Alcohol use disorder: clinical features, neurobiology, and evidence-based treatment

Anne Lingford-Hughes
Professor of Addiction Biology, Imperial College.

Consultant Psychiatrist, CNWL NHS Foundation Trust.

Imperial College London

Central and North West London NHS
NHS Foundation Trust

Harmful Substance use

ICD 11 criteria

A pattern of substance 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 substance 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.

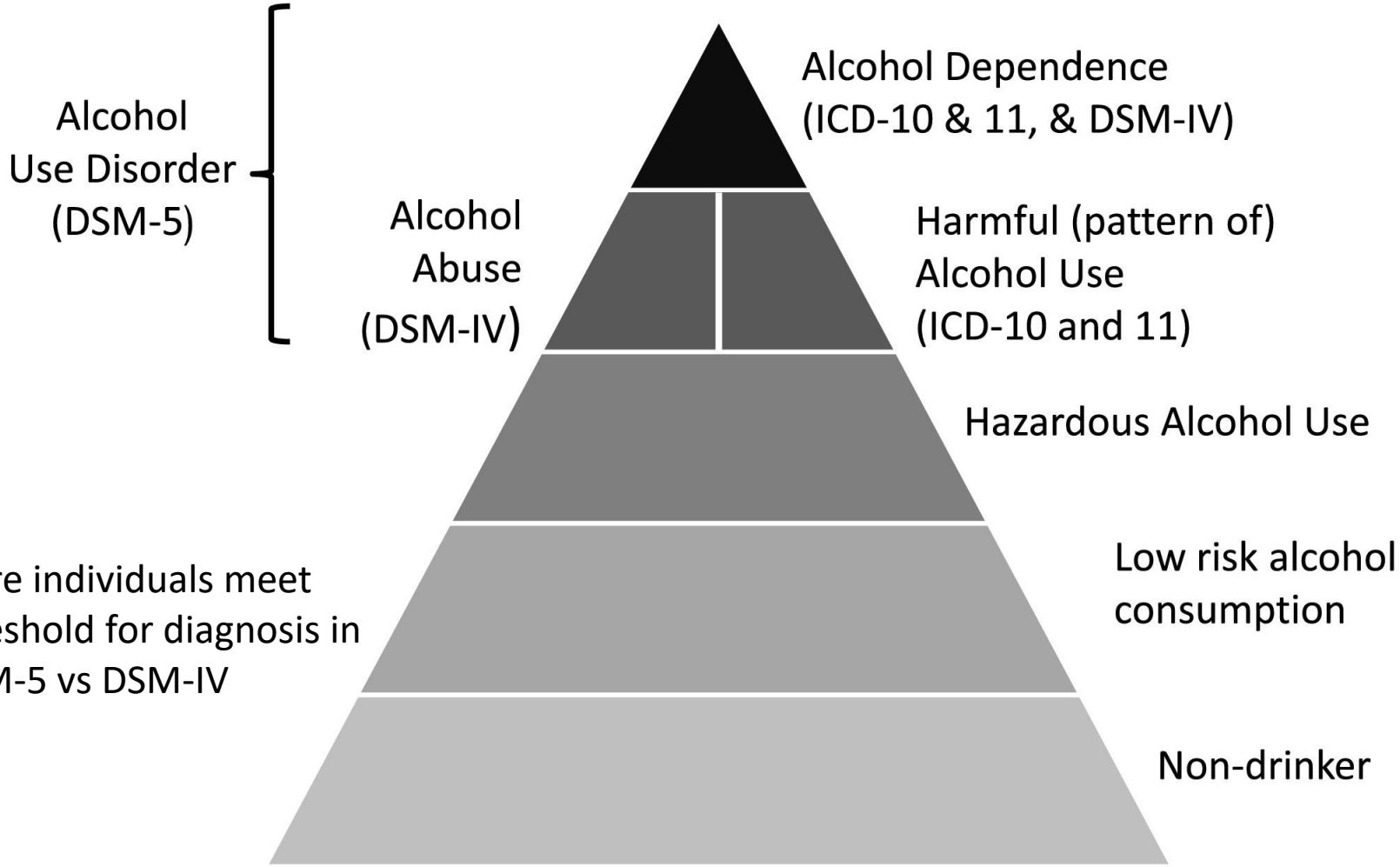
ICD-11: Dependence syndrome.

- Substance dependence is a disorder of regulation of substance use arising from repeated or continuous use of substance. The characteristic feature is a strong internal drive to use substance, 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.

DSM vs ICD
continuum vs separate



s:

e: 4-5
6+

more individuals meet threshold for diagnosis in DSM-5 vs DSM-IV

Addiction vs dependence?

- Addiction - compulsive drug use despite harmful consequences, characterized by an inability to stop using a drug; failure to meet work, social, or family obligations; and, sometimes (depending on the drug), tolerance and withdrawal.

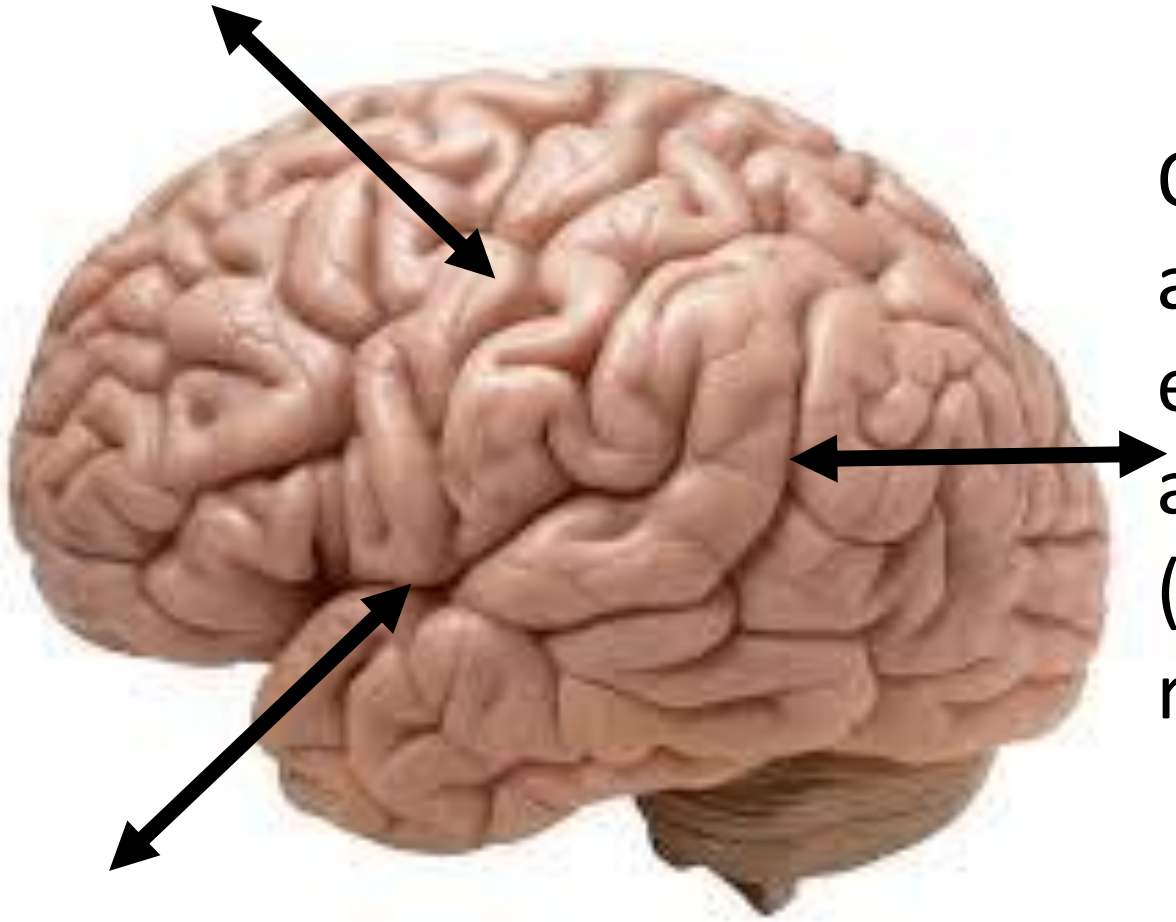
- In biology/pharmacology, dependence refers to a physical adaptation to a substance
  - Tolerance/withdrawal
    - Eg opioid, benzodiazepine, alcohol
  - ➢ So can be dependent and not addicted

- Antidepressants?
  - Withdrawal but no other features of addiction

➢ Confusion with terminology so be clear in how you are using either term 'addiction' or 'dependence' to other professionals and individual concerned.

Models of Addiction:
Overlap to some extent

Reward deficiency
(positive reinforcement)



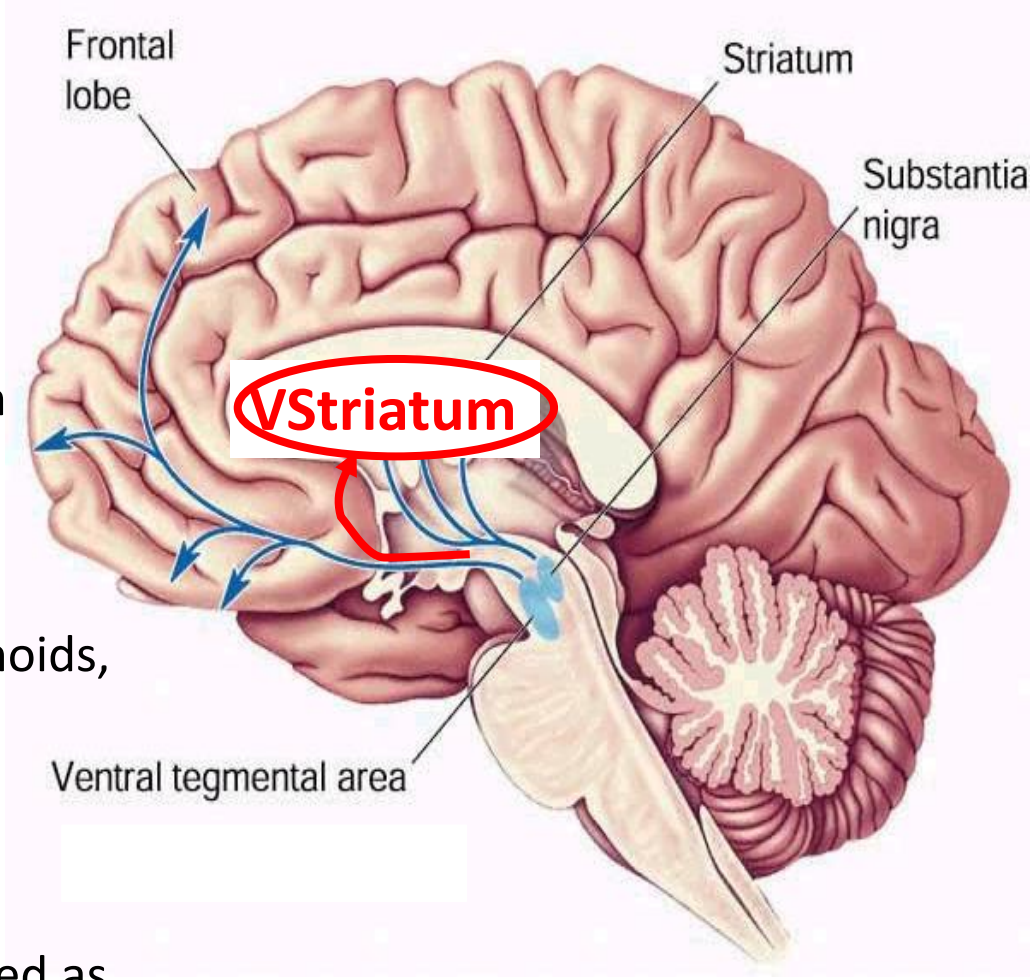
Overcoming
adverse state
eg withdrawal,
anxiety
(negative
reinforcement)

Impulsivity/
compulsivity

Natural rewards such as food, sex increase levels of a chemical – dopamine - in a part of the brain called ventral striatum.
Drugs of abuse also increase levels of dopamine here.

Mesolimbic dopamine pathway has been referred to as the 'pleasure-reward-motivation' system:

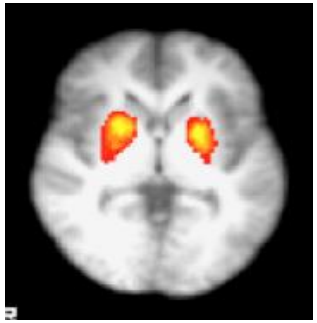
A key modulator is opioid system – particularly mu opioid that mediates pleasurable effects (eg of alcohol, 'endorphin 'rush'); others include GABA-B, cannabinoids, glutamate etc that are targets for treatment

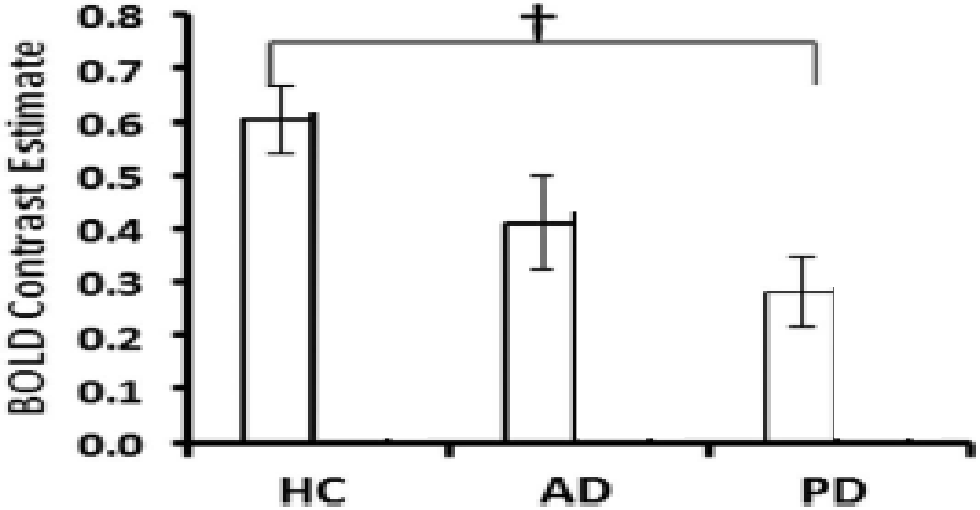


Addiction has been conceptualized as a 'reward deficient' state

Assessing function in the reward pathway with fMRI:
Monetary Incentive delay task - anticipation of winning money

- Blunted activation of reward system in abstinent addicts compared with controls.
  - Blunted responses shown in 14yr olds who went on to develop problematic drug use at 16yrs (IMAGEN; Buchel et 2017)



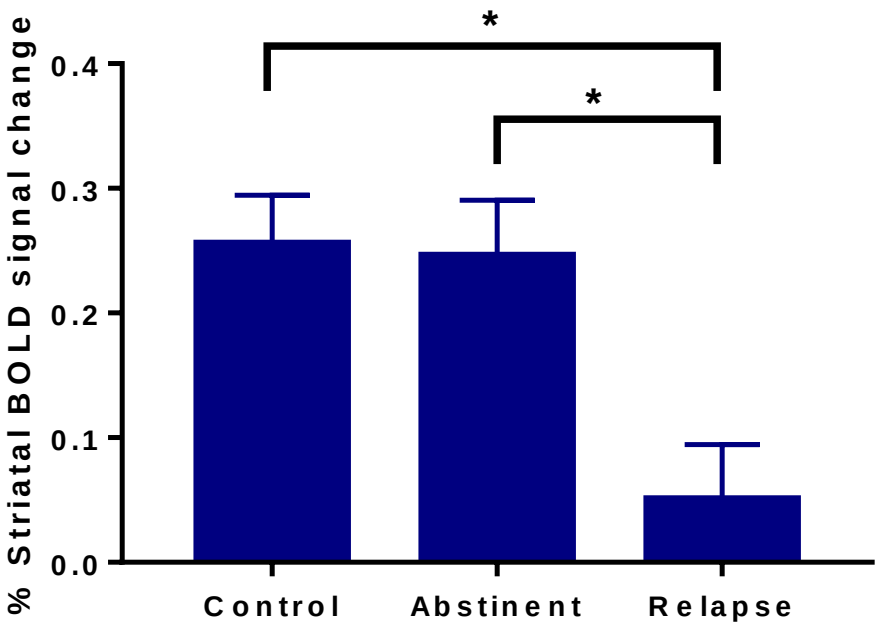


ICCAM
Imperial College London
UNIVERSITY OF CAMBRIDGE
MANCHESTER

Paterson, Lingford-Hughes, Nutt et al

HC=Healthy Control, AD=abstinent alcohol dependent, PD=abstinent polydrug (alcohol, cocaine, opiate) dependent

Higher activity in reward pathway is associated abstinence at follow-up:



- in abstinent addicts, those with blunted response in the brain to 'anticipation of reward' are more likely to relapse
  - consistent with 'reward deficiency' theories of addiction

Paterson, Lingford-Hughes, Nutt et al

ICCAM
Imperial College London
UNIVERSITY OF CAMBRIDGE
MANCHESTER

Acute D3 Antagonist GSK598809 Selectively Enhances Neural Response During Monetary Reward Anticipation in Drug and Alcohol Dependence

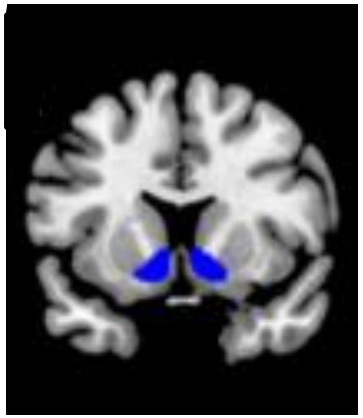
Neuropsychopharmacology (2017), 1–9

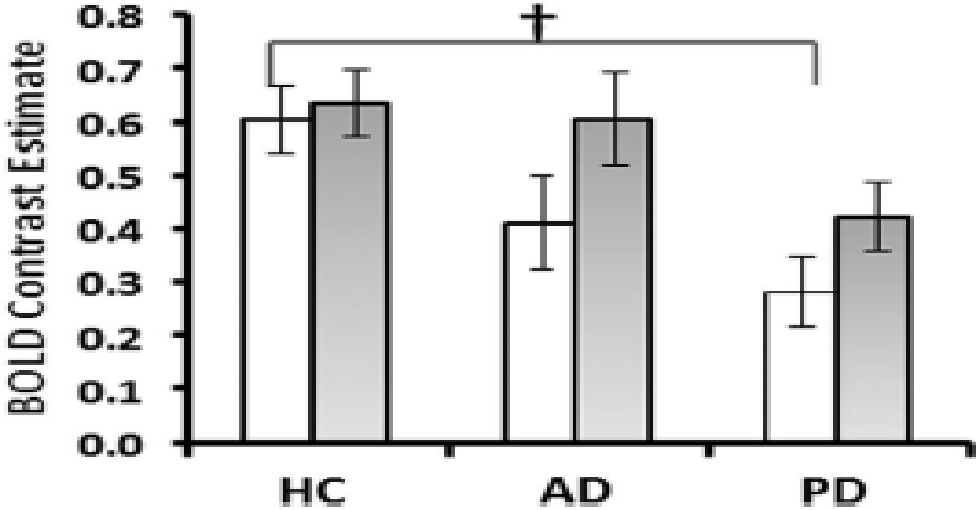
Anna Murphy*,[1], Liam J Nestor[2,3], John McGonigle[2], Louise Paterson[2], Venkataramana Boyapati[1],

ICCAM

Imperial College London · University of Cambridge · Manchester

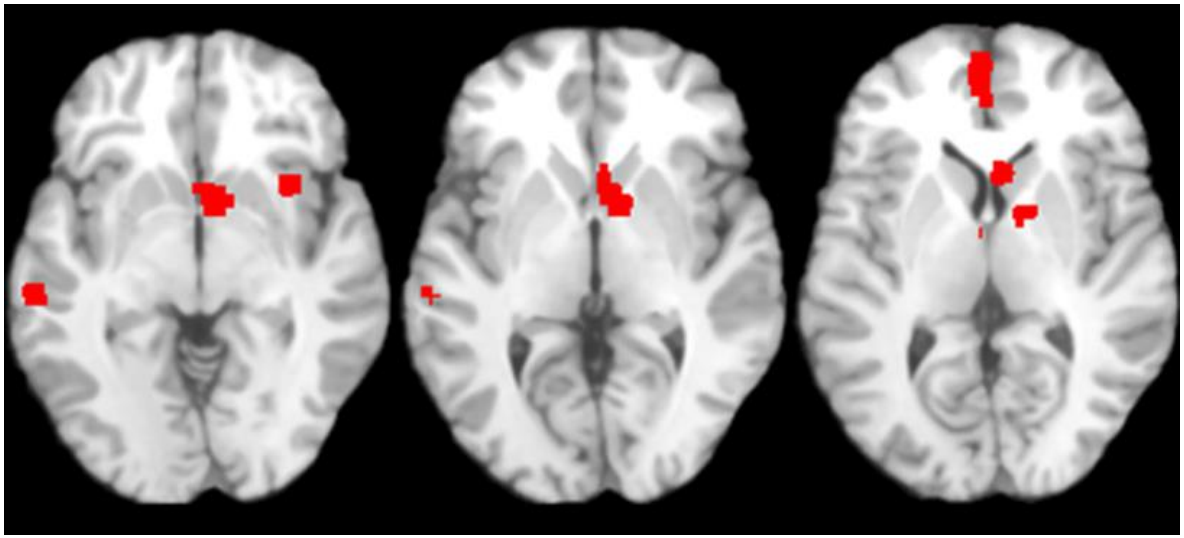
- DRD3 antagonism 'normalises' response in addiction
  - Presynaptic D3 receptor – increase dopamine





HC=Healthy Control, AD=abstinent alcohol dependent, PD=abstinent polydrug (alcohol, cocaine, opiate) dependent

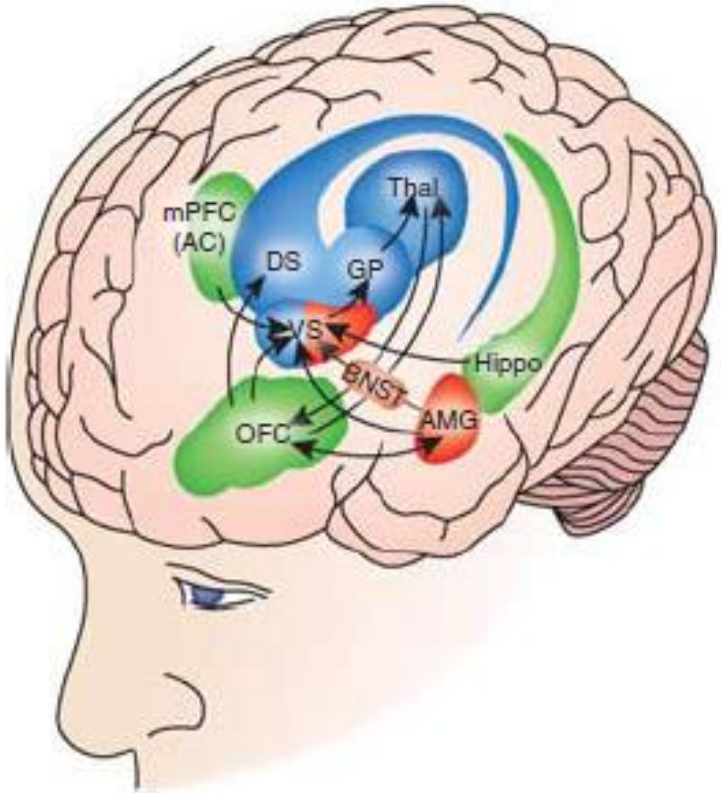
Alcohol cue reactivity

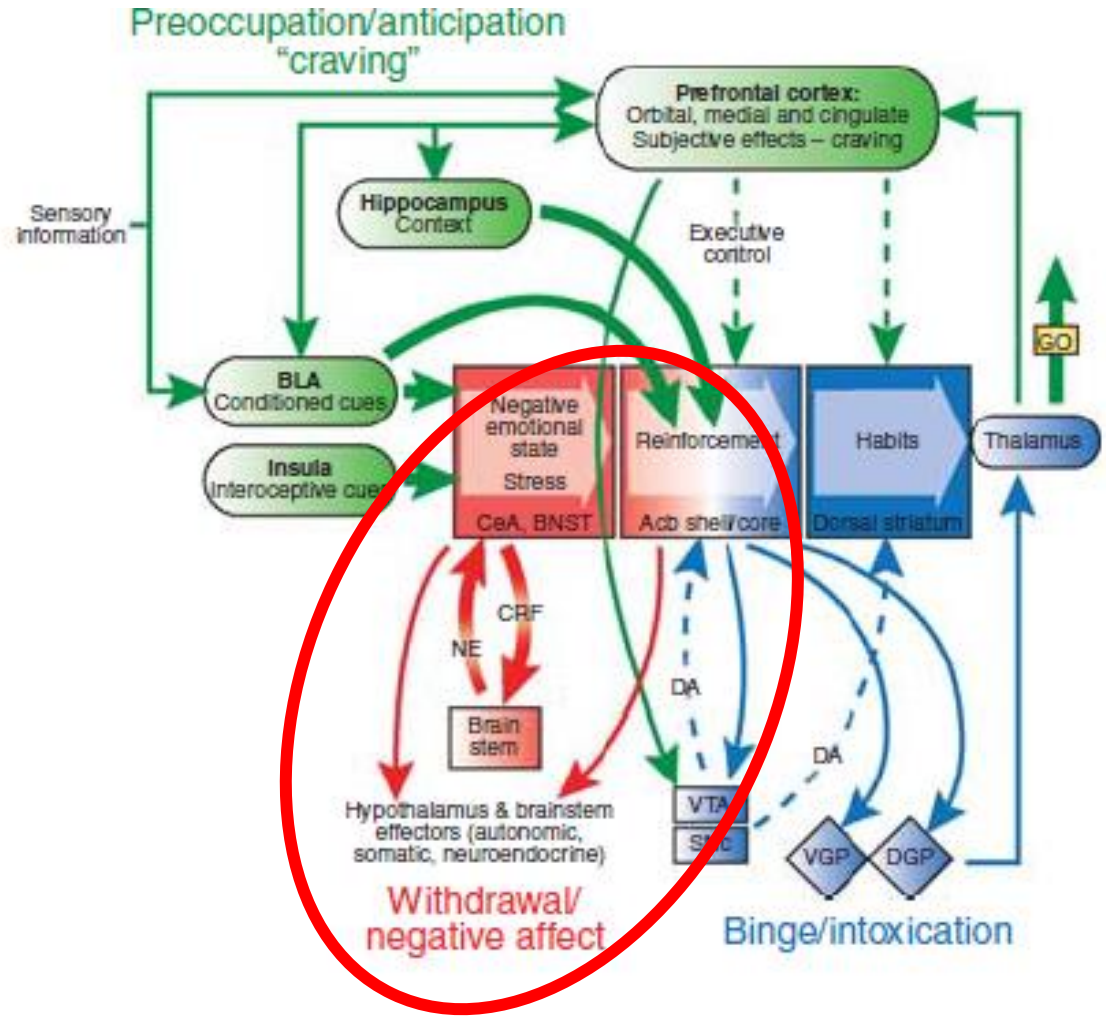


- In alcoholics: alcohol cues resulted in greater activation in
  - ventral striatum, anterior cingulate and ventromedial prefrontal cortex.
- Cue-elicited activation of ventral striatum was most frequently correlated with behavioural measures and most frequently reduced by treatment eg naltrexone
  - However there is little consistency across addictions and different paradigms to assist with prediction of treatment efficacy

Schacht et al; Courtney et al Addiction Biology

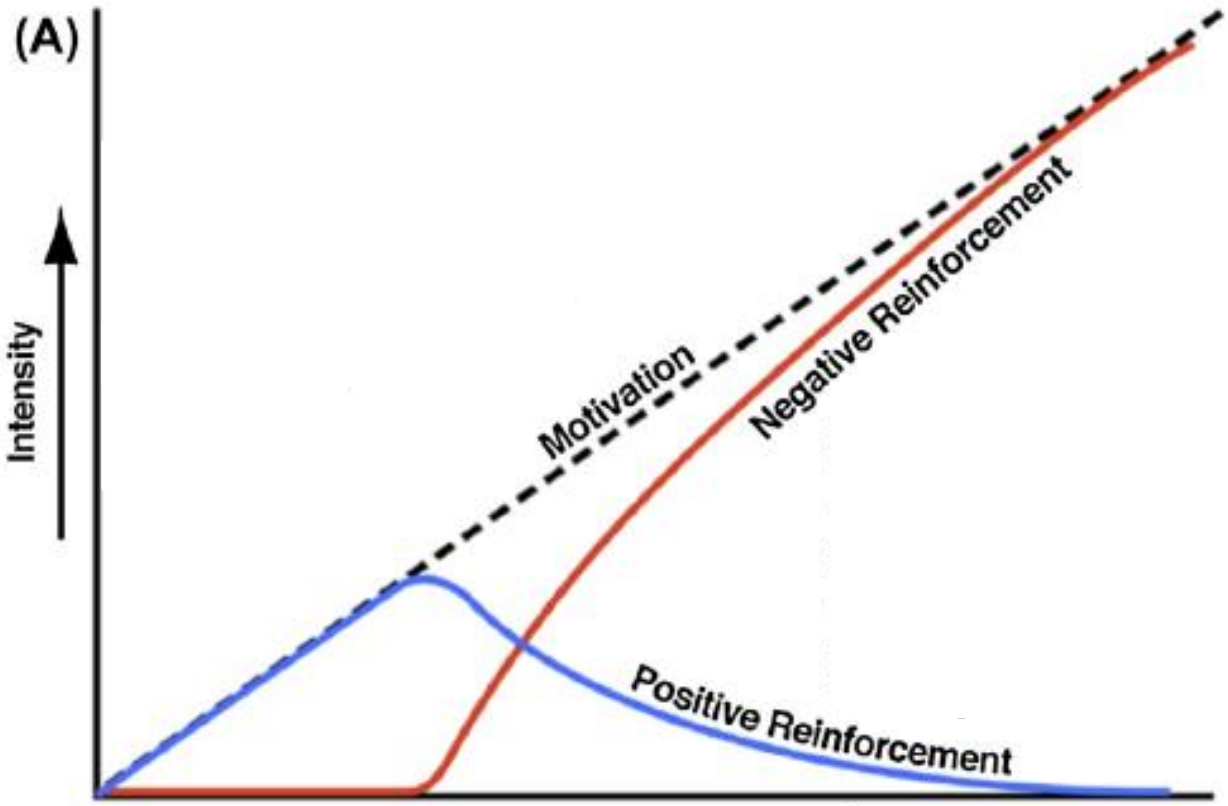
Regions of brain involved in different stages:
- binge/intoxication,
- withdrawal/negative affect,
- preoccupation/anticipation 'craving'.





Koob & Volkow

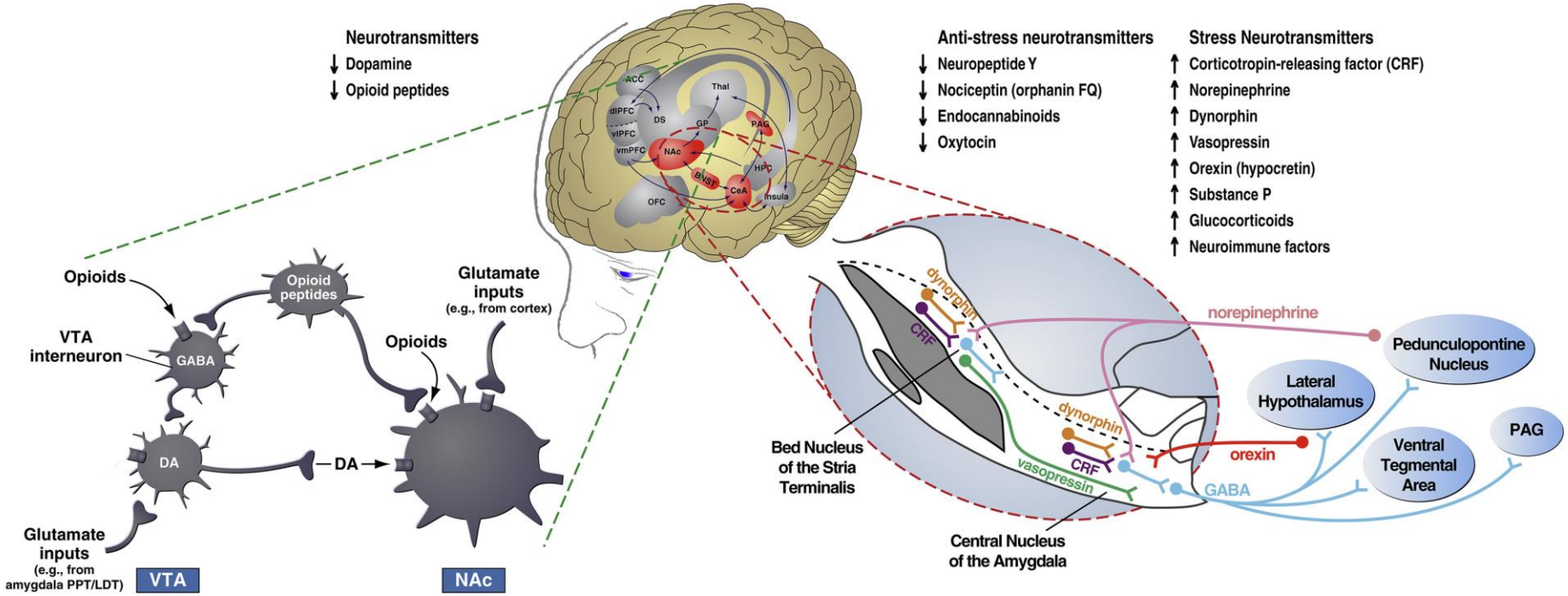
Change from positive to negative reinforcement as addiction/dependence develops.



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

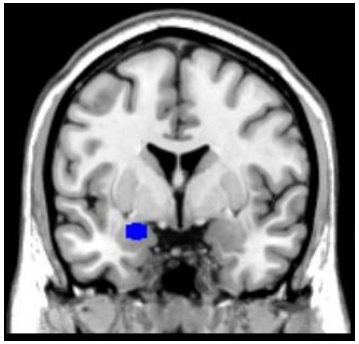
The ‘stress’ system: increased activity in many including kappa opioid (dynorphin), noradrenaline (arousal system) CRF (stress) etc

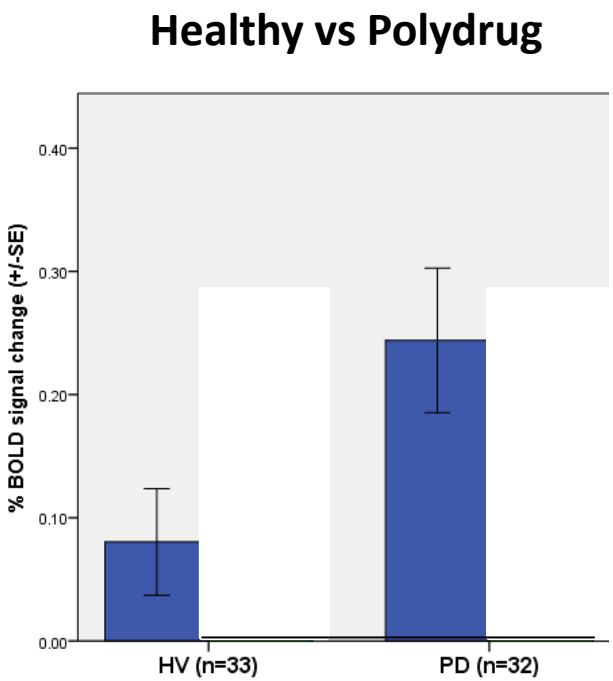


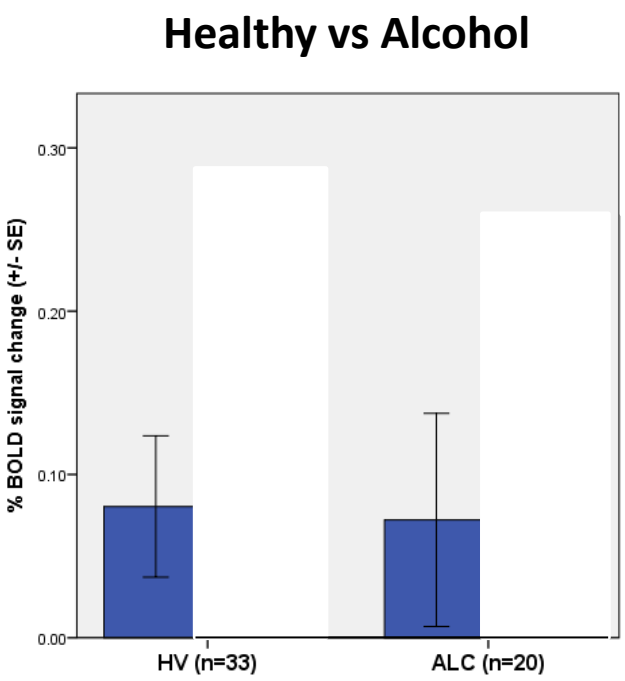
Dysregulation in amygdala is key

From Koob, Biol Psychiatry 2020 87(1):44-53.

Heightened brain response in left amygdala in abstinent polydrug addicts to aversive vs neutral images but not in alcoholism.







Paterson et al in prep

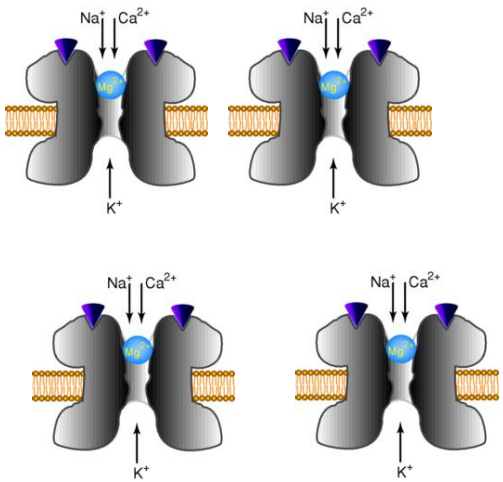
ICCAM
Imperial College London
UNIVERSITY OF CAMBRIDGE
MANCHESTER

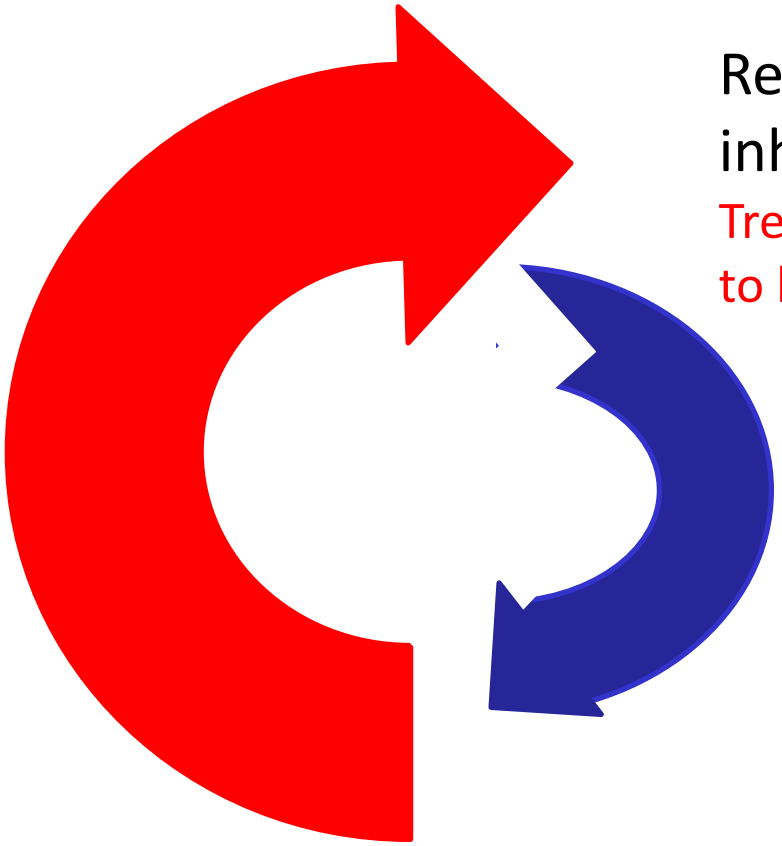
Withdrawal: a negative emotional state

Chronic alcohol exposure results in neuroadaptations:

in absence of alcohol GABA & glutamate are no longer in balance

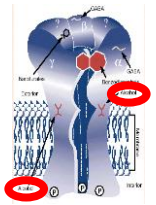
Upregulation of excitatory system





Reduced function in inhibitory system:

Treat with benzodiazepines to boost GABA function



GABA-A receptor:

NMDA receptor:

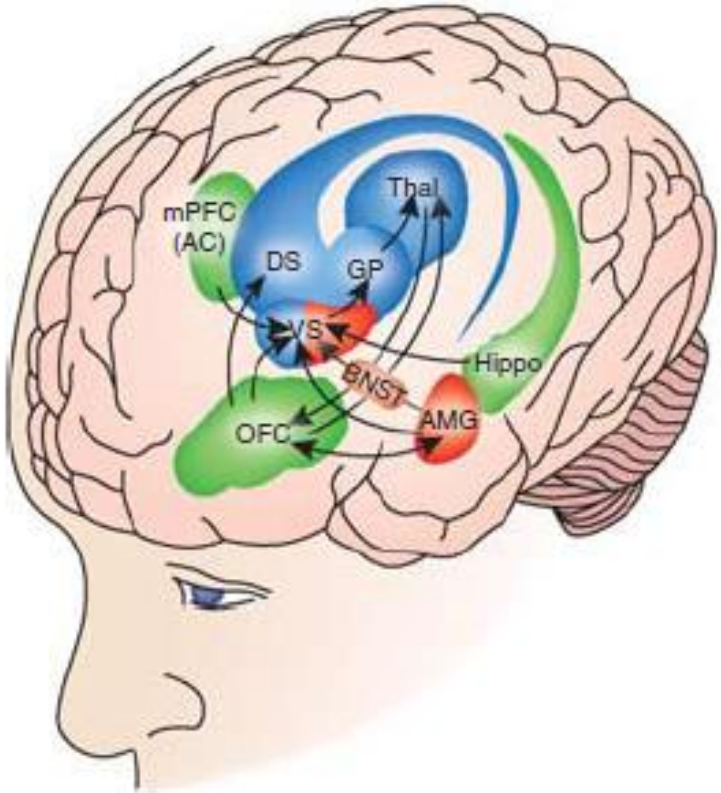
In detox:- increase in Ca^{2+}: toxic leading to hyperexcitability (seizures) and cell death (atrophy)

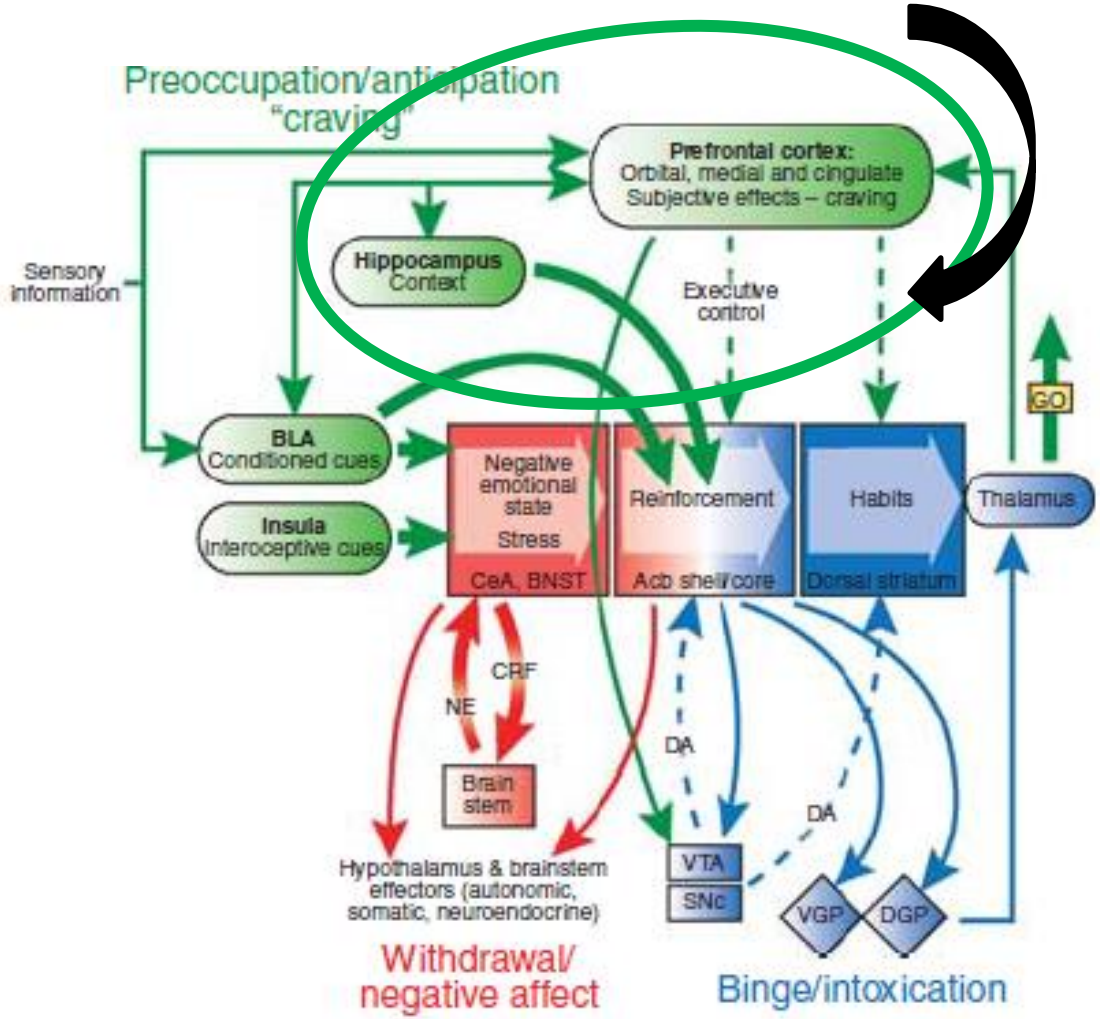
treatment: Mg loss – replenish?; thiamine – oral or parenteral?

For relapse prevention and consider for detox: acamprosate (functional NMDA antagonist)

Regions of brain involved in different stages:
- binge/intoxication
- withdrawal/negative affect
- preoccupation/anticipation 'craving'

Naltrexone: +ve
DRD3: no





Koob & Volkow

Implications from neurobiology for treatment in alcoholism

Psychosocial and pharmacological treatments to

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

- Medication is essential for some eg for detox and should always be used alongside psychosocial treatment
  - Active consideration for relapse prevention in moderate-severe alcoholism

Relapse prevention medications in alcoholism

	Medication	Pharmacology	Effect	Comments
Licensed & recommended	Acamprosate start: abstinent	Functional NMDA antagonist	Increases abstinence Possible neuroprotective effect (use during detox)	Generally well tolerated.
	Naltrexone start: abstinent	Nonselective opiate antagonist	Reduces risk of relapse from lapse	Generally well tolerated. Cannot be used with opiate analgesia
	Disulfiram start: abstinent	Aldehyde dehydrogenase inhibitor	Abstinence	Interaction with alcohol etc – more limited
	Nalmefene start: drinking	Mu opiate antagonist/ partial kappa agonist	Reduction of drinking in those who do not need a detox	Side effects – nausea, insomnia can be troublesome but 1-2d for most

Relapse prevention medications in alcoholism

	Medication	Pharmacology	Effect	Comments
Licensed & recommended	Acamprosate start: abstinent	Functional NMDA antagonist	Increases abstinence Possible neuroprotective effect (use during detox)	Generally well tolerated.
	Naltrexone start: abstinent	Nonselective opiate antagonist	Reduces risk of relapse from lapse	Generally well tolerated. Cannot be used with opiate analgesia
	Disulfiram start: abstinent	Aldehyde dehydrogenase inhibitor	Abstinence	Interaction with alcohol etc – more limited
	Nalmefene start: drinking	Mu opiate antagonist/ partial kappa agonist	Reduction of drinking in those who do not need a detox	Side effects – nausea, insomnia can be troublesome but 1-2d for most
Off-label	Baclofen start: abstinent (not drinking)	GABA-B agonist	Abstinence. Particularly in those with anxiety	Sedation main initial side-effect, dose - <60mg/d; taper reduction.

Relapse prevention medications in alcoholism

	Medication	Pharmacology	Effect	Comments
Licensed & recommended	Acamprosate start: abstinent	Functional NMDA antagonist	Increases abstinence Possible neuroprotective effect (use during detox)	Generally well tolerated.
	Naltrexone start: abstinent	Nonselective opiate antagonist	Reduces risk of relapse from lapse	Generally well tolerated. Cannot be used with opiate analgesia
	Disulfiram start: abstinent	Aldehyde dehydrogenase inhibitor	Abstinence	Interaction with alcohol etc – more limited
	Nalmefene start: drinking	Mu opiate antagonist/ partial kappa agonist	Reduction of drinking in those who do not need a detox	Side effects – nausea, insomnia can be troublesome but 1-2d for most
Off-label	Baclofen start: abstinent (not drinking)	GABA-B agonist	Abstinence. Particularly in those with anxiety	Sedation main initial side-effect, dose - <60mg/d; taper reduction.
Future?	Gabapentin, sodium oxybate, topiramate; new targets: 'anti-stress', appetitive hormones, inflammation	various	Various: support abstinence, reduce drinking etc	

Guidelines:
NICE
BAP

The National Clinical Guideline Centre

for acute and chronic conditions

Funded to produce guidelines for the NHS by NICE

ALCOHOL USE DISORDERS: DIAGNOSIS AND CLINICAL MANAGEMENT OF ALCOHOL-RELATED PHYSICAL COMPLICATIONS

Clinical Guideline 100

Royal College of Physicians

Setting higher medical standards

NHS

National Institute for Health and Clinical Excellence

Issue date: February 2011

Alcohol-use disorders

Diagnosis, assessment and management of harmful drinking and alcohol dependence

NICE clinical guideline 115

Developed by the National Collaborating Centre for Mental Health

BAP Guidelines

BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP

Psychopharm

Journal of Psychopharmacology
0(0) 1–54

DOI: 10.1177/0269881112444324
jop.sagepub.com
SAGE

AR Lingford-Hughes[1], S Welch[2], L Peters[3] and DJ Nutt[1]
With expert reviewers (in alphabetical order): Ball D, Buntwal N, Chick J, Crome I, Daly C, Dar K, Day E, Duka T, Finch E, Law F, Marshall EJ, Munafo M, Myles J, Porter S, Raistrick D, Reed LJ, Reid A, Sell L, Sinclair J, Tyrer P, West R, Williams T, Winstock A

Coming in 2021:
'Alcohol' guidelines from Public Health England