

# Introduction to substance use and addiction

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# Learning objectives.

- To understand what is substance use, harmful use and dependence/addiction
- To be aware of different models of addiction
- To understand how alcohol/drugs may impact on the brain's function and neurochemistry

Figure 1: The alcohol-specific death rate for 2020 was 18.6% higher than the previous year

Age-standardised alcohol-specific death rates per 100,000 people, by sex; UK, deaths registered between 2001 and 2020

Alcohol related deaths are rising.

Many from alcoholic liver disease

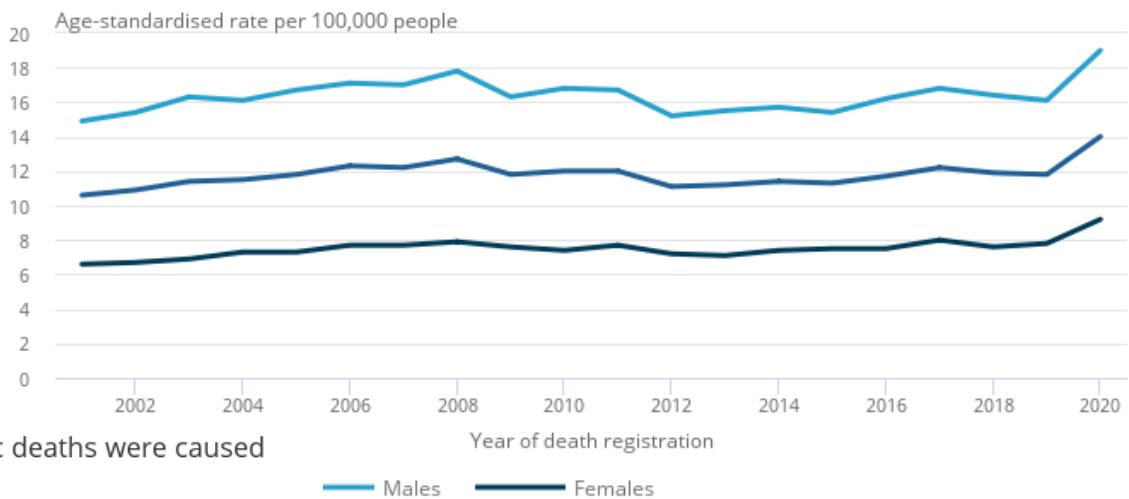
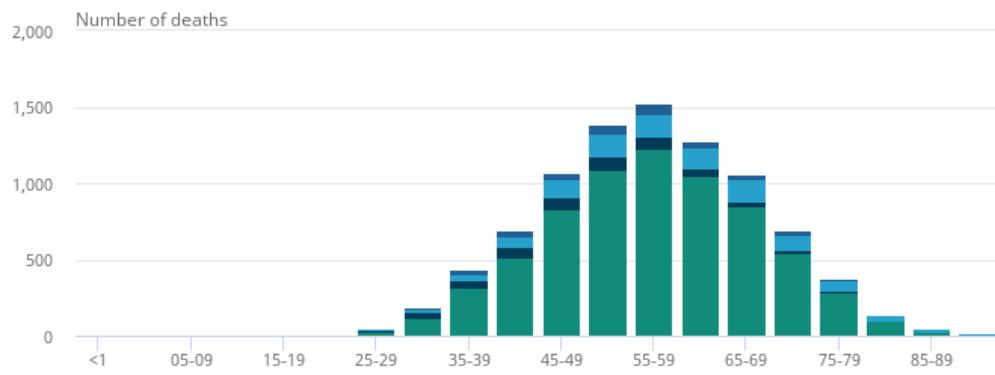


Figure 2: More than three-quarters of alcohol-specific deaths were caused by alcoholic liver disease

Numbers of alcohol-specific deaths, by five-year age group and individual cause; UK, deaths registered in 2020



- All other alcohol-specific causes
- Mental and behavioural disorders due to the use of alcohol
- External causes
- Alcoholic liver disease

Liver mortality rates in England have increased 43% between 2001 and 2019,  
liver disease is now the second leading disease causing premature death among people of working age

Source: Office for National Statistics - Alcohol-specific deaths in the UK: registered in 2020, National Records of Scotland and Northern Ireland Statistics and Research Agency

# Age-specific mortality rates for deaths related to drug misuse, by age group, England and Wales, registered between 1993 to 2020

Deaths per million people

over 110  
90 to 109  
80 to 89  
70 to 79  
50 to 69  
40 to 49  
30 to 39  
3.4 to 29

1993 |

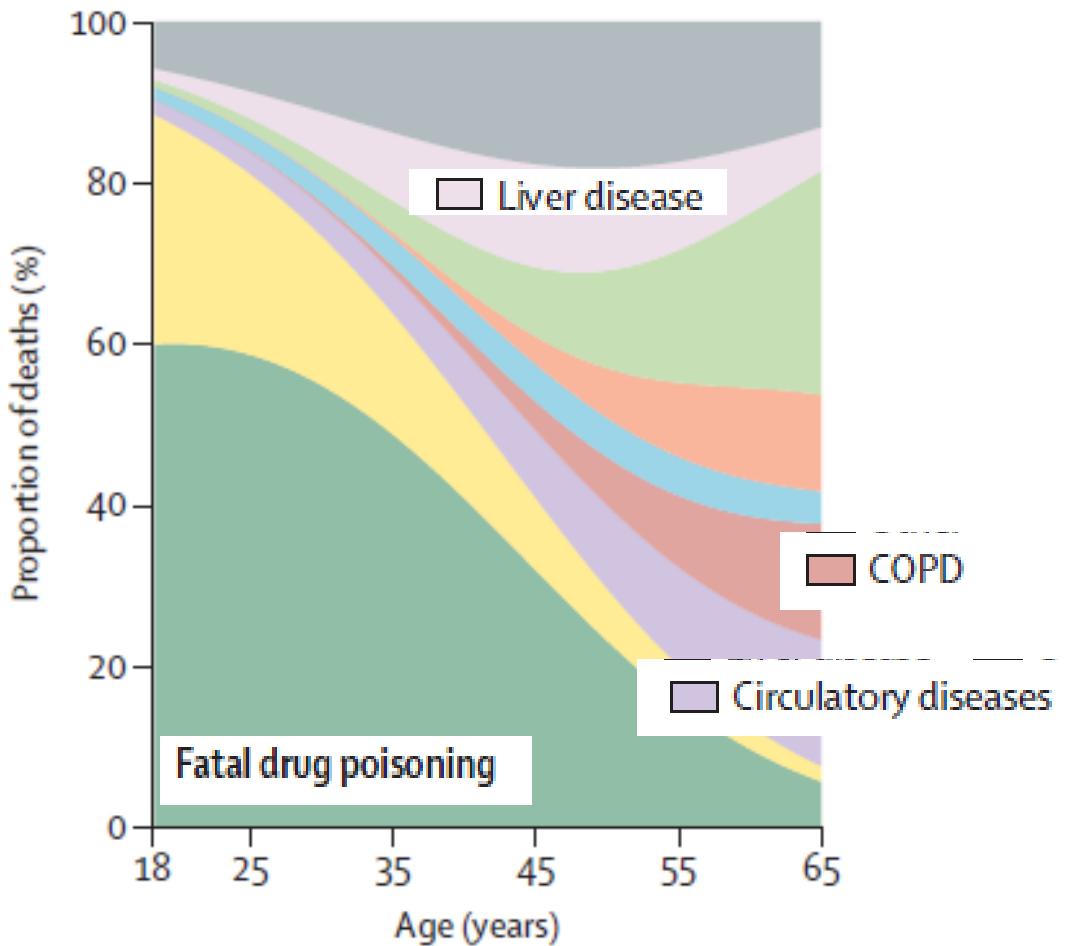
2020 |

15 to 19  
20 to 24  
25 to 29  
30 to 34  
35 to 39  
40 to 44  
45 to 49  
50 to 54  
55 to 59  
60 to 64  
65 to 69  
70 to 74  
75 to 79  
80 to 84  
85+

Increasing  
rates in  
older  
individuals

- Role of chronic opioid exposure to methadone?
  - Immunosuppressant, respiratory depressant

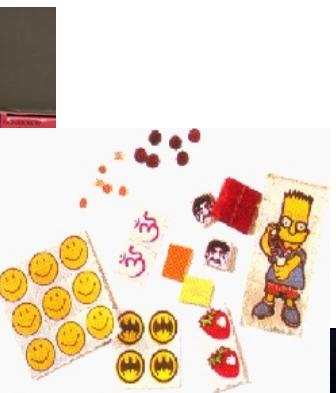
Cause-specific mortality rates by age, among participants with a history of using illicit opioids, standardised for calendar time period, duration after cohort entry, and sex



#### Underlying cause of death

- Other
- Liver disease
- Other cancers
- Respiratory cancers
- Other respiratory diseases
- COPD
- Circulatory diseases
- External causes
- Fatal drug poisoning

What is a drug of abuse?



Why take a recreational drug?

# Course of alcohol/drug use, harmful use, addiction

Experimental/'recreational' use:  
causing no/limited difficulties  
(majority of population)

Why take a 'recreational' drug?

Reduce anxiety

Get high

Boredom

Stay awake

To fit in

Rebel

Escapism

Like it

To get to sleep

Why not?

Feel better

Everyone does

Curious

# Course of alcohol/drug use, harmful use, addiction

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Curious

# Positive reinforcement:

"gain positive state"

Escapism

Get high

Stay awake

Like it

Good

'normal'

Boredom

To get to sleep

Bad

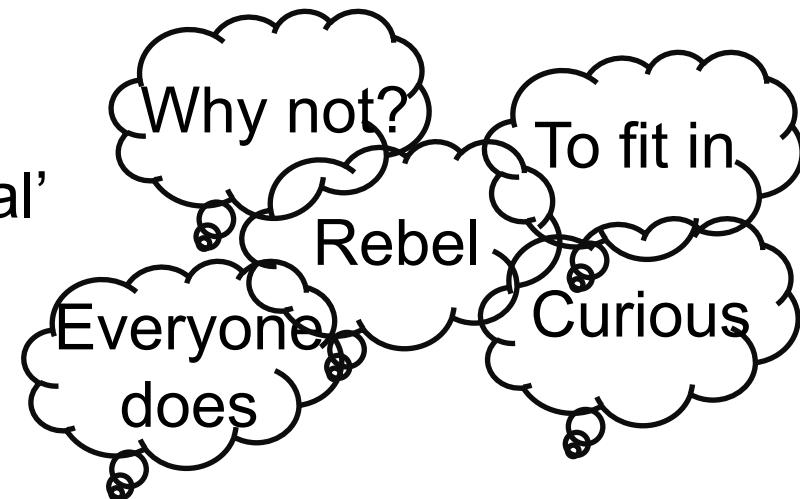
Reduce anxiety

Feel better

Negative reinforcement:  
'overcome adverse state'

# Why do you need to know?

- Informs treatment



# Course of alcohol/drug use, harmful use, addiction

Experimental/'recreational' use,  
causes no/limited difficulties  
(majority of population)

'like'

↳ 'want'

↳ 'need'

Increasingly  
regular use  
(fewer people)

harmful

Increasing problems

# Harmful Substance use

## ICD 11 criteria

A pattern of alcohol/drug use that has caused damage to a person's physical or mental health or has resulted in behaviour leading to harm to the health of others.

The pattern of alcohol/drug use is evident over a period of at least 12 months if substance use is episodic or at least one month if use is continuous.

Harm to health of the individual occurs due to one or more of the following:

- (1) behaviour related to intoxication;
- (2) direct or secondary toxic effects on body organs and systems; or
- (3) a harmful route of administration.

# Course of alcohol/drug use, harmful use, addiction

Experimental/'recreational' use,  
causes no/limited difficulties  
(majority of population)

'like'

↳ 'want'  
↳ 'need'

Increasingly  
regular use  
(fewer people)

harmful

'need'

Spiralling:  
dependence  
(smaller  
number)

Increasing problems

# ICD-11: Dependence syndrome.

- Alcohol/drug dependence is a disorder of regulation of alcohol/drug use arising from repeated or continuous use of alcohol/drug. The characteristic feature is a strong internal drive to use alcohol/drug, which is manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences.

2 of the following:

- *Impaired control over substance use*

- in terms of the onset, level, circumstances or termination of use, often but not necessarily accompanied by a subjective sensation of urge or craving.

- *Substance use becomes an increasing priority in life*

- takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or personal care. Substance use takes an increasingly central role in the person's life and relegates other areas of life to the periphery; continues despite the occurrence of problems.

- *Physiological features (indicative of neuroadaptation to the substance) as manifested by*

- (i) tolerance, (ii) withdrawal symptoms following cessation or reduction in use of that substance or (iii) repeated use of the substance (or pharmacologically similar substance) to prevent or alleviate withdrawal symptoms.

# Addiction vs dependence?

- **Addiction** - compulsive alcohol/drug use despite harmful consequences, characterized by an inability to stop using a drug/alcohol; failure to meet work, social, or family obligations; and, (depending on the drug/alcohol) tolerance and withdrawal.
- In biology/pharmacology, **dependence** refers to a physical adaptation to a substance
  - Tolerance/withdrawal
    - Eg opioid, benzodiazepine, alcohol
  - So can be dependent and not addicted
  - Drug can have withdrawal symptoms and not be addictive eg antidepressants
- NB: Terms are used interchangeably resulting in confusion – so YOU need to be clear when using these terms.

# Behavioural addictions



Roulette

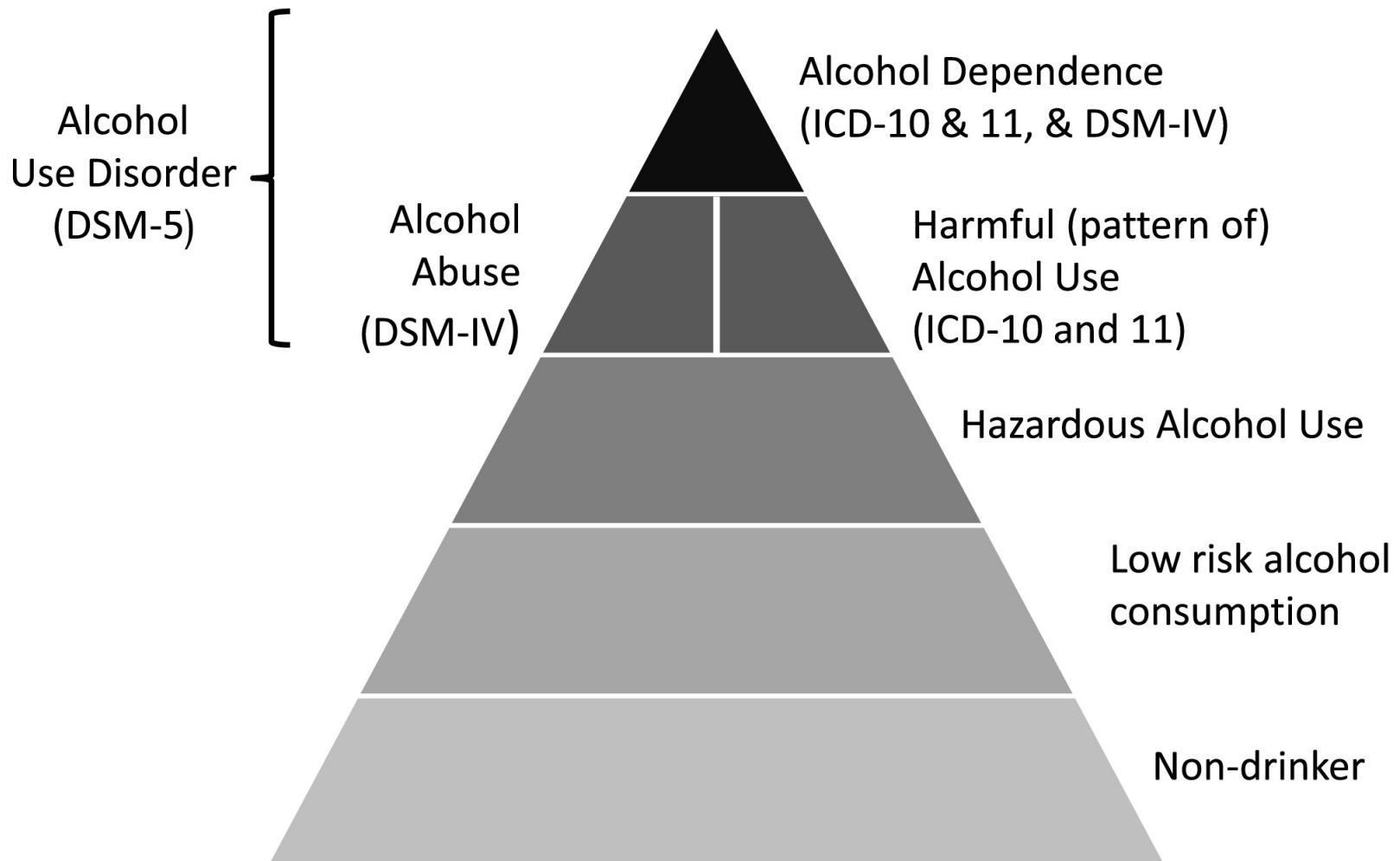
Slots

Sports

Bookmakers

- Gambling disorder
  - Many similarities in aetiology, neurobiology and treatment approaches, as well as comorbidity, with substance dependence
  - Reclassified as behavioural addiction in DSM-5/ICD-11 from an ‘impulse control disorder’ previously.
- Internet gaming disorder
  - added to ICD-11 under addictive disorders
  - in the DSM-5 is under “Conditions for Further Study”

# DSM vs ICD continuum vs separate



## A Comparison Between DSM-IV and DSM-5

DSM-IV		DSM-5	
In the past year, have you:		In the past year, have you:	
<b>Any 1 = ALCOHOL ABUSE</b>	Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?	1	Had times when you ended up drinking more, or longer, than you intended?
	More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	2	More than once wanted to cut down or stop drinking, or tried to, but couldn't?
	More than once gotten arrested, been held at a police station, or had other legal problems because of your drinking?  **This is not included in DSM-5**	3	Spent a lot of time drinking? Or being sick or getting over other aftereffects?
	Continued to drink even though it was causing trouble with your family or friends?	4	Wanted a drink so badly you couldn't think of anything else?  **This is new to DSM-5**
	Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	5	Found that drinking—or being sick from drinking—often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
	Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	6	Continued to drink even though it was causing trouble with your family or friends?
	Had times when you ended up drinking more, or longer, than you intended?	7	Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
	More than once wanted to cut down or stop drinking, or tried to, but couldn't?	8	More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
	Spent a lot of time drinking? Or being sick or getting over other aftereffects?	9	Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
	Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?	10	Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
	Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	11	Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?

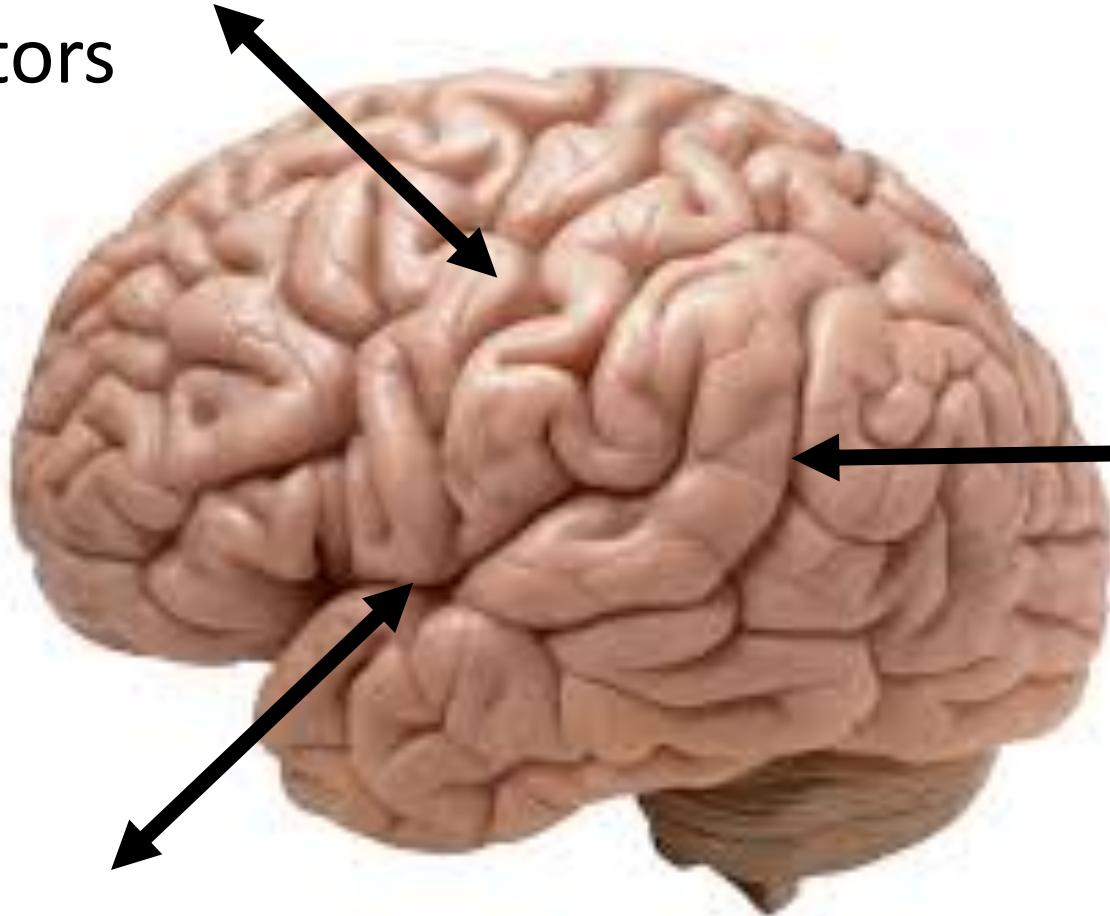
DSM-5 differs from  
DSM-IV:

a continuum  
between abuse  
and dependence

- more individuals  
meet threshold for  
diagnosis now

differs from ICD-11

Social,  
environmental  
factors

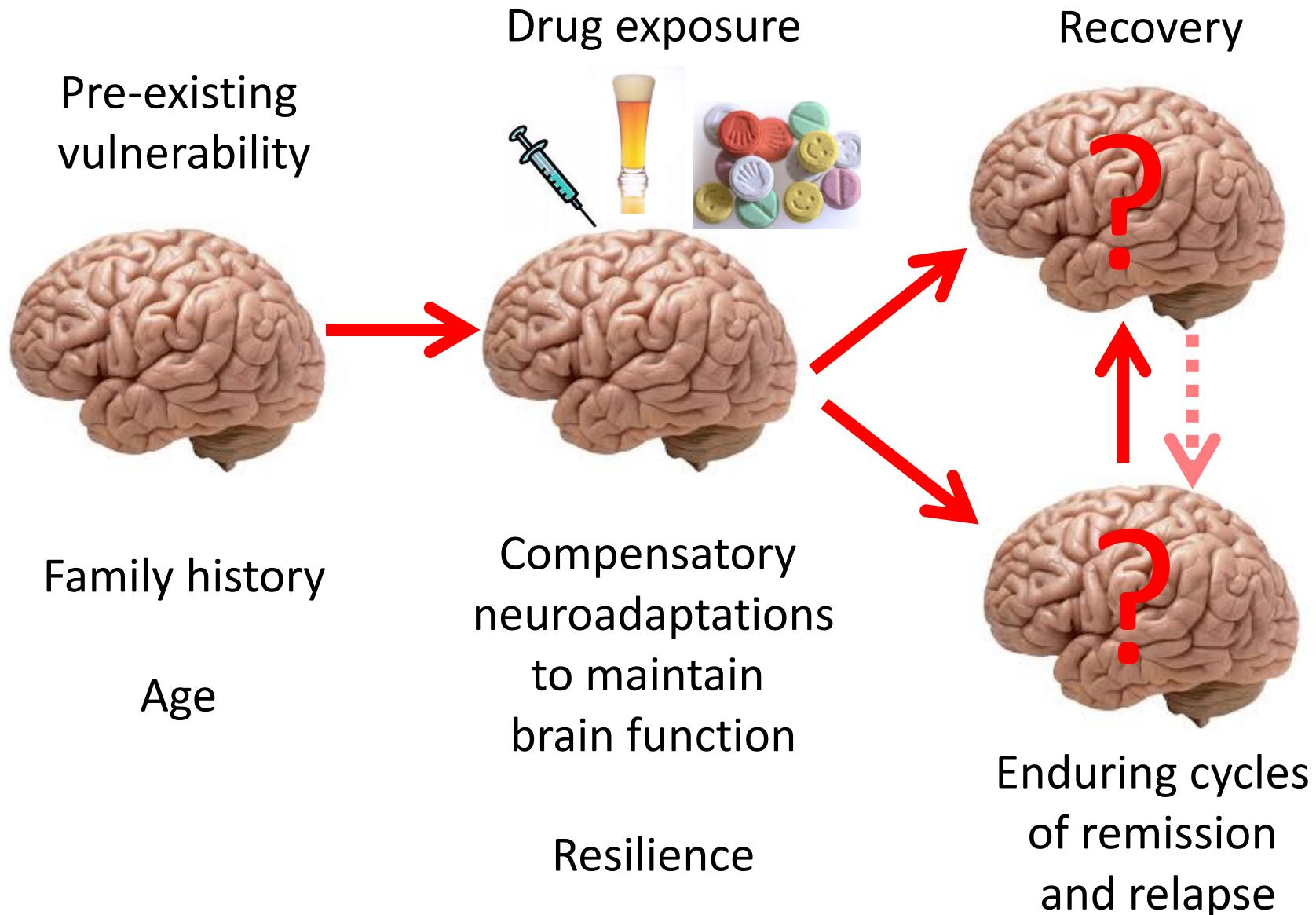


Drug factors

Elements involved in  
alcohol/drug use and  
addiction

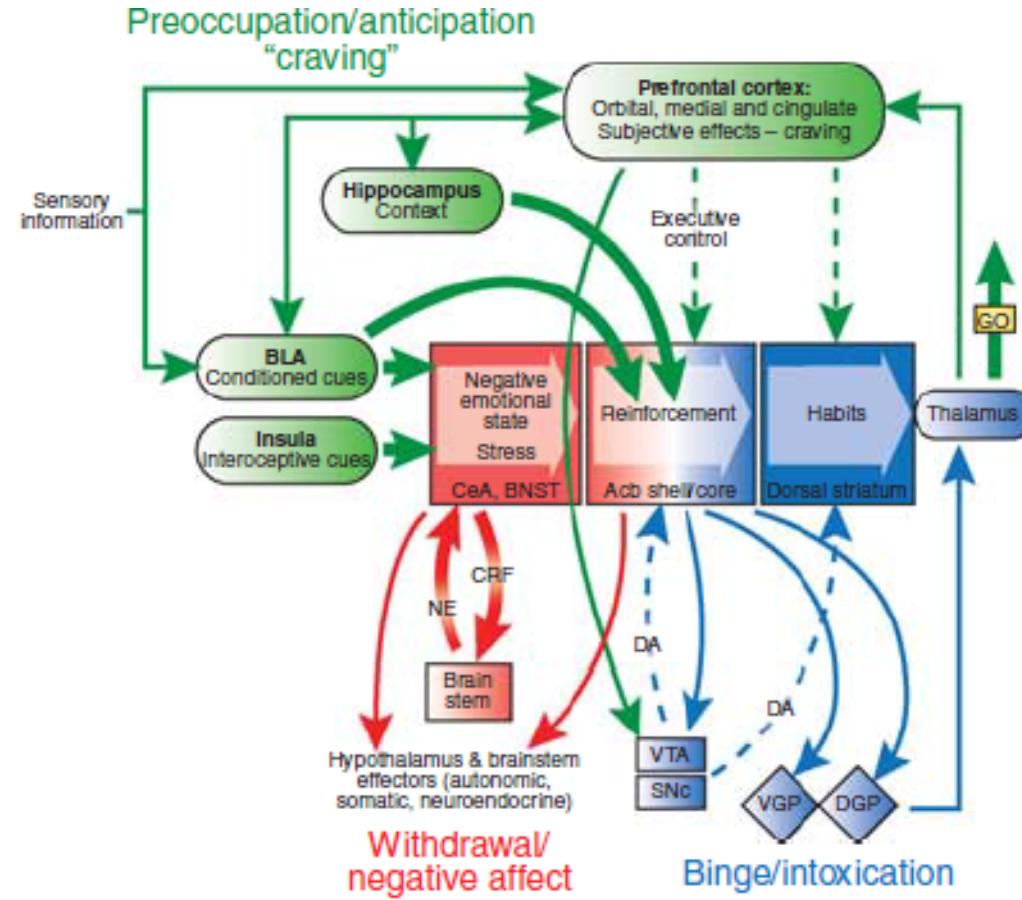
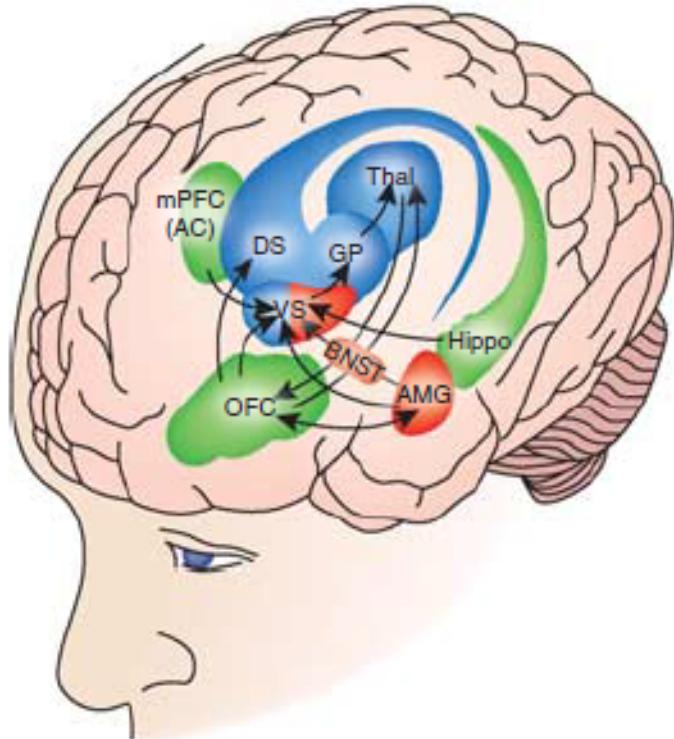
Personal  
factors eg  
genetic,  
personality  
traits eg  
impulsivity

# The brain in addiction:



# Regions of brain involved in different stages:

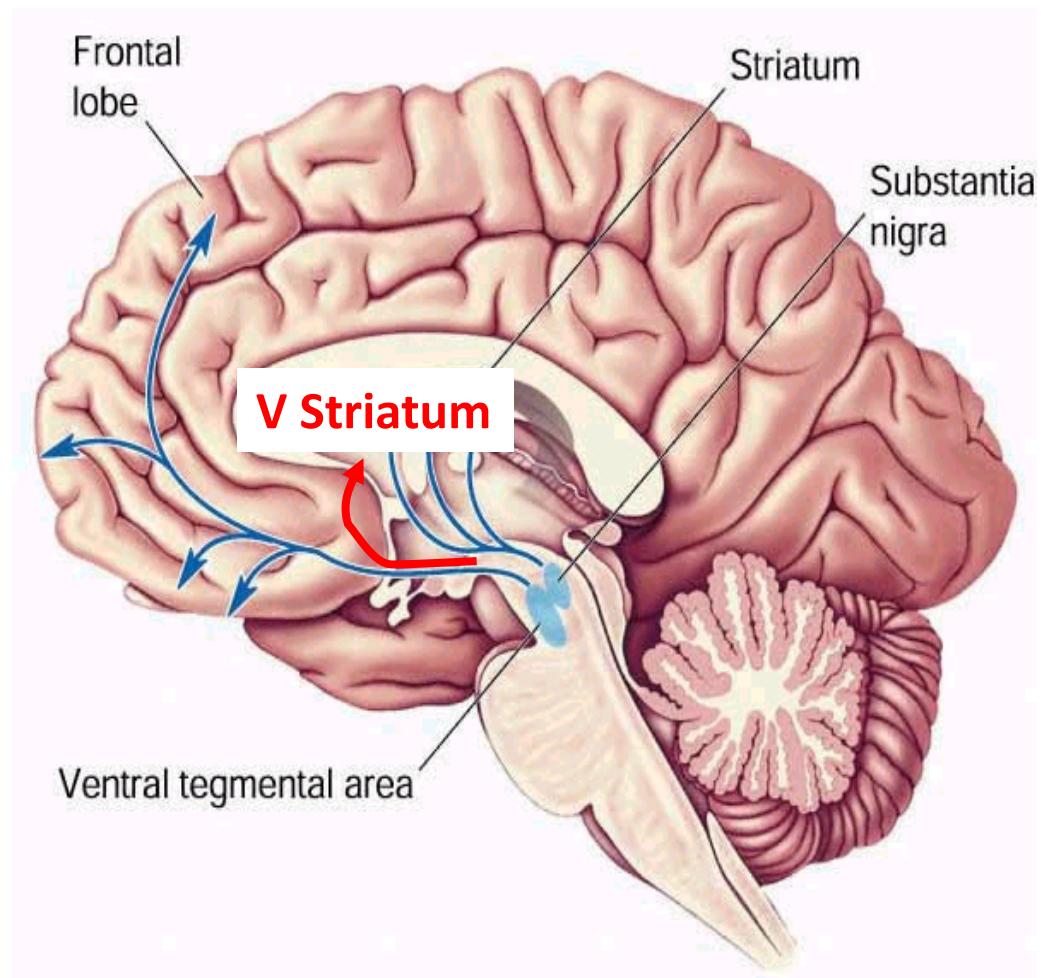
- binge/intoxication: striatum
- withdrawal/negative affect: extended amygdala
- preoccupation/anticipation ‘craving’: prefrontal cortex



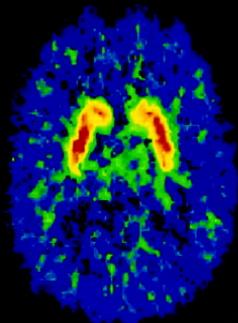
Koob, Volkow

# Natural rewards such as food, sex increase dopamine in ventral striatum: mesolimbic system

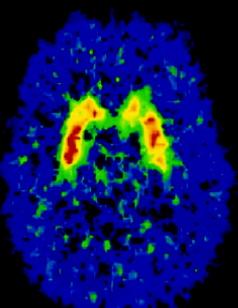
- Drugs of abuse also increase dopamine in ventral striatum either directly (eg cocaine – dopamine transporter blocker) or indirectly (eg alcohol, opioids – increasing DA neuronal firing rate).
- Drugs of abuse ‘hijack’ the mesolimbic system
  - Pleasure-reward-motivation system



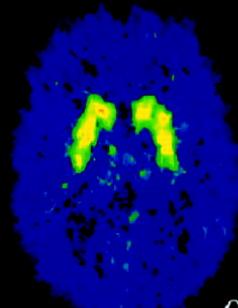
Intravenous Methylphenidate



placebo



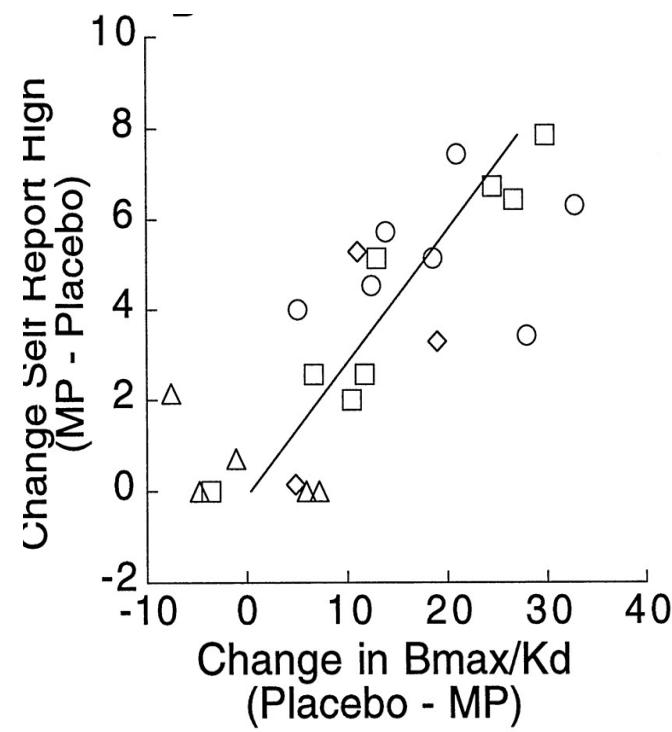
0.025 mg/kg



0.1 mg/kg

[C-11]Raclopride

Increases in dopamine levels in striatum are associated with positive reinforcing effects ('pleasurable') of stimulants in man.



# PERSPECTIVES

OPINION

## The dopamine theory of addiction: 40 years of highs and lows

David J. Nutt, Anne Lingford-Hughes, David Erritzoe and Paul R. A. Stokes

explore the current evidence for this theory and suggest that initial optimism must now be cautioned with a more objective view of the role of dopamine in addiction.

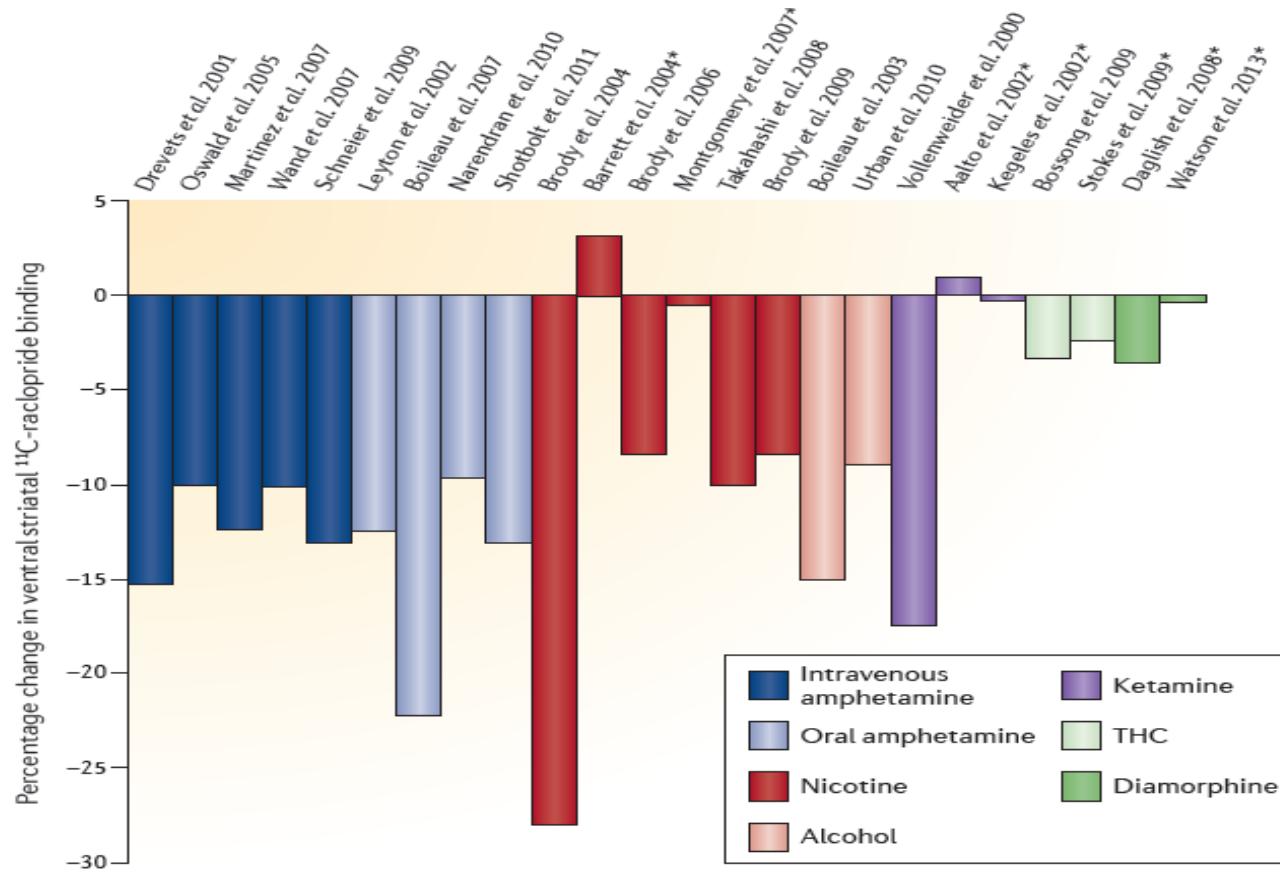
### Dopamine and the drug high

Studying *in vivo* dopamine function in humans became possible in the mid-1990s with the development of radiotracer im-

Nature Reviews Neuroscience 2015

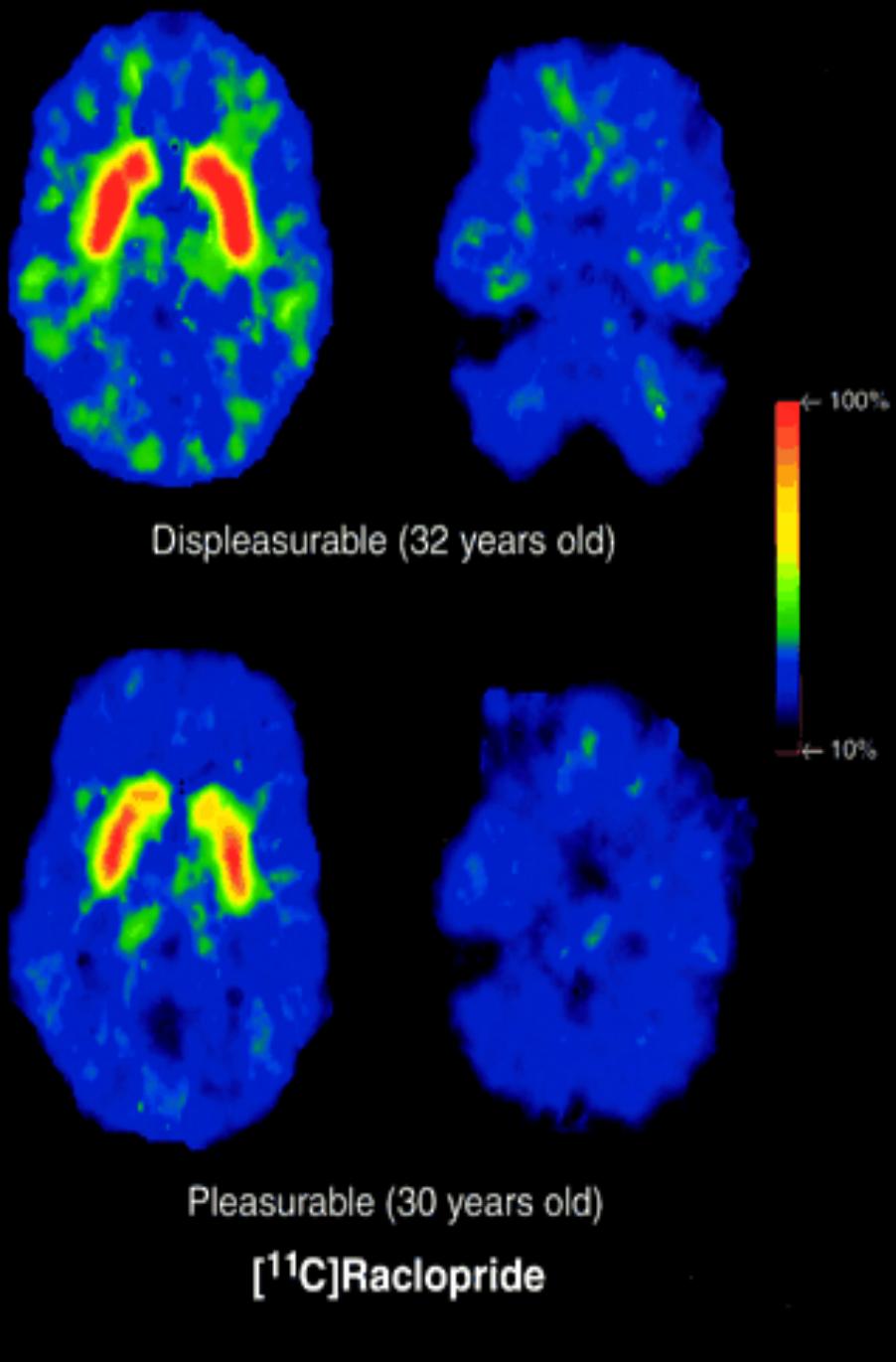
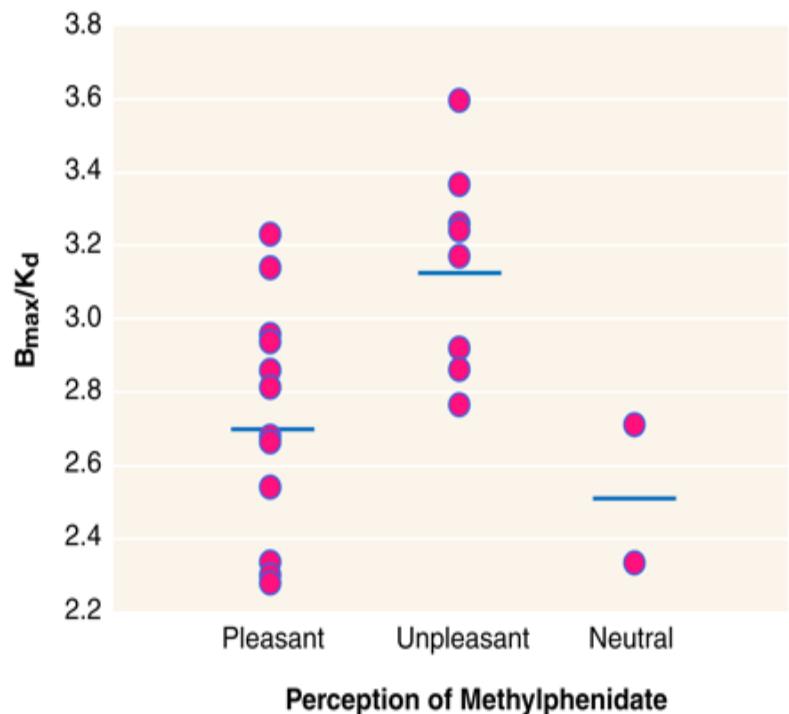
Alcohol and stimulants result in increase in dopamine levels – but for some drugs of abuse: eg opioids, THC change in dopamine is less convincing.

- And relationship between ‘high’ and change in dopamine levels less clear

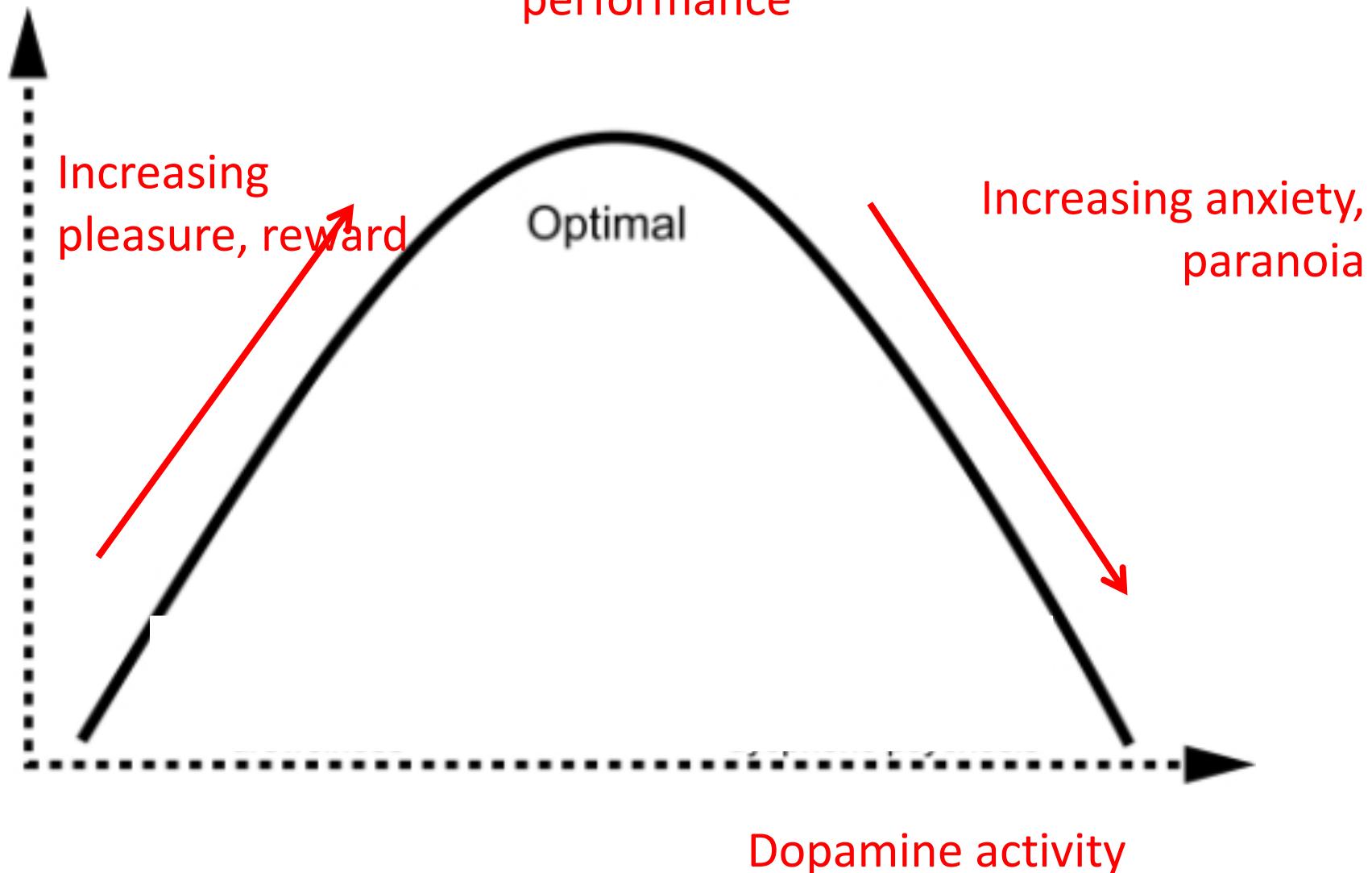


# Prediction of reinforcing responses – ‘liking’ to psychostimulants in humans by brain dopamine D2 receptor levels.

Volkow et al 1999



This relationship also appears to apply to cognitive performance

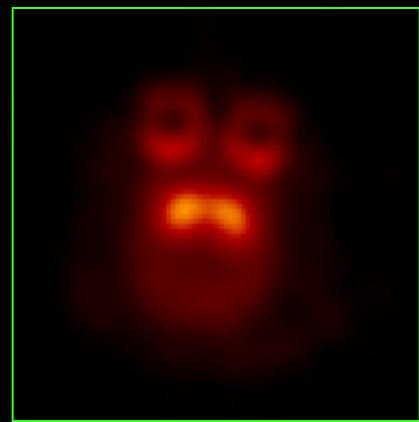


Also modifiable by stress, childhood experiences etc

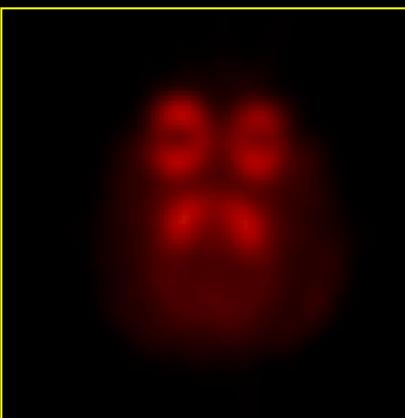
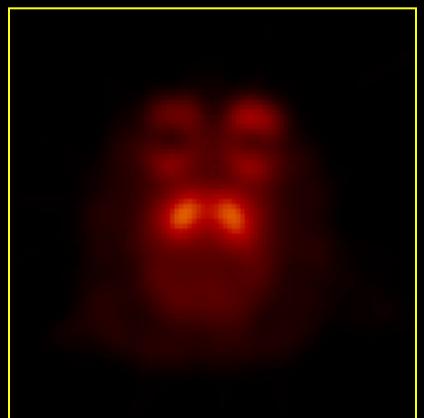
# Social dominance in monkeys: dopamine D<sub>2</sub> receptors and cocaine self-administration.

Individually Housed

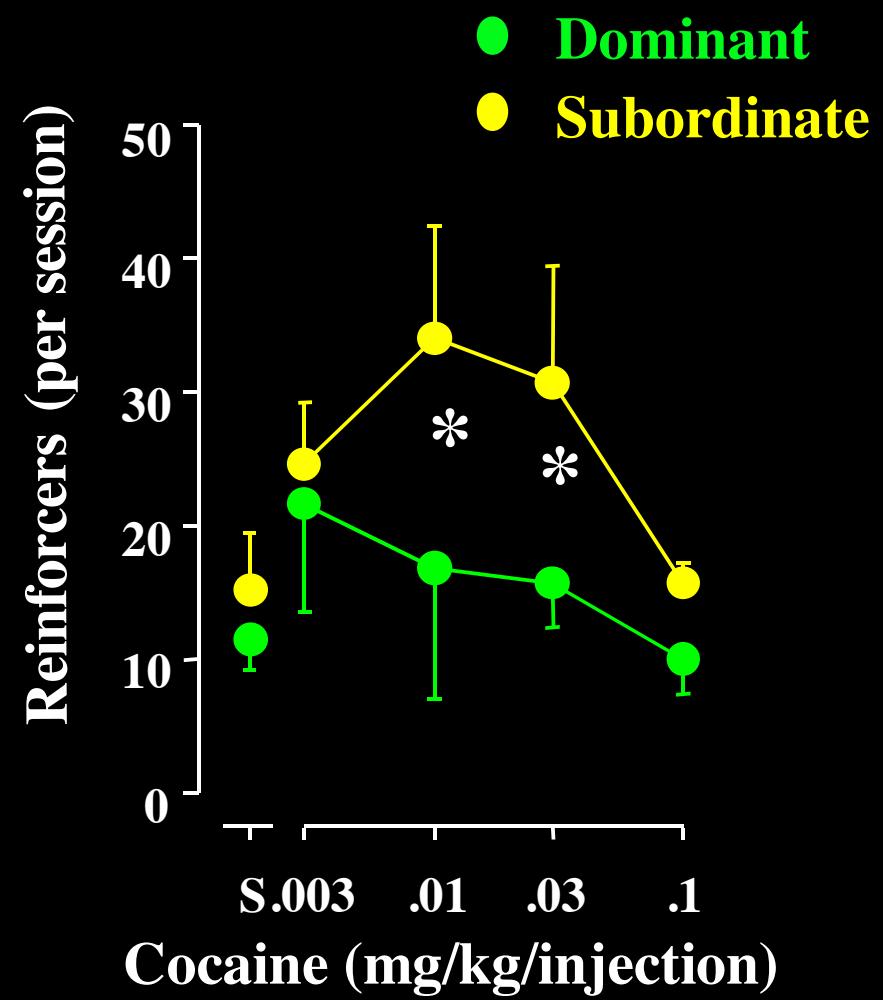
Group Housed



Dominant



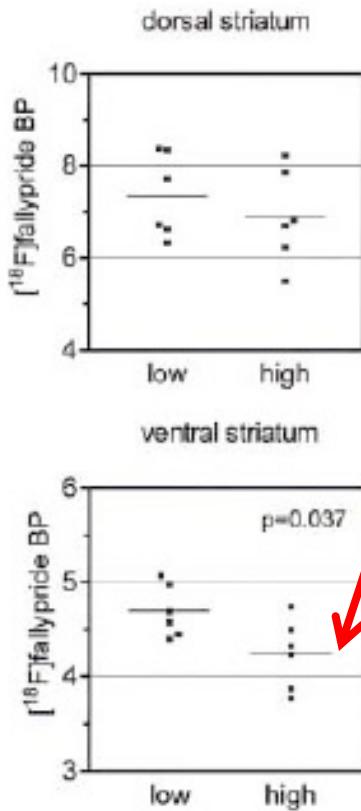
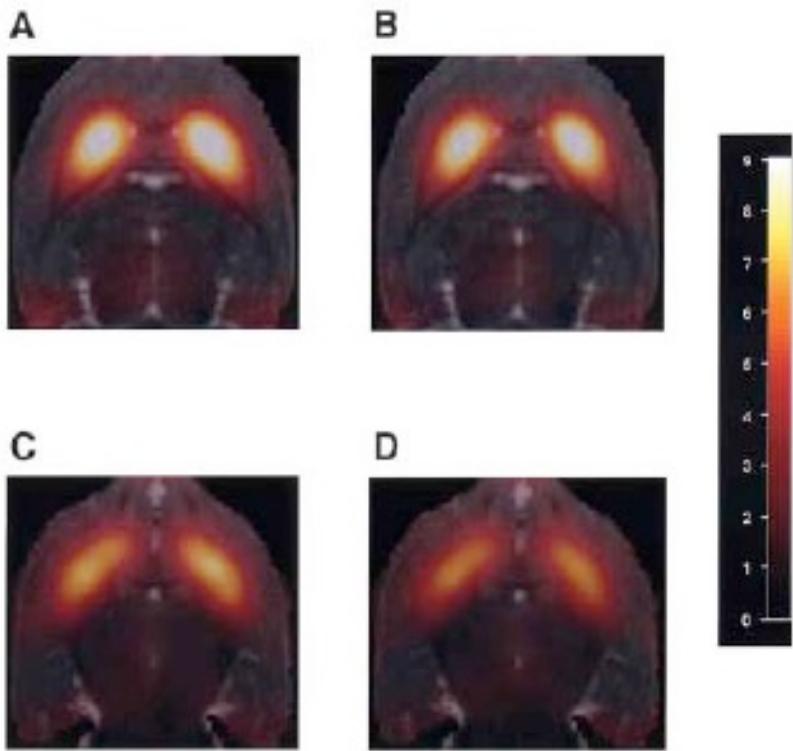
Subordinate



Morgan, et al. 2002.

# Nucleus Accumbens D2/3 Receptors Predict Trait Impulsivity and Cocaine Reinforcement

Jeffrey W. Dalley,<sup>1,2\*</sup> Tim D. Fryer,<sup>1,3</sup> Laurent Brichard,<sup>1,†</sup> Emma S. J. Robinson,<sup>1,‡</sup>  
David E. H. Theobald,<sup>1,2</sup> Kristjan Lääne,<sup>1,2</sup> Yolanda Peña,<sup>1,§</sup> Emily R. Murphy,<sup>1,2</sup> Yasmene Shah,<sup>4</sup>  
Katrín Probst,<sup>1,3</sup> Irina Abakumova,<sup>1,3</sup> Franklin I. Aigbirhio,<sup>1,3</sup> Hugh K. Richards,<sup>1,5</sup> Young Hong,<sup>1,3</sup>  
Jean-Claude Baron,<sup>1,6</sup> Barry J. Everitt,<sup>1,2</sup> Trevor W. Robbins<sup>1,2</sup>



Highly impulsive rats have lower D2/D3 receptors - particularly in ventral striatum

And

consume more cocaine but not heroin

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**OPINION**

## Opiate versus psychostimulant addiction: the differences do matter

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Aldo Badiani, David Belin, David Epstein, Donna Calu and Yavin Shaham

Nature Reviews Neuroscience 2011

cognitive and neurobiological data from laboratory animals and humans. We first discuss differences in the cognitive and neurobiological effects of opiate and psychostimulant administration. We then review data from animal models of addiction showing behavioural and neurobiological differences between opiates and psychostimulants. Next, we consider selected studies in humans

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**OPINION**

## The dopamine theory of addiction: 40 years of highs and lows

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David J. Nutt, Anne Lingford-Hughes, David Erritzoe and Paul R. A. Stokes

explore the current evidence for this theory and suggest that initial optimism must now be cautioned with a more objective view of the role of dopamine in addiction.

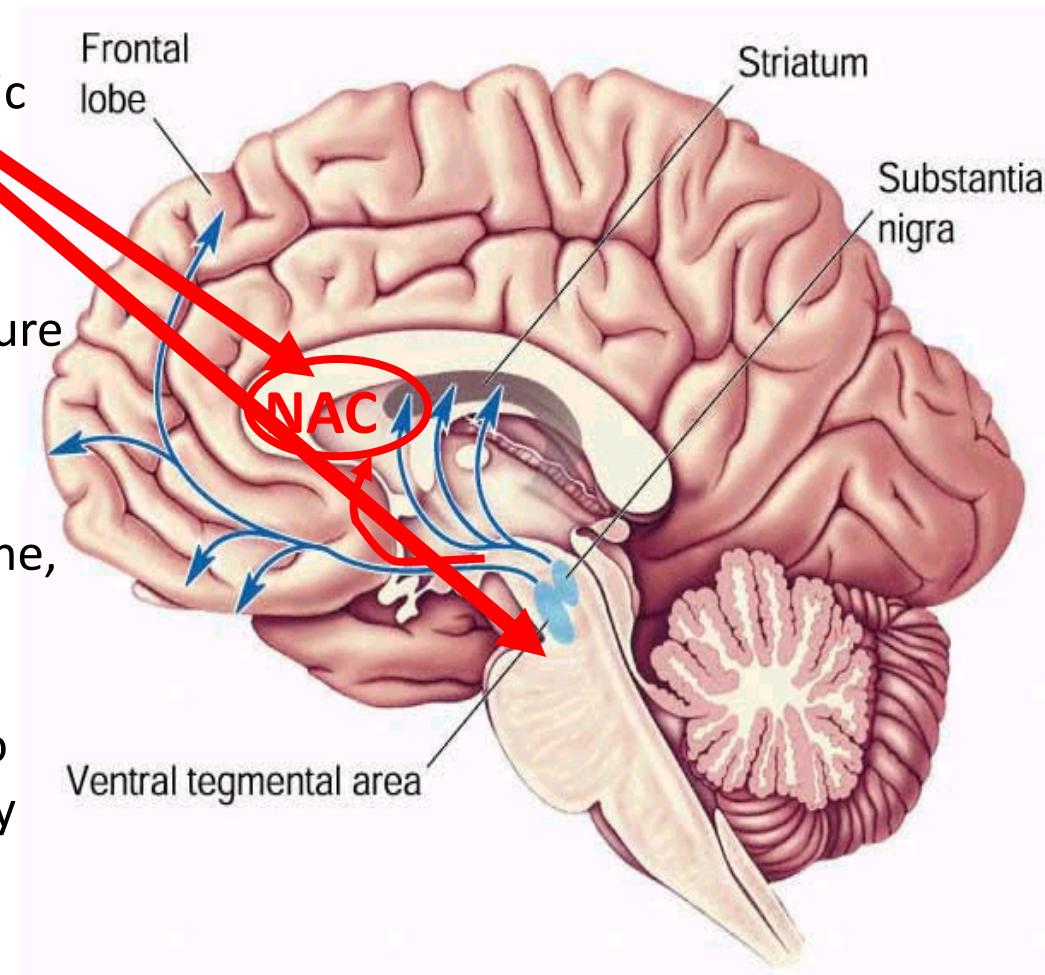
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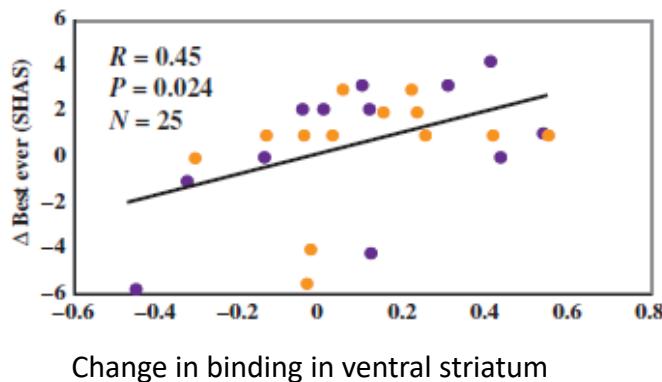
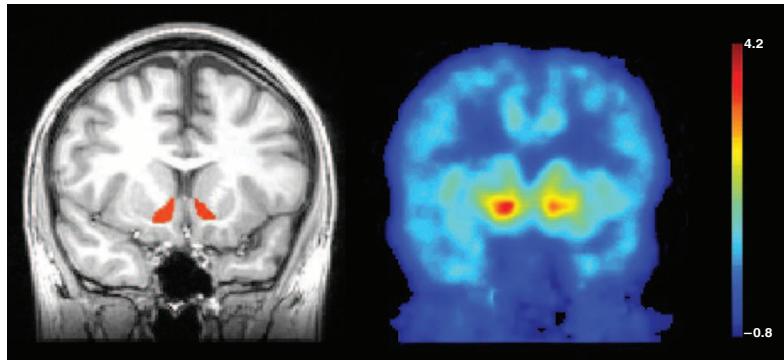
# Important modulators of the dopaminergic system: opioids.

- Opioids modulate dopaminergic function.
- Alcohol & stimulants release 'endorphins' – related to pleasure (mu receptor)
  - Increase firing of DA neurons
- Opioid antagonists eg naltrexone, naloxone used for treatment
- Opioid 'deficiency' proposed to be associated with vulnerability to addiction



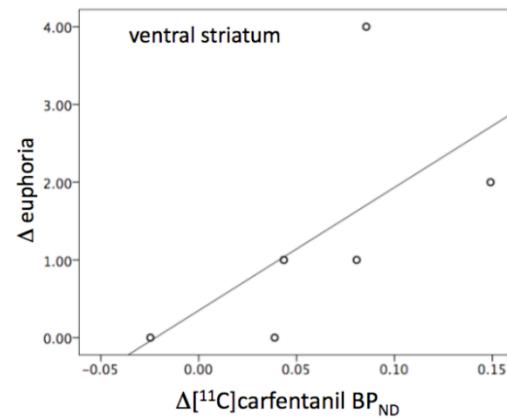
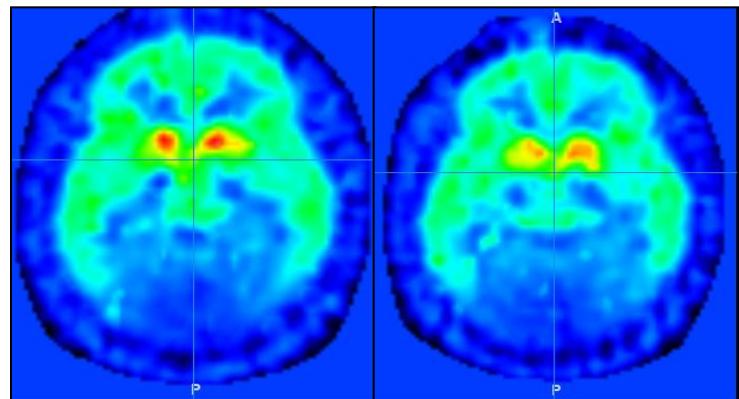
# Using PET imaging to show increases in opioids

Alcohol acutely increases opioids in social drinkers: associated with 'best ever' experience:

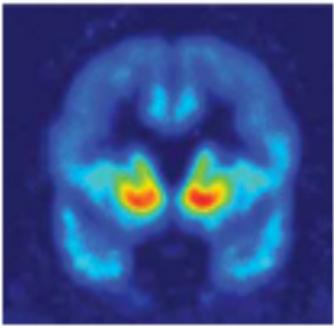


Mitchell et al 2012

Amphetamine acutely increases opioids: associated with 'euphoria'



Colasanti et al 2012



Alcohol  
dependent      Control

## Opioid PET imaging in substance addiction:

- higher availability of mu opiate receptors (MOR)
  - consistent with low endogenous opioid levels
- positively correlated with craving
- blunted endogenous opioid levels present in alcoholism and gambling disorder (though no difference in MOR levels probably due to longer abstinence and 'recovery').

### Correlation of Stable Elevations in Striatal $\mu$ -Opioid Receptor Availability in Detoxified Alcoholic Patients With Alcohol Craving

A Positron Emission Tomography Study Using Carbon 11-Labeled Carfentanil

Andreas Heinz, MD; Matthias Reimold, MD; Jana Wräse; Derik Hermann, MD; Bernhard Croissant, MD; Gotz Mundt, MD; Bernhard M. Dohmen, MD; Dieter H. Braus, MD; Gunter Schumann, MD; Hans-Jürgen Machulla, MD; Roland Bares, MD; Karl Mann, MD

### Brain opioid receptor binding in early abstinence from opioid dependence

Positron emission tomography study

TIM M. WILLIAMS, MARK R. C. DAGLISH, ANNE LINGFORD-HUGHES, LINDSAY G. TAYLOR, ALEXANDER HAMMERS, DAVID J. BROOKS, PAUL GRASBY, JUDITH S. MYLES and DAVID J. NUTT

## Imaging Brain Mu-Opioid Receptors in Abstinent Cocaine Users: Time Course and Relation to Cocaine Craving

David A. Gorelick, Yu Kyong Kim, Badreddine Bencherif, Susan J. Boyd, Richard Nelson, Marc Copersino, Christopher J. Endres, Robert F. Dannals, and J. James Frost

## Blunted endogenous opioid release following an oral dexamphetamine challenge in abstinent alcohol-dependent individuals

Samuel Turton<sup>1</sup> · James FM Myers<sup>1</sup> · Inge Mick<sup>1,2</sup> · Alessandro Colasanti<sup>3,4</sup> · Ashwin Venkataraman<sup>1</sup> · Claire Durant<sup>1</sup> · Adam Waldman<sup>5</sup> · Alan Brailsford<sup>6</sup> · Mark C Parkin<sup>6</sup> · Gemma Dawe<sup>7</sup> · Eugenii A Rabiner<sup>8,9</sup> · Roger N Gunn<sup>9,10</sup> · Stafford L Lightman<sup>11</sup> · David J Nutt<sup>1</sup> · Anne Lingford-Hughes<sup>1</sup>

## Blunted Endogenous Opioid Release Following an Oral Amphetamine Challenge in Pathological Gamblers

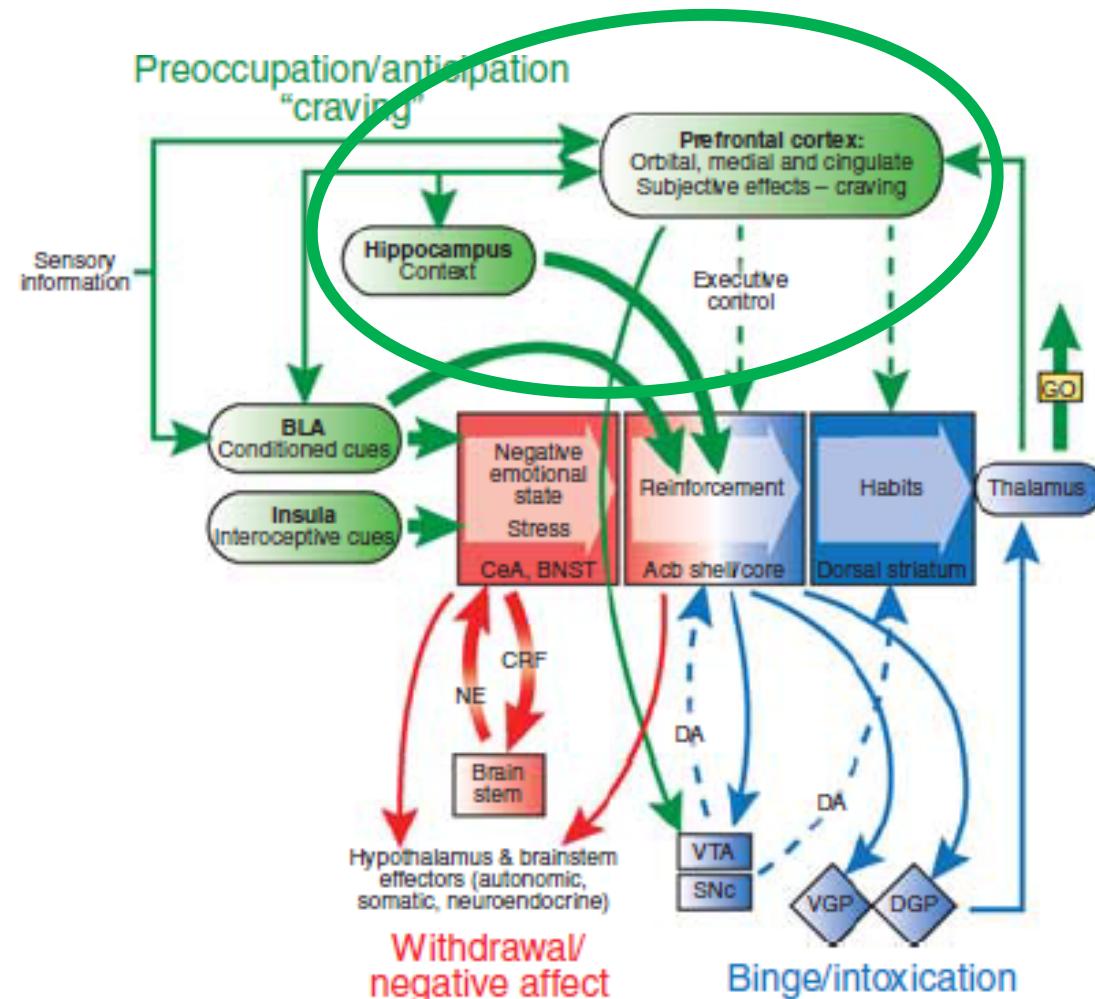
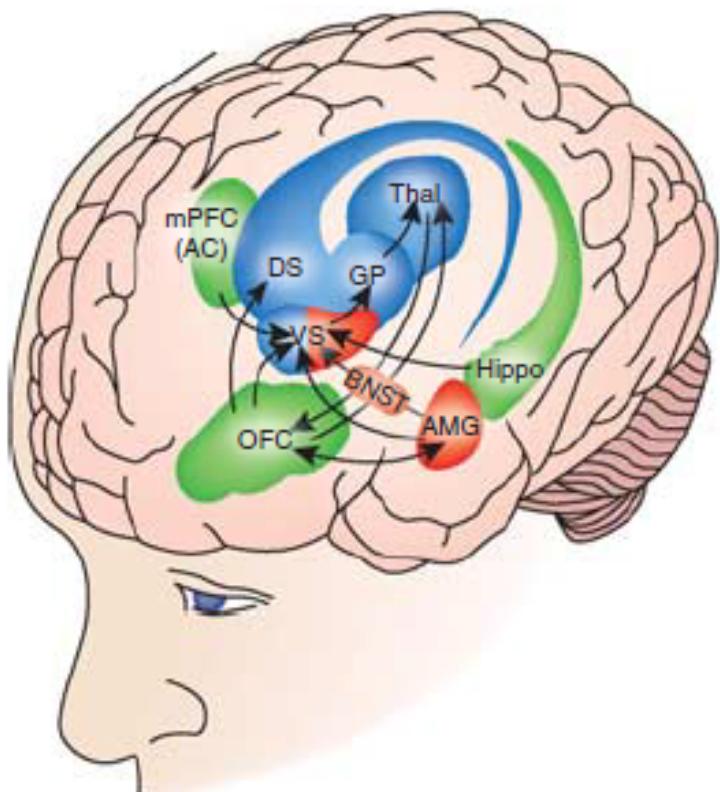
Inge Mick<sup>1</sup>, Jim Myers<sup>1</sup>, Anna C Ramos<sup>1,2</sup>, Paul RA Stokes<sup>1,3</sup>, David Erritzoe<sup>1</sup>, Alessandro Colasanti<sup>1,3,4</sup>, Roger N Gunn<sup>1,4</sup>, Eugenii A Rabiner<sup>4,5</sup>, Graham E Searle<sup>4</sup>, Adam D Waldman<sup>6</sup>, Mark C Parkin<sup>7</sup>, Alan D Brailsford<sup>7</sup>, José CF Galdróz<sup>2</sup>, Henrietta Bowden-Jones<sup>8</sup>, Luke Clark<sup>9</sup>, David J Nutt<sup>1</sup> and Anne R Lingford-Hughes<sup>9,1</sup>

# Opiate system in addiction

- Early studies showed increased availability of mu opiate receptors in alcohol, cocaine, heroin addiction
  - We have recently shown blunted endorphin release consistent with this increased availability.
    - However in these studies we saw no difference with opiate receptor availability
- What could contribute to the differences between earlier and recent studies: recovery?
  - Those in early studies were abstinent for days – weeks, in our recnet study, they were abstinent for months-years
- We scanned ‘successful’ recovered/ing alcoholics
  - Higher mu opioid receptor availability has been associated with craving and response to naltrexone (opiate antagonist)
- Role in impulsivity as well
  - Higher mu receptors associated with greater impulsivity.

# Regions of brain involved in different stages:

- binge/intoxication: striatum
- withdrawal/negative affect: extended amygdala
- preoccupation/anticipation ‘craving’: prefrontal cortex



Koob, Volkow

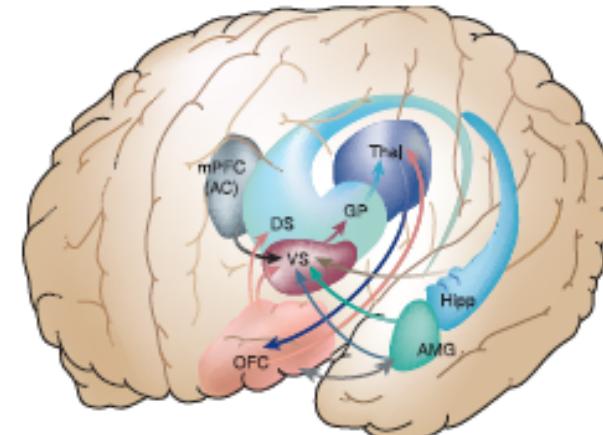
# Neural systems of reinforcement for drug addiction: from actions to habits to compulsion

Barry J Everitt & Trevor W Robbins

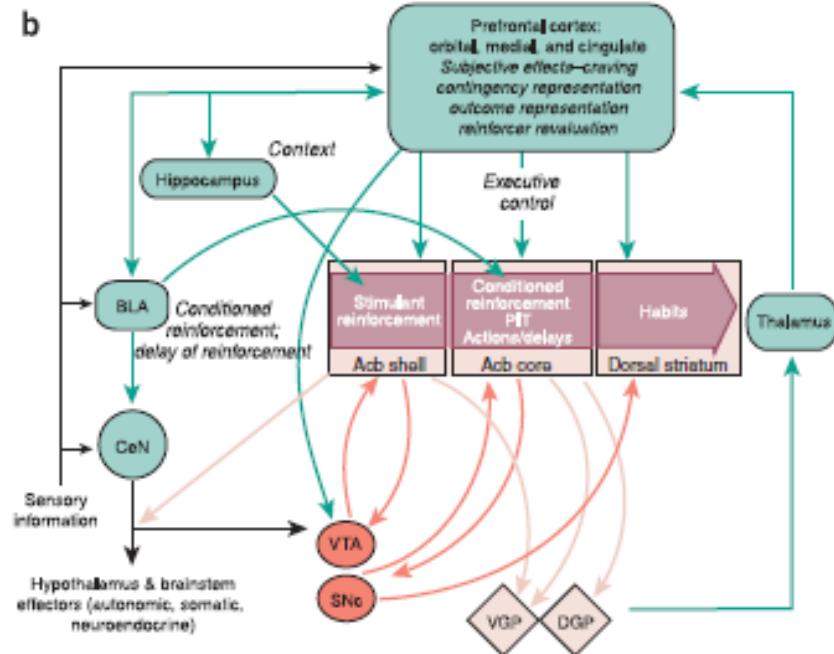
Change from voluntary drug use to more habitual and compulsive drug use involves transition from:

- prefrontal to striatal control over drug taking
- &
- ventral (limbic) to dorsal (habit) striatum.

a



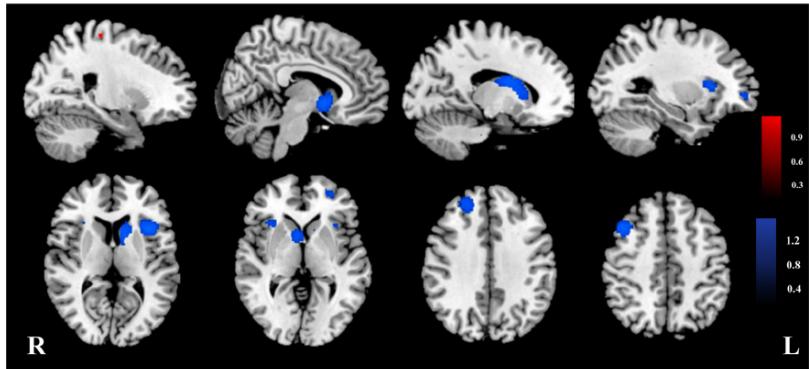
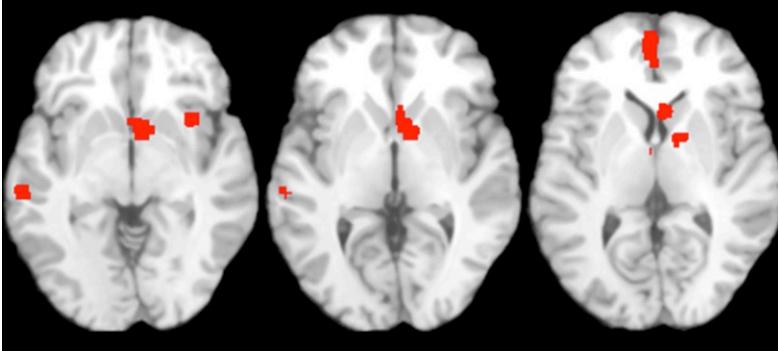
b



# Reward pathway & fronto-striatal

function:

## Cue reactivity meta-analyses in alcoholism



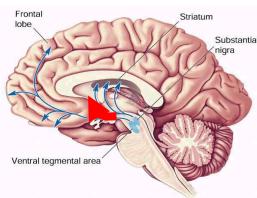
- Alcohol cues resulted in greater activation in
  - ventral striatum, anterior cingulate and ventromedial prefrontal cortex.

Schacht et al 2021

- Post treatment (naltrexone, cue-exposure therapy)
  - decreased cue-elicited activation of right DLPFC, right middle frontal gyrus, bilateral caudate nucleus, bilateral insula
  - increased in right precentral gyrus and SMA

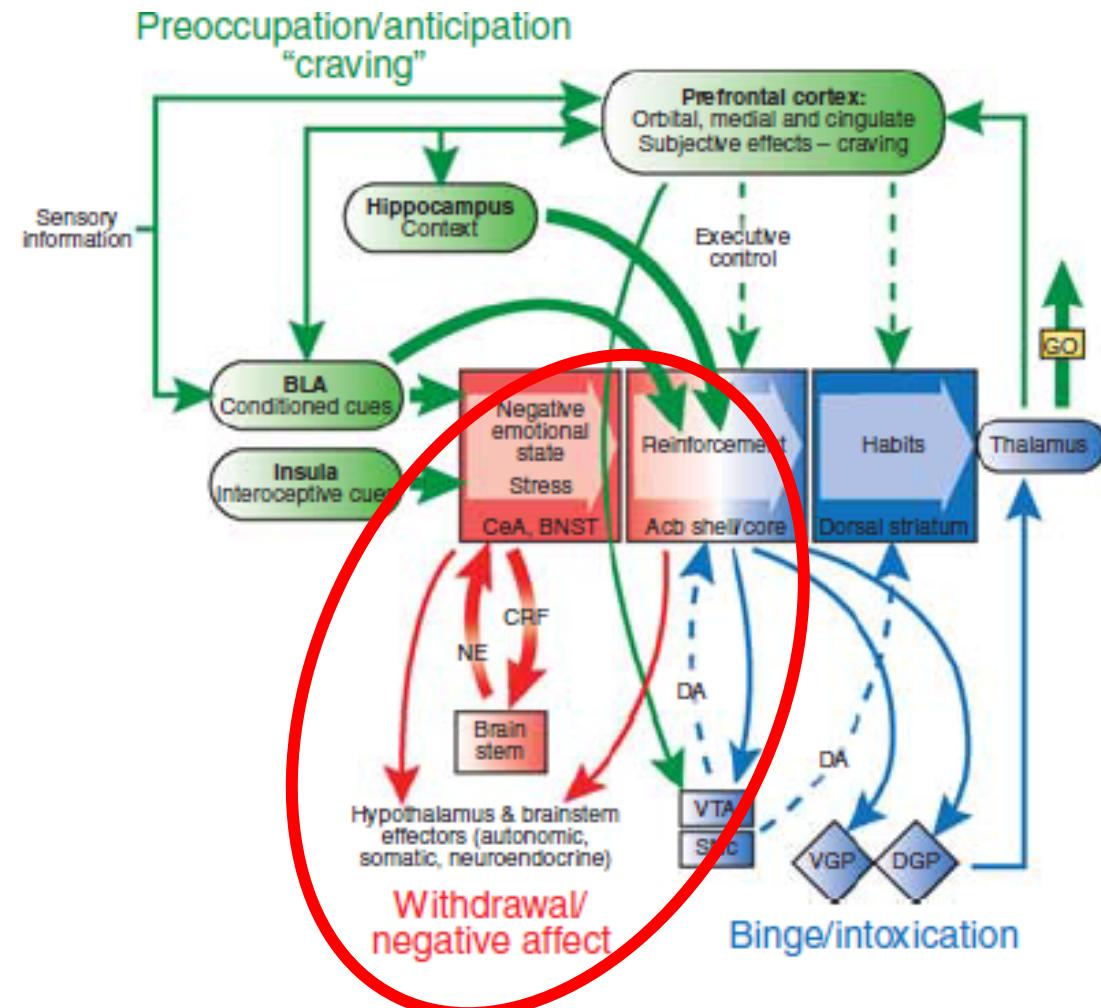
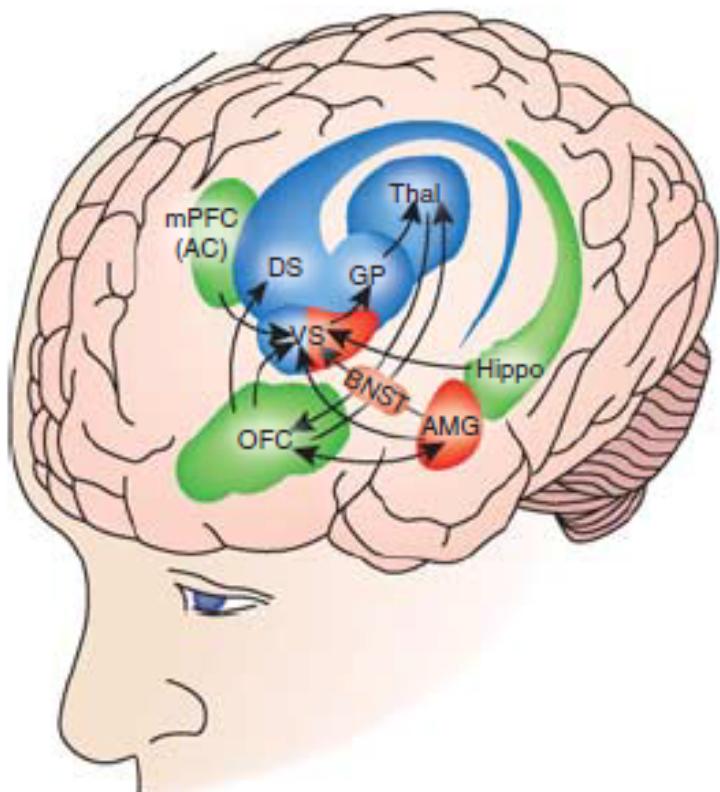
Zeng et al 2021

- NB: earlier showed that activation to money ie non-drug cue is *blunted*



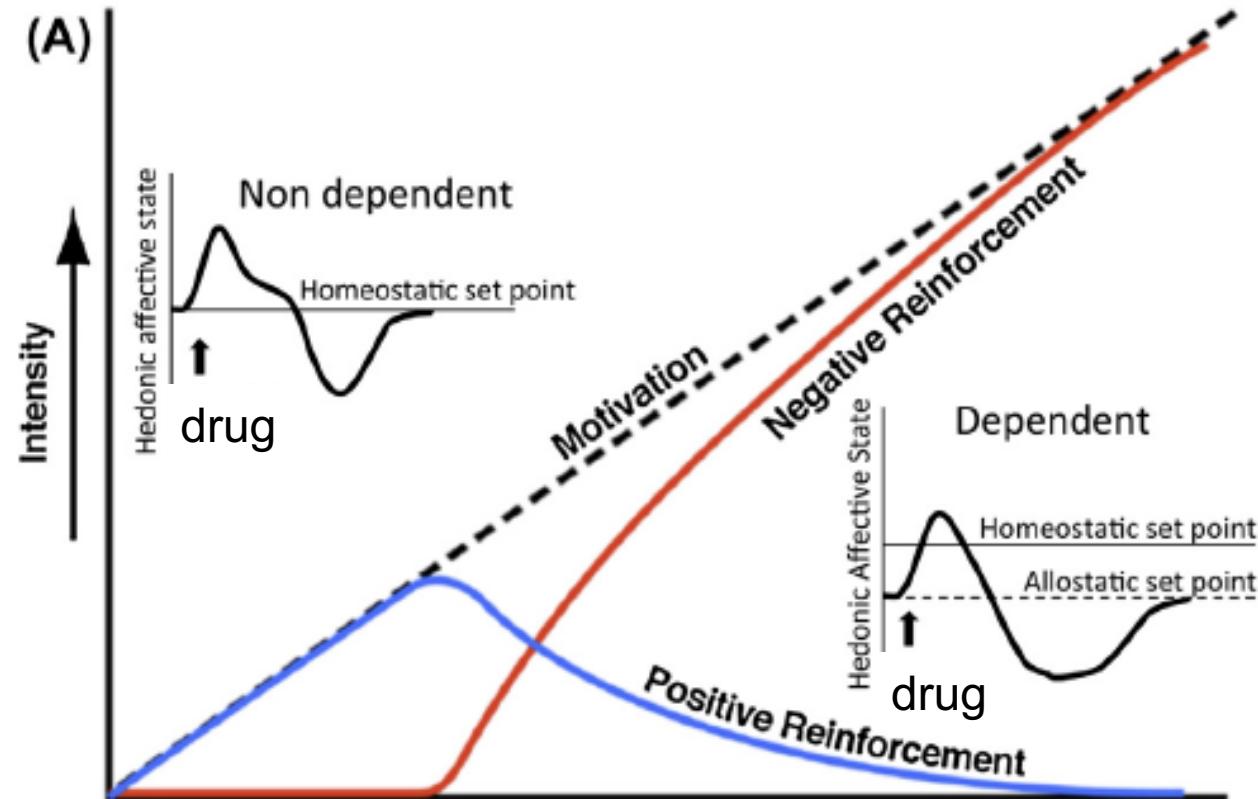
# Regions of brain involved in different stages:

- binge/intoxication: striatum
- withdrawal/negative affect: extended amygdala
- preoccupation/anticipation ‘craving’: prefrontal cortex



Koob, Volkow

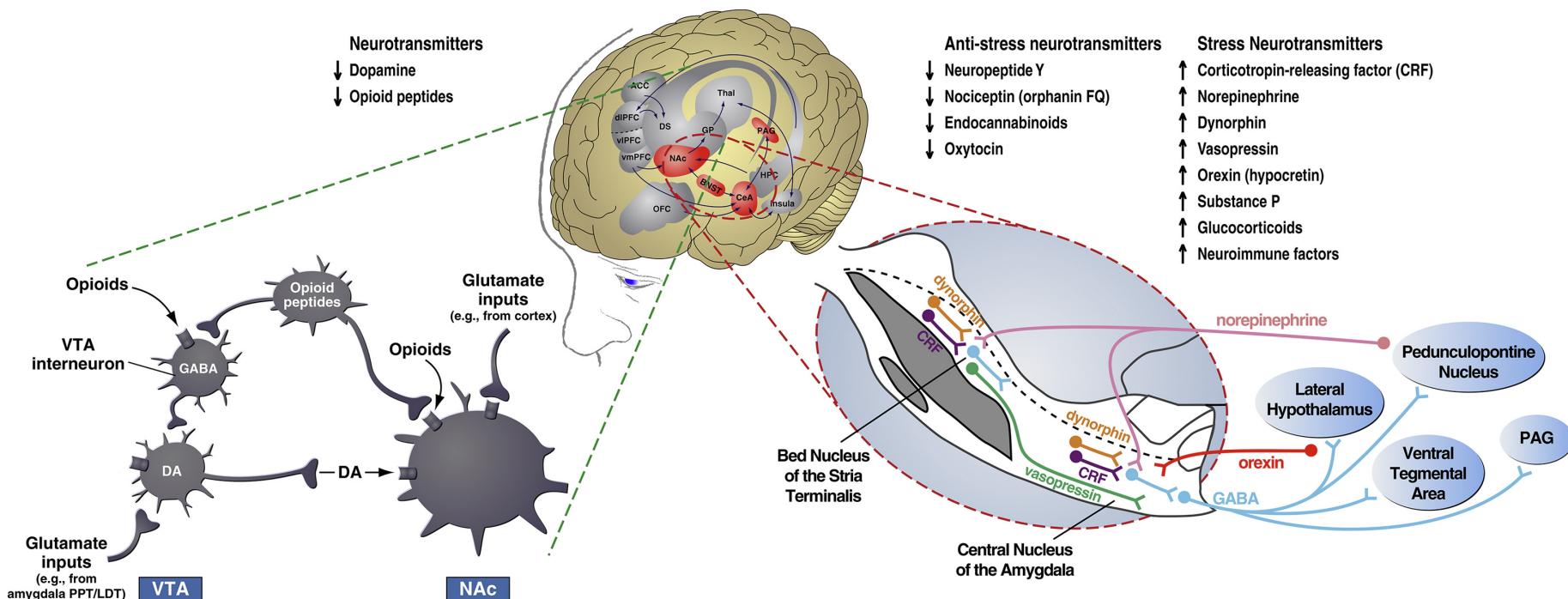
Change from positive to negative reinforcement as addiction/dependence develops.



# Neuropharmacology and brain regions associated with withdrawal and negative emotional states in addiction: targets for treatment.

The 'reward' system:  
reduced dopamine and mu  
opioid function

*The 'stress' system: increased activity  
in many including kappa opioid  
(dynorphin), noradrenaline (arousal  
system; treat with lofexidine (a2  
agonist) CRF (stress) etc*

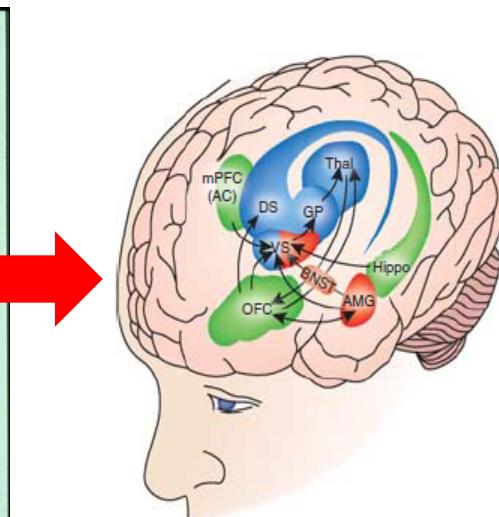
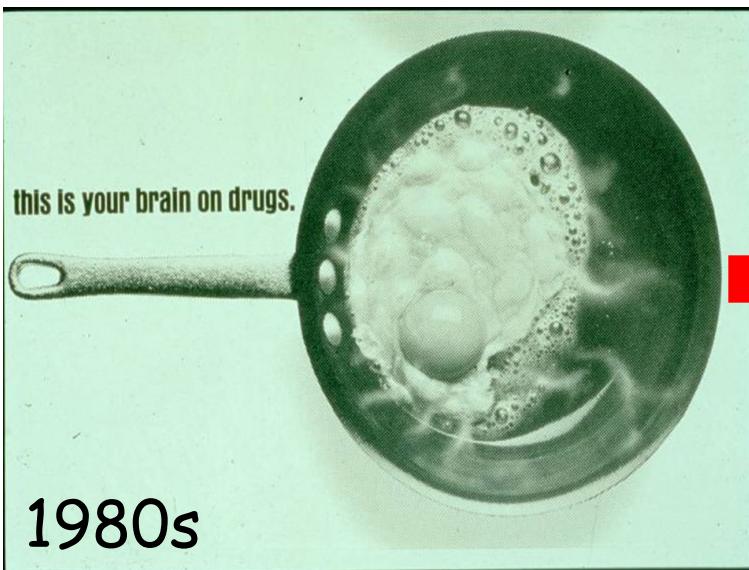


*Dysregulation in amygdala is key*

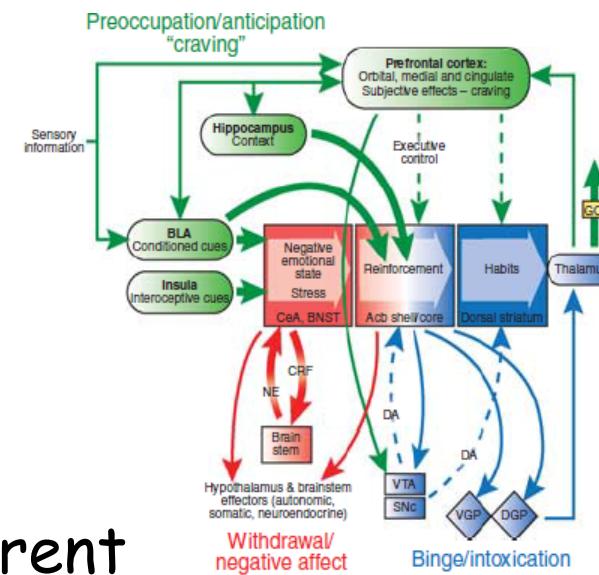
# Addiction Is a Brain Disease, and It Matters

Alan I. Leshner

Scientific advances over the past 20 years have shown that drug addiction is a chronic, relapsing disease that results from the prolonged effects of drugs on the brain. As with many other brain diseases, addiction has embedded behavioral and social-context aspects that are important parts of the disorder itself. Therefore, the most effective treatment approaches will include biological, behavioral, and social-context components. Recognizing addiction as a chronic, relapsing brain disorder characterized by compulsive drug seeking and use can impact society's overall health and social policy strategies and help diminish the health and social costs associated with drug abuse and addiction.



current



## Implications for treatment

Psychosocial and pharmacological treatments to

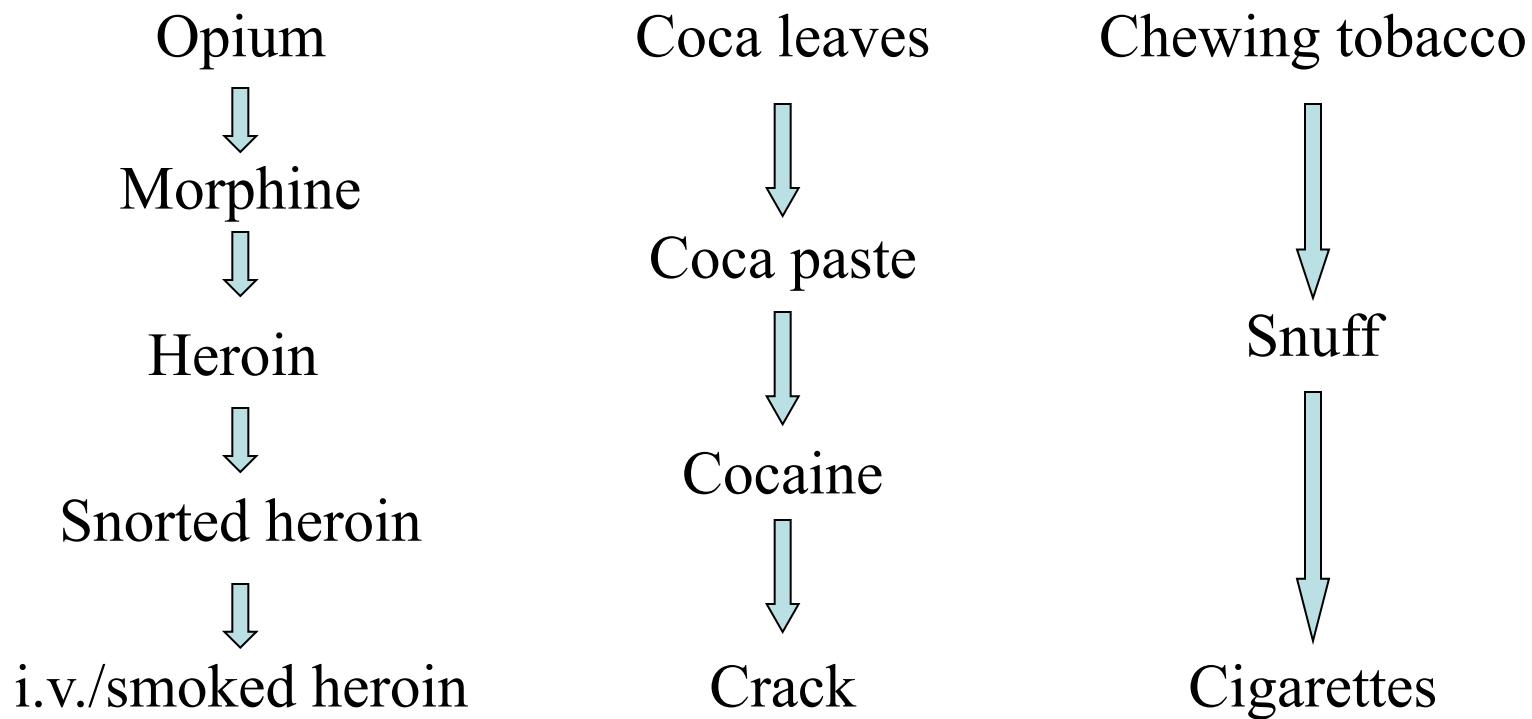
- decrease reward value of drugs
- increase value of non-drug rewards
- weaken learned associations between drug and drug cues
- strengthen frontal-striatal control
- regulate brain stress systems
- gender differences for treatment

# Appendix

Extra information

# Speeding up brain entry

Faster brain entry → more “rush” and more addiction



# Incentive -Sensitization Model

(Robinson and Berridge, 1993)

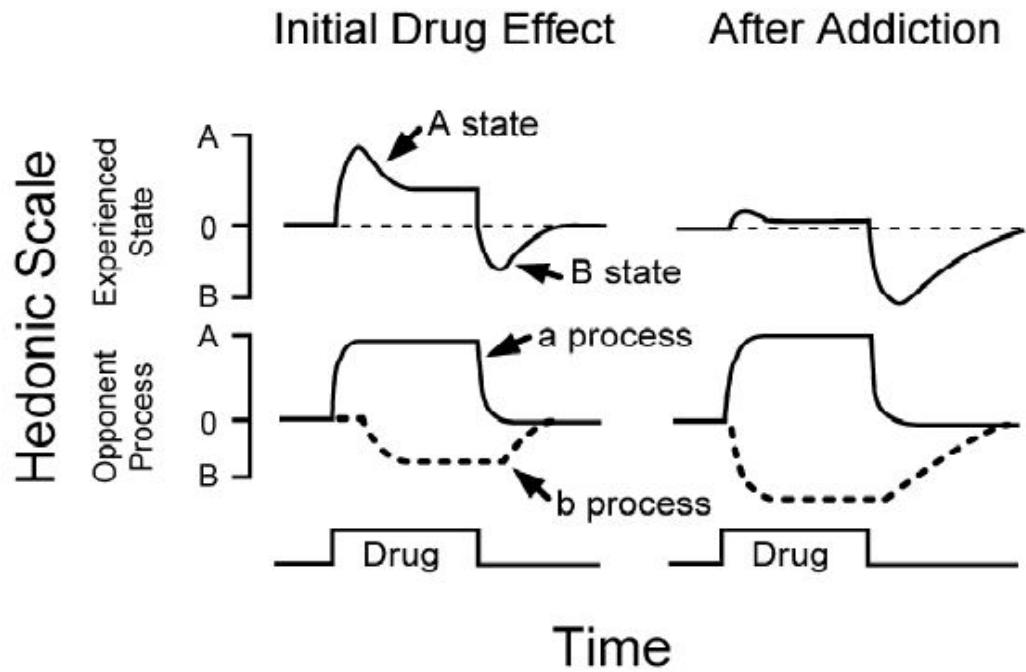
- Addiction renders systems hypersensitive ("sensitized") to drugs and drug-associated stimuli
  - Mesolimbic dopaminergic system
- These sensitized systems mediate a component of reward termed incentive salience or "wanting" (not pleasure or "liking").
- Drug-induced sensitization of brain systems (DA) that mediate incentive-salience causes drugs and drug-associated stimuli to become compulsively "wanted"
- The activation of the sensitized system can occur both implicitly or explicitly
- Challenges:
  - Applied to stimulants primarily
  - Harder to show in man

# Physical dependence: negative reinforcement.

- Some drugs produce physical dependence and withdrawal symptoms upon cessation of drug-taking.
  - Withdrawal symptoms are produced by the body in order to compensate for the unusual effects of the drug.
  - Withdrawal symptoms are generally the opposite of the effect produced by the drug.
- Addicts continue to use drugs in order to avoid withdrawal.
- Over time, drugs no longer have the same rewarding effects - they merely allow the person to feel "normal."

# Difficulties with physical dependence / negative reinforcement model

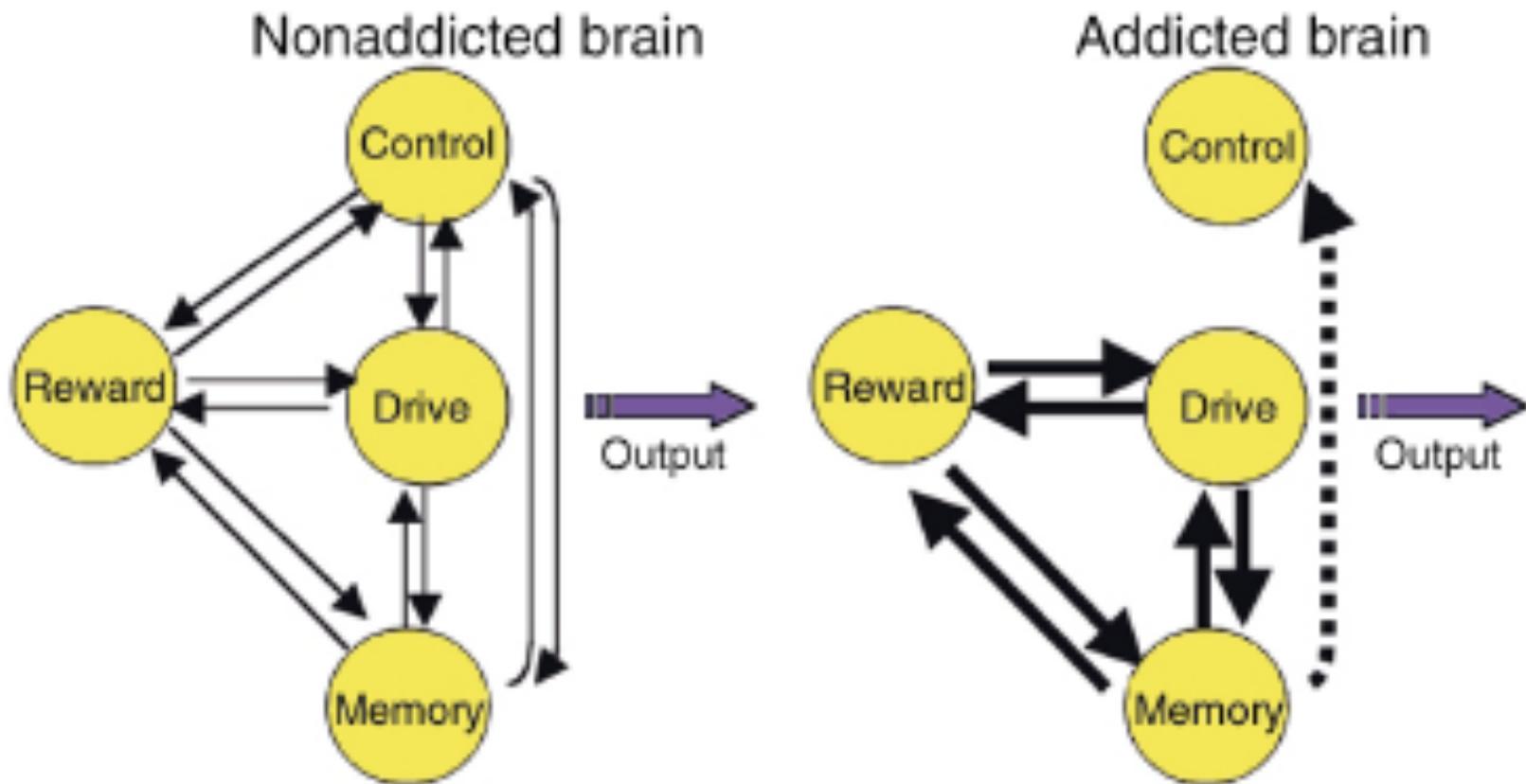
- Not all abused drugs generate withdrawal symptoms (cocaine, amphetamine).
- Different drugs produce different withdrawal symptoms with different neural bases.
- Once dependent you should continue taking drug, but people spontaneously stop.
- Once drug-abstinent and withdrawal symptoms gone, users should not relapse, but they do.
- No explanation as to why people take drugs in the first place.
  - They generally want a positive effect



## Opponent process model of addiction.

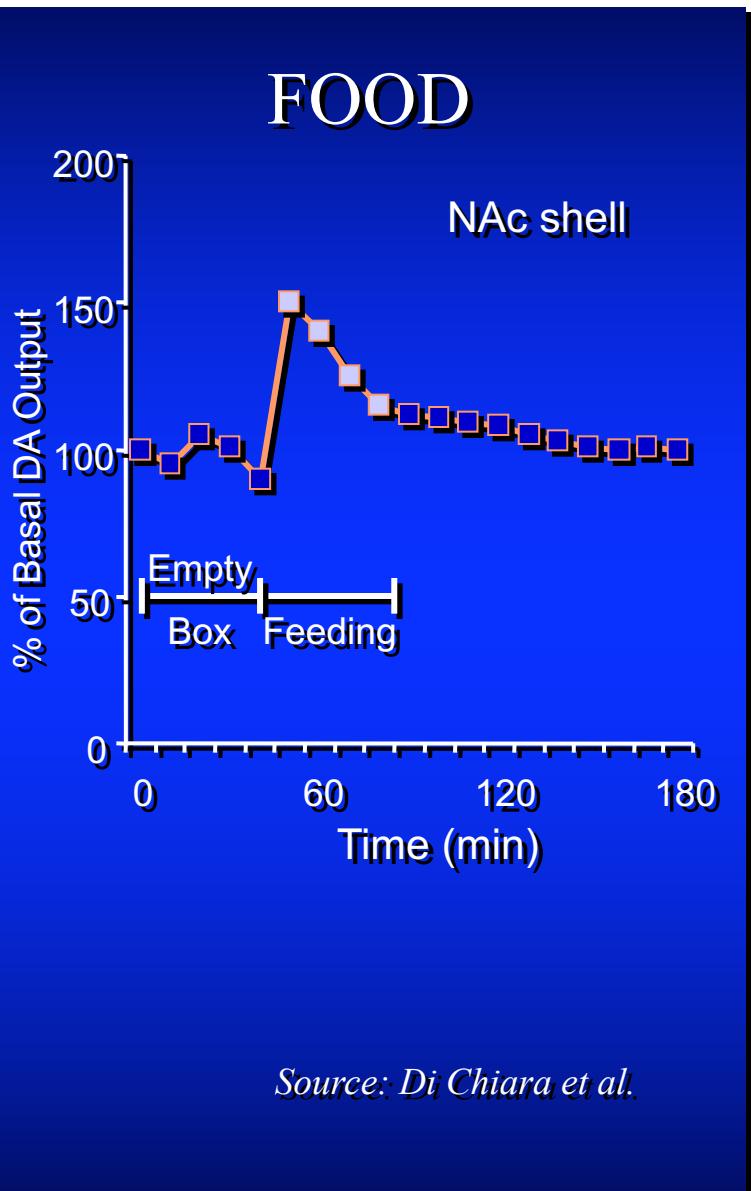
- The affective or hedonic response ('a') to a stimulus drives initial use.
- An unpleasant ('b') state follows.
- Initially 'a' is large and 'b' is small
- With repeated drug use and in addiction, the opponent 'b' increases in magnitude and duration
  - leads to individual experiencing unpleasant symptoms ie withdrawal

# Model proposing a network of four circuits involved with addiction: reward, motivation/drive, memory, control

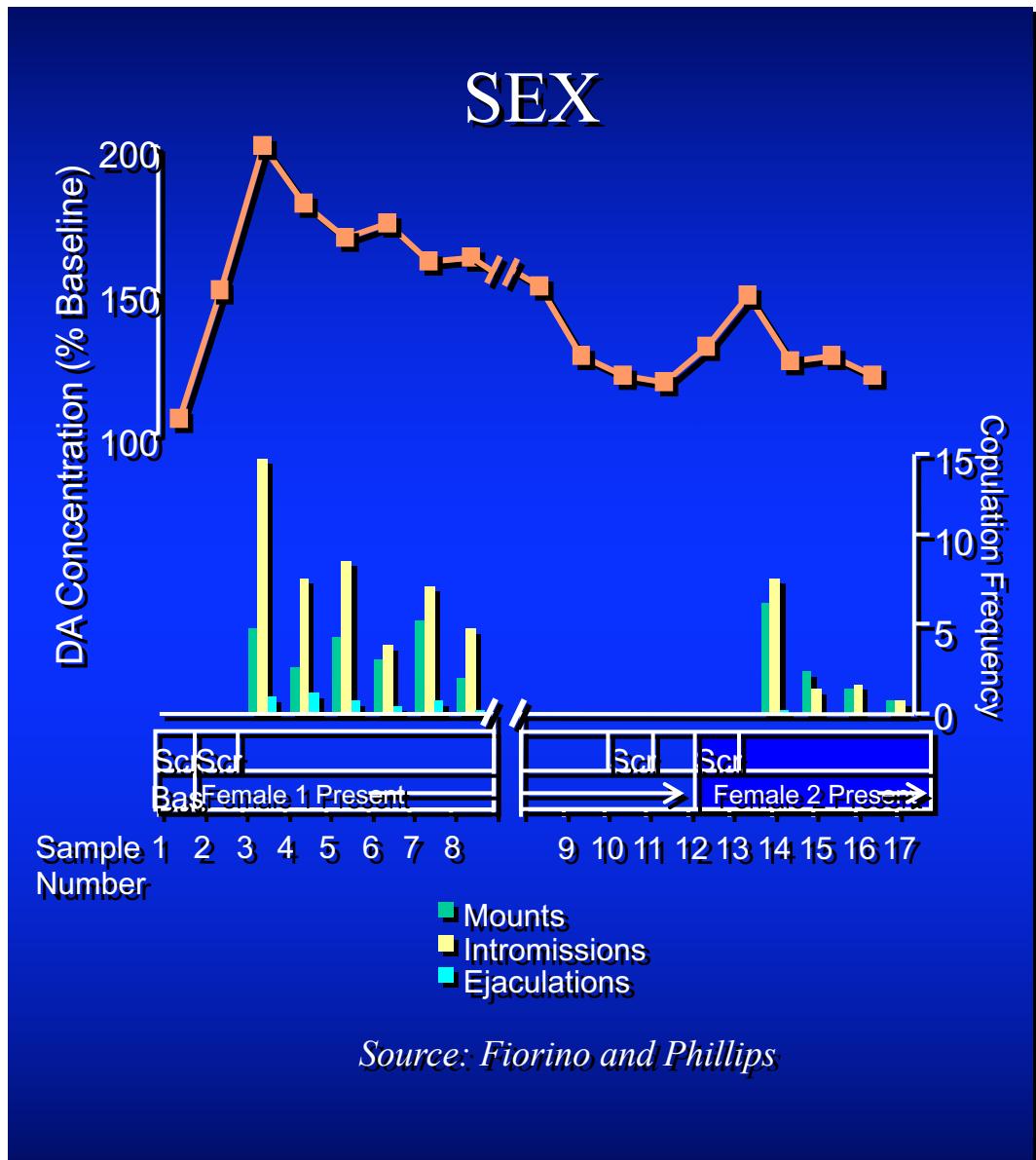


Volkow

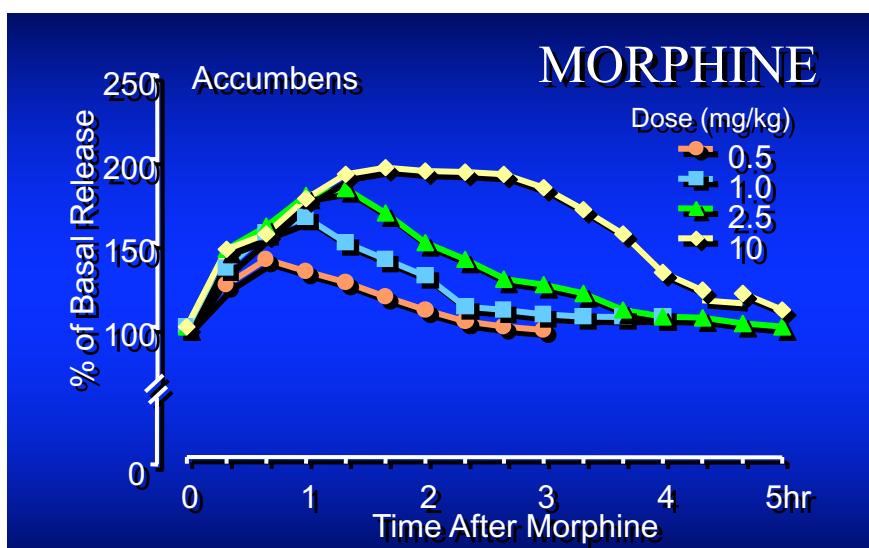
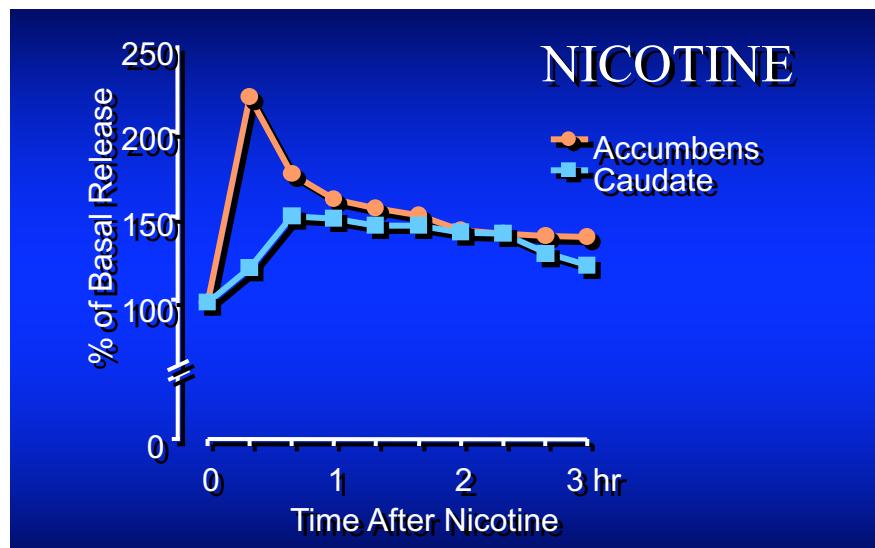
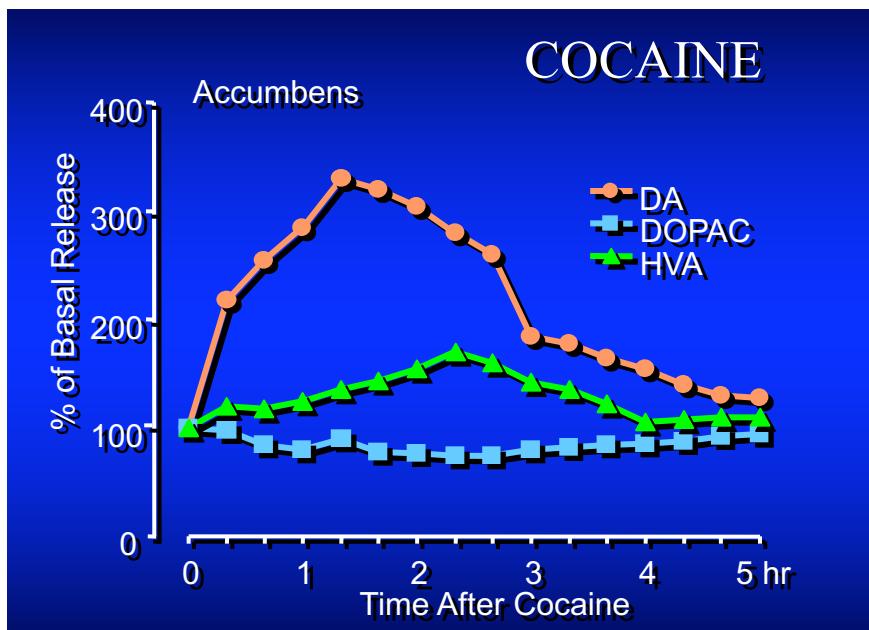
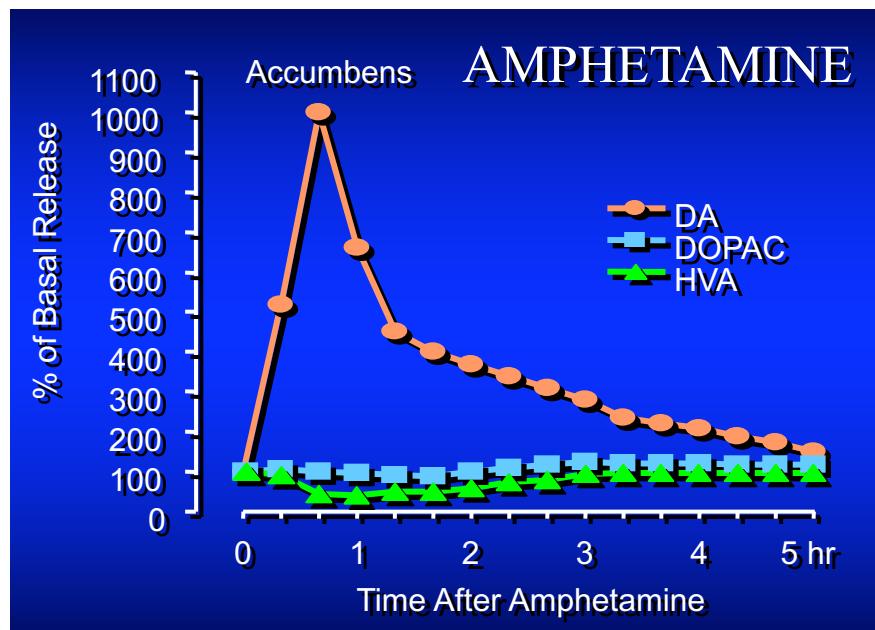
# Natural rewards increase dopamine levels.



Source: Di Chiara et al.



# Substances of abuse also increase dopamine levels.

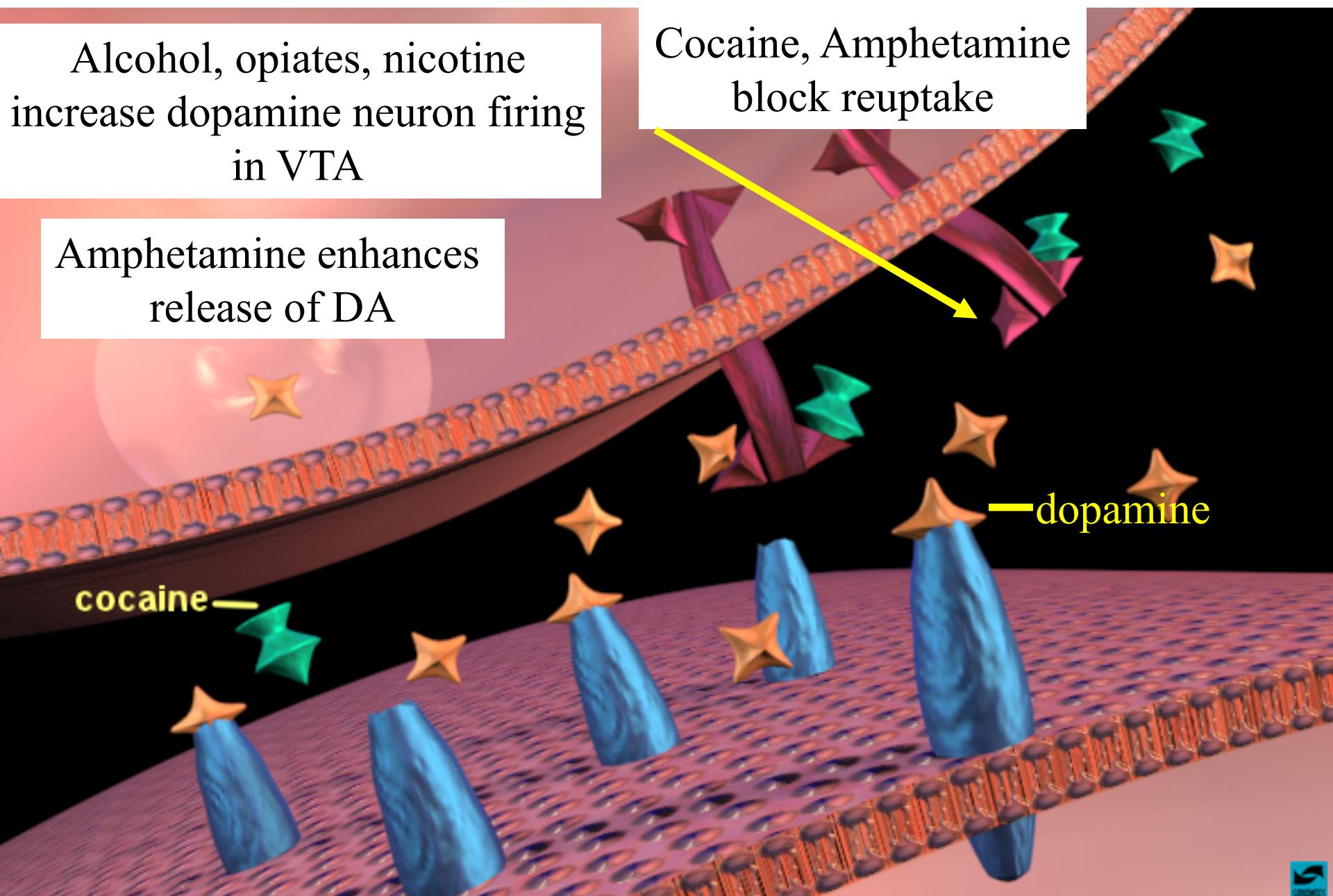


# Interaction between substances and dopamine

Alcohol, opiates, nicotine  
increase dopamine neuron firing  
in VTA

Cocaine, Amphetamine  
block reuptake

Amphetamine enhances  
release of DA



Drug	Primary target	Main effects / transmitters	Other targets/effects
Alcohol	GABA/glutamate	Inc GABAergic function; dec glutamate (NMDA)	Modulates many systems; Inc DA via opioid modulation
Opiates eg heroin, morphine	Opiate receptor (mu)	Kappa and delta opiate receptors	DA system may play lesser role
Stimulants			
Cocaine	DA transporter (DAT) blocker	Incr DA	Releases opioids, modulation of glutamate
Amphetamine	DAT blocker + stimulates DA release	Incr DA	Ditto
Nicotine	Nicotinic receptors	Incr DA	Many
Ecstasy	5HT transporter	Incr 5HT	

Drug	Primary target	Main effects / transmitters	Other targets/effects
Benzodiazepines	GABA	Inc GABAergic function	unclear if DA increases
Cannabis	CB1 receptor		CB2, Linked with opiate system
GHB/GBL	GHB receptor, GABA-B receptor		
Ketamine	NMDA receptor	Decr glutamate	
Hallucinogens eg LSD, psilocybin	5HT2 receptor		

Other targets eg appetitive hormones, HPA axis, inflammation