Neuropsychological Functioning in Adolescent Marijuana Users

Krista Lisdahl Medina, Ph.D.
University of Cincinnati

Susan Tapert, Ph.D.
University of California, San Diego

Disclosures

Faculty Disclosure Information
I have had NO financial relationships with manufacturer(s) of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity.

I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions
Frequency of Drug Use

Adolescent Brain Development

Gray Matter Development

Monitoring the Future, 2008

Adolescent Brain Development

Volume
Metabolism
Myelination

Blood Flow
Receptors
Synaptic Refinement

Prenatal
Post-birth Age

Adolescence

RATe OF CANGE

Gray Matter Development

Gogtay et al., 2004
Adolescent Brain Development

Adolescent Neurodevelopment

Theoretical Model

Abnormal Cognition and Mood

Heavy Drug Use

Altered Neurodevelopment

SUD Risk Factors

Biological Factors

Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions
Studies Overview: Participants

- 16.0 - 18.9 years old
- Parent/Guardian Permission
- Fluent English Speakers

Marijuana Users
- Used marijuana >200 times
- Never met Cahalan criteria for Heavy Drinker
- Haven't used other drugs >25 times

Controls
- Used marijuana <5 times
- Never met criteria for Heavy Drinker
- Never used other illicit drugs

Exclusion Criteria

- MRI contraindication
- Axis I psychiatric disorder
- Psychiatric medications
- Family hx bipolar or psychosis
- Complicated/premature birth
- Prenatal alcohol/drug exposure
- Neurologic illness or injury

Marijuana Study Procedure

- Recruitment at local high schools
- Youth screen
- Parent screen
- Youth diagnostic interview
- Parent diagnostic interview
- 28 days of monitored abstinence
- Neuropsych test and scan
Staying Abstinent

- 2-3x/wk urine samples
- 2/3 stay abstinent 1 month
- Non-abstainers:
  - Heavier users

MJ & Cognition

- MJ users (n=31) different than Controls (n=34), p<.05
- After 1 month abstinence

Medina, et al., 2007

MJ & Cognition

\[ r = -0.46 \]
\[ p < 0.009 \]

Medina, Hanson et al., 2007
MJ & Cognition

\[ r = -0.40 \]
\[ p < 0.03 \]

MJ Use & Emerging Adulthood

- Controls (n=42), MJ (n=21)
- Ages 18-25
- Neuropsychological battery
  - Axis I psychiatric disorder
  - Psychiatric medications
  - Family hx bipolar or psychosis
  - Neurologic Illness
  - Major medical illness
  - Minimum 1 week abstinence

MJ Use & Emerging Adults

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=42)</th>
<th>MJ Users (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.8±2.2</td>
<td>21.4±2.7</td>
</tr>
<tr>
<td>Education</td>
<td>13.8±1.7</td>
<td>13.4±2.2</td>
</tr>
<tr>
<td>% Female</td>
<td>52%</td>
<td>48%</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>69%</td>
<td>62%</td>
</tr>
<tr>
<td>Reading</td>
<td>100.7±8.6</td>
<td>106.6±11.9</td>
</tr>
<tr>
<td>BDI-2*</td>
<td>4.0±3.8</td>
<td>9.5±8.4</td>
</tr>
</tbody>
</table>

*\[ p < 0.001, \text{ Controls < MJ} \]
**MJ Use & Emerging Adults**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Controls (n=42)</th>
<th>MJ Users (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>105.8±172.3</td>
<td>261.6±326.5</td>
</tr>
<tr>
<td>Inhalants</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>0.2±0.9</td>
<td>1.9±4.2</td>
</tr>
<tr>
<td><em>MJ</em></td>
<td>1.0±2.7</td>
<td>169.9±195.9</td>
</tr>
<tr>
<td>MDMA</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>Stimulants</td>
<td>0.1±0.5</td>
<td>1.6±4.5</td>
</tr>
<tr>
<td>Sedatives</td>
<td>0.2±1.1</td>
<td>0.0±0.6</td>
</tr>
<tr>
<td>Opioids</td>
<td>0.0±0.0</td>
<td>0.1±0.3</td>
</tr>
</tbody>
</table>

*<p><.001, Controls < MJ>*

---

**MJ & Cognitive Function**

... not related to verbal memory, inhibition, or fluency

**MJ & Cognition: Summary**

- After 7-30 days abstinence
  - Poorer psychomotor speed, sustained attention, verbal memory, and sequencing ability in adolescents
  - Poorer sustained attention in emerging adults
  - Increased symptoms depression, poorer grades, increased school problems
- MJ may interrupt neuromaturation
  - Hippocampus
  - PFC
  - Cerebellum
- Is there recovery of function in that first month?
MJ & Cognition Over Time

Group p<.05
Group x Time p<.01

Hanson et al., in prep

MJ & Cognitive Function

Group p<.05

Hanson et al., in prep

MJ & Cognition: Summary

- MJ use associated with poorer
  - Verbal list learning: significant improvements
  - Attention: continued deficits
- Some cognitive recovery may occur with abstinence, even after only a few days.
- Future studies needed to assess longer periods of abstinence
Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions

Hippocampal Volume

- Larger left hippo
- Control (n=16)
- Alc (n=21)
- MJ+Alc (n=26)

Medina, Nagel et al., 2007. NTT

MJ & PFC Structure

Prefrontal Cortex – Executive Functioning
MJ users vs. Controls (N=32)

Medina, Nagel et al., In Press
Gender marginally moderated affects of MJ, p<.09

Girl MJ users, bigger NOT better

MJ users vs. Controls (N=32)
MJ & Cerebellar Structure

- Group p < .05

Brain Structure & MJ

- MJ use associated with increased hippocampal, PFC, and cerebellar volumes
  - Girls appear most affected
  - Pattern is consistent with cognitive deficits

- Bigger was NOT better!
- Interrupted gray matter pruning?

...controlled alcohol, gender, ethnicity, reading level
Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions

Brain Function & MJ Use

- FMRI Tasks
  - Spatial working memory
  - Verbal encoding
- UCSD 3T GE magnet
  - BOLD-weighted EPIs
- AFNI

Spatial Working Memory Task

SWM: Adolescent MJ Users

24 MJ users
24 Controls

L Parietal
MJ>C

L Frontal
MJ>C

L Temporal
MJ>C

L Cerebellum
MJ<C

Winward et al., in preparation

Performance same, MJ used more of the brain
Go/No-Go Task

**Instructions:**
- Press the button as soon as you see a blue shape EXCEPT the SMALL blue square.
- Respond as FAST as you can!

Schweinsburg et al., 2004; Anderson et al., 2005; Tapert et al., 2007

---

Inhibition: Adolescent MJ Users

MJ teens (n=16) had more no-go response than controls (n=17)

MJ>C

Left posterior parietal cortex

Tapert et al., 2007, Psychopharmacology

---

Inhibition: Adolescent MJ Users

MJ teens had more inhibition response than controls

Right dorsolateral prefrontal cortex

Left posterior parietal cortex

Left dorsolateral prefrontal cortex

Tapert et al., 2007, Psychopharmacology
Inhibition: Adolescent MJ Users
- Right dorsolateral prefrontal cortex
- Left posterior parietal cortex
- Left dorsolateral prefrontal cortex

MJ teens showed more disinhibition and brain effort...
MJ effects or premorbid differences?

Adolescent Marijuana Use
- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions
Adolescent MJ Use: Summary

<table>
<thead>
<tr>
<th>Marijuana</th>
</tr>
</thead>
</table>
| Cognition          | ↓1st trial, speed, and attention  
| Volume             | ↑left hippo; Gender moderated PFC  
| SWM                | ↑in inferior posterior vermis  
| Go/No-go           | ↑errors; ↑parietal, PFC  

Limitations

- Do preexisting differences explain findings?
  - Risk factors for using marijuana explain this?
  - Subclinical conduct, attentional, mood problems
  - Preexisting executive functioning deficits
  - Family history and genetics

- Need...
  - Larger sample of female users
  - Marijuana users without comorbid alcohol use
  - More diverse samples (SES, ethnicity)
  - Longitudinal studies of at-risk adolescents

Future Directions

- Targeting individual differences:
  - Do protective and/or risk factors exist?
    - Prenatal environment
    - Genetics
    - Gender
      - Hormone interactions?
    - Comorbid disorders
    - Sleep architecture
    - Stress
Future Directions

- **Do combinations of drugs matter?**
  - Independent and interactive effects of drugs, especially nicotine, alcohol and marijuana

- **Do teens improve with abstinence?**

- **Are neurocognitive abnormalities related to treatment outcome?**

- **Interventions to treat adverse neural reactions?**
  - Pharmacological
  - Enriched environments (e.g., exercise)

Acknowledgements

- **NIH Funding Institutes**
  - NIDA/NIH: R21 DA021182 (PI: Tapert); DA202166 (PI: Medina); 2008 NIDA Travel funding (Medina)
  - Center for Environmental Genetics P30 ES06096 (PI: Medina)

- **UCSD Adolescent Brain Imaging Project (past & present)**
  - Susan Tapert (PI), Bonnie Nagel (OSU), Karen Hanson, Matthew Cohen-Zin, MJ Meloy, Binita Banerjee, Alexia Schweinsburg (Yale), Carmen PubMed, Andrea Spadoni, Larry Frank, Gregory Brown, Sandra Brown, Martin Paulus, Marc Schuckit, Brian Schweinsburg (Yale).

- **UC Brain Imaging & Neuropsychology (Brain) Lab**
  - Faculty collaborators: Drs. Paula Shear, James Eliassen, Judith Strong.

References


