

Are psychedelic drugs the future of psychiatric treatments?

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Declaration of interests – 2022-2023

- Advisor - British National Formulary
- **Chair – DrugScience [UK] and PAREA Europe**
- Member International Centre for Science in Drug Policy
- **CRO Awaknlifesciences**
- Editor of the Journal: Drug Science policy and law
- Member of the Lundbeck Foundation Neurotorium programme and Chair of the editorial board
- Grants or clinical trial payments: Wellcome Trust, MRC, **COMPASSPathways, Usona**
- Speaking honoraria Lundbeck, Takeda, Otsuka
- Share options – P1vital, **Awakn, Psyched Wellness , Neurotherapeutics**
- Director Equasy Enterprises and GABA Labs
- Expert witness in a number of legal cases relating to psychotropic drugs
- Edited/written about 40 books - some purchased by pharma companies

Psychedelics are an enduring feature of human existence

Peyote /mescaline



Magic mushrooms/psilocybin



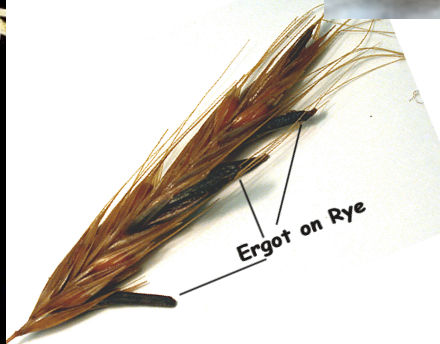
Ayahuasca/ DMT



Ancient Greeks/ ergots in wine



K26.1 PLOUTOS ENIAUTOS, DEMETER ELEUSIS



Morning glory/ lysergamide



Amanita Muscaris/muscimol

LSD – the first synthetic psychedelic

LSD

- synthetic and more potent psychedelic
- wide medical and research use

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

Joel Elkes – first psychiatrist to try LSD
in 1953 – lived to 103

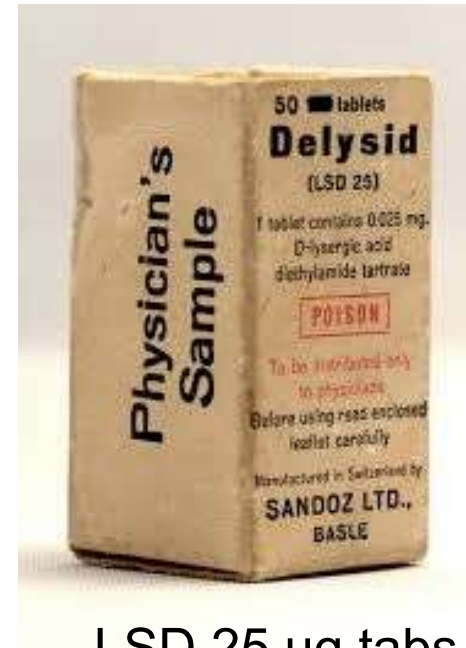


Clinical interest in LSD and psilocybin in the 1950s and 1960s

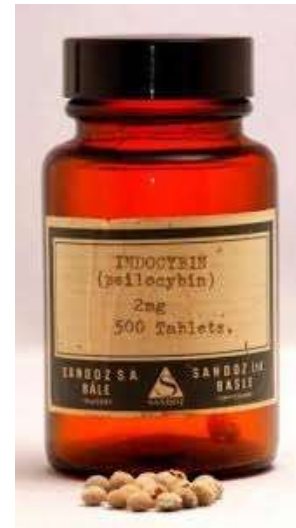
- Hundreds of psychiatrists worldwide
- 140 NIH grants
- 1000 clinical papers
- 40,000 patients
- 40 books
- 6 International conferences

Results were overwhelmingly positive, describing safe and effective treatments.

(Masters and Houston, 1971)



LSD 25 ug tabs



Psilocybin
2 mg tabs

Back to the future?

Pooled analyses in the 1960s

- **44 psychiatrists, 5000 subjects and 25,000 drug sessions:**

Rate of psychosis: 0.2%

Rate of suicide of 0.04%

(Cohen S. (1960) LSD: side e

"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,"

- **700 psych**

One case of pro

(Chandler Al. & Hartman M

- **350 patients**

One attempted suicide

(Ling TM, Buckman J (1963) The Treatment of Anxiety with Lysergic Acid and Methylphenidate. Practitioner 191: 201-4)

- **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)

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

Six LSD trials in alcoholism

1970

problems and treatment
intentions

quiet room

group therapy

Since the 1971 ban I estimate over 100 million excess deaths globally from alcohol dependence

Suppose LSD had successfully treated 10% = 10 million lives saved

How many lives saved by LSD ban – probably none but say 1000

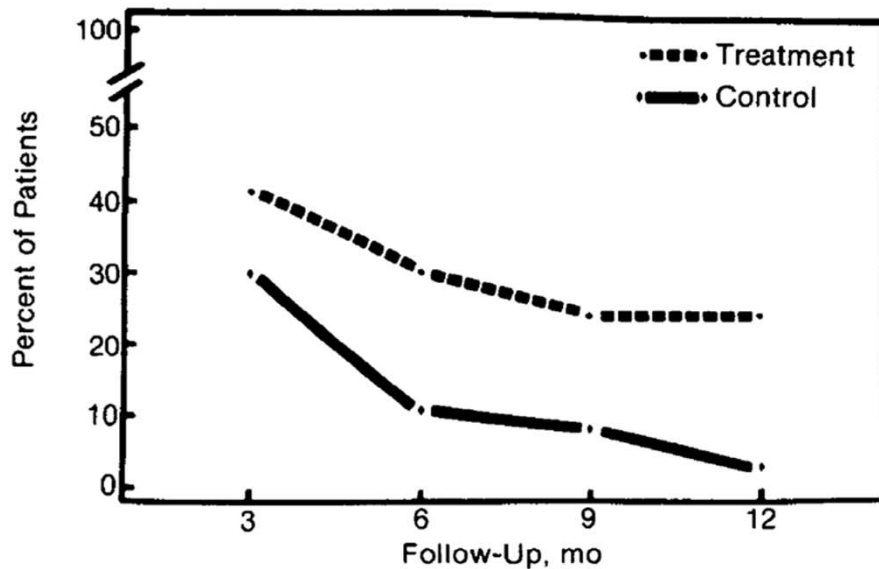
Benefit – risk ratio = 1000x – ? Any medicine has a comparable ratio?

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

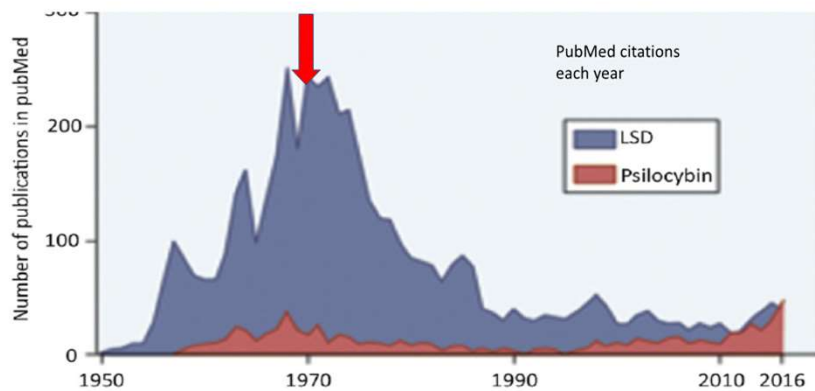
Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

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

LSDs and psilocybin – introduced into medicine in 1950s

Impact of the 1971 UN Psychotropics Convention on psychedelic research

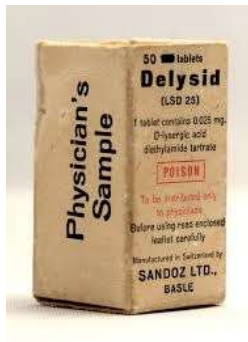


Kyzar et al 2017 TIPS

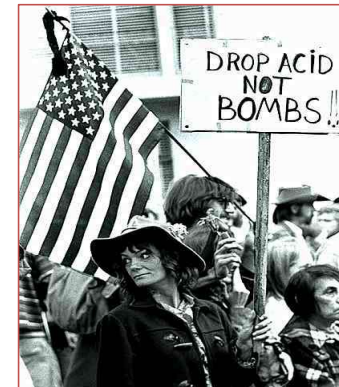
After fifteen years of successful research LSD Put into Schedule 1 – “highly dangerous and no medical use” despite massive medical value data

Psilocybin also banned as had similar pharmacology though no evidence of recreational use

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



LSD banned as it was changing art, music and culture and was associated with the anti-Vietnam war movement



MDMA - How attitudes have changed in twenty years

Then → ecstasy causes brain damage – fabrication of evidence to justify ban

Now → MDMA can heal the brain

War-induced PTSD has been the driver



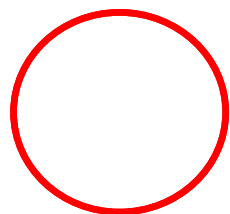
More US and Australian soldiers kill themselves than are killed by enemy



Civilian victims

Chechnya, Sri Lanka, Syria, Ukraine...

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

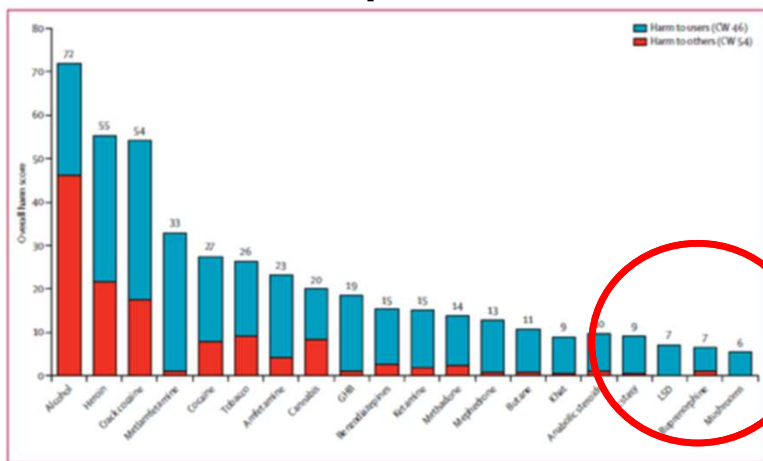


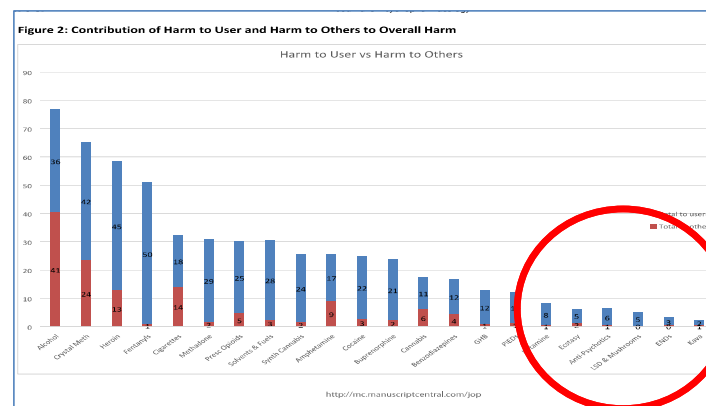
Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others. The weights after normalisation (0-100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users,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



van Amsterdam et al J Psychopharmacology 2014

EU
experts



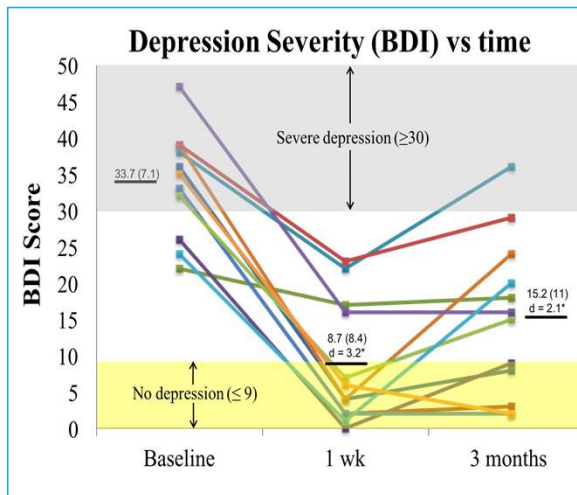
Bonomo et al J Psychopharmacology 2018

Australian
experts

Latest clinical data

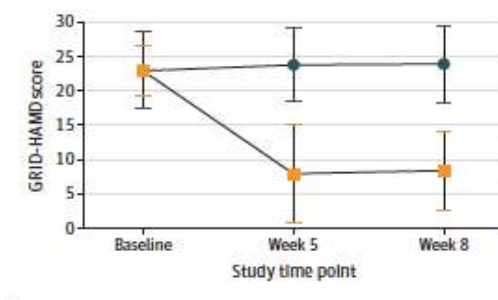
What we know- clinical 1.

Many studies psilocybin has been shown to improve mood in depression – just hours after a single dose – and these effects may last for many months

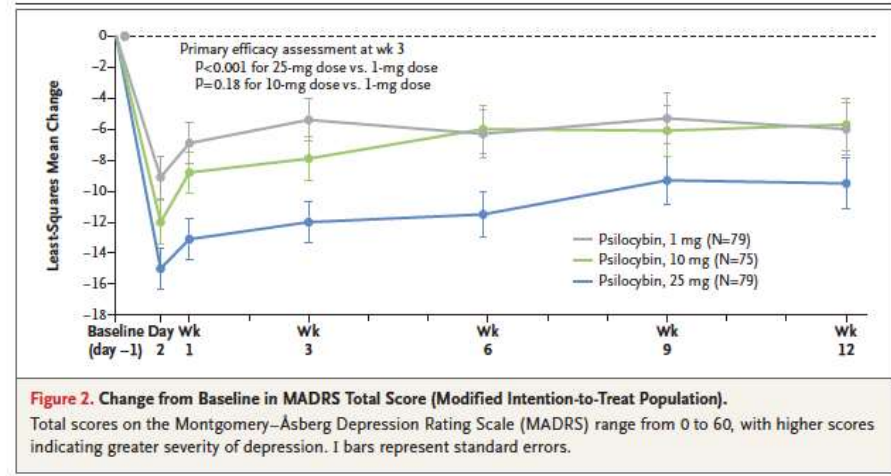


Carhart-Harris et al 2016.

Figure 3. Comparison of GRID Hamilton Depression Rating (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups



Davis et al 2021

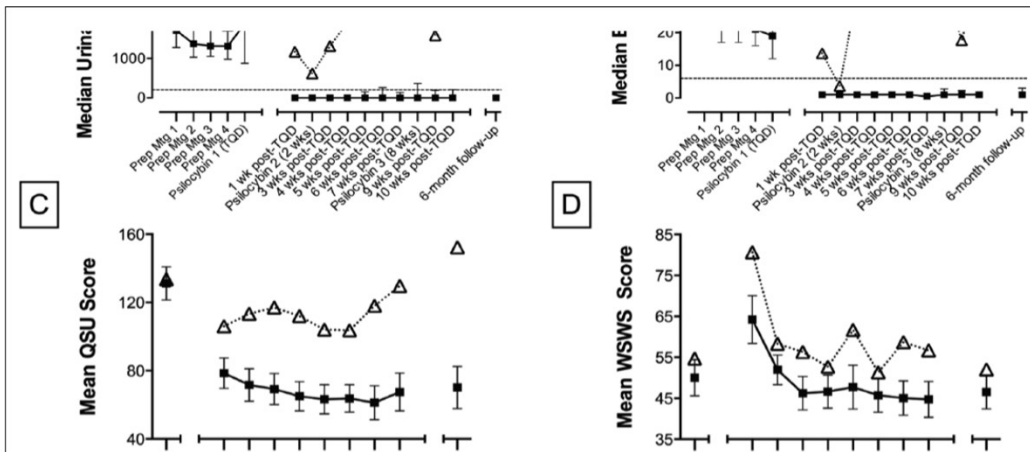


Goodwin et al 2022

+ several others and also with ayahuasca and recently DMT (press release)

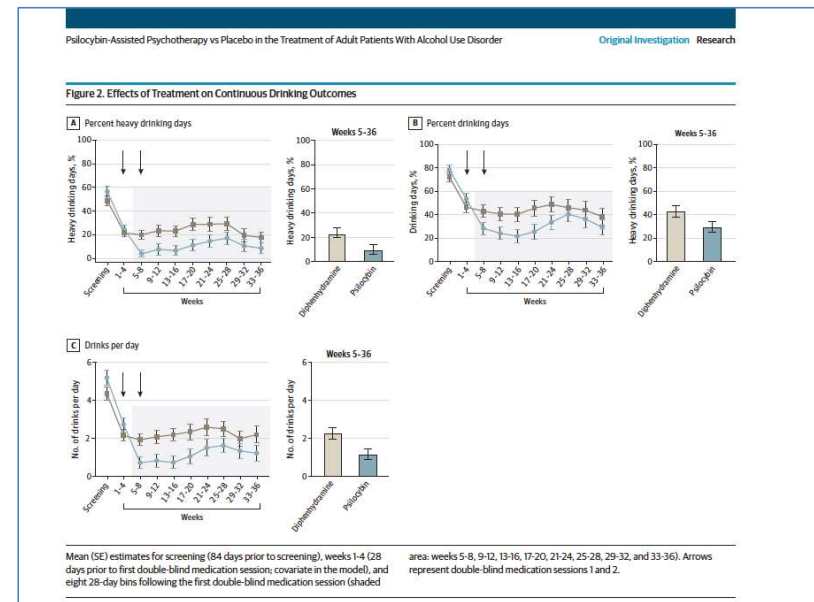
What we know- clinical 2.

Serotonin psychedelics are not addictive and they can be used to treat addictions e.g. to alcohol and tobacco



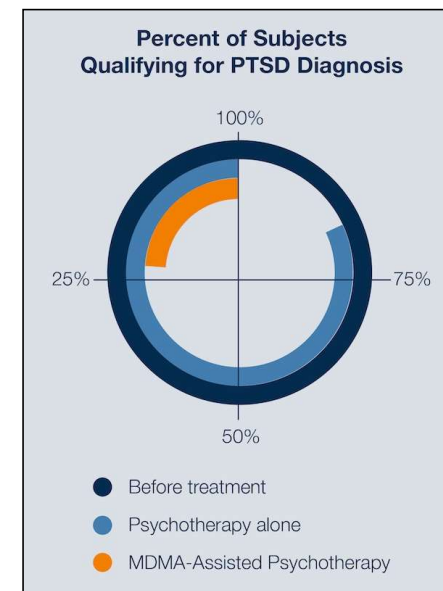
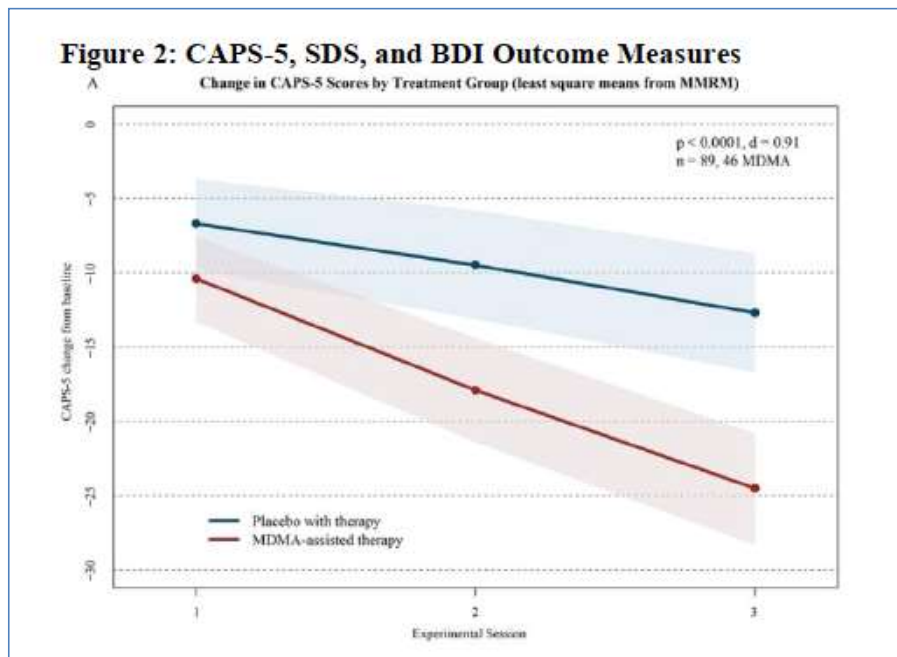
Tobacco quitting – Johnson et al 2014

Johnson – unpublished data on 100 treatment-resistant smokers
 1 dose psilocybin -v- nicotine patch
 59% psilocybin – abstinent -v- 28 patch



Alcohol dependence
 Bogenschutz et al 2022

MDMA-Assisted Psychotherapy for PTSD trials: Phase 3 first study



Mitchell et al Nature Medicine 2021

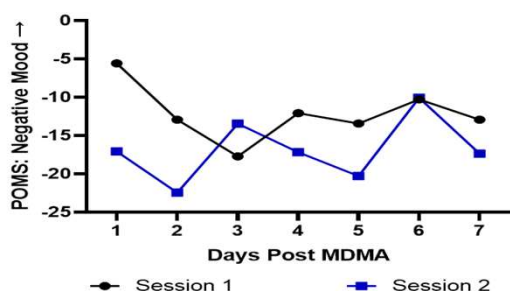
MAPS 2nd phase 3 study just completed – data in new year - if positive then likely to get FDA approval

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

Much alcohol use is to
deaden memories of trauma

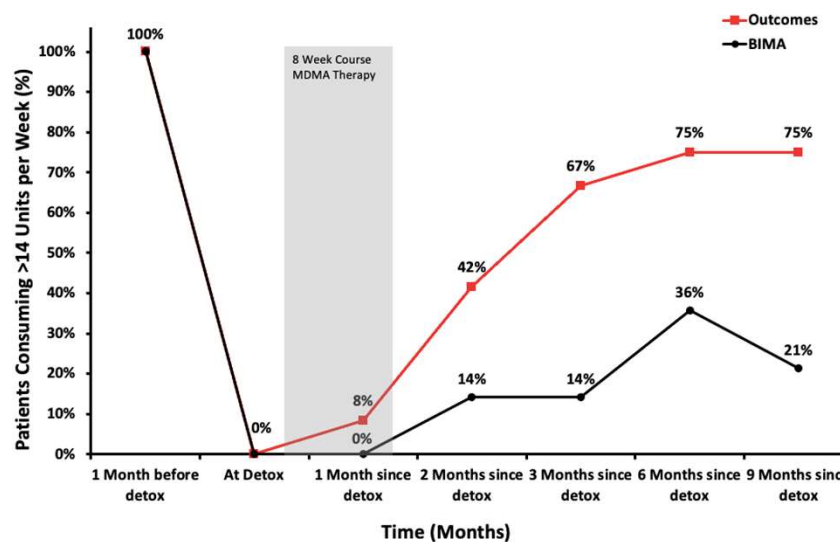
Very high levels in veterans

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 → reduced drinking and increased abstinence rate



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

Sessa et al 2021 Journal of Psychopharmacology

What about harms?

Harms of psilocybin and other psychedelics

A recent review by Drug Science UK

Review

Adverse effects of psychedelics: From anecdotes and misinformation to systematic science

Anne K Schlag^{1,2,3} , Jacob Aday^{1,4,5} , Iram Salam¹, Jo C Neill^{1,6} 
and David J Nutt^{1,2}



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Modern neuroimaging research reveals how
these drugs work

How MDMA works in PTSD

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 *Nature Medicine*, Mitchell et al. report the first phase 3 study of MDMA, which reveals significant efficacy and an excellent safety profile in people with severe PTSD¹. It now seems likely that it will be an approved medication in a few years.

MDMA was invented by Merck in 1912 as a precursor in a new synthesis for hemostatic substances²; Merck tested MDMA in animal models in 1927 and in 1959 but found nothing of interest. It was then resurrected by Alexander Shulgin

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 use continued, although clinical research effectively stopped. In 1986, a group of therapists established the Multidisciplinary Association for Psychedelic Studies (MAPS) to continue to explore the therapeutic utility of MDMA. By the end of the 1980s, MDMA was banned in most Western countries.

Despite the vast extra costs and bureaucratic constraints that the illegal status of MDMA introduced, clinical research by MAPS progressed. The first clinical study of MDMA, undertaken by

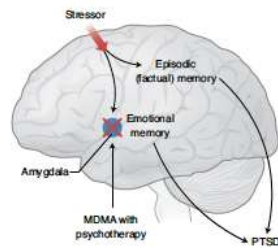
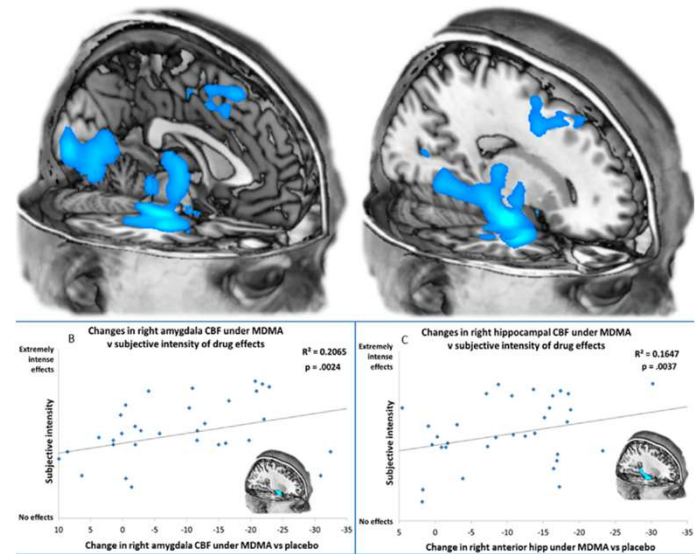


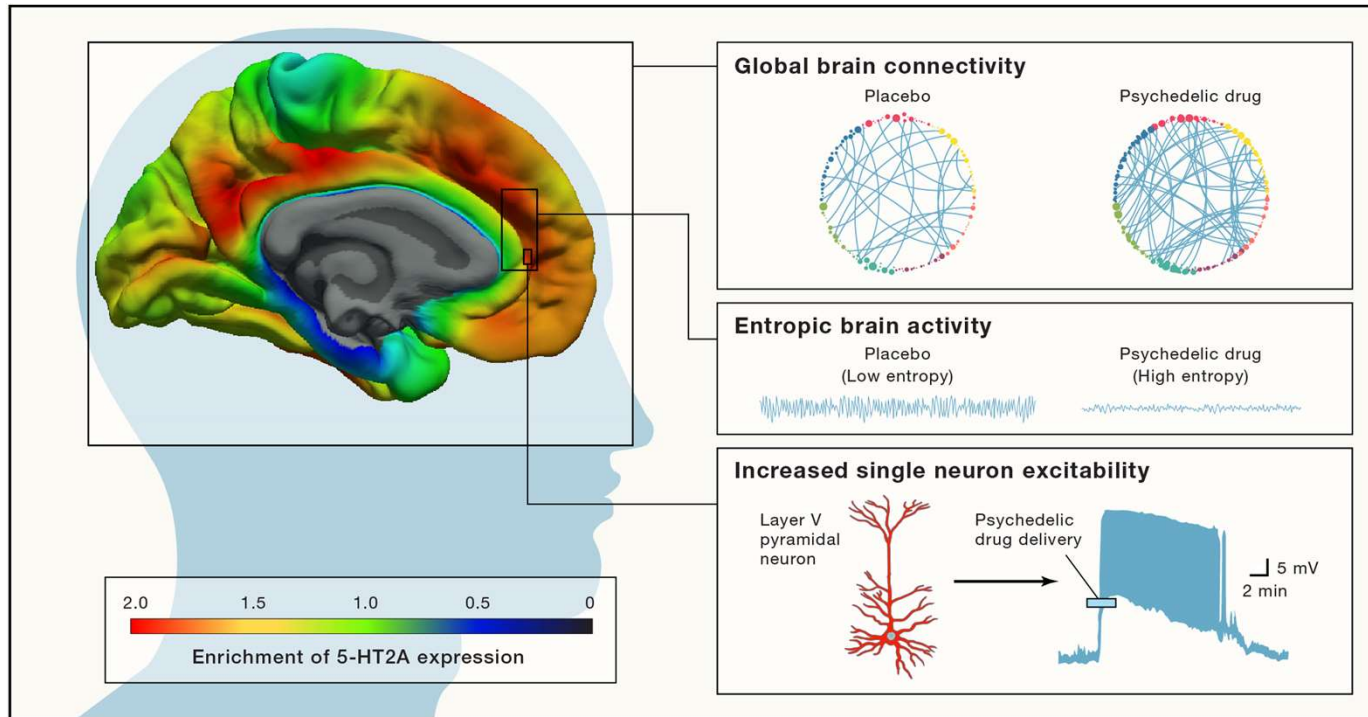
Fig. 1 | The brain pathways of PTSD and site of action of MDMA in therapy. A severe, life-threatening stressor (trauma) leaves an emotional trace as well as a factual trace in different parts of the brain. Negative emotions are reactivated by remembering the trauma or as part of a conditioned fear reflex—for example, a car backfiring activates the memory and emotions of experiencing a gunshot. MDMA treatment facilitates the extinction of these emotional resurgences.



Nutt and de Wit
Nature Medicine June 2021

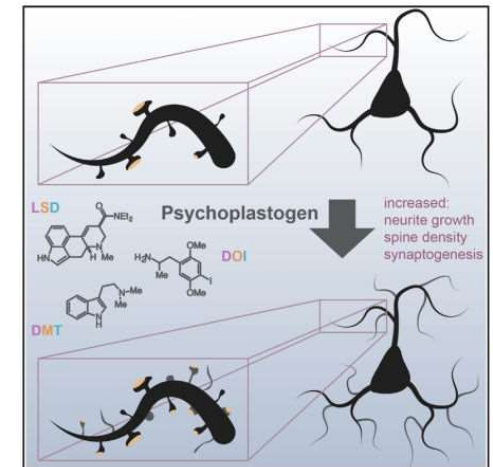
Carhart-Harris, R. L., Kevin, M., Robert, L., David, E., Wall, M. B., Bart, F., ... Nutt, D. J. (2015). *Biological Psychiatry*, 78(8), 554–562.

Brain mechanisms of psilocybin



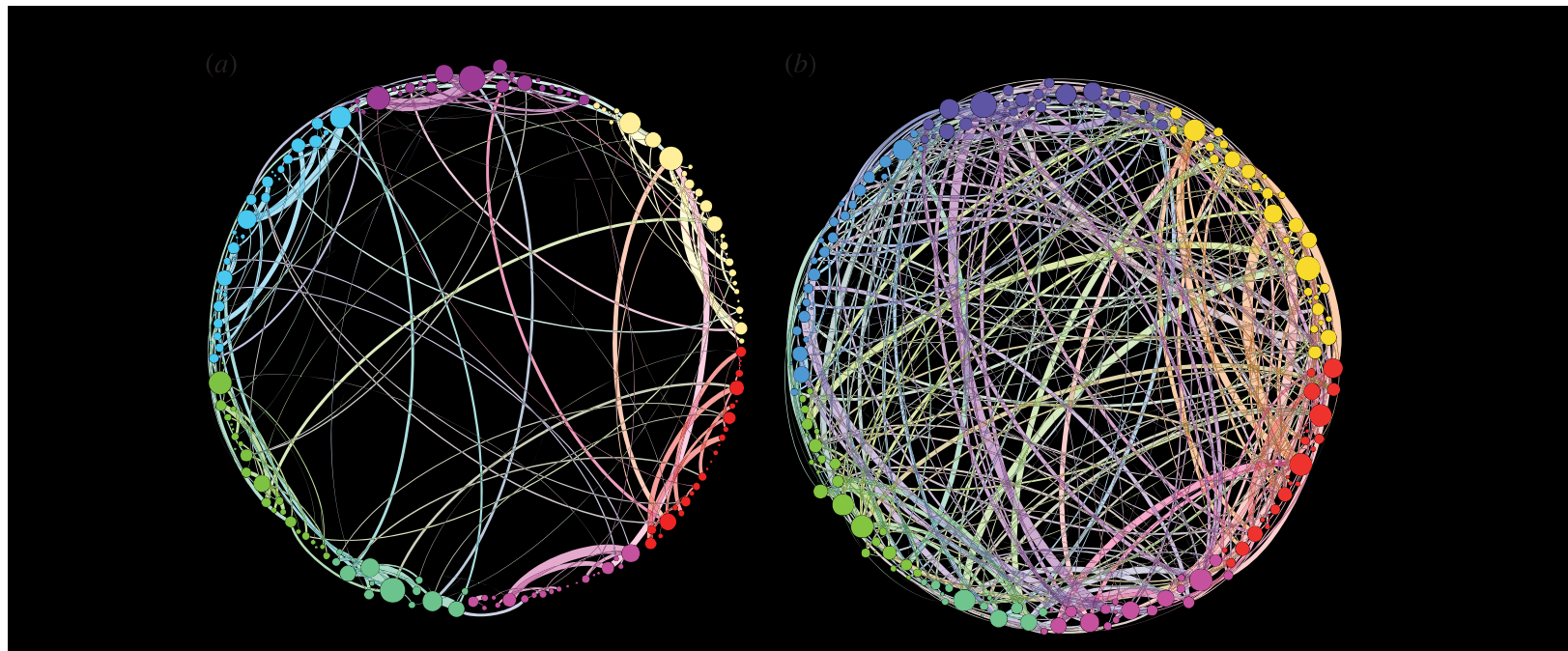
Nutt et al Cell 2020

+ neuroplasticity



Ly et al Cell Reports 2018

Psilocybin increases brain connectivity



Placebo

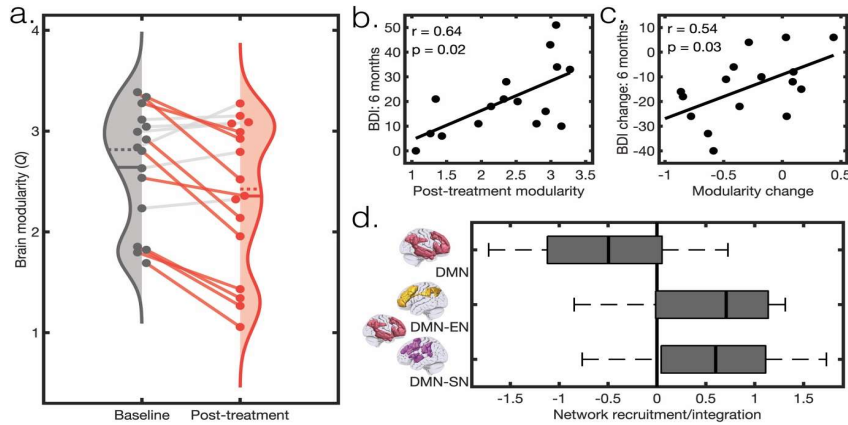
Psilocybin

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

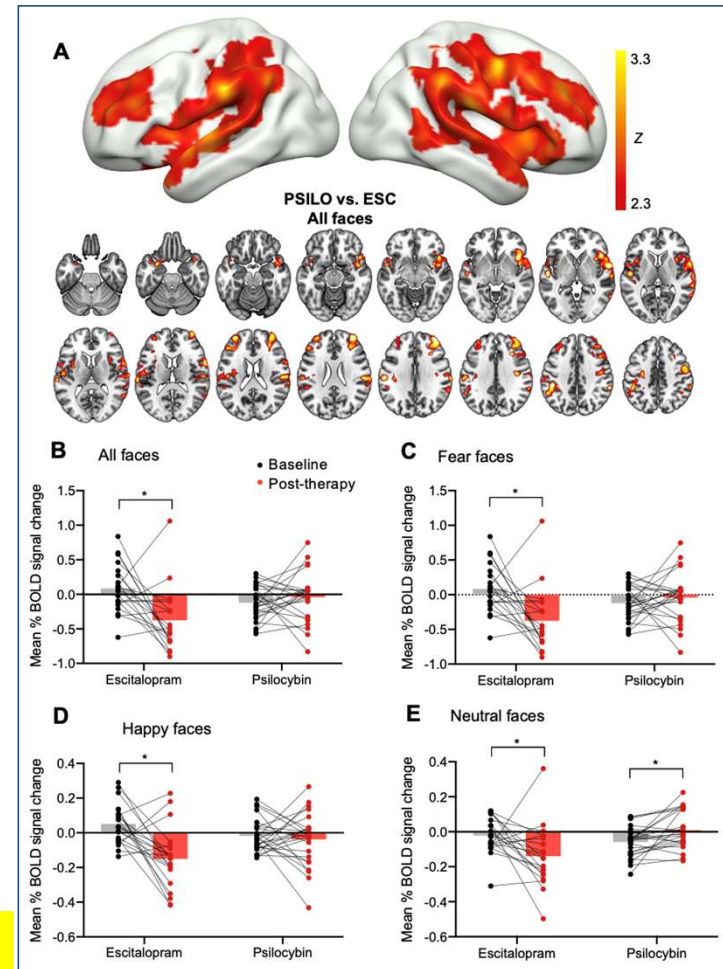
Psilocybin and escitalopram appear to have fundamentally different mechanisms

Psilocybin decreases modularity

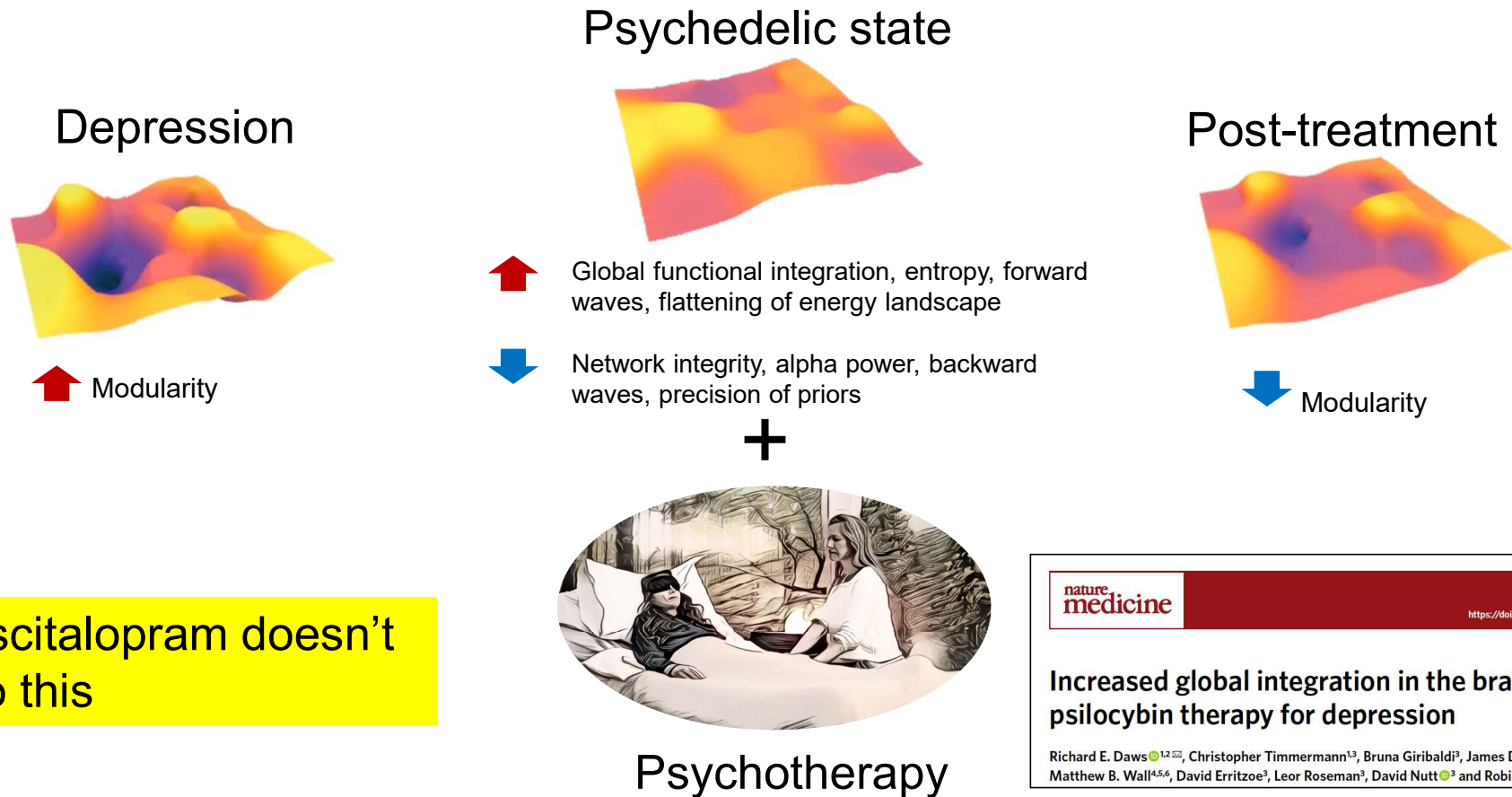
Daws et al 2022



Escitalopram blunts emotional responses
Wall et al submitted



A theory of how psychedelics work in depression



Escitalopram doesn't do this

nature medicine ARTICLES
<https://doi.org/10.1038/s41591-022-01744-z>
[Check for updates](#)

Increased global integration in the brain after psilocybin therapy for depression

Richard E. Daws^{1,2}, Christopher Timmermann^{1,3}, Bruna Giribald³, James D. Sexton³, Matthew B. Wall^{4,5,6}, David Erritzoe³, Leor Roseman³, David Nutt³ and Robin Carhart-Harris^{3,7}

Addicted brain

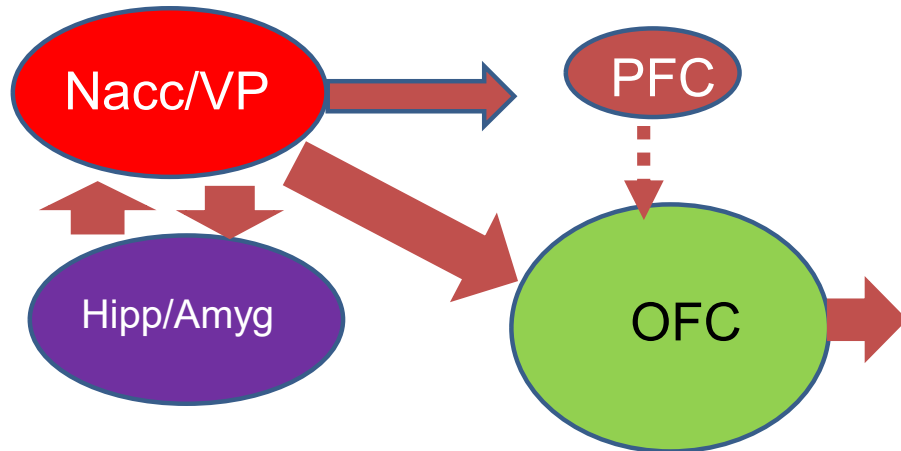
Red = reward prediction and pleasure

Blue = cognitive control

Green = motivation drive and salience attribution

Purple = learning and memory

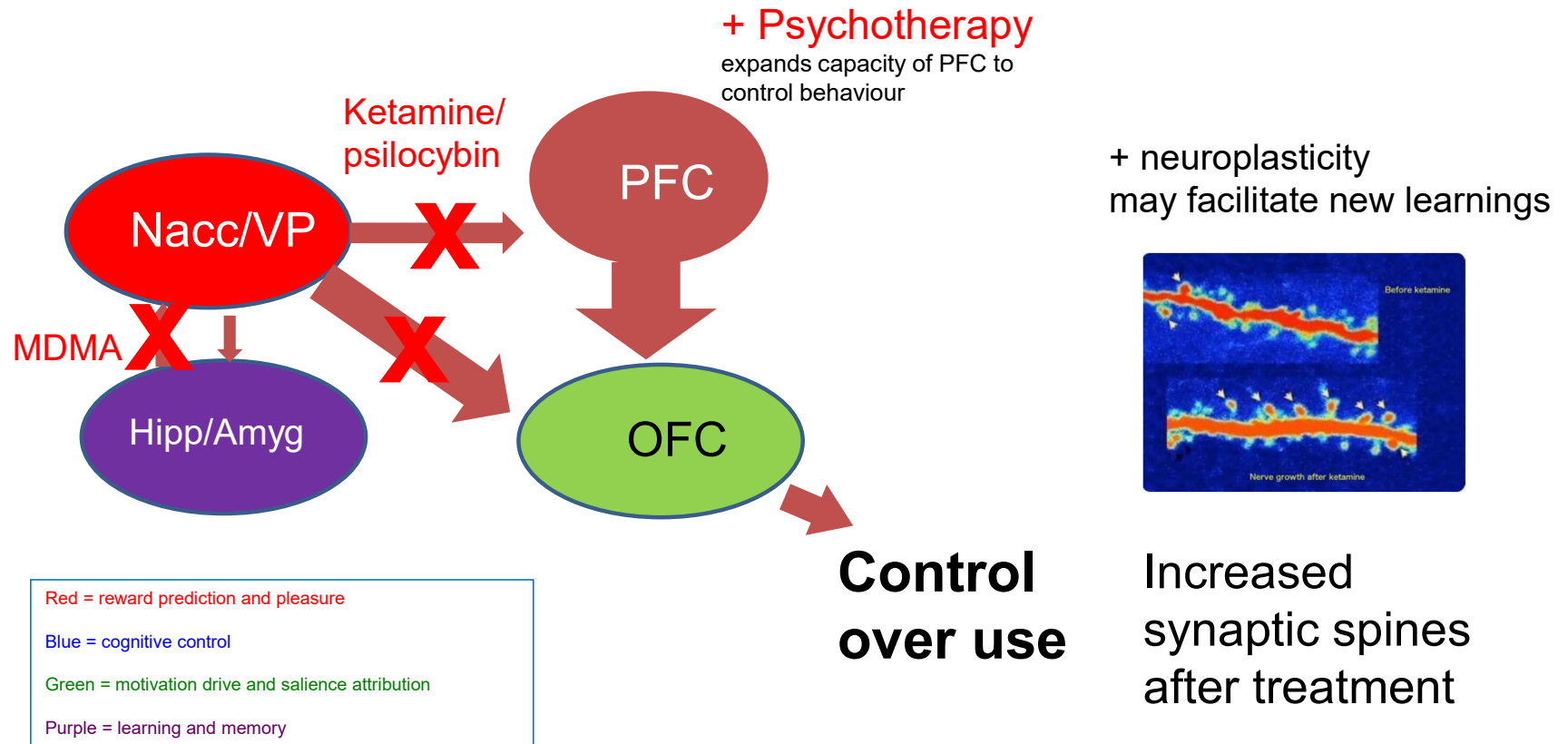
PFC – prefrontal cortex
OFC = orbitofrontal cortex
Nacc = nucleus accumbens
VP = ventral pallidum
Hipp = hippocampus
Amy = amygdala



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

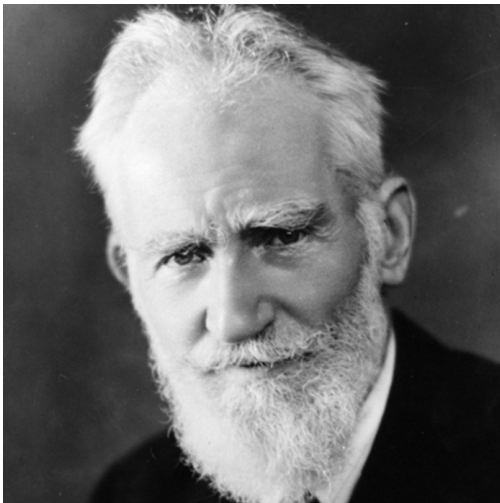
Disrupting these overactive addiction circuits can restore balance in the brain



Adapted from Baler and Volkow 2006

“Those who cannot change their minds cannot change anything”

George Bernard Shaw (1856-1950)



Psychedelic treatment has changed the minds of our patients through changing their brains

What we need to do now is change the minds of health care professionals and politicians about these therapies and bring them back into medical practice

And it has in some countries!

Feb 2023

Australia TGA announce re-scheduling psilocybin and MDMA for treatment-resistant depression and PTSD from July 2023



Magic mushrooms legal in several US states for therapeutic use

Biden says in USA psilocybin and MDMA will be registered medicines in 2 years

Acknowledgements

Alexander Mosley
Charitable Trust



THE CENTRE FOR
PSYCHEDELIC RESEARCH

Imperial College London



Time to rebalance the scales
of justice for psychedelics?

... and further reading

