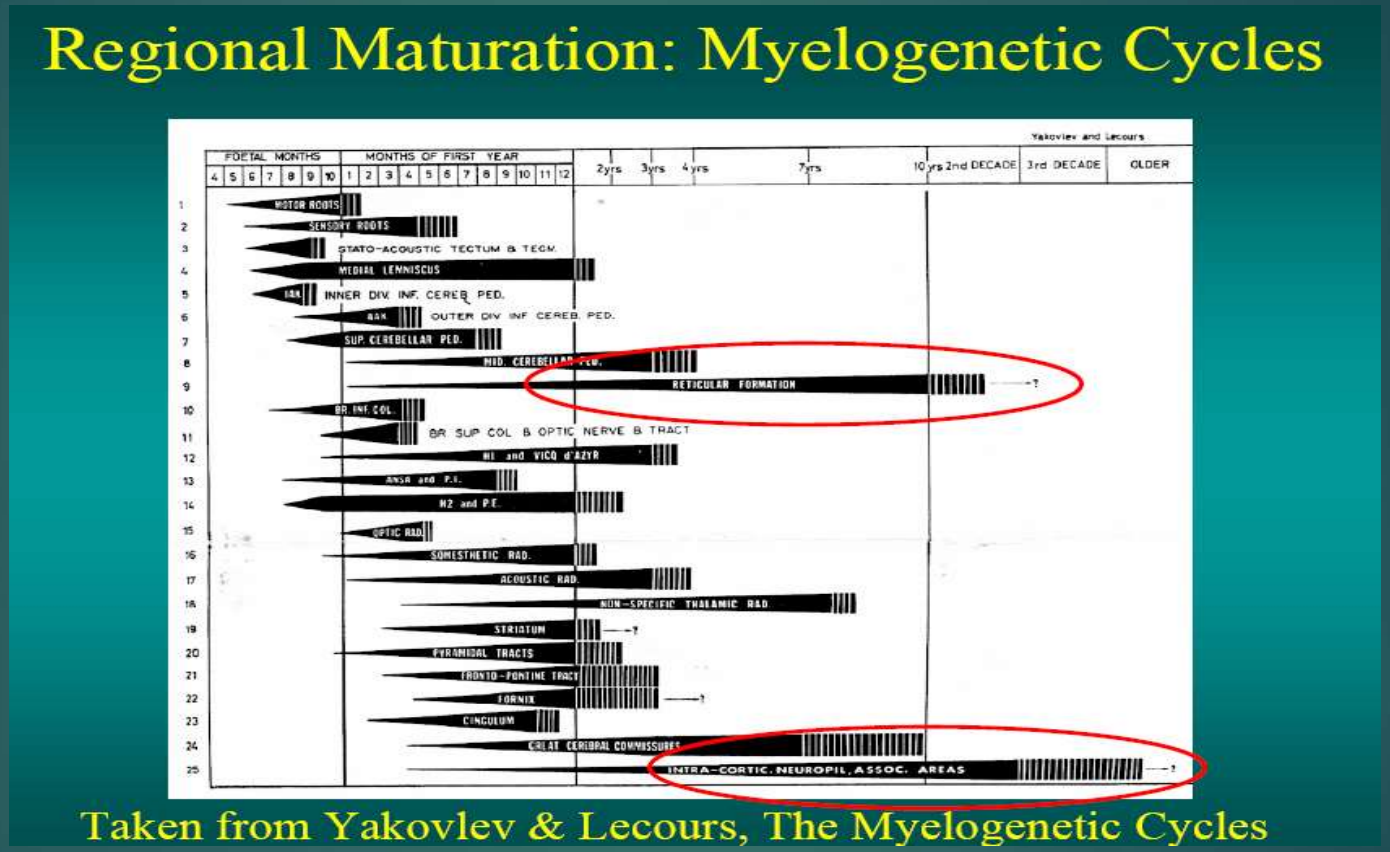




White matter, (tracts and fibers), is tissue found in the brain that contains nerve fibers, and is **responsible for transmitting information from one brain region to another.**

IMAGE SOURCES: http://brain.oxfordjournals.org/content/early/2012/10/28/brain.aws222 and http://openi.nlm.nih.gov/imgs/512/188/3190544/3190544_MSM-06-110-g002.png

Myelin Sheets on Axons Mature Slowly in Frontal Lobes; may increase into 30s.



Amount of white matter (axon interconnections) distinguishes us from primates, not size of prefrontal lobes. Creates “greater bandwidth” and processing speed. Einstein had more white matter, not neurons.

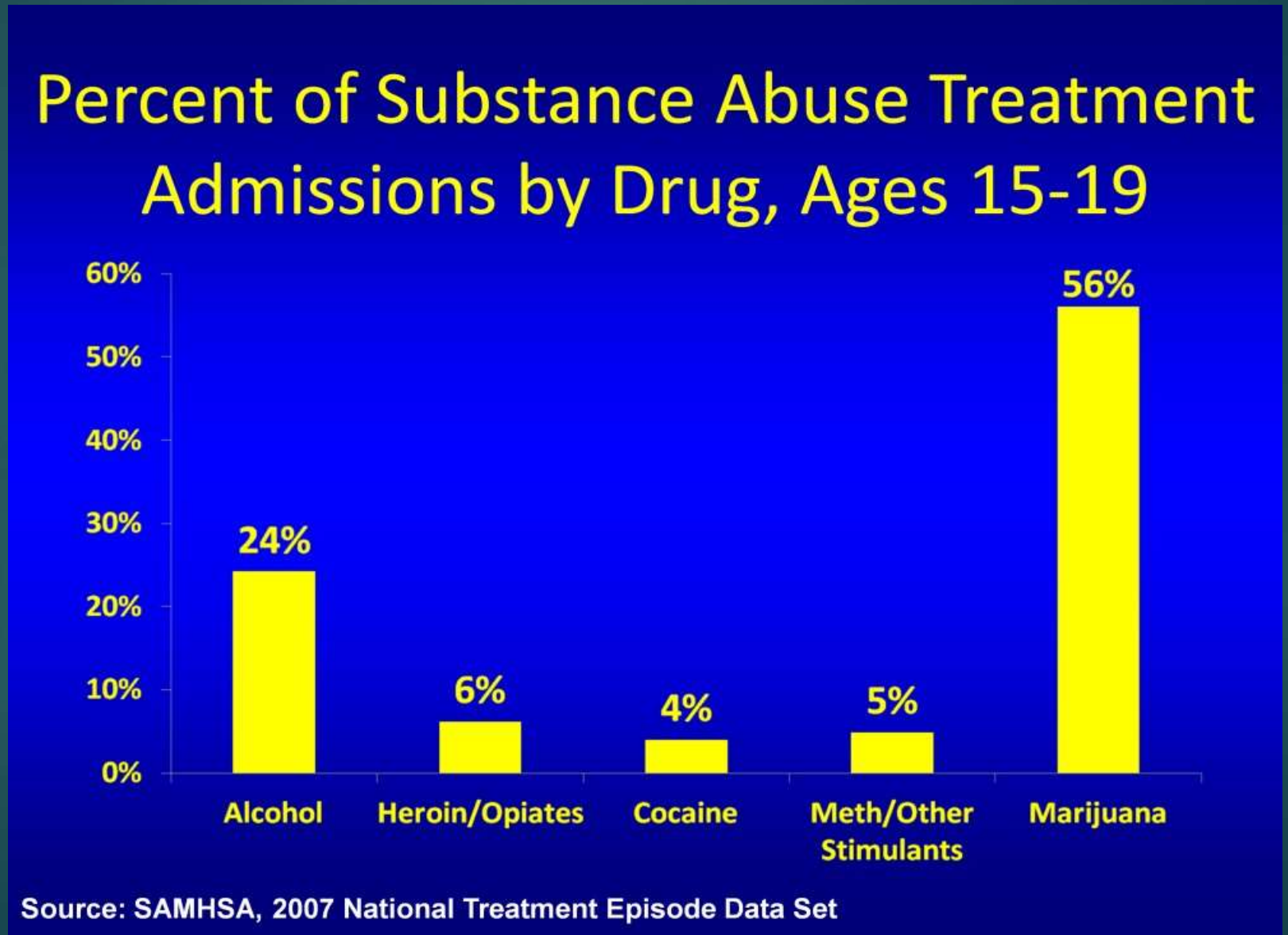
Yakovlev & Lecours 1967

All Drugs Attack the Prefrontal Cortex

- Drug Dependence Consequences are related to dysfunctions in the Prefrontal Cortex

- Unfortunately the Prefrontal Cortex is Critical for:
  - Decision-making
  - Weighing of risks vs. rewards
  - Assigning emotional valence to stimuli
  - Suppressing limbic impulses
  - Goal-directed behaviors

MJ accounts for more teens in substance abuse treatment than any of the other substances combined.

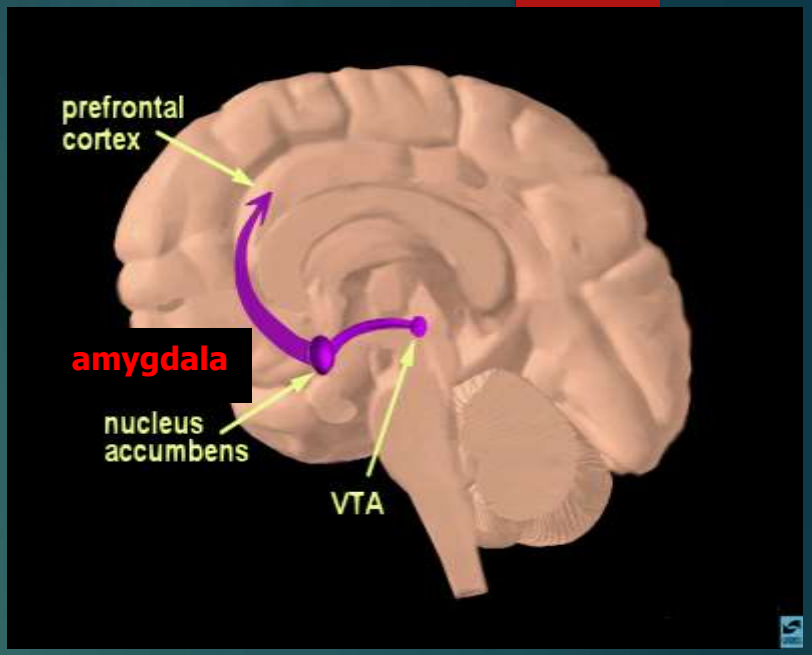


Negative consequences of MJ

- The potential harms associated with MJ use depend on two major factors:
- 1 -Age of onset of use of MJ: particularly if it's before 18. Using cannabis during key stages of brain development can impact on synaptic pruning and the development of white matter.
-
- 2 - Patterns of use: the frequency, dose and duration, particularly if you're using at least weekly. The bigger or more potent the dose, the more THC you are ingesting.

Adolescent Brain Changes

- These brain changes are relevant to adolescent behavior
  - Prefrontal cortex (PFC - Judgment) is being pruned; not fully developed until mid-20's
  - Limbic reward region: Amygdala (and Nucleus accumbens) show less pruning and tend to dominate the PFC



Risk factors for developing an addiction

- Greater activation of the brain's reward circuit accompanied by blunted executive control systems

- Greater impulsivity, poor affect regulation, and poor executive function

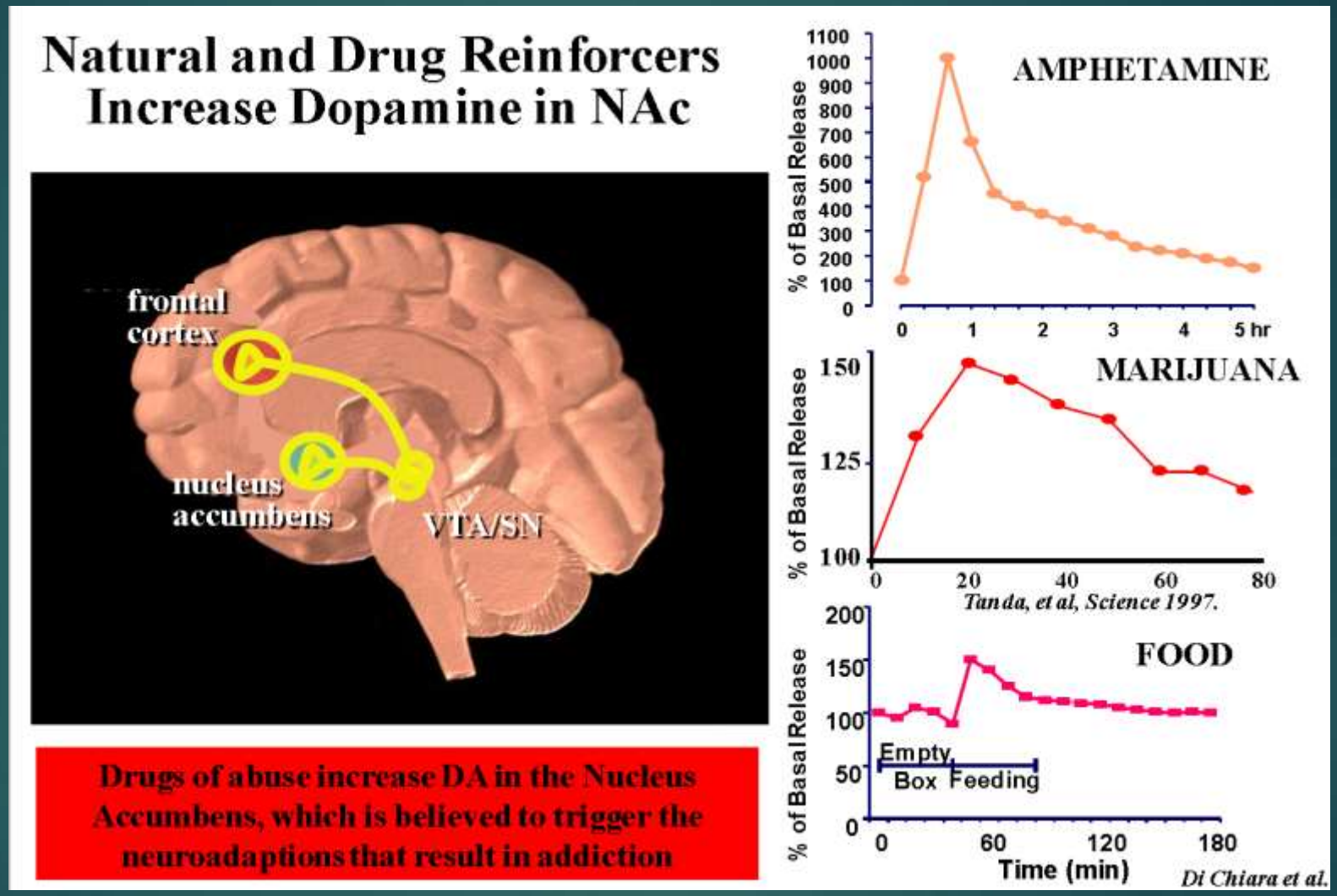
- Antisocial tendencies
- Early adversity (higher ACEs)
- Genetics (e.g., family history, genotypes)

Jacobus & Tapert, 2013, *Annual Review of Clinical Psychology, 9,* 703-721.
LovalloWR, 2013, *International Journal of Psychophysiology, 90,* 8-16.
PeetersM, 2014, *Alcohol and Alcoholism, 49,* 182-186.

Addictive Drugs in the brain

- All drugs are Trojan horses in the brain
- All addictive chemicals are mimics which look and act like an existing brain neurotransmitter, esp. dopamine (anticipation & reward chemical) & anandamide (endocannabinoid)
- Increases available amount of dopamine which produces a high; brain responds by reducing dopamine receptors; MJ reduces cannabanoid receptors
- Drugs capture reward pathways in the brain which control motivation & compulsion
- About 15% of anyone trying a drug will become addicted

Routine increase of dopamine in Nucleus Accumbens triggers Addiction



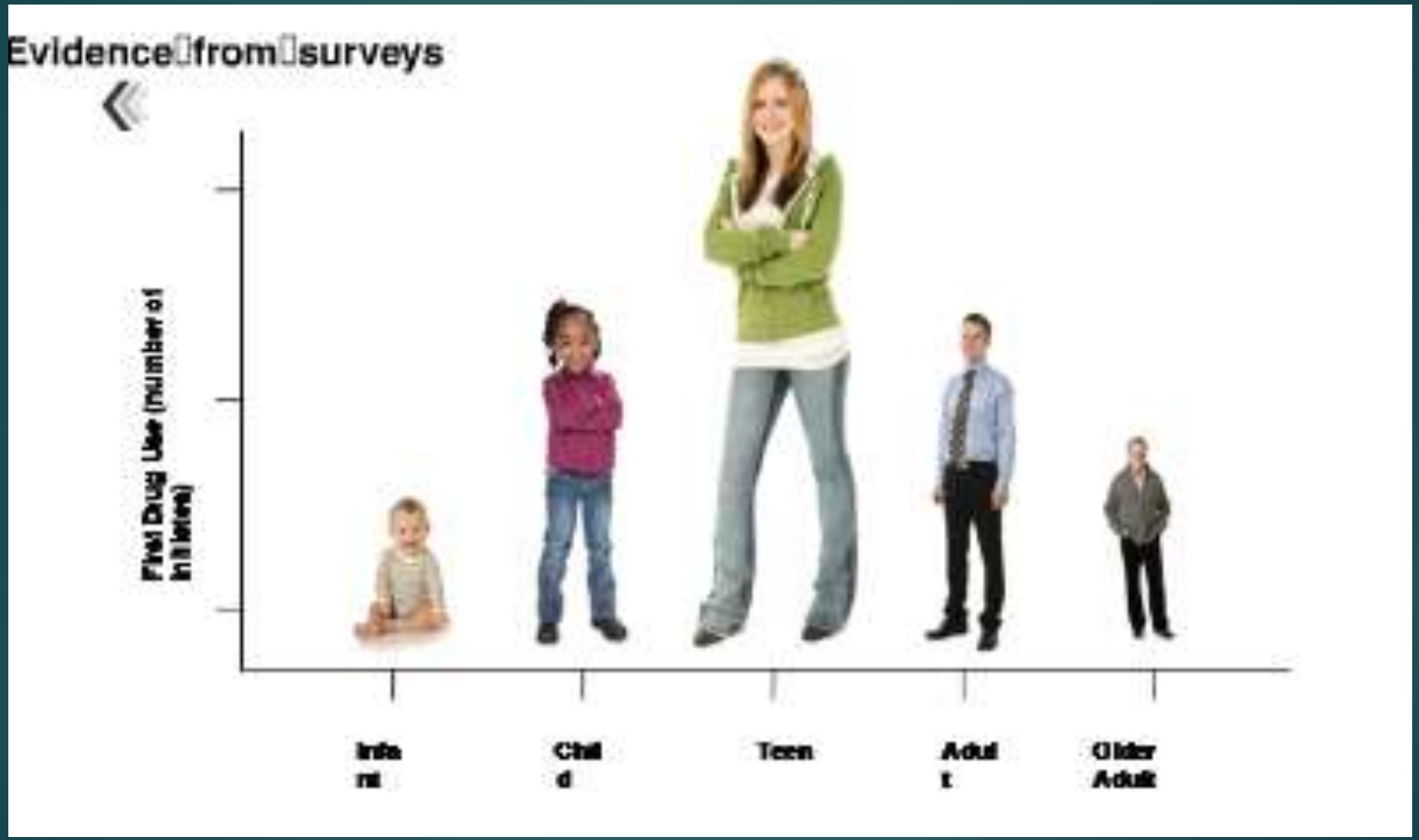
THC increase dopamine release in the “reward” or pleasure circuit of the brain, just like every other addictive drug.

Neurobiology of Risk in Adolescence: A Tale of Two Systems

- Adolescent risk taking related to two systems:
  - a) earlier maturation of subcortical limbic region (amygdala, NA)
  - b) later maturation of top-down prefrontal control region,
  - c) & context.
- Improved cognitive & behavioral control with maturation of prefrontal cortex.
- Context of behavior increases in importance (presence of other teens, alcohol & drugs, sex, etc.)
- Larger dopamine release in adolescence leads to hypersensitivity to reward which leads to risker behavior (despite knowing better)

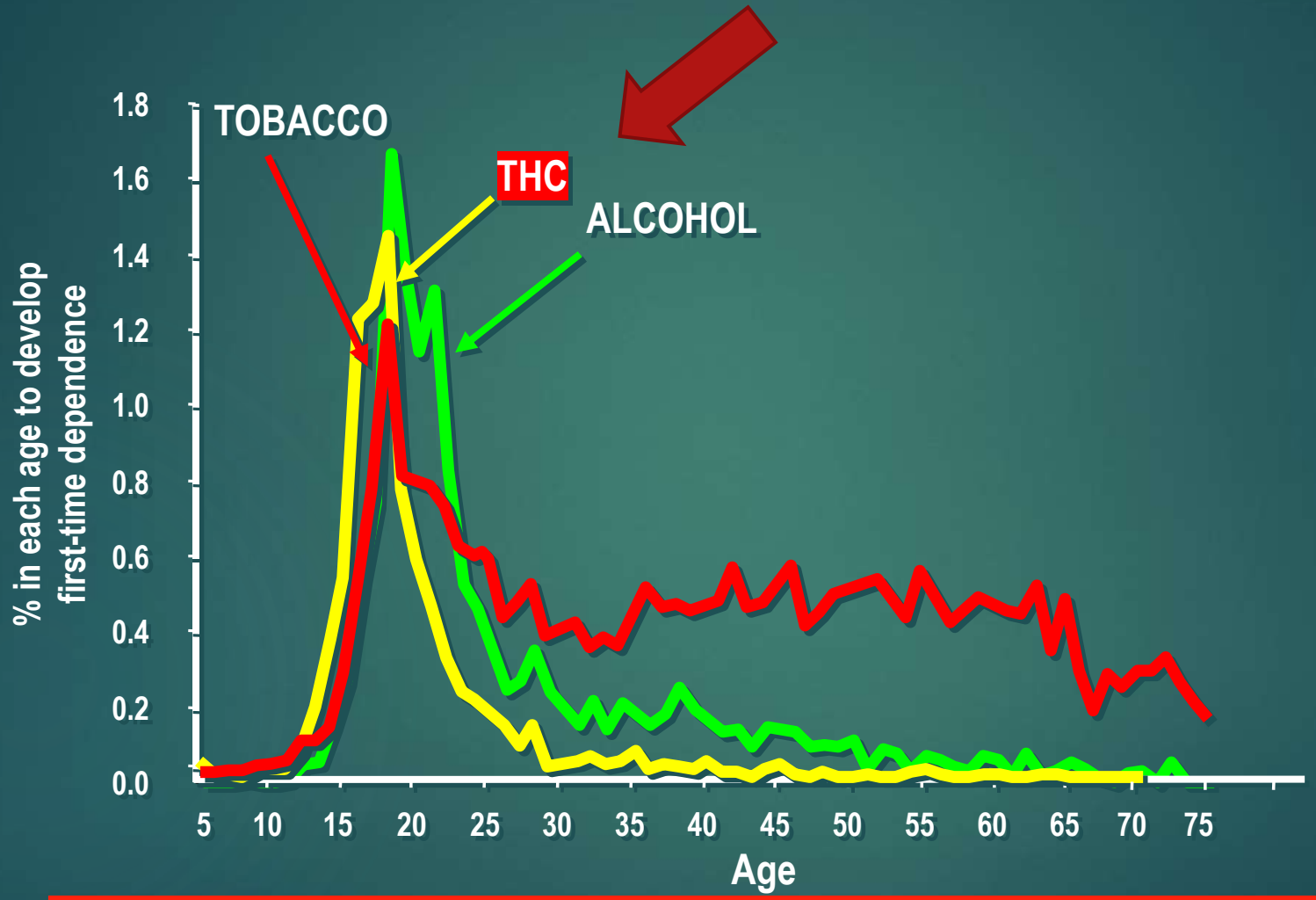
A. Galvan, 2011

Drug Use starts early and peaks in Adolescence



67% **26%**

THC addiction is a Developmental Disease

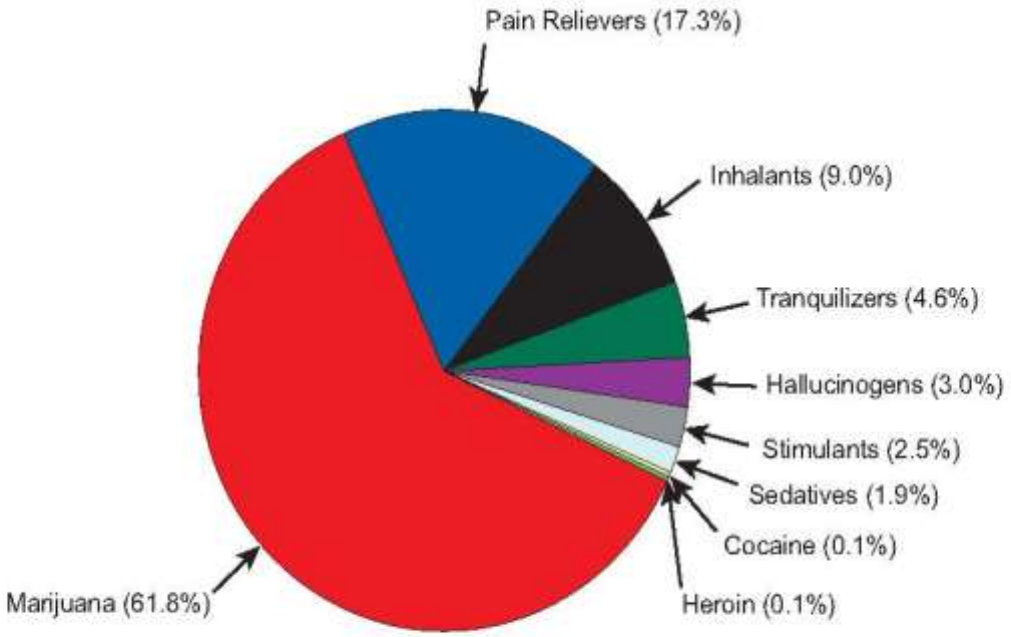


Age at tobacco, at alcohol and at cannabis dependence

National Epidemiologic Survey on Alcohol and Related Conditions, 2003

MJ leads the pack of first time use (61%) of any illicit drug

Figure 5.1 First Specific Drug Associated with Initiation of Illicit Drug Use among Past Year Illicit Drug Initiates Aged 12 or Older: 2010



3.0 Million Initiates of Illicit Drugs

Note: The percentages do not add to 100 percent due to rounding or because a small number of respondents initiated multiple drugs on the same day. The first specific drug refers to the one that was used on the occasion of first-time use of any illicit drug.

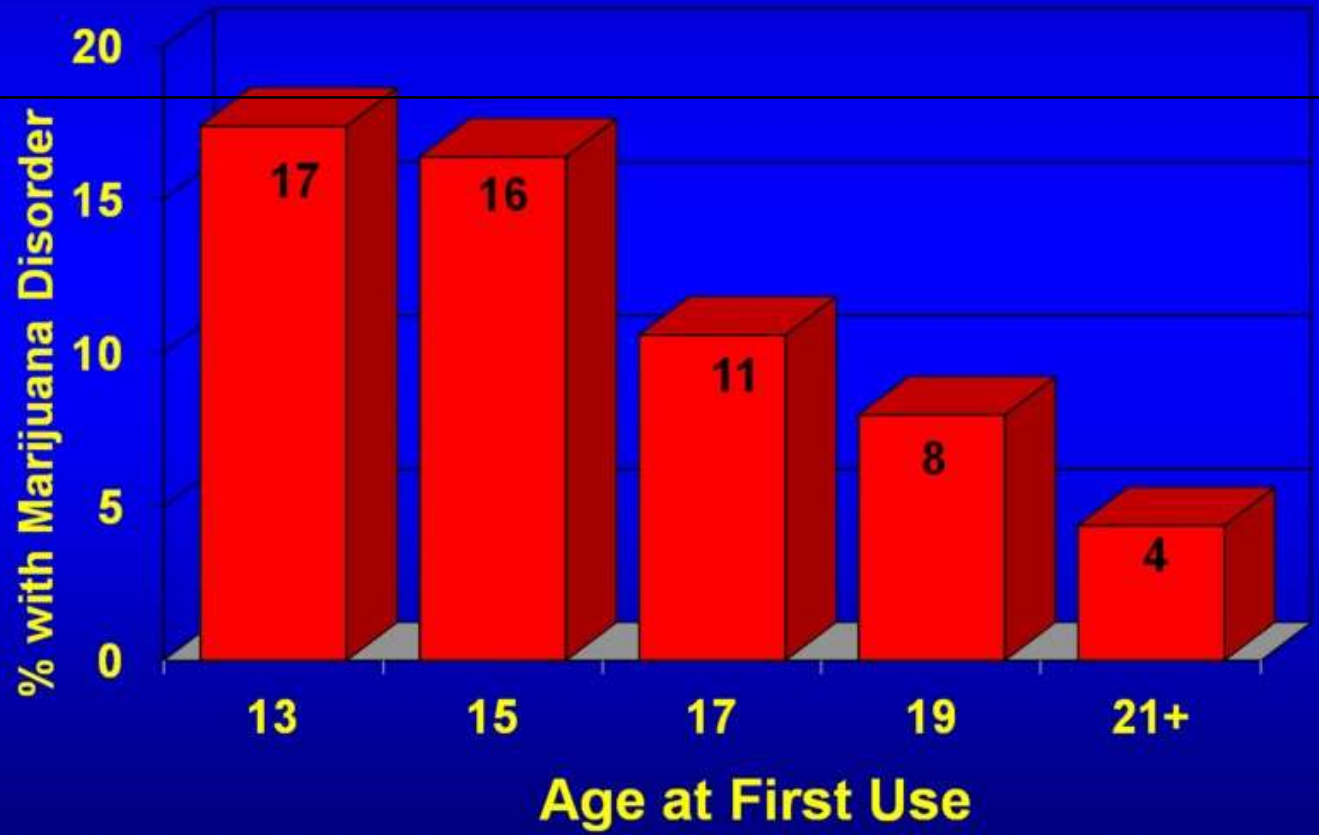
Marijuana Interactions with Addictive Substances

- Not a gateway drug per se:
- but it is often the first illicit drug used
- & those who use it are much more likely to become cocaine or heroin addicted.

- Marijuana is an addictive drug

- Use of marijuana by a recovering alcoholic or a drug addict is correlated with a greater incidence of slips and relapses

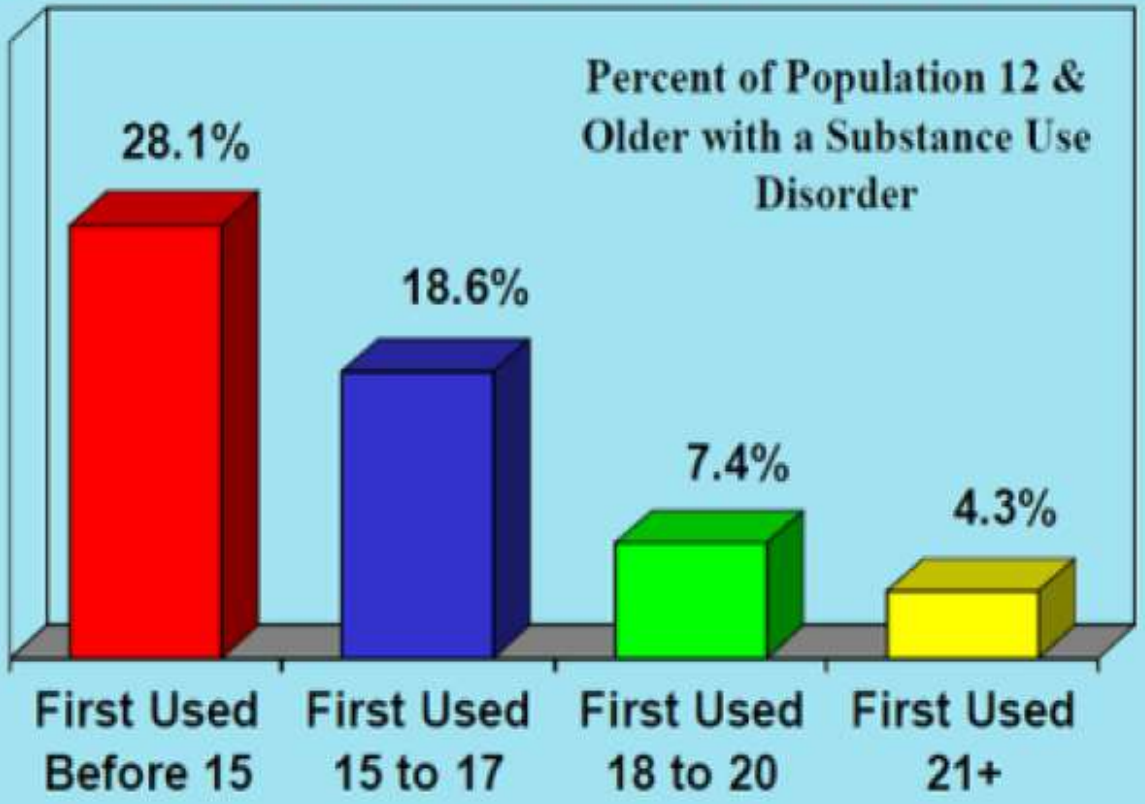
Younger Age at First Use Has Higher Risk of Marijuana Dependence



Source: Substance Abuse and Mental Health Services Administration. (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings* (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586Findings). Rockville, MD.

COLUMBIA

The Earlier Teens Use Any Substance, the Greater the Risk of Addiction



Source: CASA analysis of the *National Household Survey on Drug Use and Health* (NSDUH), 2009.

Tolerance and Tissue Dependence

Marijuana Tolerance

- Rapid development to most marijuana effects

Tissue Dependence

- Seen with daily use of 2-3 “joints” over several weeks (500mg ave. X 15% = 75 mg)

- 3 C’s: Classic loss of control, compulsive use, cravings and continued use despite development of negative consequences

- Abstinence induces physical withdrawal syndrome

Relation Between Marijuana & other Drug Use

- Early age of onset is a major predictor both of continued frequent marijuana use & of likelihood of using other drugs

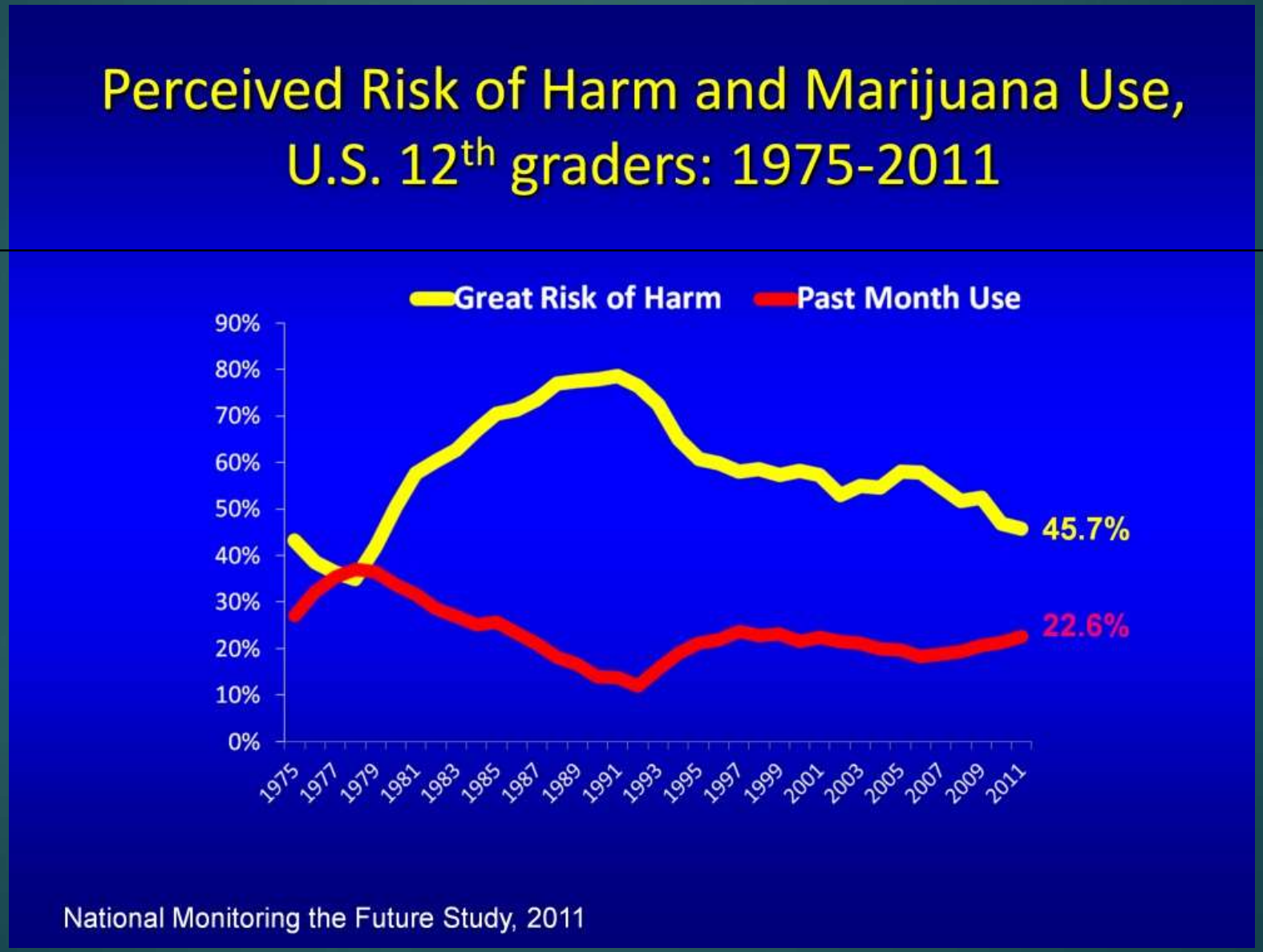
- The increased potency of marijuana may make the brain less responsive to endogenous cannabinoids.

- Combination of earlier onset & stronger potency may increase anxiety & apathy in teens & make other drug use more attractive

- Twin studies found early marijuana users had increased rates of other drug use and problems later on; odds of other drug use ranged from 2.1-5.2 times higher

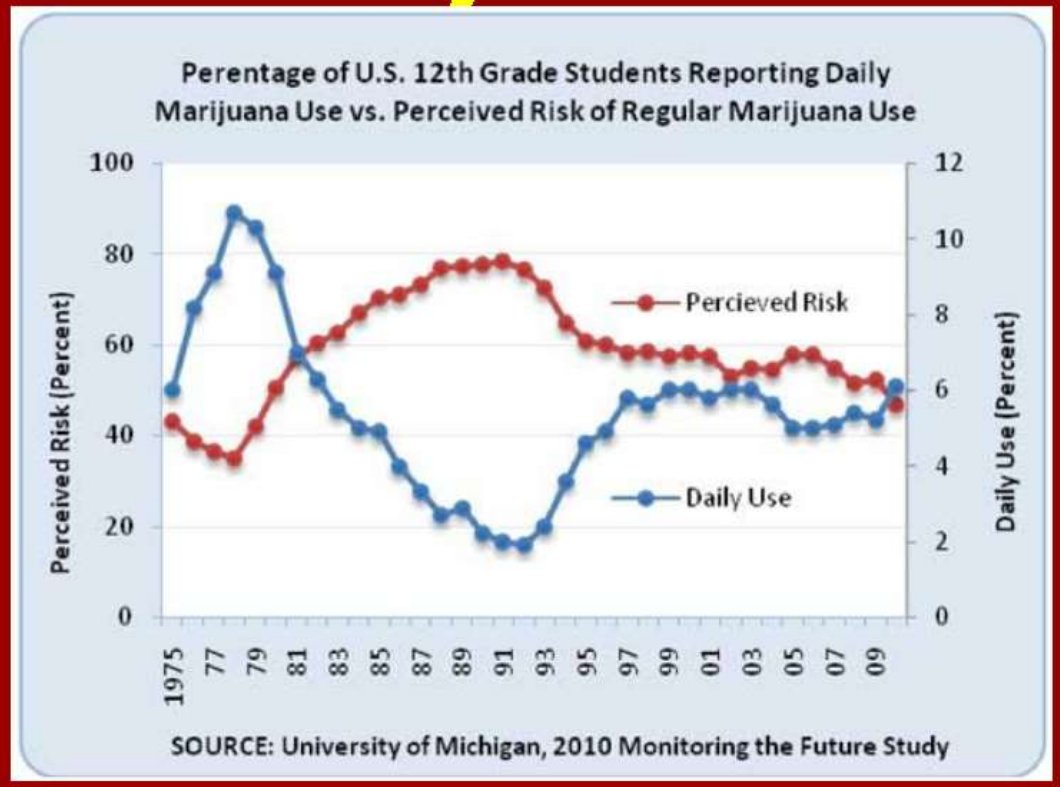
(Denenhardt, et al. 2001, Lynsky, et al. 2003)

46% of adolescents now think MJ is less harmful



2013: 61% of HS Seniors don't view MJ as harmful

Correlation of Perceived Risk and Marijuana abuse



2013

60.5% HS Seniors in 2013 Don't View regular Pot Use As Harmful & 6.5% use daily Monitoring the Future Survey 2013

Statistics

- Teenagers and young adults are now using MJ more frequently than smoking cigarettes

- 1 in 6 (17%) teenagers who regularly smoke the drug become dependent

- It doubles risk of developing psychotic disorders, including schizophrenia

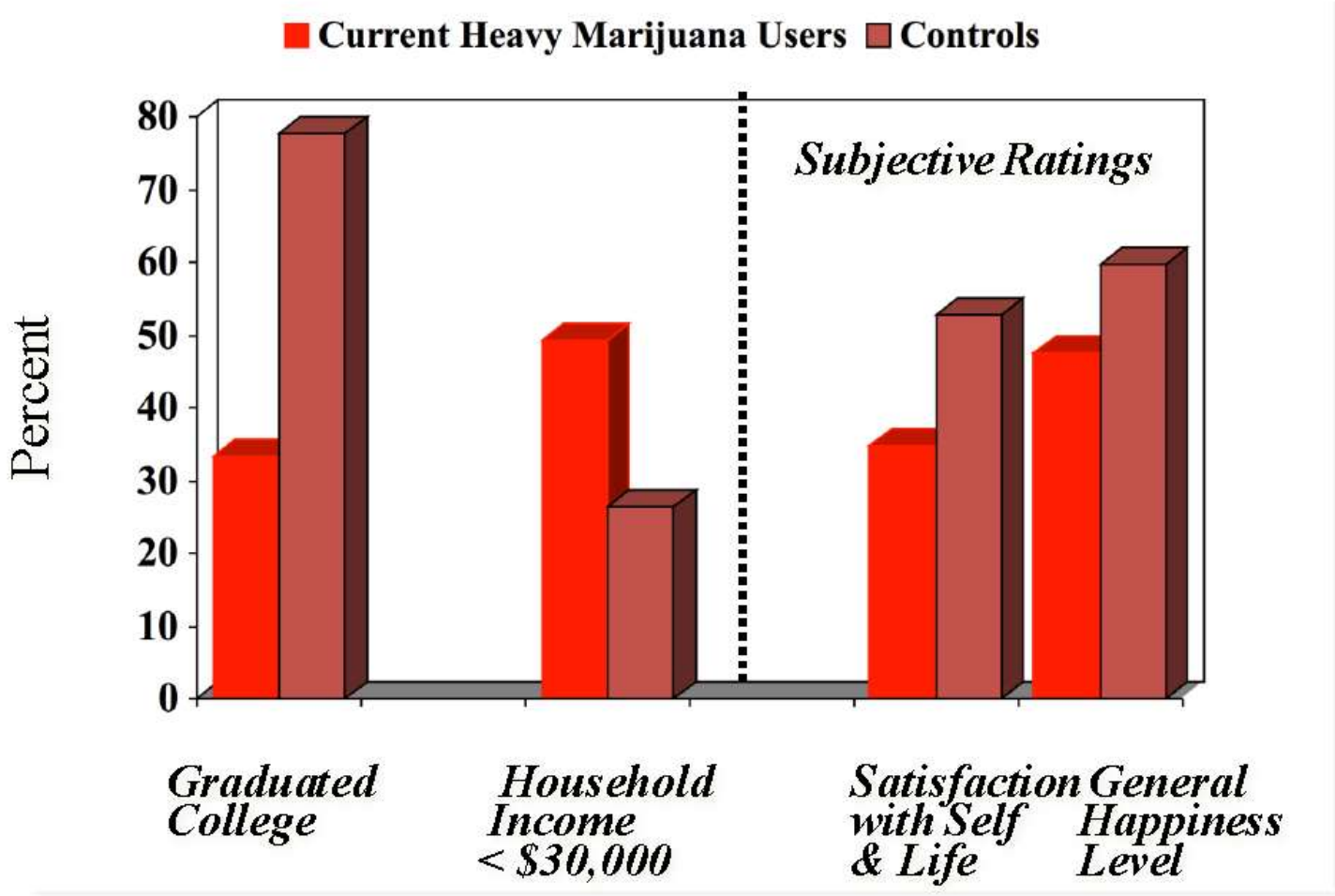
- Cannabis users do worse academically.

- Heavy use in adolescence appears to create long term NP deficits.

Statistics 2

- Driving after smoking cannabis doubles risk of having a car crash
- Smoking it while pregnant reduces the baby's birth weight
- MJ is addictive: heavy users experience a withdrawal syndrome as with alcohol and heroin.
-
- Rates of recovery among those seeking treatment are similar to those for alcohol (50%)

Negative consequences of heavy MJ use



Source: Gruber, AJ et al., Psychological Medicine, 33, pp. 1415-1422, 2003.

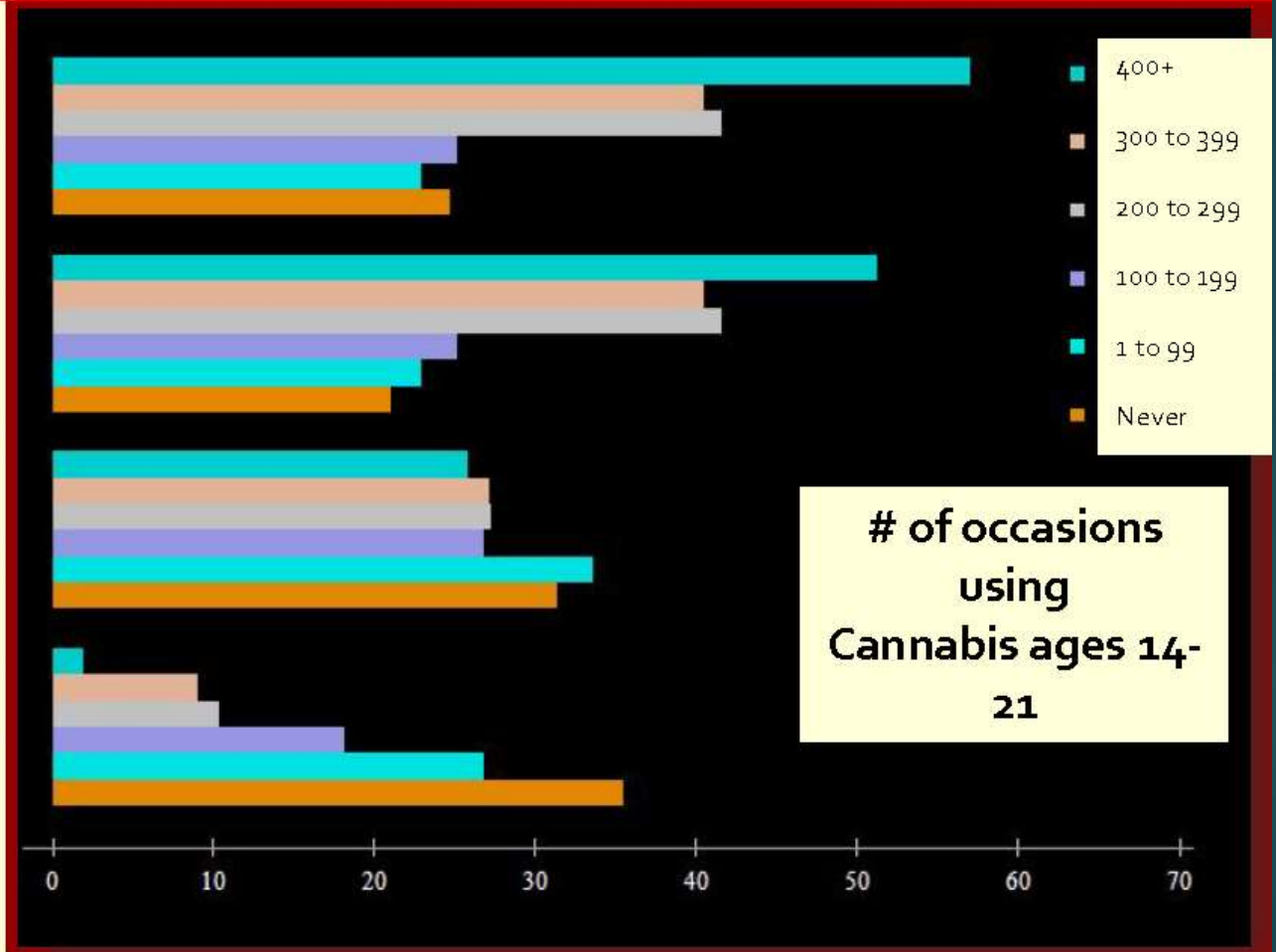
More Use of Cannabis Associated with Worse Social Outcomes at Age 25 (New Zealand Study)

% welfare dependent (ages 21-25)

% Unemployed (ages 21-25)

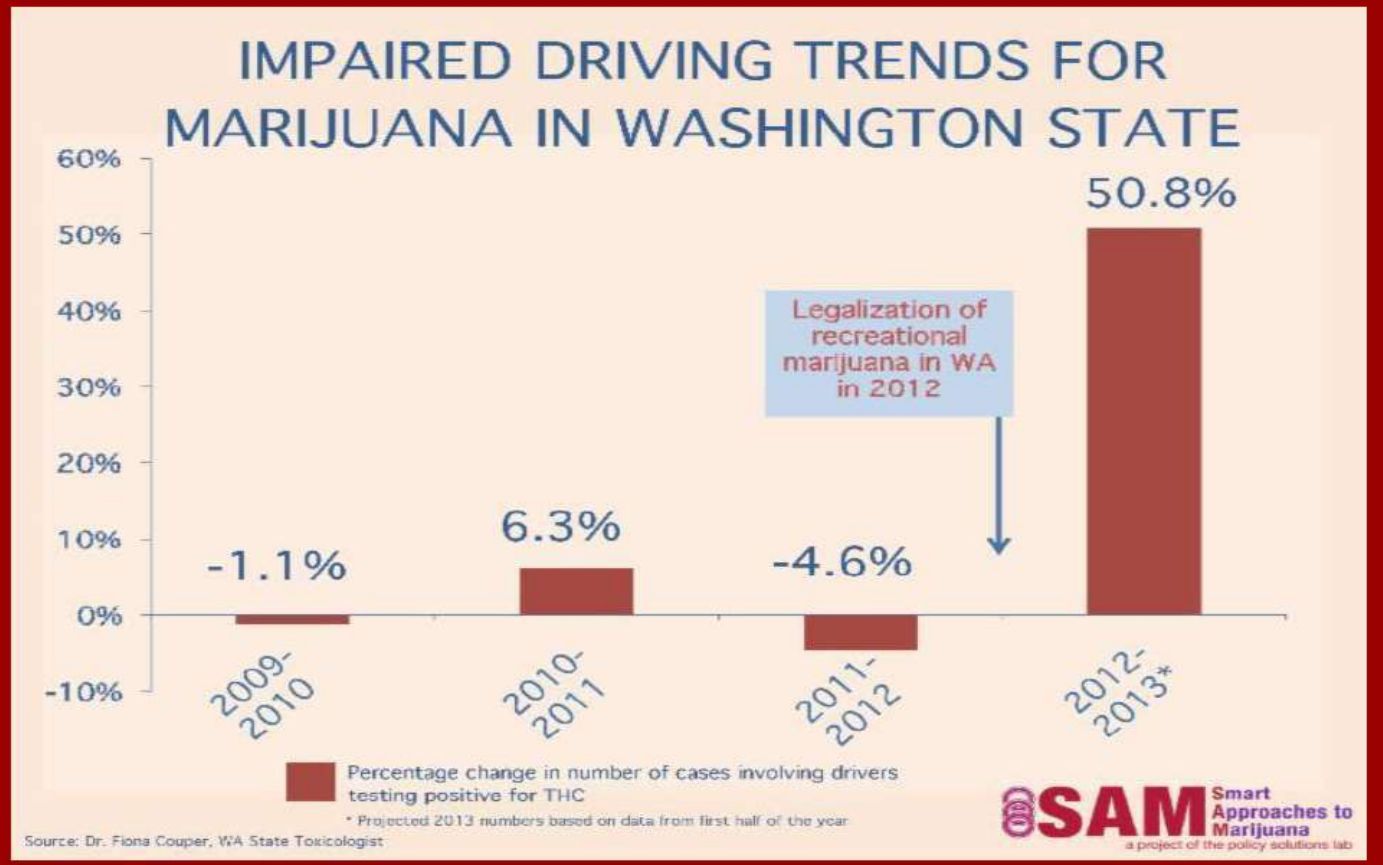
mean personal income in thousands of NZ $ at age 25

% gained university degree by age 25

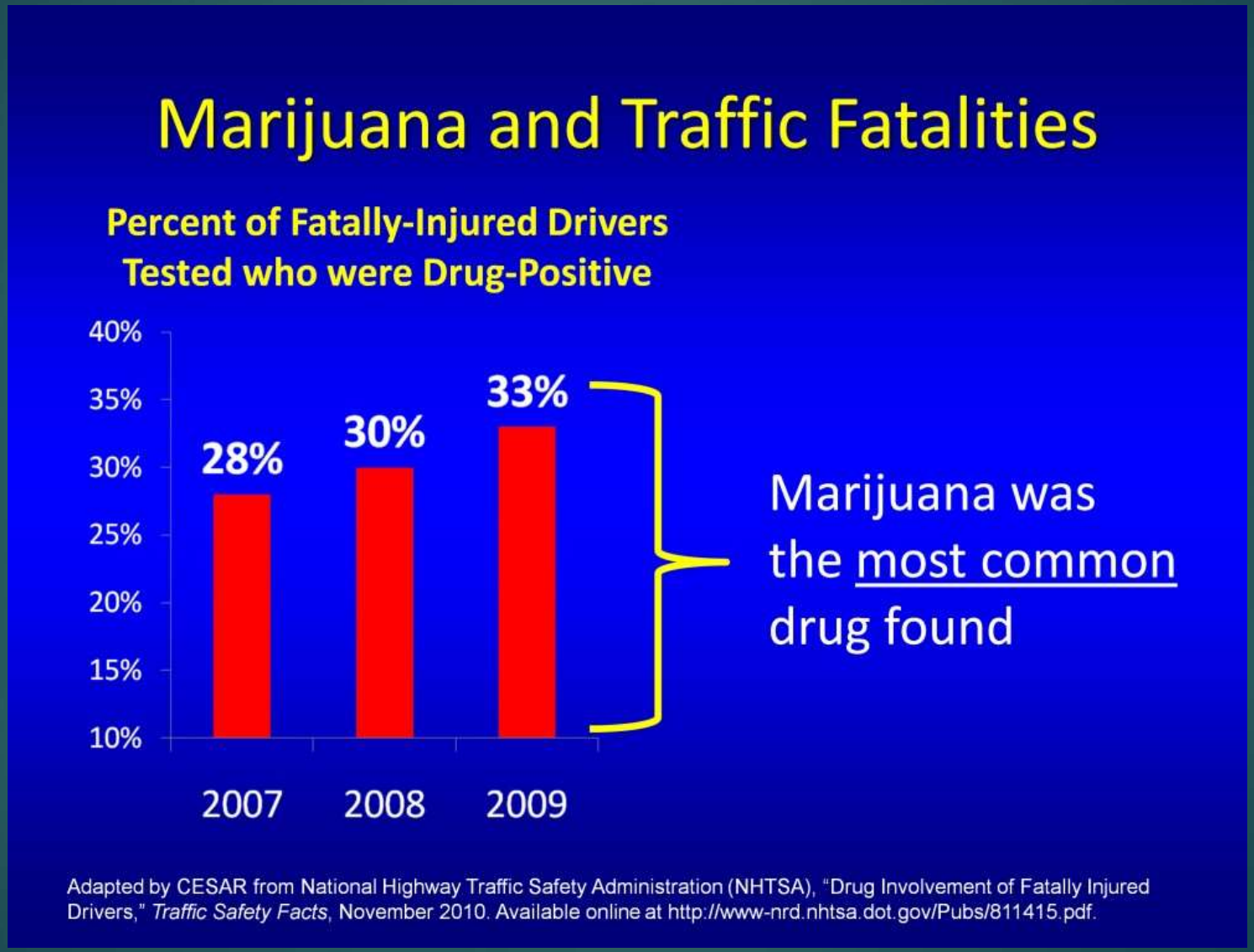


Source: Fergusson and Boden. Addiction, 103, pp. 969-976, 2008.

50% Projected Increase in Marijuana-Impaired Auto Accidents in 2013



Increasing Fatal MJ Drugged while Driving

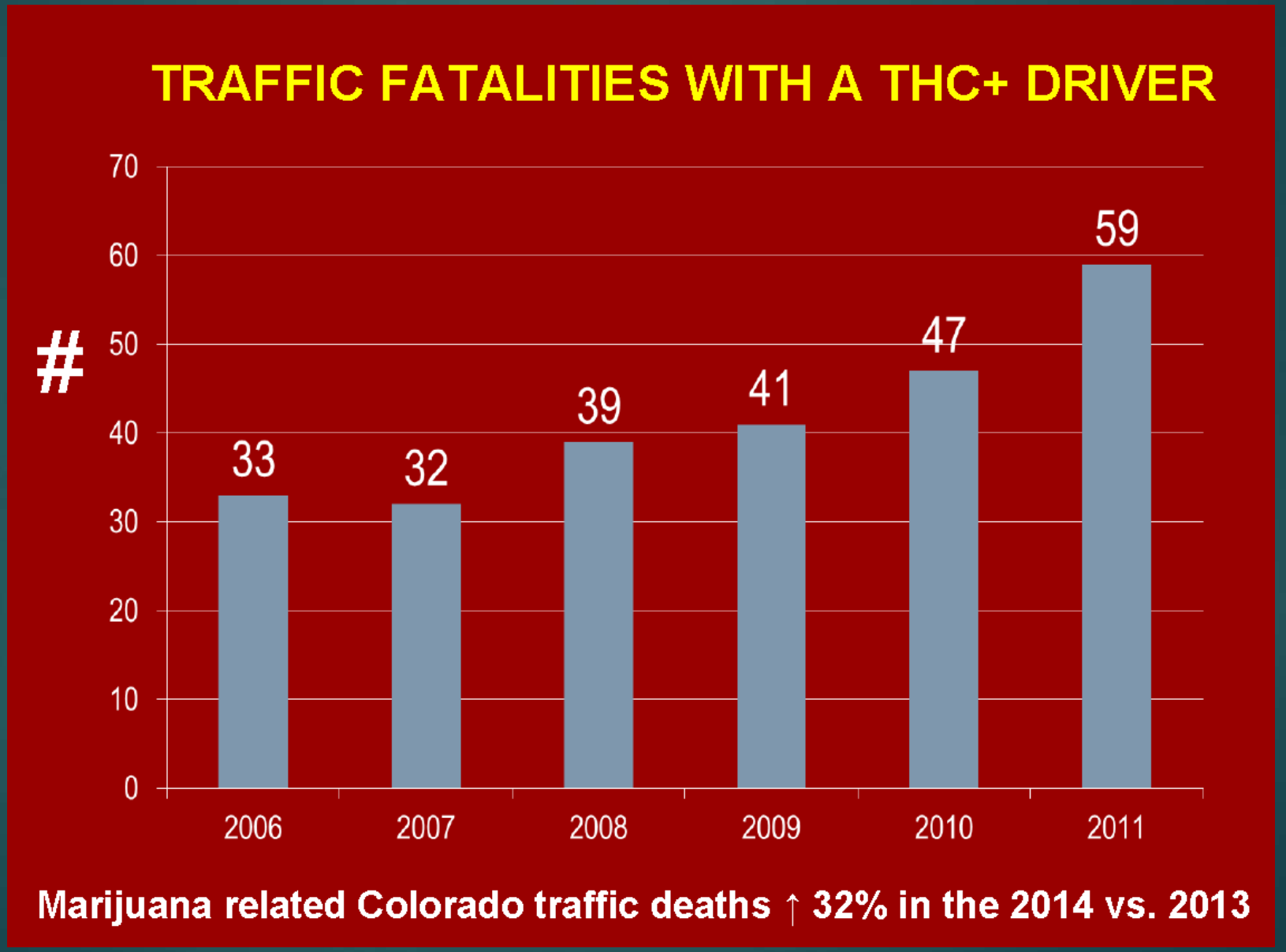


Cannabis – most prevalent illicit drug identified in impaired drivers

- Risk of involvement in a motor vehicle accident (MVA) increases 2-fold after cannabis smoking.
- Vision, coordination, judgement, movement, memory are all affected by THC. These are all, of course, important for driving.
- Cannabis smoking increases lane weaving and impaired cognitive function.
- Combining cannabis with alcohol enhances impairment, especially lane weaving.

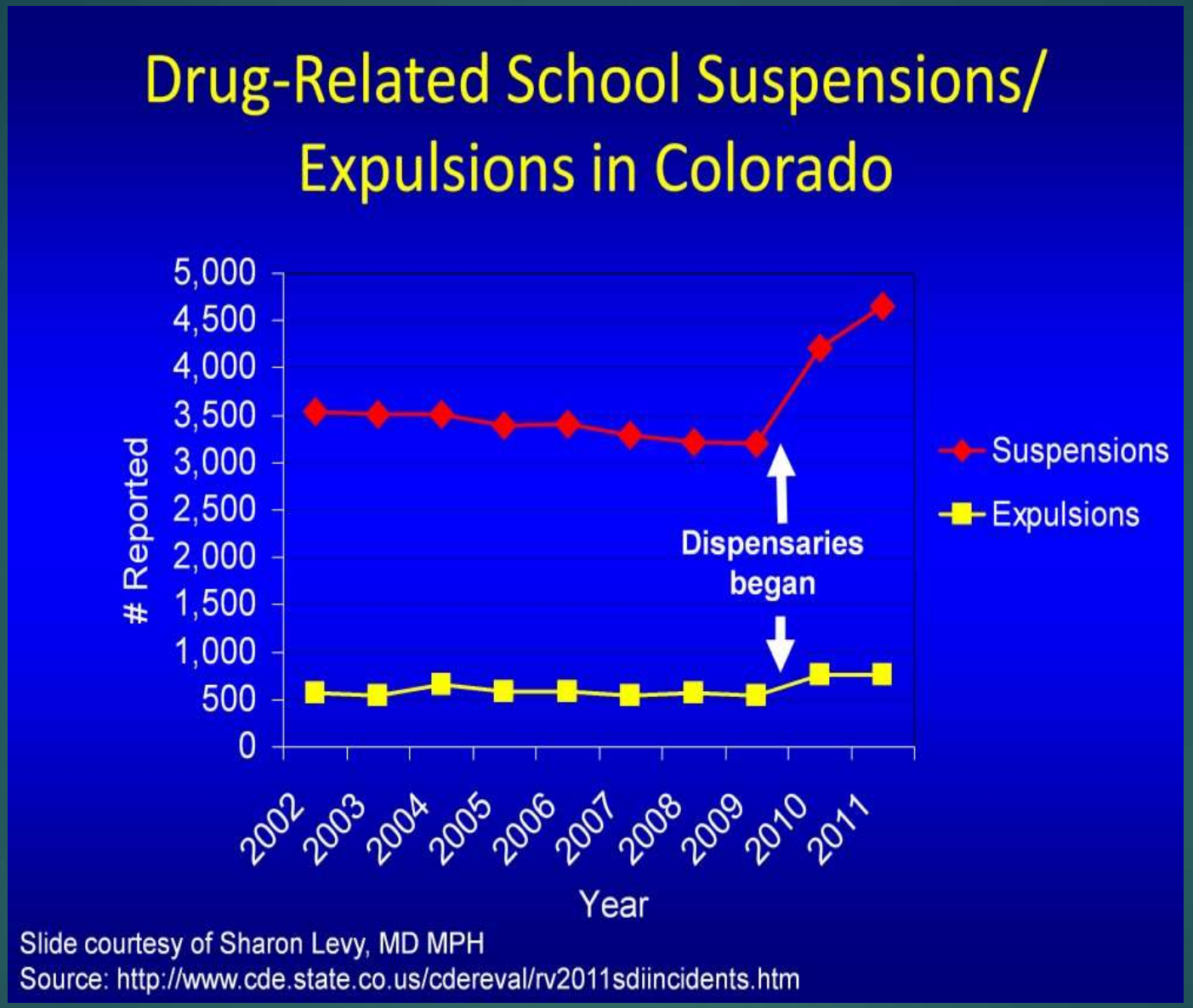
Hartman RL, Huestis MA. Cannabis Effects on Driving Skills. 2013; 59(3): 478-492.

No field sobriety test for MJ



25 States and D.C with Medical MJ Laws 2014 & 2 (CO, WA) permit Recreational Use as of 2013

- Residents of Medical MJ States have:
  - Higher rates of MJ Use
  - Higher rates of MJ abuse/dependence
  - Much Lower Adolescent Perception of MJ being Harmful
  - Much Higher Adolescent Average MJ Use



Curiously, the Colorado Department of Education also saw a steep increase in the number of drug-related school suspensions and expulsions starting between 2009 and 2010, right when the dispensary system started.

MJ and greater Neuropsychological deficits

- Increasing evidence that adolescent cannabis use onset results in greater neurocognitive deficits compared with adult onset, especially very early onset

- Regular exposure to exogenous cannabinoids may disrupt healthy neurodevelopment, especially in the PFC and parietal cortices, which underlie higher-order cognitive functioning. This early initiation during the sensitive period of adolescence may place individuals at risk

- Weekly cannabis use before age 18 has been linked with deficits neuropsychological tasks.

Importance of Neuropsychological Deficits to TX

- Neuropsychological Deficits interfere with Treatment:
  - Memory limitations
  - Executive Functional Deficits

- Psychogenic or Neurogenic Interpretation:
  - Psychological lack of motivation vs. neurological impairment:
    - Nature of denial/lack of awareness: anosognosia
      - MJ users, esp. early onset types, with significant PFC deficits will exhibit neurogenic denial of deficits (anosognosia) – they truly do not know they have a problem

Modal Neuropsychological Findings in all SA

Big 4 Major Neuropsychological Deficits:

Executive Functioning
Explicit Memory, esp. nonverbal
Visual Spatial
Motor Ability

Deficits are mild to severe

Negative Neuropsychological effects of MJ use

- Marijuana use has been shown to impair functions such as attention, memory, learning and decision-making. Those effects can last for days to years after the high wears off.

- Heavy marijuana use in adolescence or early adulthood has been associated with a dismal set of life outcomes including:
  - poor school performance & lower educational attainment,
  - increased truancy & higher dropout rates,
  - amotivational behavior
  - increased welfare dependence,
  - greater unemployment
  - and lower life satisfaction.

- Is MJ to blame?: Causal agent in these outcomes, or is it part of a number of vulnerability factors?

Note of caution about NP research

- Correlation is not causation.
- MJ use does not occur in a vacuum: less stable background (higher ACEs), behavioral issues, school issues, etc.
- Deficit cognitive performance of cannabis users may result from other factors associated with cannabis use, rather than cannabis use itself.
- Teenagers who use cannabis are much more likely to use cigarettes, alcohol and other illicit drugs, which have own NP deficits
- It's a classic chicken-egg question.

Adverse Childhood Experiences Are Common

Household dysfunction:

Substance abuse	27%
Parental sep/divorce	23%
Mental illness	17%
Battered mother	13%
Criminal behavior	6%

Abuse:

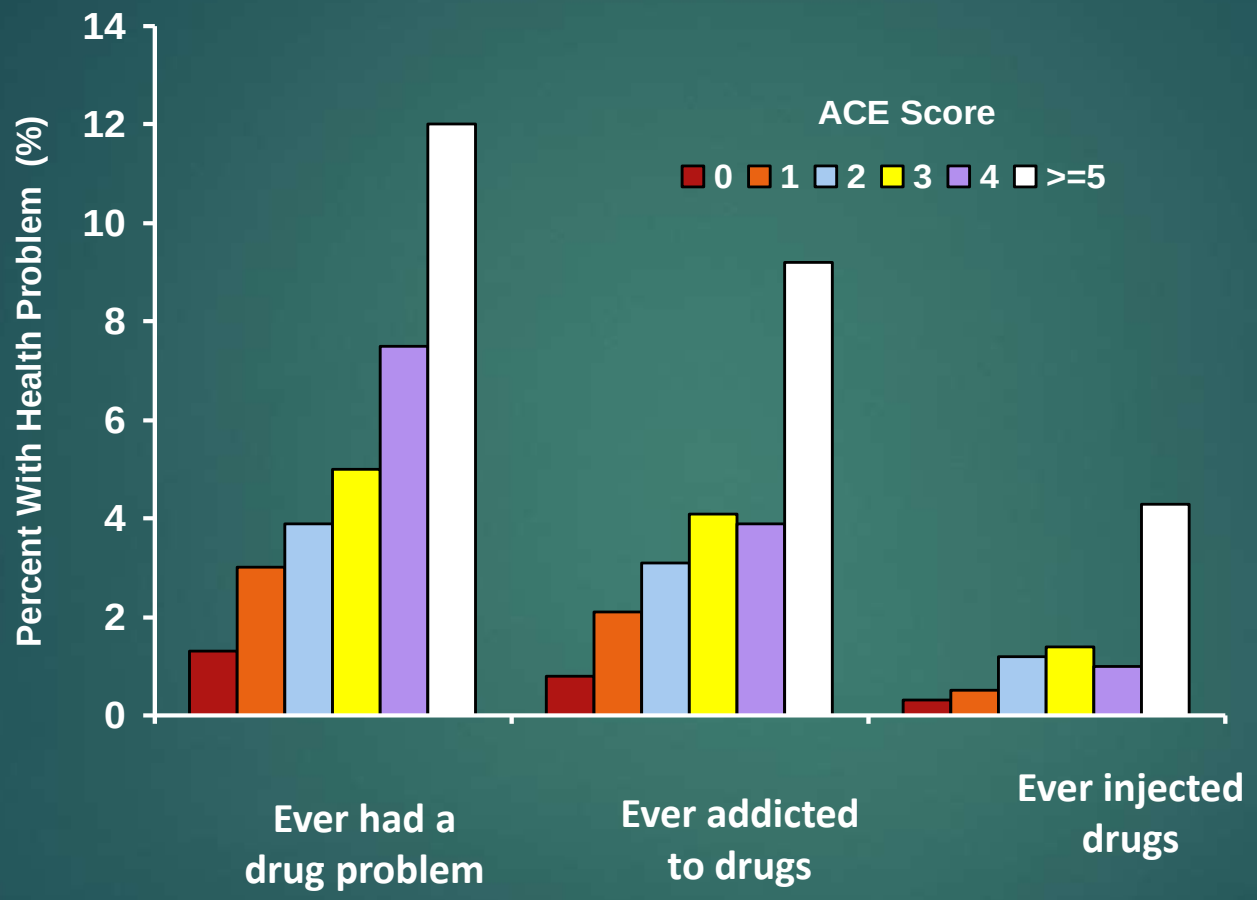
Psychological	11%
Physical	28%
Sexual	21%

Neglect:

Emotional	15%
Physical	10%

V. Felletti

ACE Score and Drug Abuse

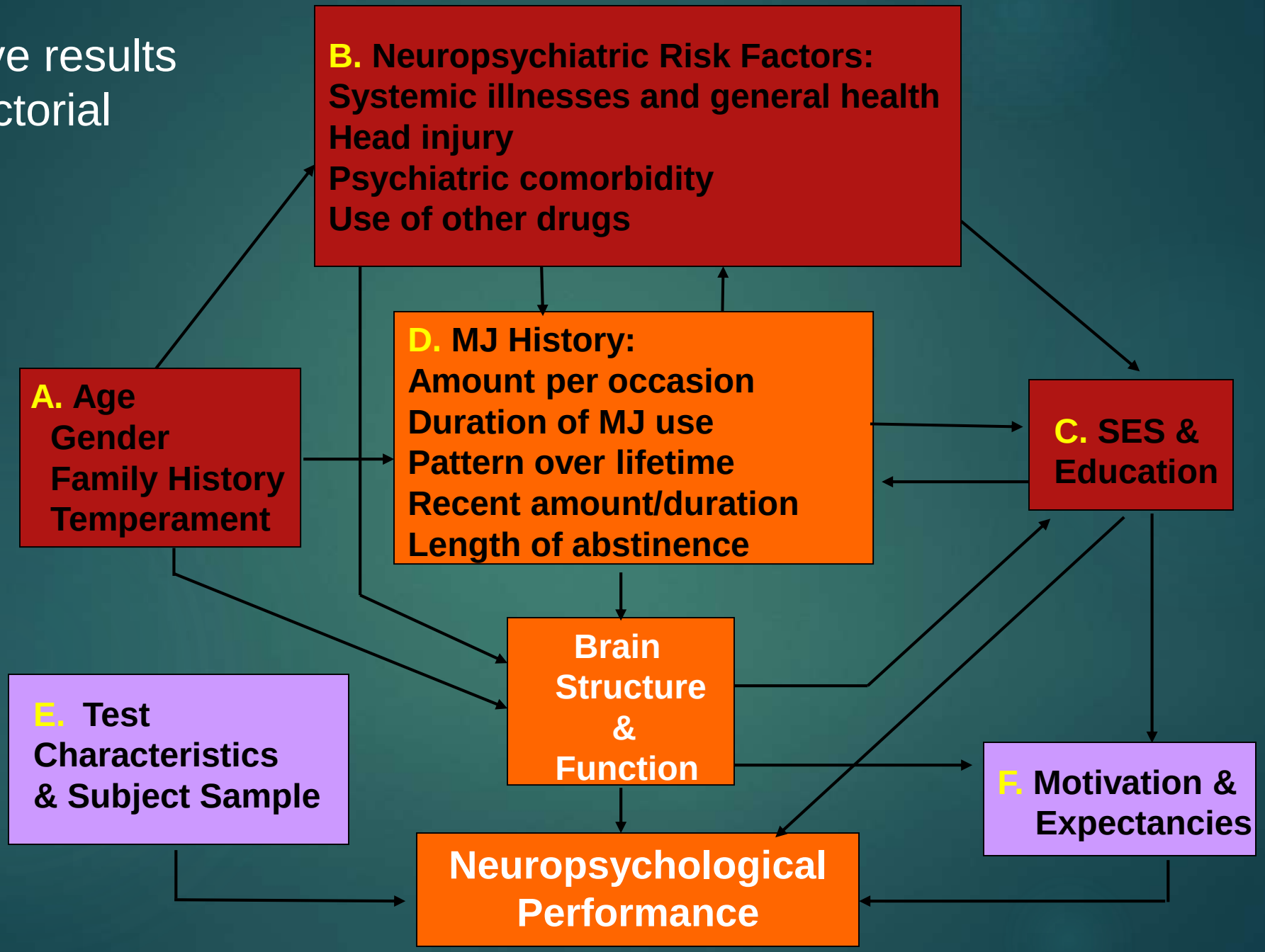


Neuropsychological Testing Performance

Neuropsychological testing performance outcome in MJ users is highly multifactorial in nature

MJ use is not the only cause of deficits.

MJ cognitive results are multifactorial

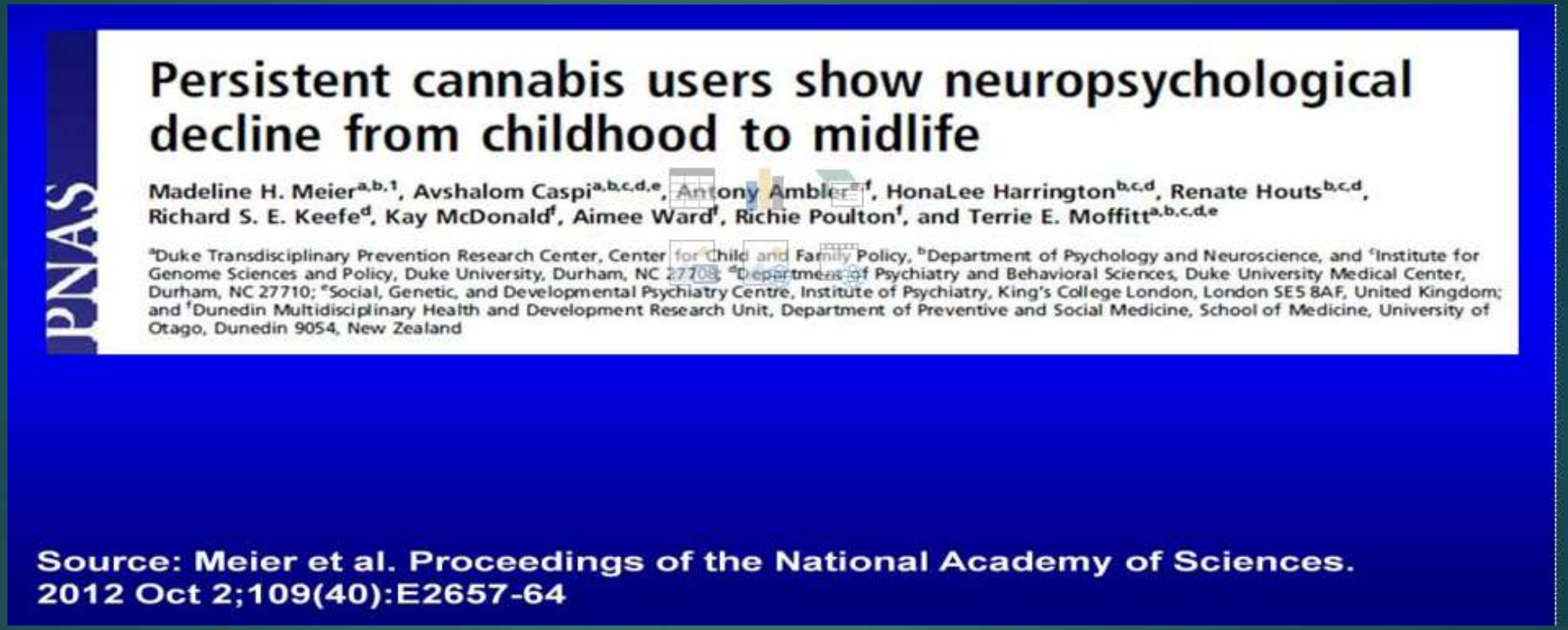


ADHD and Chemical Dependency

- Compared with controls, adults with ADHD have a:
  - 3 to 4-fold higher rate of marijuana and cocaine use
  - 3-fold higher rate of alcohol abuse
  - utilize tobacco 40% more

- ADHD Treatment with stimulants reduces CD relapses

The 2012 Controversial Study



PNAS

Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

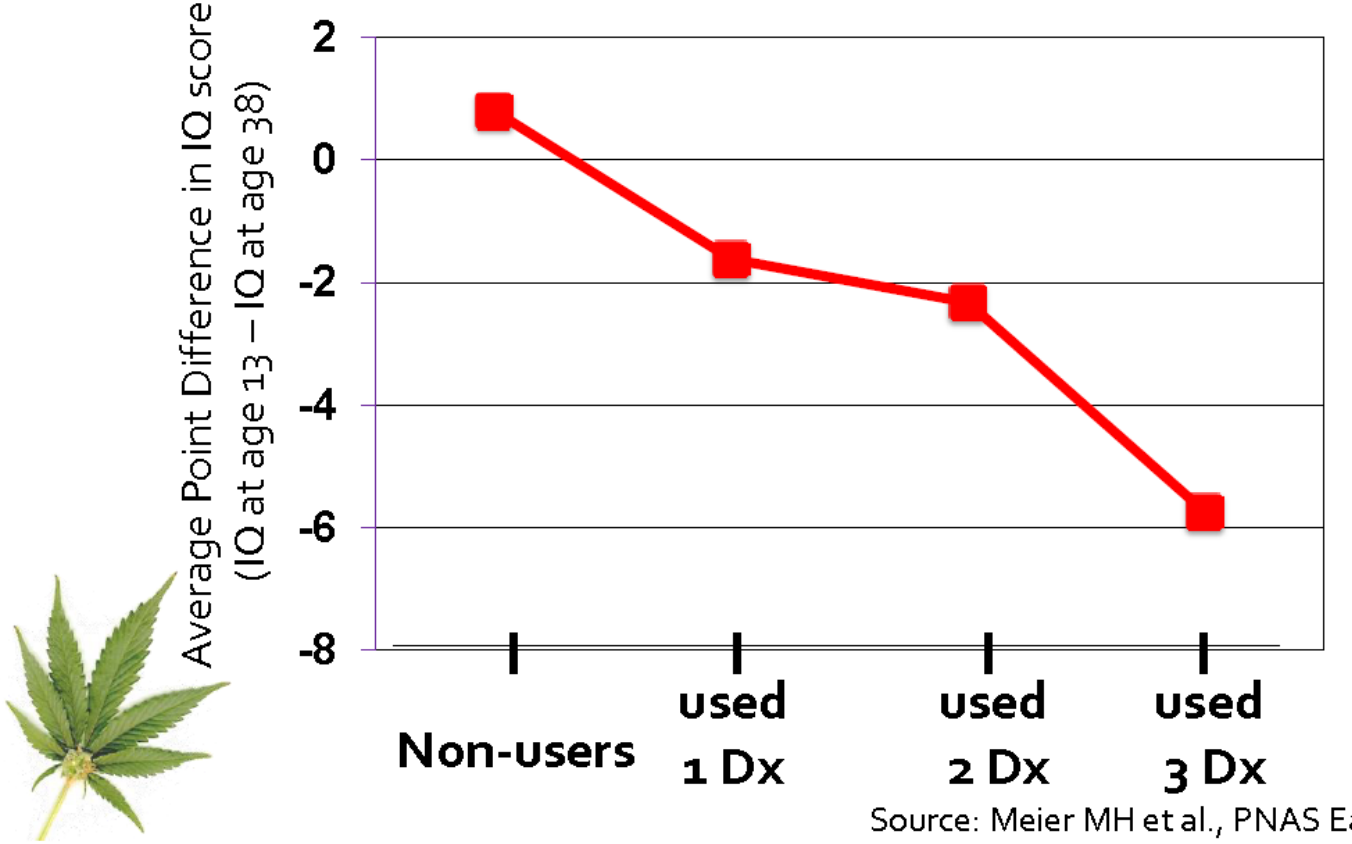
[a]Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, [b]Department of Psychology and Neuroscience, and [c]Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; [d]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; [e]Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and [f]Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Source: Meier et al. Proceedings of the National Academy of Sciences. 2012 Oct 2;109(40):E2657-64

2012 Meier study that set off alarm bells: 6% IQ drop

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

MJ and IQ decline

- In the largest prospective, longitudinal study to date, Meier and colleagues, 2012, followed a sample of 1,037 from birth to age 38 and found that 153 participants met criteria for cannabis-use disorders (CUD) at least once during the follow-up and individuals with more persistent cannabis use demonstrated the greatest reduction in IQ. Used self report of use.

- 2012 Dunedin, New Zealand, study (Meier): significant declines in IQ between ages 13 and 38 in heavy users compared with those who used marijuana occasionally before age 18 or not at all. Decline in Verbal IQ and Digit Symbol. Deficits persisted after 1 y cessation.

- Many dxed with MJ addiction. Study failed to rule out other potential explanations for the decline in IQ, such as a teen's family environment, whether they dropped out of school. Did not occur solely because cannabis users completed fewer years of education.

- They also found specific deficits in executive functioning, sustained attention, verbal list learning, and psychomotor speed associated with persistent cannabis dependency

Other research shows no IQ decline

- But then…
- 2016 twin study, 789 twins: analyzed long-term marijuana use in teens, comparing IQ changes (Vocabulary & Information) in twin siblings who either used or abstained from marijuana for 10 years.
- While MJ users showed greater decline than nonusers, no measurable link between marijuana use and lower IQ. Both groups lost 4 IQ pts.
- Attributable to familial factors that underlie both marijuana initiation and low intellectual attainment.
- But flaw is that they did not measure quantity of use and 2 subtests are best hold tests in brain damage

Jackson, et al., 2015

MJ and IQ

- 3rd Study, 2016: 2235 British adolescents of pre-15 age users (2 year follow up, only 3% had 50x of use; these used in last 3 days before age 15 testing):
  - cannabis users had lower teenage IQ scores and poorer educational performance than teenagers who had never used cannabis
  - higher rates of childhood behavioral problems, childhood depressive symptoms, other substance use (including use of cigarettes and alcohol) and maternal use of cannabis during pregnancy.
  - No IQ decline: teenage cannabis use alone does not appear to predict worse IQ outcomes in adolescents;
  - cigarettes more important for IQ and education outcome; Brits smoke MJ with tobacco

- Does not proves that marijuana—particularly heavy, or chronic use—is safe for teenagers. Need studies of duration, frequency, and dose affect on the brain. All prior studies use self report of use.

- Impossible to tell which came first: drug use or poor cognitive performance. It's a classic chicken-egg scenario.

C Mokrysz, et al. 2016

MJ and Cognitive deficits

- Evidence is building to suggest that regular cannabis use during the teenage or emerging adult years (typically ages 15–25 years) is associated with cognitive deficits.

- Two longitudinal studies that followed adolescents with substance use disorders over 8 years found that increased cannabis use during the follow-up period significantly predicted poorer attention and verbal memory.

- Early-onset cannabis users exhibit poorer cognitive performance than late-onset users or control subjects

Cannabis / Marijuana/ THC

- Intoxication: widespread Cognitive ↓
- Acute Deficits (24 hours):
  - Attention, Executive, immediate recall, RT, time underestimation
- Long Term Deficits, Chronic Use:
  - subtle working memory↓, Digit Symbol ↓, EF ↓,
  - amotivational syndrome?
- Dependence: Memory, sustained attention, EF, RT ↓

Schwartz, 1991; I. Grant, 1978

Acute Effects of MJ

- Produces sedation, mood elevation & occasionally hallucinations.
- There is no dispute that cannabis produces cognitive impairment during acute intoxication; effects can be shown using driving or flight simulators; esp. memory & learning
- Primary immediate cognitive effect: adverse effects on learning & memory, etc.
- Primary adverse effect of acute marijuana use is diminished psychomotor performance: marijuana has been found to play a significant role in car accidents with 33 percent of drivers arrested at the scene of the accident being positive for marijuana

Temporary Residual Effects (1996-2003): Definite Negative NP effects

Pope & Yurgelun-Todd (1996)	Yes (24 hrs)
Fletcher et al. (1996)	Yes (72 hrs)
Pope et al., 2001,2002, 2003	Yes (7 days)
Solowij et al., 1998, 2002	Yes (17 hrs)
Grant et al. (meta-analysis, 2003)	No, overall

Long-term Residual Effects (1998-2003): Mixed results

Lyketsos et al., 1999	No (10-yr follow-up)
Pope et al., 2001,2002, 2003	No (28 days)
Solowij et al., 1998, 2002	Yes (Up to 2 years)
Bolla et al., 2002	Yes (25 days)
Grant et al. (2003)	No, overall
Korver et al. (2010)	Yes
Shrivastava (2011)	No, overall
Lishadl, et al. (2014)	Yes

Latest studies

- 2014 Lisdahl Review:
  - Grey matter abnormalities
    - Both smaller and larger hippocampal & other area volumes - these structural alterations in gray matter were associated with increased executive dysfunction, mood symptoms, poor verbal memory, and novelty seeking suggesting that these structural abnormalities were not advantageous
    - abnormalities in gray matter architecture, including reduced cortical gyrification complexity, increased volume that may reflect disrupted healthy gray matter pruning, and decreased structure that may reflect reduced dendritic branching or neuronal atrophy
  - White matter abnormalities: Less white matter integrity
    - reductions in white matter
    - reduced white matter quality in several PFC, limbic, parietal and cerebellar tracts

Krista Lisdahl, et al., 2014

2014 Lisdahl Review

- Other:
  - Increased network connectivity with increased task complexity
  - neuronal and microglia toxicity
  - Changes in multiple neurotransmitter functioning
- Adolescent cannabis use onset results in greater neurocognitive deficits compared with adult onset & greater structural and functional brain abnormalities

DARE TO DELAY? THE IMPACTS OF ADOLESCENT ALCOHOL AND MARIJUANA USE ONSET ON COGNITION, BRAIN STRUCTURE, AND FUNCTION

(LISDAHL ET AL. JULY 2013 | VOLUME 4 | ARTICLE 53 | 1, WWW.FRONTIERSIN.ORG)

This article provides a comprehensive review of studies of MJ and cognitive functioning. Thus far, human findings suggest that earlier MJ use onset (MUO), typically defined as **use starting before16–18years old**, is associated with more **severe cognitive consequences**.

Results suggest:

- ↓ IQ
- ↓ Visual search
- ↓ Processing speed
- ↓ Verbal memory

↓ Attention: complex and simple

↓ Executive functions

↓ Sequencing ability

↓ Cognitive inhibition

- ↑"Risky" sexual behavior
- ↑ Depressive symptoms

↑ Impulsivity

Latest studies

- Abnormalities in gray matter have been found in 16- to 19-year-olds who increased their marijuana use in the past year.

- Recent 2015 study: Marijuana use may be major predictor of bipolar cycling in at risk bipolar individuals

Chronic cannabis users, by their own admission, are not happy campers

What effect has marijuana had on your…

	Positive	Neutral	Negative
Social Life?	**5%**	**25%**	**70%**
Physical Health?	**0**	**19%**	**81%**
Mental Health?	**24%**	**16%**	**60%**

Unhappy campers 2

What effect has marijuana had on your…

	Positive	Neutral	Negative
Cognition?	**2%**	**8%**	**91%**
Memory?	**0**	**8%**	**91%**
Career?	**0**	**21%**	**79%**

Marijuana Effects

- Dose relationship with negative effects.
- Reduced memory efficiency, at least during THC use
- Subtle chronic effects even with adolescent users

MJ and Cognitive deficit

- Cross-sectional studies in cannabis-using youth without psychiatric comorbidities report:

- Cannabis-related cognitive deficits in:
  - processing speed,
  - complex attention,
  - verbal memory,
  - executive functioning
  - risky sexual behavior

2002: Dose-related neurocognitive effects of marijuana use

- Study of 28-day abstinent heavy marijuana abusers.
- Persistent, negative dose-related effects are found on tests measuring verbal and visual memory, executive functioning, visuoperception, psychomotor speed, and manual dexterity.
- There was also an association between increasing marijuana use and decreasing executive cognitive functioning. Performance was not clinically abnormal.
- The hippocampus, prefrontal cortex, and cerebellum play a major role in these functions. All of these regions are dense with cannibinoid receptors, and these results are biologically plausible because THC has been shown to cause deleterious effects on these brain regions

K.I. Bolla, et al., 2002

Age of Onset of MJ use and Cognitive Dysfunction

- Severity of the effects of cannabis use on cognitive development is dependent on the age when cannabis use begins.

- From a more biological perspective, however, use of cannabis during critical developmental periods in the still maturing brain may induce persistent alterations in brain structure and brain function.

- Most commonly and consistently reported are response time, prolongation of word viewing time, basic oculomotor deficit, residual verbal memory and executive functioning

Korver N, et al., 2010

Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions

- These deficits differ in severity depending on the quantity, recency, age of onset and duration of marijuana use.

- Individuals with cannabis-related impairment in executive functions have been found to have trouble learning and applying the skills required for successful recovery, putting them at increased risk for relapse to cannabis use

Rebecca D. Crean, et al., 2011

Earlier Age of onset: more EF deficits

- Earlier published reports using traditional neuropsychological assessment methods typically show a resolution of deficits by 28 days of abstinence.
- Newer neuroimaging research: subtle, long-term effects of cannabis on cognition and brain functioning
- Deficits change as a function of the quantity of cannabis consumed and duration of use .
- Starting between 14–22 years old and stopped by age 22: significantly more cognitive problems at age 27 than their non-using peers
- Users who began smoking before the age of 17 had significant impairments in measures of executive functioning, including abstract reasoning, verbal fluency, and verbal learning and memory

Bolla et al., 2005; Solowij et al., 1995; 2002; Grant et al., 2003; Brook et al., 2008; Pope et al., 2003

MJ and EF: acute effects

- Acute Effects of MJ on EF (0 to 6 hours after use):
- Disruptions in
  - Attention/concentration ↓↓ in light users
  - Sustained attention ↓↓
  - Learning and memory functions ↓↓
  - information processing speed ↓↓
  - planning and decision making ↓↓
  - inhibition ↓↓
  - working memory ↓↓ ↓↓

Rebecca D. Crean, et al., 2011

MJ and EF: long term effects

- Long-term effects of MJ on EF (3 weeks or longer since last use):
  - Normal attention or concentration (28 days to 1 y) vs impaired
  - Impaired decision-making and risk-taking
  - Impulsivity & inhibition: Normal Stroop, Impaired WCST - intact set shifting and maintenance but impairment in concept formation, planning and sequencing
  - Normal Working Memory
  - Impaired Verbal Fluency in onset pre-17

Rebecca D. Crean, et al., 2011

Rebecca D. Crean, et al., 2011: Meta-analysis

A Summary of Research Findings on the Effects of Cannabis on Executive Functions

Executive Function Measured	Acute Effects	Residual Effects	Long-Term Effects
Attention/Concentration	Impaired (light users) Normal (heavy users)	Mixed findings	Largely normal
Decision Making & Risk Taking	Mixed findings	Impaired	Impaired
Inhibition/Impulsivity	Impaired	Mixed findings	Mixed findings
Working Memory	Impaired	Normal	Normal
Verbal Fluency	Normal	Mixed findings	Mixed findings

Note: Acute Effects denotes 0–6 hours after last cannabis use; Residual Effects denotes 7 hours to 20 days after last cannabis use; Long-Term Effects denotes 3 weeks or longer after last cannabis use.

MJ and Brains: Prefrontal Working Harder

- Brains of teens that use marijuana are working harder than the brains of their peers who abstain from the drug

- Heavy marijuana use during adolescence is associated with:
  - poorer performance on thinking tasks,
  - including slower psychomotor speed
  - poorer complex attention, verbal memory and planning ability.

- Adolescent marijuana users are using more of their frontal and parietal cortices to complete cognitive tasks

Medina, 2008

MJ & Cognition Conclusions

- There is no clear consensus on whether cannabis produces long-term IQ decline.
- Regular cannabis use (several times a week) is associated with impaired NP functioning – both by objective measures and by the admissions of users themselves
- MJ use, esp. chronic and early onset, appears to predict long-term NP deficits; leaning toward negative consequences but more research needed

Tips about cognitive functioning in your patient

- Need to know:
  - Age of onset of MJ use
  - Duration of use
  - Quantity of use
  - Recency of use

- Check for Executive Functioning: do a MoCA or refer for NP testing

- EF deficits have a negative impact on self basement and treatment success

Clinical Recommendations

- If MJ user had early onset and heavy usage:
  - Need to do some brief cognitive assessment early
- MoCA: Montreal Cognitive Assessment
- http://www.mocatest.org/
- If significant deficit, may need formal NP testing.

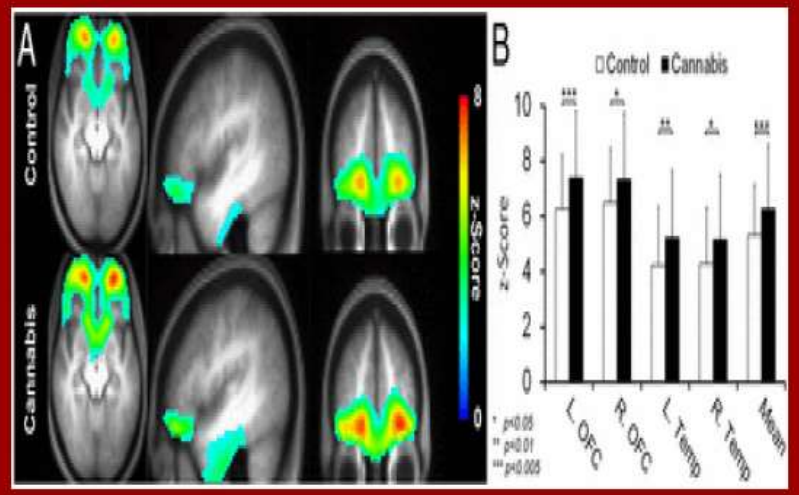
Neuroimaging Research

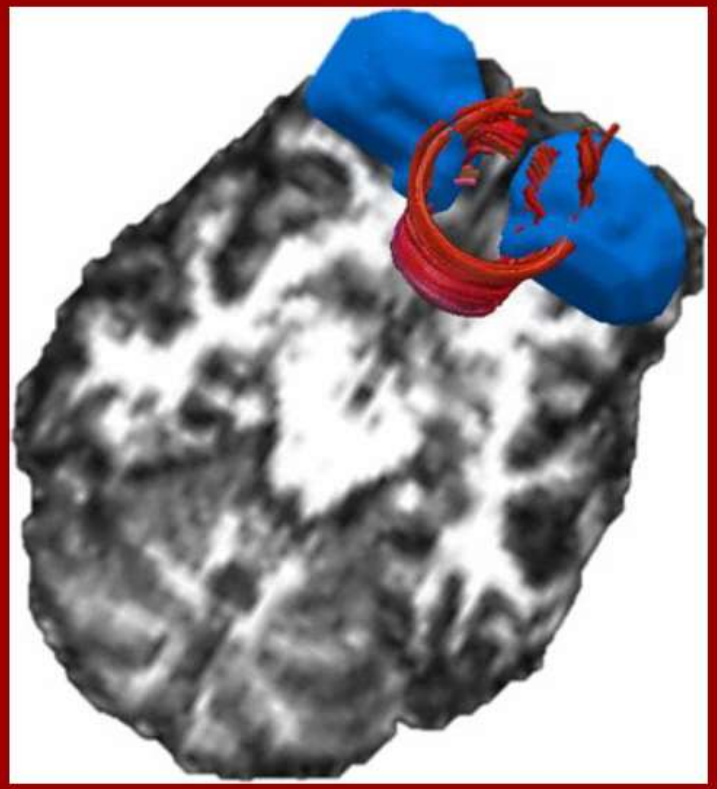
Long-term effects of marijuana use on the brain

Filbey, FM et al. (2014) PNAS 111(47):16913-16918 UC Davis

Significant reduction in gray matter volume of bilateral orbitofronto gyri of Marijuana uses compared with controls

Also, Structural/functional connectivity of OFC regions and OFC with Temporal Gyri increased in pot users



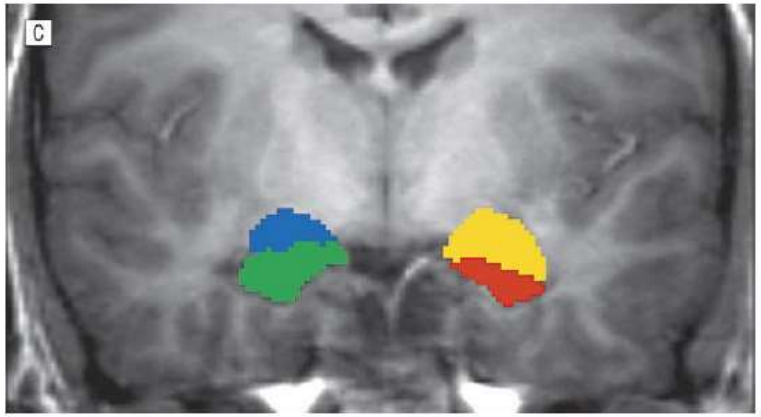


Too much or too little connectivity isn't Good for brain function. An equal Balance is needed Filbey, FM et al. 2014, PNAS

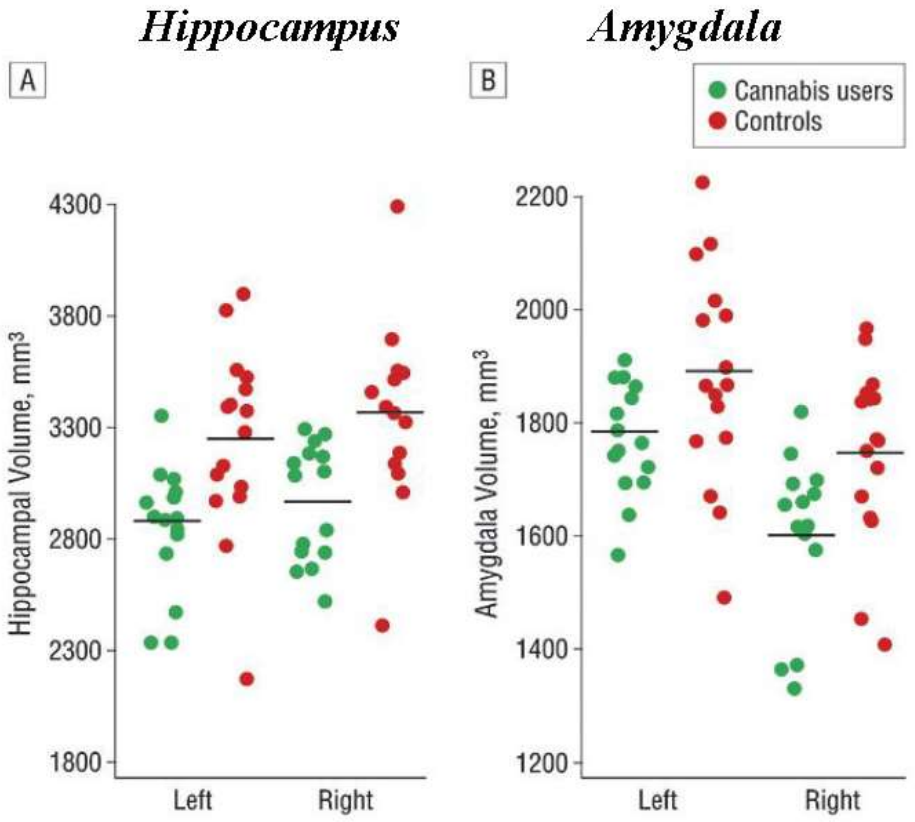
Overconnectivity is negative

Chronic MJ use reduces size of hippocampus and amygdala

Brain abnormalities associated with long-term heavy cannabis use



Tracings of left (yellow) and right (blue) amygdalae and left (red) and right (green) hippocampI.



Hippocampal (A) and amygdalar (B) volumes were smaller in cannabis users than in non using control subjects.

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

MJ and Memory: Odd shaped hippocampus

- Memory and MJ: Study of 97 people in their early 20s who used the drug daily for three years in their teens: found they had an odd-shaped hippocampus, which is vital to memory.

- They performed 18 per cent worse in long-term memory tests compared to those who had never smoked the drug.

- Longer the participants were abusing marijuana, the greater the differences in hippocampus shape.

-

Hippocampus

- The hippocampus is critical for memory formation and retrieval
  - particularly sensitive to THC;
  - lots of cannabanoid receptors;
  - CBD receptors involved in neurogenesis

- THC dampens down the activity of hippocampal neurons, below the level needed to trigger the formation of a memory.

- Brain imaging studies have found that regular marijuana users actually have, on average, smaller hippocampi, and poorer memory performance

Meta-analysis of neuroimaging studies

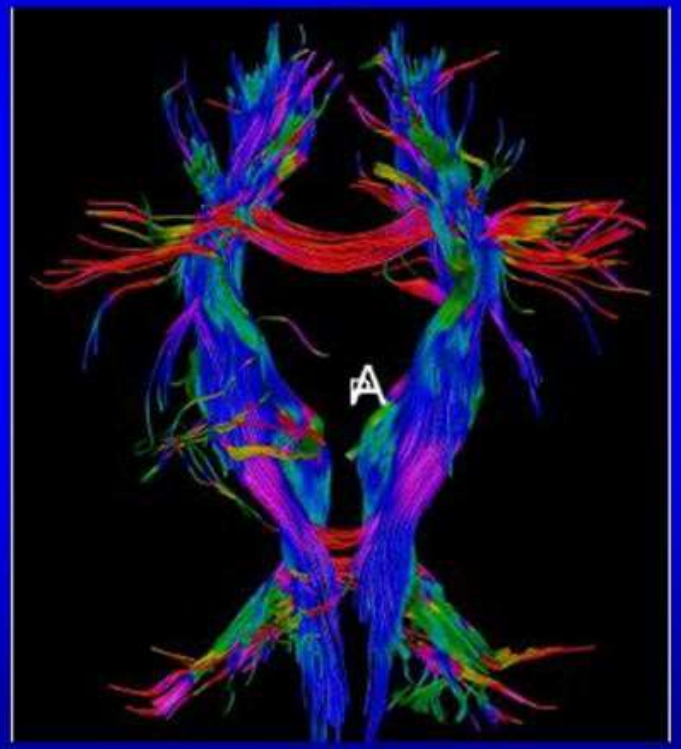
- 2013 meta-analysis of 43 studies of chronic MJ use: consistent evidence of both structural brain abnormalities and altered neural activity in marijuana users.
- Only 8 studies focused on adolescents; these suggested that both structural and functional brain changes emerge soon after adolescents start using the drug. Those changes may still be evident after a month of abstaining from the drug
- Most consistently reported:
  - brain alteration was reduced hippocampal volume, which was shown to persist even after several months of abstinence; related to the amount of cannabis use
  - amygdala, the cerebellum and the frontal cortex reductions
  - Alteration of WM integrity: DTI studies found differences in connectivity of corpus callosum and the frontal white matter fiber tracts

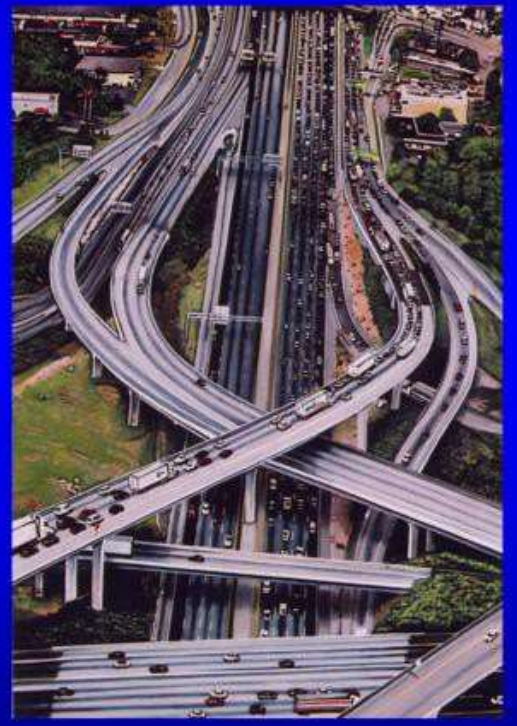
Rocío Martín-Santos, et al., 2013

Meta-analysis 2

- In adolescents, structural change effects of chronic cannabis use
  - may appear soon after starting the drug use,
  - persist after a month of abstinence
  - moderated by gender (female cannabis users may be at increased risk for cannabis-induced morphological effects)
- Evidence of neuropsychological impairments in chronic cannabis users, such as in attention and working memory, decision making, and psychomotor speed
- Brain seems able to achieve some degree of reorganization, activating brain regions (esp. frontal) not usually needed to perform the cognitive task in response to an impaired ability of the normally engaged task network

The Brain's Information Superhighway: Myelin = White Matter Tracts





Source: Gordon J. Harris, PhD.

Early MJ onset impairs White Matter and increases impulsivity

WORTH THE WAIT: EFFECTS OF AGE OF ONSET OF MARIJUANA USE ON WHITE MATTER AND IMPULSIVITY

(GRUBER, ET AL., PSYCHOPHARMACOLOGY (2014) 231:1455–1465)

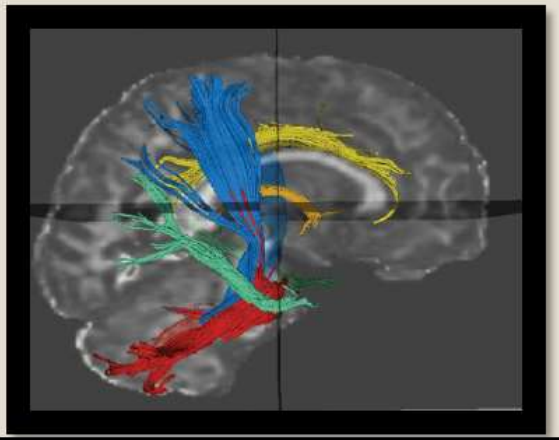
Fractional anisotropy (FA), is a measure of directionality & coherence in white matter fibers & can be measured using DTI/MRI.

The aim of this study was to examine the relationship between:

- **age of onset of MJ use**
- **white matter microstructure**, and
- reported **impulsivity** in chronic, heavy MJ smokers.

Results (n=43) : MJ use was associated with ↓ **FA,** ↑ **impulsivity**, and the pattern was amplified the younger the age of onset.

Conclusions: MJ use is associated with white matter development and reported impulsivity, particularly in early onset smokers. "These findings reinforce the idea that **early onset of MJ use negatively impacts white matter development and is associated with behavioral impulsivity**, a combination that may have enduring negative effects, particularly on the developing brain (p. 1463)."



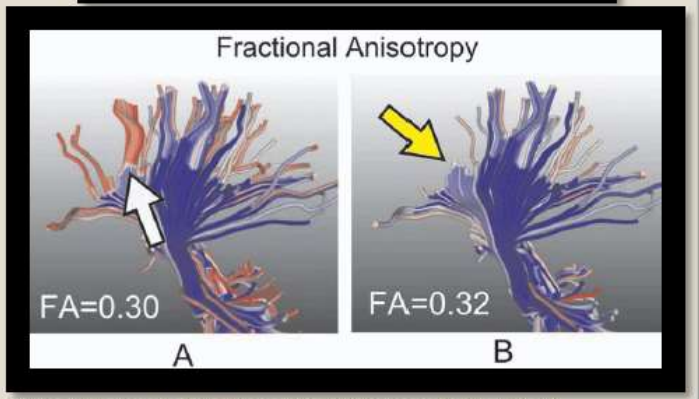
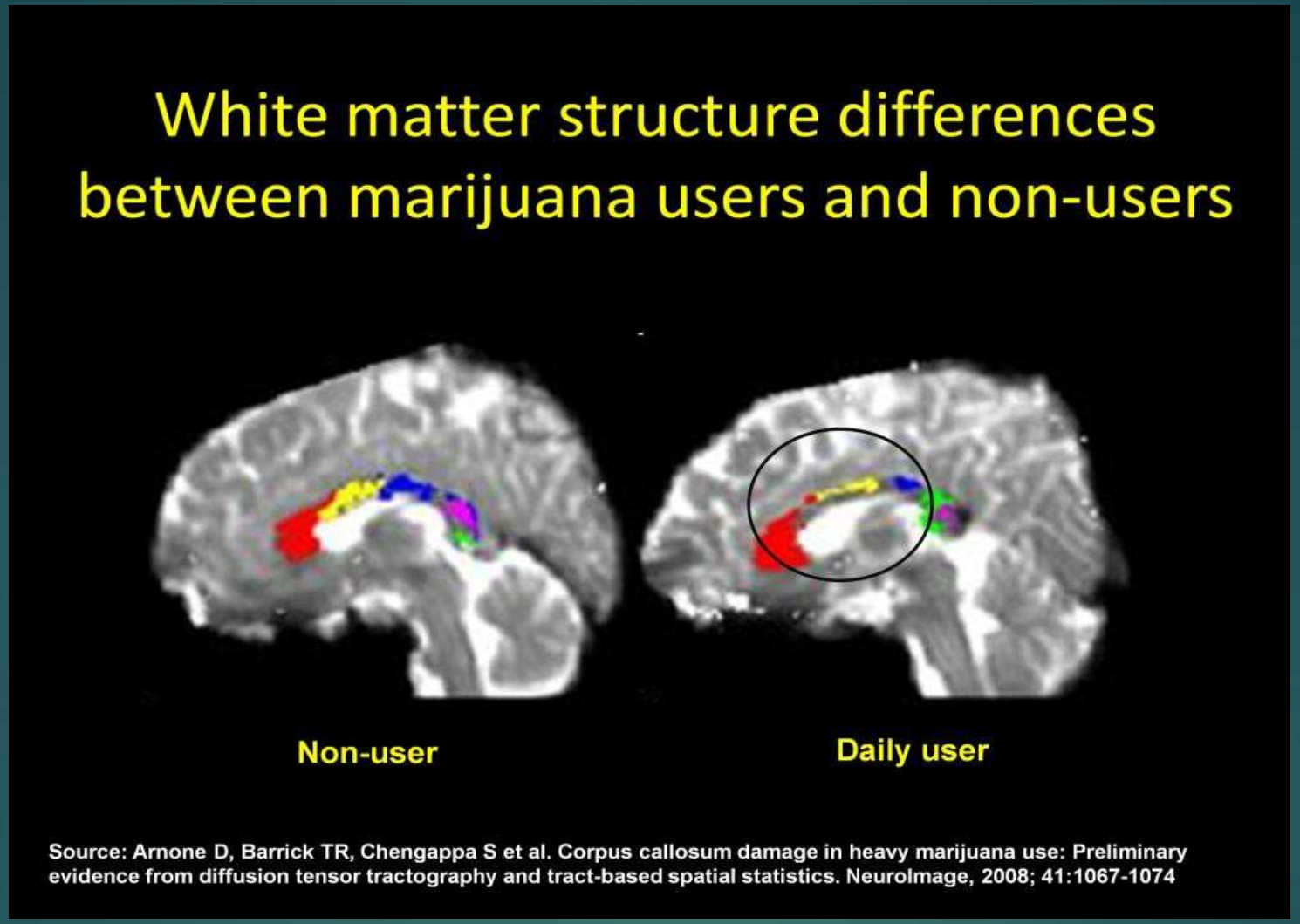
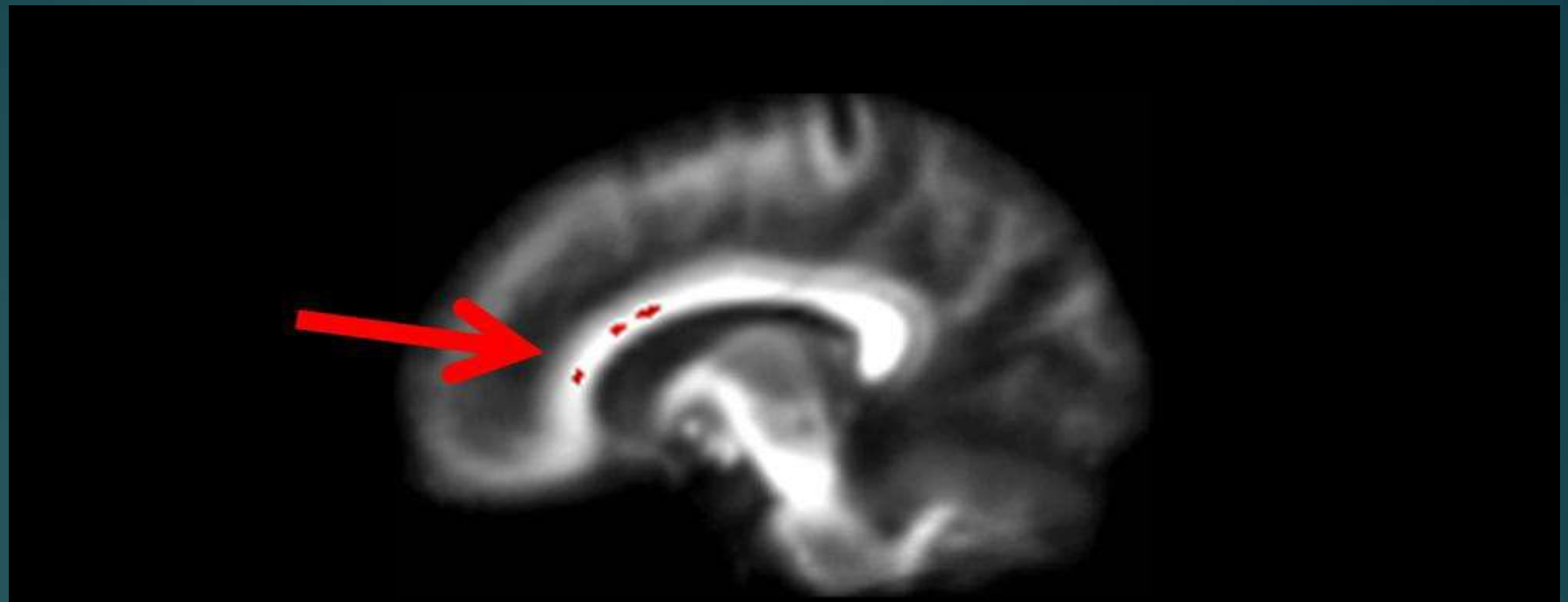


IMAGE SOURCES: : https://ieeexplore.ieee.org/ieee_pilot/articles/06/ttg2009061441/assets/img/artide_1/fig_10/large.gif & http://pubs.niaaa.nih.gov/publications/arh40/images/Sullivan4.gif



Young adult males who smoked marijuana daily
(and started at an average age of 15 yrs):
thinner corpus callosum fibers



Similar altered white matter structure found in the brains of schizophrenics and teen marijuana users

Bava S, Frank LR, McQueeny T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. *Psychiatry Research Neuroimaging*. 2009;173:228-237.

CORPUS CALLOSUM DAMAGE IN HEAVY MARIJUANA USE: PRELIMINARY EVIDENCE FROM DIFFUSION TENSOR TRACTOGRAPHY AND TRACT-BASED SPATIAL STATISTICS (D. ARNONE ET AL. / NEUROIMAGE 41 (2008) 1067–1074).

The use of the cannabis is **associated with an increased risk of developing schizophrenia, depression, anxiety disorders** and more generally with **aberrant prefrontal cortex-guided executive processes** responsible for:

- Memory,
- Executive functioning,
- Psychomotor speed and
- Selective/divided attention

These findings (n=22) suggest that cannabis exercises a **small but significant effect on white matter structural integrity.**

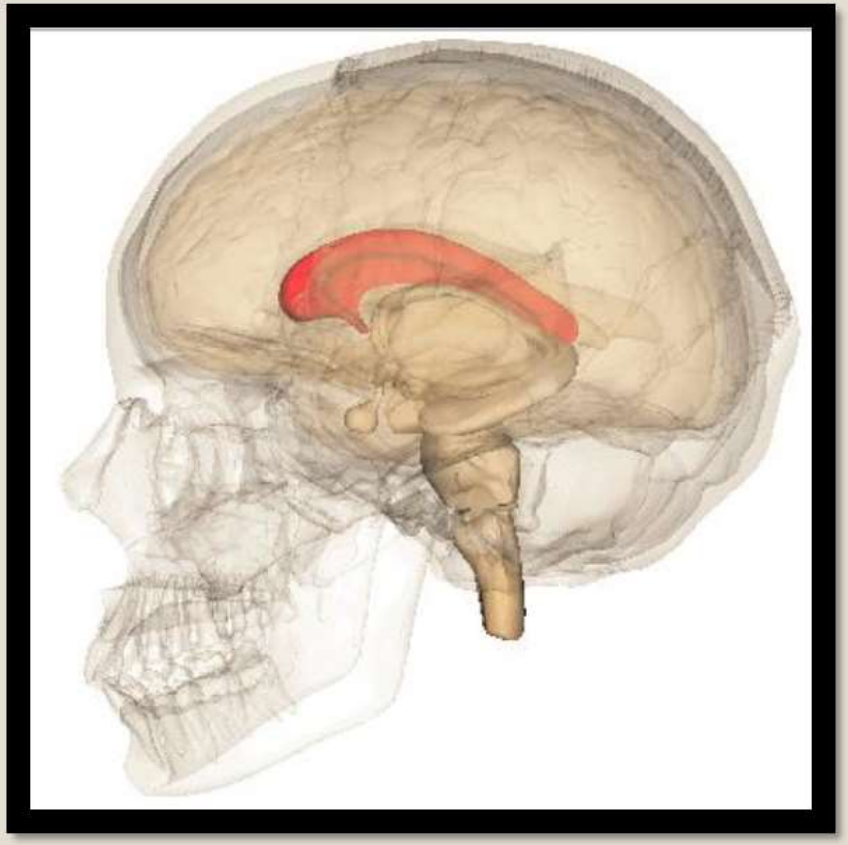


IMAGE SOURCE: http://d3k4erco76x75g.cloudfront.net/wp-content/uploads/2011/11/corpus-callosum.png

3 studies that indicate premorbid brain status may lead to MJ use vulnerability

ORBITOFRONTAL VOLUMES IN EARLY ADOLESCENCE PREDICT INITIATION OF CANNABIS USE: A 4-YEAR LONGITUDINAL AND PROSPECTIVE STUDY

(A. CHEETHAM *ET AL.*, BIOL PSYCHIATRY 2012;71:684–692, WWW.SOBP.ORG/JOURNAL)

This study (n=121) **aimed to determine whether earlier use was correlated with premorbid structural abnormalities in the amygdala, hippocampus, orbitofrontal cortex, and anterior cingulate cortex.**

The findings suggest that structural **abnormalities** in the **orbitofrontal cortex might contribute to risk for cannabis exposure**. Although the results have important implications for understanding neurobiological predictors of cannabis use, further research is needed to understand their relationship with heavier patterns of use in adulthood as well as later abuse of other substances.

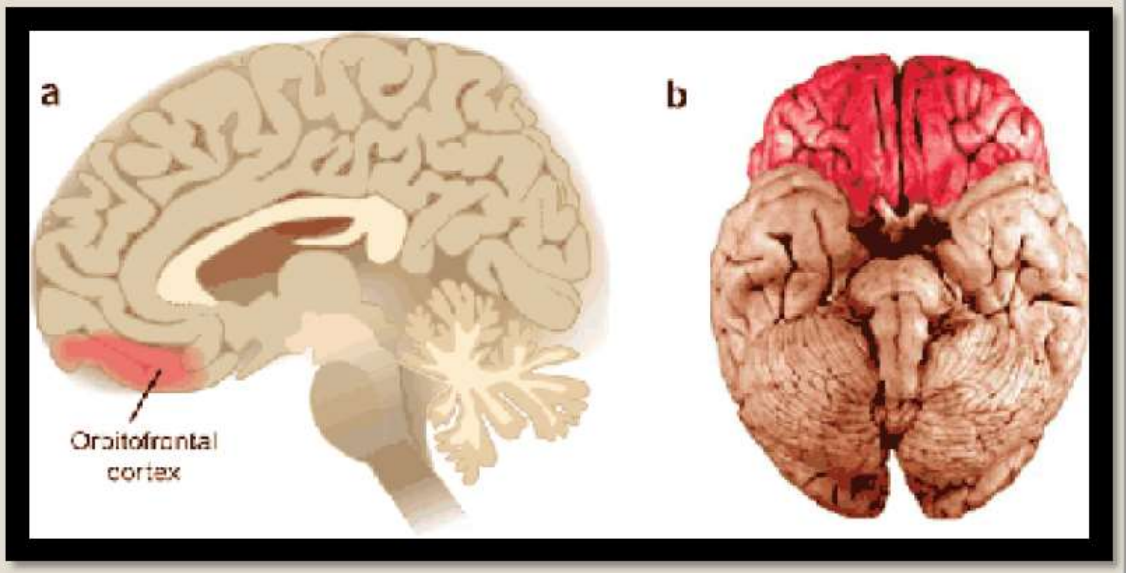


IMAGE SOURCE: http://www.psych-it.com.au/Psychlopedia/article.asp?id=423

ALTERED FRONTAL CORTICAL VOLUME AND DECISION MAKING IN ADOLESCENT CANNABIS USERS (CHURCHWELL ET AL., DECEMBER 2010 | VOLUME 1 | ARTICLE 225, WWW.FRONTIERSIN.ORG)

- **Results** (n=36) **indicate that cannabis abusing adolescents have decreased right moPFC volume**
- Cannabis abusing adolescents also show **decreased future orientation.**
- Moreover, total moPFC **volume was positively correlated with age of first use** suggesting that **alterations in this region may be related to initiation of cannabis use** or that early initiation may lead to reduced moPFC volume.

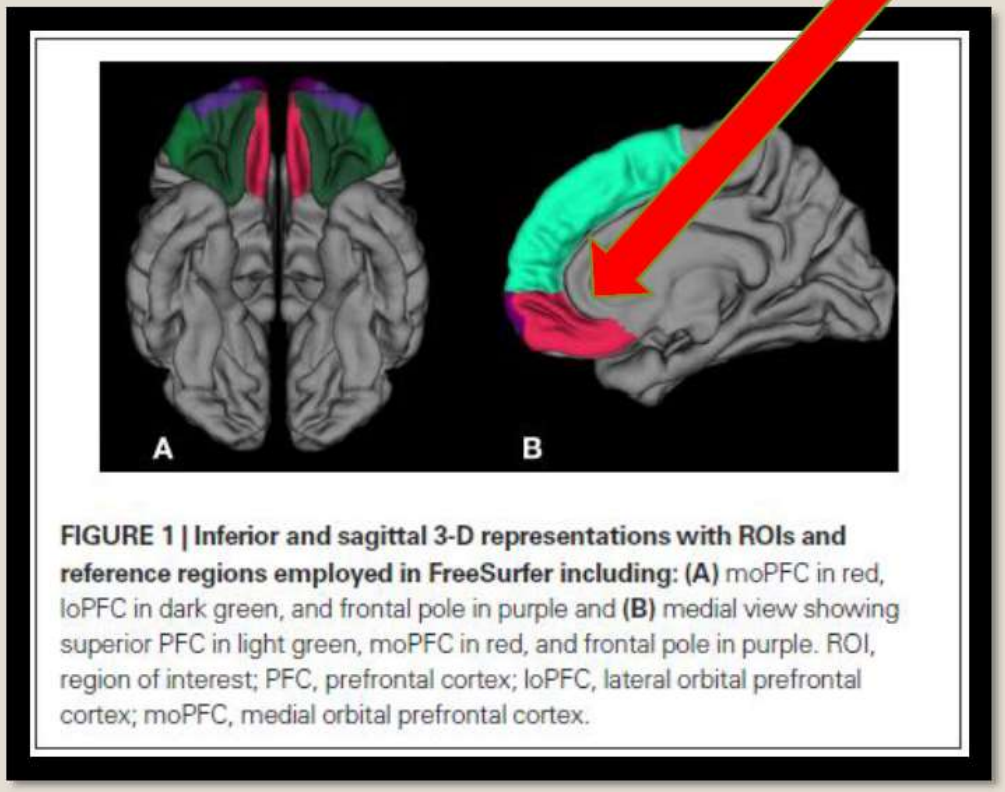
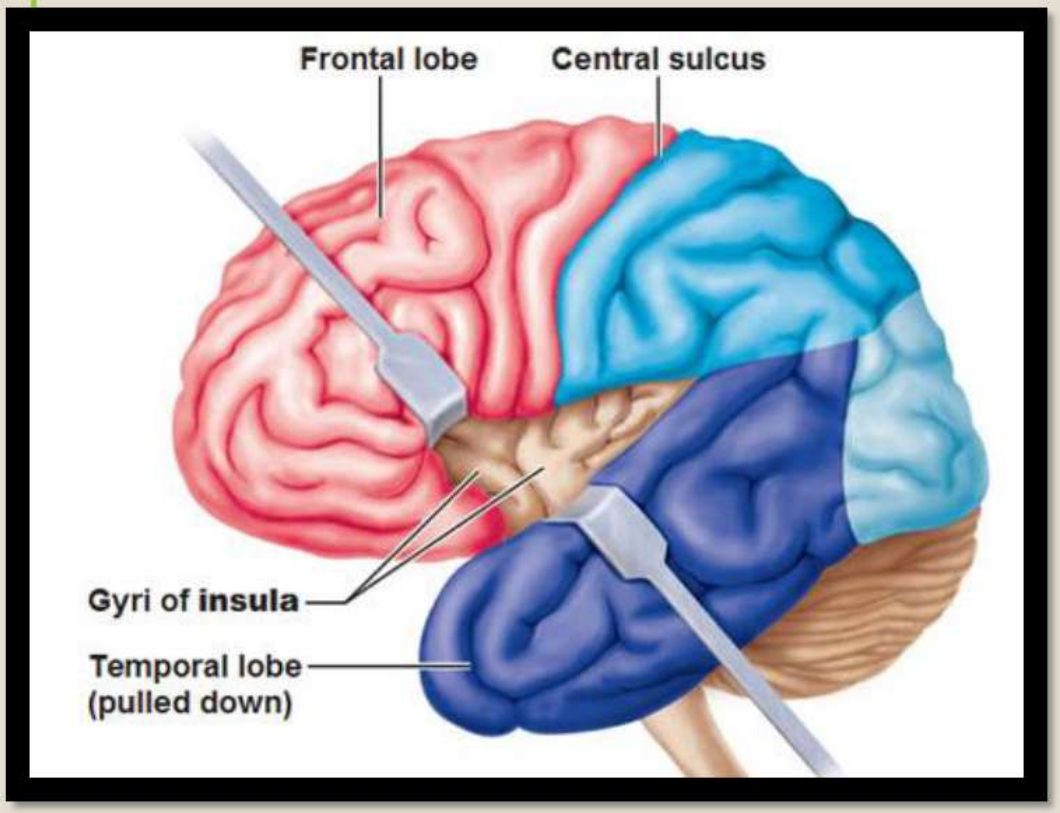
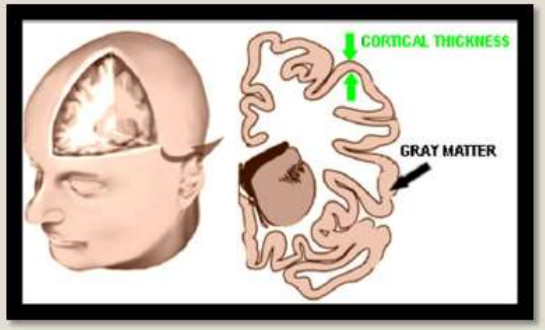


FIGURE 1 | Inferior and sagittal 3-D representations with ROIs and reference regions employed in FreeSurfer including: (A) moPFC in red, loPFC in dark green, and frontal pole in purple and **(B)** medial view showing superior PFC in light green, moPFC in red, and frontal pole in purple. ROI, region of interest; PFC, prefrontal cortex; loPFC, lateral orbital prefrontal cortex; moPFC, medial orbital prefrontal cortex.

ALTERED PREFRONTAL AND INSULAR CORTICAL THICKNESS IN ADOLESCENT MARIJUANA USERS

(LOPEZ-LARSON ET AL., BEHAV BRAIN RES. 2011 JUNE 20; 220(1): 164–172).





Conclusion (n=36)

Reduced insular cortical thickness may be a biological marker for increased risk of substance dependence.

Documented abnormalities in prefrontal and insular regions, suggest age of regular use may be associated with altered prefrontal cortical gray matter development in adolescents.

IMAGE SOURCE: http://antranik.org/wp-content/uploads/2011/11/insula-lobe-frontal-lobe-central-sulcus-gyri-of-insula.jpg and http://www.inner-light-in.com/wp-content/uploads/2015/05/Cortical-Thickness.png

Major future ABCD study

- In hopes of painting a clearer picture of marijuana's potential risks to youth, NIDA plans to launch the Adolescent Brain and Cognitive Development (ABCD) study later this year.

- The prospective longitudinal study will follow 10,000 individuals across the United States over a decade, starting when they're 9 or 10.

Negative Impacts of Marijuana on Health

- Behavioral: “Amotivational syndrome”
- Cognitive: impaired memory, attention, EF
- Psychiatric: rare but real permanent psychosis (likely “flips” those genetically predisposed)
- Respiratory: cancer, COPD
- Cardiovascular: HTN, tachycardia, MI (↑ Heart rate in 20%-100% and persists for 3 hrs; ↑ risk of heart attack 5 fold in first hour of use)
- Decreased Immunity (decrease T cells & viral resistance)
- Teratogenicity: unknown extent of fetal neurotoxicity
- Reproductive: decreased testosterone, sperm count/motility; inhibits prolactin, LH, GH

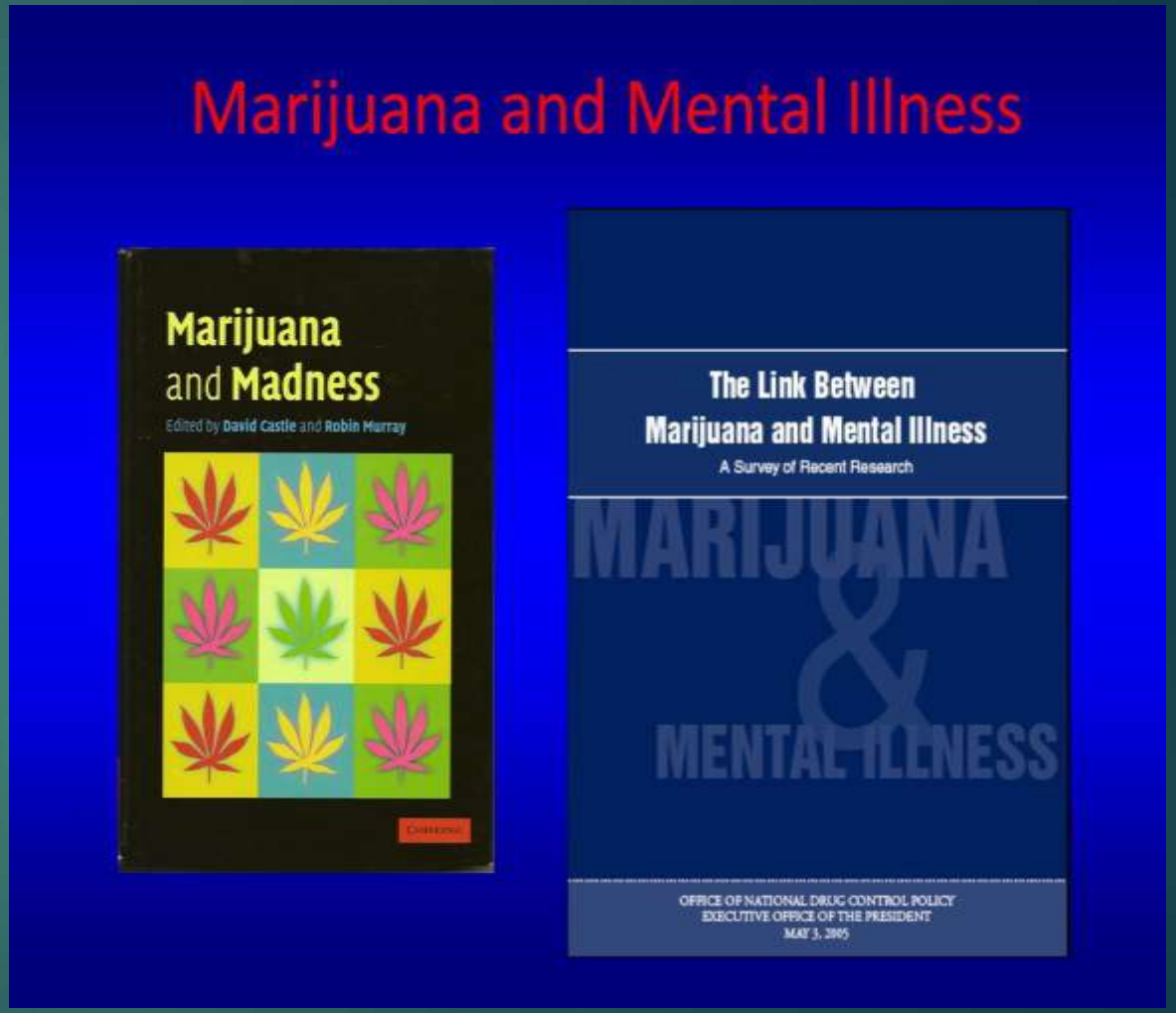
Growth and Fertility

- Marijuana affects glands, organs and hormones involved in overall growth, pubertal development, and energy levels
- People who used regularly before 16 had shorter height
- Possible increased risk for testicular cancer

Source: Wenger T, Croix D, Tramu G. The effect of chronic prepubertal administration of marijuana (delta-9-tetrahydrocannabinol) on the onset of puberty and the post-pubertal reproductive functions in female rats. *Biology of Reproduction*. 1988;39:540-545.; Trabert B, Sigurdson AJ, Sweeney AM et al. Marijuana use and testicular germ cell tumors. Cancer. 2011 Feb 15;117(4):848-53.

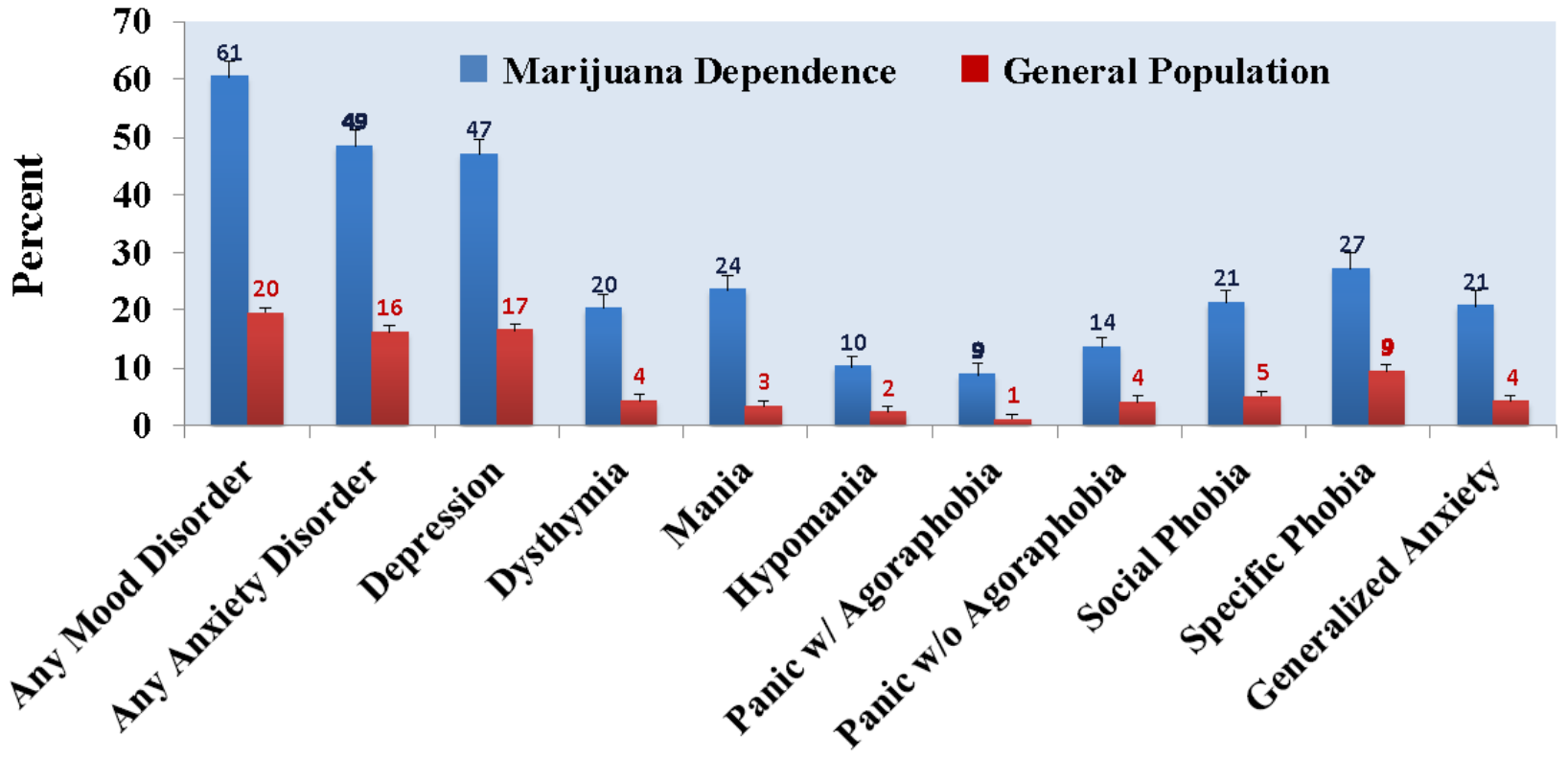
MJ and Psychiatric conditions

- There is a growing body of evidence suggesting that marijuana may increase risk for mental illness.
- The two reports shown on this slide summarize the results of over three decades of research studies showing this link between marijuana and later mental illness.



Chronic MJ use comes with comorbid Psych issues

High Rates of Comorbid Mood & Anxiety Disorders Among Respondents with Marijuana Dependence (NESARC)



2004: Marijuana and Anxiety Disorder:

- 14 yr olds using occasionally, weekly, or daily over 15 yrs are 2.5 x as likely to have anxiety disorder at age 29.
- If non-using at age 29, they are still 2 x as likely to have anxiety disorder

Depression and Suicidality

- Discordant Twin with early marijuana use (<17) was 3.5 times more likely to attempt suicide than their non early use twin

Linskey, MT, et al. (2004), Arch. Gen. Psych. 61(10):1026

2014 Meta-analysis: MJ and depression

- 14 studies, (total number of subjects = 76058).

- Cannabis use, and particularly heavy cannabis use, may be associated with an increased risk for developing depressive disorders; using cannabis placed an individual at moderate risk of developing depression.

- Could not determine if cannabis use was *causing* depression or if the relationship instead reflects the association between cannabis use and social problems

S. Lev-Ran, et al., 2015

2016 study: MJ not associated with Anxiety

- 3-year prospective study
- Results indicate that cannabis use was not associated with increased incidence of any anxiety disorder

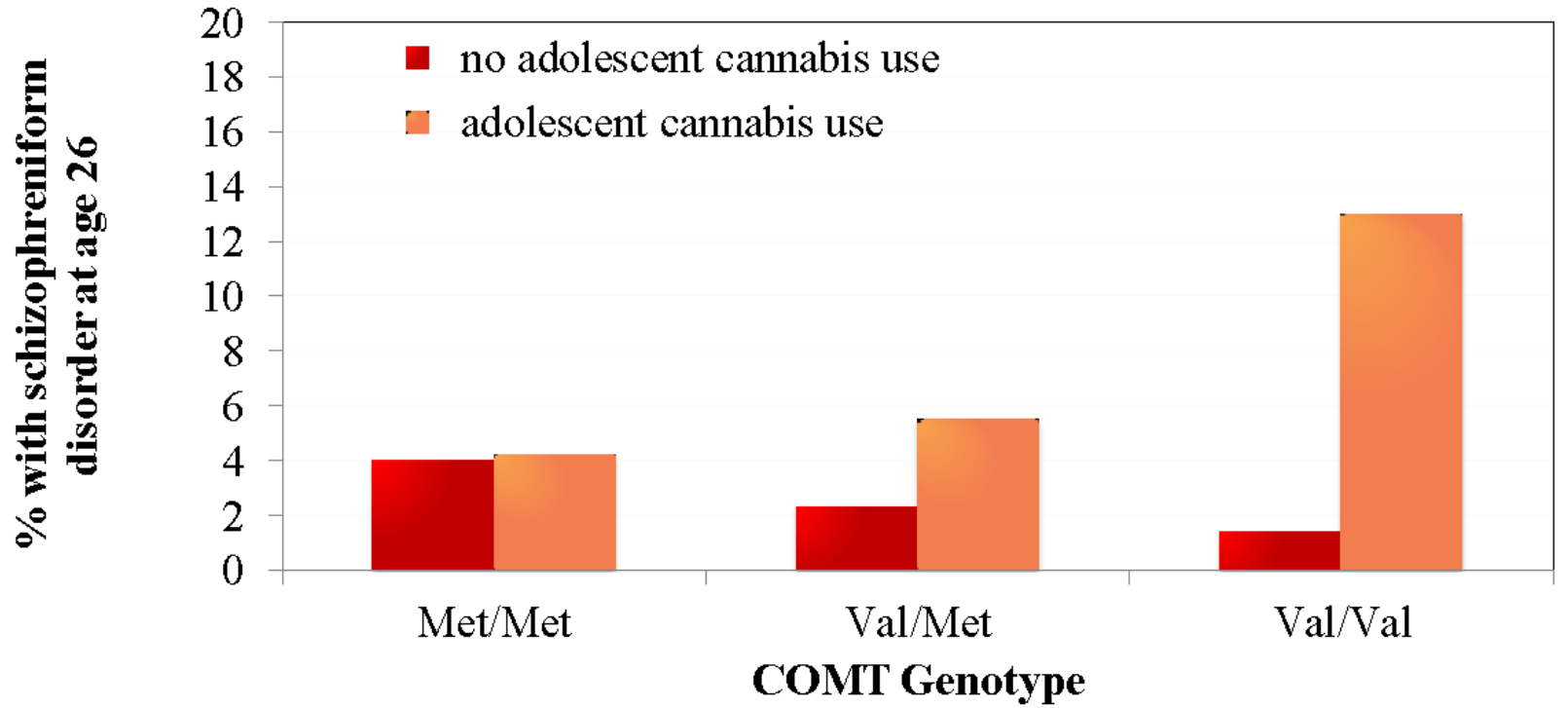
- Any baseline anxiety disorder was not associated with future initiation of cannabis use or onset of a CUD, yet individuals with baseline panic disorder were more prone to initiate cannabis use at follow-up possibly as a means of self-medication.

- Concluded that cannabis use and CUDs are not associated with increased incidence of most anxiety disorders and inversely, most anxiety disorders are not associated with increased incidence of cannabis use or CUDs.

Daniel Feingold, et al., 2016

Risk of Adult Psychosis

Adolescent Cannabis Use Increases the Risk for Adult Psychosis in Genetically Vulnerable Individuals



Source: Caspi, A. et al., Biol. Psychiatry, 57: 1117-1127; 2005.

Longitudinal studies:

- An increased risk of developing schizophrenia or mood disorders (depression, anxiety) in adulthood if individuals regularly smoked marijuana during adolescence.

- Especially if any family history of mental illness (i.e., “genetics provided the loaded gun and marijuana pulled the trigger”). Also, mental illness, among those at risk, tended to show up earlier with marijuana use.

- Regular MJ use during adolescence found to increase risk 2 to 5 x of developing psychosis, schizophrenia, anxiety & depression in adulthood.

Malone DT et al., 2010

Schizophrenia

- In contrast, the relationship between cannabis use and risk of developing symptoms of psychosis has been well established

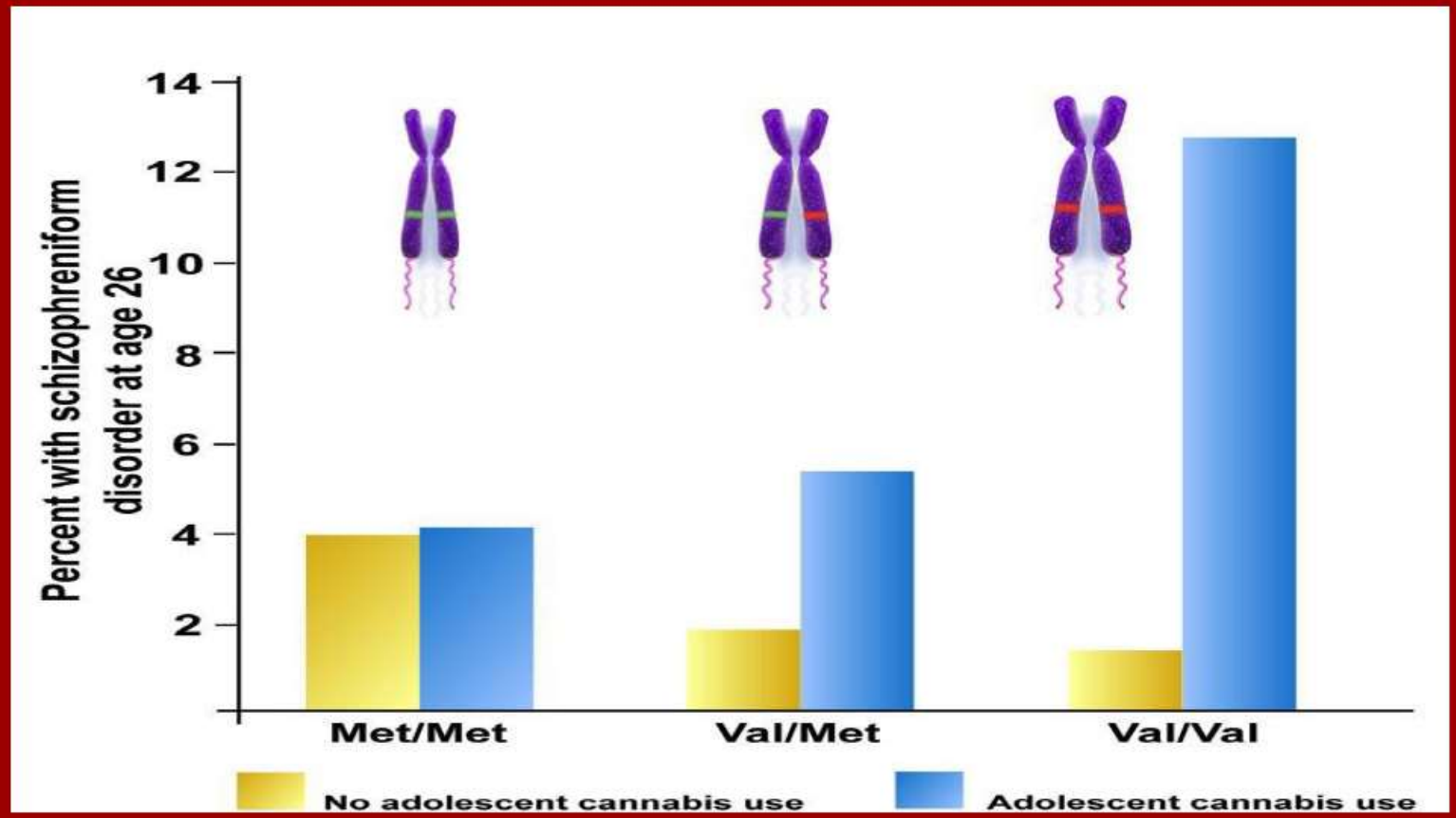
- Early and frequent cannabis use is a cause of psychosis, which interacts with other risk factors such as family history of psychosis, history of childhood abuse and expression of the COMT and AKT1 genes.

- THC effects neurodevelopment via immune processes; schizophrenia is know suspected of being due to immune driven synaptic over-pruning

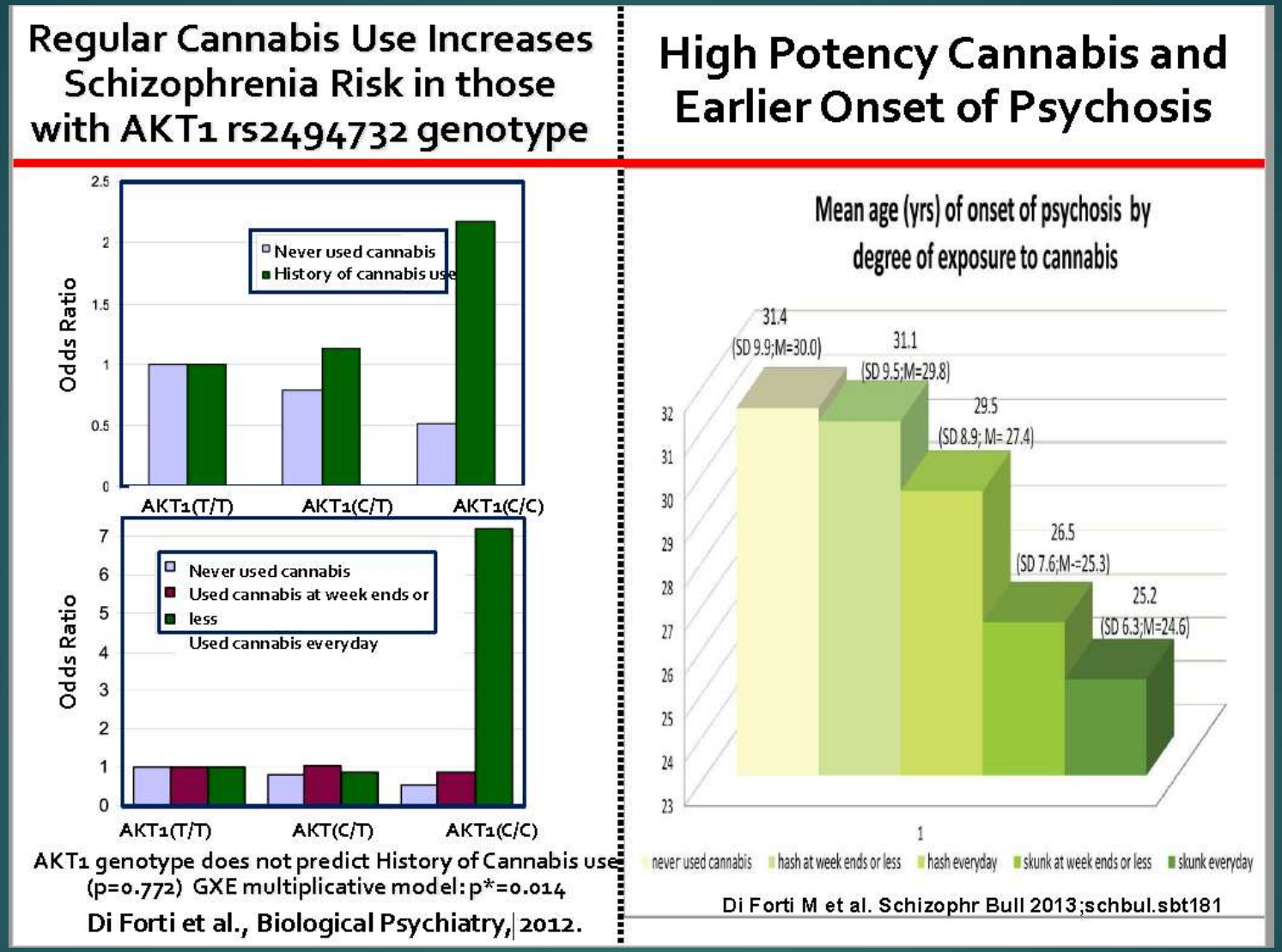
- There is a strong resemblance between the acute and transient effects of cannabis use and symptoms of psychosis, including impaired memory, cognition and processing of external stimuli.

Moore TH, et al., 2007; Matthew Large, et al., 2011

Adolescents who Smoke Cannabis have Increased Risk of Schizophreniform Disorder, Depending on the COMT Gene



Caspi et al., 2005

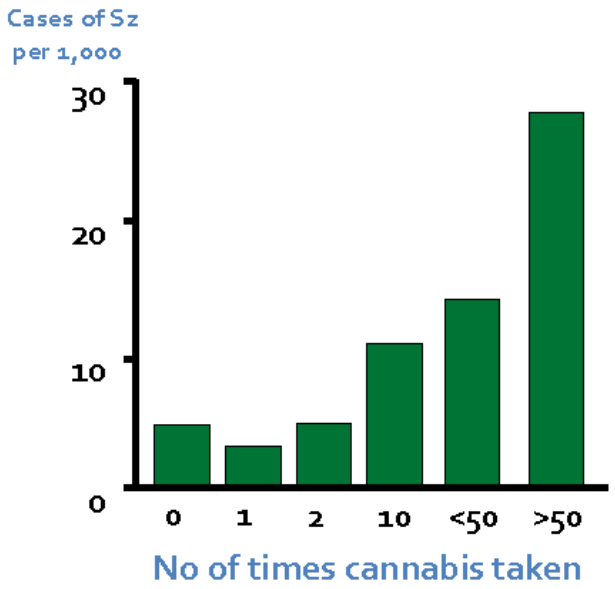


DiForti, M, et al. (2013) – 6 year earlier onset of psychosis if daily use started age 15 or less

Cannabis-Associated Psychosis

CANNABIS AND SCHIZOPHRENIA

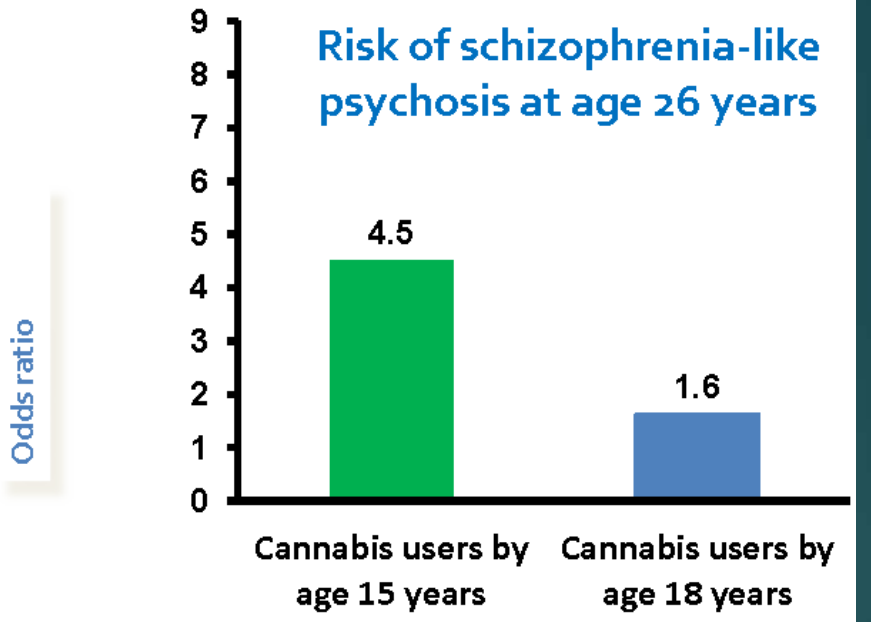
Study of Swedish Conscripts (n=45570)



Andréasson et al Lancet, 1987.

CANNABIS AND SCHIZOPHRENIA-Like

Longitudinal prospective Dunedin study (n=1037)



Arseneault et al BMJ 2002

Increased frequency of use

Early use onset

“Skunk & Psychosis

- “Skunk” (16% THC) Marijuana and Risk of Psychosis
- 2015 British Study: English “Skunk” pot is high potency pot ~ 16% THC, low CBD
- N = 410 first episode psychosis, 370 controls Di Forti, M et al. (2015) The Lancet On-line
- Occasional or weekend use increased psychosis risk 3X more than non users
- Daily use increased risk is 5X more than non users

- Welch, KA, et al (2010) – increased ventricular volume associated with marijuana use in 16-25 yo

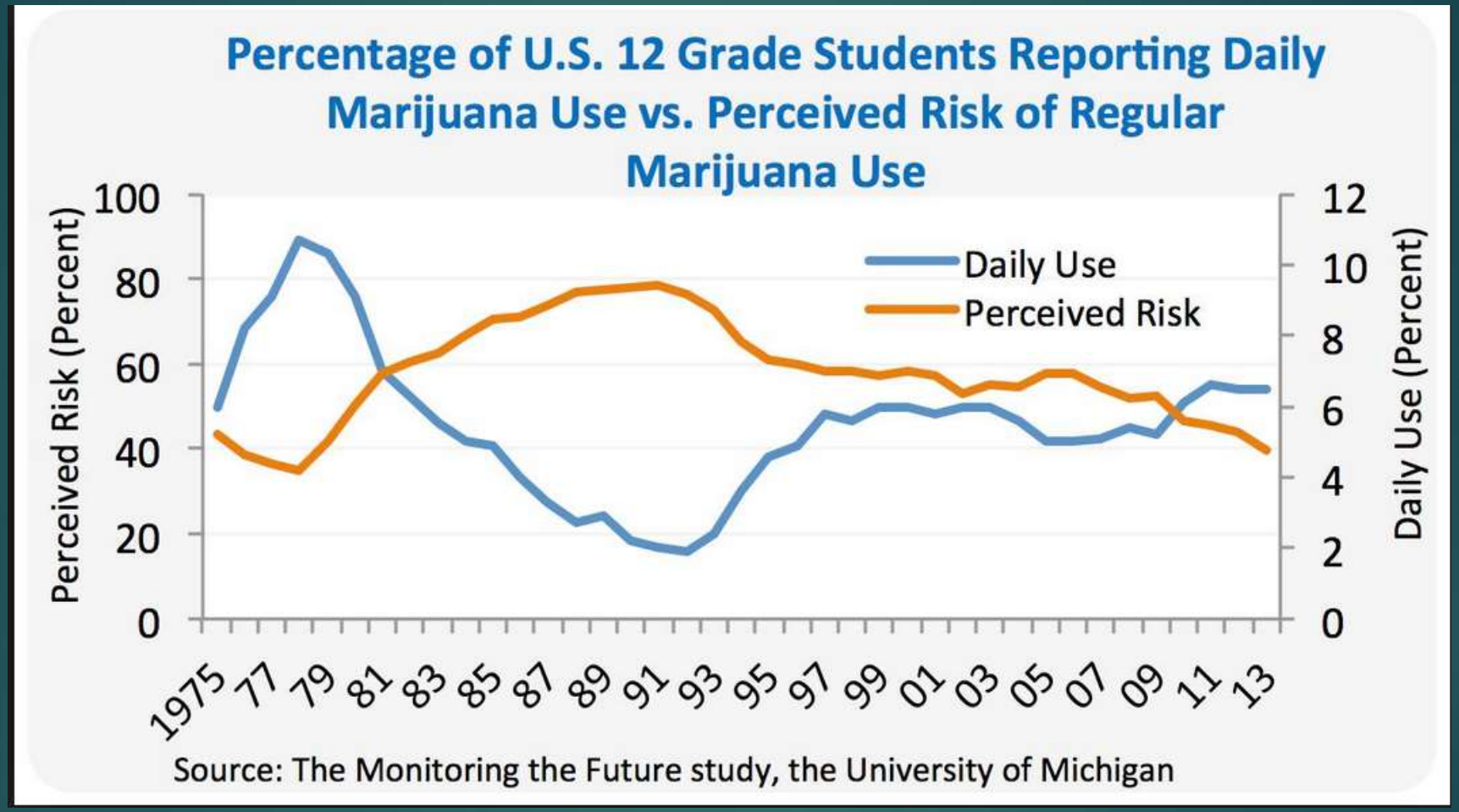
Schizophrenia

- We also know that cannabis use by people with established psychotic disorder can exacerbate symptoms.

- Overall, the evidence suggests cannabis use will bring forward diagnosis of psychosis by an average of 2.7 years.

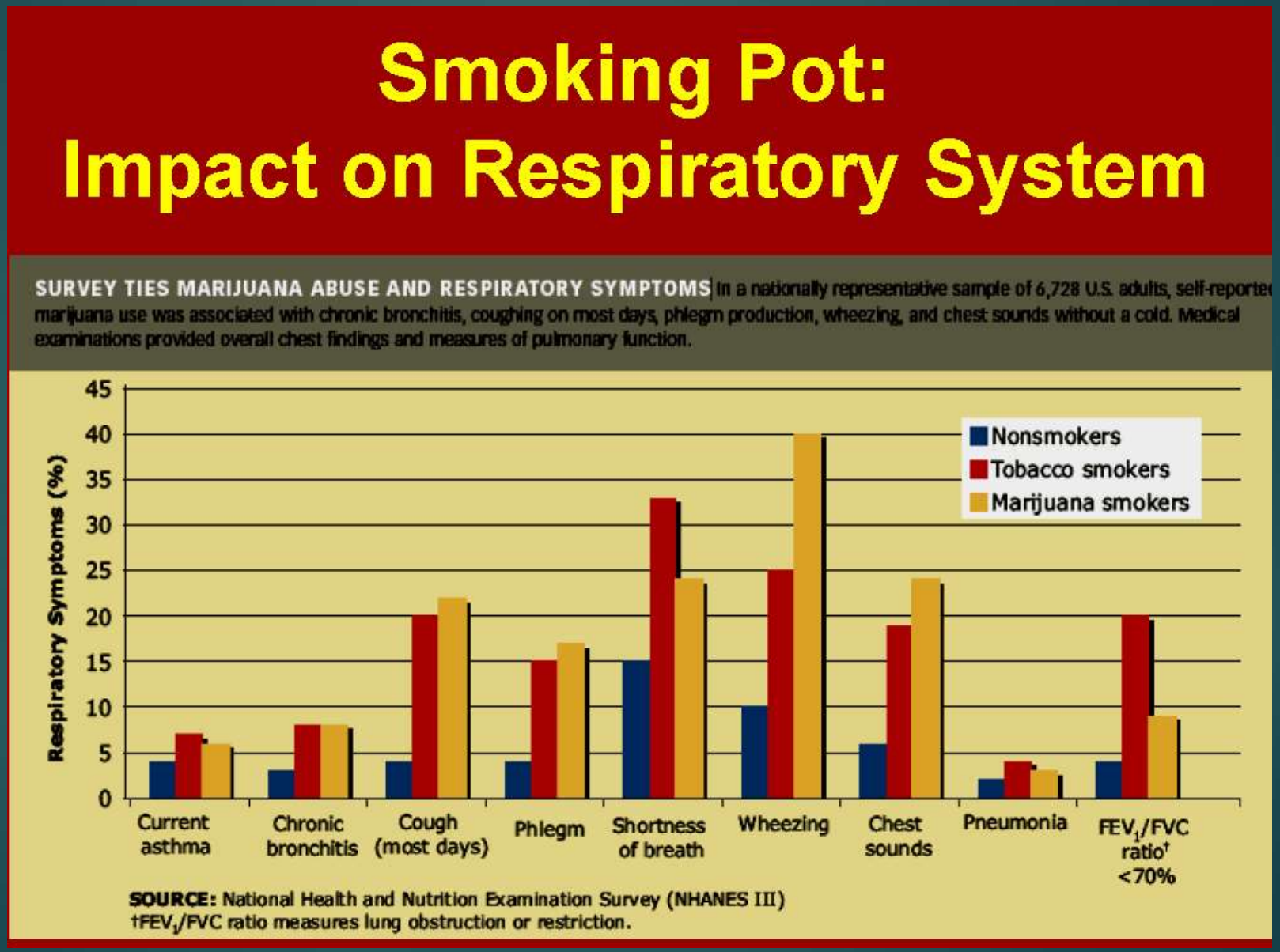
- The risk of developing schizophrenia increases with the duration and dose of cannabis use. Regular cannabis users have double the risk of non-users. Those who have used cannabis at some point in their life have a 40% increased risk compared with non-users.

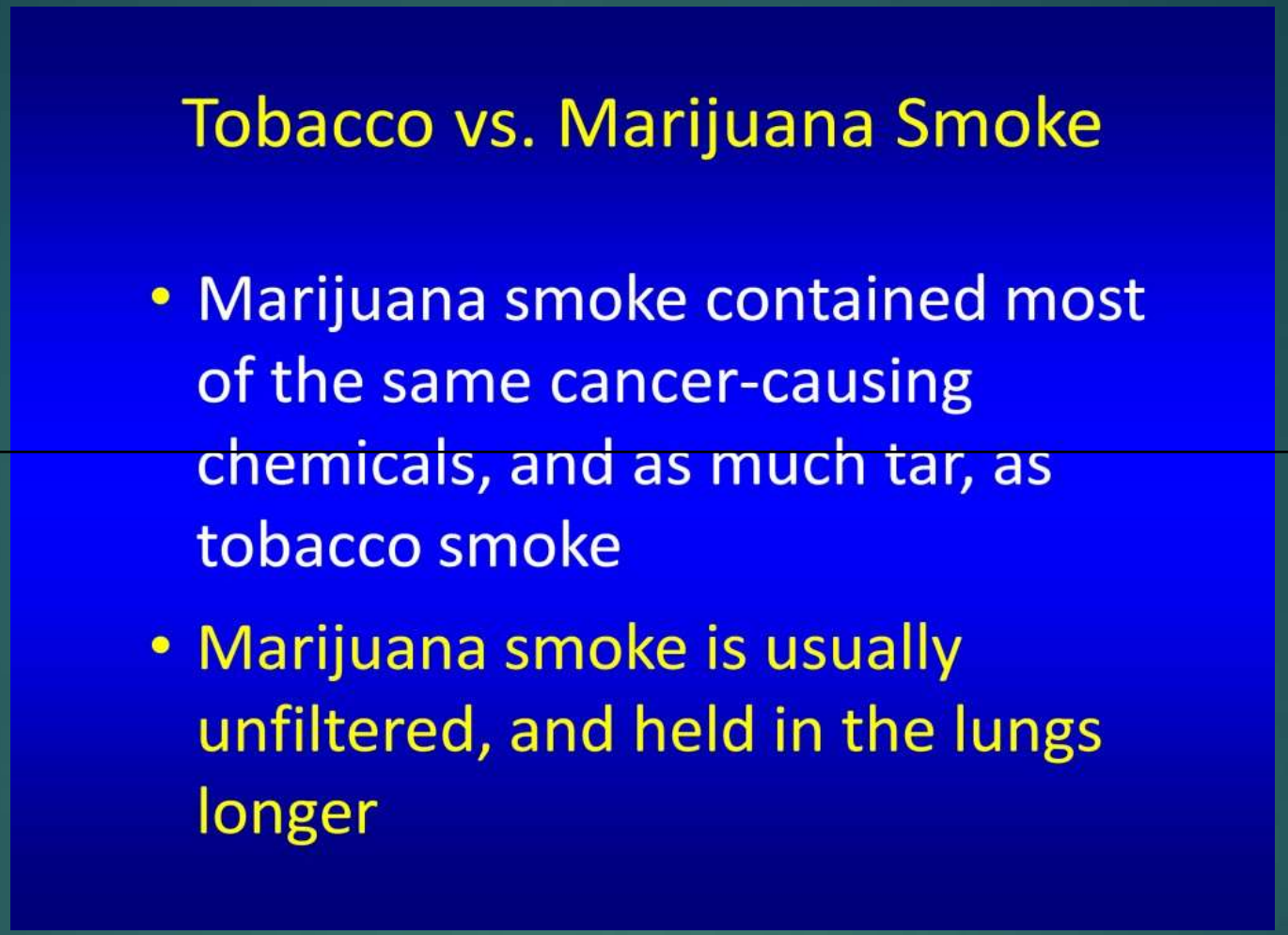
More MJ than cigarette smoking in 12th graders



Smoking tobacco and cannabis are both carcinogens

Marijuana Health Effects





Marijuana smokers are actually exposed to more of these chemicals per puff than tobacco smokers because tobacco cigarettes typically have filters through which smokers inhale, whereas marijuana joints do not. Also, marijuana smokers tend to inhale and hold the smoke in their lungs longer than cigarette smokers.

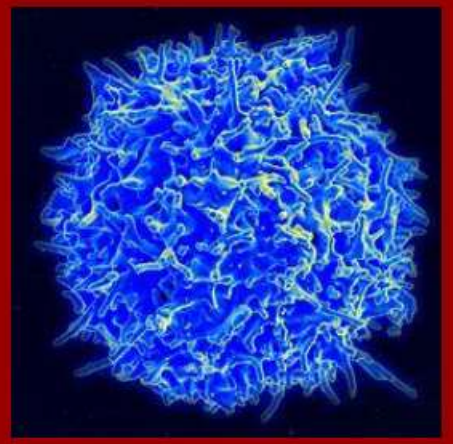
Marijuana and Respiratory Health

Regular marijuana smokers report more cough, bronchitis, wheezing, shortness of breath, and more days sick than non-smokers (regardless of tobacco use)

Regular marijuana smokers report more of a range of common respiratory health issues, and more days sick than non-users, regardless of whether they smoked cigarettes.

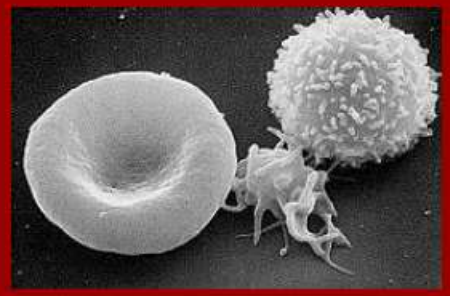
Immune System suppression

Marijuana (cannabinoids) suppression of Immune System



T lymphocyte
(T-Cell)

THC and other cannabinoids trigger massive mobilization of myeloid derived suppressor cells (MDSCs) to suppress the human immune system to infections and cancer



Blood Cell, Platelet, T-Cell

Marijuana (THC) & Pregnancy

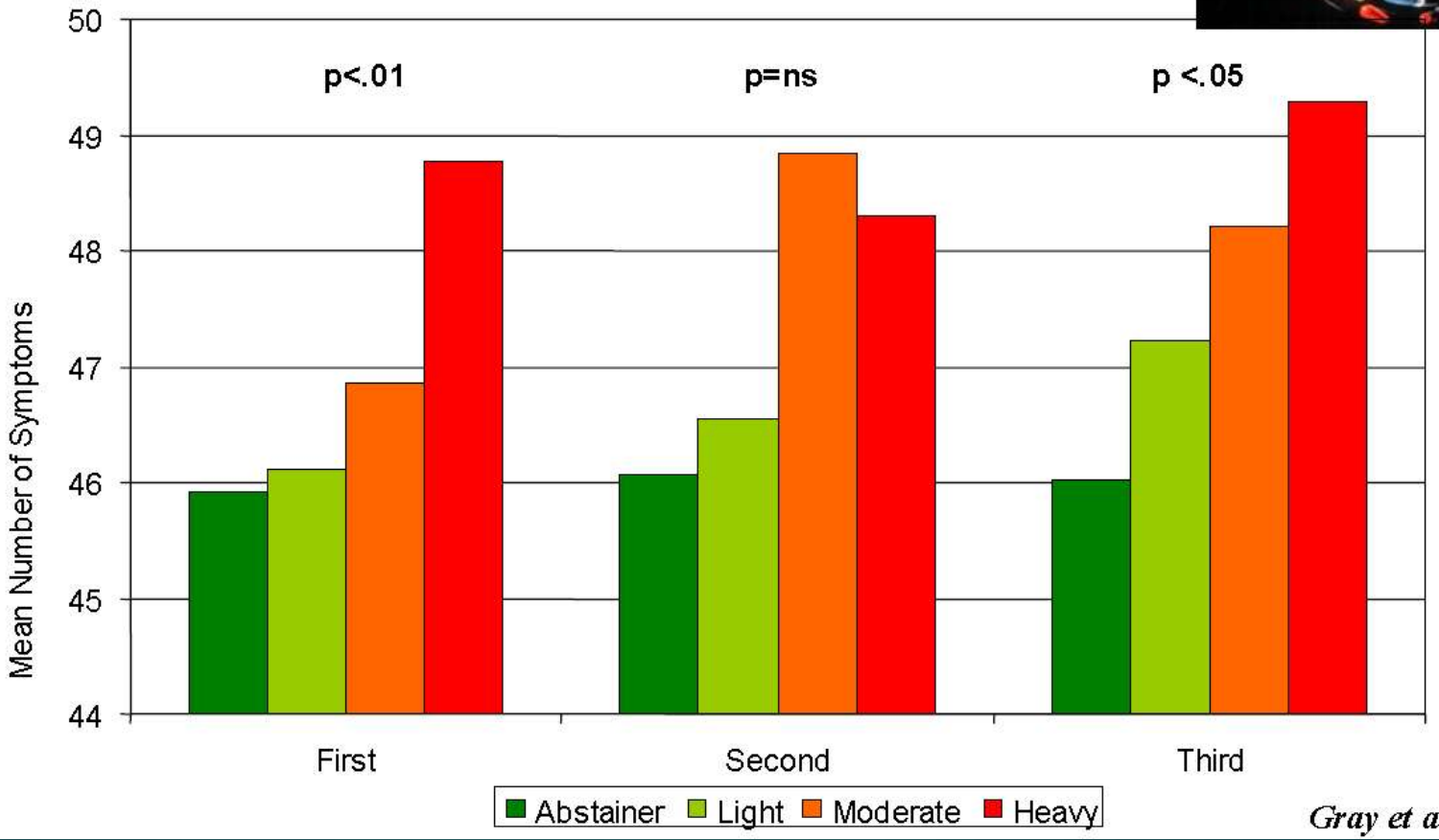
- 7.6-9% of U.S. used marijuana in past 30d
- 3-16% of pregnant women used in past 30d
- Compared to nicotine and alcohol, MJ use is least likely to be reduced during pregnancy
- THC half-life is 25-57 hours and can be detected in body for 1 to several months

Prenatal MJ exposure

- There were significant negative effects of prenatal marijuana exposure on the performance of 3-year-old children on the Stanford-Binet Intelligence Scale.
- Slower motor development
- The effects were associated with exposure during the first and second trimesters of pregnancy.

N.L. Day, et al., 1994

Depression Symptoms at Age 10 by Trimester of Prenatal Marijuana Exposure



Gray et al., 2005.

Marijuana Effects on Pregnancy Controversy

- Research difficulty: Controlled human studies impossible and most use alcohol or other drugs along with MJ
- Lower birth weight and gestational period
- Neonate abnormal response to light or visual stimulus, “startles”, tremulousness, drug withdrawal high pitch cry
- Attention, concentration, judgment, and problem solving difficulties; increased ADHD; some link with stillbirths & SID

Genetics of MJ

- Three genetic variants that were linked with symptoms of marijuana dependence.

- 1 Gene related to calcium signaling

- 2 Gene called CSMD1, involved in the growth of the central nervous system. Genetic variants within CSMD1 have also been linked with schizophrenia risk

- Findings suggest that marijuana dependence, depression and schizophrenia might share some underlying genetic factors,

Sherva R, et al., 2016

Urine Analysis (UA) Complications from Rewood Toxicology Lab Information Sheet

- THC and its metabolites take 2-4 hours after smoking to be detectable in urine

- They can persist in levels above the usual 50 ng/ml cut-off concentrations for up to 30 days (lower levels up to 6 months detectable in brain tissues)

- 1-3 days detectable from infrequent use

- 7-10 days regular use (several times/week)

- 30 days heavy/daily use (if 50 ng/ml, longer if lower cut-off)

Marijuana as a Drug

SUBSTANCE	DRUG	MEDICAL USES	ADDICTION
Tobacco Nicotiana tabacum	nicotine	some	yes
Booze Saccharomyces cerevisiae	ethanol	limited	yes
Opium Papaver somniferum	opioids	vital uses	yes
E. Coca Erythroxylaceae coca	cocaine	yes	yes
Marijuana Cannabis sativa, indica	THC	potential	yes

Clinical Recommendations

- Dissociation:
  - Knowledge or ability to describe appropriate behavior does not equal ability to do it appropriately
- Implications: Don't depend on verbal insight
- Neurologically challenged/impaired, not unmotivated
- Do a MoCA!

Clinical Recommendations

- Caution: when making inferences about motivation based on observed behaviors.
- Non-compliance may not arise from lack of motivation or resistance.
- Unawareness of deficits can be due to executive dysfunction and may not always be due to psychological denial.

AMERICAN ACADEMY OF PEDIATRICS (AAP) 2015 POLICY STATEMENT ON IMPACT OF MARIJUANA POLICIES ON YOUTH

- Earlier onset of use associated with ↑ risk of drug dependence/addiction in adulthood

- **Poorer functional outcomes**
  - ↓ rate of high school completion
  - ↓ rate of getting a college degree
  - ↑ use of other illicit drug use
  - ↑ in suicide attempts (dose dependent)
- **Poorer learning**
  - ↓ short term memory
  - ↓ concentration
  - ↓ attention span
  - ↓ problem solving

DSM-5: Substance/Medication-Induced Mild Neurocognitive Disorder

- A. Criteria met for major or mild NCD
- B. Neurocognitive impairments do not occur during course of a delirium and persist beyond usual duration of intoxication and acute withdrawal
- C. Involved substance or medication & duration and extent of use are capable of producing neurocognitive impairment.
- D. Temporal course of the neurocognitive deficits is consistent with the timing of substance or medication use & abstinence
- E. Not due to another mental disorder.

- Specify if: Persistent (NCD continues to be significant after extended abstinence)

DSM-5: Cannabis-Related Disorders Tolerance, Dependence, Withdrawal

Diagnostic Statistical Manual of Mental Disorder 5th Edition (DSM-5):

- Cannabis Use Disorder
- Cannabis Intoxication
- Cannabis Withdrawal
- Other Cannabis-induced Disorders
- Unspecified Cannabis-Related Disorders

Cannabis Use Disorder Diagnostic Criteria DSM-5

1. Larger amounts and longer than intended
2. Inability to decrease or control use
3. Excessive time to get, use, and recover
4. Cravings or urge to use
5. Failure to fulfill work, school, home roles
6. Continued despite negative consequences
7. Important activities ceased or reduced
8. Continued in physically hazardous situations
9. Continued despite physical/psychological problems
10. Tolerance: ↑ amount needed to get desired effects or decreased effects from same amount of cannabis consumed
11. Occurrence of withdrawal or use to relieve or avoid withdrawal

Mild = 2-3 of symptoms of criteria; Moderate = 4-5; Severe = 6 or more

Marijuana Withdrawal Syndrome

Symptoms occur within 8 hours of abstinence but can be delayed up to 72 hours. Usually peak in severity on day 10 and may last for up to 45 days or longer.

Symptoms: irritability, anger, anxiety, restlessness, nightmares/sleep disturbances (REM rebound), headaches, depressed mood, craving, decreased appetite, sweating, chills, pain, mild tremors (“cold dog shakes”)

Challenges to Maintenance of Continued Abstinence

- Cognitive Impairment (30-80%)
- Endogenous Craving
- Environmental Triggers or Cues
- Post Acute Withdrawal Symptoms
- Unaddressed Mental Health Issues

TALKING TO PATIENTS ABOUT MARIJUANA

- Benefits of MJ use?
- Acknowledge/validate the short-term benefits
- Negative effects of MJ use?
- Risks?
  - MJ use compromising the benefits of medications
  - MJ can cause acute and chronic psychiatric difficulties and cognitive impairment
- MJ withdrawal symptoms, 1-6 days, up to 2-3 weeks

(https://teens.drugabuse.gov/blog/post/marijuana-withdrawal-real)

- Irritability
- Depression
- Insomnia/Fatigue
- Anxiety
- Restlessness
- Decreased appetite

TREATMENT APPROACHES IDENTIFIED AS BENEFICIAL

FUNCTIONAL CONNECTIVITY AND CANNABIS USE IN HIGH-RISK ADOLESCENTS (HOUCK ET AL., *AM J DRUG ALCOHOL ABUSE*. 2013 NOVEMBER ; 39(6): 414–423.)

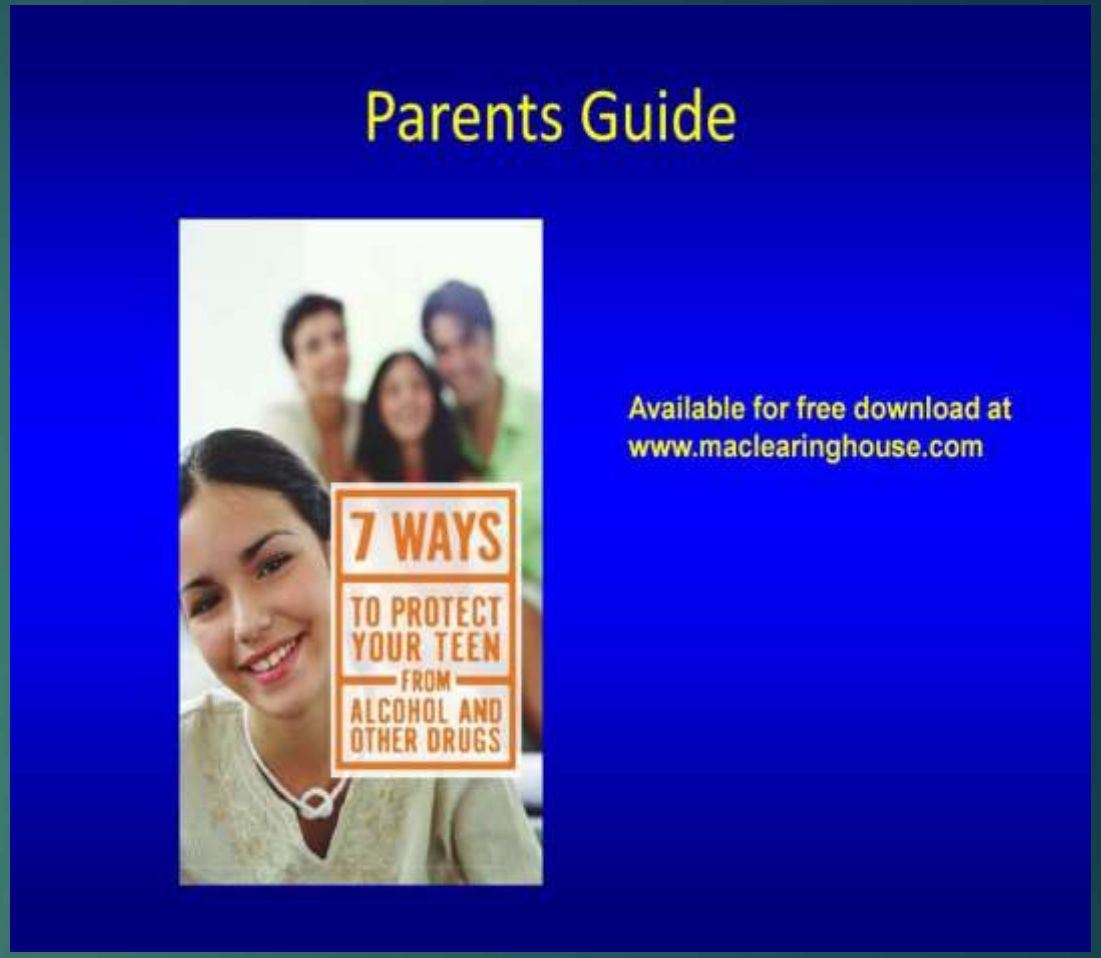
- **Motivational interviewing techniques** to decrease use (harm reduction model)
- **Contingency management** (tangible rewards to reinforce abstinence), and
- **Behavioral skills** training
- Encourage **exercise and cardiorespiratory activities** to increase blood flow to the brain and potentially impact neuronal neuroplasticity.
- Instill lifelong **exercise routines** as a way to counteract the negative impact of marijuana use.

Clinical Interventions

- National Registry of Evidence-Based Program and Practices: SAMHSA & State
- Cognitive Behavioral Therapies: Motivational Interview/Enhancement, DBT coping skills, Contingency Management (CM) & relapse prevention tools
- Levels of Change
- Marijuana Anonymous or other 12-Step group involvement

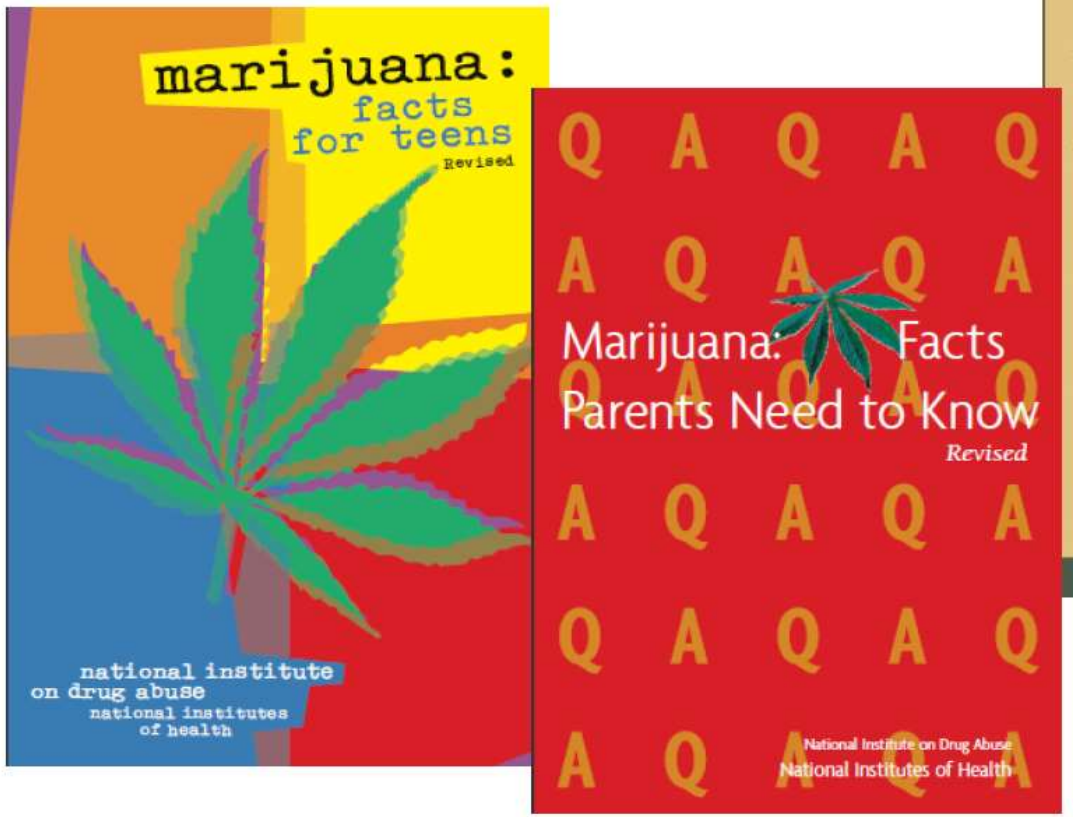
Good websites:

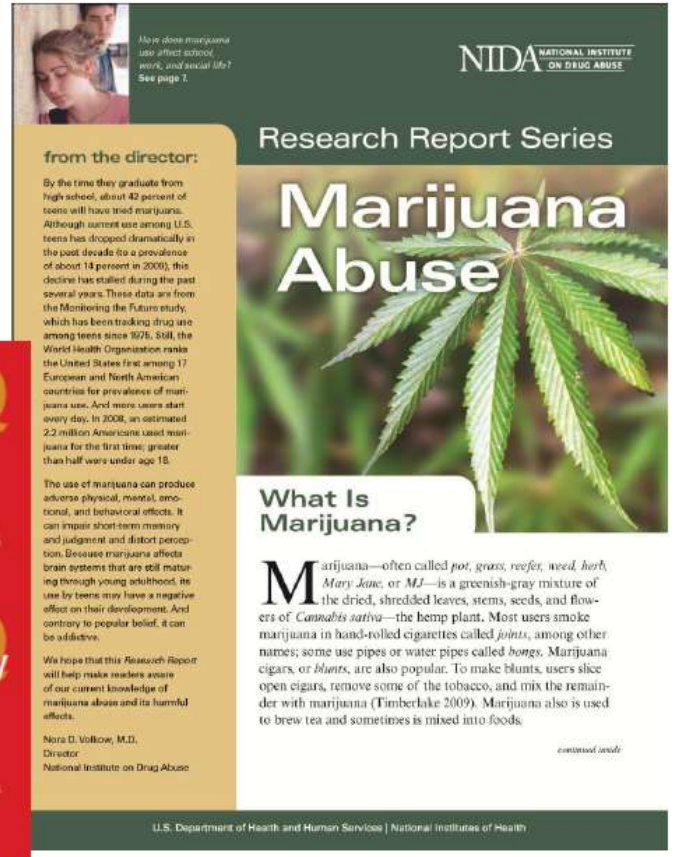
- www.nida.nih.gov
- , www.thecoolspot. gov
- , www.drugfreeamerica.org
- , www.Teen-Safe.org



For More Info Visit NIDA's Website @

www.drugabuse.gov





- Download this talk at:
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