



JOHNS HOPKINS  
M E D I C I N E

# Psychedelics as change agents in addiction and mood disorders

**Society for the Study of Addiction**

2017 Annual Conference

Newcastle upon Tyne

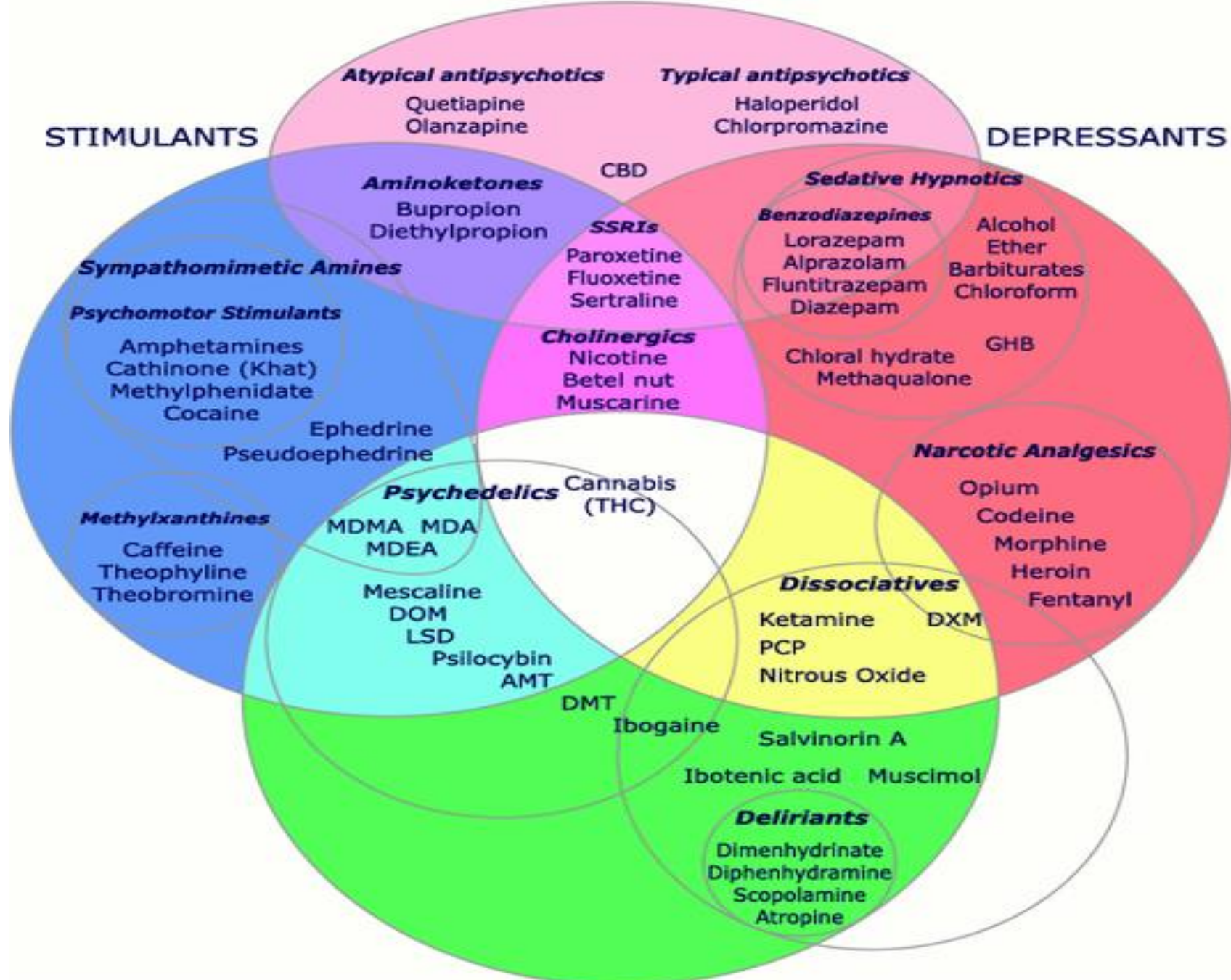
Albert Garcia-Romeu, PhD

November 10, 2017

# ANTIPSYCHOTICS

## STIMULANTS

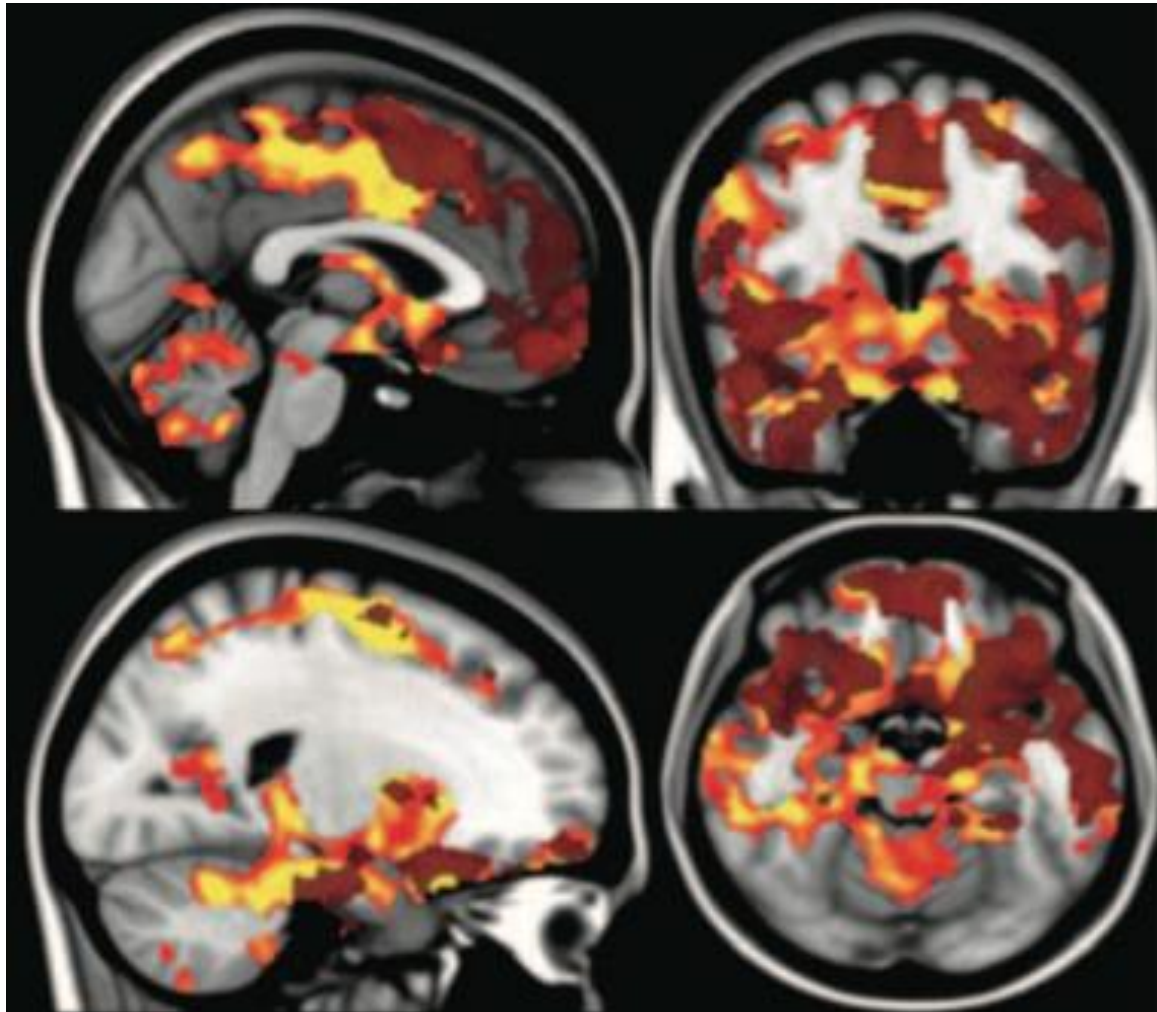
## DEPRESSANTS



## HALLUCINOGENS

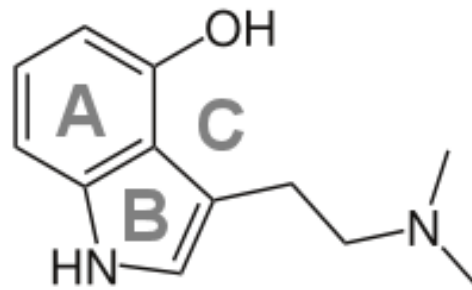
# Psychedelics (Psilocybin, LSD)

★ Primarily serotonergic, acting as agonists at 5-HT<sub>2A</sub> receptor subtypes (among others)

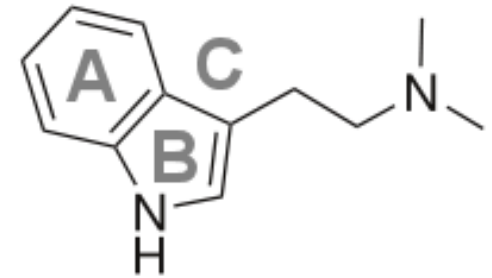


Memory activations under psilocybin

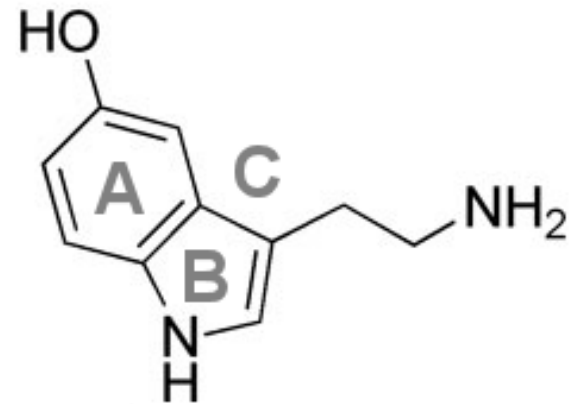
Structural similarities between psychedelics and serotonin



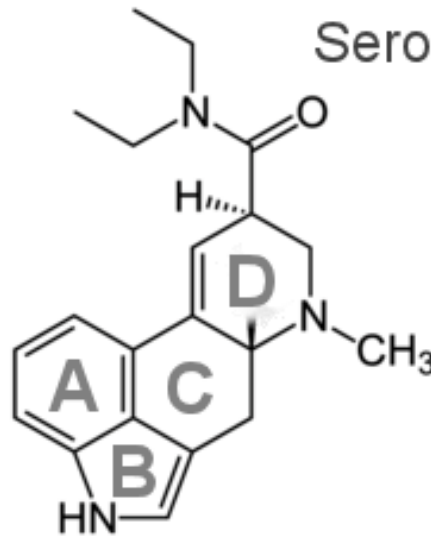
Psilocin



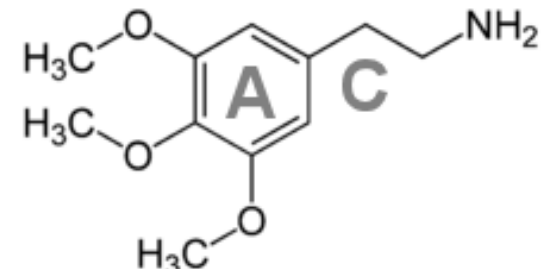
DMT



Serotonin (5-HT)



LSD

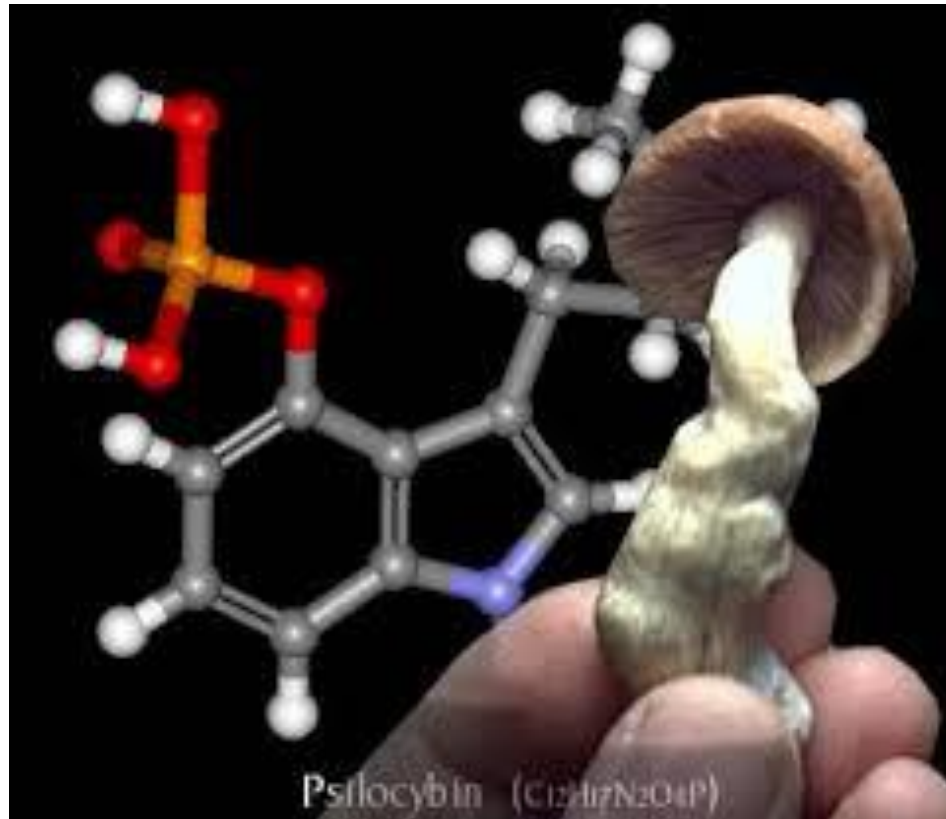


Mescaline



# Psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine)

- Psychoactive agent in over 100 species of mushrooms, most in *Psilocybe* genus



# Psychedelics = Mind manifesting?

“To fathom hell, or soar angelic, take a pinch of psychedelic.”

-Dr. Humphrey Osmond in a letter to Aldous Huxley, (1957)  
From Greek ‘psyche’ for mind, and ‘delos’ for manifest.



Humphry Osmond . . . drug pioneer



# Psychedelics

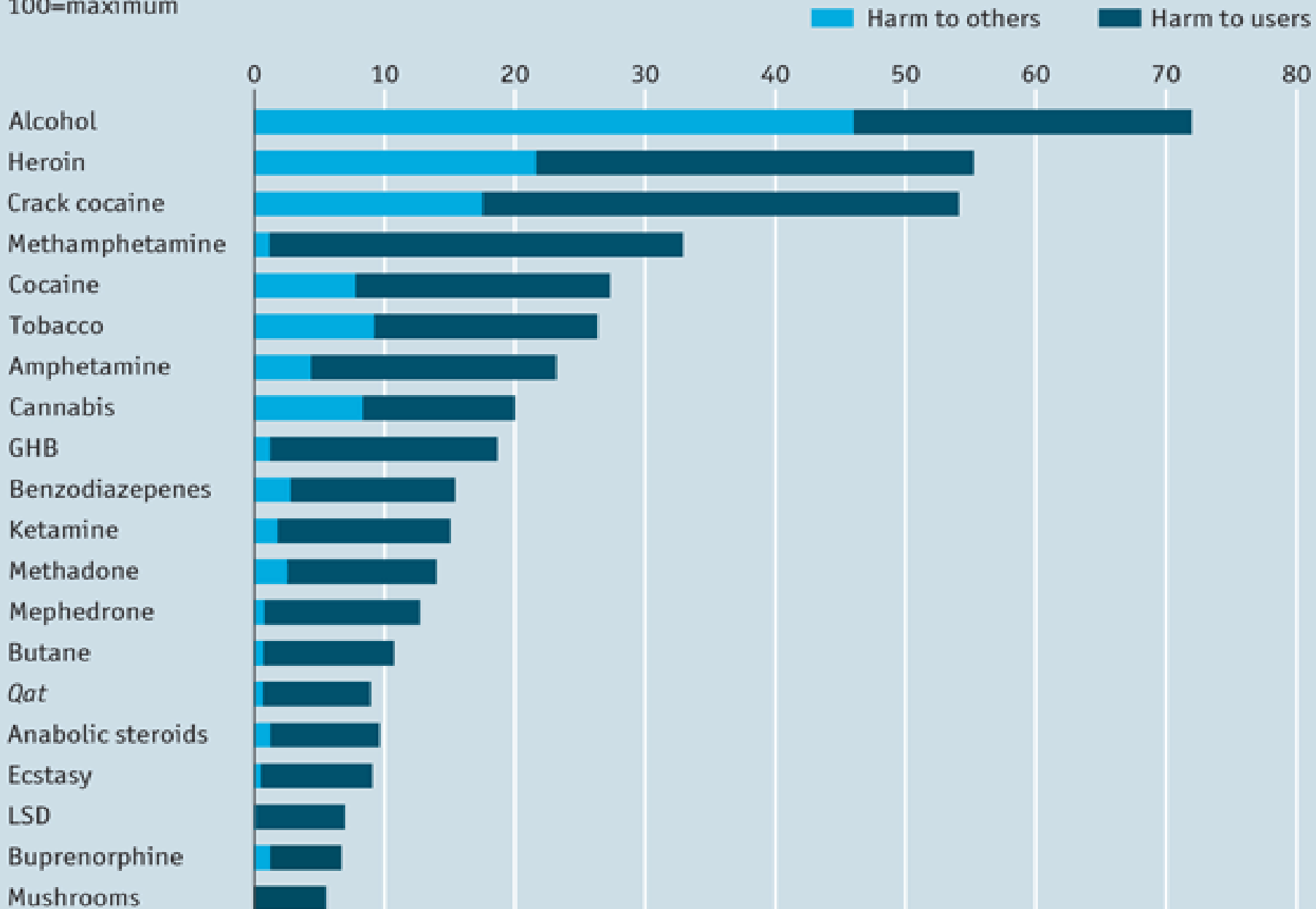
“A psychedelic drug is one which has small likelihood of causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, produces thought, mood, and perceptual changes otherwise rarely experienced except perhaps in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory and acute psychoses.”



- Dr. Lester Grinspoon

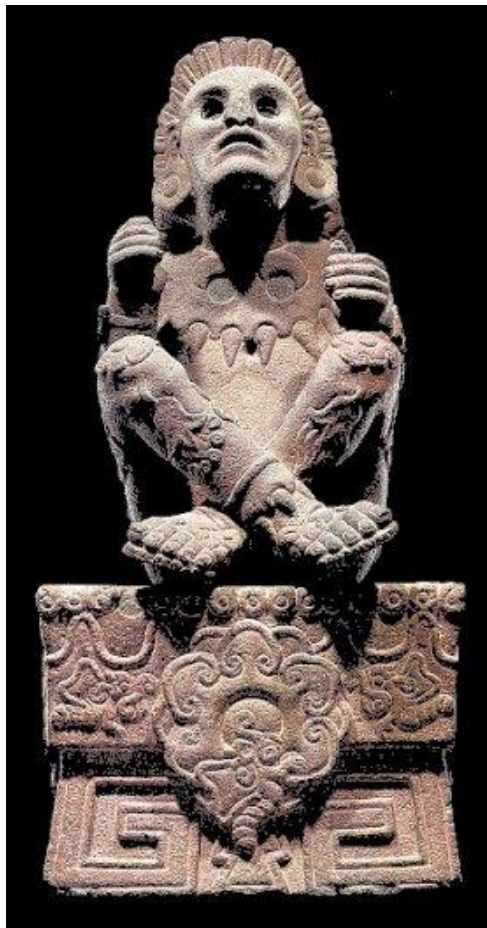
# Harm caused by drugs

100=maximum



Source: "Drug harms in the UK", by David Nutt et al. *The Lancet*





Various Mushroom Stones (approx 1 ft tall - 1000 B.C. to 500 A.D.)  
Images from Plants of the Gods by Schultes & Hofmann











ANNALS OF MEDICINE | FEBRUARY 9, 2015 ISSUE

## THE TRIP TREATMENT

*Research into psychedelics, shut down for decades, is now yielding exciting results.*

BY MICHAEL POLLAN



**O**n an April Monday in 2010, Patrick Mettes, a fifty-four-year-old television news director being treated for a cancer of the bile ducts, read an article on the front page of the *Times* that would change his death. His diagnosis had come three years earlier, shortly after his wife, Lisa, noticed that the whites of his eyes had



AD

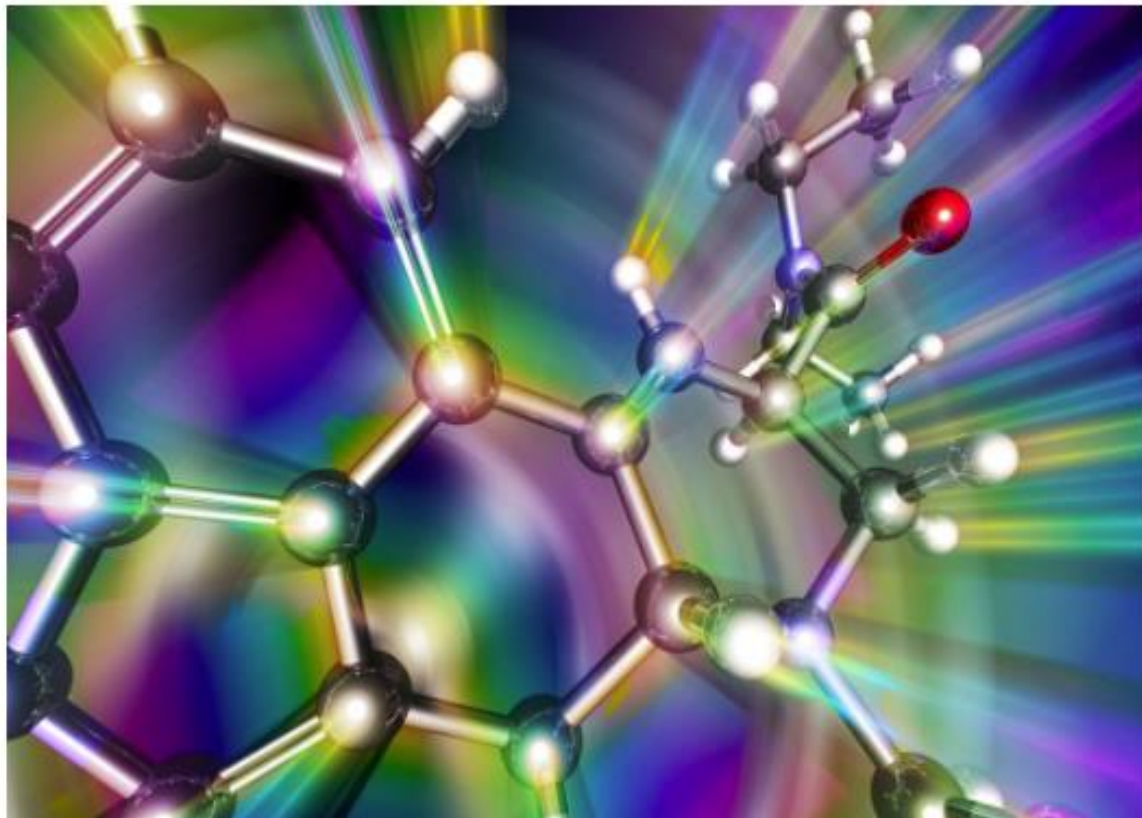
# Do LSD and Magic Mushrooms Have a Place In Medicine?

Alexandra Sifferlin @acsifferlin | May 26, 2015



## Experts say it's hard to do research on the drugs under their current status

LSD and magic mushrooms are illegal for recreational use, but some medical experts see major benefits from the drugs. In a commentary [published in the journal \*The BMJ\*](#) on Tuesday, a London-based psychiatrist argues in favor of legally reclassifying the drugs so that they can more easily be



# Research at Johns Hopkins

- Initial psilocybin study in 36 healthy volunteers (2006)
- 14 month persisting effects of psilocybin (2008)
- Dose effects of psilocybin in 18 healthy volunteers (2011)
- Effects of psilocybin on personality (2011)
- Psilocybin for smoking cessation in 15 smokers (2014)
- Psilocybin for anxiety in 44 cancer patients (2016)
- Psilocybin's effects on spirituality and meditation in 75 healthy volunteers (2017)

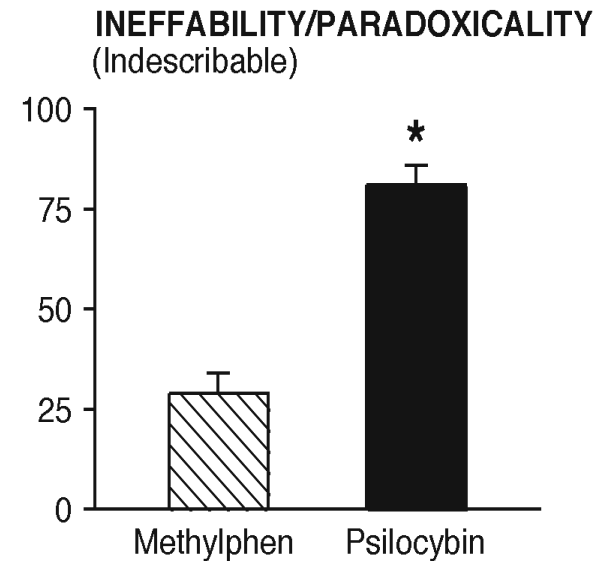
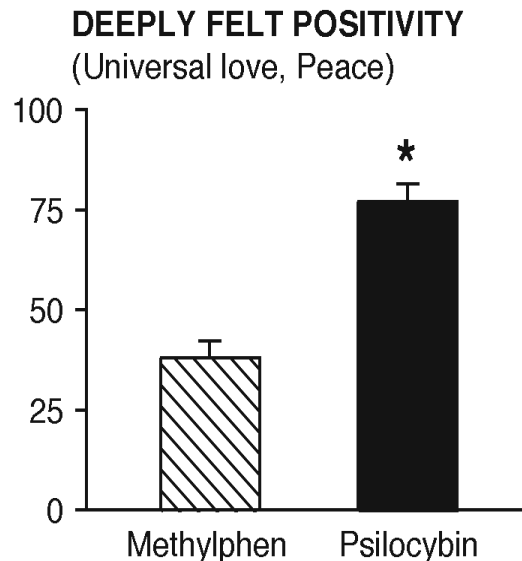
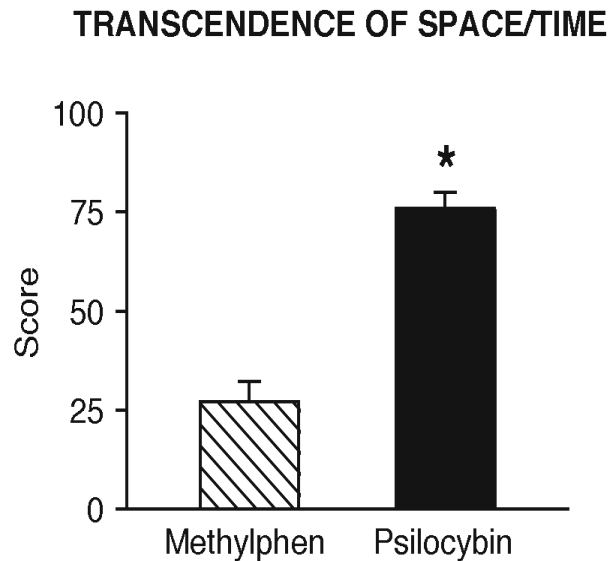
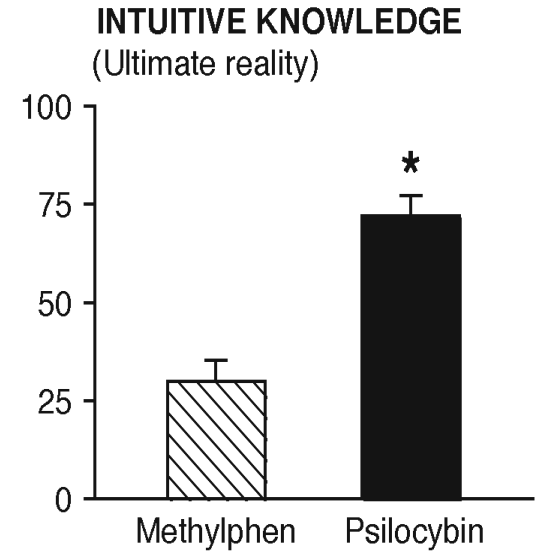
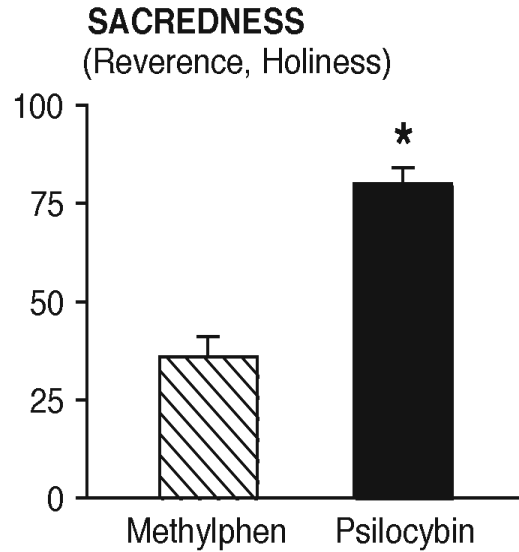
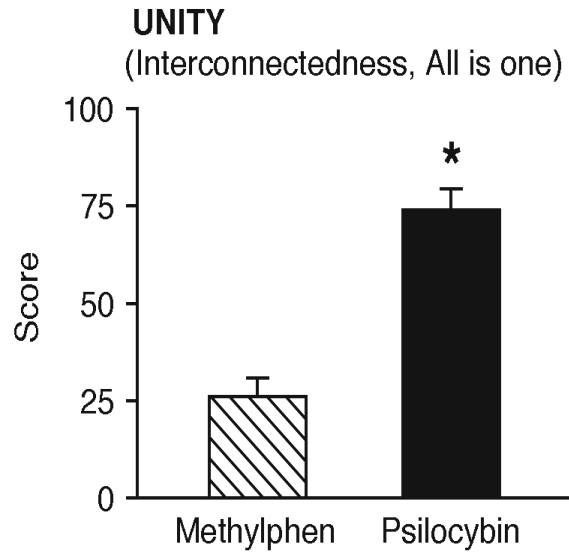


# Drug Sessions

- The 8-hr drug sessions are conducted in a living-room-like environment
- Two monitors are present throughout the session
- Participants asked to:
  - lie on the couch
  - wear eye masks and headphones
  - listen to a program of music
  - focus attention inward
  - trust, let go, be open



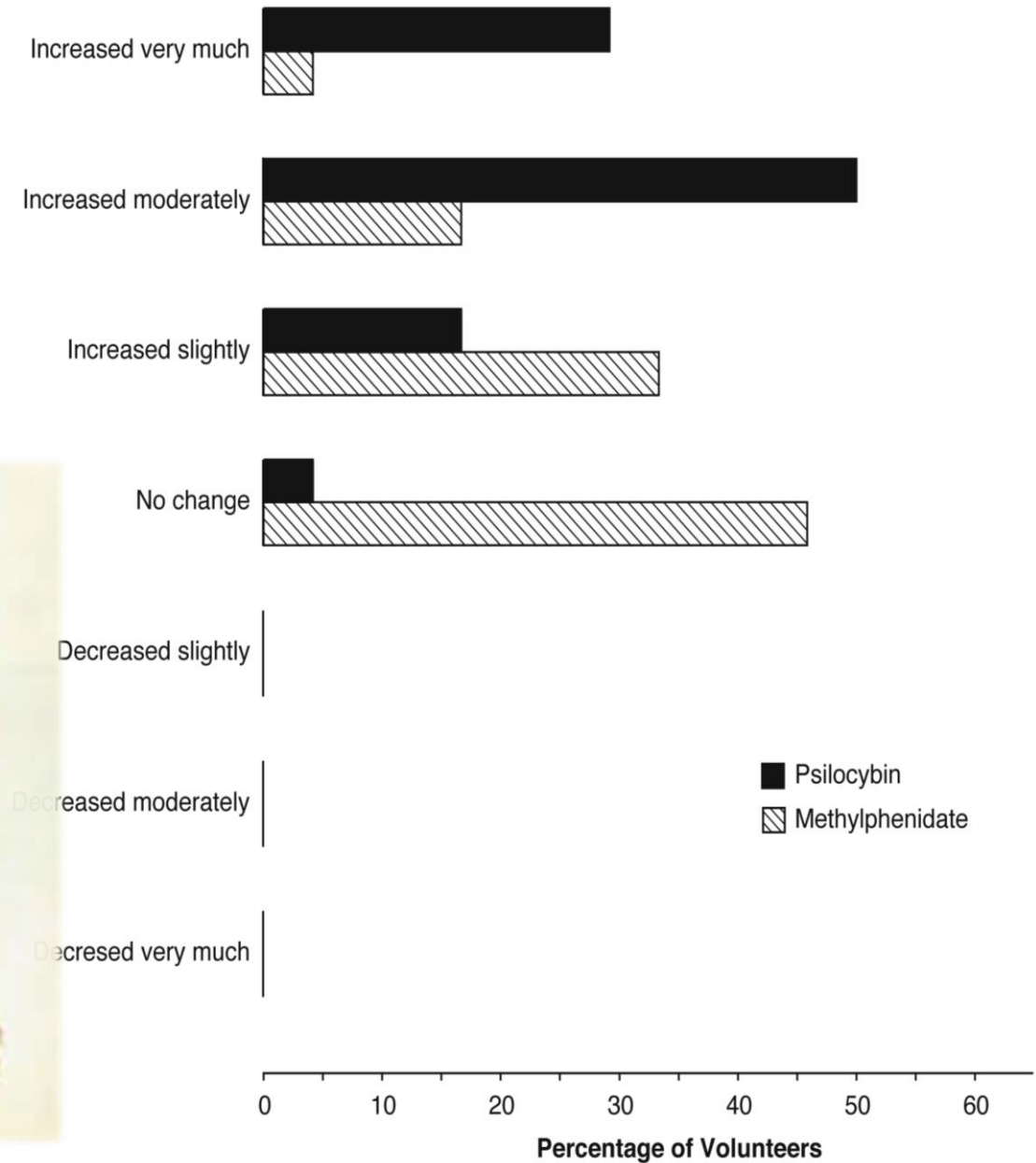
# Pahnke-Richards Mystical Experience Questionnaire – 7 hours after session



# Change in Well-Being: 2 Months after sessions

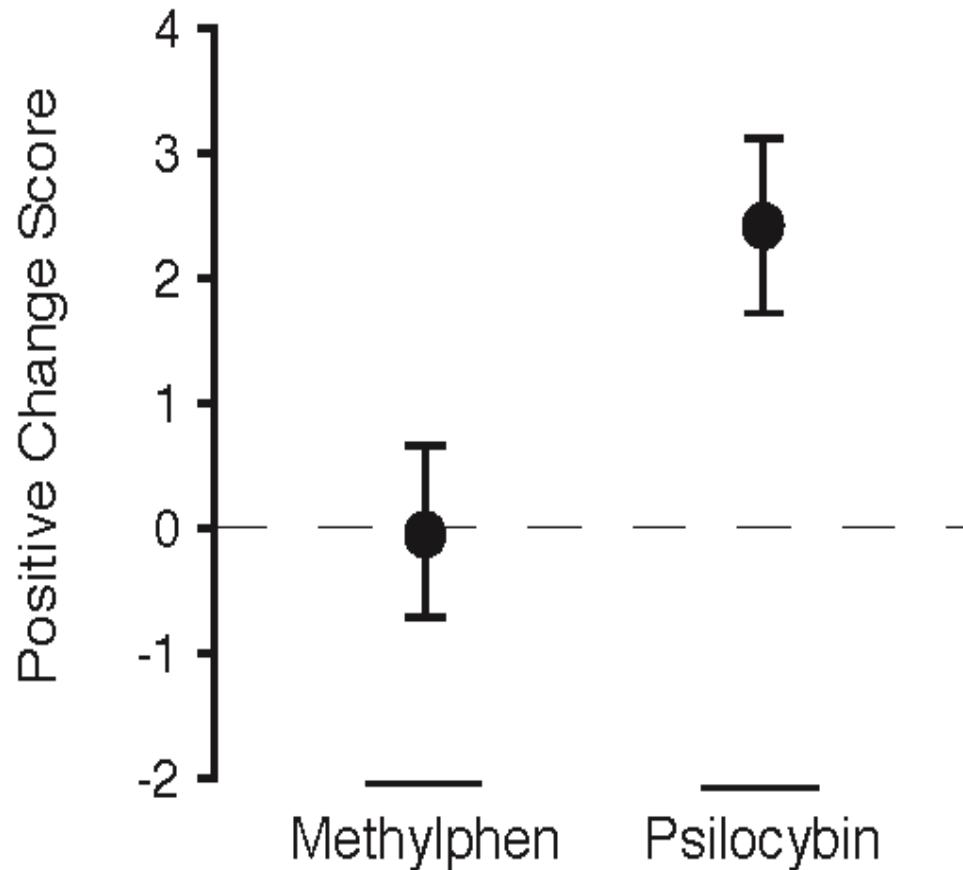


Change in Personal Well-Being or Life Satisfaction  
(Rated 2 months after session, N=24)



# Community ratings of participants' behavior & attitudes 2 months after sessions

Community Observer Ratings

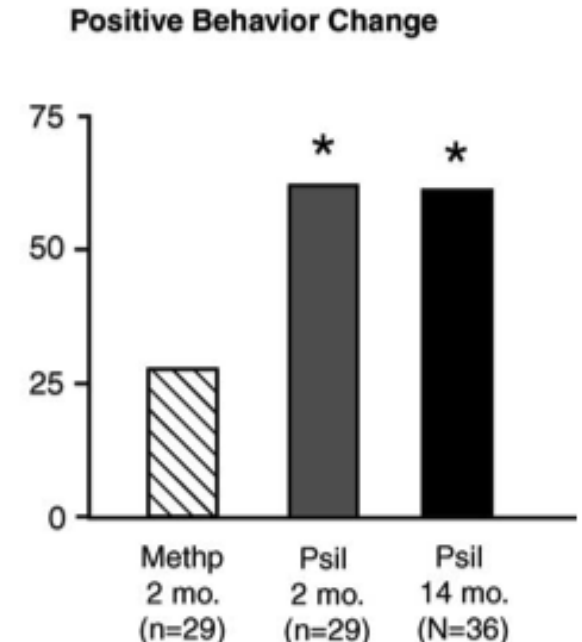
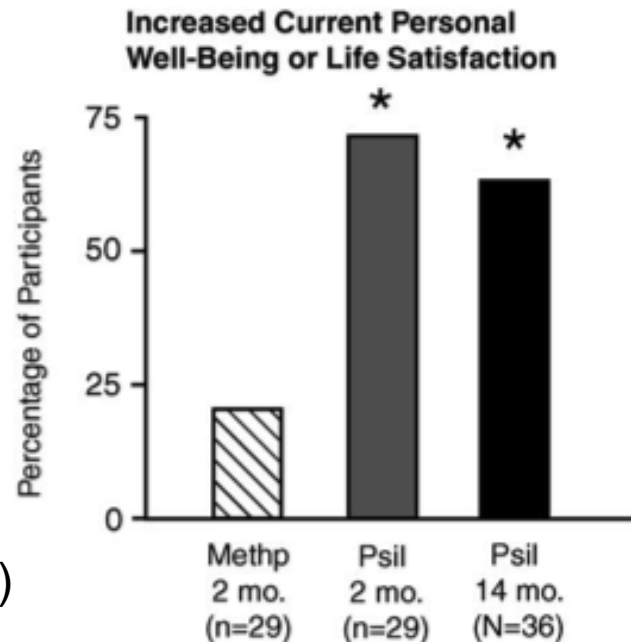
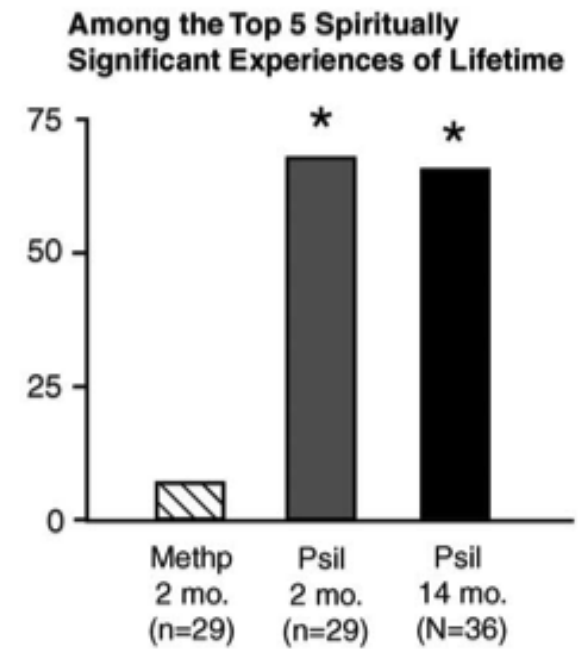
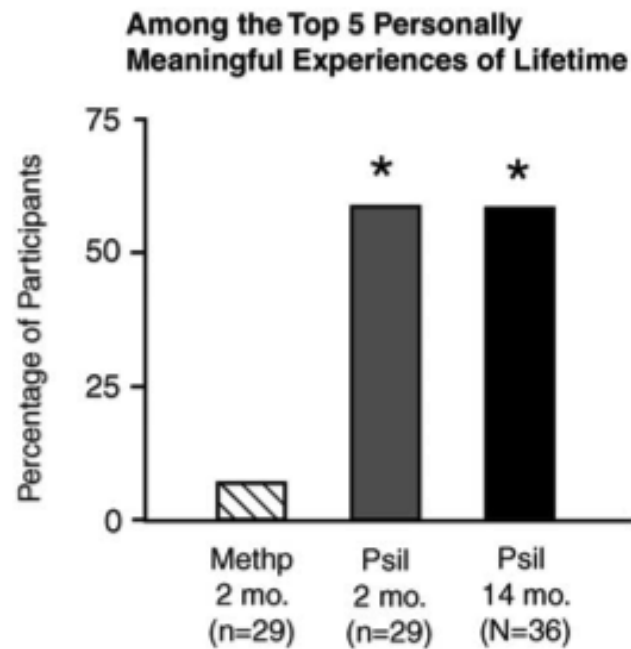




**Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later.**



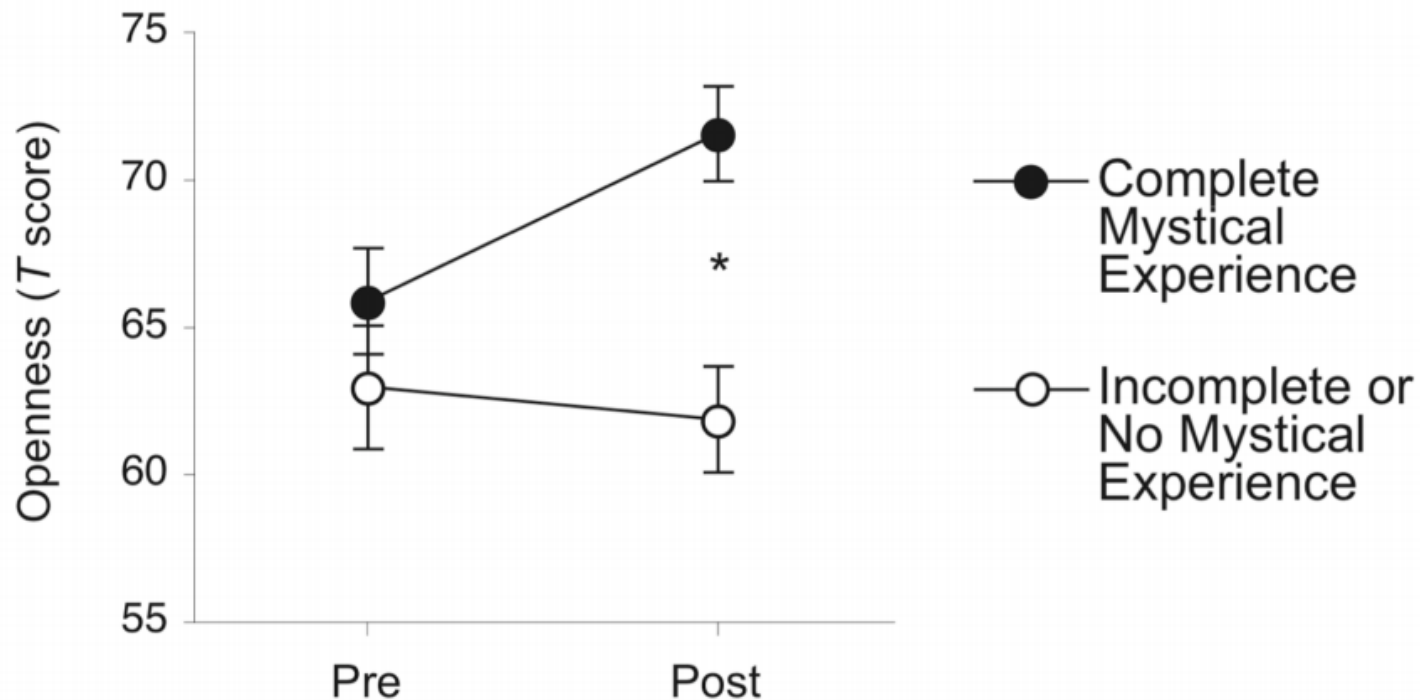
Griffiths et al. (2006, 2008)



# Psilocybin can change personality

**NEO Personality Inventory:** Neuroticism, Openness, Extroversion, Agreeableness, and Conscientiousness

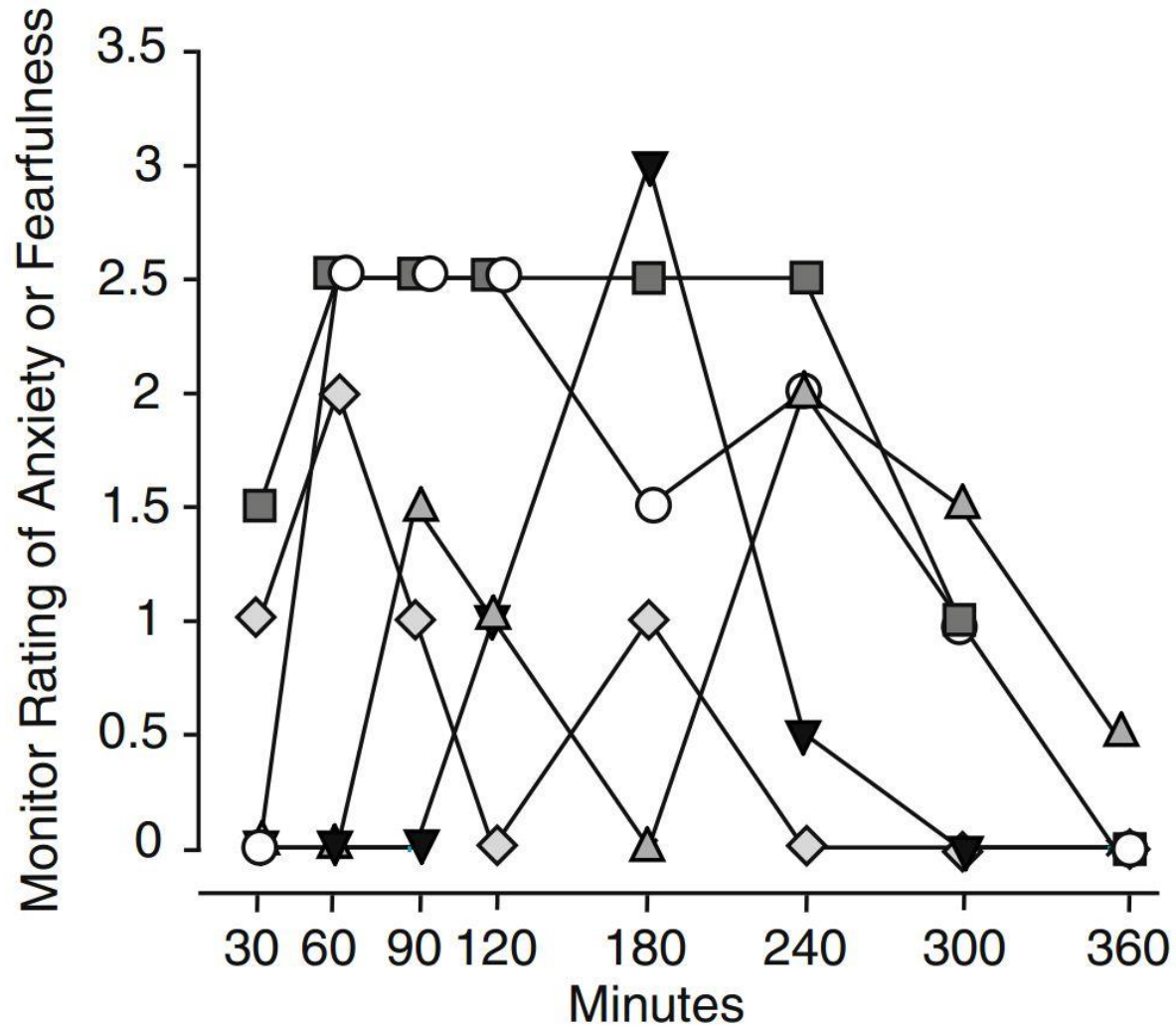
**Openness:** aesthetic appreciation and sensitivity, imagination and fantasy, and broad-minded tolerance of others' viewpoints and values



# The Dark Side

- 39% of participants (7 of 18) had extreme ratings of fear, fear of insanity, or feeling trapped
- 6 cases: 30 mg/70 kg
- 1 case: 20 mg/70 kg
- Small increase in mystical experience scores
- Potential for dangerous behavior if unsupervised
- No recorded cases of HPPD in our studies (>700 sessions with >300 participants).

# Unpredictable Timing





# Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths<sup>1,2</sup>, Matthew W Johnson<sup>1</sup>, Michael A Carducci<sup>3</sup>, Annie Umbricht<sup>1</sup>, William A Richards<sup>1</sup>, Brian D Richards<sup>1</sup>, Mary P Cosimano<sup>1</sup> and Marqaret A Klinedinst<sup>1</sup>

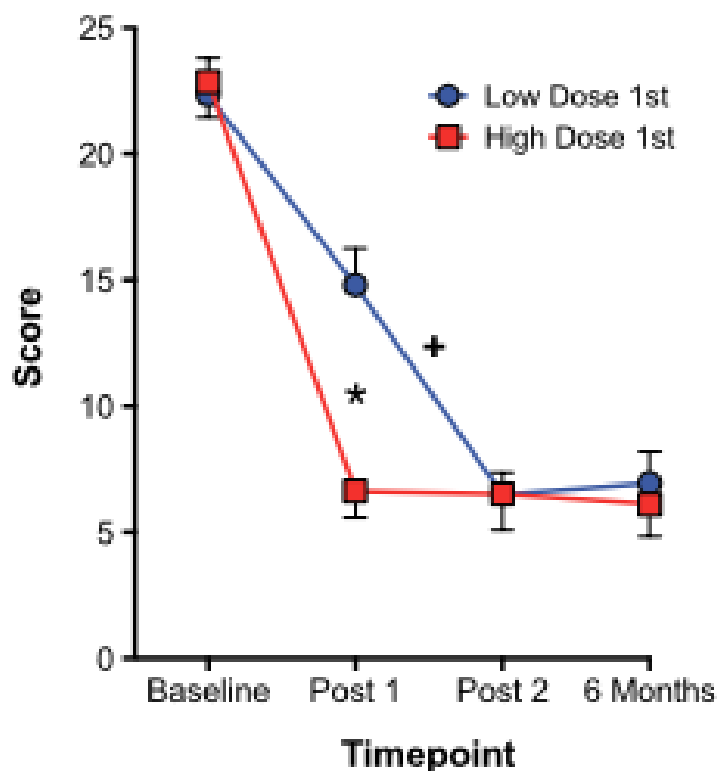
Journal of Psychopharmacology  
2016, Vol. 30(12) 1181–1197  
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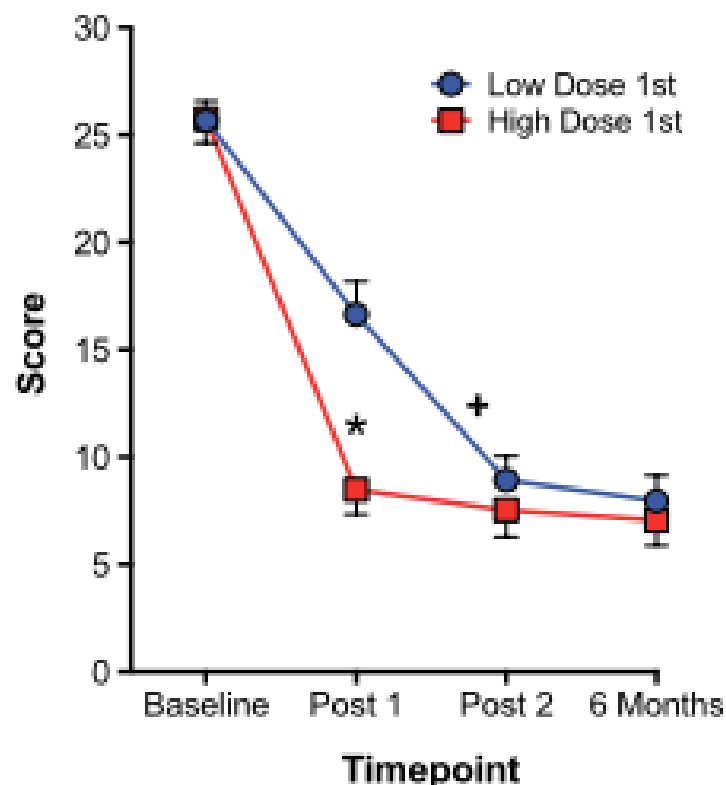
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### GRID-HAMD (Depression)



### HAM-A (Anxiety)





# Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths<sup>1,2</sup>, Matthew W Johnson<sup>1</sup>, Michael A Carducci<sup>3</sup>, Annie Umbricht<sup>1</sup>, William A Richards<sup>1</sup>, Brian D Richards<sup>1</sup>, Mary P Cosimano<sup>1</sup> and Marqaret A Klinedinst<sup>1</sup>

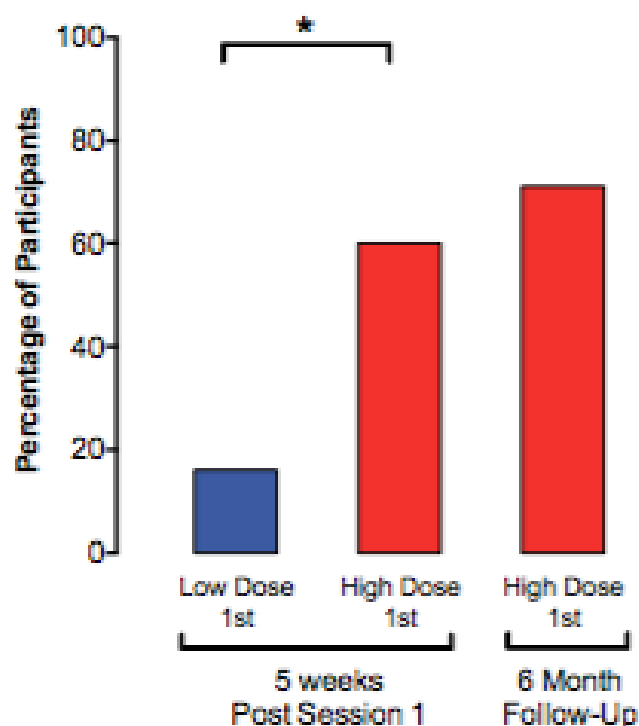
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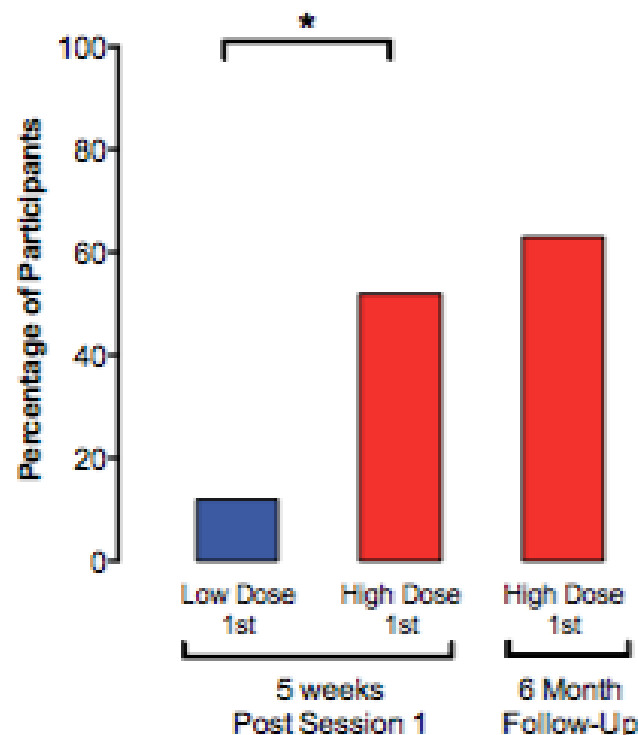
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DOI: 10.1177/0269881116675513  
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GRID-HAMD (Depression)  
Remission to Normal Range



HAM-A (Anxiety)  
Remission to Normal Range

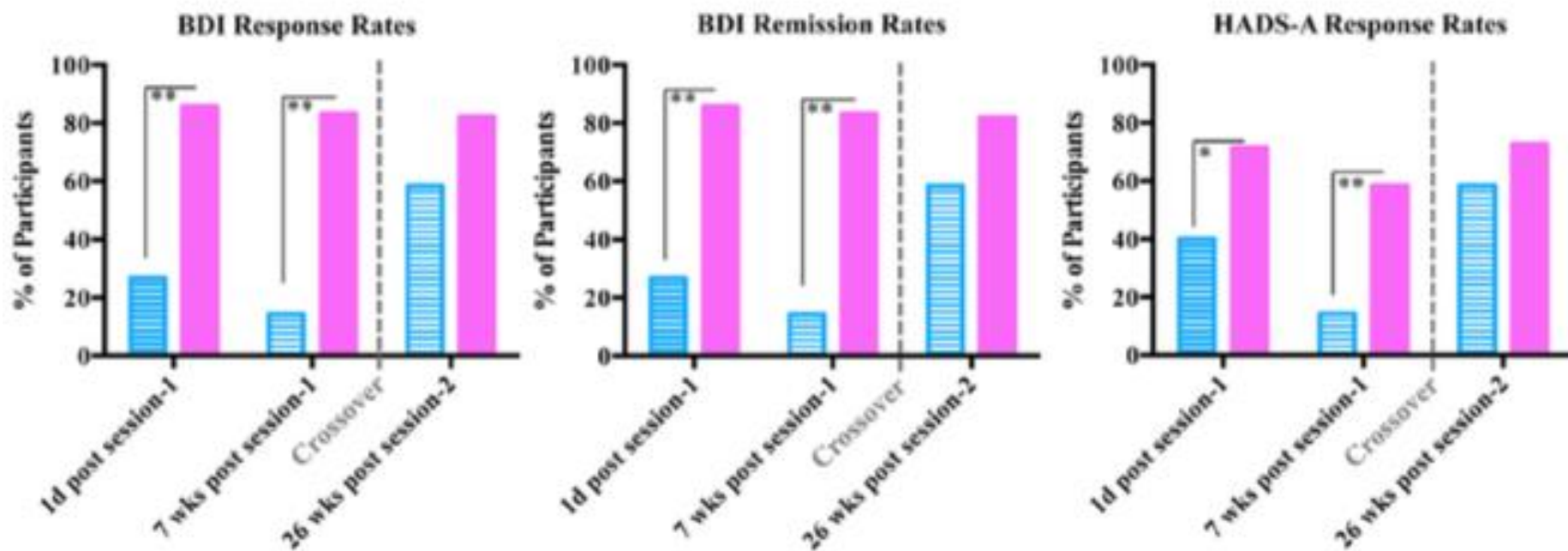




# Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

Stephen Ross<sup>1,2,3,4,5,6</sup>, Anthony Bossis<sup>1,2,4</sup>, Jeffrey Guss<sup>1,2,4</sup>, Gabrielle Agin-Liebes<sup>10</sup>, Tara Malone<sup>1</sup>, Barry Cohen<sup>7</sup>, Sarah E Mennenga<sup>1</sup>, Alexander Belser<sup>8</sup>, Krystallia Kalliontzi<sup>2</sup>, James Babb<sup>9</sup>, Zhe Su<sup>3</sup>, Patricia Corby<sup>2</sup> and Brian L Schmidt<sup>2</sup>

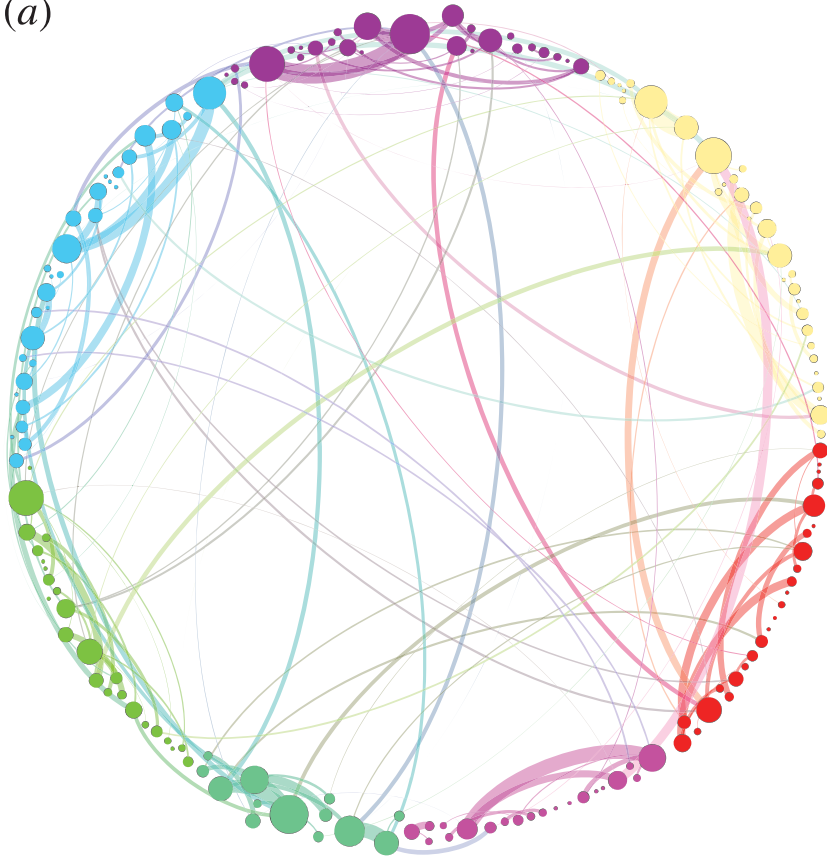
## Response/Remission Rates by Treatment Group



# Homological scaffolds of brain functional networks

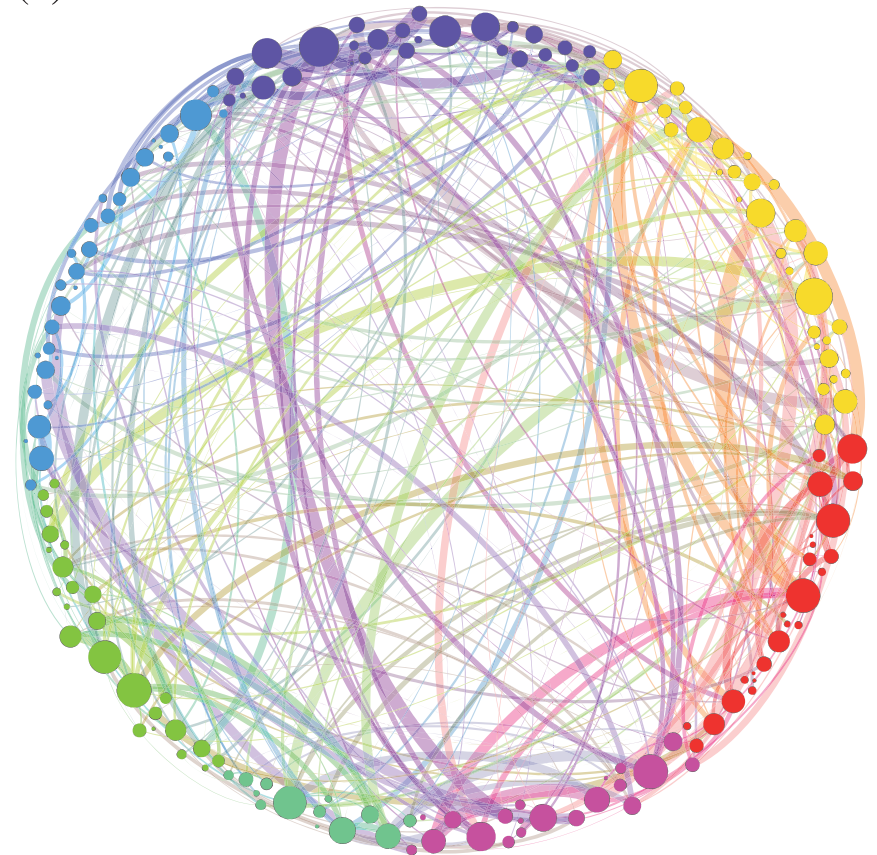
G. Petri<sup>1</sup>, P. Expert<sup>2</sup>, F. Turkheimer<sup>2</sup>, R. Carhart-Harris<sup>3</sup>, D. Nutt<sup>3</sup>, P. J. Hellyer<sup>4</sup>  
and F. Vaccarino<sup>1,5</sup>

(a)



Placebo

(b)



Psilocybin

# 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

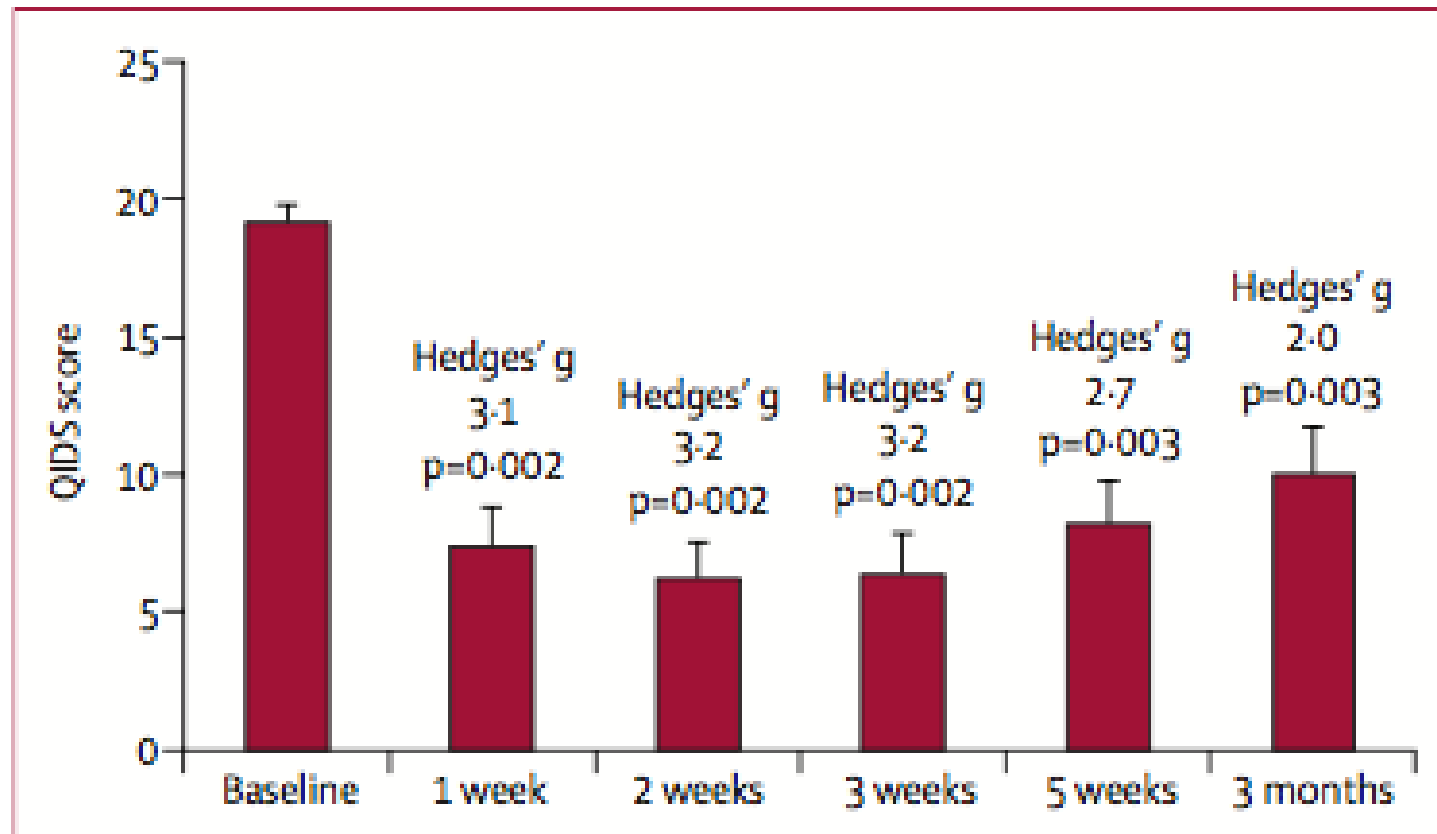


Figure 3: Mean depression severity (QIDS) over time

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

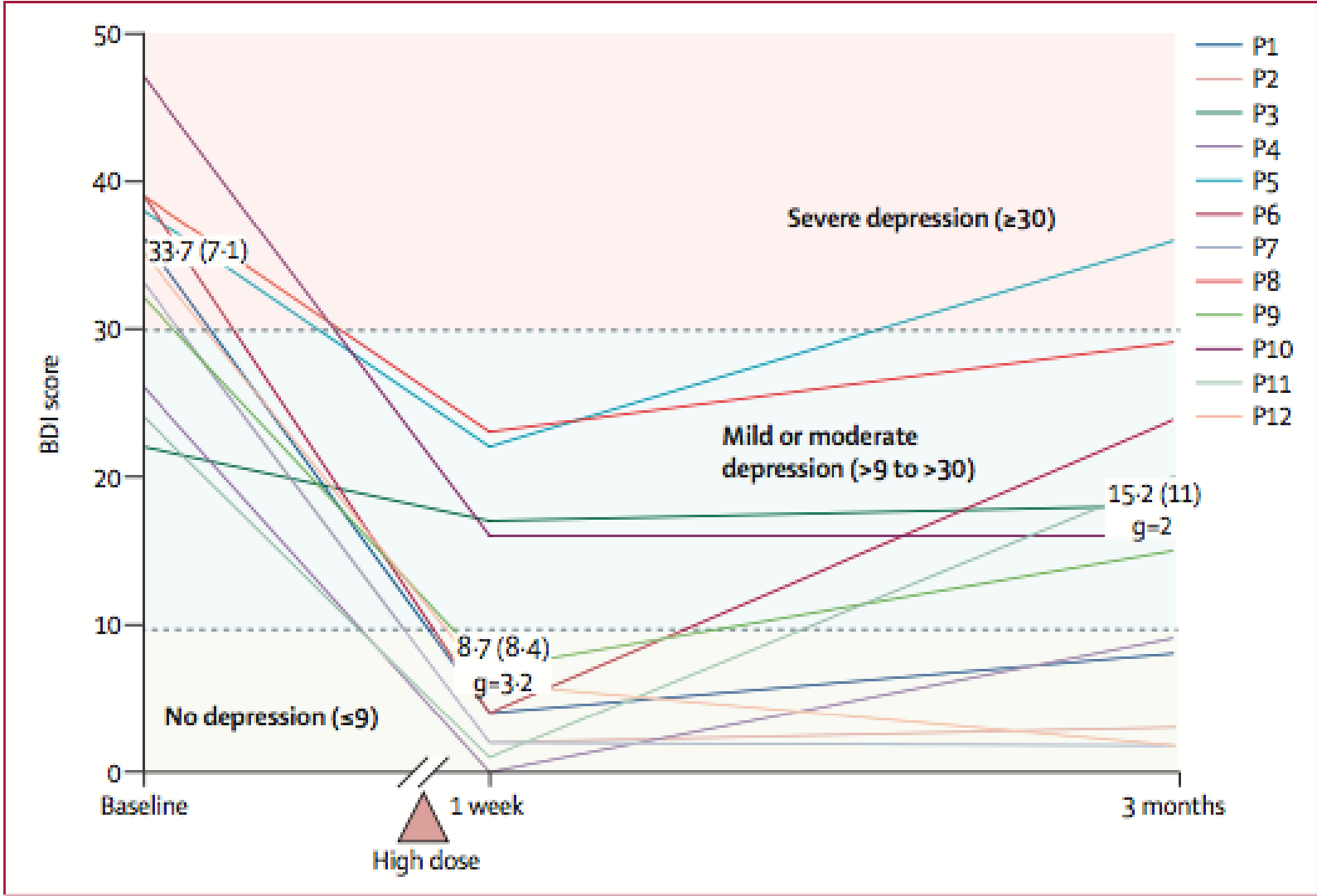
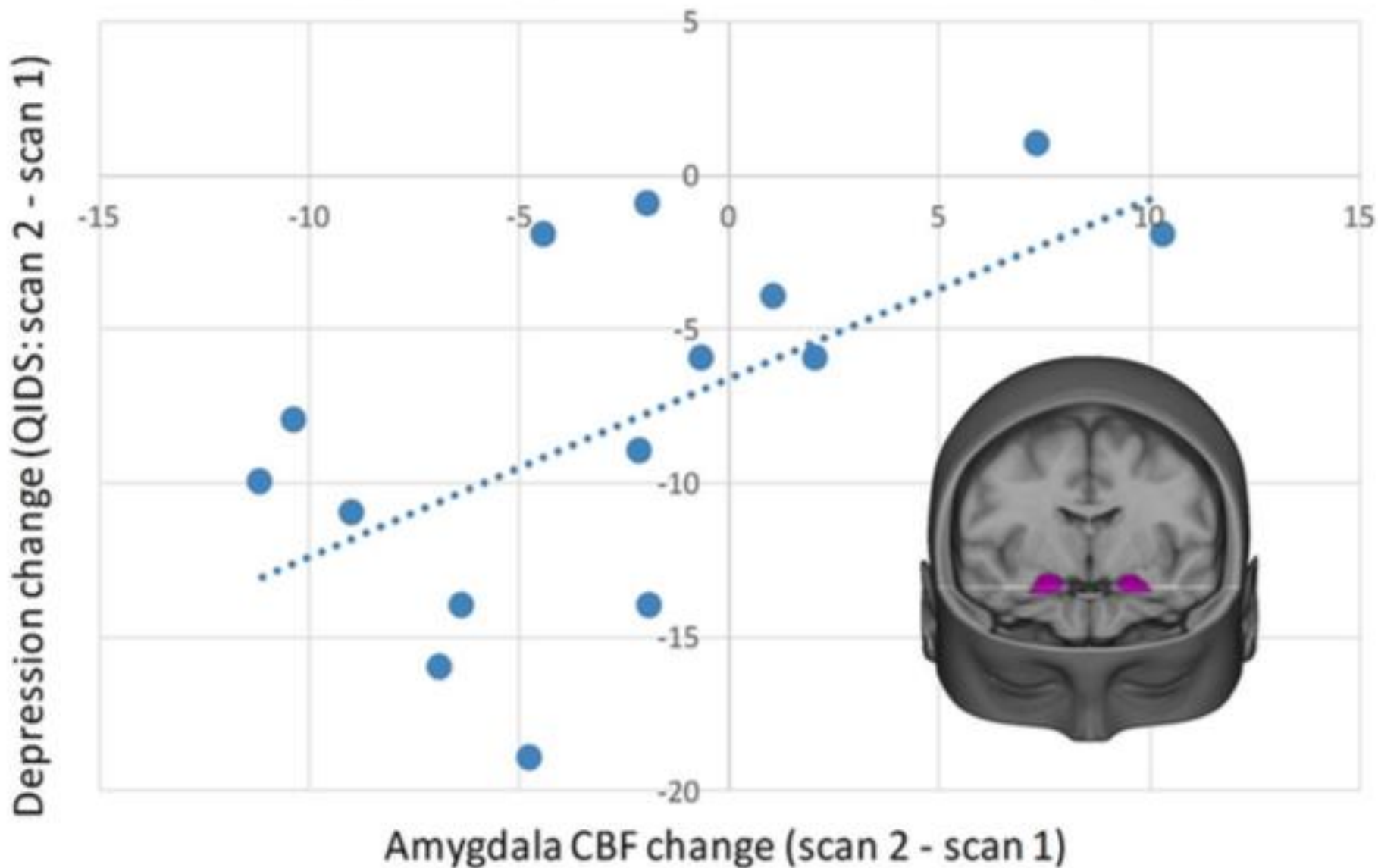


Figure 4: Depression severity (BDI) over time, by patient



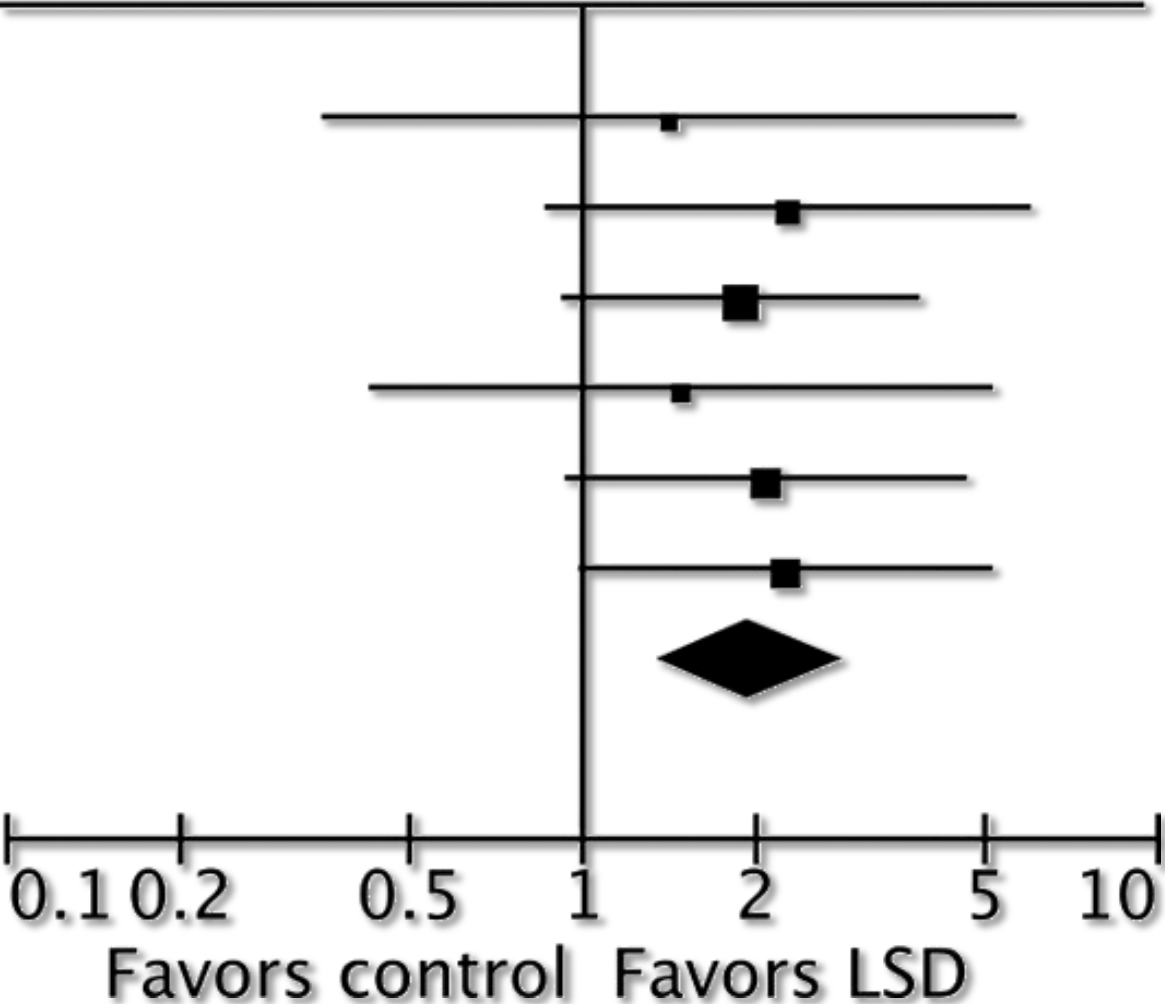
# Psilocybin for treatment-resistant depression: fMRI-measured brain

## Change in amygdala CBF v depression change



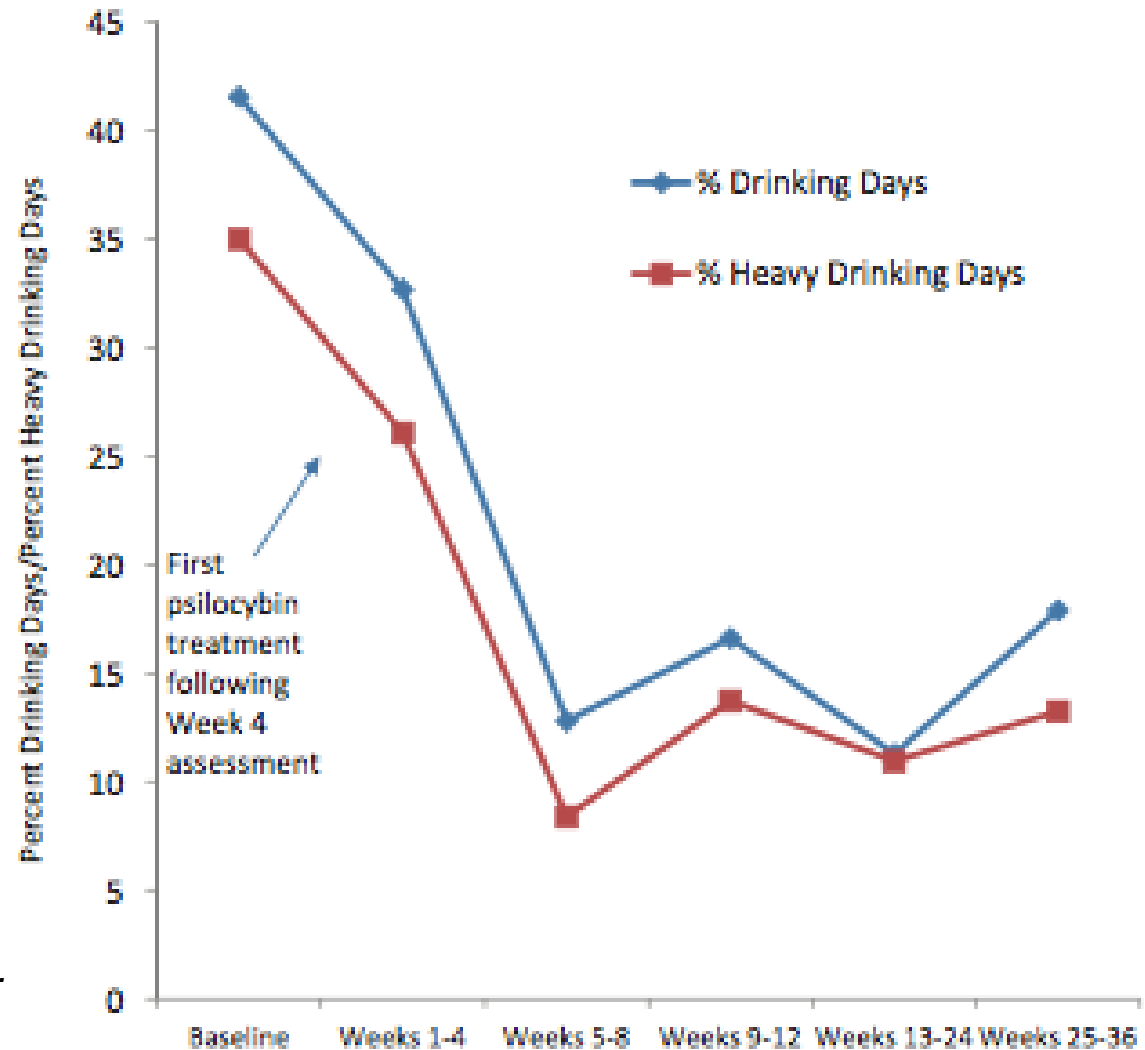
# Meta-Analysis of controlled trials of LSD for Alcoholism: Across studies, LSD doubled the odds a patient would be alcohol free at the 1<sup>st</sup> follow up (N=536)

Krebs T S , Johansen P J Psychopharmacol 2012;26:994-1002



# Psilocybin for Alcoholism

- Open-label pilot study ( $N=10$ ) of 1-2 doses psilocybin + MET for alcohol dependence
- Significantly decreased drinking up to 36 weeks later



# Pilot study of the 5-HT<sub>2A</sub>R agonist psilocybin in the treatment of tobacco addiction

Matthew W Johnson<sup>1</sup>, Albert Garcia-Romeu<sup>1</sup>, Mary P Cosimano<sup>1</sup>  
and Roland R Griffiths<sup>1,2</sup>

*Journal of Psychopharmacology*

1–10

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DOI: 10.1177/0269881114548296

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## Abstract

Despite suggestive early findings on the therapeutic use of hallucinogens in the treatment of substance use disorders, rigorous follow-up has not been conducted. To determine the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment we conducted an open-label pilot study administering moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin within a structured 15-week smoking cessation treatment protocol. Participants were 15 psychiatrically healthy nicotine-dependent smokers (10 males; mean age of 51 years), with a mean of six previous lifetime quit attempts, and smoking a mean of 19 cigarettes per day for a mean of 31 years at intake. Biomarkers assessing smoking status, and self-report measures of smoking behavior demonstrated that 12 of 15 participants (80%) showed seven-day point prevalence abstinence at 6-month follow-up. The observed smoking cessation rate substantially exceeds rates commonly reported for other behavioral and/or pharmacological therapies (typically <35%). Although the open-label design does not allow for definitive conclusions regarding the efficacy of psilocybin, these findings suggest psilocybin may be a potentially efficacious adjunct to current smoking cessation treatment models. The present study illustrates a framework for future research on the efficacy and mechanisms of hallucinogen-facilitated treatment of addiction.

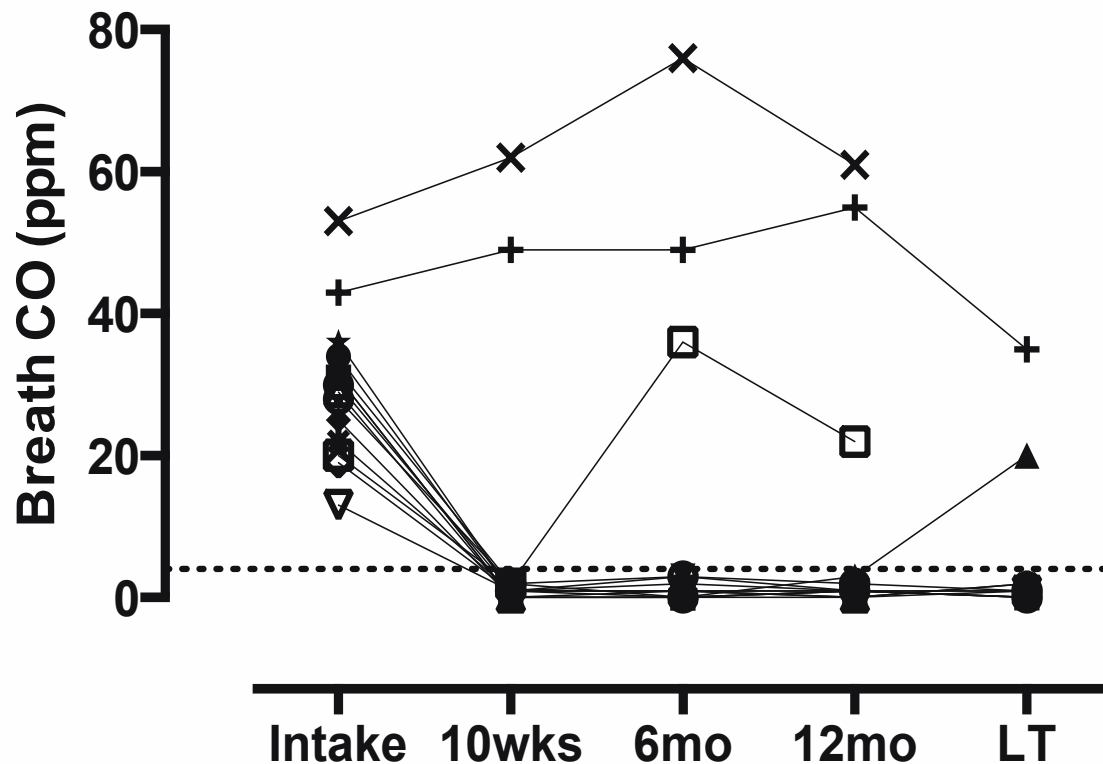
## Keywords

Hallucinogen, tobacco, smoking cessation, nicotine, addiction, psilocybin, psychedelic

# Psilocybin Smoking Cessation

- Open-label pilot study ( $N=15$ ) of 2-3 doses psilocybin + CBT for smoking cessation
- 12 (80%) abstinent at 6mo.
- 10 (67%) abstinent at 12mo.
- 9 (60%) abstinent at ~30mo.

## Exhaled Carbon Monoxide

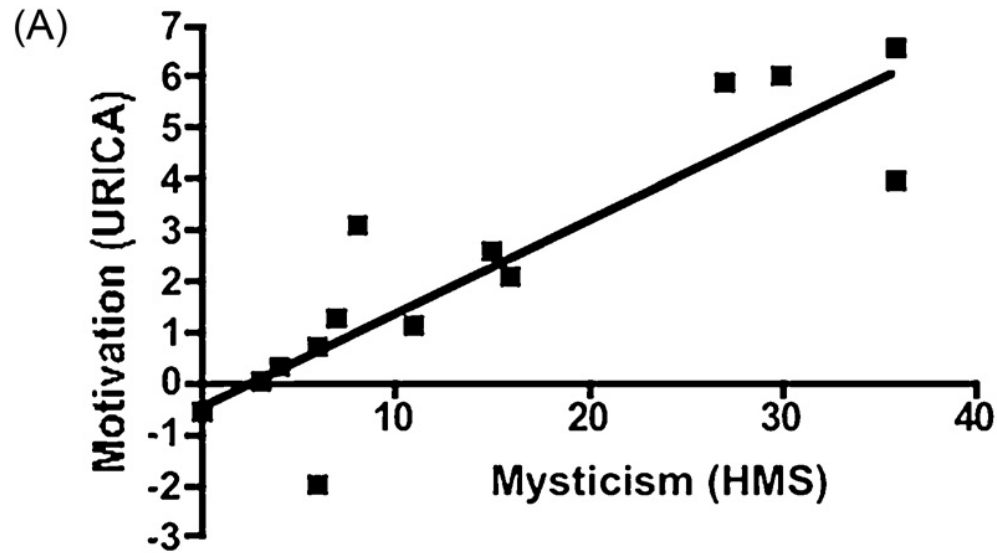






# Therapeutic infusions of ketamine: Do the psychoactive effects matter?

E Dakwar, C Anerella, CL Hart, FR Levin et al. Drug & Alcohol Dependence, 2014.

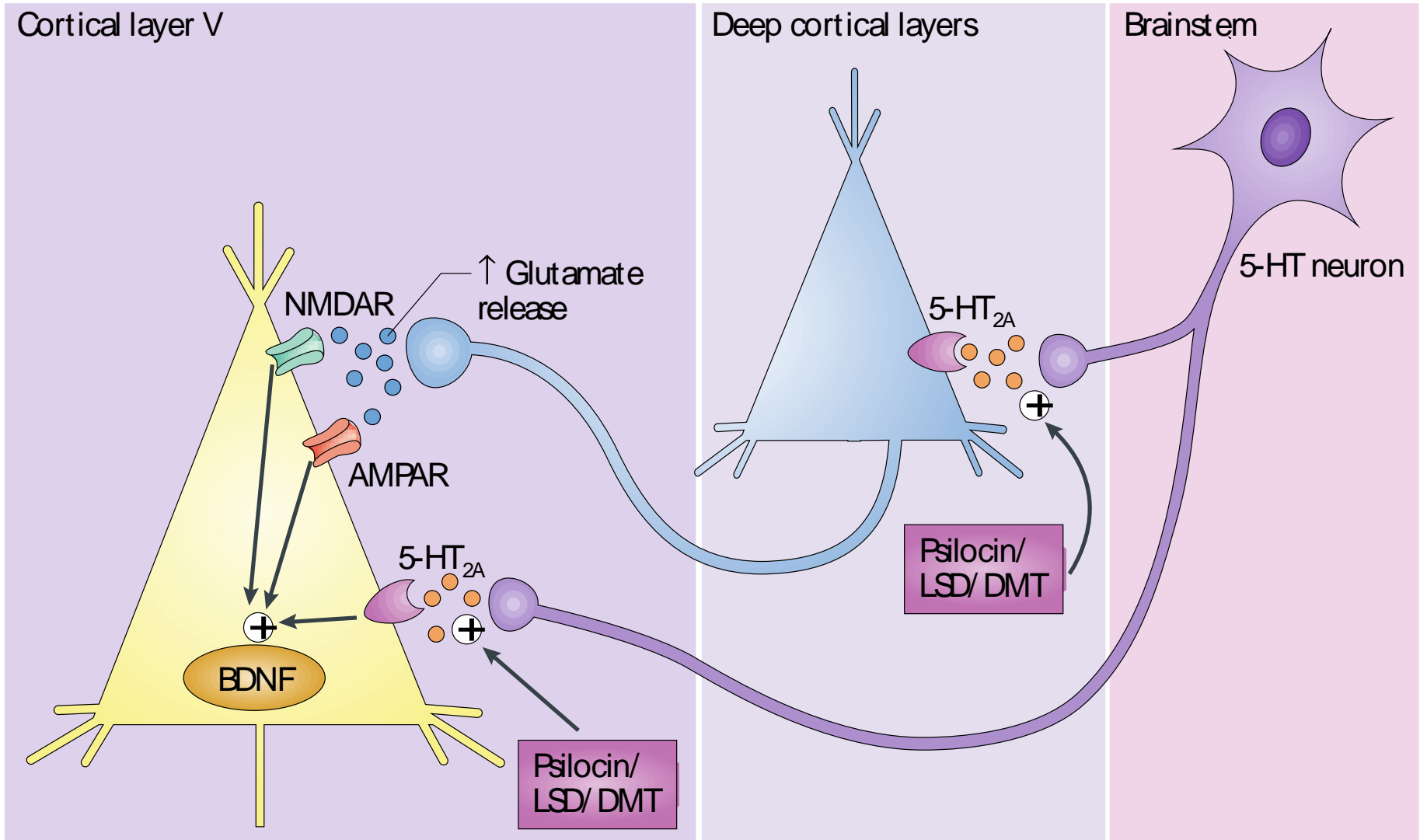


(B)

	Simple Regression		Mediation Analysis		
	Infusion Type ( $\beta$ )	Psychoactive Effect ( $\beta$ )	Infusion Type ( $\beta$ )	Psychoactive Effect ( $\beta$ )	
Dissociation	0.776*	0.681**	0.329	0.535	Motivation
	0.580	0.655**	0.287	0.479	Craving
Mysticism	0.776*	0.881***	0.274	<b>0.678****</b>	Motivation
	0.580	0.647**	0.223	0.482	Craving

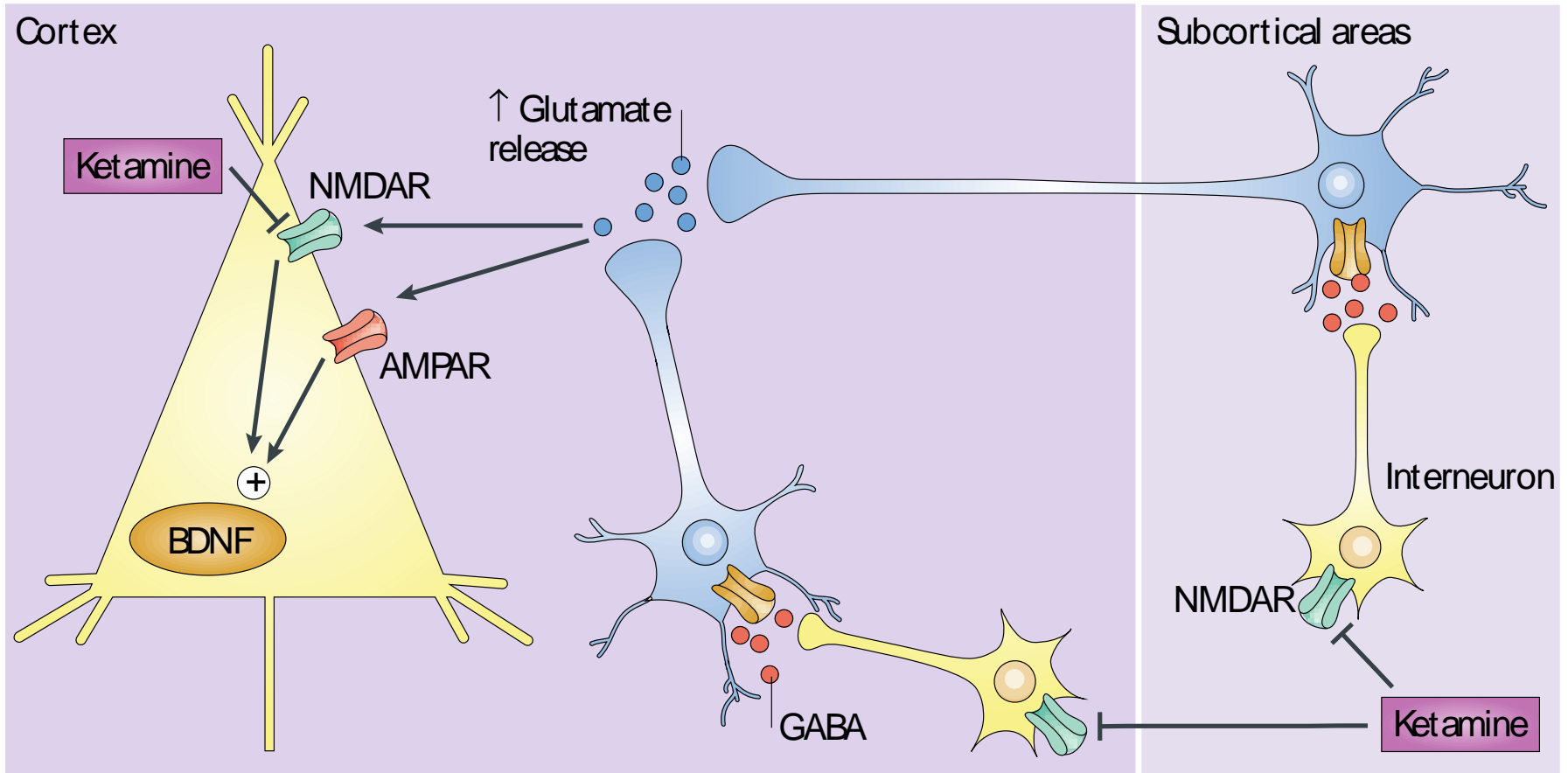
# The neurobiology of psychedelic drugs: implications for the treatment of mood disorders

Franz X. Vollenweider and Michael Komater



# The neurobiology of psychedelic drugs: implications for the treatment of mood disorders

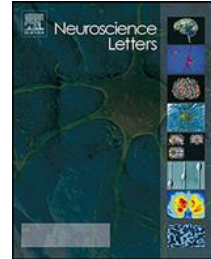
Franz X. Vollenweider and Michael Kometer





Contents lists available at ScienceDirect

## Neuroscience Letters

journal homepage: [www.elsevier.com/locate/neulet](http://www.elsevier.com/locate/neulet)

# Metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects induced by hallucinogenic 5-HT<sub>2A</sub> receptor agonists

José L. Moreno<sup>a</sup>, Terrell Holloway<sup>a</sup>, Laura Albizu<sup>b</sup>, Stuart C. Sealfon<sup>b,d</sup>, Javier González-Maeso<sup>a,b,c,\*</sup>

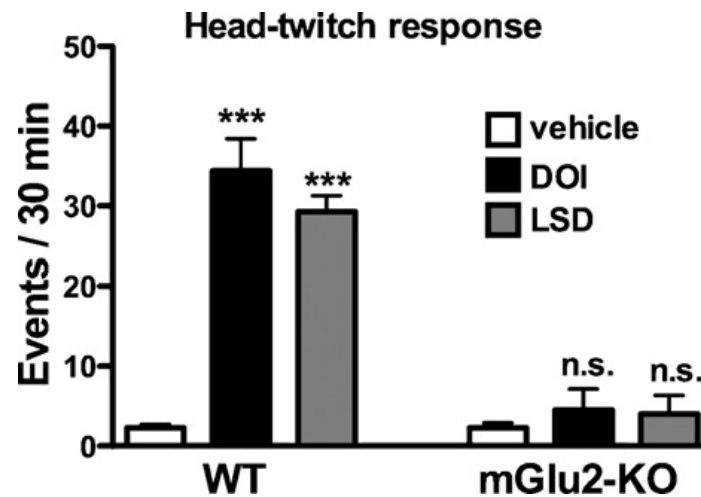


Fig. 1. Behavioral response to hallucinogens DOI and LSD. Wild type and mGluR2-KO mice ( $n=4-5$  per treatment group) were injected with vehicle, DOI (2 mg/kg) or LSD (0.24 mg/kg), and the head-twitch response was scored 15 min after injection for 30 min. \*\*\* $p < 0.001$ ; Bonferroni's post hoc test of two-way ANOVA. Data are means  $\pm$  S.E.M. n.s., not significant.

## RESEARCH ARTICLE

# Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning

Briony J. Catlow · Shijie Song · Daniel A. Paredes · Cheryl L. Kirstein · Juan Sanchez-Ramos

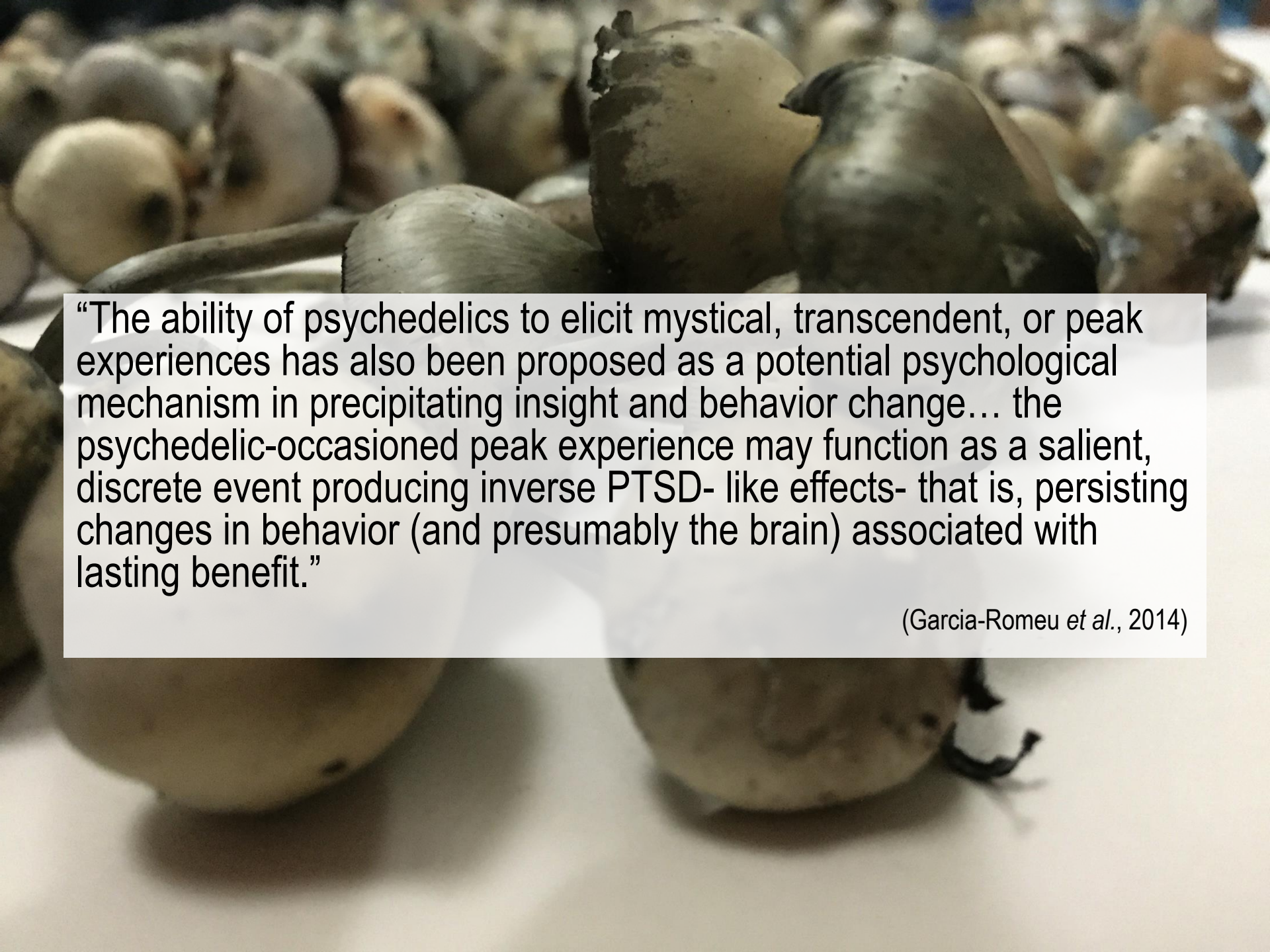
**Abstract** Drugs that modulate serotonin (5-HT) synaptic concentrations impact neurogenesis and hippocampal (HPC)-dependent learning. The primary objective is to determine the extent to which psilocybin (PSOP) modulates neurogenesis and thereby affects acquisition and extinction of HPC-dependent trace fear conditioning. PSOP, the 5-HT<sub>2A</sub> agonist 25I-NBMeO and the 5-HT<sub>2A/C</sub> antagonist ketanserin were administered via an acute *intraperitoneal* injection to mice. Trace fear conditioning was measured as the amount of time spent immobile in the presence of the conditioned stimulus (CS, auditory tone), trace (silent interval) and post-trace interval over 10 trials. Extinction was determined by the number of trials required to resume mobility during CS, trace and post-trace when the shock was not delivered. Neurogenesis was determined by unbi-

significant dose-dependent decreases in number of new-born neurons in hippocampus. At the low doses of PSOP that enhanced extinction, neurogenesis was not decreased, but rather tended toward an increase. Extinction of “fear conditioning” may be mediated by actions of the drugs at sites other than hippocampus such as the amygdala, which is known to mediate the perception of fear. Another caveat is that PSOP is not purely selective for 5-HT<sub>2A</sub> receptors. PSOP facilitates extinction of the classically conditioned fear response, and this, and similar agents, should be explored as potential treatments for post-traumatic stress disorder and related conditions.

**Keywords** Neurogenesis · Psilocybin · Serotonin · Hippocampus · Learning · Memory · Trace conditioning

Participant ID	Verbatim Comments
402	Feelings of gratefulness, a great (powerful) remembrance of humility... of my experience of being, the experience of my being in and within the infinite.
403	Not at all religious but significant in motivating me to nurture my spiritual life.
405	It changes what I believe... We are all one and divine.
406 <sup>1</sup>	The awareness that all is one and then the realization that I am an integral piece of the one's puzzle.
410	Oneness with universe; being forgiven.
413	Rich joy and awe. My body melting and becoming one with the universe felt both painless and profound... Feeling complete as a person and physically a part of all thin
416	There is a meaningful presence that humbles any human heart.
417	Simultaneously being aware and saturated in the majesty of existence.
421	Seeing God speaks for itself; seeing and feeling forever was like traveling through space-time.
422	The sessions permitted me to go inside and see and feel the nature of the mind.
423	Recognizing the source and manifestation of visions... source of unconscious content.
427	I believe I channeled the power of the Goddess and that I hold that power in me. I believe she exists everywhere and I look for her to add spark, life, and joy to everyday ordinary situations.





“The ability of psychedelics to elicit mystical, transcendent, or peak experiences has also been proposed as a potential psychological mechanism in precipitating insight and behavior change... the psychedelic-occasioned peak experience may function as a salient, discrete event producing inverse PTSD- like effects- that is, persisting changes in behavior (and presumably the brain) associated with lasting benefit.”

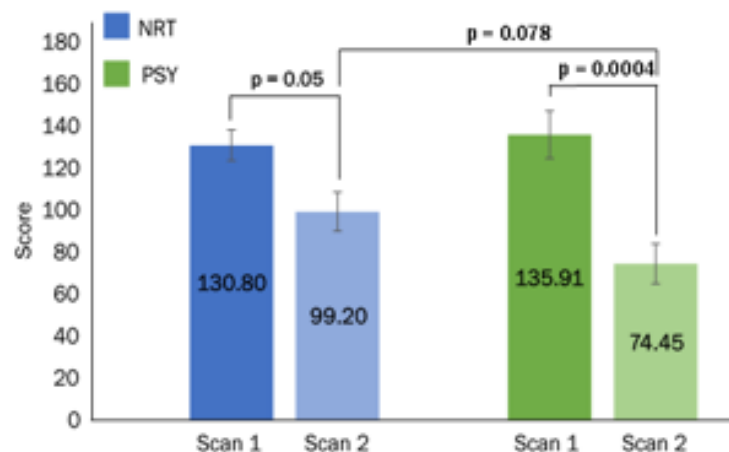
(Garcia-Romeu *et al.*, 2014)

# Psilocybin-assisted Smoking Cessation follow-up RCT

- Randomized controlled trial
- Participants receive 4 sessions CBT for smoking cessation prior to a Target Quit Date in week 5
- Randomly assigned to receive 1 high dose of psilocybin or 8-10 weeks of nicotine patch
- Follow up meetings continue weekly or biweekly until 8 weeks post-quit, and 3, 6, 12 months.
- MRI scans occur in weeks 2 (pre), 5 (24 hours post-quit), and 19 (3 months post-quit for abstinent individuals)

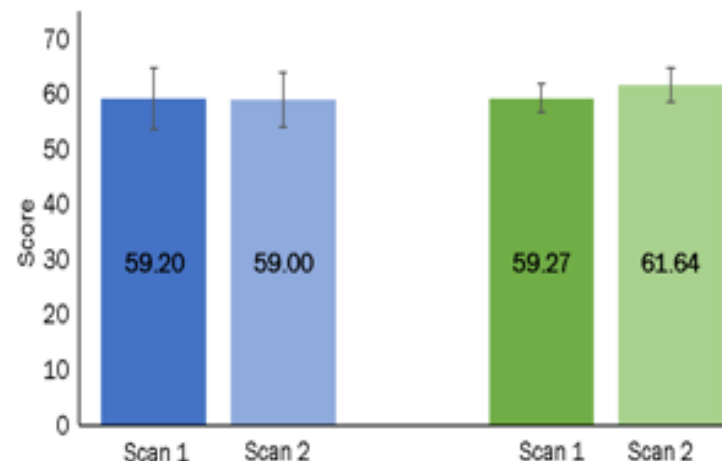
## QSU Total (Craving)

Average Total QSU Score Across Session



## WSWS Total (Withdrawal)

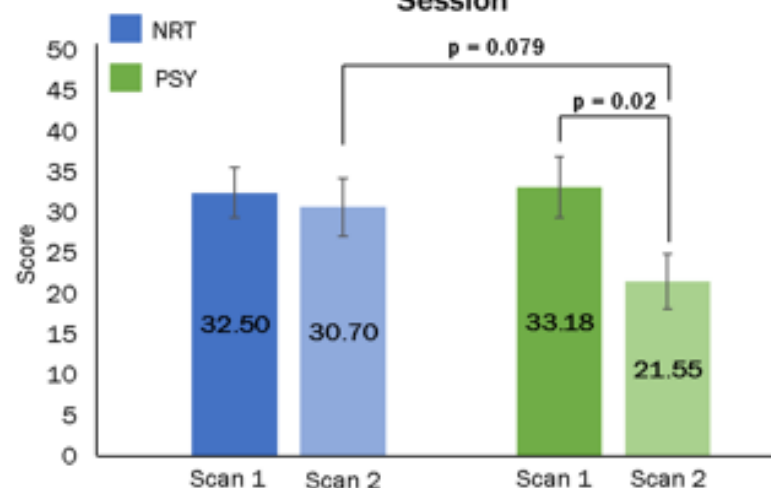
Average Total WSWS Scores Across Session



- **PSY & NRT:** Craving dropped from scan 1, withdrawal did not change.
- **Scan 2:** PSY has a trend towards lower craving than NRT, but similar withdrawal ratings.

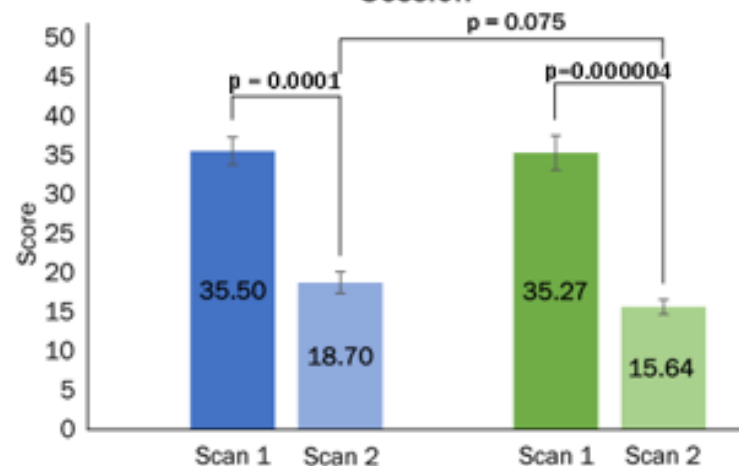
## QSU Desire

Average Desire to Smoke Score Across Session



## QSU Intent

Average Intent to Smoke Score Across Session







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