MIND MEDICINE AUSTRALIA

Psilocybin

By Drug Science and Mind Medicine Australia

Part 2 - Pharmacology

Drug Science

Drug Science

Drug Science was formed by a committee of scientists with a passionate belief that the pursuit of knowledge should remain free of all political and commercial interest.

Founded in 2010 by Professor David Nutt, following his removal from his post as Chair of the Advisory Council on the Misuse of Drugs, Drug Science is the only completely independent, science-led drugs charity, uniquely bringing together leading drugs experts from a wide range of specialisms to carry out ground-breaking research into drug harms and effects.

The Drug Science mission is to provide an evidence base free from political or commercial influence, creating the foundation for sensible and effective drug laws. Equipping the public, media and policy makers with the knowledge and resources to enact positive change.

Drug Science want to see a world where drug control is rational and evidence-based; where drug use is better informed and drug users are understood; where drugs are used to heal not harm

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Mind Medicine Australia is seeking to establish safe and effective psychedelic-assisted treatments for mental illness in Australia. As a registered charity (DGR-1 status), Mind Medicine Australia are supporting clinical research and working towards regulatory-approved and evidence-based psychedelic-assisted therapies. Mind medicine Australia operate as a nexus between medical practitioners, academia, government, regulatory bodies, philanthropists, and other partners.

Mind Medicine Australia is focused specifically on the clinical application of medicinal psilocybin and medicinal MDMA for certain mental illnesses. They do not advocate for recreational use of psychedelics, MDMA, or any other prohibited substances, nor do they advocate for any changes to the law with respect to recreational use. Their focus is wholly clinical.

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What is Psilocybin?

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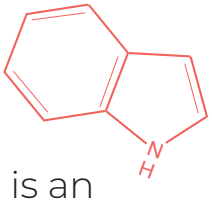
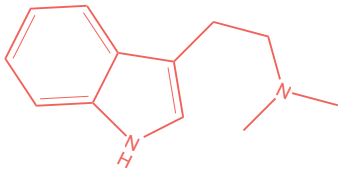
Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is an indole alkaloid, chemically similar to the neurotransmitter **serotonin** (5-HT).

It falls within the tryptamine class of classical psychedelics



An indole is an aromatic double-ring system containing a nitrogen atom in the five-membered ring, which is fused to a benzene ring.

A tryptamine is an indole molecule with an ethylamine group attached to carbon 3 of the 5-membered ring



Psilocybin occurs naturally in up to 100 species of mushrooms belonging to the genus Psilocybe

Psilocybin can also be synthesised chemically, or via biochemical synthesis, both in vivo and in vitro

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How does Psilocybin act?

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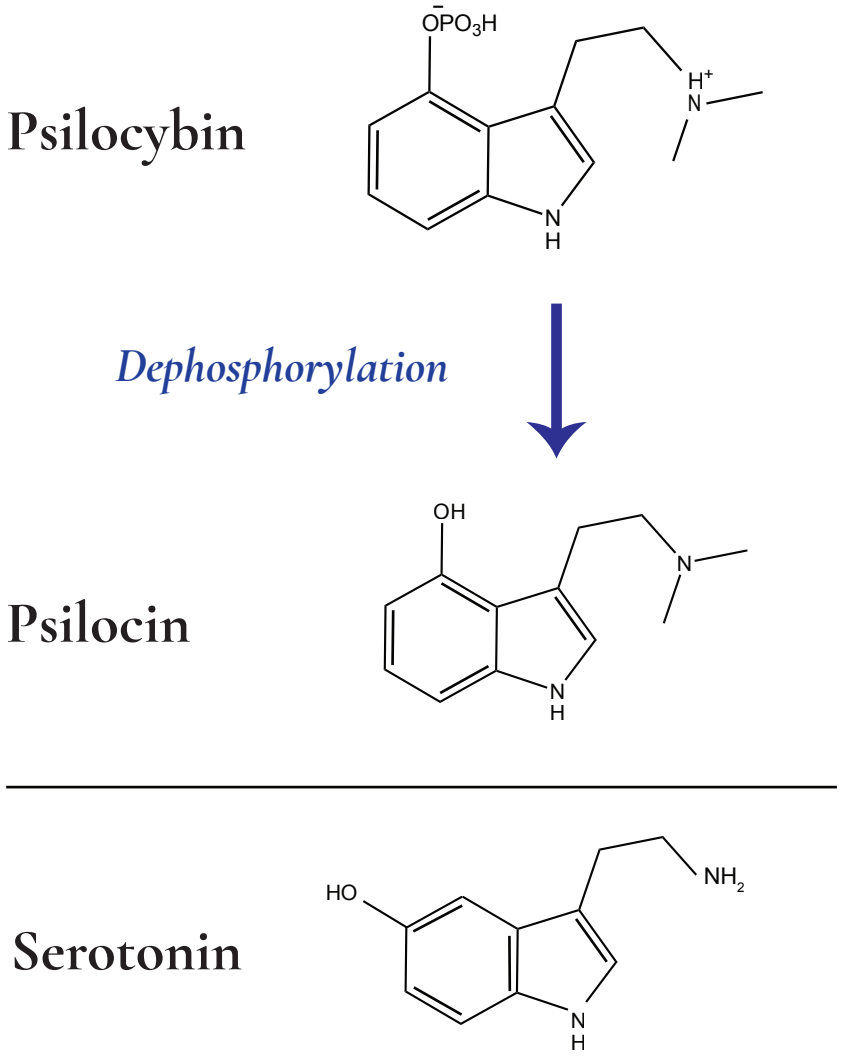
Psilocybin is easily converted within the body to the simpler compound, psilocin via dephosphorylation. **Psilocybin is therefore a "prodrug" of psilocin.**

Psilocin acts to stimulate (is an agonist of) the **5-HT2A** receptor

Thus, in some ways psilocin acts to **mimic the effects of serotonin.**

However, the binding of psilocin to serotonin receptors can also elicit different effects from the binding of serotonin to the same receptors due to the phenomenon of **functional selectivity**.



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Introduction to Serotonin

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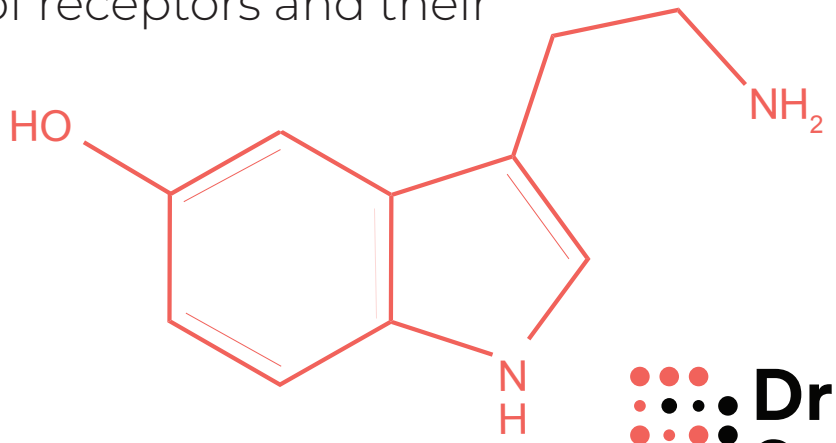
Serotonin (or 5-hydroxytryptamine, 5-HT) is one of several endogenous monoamine neurotransmitters in living organisms that have very fundamental functions in basic physiology. In humans, these neurotransmitters are also important for psychological function.

In humans, serotonin is involved in sleep regulation, appetite, mood and a host of other higher-level functions.

Serotonin was the first of the monoamine neurotransmitters to be discovered, as a consequence of LSD research in the 1950s. The discovery of serotonin led to the elucidation of receptors and their fundamental role in neurological function.



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Serotonin Formation and Breakdown

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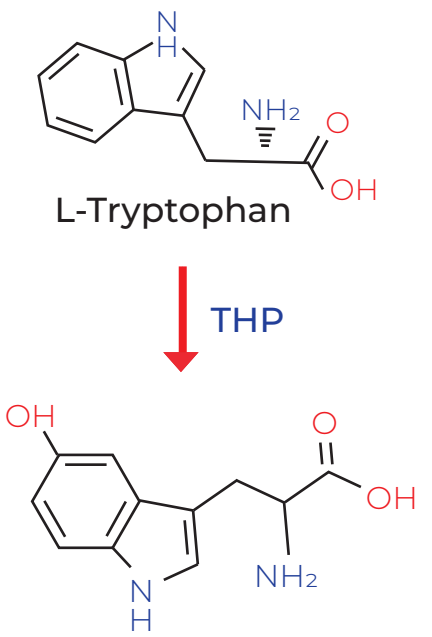
Serotonin biosynthesis initially involves the conversion of **L-tryptophan** to **5-hydroxytryptophan** by **L-tryptophan hydroxylase (TPH)**. The subsequent metabolic step involves the decarboxylation of 5-hydroxytryptophan by the action of the cytosolic enzyme **L-aromatic amino acid decarboxylase (AADC)**.

Monoamine oxidase (MAO)
Both subtypes (-A & -B) occur widely in the brain and peripheral tissues. MAO-A is more selective for serotonin oxidation by being able to metabolise serotonin with lower Km and higher affinity than MAO-B.

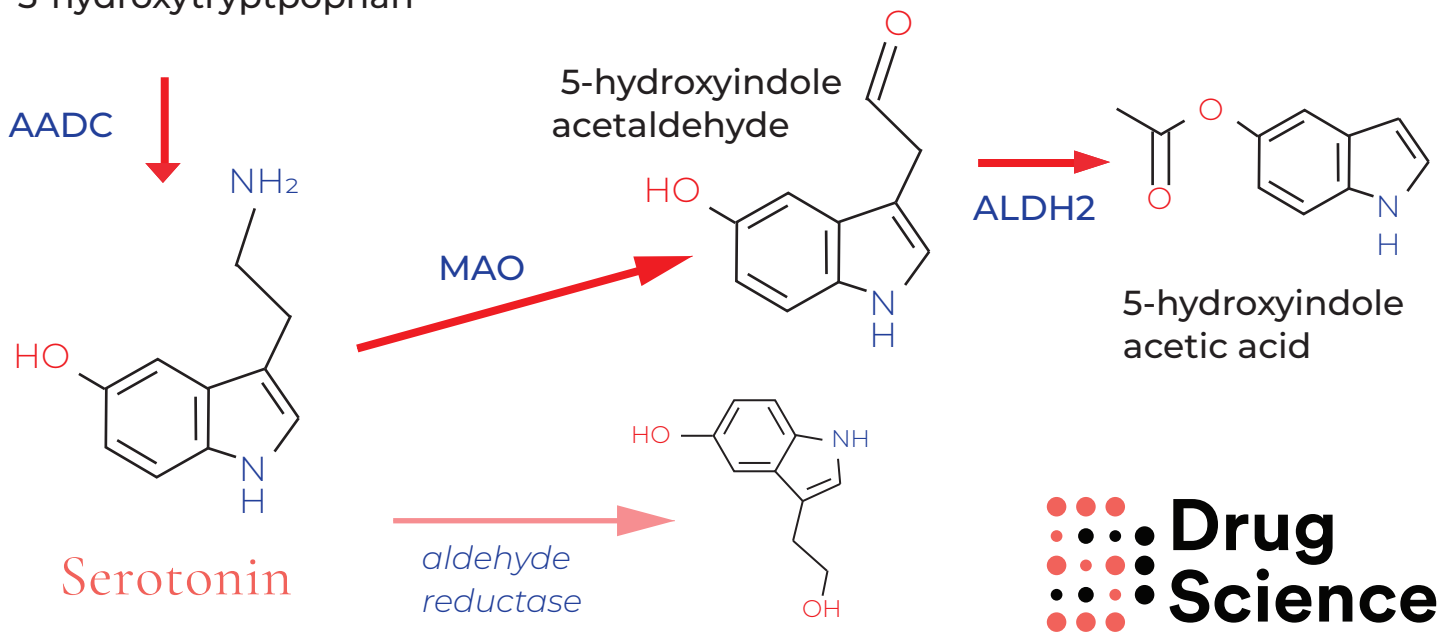
Interestingly, however, immunohistochemical studies have suggested that serotonin-containing neurons may themselves contain only MAO-B.



Metabolism of serotonin is carried out primarily by the outer mitochondrial membrane enzyme **monoamine oxidase (MAO-A & MAO-B**).

MAO converts **serotonin** to **5-hydroxyindole acetaldehyde**, which in turn is readily metabolised, principally by an isoform of **aldehyde dehydrogenase (ALDH2)** located in mitochondria, to produce **5-hydroxyindole acetic acid** as the major excreted metabolite of serotonin.

An alternative metabolic route via aldehyde reductase can convert 5-hydroxyindole acetaldehyde to **5-hydroxytryptophol,** but this pathway is normally considered to be insignificant.



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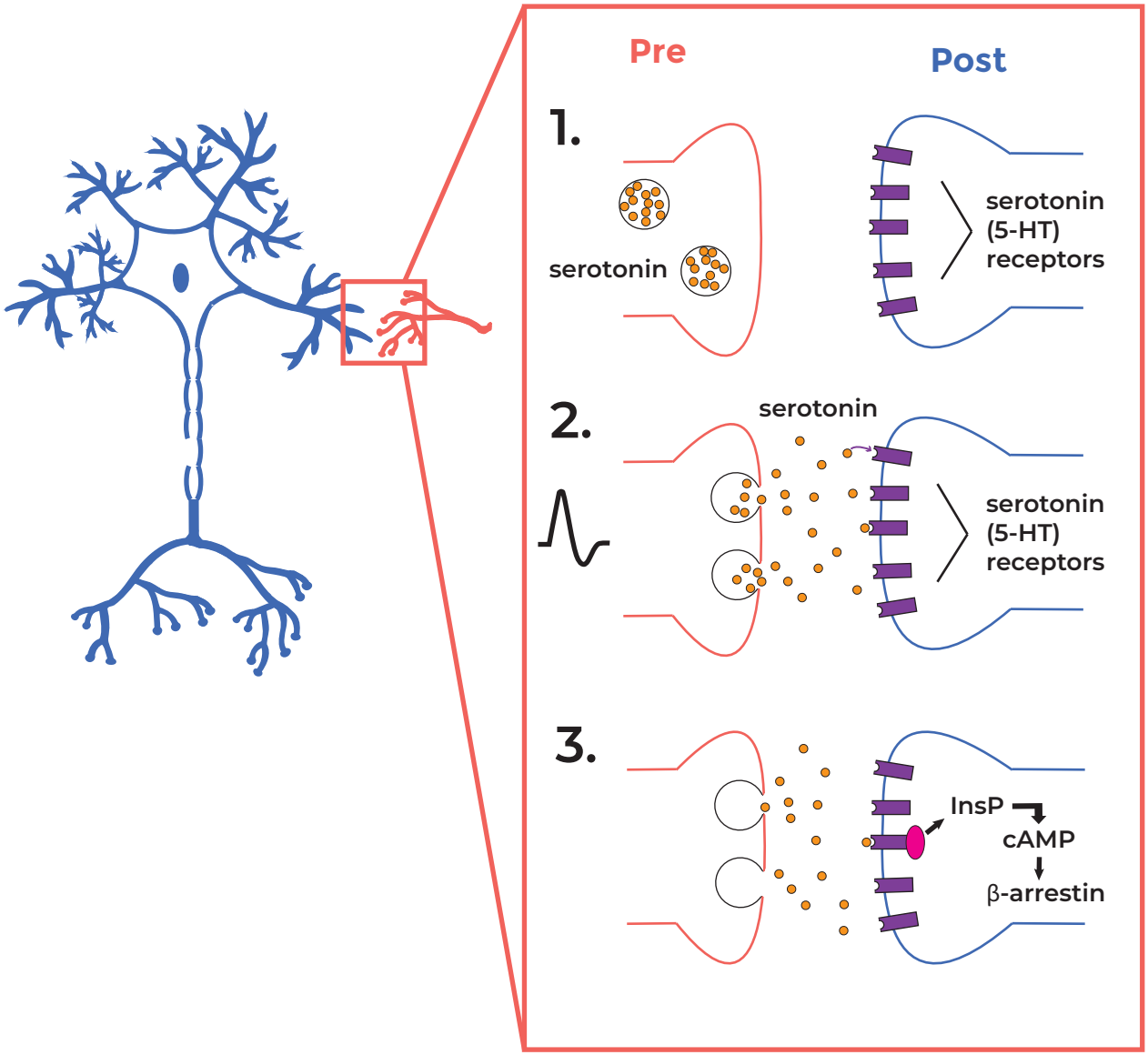
Serotonin Signalling



Neurotransmitters generally travel from the **presynaptic bouton** across the synaptic cleft to act on **postsynaptic receptors**. Serotonin is stored in vesicles at the bouton of the presynaptic neuron.

In response to an action potential transmitted within the presynaptic neuron, serotonin is released from the storage vesicles into the synaptic cleft. serotonin molecules diffuse across to bind to serotonin (5-HT) receptors on the surface of the postsynaptic neuron.

Serotonin binds to its orthosteric binding site on the extracellular domain of the membrane-bound 5-HT receptor molecule, which elicits a characteristic conformational change resulting in a cascade of events related to G-protein cleavage and downstream interactions and catalysis involving second-messenger molecules such as inositol phosphate and cyclic AMP, and proteins such as β-arrestin.

Serotonin Receptors

The **serotonin (5-HT) receptors** are postsynaptic receptors that exist as **14 subtypes** in mammals. All but one (the 5-HT3 receptor) are metabotrophic, **G protein-coupled receptors**.

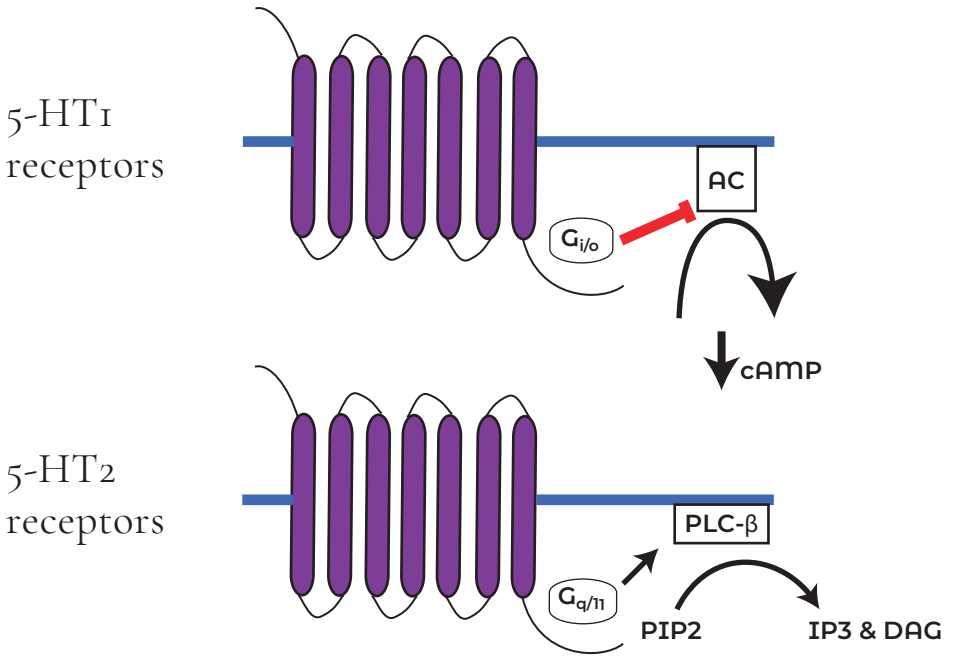
The G protein-coupled 5-HT receptors all have seven transmembrane spanning domains. They couple to different G proteins, including the **Gi/o, Gq/$_{11}$ and Gs** families of G proteins, to cause either a change in cellular cAMP levels, or in the case of 5-HT2 receptors, increase levels of inositol trisphosphate (IP3) and diglyceride (DAG).

5-HT receptors are located throughout the body, including on platelets in the blood. 5-HT receptors are also widespread in the brain.

5-HT receptors have diverse functions in the brain, including regulation of sleep, mood, appetite and social functioning.

There are 14 serotonin (5-HT) receptor subtypes

5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT5A, 5-HT5B, 5-HT6, & 5-HT7



5-HT Receptors in the Brain

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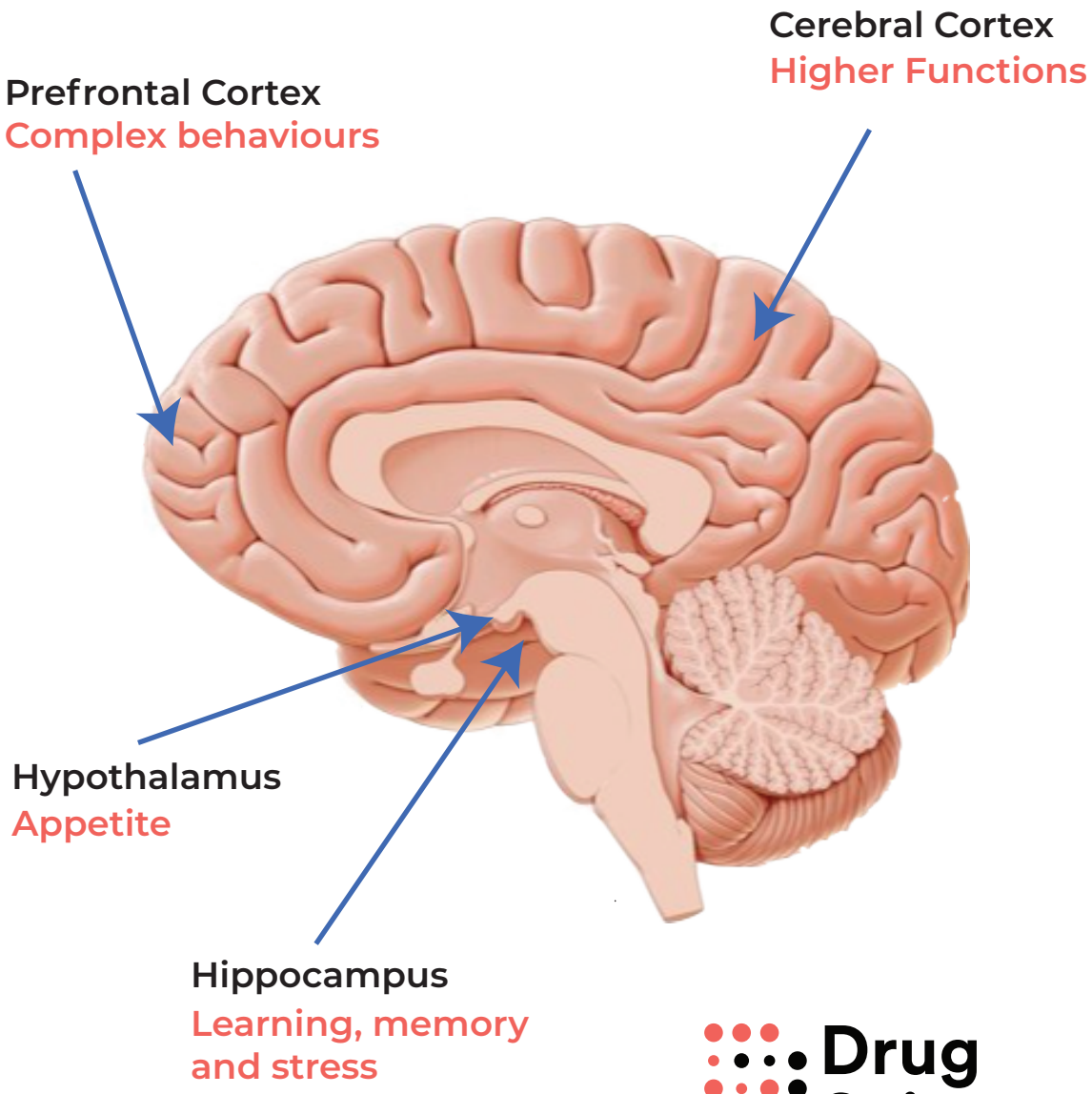
In the brain, 5-HT receptors are widespread although they feature particularly prominently in the **cortical regions**.

5-HT receptors have diverse functions in the brain, including regulation of **sleep, mood, appetite and social functioning**.

5-HT receptor expression is tightly controlled through the processes of transcription and translation, and may be up- or down-regulated in response to neurochemical influences.

5-HT2A and **5-HT2C** receptors are located predominantly in the "higher" areas, on cortical **layer V pyramidal neurons**, on cortical **glutamatergic neurons** and **GABAergic interneurons** of the pre-frontal cortex.



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Modulating 5-HT2A/2C Receptors

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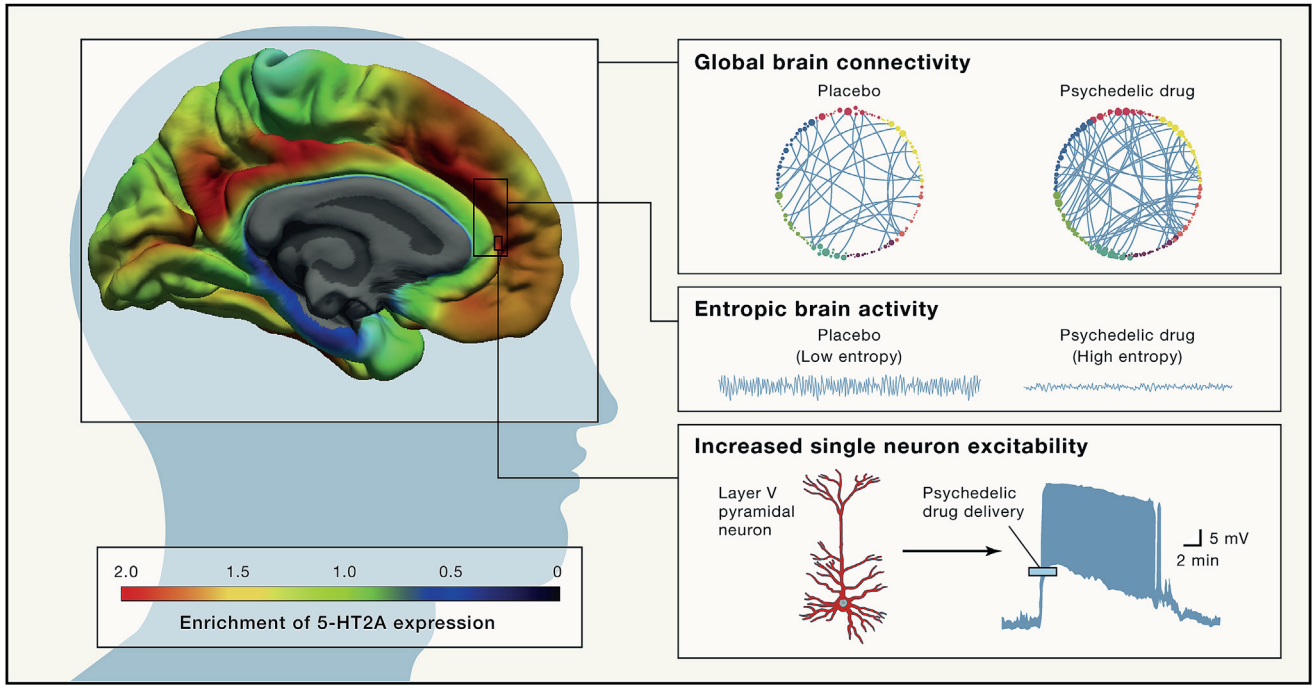
Besides being targets for the endogenous neurotransmitter, **serotonin**, the **5-HT2A** and **5-HT2C** receptors are activated by a wide range of serotonergic compounds including **psilocybin**, **mescaline** and **LSD**. Many of these compounds elicit distinctive effects on consciousness, although some (e.g. lisuride and 1-methylpsilocin) have been found to bind to the 5-HT2A/2C receptors but do not have psychoactive effects.

Those serotonergic compounds that exert psychedelic effects are commonly called the "**classical psychedelics**" The psychoactive effects of classical psychedelics appear to be mediated by interactions between the postsynaptic 5-HT2A and presynaptic **mGlu2 receptors** on glutamatergic neurons in the cortex. This has been supported by experiments using **5-HT2A antagonists that were shown to block the psychedelic effects** of psilocybin. However, the exact mechanisms are not yet clear, and are subject to ongoing research.



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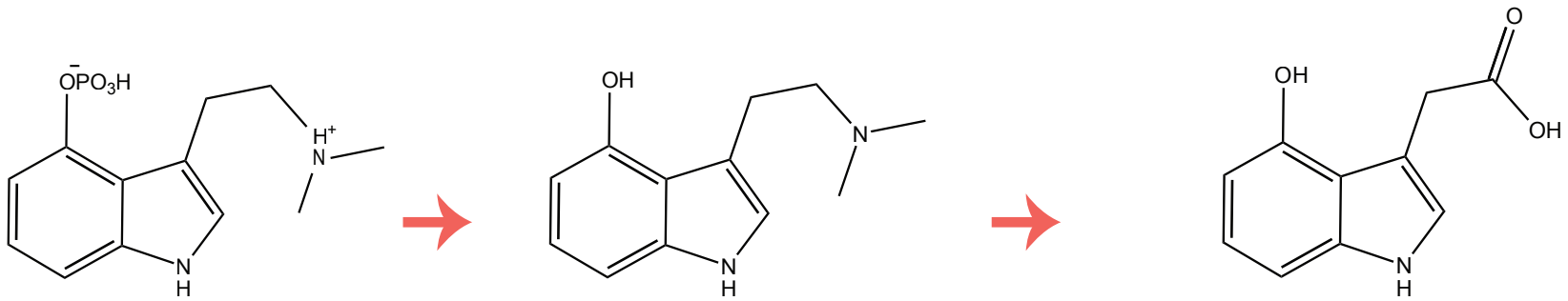
Psilocybin Pharmacology

Psilocin is a relatively unstable compound, being susceptible to oxidation due to its exposed 4-hydroxy functional group. Psilocybin is substantially more stable as the hydroxyl oxygen atom is protected by a phosphate group.

Psilocybin and psilocin are highly water-soluble, hence orally available and are quickly absorbed into the bloodstream through the stomach wall.

The 4-phosphoryloxy group of psilocybin is quickly hydrolysed to form psilocin under physiological conditions. Psilocin is metabolised by **monoamine oxidase (MAO-A & MAO-B)** throughout the body, being oxidised to **4-hydroxyindoleacetic acid**. In healthy humans, psilocybin/psilocin has a half-life of 3 hours.



Psilocybin **Psilocin** **4-hydroxyindoleacetic acid**

Psilocin – Psychoactive Properties

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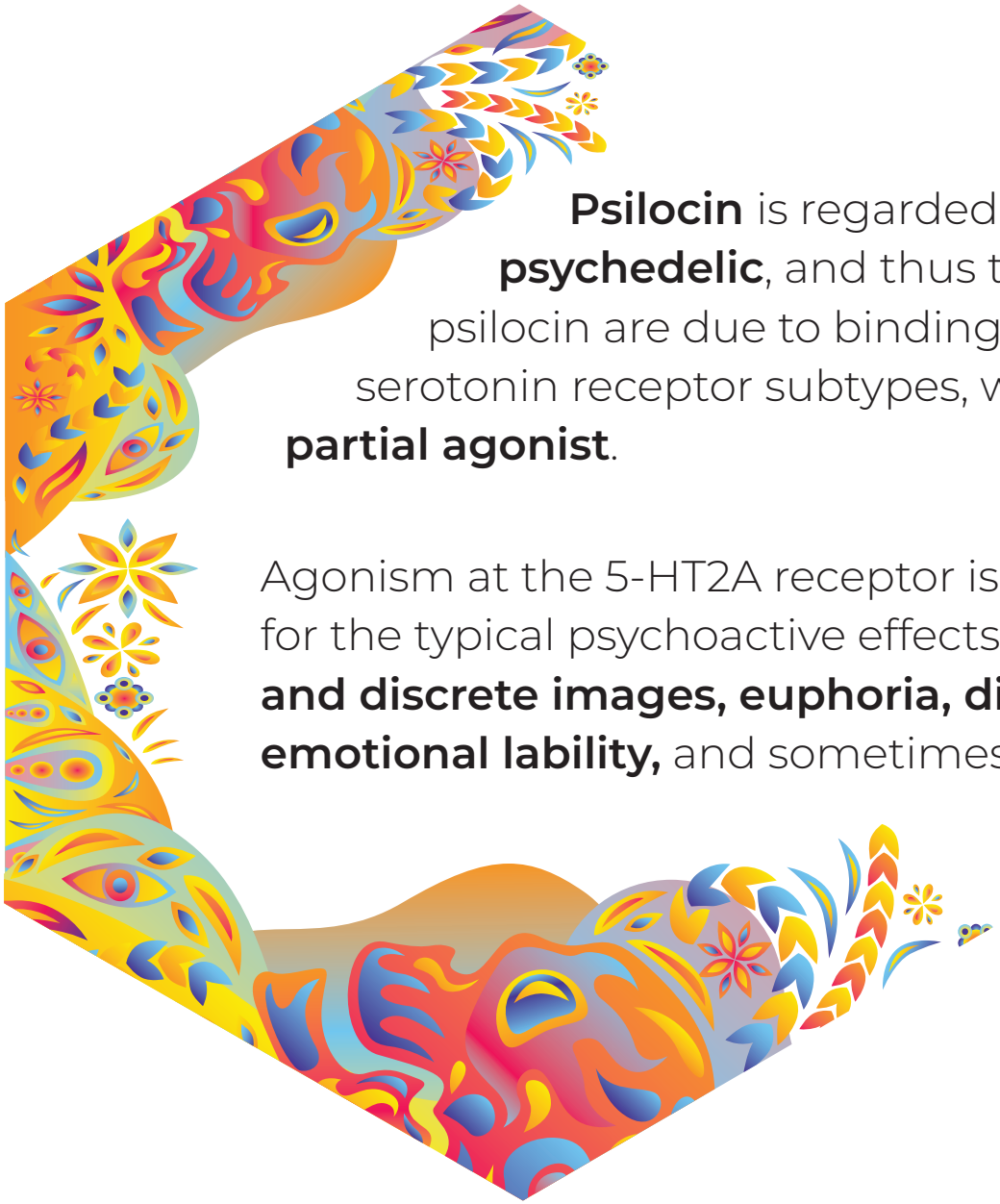

Psilocin is regarded as a prototypic **classical psychedelic**, and thus the main psychoactive effects of psilocin are due to binding to the **5-HT2A** and **5-HT2C** serotonin receptor subtypes, where it acts with high specificity as a **partial agonist**.

Agonism at the 5-HT2A receptor is thought to be most directly responsible for the typical psychoactive effects of changes in **perception, visual patterns and discrete images, euphoria, distorted sense of time, synesthesia, emotional lability,** and sometimes **mystical or spiritual experiences**.

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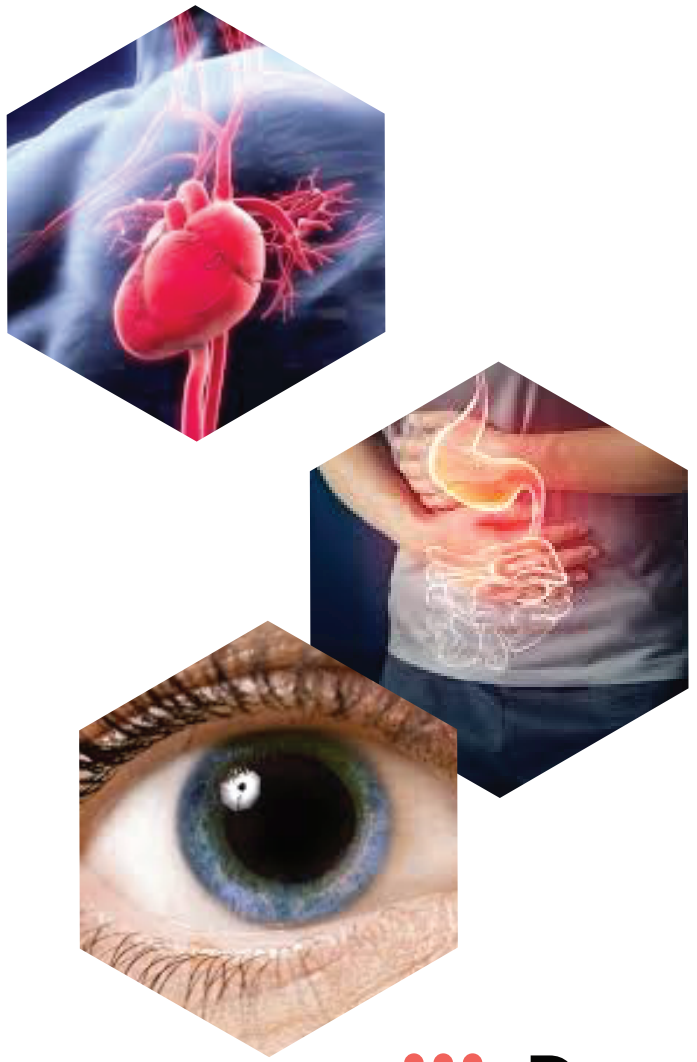
Psilocin - Physiological effects

The physiological effects of psilocin are primarily related to its activity at 5-HT receptors throughout the body, including the brain.

The most common **physiological effects** of psilocin include increased **heart rate, pupil dilatation, and increased gastrointestinal motility** due to the presence of 5-HT receptors throughout the gut. Nausea is also a relatively common, though not ubiquitous, effect of psilocin, and headaches are sometimes reported.

Psilocin has **no established toxicity** in humans. It is rapidly metabolised to harmless metabolites that are excreted in the urine.



How the psychoactive effects may affect psychological change

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At the core of mental illness often exists rigid negative self and world narratives (e.g. I am a bad person, other people are abusive, the world is a dangerous place). Psychedelics relax this rigid thinking, allowing space for new and more helpful narratives to be established (e.g. perhaps I'm not a bad person, sometimes I do good things).

Mental illness can also be caused by **unhealthy repression** and **avoidance of traumatic and unpleasant thoughts/feelings**.

During the psychedelic mental state, the **psychological defences that are usually deployed to avoid these thoughts/feelings are weakened**.

Without these defences in play, the patient is able to face and **process these repressed thoughts/feelings**, and hopefully adopt healthier coping mechanisms moving forward.

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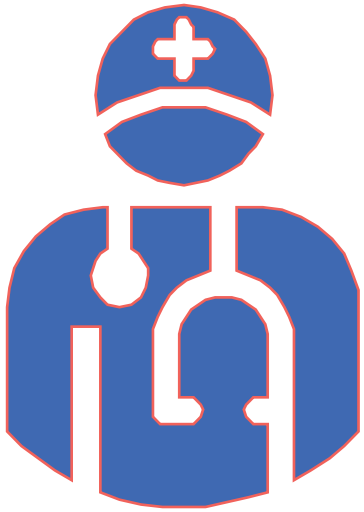
Psilocin - Risks and Adverse Effects

There is no established toxicity with psilocin due to:

- Structural similarity to serotonin
- Harmless metabolites



However, adverse effects can include:

- Transient fear and/or anxiety, sometimes panic
- Brief increase in heart rate and blood pressure
- Paranoia
- Risk of psychosis – generally in susceptible individuals and/or with extended use

Psilocybin – Therapeutic Applications

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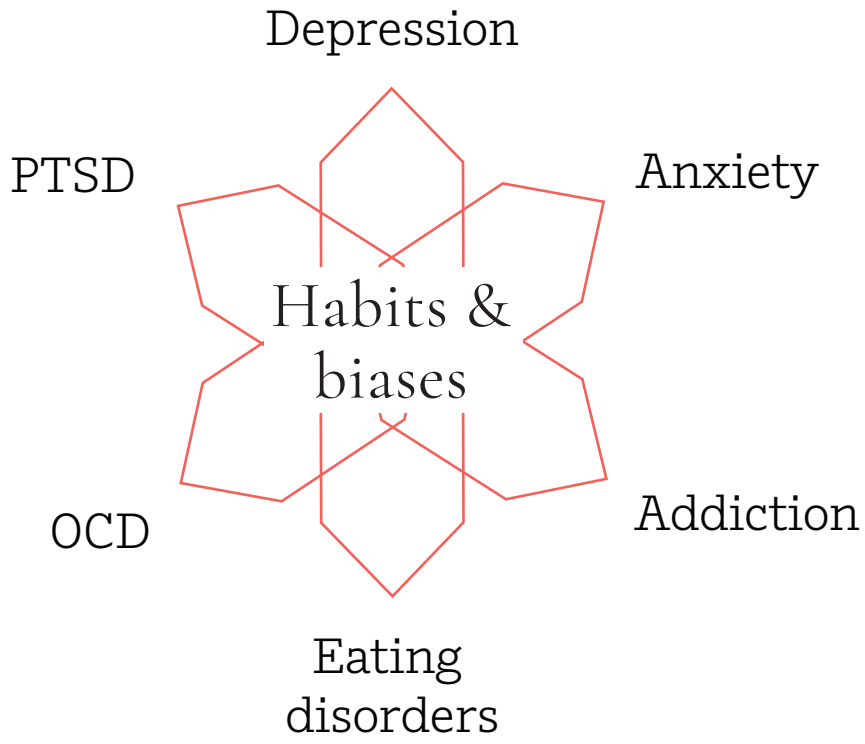
Psilocybin is thought to be an effective treatment for disorders related to rigid modes of thinking - those disorders based in habits & biases

These include:

- Anxiety
- Depression
- OCD
- Eating disorders
- Addictions
- It may also be effective for the prevention of cluster headaches, a form of migraine



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Psilocybin – Therapeutic Mechanisms

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Neuroplasticity

- Neuritogenesis, spinogenesis, synaptogenesis
- TrkB, mTOR, and 5-HT2A signaling pathway modulation, possibly through BDNF upregulation

■ Ly et al (2018). Cell Rep. 23(11):3170-3182

Functional connectivity & modulation of the Default Mode Network (DMN)

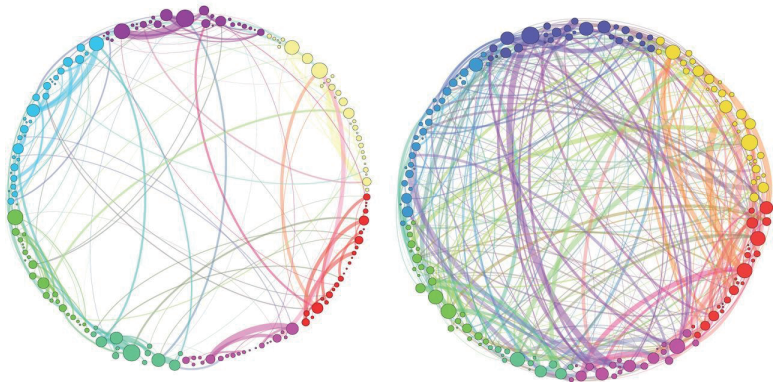
■ Carhart-Harris et al (2017). Sci Rep. 7:13187

■ Petri et al (2014). J R Soc Interface 11:20140873

Intensity of psychedelic experience correlates with positive therapeutic outcome

- Suggestibility
- Wonder
- Ineffability
- Boundlessness
- Noetic sense

CLICK HERE TO WATCH MICHAEL POLLAN TALK ABOUT HOW PSYCHEDELICS WORK



A high-dose psychedelic experience is like shaking up a snow globe, disrupting unhealthy patterns of thought and providing an opportunity for them to resettle differently

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Psilocybin – Therapeutic Practicalities

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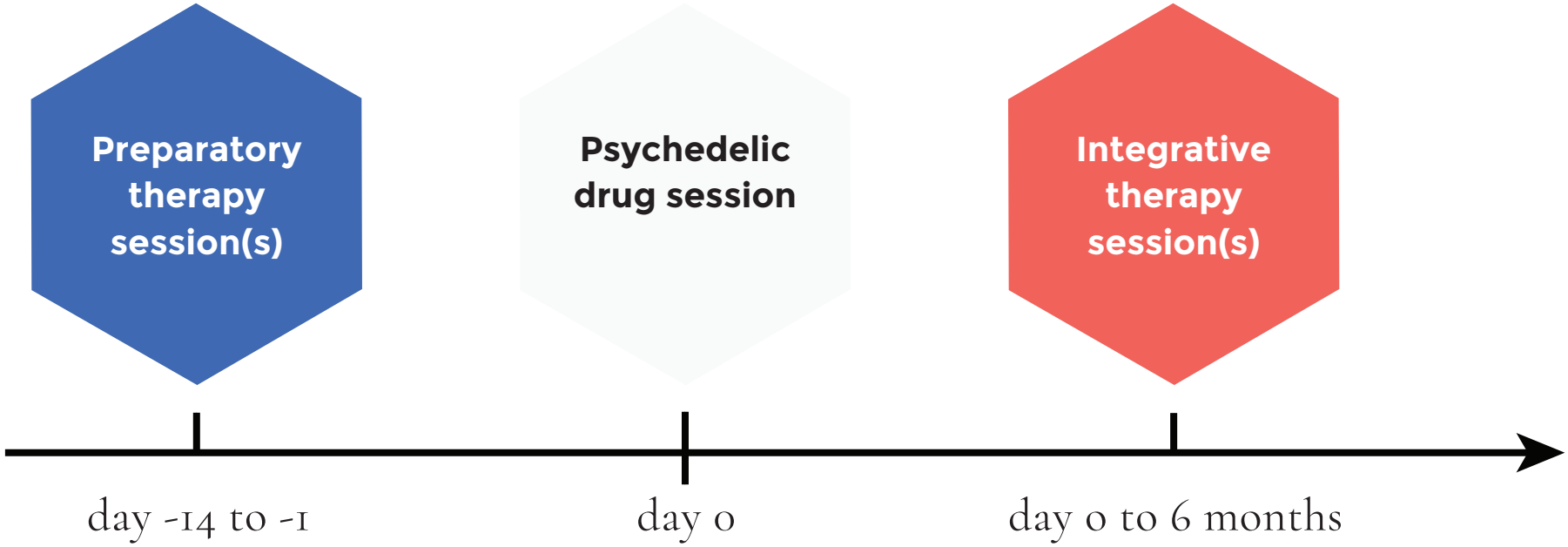
Psilocybin is generally utilised therapeutically in conjunction with a form of meaning-centred/psychodynamic psychotherapy commonly termed **Psychedelic-Assisted Psychotherapy (PAP)**

Psychedelic-Assisted Psychotherapy involves:



Preparatory and integrative therapy are considered equally crucial to the active drug session for positive outcomes. Typically preparation begins a couple of weeks before the psychedelic dosing day, with integration sessions occuring multiple times over a set follow-up period that may last for 6 months.

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Preparatory psychotherapy

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Preparatory psychotherapy:

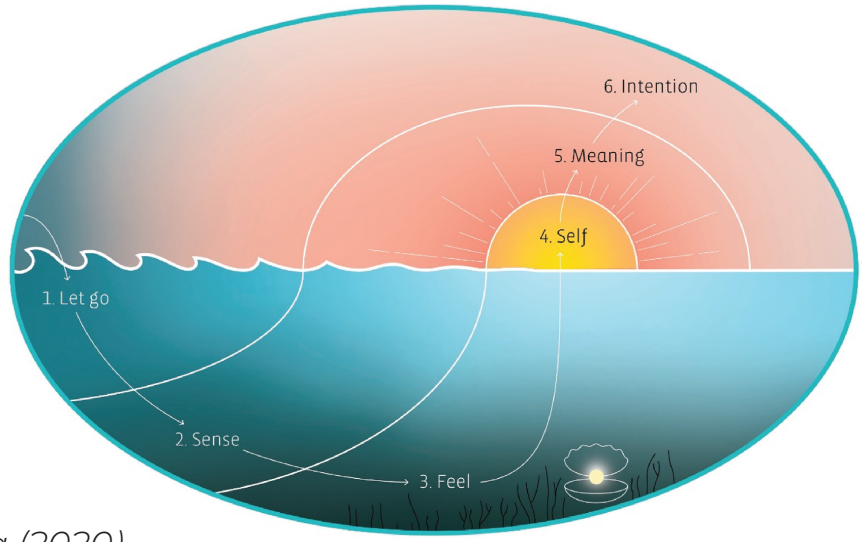
- **prepares the participant/patient for the overall process**, particularly the psychedelic experience to come. This is especially important for psilocybin-naïve patients

- it establishes a **therapeutic alliance**

- it allows for discussion of the **participant's condition and broader context**

- makes participants aware of possible **mind-states, transient anxiety, breakthroughs** etc. that can occur during the active drug session

The ACE model is a way to manage the experience and optimise outcomes



Watts & Luoma (2020)
J Context. Behav. Sci. 15:92-102.

CLICK HERE TO WATCH ROSALIND WATTS EXPLAIN THE ACE MODEL

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Active psilocybin session

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SET: the patient's emotional/cognitive/behavioral mindset and expectations

SETTING: the physical environment in which the exposure occurs

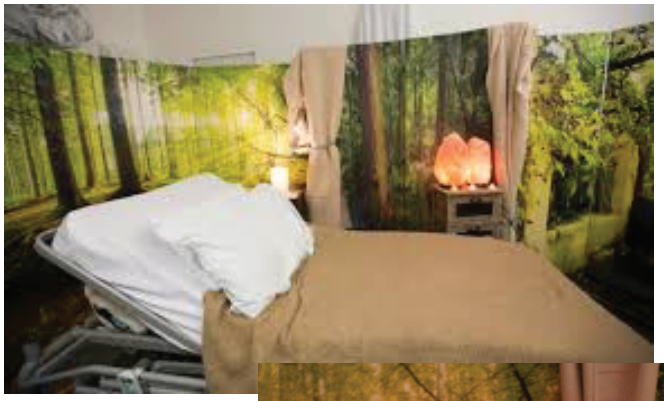
The importance of Set and Setting

Set is optimised through preparatory session(s), so that the patients feel comfortable with their therapists and familiar with the location, so they are able to relax. The therapists present are there to "support, not guide" the experience.

Setting is optimised by creating a comfortable space, using muted lighting, calming décor and elements of ceremony/ritual.

The importance of music has also been established in creating the right set and setting.

See Carhart-Harris 2018. Psychedelics and the essential importance of context, Journal of Psychopharmacology



An example of the room (left) and active session (below) at Imperial College London

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Integrative psychotherapy

Integration sessions are considered critical for optimal therapeutic outcomes with regards to psychedelic therapy because:

- Analysis is very difficult during the acute phase of the psychedelic experience, and so dedicated time afterwards allows participants to examine their experience

- They help participants to make sense of what they experienced

- Therapists can help frame the experience in broader perspective of the participant's condition

Why We Need More Research

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- **Clinical research** is fundamental to government approval of new drugs and medical interventions
- Research into therapeutic applications was **interrupted by global War on Drugs,** but many research questions were left unanswered
- **Mechanisms of action** still need to be elucidated
- Exploration of the **scope of psychedelic-assisted psychotherapy**, e.g. beyond treatment of mood disorders to other mental health conditions
- Exploration of **applicability beyond the adult population**
- Research is an effective means to **promote awareness and acceptance** of new approaches within the medical, and broader, community
- There is the potential to shed light on **mechanisms of mental illness, and brain function more broadly**

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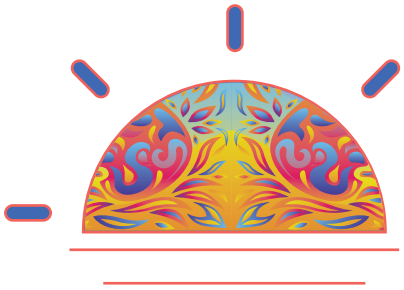
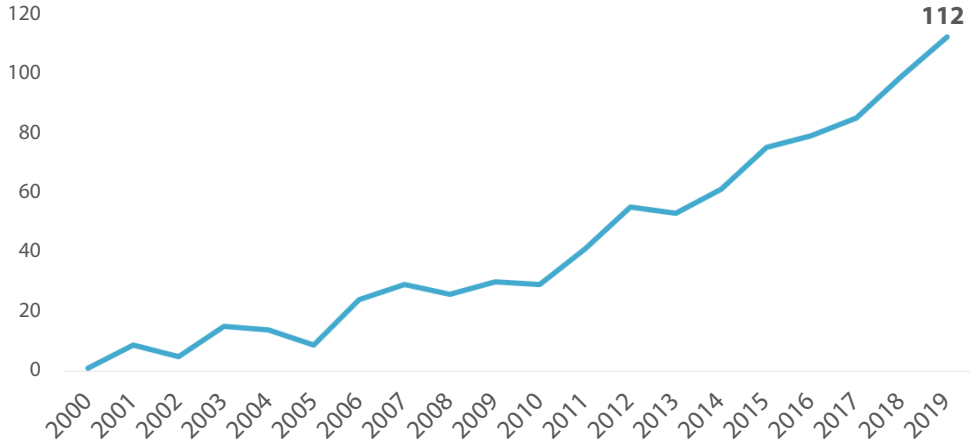
Into the future



The future of psychedelic medicine is looking promising, although there is a need for mid to long-term strategic planning to manage the process

1. Psychedelic research is now blossoming globally
2. There are realistic prospects of regulatory approval
3. There is potential for widespread application within public health models
4. The health insurance industry is already paying attention to the field

Psychedelics are being studied more than ever before



Number of interventional clinical trials launched in the US per year, 2000-2019 (from CB INSIGHTS)

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