Addiction:
From Brain Mechanisms to New Treatments

SSA York 2016

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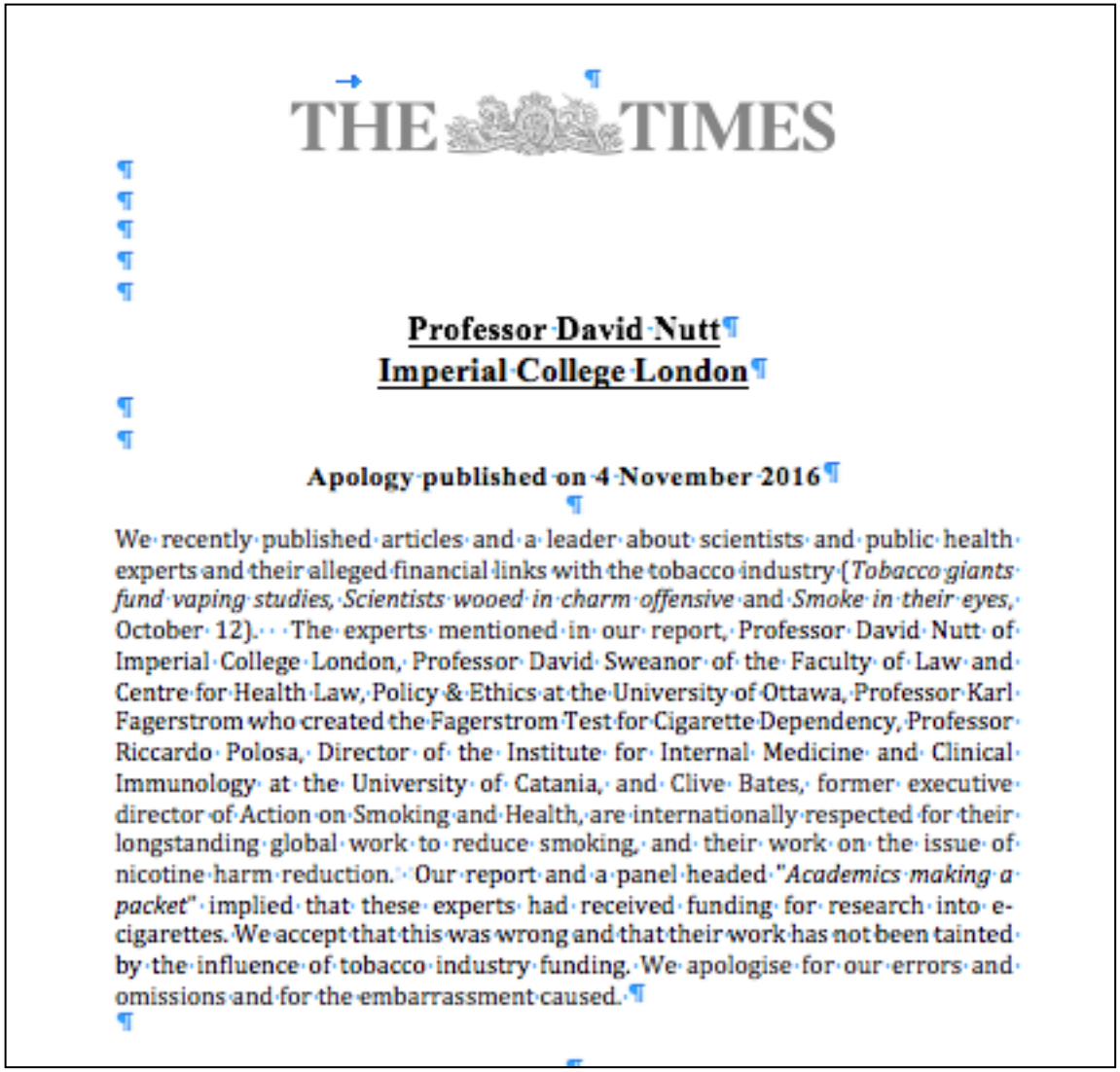
Health Warning:
Please don't lie about my research and funding



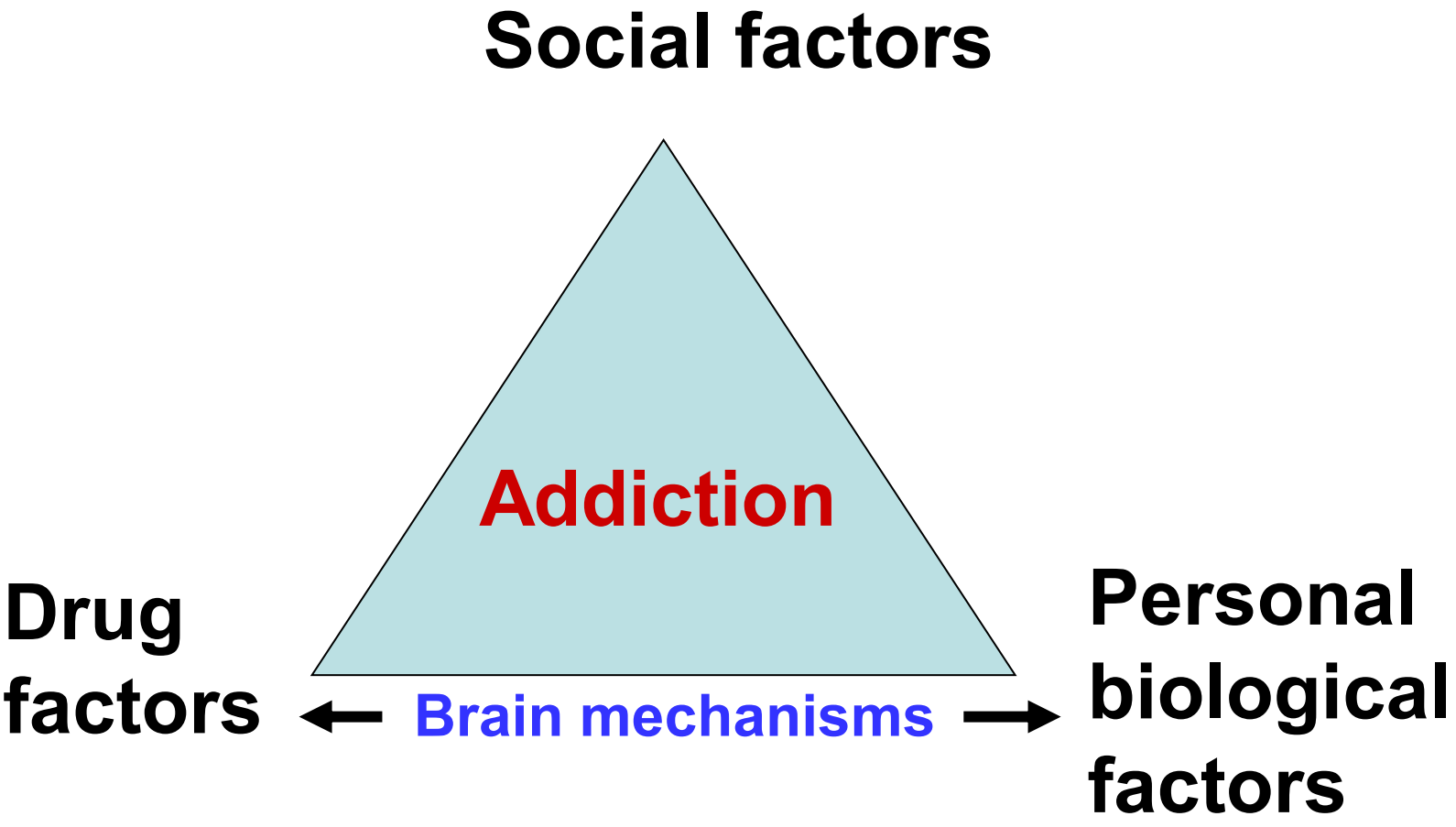
THE TIMES

Professor David Nutt
Imperial College London

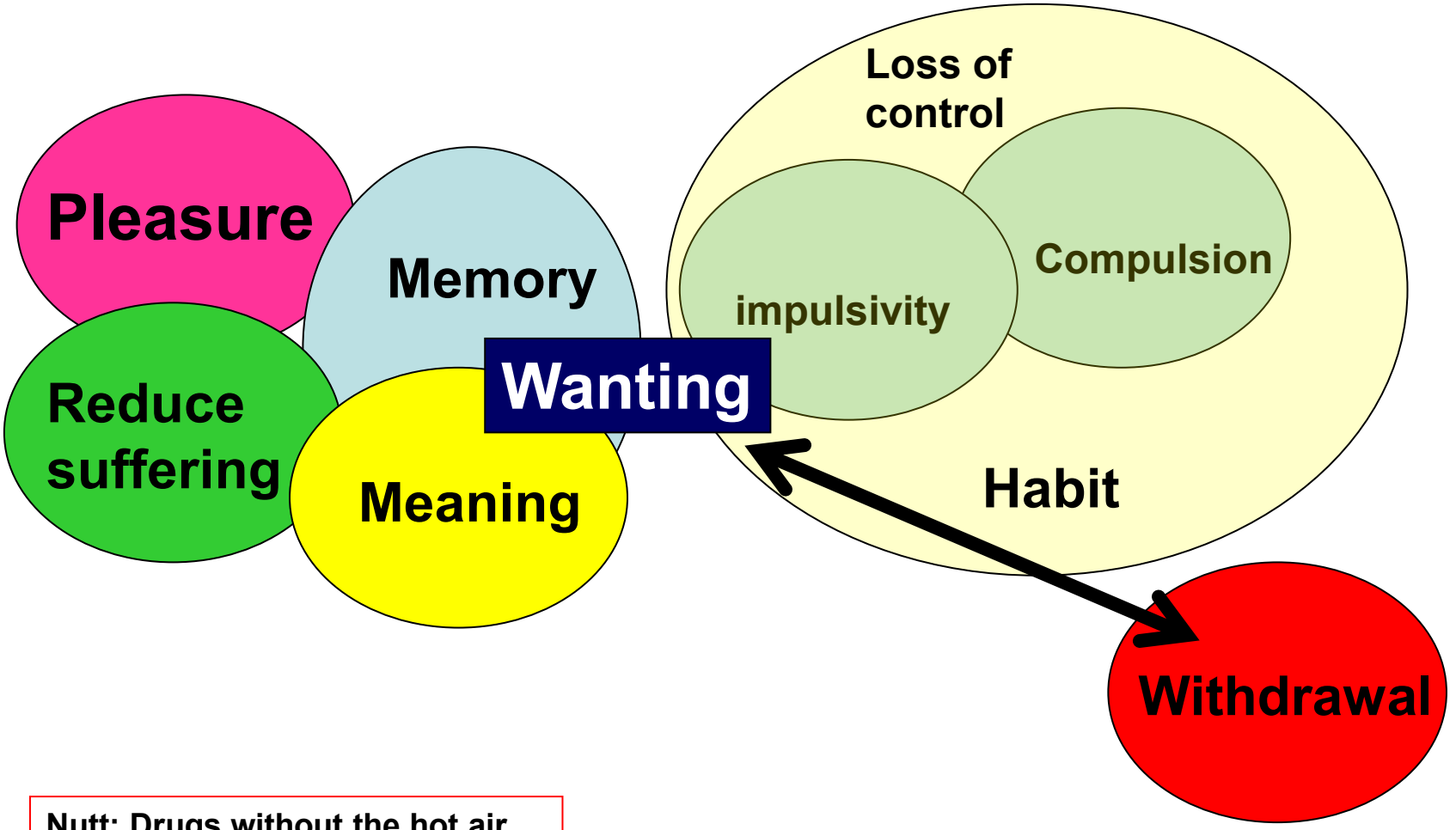
Apology published on 4 November 2016

We recently published articles and a leader about scientists and public health experts and their alleged financial links with the tobacco industry (*Tobacco giants fund vaping studies, Scientists wooed in charm offensive* and *Smoke in their eyes*, October 12). The experts mentioned in our report, Professor David Nutt of Imperial College London, Professor David Sweanor of the Faculty of Law and Centre for Health Law, Policy & Ethics at the University of Ottawa, Professor Karl Fagerstrom who created the Fagerstrom Test for Cigarette Dependency, Professor Riccardo Polosa, Director of the Institute for Internal Medicine and Clinical Immunology at the University of Catania, and Clive Bates, former executive director of Action on Smoking and Health, are internationally respected for their longstanding global work to reduce smoking, and their work on the issue of nicotine harm reduction. Our report and a panel headed "*Academics making a packet*" implied that these experts had received funding for research into e-cigarettes. We accept that this was wrong and that their work has not been tainted by the influence of tobacco industry funding. We apologise for our errors and omissions and for the embarrassment caused.

Triangulating addiction



Elements of addiction



Nutt: Drugs without the hot air

El diction

Pleasure

Reduce suffering

s of
rol

Compulsion

Habit

Withdrawal

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

f Tatum O’Neal

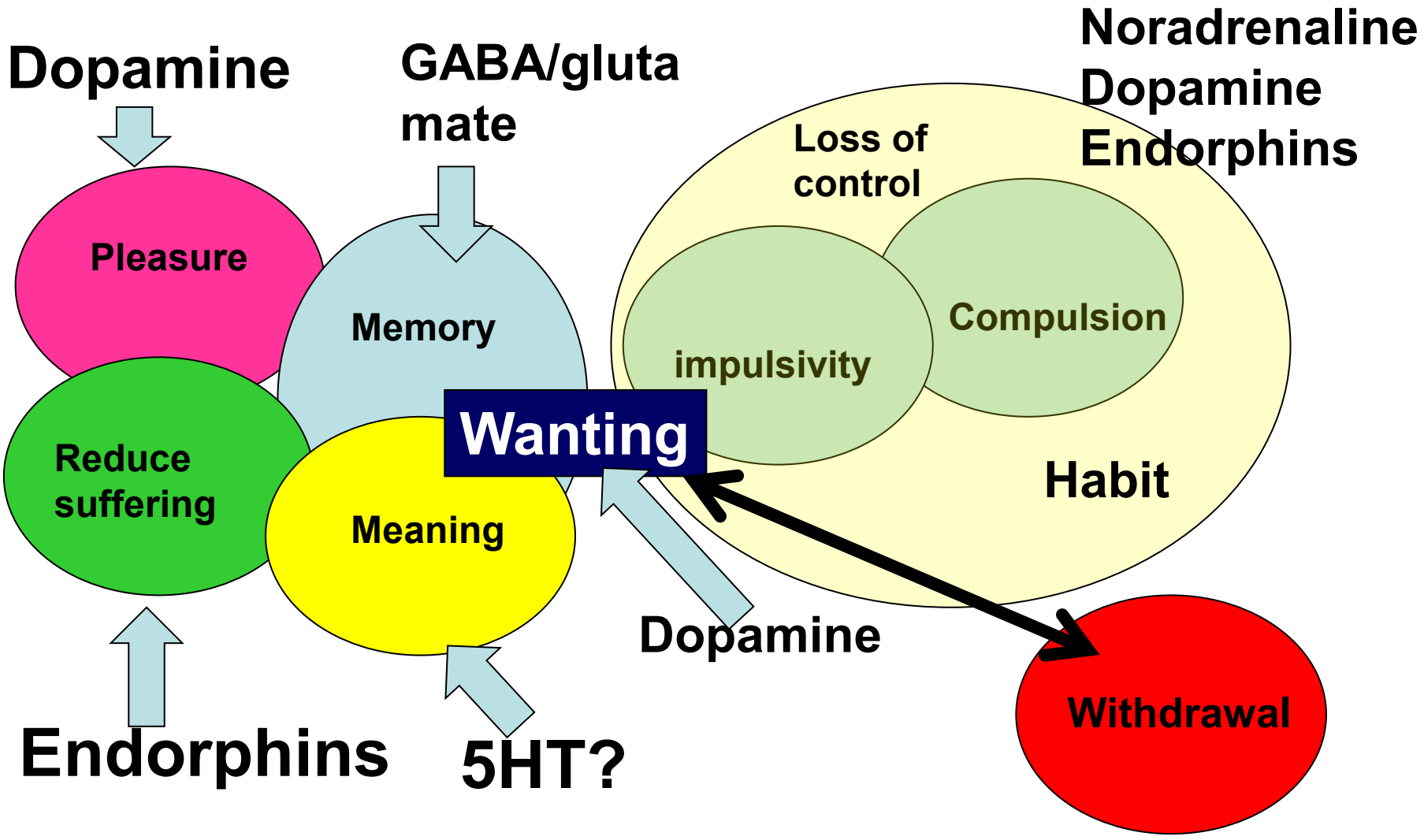
Loss of control

suffering

Meaning

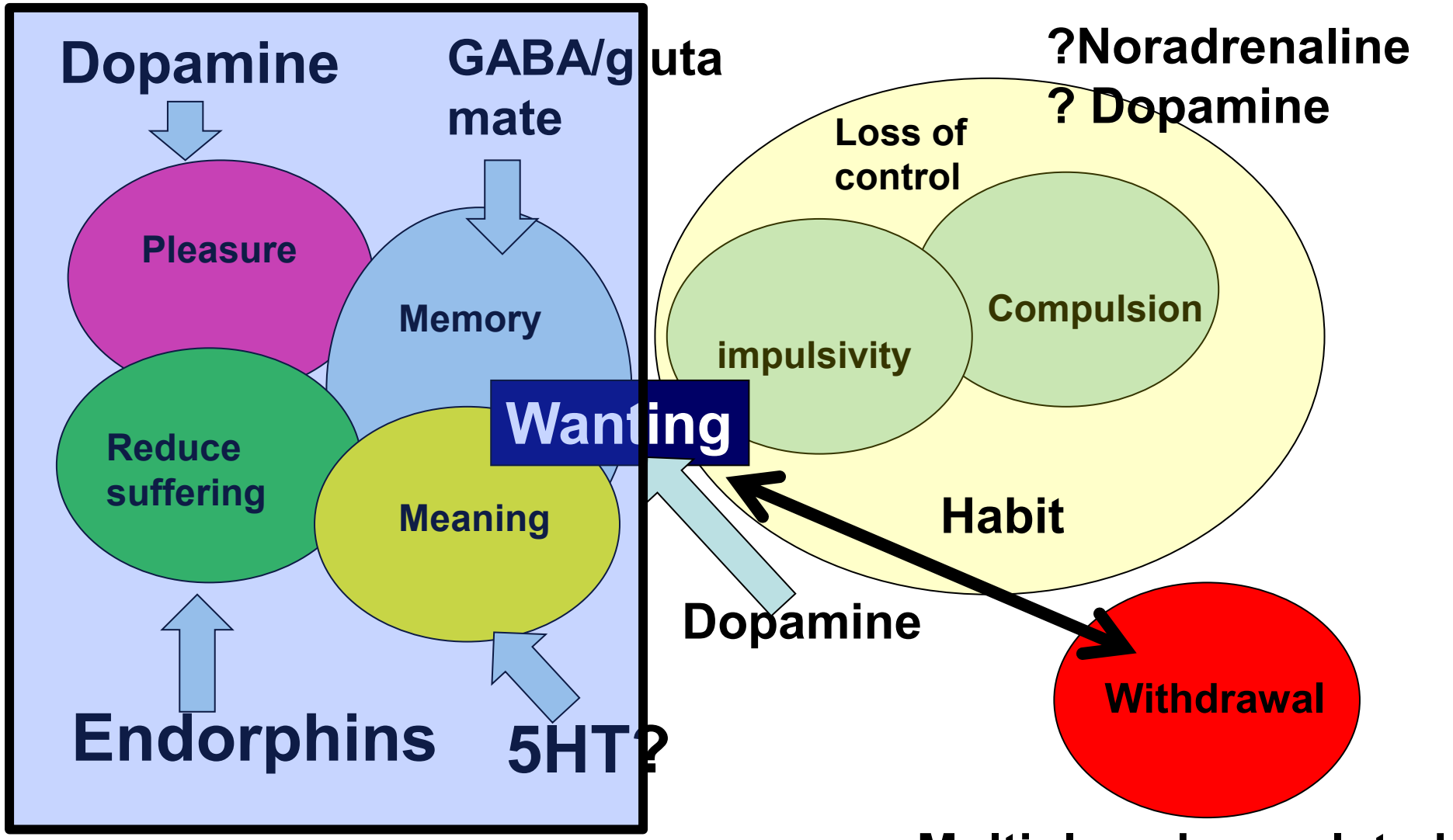
The only time I felt whole was on heroin
Tatum O’Neal

Possible neurotransmitters



Nutt: Drugs without the hot air

Stopping use?



Stopping 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)

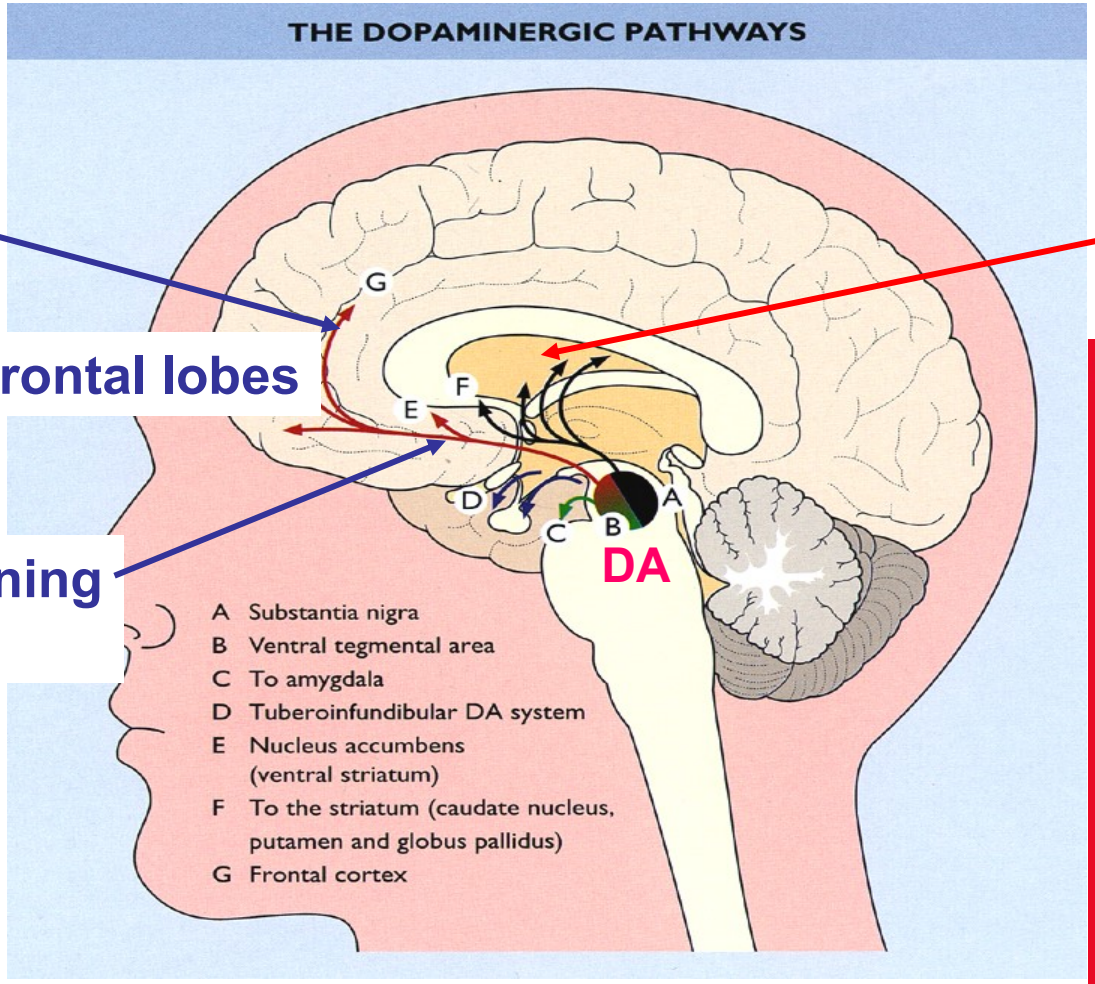
Block elements of drugs effects

- Opioid antagonists for alcohol – nalmefene naltrexone
  - ? Prevent loss of control

Substitution therapy

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

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



Planning and control

Frontal lobes

Reward learning

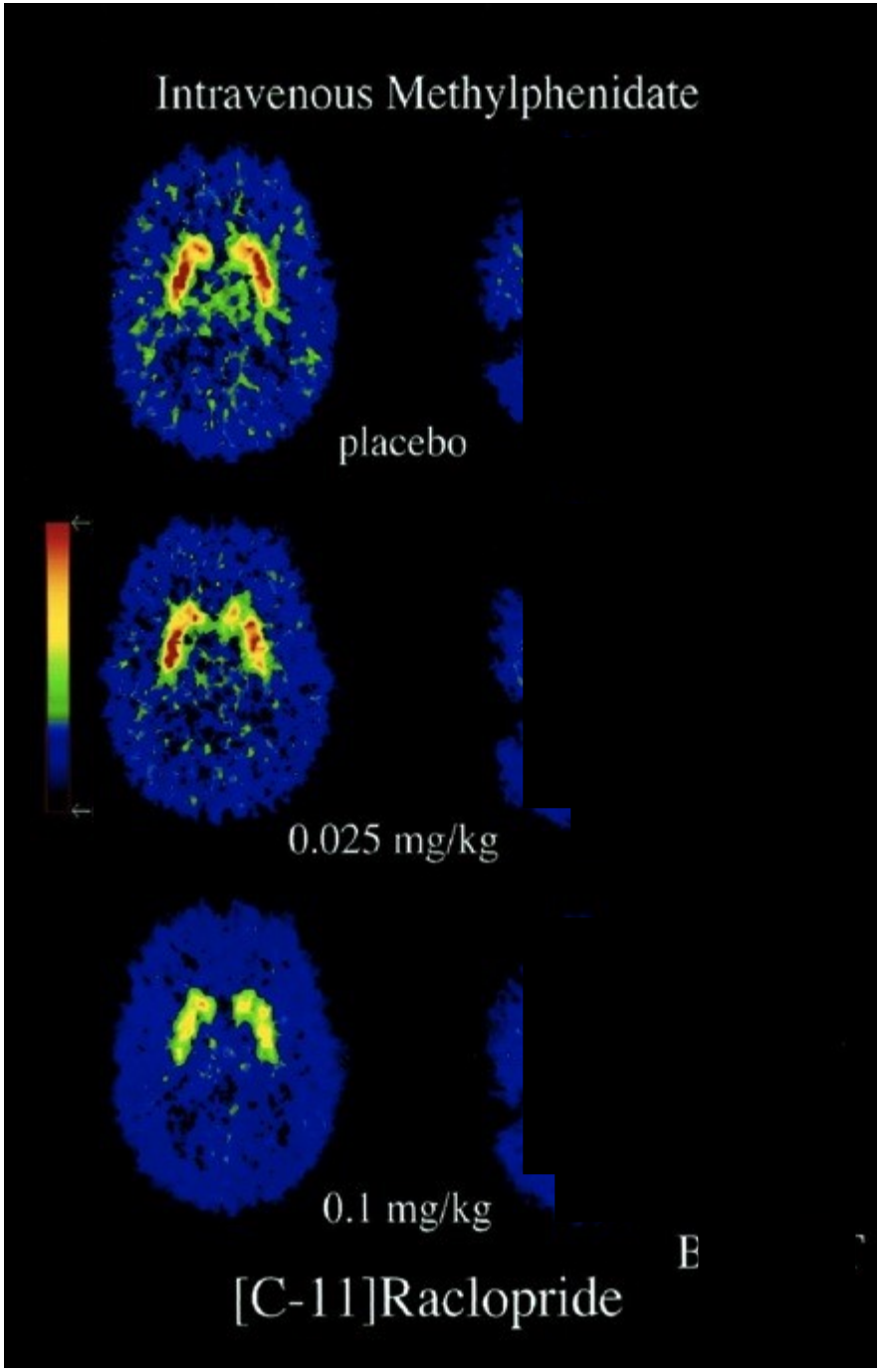
Drug abuse

Movement

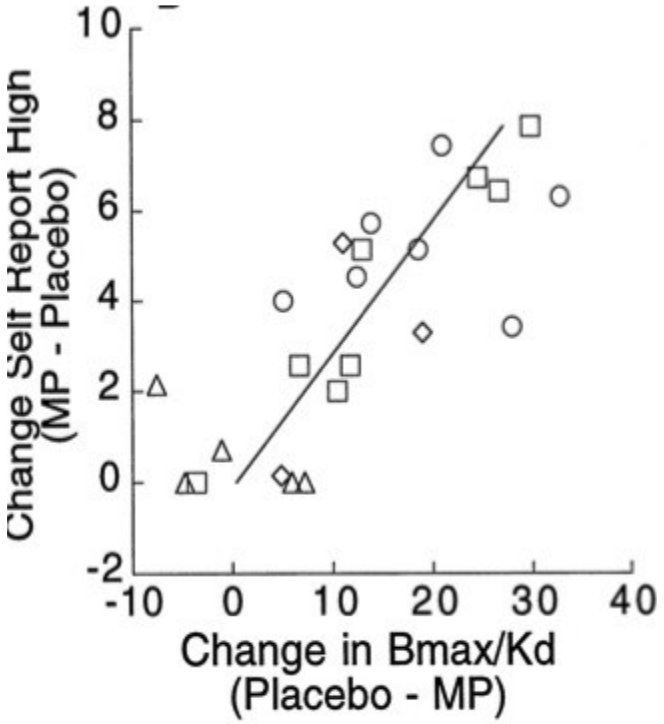
Basal ganglia

(Parkinson's)

Adapted from Stefan et al



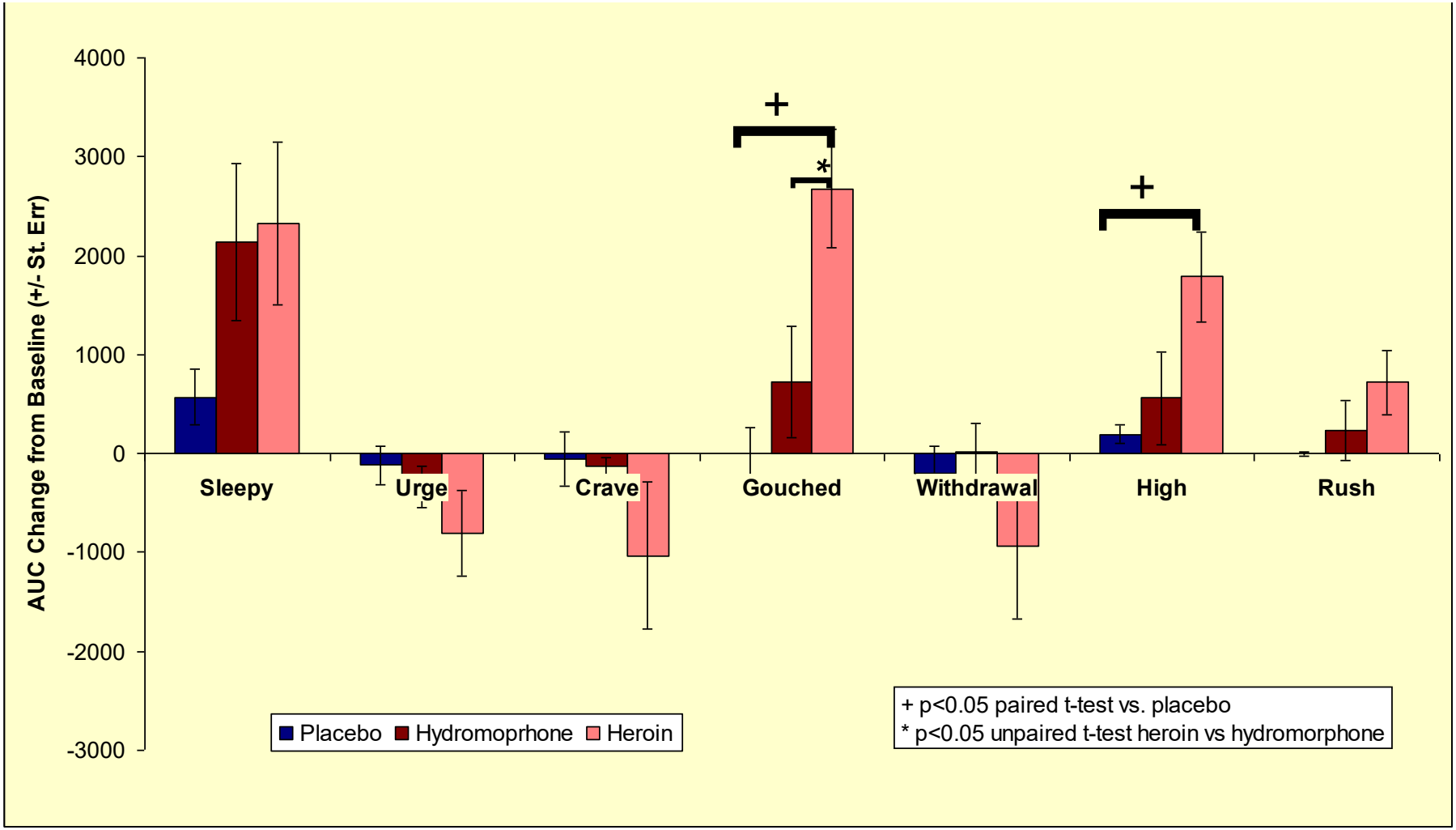
For stimulants dopamine = reward



Volkow et al 1999

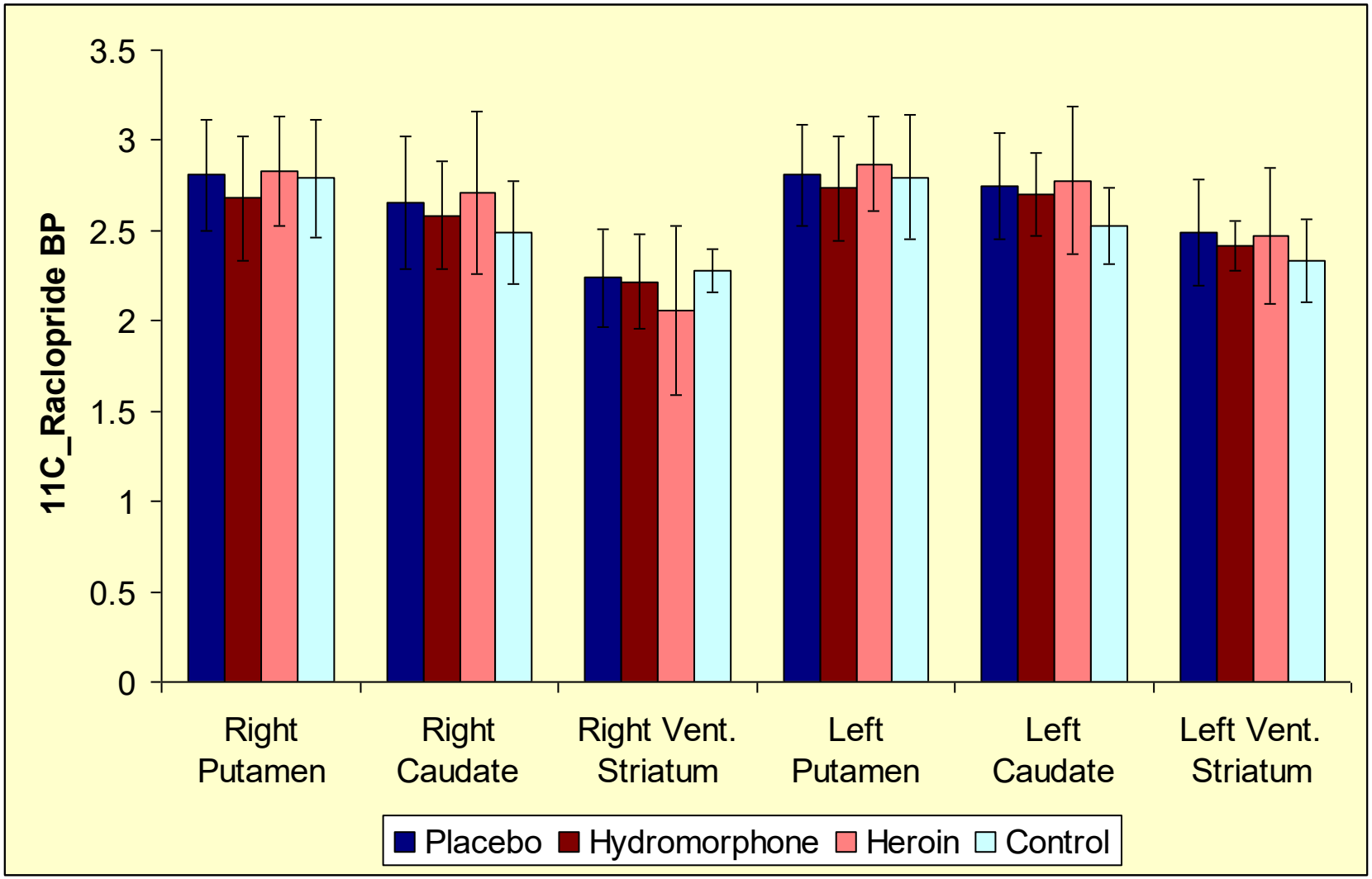
But not all drugs release dopamine

Heroin 50mg i.v. gives a good "high"



Daglish MRC, Williams TM, Wilson SJ, Taylor LG, Eap CB, Augsburger M, Giroud C, Brooks DJ, Myles JS, Grasby P, Lingford-Hughes AR, Nutt DJ [2008] Brain dopamine response in human heroin addiction. Brit J Psychiatry 193: 65-72 PMID: 18700222

But there is NO release of dopamine



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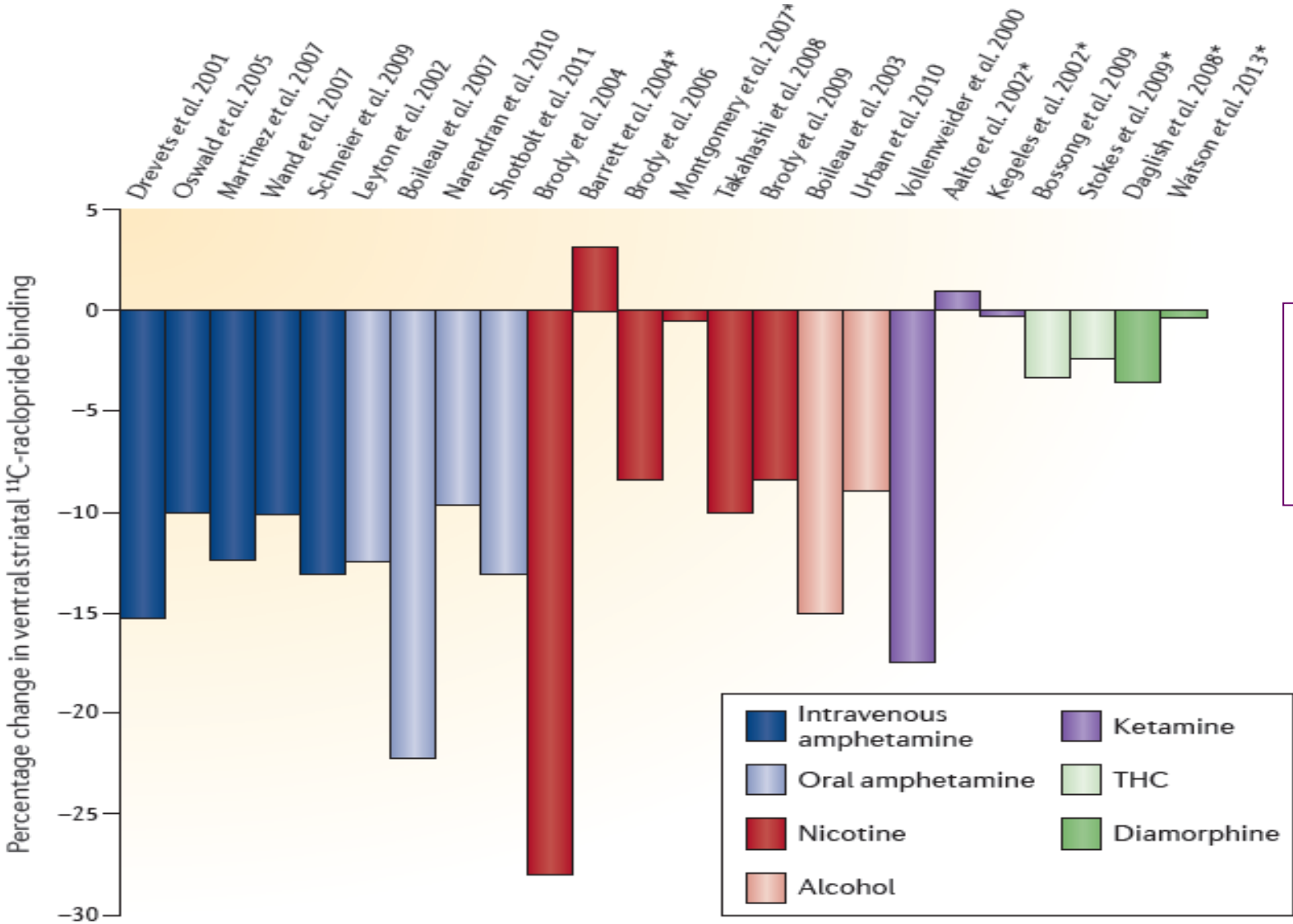
Not all drugs of abuse result in detectable increases in dopamine in man



Nutt et al Nature Reviews Neuroscience 2015

Dopamine and human addiction

What we can be sure of

- Only stimulants reliably release dopamine (Volkow etc)

- Dopamine-rich areas esp n accumbens respond to stimulant drugs + their drug cues and reward - why ?motivation

- Dopamine promoting drugs eg agonists and L-DOPA in Parkinson's can lead to addiction-like compulsive behaviour

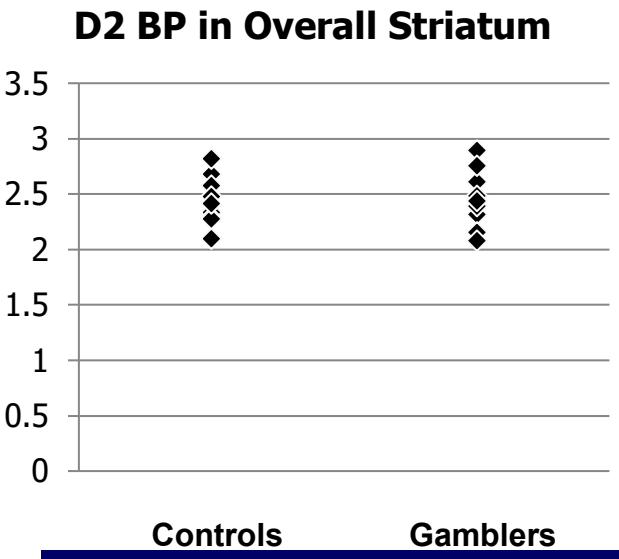
- Dopamine receptor and uptake blockers have disappointingly little therapeutic value

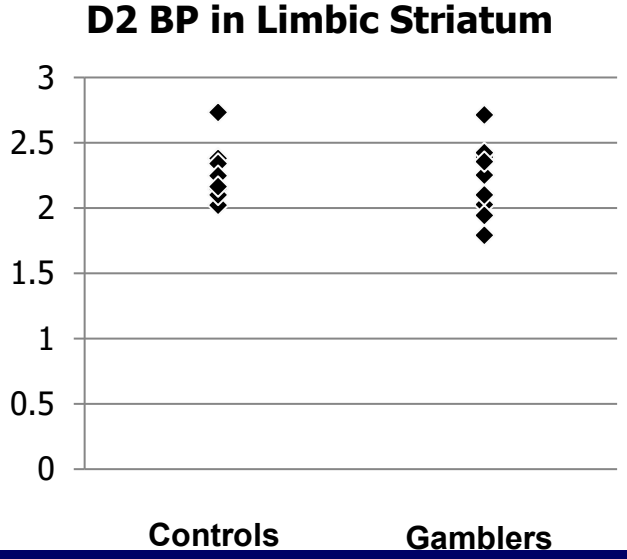
  ➔ exception = bupropion (Zyban) in smoking

Dopamine and addiction- other roles?

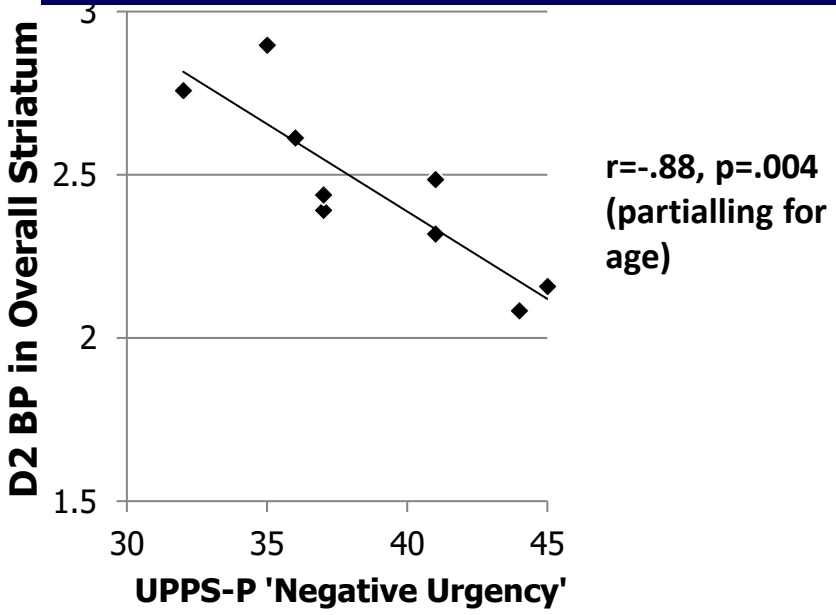
So – dopamine for reward? – no
or anticipation? – no
or habit? - probably
or impulsivity/compulsivity? - maybe

Or something else
? urges/motivation/excitement/mood
? psychotic experiences

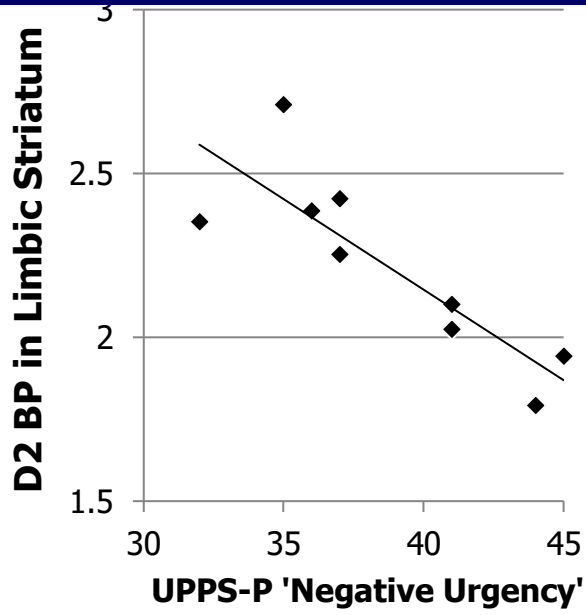




No change in DRD2 binding but lower receptor number predicts "urges"



r=-.88, p=.004 (partialling for age)



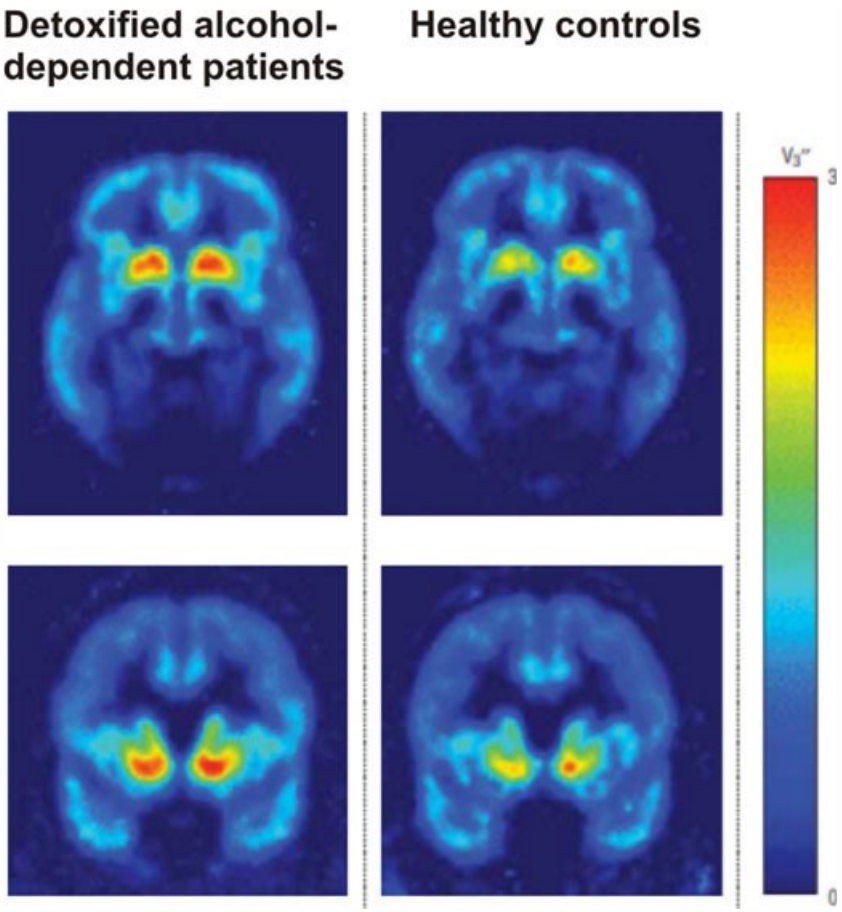
r=-.87, p=.005 (partialling for age)

Imaging opioid receptors in addiction

Density of brain receptors in relation to symptoms

Measuring endorphin release

Increased mu opioid receptors in alcoholism and correlation with craving



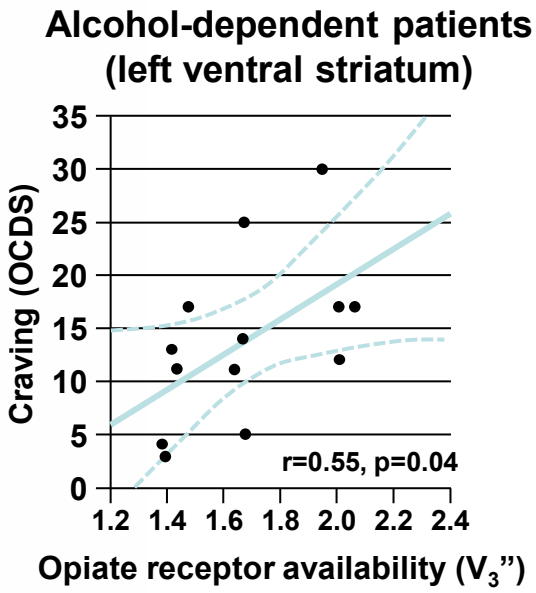
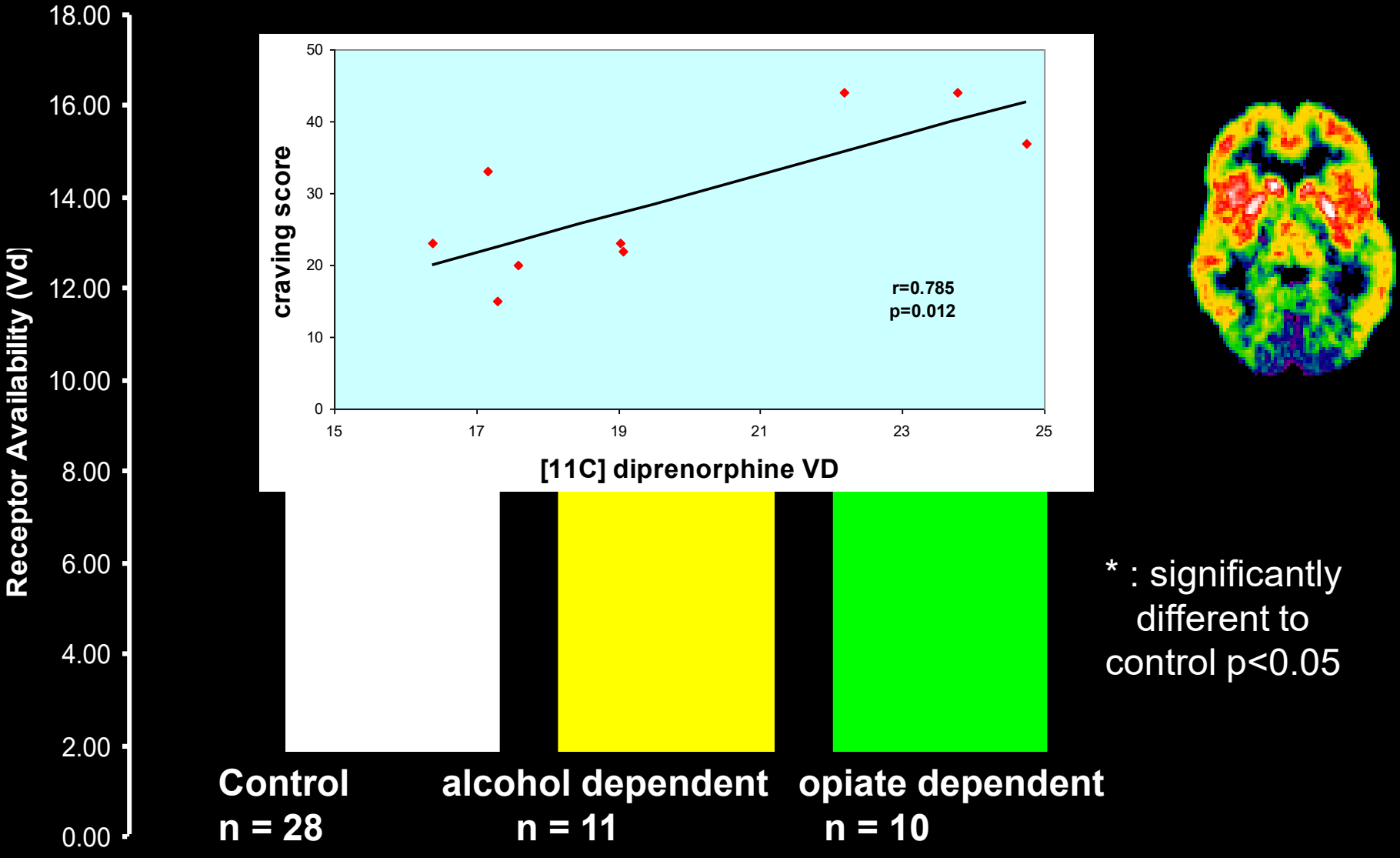


Fig. 4. Results of a [11C] Carfentanil PET study in detoxified alcohol-dependent patients. Availability of μ-Opiate-receptors in the ventral striatum of alcohol-dependent patients (left-hand side) was significantly elevated compared to healthy controls (right-hand side) and remained elevated during 6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

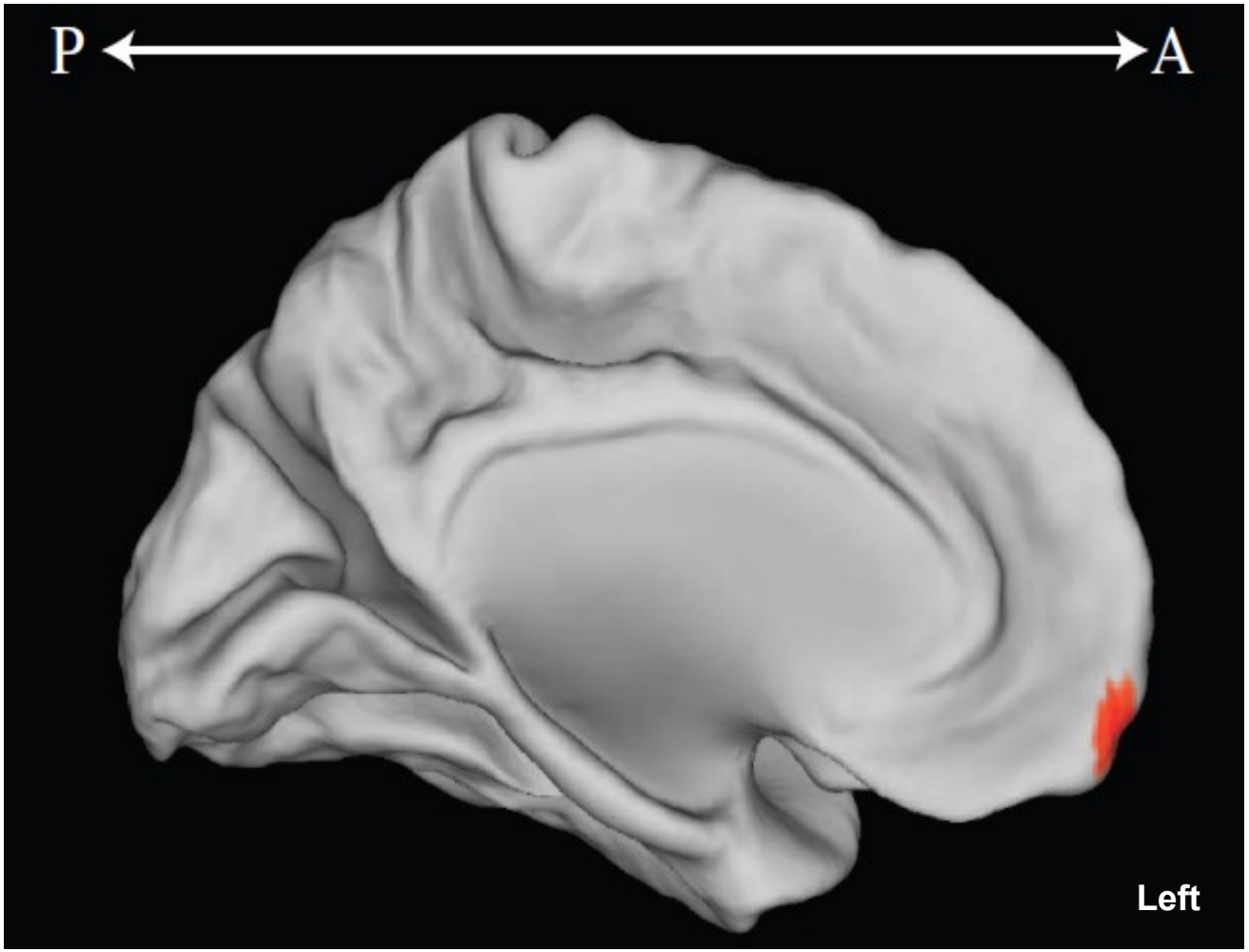
Increase in opiate receptor availability in the brain in early abstinence from alcohol and opiates.



* : significantly different to control $p<0.05$

Bristol studies Williams et al Brit J Psychiatry 2007

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

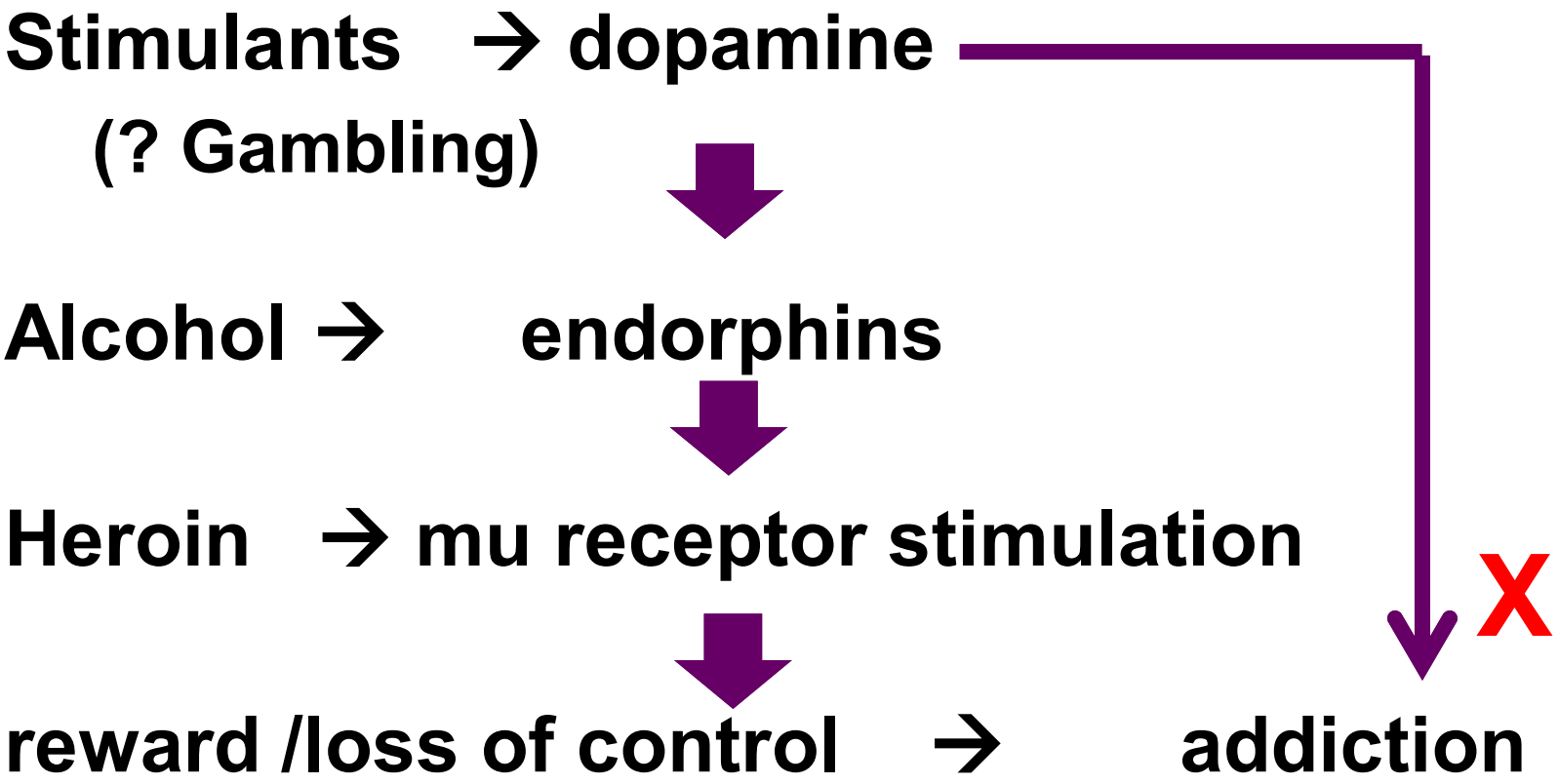


In non-dependent alcohol drinkers following alcohol consumption (~24 g)

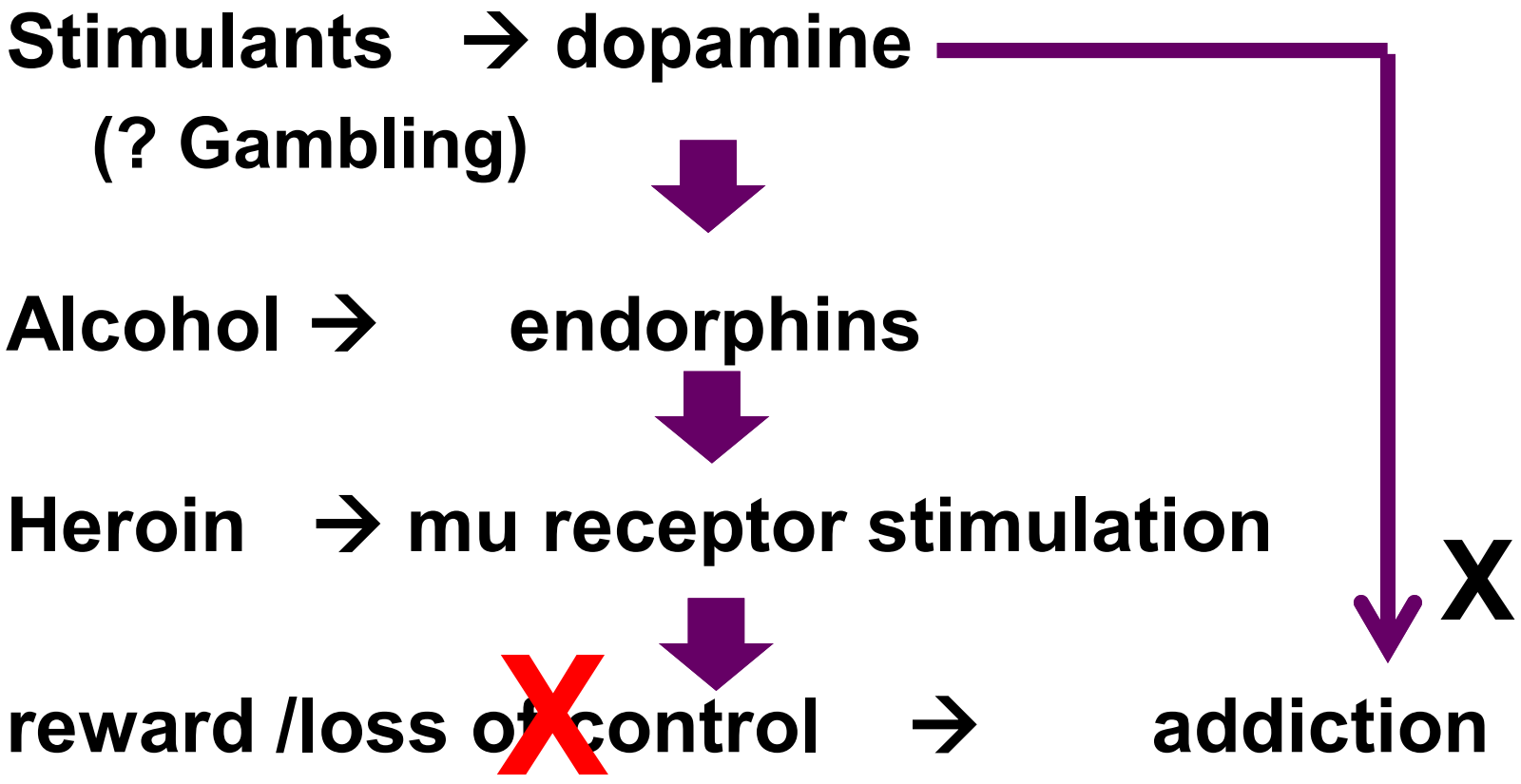
p<0.001; n=25;
P=posterior; A=anterior

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

Endorphins theory of addiction

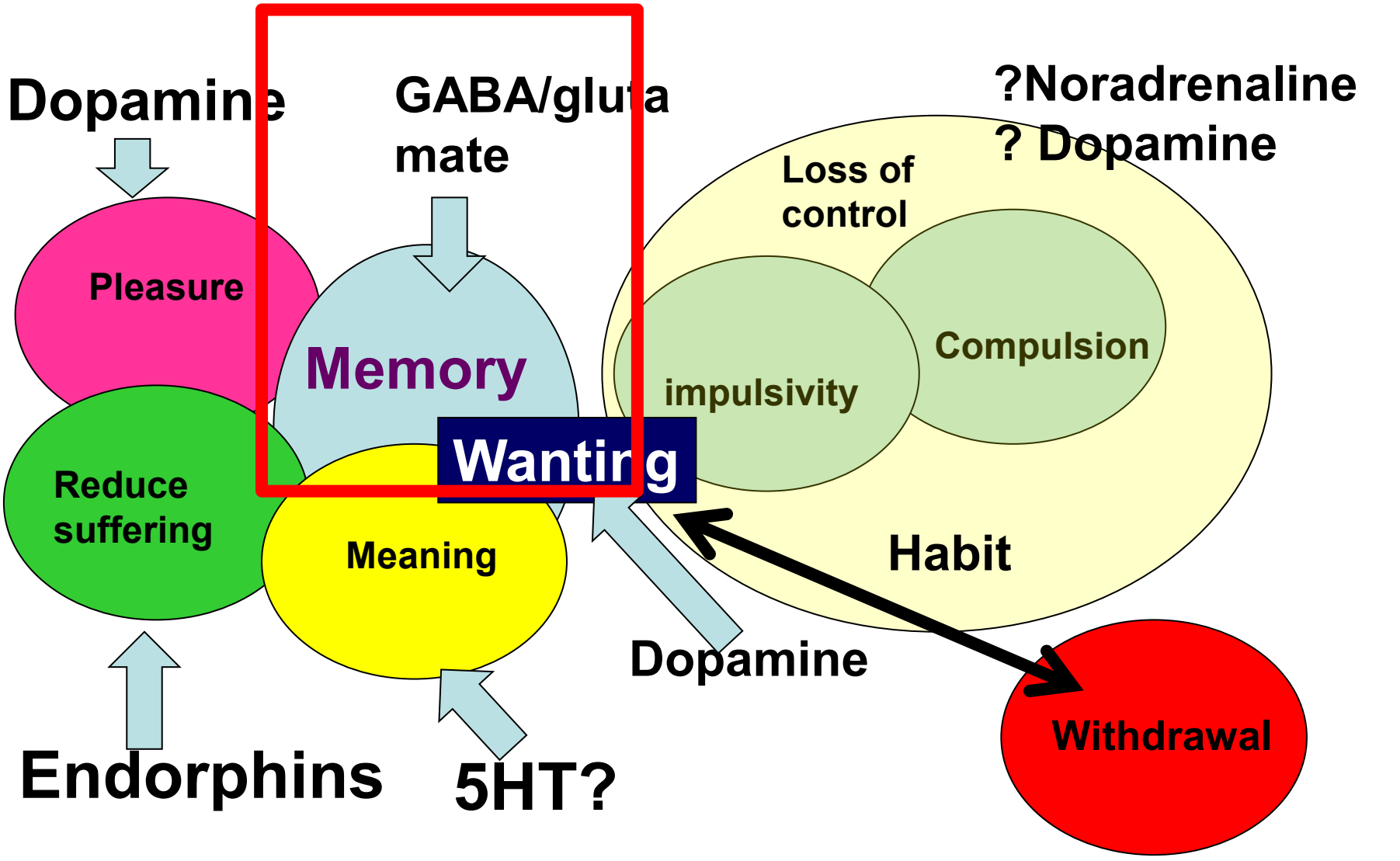


Endorphins theory of addiction



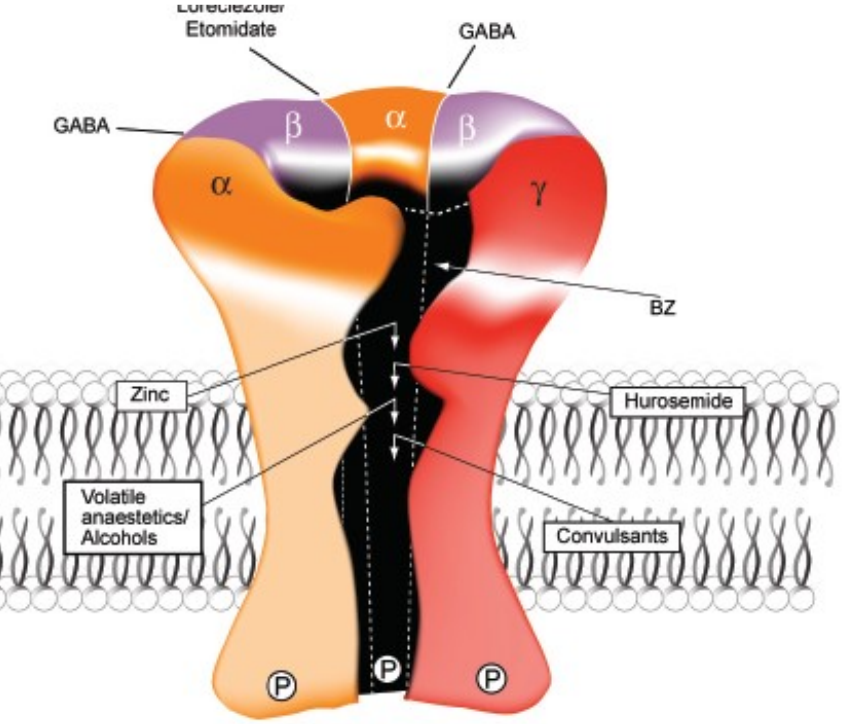
Nalmefene and naltrexone block this in alcoholism

Memory neurotransmitters

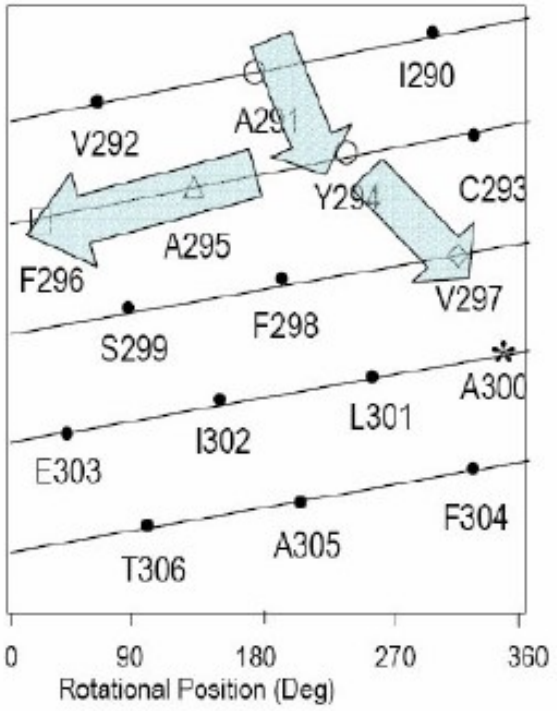


GABA

- Major inhibitory neurotransmitter in brain
- Receptors are target for alcohol, benzodiazepines, GHB, other sedatives

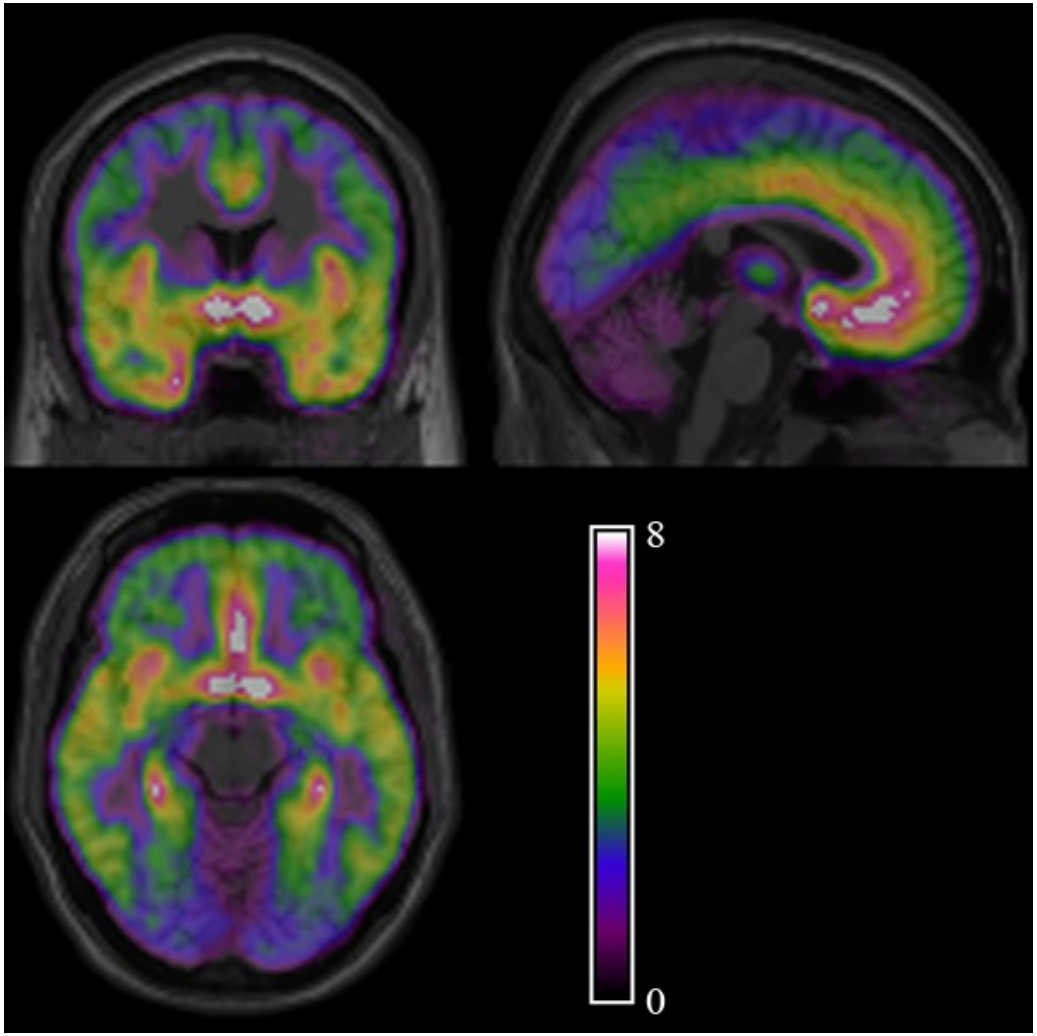


Molecular site of alcohol action is known – in 3rd transmembrane region



Jung and Harris 2006 J Neurochem

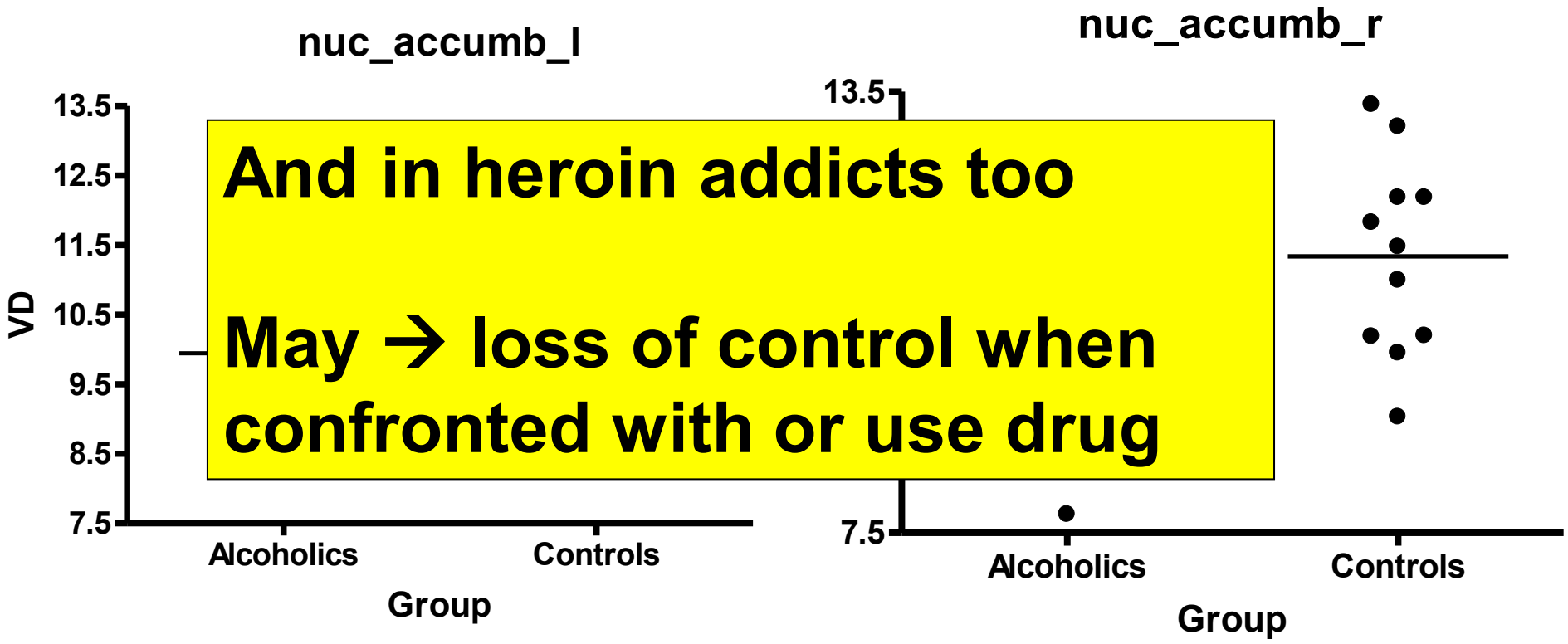
Imaging human - α5 GABA-A receptors
^{11}C-Ro 15-4513 - a selective tracer



Note – not in the rat accumbens where is α2

Lingford-Hughes et al 2002 J Cereb Blood Flow Metab

^{11}C-Ro15 4513 binding in n accumbens reduced in alcoholics



And in heroin addicts too

May → loss of control when confronted with or use drug

L Nuc Accumbens
t = 4.18; p < 0.01

R Nuc Accumbens
t = 4.23; p < 0.01

Lingford-Hughes et al 2011 Journal of Psychopharmacology

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

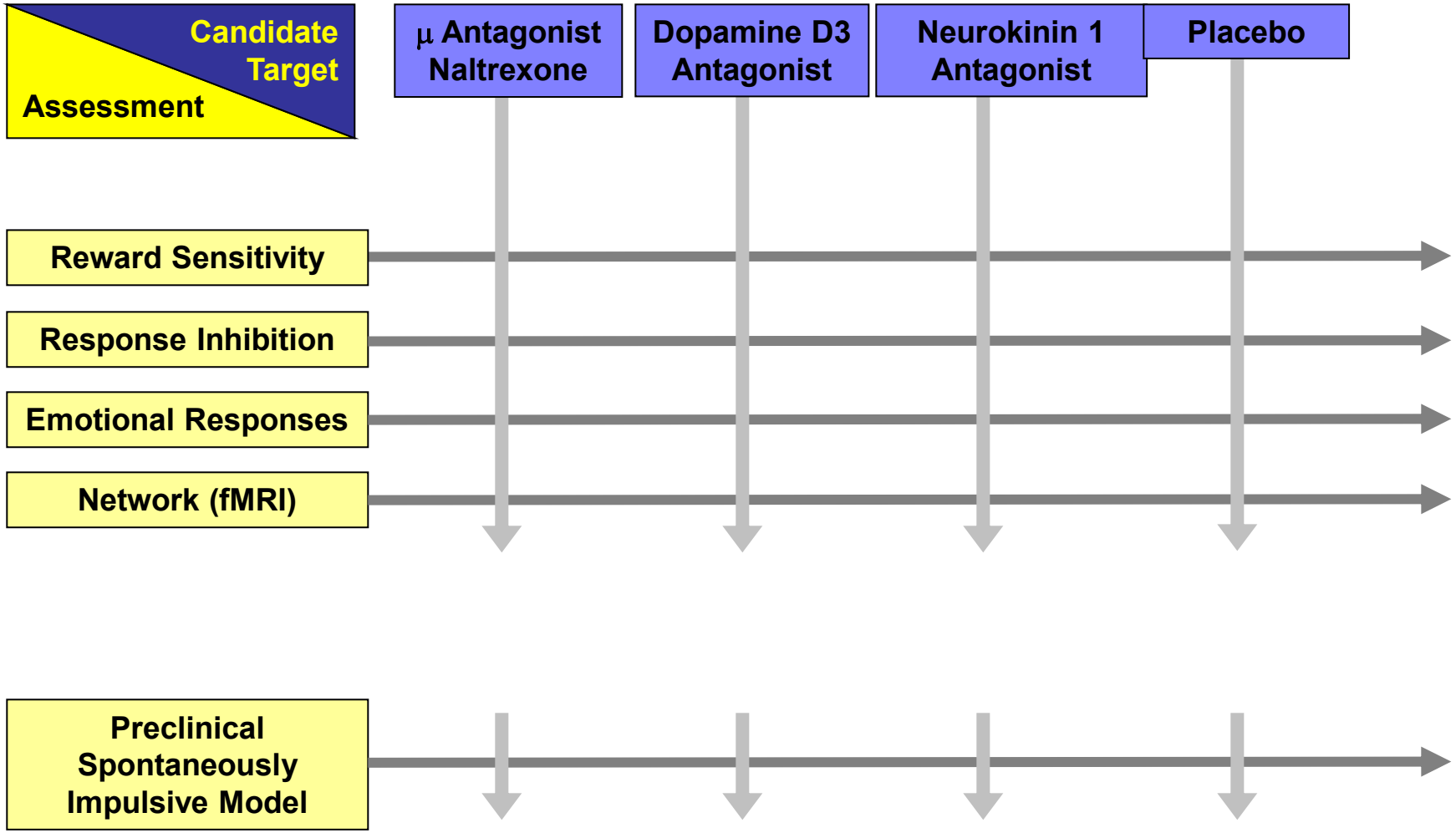
imanova Centre for Imaging Sciences

gsk GlaxoSmithKline

Mental Health Research Network

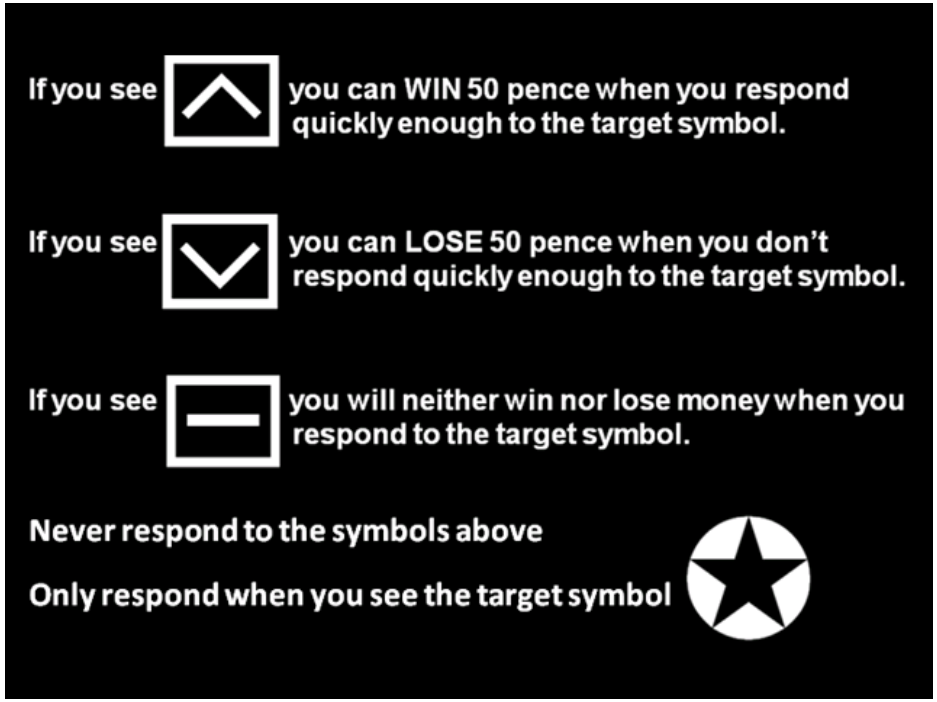
NHS National Institute for Health Research

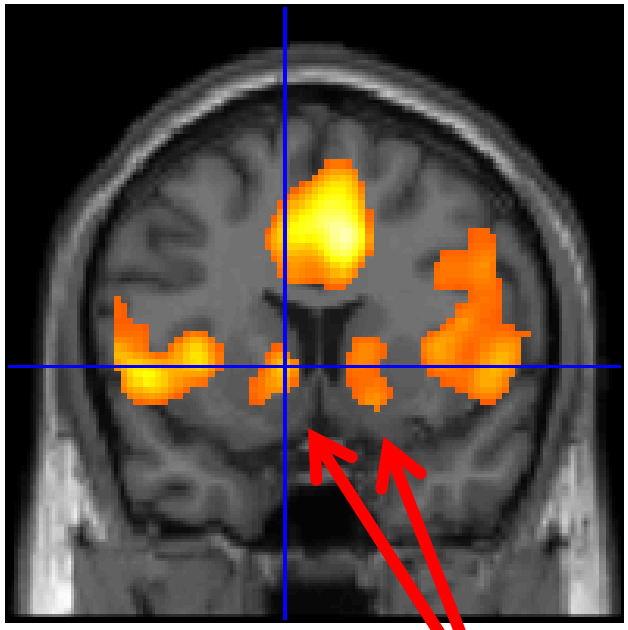
ICCAM Platform – Mechanisms of Relapse

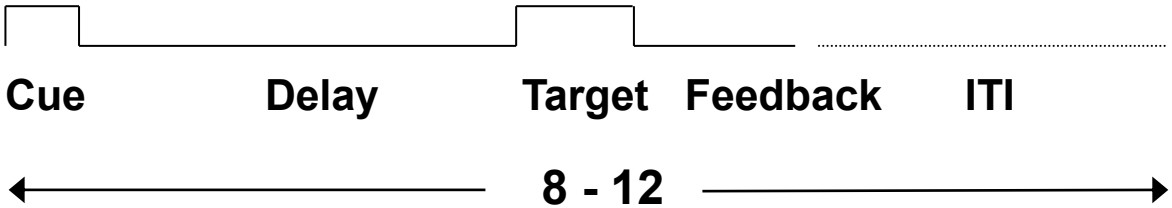


Paterson et al 2015 Journal of Psychopharmacology

Anticipation of reward
Monetary Incentive delay task



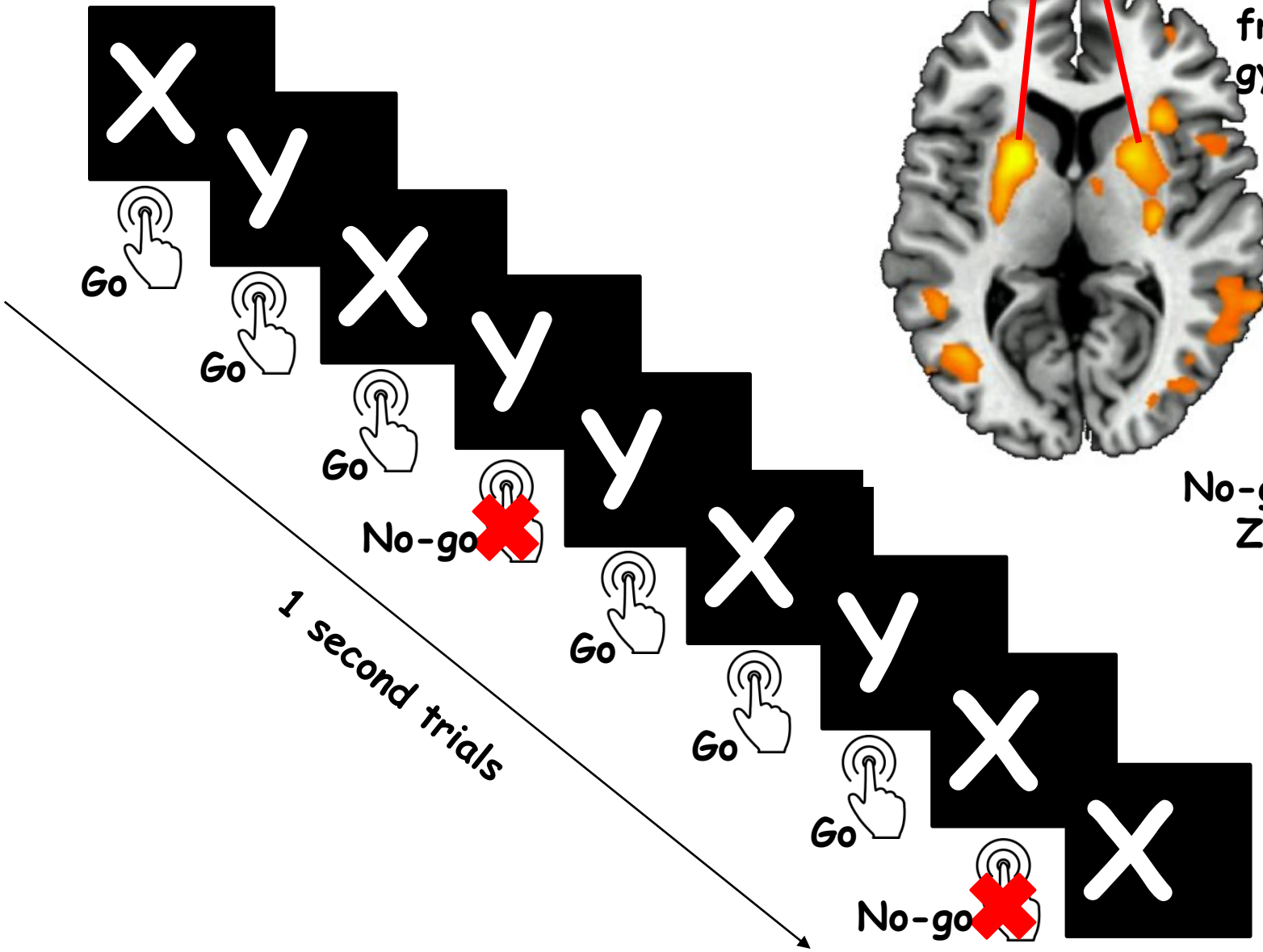


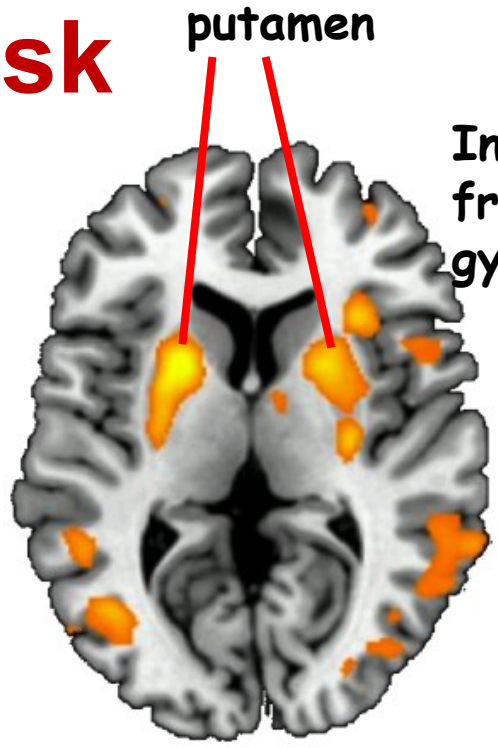


ventral striatum

Reward > neutral
Z > 4

Impulsivity: Go/No-go Task





No-go > go
Z > 5

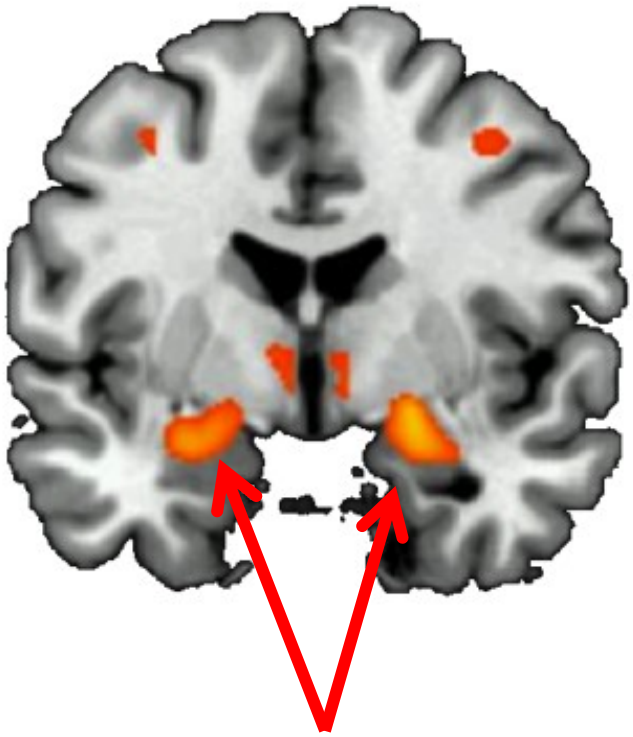
Emotional processing task

Selected neutral and aversive images from IAPS

- did not choose any images with alcohol/drug

Neutral

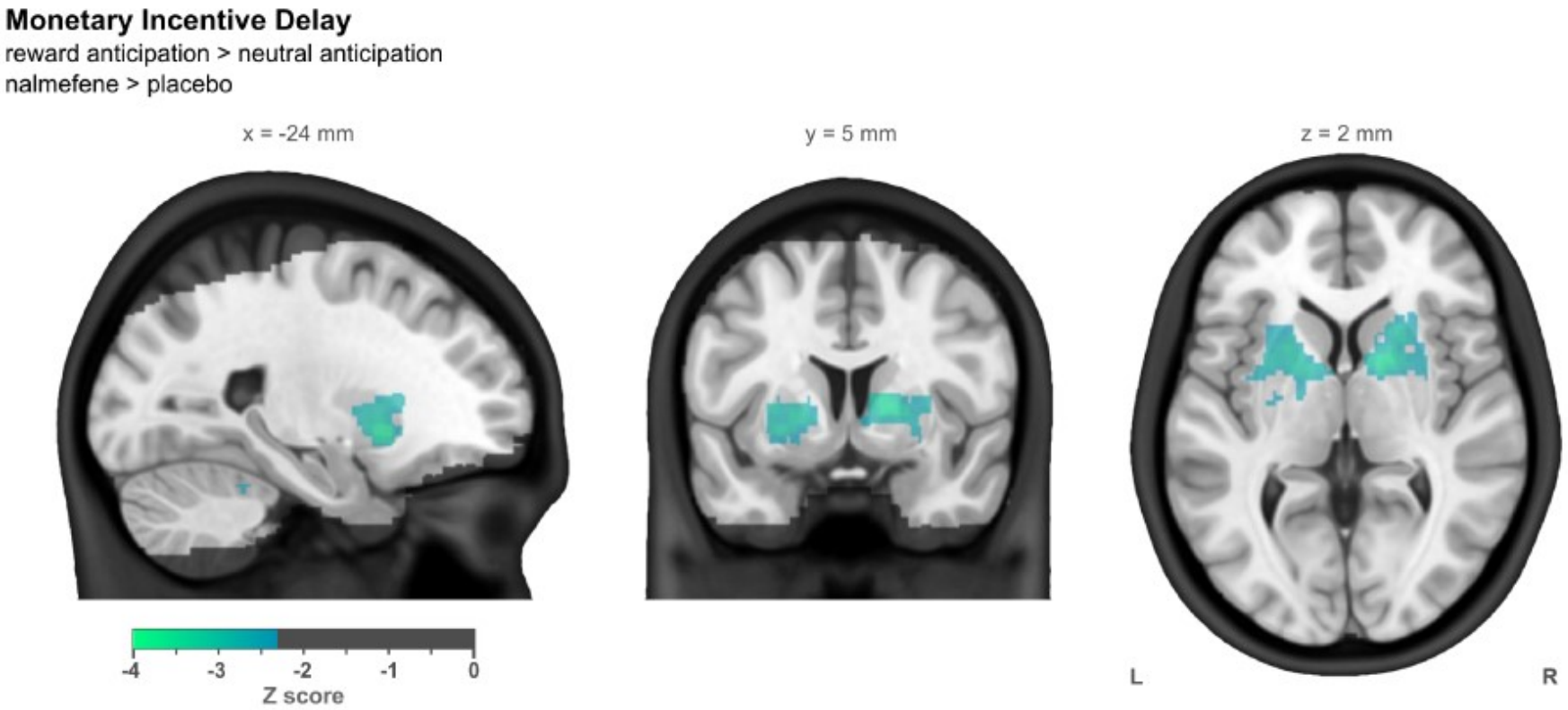
Aversive



amygdala

Aversive > neutral
Z > 4

Nalmefene and MID task during alcohol intoxication fMRI



Significant decrease in globus pallidus and putamen and in brain stem

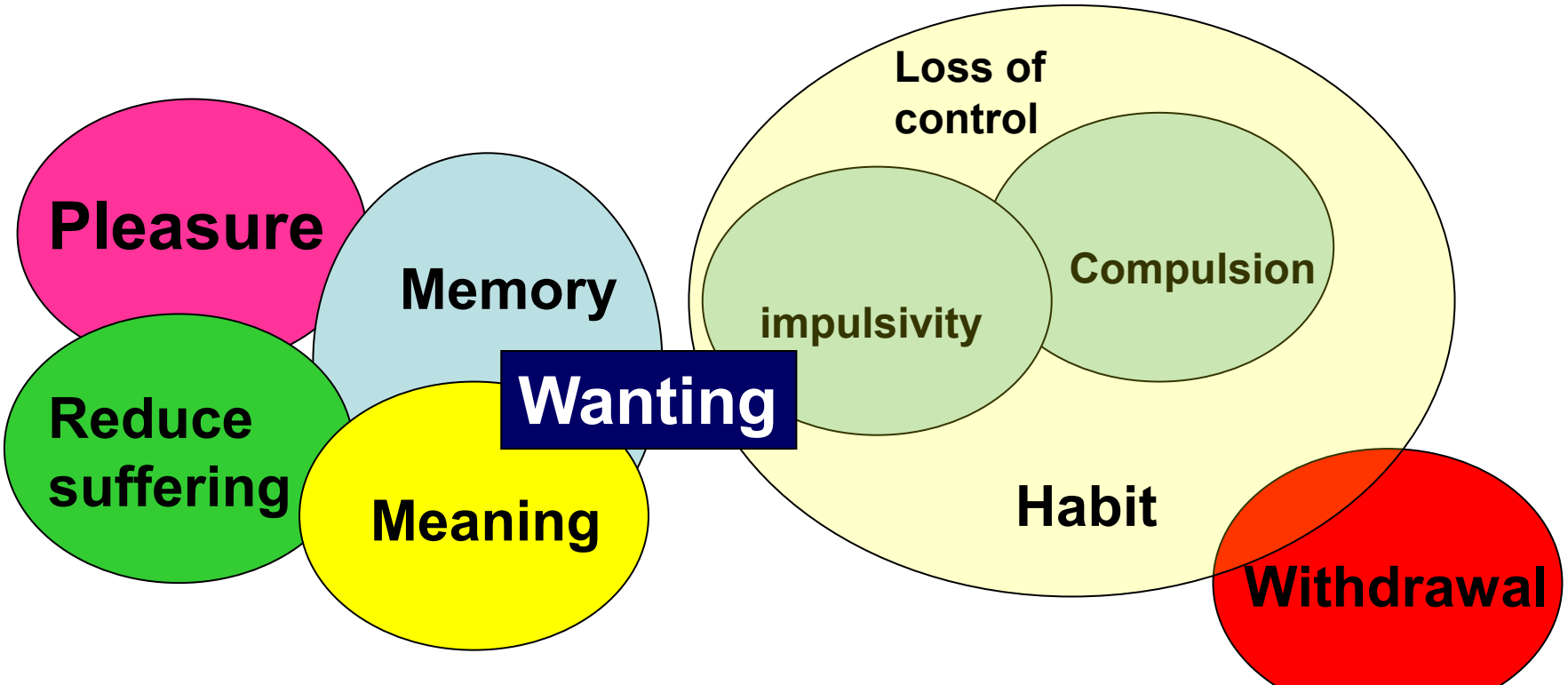
Nutt and Lingford-Hughes – in prepn

Addiction is a complex, multifaceted and enduring state

Different elements with different behavioural and molecular mechanisms

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

Personalised treatment may be the best way forward



Thanks and questions

Further reading

All proceeds to DrugScience.org.uk

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