Psychedelics for addiction

Rotterdam 2023

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Declaration of interests – 2019-2023

- Advisor - British National Formulary
- Past President - British Neuroscience Association - European Brain Council
- Past President - European College of Neuropsychopharmacology
- **Chair – DrugScience [UK] - & PAREA Europe (Psychedelic Access and Resea**
- Member International Centre for Science in Drug Policy
- Editor of the journal Drug Science policy and law
- Advisory Boards - AWAKN, Psyched Wellness, Neural Therapeutics
- Speaking honoraria (in addition to above) Lundbeck, BMS/Otsuka, Janssen, Take
- Member of the Lundbeck Foundation Neurotorium programme and Chair of the
- Grants or clinical trial payments: Wellcome Trust, MRC
- Share options – P1vital, Awakn, Psyched Wellness Director Equasy Enterprises
- Expert witness in a number of legal cases relating to psychotropic drugs
- Edited/written >38 books - some purchased by pharma companies

Two translated into Flemish

Dranke? 2022

Psychedelics - out in 2024

Psychedelics are an enduring feature of human existence

5-HT2A psychedelics

Peyote /mescaline

Ancient Greeks/ ergot in wine

K26.1 PLOUTOS ENIATOS, DEMETER ELEUSIS

Magic mushrooms/ psilocybin

Morning glory

Ayahuasca

Amanita Muscaris

GABA psychedelic – muscimol

A (cholinergic) psychedelic experience led to the founding of AA in 1933 by Bill Wilson

"Suddenly the room lit up with a great white light. I was caught up in an ecstasy which there are no words to describe. It seemed to me in my mind's eye, that I was on a mountain and that a wind not of air but of spirit was blowing. ***And then it burst upon me that I was a free man."***

Years after this psychedelic-induced sobriety conversion Bill Wilson experienced LSD (with Huxley) and came to believe that it could help "cynical alcoholics" achieve spiritual awakening …. more later

Aldous Huxley and mescaline

Peyote cactus

" the brain is an instrument for focusing the mind"

"a reducing valve"

If the doors of perception were cleansed every Thing would appear to man as it is, infinite. For man has closed himself up, till he sees all Things thro' narrow chinks of his cavern.

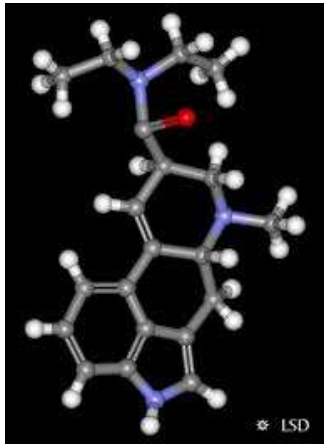
William Blake, 1793

LSD – the big breakthrough

LSD

→ synthetic and more potent psychedelic

→ wide medical and research use



Albert Hofmann – the discoverer of the chemistry of LSD and psilocybin - at 100

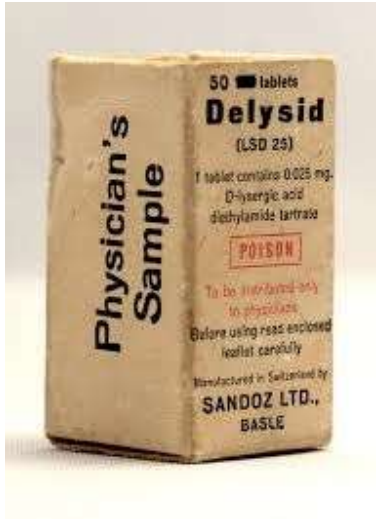
Early Psychiatric Uses for LSD and psilocybin

1. **Psychotomimetic**

2. **Self-experimentation by mental health professionals**

3. **Psychedelic Psychotherapy**
   - **High dose single drug session**
   - **Mystical / Peak experience**
   - **Favoured in the US**

4. **Psycholytic Psychotherapy**
   - **Low doses**
   - **Frequent, regular sessions**
   - **Favoured in the UK**



Clinical Interest in LSD in the 1950s and 1960s

- Hundreds of psychiatrists worldwide
- 140 NIH grants
- 1000 clinical papers
- 40,000 patients
- 40 books
- 6 International conferences

Results were overwhelmingly positive, describing safe and effective treatments

(Masters and Houston, 1971)

Pooled analyses in the 1960s

- **44 psychiatrists, 5000 subjects and 25,000 drug sessions:**
  Rate of psychosis: 0.2%
  Rate
  (Cohen S
- **700**
  One
  (Chandle
- **350**
  One
  (Ling TM,

"Treatment with LSD is not without acute adverse reactions, but given adequate psychiatric supervision and proper conditions for its administration, the incidence of such reactions is not great,"

- **Review of 20 years of psychedelic therapy in the UK, 4000 patients and 50,000 psychedelic drug-assisted sessions.**
  Two completed suicides
  Thirty-seven patients with a prolonged psychosis

(Malleson, N. (1971) 'Acute Adverse Reactions to LSD in clinical and experimental use in the UK.' Br J Psychiatry. 18(543): 229-30)

Recent review

Schlag AK, Aday J, Salam I, Neill JC, Nutt DJ et al., 2022, Adverse effects of psychedelics: From anecdotes and misinformation to systematic science, *JOURNAL OF PSYCHOPHARMACOLOGY*, Vol: 36, Pages: 258-272, ISSN: 0269-8811

6 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: $Z = 3.59$ ($P = 0.0003$)

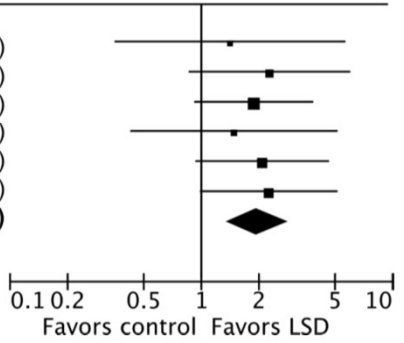


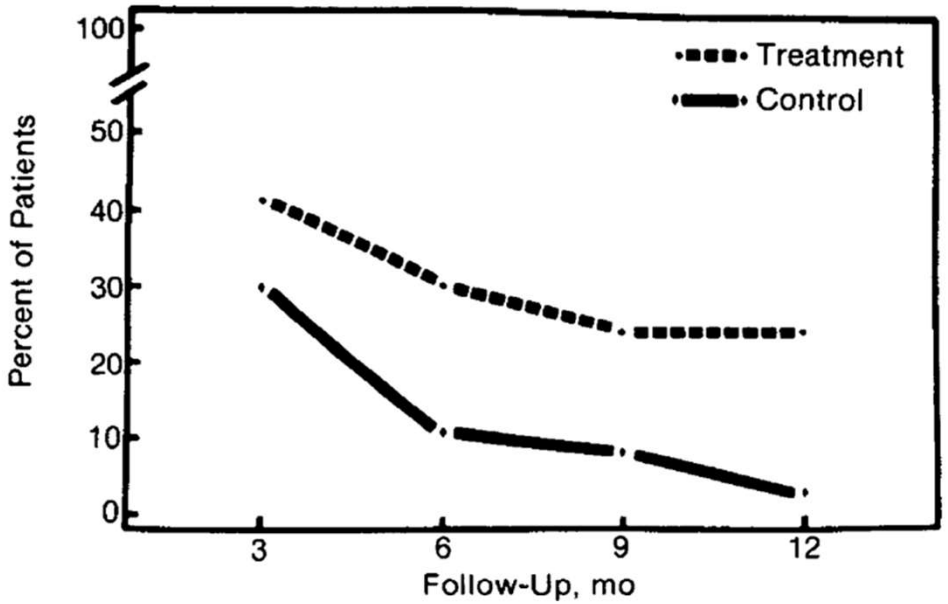
Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.
[a]Continuous outcome data.

Effect size >= all current therapies

Journal of Psychopharmacology 2012 Krebs and Johanssen

LSD for heroin addiction

Fig 1.—Percent of patients maintaining total abstinence at 3-, 6-, 9-, and 12-month follow-up.



Leonard N

The two experiences of heroin and LSD are like night and day. Heroin is night, a time to sleep and with sleep nothing comes. But with LSD it is like dawn, a new awakening, it expands your mind, it give you a brand-new outlook on life.

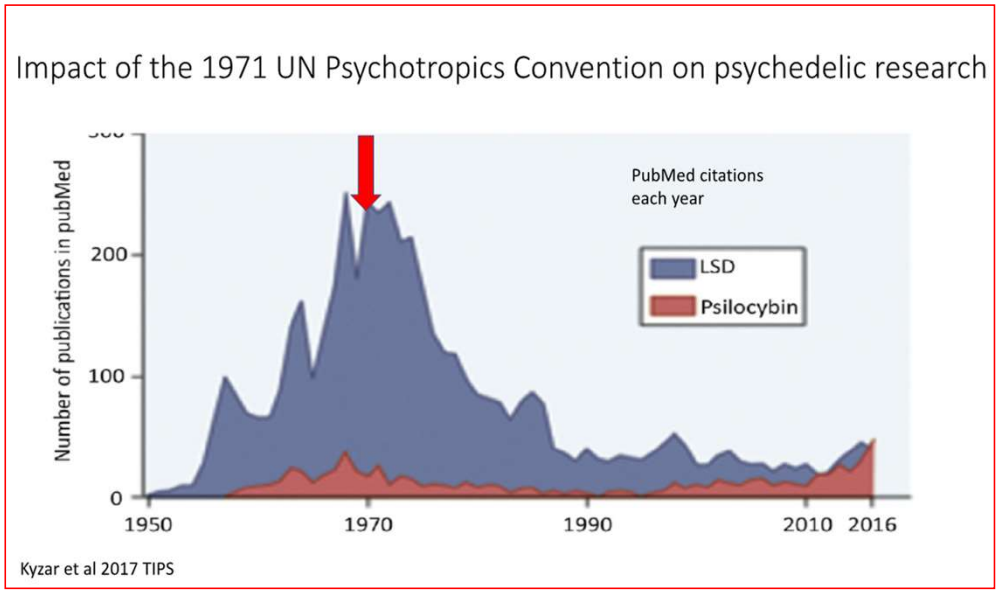
Arch Gen Psych 1973

Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

Charles Savage, MD, O. Lee McCabe, PhD, Baltimore

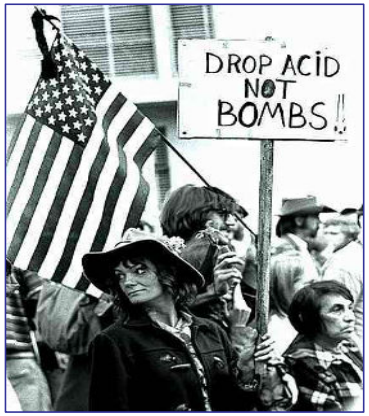
How the 1967 US ban and the 1971 UN Conventions destroyed psychedelic research



Put into Schedule 1 – "highly dangerous and no medical use"

➔ the worst censorship of ANY research in the history of the world

Psychedelics banned as they were changing art, music and culture and were associated with the anti-Vietnam war movement



In 1967 LSD (and most other psychedelics) were banned in face of opposition from senators

Bobby Kennedy:

Why if [clinical LSD projects] were worthwhile six months ago, why aren't they worthwhile now? . . . We keep going around and around. . . . If I could get a flat answer about that I would be happy. Is there a misunderstanding about my question?

I think perhaps we have lost sight of the fact that LSD can be very, very helpful in our society if used properly."

quoted in Lee & Shlain, 1985, p. 93)

Has there ever been a worst example of research censorship? NO!

For over 50 years the ban has persisted based on the myth of serious harms despite overwhelming evidence to the contrary

Psychedelics and MDMA

UK experts

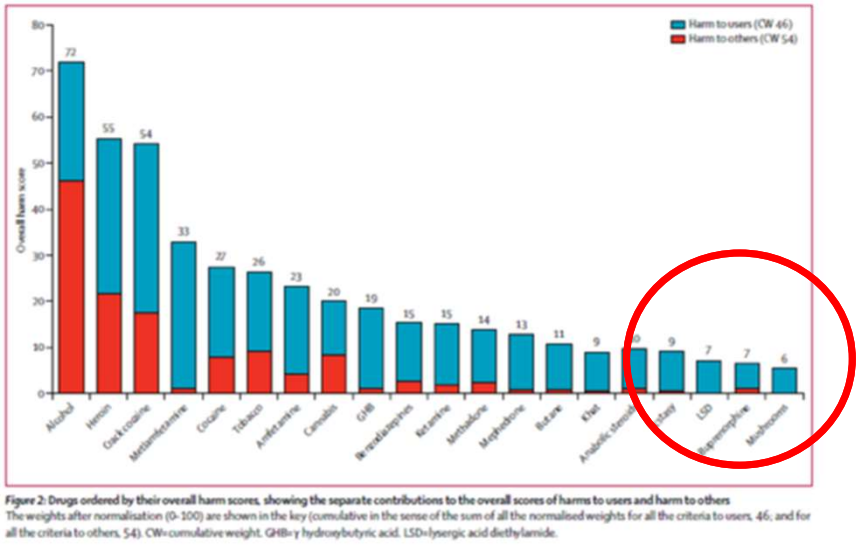
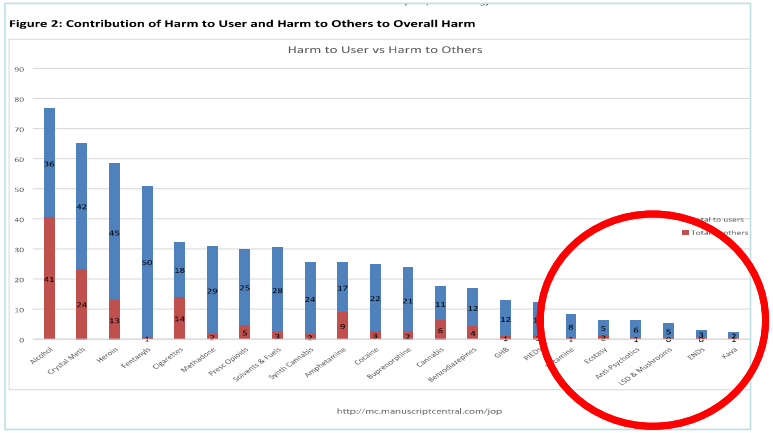


Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others
The weights after normalisation (0-100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 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

EU experts

van Amsterdam et al J Psychopharmacology 2014

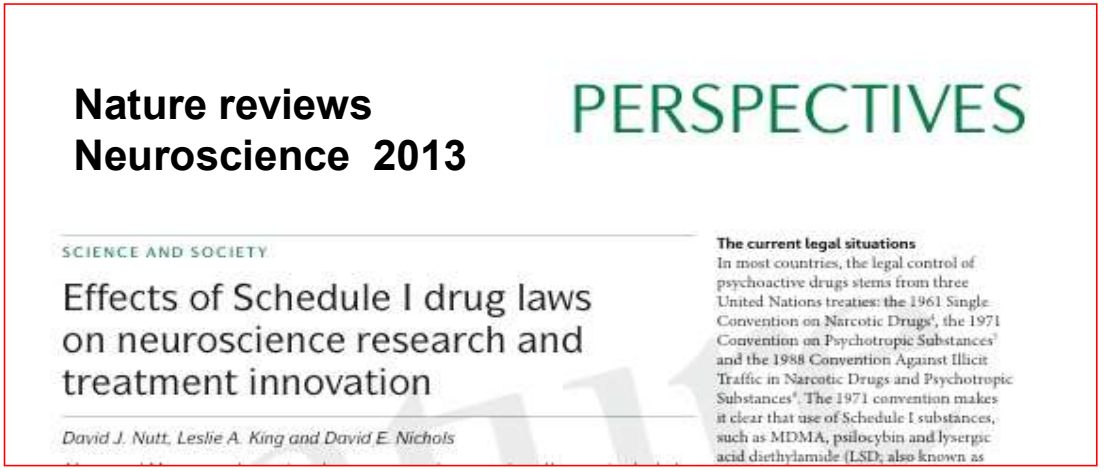


Australian experts

Bonomo et al J Psychopharmacology 2018

To read more about it

Nature reviews Neuroscience 2013



PERSPECTIVES

SCIENCE AND SOCIETY

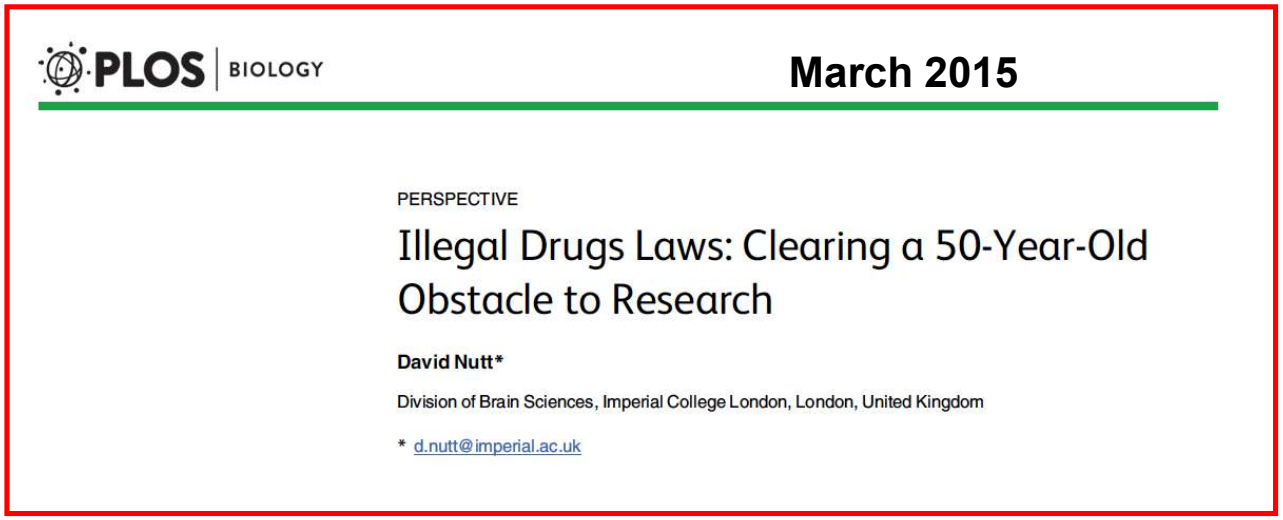
Effects of Schedule I drug laws on neuroscience research and treatment innovation

David J. Nutt, Leslie A. King and David E. Nichols

The current legal situations

In most countries, the legal control of psychoactive drugs stems from three United Nations treaties: the 1961 Single Convention on Narcotic Drugs[4], the 1971 Convention on Psychotropic Substances[5] and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances[6]. The 1971 convention makes it clear that use of Schedule I substances, such as MDMA, psilocybin and lysergic acid diethylamide (LSD; also known as

March 2015



PLOS | BIOLOGY

PERSPECTIVE

Illegal Drugs Laws: Clearing a 50-Year-Old Obstacle to Research

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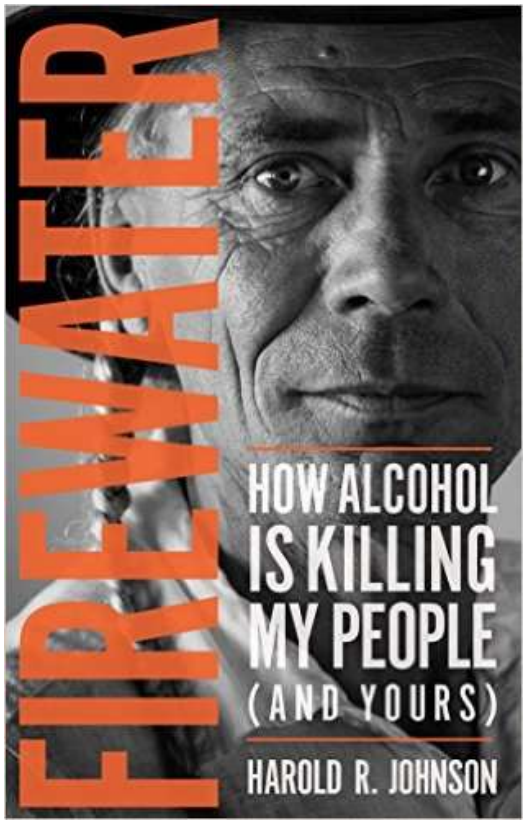
Why we need new treatments for addiction



>400 million people with addiction in the world

>90% do not get treatment

And treatment success rates < 30%

Alcohol responsible for over half of all crime and health problems in some Canadian First Nation peoples

Evgeny Krupitsky pioneers ketamine treatment of addiction

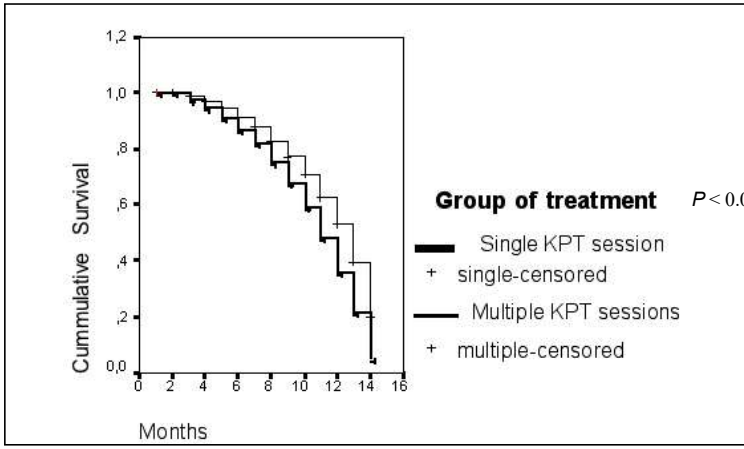
Ketamine Psychedelic Therapy (KPT): A Review of the Results of Ten Years of Research

E.M. Krupitsky, M.D., Ph.D.* & A.Y. Grinenko, M.D., Ph.D.*

Abstract—Ketamine is a prescription drug used for general anesthesia. In subanesthetic doses, it induces profound psychedelic experiences and hallucinations. The subanesthetic effect of ketamine was the hypothesized therapeutic mechanism in the authors' use of ketamine-assisted psychotherapy for alcoholism. The results of a controlled clinical trial demonstrated a considerable increase in efficacy of the authors' standard alcoholism treatment when supplemented by ketamine psychedelic therapy (KPT). Total abstinence for more than one year was observed in 73 out of 111 (65.8%) alcoholic patients in the KPT group, compared to 24% (24 out of 100 patients) of the conventional treatment control group ($p<0.01$). The authors' studies of the underlying psychological mechanisms of KPT have indicated that ketamine-assisted psychedelic therapy of alcoholic patients induces a harmonization of the Minnesota Multiphasic Personality Inventory (MMPI) personality profile, positive transformation of nonverbalized (mostly unconscious) self-concept and emotional attitudes to various aspects of self and other people, positive changes in life values and purposes, important insights into the meaning of life and an increase in the level of spiritual development. Most importantly, these psychological changes were shown to favor a sober lifestyle. The data from biochemical investigations showed that the pharmacological action of KPT affects both monoaminergic and opioidergic neurotransmitter metabolism, i.e., those neurochemical systems which are involved in the pathogenesis of alcohol dependence. The data from EEG computer-assisted analysis demonstrated that ketamine increases theta activity in cerebrocortical regions of alcoholic patients. This is evidence of the reinforcement of limbic cortex interaction during the KPT session.

Keywords—alcoholism, hallucinogen, ketamine, psychedelics, psychotherapy, Russia

Journal of Psychoactive Drugs 165 Vol. 29 (2), April - June 1997



Positive results in heroin and alcohol addiction

The new UK trial

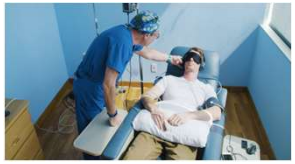
KARE Trial Design

Multi-site Phase II a/b

n=96

Patients with moderate/severe alcohol use disorder

3*Ketamine
(IV 0.8 mg/kg)
over 40 mins
n=48



3*Placebo
(IV saline)
over 40 mins
n=48

n=24
+ KARE therapy

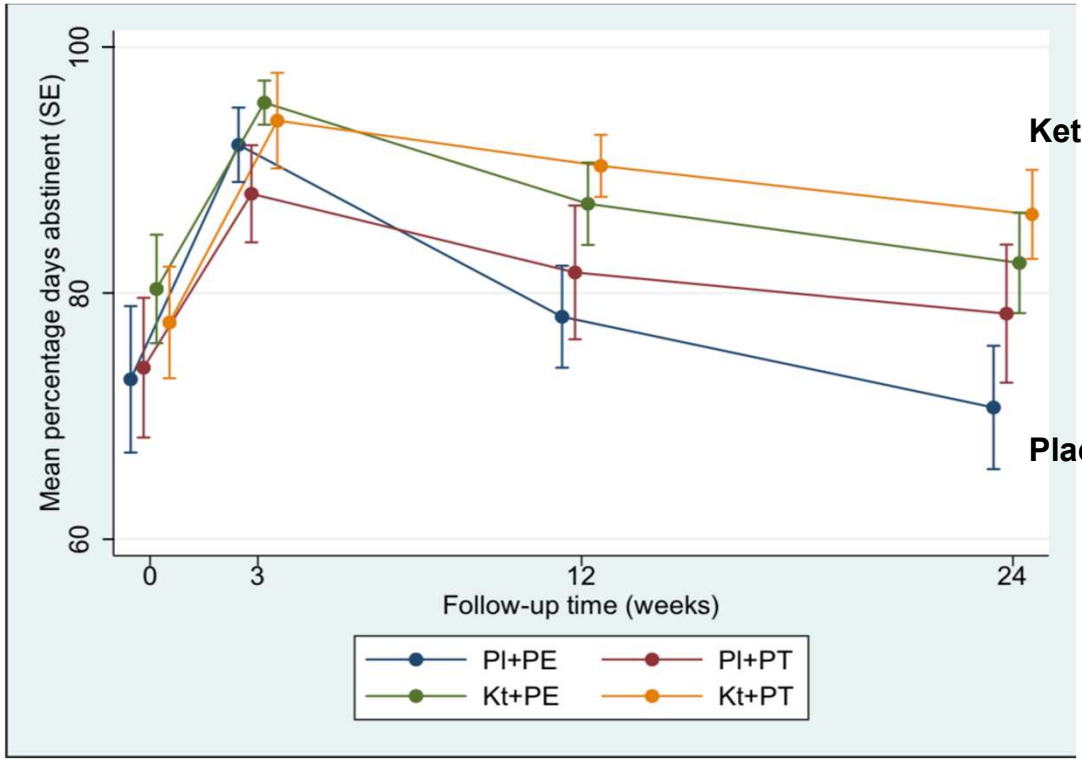
n=24
+ Alcohol Education

n=24
+ KARE Therapy

n=24
+ Alcohol Education

Grabski et al. JAMA Psychiatry 2022

Main results: Drinking Outcomes



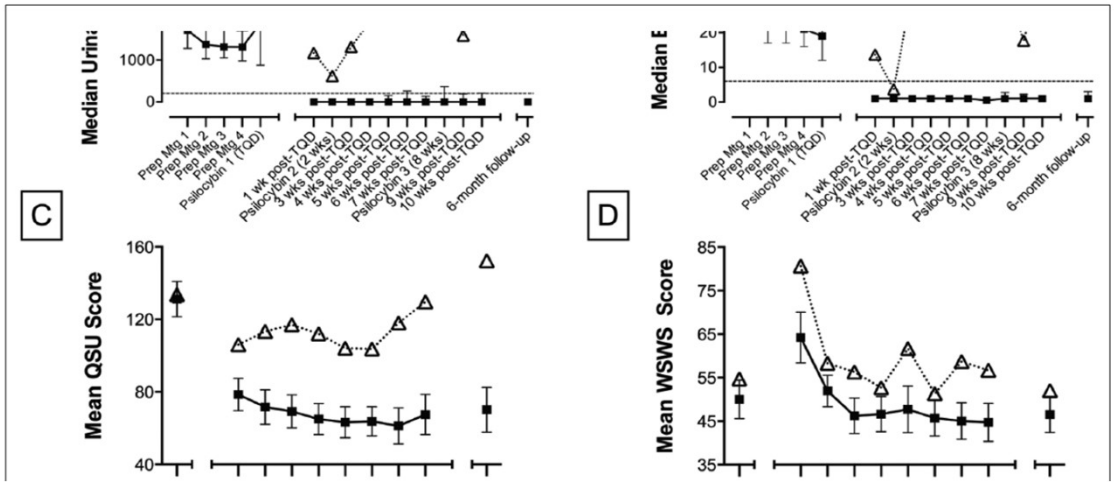
Ketamine + psychotherapy

Placebo + education

Grabski et al. JAMA Psychiatry 2022

Psilocybin for tobacco quitting

Tobacco quitting – Johnson 2014 – J of Psychopharmacology



Johnson – unpublished data on 100 treatment- resistant smokers
1 dose psilocybin -v- nicotine patch
59% psilocybin – abstinent -v- 28 patch
Stops mood symptoms of nicotine withdrawal – no effect on physical ones
Improved cognition in oddball task = less cognitive interference = less automaticity

US National. Institute for Drug Abuse now funding a new larger quitting study

Psilocybin for alcohol dependence

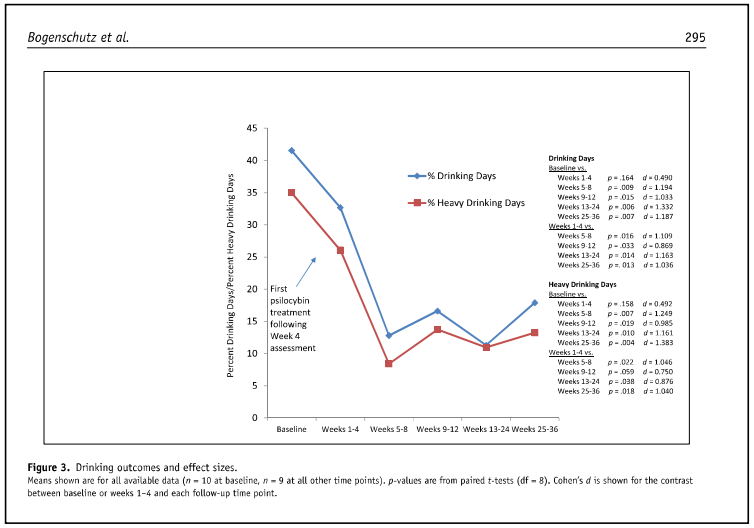


Figure 3. Drinking outcomes and effect sizes.
Means shown are for all available data (n = 10 at baseline, n = 9 at all other time points). p-values are from paired t-tests (df = 8). Cohen's d is shown for the contrast between baseline or weeks 1–4 and each follow-up time point.

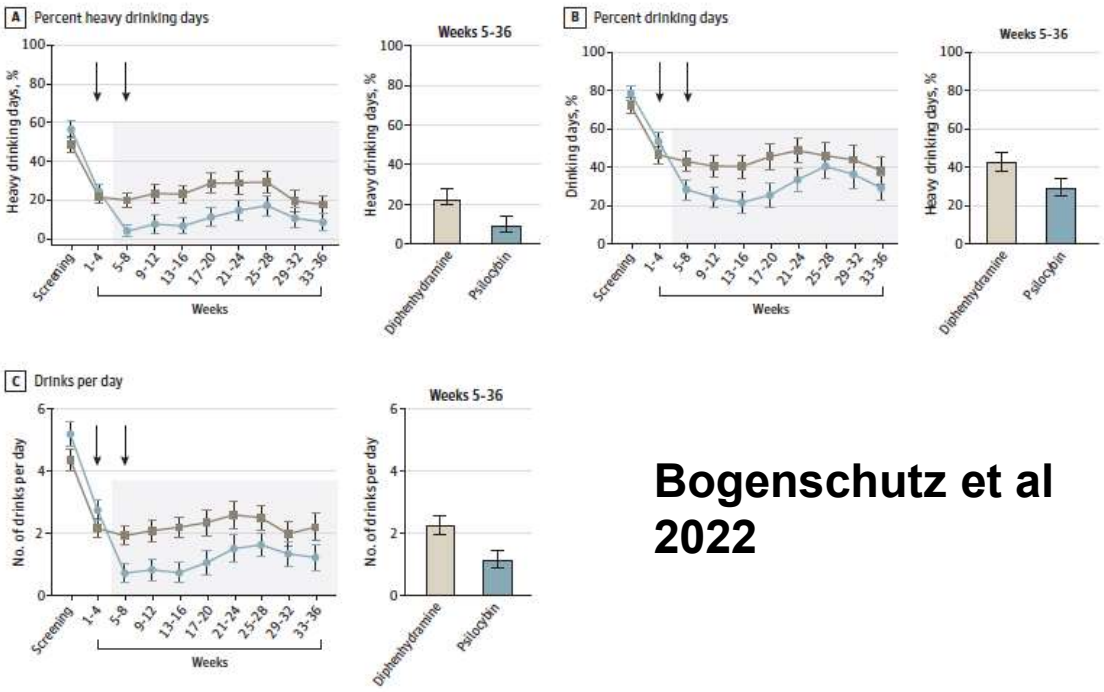
Bogenschutz et al
J of Psychopharmacology 2015

JAMA Psychiatry | Original Investigation

Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder
A Randomized Clinical Trial

Michael P. Bogenschutz, MD; Stephen Ross, MD; Snehal Bhatt, MD; Tara Baron, MA; Alyssa A. Forcehimes, PhD; Eugene Laska, PhD; Sarah E. Mennenga, PhD; Kelley O'Donnell, MD, PhD; Lindsey T. Owens, MA; Samantha Podrebarac, MA; John Rotrosen, MD; J. Scott Tonigan, PhD; Lindsay Worth, MA

Figure 2. Effects of Treatment on Continuous Drinking Outcomes



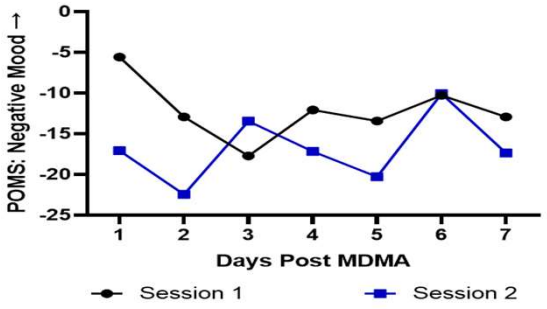
Mean (SE) estimates for screening (84 days prior to screening), weeks 1-4 (28 days prior to first double-blind medication session; covariate in the model), and eight 28-day bins following the first double-blind medication session (shaded area: weeks 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, and 33-36). Arrows represent double-blind medication sessions 1 and 2.

Bogenschutz et al 2022

The Bristol-Imperial MDMA-Alcoholism ('BIMA') Study

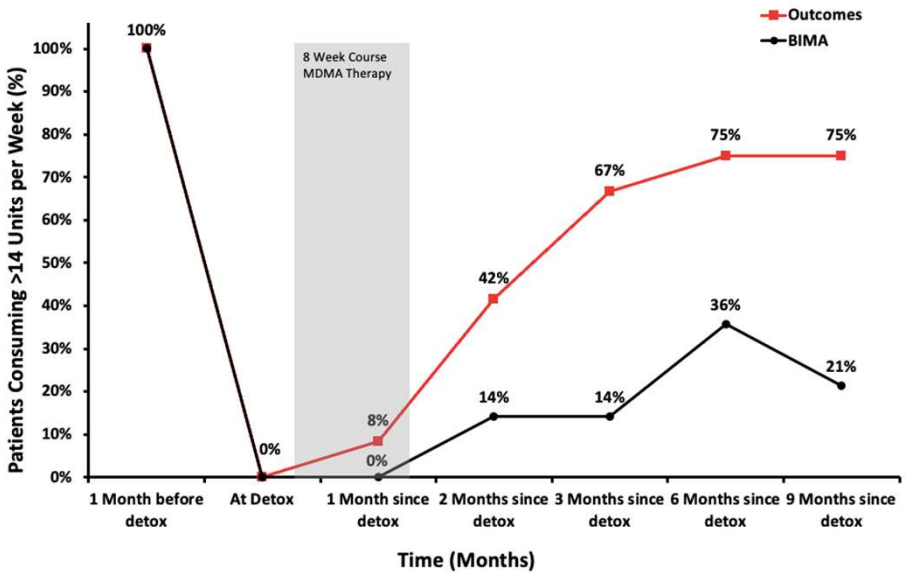
125mg +62.5 top up at 2 hours in a 12 week abstinence-based prog

No mood reduction after the MDMA sessions



Profile of Mood States (POMS) carried out by daily telephone calls for 7-days after each MDMA session (Average scores across 26 MDMA sessions)

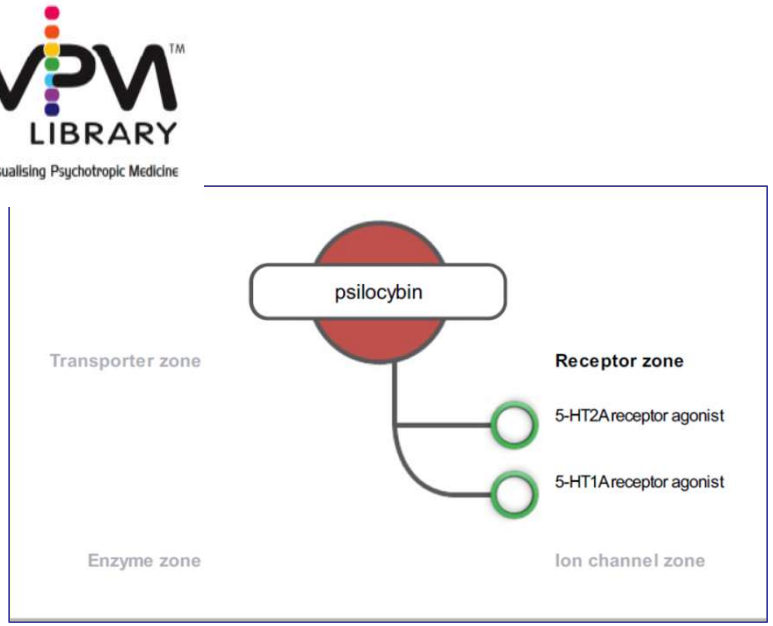
MDMA x 2 increased abstinence rates

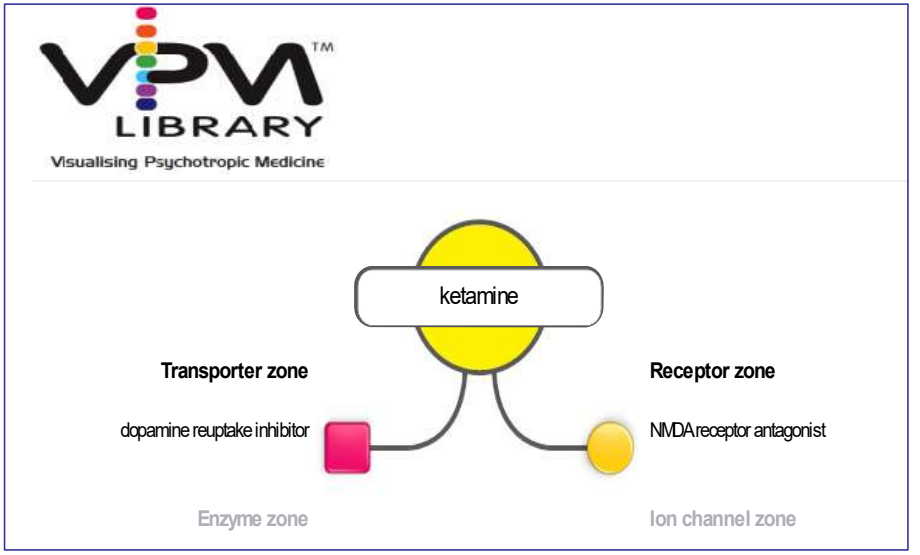


Comparison of MDMA Therapy against Treatment As Usual for Alcohol Use Disorder

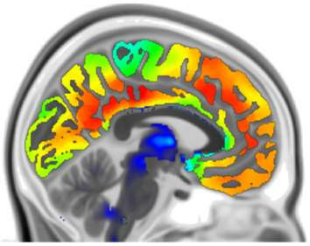
Sessa et al 2021 Journal of Psychopharmacology

How do these drugs with very different pharmacologies work?





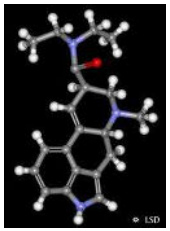
All serotonergic psychedelics are 5-HT2A receptor agonists



5-HT2A receptors in human brain

Affinity for the 5-HT2A receptor

Ayahuasca/DMT



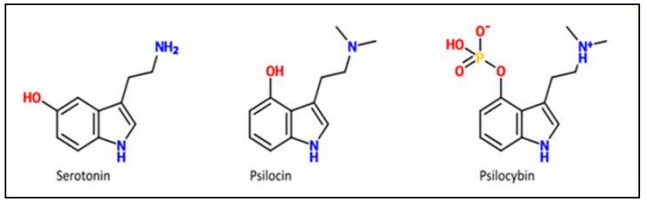
LSD

Mescaline

Potency in humans

Psilocybin – magic mushrooms – note active ingredient is psilocin

Glennon et al. 1984. Human dose data from Shulgin 1978

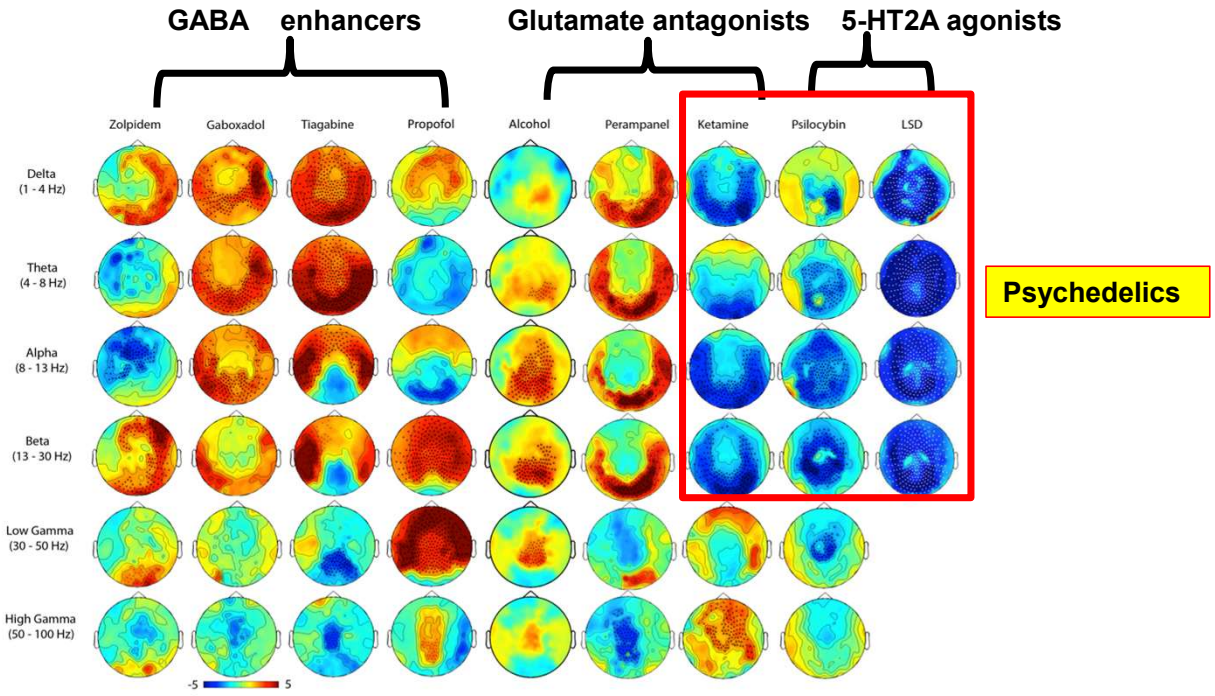


Both serotonin psychedelics and ketamine increase cortical entropy - MEG brain prints

Spectral power changes

Hot = more power = less entropy

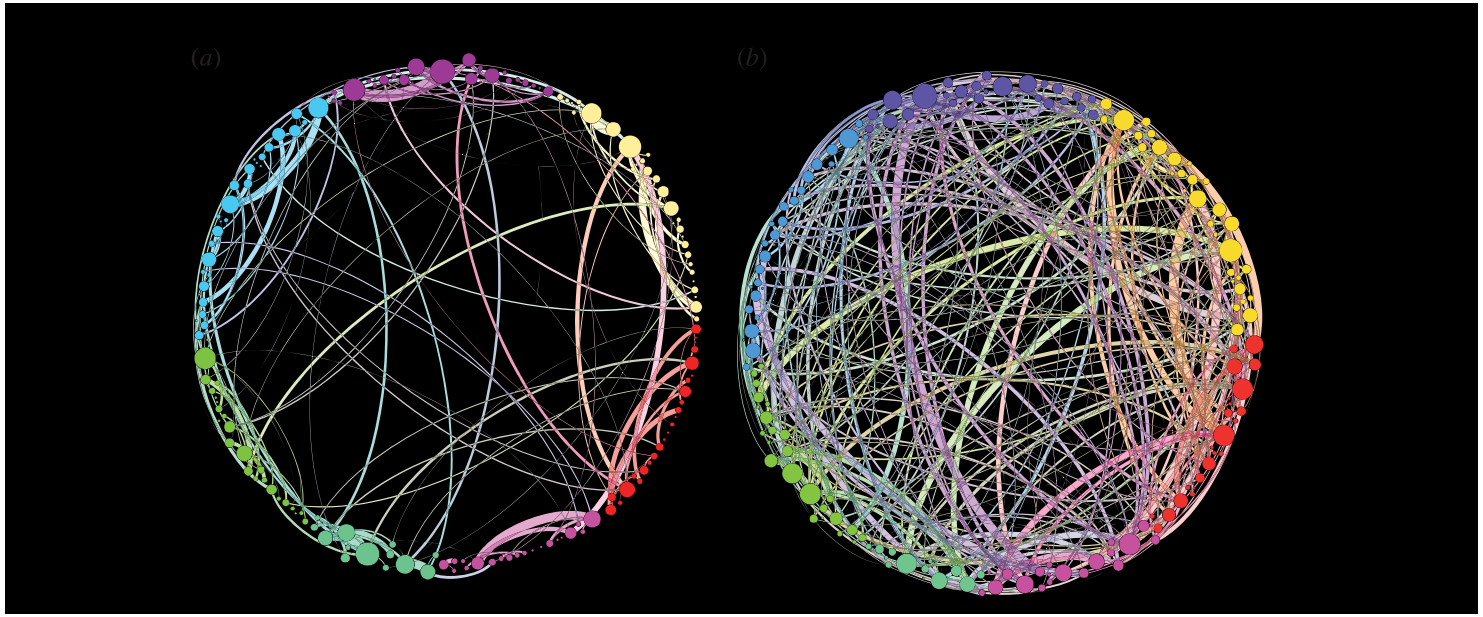
Cold = less power = more entropy



Ketamine and serotonin psychedelics induce profound disruption of cortical rhythms

Muthukumaraswamy et al., 2013 J Neuroscience, and others

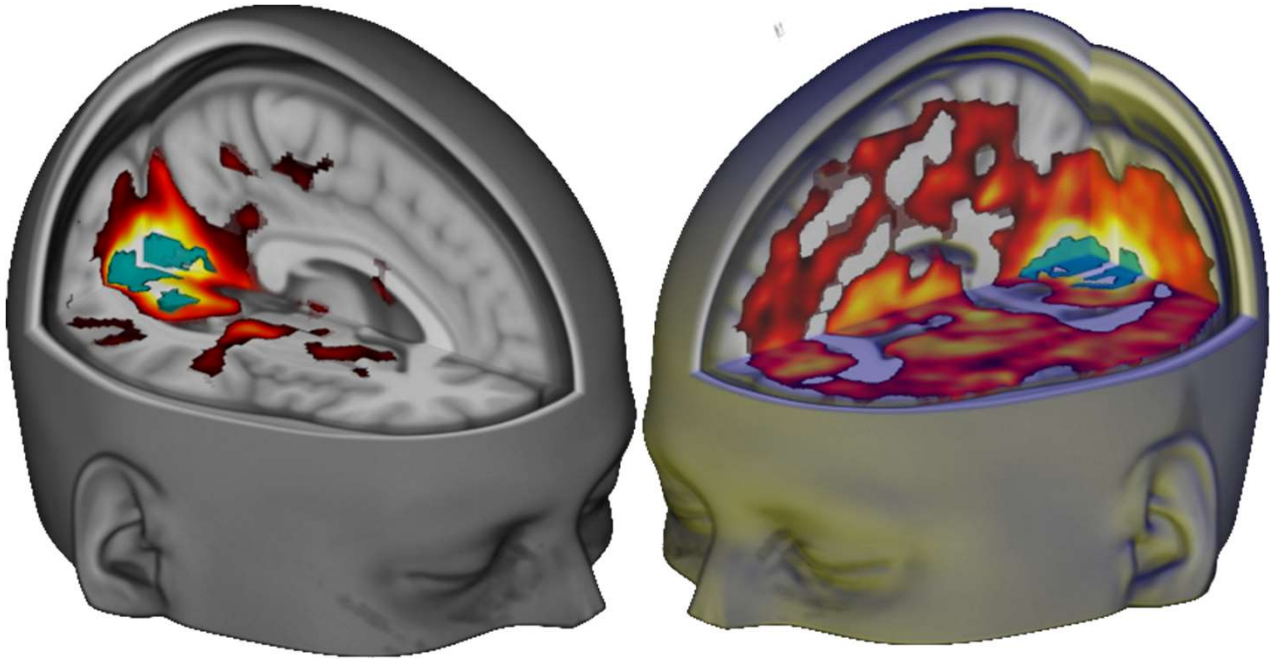
Psilocybin increases brain connectivity
→ new solutions to old problems?



Normal (small world brain) **Psilocybin (open brain)**

Petri et al J. R. Soc. Interface 11: 20140873. http://dx.doi.org/10.1098/rsif.2014.0873

Increased connectivity under LSD
→ insights as well as visions?

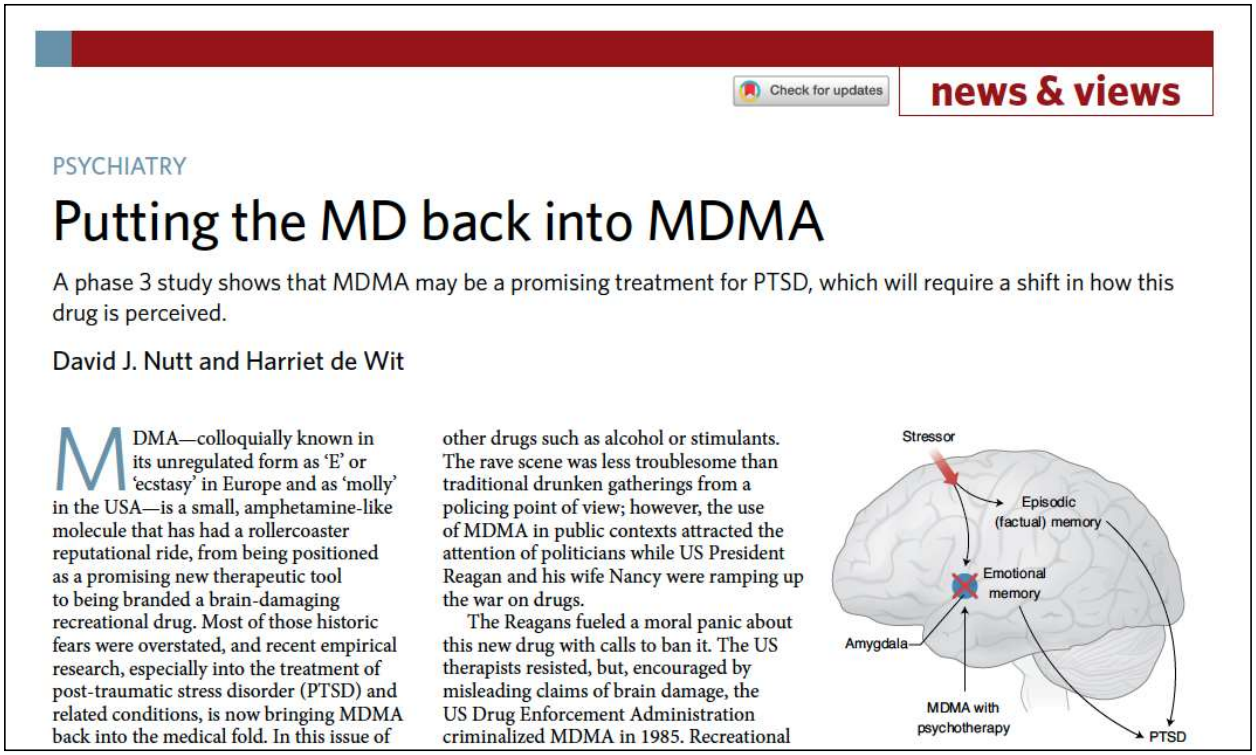


from Carhart-Harris et al 2016 PNAS

Image courtesy of Leor Roseman

MDMA – overcoming PTSD

Exposure → extinction of fear/anxiety responses without affecting declarative memory → top down executive control over bottom up fear cognition. MDMA acutely reduces amygdala activation to fearful faces



Check for updates

news & views

PSYCHIATRY

Putting the MD back into MDMA

A phase 3 study shows that MDMA may be a promising treatment for PTSD, which will require a shift in how this drug is perceived.

David J. Nutt and Harriet de Wit

MDMA—colloquially known in its unregulated form as 'E' or 'ecstasy' in Europe and as 'molly' in the USA—is a small, amphetamine-like molecule that has had a rollercoaster reputational ride, from being positioned as a promising new therapeutic tool to being branded a brain-damaging recreational drug. Most of those historic fears were overstated, and recent empirical research, especially into the treatment of post-traumatic stress disorder (PTSD) and related conditions, is now bringing MDMA back into the medical fold. In this issue of other drugs such as alcohol or stimulants. The rave scene was less troublesome than traditional drunken gatherings from a policing point of view; however, the use of MDMA in public contexts attracted the attention of politicians while US President Reagan and his wife Nancy were ramping up the war on drugs.

The Reagans fueled a moral panic about this new drug with calls to ban it. The US therapists resisted, but, encouraged by misleading claims of brain damage, the US Drug Enforcement Administration criminalized MDMA in 1985. Recreational

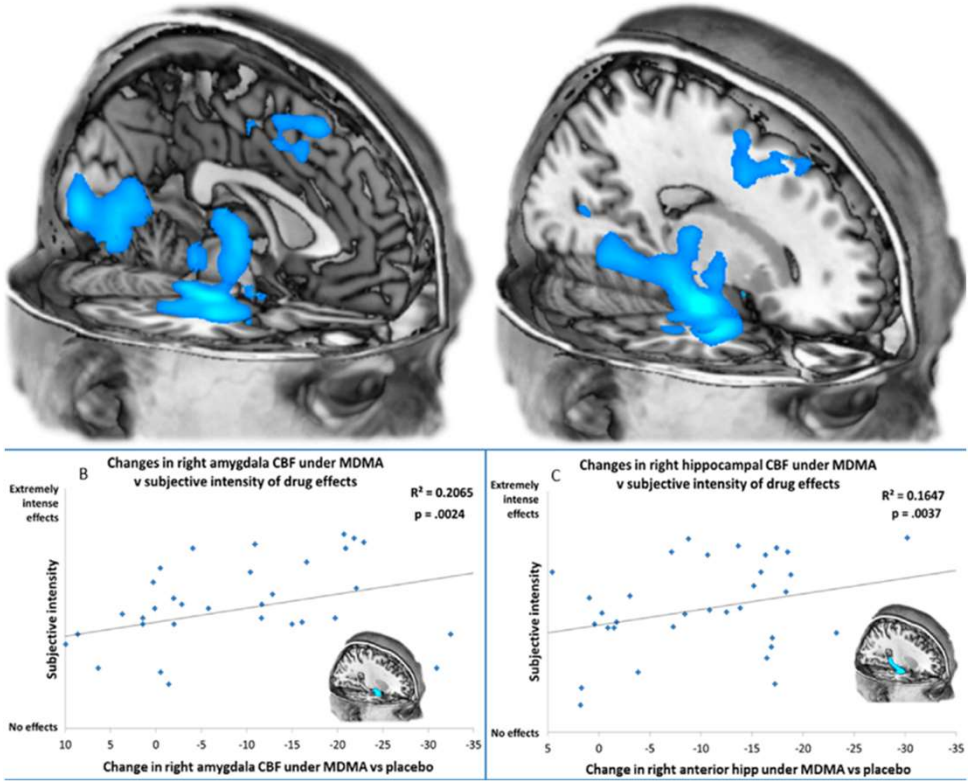
Nature Medicine 2021

Many people with PTSD turn to alcohol

Alcohol dependence itself is very traumatic

So can MDMA therapy "reset" these trauma processes and reduce drinking? As in BIMA study

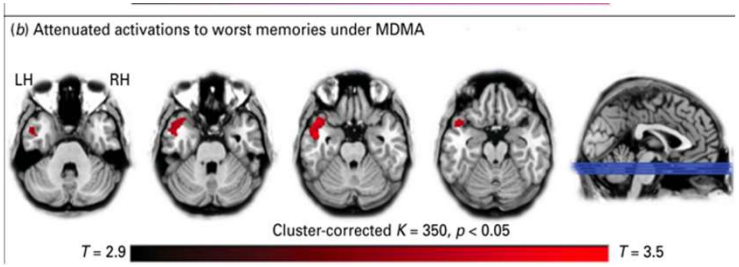
MDMA reduces brain activity in the stress circuit



Carhart-Harris, R. L., Kevin, M., Robert, L., David, E., Wall, M. B., Bart, F., … Nutt, D. J. (2015). *Biological Psychiatry*, *78*(8), 554–562.

Hippocampus and amygdala

→ ability to cope with emotional memories during therapy



Carhart-Harris, R. L., Wall, M. B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., … Nutt, D. J. (2014). *Int J Neuropsychopharmacol*, *17*(4), 527–540.

So how do these drugs work clinically?

Theory → disrupt the brain processes of addiction (and depression)

- rather than block or replicate single neurotransmitter effects

Addiction - current medicines target the receptors drugs act on

drug ➔ receptor

Block the drug getting to its binding site

- **Antagonists – e.g. naltrexone for heroin (low compliance)**

Block elements of drugs effects

- **Opioid antagonists nalmefene/ naltrexone for alcohol**

Substitution therapy – give less harmful drug/stop craving

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

Limited efficacy - especially for behavioural addictions

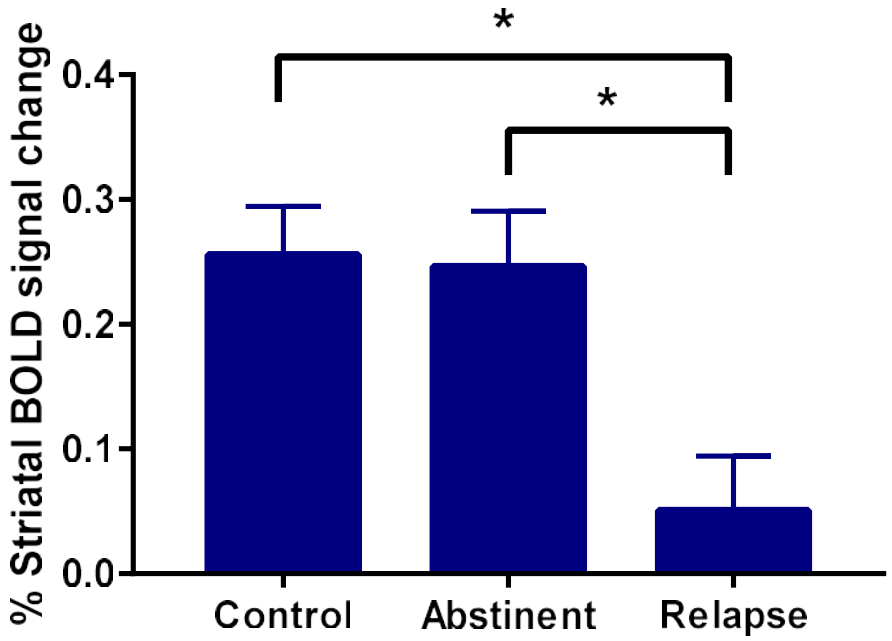
Newer approaches target brain control mechanisms

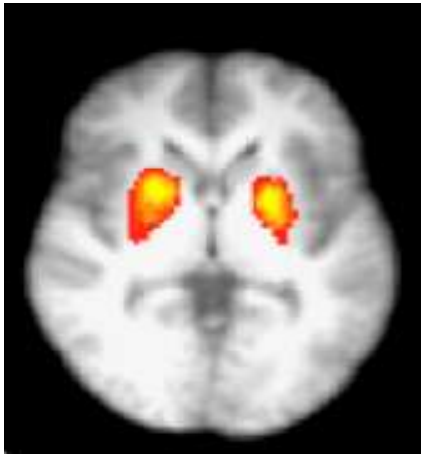
E.g.

1. Reward systems deficit
2. Impulse control deficit
3. Stress sensitivity
   - D3 antagonist, NK1 antagonist (ICCAM study)

4. Reduce appetite for drugs with gut hormones e.g. GLP1 agonists [exenatide semaglutide) or ghrelin antagonists (GHAD study)

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

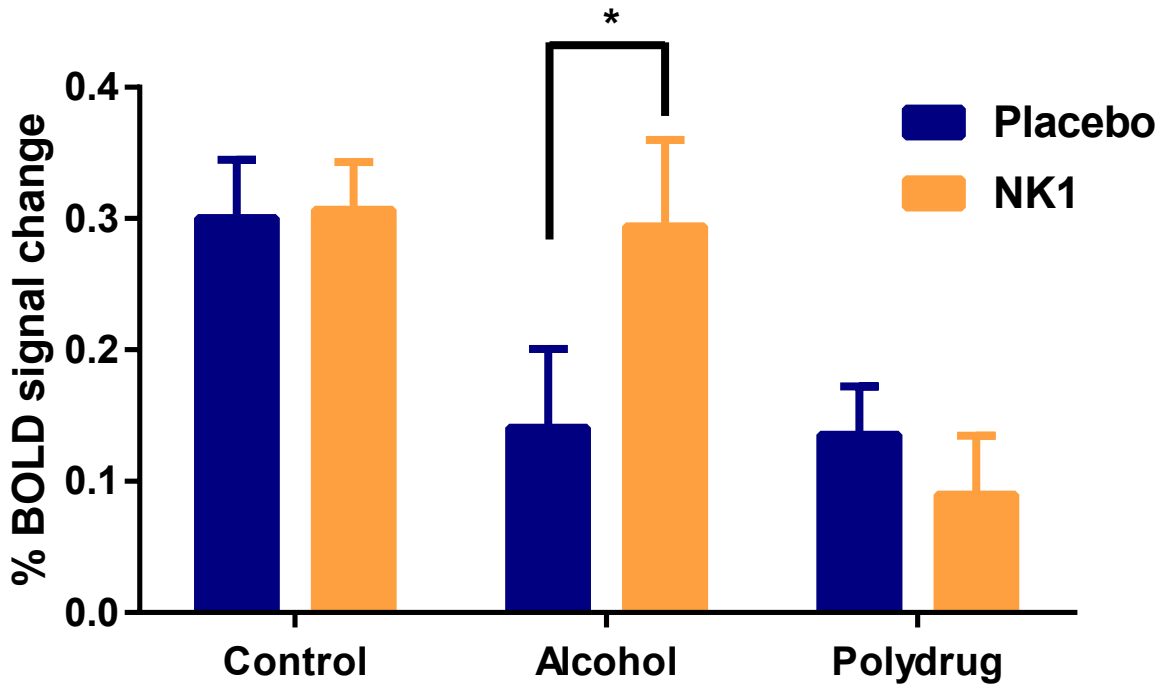




Monetary Incentive Delay (MID) task

Paterson et al ICCAM

NK1 antagonism (aprepitant) significantly 'normalises' blunted reward anticipation in alcoholism



Clinical study underway

Paterson et al

GHADD
Gut Hormones in Addiction

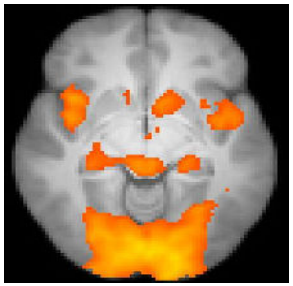
www.ghadd.co.uk

Recently
ex-smokers (n=24)

Abstinent alcohol
dependent (n=24)

Obese subjects actively
dieting (n=24)

Saline infusion
Exendin-4 (GLP-1 analogue) infusion



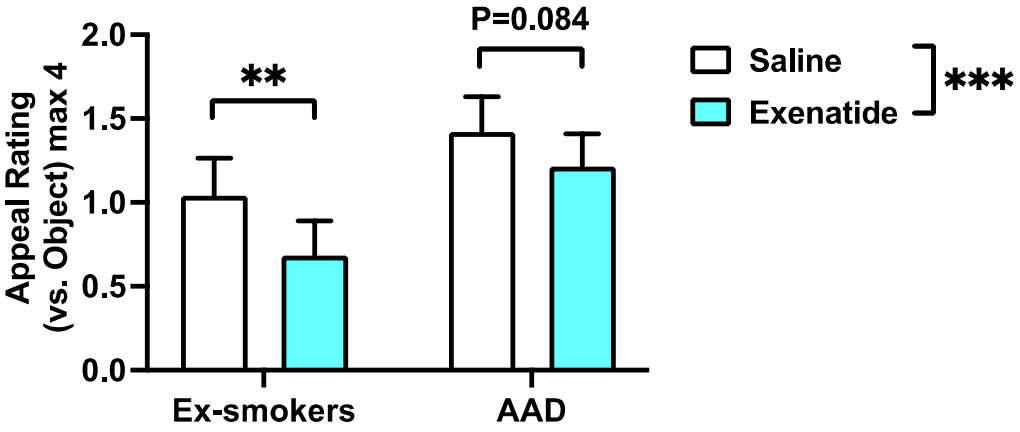
Healthy, non-obese
controls for functional
ROIs (n=26)

Appetitive cues

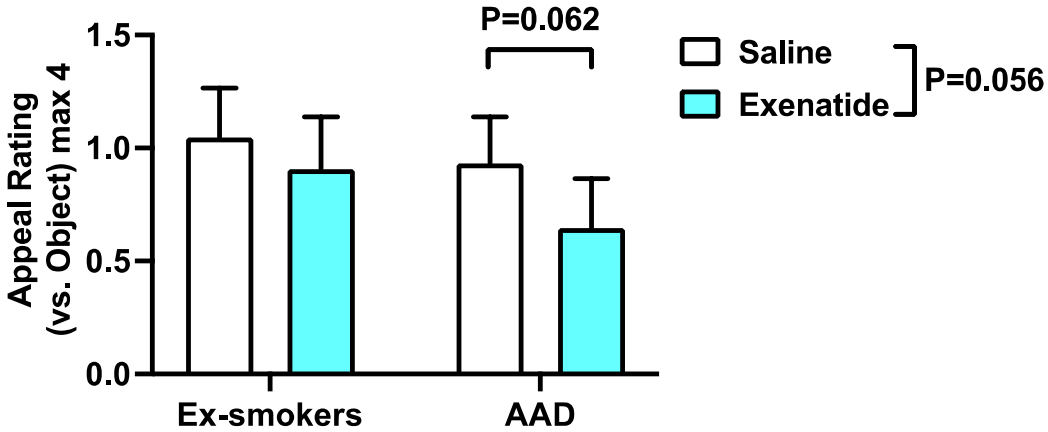
Herlinger Goldstone and Nutt in preparation

Exenatide Decreased Food Picture Appeal in ex-smokers

HE Food



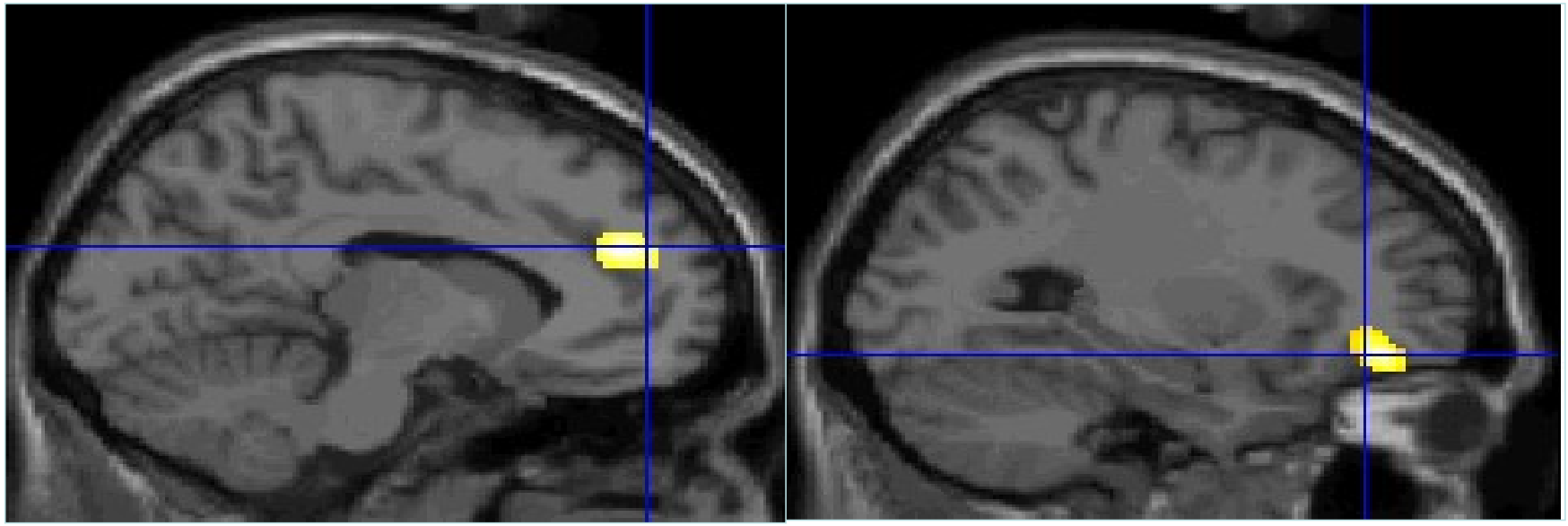
Alcohol



n=23-26, **P<0.01, ***P<0.005

Associated with reduced food intake in test meal

Would a focus on brain circuits do better?
All addictions share a common brain circuit



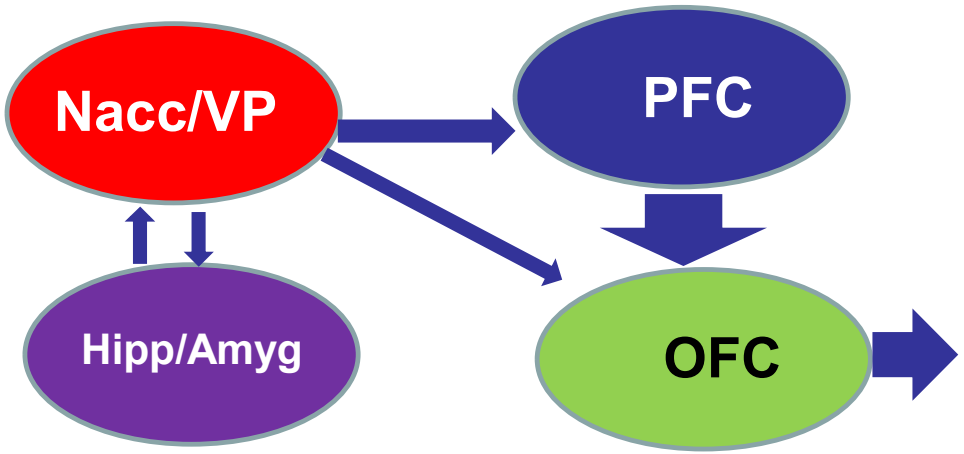
Remembering use

Urge to use

Daglish et al 2001 Am J Psychiatry

^{15}O2 water PET

Balanced brain state – no addiction



Behavioural control

Red = reward prediction and pleasure

Blue = cognitive control

Green = motivation drive and salience attribution

Purple = learning and memory

PFC – prefrontal cortex
OFC = orbitofrontal cortex
Nacc = nucleus accumbens
VP = ventral pallidum
Hipp = hippocampus
Amy = amygdala

PFC controls final decision making

Adapted from Baler and Volkow 2006

Addicted brain

Red = reward prediction and pleasure

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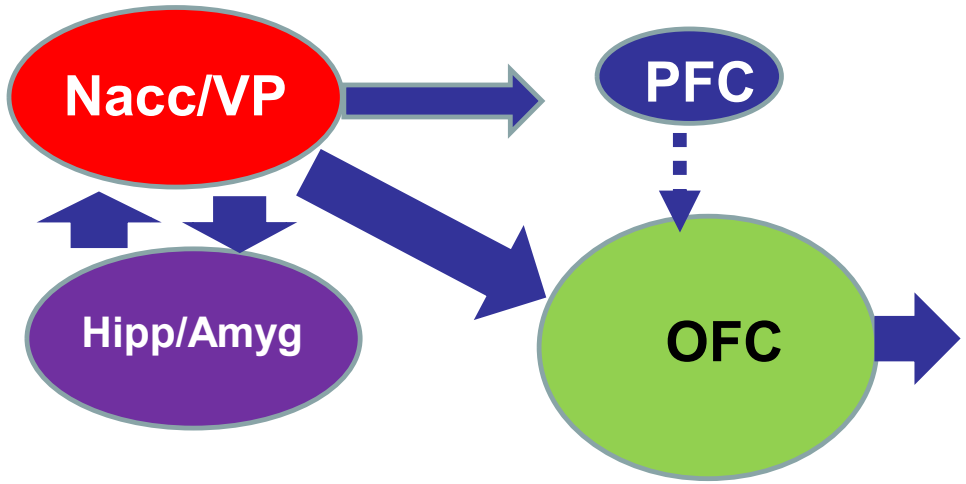


Go →drugs and other addictive behaviours

Excessive drives from memory and reward circuits depress PFC and enhance OFC functioning so PFC no longer controls behaviour

Adapted from Baler and Volkow 2006

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

Received: 21 July 2019 | Revised: 31 July 2020 | Accepted: 5 October 2020
DOI: 10.1111/adb.12980

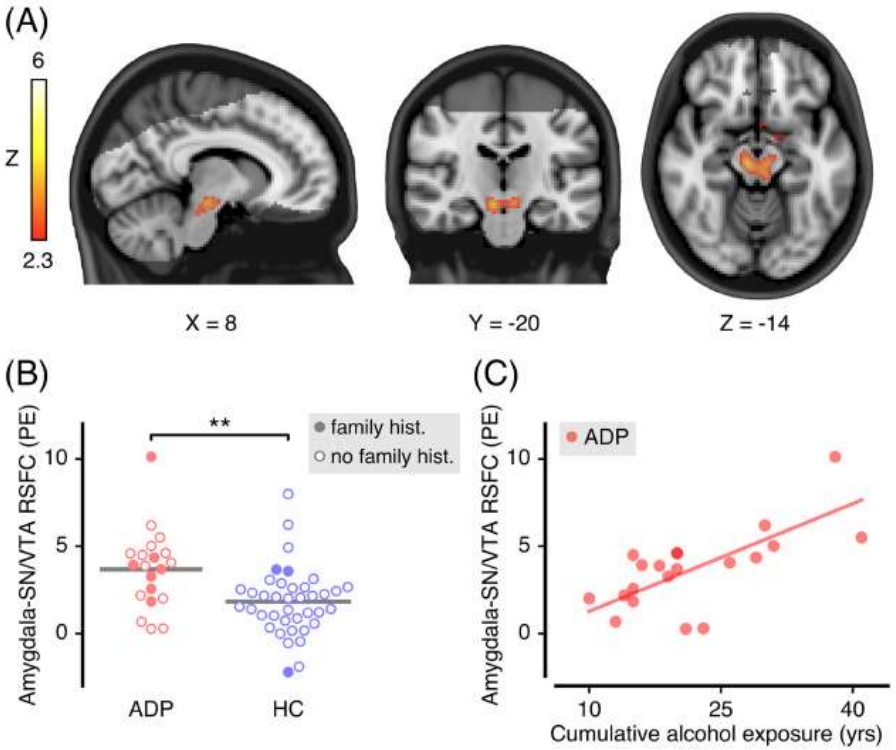
ORIGINAL ARTICLE

Addiction Biology WILEY

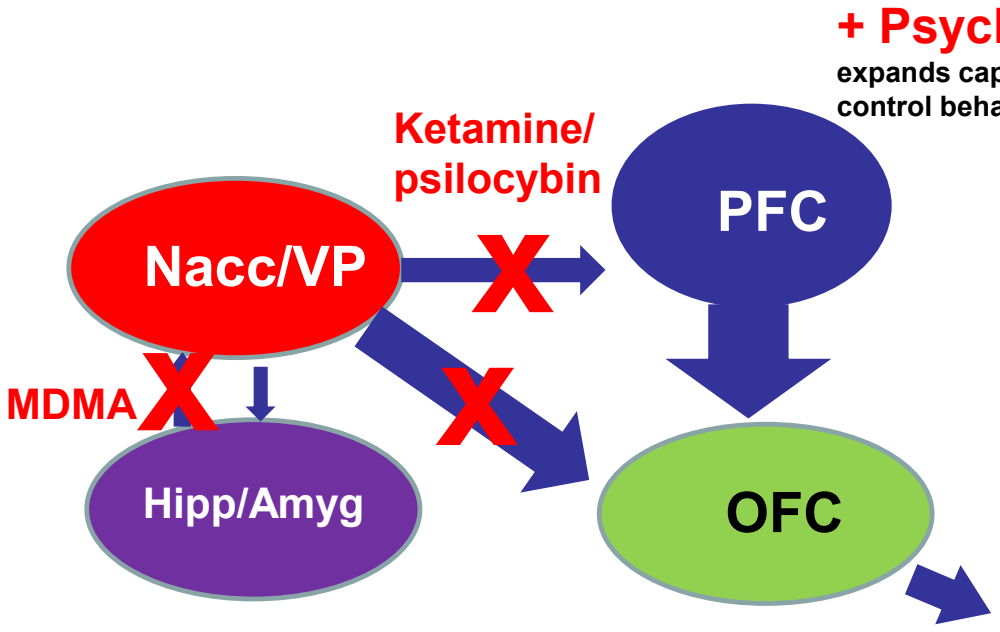
Chronic alcohol exposure differentially modulates structural and functional properties of amygdala: A cross-sectional study

Csaba Orban[1,2,3] | John McGonigle[1] | Remy S.A. Flechais[1] | Louise M. Paterson[1] | Rebecca Elliott[4] | David Erritzoe[1] | Karen D. Ersche[5,6] | Anna Murphy[4] | Liam J. Nestor[1,6] | Filippo Passetti[1,5,6] | Laurence J. Reed[1] | Andre S. Ribeiro[1] | Dana G. Smith[5,7] | John Suckling[5,6,8] | Eleanor M. Taylor[4] | Adam D. Waldman[9] | Victoria C. Wing[1] | J.F. William Deakin[4] | Trevor W. Robbins[5,7] | David J. Nutt[1] | Anne R. Lingford-Hughes[1] | ICCAM Platform*

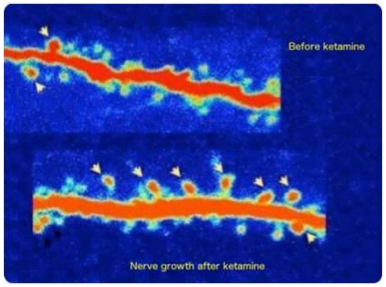
ICCAM
Imperial College London | University of Cambridge | Manchester 1824 The University of Manchester



Disrupting these overactive addiction circuits can restore balance in the brain



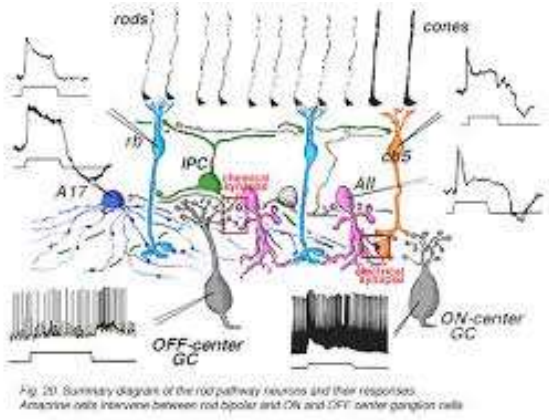
+ neuroplasticity may facilitate new learnings



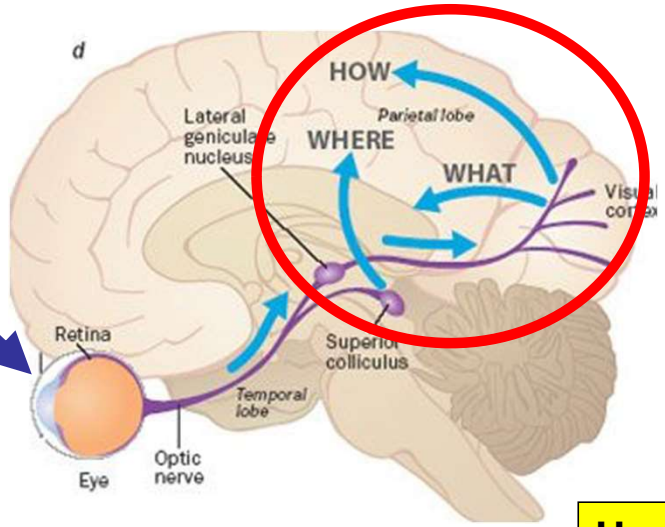
Increased synaptic spines after ketamine

Adapted from Baler and Volkow 2006

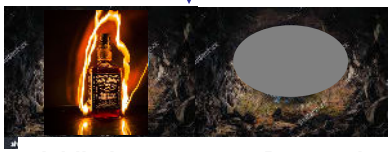
Neuroscience explains how psychedelics work in depression and addiction



The brain reconstructs the image to what it expects - or wants to see



But always with limitations
"Man sees thro' the chinks of his cavern" William Blake 1793

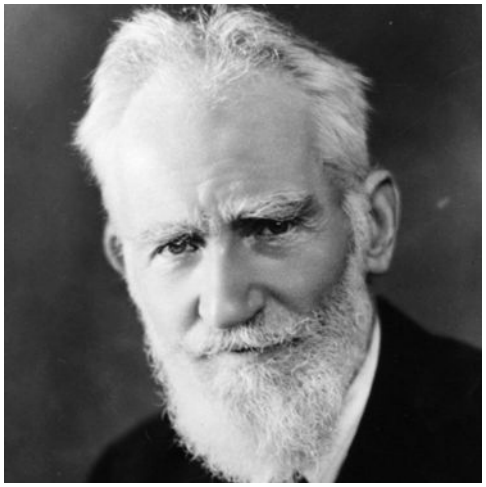


Addiction **Depression**

Humans make "mind-forged manacles" also William Blake

A psychedelic experience can break these…..like they did for Bill Wilson

"Those who cannot change their minds cannot change anything"



George Bernard Shaw
(1856-1950)

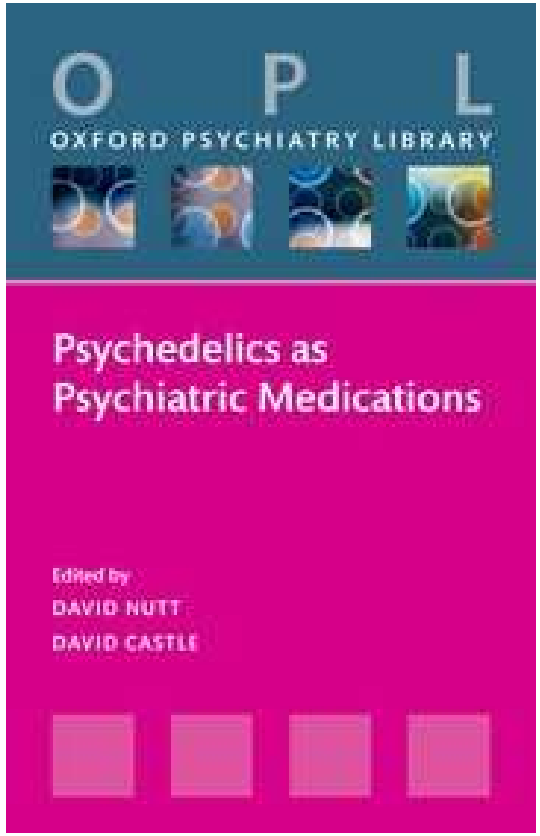
The Scales of Justice being built

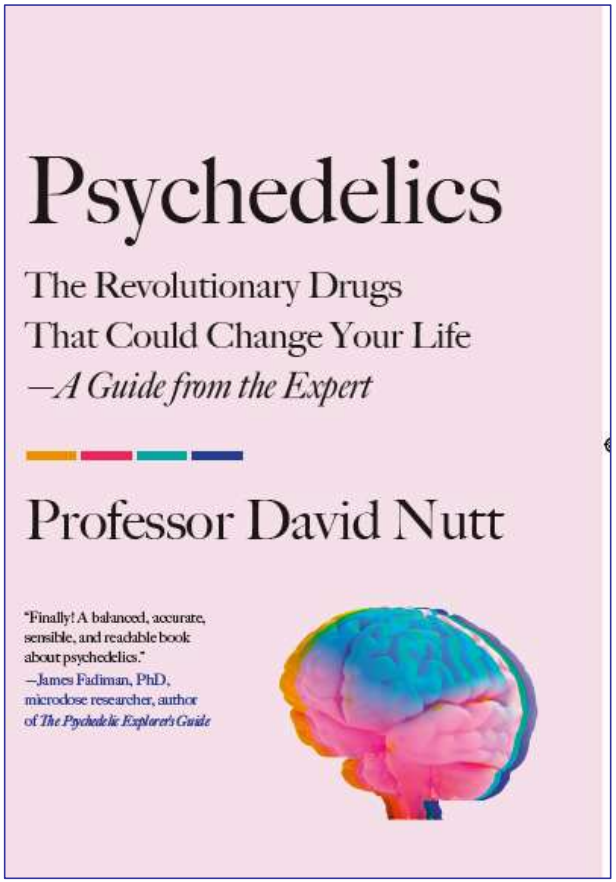
Time now to apply too psychedelics!

Treatment with psychedelics such as ketamine and psilocybin has changed the minds of our patients → through changing their brains

We hope that this research can now change the public and politicians' minds and bring those still controlled under the UN Conventions back into medical practice

If you want to change (or confirm) your mind?





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Acknowledgements and questions

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