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Chapter 2
The Therapeutic Potentials of Ayahuasca in the Treatment of Depression

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Abstract Major depressive disorder (MDD) is generally classified as a mood disorder with a profound effect on the individual's behavior and quality of life. According to the World Health Organization, in about 20 years, depression will be the disorder with the most significant repercussions, both socially and economically. Despite the substantial progress in the development of new antidepressants, their effectiveness remains low, with remission of about 50 % after a single regime of treatment. The most common form of pharmacological treatment of MDD is based

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on selective serotonin reuptake inhibitors (SSRIs), designed to increase extracellular levels of the neurotransmitter serotonin. Unfortunately, antidepressants currently available based on SSRIs may take several weeks to achieve the desired therapeutic effects. Therefore, massive effort has been devoted to find alternative treatments for MDD. For example, the use of ketamine, of (±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI), and β-carbolines is under current investigation. Based on evidence from the literature and a pilot study conducted by our group, we speculate about the possible therapeutic potential of ayahuasca for MDD. In part, such conjecture is based on the fact that ayahuasca combines N,N-dimethyltryptamine (DMT), acting particularly on serotonin neurotransmission through 5-HT_{2A} receptors and monoamine oxidase inhibitors (MAOI), both involved, at least indirectly, with pharmacological formulations intended for MDD treatment. In this chapter, we will review the major aspects of MDD such as diagnosis, current pharmacological treatments, and the motivations to use ayahuasca as a novel alternative.

Major Depressive Disorder: Causes and Diagnosis

Major depressive disorder (MDD) is generally classified as a mood disorder with a profound effect on the individual's behavior and quality of life. It has a prevalence of 17 % throughout life, being twice as common in women as it is in men and usually begins in the third decade of life. For most people, MDD presents itself in recurrent episodes. However, about 20–25 % of patients are chronically ill. According to the World Health Organization (WHO), MDD is the fourth leading cause of morbidity, and they predict that by 2020, it will be ranked second disease burden worldwide (Fava and Kendler 2000).

MDD is associated with intense personal suffering, high morbidity, and increased mortality (Ebmeier et al. 2006). The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV-TR) defines this condition based on the presence of depressed mood (irritable mood in children and adolescents) and/or loss of interest or pleasure (anhedonia) for at least 2 weeks, accompanied by at least four of the following symptoms: (a) considerable change in weight (5 % of body weight), (b) frequent insomnia or hypersomnia, (c) psychomotor agitation or retardation, (d) fatigue or loss of energy, (e) low self-esteem or inappropriate guilt, (f) diminished capacity to think, concentrate, or make decisions, (g) recurrent thoughts of death, suicidal ideation, or suicide attempts. In addition, the diagnosis requires that the symptoms cause significant distress and/or impairment in social, occupational, or other areas of life, and should not be directly caused by another general medical condition or psychoactive substance use and must not meet the criteria for mixed episode (in which the diagnostic criteria of depression and mania occur concurrently) (American Psychiatric Association [APA] 2000b).

Multiple theories attempt to explain the etiology of depression, but the most widely accepted one is the monoamine hypothesis. This theory suggests that MDD

is a result of decreased brain levels of monoamines, such as dopamine, norepinephrine, and serotonin (Wong and Licinio 2001). Among these, serotonin has received the most attention. Besides the reduction of serotonin levels found in depression, studies also point to an altered expression of $5HT_{1A}$ autoreceptors and heteroreceptors. The most consistent finding is an increase in pre-synaptic $5HT_{1A}$ autoreceptors, which inhibit the release of serotonin, and consequently reduce serotonin levels in the synaptic cleft. A reduced number of postsynaptic $5HT_{1A}$ heteroreceptors in the hippocampus and prefrontal cortex, presumably induced by high cortisol levels also found in these patients, is also associated with MDD.

On the other hand, the monoamine hypothesis does not explain important matters such as the causes of the monoaminergic disturbance and the elevated refractoriness to the treatment of MDD with antidepressant drugs that target the increase of the monoamine levels in the synaptic cleft. In this scenario, several alternative hypotheses were brought to focus such as hypothalamic–pituitary–adrenal (HPA) axis dysfunctions and the inflammatory and neurodegenerative hypotheses.

One of the most common HPA abnormalities observed in depressed patients is an increase in reactivity of this axis. Scientific evidence indicates that MDD patients have impaired glucocorticoid receptor (GR) function, which results in reduced negative feedback in the HPA system, leading to chronically high levels of adrenocorticotrophic hormone-releasing factor (CRF), and increased cortisol in the plasma, urine, and cerebrospinal fluid (Zunszain et al. 2011).

Complementarily, the inflammatory theory is based on the strong mutual regulation and communication between the immune and HPA systems (Leuchter et al. 2010). Chronic activation of the HPA axis also provokes GR resistance in immune cells (Leonard 2007). Normally, basal cortisol induces the production of lymphocytes T CD4 Th2, but chronicle GR resistance leads to an imbalance in the immune system, displacing the production of these lymphocytes to a Th1 subtype, thus reducing the concentration of anti-inflammatory cytokines (IL-4, IL-10), and increasing the pro-inflammatory cytokines (IL-1, IL-6, TNF-a) (Leuchter et al. 2010; Li et al. 2011). In turn, the massive liberation of pro-inflammatory cytokines induces a decrease in GR function (Pace et al. 2007).

Taken together, a link between these three theories has been observed: The excess of circulating corticosteroids and pro-inflammatory cytokines increases activity of indoleamine 2,3-dioxygenase (IDO), an enzyme which induces formation of kynurenine in the tryptophan-kynurenine pathway, resulting in the deficiency of serotonin commonly observed in depression (Miura et al. 2008).

The neurodegenerative hypothesis is based on the fact that many depressed patients have reduced hippocampal volume (Bremner et al. 2000). Studies suggest that such reduction does not come only as a consequence of neuronal death (Sapolsky 2004). Instead, it can be a result of a reduction in neurogenesis induced by high glucocorticoid, pro-inflammatory cytokine levels and reduced serotonin availability, which in turn can inhibit the production of cell growth factors such as brain derived neurotropic factor (BDNF) (Shimizu et al. 2003). Animals models of depression (Berry et al. 2012) have shown that social deprivation in mice leads to increased depressive-like behaviors, elevated corticosterone levels, and reduced BDNF levels (Zhou et al. 2008).

Despite the dysregulation of the inflammatory proteins, stress hormones, and brain factors associated with depression, one of the main challenges regarding MDD diagnosis is the absence of a specific biomarker related to this disease. The use of biomarkers has an important role in understanding and monitoring conventional and alternative treatments (Leuchter et al. 2010). The current consensus is that no biomarker alone is sufficient to predict and identify individuals at risk, make the diagnosis, or direct clinical treatment decisions concerning depression. Accordingly, the construction of a multimodal panel of biomarkers is recommended to obtain the accuracy required in clinical practice or research protocols (Lakhan et al. 2010). For MDD, there are several candidates for identifying biomarkers, including neuropsychological assessment, electroencephalography (EEG), polysomnography (PSG), biochemical markers, medical imaging, genomics, proteomics, and metabolomics, among others.

Biochemical Markers

Information on biochemical markers is accessed indirectly by measurements of the cerebrospinal fluid (CSF), saliva, or blood. In this scenario, CSF may be considered the source that best reflects brain activity. However, it is not easily accessible on a risk-free basis. On the other hand, although urine and feces are easily collected, it is difficult to associate levels of metabolites present in these two vehicles with the ones found in the brain. Saliva has also been used with success for the measurement of steroid hormones, such as cortisol (Dziurkowska et al. 2013). However, this is generally not considered a reliable strategy for use with depressed patients (Knorr et al. 2010). Therefore, biochemical markers have been sought in the blood, both for its easy accessibility and for the fact that many molecules found in the brain are excreted via the route of blood circulation.

Curiously, plasmatic factors which target the serotoninergic system are not considered good biomarkers for chronic depression (Pivac et al. 2002). On the other hand, high concentration of cortisol in the plasma has frequently been read as a biomarker indicative of depression, in agreement with the hypercortisolemia theory (Leonard 2007; Tadić et al. 2011). Moreover, plasmatic pro-inflammatory cytokine levels, which are reported to be increased in MDD, are also considered reliable biomarkers, in accordance with inflammatory theory (Li et al. 2011).

Polysomnographic Markers

Sleep abnormalities are consistently revealed in EEG findings in patients suffering from MDD. Although there is no single marker of sleep specifically associated with depression, many studies have found differences in sleep between MDD patients and healthy control subjects. The use of polysomnography (PSG) in these

patients has revealed impaired sleep continuity, reduced latency to REM sleep (interval between sleep onset and the occurrence of the first REM period), increased amount of REM sleep, longer first REM period, increased REM density (number of eye movements during REM), and reduced slow-wave sleep (Benca et al. 1992; Riemann et al. 2001; Tsuno et al. 2005).

The reduction in the latency to REM sleep associated with depression has been observed since the 1970s. Several studies have reported that this change is related to the secretion of cortisol at night, suggesting that dysregulation of mood, sleep, and HPA may be interconnected (Poland et al. 1992). An inverse relationship is observed between cortisol level and the latency shortening: Subjects showing the shortest REM latency also have the greatest degree of HPA activity (Asnis et al. 1983). Asnis and colleagues speculate that the association between REM latency and the HPA axis is caused by a dysregulation of the muscarinic cholinergic system, which exerts a role in both physiologic systems (Asnis et al. 1983).

In addition, it has been proposed that the decreased latency to REM sleep associated with depression may be a familiar trait (Giles et al. 1987). Giles and her co-researchers investigated risk factors in patients with a lifetime history of depression. They reported that the relative risk for MDD in relatives with reduced REM latency was almost three times greater than for relatives with non-reduced REM latency (Giles et al. 1988). They also found shortened REM latency, even in psychiatrically asymptomatic first-degree relatives of depressed probands (Giles et al. 1989). Other investigators reported sleep disorders (Lauer et al. 1995) and dysregulation of the HPA axis (Mannie et al. 2007) in otherwise healthy adults, but whose first-degree relatives had a history of depressive disorder.

Furthermore, the connection between REM sleep and depression has been demonstrated by the fact that acute sleep deprivation (total, partial, or specifically REM sleep) alleviates depressive symptoms (Benca et al. 1992; Riemann et al. 2001). Pharmacological treatment also influences REM sleep. It has been shown that antidepressants decrease the amount of REM sleep. In addition, such changes in the initial stages of antidepressant treatment are a predictor of treatment outcome (Riemann et al. 2001).

Magnetic Resonance Imaging Markers

The use of magnetic resonance imaging has helped to identify the psychopathological mechanisms underlying MDD. Recent studies show that depressed patients present neuroanatomical and functional alterations when compared to healthy controls. One of the most consistent results is the reduction of hippocampal volume in MDD (Bremner et al. 2000; Lorenzetti et al. 2009; MacQueen 2009). Another common finding is the volume reduction in some of the basal ganglia structures, such as the caudate and putamen (Lorenzetti et al. 2009). Although the results are not always convergent, such morphological changes are an indication that structural images can provide information relevant to the characterization of depression.

In addition to brain anatomy changes, some studies used functional neuroimaging techniques to evaluate the brain function of MDD patients. The amygdala, a medial temporal lobe structure that is highly sensitive to emotional stimuli, has been repeatedly implicated in depression symptoms. Studies using functional magnetic resonance imaging (fMRI) showed hyperactivity of the amygdala of depressed patients (Davey et al. 2011; Sheline et al. 2001).

Moreover, the ventromedial prefrontal cortex, the anterior cingulate cortex, and the inferior parietal cortex have been the subject of many studies on depression. These regions constitute a network known as the Default Mode Network (DMN), which is characterized by greater activity during rest than during the execution of a goal-specific task (Raichle et al. 2001). The DMN has been implicated in processes involving self-judgments, recall of autobiographical memories, mental simulations, mind-wandering, and daydreaming (Buckner et al. 2008; Northoff et al. 2006). Using an emotional regulation task, Sheline and colleagues examined the functionality of the DMN in patients with MDD, investigating whether the ability to regulate its activity, and therefore the self-referential processing, was impaired. The results showed that the individuals with depression failed to modulate different regions of the DMN, including the anterior cingulate cortex, lateral parietal cortex, the medial prefrontal cortex, and the lateral temporal cortex. Furthermore, some studies showed alterations in the functional connectivity patterns of the DMN. For instance, Greicius et al. (2007) reported a significant increase in functional connectivity in the subgenual cingulate cortex and precuneus in depressed patients when compared with healthy controls. These results are consistent with clinical symptoms, such as rumination, in which MDD patients are impulsively focused on the past and/or future negative consequences, rather than reflecting on the present moment (Devilbiss et al. 2012).

Abnormalities in functional connectivity of other networks were also found in depressive patients (Anand et al. 2005; Sheline et al. 2010; Veer et al. 2010). For example, Veer and colleagues showed that there is: (1) a decrease in connectivity between the amygdala and the left anterior insula, structures related to affection; (2) reduction in the connectivity of the left frontal pole, a network associated with attention and working memory; and (3) a decrease in bilateral connectivity of lingual gyrus and ventromedial visual areas (Veer et al. 2010). The connectivity has also been related to the response to antidepressant treatment. A study by Anand et al. (2005), evaluated the effect of sertraline, a commonly used antidepressant, in cortico-limbic connectivity. After treatment, patients showed increased connectivity between the anterior cingulate cortex and the limbic regions, a circuit that has been linked to emotional regulation.

Pharmacological Treatments

Several alternatives are available for treatment of MDD. The most common ones are the use of antidepressant medications (Uppal et al. 2010), psychotherapy (Cuijpers et al. 2011), electroconvulsive therapy (Andrade et al. 2010), and other

somatic therapies (Segal et al. 2010). The goal of treatment is the remission of the depressive episodes, defined by the DSM-IV as the absence of MDD symptoms for at least 2 months (Kennedy et al. 2001). A treatment response is considered when depressive symptoms are reduced by 50 % or more, usually evaluated by the Hamilton Scale (HAM-D), and not necessarily mean remission (Ebmeier et al. 2006).

In general, pharmacological treatment has a number of phases. The first, known as acute, lasts about 8 weeks, and is essential to evaluate the patient's response to the treatment (Bolland and Keller 2004). If this first step is successful, there is another period that lasts 16–20 weeks and aims to prevent possible recurrence of depressive episodes (Kennedy et al. 2001). Some cases go through the maintenance phase indefinitely, for example, individuals at high risk of recurrence, such as those who have had multiple episodes or partial response to treatment, and patients who have episodes of high severity with psychotic symptoms and suicidal risk (APA 2000a).

The discovery of antidepressants in the 1950s drastically transformed the treatment of depression, and they remain the leading strategy (Ebmeier et al. 2006). Several classes of antidepressants are available, classified according to their chemical structure, effect on the synapses, and action on reuptake and metabolism of neurotransmitters.

The first generation of antidepressants can be divided into tricyclics (TCA) and monoamine oxidase inhibitors (MAOI). Both act by increasing extracellular levels of monoamines; TCA by inhibiting the reuptake of dopamine, noradrenaline, and serotonin, and MAOI by preventing the action of MAO, thereby avoiding the degradation of monoamine neurotransmitters (Bolland and Keller 2004).

In addition to the therapeutic action, TCA acts on several other receptors, leading to antimuscarinic, antihistaminic, and anti-α2 adrenergic effects that lead to undesirable outcomes such as urinary retention, constipation, orthostatic hypotension, weight gain, and somnolence. Furthermore, TCA block sodium channels interfering with nerve conduction, becoming potentially arrhythmogenic. Although recently questioned, it is classically believed that the main side effect of MAOI is the high risk of hypertensive crisis triggered by its combined ingestion with foods containing tyramine, a sympathomimetic amine, which is metabolized by MAO (Grady and Stahl 2012).

Given the low selectivity of classic antidepressants, newer antidepressants were developed. Among these are the selective serotonin reuptake inhibitors: SSRIs (fluoxetine, paroxetine, etc.), selective noradrenaline reuptake inhibitors (reboxetine), and serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine, and desvenlafaxine). Moreover, there are antidepressants with multiple action mechanisms, such as mirtazapine, which acts as a noradrenergic pre-synaptic α2-receptor antagonist and serotonin ($5HT_2$ and $5HT_3$) antagonist, and nefazodone which act by inhibiting the reuptake of serotonin and norepinephrine, and as a 5HT and α2 antagonist (Cipriani et al. 2009).

The newer antidepressants, such as SSRIs, have essentially the same mechanism of action as the first generation, i.e., they increase the level of monoamines in

the brain (Zarate 2011; Zarate et al. 2006). However, this new generation offers more safety. Side effects, although milder, are still present, and are specific to different classes of medications. For example, sexual dysfunction and gastrointestinal disorders are common with the use of SSRIs, and sleepiness and weight gain are associated with the use of mirtazapine (Cipriani et al. 2009). Given that the effectiveness of the various antidepressants is similar, the choice of medication is made based on side effects, safety, tolerability, patient's individual preferences, quantity and quality of clinical trial data, and cost (APA 2000a).

With respect to the modulation on the HPA axis made by different antidepressants, evidence indicates that it depends on the type of antidepressant and length of treatment. Increased adrenocorticotropic hormone (ACTH) and cortisol levels have been reported 5 hours after a single oral administration of reboxetine, and a decrease of these hormones after a single oral administration of mirtazapine in both healthy individuals and in subjects with depression (Schüle 2006). Moreover, a gradual and significant reduction of HPA activity has been found after 5 weeks of treatment with reboxetine in depressed patients (Schüle et al. 2006). On the other hand, treatment with mirtazapine only reduces HPA activity during the first week; after that, HPA activity increases again (Pariante et al. 2004).

Despite substantial progress in the development of new drugs, less than 50 % of patients achieve remission as a result of antidepressant use, even after four different pharmacological treatment regimes (Warden et al. 2007). Besides low effectiveness, the pharmacological treatments that are currently available carry another limitation associated with the chronology of the drug action: It takes several weeks to reach the desired therapeutic effects (Zarate 2011; Zarate et al. 2006). Thus, enormous effort has been devoted to the search for alternative pharmacological treatments that could improve treatment efficiency and accelerate the onset of therapeutic effects (Uppal et al. 2010). For instance, studies conducted with ketamine, an NMDA antagonist, showed antidepressant effects after a single intravenous injection, which persisted significantly after 1 week (Liebrenz et al. 2007). Furthermore, the use of (±)-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a powerful $5HT_{2A/2C}$ agonist, resulted in positive responses in two models of anxiety in mice (Dhonnchadha et al. 2003). In another study, mice subjected to the forced swimming test, a common paradigm used to study depression in rodents, exhibited decreased immobility time 6 h after receiving DOI, an effect that is considered predictive of antidepressant response (Masuda and Sugiyama 2000).

Another serotonergic agonist, N,N-dimethyltryptamine (DMT), has also been considered a potential antidepressant. Some hypotheses have emerged that, at low doses, the anxiolytic mechanism associated with DMT would be mediated by a trace amine receptor, which could be one of the sites of action of endogenous DMT (Jacob and Presti 2005).

Anxiolytic and antidepressant effects are also related to β-carbolines. In a recent study, the use of harmane, norharmane, and harmine in an animal model was capable of reducing the time of immobility in the forced swimming test (Farzin and Mansouri 2005). Similar effects were observed in animal models using the

elevated plus maze test, a common paradigm for the study of anxiety in rodents (Aricioglu and Altunbas 2003). It has recently been found that the use of harmine alone in rodent models leads to the reduction of various signs and symptoms associated with depression, such as anhedonia, and regulation to normal levels of ACTH and hippocampal BDNF (Fortunato et al. 2010).

Based on the evidence presented here, and in a pilot study conducted by our group, described below, the question arose regarding the use of substances that combine DMT and MAOI, as is the case of ayahuasca, in MDD treatment. There are several anecdotal reports that the ritual use of ayahuasca is associated with the relief of depression symptoms.

Ayahuasca tea is traditionally prepared by decoction of the bark and stem of the *Banisteriopsis caapi* vine with leaves of the *Psychotria viridis* bush. The *B. caapi* contains the alkaloids harmine, tetrahydroharmine (THH), and harmaline; the three belonging to the β-carbolines group, and corresponding to 0.05–1.95 % of the dry weight of the plant. In addition, *P. viridis* provides the hallucinogenic tryptamine DMT, which corresponds to 0.1–0.66 % of the dry weight of the plant (McKenna et al. 1984; Riba et al. 2003).

Ayahuasca's activity is dependent on the synergistic interaction between these components. β-carbolines are potent reversible and competitive MAOI (Mckenna et al. 1984) and can increase serotonin levels, blocking its deamination. Their main action in ayahuasca is apparently to protect DMT from peripheral degradation, preventing oxidative deamination of the orally ingested DMT and enabling it to reach the central nervous system (McKenna 2004). The pharmacological effects of DMT also depend on its interaction with the serotoninergic system. DMT is the substrate for both cell-surface serotonin uptake transporters (SERTs) and neuronal vesicle monoamine transporters (VMAT2). Unlike drugs that are uptake inhibitors, DMT is transported into the cytosol or vesicle by SERT or VMAT2, respectively (Cozzi et al. 2009). Therefore, high intracellular and vesicular concentrations of DMT may be achieved inside of neurons, and can interact with intracellular sigma-1 receptors located in the mitochondria-associated endoplasmic reticulum membrane (Su et al. 2009). Hence, the DMT can be released into the synaptic cleft upon vesicular fusion to interact with cell-surface sigma-1 receptors or serotonin postsynaptic receptors (Cozzi et al. 2009).

The effects of ayahuasca are heterogeneous (Riba et al. 2001), and encompass sensory, cognitive, and affective changes (Prado et al. 2009), rich visual experiences (de Araujo et al. 2011), and entheogenic experiences (Shanon 2003). These effects begin between 35 and 40 min after tea ingestion, reaching their height between 90 and 120 min, and lasting for 4 h (Riba et al. 2003). Thus far, all studies to date have demonstrated the safety of ayahuasca, with reports of individuals who have used it for more than 30 years without evidence of harm to health (Callaway et al. 1999; Grob et al. 1996; Riba et al. 2001; Riba et al. 2003). Changes in both blood pressure—systolic, diastolic, and mean—and heart rate are not significant (Riba et al. 2003). Furthermore, a recent study showed that the ritual use of the tea is not associated with the psychosocial problems that are usually found with other drugs (Fábregas et al. 2010).

Preliminary evidence of its potential use as an antidepressant is encouraging. A double blind, placebo controlled experiment indicated that the use of ayahuasca significantly reduces the scores of behavioral scales of panic and hopelessness in participants who were under the influence of the tea compared to a control group (Santos et al. 2007).

Ayahuasca and MDD Biomarkers

In addition to the pharmacological evidence described previously, other evidence might also support the use of ayahuasca as an antidepressant. Recent studies have indicated that regular ayahuasca use is involved in long-term modulation of the serotonin systems in the brain, specifically in SERTs levels. Such modulation can increase the serotoninergic system's function, which might be a mechanism for its possible positive effect in depressed patients. Ayahuasca also has significant effects on the endocrine system, mainly in the HPA axis, and the immune system. Studies have found increases in prolactin and cortisol levels approximately 2 hours after a single ayahuasca dose. This increase of cortisol has an impact on cell immunity and reduces CD3 and CD4 lymphocytes after ayahuasca use (Dos Santos et al. 2011). Another study used two sequential doses of ayahuasca with an interval of 4 hours and found endocrine and immunomodulatory effects analogous to those previously reported (Dos Santos et al. 2012). In line with this evidence, rapid increase in cortisol levels was observed in a single acute treatment with antidepressants like reboxetine that act on the serotoninergic system (Schüle 2006).

Barbanoj and colleagues investigated the effect of ayahuasca on sleep. They evaluated sleep quality, polysomnography, and spectral analysis in 22 healthy volunteers following a unique ayahuasca dose administration during the day. Results indicated that ayahuasca had no significant effects on sleep initiation or continuity as assessed by subjective and objective measures. Furthermore, it was found that the tea inhibits REM sleep, decreasing its duration in absolute values and in percentage of REM sleep. A trend increase in REM latency was also reported (Barbanoj et al. 2008). Based on these results, one can further speculate that ayahuasca might have therapeutic potential, as evidence from the literature points out that PSG changes in depression (increased amount of REM sleep and reduction in REM latency) go in the opposite direction from the changes induced by ayahuasca (Benca et al. 1992; Riemann et al. 2001; Tsuno et al. 2005).

There is also fMRI evidence of the potential antidepressant effects of ayahuasca. In a study conducted by our group, which aimed at evaluating the changes induced by ayahuasca in the DMN, 10 healthy subjects submitted to two fMRI sessions: one before and one right after tea intake. It was observed that ayahuasca caused a reduction in the fMRI signal of central nodes of the DMN, such as the anterior cingulate cortex, the medial prefrontal cortex, the posterior cingulate cortex, the precuneus, and the inferior parietal lobe. Moreover, changes in connectivity patterns of the DMN were observed (Fig. 2.1), especially a decrease in

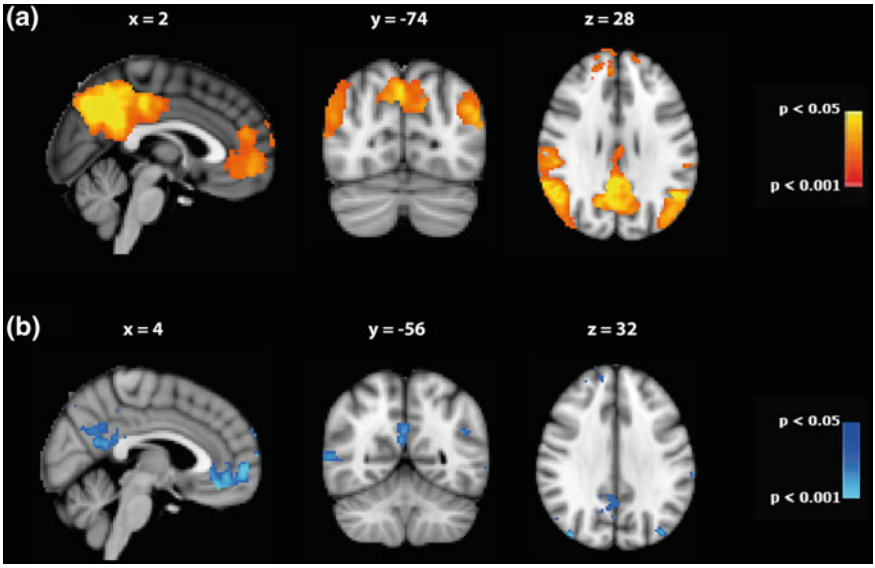

Fig. 2.1 Ayahuasca effects on the DMN. **a** An fMRI image showing the set of regions that comprise the DMN. **b** Regions where ayahuasca caused a BOLD signal reduction. Statistical maps were obtained comparing the groups before and after ayahuasca intake ($p < 0.05$ uncorrected)

the functional connectivity of the precuneus (Fontes et al. 2012). However, some studies show an opposite modulation in patients with depression, i.e., increased DMN activity and functional connectivity (Greicius et al. 2007; Sheline et al. 2009).

Our group has been conducting an exploratory study of the feasibility of the use of ayahuasca as an antidepressant. The ethics committee of the Clinical Hospital of Ribeirao Preto approved this study (No. 2484/2008). Preliminary evaluations were conducted in three female subjects with a clinical diagnosis of recurrent depressive disorder and current mild to severe depressive episodes without psychotic symptoms. The subjects were in the washout period between medication changes, and had been without antidepressant medication for 2 weeks.

Patients received a single oral dose of 2 ml/Kg of ayahuasca tea and were assessed using psychiatric scales, including the HAM-D, 10 min before administration of tea, and 40, 80, 140, and 180 min after ingestion, and on days 1, 2, 7, 14, and 28 after the experimental session. Results showed a significant decrease of HAM-D scores over time, beginning at 40 min after intake and lasting for 14 days (de Lima Osório et al. 2011).

It is interesting to notice that the improvement observed in HAM-D scale can also be further corroborated by the patient's testimonials. One patient stated: "I stayed huddled and crying softly, I was completely huddled and I could not answer because I felt as if the devil and Our Lady were battling for my soul and I could not

interfere. After a long battle Our Lady won and pulled me to her side and I felt an intense joy." Another said: "I felt as if I was trying to hold a ball of blue energy. I did not succeed because it was like my hands were different poles of a magnet, moving them apart. When I finally got to hold it, the energy came over me and it all made sense. From then on, I was no longer feeling depressed."

Although this evidence must be considered with caution due to the inherent limitations of exploratory studies, the results suggest that ayahuasca has antidepressant properties presenting an interesting acute effect.

Final Remarks

New pharmacological approaches to MDD treatment have expanded beyond the model of serotonin reuptake, including the use of ketamine as well as the potential use of novel substances such as ayahuasca. Different aspects related to the identification of biomarkers and theories about the psychophysiological action of ayahuasca were characterized and presented as part of the *zeitgeist* of depression. Although the evidence presented herein was supported by international studies, more research is necessary to support the pharmacological use of ayahuasca and of similar DMT/MAOI combinations in the treatment of MDD. Based on that evidence, and on studies conducted by our group, it is possible to glimpse promising pharmacological implications for the use of ayahuasca in treating depression.

There is an interesting aspect to consider about the use of ayahuasca in depression: A closer look at our preliminary results reveals that the depressive signs and symptoms are reduced after a single ayahuasca intake, and that the effects last for about 14 days. Curiously, in the context of the Brazilian ayahuasca religions, the interval between sessions is exactly 2 weeks. One must also consider the number of anecdotal reports from experienced ayahuasca drinkers, and also from naïve ayahuasca drinkers, supporting the notion that ayahuasca has antidepressant potentials. From a broader reflection on how knowledge is transformed, the discovery of ayahuasca's antidepressant effects might be considered a thought-provoking example of a successful dialog between science and cultural tradition.

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