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 = 0.5 grams
- 1 blunt = 1-2 grams
- 1 bowl = 0.25-0.5 grams
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
Synthetic Cannabinoids

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

Use ↑ $8^{th}$ to $12^{th}$ Grade

Alcohol + Cannabis often used together

% using in past month

Age

Monitoring the Future, 2017
Cannabis Use Trajectories

Caldeira et al, 2012, Drug Alc Dep
Perceived Risk of Harm

Perceived Risk = \uparrow Substance Use

% say regular MJ use is a "great risk"

Percentage Saying Great Risk


Monitoring the Future, 2017
Synthetic Cannabinoids

Use
% who used in last 12 months

Risk
% seeing "great risk" in using once or twice

Monitoring the Future, 2016
Prevalence Across States

Past Month Cannabis Use: Ages 12-17

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
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What’s in the Cannabis?

Increase in High Potency Marijuana

El Sohly et al. (2016). *Biological Psychiatry.*
Marijuana plant:
- 100+ cannabinoids
  - Δ-9-tetrahydrocannabinol (THC)
  - cannabidiol (CBD)
  - cannabinol (CBN)

Cannabis ➔ CB1 receptor
- Cortex, hippocampus
- Mediates inhibitory actions

Atakan, 2012. Ther Adv Psychopharm
Increase in THC / CBD

El Sohly et al., 2016. Biological Psychiatry.
Gray & White Matter

Top view

Side view
Brain Development Processes

Volume
Metabolism
Myelination
Blood Flow
Receptors
Synaptic Refinement

Adolescence

Prenatal
Post-birth Age

Prefrontal Gray Matter

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

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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.

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**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

Overview

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

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

*p < .05
Prospective Study Design

1. Recruitment at local high schools
2. Youth screen
3. Parent screen
4. Youth diagnostic interview
5. Parent diagnostic interview
6. 28 days of monitored abstinence
7. Neuropsych test and scan
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)

Fractional Anisotropy

Nonuser

MJ+ALC

Alc

* p<.01

Jacobus et al., 2009, Neurotoxicol Teratol
NP and Imaging Markers

Digit Symbol Raw Scores

Better White Matter

Better Cognitive Performance

Jacobus et al., 2013, Psychiatry Research
Substance Use over Time

Alcohol, Drinks Per Month

Baseline  | 1.5 Years  | 3 Years
---|---|---
~age 17 | ~age 19 | ~age 20

Marijuana, Days Per Month

Baseline  | 1.5 Years  | 3 Years
---|---|---
~age 17 | ~age 19 | ~age 20

Jacobus, et al., 2013, Psychiatry Research
White Matter, Marijuana, & Alcohol (~Age 20)

**R Sup. Longitudinal Fasciculus**

![Bar chart for R Sup. Longitudinal Fasciculus](chart1)

**R Superior Corona Rac**

![Bar chart for R Superior Corona Rac](chart2)

*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**
• Education, prevention, and treatment
Cognition in Abstinent Users (Age ~17)

Medina, Hanson, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007
Neurocognition & Age of Onset

**TMT Number Sequencing**

**TMT Letter Sequencing**

**TMT Switching**

**WAIS-III Digit Symbol Coding**

Pearson’s $r = .33-.44$

Jacobus et al., 2015, Neuropsychology
Neurocognitive Performance over 3 Years

**Logical Memory I**

- CON
- MJ

- Scaled Score
- Raw Score

**Logical Memory Recognition**

- Scaled Score

**Digit Span Backwards**

- Scaled Score

* * * * * *

*p < .05

Jacobus et al., 2015, Neuropsychology
What Types of Cognition Appear Affected?

Average Effect Size (Cohen's $d$) for Between Group Comparisons Over Three Years

- **Attention**: $*p<.05$
- **Processing Speed**: $*p<.05$
- **Memory**: $*p<.05$
- **Spatial Fx**: $*p<.05$
- **Executive Fx**

*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 $r = -0.39^*$

Partial $r = -0.40^*$

<table>
<thead>
<tr>
<th>Relationship</th>
<th>$\beta$</th>
<th>$\Delta R^2$</th>
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</thead>
<tbody>
<tr>
<td>Fornix FA</td>
<td>-.42**</td>
<td>.12*</td>
</tr>
<tr>
<td>Superior Corona Radiata FA</td>
<td>-.40**</td>
<td>.12*</td>
</tr>
</tbody>
</table>

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

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*
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

Verbal Memory

Working Memory

Attention

Hanson et al., 2010, Addict Behav
Arterial Spin Labeling

Brain blood flow after 28 days of monitored abstinence

Mean CBF (ml/100g/min)

- Marijuana Users
- Controls

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

Left Insula
Medial Frontal Gyrus

Jacobus, Goldenberg, Wierenga, Tolentino, Liu, & Tapert, 2012, Psychopharmacology
28 Days of MJ Abstinence

Jacobs et al., 2017, Pharmacology
Jacobus et al., 2017, Pharmacology
Overview

- Rates of marijuana use and disorders
- Does cannabis use affect the adolescent brain
- Negative outcomes of marijuana use
- Education, prevention, and treatment
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](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)
Administration:
- 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

>50,000 school and community recruitment

>7,500 screened

831 baseline MRIs completed

53% Representative

47% High Risk

Annual follow-ups:
Interview, Neuropsych, MRI / DTI / rsfMRI, DNA
## ABCD Study Timeline of Events

### Adolescent Brain Cognitive Development

**Teen Brains. Today’s Science. Brighter Future.**

<table>
<thead>
<tr>
<th>Student Age</th>
<th>9-10</th>
<th>10-11</th>
<th>11-12</th>
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<tbody>
<tr>
<td><strong>Student Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Student Payment</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Student Activity</strong></td>
<td>![Icon]</td>
<td>![Icon]</td>
<td>![Icon]</td>
</tr>
<tr>
<td></td>
<td>every 3-6 months</td>
<td>every 3-6 months</td>
<td></td>
</tr>
<tr>
<td><strong>Parent Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parent Payment</strong></td>
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<td>![Icon]</td>
<td>![Icon]</td>
<td>![Icon]</td>
</tr>
<tr>
<td></td>
<td>Interview</td>
<td>Tablet Scan</td>
<td>iPad Tasks</td>
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</tbody>
</table>

**Legend:**
- In-Person Visit
- Biosamples
- Phone Call
- Brain Scan
- iPad Tasks
- Interview

**Repeat ... until age 19-20**
Funding Support: NIDA & NIAAA
• Youth at Risk: R01 AA013419 (Tapert)
• NCANDA: U01 AA021692 (Tapert) and U01 AA021695 (Brown/Tapert)
• ABCD: U01 DA041089 (Tapert/Paulus) and U24 DA041147 (Jernigan/Brown)

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Kara Bagot, MD, Asst Prof
Sonja Eberson, MA, Lab Manager
MJ Meloy, PhD, Lead MR Techologist
Norma Castro, MA, Project Coordinator
Alyssa Lopez, Project Coordinator
Fellows: Kelly Courtney PhD, Alejandra Infante PhD, Alejandro Meruelo, MD PhD.
Grad students: Tam Nguyen-Louie MA, April May, MS.
RAs: Clarisa Coronado, Claudia Cota, Vanessa Diaz, Jackie Goetz, Irene Li, Mattie Monroe, Margie Hernandez
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Krista Lisdahl, PhD, UWM
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Jay Giedd MD, Terry Jernigan PhD,
Marc Schuckit MD, Alan Simmons PhD

THANK YOU!