Chapter 2
Recent Evidence on the Antidepressant Effects of Ayahuasca

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What is Major Depressive Disorder?

According to the World Health Organization, approximately 350 million people meet the clinical criteria for major depressive disorder (MDD), which is the main cause of disability worldwide and is significantly linked to suicidal risk (World Health Organization, 2017). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), MDD is characterized by the presence of depressed mood (irritable mood in children and adolescents) and/or anhedonia for at least 2 weeks, together with at least four of the following possible symptoms: (a) considerable change in weight, (b) insomnia or hypersomnia, (c) psychomotor agitation or retardation, (d) fatigue/loss of energy, (e) low self-esteem or inappropriate guilt, (f) diminished capacity to think, concentrate, or make decisions, (g) recurrent thoughts

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of death, suicidal ideation, or suicide attempts (American Psychiatric Association, 2013).

Many hypotheses have been proposed to explain the physiology of depression, and it is becoming more evident that depression is a multidimensional condition (Liu et al., 2017). The most widely accepted hypothesis states that depression is a result of disturbances in serotonin (5-HT), noradrenaline, and dopamine neurotransmitters in the brain (Wong & Licinio, 2001). In fact, the use of antidepressant drugs, such as iproniazid or imipramine, has been associated with increased levels of 5-HT and noradrenaline (Wong & Licinio, 2001). Besides, low concentrations of postsynaptic serotonin 1A receptor (5-HT_{1A}) in the hippocampus and prefrontal cortex have been reported in patients with depression (Stahl, 2013). Changes in the 5-HT transporter were also observed in depression, as studies with monozygotic twins show that some types of polymorphism in the promoter region of its gene are more likely to develop depression (Caspi et al., 2010; Frodl et al., 2010; Starr et al., 2012).

The hypothalamic–pituitary–adrenal (HPA) axis has also been used to explain some aspects of the pathophysiology of depression, mainly based on the frequent observations of altered cortisol levels in depressive patients (Tadić et al., 2011). One view of the problem points to resistance in glucocorticoid receptor (GR), which leads to decreased negative feedback of the HPA axis, and thus result in elevated concentrations of cortisol in the plasma, urine, and cerebrospinal fluid (Zunszain et al., 2011). Although hypercortisolemia is the most common finding, hypocortisolemia has also been observed in MDD (Bremmer et al., 2007; Vreeburg et al., 2013). In this case, reduced cortisol levels would be a consequence of HPA axis fatigue, due to the recurrent depressive episodes. In fact, hypocortisolemia has proven to be dependent on depression severity, socioeconomic status, sex, age, temperament, and coping style (Moreira et al., 2016; Schuch et al., 2014; Tu et al., 2013).

Another hypothesis associates depression with changes in the immune system. Some depressive patients present increased levels of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) in the blood, showing a low-grade inflammatory profile (Leonard, 2007; Li et al., 2011; Osimo et al., 2019). It is suggested that GR resistance in immune cells leads to decreased levels of anti-inflammatory cytokines (IL-10, IL-4, examples) and enhances inflammation (Leonard, 2007; Li et al., 2011). Neurodegeneration may also be related to the pathophysiology of depression. This hypothesis is supported by evidence of reduced volume in the hippocampus and prefrontal cortex in depressive patients (Serafini, 2012). It is suggested that these volume changes would be caused by decreased neurogenesis secondary to hypercortisolemia and inflammation, which impairs the synthesis of neurotrophins like the brain-derived neurotrophic factor (BDNF) (Cai et al., 2015; Otte et al., 2016). Moreover, some studies have shown that patients with depression express low levels of BDNF (Kotan et al., 2012), although this finding is not a consensus (Elfving et al., 2012). An important observation corroborating this hypothesis is that the use of antidepressants in rats increases hippocampal volume as a consequence of increased BDNF expression (Foltran & Diaz, 2016).

Neuroimaging and Depression

Neuroimaging techniques have also helped understand the physiology of depression. Several studies have reported that major depression patients show alterations in brain anatomy and function (Dai et al., 2019). Structural magnetic resonance imaging (MRI) has consistently shown reduced hippocampal volume in MDD (Bremner et al., 2000; Lorenzetti et al., 2009; MacQueen, 2009), as well as reduced basal ganglia, caudate nucleus, and putamen (Lorenzetti et al., 2009), thalamus (Nugent et al., 2013), amygdala (Bora et al., 2012), insula (Soriano-Mas et al., 2011), and anterior cingulate cortex (Bora et al., 2012). Deficits in both global and local white matter integrity are also observed (Shen et al., 2017).

Functional brain changes have involved particularly the limbic system, a set of brain regions fundamental to emotion processing and mood regulation (Davidson et al., 2002; Groenewold et al., 2013; Joormann & Stanton, 2016). The amygdala, for instance, is a brain structure highly sensitive to negative emotional stimuli that have been repeatedly implicated in depression. Amygdala hyperactivity has been correlated with depressive symptoms and its regulation has been associated with antidepressant effects (Godlewska et al., 2012; Murphy et al., 2009; Sheline et al., 2001; Williams et al., 2015). For instance, selective serotonin reuptake inhibitors (SSRI), such as citalopram, lead to reduced amygdala response to fearful facial expressions compared to placebo (Godlewska et al., 2012; Murphy et al., 2009).

Another structure of the limbic system, the anterior cingulate cortex (ACC), appears to be involved in depression. Positron emission tomography (PET) has found the decreased metabolic activity of the subgenual portion of the ACC in patients with depression when compared to healthy controls (Drevets et al., 1997; Videbech, 2000). This region has also been an indicator of the antidepressant response to different interventions, such as antidepressants, psychotherapy, and deep brain stimulation (Delaveau et al., 2011; Siegle et al., 2012). For example, increased functional connectivity between the ACC and the limbic system has been reported after successful antidepressant treatment with the SSRI sertraline (Anand et al. 2005).

Other brain regions, such as the ventromedial prefrontal cortex (vmPFC), the posterior cingulate cortex (PCC), and the inferior parietal cortex, also seem to be important in depression. Together with the medial prefrontal cortex (mPFC) and the ACC, these regions form a brain network known as the default mode network (DMN), which is characterized by greater activity during periods of rest than during a goal-directed task (Raichle et al., 2001). The DMN has been used as a consistent marker for self-referential processes, including spontaneous thoughts, autobiographical memories, mental simulations, and mind-wandering (Buckner et al., 2008; Northoff et al., 2006). MDD has been associated with hyperconnectivity within the DMN and hyperconnectivity between frontoparietal control systems and regions of the DMN (Kaiser et al., 2015). These results are consistent with clinical symptoms, such as rumination, in which MDD patients are impulsively focused on the past and future negative consequences, rather than reflecting on the present

moment (Papageorgiou & Wells, 2004). Furthermore, evidence suggests that patients with depression fail to modulate different regions of the DMN during an emotional regulation task (Sheline et al., 2009).

Other brain networks have also been implicated in depression (Kaiser et al., 2015). Typically, patients present reduced functional connectivity within the frontoparietal network, involved in cognitive control of attention and emotion regulation, and decreased connectivity between frontoparietal and the dorsal attention networks (Kaiser et al., 2015).

Sleep and Depression

Sleep disturbances are observed in about 75% of patients with depression (Minkel et al., 2017). Changes in sleep may be the first sign of a depressive episode and, for many patients, it persists even after treatment. Besides, patients with sleep disturbances have poorer outcomes than those without (Murphy & Peterson, 2015). Sleep complaints in MDD patients include difficulty falling asleep, frequent nocturnal awakenings, early-morning awakening, nonrestorative sleep, and recurrent nightmares (Minkel et al., 2017).

Most consistently, studies have found the following differences when comparing MDD patients with healthy controls (Minkel et al., 2017):

1. Prolonged sleep onset latency, increased wake time during sleep, increased number of awakenings during sleep (i.e., fragmentation or discontinuity of sleep), increased early morning wake-up time, and decreased total sleep time;
2. Reduced rapid eye movement sleep (REMS) latency (i.e., shorter interval between sleep onset and the first REMS episode), increased amount of REMS, longer first REMS period, and increased REM density (i.e., higher number of eye movements during REMS);
3. Decreased amount of deep sleep (DS) and of DS percentage over total sleep (Minkel et al., 2017; Murphy & Peterson, 2015).

Reduced REMS latency has been the most robust polysomnographic finding in depression (Minkel et al., 2017; Murphy & Peterson, 2015). Some suggest that these changes are due to low levels of serotonin (Siegel, 2017), somewhat related to the secretion of cortisol at night (Poland et al., 1992). In fact, an inverse correlation between cortisol level and REMS latency has been observed, as subjects with shorter REMS latency are the ones with higher HPA activity (Asnis et al., 1983), while SSRI treatment may stabilize HPA functioning (Hinkelmann et al., 2012).

A recent study suggests that cortisol changes may be a physiological target that links sleep disturbance and depression (Santiago et al., 2020). The authors found that treatment-resistant depressive patients had lower salivary cortisol awakening response and sleep duration, with higher latency to sleep than healthy volunteers with a good sleep profile. Furthermore, a low cortisol profile was associated with more severe depressive symptoms and worse sleep quality. However, although

BDNF has been proposed as a biomarker of good sleep quality, no difference in serum BDNF levels was observed (Santiago et al., 2020).

Sleep changes in MDD have been treated with psychotherapy, medication, or both (Minkel et al., 2017; Murphy & Peterson, 2015). Psychotherapy includes cognitive behavioral therapy for insomnia and sleep hygiene, such as (a) using the bed only for sleep and sex, (b) going to sleep only when really tired, (c) leaving the bed after 15 min if unable to fall asleep, (d) establishing regular sleep and wake up time, and (e) avoid napping during the day (Perlis et al., 2010). Pharmacological strategies include hypnotics and sedating agents, such as non-benzodiazepine GABA agonists, and melatonin. Antidepressants are also useful, especially tricycles and MAO inhibitors (Schutte-Rodin et al., 2008).

Ayahuasca and Depression

Thus far, a few clinical trials have been designed to test the antidepressant effects of ayahuasca. In a first open-label trial, 17 patients with refractory depression participated in a single dosing session with ayahuasca (Osório et al., 2015; Sanches et al., 2016). Depressive symptoms were monitored by clinical psychiatric scales (Carneiro et al., 2015). Assessments occurred before the session (baseline), during the session, and following 1, 2, 7, 14, and 21 days after the session. A significant decrease in depressive symptoms was observed already during the ayahuasca session (40 min after ingestion), which remained significantly reduced for 21 days (Osório et al., 2015; Sanches et al., 2016). Subacute changes in cerebral blood flow were also assessed 8 h after the session, and significant increased cerebral blood flow was observed in the nucleus accumbens, right insula, and the subgenual portion of the anterior cingulate cortex (sgACC); brain areas recurrently involved in depression (Sanches et al., 2016).

Although promising, this study did not control for the placebo effect, which is high and can benefit up to 40% of the patients in clinical trials for depression (Sonawalla & Rosenbaum, 2002). The follow-up randomized placebo-controlled trial (RCT) with ayahuasca for treatment-resistant depression was conducted from January 2014 to June 2016 (registered at http://clinicaltrials.gov/NCT02914769). The trial was a parallel two-arm design, in which half of the patients were dosed with ayahuasca and the other half with placebo (Palhano-Fontes et al., 2019).

We assessed 218 patients for eligibility, and 35 met clinical criteria for the trial. All patients had used at least two different antidepressant medications unsuccessfully (referred to as "treatment-resistant depression") and were all naïve to ayahuasca. Six patients had to be excluded during the washout period,[1] leaving 29 patients in the trial: 14 in the ayahuasca group and 15 in the placebo group. We

[1] Before the dosing session, patients remained abstinent from any antidepressant medication, for a period of 2 weeks, typically.

assessed depression severity with the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Hamilton Depression Scale (HAM-D), this time at baseline, and followed-up at 1, 2, 7, 14 days and monthly for the next 6 months after the session.

The substance used as a placebo was a brownish liquid, with a bitter and sour taste that came from water, beer yeast, citric acid, zinc sulfate, and caramel colorant. It was designed to mimic some of the characteristics of ayahuasca, including modest gastrointestinal distress due to the presence of zinc sulfate. We used a single batch of ayahuasca, prepared by our friend and leader of a Barquinha church, Edilsom Fernandes da Silva, from Ji-Paraná, Rondônia, Brazil. Patients received a single dose of 1 ml/kg of placebo or ayahuasca at an adjusted dose of 0.36 mg/kg of N,N-DMT (Palhano-Fontes et al., 2019).

All participants gave written informed consent before the trial, which was conducted in accordance with the Declaration of Helsinki that guides ethical principles for medical research, and with the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2011; World Medical Association, 2001). The trial was approved by the Ethics Committee of the Hospital Universitário Onofre Lopes (HUOL), from the Universidade Federal do Rio Grande do Norte (UFRN), in Natal, Brazil.

Prior to participation they were informed about different aspects of the trial, including the 50% possibility of taking ayahuasca and 50% of taking the placebo. Possible effects were extensively presented and discussed.

Patients then underwent a washout period of about 2 weeks prior to the dosing session to reduce interaction between their medications and ayahuasca. During this period, patients were followed by our psychiatrists for medication weaning.

Our trial was also designed to explore the nature of the subacute effects of ayahuasca. In other words, we were interested in understanding changes happening 1 day after the session. For that, we made a number of assessments 1 day before and 1 day after the session with ayahuasca or placebo.

Patients arrived at the hospital on Tuesday at around 2 p.m. They were always received by a member of our crew, and had their baseline psychiatric evaluation, which included depression severity checked with the HAM-D and MADRS scales (Palhano-Fontes et al., 2019). In the same afternoon, patients had a neuropsychological evaluation, followed by a magnetic resonance imaging (MRI) scanning session for functional MRI (fMRI). We also used linguistic analysis based on participants' free reports on their thoughts during the fMRI session, as well as on four stories created based on images with different emotional contents (Mota et al., 2017). They had dinner, and at around 9 pm, they were prepared with the EEG cap system, and then allowed to go to sleep. Brain (EEG), heart (ECG), and muscle (EMG) activities were recorded continuously throughout the night, and were followed by two health professionals: a nurse and a physician.

On the next day (Wednesday), patients were awakened at 6 am to collect saliva, and blood was collected about 45 min later, both at fasting and at rest. After a light breakfast, participants were prepared for the dosing session, when they would receive either ayahuasca or placebo. Each session lasted approximately 9 h, usually going from 7 am to 4 pm. Sessions took place in a bedroom-like environment

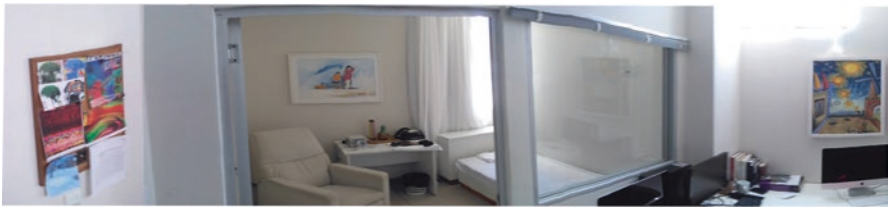

Fig. 2.1 Setting where dosing sessions took place consisted of a bedroom-like hospital site equipped with a recliner, a bed, and a desk, controlled temperature, natural and dimmed light

specifically designed for the study, equipped with a recliner, a bed, and a desk, controlled temperature, and natural and dimmed light (Fig. 2.1). Throughout the dosing session, at least two members of our team accompanied the participant, giving assistance when necessary.

At around 10 am, participants were interviewed by a trained psychiatrist for clinical evaluation and another session of clinical scales, this time including evaluating for dissociative, mania-like, and psychotomimetic symptoms, with three scales: Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), and Young Mania Rating Scale (YMRS) (Palhano-Fontes et al., 2019). Before dosing, we reinforced that they could drink ayahuasca and feel little, or drink placebo and feel something. The transitory nature of the effects was also reinforced. We also mentioned a set of helpful attitudes and strategies to be taken, such as maintaining an open attitude toward the experience. Participants were asked to remain silent, calm, with their eyes closed, while maintaining attention on their body, thoughts, and emotions. We told them we were going to ask for every detail they experienced; "so, please, pay attention."

Ayahuasca or placebo was taken at around 10:30 a.m. Participants were monitored throughout the session with EEG, ECG, and EMG. They listened to music during most of the session, and the soundtrack included Brazilian singers. Instrumental, classical, and Andean music were also present. A link to the adapted playlists, created by L. F. Tofoli, is in the footnote.[2] Saliva and psychiatric scales were also applied at three time points along the session. These assessments occurred 1h40, 2h40, and 4h after intake. At these assessments, psychiatrists monitored depressive, dissociative, psychotic, and mania-like symptoms.

When the acute effects had ceased, at around 3 pm, patients described their experiences in detail (recorded in video). They also responded to three questionnaires, two of which are sensitive to the effects of classical psychedelics, the Hallucinogenic Rating Scale (HRS) (Mizumoto et al., 2011) and the Mystical Experience Questionnaire (MEQ30) (Maclean et al., 2012), and one to assess changes in spontaneous thinking, the Amsterdam Resting State Questionnaire (ARSQ) (Diaz et al.,

[2] https://open.spotify.com/user/lftofoli/playlist/6sRsIxM4oNEpCPSFDQxAJB?si=THVcUA_tRPSIFIgZmMSvtg https://open.spotify.com/user/lftofoli/playlist/5wAyiC2RvBpbZUZeLMERza?si=H999tZ1LSJ6FyUCFgrSnJw

2013). After psychiatric evaluation, they were allowed to go home at around 4:00 pm. To get a feeling of how the session was, access: https://vimeo.com/246973683.

On the following afternoon (Thursday), they returned for psychiatric evaluation (MADRS), neuropsychological, MRI/fMRI, and another sleep EEG, from Thursday to Friday. The next morning (Friday), they repeated blood and saliva exams. After breakfast, they retrospectively described their experience, reported any perceived changes following dosing, and, at around 9 am, they were discharged by a psychiatrist. Patients were asked to return for follow-up assessments at 7 days (D7), 14 days (D14), 1 month (M1) and from then on, every month, for 6 months (M2, M3, M4, M5, M6). Also, 7 days after the session (following Tuesday), they were introduced to a new treatment scheme based on a different commercially available antidepressant.

During the session with ayahuasca, patients showed slight transient changes in dissociative and psychotomimetic symptoms, and we did not observe significant increases in mania-like symptoms. We also observed significant transient nausea (ayahuasca = 71%, placebo = 26%), vomiting (ayahuasca = 57%, placebo = 0%), transient anxiety (ayahuasca = 50%, placebo = 73%), and transient headache (ayahuasca = 42%, placebo = 53%).

Figure 2.2 shows changes in depression severity over time. We observed significantly reduced depressive symptoms 1 day (D1) after the session with ayahuasca that persisted for at least 7 days (D7) when compared to placebo (Palhano-Fontes et al., 2019). We did not find significant differences in the follow-up assessments, possibly due to the small number of patients who returned to the hospital for the psychiatric evaluations (Fig. 2.2). Nonetheless, it is worth mentioning that other recent studies using psychedelics found reduced symptoms of depression and anxiety for longer periods after the psychedelic session (Gasser et al., 2014; Griffiths et al., 2016; Ross et al., 2016).

One day after the session, response rates[3] were 50% in the ayahuasca group and 46% in the placebo group. Two days after dosing, the response rate was 77% in the ayahuasca group and 64% in the placebo. A significant between-groups difference was observed 7 days after dosing, with 64% of responders in the ayahuasca group, and 27% in the placebo (Palhano-Fontes et al., 2019). Also, 7 days after dosing, remission rate (MADRS$\leq$10) was statistically different between-groups, with 36% of remitters in the ayahuasca group and 7% in the placebo (Palhano-Fontes et al., 2019).

Our results are comparable with trials that used ketamine, although the dynamic is different. While ketamine effect size is largest 1 day after the session (Cohen's d = 0.89) and reduces toward 1 week after the session (Cohen's d = 0.41), the effect sizes observed for ayahuasca is smallest and compatible to ketamine at day 1 (Cohen's d = 0.84), but it increases and is largest 7 days after the session (Cohen's d = 1.49) (Palhano-Fontes et al., 2019). Furthermore, our results suggest that the

[3] Response was defined as a reduction of 50% or more in MADRS baseline scores.

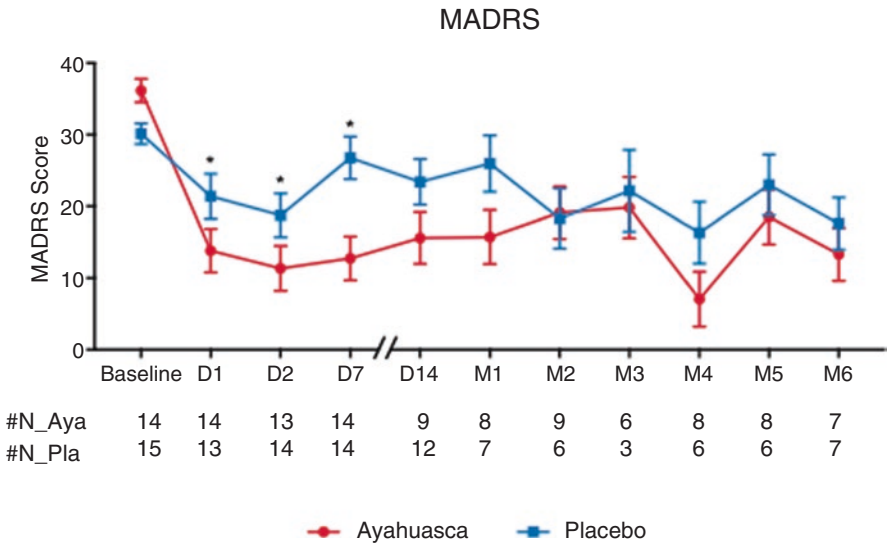

Fig. 2.2 Depression severity as a function of time. Significant differences are observed between ayahuasca (red circles) and placebo (blue squares) at D1 (p = 0.04), D2 (p = 0.04) and D7 ($p < 0.0001$). No differences were found after D7. #N_Aya and #N_pla are the numbers of patients in ayahuasca and placebo groups who attended psychiatric evaluation at that time point. Values are (mean ± SEM). MADRS scores: mild depression (11–19), moderate (20–34), severe (≥ 35) *$p < 0.05$

ayahuasca session significantly reduced suicidality (i.e., suicide attempts, suicide planning, and suicidal ideation), from baseline to 1, 2, and 7 days after the dosing session (Zeifman et al., 2019).

Neurobiological Bases Supporting the Antidepressant Effects of Ayahuasca

During the last few decades, the scientific exploration of ayahuasca and its effects has allowed insights about its biological mechanisms, safety limits, and potential therapeutic effects. Ayahuasca preparations contain N,N-dimethyltryptamine (N,N-DMT), a serotonin and sigma-1 receptors agonist (Carbonaro & Gatch, 2016), both of which have been implicated in depression. Furthermore, the MAOI present in ayahuasca directly affects the monoaminergic systems, increasing the viability of monoamines, such as serotonin, noradrenaline, and dopamine in the synaptic cleft, and tetrahydroharmine, one of these MAOI, is also a serotonin reuptake inhibitor (McKenna et al., 1984).

Cellular and systemic levels studies have been developed using models of neural cells on a dish, human stem cells, and cerebral organoids. Using human neural cells

and cerebral organoids derived from stem cells, a recent study has observed that harmine is associated with proliferation of neural cells (neurogenesis), linked to the inhibition of an enzyme called DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase) (Dakic et al., 2016). In another study, harmine, tetrahydroharmine, and harmaline were found to stimulate neural stem cell proliferation, migration, and differentiation into adult neurons, using brain progenitor cells from adult mice (Morales-García et al., 2017).

Changes in protein expression in brain organoids has also been observed after being exposed to 5-MeO-DMT, an analog of N,N-DMT (Dakic et al., 2017), naturally occurring in plants and in the Sonoran Desert toad (*Incilius alvarius*) (Davis et al., 2019). A cascade of proteins was changed that were involved in processes of novel dendritic spine formation, neuronal plasticity, and memory (Dakic et al., 2017). Furthermore, 5-MeO-DMT was also shown to induce increased dendritic complexity and to change electrophysiological properties of these newborn neurons (Lima da Cruz et al., 2018).

Animal models have also allowed for a more comprehensive exploration of the antidepressant effects of ayahuasca. These models have been extensively used as a tools to understand the biological bases of neuropsychiatric conditions as well as the effects of new treatments (Cardoso et al., 2004; Coimbra et al., 2017; Figueiredo et al., 2011; França et al., 2015; Ramaker & Dulawa, 2017; Willner & Belzung, 2015). Such studies allow for a deeper knowledge not accessible in human individuals and are conducted according to national and international regulations of animal welfare and ethical considerations.

Studies with ayahuasca and its components have shown promise in decreasing anxiety and depressive-like behavior in different animal models, such as in zebrafish, mice, and nonhuman primates (Cameron et al., 2018; Fortunato et al., 2010a; Fortunato et al., 2009, 2010b; Savoldi et al., 2017; Winne et al., 2020).

Studies in nonhuman primates have also been important, since they show similar brain morphology, function, and social organization with humans, fitting better as a translational animal model to psychiatric conditions (Galvão-Coelho et al., 2008; Galvão-Coelho et al., 2017). For instance, young common marmosets subjected to social isolation were used as a model of depression, upon which the effects of ayahuasca were tested. Results suggest reduced depressive-like behaviors and fecal cortisol levels improvements after a single session with ayahuasca compared to placebo. The effects were faster and more robust than in animals treated with the antidepressant nortriptyline (da Silva et al., 2018).

In humans, ayahuasca also seems to have a significant impact on the endocrine and immune systems. Evidence suggests increased prolactin and cortisol levels, and reduced lymphocytes CD3 and CD4, 2 h after a single ayahuasca intake in healthy volunteers (Dos Santos et al., 2011). Patients from our recent RCT with ayahuasca presented hypocortisolemia and blunted salivary cortisol awakening response at baseline. We found that patients treated with ayahuasca, but not with placebo, stabilized their salivary cortisol awakening response to the same level found in the healthy participants, 2 days after treatment (Galvao et al., 2018). These same patients treated with ayahuasca (but not with placebo) also presented an increase in

serum BDNF levels, which was correlated with lower depressive symptoms (MADRS scores) (rho = −0.55). This finding suggests that, most probably, ayahuasca affects the fast expression of this critical molecule, as is suggested for the new fast-acting antidepressants, such as ketamine (Ly et al., 2018).

Data from our RCT revealed changes in blood inflammatory biomarkers: C-reactive protein (CRP) and IL-6. At baseline, patients displayed higher CRP levels than healthy controls. Two days after ayahuasca ingestion, CRP levels decreased in both patients and healthy individuals treated with ayahuasca (but not with placebo). In addition, we found a significant positive correlation (rho = 0.70) between decreased inflammation and depressive symptoms (MADRS). No relevant variation was detected in IL-6 levels. Although usually, IL-6 and CRP are physiologically linked, some trials have shown isolated increases in CRP, which can be stimulated independently of IL-6 (Harris et al., 1999; Saito et al., 2016; Więdłocha et al., 2018). Since depression is also considered a pro-inflammatory disease, this work indicates that psychedelics can also have direct or indirect impact on the immune system involved in depressive processes, and also opens a new road for testing psychedelics on other inflammatory diseases (Galvão-Coelho et al. 2020).

The effects of ayahuasca on sleep also corroborate with its antidepressant effects. Barbanoj et al. (2008) investigated the impact of ayahuasca on sleep in the night following a single diurnal ayahuasca session. Results indicate that ayahuasca decreases REMS duration, and tends to increase REMS latency (Barbanoj et al., 2008). As mentioned before, increased amount of REMS and reduced REMS latency are common findings in depression (Minkel et al., 2017; Riemann et al., 2001; Tsuno et al., 2005).

The default mode network (DMN) has also been implicated in the pathophysiology of depression and changes in its activity and connectivity have been consistently observed during the effects of psychedelics. A previous fMRI study conducted by our group suggests that ayahuasca reduces the activity of most DMN nodes (Palhano-Fontes et al., 2015), while patients with depression tend to demonstrate increased DMN activity and functional connectivity in this region (Sheline et al., 2009).

The DMN has also been playing center stage in a recent entropic brain theory, which holds that the altered state of consciousness induced by psychedelics is characterized by higher entropy of the brain's functional connectivity (Carhart-Harris, 2018; Carhart-Harris et al., 2014). Entropy is a physical quantity associated with the level of uncertainty of a system. According to this theory, while in an ordinary state of consciousness, the DMN would act by restricting and maintaining the efficient functioning of the brain; under the psychedelic influence, the decreased activity and connectivity within the DMN would reduce such restrictions. With these constraints temporarily gone, the more flexible experiences under the influence of psychedelics would be represented by a state of increased entropy. In line with this theory, previous studies have observed increased entropy of brain connections while under the influence of psychedelics (Petri et al., 2014; Viol et al., 2017; Viol et al., 2019).

More recently, we have suggested that ayahuasca may exert its long-lasting effects on mood by modulating neural networks supporting interoceptive, affective,

and self-referential functions, such as the DMN and the salience networks (Pasquini et al., 2020). We found increased functional connectivity of the salience network and decreases in the DMN 1 day after the dosing session in healthy individuals (Pasquini et al., 2020), consistent with our previous observation that the activity and connectivity within the salience network is increased during the acute effects of ayahuasca (Fig. 2.3), together with changes in the DMN (Palhano-Fontes et al., 2015). Similar increased functional connectivity within the DMN was also observed following psychedelic psilocybin in an open-label trial for depression (Carhart-Harris et al., 2017). Altogether, these studies suggest that brain changes could be a mechanism influencing the therapeutic response we observe in the use of psychedelics for depression.

The therapeutic benefit of psychedelics also seems to depend on the quality of psychedelic experience, such as the peak experience (Bogenschutz et al., 2015; Garcia-Romeu et al., 2015; Griffiths et al., 2016; Majić et al., 2015; Ross et al., 2016). An open-label trial with psilocybin for tobacco addiction found a significant correlation between cessation outcomes and mystical experience measures (Garcia-Romeu et al., 2015). The same was found in another trial with psilocybin for alcohol dependence, where mystical experiences were correlated with decreased craving and increased abstinence (Bogenschutz et al., 2015). Furthermore, recent RCT with psilocybin for depression and anxiety in patients with life-threatening cancer showed that mystical experiences mediate the therapeutic effects (Griffiths et al., 2016; Ross et al., 2016).

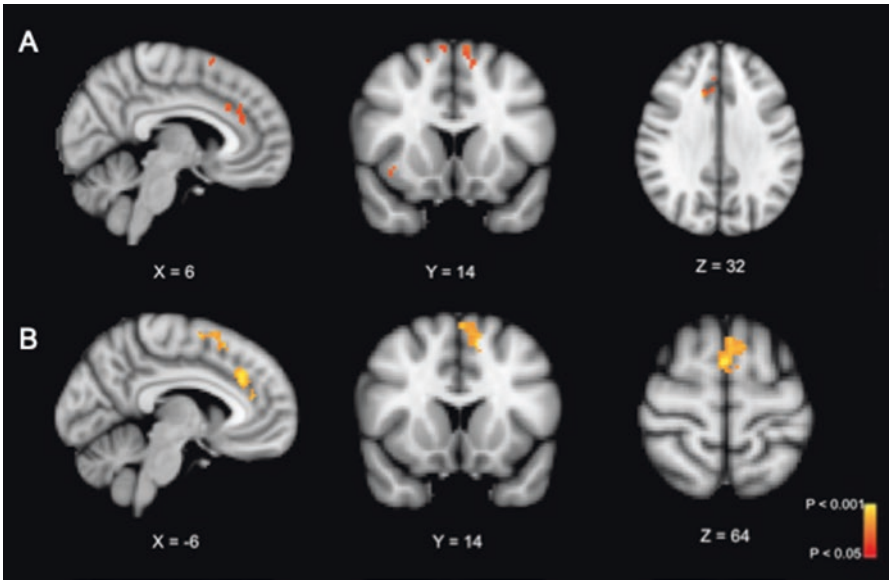

Fig. 2.3 Activity (panel A) and functional connectivity (panel B) increases within the salience network during acute effects of ayahuasca

In our recent RCT with ayahuasca for depression, out of the 29 patients, 27 patients responded to the HRS and 15 patients responded to the MEQ. We found that the HRS dimension that assesses changes in visual perception was the only one to show relationship with the antidepressant outcome (Palhano-Fontes et al., 2019). In fact, it has been argued that visions may play a crucial role in the therapeutic benefits of ayahuasca, as a mechanism to provide personal insights (Frecska et al., 2016). Our results give support to this hypothesis. In addition to a previous fMRI study that found increased activity in vision-related cortices during the acute effects of ayahuasca (de Araujo et al., 2012), we also found a negative correlation between changes in depressive symptoms after the ayahuasca session and the MEQ factor related to perception of time and space (Palhano-Fontes et al., 2019).

Final Remarks

Psychedelic substances from different plants and fungi have been used for a long time for healing purposes, and form a central pillar of different ancient cultures (Schultes & Hofmann, 1979). Despite the presence of these substances throughout nature and history, they have attracted little scientific attention until the 1940s, with the discovery of lysergic acid diethylamide (LSD) (Hofmann, 1979). During that period, LSD was regarded with great interest by psychiatry due to its therapeutic potential (Oram, 2014). Between the 1950s and mid-1960s, more than 1000 articles had been published, with more than 40,000 subjects having participated in clinical trials with LSD (Bakalar & Grinspoon, 1997). Due to the Drug War policy under Richard Nixon's presidency in the 1970s, all research with psychedelics was practically shut down, and psychedelics became schedule I substances, defined as drugs with severe safety concerns, no medical use, and high risk of abuse. Back then, there were no controlled trials with psychedelics for any human condition.

After a few decades of discontinuation, research involving psychedelics has once again gained momentum. Recent studies suggest that it is safe when used in appropriate set and setting. In the case of ayahuasca, its clinical potential has been tested in recent studies on anxiety and depression (dos Santos et al., 2016; Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016), and alcohol addiction (Thomas et al., 2013).

Our recent study was the first RCT to test a classic psychedelic against treatment-resistant depression (Palhano-Fontes et al., 2019). One point worth mentioning is the rapid nature of the observed antidepressant effects of ayahuasca. Currently available antidepressants, such SSRIs and tricyclics, take around 2 weeks for the onset of the desired therapeutic response (Cai et al., 2015; Otte et al., 2016), while our study suggests significant antidepressant effects of ayahuasca already 1 day after dosing.

The placebo effect observed in our study was higher than usually seen in clinical trials for depression, including those with ketamine (Palhano-Fontes et al., 2019; Romeo et al., 2015). While we found a placebo response rate of 46% 1 day after

dosing, and 26% 7 days after, studies with ketamine found placebo responses on the order of 0–6% at 1 day and 0–11% 7 days after dosing.

Several factors contribute to the high placebo effects observed in our study. First, most of our patients come from low socioeconomic status, and most live under intense and constant stress, in insecure environments, under intense financial and psychosocial stressors. During our trial, they stayed in a very comfortable and supportive environment for a period of 4 days. It seems as though this is more of a care effect than a typical placebo effect. For several of them, our laboratory was like staying in a five-star hotel.

Most of our patients (76%) had concurrent personality disorder, most of them from cluster B (borderline and histrionic), and other studies have related personality disorder to higher placebo responses (Palhano-Fontes et al., 2019). This was the first clinical trial with psychedelics to report including individuals with personality disorder. No serious adverse events were observed, although the session tended to be more challenging for these individuals. The number of individuals with personality disorder included in our trial was small, but the preliminary results found are promising, which warrants additional research exploring the safety and clinical utility of ayahuasca as an intervention for personality disorder (Zeifman et al., 2019).

For many years, indigenous knowledge and ayahuasca communities have been pointing out the therapeutic benefits of ayahuasca. This wisdom is now being explored with scientific methods and new interpretations are being made in light of new findings. Preliminary evidence supports many claims and previous anecdotal reports. The evidence reviewed here suggests good support for the use of ayahuasca for treatment-resistant depression. The antidepressant effects we observed were accompanied by changes in a variety of systems, including hormonal, inflammatory, and immune systems, and brain functions related to perception, memory, attention, emotion, and cognition. Such observations reveal that the nature of the effects of ayahuasca are indeed multifactorial, and spans from gross biochemical changes to subtle cognitive processes.

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