Psychedelics in Psychiatry

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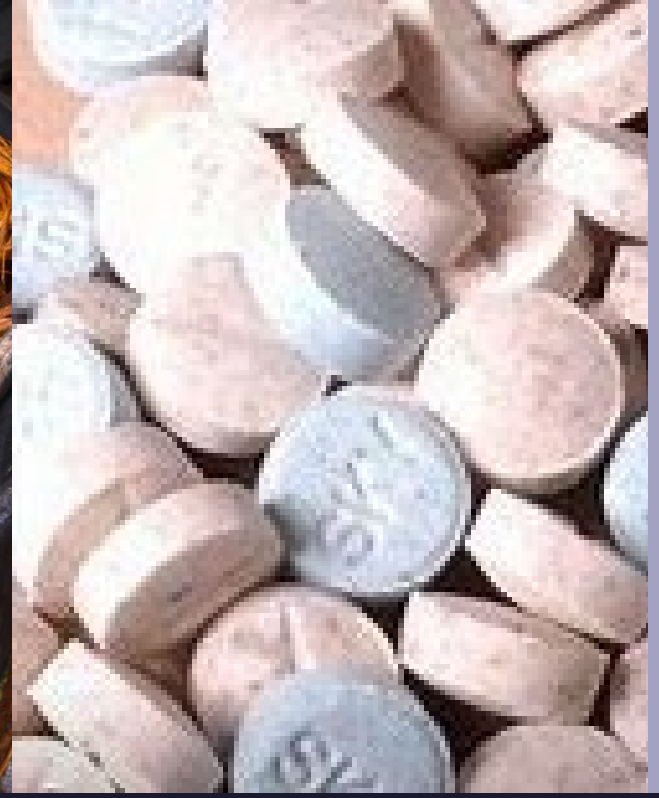


Disclosures

- I have no disclosures.

"**What we ordinarily call 'reality'** is merely that slice of total fact which our biological equipment, our linguistic heritage and our social conventions of thought and feeling make it possible for us to apprehend."

-Aldous Huxley

Agenda

- Definitions
- History
- Psychedelic Renaissance
- Highlights
  - Classical psychedelics
  - Entactogens / Empathogens
  - Dissociative substances
- Session Overview
- Challenges
- Research Directions

The Psychedelics:

a few definitions

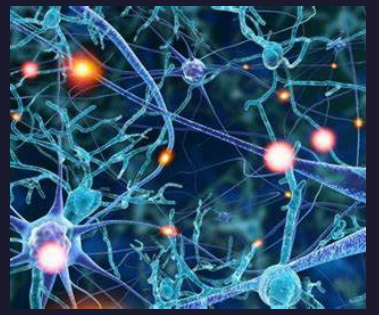
- psychomimetic: drug or substance that produces psychological and behavioral changes resembling those of psychosis
- mind altering substances: something that changes a mood or perceptions
- psychosis inducer: a substance that produces psychosis
- entheogens: a substance, typically of plant origin, that is ingested to produce a non-ordinary state of consciousness for religious or spiritual purposes

History

Ancient Times and Indigenous Use

Early Science

Prohibition



Renaissance

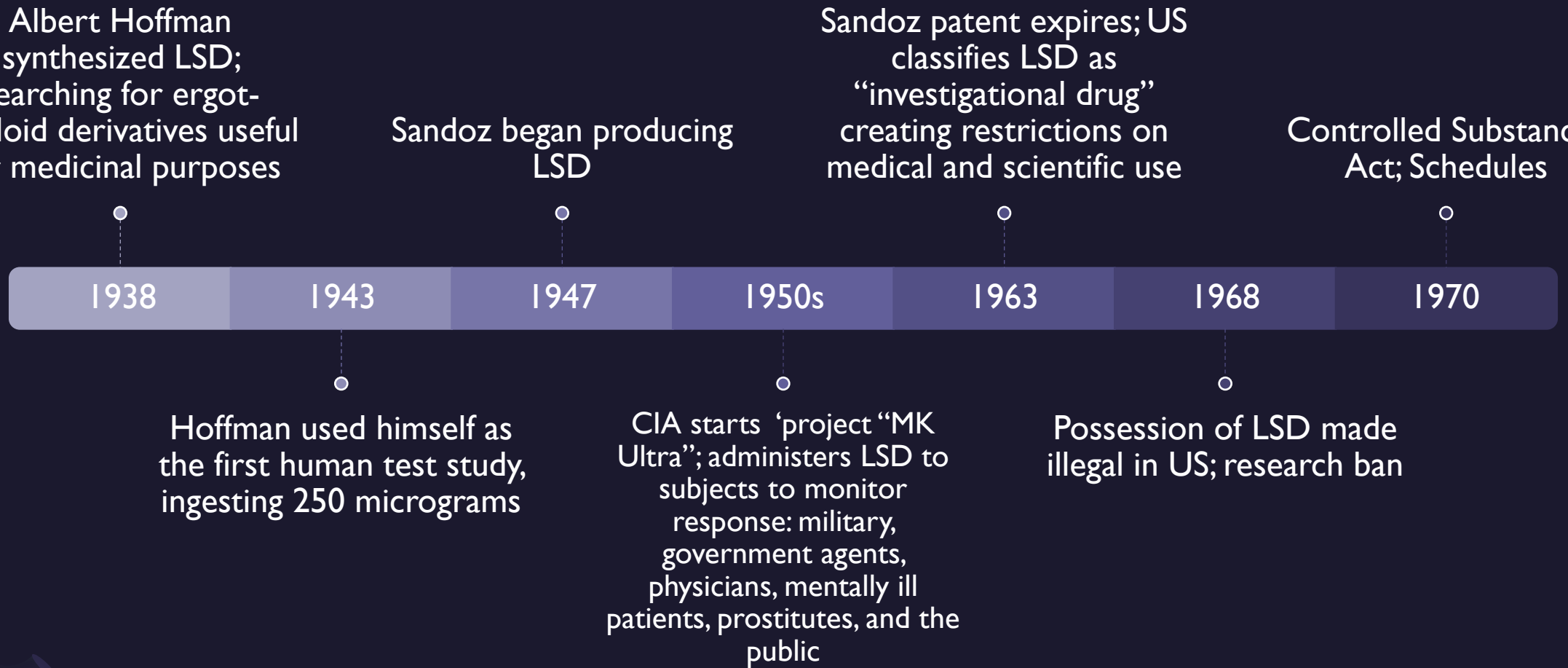
Ancient Times and Indigenous Use

- Evidence points to the use of psychedelic plants as early as 3500 BCE
- Traditional uses were tied to religious ceremonies, used for pain control and to prepare for battle
- Cacti including peyote, san pedro and peruvian torch containing mescaline which can be dried and smoked or infused into water or alcohol (mescal)
- Psilocybin, a mushroom native to the Americas ingested through chewing or creating a tea, to treat pain and participate in ceremonies
- Cannabis, typically from the marijuana plant, which has milder psychedelic properties
- Ayahuasca, a brew made from plants in the Amazon rainforest; contains the potent psychedelic DMT
- Salvia, a flowering plant which is a dissociative whose leaves can be smoked, chewed or made into a tea

Early Science: late 1800s-1960s

- 1895 first scientific trial involving peyote in Washington, DC at (now) George Washington University
- 1912 Anton Köllisch, a German chemist, became the first person to synthesize MDMA
- 1919 Ernst Spath synthesizes mescaline
- 1931 Richard Manske, a Canadian chemist, is the first to synthesize DMT
- 1938 chemist Albert Hoffman created d-lysergic acid diethylamide, aka LSD
- 1943 Hoffman self administers; starts to publish on methodologies and findings
- 1947 Sandoz Laboratories markets LSD and distributes it to psychiatrists to study effects on mental disorders
- 1958 Hofmann isolates and figures out the structure of psilocybin and psilocin
- 1960s Stanislav Grof, MD, PHD carried out more than 4,000 LSD-assisted therapy sessions
- **1966** ban on manufacturing and sales of peyote, mescaline, LSD, and DMT were prohibited in the US
- 1968 ban on personal use or possession for any reason
- 1970 Controlled Substances Act- schedules

Timeline of LSD



Schedule 1 substance

1) Is deemed to have a high abuse potential
2) Has no legitimate medical use and treatment
3) There is a lack of accepted safety for its use under medical supervision

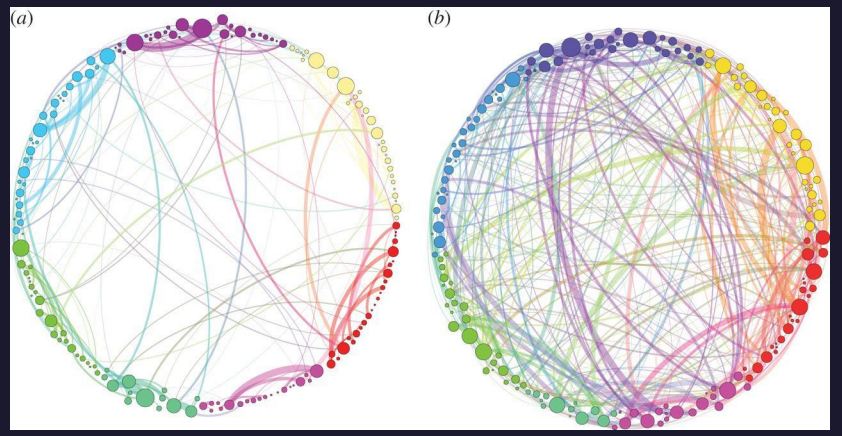
"the DEA's definition for high potential for abuse really means that people will take it without a prescription. It doesn't necessarily mean that it has the possibility of people getting addicted"
–David Nichols, PhD, Professor of Medical Chemistry and Molecular Pharmacology

What Happened?

- Before LSD was banned, the NIH funding more than 130 studies into the use of LSD for a variety of mental health conditions including anxiety, depression and alcohol use disorder
- Led to rapid advancements in brain science
- Adoption by the public of recreational use, and association with Vietnam era anti-war sentiments, led to fear, altered political landscape and ultimately banning of further study.

Psychedelics Renaissance: Current State of Study

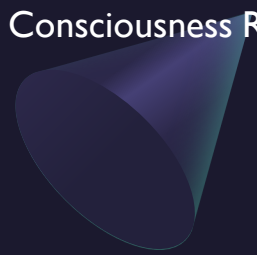
- The efforts of a dedicated few early on, paved the way to the recent resurrection of psychedelics study and renaissance
- Roland Griffiths et al discovered that a dose of psilocybin led to enduring improved mood and sense of well being when administered therapeutically
- Neuroimaging studies by Carhart-Harris and Nutt found that psilocybin dosing produced alterations in brain function, particularly in the default mode network, similar to an anti-depressant effect
- Studies paved the way for further investigation into depression, anxiety, substance use disorders, etc
- Likely future state, licensed for medicinal use in approved diagnoses



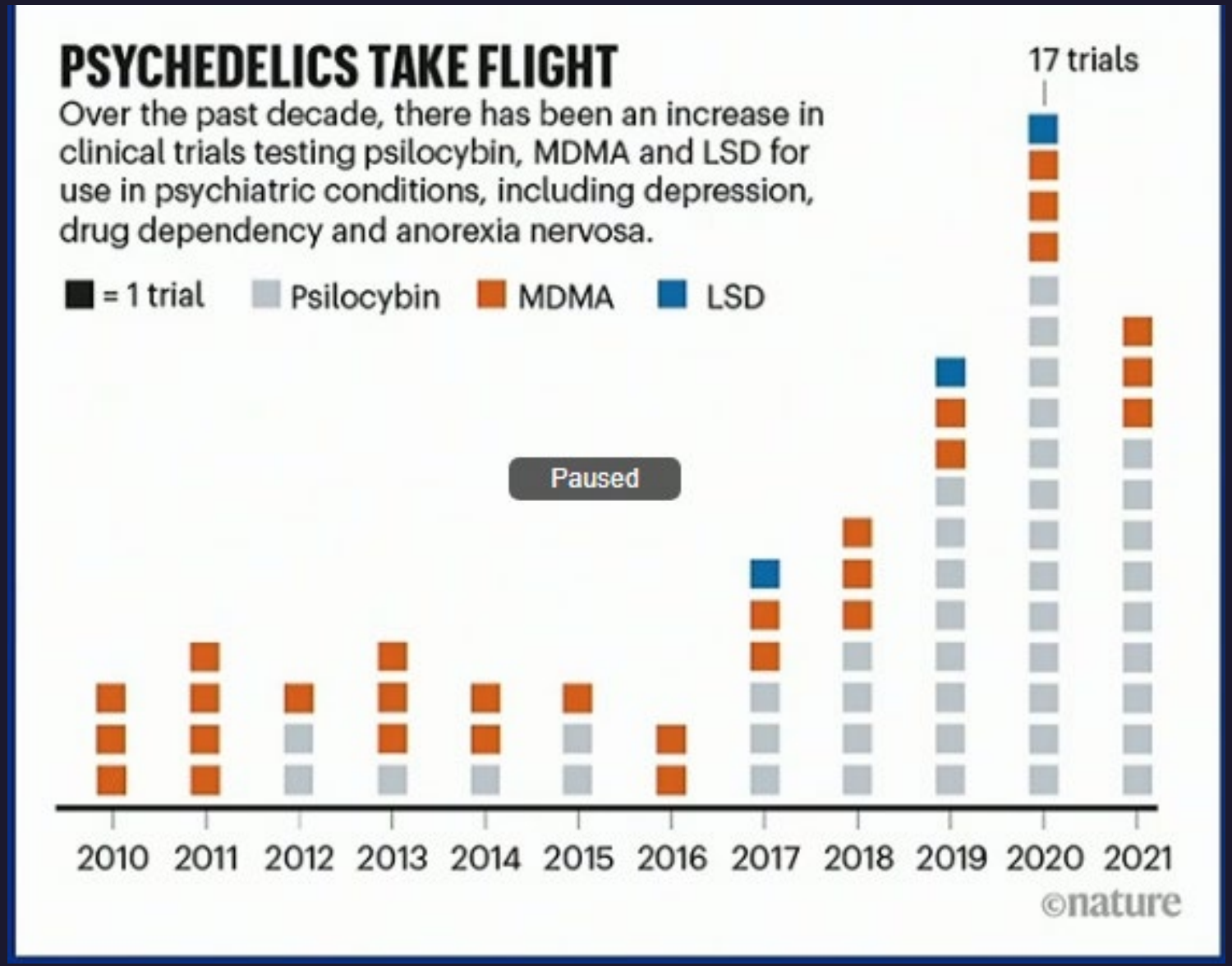
Petri G, Expert P, Turkheimer F, Carhart-Harris R, Nutt D, Hellyer PJ, Vaccarino F. 2014 Homological scaffolds of brain functional networks. J. R. Soc. Interface 11: 20140873.

Psychedelics Renaissance Timeline

- **1998** Franz Vollenweider discovers LSD and psilocybin bind 5-HT2A receptor
- **1999** Roland Griffiths, PhD establishes research at Johns Hopkins University to study the effects of psilocybin
- **2006** Griffiths publishes paper showing that psilocybin can induce mystical experiences
- **2009** Robin Carhart-Harris, PhD studies psilocybin in the UK
- **2011** Charles Grob, MD, publishes research on psilocybin reducing anxiety in cancer patients
- **2014** Petri et al demonstrates with imaging that psilocybin increases neuronal connectivity.
- 2016 Robin Carhart-Harris, PhD publishes on LSD increasing connectivity
- **2018** Study illustrates that ayahuasca leads to significant decreases in symptoms of depression
- **2019** Imperial College London launches Centre for Psychedelics Research*
- 2019 Launch of Hopkins Center for Psychedelic and Consciousness Research*



Current Wave



Psychiatric indications* under evaluation

	Depression	Social Anxiety	OCD	SUDS	PTSD	Eating Disorders	End of Life Distress	
Ayahuasca	√			√	√			
Ibogaine				√				
Ketamine	√							
LSD							√	
MDMA		√		√	√	√	√	
Psilocybin	√		√	√	√	√	√	

** Non-psychiatric indications under study as well including neurodevelopmental disorders (autism spectrum disorders), neurodegenerative disorders (Alzheimer's, Parkinson's, MS), pain conditions like headache, phantom limb and fibromyalgia, etc*

Psychedelic medicine: a re-emerging therapeutic paradigm

Kenneth W. Tupper PhD, Evan Wood MD PhD, Richard Yensen PhD, Matthew W. Johnson PhD

Table 1: Psychedelic agents currently under investigation for their potential benefits as adjuncts to psychotherapy

Substance	Derivation or chemical analogues	General effects and properties	Potential harms*	Potential therapeutic uses†
LSD	Ergot fungus (*Claviceps purpurea*); morning glory (*Turbina corymbosa*); Hawaiian baby woodrose (*Argyreia nervosa*) — sources of ergine or lysergic acid amide	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Hallucinogen persisting perception disorder	• Addiction (e.g., alcohol)[3] • Anxiety associated with terminal illness[4,5]
Psilocybin	Psilocybe and other genera of mushrooms (various species)	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Hallucinogen persisting perception disorder	• Addiction (tobacco, alcohol)[6,7] • Anxiety associated with terminal illness[8]
Ayahuasca brew (admixtures contain DMT)	Chacruna leaf (*Psychotria viridis*); Chagropanga vine (*Diplopterys cabrerana*); ayahuasca vine (*Banisteriopsis caapi*); assorted other admixture plants	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Nausea, emesis • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Serotonin syndrome and other dangers from medication interactions due to monoamine oxidase inhibitory activity	• Addiction (alcohol, cocaine, tobacco)[9,10] • Depression, anxiety[11–14]
Mescaline	Peyote cactus (*Lophophora williamsii*); San Pedro cactus (*Echinopsis pachanoi*)	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis	• Addiction (alcohol)[15]
MDMA	Sassafras tree (*Sassafras albidum*) — source of safrole, precursor chemical	• Serotonin, dopamine and noradrenaline agonist • Euphoria • Arousal • Perceptual alteration • Enhanced empathy and sociability	• Potential neurocognitive deficits (e.g., memory impairment) • Sleep disruption • Short-term depression	• PTSD[16–18]

Note: DMT = dimethyltryptamine, LSD = lysergic acid diethylamide, MDMA = methylenedioxymethamphetamine, PTSD = posttraumatic stress disorder.
*Potential harms identified here are associated with illicit and unsupervised nonmedical uses of psychedelic substances (often in the context of polysubstance use); current clinical studies on psychedelic agents have not reported such chronic adverse sequelae.
†Potential therapeutic uses are identified based on evidence from past (i.e., 1950s–1960s) and current research on psychedelic drugs.

Psychedelic drugs—a new era in psychiatry?

David Nutt, DM, FRCP, FRCPsych, FMedSci

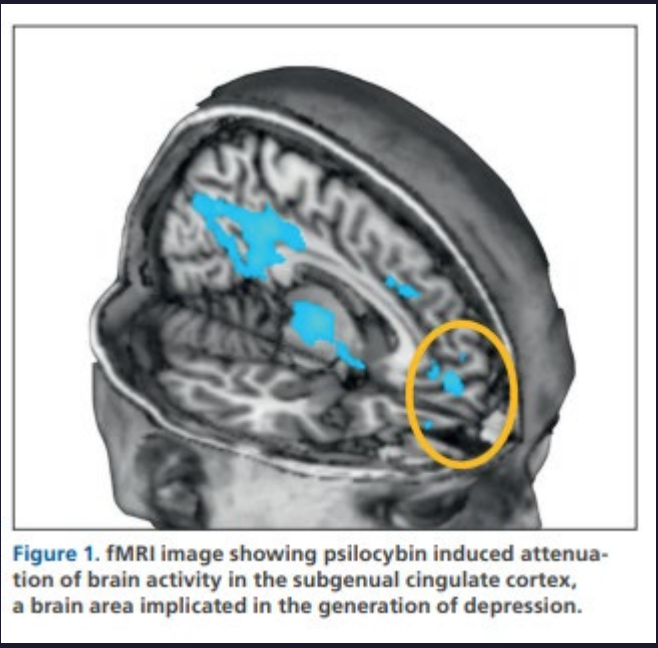


Figure 1. fMRI image showing psilocybin induced attenuation of brain activity in the subgenual cingulate cortex, a brain area implicated in the generation of depression.

STUDY AUTHOR AND REF	STUDY TYPE AND DOSE	TARGET ILLNESS	PRIMARY OUTCOME	STATISTICAL SIGNIFICANCE	PLACEBO
Moreno[22]	OCD	OCD	Reduced Y-BOCS	Effects at all doses	Low dose
Johnson et al[23]	Open 2-3 fixed 25-mg doses	Tobacco dependence	Abstinence	12/15 fully stopped	None
Bogenschutz et al[24]	Open 2-3 fixed 25-mg doses	Alcoholism	Reduced heavy drinking days		None
Carhart-Harris et al[26]	Open single dose 25-mg	Resistant depression	QIDS-SR	Max at 5 weeks	None
Grob et al[28]	Double-blind crossover	Cancer + acute stress reactions	Beck and POMS		Niacin
Griffiths et al[29]	2016 double-blind fixed-dose 25-mg	End of life mood changes	HAM-D and HAM-A	Max at 5 weeks	Low-dose psilocybin
Ross et al[30]	2016 double-blind fixed-dose 25-mg	End of life mood changes	Beck and STAI	6 weeks	Niacin
ONGOING STUDIES					
Carhart-Harris et al, unpublished	Reporting 2020 2 x 25-mg dose	Depression Psilocybin -v- escitalopram	fMRI brain measures and QIDS-SR	n/a	1-mg dose
COMPASS Pathways[31]	Reporting 2020 single 1, 10, 25-mg dose	Resistant depression Multicenter European study	MADRS	n/a	1-mg dose
BIMA Bristol University MDMA for Alcoholism, unpublished	MDMA 125-mg + 62.5 after 2 h	Alcoholism with significant trauma	Days of drinking	n/a	Open trial

Table I. Recent published and some current psilocybin studies. Y-BOCS, Yale Behaviour in Obsessive Compulsive Disorder Scale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; QIDS-SR, Quick Inventory overdose Depression Scale – Self Report; POMS, Profile of Mood States; STAI, Spielberg State Anxiety Inventory.

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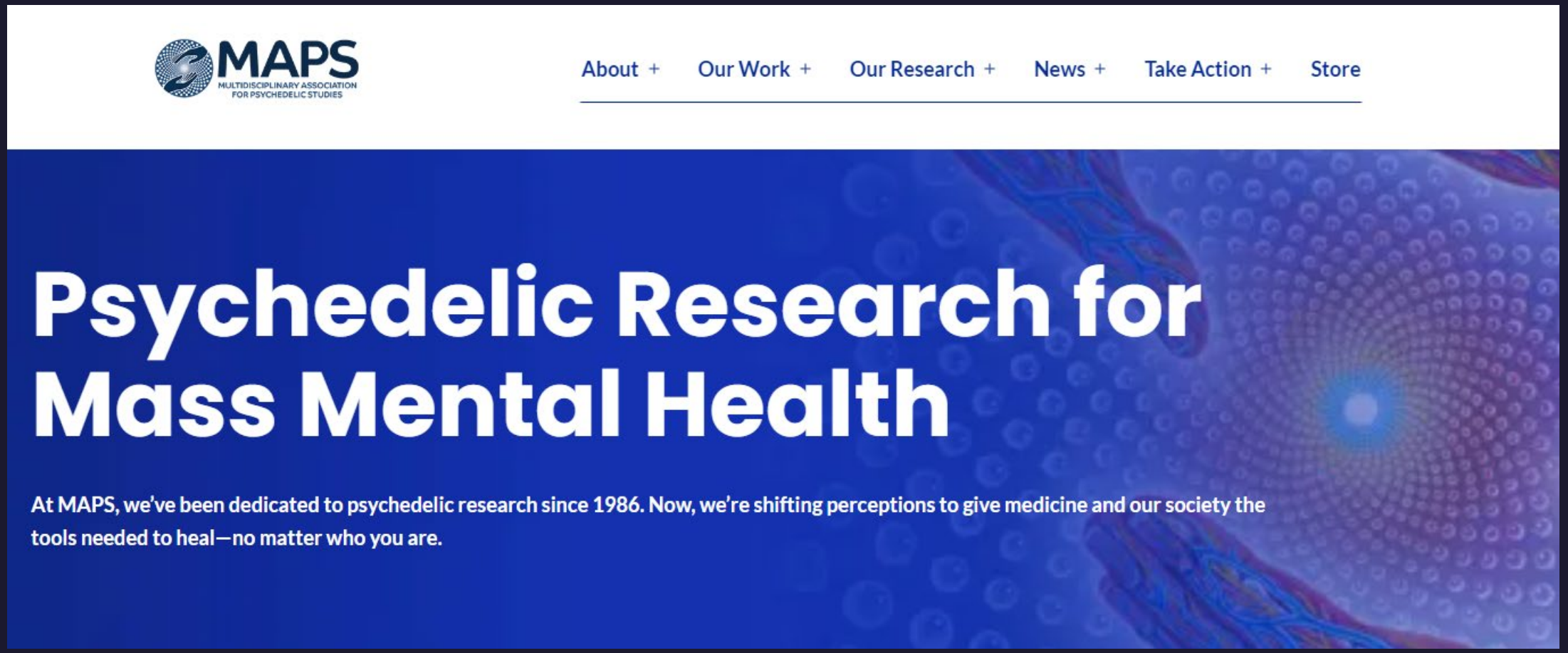
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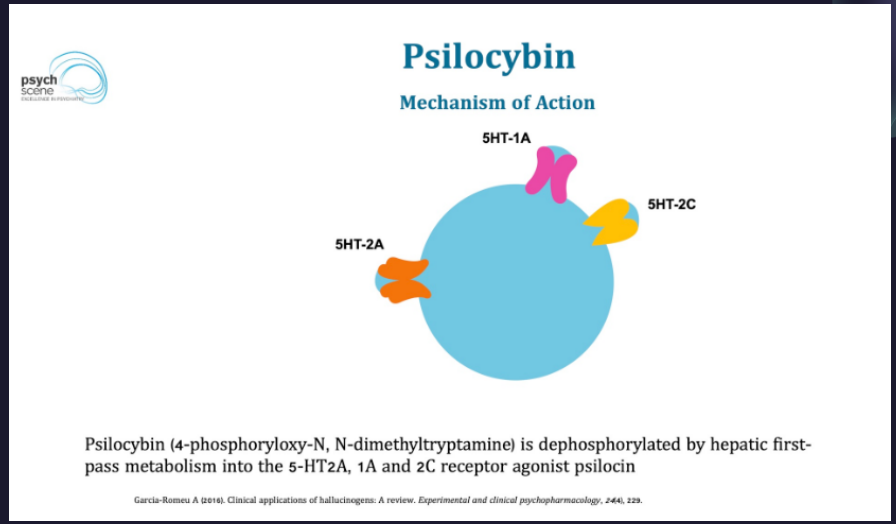
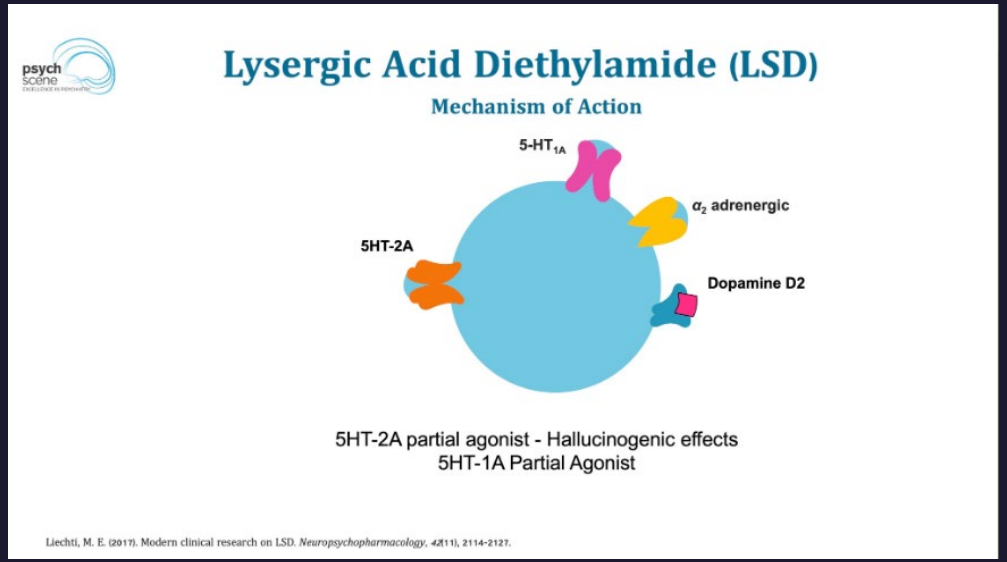
At MAPS, we've been dedicated to psychedelic research since 1986. Now, we're shifting perceptions to give medicine and our society the tools needed to heal—no matter who you are.

Classic Psychedelics

- Examples: LSD, Psilocybin, DMT (N,N-dimethyltryptamine)

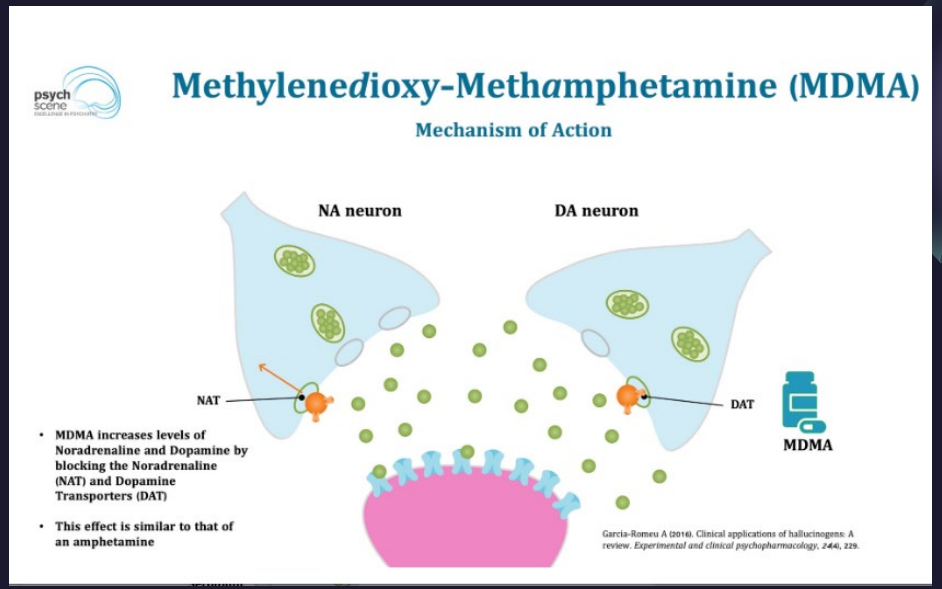
- Serotonergic hallucinogens
- Full or partial agonists of serotonergic 5-HT2a receptors
- Induce a state of altered perception, thought and feeling

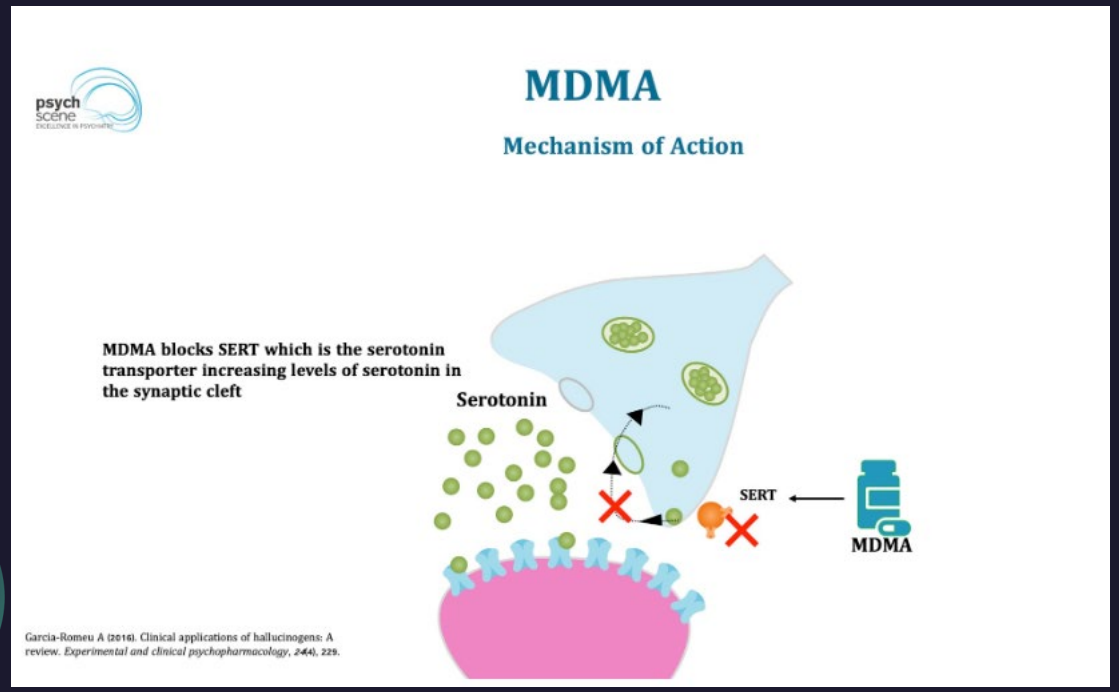




Empathogens / Entactogens

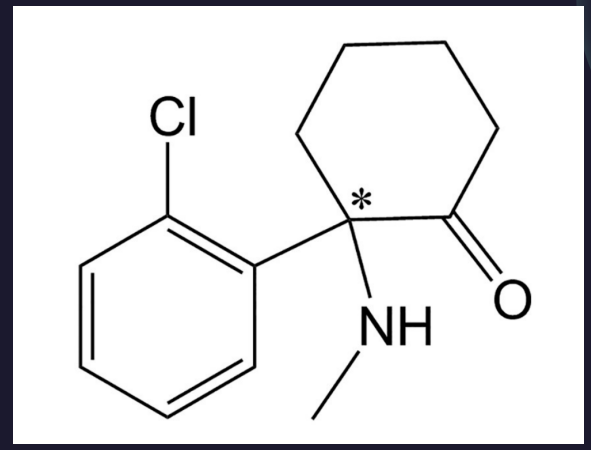
- Example: MDMA aka ecstasy (3,4-methylenedioxymethamphetamine)
- Mixed serotonin and dopamine reuptake inhibitors and releasers
- Induce a sense of emotional connectivity and increased sociability



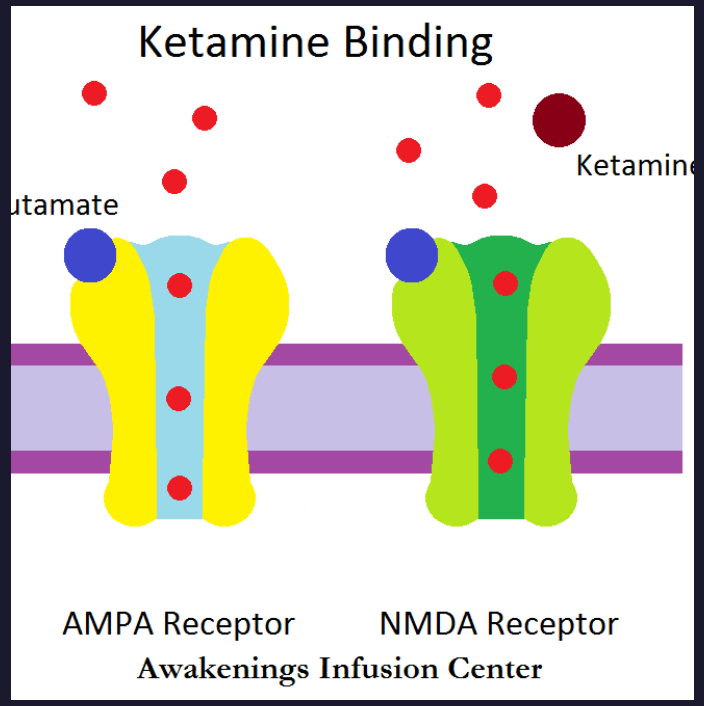


Dissociatives

- Example: Ketamine



- Reduces excitation, causes sedation and perceptual distortion
- Overly simplified: antagonism at NMDA receptor
- Leads to an increase in glutamate in the PFC
- Glutamate cascade stimulate receptors downstream that may increase expression of synaptic proteins leading to remodeling, e.g., increased synaptic plasticity

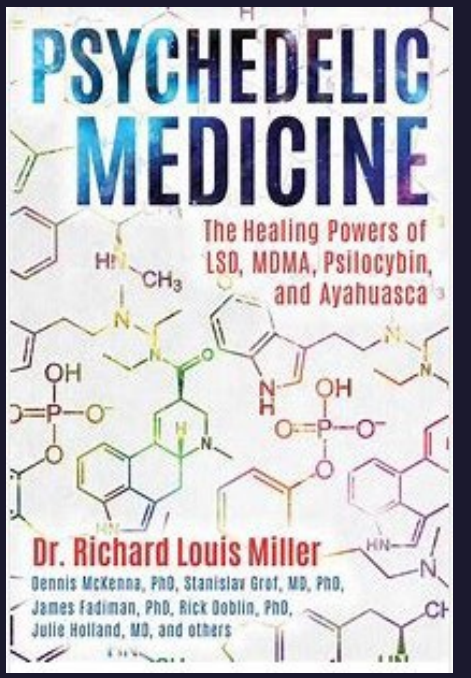


Book Excerpt:

"I received my first license to practice clinical psychology in 1966 while teaching psychology at the University of Michigan in Ann Arbor. One evening a colleague invited me to his home where he offered me the opportunity to experience DMT (dimethyltryptamine). I took one puff of the normal appearing cigarette, immediately closed my eyes, lay back, and explored the very deepest core of my consciousness and the very borders of the universe.

I had a clear sense that within the infinite universes I was smaller than what I see while using an electron microscope. I experienced being and nothingness. The experience lasted about twelve minutes. I sat up and asked for another puff. Once again I embarked on inner-space travel. I became a dematerialized inner-space traveler transcending time. I soared through the universe in search of the Source. I had a clear sense that I was a part of, and expression of, the whole of it all. My journey had begun."

-Dr. Richard Louis Miller, Psychedelic Medicine: the healing powers of LSD, MDMA, psilocybin and ayahuasca



Sessions

- A preparation session with a trained therapist, known as a guide is typical
- Explores the potential experience and approaches to any challenges
- In session, the patient may be offered eye shades and headphones with music compiled in advance
- Psilocybin sessions may last 4-5 hours
- The guide is present for assurance; however, the patient is not typically expected have significant engagement with the therapist
- Patients will typically experience an inner journey into visions, memories, thoughts
- Post session follow up: integration of experience + plan for ongoing psychotherapy

Challenges?

- Substances highly regulated: scheduled as dangerous, illegal drugs.
- How do you train an adequate number of therapists to act as guides?
- How do you ensure fidelity to good practice through structured, manualized treatment?
- How do you keep patients safe from those who would take advantage of "the next best thing?" without adequate training and knowledge?
- What is that necessary training and knowledge?
- How do you monitor outcomes in non-study environments?
- How do you prevent another prohibition?
- Other challenges you've identified?

Future Research Directions

Can psychedelics provide therapeutic effects without the "trip"; e.g., can the hallucinogenic and "mind-altering properties" be disentangled from the inner journey or is it the inner journey that provides therapeutic benefit?

But how do they really work?

What is consciousness?

What is reality?

How does my view of the world inform my response to it?

“Consciousness does not just passively reflect the objective material world; it plays an active role in creating reality itself.”

- Stanislav Grof, MD, PhD

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Thank You