ARBDAlcohol and the brain conference 2023

David Nutt DM FRCP FRCPsych FBPs FMedSci DLaws
Prof of Neuropsychopharmacology
Imperial College London
d.nutt@imperial.ac.uk
profdavidnutt@twitter.com

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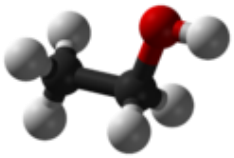
Alcohol is a small molecule, toxic to most organs



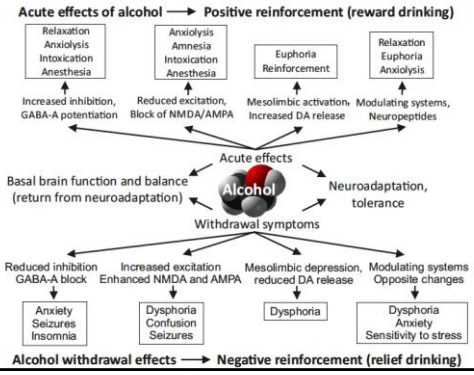
Toxicological safe limit is about 50mls/per year

- Alcohol molecule easily penetrates into the brain
- Alcohol is toxic to most organs of the body
- Alcohol consumption is strongly correlated with the risk of short- and long-term morbidity and mortality

Gabathuler. Neurobiol Dis 2010;37:48–57.
Oldendorf. NIDA Res Monograph 1992;120:13–25.
WHO. Alcohol fact sheet, 2011; Rehm et al. Eur Addict Res 2003;9:147–156

2

Complex brain effects of alcohol



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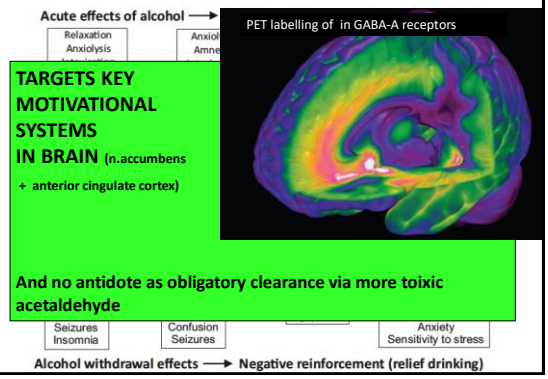
Complex brain effects of alcohol



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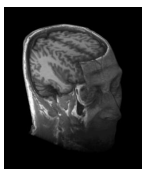
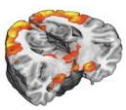
Neuroimaging approaches to understanding the impact of alcohol on the brain

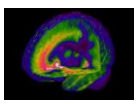
Structural v functional v chemical imaging



Brain shrinkage in alcoholism



Activation with stress



GABA receptor density

5

Structural changes in addiction

Really only seen with alcoholism

First described using X-ray air encephalography

How can we minimise this?

Effective treatment of alcohol abuse / dependence and prevention of complications

Healthy control volunteers

Abstinent 'healthy' alcohol-dependent patients

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Wernicke Encephalopathy

Wernick, C. (1881) described

- Abrupt onset confusional state
- Impairment of consciousness
- Ataxia and ophthalmoplegias

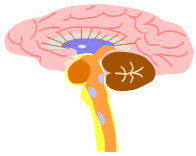
Pathology showed

- Numerous punctate haemorrhage symmetrically situated in the grey matter around third and fourth ventricles and aqueduct of Sylvius

7

How common is Wernicke's in the general population?

In a review of 26 691 general post-mortems



367 or 1.4% of cases had lesions indicative of Wernicke's Encephalopathy

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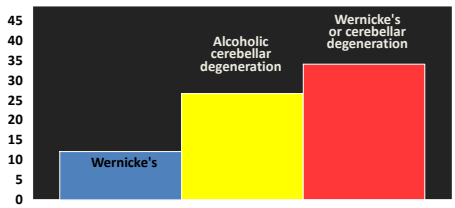
How Common is Wernicke's Encephalopathy in alcoholics?



% prevalence

Up to 35% of chronic alcoholics may develop lesions indicative of W-K syndrome

Adapted from Torvik 1982 and Victor et al., 1989

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Outcome of Wernicke's Encephalopathy

- **20% Die**
- **70%** **i.e. (85% of 80%)**
  Korsakoff's dementias
  – 50% of these require long-term care
- **10% recover**

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Treatment & prevention of WE

- Management of established or suspected WE:
  - High index of suspicion (particularly in A&E setting)
  - 2 pairs of vials of vitamins B+C (Pabrinex) i.v. t.d.s for 3 days
  - 1 pair of vials per day for 3-5 days
  - Administer in 100mls N/Saline or dextrose over 30mins
  - Resuscitation facilities readily available (anaphylaxis)
- High risk group (malnourished, weight loss, poor diet, requiring glucose infusion)
  - 1 pair of vials immediately then 1 per day for 3-5 days
- Low risk
  - Thiamine 200mg q.i.d. during detoxification admission

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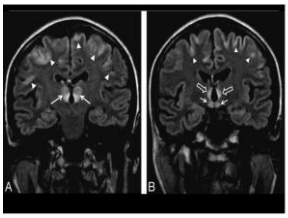
MRI of Wernicke's disease



(A) Signal-intensity alterations with different intensity patterns are seen in the thalami (arrows). Diffuse signal-intensity alterations of the frontal cortex (arrowheads) are present. (B) Note signal-intensity alterations in the mamillary bodies (arrows), periventricular region of the third ventricle (empty arrows), and brain cortex (arrowheads).

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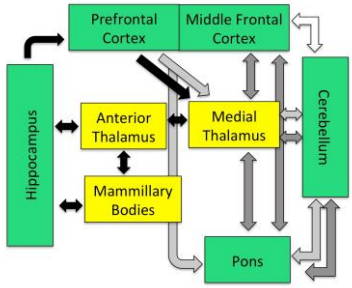

Added harms from alcohol

Figure 7.1: Brain regions damaged by thiamine deficiency (yellow) and by alcohol and thiamine deficiency (green). Arrows mark circuits (black= limbic/Papez circuit; gray=frontocerebellar loops [see Chanraud et al., 2013; light gray= executive loop; dark gray=motor loop; white= novel compensatory loop] that become altered in WKS patients (black and gray arrows) and in uncomplicated alcoholics (gray and white arrows).

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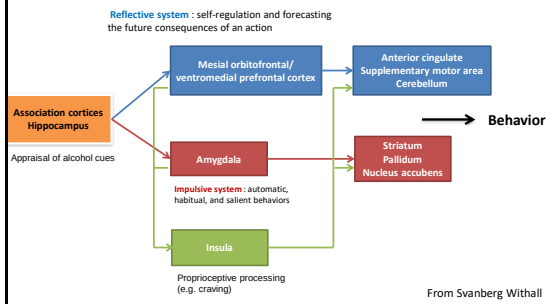

Figure 8.5. A brain network of alcohol addiction illustrating functional role for three key neural systems : impulsive system (in red), reflective system (in blue) and the insula (in green). Based on Noel et al. (2013).

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Reduced grey-matter → poorer decision making

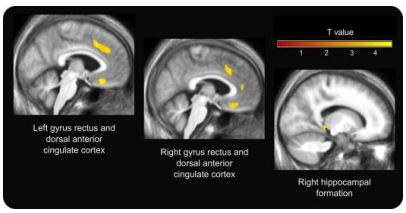

Figure 8.6. Positive correlations between the decision-making measure and brain voxels with reduced gray matter volume in the alcoholic group.

Reproduced from *Le Berre, A. P., Rauchs, G., La Joie, R., Mézenge, F., Boudehent, C., Vabret, F., Segobin, S., Viader, F., Allain, P., Eustache, F., Piiel, A-L., & Beaunieux, H. Impaired decision-making and brain shrinkage in alcoholism. European Psychiatry: The Journal of the Association of European Psychiatrists, 29(3), 125–133.* Copyright © 2014 Elsevier Masson SAS. All rights reserved.

From Svanberg Withall Draper and Bowden 2014

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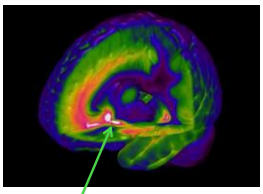
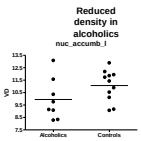
Lower GABA-A receptors in alcoholics in motive circuit → less control over decision-making?



Highest density in nucleus accumbens

Extra-synaptic GABA-A α5 receptors visualised by PET with [11C]Ro15-4513



Lingford-Hughes et al 2012 J Psychopharmacology

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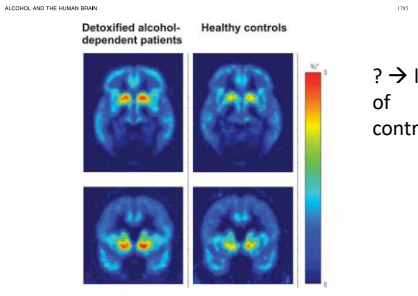
Increased number of opioid receptors in alcoholism



? → loss of control

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MANCHESTER 1824 · Imperial College London · UNIVERSITY OF CAMBRIDGE

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 · gsk GlaxoSmithKline

Mental Health Research Network · NHS National Institute for Health Research

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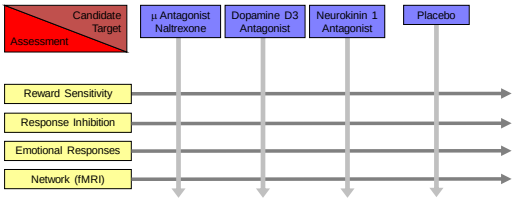
ICCAM Platform – Mechanisms of Relapse



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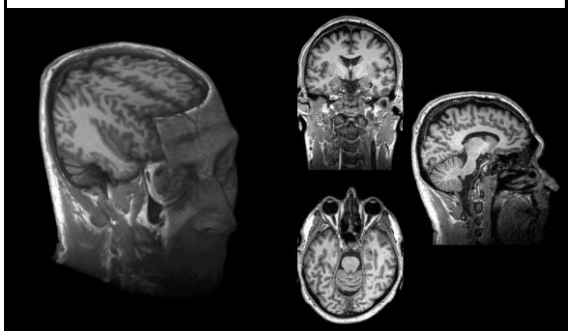
High Resolution Structural Imaging



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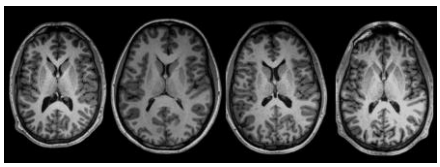
Alcohol related brain damage:

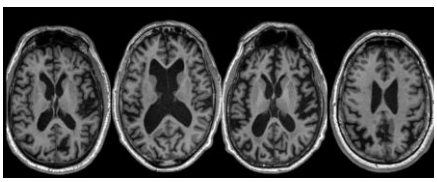
How can we minimise this?

Effective treatment of alcohol abuse / dependence and prevention of complications

Healthy control volunteers



Abstinent 'healthy' alcohol-dependent patients



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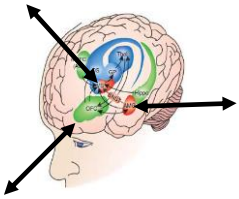
Reward deficiency = loss of positive reinforcement

Brain mediators of addiction:



Overcoming adverse state eg withdrawal, anxiety, stress

Impulsivity/ compulsivity; memory
Preoccupation / anticipation, craving

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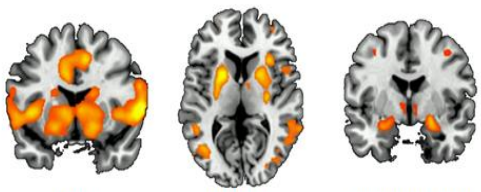
Brain signatures of each task

Figure 1. Patterns of brain activation in ICCAM tasks.



Reward
(Monetary Incentive Delay)
Reward > neutral
Z > 4

Impulsivity
(Go/No-go)
No-go > go
Z > 5

Emotional salience
(Evocative images)
Stress > neutral
Z > 4

Nutt et al ICCAM platform study

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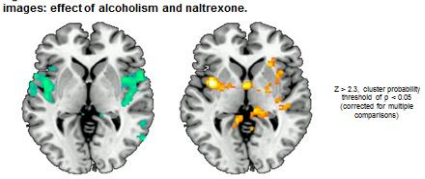
Differential impact of naltrexone on emotional images

Figure 3. Pattern of brain activation with evocative images: effect of alcoholism and naltrexone.



Healthy controls
Response goes down with naltrexone

Alcohol group
Response goes up with naltrexone

Z > 2.3, cluster probability threshold of $p < 0.05$ (corrected for multiple comparisons)

Nutt et al ICCAM platform study

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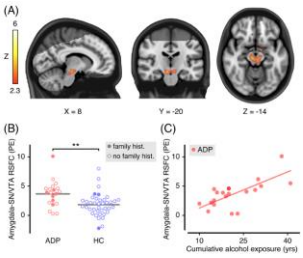
Enhanced connectivity between amygdala and dopamine nuclei in alcohol use disorder → loss of control?



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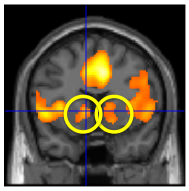
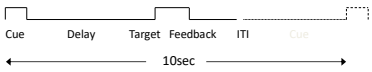
Reward Responding - Monetary Incentive Delay Task

N accumbens activation presumed due to increase in dopamine neuronal firing





Knutson et al. (2001) J Neurosci

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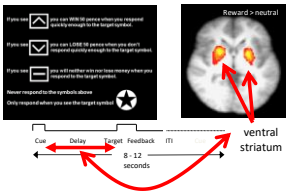
Assessing function in the mesolimbic reward pathway with fMRI

Monetary Incentive delay task - anticipation of winning money



ICCAM

Knutson et al

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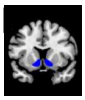
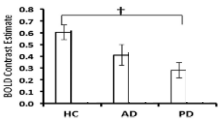
ICCAM

Blunted activation of reward pathway during anticipation of winning money in abstinent addicts





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

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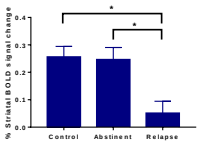
ICCAM

Higher activity in reward pathway during anticipation of winning money is associated with abstinence at 1yr follow-up:



Paterson et al

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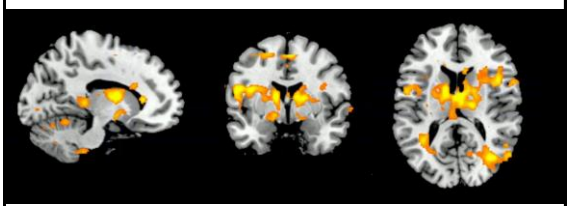
Monetary Incentive Delay task

Win anticipation > neutral anticipation

GSK598809 > placebo

Alcohol group

Analysis: control v alcohol
n: 18 + 18 = 36



GSK598809 increases response to win anticipation in alcohol group

? → Improved motivation

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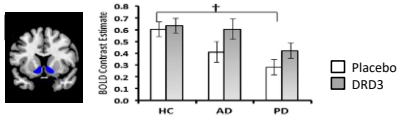
Acute D3 Antagonist GSK598809 Selectively Enhances Neural Response During Monetary Reward Anticipation in Drug and Alcohol Dependence

Neuropsychopharmacology (2017), 1–9

Anna Murphy[1,2], Liam J Nestor[1,2], John McGonigle[1], Lysia Paterson[1], Venkataramana Bogapati[1], ...

- 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

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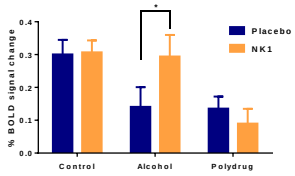
NK1 antagonism (aprepitant) also significantly 'normalises' blunted reward anticipation in alcoholism but not healthy controls or polydrug addicts.



Paterson et al

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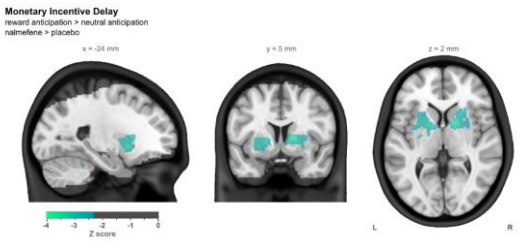
Nalmefene and MID task during alcohol intoxication fMRI



Significant decrease in globus pallidus and putamen and in brain stem

Quelch Lingford-Hughes and Nutt Biological Psychiatry

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Putting chemistry in charge?

A safer "synthetic" alcohol
- with antidote
New Scientist 2006
The Scientist Jan 2011

Should this not be a global health challenge?

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Now available – the first active botanical GABA-spirit

GABA Labs launches an active botanical spirit alcohol alternative in Jan 2021

The first GABA Spirit

Approved food grade ingredients

To sample
https://www.sentiaspirits.com

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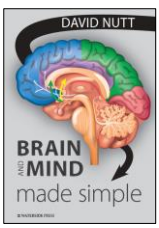
Thanks – questions and further reading



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