How Cannabis Affects the Body & the Brain

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October 2, 2018

The University of Vermont
LARNER COLLEGE OF MEDICINE

Outline:

Part I: Cannabis Effects on Pain and Pleasure Pathways

Dr. Karen Lounsbury

Part II: Cannabis and the Developing Brain

Dr. Peter Jackson

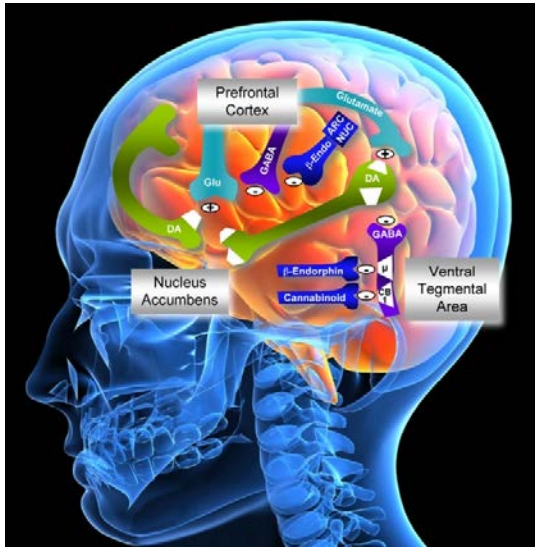
Disclaimer

We are members of the faculty at the University of Vermont

Materials presented here represent our own research, views and opinions and are in no way a reflection of the legal views or opinions of the University of Vermont

Conflict of Interest: Pharmaceuticals will be presented according to their FDA approvals. We have no financial interests to disclose.

Cannabis Effects on Pain and Pleasure Pathways



Karen M. Lounsbury, PhD

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https://www.youtube.com/watch?v=O5RdMvgk8b0

Cannabis: Medicine or Drug of Abuse?

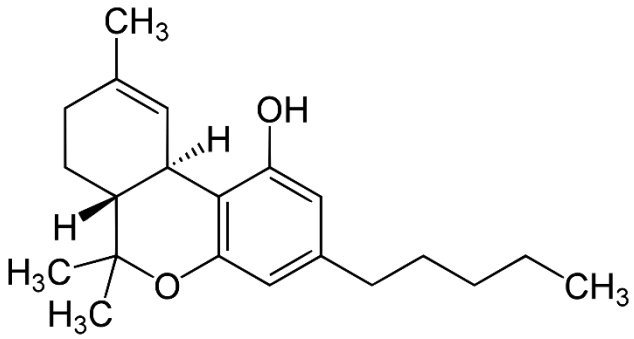
Cannabis and Phytocannabinoids

- *Cannabis* sativa produces many compounds that are secreted by trichromes in the flowers and leaves
- Different strains of *Cannabis* can produce different levels of biologically active components
  - Hemp
  - Charlotte's Web
  - Sativa/Indica

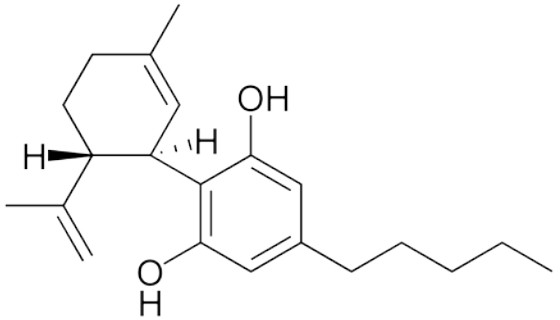
Biologically Active Cannabinoids

Cannabis produces over 100 cannabinoids

- Delta-9-tetrahydrocannabinol (THC)
  - Partial Agonist CB1/CB2 receptors
  - Psychoactive
  - Anti-pain, anti-nausea
  - Anti-spasm, anti-inflammatory



- Cannabidiol (CBD)
  - Weak antagonist CB1/CB2 receptors
  - TRP channels or 5-HT receptors?
  - Not psychoactive, moderates THC
  - Anti-seizure activity, anti-pain activity
  - Possible non-receptor activities



- Activated by heating the plant (smoking, vaping, baking, heat extraction)

Cannabis as a Medicine

- Proven effectiveness (THC):
  - Chronic Pain
  - Chemotherapy-induced Nausea
  - Seizures
  - Spasticity (MS and Cerebral Palsy)
  - Cachexia (wasting disorder)
- Likely effective and in clinical trials (THC):
  - Eating Disorders
  - Glaucoma
  - Anxiety Disorders (OCD, PTSD)
- Possibly effective, but needs more research (THC)
  - Addiction
  - Parkinson's/Alzheimer's
  - Inflammatory Diseases
  - Cancer

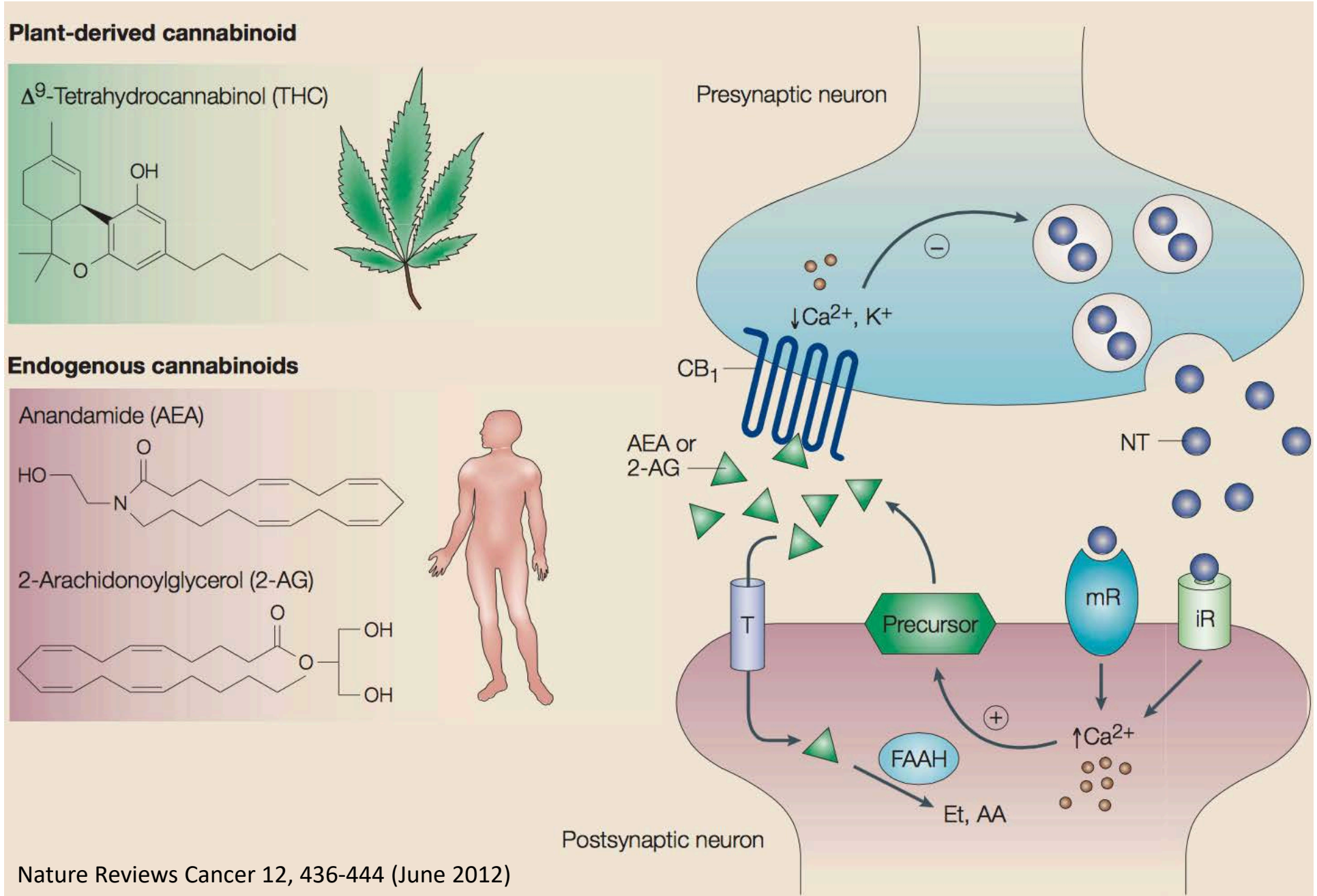
*Proven effectiveness is through randomized clinical trials using **THC**. Whole plant cannabis has been found effective for Pain, Nausea and Seizures, but these trials are sparse and nonexistent for other conditions.*

***CBD** has only been found effective against seizures, other trials have not shown significant effectiveness, but more are needed*

Lynch and Ware. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. Journal of Neuroimmune Pharmacology 10: 293-301, 2015

Wilsey et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008

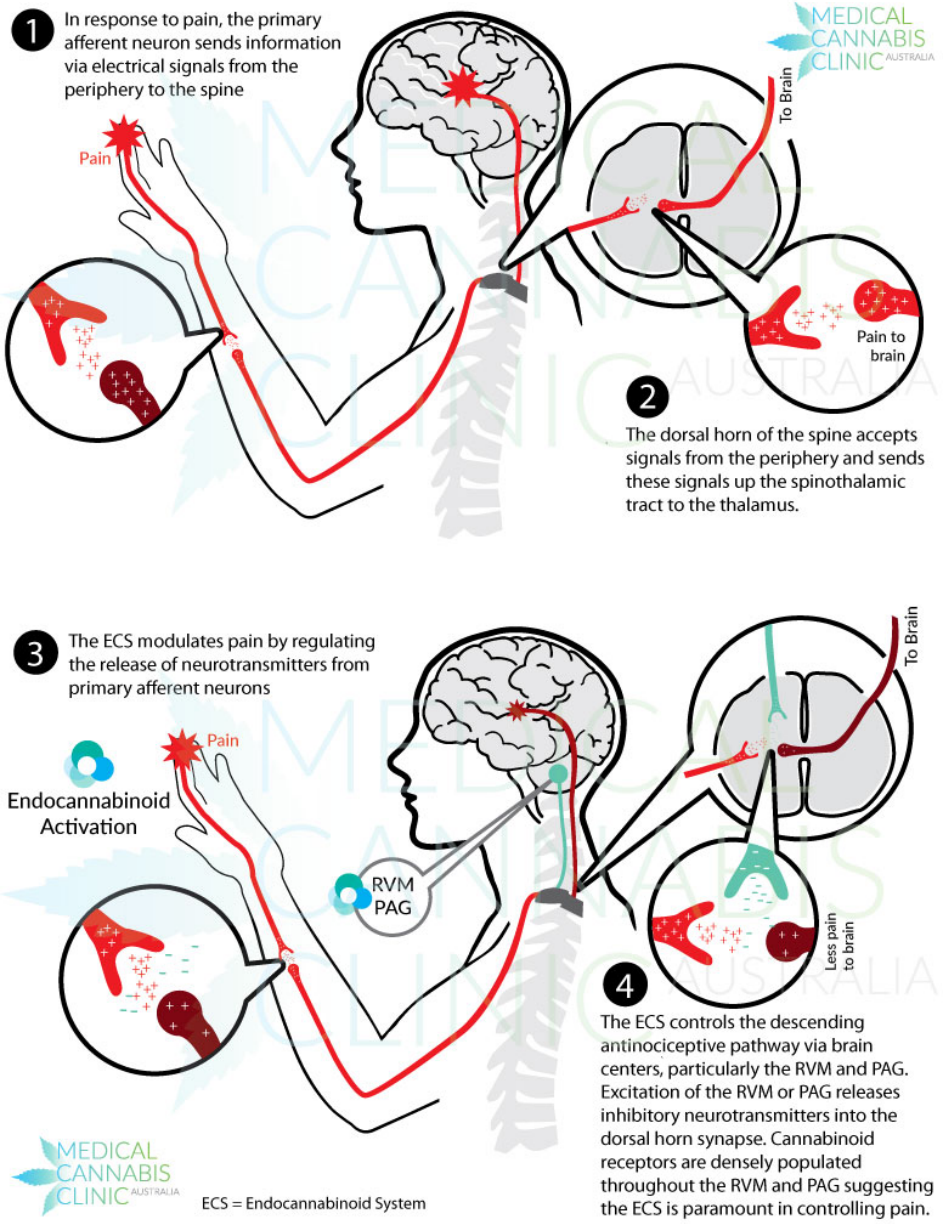
Your body makes its own cannabinoids



Nature Reviews Cancer 12, 436-444 (June 2012)

Cannabinoid Receptors reduce neuronal activity in response to pain, nausea, and anxiety

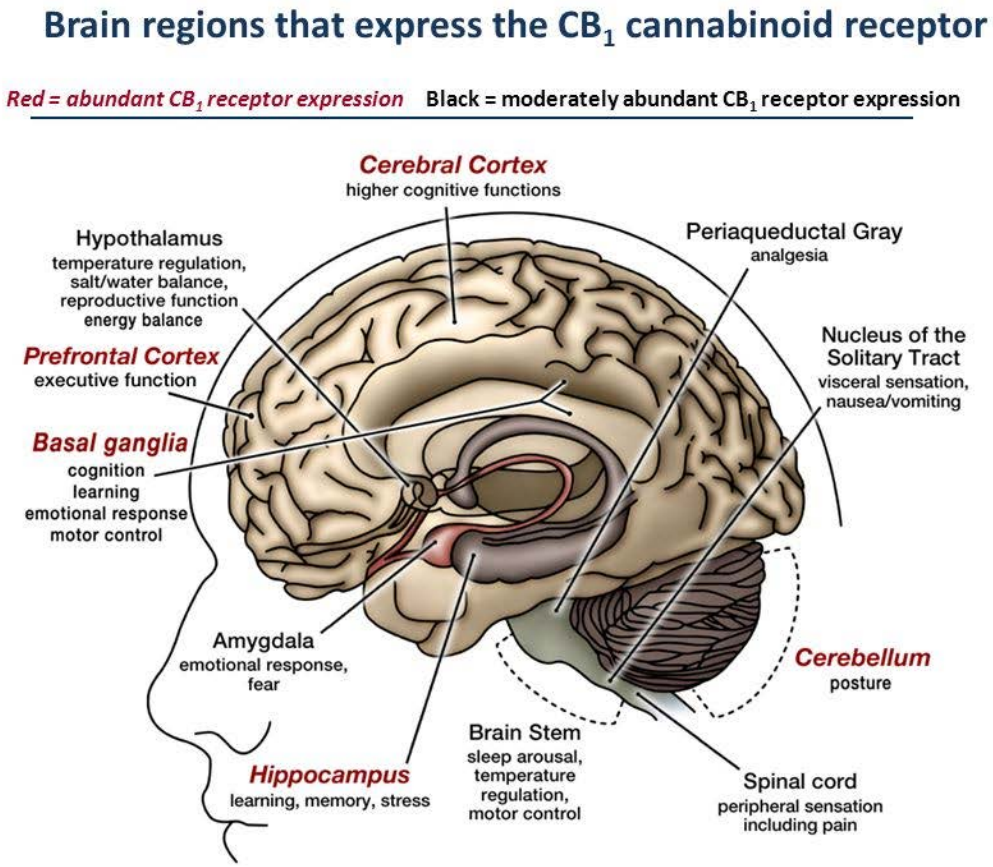
- Both endocannabinoids and cannabis reduce both pain signal and interpretation of pain
- Similar to the action of opioids
  - Not as effective
  - Produce less tolerance
  - Less risk of addiction
  - Low risk of overdose



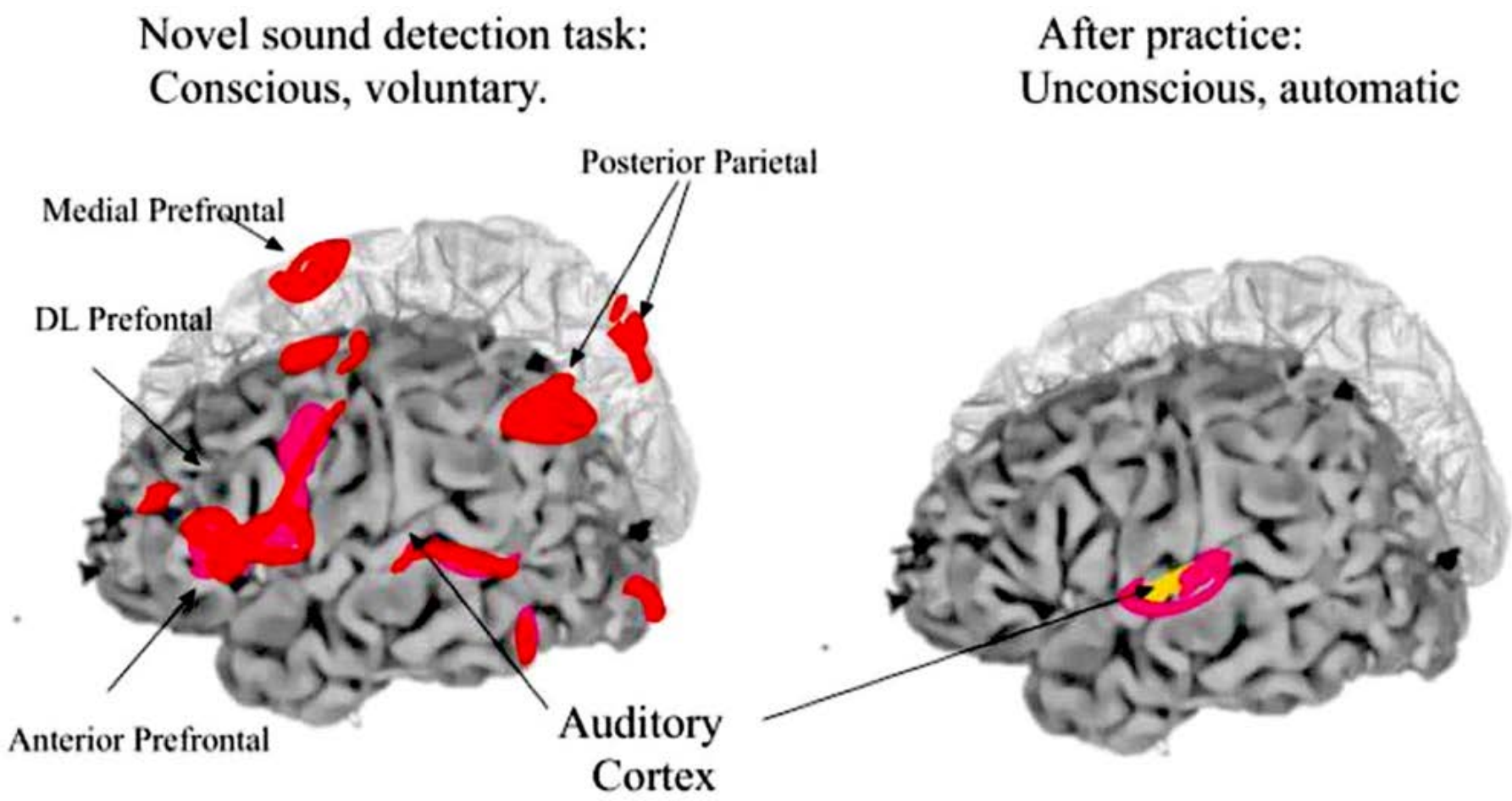
Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain, 2012
http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.html

Cannabis Intoxication:

- *Attributed to THC action in the brain*
- Head rush and euphoria (Reward Pathway)
- Appetite increase (Hypothalamus)
- Decreased attention, sedation (Hippocampus-Prefrontal cortex)
- Altered Perceptions (Pre-frontal cortex inhibition)
  - Awareness of the senses and of music may be increased
  - Distorted sense of time
  - Preoccupation with distractions
  - Giggles



Pre-frontal Cortex is primarily active in response to new experiences



“Executive” functions of the Pre-frontal Cortex

- Planning, organization and execution of complex behavioral sequences (Working Memory)
- Flexible responses to changing environmental contingencies
- Selective attention, noticing change
- Persistence in a task despite distraction
- Creative problem solving

Perception is a combination of sensory input and pre-frontal cortex executive function


Through learning, we are able to distinguish errors in the environment

Activities that can Reduce the Activity of Pre-Frontal Cortex

- Meditation
- Intense Exercise
  - Runner's High
  - reduction of pain sensations
  - widespread activation of motor and sensory systems during exercise shunts activity from the higher cognitive centers of the prefrontal cortex.
- Daydreaming
  - Frontal cortex is disengaged
  - Activities are controlled by automatic functions
  - Can perform complex automatic activities (like driving a normal route)
- Some Drugs of Abuse
  - Cannabis, Opioids

Cannabis Effects on Attention: Impaired ability to drive

- Peripheral attention reduced
  - A person who is high may become absorbed in an object, event, or process to the exclusion of everything else
- Memory
  - Both short-term and long-term memory impairment
- Color/Image Perception
  - Hallucinogenic effects
- Motor Coordination
  - Impaired, but much less than alcohol or opioids

States with legalized recreational use have seen increased car accidents in the population that has combined alcohol and cannabis, but there is no significant difference in fatal car accidents in states with legalized cannabis

Frontal Cortex Impairment: The Problem with Distractors

Stroop task: Identify the color of the words

RED

GREEN

RED

BLUE

BLUE

GREEN

BLUE

RED

Again: Identify the color of the words

GREEN

BLUE

RED

BLUE

GREEN

RED

GREEN

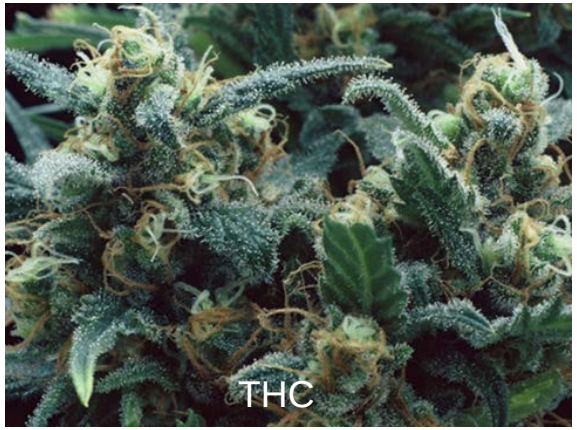
BLUE

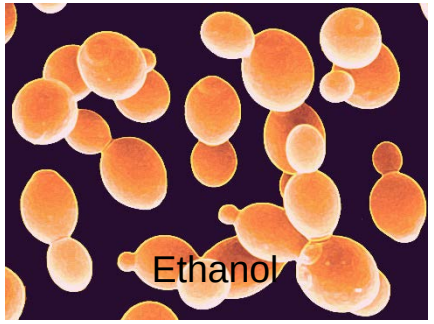
Subjects intoxicated by THC have a much longer delay in completing the Stroop Test

Cannabis Addiction in Perspective

- 30 million drugs are currently known
- Approximately 100 are addicting
- Many are natural products

- What properties make drugs addicting?



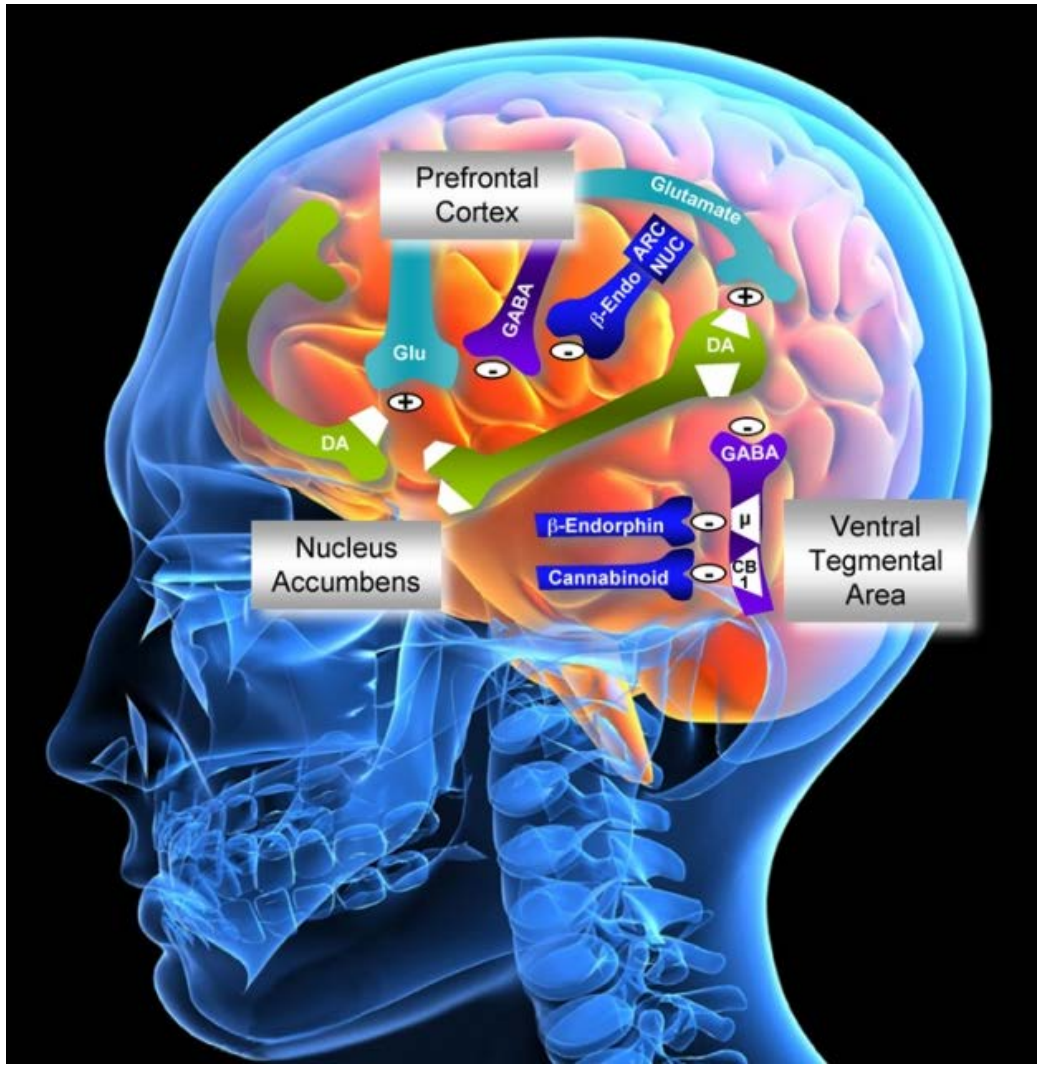


Common Properties of Addicting Drugs

- Stimulate Dopamine signaling in the Reward Pathway
- Rapid acting, can get into the brain
- Withdrawal of drug inhibits the Reward Pathway
- Voluntarily administered (specifically to the reward center in animal models)
- Trigger relapse to drug-seeking behavior

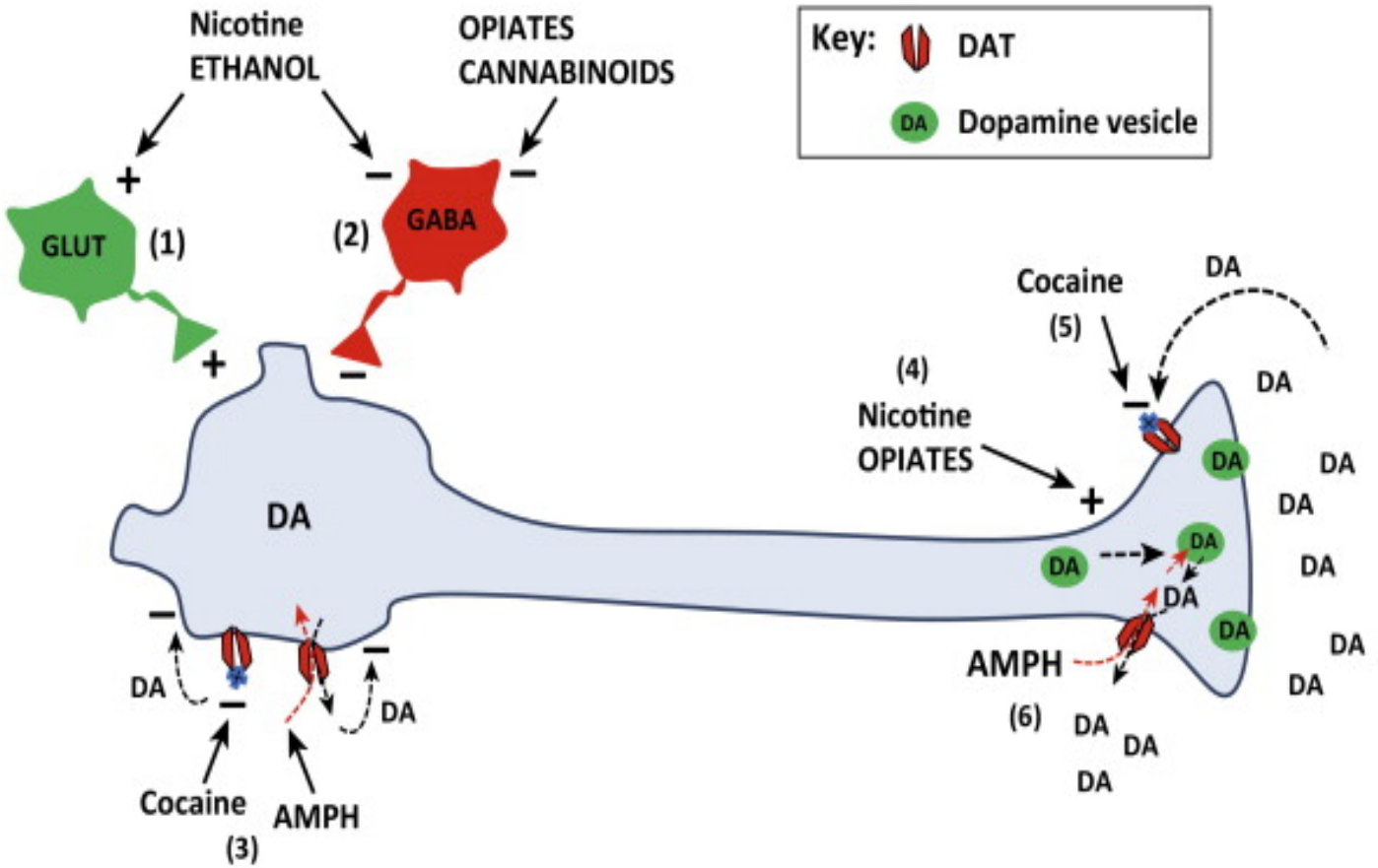
The Reward Pathway:

- Connects limbic regions of the brain
  - Ventral tegmental area
  - Nucleus accumbens
  - Pre-frontal cortex
- Dopamine receptor signaling tracts
- Overactivity is linked to psychologic addiction



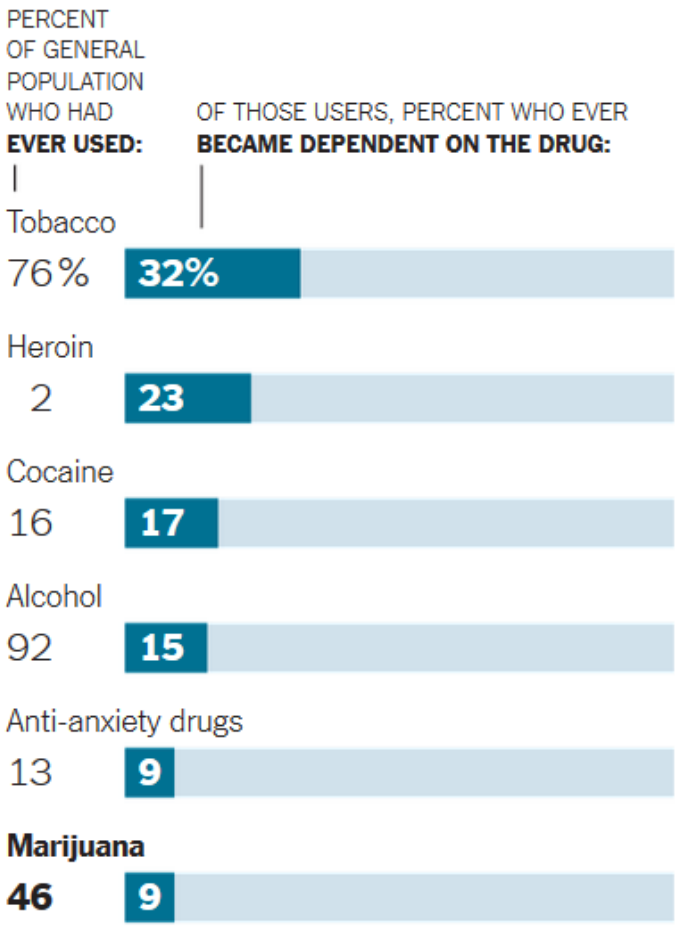
https://inside-the-brain.com/2014/10/17/drugs-addiction-and-the-brain/

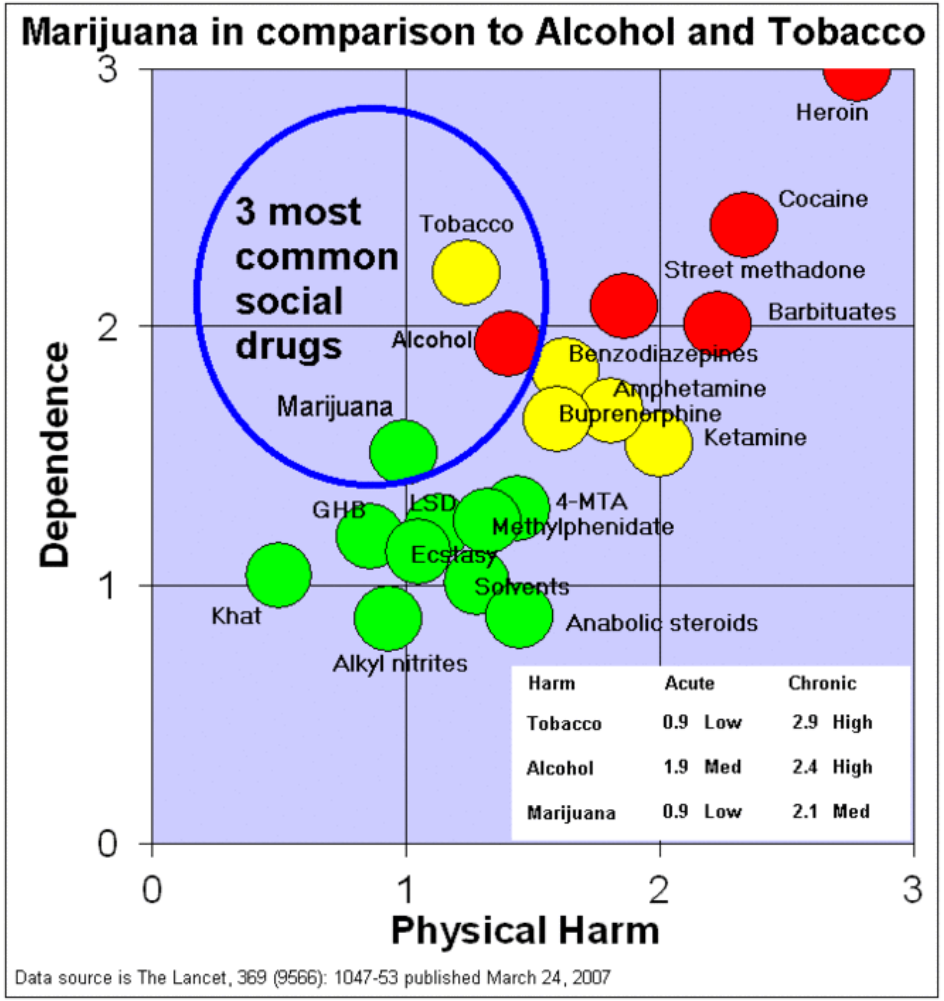
Effects of Addicting Drugs on DA signaling: Highjacking reward



Trends in Neuroscience, Volume 37, April 2014

Cannabis Addiction Potential





Young People are Particularly Vulnerable

- Substantially higher risk for Substance use disorder when an addicting drug is started before the age of 18, even higher risk with younger patients
- Chronic adverse effects of cannabis are more likely to develop in younger patients

- Dr. Jackson will now provide the viewpoint of a child psychiatrist

Cannabis and the Developing Brain

Peter R Jackson, MD

Community Medical School

October 2, 2019

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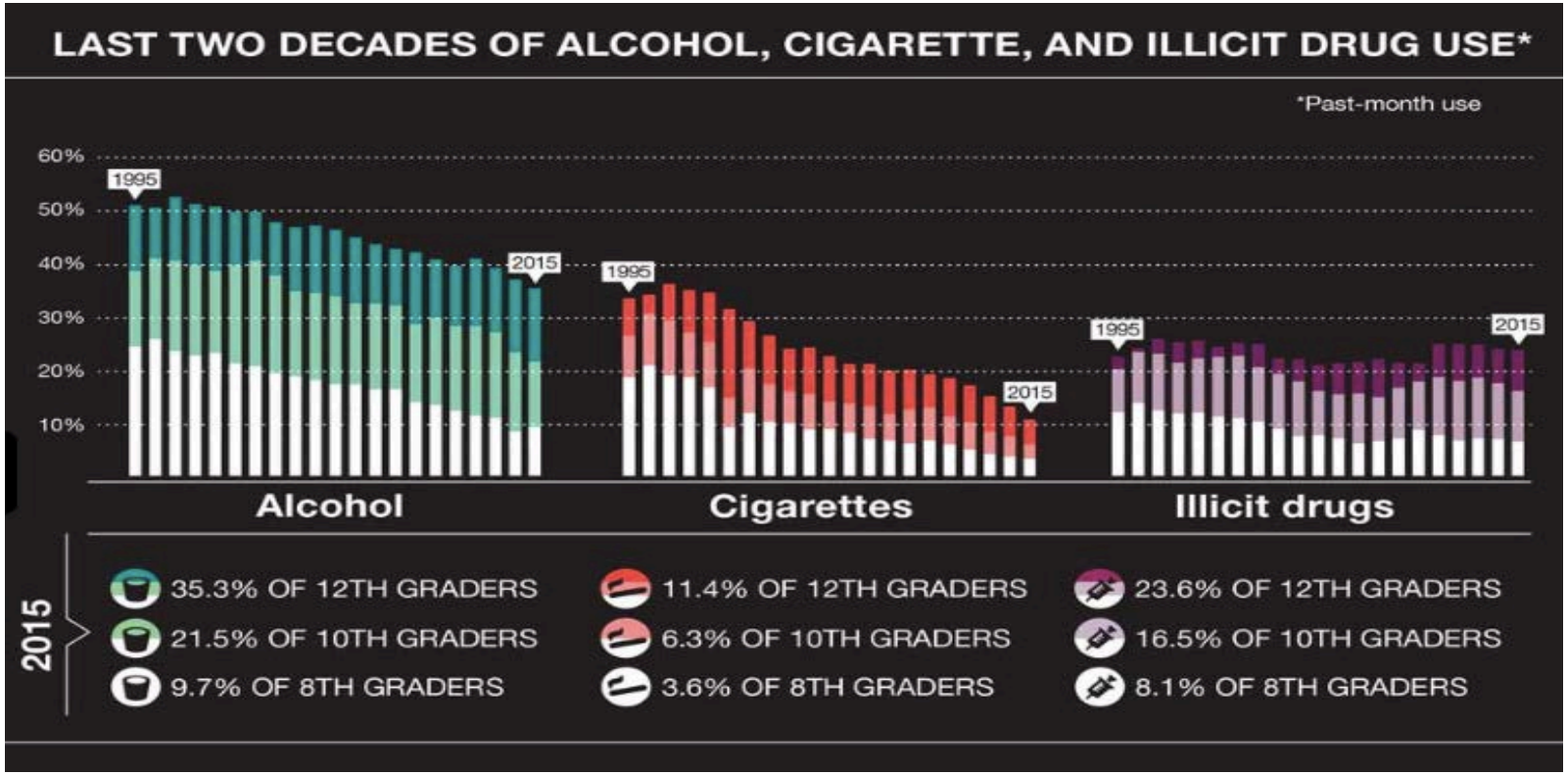
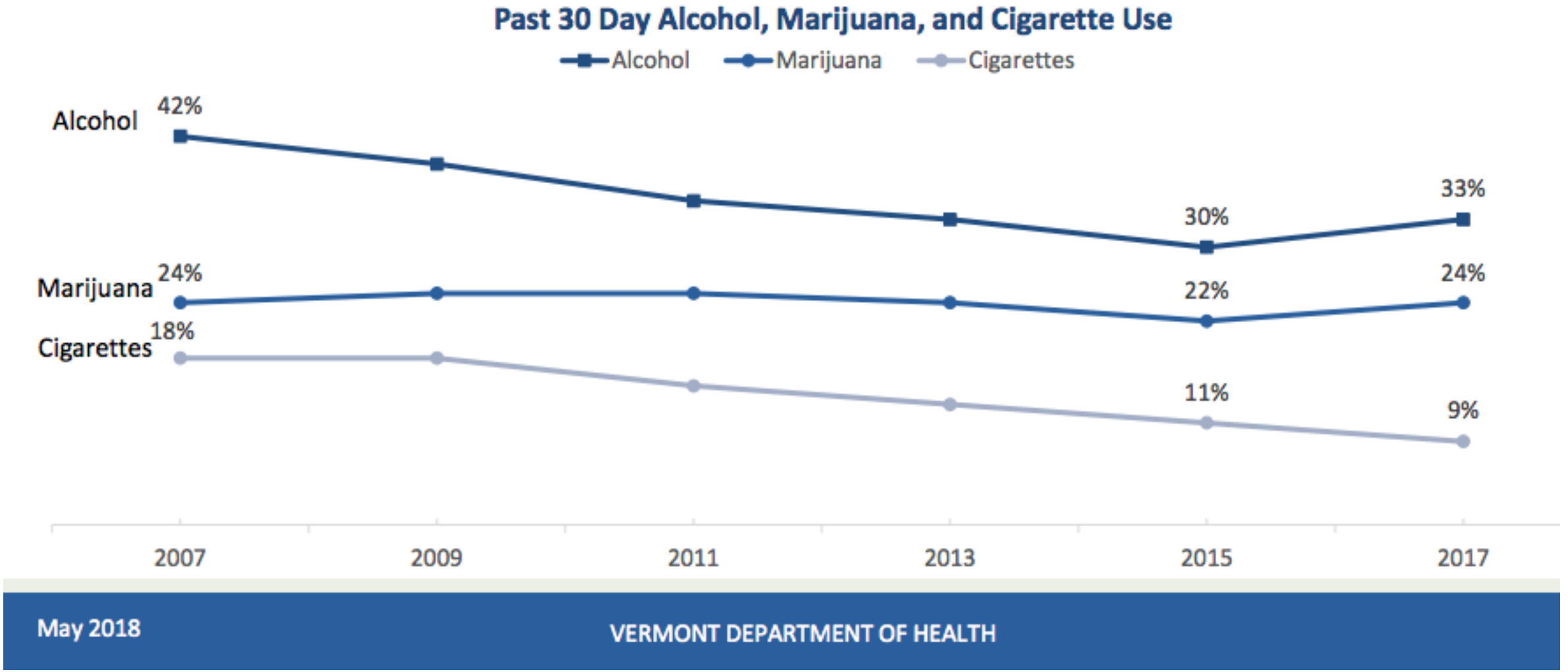
Outline: Cannabis use and the teenage brain

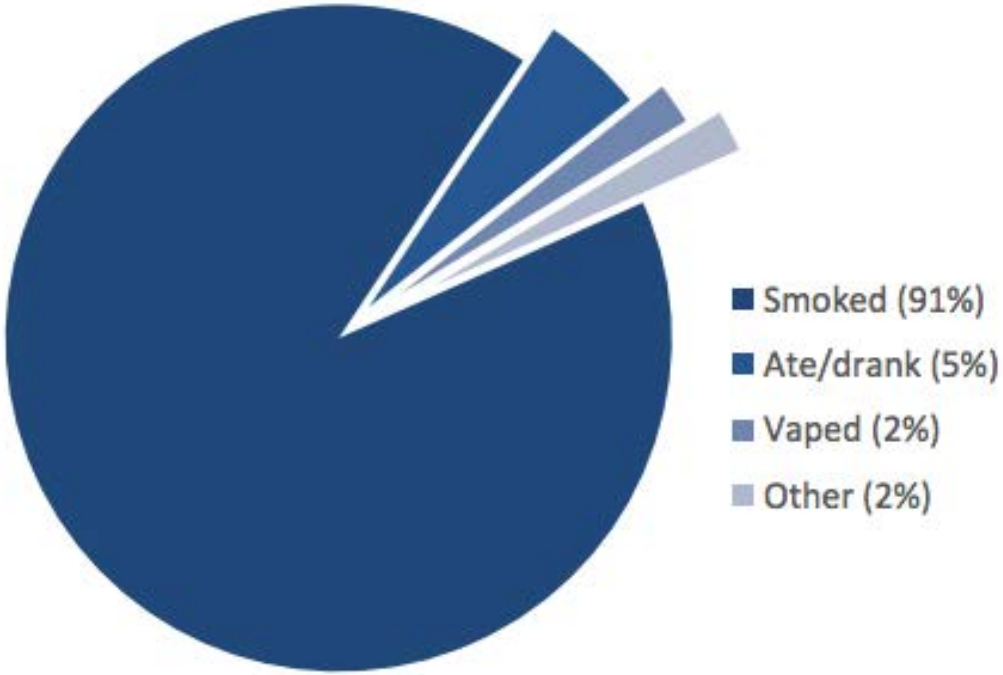
- What's the trend?
- What's great (different) about the adolescent brain and why it matters
- Potential therapeutic benefits vs. well known risks
- A word to the parents in behalf of the kids
- Seeking solid ground

National trends




Past 30 Day Alcohol, Marijuana, and Cigarette Use
Alcohol
Marijuana
Cigarettes
Alcohol
42%
30%
33%
Marijuana
24%
22%
24%
Cigarettes
18%
11%
9%
2007
2009
2011
2013
2015
2017
May 2018
VERMONT DEPARTMENT OF HEALTH

Primary Methods Used to Consume Marijuana, Among Current Users



May 2018

VERMONT DEPARTMENT OF HEALTH

Vermont trends: Middle school

Middle school students believing their parents would think it was wrong to:

Use alcohol: 85% (down from 91% in 2015)

Use marijuana: 92% (down from 94% in 2015)

Current middle school student marijuana use: 4% (unchanged)

Vermont Trends: High School

High School students believing their parents would think it was wrong to:

Use alcohol: 66% (down from 72% in 2015)

Use marijuana: 76% (down from 80% in 2015)

Current high school student marijuana use: 24% (up from 22%)

Vermont Trends: High School

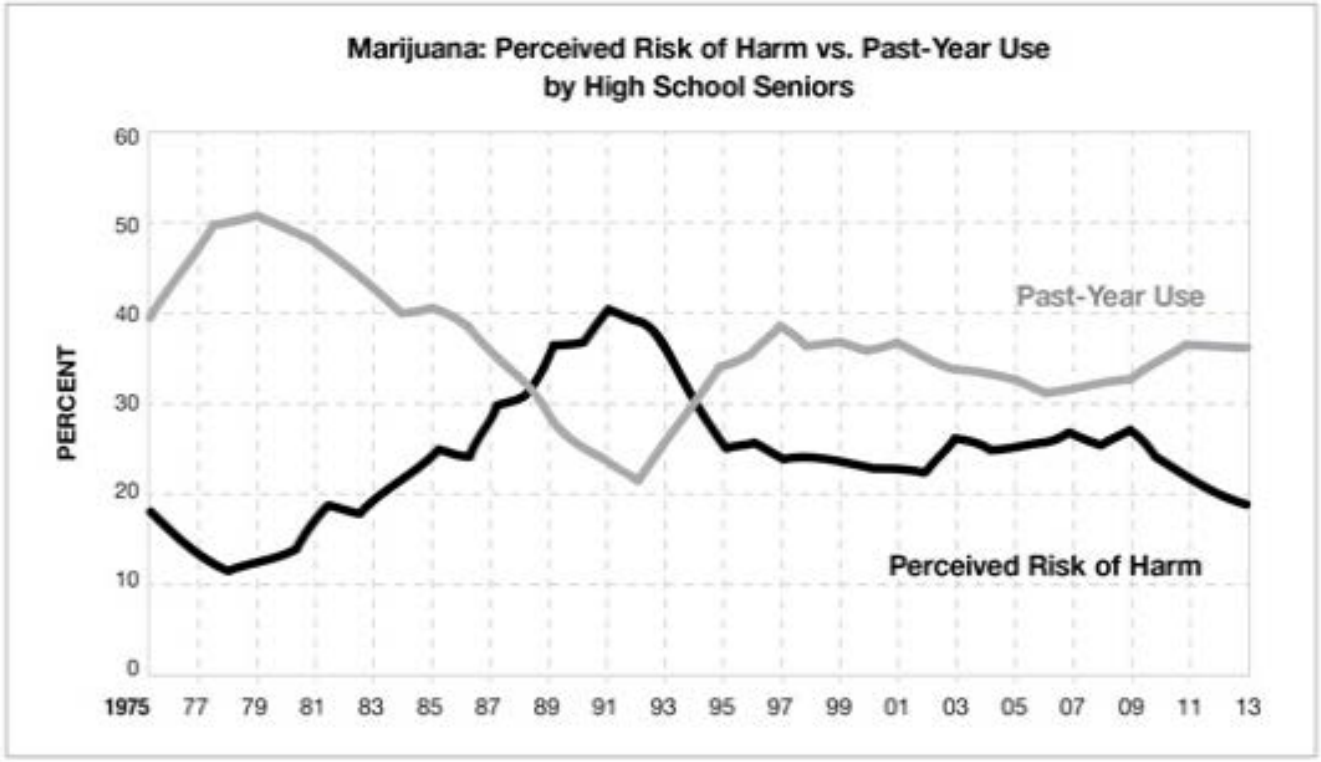
High School students believing there is a great risk of harm from:

Binge drinking regularly: 36%

Smoking a pack or more of cigarettes: 68%

Using marijuana regularly: 24%

Perception of harm and rates of use



High school graduation isn't the finish line

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Source: National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services.

What's happening where recreational use is legal?

Those states have higher than average rates of adolescent use (they were already near the top)

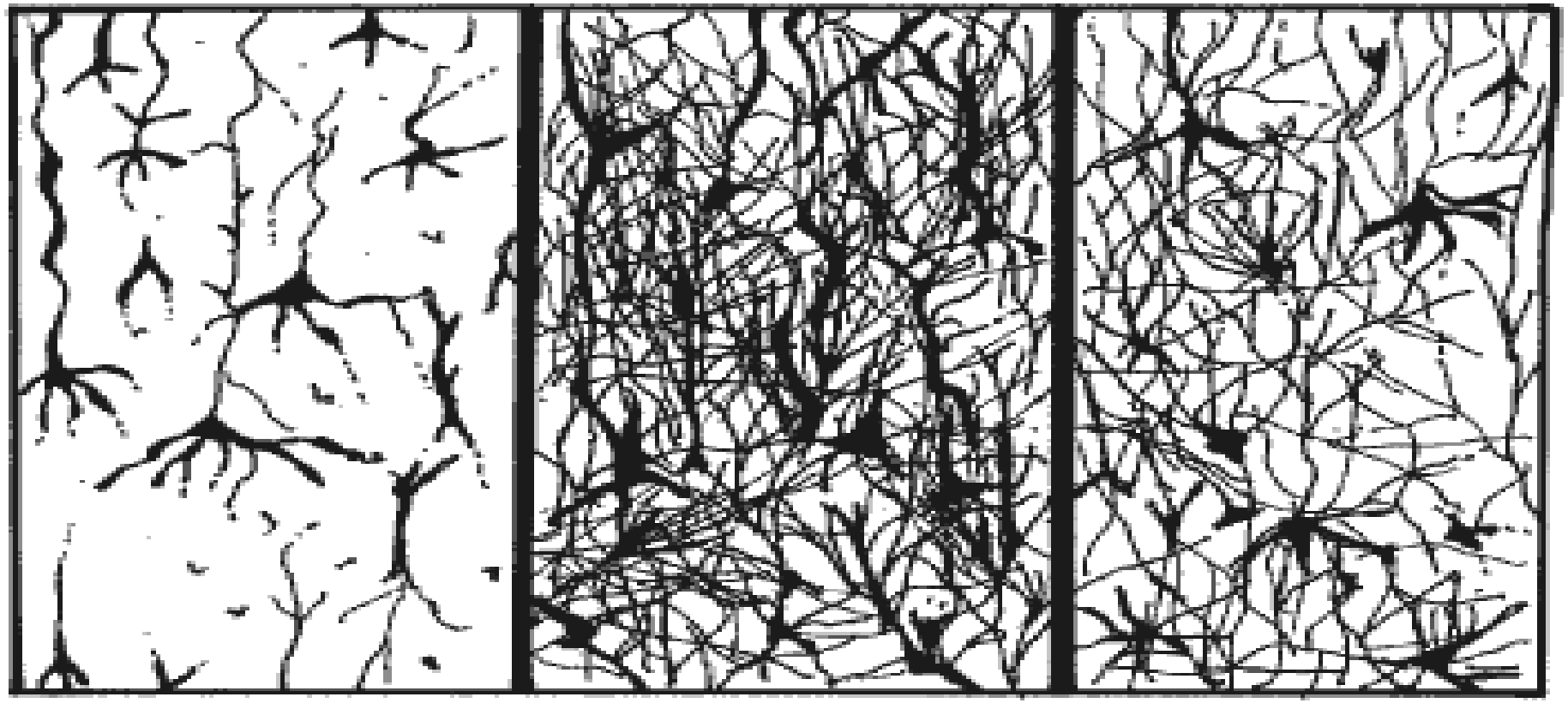
Adolescent use trend is increasing in some states where legalized compared to holding steady for most states. (NSDUH) Conflicting studies abound

The rate of college age use, which is increasing nationally is increasing faster than the national average

Adolescent use rates correlate with availability (density of dispensaries: Colorado data)

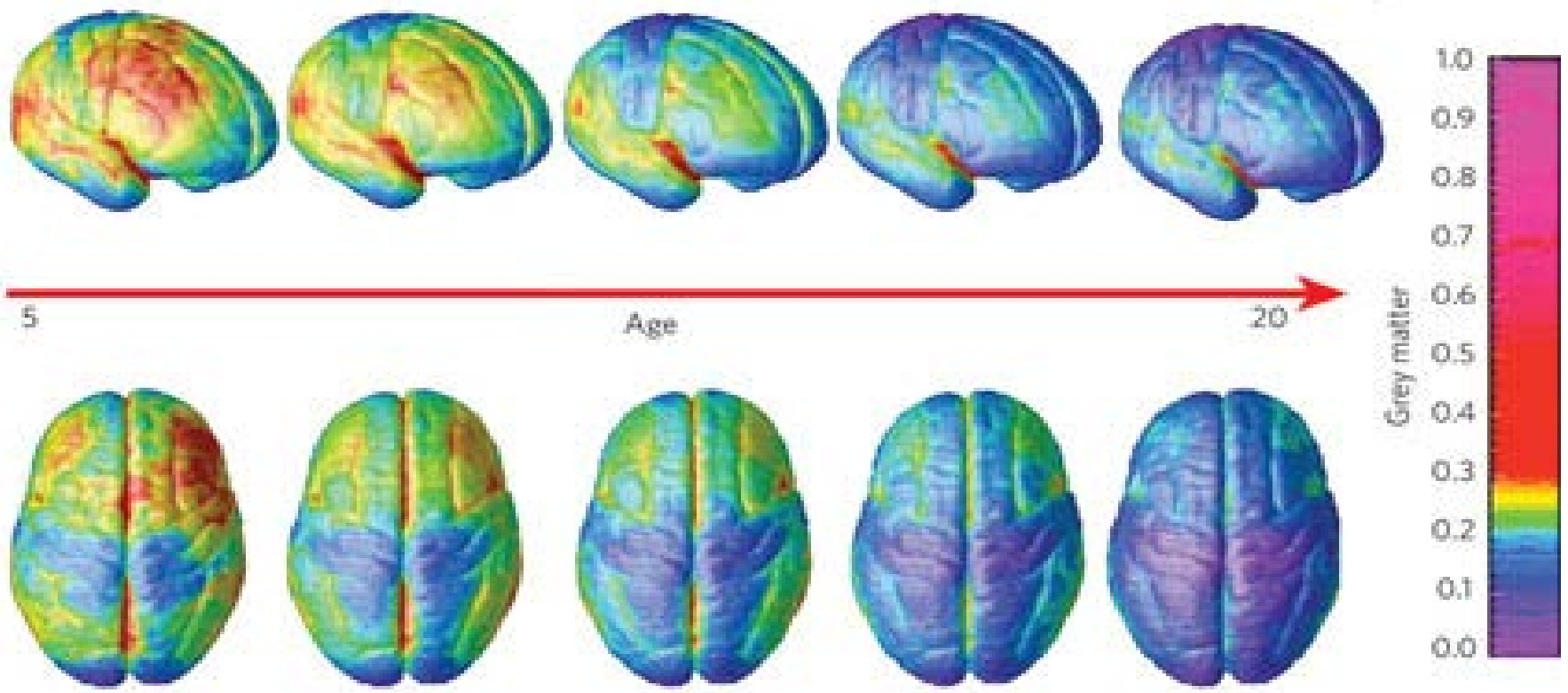
Marketing targets all audiences, including young people

Marketing



at a child's birth at 7 years of age at 15 years of age

Brain development: Efficiency and connectivity



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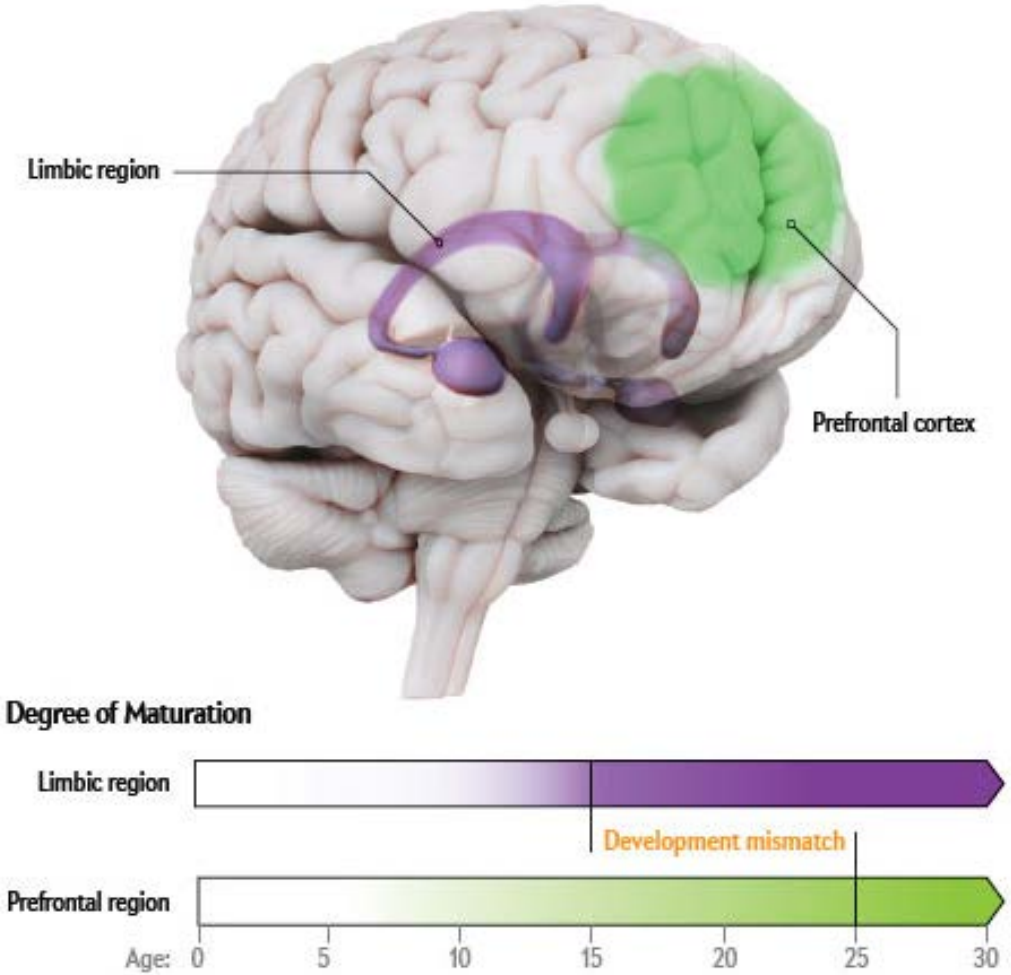
Staggered development: Gas before brakes



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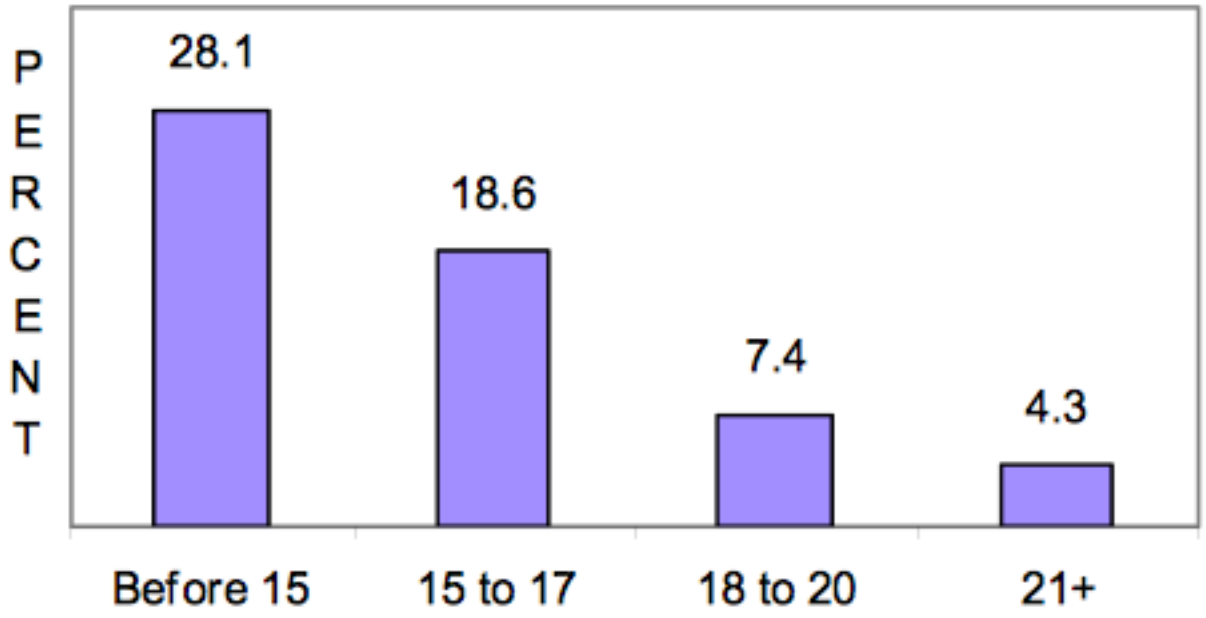
Geidd 2015

Substance Use Disorders Among Persons 12 and Older, by Age of First Use



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

Higher risk for earlier use

4 to 7 times more likely to develop a use disorder if you use cannabis prior to age 18 compared to in adulthood. (Winters et al)

1 in 6 adolescents who use will develop a use disorder

What's the upside… What's the downside?

Adverse effects of early use

Negative impact on synaptic pruning and myelination

Cognitive effects:

- Verbal learning, recall, attention most impacted
- some studies showing measurable IQ decrease later in life (Meier et al)
- Some studies showing deficits improve after abstinence

Association with increased incidence of psychosis

Increase likelihood of anxiety disorders (Degenhardt et al)

Increased likelihood of depression (Rubino et al)

Amotivation, related to blunting of the dopaminergic system with chronic use (Bloomfield et al)

Adverse effects of use: short term

Inattention

Impaired reaction time: doubled risk of car accident

Short term memory impairment

Adverse effect of adolescent use: long term

Decreased white matter integrity: poorer connectivity

Poorer attention, processing speed, working memory

Impaired memory: decreased hippocampus volume

Effect on the brain: Hot topics

Cognition

Potential neuropsychological decline into the late 30s for adolescent users compared to adult onset use

Some studies show that this can recover with abstinence

Motivation

Long term heavy use particularly associated with educational underachievement and impaired motivation

Psychosis

Consistent association between adolescent cannabis use and psychosis. Could come from direct causality, gene-environment interaction, shared etiology.

Medical Use of Cannabinoids in Children or Adolescents

Marijuana not FDA approved for the prevention or treatment of any disease process in kids

Evidence for cannabinoids

- Rare and severe forms of epilepsy: Recent FDA approval: Epidiolex (highly purified CBD) approved June 2018 for pediatrics seizures (Lennox Gastaut, Dravit Syndrome)
- Stronger signal: Chemotherapy induced nausea and vomiting (THC)
- Weaker signal/anecdotal: Tourette Syndrome, Spasticity, neuropathic pain, PTSD

“What should I tell parents about the medical benefits for adolescents or children?”

- Benefits have been primarily in case reports, risks are well established
- We will likely learn more as research continues

Note the process of prescribing any medication

- medication, dose, route, frequency

American Academy of Pediatrics

- Opposes medical marijuana outside FDA process
- Opposes legalization for recreational use
- Supports research (move from schedule I to schedule II)
- Strict enforcement of rules against marketing and sale to children (age 21 minimum)
- Supports decriminalization for both adults and youth
- Opposes smoking in any form
- Strongly Discourages any use in the presence of children

AMA position statement: Cannabinoid research

1. Study proposed/promising areas for benefit, see if we can expand the evidence from anecdotal to controlled trials
    1. Reconsider the schedule I status
    2. Put more funding towards it
2. Study the consequences of long term use, particularly in high risk groups
3. Don’t legalize recreational use until we know more about the public health, medical, social and economic consequences of use

AMA position statement: Legalization for medical use

1. Any treatment should be studied to assure safety
2. Should not be done through state legislative, referendum or ballot initiatives
3. Anything not approved labeled “marijuana has a high potential for abuse.”
4. Protect physicians working within state laws
5. Don’t legalize recreational use until we know more about the public health, medical, social and economic consequences of use

What aspects convey the highest risks?

Age of onset of use?

Frequency of use?

Duration of use?

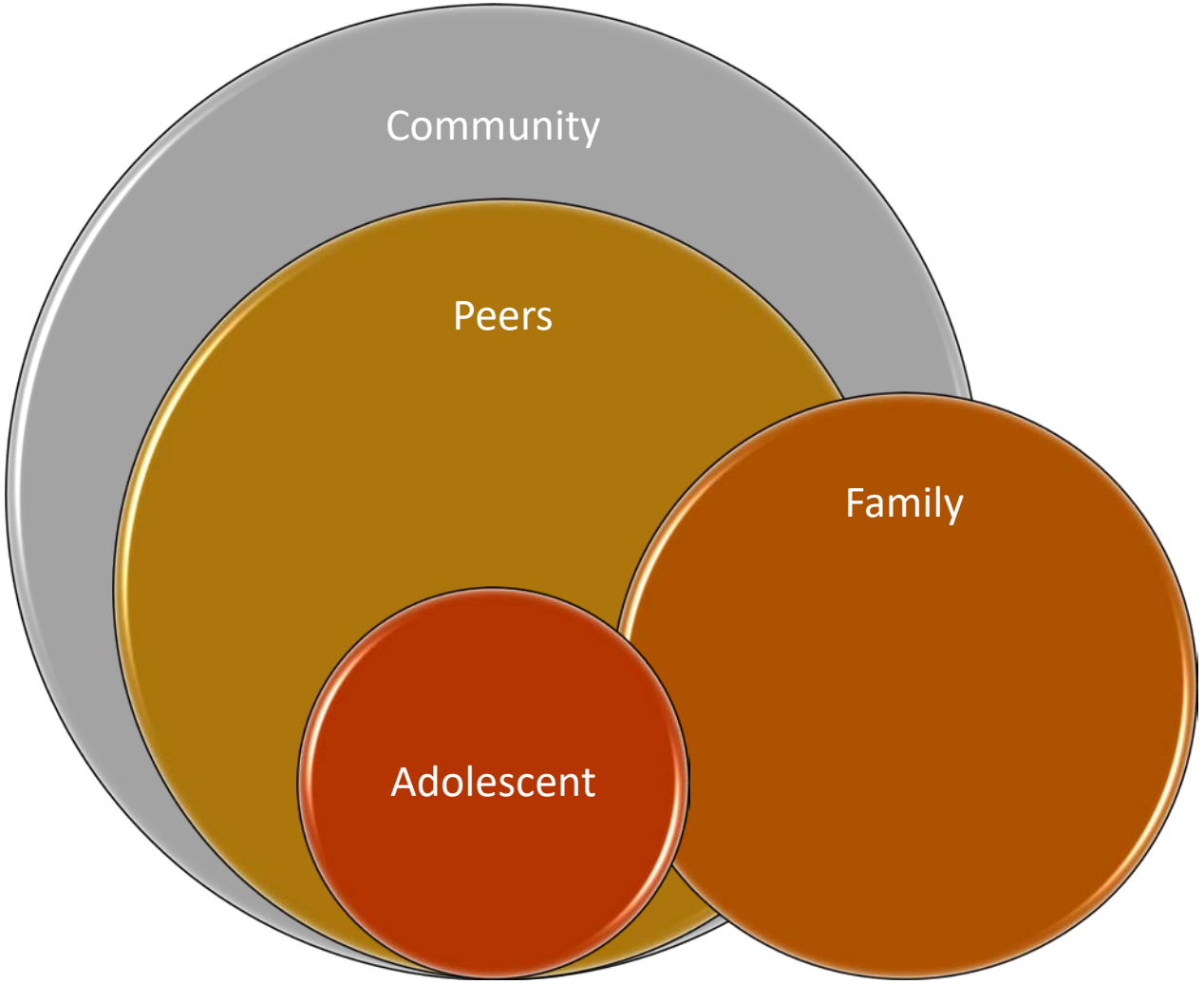
Quantity used?

Strength/potency?

Composition (THC vs. CBD vs. other cannabinoids)?

Teaching, Nurturing, Protecting

Importance of Family



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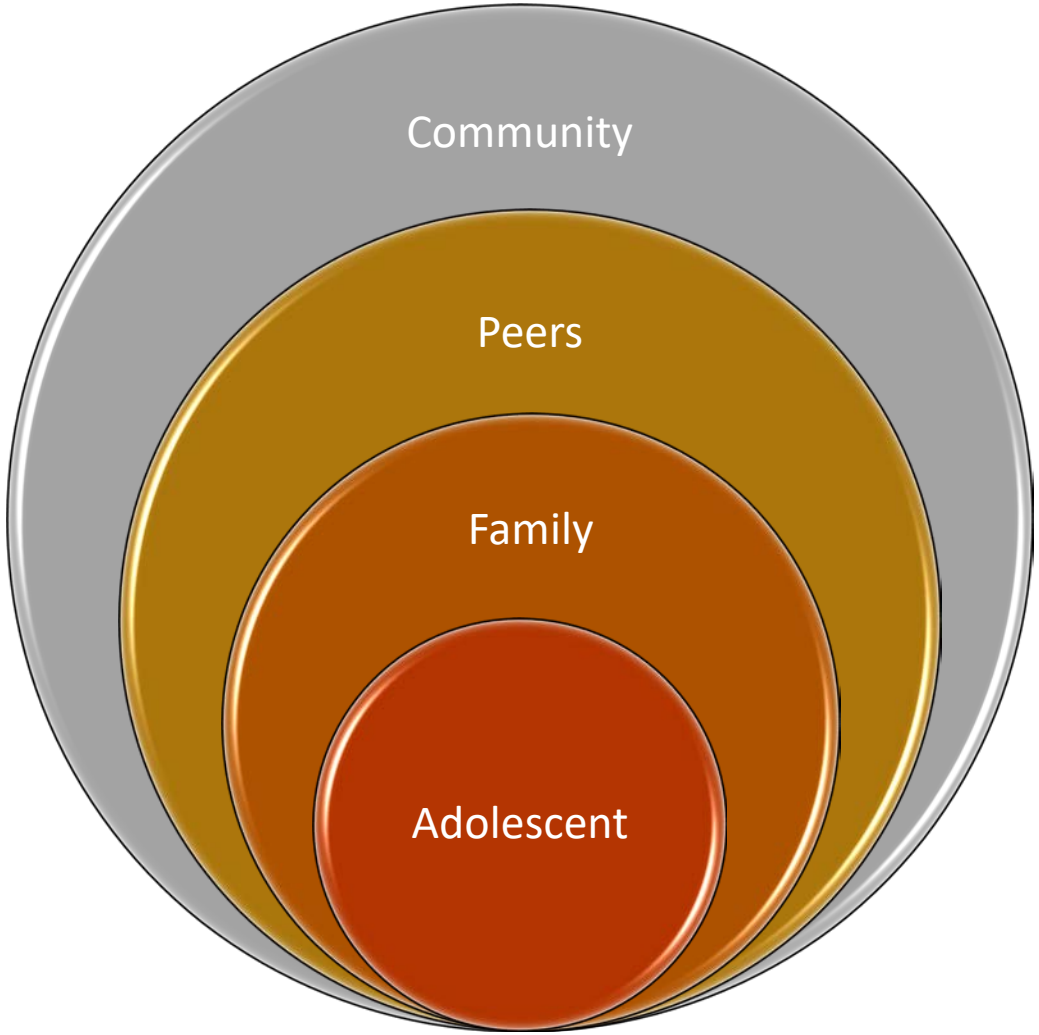
Importance of Family



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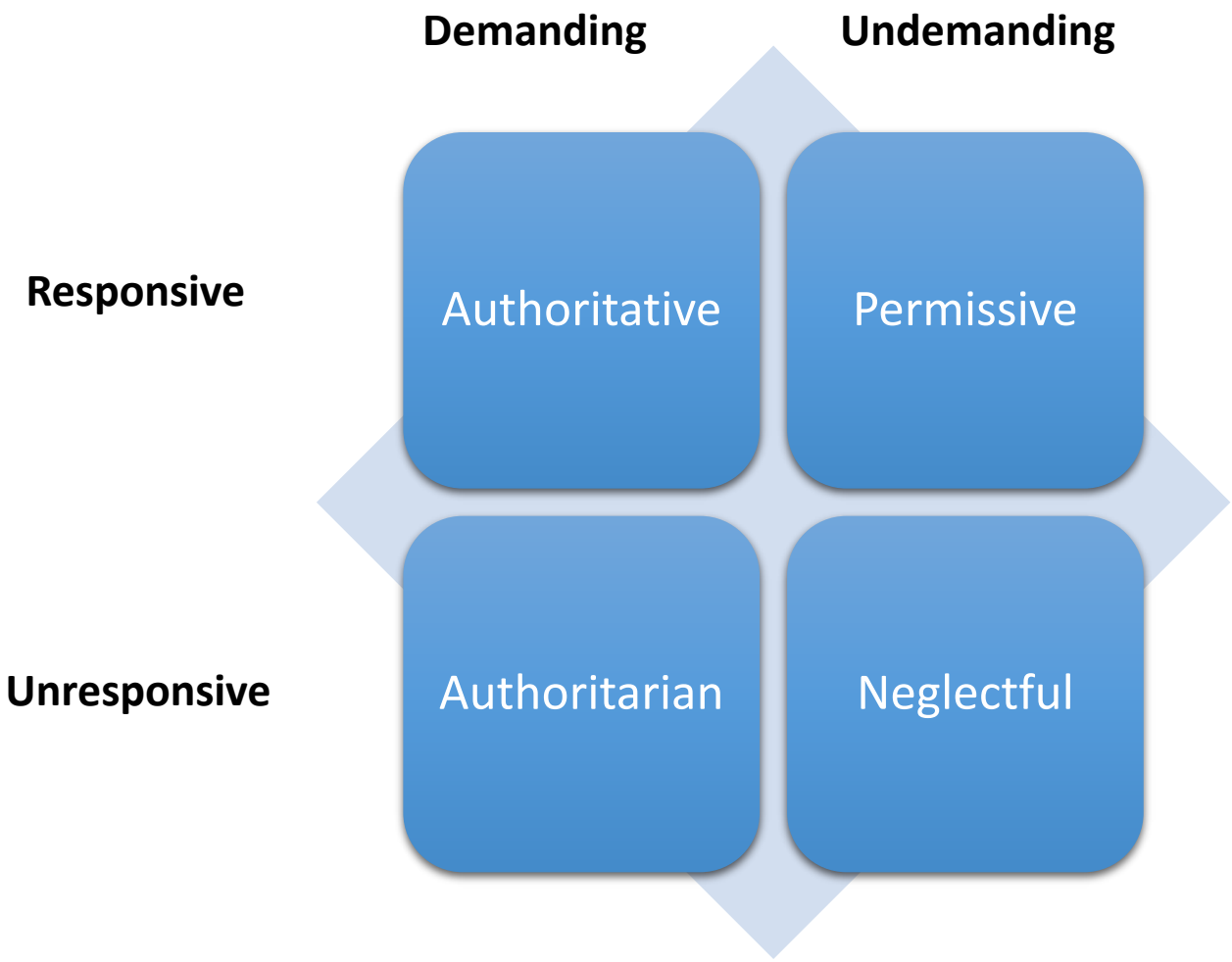
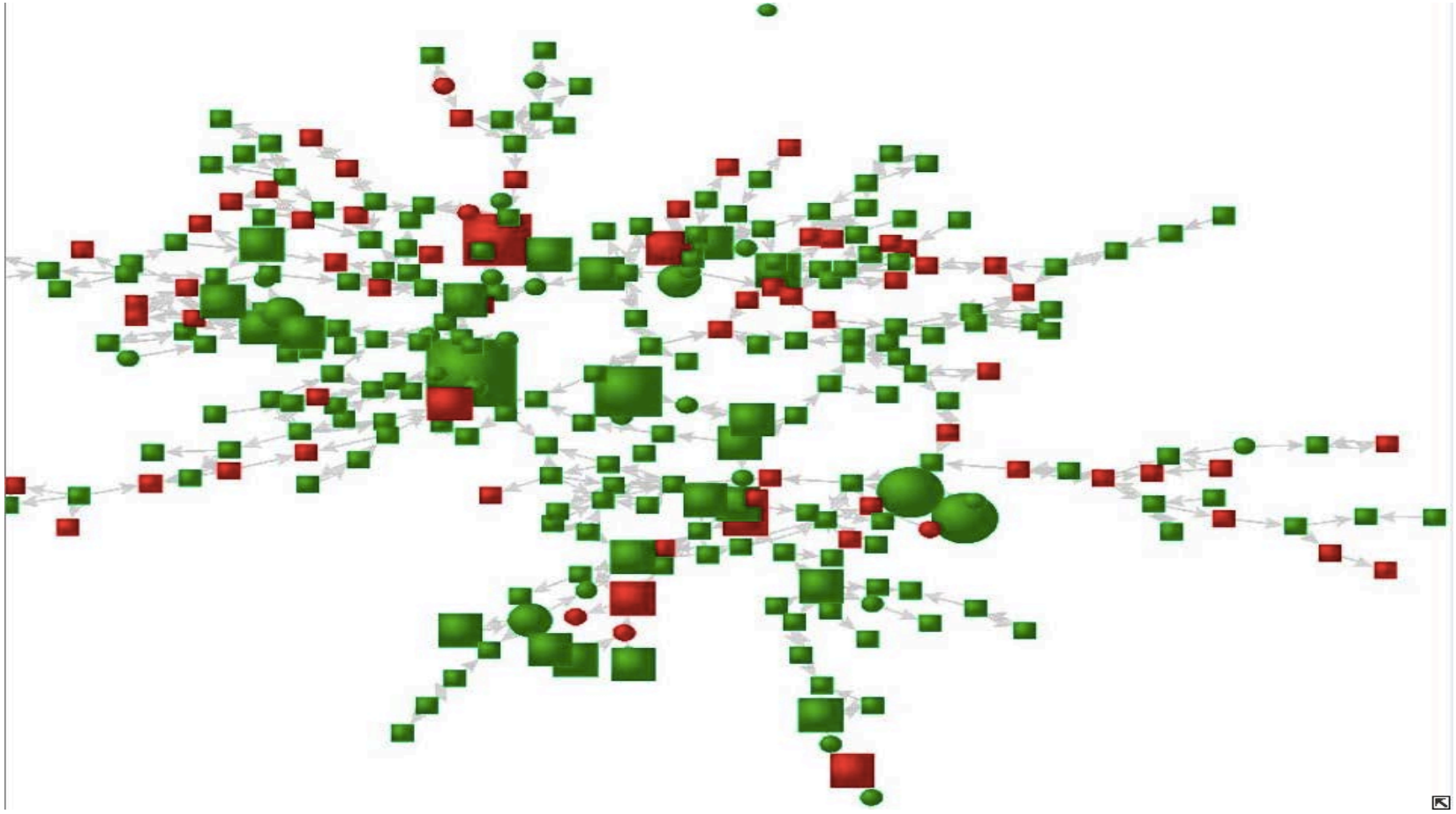
Parenting Style



Parental Influence



Shakya, Christakis and Fowler, 2012

Positive Parenting

Communication: calm and clear

Encouragement: of positive behaviors

Negotiation: working towards solution when conflict arises

Setting Limits: calmly and in proportion to behaviors

Supervision: know friends and schedule

Dishion T et al 2003

How do I talk about this with my kids?

Talk early, talk often

Talk with them when calm, not when angry or “high”

Stay calm but serious, not angry

Tell them what you’re worried about, then listen

ParentupVT.org (parent monitoring checklist, “Free marijuana talk kit”)

Warning signs:

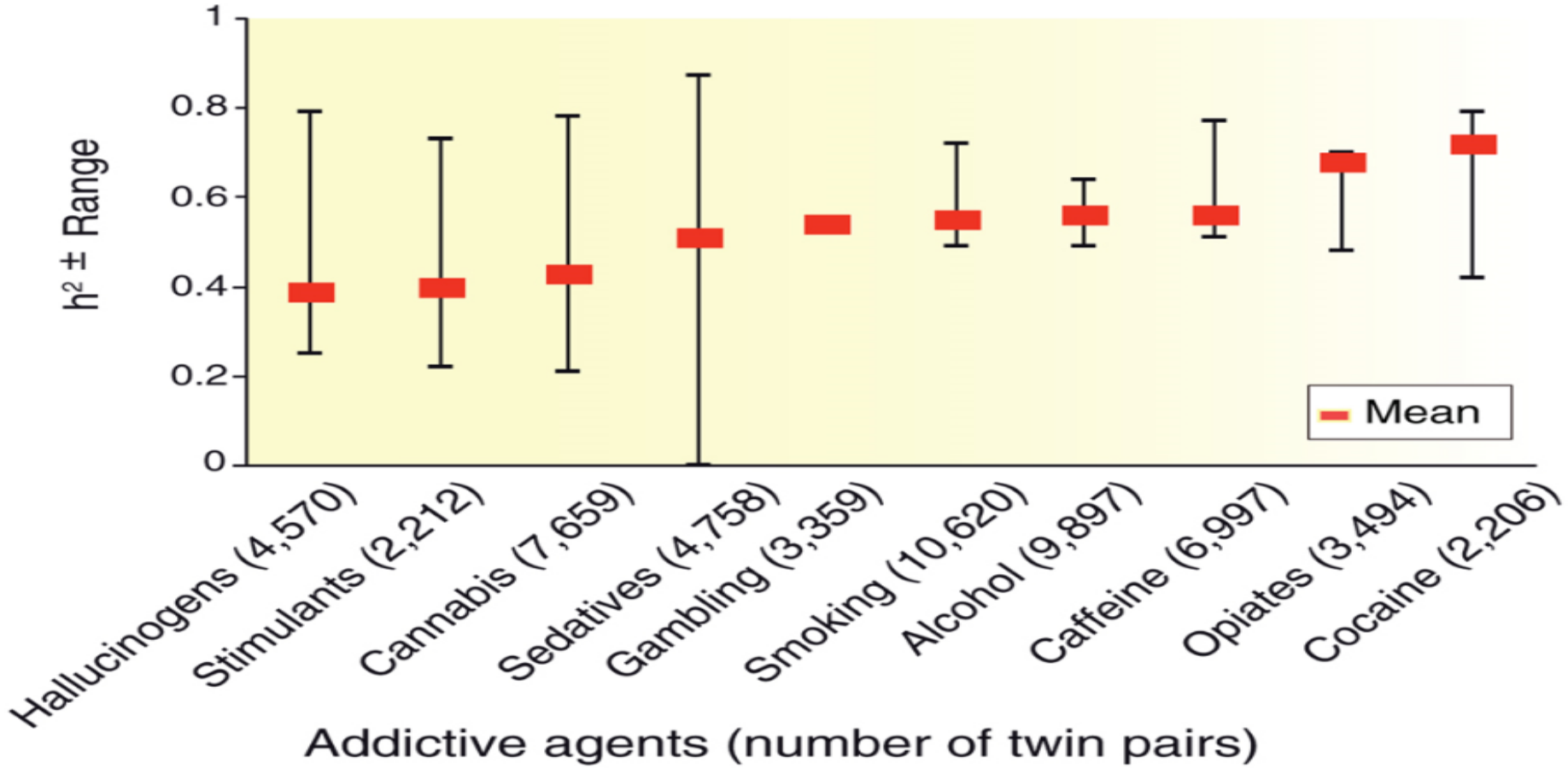
Mood and behavior changes: restlessness, paranoia, loss of interest

Rapid peer change and reluctance to introduce new peers

Notable drop in grades, declining participation in school

Significant change in concentration, memory lapses

Genes and addiction



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Bevilaqua L et al 2009

For Parents

Actions speak louder than words

Words speak louder than no words

If substance use disorders have been a problem in the family, give good consideration to educating younger generations early on.

There ARE “sober kids” at school.

Seeking Solid Ground

How have we gotten here?

Grassroots activism

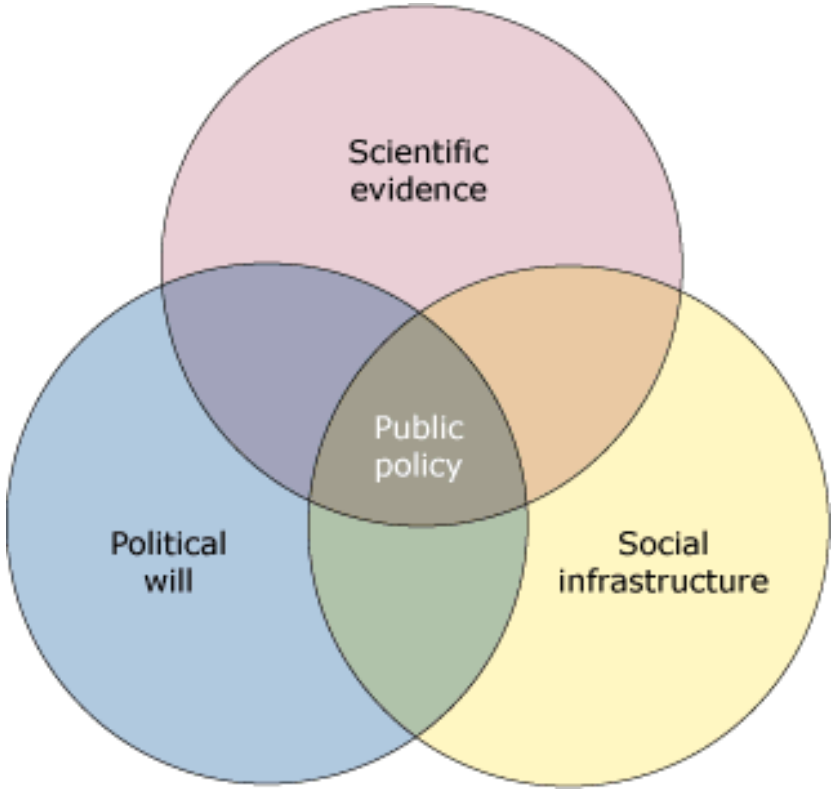
Pharmacological ingenuity

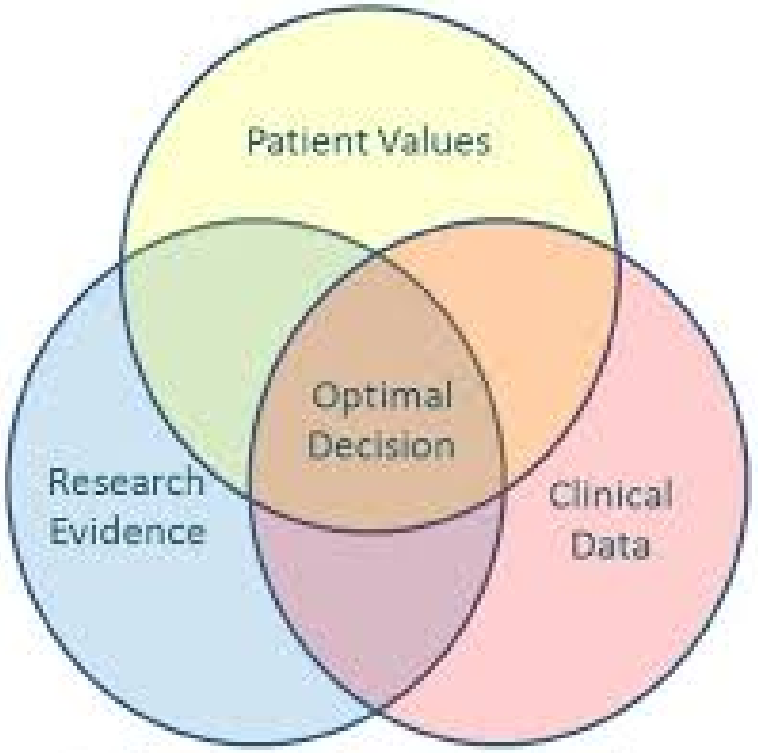
Private Profiteering

Policy moving ahead of science, with gaps in knowledge, underestimation of unintended consequences.

Volkow et. al, JAMA Psychiatry 2016

Seeking Solid Ground





Evidence Based Medicine: when best evidence from research meets clinical information and patient values, optimal decisions are possible.
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