Degree project

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A Systematic Review of the Neural Correlates and the Psychedelic Experience Induced by Ayahuasca and N, N-Dimethyltryptamine (DMT)

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Abstract

Background: Ayahuasca is a South American psychoactive brew that contains Dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOIs). Research has experienced a resurgence of interest in exploring the potential of these substances in the last decade. Thus, the aim of this review was to systematically review studies that used a placebo-controlled design to explore the neural correlates and *psychedelic experience* induced by DMT and ayahuasca. ***Method***: The search was conducted using the Web of Science and Scopus databases to select studies published between January 2000 and February 2022 that used neuroimaging techniques and recruited healthy participants. Thus, 7 papers were selected. ***Results***: Ayahuasca alters electrical activity in the brain by decreasing spectral power in all EEG frequency bands, predominantly in the *alpha* band. DMT caused a spatially widespread decrease in *alpha* bands and a more modest decrease in *beta* bands. Ayahuasca caused an increase in the flow of information in the brain from posterior regions to more frontal regions and an increase in scores in all the Hallucinogen Rating Scale (HRS) subscales. Ayahuasca decreased connectivity in the Default Mode Network (DMN) and increases connectivity between DMN and the salience network. ***Conclusion***: Ayahuasca and DMT can reliably produce profound changes in perception, emotions, and sense of self. Moreover, the decrease in the *alpha* band, the alteration of information flow between posterior and frontal regions, and the decrease in connectivity in the DMN could be the keys to understanding the neural correlates and the *psychedelic experience* induced by DMT and ayahuasca.

Keywords: n,n-dimethyltryptamine, ayahuasca, neural correlates, neuroimaging, psychedelic experience

A Systematic Review of the Neural Correlates and the Psychedelic Experience Induced by Ayahuasca and N, N-Dimethyltryptamine (DMT)

The use of hallucinogenic plants in ceremonial contexts for recreational, spiritual, and healing purposes in human cultures dates back thousands of years (dos Santos & Hallak, 2021; Nichols, 2016; Strassman, 1984) and continues today (Hartogsohn, 2021; Sexton et al., 2019). The term *psychedelic* means *mind-manifesting* and was first coined by psychiatrist Humphry Osmond (1957). Psychedelics are psychoactive substances and a subcategory of hallucinogenic drugs that profoundly affect cognition, emotions, sense of self, perception, and human consciousness (Nichols, 2016; Swanson, 2018). Moreover, psychedelics can induce different subjective effects that can be divided generally into two categories. The first relates to their long-term therapeutic potential (for review see Johnson et al., 2019), and the second relates to the immediate state of consciousness induced by these substances which will be referred to as the *psychedelic experience* in this review. Although these two aspects of the subjective effects of psychedelics are relevant to understanding the potential of these substances, they have different mechanisms of action in the brain. Therefore, this systematic literature review will focus exclusively on the neural correlates and the immediate *psychedelic experience* induced by DMT and ayahuasca to provide a more comprehensive understanding of the effects of these substances on consciousness and offer deeper insights into their neuroanatomical properties.

Classical psychedelics can be divided chemically into two main categories. The first category consists of *phenethylamine* variations, such as mescaline, which is the main psychoactive ingredient in the plant *peyote*. In the second category, we find variations of the *tryptamine* structure, such as lysergic acid diethylamide (LSD), psilocybin which is the main psychoactive ingredient of *magic mushrooms*, and N, N-dimethyltryptamine (DMT) which is the main psychoactive component of the plant *Psychotria Viridis* (Nichols, 2016). These substances act as agonists or partial agonists at the serotonin (5-hydroxytryptamine) 5-HT2A receptors in the brain (Nichols, 2016). The discovery of the function of serotonin in the brain was first catalysed by the discovery of LSD in the 1950s (Woolley & Shaw, 1954). Accordingly, the effects of LSD were found to be attributed to its involvement in interfering with the availability of serotonin in the brain (Woolley & Shaw, 1954). Interestingly, the majority of 5-HT is synthesized in the gastrointestinal tract, while a small percentage of it is synthesized in the nervous system (Bertrand & Bertrand, 2010; Lesurtel et al., 2007). In the brain, the 5- HT cell bodies, consisting of approximately 350000 cells, are mainly concentrated in the brainstem. A large proportion of these cells are located in the raphe nuclei, which extend from the caudal level of the medulla oblongata to the middle level of the mesencephalon (Charnay & Leger, 2010). There are two groups of 5 HT neurons, distinguished by the location of their cell bodies. The first is located in the mesencephalic and rostral pons and sends axons to the

forebrain; the second group is located in the rostral pons and medulla oblongata and sends axons to the brainstem and spinal cord (Charnay & Leger, 2010).

Psychedelic research has experienced a resurgence of interest in the last decade, and scientists and mainstream media now use the term *psychedelic renaissance* to describe this resurgence (George et al., 2019; Kohli, 2013). The scientific study of DMT and ayahuasca provides a unique opportunity for cognitive neuroscientists to investigate the mechanism of serotonergic pathways, sense of self, and the nature of consciousness and its altered states. Moreover, this revival of scientific exploration may also pave the way for a new multidisciplinary field of cognitive neuroscience dedicated to exploring the potential of these substances at multiple levels. Furthermore, the importance of exploring the 5-HT systems comes from the fact that these chemical messengers play an essential role in the most fundamental physiological functions of the body such as cardiovascular regulation, thermoregulation, reproduction sleep-wake cycle, and responses to stressors (Charnay & Leger, 2010). Accordingly, the study of ayahuasca and DMT not only provides a great opportunity into understanding the human mind but also its physiology.

The Aim

Although scientific research on ayahuasca and DMT is still in its infancy and the mechanism of their action in the brain is not fully elucidated, there is no shortage of electrophysiological and neuroimaging studies investigating the neural correlates and the *psychedelic experience* induced by these hallucinogens (Acosta-Urquidi, J, 2015; Alamia et al., 2020; Alonso et al., 2015; Daumann et al., 2009; de Araujo et al., 2011; Palhano-Fontes et al., 2015; Pallavicini et al., 2021; Pasquini et al., 2020; Riba et al., 2001, 2002, 2003, 2004, 2006; Schenberg et al., 2015; Stuckey et al., 2005; Timmermann et al., 2019; Valle et al., 2016). To this end, and to provide clarity to the reader, current psychedelic research cannot be fully appreciated without reference to other areas of research, including clinical psychology, psychiatry, chemistry, anthropology, ethnopharmacology, sociology, spirituality, philosophy, and others. However, such an undertaking is impossible to accomplish in this review. Therefore, the aim of this review is to focus exclusively on the neural correlates and *psychedelic experience* induced by DMT and ayahuasca from the perspective of cognitive neuroscience by reviewing original studies that used a placebo-controlled design.
Further and to introduce the reader to the topic, the first part of this review contains a brief description of DMT and ayahuasca, followed by an overview of some of the major scientific concepts related to psychedelic research. The second part contains an overview of electrophysiological and neuroimaging studies investigating the neural correlates and the *psychedelic experience* induced by DMT and ayahuasca. Finally, in the Discussion section, the main findings, ethical considerations, and the limitations of this research are highlighted.

DMT and Ayahuasca

As for modern science, DMT was first synthesized in 1931 by chemist Richard Manske (Manske, 1931) and its occurrence in plants was discovered in 1946 by microbiologist Oswaldo Gonçalves de Lima (cited in Barker, 2018). In 1956, chemist Stephen Szara first discovered and demonstrated the hallucinogenic properties of DMT by extracting it from the *Mimosa hostilis* plant and administering it intramuscularly to himself (Szára, 1956). Consumers of DMT report experiencing visual illusions and hallucinations, distortion of body image, speech disturbances, mood changes, and euphoria (Szára, 1956). The effects of DMT given intramuscularly at a dose of 0.2–1 mg/kg have a rapid onset (2–5 min) and last between 30–60 min (Barker, 2018). Undoubtedly, the discovery of DMT has led to building a cultural bridge between modern science and indigenous cultures. Moreover, it has sparked the interest of contemporary scientists in exploring its effect on the brain and the states of consciousness.

The word ayahuasca comes from the *Quechua* language and is composed of two parts - *aya*, meaning soul, and *waska*, meaning vine (dos Santos & Hallak, 2021). In northwestern Amazonian countries such as Brazil, Peru, and Ecuador, the word refers to a brown beverage derived from the fermentation of two plants. *Psychotria viridis,* which contains DMT and binds to serotonin receptors, and *Banisteriopsis caapi,* which contains harmine, tetrahydroharmine (THH), and harmaline, which act as inhibitors of monoamine oxidase (MAO) and degrade DMT, allowing its oral ingestion and leading to longer-lasting effects (McKenna et al., 1984; Nichols, 2016). However, DMT is not only present in *Psychotria Viridis* but also in over fifty other plants (cited in Domínguez-Clavé et al., 2016). Consumers of DMT-containing ayahuasca report a state of consciousness described as feelings of oneness, euphoria, transcendence of time and space, and meaningful encounters with non-human entities (Riba et al., 2002, 2003).

The first effects of ayahuasca usually occur within 30 minutes to two hours. According to Riba et al. (2001, 2003), individuals experience altered skin sensitivity, heat, and cold sensations, gastrointestinal distress, and profound visions. However, some individuals do not report experiencing visual images. Within approximately four to six hours after ingestion, the overall intensity of the experience begins to decrease and diminish (Riba et al., 2001, 2003).

The psychedelic Experience

Psychedelics seem to be capable of causing profound altered states of consciousness (ASC) that differ from normal states of consciousness. Since the 1990s, researchers have become increasingly interested in exploring the phenomenology of hallucinogenic ASC in humans (Vollenweider & Geyer, 2001). Over the years, several attempts have been made to

describe the phenomenology of these ASCs, and various measurement tools have been used to assess them. Among these instruments is the Phenomenology of Consciousness Inventory (PCI) developed by Pekala et al. (1986), the Hallucinogen Rating Scale (HRS) developed by Strassman (1994), the Altered State of Consciousness Questionnaire revised version (APZ-OAV) developed by Dittrich (1998), the 30-item Mystical Experience Questionnaire (MEQ30) developed by Roland R. Griffiths (Griffiths et al., 2006), and the 5-Dimensional Altered States of Consciousness Rating Scale 5D-ASC developed by Studerus et al. (2010). Some of these scales are discussed in more detail in the results section since they are used as tools for measuring the immediate subjective effects of DMT and ayahuasca in the studies on which this review focuses.

The effects of the *psychedelic experience* induced by ayahuasca can be divided into two categories. The physical effects include increases in blood pressure, cardiac and respiratory rates, fluctuation of skin temperature, pupil diameter, spatiotemporal scaling, and gastrointestinal distress (Riba et al., 2002, 2003). The psychological effects include increased sense of well-being, changes in self-perception, insights, feelings of apprehension, heightened introspection, and profound vivid visual hallucinations called mirações (seeing) with which some people report meaningful encounters with non-human entities (Riba et al., 2001, 2003, 2006).

The major physiological effects of intravenous DMT are increased blood pressure, body dissociation, and heart rate, as well as increased levels of β-endorphin and cortisol in the blood (Strassman, 1994). Psychological effects include visual hallucinations, shifts in mood, auditory hallucinations, euphoria, and anxiety depending on the set and setting (Strassman, 1994; Szára, 1956). Moreover, users of ayahuasca and DMT report similar experiences to other non-ordinary states of consciousness, such as near-death experiences, transcendental experiences, and mystical experiences (Martial et al., 2019; Timmermann et al., 2018).

Set and Setting

Several factors influence a person's reaction to a hallucinogen, including both pharmacological and non-pharmacological factors. In addition to chemical effects, psychological factors such as mood, anticipation, and intention also have a direct effect on the person's experience with the hallucinogen. These psychological factors are commonly referred to as the *set* (Hartogsohn, 2016). In addition to chemical effects and psychological factors, environmental factors such as physical, social, and cultural factors also influence how a person responds to the hallucinogen. These environmental factors are referred to as the *setting* (Hartogsohn, 2016). Psychologist Timothy Leary (Leary et al., 1963) coined the term (set and setting) in 1963, and it is still used now a day in psychedelics research (Hartogsohn, 2017; Kaelen et al., 2018) and pharmacology to account for the effects of psychological and

environmental factors on a person's response to psychedelics. In conclusion and in order to understand the effects of psychedelics, it is crucial to bear in mind that the three factors, namely the dose of the psychedelic substance, the *set*, and the *setting* are essential to the overall experience.

Default Mode Network (DMN)

Researchers have discovered through experimental studies using positron emission tomography (PET) that certain brain regions, known as the *default mode network*, are active when people are engaged in self-referential processing and self-projection such as thinking of the past or contemplating the future (Raichle et al., 2001). The major regions of the DMN are: 1) the medial prefrontal cortex (MPFC), 2) the posterior cingulate cortex 3) the inferior parietal lobule (IPL), 4) the retrosplenial cortex (RSP), 5) the medial temporal lobule (MTL), and 6) the parahippocampal cortex (PHC) (Raichle, 2015; Raichle et al., 2001). When we are resting and thinking about ourselves, these regions seem to be more active, whereas they become less active when we are engaged in a particular activity or task. It has been shown that there is increased activity in DMN in patients who suffer from schizophrenia (Garrity et al., 2007), social phobia (Gentili et al., 2009), and depression (Sheline et al., 2009). There is some interesting evidence that these regions are associated with 5HT2A receptor sites, which are considered to be cellular targets of classical psychedelics (Barrett & Griffiths, 2017), which explains the decreased activity in the DMN in psilocybin intake (Carhart-Harris et al., 2012). The association between DMN and psychedelics will be further explored in the results section.

Methods

This systematic review utilized the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009) for data collection and organization.

Search strategy

The electronic search was conducted using Web of Science, and Scopus was scrutinized based on the title, abstract, and full text in February 2022. The following search terms were used to identify the relevant studies; (DMT OR N, N-Dimethyltryptamine OR Ayahuasca*) AND (Neural correlates* OR neuroimaging* OR functional brain imaging* OR structural brain imaging* OR Electroencephalography OR Magnetoencephalograph OR Positron emission tomography* OR Single-photon emission computed tomography* OR EEG* OR MEG* OR PET* OR SPECT*) AND (psychedelic experience* OR subjective effects*).

Inclusion and Exclusion Criteria

Experimental studies that assessed psychological or/and neurological outcomes conducted on human subjects were included in this review. The included studies were published in peer-reviewed journals written in English and published between January 2000 and February 2022. Additionally, the following criteria were considered: Participants: healthy individuals over the age of 18 years. Interventions: ayahuasca and/or DMT. Control: comparisons with placebo groups/dose. Outcome: EEG measurements, functional magnetic resonance imaging (fMRI), single-photon emission tomography (SPECT), and psychometric questionnaires measuring *psychedelic experience* induced by DMT and ayahuasca. Last but not least, clinical studies that examined the therapeutic effects of DMT/ayahuasca on mental disorders and those that did not examine the neural correlates and *psychedelic experience* were excluded.

Data Extraction

Based on all included studies, the following data were extracted: study design, intervention/dose, number of participants, and outcomes.

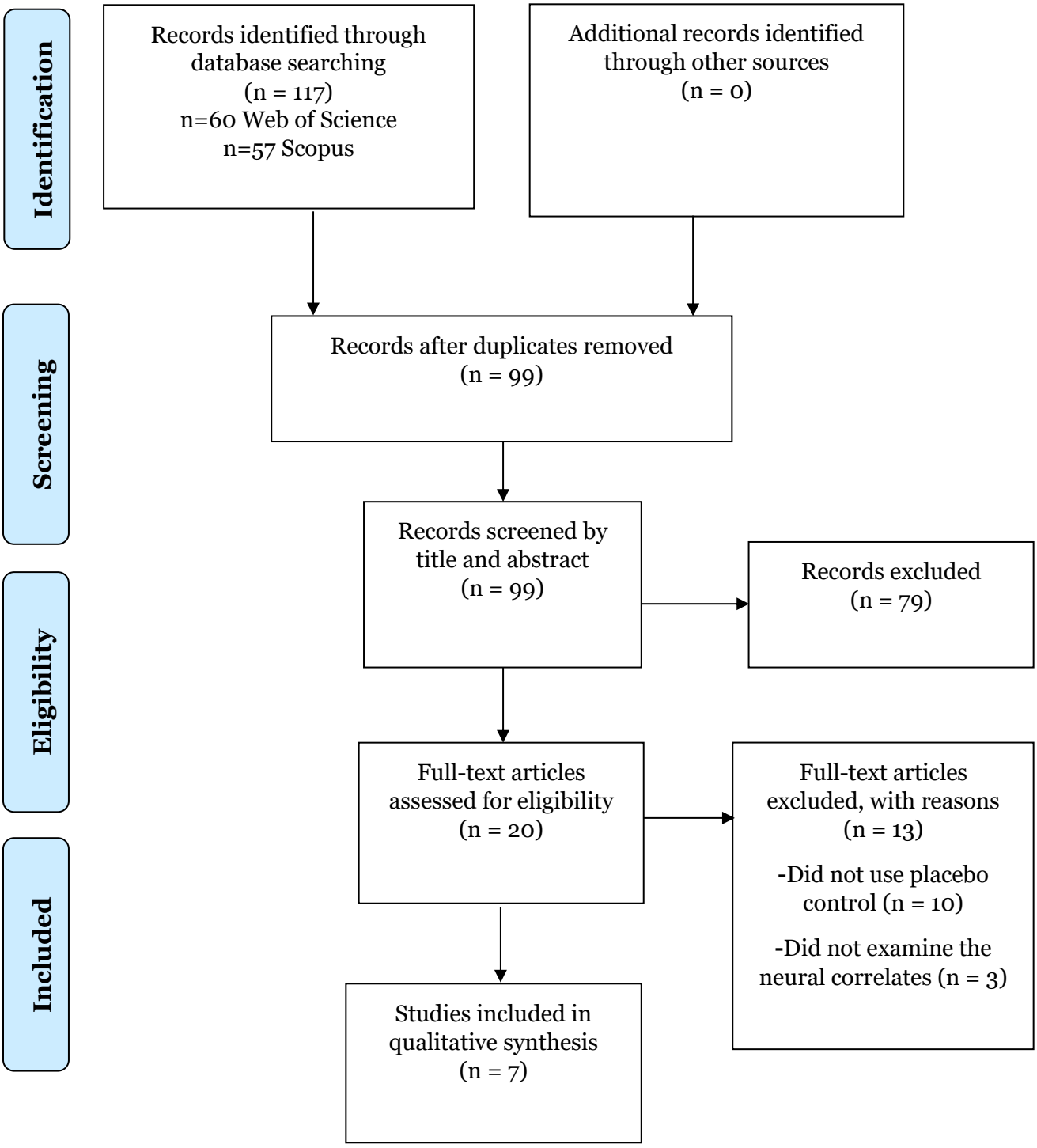
Results

Search Results

Using the previously mentioned search strings, the literature search uncovered 117 records in the Web of Science and Scopus databases (Figure 1). Eighteen duplicate records were excluded. Ninety-nine records were scanned by title and abstract and seventy-nine records of them were excluded. Twenty full texts were scanned for eligibility and 13 were excluded because they either examined the therapeutic effects of DMT and ayahuasca or other types of studies that did not examine the neural correlates and *psychedelic experience* induced by DMT and ayahuasca or did not use placebo control in the study design. One study used DMT and 6 studies used ayahuasca were included in the final analyses of this review and are summarized in Table 1.

Figure 1

PRISMA flow char



Note: This flow diagram follows the structure and guidelines of (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*) (Moher et al., 2009).

Table 1

Summary of studies included

Reference by drug	N	Drug dose	Study design	Measurements
DMT				
Timmermann et al. (2019)	13	(7- 20 mg) P (saline)	Single-blind fixed-order	Power spectral density PE (VAS)
Ayahuasca				
Riba et al. (2002)	18	0.85 mg DMT/kg P (0.75 g lactose)	RCT	Power spectral density PE (HRS)
Riba et al. (2004)	18	0.85 mg DMT/kg P (0.75 g lactose)	RCT	Power spectral density PE (HRS)
Riba et al., (2006)	15	1 mg DMT/kg P (0.75 g lactose)	RCT	Cerebral blood flow PE (HRS+ ARCI)
Alonso et al. (2015)	10	0.75 mg DMT/kg P(not-mentioned)	RCT	Transfer entropy PE (HRS+ APZ)
Valle et al. (2016)	12	0.75 mg DMT/kg 40 mg ketanserin P (lactose)	RCT	Power spectral density PE (HRS+ APZ+ ARCI)
Pasquini et al. (2020)	43	0.36 mg/ml DMT	Randomized, single-blind, placebo	Functional connectivity PE (HRS)

Note. DMT = N,N-dimethyltryptamine; P= Placebo; PE: Psychedelic experience; RCT = Randomized double-blind control; HRS = Hallucinogenic Rating Scale; APZ = Altered state of consciousness questionnaire; ARCI=Addiction research center inventory.

The Effects of DMT on Spectral Power and Signal Diversity

In this review, one study used an electroencephalogram (EEG) and a comparison with a placebo to examine the neural correlates of DMT has been identified. Timmermann et al. (2019) used EEG techniques in a fixed-order, single-blind design of intravenous administration of DMT and placebo (sterile saline) in 13 healthy volunteers to determine how intravenous DMT affects the power spectrum and signal diversity of brain activity. Subjects participated in two sessions, receiving the placebo in the first session and DMT in the second. Each of the participants received one of four doses of DMT due to the paucity of data on intravenous administration of DMT and to ensure an appropriate DMT dose for brain imaging purposes. Three participants received 7 mg, four received 14 mg, one received 18 mg, and five received 20 mg. The researchers measured the intensity of the DMT experience by asking participants to provide a rating of the subjective effect of each minute of the experience. In addition, participants were asked to rate different aspects of the experience using various visual analogue scales (VAS), including statements such as "I experienced a different reality or diminution" Finally, one day after the DMT session, participants participated in micro-phenomenological interviews (for review see Petitmengin, 2006) to discover a distinct ‘core’ component of the subjective experience and to reduce subjective biases influencing the first-person report (Timmermann et al., 2019). In comparison with the placebo condition, the DMT condition showed a spatially widespread decrease in *alpha* bands and a more modest decrease in *beta* bands. The power decreases in the *alpha* bands were pronounced in all channels (Timmermann et al., 2019). In addition, when the EEG spectrum was decomposed into its oscillatory and fractal (1/f) components, the decreases in total *alpha* and *beta* total power were consistent, whereas the fractal component showed significantly reduced power in all frequency bands. Signal diversity was significantly increased under DMT compared with placebo. Additionally, a sustained *alpha* peak was observed during the placebo condition. When time-dependent EEG analyses were considered, a stable decrease in power for *alpha* activity was observed throughout the 5 minutes after DMT injection. In addition, a decrease in power for the *delta* and *theta* bands was observed 1-minute post- DMT injection. Considering the rating of the intensity of the experience by the subjective reports, a negative correlation was noted between the changes in total *alpha* power in the DMT condition and the subjective reports. In addition, decreases in *beta* power correlated negatively with higher intensity ratings. Finally, regarding oscillatory power, both *delta* and *theta* power showed significant positive correlations with subjective reports of intensity (Timmermann et al., 2019).

The Effects of Ayahuasca on Spectral Power

Three studies examining the effects of ayahuasca on the spectral power we identified in this review (Table 2). To explore the effects of ayahuasca on brain electrical

activity, Riba et al. (2002) used topographic quantitative electroencephalography (q-EEG), a non-invasive method to assess the main effects of ayahuasca in a randomized, double-blind, placebo-controlled study. Study participants included 18 healthy volunteers who had previous experience with psychedelic drugs. Volunteers took part in four experimental sessions during which they received a single dose of encapsulated freeze-dried ayahuasca each day (equivalent to a low dose of 0.6 mg DMT kg^{-1}, a high dose of 0.85 mg kg^{-1} body weight, and a placebo consisting of capsules containing 0.75 g lactose). To familiarize volunteers with the experimental environment, they all received a placebo in a single-blinded condition on day 1, followed by one of the three treatment options in a double-blinded condition on days 2 to 4. EEG was recorded at baseline (prior to the treatment) and periodically after treatment administration. Volunteers were asked to complete the questionnaire HRS four hours after the most prominent subjective effects of the drug had subsided to quantify the *psychedelic experience* induced by ayahuasca. HRS is a self-report questionnaire intended to measure various aspects of the subjective effects of psychedelics. This questionnaire contains six subscales: *Somaesthesia*, which measures somatic experiences; *Affect*, which measures emotional experiences; *Volition*, which measures the person's willingness to interact with themselves and their environment; *Cognition*, which measures changes in thoughts and mental processes; *Perception*, which measures auditory, visual, gustatory, and olfactory changes; and finally, *Intensity*, which measures how strong the experience is (Strassman, 1994). The effects of ayahuasca began to appear 1 hour after administration, peaked between 1.5 and 2 hours, and were gradually decreased hourly to disappear between 6 and 8 hours (Riba et al., 2002). Researchers found that ayahuasca produced central effects as reflected by EEG variables after a low dose compared with placebo only at isolated electrode sites between 45 minutes and 2.5 hours after administration. On the other hand, subsequent to the high dose, EEG changes were observed over a wide area of the scalp. Ayahuasca-induced reductions in power were observed in all measured frequency bands-*delta*, *theta*, and *beta*. Furthermore, decreases in the *alpha* band were most marked at the left temporal and centro-parieto-occipital electrodes at the high dose, where the maximum decrease was observed 90 minutes after administration. The HRS results revealed that ayahuasca resulted in significant increases across all subscales at the high dose. The Volition subscale, however, showed no increase relative to placebo at the low dose, thus demonstrating that of all HRS subscales, *Volition* is the least modified by ayahuasca (Riba et al., 2002).

Riba et al. (2004) investigated the differential involvement of cortical brain regions in the acute main effects of ayahuasca using EEG and low-resolution electromagnetic tomography (LORETA). The researchers tested 18 volunteers with prior experience with psychedelic drugs in a double-blind, randomized, placebo-controlled crossover design.

Subjects were administered freeze-dried ayahuasca capsules, each containing 0.85 mg DMT/kg body weight, and placebo capsules containing 0.75 g lactose. The EEG was recorded at baseline and at regular intervals, with the last recording taking place 8 hours post drug administration (Riba et al., 2004). Similar to the previously mentioned study (Riba et al., 2002), volunteers were asked to answer the questionnaire HRS approximately 240 minutes post ayahuasca and placebo administration to test the subjective effects of the *psychedelic experience* induced by ayahuasca. A voxel-by-voxel statistical analysis showed significant decreases in *alpha* bands, mainly 60 minutes post-drug administration. In addition, statistically significant decreases were seen in the *delta*, *theta*, and *beta*-1 frequency bands 90 minutes post-drug administration (Riba et al., 2004). The decrease in power was observed bilaterally in the limbic lobe mainly in the cingulate and parahippocampal gyrus, in the temporal lobe mainly in the superior and middle temporal gyri and fusiform gyrus, in the occipital lobe mainly in the superior and middle occipital gyrus, and in the parietal lobe mainly in the angular gyrus, supramarginal gyrus, precuneus, and in the left frontal lobe. Additionally, decreases in the *delta* frequency band were observed in a small area covering only 15 suprathreshold voxels between the left occipital and temporal lobes mainly in Brodmann Area (BA) 19 and BA 21 areas. Also, decreases in the *theta* band were observed in the medial frontal cortex mainly in area BA 24, however, these results were not statistically significant (Riba et al., 2004). Lastly and regarding subjective reports, all participants reported an increase in all subscales of the HRS questionnaire in the ayahuasca condition compared with placebo. Subjects reported a change in their subjective experience approximately 15 minutes post-drug administration, the effect became more pronounced between 30 and 45 minutes, was even stronger at 60 minutes, peaked between 90 and 120 minutes, and began to gradually diminish and disappear at 360 minutes.

Valle et al. (2016) investigated the effects of ayahuasca on regional power in the brain by using the standardized LORETA (sLORETA). Twelve healthy volunteers who had previously experienced psychedelics participated in a double-blind, randomized, balanced, placebo-controlled crossover design. Participants attended 4 experimental sessions, 1 week apart, receiving 1 dose of freeze-dried ayahuasca containing 0.75 mg DMT per kilogram of body weight (which was considered a medium intensity dose) or a placebo consisting of lactose, or 40 mg ketanserin (an antagonist of 5-HT_{2A}). Participants received one of 4 different treatment combinations on each day of the trial: Placebo + Placebo, Placebo + Ayahuasca, Ketanserin + Placebo, and Ketanserin + Ayahuasca. Participants were asked to complete the HRS, the Addiction Research Center Inventory (ARCI), and the Altered States of Consciousness (APZ) questionnaires 4 hours after administration of the drug (Valle et al., 2016). The ARCI is divided into five groups; *MBG*, the morphine-benzedrine group, which pertains to positive mood and euphoria; *PCAG*, the pentobarbital-chlorpromazine-alcohol

group, which pertains to sedation; *BG*, the benzedrine group, which measures intellectual energy and performance; *LSD*, the lysergic acid diethylamide group, which measures somatic-dysphoric effects; and *A*, the group that measures amphetamine-like effects (Martin et al., 1971). The APZ questionnaire consists of 3 subscales; *OSE*, oceanic boundlessness, which assesses alteration of the sense of time and depersonalization phenomena; *AIA*, dread of ego- dissolution, which refers to thought disturbances and decreased body and thought control associated with anxiety; and *VUS*, visionary restructuration, which measures hallucinations, illusions, and synaesthesia (Dittrich, 1998). The sLORETA analysis showed that ayahuasca significantly decreased power in the *delta*, *theta*, and *alpha* frequency bands compared to placebo with no effect observed in the *beta* band (Valle et al., 2016). The power decreases in *alpha* were mainly localized in the occipital, parietal, and temporal regions with the greatest decrease found in the primary visual cortex, at BA 18. The power decreases in *theta* bands were mainly localized in the lateral and medial frontal lobes with the greatest decrease occurring at BA 10. *Delta* bands decreased in the temporal lobe, with the greatest decrease occurring in the inferior temporal gyrus at BA 20. In addition, administration of ketanserin prior to ayahuasca as a pretreatment reversed the ayahuasca-induced reduction of the *alpha* band. In addition, ayahuasca significantly increased the scores on all HRS subscales, except for *Volition*. The administration of ketanserin alone did not promote a significant increase in the HRS scale. Treatment with ketanserin + ayahuasca significantly decreased the *Affect* subscales by 62%, *Perception* by 56%, and *Intensity* by 36%. Regarding the results of the ARCI questionnaire, ayahuasca resulted in significant increases in the *LSD, A,* and *MBG,* subscales. The *MBG* subscale was reduced by 80% and the *A* subscale by 53% after treatment with ketanserin + ayahuasca. Ayahuasca markedly increased the scores on all three subscales of the *APZ* questionnaire, furthermore, ketanserin + ayahuasca caused a significant reduction in scores on all subscales, whereas treatment with ketanserin alone had no effect.

Table 2

Summary of results of the effect of ayahuasca on Spectral power

Study	Main results
Riba et al. (2002)	-Absolute power decrease in all frequency bands - Power decreases in the *alpha* band were noted at the left temporal and centro-parieto-occipital electrodes at the high dose
Riba et al. (2004)	- Power decreases in *alpha, delta, theta*, and *beta* bands - Power decreases in *alpha*, delta and *beta* were noted in the tempro-parietal-occipital junction - Power decreases in the *theta* band were noted in the temporomedial cortex and in frotomedial regions
Valle et al. (2016)	- Power decreases in *alpha, delta*, and *theta*, bands - Power decreases in the *alpha* band were noted in the occipital, parietal, and temporal regions. - Power decreases in the *theta* band were noted in the lateral and medial frontal lobes - No effect was noted in the beta band

The Effects of Ayahuasca on Cerebral blood flow

One study that investigated the effect of ayahuasca on cerebral blood flow was identified in this review. Riba et al., (2006) studied the effect of ayahuasca on cerebral blood flow using single-photon emission computed tomography (SPECT) in a double-blind, placebo-controlled design. Study participants included 15 healthy volunteers with previous psychedelic experiences. Participants attended two experimental sessions 1 week apart, during which they received a single dose of encapsulated freeze-dried ayahuasca containing 1 mg DMT/kg or a placebo consisting of capsules containing 0.75 g lactose. The SPECT image acquisition took place 3 hours after drug administration. To test the subjective effects of the *psychedelic experience* induced by ayahuasca, two self-assessment questionnaires were used. The first is the HRS questionnaire, which participants were asked to answer 4 hours post-

administration, and the second is the ARCI, which participants were asked to answer immediately before and 4 hours post-administration of the drug. The SPECT imaging analysis showed significant activation of frontal and paralimbic brain regions after ayahuasca administration compared with placebo. More specifically, ayahuasca administration resulted in bilateral activation of the inferior frontal gyrus and anterior insula with greater activation in the right hemisphere. Increased activation of the left amygdala and parahippocampal gyrus was also observed. In addition, increased activation was observed in the anterior cingulate and frontal medial cortex of the right hemisphere. The subjective reports of all participants indicated that ayahuasca significantly improved all subscales of the HRS questionnaire compared to placebo. In addition, ARCI scores showed statistically significant increases in the *A* group, *MBG* group, and *LSD* group. However, no statistically significant results were obtained in the *BG* and *PCAG* groups.

The Effect of Ayahuasca on Functional Connectivity

Two studies testing the effects of Ayahuasca functional connectivity were identified in this review (Tabel 3). Alonso et al. (2015) investigated the directed functional connectivity of brain oscillations induced by ayahuasca using transfer entropy (TE) measurement. Ten healthy male participants with previous psychedelic experiences participated in a double-blind, randomized, balanced crossover design. Participants attended 2 experimental sessions 1 week apart in which they received a single dose of encapsulated freeze-dried ayahuasca containing what is equivalent to 0.75 mg DMT/kg body weight (which was considered a medium dose) or placebo. EEG recordings were obtained at baseline (before drug administration) and at regular intervals (15, 30, 45 minutes, and 1, 1.5, 2, 2.5, 3, and 4 hours) after drug administration. Four hours following the administration of the drug, participants completed the Spanish version of the HRS, as well as the APZ questionnaire. The results showed that ayahuasca produced significant TE changes 1.5, 2, and 2.5-hours post-treatment administration compared to placebo (Alonso et al., 2015). Topographic representations showed that increases 2 hours post-administration originated in posterior regions and affected signals in more frontal regions. In other words, information flow increased from posterior to anterior regions. In contrast, significant decreases were observed at 1.5 and 2.5 hours after administration at TE as information flow decreased from anterior to posterior regions. This pattern of increased information flow from posterior to anterior regions and decrease in information flow from anterior to posterior regions was observed at all time points between 45 minutes and 4 hours post- ayahuasca administration (Alonso et al., 2015). In addition, ayahuasca was shown to elicit statistically significant increases in all HRS subscales compared to placebo. Moreover, increases were observed in all APS subscales, except for nonsignificant results in the OSE and AIA subscales.

Pasquini et al. (2020) used a randomized, placebo-controlled study design with 46 participants. They used task-free functional magnetic resonance imaging (tf-fMRI) to investigate the effects of ayahuasca on networks supporting higher-order affective and self-referential processes in the brain. More specifically, they investigated the effects of ayahuasca on the functional connectivity of the DMN, sensorimotor network, and salience network (a brain system mainly responsible for supporting socioemotional functions). Twenty-two participants received a single dose of ayahuasca containing 0.36 mg/ml DMT and 21 participants received a placebo, which was a liquid designed to simulate the organoleptic properties of ayahuasca. Participants were assessed with the tf-fMRI 1 day before and 1 day after ingestion. Participants were asked to complete the questionnaire HRS to assess the *psychedelic experience* elicited by ayahuasca approximately 4 hours after administration of the drug (Pasquini et al., 2020). The researchers found that ayahuasca caused a significant increase in functional connectivity in the salience network compared with placebo. The increase was observed in the anterior cingulate cortex and superior frontal gyrus (Valle et al., 2016). In contrast, a decrease in functional connectivity in the DMN was observed in the ayahuasca group, particularly in the posterior cingulate cortex. Interestingly, connectivity in sensory networks, mainly visual and sensorimotor networks, did not differ between groups. In addition, the analyses showed increased functional connectivity between the DMN and the salience network. Furthermore, a positive correlation was found between the increased functional connectivity of the salience network and the Somesthesia and Affect subscales in the HRS questionnaire in the ayahuasca group compared with the placebo group. In addition, a positive correlation was found between the placebo group and the Volition subscale compared with the ayahuasca group. In addition, the decrease in functional connectivity of the DMN correlated negatively with the Volition subscale in the ayahuasca group.

Table 3

Summary of results of the effect of ayahuasca on functional connectivity

Study	Main results
Alonso et al. (2015)	-Increased information flow from posterior to anterior regions 2 hours post-administration. -Decreased information flow from anterior to posterior regions at 1.5- and 2.5-hours post-administration.

Pasquini et al. (2020)	-Increased anterior cingulate cortex connectivity within the salience network -Decreased posterior cingulate cortex connectivity in the DMN -Increased connectivity between the DMN and the salience network -No effect of ayahuasca was noted on the sensory networks

Note. DMN = Default mode network

Discussion

The purpose of this paper was to systematically review studies that used a placebo-controlled design to evaluate the neural correlates and the immediate *psychedelic experience* induced by DMT and ayahuasca. The results of the 7 included studies are contextualized with respect to previous and current research findings in this section. In addition, this section discusses the limitations, societal and ethical considerations, and conclusion of this review.

The Effects of DMT and Ayahuasca on Spectral Power

The three included studies that examined the effect of ayahuasca on spectral power (Riba et al., 2002, 2004; Valle et al., 2016) showed a consistent pattern of decreased spectral power in all frequency bands, predominantly in the *alpha* band. This is consistent with the results shown by Schenberg et al. (2015), who investigated the effects of ayahuasca in an open-label study design. Decreases in spectral power in the *alpha* band were observed in temporal, parietal, and occipital regions. However, in other studies (dos Santos, Grasa, et al., 2011; dos Santos, Valle, et al., 2011), no decrease in *alpha* power was observed. Thus, based on this review, the existing research is insufficient to determine a consistent pattern of how exactly ayahuasca affects spectral power. Regarding the effect of DMT on spectral power, the significant decrease in *alpha* power and increase in *delta* band found in (Timmermann et al., 2019) are congruent with the results found by (Pallavicini et al., 2021). In an open-label, naturalistic design, Pallavicini et al. (2021) measured the effect of DMT on spectral power by testing 35 participants. The researchers also found a significant decrease in *alpha* power and the *delta* power as an effect of DMT when participants closed their eyes. Despite some inconsistencies between the ayahuasca studies, this pattern of *alpha* power reduction is consistent with other neuroimaging studies of other psychedelic substances such as LSD (Carhart-Harris, Muthukumaraswamy, et al., 2016) and psilocybin (Muthukumaraswamy et al., 2013). Moreover, this pattern is also reported with the use of ketamine (Muthukumaraswamy et al., 2015), suggesting that ketamine and other psychedelics share some similarities in their effects on brain electrical activity.

The effect of ayahuasca on cerebral blood flow

The results shown by Riba et al., (2006) using SPECT were the first of their kind to show the effect of ayahuasca in measuring blood flow in regions related to introspection; the right anterior insula, memories; the parahippocampal gyrus, self-awareness; frontal gyrus/frontal medial cortex and emotions; anterior cingulate cortex, amygdala/ parahippocampal gyrus. Similar results were found by de Araujo et al. (2011) in an open-label design using fMRI and an imagery task to investigate how ayahuasca affects visual imagery. The result showed that ayahuasca caused increased activation in the parahippocampal and frontopolar cortex, similar to the results shown by Riba et al., (2006). In addition, the researchers noted an increase in the primary visual area during the imagery task when participants were only imagining some natural images. The results of these two studies may explain the visionary images people report under the effects of ayahuasca and why they are associated with emotional and meaningful experiences.

The Effect of Ayahuasca on Functional Connectivity

Ayahuasca appears to be able to alter the flow of information between anterior and posterior regions of the brain. According to Alonso et al. (2015), a measure of directional functional connectivity called transfer entropy indicated that under the effects of ayahuasca, the frontal regions of the brain had decreased their influence on the central, parietal, and occipital regions of the brain. Moreover, at a different time point, the influence of posterior regions on signals measured in anterior regions increased. In other words, ayahuasca altered the interactions between the higher-order frontal regions and the more sensory-selective posterior regions. de Araujo et al. (2011) reported similar findings in an fMRI study using ayahuasca, which demonstrated a reversal in the functional connectivity between the frontal and parietal lobes. The results of these two studies shed light on how executive regions in the brain alter their influence on more sensory regions at different time points under the effect of ayahuasca.

The results of the study by Pasquini et al. (2020) regarding the decreased activity of DMN connectivity within the posterior cingulate cortex are consistent with what was previously shown by (Palhano-Fontes et al., 2015). The researchers found that ayahuasca decreased the activation of key hubs in the DMN, including the posterior cingulate cortex, the medial prefrontal cortex, and the precuneus. This pattern of decreased activity in the DMN has also been observed with other psychedelics such as LSD (Carhart-Harris et al., 2016) and psilocybin (Muthukumaraswamy et al., 2013). In light of these studies, it is evident that DMN plays an important role in understanding the effects of psychedelics on the brain.

Measurements of the psychedelic experience generated by ayahuasca

All studies included in this review that examined the *psychedelic experience* induced by ayahuasca used the questionnaire HRS. Interestingly, all of these studies reported

an increase in all HRS questionnaires, with the exception of Riba et al. (2002), which found no increase in the *Volition* subscale at the low dose, which was interpreted by the researchers as the subscale least mediated by ayahuasca. In addition, the study by Pasquini et al. (2020) showed a negative correlation between decreased DMN connectivity in the posterior cingulate cortex and the *Volition* subscale in the ayahuasca group compared with the placebo group. This can be interpreted to mean that the more the connectivity in the DMN is decreased, the more the participant is willing to interact with his/herself during an ayahuasca-induced *psychedelic experience*. Furthermore, increases in all HRS subscales indicate that ayahuasca is able to effectively induce a temporary altered state of consciousness characterized by increased introspection and affectivity, changes in self-awareness, insight, and feelings of apprehension.

Two of the included studies that examined the *psychedelic experience* induced by ayahuasca used the ARCI questionnaire (Riba et al., 2006; Valle et al., 2016). Both studies reported significant increases in the *LSD* (measures somatic-dysphoric effects), *A* (measures amphetamine-like effects), and *MBG* (measures morphine-benzedrine-like effects) subscales after ayahuasca administration. One possible explanation for these increases is that ayahuasca interacts with receptors other than 5-HT_{2A} yet to be explored.

Two of the included studies that examined the *psychedelic experience* induced by ayahuasca used the ARCI questionnaire (Alonso et al., 2015; Valle et al., 2016). Valle et al. (2016) reported significant increases in all three subscales, *OSE* (measures alteration of the sense of time), *AIA* (measures thought disturbances and decreased body and thought control associated with anxiety), and *VUS* (measures hallucinations and illusions). Only Alonso et al. (2015) reported statistically significant increases in the *VUS* subscale, but not in *OSE* and *AIA*, although the same dose of ayahuasca was administered in both studies, 0.75 mg DMT/kg body weight.

Limitations

The results of this study must be interpreted in light of several limitations. The studies were selected from only two databases (Web of Science and Scopus). Only studies that were written in English were considered. To our knowledge, none of the included studies has been replicated, which cast doubt on the generalizability of the results. Only one study was included in which DMT was used in a placebo-controlled design, making it impossible to compare with other studies with the same design as well as to identify similarities and differences between the effects of DMT and ayahuasca. The fact that only studies with a placebo-controlled design were included may be deemed to limit the number of studies included. The small sample size used in all the included studies ranging from 13 to 43 cast a doubt on the reliability of statistical significance of the results. In addition, all included studies conducted their experiments in a laboratory setting, and since the (set and setting)

are essential factors for the effects of psychedelic substances, this may have led to misleading results about the natural effects of ayahuasca and DMT. Different brain imaging techniques and methods of data analysis in the studies could lead to different results. It should also be noted that differences in the doses used and the time chosen to obtain brain images in the different studies, as in the case of EEG, are significant limitations and may explain some of the inconsistencies in the results. Although all studies that examined the effects of ayahuasca used the HRS questionnaire to assess the *psychedelic experience*, not all studies used the ARCI and APZ questionnaires, making the comparison between studies quite difficult, if not insignificant.

Ethical concerns and considerations

Interest in exploring the potential of psychedelic substances is rising in the scientific community and in the general public and mainstream media (Johnson et al., 2019). There is a concern that may be directly related to the increasing interest in psychedelic science. I think that it is probable that pharmaceutical companies and 'new age healers/shamans' may take advantage of the research produced by science to their advantage, especially since researchers tend to use 'fancy' titles to attract readers. It is difficult to discern a causal effect here, but it is safe to say that researchers have an ethical responsibility in educating the general public about the potential and side effects of these substances.

Conclusion

The present review has shown that the *psychedelic experience* induced by ayahuasca and DMT can reliably produce profound changes in perception, emotions, cognition, and sense of self-awareness. Moreover, the decrease in the *alpha* band, the alteration of information flow between posterior regions, and the decrease in connectivity in the DMN could be the keys and the foundation of understanding the neural correlates and the *psychedelic experience* induced by DMT and ayahuasca. Although there are some inconsistencies in the results and none of the included studies have been replicated, this review nevertheless provides the reader with an overview of current research on ayahuasca and DMT and demonstrates that ayahuasca and DMT offer neuroscientists a unique opportunity to investigate the neural correlates of profound altered states of consciousness.

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