N,N-dimethyltryptamine (DMT) and Ayahuasca

By Drug Science and Small Pharma

Part 2 - Pharmacology

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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Small Pharma

Led by an experienced team committed to making a difference for people suffering from mental health conditions, Small Pharma believes that together, as a community, we can help unlock cutting edge science and bring new therapies to treat mental health disorders.

Small Pharma is a virtual biopharmaceutical company on a mission to improve mental health by progressing psychedelic therapies to the clinic. At Small Pharma, they have identified the field of psychedelic medicine as an exciting and unexplored area of drug discovery, with the ability to completely transform our understanding and approach to mental health. As compounds neglected by risk averse traditional pharma, the Small Pharma team are passionate about becoming the R&D leaders of psychedelic drug discovery and development.

Small Pharma funds clinical trials of DMT and related psychedelic compounds as a tool to augment psychotherapy for the treatment of depression and other mental health conditions. Their current focus is to unlock the exciting potential of DMT therapy as a treatment for Major Depressive Disorder.

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What is DMT?

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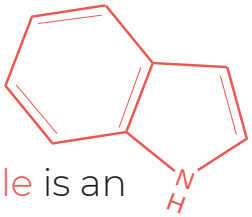
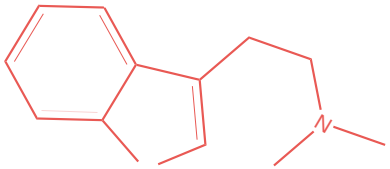
DMT (N,N-dimethyltrypta-mine) is an indole alkaloid, chemically similar to the neurotransmitter **serotonin** (5-HT).

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.



DMT **occurs naturally** in various plants in relatively small amounts.

DMT has also been found in rat brains, suggesting mammalian brains might be able to produce DMT endogenously.

The molecule has been reported to be produced by the human brain in very small quantities.

DMT can be synthesised chemically as a base or salt form.

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How does DMT act?

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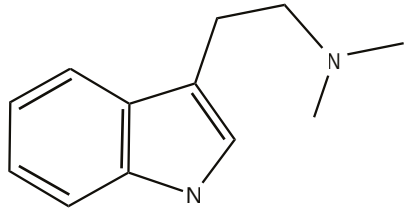
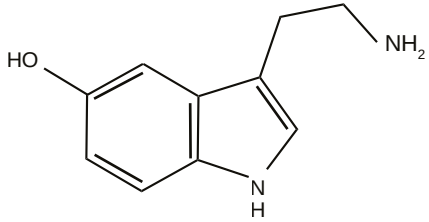
In vitro, DMT has shown an affinity to a range of receptors, including **serotonin** (5-hydroxytryptamine; 5-HT). The chemical structure of DMT is similar to that of serotonin, allowing DMT to bind with 5-HT receptors.

DMT acts to stimulate (is an agonist of) the **5-HT2A** receptor, in particular.

DMT



Serotonin



Besides being targets for the endogenous neurotransmitter **serotonin**, the **5-HT2A** (as well as the 5-HT2C) receptors are activated by a wide range of serotonergic compounds including **psilocybin**, **mescaline** and **LSD**.

However, the binding of DMT to 5-HT 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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What is 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, serotonin plays an important role in **psychological function,** involved in sleep regulation, appetite, mood and a host of other **higher-level functions**.

Like other classical psychedelics, the primary psychological effects of DMT are believed to be induced through its **activation of 5-HT2A receptors**. Specifically, 5-HT2A receptor agonism is believed to be primarily responsible for the hallucinogenic effects of DMT.

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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Serotonin Formation and Breakdown

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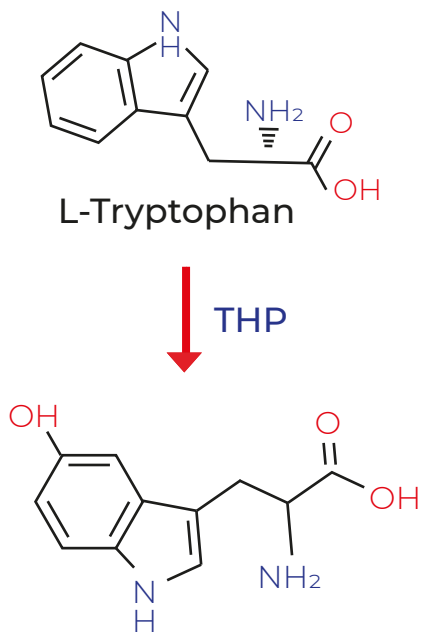
Serotonin biosynthesis initially involves the conversion of **L-tryptophan** to **5-hydroxytryptophan** by **L-tryptophan hydroxylase (TPH)**. The subsequent metabolic step involves the decarboxylation of 5-hydroxytryptophan by the action of the cytosolic enzyme **L-aromatic amino acid decarboxylase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

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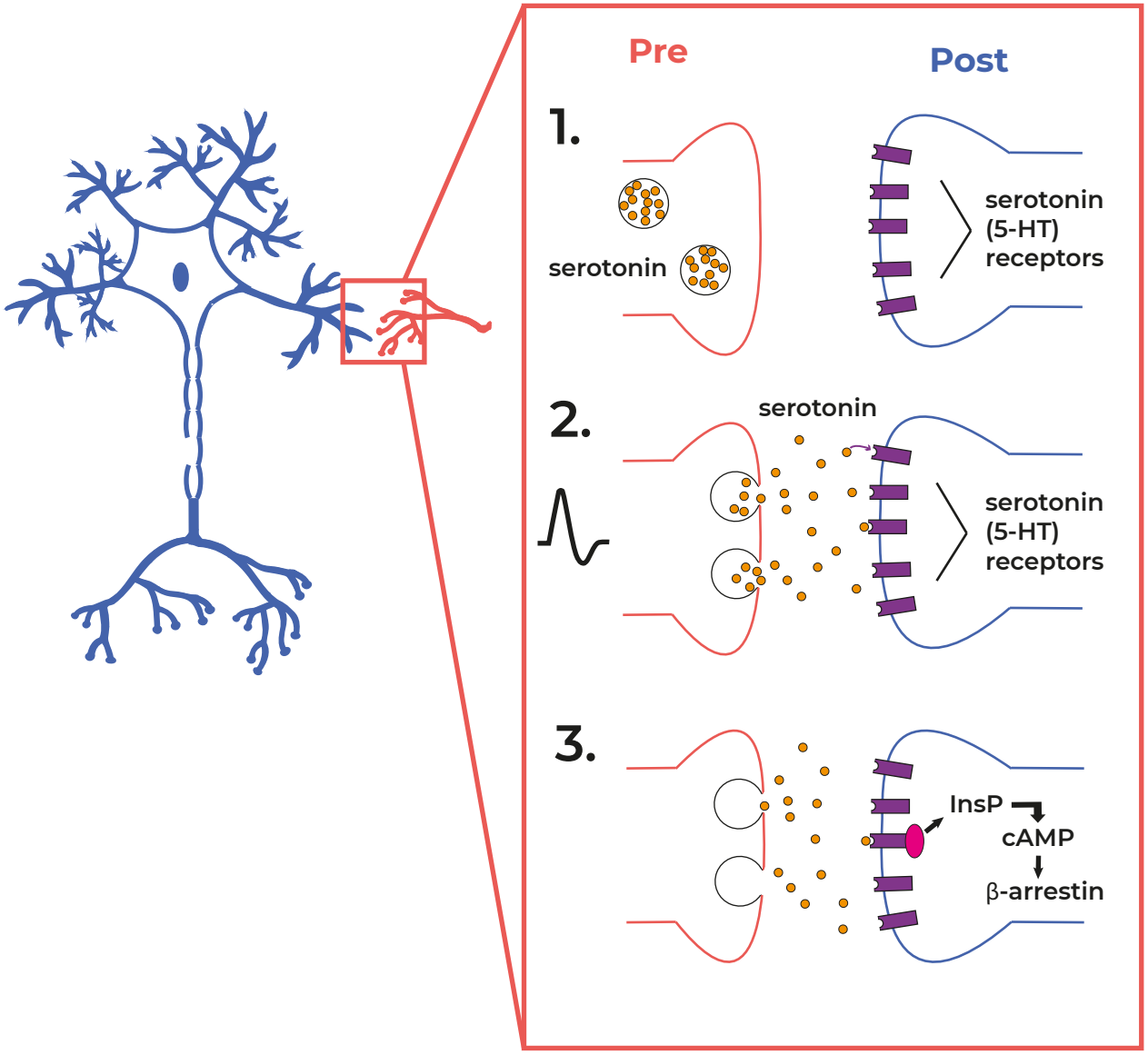

Neurotransmitters generally travel from the **presynaptic bouton** across the synaptic cleft to act on **postsynaptic receptors**. Serotonin is stored in vesicles at the bouton of the presynaptic neuron.

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 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.

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Serotonin Receptors

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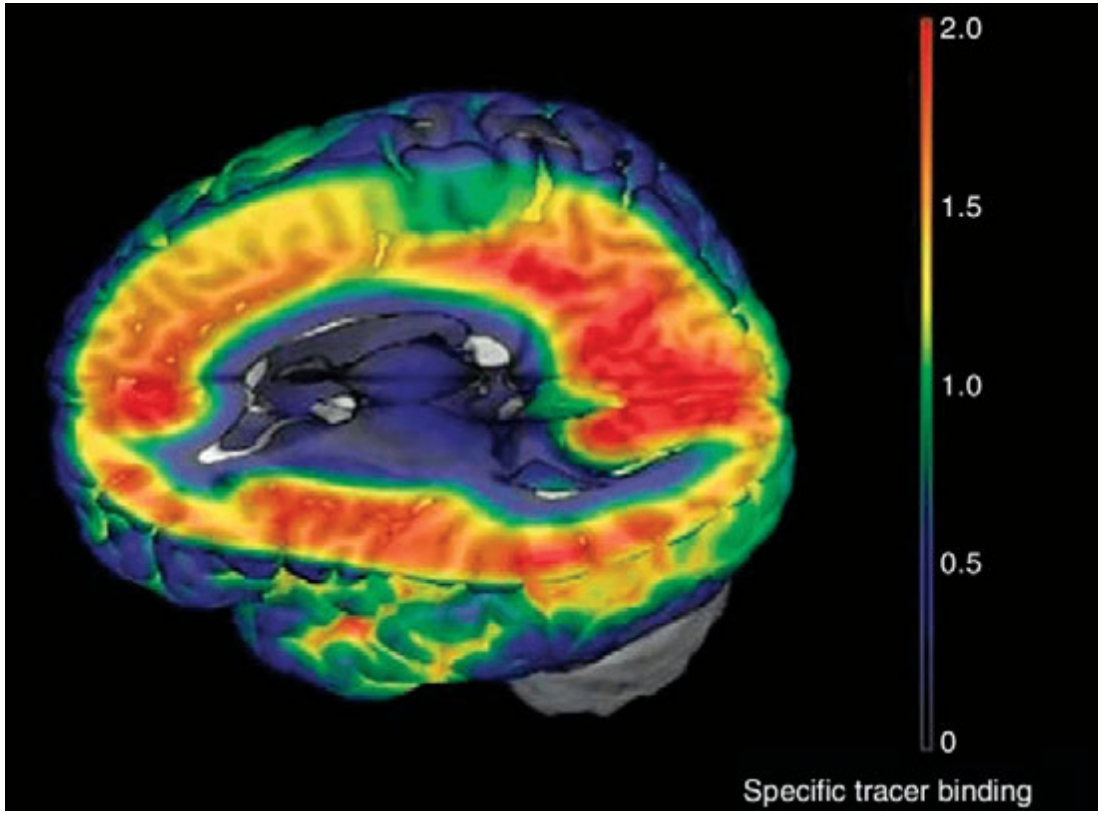
The **serotonin (5-HT) receptors** are postsynaptic receptors that exist as **14 subtypes** in mammals. All but one (the 5-HT3 receptor) are metabotropic, **G protein-coupled receptors**.

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



PET image of the averaged serotonin 5-HT 2A binding potential in 30 healthy subjects. Note that in cortical areas the 5-HT 2A receptor density is very pronounced (high tracer uptake) whereas it is lower in subcortical areas and negligible in cerebellum.
(Ebdrup et al., 2011)

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Serotonin Receptors

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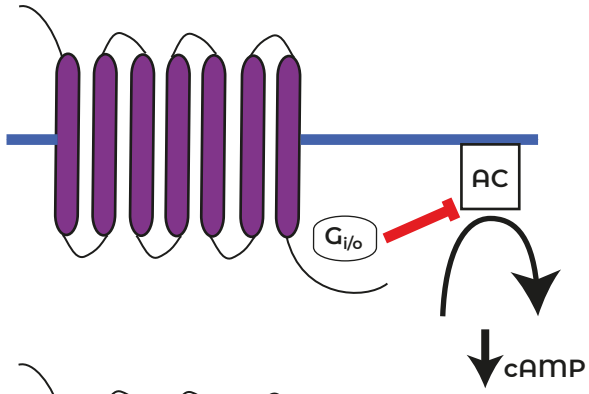
The G protein-coupled 5-HT receptors all have seven transmembrane spanning domains. They couple to different G proteins, including the **Gi/o, Gq/$_{11}$ and Gs** families of G proteins, to cause either a change in cellular cAMP levels, or in the case of 5-HT2 receptors, increase levels of inositol trisphosphate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

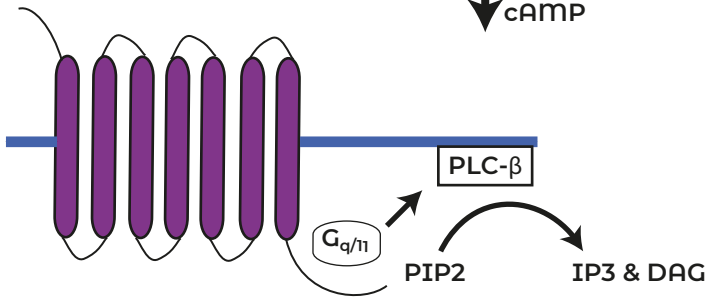
There are 14 serotonin (5-HT) receptor subtypes

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-HT1 receptors



5-HT2 receptors



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Metabolism of DMT

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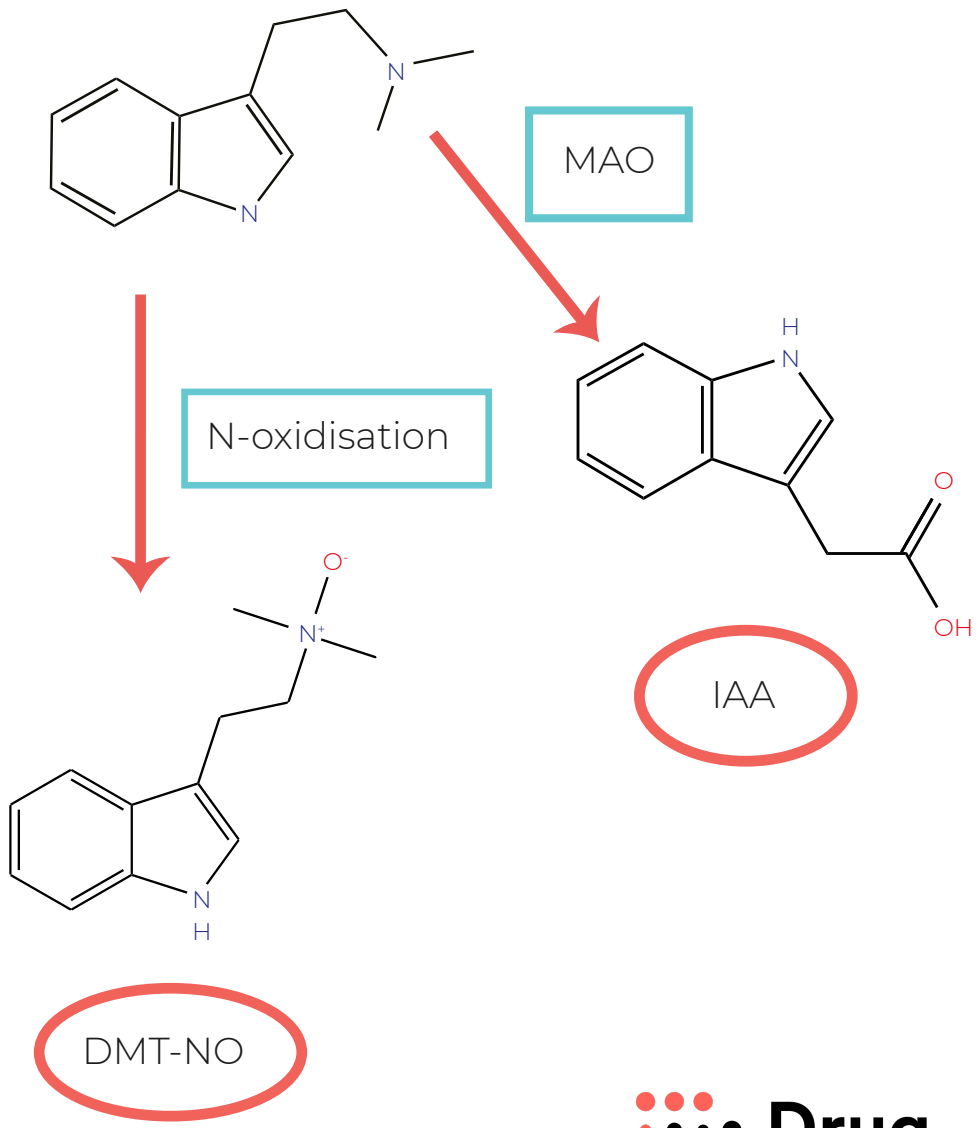
DMT is **metabolized via multiple routes**, including: **MAO, aldehyde dehydrogenase, kyneurinase, and N-oxidase**.

DMT is primarily metabolised by MAO to **indole-3-acetic acid** (IAA). DMT is also converted to **DMT-N-oxide** (DMT-NO) as the second most abundant metabolite.

Depending on the method of administration, DMT is metabolized by different routes:
- When administered orally, DMT is broken down by MAOs and the two primary metabolites are **IAA** and **DMT-NO**;
- When smoked, **higher levels of DMT-NO** can be found in human urine, showing more activity in the N-oxidation metabolic pathway.

More recently, *in vitro* evidence has shown that DMT can also be metabolised by peroxidase or peroxidase-like enzymes, producing **N,N-dimethyl-kynuramine** (DMK), **N,N-dimethyl-N-formyl-kynuramine** (DMFK) and **hydroxyl-DMT** (OH-DMT) (Gomes et al 2014).



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DMT: Duration of action

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Depending on how DMT is administered, its **effects last between 5 and 45 minutes.** Regardless of administration method, the subjective effects of DMT are closely correlated with blood concentration. The prompt cessation of the effects of DMT is due to its **rapid metabolism** via the aforementioned routes.

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5-HT Receptors in the Brain

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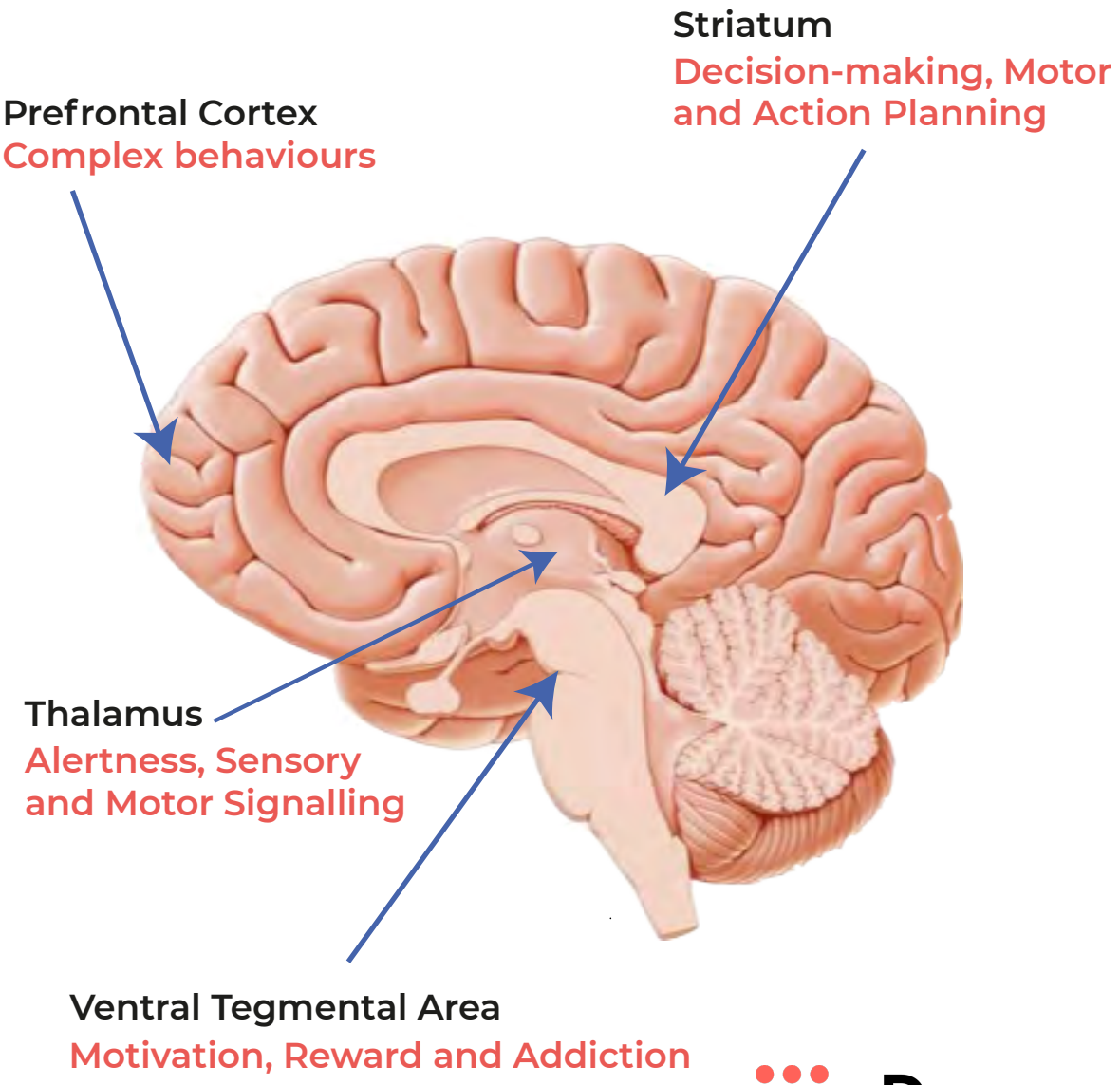
DMT acts as a non-selective agonist on a variety of serotonin receptors including 5-HT2A, as well as: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2B, 5-HT2C, 5-HT5A and 5-HT7

In the brain, 5-HT receptors feature particularly prominently in the **cerebral cortex**.

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 receptors are located predominantly in the **prefrontal cortex, striatum, ventral tegmental area and thalamus.**

They have been identified on cortical **layer V pyramidal neurons,** on cortical **glutamatergic neurons** and **GABAergic interneurons** of the pre-frontal cortex.



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DMT: Psychoactive Properties

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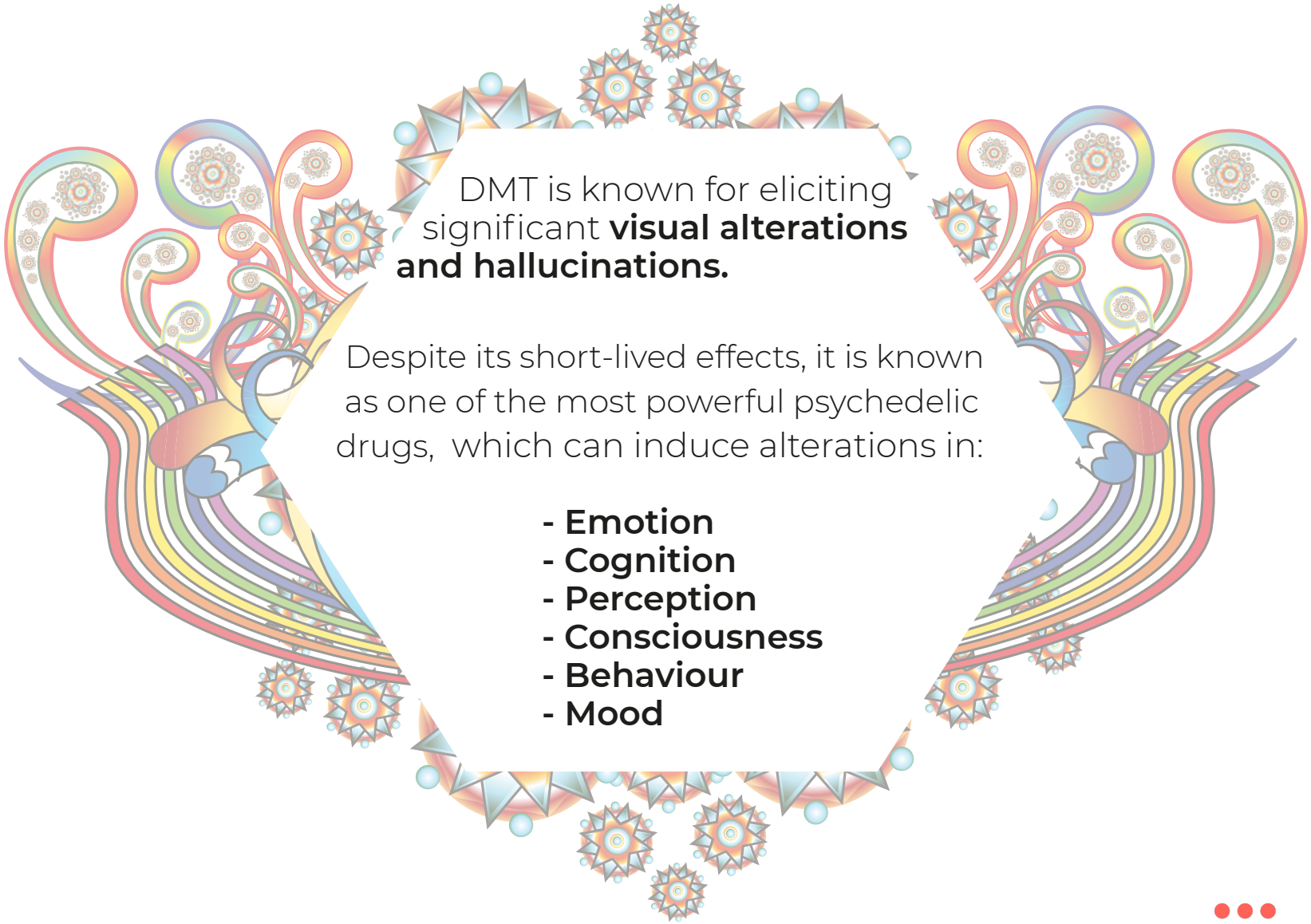

DMT is known for eliciting significant **visual alterations and hallucinations.**

Despite its short-lived effects, it is known as one of the most powerful psychedelic drugs, which can induce alterations in:

- **Emotion**
- **Cognition**
- **Perception**
- **Consciousness**
- **Behaviour**
- **Mood**

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DMT: Physiological Properties

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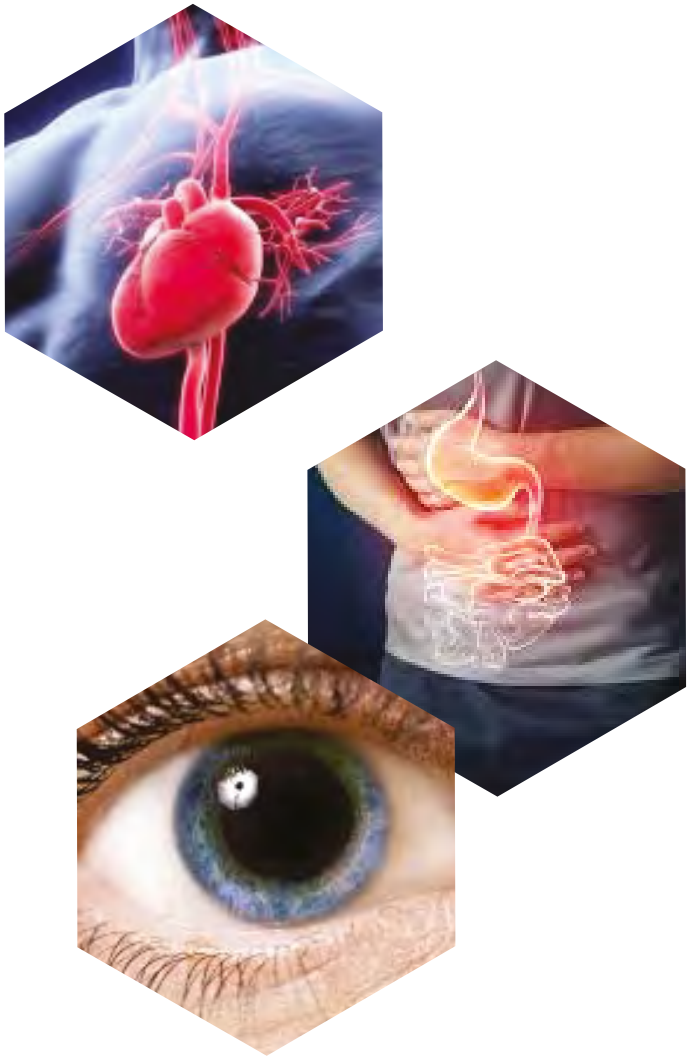
Depending on the method of administration, physiological effects may vary. These include:

- Decreased motor activity
- Impaired cognitive function
- Sympathomimetic effects
- Increased pupil diameter
- Heightened rectal temperature

- Increased cortisol levels
- Increased beta-endorphin / β-endorphin
- Increased corticotropin

- Increased prolactin levels
- Raised growth hormone blood levels

- Elevated blood pressure
- Increased heart rate



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Ayahuasca: What is it?

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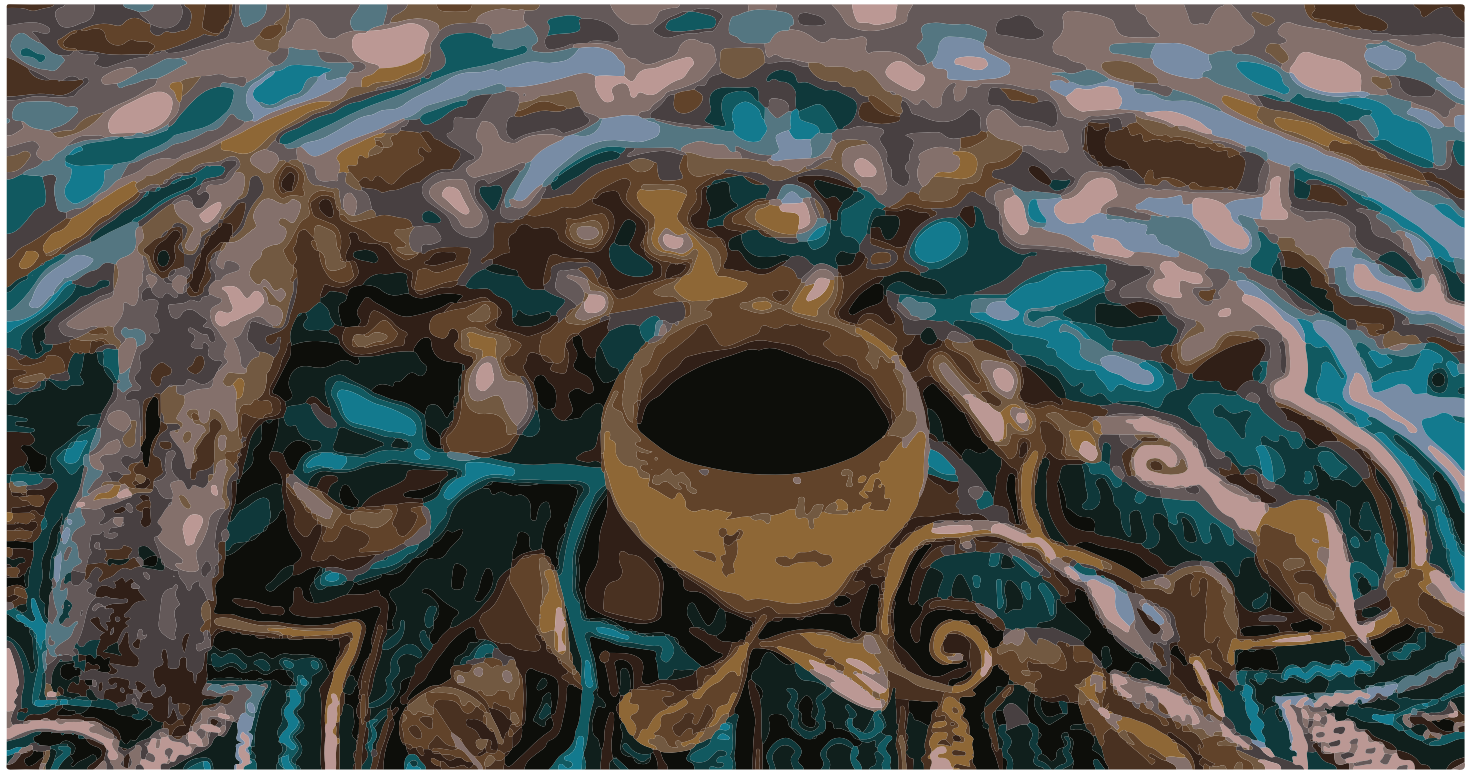
DMT is also present in the **Amazon brew Ayahuasca** – a psychoactive tea consisting of a combination of plants. This botanical hallucinogenic beverage is typically brewed in the Amazon rainforest for ritualistic purposes by indigenous groups.



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What is in Ayahuasca?

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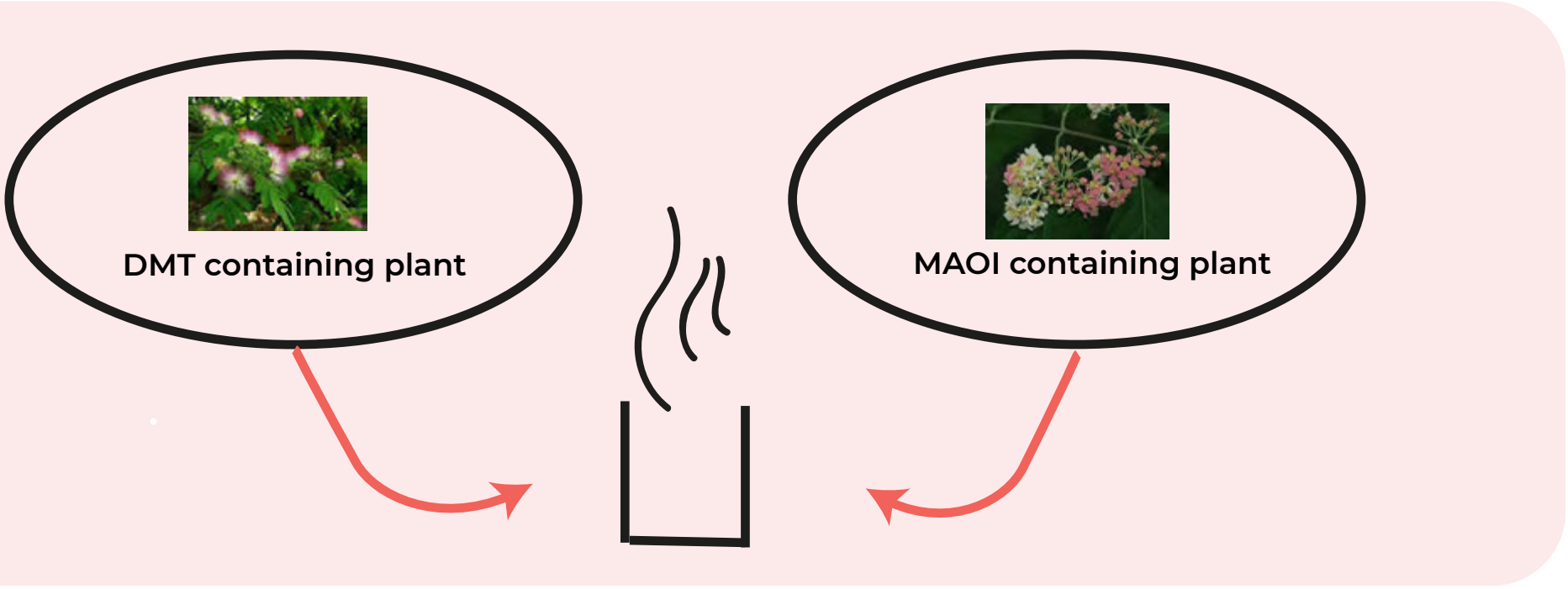
When taken orally, DMT is reportedly **rapidly degraded** by peripheral **monoamine oxidase (MAO)** present in the gatrointestinal wall and liver. This enzyme is located in mitochondria and **catalyses the oxidative deamination of endogenous biogenic amines.** Therefore, DMT is not orally active.

When a DMT-containing plant, such as *Banisteriopsis caapi*, is brewed with another that contains monoamine oxidase inhibiting carboline alkaloids, such as leaves of the shrub *Psychotria viridis*, the rapid degradation of DMT is prevented, allowing for a longer psychedelic experience than taking DMT alone.



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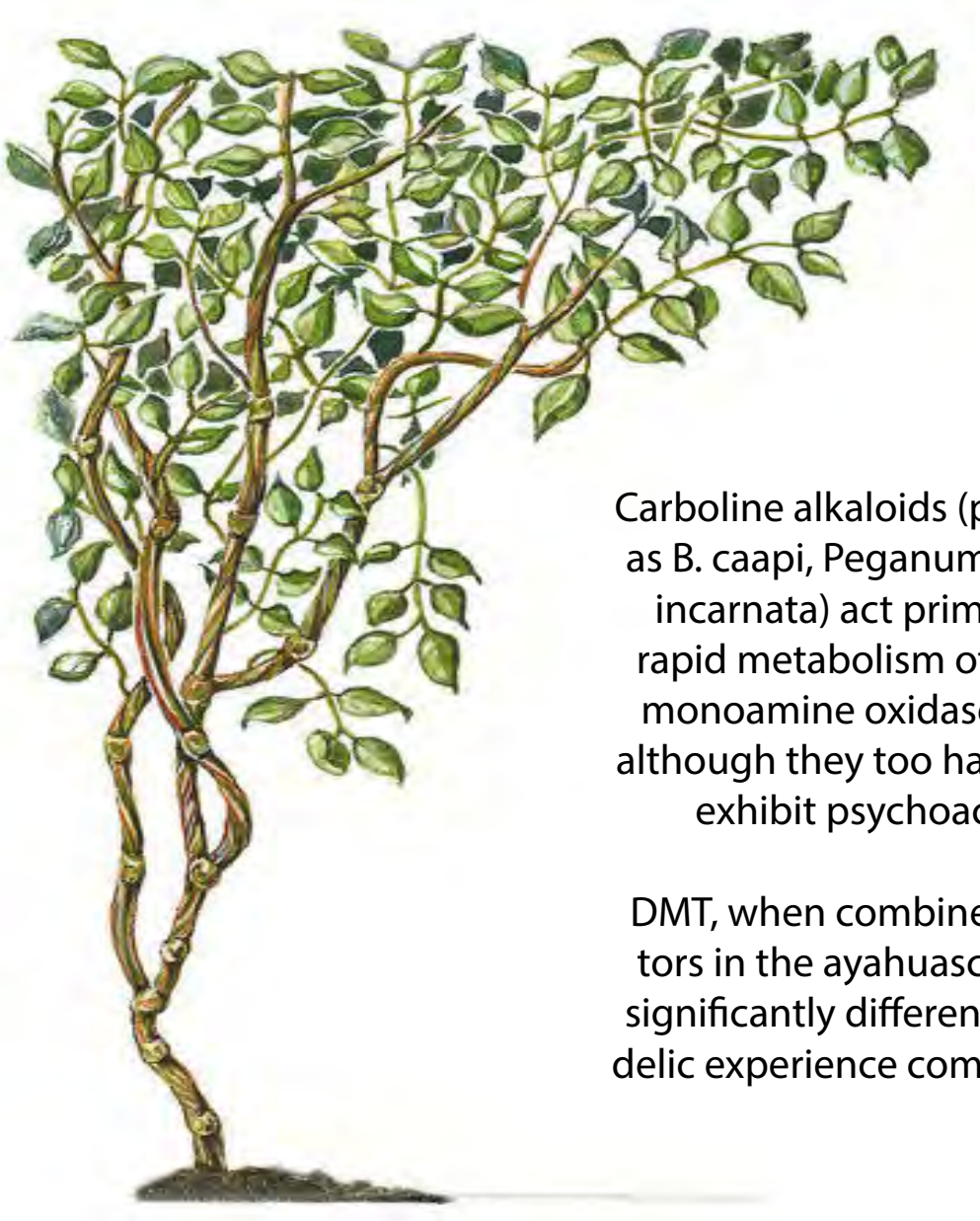
MAOI-DMT interaction in Ayahuasca



Banisteriopsis caapi

Carboline alkaloids (present in plant such as B. caapi, Peganum harmala, Passiflora incarnata) act primarily to inhibit the rapid metabolism of DMT by inhibiting monoamine oxidase enzymes (MAOs), although they too have been reported to exhibit psychoactive properties.

DMT, when combined with MAO inhibitors in the ayahuasca brew, produces a significantly different effect and psychedelic experience compared to DMT alone.

Psychotria viridis

Ayahuasca: What psychological effects?

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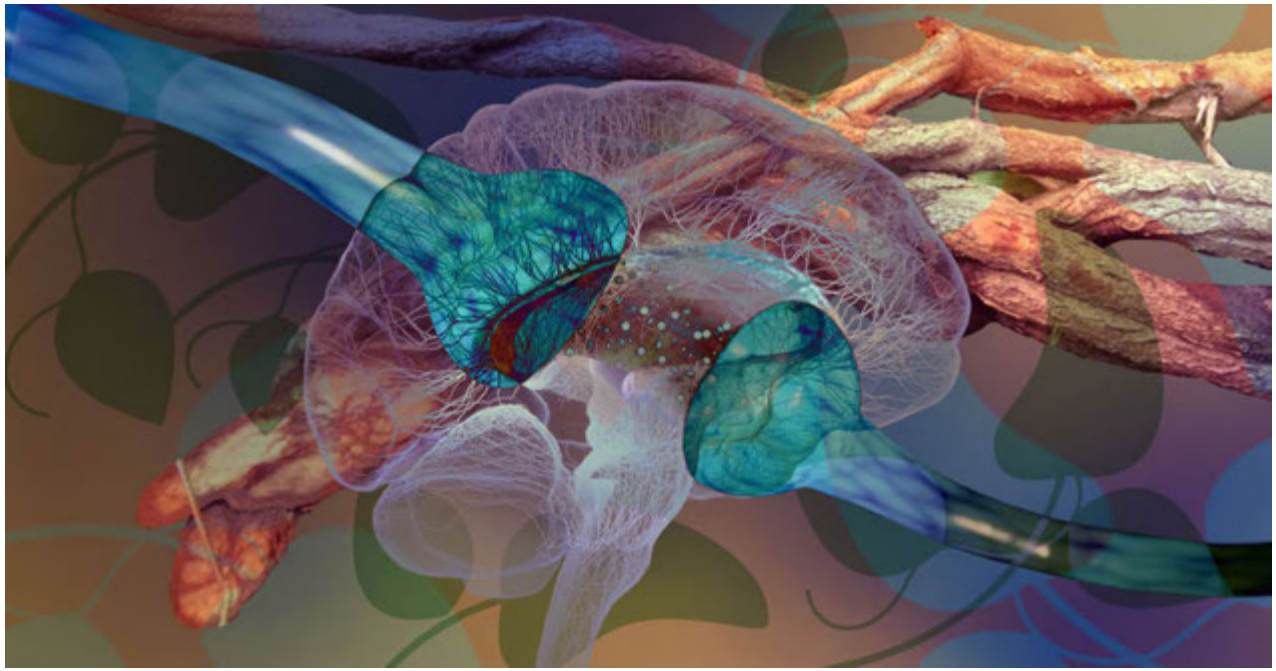
The effects of ayahuasca can last between 4 and 6 hours in humans, and typically take 30 min to 1 hr to begin.

Ayahuasca produces a range of psychoactive effects, including:

- **Hallucinations**
- **Altered perception**
- **Feelings of euphoria**



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Ayahuasca: What physiological effects?

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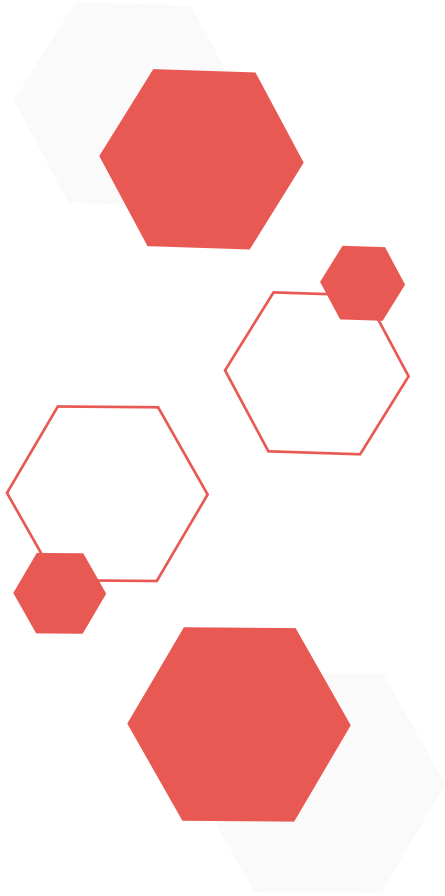
Ayahuasca produces intense physiological effects.

Quickly after consuming the brew, subjects normally experience nausea, vomiting and diarrhoea - a process typically reffered to as “**purging**”.

Other physiological reactions can include:

- **Increased heart rate**
- **Dizziness**
- **Agitation**
- **Increased blood pressure**
- **Increased body temperature**
- **Dilated pupils**
- **Chest pain**



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Ayahuasca and DMT: Risks and Adverse Effects

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Both DMT and ayahuasca can cause:

- **Mild headaches**
- **Hypotonia**
- **Anxiety**
- **Paranoia**

At high doses, severe side effects can happen such as:

- **Seizures**
- **Respiratory arrest**
- **Coma**

In people who have **pre-existing mental disorders** like schizophrenia, there can also be severe psychological side effects when using ayahuasca.

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Ayahuasca: Traditional Medicinal Use

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Ayahuasca is often referred to as a medicine or “plant spirit”.

The use of ayahuasca is widespread and represents the basis of traditional medicine practice for at least **75 different indigenous tribes across the Lower and Upper Amazon**.

The psychedelic is also allowed for religious use **in some churches during ceremonies led by experienced individuals often called shamans.**

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Ayahuasca-assisted psychotherapy

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Ayahuasca has a long history of therapeutic usage, which may give **promises for its application to medical and psychiatric practice.**

Ayahuasca is thought to **facilitate therapy through the induction of altered states of consciousness**. DMT may therefore hold significant potential to be used as a **facilitating tool in psychotherapy.**

Tested in clinical settings, studies revealed a **significant reduction in depressive symptoms** following **a single dose** of ayahuasca. In patients with Major Depressive Disorder, ayahuasca administration was associated with a **reduction in feelings of guilt, depressed mood and suicide ideation** specifically.

- Osorio et al (2015) Brazilian Journal of Psychiatry, 37(1)

It has previously been found that ratings of **depression and stress dramatically drop** after a single ayahuasca ceremony, and persist for four weeks.

- Uthaug et al (2018) Psychopharmacology, 235(10), 2979–2989

Additionally, four weekly ayahuasca sessions were shown to **increase mindfulness and acceptance** more than an eight-week mindfulness training program.

- Soler et al (2018) Front. Pharmacol. 9(224), 1-5

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How do psychedelics work?

Small Pharma

The leading theory of how psychedelics work in mental health disorders is that they increase disorder (entropy) within brain networks, disrupting unhealthy patterns of thought and providing an opportunity for them to resettle differently.

This is why psychedelics have shown therapeutic benefits in disorders that have **rumination, habits and biases** as key symptoms, such as Depression, OCD or Eating Disorders.

Neuroplasticity

- Neuritogenesis, spinogenesis, synaptogenesis
- TrkB, mTOR, and 5-HT2A signalling 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

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How does DMT work?

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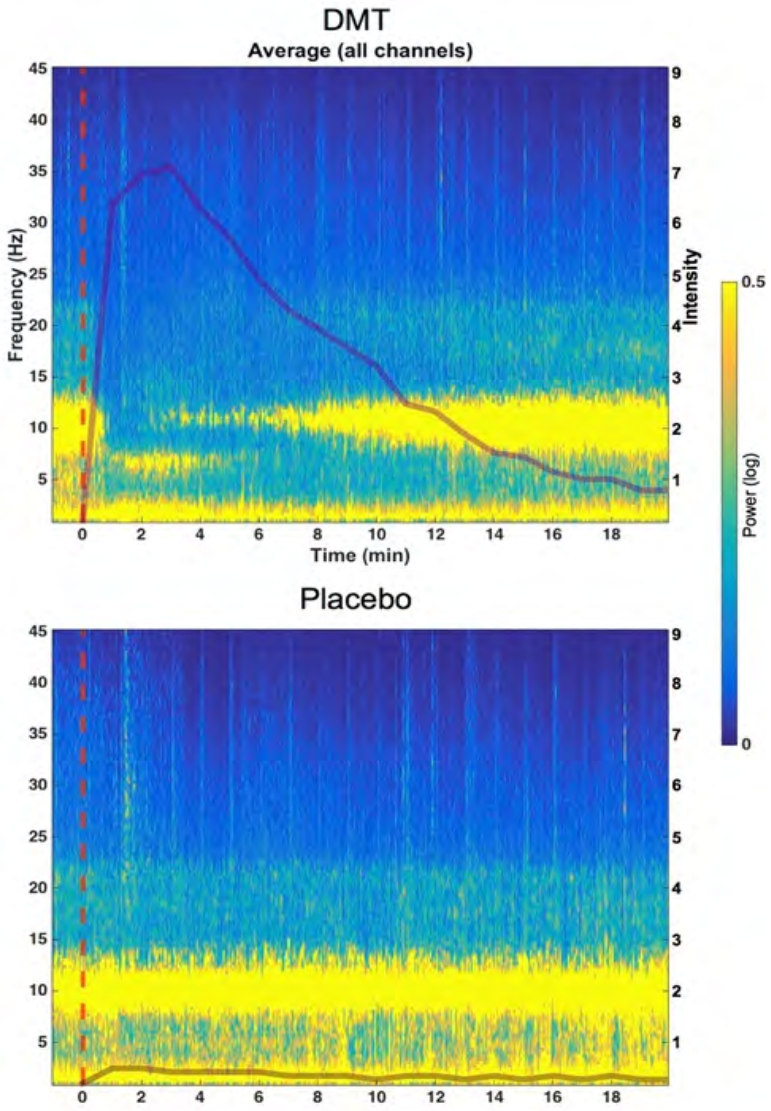
Research into DMT revealed a negative correlation between changes in total *alpha* power across the brain and ratings of subjective intensity under DMT.

A positive relationship was found between subjective intensity and power at *delta* and *theta* bands.

Increased signal diversity also correlated positively with subjective intensity of DMT.

CLICK HERE TO WATCH CHRIS TIMMERMANN DISCUSS THE EFFECTS OF DMT ON THE BRAIN



Time frequency plot illustrating the associations between intensity ratings and spectral activity for DMT and placebo (red line marks beginning of injection)(Timmerman et al 2019)

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DMT's therapeutic potential

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In terms of mystical experience, **DMT is comparable to psilocybin.**

- Griffiths et al (2019) PLoS ONE, 14(4)

Imaging data shows that **DMT may also enable the brain to 'reset'** in a similar way to psilocybin. As DMT causes similar changes in brain activity as psilocybin, it may have a comparable antidepressant potential.

- Timmermann et al (2019) Scientific Reports, 9, 16324
- Nutt et al (2020) Cell, 181(1): 24-28

Rodent studies have shown that **DMT reduces behavioural despair in the forced swim test**. This test is typically used to assess the efficacy of antidepressants.

- Cameron et al (2018) ACS Chem Neurosci, 9(7): 1582-1590

In vivo and in vitro work demonstrated that **DMT enhances adult neurogenesis, improving spatial learning and memory tasks**.

- Morales-Garcia et al (2020) Translational Psychiatry, 10(331)

Trials with ayahuasca have shown antidepressant activity. Given that ayahuasca contains DMT, the data is encouraging for the **therapeutic potential of DMT.**

- Palhano-Fontes et al (2019)Psychol Med., 49(4): 665-663

Future research

Small Pharma

We still need to understand:

- **The correct dosage, mechanism of action, health and safety profile**
- **How many sessions** are required for optimal efficacy
- The **therapy paradigm** surrounding the psychedelic experience

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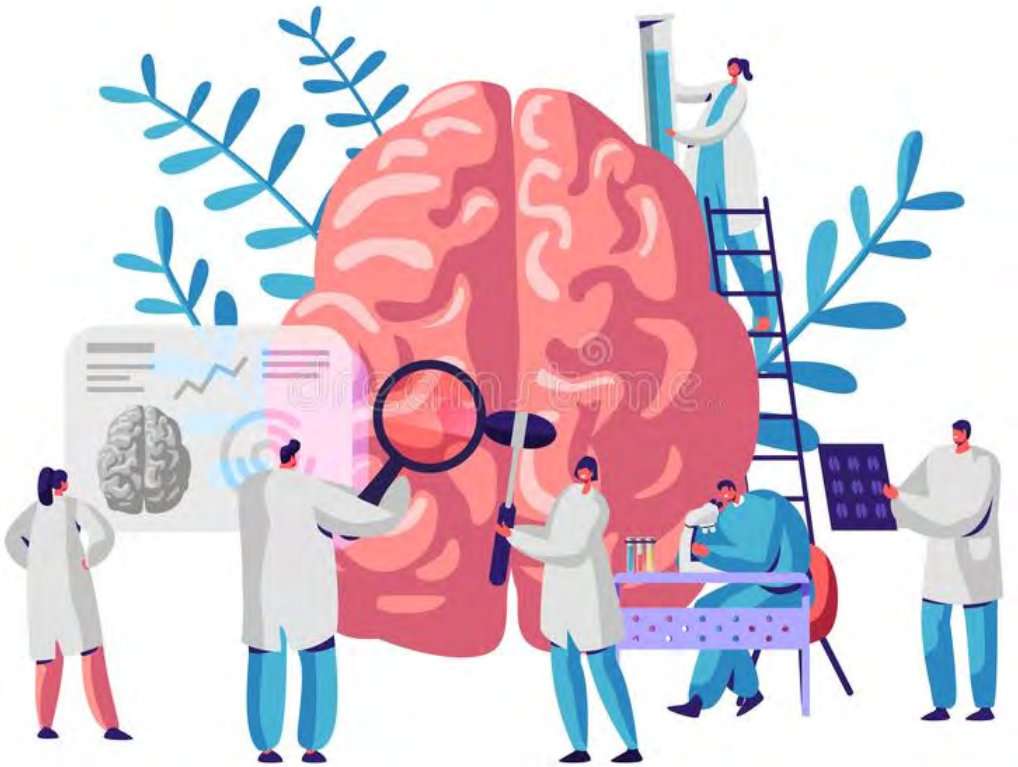
Where are we at now?

Small Pharma

Before any DMT-assisted psychotherapy can be safely developed and administered, **more evidence needs to be gathered about the effects and safety of DMT.**

Small Pharma, a London-based neuropharmaceutical company, has obtained approval for **a regulatory-approved Phase 1/2a clinical trial with DMT in healthy volunteers and patients with Major Depressive Disorder in 2021** and is set to begin in January 2021.



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