Policy reform, personalised medicine and brain science: why we need a multifaceted approach to reducing the harms of alcohol and other drugs

VAADA 2019

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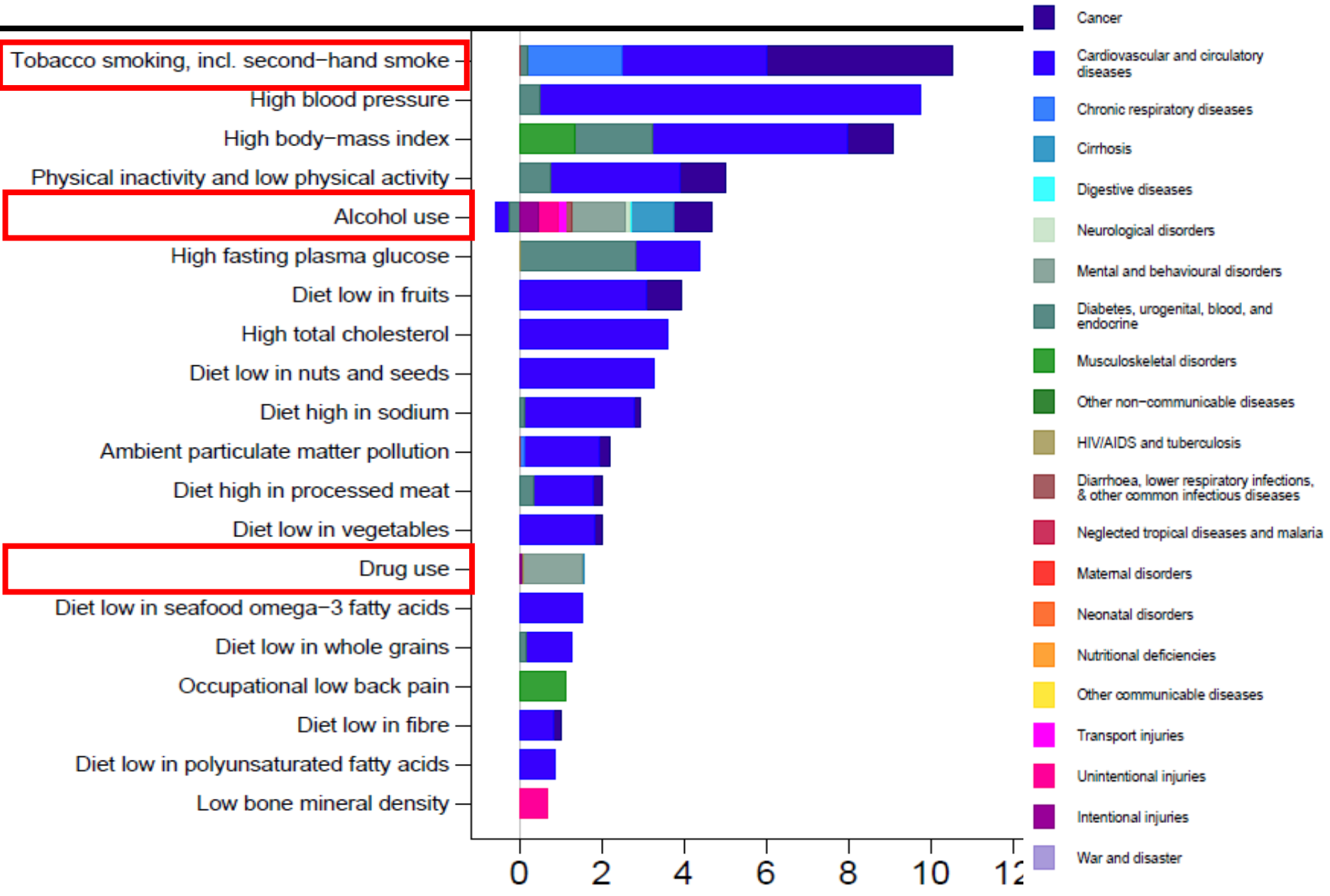
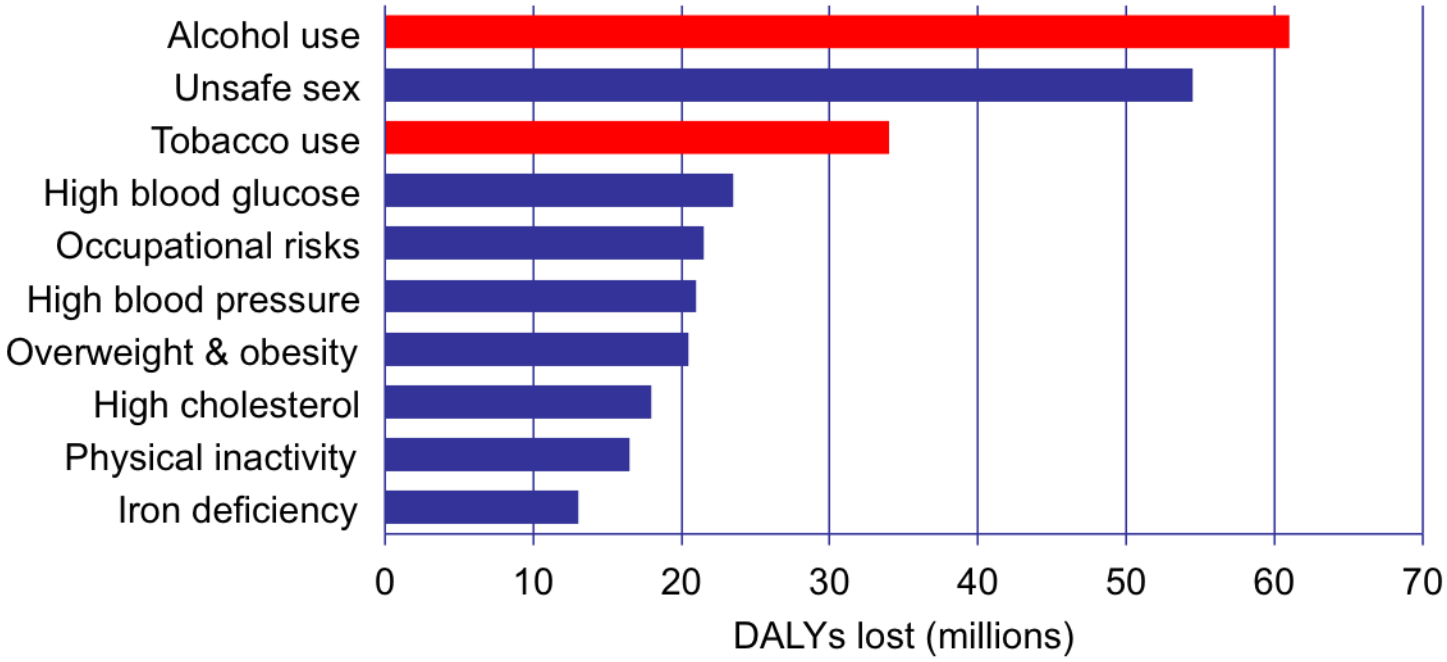
Drug use leads the Global Burden of disease 2010



Alcohol is the leading risk factor for overall burden of disease among men aged 15–59

DALYs lost attributable to 10 leading risk factors, for the age group 15–59 years (2004)

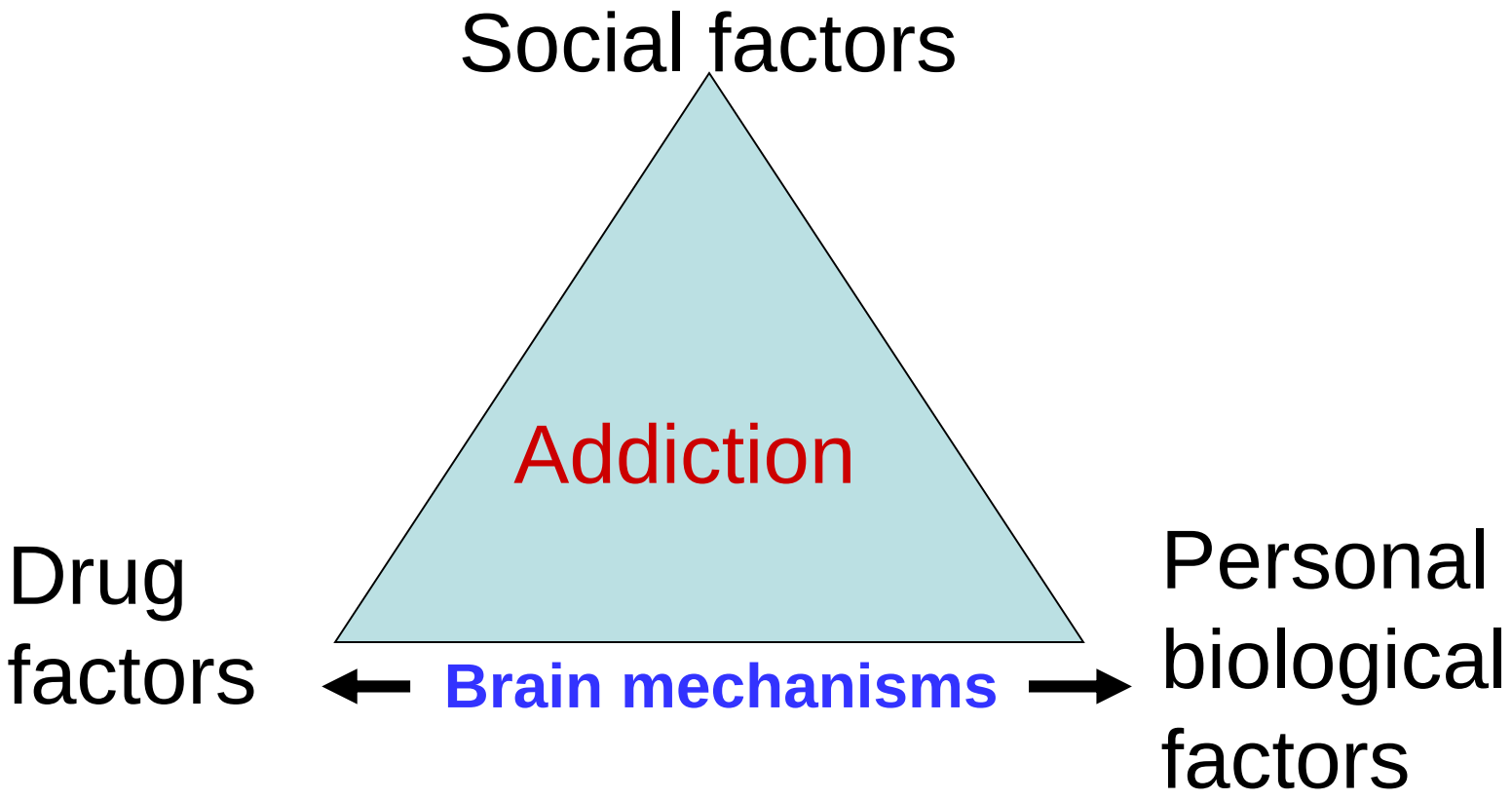


In 2004, 4.5% of the global burden of disease and injury was attributable to alcohol: 7.4% for men and 1.4% for women

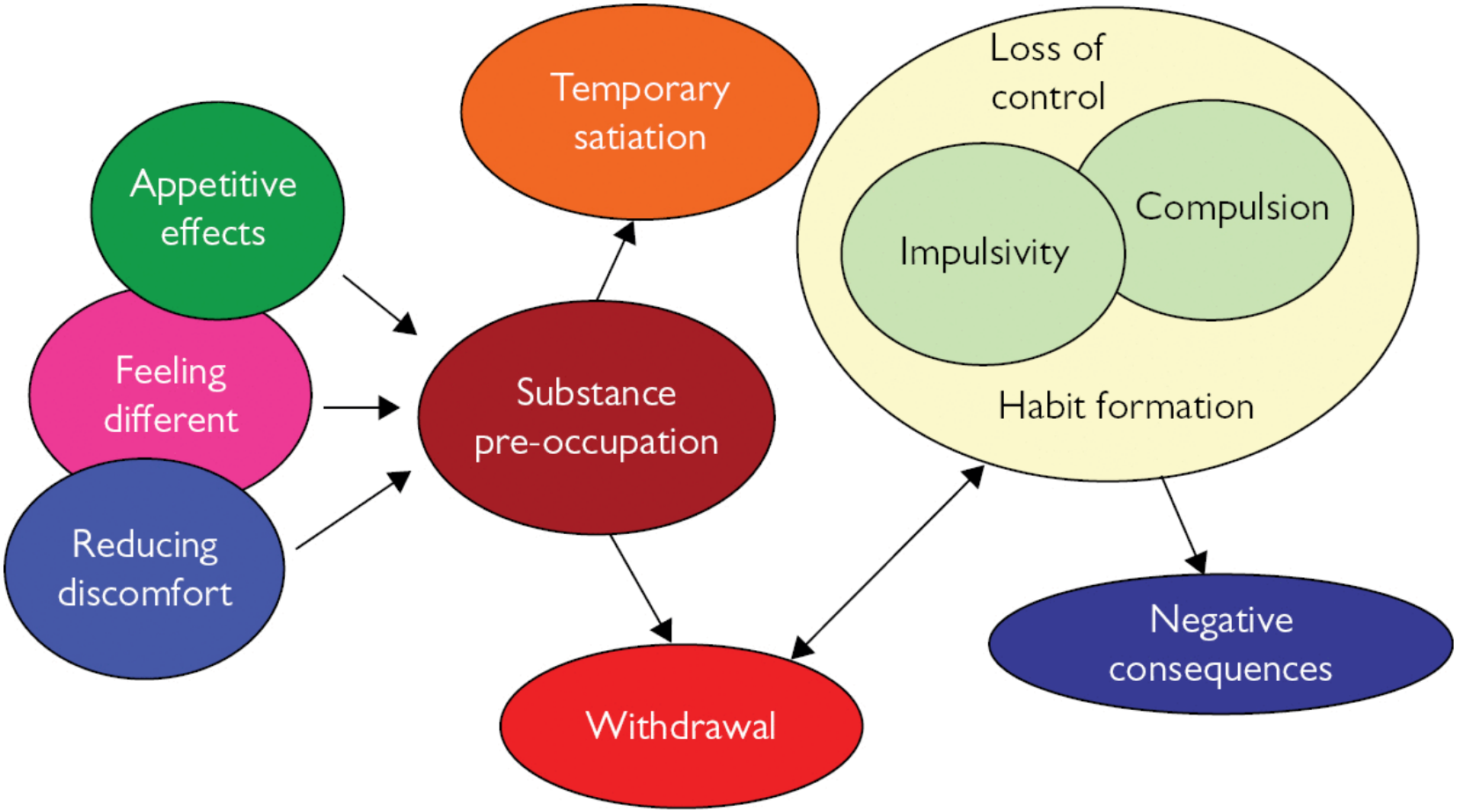
DALY=disability-adjusted life year

WHO. Global status report on alcohol and health, 2011

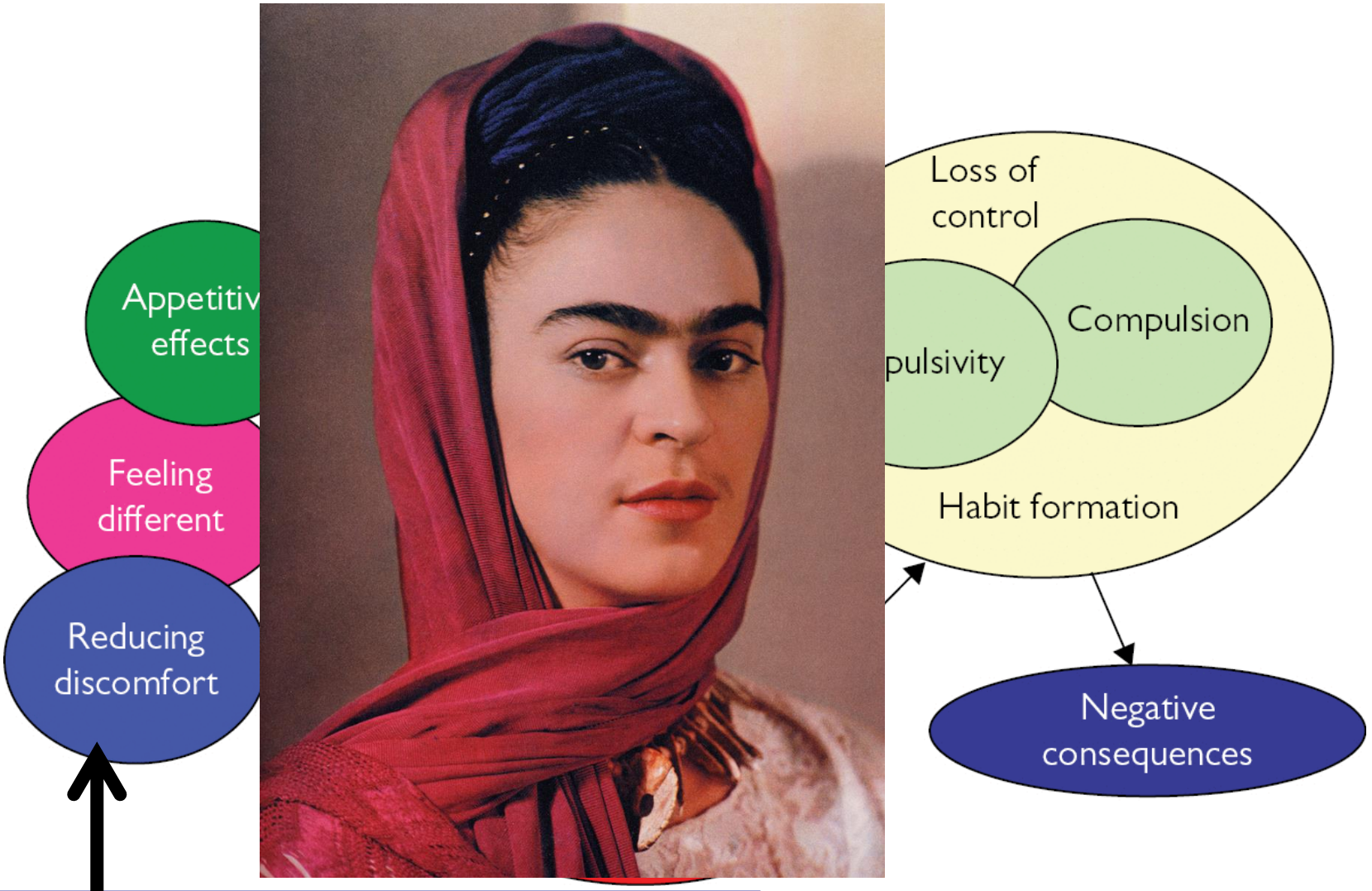
Triangulating addiction



The multiple stages of addiction



Chapter: What is addiction?
Author(s): David J. Nutt and Liam J. Nestor
From: Addiction (Oxford Psychiatry Library)



I tried to drown my sorrows in alcohol, but they learned to swim - Frida Kalho

Chapter: What is addiction?
Author(s): David J. Nutt and Liam J. Nestor
From: Addiction (Oxford Psychiatry Library)

The only time I felt whole was on heroin
Tatum O'Neal

Temporary satiation

Appetitive effects

Feeling different

Reducing discomfort

formation

Negative consequences

Withdrawal

Chapter: What is addiction?
Author(s): David J. Nutt and Liam J. Nestor
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What do we know about the neuropsychopharmacology of drug use?

Addictive drugs are usually pleasurable when first taken
- Not tobacco or alcohol

Pleasurable effects determined by
- dose
- faster speed of brain entry
- receptor sensitivity (nicotine)
- metabolism – alcohol – Aldehyde dehydrogenase gene

Withdrawal by
- duration and dose
- speed of clearance (CYP450 genes)

How does this help us reduce harms?

Addictive drugs are usually pleasurable when first taken

- Not tobacco or alcohol

Ban alcopops

Pleasurable effects determined by

- dose
- faster speed of brain entry
- receptor sensitivity (nicotine)
- metabolism – alcohol

Slow release opioid analgesics
Safer alternatives eg cannabis

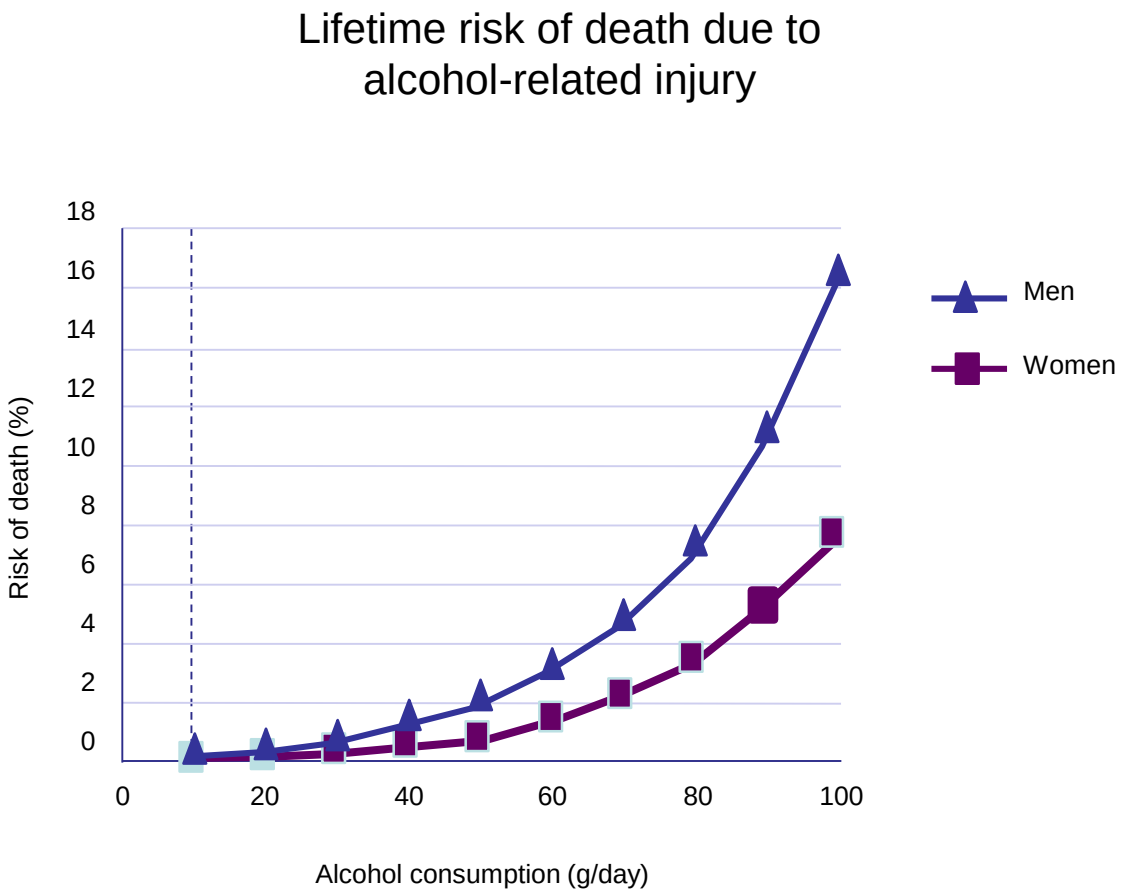
Withdrawal by

- duration and dose
- speed of clearance (CYP450

Short course prescribing of opioids

Reducing use reduces harm

Use increases mortality: with alcohol consumption → exponential rise



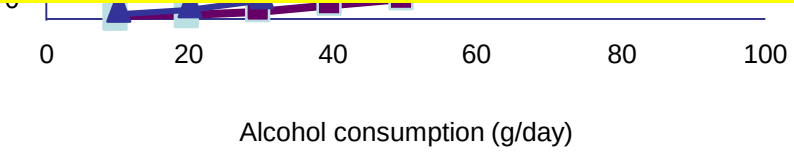
Rehm et al. Addiction 2011;106(Suppl 1):11–19

Reducing use reduces harm

Use increases mortality: with alcohol consumption
→ exponential rise

Is it now time to replace the concept of addiction with one of
Heavy use over time?

ALICERAP project 2017

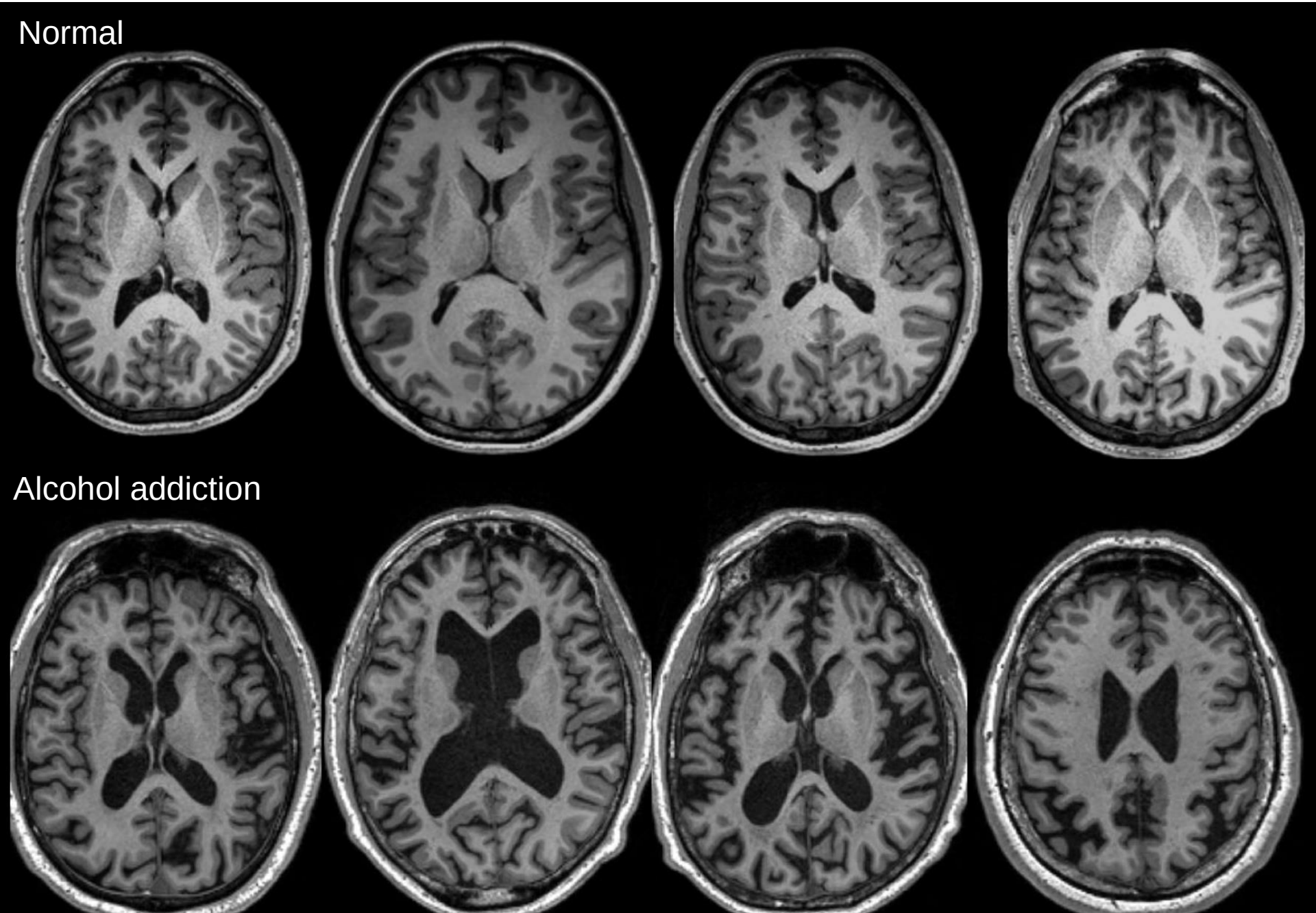


Alcohol consumption (g/day)

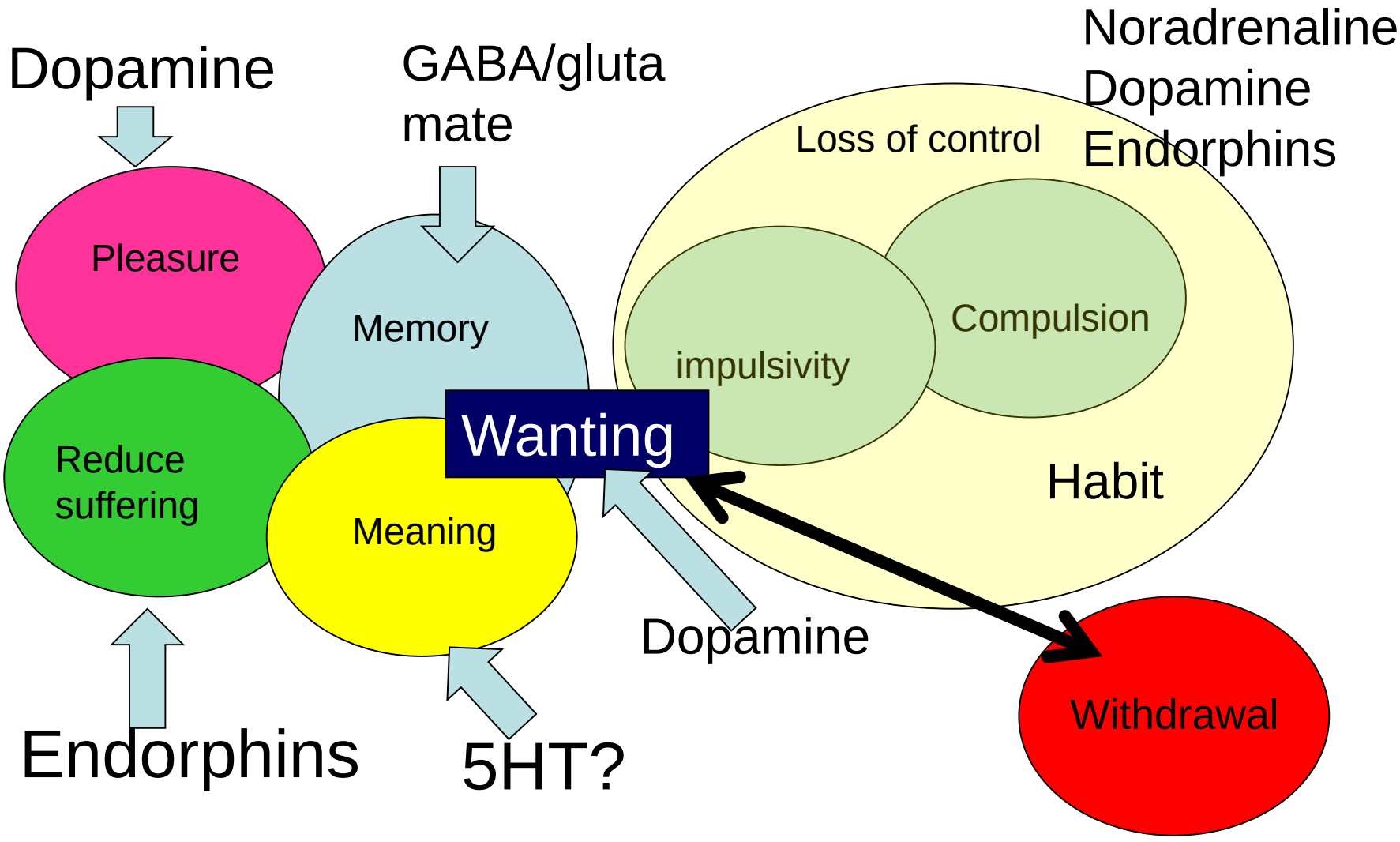
ductions in high
sumers → big
ealth benefits

Rehm et al. Addiction 2011;106(Suppl 1):11–19

Alcohol is the most destructive drug to the brain

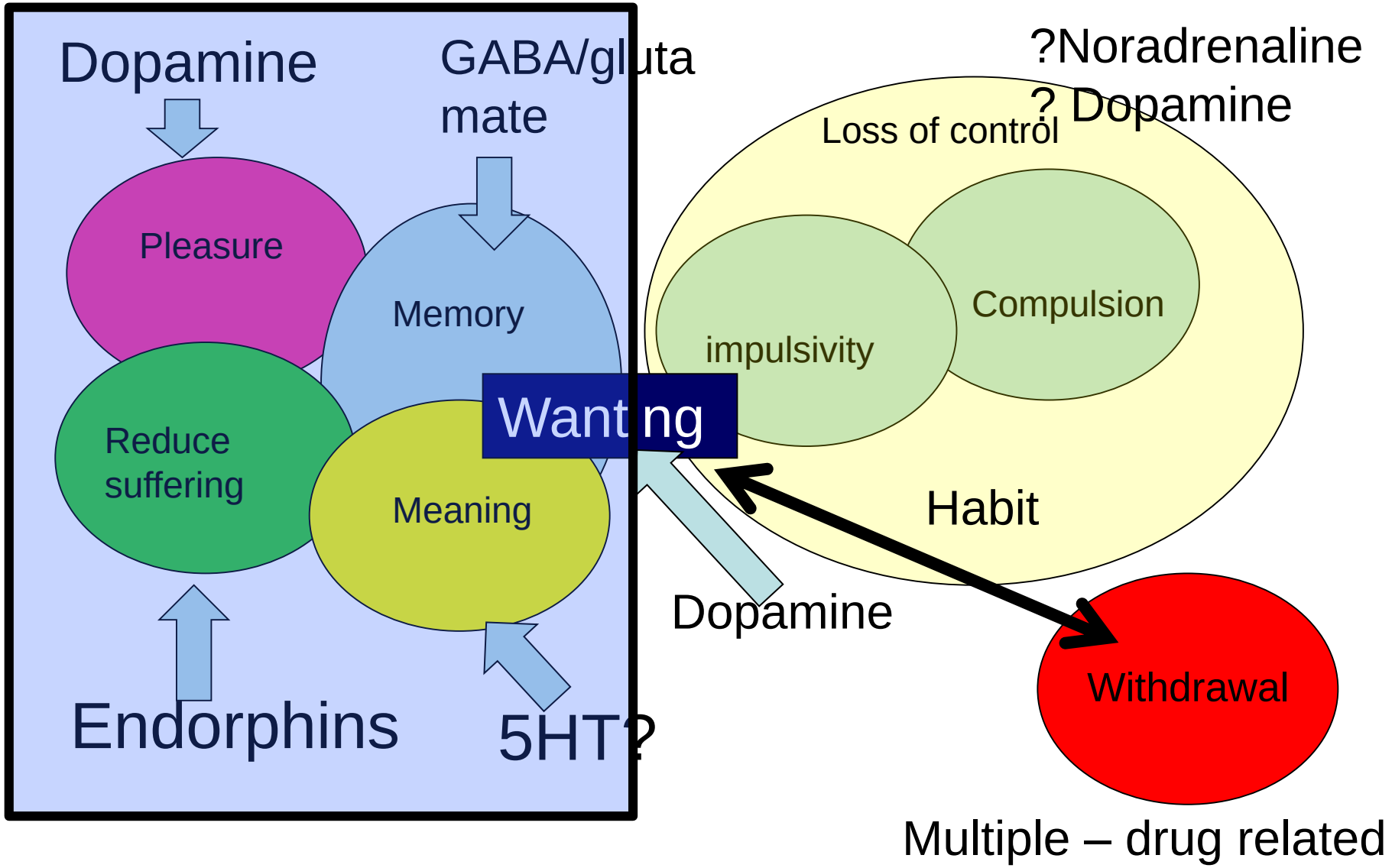


Possible neurotransmitters



Nutt: Drugs without the hot air

Reducing use?



Ways to reduce use

Block the drug getting to its binding site

- Antagonists - naltrexone for heroin (low compliance)
- (Dopamine reuptake blockers failed for cocaine)
- Vaccines – nicotine, cocaine (under study)

Block elements of drugs effects

- Opioid antagonists for alcohol – nalmefene naltrexone

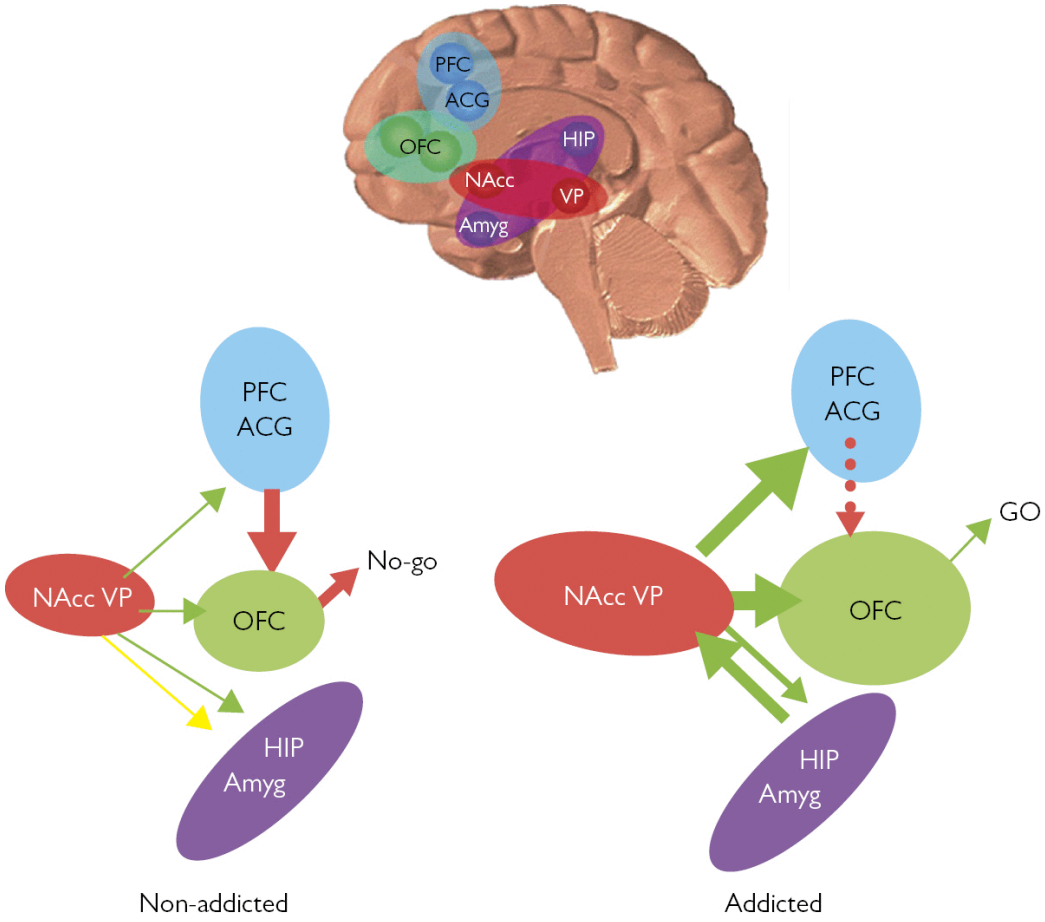
Substitution therapy

- Methadone, buprenorphine for opiates
- Sodium oxybate, baclofen for alcohol
- Varenicline for tobacco

Relapse prevention – just for alcohol so far

- Naltrexone and nalmefene, acamprosate

Brain systems in drug use



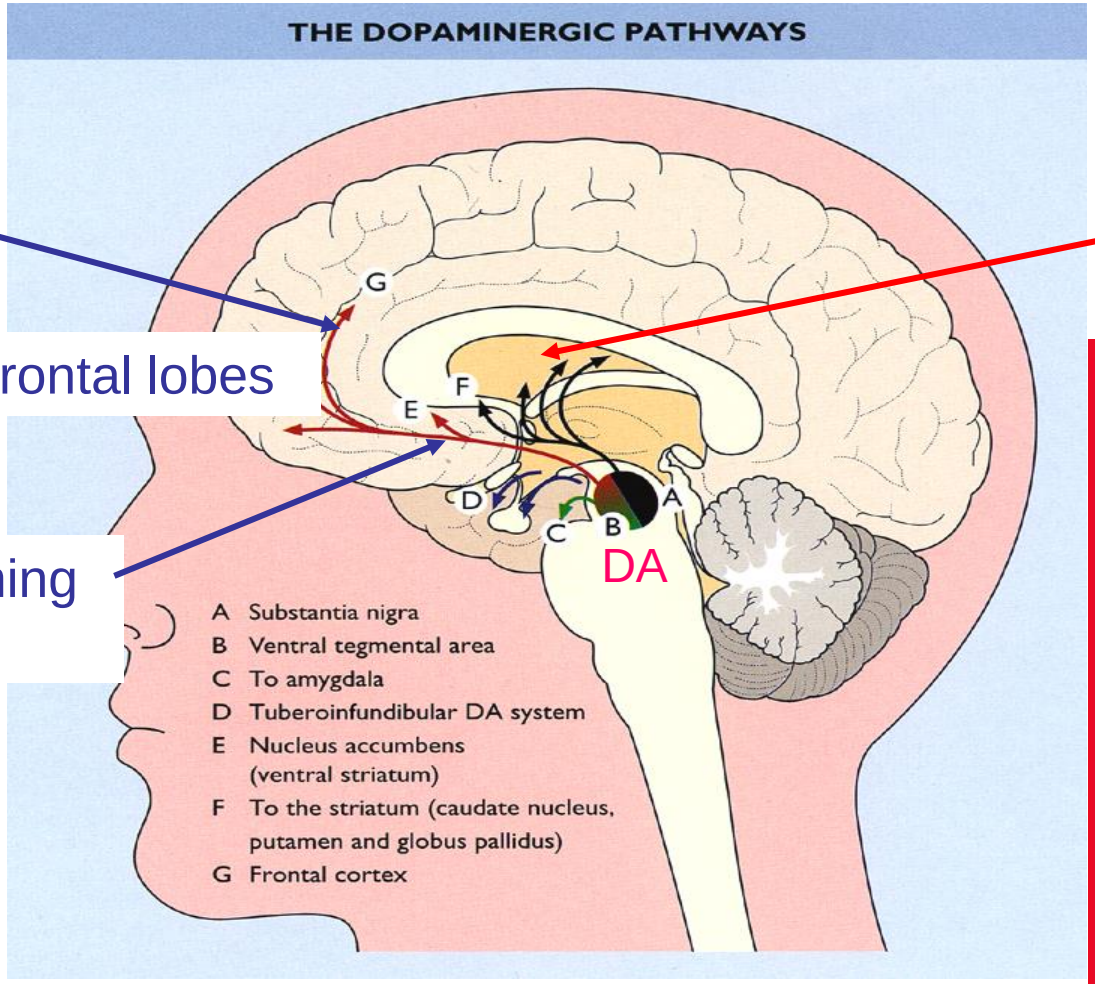
Chapter: Neurobiological processes in addiction
Author(s): David J. Nutt and Liam J. Nestor
From: Addiction (Oxford Psychiatry Library)

Dopamine: The midbrain dopamine system may be a common reward system for stimulants – but ? other drugs

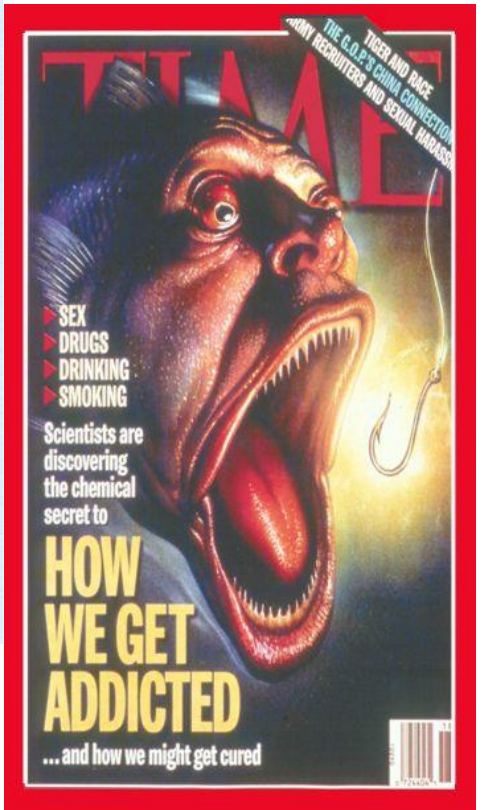
Planning and control

Frontal lobes

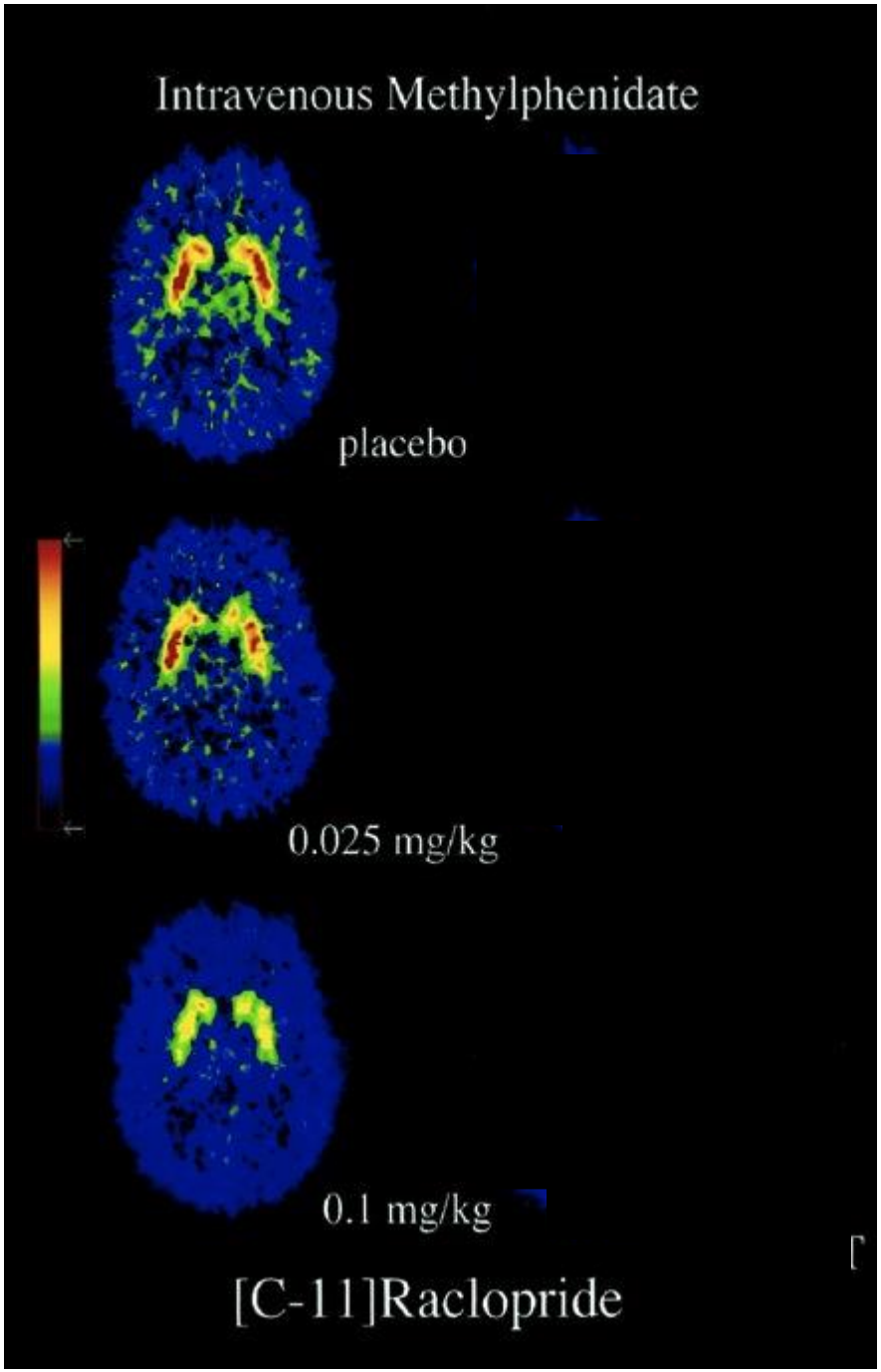
Reward learning
Drug abuse



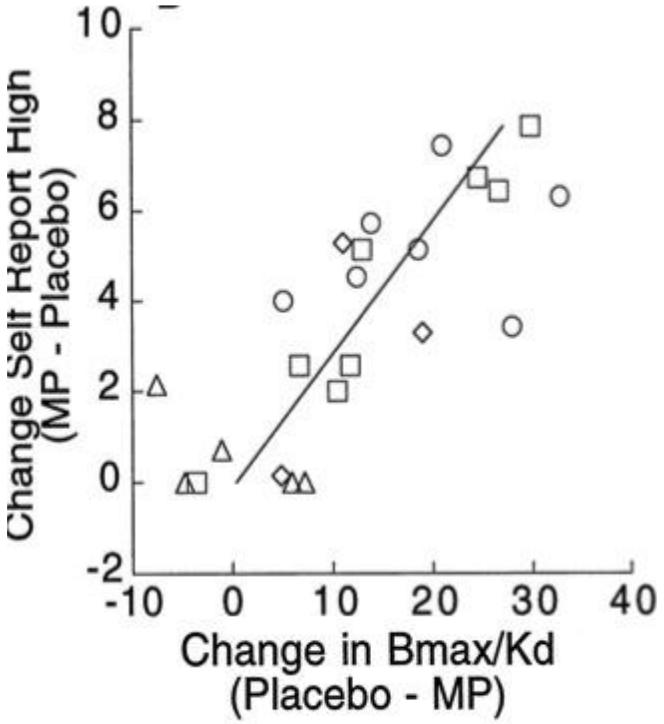
Movement
Basal ganglia
(Parkinson's)



Adapted from Stefan et al

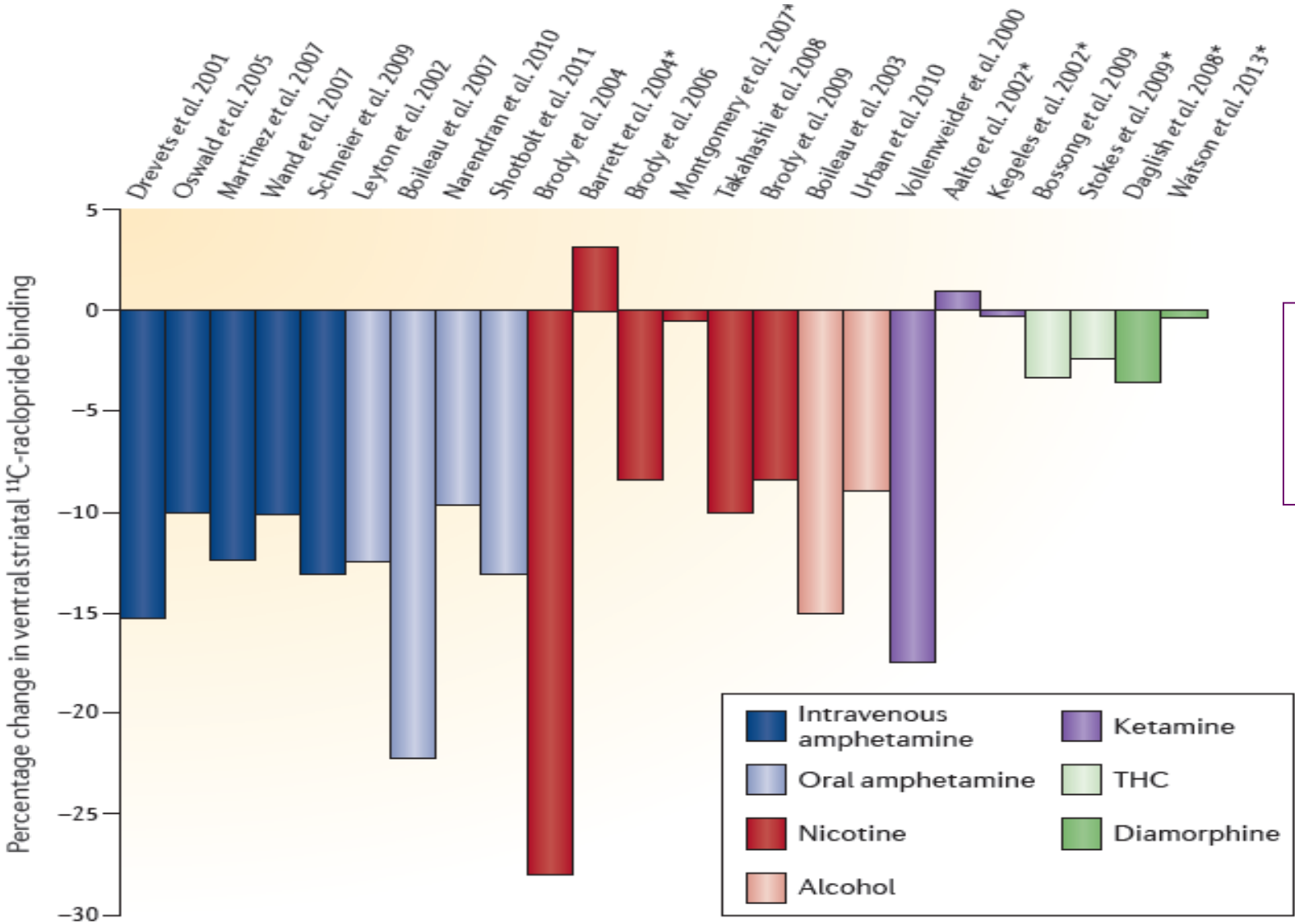


For stimulants dopamine linked to reward



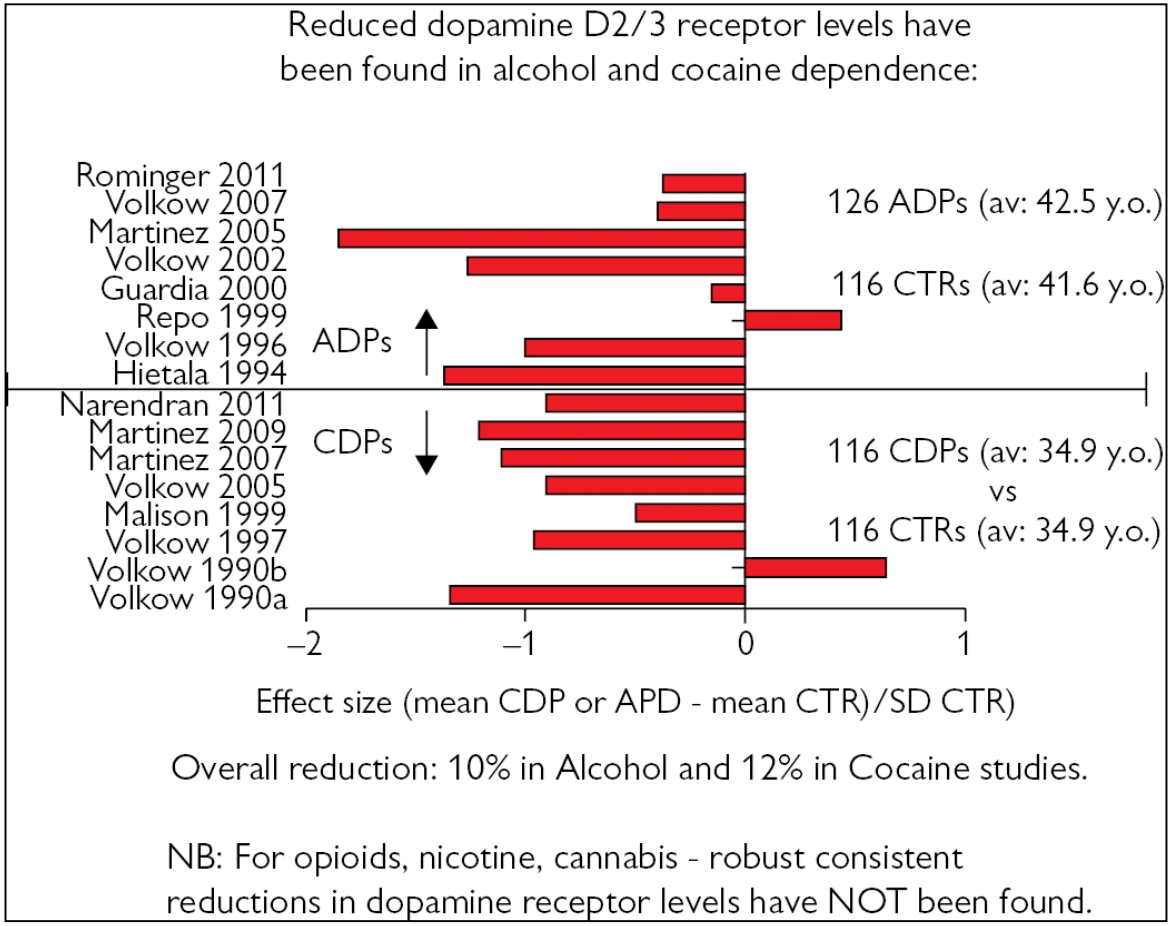
Volkow et al 1999

Not all drugs of abuse result in detectable increases in dopamine in man



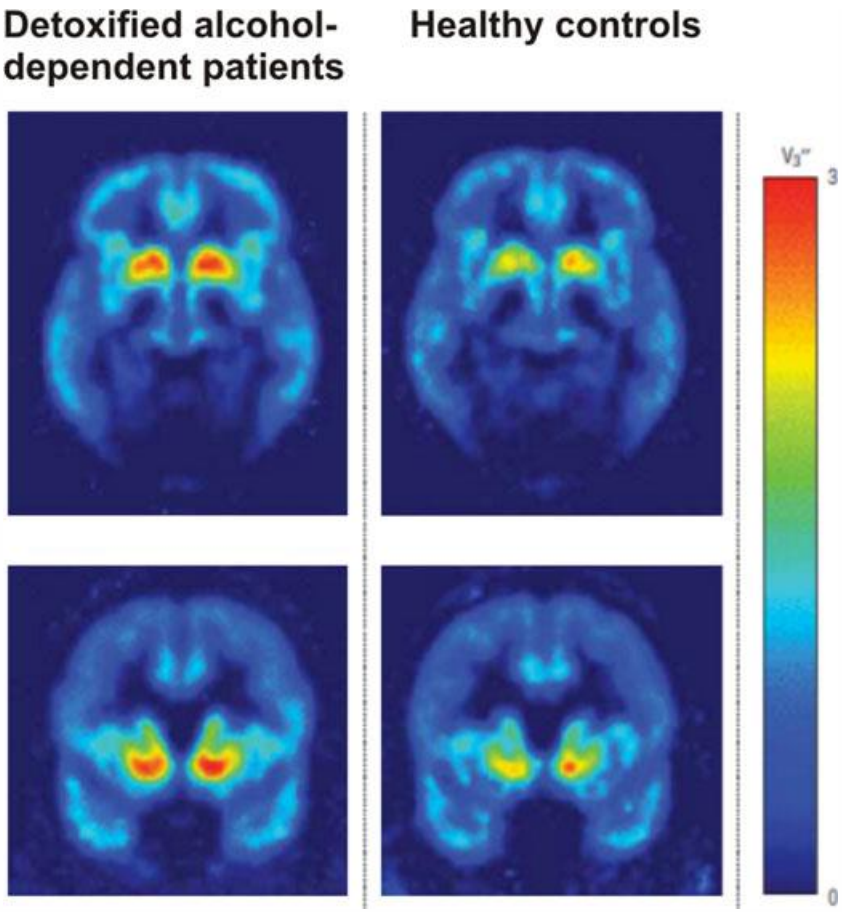
Nutt et al
Nature Reviews
Neuroscience
2015

Deficits in dopamine receptors predispose to addiction .



Chapter: The dopamine system and addiction
Author(s): David J. Nutt and Liam J. Nestor
From: Addiction (Oxford Psychiatry Library)

Increased mu opioid receptors in alcoholism and correlation with craving



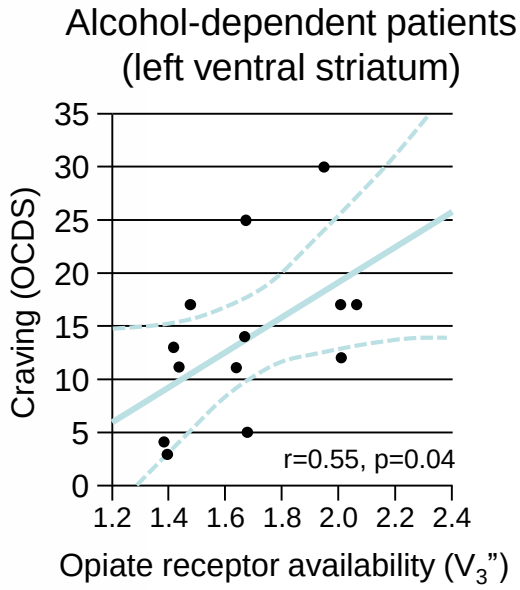
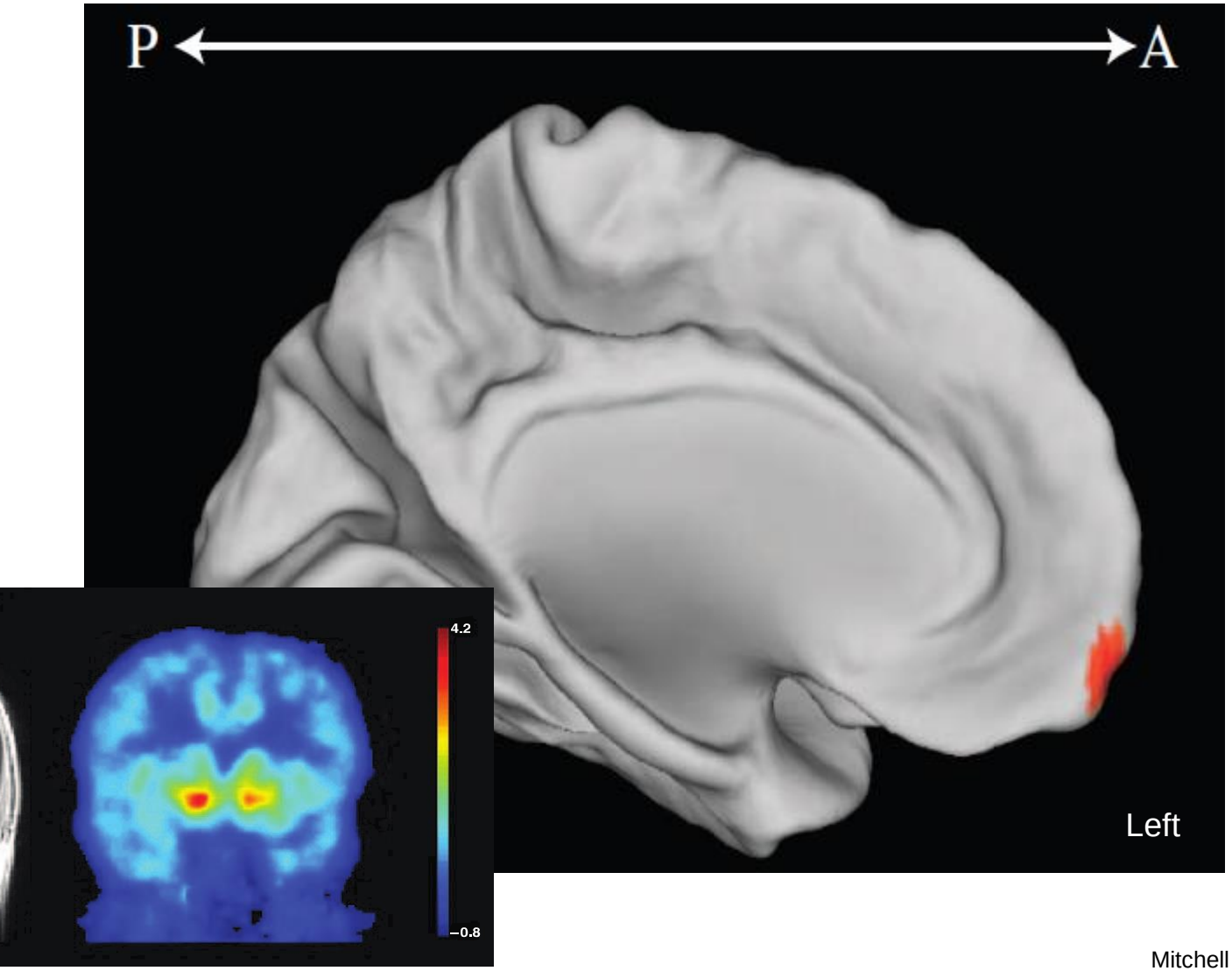


Fig. 4. Results of a [11C] Carfentanil PET study in detoxified alcohol-dependent patients. Availability of μ-Opiate-receptors in the ventral striatum of alcohol-dependent patients (left-hand side) was significantly elevated compared to healthy controls (right-hand side) and remained elevated during 6 weeks of abstinence (not shown) (Heinz et al. 2005a).

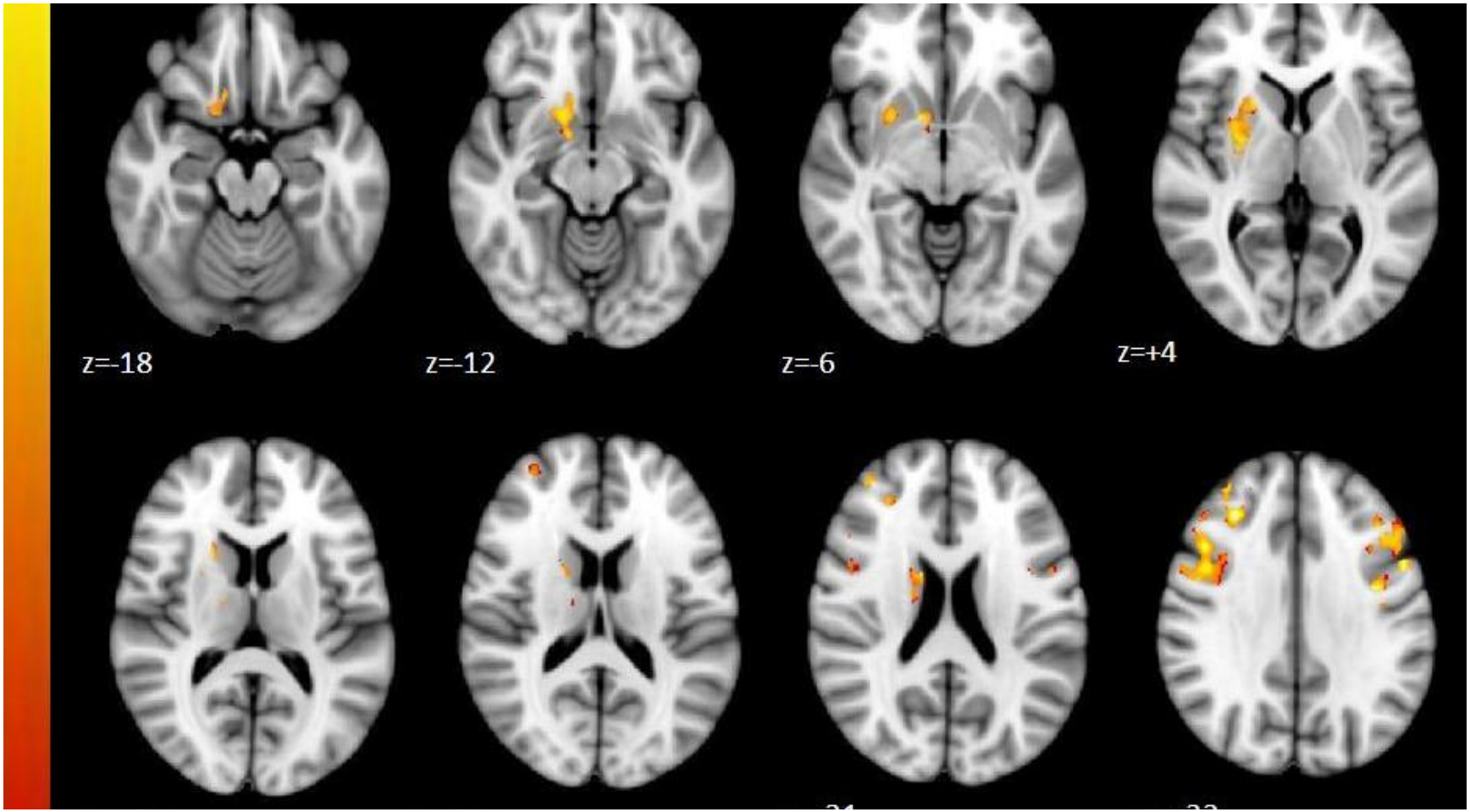
Alcohol consumption induces endorphin release in the human orbitofrontal cortex and nucleus accumbens



In non-dependent alcohol drinkers following alcohol consumption (~24 g)

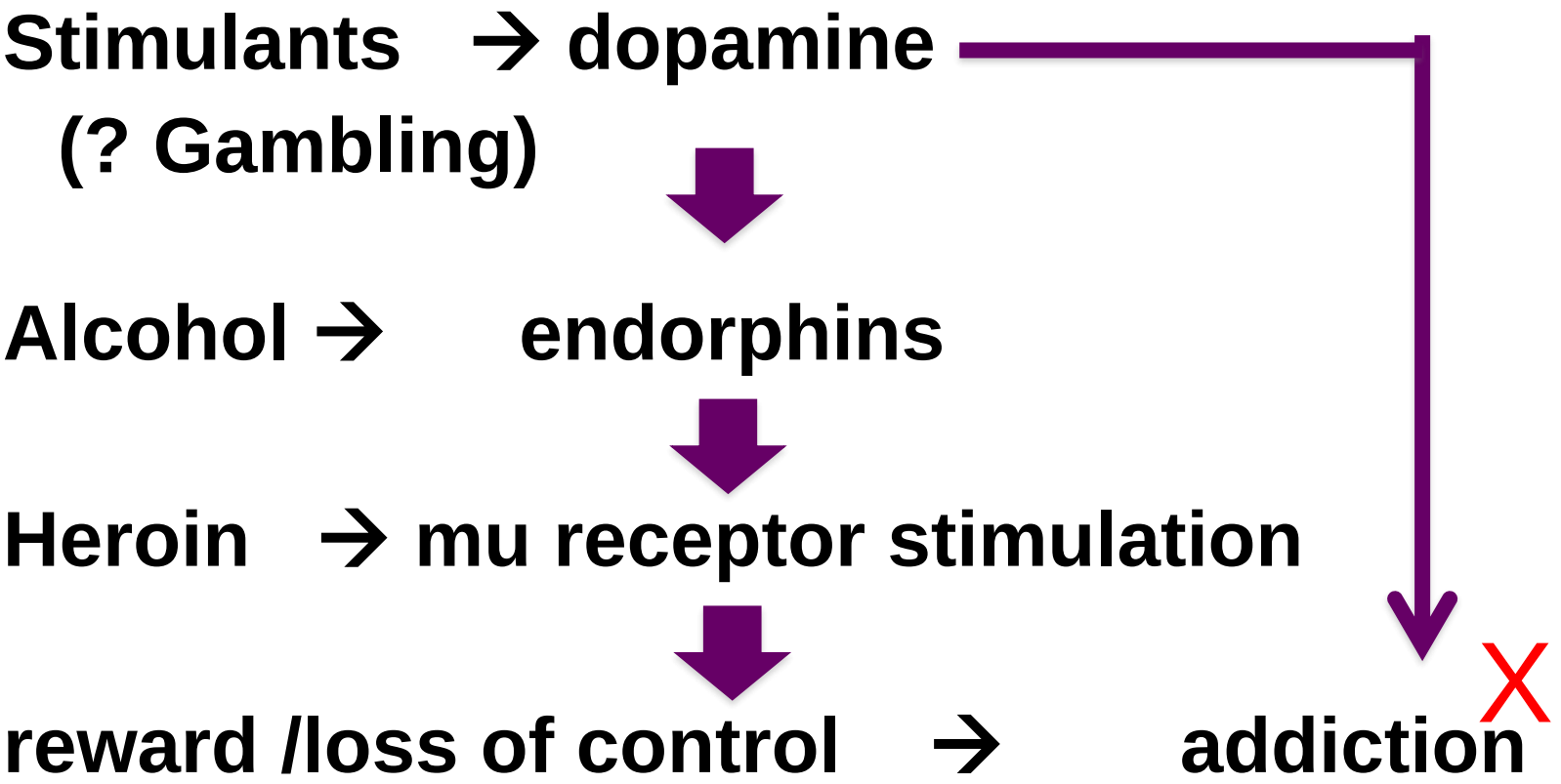
Mitchell et al. Sci Transl Med 2012;4(116):116ra6

Amfetamine releases endorphins – reduced 11C-carfentanil binding

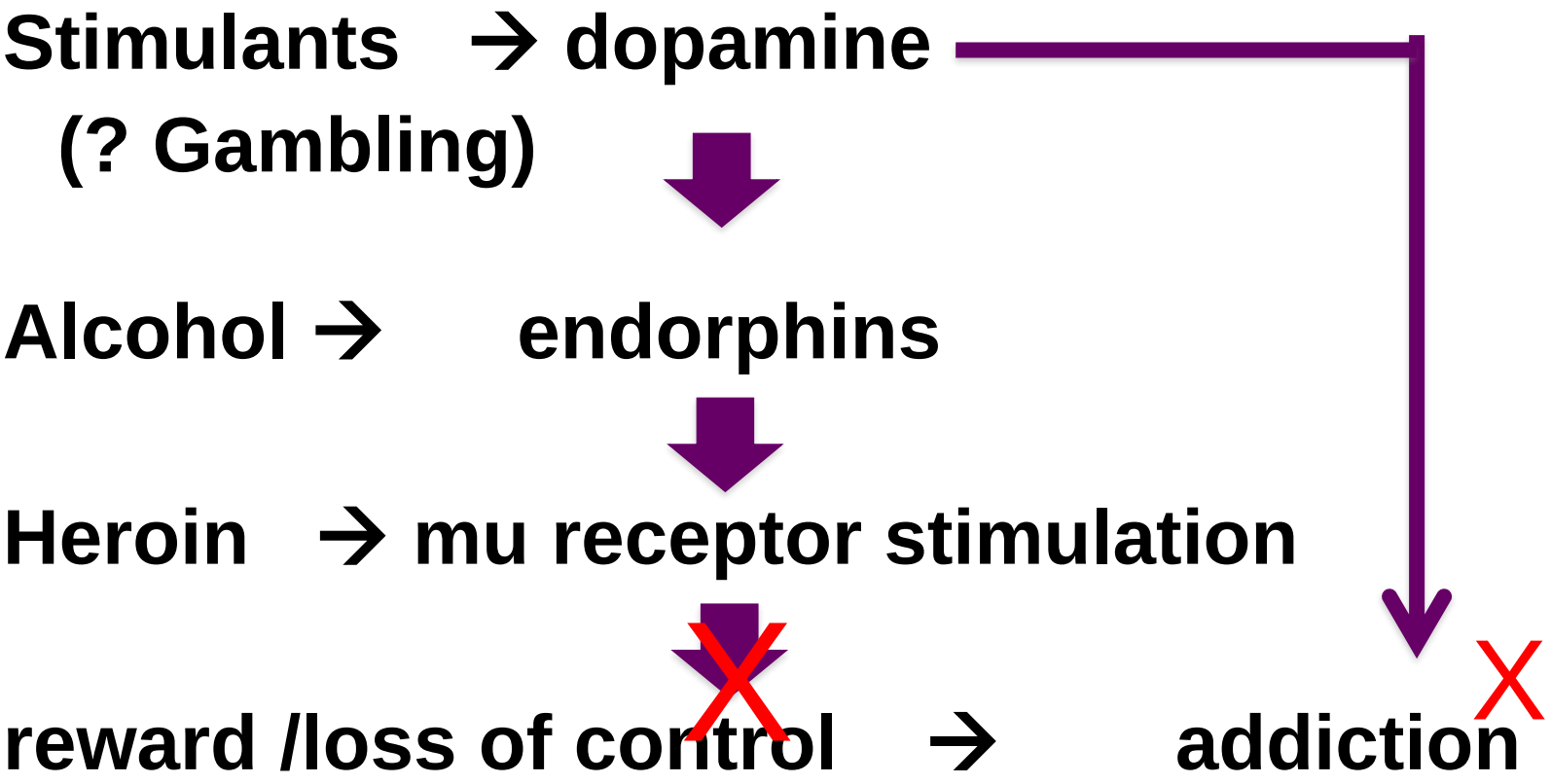


Colasanti et al 2011 replicated Mick et al 2016

Endorphins theory of addiction



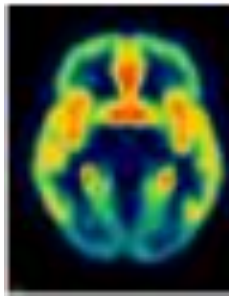
Endorphins theory of addiction

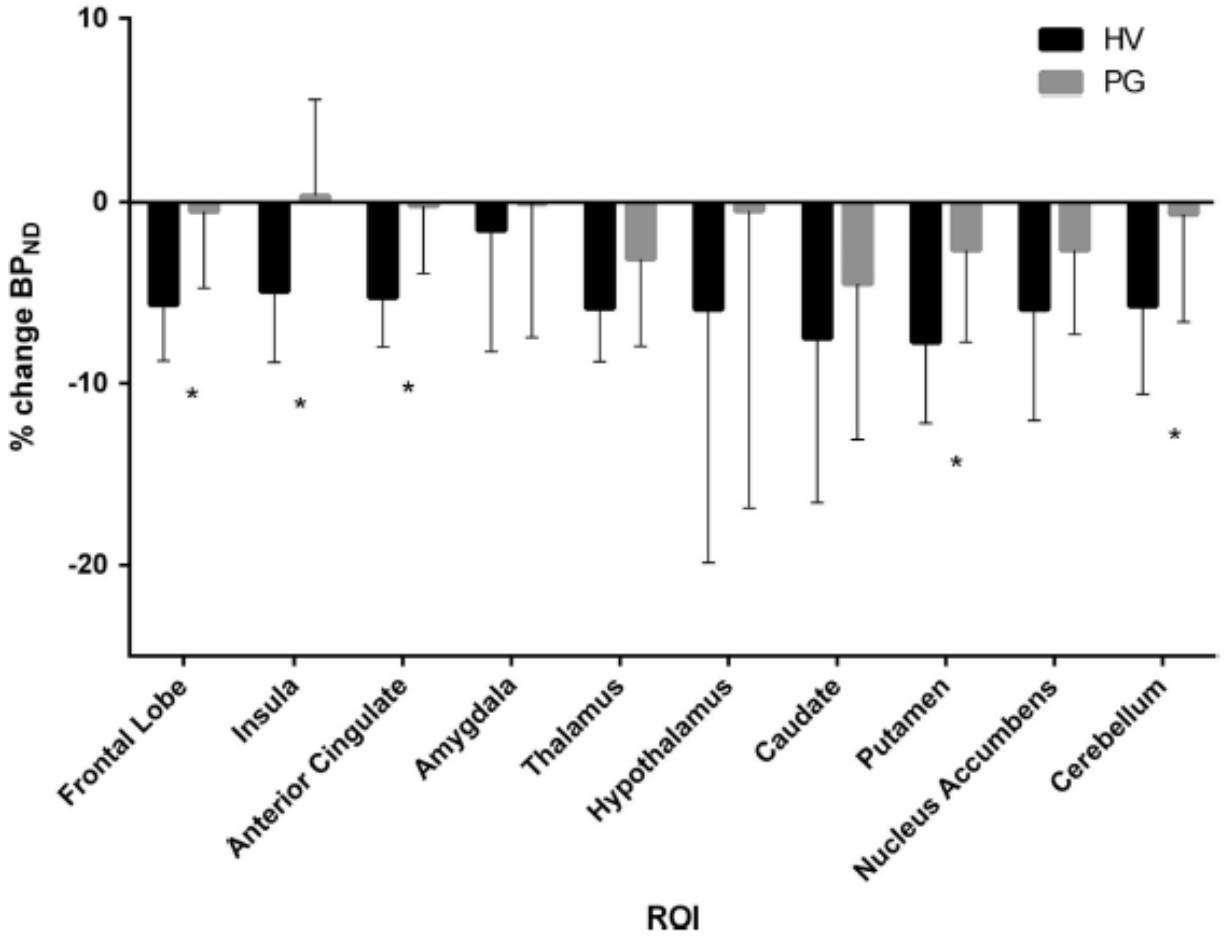


Nalmefene and naltrexone block this in alcoholism

Blunted endorphin release in pathological gamblers

[11C]Carfentanil PET amphetamine challenge



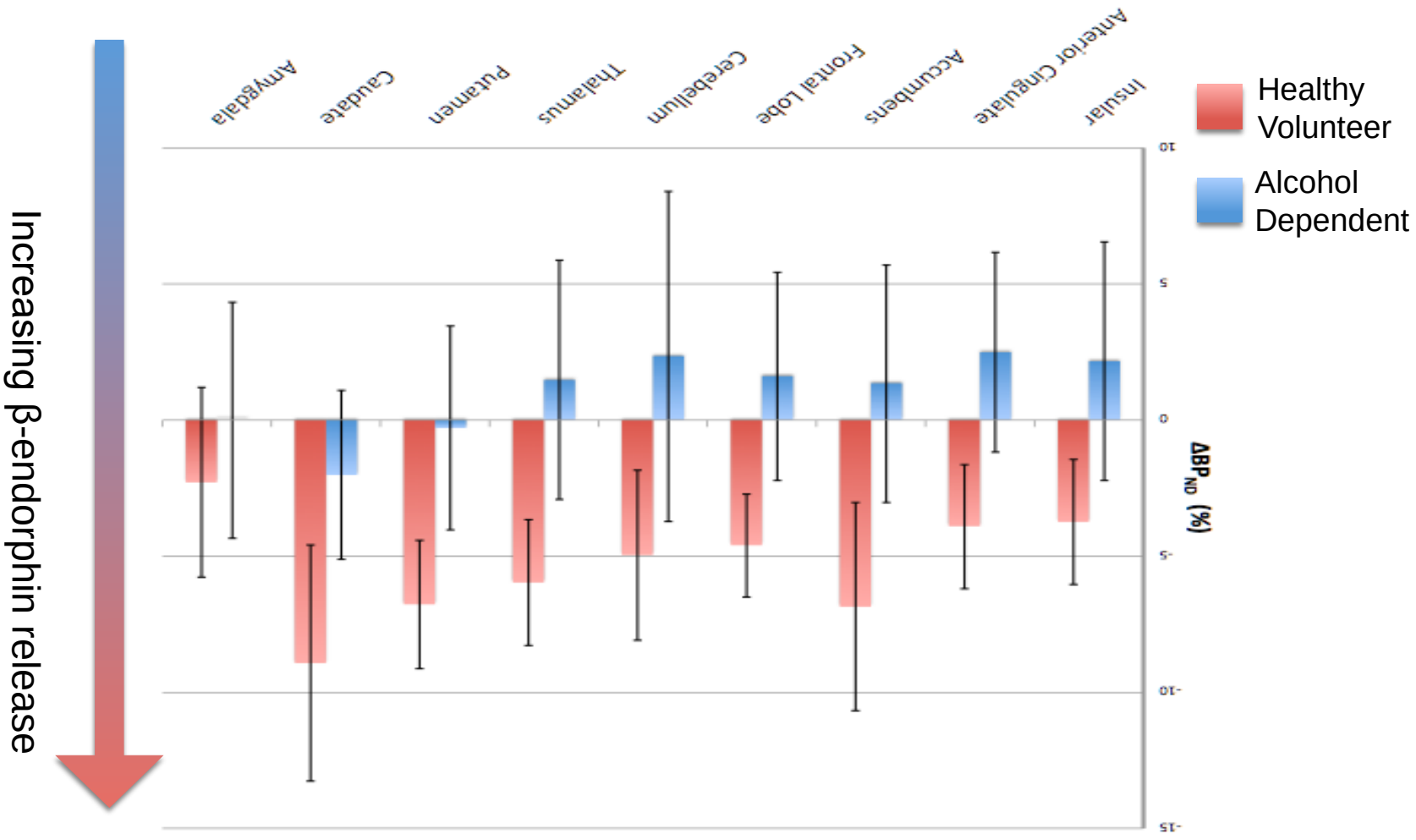


OPEN

Neuropsychopharmacology (2015), 1–9
Official journal of the American College of Neuropsychopharmacology. 0893-133X/15

www.neuropsychopharmacology.org

Blunted β-endorphin release in abstinent alcoholics



Turton - Molecular Psychiatry 2018

Are addictions an endorphin deficiency state?

- And does only the addiction activate endorphin release?

- How can we test?
  - alcohol in alcoholics – unethical
  - Maybe gambling in pathological gambling?

Abstinence is not enough

Amy Winehouse's death due to acute alcohol poisoning in relapse

Blood alcohol 450 mg/%
= 5.5 x legal driving limit

Relapse after 23 years abstinence

Philip Seymour Hoffman Feb 2014

http://www.theguardian.com/society/2014/feb/04/philip-seymour-hoffman-curing-addiction-david-nutt

How to prevent relapse? = The ICCAM Platform

New Drugs to Treat Addiction:

Can a Knowledge of Brain Mechanisms Help?

Imperial College London: David Nutt (PI), Anne Lingford-Hughes, Laurence John Reed, Louise Paterson and John McGonigle

Cambridge University: Trevor Robbins, Barry Everitt, Ed Bullmore, Karen Ersche, Jeff Dalley and Franklin Aigbirhio

Manchester University: Bill Deakin, Rebecca Elliott and Anna Murphy.

Imanova: Ilan Rabiner and Rexford Newbould

GSK: Pradeep Nathan

MRC Medical Research Council

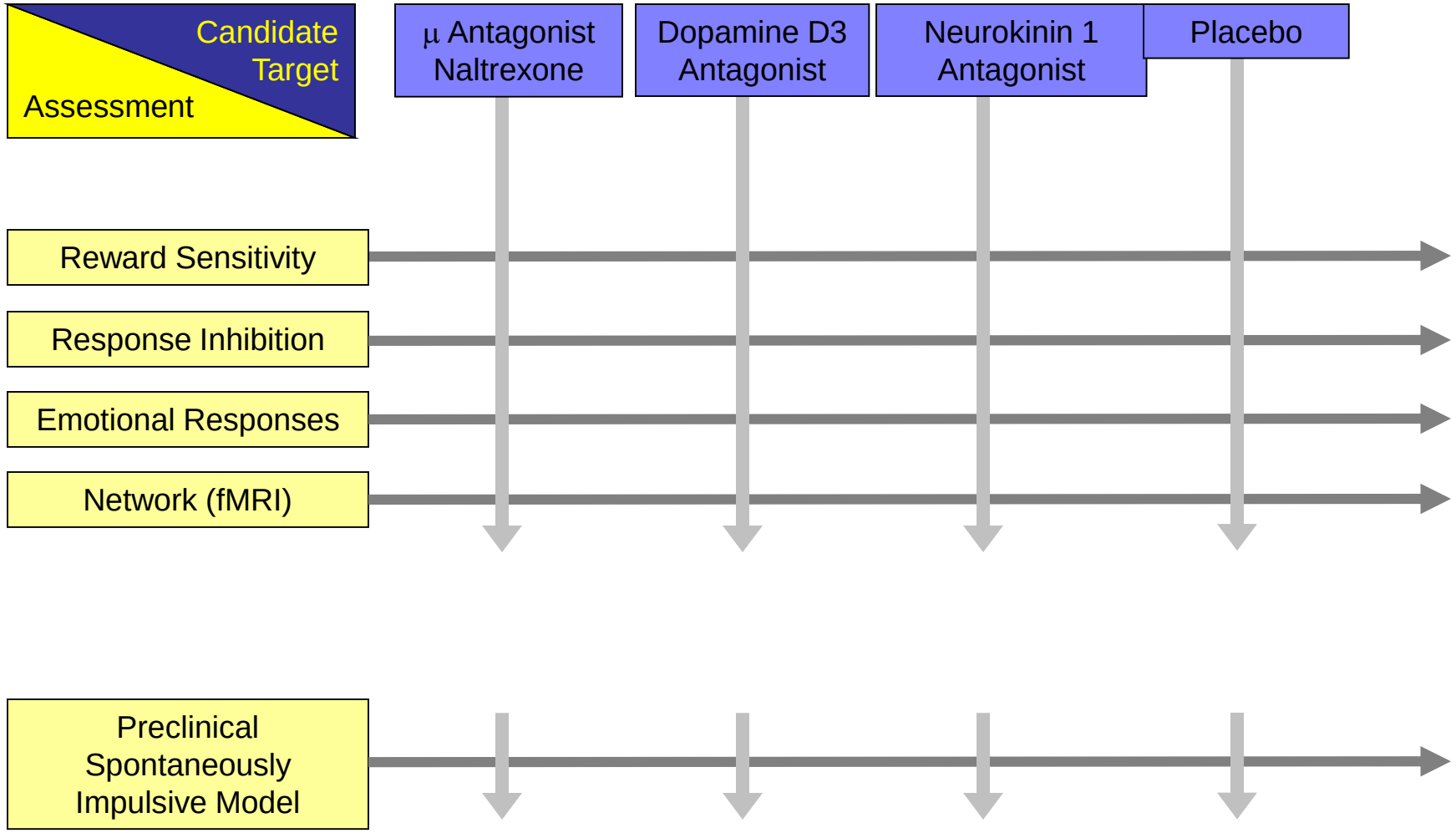
imanova Centre for Imaging Sciences

gsk GlaxoSmithKline

Mental Health Research Network

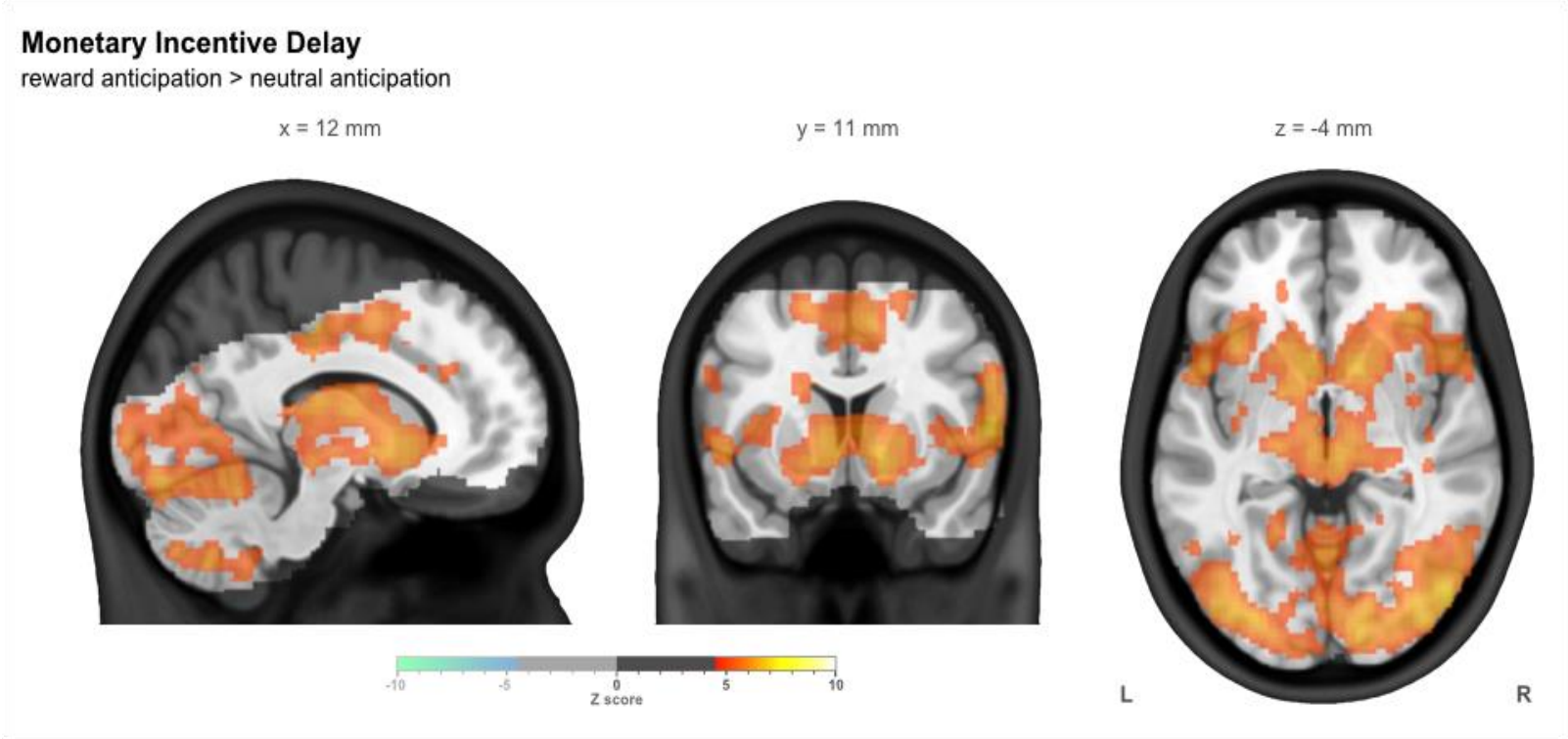
NHS National Institute for Health Research

ICCAM Platform – Mechanisms of Relapse



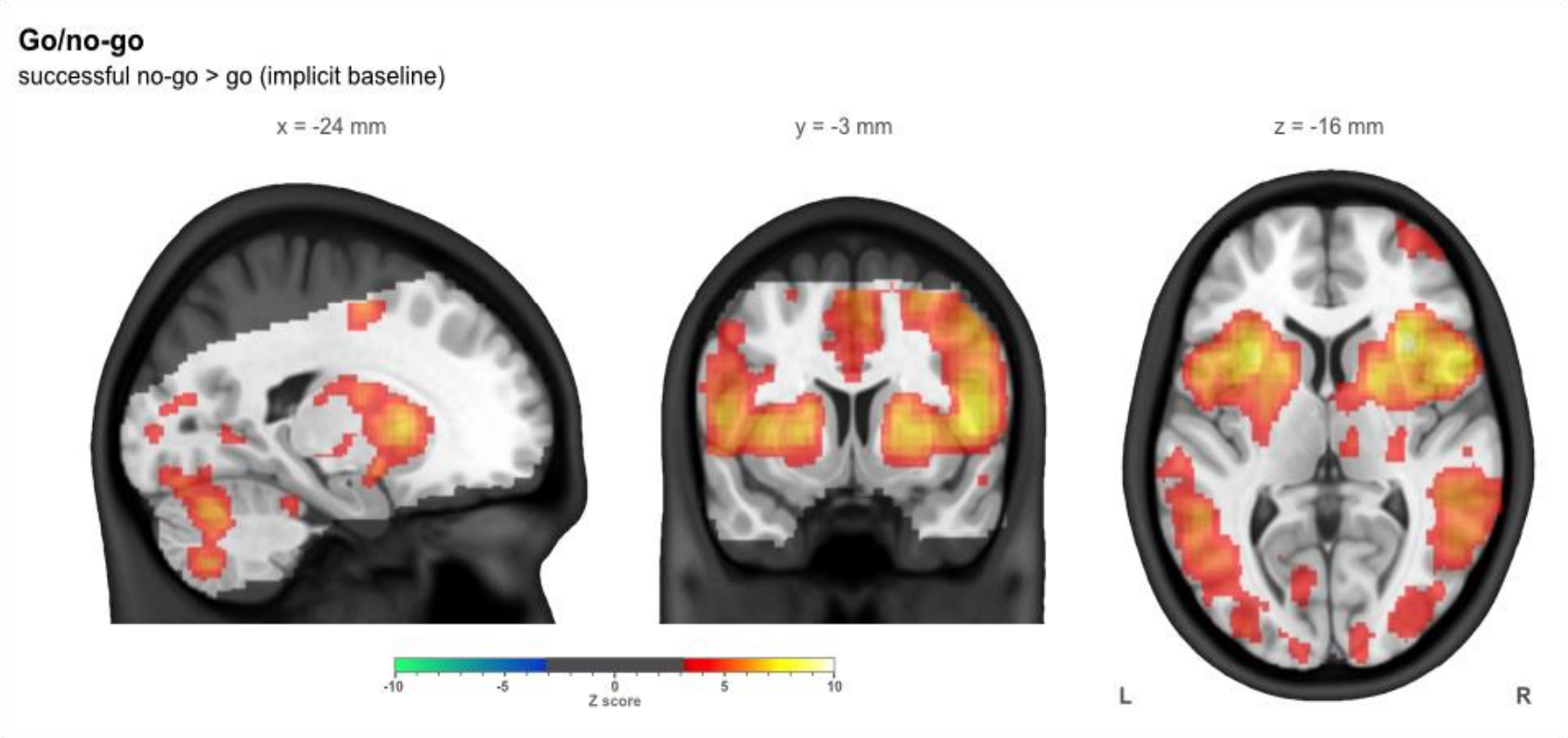
Paterson et al 2015 Journal of Psychopharmacology

Monetary Incentive Delay task = reward mechanisms



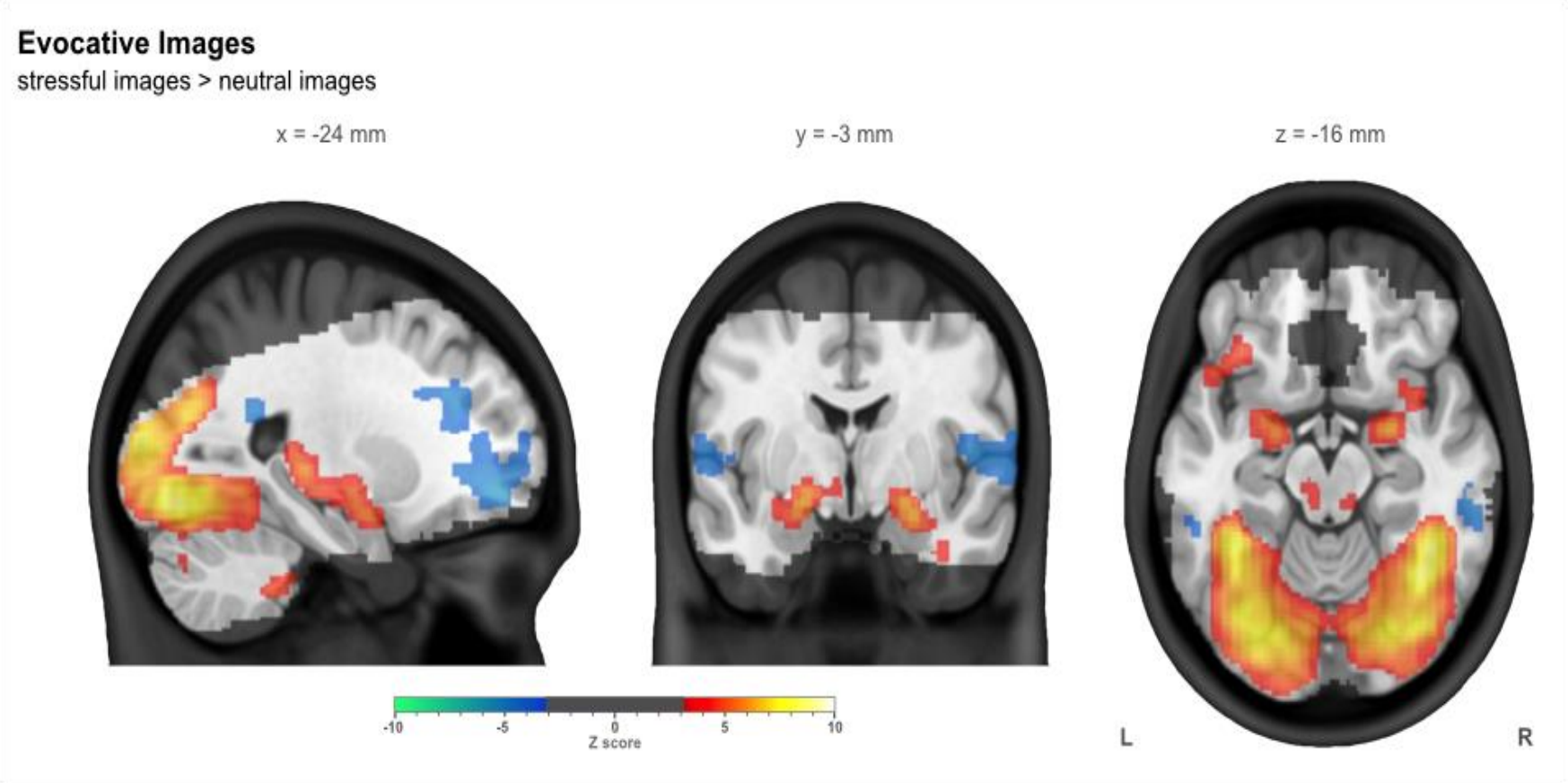
Paterson et al 2015 Journal of Psychopharmacology

Go/NoGo task = impulse control



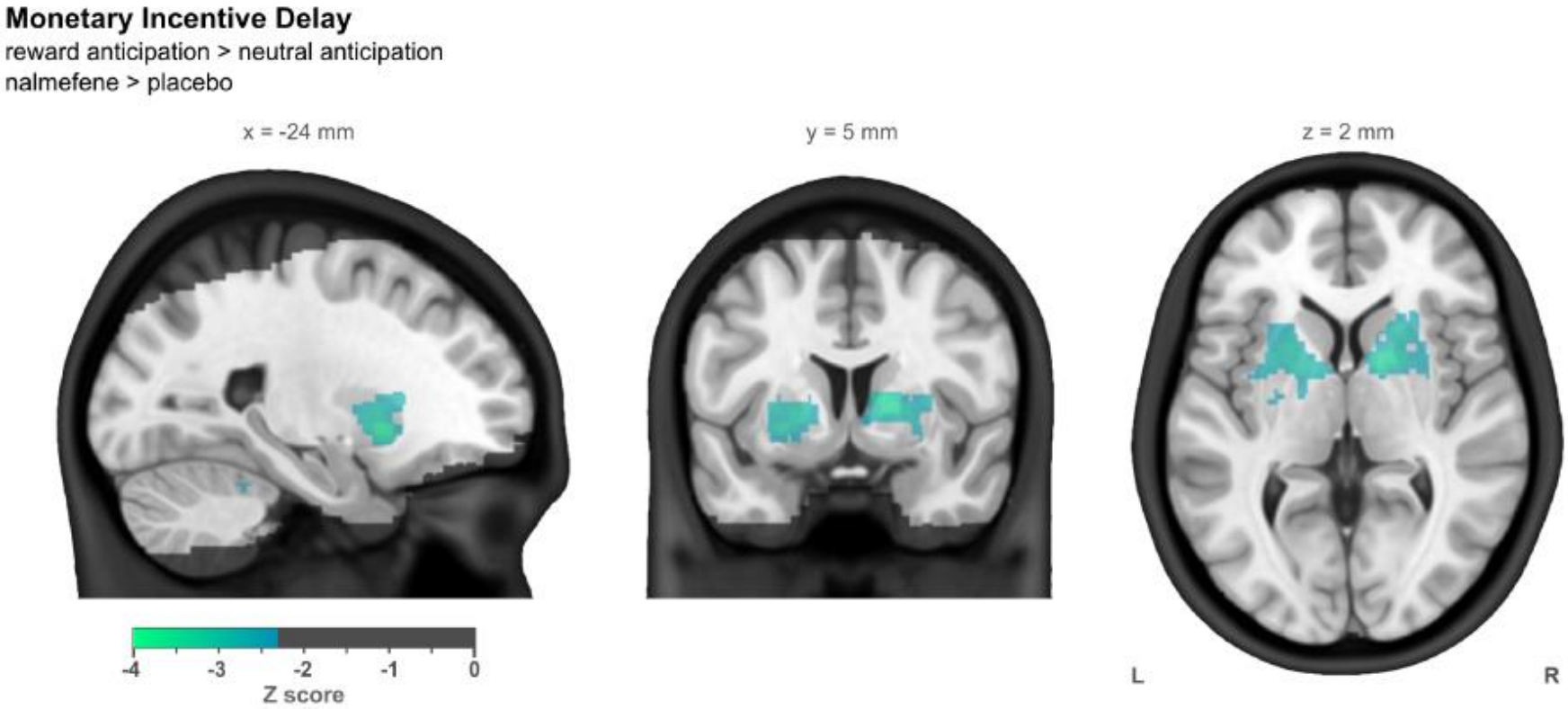
Paterson et al 2015 Journal of Psychopharmacology

Evocative task
= emotional images responding



Paterson et al 2015 Journal of Psychopharmacology

Nalmefene and MID task during alcohol intoxication fMRI



Significant decrease in globus pallidus and putamen and in brain stem

Quelch Nutt and Lingford-Hughes –Biological Psychiatry 2018

NK1 antagonism (apipretant) significantly attenuates blunted reward anticipation in alcoholics

Apipretant is available as a medicine – for chemo-induced nausea - But v expensive

Should be cheaper once off-license

And grant to study it now awarded by MRC

Control Alcohol Polydrug

Significant drug by group interaction [F = 3.514 (77,2), p=0.035]

Significant group effect [F = 7.527 (77,2), p=0.001]

New approaches to tobacco and alcohol harm reduction using safer alternatives

Nicotine
= vaping/e-cigarettes
= snus [Swedish safe oral tobacco)

Alcohol
= Alcarelle = less harmful drink (cf aspartame for sugar)

Revisit ”illegal” drugs for addiction?

Review

Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials

Teri S Krebs[1,2] and Pål-Ørjan Johansen[1,2]

Psychopharm

Journal of Psychopharmacology
0(0) 1–9

DOI: 10.1177/0269881112439253
jop.sagepub.com
SAGE

Abstract

Assessments of lysergic acid diethylamide (LSD) in the treatment of alcoholism have not been based on quantitative meta-analysis. Hence, we performed a meta-analysis of randomized controlled trials in order to evaluate the clinical efficacy of LSD in the treatment of alcoholism. Two reviewers independently extracted the data, pooling the effects using odds ratios (ORs) by a generic inverse variance, random effects model. We identified six eligible trials, including 536 participants. There was evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI, 1.36–2.84; p = 0.0003). Between-trial heterogeneity for the treatment effects was negligible (I^2 = 0%). Secondary outcomes, risk of bias and limitations are discussed. A single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse.

Keywords

Alcoholism, alcohol-related disorders, hallucinogens, meta-analysis, psychedelics, substance-related disorders

Six LSD trials in alcoholism

1970	problems and treatment intentions		quiet room	group therapy

	Follow-up (months)	LSD (n/N)	Control (n/N)	Weight	Odds Ratio (95% CI)
First follow-up					
Smart *et al.*, 1966	6	[a]/10	[a]/20	7.2%	1.41 (0.36-5.60)
Hollister *et al.*, 1969	2	18/36	11/36	14.7%	2.27 (0.87-5.94)
Ludwig *et al.*, 1969	1	88/132	31/44	27.3%	1.88 (0.93-3.81)
Bowen *et al.*, 1970	12	9/22	7/22	8.9%	1.48 (0.43-5.10)
Pahnke *et al.*, 1970	6	34/73	13/44	21.6%	2.08 (0.94-4.60)
Tomsovic & Edwards, 1970	3	30/52	17/45	20.4%	2.25 (0.99-5.10)
Total		**325**	**211**	**100%**	**1.96 (1.36-2.84)**

Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.65$, df = 5 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: Z = 3.59 ($P = 0.0003$)

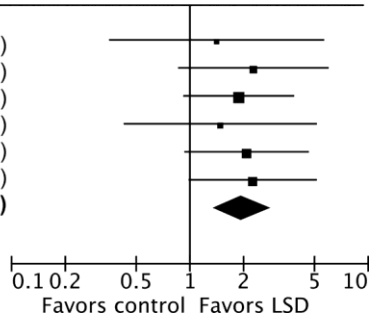


Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.
[a]Continuous outcome data.

Effect size >= all current therapies

Krebs and Johansen 2012 Journal of Psychopharmacology

The future? 2.
Revisit ”illegal” drugs for addiction

Recent positive open trials of psilocybin (magic mushrooms) in addiction to

- Tobacco (John Hopkins)
- Alcohol (New Mexico)

- and ketamine for alcohol and heroin
- And MDMA for alcoholism starting in Bristol

But illegal status profoundly limits research and clinical roll out

Effect size >= all current therapies but banned for 50 years!

Modern replication study

Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study

J Psychopharmacol March 2015 29: 289-299, first published on January 13, 2015

Bogenschutz MP1, Forcehimes AA2, Pommy JA2, Wilcox CE2, Barbosa PC3, Strassman RJ2.

Psilocybin and smoking cessation

Original Paper

Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction

Matthew W Johnson[1], Albert Garcia-Romeu[1], Mary P Cosimano[1] and Roland R Griffiths[1,2]

Psychopharm

Journal of Psychopharmacology
1–10

DOI: 10.1177/0269881114548296
jop.sagepub.com
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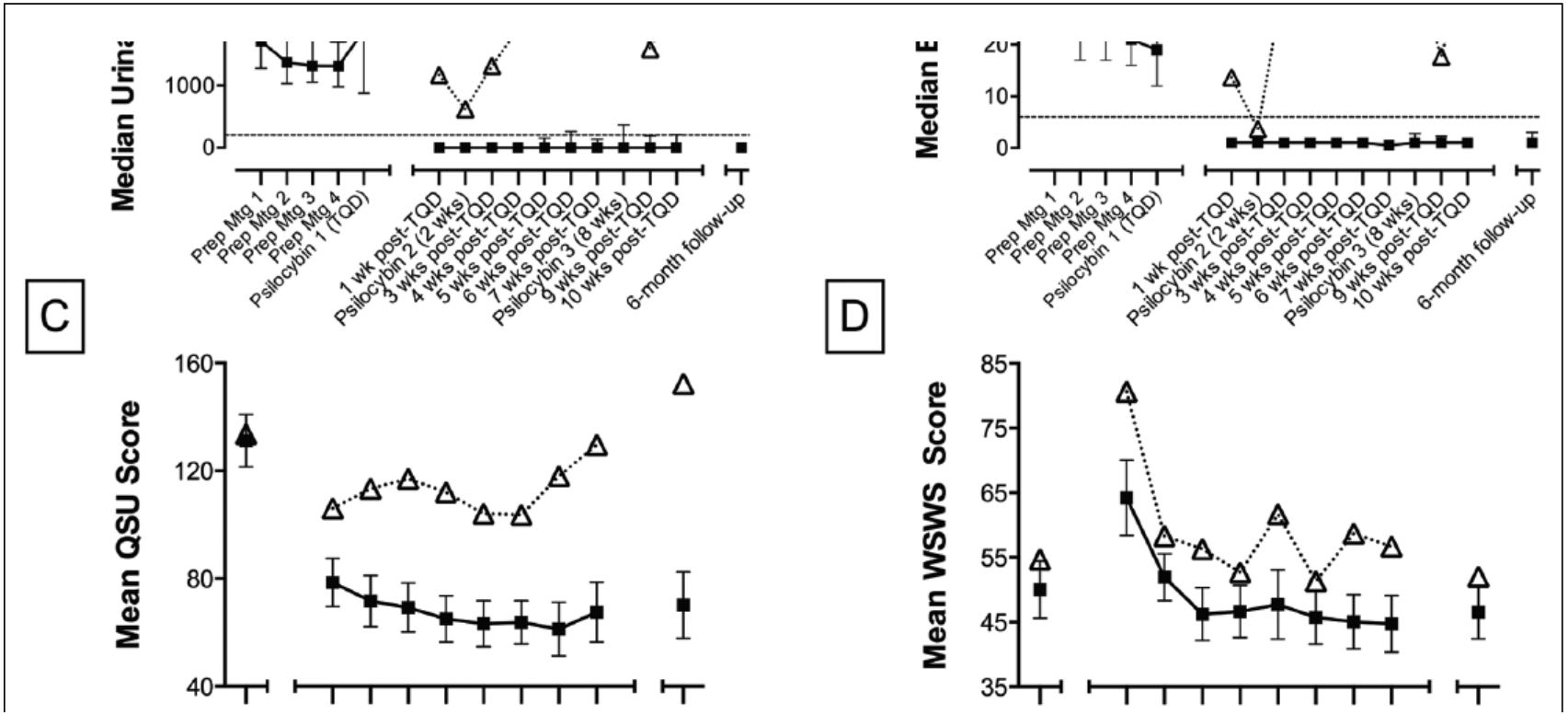
Psilocybin and smoking cessation - Results 1.



Drugs ranked according to total harm

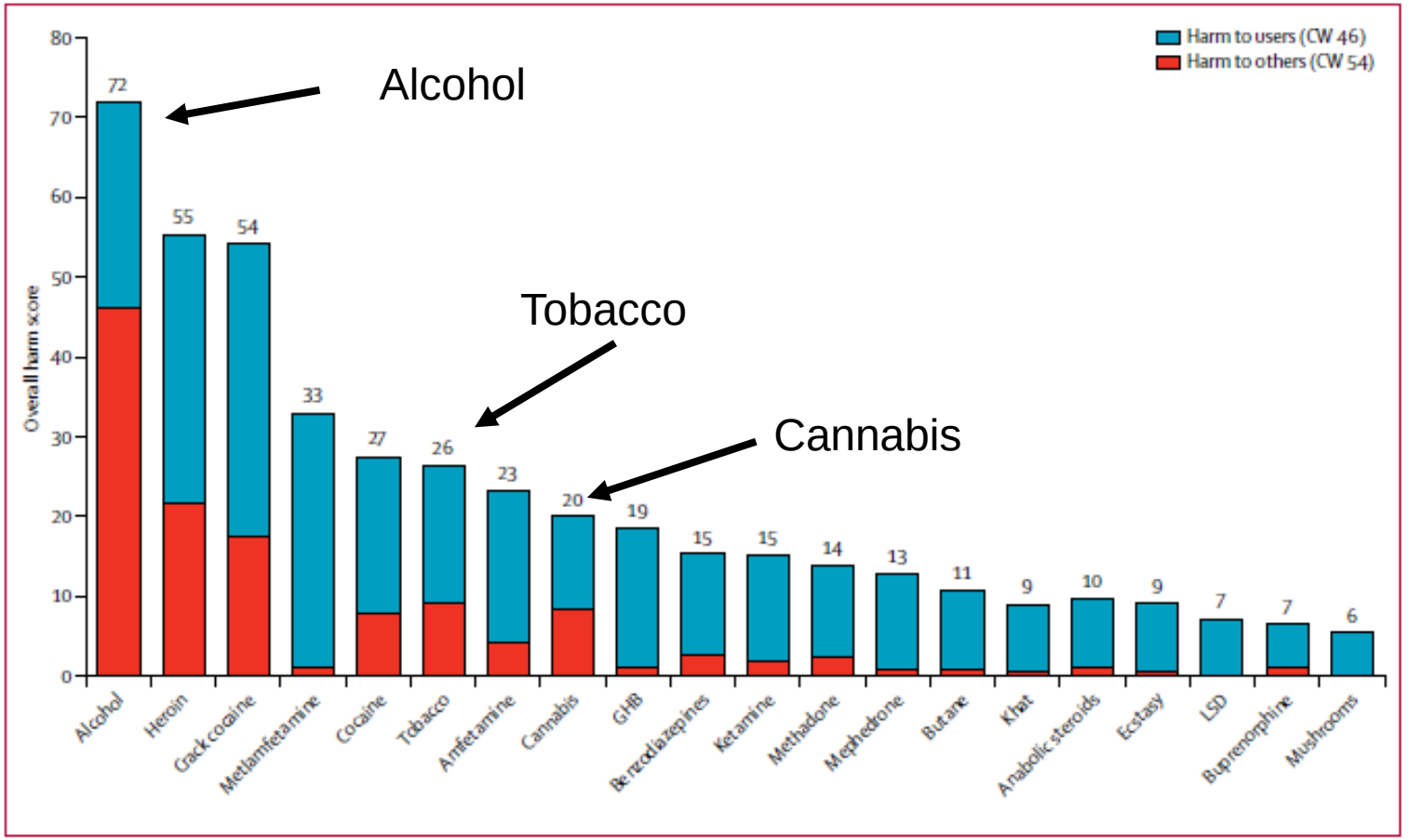


Figure 2: **Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others**
The weights after normalisation (0–100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 46; and for all the criteria to others, 54). CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide.

Nutt King & Phillips Lancet Nov 2010

Managing the media very important

Note in newspaper

Gavin Britton

Alcohol poisoning

(Drinking game after Exeter University golf match)

Billboards all over the UK

Leah Betts

Water poisoning following MDMA use

A plea for a regulated market

Robert Fraser

Robert goes to score some cannabis

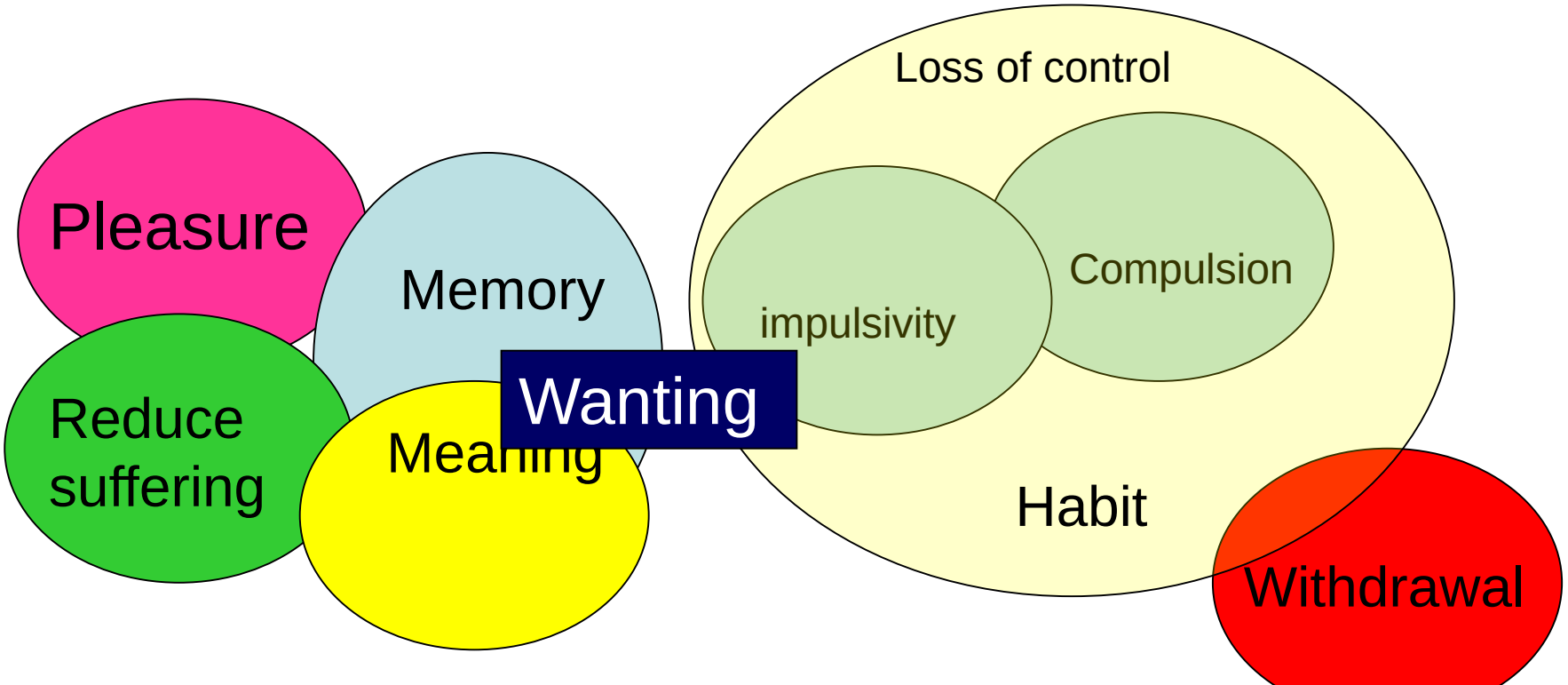
Gets offered “ecstasy” as well -- takes it

Dies as its fentanyl not ecstasy

Dru use and addiction is a complex, multifaceted issue

Different elements with different behavioural and molecular mechanisms

New treatments may require a more fine-grained analysis of these factors – and clarity of processes and policies



Thanks, questions and further reading