Understanding Reward Value and Motivation in Cannabis Use Disorder

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St. Joseph's Healthcare Hamilton | 125 YEARS

McMaster University
PSYCHIATRY AND BEHAVIOURAL NEUROSCIENCES

COI/Disclosures

I have no conflicts of interest

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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

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REPORT

OF THE

INDIAN HEMP DRUGS COMMISSION,

1893-94.

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The Hon'ble W. MACKWORTH YOUNG, M.A., C.S.I., First Financial Commissioner, Punjab.

Members:

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"Heavy" cannabis use causes "lethargy" "apathy" "Inactivity" and "loss of goal-directed behaviour"

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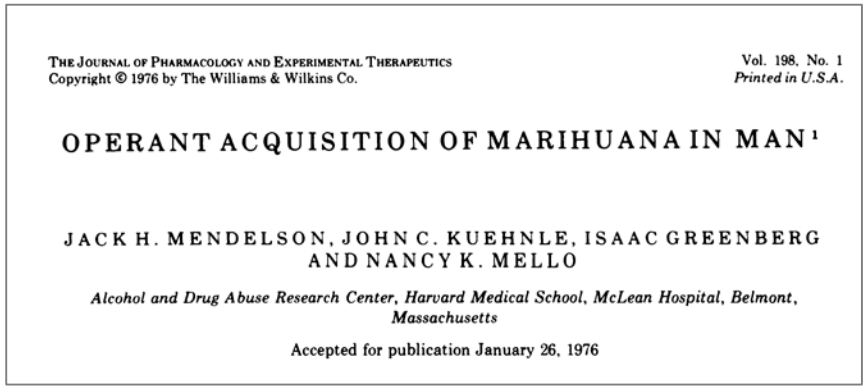
Motivation Studies with Cannabis



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Printed in U.S.A.

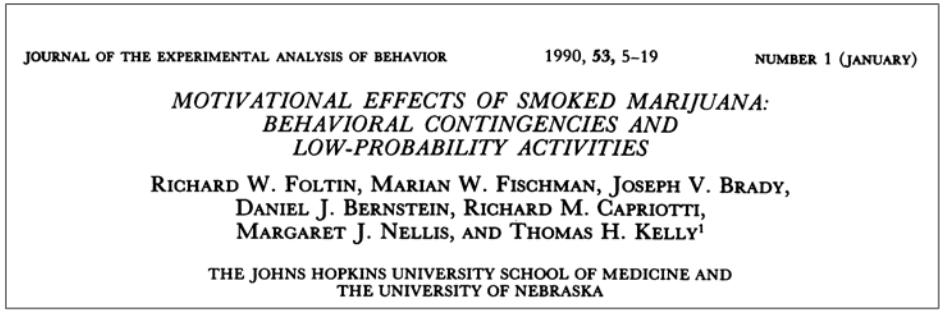
OPERANT ACQUISITION OF MARIHUANA IN MAN[1]

JACK H. MENDELSON, JOHN C. KUEHNLE, ISAAC GREENBERG AND NANCY K. MELLO

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

Accepted for publication January 26, 1976

Marijuana ↑ motivation



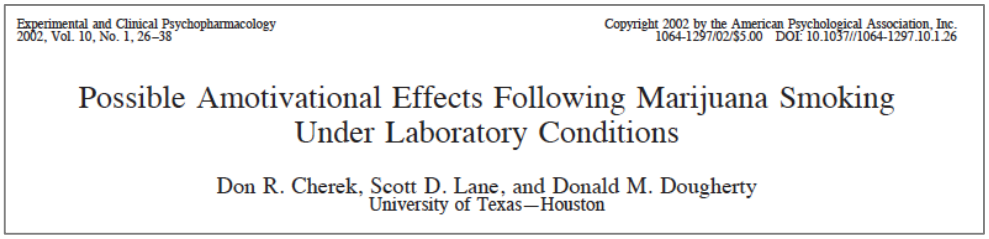
JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1990, 53, 5–19 NUMBER 1 (JANUARY)

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

RICHARD W. FOLTIN, MARIAN W. FISCHMAN, JOSEPH V. BRADY, DANIEL J. BERNSTEIN, RICHARD M. CAPRIOTTI, MARGARET J. NELLIS, AND THOMAS H. KELLY[1]

THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE AND THE UNIVERSITY OF NEBRASKA

Marijuana ↑ motivation



Experimental and Clinical Psychopharmacology
2002, Vol. 10, No. 1, 26–38

1064-1297/02/$5.00 DOI: 10.1037//1064-1297.10.1.26

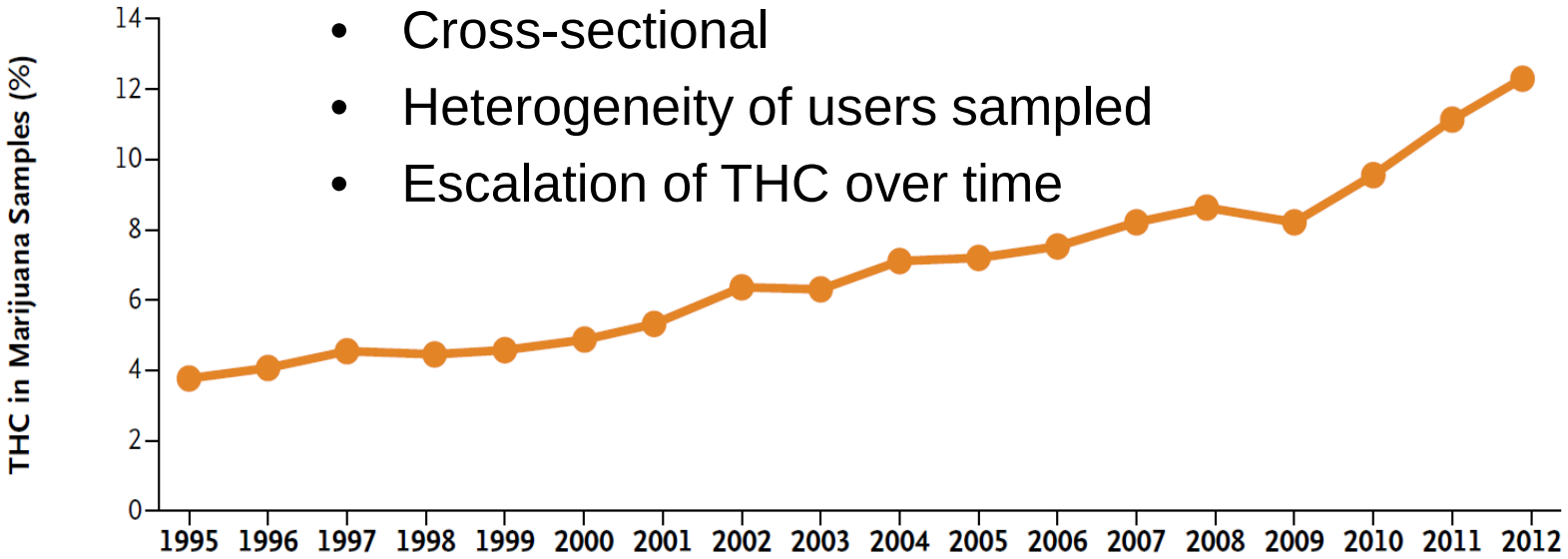
Possible Amotivational Effects Following Marijuana Smoking Under Laboratory Conditions

Don R. Cherek, Scott D. Lane, and Donald M. Dougherty
University of Texas—Houston

Marijuana ↓ motivation

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

El-Sohly, 2014

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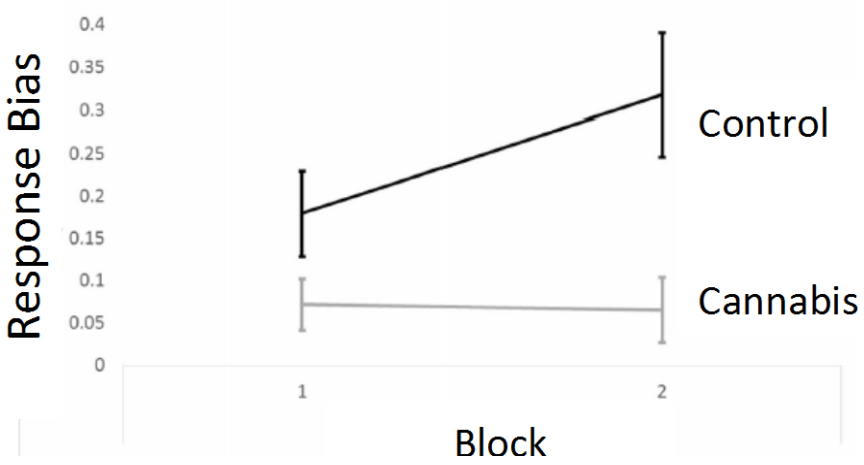
Lawn et al., 2016 *Psychopharmacology*

- Chronic effects of cannabis on reward learning



  - CUD group did not develop a response bias

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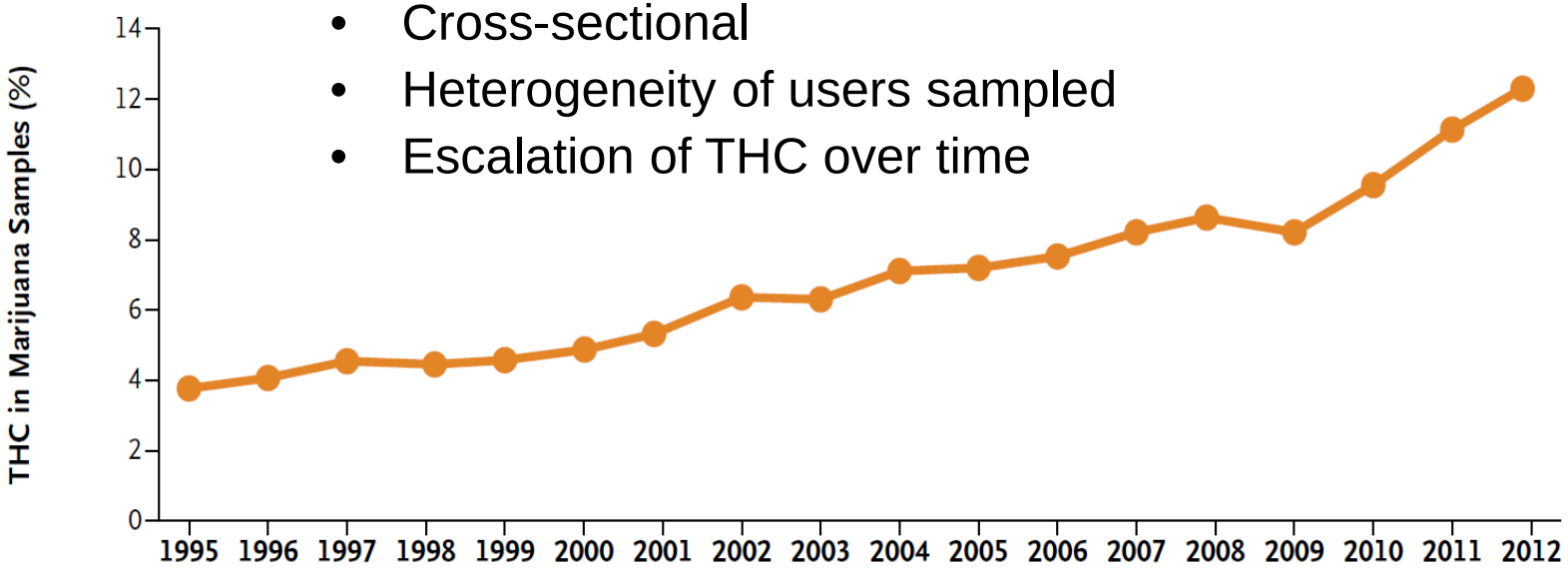
Limitations in Studies of Motivation

- 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

El-Sohly, 2014

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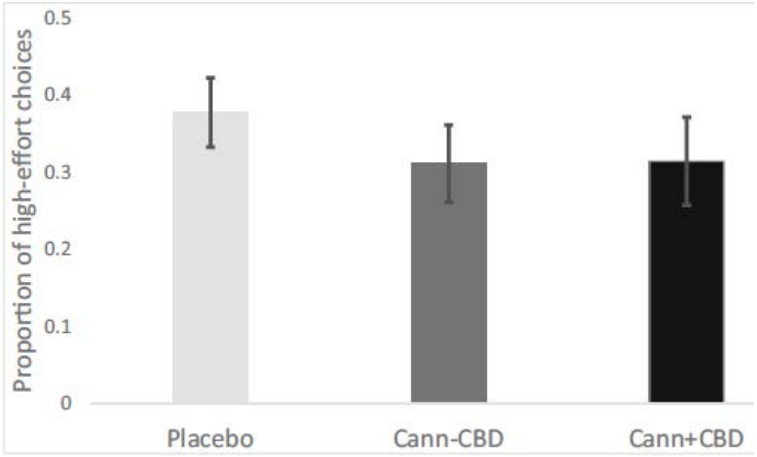
Lawn et al., 2016 *Psychopharmacology*

- 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

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Silins et al., 2014 *Lancet Psychiatry* 1:286-93

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
- Assessed up to age 30

- High School Completion
- University degree attainment
- Cannabis dependence
- Use of other illicit drugs
- Suicide attempt
- Depression
- Welfare Dependence

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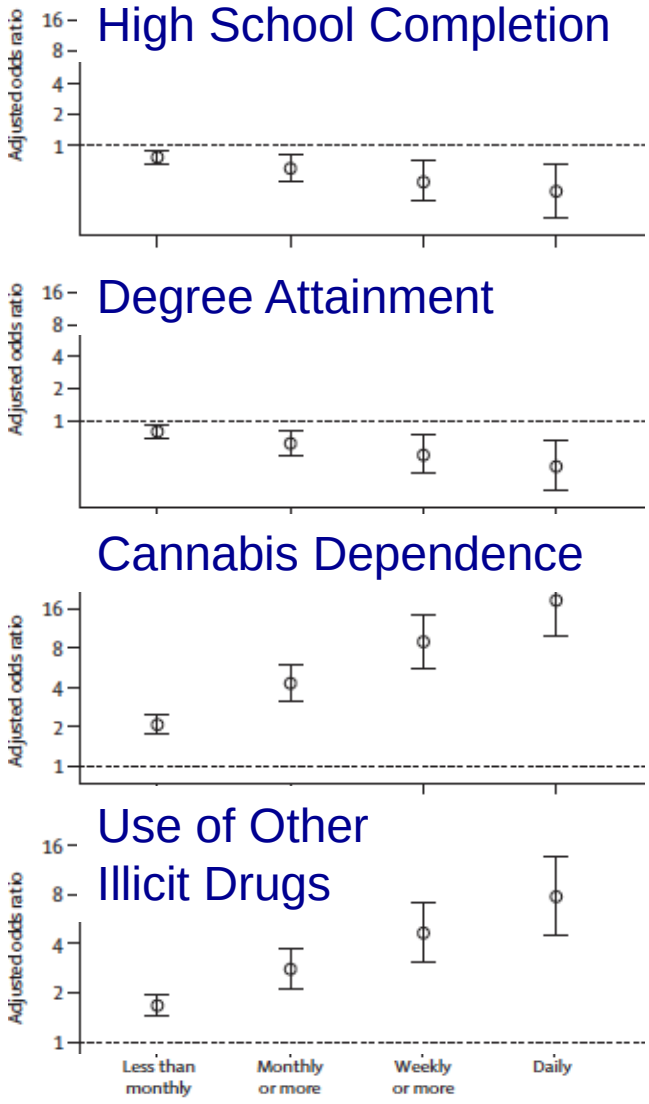
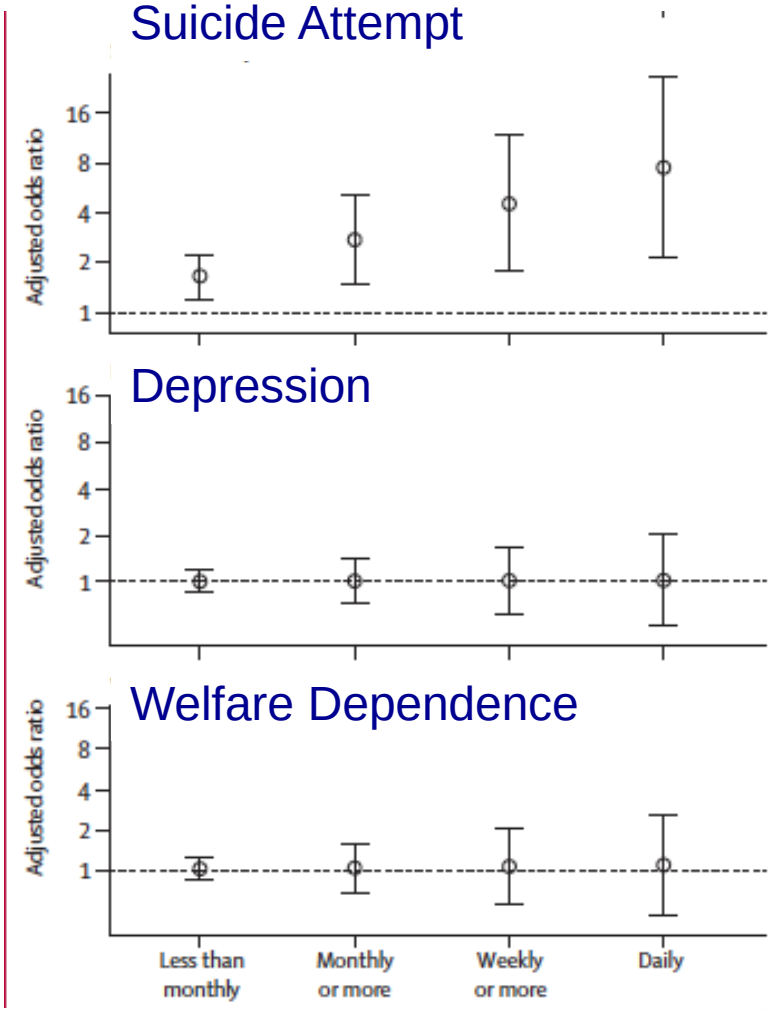
Silins et al., 2014 *Lancet Psychiatry* 1:286-93





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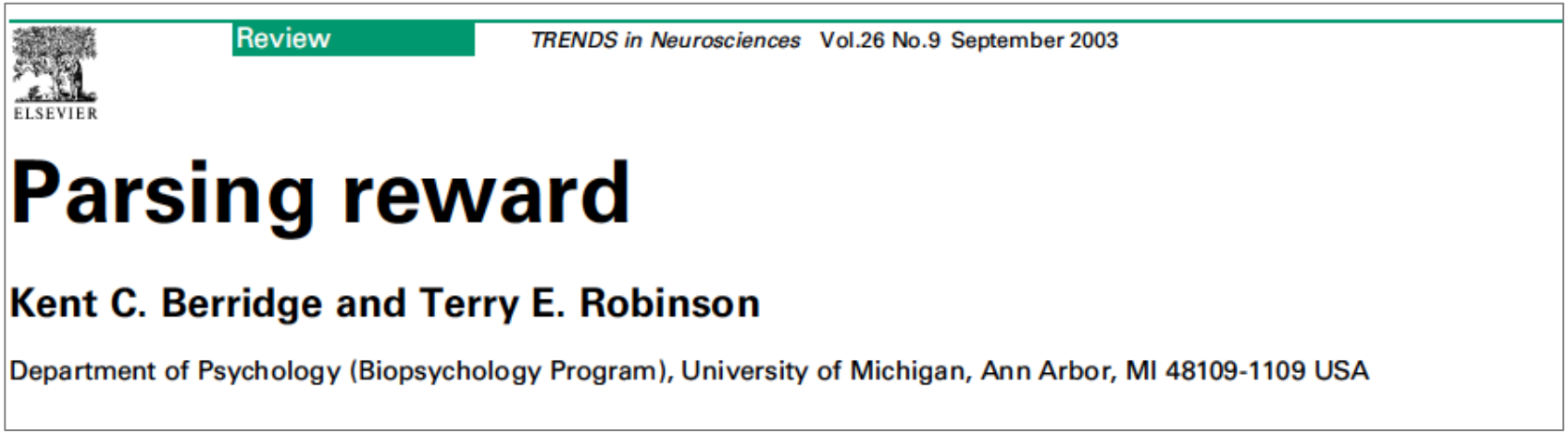
Silins et al., 2014 *Lancet Psychiatry* 1:286-93

- Support for causal relationship
- Consistent frequency → adverse outcomes
- Dose-response characteristics
  - » strongest effects for daily users
- Resilient associations
  - » Even when controlling for confounding factors
- **Mechanisms?**

Reward Processing in the Brain



Review TRENDS in Neurosciences Vol.26 No.9 September 2003

ELSEVIER

Parsing reward

Kent C. Berridge and Terry E. Robinson

Department of Psychology (Biopsychology Program), University of Michigan, Ann Arbor, MI 48109-1109 USA

- Advances in neuroscience permit parsing reward into specific psychological components
  - Reward Learning (explicit & implicit knowledge)
  - Affect or emotion
  - Motivation

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Neurobiology of Motivation

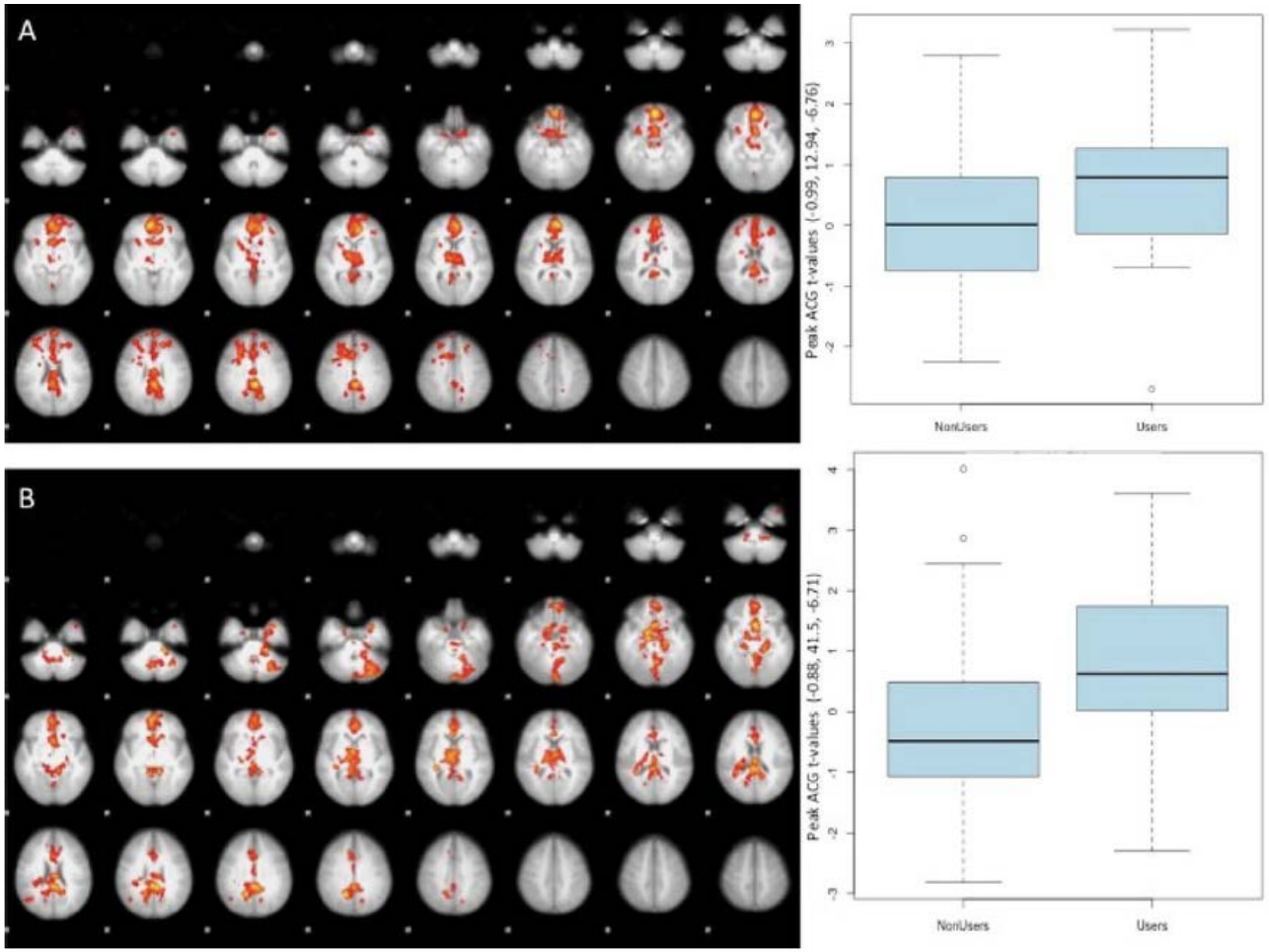
- Amotivation may reflect that cannabis itself is a huge motivator

- Measure valuation of cannabis cues

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

◆ Human Brain Mapping 37:3431–3443 (2016)

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



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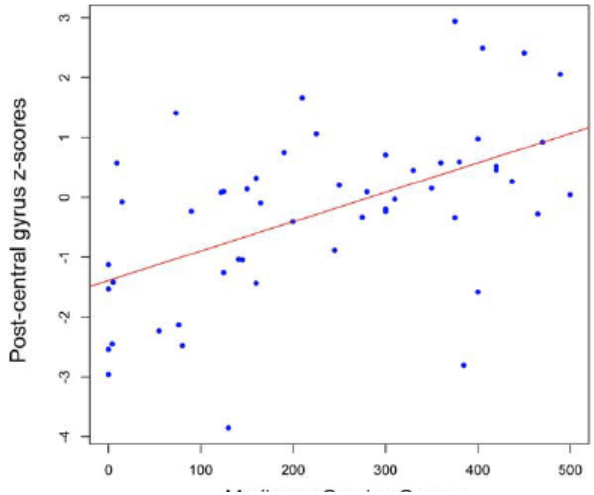
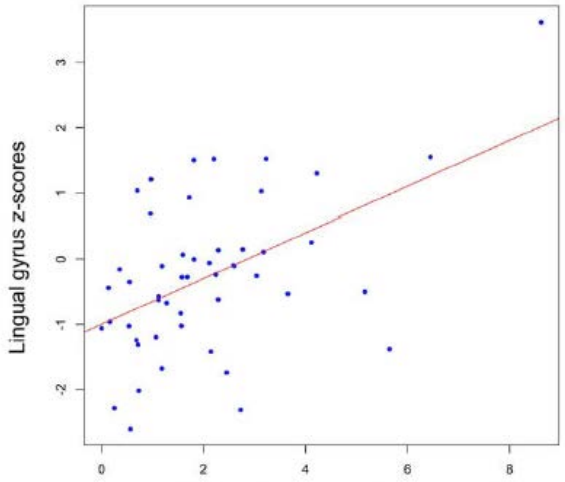
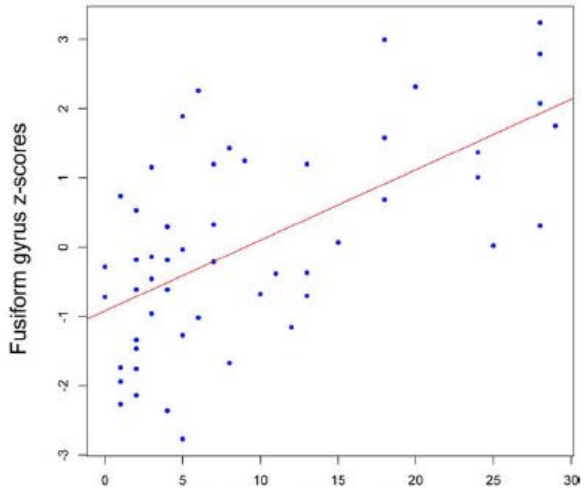


Marijuana Craving Scores



THC/creatinine ng/ml (abstinent state)



Marijuana Withdrawal Scores

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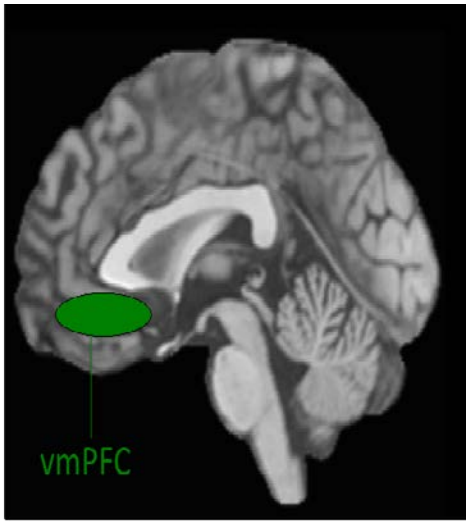
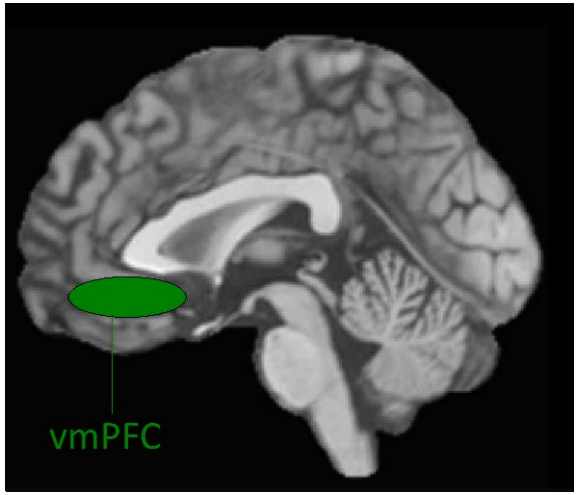
Neurobiology of Motivation

- 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

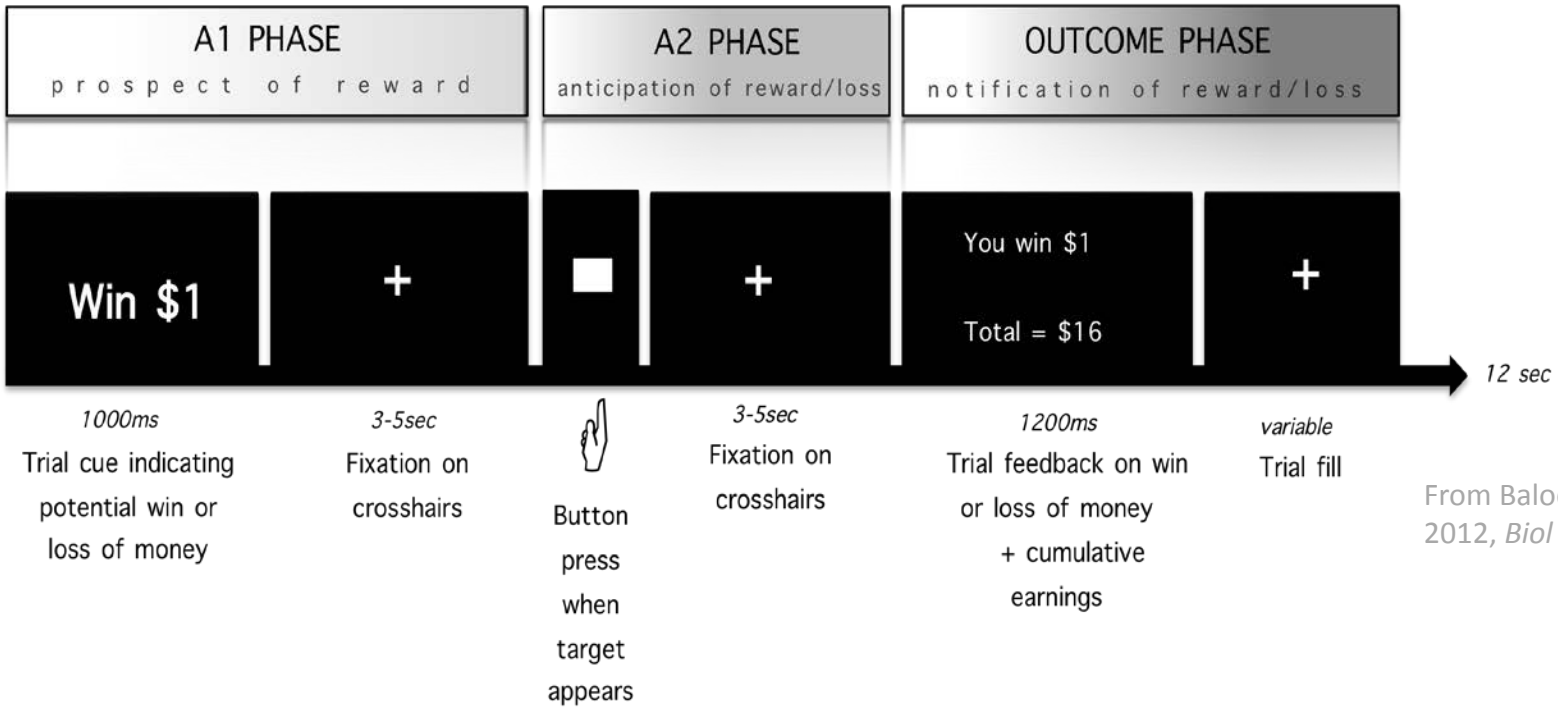
Reward Processing





Anticipation time Outcome

Monetary Incentive Delay Task



From Balodis et al., 2012, *Biol Psychiat*

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

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Biological Psychiatry

Anticipatory Reward Processing in Addicted Populations: A Focus on the Monetary Incentive Delay Task

Iris M. Balodis and Marc N. Potenza

Table 1. Continued

Population	Author (Year)	Clinical Group M/F	HC M/F	Urine Screen?	Image Analysis	MC Correction	Phase/ Contrast	Striatal Response	Coordinates	Correlations with Striatal Response	Comments
MD	van Hell *et al.*, 2010 (48)	13M 1F Smokers: 11M 3 F	11M 2F	U	WB ROI	✓	Gain > neutral	↓	±14, 14, −8 (TC)	—	Non–treatment seeking Loss trial results not included in MIDT task Negative urine screens for THC in almost all participants Decreased VS in both smokers and cannabis users relative to HCs
	Nestor *et al.*, 2010 (49)	14M	14M	U + THC	WB	✓	Gain > baseline	↑	20, 8, −4	VS activity during win correlates positively with number of reported lifetime joints smoked	MIDT version collapsed across magnitude All MD participants had positive THC urine toxicology
							Loss > baseline	—			
	Filbey *et al.*, 2013 (63)	47M 12F	5M 22F	U + THC	WB	✓	Gain > neutral	—	MNI[a] extents on x, 8–16; y, 15–6; z, −4 to −12		Required positive urinalysis for THC metabolites but excluded for other drugs HC group showed no significant difference during either incentive condition (gain or loss) —may be driving effect?
							Loss > baseline	—			
	van Hell *et al.*, 2012 (61)		11M	U	ROI	✗	Gain > neutral	—	Dorsal caudate −8, 4, 4 and 12, 8, 0		6 mg THC administration or placebo ROI based on pooled group activation maps Loss trial results not included in MIDT task

JAMA Psychiatry | Original Investigation

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

JAMA Psychiatry | Original Investigation

Association of Marijuana Use With Blunted Nucleus Accumbens Response to Reward Anticipation

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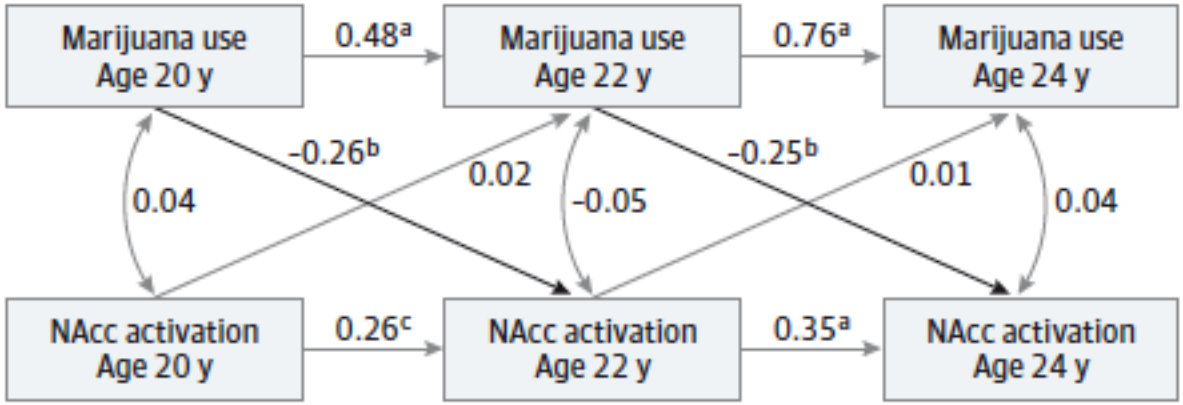
Figure 1. Longitudinal Cross-lagged Associations Between Marijuana Use and Nucleus Accumbens (NAcc) Activation During Reward Anticipation



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.

JAMA Psychiatry | Original Investigation

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- 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

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Research Priorities

1. Longitudinal studies in cannabis use
2. Studies in the context of other substances and behaviours

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Research Priorities

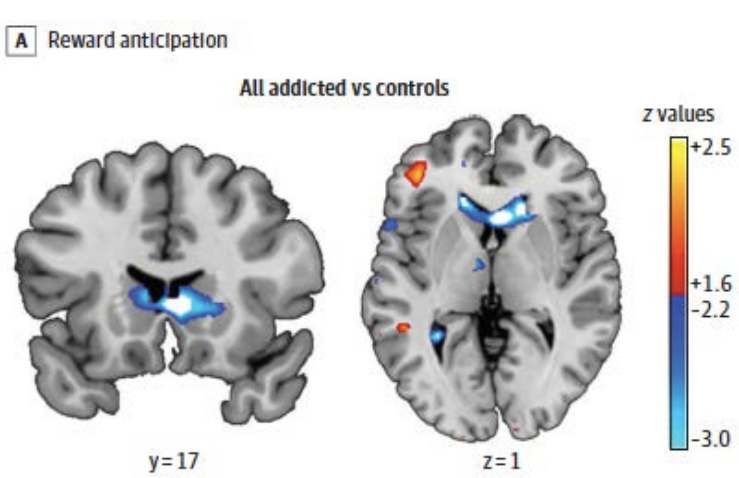
1. Longitudinal studies in cannabis use
2. Studies in the context of other substances and behaviours
3. Studies directly comparing different types of reinforcers and their motivational effects

JAMA Psychiatry | Original Investigation | META-ANALYSIS

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



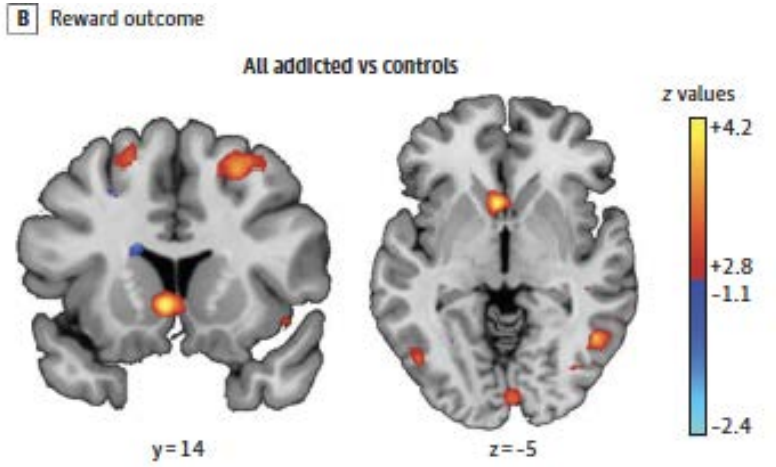


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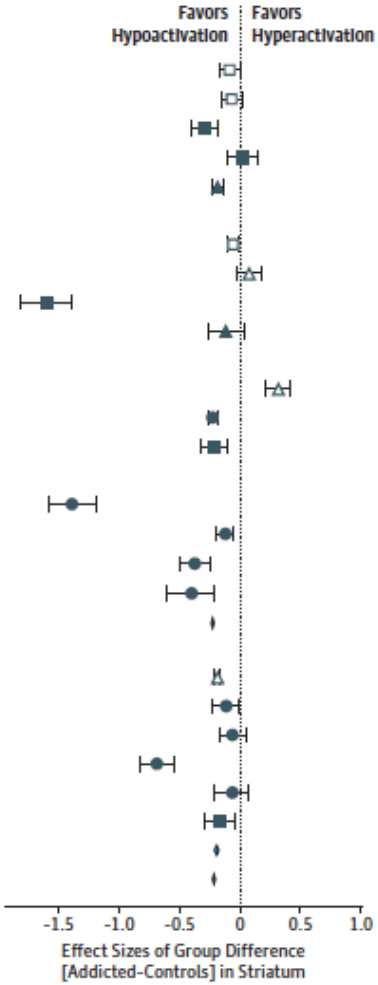
Figure 3. Forest Plot Illustrating Reward Anticipation Meta-analytic Results in the Striatum

Noncomorbid addicts
- Abstinent
- Active
- Mix abstinent/active

Comorbid addicts
- Abstinent
- Mix abstinent/active

Reward Anticipation

Substance Addiction	Mean Effect Size (Variance of Effect Size)
Alcohol	
Bjork et al,[17] 2012	-0.08 (±0.08)
Bjork et al,[39] 2008	-0.07 (±0.09)
Van Holst et al,[59] 2014	-0.29 (±0.11)
Romanczuk et al,[53] 2014	0.02 (±0.13)
Hagele et al,[16] 2014	-0.18 (±0.06)
Cannabis	
Filbey et al,[44] 2013	-0.06 (±0.05)
Yip et al,[60] 2014	0.08 (±0.10)
Van Hell et al,[57] 2010	-1.6 (±0.21)
Nestor et al,[51] 2010	-0.11 (±0.14)
Cocaine	
Jia et al,[48] 2011	0.32 (±0.10)
Patel et al,[52] 2013	-0.22 (±0.05)
Bustamante et al,[40] 2013	-0.22 (±0.12)
Nicotine	
Van Hell et al,[60] 2010	-1.39 (±0.20)
Rose et al,[54] 2013	-0.12 (±0.07)
Martin et al,[49] 2014	-0.37 (±0.12)
Jansma et al,[47] 2013	-0.40 (±0.20)
Average substance	-0.23 (±0.01)
Gambling addiction	
Fauth-Buhler et al,[43] 2014	-0.19 (±0.02)
Sescousse et al,[56] 2013	-0.11 (±0.11)
Romanczuk et al,[53] 2014	-0.06 (±0.11)
Choi et al,[41] 2012	-0.69 (±0.14)
Balodis et al,[37] 2012	-0.06 (±0.14)
Van Holst et al,[58] 2012	-0.17 (±0.13)
Average gambling	-0.19 (±0.01)
Average all studies	-0.21 (±0.006)



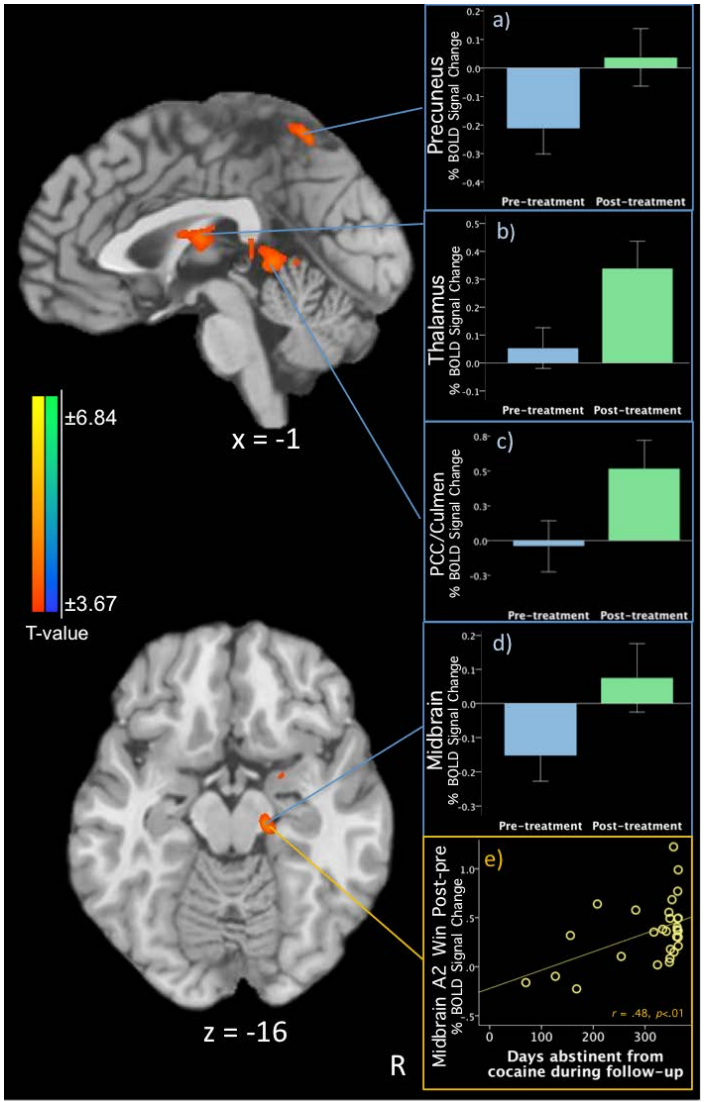
Research Priorities

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 Balodis[1], Hedy Kober[1], Patrick D Worhunsky[1], Michael C Stevens[2], Godfrey D Pearlson[1,2,3], Kathleen M Carroll[1] and Marc N Potenza*[,1,3,4]

Neuropsychopharmacology, 2016



$p<0.001$, FWE

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Thank You

James MacKillop
Michael Amlung

Marc Potenza
Patrick Worhunsky
Hedy Kober
Godfrey Pearlson
Michael Stevens

Thank You

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