Cannabinoids and the Adolescent Brain

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Disclosures

- Dr. Tapert does not have financial or other relationship with the manufacturer(s) of any commercial product(s) or provider(s) of any commercial service(s) discussed in this CE activity.
- This presentation will not include discussion of off-label, experimental, and /or investigational use of drugs or devices.

Learning Objectives

1. Review the rates of marijuana use and marijuana use disorders, particularly with focus on the adolescent population.

2. Describe and understand brain structure and function affected by the illicit use of marijuana among adolescents.

3. Summarize negative outcomes of marijuana use including poor cognition, behavior, academic and social functioning and explain why the adolescent population still developing neural connections, is particularly susceptible to poor long term outcomes.

4. Design a plan for providers' role in the education and treatment of marijuana use disorders and how better to identify and comprehensively manage teens using marijuana.

Overview

- Rates of marijuana use and disorders
- Does cannabis use affect the adolescent brain?
- Negative outcomes of marijuana use
- Education, prevention, and treatment

Cannabis: Smoking Joints, Bowls, Pipes

- Measure in grams per occasion
- 1 joint= .5 grams
- 1 blunt= 1-2 grams.
- 1 bowl=.25-.5 grams.

Blunts (+/- tobacco)

Bong

Joints

Bowl

Cannabis: Edibles

- Cookies, brownies, candies…
- Measure in times used and mg of THC
- Standard “serving size” in Colorado is 10 mg

Hash & Concentrates

- Concentrated marijuana with high THC content
- Hash: purified cannabis resin
- Wax/Dabs: ~40mg; 1 gram has 25 40mg doses
- Kief: dry concentrate
- Water hash: bubble hash, solventless wax, ice wax
- C02 Oil: BHO (solvent extracted): wax, shatter, crumble, oil, honeycomb

Bubble hash

Wax

Budder

Dabs

Vape pen

Shatter

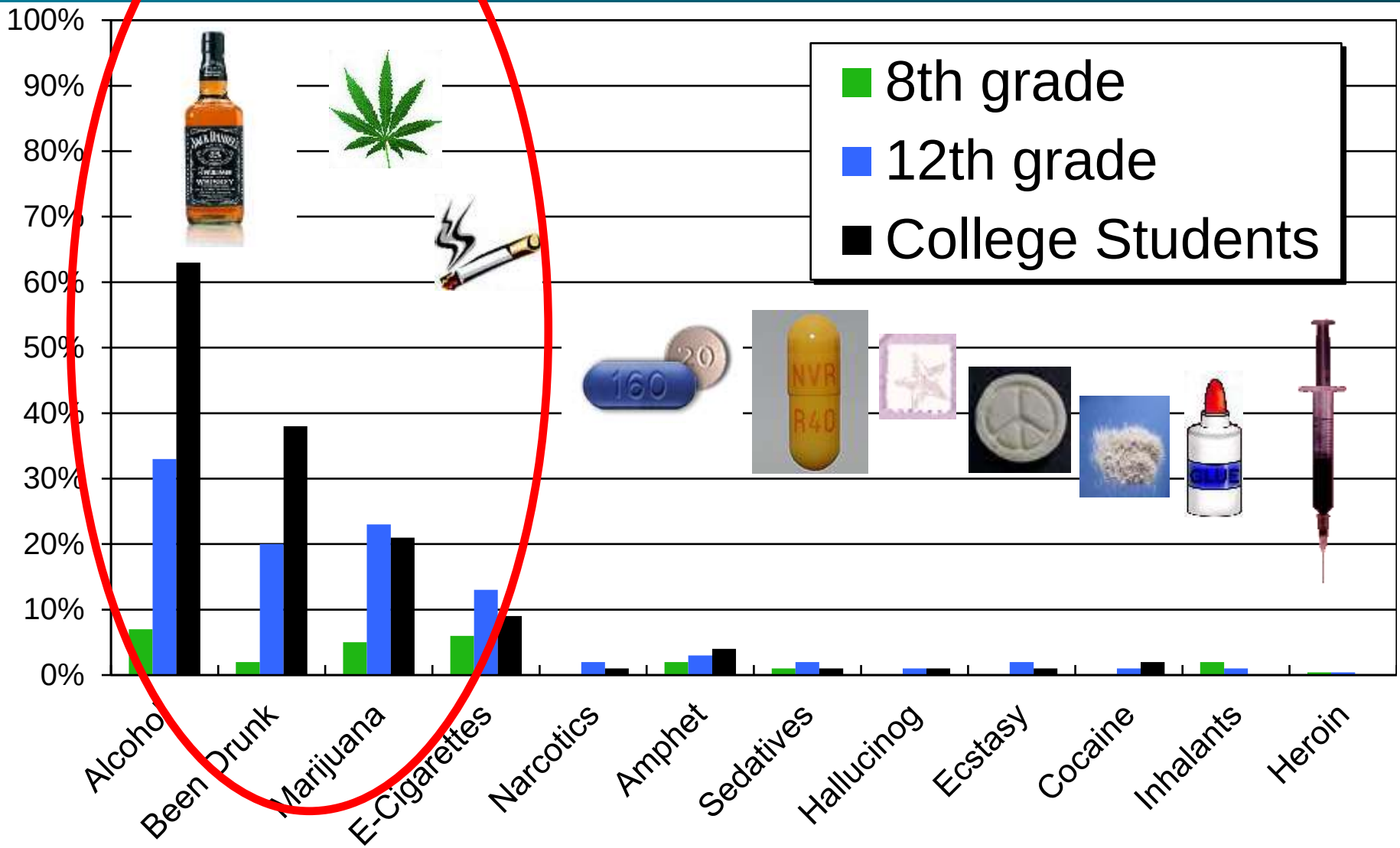
Honeycomb

Synthetic Cannabinoids

- Fake weed, synthetics, herbal incense, Spice, K2

1 Gram K2

Past Month Use of Intoxicants



Monitoring the Future, 2017

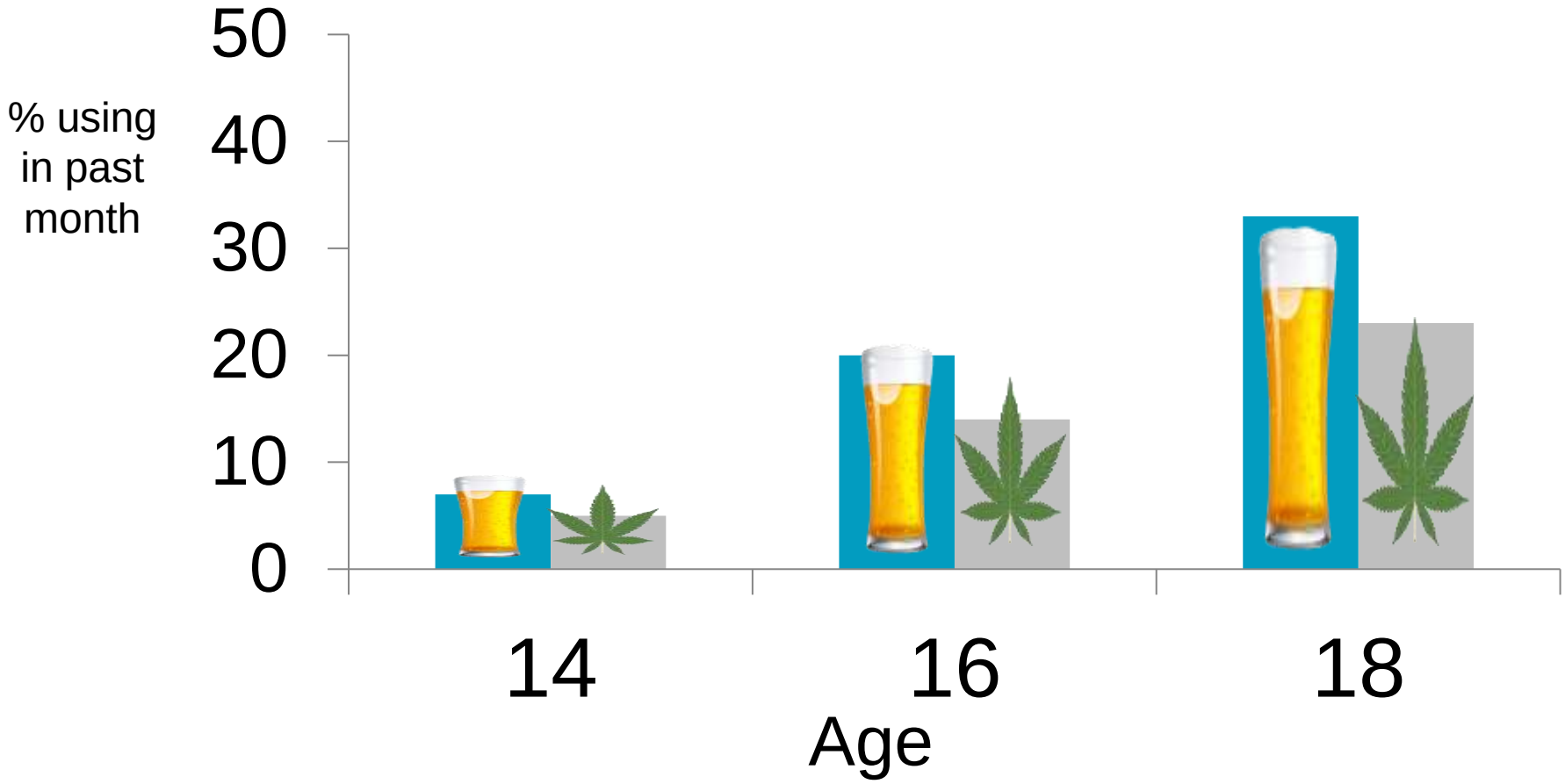
Cannabis: Prevalence

- 34% of young adults (18-28) used in past year
- Downward/stable trend since 2013:
  - 24% of 10th graders
  - 9% of 8th graders
- Dependence in ~9% of users
- #2 reason for SUD treatment (#1=alcohol)
- 12% users drove high in past 2 weeks

SAMHSA, National Surveys on Drug Use and Health, 2013 and 2014.
Johnston et al., 2017. Monitoring the Future.

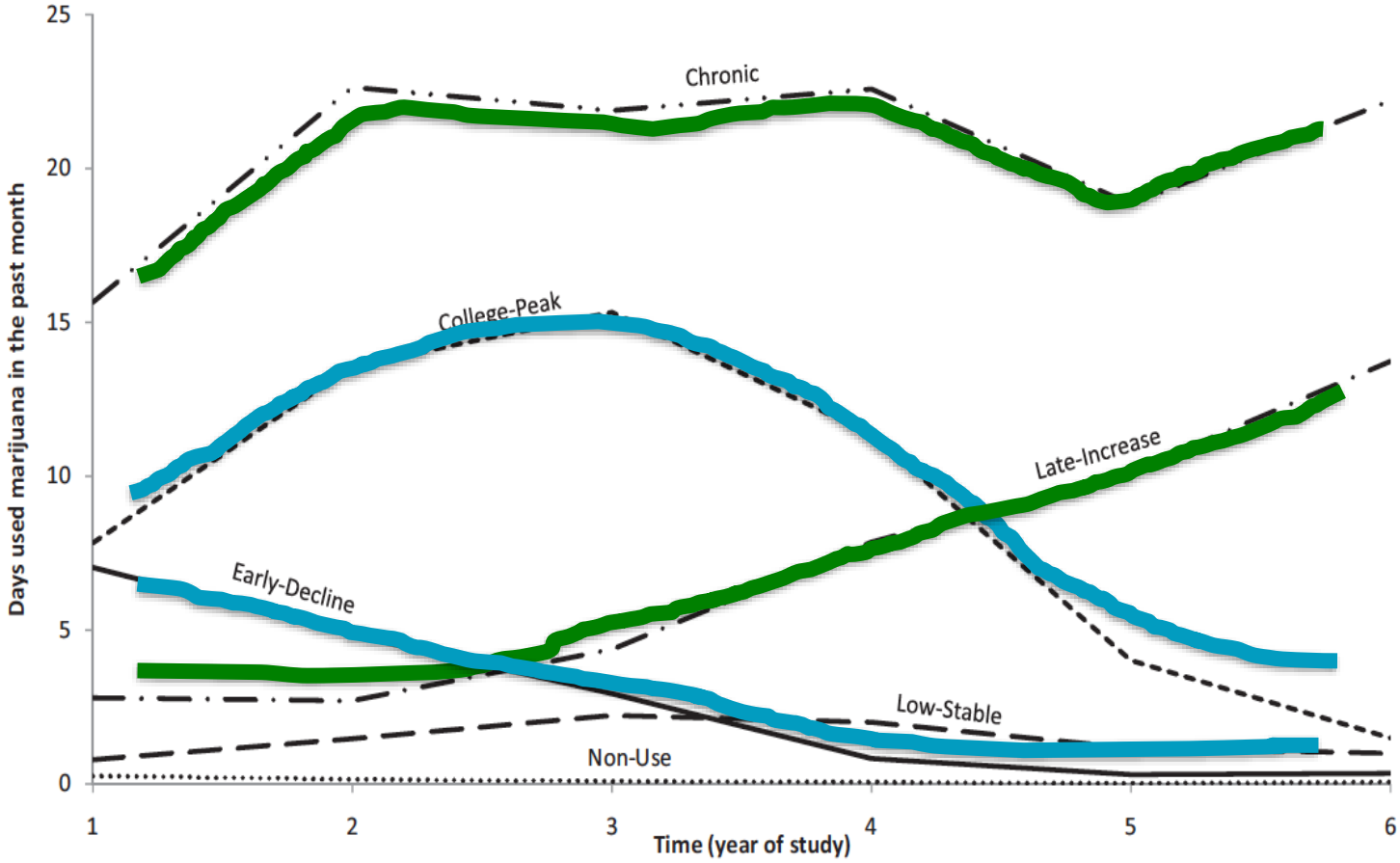
Use ↑ 8th to 12th Grade

Alcohol + Cannabis often used together



Monitoring the Future, 2017

Cannabis Use Trajectories

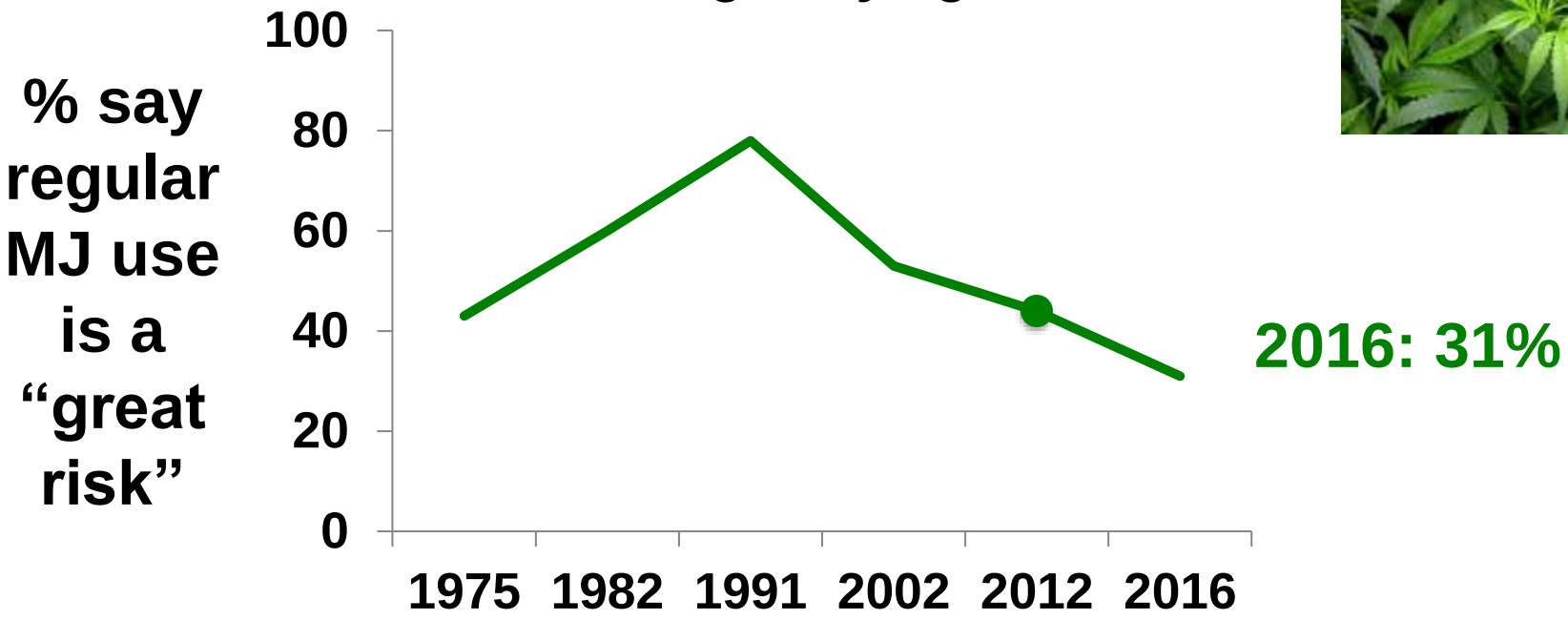


Age ~18 → Age ~25

Caldeira et al, 2012, Drug Alc Dep

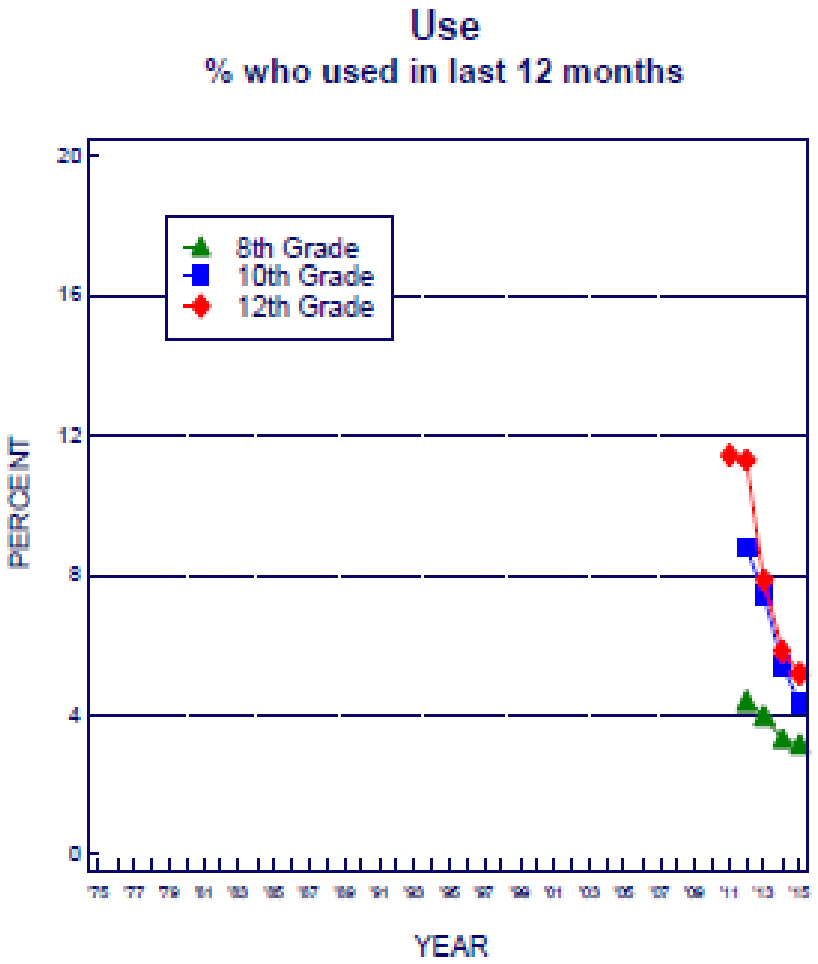
Perceived Risk of Harm

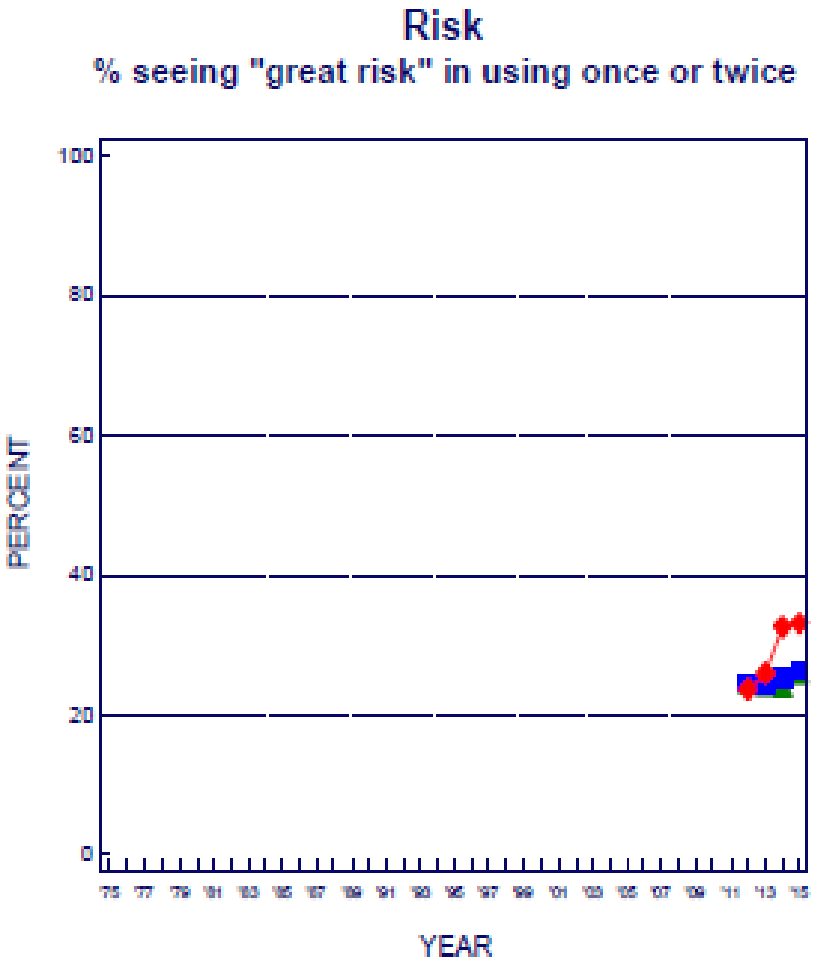
↓ Perceived Risk= ↑ Substance Use



Monitoring the Future, 2017

Synthetic Cannabinoids

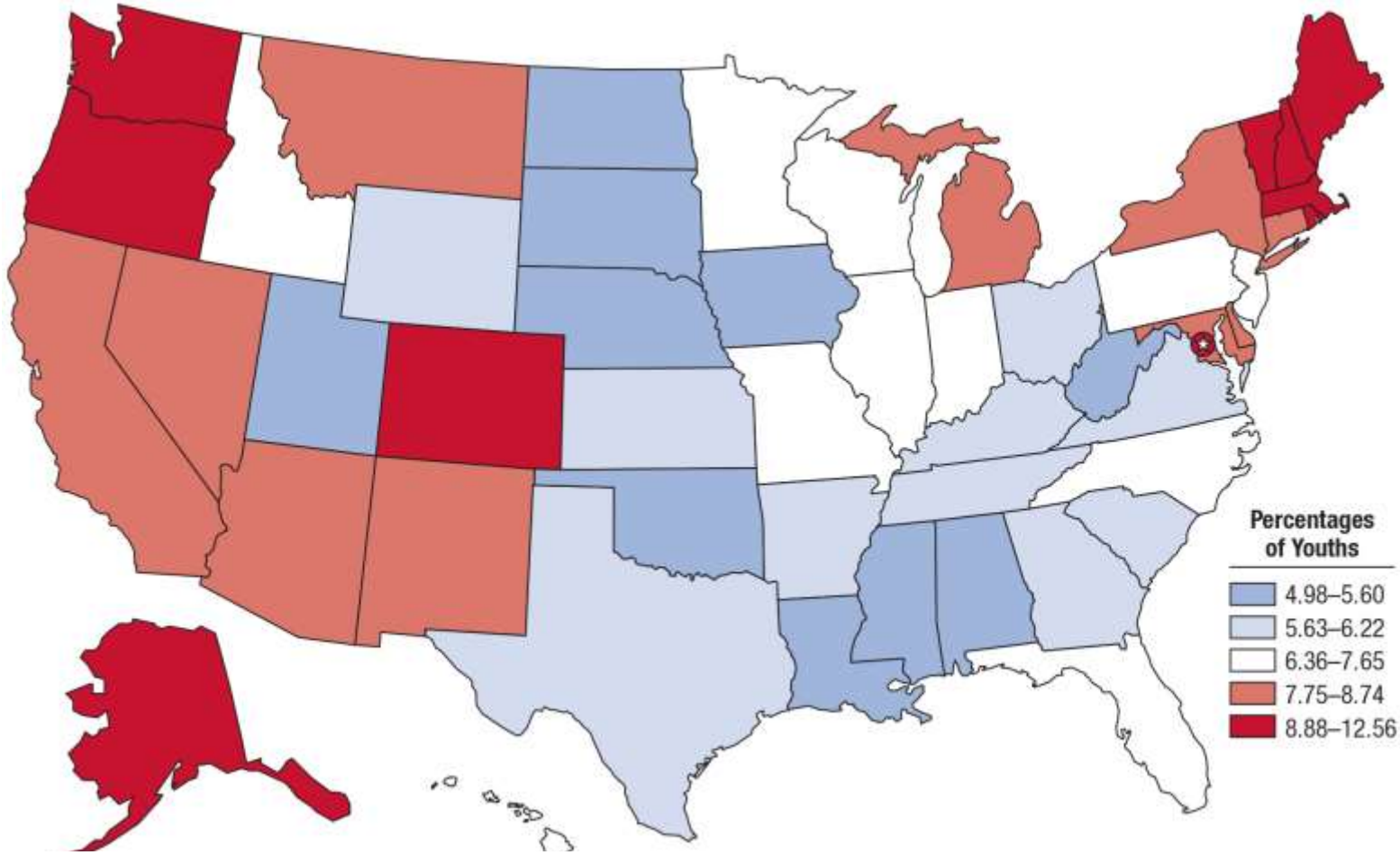




Monitoring the Future, 2016

Prevalence Across States

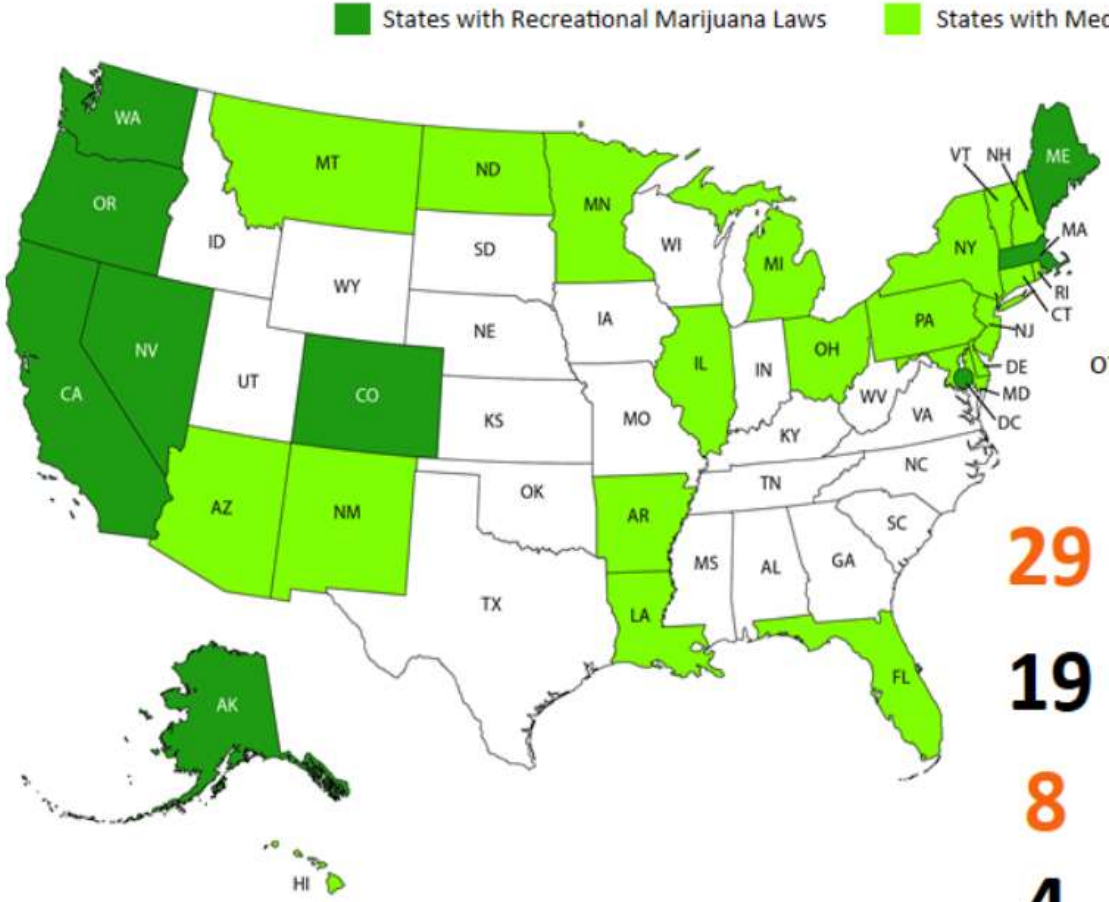
Past Month Cannabis Use: Ages 12-17



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

Legal Status

Marijuana Legalization by State



Key Statistics

59.3%

of the U.S. population now lives in a state where marijuana has been legalized

29 states plus Washington DC have medical marijuana laws ...

19 plus Washington DC have operating dispensaries

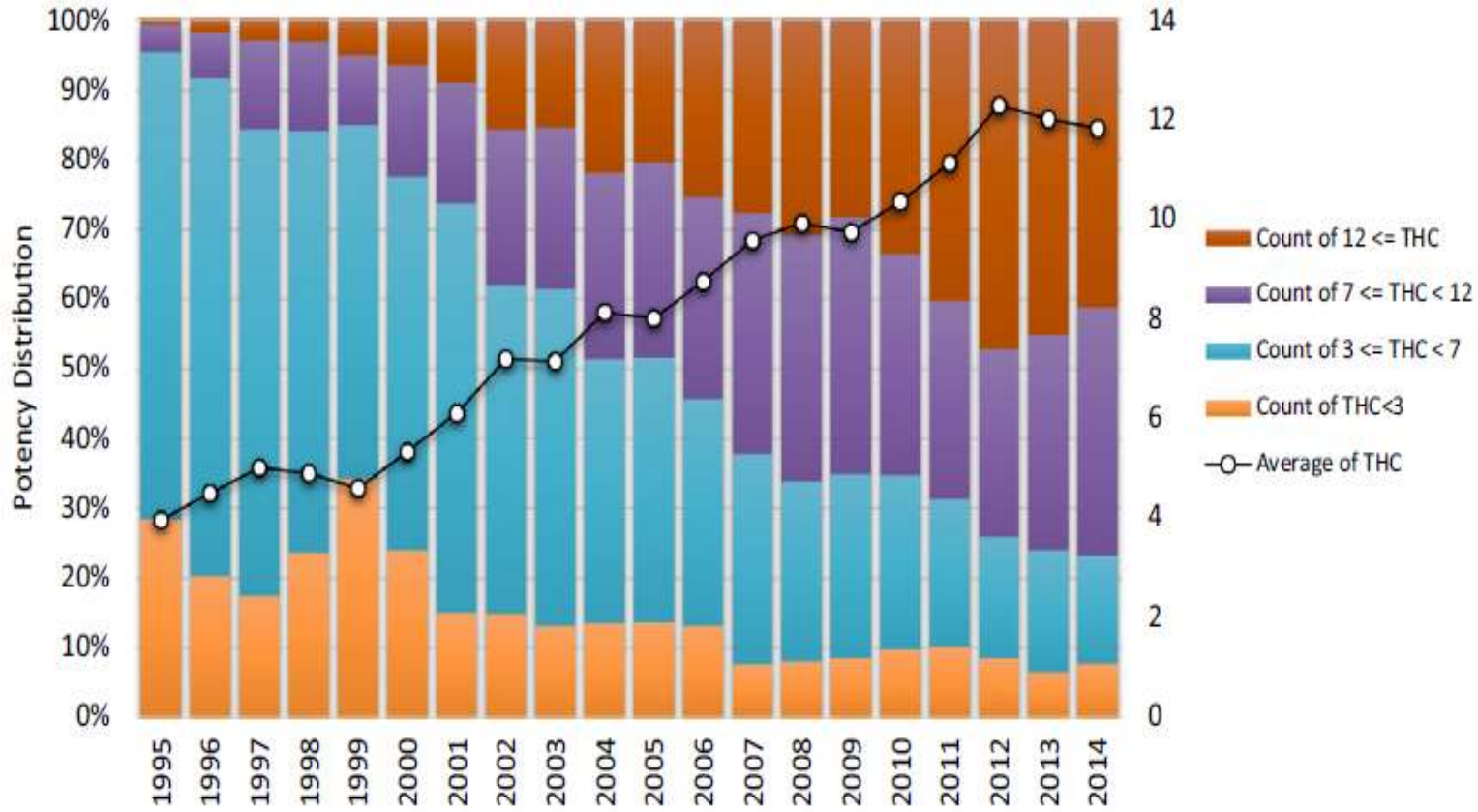
8 states plus Washington DC have recreational marijuana laws ...

4 with operating retail stores

Source: Marijuana Business Daily, U.S. Census Bureau

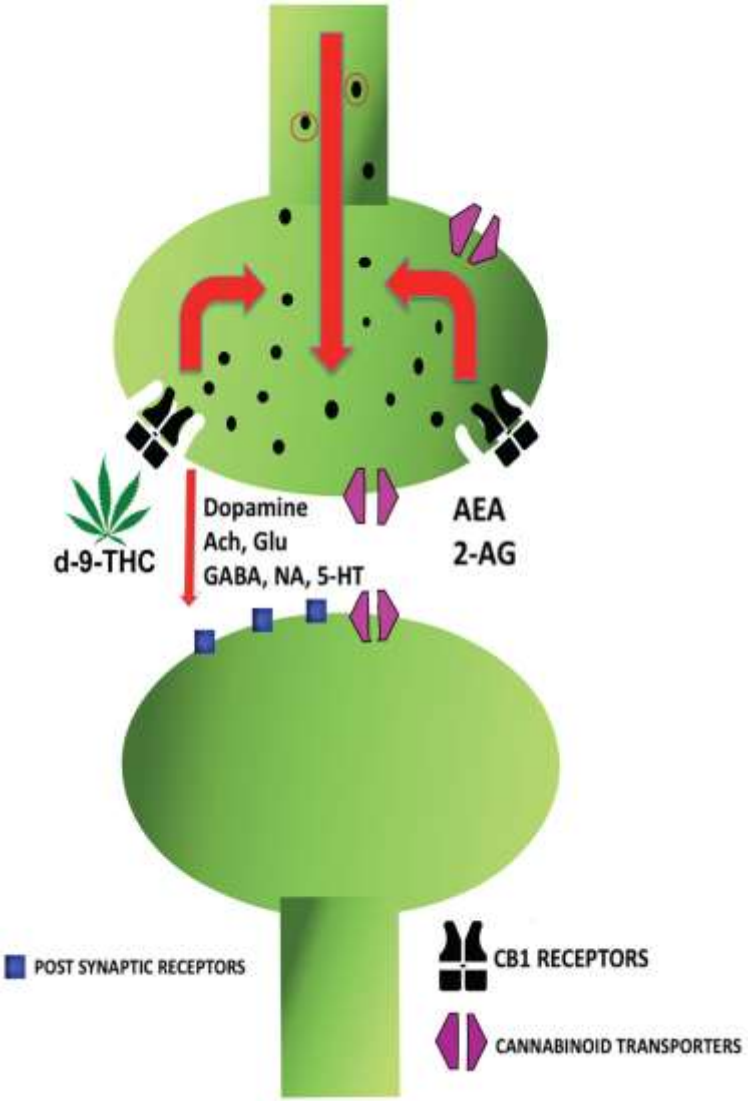
What's in the Cannabis?

Increase in High Potency Marijuana



El Sohly et al. (2016). *Biological Psychiatry.*

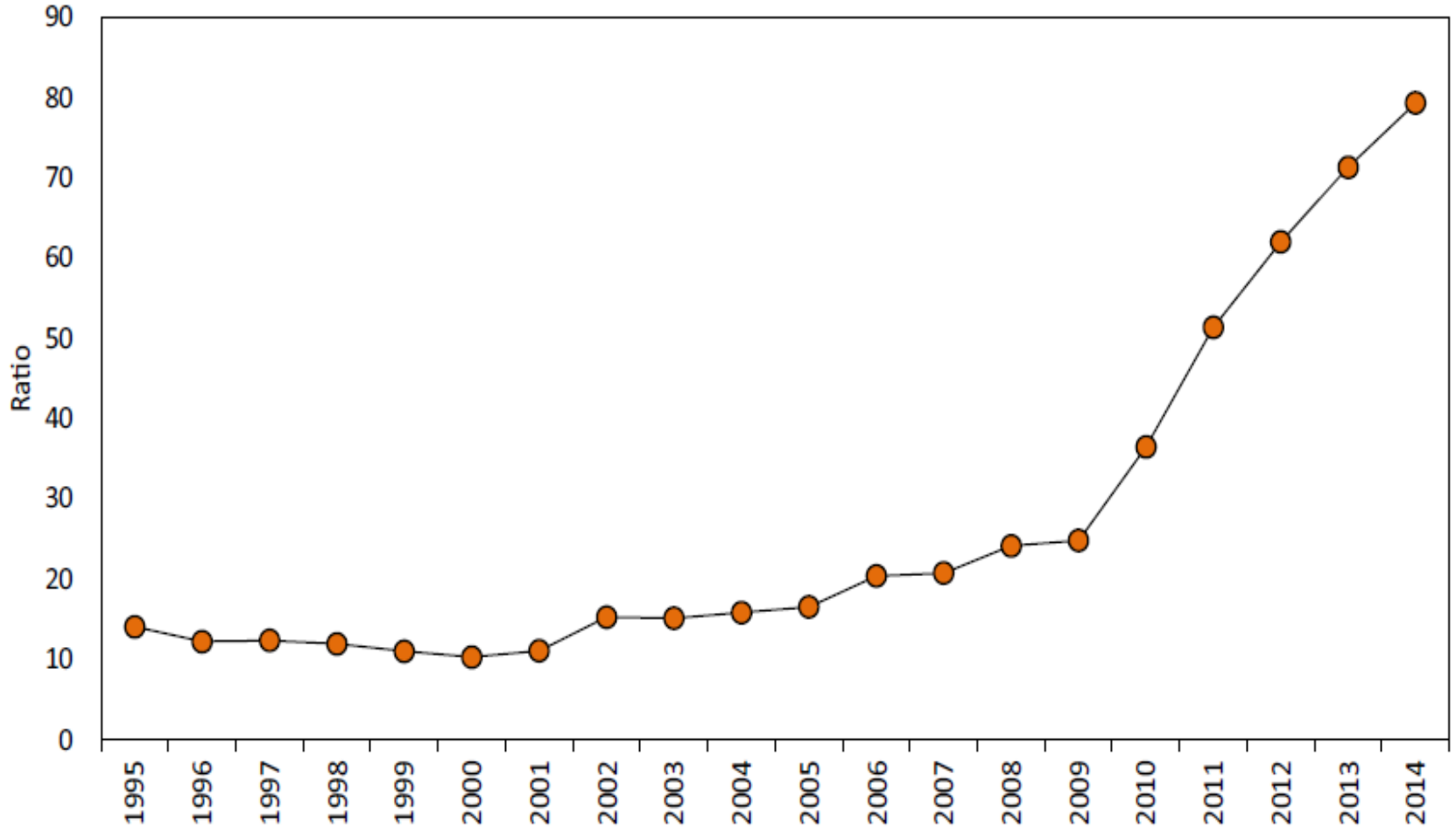
Cannabis Biochemistry



Atakan, 2012. Ther Adv Psychopharm

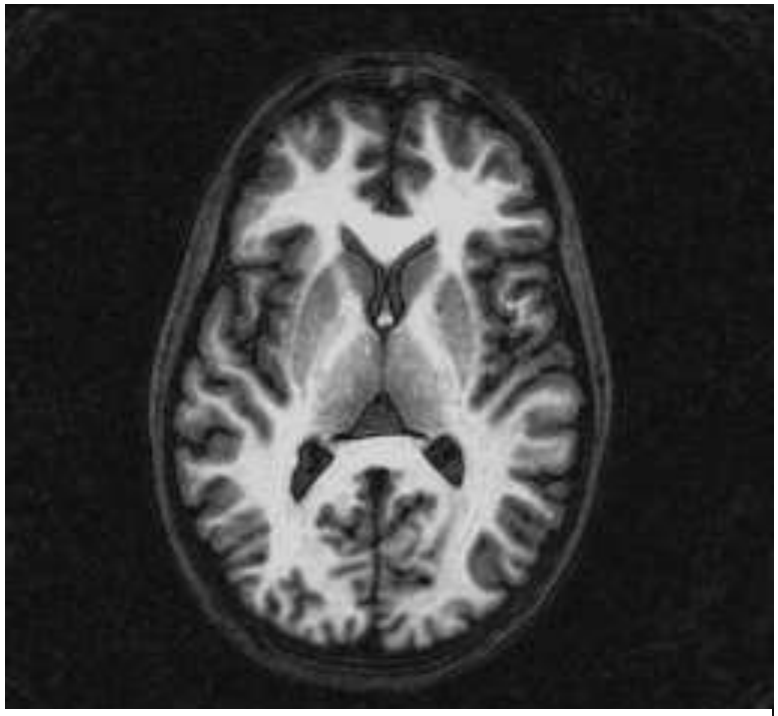
- Marijuana plant:
  - 100+ cannabinoids
  - Δ-9-tetrahydrocannabinol (THC)
  - cannabidiol (CBD)
  - cannabinol (CBN)
- Cannabis➔CB1 receptor
  - Cortex, hippocampus
  - Mediates inhibitory actions

Increase in THC / CBD



El Sohly et al., 2016. *Biological Psychiatry.*

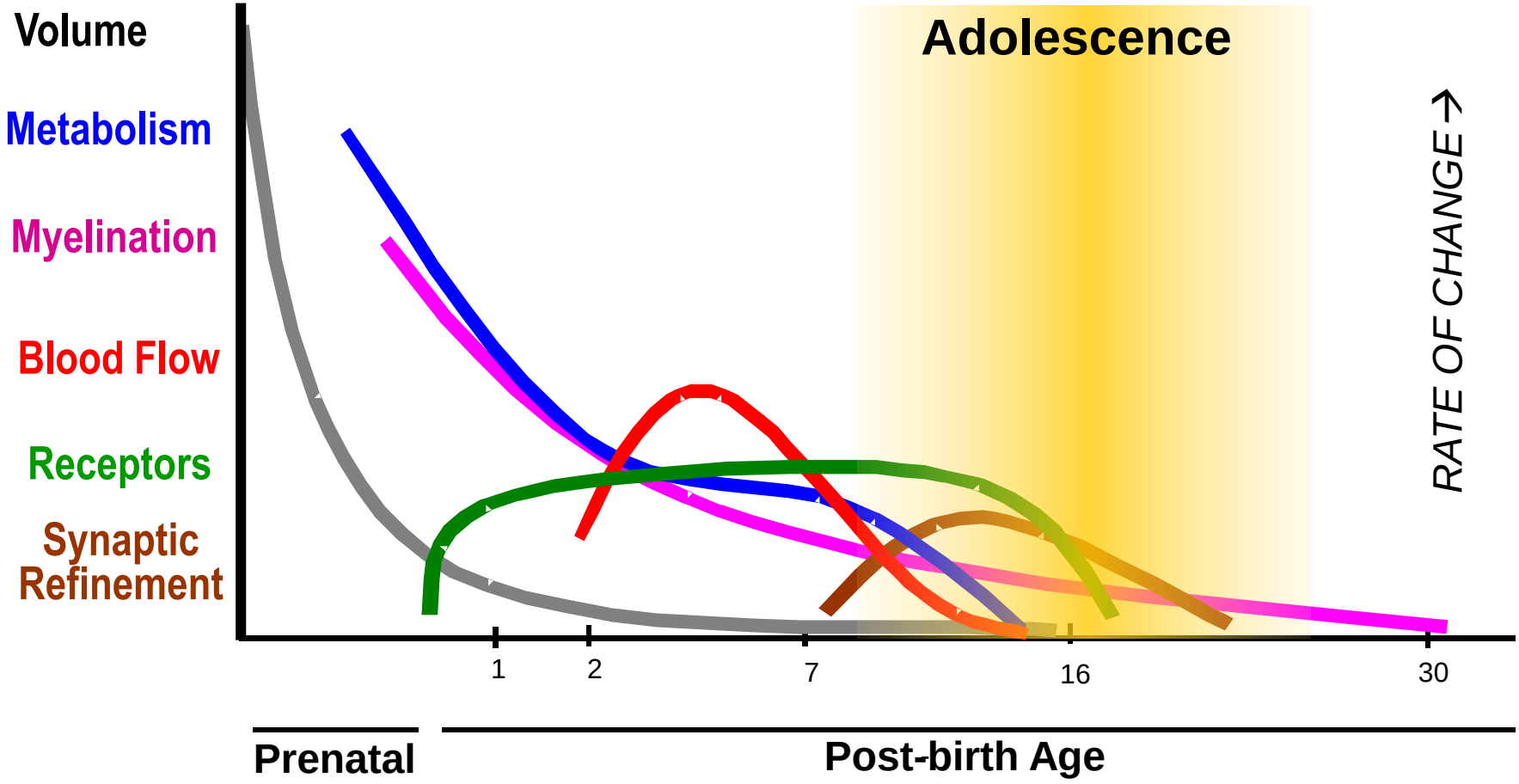
Gray & White Matter



Top view

Side view

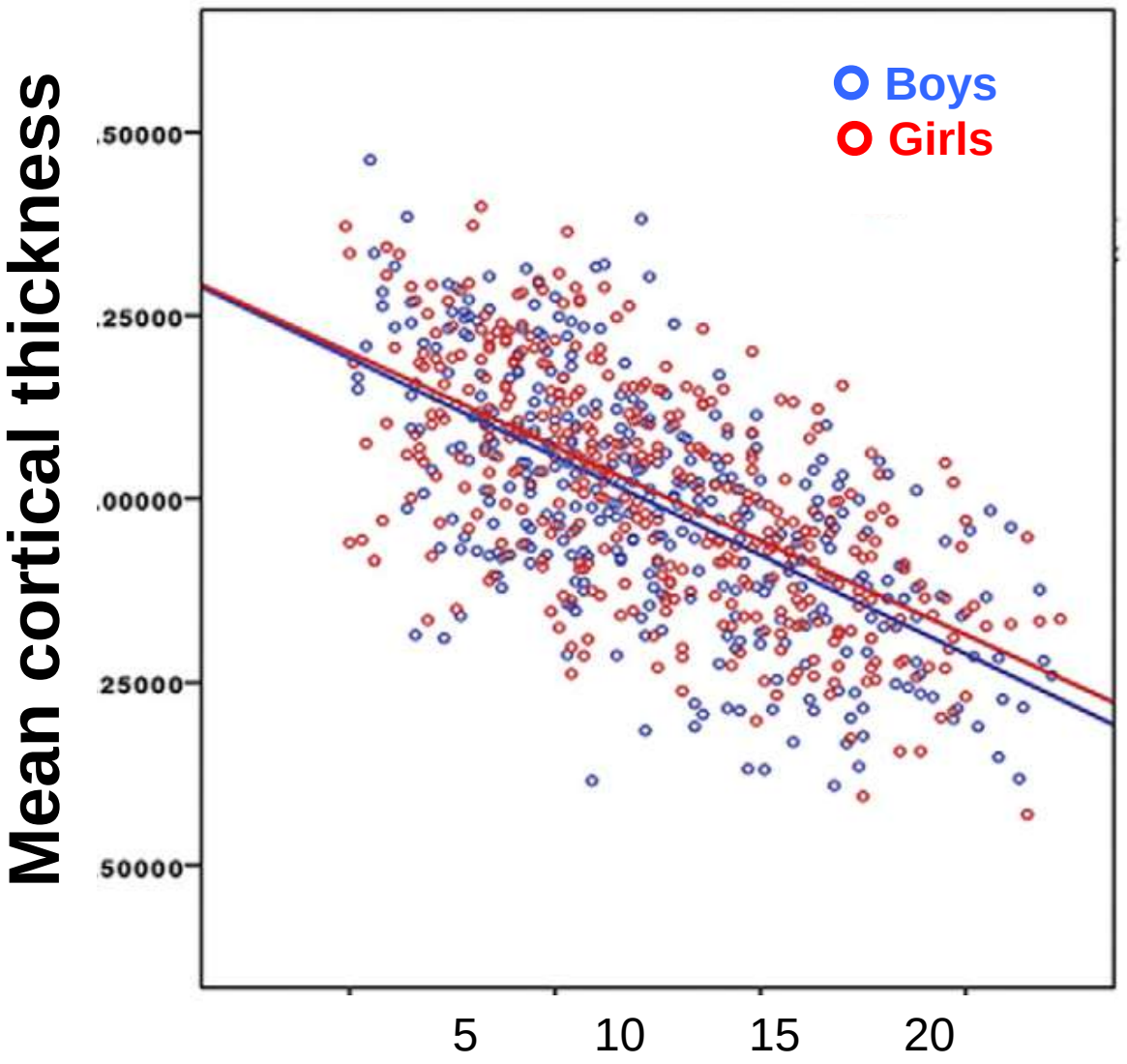
Brain Development Processes



Tapert & Schweinsburg, 2005. Recent Dev Alcoholism.

Prefrontal Gray Matter

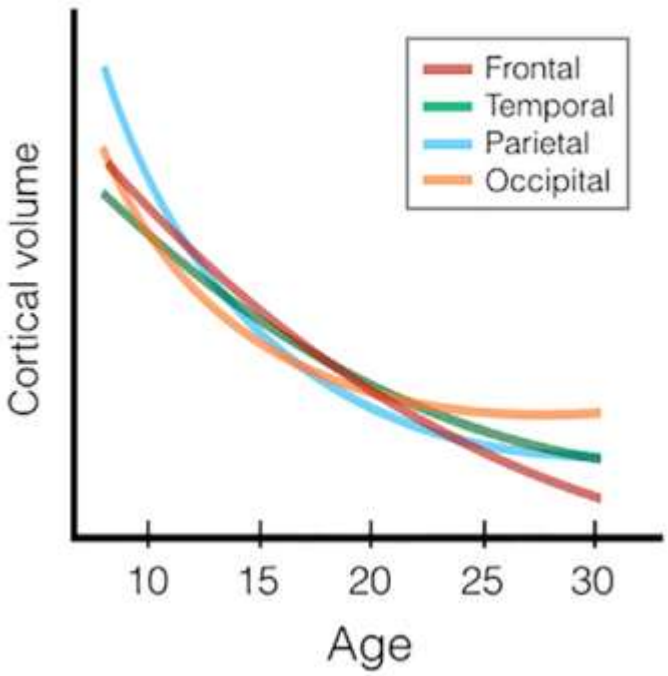
- Developmental trajectories of cortical thickness
- Ages 4-22
- Control for total brain volume, sex and scanner
- N=753



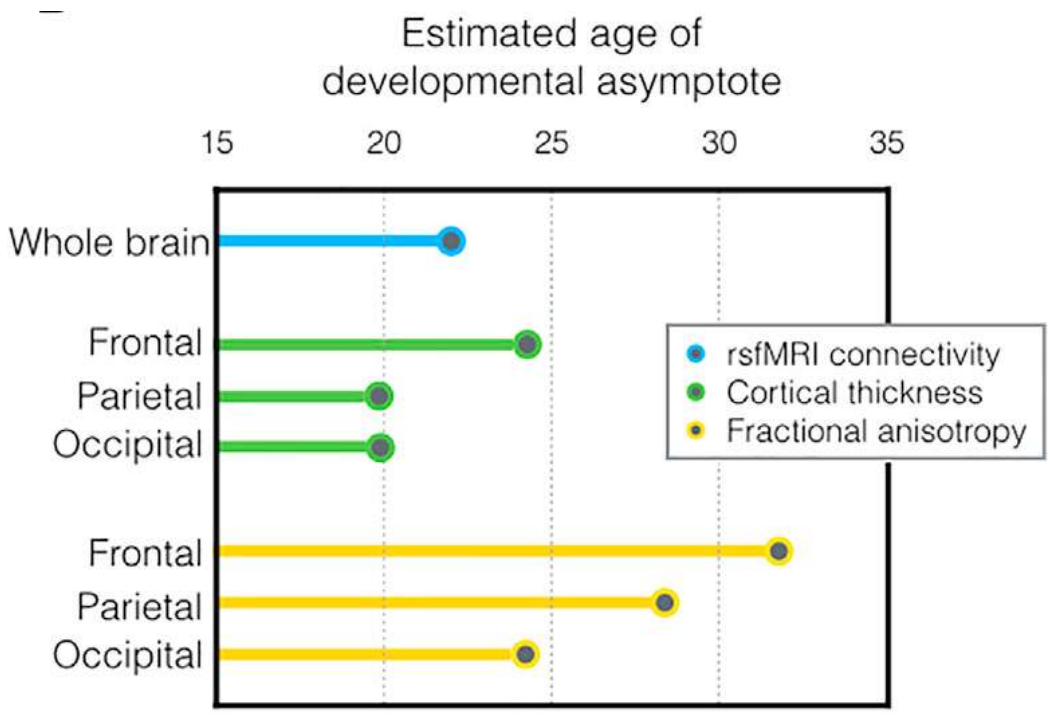
Ducharme et al., 2016, NeuroImage

Adolescent Brain Development

Trajectories of cortical volume adjusting for total brain volume *(schematized from data in Ostby et al., 2009).*

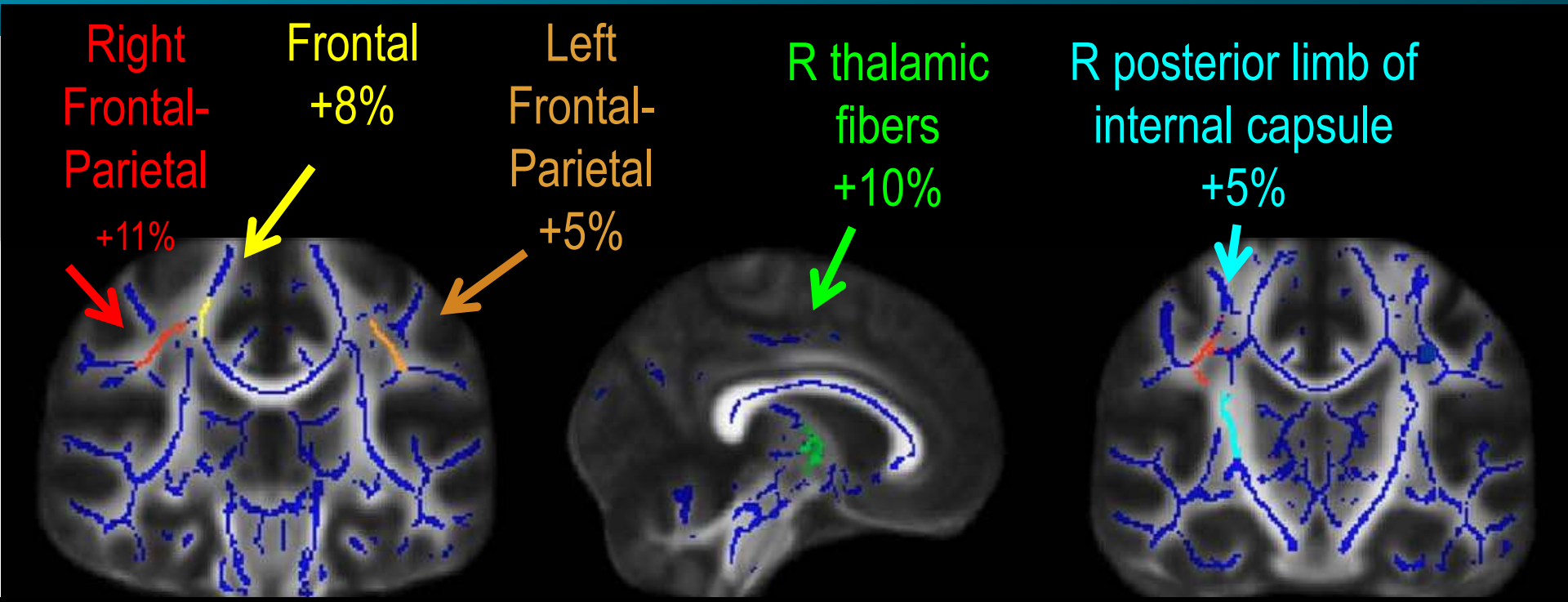


Age of asymptote for connectivity *(Dosenbach et al., 2010)* and structural *(Tamnes et al., 2010)* development.



Somerville, 2016, Neuron

White Matter Change



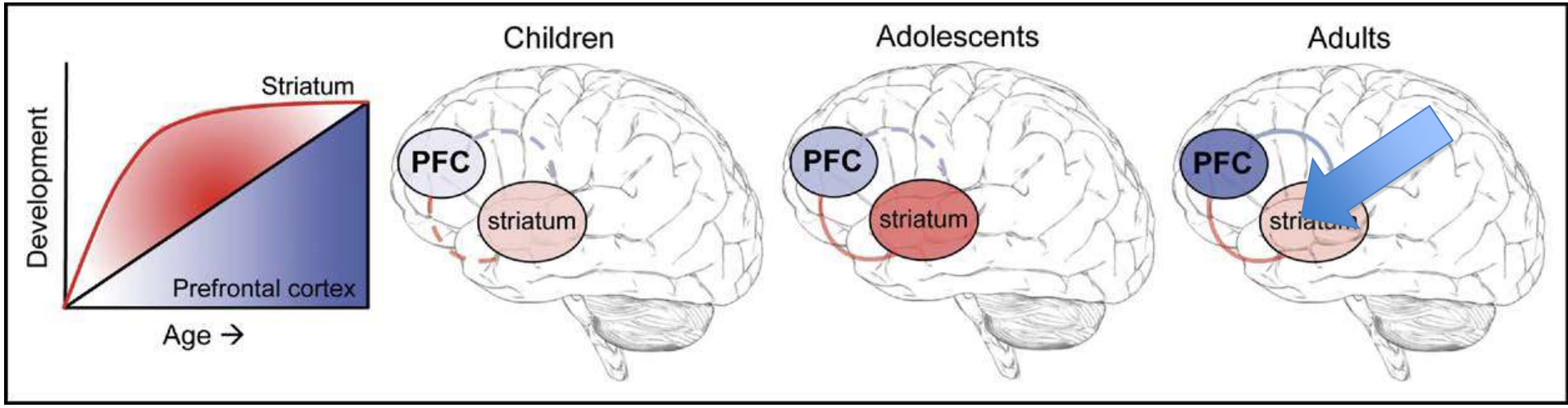
Significant fiber improvement, age 17.5 to 19

***N*=22**

Bava, Thayer, Jacobus, Ward, Jernigan, & Tapert, 2010, Brain Research

Neurobiology of Adolescent Risk Taking

- Development prefrontal (control) and limbic (reward)
  - ↑ subcortical activation
  - More diffuse prefrontal recruitment
- Inefficient connectivity



Somerville & Casey, 2010, Curr Opin Neurobiol.

Overview

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- Negative outcomes of marijuana use
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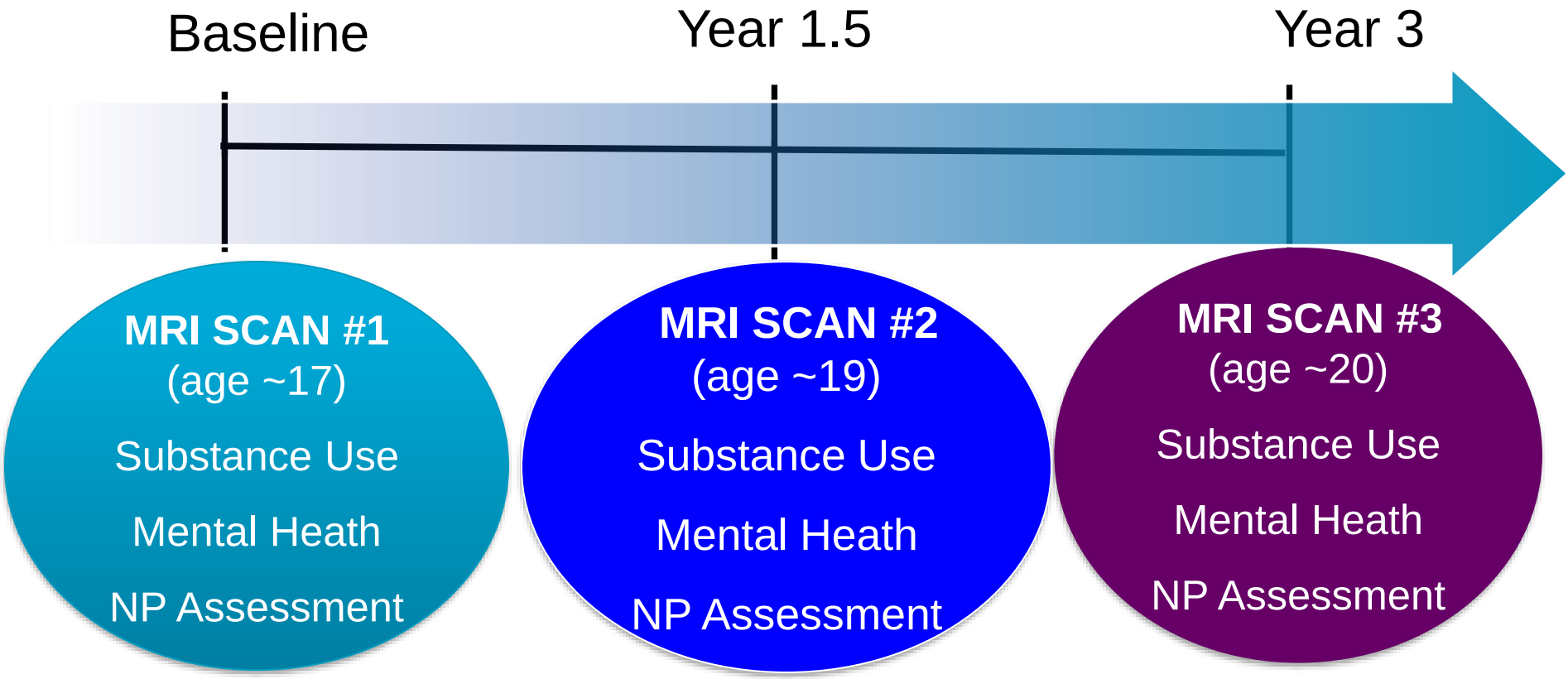
Design of 3-Year Study



1. **Groups defined by substance use patterns**
2. **All participants followed for 3 years**

R01 DA021182 (PI: Tapert)

Inclusion Criteria

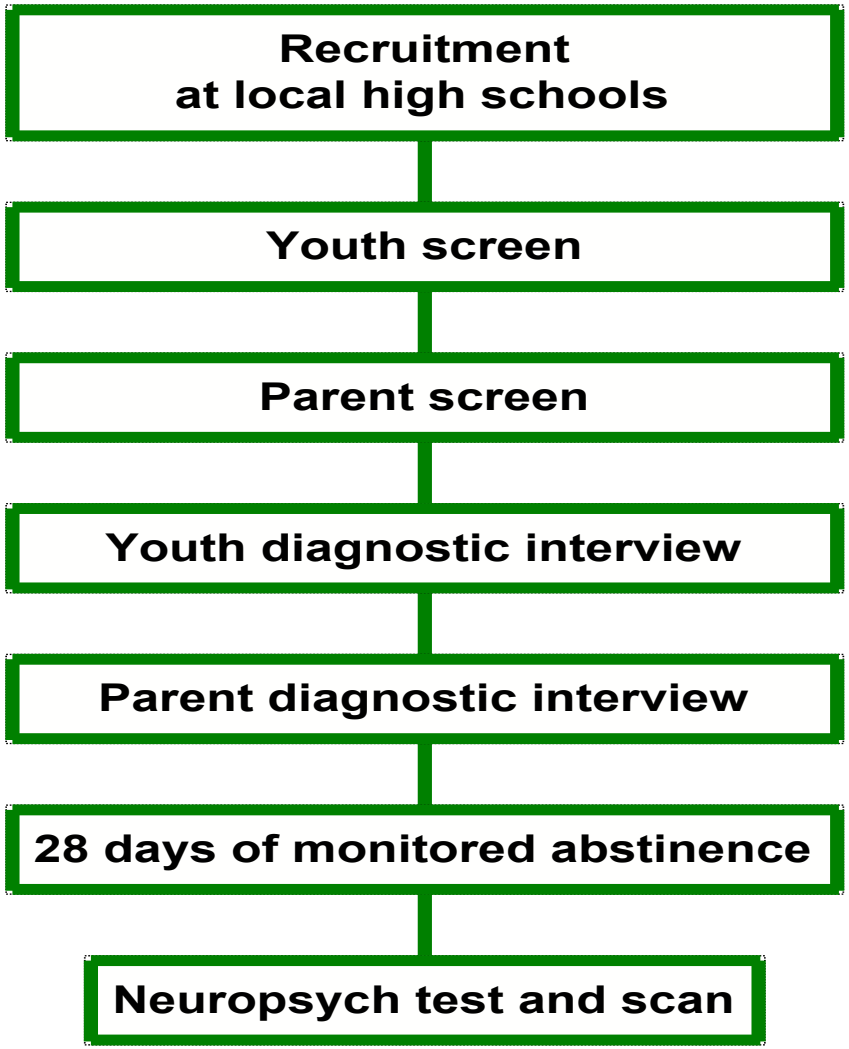
- Age 15-18
- Right-handed
- Lifetime marijuana use:
  - > 200 for “MJ Users”
  - < 5 for “Controls”
- < 150 lifetime drinks
- < 10 cigs/day
- < 30 lifetime other drugs

Participants (N=108)

	Light Drinkers	Heavy Drinkers	MJ+Alc Users
Age (15-19)	17.2	16.8	17.7
Female	35%	37%	29%
No FH of alcoholism	46%	42%	45%
IQ	111	113	109
Cigarettes/day	<1	2	2
Drinks/month	4	42*	44*
Lifetime MJ use	1	11	541*

*p<.05

Prospective Study Design



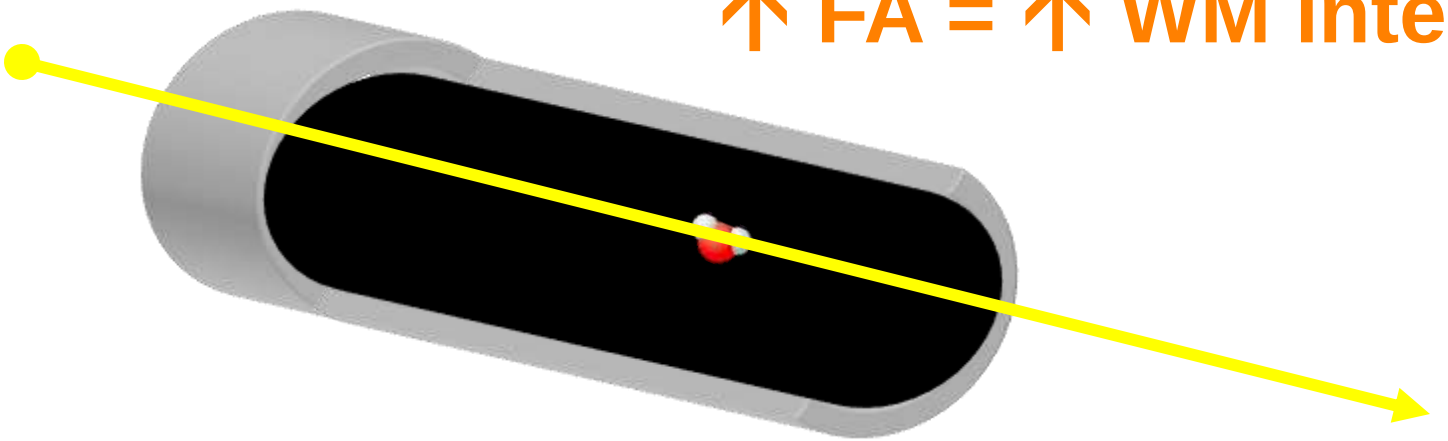
MRI

- Safe
  - Non-invasive
  - No radioactivity
- Issues
  - Motion
  - Artifact

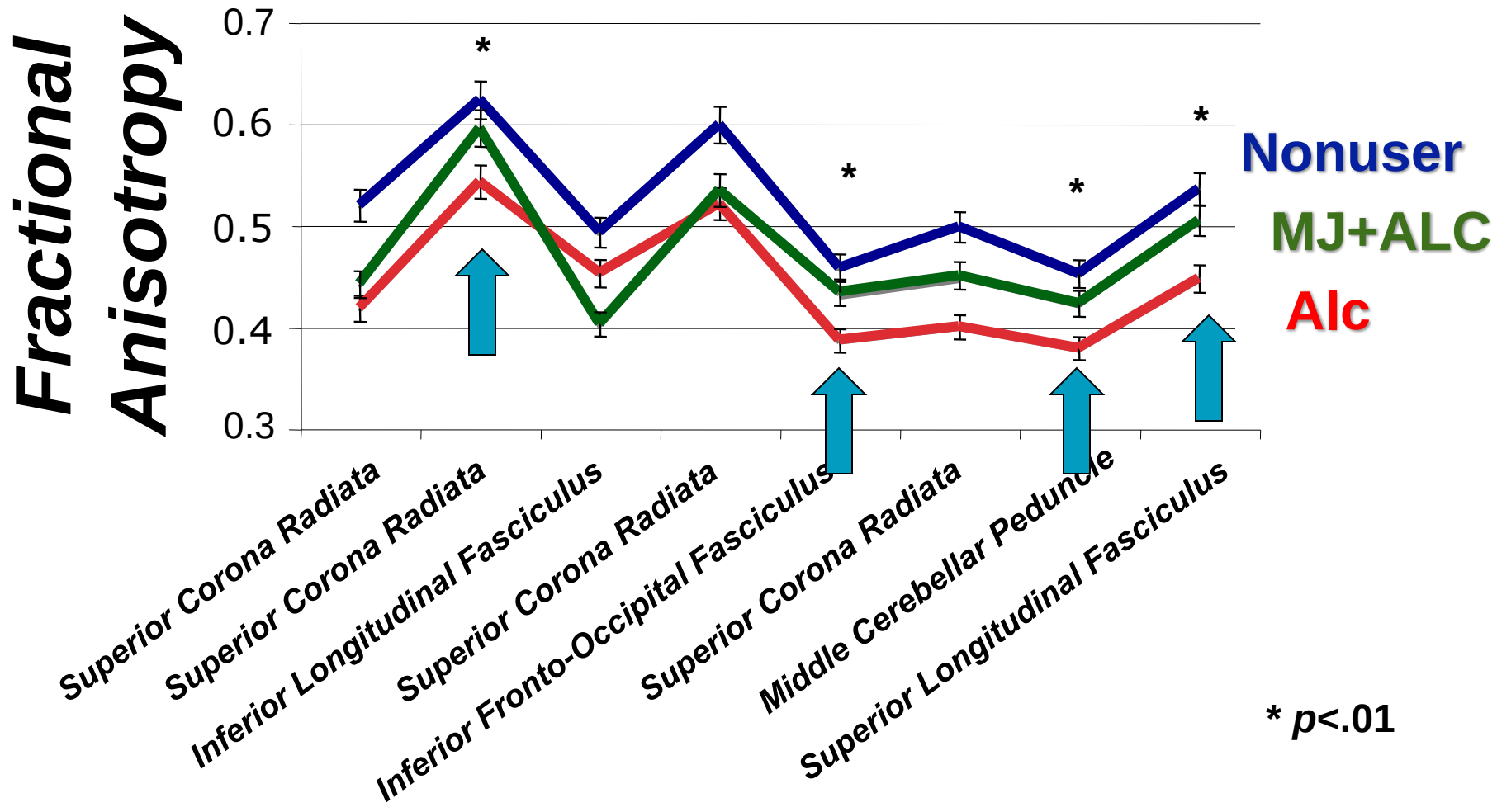
White Matter Microstructure

- Diffusion tensor imaging
  - Changes in tissue microenvironment
    - Myelination, density, coherence, compactness, diameter
  - ↑ **fractional anisotropy (FA)**
    - Related to cognitive status

↑ FA = ↑ WM integrity

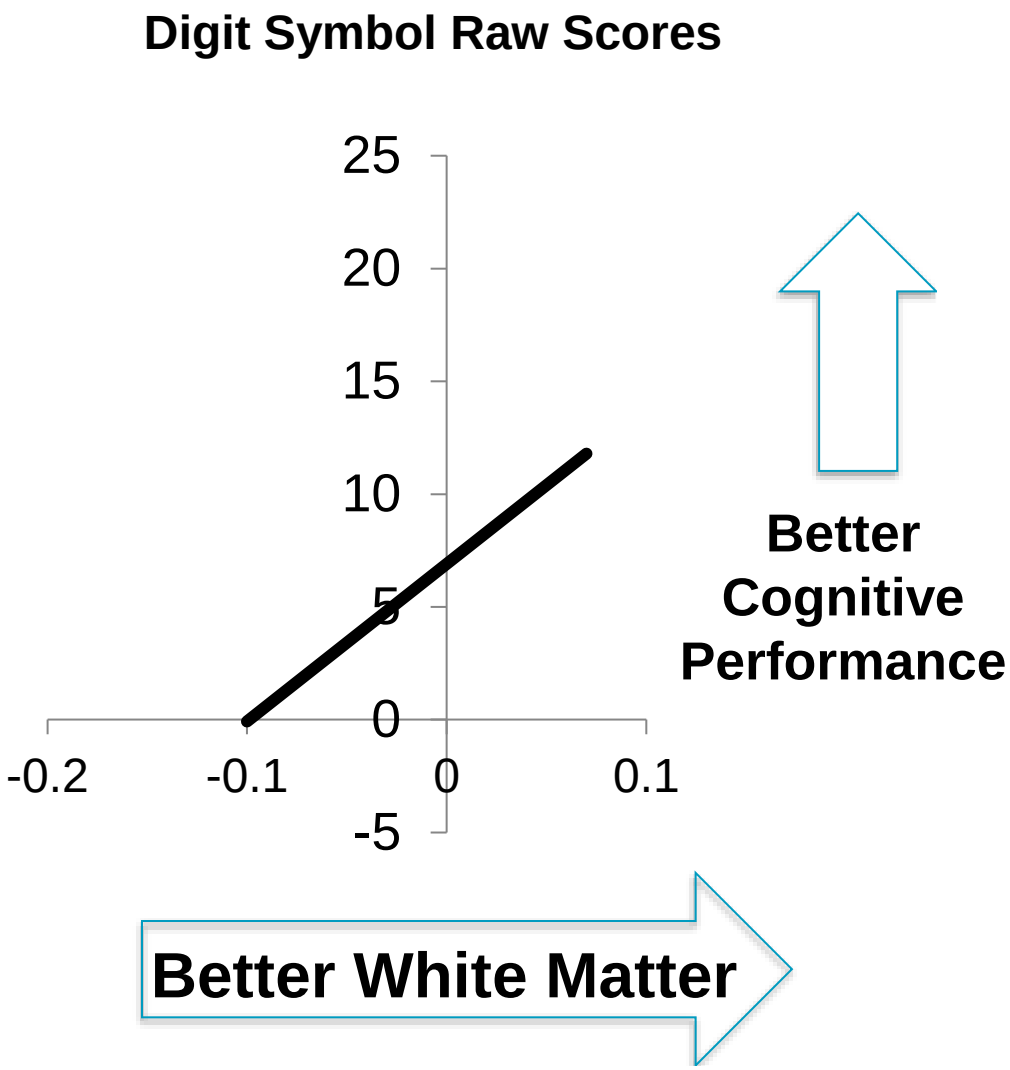


White Matter, Marijuana & Binge Drinking (age ~17)



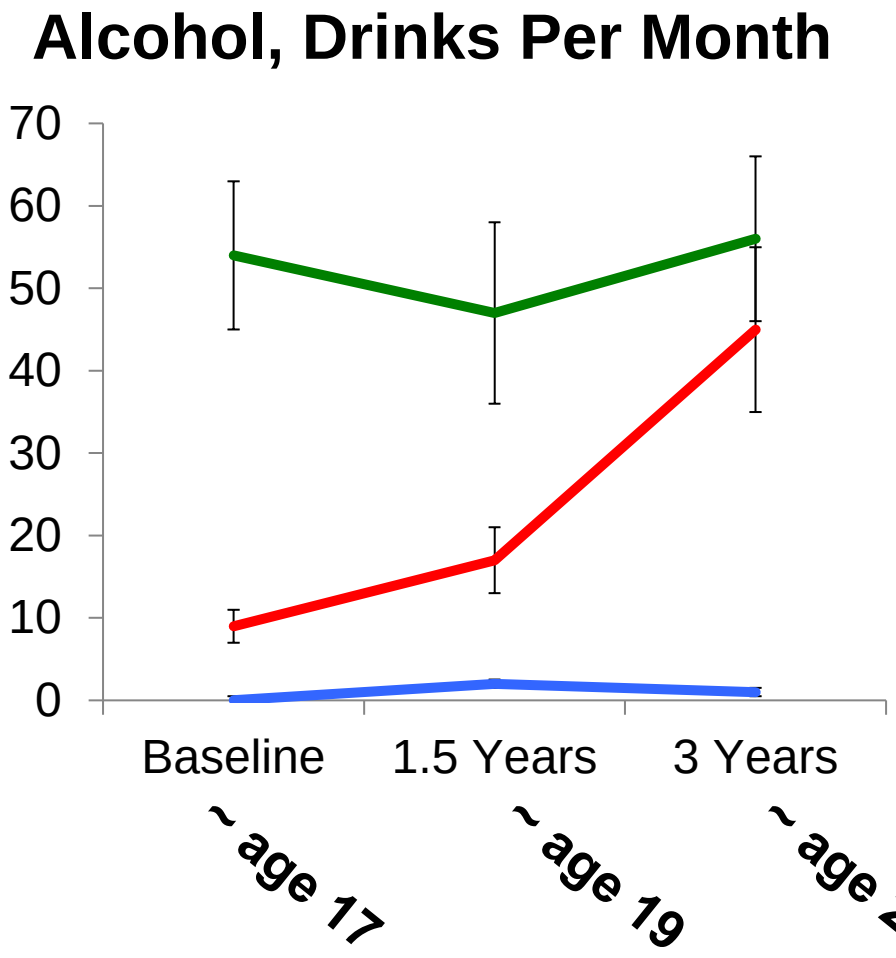
Jacobus et al., 2009, Neurotoxicol Teratol

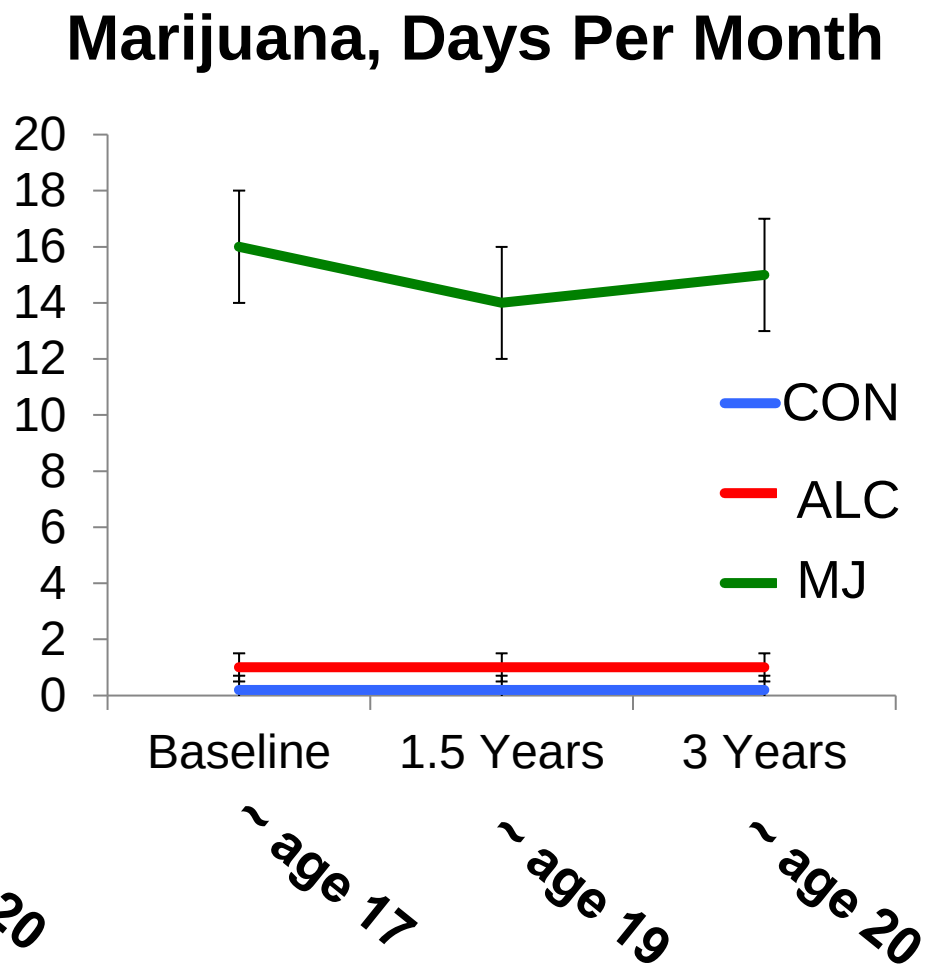
NP and Imaging Markers



Jacobus et al., 2013, Psychiatry Research

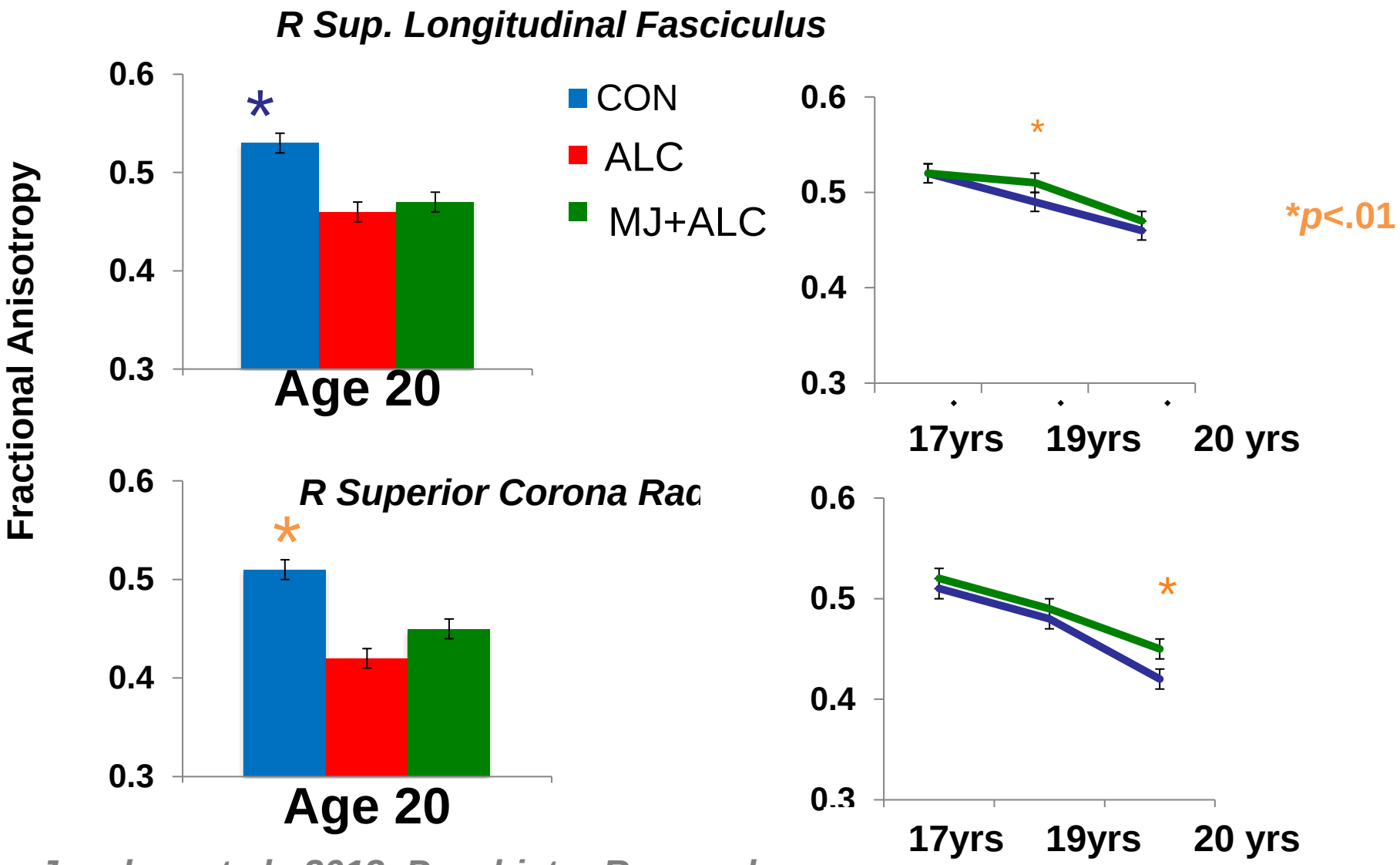
Substance Use over Time





Jacobus, et al., 2013, Psychiatry Research

White Matter, Marijuana, & Alcohol (~Age 20)



Jacobus et al., 2013, Psychiatry Research

Overview

- Rates of marijuana use and disorders
- Does cannabis use affect the adolescent brain
- Negative outcomes of marijuana use
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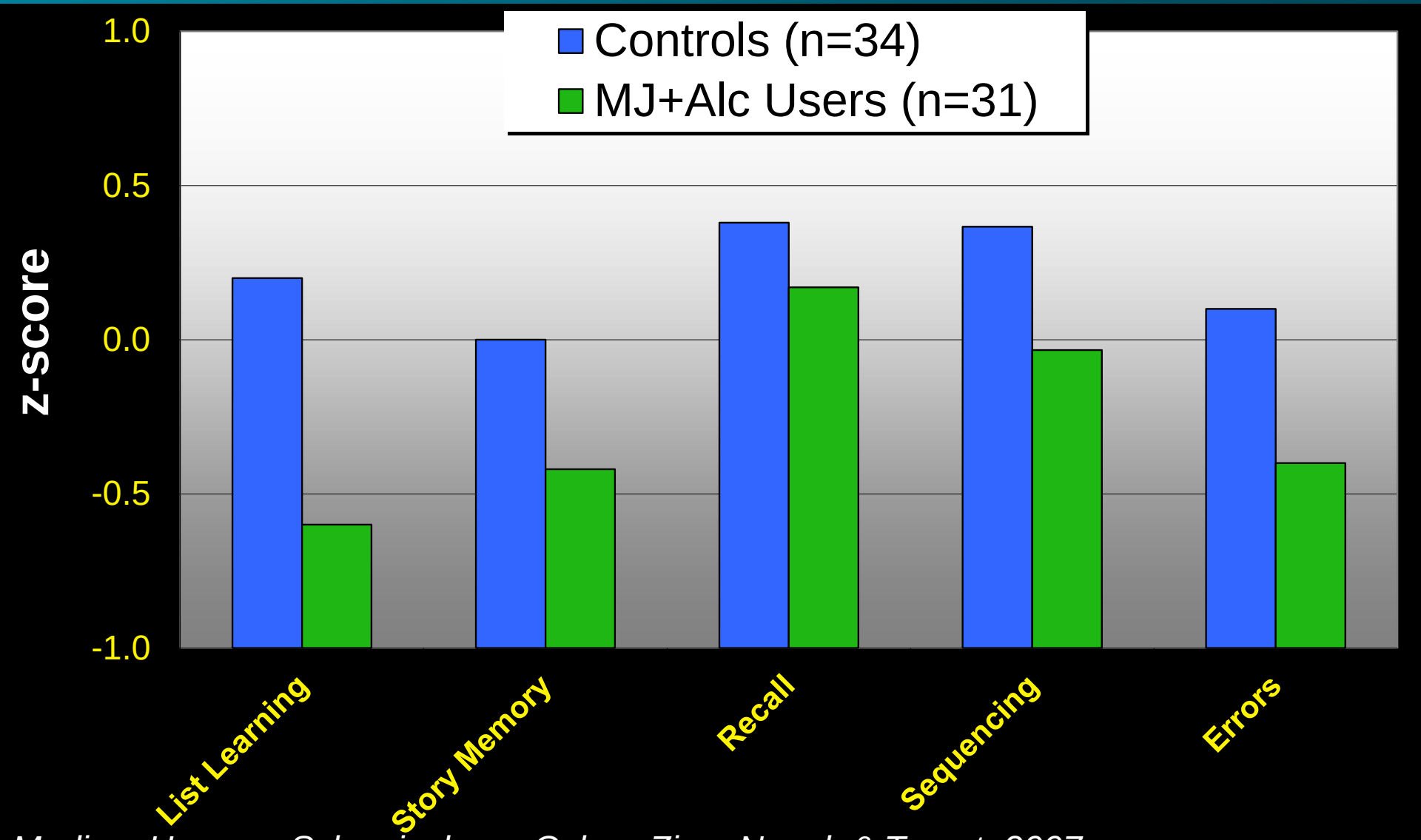
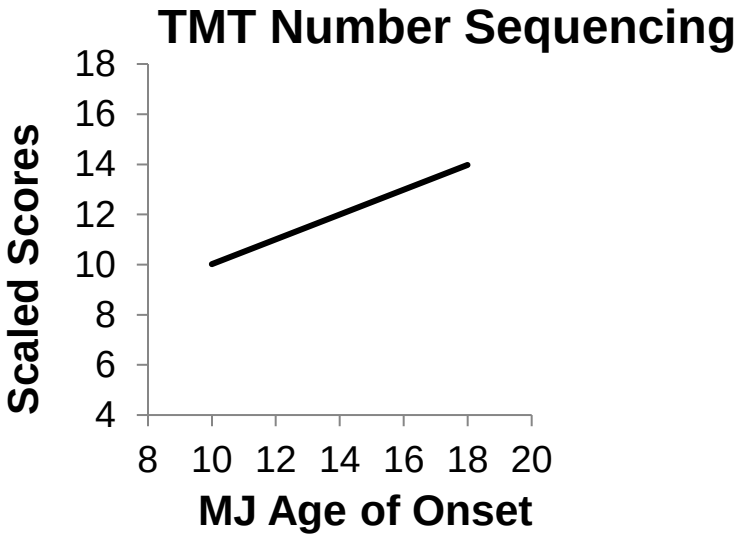
Cognition in Abstinent Users (Age ~17)

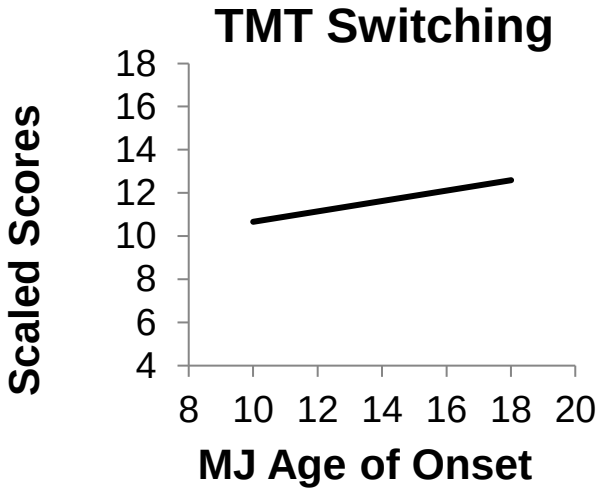


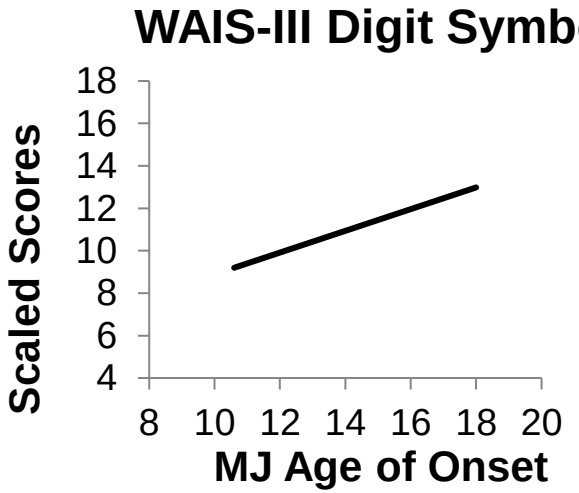
Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007

Neurocognition & Age of Onset



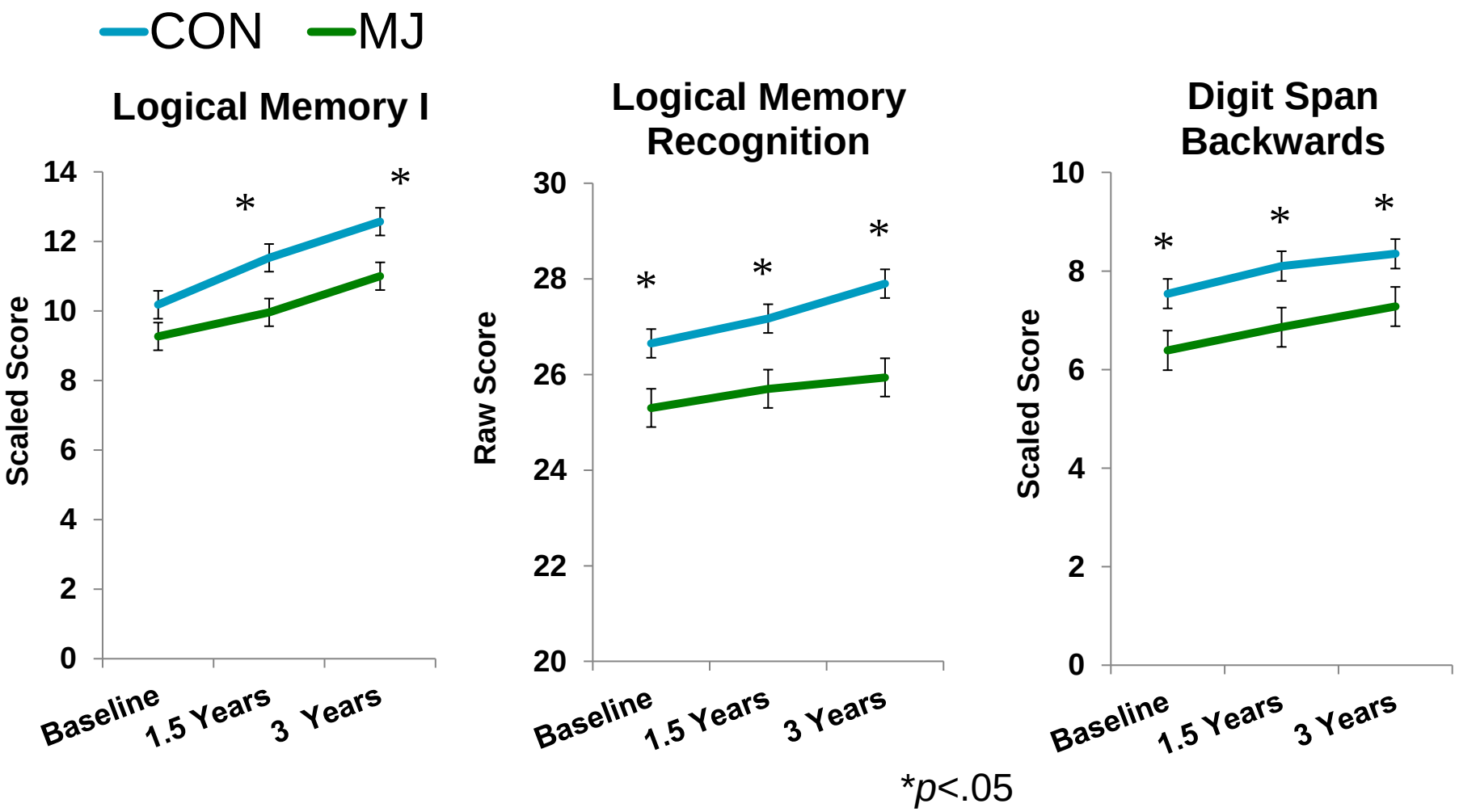
***Pearson's r*=.33-.44**





Jacobus et al., 2015, Neuropsychology

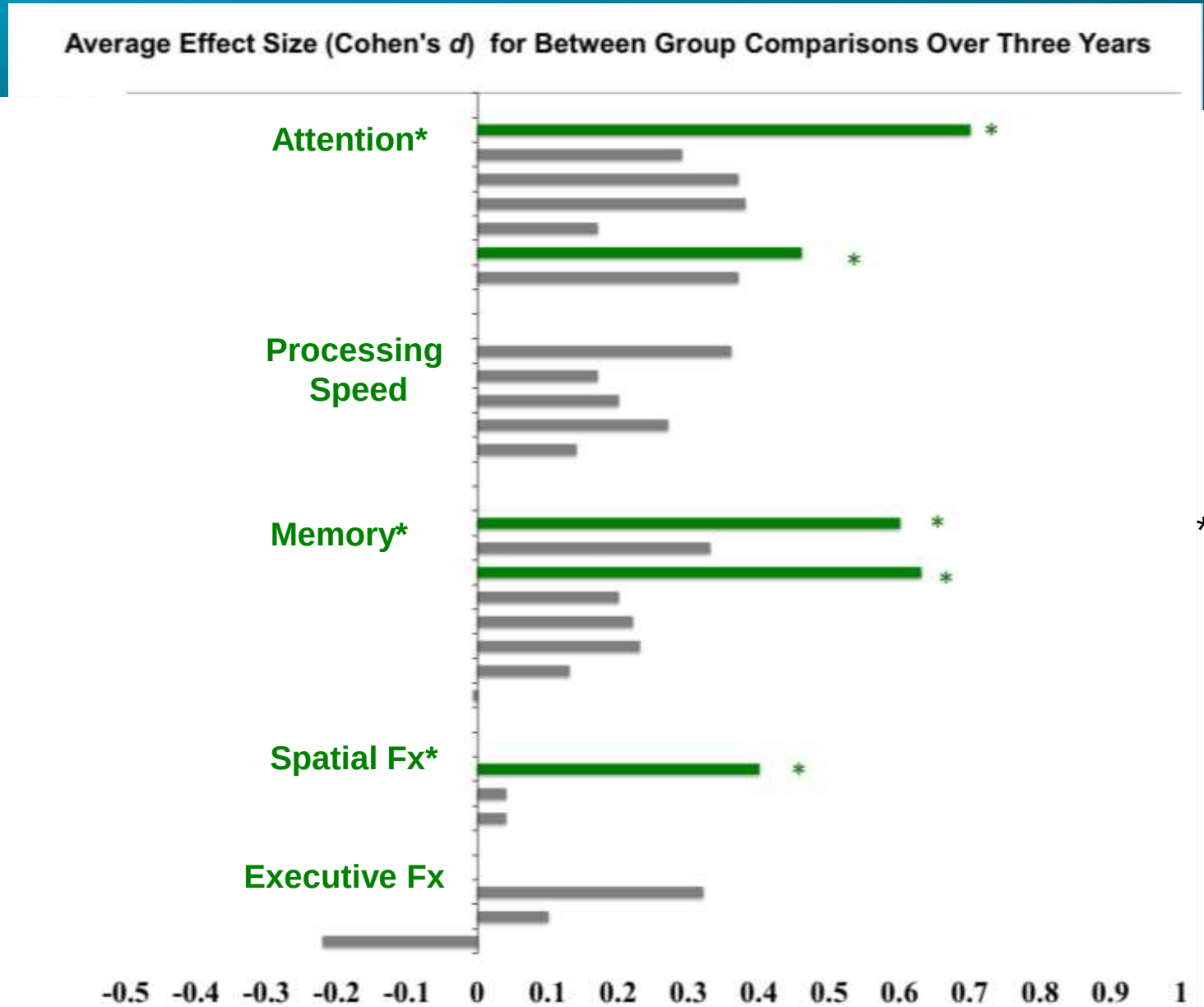
Neurocognitive Performance over 3 Years



*p<.05

Jacobus et al., 2015, Neuropsychology

What Types of Cognition Appear Affected?

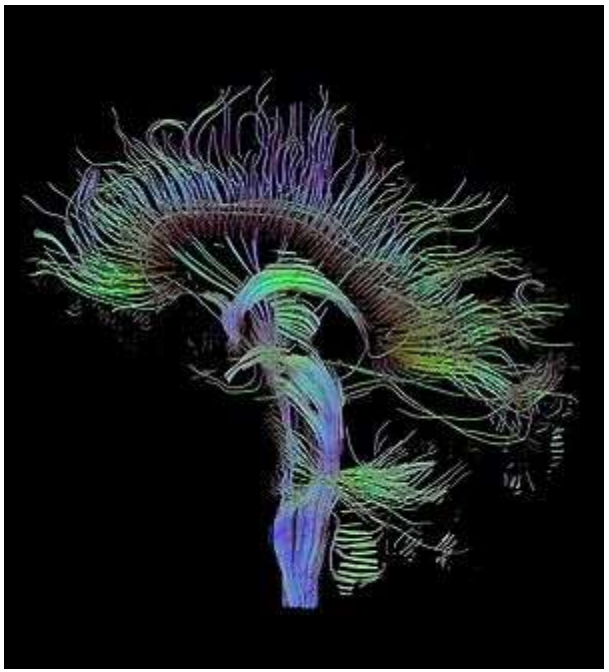


*p<.05

Jacobus et al., 2015, Neuropsychology

White Matter Predicts Future Use

White Matter Integrity



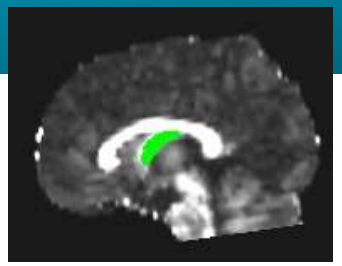
Substance Use

Baseline
Ages 16-19

18-month Follow-up
Ages 17-20

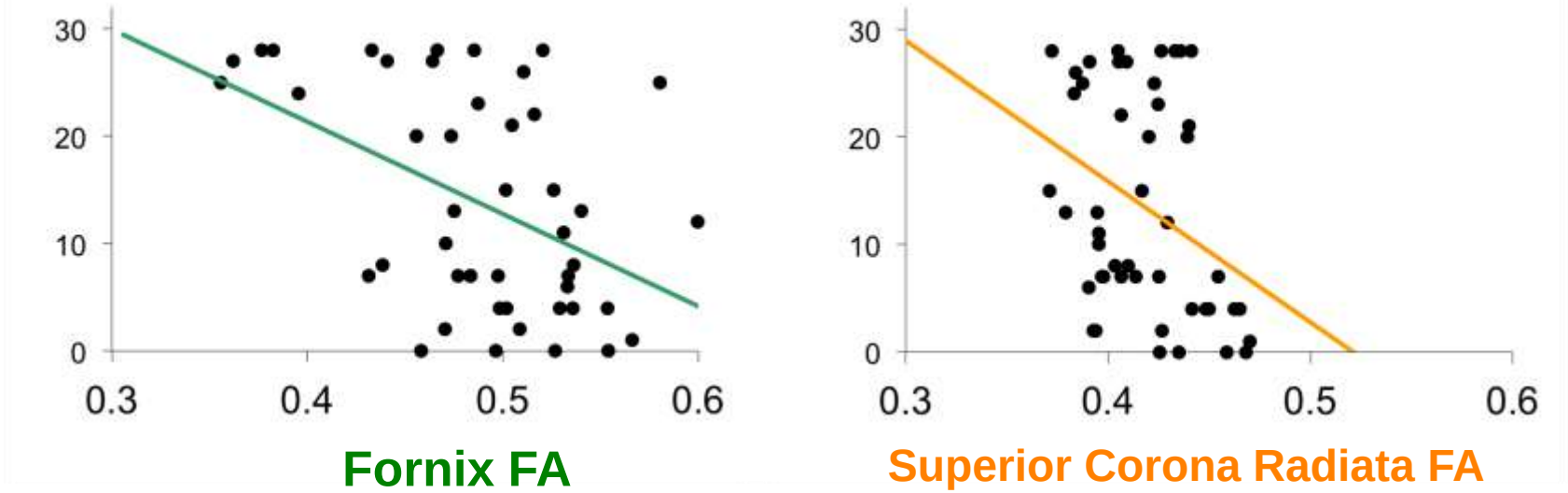
Jacobus et al., 2012; Psych Add Beh

White Matter Predicts MJ Use



partial *r* = -.39*

partial *r* = -.40*

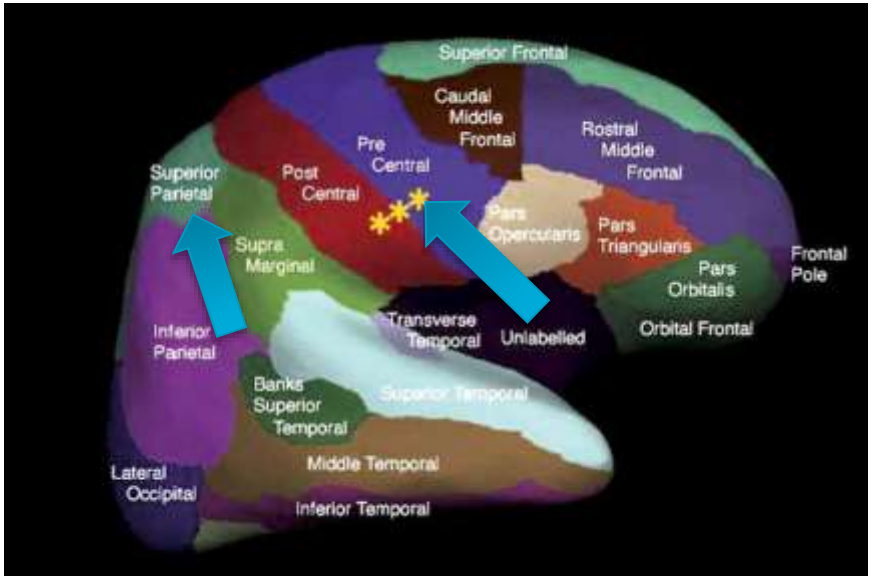


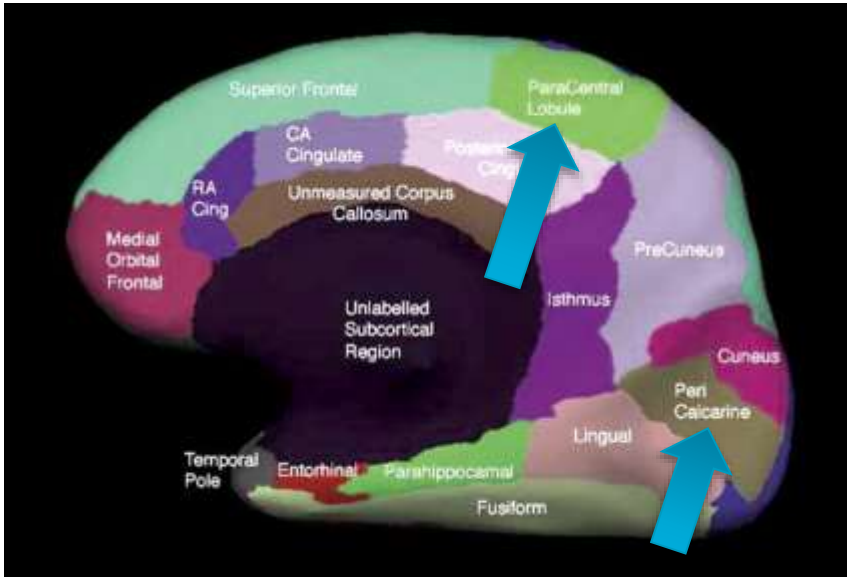
Relationship	ß	ΔR^2
Fornix FA	-.42**	.12*
Superior Corona Radiata	-.40**	.12*

* $p < .05$
** $p < .01$

Jacobus et al., 2012; Psych Add Beh

Pre- and Post MJ Initiation Dose-dependent Effects





- Less cortical thinning = MJ use at follow-up
  - *Left and right* superior parietal cortex, *r*=-.40, *p*=.01
  - *Right* paracentral gyrus, *r*=-.41, *p*<.01
  - *Left pericalcarine*, *r*=-.41, *p*<.01
  - *Right* precentral= r=-.30, *p=.04*

Jacobus et al., 2016, Neurotoxicol Teratol

Design of 4-Week Study

Day 1

Day 28

2x Weekly Urine Toxicology

SCAN #1
(age ~17)

Substance Use

Mental Heath

NP Assessment

SCAN #2
(age ~17)

Substance Use

Mental Heath

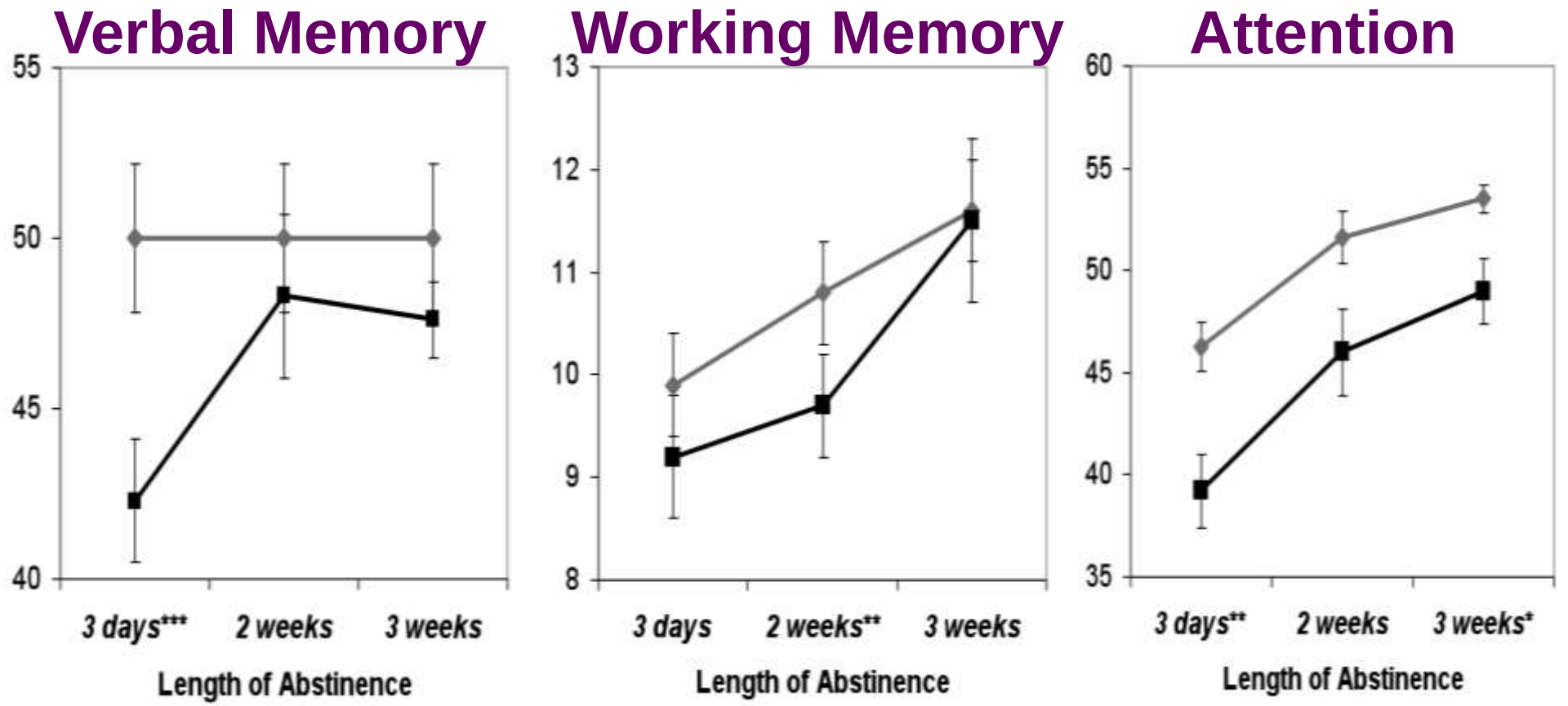
NP Assessment

1. Groups defined by substance use patterns
2. All were asked to stop all substance use

P20 DA024194; Center PI: Mason,
Subcontract PI: Tapert

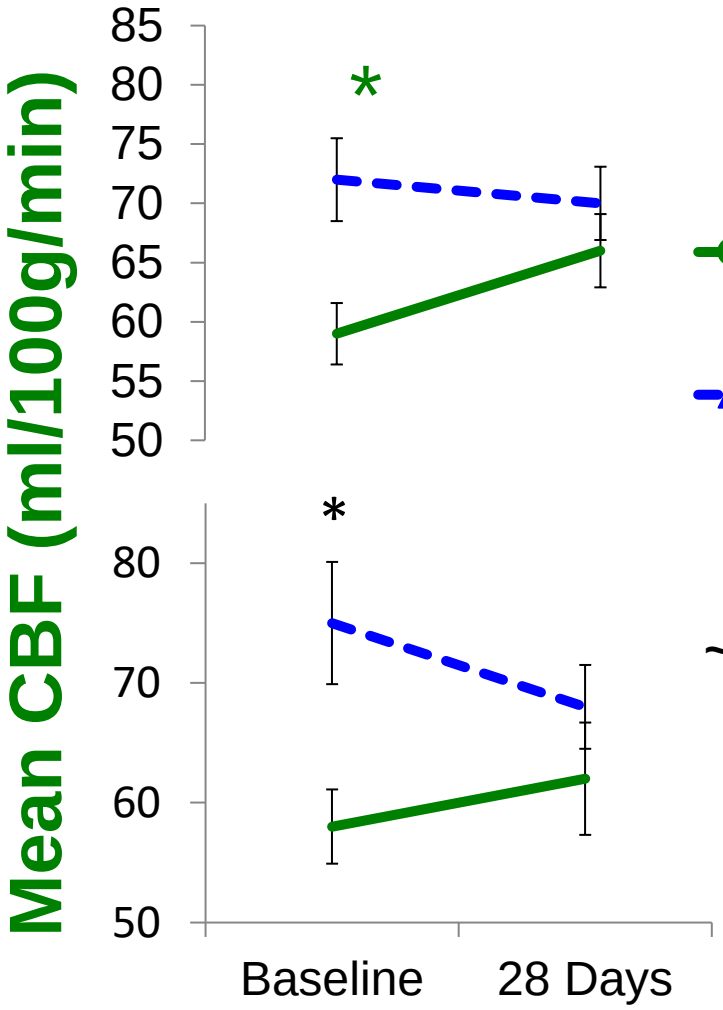
Recovery with Abstinence

■19 users ◆21 non-users



Hanson et al., 2010, Addict Behav

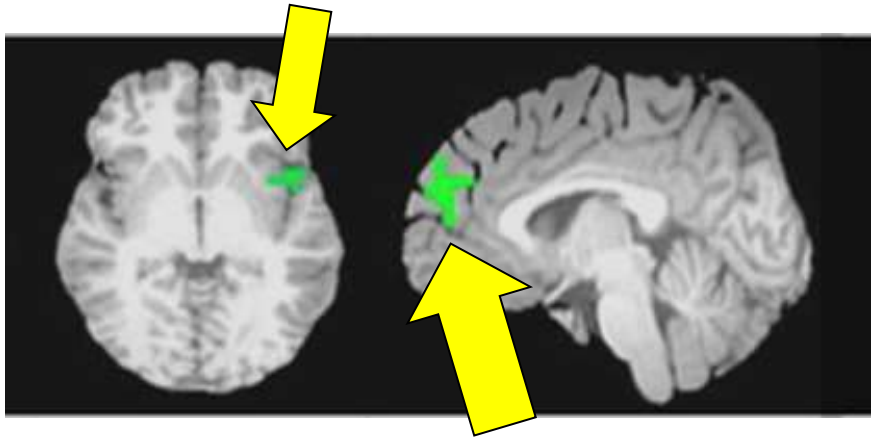
Arterial Spin Labeling



Brain blood flow after 28 days of monitored abstinence

*p<.01
~Age 17
***N*=46**

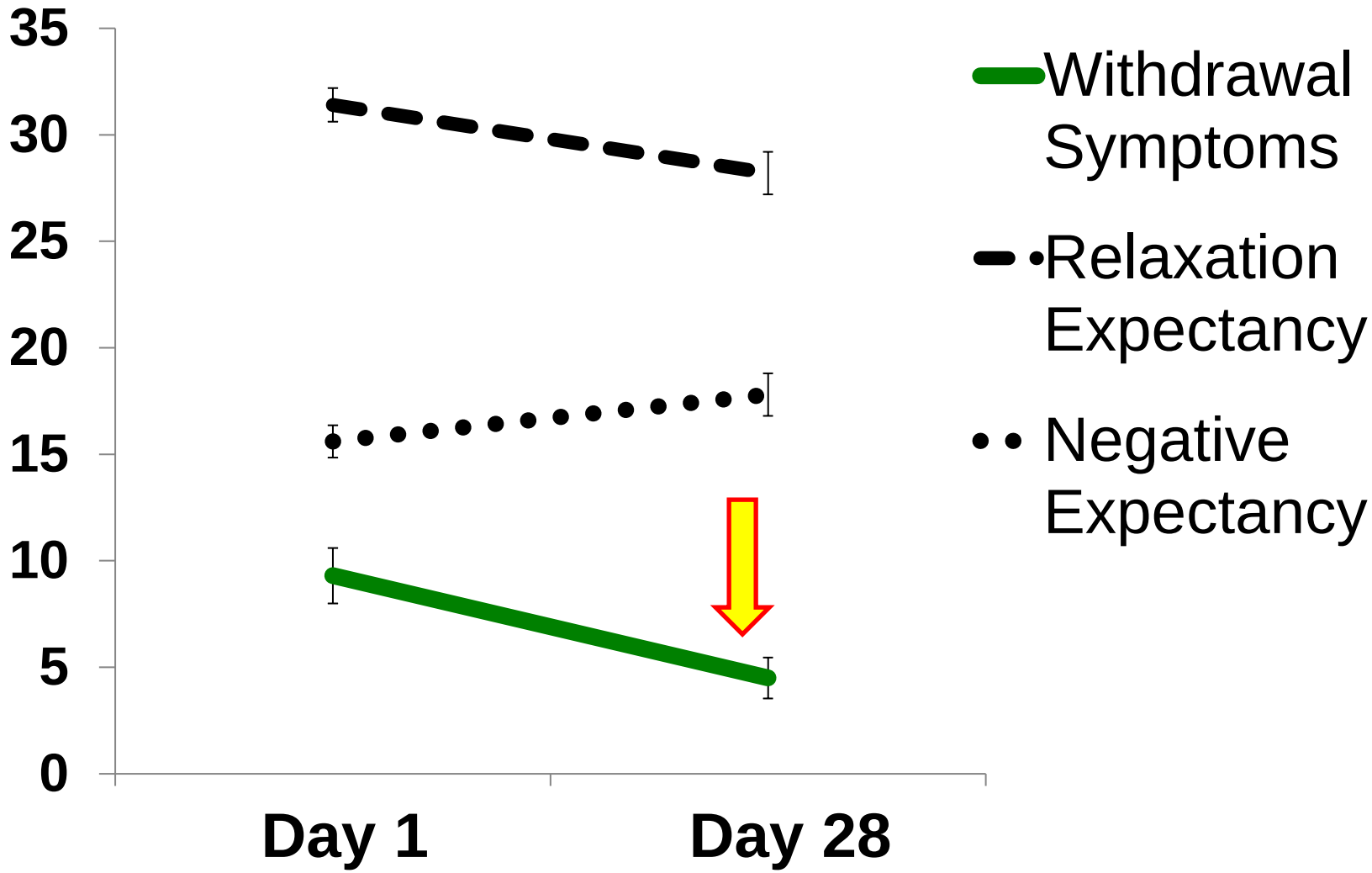
Left Insula



Medial Frontal Gyrus

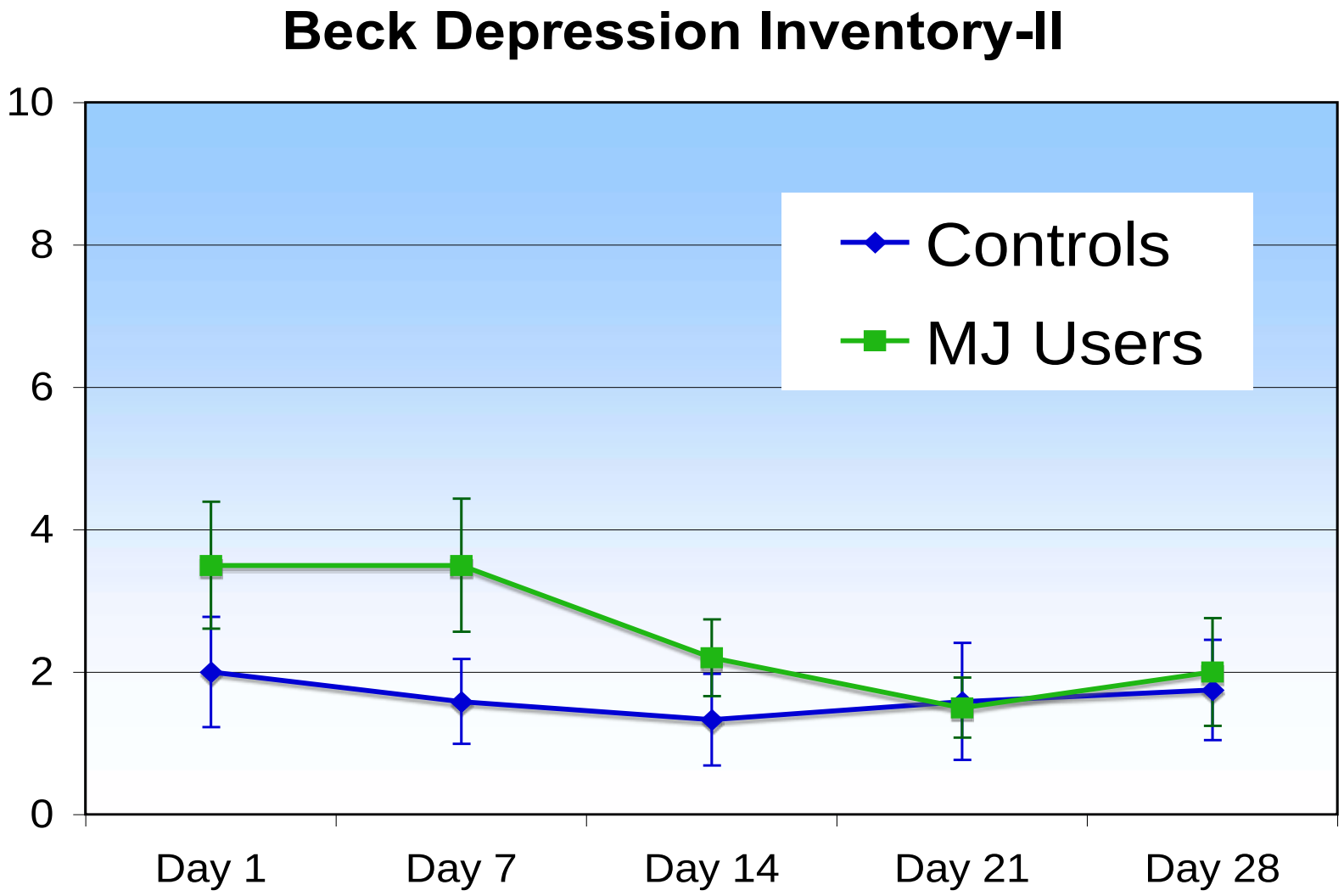
Jacobus, Goldenberg, Wierenga, Tolentino, Liu, & Tapert, 2012, Psychopharm

28 Days of MJ Abstinence



Jacobus et al., 2017, Pharmacology

Mood



Jacobus et al., 2017, Pharmacology

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Clinical Considerations

Problem vs. experimentation?

- Frequency
- Age of onset
- Pre-existing differences
- Co-occurring other substance use
- *Generally*, poorer cognitive performance (compared to demographically matched controls) observed in learning, memory, & complex attention
  - Likely to resolve with abstinence

Jacobus et al., 2017, Pharmacology

Treatment

- Motivational Enhancement Therapy (MET) with Cognitive Behavioral Therapy (CBT)
  - Kaminer, Sampl, Kadden
  - *https://store.samhsa.gov*
- 5 45-75-minute sessions:
  1. Motivation building
  2. Goal setting
  3. Marijuana refusal skills
  4. Enhancing social support and pleasant activities
  5. Planning for emergencies and coping

Therapeutic Effects of Cannabis?

- Substantial evidence (adults):
  - +Chronic pain
  - +Anti-emetic for chemo-induced nausea
  - +Improving multiple sclerosis spasticity

  - -Increased risk of psychoses (esp frequent use)
  - -Worsened respiratory symptoms
  - -Risk of MVA and overdose
  - -Lower birthrate with prenatal exposure

National Academy of Sciences, 2017

Therapeutic Effects of Cannabis?

- Moderate evidence:
  + Improving sleep short-term in apnea, pain, and MS
- Limited evidence:
  + improved appetite
  + improvements in Tourette's, anxiety, PTSD, TBI symptoms
- Ineffective for:
  -dementia, glaucoma, depression
- Inconclusive:
  ? cancer, IBS, epilepsy, ALS, HD, PD, SUD, schizophrenia

National Academy of Sciences, 2017

How Harmful Is Marijuana?

- Pre-existing differences
- Objective measures
- Links to functional impairment

✓ Generally, risks outweigh any possible benefit during *typical* adolescent development

- We need large, prospective studies (ABCD, NCANDA)

NCANDA

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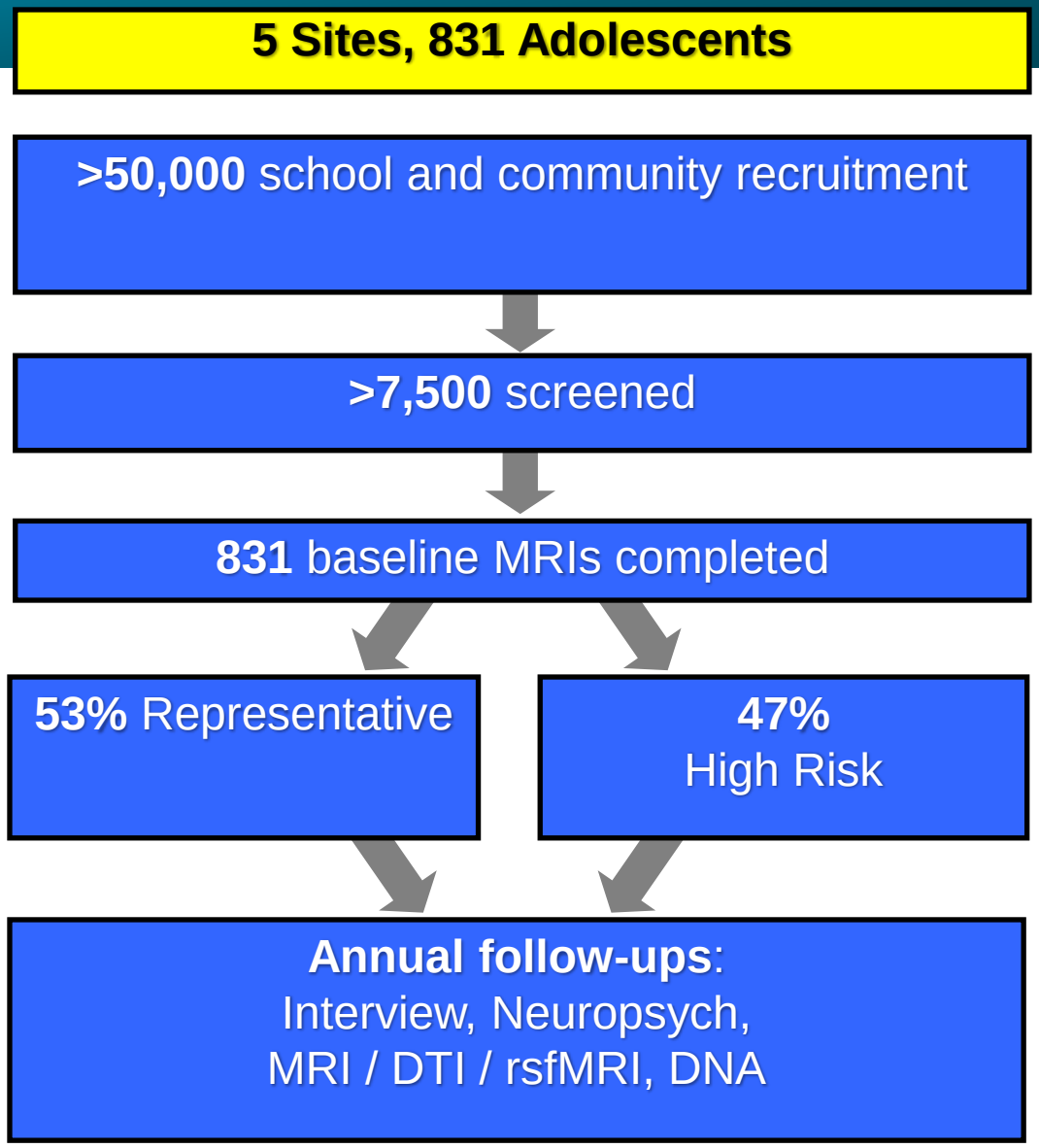
- Sandy Brown - Coordinator
- Susan Tapert – Scientific Director

Data:
- Dolf Pfefferbaum
- Kilian Pohl
- Edie Sullivan

Sites:
- Duncan Clark - U Pittsburgh
- Ian Colrain & Fiona Baker – SRI
- Mike DeBellis - Duke University
- Bonnie Nagel – OHSU
- Susan Tapert – UC San Diego



Adolescent Brain Cognitive Development

Teen Brains. Today's Science. Brighter Future.

ABCD Study

TIMELINE OF EVENTS

STUDENT AGE	9-10		10-11		11-12	
STUDENT TIME						
STUDENT PAYMENT						
STUDENT ACTIVITY		every 3-6 months		every 3-6 months		
PARENT TIME						
PARENT PAYMENT						
PARENT ACTIVITY						

REPEAT ... until age 19-20

LEGEND In-Person Visit · Biosamples · Phone Call · Brain Scan · iPad Tasks · Interview

THANK YOU!

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