Chapter 7
Acute and Long-Term Effects of Ayahuasca on (Higher-Order) Cognitive Processes

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Introduction

Ayahuasca is a South American psychotropic plant brew, generally consisting of the boiled stems of the *Banisteriopsis caapi* vine, and the leaves of the *Psychotria viridis* bush. *B. Caapi* contains the β-carboline alkaloids harmine, tetrahydroharmine, and harmaline, while *P. Viridis* contains the tryptamine N,N dimethyltryptamine (DMT), a hallucinogen that is structurally similar to serotonin (5-HT). When taken orally, DMT is rendered inactive via monoamine oxidase activity in the gastrointestinal tract (McKenna 2004; McKenna et al. 1984). However, when combined with *B. caapi*, the β-carboline alkaloids inhibit monoamine oxidase activity, allowing DMT to reach the systemic circulation and cross the blood-brain barrier, where it activates 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors (Dos Santos et al. 2016a, b; Fantegrossi et al. 2008; Riba et al. 2003; Smith et al. 1998).

Similar to other serotonergic hallucinogens, the 5-HT_{2A} receptor activation is the suggested mechanism for the acute subjective effects of ayahuasca, which include perceptual modifications, increased rates of thinking when eyes are closed, and increased emotional lability (Bickel et al. 1976; Riba et al. 2001; Riba et al. 2003). These acute effects usually start between 45 and 60 min post-administration, peak between 60 and 120 min, end after 4 h, and follow a dose-response pattern (Riba et al. 2001).

Ayahuasca has been traditionally used for centuries by indigenous and mestizo populations throughout the Amazon Basin for magical, ritual, and medicinal purposes (Luna 2011; Schultes and Hofmann 1979). However, in the last few decades, there has been an increase in the availability of the brew to non-Amazonian populations (Tupper 2009). Subsequently, there has been an increase of anecdotal reports

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B. C. Labate, C. Cavnar (eds.), *Ayahuasca Healing and Science*,
https://doi.org/10.1007/978-3-030-55688-4_7

from ayahuasca users regarding the acute and long-term effects of the substance, with many claiming that the substance has positive and therapeutic potential for psychosocial, emotional, and substance-related problems (Barbosa et al. 2005; Kjellgren et al. 2009; Winkelman 2005).

Over the past few years, there has been a renewed interest in psychedelic drugs as potential tools in therapy (Dominguez-Clave et al. 2016; Vollenweider and Kometer 2010). Double-blind experimental studies on the acute and long-term effects of psilocybin, a classic hallucinogen whose psychoactive mechanism is also mediated through 5-HT_{2A} receptor activation, have suggested that a psychedelic session can produce life-altering experiences and long-term improvements in well-being and behavior in healthy volunteers (Griffiths et al. 2006; Hasler et al. 2004).

Case-control studies and surveys have suggested that psychedelic users suffer from less psychopathology (Da Silveira et al. 2005; Grob et al. 1996; Hendricks et al. 2015) and display lower patterns of alcohol use (Doering-Silveira et al. 2005). Importantly, clinical trials have suggested that, when taken in an appropriate psychotherapeutic setting, psychedelics such as ayahuasca elicit anxiolytic, antidepressive, and anti-addictive effects (Dos Santos et al. 2016a, b; Palhano-Fontes et al., this volume, Chap. 2), even for patients with treatment-resistant psychopathologies (Carhart-Harris et al. 2017; Oehen et al. 2013; Palhano-Fontes et al. 2019), with symptom reduction persisting weeks after ingestion (Osorio et al. 2015).

The main outcome of interest for the abovementioned studies in both healthy participants and patients has been subjective effects and symptom alleviation, with little attention being paid to the (higher-order) cognitive processes that may be enhanced or that may play a role in subjective experience or symptom alleviation of the disorders. For example, changes in behavior and lifestyle may result from a psychedelic's capacity to stimulate processes, such as flexible (creative) thinking, empathy, and emotion regulation, which are crucial for everyday interactions, and have been found to be decreased in certain disorders like depression, anxiety, and post-traumatic stress disorder (PTSD) (Aldao et al. 2010; Baas et al. 2008; Davis 2009; Nietlisbach et al. 2010; Parlar et al. 2014; Todd et al. 2015; Tull et al. 2007). For instance, individuals with these pathologies display repetitive, rigid, and pathological patterns of negative and compulsive thoughts (Chamberlain et al. 2006; Dos Santos et al. 2016a, b). Similarly, empathic changes are particularly evident in mood disorders, like depression, and have even been associated with symptom severity. Donges et al. (2005), for example, demonstrated that inpatients with major depressive disorder (MDD) displayed reduced awareness of other's emotions; this decrease was associated with elevated symptoms of depression. Similarly, Cusi et al. (2011) found that MDD outpatients reported significantly reduced levels of empathy compared to matched controls, with greater reductions in emotion recognition related to a greater number of past depressive episodes. Finally, emotion regulation is considered a primary feature of mental health (Gross and Muñoz 1995), with maladaptive patterns of emotion regulation impairing daily life functioning and supporting symptoms of psychopathology (Cole et al. 1994) in disorders like depression and PTSD (Joormann and Gotlib 2010; Tull et al. 2007).

The aim of the present chapter was therefore to review the acute and long-term effects of ayahuasca on (higher-order) cognitive processes, such as flexible (creative) thinking, empathy, and emotion regulation, and look for the link between these cognitive effects and subjective mood state and well-being. To that end, the literature has been searched for anecdotal reports and studies in which ayahuasca was administered either in a controlled experimental setting or a quasi-experimental setting, where participants took the substance at an ayahuasca retreat or ceremony. For a summary of included studies, refer to Table 7.1.

Flexible, Creative Thinking

Cognitive flexibility is the readiness with which one can selectively switch between mental processes to generate appropriate behavioral responses and is an important skill that allows individuals to accurately respond to their changing environment (Dajani and Uddin 2015). Within cognitive flexibility is creative thinking, a multicomponent construct that includes convergent (CT) and divergent thinking (DT). CT is considered a process of generating a single optimal solution to a particular problem, emphasizing speed, accuracy, and logic. In contrast, DT is a process used to generate many new ideas in a context where more than one solution is correct, like in a brainstorming session, where generating as many innovative ideas or solutions on a particular issue as possible is the ultimate goal. Although both CT and DT are important in creative activities, DT is a more useful estimate of the potential for creative thought in daily life (Runco and Acar 2012).

In order to assess DT and creativity, researchers employ two categories of tests, namely, objective, psychometric tests, and more subjective, expert opinions (Sessa 2008). Psychometric tests typically assess DT, focusing on three different parameters: fluency, defined as the number of ideas an individual gives; originality, defined as the statistical infrequency or uniqueness of ideas; and flexibility, which represents the number of different conceptual categories the ideas cover (Beketayev and Runco 2016). Examples of these tests include Guilford's Alternative Uses Test (1967) Torrance Tests of Creative Thinking, the Pattern/Line Meanings Task, and the Picture Concept Test, composed of stimuli from the Wechsler Preschool and Primary Scale of Intelligence and the Wechsler Intelligence Scale for Children. Conversely, the expert opinion method employs a group of judges assessing persons' creative output. The judges make their assessments individually and then collate their views to establish an overall rating or measure. An example of this is the Consensual Assessment Technique (Amabile 1982).

There is a notable amount of anecdotal reports of increased creative capacity after psychedelic use (Frecska et al. 2012; Harman et al. 1966). Numerous writers and artists, including the likes of Aldous Huxley and Ken Kesey, have acknowledged the influence psychedelic drugs had on their work (Nutt 2012). Accordingly, a survey of 91 artists with at least one psychedelic experience reported that 70% had claimed that the psychedelic experience had affected the content of their work, with

Table 7.1 Summary of studies assessing effects of ayahuasca on cognitive processes

Type of study	Design (BS/WS)	Participants (#)	Reference measure/group	User (type)	Effect (type)	Cognitive/emotional tests and effect	Mood/well-being measures and effect	References
QE	WS	26	Baseline	E	A	PCT: CT ↓↓; DT ↑↑ PLMT: -	Mood and well-being ↑↑	Kuypers et al. (2016)
QE	WS	57 at baseline; 31 at 4 weeks	Baseline	E and N	S;L	PCT: DT -; CT ↑↑	Depression, anxiety, and stress measures↓↓; well-being measures ↑↑	Uthaug et al. (2018)
QE	BS	Ayahuasca users (40); control (21)	Control group	E	L	Torrance tests of creative thinking: originality ↑↑	No	Frecska et al. (2012)
QE	WS	45	Baseline	E and N	S	DERS: emotional nonacceptance, emotional interference, lack of control subscales ↓↓	Mindfulness measures: ↑↑ in observing, acting with awareness, non-judging, non-reacting, and decentering	Domínguez-Clavé et al. (2019)
QE	WS	12	Baseline	N	L	DERS ↓↓ (ns)	No	Thomas et al. (2013)
QE	BS	Ayahuasca users (127); controls (115)	Control group	E	L	The frontal systems behavior scales: users ↓↓ disinhibition/emotional dysregulation scale	Well-being test ↑↑; psychopathology measures ↓↓	Bouso et al. (2012)
E	WS and BS	24 (12 received ayahuasca; 12 received placebo)	Baseline and control group	N	S	fMRI; emotion regulation task Δ in activity in subgenual anterior cingulate cortex, amygdala, insula, and ventrolateral prefrontal cortex after ayahuasca intake	Depression ratings ↓↓	Palhano-Fontes et al. (2017)

E experimental, *QE* quasi-experimental, *A* acute, *S* subacute, *L* long term, *O* observational, *E* experienced, *N* naïve, *PCT* Picture Concept Test, *PLMT* Pattern/Line Meaning Test, *DERS* Difficulties in Emotion Regulation Scale, *VAS* Visual Analog Scale

54% claiming there had been a noticeable improvement in their artistic technique (Krippner 1968). Similarly, a recent review of past experimental studies suggests that, albeit with limited evidence, there is a positive association between creativity and psychedelic use (Iszáj et al. 2017). However, due to different objectives and varying methodological details, like timing of the measurements relative to dosing (e.g., immediately after intake or longer-term effects), the nature of this relationship was not clarified. More recent observational studies provide stronger objective evidence that psychedelics like psilocybin and 5-MeO-DMT have acute (Prochazkova et al. 2018) and persisting effects (Mason et al. 2019; Uthaug et al. 2019) on creativity.

Anecdotal reports suggest that ayahuasca also elicits similar effects as other psychedelic substances (Narby and Huxley 2004; Shanon 2000), with ayahuasca users scoring higher on creativity-related variables versus nonusers (Franquesa et al. 2018). However, to date, only three studies have objectively assessed the effect of ayahuasca on creativity. In order to address this gap in knowledge, a recent study by our group (Kuypers et al. 2016) employed a quasi-experimental design to assess the acute effect of ayahuasca on creative thinking in participants of ayahuasca sessions. Twenty-six experienced ayahuasca users from two spiritual ayahuasca workshops were invited to complete the Patterns/Line Meaning Task (PLMT), assessing CT, and the Picture Concept Test (PCT), assessing both CT and DT, both before ayahuasca intake and during acute inebriation, around 2 h after ayahuasca intake. While no statistically significant effects for the PLMT were found, ayahuasca intake significantly modified DT and CT as measured by the PCT. Specifically, CT was decreased after intake, whereas DT increased. Additionally, participants showed significant increases in visual analog scales assessing subjective effects in mood, like happiness, euphoria, fear, and well-being. Subsequently, another study by our group assessed the subacute and longer-term effects of ayahuasca on creative thinking by utilizing a similar approach (Uthaug et al. 2018). In this study, 57 participants from ayahuasca ceremonies in the Netherlands and Colombia were invited to complete the PCT before ayahuasca intake, the day after ayahuasca intake, and 4 weeks after ayahuasca intake. While no significant effects on DT were found, CT was increased the morning after and 4 weeks after use. The finding that ayahuasca did not have lasting effects on DT is in contrast to a previous study by Frecska (2012), in which 40 participants from an ayahuasca ritual in Brazil completed a creativity test before, and 2 days after, a 2-week-long ayahuasca ceremony. Frecska et al. (2012) found that ingestion of ayahuasca significantly increased the number of original solutions participants gave on the Torrance Tests of Creative thinking, a test assessing DT. An important difference between the two studies is the amount of ayahuasca consumed, with the latter study measuring DT after repeated ingestion of ayahuasca. Thus, taken together, these studies provide evidence that ayahuasca acutely enhances DT, with potential dose-dependent persisting effects.

In accordance with the aforementioned behavioral evidence, a neuroimaging study showed that ayahuasca causes an acute decrement in the functional connectivity in parts of the default mode network, a cluster of brain areas that is active when an individual is awake but not focused on the external environment (Palhano-Fontes

et al. 2015). It was suggested that this decrease in distinction between brain networks allows the brain to operate with greater interconnectedness, resulting in a more cognitively flexible state that could therapeutically interrupt the maladaptive patterns seen in cognitively inflexible disorders (Carhart-Harris et al. 2012, 2014a, b; Dos Santos et al. 2016a, b; Tagliazucchi et al. 2014).

Empathy

Empathy, a multifaceted construct consisting of emotional empathy and cognitive empathy—respectively, the ability to feel and understand what another person is experiencing—is thought to play a key role in motivating moral and prosocial behavior (Decety 2011). Importantly, it has been suggested that cognitive flexibility is a prerequisite for empathy and, thus, impaired cognitive flexibility could mediate impaired empathy (Cusi et al. 2011; Grattan and Eslinger 1989).

Commonly used assessments of empathy include questionnaires and paradigms using nonverbal static stimuli. Questionnaires like the Interpersonal Reactivity Index (Davis 1983) provide a trait measure of both cognitive and emotional empathy. Paradigms like the Reading the Mind in the Eyes Test (Baron-Cohen et al. 2001) or the Facial Emotion Recognition Test (Kemmis et al. 2007) provide a state measure of cognitive empathy. Due to the limitations of these paradigms, a further photo-based paradigm, the Multifaceted Empathy Test (MET), was designed to assess state measures of both cognitive and emotional empathy (Dziobek et al. 2008). The MET has since been shown to be sensitive to the effects of psychedelic substances (Dolder et al. 2016; Hysek et al. 2014; Kuypers et al. 2014; Pokorny et al. 2017; Preller et al. 2015; Schmid et al. 2014).

Recent studies assessing the acute effects of serotonergic psychedelics indicate that ±3,4-methylenedioxymethamphetamine (MDMA), psilocybin, and LSD similarly alter empathy. Specifically, MDMA and psilocybin have been found to enhance emotional empathy on the MET (Hysek et al. 2014; Kuypers et al. 2014; Kuypers et al. 2017; Preller et al. 2015; Schmid et al. 2014), with MDMA also impairing the identification of negative emotions (fearful, angry, and sad faces) as measured by the Facial Emotion Recognition Task (FERT) (Hysek et al. 2014). Similarly, LSD has been found to enhance emotional empathy on the MET and decrease recognition of fearful and sad faces, as measured by the FERT (Dolder et al. 2016). Interestingly, a recent study also suggests that enhancement of *emotional* empathy may outlast the acute phase, with increases found up to 7 days after use of psilocybin in a naturalistic setting (Mason et al. 2019). The specificity of emotional and cognitive empathy suggests that emotional empathy is dependent on state variables, and cognitive empathy requires a (trait) ability to identify another's emotions (Pokorny et al. 2017).

Although anecdotal reports suggest that ayahuasca increases empathy (Dobkin de Rios and Rumrrill 2009), there have been no objective studies to date that have assessed this. Due to similarities in the mechanisms of action—namely, activation

through the 5-HT system—findings from the previous psychedelic studies add strength to the hypothesis that ayahuasca would enhance emotional empathy. Currently, our group is assessing this hypothesis. To do this, we are visiting ayahuasca ceremonies throughout the Netherlands and administering the MET, as well as measures of creativity and subjective well-being, to participants at three different time points: before they take ayahuasca, the morning after they have taken ayahuasca, and 7 days after they have taken ayahuasca. With this, we hope to assess both the short- and longer-term effects of ayahuasca on emotional and cognitive empathy, as well as the correlation with creativity and subjective well-being.

Emotion Regulation

Emotion regulation is defined as the ongoing processes by which individuals influence the emotions they have, when they have them, and how they experience and express them (Gross 1998). According to Gratz and Roemer (2004), emotion regulation can be conceptualized as involving multiple processes, including the ability to be aware of, to understand, and to accept our emotions, to control impulsive behaviors when feeling negative emotions, and to choose suitable emotion regulation strategies in order to meet personal goals and situational demands. The process model of emotion regulation proposes five strategies individuals use during emotion regulation (Gross 1998). These strategies include "situation selection," which involves choosing to physically approach or avoid an emotionally relevant situation; "situation modification," which involves modification of the emotional impact of the situation; "attentional deployment," which involves directing ones attention towards or away from an emotional situation; "cognitive change or reappraisal," which involves choosing what meaning you attach to the emotional situation; and "response modification," which involves influencing your behavioral, physiological, and experiential response tendencies once they have been elicited. Importantly, these strategies can be either explicit, conscious, and voluntary, or implicit, nonconscious, and automatic (Gyurak et al. 2011). Interestingly, empathy deficits have been suggested to serve as a potential trigger of emotion dysregulation (Schipper and Petermann 2013).

Assessments of emotion regulation include self-report questionnaires, psychophysiological measurements, and responses to emotional stimuli. Questionnaires include the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer 2004), developed to assess each of the proposed multiple processes of emotion regulation, as well as the flexible use of strategies to modulate emotional strategies. Psychophysiological assessments include measurements of heart rate variability, which has been proposed as a psychophysiological marker of emotion regulation capacity (Visted et al. 2017; Williams et al. 2015). In addition, neuroimaging studies investigating the underlying circuitry of emotion regulation have employed various tasks consisting of basic emotional stimuli in order to provoke certain emotions in participants (Goldin et al. 2008; McRae et al. 2008).

Anecdotal reports, animal models, and observational and experimental studies suggest that ayahuasca has emotion and mood-altering properties (Dos Santos et al. 2016a, b; Nunes et al. 2016). A within-subjects, double-blind, placebo-controlled study found that, acutely, ayahuasca was associated with lower scores on scales assessing panic and hopelessness-related states in individuals with over 10 years of ayahuasca experience (Santos et al. 2007). Furthermore, a study by Barbosa et al. (2016) found that, relative to non-ayahuasca using controls, ayahuasca users displayed lower depression scores. Similarly, an open-label trial with major depressive patients found that, under the acute influence of ayahuasca, patients displayed improvements in emotional withdrawal and blunted affect and significantly decreased scores in depression-related scales, with depression symptoms remaining decreased up until 21 days after administration (Osorio et al. 2015; Sanches et al. 2016). In addition, the study reported increased blood perfusion in areas of the brain implicated in the regulation of mood and emotional states, a response associated with antidepressive effects (Sanches et al. 2016). Furthermore, providing perhaps the strongest experimental evidence to date, a recent randomized, double-blind, placebo-controlled trial found that a single dose of ayahuasca reduced symptoms of depression (Palhano-Fontes et al. 2019) and feelings of suicidality (Zeifman et al. 2019) for up to 7 days in a treatment-resistant depression population. Another recent interview study with individuals who were diagnosed with eating disorders found that the majority of the interviewees reported improvements in psychological symptoms following ceremonial ayahuasca drinking, which they partially attributed to increased emotion regulation and processing (Lafrance et al. 2017).

Despite evidence for ayahuasca's emotion and mood-altering properties, studies directly assessing the effects of ayahuasca on emotion regulation are sparse. The most recent study utilized an observational design to assess the impact of one ayahuasca session on emotion regulation (Domínguez-Clavé et al. 2019). Forty-five volunteers completed the DERS prior to and 24 h after the session. Findings showed that volunteers scored lower in emotional nonacceptance, emotional interference, and lack of control 24 h after ayahuasca ingestion. Interestingly, a subset of participants displaying borderline personality disorder traits also demonstrated lower scores in emotional interference after ayahuasca ingestion. Accordingly, a previous observational study found similar results in a separate clinical group. Namely, 12 participants in an ayahuasca-assisted addiction treatment retreat were assessed at baseline and at 6-month follow-up on several psychological and behavioral factors, including emotion regulation (Thomas et al. 2013). Findings showed that participants' scores improved (albeit not significantly) on the DERS. Finally, a study by Bouso et al. (2012) assessed the even longer-term impact of repeated ayahuasca use on various factors, including general psychological well-being and mental health. They found that, compared to controls, ayahuasca users scored higher in emotion regulation at both baseline and 1-year follow-up, as shown by lower values on the items in the Frontal Systems Behavior Scale assessing disinhibition and emotional dysregulation. Users also scored higher on subjective psychological well-being and lower on psychopathology measures.

A recent imaging study evaluated the mechanisms by which ayahuasca modulates emotion processing of patients with depression (Palhano-Fontes et al. 2017). Twenty-four patients with treatment-resistant depression completed two fMRI sessions 1 day before and 1 day after ayahuasca or placebo intake. During the fMRI session, participants performed an emotion regulation task (Ochsner et al. 2012) in which they viewed a series of images with different emotional content and were instructed to passively look at neutral and negative images, as well as to positively reappraise negative images (e.g., by imagining a happy ending). Behavioral data suggested that the group who received ayahuasca rated all images (neutral, negative, and reappraised) more positively after treatment, compared to the placebo treatment. Analysis of the imaging data showed that brain areas involved in emotion regulation processes, such as the subgenual anterior cingulate cortex, amygdala, insula, and ventrolateral prefrontal cortex, were differently modulated in the patients treated with ayahuasca when compared to placebo. Interestingly, pre-posttreatment increases in subgenual anterior cingulate cortex activity, in particular, also positively correlated with reductions in depressive symptoms 1 day posttreatment.

Recent evidence also suggests that ayahuasca can enhance mindfulness abilities, which involve nonjudgmental attention to present-moment experience (Farb et al. 2012). In a study by Soler et al. (2016), 25 individuals were assessed on a measure of mindfulness capacity (the Five Facets of Mindfulness Questionnaire; FFMQ) before and 24 h after they attended an ayahuasca session. After ayahuasca intake, individuals displayed a significant reduction in automatic negative judgmental processing of experiences and inner reactivity, two facets of the FFMQ. These results were replicated by Domínguez-Clavé et al. (2019), who found the same decrease in judgmental processing and reactivity 24 h after an ayahuasca session, and Sampedro et al. (2017), who found similar results at both 24 h and 2 months after ayahuasca intake.

Although these studies do not directly assess emotion regulation, evidence suggests that mindfulness and emotion regulation have a strong, possibly overlapping, relationship. Specifically, studies suggest that the practice of mindfulness (cultivating awareness and acceptance of the present moment) is associated with healthy emotion regulation and may play a causal role (Roemer et al. 2015). Biological evidence supporting this relationship also stems from a previous study investigating the neural correlates of increased mindfulness capacities after ayahuasca intake (Sampedro et al. 2017). Findings suggested that enhanced connectivity between the anterior cingulate cortex (previously implicated in ayahuasca-enhanced emotion regulation and depressive symptom reduction in Palhano-Fontes et al. (2019)) is associated with increased nonjudgmental processing 1 day and 2 months after ayahuasca use.

Discussion

The aim of this review was to assess whether ayahuasca has the ability to enhance (higher-order) socio/cognitive processes, like creative, flexible thinking, empathy, and emotion regulation, and to look for the link between these cognitive effects and subjective mood states and well-being. Although objective evidence is limited, previous studies with ayahuasca and similar psychedelics, like psilocybin and LSD, support the notion that ayahuasca can enhance these processes. Importantly, evidence is given to suggest that this enhancement outlasts the acute stage, thus potentially persisting over time. These findings have important implications for the therapeutic utility of ayahuasca.

Previously, it has been shown that creative DT can enhance and strengthen psychological flexibility by allowing individuals to generate new and effective cognitive, emotional, and behavioral strategies on their own, ultimately helping them to adopt adaptive interpretations and coping styles (Forgeard and Elstein 2014). Since ayahuasca promotes flexible cognition, it was suggested that ayahuasca possesses qualities that can facilitate a therapeutic process (Kuypers et al. 2016) and make it suited, for example, to psychedelic-assisted psychotherapy (Bouso et al. 2008). Specifically, the ability of ayahuasca to increase DT acutely (Kuypers et al. 2016) and in the longer term (Frecska et al. 2012) could help patients relive events, recalling various associations without inhibition (Bouso et al. 2008; Frecska et al. 2012, 2016). The subacute effects, e.g., longer-term enhancements in CT (Uthaug et al. 2018), could then be suited in a second "integration" session, in which patients discuss the experiences they had on ayahuasca and find strategies that help them cope with intensive emotions (Kuypers et al. 2016; Mason et al. 2019).

Empathy has been implicated as a factor in symptom severity of disorders like depression. Thus, it could be hypothesized that enhancing an individual's empathic abilities could play a role in symptom alleviation. Furthermore, the addition of a pharmacological agent that can enhance empathy could play an important role in psychotherapy and in the patient-therapist relationship. Namely, the increase in empathy could enhance feelings of openness and trust in the patient that could strengthen the therapeutic alliance between patient and therapist (Oehen et al. 2013). The quality of this relationship has been seen to be particularly important for disorders like PTSD (Charuvastra and Cloitre 2008). Previous research suggests that 5-HT_{2A} agents have the potential to enhance empathy, with enhancements even outlasting the acute phase and positively correlating with increased feelings of well-being (Mason et al. 2019). However, in the case of ayahuasca, this has yet to be shown.

Collectively, being able to monitor and evaluate our emotional experience, accept our emotional reactions, and modulate our emotional responses to meet goals and situational demands is crucial for everyday interactions (Visted et al. 2017). Ayahuasca's ability to reduce symptom pathology of disorders like depression may be due to its ability to alter an individual's engagement with their emotions. For example, enhancing nonjudgmental awareness and reducing reactivity to emotional

events may facilitate a healthy engagement with emotions and emotional memories that may lead to an individual experiencing their emotions in a less reactive state instead of avoiding them or responding negatively (Chambers et al. 2009; Hayes and Feldman 2004; Soler et al. 2016). This avoidance, termed "experiential avoidance," is a problem of emotion regulation (Hayes and Feldman 2004), with those displaying higher experiential avoidance also reporting higher emotional reactivity (Sloan 2004).

The reviewed studies are not without their limitations. Most studies employed a quasi-experimental, naturalistic design with experienced ayahuasca users (Bouso et al. 2012; Domínguez-Clavé et al. 2019; Frecska et al. 2012; Kuypers et al. 2016; Uthaug et al. 2018). In such a design, factors like composition of the brew (dose) and the context of the experience differ between studies and need to be considered when looking at the effects of ayahuasca on cognition and subjective experience.

Ayahuasca has previously been shown to display dose-dependent subjective (Riba et al. 2001) and physiological effects (Riba et al. 2003). In accordance with this, a neuroimaging study showed decreased amygdala activity after a low dose of ayahuasca, while another study using a higher dose found increased activity in the same region (Riba et al. 2006). For further information regarding underlying neural correlates, see Dominguez-Clavé et al., this volume, Chap. 1.

Additionally, the context of the experience, or the "set" and the "setting," are two proposed key factors in elucidating the positive and therapeutic potential of psychedelics. "Set" refers to the mental state of the individual prior to and during the experience, like thoughts, mood, and expectations. "Setting" is the physical and social environment that the drug is taken in (Leary et al. 1963). Previous research and anecdotal evidence have shown that both mindset and the social environment play an important role in the outcome of the experience (Shewan et al. 2000). Participants regularly attending ayahuasca ceremonies could inherently have a biased mindset, in that individuals who seek ayahuasca are predisposed to do so for personal growth or to treat an illness. Setting is also of particular importance, as ayahuasca is commonly taken in supportive and ceremonial or religious settings (Lawn et al. 2017).

The aforementioned factors can be controlled for by assessing the effects of ayahuasca in a randomized, double-blind, placebo-controlled experimental design. This design is the gold standard of psychopharmacological research, allowing for control over factors that could affect the study results. To demonstrate this, we will sketch a hypothetical study in which the aim is to assess the effects of ayahuasca on a (higher-order) cognitive process, for example, empathy. As a researcher, you recruit participants, screen them according to your inclusion criteria and, if those are met, you randomly assign them to a drug condition (ayahuasca or placebo), subsequently eliminating selection bias from the researcher and balancing the groups with respect to known (e.g., social differences) and unknown (e.g., genetic differences) factors. On the testing day, the participant comes to the lab, a standardized, "sterile" space identical for each participant (thus controlling for setting), where they are given a drug by the researcher. The drug will be controlled, i.e., it will either be a standardized placebo or a "pharmaceutical" version of ayahuasca,

where purity and dose have been established. Importantly, neither the participant nor the researcher knows whether they received ayahuasca or placebo (hence "double blind"), subsequently controlling for expectation effects (e.g., *expecting* that ayahuasca increases empathy). If all of these steps are followed, the researcher has effectively cancelled out the potential influence of confounding variables that can skew study results (e.g., bias, setting, drug composition, and expectation) and thus is able to directly assess the effect of ayahuasca alone. If the data show that participants who took ayahuasca scored higher in empathy compared to the placebo, we can say with more certainty that it is the ayahuasca increasing this cognitive process, and not other external factors.

That being said, a placebo-controlled, double-blind experimental design is currently difficult to implement due to multiple issues related to this scheduled substance. First, approval (e.g., by an institutional review board) is needed to be able to work with the substance, and due to the scheduling of, and stigma surrounding, psychedelic substances, crucial information required to gain such approval is missing. This information includes (but is not limited to) scientific data demonstrating their biological and psychological safety. Furthermore, due to scheduling of these substances in most countries, special licenses are required in order to obtain them for an experimental study, and "pharmaceutical" versions of the drug are required in order to be allowed to administer them to participants. All of these factors together can lead to a vicious cycle: the lack of scientific data results in an inability to study these substances, which means no data can be acquired.

Thus, although less able to assess "cause and effect," the quasi-experimental, naturalistic designs that have been reviewed in this chapter offer a unique opportunity to explore the effects of ayahuasca, overcoming some of the hurdles that scientists face. Namely, via an observational design, scientists can gather necessary data (like safety data) without the need to acquire a special license or a pharmaceutical version of the drug, as the scientist is not the person organizing the ayahuasca ceremony or administering the substance. Additionally, with this design some of the limitations that controlled designs face can be overcome; namely, collecting data in a more externally valid setting, i.e. the cultural or social setting in which people usually consume the substance, versus a "sterile" laboratory. Overall, future studies should employ both types of designs in a complementary approach, with naturalistic studies acquiring externally valid data that researchers can reference when applying for approval for experimental studies that more accurately assess cause and effect.

Future avenues of research include the impact of enhanced cognitive processes on mood and well-being. Although most of the studies assessed participants' mood and well-being in some form, none of them showed the relationship between subjective states and measures of creativity and emotion regulation. Additionally, as studies found a time-related differentiation of effects of ayahuasca on these outcomes—for example, enhancements in emotion regulation were seen both acutely and long term, whereas decrements in CT were seen acutely and enhancement long term—future studies could take both stages into account. Specifically, studies assessing the longevity of the effects are warranted, to see how long ayahuasca's "window of opportunity" lasts.

Conclusion

This review assessed literature to determine whether ayahuasca has the ability to enhance (higher-order) socio/cognitive processes, like creative, flexible thinking, empathy, and emotion regulation and, consequently, also, mood and well-being. While the number of studies is small, findings suggest that ayahuasca enhances socio-cognitive skills acutely and in the longer term. Future clinical research into the therapeutic effects of ayahuasca could assess the relationship between the effect on (higher-order) cognitive and emotional processes and the role both play in the symptom alleviation in the pathological population.

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