

Let's take a trip.

Psychedelics



Julie Ayad, Kaila Kosuljandic, Nicole Benedictson, and Sunaina Ajit Kumar



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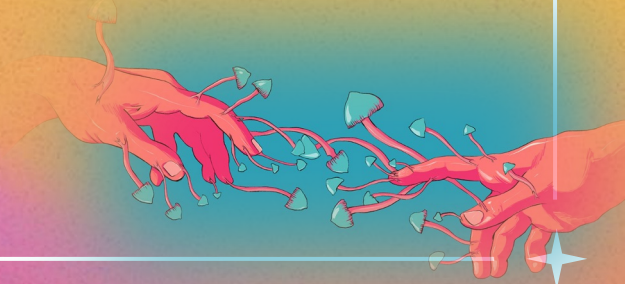
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What are Psychedelics?

Psychedelics are powerful psychoactive compounds that **alter perception, mood, and numerous cognitive processes**.

Common types of psychedelics include Mescaline, Lysergic Acid Diethylamide (LSD), Psilocybin, Dimethyltryptamine (DMT), and Methylenedioxymethamphetamine (MDMA, ecstasy).

The term “Psychedelics” was coined by **Humphrey Osmond in 1956** and was derived from ancient Greek words “Psyche” meaning soul or mind and “Delein” meaning to reveal or to manifest



Different types of Psychedelics:

Mescaline



Consumed orally: chewing, brewing, capsule, or tablet form.

Metabolized in the **liver.**

Active dosage: 200-400 milligrams.

Has a **longer half-life** than other psychedelics. Mescaline reaches its peak approximately two hours after ingestion, and **the entire experience can last eight to twelve hours.**

Possible effects: spatial distortion, altered colours, closed-eye visual hallucinations, synesthesia, anxiety, panic, disorganized behaviour, pleasant feelings, euphoria, and transcendence.

Lysergic Acid Diethylamide (LSD)

Consumed orally: swallowing or placing the blotter paper under the tongue, liquid form (dropper bottles), and micro-dosing.

Metabolized in the **liver.**

Active dosage: 0.5 and 2 milligrams per kilogram of body weight.

LSD's **half-life** is approximately three hours, although it can vary between two to five hours. The psychoactive effects of LSD can last up to twelve hours.

Possible effects: time and identity distortion, altered depth and time perception, visual hallucinations, a sense of euphoria or certainty, and distorted perceptions of object size, shape, movements, colours, sounds, touch, body image, and delusions.

"**Bad trips**" occur which are characterized by: anxiety, dysphoria, and confusion.



Psilocybin

Consumed orally: eating raw magic mushrooms, eating dried magic mushrooms (mixed into food), brewed, capsule or tablet form, and micro-dosing.

Metabolized in the **liver** (converted to psilocin).

Active dosage: Doses greater than 30 micrograms are more likely to lead to psychologically challenging experiences. It is essential to be mindful of dosages when exploring psilocybin.

Psilocybin's **half-life** is approximately three hours. Psilocybin reaches it's peak approximately 60-90 minutes after ingestion, and the overall experience subsides over the following six hours.

Possible effects: hypertension, tachycardia, mild headaches, prolonged psychosis (rarely), elevated blood pressure, and gastrointestinal distress including nausea and vomiting.

"**Bad trips**" occur which are characterized by: delirium, panic attacks, depersonalization, extreme stress, and symptoms resembling schizophrenia.



Dimethyltryptamine (DMT)

Consumed orally: inhaling, smoking, vaporizing, and brewing.

Metabolized in the **liver**.

Active dosage and half life vary based on consumption type.

Possible effects: intense fear, paranoia, anxiety, grief, and depression (posses risks to the user and others).



Methylenedioxymethamphetamine (MDMA)



Consumed orally: swallowing, snorting, or dissolving and drinking.

Metabolized in the **liver**.

Active dosage: 50 to 150 micrograms.

MDMA's **half-life** is approximately eight hours. MDMA reaches it's peak approximately 2 hours after ingestion.

Possible effects: enhances feelings of empathy, bonding, and offers users an opportunity to access and process memories of emotional trauma.



Three Categories of Psychedelics

1. **Hallucinogens** (mescaline, LSD, psilocybin, and DMT)
2. **Mixed Stimulant Psychedelics** (DMT)
3. **Disassociates** (phencyclidine, ketamine, and dextromethorphan)



History of Psychedelics

Arthur Heffter and Mescaline

Albert Hofmann and Psilocybin/Psilocin



1898

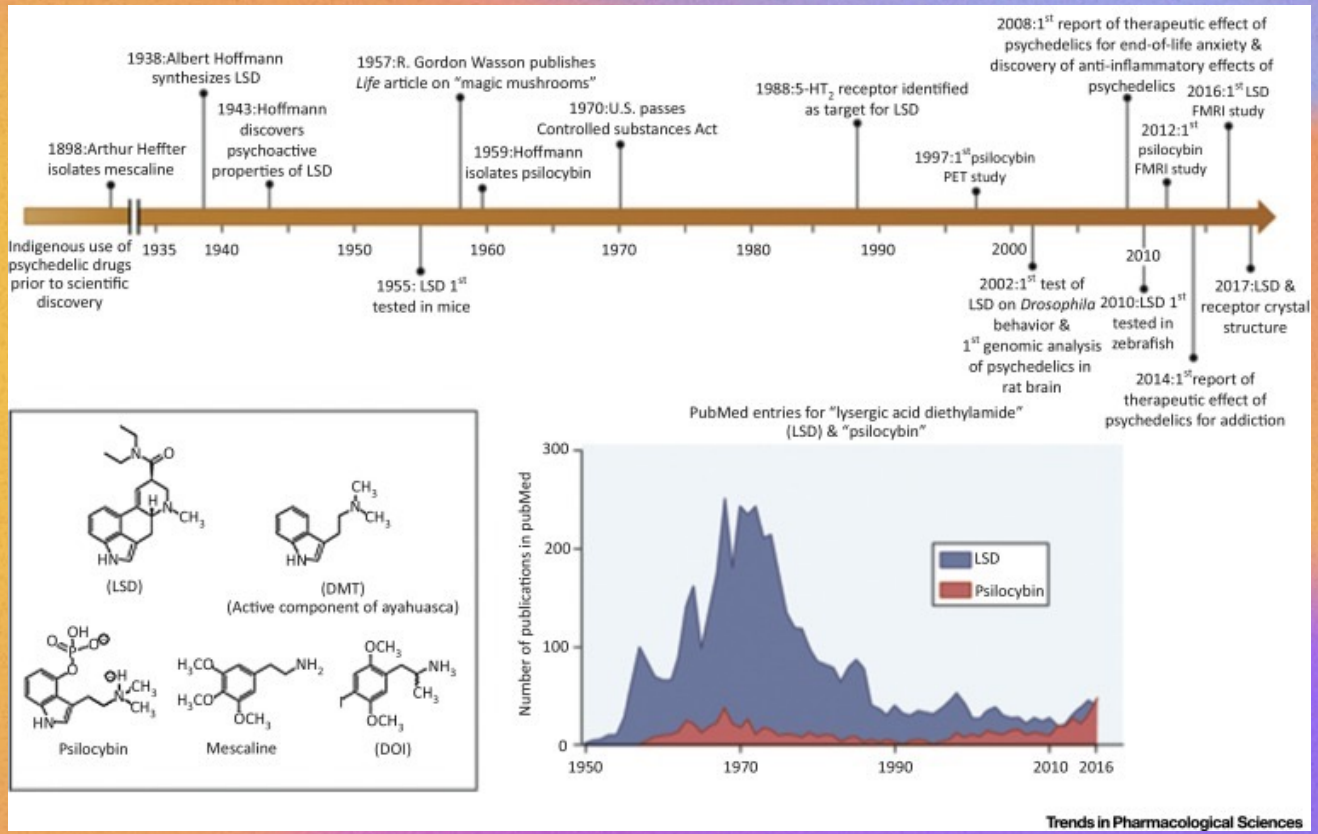
1938/1943

1959



Albert Hofmann and Lysergic Acid Diethylamide (LSD)

The next slide will show a more recent timeline!

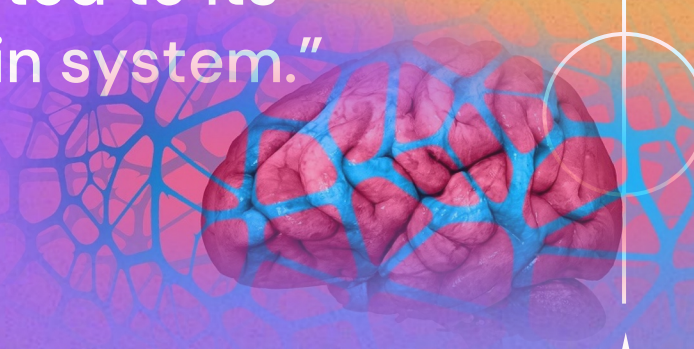

1898:Arthur Heffter isolates mescaline
1938:Albert Hoffmann synthesizes LSD
1943:Hoffmann discovers psychoactive properties of LSD
1957:R. Gordon Wasson publishes *Life* article on "magic mushrooms"
1959:Hoffmann isolates psilocybin
1970:U.S. passes Controlled substances Act
1988:5-HT2 receptor identified as target for LSD
1997:1st psilocybin PET study
2008:1st report of therapeutic effect of psychedelics for end-of-life anxiety & discovery of anti-inflammatory effects of psychedelics
2012:1st psilocybin FMRI study
2016:1st LSD FMRI study
Indigenous use of psychedelic drugs prior to scientific discovery
1935
1940
1950
1955: LSD 1st tested in mice
1960
1970
1980
1990
2000
2002:1st test of LSD on *Drosophila* behavior & 1st genomic analysis of psychedelics in rat brain
2010
2010:LSD 1st tested in zebrafish
2014:1st report of therapeutic effect of psychedelics for addiction
2017:LSD & receptor crystal structure
(LSD)
(DMT)
(Active component of ayahuasca)
Psilocybin
Mescaline
(DOI)
PubMed entries for "lysergic acid diethylamide" (LSD) & "psilocybin"
Number of publications in pubMed
300
200
100
0
1950
1970
1990
2010
2016
LSD
Psilocybin
Trends in Pharmacological Sciences



Let's talk about **biological mechanisms**. But first, a quote.

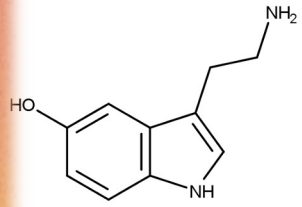
"If neuroscience can be said to have a beginning, one could argue that it occurred in 1954, with the idea that the action of LSD might be related to its effects on the brain serotonin system."

– Dr. David E. Nichols

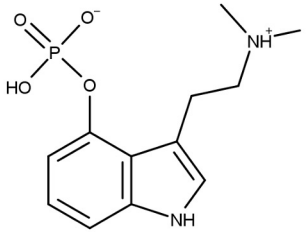


Look at these chemical structures.

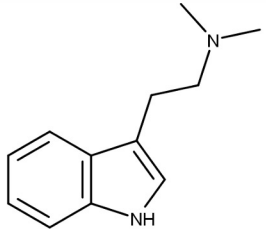
Do you notice anything interesting here?



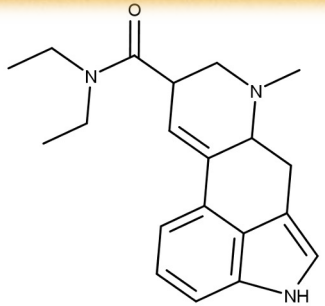
Serotonin



Psilocybin



Dimethyltryptamine (DMT)



Lysergic Acid Diethylamide (LSD)

... If you guessed that they all look similar – **you're correct!**

How do psychedelics interact with receptors?

Psychedelic compounds interact with specific receptors in the brain, initiating their effects (triggering cellular responses). Their interactions with these distinct receptors contribute to their unique psychological experiences (we'll get into some examples of this later).

Serotonin plays a big role!

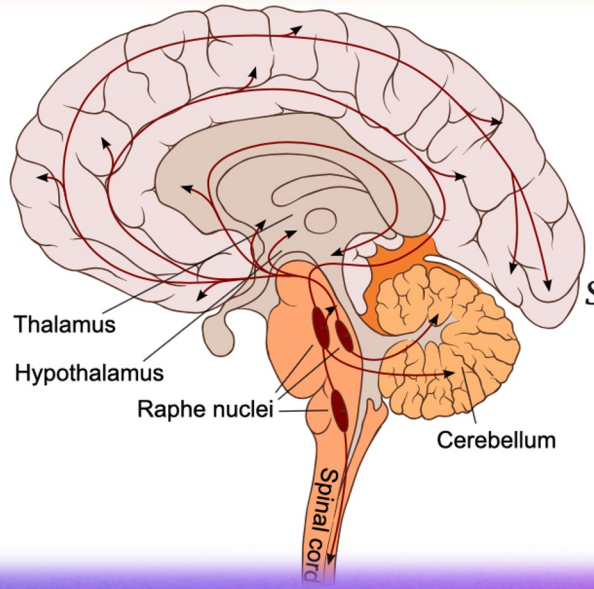
- Serotonin receptors **(serotonin 2A receptor (5-HT2A))** are the key targets for psychedelics – and this is their primary mechanism of action.
- 5-HT2A receptors are very distributed in our brain (they're everywhere!)



Structural Resemblance:

- Psychedelics have a chemical structure similar to serotonin.
- This structural resemblance allows psychedelics to mimic serotonin's actions in the brain.

Serotonergic Pathways



Serotonergic pathways in the brain[5]

- Serotonin receptors come from the ***raphe nuclei*** in the brainstem
- Plays a key role in regulating mood, sexual behaviour, aggression, impulsivity, cognitive function, appetite, pain, sleep, memory, and more.
- Many drugs target the serotonergic system
- Psychedelics raise serotonergic activity in the brain.

Mechanism of Action

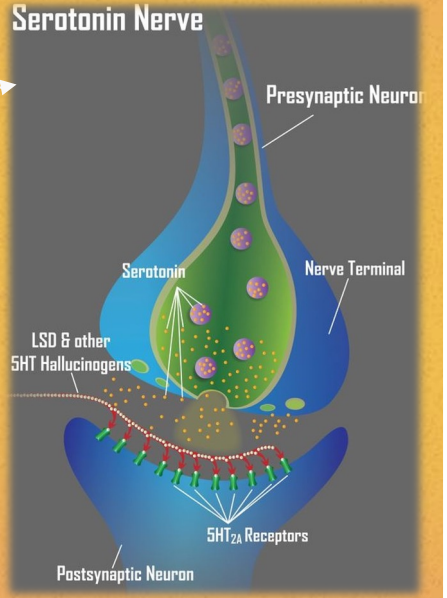
Note, psychedelics is a blanket term. Different kinds of psychedelics have varying mechanisms of action:

- **Hallucinogenic psychedelics:** full or partial agonists of serotonergic 5-HT2A receptors
- **Empathogens/entactogens:** mix of serotonin and dopamine reuptake inhibitors as well as releasers
- **Dissociative anesthetics:** glutamatergic NMDA receptor antagonists

e.g., **LSD, psilocybin, DMT** – induce a state of altered perception

e.g., **MDMA** – increase sociability and emotional connectivity

e.g., **Ketamine** – reduce excitation, causes sedation, perceptual distortion



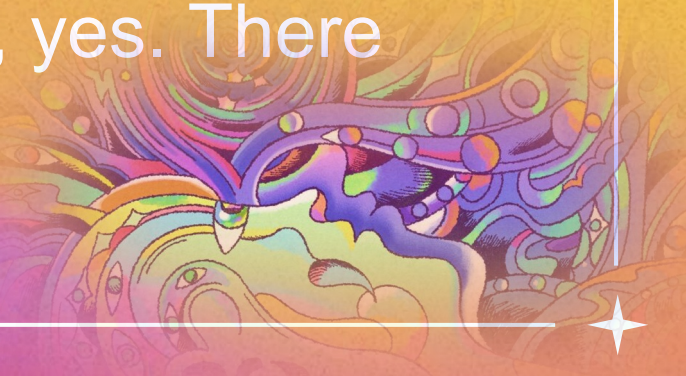
Neural Activity & Brain Networks

Let's recap what we know so far:

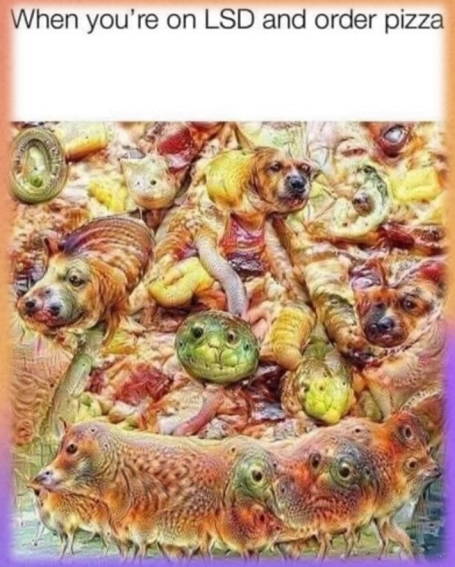
1. Psychedelics is a blanket term. For ease, we can divide them into two groups - classical psychedelics and non-classical psychedelics.
2. Classical psychedelics work by being full or partial agonists of serotonergic 5-HT2A receptors

This leaves one question: is there a commonality between all psychedelic (or hallucinogenic) drugs when we're looking at brain network modulation?

The answer is **yes**. There's still a lot more to be investigated, but so far, yes. There is.



Neural Activity & Brain Networks



Researchers (Gattuso et. al., 2023) wanted to identify **functional connectivity** patterns that are common across different psychedelic drugs. They examined brain activity using a technique called **resting state fMRI**.

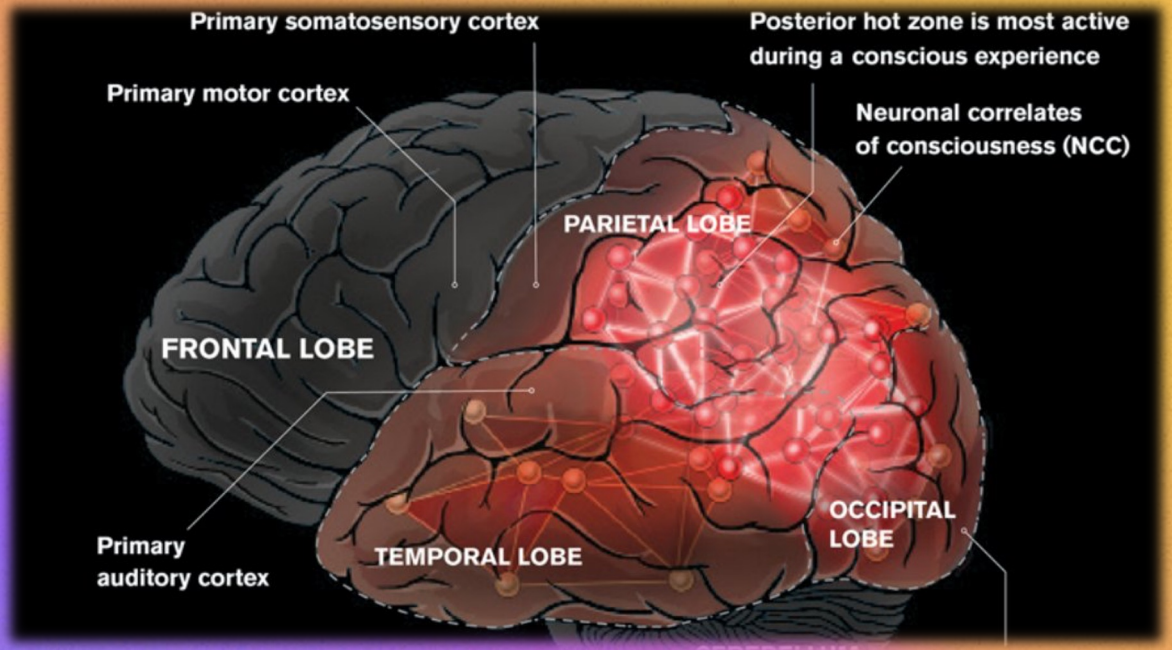
Data was collected from healthy human volunteers both before and after they were given nitrous oxide, ketamine, and lysergic acid diethylamide (LSD).

Functional Connectivity: the relationship between different regions of the brain based on their activity patterns.

Findings?

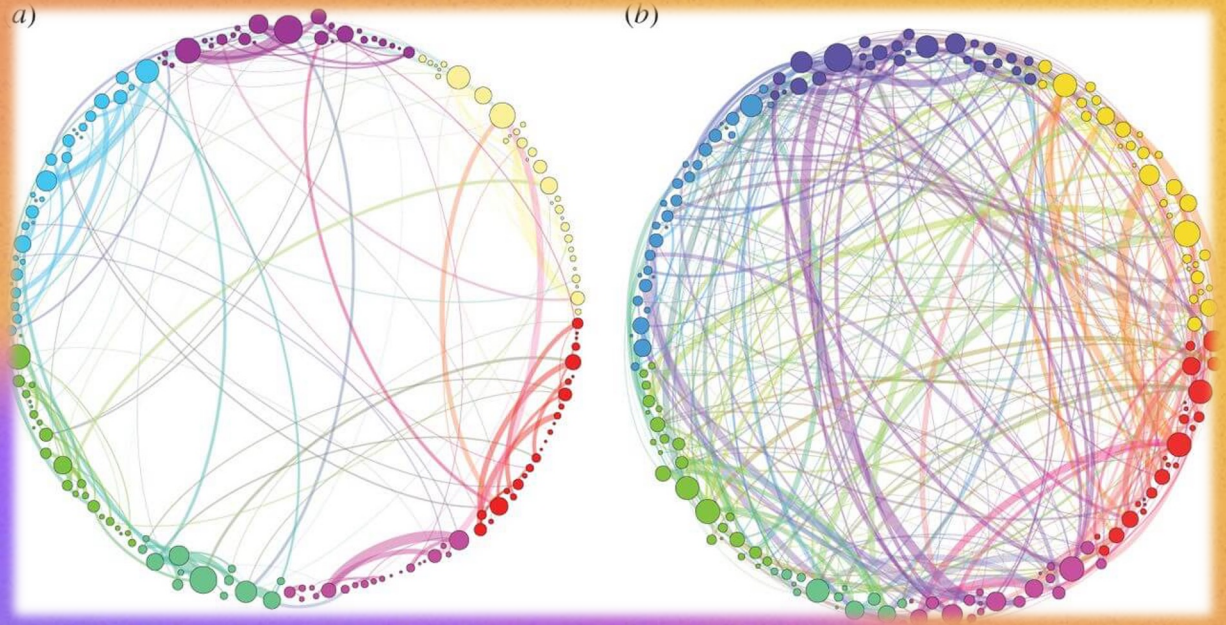
- Both classical psychedelic drugs and non-classical psychedelic drugs have similar effects on brain connectivity.
- Suggests that there may be a commonality in biological mechanisms that explains the effects of both classical and non-classical psychedelics on large-scale brain networks.
- All three substances reduced the connections ***within*** specific brain networks while increasing the connections ***between*** different networks (Gattuso et. al., 2023).

The Posterior Cortical “Hot Zone”



Changes in Brain Network Connectivity

This is a diagram of communication pathways in the brain after **a) a placebo** and **b) psilocybin.**



What do you see happening here?

Pharmacogenetics



- Genetic variations in specific genes, such as **CYP2D6** can impact the metabolism and efficacy of psychedelics.
- The 5-HT2A receptor gene (HTR2A) is also relevant, since it modulates sensitivity to psychedelics.
- Research on psychedelic pharmacogenetics is **still in its early stages**, and more studies are needed to fully understand the genetic domain.

Am I tripping out?



I've heard that this psychedelic simulation on YouTube is 'frighteningly accurate.'

It attempts to replicate the **visual and auditory** subjective effects of a psychedelic experience.

Feel free to pause the seminar and check it out.

https://www.youtube.com/watch?v=ARKoc6P6FAQ

That’s all for biological mechanisms. Now, let’s discuss science and research.



History and Resurgence of Interest in Psychedelic Research



History

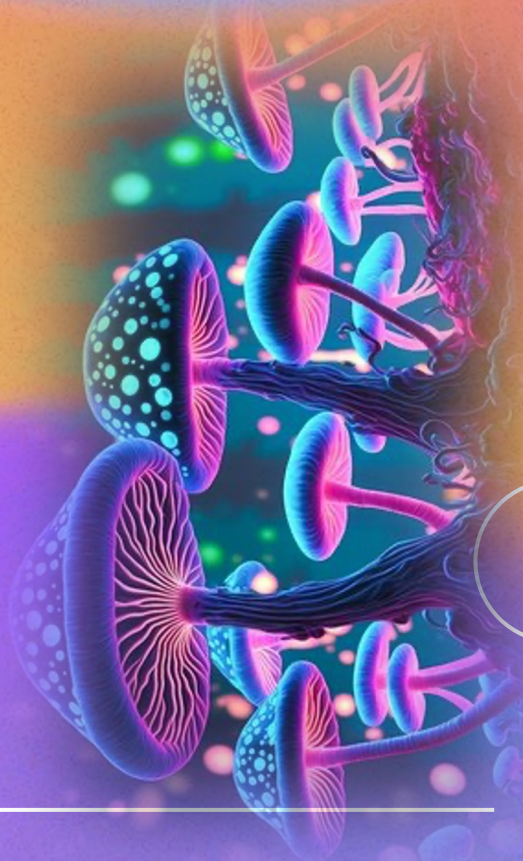
- **First period of research interest spanned between the 1950's-1970's.**
- Research declined in the mid 1970's due to political and social concerns, ethical breaches in research practice, and new regulatory restrictions.

Renewed Interest

- **Renewed interest on psychedelic research in the past two decades.**
- Growing urgency for new safe and effective therapy alternatives.
- Current research focusing on therapeutic potential of both classic and non-traditional psychedelics.

Therapeutic Potential and Research of **Psilocybin**

- **Most researched psychedelic substance.**
- Current research has examined its therapeutic potential for **treatment of mood disorders, end-of-life anxiety and depression, OCD, and substance-use disorders.**
- Granted "breakthrough therapy" designation by the FDA for treatment of PTSD and treatment-resistant depression.
- **Psilocybin combined with therapy successfully alleviated anxiety and depression in Johns Hopkins and NYU studies participants.**
- Greater reduction in anxiety and depression symptoms with a high dose of psilocybin.
- Provides an alternative to other more conventional treatments.



Therapeutic Potential and Research of **Psilocybin**

- **Psilocybin can help individuals understand their addiction and confront the psychological issues contributing to it.**
- Johns Hopkins smoking addiction study – participants smoke-free after three doses of psilocybin.
- **Combining psilocybin with Cognitive Behavioral Therapy helped individuals quit smoking.**
- **Psilocybin with standard therapy led to drinking reductions for those with alcohol dependency.**
- **Decreased alcohol dependency** after first session of psilocybin and motivational enhancement therapy.



Therapeutic Potential and Research of Lysergic Acid Diethylamide **"LSD"**



- Obstacles in conducting research due to **schedule 1 classification.**
- Studies have explored its potential therapeutic benefits for mood disorders, migraine headaches, and anxiety.
- LSD-assisted psychotherapy reduced anxiety levels for patients with medical-related anxiety.
- LSD contributed to lasting **positive effects** on behaviour, attitudes, and moods **for up to a year.**
- Neuroimaging research suggests that LSD might alter how the brain processes negative stimuli.
- Claims that micro-dosing LSD can influence positive mood and increased creativity?

Therapeutic Potential and Research of **Ketamine**

- Widely used for anesthesia and pain management.
- Observed fast-acting antidepressant effects led to an increase in research to explore its other therapeutic potential.
- Current research exploring its therapeutic potential for anxiety, depression, OCD, PTSD, and substance-use disorders has yielded promising results. However, **treatment effects aren't long-lasting.**
- Maintenance ketamine treatments were shown to improve anxiety levels in patients with anxiety disorders, but most participants reported that most of their symptoms returned after treatment stopped.



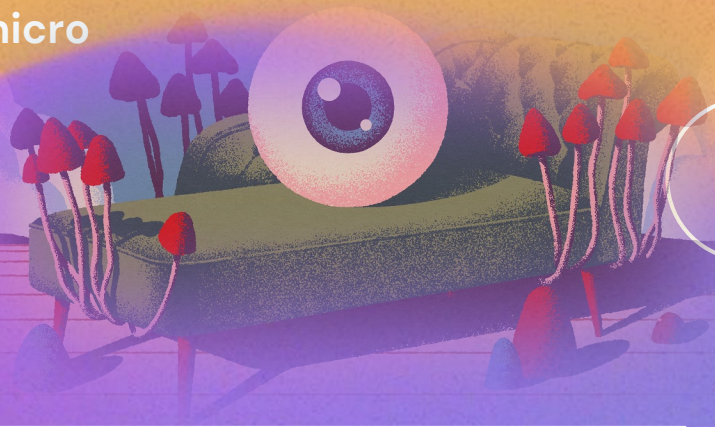
Therapeutic Potential and Research of **MDMA**



- Concerns about neurotoxicity and abuse potential led to its classification as a Schedule 1 controlled substance in 1985, making it illegal in the US and posing challenges for future research.
- MDMA is recognized for its ability to promote happiness, sociability, emotional connection, and trust, **making it a promising candidate for treating PTSD.**
- Clinical trials using **MDMA-assisted psychotherapy** to treat **PTSD** have demonstrated promising outcomes showing substantial **reductions in PTSD symptoms** and overall improvement in well-being.
- **Moderate to high dose** = greater impact on **reducing symptoms associated with PTSD.**
- MDMA-assisted psychotherapy has received “Breakthrough Therapy” status for the treatment of PTSD.

Benefits of Psychedelic use

- Promising therapeutic abilities for treating mental health and substance use disorders.
- Provides alternative solutions for individuals with treatment-resistant disorders.
- Contributes to positive emotional effects.
- Can **improve cognitive performance – micro dosing.**
- Boosts **creative thinking.**
- Enhances aspects of thinking that can benefit the therapy process.



Risk and Safety Considerations

- Potential for overdose when taken in large amounts and when combined with other substances.
- Higher risk posed for those taking medications that may interact negatively with psychedelics.
- Higher risk for individuals who have or are **predisposed to psychotic disorders.**
- Appropriate dosage minimizes risks of over-dose, negative experiences, and supports successful therapeutic outcomes.
- Substance purity prevents unexpected events.
- "Set and Setting" plays an important role in ensuring a safe experience.

Safety Considerations of using Psychedelics to treat **Minors**

- **Controversial topic with limited information available.**
- Studies focus on the **adult population** – these findings can't be directly applied to the safety of minors.
- Impacts on earlier stages of cognitive development?
- Understanding and management of the intense psychological experiences caused by psychedelics.
- What is the appropriate dosage for children?

Behavioral Effects







- Minimal with most psychedelics
- Most effects are **internal and subjective**
- Behavioral changes will **depend on the trip**
- Some (such as MDMA) have **reinforcing effects** (i.e. subject wants to take more).

Experiences Related to Altered Perception

- Synesthesia
- Pseudo-hallucinations
- True hallucinations
- Flashbacks and longer-lasting effects
- Psychedelic effects of other types of drugs (opium, cannabis, alcohol, etc.).



Ego Dissolution & Mystical Experiences

- Very **subjective**
- Used in religious practices
- Modern "**shamanistic**" practice by Westerners.

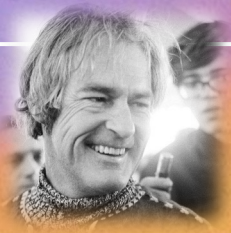


Set and Setting

- **Can affect** trip expectations.
- **Outside party leading your trip.**









Famous People on Psychedelics

- Hunter S. Thompson, Aldous Huxley, Timothy Leary, William Blake
- Syd Barrett and Pink Floyd, Jimi Hendrix, Janis Joplin
- Maynard Ferguson, Charlie Rouse, Thelonious Monk, others
- Leary, Allen Ginsberg, Jack Kerouac













Cults and Psychedelics

- **Suggestibility**
- **Manson Family**
- **NXIVM**



In Conclusion

1. Psychedelics can be natural or synthetic
2. Experience of psychedelics is subjective
3. Many people throughout history have used them for various purposes.
4. They show some promise in therapy, but their use is controversial.



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