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PII: S0361-9230(16)30045-4
DOI: http://dx.doi.org/doi:10.1016/j.brainresbull.2016.03.002
Reference: BRB 8974

To appear in: *Brain Research Bulletin*

Received date: 15-2-2016
Revised date: 1-3-2016
Accepted date: 9-3-2016

Please cite this article as: Elisabet Domínguez-Clavé, Joaquim Soler, Matilde Elices, Juan C.Pascual, Enrique Álvarez, Mario de la Fuente Revenga, Pablo Friedlander, Amanda Feilding, Jordi Riba, Ayahuasca: pharmacology, neuroscience and therapeutic potential, Brain Research Bulletin http://dx.doi.org/10.1016/j.brainresbull.2016.03.002

Highlights

Ayahuasca is a psychotropic tea obtained from Amazonian plants.

Ayahuasca induces visions, intense emotion and recollection of personal memories.

Ayahuasca enhances self-acceptance and beneficial mindfulness capacities.

Available evidence suggests its potential to treat various psychiatric disorders.

Ayahuasca: pharmacology, neuroscience and therapeutic potential

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Abstract

Ayahuasca is the Quechua name for a tea obtained from the vine *Banisteriopsis caapi,* and used for ritual purposes by the indigenous populations of the Amazon. The use of a variation of the tea that combines *B. caapi* with the leaves of the shrub *Psychotria viridis* has experienced unprecedented expansion worldwide for its psychotropic properties. This preparation contains the psychedelic 5-HT_{2A} receptor agonist *N*,*N*-dimethyltryptamine (DMT) from *P. viridis*, plus β-carboline alkaloids with monoamine-oxidase-inhibiting properties from *B. caapi*. Acute administration induces a transient modified state of consciousness characterized by introspection, visions, enhanced emotions and recollection of personal memories. A growing body of evidence suggests that ayahuasca may be useful to treat substance use disorders, anxiety and depression. Here we review the pharmacology and neuroscience of ayahuasca, and the potential psychological mechanisms underlying its therapeutic potential. We discuss recent findings indicating that ayahuasca intake increases certain mindfulness facets related to acceptance and to the ability to take a detached view of one's own thoughts and emotions. Based on the available evidence, we conclude that ayahuasca shows promise as a therapeutic tool by enhancing self-acceptance and allowing safe exposure to emotional events. We postulate that ayahuasca could be of use in the treatment of impulse-related, personality and substance use disorders and also in the handling of trauma. More research is needed to assess the full potential of ayahuasca in the treatment of these disorders.

Keywords: Ayahuasca, DMT, beta-carbolines, pharmacology, neuroscience, therapeutic potential

1. A brief introduction to the history, plant sources and chemical composition of ayahuasca

1.1. History and botany

Ayahuasca, *yajé*, *Daime* and *Vegetal* are four of the many names used to describe the Amazonian liana *Banisteriopsis caapi* (Malpighiaceae), and a wide range of water infusions and decoctions prepared from this vine, alone or in combination with other plants (Ott, 1993; Schultes, 1980). The use of this psychotropic plant tea is experiencing unprecedented expansion worldwide, and is the object of increasing biomedical research (Frood, 2015). This preparation is a remarkable member of the indigenous pharmacopoeias of the Americas, which is rich in psychotropic plants able to induce visionary states of consciousness. These plants were central to the world view of indigenous cultures in the New World and were used in their medicine, religious ceremonies and rites of passage (Schultes, 1987). Such practices gradually disappeared, however, with the expansion of European colonization and Christianity. In the early and mid-twentieth century small pockets of native users continued to use plants such as the mescaline-containing p*eyote* cactus (*Lophophora williamsii*), psilocybin-containing mushrooms (*Psilocybe spp*.) and salvinorin-A-containing *Salvia divinorum* (Ott, 1993; Valdés et al., 1983).

Perhaps as a result of the greater isolation of human groups living in the relatively inaccessible Upper Amazon, ceremonial use of ayahuasca brews continued without external interference until more recent times. Different indigenous groups developed complex variations of the basic *B. caapi* infusion, adding as admixtures up to 90 different plants (Ott, 1993). In the 1980s, anthropologist Luis Eduardo Luna recorded over 70 different indigenous names for ayahuasca preparations, underscoring its widespread use by unconnected human groups. In Peru he also witnessed that rather than fading, knowledge of ayahuasca had passed from the Amerindian shamans to mestizo healers known as *vegetalistas*, who used the brew to diagnose and treat patients in the frontier cities of the Amazon (Luna, 1984). In Brazil, ayahuasca use underwent an even more radical cultural transformation, blending with Christian and Afro-Brazilian religious beliefs to give birth to the *Santo Daime*, the *União do Vegetal*, the *Barquinha* and other spiritual

movements. (Labate et al., 2009). These new forms of use have contributed to the expansion of ayahuasca use to mainstream South American society and also to many other parts of the world in the last two decades (Tupper, 2008).

Insert Figure 1 about here

1.2. Chemistry of B. caapi and P. viridis

One of the most common versions of the ayahuasca tea found on the global scene is that combining *B. caapi* with the leaves of the shrub *Psychotria viridis* (Rubiaceae).

Insert Figure 2 about here

In contrast with *peyote*, *Psilocybe* mushrooms and *S. divinorum*, whose active principles can elicit psychedelic effects on their own, the *B. caapi* - *P. viridis* combination relies on an interesting pharmacological interaction between substances present in each plant. *B. caapi* contains the alkaloids harmine, tetrahydroharmine (THH), and small amounts of harmaline (McKenna et al., 1984; Rivier and Lindgren, 1972). These compounds share a common tricyclic β-carboline structure. For this reason they are commonly referred to as "beta-carbolines", but also as "harmala alkaloids", because harmine was originally isolated from the unrelated plant, *Peganum harmala*. These beta-carbolines have various

pharmacological properties. In humans, they can reversibly block the activity of subtype A of the monoamine-oxidase (MAO) enzyme (Undenfriend et al., 1958; Buckholtz and Boggan, 1977a, Wang et al., 2010; Herraiz et al., 2010). MAO naturally degrades endogenous neurotransmitters and potentially dangerous exogenous amines that could be accidentally consumed in the diet. One of these "potentially dangerous" alien amines is the psychedelic *N,N*-dimethyltryptamine or DMT, present in large amounts in the leaves of *P. viridis* (Rivier and Lindgren, 1972; Schultes, 1980). The chemical structures of DMT and the main beta-carbolines are shown in Figure 3.

Insert Figure 3 about here

DMT is a rather common alkaloid, present not only in *P. viridis* but also in over fifty other plant species pertaining to various families (Ott, 1993). It was first isolated from the roots of *Mimosa tenuiflora* by the Brazilian chemist Oswaldo Gonçalves de Lima in 1946, who was not aware of its chemical identity and named it nigerine (cited in McKenna and Riba, 2015). This alkaloid was later found to be identical to DMT by another group (Pachter et al., 1959). The first unequivocal identification of DMT as a natural compound was conducted by Fish and coworkers (Fish et al., 1955). These authors identified DMT in the seeds of the tree *Anadenanthera peregrina*, which they were studying as the putative source of a psychotropic snuff. The presence of DMT in the seeds caught the attention of Stephen Szára, who conducted the first administration studies in humans and found that DMT had powerful visionary effects (Szara, 1956). Studies by Szára and others showed that 30 mg of DMT administered parenterally induced brief but intense psychedelic effects with visual illusions, changes in thought content and mood, and a series of physiological modifications such as tingling sensations, tremors, mydriasis and elevations of

blood pressure and pulse rate. Remarkably, the drug was not orally active even in doses as high as 150 mg (Szara, 1957).

1.3. The beta-carboline DMT interaction

After confirming the presence of the orally inactive DMT in *Diplopterys cabrerana* (another ayahuasca admixture plant used predominantly in Colombia), Agurell and coworkers postulated that "The combination in *yajé* of monoamine oxidase inhibiting harman alkaloids with *N,N*-dimethyltryptamine might result in specific pharmacological effects" (Agurell et al., 1968). Thus was born the interaction hypothesis stating that MAO-inhibiting beta-carbolines prevent the gastrointestinal and hepatic degradation of DMT, allowing it to reach the general circulation and the central nervous system (McKenna et al., 1984).

2. General pharmacology of ayahuasca in humans

2.1. Subjective effects

After ayahuasca intake there is usually a half-hour lag time until the first effects are felt (Riba et al., 2001; Riba et al., 2003). It is not uncommon to experience an unpleasant burning sensation in the stomach, which can be readily attributed to the acidity of the brew (Riba et al., 2001). Users also report changes in skin sensitivity, pins and needles, heat and cold waves and yawning. This is followed by a strong desire to close the eyes, and the onset of visual imagery at 45-60 min, although some individuals report they do not experience any visual effects. If present, images are usually compared to those in dreams, with complex scenes at times involving places and people they know or the recollection of past events. Despite their vividness, these images clearly differ from "true hallucinations". Participants are aware that the visions are drug-induced, usually disappearing when eyes are open and when attention is directed to external cues. Auditory perception rarely involves hearing internally-generated complex

phenomena such as voices, but rather modifications of external stimuli, with music being more intensely felt and deeply influencing the experience (Riba et al., 2001).

In addition to visual and auditory effects, ayahuasca increases thought speed and facilitates new associations. The introspective state induced by ayahuasca promotes reflection on personal issues. Memories of personal matters may trigger intense emotions (Riba et al., 2001). This interplay between thoughts, memories and emotions is highly valued by ayahuasca users. They consider that the experience can provide new insights into personal concerns, and it is not uncommon that they characterize the ayahuasca-induced experience as analogous to a psychotherapeutic intervention.

These subjective effects typically come and go in waves with alternating periods of higher and lower intensity. However, in average terms and based on laboratory studies, after the intake of a single ayahuasca dose, psychological effects reach a maximum intensity after one and a half to two hours. The overall intensity then gradually decreases, returning to baseline between four and six hours after intake (Riba et al., 2001, Riba et al., 2003). A series of studies implementing a within-subjects design, and using known doses of ayahuasca and quantitative assessment measures, such as subjective effects questionnaires, shows that ayahuasca effects are dose-dependent, although they may reach a ceiling effect past a certain dose. Despite this dose-dependent pattern seen when data from a pool of individuals are analyzed together, the "qualitative" aspects of the experience may vary greatly for one individual from one intake to the next.

2.2. Pharmacokinetics

The rise and fall of subjective effects and other pharmacodynamic variables fits nicely to that of DMT pharmacokinetics. In a study involving both types of measures, we did not find statistically significant differences between the time of the peak intensity of psychological effects (1.5-2h), measured using visual analogue scales, and the time of the peak DMT plasma concentrations (1.5 h) (Riba et al., 2003). In contrast, the pharmacokinetics of the beta-carbolines is dissociated from the global increase and

decrease of subjective effects. Thus, concentrations of harmaline and THH peak later, when the acute visionary effects have resolved. These findings support a major role for DMT in the pharmacology of such a complex alkaloid combination as ayahuasca. Another interesting aspect of ayahuasca pharmacokinetics is that harmine, the main MAO inhibitor present in the tea, appears to be readily metabolized in some individuals who show undetectable levels of this compound in plasma (Riba et al., 2003). Despite the absence of measurable concentrations of harmine in plasma, participants report fully psychoactive effects. This finding suggests that MAO inhibition is mainly peripheral and short-lived, barely enough to allow around 15% of the DMT to reach systemic circulation (Riba, 2003). Thus, partial MAO inhibition by the beta-carbolines would be enough to experience psychoactive effects after ayahuasca intake.

2.3. Physiological effects and tolerability

From a physiological perspective, ayahuasca exerts sympathomimetic effects increasing norepinephrine turnover (Riba et al., 2003) and causing mydriasis (dos Santos et al., 2011). It also increases blood levels of the stress hormones cortisol and prolactin (dos Santos et al., 2011). However, in contrast with the prominent cardiovascular effects reported for pure DMT in studies involving intravenous administration, we observed only moderate increases in systolic (SBP) and diastolic blood pressure (DBP) after ayahuasca, and practically no changes in heart rate. In a first pilot study involving 6 participants, we found a marginally significant increase in SBP at a dose of 1 mg DMT/kg body weight. On average this increase was of 14 mm Hg. Average increases in DBP were of 10 mm Hg and 9 beats per minute in heart rate (Riba et al., 2001). In a subsequent study involving 18 participants and a lower 0.85 mg DMT/kg dose, we obtained inconsistent results. Blood pressure increased but only DBP reached statistical significance. SBP increased an average of 6 mm Hg, DBP an average 10 mm Hg, and heart rate only 4 beats per minute (Riba et al., 2003). This low-to-moderate cardiovascular impact was further supported by a subsequent study in which we administered two consecutive 0.75 mg DMT/kg ayahuasca

doses. The second dose led to higher DMT plasma levels than the first, but the increase was linear, showing a mere superposition over the DMT levels remaining from the first dose. This produced linear increases in subjective, neurophysiological and autonomic effects. However, there was a trend to reduced SBP and heart rate, suggesting tolerance for cardiovascular effects (dos Santos et al., 2012).

Based on the above studies, the *B. caapi* - *P. viridis* version of ayahuasca appears to be reasonably safe in terms of physiological impact when administered to healthy individuals. The most common side effects are nausea and vomiting (Riba et al., 2001). And even this aspect of the experience is perceived in some contexts as beneficial 'purging'. Several factors may contribute to its low toxicity, such as selectivity of the beta-carbolines for the MAO-A isoenzyme, the rapid clearance of harmine from the organism, and the availability of MAO-independent biotransformation routes for DMT (Riba et al., 2015). These factors would explain the absence of reports of adverse reactions following the ingestion of foodstuffs containing tyramine after an ayahuasca session. However, as a precautionary measure, combining ayahuasca with other MAO inhibitors and serotonergic drugs such as antidepressants should always be avoided (dos Santos, 2013). Finally, from the perspective of psychological safety, there is the potential risk of anxiety reactions during the experience, as occurs with other psychedelics. Transient dissociative episodes have also been documented during ayahuasca intake. These effects are usually observed at high doses. In a clinical context, verbal support seems to be sufficient to help participants navigate these situations (Riba et al., 2001). More infrequently, longer-lasting psychotic symptoms have been reported in association with ayahuasca use (dos Santos and Strassman, 2011).

3. Neural mechanisms of ayahuasca effects

3.1. DMT and beta-carboline molecular-level and cellular-level interactions

At the receptor level, DMT shows a series of potential molecular targets. It interacts with serotonergic neurotransmission due to its structural similarity with the endogenous neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) and its affinity for some serotonin receptors. DMT shows agonist activity, at the 5-HT_{2A} and 5-HT_{1A} receptors sites (González-Maeso and Sealfon, 2009). The 5-HT_{1A} receptor is mainly pre-synaptic and has been associated with inhibitory activity. It is present in high levels in the raphe nuclei of the brain stem, and its activation reduces serotonergic tone. Although this mechanism may modulate the overall effects of DMT, it is not considered central to the drug's psychedelic effects.

On the other hand, there is a good correlation between the potency of the classical psychedelics, i.e, mescaline, DMT, LSD, psilocybin, etc and their affinity for the 5-HT_{2A} receptor (Glennon et al., 1984) where they display agonist activity (González-Maeso and Sealfon, 2009; Smith et al., 1998). The interaction between psychedelics and the 5-HT_{2A} receptor increases neural firing through excitatory postsynaptic potentials and currents (Kłodzinska et al., 2002). Stimulation of the 5-HT_{2A} may have longer-lasting implications besides the more immediate electrophysiological changes. Several studies have shown that psychedelic 5-HT_{2A} agonists stimulate the expression of immediate early genes. These genes encode transcription factors, such as c-fos (Frankel and Cunningham, 2002), egr-1 and egr-2 (González-Maeso et al., 2007). They also increase the expression of the brain-derived neurotrophic factor (BDNF) (Gewirtz et al., 2002). These transcription factors are involved in synaptic plasticity (O'Donovan et al., 1999) and have been associated with various aspects of cognition, such as memory (Jones et al., 2001) and attention (DeSteno and Schmauss, 2008).

DMT also interacts with other non-serotonergic molecular targets. Fontanilla and coworkers discovered that it has micromolar affinity for the intracellular sigma-1 receptor (S1R) (Fontanilla et al., 2009). The SR1 is associated with the endoplasmic reticulum, modulating the activity of other proteins and promoting neural plasticity through dendritic spine formation. DMT exerts molecular and behavioral effects in animals through sigma-1 activation. It blocks sodium channels and induces hypermobility in

mice. These behavioral effects are absent in sigma-1 knockout mice (Fontanilla et al., 2009). DMT is also an agonist at the trace amine associated receptor (TAAR) (Bunzow et al., 2001) and a substrate of the vesicle monoamine and serotonin transporters (Cozzi et al., 2009). These uptake mechanisms could potentially increase intracellular DMT to pharmacologically significant levels for the sigma-1 receptor.

While the more immediate electrophysiological changes induced by 5-HT_{2A} agonists have been related to the acute effects induced by ayahuasca and other psychedelics, changes in transcription and growth factors may underlie the structural and personality changes observed in long-term users of ayahuasca (Bouso et al., 2015). Bouso and coworkers found that regular ayahuasca users showed decreased cortical thickness (CT) in the posterior cingulate cortex (PCC), a key structure within the default mode network. Additionally, ayahuasca users scored higher than controls on Self-transcendence, a personality trait that measures the tendency towards religiousness and spirituality. Interestingly, CT values in the PCC were inversely correlated with lifetime use of ayahuasca and with scores on Self-transcendence. The authors postulated that repeated exposure to ayahuasca could underlie the observed structural changes in the PCC, and these, in turn, lead to a shift in attitudes and interests towards less materialistic values and greater open-mindedness. The S1R could also be involved in these differences in life attitudes and views. Considering that certain antidepressants, such as fluvoxamine, stimulate the S1R, it is plausible that the antidepressant effects recently reported for ayahuasca (Osório et al., 2015; Sanches et al., 2016) are mediated, at least in part, by S1R agonism.

It is worth pointing out that in addition to the effects of DMT on the CNS, the ayahuasca experience may be modulated by the pharmacological effects of the beta-carbolines. Following an ayahuasca dose, THH, harmaline, harmol and harmalol can be measured in plasma (Riba et al., 2003). While the presence of harmine in the organism appears to be short-lived, THH levels in plasma increase dose-dependently and disappear relatively slowly, with an elimination half-life of about 5 hours (Riba et al., 2003). Although weaker than harmine, THH inhibits MAO in the nanomolar range (Wang et al., 2010), and it also acts as an inhibitor of the serotonin transporter (Buckholtz and Boggan, 1977b).

3.2. Neurophysiological and neuroimaging correlates of ayahuasca effects in humans

Neurophysiological recordings in healthy volunteers have shown that within the time frame of acute inebriation, ayahuasca produces broad-band power decreases in spontaneous brain electrical activity (Riba et al., 2002). Intracerebral current source density (CSD) decreases are particularly pronounced in the delta (1.5-6 Hz), theta (6-8 Hz) and alpha-2 bands (10-12 Hz) and involve two main regions: a) a posterior area including medial and lateral aspects of the parietal, occipital and temporal cortex; and b) the frontomedial cortex including the anterior cingulate (see Figure 4) (Riba et al., 2004). Decreases in alpha-band oscillations correlate inversely with the intensity of the visual effects and can be blocked by the 5-HT_{2A} receptor antagonist ketanserin (Valle et al., under review). Analogous reductions in alpha oscillations have also been reported for another psychedelic tryptamine, psilocybin (Kometer et al., 2013; Muthukumaraswamy et al., 2013).

Insert Figure 4 about here

Energy decreases in brain oscillations suggest an excitatory effect of ayahuasca on the cerebral cortex (Romei et al., 2008b). The physiologic alpha rhythm inhibits visual areas in the occipital and parietal lobes (Romei et al., 2010, 2008a). Decreases in alpha rhythm are coupled with increased blood flow and metabolism (Buchsbaum et al., 1984; Moosmann et al., 2003). The blood oxygenation level dependent response (BOLD) measured by functional MRI shows a negative correlation with alpha oscillations in the anterior cingulate and in the parieto-occipital cortex (de Munck et al., 2007; Goldman

et al., 2002; Laufs et al., 2003). This negative relationship has been extended to the theta band of the EEG (de Munck et al., 2009).

The above neurophysiological measures detect changes mainly in: a) posterior sensory processing regions; b) frontal areas involved in emotional processing and cognitive control; and c) the medial temporal lobe involved in memory processing and affect. In contrast, nuclear medicine studies of serotonergic psychedelics found no changes in blood flow or glucose metabolism in posterior brain regions (Gouzoulis-Mayfrank et al., 1999; Hermle et al., 1992; Vollenweider et al., 1997). In the specific case of ayahuasca, we conducted a neuroimaging study to assess the acute effects of a high 1 mg DMT/kg dose in regional blood flow using single photon emission tomography (SPECT). Contrary to our expectations, we did not see changes in visual or auditory areas. We obtained only a partial overlap with the neurophysiological data. This overlap involved clusters of activation in the medial frontal lobe (see Figure 4), and in the medial temporal lobe (MTL) around the amygdala, hippocampus and parahippocampal gyrus (Riba et al., 2006).

In our most recent lab study, we were able to reconcile these seemingly contradictory findings from the nuclear medicine and neurophysiological studies (Alonso et al., 2015). Using a measure of directed functional connectivity known as Transfer Entropy, we analyzed the coupling of electrical signals between recording sites. This approach allows inferences regarding the directionality of information flow. Our results showed that ayahuasca modified the flow of information between anterior and posterior recording sites. Frontal sources decreased their influence over central, parietal and occipital sites. At the same time, sources in posterior locations increased their influence over signals measured at anterior locations (see Figure 4). In this way, the dynamics of the interaction between the higher order frontal regions and the more sensory-selective posterior areas was modified. Analogous findings have been reported using MRI. Araujo and coworkers found a reversal of the functional connectivity between the frontal and parietal cortices (de Araujo et al., 2012). We interpreted our findings on Transfer Entropy as reflecting a modification of the normal hierarchical structure regulating the flow of information in the

brain. While feed-back or top-down control is reduced, feed-forward and bottom-up information transfer is increased (Alonso et al., 2015).

Interestingly, in a study we conducted on long-term ayahuasca users we found structural brain differences in two main clusters of the brain. Analyzing magnetic resonance images we found a cluster of cortical thickness decrease in the posterior cingulate cortex and neighboring areas (Bouso et al., 2015). This region is a key hub of the so-called Default Mode Network or DMN (Raichle et al., 2001). Hyperactivity of this region has been associated with psychopathology, for instance with ruminations in depression (Dutta et al., 2014). In contrast, we also found in long-term users an increase in cortical thickness in the medial frontal lobes, specifically in the anterior cingulate cortex. Thus, we found a parallel between the anterior-posterior dynamics observed in the functional connectivity analysis, and the opposite pattern of structural differences between anterior and posterior brain regions.

3.3. A model of ayahuasca effects in the human brain

Based on the extensive data we obtained using the assessment and analysis techniques described above, we recently proposed a model of how ayahuasca and other psychedelics work on the human brain (McKenna and Riba, 2015).

Classical models of brain dynamics have emphasized the bottom-up or feed-forward transfer of information through various stages of increasing processing complexity, from sensory-specific areas up to multimodal association hubs that combine information from different channels into a meaningful whole. However, more recent views postulate that top-down control also plays a significant role in the interpretation of internal and external information. According to this alternative model, the experience of reality would be heavily dependent on previous knowledge and expectations (Friston, 2005; Mesulam, 2008). These constraints would be present at all levels of the hierarchy of feed-forward and feedback loops and the whole system would be under the executive control of the frontal cortex.

We postulate that ayahuasca and psychedelics in general will reduce top-down constraints or expectations and increase excitability in areas involved in sensory, memory and emotional processing. The reduction of the cognitive grip exerted by the frontal cortex combined with increased activation in the mentioned areas will allow weak endogenous activity to become consciously perceptible. This would explain that visions emerge with eyes closed but virtually disappear with eyes open, when they have to compete with strong external stimuli. Increased excitability in multimodal brain areas such as the temporo-parieto-occipital junction and the MTL (Riba et al., 2004; Riba et al., 2006) would explain the rapidly evolving modifications in thought content, the recollections and the novel associations reported by users. The stimulation of areas associated with emotional processing such as the amygdala, the insula and the anterior cingulate cortex, would be responsible for the intensely emotional nature of the experience.

The collapse of top-down constraints (McKenna and Riba, 2015) will give the experience an overall sense of novelty. Ayahuasca users commonly report using ayahuasca to facilitate insight into personal issues or to gain a new perspective into a given matter (Riba et al., 2001). Supporting these claim, we recently found that in the 24 hours following an ayahuasca session, certain psychological capacities such as self-acceptance and taking a detached view of one's own thoughts and emotions are increased (Soler et al., 2016). These interesting findings open an avenue for the exploration of the potential therapeutic applications of ayahuasca, and will be discussed in the next section.

4. Potential therapeutic uses of Ayahuasca

As described in the previous section, acute ayahuasca intake leads to a transient modified state of awareness characterized by introspection, visions, and autobiographic and emotional memories (Riba et al. 2001). Both naïve and regular ayahuasca users have described the experience as positive and valuable, and some individuals have reported health improvements associated with ayahuasca intake (Loizaga-Velder, 2013; Barbosa et al., 2009). Reports of decreased consumption of alcohol, cocaine and other

addictive drugs are common in regular ayahuasca users (Fábregas et al. 2010; Thomas et al. 2013). Anecdotal data also suggest an antidepressant effect for ayahuasca (Palhano-Fontes et al, 2014; Schmid, 2014). These testimonies have stimulated research into the potential benefits of ayahuasca in the treatment of substance use disorders and other psychiatric conditions.

The available literature examining the therapeutic potential of ayahuasca can be classified into three main groups. In a first group we find studies on the molecular mechanisms of ayahuasca alkaloids: receptor binding studies and in vitro assays, as well as pharmacological studies in animal models. This group of investigations has examined the mechanisms of action that could explain the psychotropic effects of ayahuasca and the beneficial effects described by users. The second group of studies includes case reports describing beneficial effects in psychiatric symptomatology. Disorders include substance use disorders, anxiety and depression. However, most of these papers provide information from few subjects usually taking ayahuasca in the context of a religious group. This confounding factor has raised doubts as to whether beneficial effects can be attributed exclusively to ayahuasca. The third and more recent group of reports includes case-control studies and open label trials with psychiatric inpatients. These new investigations constitute a step forward in terms of methodological rigor, but designs are still not ideal, as will be discussed below.

4.1 Molecular mechanisms potentially associated with therapeutic effects

As mentioned in previous sections, ayahuasca is a complex mixture of alkaloids. Thus, the molecular mechanisms potentially involved in its therapeutic effects are numerous.

Agonism of DMT at the 5-HT_{2A} receptor sites may already have antidepressant and anxiolytic effects. This has been shown in animals using the selective agonist DOI (Masuda and Sugiyama, 2000; Nic Dhonnchadha, et al., 2003). This possibility is supported by the success of recent therapeutic trials that have used various psychedelics which have the common feature of stimulating this receptor (Grob et al., 2011; Gasser et al., 2015). In addition to increased glutamatergic transmission and rapid

electrophysiological changes, agonism at this level has been shown to stimulate BDNF release and neurogenesis (Baumeister et al., 2014). These slower secondary events may also play a role in the beneficial effects of 5-HT_{2A} agonists.

As mentioned above, the recently uncovered modulatory role of DMT at the orphan receptor sigma-1 receptor (S1R) (Fontanilla et al., 2009) could also be involved in the effects of ayahuasca. As discussed above, the SR1 is a chaperone receptor promoting neural plasticity. Long-term exposure to ayahuasca could potentially lead to neural changes mediated through this mechanism.

The pharmacology of the beta-carbolines can be directly associated with therapeutic effects in depression and anxiety. MAO inhibition is a known therapeutic approach to treat these disorders. All three major beta-carbolines, harmol, harmalol and tetrahydroharmol have MAO-inhibiting properties (Buckholtz and Boggan, 1977a). Additionally, THH is a serotonin reuptake inhibitor (Buckholtz and Boggan, 1977b). Inhibition of the serotonin transporter is the main pharmacological mechanism of many of the antidepressants currently used in clinical practice. Increased monoamine concentrations in the synapse following ayahuasca intake could contribute to the antidepressant and antianxiety properties of B. caapi preparations. Harmine is also known to inhibit DYRK1A (dual specificity tyrosine-(Y)-phosphorylation regulated kinase 1A) in a potent and specific manner (Adayev et al., 2011). This kinase that affects neurite formation and maturation is up-regulated in Down Syndrome as a result of the trisomy (Mazur-Kolecka et al., 2012).

4.2 Studies in animals

There are several studies in animals addressing the potential antidepressant and axiolytic effect of ayahuasca and also its potential effect on substance use disorders.

Aricioglu and Altunbas, (2003) observed that the β-carboline harmane induced an antidepressant effect in the forced swim test. This effect seems to be induced by an inverse-agonist mechanism on the benzodiazepine receptor. Farzin and Mansouri (2006) showed the same antidepressant-like effects for

harmane, norharmane and harmine. Similarly, Fortunato et al. (2009) reported antidepressant activity following the acute administration of harmine in the forced swimming and open-field tests. In contrast with the antidepressant imipramine, harmine increased BDNF levels in the hippocampus. In another study by the same group (Fortunato et al. 2010a), the authors assessed harmine in rats exposed to the Chronic Mild Stress (CMS) procedure, an animal model for depression. Interestingly, treatment with harmine reversed anhedonia, reversed hypertrophy of adrenal glands, and normalized blood ACTH and BDNF protein levels. In a later study (Fortunato et al., 2010b), they also demonstrated that chronic treatment with all examined doses of harmine (see table) decreased immobility time of rats in the forced swimming test. They also showed increases in swimming and climbing time after harmine. Finally, chronic treatment with harmine, but not imipramine, increased BDNF protein levels in the rat hippocampus. Pic-Taylor et al. (2015) reported antidepressant effects of an ayahuasca infusion (*B. caapi* and *P. viridis* combination) as measured using the forced swimming test. This was evidenced as increased swimming behavior and lower immobility than the controls. Lima et al. (2007) reported decreased immobility time in the forced swimming test. The sample contained various beta-carbolines and DMT. Another study evaluated the positive effects of imipramine and harmine on oxidative stress parameters, thought to be involved in depression. The study reported harmine-induced increases in superoxide dismutase (SOD) and catalase (CAT) activities and decreased lipid and protein oxidation (Réus et al., 2010). The same authors reported increased mitochondrial activity by harmine, and commented that mitochondrial function is impaired in depressive disorders (Réus et al., 2012).

Regarding anxiety symptoms, Aricioglu and Altunbas (2003) reported that harmane attenuated, in a dose-dependent manner, behaviors associated with anxiety in the elevated plus maze test, a common paradigm for the study of anxiety in rodents. Similarly, Hilber and Chapillon (2005) reported mixed results for harmaline in the elevated plus maze anxiety test. Pic-Taylor et al. (2015) reported decreases in locomotor and exploratory activities in the open field and elevated plus-maze tests that were similar to those of fluoxetine. Additionally, increased *c-fos* expression in specific brain areas confirmed an effect of

ayahuasca alkaloids on areas involved in emotional processing and that are innervated by serotonergic pathways.

As for studies on substance use disorders, Oliveira-Lima et al. (2015) showed that the ayahuasca brew (*B. caapi* and *P. viridis* combination) not only inhibited early behaviors associated with the initiation and development of ethanol addiction, but was also effective for reversing the behavioral sensitization associated with chronic ethanol administration.

Table 1

Therapeutic effects of Ayahuasca: studies in animals.

Publication	Sample	Effects	Treatment	Method
Aricioglu and Altunbas (2003)		Decreased dose-dependently immobility time in the forced swimming test. Increased the time spent in open arms in the elevated plus maze test.	Harmane (compared to imipramine)	Elevated plus maze test (anxiety), and forced swimming test (depression)
Hilber and Chapillon (2005)		Changes in emotional reactivity (anxiolytic or anxiogenic depending on dose).	Harmaline	Elevated plus maze test (anxiety)
Farzin and Mansouri (2006)		Antidepressant-like effect in the forced swim test	Harmane, norharmane and harmine	Forced swimming test (depression)
Lima et al. (2007)		Decreased immobility time in the forced swimming test	Ayahuasca brew sample	Forced swimming test (depression)
Fortunato et al. (2009)		Reduced immobility time, and increased climbing and swimming time at the higher dose. Only harmine increased BDNF protein levels in the hippocampus	Harmine and imipramine	Forced swimming test and open field test (depression)
Fortunato et al. (2010a)		Reversed anhedonia, increased adrenal gland weight. Normalized ACTH blood levels and BDNF protein levels	Harmine	CMS Procedure (depression)
Fortunato et al. (2010b)		Decreased immobility time, and increased BDNF levels in hippocampus	Harmine and imipramine	Forced swimming test (depression)
Réus et al. (2010)		Increased SOD and CAT activities and decreased lipid and protein oxidation	Harmine and imipramine	Oxidative stress parameters (depression)
Réus et al. (2012)		Modulation of energy metabolism (mitochondrial activity)	Harmine and imipramine	Mitochondrial respiratory chain and creatine kinase activities (depression)
Oliveira-Lima et al. (2015)		Inhibition of early behaviors associated with the initiation and development of ethanol addiction. Reversion of behavioral sensitization associated with chronic ethanol	ayahuasca	Ethanol-induced hyperlocomotion and subsequent locomotor sensitization (substance use disorder)
Pic-Taylor et al. (2015)		Increased swimming behavior and lower immobility. Decreased locomotor and exploratory activities in the open field and elevated plus-maze tests. Activation of c-fos expression	Ayahuasca compared to fluoxetine	Forced swimming test, open field and elevated plus-maze tests. c-fos expression (depression and anxiety)

4.3 Studies in humans

Similar to the studies conducted to date in animals, studies in humans have assessed the impact of ayahuasca on: a) substance use disorders (Fabregas et al., 2010; Grob et al., 1996; Halpern et al., 2008; Thomas et al., 2013); and b) depression-anxiety (Barbosa et al., 2005; Sanches et al., 2016; dos Santos et al., 2007; Osório et al., 2015).

Halpern, et al. (2008) reported a remission of drug or alcohol abuse/dependence in an ayahuasca community sample (6.5 years average of membership). In another case series study (Thomas et al., 2013), the authors found statistically significant reductions in cocaine use after an ayahuasca-assisted therapy in a sample of members of a First Nations community in Canada with no prior experience with ayahuasca. They also reported improvements in mindfulness, empowerment, hopefulness, quality of life-outlook and quality of life-meaning. Similar effects on substance use were found in two case-control studies (Fabregas et al., 2010; Grob et al., 1996). Grob et al. (1996) reported remission of alcohol, depressive, or anxiety disorders and changes in behavior, attitude toward others and outlook on life in a 15 long-term sample of ayahuasca users, compared to 15 matched controls with no prior history of ayahuasca ingestion. Fabregas et al. (2010) reported an improvement in alcohol use and cessation of drug use (except cannabis) in two groups of jungle and urban-based ayahuasca users compared to non ayahuasca users. These findings were maintained at one-year follow-up. Other descriptive studies, such as observational pilot studies, reports and informal interviews (i. e. Bouso and Riba, 2014, p.101; Doering-Silveira et al., 2005; Labate et al., 2014, p.153), have presented preliminary evidence, suggesting a potential beneficial role for ayahuasca in the treatment of substance use disorders.

As regards anxiety and depression, Barbosa, et al. (2005) reported reductions in associated symptomatology after a first consumption of ayahuasca in a sample of Santo Daime members. They also reported behavioral changes, such as increased assertivity, vivacity and joy in members of two groups of ayahuasca users: the *União do Vegetal* and the *Santo Daime*. A case-control study (dos Santos et al.,

2007) used psychometric measures of anxiety, panic-like and hopelessness in regular (10 years) ayahuasca users, members of the Santo Daime. While under the acute effects of ayahuasca, participants scored lower on the scales for panic- and hopelessness-related states, but no modification of state- or trait-anxiety was reported following ayahuasca ingestion.

More recently, two open-label trials (Osório et al., 2015; Sanches et al., 2016) evaluated the effects of a single dose of ayahuasca in psychiatric depressive inpatients. Osório et al. (2015) observed statistically significant reductions of up to 82% in depressive scores (HAM-D, MADRS, and the Anxious-Depression subscale of the BPRS) between baseline and 1, 7, and 21 days after the administration. Furthermore, ayahuasca administration did not trigger episodes of mania or hypomania as measured by the Young Mania Rating Scale (YMRS). Neither did it lead to increases in the Thinking disorder subscale of the Brief Psychiatric Rating Scale (BPRS). In a subsequent study by the same group (Sanches et al., 2016), the authors reported significant decreases in scores on the same depression scales (HAM-D, MADRS, BPRS- Anxious-Depression), from 80 minutes after administration to day 21. No effects were observed on the YMRS and Activation BPRS subscale. Nevertheless, they reported increases in dissociative symptoms as measured by the Clinician Administered Dissociative States Scale (CADSS). The study included a SPECT assessment that found increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area, a series of brain regions related to the regulation of mood and emotional states.

Table 2

Therapeutic effects of Ayahuasca: studies in humans.

Publication	Sample size	Effects	Treatment components	Method
Grob et al. (1996)	n=30	Remission of alcohol, depressive, or anxiety disorders. Changes in behavior, attitudes toward others, and in outlook on life after joining the group	Ayahuasca	15 long term ayahuasca-users vs. 15 matched controls with no prior history of ayahuasca ingestion
Barbosa et al. (2005)	n=28	Reductions in minor psychiatric symptoms (including anxiety and depression) only in the *Santo Daime* subgroup. Behavioral changes, increased assertivity and vivacity/joy (in both groups)	Ayahuasca (first time consumption)	Samples from ayahuasca-using groups (*Santo Daime*, n=19 and *União do Vegetal*, n=9) Pre-post intake (2 weeks after)
dos Santos et al. (2007)	n=9	Lower scores on scales measuring panic and hopelessness. No modification of state- or trait-anxiety	Ayahuasca and ayahuasca-flavored solution (placebo)	Religious long-term users (double-blind, placebo-controlled procedure)
Halpern et al. (2008)	n=32	Reported remission of drug or alcohol abuse or dependence after joining the group	Ayahuasca	Community long term users
Fabregas et al. (2010)	n=127	Lower scores on the ASI Alcohol Use and Psychiatric Status subscales, cease of drug use (except cannabis) maintained at the follow-up, and worsening in the Family/Social relationships subscale only in the jungle group	Ayahuasca	Jungle and urban-based community users vs. controls non-ayahuasca users
Thomas et al. (2013)	n=12	Statistically significant reductions in cocaine use. Improvements in measures of mindfulness, empowerment, hopefulness and quality of life-outlook and quality of life-meaning	Ayahuasca -assisted therapy (first time consumption)	Individuals with substance use disorders or other behavioral problems Pre-treatment and 6 months after
Osório et al. (2015)	n=6	Up to 82% reductions in depressive scores between baseline and 1, 7, and 21 days after AYA administration.	Single dose ayahuasca	Psychiatric inpatients with acute depression. Open-label trial
Sanches et al. (2016)	n=17	Significant decreases in depression-related scales (HAM-D, MADRS, BPRS) from 80 minutes to day 21. Increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area.	Single dose ayahuasca (2.2 mL/kg)	Psychiatric inpatients with recurrent depression. Open-label trial

5. Potential psychological mechanisms underlying the therapeutic effects of ayahuasca

In addition to the aforementioned reports of beneficial experiences and the improvements in psychiatric symptomatology following ayahuasca intake, a recent work by Soler et al. (2016) suggested the increase of mindfulness-related capabilities as a possible psychological mechanism underlying the therapeutic effects of ayahuasca. The exploratory study assessed twenty-five individuals before and 24 hours after an ayahuasca session using the Five Facets Mindfulness Questionnaire (FFMQ, Baer et al., 2006; Cebolla et al., 2012) and the Experiences Questionnaire (EQ, Fresco et al., 2007a; Soler et al., 2014). Results showed significant reductions in the FFMQ facets "non-judge" and "non-react to inner experience", both related to self-acceptance. Changes in the first of these two facets indicate decreases in the tendency to be evaluative and judgmental. Changes in the second indicate decreased reactivity in the face of thoughts and feelings regardless of their pleasant or unpleasant nature. Finally, the study also found significant increases in "decentering ability" as measured by the EQ, which will be discussed later.

Analogous benefits in these three psychological domains have been observed in meditators, with a direct association between enhanced mindfulness capacities and the frequency and lifetime practice of meditation (Bergomi et al., 2013; Soler et al., 2014). This association suggests a connection between mindfulness techniques and the ayahuasca-induced experience. In this respect, previous data also show an overall increase in mindfulness scores after ayahuasca administration to substance users (Thomas et al., 2013). These findings are of special interest, if we consider that psychiatric populations score lower than healthy individuals on trait mindfulness (Cardaciotto et al., 2008; Lavender et al., 2011; Tejedor et al., 2014).

Decentering, also called "defusion", is considered a byproduct of mindfulness practice (Gecht et al., 2014; Tanay et al., 2012) and refers to the ability to observe one's own thoughts and feelings in a detached manner. When improving the capacity of decentering the individual gains mastery over their thoughts and emotions, preventing the identification with them (Safran and Segal, 1990; Shapiro et al.,

2006). Recent studies also indicate that the capacity to decenter may be protective against suicidal ideation and is predictive of the intensity of depressive symptoms at a 6-month follow-up (Bieling et al., 2012; Hargus et al., 2010). Mindfulness based approaches, and particularly mindfulness-based cognitive therapy for depression (MBCT) seem to improve the capacity of decentering. However, enhancement on this ability has also been reported as consequence of standard Cognitive Behavioral Therapy (CBT) (Fresco et al., 2007). These studies have reported greater gains in decentering with psychotherapeutic interventions than with antidepressant medications in drug-responders (Fresco et al., 2007). Benefits were also greater than those induced by antidepressant drugs and placebo in the maintenance phase (Bieling et al., 2012). These results suggest that promoting decentering could be the common mechanism underlying the effectiveness of different psychological treatments for depression. Impaired decentering has mainly been reported in relation to mood disorders (Bieling et al., 2012; Fresco et al., 2007b; Gecht, 2014; Hargus et al., 2010; Teasdale et al., 2002), but also in generalized anxiety disorder (Hayes-Skelton et al., 2015; Hoge et al., 2015), social anxiety (Hayes-Skelton and Graham, 2013), eating disorders, substance use disorders (Shapiro et al., 2006; Soler et al., 2014) and borderline personality disorders (Soler et al., 2014). With regard to impulsive-related disorders (such us drug abuse or borderline personality disorder), an increased capacity to observe thoughts, emotions, and desires more clearly, would diminish mood-dependent behavior by interrupting habitual and automatic maladaptive habits (Shapiro et al., 2006). Similarly, ayahuasca may be useful in the treatment of drug addiction by enhancing the individual's ability to make conscious healthy choices and resist unhealthy urges (Thomas et al., 2013). Liester and Prickett (2012) have proposed that ayahuasca may help treat addiction by acting at various levels from the biochemical and physiological, to the psychological and transcendent (Liester and Prickett, 2012). Moreover, as pointed out by Winkelman (2014, p.13-14), a significant feature of the pharmacological effects of psychedelics in the treatment of addictions is manifested in the so-called ''after glow'' that goes beyond the acute effects. These after-effects are characterized by positive mood, and increased openness to therapeutic intervention that lasts for several weeks after the intake.

Also, an enhancement of acceptance attitude may promote cessation of maladaptive behavior (abstinence from substance use) and improvements in other areas, such as anxiety sensitivity, and psychological flexibility (Villagra-Lanza and Gonzalez-Menendez, 2013; Skanavi et al.; 2011). Acceptance consists in being willing to notice, feel and connect with what is offered in the present, according to each individual's personal history (Villagra-Lanza and Gonzalez-Menendez, 2013). In addition to substance use disorders, there is growing empirical evidence of the effectiveness of acceptance-based therapies in the treatment of anxiety disorders and trauma (Roemer and Orsillo, 2007; Skanavi et al., 2011; Vujanovic et al., 2009). These studies emphasize that the effectiveness of these therapies relies on mitigating experiential avoidance, the major cause of chronification. Likewise, ayahuasca intake seems to induce a similar pattern of change. In fact, the two facets improved after ayahuasca use (i.e. "non-judge" and "non-react to inner experience") (Soler, et al., 2016), are the acceptance-measuring components of FFMQ (Baer et al., 2006).

Similar to mindfulness interventions and other therapeutic approaches such as prolonged exposure therapy that target traumatic memories (PE; Foa, Hembree, & Rothbaum, et al., 2007), ayahuasca appears to facilitate introspection, the processing of unconscious psychological material, and emotional catharsis (Loizaga-Velder, 2013). This introspective state would facilitate the detached view of one's own thoughts and emotions (Shanon, 2003). Levine and Frederick (1997; as cited in Nielson and Megler, 2014, p.44) point out that in posttraumatic stress disorder (PTSD) maladaptive patterns cease when subjects are able to slow down and experience all the elements, sensation and feelings that accompany them. If victims allow themselves to acknowledge the thoughts and sensations associated with their traumas, the perceptions will have their natural flow, peak, and then begin to diminish and resolve. This process will allow the nervous system to regain its capacity for self-regulation. According to Luciano et al. (2013), exposure can be conceived of as a strategy intended not only to cause the extinction of conditioned fear responses, but also to disconfirm the avoidance rules associated with the feared situation or event.

Brain imaging studies in humans suggest that ayahuasca significantly activates brain regions, such as the left amygdala and parahippocampal gyrus (Riba et al., 2006), which play a prominent role in emotional processing and the formation of memories. Activation of these areas potentially opens the limbic pathways of the brain to influence the emotional core of trauma in a way similar to affective psychotherapy. Ayahuasca also modulates activity in higher cognitive regions (Riba et al., 2006, de Araujo et al., 2012). Thus, users feel that the visions and emotions that emerge under the effects of ayahuasca are ‘‘real,’’ and, if they are real, then one may work therapeutically toward ‘‘real’’ new behaviors in the future (Bouso and Riba, 2014, p.102). This process may assign a new context to trauma and help patients understand traumatic memories and move past them (Nielson and Megler, 2014, p.50). However, ayahuasca might have the associated risk of re-traumatization by introducing traumatic memories or triggers. Special care should thus be taken to ensure the adequate state of mind of patients and a safe setting to maximize the individual's ability to look at each aspect of the self in order to resolve traumatic symptoms (Nielson and Megler, 2014, p.50).

The autobiographical aspects of the ayahuasca experience would be analogous to the "imaginal exposure" procedure, with the additional benefit of a relatively long duration (4-6 hours) and vividness of the visual effects. With regard to the visions, it is possible to temporarily interrupt them (escape) by opening the eyes, which allows taking control over the situation, but not avoiding it. In this respect, avoidance is a key variable in the maintenance of anxiety and PTSD symptoms as stated in several studies and treatment guidelines (i.e. Dunmore et al., 1999; Ehlers, 2000; Eifert and Forsyth, 2005; Foa, 2011; Forsyth et al., 2007; Moran et al., 2013; Steil and Ehlers, 2000; Walser and Westrup, 2007). Escape, on the other hand, may occur during Systematic Desensitization procedure. The goal is actually to expose gradually to the phobic object until it can be tolerated. In that sense, escape is part of a progressive process of change. Some reports on trauma sufferers who have used ayahuasca suggest that the beneficial effect of the drug could rely on the combination of several psychological factors: a) the non-identification with the content of the visions, which they regard as "safe" (i.e. decentering); b) imaginal exposure; and

c) acceptance. In this positive context, acceptance can arise. Therefore, ayahuasca may act as an enhancer of acceptance and exposure to thoughts and sensations in a detached context. These psychological mechanisms suggest its potential to treat trauma-related conditions and other disorders like borderline personality disorder (Bohus et al., 2011, Bohus et al., 2013, Harner and Burgess, 2011; Harner et al, 2015), obsessive-compulsive disorder (OCD), and phobias, in a structured, safe and comfortable setting.

6. Closing remarks

Ayahuasca has a long history of ceremonial use and its recent worldwide expansion is providing an unprecedented opportunity to study its impact on human health. An increasing number of papers suggest reasonable safety and benefits in mood and psychiatry symptoms in the areas of substance use disorders, anxiety and depression.

Preliminary findings on the potential psychological mechanisms associated with therapeutic benefits indicate similarities with mindfulness-based therapy. Ayahuasca appears to enhance self-acceptance and decentering, crucial aspects associated with psychotherapeutic treatment outcome in several psychiatric disorders. From a neural perspective, neuroimaging studies after an ayahuasca intake have reported activation in areas associated with emotional processing and memory formation. These results suggest that similarly to exposure therapies, ayahuasca allows reviewing emotional events, but with increased vividness and sense of "reality". We postulate that the state induced by ayahuasca could be useful in the treatment of trauma, substance use disorders, impulsive-related disorders, and certain patients suffering from borderline personality disorder.

More research is warranted in clinical populations, using larger samples, matched comparison groups, randomized designs and blinded raters to confirm its efficacy. Finally, it will be necessary for future studies to implement adequate settings and involve clinicians with specific training to ensure the safety of participants.

Acknowledgements

This work was supported in part by the Beckley Foundation. The authors with to thank all individuals who have participated in the studies mentioned in this review.

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Figure legends

Figure 1: *Banisteriopsis caapi*. Photo courtesy of Dr. Josep Maria Fericgla.

Figure 2: *Psychotria viridis*. Photo courtesy of Dr. James C. Callaway.

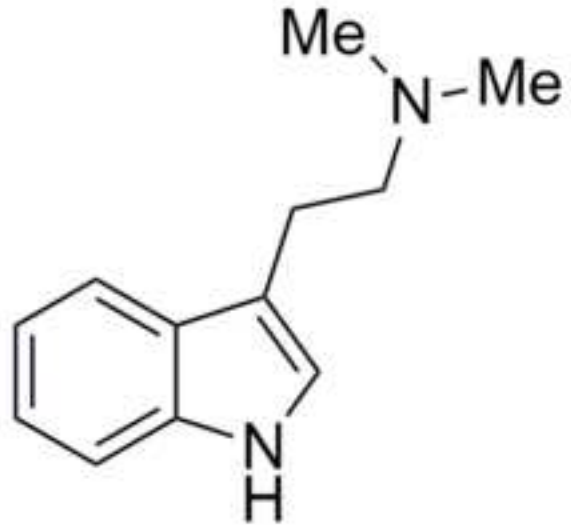
Figure 3: Chemical structures of the main alkaloids found in *Psychotria viridis* (*N*,*N*-dimethyltryptamine) and Banisteriopsis caapi (harmine, harmaline and tetrahydroharmine).

Figure 4: Neuroimaging and neurophysiological correlates of acute ayahuasca effects in humans. A) Blood flow increases in frontal brain regions measured using SPECT (Riba et al., 2006); B) Current source density decreases (EEG alpha band) in posterior brain regions (McKenna and Riba, 2015); C) Functional connectivity increases measured using Transfer Entropy (TE). With eyes closed, sources in posterior brain regions increase their influence over anterior brain regions (Alonso et al., 2015).

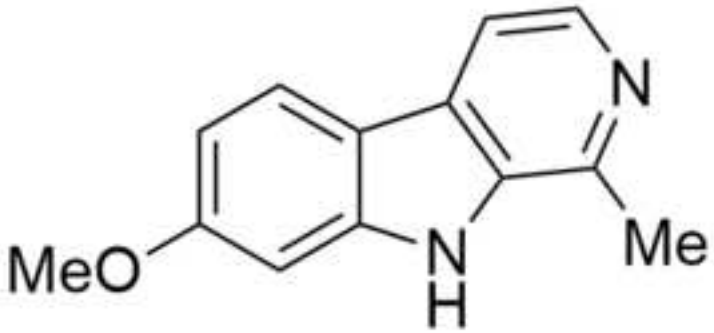
Figure_1

Figure_2

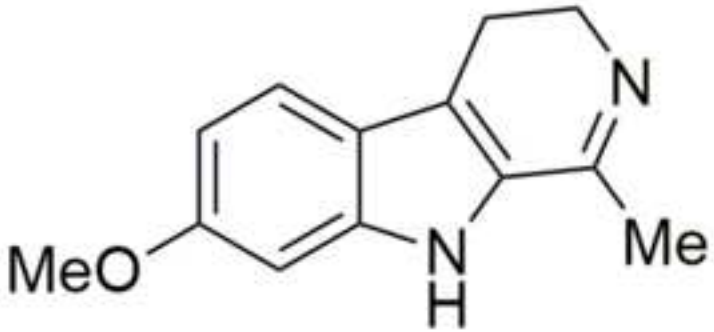
Figure_3



N,N-**Dimethyltryptamine**



Harmine



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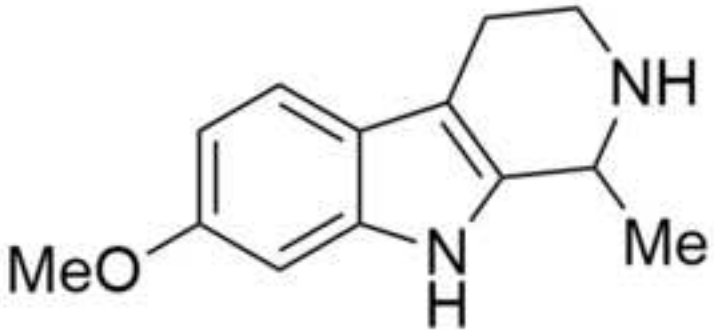
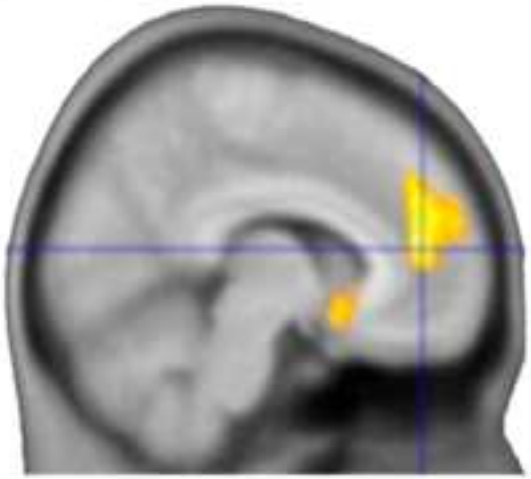


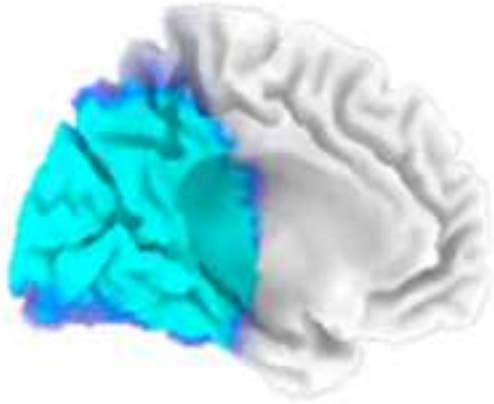
Tetrahydroharmine

Figure_4

A) Regional Cerebral Blood Flow



B) Current Source Density



C) Functional Connectivity (TE)