

The ghost in the machine? examining change phenomena in psychedelic assisted psychotherapy



Andrew Penn, RN, MS, NP, APRN-BC
Psychiatric Nurse Practitioner
Kaiser Permanente
Redwood City, California
Assistant Clinical Professor
University of California, San Francisco,
School of Nursing
San Francisco, California

Charles L. Raison, MD
Mary Sue and Mike Shannon Chair for Healthy
Minds, Children & Families
Professor, Human Development and Family
Studies, School of Human Ecology
Professor, Department of Psychiatry, School of
Medicine and Public Health
University of Wisconsin-Madison
Madison, Wisconsin

Early History: Ceremonial

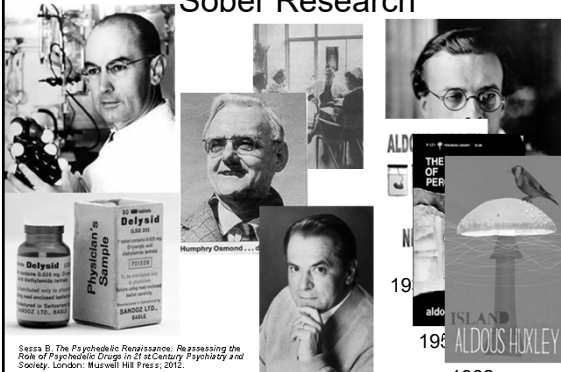
Mushroom Ceremony of the Mazatec Indians of Mexico



Sessa B. *The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in 21st Century Psychiatry and Society*. London: Muswell Hill Press; 2012.



1943–1960: Discovery of LSD, Sober Research



Sessa B. *The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in 21st Century Psychiatry and Society*. London: Muswell Hill Press; 2012.
Hofmann A, et al. *LSD: My Problem Child*. McGraw-Hill; 1980.

1960s: The Genie is Out of the Bottle



Sessa B. *The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in 21st Century Psychiatry and Society*. London: Muswell Hill Press; 2012. Lattin D. *The Harvard Psychedelic Club*. New York, New York: Harper Collins; 2010.

After a long winter, a cultural re-emergence of psychedelics and a spring of research is upon us...

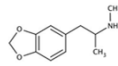


ClinicalTrials.gov

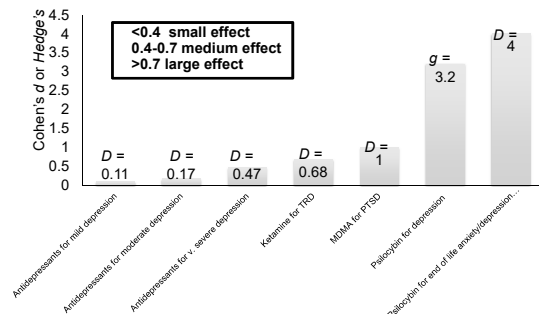


What is being studied?

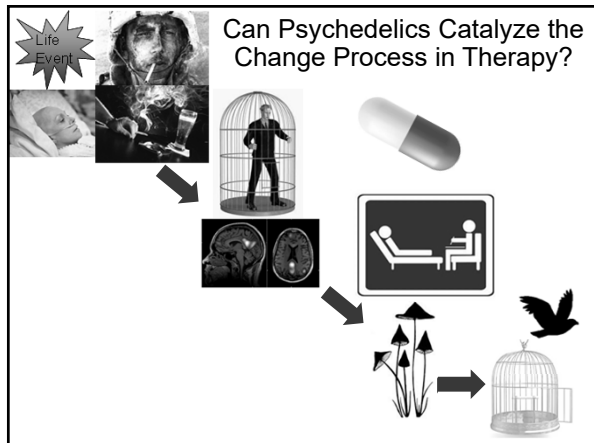
	Ketamine	MDMA	Psilocybin
Indication(s)	<ul style="list-style-type: none"> Treatment-resistant depression 	<ul style="list-style-type: none"> Treatment-resistant PTSD Social anxiety in autistic adults Anxiety at end of life 	<ul style="list-style-type: none"> Depression/Anxiety at end of life Alcohol dependence Nicotine dependence Depression
FDA/DEA	Off-label/CS III	Research only/CS I	Research only/CS I
Research status	Many centers and private practitioners already provide ketamine infusions	Phase II trials wrapping up, phase III likely soon	Phase II
MOA	NMDA receptor antagonist	Releaser of 5-HT ₁ , prolactin, oxytocin	5-HT _{2A} receptor agonist



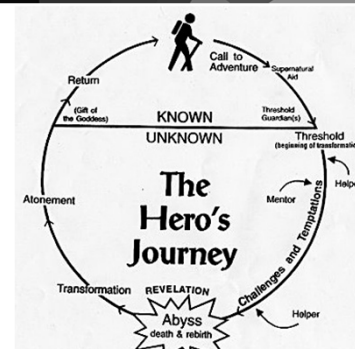
Comparative Effect Sizes for Different Treatments



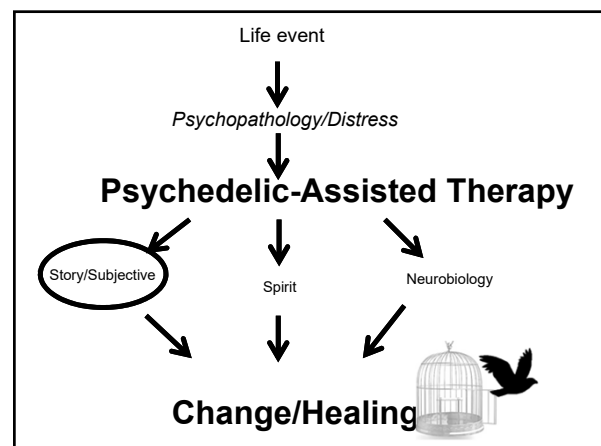
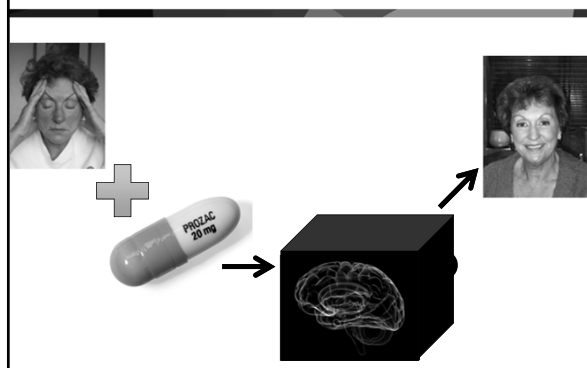
Fournier JC, et al. JAMA. 2010;303(1):47-53. Zarate CA Jr, et al. Arch Gen Psychiatry. 2006;63(8):856-864. Mithoefer M, et al. Presented at: American Psychiatric Association 168th Annual Meeting; May 16-20, 2015; Toronto, Canada. Mithoefer M. Personal Communication. April 16, 2015. ClinicalTrials.gov Identifier: NCT01211405. Carhart-Harris RL, et al. Lancet Psychiatry. 2016;3(7):619-627. Ross S. Presented at: HORIZONS; October 10-11, 2015; New York, NY.



The psychedelic experience as archetype of the hero's journey, a trip



When was the last time someone told you about their mystical transformative journey on Prozac?



Vitalism vs Mechanism

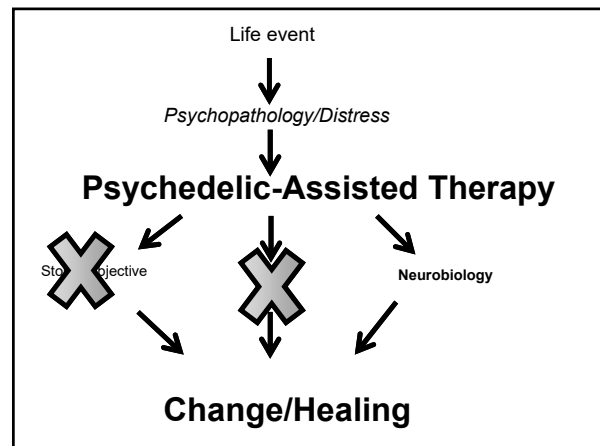
Mechanism – “the machine”

- “A doctrine that holds **natural processes (as of life) to be mechanically determined** and capable of complete explanation by the laws of physics and chemistry”
- The black box
- Deterministic/limited by observational ability
- Historic explanatory model of western medicine

Vitalism – “the ghost in the machine”

- “A doctrine that the processes of life are **not entirely explicable by the laws of physics and chemistry** and that life is in some part self determining”
- Soul/Story/Journey
- Holistic/vague
- Historic explanatory model of psychedelic induced change

www.merriam-webster.com/.



But what is actually happening inside the brain?

The diagram shows a person's head with a plus sign over the eye area, leading to a 3D brain model. An arrow points from the brain model to a person's face, suggesting a connection between internal brain activity and external perception.

If PTSD, Depression, and Addiction are Examples of Overly Rigid Brain States, Psychedelics May Be a Way to Loosen Them

The diagram shows a funnel representing different levels of consciousness. At the top is "primary consciousness" with "CRITICALITY" described as "a less rigid, slightly unpredictable brain more 'in the flow' and happier?". Below this is "Normal adult healthy waking consciousness". At the bottom is "reduced consciousness". To the left of the funnel are "High Entropy States" (more chaos, more unpredictable) including "Psychodelic state", "Infant consciousness", "Early psychosis", "Dreaming/ REM sleep", "Magical thinking", and "Highly creative/ fluid thinking". To the right are "Low Entropy States" (more rigid, more predictable) including "Depression", "PTSD", "OCD", "Addiction", "Later psychosis", "Seizure", and "Rigid thinking". A central question asks "Does this 'loosen' 'stuck mental patterns'?". A quote from Carhart-Harris RL, et al. (2014) is at the bottom: "Front Hum Neurosci. 2014;8:20."

Psilocybin

CCN(C)CCc1c[nH]c2cc(O)ccc12

Psilocybin

\rightarrow

CCN(C)Cc1c[nH]c2cc(O)ccc12

Psilocin

NC1=CC=C2C(=C1)C(=C(C=C2)O)N

Serotonin

- Potent agonist at
 - 5-HT_{1A}
 - 5-HT_{2C}
 - 5-HT_{2A}
 - Psychedelic effects blocked by **ketanserin** (selective 5-HT_{2A} antagonist)

Nichols DE. *Pharmacol Ther*. 2004;101(2):131-181. Vollenweider FX, et al. *Nat Rev Neurosci*. 2010;11(9):642-651. Passie T, et al. *Addict Biol*. 2002;7(4):357-364.

Psilocybin Decreases Activity in Key Connectivity Hubs (proportionate to subjective effects)

Thalamus

Anterior cingulate

Posterior cingulate

“To make survival possible, mind... has to be funneled through the **reducing valve** of the brain”

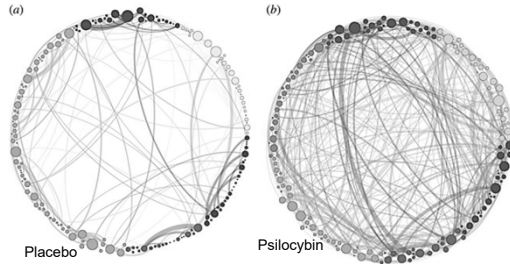
(and that psychedelics open the reducing valve)

—A. Huxley, 1954

Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2012;109(6):2138-2143.

Psilocybin: Less Constrained, More Intercommunicative Brain Communication

Simplified visualization of the persistence homological scaffolds.



Petri G, et al. *J R Soc Interface*. 2014;11(101):20140873.

Connectivity Hubs: Constrain, Route, Allow for Predictability



Leech R, et al. *PLoS One*. 2014;9(6):e98500. Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2012;109(6):2138-2143. Sood A, et al. *Explore*. 2013;9(3):136-141.

Does psilocybin loosen brain network rigidity found in depression?

Active in introspective, self-referential, complex mental imagery, metacognition, future predicting tasks

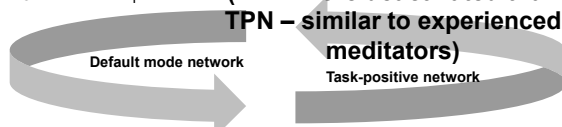
Active in external, task-oriented activities

Important connectivity hub

Home of the ego?

"Overstable" in depression?

Under Psilocybin – both networks become underactive and noncompetitive (DMN more deactivated than TPN – similar to experienced meditators)



DMN = default mode network; TPN = task-positive network. Sheline YI, et al. *Proc Natl Acad Sci U S A*. 2009;106(6):1942-1947. Leech R, et al. *PLoS One*. 2014;9(6):e98500. Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2012;109(6):2138-2143. Sood A, et al. *Explore*. 2013;9(3):136-141.

Rapid Reduction of Depression Lasting at Least 3 Months

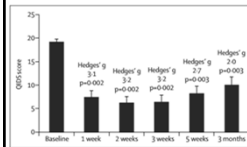


Figure 3: Mean depression severity (QIDS) over time
Depression severity determined by self-rated 16-item QIDS. QIDS scores of 16-20 are considered to reflect severe depression, scores of 11-15 are considered moderate depression, scores of 6-10 are considered mild depression, and scores of 5 and less are considered absent depression. All post-treatment assessments were obtained after the high-dose session (ie, 1 week post-treatment refers to 1 week after the high-dose session). Hedge's g values versus baseline are shown. QIDS=Quick Inventory of Depressive Symptom.

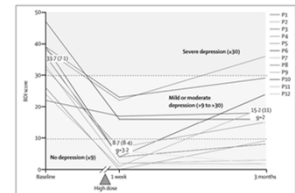
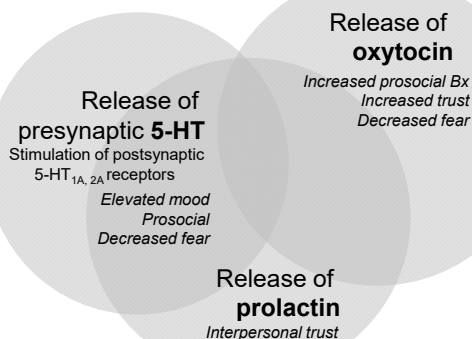


Figure 4: Depression severity (QIDS) over time, by patient
Figure shows depression severity (QIDS) over time plotted for each of the 12 patients. Mean values (SD) are shown as well as the relevant effect sizes (Hedge's g) versus baseline. QIDS=Quick Inventory of Depressive Symptom.

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627.

What Does MDMA Do?



Mas M, et al. *J Pharmacol Exp Ther*. 1999;290(1):136-145. McGregor IS, et al. *Br J Pharmacol*. 2008;154(2):358-368. Rudnick G, et al. *Proc Natl Acad Sci U S A*. 1992;89(5):1817-1821. Carhart-Harris RL, et al. *Biol Psychiatry*. 2015;78(8):554-562.

Optimal Arousal Zone

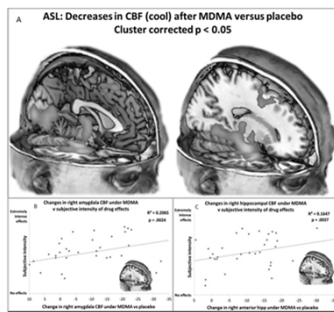
Flooded, overwhelmed, treatment is intolerable

Optimal arousal zone?

Reluctant, emotional numbing, treatment is avoided

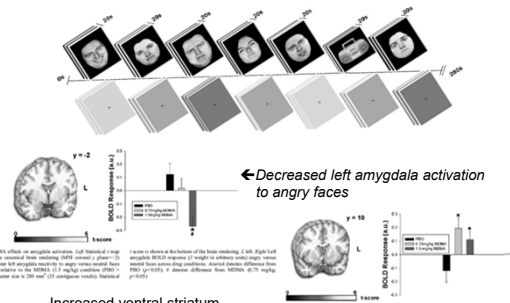
Siegel DJ. *The Developing Mind: Toward Neurobiology of Interpersonal Experience*. New York, NY: Guilford Press; 1999. Ogden P. *Trauma and the Body: A Sensorimotor Approach to Psychotherapy*. New York, NY: W.W. Norton; 2006.

MDMA Results in Decreased Activity in the Hippocampus and Right Amygdala



CBF = cerebral blood flow.
Carhart-Harris RL, et al. *Biol Psychiatry*. 2015;78(8):554-562.

MDMA May Quiet the Fear Response of the Amygdala



Bedi G, et al. *Psychopharmacology*. 2009;207(1):73-83.

Does MDMA Change the Emotional Distress Associated with Negative Memories?

No decrease in amygdala activity, but lowered connectivity between the left anterior temporal cortex and amygdala (an area associated with negative memory evoked emotion)

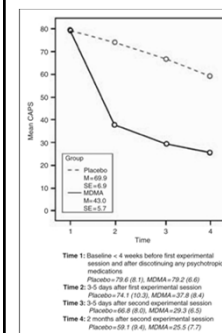
(b) Attenuated activations to worst memories under MDMA



Subjectively: worst memories rated less negative, positive memories rated more positively, vivid, and emotional on MDMA vs placebo (non-PTSD sample)

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

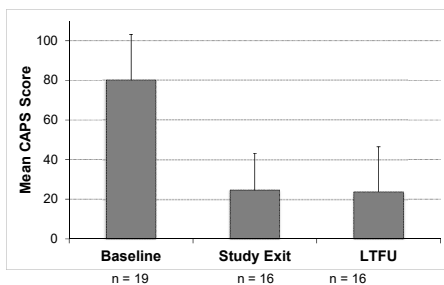
Change from Baseline after First and Second MDMA Session and at 2 Months Post-treatment



At endpoint, 83% of Treatment/MDMA Group (vs 25% placebo) No Longer Met DSM-IV PTSD Diagnosis

CAPS = Clinician-Administered PTSD Scale.
Mithoefer MC, et al. *J Psychopharmacol*. 2011;25(4):439-452.

Long-Term Follow-Up: Mean Global CAPS Scores 17 to 74 Months Post Final MDMA Session (Mean = 45.4 Months, SD = 17.3)



Error bars represent SD.
LTFU = long-term follow up.
Mithoefer MC, et al. *J Psychopharmacol*. 2013;27(1):28-39.

Upcoming Findings on Psilocybin for Depression/Anxiety in Cancer

Psilocybin, found in magic mushrooms, decreased anxiety and depression in patients diagnosed with life-threatening cancer. New research shows that patients who received a psilocybin dose that altered perception and produced mystical-type experiences reported significantly less anxiety and depression compared with patients who received a low dose of the drug. The positive effects lasted 6 months.

Griffiths R, et al. Active ingredient in magic mushrooms reduces anxiety, depression in cancer patients. Presented at: 49th Annual Meeting of the American College of Neuropsychopharmacology; December 10, 2015; Hollywood, FL.

Caveats and Cautions

- Psychedelic medicines do not have any currently recognized therapeutic usages per the US Food and Drug Administration, and all available data derive from small studies
- Multiple alternative treatments exist for both major depressive disorder and posttraumatic stress disorder that are far better studied, including the novel agent ketamine
- Although adverse events associated with psilocybin and MDMA are generally mild (eg, transient increase in blood pressure, nausea, anxiety, headache), limited data are available compared to currently approved medications
- It is unknown how many treatments patients would need to maintain long-term benefits or whether and/or how treatment with psychedelics might be combined with use of standard agents

Carhart-Harris RL, et al. *Lancet Psychiatry*. 2016;3(7):619-627. Johnson M, et al. *J Psychopharmacol*. 2008;22(6):603-620.

How is the psychedelic experience a hero's journey?

Winkler M. December 4, 2012. www.youtube.com/watch?v=Hhk4N9A0oCA. Accessed July 26, 2016.

What if the story/consciousness doesn't matter?

And the clinical outcome is the same, regardless of subjective experience?

What if the subjective experience ("trip") was just a "side effect" (epiphenomenon), and not the actual cause of the change?

How would this change our conversation around the re-imagination of psychedelics?

Does one need the subjective experience, the change of consciousness to experience healing?



What if the drug were administered under general anesthesia?

What if the healing was just "biological", and had nothing to do with the subjective narrative?

Raison CL. Personal communication. 2015.

The "Campfire" vs "Gas Grill" Approaches to Mental Health



A campfire requires external resources to continue, but burns under its own self-sustaining power. It is resistant to perturbations in its fuel source.



A gas grill requires external resources and an ongoing external source of fire. It stops the minute the gas stops.

Embracing non-duality and shadow

"And this too..." —Tara Brach, Buddhist teacher

- Psychedelic psychotherapy has the potential to bring non-dualistic (physiologic/mechanistic action AND narrative therapeutic journey/vitalism) to psychiatry
- What are the shadow aspects of mechanistic, western thinking?
- What are the shadow aspects of vitalistic, psychedelic-informed thinking?

Practical Take-Aways

1. Psychedelic drugs, such as psilocybin and MDMA, are far more than mere intoxicants and have a growing research base supporting their use in carefully controlled clinical settings as an adjunct to psychotherapy
2. The importance of conscious experience in the change process of psychiatric treatment remains unanswered, but the answers to this question hold broad implications for our treatment models
3. Functional network rigidity is a useful explanatory framework for helping patients understand the subjective experience of depression and anxiety and can become part of the education we provide to patients about their conditions