Advancing preclinical models to accelerate the discovery of novel psychedelic therapeutics

Transpharmation
Science that translates into results

Dr Jack Prenderville
Neuroscience Ireland Meeting
10th September 2021

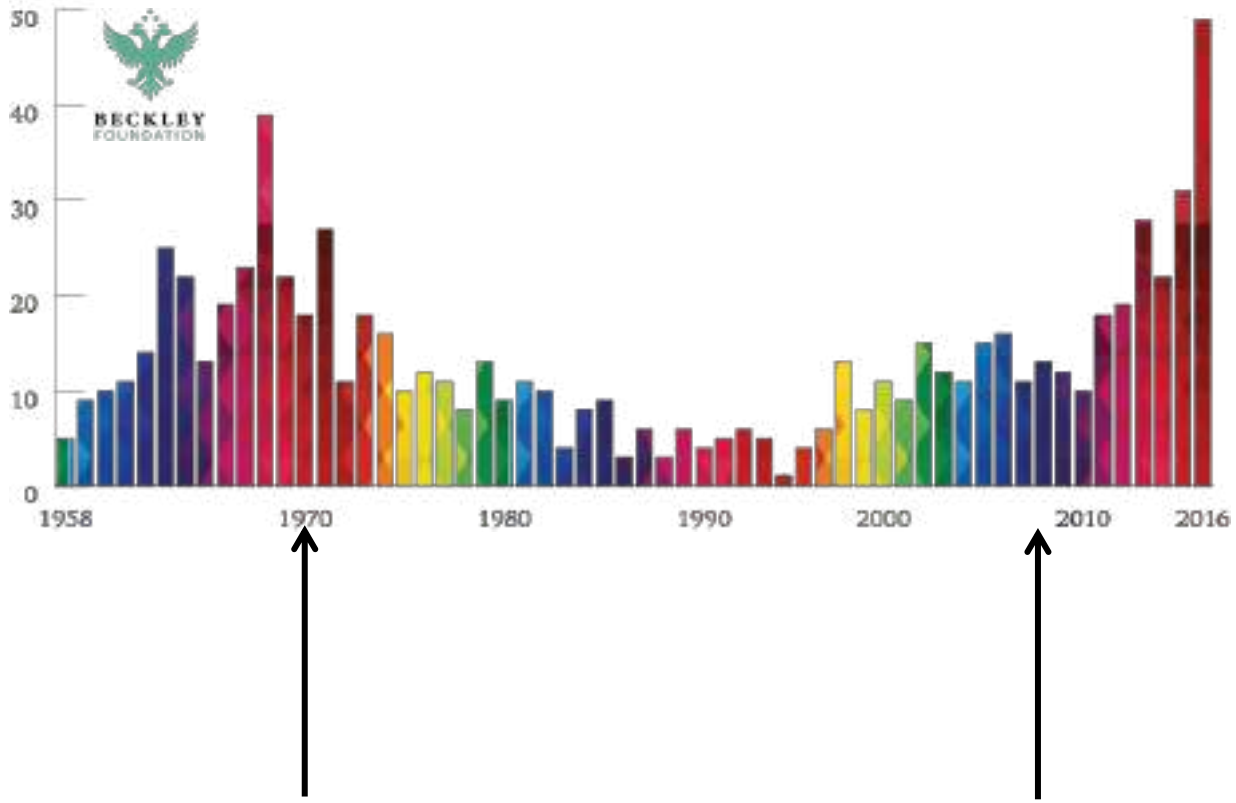
The oldest and least understood psychopharmacological agent

Psychedelics are powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes (Nichols, 2016)

"...was seized by a peculiar sensation of vertigo and restlessness... In a dreamlike state... With my eyes closed, fantastic pictures of extraordinary plasticity and intensive colour seemed to surge towards me."
Albert Hofmann, on his accidental exposure to LSD, 1943

"I lost all control of time: space and time became more and more disorganised and I was overcome with fears that I was going crazy... Occasionally I felt as being outside my body. I thought I had died. My 'ego' was suspended somewhere in space and I saw my body lying dead on the sofa."
Albert Hofmann, on his deliberate exposure to LSD, 1943

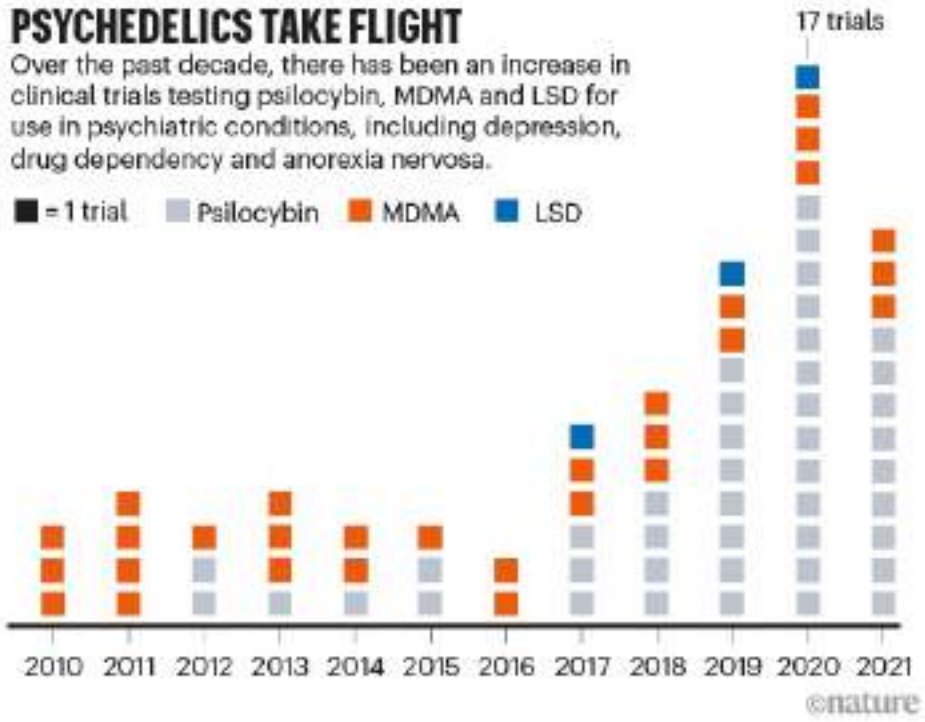
Number of scientific articles published about psilocybin



USA passes Controlled Substances Act
Psychedelic drugs - Schedule 1
(most restrictive category)

Therapeutic effect of psychedelics
End-of-life anxiety

Psychedelics in the clinic



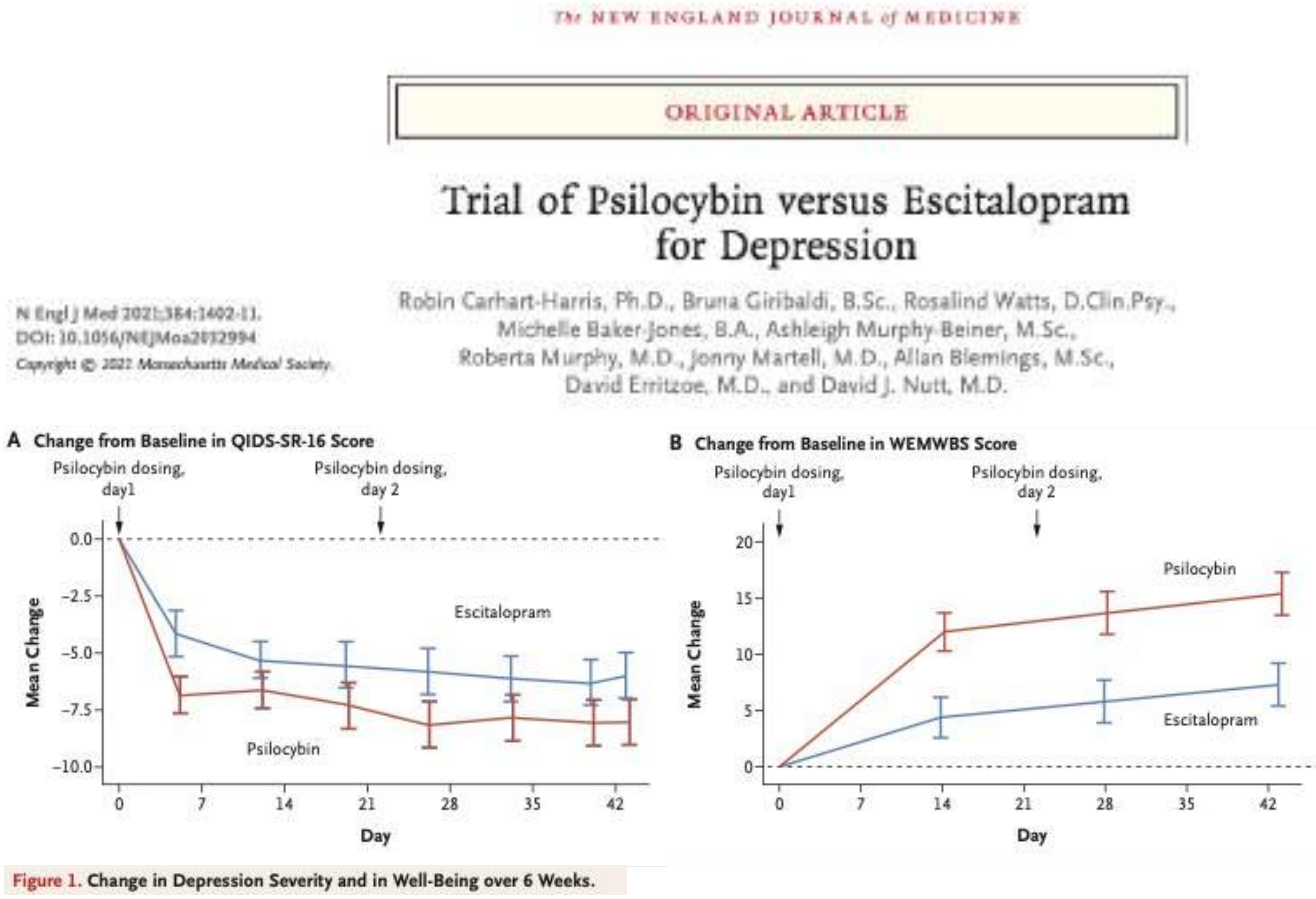
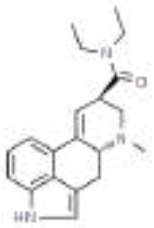


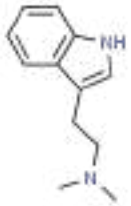
Figure 1. Change in Depression Severity and in Well-Being over 6 Weeks.

Psychedelics (classic serotonergic 'hallucinogens')

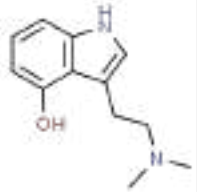
Agonist or partial agonist



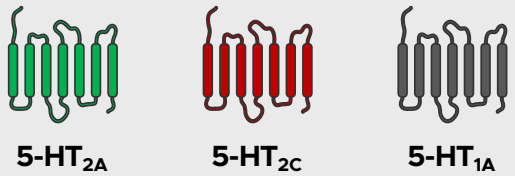
LSD

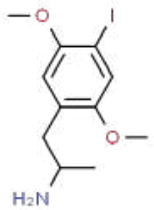


DMT



Psilocin
(Psilocybin)





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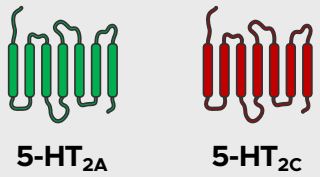
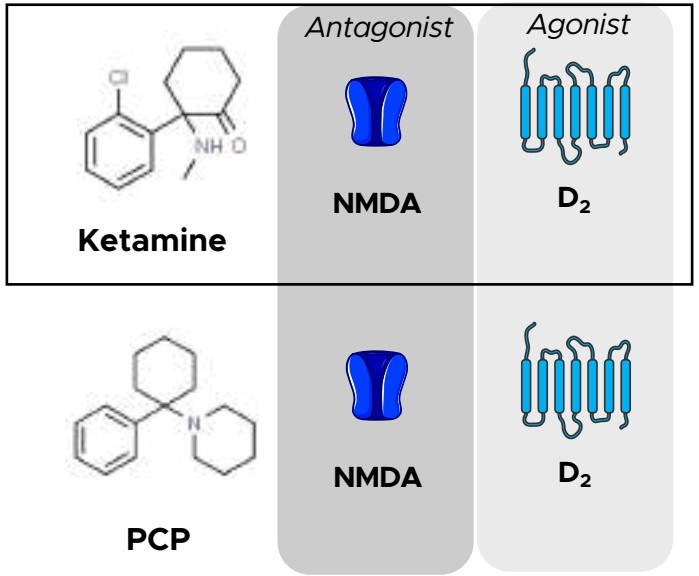


Dissociatives



How can preclinical models support (psychedelic) discovery?

I. Target engagement

II. Preclinical efficacy testing

III. Safety pharmacology

IV. Mechanism of action / biomarkers

5HT-2A receptor target engagement – Head Twitch Response

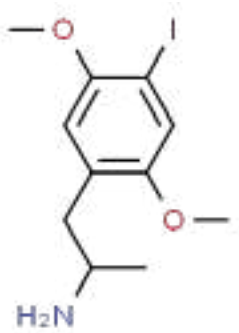
Science 8 September 1956

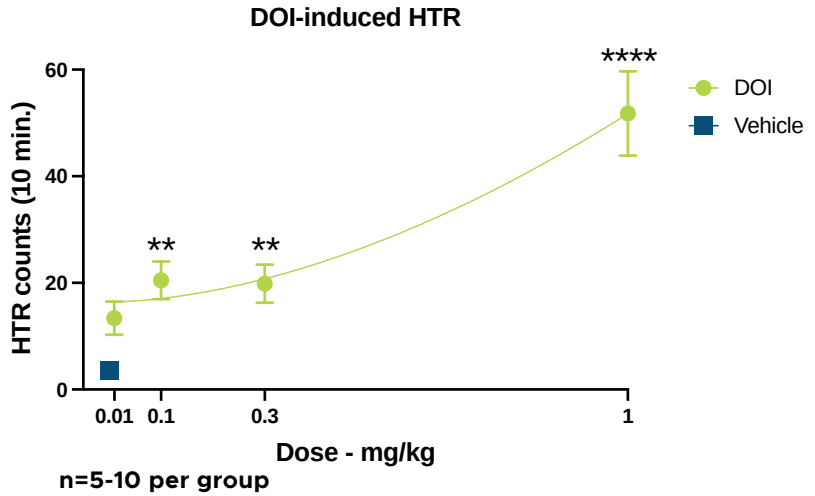
"Permanent" Alteration of Behavior in Mice by Chemical and Psychological Means

Doris L. Keller
Wayne W. Umbreit
Merck Institute for Therapeutic Research, Rahway, New Jersey

The response consists of a rapid and violent head shaking when any area about the back of the head is touched very lightly with a small stick or pencil point. The head-twitch response does not occur in normal mice, and with a little experience the response is easy to detect. It is only rarely that one is uncertain whether a particular animal possesses the head twitch or not, and

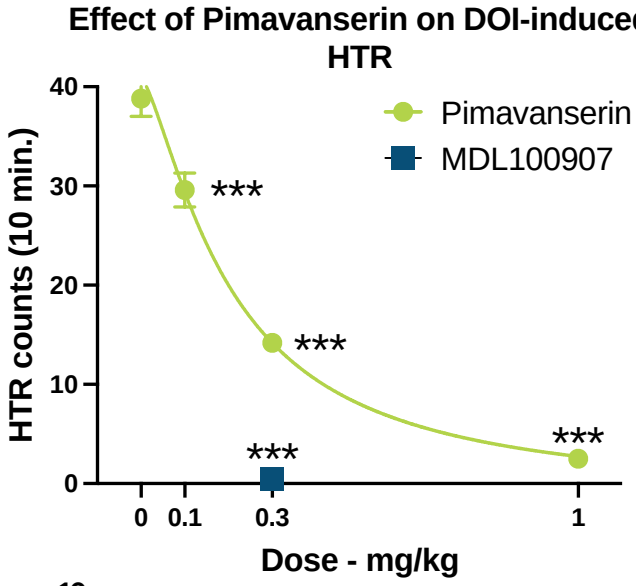
DOI



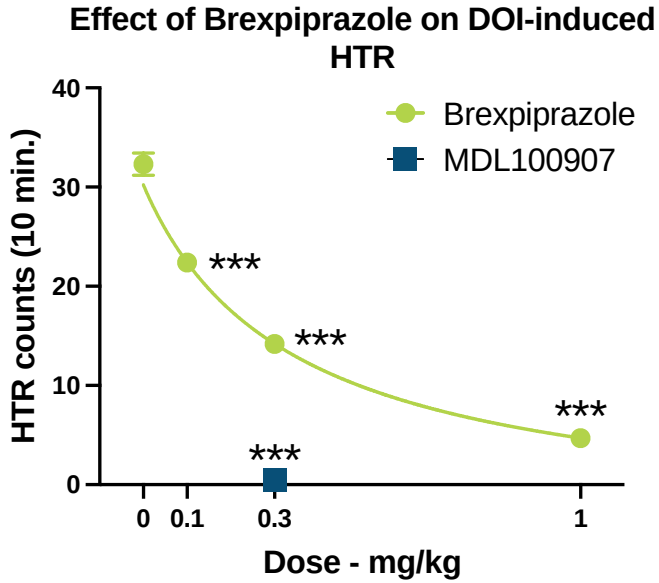


n=5-10 per group

DOI-induced HTR: 5-HT$_{2A}$ receptor antagonists

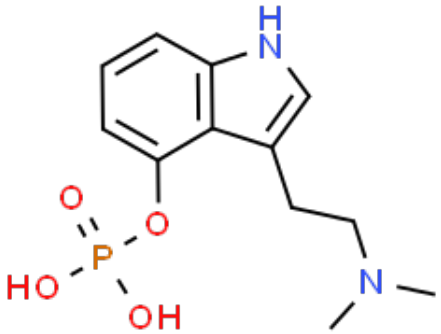


n=10 per group

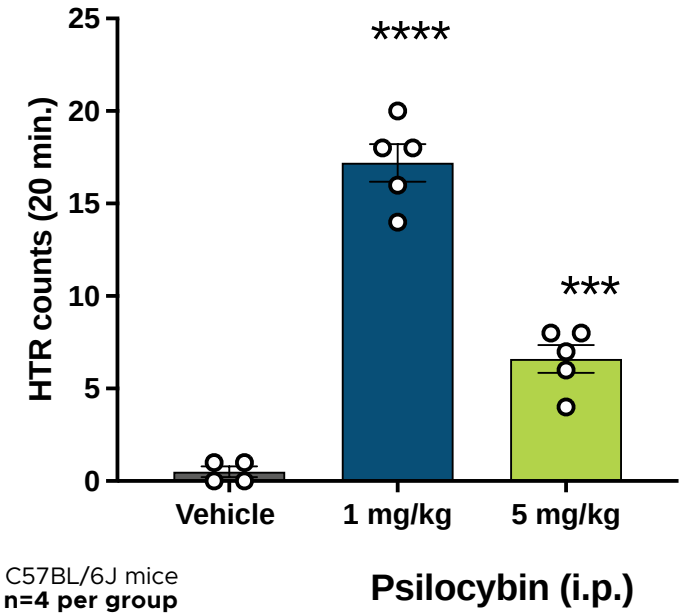


Target engagement - HTR

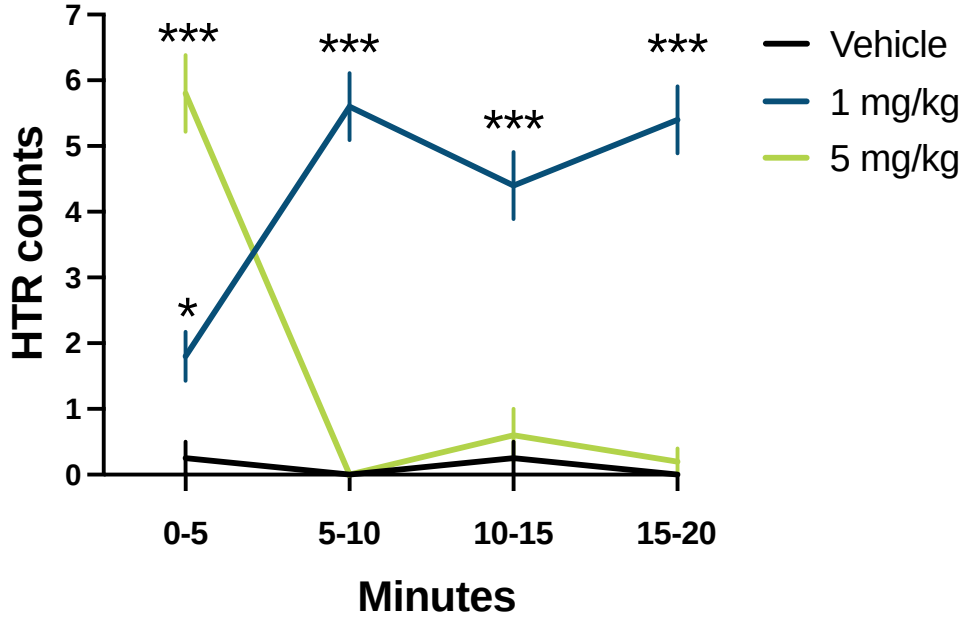
Psilocybin



Psilocybin-induced HTR



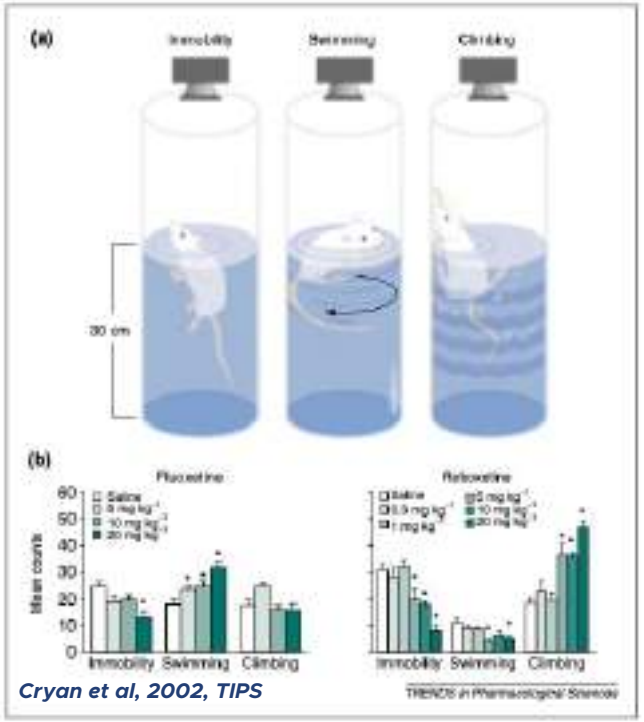
C57BL/6J mice
n=4 per group



* Significant effect compared to Vehicle. One-way ANOVA or one-way repeated measures ANOVA with Fishers LSD.

Preclinical Efficacy testing - Depression

The forced swim test (FST): monoaminergic antidepressants



Cryan et al, 2002, TIPS

Drug	Mechanism of action	Effect on FST immobility (rat)
Fluoxetine	SSRI	↓
Sertraline	SSRI	↓
Paroxetine	SSRI	↓
Desipramine	NRI	↓
Maprotiline	NRI	↓
Reboxetine	NRI	↓
Bupropion	NDRI (?)	↓
Venlafaxine	SNRI	↓
Milnacipran	SNRI	↓
Duloxetine	SNRI	↓
Mianserin	NaSSA (?)	↓

Adapted from Cryan et al, 2005, Neurosci. Biobehav. Rev.

The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior

Kathryn G. Commons,* Aram B. Cholanians, Jessica A. Babb, and Daniel G. Ehlinger

Immobility in the forced swim test is adaptive and does not reflect depression

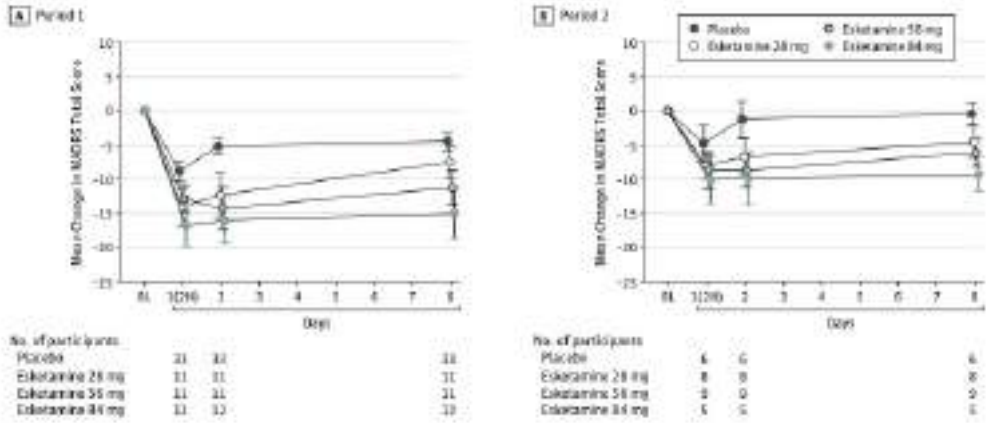
Marc L. Molendijk[a,c,1], E. Ronald de Kloet[b,1]

Depression researchers rethink mouse swim test

Too Depressed to Swim or Too Afraid to Stop? A Reinterpretation of the Forced Swim Test as a Measure of Anxiety-Like Behavior

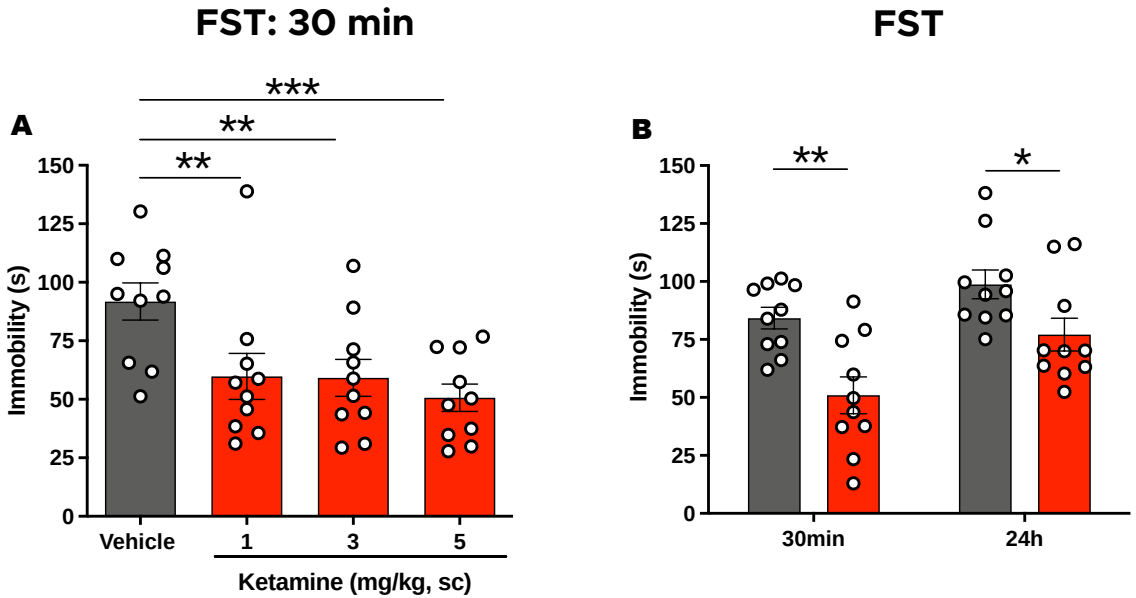
Novel antidepressants and the FST: (es)ketamine

Daly et al, 2018, JAMA Psychiatry



The FST: glutamatergic antidepressants - ketamine

(McDonnell et al, 2021, Frontiers in Psychiatry)

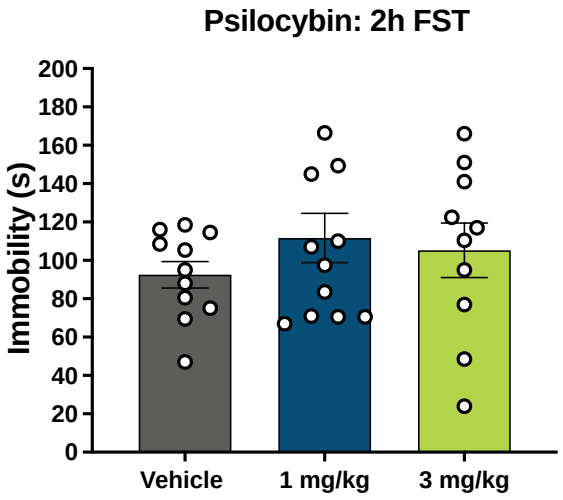


Wistar K yoto rats
n=9-10 per group

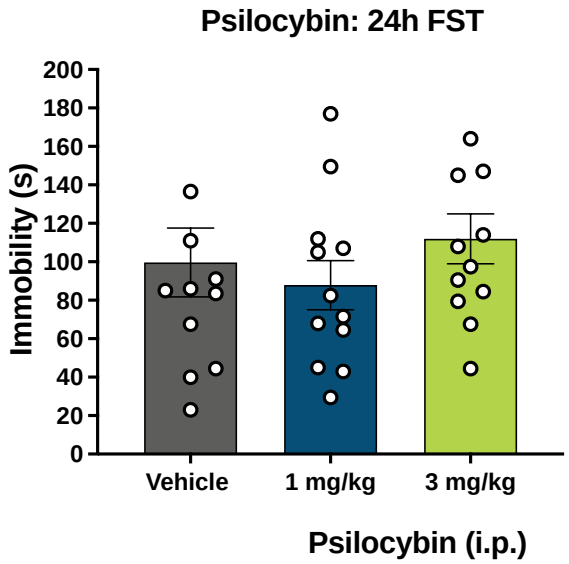
* Significant effect compared to Vehicle. One-way ANOVA with Fishers LSD.

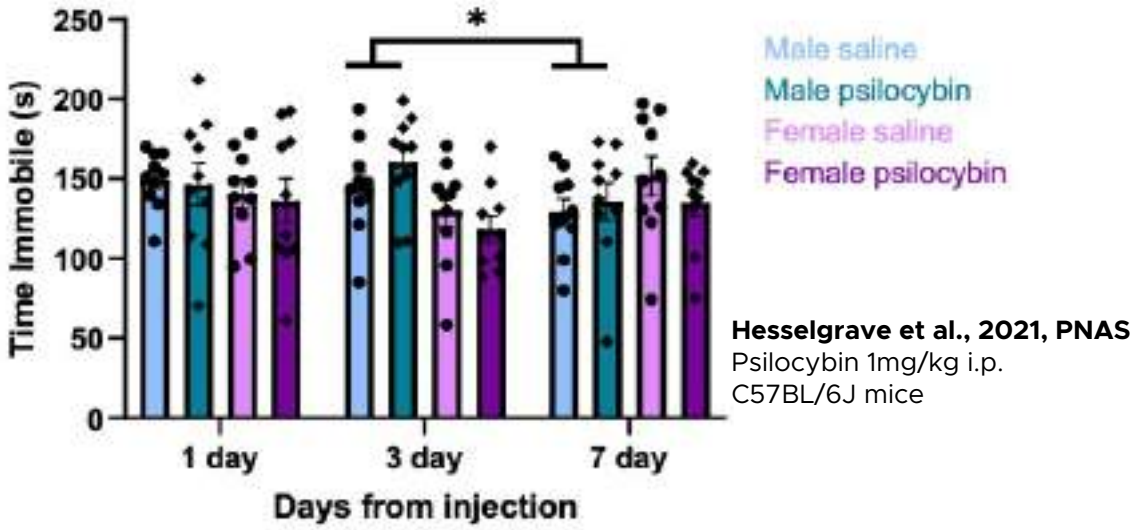
Key question: is the FST a suitable tool for psychedelic research?

Psilocybin and the forced swim test



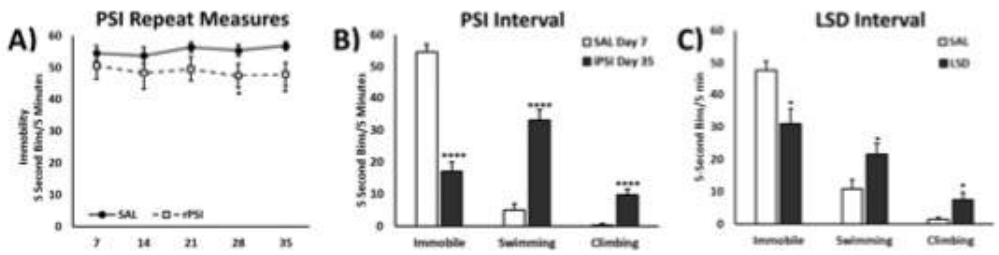
C57BL/6J mice
n=10-12 per group

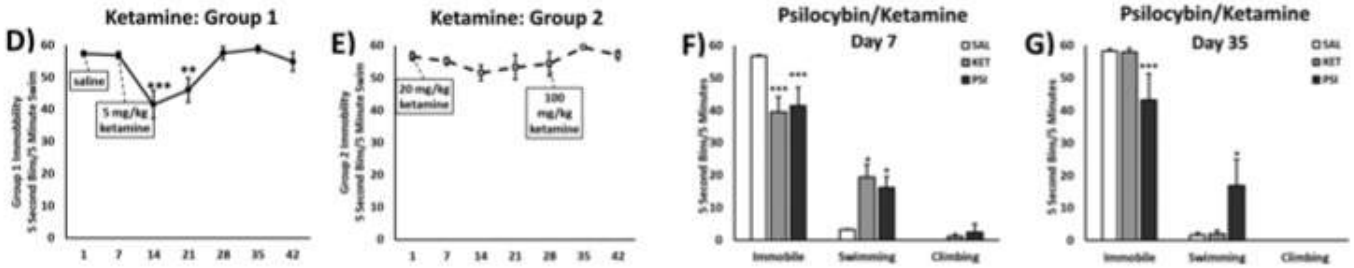




Hesselgrave et al., 2021, PNAS
Psilocybin 1mg/kg i.p.
C57BL/6J mice

Psilocybin (and LSD) produce persistent antidepressant-like effects in the FST





Hibicke et al., 2020, ACS Chem. Neuro.
Psilocybin 1mg/kg i.p.; LSD 0.15mg/kg i.p.
WKY rats

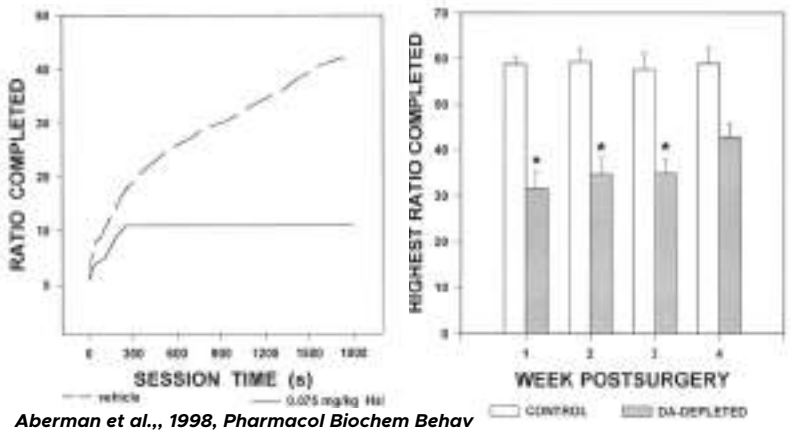
Measuring rodent motivation: the progressive ratio task

Anhedonia: Inability to feel pleasure in normally pleasurable activities

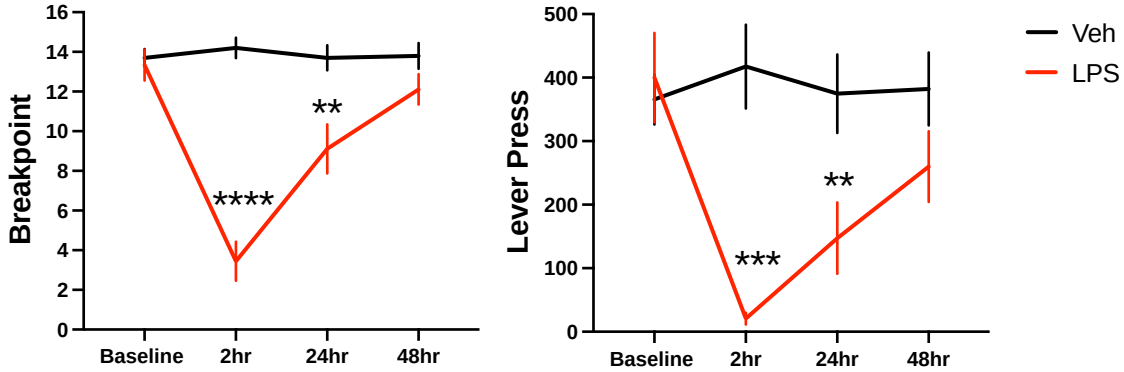
'Markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day' (symptom of depression as in DSM-5)

Motivational anhedonia: loss of interest or absence of anticipatory pleasure
Consummatory anhedonia: loss of pleasure in response to previously rewarding stimuli

Rat progressive ratio (PR) task



Aberman et al.,, 1998, Pharmacol Biochem Behav



* Significant effect compared to baseline. One-way repeated measures ANOVA with Fishers LSD post-hoc (n=9-10 per group)

- Responses for successive reinforcers (sucrose pellet) increases according to the progression: 2, 4, 6, 9, 12, 15, 20, etc.
- Endpoints: **Lever Press** and **Breakpoint**

Micro doses of psilocybin enhance motivation

frontiers in Pharmacology

ORIGINAL RESEARCH

Low Doses of Psilocybin and Ketamine Enhance Motivation and Attention in Poor Performing Rats: Evidence for an Antidepressant Property

Guy A. Higgins[1,2*], Nicole K. Carroll[1], Matt Brown[1], Cam MacMillan[1], Leo B. Silenieks[1], Sandy Thevarkunnel[1], Julia Ulhaleva[1], Lilia Magomedova[1], Ines DeLannoy[1,3] and Edward M. Sellers[2,3]

[1]Intervivo Solutions Inc., Angus, ON, Canada, [2]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada, [3]Intervivo Solutions Inc., Mississauga, ON, Canada, [4]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [5]3-D Global Partners Inc., Toronto, ON, Canada

OPEN ACCESS

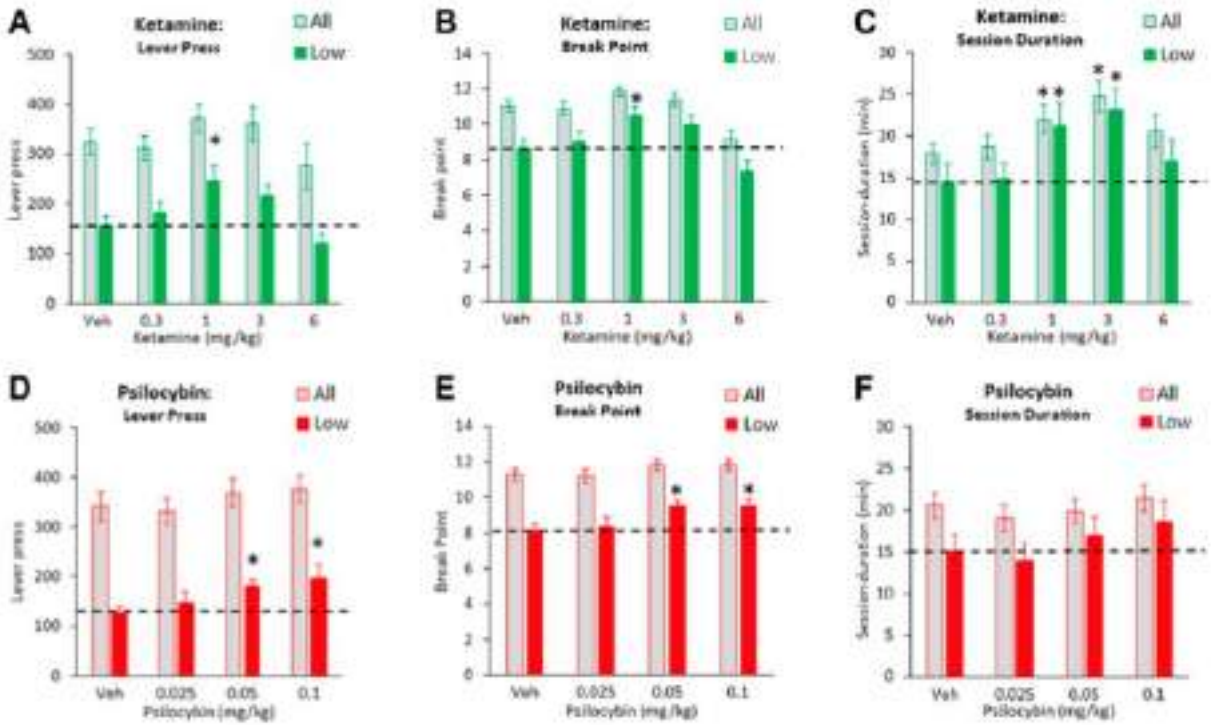
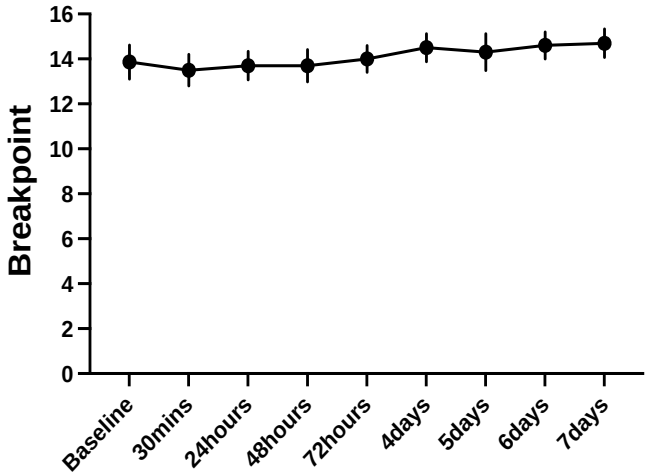
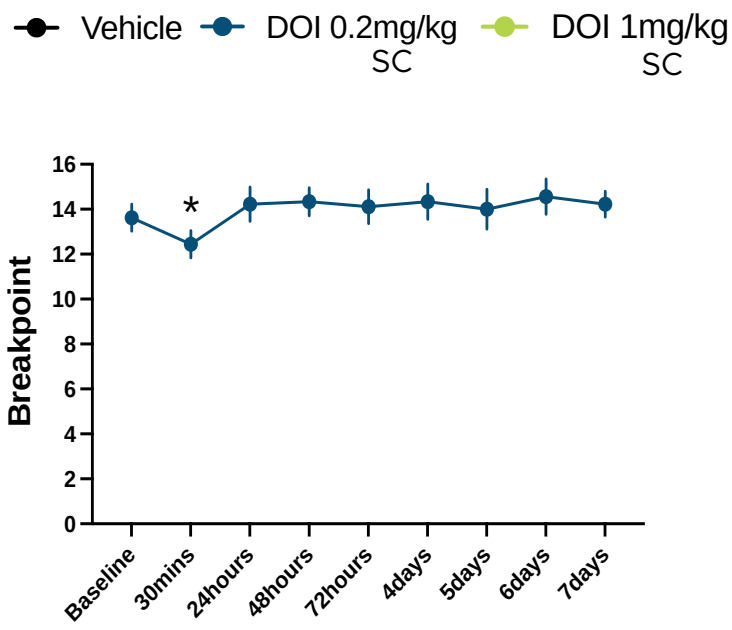


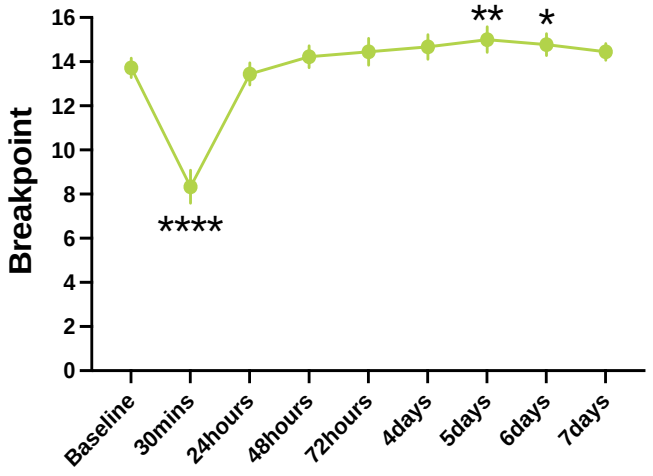
FIGURE 2 | Characterisation of ketamine (0.3–6 mg/kg IP) and psilocybin (0.025–0.1 mg/kg SC) on food responding made available under a progressive schedule of reinforcement. Data is presented for both drugs as total number of lever presses recorded during the test session **(A and D)**, final break point **(B and E)**, and total session duration **(C and F)**. Data for each drug is presented both as all test subjects (ketamine: N = 68; psilocybin: N = 72), and subjects characterized as "low performers" based on having the lowest tertile on lever presses/break point based on performance measured over 7 days prior to onset of drug testing (ketamine: N = 23; psilocybin: N = 24). The hashed line is to highlight the level of the "low performer" subgroup following vehicle pretreatment. *$p < 0.05$ vs. vehicle control (Dunnetts test following significant ANOVA).

DOI and motivation

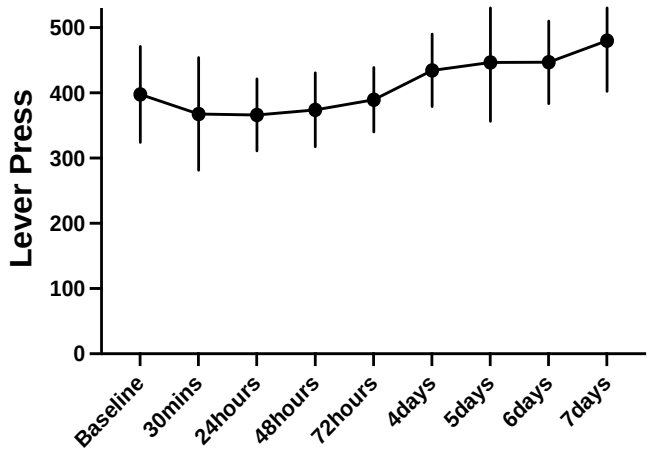
Breakpoint

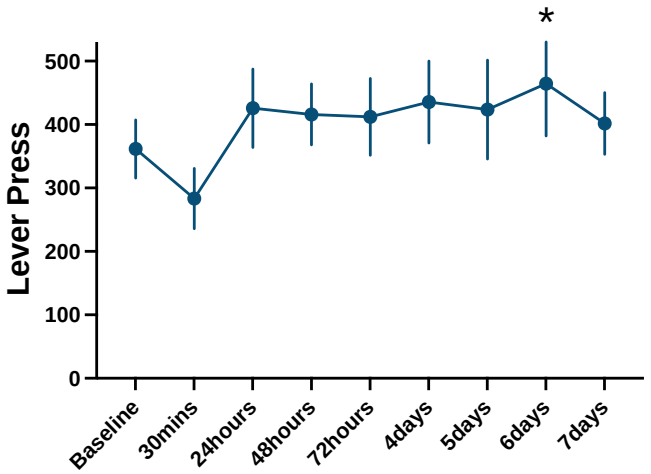


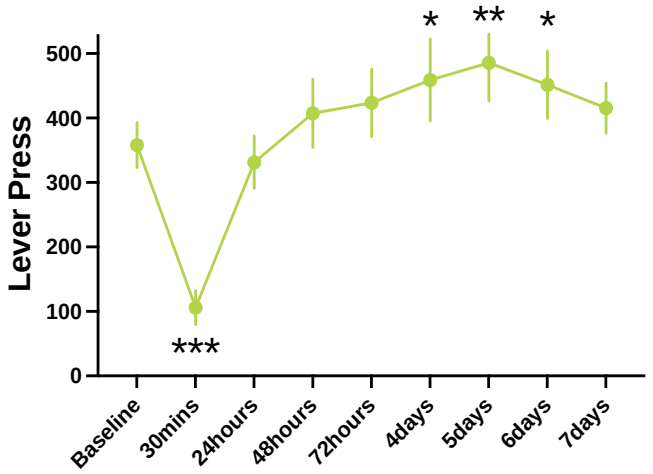




Lever Presses





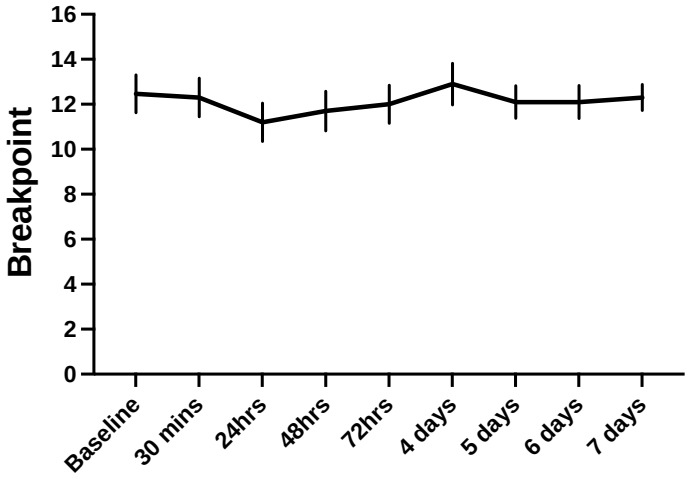


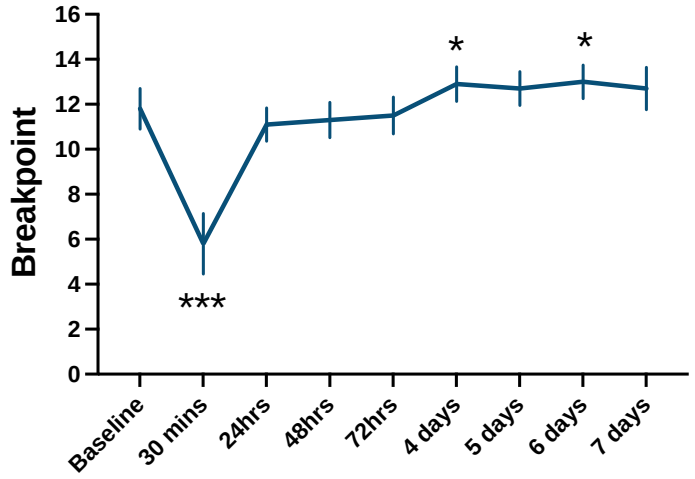
* Significant effect compared to baseline. One-way repeated measures ANOVA with Fishers LSD post-hoc (n=9-10 per group). Drugs administered by subcutaneous (SC) injection.

Psilocybin and motivation

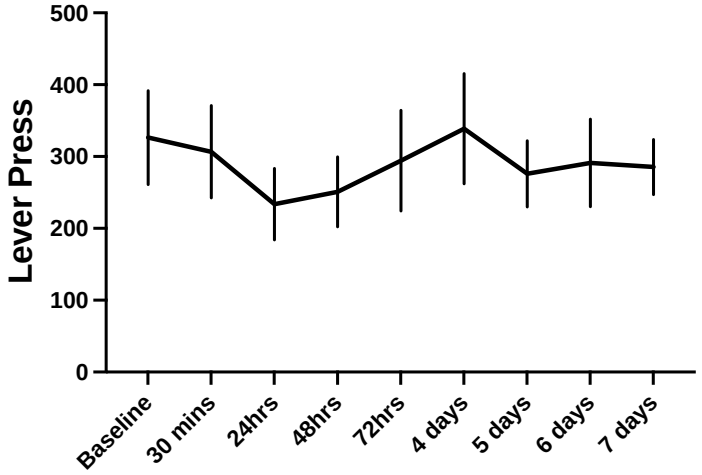
Vehicle | Psilocybin 1mg/kg SC | Psilocybin 3mg/kg SC

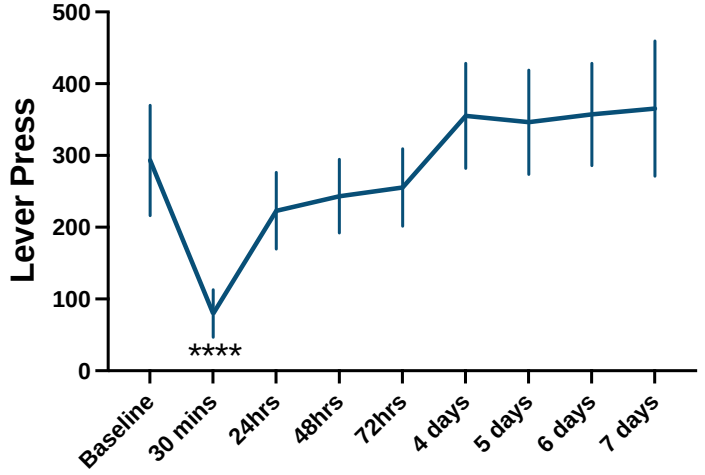
Breakpoint

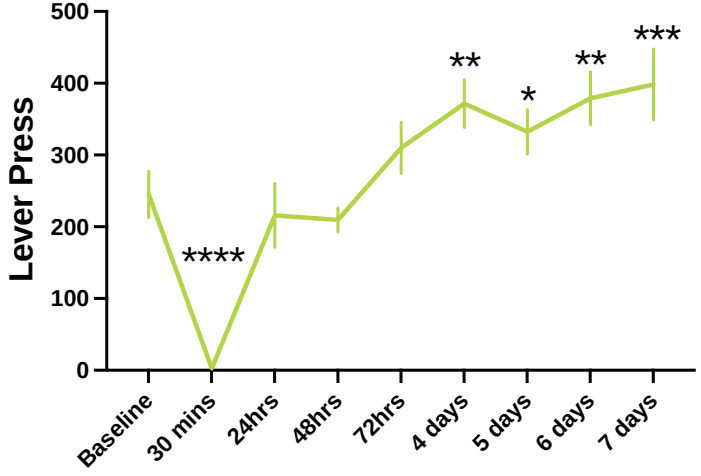




Lever Presses





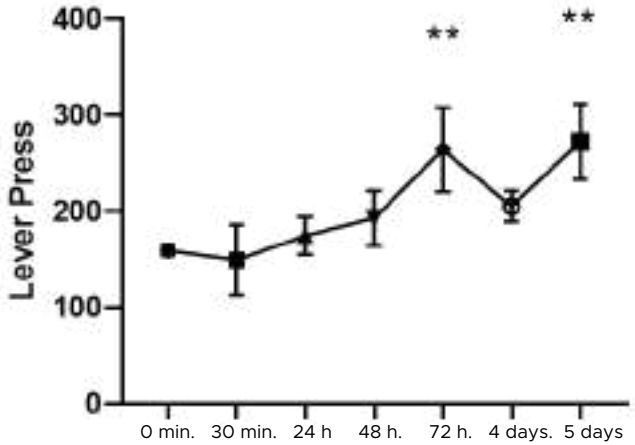


* Significant effect compared to baseline. One-way repeated measures ANOVA with Fishers LSD post-hoc (n=9-10 per group). Drugs administered by subcutaneous (SC) injection.

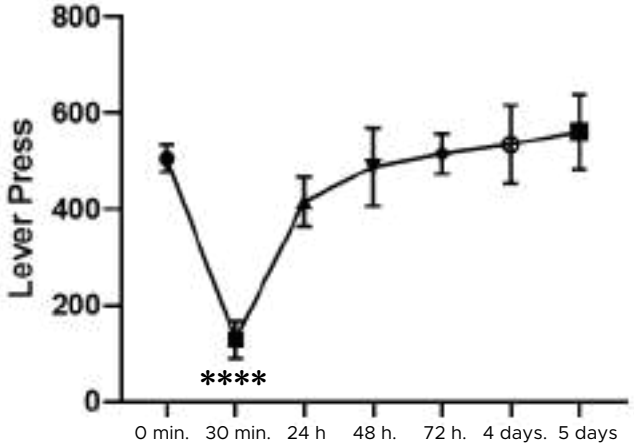
DOI (1mg/kg sc) and motivation

Lever Presses

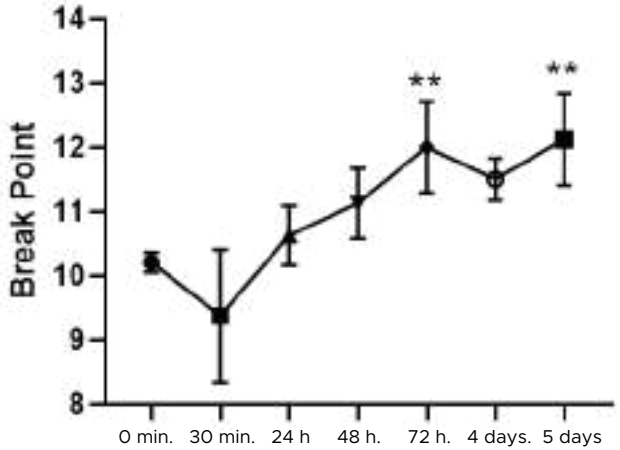
Low responders

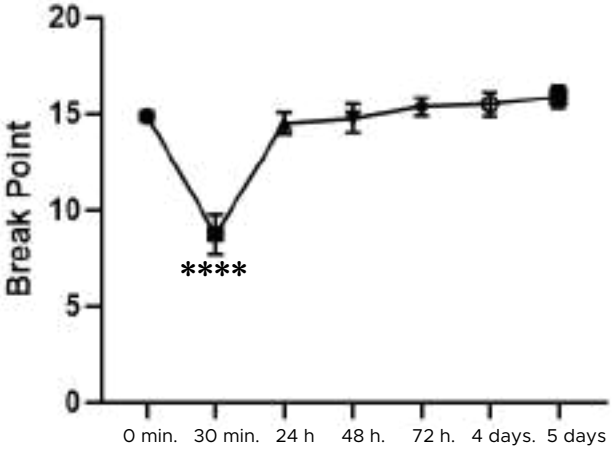


High responders



Breakpoint





* Significant compared to Baseline group. One-way repeated measures ANOVA with Fishers LSD post-hoc (n=8 per group)

"It gave me an inner joy, an open mindedness, a gratefulness, open eyes and an internal sensitivity for the miracles of creation."
Albert Hofmann, on LSD

Acknowledgements

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Kerry Waters

Colleen Taylor

Dr. Neil Upton

Dr. Mark Duxon

Slides 4, 6, 7 contain figures provided by smart.servier.com and chemspider.com