REVIEW ARTICLE

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# N,N-dimethyltryptamine and Amazonian ayahuasca plant medicine

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## Abstract

**Objective:** Reports have indicated possible uses of ayahuasca for the treatment of conditions including depression, addictions, post-traumatic stress disorder, anxiety and specific psychoneuroendocrine immune system pathologies. The article assesses potential ayahuasca and N,N-dimethyltryptamine (DMT) integration with contemporary healthcare. The review also seeks to provide a summary of selected literature regarding the mechanisms of action of DMT and ayahuasca; and assess to what extent the state of research can explain reports of unusual phenomenology.

**Design:** A narrative review.

**Results:** Compounds in ayahuasca have been found to bind to serotonergic receptors, glutaminergic receptors, sigma-1 receptors, trace amine-associated receptors, and modulate BDNF expression and the dopaminergic system. Subjective effects are associated with increased delta and theta oscillations in amygdala and hippocampal regions, decreased alpha wave activity in the default mode network, and stimulations of vision-related brain regions particularly in the visual association cortex. Both biological processes and field of consciousness models have been proposed to explain subjective effects of DMT and ayahuasca, however, the evidence supporting the proposed models is not sufficient to make confident conclusions. Ayahuasca plant medicine and DMT represent potentially novel treatment modalities.

**Conclusions:** Further research is required to clarify the mechanisms of action and develop treatments which can be made available to the general public. Integration between healthcare research institutions and reputable practitioners in the Amazon is recommended.

**KEYWORDS**
Amazonian practices, ayahuasca, consciousness, DMT, medical uses

## 1 | INTRODUCTION

Ayahuasca is becoming more well-known as a potential medicine among the general populations of developed countries such as the United States and the United Kingdom (Larbi, 2020). Every year, many people travel to the Amazonian region, often with the aim to improve some form of psychological issue they have been struggling to overcome (Winkelman, 2005). Anecdotal reports of ayahuasca's healing and transformative potential have led to increasing interest in the substance worldwide (Frecska, Bokor, & Winkelman, 2016). Furthermore, outside of the Amazon, one of the primary psychoactive compounds in ayahuasca, N,N-dimethyltryptamine (DMT), maintains popularity as a recreational drug among psychedelic subcultures globally and 'underground' ayahuasca ceremonies are sometimes conducted in countries such as the UK (Carbonaro & Gatch, 2016; Pallavicini et al., 2021). Therefore, ayahuasca and DMT represent an issue of relevance to health and wellbeing as they could be potentially abused and allegedly have the potential to aid and catalyse the healing of physical and psychological disorders (Bouso et al., 2012; Tupper, 2008).

This article seeks to review the literature on ayahuasca and DMT, assessing their potential therapeutic applications and risks of use, providing insight into their mechanism of action and outlining possible future directions for research. The review is also intended to focus on the mechanisms of action underlying the phenomenology which, after reviewing the literature, is not widely discussed in scientific publications as the scientific literature has predominantly focused on the neurochemistry, brain imaging studies and medical applications rather than the genesis of the highly unusual phenomenology. A narrative review style was chosen as opposed to a systematic review as the latter limits the discussion to papers yielded by specific searches. The approach chosen leaves the review open to consider literature that may have no obvious connection with the topic but which may ultimately be relevant.

In this paper we aim to evaluate the literature and first hand reports rationally, whilst being aware that not acknowledging the potential existence of phenomena which cannot be verified using current analytical techniques can be misguided; an example of this would be asking someone from the 16th century about the existence of radio waves as they would neither have been able to prove their existence nor accurately contest that they do not exist due to the fact that they could not be measured at that time. Similarly, it is not impossible that there could be some validity to frequent reports of allegedly 'inter-subjectively verified' unusual phenomena and that human consciousness and no currently available technology is the only presently viable method of detecting them (Luke et al., 2018; Michael et al., 2021; Strassman, 2001; Winkelman, 2018). Conversely, if all such unusual phenomenological experiences are entirely non-veridical hallucinations, the mechanism of the genesis of the hallucinations and other subjective experiences requires elucidation and evidence-based validation to understand the mode of action. A comprehensive understanding of how such hallucinations are generated by the brain would be preferable than the source of such visions remaining unknown if medical healthcare professionals are to integrate DMT-based therapies into modern medicine and be able to explain with authority to patients what they are likely to experience and why. Otherwise, if such treatments become approved and the medical healthcare profession is unable to adequately explain the phenomenology, patients will have little option but to consult non-medical sources in order to develop an understanding of and integrate their experiences.

## 2 | POSSIBLE ROLES FOR ENDOGENOUS DMT

DMT, a derivative of the amino acid tryptophan, has been found to be endogenously synthesised in many species (Barker, 2018a; Barker et al., 1981; Cozzi et al., 2009). DMT is found in both plants and animals, including humans (Barker et al., 2012; Carbonaro & Gatch, 2016). The precise roles of DMT in the large assortment of species in which it is found remain unknown although some research has been conducted to resolve these questions (Barker, 2018a; Chu et al., 2014; Luke et al., 2018; Rodrigues et al., 2019).

Early work on DMT's role within humans involved studies of pathopsychology. It had been hypothesised people with schizophrenia or individuals experiencing other forms of psychosis may have elevated levels of DMT or other proposed 'schizotoxins', but analyses of DMT concentrations in patients and controls found this not to be the case (Barker et al., 2012; Carbonaro & Gatch, 2016; Gillin et al., 1976). The hallucinations in schizophrenia are more commonly reported to be auditory in contrast to DMT-induced hallucinations, which further adds doubt to such hypotheses (Brito-da-Costa et al., 2020). To date, no clear link has been found with endogenous DMT levels and any psychiatric disorder (Barker, 2018a; Checkley et al., 1980; Grammenos & Barker, 2015). DMT expression may be modulated at critical times such as during naturally occurring pivotal mental states, which can lead to psychosis, although such a function is speculative and not supported by any reliable studies (Barker, 2018a; Brouwer & Carhart-Harris, 2020). Other suggested roles for endogenous DMT have included dreams, creativity, mystical-type phenomena, imagination, near-death experiences (NDE) and a regulatory function in conventional waking consciousness (Carbonaro & Gatch, 2016; Davis, Barrett et al., 2020; Frecska, Bokor et al., 2016; Strassman, 2001).

In humans, DMT has been detected in cerebrospinal fluid, urine and blood using a number of analytical techniques and can be synthesised de novo (Barker, 2018a; Barker et al., 2012). DMT could play a role in the functioning of the central nervous system (CNS) as it has been reported to be transported into the brain across the blood brain barrier (Barker, 2018a; Barker et al., 2012; Cozzi et al., 2009). DMT levels have been directly measured from peripheral fluids such as blood, however, if DMT is endogenously synthesised, stored and metabolised in discrete brain regions then these types of analyses will only elicit limited relevant information (Barker, 2018a).

Endogenous DMT may be synthesised in the lung, spinal cord, brain, retina and pineal gland as an enzyme proposed as being

responsible for its synthesis, indolethylamine N-methyltransferase (INMT), has been detected in these locations (Barker et al., 2012; Cozzi et al., 2011; Dean, 2018; Thompson & Weinshilboum, 1998). DMT may have a role in prenatal and neonatal development due to the presence of high levels of INMT during foetal development and up-regulation of DMT levels after birth (Barker, 2018a). Additionally, INMT has been located in numerous regions of the CNS including the amygdala and frontal cortex (Barker, 2018a; Carbonaro & Gatch, 2016; Morgan & Mandell, 1969). However, detecting INMT expression does not equate to detecting the presence of DMT as INMT has other substrates, besides tryptamine, including histamine for which INMT has a higher affinity (Barker, 2018a; Dean, 2018; Nichols, 2017).

Some evidence has accumulated of DMT, and structurally related compounds, acting as a neurotransmitter which may participate in cell signalling in processes involved in sensory perception and modulate serotonin (5-hydroxytryptamine or 5-HT) receptors including 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6 and 5-HT7 with varying degrees of affinity (Carbonaro & Gatch, 2016; Cozzi et al., 2009; Dean et al., 2019). DMT has been demonstrated to be taken up into neurons via serotonin uptake transporters (SERT) on neuronal plasma membranes, thus providing a mechanism for accumulation of DMT in neuronal cells (Barker, 2018a; Carbonaro & Gatch, 2016; Cozzi et al., 2009). DMT can be sequestered into synaptic vesicles from the cytoplasm by the neuronal vesicle monoamine transporter 2 (VMAT2) and thus stored in storage vesicles in pharmacologically relevant concentrations (Barker, 2018a; Carbonaro & Gatch, 2016; Cozzi et al., 2009). Additionally, following experimentally-induced cardiac arrest, higher DMT levels have been observed in the visual cortex (Dean et al., 2019). However, while endogenous DMT may play some form of regulatory psychophysiological role, there is no consensus whether or not DMT acts as a neurotransmitter, neurohormone and/or a neuroregulator (Barker, 2018a; Carbonaro & Gatch, 2016; Frecska et al., 2013; Nichols, 2017; Wallach, 2009). Furthermore, despite DMT being found to be uptaken by serotonin uptake transporters, this may be a secondary consequence of its structural similarity to serotonin (Cozzi et al., 2009).

INMT has been detected in postsynaptic sites of C-terminals of motor neurons in close proximity to sigma-1 receptors (Barker, 2018a; Mavyultov et al., 2012). It has been suggested that DMT is an endogenously synthesised sigma-1 receptor modulator which can be stored in neurons and bind to sigma-1 receptors (Barker, 2018a; Cozzi et al., 2009; Fontanilla et al., 2009; Su et al., 2009). Sigma-1 receptors have been located in the human brain, with highest densities in the cerebellum, orbitofrontal cortex, nucleus accumbens, occipital cortex and frontal cortex, in addition to the retina, liver, lung, heart and immune system (Cozzi et al., 2009; Frecska, Bokor et al., 2016). Inside cells, sigma-1 receptors are located mainly at the interface of the endoplasmic reticulum and mitochondria (Frecska, Bokor et al., 2016). The function of sigma-1 receptors is not well understood although it is known that DMT can inhibit voltage-gated sodium (Na+) channels via sigma-1 receptor

agonism and sigma-1 receptors modulate neuronal differentiation, can act as intracellular signal transduction amplifiers, protect cells against reactive oxygen species, modulate inflammation, regulate brain-derived neurotrophic factor (BDNF) secretion and can inhibit apoptosis signalling, with potential roles for DMT in modulating these functions and others (Fontanilla et al., 2009; Frecska et al., 2013; Frecska, Bokor et al., 2016; Fujimoto et al., 2012; Hayashi, 2019; Nardai et al., 2020; Su et al., 2009; Su & Hayashi, 2003). Studies have suggested that DMT agonism of sigma-1 receptors leads to reduced damage to neurons induced by hypoxia and oxidative stress and may up-regulate neuroregeneration and promote plasticity via increased expression of BDNF (Barker, 2018a; Szabo et al., 2014; Szabo and Frecska, 2016; Szabo et al., 2016). It is possible that DMT may also play a role in immunoregulation via sigma-1 receptor modulation as sigma-1 receptors are also expressed on many cells of the immune system (Carbonaro & Gatch, 2016; Frecska et al., 2013). DMT could have an immunoregulatory role via sigma-1 receptor modulation as DMT has been found to inhibit pro-inflammatory cytokine (IL-1β, IL-6, TNFα) production and enhance release of anti-inflammatory cytokine IL-10 (Brito-da-Costa et al., 2020; Frecska et al., 2013). However, DMT has a comparably low affinity for sigma-1 receptors which calls into question any role of endogenous DMT and sigma-1 receptors (Carbonaro & Gatch, 2016; Fontanilla et al., 2009). Therefore, the many hypothesised roles of DMT with sigma-1 receptors may be due to the fact that the sigma-1 receptor has only been discovered relatively recently and its exact functions are not well understood (Hayashi, 2019; Rossino et al., 2021; Su & Hayashi, 2003).

An additional potential role of sigma-1 receptor agonism by endogenous DMT may involve potentiation of N-methyl-D-aspartate (NMDA) receptors (Carbonaro & Gatch, 2016; Cozzi et al., 2009). DMT has been found to modulate ionotropic and metabotropic glutamate receptors including NMDA receptors (Carbonaro & Gatch, 2016). Glutamate receptors are responsible for glutamate-mediated postsynaptic excitation of neural cells and have been found to be involved in neural communication, the formation of memories, and learning (Barco et al., 2006; Reiner & Levitz, 2018).

Poorly understood possible neurochemical roles of endogenous DMT include that DMT has been shown to be an agonist in binding to trace amine associated receptors (TAAR) including TAAR-1 and TAAR-6, although the downstream effects of binding to TAAR-1 and their relevance beyond accumulation of cyclic adenosine monophosphate (cAMP), a ubiquitous cell signalling molecule involved in many biological processes, are unknown (Barker, 2018a; Wallach, 2009). The TAAR-6 receptor has been located in relatively high occurrence in the amygdala, hippocampus and prefrontal cortex, and endogenous hallucinogens such as DMT have been speculated to be ligands of these receptors (Wallach, 2009). DMT appears to have effects on the dopaminergic system and acetylcholine signalling although such effects are reportedly not significant and any role of endogenous DMT and dopamine and acetylcholine function is unclear (Carbonaro & Gatch, 2016; Haubrich & Wang, 1977; Smith, 1975,

1977). Additionally, DMT could bind to and modulate proteins which are yet to be discovered.

Rick Strassman's studies in the 90s, and his subsequent book on the study, *DMT: The Spirit Molecule*, led to much interest in the role of DMT and the pineal gland and its link with hallucinatory experiences and potential metaphysical roles (Luke et al., 2018; St John, 2016; Strassman, 2001). This interest has been partly based on René Descartes' hypotheses on the role of the pineal and the observation that INMT and DMT have been detected in the pineal gland (Barker, 2018b; Cozzi et al., 2011; Nichols, 2017; Shoja et al., 2016; Strassman, 2001). Strassman hypothesised that DMT secreted in the pineal gland during foetal development and death may act as a form of mechanism for the 'mindstream' (i.e. soul) of an individual to enter and leave the body (Lama, 2005; Nichols, 2017; St John, 2016; Strassman, 2001). However, even allowing for the hypothesised existence of a mindstream (Alexander, 2012; Frecska et al., 2011; Lama, 2005; Long, 2014; Moody, 1988; Parnia et al., 2001; Tucker, 2009; van Lommel et al., 2001), a concept which is generally not supported by contemporary neuroscientific researchers (Metzinger, 2009; Pyysiäinen, 2009; Timmermann et al., 2018; Winkelman, 2017), there are some basic difficulties with such a model. For example, if a developing foetus had a genetic abnormality that resulted in the absence of a pineal gland, would that mean that the individual would have no mindstream? Furthermore, at the point of death, if the pineal gland was destroyed, that is, if there was a severe traumatic brain injury, would that mean that the mindstream cannot leave the body? If the concept of a mindstream were to have any validity, by definition its function would be unlikely to be dependent upon adequate functioning of the physiology or neurochemistry of a living organism during the process of dying. In rare cases of humans and other animals which normally possess a pineal gland not having one, there is little evidence to suggest that the pineal has such a major function as implicated by these hypotheses (Nichols, 2017, 2018). Furthermore, it is difficult to conceive of a mechanism by which an organic molecule would reach a threshold concentration in a specific region of a developing or dying human body and enable, or otherwise be associated with, the hypothetical mindstream entering or exiting the body. Therefore, whilst there may be a physiological function of endogenous DMT, conceptual problems render this hypothesised DMT and pineal gland function unlikely (Checkley & Park, 1987).

Considering other DMT and pineal gland hypotheses, whilst DMT could play a role in dreaming, no studies of DMT expression and circadian rhythms have been conducted and pinealectomised rats did not display differences in rapid-eye movement (REM) sleep which casts doubt on the relevance of DMT synthesis in the pineal and dreaming (Barker, 2018b; Barker et al., 2013; Nichols, 2017). Considering the light sensitive cells in the pineal, which are present as the gland derived from a third eye which atrophied to the brain (Shoja et al., 2016), there is a possibility, at least hypothetically, for a role of the pineal and closed eye hallucinations or images during dreaming although such a hypothesis remains highly speculative and is not corroborated by any reliable studies.

Finally, as no clear role for endogenous DMT has been established, it may be that the DMT that has been detected in human studies plays no significant psychophysiological role and that the DMT detected is an intermediary compound in biosynthetic metabolic processes.

## 3 | EXOGENOUS DMT

DMT has been found to be synthesised in at least 50 species of plants (Dominguez-Clave et al., 2016). When consumed via ingestion, DMT is not psychoactive due to its rapid breakdown by monoamine oxidase (MAO) enzymes which catalyse its degradation prior to reaching the brain in sufficient concentrations in order to elicit a psychoactive response (Alamia et al., 2020; Barker, 2018a). However, some Native American cultures have developed snuffs, such as *yopo and epená*, which contain enough DMT to induce an altered state of consciousness (Fontanilla et al., 2009; Luke et al., 2018). Typically in contemporary recreational settings, DMT is consumed via vaporisation and smoking (Winstock et al., 2014), additionally DMT can be administered as an intravenous (IV) or intramuscular (IM) injection and these methods bypass the enzymatic degradation associated with ingestion (Barker, 2018a; Riba et al., 2015). The earliest recorded example of intramuscular injection of DMT was conducted by the Hungarian researcher Stephen Szara in the 1950s who found DMT has powerful hallucinatory effects (Barker, 2018a; Dominguez-Clave et al., 2016; Szára, 1956). A smoking blend called *changa* also has some popularity among psychedelic subcultures and the mixture contains both DMT and monoamine oxidase inhibitors (MAOIs) derived from plant sources (St John, 2017). Onset of the effects of DMT typically occurs within seconds of administration and the subjective effects usually dissipate in 15–60 min depending on the dose and route of administration (Barker, 2018a; Strassman & Qualls, 1994). In Rick Strassman's studies, DMT was administered via IV injection and one of the motivations for this as opposed to smoking was that it was less problematic to administer the desired dose (Strassman, 2001; Strassman & Qualls, 1994). Studies have shown that DMT does not induce tolerance and therefore extended and repeated administrations are possible (Brito-da-Costa et al., 2020; Carbonaro & Gatch, 2016; Strassman and Qualls, 1994; Strassman, 1996, 2001).

## 4 | AYAHUASCA

The brew *ayahuasca*, meaning Vine of Souls or Vine of the Dead in the Incan Quechua language, also called *yagé, daime* and *hoasca* among other names (Brito-da-Costa et al., 2020; Strassman et al., 2008), has been used for thousands of years in the Amazonian region as a form of medicine and source of knowledge (Frecska, Bokor et al., 2016; McKenna et al., 1998). Ayahuasca is used by indigenous and mestizo (ethnically mixed) groups and its use has been incorporated into Christian and Afro-Brazilian religious practices with such ayahuasca-

using religious groups including the *Santo Daime*, the *União do Vegetal* and the *Barquinha* which have expanded to Europe and North America in recent years (Dominguez-Clave et al., 2016; dos Santos et al., 2019b; Fabregas et al., 2010; Frecska, Bokor et al., 2016). Ayahuasca is a brew which consists of the β-carboline harmala alkaloid containing vine *Banisteriopsis caapi*, after which the brew is generally named, and often, but not always, an additional admixture plant or plants are added such as *Psychotria viridis* or *Diplopterys cabrerana* which contain tryptamines such as DMT (Bouso et al., 2015; Brito-da-Costa et al., 2020). The harmala alkaloids have many physiological effects although one of their earliest recognised roles is to inhibit the degradation of DMT by MAO enzymes in the gut and liver and thus make it orally active (Agurell et al., 1968; Barker, 2018a; Bilhimer et al., 2018; McKenna, 2004; McKenna et al., 1984; Riba et al., 2003).

In contrast to the effects of inhaled DMT being observed within seconds of inhalation, it can take around 30 min for the subjective effects of ayahuasca to begin to be felt and in contrast to inhaling pure DMT, the subjective effects of which typically dissipate after 20 min, ayahuasca sessions often last between 4 and 6 h with peak intensity of effects often felt at around 1.5 h after consumption (Dominguez-Clave et al., 2016; Riba et al., 2001, 2003; Tafur, 2017). In addition to hallucinations, somatic symptoms such as vomiting, dizziness and diarrhea are also frequently reported, however, many attest that such 'purging' is a beneficial cathartic aspect of the experience (Bilhimer et al., 2018; Dominguez-Clave et al., 2016; Frecska, Bokor et al., 2016; Riba et al., 2001; Tafur, 2017). As is comparable with DMT, ayahuasca does not induce tolerance upon repeated dosing and therefore extended and repeated sessions are possible (dos Santos et al., 2012). Capsules, referred to as pharmahuasca, containing freebase DMT and MAOIs such as synthetic harmaline or Syrian Rue have been consumed, but these admixtures cannot be viewed as being equivalent to regular ayahuasca due to the other components of the plants which are not present in pharmahuasca (Carbonaro & Gatch, 2016). In Amazonian traditions, the ritual or ceremonial elements are considered to impact the experience beyond the recognised pharmacological properties of the plants (Tafur, 2017).

## 4.1 | Reported medical applications of Amazonian ayahuasca plant medicine

Ayahuasca use has been found to be associated with high levels of overall wellbeing in healthy individuals (Brito-da-Costa et al., 2020; dos Santos et al., 2016a; Frecska et al., 2012; Gonzalez et al., 2021). Ayahuasca users exhibit reduced psychopathology with lower ratings for obsessive-compulsive, somatic, interpersonal sensitivity, depressive, neurotic, hopeless, hostile, phobic, anxious, paranoid and psychotic symptoms (Bouso et al., 2012; Brito-da-Costa et al., 2020; dos Santos et al., 2007; Grob et al., 1996; Netzband et al., 2020; Weiss et al., 2021). Long-term ayahuasca use has been associated with better performance on neuropsychological tests, including working

memory and attention, compared to matched controls (Bouso et al., 2012, 2015; Brito-da-Costa et al., 2020; Carbonaro & Gatch, 2016). Additional reported benefits of ayahuasca use include enhanced creativity, greater ability to overcome grief and reduced concerns for body image in adolescents (Brito-da-Costa et al., 2020; da Silveira et al., 2005; Frecska et al., 2012; Gonzalez et al., 2020).

Interestingly, despite being a psychoactive drug, ayahuasca has been found to not elicit dependence in consumers and can aid in the treatment of addictions to other substances including alcohol and cocaine (Barbosa et al., 2018; Bouso et al., 2012; Dominguez-Clave et al., 2016; Fabregas et al., 2010; Grob et al., 1996; McKenna, 2004; Tafur, 2017; Thomas et al., 2013). Ayahuasca has been found to both reduce early behaviours associated with the initiation and development of alcohol use disorder and also reverse the behaviours associated with chronic ethanol administration (Dominguez-Clave et al., 2016; Lawn et al., 2017; Oliveira-Lima et al., 2015). Ayahuasca users, in a variety of environmental contexts including in jungle and urban settings, have demonstrated less addictive tendencies, substance abuse and fewer associated psychiatric/psychosocial problems than matched controls (Barbosa et al., 2018; Bouso et al., 2012; Carbonaro & Gatch, 2016; Fábregas et al., 2010).

Several small contemporary studies of people in syncretic religions, in indigenous ceremonial contexts and in clinical settings have shown that ayahuasca may be beneficial for individuals experiencing psychiatric problems such as stress-related disorders, depression and anxiety (Barbosa et al., 2005; Dominguez-Clave et al., 2016; dos Santos & Bouso, 2019; dos Santos & Hallak, 2019; dos Santos et al., 2016c, 2018, 2016a; Jimenez-Garrido et al., 2020; Palhano-Fontes et al., 2019; Sanches et al., 2016; Zeifman et al., 2021). Ayahuasca use has shown marked improvements in depressive symptoms with no concomitant mania or hypomania for up to 21 days after a single dose (Bouso et al., 2012; Carbonaro & Gatch, 2016; dos Santos et al., 2007; Osório et al., 2015). A single dose of ayahuasca in patients diagnosed with treatment-refractory depression has been found to elicit therapeutic effects and in two larger scale studies, ayahuasca decreased ratings of anxiety in depressive-disorder patients (Brito-da-Costa et al., 2020; Carbonaro & Gatch, 2016; Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016). Ayahuasca may be applicable to the treatment of post-traumatic stress disorder (PTSD), as indicated in a number of case reports, although the evidence supporting this application is anecdotal and preliminary (Inserra, 2018; Nielson & Megler, 2014; Tafur, 2017). Ayahuasca has been found to help people take a detached, or mindful, view of their thoughts and emotions and such mindful awareness attributes are well-known to be associated with improved psychological and physical wellbeing (Dominguez-Clave et al., 2016, 2021, 2016; Sampedro et al., 2017; Soler et al., 2016, 2018; Tafur, 2017).

Additionally, ayahuasca has been found in case studies to be beneficial for the treatment of conditions relating to the psychoneuroendocrine immune (PNEI) system including psoriasis, eczema and Crohn's disease (Shenefelt & Shenefelt, 2014; Tafur, 2017).

Crohn's disease, for example, has no reliably effective treatments in contemporary medicine and novel therapeutic approaches are required (Shi & Ng, 2018). The PNEI network links the limbic region of the brain, the autonomic nervous system (ANS), the endocrine system and the immune system (Gonzalez-Diaz et al., 2017). Emotional disturbances are often expressed through the autonomic nervous system and the immune system and such dysfunction can generate a number of inflammatory problems such as eczema and psoriasis (Chen & Lyga, 2014; Suarez et al., 2012; Tafur, 2017). Ayahuasca has been proposed as being capable of clearance of the 'allostatic load' - the psychobiological impact of chronic exposure to elevated or fluctuating endocrine or neural responses resulting from chronic or repeated stress - and thus able to treat disorders such as migraines, chronic cough and menstrual pain which, like psoriasis, are thought to be caused in part by neurogenic inflammation (Chiu et al., 2012; Guidi et al., 2021; Tafur, 2017). However, reports of ayahuasca's applicability to treat disorders relating to the PNEI system, including Parkinson's, are mostly anecdotal and studies are very preliminary (de Araújo, 2019; de Pablo-Fernandez et al., 2017; Tafur, 2017; Willis, 2008).

Ayahuasca has been found to enable people to have cathartic psycho-spiritual experiences which can catalyse long-term alterations in psychological outlook (Bouso et al., 2012). Increased measures of 'self-transcendence',[1] reported feelings of an enhanced sense of spirituality and being connected to a larger spiritual consciousness have been associated with ayahuasca use (Bouso et al., 2012; Frecska, Bokor et al., 2016; Luke et al., 2018; Tafur, 2017). Such psycho-spiritual experiences and long-term alterations in perception reportedly enable forgiveness and compassion for the people in their lives (Bouso et al., 2012; dos Santos et al., 2018; Tafur, 2017). In addition to forgiveness of others, ayahuasca has been found to increase self-acceptance and acceptance of one's own life situation and history with such changes in psychological outlook perhaps underpinning remission of psychiatric disorders (Bouso et al., 2012; Dominguez-Clave et al., 2016; dos Santos et al., 2018; Soler et al., 2018). Reported benefits of ayahuasca use include a greater sense of meaning and purpose in life ($p < 0.001$), sacredness of life ($p < 0.001$) and altruism ($p < 0.001$) when compared with non-ayahuasca using controls (Bouso et al., 2012).

## 5 | PHENOMENOLOGY

### 5.1 | N,N-dimethyltryptamine

As is consistent with classic psychedelics, the subjective effects of DMT are strongly influenced by set and setting in which a negative environment and mindset prior to consumption is more likely to lead to negative subjective effects and conversely a positive build up and environment is generally more likely to lead to a positive subjective experience (Brito-da-Costa et al., 2020; dos Santos et al., 2021; Hartogsohn, 2016). However, the subjective effects of DMT are reportedly very unpredictable and first-hand reports indicate that the subjective effects of DMT are less predictable than other psychedelics such as psilocybin (Brito-da-Costa et al., 2020; Strassman, 2001).

Initial effects are typically of a stimulant-type sometimes accompanied by anxiety, elevated heart rate and blood pressure, confusion and a sense of being overwhelmed (Brito-da-Costa et al., 2020; Cott & Rock, 2008; Strassman, 2001). Soon after inhaling DMT, the consumer often sees kaleidoscopic interlaced geometric patterns, kinaesthetic hallucinations can occur such as feelings of vibrations, auditory hallucinations can also arise including '8-bit-Super-Nintendo-like' music and vibrational sounds (Cott & Rock, 2008; Strassman, 2001). The external world can appear brighter with rippling effects which can be overlaid by multicoloured fractal imagery (Cott & Rock, 2008; Strassman, 2001). Synesthesia can be experienced in which stimulation of one sense or part of the body can produce a sense impression relating to another sense or part of the body. Typical synesthetic experiences include seeing sounds in the mind's eye as colours (dos Santos et al., 2019b).

Subjective effects are often reported to have a dream-like quality, yet participants frequently report feeling lucid and able to appreciate the experience as if in a non-drug-induced state of consciousness (Cott & Rock, 2008; Davis, Clifton et al., 2020; Strassman, 2001). Intense emotions and mood changes can arise with powerful emotional responses such as bliss and fear being frequently reported (Cozzi et al., 2009; Davis, Clifton et al., 2020; Strassman, 2001).

Altered perceptions of time and space are common, with people reporting a dissolution of conventional space-time, a sense of detachment from the body and merging into an all-pervading consciousness (Davis, Clifton et al., 2020; Strassman, 2001). Such anecdotes include reportedly learning how consensus three dimensional reality is a subset of reality composed of more dimensions (Cott & Rock, 2008). Many DMT users report a sense of familiarity with the altered perceptions of space and time and a feeling of having perceived these domains before (Cott & Rock, 2008; Davis, Clifton et al., 2020; Michael et al., 2021; Strassman, 2001).

Unitive mystical-type experiences are often reported which are complemented by profound sensations of bliss and a loss of ego identity (Cott & Rock, 2008; Milliere et al., 2018; Strassman, 2001). NDE-type states have also been reported with subjective experiences including going through a tunnel and entering blinding white light - as consistent with classic near-death experiences (Michael et al., 2021; St John, 2018; Strassman, 2001). Additionally, consumers have reported speaking with deceased people who they have previously known and reaching a staging zone for mindstreams to incarnate into a body (Michael et al., 2021; Strassman, 2001). An inability to explain the experience using words, ineffability, is a common feature of subjective DMT reports which is also typical of classic mystical and near-death experiences (Cott & Rock, 2008; Davis,

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[1]*Self-transcendence* has been defined as: Overcoming the limits of the individual self and its desires in contemplation and realisation, and potentially experiencing ideas such as considering oneself an integral part of the universe.

Clifton et al., 2020; James et al., 2020; Strassman et al., 2001). DMT users frequently describe some form of acute psycho-spiritual changes during the subjective experience which they later incorporate into their long-term perception of the cosmos (Cott & Rock, 2008; Griffiths et al., 2019).

DMT consumers often report being transported to an alternative 'world', 'reality' or 'universe' and in many cases these alternate realms or domains are perceived to be more real than everyday reality even after the subjective effects of the drug have dissipated (Cott & Rock, 2008; Strassman, 2001). Around half of the participants in Strassman's studies perceived 'invisible worlds' which are reportedly often inhabited by entities or intelligences (Davis, Clifton et al., 2020; Strassman, 2001). Common descriptive labels for the entities encountered include beings, guides, spirits, aliens, machine elves and helpers (Davis, Clifton et al., 2020; Luke et al., 2018). The entities are often perceived as having initiated the interaction rather than the individual under the effects of DMT (Davis, Clifton et al., 2020). Encounters with perceived entities can induce strong emotional responses including fear, kindness, friendship and love with the entities themselves also often reportedly having a, usually positive, emotional reaction to the encounter (Davis, Clifton et al., 2020). Such entities are commonly described as attempting to impart useful information typically via some form of extrasensory (i.e. telepathic) and/or auditory means (Cott & Rock, 2008; Davis, Clifton et al., 2020; Strassman, 2001). Communication between the entity and the perceiver is typically reported as from the entity to the perceiver or 2-way but rarely solely from the perceiver to the entity (Davis, Clifton et al., 2020).

Intriguingly, a recent study of DMT inhalation suggests that of individuals who have entity encounter experiences, around 96% and 72% contest that these entities are conscious and intelligent, and continue to exist after the effects of the drug have worn off, respectively (Cott & Rock, 2008; Davis, Clifton et al., 2020). This is an unusual statistic for a drug-induced hallucination because in other circumstances hallucinations are more frequently determined to have been non-veridical creations of the mind and in no way real. Furthermore, many people report the entity encounter experience as being more real than everyday waking consciousness (Davis, Clifton et al., 2020). DMT occasioned entity encounters have been associated with reduced atheistic attitudes, with a majority of people having DMT-induced entity experiences reporting that the encounter catalysed long-term alterations in perceptions of the functioning of reality (Davis, Clifton et al., 2020). Entity encounters are often associated with increased life satisfaction and meaning; however, in a study by Davis, Clifton et al. (2020) it was found that DMT-induced entity encounters were statistically significantly less likely ($p < 0.001$) to be associated with positive enduring effects compared to merging with 'God/ultimate reality' (as in a classic mystical experience) when compared to results of a similar study (Davis, Clifton et al., 2020; Griffiths et al., 2019).

Rick Strassman classified DMT experiences into the following subtypes: Personal, Transpersonal, and Invisible Worlds; and DMT experiences can consist of varying combinations of the three subsets

for example, encounter with seemingly autonomous entities followed by a mystical-type experience (Strassman, 2001). In Strassman's studies, the participants were all administered DMT in the same sterile hospital environment, however, the subjective effects were sometimes very different from one person to another, with some experiencing classic unitive mystical-type experiences and others having confusing entity encounter experiences with no apparent psychological benefits (Strassman, 2001).

## 5.2 | Ayahuasca

Many similar themes occur in first-hand ayahuasca reports although the phenomenology of DMT and ayahuasca are not completely equivalent. A significant difference between DMT and ayahuasca is the length of time of the experience as, whilst inhaled or injected DMT experiences last around 20 min, ayahuasca sessions last several (approximately 4) hours (Frecska, Bokor et al., 2016). As the subjective effects begin to be felt strongly, the experience is often accompanied by emotions such as fear and confusion with frequent vomiting and diarrhea; the perception of time is altered, and a sense of entering altered domains of existence (i.e. the 'spirit world') is often reported with subjective experiences including entity encounters and a sense of merging with the cosmos (Brito-da-Costa et al., 2020; Frecska, Bokor et al., 2016; Tafur, 2017).

Perceptions of geometric patterns (Figure 1), mythological beings, chimeras or hybrids, extraterrestrials, celestial beings, semi-divine beings (such as Hindu deities), spirit guides, demons or monsters, plant spirits and also animals including snakes and black pumas are often reported under the influence of ayahuasca (Frecska, Bokor et al., 2016; Luke, 2020; Narby, 1998; Shanon, 2002; Strassman et al., 2008; Tafur, 2017). When consuming ayahuasca in the Amazonian region, many consumers attest that they establish a relationship with 'the spirit of ayahuasca' which is often perceived to
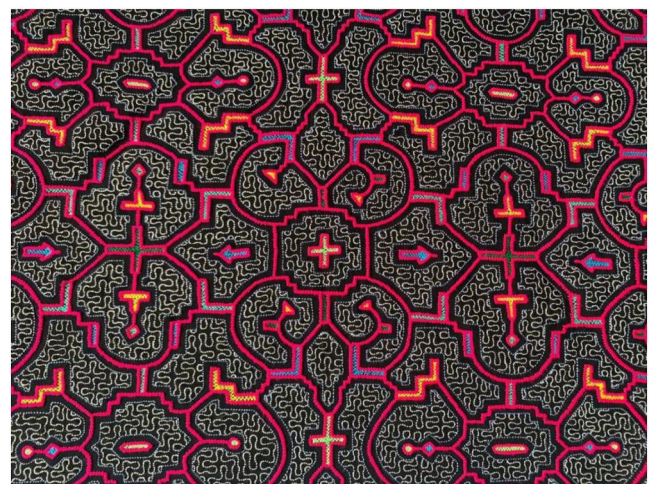


**FIGURE 1** Shipibo kene which is a representation of some of the visual aspects of ayahuasca experience (image courtesy of Dr Joseph Tafur)

be female, but in some cases is male (Hoffman, 2019; Narby, 2021; Tafur, 2017). Consumers of ayahuasca talk about being communicated with and taught by the spirit of ayahuasca through visions (Luke et al., 2018; Narby, 2021; Tafur, 2017). Visions of landscapes of what appear to be other worlds are frequently reported (Luke et al., 2018; Strassman et al., 2008). Perceptions of and conversations with the deceased are not uncommon in ayahuasca sessions (dos Santos et al., 2018; Tafur, 2017). Many *pasajeros* (Spanish: travellers or journeyers) attest that ayahuasca visions feel real despite the hallucinations often having little relation with everyday waking consciousness (Narby, 1998; Tafur, 2017).

Ayahuasca sessions are often reported to be highly introspective and dream-like with interplay between thoughts, memories and emotions (Bilhimer et al., 2018; Dominguez-Clave et al., 2016; Frecska, Bokor et al., 2016; Tafur, 2017). Autobiographical streams of consciousness are common and retrieval of forgotten memories can occur, for example, someone in their 70s reported remembering events which took place when they were 8 months old (Frecska, Bokor et al., 2016; Tafur, 2017). Additionally, some people report a sense of experiencing events from another person's perspective, for example, seeing events in the lives of people they know which were formative in their personality and enabling a greater empathy for people they had previously felt antipathy towards (Roseman et al., 2021; Tafur, 2017). Psychological issues such as traumatic memories can become illuminated with the capacity to view the problems from numerous perspectives and therefore allowing greater insight into maladaptive cognitive, emotional and behavioural patterns and a sense of psychological restructuring (Frecska, Bokor et al., 2016). In addition to past events, ayahuasca can enable consumers to perceive future outcomes of their behaviours, which can provide motivation for changing behavioural patterns such as addiction (Frecska, Bokor et al., 2016; Tafur, 2017).

Ayahuasca sessions are often associated with an 'afterglow' of several days in which greater positive mood and openness are felt (Dominguez-Clave et al., 2016). The phenomenology of ayahuasca has led people to attest that their experiences with ayahuasca are some of the most deeply important and meaningful of their lives with transformative long-term beneficial effects including themes of redemption and forgiveness (dos Santos, Sanches, et al., 2018; Frecska, Bokor et al., 2016; Tafur, 2017).

# 6 | AMAZONIAN SCIENCE, PRACTICES AND BELIEFS

This section summarises the science, practices and beliefs of many ayahuasca using groups in the Amazon. This section is included to present selected medical and ceremonial practices of indigenous ayahuasca using peoples and how they view reality through their use of ayahuasca. Such information highlights some of the challenges involved in incorporating Amazonian ayahuasca plant medicine into contemporary medical practices (Tafur, 2017; Winkelman, 2021).

People in the Amazon have been cultivating and domesticating plants in the rainforest since pre-Columbian times with many of the plants being used in indigenous healing practices (Levis et al., 2017). There are numerous ayahuasca consuming peoples in the Amazonian region and amongst the Amazonians the Shipibo-Conibo, the Tukano, the Kamsa and the Huitoto are particularly well-renowned for their science and knowledge of ayahuasca and plant medicine in general, according to anthropologist Jeremy Narby (1998). The use of plant hallucinogens in these types of practices is one variant of a group of practices that in contemporary English are known collectively as shamanism; however, the word shamanism derives from a Siberian Tungus-Mongol word, *saman*, and is now used as an all-encompassing term to describe generalised belief systems which have many similarities across the world in cultures which have no apparent connection with each other (Frecska, Hoppál et al., 2016).

In Amazonian ayahuasca using cultures, ayahuasca is generally viewed with respect and is not used casually in a way that could be described as recreational but, rather, in a social and functional context such as for information gathering and healing (Cott & Rock, 2008; Frecska, Bokor et al., 2016; Tafur, 2017). In order to become an established *ayahuasquero*, arguably the equivalent of a doctor of ayahuasca, trainees have to undergo several years of training, with training often lasting 6 or 7 years as is comparable with medical degrees in North America and Europe (Tafur, 2017). Ayahuasca is typically ingested by an ayahuasquero in order to journey to the 'spirit world' and access information (e.g. the remote location of a plentiful food source) not usually attainable (Cott & Rock, 2008; Frecska, Hoppál et al., 2016; Luke et al., 2018). In many indigenous-type communities a specialised building, in some regions referred to as a maloca, is the setting for people to use ayahuasca in ceremony. Malocas often are circular and spacious with a high ceiling (Figure 2). Ayahuasca ceremonies are usually conducted at night and are often followed up by further processes, sometimes including cleansing flower baths, with discussion and psychological integration (Frecska, Bokor et al., 2016; Gonzalez et al., 2021; Tafur, 2017).



**FIGURE 2** Interior of a contemporary maloca that has been used to provide ayahuasca ceremonies for international non-Amazonian people in the Peruvian Amazon (image courtesy of Dr Joseph Tafur)

The medical beliefs of ayahuasqueros differ from contemporary 'western' medicine as, in addition to biological mechanisms of action, concepts such as emotional and healing energies, interactions with consciousnesses present in alternate domains of existence and ancestral traumas, amongst others, are held to be relevant to healing processes (Tafur, 2017). For example, if an illness is of an energetic nature, chemical and physical approaches like medications and surgery are believed to be unlikely to solve the problem and a shaman or spiritual healer will be needed to interact with the energy body and help to heal dysfunction in the emotional body (Tafur, 2017). The vomiting and purging involved in ayahuasca sessions are believed in Amazonian medicine to be a mechanism of releasing emotional and mental pathologies (Frecska, Bokor et al., 2016; Tafur, 2017). Ayahuasqueros have concepts such as cleaning the energies of emotional trauma, childhood trauma, in utero trauma and ancestral trauma; and a process of healing involving spiritual cleansing, reconciliation, love and acceptance (Tafur, 2017). Another aspect of Amazonian ayahuasca healing practices is generating a sense of connection to community, to nature and to 'spirit' (Tafur, 2017). Such practices in the Amazon are believed to be applicable to some ailments which are not served well by contemporary medicine including depression, PTSD, idiopathic chronic cough, psychosomatic pain, psoriasis and other inflammatory skin conditions, addiction, migraine headaches, inflammatory bowel disease and anxiety (Frecska, Bokor et al., 2016; Tafur, 2017).

According to Amazonian practices, plants possess consciousness and there are numerous conscious beings that humans are unable to detect in everyday waking consciousness (Gardiner, 2012; Tafur, 2017). Many Amazonians claim that their extensive knowledge of the applications of many plants in the Amazon were taught to them by the plants themselves rather than through a process of trial and error, as would be expected in contemporary science as it is generally understood in North America and Europe, and that the numbers of plants and potential combinations of them are too great for all their discoveries to have been made through trial and experimentation (Narby, 1998; Tafur, 2017). According to Amazonian beliefs, ayahuasca enables the consumer to perceive domains of existence and conscious entities which inhabit these alternate domains and engage in communication with these consciousnesses (Tafur, 2017). Additionally, many Amazonians believe that ayahuasca enables people to converse with the dead in the 'spirit world' (dos Santos, Sanches et al., 2018; Frecska, Hoppál et al., 2016; Tafur, 2017). In some Amazonian cultures, practitioners sing songs referred to as *icaros* which are believed to help guide healing experiences by scanning *pasajeros'* bodies for energetic blockages and helping to clear harmful energies; additionally, these songs are at least partly conducted by channelling tunes intuited through interactions with perceived beings or energies (Tafur, 2017; Weiss et al., 2021).

In Peruvian *vegetalismo* Shipibo tradition, people take a purgative brew and have a strict diet including dieting specific plants prior to taking ayahuasca (Frecska, Bokor et al., 2016; Gonzalez et al., 2021; Tafur, 2017). People often diet additional plants over an extended period of time to be taught by the plants which are often incorporated into ayahuasca brews. Examples of at least 90 plants, referred to as teacher, or master, plants, which are often used in conjunction with ayahuasca in healing and self-development practices include nihue rao, coca, piñon blanco, ajo sacha and bobinsana (Dominguez-Clave et al., 2016; Frecska, Bokor et al., 2016; Tafur, 2017). Although some perceive ayahuasca as a means of administering orally active DMT to enable a hallucinogenic experience, this contrasts with the general Amazonian perspective which holds that such a view is excessively reductionist (Tafur, 2017). Rather than administering a single psychoactive drug, ayahuasqueros do not tend to think of ayahuasca as a drug experience but use ayahuasca to 'facilitate deep healing through the master plants, allowing for the possibility of dialogue with the realm of spirit' (Tafur, 2017).

Many of the Amazonian beliefs highlighted in this section, such as in what has been described as 'the spirit world', are based on subjective experiences and are not supported by contemporary scientific understanding. However, the scientific method cannot generally be used to demonstrate the absence of the existence of something. Therefore, many of these notions cannot be dismissed as being false with absolute certainty as available technologies would be incapable of providing additional empirical evidence that could be used to corroborate or disprove the anecdotal reports.

## 7 | MECHANISM OF ACTION

### 7.1 | Biochemistry and neuropsychopharmacology

#### 7.1.1 | N,N-dimethyltryptamine

Psychedelic states arise when the regulation of normal states of consciousness correlating with events in the exterior world, as detected by the senses, is decoupled in some way (Swanson, 2018). As previously highlighted, DMT (Figure 3) can bind to many proteins including sigma-1 receptors, trace amine-associated receptors, serotonergic receptors (e.g. 5-HT2A, 5-HT1A and 5-HT2C), glutaminergic receptors and modulates the dopaminergic system (Brito-da-Costa et al., 2020; Carbonaro & Gatch, 2016; Ray, 2010; Riba et al., 2002). Understanding of the neurochemistry of DMT is limited and it is not clear whether exogenously administered DMT binds to any additional receptors beyond those that have been proposed to be
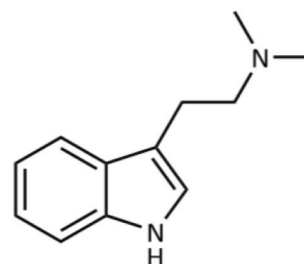


**FIGURE 3** Chemical structure of N,N-dimethyltryptamine

relevant to endogenous DMT. Thus, due to the state of research in the area it is difficult to differentiate the binding profiles of endogenous and exogenous DMT.

DMT interacts with a variety of ionotropic and metabotropic receptors, the most well understood being serotonin receptors, in particular 5HT2A (Alamia et al., 2020; Cozzi et al., 2009). Serotonin receptors have a vast range of functions, and balancing between endogenous and exogenous information involved in the construction of conscious experience is heavily mediated by the interplay between 5-HT1A and 5-HT2A receptors (Carhart-Harris & Nutt, 2017; Schartner & Timmermann, 2020). Pre-treatment with the 5-HT1A antagonist pindolol can significantly increase the reported psychological response to DMT, indicating that 5-HT1A agonism may downregulate the psychedelic effects (Strassman, 1996, 2001; Wallach, 2009). Additionally, it is understood that DMT can exert anxiolytic effects via 5-HT1A receptor agonism (Frecska, Bokor et al., 2016; Wallach, 2009).

G protein-coupled 5-HT2A receptors are found in many brain regions including the cortex, striatum, hippocampus and amygdala (Brito-da-Costa et al., 2020; Vollenweider & Preller, 2020). Psychedelics are particularly known to be agonists of 5-HT2A receptors expressed in deep-layer pyramidal neurons in the fronto-parieto-occipito-temporal cortex (dos Santos et al., 2016b). 5-HT2A receptor agonism by psychedelics, including DMT, is associated with an increase in both the frequency and amplitude of spontaneous excitatory postsynaptic currents (Brito-da-Costa et al., 2020; Dominguez-Clave et al., 2016). 5-HT2A receptor agonism by psychedelics has also been found to be involved in gene expression and can upregulate transcription factors such as c-fos, egr-1, egr-2 and BDNF which are involved in synaptic plasticity, memory and learning (Dominguez-Clave et al., 2016). Furthermore, DMT has been found to modulate functional plasticity in prefrontal cortical neurons with increased dendritic spine density which may be mediated via 5-HT2A receptor modulation (Brito-da-Costa et al., 2020). The 5-HT2A receptor has been associated with visual hallucinations in neurological disorders, however, how hallucinations are generated by 5-HT2A receptor agonism is not understood (Alamia et al., 2020). Although administration of the 5-HT2A receptor antagonist ketanserin inhibits many of the effects of DMT in humans, other compounds bind with higher affinity to 5-HT2A receptors than DMT which do not induce hallucinations. Therefore, 5-HT2A receptor agonism alone is not sufficient to explain the entirety of DMT phenomenology (Barker, 2018a; Brito-da-Costa et al., 2020; Carbonaro & Gatch, 2016; Nichols, 2016; Valle et al., 2016; Vollenweider & Preller, 2020; Wallach, 2009). Finally, all classic psychedelics, including DMT, which act upon 5-HT2A receptors are understood to cause consumers to be sensitised to set and setting, however, the mechanism of this sensitisation and its link with 5-HT2A receptor binding is not clear (Carhart-Harris & Nutt, 2017; Hartogsohn, 2016; James et al., 2020).

DMT triggers a complex cascade of receptor activations resulting in the modulation of the overall glutamate concentration via agonism of mGlu receptors 2 and 3 in certain brain areas, including the frontal cortex, which may contribute to the observed physiological and psychological psychedelic effects, but how such modulation induces hallucinations is unknown (Barker, 2018a; Carbonaro & Gatch, 2016; dos Santos et al., 2016a, 2016b; Gonzales-Maeso et al., 2007, 2008; Marek, 2018; Nichols, 2004). A study with mGluR2 knockout mice suggested that mGluR2 is necessary for psychedelic effects as measured by head-twitch response, although such a measure of psychedelic effects does have limitations (Canal & Morgan, 2012; Carbonaro & Gatch, 2016; Moreno et al., 2011). The 5-HT2A receptor mediated hallucinogen-specific intracellular pathway may require a complex of the 5-HT2A receptor with the mGlu2 receptor (Frecska, Bokor et al., 2016; Gonzalez-Maeso et al., 2008; Moreno et al., 2011). Agonism of 5HT2A receptors in the medial prefrontal cortex increases pyramidal cell activity and has been proposed to stimulate corticotegmental glutamatergic projection neurons via co-localisation with 5-HT2A receptors to form heteroreceptor complexes, and such heteroreceptors may induce a psychedelic-specific second messenger cascade (Aghajanian & Marek, 1997; Carbonaro & Gatch, 2016; Delille et al., 2012; Gonzalez-Maeso et al., 2007, 2008).

As previously highlighted, DMT can modulate sigma-1 receptors, however, the role of these receptors and the downstream effects of DMT binding to these receptors are not well understood (Barker et al., 2012; Fontanilla et al., 2009; Hayashi, 2019; Rossino et al., 2021; Su et al., 2009; Su & Hayashi, 2003). The sigma-1 receptor plays a role in neural plasticity through dendritic spine formation which could be relevant for DMT's reported potential for promoting neurogenesis and personality change (Dominguez-Clave et al., 2016; Morales-Garcia et al., 2020). Certain antidepressants have been found to modulate the sigma-1 receptor which could be a factor in DMT and ayahuasca's reported antidepressant effects (Dominguez-Clave et al., 2016). It has been observed that at higher concentrations, DMT can inhibit voltage-gated sodium ion channels via sigma-1 receptor agonism, but such a role in psychedelic effects is unknown (Cozzi et al., 2009). The sigma-1 receptor has been associated with the psychopathology of a number of disorders including addiction and depression which, when considering some of the applications of psychedelics, could indicate a link between sigma-1 receptor modulation and the subjective effects of psychedelics (Carbonaro & Gatch, 2016). However, the most widely understood functions of the sigma-1 receptor relate to bioenergetic cellular function and signal transduction, and the neuromechanistic relationship between sigma-1 receptor agonism and psychedelic effects is unclear (Carbonaro & Gatch, 2016; Frecska, Bokor et al., 2016; Hayashi, 2019; Su & Hayashi, 2003).

The affinity of DMT to TAA receptors has been associated with anxiolytic effects (Brito-da-Costa et al., 2020). It has been proposed that TAAR-6 could be relevant for psychedelic effects due to it being present in high concentrations in limbic regions and the frontal cortex (Wallach, 2009). However, after binding to TAARs it is not well understood what happens besides the release of cAMP and this alone cannot explain hallucinatory phenomena as administration of cAMP would not elicit DMT-like effects and such phenomenology will be a

result of downstream processes (Barker et al., 2012). Therefore, more research is required to determine the significance of TAAR modulation and psychedelic effects (Carbonaro & Gatch, 2016).

## 7.1.2 | Ayahuasca

*Banisteriopsis caapi* contains the alkaloids harmine, tetrahydroharmine (THH), harmaline, harmol and harmalol (Figure 4) (Dominguez-Clave et al., 2016; McKenna et al., 1984). As the preparation of ayahuasca is not standardised across the Amazonian region, varying concentrations and relative amounts of the different known psychoactive compounds harmine, DMT, THH and harmaline have been found in different brews which will inevitably lead to different pharmacological profiles and subjective effects (Brito-da-Costa et al., 2020).

There has been the perception by some scholars that ayahuasca is principally DMT and that the β-carboline harmala alkaloids just act purely to inhibit the action of the enzymes which catalyse DMT's degradation. However, monoamine oxidase inhibitors are an established class of antidepressants which can increase serotonin and noradrenaline (norepinephrine) levels and thus likely contribute to ayahuasca's therapeutic profile (Barker, 2018a; Dominguez-Clave et al., 2016; dos Santos et al., 2007, 2019). Additionally, THH is also a serotonin reuptake inhibitor which is another well-established form of antidepressant (Dominguez-Clave et al., 2016; dos Santos et al., 2007). The harmala alkaloids have structural similarities with serotonergic receptor agonists and have been found to bind to 5-HT receptors with significant affinities (dos Santos et al., 2007; Grella et al., 2003). Harmala alkaloids can also induce psychoactive effects without the presence of DMT possibly via 5-HT2A receptor agonism
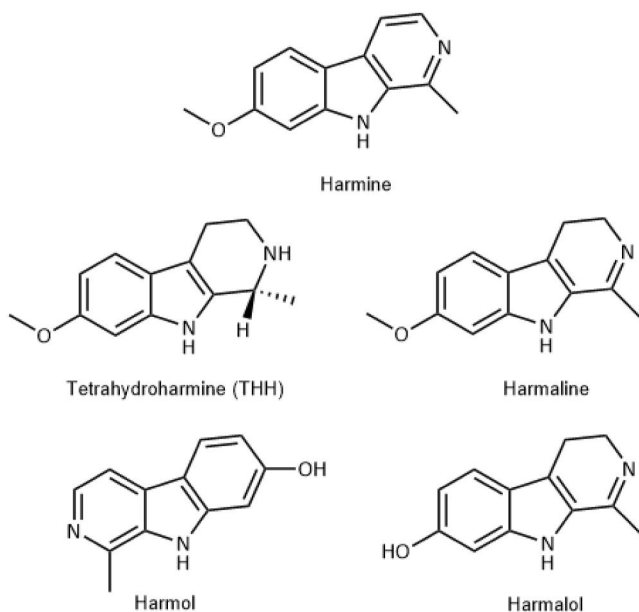
(Brito-da-Costa et al., 2020; Frecska, Bokor et al., 2016; Narby, 2021; Tafur, 2017). Harmine has been suggested to inhibit dopamine transporters leading to high levels of dopamine in the synaptic cleft; additionally both harmine and harmaline have been found to induce dopamine release and inhibit enzymatic degradation of dopamine with likely effects on the amygdala and induction of dream-like states, although dopamine has a wide range of functions and its exact role in the subjective effects of ayahuasca is unclear (Figure 6) (Brito-da-Costa et al., 2020; Solms, 2000). Harmine has been found to up-regulate BDNF expression, including in the hippocampus, and can increase proliferation of neural progenitor cells and therefore likely plays a role in the neuroplasticity associated with ayahuasca use (Dominguez-Clave et al., 2016; dos Santos et al., 2019b, 2016a; Fortunato et al., 2009; Morales-Garcia et al., 2017). Little research has been conducted on the pharmacological and therapeutic effects of these compounds and they may contribute significantly to ayahuasca's phenomenological and therapeutic profile.

Biochemically, consuming an ayahuasca brew is significantly more complex than inhaling pure DMT vapour due to the many chemical compounds present in the drink (Frecska, Bokor et al., 2016). As with consuming herbal cannabis as opposed to pure THC (James et al., 2021), the various compounds in ayahuasca will induce a synergistic entourage effect in which the many different chemical constituents combine to induce an effect which is distinct from that which would be elicited by consuming the individual compounds (such as DMT and harmaline) in isolation (dos Santos et al., 2019b; Ona et al., 2020). Whilst DMT and the harmines have been the subject of most of the chemical analyses, it has become clear that in the case of cannabis, often overlooked compounds such as terpenes have an impact on the subjective effects and therapeutic applications. Likewise there may be numerous other compounds present in ayahuasca whose presence and role are yet to be determined.

Different species of toad produce the structurally different yet related compound 5-methoxydimethyltryptamine (5-MeO-DMT) which has also been used deliberately to induce altered states of consciousness which can include mystical-type experiences, awe and sensations of pure awareness (Figure 5) (Barsuglia et al., 2018; Davis et al., 2018). 5-MeO-DMT has been found to be present in some ayahuasca brews and therefore will occasionally be a contributory molecule to ayahuasca's entourage effect (Davis et al., 2018; Riga et al., 2014). As with other serotonergic psychedelics, 5-MeO-DMT has been reported to be potentially beneficial in treating
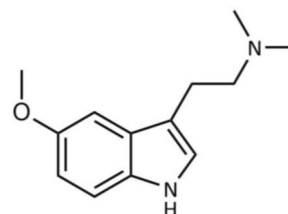
**FIGURE 4** Chemical structures of harmala alkaloids present in ayahuasca

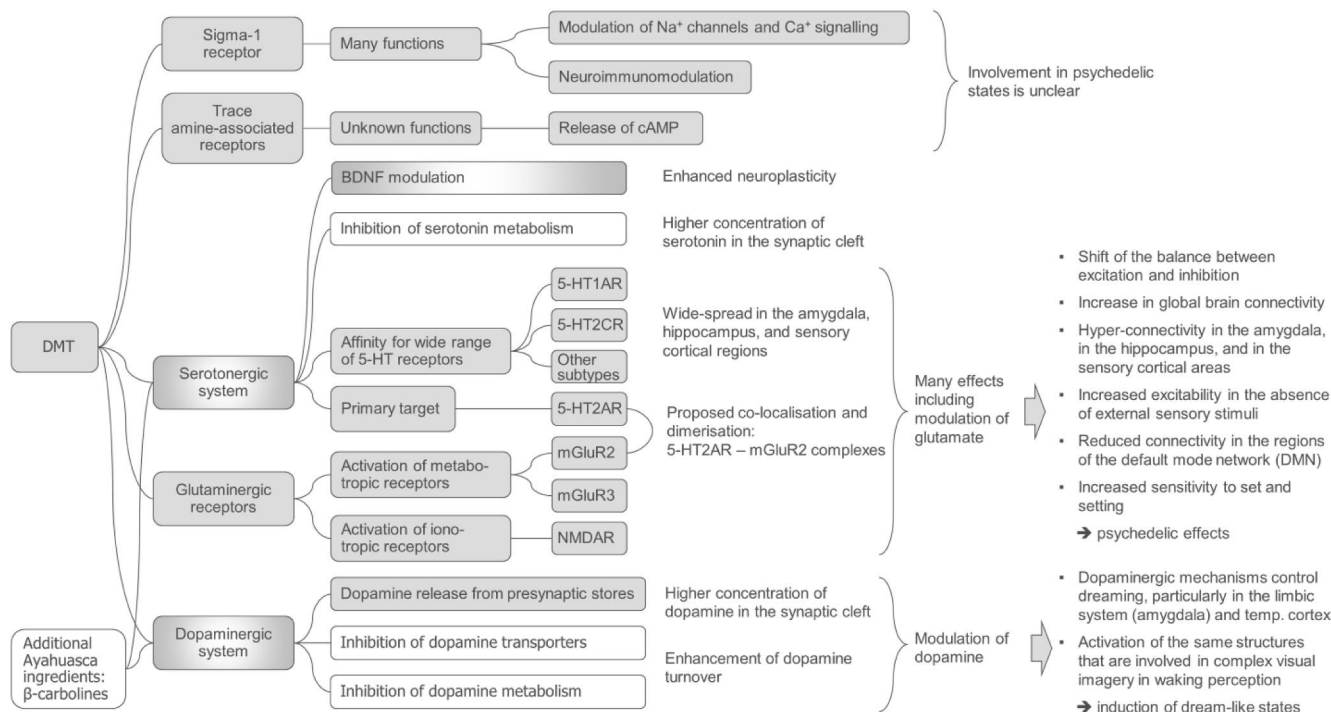**FIGURE 5** Chemical structure of 5-MeO-DMT

**FIGURE 6** A simplified general overview of contemporary understanding of the neurochemistry and psychopharmacology of N,N-dimethyltryptamine and ayahuasca. Grey boxes = DMT mediated; White boxes = β-carboline mediated; White/grey boxes = both DMT and β-carboline mediated

psychiatric illnesses including PTSD, depression, anxiety and substance use disorders (Davis et al., 2018, 2019), can bind to several serotonin receptors including 5-HT1A and 5-HT2A and inhibit serotonin reuptake (Davis et al., 2018).

Ayahuasca consumption increases blood cortisol and prolactin levels which have many different biological functions including modulation of the immune system (Bouso et al., 2012). Abnormally low levels of cortisol, hypocortisolemia, has been observed in some types of depression and up-regulation of cortisol expression upon ayahuasca consumption may play a role in ayahuascas's function as an antidepressant (Galvao et al., 2018). Ayahuasca consumption can lead to increased levels of natural killer cells (Carbonaro & Gatch, 2016; dos Santos & Strassman, 2011) and lymphocyte redistribution (Bouso et al., 2012). Such observations suggest a possible anti-inflammatory mechanism of action with potential roles in aiding disorders of the PNEI system including specific types of depression (Galvao-Coehlo et al., 2020).

Ayahuasca has been proposed to exert anti-addictive effects via direct and indirect effects on serotonergic and dopaminergic neurons in the mesolimbic pathway (Frecska, Bokor et al., 2016; Liester & Prickett, 2012). Moreover, ayahuasca has been found to modulate concentrations of the neurotransmitter γ-aminobutyric acid (GABA), with decreased GABA release in the hippocampus and increased GABA release in the amygdala with implications for emotional, memory and learning processes (Brito-da-Costa et al., 2020). Ayahuasca increases blood flow in frontal and paralimbic regions and activates prefrontal and temporal regions of the brain, potentially mediated by glutamate release (Bouso et al., 2012). Modulation of

both GABAergic and glutamatergic systems has been proposed to affect BDNF expression with implications for neuroplasticity and possible mechanistic relevance to remission of depressive and addictive symptoms (Frecska, Bokor et al., 2016). Additionally, increased serum BDNF levels after ayahuasca administration have been associated with antidepressant effects (de Almeida et al., 2019).

The fast-acting antidepressant effects of ayahuasca have been associated with increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area which are brain regions that have been implicated in the regulation of mood and emotions and the mechanism of action of some established antidepressants (dos Santos et al., 2019, 2016a; Sanches et al., 2016). Ayahuasca has been found to increase bilateral activation of the anterior insula frontal gyrus (involved in interoception and self-awareness), the anterior cingulate cortex (ACC) (emotion processes) and frontomedial cortex (self-awareness) in the right hemisphere, and activate the amygdala (emotion processes) and parahippocampal gyrus (involved in memory processes and emotion) in the left hemisphere (dos Santos et al., 2019; McKenna & Riba, 2015; Riba et al., 2006).

Long-term ayahuasca users show differences in cortical thickness in midline brain structures, with decreased thickness in the posterior cingulate cortex (PCC), a key node of the default mode network, and an increase in the thickness of the precentral gyrus and the anterior cingulate cortex using magnetic resonance imaging (MRI) versus matched controls (Bouso et al., 2015; Brito-da-Costa et al., 2020; Carbonaro & Gatch, 2016). Reduced cortical thickness of the PCC has been associated with reported long-term personality modulation

and higher scores of self-transcendence and spirituality and such findings indicate a relevance for the PCC and self-referential thought and cognitive function (Bouso et al., 2015). These changes in the structure of the brain might be at least partly mediated by 5-HT2A receptor agonism induced up-regulation of BDNF and transcription factors involved in synaptic plasticity and memory (Bouso et al., 2015); and activation of frontocortical glutamate networks leading to enhanced expression of egr-1, egr-2, BDNF and glial cell line-derived neurotrophic factor (GDNF) (dos Santos et al., 2016a).

As previously shown, ayahuasca can modulate functions of the limbic system, including the amygdala and anterior cingulate cortex, which is involved in many cognitive processes including emotion, interoception and long-term memory (Riba et al., 2004, 2006). Emotion-based problems such as depression, anxiety, PTSD, addiction and many psychosomatic disorders are associated with limbic system dysfunction, within the PNEI network, which can benefit from the emotional healing capacities of ayahuasca plant medicine (dos Santos et al., 2016; Tafur, 2017). The limbic system has been proposed as being a potential hub of profound subjective emotional experiences, such as mystical-type experiences, and modulation of the limbic system in the sometimes intensely emotion-rich cathartic ayahuasca sessions can affect the size and thickness of the areas associated with impulse control, emotion, decision making and memory, thus partially explaining ayahuasca's reported long-term antidepressant and anti-addictive potentials (dos Santos et al., 2016a; Saver & Rabin, 1997; Tafur, 2017).

Psychiatric disorders such as depression and trauma have been found to be modulated and maintained by epigenetic mechanisms (Smart et al., 2015; Sun et al., 2013). Epigenetic modifications can be mediated via psychological and emotional events and therefore it has been hypothesised that emotional experiences characterised by love, compassion, forgiveness and gratitude elicited by ayahuasca can influence the expression and regulation of genes (Carey, 2012; Dias & Ressler, 2014; Inserra, 2018; Kaliman et al., 2014; Tafur, 2017). Serotonin receptor-dependent signalling has been linked with epigenetic mechanisms involving psychiatric disorders such as schizophrenia and depression, however, the specific mechanisms of the compounds or the emotions involved in ayahuasca sessions interacting with such functions are not clear (Holloway & González-Maeso, 2015; Inserra, 2018). Ayahuasquero concepts such as cleaning the energies of emotional trauma, childhood trauma, in utero trauma, and ancestral trauma can be linked to some extent through contemporary conventional medical understanding of epigenetic processes including, but not limited to, cytosine methylation/hydroxymethylation and modification of histone proteins such as acetylation of lysine residues and serine phosphorylation (Carey, 2012; Dupont et al., 2009; Sadakierska-Chudy & Filip, 2015; Tafur, 2017). Therefore, there is, at least in principle, some contemporary scientific basis for how ayahuasca can be used to resolve problems associated with intergenerational stress, that is, how traumatic events in the lives of a person's ancestors can be influencing them now and that such influences can be remedied through ayahuasca (Bird, 2007; Bowers & Yehuda, 2016; Inserra, 2018; Tafur, 2017).

## 7.2 | Neural correlates of consciousness

The activity patterns constituting the neural correlates of consciousness (NCC) correspond to the observable concomitants of subjective experiences. As such, the neural correlates reflect the macroscopic system behaviour of the brain while forming conscious states. In the following, the system behaviour under the influence of DMT and ayahuasca is first described on the basis of general findings about the activity and connectivity features of the brain, before the neurophysiological body of evidence in the individual frequency bands is discussed in more detail. The neurophysiological findings presented here are relevant to the following section which is devoted to models for explaining the phenomenological features of psychedelic states.

The spatio-temporal dynamics and neural activity patterns occurring in connection with DMT-induced altered states of consciousness bear a high degree of resemblance to the patterns evoked by visual stimulation (Alamia et al., 2020). In the same manner, strong stimulations of vision-related brain regions brought about by ayahuasca, particularly in the visual association cortex, are 'comparable to the effect of natural images with the eyes open', resulting in vivid visual experiences that are felt to be equivalent to sensory perceptions and, hence, are assigned a status of reality (de Araújo et al., 2012). A general insight is that psychedelics increase the global brain connectivity across sensory areas, a phenomenon termed *hyper-connectivity* (Preller et al., 2018; Tagliazucchi et al., 2016). In this context, a high overlap is found between regions of increased global connectivity and those that express 5-HT2A receptors (Tagliazucchi et al., 2016), explaining that also the amygdala, which abundantly expresses these receptors, belongs to those regions that exhibit hyper-connectivity under consumption of psychedelic substances (Preller et al., 2018). Notably, however, the expansion of global connectivity, being indicative of highly integrated brain states, disrupts the integrity of individual functional modules (Tagliazucchi et al., 2016). A consistent finding is that the functioning of the default mode network (DMN), which is associated with self-referential mental processes, is disabled by all classic psychedelics, meaning that LSD, psilocybin as well as DMT and ayahuasca cause a significant decrease in activity and functional connectivity across the core structures of the DMN, giving rise to the de-synchronisation and disintegration of this network (Carhart-Harris et al., 2014; Frecska, Bokor et al., 2016; Muthukumaraswamy et al., 2013; Palhano-Fontes et al., 2015; Tagliazucchi et al., 2016). Importantly, the induced changes in connectivity are highly correlated with the reported subjective effects, in particular vivid imagery, bliss, disembodiment, and ego dissolution (Preller et al., 2018; Tagliazucchi et al., 2016). Altogether, it can be summarised that psychedelics diminish the functional connectivity within resting-state networks and heighten the functional connectivity between nodes that under normal conditions belong to distinct resting-state networks. In this way, psychedelics increase the functional complexity of the brain by decoupling the functional connectivity from 'the underlying structural connectome', resulting in interactions between brain regions

that are 'less constrained than usual by the presence or absence of an underlying anatomical connection' (Luppi et al., 2021).

These essential characteristics of psychedelic states suggest a link to *dreamlike states*, especially as it has been pointed out that the mechanisms of dreaming and the mechanisms of action underlying psychedelics may share a common basis (Barr et al., 1972; Kraehenmann, 2017; Kraehenmann et al., 2017; Sanz et al., 2018; Vollenweider & Preller, 2020). Thus, it is significant that all dreamlike states feature complex imagery with rich emotional undertones and entail activity in the visual association cortex and the medial temporal regions, comprising in particular the amygdala and the hippocampus (Carhart-Harris, 2007; Solms, 2000). Emanating from these temporal core regions, dream imagery takes place with the participation 'of the same structures that generate complex visual imagery in waking perception' (Solms, 2000). It is also typical that, due to the disabled DMN, dreams are accompanied by reduced self-awareness and self-reflection, so that 'the dream sequence is not within the dreamer's voluntary control' (Zhao et al., 2018). Moreover, insights from deep brain stimulations suggest that the amygdala in interaction with other network nodes, such as the hippocampus, the temporal cortex, and the visual association cortex, plays an important role in the formation of vivid mental imagery and integrated sensory experiences. Interestingly, some of the evoked experiences are associated with autobiographical content, some with subconscious feelings of déjà vu, while a significant portion of the experienced states is distinguished by novelty, which are frequently encountered hallmarks of dreamlike states (Lai et al., 2020). On the one hand, these findings give rise to the conjecture that the role of dreaming consists in 'off-line memory reprocessing' and 'memory consolidation', with the amygdala and the hippocampus being crucially involved in the reactivation of emotional episodic memory (Zhao et al., 2018). On the other hand, the amygdala is hypothesised to function as the 'final integration center of dream phenomena', implying that this center channels 'creative novel features' into the dream experience and 'determines the emotional load of dreams' by enriching the experienced states with a broad spectrum of emotional nuances (Lai et al., 2020).

Turning to the neurophysiological body of evidence, the subjective experiences evoked by DMT are tightly correlated with increased oscillatory activity in the delta and theta bands (Alamia et al., 2020; Pallavicini et al., 2021; Timmermann et al., 2019), with the phase synchronisation of delta oscillations extending over cortical and hippocampal areas (Kometer et al., 2013). In addition to these features, elevated power and global synchrony are observed in the gamma band, where complex imagery is correlated with central gamma power, experiences of unity and disembodiment are correlated with occipital gamma power, the perceived transcendence of space and time is accompanied by occipital and frontal gamma power, and ND-type experiences are associated with enhanced occipital, frontal, and temporal gamma power (Pallavicini et al., 2021; Tagliazucchi et al., 2021). Moreover, there is a cross-frequency coupling between the delta/theta oscillations and the gamma oscillations. While theta-phase-gamma-amplitude coupling is characteristic of the waking state, the release of dopamine, which is triggered in sleep phases and initiated by DMT and ayahuasca, strengthens the phase-amplitude relationship between delta and gamma oscillations and induces a shift to delta-phase-gamma-amplitude coupling in regions of the hippocampus and frontal cortex (Andino-Pavlovsky et al., 2017).

Thus, also at the neurophysiological level, the close relationship between psychedelic and dreamlike states becomes apparent, resulting in the conclusion that the neural correlates of such states can be best described in terms of synchronised patterns of delta/theta and gamma activity in medial temporal regions, comprising the amygdala and the hippocampus, and cortical areas, particularly the visual association cortex, with the onset of conscious experiences requiring the propagation of activity from the medial temporal regions to the cortical regions (Figure 7) (Carhart-Harris, 2007; Riba et al., 2002). This fits in with the interpretation of activity in the delta and theta frequency bands during sleep as a signature for the replay of memory traces (Kim et al., 2019; Langille, 2019). More specifically, given the known involvement of the amygdala and the hippocampus in emotional memory encoding and retrieval, the dream-related occurrence of theta and gamma oscillations in both structures implies that coupled theta-gamma activity reflects the reactivation of emotional memories (Scarpelli et al., 2019). With regard to psychedelic and NDE-type states, this suggests that sequences of emotionally charged experiences induced by DMT and ayahuasca (those with autobiographical content as well as those with novel features) are correlated with coherent activity patterns in the delta/theta and gamma frequency bands involving the amygdala, the hippocampus, and experience-specific areas of the cortex.

To complete the picture, suppression of alpha waves has been identified as the most robust effect brought about by serotonergic psychedelics, as evidenced by a marked decrease in oscillatory alpha power and alpha-band coherence across the entire brain (Alamia et al., 2020; Pallavicini et al., 2021; Riba et al., 2004; Schenberg et al., 2015; Timmermann et al., 2019; Valle et al., 2016). The significant reduction in alpha power reaches its maximum within the key structures of the DMN, that is, the network that displays the most pronounced decline of alpha activity strongly overlaps with the DMN, causing a disruption of its integrity (Kometer et al., 2013; Pasquini et al., 2020), which is highly correlated with ego dissolution (Nour & Carhart-Harris, 2017; Tagliazucchi et al., 2016).

## 7.3 | Models of consciousness used to explain N,N-dimethyltryptamine and ayahuasca phenomenology

> "Behind the scientific community's unified facade are deep intellectual divergences, which are all the more important given that they are rarely expressed." - Jean-Marc Levy-Leblond (Ricard & Xuan Thuan, 2001).

In the academic and popular literature there are essentially two main approaches to interpreting the unusual reported subjective effects of DMT and ayahuasca such as entity encounters and perceiving alternate realities:
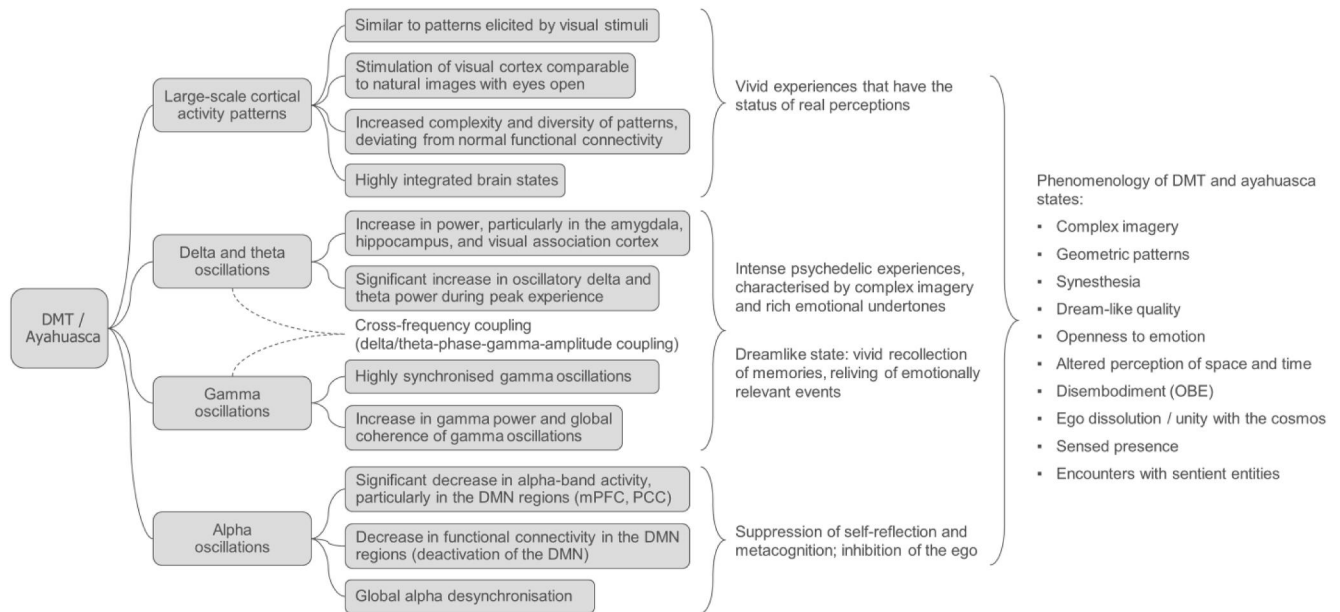
**FIGURE 7** Overview of contemporary understanding of the neural correlates of consciousness, activity features and organisational characteristics of the brain related to the administration of N,N-dimethyltryptamine and ayahuasca and their mapping onto the phenomenology of psychedelic states

1. The subjectively experienced events solely occur in the minds of the participants and are the product of biological processes in the brain: *This model appears to be supported by the majority of contemporary researchers.*

2. The subjective effects are based on the interaction with existing phenomena and can be attributed to the participants' consciousness becoming more receptive or attuned to alternate domains of existence which are not readily accessible during everyday waking consciousness. This approach includes the possibility that the person's brain, with its given neurophysiological constraints, acts as a form of filter that distorts or post-processes the information received through the interaction: *This 'field of consciousness' approach has been proposed by researchers who advocate that consciousness is embedded in the cosmic blueprint* (Frecska, Hoppál, & Luna, 2016; Grof, 2006; Keppler & Shani, 2020; Laszlo, 1995, 2007).

In the subsequent subsections we provide an overview of these two general approaches, followed by a critical assessment of the models. In order to fully explain the 'field of consciousness' approach and allow it to be given an accurate presentation and assessment, a representative of this school of thought, Joachim Keppler, was invited to co-author the article. This section of the review is unusual with regard to the intended explanatory depth as very few contemporary publications on the topic address the nature of consciousness itself and discuss the foundational mechanism of the genesis of the phenomenology of DMT and ayahuasca.

### 7.3.1 | Consciousness as an internal biological process model

The model that relies on an intimate link between consciousness and biological processes has a long tradition in the scientific community

(Place, 1956; Smart, 1959). In the more recent past, several subtypes of this interpretative approach have evolved, according to which consciousness is assumed to be associated with synchronously firing coalitions of neurons (Crick & Koch, 1990, 2003), with a dynamic core forming a transiently stable functional cluster of neurons (Tononi & Edelman, 1998), with recurrent processing (Lamme, 2006), with a dynamic process that can be quantified using measures of complexity (Seth et al., 2006), with a particular biological level of organisation that is realised in the brain (Revonsuo, 2006), or with the operational architectonics of brain organisation (Fingelkurts et al., 2013), to list some prominent representatives. Although this list is not exhaustive, it may be summarised that most neuroscientific approaches can ultimately be divided into two main camps. The first camp posits that consciousness is the final outcome of complex neural interactions, as reflected in the view that phenomenal states *emerge* from specific neural activity patterns, while the proponents of the second camp argue that phenomenal states *are identical with* specific neural activity patterns. Both schools of thought are founded on the conviction that the activity patterns constituting the NCC are not just observable concomitants of subjective experience in highly complex animals but, rather, the ultimate foundation of consciousness (Keppler & Shani, 2020).

In order to explain the hallucinations that the substances can elicit, it has been suggested that the mechanism of the frequent occurrences of entity encounters could be biological and DMT may modulate a region or regions of the brain involved in the perception of entities such as particular fundamental, or low-level, areas of the brain associated with the representation of humanoid beings; and/or psychological in which cortical regions associated with one's life experiences are stimulated (Rodriguez, 2007). Sleep paralysis has been associated with the perception of the presence of autonomous entities and has been used to explain other reported, not drug-induced, entity encounters (Clancy, 2005). Likewise, in dreams people perceive

the existence of seemingly free-thinking autonomous beings, typically humans, which generally appear to be real during dreaming, however, upon waking the individuals encountered in most dreams are believed to have not existed anywhere other than through fabrication of the mind. In schizophrenia and other forms of psychosis, patients often report the perception of seemingly real autonomous beings who communicate with them (de Vries et al., 2013). Proposed 'innate modules' of the brain with an evolutionary psychological basis including hyperactive agency detection, coupled with a hypothesised role for mirror neurons[2] have also been speculated as underlying psychedelic phenomenology including entity encounters (Barrett, 2000; Ernandes, 2013; Gardner, 2000; Pyysiäinen, 2009; Winkelman, 2017, 2018). Based on these examples, proponents of biological process models of consciousness argue that the human brain is capable of producing subjectively convincing experiences of free-thinking beings and other delusions that can be used to explain unusual phenomenology associated with DMT and ayahuasca (Branković, 2019; Peters et al., 2004; Winkelman, 2017, 2018).

### 7.3.2 | Ubiquitous field of consciousness model

> "There is obviously only one alternative, namely the unification of minds or consciousnesses."

> "For consciousness is absolutely fundamental. It cannot be accounted for in terms of anything else."

> - Erwin Schrödinger (Schrödinger, 1931, 1958)

As an antipole to the conventional biological process models, a new avenue to the scientific understanding of consciousness has been explored (Keppler, 2012, 2013, 2016, 2018, 2020, 2021; Keppler & Shani, 2020; Shani & Keppler, 2018). It accepts consciousness as ontologically fundamental, that is, an irreducible feature of ultimate reality, and is predicated on the hypothesis that the whole range of phenomenal nuances is inherent in the frequency spectrum of a ubiquitous background field. Following this line of thought, it is postulated that the brain employs a universal mechanism through which it taps into the phenomenal colour palette predetermined by the omnipresent field, thereby acquiring phenomenal qualities (Keppler, 2013, 2016, 2018; Keppler & Shani, 2020).

The rationale of the presented approach derives from stochastic electrodynamics (SED), a branch of physics that provides an in-depth understanding of quantum phenomena (de la Peña & Cetto, 1994, 1995, 1996, 2001, 2006; de la Peña et al., 2009, 2015), thus unveiling a deeper level of reality behind the formalism of quantum theory.

SED is based on the notion that the universe is permeated by a ubiquitous electromagnetic background field, termed *zero-point field* (ZPF), which in its ground state represents a maximally disordered ocean of activity with completely uncorrelated field modes. In summary, the crucial insight from SED is that the properties of quantum systems originate from the resonant interaction between the system components and the ZPF, with each system responding to a specific set of relevant field modes selectively filtered from the full frequency spectrum of the ZPF (de la Peña et al., 2015). In the event that the resonant system-ZPF interaction leads to the formation of a transiently stable attractor state, a partial organisation of the local field is established in such a way that the relevant ZPF modes for which the system exhibits a strong resonant behaviour become highly correlated (de la Peña & Cetto, 2006; de la Peña et al., 2009). On the part of the material system, the dynamic interplay with the ZPF leads to *long-range coherence* (de la Peña & Cetto, 2001). Viewed in this light, quantum systems acquire their properties by dynamically interacting with the ZPF and modulating its internal structure, with each coherent system state being accompanied by a partially ordered ZPF state, hereafter referred to as *ZPF information state*. Moreover, the finding that long-term memory is decisive for explaining the behaviour of quantum systems (de la Peña-Auerbach & Cetto, 1977) suggests the persistence of such ZPF information states.

As discussed in previous works, its unique properties make the ZPF a contender for the *ubiquitous field of consciousness*, just as the interaction and modulation mechanism underlying quantum systems qualifies as the universal mechanism that governs conscious systems (Keppler, 2012, 2016; Keppler & Shani, 2020). Accordingly, the undisturbed ZPF may be looked upon as an unstructured ocean of consciousness in which all conceivable shades of phenomenal awareness lie dormant in undifferentiated form. This gives rise to the conjecture that *each ZPF information state is associated with a specific conscious state*, resulting in the hypothesis that the recurring formation of transiently stable coherent states is an essential prerequisite for conscious systems (Keppler, 2013, 2016, 2018, 2020), which is well in accordance with empirical findings (Desmedt & Tomberg, 1994; Doesburg et al., 2009; Engel & Singer, 2001; Gaillard et al., 2009; Melloni et al., 2007; Rodriguez et al., 1999; Singer, 2015). In particular, the studies of Freeman and collaborators revealed that the neural correlates of waking consciousness can be equated with large-scale patterns of coherent gamma-band activity locked to the theta rhythm and that the rigorous explanation of these macroscopic activity patterns (attractors) requires the framework of quantum physics (Freeman, 2004, 2005, 2007, 2009; Freeman & Vitiello, 2006, 2007). From the vantage point of the SED-based model, each of these periodically occurring attractors is accompanied by an attractor-specific ZPF information state, implying that ultimately our streams of consciousness, and consequently all consciously perceived memory traces, are represented by sequences of ZPF information states (Keppler, 2018, 2020).

Building on this conceptual basis, the phenomenology of DMT and ayahuasca states will subsequently be discussed. To this end, we are following up on previous findings, according to which sequences

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[2]Mirror neurons: Brain cells that have the property of being activated when a person performs a particular motor movement, as well as when a person observes another person engaging in the same movement (Rizzolatti & Sinigaglia, 2016; Winkelman, 2017).

of experiences induced by DMT and ayahuasca are associated with coherent activity patterns exhibiting delta/theta-phase-gamma-amplitude coupling involving the amygdala, the hippocampus and experience-specific areas of the cortex (Alamia et al., 2020; Andino-Pavlovsky et al., 2017; Kometer et al., 2013; Pallavicini et al., 2021; Timmermann et al., 2019). As will become apparent, these findings are compatible with the SED-based interpretation of the NCC given above.

A consistent feature that characterises psychedelic states is the presence of a complex imagery manifesting itself in vivid geometric patterns shining with an intrinsic brightness, often accompanied by the perceptual phenomenon of synesthesia which arises when the activation of one sensory pathway leads to experiences in a second sensory pathway. Such phenomena can be attributed to the insight that psychedelics enhance the global brain connectivity across sensory areas (hyper-connectivity), resulting in increased excitability and cross-activation of adjacent regions of the cortical map (Hubbard et al., 2011; Luke, 2020).

Conscious states elicited by DMT and ayahuasca have dreamlike qualities with rich emotional undertones, part of the experiences being dominated by encounters with one's own deep-seated issues, while on the other hand novel experiences surface arising from one's previous experiences (Frecska, Bokor et al., 2016). As pointed out in the section on the neural correlates, hypotheses have been formulated according to which the specific activity patterns during dreamlike states are viewed as signatures indicating the reactivation of emotional memories (Kim et al., 2019; Langille, 2019; Scarpelli et al., 2019; Zhao et al., 2018), with the amygdala playing a central role as the 'final integration center of dream phenomena' (Lai et al., 2020). In the SED-based model, these activity patterns can be interpreted such that the amygdala, in concert with other brain areas, functions as a receiving unit or read head capable of accessing previously generated memory traces, represented by sequences of ZPF information states. The hypothesised operating principle of the receiving unit rests on the notion that a ZPF information state induces a resonant ZPF-neurotransmitter interaction that triggers the activation of receptors (Keppler, 2020, 2021). In this process, those nuclei and subareas of the amygdala are activated whose specific neurotransmitter and receptor profiles have the highest vibrational correspondence to the set of phase-locked ZPF modes that defines the ZPF information state. In this bottom-up process, the retrieved information is channelled to hippocampal and cortical regions, resulting in large-scale coherent oscillations and the formation of a multimodal conscious state (see Figure 8) (Alonso et al., 2015). The physiological findings and user reports suggest that these postulated mechanisms underlying dreamlike states are amplified by DMT and ayahuasca intake (Blake et al., 2019; Brito-da-Costa et al., 2020; Frecska, Bokor et al., 2016; Kraehenmann, 2017; Kraehenmann et al., 2017; Sanz et al., 2018; Solms, 2000; Strassman, 2001; Tafur, 2017; Vollenweider & Preller, 2020). It should be emphasised that these mechanisms are quite different from the mechanisms governing the retrieval of memory traces in the waking state. Intentionally initiated memory retrieval processes during

wakefulness rely on the alpha cycle involving the DMN (Knyazev et al., 2015; Sestieri et al., 2011; Sutterer et al., 2019). In dreamlike states, however, the DMN is largely deactivated, which leads to significantly reduced self-reflection and voluntary control (Pasquini et al., 2020). Instead, following the explanatory approach building on SED, the amygdala assumes the prominent role in extracting emotionally charged conscious states from the ZPF, which are projected directly to the sensory areas of the cortex, bypassing self-reflection.

In addition, under the influence of DMT and ayahuasca, profound spiritual (also referred to as peak, unitive, mystical, mystical-type and, as is highlighted in this article, henosis[3]) experiences can emerge, hallmarked by an altered perception of space and time, disassociation from the body, ego dissolution, a sense of entering into pure awareness and unity with the cosmos (Griffiths et al., 2019; James, 1902; James et al., 2020; Pallavicini et al., 2021; Stace, 1960; Strassman, 2001). In the light of the zero-point field hypothesis, this suggests that DMT and ayahuasca modify the receiving characteristics of the brain, allowing the receiving unit to resonate with a larger set of ZPF modes and to tap into a wider spectrum of the phenomenal colour palette furnished by the ZPF (Figure 9). In other words, a major effect of psychedelics consists in *opening the ZPF filter*, which under normal conditions is restricted to a narrow window of ZPF modes (Keppler, 2018), implying that henosis reflects an awareness of the unrestricted ground state of the zero-point field from which all physical matter and perspectival conscious selves are selectively restricted into existence (Keppler, 2012, 2018, 2020). Such a general description is consistent with interpretations in eastern contemplative traditions of such experiences which suggest a unified source of matter and consciousness and that consciousness pervades the universe (Carter, 2002; Dubashia, 2018; Lama, 2005; Ricard & Xuan Thuan, 2001).

Among the most remarkable phenomena triggered by DMT and ayahuasca are perceived encounters with sentient entities (Davis, Clifton et al., 2020). DMT and ayahuasca users sometimes report that they have the feeling of having entered or perceived parallel domains of existence (Cott & Rock, 2008; Luke et al., 2018; Strassman, 2001). Some of the 'invisible worlds' described are inhabited by alien beings capable of direct interaction and communication (Cott & Rock, 2008; Davis, Clifton et al., 2020; Frecska, Bokor et al., 2016; Luke, 2011, 2020; Luke et al., 2018; Michael et al., 2021; Strassman, 2001; Strassman et al., 2008). One explanatory framework for such phenomena lies in the proposition that these beings, whose identity remains speculative, exist (Frecska, Hoppál et al., 2016; Luke, 2011, 2020; Luke et al., 2018). The SED-based explanatory model lends

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[3] The word *henosis* (adjective: henotic), derived from the Ancient Greek word ἕνωσις, refers to unitive mystical-type union with fundamental reality and matches well the definition of subjective mystical experiences. Many words used in biology are derived from Latin and Greek and the use of such a word would be consistent with scientific terminology. Words such as 'spiritual' and 'mystical' are perhaps too open to interpretation with the concept of mystical experiences having been found to be an objection towards legislated psilocybin use (James et al., 2019; Jylkka, 2021; Sanders & Zijlmans, 2021). Consequently the use of an alternate word may be preferable. Henosis is less likely to be misinterpreted than the word 'peak' due to the latter's potential to be confabulated with intensity of drug action.
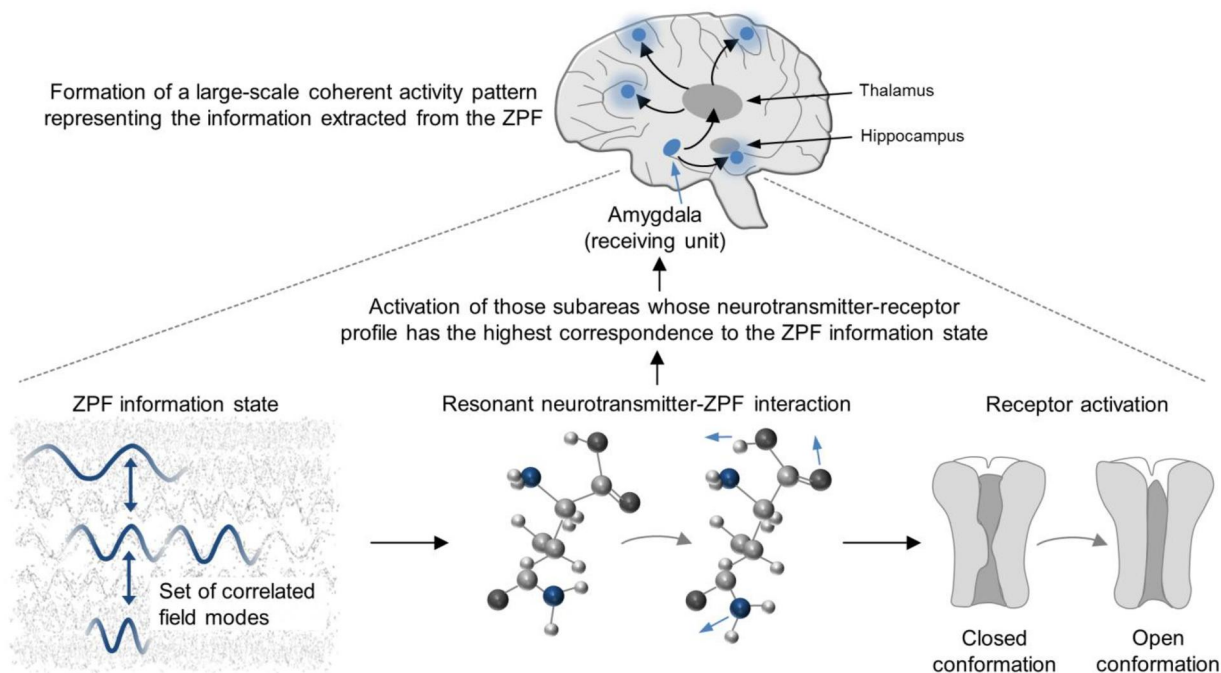
**FIGURE 8** Proposed general mechanism underlying the extraction of conscious states from the zero-point field (ZPF) in N,N-dimethyltryptamine, ayahuasca and dream states. The mechanism is based on the conception that the ZPF is the substrate of consciousness and that a particular conscious state is represented by a particular ZPF information state (i.e., by a set of correlated field modes). A ZPF information state induces a resonant interaction with neurotransmitter molecules (e.g. glutamate as shown here) that triggers the activation of receptors, driving the emergence of neuronal avalanches and the formation of a large-scale coherent activity pattern. This large-scale activity pattern represents the information extracted from the ZPF. In this bottom-up process, the amygdala is assumed to play the role of a central receiving unit and integration center, involving those subareas whose neurotransmitter-receptor profile has the highest correspondence to the ZPF information state. Note that this is a simplified model that is intended only to illustrate the basic principles of the process
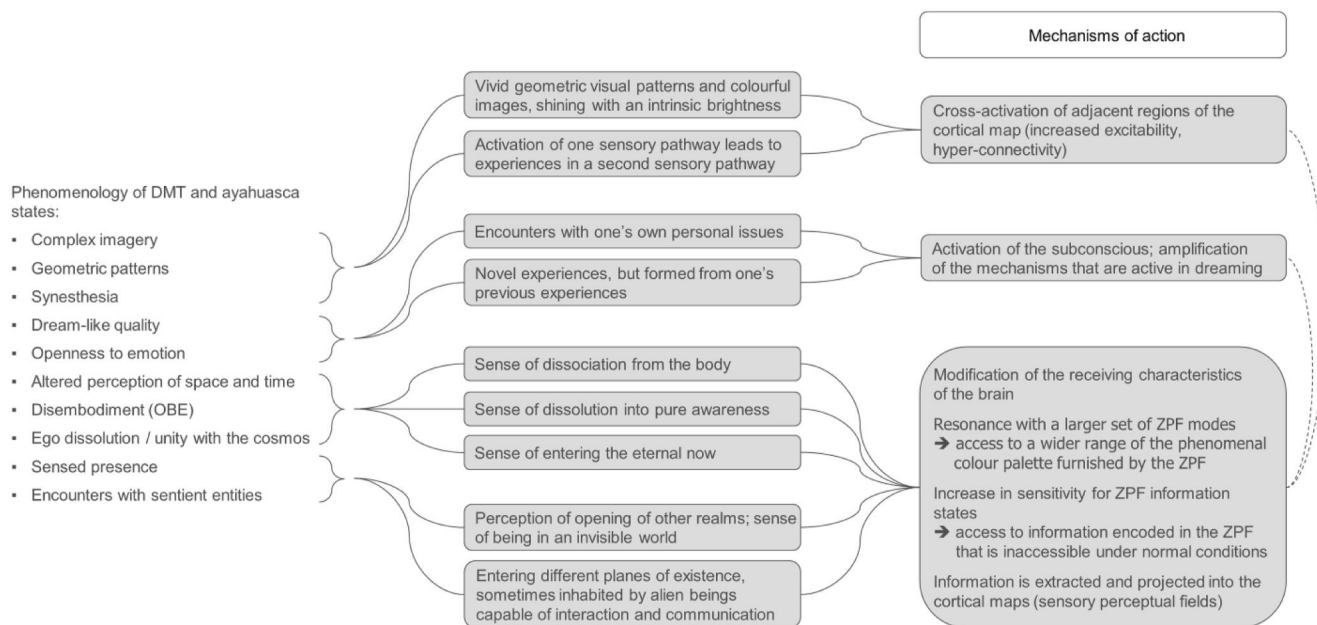


**FIGURE 9** Overview of the main phenomenological facets of psychedelic states and their mapping onto the proposed mechanisms of action based on the zero-point field hypothesis

support to this proposition by relying on the notion that all sentient entities continually generate ZPF information states preserved in the field (Keppler, 2018, 2020). From this perspective, it is conceivable that the ZPF, while respecting all the laws of physics, may be harnessed as a direct *communication channel* between conscious beings, provided that the beings are equipped with a suitable, highly

sensitive receiving unit which allows them to read the information states of other entities. These conditions may be fulfilled under the influence of DMT and ayahuasca, as these substances increase the excitability of neural networks and thus affect the hypothesised read mechanism such that the user gains access to information encoded in the ZPF that is inaccessible in the normal operating mode of the brain (dos Santos et al., 2016b). Additionally, according to the SED-backed approach, the ZPF functions as a cosmic repository of memory traces left by conscious entities (Keppler, 2018, 2020), which offers a possible basis of an explanation for occasional DMT and ayahuasca-induced phenomenological experiences of the sensed presence and perceived interaction with deceased beings (Frecska, Bokor et al., 2016; Frecska, Hoppál et al., 2016; Tafur, 2017).

### 7.3.3 | Critical analysis of different models of consciousness used to explain N,N-dimethyltryptamine and ayahuasca phenomenology

> "The existing scientific concepts cover always only a very limited part of reality, and the other part that has not yet been understood is infinite." - Werner Heisenberg (1958)

In the previous sections, two primary models used to explain the phenomenology of DMT and ayahuasca by contemporary researchers were presented. In this section we aim to critically assess the strengths and weaknesses of the models used to explain the subjective effects of the substances, taking into account the evidence that has been reviewed and the lucidity of the explanations of the models. The assessment of the models is based on criteria that are commonly used by philosophers of science to evaluate theories (Baker, 2016; Cartwright, 2004; Craver, 2002; Hempel, 1965; Salmon, 1984; Schulz, 2012; Schupbach & Sprenger, 2011; Ylikoski & Kuorikoski, 2010).

The first cluster of criteria examines the extent to which a model provides *insight into the nature of consciousness*. This can be judged, on the one hand, by whether the model is able to establish clarity about the psychophysical nexus, that is, the precise character of the connection between particular conscious states and particular neural activity patterns. Put another way, this aspect reflects the capability of a model to achieve a seamless integration of phenomenal qualities into the scientific worldview. On the other hand, the criterion looks at the *explanatory power* of a model. In this context, it is considered whether the model, regarding the formation of conscious states, offers convincing and logically interconnected cause-effect relationships, being indicative of the capability of a model to *unveil the mechanism* by which conscious states are produced or realised.

As previously discussed, the conventional model relies on an intimate link between consciousness and biological processes and is founded on the conviction that the activity patterns constituting the NCC are not just observable concomitants of subjective experience

in highly complex animals but, rather, the ultimate foundation of consciousness. The proponents of this model can ultimately be divided into two main camps. While the first camp posits that consciousness is the final outcome of complex neural interactions, as reflected in the view that phenomenal states *emerge* from specific neural activity patterns, the second camp argues that phenomenal states *are identical with* specific neural activity patterns (Seager, 1999).

It has long been pointed out that each of the two views is afflicted with an *explanatory gap*, due to the existence of general arguments against the phenomenal properties of a system being necessitated by purely structural or organisational principles, no matter what type of structure or organisation is involved (Chalmers, 1995, 1996; Levine, 1983; Shani & Keppler, 2018). This is reflected in the fact that the proponents of the emergence hypothesis have failed to specify an intelligible generation mechanism that explains the genesis of phenomenal qualities from purely physical (or chemical, or biological) properties. Therefore, it remains mysterious in which way a material system, however complexly it may be organised, could give rise to consciousness starting from insentience and what it is about neural activity patterns that 'suddenly switches consciousness on' (Velmans, 2007). The situation is no better for identity theorists who are faced with the challenge of presenting a conclusive and convincing model that explains 'why a *certain* level of functional description, or the functioning of a system described at *this* level, is appropriately *identified* with consciousness' (Seager, 1999). In summary, all models that regard biological processes as the source of consciousness run into the same core problem, namely the problem that regardless of the indisputable connection between consciousness and the brain, and notwithstanding the relevant neuroscientific evidence, the precise *nature* of this connection remains an open question (Keppler & Shani, 2020). This observation, which is known as the hard problem of consciousness, has led Tenzin Gyatso, also referred to as the Dalai Lama, the head of an organisation of which the direct study of consciousness is a prominent field of investigation, to conclude that 'despite tremendous success in observing close correlations between parts of the brain and mental states, I do not think current neuroscience has any real explanation of consciousness itself' (Lama, 2005), just as other researchers acknowledge contemporary science's inability to explain how consciousness can arise from what is generally believed to be insentient matter (Carter, 2002; Yaden et al., 2021).

While conventional biological process models cannot offer convincing explanations for consciousness, the approach based on the zero-point field hypothesis arguably circumvents the hard problem of consciousness and leads to more consistent interpretations of the NCC. This is achieved because in the latter model the organisational principles essential to conscious processes are not accountable for the generation of conscious awareness per se but, rather, for the modulation and selective restriction of a cosmic field of consciousness that is identified with the radiative background of quantum field theory (Laszlo, 1995; Shani & Keppler, 2018). The modulation mechanism underlying the formation of phenomenal states is

identical with the fundamental mechanism underlying quantum systems, resulting in the notion (see Figure 8) that a coherently oscillating neural cell assembly acquires its phenomenal properties by tapping into the universal pool of phenomenal nuances predetermined by the ZPF (Keppler & Shani, 2020), which is substantiated by a multitude of empirical findings that point to the significance of large-scale coherent activity patterns for the emergence of conscious states (Doesburg et al., 2009; Engel & Fries, 2016; Melloni et al., 2007; Rodriguez et al., 1999). On this basis, the ZPF-based model accomplishes to convey a clearer picture of the nature of consciousness, to the effect that experientiality is built into the fabric of the cosmos and that the universe is imbued with an inherently sentient medium, the extrinsic manifestation of which is physical and the intrinsic appearance of which is phenomenological (Keppler, 2021).

The second cluster of criteria addresses the ontological simplicity of a theory. The purpose of this cluster is to evaluate whether a model meets the *principle of parsimony*, which manifests itself in postulating one fundamental, species-independent causal mechanism. This principle is closely related to the *universality* of the postulated mechanism and includes an assessment to what degree a model is integrated into existing theories, that is, connected to a larger theoretical framework.

In terms of perceived simplicity, the biological process model, which views all conscious states as the final outcome of neural interactions, offers the supposedly most attractive explanation for the majority of researchers. Such an explanation does not require the acknowledgement that there may be more to reality and consciousness than has been measured to date. In this respect, it is often pointed out that consciousness research is well integrated into the overall framework of cognitive neuroscience (Crick & Koch, 1990, 2003; Lamme, 2006; Revonsuo, 2006; Seth et al., 2006; Tononi & Edelman, 1998). However, as already discussed, it is often overlooked that this framework has not yet brought forth any plausible and testable mechanism that could account for the phenomenal properties of conscious states. Moreover, the focus on known neural or biological mechanisms ignores the possibility that in the expanses of the cosmos conscious life forms could have developed that are independent of the structural underpinnings of conscious organisms on Earth, which is an argument against the universality of neuroscientific theories of consciousness, given that the ultimate ambition of a satisfying theory must be that its laws are 'universal, unrestricted and exceptionless' (Craver, 2002).

In contrast to conventional biological process models, the ZPF-based approach is built on the premise that conscious systems must be equipped with a fundamental modulation mechanism by means of which they are able to influence the internal structure of a ubiquitous field of consciousness. In conjunction with knowledge of the dynamical properties of the field, this premise can be used to derive distinctive features of the modulation mechanism that are in accord with empirical evidence (Keppler, 2013, 2018, 2020). The appeal of this approach lies in its adherence to the principle of parsimony, which is reflected in the idea that quantum systems acquire both their physical properties and their phenomenal qualities employing one and the same mechanism. A pivotal feature of this mechanism is its universality, in the sense that it is available throughout the universe and provides access to the ubiquitous substrate of consciousness. Due to its universality, the mechanism leads to a clear demarcation line between conscious and unconscious processes in such a way that the formation of transiently stable coherent states is an essential prerequisite for conscious awareness, which is supported by neuroscientific findings (Keppler, 2016, 2021).

The last group of criteria is specifically focused on the phenomenological peculiarities of DMT and ayahuasca-induced states, especially since the explanation of psychedelic states presents special challenges to models of consciousness. The task here is to assess how well a model deals with the subjective reports given by the drugs' users and whether a model is capable of explaining the different phenomenological aspects that are reported by the users.

By interpreting hallucinations simply as the result of an interaction of the drug molecules with the participant's biological processes (Winkelman, 2018), the conventional model offers what is at first sight thought to be the most straightforward explanation. However, taking the vast stock of first-person reports into account, it becomes clear that the model does not really explain any details of the experiences induced by DMT and ayahuasca (Strassman, 2001; Tafur, 2017). Most notably, there is one aspect related to dreamlike states in general and to psychedelic states in particular that poses an enormous hurdle to conventional explanations. While in conscious perception the stream of consciousness is triggered by the sensory organs and their interactions with the external world, the complex imagery induced by DMT, which unfolds when the user's eyes are closed, has the status of real perceptions, without stimuli being fed in from the environment. This raises the question of where the storyboard for these conscious experiences originates from, especially since the altered states of consciousness do not manifest themselves as disconnected flashes of awareness but predominantly as coherent sequences of events that appear highly realistic (Strassman, 2001). It is precisely this coherence which is difficult to reconcile with the idea that nothing but the presence of DMT molecules in the brain initiates the orchestration of neural processes, culminating in the choreography of long sequences of activity patterns and the generation of streams of consciousness. Furthermore, arguments based on mirror neurons and hyperactive agency detection would be applicable to hallucinations which have some form of resemblance to real-world events, however, many of the hallucinations elicited by DMT and ayahuasca have no resemblance to events which could realistically take place during the lives of either modern or prehistoric humanity (Davis, Clifton et al., 2020; Michael et al., 2021; Strassman, 2001; Tafur, 2017; Winkelman, 2017, 2018). As a consequence, in their current state, biological process models are not capable of providing a plausible explanation for the entirety of empirical findings.

Further drawbacks of the conventional approach to explaining DMT experiences include, on the one hand, the fact that the majority of individuals who report meeting beings and witnessing alternate realities, many of whom are university-educated high functioning

members of society, believe that they exist and are not the product of biological processes in their brain (Davis, Clifton et al., 2020; Griffiths et al., 2019; Michael et al., 2021), which is in contrast to most dream states. On the other hand, there is the consistency, or intersubjective verifiability, of reports by people having the same or similar experiences (Luke et al., 2018). Such allegedly independently verified reports include different people reporting meeting the same beings, shared visions/hallucinations and the attainment of verifiable knowledge which is unlikely to be previously present in the subconscious (Strassman, 2001; Strassman et al., 2008; Tafur, 2017). Accordingly, there is little explanation for how two people could have a shared vision or hallucination, or for past events in someone else's life to be correctly deduced as there is no physical basis for their minds to be linked or share any kind of connection. In biological process models, such phenomena would typically be explained by coincidence, intuition, confabulation and the fact that such stories are unverifiable anecdotes.

As demonstrated in the previous section, the ZPF-based model is able to provide arguably more plausible explanations for some of the core aspects of psychedelic states. According to this model, a major effect of psychedelics is posited to consist in modifying the receiving characteristics of the brain and opening the ZPF filter, which allows the receiving unit to resonate with a larger set of ZPF modes and is seen as the underlying cause of profound henosis or mystical-type experiences (Keppler, 2018). Furthermore, since DMT and ayahuasca increase the excitability of neural networks (dos Santos et al., 2016b), it is assumed that the hypothesised read mechanism is significantly affected (Keppler, 2018, 2020), causing the user to gain access to ZPF information states that have been generated by other conscious entities, thus offering a possible explanation for the sensed presence and perceived interaction with sentient beings. Apart from these very general lines of thought, however, many details remain to be clarified. Representative of the numerous open issues is, for example, the question as to why a person senses only certain entities and how specific entities are selected for interaction.

As far as the comparison of the models is concerned, it can be summarised that the field of consciousness approach, whilst speculative, has greater potential than biological process models in explaining the experience accounts given by the drugs' users. This can be attributed to the ZPF-based model proposing a universal mechanism for the formation of all types of conscious states, which provides a rudimentary explanation for the reported features of psychedelic states, while in biological process models there is no conceptual basis for how the reported experiences are generated and from where they would derive. Accordingly, regarding the understanding of psychedelic states, the field of consciousness model more closely meets the requirements formulated by other researchers, namely that 'any complete theory will likely also require a deep consideration of the ontological and philosophical perspectives regarding the hard problem of consciousness and not just neurocognitive viewpoints' (Luke, 2020). In particular, the model proposed by Keppler and Shani (2020) could be looked upon as a refinement of a more general explanatory approach, as proposed by

researchers including Ede Frecska and Ervin Laszlo, that refers to the zero-point field (also known as the Akashic field) as a cosmic matrix, views sentient beings as specific information-bearing structures in this matrix, and considers the induction of psychedelic states as the result of an integrative information-gaining process (Grof, 2006; Luke et al., 2018; Strassman et al., 2008). At the present time, however, all such models are at a preliminary and very elementary stage of development (Frecska, Hoppál et al., 2016; Keppler, 2021; Laszlo, 2007; Luke et al., 2018; Strassman et al., 2008). This leads to the conclusion that there is considerable work to be done and that, from an empirical point of view, none of the existing models is sufficiently supported by experimental evidence (Swanson, 2018).

### 7.3.4 | Future research avenues

From the discussion of the explanatory approaches it has become clear that there is a wide range of different perspectives within the research community. In order to achieve greater consensus and certainty among the researchers, projects are needed that strictly follow the scientific process of knowledge acquisition and are guided by the principles of repeatability and reproducibility. In particular, the focus of future research efforts must be on elucidating the mechanisms underlying conscious states, which will enable falsification of some of the circulating theories of consciousness and narrow down the search space for a fundamental theory of consciousness. The systematic study of psychedelic states can make a significant contribution to this endeavour.

From the viewpoint of field theories of consciousness, the research agenda can be divided into physical, neurochemical, neurophysiological and phenomenological avenues of collecting evidence. While at the basic physical level the crucial point is to demonstrate the modulation of the ZPF during conscious states, the initiatives at the neurochemical and neurophysiological level are primarily concerned with the exploration of the neurotransmitter-ZPF interface and the derivation of theoretical predictions about the dynamical characteristics of the NCC that, provided they are empirically confirmed, lend further support to the notion of the ZPF being instrumental in the formation of the activity patterns constituting the NCC (Keppler, 2021).

These research directions, which concentrate on the objectively observable aspects of conscious states, should be complemented by systematic studies of first-person accounts. In principle, there are a lot of anecdotes which could be used to support the field of consciousness approach, such as ayahuasca visions apparently eliciting verifiable information including the location of missing objects or people, and external events that have taken place, that are taking place or are yet to take place (Frecska, Hoppál et al., 2016; Luke et al., 2018; Strassman et al., 2008; Tafur, 2017). However, there is currently a lack of rigorous well-controlled studies with statistically significant results, which is why this approach cannot be accepted as correct without further investigation.

In classical eastern experiential studies of consciousness, investigators adhere to the following scientific methodology (Lama, 2005): 'All meditatively valid subjective experiences must be verifiable both through repetition by the same practitioner and through other individuals being able to attain the same state by the same practice. If they are thus verified, such states may be taken to be universal, at any rate for human beings.' Possible future studies could involve experienced meditators knowledgeable in taking such an approach, based on first-hand experience, to the study of DMT and ayahuasca states. Such studies could, in theory, yield statistically significant results using validated questionnaires with empirical findings subjected to statistical analyses as is typical in contemporary psychological research methods (Winkelmann, 2018).

Experienced meditators who can reportedly elicit spontaneous near death-type experiences and henosis (mystical experiences) could, hypothetically, investigate how DMT and ayahuasca occasioned henosis and near death-type experiences compare (Van Gordon et al., 2018). Recent research has demonstrated the neural correlates of henosis and near death-type experiences, and demonstrating being able to induce these states in non-drug conditions as detected via brain imaging could aid in participant recruitment (Pallavicini et al., 2021). Such studies would also be applicable to people who report having had conventional near-death and spontaneous henosis experiences.

Blinded cross-cultural studies in DMT and ayahuasca naive participants could be conducted to investigate the alleged intersubjective verifiability of unusual phenomenology such as entity encounters. Additionally, target-controlled intravenous infusions of DMT could be conducted for a prolonged immersive DMT psychedelic experience in experimental settings, and such experimental conditions could aid studies to further elucidate the mechanisms (e.g., using brain imaging techniques) and assess the alleged intersubjective verifiability using psychological research methods (Gallimore & Strassman, 2016; Luke et al., 2018).

## 8 | INTEGRATION WITH CONTEMPORARY MEDICINE

### 8.1 | N,N-dimethyltryptamine

The consumption of psychoactive quantities of DMT has been found to be both psychologically and physically risky for certain susceptible individuals with the risk of dangerously elevated heart rate and blood pressure, and possible cardiac arrest (Bilhimer et al., 2018; Strassman, 2001; Strassman & Qualls, 1994). Furthermore, some of the subjective effects can be traumatising in certain cases (Strassman, 2001). Therefore, when consumed in non-controlled settings without adequate preparation, support and integration, DMT could potentially present risks to the user (Strassman, 2001).

It has been proposed that DMT could be used to treat disorders modulated by DMT sigma-1 receptor agonism such as inflammation, ischemia and cancer (Szabo et al., 2021); however, DMT's potential endogenous roles in these processes are not well understood and neither is the potential role for exogenously administered DMT in treating these conditions (Barker, 2018a; Nardai et al., 2020; Nemes et al., 2019; Szabo & Frecska, 2016). DMT could be applicable to the treatment of neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's) due to DMT's anti-inflammatory and neurogenesis promoting properties but such applications are speculative (Brito-da-Costa et al., 2020; dos Santos et al., 2019b; Frecska, Bokor et al., 2016; Nardai et al., 2020; Penke et al., 2017). Other non-psychedelic uses include microdosing DMT which may have antidepressant and creative performance-enhancing potentials, however, most reports are anecdotal and such research is preliminary and further research is required (Cameron et al., 2019; Kuypers et al., 2019).

The 'ontological shock' caused by DMT has been hypothesised as leading to increased psychological flexibility, which has in turn been demonstrated to be associated with positive alterations in mental wellbeing (Davis, Barrett and Griffiths, 2020; Davis, Clifton et al., 2020). Thus, the radical shift in perception of the functioning of the cosmos as induced by DMT could possibly be utilised in psychiatric treatments. Unitive mystical-type experiences or henosis appear to be less predictably inducible on DMT than in psilocybin sessions, therefore psilocybin is presumably a more reliable catalyst for these kinds of psychotherapeutic processes (James et al., 2020; Strassman, 2001). Nonetheless, in Strassman's studies, in spite of using DMT, some participants had personally meaningful healing experiences despite being in an un-aesthetically pleasing clinical setting which suggests possible applications for hospitalised patients (Strassman, 2001).

### 8.1.1 | Near-death experience model in palliative care

> "I think the high dose is like death trauma. It knocks you out of your body. I could have tolerated death or some major physical leaping-out-of-this-plane type of experience under DMT. This would be a good drug for people in a hospice program or the terminally ill to have some acquaintance with." (Strassman, 2001).

During the process of dying, surges in the coherence and connectivity within the brain have been detected (Borjigin et al., 2013). Such observations have been used to suggest a correlation relationship between such brain activity and near-death experiences. It is well reported in the scientific literature that many people who have been determined to be clinically dead or otherwise on the cusp of death report out of body experiences, a sense of harmony and sequences of events which can include entering a white light (Long, 2014; Martial et al., 2017; Parnia et al., 2001; Potts, 2002; Schwaninger et al., 2002). Whilst it is not within the scope of the article to discuss in detail the mechanisms of such events, there is

consensus among the scientific community that many people do report such experiences after having been in a transitory near-death state (Britton & Bootzin, 2004; Greyson, 2003; Thonnard et al., 2013). Additionally, whilst not the focus of this article, it is worth highlighting that some established researchers in the physical, biomedical and psychological sciences support some form of non-entirely illusory model of the experiences, including such research being published in the medical journal *The Lancet* (Alexander, 2012; Long, 2014; Moody, 1988; Tucker, 2009; van Gordon et al., 2018; van Lommel et al., 2001); which are likewise offset by other researchers in the same fields who disagree with any possibility of such reports having any non-illusory nature (Bardi, 2002; Borjigin et al., 2013; Bryant, 2018; Saver & Rabin, 1997). As such, there are some similarities between the state of discourse on explaining DMT phenomenology and that of near-death experiences.

Anecdotal reports and studies have suggested that DMT can act as a model for near-death experiences (Strassman, 2001; Timmerman et al., 2018). Endogenous release of DMT during dying has been proposed as being a cause of the phenomenology of near-death experiences (Dean et al., 2019; Strassman, 2001), although many other potential neurochemical contributory factors have been highlighted (Greyson, 2003; Martial et al., 2019; Nichols, 2017). As a result, it has been proposed that administered DMT could be useful in palliative care for patients who wish to become more familiar with the subjective experience of the process of dying and alleviate death anxiety (Martial et al., 2019; Strassman, 2001). However, it is not clear how to prepare someone to have a classic near death-type experience instead of personal or invisible world entity encounter experiences as it is reportedly not facile for consumers of DMT to influence the subjective effects (Strassman, 2001). Rick Strassman attempted to advise people how to 'navigate the DMT realm' but many participants had experiences which were simply bizarre and had no similarity to classic mystical or near-death experiences (Strassman, 2001). Thus, such a role for DMT in palliative care would require well supported and controlled studies, as has been the case for psilocybin, to determine whether DMT could be used in such a novel psychiatric treatment (James et al., 2020; Yaden et al., 2020).

## 8.2 | Ayahuasca

For most people, consuming ayahuasca is physiologically low-risk with milder reported cardiovascular effects than intravenous DMT (Bilhimer et al., 2018; Dominguez-Clave et al., 2016). However, generally accepted contraindications for ayahuasca use include cardiovascular problems such as coronary artery disease (as ayahuasca consumption can trigger a heart attack or stroke), endocrine problems, abnormal lipid metabolism, glaucoma, fever and pregnancy (Degan, 2016; Frecska, Bokor et al., 2016; Strassman, 2001; Tafur, 2017). As with other psychedelics, ayahuasca can cause anxiety but this can typically be mitigated with adequate verbal support and preparation (Dominguez-Clave et al., 2016). In rare cases, long-lasting psychotic symptoms have been associated with ayahuasca

use and, in a case report, a patient suffering from schizophrenia was arrested and hospitalised due to a negative reaction to ayahuasca and dangerous behaviour, which adds weight to the general perception that such patients are at higher risk of adverse effects to psychedelics in general (Bilhimer et al., 2018; Carhart-Harris, 2013; Dominguez-Clave et al., 2016; dos Santos & Strassman, 2011; James et al., 2020). Furthermore, in other case reports, an individual with no personal or family history of psychosis experienced psychosis elicited by ayahuasca which may have been exacerbated or catalysed by regular and concomitant cannabis use - although the influence, if any, of cannabis is unknown (dos Santos & Strassman, 2011); and an individual with bipolar disorder taking part in an ayahuasca ceremony resulted in a manic episode (Szmulewicz et al., 2015). In addition, there is a risk of drug-drug interactions between the MAOIs in ayahuasca and serotonergic medications resulting in serotonin toxicity (Bilhimer et al., 2018; Brito-da-Costa et al., 2020; Dominguez-Clave et al., 2016). Thus, these examples demonstrate the need for screening and sufficient preparation prior to ayahuasca sessions as some people with underlying health conditions including a personal or family history of psychosis are at greater risk (dos Santos et al., 2017; Frecska, Bokor et al., 2016). However, regular use in healthy individuals has not been associated with deterioration of mental health or cognitive function and incidences of psychosis in ayahuasca users are reported to occur in less than 0.1% of consumers (Bouso et al., 2012; dos Santos et al., 2016a).

After consuming ayahuasca in traditional Amazonian healing practices, post-ayahuasca integration sessions and long-term behavioural change are needed to facilitate maintained healing and wellbeing (Frecska, Bokor et al., 2016; Tafur, 2017). However, as ayahuasca is currently illegal in most developed countries, many people need to travel to the Amazonian region to experience ayahuasca with integration and behavioural change needing to take place in their usual country of residence. Currently, although the number of professionally trained psychedelic therapists is growing, professional psychiatric assistance for the integration is effectively non-existent in most countries as there are very few therapists trained in managing ayahuasca experiences. As the number of people seeking ayahuasca ceremonies has seen a steady increase, the need for an availability of professional post-ayahuasca services is becoming more pressing (Frecska, Bokor et al., 2016). Therefore, post-Amazon integration sessions with trained psychiatric specialists would likely need to be incorporated into any long-term global ayahuasca treatment program.

As with other psychedelics, set and setting are major factors in ayahuasca experiences and must be well controlled for in clinical applications (Barbosa et al., 2005; Hartogsohn, 2016). Ayahuasca therapies would require adequate screening, preparation, monitoring during the experience and integration sessions (Brito-da-Costa et al., 2020; dos Santos et al., 2017). Monitoring during the session is important to ensure safety as well as efficacy as greater likelihood of long-term psychological harm from ayahuasca use is reported when used in unsupervised settings (Brito-da-Costa et al., 2020; dos Santos et al., 2017). Whilst set and setting is important in ayahuasca therapy,

ayahuasca-based treatments have been shown to be possible in jungle, urban and clinical environments which suggests applicability to locations and cultures outside the Amazon with adequate preparation, supervision and follow up (Fabregas et al., 2010; Palhano-Fontes et al., 2019). Ayahuasca is usually used in groups and the supportive community environment likely plays an important role in the overall efficacy of ayahuasca medicine (dos Santos et al., 2021; Frecska, Bokor et al., 2016). Such supportive communal environments are understood to often be helpful in overcoming addiction (Frecska, Bokor et al., 2016). Consequently, if ayahuasca is to be introduced into conventional medical practices, the community and interpersonal aspects of ayahuasca retreats should likely be incorporated into the therapy in many treatments.

Although recent studies suggest a potential role for ayahuasca in the treatment of psychiatric disorders such as depression, such studies are preliminary and larger well-controlled, randomised, blinded studies need to be conducted as the evidence so far is mainly anecdotal, observational and based on small preclinical studies (dos Santos et al., 2019; Orsolini et al., 2020; Rodrigues et al., 2021; Yaden and Griffiths, 2021). Ayahuasca could possibly be used to treat very care cases of individuals with a disorder called aphantasia who perceive no visual imagery associated with cognitive processes such as memory, dreaming and imagination although no clinical studies have been conducted for this application (dos Santos et al., 2018).

Ayahuasca sessions could be complemented with meditation and mindfulness interventions to improve therapeutic clinical outcomes by helping to reduce anxiety and avoidant responding during the experience and help to maintain and cultivate the psychotherapeutic benefits after the experience (Barrett & Griffiths, 2018; Fox et al., 2016; Payne et al., 2021; Williams & Penman, 2011). Ayahuasca could additionally be used prophylactically and in positive psychology interventions in healthy individuals due to the many reported benefits of ayahuasca use including reduced ratings of hopelessness, improved neurocognitive function and an association with positive personality attributes (Brito-de-Costa et al., 2020; Gonzalez et al., 2021; James et al., 2020; Kočárová et al., 2021; Netzband et al., 2020).

Whilst there are many reports of successful therapeutic experiences by people who journey to the Amazon to take part in ayahuasca healing ceremonies, there is no form of regulatory oversight by the established medical field. There have been reports of traumatised individuals, such as victims of rape, being sexually abused by ayahuasqueros in the Amazonian region (Maybin & Casserly, 2020). Currently, people who wish to travel to the Amazon to be healed must conduct their own research into the treatment centers or certain practitioners are recommended by referral from a friend or online forum. This system is suboptimal and can lead to poor therapeutic outcomes and, in extreme cases, extortion and abuse (Gonzalez et al., 2021). Therefore, greater integration between the established medical healthcare profession and reputable practitioners in the Amazon will ultimately be required to provide an acceptable level of safety and efficacy.

For practical purposes, for patients to experience authentic Amazonian healing practices, it might be preferable to have a health service-approved list of healing centers that doctors can recommend. However, it would be difficult to generate an official list that governmental national health services might approve of. Therefore, it may be more practical for such referrals to be conducted via private healthcare organisations. It would be challenging to develop a series of criteria that Amazonian ayahuasca centers could adhere to and prove that they meet without adding unnecessary pressure and bureaucracy. However, due to the potential for abuse and poor therapeutic outcomes, if Amazonian healing is to be integrated with modern healthcare systems then safety and efficacy criteria would have to be met and some kind of regulatory oversight would need to be established. If patients are travelling from countries such as the UK to Latin America, organisations such as *Santo Daime* or *União do Vegetal* would introduce religious ideas and doctrines which will likely cause problems with patients, and it is therefore probably inadvisable to recommend these organisations as places to undergo therapy. Due to the interpersonal psycho-spiritual nature of ayahuasca, and psychedelics' potential induce psychological alterations in perceptions of reality which can often include changes from 'materialist' to more 'panpsychist' perspectives, great care needs to be taken to maintain professional boundaries and for practitioners to not introduce unverified beliefs to the patients (Johnson, 2020; Timmermann et al., 2021).

Potentially, in the long-term, if ayahuasca is to be integrated fully into international medical systems, practitioners to be based outside the Amazon should be trained medical doctors, psychiatrists or psychologists who could specialise and receive complementary training in the Amazon. Medical doctors and psychiatrists could train in the Amazonian region with groups such as the Shipibo-Conibo, the Tukano, the Kamsa, and the Huitoto who have been asserted as being Amazonian equivalents of institutions such as Oxford, Cambridge and Harvard (Narby, 1998). Proficiency in Spanish and/or Portuguese, and a willingness to learn indigenous languages, will likely be a prerequisite for medical practitioners undergoing training in the Amazon to specialise in ayahuasca medicine. Regarding ayahuasca use outside the Amazon, as some of the components of ayahuasca can degrade during storage, transportation of the materials from the Amazon to other countries will likely lead to problems regarding quality. Growing the plants in the country where the session is to take place and the plant materials being fresh is likely to be important in ensuring quality (de Oliveira Silveira et al., 2020). However, freeze-dried ayahuasca can be safely administered with the desired effects (dos Santos et al., 2020). Ultimately, integration of Amazonian medical practices to countries such as the UK is inherently challenging but worthwhile and interesting.

## 9 | CONCLUSIONS

DMT and ayahuasca, could form the basis for a number of new therapies to treat disorders which are not always served by contemporary western medicine such as certain psychiatric and psychoneuroendocrine pathologies. However, the evidence base for

such treatments in many cases is at this stage anecdotal and further investment in research would be required in order to develop treatments which can be made available to the general public by the conventional Food and Drug Administration and European Medicines Agency approval routes. A change of Schedule from Schedule 1, acknowledging potential medical applications of DMT is justifiable at this point and such a change in Schedule would facilitate further medical studies (dos Santos et al., 2021). As is the case with cannabis (James et al., 2021) and psilocybin (James et al., 2020), the investment route is challenging due to the compounds being natural products and the lack of financial incentive for private companies to conduct such research as a result of this (dos Santos et al., 2021). Patenting of ayahuasca as it is consumed in the Amazon, whilst being legally difficult, would also be highly ethically questionable and represent a form of 'biopiracy' that should not be pursued by the pharmaceutical industry (Frecska, Bokor et al., 2016). However, such a legal stance highlights the financial challenges associated with integrating ayahuasca with western-style medicine. As an alternative to conventional approval as a medicine, ayahuasca could receive legal approval on religious grounds via a religious exemption, as has happened in the US for mescaline-containing cacti in certain religious organisations, but such a system would inevitably bring with it numerous uncertainties including safety and efficacy concerns when applied to people diagnosed with a medical disorder. Therefore, approval and assimilation within legal medical frameworks remains the optimal solution for the treatment of medical conditions.

As stated in the introduction, we have attempted to be critical yet open-minded in our discussion of DMT and ayahuasca. However, from review of the available literature it appears that the mechanisms underlying the subjective effects of DMT and ayahuasca remain largely unanswered by contemporary science. The role and relative significance of endogenous DMT in the functioning of humans and other organisms is not understood and consequently how exogenously administered DMT differs in its mechanism of action is likewise not clear. Regarding the phenomenology, the standard biological models of consciousness, which posit that conscious states emerge from or are identical with specific neural activity patterns, were found to be lacking in their explanatory power. The field of consciousness models discussed in this article provide arguably more plausible explanations for many of the core aspects of DMT and ayahuasca states and, hence, may be more convincing to those who adhere to commonly accepted evaluation criteria for theories; however, whilst conceptually intriguing and comparatively coherent, such models have not been verified in well-designed and controlled studies as neuroscientific studies have thus far only yielded superficial observations regarding receptor binding and alterations in brain function. The phenomenology of DMT and ayahuasca experience leads to questions on the nature of consciousness, consensus material reality and mechanisms in medicine (Strassman, 2001; Tafur, 2017; Timmermann et al., 2021). Until a general consensus is reached among the scientific community, backed by a solid base of empirical model tests, the fundamental nature of the mechanisms of action of DMT and ayahuasca will remain unexplained.

## CONFLICT OF INTEREST

Dr Sessa is Chief Medical Officer of Awakn Life Sciences and has authored and co-authored several books on psychedelics.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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## REFERENCES

Aghajanian, G. K., & Marek, G. J. (1997). Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropharmacol*, *36*, 589–599.

Agurell, S., Holmstedt, B., & Lindgren, J. E. (1968). Alkaloid content of Banisteriopsis rusbyana. *The American Journal of Pharmacy*, *140*(5), 148–151.

Alamia, A., Timmermann, C., Nutt, D. J., VanRullen, R., & Carhart-Harris, R. L. (2020). DMT alters cortical travelling waves. *eLife*, *9*, e59784. https://doi.org/10.7554/eLife.59784

Alexander, E. (2012). *Proof of heaven: A neurosurgeon's journey into the afterlife*. Piatkus.

Alonso, J., Romero, S., Mañanas, M., & Riba, J. (2015). Serotonergic psychedelics temporarily modify information transfer in humans. *International Journal of Neuropsychopharmacology*, *18*, 1–9. https://doi.org/10.1093/ijnp/pyv039

Andino-Pavlovsky, V., Souza, A. C., Scheffer-Teixeira, R., Tort, A. B. L., Etchenique, R., & Ribeiro, S. (2017). Dopamine modulates delta-gamma phase-amplitude coupling in the prefrontal cortex of behaving rats. *Frontiers in Neural Circuits*, *11*(29), 1–13.

Baker, A. (2016). Simplicity. In E. N. Zalta (Ed.), *The stanford Encyclopedia of philosophy* (Winter 2016 Edition). https://plato.stanford.edu/archives/win2016/entries/simplicity/

Barbosa, P. C. R., Giglio, J. S., & Dalgalarrondo, P. (2005). Altered states of consciousness and short-term psychological after-effects induced by the first time ritual use of ayahuasca in an urban context in Brazil. *Journal of Psychoactive Drugs*, *37*(2), 193–201.

Barbosa, P. C. R., Tófoli, L. F., Bogenschutz, M. P., Hoy, R., Berro, L. F., Marinho, E. A. V., Areco, K. N., & Winkelman, M. J. (2018). Assessment of alcohol and tobacco use disorders among religious users of ayahuasca. *Frontiers in Psychiatry*, *9*, 136. https://doi.org/10.3389/fpsyt.2018.00136

Barco, A., Bailey, C. H., & Kandel, E. R. (2006). Common molecular mechanisms in explicit and implicit memory. *Journal of Neurochemistry*,

97(6), 1520–1533. PMID: 16805766. https://doi.org/10.1111/j.1471-4159.2006.03870.x

Bardi, A. H. (2002). Near death experiences. *The Lancet, 359*(9323), 2116–2117. https://doi.org/10.1016/S0140-6736(02)08926-2

Barker, SA. (2018a). N, N-dimethyltryptamine (DMT), an endogenous hallucinogen: Past, present, and future research to determine its role and function. *Frontiers in Neuroscience, 12*(536), 1–17.

Barker, SA. (2018b). N,N-dimethyltryptamine facts and myths. *Journal of Psychopharmacology, 32*(7), 820–821. https://doi.org/10.1177/0269881118767648

Barker, S. A., Borjigin, J., Lomnicka, I., & Strassman, R. (2013). LC/MS/MS analysis of the endogenous dimethyltryptamine hallucinogens, their precursors, and major metabolites in rat pineal gland microdialysate. *Biomedical Chromatography, 27*, 1690–1700. https://doi.org/10.1002/bmc.2981

Barker, S. A., McIlhenny, E. H., & Strassman, R. (2012). A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955-2010. *Drug Testing and Analysis, 4*(7–8), 617–635. Epub 2012 Feb 28. PMID: 22371425. https://doi.org/10.1002/dta.422

Barker, S. A., Monti, J. A., & Christian, S. T. (1981). N,N-Dimethyltryptamine: An endogenous hallucinogen. In *International review of neurobiology* (pp. 83–110). International Review of Neurobiology. https://doi.org/10.1016/s0074-7742(08)60291-3

Barr, H. L., Langs, R. J., Holt, R. R., Goldberger, L., Klein, L., & George, S. (1972). *LSD: Personality and experience.* John Wiley.

Barrett, F. S., & Griffiths, R. R. (2018). Classic hallucinogens and mystical experiences: Phenomenology and neural correlates. *Current Topics in Behavioral Neurosciences, 36*, 393–430. PMID: 28401522; PMCID: PMC6707356. https://doi.org/10.1007/7854_2017_474

Barrett, J. (2000). Exploring the natural foundations of religion. *Trends in Cognitive Sciences, 4*(1), 29–34. https://doi.org/10.1016/S1364-6613(99)01419-9

Barsuglia, J., Davis, A. K., Palmer, R., Lancelotta, R., Windham-Herman, A.-M., Peterson, K., Polanco, M., Grant, R., & Griffiths, R. (2018). Intensity of mystical experiences occasioned by 5-MeO-DMT and comparison with a prior psilocybin study. *Frontiers in Psychology, 9*(2459), 6.

Bilhimer, M. H., Schult, R. F., Higgs, K. V., Wiegand, T. J., Gorodetsky, R. M., & Acquisto, N. M. (2018). Acute intoxication following dimethyltryptamine ingestion. *Case Reports in Emergency Medicine, 2018*, 1–3. vol. 2018, Article ID 3452691, 3 pages. https://doi.org/10.1155/2018/3452691

Bird, A. (2007). Perceptions of epigenetics. *Nature, 447*(7143), 396–398.

Blake, Y., Terburg, D., Balchin, R., van Honk, J., & Solms, M. (2019). The role of the basolateral amygdala in dreaming. *Cortex, 113*, 169–183.

Borjigin, J., Lee, UnC., Liu, T., Pal, D., Huff, S., Klarr, D., Sloboda, J., Hernandez, J., Wang, M. M., & Mashour, G. A. (2013). Surge of neurophysiological coherence and connectivity in the dying brain. *Proceedings of the National Academy of Sciences, 110*(35), 14432–14437. https://doi.org/10.1073/pnas.1308285110

Bouso, J. C., Gonzalez, D., Fondevila, S., Cutchet, M., Fernandez, X., Ribeiro Barbosa, P. C., Alcazar-Corcoles, M. A., Araujo, W. S., Barbonoj, M. J., Fabregas, J. M., & Riba, J. (2012). Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of ayahuasca: A longitudinal study. *PLoS One, 7*, e42421.

Bouso, J. C., Palhano-Fontes, F., Rodríguez-Fornells, A., Ribeiro, S., Sanches, R., Crippa, J. A. S., Hallak, J. E. C., de Araujo, D. B., & Riba, J. (2015). Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. *European Neuropsychopharmacology, 15*, 483–492.

Bowers, M. E., & Yehuda, R. (2016). Intergenerational transmission of stress in humans. *Neuropsychopharmacology, 41*(1), 232–244. https://doi.org/10.1038/npp.2015.247

Branković, M. (2019). Who believes in ESP: Cognitive and motivational determinants of the belief in extra-sensory perception. *Europe's Journal of Psychology, 15*(1), 120–139. Published 2019 Feb 28. https://doi.org/10.5964/ejop.v15i1.1689

Brito-da-Costa, A. M., Dias-da-Silva, D., Gomes, N. G. M, Dinis-Oliveira, R. J., & Madureira-Carvalho, Á. (2020). Toxicokinetics and toxicodynamics of Ayahuasca alkaloids N,N-Dimethyltryptamine (DMT), harmine, harmaline and tetrahydroharmine: Clinical and forensic impact. *Pharmaceuticals, 13*, 1–36.

Britton, W. B., & Bootzin, R. R. (2004). Near-death experiences and the temporal lobe. *Psychological Science, 15*(4), 254–258. PMID: 15043643. https://doi.org/10.1111/j.0956-7976.2004.00661.x

Brouwer, A., & Carhart-Harris, R. L. (2020). Pivotal mental states. *Journal of Psychopharmacology, 35*, 319–352. https://doi.org/10.1177/0269881120959637

Bryant, B. (2018). A DMT trip feels like dying - and scientists now agree. BBC. Article found at: https://www.bbc.co.uk/bbcthree/article/dd52796e-5935-414e-af0c-de9686d02afa (accessed April 2021).

Cameron, L. P., Benson, C. J., DeFelice, B. C., Fiehn, O., & Olson, D. E. (2019). Chronic, intermittent microdoses of the psychedelic n,n-dimethyltryptamine (DMT) produce positive effects on mood and anxiety in rodents. *ACS Chemical Neuroscience, 10*, 3261–3270.

Canal, C. E., & Morgan, D. (2012). Head-twitch response in rodents induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine: A comprehensive history, a re-evaluation of mechanisms, and its utility as a model. *Drug Testing and Analysis, 4*(7–8).

Carbonaro, T. M., & Gatch, M. B. (2016). Neuropharmacology of N,N-dimethyltryptamine. *Brain Research Bulletin, 126*(Pt 1), 74–88. https://doi.org/10.1016/j.brainresbull.2016.04.016

Carey, N. (2012). *The epigenetics revolution.* Icon Books.

Carhart-Harris, R. (2007). Waves of the unconscious: The neurophysiology of dreamlike phenomena and its implications for the psychodynamic model of the mind. *Neuro-psychoanalysis, 9*(2), 183–211.

Carhart-Harris, R. (2013). Psychedelic drugs, magical thinking and psychosis. *Journal of Neurology, Neurosurgery & Psychiatry, 84*, e1.

Carhart-Harris, R., & Nutt, D. (2017). Serotonin and brain function: A tale of two receptors. *Journal of Psychopharmacology, 31*(9), 1091–1120.

Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., & Nutt, D. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience, 8*, 20. https://doi.org/10.3389/fnhum.2014.00020

Carter, R. (2002). *Consciousness.* Weidenfield & Nicholson.

Cartwright, N. (2004). From causation to explanation and back. In B. Leiter (Ed.), *The future for philosophy* (pp. 230–245). Oxford University Press.

Chalmers, D. J. (1995). Facing up to the problem of consciousness. *Journal of consciousness studies, 2*, 200–219.

Chalmers, D. J. (1996). The conscious mind. In *Search of a fundamental theory.* Oxford University Press.

Checkley, S. A., Murray, R. M., Oon, M. C. H., Rodnight, R., & Birley, J. L. T. (1980). A longitudinal study of urinary excretion of N,N,-Dimethyltryptamine in psychotic patients. *The British Journal of Psychiatry, 137*, 236–239. https://doi.org/10.1192/bjp.137.3.236

Checkley, S. A., & Park, S. B. G. (1987). The psychopharmacology of the human pineal. *Journal of Psychopharmacology, 1*(2), 109–125. https://doi.org/10.1177/026988118700100208

Chen, Y., & Lyga, J. (2014). Brain-skin connection: Stress, inflammation and skin aging. *Inflammation and Allergy - Drug Targets, 13*(3), 177–190. https://doi.org/10.2174/1871528113666140522104422

Chiu, I. M., von Hehn, C. A., & Woolf, C. J. (2012). Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nature Neuroscience, 15*(8), 1063–1067. https://doi.org/10.1038/nn.3144

Chu, U. B., Vorperian, S. K., Satyshur, K., Eickstaedt, K., Cozzi, N. V., Mavlyutov, T., Hajipour, A. R., & Ruoho, A. E. (2014). Noncompetitive inhibition of indolethylamine-N-methyltransferase by N,N-dimethyltryptamine and N,N-dimethylaminopropyltryptamine. *Biochemistry*, *53*(18), 2956–2965.

Clancy, S. (2005). *Abducted: How people come to believe they were kidnapped by aliens*. Harvard University Press.

Cott, C., & Rock, A. (2008). Phenomenology of N,N-dimethyltryptamine use: A thematic analysis. *Journal of Scientific Exploration*, *22*(No. 3), 359–370.

Cozzi, N. V, Mavlyutov, T. A., Thompson, M. A., & Ruoho, A. E. (2011). Indolethylamine N- methyltransferase expression in primate nervous tissue. *Society for Neuroscience Abstracts*, *37*, 840–919.

Cozzi, N. V., Gopalakrishnan, A., Anderson, L. L., Feih, J. T., Shulgin, A. T., Daley, P. F., & Ruoho, A. E. (2009). Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. *Journal of Neural Transmission*, *116*(12), 1591–1599. Epub 2009 Sep 12. PMID: 19756361. https://doi.org/10.1007/s00702-009-0308-8

Craver, C. F. (2002). Structures of scientific theories. In P. K. Machamer & M. Silberstein (Eds.), *blackwell Guide to the Philosophy of science* (pp. 55–79). Blackwell. https://doi.org/10.1002/9780470756614.ch4

Crick, F., & Koch, C. (1990). Towards a neurobiological theory of consciousness. *Seminars in the Neurosciences*, *2*, 263–275.

Crick, F., & Koch, C. (2003). A framework for consciousness. *Nature Neuroscience*, *6*, 119–126. https://doi.org/10.1038/nn0203-119

da Silveira, D. X., Grob, C. S., Rios, M. D., Lopez, E., Alonso, L. K., Tacla, C., & Doering-Silveira, E. (2005). Ayahuasca in adolescence: A preliminary psychiatric assessment. *Journal of Psychoactive Drugs*, *37*, 129–133.

Davis, A. K., Barrett, F., & Griffiths, R. R. (2020). Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *Journal of contextual behavioral science*, *15*, 39–45.

Davis, A. K., Barsuglia, J. P., Lancelotta, R., Grant, R. M., & Renn, E. (2018). The epidemiology of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption. *Journal of Psychopharmacology*, *32*(7), 779–792. https://doi.org/10.1177/0269881118769063

Davis, A. K., Clifton, J. M., Weaver, E. G., Hurwitz, E. S., Johnson, M. W., & Griffiths, R. R. (2020). Survey of entity encounter experiences occasioned by inhaled N,N-dimethyltryptamine: Phenomenology, interpretation, and enduring effects. *Journal of Psychopharmacology*, *34*(9), 1008–1020. https://doi.org/10.1177/0269881120916143

Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P., & Griffiths, R. R. (2019). 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *The American Journal of Drug and Alcohol Abuse*, *45*(2), 161–169. https://doi.org/10.1080/00952990.2018.1545024

de Almeida, R. N., Galvao, A. C. M., da Silva, F. S., Silva, E. A. D. S., Palhano-Fontes, F., Maia-de-Oliveira, J. P., de Araújo, L.-S. B., Lobão-Soares, B., & Galvão-Coelho, N. L. (2019). Modulation of serum brain-derived neurotrophic factor by a single dose of ayahuasca: Observation from a randomized controlled trial. *Frontiers in Psychology*, *10*, 1234. https://doi.org/10.3389/fpsyg.2019.01234

de Araújo, D. B., Ribeiro, S., Cecchi, G. A., Carvalho, F. M., Sanchez, T. A., Pinto, J. P., de Martinis, B. S., Crippa, J. A., Hallak, J. E. C., & Santos, A. C. (2012). Seeing with eyes shut: Neural basis of enhanced imagery following ayahuasca ingestion. *Human Brain Mapping*, *33*, 2550–2560.

de Araújo. (2019). Evidence for the therapeutic effects of ayahuasca. In Winkelman & Sessa (Eds.), *Advances in psychedelic medicine: State-of-the-art therapeutic applications*. Praeger.

de la Peña, L., & Cetto, A. M. (1994). Quantum phenomena and the zeropoint radiation field. *Foundations of Physics*, *24*, 917–948. https://doi.org/10.1007/BF02067655

de la Peña, L., & Cetto, A. M. (1995). Quantum phenomena and the zeropoint radiation field II. *Foundations of Physics*, *25*, 573–604. https://doi.org/10.1007/BF02059007

de la Peña, L., & Cetto, A. M. (1996). *The quantum dice: An introduction to stochastic electrodynamics*. Kluwer Academic Publishers. https://doi.org/10.1007/978-94-015-8723-5

de la Peña, L., & Cetto, A. M. (2001). Quantum theory and linear stochastic electrodynamics. *Foundations of Physics*, *31*, 1703–1731. https://doi.org/10.1023/A:1012670800317

de la Peña, L., & Cetto, A. M. (2006). The foundations of linear stochastic electrodynamics. *Foundations of Physics*, *36*, 350–368. https://doi.org/10.1007/s10701-005-9020-1

de la Peña, L., Cetto, A. M., & Valdés-Hernández, A. (2015). *The emerging quantum. The physics behind quantum mechanics*. Springer International Publishing.

de la Peña, L., Valdés-Hernández, A., & Cetto, A. M. (2009). Quantum mechanics as an emergent property of ergodic systems embedded in the zero-point radiation field. *Foundations of Physics*, *39*, 1240–1272. https://doi.org/10.1007/s10701-009-9348-z

de la Peña-Auerbach, L., & Cetto, A. M. (1977). Derivation of quantum mechanics from stochastic electrodynamics. *Journal of Mathematical Physics*, *18*, 1612–1621. https://doi.org/10.1063/1.523448

de Oliveira Silveira, G., Guimarães dos Santos, R., Rebello Lourenço, F., Novak Rossi, G., Hallak, J., & Yonamine, M. (2020). Stability evaluation of DMT and harmala alkaloids in ayahuasca tea samples. *Molecules*, *25*, 2072. https://doi.org/10.3390/molecules25092072

de Pablo-Fernández, E., Breen, D. P., Bouloux, P. M., Barker, R. A., Foltynie, T., & Warner, T. T. (2017). Neuroendocrine abnormalities in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry*, *88*(2), 176–185. Epub 2016 Oct 31. PMID: 27799297. https://doi.org/10.1136/jnnp-2016-314601

de Vries, R., Heering, H. D., Postmes, L., Goedhart, S., Sno, H. N., & de Haan, L. (2013). Self-disturbance in schizophrenia: A phenomenological approach to better understand our patients. *The primary care companion for CNS disorders*, *15*(1), PCC.12m01382. https://doi.org/10.4088/PCC.12m01382

Dean, J., Liu, T., Huff, S., Sheler, B., Barker, S. A., Strassman, R. J., Wang, M. M., & Borjigin, J. (2019). Biosynthesis and extracellular concentrations of N,N-dimethyltryptamine (DMT) in mammalian brain. *Scientific Reports*, *9*, 9333.

Dean, J. G. (2018). Indolethylamine-*N*-methyltransferase polymorphisms: Genetic and biochemical approaches for study of endogenous N,N,-dimethyltryptamine. *Frontiers in Neuroscience*, *12*, 232. https://doi.org/10.3389/fnins.2018.00232

Degan, R. (2016). *The last shaman*. Netflix.

Delille, H. K., Becker, J. M., Burkhardt, S., Bleher, B., Terstappen, G. C., Schmidt, M., Meyer, A. H., Unger, L., Marek, G. J., & Mezler, M. (2012). Heterocomplex formation of 5-HT2A-mGlu2 and its relevance for cellular signaling cascades. *Neuropharmacol*, *62*, 2184–2191.

Desmedt, J. E., & Tomberg, C. (1994). Transient phase-locking of 40 Hz electrical oscillations in prefrontal parietal cortex reflects the process of conscious somatic perception. *Neuroscience Letters*, *168*, 126–129. https://doi.org/10.1016/0304-3940(94)90432-4

Dias, B., & Ressler, K. (2014). Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neuroscience*, *17*, 89–96. https://doi.org/10.1038/nn.3594

Doesburg, S. M., Green, J. J., McDonald, J. J., & Ward, L. M. (2009). Rhythms of consciousness: binocular rivalry reveals large-scale oscillatory network dynamics mediating visual perception. *PLoS One*, *4*, e6142. https://doi.org/10.1371/journal.pone.0006142

Dominguez-Clave, E., Soler, J., Elices, M., Franquesa, A., Álvarez, E., & Pascual, J. C. (2021). Ayahuasca may help to improve self-compassion and self-criticism capacities. *Human Psychopharmacology: Clinical and Experimental*, 37(2), e2807. https://onlinelibrary.wiley.com/doi/10.1002/hup.2807

Dominguez-Clave, E., Soler, J., Elices, M., Pascual, J. C., Álvarez, E., de la Fuente Revenga, M., Friedlander, P., Feilding, A., & Riba, J. (2016). Ayahuasca: Pharmacology, neuroscience and therapeutic potential. *Brain Research Bulletin*, 126, 89–101.

dos Santos, R. G., Araujo, D. B., Sanches, R. F., & Hallak, J. E. (2020). Unveiling ayahuasca psychopharmacology: The accomplishments of Jordi Riba (1968-2020). *Brazilian Journal of Psychiatry*, 43(6). https://doi.org/10.1590/1516-4446-2020-0021

dos Santos, R. G., Balthazar, F. M., Bouso, J. C., & Hallak, J. E. (2016a). The current state of research on ayahuasca: A systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging. *Journal of Psychopharmacology*, 30(12), 1230–1247. https://doi.org/10.1177/0269881116652578

dos Santos, R. G., & Bouso, J. C. (2019). Translational evidence for ayahuasca as an antidepressant: what's next? *Brazilian Journal of Psychiatry*, 41, 275–276. https://doi.org/10.1590/1516-4446-2019-4104

dos Santos, R. G., Bouso, J. C., & Hallak, J. E. C. (2017). Ayahuasca, dimethyltryptamine, and psychosis: A systematic review of human studies. *Therapeutic Advances in Psychopharmacology*, 7, 141–157. https://doi.org/10.1177/2045125316689030

dos Santos, R. G., Bouso, J. C., Rocha, J. M., Rossi, G. N., & Hallak, J. E. (2021). The use of classic hallucinogens/psychedelics in a therapeutic context: Healthcare policy opportunities and challenges. *Risk Management and Healthcare Policy*, 14, 901–910. https://doi.org/10.2147/rmhp.s300656

dos Santos, R. G., Enyart, S., Bouso, J. C., Pares, Ò., & Hallak, J. E. C. (2018). "Ayahuasca turned on my mind's eye": Enhanced visual imagery after ayahuasca intake in a man with "blind imagination" (aphantasia). *Journal of Psychedelic Studies*, 2(2), 1–4.

dos Santos, R. G., Grasa, E., Valle, M., Ballester, M. R., Bouso, J. C., Nom-dedéu, J. F., Homs, R., Barbanoj, M. J., & Riba, J. (2012). Pharmacology of ayahuasca administered in two repeated doses. *Psychopharmacology (Berl)*, 219(4), 1039–1053. Epub 2011 Aug 13. PMID: 21842159. https://doi.org/10.1007/s00213-011-2434-x

dos Santos, R. G., & Hallak, J. E. C. (2019). *Ayahuasca, an ancient substance with traditional and contemporary use in neuropsychiatry and neuroscience* (p. 106300). Epilepsy Behav.

dos Santos, R. G., Landeira-Fernandez, J., Strassman, R. J., Motta, V., & Cruz, A. P. (2007). Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *Journal of Ethnopharmacology*, 112, 507–513. https://doi.org/10.1016/j.jep.2007.04.012

dos Santos, R. G., Osório, F. L., Crippa, J. A. S., & Hallak, J. E. C. (2016b). Classical hallucinogens and neuroimaging: A systematic review of human studies. Hallucinogens and neuroimaging. *Neuroscience & Biobehavioral Reviews*, 71, 715–728. https://doi.org/10.1016/j.neubiorev.2016.10.026

dos Santos, R. G., Osório, F. L., Crippa, J. A., & Hallak, J. E. (2016c). Antidepressive and anxiolytic effects of ayahuasca: A systematic literature review of animal and human studies. *Braz J Psychiatry*, 38(1), 65–72. PMID: 27111702; PMCID: PMC7115465. https://doi.org/10.1590/1516-4446-2015-1701

dos Santos, R. G., & Strassman, R. (2011). Ayahuasca and psychosis. In R. G. dos Santos (Ed.), *The ethnopharmacology of ayahuasca* (p. 97). Transworld Research Network.

dos Santos, R. G., Sanches, R. F., Osório, F. D. L., & Hallak, J. E. C. (2018). Long-term effects of ayahuasca in patients with recurrent depression: A 5-year qualitative follow-up. *Archives of Clinical Psychiatry (São Paulo)*, 45, 22–24. https://doi.org/10.1590/0101-60830000000149

Dubashia, N. (2018). *The unity of everything: A conversation with David Bohm*. Tredition.

Dupont, C., Armant, D. R., & Brenner, C. A. (2009). Epigenetics: Definition, mechanisms and clinical perspective. *Seminars in Reproductive Medicine*, 27(5), 351–357. https://doi.org/10.1055/s-0029-1237423

Engel, A. K., & Fries, P. (2016). Neuronal oscillations, coherence, and consciousness. In S. Laureys, O. Gosseries, & G. Tononi (Eds.), *The Neurology of conciousness* (2nd ed., pp. 49–60). Academic Press. https://doi.org/10.1016/B978-0-12-800948-2.00003-0

Engel, A. K., & Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends in Cognitive Sciences*, 5, 16–25. https://doi.org/10.1016/S1364-6613(00)01568-0

Ernandes, M. (2013). The triune brain and the neurobiological bases of thought and behaviour. In R. Cuoghi & M. Farronato (Eds.), *De incontinentia* (p. 52–87). Mouse Publishing.

Fábregas, J. M., González, D., Fondevila, S., Cutchet, M., Fernán- dez, X., Barbosa, P. C. R., Alcázar-Córcoles, M. Á., Barbanoj, M. J., Riba, J., & Bouso, J. C. (2010). Assessment of addiction severity among ritual users of ayahuasca. *Drug and Alcohol Dependence*, 111, 257–261.

Fingelkurts, A. A., Fingelkurts, A. A., & Neves, C. F. (2013). Consciousness as a phenomenon in the operational architectonics of brain organization: Criticality and self-organization considerations. *Chaos Soliton Fract*, 55, 13–31. https://doi.org/10.1016/j.chaos.2013.02.007

Fontanilla, D., Johannessen, M., Hajipour, A. R., Cozzi, N. V., Jackson, M. B., & Ruoho, A. E. (2009). The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. *Science*, 323(5916), 934–937. https://doi.org/10.1126/science.1166127

Fortunato, J. J., Reus, G. Z., Kirsch, T. R., Stringari, R. B., Stertz, L., Kapczinski, F., Pinto, J. P., Hallak, J. E., Zuardi, A. W., Crippa, J. A., & Quevedo, J. (2009). Acute harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus. *Progress In Neuro-Psychopharmacology & Biological Psychiatry*, 33, 1425–1430. https://doi.org/10.1016/j.pnpbp.2009.07.021

Fox, K., Dixon, M., Nijeboer, S., Girn, M., Floman, J., Lifshitz, M., Ellamil, M., Sedlmeier, P., & Christoff, K. (2016). Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. *Neuroscience & Biobehavioral Reviews*, 65, 208–228. https://doi.org/10.1016/j.neubiorev.2016.03.021

Frecska, E., Bokor, P., & Winkelman, M. (2016). The therapeutic potentials of ayahuasca: Possible effects against various diseases of civilization. *Frontiers in Pharmacology*, 7(35), 1–17.

Frecska, E., Hoppál, M., & Luna, L. E. (2016). Nonlocality and the shamanic state of consciousness. *NeuroQuantology*, 14(2), 155–165.

Frecska, E., Móré, C. E., Vargha, A., & Luna, L. E. (2012). Enhancement of creative expression and entoptic phenomena as after-effects of repeated ayahuasca ceremonies. *Journal of Psychoactive Drugs*, 44, 191–199.

Frecska, E., Móró, L., & Wesselman, H. (2011). The soul cluster: Reconsideration of a millennia old concept. *World Futures*, 67(2), 132–153. https://doi.org/10.1080/02604027.2010.532464

Frecska, E., Szabo, A., Winkelman, M. J., Luna, L. E., & McKenna, D. J. (2013). A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity. *Journal of Neural Transmission*, 120, 1295–1303.

Freeman, W. J. (2004). Origin, structure, and role of background EEG activity. Part 1. Analytic Amplitude. *Clinical Neurophysiology*, 115, 2077–2088. https://doi.org/10.1016/j.clinph.2004.02.029

Freeman, W. J. (2005). Origin, structure, and role of background EEG activity. Part 3. Neural frame classification. *Clinical Neurophysiology*, 116, 1118–1129. https://doi.org/10.1016/j.clinph.2004.12.023

Freeman, W. J. (2007). Indirect biological measures of consciousness from field studies of brains as dynamical systems. *Neural Networks*, *20*, 1021–1031. https://doi.org/10.1016/j.neunet.2007.09.004

Freeman, W. J. (2009). Deep analysis of perception through dynamic structures that emerge in cortical activity from self-regulated noise. *Cognitive Neurodynamics*, *3*, 105–116. https://doi.org/10.1007/s11571-009-9075-3

Freeman, W. J., & Vitiello, G. (2006). Nonlinear brain dynamics as macroscopic manifestation of underlying many-body field dynamics. *Physics of Life Reviews*, *3*, 93–118. https://doi.org/10.1016/j.plrev.2006.02.001

Freeman, W. J., & Vitiello, G. (2007). The dissipative quantum model of brain and laboratory observations. *Electronic Journal of Theoretical Physics*, *4*, 1–251. https://doi.org/10.1142/9789812779953_0009

Fujimoto, M., Hayashi, T., Urfer, R., Mita, S., & Su, T. P. (2012). Sigma-1 receptor chaperones regulate the secretion of brain-derived neurotrophic factor. *Synapse*, *66*, 630–639. https://doi.org/10.1002/syn.21549

Gaillard, R., Dehaene, S., Adam, C., Clemenceau, S., Hasboun, D., Baulac, M., Cohen, L., & Naccache, L. (2009). Converging intracranial markers of conscious access. *PLoS Biology*, *7*, e1000061. https://doi.org/10.1371/journal.pbio.1000061

Gallimore, A. R., & Strassman, R. J. (2016). A model for the application of target-controlled intravenous infusion for a prolonged immersive DMT psychedelic experience. *Frontiers in Pharmacology*, *7*, 211.

Galvao, A. C. M., de Almeida, R. N., Silva, E., Freire, F. A. M., Palhano-Fontes, F., Onias, H., Arcoverde, E., Maia-de-Oliveira, J. P., de Araújo, D. B., Lobão-Soares, B., & Galvão-Coelho, N. L. (2018). Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. *Frontiers in Psychiatry*, *9*, 185. https://doi.org/10.3389/fpsyt.2018.00185

Galvão-Coelho, N. L., de Menezes Galvão, A. C., de Almeida, R. N., Palhano-Fontes, F., Campos Braga, I., Lobão Soares, B., Maia-de-Oliveira, J. P., Perkins, D., Sarris, J., & de Araujo, D. B. (2020). Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca. *Journal of Psychopharmacology*, *34*(10), 1125–1133. https://doi.org/10.1177/0269881120936486

Gardiner, J. (2012). Insights into plant consciousness from neuroscience, physics and mathematics: A role for quasicrystals? *Plant Signaling & Behavior*, *7*(9), 1049–1055. https://doi.org/10.4161/psb.21325

Gardner, H. E. (2000). *Intelligence reframed: Multiple intelligences for the 21st century*. Basic Books.

Gillin, J. C., Kaplan, J., Stillman, R., & Wyatt, R. J. (1976). The psychedelic model of schizophrenia: The case of N,N-dimethyltryptamine. *American Journal of Psychiatry*, *133*, 203.

Gonzalez, D., Cantillo, J., Perez, I., Carvalho, M., Aronovich, A., Farre, M., Feilding, A., Obiols, J. E., & Bouso, J. C. (2021). The Shipibo ceremonial use of ayahuasca to promote well-being: An observational study. *Frontiers in Pharmacology*, *12*, 623923.

Gonzalez, D., Cantillo, J., Perez, I., Farré, M., Feilding, A., Obiols, J. E., & Bouso, J. C. (2020). Therapeutic potential of ayahuasca in grief: A prospective, observational study. *Psychopharmacology (Berl)*, *237*(4), 1171–1182. https://doi.org/10.1007/s00213-019-05446-2

González-Díaz, S. N., Arias-Cruz, A., Elizondo-Villarreal, B., & Monge-Ortega, O. P. (2017). Psychoneuroimmunoendocrinology: Clinical implications. *World Allergy Organization Journal*, *10*, 19. https://doi.org/10.1186/s40413-017-0151-6

Gonzalez-Maeso, J., Ang, R. L., Yuen, T., Chan, P., Weisstaub, N. V., Lopez-Gimenez, J. F., Zhou, M., Okawa, Y., Callado, L. F., Milligan, G., Gingrich, J. A., Filizola, M., Meana, J. J., & Sealfon, S. C. (2008). Identification of a serotonin/glutamate receptor complex implicated in psychosis. *Nature*, *452*, 93–97.

Gonzalez-Maeso, J., Weisstaub, N. V., Zhou, M., Chan, P., Ivic, L., Ang, R., Lira, A., Bradley-Moore, M., Ge, Y., Zhou, Q., Sealfon, S. C., & Gingrich, J. A. (2007). Hallucinogens recruit specific cortical 5-HT(2A)

receptor- mediated signaling pathways to affect behavior. *Neuron*, *53*, 439–452.

Grammenos, D., & Barker, S. A. (2015). On the transmethylation hypothesis: Stress, N,N-dimethyltryptamine, and positive symptoms of psychosis. *Journal of Neural Transmission*, *122*, 733–739. https://doi.org/10.1007/s00702-014-1329-5

Grella, B., Teitler, M., Smith, C., Herrick-Davis, K., & Glennon, R. A. (2003). Binding of β-Carbolines at 5-HT 2 serotonin receptors. *Bioorganic & Medicinal Chemistry Letters*, *13*, 4421–4425. https://doi.org/10.1016/j.bmcl.2003.09.027

Greyson, B. (2003). Incidence and correlates of near-death experiences in a cardiac care unit. *General Hospital Psychiatry*, *25*(4), 269–276. PMID: 12850659. https://doi.org/10.1016/s0163-8343(03)00042-2

Griffiths, R. R., Hurwitz, E. S., Davis, A. K., Johnson, M. W., & Jesse, R. (2019). Survey of subjective "God encounter experiences": Comparisons among naturally occurring experiences and those occasioned by the classic psychedelics psilocybin, LSD, ayahuasca, or DMT. *PLoS ONE*, *14*(4), e0214377. https://doi.org/10.1371/journal.pone.0214377

Grob, C. S., McKenna, D. J., Callaway, J. C., Brito, G. S., Neves, E. S., Oberlaender, G., Saide, O. L., Labigalini, E., Tacla, C., Miranda, C. T., Strassman, R. J., & Boone, K. B. (1996). Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *The Journal of Nervous and Mental Disease*, *184*(2), 86–94.

Grof, S. (2006). Ervin Laszlo's Akashic field and the dilemmas of modern consciousness research. *The Journal of New Paradigm Research*, *62*(1), 86–102.

Guidi, J., Lucente, M., Sonino, N., & Fava, G. A. (2021). Allostatic load and its impact on health: A systematic review. *Psychotherapy and Psychosomatics*, *90*, 11–27.

Hartogsohn, I. (2016). Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology*, *30*(12), 1259–1267.

Haubrich, D., & Wang, P. (1977). N,N-dimethyltryptamine lowers rat brain acetylcholine and dopamine. *Brain Research*, *131*(1), 158–161.

Hayashi, T. (2019). The sigma-1 receptor in cellular stress signaling. *Frontiers in Neuroscience: Neuropharmacology*, *13*(733), 1–5.

Heisenberg, W. (1958). *Physics and philosophy: The revolution in modern science (1958)*. Lectures delivered at University of St. Andrews, Scotland, Winter 1955-56. Penguin.

Hempel, C. (1965). *Aspects of scientific explanation and other essays in the philosophy of science*. Free Press.

Hoffman, G. (2019). The nature of ayahuasca. Documentary film. YouTube. https://www.youtube.com/watch?v=6j0_glRnJxI

Holloway, T., & González-Maeso, J. (2015). Epigenetic mechanisms of serotonin signaling. *ACS Chemical Neuroscience*, *6*(7), 1099–1109. Epub 2015 Mar 10. PMID: 25734378; PMCID: PMC4838281. https://doi.org/10.1021/acschemneuro.5b00033

Hubbard, E. M., Brang, D., & Ramachandran, V. S. (2011). The cross-activation theory at 10. *Journal of Neuropsychology*, *5*, 152–177. https://doi.org/10.1111/j.1748-6653.2011.02014.x

Inserra, A. (2018). Hypothesis: The psychedelic ayahuasca heals traumatic memories via a sigma 1 receptor-mediated epigenetic-mnemonic process. *Frontiers in Pharmacology*, *9*(330), 1–13.

James, E., Robertshaw, T. L., Hoskins, M., & Sessa, B. (2020). Psilocybin occasioned mystical-type experiences. *Human Psychopharmacology: Clinical and Experimental*, *35*, . https://doi.org/10.1002/hup.2742

James, E., Robertshaw, T. L., Pascoe, M. J., Chapman, F., Westwell, A., Barrow, J., Sessa, B., Hoskins, M., Doblin, R., Rosky, R., & Smith, A. (2021). Online survey into developing a model for a legal cannabis market in the United Kingdom. *Drug Science, Policy and Law*, *7*, 1–22.

James, E., Robertshaw, T. L., Pascoe, M. J., Chapman, F. M., Westwell, A. D., & Smith, A. P. (2019). Using the pharmacy retail model to examine perceptions and biases of a UK population sample towards

regulation of specific psychoactive drugs. *Drug Science, Policy and Law, 5*, 1–14.

James, W. (1902, republished 1958). *The varieties of religious experience.* : Penguin Books.

Jiménez-Garrido, D. F., Gómez-Sousa, M., Ona, G., dos Santos, R. G., Hallak, J. E. C., Alcázar-Córcoles, M. Á., & Bouso, J. C. (2020). Effects of ayahuasca on mental health and quality of life in naïve users: A longitudinal and cross-sectional study combination. *Scientific Reports, 10.* https://doi.org/10.1038/s41598-020-61169-x

Johnson, M. (2020). Consciousness, religion, and gurus: Pitfalls of psychedelic medicine. *ACS Pharmacology and Translational Science, 4*(2), 578–581. https://pubs.acs.org/doi/10.1021/acsptsci.0c00198

Jylkka, J. (2021). Reconciling mystical experiences with naturalistic psychedelic science: Reply to Sanders and Zijlm11. *ACS Pharmacology & Translational Science, 4*, 1468–1470. https://doi.org/10.1021/acsptsci.1c00137

Kaliman, P., Alvarez-López, M. J., Cosín-Tomás, M., Rosenkranz, M. A., Lutz, A., & Davidson, R. J. (2014). Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators. *Psychoneuroendocrinology, 40*, 96–107. Epub 2013 Nov 15. PMID: 24485481; PMCID: PMC4039194. https://doi.org/10.1016/j.psyneuen.2013.11.004

Keppler, J. (2012). A conceptual framework for consciousness based on a deep understanding of matter. *Philosophy Study, 2*, 689–703.

Keppler, J. (2013). A new perspective on the functioning of the brain and the mechanisms behind conscious processes. *Frontiers in Psychology, 4*, 242. https://doi.org/10.3389/fpsyg.2013.00242

Keppler, J. (2016). On the universal mechanism underlying conscious systems and the foundations for a theory of consciousness. *Open Journal of Philosophy, 6*, 346–367. https://doi.org/10.4236/ojpp.2016.64034

Keppler, J. (2018). The role of the brain in conscious processes: A new way of looking at the neural correlates of consciousness. *Frontiers in Psychology, 9*, 1346. https://doi.org/10.3389/fpsyg.2018.01346

Keppler, J. (2020). The common basis of memory and consciousness: Understanding the brain as a write–read head interacting with an omnipresent background field. *Frontiers in Psychology, 10*, 2968. https://doi.org/10.3389/fpsyg.2019.02968

Keppler, J. (2021). Building blocks for the development of a self-consistent electromagnetic field theory of consciousness. *Frontiers in Human Neuroscience, 15*, 723415. https://doi.org/10.3389/fnhum.2021.723415

Keppler, J., & Shani, I. (2020). Cosmopsychism and consciousness research: A fresh view on the causal mechanisms underlying phenomenal states. *Frontiers in Psychology, 11*, 371. https://doi.org/10.3389/fpsyg.2020.00371

Kim, J., Gulati, T., & Ganguly, K. (2019). Competing roles of slow oscillations and delta waves in memory consolidation versus forgetting. *Cell, 179*, 514–526.

Knyazev, G. G., Savostyanov, A. N., Bocharov, A. V., Dorosheva, E. A., Tamozhnikov, S. S., & Saprigyn, A. E. (2015). Oscillatory correlates of autobiographical memory. *International Journal of Psychophysiology, 95*, 322–332. https://doi.org/10.1016/j.ijpsycho.2014.12.006

Kočárová, R., Horacek, J., & Carhart-Harris, R. (2021). Does psychedelic therapy have a transdiagnostic action and prophylactic potential? *Frontiers in Psychiatry, 12*, 1–18.

Kometer, M., Schmidt, A., Jancke, L., & Volleinweider, F. X. (2013). Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. *Journal of Neuroscience, 33*(25), 10544–10551.

Kraehenmann, R. (2017). Dreams and psychedelics: Neurophenomenological comparison and therapeutic implications. *Current Neuropharmacology, 15*, 1032–1042. https://doi.org/10.2174/1573413713666170619092629

Kraehenmann, R., Pokorny, D., Vollenweider, L., Preller, K. H., Pokorny, T., Seifritz, E., & Vollenweider, F. X. (2017). Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. *Psychopharmacology, 234*, 2031–2046.

Kuypers, K. P., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology, 33*(9), 1039–1057. https://doi.org/10.1177/0269881119857204

Lai, G., Langevin, J.-P., Koek, R. J., Krahl, S. E., Bari, A. A., & Chen, J. W. Y. (2020). Acute effects and the dreamy state evoked by deep brain electrical stimulation of the amygdala: Associations of the amygdala in human dreaming, consciousness, emotions, and creativity. *Frontiers in Human Neuroscience, 14*, 61. https://doi.org/10.3389/fnhum.2020.00061

Lama, D. (2005). *The universe in a single atom: How science and spirituality can serve our world.* Abacus.

Lamme, V. A. F. (2006). Towards a true neural stance on consciousness. *Trends in Cognitive Sciences, 10*, 494–501. https://doi.org/10.1016/j.tics.2006.09.001

Langille, J. J. (2019). Remembering to forget: A dual role for sleep oscillations in memory consolidation and forgetting. *Frontiers in Cellular Neuroscience, 13*(71), 1–21.

Larbi, M. (2020). Frogs, brain noodles and a lot of vomit - I took ayahuasca and finally found inner peace. Metro. https://metro.co.uk/2020/01/08/what-its-like-to-do-ayahuasca-trip-12003574/ (accessed April 2021).

Laszlo, E. (1995). *The interconnected universe: Conceptual foundations of transdisciplinary unified theory.* World Scientific Publishing.

Laszlo, E. (2007). *Science and the akashic field: An integral theory of everything.* Inner Traditions.

Lawn, W., Hallak, J. E., Crippa, J. A., dos Santos, R., Porffy, L., Barratt, M. J., Ferris, J. A., Winstock, A. R., & Morgan, C. J. A. (2017). Well-being, problematic alcohol consumption and acute subjective drug effects in past-year ayahuasca users: A large, international, self-selecting online survey. *Scientific Reports, 7*. https://doi.org/10.1038/s41598-017-14700-6

Levine, J. (1983). Materialism and qualia: The explanatory gap. *Pacific Philosophical Quarterly, 64*, 354–361.

Levis, C., Costa, F. R. C., Bongers, F., Peña-Claros, M., Clement, C. R., Junqueira, A. B., Neves, E. G., Tamanaha, E. K., Figueiredo, F. O. G., Salomão, R. P., Castilho, C. V., Magnusson, W. E., Phillips, O. L., Guevara, J. E., Sabatier, D., Molino, J.-F., Cárdenas López, D., Mendoza, A. M., Pitman, N. C. A., … Ter Steege, H. (2017). Persistent effects of pre-Columbian plant domestication on Amazonian forest composition. *Science, 355*(6328), 925–931.

Liester, M. B., & Prickett, J. I. (2012). Hypotheses regarding the mechanisms of ayahuasca in the treatment of addictions. *Journal of Psychoactive Drugs, 44*, 200–208. https://doi.org/10.1080/02791072.2012.704590

Long, J. (2014). Near-death experience. Evidence for their reality. *Missouri Medicine, 111*(5), 372–380.

Luke, D. (2011). Discarnate entities and dimethyltryptamine (DMT): Psychopharmacology, phenomenology and ontology. *Journal of the Society for Psychical Research, 75*(1), 26–42. ISSN 0037-9751.

Luke, D. (2020). Anomalous psychedelic experiences: At the neurochemical juncture of the humanistic and parapsychological. *Journal of Humanistic Psychology, 62*, 257–297. https://doi.org/10.1177/0022167820917767

Luke, D., Spowers, R., McKenna, D., Jeremy, J., Davis, E., Sheldrake, R., Hancock, G., & Strassman, R. (2018). *DMT Dialogues: Encounters with the spirit molecule.* Park Street Press.

Luppi, A. I., Carhart-Harris, R. L., Roseman, L., Pappas, I., Menon, D. K., & Stamatakis, E. A. (2021). LSD alters dynamic integration and

segregation in the human brain. *NeuroImage*, *227*, 117653. https://doi.org/10.1016/j.neuroimage.2020.117653

Marek, G. J. (2018). Interactions of hallucinogens with the glutamatergic system: Permissive network effects mediated through cortical layer V pyramidal neurons. *Current Topics in Behavioral Neurosciences*, *36*, 107–135.

Martial, C., Cassol, H., Charland-Verville, V., Pallavicini, C., Sanz, C., Zamberlan, F., Vivot, R. M., Erowid, F., Erowid, E., Laureys, S., Greyson, B., & Tagliazucchi, E. (2019). Neurochemical models of near-death experiences: A large scale study based on semantic similarity of written reports. *Consciousness and Cognition*, *69*, 52–69.

Martial, C., Cassol, H., Antonopoulos, G., Charlier, T., Heros, J., Donneau, A.-F., Charland-Verville, V., & Laureys, S. (2017). Temporality of features in near-death experience narratives. *Frontiers in Human Neuroscience*, *11*(311), 1–6.

Mavlyutov, T. A., Epstein, M. L., Liu, P., Verbny, Y. I., Ziskind-Conhaim, L., & Ruoho, A. E. (2012). Development of the sigma-1 receptor in C-terminals of motoneurons and colocalization with the N, N-dimethyltryptamine forming enzyme, indole-N-methyl transferase. *Neuroscience*, *206*, 60–68.

Maybin, S. & Casserly, J. (2020). I was sexually abused by a shaman at an ayahuasca retreat. BBC News. https://www.bbc.com/news/amp/stories-51053580?fbclid=IwAR3tHP0vd7PSOwEnMm4JrbsGgGsFuaouYilFwIDbV9Od_SCHShOYHeQkj4Y (accessed July 2021).

McKenna, D., & Riba, J. (2015). New world tryptamine hallucinogens and the neuroscience of ayahuasca. *Current Topics in Behavioral Neurosciences*, *36*. https://doi.org/10.1007/7854_2015_368

McKenna, D., Towers, G., & Abbott, F. (1984). Monoamine-oxidase inhibitors in south-american hallucinogenic plants – tryptamine and beta-carboline constituents of ayahuasca. *Journal of Ethnopharmacology*, *10*(2), 195–223. https://doi.org/10.1016/0378-8741(84)90003-5

McKenna, D. J. (2004). Clinical investigations of the therapeutic potential of ayahuasca: Rationale and regulatory challenges. *Pharmacology & Therapeutics*, *102*(2), 111–129. PMID: 15163593. https://doi.org/10.1016/j.pharmthera.2004.03.002

McKenna, D. J., Callaway, J. C., & Grob, C. S. (1998). The scientific investigation of ayahuasca: A review of past and current research. *The Heffter Review of Psychedelic Research*, *1*, 65–77.

Melloni, L., Molina, C., Pena, M., Torres, D., Singer, W., & Rodriguez, E. (2007). Synchronization of neural activity across cortical areas correlates with conscious perception. *Journal of Neuroscience*, *27*, 2858–2865. https://doi.org/10.1523/JNEUROSCI.4623-06.2007

Metzinger, T. (2009). *The ego tunnel: The science of the mind and the myth of the self*. Basic Books.

Michael, P., Luke, D., & Robinson, O. (2021). An encounter with the other: A thematic analysis of DMT experiences from a naturalistic field study. *Frontiers in Psychology*, *12*, 1–20.

Millière, R., Carhart-Harris, R. L., Roseman, L., Trautwein, F.-M., & Berkovich-Ohana, A. (2018). Psychedelics, meditation, and self-consciousness. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.01475

Moody, R. (1988). *Life after life: The investigation of a phenomenon - survival of bodily death*. Christian Large Print.

Morales-Garcia, J. A., Calleja-Conde, J., Lopez-Moreno, J. A., Alonso-Gil, S., Sanz-SanCristobal, M., Riba, J., & Perez-Castillo, A. (2020). N, N-dimethyltryptamine compound found in the hallucinogenic tea ayahuasca, regulates adult neurogenesis in vitro and in vivo. *Translational Psychiatry*, *10*(1), 1–14. https://doi.org/10.1038/s41398-020-01011-0

Morales-Garcia, J. A., De La Fuente Revenga, M., Alonso-Gil, S., RodriguezFranco, M. I., Feilding, A., Perez-Castillo, A., & Riba, J. (2017). The alkaloids of Banisteriopsis caapi, the plant source of the Amazonian hallucinogen Ayahuasca, stimulate adult neurogenesis in

vitro. *Scientific Reports*, *7*, 5309. https://doi.org/10.1038/s41598-017-05407-9

Moreno, J. L., Holloway, T., Albizu, L., Sealfon, S. C., & González-Maeso, J. (2011). Metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects induced by hallucinogenic 5-HT2A receptor agonists. *Neuroscience Letters*, *493*, 76–79.

Morgan, M., & Mandell, A. J. (1969). Indole(ethyl)amine N-methyltransferase in the brain. *Science*, *165*, 492–493.

Muthukumaraswamy, S. D., Carhart-Harris, R. L., Moran, R. J., Brookes, M. J., Williams, T. M., Errtizoe, D., Sessa, B., Papadopoulos, A., Bolstridge, M., Singh, K. D., Feilding, A., Friston, K. J., & Nutt, D. J. (2013). Broadband cortical desynchronization underlies the human psychedelic state. *Journal of Neuroscience*, *33*, 15171–15183. https://doi.org/10.1523/JNEUROSCI.2063-13.2013

Narby, J. (1998). *The cosmic serpent: DNA and the origins of knowledge*. Orion Books LTD.

Narby, J. (2021). *Plant teachers: Ayahuasca, tobacco, and the pursuit of knowledge*. New World Library.

Nardai, S., László, M., Szabó, A., Alpár, A., Hanics, J., Zahola, P., Merkely, B., Frecska, E., & Nagy, Z. (2020). N,N-dimethyltryptamine reduces infarct size and improves functional recovery following transient focal brain ischemia in rats. *Experimental Neurology*, *327*, 113245. https://doi.org/10.1016/j.expneurol.2020.113245

Nemes, B., Pető, K., Németh, N., Mester, A., Magyar, Z., Ghanem, S., Sógor, V., Tánczos, B., Deák, Á., Kállay, M., Bidiga, L., & Frecska, E. (2019). N, N-dimethyltryptamine prevents renal ischemia-reperfusion injury in a rat model. *Transplantation Proceedings*, *51*, 1268–1275. https://doi.org/10.1016/j.transproceed.2019.04.005

Netzband, N., Ruffell, S., Linton, S., Tsang, W. F., & Wolff, T. (2020). Modulatory effects of ayahuasca on personality structure in a traditional framework. *Psychopharmacology*, *237*, 3161–3171. https://doi.org/10.1007/s00213-020-05601-0

Nichols, D. E. (2004). Hallucinogens. *Pharmacology & Therapeutics*, *101*(2), 131–181. PMID: 14761703. https://doi.org/10.1016/j.pharmthera.2003.11.002

Nichols, D. E. (2016). Psychedelics. *Pharmacological reviews*, *68*, 264–355. https://doi.org/10.1124/pr.115.011478

Nichols, D. E. (2018). Author's reply. *Journal of Psychopharmacology*, *32*(7), 821–822. https://doi.org/10.1177/0269881118767648a

Nichols, DE. (2017). N,N-dimethyltryptamine and the pineal gland: Separating fact from myth. *Journal of Psychopharmacology*, *32*(1), 30–36. https://doi.org/10.1177/0269881117736919

Nielson, J. L., & Megler, J. D. (2014). Ayahuasca as a candidate therapy for PTSD. In C. C. B. Labate (Ed.), *The therapeutic use of ayahuasca*. Springer.

Nour, M., & Carhart-Harris, R. (2017). Psychedelics and the science of self-experience. *The British Journal of Psychiatry*, *210*(3), 177–179. https://doi.org/10.1192/bjp.bp.116.194738

Oliveira-Lima, A. J., dos Santos, R., Hollais, A. W., Gerardi-Junior, C. A., Baldaia, M. A., Wuo-Silva, R., Yokoyama, T. S., Costa, J. L., Malpezzi-Marinho, E. L. A., Barbosa, P. C. R., Berro, L. F., Frussa-Filho, R., & Marinho, E. A. V. (2015). Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a post-sensitization treatment in mice. *Physiology & Behavior*, *142*, 28–36.

Ona, G., dos Santos, R. G., Hallak, J. E. C., & Bouso, J. C. (2020). Polypharmacology or "pharmacological promiscuity" in psychedelic research: What are we missing? *ACS Chemical Neuroscience*, *11*, 3191–3193. https://doi.org/10.1021/acschemneuro.0c00614

Orsolini, L., Chiappini, S., Papanti, D., Latini, R., Volpe, U., Fornaro, M., Tomasetti, C., Vellante, F., & De Berardis, D. (2020). How does ayahuasca work from a psychiatric perspective? Pros and cons of the entheogenic therapy. *Human Psychopharmacology: Clinical and Experimental*, *35*, e2728. https://doi.org/10.1002/hup.2728

Osório Fde, L., Sanches, R. F., Macedo, L. R., Santos, R. G., Maia-de-Oliveira, J. P., Wichert-Ana, L., Araujo, D. B., Riba, J., Crippa,

J.A., & Hallak, J. E. (2015). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A preliminary report. *Brazilian Journal of Psychiatry*, *37*(1), 13–20. PMID: 25806551. https://doi.org/10.1590/1516-4446-2014-1496

Palhano-Fontes, F., Andrade, K. C., Tofoli, L. F., Santos, A. C., Crippa, J. A. S., Hallak, J. E. C., Ribeiro, S., & de Araujo, D. B. (2015). The psychedelic state induced by Ayahuasca modulates the activity and connectivity of the default mode network. *PLoS ONE*, *10*(2), 1–13.

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L., Lobão-Soares, B., ..., & Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. *Psychological medicine*, *49*(4), 655–663. https://doi.org/10.1017/S0033291718001356

Pallavicini, C., Cavanna, F., Zamberlan, F., de la Fuente, L. A., Ilksoy, Y., Perl, Y. S., Arias, M., Romero, C., Carhart-Harris, R., Timmermann, C., & Tagliazucchi, E. (2021). Neural and subjective effects of inhaled N,N-dimethyltryptamine in natural settings. *Journal of Psychopharmacology*, *35*(4), 406–420. https://doi.org/10.1177/0269881120981384

Parnia, S., Waller, D. G., Yeates, R., & Fenwick, P. (2001). A qualitative and quantitative study of the incidence, features and aetiology of near death experiences in cardiac arrest survivors. *Resuscitation*, *48*(2), 149–156. PMID: 11426476. https://doi.org/10.1016/s0300-9572(00)00328-2

Pasquini, L., Palhano-Fontes, F., & Araujo, D. B. (2020). Subacute effects of the psychedelic ayahuasca on the salience and default mode networks. *Journal of Psychopharmacology*, *34*(6), 623–635. https://doi.org/10.1177/0269881120909409

Payne, J. E., Chambers, R., & Liknaitzky, P. (2021). Combining psychedelic and mindfulness interventions: Synergies to inform clinical practice. *ACS Pharmacology & Translational Science*, *4*(2), 416–423. https://doi.org/10.1021/acsptsci.1c00034

Penke, B., Fulop, L., Szucs, M., & Frecska, E. (2017). The role of sigma-1 receptor, an intracellular chaperone in neurodegenerative diseases. *Current Neuropharmacology*, *16*. https://doi.org/10.2174/1570159x15666170529104323

Peters, E., Joseph, S., Day, S., & Garety, P. (2004). Measuring delusional ideation: The 21-item Peters et al. Delusions inventory (PDI). *Schizophrenia Bulletin*, *30*(4), 1005–1022. PMID: 15954204. https://doi.org/10.1093/oxfordjournals.schbul.a007116

Place, U. T. (1956). Is consciousness a brain process? *British Journal of Psychology*, *47*, 44–50.

Potts, M. (2002). The evidential value of near-death experiences for belief in life after death. *Journal of Near-Death Studies*, *20*, 233–258. https://doi.org/10.1023/A:1015210902730

Preller, K. H., Burt, J. B., Ji, J. S, Preller, K. H., Burt, J. B., Ji, J. L., Schleifer, C. H., Adkinson, B. D., Stämpfli, P., Seifritz, E., Repovs, G., Krystal, J. H., Murray, J. D., Vollenweider, F. X., & Anticevic, A. (2018). Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. *eLife*, *7*, 1–35.

Pyysiäinen, I. (2009). *Supernatural agents. Why we believe in souls, gods, and buddhas*. Oxford University Press.

Ray, T. S. (2010). Psychedelics and the human receptorome. *PLoS ONE*, *5*(2), e9019. https://doi.org/10.1371/journal.pone.0009019

Reiner, A., & Levitz, J. (2018). Glutamatergic signaling in the central nervous system: Ionotropic and metabotropic receptors in concert. *Neuron*, *98*, 1080–1098.

Revonsuo, A. (2006). *Inner presence: Consciousness as a biological phenomenon*. MIT Press.

Riba, J., Anderer, P., Jane, F., Saletu, B., & Barbanoj, M. J. (2004). Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: A functional neuroimaging study using low-resolution electromagnetic tomography. *Neuropsychobiology*, *50*, 89–101.

Riba, J., Anderer, P., Morte, A., Urbano, G., Jané, F., Saletu, B., & Barbanoj, M. J. (2002). Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers. *British Journal of Clinical Psychology*, *53*, 613–628.

Riba, J., McIlhenny, E. H., Bouso, J. C., & Barker, S. A. (2015). Metabolism and urinary disposition of N,N-dimethyltryptamine after oral and smoked administration: A comparative study. *Drug Testing and Analysis*, *7*(5), 401–406. https://doi.org/10.1002/dta.1685

Riba, J., Rodriguez-Fornells, A., Urbano, G., Morte, A., Antonijoan, R., Montero, M., Callaway, J. C., & Barbanoj, M. J. (2001). Subjective effects and tolerability of the south american psychoactive beverage ayahuasca in healthy volunteers. *Psychopharmacology (Berl.)*, *154*(1), 85–95. https://doi.org/10.1007/S002130000606

Riba, J., Romero, S., Grasa, E., Mena, E., Carrió, I., & Barbanoj, M. J. (2006). Increased frontal and paralimbic activation following ayahuasca the pan-Amazonian inebriant. *Psychopharmacology (Berl.)*, *186*(1), 93–98. https://doi.org/10.1007/s00213-006-0358-7

Riba, J., Valle, M., Ubrano, G., Yritia, M., Morte, A., & Barbanoj, M. J. (2003). Human pharmacology of ayahuasca: Subjective and cardiovascular effects, monoamine metabolite excretion, and pharmacokinetics. *Journal of Pharmacology and Experimental Therapeutics*, *306*, 73–83.

Ricard, M., & Xuan Thuan, T. (2001). *The quantum and the Lotus*. Three Rivers Press.

Riga, M. S., Soria, G., Tudela, R., Artigas, F., & Celada, P. (2014). The natural hallucinogen 5-MeO-DMT, component of ayahuasca, disrupts cortical function in rats: Reversal by antipsychotic drugs. *International Journal of Neuropsychopharmacology*, *17*(8), 1269–1282. Epub 2014 Mar 20. PMID: 24650558. https://doi.org/10.1017/S1461145714000261

Rizzolatti, G., & Sinigaglia, S. (2016). The mirror mechanism: A basic principle of brain function. *Nature Reviews Neuroscience*, *17*, 757–765.

Rodrigues, A. V. S. L., Almeida, F. J., & Vieira-Coelho, M. A. (2019). Dimethyltryptamine: Endogenous role and therapeutic potential. *Journal of Psychoactive Drugs*, *51*(4), 299–310. https://doi.org/10.1080/02791072.2019.1602291

Rodrigues, L. S., Rossi, G. N., Rocha, J. M., L Osório, F., Bouso, J. C., Hallak, J. E. C., & dos Santos, R. G. (2021). Effects of ayahuasca and its alkaloids on substance use disorders: An updated (2016–2020) systematic review of preclinical and human studies. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-021-01267-7

Rodriguez, E., George, N., Lachaux, J. P., Martinerie, J., Renault, B., & Varela, F. J. (1999). Perception's shadow: Long distance synchronization of human brain activity. *Nature*, *397*, 430–433. https://doi.org/10.1038/17120

Rodriguez, M. A. (2007). A methodology for studying various interpretations of the N,N-dimethyltryptamine-Induced alternate reality. *Journal of Scientific Exploration*, *21*(1), 67–84.

Roseman, L., Ron, Y., Saca, A., Ginsberg, N., Luan, L., Karkabi, N., Doblin, R., & Carhart-Harris, R. (2021). Relational processes in Ayahuasca groups of Palestinians and Israelis. *Frontiers in Pharmacology*. *12*. https://www.frontiersin.org/articles/10.3389/fphar.2021.607529/full

Rossini, G., Rui, M., Linciano, P., Rossi, D., Boiocchi, M., Peviani, M., Poggio, E., Curti, D., Schepmann, D., Wünsch, B., González-Avendaño, M., Vergara-Jaque, A., Caballero, J., & Collina, S. (2021). Bitopic sigma 1 receptor modulators to shed light on molecular mechanisms

underpinning ligand binding and receptor oligomerization. *Journal of Medicinal Chemistry*, 64(20), 14997–15016.

Sadakierska-Chudy, A., & Filip, M. (2015). A comprehensive view of the epigenetic landscape. Part II: Histone post-translational modification, nucleosome level, and chromatin regulation by ncRNAs. *Neurotoxicity Research*, 27(2), 172–197. https://doi.org/10.1007/s12640-014-9508-6

Salmon, W. (1984). *Scientific explanation and the causal structure of the world*. Princeton University Press.

Sampedro, F., Revenga, M. F., Valle, M., Roberto, N., Domínguez-Clavé, E., Elices, M., Luna, L. E., Crippa, J. A. S., Hallak, J. E. C., de Araujo, D. B., Friedlander, P., Barker, S. A., Álvarez, E., Soler, J., Pascual, J. C., Feilding, A., & Riba, J. (2017). Assessing the psychedelic "after-glow" in ayahuasca users: Post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities. *International Journal of Neuropsychopharmacology*, 20(9), 698–711. https://doi.org/10.1093/ijnp/pyx036

Sanches, R. F., de Lima Osorio, F., dos Santos, R. G., Macedo, L. R. H., Maia-de-Oliveira, J. P., Wichert-Ana, L., de Araujo, D. B., Riba, J., Crippa, J. A. S., & Hallak, J. E. C. (2016). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A SPECT study. *Journal of Clinical Psychopharmacology*, 36(1), 77–81.

Sanders, J. W., & Zijlmans, J. (2021). Moving past mysticism in psychedelic science. *ACS Pharmacology & Translational Science*, 4(3), 1253–1255.

Sanz, C., Zamberlan, F., Erowid, E., Erowid, F., & Tagliazucchi, E. (2018). The experience elicited by hallucinogens presents the highest similarity to dreaming within a large database of psychoactive substance reports. *Frontiers in Neuroscience*, 12, 7. https://doi.org/10.3389/fnins.2018.00007

Saver, J. L., & Rabin, J. (1997). The neural substrates of religious experience. *Journal of Neuropsychiatry and Clinical Neurosciences*, 9(3), 498–510. PMID: 9276850. https://doi.org/10.1176/jnp.9.3.498

Scarpelli, S., Bartolacci, C., D'Atri, A., Gorgoni, M., & De Gennaro, L. (2019). The functional role of dreaming in emotional processes. *Frontiers in Psychology*, 10, 459. https://doi.org/10.3389/fpsyg.2019.00459

Schartner, M. M., & Timmermann, C. (2020). Neural network models for DMT-induced visual hallucinations. *Neuroscience of Consciousness*, Issue 1, 2020. niaa024. https://doi.org/10.1093/nc/niaa024

Schenberg, E. E., Alexandre, J. F. M., Filev, R., Cravo, A. M., Sato, J. R., Muthukumaraswamy, S. D., Yonamine, M., Waguespack, M., Lomnicka, I., Barker, S. A., & da Silveira, D. X. (2015). Acute biphasic effects of ayahuasca. *PLoS One*, 10, e0137202. https://doi.org/10.1371/journal.pone.0137202

Schrödinger, E. (1931). *Psychic Research*, 25, 91.

Schrödinger, E. (1958). *Mind and matter*. Cambridge University Press.

Schulz, D. B. (2012). *Simplicity in science*. Dissertation, University of Iowa. https://doi.org/10.17077/etd.tovd78md

Schupbach, J. N., & Sprenger, J. (2011). The logic of explanatory power. *Philosophy of Science*, 78, 105–127. https://doi.org/10.1086/658111

Schwaninger, J., Eisenberg, P. R., Schechtman, K. B., & Weiss, A. N. (2002). A prospective analysis of near-death experiences in cardiac arrest patients. *Journal of Near-Death Studies*, 20, 215–232.

Seager, W. (1999). *Theories of Consciousness: An Introduction and Assessment*. Routledge.

Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: Functional and topographic analyses. *Journal of Neuroscience*, 31, 4407–4420. https://doi.org/10.1523/JNEUROSCI.3335-10.2011

Seth, A. K., Izhikevich, E., Reeke, G. N., & Edelman, G. M. (2006). Theories and measures of consciousness: An extended framework. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 10799–10804. https://doi.org/10.1073/pnas.0604347103

Shani, I., & Keppler, J. (2018). Beyond combination: How cosmic consciousness grounds ordinary experience. *Journal of the American Philosophical Association*, 4(3), 390–410. https://doi.org/10.1017/apa.2018.30

Shanon, B. (2002). *The antipodes of the mind: Charting the phenomena of the ayahuasca experience*. Oxford University Press.

Shenefelt, P. D., & Shenefelt, D. A. (2014). Spiritual and religious aspects of skin and skin disorders. *Psychology Research and Behavior Management*, 7, 201–212. https://doi.org/10.2147/PRBM.S65578

Shi, H. Y., & Ng, S. C. (2018). The state of the art on treatment of Crohn's disease. *Journal of Gastroenterology*, 53(9), 989–998. https://doi.org/10.1007/s00535-018-1479-6

Shoja, M. M., Hoepfner, L. D., Agutter, P. S., Singh, R., & Tubbs, R. S. (2016). History of the pineal gland. *Child's Nervous System*, 32, 583–586.

Singer, W. (2015). The ongoing search for the neuronal correlate of consciousness. In T. Metzinger & J. M. Windt (Eds.), *open MIND*. MIND Group. https://doi.org/10.15502/9783958570344

Smart, C., Strathdee, G., Watson, S., Murgatroyd, C., & McAllister-Williams, R. H. (2015). Early life trauma, depression and the glucocorticoid receptor gene- an epigenetic perspective. *Psychological medicine*, 45(16), 3393–3410. Epub 2015 Sep 21. PMID: 26387521. https://doi.org/10.1017/S0033291715001555

Smart, J. J. C. (1959). Sensations and brain processes. *Philosophical Review*, 68, 141–156.

Smith, T. L. (1975). Some neurochemical effects of N,N-dimethyltryptamine and their possible relation to acute schizophrenia. *Thesis*, Reno, Nevada USA, 35, 4374B–4375B. report Dissertation Abst Intern. 1975;B.

Smith, T. L. (1977). Increased synthesis of striatal DA by N,N-DMT. *Life Sciences*, 21, 1597–1601.

Soler, J., Elices, M., Dominguez-Clave, E., Pascual, J. C., Feilding, A., Navarro-Gil, M., García-Campayo, J., & Riba, J. (2018). Four weekly ayahuasca sessions lead to increases in "acceptance" capacities: A comparison study with a standard 8-week mindfulness training program. *Frontiers in Pharmacology*, 9, 224. https://doi.org/10.3389/fphar.2018.00224

Soler, J., Elices, M., Franquesa, A., Barker, S., Friedlander, P., Feilding, A., Pascual, J. M., & Riba, J. (2016). Exploring the therapeutic potential of ayahuasca: Acute intake increases mindfulness-related capacities. *Psychopharmacology (Berl.)*, 233(5). https://doi.org/10.1007/s00213-015-4162-0

Solms, M. (2000). Dreaming and REM sleep are controlled by different brain mechanisms. *Behavioral and Brain Sciences*, 23, 843–850.

St John, G. (2016). The DMT gland: The pineal, the spirit molecule, and popular culture. *International Journal for the Study of New Religions*, 7, 153–174.

St John, G. (2017). Aussiewaska: A cultural history of changa and ayahuasca analogues in Australia. In B. C. Labate, C. Cavnar, & A. K. Gearin (Eds.), *The world ayahuasca diaspora: Reinventions and controversies* (pp. 143–164). Routledge.

St John, G. (2018). The breakthrough experience: DMT hyperspace and its liminal aesthetics. *Anthropology of Consciousness*, 29, 57–76.

Stace, W. T. (1960). *Mysticism and philosophy*. Lippincott.

Strassman, R. (2001). *DMT: The spirit molecule*. Park Street Press.

Strassman, R., Wojtowicz, S., Luna, L. E., & Frecska, E. (2008). *Inner paths to outer space: Journeys to alien worlds through psychedelics and other spiritual technologies*. Park Street Press.

Strassman, R. J. (1996). Human psychopharmacology of N,N-dimethyltryptamine. *Behavioural Brain Research*, 7, 121–124.

Strassman, R. J., & Qualls, C. R. (1994). Dose-response study of N,N-dimethyltryptamine in humans: I. Neuroendocrine, autonomic, and cardiovascular effects. *Archives of general psychiatry*, 51(2), 85–97.

Su, T. P., & Hayashi, T. (2003). Understanding the molecular mechanism of sigma-1 receptors: Towards A hypothesis that sigma-1 receptors are intracellular amplifiers for signal transduction. *Current Medicinal Chemistry*, 10, 2073–2080.

Su, T. P., Hayashi, T., & Vaupel, D. B. (2009). When the endogenous hallucinogenic trace amine N,N-dimethyltryptamine meets the sigma-1 receptor. *Science Signaling*, *2*(61), 1–7.

Suárez, A. L., Feramisco, J. D., Koo, J., & Steinhoff, M. (2012). Psycho-neuroimmunology of psychological stress and atopic dermatitis: Pathophysiologic and therapeutic updates. *Acta Dermato-Venereologica*, *92*(1), 7–15. https://doi.org/10.2340/00015555-1188

Sun, H., Kennedy, P., & Nestler, E. (2013). Epigenetics of the depressed brain: Role of histone acetylation and methylation. *Neuropsychopharmacology*, *38*, 124–137. https://doi.org/10.1038/npp.2012.73

Sutterer, D. W., Foster, J. J., Serences, J. T., Vogel, E. K., & Awh, E. (2019). Alpha-band oscillations track the retrieval of precise spatial representations from long-term memory. *Journal of Neurophysiology*, *122*, 539–551.

Swanson, L. R. (2018). Unifying theories of psychedelic drug effects. *Frontiers in Pharmacology*, *9*(172), 1–23.

Szabo, A., & Frecska, E. (2016). Dimethyltryptamine (DMT): A biochemical Swiss Army knife in neuroinflammation and neuroprotection? *Neural Regeneration Research*, *11*, 396. https://doi.org/10.4103/1673-5374.179041

Szabo, A., Kovacs, A., Frecska, E., & Rajnavolgyi, E. (2014). Psychedelic N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. *PLOS ONE*, *9*, e106533. https://doi.org/10.1371/journal.pone.0106533

Szabo, A., Kovacs, A., Riba, J., Djurovic, S., Rajnavolgyi, E., & Frecska, E. (2016). The endogenous hallucinogen and trace amine N, N-dimethyltryptamine (DMT) displays potent protective effects against hypoxia via sigma-1 receptor activation in human primary iPSC-derived cortical neurons and microglia-like immune cells. *Frontiers in Neuroscience*, *10*, 423. https://doi.org/10.3389/fnins.2016.00423

Szabo, I., Varga, V., Dvoracsko, S., Farkas, A. E., Körmöczi, T., Berkecz, R., Kecskés, S., Menyhárt, Á., Frank, R., Hantosi, D., Cozzi, N. V., Frecska, E., Tömböly, C., Krizbai, I. A., Bari, F., & Farkas, E. (2021). N,N-Dimethyltryptamine attenuates spreading depolarization and restrains neurodegeneration by sigma-1 receptor activation in the ischemic rat brain. *Neuropharmacology*, *192*(2), 108612.

Szára, S. (1956). Dimethyltryptamine: Its metabolism in man; the relation to its psychotic effect to the serotonin metabolism. *Experientia*, *12*, 441–442.

Szmulewicz, A. G., Valerio, M. P., & Smith, J. M. (2015). Switch to mania after ayahuasca consumption in a man with bipolar disorder: A case report. *International Journal of Bipolar Disorders*, *3*, 4. https://doi.org/10.1186/s40345-014-0020-y

Tafur, J. (2017). *The fellowship of the River: A medical doctor's exploration into traditional amazonian plant medicine*. Espiritu Books.

Tagliazucchi, E., Zamberlan, F., Cavanna, F., de la Fuente, L., Romero, C., Sanz Perl, Y., & Pallavicini, C. (2021). Baseline power of theta oscillations predicts mystical-type experiences induced by DMT in a natural setting. *Frontiers in Psychiatry*, *12*, 1–9.

Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S. D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., Bullmore, E., Williams, T., Bolstridge, M., Feilding, A., Nutt, D. J., & Carhart-Harris, R. (2016). Increased global functional connectivity correlates with LSD-induced ego dissolution. *Current Biology*, *26*, 1043–1050.

Thomas, G., Lucas, P., Capler, N. R., Tupper, K. W., & Martin, G. (2013). Ayahuasca-assisted therapy for addiction: Results from a preliminary observational study in Canada. *Current Drug Abuse Reviews*, *6*(1), 30–42.

Thompson, M. A., & Weinshilboum, R. M. (1998). Rabbit lung indolethylamine N-methyltransferase. cDNA and gene cloning and characterization. *Journal of Biological Chemistry*, *273*, 34502–34510.

Thonnard, M., Charland-Verville, V., Brédart, S., Dehon, H., Ledoux, D., Laureys, S., & Vanhaudenhuyse, A. (2013). Characteristics of near-death experiences memories as compared to real and imagined events memories. *PLoS ONE*, *8*(3), e57620. https://doi.org/10.1371/journal.pone.0057620

Timmermann, C., Kettner, H., Letheby, C., Roseman, L., Rosas, F., & Carhart-Harris, R. (2021). Psychedelics alter metaphysical beliefs. *Scientific Reports*, *11*, 22166. https://doi.org/10.1038/s41598-021-01209-2

Timmerman, C., Roseman, L., Williams, L., Erritzoe, D., Martial, C., Cassol, H., Laureys, S., Nutt, D., & Carhart-Harris, R. (2018). DMT models the near-death experience. *Frontiers in Psychology*, *9*(1424), 1–12.

Timmermann, C., Roseman, L., Schartner, M., Milliere, R., Williams, L. T. J., Erritzoe, D., Muthukumaraswamy, S., Ashton, M., Bendrioua, A., Kaur, O., Turton, S., Nour, M. M., Day, C. M., Leech, R., Nutt, D. J., & Carhart-Harris, R. L. (2019). Neural correlates of the DMT experience assessed with multivariate EEG. *Scientific Reports*, *9*, 16324. https://doi.org/10.1038/s41598-019-51974-4

Tononi, G., & Edelman, G. M. (1998). Consciousness and complexity. *Science*, *282*, 1846–1851. https://doi.org/10.1126/science.282.5395.1846

Tucker, J. B. (2009). *Life before life: A scientific investigation of children's memories of previous lives*. Piatkus.

Tupper, K. W. (2008). The globalization of ayahuasca: Harm reduction or benefit maximization? *International Journal of Drug Policy*, *19*, 297–303.

Valle, M., Maqueda, A. E., Rabella, M., Rodríguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mañanas, M. À., Barker, S., Friedlander, P., Feilding, A., & Riba, J. (2016). Inhibition of alpha oscillations through serotonin 2A receptor activation underlies the visual effects of ayahuasca in humans. *European Neuropsychopharmacology*, *26*(7), 1161–1175.

Van Gordon, W., Shonin, E., Dunn, T. J., Sheffield, D., Garcia-Campayo, J., & Griffiths, M. D. (2018). Meditation-induced near-death experiences: A 3-year longitudinal study. *Mindfulness (N Y)*, *9*(6), 1794–1806. https://doi.org/10.1007/s12671-018-0922-3

van Lommel, P., van Wees, R., Meyers, V., & Elfferich, I. (2001). Near-death experience in survivors of cardiac arrest: A prospective study in The Netherlands. *Lancet*, *358*(9298), 2039–2045. Erratum in: Lancet 2002 Apr 6;359(9313):1254. PMID: 11755611. https://doi.org/10.1016/S0140-6736(01)07100-8

Velmans, M. (2007). The co-evolution of matter and consciousness. *Synthesis Philosophica*, *44*, 273–282.

Vollenweider, F. X., & Preller, K. H. (2020). Psychedelic drugs: Neurobiology and potential for treatment of psychiatric disorders. *Nature Reviews Neuroscience*, *21*, 611–624.

Wallach, J. V. (2009). Endogenous hallucinogens as ligands of the trace amine receptors: A possible role in sensory perception. *Medical Hypotheses*, *72*, 91–94.

Weiss, B., Miller, J. D., Carter, N. T., & Keith Campbell, W. (2021). Examining changes in personality following shamanic ceremonial use of ayahuasca. *Scientific Reports*, *11*. https://doi.org/10.1038/s41598-021-84746-0

Williams, M., & Penman, D. (2011). *Mindfulness: A practical guide to finding peace in a frantic world*. Piatkus.

Willis, G. L. (2008). Parkinson's disease as a neuroendocrine disorder of circadian function: Dopamine-melatonin imbalance and the visual system in the genesis and progression of the degenerative process. *Reviews in the Neurosciences*, *19*(4–5), 245–316. PMID: 19145986. https://doi.org/10.1515/revneuro.2008.19.4-5.245

Winkelman, M. (2005). Drug tourism or spiritual healing? Ayahuasca seekers in Amazonia. *Journal of Psychoactive Drugs*, *37*, 209–218.

Winkelman, M. J. (2017). The mechanisms of psychedelic visionary experiences: Hypotheses from evolutionary psychology. *Frontiers in Neuroscience*, *11*, 539. https://doi.org/10.3389/fnins.2017.00539

Winkelman, M. J. (2018). An ontology of psychedelic entity experiences in evolutionary psychology and neurophenomenology. *Journal of Psychedelic Studies*, *2*, 1–19.

Winkelman M. J. (2021). The evolved psychology of psychedelic set and setting: Inferences regarding the roles of shamanism and entheogenic ecopsychology. *Frontiers in Pharmacology*, *12* https://doi.org/10.3389/fphar.2021.619890

Winstock, A. R., Kaar, S., & Borschmann, R. (2014). Dimethyltryptamine (DMT): Prevalence, user characteristics and abuse liability in a large global sample. *Journal of Psychopharmacology*, *28*, 49–54.

Yaden, D. B., Johnson, M. W., Griffiths, R. R., Doss, M., Garcia-Romeu, A., Nayak, S., Gukasayan, N., Mathur, B. N., Barrett, F. S. (2021). Psychedelics and consciousness: Distinctions, demarcations, and opportunities. *International Journal of Neuropsychopharmacology*, *24*(8), 615–623. 2021:pyab026. Epub ahead of print. PMID: 33987652. https://doi.org/10.1093/ijnp/pyab026

Yaden, D. B., Yaden, M. E., & Griffiths, R. R. (2020). Psychedelics in psychiatry—keeping the renaissance from going off the rails. *JAMA Psychiatry*, *78*(5). https://doi.org/10.1001/jamapsychiatry.2020.3672

Ylikoski, P., & Kuorikoski, J. (2010). Dissecting explanatory power. *Philosophy Study*, *148*, 201–219. https://doi.org/10.1007/s11098-008-9324-z

Zeifman, R. J., Singhal, N., dos Santos, R. G., Sanches, R. F., De Lima Osório, F., Hallak, J. E. C., & Weissman, C. R. (2021). Rapid and sustained decreases in suicidality following a single dose of ayahuasca among individuals with recurrent major depressive disorder: Results from an open-label trial. *Psychopharmacology*, *238*, 453–459. https://doi.org/10.1007/s00213-020-05692-9

Zhao, H., Li, D., & Li, X. (2018). Relationship between dreaming and memory reconsolidation. *Brain Sciences Advances*, *4*(2), 118–130.