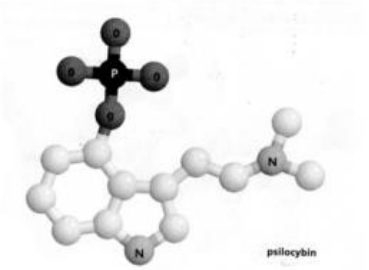
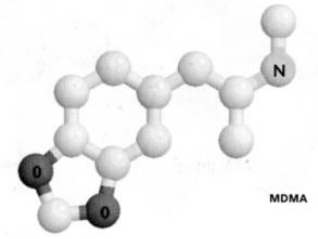
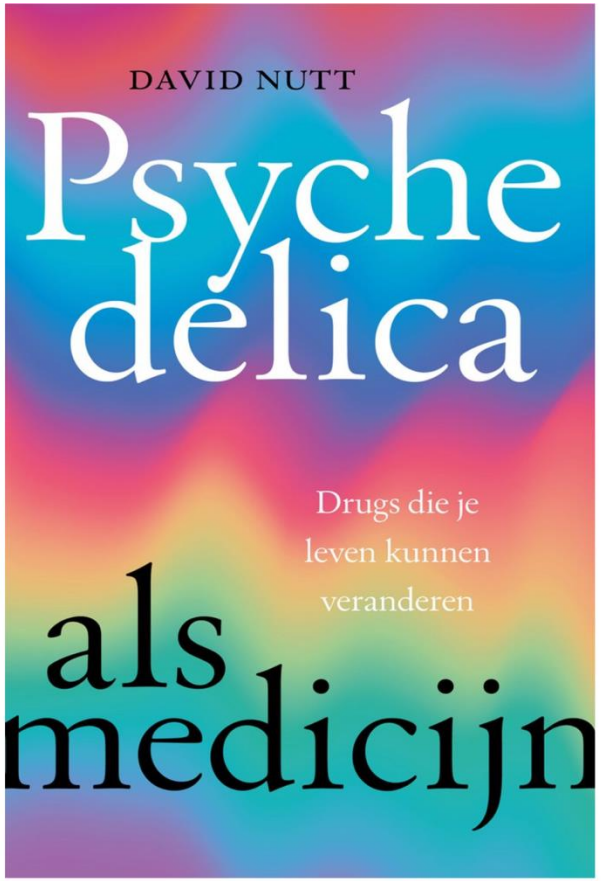


Psychedelics for depression
From neuroscience to clinical trials





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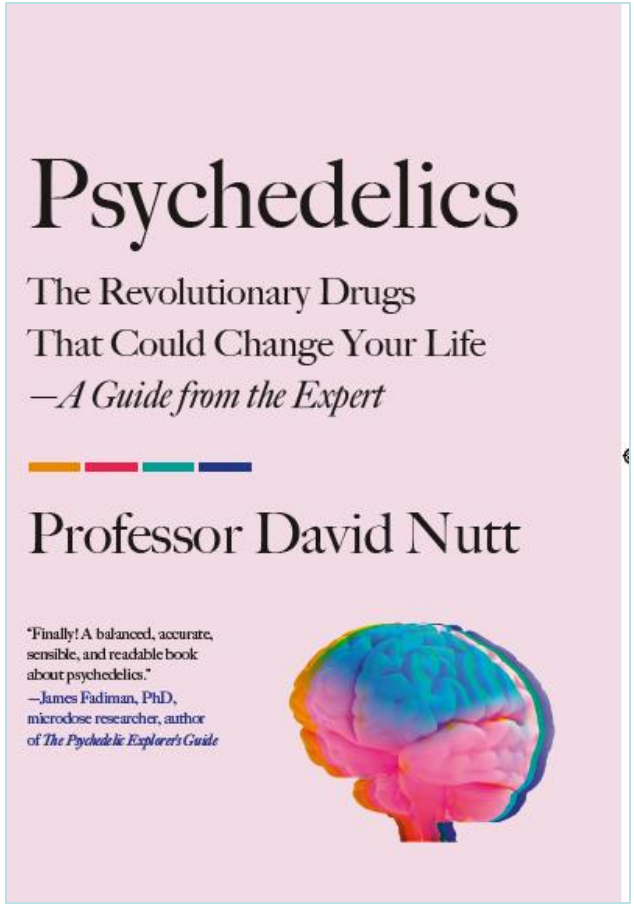
Imperial College London

d.nutt@imperial.ac.uk

CRO Awaknlifesciences

profdavidnutt@twitter.com

Podcasts on www.drugscience.org.uk



Declaration of interests – 2022-2024

- **Chair – DrugScience [UK] - & PAREA Europe (Psychedelic Access and Research European Alliance)**
- 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 - Lundbeck, BMS/Otsuka, Janssen, Takeda
- Grants and clinical trial support - Wellcome Trust, MRC, Compass Pathways, Usona, Filament
- Director Equasy Enterprises and GABA Labs. Share options – Psyched Wellness
- Expert witness in some legal cases relating to psychotropic drugs
- Edited/written 40 books - some purchased by pharma companies

Widening European interest in psychedelics as therapy

December 2023 – Vatican conference on neuromodulation – included me talking on psychedelics

The Vatican conference venue

St Peter overseeing his church ……..as well as the gates to Heaven

The Blessed at the gate to heaven with St. Peter(1467–1471) by Hans Memling

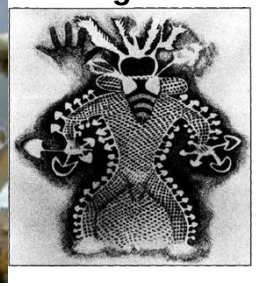
Psychedelics have always been with us
→ understanding, personal growth, wellbeing, healing

Peyote /San Pedro cacti
mescaline

Native American churches

Magic mushrooms/ psilocybin

Mushroom man
Algeria 5000 BCE



Ayahuasca = DMT drink

Serpent and jaguar indigenous gods
Now used in several "Christian" churches

K26.1 PLOUTOS ENIATOS, DEMETER ELEUSIS

Ancient Greeks
Kykeon drink = ergot + wine

Demeter sharing magic mushrooms with her daughter Persephone

Hinduism

Soma = Cannabis + magic mushrooms +ephedra

Amanita Muscaris muscimol

Roman mosaic for Amanita tea

May have helped the early Christians survive persecution

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.

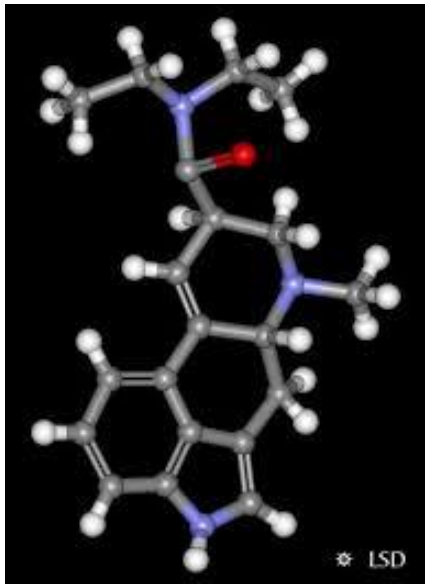
William Blake, 1793

LSD – the big breakthrough

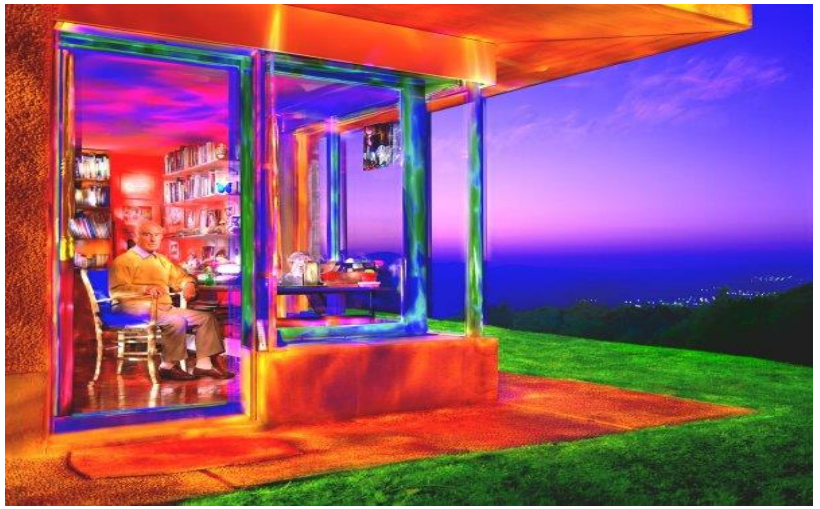
LSD

→ synthetic and more potent psychedelic

→ wide medical and research use

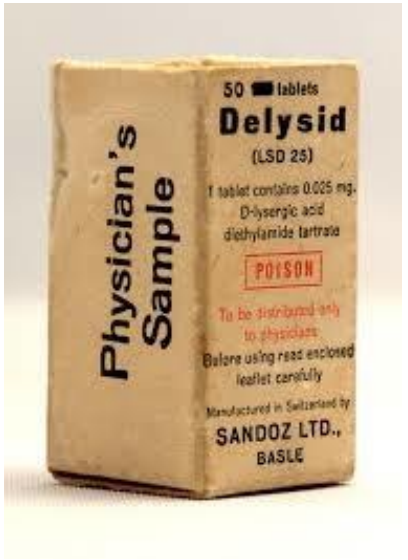


Albert Hofmann – the discoverer of the chemistry of LSD and psilocybin - at 100



Research with LSD and psilocybin in the 1950s and 1960s

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



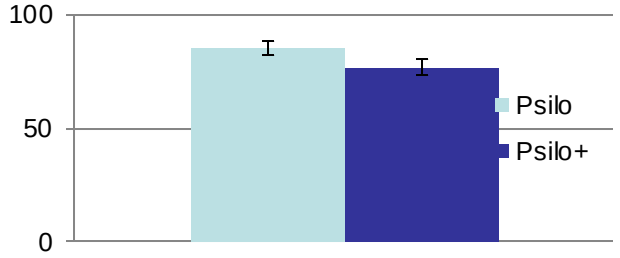
LSD

Psilocybin

Results were overwhelmingly positive, describing safe and effective treatments

(Masters and Houston, 1971)

Early Psychiatric Uses for LSD and psilocybin



Mehta et al Saracatanib reduces effects of psilocybin → trial in psychosis with Parkinson's disease

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**

Current major approach –
e.g. 25 mg psilocybin

Use starting at Imperial College
– e.g. 10 mg psilocybin for OCD – first data in Masterclass
- 5mg for young people who self harm by cutting to aid cognitive reframing

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

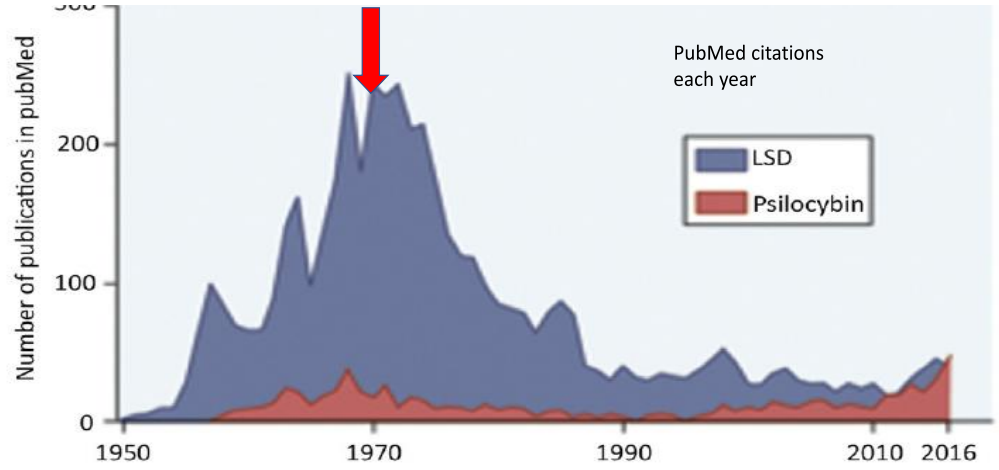
(Malleson, N. (1971) 'Acute Adverse Reactions to LSD in clinical and experimental use in the UK.' Br J Psychiatry. 18(543): 229-30)

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

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

Impact of the 1971 UN Psychotropics Convention on psychedelic research

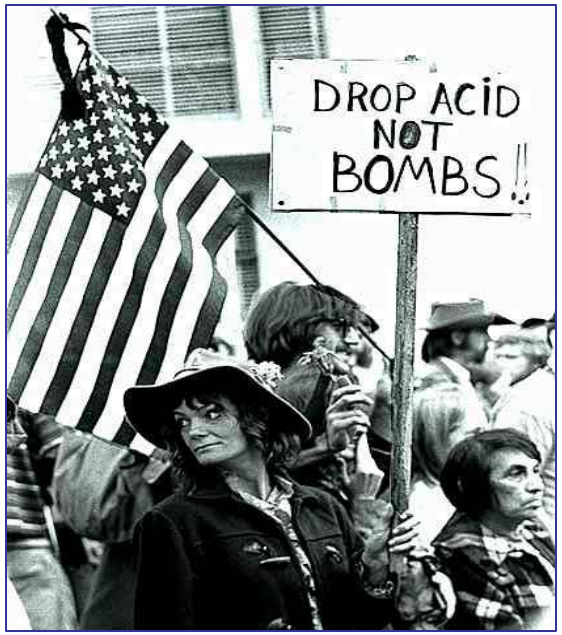


Kyzar et al 2017 TIPS

Put into Schedule 1 – "highly dangerous, addictive 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



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

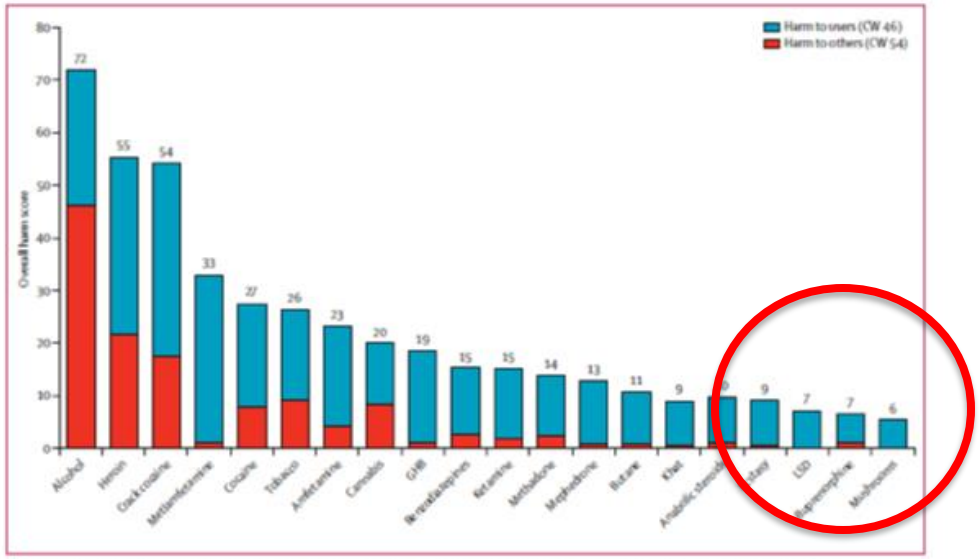
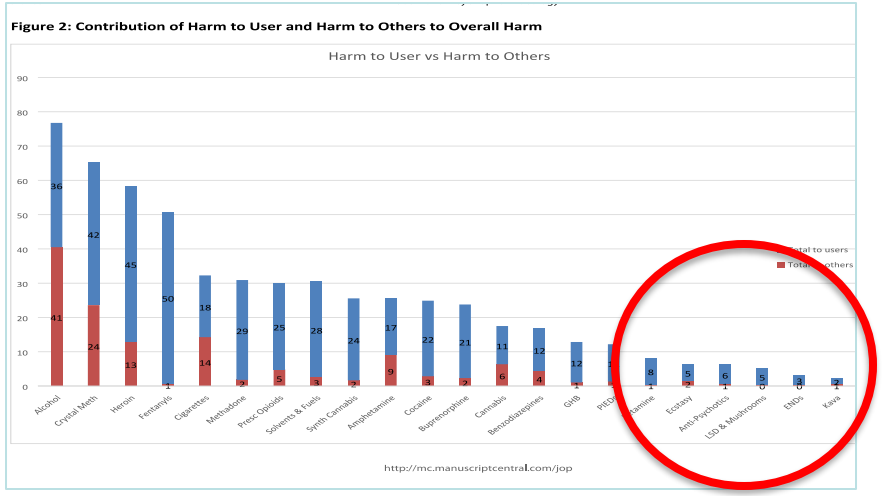


Figure 2: Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others
The weights after normalisation (0–100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 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[1], the 1971 Convention on Psychotropic Substances[2] and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances[4]. The 1971 convention makes it clear that use of Schedule I substances, such as MDMA, psilocybin and lysergic acid diethylamide (LSD; also known as

PLOS | BIOLOGY

March 2015

PERSPECTIVE

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

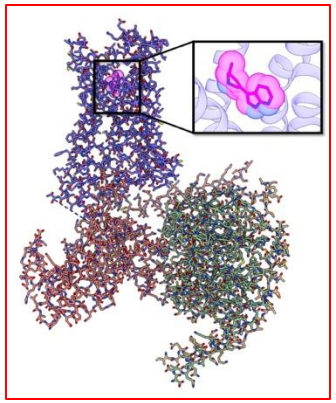
David Nutt*

Division of Brain Sciences, Imperial College London, London, United Kingdom

* d.nutt@imperial.ac.uk

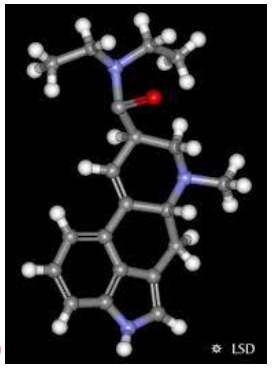
All serotonergic psychedelics are 5-HT2A receptor agonists

Crystal structure of the 5-HT2A receptor

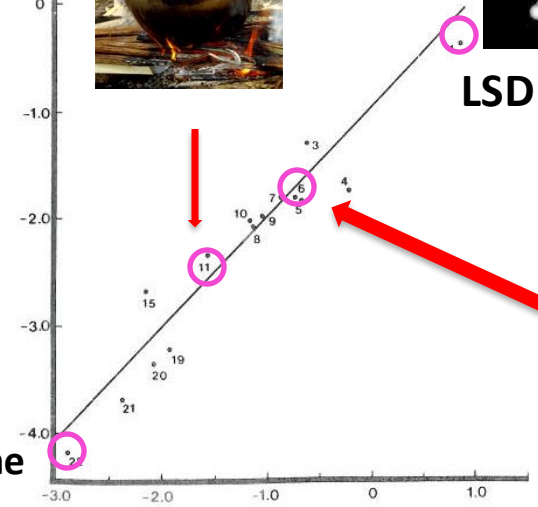


Affinity for the 5-HT2A receptor

Ayahuasca/DMT

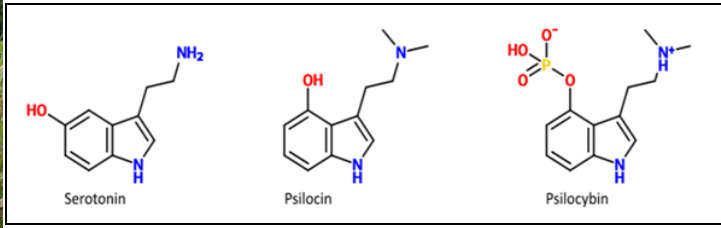


LSD



Mescaline

Psilocybin – magic mushrooms – note active ingredient is psilocin



Potency in humans

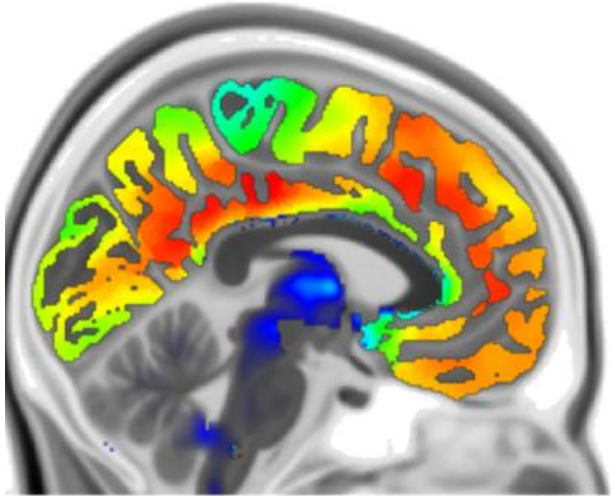
Glennon et al. 1984. Human dose data from Shulgin 1978

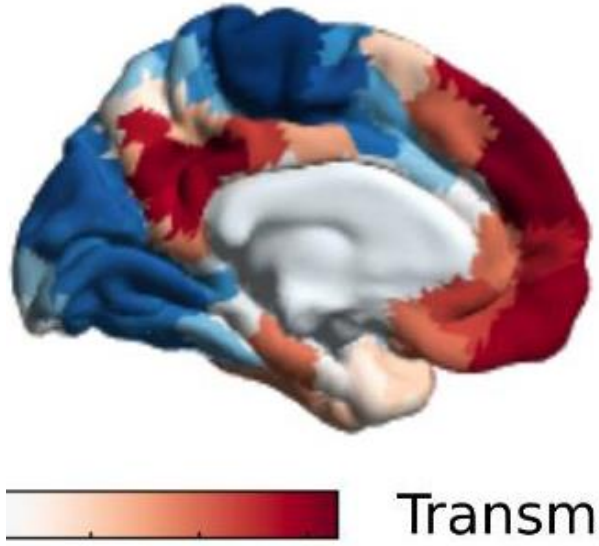
5-HT2A receptor antagonists e.g. ketanserin, risperidone, mirtazapine block effects

The 5-HT2A receptor in human brain

PET image
[11C]Cimbi-36
5HT2A receptor agonist

Copenhagen PET centre





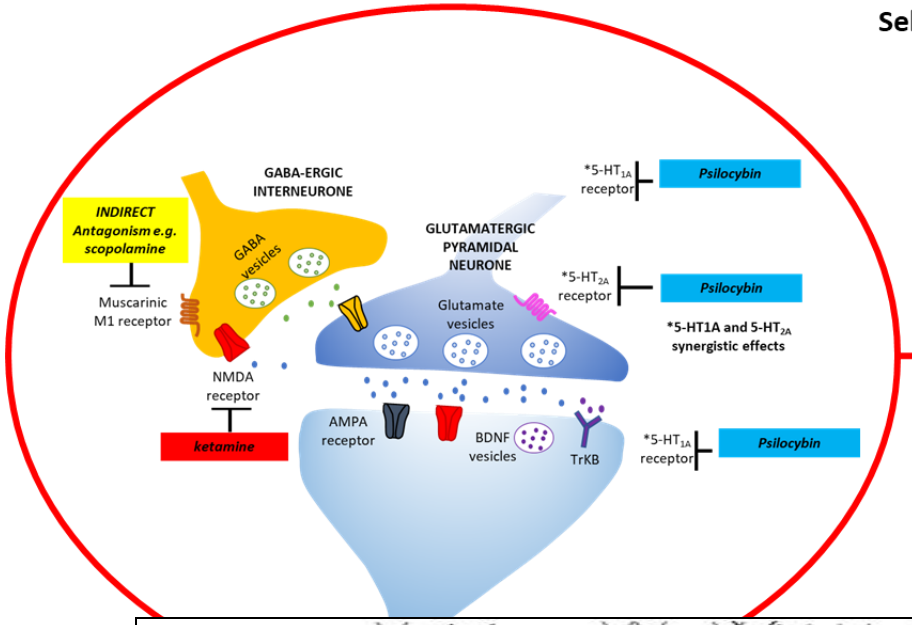
Evolution of human brain – red = latest

Human brain has highest 5-HT2A density of any brain

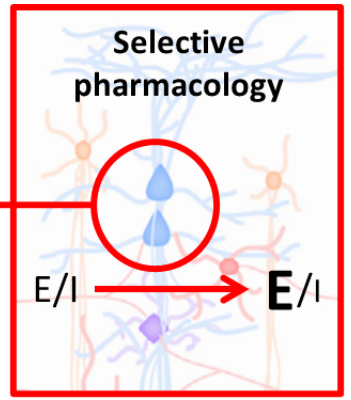
5HT2A receptors most densely expressed in recently evolved transmodal cortex – maybe patterns it? Luppi et al Brain 2024

Synaptic pharmacology of psychedelics including ketamine and scopolamine

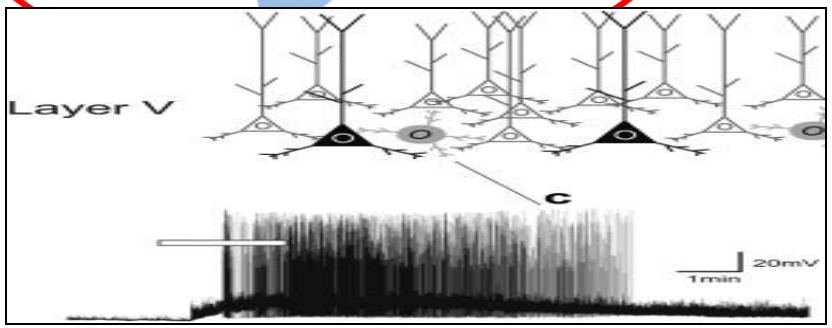
Axonal synapse of pyramidal neurons



Phase I
Selective modulation of affective biases
Protein synthesis independent



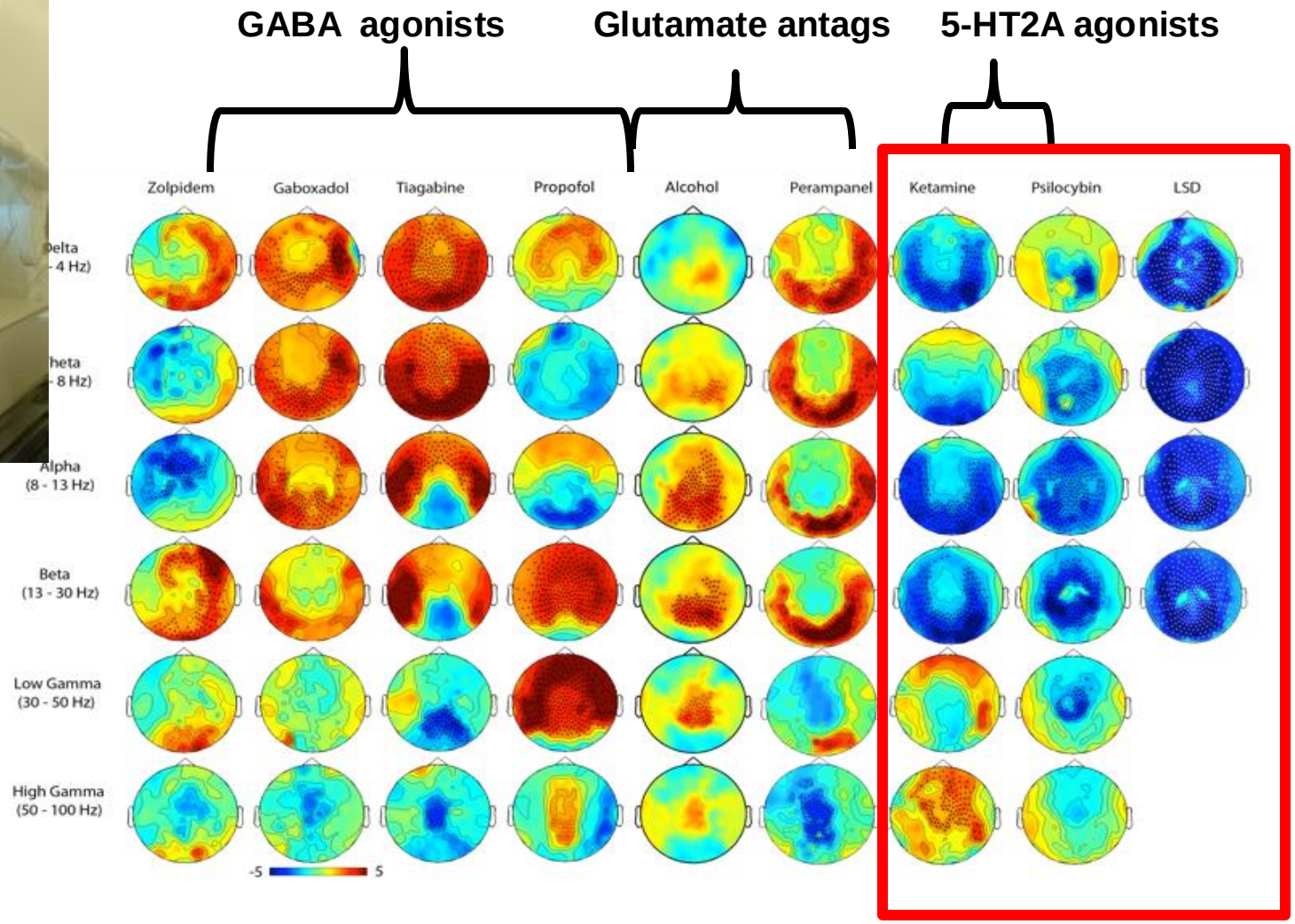
Massive depolarisations



➔ Entropic brain state

Brain-prints = How drugs compare on MEG

Sedatives synchronize brain activity

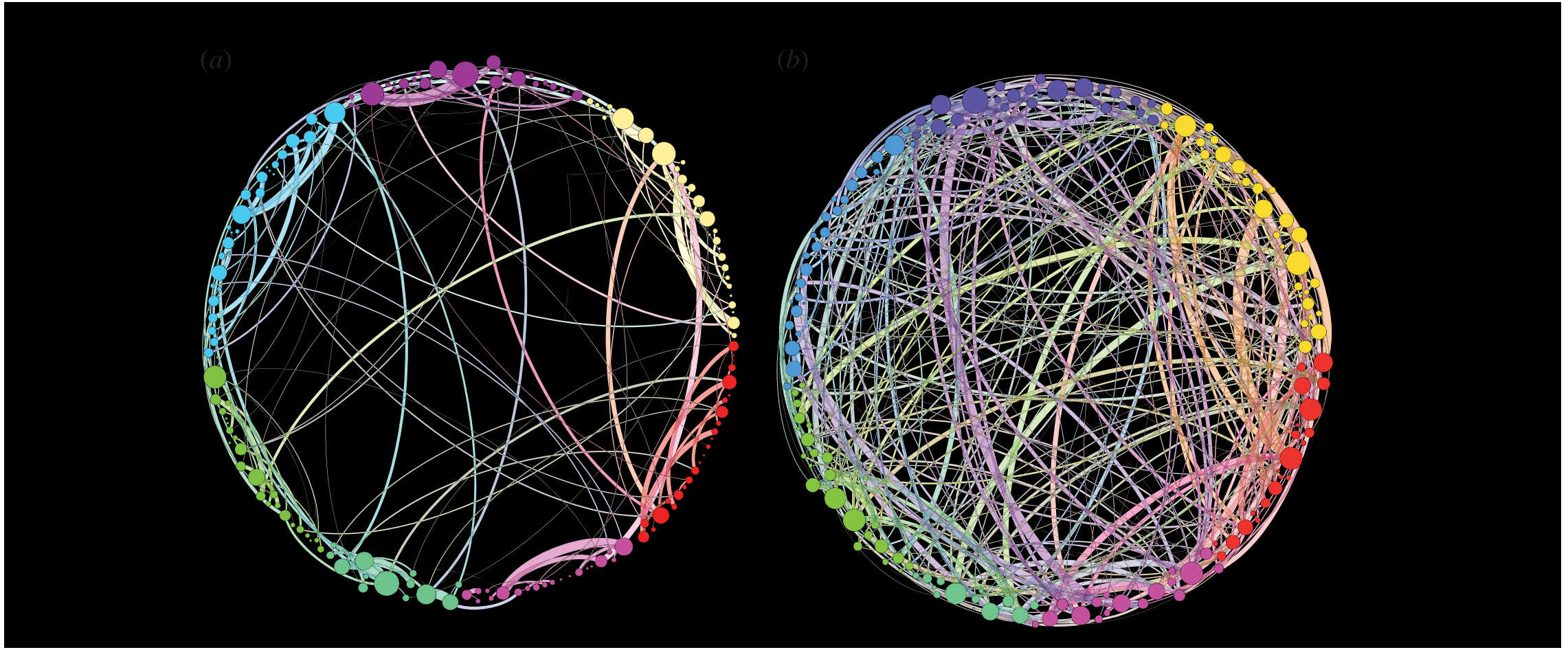


Psychedelics

desynchronize brain activity = entropic brain

Muthukumaraswamy et al 2013 Journal of Neuroscience

Psychedelics increase brain connectivity
→ new solutions to old problems?

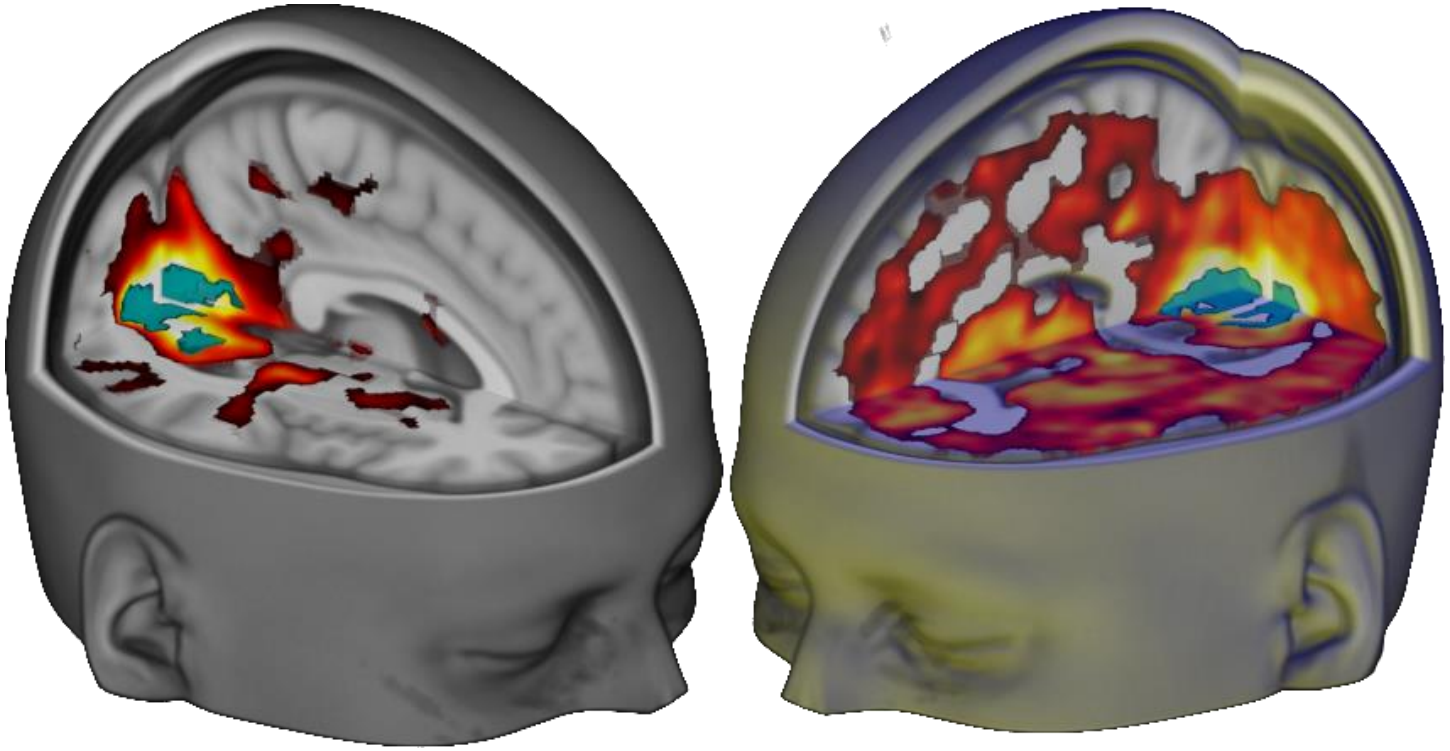


Normal (small world brain)

Psilocybin (child's brain)

Petri et al J. R. Soc. Interface 11: 20140873

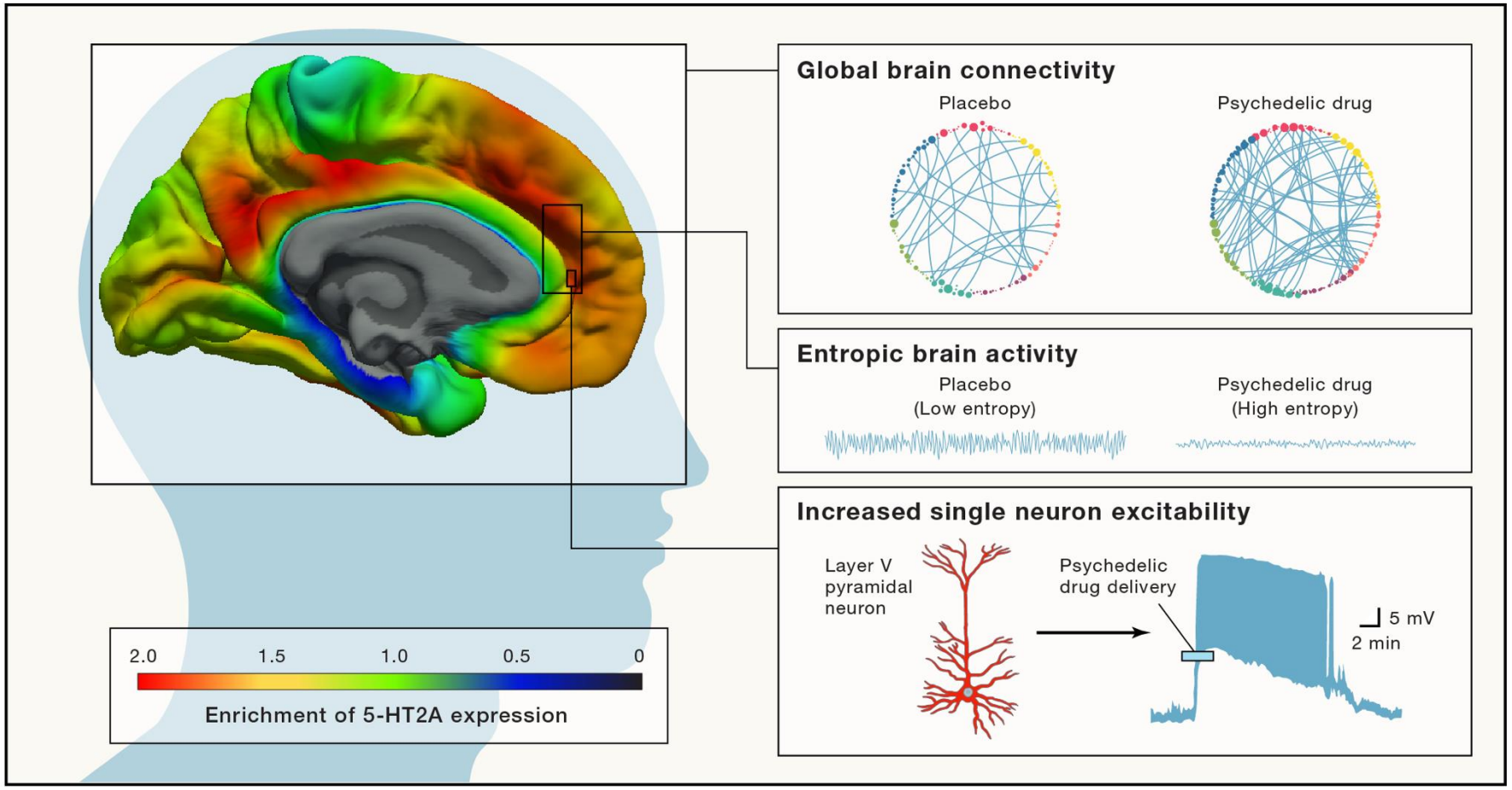
Increased connectivity under LSD
→ insights as well as visions?



from Carhart-Harris et al 2016 PNAS

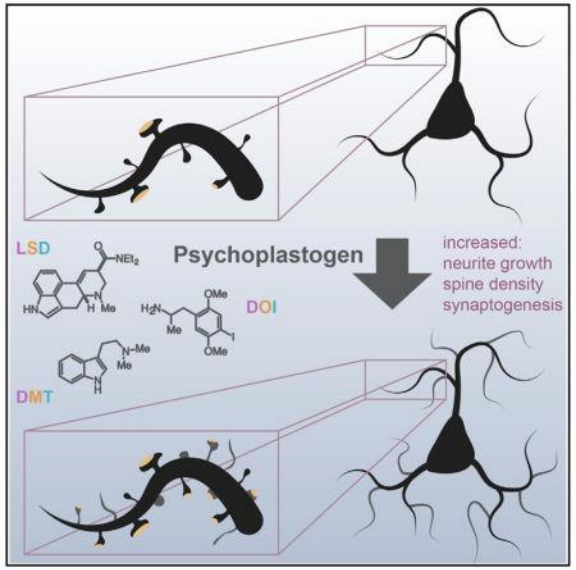
Image courtesy of Leor Roseman

Brain mechanisms of psilocybin



Nutt et al, Cell 2020

+ neuroplasticity

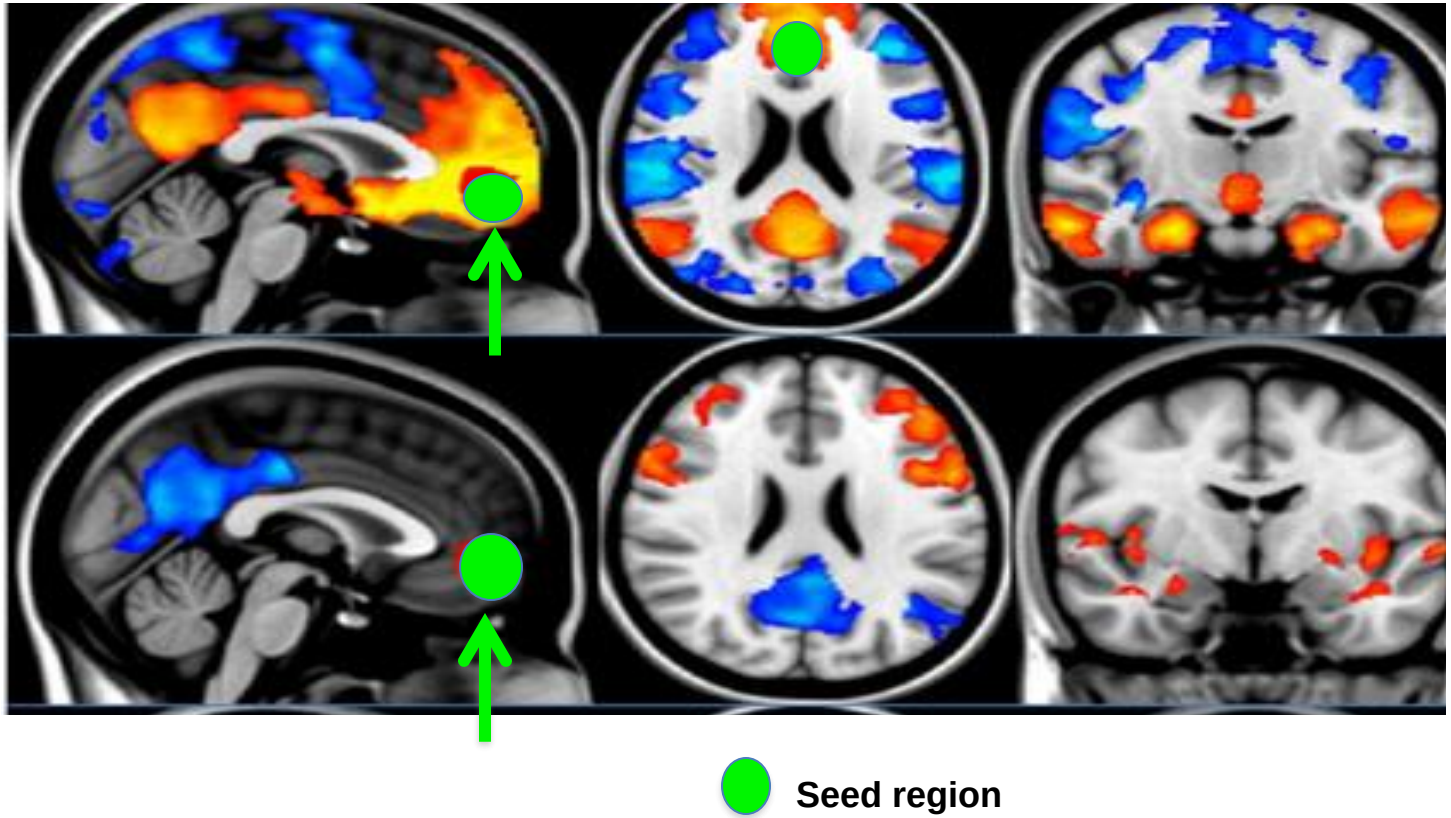


Ly et al, Cell Reports 2018

Psilocybin uncouples the default mode network, DMN)

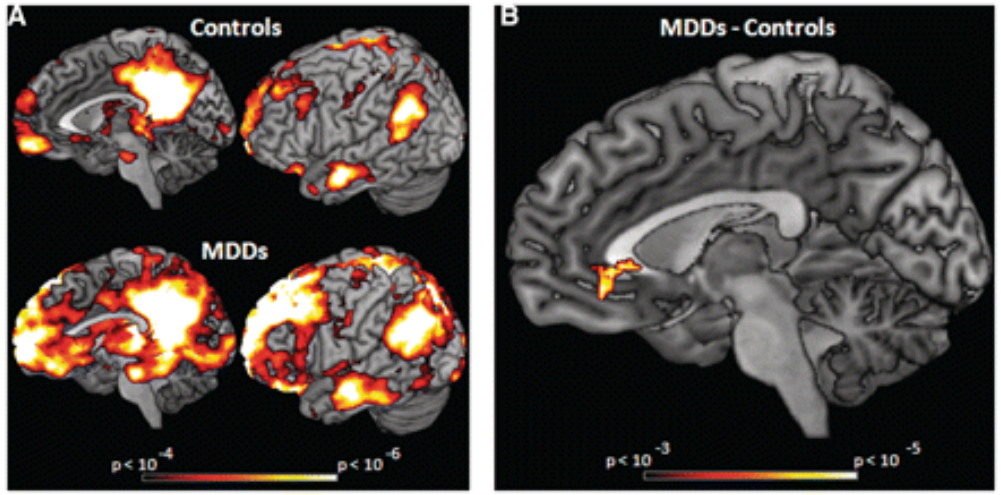
Saline – strong correlations in activity in these regions

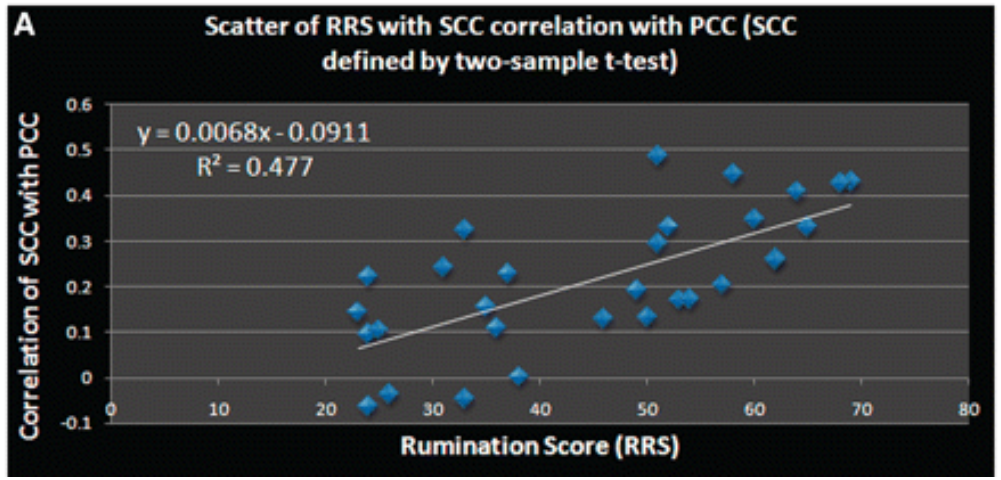
Psilocybin – correlations lost or even negative



Carhart-Harris et al PNAS 2012

The default mode network is overconnected in depression





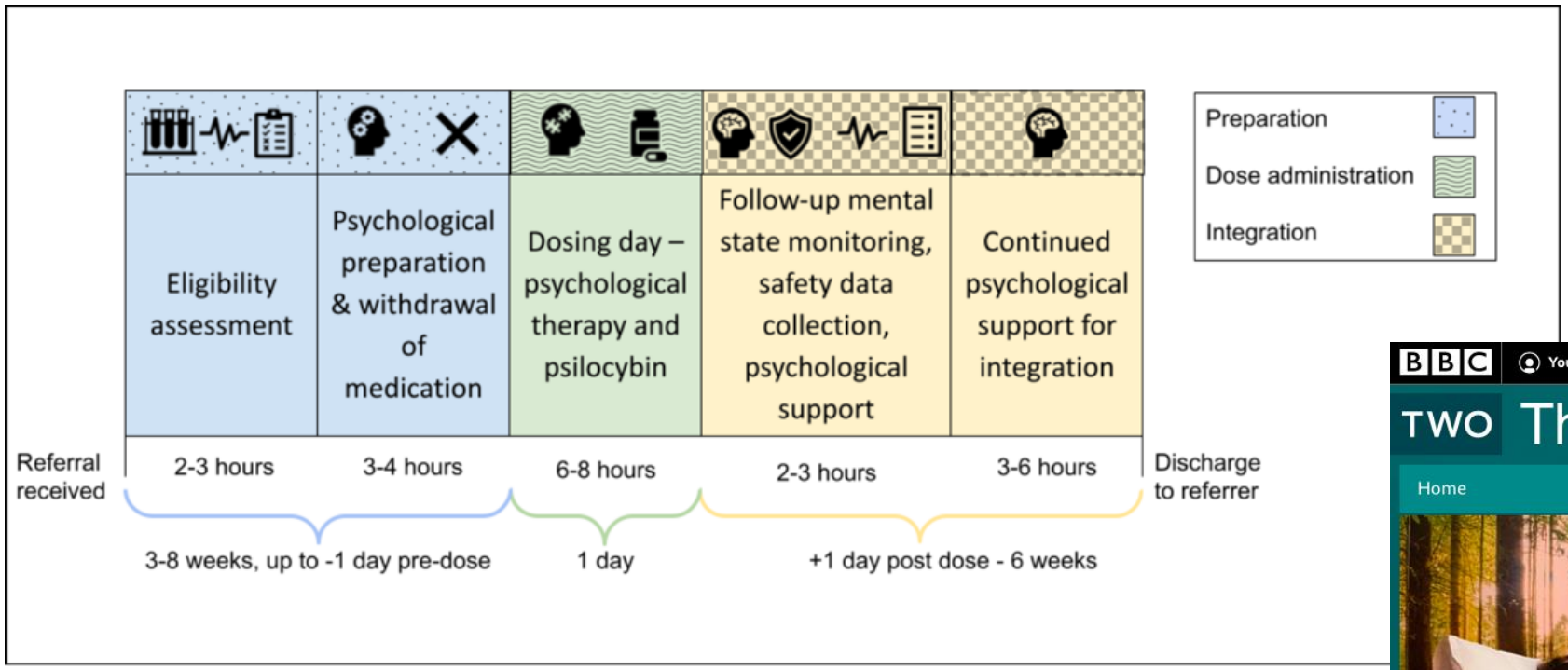
(Berman et al. 2011)

A) PCC functional connectivity

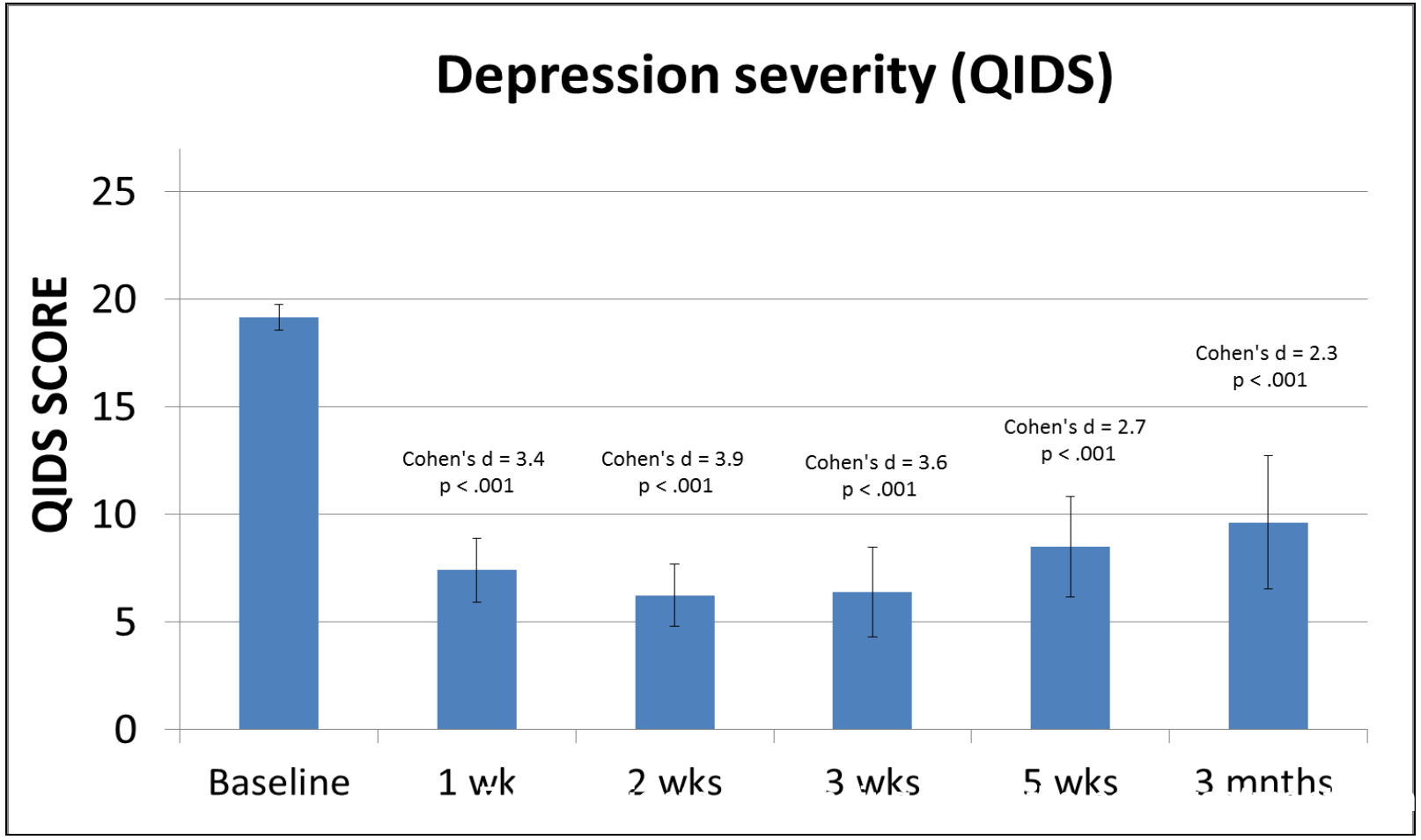
B) Greater PCC to SCC (subgenual cingulate cortex) connectivity in depression

PCC - SCC functional connectivity predicts rumination

How we do psychedelic therapy



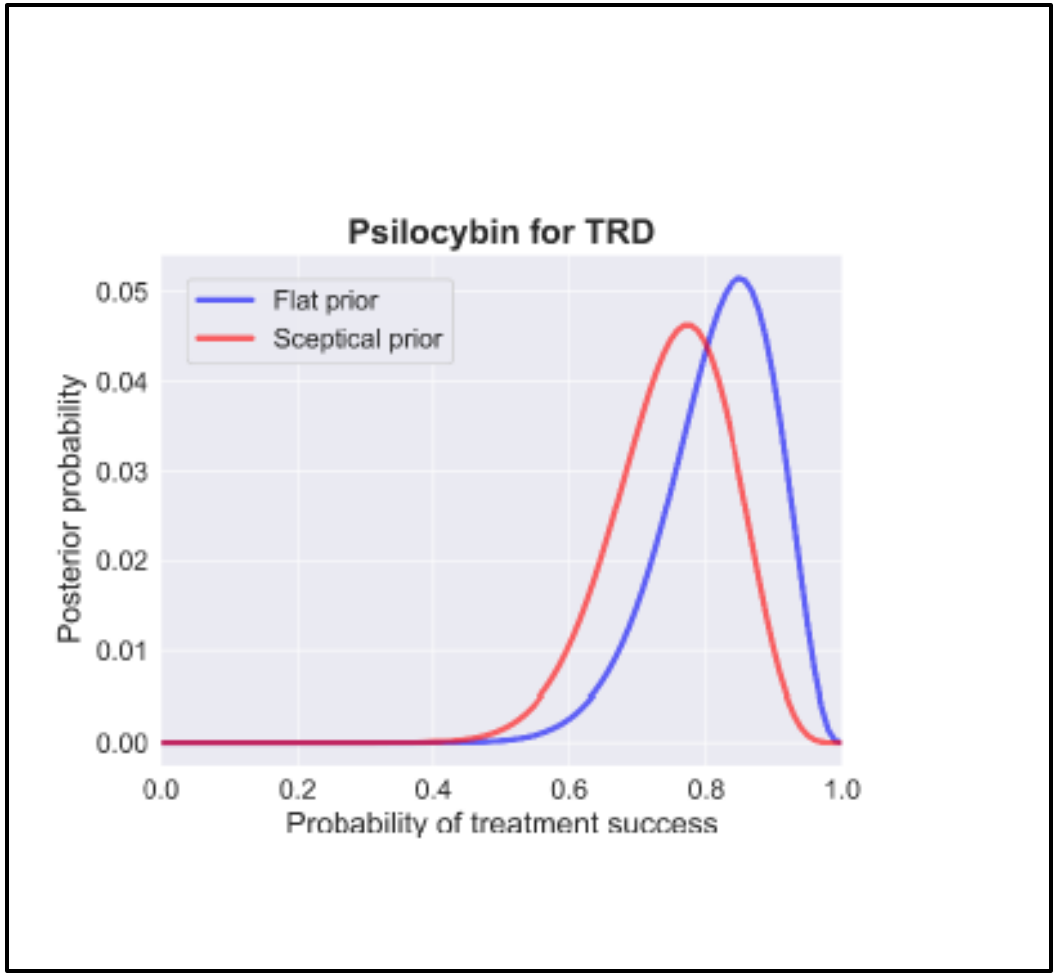
Powerful and enduring effects of single 25mg dose of psilocybin in treatment-resistant depression



All failed > 2 antidepressants and CBT`

Carhart-Harris Lancet psychiatry 2016

Bayesian analysis of psilocybin in treatment-resistant depression



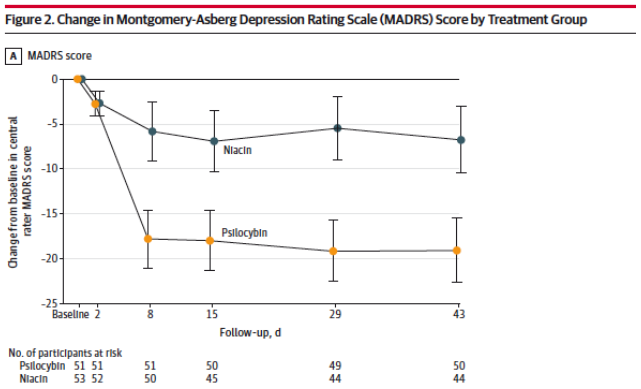
20 patients all failed on >2 antidepressants and on CBT

Data from Carhart-Harris et al 2016 Lancet Psychiatry

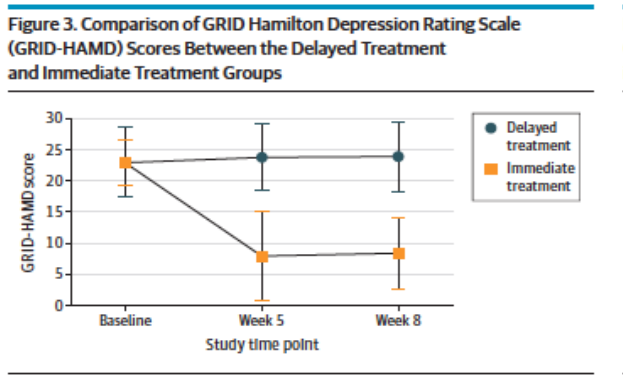
Szegeti, Philips and Nutt 2023 Brit Journal Clinical Pharmacology

Replications

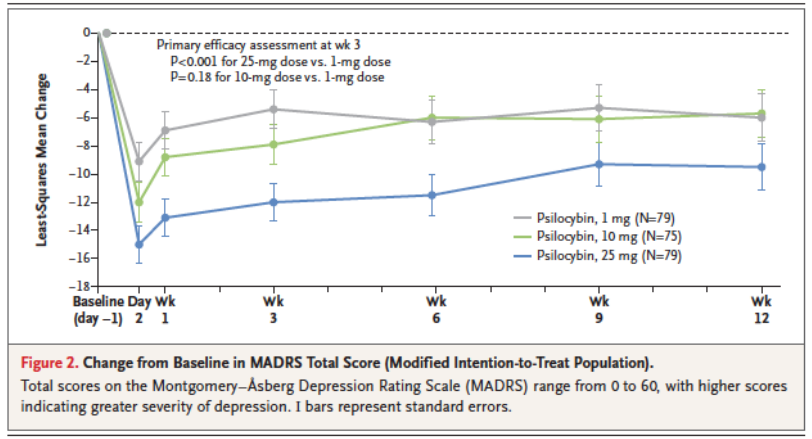
Many studies psilocybin has been shown to improve mood in depression – just hours after a single dose – and these effects may last for many months



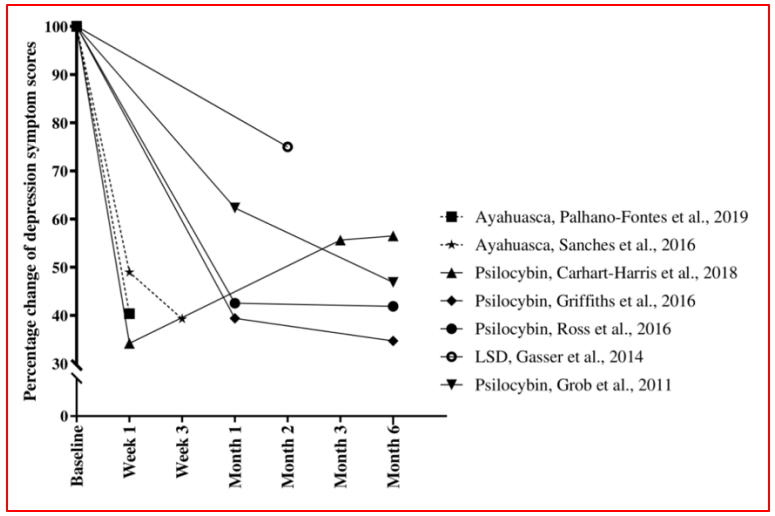
Raison et al 2023.



Davis et al 2021



Also with ayahuasca LSD and recently i.v. DMT (press release)



Many other trials with psychedelics - all positive

End of life anxiety and depression – 2 double-blind RCTs:

- **Griffiths - Johns Hopkins and**
- **Ross - NYU**

Seven depression trials – psilocybin
One – DMT
One - ayahuasca

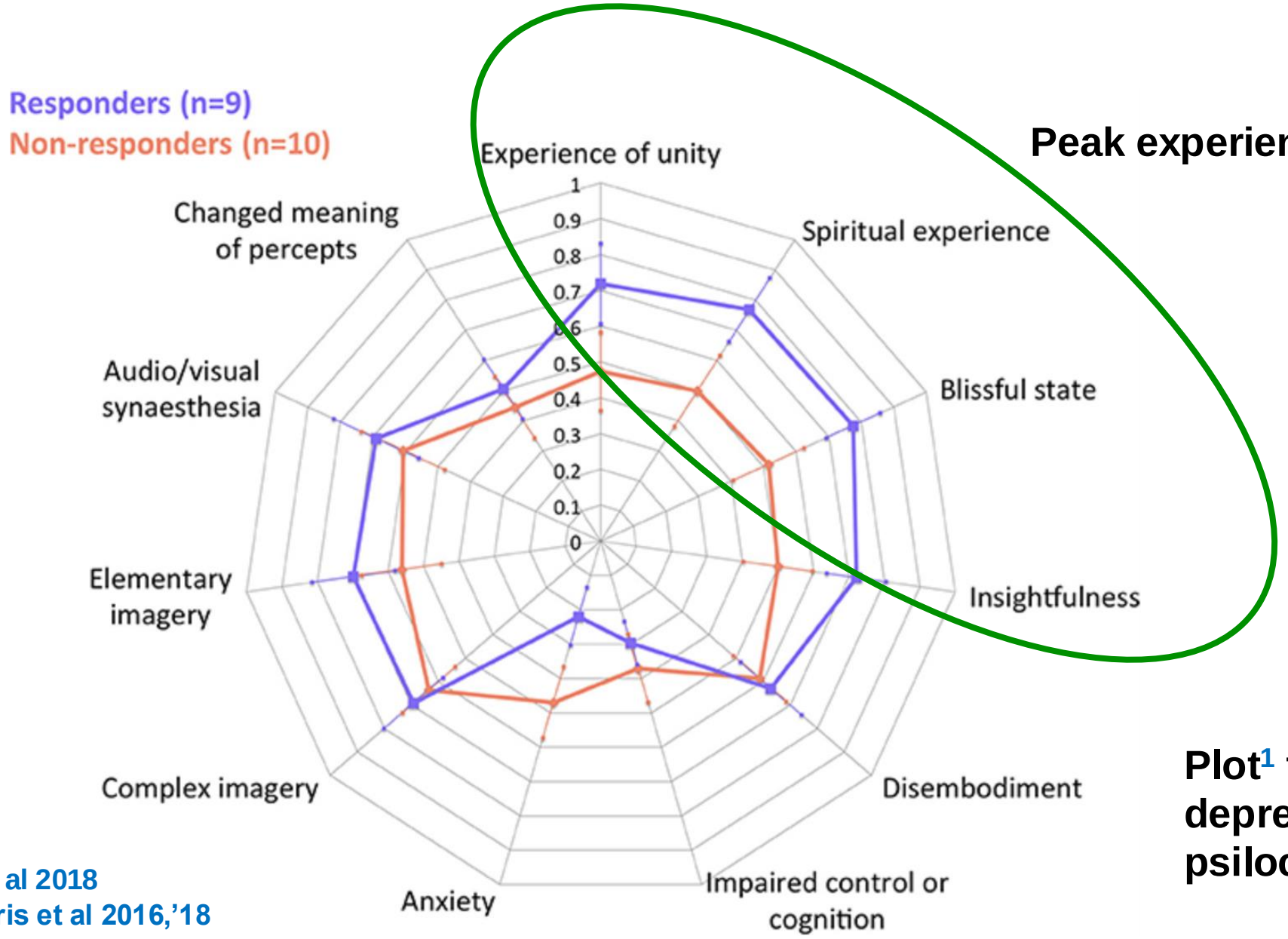
Smoking quitting - Johnson - Johns Hopkins
Alcoholism – Bogenschutz - NYU

LSD in GAD

Many others now underway including in anorexia, OCD, pain syndromes

These are all internalizing disorders – cognitions are self-referential and ruminative - psychedelic can break these down

The psychedelic experience and depression outcomes



Plot[1] from our first depression trial with psilocybin[2]

[1]Roseman et al 2018
[2]Carhart-Harris et al 2016,'18

ORIGINAL ARTICLE FREE PREVIEW

Trial of Psilocybin versus Escitalopram for Depression

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.

Abstract

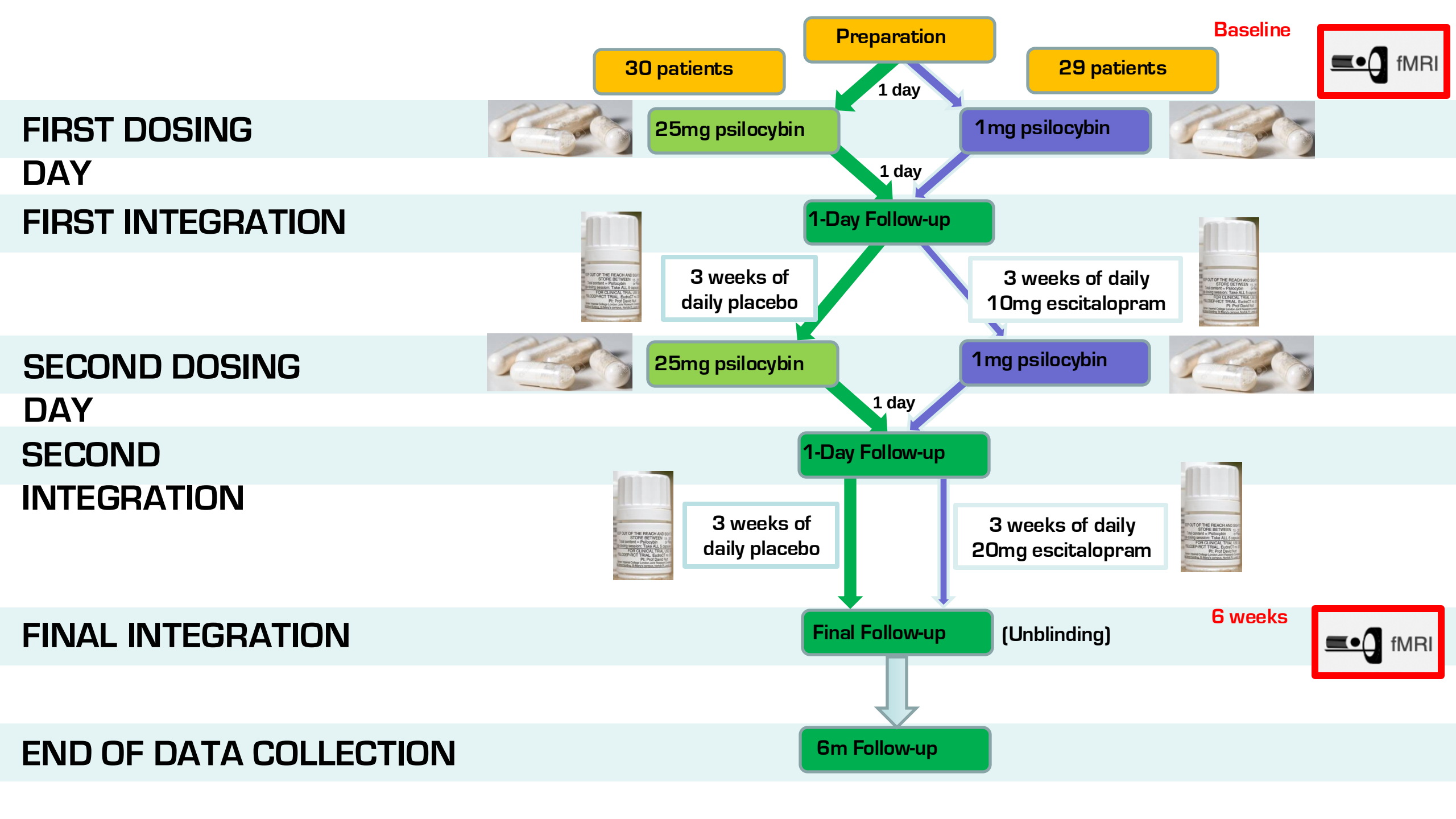
April 15, 2021
N Engl J Med 2021; 384:1402-1411
DOI: 10.1056/NEJMoa2032994

The first comparative trial - aims

1. Use fMRI to compare therapeutic mechanisms of psilocybin therapy with a prototypical selective serotonin reuptake inhibitor (SSRI) antidepressant

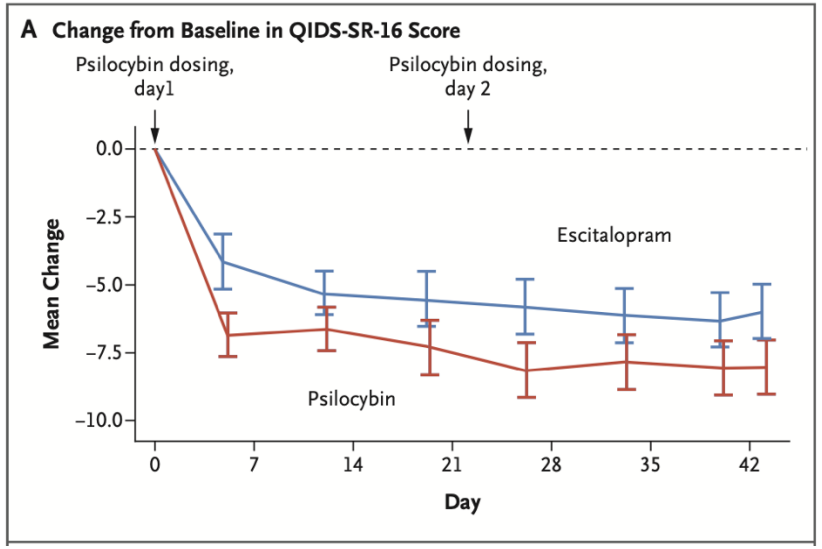
2. To compare side effects

3. To compare efficacy in depression + ancillary symptoms

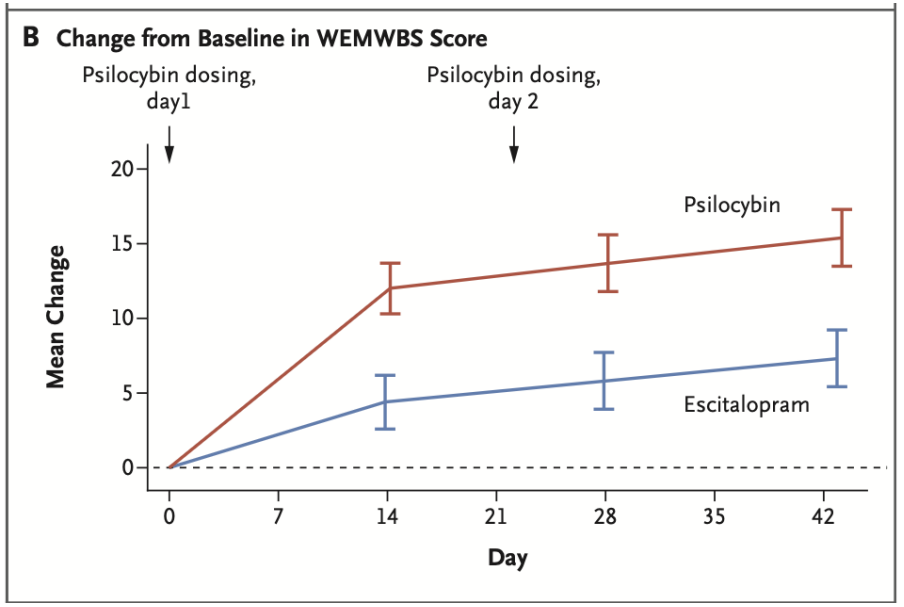

Baseline
fMRI
Preparation
30 patients
29 patients
1 day
25mg psilocybin
1mg psilocybin
1 day
FIRST DOSING DAY
FIRST INTEGRATION
1-Day Follow-up
3 weeks of daily placebo
3 weeks of daily 10mg escitalopram
SECOND DOSING DAY
25mg psilocybin
1mg psilocybin
1 day
SECOND INTEGRATION
1-Day Follow-up
3 weeks of daily placebo
3 weeks of daily 20mg escitalopram
FINAL INTEGRATION
Final Follow-up
(Unblinding)
6 weeks
fMRI
END OF DATA COLLECTION
6m Follow-up

Psilocybin –v-escitalopram trial

Reductions in depression scores



Improvements in wellbeing



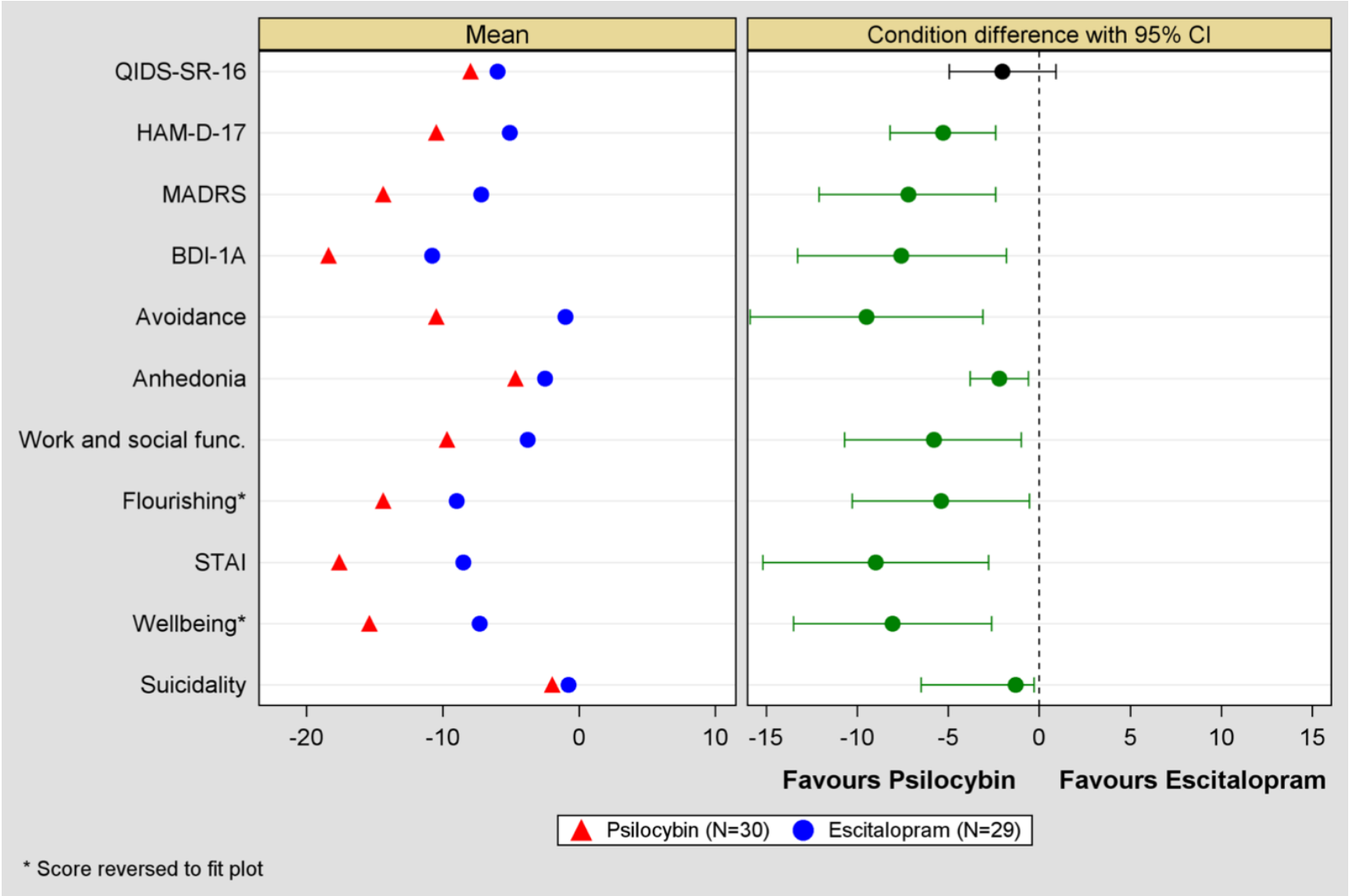
Remission rates % patients

Scale	Psilocybin	Escitalopram
QIDS	57	29
BDI	58	18
HAMD	49	10
MADRS	29	7

Psilocybin better tolerability on sleep and gut measures over the 6 weeks

Carhart-Harris et al NEJM 2021

Efficacy: Green = >95% confident of difference



Carhart-Harris et al NEJM 2021

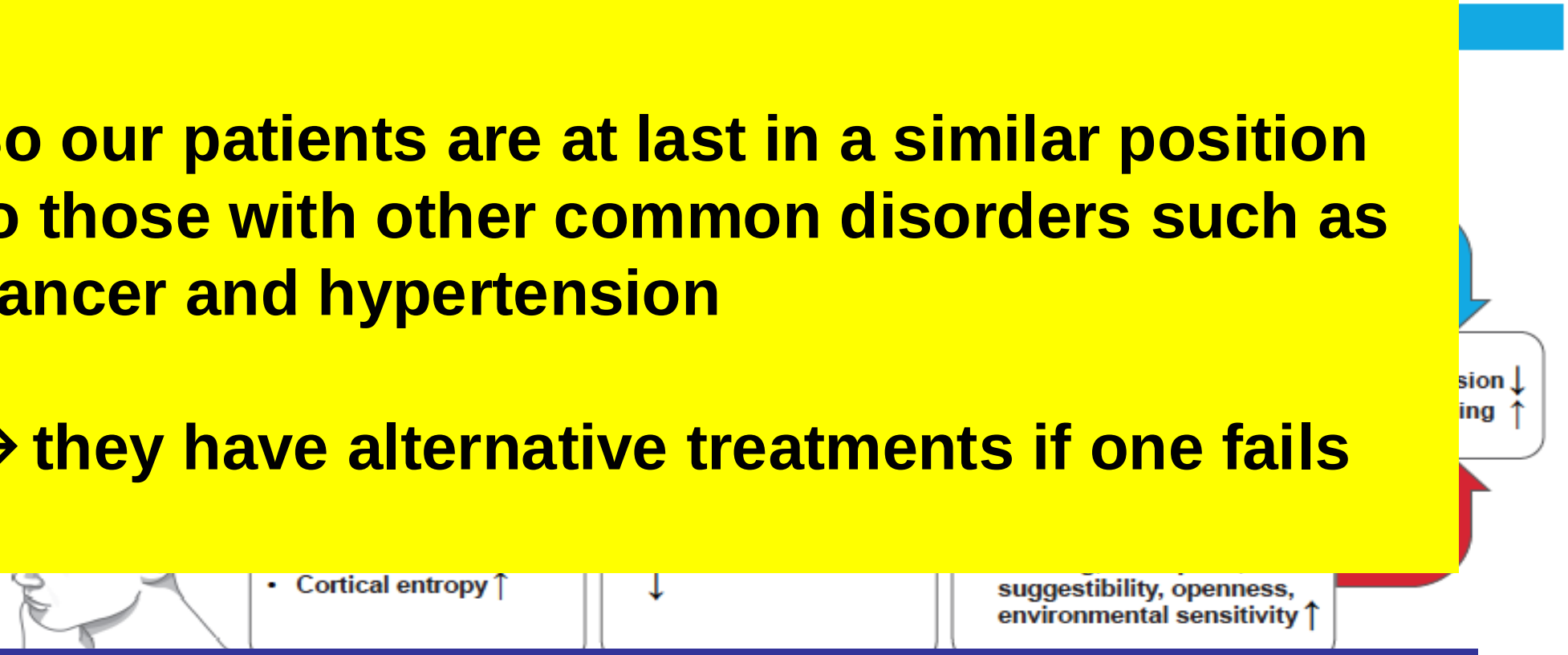
We now have two ways to treat depression

Conventional Antidepressants

Ketamine and psilocybin

So our patients are at last in a similar position to those with other common disorders such as cancer and hypertension

→ they have alternative treatments if one fails

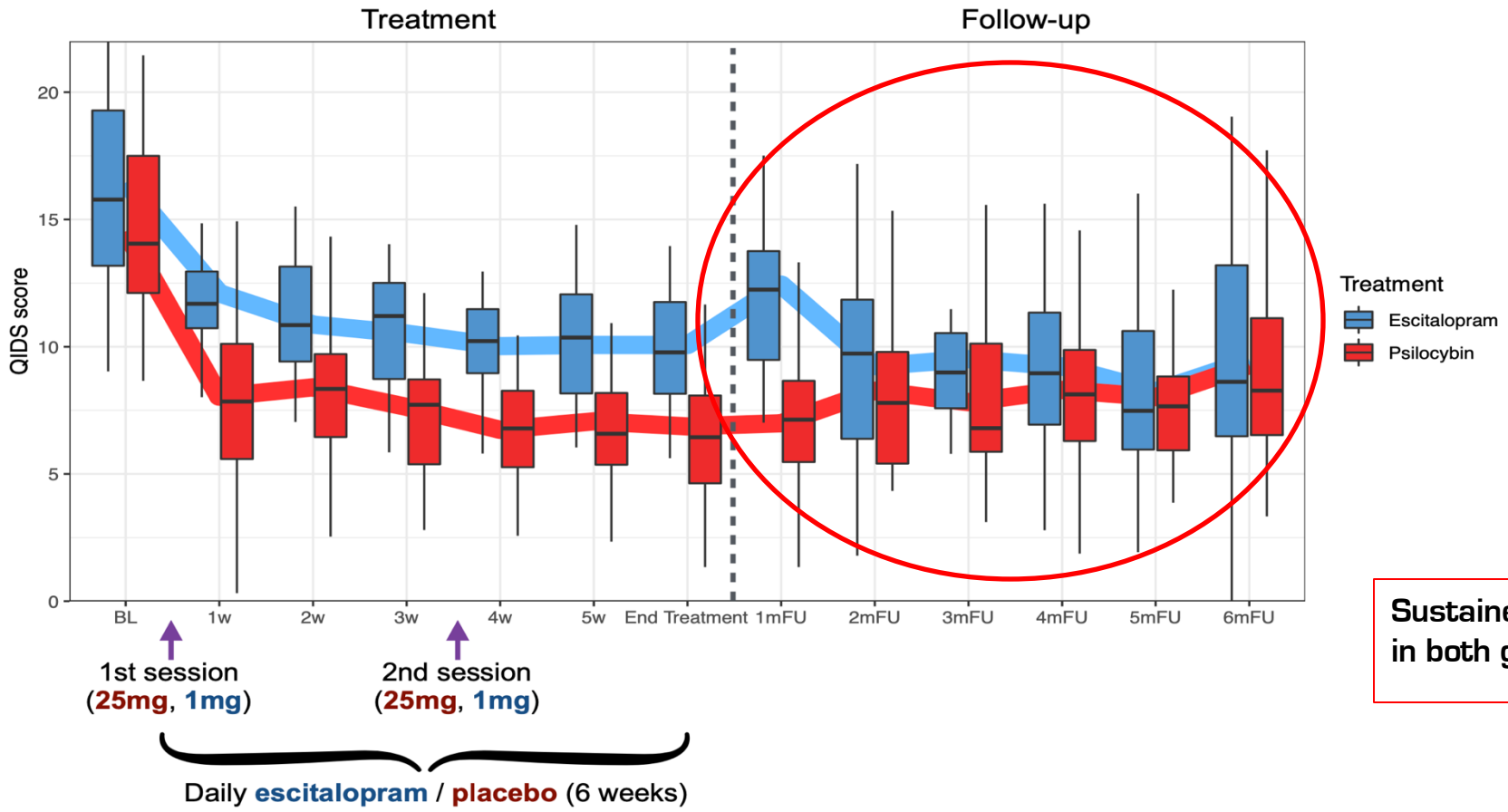


Antidepressants – blunt emotions *"Where escitalopram nulled me to be less scared, psilocybin has made me realise that fear is not something to be feared*

Psilocybin vs Escitalopram - 6 months follow up

QIDS scores (after mixed-model cleaning)

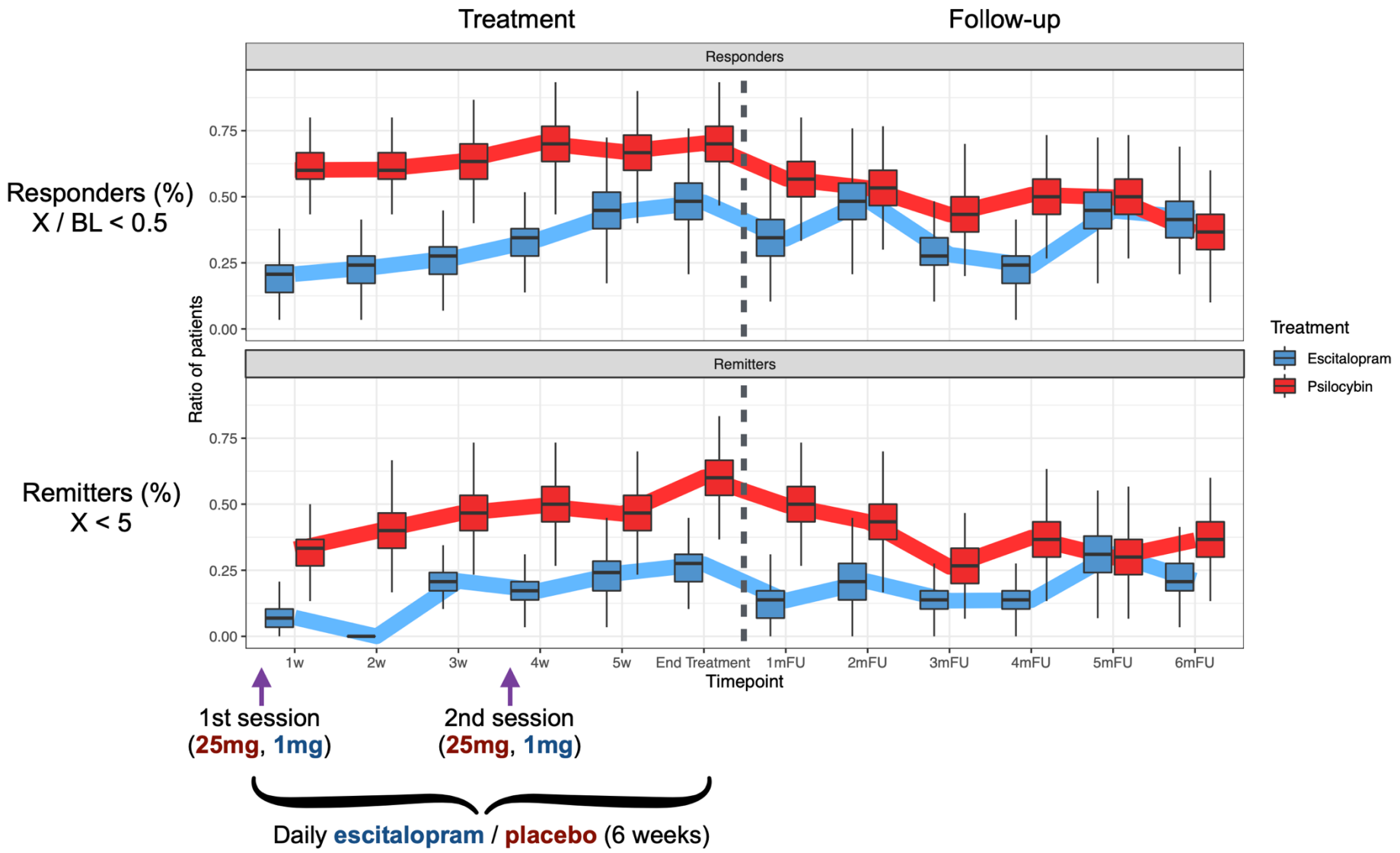
Psilocybin: 30 patients
Escitalopram: 29 patients



Sustained antidepressant effects in both groups

Erritzoe et al eClinicalMedicine 2024 102799

Psilocybin vs Escitalopram - 6 months follow up

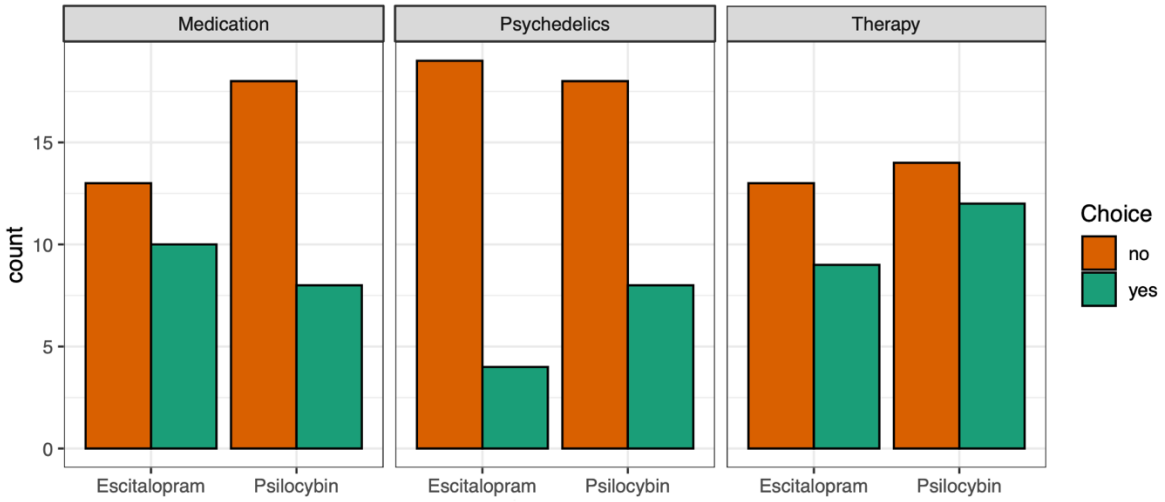


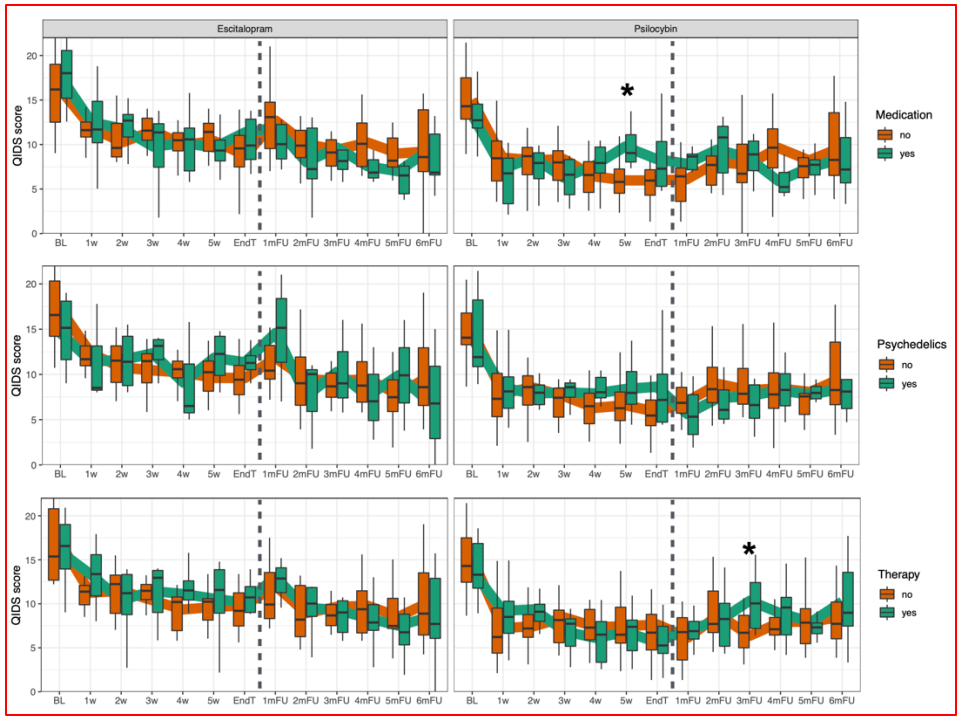
Erritzoe et al eClinicalMedicine 2024 102799

The 6 months follow up (cont.)

What people do after the trial ended?

There were found no significant difference between treatment arms…



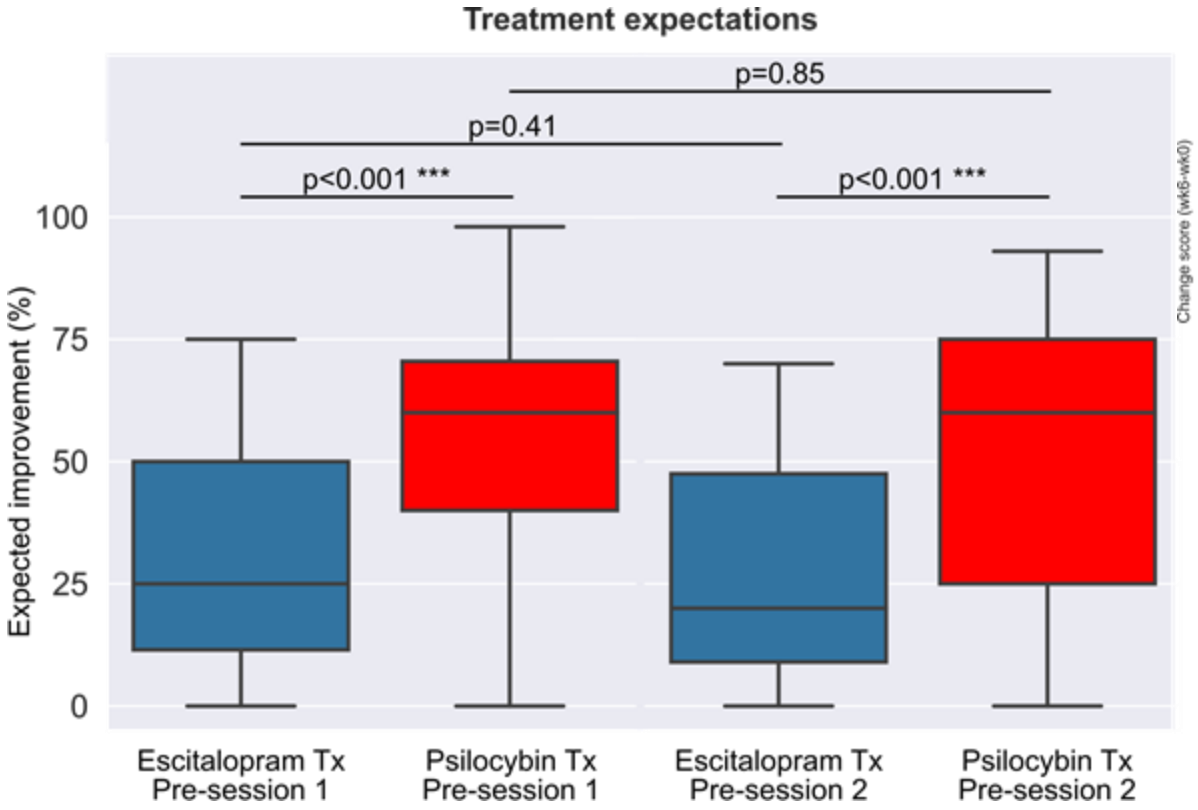


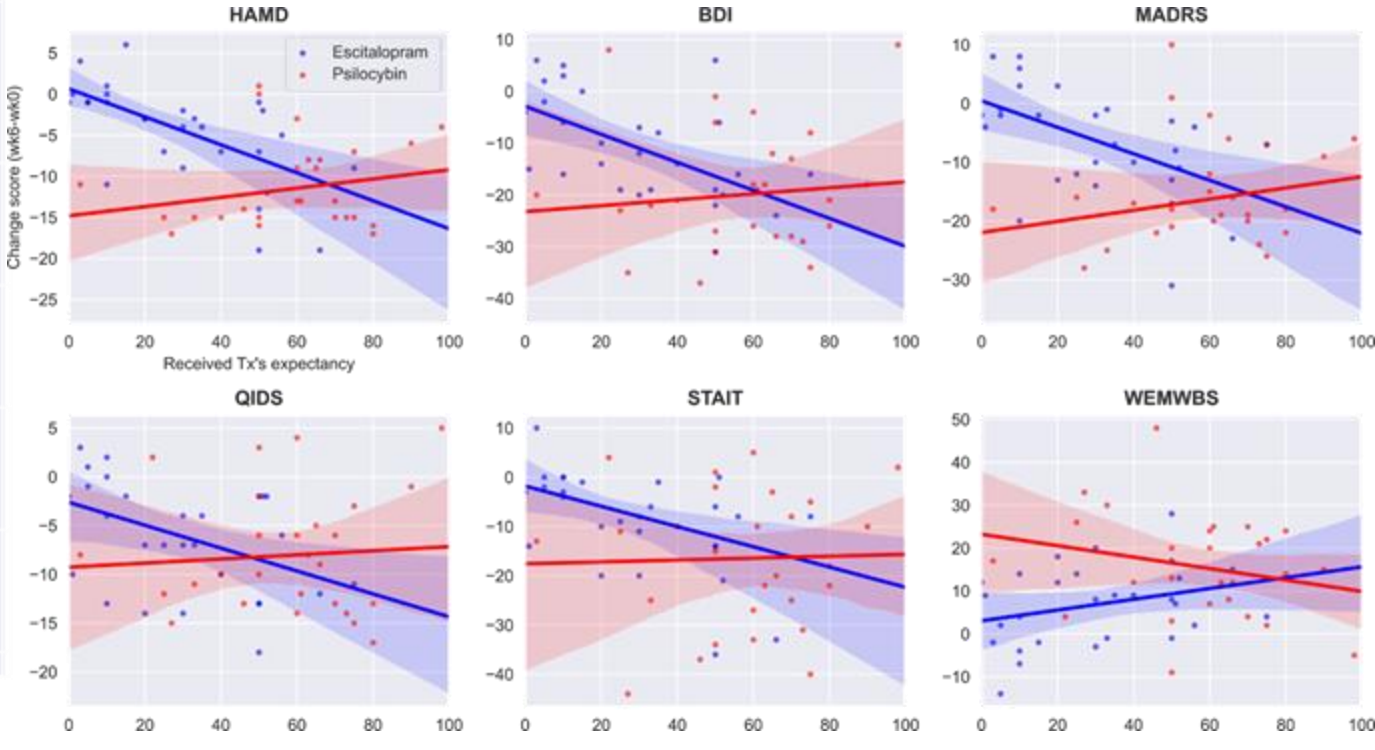
	Yes psilocybin	No psilocybin	Yes escitalopram	No escitalopram	p-value
Medication	8	18	10	13	0.533
Psychedelics	8	18	4	19	0.451
Therapy	12	14	9	13	0.942

Our data don't offer a good explanation to why sustained effects in both groups

Erritzoe et al eClinicalMedicine 2024 102799

Effects of expectancy





- **Patients in our study had higher expectations of the effects of psilocybin !**
- **However the effects of expectancy were only significant in the escitalopram arm**

Szigeti et al 2024 Psychological Medicine

Brain mechanisms in afternoon Masterclass

Many other trials with psychedelics - all positive

End of life anxiety and depression – 2 double-blind RCTs:

- **Griffiths - Johns Hopkins**
- **Ross - NYU**

Seven depression trials – psilocybin
One – DMT
One - ayahuasca

These are all internalizing disorders – cognitions are self-referential and ruminative
- psychedelics can break these down

Smoking quitting - Johnson - Johns Hopkins
Alcoholism – Bogenschutz - NYU

LSD in GAD

Many others now underway including in anorexia, OCD, pain syndromes

MDMA (ecstasy)

Invented 1904 – never tested in humans

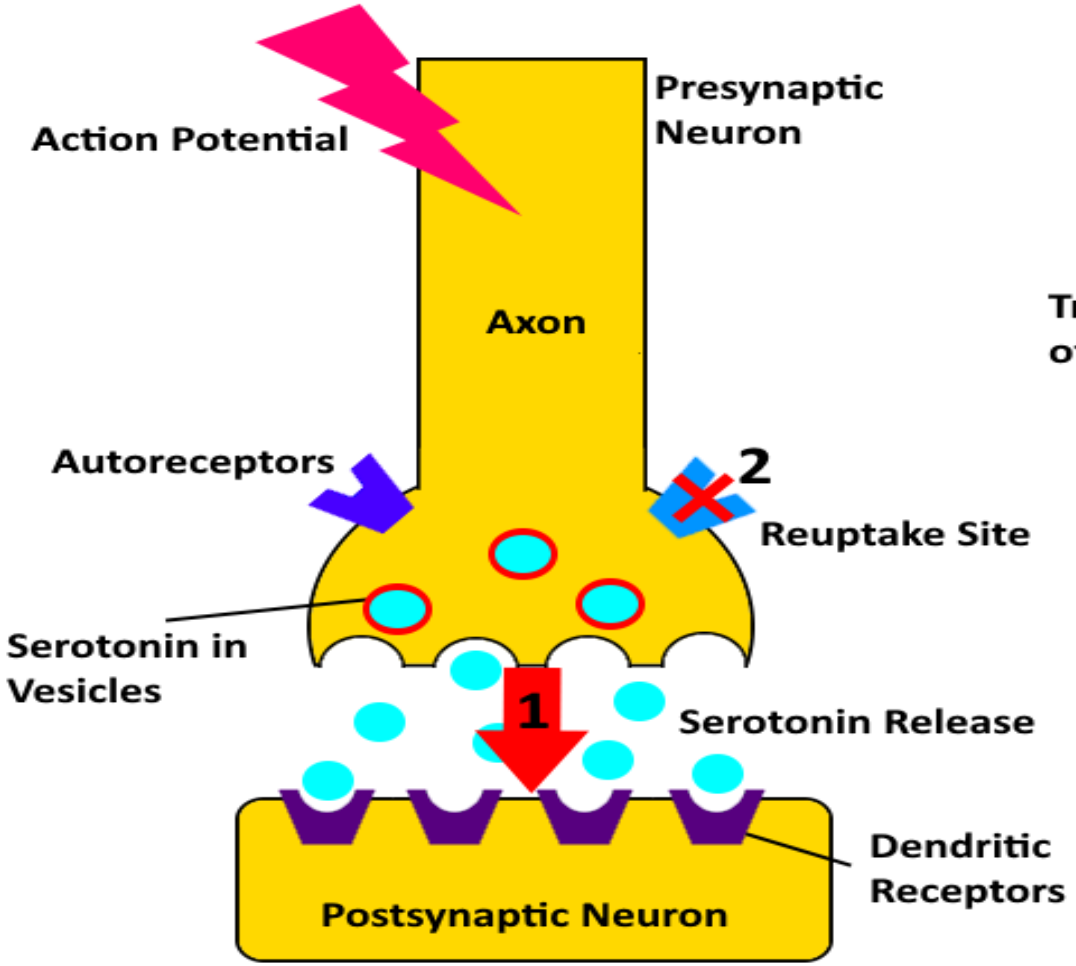
1970s - Sasha Shulgin synthesized MDMA & gave it to himself, his wife and friends who were psychotherapists.

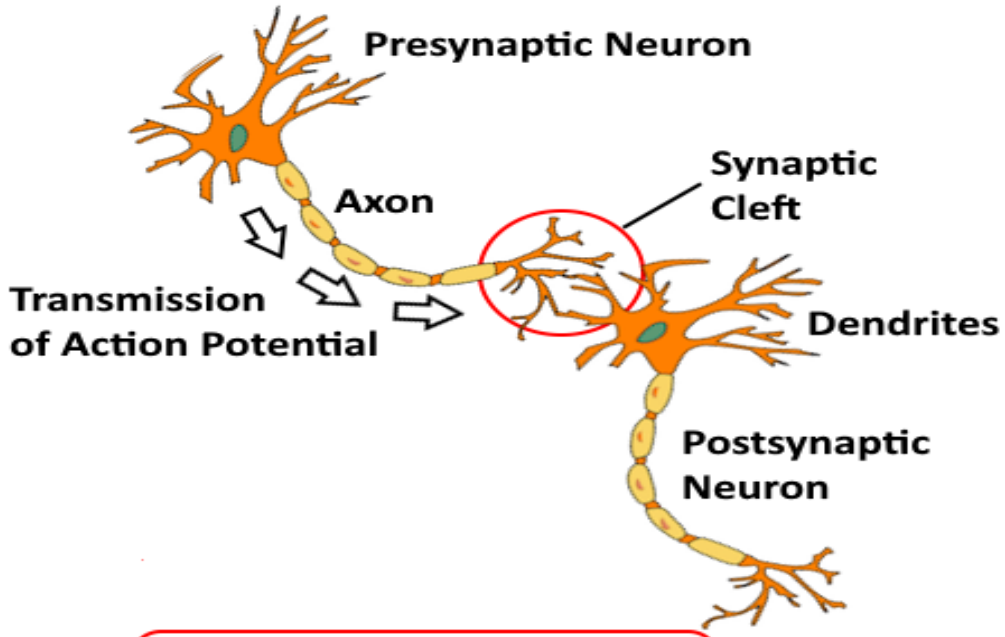
Positive reports of MDMA as adjunct to psychotherapy; no controlled trials.

Recreational use – MDMA ('ecstasy') made illicit in US 1985 for political reasons supported by dishonest "science"

Now back in clinical trials for trauma related disorders

The pharmacology of MDMA

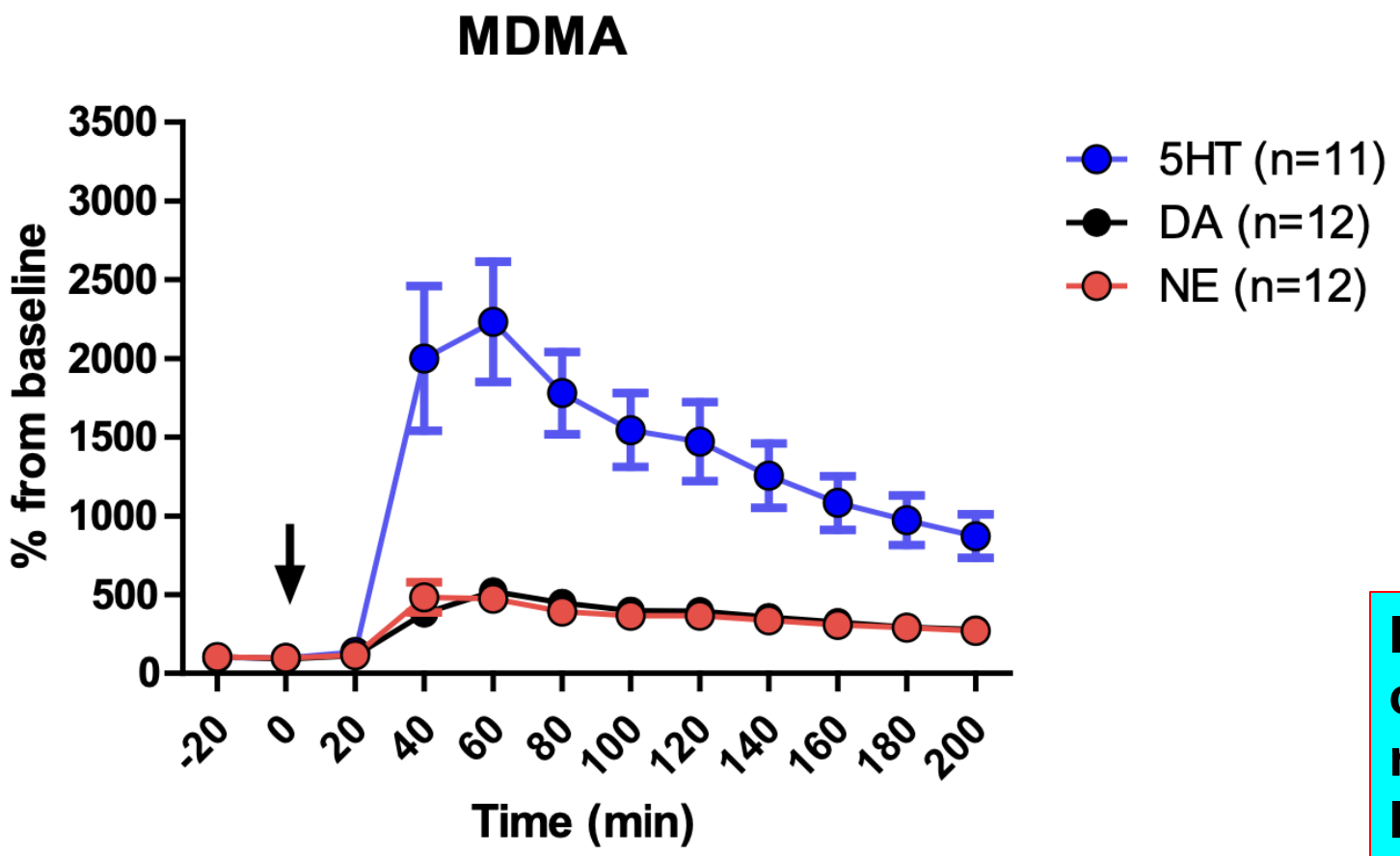




1. MDMA promotes the release of serotonin

2. MDMA blocks serotonin reuptake

MDMA predominantly releases 5-HT not dopamine



Rat brain microdialysis

Awaknlifescience data on file

Which is why it is not addictive (and may be anti-addictive)

In-vitro MDMA has 5x less effect on dopamine than serotonin release.
In contrast metamfetamine has 15x higher effect on dopamine than serotonin release

MDMA - How attitudes have changed in twenty years

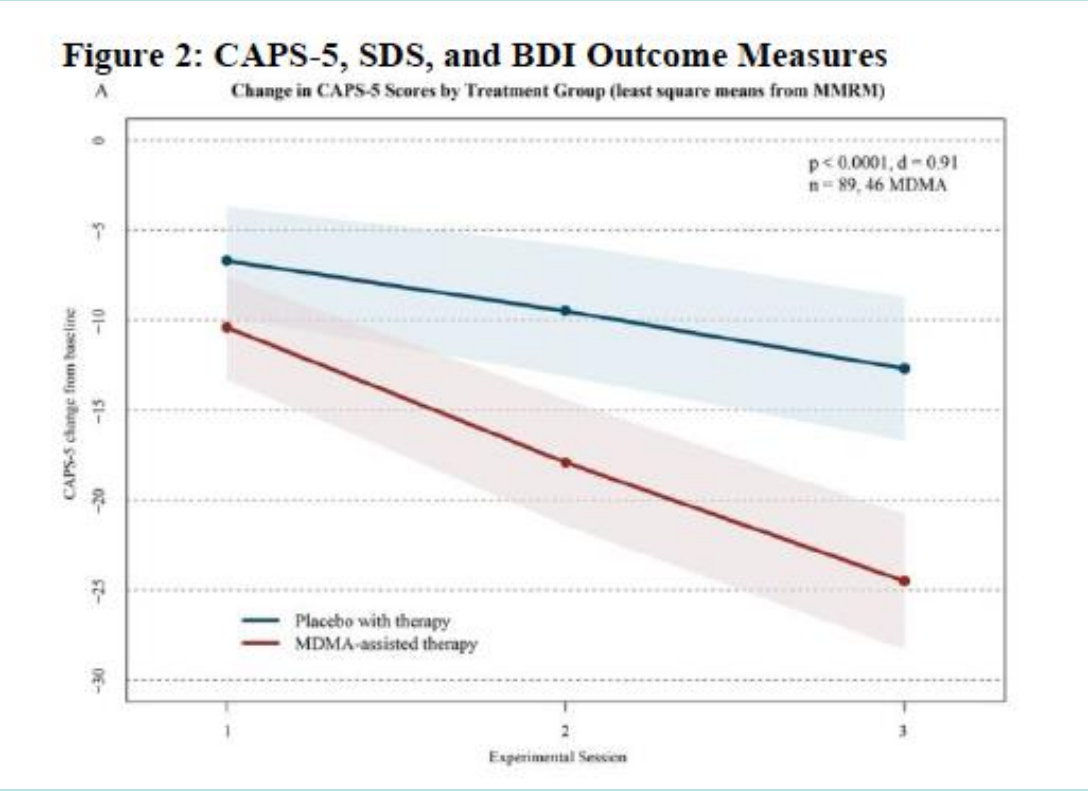
Then → ecstasy causes brain damage – fabrication of evidence to justify ban
Now → MDMA can heal the brain

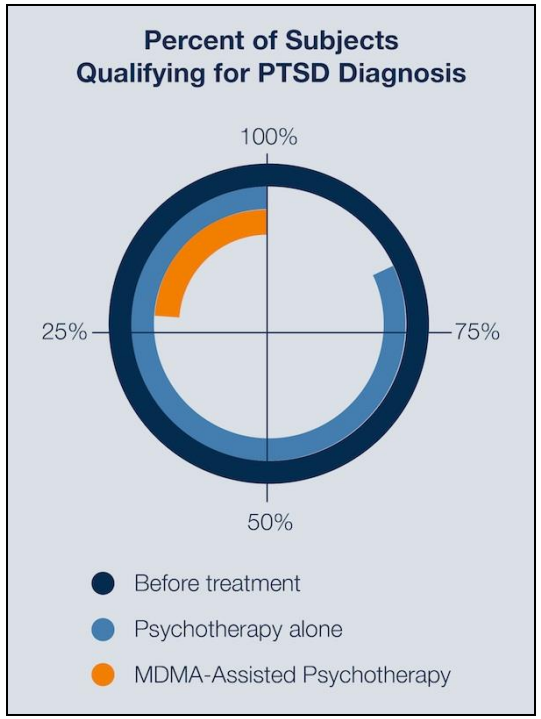
War-induced PTSD has been the driver

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

Civilian victims
Chechnya, Sri Lanka, Syria, Ukraine, Gaza, Lebanon …

MDMA-Assisted Psychotherapy for PTSD trials

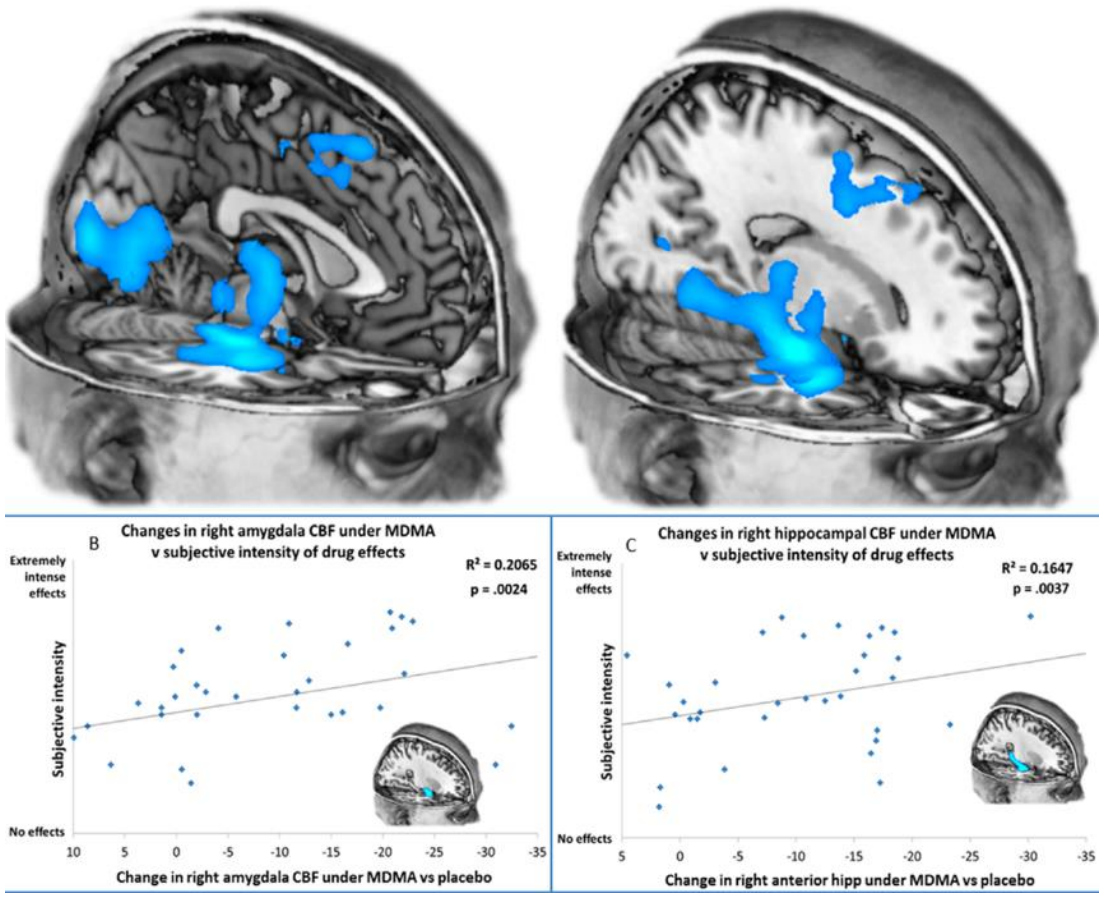




Mitchell et al Nature Medicine 2021

Now under FDA review

MDMA reduces brain activity in the limbic stress circuit

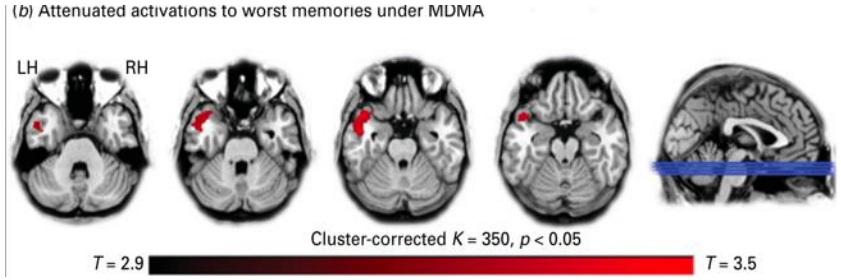


Carhart-Harris et al *Biological Psychiatry*, *78*(8), 554–562.

Hippocampus and amygdala

→ ability to cope with emotional memories during therapy

→ Reduced insula activity also ? Better mind-body integration



Carhart-Harris et al (2014). *Int J Neuropsychopharmacol*, *17*(4), 527–540.

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

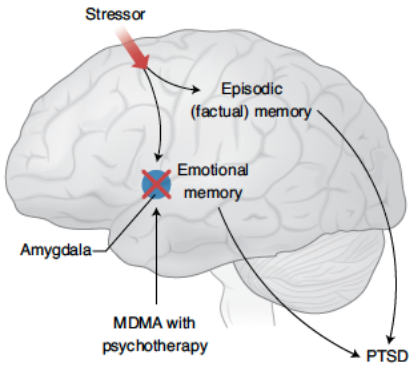
Putting the MD back into MDMA

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

Sessa et al 2022 – see materclass

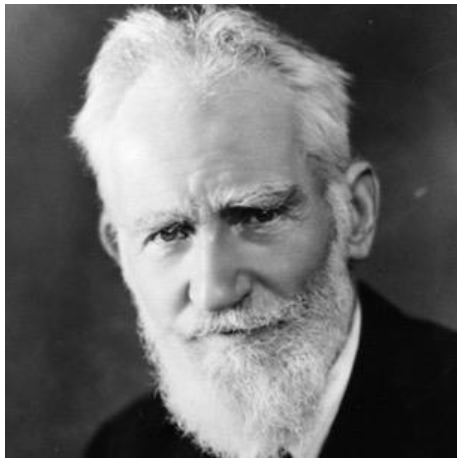
“Those who cannot change their minds cannot change anything”

George Bernard Shaw (1856-1950)

Well it has in Australia!

July 2023

Australian FDA equivalent re-schedules psilocybin and MDMA for treatment-resistant depression and PTSD respectively



ed the minds of our patients through changing their brains

public and politicians’ minds about psychedelics and bring n back into medical practice?

Acknowledgements, further reading and questions

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MRC Medical Research Council

ICCAM
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NIHR UK addictions mission

BECKLEY FOUNDATION