Understanding Reward Value and Motivation in Cannabis Use Disorder

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I have no conflicts of interest
Public health relevance of cannabis use is intensifying

• Understanding cannabis’ effects is critical
  – Cannabis use disorder (CUD)
    • prevalence especially high in US and Canada
      • peaking during ‘emerging adulthood’
  – Changes in motivation
  – Understand underlying neurobiology

Degenhardt et al., 2004; 2013; UNODC, 2015
“Heavy” cannabis use causes “lethargy” “apathy” “Inactivity” and “loss of goal-directed behaviour”
Motivation Studies with Cannabis

**OPERANT ACQUISITION OF MARIHUANA IN MAN**

Jack H. Mendelson, John C. Kuehnle, Isaac Greenberg, and Nancy R. Mello

Alcohol and Drug Abuse Research Center, Harvard Medical School, McLean Hospital, Belmont, Massachusetts

Accepted for publication January 26, 1976

**MOTIVATIONAL EFFECTS OF SMOKED MARIJUANA: BEHAVIORAL CONTINGENCIES AND LOW-PROBABILITY ACTIVITIES**


The Johns Hopkins University School of Medicine and The University of Nebraska

**Possible Amotivational Effects Following Marijuana Smoking Under Laboratory Conditions**

Don R. Cherek, Scott D. Lane, and Donald M. Dougherty

University of Texas—Houston
Limitations in Studies of Motivation

- Small sample sizes
- Cross-sectional
- Heterogeneity of users sampled
- Escalation of THC over time

- Motivation tasks may not adequately capture the affected behaviour
• Chronic effects of cannabis on reward learning

• CUD group did not develop a response bias
Limitations in Studies of Motivation

- Small sample sizes
- Cross-sectional
- Heterogeneity of users sampled
- Escalation of THC over time

- Motivation tasks may not adequately capture the affected behaviour
- Heterogeneity in the active cannabis concentrations and compounds
• Acute effects of THC and cannabidiol (CBD) on effort-related decision-making

• Reduced mean number of high-effort choices
• Cann-CBD increased sensitivity to expected value
Young adult sequelae of adolescent cannabis use: an integrative analysis

Edmund Silins, L John Horwood, George C Patton, David M Fergusson, Craig A Olsson, Delyse M Hutchinson, Elizabeth Spry, John W Toumbourou, Louisa Degenhardt, Wendy Swift, Carolyn Coffey, Robert J Tait, Primrose Letcher, Jan Copeland, Richard P Mattick, for the Cannabis Cohorts Research Consortium*

- Integrated 3 longitudinal studies (N=~3000)
- Max frequency of cannabis <17
- Developmental outcomes
  - High School Completion
  - University degree attainment
  - Cannabis dependence
  - Use of other illicit drugs
  - Suicide attempt
  - Depression
  - Welfare Dependence
- Assessed up to age 30
High School Completion

Degree Attainment

Cannabis Dependence

Use of Other Illicit Drugs

Suicide Attempt

Depression

Welfare Dependence
• Support for causal relationship

• Consistent frequency $\rightarrow$ adverse outcomes

• Dose-response characteristics
  » strongest effects for daily users

• Resilient associations
  » Even when controlling for confounding factors

• Mechanisms?
• Advances in neuroscience permit parsing reward into specific psychological components
  – Reward Learning (explicit & implicit knowledge)
  – Affect or emotion
  – Motivation
Neurobiology of Motivation

- Amotivation may reflect that cannabis itself is a huge motivator

- Measure valuation of cannabis cues
fMRI Study of Neural Sensitization to Hedonic Stimuli in Long-Term, Daily Cannabis Users

Francesca M. Filbey,* Joseph Dunlop, Ariel Ketcherside, Jessica Baine, Tyler Rhinehardt, Brittany Kuhn, Sam DeWitt, and Talha Alvi

Marijuana Craving Scores

THC/creatinine ng/ml (abstinent state)

Marijuana Withdrawal Scores
Neurobiology of Motivation

• Emerging theoretical and empirical sophistication in understanding the cognitive components of addiction neurobiology

• Advances in neuroscience show dissociable neural systems mediate specific psychological components of reward
Reward Processing

Anticipation → time → Outcome

vmPFC
Monetary Incentive Delay Task

- Separates motivational from hedonic stages of reward processing
- Probabilistic reward delivery increases anticipatory signaling
- Can gauge neural sensitivities to reward anticipation and receipt

From Balodis et al., 2012, *Biol Psychiat*
Anticipatory Reward Processing in Addicted Populations: A Focus on the Monetary Incentive Delay Task

Iris M. Balodis and Marc N. Potenza

Table 1. Continued

<table>
<thead>
<tr>
<th>Population</th>
<th>Author (Year)</th>
<th>Clinical Group M/F</th>
<th>HC M/F</th>
<th>Urine Screen?</th>
<th>Image Analysis</th>
<th>MC Correction</th>
<th>Phase/Contrast</th>
<th>Striatal Response</th>
<th>Coordinates</th>
<th>Correlations with Striatal Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>van Hell et al., 2010 (46)</td>
<td>13M 1F Smokers: 11M 3 F</td>
<td>11M 2F</td>
<td>U</td>
<td>WB ROI</td>
<td>✓</td>
<td>Gain &gt; neutral</td>
<td>±14, 14, −8 (TC)</td>
<td>—</td>
<td>Non-treatment seeking</td>
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<td>Loss trial results not included in MIDT task</td>
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<td>Negative urine screens for THC in almost all participants</td>
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<td>Decreased VS in both smokers and cannabis users relative to HCs</td>
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<tr>
<td>Nestor et al., 2010 (49)</td>
<td>14M</td>
<td>14M U + THC</td>
<td>WB</td>
<td>✓</td>
<td>Gain &gt; baseline</td>
<td>20, 8, −4</td>
<td>VS activity during win correlates positively with number of reported lifetime joints smoked</td>
<td>MIDT version collapsed across magnitude</td>
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<td>All MD participants had positive THC urine toxicology</td>
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<tr>
<td>Filbey et al., 2013 (63)</td>
<td>47M 12F</td>
<td>5M 22F U + THC</td>
<td>WB</td>
<td>✓</td>
<td>Gain &gt; neutral</td>
<td>MNI extent on x, 8–16; y, 15–6; z, −4 to −12</td>
<td>Required positive urinalysis for THC metabolites but excluded for other drugs</td>
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<td>HC group showed no significant difference during either incentive condition (gain or loss) — may be driving effect?</td>
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<tr>
<td>van Hell et al., 2012 (61)</td>
<td>11M</td>
<td>U ROI</td>
<td>x</td>
<td>Gain &gt; neutral</td>
<td>Dorsal caudate −8, 4, 4 and 12, 8, 0</td>
<td>6 mg THC administration or placebo</td>
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<td>ROI based on pooled group activation maps</td>
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</tbody>
</table>
Association of Marijuana Use With Blunted Nucleus Accumbens Response to Reward Anticipation

Meghan E. Martz, MS; Elisa M. Trucco, PhD; Lora M. Cope, PhD; Jillian E. Hardee, PhD; Jennifer M. Jester, PhD; Robert A. Zucker, PhD; Mary M. Heitzeg, PhD

- Longitudinal study to prospectively examine striatal changes following cannabis use
- N=108 young adults
- Scanned:
  - 20 (T1)
  - 22 (T2)
  - 24 (T3)
- Focus on striatum during reward anticipation
Association of Marijuana Use With Blunted Nucleus Accumbens Response to Reward Anticipation

Meghan E. Martz, MS; Elisa M. Trucco, PhD; Lora M. Cope, PhD; Jillian E. Hardee, PhD; Jennifer M. Jester, PhD; Robert A. Zucker, PhD; Mary M. Heitzeg, PhD

Figure 1. Longitudinal Cross-lagged Associations Between Marijuana Use and Nucleus Accumbens (NAcc) Activation During Reward Anticipation

Results are shown from cross-lagged analysis of past-year marijuana use at each scan date and NAcc activation during reward anticipation. The coefficients indicated are standardized path coefficients with covariates of sex, age at time 1, parental history of substance use disorder, previous marijuana use and binge drinking up to 12 months before time 1, and past-year binge drinking corresponding to each time (covariances of exogenous variables are not depicted). Straight arrows represent causal paths; curved arrows, covariances.
Blunted striatal response was only present with escalating drug use

» Suggests cannabis is triggering these changes

• Supports the incentive sensitization model of addiction
5 Research Priorities

Unfortunately, the Johnsons never noticed the early warning signs that their teen-age son had a gambling problem.
1. Longitudinal studies in cannabis use
2. Studies in the context of other substances and behaviours
Research Priorities

1. Longitudinal studies in cannabis use
2. Studies in the context of other substances and behaviours
3. Studies directly comparing different types of reinforcers and their motivational effects
Disruption of Reward Processing in Addiction
An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies

Maartje Luijten, PhD; Arnt F. Schellekens, MD, PhD; Simone Kühn, PhD; Marise W. J. Machielse, MD, PhD; Guillaume Sescousse, PhD

A Reward anticipation

All addicted vs controls

B Reward outcome

All addicted vs controls

z values

+2.5
+1.6
0.0
-2.2
-3.0
-4.2
+2.8
0.0
-1.1
-2.4
-3.2
Figure 3. Forest Plot Illustrating Reward Anticipation Meta-analytic Results in the Striatum

<table>
<thead>
<tr>
<th>Substance Addiction</th>
<th>Mean Effect Size (Variance of Effect Size)</th>
<th>Favors Hypoactivation</th>
<th>Favors Hyperactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
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<tr>
<td>Bjork et al.</td>
<td>-0.08 (±0.08)</td>
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<tr>
<td>Bjork et al.</td>
<td>-0.07 (±0.09)</td>
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<tr>
<td>Van Holst et al.</td>
<td>-0.29 (±0.11)</td>
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<td>Romanczuk et al.</td>
<td>0.02 (±0.13)</td>
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<tr>
<td>Hagele et al.</td>
<td>-0.18 (±0.06)</td>
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<td>Cannabis</td>
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<tr>
<td>Filbey et al.</td>
<td>-0.06 (±0.05)</td>
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<tr>
<td>Yip et al.</td>
<td>0.08 (±0.10)</td>
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<tr>
<td>Van Hell et al.</td>
<td>-1.16 (±0.21)</td>
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<tr>
<td>Nestor et al.</td>
<td>-0.11 (±0.14)</td>
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<td>Cocaine</td>
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<td>Jia et al.</td>
<td>0.32 (±0.10)</td>
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<td>Patel et al.</td>
<td>-0.22 (±0.05)</td>
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<td>Bustamante et al.</td>
<td>-0.22 (±0.12)</td>
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<td>Nicotine</td>
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<tr>
<td>Van Hell et al.</td>
<td>-1.39 (±0.20)</td>
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<td>Rose et al.</td>
<td>-0.12 (±0.07)</td>
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<td>Martin et al.</td>
<td>-0.37 (±0.12)</td>
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<td>Jansma et al.</td>
<td>-0.40 (±0.20)</td>
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<tr>
<td>Average substance</td>
<td>-0.23 (±0.01)</td>
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<td>Gambling addiction</td>
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<tr>
<td>Fauth-Buhler et al.</td>
<td>-0.19 (±0.02)</td>
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<td>Sescousse et al.</td>
<td>-0.11 (±0.11)</td>
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<tr>
<td>Romanczuk et al.</td>
<td>-0.06 (±0.11)</td>
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<tr>
<td>Choi et al.</td>
<td>-0.69 (±0.14)</td>
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<tr>
<td>Balodis et al.</td>
<td>-0.06 (±0.14)</td>
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<tr>
<td>Van Holst et al.</td>
<td>-0.17 (±0.13)</td>
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<tr>
<td>Average gambling</td>
<td>-0.19 (±0.01)</td>
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<tr>
<td>Average all studies</td>
<td>-0.21 (±0.006)</td>
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</table>
Research Priorities

1. Longitudinal studies in cannabis use
2. Studies in the context of other substances and behaviours
3. Studies directly comparing different types of reinforcers and their motivational effects
4. How do changes in THC concentrations and other cannabinoids affect motivation?
5. How does the brain recover?
Neurofunctional Reward Processing Changes in Cocaine Dependence During Recovery

Iris M Balodis¹, Hedy Kober¹, Patrick D Worhunsky¹, Michael C Stevens², Godfrey D Pearlson¹,²,³, Kathleen M Carroll¹ and Marc N Potenza*¹,²,³,⁴

Neuropsychopharmacology, 2016
Thank You

James MacKillop
Michael Amlung

Marc Potenza
Patrick Worhunsky
Hedy Kober
Godfrey Pearlson
Michael Stevens

St. Joseph’s Healthcare Hamilton

McMaster University
Psychiatry and Behavioural Neurosciences

Michael G. DeGroote Centre for Medicinal Cannabis Research

Gambling Research Exchange Ontario
Driving Knowledge into Action
Thank You