PSYCHEDELIC THERAPY IN MENTAL HEALTH
- CURRENT STATUS, FUTURE POTENTIAL AND POSSIBLE MECHANISMS

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Collaborations @ Usona Institute and Compass Pathways – for study drug

Lisbon Addictions
24th November 2022

THE CENTRE FOR PSYCHEDELIC RESEARCH
Imperial College London

CIPPRes CLINIC
CNWL - IMPERIAL PSYCHOPHARMACOLOGY & PSYCHEDELIC RESEARCH CLINIC

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Psychedelic compounds

Classic serotonergic psychedelics

Oral: ~12hrs

Mescaline

DOI

Serotonin; 5-HT

2C-T-2

DOB

"Atypical" psychedelics
– also being clinically developed"

"Enactogen/ Emphatogen"

MDA

MDMA

"Stimulant/ psychedelic hybrid"

Oral: ~4-5hrs

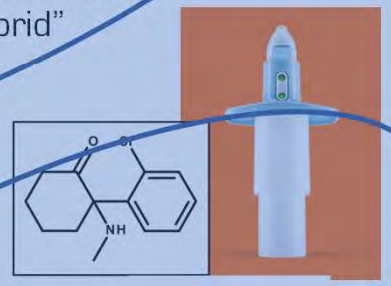
DMT

DMT (alone)
Smoke or IV:
~10-20min

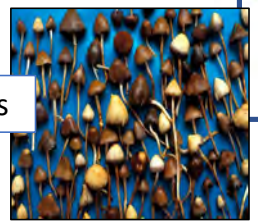
5-MeO-DMT

5-MeO-MiPT

DiPT



Ketamine

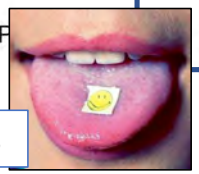


Oral: ~4-5hrs

Psilocin

DP

LSD



Oral: ~10-12hrs

Ibogaine

"Dissociative psychedelics"

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Different from other drugs – both in effects and safety profile

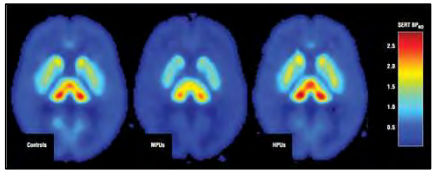
EFFECTS

Psyche-delic: "mind" – "revealing/manifesting"

"Oceanic boundlessness"
Sense of unity
Insightfulness
Spiritual experience
Blissful state
Sense of sacredness / noetic quality
Ineffability
Transiency
Deeply felt positive mood
Paradoxicality
Transcendence of time and space

"Psychological peak / mystical type experiences"

SAFETY[1]



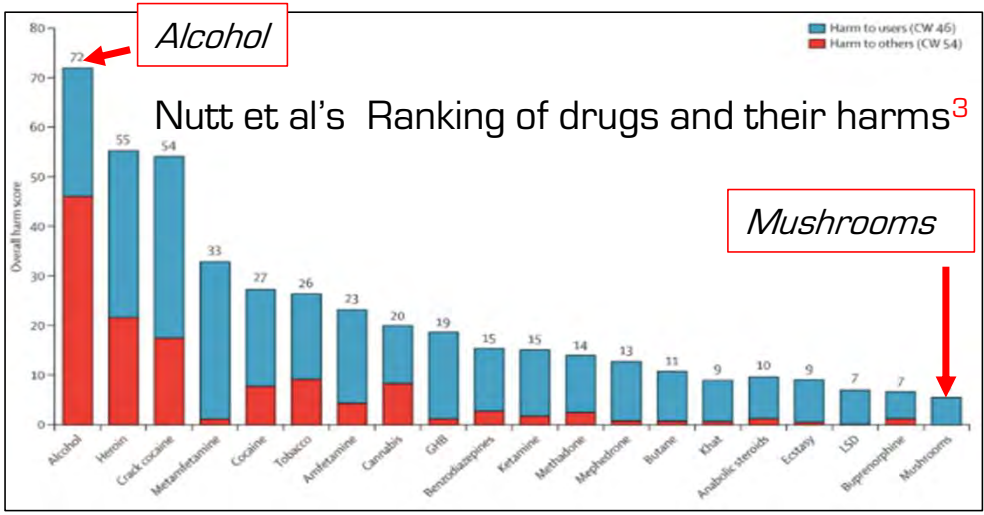
Brain PET in recreational psychedelic users[2]

Safe +++

Non-addictive, **L**ow physiological & brain toxicity[1,2]
Good therapeutic index[3]

Risks/SEs

Dysphoria/**a**nxiety, **n**ausea, **h**eadache, **f**alse memories?



Nutt et al's Ranking of drugs and their harms[3]

1. Rucker et al. 18; 2. Erritzoe et al 2011; 3. Nutt et al. 2010

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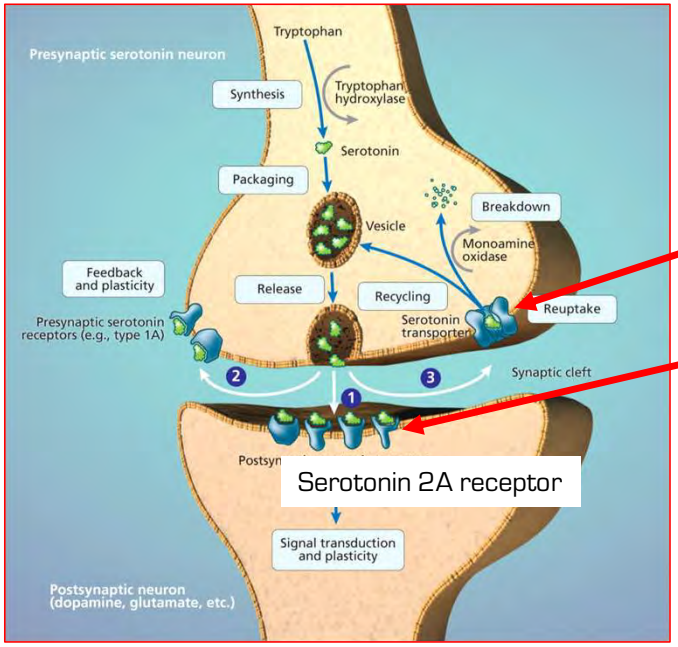
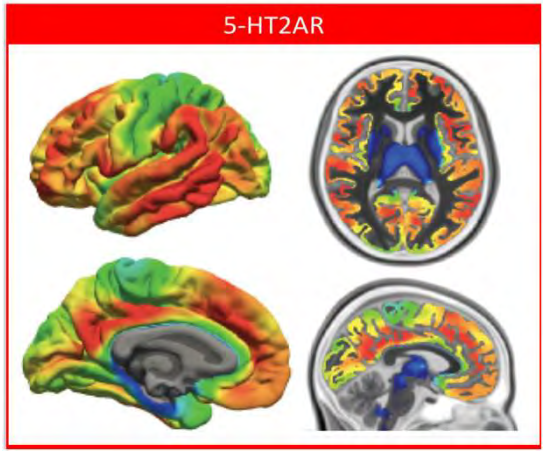
Basic pharmacology of classic 5-HT psychedelics

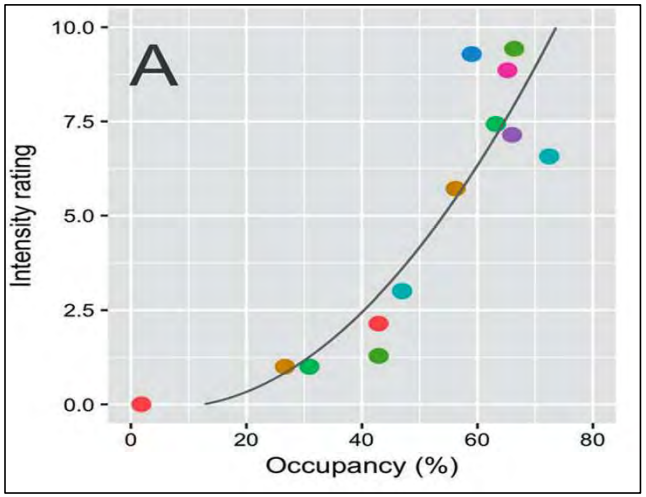


SSRIs

Psychedelics



Beliveau et al. 16



Madsen et al. 19

Classic 5-HT psychedelics have their action in the brain's serotonin system (2A receptor+++)
Medications such as "SSRIs" also work in this system but different mechanisms (Reuptake+++)

5-HT2AR agonist **affinity** ↑ Potency ↑ Glennon et al. 84

5-HT2AR occupancy ↑ subjective effects ↑ Madsen et al. 19

Blocking **5-HT2AR** mutes effects Vollenweider et al. 98

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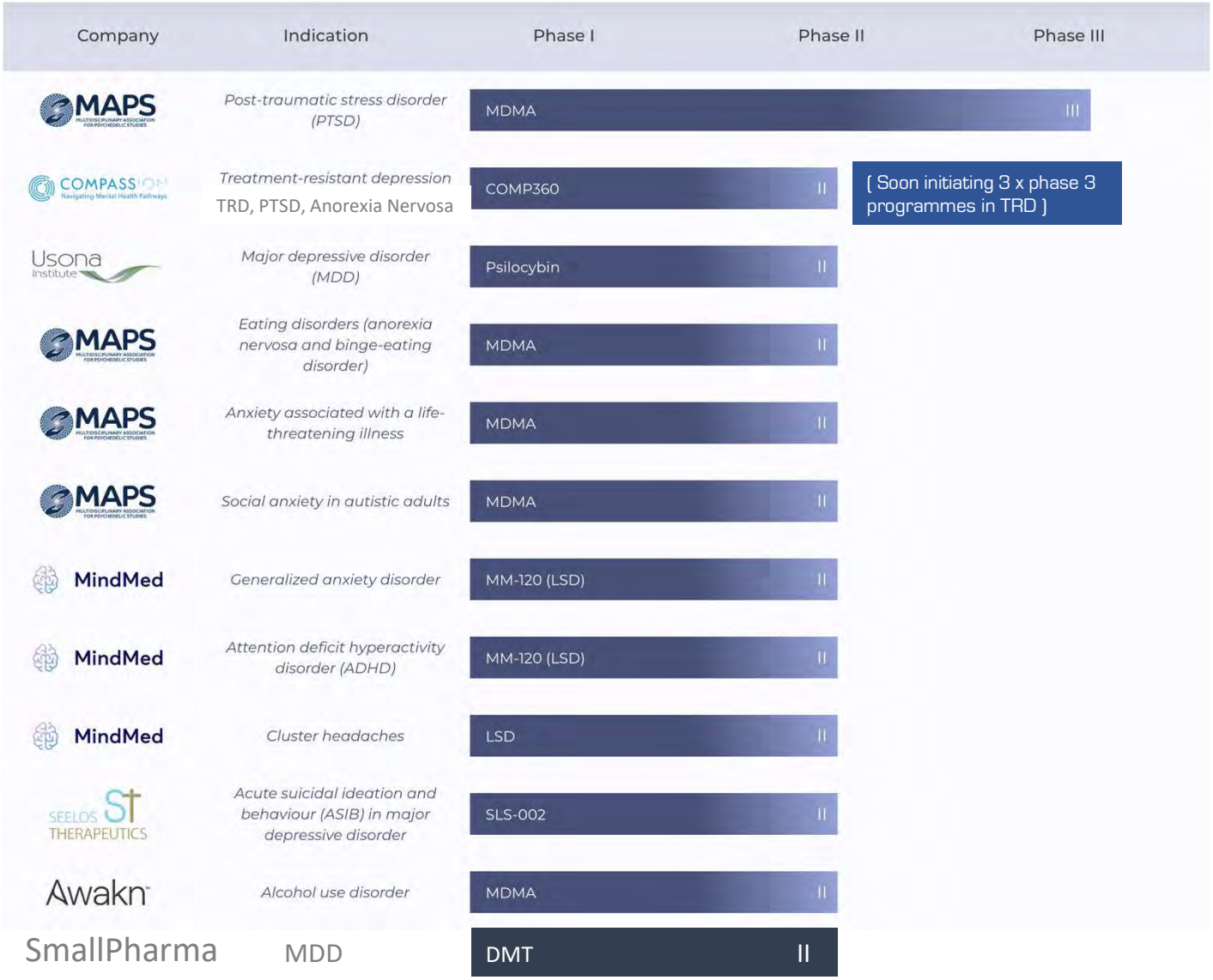
The psychedelic renaissance – seen through current pharma development

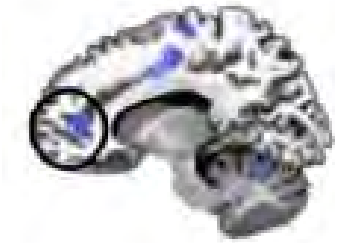


Listed on clinicaltrials.gov

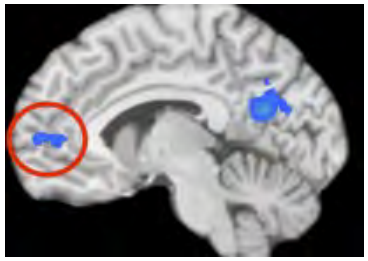
- 96 Psilocybin
- 112 MDMA
- 132 LSD
- 20 DMT
- >250 Ketamine

Pre-existing evidence in depression & rumination

Excisting treatments for depression reduce activity in the Anterior Cingulate Ctx (ACC)/ medial Prefrontal Ctx (mPFC) area

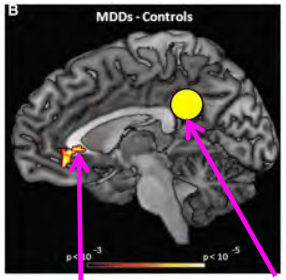


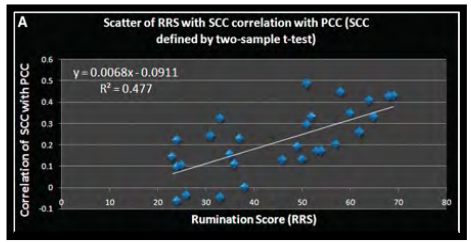
Hasenkamp et al. 12



Brewer et al. 11

- SSRIs Kennedy et al. 01
- CBT Goldapple et al. 04
- Sleep deprivation Gillin et al. 01
- ECT Bonne et al. 96
- Placebo Mayberg et al. 02
- Deep brain stim'
- Mindfulness medit'
- Ketamine Deakin et al. 08

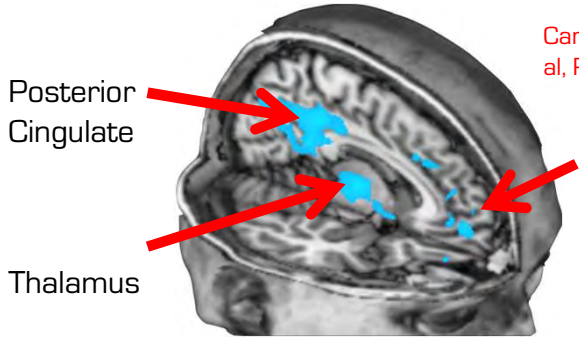




Evidence of ***greater*** PCC to mPFC ***connectivity*** in ***depression***

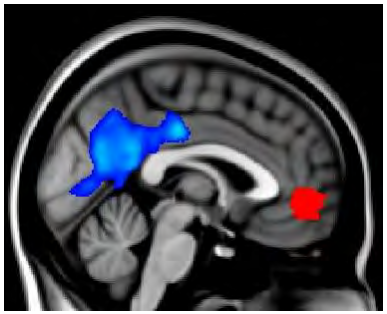
PCC – mPFC functional connectivity predicts ***rumination***

Early fMRI work in healthy subjects at Imperial College



Carhart-Harris et al, PNAS 2012

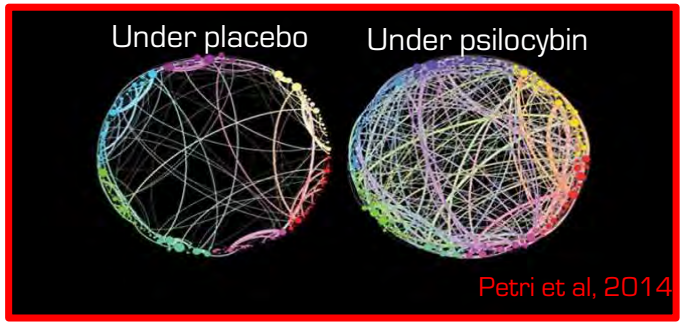
Carhart-Harris et al, PNAS 2012



Decreased PCC to mPFC coupling after psilocybin.

Reduced ACC and mPFC activity after psilocybin.

Reduced connectivity *within* in default mode network, and increased global connectivity/ connectivity *between* networks

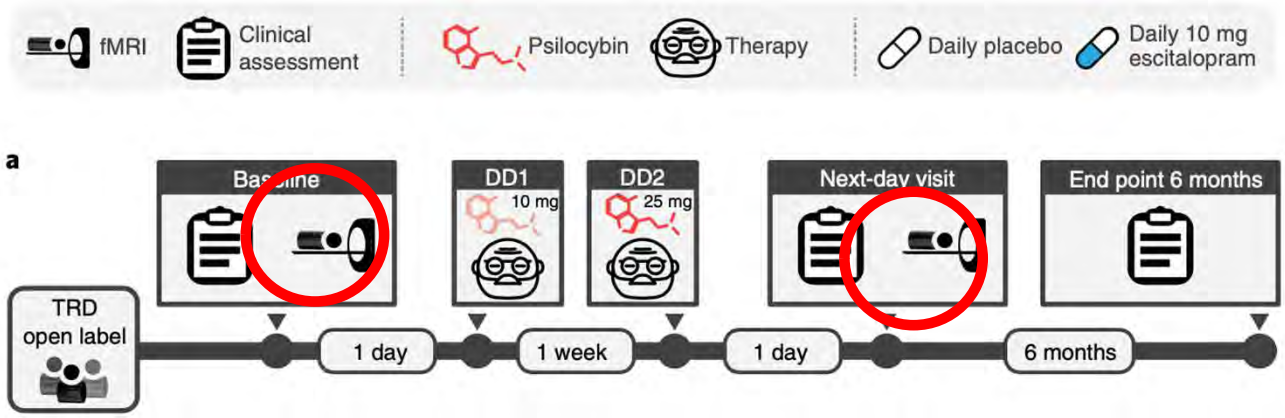


Petri et al, 2014

Broadly speaking, early brain imaging studies in healthy volunteers at Imperial suggested effects of acute administration of psilocybin (and other psychedelics) in the **opposite direction to what seen by others in the study of depression & rumination.**

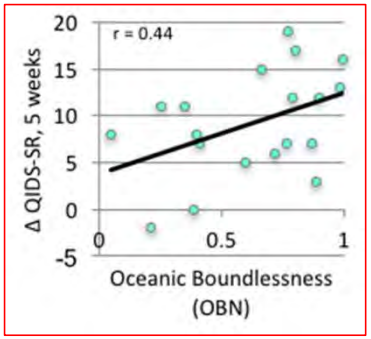
1st depression study at Imperial with psilocybin therapy

Imperial N=20 depression study 1



Acute state predicting outcomes

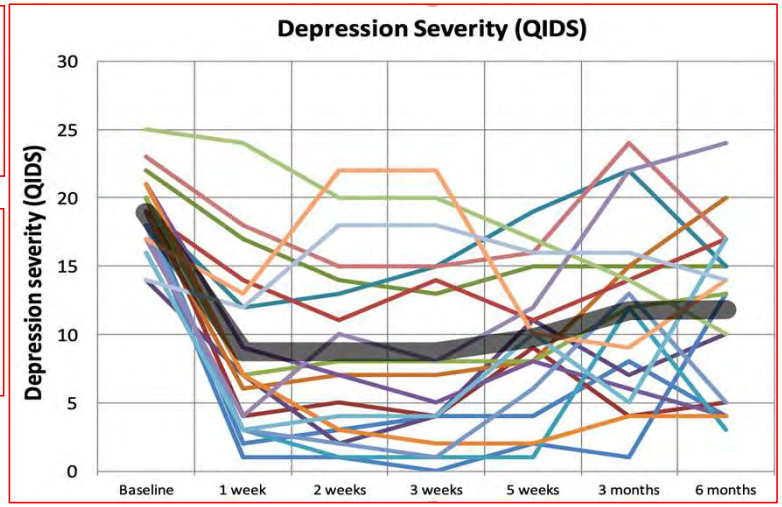
Roseman et al 2018



Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study

Robin L Carhart-Harris, Mark Bolstridge, James Rucker, Camilla M J Day*, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt*

Imperial's open label pilot study in 20 patients with treatment-resistant moderate-severe major depression[4]



3 factors suggestive of an important **new paradigm**

- **Single** treatment session(s)
- **Sustained effects** for some patients
- The nature of the pharmacologically induced **experience seemingly play a role** for the therapeutic outcome

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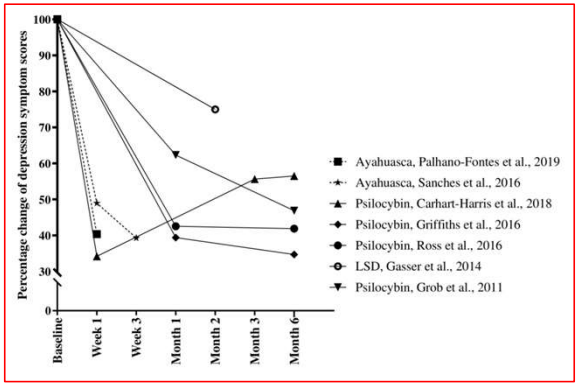
Full dose interventions – early evidence for therapeutic value

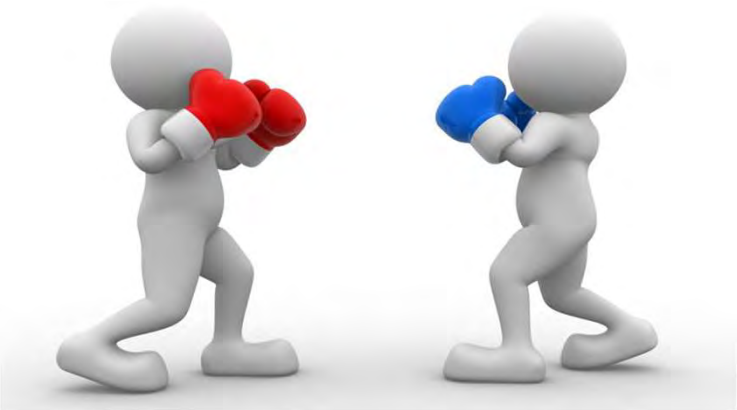
- ✔ **Rapid & enduring mood improvement**
- ✔ Well-being ↑[2,3]
- ✔ OCD ↓[5]
- ✔ End-of-life distress ↓[6-9]
- ✔ Anxiety↓[18-19]
- ✔ Addiction ↓[10,11,22]
- ✔ Depression ↓[4,6–9,12, 16,17]
- ✔ Suicidality ↓[3,4,5,13]



Across early studies; long-lasting antidepressans effects after single interventions[15]

2. Griffiths et al. 06; **3**. Haijen et al. 18; **4**. Hendricks et al. 15; **4**. C-H et al. 17; **5**. Moreno et al. 06; **6**. Grob et al. 11; **7**. Gasser et al. 13; **8**. Griffiths et al. 16; **9**. Ross et al. 16; **10**. Johnson et al. 14; **11,19**. Bogenschutz et al. '15, '22; **12**. Osorio Fde et al. 15; **13**. Argento et al. 17; **14**. C-H et al. 18; **15.** Andersen et al 20.; **16.** CompassPathways 22; **17**. Davis et al. 21; **18** Gasser et al '15; Holze et al '22;

2nd depression study at Imperial
Psilocybin vs Escitalopram (n=59)



2 psilocybin (COMP360) therapy sessions

6 weeks of escitalopram + therapy

The NEW ENGLAND JOURNAL of MEDICINE

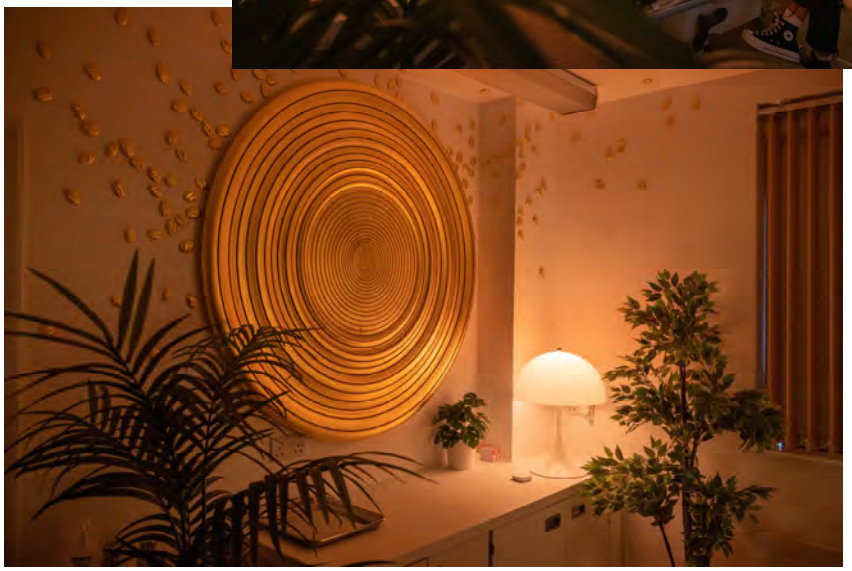
Carhart-Harris et al., 2021

Carhart-Harris et al., 2021

New setting – CIPPRes Clinic at St Charles Hospital

CIPPRes
CLINIC

CNWL - IMPERIAL PSYCHOPHARMACOLOGY
& PSYCHEDELIC RESEARCH CLINIC



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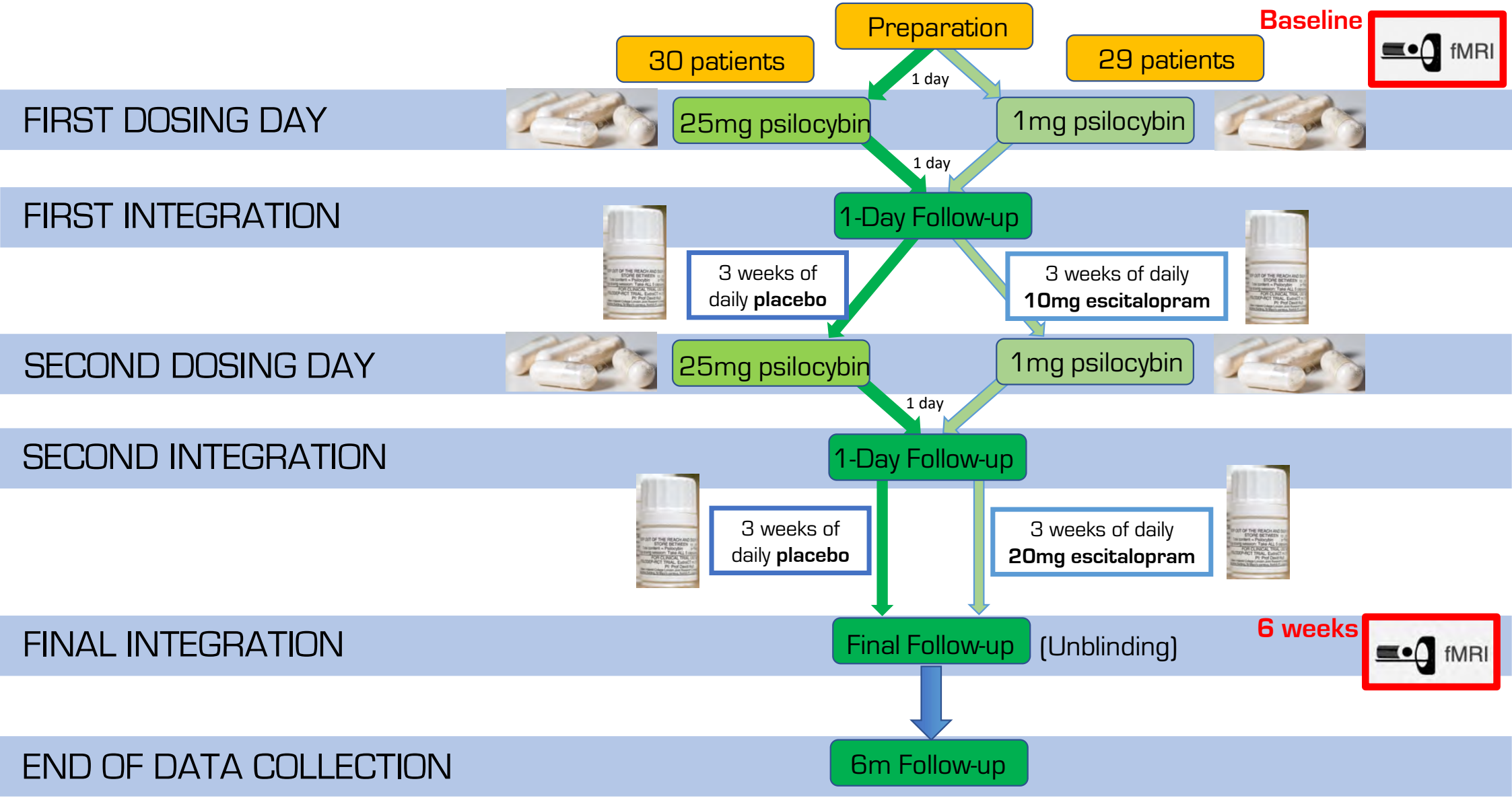
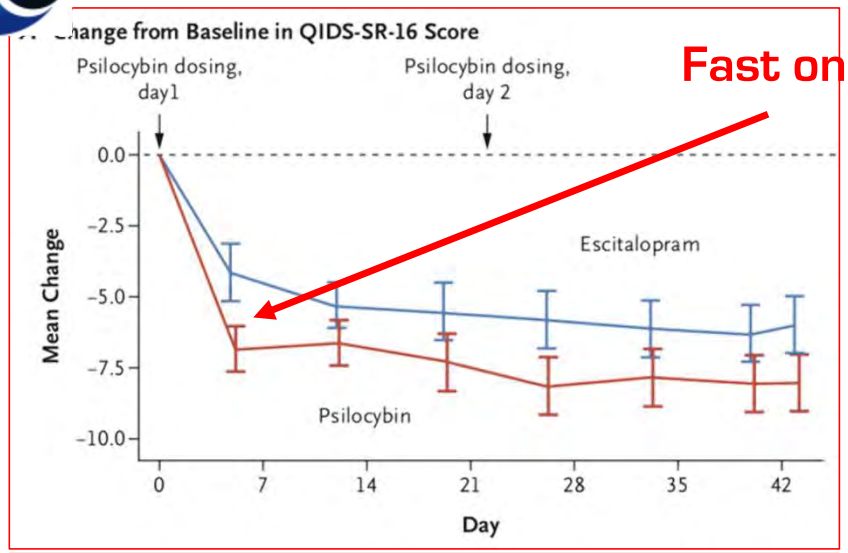
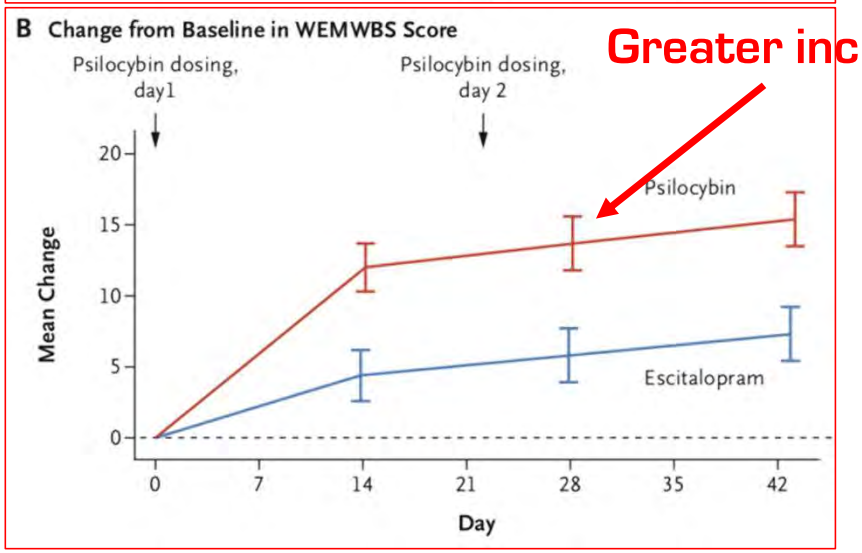

Preparation
Baseline
fMRI
30 patients
29 patients
1 day
FIRST DOSING DAY
25mg psilocybin
1mg psilocybin
1 day
FIRST INTEGRATION
1-Day Follow-up
3 weeks of daily placebo
3 weeks of daily 10mg escitalopram
SECOND DOSING DAY
25mg psilocybin
1mg psilocybin
1 day
SECOND INTEGRATION
1-Day Follow-up
3 weeks 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 vs Escitalopram for depression (n=59)

Treatment phase - key results...

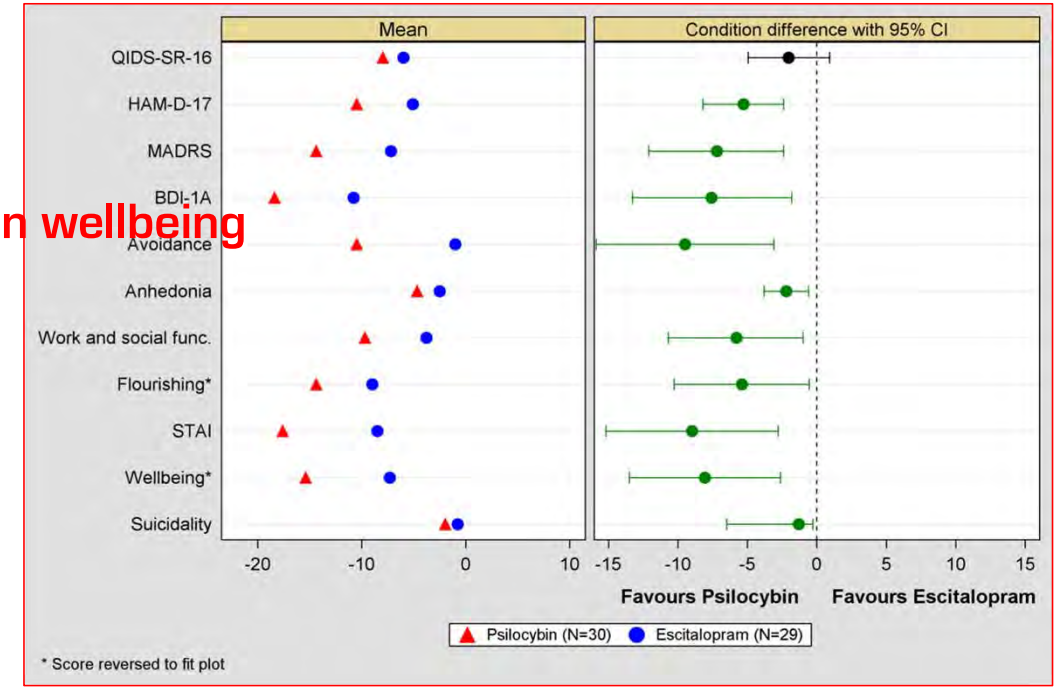




Remission rates:

29.1%

57.1%

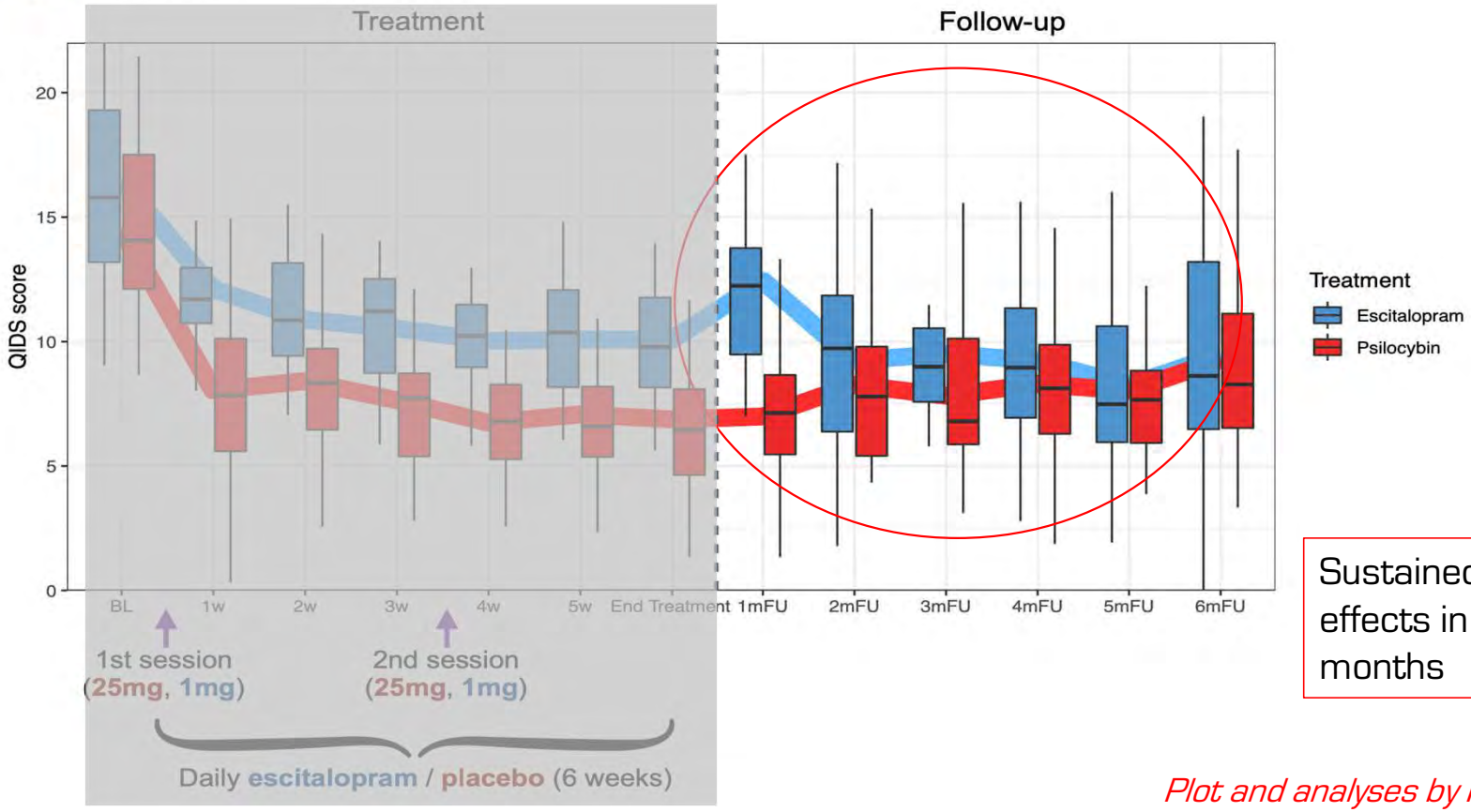


Carhart-Harris et al., 2021

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 at 6 months

Plot and analyses by F. Rosas (In prep.)

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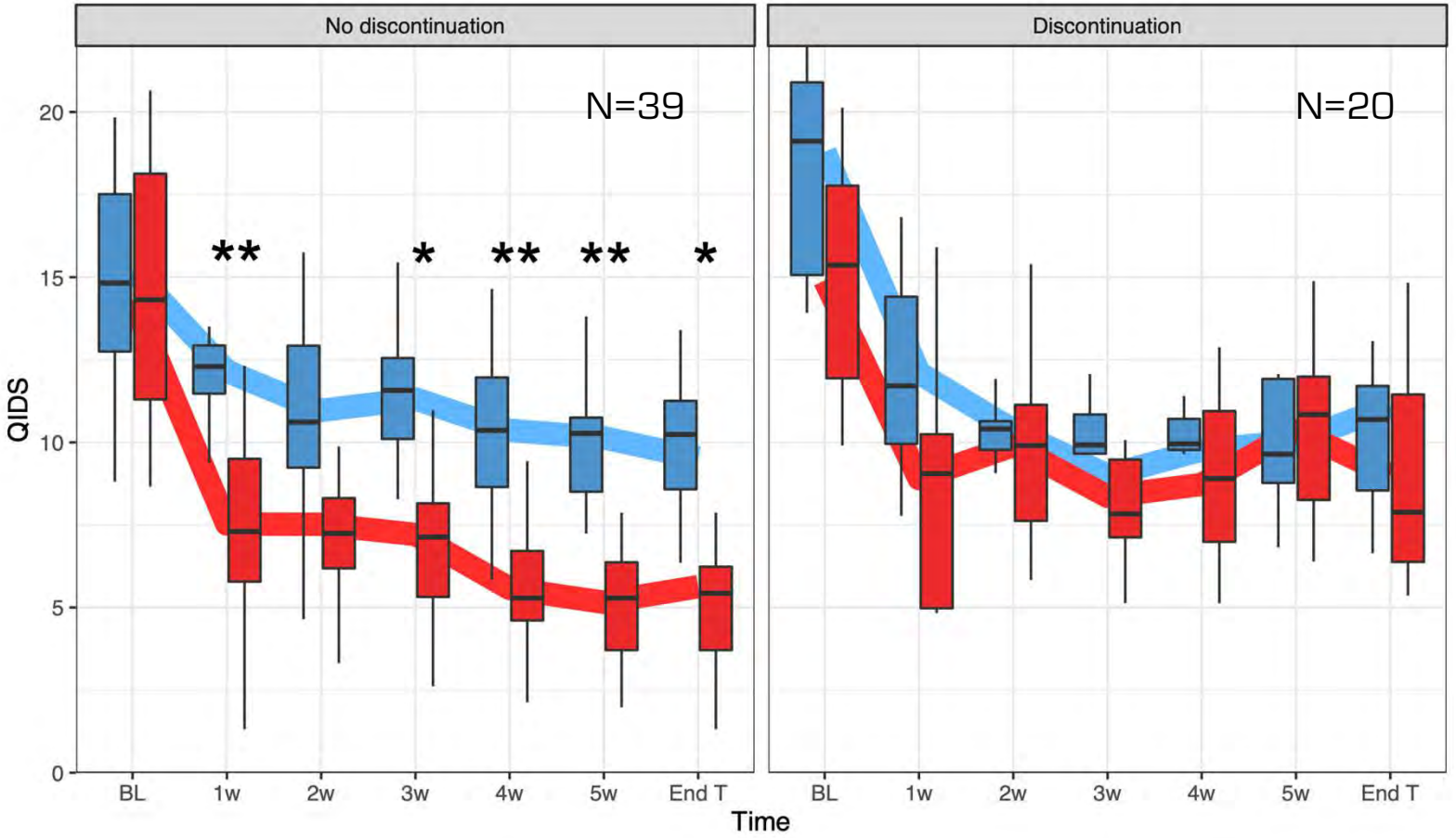
Effects of discontinuation of medication

NOT tapered off (not on AD meds before trial)

Tapered off (on AD meds before trial)

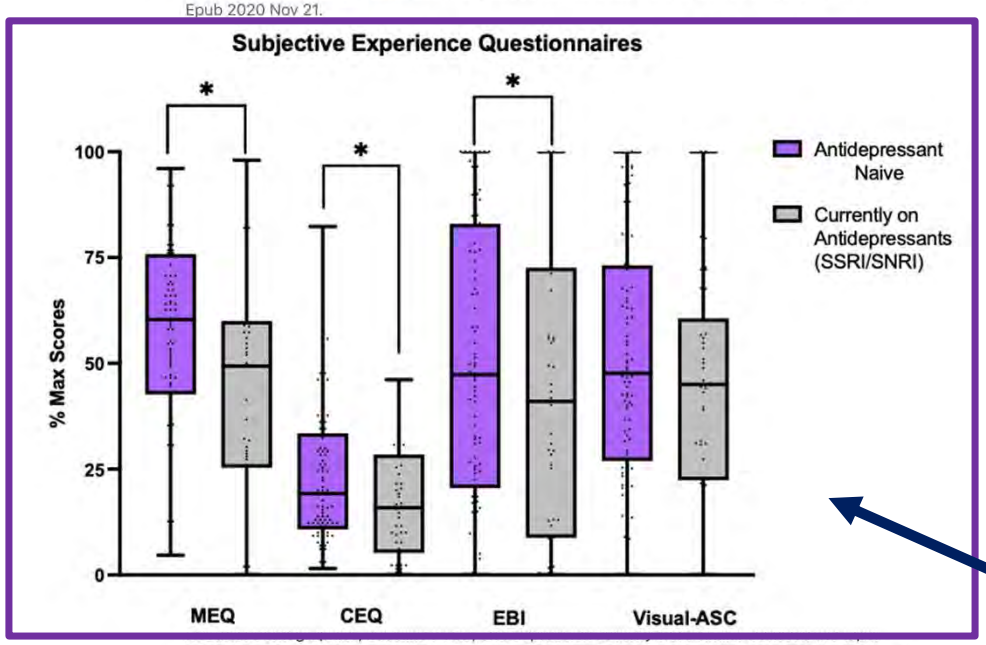


(Post-hoc) significant difference between treatment conditions for people that didn't discontinue antidepressants going into the trial

In prep. Plot and analyses by M. Spriggs and F. Rosas

The issue of discontinuation of medication

Psychopharmacology (Berl). 2021 Feb;238(2):581-588. doi: 10.1007/s00213-020-05710-w. Epub 2020 Nov 21.



and non-taper groups. At the primary endpoint, the non-taper group (mean = 45.7, SD = 27.17) had a significantly (p = 0.009) lower CAPS-IV total scores compared to the taper group (mean = 70.3, SD = 33.60). More participants in the non-taper group (63.6%) no longer met PTSD criteria at the primary endpoint than those in the taper group (25.0%). The non-taper group (mean = 12.7, SD = 10.17) had lower depression symptom severity scores (p = 0.010) compared to the taper group (mean = 22.6, SD = 16.69). There were significant differences between groups in peak systolic blood pressure (p = 0.043) and diastolic blood pressure (p = 0.032).

Conclusions: Recent exposure to antidepressant drugs that target reuptake transporters may reduce treatment response to MDMA-assisted psychotherapy.

Keywords: Discontinuation syndrome; MDMA; MDMA-assisted psychotherapy; PTSD; Psychedelics; SNRI; SSRI; Taper.

- Work from Basel team (*Becker et al*) in healthy subjects **and** from Compass Pathways (*online info*) in TRD subjects both suggest that it might be possible to stay on SSRIs for psilocybin treatment.
- MAPS looking into whether ok to stay on SSRIs but then give higher MDMA doses ?
- Preliminary data from Imperial's online prospective surveys suggest that being under SSRIs/SNRIs treatment is associated with reduced psychedelic experience (i.e. lower scores on peak component of acute scales). (*Barbut, Barba et al, in prep*)

More work needs to be done to conclude on best strategy regarding SSRIs in these trials !!

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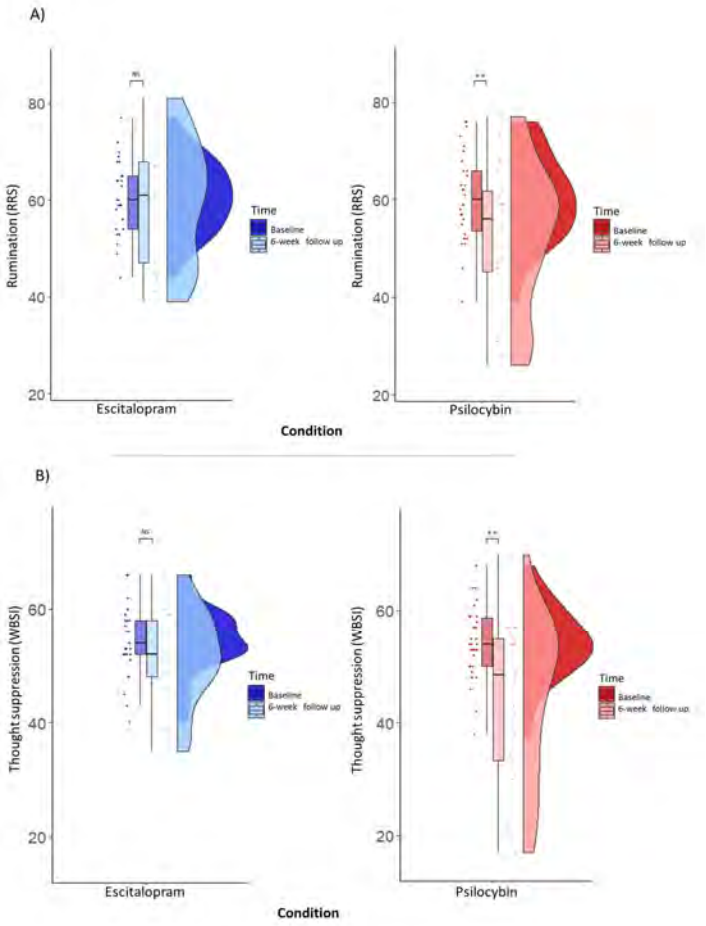
Mechanisms – lid off ?



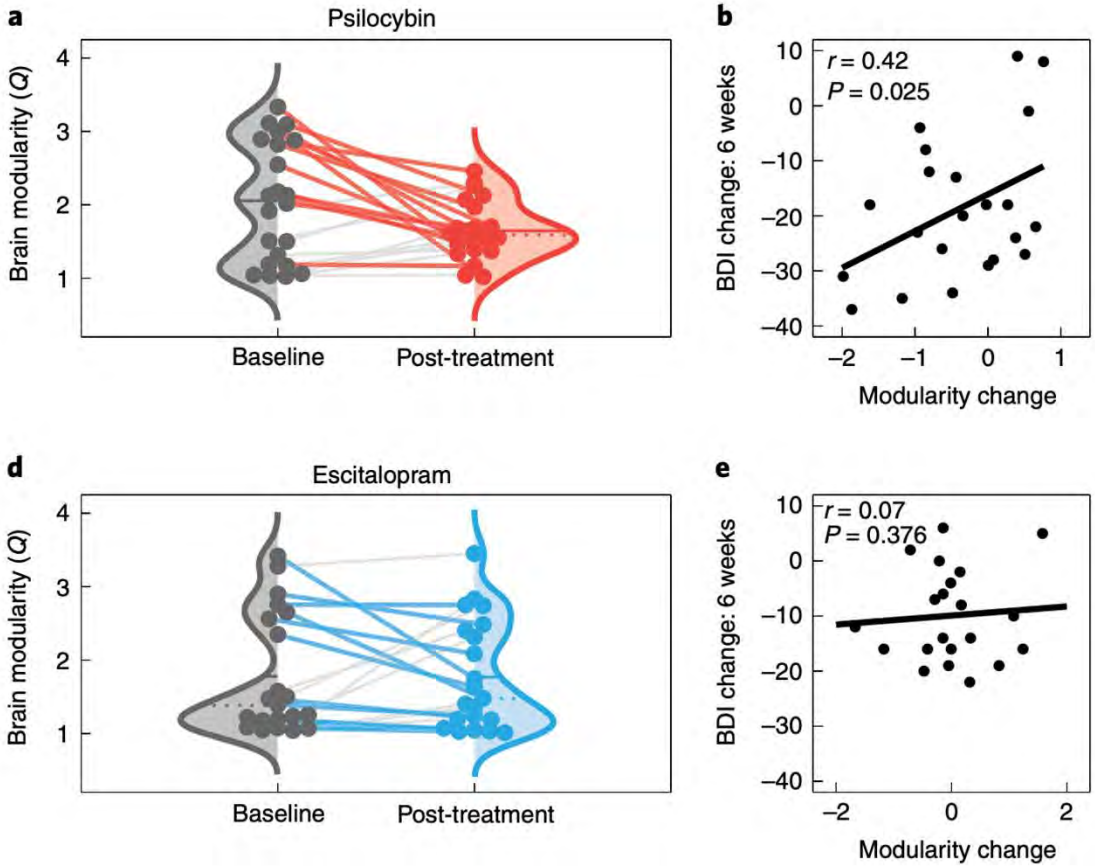
Rumination & Thought Suppression

- Patients in the **psilocybin arm** experienced a significant **decrease in rumination and thought suppression** scores after treatment but patients in the escitalopram arm did not.

- In the psilocybin arm, decreases in rumination and thought suppression **correlated positively with the degree of ego dissolution and psychological insights** reported after the psilocybin dosing sessions.

Barba et al (in press)

Mechanisms - explored via fMRI across 2 Imperial College depression trials



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 Giribaldi[3], James D. Sexton[3], Matthew B. Wall[4,5,6], David Erritzoe[3], Leor Roseman[3], David Nutt[3] and Robin Carhart-Harris[3,7]

Based on fMRI analysis from two separate psilocybin studies in depression:

fMRI modularity results suggest – but cannot conclude - different brain mechanisms psilocybin vs SSRI

Additionally;
using task based fMRI, amygdala BOLD response to emotional faces was reduced (across emotions) following escitalopram , but NOT psilocybin
Lid off?

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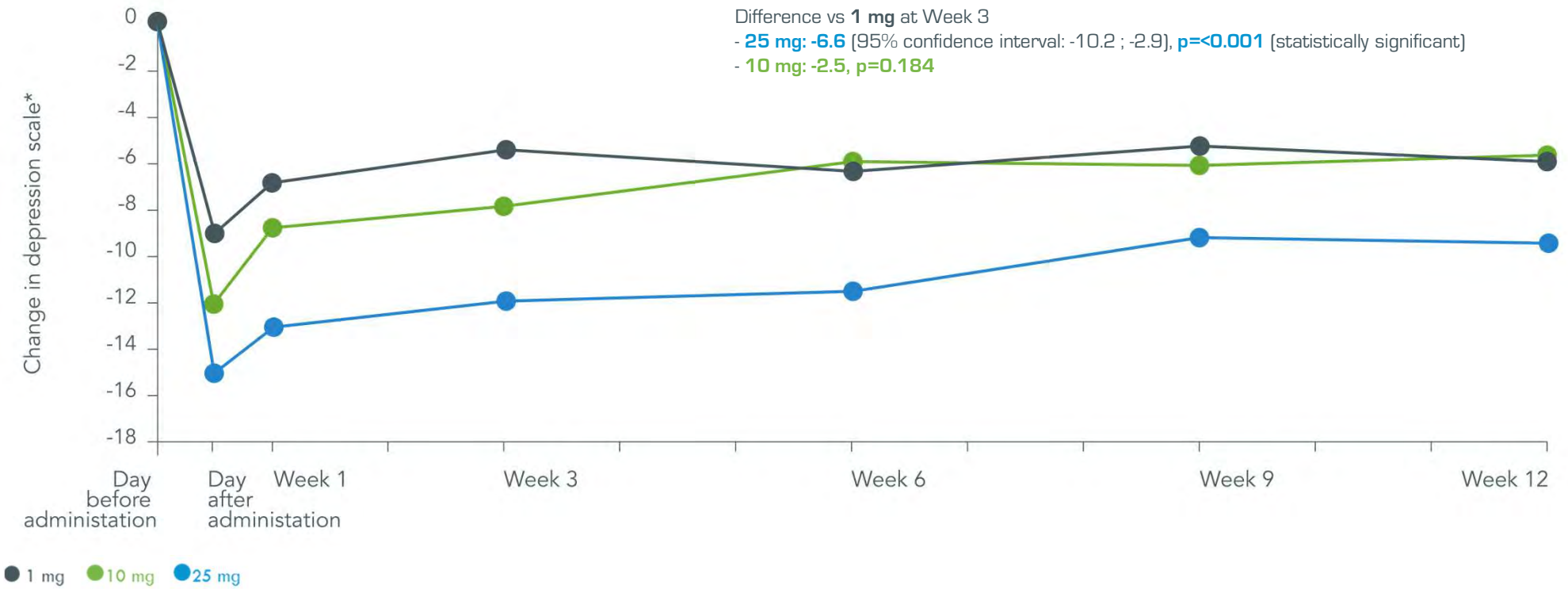
Recent COMPASS Phase 2b trial in TRD patients (N=233)

Results demonstrated the potential for a rapid, sustained response



Efficacy: saw a statistically significant and clinically meaningful reduction in depression symptoms

Rapid onset action: the effect occurred the day after the administration

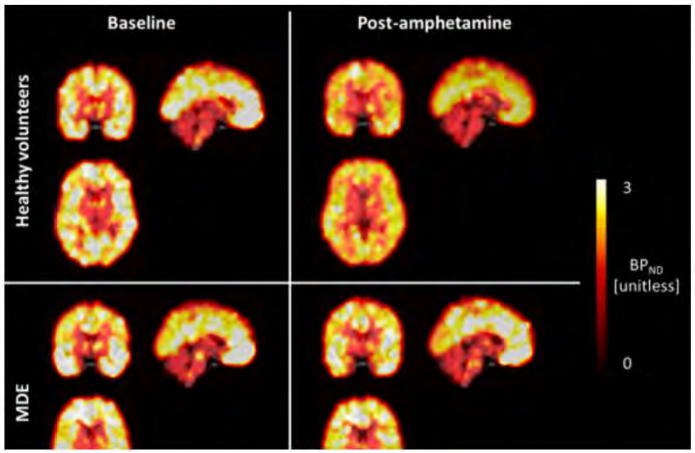
Durability: saw a sustained response at week 12 – a positive indication for high potential as a monotherapy

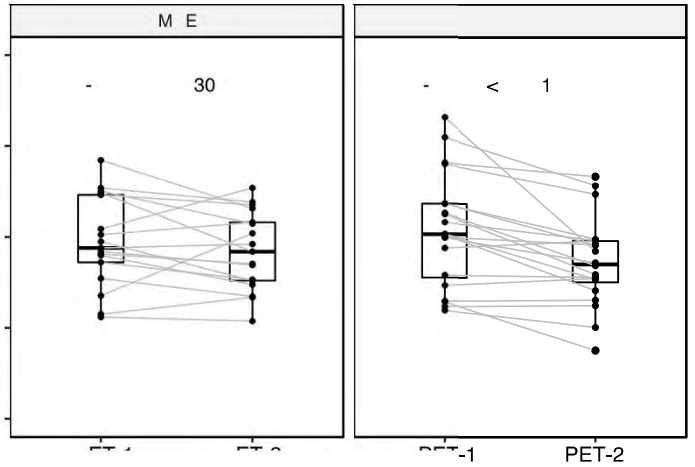
Note: MADRS =Montgomary-Åsberg Depression Rating Scale; SE =standard error

Other new work related to serotonin 2A receptor agonists and depression

- novel PET imaging method with a "psychedelic radioligand" to measure serotonin release in the brain

Biological Psychiatry
Available online 29 October 2022
In Press, Journal Pre-proof





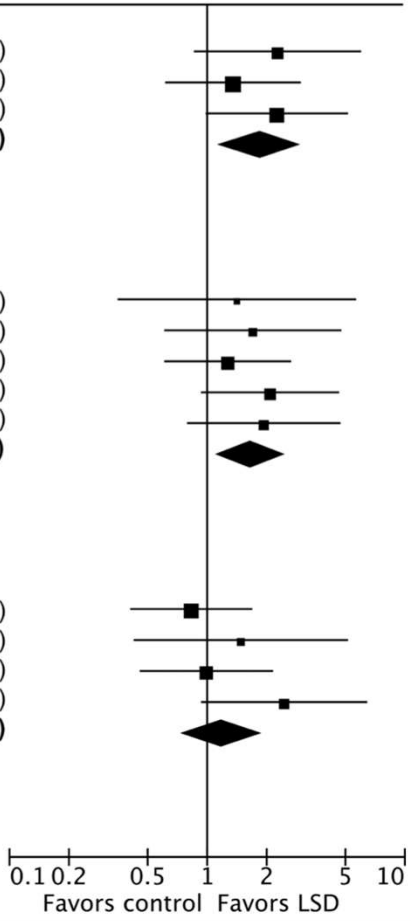
Archival Report

BRAIN SEROTONIN RELEASE IS REDUCED IN PATIENTS WITH DEPRESSION: A [11C]Cimbi-36 PET STUDY WITH A D-AMPHETAMINE CHALLENGE.

David Erritzoe [1], Beata R. Godlewska [2], Gaia Rizzo [3], Graham E. Searle [3], Claudio Agnorelli [1, 4], Yvonne Lewis [3], Abhishekh H. Ashok [5, 6], Alessandro Colasanti [7], Iro Boura [5], Chloe Farrell [5], Hollie Parfit [1], Oliver Howes [5], Jan Passchier [3], Roger N. Gunn [3], David J. Nutt [1], Philip J. Cowen [2], Gitte Knudsen [8], Eugenii A. Rabiner [3, 5]

Addiction studies

	Follow-up (months)	LSD (n/N)	Control (n/N)	Weight	Odds Ratio (95% CI)
Short-term follow-up					
Hollister *et al.*, 1969	2	18/36	11/36	25.5%	2.27 (0.87-5.94)
Ludwig *et al.*, 1969	3	41/132	11/44	39.1%	1.35 (0.62-2.94)
Tomsovic & Edwards, 1970	3	30/52	17/45	35.4%	2.25 (0.99-5.10)
Total		**220**	**125**	**100%**	**1.85 (1.14-3.00)**
Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.02$, df = 2 ($P = 0.60$); $I^2 = 0\%$					
Test for overall effect: Z = 2.47 ($P = 0.01$)					
Medium-term follow-up					
Smart *et al.*, 1966	6	[a]/10	[a]/20	8.4%	1.41 (0.36-5.60)
Hollister *et al.*, 1969	6	13/36	9/36	15.4%	1.70 (0.61-4.71)
Ludwig *et al.*, 1969	6	49/132	14/44	30.2%	1.27 (0.61-2.63)
Pahnke *et al.*, 1970	6	34/73	13/44	25.4%	2.08 (0.94-4.60)
Tomsovic & Edwards, 1970	6	20/52	11/45	20.6%	1.93 (0.80-4.66)
Total		**303**	**189**	**100%**	**1.66 (1.11-2.47)**
Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.00$, df = 4 ($P = 0.91$); $I^2 = 0\%$					
Test for overall effect: Z = 2.47 ($P = 0.01$)					
Long-term follow-up					
Ludwig *et al.*, 1969	12	48/132	18/44	35.2%	0.83 (0.41-1.67)
Bowen *et al.*, 1970	12	9/22	7/22	13.3%	1.48 (0.43-5.10)
Pahnke *et al.*, 1970	12	28/73	17/44	30.5%	0.99 (0.46-2.13)
Tomsovic & Edwards, 1970	12	18/52	8/45	21.0%	2.45 (0.94-6.38)
Total		**279**	**155**	**100%**	**1.19 (0.74-1.90)**
Test for heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 3.54$, df = 3 ($P = 0.32$); $I^2 = 15\%$					
Test for overall effect: Z = 0.72 ($P = 0.47$)					



Alcohol

Review of **early studies** of alcohol addiction treated with LSD-assisted therapy.

Meta-analysis evidence for a beneficial effect of LSD on alcohol misuse (OR, 1.96; 95% CI, 1.36–2.84; p = 0.0003)

Krebs, Johansen 2012

This model was also initially thought into the AA program !!

Bill Wilson

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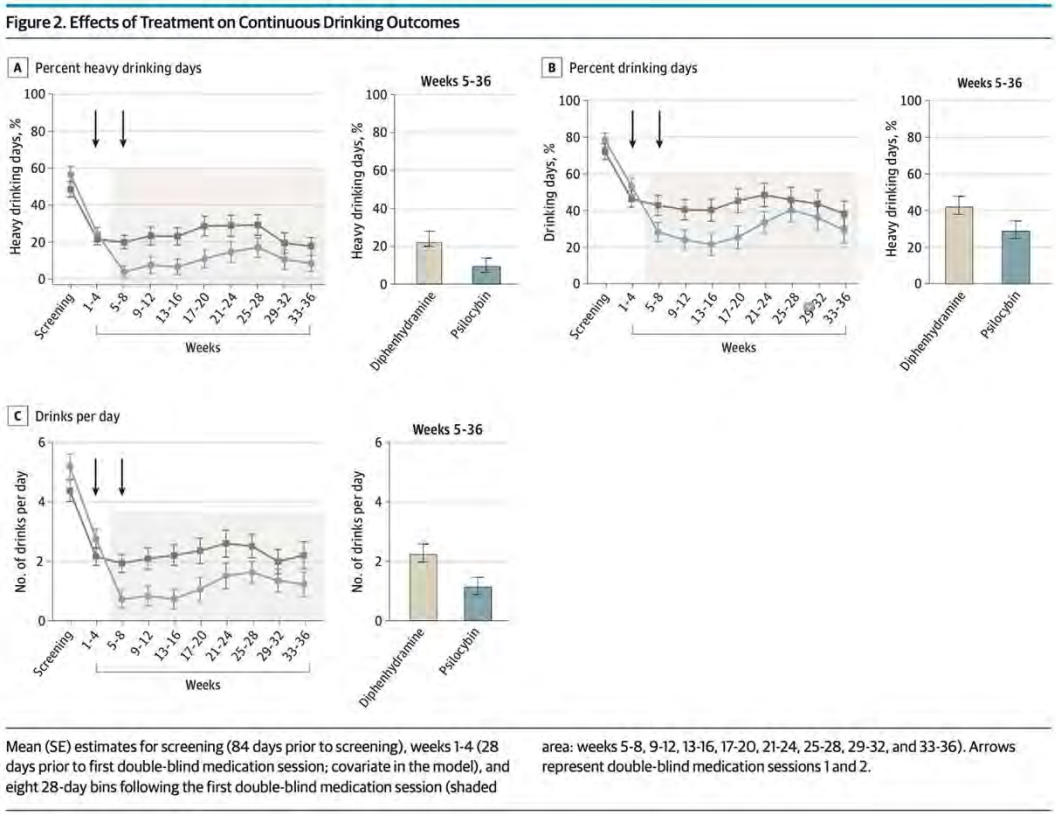
Alcohol studies - cont

Psilocybin-assisted treatment for alcohol dependence: Larger study

Bogenschutz et al, 2022

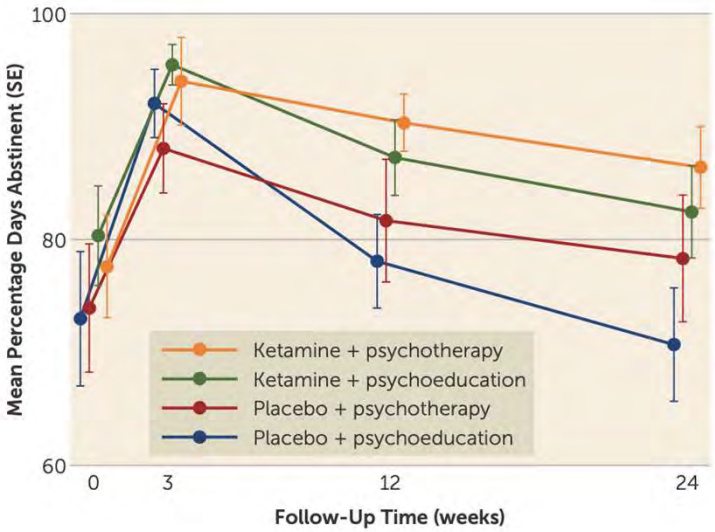


Mean (SE) estimates for screening (84 days prior to screening), weeks 1-4 (28 days prior to first double-blind medication session; covariate in the model), and eight 28-day bins following the first double-blind medication session (shaded area: weeks 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, and 33-36).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

- N=95, randomised
- Psilocybin 25mg/70kg vs diphenhydramine 50mg sessions

Percentage of heavy drinking days during the 32-week double-blind period was 9.7% for the psilocybin group and 23.6% for the diphenhydramine group, a mean difference of 13.9%; (95% CI, 3.0–24.7; $F1,86 = 6.43$; $P = .01$).

Alcohol studies - cont



- Significantly greater number of days abstinent from alcohol in the ketamine group compared with the placebo group at 6-month follow-up (mean difference510.1%, 95% CI51.1, 19.0)
- Greatest reduction in the ketamine plus therapy group compared with the saline plus education group (15.9%, 95% CI53.8, 28.1).

Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder

Meryem Grabski, Ph.D., Amy McAndrew, Ph.D., Will Lawn, Ph.D., Beth Marsh, B.Sc., Laura Raymen, M.Sc., Tobias Stevens, Ph.D., Lorna Hardy, Ph.D., Fiona Warren, Ph.D., Michael Bloomfield, Ph.D., Anya Borissova, M.D., Emily Maschauer, M.Sc., Rupert Broomby, M.D., Robert Price, M.D., Rachel Coathup, M.D., David Gilhooly, M.D., Edward Palmer, M.D., Richard Gordon-Williams, M.D., Robert Hill, Ph.D., Jen Harris, D.Clin.Psych., O. Merve Mollaahmetoglu, M.Sc., H. Valerie Curran, D.Clin.Psych., Brigitta Brandner, M.D., Anne Lingford-Hughes, M.D., Ph.D., Celia J.A. Morgan, Ph.D.

Objective: Early evidence suggests that ketamine may be an effective treatment to sustain abstinence from alcohol. The authors investigated the safety and efficacy of ketamine compared with placebo in increasing abstinence in patients with alcohol use disorder. An additional aim was to pilot ketamine combined with mindfulness-based relapse prevention therapy compared with ketamine and alcohol education as a therapy control.

Methods: In a double-blind placebo-controlled phase 2 clinical trial, 96 patients with severe alcohol use disorder were randomly assigned to one of four conditions: 1) three weekly ketamine infusions (0.8 mg/kg i.v. over 40 minutes) plus psychological therapy, 2) three saline infusions plus psychological therapy, 3) three ketamine infusions plus alcohol education, or 4) three saline infusions plus alcohol education. The primary outcomes were self-reported percentage of days abstinent and confirmed alcohol relapse at 6-month follow-up.

Results: Ninety-six participants (35 women; mean age, 44.07 years [SD=10.59]) were included in the intention-to-treat analysis. The treatment was well tolerated, and no serious adverse events were associated with the study drug. Although confidence intervals were wide, consistent with a proof-of-concept study, there were a significantly greater number of days abstinent from alcohol in the ketamine group compared with the placebo group at 6-month follow-up (mean difference=10.1%, 95% CI=1.1, 19.0), with the greatest reduction in the ketamine plus therapy group compared with the saline plus education group (15.9%, 95% CI=3.8, 28.1). There was no significant difference in relapse rate between the ketamine and placebo groups.

Conclusions: This study demonstrated that treatment with three infusions of ketamine was well tolerated in patients with alcohol use disorder and was associated with more days of abstinence from alcohol at 6-month follow-up. The findings suggest a possible beneficial effect of adding psychological therapy alongside ketamine treatment.

Am J Psychiatry 2022; 179:152–162; doi: 10.1176/appi.ajp.2021.21030277

Alcohol studies - cont

"It helped family wise, relationship wise, in every, every single avenue of my life, It's changed it."

"I feel I have much less desire to drink now than I used to. And I think what it is, I actually, I think I enjoy it less now"

"*I think before the trial all my life was sort of focused on alcohol. I was either drinking it at home or selling it to students or working in an event where there was alcohol, the alcohol was a focus of it. So, it was sort of everything and then afterwards, it just sort of stopped."*

Morgan et al 2021

Alcohol studies - cont

Original Paper

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder

Ben Sessa[1], Laurie Higbed[1], Steve O'Brien[1], Claire Durant[1], Chloe Sakal[2], Daniel Titheradge[3], Tim M Williams[4], Anna Rose-Morris[4], Elsa Brew-Girard[4], Sam Burrows[4], Chantelle Wiseman[5], Sue Wilson[1], James Rickard[6] and David J Nutt[1,2]

Psychopharm

Journal of P
2021, Vol. :
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DOI: 10.11
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N=14 suffering AUD
2 sessions with MDMA 187.5mg

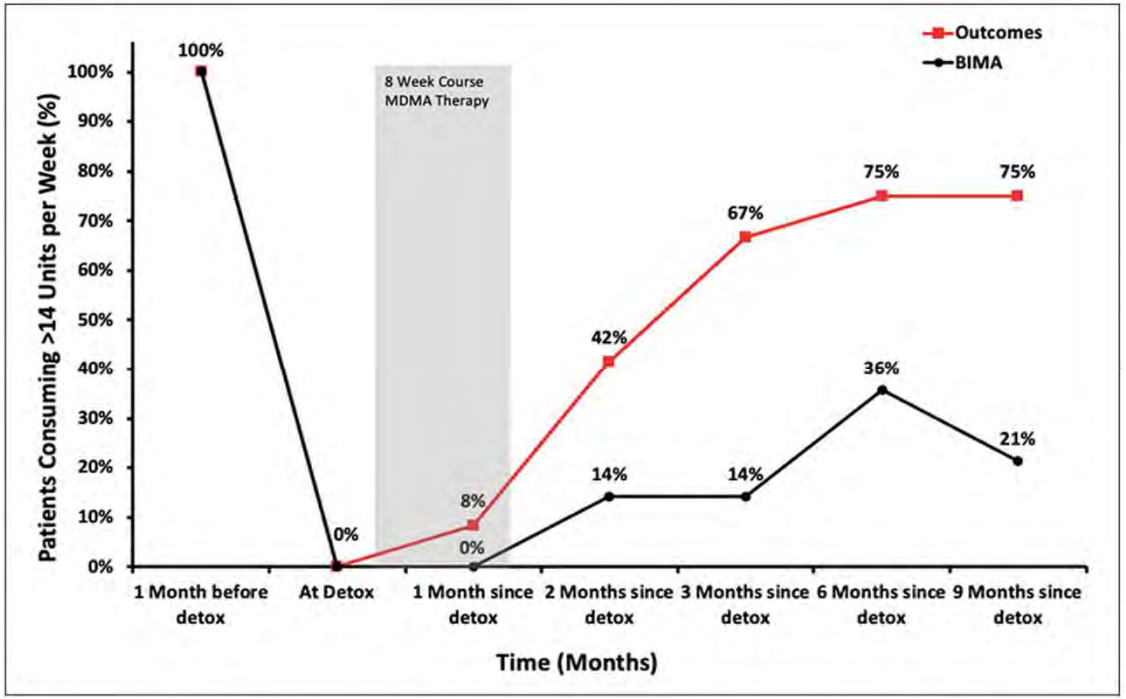


Figure 6. TLFB showing % of patients consuming more than the 14 recommended daily units of alcohol (Sessa et al., 2020).

Nine months post detox, the average units of alcohol consumption by participants was 18.7 units per week compared to 130.6 units per week before the detox.

Sessa et al 2021

Smoking cessation studies

Original Paper

Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction

Matthew W Johnson[1], Albert Garcia-Romeu[1], Mary P Cosimano[1] and Roland R Griffiths[1,2]

Psychopharm

Journal of Psychopharmacology
1–10

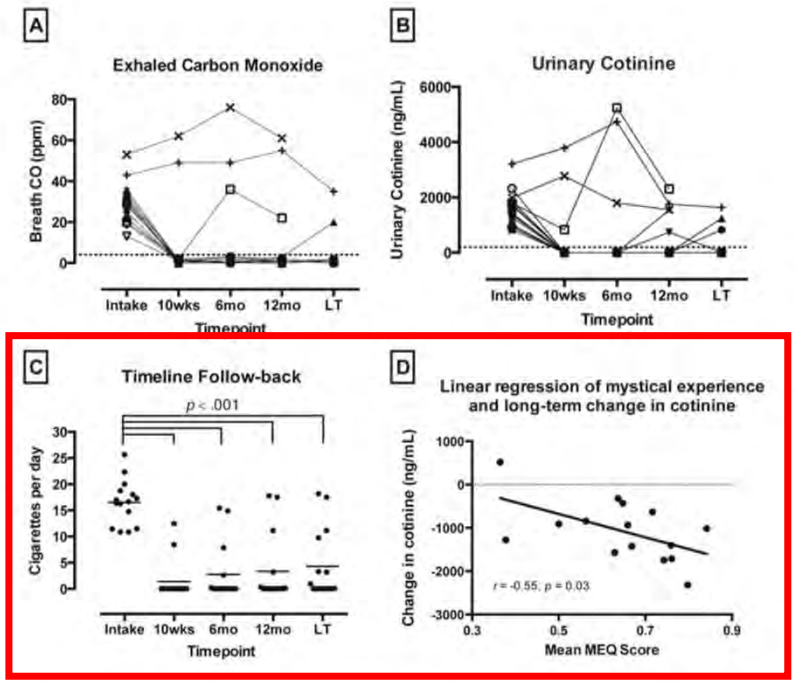
DOI: 10.1177/0269881114548296
jop.sagepub.com
SAGE

Am J Drug Alcohol Abuse. 2017 January ; 43(1): 55–60. doi:10.3109/00952990.2016.1170135.

Long-term Follow-up of Psilocybin-facilitated Smoking Cessation

Matthew W. Johnson, PhD[1], **Albert Garcia-Romeu, PhD**[1], and **Roland R. Griffiths, PhD**[1,2]
[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

Figure 1



(A) Exhaled carbon monoxide (CO) shown for each participant from baseline through long-term follow-up (LT). (B) Urine cotinine levels shown for each participant from baseline through long-term follow-up. (C) Timeline Follow-back (TLFB) data of self-reported daily smoking; individual data points show individual participant data, with the group mean indicated by horizontal line; horizontal brackets indicate significant reductions between intake and each of 4 follow-up assessments (2-tailed paired *t*-tests, $p < 0.001$). (D) Relationship between average scores on the Mystical Experience Questionnaire (MEQ30) at the conclusion of each psilocybin session, and change in urinary cotinine levels from study intake to long-term follow-up. Data points show data from each of the 15 individual participants with best-fit linear regression.

Opiate studies

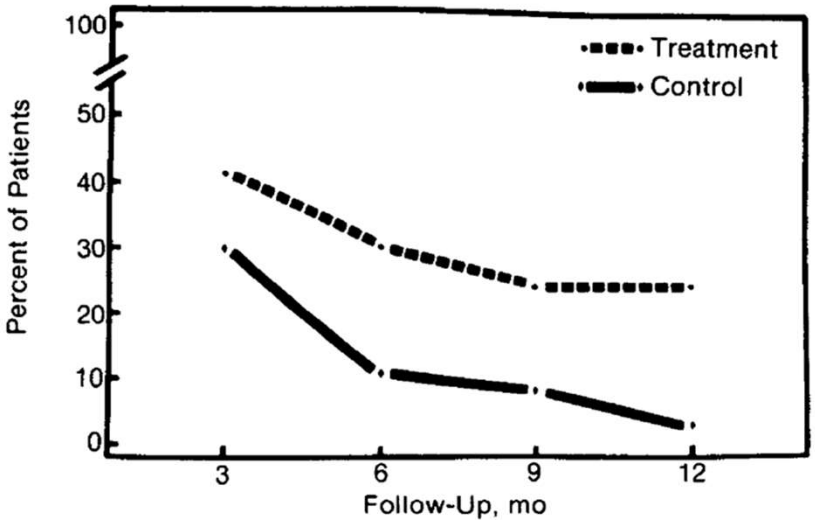
Residential Psychedelic (LSD) Therapy for the Narcotic Addict

A Controlled Study

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

Arch Gen Psych 1973

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



Morris N.

Heroin has a numbing-like effect on you. It tends to relax you and somewhat takes you out and away from your surroundings and yourself. LSD makes you more aware of yourself and puts you right into whatever has been troubling you.

Robert W.

Comparing LSD to heroin is like comparing a speck of dust with a mountain. The difference is that heroin helps you to turn from yourself and LSD shows you how to face yourself.

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 a dream. But with LSD, it is like dawn, a new awakening, it expands your mind, it gives you a brand new outlook on life.

Other theoretical concepts – reward circuits

Addiction and Transcendence as altered states of consciousness (Metzner, 1994)

'Transcendent or ecstatic experiences, like the classic accounts of mystical or cosmic consciousness, involve a widening of the focus of attention, an expansion of awareness beyond the boundaries of the ordinary or baseline state. Thus, such experiences involve the opposite of the addictive contractions of consciousness.'

FIGURE 1
BASELINE AND CONTRACTED STATES

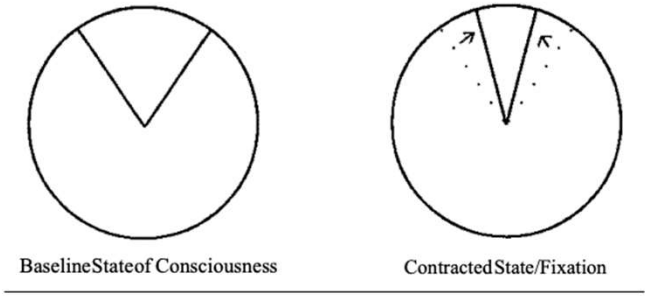


FIGURE 2
BASELINE AND EXPANDED STATES

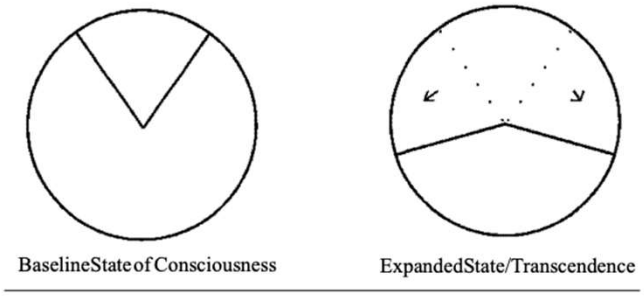
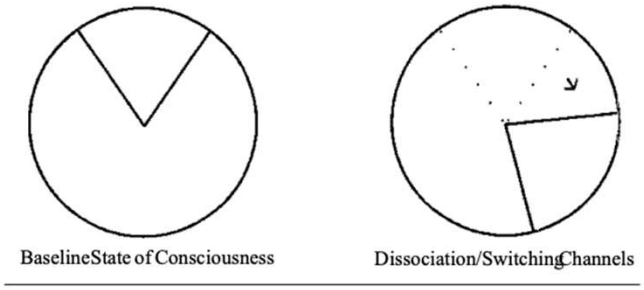


FIGURE 3
BASELINE AND CHANNEL-SWITCHING STATES



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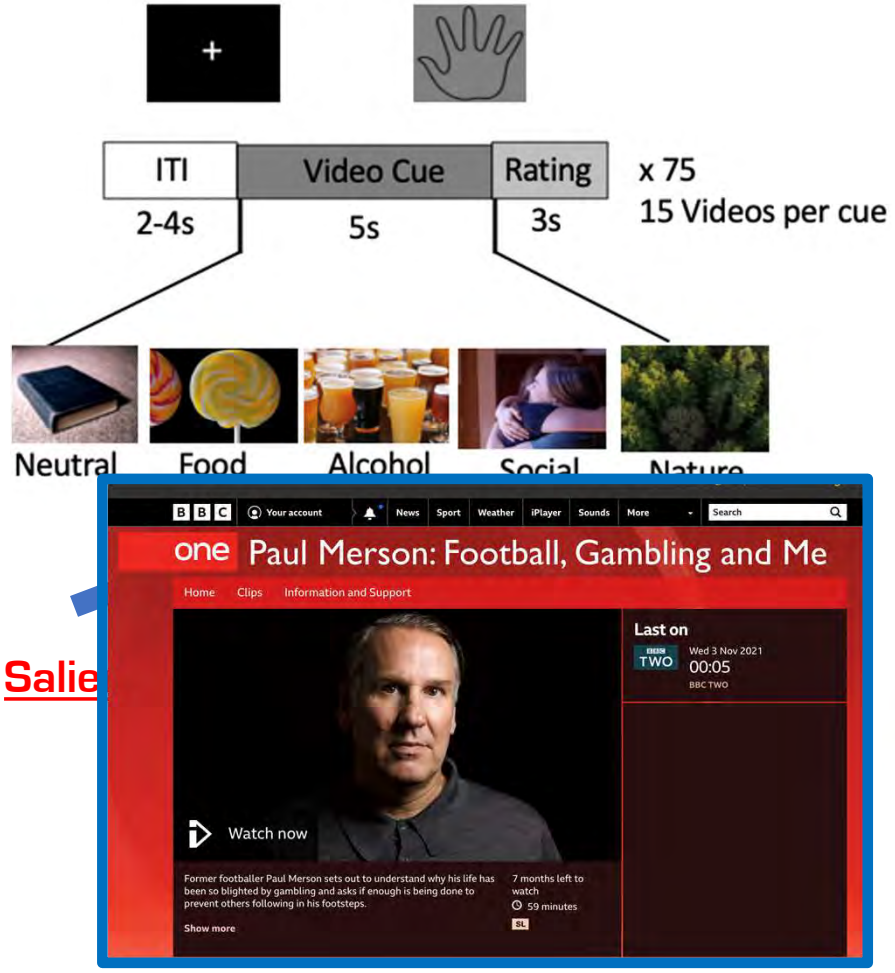
5-Arm Cue Reactivity Paradigm

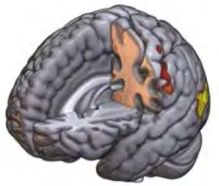
Hypotheses:

1. Increased BOLD activation in cue-associated brain regions of the reward and salience networks in response to Gambling cues will be greater in GD > HC

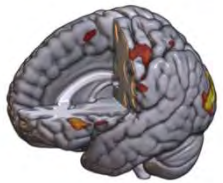
2. Lower BOLD activation in reward and salience networks in response to Social, Art, Nature, Food and Aversive cues in GD < HC



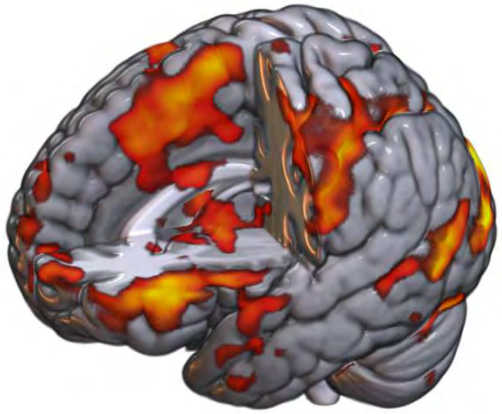
Food cues



Nature cues



Gambling cues

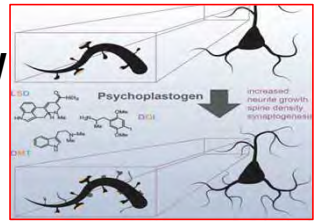


Possible mechanisms

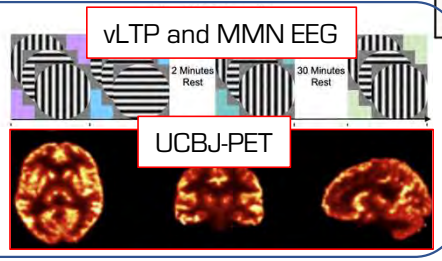
Serotonin 2A receptor stimulation

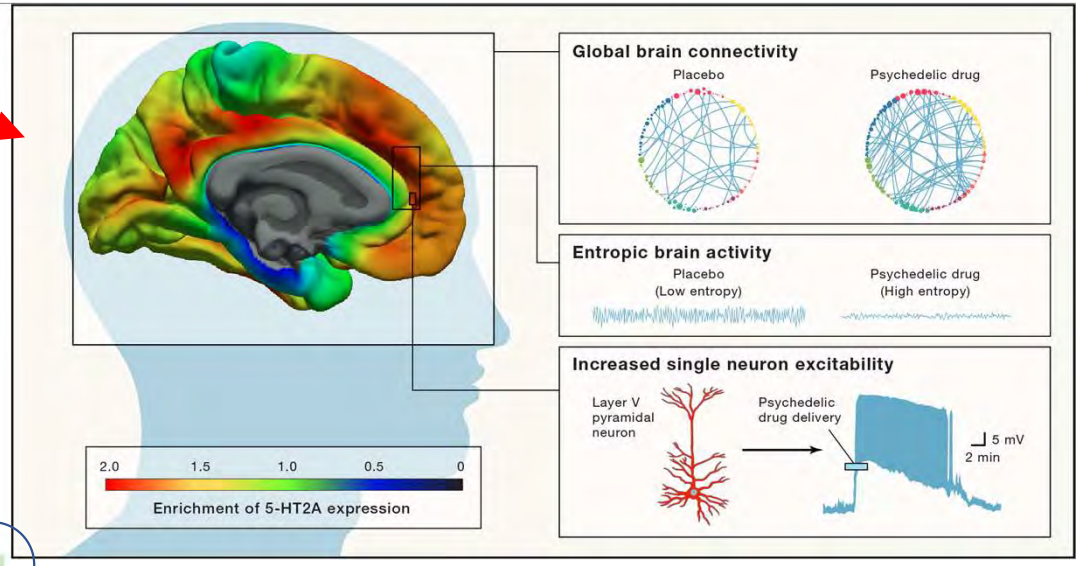
Serotonin & 2A receptor: plasticity

- Neuroplasticity (cortex) ↑
- Brain development
- Associative Learning/unlearning



Ly et al. 18. Cell





Nutt, Erritzoe, Carhart-Harris, Cell 2020

Bottom-up re-structuring of ingrained models of the world ?

Cahart-Harris: REBUS & anarchic brain

- ↓ Expectations about standard tones with MMN EEG paradigm [Timmermann et al., 2017]
- ↓ Hierarchical differentiation of trans-v unimodal cortex [Girn et al., 2022, & Timmermann in press]

Key psychological effects:

↑ Connectedness & acceptance Watts,2017

↓ Negative cognitive biases Lyons, 2018

↓ Rumination & thought suppression Barba (in press)

↑ Trait openness Erritzoe 2018,19

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Project overview at Centre for Psychedelic Research at Imperial

In CIPPRes Clinic:

- Test and validate fMRI reward paradigms in problem gamblers vs matched controls (*AMS grant*)
- Test plasticity EEG and synaptogenesis PET-MRI before and after ketamine infusion (*GE grant*)
- Test the same following DMT intervention (*Drug Science support*)
- Test effects of moderate dose of (COMP360) psilocybin on EEG plasticity and cognitive flexibility in OCD (*Charity*)
- Naturalistic microdosing w self-blinding) (*NIHR BRC grant and Mydecine support*)

Additional studies in the Centre:

- Anorexia nervosa, oral (COMP360) psilocybin
- Chronic pain, oral (Usona psilo) psilocybin
- **DMT SmallPharma depression phase1&2a study**
- DMT constant infusion study
- 5MEO-DMT EEG
- **Opiate study with psilocybin in prep**
- Online surveys and field work

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www.imperial.ac.uk/psychedelic-research-centre/

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Tommaso Barba

Research Intern; ERASMUS Masters Student in Neuroscience

Dr Alan Cross

Honorary Clinical Research Fellow; Specialist Registrar in Psychiatry

Dr David Erritzoe

Director of CIPPRes Clinic, Clinical Senior Lecturer and Consultant Psychiatrist

Dr Elinor Farrell

Honorary Clinical Research Fellow; Specialist Registrar in Psychiatry

Marion Gildea

Research Intern; ERASMUS Masters Student in Neuroscience

Bruna Giribaldi

Pharmacologist; Clinical Trial Manager

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Dr Mamas Pipis

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THE CENTRE FOR PSYCHEDELIC RESEARCH

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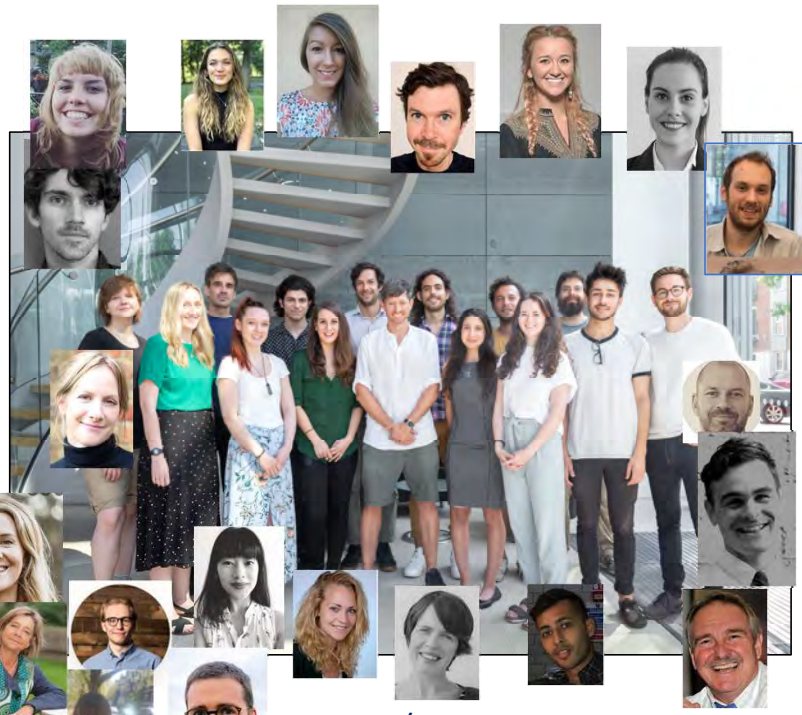

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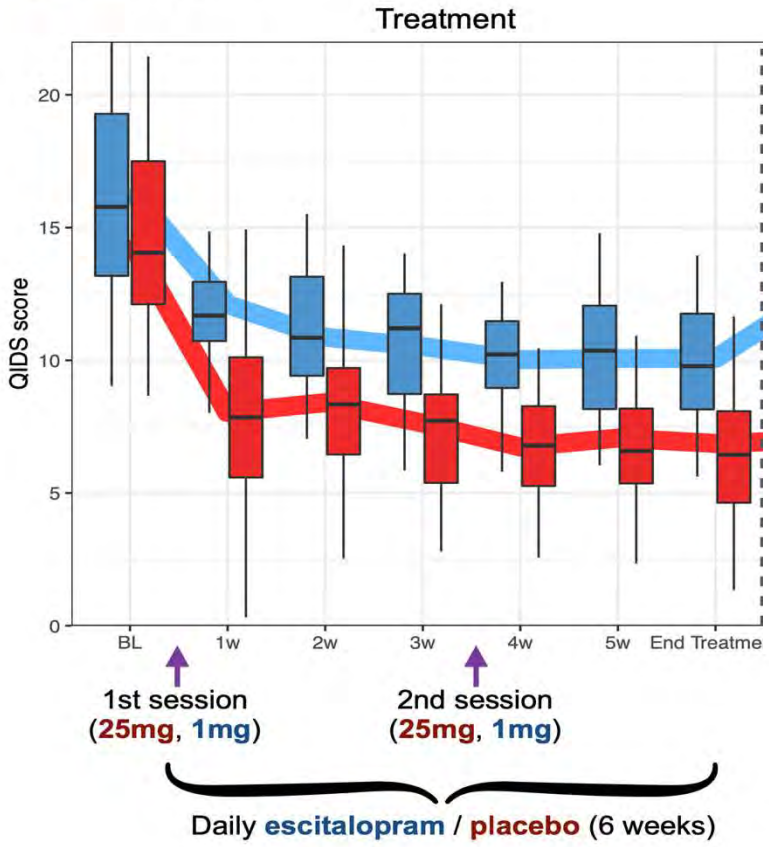
Psilocybin vs Escitalopram - 6 months follow up

QIDS scores (after mixed-model cleaning)

Psilocybin: 30 patients
Escitalopram: 29 patients



What happens after patients leave the 6 week treatment phase of the study ?

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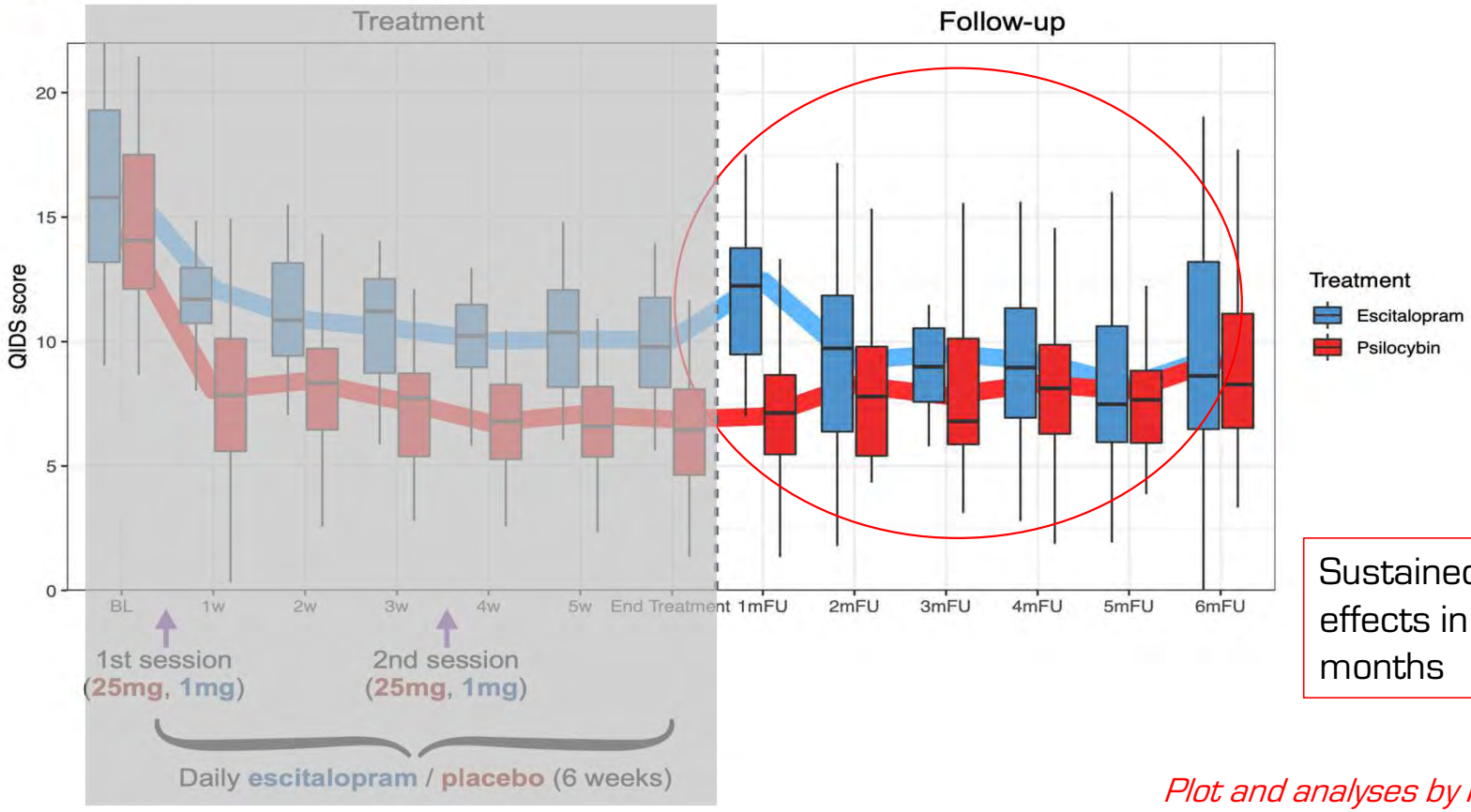
Psilocybin vs Escitalopram - 6 months follow up

QIDS scores (after mixed-model cleaning)

Psilocybin: 30 patients
Escitalopram: 29 patients



Sustained antidepressant effects in both groups at 6 months

Plot and analyses by F. Rosas (In prep.)

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Psilocybin vs Escitalopram - 6 months follow up

	Change psilocybin	Change p-value	Change escitalopram	Change p-value	Treatment difference	(Uncorrected) p-value
(Baseline)	14.5	-	16.4	-	1.9	0.184
1 week	-6.5	**<.001**	-4.3	**<.001**	2.2	0.110
2 week	-6.1	**<.001**	-5.6	**<.001**	0.6	0.684
3 week	-6.9	**<.001**	-5.9	**<.001**	1.0	0.461
4 week	-7.8	**<.001**	-6.4	**<.001**	1.4	0.307
5 week	-7.5	**<.001**	-6.4	**<.001**	1.1	0.415
6 week	-7.7	**<.001**	-6.4	**<.001**	1.3	0.328
1m FU	-7.5	**<.001**	-4.0	**<.001**	3.5	**0.009**
2m FU	-6.3	**<.001**	-7.2	**<.001**	-0.9	0.485
3m FU	-6.7	**<.001**	-7.0	**<.001**	-0.2	0.881
4m FU	-6.2	**<.001**	-7.2	**<.001**	-1.0	0.489
5m FU	-6.5	**<.001**	-8.2	**<.001**	-1.7	0.227
6m FU	-5.3	**<.001**	-7.0	**<.001**	-1.7	0.223

The 6 week treatment phase

The 6 month follow-up period

Sustained antidepressant effects in both groups

Plot and analyses by F. Rosas (In prep.)

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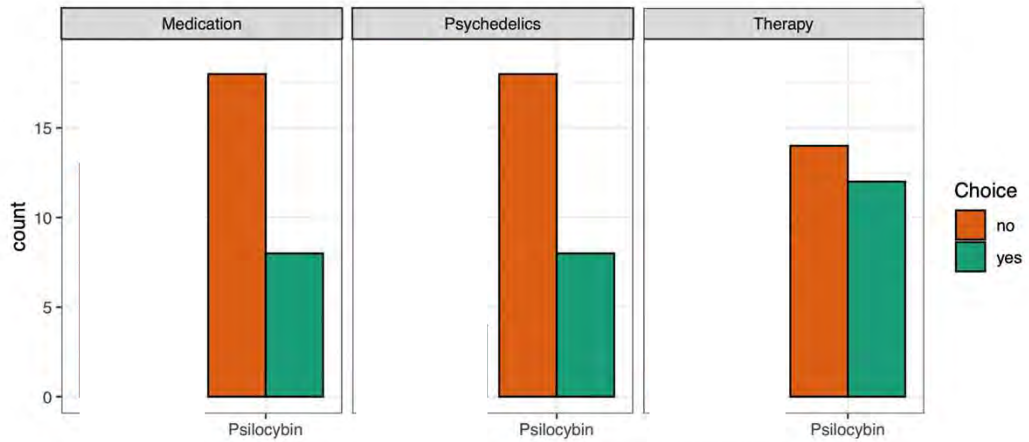
The 6 months follow up (cont.)

What people do after the trial ended?

(We only have such info from n=49, so we don't have from n=10)



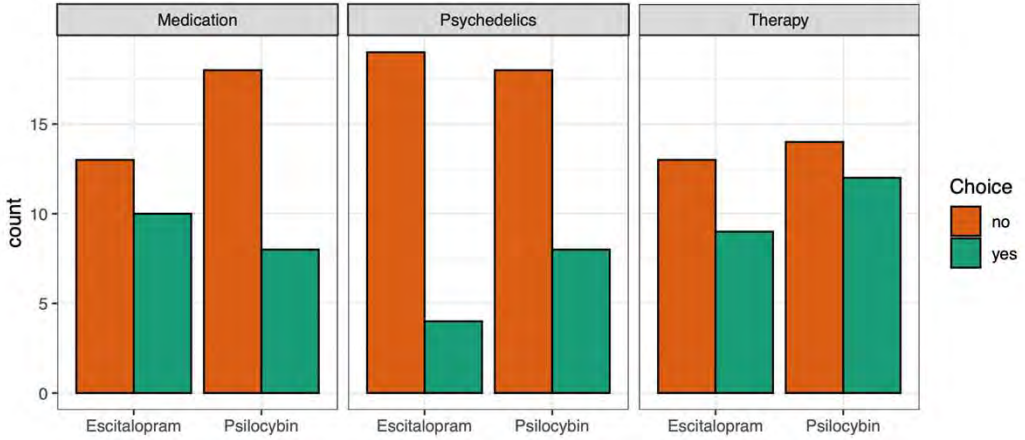
From psilocybin arm

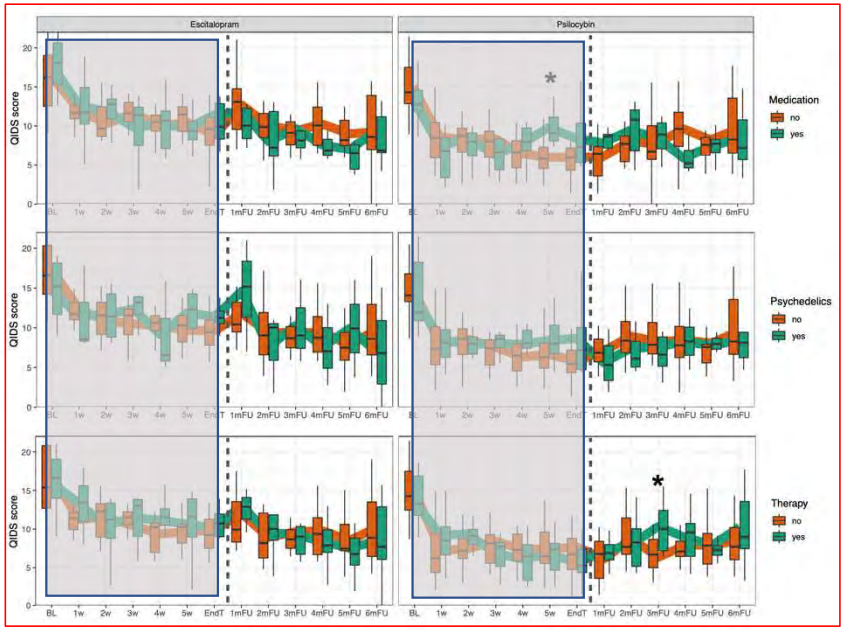
	Treatment +	Treatment -
Medication	8	18
Psychedelics	8	18
Therapy	12	14

The 6 months follow up (cont.)

What people do after the trial ended?

(We only have such info from n=49, so we don't have from n=10)





	From psilocybin arm		From escitalopram arm		
	Treatment +	Treatment -	Treatment +	Treatment -	p-value
Medication	8	18	10	13	0.533
Psychedelics	8	18	4	19	0.451
Therapy	12	14	9	13	0.942

The pattern in the long-term data is not clearly explained by the information available about participants' treatment behaviour in the follow-up period

Plot and analyses by F. Rosas (In prep.)

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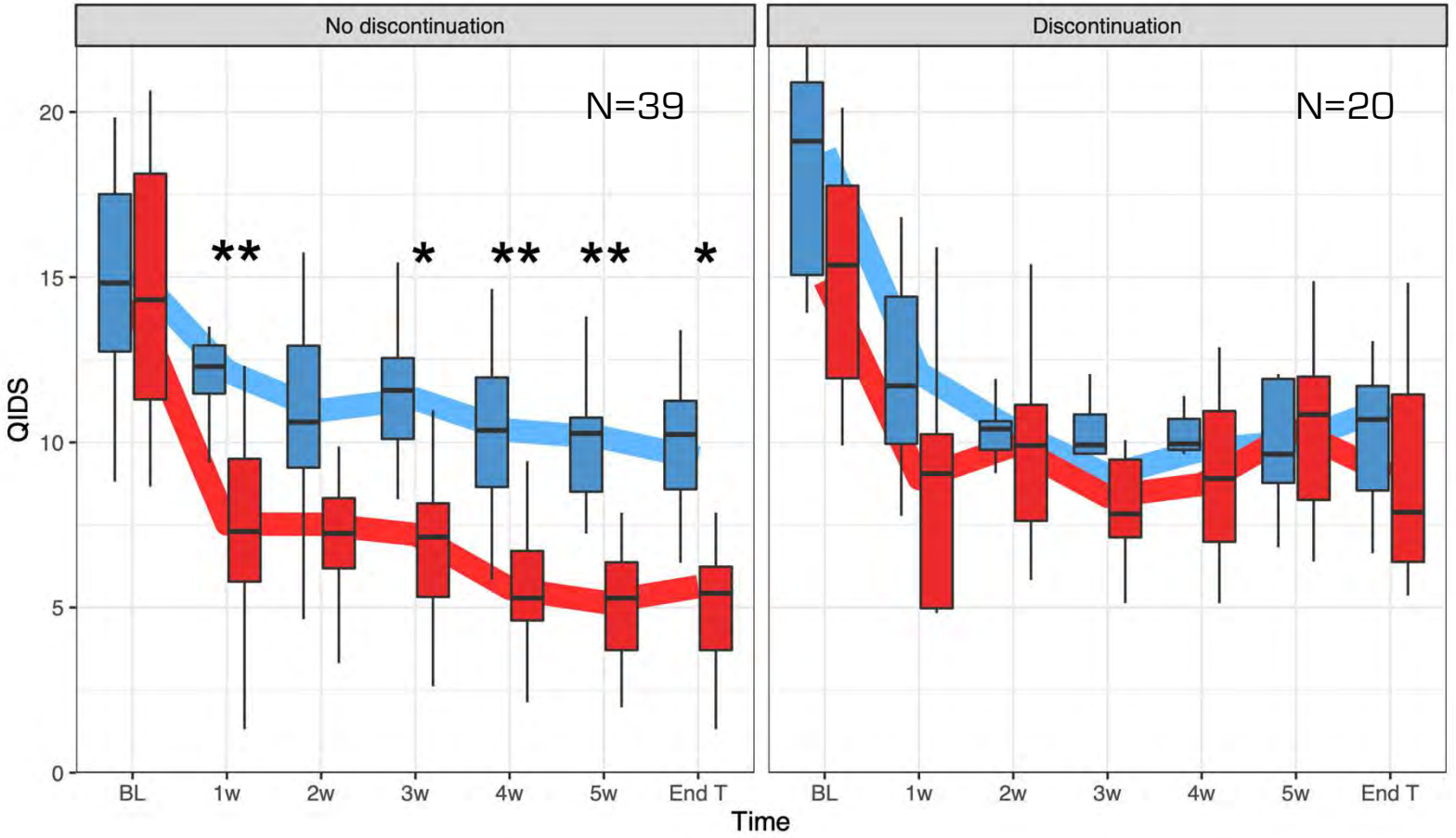
Effects of discontinuation of medication

NOT tapered off (not on AD meds before trial)

Tapered off (on AD meds before trial)

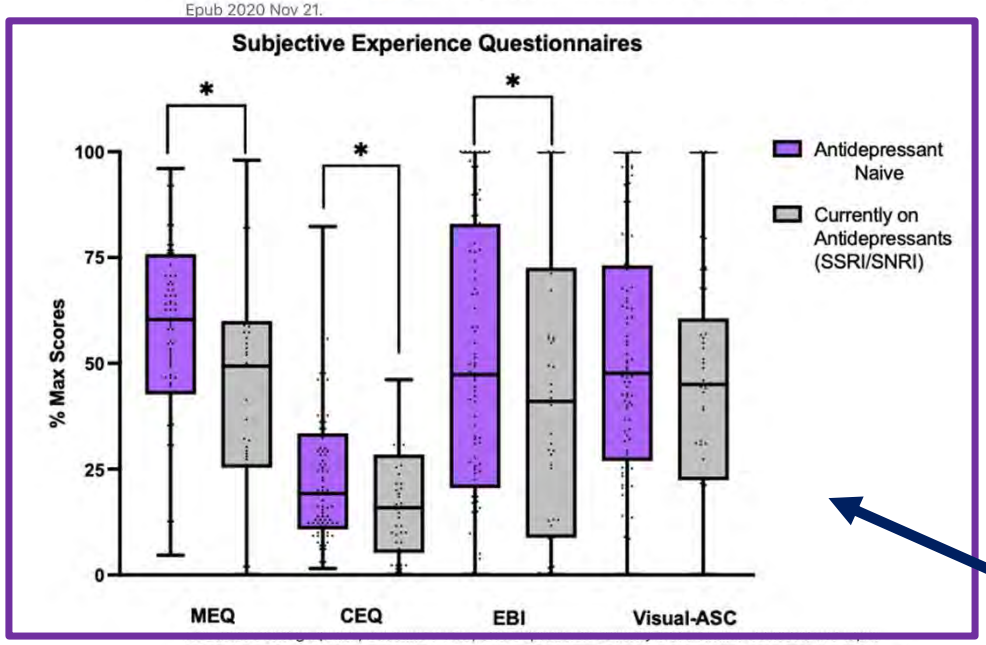


(Post-hoc) significant difference between treatment conditions for people that didn't discontinue antidepressants going into the trial

In prep. Plot and analyses by M. Spriggs and F. Rosas

The issue of discontinuation of medication

Psychopharmacology (Berl). 2021 Feb;238(2):581-588. doi: 10.1007/s00213-020-05710-w. Epub 2020 Nov 21.



and non-taper groups. At the primary endpoint, the non-taper group (mean = 45.7, SD = 27.17) had a significantly (p = 0.009) lower CAPS-IV total scores compared to the taper group (mean = 70.3, SD = 33.60). More participants in the non-taper group (63.6%) no longer met PTSD criteria at the primary endpoint than those in the taper group (25.0%). The non-taper group (mean = 12.7, SD = 10.17) had lower depression symptom severity scores (p = 0.010) compared to the taper group (mean = 22.6, SD = 16.69). There were significant differences between groups in peak systolic blood pressure (p = 0.043) and diastolic blood pressure (p = 0.032).

Conclusions: Recent exposure to antidepressant drugs that target reuptake transporters may reduce treatment response to MDMA-assisted psychotherapy.

Keywords: Discontinuation syndrome; MDMA; MDMA-assisted psychotherapy; PTSD; Psychedelics; SNRI; SSRI; Taper.

- Work from Basel team (*Becker et al*) in healthy subjects **and** from Compass Pathways (*online info*) in TRD subjects both suggest that it might be possible to stay on SSRIs for psilocybin treatment.
- MAPS looking into whether ok to stay on SSRIs but then give higher MDMA doses ?
- Preliminary data from Imperial's online prospective surveys suggest that being under SSRIs/SNRIs treatment is associated with reduced psychedelic experience (i.e. lower scores on peak component of acute scales). (*Barbut, Barba et al, in prep*)

More work needs to be done to conclude on best strategy regarding SSRIs in these trials !!

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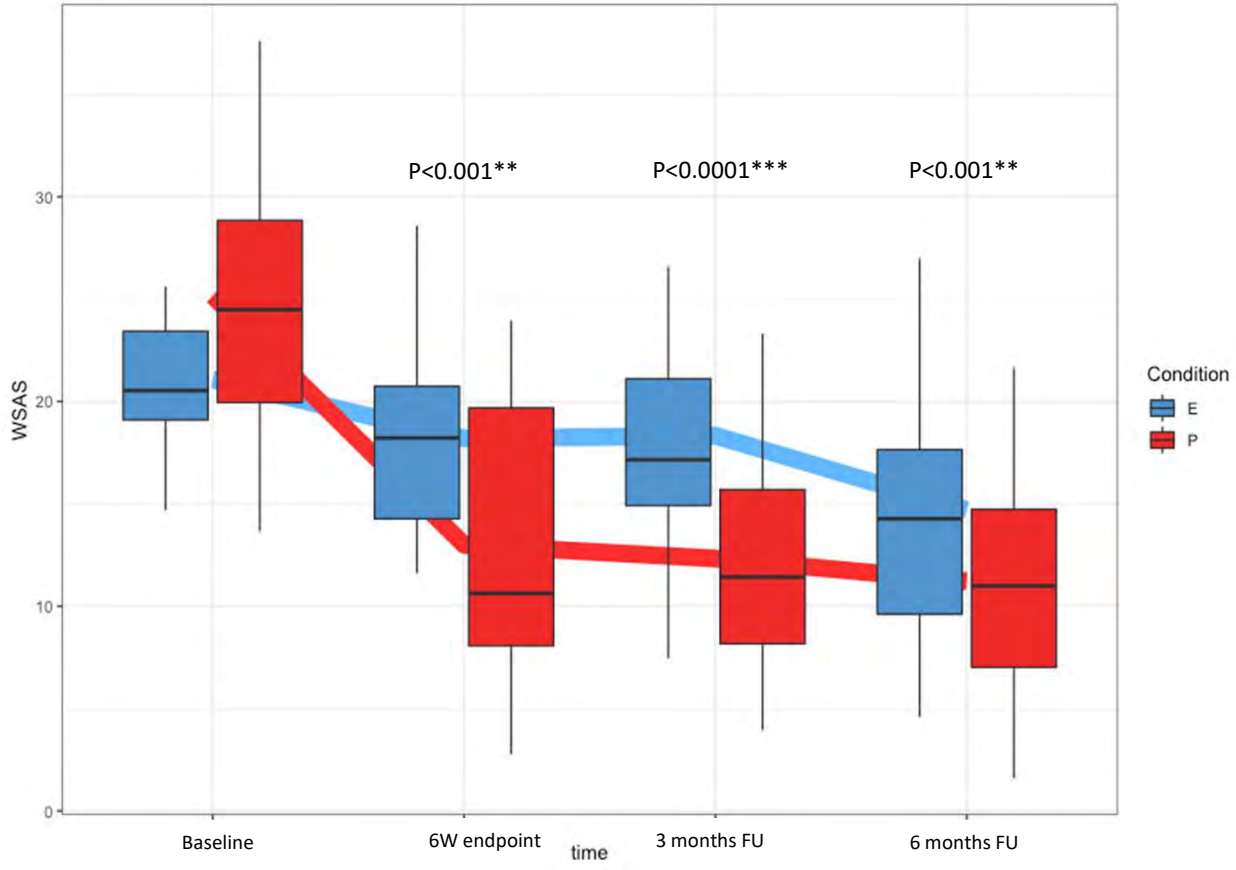
Other long-term follow up measures - WSAS

Work and Social Functioning Scale

The impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships.

LOWER SCORES: LOWER IMPAIRMENT.



Preliminary data from Barba, Weiss, Spriggs, Rosa et al

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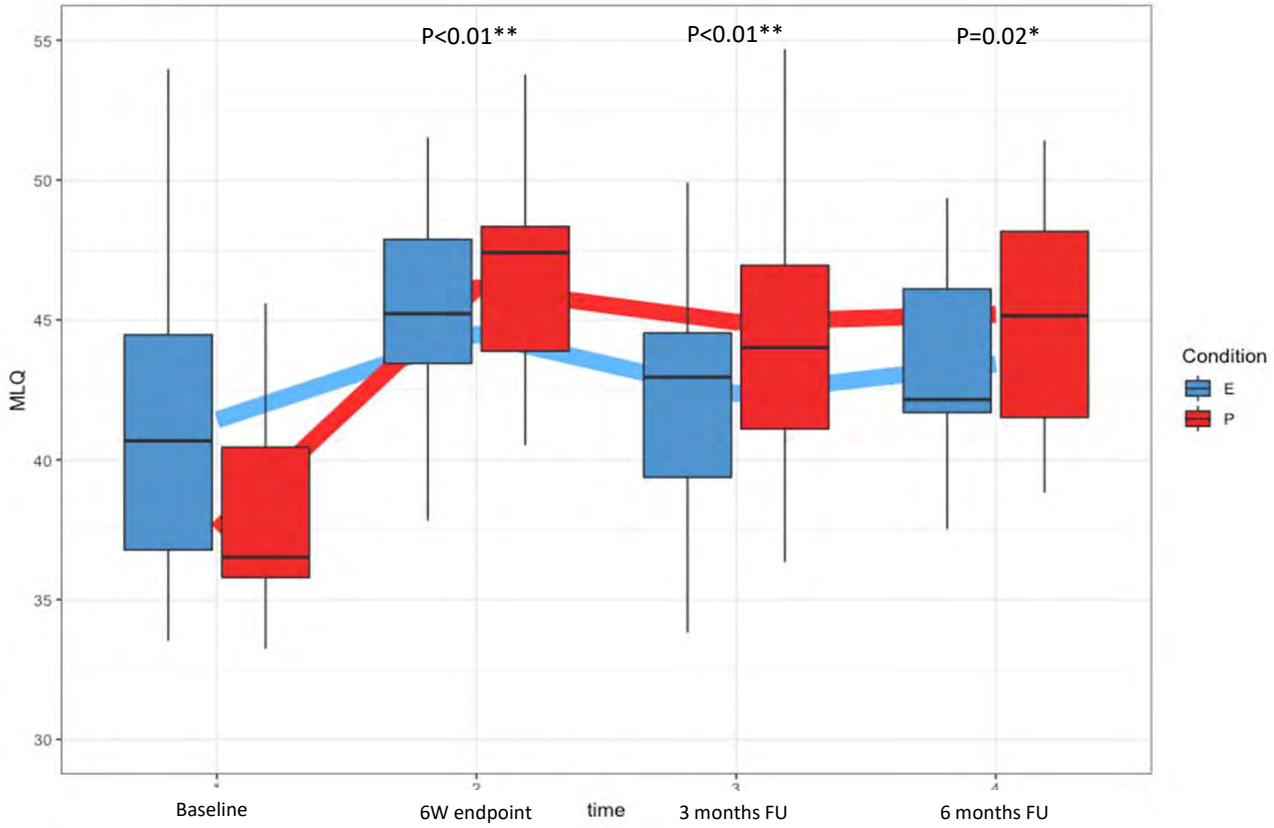
Other long-term follow up measures - MLQ

Meaning in Life Questionnaire

Measures the presence of meaning in life, that is the subjective sense that one's life is meaningful, and the search for meaning in life, reflecting one's drive and orientation toward finding such meaning.

HIGHER SCORES: HIGHER MEANING.



Preliminary data from Barba, Weiss, Spriggs, Rosa et al

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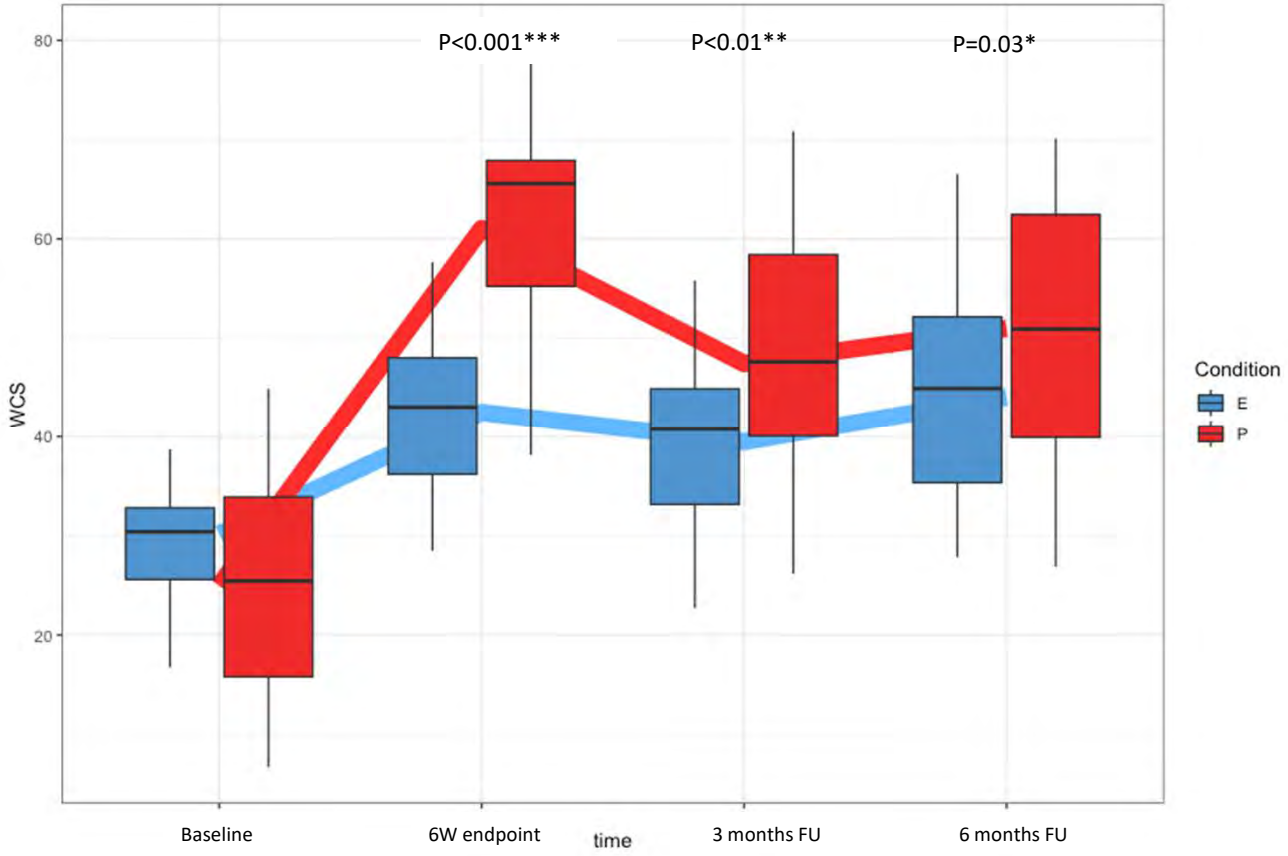
Other long-term follow up measures - WCS

Watts' Connectedness Scale

The scale measures 'a state of feeling connected to self, others and the wider world'.

HIGHER SCORES: HIGHER CONNECTEDNESS.



Preliminary data from Barba, Weiss, Spriggs, Rosa et al

Other long-term follow up measures - FS

Flourishing Scale

The scale measures the respondent's self-perceived success in important areas such as relationships, self-esteem, purpose, and optimism. The scale provides a single psychological well-being score.

HIGHER SCORES: HIGHER FLUORISHING.

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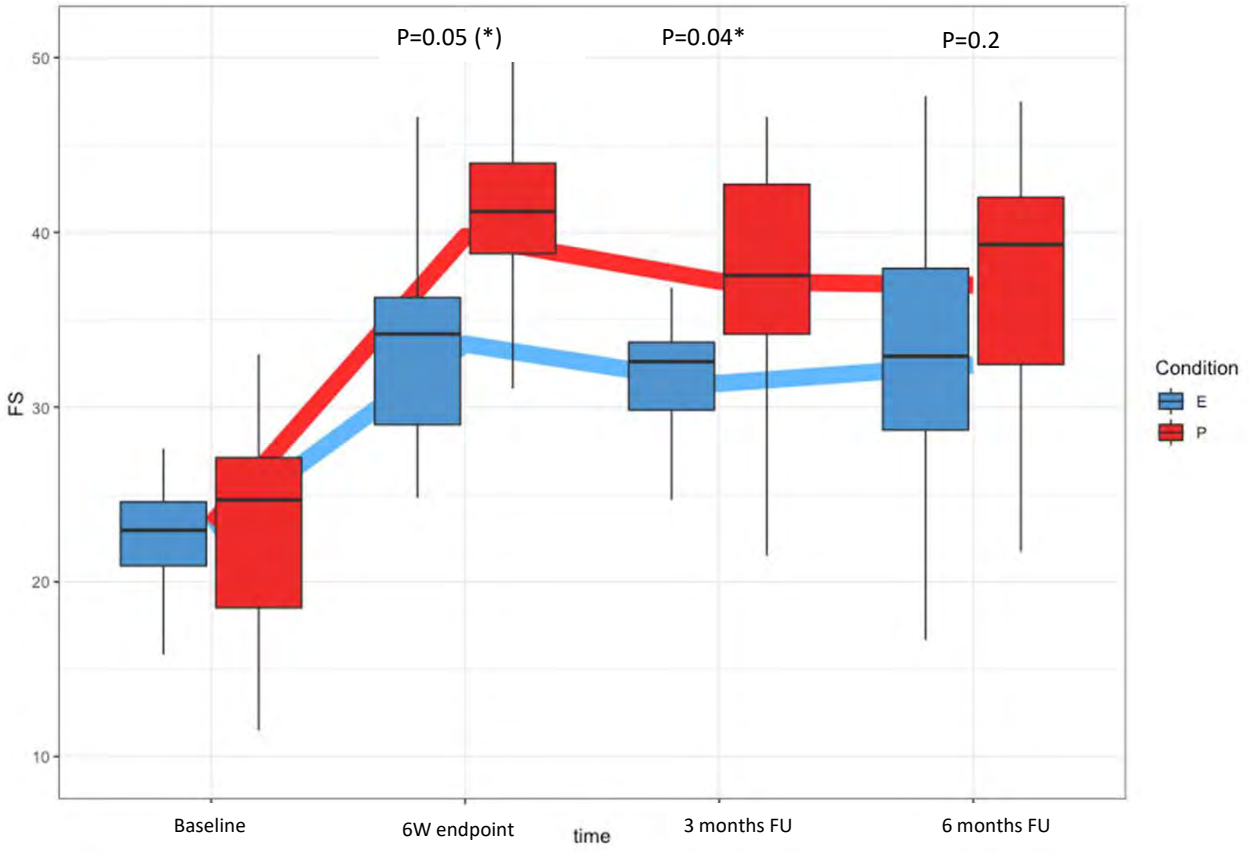
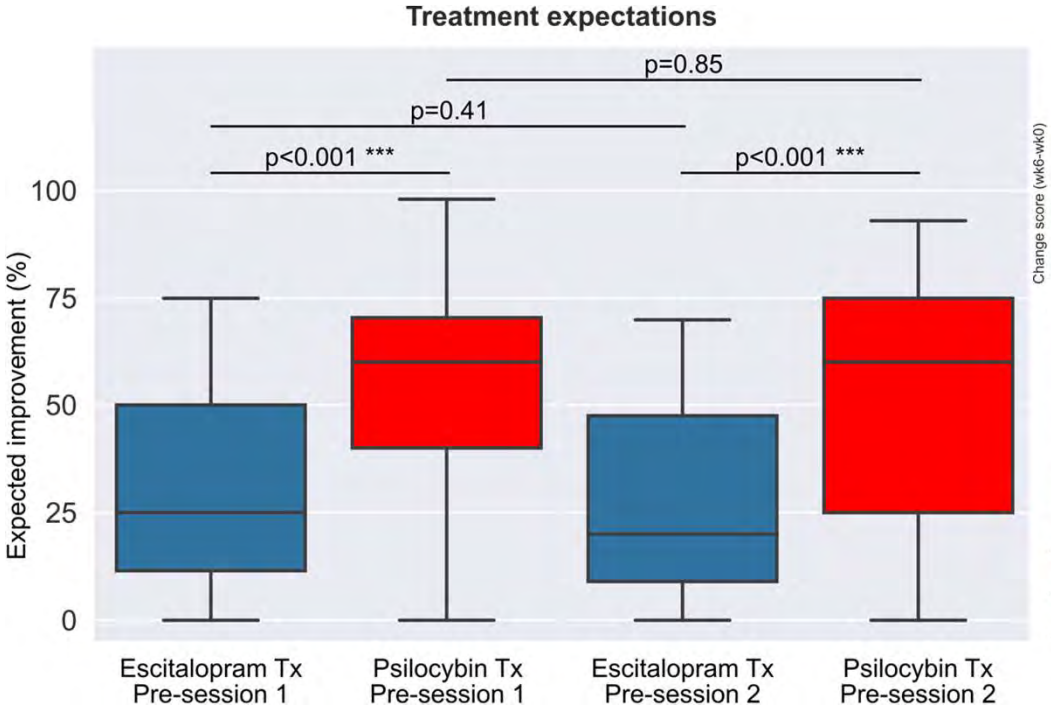
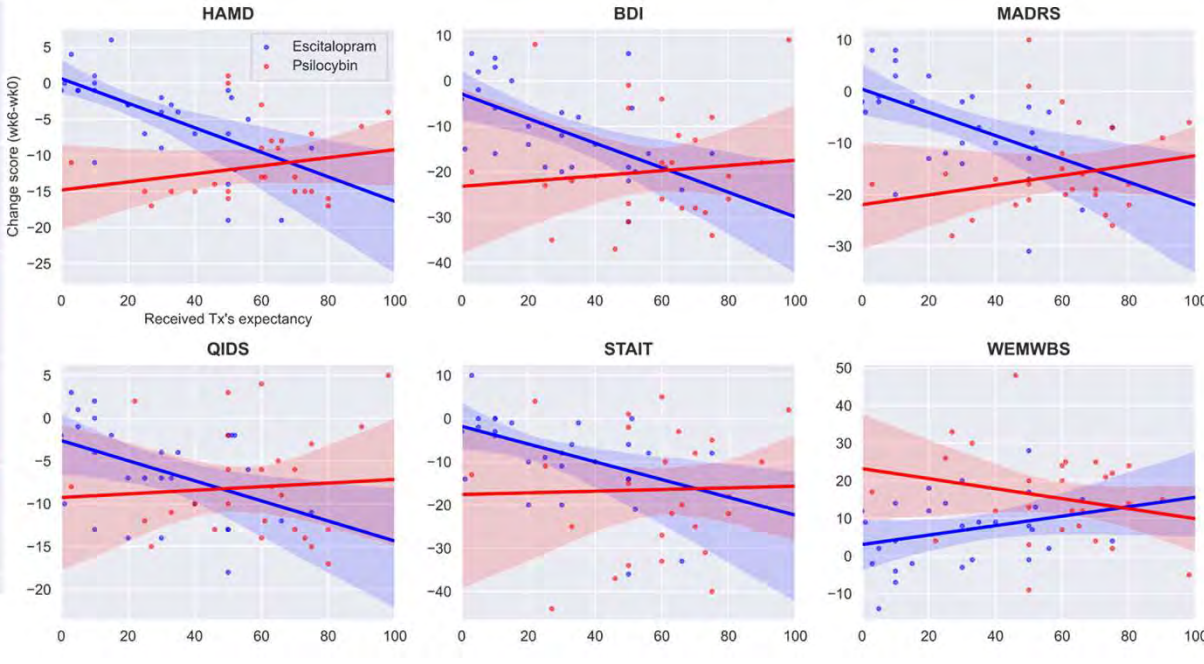


Preliminary data from Barba, Weiss, Spriggs, Rosa et al

Effects of expectancy





- (Expectedly) patients in our study had higher expectations to the effects of psilocybin
- However, the effects of expectancy were more pronounced for treatment in the escitalopram arm

B Szigeti (in prep)

Alcohol studies - cont

Possible mechanism:

- Reduced prefrontal mGluR2 function impaired executive control AND alcohol craving
- This is reverted with psilocybin treatment in knock-down rodent model

SCIENCE ADVANCES | RESEARCH ARTICLE 2021

NEUROSCIENCE

Psilocybin targets a common molecular mechanism for cognitive impairment and increased craving in alcoholism

Marcus W. Meinhardt[1]*†, Simone Pfarr[1]†, Grégory Fouquet[2]†, Cathrin Rohleder[3,4,5,6], Manuela L. Meinhardt[1], Janet Barroso-Flores[1], Rebecca Hoffmann[1], Jérôme Jeanblanc[2], Elisabeth Paul[1], Konstantin Wagner[1], Anita C. Hansson[1], Georg Köhr[1,7], Nils Meier[8], Oliver von Bohlen und Halbach[8], Richard L. Bell[9], Heike Endepols[4,5,10,11], Bernd Neumaier[4,8], Kai Schönig[12], Dusan Bartsch[12], Mickaël Naassila[2]‡, Rainer Spanagel[1]*‡, Wolfgang H. Sommer[1,13]*‡

Alcohol-dependent patients commonly show impairments in executive functions that facilitate craving and can lead to relapse. However, the molecular mechanisms leading to executive dysfunction in alcoholism are poorly understood, and new effective pharmacological treatments are desired. Here, using a bidirectional neuromodulation approach, we demonstrate a causal link between reduced prefrontal mGluR2 function and both impaired executive control and alcohol craving. A neuron-specific prefrontal mGluR2 knockdown in rats generated a phenotype of reduced cognitive flexibility and excessive alcohol seeking. Conversely, virally restoring prefrontal mGluR2 levels in alcohol-dependent rats rescued these pathological behaviors. In the search for a pharmacological intervention with high translational potential, psilocybin was capable of restoring mGluR2 expression and reducing relapse behavior. Last, we propose a FDG-PET biomarker strategy to identify mGluR2 treatment-responsive individuals. In conclusion, we identified a common molecular pathological mechanism for both executive dysfunction and alcohol craving and provided a personalized mGluR2 mechanism-based intervention strategy for medication development for alcoholism.

THE THERAPEUTIC POTENTIAL OF PSYCHEDELICS

- CURRENT STATUS AND POSSIBLE MECHANISMS

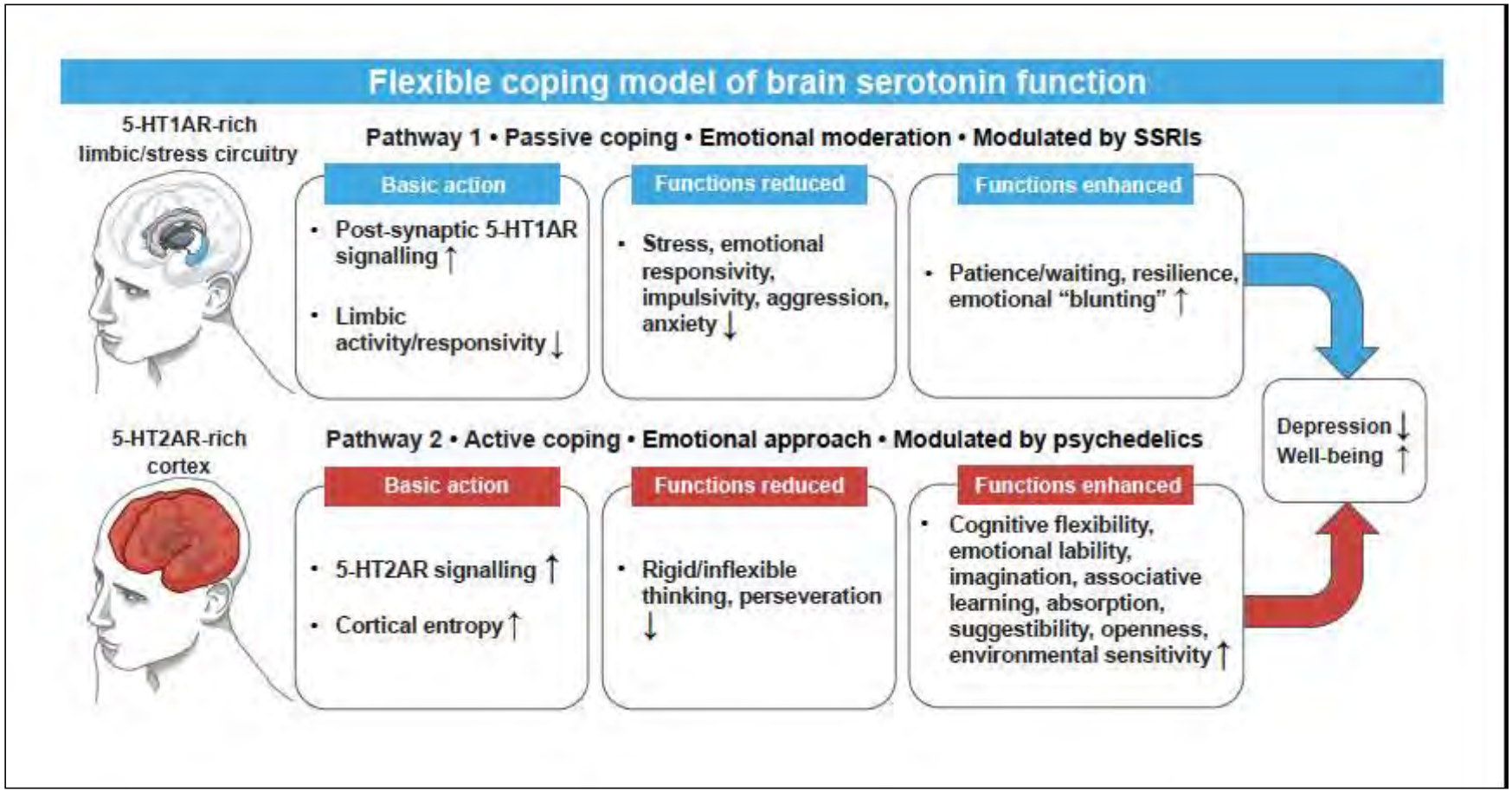
David Erritzoe, MD, PhD, MRCPsych

Universidad Complutense, Madrid
27th October 2022

Envia tus preguntas en ingles o en espanol en este codigo QR.

Why test Psilocybin assisted therapy vs an SSRI ?

Two ways to lift depression? Different brain regions and different 5-HT receptors



Carhart-Harris & Nutt – Journal of Psychopharmacology 2017 – free download

DMT for depression – RCT Imperial with SmallPharma

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Drugs

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Psychedelic drug DMT to be trialled in UK to treat depression

Exclusive: UK regulators give go-ahead for drug to be trialled ahead of possible treatment alongside psychotherapy

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nda Geddes

d 9 Dec 2020 17.28 GMT

▲ DMT is found in several plants and is one of the active ingredients in ayahuasca, pictured. Photograph: Michal Moravcik/Alamy

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ClinicalTrials.gov

Find Studies

Home > Search Results > Study Record Detail

SPL026 (DMT Fumarate) in Healthy Subjects and MDD Patients

Contacts

Contact: Recruitment Manager 08007838792 recruit@hmrlondon.com

Phase 1 completed – phase 2A (MDD) soon complete

Locations

United Kingdom

MAC Clinical Research — Recruiting
Liverpool, United Kingdom, L34 1BH
Contact: Paul Westhead, MD info@researchforyou.co.uk

Hammersmith Medicines Research — Recruiting
London, United Kingdom
Contact: Malcolm Boyce, MD

Sponsors and Collaborators

Small Pharma Ltd

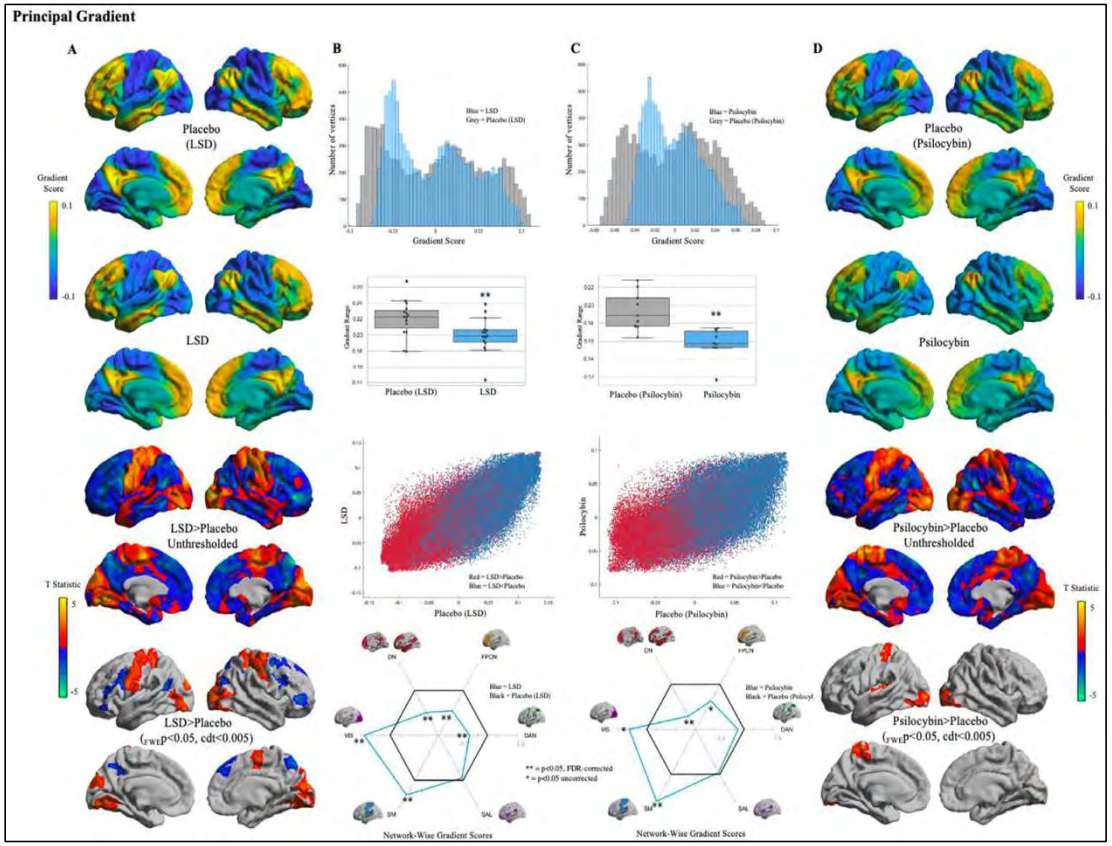
Investigators

Study Director:	Jan Steiner, MD	Oxford Therapeutics Consulting
Principal Investigator:	David Erritzoe, MD	Imperial College London
Principal Investigator:	Malcolm Boyce, MD	Hammersmith Medicines Research

DMT for depression study:
and Imperial College London, ongoing in CROs in London and Liverpool

Bottom-up re-structuring of ingrained models of the world ?

- LSD weakens expectations about standard tones in the auditory mismatch negativity paradigm, making deviant tones seem less anomalous or surprising (Timmerman et al., 2017).
    - Using dynamic causal modelling, it appeared that this result could be best accounted for by reduced top-down information flow from the frontal cortex.
- LSD, psilocybin and DMT induce an acute reduction in the hierarchical differentiation of transmodal versus unimodal cortex (Girn et al., 2022; Timmermann et al., in press).
    - These alterations of transmodal activity and connectivity lead to reduced top-down control of lower-order areas, leading to increased influence of unimodal sensory inputs on high level transmodal representations.



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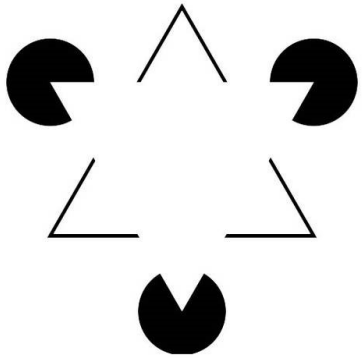
Bottom-up re-structuring of ingrained models of the world ?

- Psilocybin reduces object completion and reduced EEG visual evoked responses to the Kanisza triangle, a visual perceptual illusion requiring object completion via top-down perceptual priors (Kometer et al., 2011).
- Psilocybin reduces binocular rivalry and increased the perception of mixed percepts when 2 different images are quickly shown to right and left eye at the same time (Carter et al., 2007).
- Psilocybin reduces the susceptibility to perceive the Hollow Mask illusion (unpublished results from Torsten Passie).
- Psilocybin induces impairments in high- but not low-level motion perception (Carter et al., 2004).



Relaxation of highly confident prior beliefs and greater influence of bottom-up sensory information?

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Bottom-up re-structuring of ingrained models of the world ?

Measuring belief confidence: the REB-Q

Examples of core belief types

Positive other:
"This person is trustworthy"

Negative other:
"This person is devious"

Positive self:
"I am loved"

Negative self:
"I am a failure"

Figure 1.
Changes in Belief Confidence Following 1 and 25 mg Psilocybin Administration

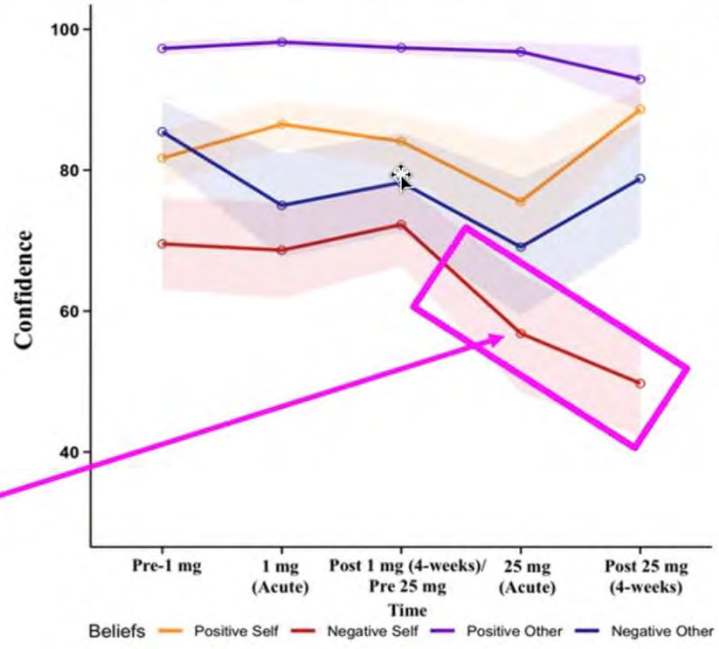
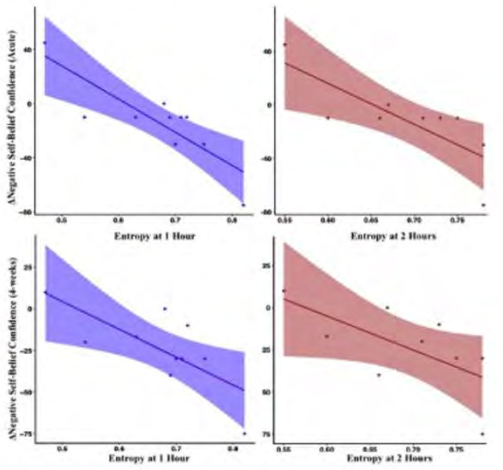


Figure 3.
Association Between Decreases in Negative Self-Belief Confidence (Acute and 4-Week Fo
During the 25 mg Psilocybin Session



Rick Zeifman & Meg Spriggs
Zeifman et al., in prep
Lyons et al. in prep

Higher acute EEG LZC was correlating with decreased confidence in negative beliefs.

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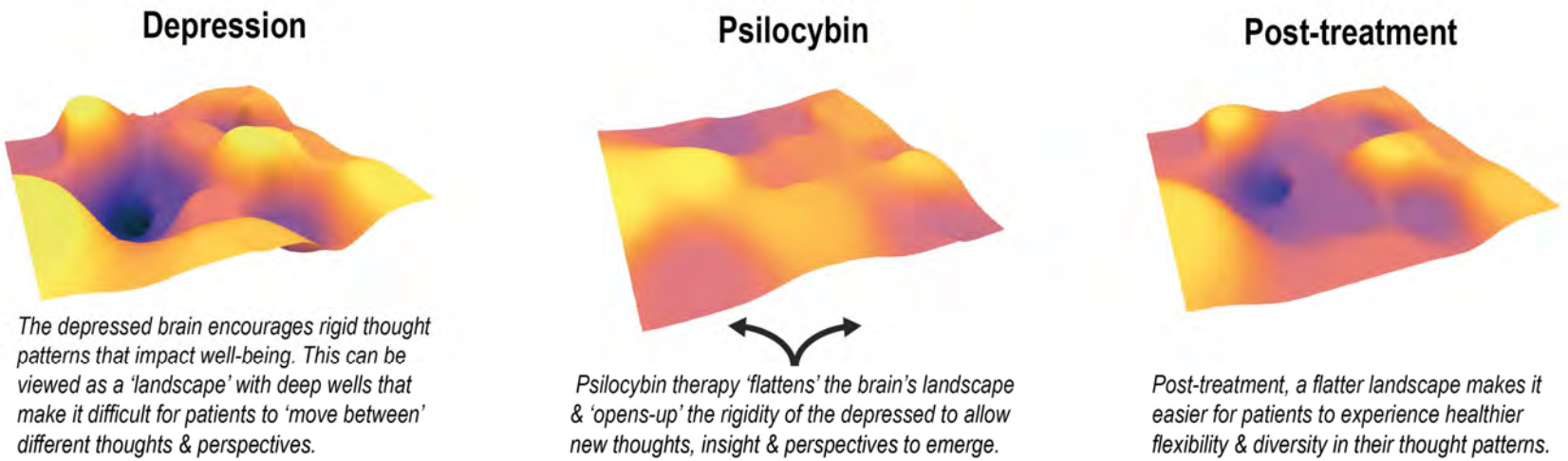
Psilocybin reduces modularity → increases cortical connectivity in depression



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 Giribaldi[3], James D. Sexton[3], Matthew B. Wall[4,5,6], David Erritzoe[3], Leor Roseman[3], David Nutt[3] and Robin Carhart-Harris[3,7]

April 2022

A VERY VERY ABRIDGED TIMELINE OF

Psychedelics as Pharmaceutical Products

1912 — MDMA Patents Filed (Merck)

1920 — Mescaline marketed (Merck)

1930s - 1966 — Lambarène (Ibogaine)

1930s — Panpeytol (Mescaline)

1930s — Le Peyotyl R.D. (Mescaline)

1946 — Delysid (LSD) marketed (Sandoz, A Novartis Division)

1949-57 — SKF #5 (MDA) (SK&F, gsk)

1952 — Sernyl (PCP) patented (Parke-Davis, Pfizer)

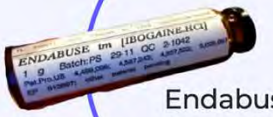
1960 — Amphedoxamine (MDA) (SK&F, gsk)

1960 — Indocybin (Psilocybin) (Sandoz, A Novartis Division)

1960s — Monase (α-Ethyltryptamine) (Upjohn)

1960s — Indopan (α-Methyltryptamine)

1985 — Endabase (Ibogaine) Howard Lotsof



1990s — Erox (2C-B) Drittewelle

2012-2020 — Belviq (Lorcaserin) (Arena Pharmaceuticals, Eisai)

2019 — Spravato (S-Ketamine) (Janssen, Johnson & Johnson)

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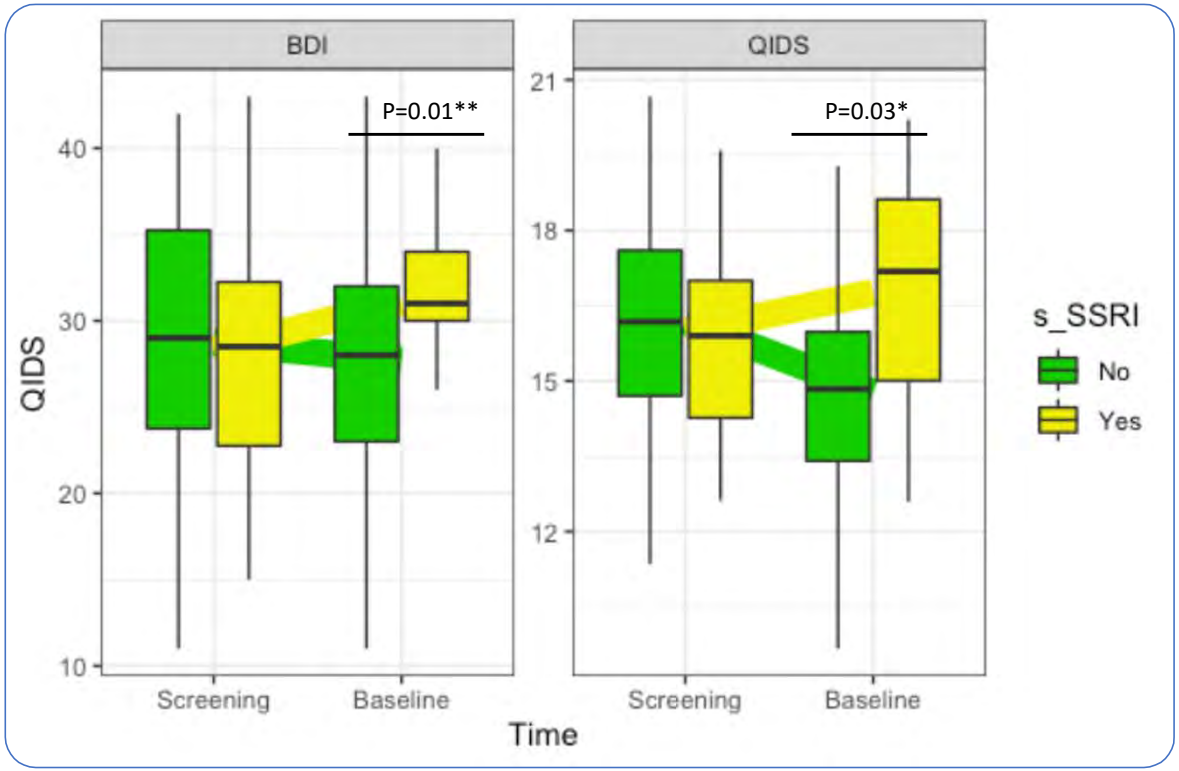
Changes in depression from screening to baseline



We do not know when exactly they discontinued after screening (minimum for 2 weeks before trial start) but this hints to an effect of discontinuation.

- Linear mixed modelling revealed that QIDS (P=0.03) and BDI (P=0.01) scores arose from screening to baseline in discontinuers, suggesting a negative effect of discontinuation before the start of the trial.
- A regression analysis using depression scores at baseline as target and discontinuation as predictor showed a trend for scales to exhibit higher baseline scores for discontinuers (*Graph not shown*)
- QIDS difference=2.00, SE=1.09, p=0.072; HAMD difference=1.99, SE=0.75, p=0.010; MADRS difference=2.25, SE=1.24, p=0.076; BDI difference=3.41, SE=1.96, p=0.052.

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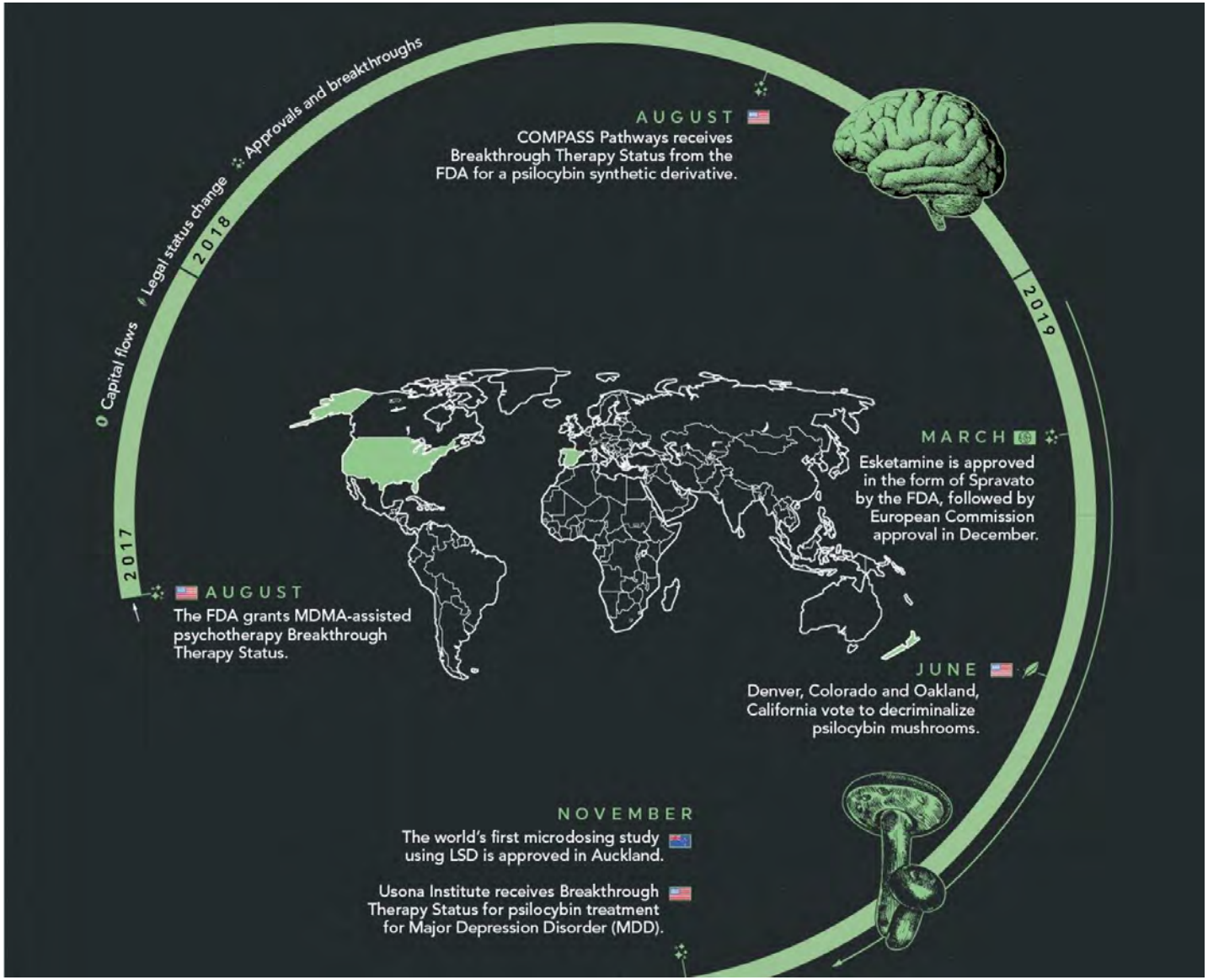
Psychedelic history - 2nd era (renaissance)



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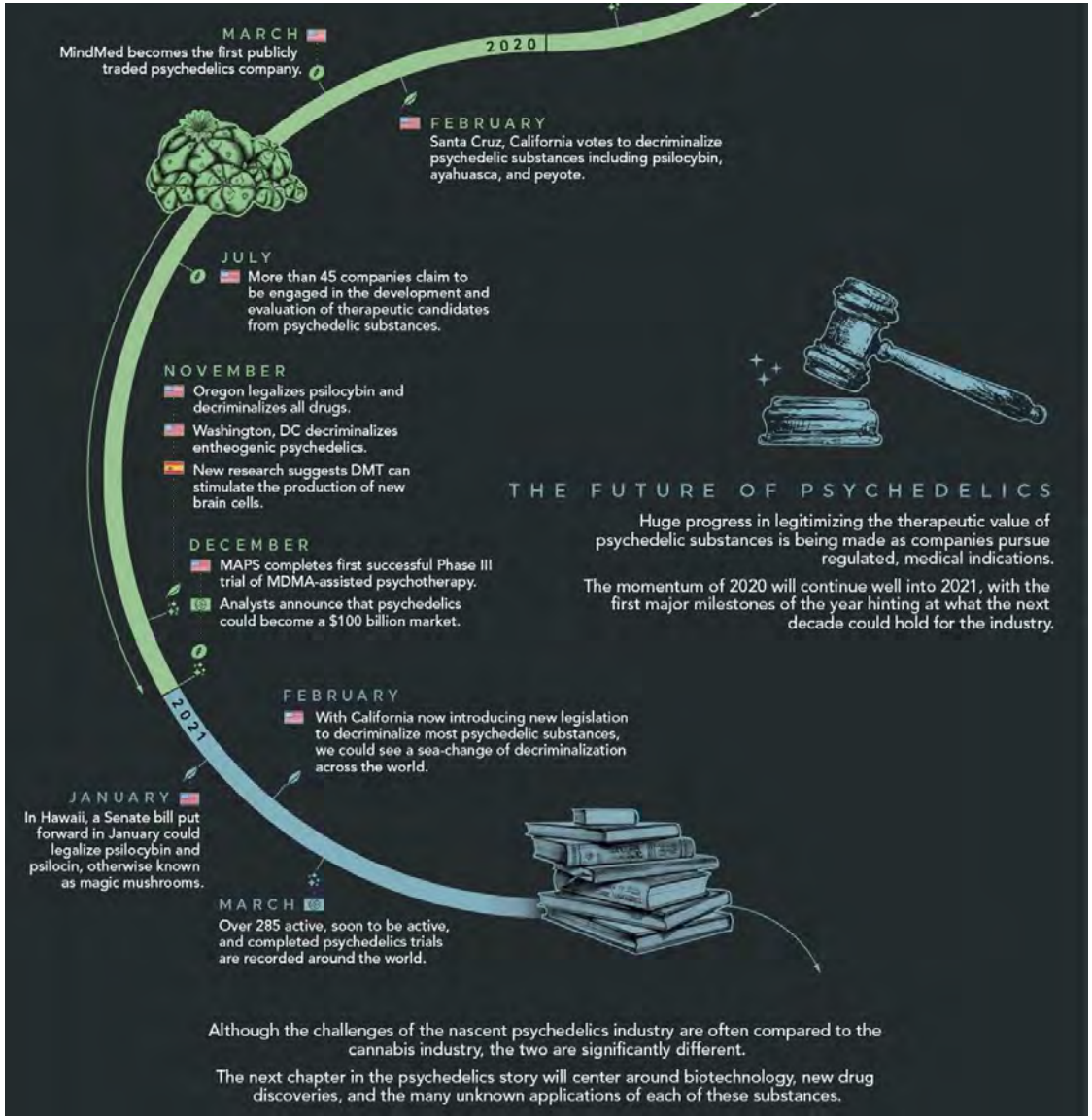
Psychedelic history
2nd era up to current



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