

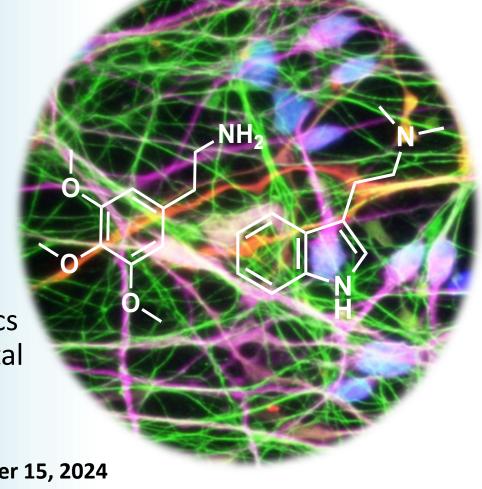
# The Neurobiology of Plant Medicine

Leveraging 21<sup>st</sup> Century Approaches to Ethnobotany

Stephen J. Haggarty, PhD

Mass General Center for the Neuroscience of Psychedelics Department of Psychiatry, Massachusetts General Hospital

Harvard Medical School, Boston, Massachusetts



4<sup>th</sup> Annual Conference on Psychedelics & Psychedelic Medicine | November 15, 2024



#### Disclosures

Dr. Stephen Haggarty: My spouse/partner and I have the following relevant financial relationships with a commercial interest to disclose.

Company	Nature of Financial Relationship	Status Past 2 Years
Souvien Therapeutics	Equity, Consultant, Scientific Advisory Board	active
Proximity Therapeutics	Equity, Consultant, Scientific Advisory Board	active
Sensorium Therapeutics	Equity, Consultant, Scientific Advisory Board	active
4M Therapeutics	Equity, Consultant, Scientific Advisory Board	active
Psy Therapeutics	Equity, Consultant, Scientific Advisory Board	active
Vesigen Therapeutics	Equity, Consultant, Scientific Advisory Board	ended
	Sponsored Research Support at MGH; Consultant, Scientific	
Entheos Labs	Advisory Board	active
Ilios Therapeutics	Consultant, Scientific Advisory Board	active
Biohaven Pharmaceuticals	Consultant, Scientific Advisory Board	ended
Alzheimers' Drug Discovery Foundation	Honorarium, Scientific Advisory Board	active
Fondazione Carpilo	Honorarium, Scientific Advisory Board	active
Lexicon Therapeutics	Sponsored Research Support at MGH	ended
Compass Pathways	Sponsored Research Support at MGH	ended
atai Life Sciences	Sponsored Research Support at MGH	ended
JW Pharmaceuticals	Sponsored Research Support at MGH	active
Stealth Biotherapeutics	Sponsored Research Support at MGH	ended

## Wide Spread Use of Psychoactive Plants in Modern Society

Coffee: Coffea arabica



Black Tea: Camellia sinensis



(Source: Köhler. Medizinal Pflanzen, 1897)

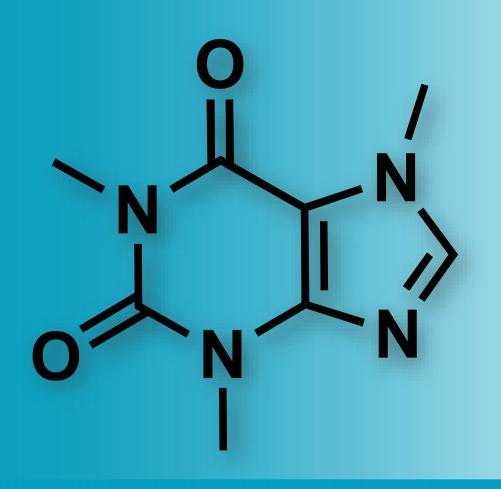


Mate: *Ilex paraguariensis* 



# Wide Spread Use of Psychoactive Plants in Modern Society



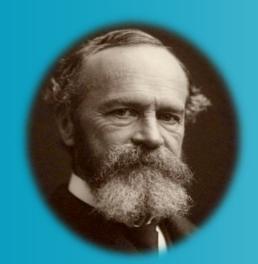


### Caffeine (1,3,7-trimethylxanthine)

- Central Nervous System Stimulant
- Antagonist of Adenosine Receptors
- Belongs to Alkaloid Compound Class

## Early Interest in Understanding Mechanisms of Human Brain Plasticity





**Dr. William James** *Principles of Psychology (1890)* 

"Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity.....phenomena of habit in living beings are due to the plasticity of the organic materials..."

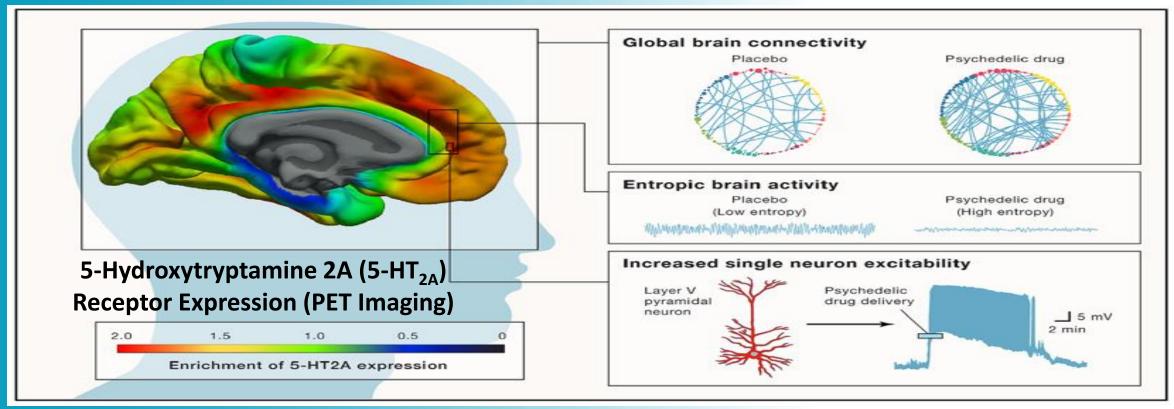
**Noetic Sense:** "profound sense of knowledge & states of insight into depths of truth unplumbed by the discursive intellect" (*The Varieties of Religious Experience, 1902*)

# Psychedelic Treatments: Imaging, Physiology & Clinical Studies Implicate Plasticity in Specific Brain Regions & Neurons



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Scientific Challenges: Neuroplasticity Operates at a Wide Range of Size Scales & Times



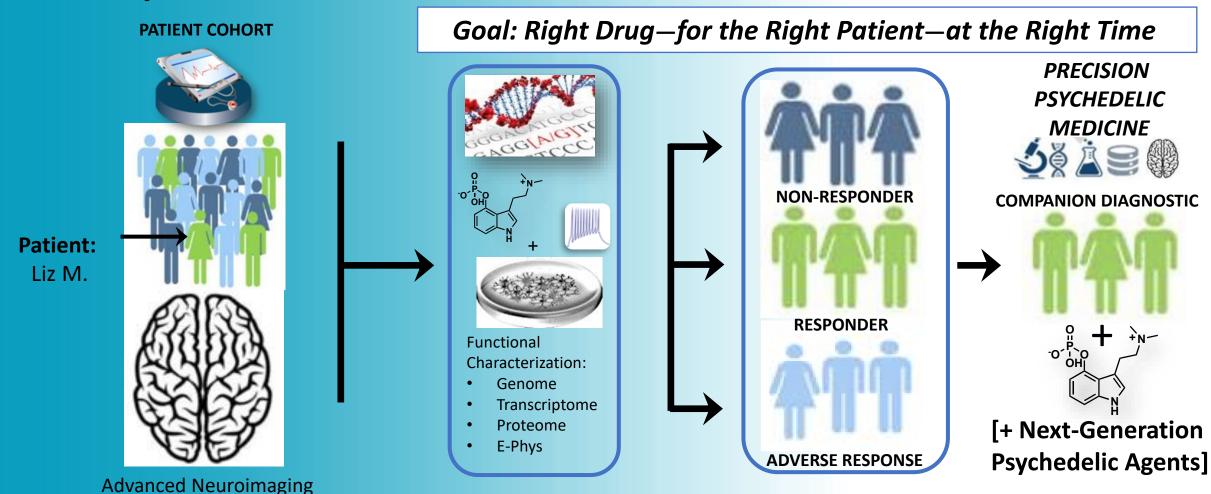
(Adapted: David Nutt, David Erritzoe & Robin Carhart-Harris. Psychedelic Psychiatry's Brave New World. Cell. 2020.)

### **Toward Optimizing the Precision** of Psychedelic Use as Medicines



**PRECISION** 

**MEDICINE** 



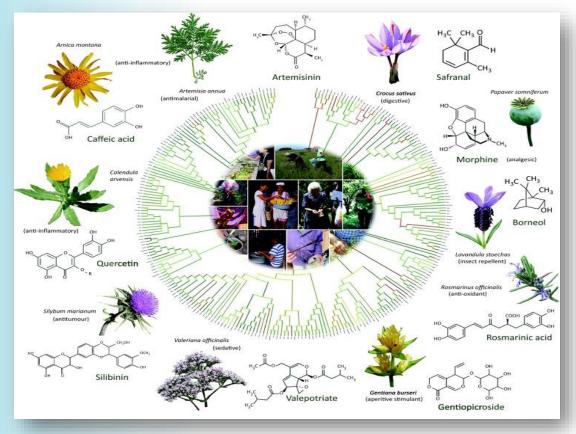
### Learning from the Fields of Ethnobotany & Ethnopharmacology



**PIONEERING the FUTURE by LEARNING FROM the PAST** 

- Ethnobotany is derived from the terms "ethnology," the study of human culture & "botany, the study of plants."
- Ethnobotany is the scientific study of the relationships that exist between people & plants

Adapted: Garnatje, et al. Ethnobotany, Phylogeny, and 'Omics' for Human Health and Food Security. *Trends in Plant Science*. 2017.

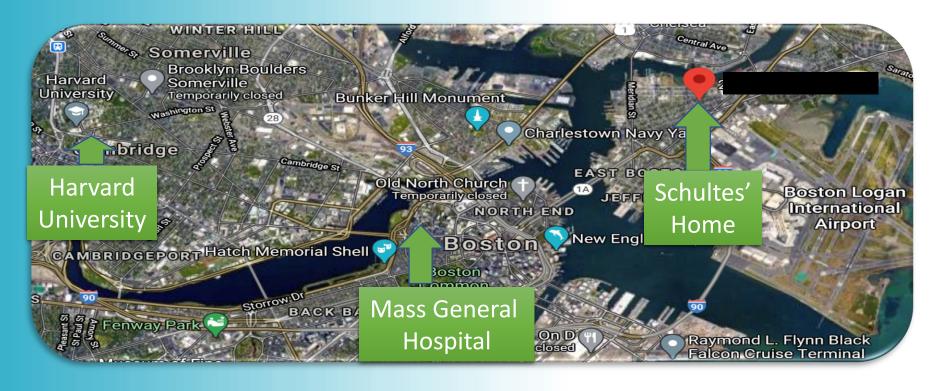


### Dr. Richard Evan Schultes: Enduring Legacy of Scientific Discovery & Collaboration GENERAL HOSPITAL PSYCHIATRY ACADEMY

In 2024: Innumerable Discoveries & Teachings Serve as Inspiration for Psychedelic Research



[January 12, 1915-April 10, 2001]



MASSACHUSETTS

(Source: https://news.harvard.edu/gazette/story/2001/04)

### Dr. Richard Evan Schultes: Enduring Legacy of Scientific Discovery & Collaboration GENERAL HOSPITAL PSYCHIATRY ACADEMY

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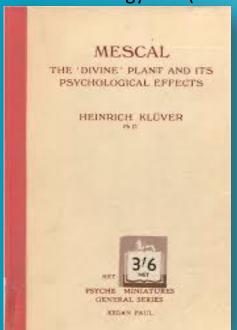
[January 12, 1915-April 10, 2001]

- Considered founder of modern ethnobotany field the study of Indigenous Peoples' uses of locally available plants in particular as medicines
- Came to Harvard as an undergraduate bound for Medical School
- Completed his AB (1937), AM (1938) & PhD (1941)
- Served at the Harvard Botanical Museum
  - 1941 to 1953: research associate (fieldwork)
  - 1958 to 1985: curator of Economic Botany
  - 1967 to 1985: executive director/director
- Served as Harvard Professor
  - Professor of biology at Harvard (1970); Mangelsdorf Professor of Natural Sciences (1973)
  - Edward C. Jeffrey Professor of Biology/Emeritus (1980/1985)
- Trained & inspired a generation of interdisciplinary scientists & in doing so (un/knowingly) helped lay the foundation for psychedelic medicine.

(Sources: Wade Davis. One River. 1996. https://news.harvard.edu/gazette/story/2001/04)

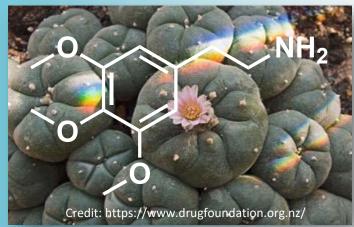


Read for Class Assignment: Harvard Biology 104 (1936)



Author: German Psychiatrist Dr. Henrich Klüver (1928)





- Native Americans as part of religious ceremonies for thousands of years
- German scientist Dr. Karl Heffter (1897) identified mescaline as active principle
- Mescaline synthesized by Austrian chemist Dr. Ernst Späth (1919)

21-year old Schultes asked to write his Harvard thesis on peyote

Prof. Oakes Ames:
Agreed <u>only if studied</u>
use by **Kiowa People** of
Oklahoma, USA

(Sources: Wade Davis. One River. 1996. https://www.arcgis.com/apps/MapJournal/; https://www.amazonteam.org/maps/schultes/en/)

MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

- Visited 15 tribes taking peyote 2-3 times/week
- Schultes learned value of inter-disciplinary collaboration (Shamans & Weston La Barre)
- Lifelong friendships with indigenous peoples
- Exposed Schultes to experiences beyond contemporary science
- Published: Peyote & Plants Used in the Peyote Ceremony (1937); The Appeal of Peyote (Lophophora williamsii) as a Medicine (1938)
- Defined path to future career



1936 Kiowa Territory, Oklahoma
21-year-old Richard E. Schultes (left)
Kiowa Shaman Belo Kozad (center)
Anthropologist Weston La Barre (right)

(Sources: Wade Davis. One River. 1996. https://www.arcgis.com/apps/MapJournal/; https://www.amazonteam.org/maps/schultes/en/)



- While researching peyote...Schultes becomes intrigued by references to a scared mushroom known as teonanácatl or
   "flesh of the gods" used by Aztecs for divinatory purposes; skeptical of claims was a cactus (peyote) & not a mushroom
- 1938: 24-year old Schultes travelled to Mexico to investigate (Harvard Master's Thesis)
- 1939: Schultes & Austrian-born/Mexican ethnobotanist Blas Pablo Reko solved 300-year old botanical mystery



# BOTANICAL MUSEUM LEAFLETS HARVARD UNIVERSITY CAMBRIDGE, MASSACHUSETTS, FEBRUARY 21, 1939 Vol. 7, No. 3 PLANTAE MEXICANAE II BY RICHARD EVANS SCHULTES THE IDENTIFICATION OF TEONANACATL, A NARCOTIC BASIDIOMYCETE OF THE AZTECS

(Sources: The Amazonian Travels of Richard Evans Schultes, by Brian Hettler & Mark Plotkin. https://www.amazonteam.org/;
Wade Davis. One River. 1996. Rolf, Singer. Mycological investigations on Teonanacatl, the Mexican hallucinogenic mushroom. Mycologia. 195.)



AMERICAN ANTHROPOLOGIST

[n. s., 42, 1940

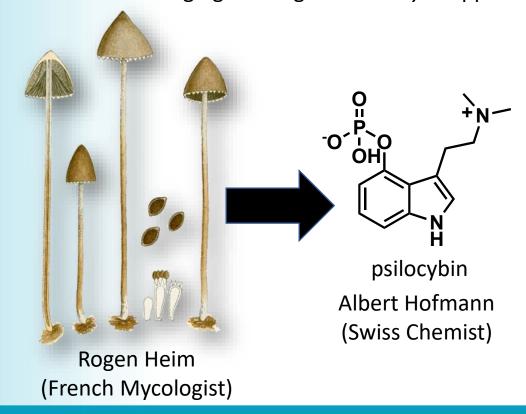
TEONANACATL: THE NARCOTIC MUSHROOM OF THE AZTECS<sup>1</sup> By RICHARD EVANS SCHULTES

BECAUSE of the important roles which they played in ceremonial and in daily life, the narcotic plants of ancient Mexico are of especial interest to the anthropologist. Mexico possessed and still possesses many plant narcotics and intoxicants, of which a few are outstanding in their uses and are extremely interesting because of their great antiquity as well as because of the important bearing their use, distribution, and history may have on questions of a theoretical nature. Of these, the most notable are the toleselo or coral-berry (Sophora secundiflora (Ort.) Lag. ex DC.), ololiuqui or piule (Rivea corymbosa (L.) Hall. f.), peyote (Lophophora Williamsii (Lem.) Coult.), and teonanacatl (Paneolus campanulatus L. var. sphinctrinus (Fr.) Bresadola).

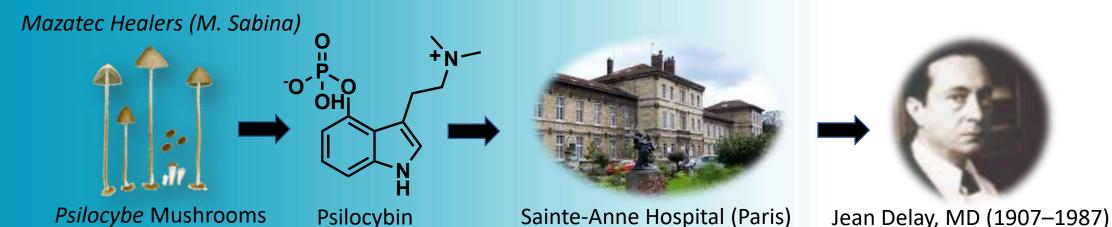
(Also: Reko BP. Teonanacatl, the Narcotic Mushroom. American Anthrop. 1940.)

- Original publications ignored for > 12 years
- World War II interrupted follow-up research
- 1952: amateur mycologist (G. Wasson) takes interest

Teonanacatl now recognized as likely > 1 species also belonging to the genus *Psilocybe* spp.







Gordon Wasson → Dr. Roger Heim (French Mycologist) → Dr. Albert Hofmann (Swiss Chemist)

- Mass production of fungal mycelia led Dr. Author Brack & Dr. Hans Kobel at Sandoz
- Isolated the two active agents (psilocybin & psilocin)
- Dr. Albert Hofmann & chemistry colleagues at Sandoz defined their molecular structure & completed total synthesis

#### **Dr. Jean Delay** (French Psychiatrist)

- Coined the word "psychopharmacology" & first trials with chlorpromazine (Thorazine) in 1952
- First clinical trials at (1958): psilocybin (10 mg) sublingually to 4 healthy controls + 14 patients with varied diagnoses
- Psilocybin caused "hallucinations, dreamlike states, reliving of emotionally charged experiences & modifications of mood"
- Manifestations varied from subject to subject



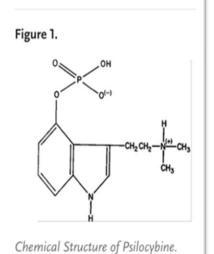
PSYCHIATRY ACADEMY

#### Experimental Psychiatry. V — Psilocybine, a New Psychotogenic Drug

Max Rinkel, M.D.<sup>†</sup>, Charles R. Atwell, M.A.<sup>‡</sup>, Albert DiMascio, M.A.<sup>§</sup>, and Jonathan Brown, B.A.<sup>¶</sup>

Psilocybin Has its First Medical Investigation In Boston

SILOCYBINE (Fig. 1), THE phosphoric ester of 4hydroxytryptamine, has been established by Hofmann et al. 1234 as the active principle of the Mexican mushroom family Psilocybe mexicana Heim. The chemists emphasize the fact that this chemical is the only phosphorylated indole compound that is known to occur in nature and that it is remarkable in that it is an indole substituted at the fourth position.



#### Footnote:

We are indebted to Dr. Harry C. Solomon, Massachusetts Commissioner of Mental Health, and Dr. Jean Delay, professor of psychiatry, Paris, France, for suggesting this research and providing us with the chemical.





**Massachusetts Mental Health Center** (Boston Psychopathic Hospital) 74 Fenwood Road, Boston

<sup>&</sup>lt;sup>†</sup> Senior research associate, Massachusetts Mental Health Center

<sup>&</sup>lt;sup>‡</sup> Instructor in psychology, Harvard Medical School; principal psychologist, Massachusetts Mental Health Center

<sup>§</sup> Research associate, Boston University and Massachusetts Mental Health Center

<sup>¶</sup> Graduate student, Psychology Department, Northwestern University, Evanston, Illinois



- Schultes next becomes intrigued by references to *ololiuqui* or "the vine of the serpent" used by the Aztecs for divination
- Schultes returned to Oaxaca in 1939 for more research leading to the identification of ololiuhqui as Rivea corymbosa (morning glory) & what becomes final chapter of Harvard PhD Thesis
- Seeds latter shown by Dr. Hofmann (1960) to contain d-lysergic acid amide (LSA)



1933: Starts Bound for Harvard Medical School Bound

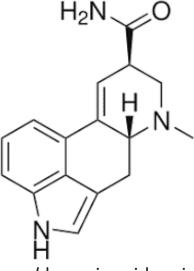


1941: Becomes Harvard Doctor of Philosophy (Botany)

Seeds of Rivea corymbosa







d-lysergic acid amide(ergine; ergoline alkaloid)

(Sources: *The Amazonian Travels of Richard Evans Schultes*, by Brian Hettler & Mark Plotkin; https://www.amazonteam.org/; Wade Davis. One River.)

### Schultes' Legacy: 12 Years >24,000 Plants Collected > 300 "New" to Science



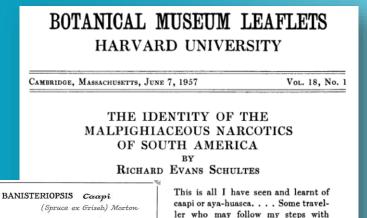
.....But Many Known for 100-1000's of Years by Indigenous Cultures



Rich Legacy of Ethnobotanical Descriptions of Medicinal Plants/Fungi: Potential Keys to **Improve Brain Health** 



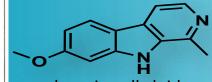
**Tetrapterys styloptera** (syn. **Tetrapterys methystica**)



ler who may follow my steps with greater resources at his command, will, it is hoped, be able to bring away materials adequate for the complete analvsis of this curious plant.

Rubiaceae: coffee family

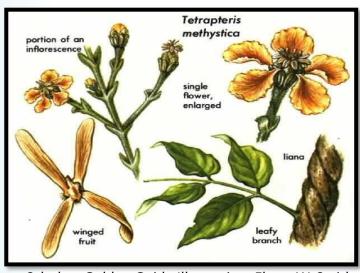
Richard Spruce



harmine alkaloid



Harvard Gray Herbarium Specimen



Schultes Golden Guide Illustration: Elmer W. Smith

"Specimens taken from a flowering vine, from the bark of which a cold water infusion was made without the admixture of any other plants...nothing is known chemically of this kind of caapi... with effects very like those induced by Banisteriopsis, I can vouch from self-experimentation."

(Sources: R.E. Schultes. Hallucinogens. 1976. R.E. Schultes & Albert Hofmann. Plants of the Gods: Their Sacred, Healing, and Hallucinogenic Powers. 1992; R.E. Schultes & Robert F. Raffauf. The Healing Forest: Medicinal and Toxic Plants of the Northwest Amazonia. 1990. W. Davis. The Lost Amazon: The Pioneering Expeditions of Richard Evans Schultes. 2016.)



#### A New Hallucinogen from Andean Colombia:

### Iochroma fuchsioides RICHARD E. SCHULTES\*



In February 1946, I made a botanical collection (Schultes 3208) in the Valley of Sibundoy to which was attached the following annotation: "Leaves crushed and taken in water by medicine-men as a narcotic." Another collection (Schultes et Villarreal 7489) made in Sibundoy in May 1946, likewise indicated use of the plant as an hallucinogen.

Richard E. Schultes. A New Hallucinogen the Andean Colombia. *Journal of Psychedelic Drugs.* vol. 9, no. 1, 1977, pp. 45–49.

### Definitive Scientific Guides to the Nature of Psychoactive Plants & Fungi

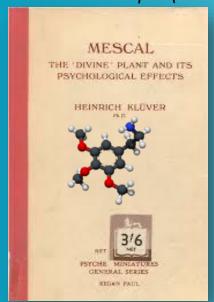


PSYCHIATRY ACADEMY

Collaborative Work by Dr. Schultes (Botanist) & Dr. Hofmann (Chemist)

**Key Demonstration of Inter-Disciplinary Collaboration** 

Schultes: Harvard Bio104 Class Term Paper (1936)

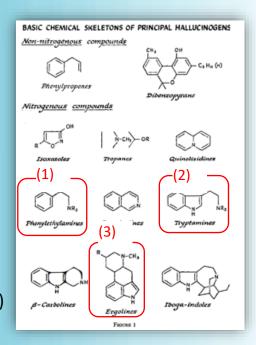


**Dr. Henrich Klüver**German Psychiatrist (1928)

Ethnobotany of 3 Major Classes of Psychedelics



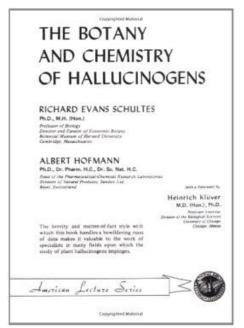
- (1) Scared Cacti (Peyote)
- (2) Teonanacatl (Psilocybe)
- (3) Ololiqui (Morning Glory)



By Age 58

**Dr. Richard E. Schultes**, Annual Review Plant Physiology, 1970

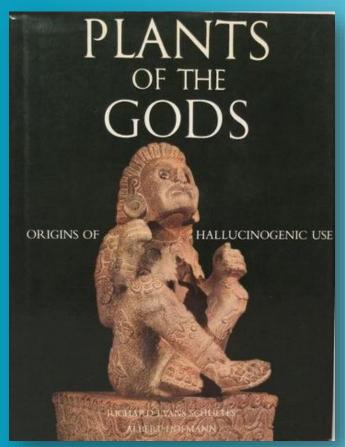
1973 (464 pages)



Foreword By: **Dr. Henrich Kluver**, Psychiatrist/Professor Emeritus



### Innumerable Discoveries & Teachings Serve as a Foundation & Inspiration for Psychedelic Research



"Can a thorough understanding of the use & chemical composition of these drugs not lead to the discovery of pharmaceutical tools for psychiatric treatment or experimentation?"

—Dr. Richard Evans Schultes & Dr. Albert Hofmann Plants of the Gods (1979)

Authors: Dr. Richard Evans Schultes & Dr. Albert Hofmann (Swiss chemist, LSD Pioneer)



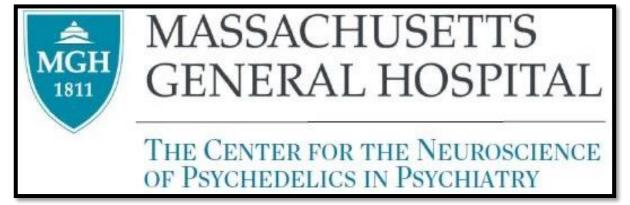
# Future of Ethnopharmacology & Personalized Medicine for Psychiatric Disorders

## Launch of the MGH Center for the Neuroscience of Psychedelics



The Harvard Gazette

Official Launch: February 2021



MISSION: The Center seeks to understand how psychedelics enhance the brain's capacity for change, to optimize current treatments, to create new treatments for mental illness & to make the term "treatment resistant" obsolete.

**HEALTH & MEDICINE** 

June 10, 2021

#### New center seeks to understand any 'magic' in mushrooms

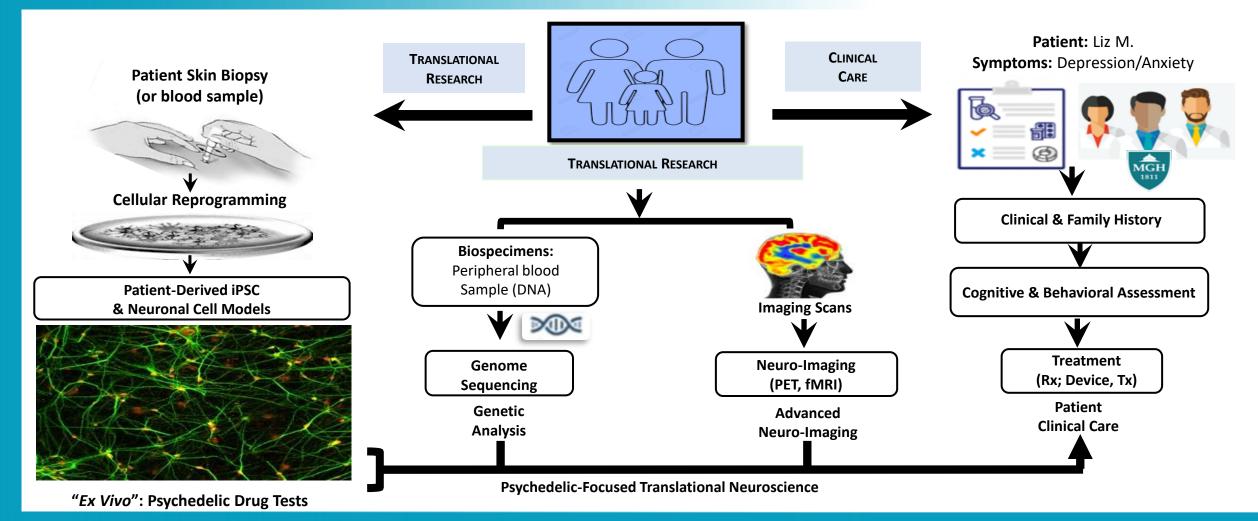
Research may help clear path for use of psychedelics in treating psychiatric patients



**Director: Dr. Jerrold Rosenbaum**, MGH's former psychiatrist-in-chief & Stanley Cobb Professor of Psychiatry at Harvard Medical School

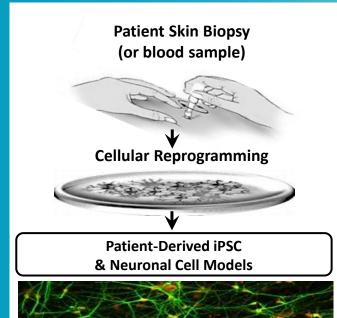
## Future: Toward Precision Psychiatric Medicines for Improved Therapy





# Rationale for Applying Human iPSC Models to Advance the Neurobiology of Brain Plasticity & Psychedelic Medicine



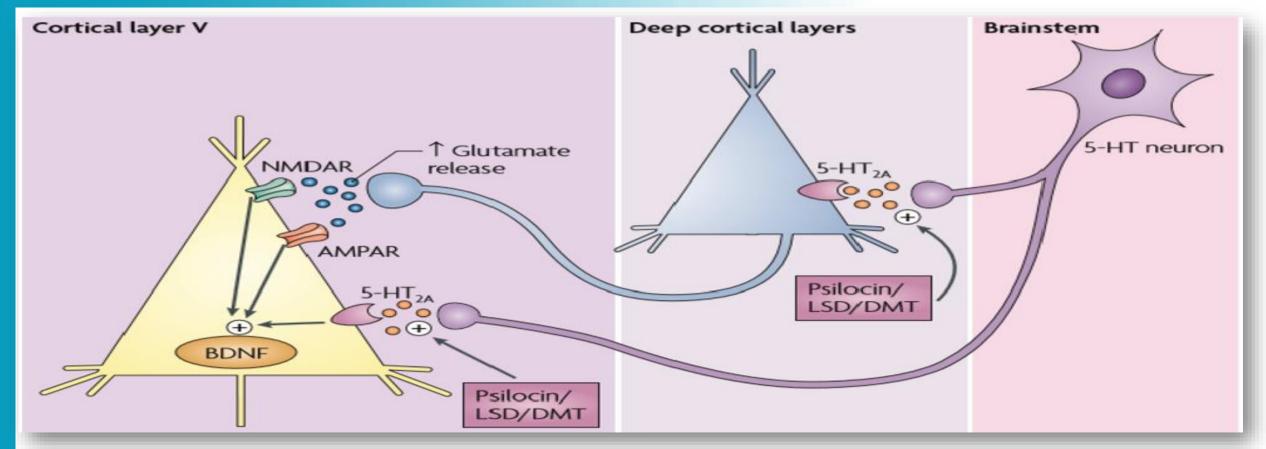


"Ex Vivo": Psychedelic Drug Tests

- 1. Study of **genetically accurate human** cell models that fully capture relevant genetic variation
- 2. Study of **different cell types** and hard to obtain cells (e.g., glutamatergic neurons with functional synapses)
- Study of developmental, maintenance, & any degenerative aspects of disorders in multiple cells
- 4. Identification of **biomarkers** for treatment response
- 5. Provide human cell models for high-throughput **drug screens** to discover next-generation medicines

# Goal: Develop Robust Functional Assays to Probe the Cellular Neurobiology & Mechanism of Diverse Psychedelic Agents

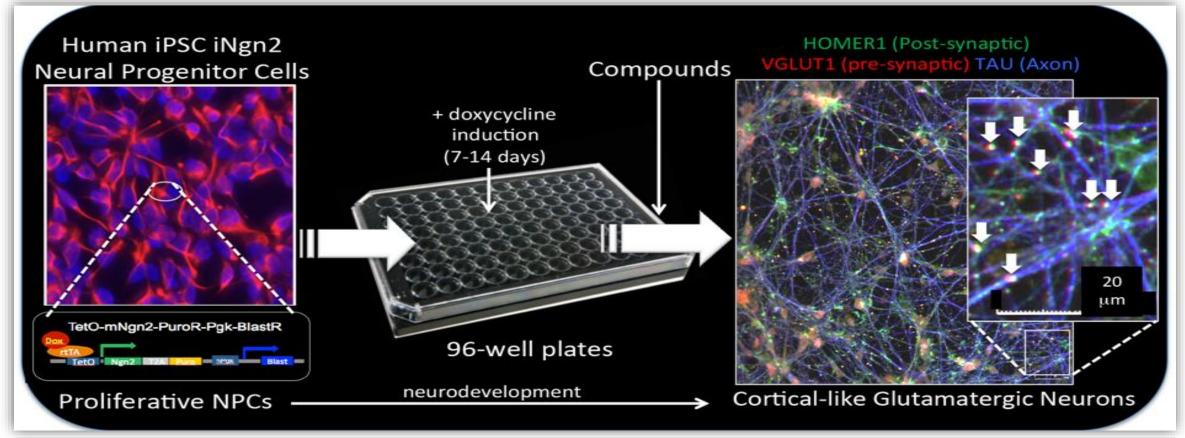




(Adapted: Vollenweider & Kometer. The Neurobiology of Psychedelic Drugs: Implications for the Treatment of Mood Disorders. Nature Review Neurosci. 2010.)

### Opportunity to Grow Human Neural Networks From Patients in the Lab



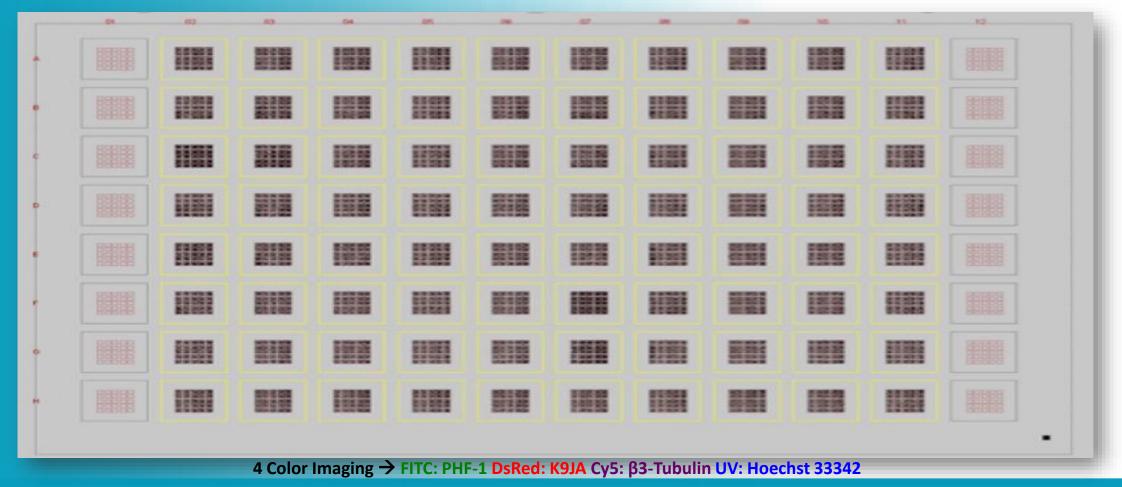


Cheng et al. Highly Expandable Human iPS Cell-Derived Neural Progenitor Cells (NPC) and Neurons for CNS Disease Modeling and High-Throughput Screening. Current Protocol Human Genetics. 2017.

# Development of High-Content Imaging Assays of Neuroplasticity: Quantifying Changes in Human Axon/Dendrite Morphology

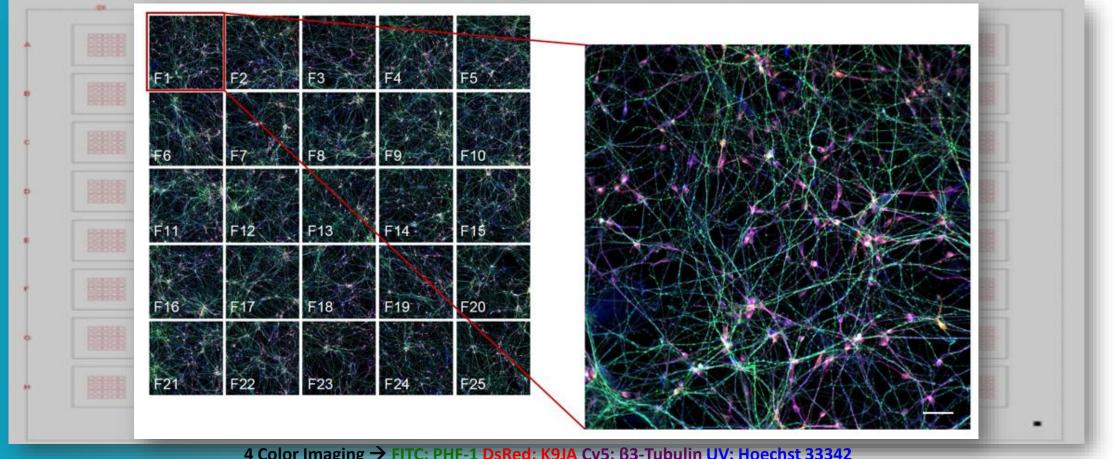


**PSYCHIATRY ACADEMY** 



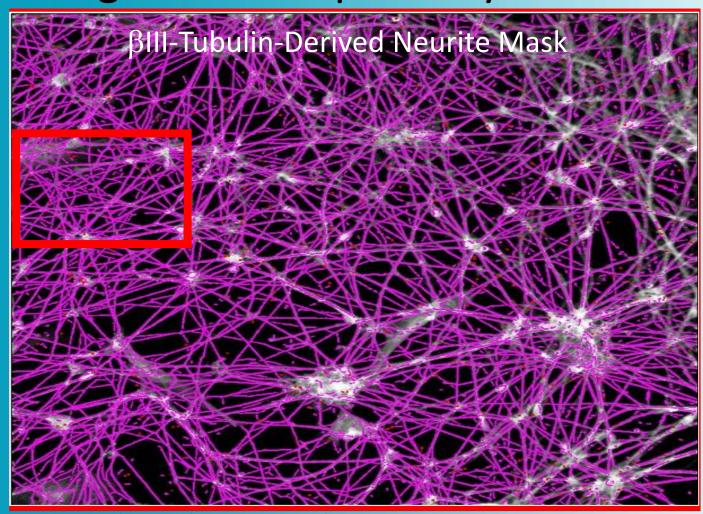
#### **Development of High-Content Imaging Assays of Neuroplasticity: Quantifying** Changes in Human Axon/Dendrite Morphology





4 Color Imaging → FITC: PHF-1 DsRed: K9JA Cy5: β3-Tubulin UV: Hoechst 33342

### Imaging Human Neurons & Quantifying Changes in Neuroplasticity



Cheng et al. Current Protocols in Human Genetics. 2017.

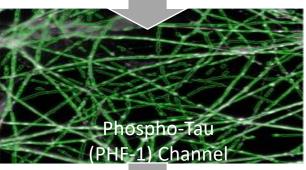


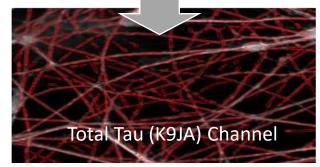


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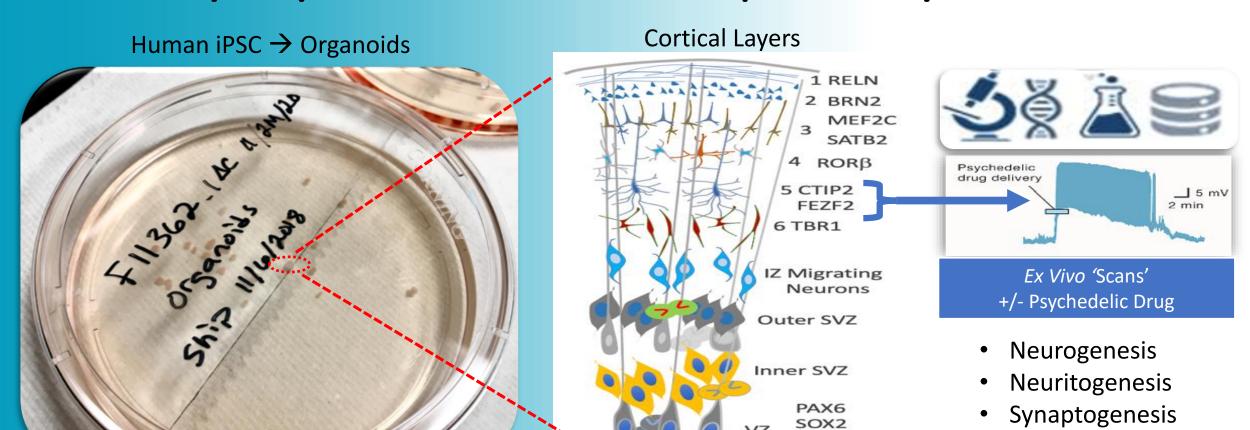
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## Use of 3-Dimensional 'Mini-Brains' to Study Psychedelics & Neuroplasticity

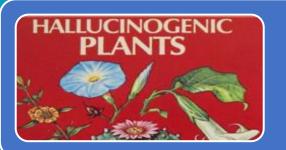




FOXG1

(Adapted: Sally Temple. NSCI)

### Toward Discovering Next-Generation Medicines HOSPITAL PSYCHIATRY ACADEMY Targeting Neuroplasticity



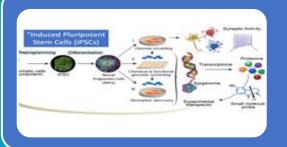
### Step I: Source Understudied Psychedelic Plants & Fungi with Medicinal Potential Based on Human Use

(Collaborations with Traditional Knowledge Keepers, Ethnobotanists, Chemists, Psychiatrists/Neurologists)



### Step 2: Create a Collection of Fractionated Extracts & Purified Compounds + Known Psychedelics

(e.g., mescaline, psilocybin, 5-MeO-DMT, salvinorin, mitragynine, ibogaine, MDMA, ketamine, novel)



### Step 3: Use Patient Stem Cell Models to Generate Molecular & Cellular Signatures in Neurons/Mini-Brains

(Working with Psychiatry & Neurology Clinicians, Neuro-Imagers & Medicine Hunters)







"Garden-to-Lab"

None of the plants are Scheduled (i.e., not known to contain an agent covered in the Controlled Substance Act)

### PSYCHEDELOME PROJECT v2.0: Revitalization of a MGH Rooftop Greenhouse to Create the MPL



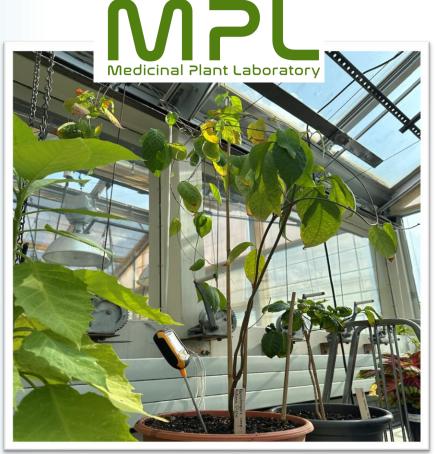


[Source: Google Earth View of Mass General Hospital/Boston]

### **PSYCHEDELOME PROJECT v2.0: Curation of a 'Living Library' of Diverse Psychoactive Plants**





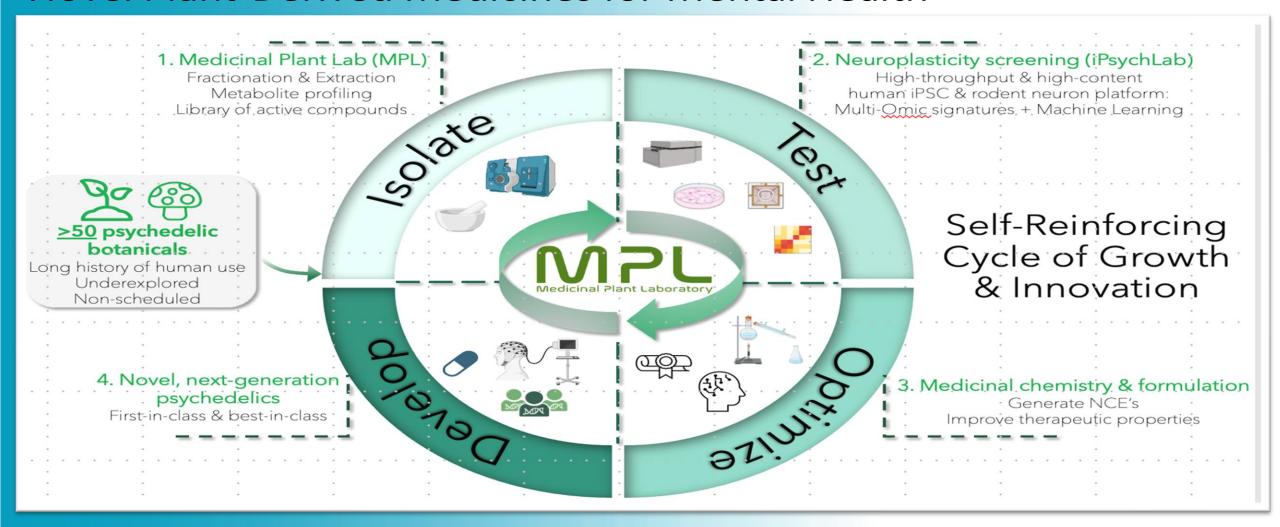


Banisteriopsis caapi vine

None of the plants are Scheduled (i.e., not known to contain an agent covered in the Controlled Substance Act)

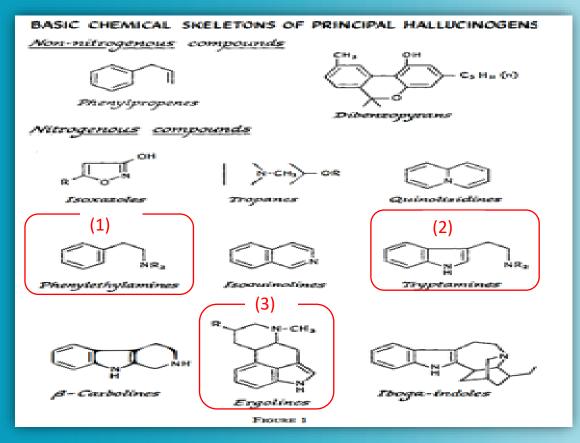
#### Toward Learning from Nature to Advance Novel Plant-Derived Medicines for Mental Health





### Natural Products As Leads for Drug Discovery & Innovation





Dr. Richard E. Schultes. Annual Review Plant Physiology. 1970.

Psychoactive Plants & Fungi(1) Scared Cacti (Peyote)(2) Teonanacatl (Psilocybe)(3) Ololiqui (Morning Glory)

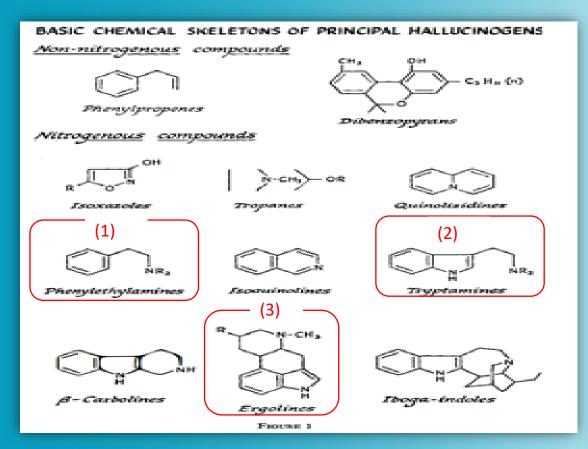


3 Major Classes of Psychedelics Under Clinical Investigation

New Targets & Chemotypes?

### Natural Products As Leads for Drug Discovery & Innovation





#### Growing the Future of Mental Health



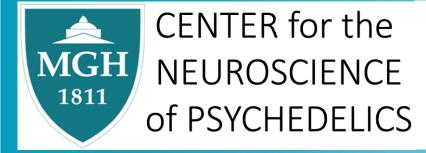
Dr. Richard E. Schultes. Annual Review Plant Physiology. 1970.



### Ethnobotany of the Future: Key Considerations & Implications

- 1) Adherence to the *United Nations' Convention on Biological*Diversity & informed consent on the use of genetic resources, including the fundamental principles of access & benefit-sharing.
- 2) Key for collaboration with keepers of traditional knowledge & Indigenous Peoples scholars to elevate their voices & contribution.
- 3) Continued importance of maintaining biodiversity & conservation efforts throughout the world.









#### **Acknowledgments**

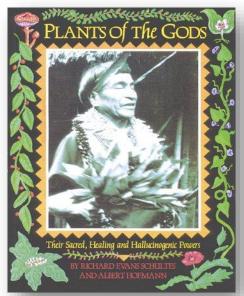
Chemical Neurobiology Lab Members & Collaborators (Past & Present)

Mass General Hospital, Departments of Psychiatry & Neurology

Harvard Medical School, Boston, Massachusetts

Psychedelic Ethnobotany/mycology & Ethnopharmacology

Communities, Traditional Knowledge Keepers, Psychiatrists, Therapists





#### Suggested Readings

- 1) Schultes, RE. *Teonanacatl: The Narcotic Mushroom of the Aztecs*. American Anthropologist, New Series, Vol. 42, No. 3, Part 1 (Jul.-Sep., 1940).
- 2) Schultes RE. The Botanical and Chemical Distribution of Hallucinogens. Annual Review of Plant Physiology. 1970. Vol. 21:571-598.
- 3) Public Lecture by Mark Plotkin, Amazon Conservation Team. The Amazonian Travels of Richard Evans Schultes.
  <a href="https://www.youtube.com/watch?v=vBqQ2SQuq68">https://www.youtube.com/watch?v=vBqQ2SQuq68</a>
- 4) Vollenweider FX & Kometer M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nature Review Neuroscience. 2010;11:642-51.
- 5) Silva MC, Haggarty SJ. Human Pluripotent Stem Cell-Derived Models and Drug Screening in CNS Precision Medicine. *Ann N Y Acad Sci.* 2020;1471:18-56.