

Psychedelics for Addiction The Past, Present & Future

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& PSYCHEDELIC RESEARCH CLINIC



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Drug
Science

Psychedelic therapy in the treatment of addiction: The past, present and future

Rayyan Zafar^{1, 2*}, Maxim Siegel^{1, 2}, Rebecca Harding³, Tommaso Barba^{1, 2}, Claudio Agnorelli^{1, 2}, Shayam Suseelan^{1, 2}, Leor Roseman^{1, 2}, Matthew Wall^{1, 4, 2}, David J. Nutt^{1, 2}, David Erritzoe^{1, 2}

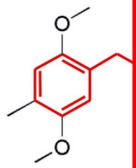
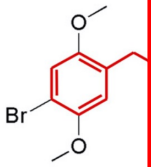
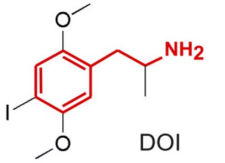
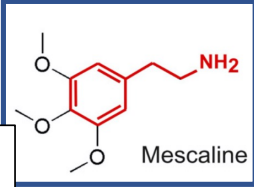
¹Centre for Psychedelic Research, Imperial College London, United Kingdom, ²Neuropsychopharmacology Unit, Department of Medicine, Faculty of Medicine, Imperial College London, United Kingdom, ³Clinical Psychopharmacology Unit, University College London, United Kingdom, ⁴Invicro (United Kingdom), United Kingdom

Out next week!

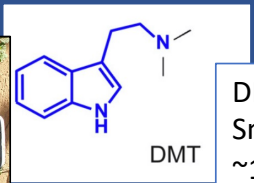
Psychedelic compounds

Classic serotonergic psychedelics

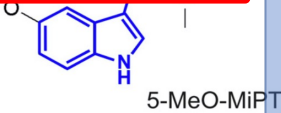
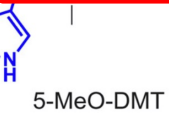
Oral: ~12hrs



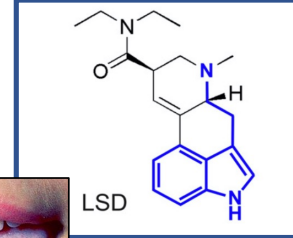
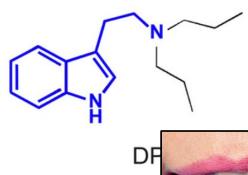
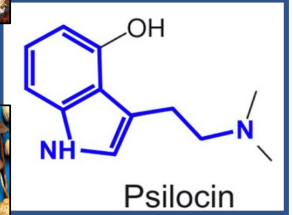
Oral: ~4-5hrs



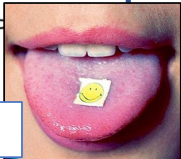
DMT (alone)
Smoke or IV:
~10-20min



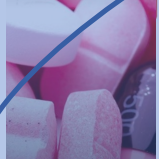
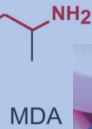
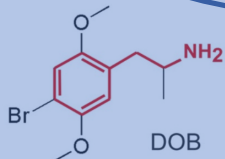
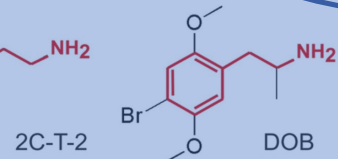
Oral: ~4-5hrs



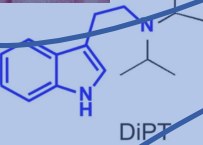
Oral: ~10-12hrs



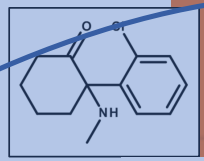
“Atypical” psychedelics
-also being clinically developed”



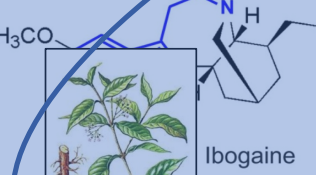
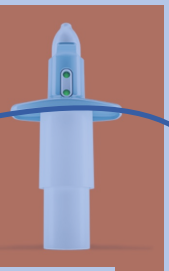
“Stimulant/
psychedelic
hybrid”



“Enactogen/
Emphatogen”



Ketamine



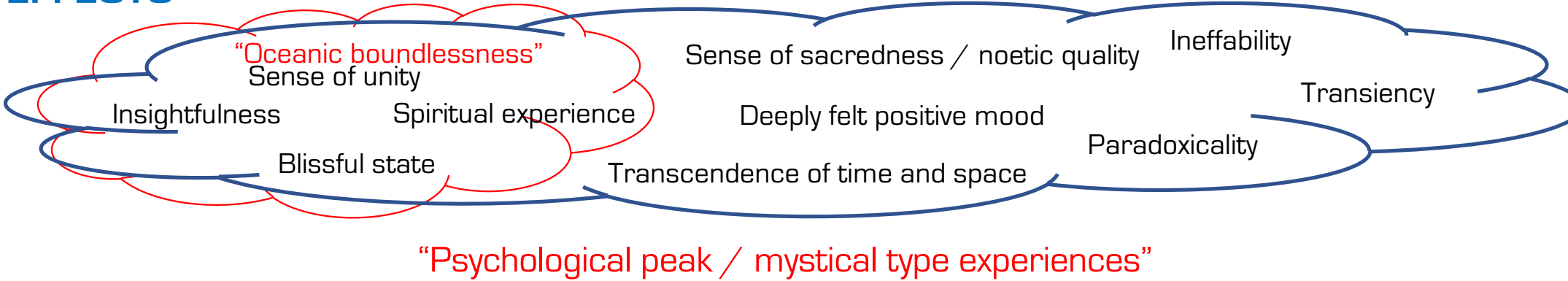
“Dissociative
psychedelics”



Psyche-delic: “mind” – “revealing/manifesting”

Different from other drugs both in **effects** and **safety** profile

EFFECTS



SAFETY¹



Safe +++

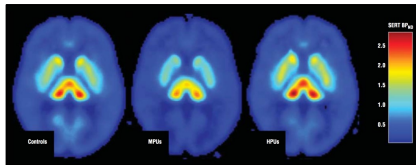
Non-addictive, Low physiological & brain toxicity^{1,2}

Good therapeutic index³

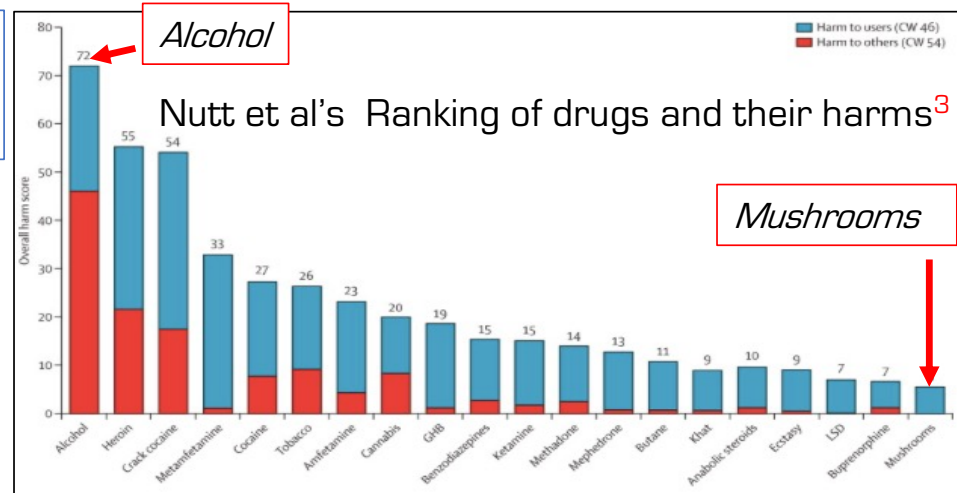


Risks/SEs

Dysphoria/ anxiety, nausea, headache, false memories?



Brain PET in recreational psychedelic users²



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

Six LSD trials in alcoholism

1970

problems and treatment intentions

quiet room

group therapy

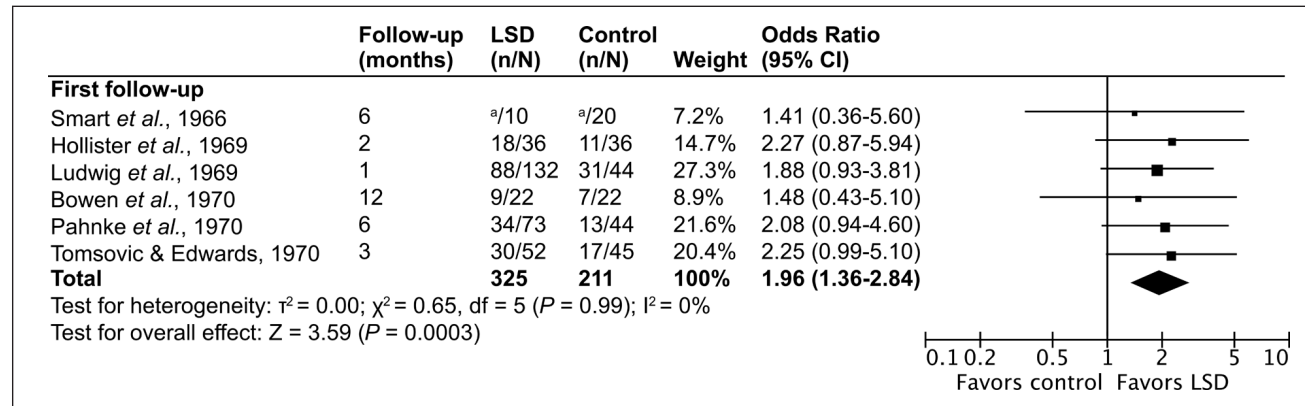


Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.

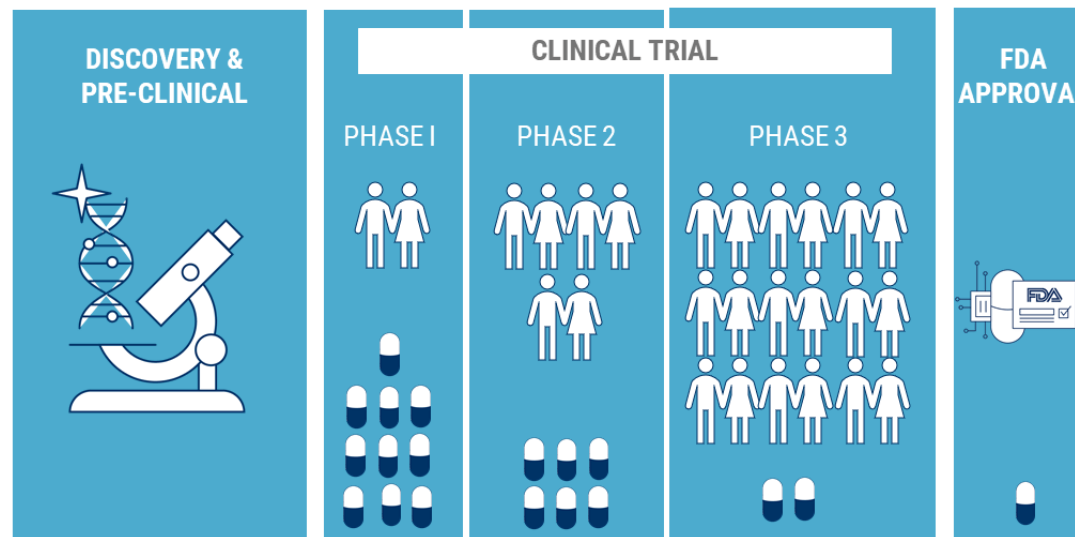
^aContinuous outcome data.

Effect size > all current therapies

The Present

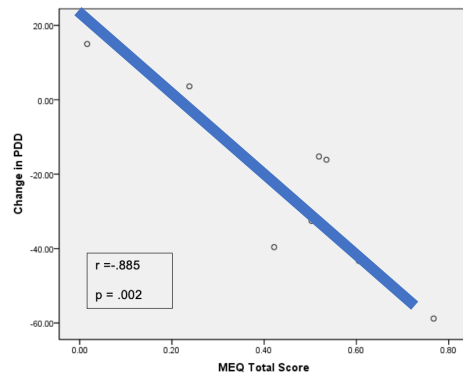
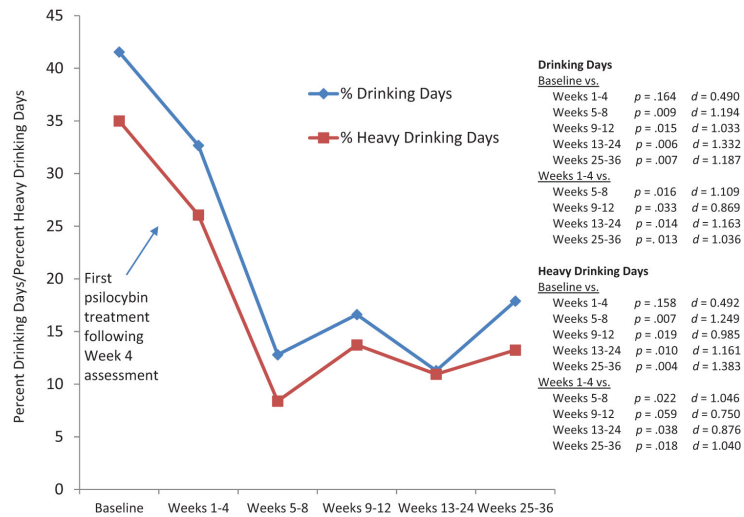
Modern clinical studies

Number of modern clinical trials in addiction & investment



Source: cbinsights.com

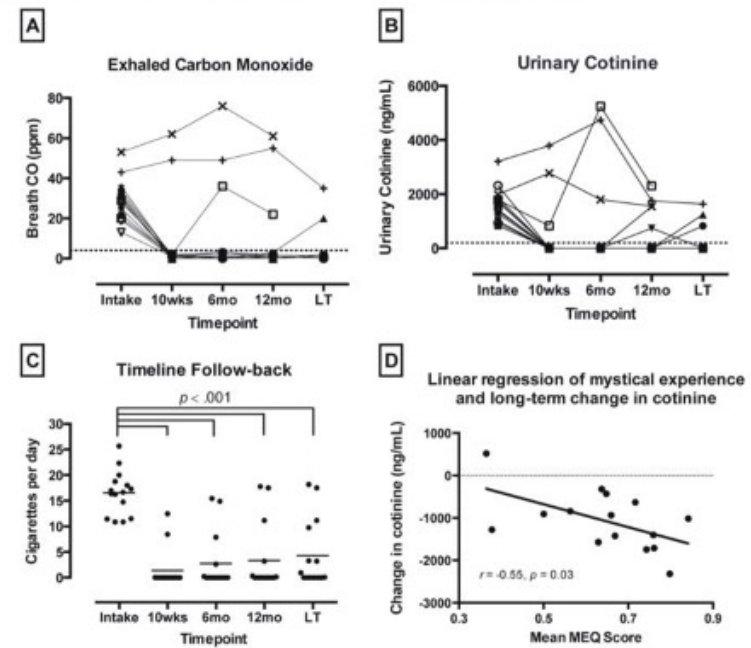
Psilocybin for alcoholism/smoking



Bogenschutz et al 2015

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}

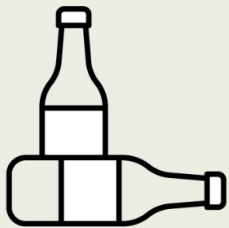


(A) Exhaled carbon monoxide (CO) shown for each participant from baseline through long-term follow-up (LT). (B) Urine cotinine levels shown for each participant from baseline through long-term follow-up. (C) Timeline Follow-back (TLFB) data of self-reported daily smoking; individual data points show 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.

RCT: Psilocybin-Assisted Treatment of Alcohol Use Disorder

POPULATION

53 Men, 42 Women



Adults with alcohol dependence
Mean age, 45.8 y

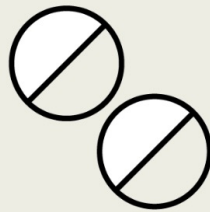
SETTINGS / LOCATIONS



2 Academic centers in New York and New Mexico

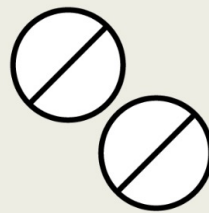
INTERVENTION

95 Individuals randomized



49 Psilocybin

Administered orally in 2 all-day sessions (dose range, 25-40 mg/70 kg)



46 Diphenhydramine control

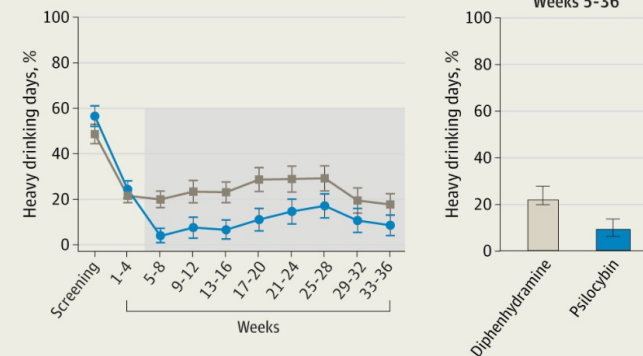
Administered orally in 2 all-day sessions (dose range, 50-100 mg)

PRIMARY OUTCOME

Percent heavy drinking days (scale, 0-100), assessed using the timeline followback interview, contrasted between groups over the 32-wk period following the first administration of study medication.

FINDINGS

Percent heavy drinking days during the 32-wk double-blind period was lower in the psilocybin group compared with the diphenhydramine group



Percent heavy drinking days

Psilocybin=9.7%

Diphenhydramine=23.6%

Mean difference, 13.9 (95% CI, 3.0-24.7; $P = .01$)



The Future

Theoretical concepts

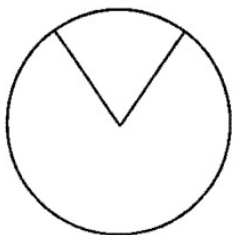


Addiction and Transcendence as altered states of consciousness (Metzner, 1994)

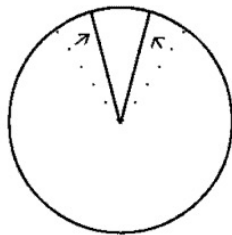


'Transcendent or ecstatic experiences, like the classic accounts of mystical or cosmic consciousness, involve a widening of the focus of attention, an expansion of awareness beyond the boundaries of the ordinary or baseline state. Thus, such experiences involve the opposite of the addictive contractions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

FIGURE 1
BASELINE AND CONTRACTED STATES

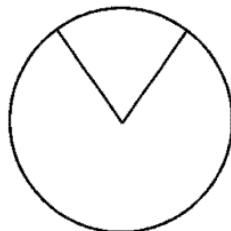


Baseline State of Consciousness

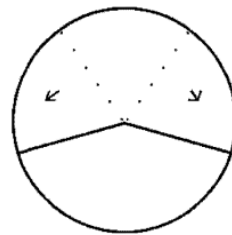


Contracted State/Fixation

FIGURE 2
BASELINE AND EXPANDED STATES

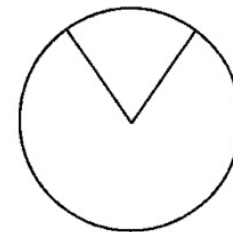


Baseline State of Consciousness

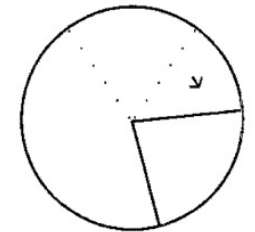


Expanded State/Transcendence

FIGURE 3
BASELINE AND CHANNEL-SWITCHING STATES



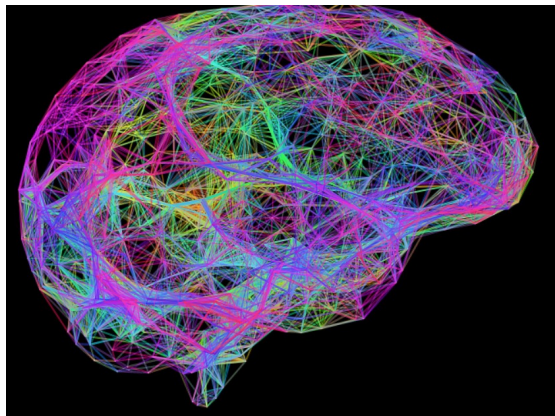
Baseline State of Consciousness



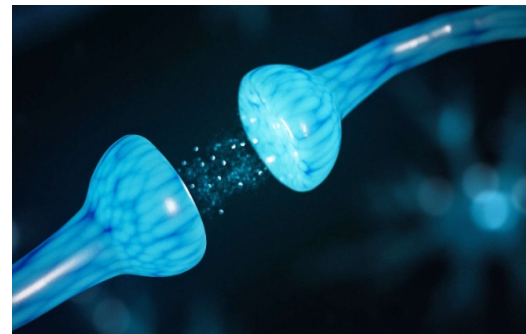
Dissociation/Switching Channels

Where can we make a start?

1. **Reward system** - Multimodal neuroimaging investigations of the mesocorticolimbic and salience system and how psychedelics modulate these
2. **Neuroplasticity** - how psychedelics can increase the efficiency of learning in neuronal tissues



Circuits/Systems



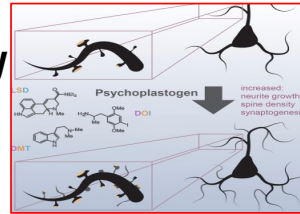
Molecular

Possible mechanisms

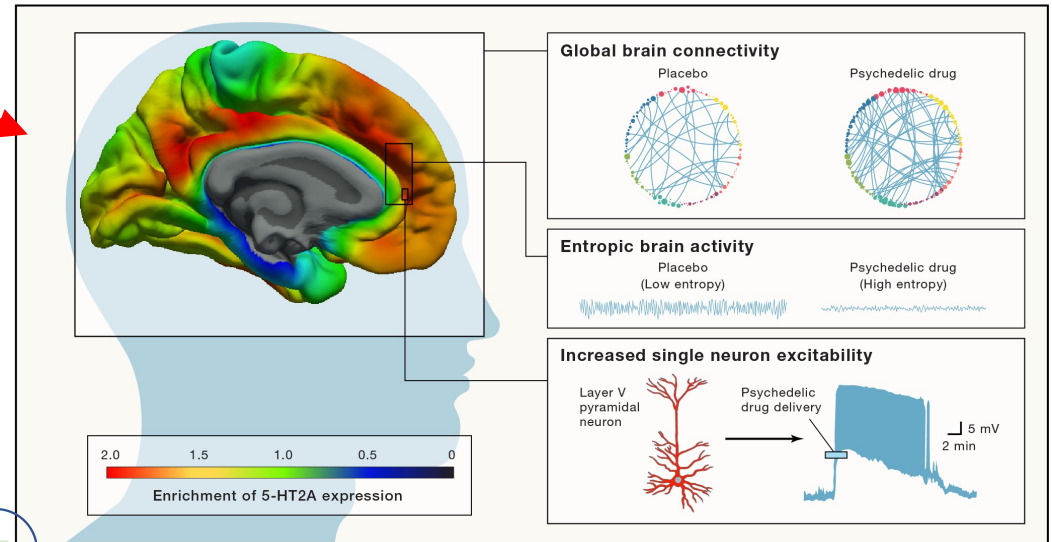
Serotonin 2A receptor stimulation

Serotonin & 2A receptor: plasticity

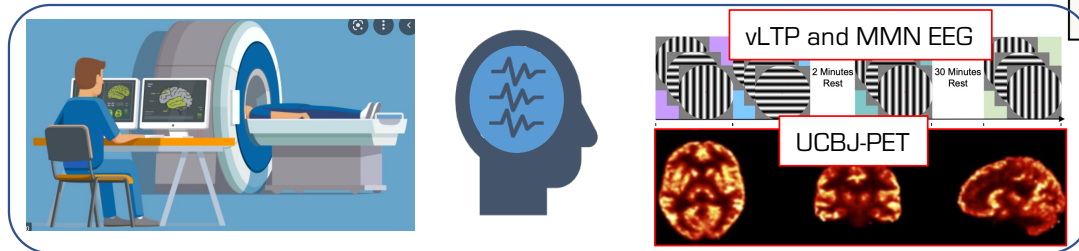
- Neuroplasticity (cortex) ↑
- Brain development
- Associative Learning/unlearning



Ly et al. 18. Cell



Nutt, Erritzoe, Carhart-Harris, Cell 2020



Key psychological effects:

- ↑ Connectedness & acceptance *Watts, 2017*
- ↓ Negative cognitive biases *Lyons, 2018*
- ↓ Rumination & thought suppression *Barba, 2021*
- ↑ Trait openness *Erritzoe 2018,19*



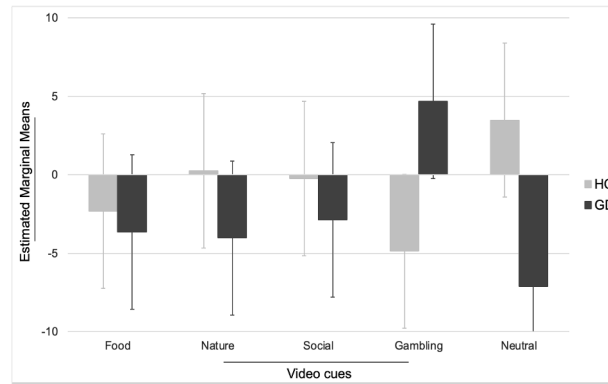
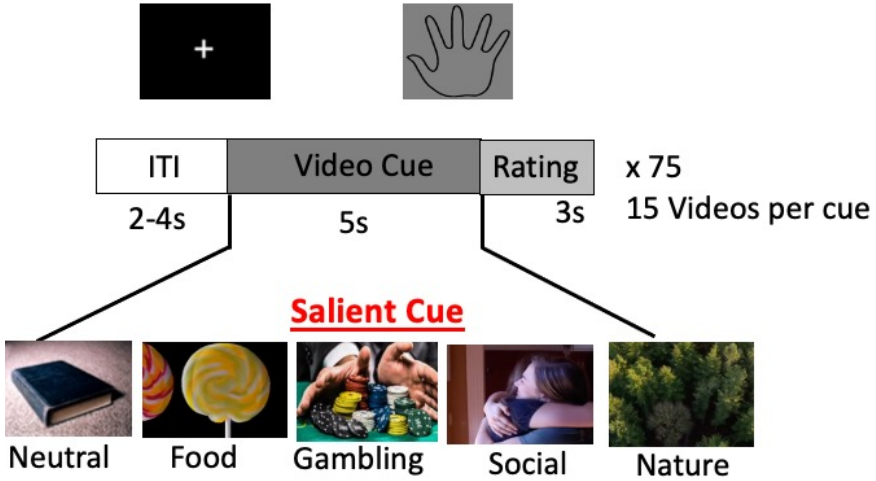
Bottom-up re-structuring of ingrained models of the world ?

Cahart-Harris: REBUS & anarchic brain

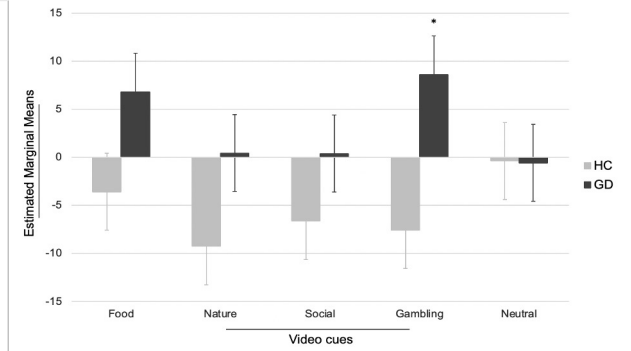
- ↓ Expectations about standard tones with MMN EEG paradigm [*Timmermann et al., 2017*]
- ↓ Hierarchical differentiation of trans-unimodal cortex [*Girn et al., 2022, & Timmermann in press*]



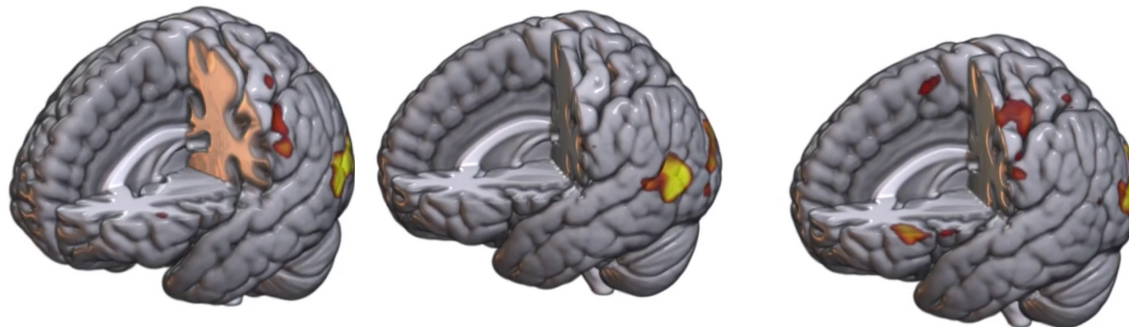
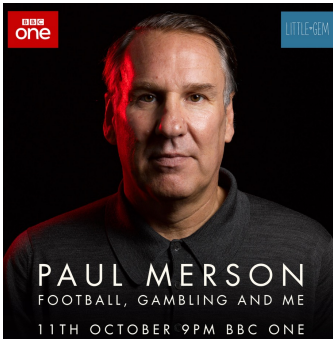
Cue-Reactivity



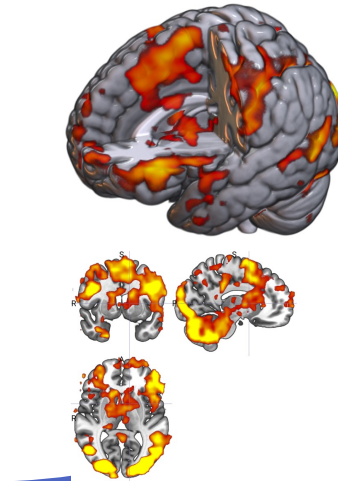
Ventral Striatum



Insula



Zafar et al unpublished



Psychedelics can expand state of consciousness and the brain states

FIGURE 1
BASELINE AND CONTRACTED STATES

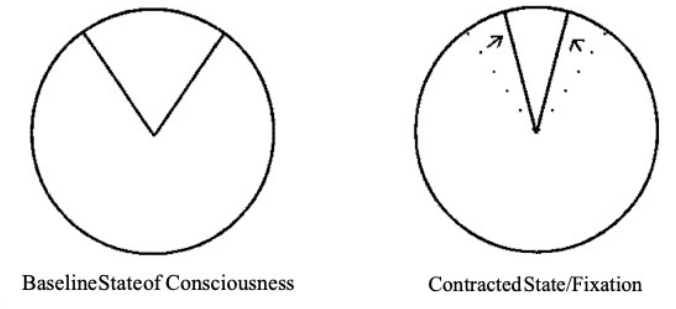
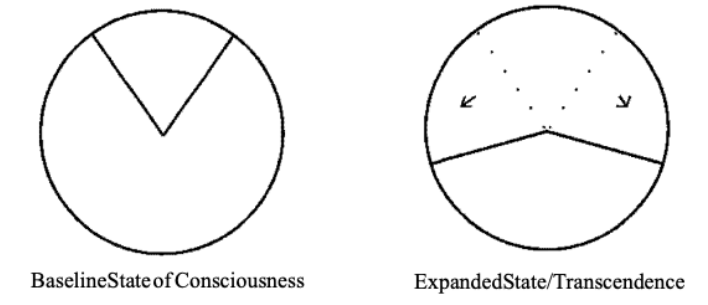


FIGURE 2
BASELINE AND EXPANDED STATES

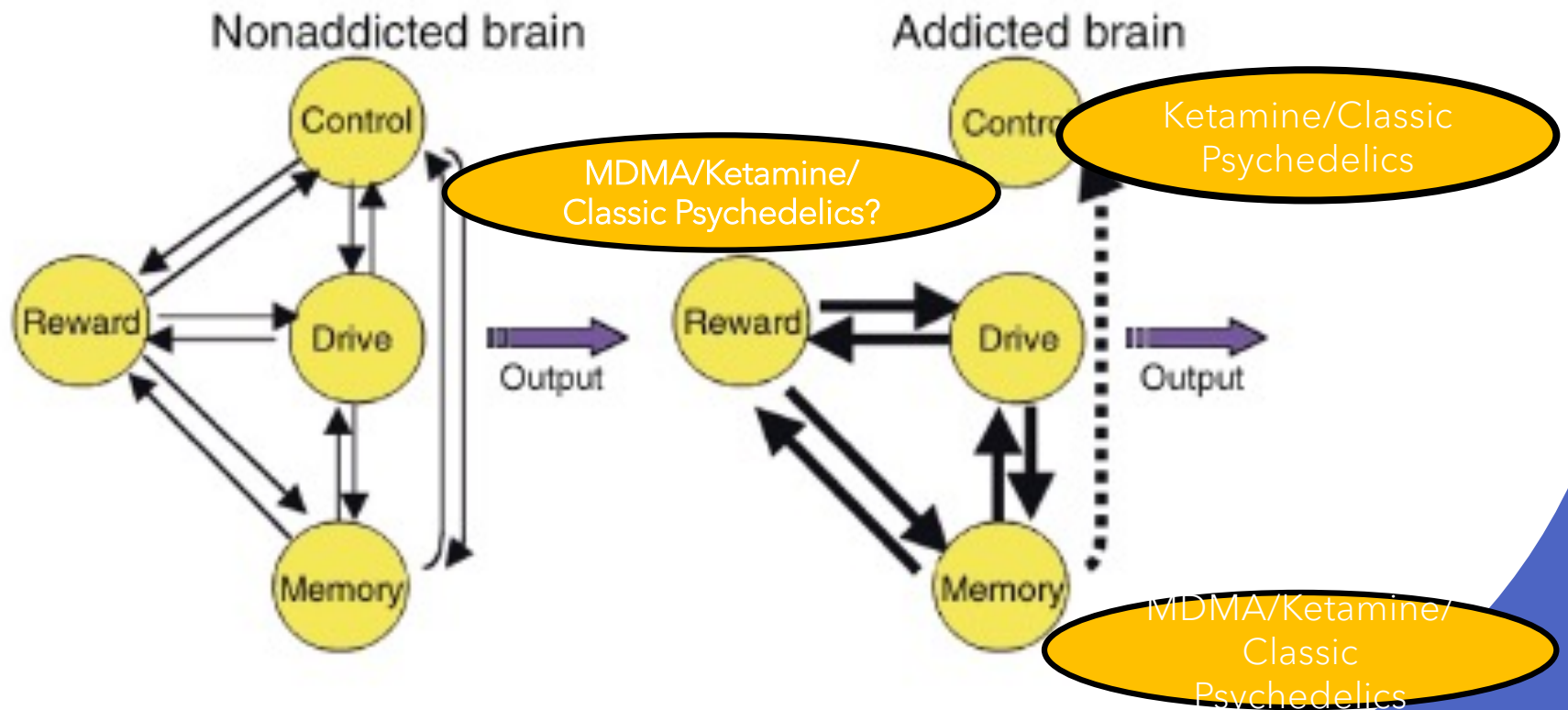


- Is this how they might treat addiction?
- Re-engage an individual with the world they live in

Re-connect - re-calibrate - re-broaden reward?

Can psychedelics change key brain pathways driving addiction?

Reward, motivation/drive, memory, control



Volkow et al 2016



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& PSYCHEDELIC RESEARCH CLINIC

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