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Why N,N-dimethyltryptamine matters: unique features and therapeutic potential beyond classical psychedelics

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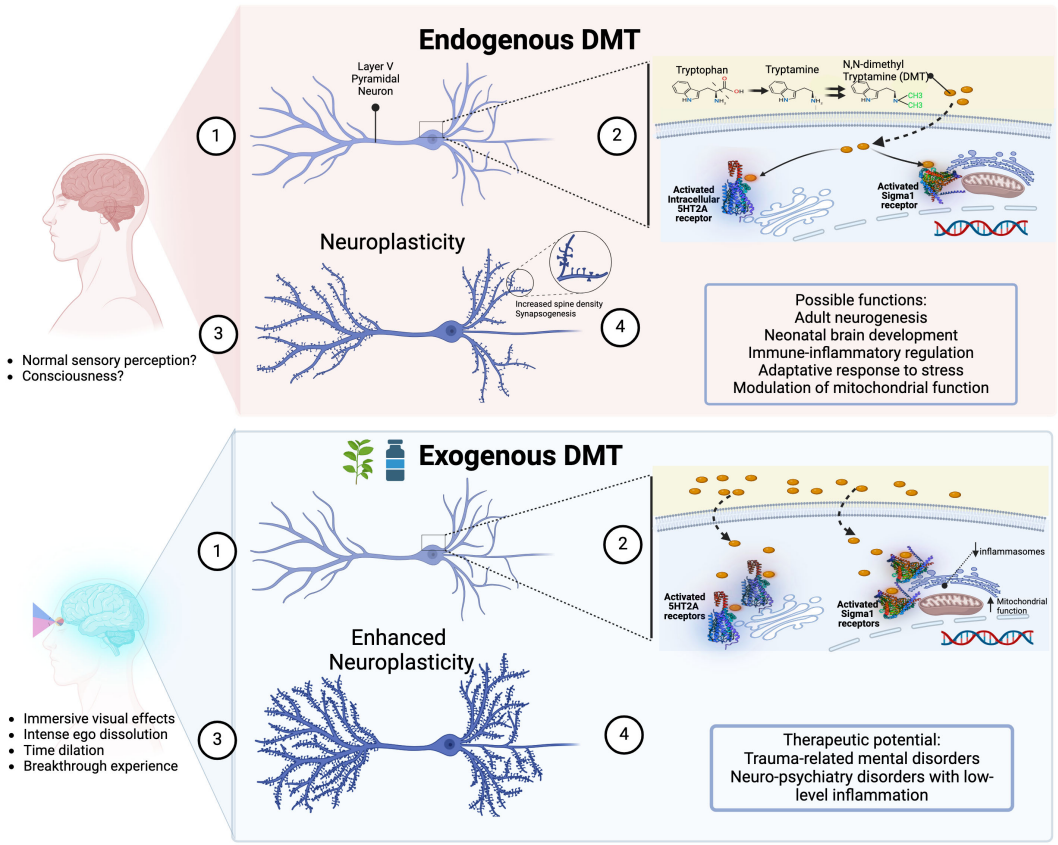

GRAPHICAL ABSTRACT

> *'Iracema comes with the pot full of the green liquor. The shaman decrees the dreams to each warrior and distributes the* ***wine of jurema****, which carries the brave Tabajara to heaven.'*[1]
> José de Alencar, in his poetic novel "Iracema" (1865)

1 Introduction

The "wine of jurema", used in ancient Brazilian shamanic rituals, is rich in N,N-dimethyltryptamine (DMT), a naturally occurring tryptamine like serotonin and melatonin. Widely found in plants and animals, DMT is the main component of some botanical tisanes used for centuries as a channel of communication with the otherworld (1, 2). Despite being classified as a "classical psychedelic" (2–4), DMT's unique effects are often overlooked due to an overemphasis on serotonin (5HT) 2A receptors as the key pharmacological feature of serotoninergic psychedelics. This simplification ignores DMT's broader receptor interactions, lack of tolerance, and distinct subjective experiences. A nuanced understanding of DMT's pharmacology and its redefinition among psychedelics is necessary to recognize its full potential.

DMT was originally synthesized by Canadian chemist Richard Manske in 1931, before it had ever been discovered in any plant (5), but its hallucinogenic properties were confirmed only in 1956 when chemist and psychiatrist Stephen Szara administered DMT intramuscularly to healthy volunteers, who experienced LSD-like effects (6). However, DMT had been identified earlier in *Mimosa hostilis* roots (the main component of the "wine of jurema") by chemist O. Gonçalves de Lima in 1946 (7) and was later recognized in 1957 as a key psychoactive ingredient in ayahuasca ("vine of the souls") (8).

These brews produce intense closed-eye (and, less frequently, open-eye) visual effects, known in Portuguese as "miração" ("seeings"), with immersive dream-like states and rich internal imagery (9–11). In contrast to other serotoninergic psychedelics, individuals who use ayahuasca and DMT report stronger visual effects, breakthrough experiences, near-death experiences, and encounters with entities (12–16).

This distinct phenomenology reflects DMT's unique pharmacological profile, defying its simplistic classification as a classical psychedelic. In fact, DMT (a) activates sigma-1 receptors, trace amine-associated receptors (TAAR1), and intracellular

1 Freely translated from the Portuguese; bold highlight not on the original.

5HT2A receptors; (b) acts as a substrate of the serotonin uptake transporter (SERT) and the vesicle monoamine transporter (VMAT2); (c) and modulates dopaminergic, noradrenergic, adrenergic and cholinergic neurotransmission (1, 4, 17–19).

Unlike LSD, which induces complete tolerance after four consecutive daily doses (20), DMT's effects remain minimally reduced with repeated use (21, 22). Moreover, DMT's endogenous presence in the human body (urine, blood, cerebrospinal fluid) suggests roles in neuroplasticity, immune function, and other physiological processes, further distinguishing it from other psychedelics.

In mental health treatment, an exploratory study with intravenous DMT has shown next-day antidepressant effects in treatment-resistant depression (23). Ayahuasca has been long used in traditional Amazonian ceremonies with the aim of facilitating profound introspection and emotional healing. Modern preliminary research suggests its therapeutic potential for treating mood, anxiety, substance use, and trauma-related disorders (24–35), as well as suicidality (34) – possibly by modulating emotion and trauma processing (36–41).

However, these studies remain in their early stages, often involving small sample sizes and variability in methodologies. In contrast, LSD has a long tradition of studies, MDMA is approved in Australia for PTSD, and psilocybin, now also approved in Australia, shows promising potential for treatment-resistant depression. Hence, this study aims to highlight the unique characteristics of DMT that make it a promising candidate for psychedelic therapeutics.

2 DMT unique features

2.1 There is an endogenous production of DMT

A distinguishing feature of DMT is its natural production in the human body. Although often associated with hallucinogenic experiences when administered exogenously, DMT's presence and role in the brain under normal physiological conditions remain an area of active investigation. Since the 1960s and 1970s we have known that mammals, including humans, endogenously produce DMT (18, 42, 43); for a comprehensive review, see Barker et al. (2012) (44). However, recent rodent studies show that DMT is present in the brain at levels akin to canonic neurotransmitters like serotonin and dopamine (45, 46).

Early research confirmed the presence of endogenous DMT in various tissues, including the liver and lungs, using techniques like gas chromatography and mass spectrometry (43). Traditionally, DMT synthesis have been attributed to the enzyme indolethylamine N-methyltransferase (INMT) (47). Nonetheless, Glynos et al. (2023) demonstrated that INMT is not essential for DMT production in rats, suggesting alternative enzymatic pathways (48).

Nichols (2018) critically examined the functional significance of endogenous DMT, particularly its secretion from the pineal gland and its link to near-death or out-of-body experiences (49). He argues that DMT concentrations in the brain are too low to produce psychoactive effects and emphasized the need for rigorous research.

Until 2018, few studies quantified DMT levels in rodent brains (50, 51), possibly losing sequestered DMT during tissue processing from whole-brain homogenates (17). However, Dean et al. (2019) provided substantial evidence of endogenous DMT in the rat brain (45), finding levels in the pineal gland and visual cortex comparable to other neuroamines. This suggests that DMT could be part of a functional system in normal brain physiology.

Dean et al. (2019) also observed a sudden increase in DMT levels in rats during cardiac arrest (45). However, Li et al. (2015) and Nichols (2018) (49, 52) noted that the time of death involves a "brainstorm" with a surge in neurotransmitters and synchronous electroencephalographic (EEG) signaling, indicative of high cognitive processing (53, 54), which aligns with experiences reported by cardiac arrest survivors.

Glynos et al. (2024) further explored DMT's effects in animal models, finding that intravenous DMT administration in rats increased serotonin and dopamine levels, altered EEG spectral power, and enhanced functional connectivity (46). Importantly, they also detected endogenous DMT in the prefrontal and somatosensory cortices at levels comparable to serotonin and dopamine. These findings suggest that endogenous DMT may have functional significance in the mammalian brain (46), supporting previous results that DMT may accumulate and be stored in neuron vesicles (19, 55).

Although the natural role of DMT remains elusive, it has been suggested that DMT may be involved in diverse normal physiological functions: synaptic plasticity (56), neonatal brain development (50), adult neurogenesis regulation (57), normal sensory perception (58), modulation of brain mitochondrial function (59), adaptative immune response to stress (60–62), and protection against hypoxia and oxidative stress (63, 64).

2.2 DMT has an unique phenomenology

Compared to the other traditional psychedelics, DMT has a distinct phenomenology. When injected intravenously, DMT induces visions so strong that having one's eyes open or closed barely affects what is seen (14). Breakthrough experiences, marked by profound changes in temporal and spatial perception, are common with ayahuasca and DMT, leading to feelings of being in a different reality, intense ego dissolution, and time dilation (15, 65, 66).

Near-death experiences (NDEs), featuring inner peace, out-of-body experiences, and exploration of otherworldly realms, closely resemble DMT-induced experiences. Accordingly, Timmermann et al. (2018) found striking parallels between actual NDEs and those induced by DMT (67).

A survey by Griffiths et al. (2019) on mystical experiences induced by classical psychedelics found that participants using DMT more often had complete mystical experiences, scoring higher on ineffability and transcendence of time and space compared to the use of psilocybin and LSD (68). In another survey by the same team, investigating interactions with sentient entities during DMT experience, 80% of respondents reported the experience profoundly altered their perception of reality, with 65% describing them as more real than typical waking consciousness (12).

Of note, although ayahuasca contains beta-carbolines, which act as monoamine oxidase inhibitors (MAOIs), its primarily psychedelic effect is mainly due to DMT. Beta-carbolines inhibit DMT's metabolization by MAO enzymes in the gut and liver, allowing DMT to reach the brain and extending its effects from minutes to several hours (22, 69, 70). However, despite differences in duration and intensity, the experiences from ayahuasca are similar to those from exogenous DMT administration (71).

Interestingly, despite the molecular similarity between DMT and its derivative 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), they have distinct characteristics. Both cause ego dissolution and time dilation, but 5-MeO-DMT often induces a sense of void or "whiteout", contrasting with DMT's vivid and intense visual phenomena (72).

2.3 DMT has unique pharmacokinetic properties

Tachyphylaxis, or rapid tolerance, is common with most classic serotoninergic psychedelics like LSD, psilocybin, and mescaline. Repeated administration of these substances quickly diminishes their subjective effects, usually within a few days, due to the downregulation and desensitization of extracellular cortical 5-HT2A receptors (73, 74). For instance, after four days of daily LSD administration, its hallucinogenic effects simply vanish (20, 75–79). Additionally, cross-tolerance between these substances is common; individuals tolerant to LSD, for example, show reduced sensitivity to psilocybin and mescaline, indicating shared mechanisms of action (80–88).

In contrast, DMT is unique in that it does not induce tolerance to its psychological effects, even with closely spaced repeated use. Studies in humans have consistently shown no significant attenuation in the subjective experiences elicited by DMT. For instance, Strassman (1995, 1996a) demonstrated that volunteers who received four closely spaced doses of DMT experienced no reduction in hallucinogenic intensity (21, 89). Similarly, Dos Santos et al. (2012) observed no tolerance to the subjective effects of two consecutive doses of ayahuasca (22). DMT also does not produce cross-tolerance to other hallucinogens like LSD, further highlighting its distinct pharmacodynamic properties (90–95). DMT's unique lack of tolerance suggests a different mechanism of action compared to other serotoninergic psychedelics, making it a valuable compound for psychopharmacological research.

As with other psychedelics, there is the possibility of pharmacodynamic drug-drug interactions between DMT and other serotoninergic drugs, especially by competition at the receptor level (96). For instance, concomitant DMT administration with serotonin and norepinephrine reuptake inhibitors, or MAO inhibitors, may reduce DMT's subjective effects by increasing serotonin levels and by downregulating 5-HT2A receptors after chronic use, and 5-HT2A antagonists may reduce the effects of DMT (96). Regarding possible toxicity in humans, human studies usually report a good tolerability profile (23), but elevations of cardiovascular parameters, anxiety, and unpleasant psychological reactions have been observed in clinical settings after acute DMT administration (4, 6, 14).

2.4 DMT has unique mechanisms of action

In 2009, Fontanilla and colleagues discovered that DMT is an endogenous ligand for sigma-1 receptors, found throughout the central nervous system and peripheral tissues (97). Initially mistaken for an opioid receptor, the sigma-1 receptor is now known as an orphan receptor because it binds synthetic compounds but not opioid peptides (97). Sigma-1 receptors act as transmembrane chaperone proteins, controlling anti-inflammatory reactions, cell survival, and neuronal differentiation (62). They have neurorestorative effects and protect cells against oxidative stress, underscoring their importance for brain health and function (60).

Unlike other classical psychedelics, DMT's interaction with sigma-1 receptors may enhance neuroplasticity, neuroprotection and cognitive function. Cheng et al. (2024) showed that long-term DMT administration improved neurogenesis and cognitive function in rat models of Alzheimer's disease by activating sigma-1 receptors, confirming its therapeutic potential in neurodegenerative disorders (59). Morales-Garcia et al. (2020) found that DMT promotes adult neurogenesis in the hippocampus via sigma-1 receptors, stimulating neural stem cell proliferation, neuroblast migration, and new neuron generation (57). These effects likely explain the improved spatial learning and memory observed in DMT-treated mice compared to controls (57).

DMT's interaction with sigma-1 receptors also influences the immune system. DMT and its derivative 5-MeO-DMT modulate human monocyte-derived dendritic cells by activating sigma-1 receptors, reducing pro-inflammatory cytokine production and increasing anti-inflammatory cytokine secretion (62). This suggests that DMT may help maintain immune homeostasis and manage autoimmune and chronic inflammatory diseases. Additionally, DMT's activation of sigma-1 receptors may offer therapeutic benefits in neuropsychiatric disorders characterized by low-level inflammation and cytokine imbalance (60).

2.5 DMT has unique effects in neuroplasticity

In a landmark study, Vargas et al. (2023) described how DMT and psilocybin activate intracellular cytoplasmic pools of 5HT2A receptors to promote neuroplasticity (98). This confirmed Cornea-Hébert et al. (1999) previous finding that 5HT2A receptors in the neuronal cortex are primarily intracellular rather than on the membrane surface (99). Remarkably, although serotonin is a potent 5HT2A receptor agonist, it cannot cross the cellular membrane to activate these receptors. However, the lipophilic nature of DMT allows it to cross cellular membranes and bind to these intracellular receptors, suggesting DMT, rather than serotonin, may be the endogenous agonist.

Moreover, downregulation and internalization of 5-HT2A receptors on the cell surface play a role in tolerance to psychedelics (20, 100–102). Interestingly, DMT's action on intracellular pools of 5HT2A receptors may partially explain the lack of tolerance with repeated use (21). Accordingly, chronic DMT use does not induce 5HT2A receptor desensitization (2, 70).

Given its ability to promote neuroplasticity, DMT may be categorized as a psychoplastogen, a group of substances that may directly and rapidly change brain structure and function. This unique characteristic makes them promising therapeutic agents for neuropsychiatric disorders. By promoting dendritic growth and synapse formation, psychoplastogens like DMT may quickly alleviate symptoms of conditions such as anxiety and depression (103).

3 Discussion

DMT stands out among serotoninergic psychedelics for its potent visual effects, lack of tolerance, and unique neurophysiological properties. Its natural production and interaction with sigma-1 and intracellular 5HT2A receptors play important roles in brain plasticity and immune regulation. Evidence of substantial DMT levels in the rat brain, including its accumulation in neuron vesicles and alternative production pathways, suggests a broader role in neurobiology. While endogenous DMT is confirmed in the rat brain, its presence in the human brain and exact physiological roles need further exploration.

Despite its therapeutic potential, research on DMT faces key limitations, including uncertainty about the optimal dose and duration of therapeutic benefits, besides the challenge of functional unblinding due to its rapid and intense effects (23, 25). Variability in dosing, administrations routes, and the combination with a MAOI (in ayahuasca) further complicates cross-study comparisons (17). The long-term impacts of repeated dosing also require further investigation (104). It is crucial to have larger, well-designed trials to better understand DMT's safety and efficacy (29, 30).

In addition to its unique pharmacological and therapeutic benefits, DMT could offer a cost-effective psychiatric treatment option if approved globally (39, 105, 106). Although the substance itself may not be patentable, like psilocybin, the processes and formulations used in different routes of administration (e.g. inhalation, intranasal, buccal or sublingual) could be, which could influence its accessibility (107). Nonetheless, DMT's potential as a widely accessible treatment is significant, particularly given its potential to yield different treatment outcomes compared to other psychedelics, such as for neuropsychiatric disorders involving low-level inflammation.

DMT's rapid onset and short duration (20-30 minutes when inhaled or injected) (17, 23) make it practical for clinical use compared to longer-acting psychedelics like psilocybin (4-6 hours), MDMA (4-6 hours), and LSD (8-12 hours) (108, 109). Its brief effects reduce supervision needs, and its lack of tolerance allows for repeated dosing. However, its short half-life and intense acute effects could complicate clinical use if frequent administration is needed, increasing demands on personnel and risk of adverse reactions (2, 3). Extended DMT infusion may address these limitations by offering more controlled, sustained effects (104, 110). While DMT shows promise in psychedelic therapy, more research is needed to explore its benefits, especially in combination with other molecules (111).

Author contributions

CC: Conceptualization, Writing – original draft, Writing – review & editing. Rd: Writing – review & editing. SD: Writing – review & editing. MT: Writing – review & editing. MC: Writing – review & editing. EB: Conceptualization, Supervision, Writing – review & editing. JH: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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