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

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
- CO2 Oil: BHO (solvent extracted): wax, shatter, crumble, oil, honeycomb

Synthetic Cannabinoids

- Fake weed, synthetics, herbal incense, Spice, 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


Use ↑ 8th to 12th Grade

Alcohol + Cannabis often used together

Monitoring the Future, 2017

Cannabis Use Trajectories

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

\[ \text{Perceived Risk} = \uparrow \text{Substance Use} \]

\[ \% \text{ say regular MJ use is a "great risk"} \]

\[ 2016: 31\% \]

Monitoring the Future, 2017

Synthetic Cannabinoids

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 have been in a state where marijuana has been legalized.

What's in the Cannabis?

Increase in High Potency Marijuana

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

Cannabis Biochemistry

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

Atakan, 2010. Ther Adv Psychopharm
El Sohly et al., 2016. Biological Psychiatry.

Increase in THC / CBD

Gray & White Matter

Top view

Side view

Brain Development Processes

Volume
Metabolism
Myelination
Blood Flow
Receptors
Synaptic Refinement

Adolescence

Rate of Change

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

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.

Ducharme et al., 2016, NeuroImage

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

**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)

<table>
<thead>
<tr>
<th></th>
<th>Light Drinkers</th>
<th>Heavy Drinkers</th>
<th>MJ+Alc Users</th>
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<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>
</tr>
<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

- Recruitment at local high schools
- Youth screen
- Parent screen
- Youth diagnostic interview
- Parent diagnostic interview
- 28 days of monitored abstinence
- 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
  - $\uparrow$ fractional anisotropy (FA)
    - Related to cognitive status

$\uparrow$ FA = $\uparrow$ WM integrity

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

<table>
<thead>
<tr>
<th>Fractional Anisotropy</th>
<th>Nonuser</th>
<th>MJ+ALC AIC</th>
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Jacobus et al., 2009, Neurotoxicol Teratol

$p < .01$
NP and Imaging Markers

Digit Symbol Raw Scores

Better Cognitive Performance

Better White Matter

Jacobus et al., 2013, Psychiatry Research

Substance Use over Time

Alcohol, Drinks Per Month

Marijuana, Days Per Month

Baseline 1.5 Years 3 Years

Baseline 1.5 Years 3 Years

Jacobus, et al., 2013, Psychiatry Research

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

R Sup. Longitudinal Fasciculus

Fractional Anisotropy

R Superior CoronaRadiata

Jacobus et al., 2013, Psychiatry Research
Overview

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Cognition in Abstinent Users (Age ~17)

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

Neurocognition & Age of Onset

Jacobus et al., 2015, Neuropsychology

Pearson’s r = .33-.44
Neurocognitive Performance over 3 Years

What Types of Cognition Appear Affected?

White Matter Predicts Future Use
White Matter Predicts MJ Use

- Partial $r = -.39^*$
- Partial $r = -.40^*$

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Fornix FA</th>
<th>Superior Corona Radiata FA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r$</td>
<td>-.42**</td>
<td>-.40**</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.12*</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 $\rightarrow$ 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
  - SCAN #1
  - Substance Use
  - Mental Health
  - NP Assessment
  - 2x Weekly Urine Toxicology

- Day 28
  - SCAN #2
  - Substance Use
  - Mental Health
  - 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

- Verbal Memory
- Working Memory
- Attention

Hanson et al., 2010, Addict Behav

Arterial Spin Labeling

- Brain blood flow after 28 days of monitored abstinence
- Left Insula
- Medial Frontal Gyrus

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

28 Days of MJ Abstinence

- Withdrawal Symptoms
- Relaxation Expectancy
- Negative Expectancy

Jacobus et al., 2017, Pharmacology
Mood

Beck Depression Inventory-II

Overview

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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

5 Sites, 831 Adolescents

>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

Administration:
- Sandy Brown - Coordinator
- Susan Tapert – Scientific Director

Data:
- Dolf Pfefferbaum
- Kilian Pohl
- Edie Sullivan

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

ABCD Study

TIMELINE OF EVENTS

PNNS Annual Conference 2019
Thank you!

Tapert Lab:
- Joanna Jacobus, PhD, Asst Prof
- Kara Bagot, MD, Asst Prof
- Sergei Efron, MA, Lab Manager
- MJ Weih, PhD, Lead MRI Technologist
- Nirsha Cenizo, MA, Project Coordinator
- Alyssa Lopez, Project Coordinator

Fellows:
- Kelly Courtney PhD, Alejandra Infante PhD, Alejandro Maceo, MD PhD.

Grad Students:
- Tam Nguyen-Loque MA, April MD

RAs:
- Clarisa Connors, Claudia Cola
- Veronica Dicz, Jackie Gratz, Irene Li, Matte
- Danielle, Margot Hernandez

Lab alumni and collaborators:
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- Maria Derog, PhD, Yale
- Krista Lasker, PhD, UWM
- Bronte Nagle, PhD, CHSU
- Martin Paulus MD, LBR
- Emily Szablewski, PhD, MUSC

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- Jay Giedd MD, Terry Jernigan PhD
- Marc Schuckit MD, Alan Simmons PhD

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