Neuropsychiatric Effects of Cannabis

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Cannabis and Neuropsychiatry: Overview

- **Purpose:** to review the effects of cannabis on the brain and behavior

- **Focus:** on those neuropsychiatric phenomena that may be particularly relevant in evaluating risk:benefit of medicinal cannabis
  - Neurocognitive – attention, perceptual, verbal, memory, processing speed, executive functions, etc.
  - Complex cognitive-behavioral – driving as an example
  - Serious psychiatric – eg., vulnerability to schizophrenia and depression

- **The time course of these neuropsychiatric effects can be grouped as:**
  - Acute – minutes to hours after dosing
  - Intermediate (residual) – days to weeks after stopping regular use
  - Long term (persistent) - months to years after stopping regular use
Acute Effects of Cannabis Use

- **Cardiovascular**: ↑HR; vasodilation; ↓BP
- **Neurological**: psychomotor slowing; cerebellar signs; drowsy; fatigued;
- **Cognitive**: memory; time sense; executive
- **Emotional**: giddy; calm; anxious; depressed
- **Ideational**: unusual insights; paranoid
- **Perceptual**: dissociation; illusions; hallucinations; synesthesia (eg., “seeing music”)
- **Appetitive**: hunger
Mean plasma concentrations of Δ9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) following administration smoked cannabis vs. oral dronabinol.

Acute Psychoactive Effects of Cannabis: subjective ratings

Neurocognitive Effects after 3 days of daily cannabis administration to neuropathy patients

Neuropsychological t-scores after active and placebo cannabis administration. Active cannabis reduced the NP T score by a median of 7.3 points (IQR = -10.6, -2.6), p<0.001. Treatment=third day; washout=2 wk after last treatment; Y axis= NP global T score

Source: Ellis et al 2008 Neuropsychopharmacology, 34:672-80.
Memory Impairments from Acute THC may have more clinical significance in those with subtle deficits: example of controls and schizophrenics

MJ intoxication slightly increases motor vehicle collision risk

Meta-analysis of observational studies investigating the association between acute cannabis consumption and motor vehicle crashes.

Source: Asbridge, et al., BMJ. 2012; 344:e536

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/Total Case</th>
<th>Control</th>
<th>Odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedard 2007</td>
<td>1106/19 511</td>
<td>541/13 032</td>
<td>1.39 (1.25 to 1.54)</td>
<td>18.0</td>
<td>1.39 (1.25 to 1.54)</td>
</tr>
<tr>
<td>Blows 2005</td>
<td>32/552</td>
<td>5/587</td>
<td>7.16 (2.77 to 18.52)</td>
<td>7.9</td>
<td>7.16 (2.77 to 18.52)</td>
</tr>
<tr>
<td>Drummer 2004</td>
<td>51/1214</td>
<td>5/376</td>
<td>3.25 (1.29 to 8.21)</td>
<td>8.1</td>
<td>3.25 (1.29 to 8.21)</td>
</tr>
<tr>
<td>Laumon 2005</td>
<td>322/3972</td>
<td>100/2793</td>
<td>2.38 (1.89 to 2.99)</td>
<td>17.0</td>
<td>2.38 (1.89 to 2.99)</td>
</tr>
<tr>
<td>Longo 2000</td>
<td>21/1038</td>
<td>23/937</td>
<td>0.82 (0.45 to 1.49)</td>
<td>12.0</td>
<td>0.82 (0.45 to 1.49)</td>
</tr>
<tr>
<td>Mathijssen 2005</td>
<td>6/108</td>
<td>148/3571</td>
<td>1.36 (0.59 to 3.15)</td>
<td>9.0</td>
<td>1.36 (0.59 to 3.15)</td>
</tr>
<tr>
<td>Mura 2003</td>
<td>49/321</td>
<td>21/310</td>
<td>2.48 (1.45 to 4.24)</td>
<td>12.8</td>
<td>2.48 (1.45 to 4.24)</td>
</tr>
<tr>
<td>Terhune 1982</td>
<td>13/129</td>
<td>4/161</td>
<td>4.40 (1.40 to 13.84)</td>
<td>6.2</td>
<td>4.40 (1.40 to 13.84)</td>
</tr>
<tr>
<td>Terhune 1992</td>
<td>16/541</td>
<td>9/258</td>
<td>0.84 (0.37 to 1.93)</td>
<td>9.1</td>
<td>0.84 (0.37 to 1.93)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1616/27 286</td>
<td>856/22025</td>
<td>1.92 (1.35 to 2.73)</td>
<td>100.0</td>
<td>1.92 (1.35 to 2.73)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=42.74$, df=8, $P<0.001$, $I^2=81$

Test for overall effect: $z=3.63$, $P<0.001$
Odds Ratios for MJ intoxication on driving sorted by type of study

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>N</th>
<th>I² (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>3</td>
<td>5449</td>
<td>71</td>
<td>2.79 (1.23 to 6.33)</td>
</tr>
<tr>
<td>Culpability</td>
<td>6</td>
<td>43 962</td>
<td>83</td>
<td>1.65 (1.11 to 2.46)</td>
</tr>
<tr>
<td>High quality</td>
<td>4</td>
<td>9444</td>
<td>60</td>
<td>2.21 (1.25 to 3.90)</td>
</tr>
<tr>
<td>Medium quality</td>
<td>5</td>
<td>39 967</td>
<td>79</td>
<td>1.78 (1.07 to 2.94)</td>
</tr>
<tr>
<td>Fatal collisions</td>
<td>5</td>
<td>42 836</td>
<td>88</td>
<td>2.10 (1.31 to 3.36)</td>
</tr>
<tr>
<td>Non-fatal collisions</td>
<td>4</td>
<td>6575</td>
<td>71</td>
<td>1.74 (0.88 to 3.46)</td>
</tr>
</tbody>
</table>

Pooled odds ratio (95% CI) of motor vehicle collision risk with tetrahydrocannabinol for subgroups of studies.

Source: Asbridge, et al., BMJ. 2012; 344:e536
Driving and Cannabis: Effects of Alcohol

Geometric mean (+SE) of time out of lane (TOL, percent) in first and second repetitions of the Road Tracking Test in every condition. Target blood alcohol level (BAC) was 0.04 g/dl.

Long Term Neurocognitive Effects of Marijuana
Results of Meta-analysis of 15 NP studies

Source: Data from Grant et al. (2003) JINS. 9;679-689
Long Term Neurocognitive Effects
Methamphetamine vs. Cannabis

Neurocognitive Domain

Verbal/Language
Reaction time
Perceptual-Motor
Motor
Learning
Forgetting
Attention
Abstraction-Executive

1Data from Grant et al. (2003) JINS. 9;679-689.
2Data from Scott et al. (2007) Neuropsychol Rev. 17;275-297.
Persisting neurocognitive deficits? Meta-analyses based on 33 Studies of nonintoxicated MJ users and subset of 13 studies with minimum 25 days abstinent

Persisting neurocognitive deficits? Meta-analyses based on 33 Studies of nonintoxicated MJ users and subset of 13 studies with minimum 25 days abstinent

Does Cannabis dependence before age 18 lower IQ 20 yrs later?

Meier M H et al. PNAS 2012;109:E2657-E2664
Alternative causal model predicting worse IQ in early onset, repetitive MJ users: predicted follow-up IQ from SES model (blue line) vs actual Dunedin data (orange triangles)

Rogeberg 2013, PNAS, Epub, Jan 14
## Brain Structure Marijuana Users vs. Non Users

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co, 1977</td>
<td>CT</td>
<td>NS</td>
</tr>
<tr>
<td>Keuhnle, 1977</td>
<td>CT</td>
<td>NS</td>
</tr>
<tr>
<td>Hannerz, 1983</td>
<td>CT</td>
<td>NS</td>
</tr>
<tr>
<td>Wiesbeck, 1991</td>
<td>CT</td>
<td>NS</td>
</tr>
<tr>
<td>Aasly, 1993</td>
<td>vMRI</td>
<td>Cerebral &amp; Cerebellar Atrophy</td>
</tr>
<tr>
<td>Wilson, 2000</td>
<td>vMRI</td>
<td>Reduced Whole Brain / Grey Volume</td>
</tr>
<tr>
<td>Block, 2000</td>
<td>vMRI</td>
<td>NS</td>
</tr>
<tr>
<td>Tzilos, 2005</td>
<td>vMRI</td>
<td>NS</td>
</tr>
<tr>
<td>Matochik, 2005</td>
<td>vMRI</td>
<td>Regional Volume Loss of Parahippocampal</td>
</tr>
<tr>
<td>Jager, 2007</td>
<td>vMRI</td>
<td>NS</td>
</tr>
<tr>
<td>Yucel, 2008</td>
<td>vMRI</td>
<td>Reduced hippocampal, amygdala volumes</td>
</tr>
<tr>
<td>Gruber, 2005</td>
<td>MRI DTI</td>
<td>NS</td>
</tr>
<tr>
<td>DeLisi, 2006</td>
<td>MRI DTI</td>
<td>NS</td>
</tr>
<tr>
<td>Arnone, 2008</td>
<td>MRI DTI</td>
<td>NS</td>
</tr>
<tr>
<td>Zalesky, 2012</td>
<td>MRI DTI</td>
<td>NS</td>
</tr>
<tr>
<td>Medina(^a), 2007</td>
<td>MRI</td>
<td>NS</td>
</tr>
<tr>
<td>Medina(^b), 2007</td>
<td>MRI</td>
<td>NS</td>
</tr>
<tr>
<td>Mata, 2010</td>
<td>MRI</td>
<td>NS</td>
</tr>
<tr>
<td>McQueeny, 2011</td>
<td>MRI</td>
<td>NS</td>
</tr>
<tr>
<td>Lopez-Larson, 2011</td>
<td>MRI</td>
<td>NS</td>
</tr>
<tr>
<td>Cousijn, 2011</td>
<td>MRI</td>
<td>NS</td>
</tr>
<tr>
<td>Ashtari, 2011</td>
<td>MRI</td>
<td>Reduced hippocampal volume, increased whole brain volume</td>
</tr>
<tr>
<td>Schacht, 2012</td>
<td>MRI</td>
<td>Reduced hippocampal volume</td>
</tr>
<tr>
<td>Batalla, 2013</td>
<td>MRI (VBM)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Daily marijuana use not associated with brain morphometric measures in 2015 study that matched MJ and non MJ users on cofactors that may be linked to brain changes, eg., alcohol use

Functional Brain Imaging Studies

- **In acutely cannabis intoxicated:**
  - ↑ cerebral blood flow
  - ↑ activation (anterior cingulate, frontal lobe, cerebellum)
  - No consistent change in cerebral metabolic rate

- **In abstinent longer term cannabis users:**
  - ↓ cerebral blood flow
  - ↓ activation on fMRI
  - No consistent change in cerebral metabolic rate
  - Note: effects of co-occurring tobacco use not always accounted

Cerebral blood flow differences between adolescent MJ users and nonusers disappear after 28 days abstinence.


(Blue = CON < MJ, Green = MJ < CON)
Cannabis and Schizophrenia

- Does cannabis cause schizophrenia?
Cannabis and Schizophrenia

- Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to ever use of cannabis in individual studies. Pooled adjusted odds ratio 1.41, 95% CI 1.20 - 1.65.

Prevalence of Cannabis Use in the U.S.

Percentages are calculated using a weighted ratio estimate. Lifetime drug use status and age group, for each specified year, were determined using the age, date of first use, and interview date for each respondent.

Source: Data from National Survey on Drug Use and Health. 2002-2013.
Schizophrenia Over Time

Change in Incidence of Schizophrenia by Study Location, 1965-1990

-66%  -49%  -48%  -54%  -50%  -40%  -37%  -37%  +0%  +18%  +38%  +64%
Canada, 1979-90
Scotland, 1969-78
Australia, 1967-77
Scotland, 1970-81
Germany, 1963-80
Denmark, 1970-84
New Zealand, 1974-84
Scotland, 1969-84
England, 1975-86
England, 1970-86
Croatia, 1965-84
England, 1974-84
England, 1965-84
England, 1975-87
Denmark, 1969-88
Scotland, 1969-88
Scotland, 1971-89
Canada, 1979-90

Effects of acute THC on “positive psychotic” symptoms in controls vs schizophrenics

Meta-analysis finds persons with Diagnosis of Schizophrenia who have histories of cannabis use tend to perform better on neurocognitive testing

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Mean d</th>
<th>SD</th>
<th># of studies used in ES</th>
<th>Overlap %</th>
<th>Nfs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General cognitive ability and intelligence</td>
<td>0.48</td>
<td>0.51</td>
<td>4</td>
<td>64</td>
<td>15</td>
</tr>
<tr>
<td>2. Selective, sustained and divided attention</td>
<td>0.35</td>
<td>0.23</td>
<td>6</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>3. Executive abilities</td>
<td>0.14</td>
<td>0.49</td>
<td>7</td>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>4. Working memory and learning</td>
<td>0.07</td>
<td>0.40</td>
<td>5</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>5. Retrieval and recognition</td>
<td>0.12</td>
<td>0.50</td>
<td>6</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>6. Receptive and expressive language abilities</td>
<td>0.06</td>
<td>0.30</td>
<td>4</td>
<td>95</td>
<td>1</td>
</tr>
<tr>
<td>7. Visuo-spatial and constructional abilities</td>
<td>0.33</td>
<td>0.27</td>
<td>3</td>
<td>76</td>
<td>7</td>
</tr>
</tbody>
</table>

ES, effect size; Nfs, Orwin's fail safe N formula.

Cannabis and Depression

- Does cannabis cause depression?
Relationship of starting MJ under age 17 and later depression

Estimated odds ratios for the association between early onset (age<17 years) cannabis use and later onset (age 17 years) of a depression spell in different countries, World Health Organization World Mental Health Survey Initiative, 2001–2005.

Is There a Cannabis Withdrawal Syndrome in Humans?

Cannabis and Neuropsychiatry Summary

- Dose related acute effects of MJ on attention, memory, perception clearly established
- MJ intoxication may increase MVA risk slightly, much less than alcohol, but MJ + alcohol heighten impairment
- Upon cessation of chronic heavy use neurocognitive effects may persist for days to weeks, and may be accompanied by a mild abstinence syndrome
- Long term brain effects of chronic MJ use in adults not demonstrated in those beyond residual MJ effect period. If present, they are subtle and of unclear clinical significance.
- Effects on developing brain [eg., heavy use by teenagers] unclear; requires more and better designed studies that address alternative causation, eg., worse IQ trajectories in those at risk for MJ abuse
- There are associations between MJ use and schizophrenia/psychosis, but the effect sizes are modest, and the direction of causality is unproven. Psychotic symptoms may be enhanced in schizophrenics during acute intoxication
Neuropsychiatric Effects of Cannabis
Thanks for your attention!

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