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AMAZONIAN AYAHUASCA

and mental health outcomes

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Amazonian Ayahuasca and Mental Health Outcomes

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Doctor of Philosophy (PhD)

Word count: 37 912

This body of work is dedicated to Nige Netzband,

WaiFung Tsang, and Noya Rao

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Abstract

Ayahuasca is a psychedelic plant brew originating from the Amazon Rainforest. It is formed from two basic components, the *Banisteriopsis caapi* vine, and a plant containing the potent psychedelic dimethyltryptamine (DMT), usually *Psychotria viridis*. There has been a dramatic increase in interest surrounding ayahuasca since the turn of the millennium. Increasing numbers of tourists are travelling to the Amazon rainforest to drink the brew, with various media outlets, celebrities, and researchers describing benefit from its consumption. Ayahuasca is now present in every continent and retreat centres offering plant medicine experiences in the Amazon rainforest has become a thriving business. Anecdotal evidence varies significantly, ranging from evangelical accounts to horror stories involving physical and psychological harm. This thesis comprises five studies investigating Amazonian ayahuasca use. Initially, the pharmacology of the brew is explored in the form of a systematic review, concluding complex synergistic mechanisms may be present, although further research is needed. The remaining studies utilise observational methodology, investigating the impact of ayahuasca retreats following a traditional Shipibo lineage adapted for ayahuasca tourists in the Peruvian Amazon. The effects of the brew on personality, mental health outcomes, epigenetics, and nature relatedness are documented. Further, a phenomenological analysis of the ayahuasca experience is included. The research in this thesis is amongst the first to investigate Shipibo-style ayahuasca retreats in the Peruvian Amazon. Various ethical issues surrounding the increasing popularity of the brew and potential medicalisation are also discussed. It is hoped that this research will add to the growing body of knowledge surrounding the potential therapeutic effects of ayahuasca, whilst considering risks, ethics, and wider applications.

Introduction

Background

Historical Overview of Ayahuasca

Ayahuasca is an *entheogenic* psychedelic plant brew originating from the Amazon rainforest (Tupper, 2009). Entheogens are used in spiritual or religious contexts and are associated with a perceived connection to the divine, or are transcendental in nature (Tupper, 2009). The term *Aya* refers to *spirit* or *soul* and *Waska* translates to *vine* or *rope* in the Quechua langue. Consequently, the brew is often referred to as the Vine of the Soul or Dead (Santos et al., 2007). The vine, or *Banisteriopsis caapi*, is also referred to as ayahuasca independently. An ayahuasca brew typically contains *Banisteriopsis caapi*, along with a plant containing dimethyltryptamine (DMT) – usually *Psychotria viridis* (Rivier & Lindgren, 1972) – often known as *Chacruna*. It must be noted that a variety of other preparations, with a vast range of admixtures, also fall under the terminological parameters of the word *ayahuasca* (Kaasik et al., 2020).

Spruce (1873) was the first to document the use of ayahuasca in the Amazon rainforest around 150 years ago, although many suspect it had been used long before this, with archaeological findings in the form of stereotypical small ceramic ceremonial vessels from around 2400 B.C. (Naranjo, 1986). Luna (2000) suggests it has been used among different indigenous groups for millennia, and Metzner (1999) states the use of ayahuasca within the human species represents *a millennia of coevolution*. It should however be noted that this claim has been critiqued, with other authors stating current indication of such use is insufficient (de Mori, 2011). It is, however, universally accepted that in the 1930s ayahuasca was introduced to the urban areas of Brazil in religious settings and by the 1980s outreach had reached international cities (Labate & Cavnar, 2014; Labate & Jungaberle, 2011). Syncretic churches known for integrating

ayahuasca into their traditions include the Santo Daime, the Barquinha, and the União do Vegetal (Labate & Jungaberle, 2011). Today, the popularity of ayahuasca is rising among Westerners who travel to South America in search of physical and emotional healing, personal growth, and improved insight (Winkelman, 2005). The empirical research within this thesis is amongst the first to investigate the use of ayahuasca in adapted traditional Shipibo-style retreat settings.

One of the primary components in ayahuasca, DMT, is a Schedule 1 drug according to the United Nations 1971 Convention on Psychotropic Substances (Van den Plas, 2011). Although worldwide DMT is largely considered a scheduled substance, a minority of countries have laws specific to ayahuasca. In the United Kingdom for example, it is illegal to cultivate, transport, sell, or possess ayahuasca (Nutt, 2015). In Peru, however, where the research included within this thesis was conducted, ayahuasca is legal, with many therapists, psychologists and doctors giving the brew to their clients for therapeutic, personal, or even spiritual reasons (Søren Ventegodt & Kordova, 2016).

Traditional Use

Before ayahuasca became popular in the West, its psychedelic properties were not the focus, and the brew was used in combination with many other healing plants to treat a variety of medical conditions (Beyer, 2008; Luna, 2000). Ayahuasca is most commonly seen as a *plant teacher* (de Rios, 1994), the *spirit* of which is often described as possessing healing properties, as well as being used as a diagnostic tool by *shamans* (Demange, 2002; Luna, 1984). Although there is no single agreed upon definition of shamanism, the term *shaman* is loosely used to describe someone who works in the world of spirits, utilising ritualistic trance states to heal and perform divination (Singh, 2018). It should be noted however that there are many names

given to those who work with ayahuasca, such as *taita, vegetalista, ayahuasquero, maestro, onaya,* and *curandero* (Roseman et al., 2021). Although *shaman* is the name most given to those who run ayahuasca ceremonies by Westerners, it actually refers to practices confined geographically to Siberia, and is derived from the Tungus *saman* (Scuro & Rodd, 2015). Although this term may be inaccurate, it is also used frequently by mestizo and indigenous peoples (Fotiou, 2012) and is therefore used throughout this thesis.

In some tribes only the shaman would consume the brew to identify the appropriate medicine, treatment, or cause of a disease (Beyer, 2008). This is believed to be achieved via the visionary state that ayahuasca produces which enhances the practitioner's capabilities beyond ordinary senses. Additionally, its uses were sometimes social, such as perceived magical wars between shamans of oppositional tribes (Beyer, 2008). Following the ingestion of ayahuasca, the *curanderos* (meaning *native healer* in Spanish) would employ other plants used in a ritualistic style of botanical wizardry, carrying out whatever is necessary to support their relative communities as both healers and protectors (Narby, 1999). Some believe the Western interest in the psychedelic experience has restricted the breadth of shamanic plant-based medical treatments (Luna, 2000).

Clinical Research Overview

It has been proposed that we are amid a psychedelic renaissance (Sessa, 2012). Many researchers have continued the work of their predecessors in the 1950s and 60s, adopting new and more sophisticated techniques. Preliminary findings show promising results in the field known as *psychedelic-assisted psychotherapy* (PAP) (Carhart-Harris et al., 2021; Jerome et al., 2020; Mitchell et al., 2021; Mithoefer et al., 2018; Mithoefer et al., 2011; Rucker et al., 2019). In these sessions, psychedelic drugs are used alongside conventional psychotherapeutic

interventions, the modality of which is not directly prescribed, to facilitate autobiographical insight and emotional release (Busch & Johnson, 1950). Many of the considerations relating to *set, setting* and *integration* are based on traditional uses of psychedelics, such as ceremonial settings. *Set* is described as the participant's mental state, where as *setting* is the environment, both physical and social (Zinberg, 1984). Hartogsohn (2017) conducted a review of the literature pertaining to LSD research in the 1950s and 60s. They concluded that depending on the way in which the drug was used, effects could range from relaxation to anxiety, joy to fear, cognitive enhancement to impairment and intimacy to suspiciousness. Hyde (1960) famously continuously modified his study design over a three-year period, with staff administering LSD to participants in a normal, cold, impersonal, and friendly way. Not only was the demeanour of staff found to significantly affect the outcomes reported, but also whether the drug was taken in a group setting, with those taking LSD alone experiencing more negative effects. Hyde concluded that certain non-pharmacological factors influenced participants' responses to LSD. These were categorised as; *familiarity-unfamiliarity of environment; rigidity–flexibility of goals; attitudes of acceptance–nonacceptance of the participant's behaviour and feelings and presence or absence of others with a common culture* (Hyde, 1960). Further evidence for the importance of *set* and *setting* is demonstrated in Alexander's rat park experiments, whereby the environment in which rodents were placed demonstrated a drastic change in morphine addiction (Alexander et al., 1978). This study has been replicated more recently with amphetamine, yielding similar results (Stairs et al., 2006).

Dos Santos et al. (2016) conducted a systematic review evaluating 28 articles investigating the brew. Despite the relatively small number of studies included in the review and the significant heterogenicity between them, the following points were made regarding ayahuasca consumption including that it: is tolerated well (Grob, 1996), increases introspection and

positive mood (Palhano-Fontes et al., 2015), alters visual perception (de Araujo et al., 2012), activates frontal and paralimbic regions (Riba et al., 2006), and decreases default mode network (DMN) activity (Palhano-Fontes et al., 2015). It also improved inhibitory control and planning (Damásio, 2015), impaired working memory (Bouso et al., 2013), and showed anti-addictive (Fábregas et al., 2010) and anti-depressant potential (Osório et al., 2015).

Preliminary research has begun to shed light on the potential long-term neurophysiological impact of ayahuasca use. In one study, 22 ayahuasca users and matched controls underwent magnetic resonance imaging (MRI) of their brains (Bouso et al., 2015). Long term ayahuasca consumption was associated with cortical thinning in the posterior cingulate cortex (PCC) and an increase in cortical thickness in the anterior cingulate cortex (ACC), with change in thickness employed as a relative, rather than an absolute measure (Bouso et al., 2015). PCC thinning showed an inverse correlation with age of initial ayahuasca use, the frequency with which it was consumed, and ratings of self-transcendence, spiritual and transpersonal feelings (Bouso et al., 2015). It should however be noted that direct causation cannot be established as a result of the cross-sectional methodology that was utilised. In addition, generalisations should be made with caution due to the relatively small sample size employed in this study. All ayahuasca users were members of a specific ayahuasca church, the Santo Daime, based in Spain. Not only are results specific to one nationality, but *Daime*, the form of ayahuasca used by the church, is prepared in a specific ritual, known as *feitio*, which takes place over days. This ritual is likely to lead to differences in the concentration of components in the brew, as the bark of the ayahuasca vine is discarded despite containing active constituents (Wang et al., 2010). Ayahuasca is commonly boiled to reduce it as part of the preparation. However, it is also sometimes reduced further to form a *gel*, which is the most efficient way it can be

transported. This is an additional procedure that may well have been employed in studies taking place outside of Brazil, such as this one (Kaasik et al., 2020).

Both the ACC and the PCC are thought to be involved in a range of cognitive functions, showing anticorrelated activity (Fox et al., 2005). Studies suggest the ACC is involved in expressing internal states vocally, assessing motivational content, determining the emotional content associated with both internal and external stimuli, conditioned emotional learning, infant-maternal interactions, the reinforcement of information to control behaviour, guiding voluntary choices with reference to historic actions, regulating autonomic and endocrine functions and outcomes, as well as error detection, referred to as the conflict monitoring hypothesis (Botvinick et al., 2004; Bush et al., 2000; Devinsky et al., 1995; Kennerley et al., 2006). There is no agreement on the specific function of the PCC, however it is hypothesised to be involved in cognitive processes such as internally directed cognition, self-referential thought, internal mentation, and attentional processes (Bouso et al., 2015; Leech & Sharp, 2014).

Carhart-Harris, Erritzoe, et al. (2012) demonstrated that activity in these regions is significantly reduced under the acute influence of psychedelics. Psilocybin, a 5-HT2A agonist and functional analogue of DMT (Gable, 2007), and the active ingredient in so called *magic mushrooms* was administered to participants in a task free functional MRI (fMRI) protocol. Results showed decreases in cerebral blood flow in prominent hub regions such as the ACC and PCC as well as decreases in positive coupling amid the PCC and the medial prefrontal cortex (mPFC). Despite the relatively small sample of 15, outcomes were largely consistent, other than an increase in glucose metabolism thought to be due to the long half-life of the 18F-fluorodeoxyglucose radiotracer used to measure it. Similar results were also obtained in 2015

when Palhano-Fontes et al. demonstrated using fMRI that ayahuasca significantly reduced activity throughout most of the DMN, specifically the PCC/precuneus and the mPFC. In addition, PCC/precuneus functional connectivity was found to decrease, largely in keeping with the results obtained after psilocybin administration (Carhart-Harris, Erritzoe, et al., 2012). Unlike psilocybin however, ayahuasca did not result in a significant reduction in coupling between the PCC and the mPFC (Palhano-Fontes et al., 2015). More recently, Daws et al. (2022) demonstrated a decrease in fMRI brain network modularity in patients suffering from either treatment resistant depression or major depressive disorder following the administration of psilocybin in a clinical setting. Results suggest the antidepressant activity of psilocybin following dosing may be due to increased global brain network integration, in contrast to the DMN disintegration observed during acute psychedelic states (Carhart-Harris et al., 2017). These results are in keeping with Pasquini et al. (2020), who after dispensing ayahuasca during a task free fMRI study found increased inter-network functional connectivity, specifically between the salience network and the DMN as well as the salience network and the ACC.

Despite these intriguing results, Daws et al. (2022) recently came under criticism in a high profile dispute featured on various news outlets such as Vice magazine (Love, 2022). The authors were criticised in terms of their statistical methodology, drawing conclusions that global network integration is increased due to psilocybin administration despite a lack of interaction between group (*S*-citalopram vs psilocybin.) and timepoint (pre- vs post-) (Daws et al., 2022; Doss, 2022). Furthermore, the claims made by Daws and colleagues that their paper *proved* psilocybin operated via a different mechanism when compared to Selective Serotonin Reuptake Inhibitors (SSRIs) were deemed premature (Doss, 2022). *Task-free* or *resting state* scanning has also come under scrutiny (Gonzalez-Castillo et al., 2021; Holiga et al., 2018), specifically in terms of variability between participants when they are left for prolonged periods

inside a scanner (Gonzalez-Castillo et al., 2021). Doss (2022) specifically raised concerns in terms of the non-specific cognitive processes participants engage in when cognition is left unconstrained in task-free studies, suggesting the decreases in modularity described by Daws et al. (2022) may represent nothing more than a decrease in the fatigue and lethargy so often associated with depression. The ambiguities surrounding task-free fMRI are particularly concerning in psychedelic research, as this methodology is so often used and is largely considered the *gold-standard* in the field (Doss, 2022).

Although the precise role of the PCC is unknown, it is widely accepted as the primary posterior node of the default mode network (Chang & Glover, 2010; Greicius et al., 2003); a group of regions that are more active at rest and are believed to support various features of self-referential thought (Andrews-Hanna et al., 2010). The PCC has been shown to be particularly metabolically active, leading some to suggest it might be involved in high level constructs, for example the *ego* (Carhart-Harris et al., 2008). In contrast, the ACC is thought to contribute to cognition in a more general manner (Bush et al., 2000). The opposing structural differences in the ACC and PCC in ayahuasca users demonstrated by Bouso and colleagues may well account for the preservation of neuropsychological function demonstrated in this study (Bouso et al., 2015). This result also aligns with findings suggesting that ayahuasca may reduce *neuroticism* in long-term users (Kaasik & Kreegipuu, 2020). Furthermore, long-term and sub-acute ayahuasca has not been found to be connected with cognitive deficits or psychopathology (Bouso et al., 2012). Rather, repeated use after one year is correlated with enhanced cognition and mood (Bouso et al., 2012), increased spirituality (Doering-Silveira et al., 2005) and reduced impulsivity (Fábregas et al., 2010).

Research into psychedelics utilising both magnetoencephalography (MEG) and electroencephalogram (EEG) has demonstrated relatively consistent results. Reductions in absolute oscillatory power have been shown following ayahuasca (Riba et al., 2002), LSD (Carhart-Harris, Muthukumaraswamy, et al., 2016), and psilocybin (Muthukumaraswamy et al., 2013), with *alpha* power suppression seemingly the most reliable change (Kometer et al., 2015; Schenberg et al., 2015; Timmermann et al., 2019), along with increased entropic brain activity (Schartner et al., 2017). Various studies have investigated the effects of ayahuasca ingestion using EEG. Don et al. (1998) detected decreased power in theta and delta bands, with increases in power in 36–44 Hz frequency bands located at the left occipito-temporo-parietal region. Riba et al. (2002) also demonstrated decreases in alpha power at the centro-parieto and left-temporal electrodes, as well as decreases in theta and delta in the parietal region and increases in beta at the parieto-temporal and central area after administering lyophilizate ayahuasca. Subsequently, Riba et al. (2004) used MEG to show that ayahuasca decreased delta, theta, and alpha power. Stuckey et al. (2005) then found that gamma bands increased in coherence globally following ayahuasca administration and Dos Santos et al. (2012) found increased beta power across the brain. Alonso et al. (2015) found that frontal regions had less impact over occipital, parietal, and central sites whilst posterior brain regions showed increased influence over signals in anterior regions. The authors concluded that ayahuasca temporarily reduced top-down processing and increased bottom-up control, transiently disrupting neural hierarchies (Alonso et al., 2015). Most recently, Schenberg et al. (2015) using ayahuasca, and Timmermann et al. (2019), using intravenous DMT, demonstrated decreases in alpha band power (8-13 Hz) following psychedelic injection.

Schenberg et al. (2015) found the brew resulted in a biphasic effect, with reductions in alpha power 50 minutes after consumption, largely at the left parieto-occipital cortex. Furthermore,

increases in fast oscillatory activity were found after 75-125 minutes in slow-gamma bands (30-50 Hz) at the right frontal, left fronto-temporal, and left centro-parieto-occipital cortices and increases in fast-gamma bands (50-100 Hz) were detected in the right parieto-occipital, right frontal, left fronto-temporal, and left centro-parieto-occipital cortices, with no significant change in theta or delta power. These changes in activity were also associated with the concentrations of beta-carbolines and DMT in the blood. On average, harmine levels peaked after 50 minutes and DMT after 75, suggesting these components may be related the reduced alpha band power at the beginning of the experience. Harmaline plateaued at 100 minutes and THH at 150, suggesting an association with gamma-band increases in the later phase. These EEG findings are in partial agreement with the studies listed above (Schenberg et al., 2015).

The reduction in power in the alpha band at the left parieto-occipital region is in keeping with increased Blood Oxygenation Level Dependent (BOLD) signal in the visual cortex demonstrated during visionary experiences with the brew (de Araujo et al., 2012). Further, the alpha asymmetries described may be associated with memory retrieval (Nelson et al., 2013) and attentional control (Alfonso et al., 2013). Gamma power increases, such as those demonstrated by Schenberg et al., have also been found in retrospective states such as lucid dreaming (Voss et al., 2009) and meditation (Lutz et al., 2004). Gamma frequencies are thought to be involved in visual domain integration (Castellano et al., 2014), the synchronisation of frontal and parietal cortices – the integration of which allows for the subjective description of experiences (Dehaene & Changeux, 2011), and both memory and attention (Jensen et al., 2007). Interestingly, stimulation of slow-gamma frequencies in the frontal brain region during dreaming has been demonstrated to result in self-awareness (Voss et al., 2014). It may be that increases in gamma power are related to internal awareness of intentions and memories via visual imagery (de Araujo et al., 2012; Schenberg et al., 2015). It should also be noted that

alpha power has been suggested to be associated with inhibition, visual and thalamic cortical generators, and the supression of top-down processing (Mayer et al., 2015), whereas increased gamma is thought to signify active processing (Jensen & Mazaheri, 2010). Furthermore, the rise in gamma power located in the frontal regions, associated with occipito-parietal region alpha power decrease, resembles patterns shown in emotional regulation during cognitive appraisal (Popov et al., 2012) and problem solving (Sandkühler & Bhattacharya, 2008), which is in keeping with the increased emotional awareness reported after drinking ayahuasca (Schenberg et al., 2015).

Although both Schenberg et al. (2015) and Stuckey et al. (2005) demonstrated gamma-band increases after drinking ayahausca, it should be noted that the validity of such findings using scalp EEG has been contested. This is largely because electromyographic (EMG) frequency bands overlap with that of gamma oscillations, making gamma signal recordings particularly vulnerable to contamination resulting from musculoskeletal activity (Muthukumaraswamy, 2013). Furthermore, studies by Näätänen et al. (2007) and Whitham et al. (2008) using neuromuscular blockades have demonstrated that EMG signals can be present in EEG traces. The results presented by Schenberg et al. (2015) and Stuckey et al. (2005) should therefore be interpreted with caution until advanced signalling separation and processing methodologies are utilised. Spatial filtering techniques or independent component analysis could help to reduce the contamination from electromyographic artifacts in future studies (Muthukumaraswamy, 2013).

Empirical research has also been carried out evaluating the impact of ayahuasca on psychiatric symptomology. In a sample of 17 participants with recurrent depression in an inpatient psychiatric unit, Sanches et al. (2016) found reductions in depression with a single dose of

ayahuasca, maintained at 21 days post dosing with results greatest at day seven (Cohen's *d* at D7 = 1.83). Reduced suicidality was found in a secondary analysis, the greatest effect size being evident after 21 days (Hedges's $g = 1.75$) (Zeifman et al., 2019). These studies built on a preliminary report by Osório et al. (2015) showing similar reductions in depression in a sample of six following the same study design and no effect sizes were reported. Although intriguing, the results from these clinical studies have numerous limitations which are worth considering. The sample sizes in each of the studies were relatively small, the studies were open label, lacking placebo and control groups, and there was no systematic investigation into potential side effects. For these reasons is it prudent to consider the findings of these studies preliminary. Furthermore, the clinical setting in which the research took place lacks ecological validity, and caution is required when generalising these results to naturalistic settings.

Studies in non-clinical populations have shown similar reductions. In a sample of nine, symptoms of *panic-like disorders* were found to decrease when compared to a placebo ayahuasca group in a Santo Daime ritualistic setting, with no effect sizes recorded and no long term follow-up (Santos et al., 2007). Open label studies utilising self-selected samples in naturalistic settings have also demonstrated significant change in psychometric outcomes. Increased mindfulness was found in a sample of 48 individuals, $\eta^2 = 0.15$ at 24 hour follow up (Murphy-Beiner & Soar, 2020), and improvements in convergent thinking and general wellbeing was recorded up to four weeks following ayahuasca administration in a sample of 31 with no effect sizes recorded (Uthaug et al., 2018).

Studies also suggest improvements in wellbeing and substance misuse following ayahuasca consumption (Fábregas et al., 2010; Thomas et al., 2013). Fábregas et al. (2010) investigated addiction severity in a population of 56 jungle-based ayahuasca users as well as in another

sample comprised of 71 urban-based ayahuasca users, both with matched controls. The jungle-based ayahuasca group were found to score lower on the Drug Use subscale of the Addiction Severity Index (ASI) at one year follow up, whereas the urban-based ayahuasca group were found to score worse than controls on the Family/Social Relationships subscale. Thomas et al. (2013) investigated ayahuasca-assisted treatment in a group of 12 participants from a rural First Nations population in British Columbia. This observational study showed significant reductions in problematic cocaine habits when two ayahuasca ceremonies were delivered alongside four days of group counselling (effect sizes were not reported).

Long-term users of ayahuasca have shown elevated platelet 5-HT transporter levels, thought to be indicative of neuronal 5-HT activity which is intimately connected to depression and other mood disorders (Callaway et al., 1994). Therefore, ayahuasca consumption may have an antidepressant effect through reversing serotonergic deficits (Liester & Prickett, 2012). Other neuroimaging evidence postulates the involvement of increased serotonin transmission after ayahuasca use (McKenna et al., 1998). Single-photon emission computed tomography (SPECT) showed increased activation in the anterior cingulate, the anterior insula, and the left amygdala in participants administered with freeze-dried ayahuasca as compared to placebo (Riba et al., 2006). These latter areas are involved in emotion regulation and processing, and the anterior cingulate is involved in interoceptive ability (Riba et al., 2006).

There are however certain methodological issues associated with the research above. Although studies into ayahuasca generally present impressive outcomes, the majority are open label (Barbosa et al., 2009; Barbosa et al., 2016; Bouso et al., 2012; Kavenská & Simonová, 2015; Murphy-Beiner & Soar, 2020; Osório et al., 2015; Uthaug et al., 2018; Zeifman et al., 2021). The impact of expectancy as well as other confounding variables, such as community support

(especially in church settings), associated therapy, and the effects of attending a retreat must be considered when interpreting these results. To date, there has been only one randomised controlled trial (RCT) comparing a single dose of ayahuasca to a placebo in a population suffering from treatment-resistant depression (TRD). This double-blind, parallel-arm, randomised placebo controlled trial included 29 participants with a history of TRD (Palhano-Fontes et al., 2019). Participants were assessed at day one, two, and seven after dosing in hospital setting in Brazil. The ayahuasca group experienced a statistically significant reduction in depressive symptomatology in comparison to the placebo group. When assessed a week later the ayahuasca group displayed a further reduction in symptoms and a non-significant trend towards the remission of depression (Cohen's *d* D7 = 1.49).

There are however various hurdles associated with blinding in psychedelic research. When psychedelic substances are given at high dose, the subjective effects are frequently extremely pronounced, often revealing the condition to which the participant has been assigned (Aday et al., 2021). Despite this, some authors have attempted to create convincing placebo ayahuasca preparations (Palhano-Fontes et al., 2019; Santos et al., 2007; Uthaug et al., 2021). Santos et al., (2007) not only developed a foul-tasting black liquid resembling ayahuasca, but also recreated a Santo Daime ritual for his control group. Similarly, Palhano-Fontes et al. (2019) created a placebo ayahuasca brew with components such as zinc oxide that irritate the gastrointestinal lining, replicating the emetic effects of the tea. The placebo effect was found to be extremely high in the latter, with 46% of the placebo group responding at time point one and five participants misclassifying it as ayahuasca. This is potentially due high rate of comorbid cluster B personality disorder (76%) in the sample, a factor which is associated with higher placebo responses (Ripoll, 2013). In addition, the majority of the sample were from low

socioeconomic status, which has also been associated with increased placebo responses (Sonawalla & Rosenbaum, 2002).

More generally, users of ayahuasca report greater increases in subjective wellbeing, quality of life and personality factors including greater optimism, confidence, and independence (Barbosa et al., 2009; Lawn et al., 2017). There has been no evidence that long-term ayahuasca use negatively impacts cognitive ability, leads to addiction, or worsens mental health problems (Barbosa et al., 2009; Bouso et al., 2012; Da Silveira et al., 2005; Fábregas et al., 2010). Rather, its use has been associated with improvements in performance on various cognitive tasks and psychopathological measures (Bouso et al., 2012). In one study, individuals drinking ayahuasca participated in a closed-eye imagery task and were found to show increased activity in neural regions associated with episodic and working memory, as well as prospective imagination (de Araujo et al., 2012). The imagery experienced by ayahuasca users may be elicited via extensive activation of regions involved in vision, memory, and intention, lending a sense of reality to the inner experience (de Araujo et al., 2012).

It is common for studies investigating the use of ayahuasca to use populations from the so called *ayahuasca churches* (Barbosa et al., 2009; Barbosa et al., 2016; Bouso et al., 2012; Santos et al., 2007). Members of these cults often have pre-held beliefs that drinking ayahuasca is beneficial, some of whom have organised their lives around the bimonthly rituals. In addition, there is a clear self-selection bias in the samples choosing to attend ayahuasca retreats in naturalistic settings (Murphy-Beiner & Soar, 2020). It has been suggested that the psychotherapeutic benefits some users experience are contingent on expectations and psychological readiness, the quality of the concoction itself and the guidance provided (Loizaga-Velder & Verres, 2014). Effect sizes do not appear to have been reported in many of

the studies investigating ayahuasca, however when documented they are often very large. Although this may appear encouraging, it must be taken into consideration that many of the studies investigating ayahuasca and psychedelics more generally are preliminary, have small sample sizes, are prone to expectancy effects and lack long-term follow up (Muthukumaraswamy et al., 2021). Although the data looks promising, further RCTs are required to see if results replicate in controlled settings.

Pharmacology

Pharmacological Overview of Ayahuasca

The psychoactive effects that users experience following ingestion of ayahuasca are largely a result of dimethyltryptamine (DMT) (McKenna et al., 1984). The compound DMT itself is a functional analogue of various psychedelic tryptamines, including 5-HO-DMT, 5-MeO-DMT, 4-AcO-DMT, psilocin (4-HO-DMT), and psilocybin (4-PO-DMT), as well as a structural analogue of melatonin and serotonin (Gable, 2007). DMT is an endogenous serotonergic compound with evidence suggesting it exists within the brain, lungs, and liver of humans, with trace amounts also being prevalent in a large range of other plant and animal species (Domínguez-Clavé et al., 2016). DMT becomes orally active as a result of monoamine oxidase inhibitors (MAOIs) in the *Banisteriopsis caapi* vine (McKenna, 2004). The brew preparation ensures that DMT is not broken down in the gastrointestinal track and therefore can enter the bloodstream in higher quantities than what could be typically produced endogenously. This allows psychoactivity to occur as the DMT becomes centrally active (Ruffell, Netzband, Bird, et al., 2020). Several major psychiatric disorders, most noticeably depression, have implicated serotonin imbalance as a potential cause (Baldwin & Rudge, 1995; Meltzer, 1990; Owens &

Nemeroff, 1994) and consequently SSRIs are the gold standard in treating many of these conditions (Carhart-Harris et al., 2018). Evidence also suggests that signalling of the 5-HT2A receptor results in processes involving neurogenesis, learning, extinction learning, neurodevelopment and cognitive flexibility (Carhart-Harris & Nutt, 2017). The psychedelic experience is hypothesised to be induced by 5-HT2A activation (Carhart-Harris & Nutt, 2017) and DMT has been shown to bind to multiple 5-HT receptors (Smith et al., 1998). Interestingly, this is also the case with two of the beta-carbolines present in the vine - harmine and harmaline (Glennon et al., 2000).

DMT falls under the category of *classical psychedelics*, which also includes psilocybin, lysergic acid diethylamide (LSD) and mescaline, all of which act as partial agonists at the 5-HT2A receptor (Carhart-Harris, 2019). Several neuroimaging studies have been conducted into a range of serotonergic psychedelics, yielding similar findings (Carhart-Harris, Muthukumaraswamy, et al., 2016a; Riba et al., 2004). These studies indicate that 5-HT2A partial agonists transiently reduce activation in the default mode network (DMN), whilst increasing connectivity to other subcortical regions of the brain. Carhart-Harris, Muthukumaraswamy, et al. (2016) published an fMRI study which showed the neurophysiological activity of 75mg of LSD against a placebo control group (Carhart-Harris, Muthukumaraswamy, et al., 2016). Overall brain connectivity was vastly increased in the LSD group, resulting in increased communication between different brain regions, along with a decrease in the DMN. Near identical findings have been observed with psilocybin (Carhart-Harris, Erritzoe, et al., 2012) and ayahuasca (Palhano-Fontes et al., 2015).

Similar psychological states cantered around disruptions of self-consciousness can also be induced through other non-pharmacological means, such as meditation,

yoga, and holotropic breathwork (Grof & Grof, 2010; Millière et al., 2018). When 5-HT2A/C receptors are activated in such a way, the brain's normal waking state can be altered and increased activity is observed in regions surrounding the DMN (Tagliazucchi et al., 2016). Using LSD, Carhart-Harris and colleagues (2016) showed with fMRI that brain activity was characterized by less segregation and a more unified form of connectivity during task-free, closed eye activity. Similar effects have been displayed with ayahuasca but with limited data (de Araujo et al., 2012; Palhano-Fontes et al., 2015) potentially because of lack of funding and the complexities of conducting brain imaging in the settings in which ayahuasca is typically used.

Epigenetics

Epigenetic change can be defined as heritable phenotypic change without permanent DNA sequence alterations (Dupont et al., 2009). The prefix *epi* originates from Greek and translates as *around* or *over*, suggesting additional elements to traditional genetic inheritance (Rutherford, 2015). The field most often concerns itself with changes in gene expression and activity, with external environmental factors leading to changes in both physiological and cellular phenotypical traits. Specific mechanisms of epigenetic change include DNA methylation and histone modification (Bollati & Baccarelli, 2010).

Tobi et al. (2018) performed a genome wide analysis of DNA methylation in a cohort of over 400 children born to mothers who underwent the atrocities of the Dutch famine in the Second World War, compared to siblings born after the famine. The authors investigated the relationship between serum triglycerides, body mass index and DNA methylation. Epigenetic

analysis revealed compelling evidence that environmental influences, in this case famine, impact epigenetic expression. Furthermore, the results suggest epigenetic changes in the short term may impact longer term health (Tobi et al., 2018). Despite these findings, conclusions are limited by methodological shortcomings, such as the incompleteness of the gene database on which the Illumina 450k array was based, and the choice of whole blood to assess DNAm, which may not be representative of tissue associated with triglycerides or body mass index (Gunderson et al., 2009). Further research is required to determine the causal mechanisms associated with change in methylation as a result of environmental influence.

The extent to which epigenetic change can be passed to subsequent generations remains unclear (Heard & Martienssen, 2014; Knopik et al., 2017). There is, however, increasing evidence that traumatic effects may be transmitted intergenerationally. Yehuda and Lehrner (2018) identify two main categories of epigenetic effect; those programmed during early development encompassing *in utero* and early care, and those effecting the germline preconceptionally. Research in animal models have provided evidence that changes in the epigenome are transmissible (Anderson et al., 2006; Carone et al., 2010; Jimenez-Chillaron et al., 2009; Zambrano et al., 2005). Results are however less clear in human studies. It has been suggested that the children of holocaust survivors have an increased susceptibility to stress (Kellermann, 2013; Yehuda et al., 2016; Yehuda et al., 2014), and those who experience trauma in early childhood may effect hypothalamic-pituitary-adrenal (HPA) axis function in subsequent generations (Brand et al., 2010 ; Juul et al., 2016). Furthermore, the physiological makers of anxiety have been found to be raised in the children of abused mothers (Jovanovic et al., 2011). However, given the lack of research in this area and associated methodological issues, conclusions cannot be drawn surrounding the role a single set of biological determinants may have intergenerationally (Yehuda & Lehrner, 2018).

Ayahuasca may impact trauma-related neurobiology pharmacologically. Fear extinction, memory reconsolidation, synaptic plasticity, and neurogenesis are hypothesised to occur as a result of sigma non-opioid intracellular receptor 1 (SIGMAR1) activity (Inserra, 2018). SIGMAR1 is a stress-responsive neuro-receptor located largely on the endoplasmic reticulum. Stress-induced SIGMAR1 activation in rodents demonstrate it could be a potential target in the management of PTSD (Ji et al., 2016). In a seminal paper by Fontanilla et al. (2009), DMT was also found to bind to SIGMAR1, inhibiting voltage-gated sodium ion channels in cardiac myocytes as well as SIGMAR1 expressing heterologous cells. These results indicate that DMT is in fact a SIGMAR1 endogenous agonist. Other candidate receptors include brain-derived neurotrophic factor (BDNF) and FKBP prolyl isomerase 5 (FKBP5). FKBP5 is primarily a glucocorticoid receptor co-chaperone, as well as being associated with stress response pathways (Binder, 2009), and is suggested to be involved in stress-related disorders (Zannas et al., 2016). Furthermore, FKBP5 methylation could be a proxy marker when assessing the effects of treating PTSD with meditation treatment (Bishop et al., 2018). BDNF encodes a protein which is involved in the growth, differentiation, and maintenance of neurons (Sun et al., 2013; Xiong et al., 2013). It is primarily active at synapses, the sites at which cells communicate (Bramham & Messaoudi, 2005; Numakawa et al., 2010). It is therefore thought to have a role in synaptic plasticity, facilitating both memory and learning through the formation of new synaptic connections (Bramham & Messaoudi, 2005). BDNF expression levels are associated with PTSD in rat models (Burstein et al., 2018), and increased BDNF promoter region DNA methylation has been correlated with PTSD (Kim et al., 2017). Depressive behaviour in general has also been associated with reduced levels in BDNF (Martis et al., 2019). Despite this, researchers and therapists alike emphasise the importance of non-pharmacological factors when administering psychedelics. In fact, many have suggested that

set and setting are essential to achieve the full therapeutic potential of psychedelic substances, potentially as a result of the placebo effect (Aday et al., 2021; Mithoefer et al., 2008).

Short-Term Effects

Phenomenology

DMT has been labelled *the spirit molecule* by Rick Strassman (Strassman, 2001), and this phrasing has filtered down into broader society colloquially. This is a result of his work in 1994 in which he dosed 60 volunteers with intravenous (IV) DMT negating the need for a MAOIs. DMT is most commonly smoked and subsequently inhaled, and similarly to IV DMT, the effects last from 10 to 30 minutes (Strassman, 2001). When DMT is ingested orally in combination with MAOIs the experience lasts between four and six hours. Users often report feelings of euphoria, as if they have transcended through space and time, and a sense of oneness (Riba et al., 2001). Many participants in Strassman's work with DMT also reported interactions with intelligent nonhuman beings, such as spirits, angels, and aliens (Strassman, 2000). Subjective descriptions of experiences with DMT show similarities with that of *near-death experiences* (NDEs). Interestingly, NDE's can also be reproduced with ketamine, via N-methyl-D-asparate (NMDA) receptor blockade in the brain, preventing the action of the neurotransmitter glutamate (Jansen, 1997). Common phenomena include reviews of past life events, travelling through a tunnel towards a light, and out-of-body experiences (Martial et al., 2019).

Changes in Perception

Those drinking ayahuasca frequently experience complex thought processes, coloured visual imagery, and a heightened state of awareness when levels of DMT are highest (Callaway & Grob, 1998; Callaway et al., 1999; Luna, 1986; Riba et al., 2001; Wolff et al., 2019). Synaesthesia is also common, with participants frequently experiencing simultaneous smells, sounds and visions (Luna & Amaringo, 1999). Psychedelic users often report deep introspection and self-awareness during sessions, as well as profound and insightful experiences (Strassman, 2000). These types of events have been ranked by participants as being as significant as life events such as falling in love, having a first child, or getting married (MacLean et al., 2011; Strassman, 2000). These reports are not anomalies when it comes to research into ayahuasca and DMT; psilocybin and LSD have also been reported to produce similar subjective effects (Nichols, 2016).

Phenomenological analyses suggest that LSD, ayahuasca and psilocybin can all result in alterations in perception, whether that be visual, auditory, or tactile (Schmid et al., 2015; Turton et al., 2014; Wolff et al., 2019). In addition, these psychedelic compounds appear to be able to induce feelings of happiness (Schmid et al., 2021; Turton et al., 2014), changes in perception of time (Wolff et al., 2019), aid in the processing of difficult emotions (Masters & Houston, 1966; Wolff et al., 2019) and to alter the capacity for recollection of memories (Turton et al., 2014; Wolff et al., 2019). Although the appearance of supportive entities/beings have been reported anecdotally in psilocybin and LSD sessions, this phenomenon appears to more specific to ayahuasca and DMT (Beyer, 2010; Luna, 1986).

Different classical psychedelics appear to lead to relatively similar subjective experiences when ingested (Pahnke, 1969). Strassman and colleagues developed the *Hallucinogen Rating Scale*

(HRS) to assess this (Strassman et al., 1994). The inventory measures the subjective effects of hallucinogens in six different domains; volition, somaesthesia, perception, affect, intensity, and cognition (Strassman et al., 1994). A similar measure, the *Mystical Experience Questionnaire* (MEQ) categorises the potential subjective effects of psychedelics slightly differently, with four subscales pertaining to; *difficulties putting the experience into words; alterations to the sense of both time and space; positively valanced feelings such as love or peace; and an authoritative sense of unity or connectedness accompanied by feelings of reverence* (Barrett et al., 2015).

Physical Effects

In response to DMT ingestion, users often experience purgative effects - a result of the disturbance to stomach enzymes caused by the MAOI alkaloids and potentially the serotonergic effect of DMT affecting 5HT receptors in the gut (Gershon, 2004). Most users experience nausea and around 57% report vomiting (Heise & Brooks, 2017). Traditionally, vomiting is not seen as a negative side effect of ayahuasca but rather as a fundamental aspect of the *purging* process (Tafur, 2017) an expelling of physical toxins and/or psychological traumas. Some traditional practitioners even refer to the beverage as *la purga* (Spanish: the purge) (MacRae, 2004). Other physiological effects commonly reported include shivering, sweating and gastrointestinal cramps, largely thought to be as a result of increased levels of serotonin (Callaway & Grob, 1998; Wolff et al., 2019).

Experiential Effects

The term *holotropic* was adapted and applied to human consciousness by psychiatrist and researcher Stanislav Grof, *meaning moving towards the whole* in ancient Greek (Grof & Grof,

2010). The term encompasses many of the effects associated with the 5-HT2A receptor. One such effect is loss or reduction of sense of self, often referred to as *ego-death* (Pahnke, 1969), which is characterized by the dissolution of the boundaries between the individual and their surroundings. Normal awareness is compromised in such states, and therefore a rationalised understanding of the experiences is often a result of retrospective thinking (Palhano-Fontes et al., 2015). A heightened sense of empathy is also common, along with distortions in sensory processing and a sense of interconnectedness (Strassman et al., 1994). Often people experience profound biographical insights, by considering novel perspectives regarding existing life problems (Baker, 2005). Such experiences are often referred to as mystical, spiritual, or peak experiences (Watts, 1968).

Mystical Experiences

Allman and colleagues define mystical experience as an extraordinary, transient incident, characterised by feelings of harmony and unity with *the divine* and all existence (Allman et al., 1992). Preliminary evidence suggests that psychoactive substances such as ayahuasca occasion such states (Palhano-Fontes et al., 2019; Ruffell, Netzband, Linton, et al., 2020; Ruffell et al., 2021). When compared to other psychedelics like psilocybin and LSD, certain features of the mystical experience appear particularly prevalent with ayahuasca. Griffiths and colleagues found that those consuming ayahuasca were more likely to report that they had encounters with non-human entities who engaged them in conversation, had two-way conversations with these entities, communicated through visual means such as gestures, engaged in extrasensory-telepathic communication and received messages/tasks from these entities (Griffiths et al., 2019). Griffiths did not, however, discover a difference in the number of people undergoing mystical experiences when comparing LSD (61%), psilocybin (62%) and ayahuasca (65%) (Griffiths et al., 2019). Furthermore, the extent to which participants undergo a mystical

experience has been found to correlate with therapeutic outcomes such as depression and anxiety in both psilocybin (Roseman, Nutt, et al., 2018) and ayahuasca (Palhano-Fontes et al., 2019; Ruffell, Netzband, Linton, et al., 2020; Ruffell et al., 2021).

Long-Term Effects

Ayahuasca and Personality Structure

An Overview of the Literature

Several studies have investigated the impact of ayahuasca on personality. These have been primarily conducted in church-based settings (Barbosa et al., 2009; Barbosa et al., 2016; Bouso et al., 2012). Grob and colleagues (1996) conducted an observational study assessing personality traits of União do Vegetal (UDV, translation: Union of the Plants) church members. 15 long-term church members and 15 controls were assessed on three main personality domains using the *Tridimensional Personality Questionnaire* (TPQ) (Cloninger, 1987), assessing reward dependence, harm avoidance, and novelty seeking. Compared to controls, the UDV congregation scored lower in harm avoidance and novelty seeking domains, but interestingly, this was not apparent for reward dependence. Barbosa et al. (2009) conducted an observational study assessing the congregation of both the Santo Daime (*N*=15) and UDV (*N*=8) churches for changes in personality. Participants were assessed using the *Temperament and Character Inventory* (TCI-125) (Cloninger et al., 1993) immediately before their first ayahuasca experience and six months following, with members of the Santo Daime showing significantly higher reward dependence scores at baseline when compared to those of the UDV. Six months

after ayahuasca use, the active groups demonstrated substantial reductions in reward dependence, which were positively correlated with the degree to which ayahuasca was used (Barbosa et al., 2009). It is, however, difficult to disentangle the relative influences of church membership and ayahuasca use, and membership of a supportive church community is likely to result in positive life changes.

Bouso et al. (2012) conducted an observational study utilising long-standing (≥15 years) users from several ayahuasca churches. 127 regular ayahuasca users were assessed alongside 115 control subjects actively participating in non-ayahuasca based religious practice. Personality was assessed using the TCI-125 (Cloninger et al., 1993) both initially and one year later. The experimental cohort scored significantly less than controls in harm avoidance and reward dependence at baseline and reduced levels of harm avoidance were maintained at one year follow-up. Effect sizes were not recorded. Kavenská and Simonová (2015) found similar results when they assessed the personality structure of tourists who had travelled to the Amazon rainforest to partake in at least one ayahuasca ceremony. The *Personality Styles and Disorders Inventory* (PSSI) (Kuhl & Kazén, 2009) was used to assess the experimental group (N=77). The experimental group showed higher scores in optimism (d = 5.04), intuition (d = >15), ambition (d = .67), helpfulness (d = .80), and charm (d = 1.52) when compared to the general Czech population (Kavenská & Simonová, 2015). The authors suggest those consuming the brew demonstrate an optimistic, pleasant, trustful, and empathic personality style. The authors did not however collect baseline data pertaining to personality, making it difficult to reliably attribute these differences to ayahuasca.

Psilocybin and Personality

Psilocybin, a 5-HT2A agonist with a similar chemical structure to DMT, is known to produce similar psychedelic effects to ayahuasca (Carhart-Harris, Erritzoe, et al., 2012). Given the commonalities in pharmacology and subjective experience it can be expected to result in similar psychological outcomes. A study by MacLean et al. (2011) investigated this concept with personality. The RCT assessed 52 participants using the *Revised NEO Personality Inventory* (NEO-PI-R; Costa & McCrae, 1992), a measurement of the *five-factor model* of personality (or *Big Five*), as well as the MEQ (Barrett et al., 2015; Costa Jr & McCrae, 1992). Volunteers were assessed before and after intravenous doses of the drug. Changes in personality scores were then monitored six- and 12-months post-dosing. Long term (12-month) increases in levels of openness were observed and correlated with high scores on the MEQ in acute response to psilocybin.

The literature suggests personality starts to stabilise at around 30 years of age, with the most heritable trait being Openness to experience (Costa Jr & McCrae, 1992; Jang et al., 1996; Terracciano et al., 2010). The above study recruited participants with a mean age of 46. Although changes in personality can develop later in life, these are usually minor and occur over time (Terracciano et al., 2010). Despite this, significant changes were observed in the domain of Openness. In a more recent study, similar methods were carried out in a population with unipolar depression (Erritzoe et al., 2018). Reduced levels of Neuroticism were observed, which showed a positive correlation with the magnitude of mystical experience reported. The mean age of subjects was 47. Neuroticism was found to significantly decrease whereas Extraversion and Openness both increased. Collectively, this suggests that psychedelics may result in long-term changes in traits historically considered stable (Costa Jr & McCrae, 1992;

Terracciano et al., 2010) and may even have therapeutic potential for conditions based in high levels of neurosis, such as affective disorders.

The above studies demonstrated that psilocybin was associated with personality change that directly correlated with perceived mystical experience (Erritzoe et al., 2018; MacLean et al., 2011). Drinking ayahuasca has also been found to correlate with reduced substance and alcohol misuse, as well as lower levels of anxiety and depression (Barbosa et al., 2009; Bouso et al., 2012; Fábregas et al., 2010). Due to the structural similarities between DMT and psilocybin, it is unsurprising that DMT appears to have a similar effect on personality structure. To date however, there has been no research investigating the effect of ayahuasca on personality in an adapted traditional shamanic retreat setting.

Connection to Nature

It is common that ayahuasca experiences contain a prominent phenomenological component related to nature (Fernández & Fábregas, 2014a; Liester & Prickett, 2012; Metzner, 2005; Trichter et al., 2009; Winkelman, 2005). These often include experiences of interconnection or connectedness with nature (Kavenská & Simonová, 2015; Loizaga-Velder & Pazzi, 2014; Prayag et al., 2016; Thomas et al., 2013). Amazonian shamanism emphasises the connection between nature and humans, and ritualistic practices are heavily influenced by the surrounding environment (de Rios, 1994; De Rios & Rumrrill, 2008). *Nature relatedness* (also called *nature connectedness*) is a measure of affinity with nature, representing prolonged understanding of

the connection between nature and self (Zylstra et al., 2014) and as the impression of *oneness* with nature (Mayer & Frantz, 2004).

An observational study investigating 12 Canadian First Nations members, a population prone to substance addiction, demonstrated involvement in ayahuasca retreats augmented the feeling of connection with nature, spirit, self and others, in addition to enhancing mindfulness (Thomas et al., 2013). Participants often describe feeling disconnected from nature prior to psychedelic use (St John, 2018), and the use of psychedelics may be able to resolve this disconnect (Fotiou, 2012; St John, 2018). *Nature relatedness* is associated with eudemonic wellbeing (i.e., a life associated with self-actualisation), particularly personal growth (Pritchard et al., 2020). Desire for personal growth is a common motivation for people seeking out ayahuasca, while also being a commonly reported outcome of usage (Fernández & Fábregas, 2014a; Franquesa et al., 2018; Kavenská & Simonová, 2015; Kjellgren et al., 2009; Loizaga-Velder & Pazzi, 2014; Shanon, 2014). Ayahuasca users have also been found to have higher ratings of life purpose, life meaning, life satisfaction and wellbeing; and usage has been found to lower anxiety and improve mood (Bouso et al., 2012; Jiménez-Garrido et al., 2020; Thomas et al., 2013; Uthaug et al., 2018). Such cognitive and affective shifts are also associated with higher ratings of nature relatedness (Gandy et al., 2020).

Ayahuasca usage is also associated with deepened spiritual beliefs and sustained spiritual self-development (Kavenská & Simonová, 2015; Trichter et al., 2009; Winkelman, 2005), with spirituality and nature relatedness showing a significant association (de Jager Meezenbroek et al., 2012; Saroglou et al., 2008; Trigwell et al., 2014). Further, spirituality acts as a mediator between nature connectedness and psychological wellbeing (Kamitsis & Francis, 2013; Trigwell et al., 2014). Despite these intriguing results, there have been no quantitative studies

investigating the impact of ayahuasca on nature connectedness and associated psychological measures.

Safety Considerations

Safety and wellbeing issues are always paramount for any intervention, therefore it is important to outline some of the wealth of research suggesting that the risks of ayahuasca use are minimal, when used appropriately. Animal studies suggest a fatal dosage of DMT would be 20 times that of the standard ritualistic ayahuasca practice (Gable, 2007). This suggests a wide therapeutic window, with neither acute nor long-term administration of ayahuasca appearing toxic in humans (Guimarães dos Santos, 2013). Ayahuasca, which typically contains harmala alkaloids and DMT, has a safety profile similar to methadone, mescaline, and codeine, with the risk of sustained psychological disturbance being minimal (Gable, 2007).

Ayahuasca has low addiction potential (Fábregas et al., 2010), and the overall cardio-vascular risk of the brew has been described as minimal (Riba et al., 2003). Further, there have been no serious negative consequences recorded when ayahuasca has been drunk by healthy individuals in sensible contexts (Guimarães dos Santos, 2013). A technical report from the International Centre for Ethnobotanical Education, Research, and Service (ICEERS) states there have not been any recorded deaths due to drinking ayahuasca or DMT/β-carboline combinations, concluding that the available literature suggests the responsible use of ayahuasca is acceptably safe, in the short-term, medium-term, and long-term (Bouso et al., 2017). Despite this, a broad range of other plant and sometimes chemical admixtures are used by charlatan shamans, some

of which can be dangerous or potentially even deadly, yet the brew is still referred to as *ayahuasca* (McKenna et al., 1995). Deaths have occurred in ceremonial settings but upon investigation it appears in all or most cases that this has been due to some form of malpractice (Guimarães dos Santos, 2013).

Research investigating physical pain within participants of the UDV concluded that there were no incidents of adverse effects in first-time users (Barbosa et al., 2009). Women have been known to drink ayahuasca when pregnant and anecdotal evidence does not suggest any negative effects (Labate & Jungaberle, 2011). There is however limited information available regarding the possibility of toxic effects in pregnancy, the offspring of pregnancy women, and toxicity following long-term consumption, suggesting that further research is required (Guimarães dos Santos, 2013).

It should be acknowledged that there is a potential risk associated with MAOIs and the chemical tyramine (Callaway et al., 1994). MAOIs prevent tyramine from being degraded and consequently may result in dangerously high blood levels when introduced into the body from exogenous sources leading to hypertensive crisis (Dalgarno, 2008). Contraindicated food and drugs containing tyramine include certain cold and flu medications, cocaine, ecstasy, and certain alcoholic beverages (Dalgarno, 2008). Ayahuasca has also been linked to serotonin syndrome, a potentially life-threatening condition characterised by the over stimulation of 5HT1a and 2a receptors, when combined with psychiatric medications such as SSRIs (Callaway & Grob, 1998; Volpi-Abadie et al., 2013). Various deaths from so called ayahuasca have made international headlines, with serotonin syndrome suggested as the cause of death (Mortimer, 2015).

Although there are reported cases of ayahuasca having life-threatening or even fatal consequences following consumption, it must be noted that these are speculative (*died from convulsions, fulminant heart attack*) and it is impossible at this stage to state a causal effect from ayahuasca consumption (Bauer, 2018). Most retreat centres working with ayahuasca in the Amazon rainforest screen participants for a variety of mental and physical conditions to avoid potential harmful effects. The Ayahuasca Foundation, where the empirical research in this thesis took place, specifically screens for a history of stroke, hypertension, previous cardiac arrests, and diabetes as well as psychotic disorders such as schizophrenia and bipolar disorder (Ayahuasca Foundation, 2022, January 3). Furthermore, it must be noted that dramatic media reports are not necessarily based on accurate data and can cause harm by propagating false and exaggerated claims (Guimarães dos Santos, 2013).

Adverse Mental Health Outcomes

Although evidence suggests the safety profile of ayahuasca is acceptable, there have been incidents in which ayahuasca consumption has been associated with psychosis (Dos Santos, Bouso, et al., 2017; Tófoli, 2011). Syncretic churches, such as the UDV, have documented such cases, however it is not possible to deduce causality. This is due to factors such as concurrent substance use, pre-existing conditions, and temporality (dos Santos & Strassman, 2011; Tófoli, 2011). In addition, the rate of psychotic episodes recorded over a period of five years within ayahuasca users in the UDV was under 1% - equivalent to the rate found in the general population at any one time (Gable, 2007; Stilo & Murray, 2010) - whilst other drugs, such as cannabis, are thought to cause a two-to-three-fold increase in the relative risk of developing psychotic disorders (Arseneault et al., 2004).

Psychedelic-Assisted Psychotherapy (PAP)

Accumulating evidence points to the potential therapeutic value of ayahuasca and psychedelics in general, especially when used in combination with conventional psychotherapy (Carhart-Harris, Bolstridge, et al., 2016; Mithoefer et al., 2019; Mithoefer et al., 2011; Mithoefer et al., 2013; Palhano-Fontes et al., 2019). The Multidisciplinary Association for Psychedelic Studies (MAPS) has designed a set protocol, known as the *California Institute of Integral Studies (CIIS) psychedelic-assisted psychotherapy protocol*, incorporating the concepts of *set* and *setting*, aiming to optimise therapeutic outcomes (Mithoefer et al., 2008). The format usually takes around six months per patient, with follow-up at 12 months, and at present has focused on 3,4-Methylenedioxymethamphetamine (MDMA) for PTSD. The six-months is split, with each patient receiving around one month of counselling before the psychedelics are integrated into the therapy protocol. Each of the sessions typically employs psychodynamic principles combined with other approaches such as *Internal Family Systems* (IFS) (Schwartz, 1995), largely dependent on the background and training of individual therapists (Mithoefer et al., 2008). Much of the framework draws upon traditional ceremonial practices which have been adapted for a Western clinical setting. For example, therapy rooms are decorated with objects such as Buddha statues, lotus flowers and various pieces of artwork with spiritual connotations and aroma therapy is often used. During the psychedelic sessions, individuals are generally encouraged to look inwards whilst listening to suitable music. PAP is said to utilise the inner healing potential of the individual, rather than the session being led by the expertise of the so-called *sitter*/psychotherapist (Mithoefer et al., 2008). Alongside MDMA, psilocybin and ayahuasca have been suggested as candidates for PAP (Reiff et al., 2020).

Biological Mechanisms of Action

In addition to changes in regional blood flow and connectivity, psychedelics have been suggested to increase brain neuroplasticity, with neurons having greater propensity to form new connections (Almeida et al., 2019; Pittenger & Duman, 2008). Both DMT and the harmala alkaloids have been demonstrated to induce neuroplastic effects when administered in isolation, as well as when combined as ayahuasca (Colaço et al., 2020; Morales-García et al., 2017). This increased neuroplasticity coupled with psychotherapy sessions appears to catalyse therapeutic processes (Carhart-Harris, Bolstridge, et al., 2016). Further, Morales-García et al. (2017) have shown that the *beta*-carbolines in the brew cause neurogenesis *in vitro* in hippocampal tissue in mice. These findings have opened new avenues in ayahuasca research in areas such as neurodegenerative disorders.

Psychological Mechanisms of Action

Ayahuasca can be seen to breed a sense of self-acceptance (Soler et al., 2016). This state could be clinically useful as in fostering a detached relationship with emotion, also known as *defusion* or *decentring*. *Decentring* can be defined as the ability to detach from emotions and thoughts, resulting in a more objective view of one's own mental state (Fresco et al., 2007). Logic would imply this process could minimise anxiety, hence its potential usefulness in clinical or therapeutic practice. Problems with decentring are thought to be a transdiagnostic index in mental illness (Feliu-Soler et al., 2016). Compared to healthy controls, Soler et al. (2016) found it to be reduced in those suffering from major depression, eating disorders, borderline personality disorder, and addiction to cocaine. This study showed that ayahuasca was associated with increased rates of decentring. Such increases may go some way in explaining the positive effects ayahuasca appears to have in those suffering from depression (Fresco et al., 2007). Carhart-Harris and Friston (2019) propose a similar mechanism in psychedelics, which

they refer to as relaxed beliefs under psychedelics (REBUS), or the anarchic brain. The authors postulate that psychedelics can induce bottom-up information flow, brought upon by relaxing the precision of higher-level beliefs. The REBUS theory is based on the entropic effects of psychedelics in cortical activity, which the authors propose has therapeutic potential. Reducing the precision of overweighted ideas is thought to allow the revision of such ideas, with clear implications for psychiatric conditions such as anxiety and other disorders of a neurotic nature (Carhart-Harris & Friston, 2019).

Ayahuasca use is associated with a temporary increase in some, but not all, mindfulness capabilities. Decentring and dimensions related to acceptance, such as the ability to observe internal experience without judgement or reaction, show the most promising results (Sampedro et al., 2017; Soler et al., 2018; Soler et al., 2016). Known as ayahuasca *after-glow*, these effects tend to be short-term, presenting 24 hours after ayahuasca consumption and lasting up to several weeks, but not observed at two-month follow-up. The small literature investigating the link between ayahuasca and mindfulness are predominantly within a non-religious context where ayahuasca use is limited to between a single dose to four ayahuasca sessions (Sampedro et al., 2017; Soler et al., 2018; Soler et al., 2016). Within religious and non-religious settings, decentring ability was significantly greater in regular drinkers compared to those not drinking ayahuasca, with effects lasting beyond the *after-glow* period (Franquesa et al., 2018). Changes in mindfulness may be beneficial within a therapeutic context, providing a window of opportunity for therapeutic growth. A large body of research has linked mindfulness and associated therapies to significant reductions in anxiety and depression (Grossman et al., 2004; Khoury et al., 2015; Vøllestad et al., 2012).

Ayahuasca and Other Psychedelics

To date, most of the work conducted into the mechanism of action of psychedelics has focused on compounds other than ayahuasca, such as psilocybin (Carhart-Harris, Bolstridge, et al., 2016) and MDMA (Green et al., 2003). Unsurprisingly, similarities in therapeutic outcome have also been observed for these compounds (Carhart-Harris et al., 2021; Jerome et al., 2020; Mithoefer et al., 2018; Mithoefer et al., 2011; Rucker et al., 2019). In a seminal paper, Ly et al. (2018) demonstrated that serotoninergic psychedelics showed both neuritogenic and spinogenic properties *in vitro* and *in vivo.* Electrophysiology and fluorescence microscopy showed such changes in neuronal structure were associated with increases in synaptic function and number, with structural changes occurring due to the stimulation of various signalling pathways including 5-HT2A, mTOR, and TrkB. As the pathophysiology of depression involves prefrontal cortex (PFC) neuronal atrophy, compounds such as serotonergic psychedelics and ketamine may induce fast acting antidepressant effects via functional and structural plasticity in the PFC (Ly et al., 2018).

MDMA

Like DMT and other classic psychedelics, MDMA is a 5-HT2A agonist causing the rapid release of serotonin from nerve endings in the brain (Green et al., 2003). The therapeutic potential of MDMA was recognised as early as the 1980s, with a small following of psychiatrists advocating its use as an adjunct in psychotherapy (Grinspoon & Bakalar, 1986). The first RCT of MDMA-assisted psychotherapy was conducted in 2008, showing a reduction in PTSD symptoms (Bouso et al., 2008). Some participants who were reportedly unresponsive to conventional treatments for PTSD have found symptomatic relief following the carefully controlled administration of MDMA (Mithoefer et al., 2013). As has been suggested by Soler

et al. (2016) when working with ayahuasca, Mithoefer et al. (2013) claimed that MDMA can give participants more flexibility in the way their brain processes both thoughts and emotions. Mithoefer and colleagues propose that this therapeutic intervention facilitates a process whereby recipients are no longer trapped by their existing thought processes. Like DMT and other psychedelics, MDMA has been suggested to work in tandem with conventional psychological treatments to expedite the therapeutic process (Mithoefer et al., 2008).

Psilocybin

Psilocybin occurs naturally the world over, found within over 200 different species of mushroom (Nichols, 2020). There is evidence that psilocybin has been used by humans for many centuries (Sayin, 2014). As in the case with ayahuasca, recent studies into psilocybin have suggested it could be particularly effective in minimising symptoms of depression and anxiety in patients once considered treatment-resistant (Carhart-Harris, Bolstridge, et al., 2016). Similar to ayahuasca, psilocybin works as a 5-HT2A agonist (Carhart-Harris, Muthukumaraswamy, et al., 2016), and is thought to decrease activity in the brain's major connector hubs, such as the PCC and mPFC in the DMN, resulting in *unconstrained cognition* (Carhart-Harris, Erritzoe, et al., 2012). Carhart-Harris, Bolstridge, et al. (2016) found significant improvements in depression, as well as decreasing anxiety and anhedonia in patients previously considered treatment-resistant. Notably, these findings were evident following one dose of psilocybin. Eight of the 12 patients were found to achieve remission from depression measured with the *Becks Depression Inventory* (BDI), with five remaining in remission at three months. *Quick Inventory of Depressive Symptomatology* (QIDS) one week after dosing decreased by 11.8 (Hedges's $g = 3.1$) and was -9.2 three months later (Hedges's $g = 2.0$). Some patients who have undergone clinical observation with psilocybin have been reported to feel

more emotionally reconnected and secure when compared to those in the placebo control group (Roseman, Demetriou, et al., 2018).

Mechanisms of Action: Antidepressants vs Psychedelics

Selective serotonin reuptake inhibitors (SSRIs) and other conventional antidepressants share some similarities with psychedelics in terms of mechanism of action, with both working via serotonergic modulation (Carhart-Harris & Nutt, 2017). Change in one's relationship with their environment - encompassing social, nature-related, and physiological aspects - has also been suggested to be key in the subjective effects of both SSRIs (Belsky, 2016; Harmer & Cowen, 2013) and psychedelics (Carhart-Harris et al., 2015; Kaelen et al., 2015). However, important differences exist. Long term use of SSRIs can result in emotional blunting and reduced responsiveness of the limbic system, thought to be mediated via the 5HT1A receptor (Cowen & Browning, 2015; McCabe et al., 2010). In contrast to these effects, psychedelics are claimed to result in greater emotional release, enhancing bottom-up emotional processing and relaxing higher-level belief precision, effects which are thought to be mediated by 5HT2A receptor signalling in areas such as the limbic system (Carhart-Harris & Friston, 2019; Carhart-Harris, Leech, et al., 2012). Such differences in mechanism of action may be responsible for the longer lasting effects of psychedelics when compared to SSRIs (Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris & Friston, 2019; Watts et al., 2017). Unlike the emotional blunting that may be occasioned by long term SSRI use, studies indicate psychedelics can give rise to increases in Openness to experience at both three (Erritzoe et al., 2018) and 12-month follow-up (MacLean et al., 2011). Increasing environmental sensitivity and emotional release, psychedelics have been hypothesized to address the root of the problem, rather than working to suppress the associated symptoms (Carhart-Harris & Nutt, 2017).

A recent study by Carhart-Harris et al. (2021) directly compared escitalopram, a commonly prescribed SSRI, to psilocybin. This double-blind RCT assessed 59 participants with moderate to severe depression. Psychotherapy was provided alongside drug treatment. The trial failed to demonstrate a significant difference between escitalopram and psilocybin in terms of antidepressant effects, however secondary measures numerically favoured psilocybin. The authors concluded that psilocybin can be at least as effective as SSRIs – the current gold standard in the treatment of depression. Despite these promising results, it should be noted that the study only lasted for six weeks, while courses of escitalopram often take longer to establish full efficacy. Although this study focuses on the use of psilocybin rather than ayahuasca, the similarities in mechanism of action and therapeutic outcomes are explored throughout this thesis.

A Note on "Hype"

In recent years there has been a considerable rise in support surrounding the use of psychedelics as medicines in the media. This form of bias to which high-dose psychedelics are extremely susceptible has also been dubbed the *Michael Pollan Effect* (Aday et al., 2021), following the release of the author's successful book outlining his experience with psychedelic substances *How To Change Your Mind* (Pollan, 2019). Furthermore, it is not unusual for leaders in the field to claim psychedelics could *change the world*, with many enthusiasts describing them as *the most important innovation in psychiatry since the discovery of SSRIs* (Dupuis, 2021). Concerns have been raised that unsubstantiated claims about therapeutic potential may mislead patients and the public alike (Aday et al., 2021; Rucker & Young, 2021). Not only are the majority of trials into psychedelics currently early-stage studies (Rucker & Young, 2021), but issues surrounding methodology, such as difficulties in maintaining blinding, exist (Aday et al., 2021). Expectancy effects, undoubtably influenced by considerable positive coverage in

the media, have led some researchers to advise caution in interpreting potentially overestimated effect sizes (Muthukumaraswamy et al., 2021). It has also been suggested that participants may feel pressured *not to let the movement down* by failing to report positive effects (Aday et al., 2021). These factors likely make psychedelic therapy particularly prone to both placebo and nocebo effects (Aday et al., 2021). Despite the exciting potential of psychedelics, a measured approach is required if these compounds are to be deemed appropriate to use in Western medicine.

Ayahuasca and Trauma

Some of the most prevalent conditions that affect Western society have been said to be rooted in developmental trauma (Van der Kolk et al., 2012). These include anxiety, depression, PTSD, and addiction. Coincidentally, it is also some of these common conditions in which treatment modalities have been considered to have stagnated under current approaches (Sessa, 2012). This has led researchers to look outside of the current medical model to identify novel treatments.

Mental healthcare is said to require more novel treatments for trauma-related disorders (Glass et al., 2020). 40-60% of adults are subject to experiences of a traumatic nature during their life, and it is estimated that 7-12% will subsequently develop PTSD (Ackerman et al., 1998). Exposure to trauma and distressing experiences increases the likelihood for developing conditions such as major depressive episodes, somatisation disorder, anxiety spectrum disorders, addiction, and a large range of other less common and/or comorbid conditions

(O'Donnell et al., 2004), including attention deficit hyperactivity disorder (ADHD) (Pallanti & Salerno, 2020). Following exposure to trauma, short-term strategies to reduce distress often include a variety of control- and avoidance-based behaviours such as hyper-vigilance to decrease one's sense of vulnerability, self-blame to rationalise the trauma, substance abuse to minimise dysphoria, and sleep avoidance to escape nightmares (Meyer et al., 2013). In more severe cases that persist in the long-term, maladaptive approaches like these can contribute to the development of PTSD (Hiraoka et al., 2015; Meyer et al., 2013). It has been suggested that reduced mindfulness and reduced cognitive flexibility are likely contributing to these symptoms (Meyer et al., 2018; Palm & Follette, 2011).

Preliminary data suggests that ayahuasca could be used to improve therapeutic targets related to trauma exposure. For example, Murphy-Beiner and Soar (2020) showed sustained increased levels of mindfulness and cognitive flexibility following ayahuasca use. Furthermore, ayahuasca may alleviate symptoms of depression, anxiety, mood disorders and drug dependence (Dos Santos et al., 2016; Galvão et al., 2018; Palhano-Fontes et al., 2019). The brew has also been associated with reduced feelings of hopelessness and improved scores on quality of life measures, with changes sustained at long-term follow-up (Thomas et al., 2013). As such, while there has yet to be direct empirical evidence exploring the impact of ayahuasca on PTSD and trauma-related symptomatology, several authors have suggested it as a likely candidate to be used alongside psychological interventions (Harris, 2017; Labate & Cavnar, 2014; Jessica L Nielson & Julie D Megler, 2014).

Setting Within the Riosbo Centre

The empirical research included within this thesis was conducted in an indigenous community called *Mishana,* in the Peruvian Amazon. This community resides in the Allpahuayo-Mishana National Reserve, near the city of Iquitos. Various members of the community are affiliated with an organisation called the *Ayahuasca Foundation*. This foundation provides *ayahuasca tourists* with Shipibo-style ceremonies. The practices of the Ayahuasca Foundation at the Riosbo centre are said to uphold the Shipibo-Conibo ayahuasca tradition (Ayahuasca Foundation, 2022). They are affiliated with MAPS who assisted financially in the construction of the research centre.

It is common for retreat centres to blend different forms of treatments into package deals for tourists. Interventions such as tobacco purges, a procedure in which tobacco mixed with water is drunk to induce vomiting and diarrhoea to clear the intestines (Berlowitz et al., 2020); Kambô, a skin secretion from the frog *Phyllomedusa bicolor*, administered transdermally in purification procedures (Aquila et al., 2018); or San Pedro, a cactus that contains the psychedelic mescaline used in ceremonial folk healing across Peru (Dobkin, 1968), are often conducted alongside ayahuasca. Practices combining such extensive ranges of treatments do not appear to have been used together conventionally in such limited timeframes (Labate & Cavnar, 2014). The Ayahuasca Foundation does not offer other such treatments, therefore more closely resembling traditional practices. Not only this, but it would also add another layer of difficulty when attempting to identify causation with other psychoactive compounds used in conjunction. The Ayahuasca Foundation and Riosbo research centre therefore allows access to practices which are at least rooted in a traditional approach to administration, whilst allowing us to be able to extrapolate useful data.

Ceremonies are run by *curanderos (shamans*), alongside two to three *facilitators*, often Western individuals who have trained in traditional medicine. Rituals begin at around 20:00, and last between five to six hours. They take place in a circular wooden building (the *maloka*), with participants evenly spaced around the outside of the structure. 10 to 12 participants are usually in attendance during rituals, with each provided with a mattress and a bucket for *the purge*. Participants are instructed to avoid contact with others during the ceremony, and to remain in silence on their mattress. Facilitators assist with the physical needs of participants, such as supporting them to the bathroom if required. After the ayahuasca has been consumed and the curandero has started to feel the effects of brew, he, or occasionally she, sings traditional medicine songs called *icaros* throughout the ceremony.

Overarching Thesis Rationale

Progress in Western psychiatry has arguably stagnated, with many pharmaceutical companies ending their funding for the research and development of psychiatric medicines since the turn of the millennium (Hyman, 2013). Psychiatry is noticeably falling behind the rest of medicine, with research into only 240 potential drug treatments in 2011, compared to 3,000 for cancer (PhRMA, 2013). With around 650 million people worldwide thought to suffer from disorders such as anxiety and depression, mental illness is proving to be both an economic and social burden (Vos et al., 2012). Furthermore, the ongoing COVID-19 pandemic has been associated with a rise in disorders such as post-traumatic symptomology, anxiety, and depression (Talevi et al., 2020). Data from the World Health Organisation has indicated that mental disorders cost over $2.5 trillion per year globally (Kleinman et al., 2016), with neuropsychiatric disorders

accounting for 22.8% of this (Murray et al., 2015). Further, many patients do not respond to the pharmaceutical and psychological treatments offered today, emphasising the need for new medicines. In fact, treatment efficacy for conditions such as depression has remained largely static over the last 50-70 years (Holtzheimer & Mayberg, 2011). Research into psychiatric treatments by pharmaceutical companies has decreased by 70% and treatments that have been developed largely rely on the same mechanisms as existing drugs (Cipriani et al., 2018; Duncan, 2016). Despite a multitude of medications available for conditions such as depression, there is insufficient evidence that those recently developed are more effective than existing treatments (Cipriani et al., 2018).

Modern-day psychiatry arguably continues to follows the biomedical model, explaining mental illness as an abnormality in biology, and advocating the use of pharmacological interventions to treat what is primarily thought of as a *disease of the brain* (Deacon, 2013). Roseman et al. (2022) emphasise the necessity of interdisciplinary integration if psychedelic medicines are to successfully enter the mainstream, suggesting a shift towards the *biopsychosocial model.* This model is based on the concept that health results from the interaction between psychological, biological, and social factors (Engel, 1977). In recent years this model has been expanded upon to include alternative therapies, a field now known as *Integrative Medicine* (Maizes et al., 2009). In addition to the factors listed above, integrative medicine considers spirituality essential in understanding an individual and their health holistically, with some even advocating for the use of *the biopsychosocial-spiritual* model (Maizes et al., 2009; Saad et al., 2017; Sulmasy, 2002). The rise in mental health concerns has also been accompanied by a decrease in spirituality in the West (Weber & Pargament, 2014). It has been suggested that the two are interlinked; whether due to the mental states achieved through spiritual practices, or

from the community aspect derived from involvement in such rituals (Weber & Pargament, 2014).

Traditional views are being adapted and incorporated into modern psychotherapeutic frameworks, blending Eastern and Western principles. Examples include yoga and mindfulness, with the latter now offered as a first line treatment for patients with *less severe depression* over medication by the National Institute for Clinical Excellence (NICE) (Gregory, 2021). Psychedelics have long been said to give access to profound spiritual experiences and are thought to have a mediator role in spirituality (Hartogsohn, 2018; Sessa, 2012). Evidence is mounting that ayahuasca may be effective in managing a variety of psychiatric conditions (Reiff et al., 2020), as well as physical illnesses such as neurodegenerative disorders (Morales-García et al., 2017) and potentially cancer (Schenberg, 2013). Furthermore, there has been a recent surge in funding into psychedelic research (Australian Government Department of Health, 2022), with a multitude of clinics arising across the globe offering psychedelic-assisted therapy (Cohen, 2021; van Wylich-Muxoll, 2021). It is possible that alternative treatments such as the Amazonian use of ayahuasca investigated in this thesis may be conducted in clinical settings in another form of cultural convergence. Recently, in the United States, ayahuasca has been granted legal exemptions for use in religious contexts, suggesting perceptions around the use of psychedelics are changing (Labate, 2012b). The pseudo-Christian framework used appears to have developed as indigenous Amazonian customs have blended with the Catholic traditions of more recent settlers (Labate, 2012b). Studies on these communities have shown lower levels of anxiety, panic-like states, and hopelessness compared to the general population (Santos et al., 2007).

Psychoactive compounds appear to have been used throughout history by a variety of traditional communities (Luna, 2000; McKenna, 1999; Naranjo, 1986; Schaefer, 2006). In northern Mexico the Huichol people use Peyote cactus which contains mescaline (Schaefer, 2006); the Mazatecs work with psilocybin mushroom (Metzner, 2005); Iboga is used by the Bantu tribes in Gabon; and ayahuasca is used ceremonially by many communities within the Amazonas (Luna, 2000). Such communities appear to have developed their own frameworks that maximise therapeutic potential by optimising set and setting, resulting in culturally sanctioned ceremonial traditions. Many of these traditions appear to share commonalities, for example the use of incense, perfumes, and guiding songs (Luna, 2011).

At this stage it cannot be determined if the therapeutic effects occasioned by ayahuasca are due to pharmacology, the shamanic framework, or a combination of the two. Irrespective of the above, scientific investigation is essential to limit the effects of anecdotal sensationalism, to develop therapeutic protocol, establish risks and to identify avenues for future research. Researchers are now exploring techniques employed by traditional practitioners to inform psychedelic-assisted psychotherapy (Schenberg, 2018). The typical PAP protocol involves psychotherapeutic sessions to prepare participants, followed by a small number of active sessions with the psychoactive compound, followed by integration sessions. This structure has been said to be similar to ayahuasca practices within retreat-based frameworks (Argento et al., 2019). In fact, many aspects of the psychedelic-assisted modality of psychotherapy have been said to have been informed by shamanic disciplines (Metzner, 1999; Mithoefer et al., 2008). Such a framework was observed in the empirical research included within this thesis, in which participants experience psychedelic states in a reasonable amount of sensory deprivation (in the dark), whilst a facilitator (*shaman*/*curandero*) sings traditional songs, believed to optimise the ayahuasca experience.

Unlike psychostimulants and opiates, psychedelic drugs are generally considered psychologically safe (Nutt et al., 2010; Rucker, 2015; Strassman, 1984). Inappropriate use has, however, been associated with psychological distress and even harm (Nichols, 2016). Evidence also suggests this extends to ayahuasca (Bouso et al., 2012; Guimarães et al., 2021). Wellbeing and life purpose has been found to be higher in long-term ayahuasca drinkers in cross-sectional studies. In addition to this, improved executive functioning and decreased levels of psychopathology have been found when compared to those not drinking ayahuasca (Bouso et al., 2012; Lawn et al., 2017). Furthermore, reduced grief, improved quality of life, and lower levels of panic and hopelessness have been identified (Gonzalez et al., 2021; González et al., 2020; Kaasik & Kreegipuu, 2020). Effects comparable to an eight-week mindfulness course have been described after one ayahuasca session, with increases in participants' mindfulness capabilities and ability to regulate emotion (Soler et al., 2016).

Ayahuasca has shown therapeutic potential when investigated in both controlled and field settings (Bouso et al., 2013; Bouso et al., 2012; Fábregas et al., 2010; Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016; Uthaug et al., 2021; Uthaug et al., 2018; Zeifman et al., 2021). To date, most research into the use of ayahuasca in humans has taken place in syncretic church settings (Barbosa et al., 2009; Barbosa et al., 2005; Bouso et al., 2012; Callaway et al., 1994; Fábregas et al., 2010; Labate, 2012a; Santos et al., 2007), with a small number of studies in neo-shamanic settings (Kavenská & Simonová, 2015; Uthaug et al., 2021; Uthaug et al., 2018) and retreat centres following a traditional framework (Gonzalez et al., 2021; González et al., 2020; González et al., 2019; Weiss et al., 2021). The research included in this thesis is amongst the first to investigate the use of ayahuasca in a traditional Shipibo setting adapted for tourists. To further understand the therapeutic potential of the brew and the

role that setting has on outcome, further research into its use in a traditional indigenous Amazonian setting is required.

Overview of Papers

Rationale for Studies Included in Thesis

The use of ayahuasca is spreading rapidly in the West, with a host of outlets discussing the therapeutic potential of the brew. Ayahuasca is thought to have first come to mainstream attention in the Global North when William Burroughs published *The Yagé Letters* (Burroughs, 1963), describing his experiences with the tea. Since this time ayahuasca has been referenced in many articles and news reports, such as the South China Morning Post (Knott, 2020) and the British Telegraph (Haigh, 2020), and has made appearances in various documentaries (BBC, 2008), films such as *Wanderlust* (2012) and *Blueberry* (2004), and reality television shows including *Extreme Celebrity Detox* (2005) and *Anthony Bourdain's No Reservations* (2006). Ayahuasca has been referenced in the health and lifestyle section of fashion magazines such as *Elle* (2014), *Vanity Fair* (2011) and *Marie Claire* (2014), as well as in travel guides including the in-flight magazine used by *Delta Airways* and on *tripadvisor.com*, where individuals can even rate their ayahuasca retreat experiences (Hudson & Walker, 2011).

In response to the dramatic increase in popularity, various academics, *shamans*, and self-proclaimed experts have devoted their time and energy to distributing information regarding the brew (Tupper, 2009). This has resulted in a multidisciplinary space, populated by artists, such as *Alex Grey* (Grey, 1990), inspired musicians such as *Sting* and Paul Simon, which has also given a voice to indigenous leaders, neuroscientists, psychiatrists, and anthropologists at conferences such as the *World Ayahuasca Conference* (ICEERS, 2019).

The multidisciplinary nature of ayahuasca is evident, with many disciplines providing a unique perspective on the brew. Despite the complexities associated with the investigation of a subject

open to multiple disciplines, to minimise harm in our current *age of misinformation* (Bessi et al., 2015), accurate information is required whilst allowing for scope in methodologies utilised. As such, this thesis is comprised of a complementary set of five studies, adopting a range of methodologies that sought to outline the mechanism of action of the brew, as well as potential therapeutic outcomes. In addition, qualitative data is included to provide a more holistic view on participants' experiences in jungle ayahuasca ceremonies. Participants included in qualitative study were from the same sample as used Ruffell et al. (2020; Appendix C), whereas for the remainder of papers in this thesis unrelated populations were used.

The Pharmacological Interaction of Compounds in Ayahuasca: A Systematic Review

Ruffell, S., Netzband, N., Bird, C., Young, A. H., & Juruena, M. F. (2020). The pharmacological interaction of compounds in ayahuasca: a systematic review. Brazilian Journal of Psychiatry, 42, 646-656. DOI:10.1590/1516-4446-2020-0884 (Appendix A).

SR contributed to the conceptualisation, design, data acquisition and analysis, and write-up of this manuscript.

Study Rationale

As various scholars and companies debate which chemicals in ayahuasca are required to achieve positive outcomes, questions remain regarding which components are essential, how they interact, and what happens if they are removed. The MAOIs in ayahuasca allow for the bioavailability of DMT (Mckenna, 2004), however, it is currently unclear as to whether these

compounds interact synergistically or merely additively. As such, I conducted a review of the available literature surrounding the pharmacology of ayahuasca.

Methodology

The PubMed, PsycINFO, and Web of Science databases were searched through September 2019 for the following terms: (ayahuasca OR DMT OR dimethyltryptamine) AND (B-carboline OR constituents OR chemistry OR harmine OR harmaline OR harmala alkaloids OR tetrahydroharmine OR harmalol OR MAOI OR monoamine oxidase inhibitor OR pharmacology OR pharmacokinetics OR pharmacodynamics OR psychopharmacology OR synergy). The reference lists of relevant studies were checked for additional papers, and secondary searches were performed using related keywords. A total of 2,141 papers were identified, of which 1,957 were extracted, following the removal of duplicates. A review of the titles and abstracts eliminated all but 202 papers, which were screened in greater detail for eligibility. The abstracts, methods, and findings of these papers were assessed, reducing the number to 57 for full text analysis. A total of 16 studies examined the pharmacology of ayahuasca as a brew or its known active compounds, either isolated or synergistically, and were included in the review. Only papers that had undergone full peer review and were published in English were included. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009).

Summary of Results

Table 1

Summary of studies included in systematic review

Authors	Title	Findings	Further comments
McKenna et al. (1984)	Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and ß-carboline constituents of ayahuasca	-Showed MAOI effect in vitro. -Proposes that inhibition experiments using mixtures of ß-carbolines indicate that their effects in combination are additive, rather than synergistic or antagonistic.	-Original proposal regarding DMT deamination prevention via MAOI in harmala alkaloids from P. viridis.
Callaway et al. (1994)	Platelet serotonin uptake sites increased in drinkers of ayahuasca	-Increased number of serotonin mRNA transporter sites in regular ayahuasca drinkers against control group.	-Shows an increased number of binding sites in platelets. -No evidence of this for DMT alone, which is suggestive of a synergistic effect.
Strassman et al. (1994)	Dose-response study of N, N-dimethyltryptamine in humans	-Peak DMT blood levels and subjective effects were seen within 2 minutes after drug administration and were negligible at 30 minutes. -DMT dose-dependently elevated blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to elevating blood concentrations of ß-endorphin, corticotropin, cortisol, and prolactin. Growth hormone blood levels rose equally in response to all doses of DMT, and melatonin levels were unaffected. -Threshold doses for significant effects relative to placebo were also hallucinogenic (> 0.2 mg/kg)	-Dose-response data for IV DMT fumarate, neuroendocrine, cardiovascular, autonomic, and subjective effects in a group of experienced hallucinogen users.

		-Subjects exposed five or more times to 3,4-methylenedioxymethamphetamine had less robust pupil diameter effects than those exposed two times of less. -Evidence that DMT is unique in the inability to develop tolerance to its psychological effects.	
Smith et al. (1998)	Agonist properties of N, N-dimethyltryptamine at serotonin 5-HT2A and 5-HT2C receptors	-DMT fully substituted for DOI. Intact choroid plexus was used to evaluate the agonist properties at endogenous 5-HT2C receptors. -DMT was a partial agonist at 5-HT2C receptors in this native preparation. -DMT behaves as an agonist at both 5-HT2A and 5-HT2C receptors. -One difference was evident in that the 5-HT2C, but not the 5-HT2A, receptor showed a profound desensitization to DMT over time (suggestive of limited application for repeat prescription).	-Evidence of DMT 5HT2a(c) agonism.
Callaway et al. (1999)	Pharmacokinetics of Hoasca alkaloids in healthy humans	-THH shows PK profile independent to harmine. -Affinities and other PK values provided.	-Evidence that THH alone may be a weak SSRI. -Implies further synergistic effects on the serotonin system.
Ott (1999)	Pharmahuasca: human pharmacology of oral DMT plus harmine	-MAO inhibition from simultaneous ingestion of ß-carbolines confirmed by eight self-experimenters. -Results of a total of some 70 bioassays are summarized and the literature on this subject is reviewed.	-Evidence that DMT and harmine in tablet form create similar effects to ayahuasca, further reinforcing the DMT MAOI interaction. -When orally ingested, DMT without harmine is non-active.
Glennon et al. (2000)	Binding of ß-carbolines and related agents at 5-HT2, 5-HT1A, dopamine (D2) and benzodiazepine receptors	-Affinity scores at 5-HT2 for harmine/harmaline.	-Shows that other harmala alkaloids also bind to the 5HT2 receptors, further suggesting synergistic potential in the serotonergic system.

Riba et al. (2003)	Human pharmacology of ayahuasca	-Diastolic blood pressure significant increase. -Heart rate moderate increase. -Increased urinary normetanephrine excretion. -Deaminated monoamine metabolite levels did-not decrease (contrary to typical MOAI effect profile). -The negligible harmine plasma levels found suggest a predominantly peripheral (gastrointestinal and liver) site of action for harmine.	-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca. -PK angle. -Small sample size (n=18).
Riba et al. (2006)	Increased frontal and paralimbic activation following ayahuasca	-Significant activation of frontal and paralimbic brain regions. -Increased blood perfusion observed bilaterally in anterior insula, gather intensity in right hemisphere, and anterior cingulate/frontal medial cortex of right hemisphere. -Increases observed in left amygdala/parahippocampal gyrus. -Concludes that ayahuasca interacts with neural systems that are central to interoception and emotional processing.	-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca. -Neuroimaging angle. -Used SPECT.
Fortunato et al. (2010)	Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus	-Increased BDNF protein levels in rat hippocampus. -Concludes that findings within support the hypothesis that harmine could bring about behavioural and molecular effects.	-Further evidence that the synergistic mechanisms of DMT + harmine are more than just effects of MAOIs.
dos Santos and	Autonomic, neuroendocrine, and immunological effects of	-Significant increases in prolactin. -Percentage of CD3/4 were decreased, natural killer cells increased.	-Focuses on the synergistic effects of ayahuasca rather than individual action of compounds.

Strassman (2011)	ayahuasca: a comparative study with D-amphetamine	-Maximum changes occurred around 2 hours, returned to baseline after 24 hours. -Ayahuasca displayed moderate sympathomimetic effects, significant neuroendocrine stimulation, and time-dependent modulatory effect on cell-mediated immunity.	-Immunological, rather than neuropsychological, perspective.
McIlhenny et al. (2011)	Methodology for determining the major constituents and metabolites of the Amazonian botanical medicine ayahuasca in human urine	-Showed that the major metabolite of a DMT is the corresponding DMT-NO, the first time this metabolite has been described in *in vivo* studies in humans. -Very little DMT detected in urine, despite the MAOI. -Major alkaloid excreted was THH. -List of other products and metabolites quantified.	-Provides methodology for identifying and quantifying constituents of ayahuasca in human urine. -PK data of tested samples provided. Excretion and metabolism of THH should be further investigated.
McIlhenny et al. (2012)	Methodology for determining major constituents of ayahuasca and its metabolites in blood	-DMT concentrations lower than DMT-NO at all time points. -Harmine and harmaline present in most samples. -Plasma DMT-NO concentrations three to four times higher than DMT. -DMT-NO forms rapidly after drug administration.	-Single methodology combining HPLC and gas chromatography to identify ayahuasca constituents in blood following oral consumption. -First report of presence of DMT-NO in human blood following ayahuasca/DMT administration. -Method for the most complete profile of DMT, harmala alkaloids, and metabolite concentrations. -THH levels peaked at around 4.5 hours.

Riba et al. (2012)	Metabolism and disposition of N, N-dimethyltryptamine and harmala alkaloids after oral administration of ayahuasca	-Less than 1% of DMT excreted unchanged. -The recovery of each harmala alkaloid plus its 0-demethylated metabolite varied greatly (between 9 and 65%). -Fifty per cent was recovered as indole-3-acetic acid or DMT-NO. -Ten per cent was other MAO-independent compounds. -Recovery of DMT plus metabolites reached 68%. -Harmol, harmalol, and THH conjugates were abundant in urine.	-PK study with implications regarding alternative metabolic routes for DMT other than biotransformation by MAO. -Freeze-dried ayahuasca. -Urine samples obtained. -Small sample (n=10).
Morales-García et al. (2017)	The alkaloids of *Banisteriopsis caapi*, the plant source of the Amazonian hallucinogen ayahuasca, stimulate adult neurogenesis *in vitro*	-Significant neurogenesis in adult hippocampal cells *in vitro* with harmine.	-Suggests that ayahuasca brew may have more complex synergistic properties than we currently understand. -Shows that harmine alone could be partially responsible for the neurological changes seen in ayahuasca users.
Sampedro et al. (2017)	Assessing the psychedelic "after-glow" in ayahuasca users: post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities	-Magnetic resonance spectroscopy showed post-acute reductions in glutamate + glutamine, creatine, and N-acetylaspartate+N-acetylaspartylglutamate in the posterior cingulate cortex. -Connectivity was increased between the posterior cingulate cortex and the anterior cingulate cortex, and between the anterior cingulate cortex and limbic structures in the right medial temporal lobe.	-DMN activity decrease and increased neural connectivity to other areas of the brain. -Supported by other studies on 5HT2a agonists.

	-Glutamate + glutamine reductions correlated with increases in the "nonjudging" subscale of the Five Facets Mindfulness Questionnaire-Increased anterior cingulate cortex-medial temporal lobe connectivity correlated with increased scores on the self-compassion questionnaire. -Post-acute neural changes predicted sustained elevations in nonjudging 2 months later.	-Long-term neurological differences found after ayahuasca administration.

BDNF = brain-derived neurotropic factor; DMN = default mode network; DMT = N,N-dimethyltryptamine; DMT-NO = DMT-N-oxide; DOI = 2,5-dimethoxy-4-iodoamphetamine; HPLC = high-performance liquid chromatography; IV = intravenously; MAO = monoamine oxidase; MAOI = MAO inhibitor; PK = pharmacokinetic; SPECT = single photon emission tomography; SSRI = serotonin reuptake inhibitor; THH = tetrahydroharmine.

Integration with extant literature

This systematic review shows that two of the constituents in ayahuasca, DMT and harmine, have been studied significantly more than the secondary harmala alkaloids (MAOIs). It appears there may be more synergistic mechanisms present than we currently understand. This is derived from data pertaining to individual constituents, which often shows overlapping biochemical and pharmacokinetic action. It is unclear at present whether these actions are of a true synergistic nature or are additive. Evidence suggests, despite the lack of solid data on synergy, that ayahuasca may have promising antidepressant qualities.

Increasing numbers of studies are being published focusing on DMT and other serotonin agonists (Carhart-Harris et al., 2021; Mitchell et al., 2021; Mithoefer et al., 2018; Palhano-Fontes et al., 2019; Ross et al., 2016; Rucker et al., 2019; Schartner & Timmermann, 2020; Strassman, 2000; Timmermann et al., 2019; Timmermann, Spriggs, et al., 2018). There is, however, a vast number of anthropological and qualitative articles which emphasise the importance of Banisteriopsis caapi. Traditional ayahuasca is composed of the Banisteriopsis caapi vine, with a DMT containing plant, usually Psychotria viridis, with the vine being the only consistent requirement for the brew (McKenna et al., 1984). In the Peruvian Amazon the term ayahuasca is also commonly used to indicate the vine only.

The harmala alkaloids reduce the deamination of DMT by MAO-A during first-pass metabolism, resulting in the subsequent absorption and distribution of this potent psychedelic (Yritia et al., 2002). The alkaloids are derived from β-carbolines, and their potential psychotropic properties have been discussed since research into psychedelic substances began (Naranjo, 1967). In recent times, researchers have started to focus their attention on the β-carbolines and their role in treating mental health conditions (Dos Santos & Hallak, 2017). The

β-carbolines have been demonstrated to have a variety of biological actions, including anxiolytic, anticonvulsant and sedative effects, largely due to their interactions with serotonin and benzodiazepine receptors (Cao et al., 2007).

Papers that assess the levels of constituents in various brews and compare these to therapeutic outcomes have been summarised in Table 2. Due to the lack of heterogeneity between the study designs it is difficult to draw meaningful conclusions by comparing the outcomes of the studies. The table does however demonstrate that the ratio of constituents, as well as the dose of the brew, has an impact on mental health outcomes.

Table 2

Summary table of studies reporting constituency and psychometrics (i.e., depression, anxiety, wellbeing, and perceived peak experiences)

Reference	Study Design			Constituent				
	Tradition	Design	Sample Size (n)	DMT (mg/ml)	THH (mg/ml)	HRL (mg/ml)	HRM (mg/ml)	Total Dosing Sessions
Osório et al. (2015)	Church - Santo Diame	Open label RCT	6	0.8	NA	NA	0.21	1
Gonzalez et al. (2021)	Traditional - Shipibo	Observational	200	2	1-2	0.37-0.65	2	1 to 12
González et al. (2020)	Traditional - Shipibo	Observational	50	2	1-2	0.37-0.65	2	4 to 9
Uthaug et al. (2018)	Neo-Shamanic	Observational	30	1.90	NA	4.9	2.4	1
Uthaug et al. (2018)	Shamanic	Observational	27	0.95	NA	0.35	6.305	1
Palhano-Fontes et al. (2019)	Church - Barquinha	Placebo Control RCT	29 (14 active, 15 control)	0.36	1.2	0.24	1.86	1
Uthaug et al. (2021)	Neo-Shamanic	Placebo Control Observational	30 (14 active, 16 control)	3.6	NA	0.7	10.1	2

THH = tetrahydroharmine, HRL = harmaline, HRM = harmine

Reference	Depression: P Value (Cohen's D)				Anxiety: P Value				Wellbeing: P Value				Peak: P Value	
	Scale	T1-T2	T1-T3	Dep T1-T4	Scale	T1-T2	T1-T3	T1-T4	Scale	T1-T2	T1-T3	T1-T3	Scale	Peak T1
Osório et al. (2015)	HAM-D MADRS	0.01 0.01	0.01 0.003	0.11 0.009	BPRS-AD	0.02	0.02	0.02	-	-	-	-	-	-
Gonzalez et al. (2021)	-	-	-	-	-	-	-	-	PWBS	0.01	0.01	0.01	-	-
González et al. (2020)	SA-45 D	0.001	0.01	0.1	SA-45 A	0.001	0.001	0.01	WHO-QOL-B	0.001	0.001	-	-	-
Uthaug et al. (2018)	DASS-21	0.001	0.001	-	DASS-21	NS	NS	-	SWLS	0.027	NS	-	EDI	0.001
Uthaug et al. (2018)	DASS-22	0.001	0.001	-	DASS-22	NS	NS	-	SWLS	0.027	NS	-	EDI	0.001
Palhano-Fontes et al. (2019)	MADRS	0.04 (0.84)	0.04 (0.84)	0.0001 (1.49)	-	-	-	-	-	-	-	-	MEQ	0.004
	HAM-D	-	-	0.019 (0.98)	-	-	-	-	-	-	-	-	HRS	0.0001
Uthaug et al. (2021)	DASS-21	0.017	-	-	DASS-21	0.032	-	-	-	-	-	-	EDI	NS

NS = non-significant

It should be noted that some of the papers did not document tetrahydroharmine levels (Osório et al., 2015; Uthaug et al., 2021; Uthaug et al., 2018). This is the only constituent in the brew that has been demonstrated to function as an SSRI and an MAOI, both used in the treatment of depression, with SSRIs being the current *gold standard* (Brunoni et al., 2009; Callaway et al., 1999). While it is unclear if this omission was from the brew altogether or simply from the constituency analysis, these particular studies coincidentally described non-significant changes in anxiety, wellbeing, and peak experience measures. Furthermore, due to inconsistencies in dose administration and consistency ratios between studies, the extent to which outcomes related to dose response and pharmacokinetics remains unclear. Nonetheless, these studies suggest that the harmala alkaloids do have a role in psychometric changes alongside DMT.

The Properties of the Harmala Alkaloids

Each of the harmala alkaloids has been associated with different effects, psychologically, pharmacologically, and pharmacokinetically. Table 3 summaries the therapeutic and psychoactive effects of each of the harmala alkaloids and Table 4 provides an overview of their pharmacokinetic profile.

Table 3

The therapeutic and psychoactive effects of the harmala alkaloids

Therapeutic and psychoactive effects	**Reference**	**Harmine**	**Harmaline**	**Tetrahydroharmine**
Antidepressant properties	(McKenna et al., 1984)	X	X	X
Anxiolytic properties	(Ebrahimi-Ghiri et al., 2019) (Khan et al., 2013)	Not assessed	X	Not assessed
Increases serotonin and norepinephrine	(McKenna et al., 1984)	X	X	X
Raises dopamine levels in CNS	(Pimpinella & Palmery, 1995)	X	X	Not assessed

Anti-addictive properties	(Aricioglu-Kartal et al., 2003; Brierley & Davidson, 2012; Owaisat et al., 2012)	X	Not assessed	Not assessed
Diabetes management - mitogenic for human beta cells (Likely target DYRK1A)	(Wang et al., 2015)	X	Not assessed	Not assessed
Induce brain plasticity and neurogenesis	(Morales-García et al., 2017)	(Harmine metabolite harmol)	X	X
Upregulates 5-HT receptor density	(Callaway et al., 1994; McKenna et al., 1998)	Not assessed but unlikely (Graham et al., 1987)	Not assessed but unlikely (Graham et al., 1987)	X
Hallucinogenic properties (at high doses)	(Buckholtz & Boggan, 1977; Naranjo, 1967; River & Lindgren, 1972)	Gunn and Marshall (1920) suggest it is at 2mg/kg i.v. or 8mg/kg po	1 mg./kg. i.v. or 4 mg./kg. po (Naranjo, 1967)	?300mg but unclear (Gunn & Marshall, 1920)
Increases the number of nerve progenitor cells (may be important in treatment of damage by drug use)	(Dakic et al., 2016)	X	Not assessed	Not assessed

X = present

Hallucinations, vomiting, confusion, and ataxia are thought to be due to central nervous system stimulation by MAOIs (Hamill et al., 2019). In a study by Glennon et al. (2000), the harmala alkaloids were found to bind to 5-HT2 receptors with a similar affinity to DMT. The psychedelic properties of both harmaline and harmine are thought to arise from their binding at the 5-HT receptors (Riba et al., 2003).

Table 4

Overview of the pharmacokinetic profile of the harmala alkaloids with DMT for comparison

Overview of Pharmacokinetics	**DMT**	**Harmine**	**Harmaline**	**Tetrahydroharmine**
Pharmacokinetics profile (Callaway et al., 1999)	-	Pharmacokinetic profile correlates with that of DMT	-	Pharmacokinetic profile independent of harmine
Cmax (ng/ml)	15.8 ± 4.4	114.8 ± 61.7	6.3 ± 3.1	91.0 ± 22.0
Tmax (min)	107.5 ± 32.5	102.0 ± 58.3	145.0 ± 66.9	174.0 ± 39.6
AUC (mg min/ml)	5.60 ± 4.53	22.88 ± 11.69	-	47.78 ± 25.88
T 1/2 (min)	259.4 ± 207.2	115.5 ± 60.1	-	531.9 ± 290.8
IC50 (μM) (Passos et al., 2014)	-	MAO IC50 = 0.013	MAO IC50 = 0.016	MAO IC50 = 1.77
	-	MAO-A IC50 = 0.002	MAO-A IC50 = 0.003	MAO-A IC50 = 0.074
	-	MAO-B IC50 = 20	MAO-B IC50 = 25	MAO-B IC50 = 100
5HT2A binding capacity (Ki) (Glennon et al., 2000)	-	397	5010	>10000

Harmine

Of all the β-carboline alkaloids in ayahuasca, harmine is present in the highest concentration. It is associated with numerous therapeutic effects, such as astrocytic function restoration, anti-inflammatory effects, human neural progenitor cell the proliferation, and increases in levels of BDNF (Abelaira et al., 2013; Dos Santos & Hallak, 2017; Liu et al., 2017; Morales-Garcia et al., 2020; Morales-García et al., 2017). Other research has also indicated the role of harmine in the treatment of addiction, specifically in reducing relapse rates from methamphetamine, cocaine, and alcohol via dopamine neurotransmission (Aricioglu-Kartal et al., 2003; Owaisat et al., 2012). Harmine also displays affinity at both the DYRK1A and imidazoline I2 binding

sites, a property which has potential in the pharmacological management of drug dependence (Brierley & Davidson, 2012). Dakic et al. (2016) also report that harmine exerts proliferative effects in human neural progenitors, by inhibiting DYRK1A. This has been suggested as a potential mechanism behind the antidepressant effects of the brew. Harmine may also have potential in the management of diabetes, and has shown potential in improving glycaemic control, increasing islet mass, and inducing beta cell proliferation (Wang et al., 2015).

Glutamine synthetase and glial-specific excitatory amino-acid transporter expression (glutamate transporter-1 (GLT-1), glutamate/aspartate transporter (GLAST)) can be altered in the brain tissue of those suffering from depression (Bernard et al., 2011; Choudary et al., 2005). Several different investigations utilising animal models have shown GLT-1 protein and gene expression are increased by harmine, as is the uptake of glutamate (Li et al., 2011; Liu et al., 2017; Sun et al., 2014). Harmine has also been found to protect against the effects of chronic unpredictable stress in mice, such as reduced levels of glial fibrillary acidic protein (Liu et al., 2017). This suggests that its antidepressant action may be due to the renewal of astrocytic function. In addition, Liu et al. (2017) found harmine enhanced outcomes in the forced swimming test and also protected mice against stress when undergoing the tail suspension test.

BDNF signal restoration is hypothesised to mediate the antidepressant effects of harmine. Fortunato and colleagues showed this by administering harmine to rats both acutely (Fortunato et al., 2009) and chronically (Fortunato et al., 2010), finding improvements in both the open field and forced swimming tests. Both studies also demonstrated increased hippocampal BDNF levels, when compared to treatment with imipramine. Liu et al. (2017) found when mice were exposed to chronic unpredictable stress and were not given harmine, levels of BDNF did not

increase, nor did hippocampal neurogenesis occur. These findings suggest harmine may result in molecular and behavioural outcomes like antidepressants drugs.

Morales-García et al. (2017) found that tetrahydroharmine, harmaline, and harmol (the metabolite of harmine), induce neurogenesis in adults *in vitro* via neural stem cell differentiation, migration, and proliferation. The authors conclude that the *Banisteriopsis caapi* β-carbolines appear to have the ability to induce brain plasticity, thereby showing potential in the treatment of various neurological and psychiatric conditions. Interestingly, in a subsequent study Morales-Garcia et al. (2020) showed that DMT led to the generation of new neurones via activation of the sub granular hippocampal dentate gyrus – the predominant neurogenic niche in adults. This research, conducted in mice, showed subsequent improvements in memory, demonstrating the functional relevance of the above findings. Furthermore, SIGMAR-1 activation appeared to underlie the neurogenic effects of DMT. The authors conclude that DMT induces the growth of new hippocampal neurones, promotes the migration of neuroblasts and regulates neural stem cell proliferation, largely via sub granular neurogenic niche activation, improving memory and spatial learning tasks as well as inducing neurogenesis (Morales-Garcia et al., 2020). The authors further highlight the potential antidepressant properties associated with neurogenesis, with DMT showing a considerably more potent neurogenic profile than the β-carbolines (Morales-Garcia et al., 2020; Morales-García et al., 2017).

Harmaline

Harmaline has been demonstrated to have numerous pharmacological functions including hypothermic and vasorelaxant activity, antitumoral, antimicrobial, antiplatelet, antileishmanial, and antiplasmodial effects (Khan et al., 2013). It has been found to be effective in managing various conditions associated with microbes, such as Candida albicans, Proteus vulgaris,

Staphylococcus aureus, Aspergillus niger, and Escherichia coli (Wink et al., 1998). Harmaline has been shown to minimise the proliferation of cells *in vitro* when investigating promyelocytic cell lines in humans, with the optimal dose being 6–10 µg/mL and higher doses of 15–30 µg/mL generally considered cytotoxic (Zaker et al., 2007). Naranjo (1967) found harmaline was hallucinogenic at 4 mg/kg when taken orally - about half the amount required to achieve psychedelic effects when compared to harmine. Of all the harmala alkaloids, harmaline is usually present in the lowest concentrations. Despite this, it exerts various pharmacological effects, such as antimicrobial and vasorelaxant properties, as well as being an anxiolytic and an antidepressant (Ebrahimi-Ghiri et al., 2019; Khan et al., 2013).

Tetrahydroharmine

Platelet serotonin uptake sites appear to increase in those who drink ayahuasca. This is thought to be associated with positive mental health effects, largely as this is deemed to be indicative of neuronal serotonin uptake activity, although the degree to which this actually reflects neuronal activity is debated (Callaway et al., 1994). Callaway hypothesised that tetrahydroharmine was responsible for the upregulation of 5HT uptake sites. He therefore commenced daily dosing with tetrahydroharmine over a six-week period, conducting SPECT scans of his own brain before and after the period of treatment. Central 5-HT receptor density was found to increase in his prefrontal cortex. Upon ceasing to consume tetrahydroharmine, SPECT scans revealed over several weeks that the density slowly returned to pre-dosing levels. Despite clear methodological issues, this one-man experiment suggests tetrahydroharmine may have potentially significant effects (McKenna et al., 1998).

Interestingly, tetrahydroharmine is the only component of the brew that is known to function as an SSRI, albeit weakly (Callaway et al., 1999). The psychoactive effects induced by

tetrahydroharmine are less prominent than that of harmine, with harmaline having the strongest effect of all the harmala alkaloids (Naranjo, 1967). Gunn and Marshall (1920) provided an oral administration of 300mg tetrahydroharmine to a single volunteer, who described similar hallucinogenic effects to 100mg of harmaline. Although limited conclusions can be derived from this single experiment, the results suggest the hallucinogenic effects of tetrahydroharmine are roughly one-third that of harmaline.

Callaway et al. (1999) noted that in the ayahuasca-using church, the UDV, teas with higher levels of tetrahydroharmine relative to harmine and harmaline were favoured by both church elders and the congregation. Findings in the Santo Daime confirm this observation (Kaasik et al., 2021). Callaway connected the variation of the relative concentration of tetrahydroharmine in ayahuasca brews to its variability in *Banisteriopsis caapi*. Kaasik et al. (2021) show that it may also depend on the preparation of the brew. Tetrahydroharmine is the reduction product of harmaline, and consequently levels of THH are generally found to be higher in preparations that are brewed for longer (Kaasik et al., 2021).

Although no quantitative data exists comparing the therapeutic effects of DMT combined with other harmala alkaloid containing plants such as *Peganum harmala* (Syrian Rue) to *Banisteriopsis caapi*, reports describing subjective experience can be consulted. Differences appear to exist and have been recorded in various forums, such as online forums and psychonautical guides to plant medicine: '*substituting, say, Syrian rue for the ayahuasca vine, even though the rue contains the same harmala alkaloids, does apparently make an experiential difference. The experience with rue has been described as crystalline, cold, overwhelming, erratic, and uncaring, compared with that of the ayahuasca vine, which has been described as warm, organic, friendly, and purposeful'* (Beyer, 2009)p253. It should

however be noted that the ratios in Syrian Rue are quite different to that of *Banisteriopsis caapi*, with Rue containing much higher levels of harmaline and lower levels of tetrahydroharmine (Moloudizargari et al., 2013). It is possible that this difference in ratio accounts for the qualitatively different experiences suggested above.

Study Relevance

Prior to this study there had not been a systematic attempt to elucidate the pharmacological basis of ayahuasca. Not only is this necessary to better understand its therapeutic effects and safety profile, but also to determine how specific components in the brew result in therapeutic outcomes. The latter is particularly important when considering the potential medicalisation of ayahuasca.

A Phenomenology of Subjectively Relevant Experiences Induced by Ayahuasca in Upper Amazon *Vegetalismo* Tourism

Wolff, T. J., Ruffell, S., Netzband, N., & Passie, T. (2019). A phenomenology of subjectively relevant experiences induced by ayahuasca in Upper Amazon vegetalismo tourism. *Journal of Psychedelic Studies*, *3*(3), 295-307. DOI: 10.1556/2054.2019.007 (Appendix B).

SR contributed to the conceptualisation, design, data collection, and write-up of this manuscript.

Study Rationale

There has been a substantial increase in the amount of quantitative research investigating the potential of ayahuasca therapeutically over the last decade. Although informative, numerical data fails to emphasise the impact that context has on the participant under study (Barbour, 2000), which is arguably essential when considering the indigenous ceremonial use of Amazonian ayahuasca. Furthermore, using only quantitative data limits our ability to determine the psychological processes underlying change in psychometrics. To address these issues, a heuristic study was conducted to further explore the phenomenology of the ayahuasca experience in a traditional setting.

Methodology

Participants underwent six ayahuasca ceremonies in a group setting at the Ayahuasca Foundation, Peru. Interviews took place in the morning, immediately after the second ayahuasca ceremony had finished. A narrative interview strategy was chosen (Küsters, 2009) to minimize any potential bias or leading questions relating to the study (Patton, 2002). Participants were asked to report what they had experienced during the ceremony, for example, "please tell me about your experiences during the ceremony as openly as possible." An open question about emotional experience was subsequently added to the narrative interview since, in contrast to traditional local ayahuasca use in the upper Amazon region (De Rios, 1972), the focus for western clients is often on psychotherapeutic processes (Beyer, 2009). Interviews were sound recorded. After transcription, interviews were analysed through qualitative content analysis (QCA) using a mixed data-driven strategy. A progressive-paraphrasing strategy was combined with a subsuming strategy (Schreier, 2012). This allowed for the extraction of themes and commonalities among subjective experiences, without prompting and overly influencing results. For the first interview, the material was cut into single statements; all statements

(coding units) were paraphrased to build up provisional main categories. Similar paraphrases with shared meaning were paraphrased again. In this way, abstract categories were formed. For the additional material, statements were used to build up subcategories, and further statements were either subsumed under these already existing subcategories or new subcategories were formed. The coding-frame was built up successively until a point of saturation was reached. After the ninth interview, no further categories had to be introduced to classify new material.

Summary of Results

One overarching topic was identified: *experiences during the ceremony* (Figure 1), along with two side categories: *appraisal of the process* (Figure 2) and *preparedness* (Figure 3). Various subthemes were identified from the main category, including *physical symptoms, received messages, visions and hallucinations, cognitive reactions, attribution of meaning, recognised meaning, emotional reactions, and reactions of the individual.*

Figure 1

Preparation, physical symptoms, phantasies, visions, received messages, cognitive reactions, and attribution of meaning reported after a shamanic ayahuasca ceremony in the Amazon region in narrative interviews of nine foreign participants using qualitative content analyses.

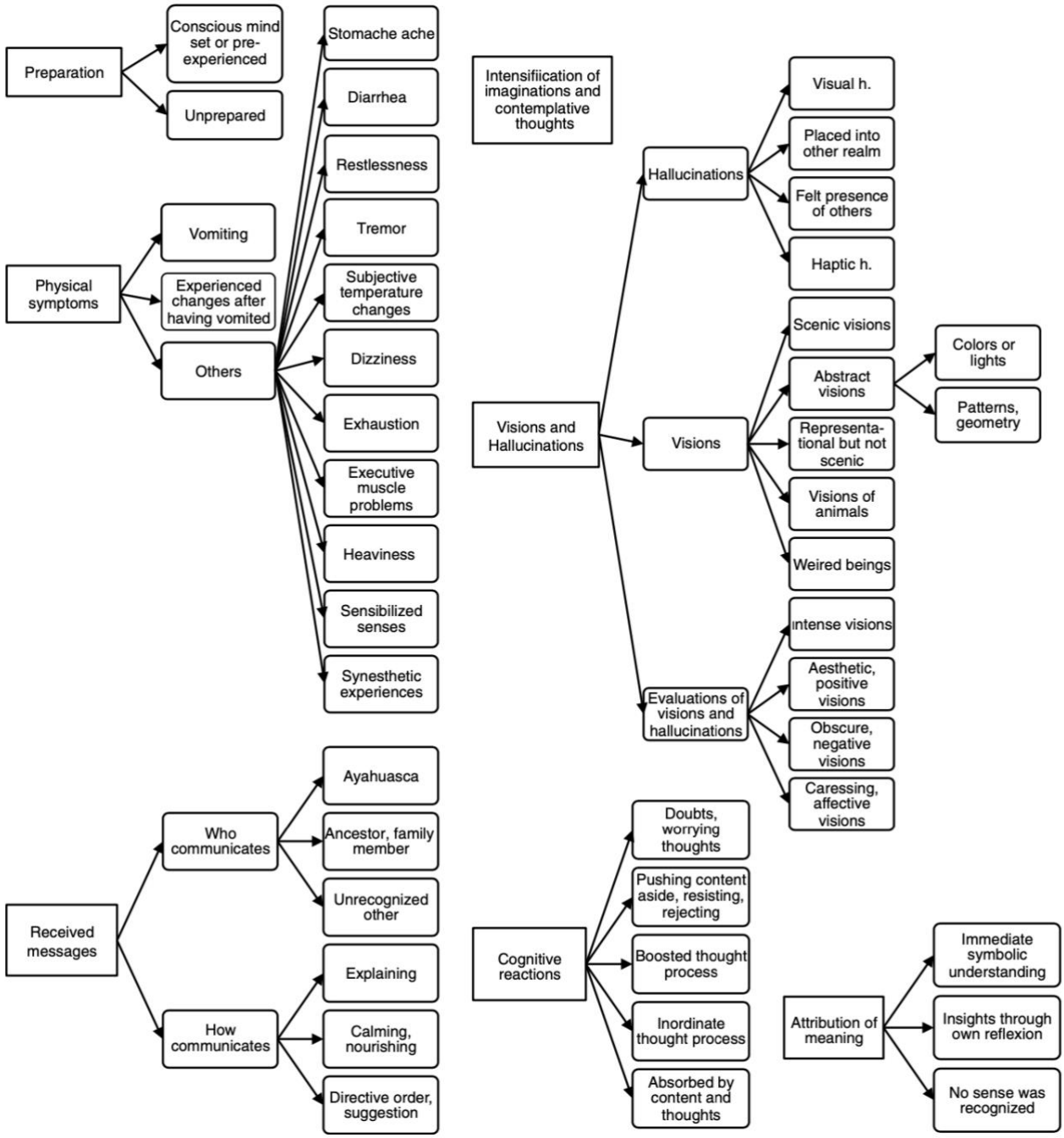


Figure 2

Recognized meaning of psychedelic content and emotional reactions reported after a shamanic ayahuasca ceremony in the Amazon region in narrative interviews of nine foreign participants using qualitative content analyses.

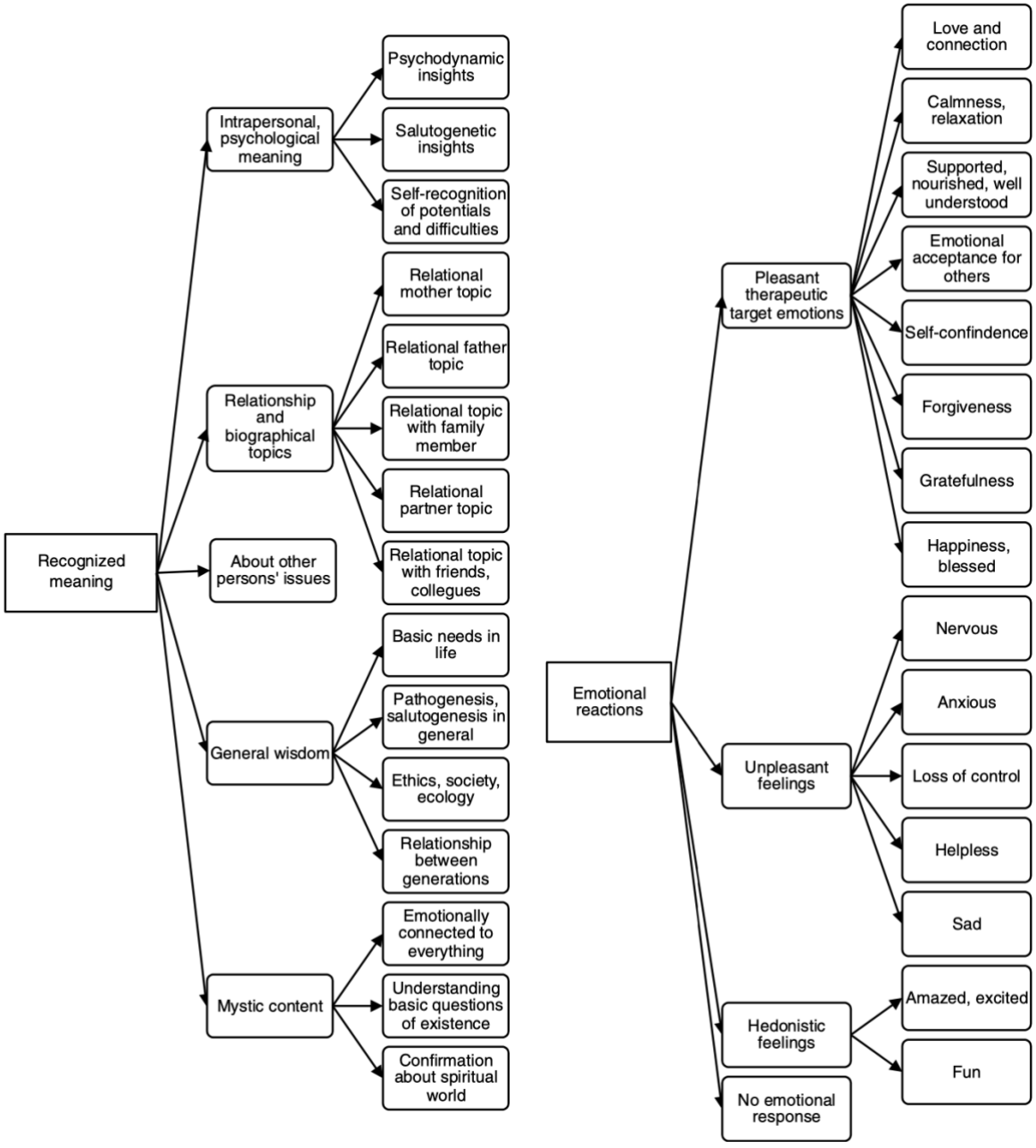
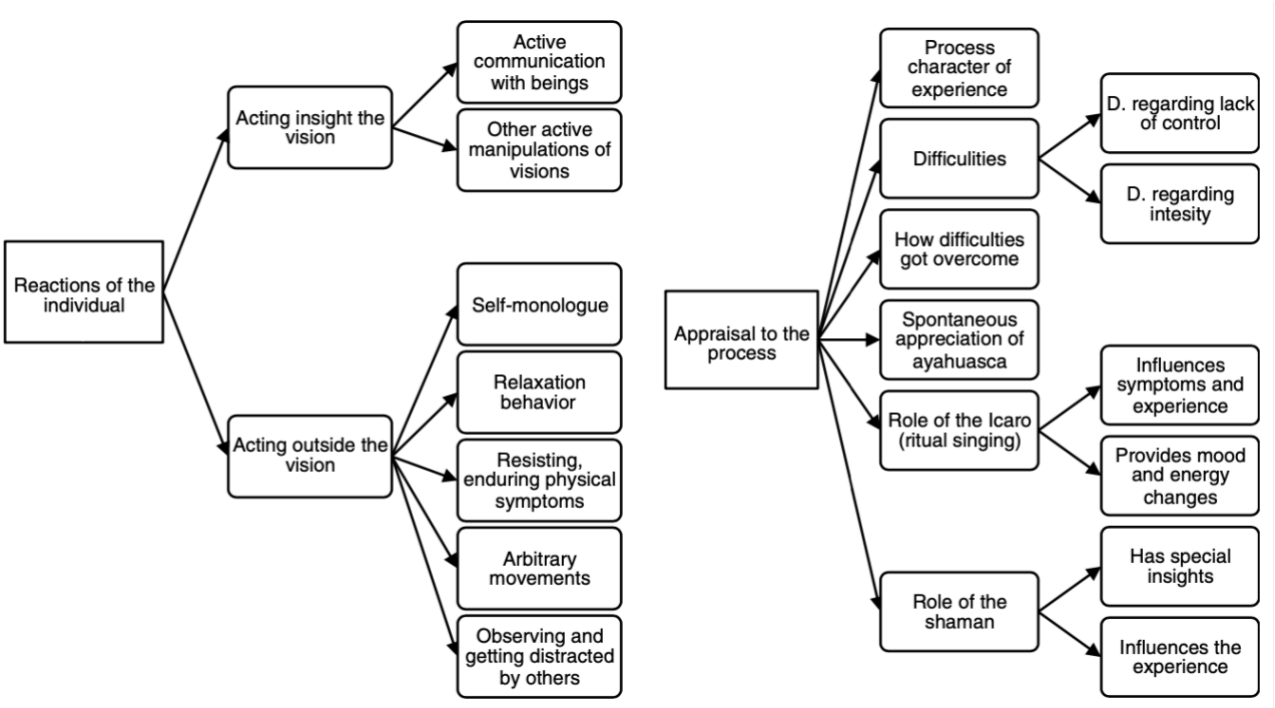


Figure 3

Appraisal of the process, role of ritual singing and of the shaman, individual reactions reported after a shamanic ayahuasca ceremony in the Amazon region in narrative interviews of nine foreign participants using qualitative content analyses.



Integration with extant literature

The study was designed to identify possible implications for psychedelic-assisted psychotherapy for Western clients using psychedelics as medicines, as well as commonalities in subjective experiences with ritualistic ayahuasca use in retreat settings. Although the use of coding manuals in QCA makes it less appropriate for deriving meaning, it does allow for rich phenomenological understanding of the participant's journey, with the potential to illuminate any psychotherapeutic processes that may have been occurring (Hsieh & Shannon, 2005).

Experiences During the Ceremony

Physical Symptoms

Although similarities exist between the subjective ayahuasca experience and other psychedelics, ayahuasca is unique in several domains. It has a prominent somatic component, with somatic symptoms comprising 12.43% of the qualitative reports. It is well established in the literature that both kinaesthetic and somatic awareness are enhanced throughout the ayahuasca experience (Espinoza, 2014; Kaufman, 2015; Shanon, 2002). Shanon (2014) describes the somatic aspect of the ayahuasca experience as the primary psychotherapeutic modality.

Those who drink ayahuasca often describe the sensation that something foreign has taken hold, frequently explained as an energetic force entering the body and nervous system at the start of ayahuasca ceremonies (Shanon, 2002). Furthermore, these physical effects can be interlinked with psychological insights and spiritual experiences (Shanon, 2002). Intimate awareness of body parts with a heightened awareness of proprioception is often connected to self-healing (Shanon, 2002, 2014). Participants engaging in ayahuasca ceremonies describe a spectrum of sensation, encompassing pain and emotional release from embodied trauma to an ecstatic sense of love and awe (Shanon, 2002).

Ayahuasca characteristically is associated with nausea and vomiting, leading some to refer to it as *la purga* (MacRae, 2004). The nauseating effects of the tea are largely due to the effect of the harmala alkaloids on stomach enzymes, and of DMT present in the intestines acting on serotonin receptors (Domínguez-Clavé et al., 2016; Gershon, 2004). Although vomiting would usually be considered a side effect of a drug, this is not so in the traditional use of ayahuasca (Tafur, 2017). Rather it is thought of as having significant therapeutic benefit, with users

reporting emotional release, psychological benefits, and even long-lasting transformative effects. Some traditions even refer to the purge as *getting well* (Gearin, 2016; Lafrance et al., 2017; Rush et al., 2021; Shanon, 2002, 2014).

Van der Kolk (2014) writes that to identify specific emotions connected to bodily sensations, one must be connected to deep psychological states. This in turn allows for better recognition, understanding and control of emotion. Brain imaging studies have shown that areas like the anterior insula and the paralimbic region are activated upon ayahuasca consumption (Riba et al., 2006). These areas are associated with emotional processing, interoception, and somatic awareness (Riba et al., 2006; Wang et al., 2019). Furthermore, disruptions in the anterior insular and consequently interoceptive processing are associated with a variety of disorders, such as depression (Wiebking et al., 2015), addiction (Paulus et al., 2013), childhood trauma and PTSD (Reinhardt et al., 2020). This theory forms the basis of somatic-orientated psychotherapies, which have recently attracted substantial interest (Davis, 2021). Interestingly, longitudinal research has also suggested decreased rates of bodily dissociation in ayahuasca drinkers (Kaufman, 2015).

Emotional Reactions

All participants interviewed in this study described emotional release and corrective emotional experiences as a result of drinking ayahuasca. These were divided into desirable, unpleasant, and hedonistic emotional states. Unpleasant emotional states were often followed by pleasant ones, suggesting potential resolution. This is in line with the psychotherapeutic processes associated with psychodynamic psychotherapy, for example, when challenging immature psychological defence mechanisms which consequently results in positive therapeutic outcomes (Drapeau et al., 2003; Owen et al., 2015; Perry & Bond, 2012). Furthermore, the

brew has been suggested to disable defence mechanisms, with participants left to face intense emotions and experiences directly (Nielson & Megler, 2014; Perkins & Sarris, 2021).

The quality of the acute psychedelic experience has been demonstrated with psilocybin to predict therapeutic efficacy (Roseman, Nutt, et al., 2018). Roseman and colleagues demonstrated that low Dread of Ego Dissolution (DED), a dimension of the Altered States of Consciousness (ACS) questionnaire assessing challenging experiences similar to anxiety, and high Oceanic Boundlessness (OBN) were found to predict positive outcomes on the Self-Reported Quick Inventory of Depressive Symptoms (QIDS-SR) at 5-week follow-up. Although this would appear to suggest challenging experiences during psychedelic sessions are negatively associated with therapeutic outcome, it appears a less simplistic viewpoint is required. In a subsequent study by Roseman et al. (2019), emotional breakthrough, a phenomena bearing similarity to the psychoanalytic principle of catharsis, was found to mediate long-term therapeutic outcome. This finding is in keeping with various therapist's accounts and modern phenomenological analyses emphasising the importance of working through challenging emotional states (Belser et al., 2017; Bonny & Pahnke, 1972; Gasser et al., 2014; Watts et al., 2017). Although challenging experiences have been shown to correlate with negative therapeutic outcomes (Roseman, Nutt, et al., 2018), it appears that if such experiences are resolved, as in the case with emotional breakthrough, they can successfully predict well-being in the long-term (Roseman et al., 2019).

Research has shown that drinking ayahuasca is associated with heightened self-love (Lafrance et al., 2021), which in turn improves interpersonal relationships and results in higher levels of empathy. Furthermore, those who consume the brew have been found to be more present in themselves, more self-aware, and have a greater degree of self-acceptance (Kjellgren et al.,

2009; Soler et al., 2016). These desirable emotional states have been found to be associated with improvements in psychological well-being (Perkins, Schubert, et al., 2021), as well as being a focus in various third wave Cognitive Behaviour Therapies (CBT), such as compassion-focused therapy, which have demonstrated positive effects in the literature (Gilbert, 2009).

Research suggests ayahuasca can improve the ability to observe thoughts and emotions from a state of detachment (Fresco et al., 2007). Known as decentring, this cognitive ability is hypothesised to be a transdiagnostic index of psychopathology and is a core component of Mindfulness-Based Cognitive Therapy (Safran & Segal, 1996; Soler et al., 2016). Interestingly, an association between self-connection and response to the treatment of addiction has been identified, as has self-acceptance and self-love in therapeutic outcomes more generally (Argento et al., 2019; Renelli et al., 2020; Thomas et al., 2013).

Received Messages

Direct communication with *entities* were reported in three of the nine qualitative accounts. The appearance of supportive entities is a key feature of traditional ayahuasca use and helps to distinguish it from western psychedelic-assisted therapy (Beyer, 2009; De Rios, 1972; Luna, 1986). It should be noted, however, that such phenomena are also rarely described in western psilocybin-assisted psychotherapy sessions, as well as non-drug assisted psychotherapy (Belser et al., 2017). In Internal Family Systems (IFS) therapy, Falconer (2021) describes supportive entities largely presenting as guiding spirits from family members. The impact of such encounters, their nature, and the role different expectations have on the phenomenology could be the subject of future research.

Recognised Meaning

Seven of the nine participants interviewed described gaining *insightful and personal meaning* during their ayahuasca ceremonies. Five subcategories were further derived, including: *interpersonal psychological insights; insights into relational issues; insights into the motives and issues of others; general social, ethical, and environmental wisdom;* and *mystical, spiritual, and religious insights and experiences*.

Many subjects spontaneously described relationship issues in their interview sessions. Like other psychedelic-assisted therapies, new perspectives in interpersonal issues are an integral part of ayahuasca-therapy (Belser et al., 2017; Gasser et al., 2014). Furthermore, psychodynamic psychotherapy often addresses preconscious intrapersonal conflicts, conflicts of the biographical past, relational conflicts, and social representations (Grawe, 2004). Ayahuasca appears to induce a state in which participants can reassess these issues and acquire new perspectives, providing potential psychotherapeutic value (Grawe, 2004).

Most who choose to engage with psychedelic therapy do so with the expectation of achieving emotional healing and a better understanding of self (Winkelman, 2014). Psychedelics have been demonstrated to lead to insightful psychodynamic, cathartic, and interpersonal experiences (Gasser et al., 2014). *New self-narration* is a common aim in psychotherapy, defined as a fresh evaluation of identity and relationship with one's surroundings, as well as the potential rescripting of life narrative (Jørgensen, 2006). Enhanced connection to nature appears to be encompassed within connection to the universe. Research suggests that connection to the planet, others, and self is a spiritual value common to psychedelic substance use (Carhart-Harris et al., 2018; Watts et al., 2017). Furthermore, these mystical, spiritual, and religious understandings appear to have therapeutic value, both in treating mental illnesses such

as addiction, as well as facilitating new perspectives on life (Kjellgren et al., 2009; Liester & Prickett, 2012; Loizaga-Velder & Verres, 2014; Renelli et al., 2018). Individuals drinking ayahuasca can also experience perceived near-death experiences (NDEs). NDEs as a result of psychedelics have been associated with improvements in psychological distress, change towards health-related behaviours, diminished death anxiety in those with terminal illnesses and improvements in wellbeing in the long-term (Loizaga-Velder, 2013; Maia et al., 2021; Timmermann et al., 2018).

Spiritual and religious counselling regarding ayahuasca consumption has been shown to be beneficial with integration, is associated with enhance mental wellbeing and can lead to larger numbers of personal insights (Perkins, Schubert, et al., 2021). It is well established in psychedelic research that the strength of participants' perceived mystical experiences predicts therapeutic outcomes (Perkins, Schubert, et al., 2021; Russ et al., 2019). Research has found that these foster the feeling of connection with plant intelligence, the natural world and an understanding pertaining to the connection between all things (Harris & Gurel, 2012; Shanon, 2002).

Attribution of Meaning

Participation in ayahuasca ceremonies often results in novel insights and perspectives which can have therapeutic value (Frecska et al., 2016; Kjellgren et al., 2009). The meaning associated with these experiences often lends itself to the re-evaluation of current and historical events. Such insights have been found to correlate with improvements in depression, anxiety, and psychological wellbeing as well as reduced drug and alcohol consumption (Perkins, Opaleye, et al., 2021; Perkins, Schubert, et al., 2021; Sarris et al., 2021). These understandings are further related to physical health, novel creative pursuits, enhanced life purpose, as well as

interpersonal and psychodynamic factors (Kavenská & Simonová, 2015; Kjellgren et al., 2009; Shanon, 2002). Research suggests insights can result in meaningful life change in the aforementioned areas (Bouso et al., 2012; Franquesa et al., 2018; Loizaga-Velder, 2013; Maia et al., 2021).

Visions and Hallucinations

Visual phenomena are a common experience in ayahuasca ceremonies, and eight of the nine participants discussed this in their interviews. Visions during ayahuasca ceremonies can result in the reprocessing of autobiographical memory, including traumatic experiences (Echenhofer, 2011; Perkins, Sarris, et al., 2021; Shanon, 2002). Despite being in an altered state of consciousness, participants' mental clarity is often described as being enhanced, allowing for an accelerated psychotherapeutic process with intense self-evaluation. The identification of dysfunctional coping strategies, as well as maladaptive emotional and behavioural patterns are often identified and addressed (Argento et al., 2019; Franquesa et al., 2018; Frecska et al., 2016; Renelli et al., 2018).

Cognitive Reactions

Ayahuasca drinkers often describe what is referred to in my qualitative analysis as *boosted thought processes*. This is in concordance with research suggesting that 90% of those who engage in ayahuasca rituals experience a dramatic increase in their perceived level of understanding (Bresnick & Levin, 2006). Although boosted thought processes can result in critical self-analysis regarding interpersonal relationships, self-care, and the potential aetiology of psychological distress (Franquesa et al., 2018; Loizaga-Velder & Verres, 2014; Maia et al., 2021), it can also result in emotional distress and discomfort as participants are forced to confront issues that may be unpleasant or fear inducing (Franquesa et al., 2018; Loizaga-Velder

& Verres, 2014; Maia et al., 2021). Despite this, such experiences are generally considered of therapeutic benefit, as is the case when confronting issues in standard talking therapies, such as psychodynamic psychotherapy and CBT (Bresnick & Levin, 2006; Kjellgren et al., 2009; Maia et al., 2021; Shanon, 2002).

Deep cognitive processes seem to be induced by providing access to otherwise unobtainable emotional material whilst activating higher cortical areas (Jessica L Nielson & Julie D Megler, 2014). Several factors have been described in psychedelic-assisted therapy, including *transpersonal experiences, corrective new experience, problem actualisation, rescripting of past behaviours, regression and the acceleration of psychological processes*, all of which are often associated with emotional activation (Passie et al., 2012). These processes can result in the reprocessing, reframing and reintegration of significant life events and emotional associations (Jessica L Nielson & Julie D Megler, 2014). This theory is supported by Carhart-Harris and Friston (2019) in their REBUS model which describes the relaxation of existing beliefs through disruption of neural hierarchies and consequently results in emotional and psychological insights. The importance of integration following such processes has been stressed to ensure insights result in beneficial change and prevent psychological harm (Perkins, Sarris, et al., 2021).

Appraisal of the Process

The importance of ceremony is currently a topic of debate as researchers work towards the medicalisation of ayahuasca and other psychedelics. There are various explanations regarding the impact of the *shaman* and the singing of *icaros*, which were mentioned by over half the participants. Participants in ayahuasca rituals could be more prone to the placebo effect (Palhano-Fontes et al., 2019), their altered state of consciousness interacting with positive

thoughts and emotions surrounding the shamanic aspect of the ceremony. An alternative explanation is that the shamanic aspect of the ceremony provides healing in a psychospiritual capacity. A study by Weiss et al. (2021) assessing ceremonial ayahuasca use suggests that the mystical states occasioned by ayahuasca act as a covariate that significantly interacts with positive prior perceptions of shamanic tradition. Furthermore, in the same study, the belief that ayahuasca was *cleaning* the body, through purging and spiritual means, was found to significantly predict long term change in both Neuroticism and Extraversion. Although purging was found to induce positive change quantitatively, this was not generally true for other shamanic features used within the ceremonial setting (Weiss et al., 2021).

Study Relevance

Although some of the ayahuasca experiences described can be difficult to interpret through a Western scientific lens, it appears that there are similarities between many of the user accounts described by Westerners on an experiential level. The majority of subjective reports focused on experiences during the ceremony, with data suggesting ayahuasca consumption does not necessary result in psychotherapeutic effects. Available literature suggests therapeutic benefit is significantly enhanced with integration sessions following psychedelic ingestion, although empirical data in this area is lacking (Earleywine et al., 2022; Perkins et al., 2022). In most participants in this study, insights were acquired without necessarily fully integrating these. This is interesting to consider, as the majority of ayahuasca retreat centres do not offer integrative psychotherapy as part of their package of care. The psychotherapeutic potential for participants to learn and process their experiences could potentially be enhanced with additional preparation and integration sessions, although further research in this area is required.

Modulatory Effects of Ayahuasca on Personality Structure in a Traditional Framework

Ruffell, S., Netzband, N., Linton, S., Tsang, W. F., & Wolff, T. (2020). Modulatory effects of ayahuasca on personality structure in a traditional framework. *Psychopharmacology, 237*(10), 3161-3171. DOI 10.1007/s00213-020-05601-0 (Appendix C).

SR contributed to the conceptualisation, design, data collection, data analysis, and write-up of this manuscript.

Study Rationale

Whilst the numbers of tourists visiting the Amazon rainforest to drink ayahuasca continues to increase, relatively few studies have evaluated the psychological impact of the brew in such settings. Open label studies suggest that psychedelics such as psilocybin may increase the personality facet of Openness and decrease that of Neuroticism (Erritzoe et al., 2018; Maclean et al., 2011). While previous research has evaluated the effects of ayahuasca on personality (Barbosa et al., 2009; Barbosa et al., 2016; Bouso et al., 2012; Grob, 1996; Kavenská & Simonová, 2015), this is, to my knowledge, the first study to collect prospective personality data in a traditional Shipibo-style retreat setting.

Methodology

Using the *NEO-PI3 personality questionnaire* (Costa Jr & McCrae, 2008), 24 participants were assessed alongside a comparison group, immediately before drinking ayahuasca, after their 12 day retreat and at six-months to assess for longer term changes. Comparison group participants were English-speaking individuals on holiday in Peru who were initially approached on the premise that they had no previous experiences with ayahuasca reported. The *Mystical*

Experience Questionnaire (MEQ; Barret et al., 2015) was administered at time-point two to assess the degree to which participants underwent a mystical experience, which was subsequently correlated with changes in personality. Written consent and demographic information were obtained the day before the first ayahuasca ceremony. The six-month follow-up NEO-PI3 scores were obtained electronically via email. This also included a follow-up questionnaire assessing the potential long-term impact of the retreat in terms of behavioural, physical, and psychological changes.

Summary of Results

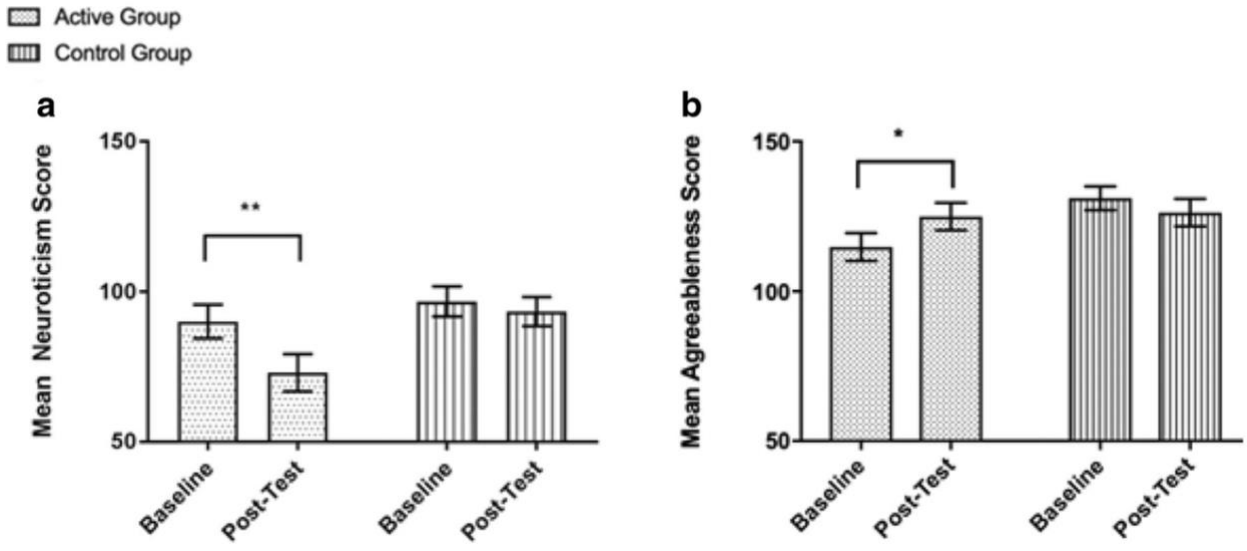
Personality changes from baseline to post-treatment

I first assessed whether the ayahuasca sessions led to changes in personality from baseline to post-test, using a mixed ANOVA, with time (baseline, post-test) and personality (neuroticism, extraversion, conscientiousness, agreeableness, openness to experience) as the within-participants variables, and group (active vs. comparison) as the between-subjects variable. To correct for multiple comparisons, the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was applied for all follow-up pairwise comparisons. Analysis observed a significant interaction between time, personality, and group. Pairwise comparisons revealed a significant reduction in Neuroticism scores from baseline measures to post-test in the active group *(d* = 0.59, $p < .001$), but not the control group ($p = .335$). Pairwise comparisons also revealed a significant increase in Agreeableness scores from baseline measures to post-test in the active group ($d = 0.45$, $p = .012$), not the comparison group ($p = .222$) (Figure 4). Given that there were non-significant differences in baseline Agreeableness and Neuroticism scores between the active and comparison groups, my results suggest a significant reduction in Neuroticism and a significant increase in Agreeableness in the active group following the ayahuasca sessions. Consistent with my original hypothesis, there was a trend towards a significant

increase in Openness scores from baseline to post-test in the active group ($p = .040$); however, this test did not survive the correction for multiple comparisons.

Figure 4

Significant reduction in Neuroticism (a) and increase in Agreeableness (b) observed in the active group from baseline to post-test, compared with the comparison group. Asterisk indicates p < .05, double asterisk indicates p < .001. Bars represent the standard error of the mean (SEM)



Relationship between neuroticism, agreeableness, and mystical experience

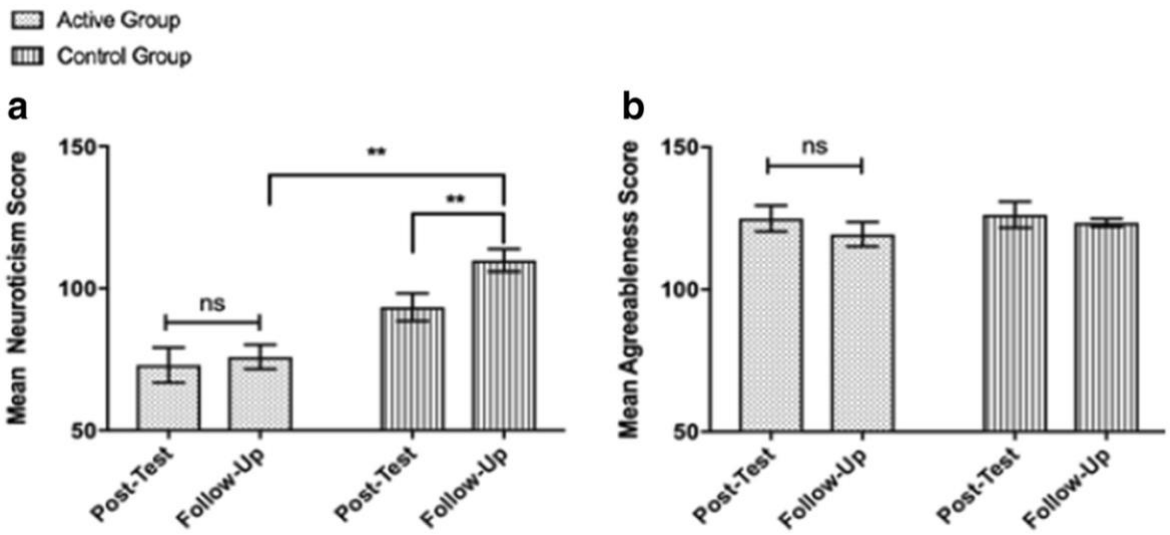
Spearman's rank-order correlation revealed a medium significant negative correlation between Neuroticism change and MEQ scores from baseline to post-test in both the active and comparison groups ($r_S(48) = -.56$, $p < .001$) (i.e. those who reported a greater degree of mysticism also experienced greater reductions in Neuroticism).

Personality changes from post-treatment to follow-up

Mixed ANOVA also indicated a significant interaction between time, personality, and group from post-treatment to follow-up. Pairwise comparisons revealed that the reduction in Neuroticism scores observed in the active group at post-test remained stable at the 6-month follow-up assessment (d = 0.08, p = .539), and remained significantly lower than those observed in the comparison group (d = 1.71, p < .001). In addition, the short-term increase in Agreeableness that was observed in the active group was maintained at 6-month follow-up (d = 0.26, p = .151) (Figure 5). Lastly, at 6-month follow- up, significantly greater Openness to experience scores in the active group compared with the comparison group was also observed (d = 2.20 p < .001).

Figure 5

Significant reduction in Neuroticism (a) and increase in Agreeableness scores (b) observed in the active group at post-test remained stable at 6-month follow-up and were significantly reduced in comparison with the comparison group at follow-up. In contrast, I observed a significant increase in Neuroticism scores in the comparison group from post-test to 6-month follow-up. Double asterisk indicates p < .001. Bars represent SEM.



Integration with extant literature

Personality is thought of as stable once the age of maturity is reached at 30 years (Costa Jr & McCrae, 1992). Change is however possible if a significant event occurs, with the usual pathways including adopting a new role in society or vocationally (Hudson et al., 2012; Lodi-Smith & Roberts, 2007), maturation (Bleidorn et al., 2009), psychotherapy (Noordhof et al., 2018), genetics (McCrae et al., 2000), general motivation to change (Allan et al., 2018) and normal development (Roberts et al., 2006). The data presented in this study suggests ayahuasca can result in significant reductions in Neuroticism as well as increases in Agreeableness, and that this change is maintained for at least six-months. Furthermore, the degree of lessening in Neuroticism scores from pre- to post-retreat were associated with higher ratings of mystical experience, as measured by the MEQ. Only trait increases were observed in Openness scores, contrary to the hypotheses. As the average participant age was 37.6, the fact change was witnessed in personality structure is significant. The results however are not directly in line with predictions, primarily based on the findings by MacLean et al. (2011), suggesting Openness would increase. It was predicted that there may be some effect on levels of Neuroticism, yet the results show that the effect was more pronounced than hypothesised.

We investigated further to establish whether the sample group tested had above average levels of Openness prior to ayahuasca sessions, implying a ceiling effect may have restricted increase in this domain. This would make sense, as all participants had chosen to participate in a series of traditional ceremonies in the Amazon, with good knowledge that the structure was based around local spiritual beliefs. Further weight to this notion is added by the fact that it is unlikely that many people would pay the $1750 USD retreat fee without doing background research into the centre itself. It was apparent that the sample group indeed had above average levels of Openness compared to the general population (mean = 129 compared to population average of

124), implying that ayahuasca users in the Amazon rainforest tend to be individuals who score higher in this domain. This, however, was also the case for the control group (mean = 133). Control group participants were backpackers travelling around Peru, therefore fulfilling the criteria of being *open to new experience* by virtue. Alternatively, it is possible they may have higher levels of *Openness* because of exercising this trait whilst travelling. In addition, the relatively small sample size could have contributed to the null results in this paper. In hindsight, it would be of benefit to have data points prior to a participant's departure from home. This would allow the impact of being abroad on personality scores to be assessed. It is plausible that both backpacking (comparison group) and events leading to booking ayahuasca sessions (active) may have raised the individuals Openness scores before initial assessment. This is, however, contrary to previous research that suggests personality is stable once maturity is reached (Costa & McCrae, 1992; Terracciano et al., 2006). To my knowledge, there have been no studies investigating the impact of travelling on personality structure. This is a concept that could be investigated by those with a specific interest in such an area. Unfortunately, testing participants in advance of their ayahuasca retreats is difficult to achieve logistically, however, my current research is attempting to implement this.

Since publication of this paper, Weiss et al. (2021) have published a similar, larger scale study also investigating personality change in ayahuasca retreat centres following a traditional framework. 256 participants were assessed partaking in ayahuasca retreats in three centres in Central and South America. Participants were evaluated at three time points; baseline, post retreat and three-month follow-up. Similarly, reductions in levels of Neuroticism were found. In addition, increases in Openness, Extraversion, Conscientiousness and Agreeableness were also observed, and all but Conscientiousness was maintained at three-month follow-up. Interestingly, the authors assessed the impact of predisposing factors on personality change.

Baseline personality, demographic characteristics, and experiential elements such as altered states of consciousness as well as affect were measured and their ability to moderate personality change assessed. Changes in Neuroticism were found to be moderated by the acute ayahuasca experience, baseline personality scores and the experience of the purge (Weiss et al., 2021).

Expectancy Effects

Expectancy effects have been shown to be influential in psychedelic research (Aday et al., 2021). Weiss et al. (2021) demonstrated that expectancy effects enhanced change in the personality domains Conscientiousness, Extraversion and Neuroticism in participants consuming ayahuasca in retreat settings. Furthermore, those who had high expectations in terms of preferable decreases in Neuroticism, anxiety and depression scored higher on baseline measures of Neuroticism and subsequently displayed greater reductions following ayahuasca consumption, both in the short and long term (Weiss et al., 2021). Moreover, those who expected increases in Conscientiousness and Extraversion scored lower in these areas before drinking ayahuasca and demonstrated larger increases following ceremonies and at follow-up. Those who scored higher on suggestibility had higher levels of Neuroticism at baseline, before showing greater reductions in this domain pre – and post retreat. Given the similarities in both setting and participants, it is likely such moderating factors were at play in the empirical data included within this thesis.

Study Relevance

The personality characteristic Neuroticism has been found to predict the development of various psychopathologies, including anxiety, depression, and addiction (Zinbarg et al., 2016), results suggesting Amazonian ayahuasca retreats may have therapeutic potential. However, implementing interventions that decrease levels of Neuroticism also gives rise to theoretical

concerns, many of which span into socio-political contexts, the question of what level of neurosis is deemed to be healthy, for instance. It could be argued that neurosis is required for individuals to function in the modern world, which requires organisation and motivation to stick to calendars and schedules. It is possible that excessive reductions in levels of Neuroticism may hinder the ability to function in such regimented societies, as was seen with the 1960s counterculture movement (Smith, 2016). This concept requires investigation but warrants consideration in respect to the findings presented in this thesis, especially in conjunction with the growing support for psychedelic-therapy. This is a trend which is evident through the increased funding being given to scientific research and positive media reports (Australian Government Department of Health, 2022; Cohen, 2021).

Participation in an Indigenous Amazonian Led Ayahuasca Retreat Associated with Increases in Nature Relatedness – a pilot study

Ruffell, S., Gandy, S., Tsang, W., Netzband, N., & Hollingdale, J. (2022). Participation in an indigenous Amazonian led ayahuasca retreat associated with increases in nature relatedness – a pilot study. *Psyarxiv.com*. DOI 10.31234/osf.io/mytnf (Appendix D).

SR contributed to the conceptualisation, design, data collection, data analysis, and write-up of this manuscript.

Study Rationale

Nature relatedness, defined as one's subjective identification with the experience of being connected to nature (Kettner et al., 2019), is a common theme in the experiential response to

ayahuasca and may function in its therapeutic efficacy. Analogous to *biophilia*, nature relatedness can be considered as the subconscious drive experienced by humans to connect with all life (Wilson, 2010). There is a notable lack of interventions which can foster robust and continued enhancements in nature relatedness (Frantz & Mayer, 2014). There is arguably a need for interventions capable of doing so to improve both planetary and human health (Frantz & Mayer, 2014; Martin et al., 2020; Wright & Matthews, 2015; Zylstra et al., 2014). Wilderness retreat experiences (Barton et al., 2016), nature-based educational programmes (Braun & Dierkes, 2017; Liefländer et al., 2013; Stern et al., 2008) and extended nature engagement programmes (Richardson et al., 2016; Richardson et al., 2018) can be effective in increasing nature relatedness, but often require substantial time and resources. Furthermore, evidence for long-term sustained enhancements in nature relatedness post intervention is lacking. Developing effective interventions capable of eliciting long-term positive change requiring less time and resource investment would be highly beneficial.

One study found that two psilocybin therapy sessions could elicit increases in nature relatedness sustained between seven and 12 months (Lyons & Carhart-Harris, 2018). While there have been previous survey studies examining the effect of classical psychedelics on nature relatedness, the study included within this thesis is the first to investigate the impact of ayahuasca usage on nature relatedness when used in an adapted traditional setting in the Amazon rainforest. Participants' perception of their connection to nature was therefore assessed utilising the *Short Form Nature Relatedness Scale* (NR-6) (Nisbet & Zelenski, 2013) in a prospective, naturalistic study design in an adapted traditional setting in the Amazon rainforest. The *State-Trait Anxiety Inventory* (STAI) and *Beck Depression Inventory* (BDI-II) were implemented alongside this measure, assessing 24 participants immediately before and after completing an ayahuasca retreat. I hypothesised that like other serotonergic psychedelics,

ayahuasca consumption would result in an increase in nature relatedness, and this change would be associated with participants' ratings of depression and anxiety (Lyons & Carhart-Harris, 2018).

Methodology

Ayahuasca was administered to participants in a traditional Shipibo setting adapted for tourists. Retreats varied in length between 8 days to 1 month, including 8-day (four ayahuasca ceremonies), 2-week (six ayahuasca ceremonies), 3-week (nine ayahuasca ceremonies), and 1-month (11 ayahuasca ceremonies) retreats. It was not compulsory for individuals to participate in all ceremonies offered, therefore the researchers recorded the number of ceremonies that each individual participated in. Participants completed inventories before their first ceremony and the morning after their final ceremony. Pre-retreat data collection took place at a hotel in Iquitos, and post-retreat data collection at the AF in the Mishana community. Participants completed the *Short form Nature Relatedness Scale* (NR-6), *Beck Depression Inventory—Second Edition* (BDI-II), *State-Trait Anxiety Inventory* (STAI), *Five Facets Mindfulness Questionnaire* (FFMQ), as well as the *Mystical Experience Questionnaire* (MEQ-30) at time-point two.

Summary of Results

Pre and Post Ayahuasca Retreat Outcomes

My first set of analyses examined whether participation in Amazonian ayahuasca retreats was associated with changes in the different research measures utilised (see Table 5 for descriptive and inferential statistics). Paired samples *t*-tests showed that participation in Amazonian ayahuasca retreats was associated with significant improvements on all measures, with medium

to large effect sizes. This suggests that participation in such retreats as a multidimensional intervention could evoke significant changes in a variety of domains.

Table 5

Descriptive and inferential statistics for research measures as a function of time point (pre- vs. post-Amazonian ayahuasca retreat attendance)

	Pre	**Post**			
Measure (*n*)	***M (SD)***	***M (SD)***	***t* (df)**	***p***	**Cohen's *d***
BDI -II (47)	18.49 (13.44)	4.26 (4.08)	8.12 (46)	<.001**	1.18
STAI-T (42)	50.28 (13.21)	37.71(14.54)	5.73 (41)	<.001**	.88
STAI-S (47)	39.38 (13.05)	25.94 (8.93)	7.01 (46)	<.001**	1.02
FFMQ (38)	122.76 (25.75)	140.13 (26.89)	4.63 (37)	<.001**	.75
NR-6 (24)	4.10 (.64)	4.36 (.62)	2.52 (23)	.019*	.51

*M = mean, df = degrees of freedom, *p < .05, **p ≤ .001*

Primary correlation analysis of change scores

A priori analyses involved correlating the NR-6 with the BDI-II, STAI-S, and STAI-T. A statistically significant negative correlation with moderate effect size was found between NR-6 change scores and BDI-II, STAI-S, and STAI-T change scores (see Table 6 for primary correlation analyses). This suggests that increases in nature relatedness are associated with

decreased scores on clinical outcome measures after attending Amazonian ayahuasca retreats in our sample.

Table 6

Primary correlation analyses of change scores

	BDI-II *n* = 47	**STAI-S** *n* = 47	**STAI-T** *n* = 42
NR-6 *n* = 24	-.623***	-.653**	-.485*

**p<.05, ** p<.01, *** p≤.001*

Exploratory Correlation Analyses

Subsequent exploratory analyses were conducted, correlating the remaining research measures, and investigating demographic and retreat variables. A statistically significant positive correlation with a large effect size was found between the NR-6 and FFMQ change scores (see Table 7 for correlation matrix of pre-post change scores), suggesting increases in nature relatedness are associated with increases in mindfulness. The MEQ was not found to significantly correlate with any of the change scores in research measures.

Table 7

Correlation matrix of pre-post change scores in research measures

	STAI-S *n* = 47	**STAI-T** *n* = 42	**FFMQ** *n* = 38	**MEQ** *n* = 50
BDI-II *n* = 47	.616**	.513**	-.192	.170
STAI-S *n* = 47	-	.490**	-.289	-.263

STAI-T *n* = 42	-	-	-.600**	-.111
NR-6 *n* = 24	-	-	.747**	-.084
FFMQ *n* = 38	-	-	-	.001

** p<.01, ** p≤.001*

Integration with extant literature

In keeping with other studies in this thesis, attending Amazonian ayahuasca retreats was found to lead to decreases in depression and anxiety. These affective shifts were associated with higher ratings of nature relatedness, in concordance with previous research assessing the impact of psychedelics on nature relatedness (Gandy et al., 2020). Previous research has found those who use ayahuasca tend to have higher scores in the self-transcendence trait (Bouso et al., 2012; Jimenez-Chillaron et al., 2009). This in turn has been shown to positively correlate with pro-environmental beliefs and nature relatedness (Dornhoff et al., 2019; Sothmann & Menzel, 2017; Tam, 2013). The dissolution of separation between other and self could lead to a perception of self/nature continuity or overlap, which may partly explain why the perceived influence of natural settings has been shown to predict greater nature relatedness (Kettner et al., 2019). Both self-transcendence and the ceremonial use of ayahuasca have been demonstrated to negatively correlate with Neuroticism (Levenson et al., 2005; Ruffell, Netzband, Linton, et al., 2020; Weiss et al., 2021). Furthermore, greater psychological benefits after being immersed in nature have been associated with lower levels of Neuroticism (Ambrey & Cartlidge, 2017).

While long-term follow up of interventions enhancing nature relatedness has not yet been assessed (Barrable & Booth, 2020), existing evidence calls into question their efficacy at

yielding sustained positive change. Some interventions may only elicit increases in nature relatedness lasting between three and eight weeks (Barrable & Booth, 2020; Chawla et al., 2020; Liefländer et al., 2013), with nature relatedness increases sustained at two months post intervention in some cases (Richardson et al., 2016; Richardson et al., 2018). However, follow-up of a national park residential programme at three months found that any increase in nature connectedness had returned to baseline (Stern et al., 2008). There is a notable lack of interventions that can elicit sustained long-term increases in nature relatedness. Given the longevity of effects elicited by ayahuasca, it is worth investigating to see if it may occasion enduring enhancements in people's connection to nature. Unfortunately, long term follow-up data was not included in this study due to a high attrition rate and is discussed further in the strengths and limitation section at the end of this thesis.

Study Relevance

These data suggest that attending Amazonian ayahuasca retreats leads to increases in nature relatedness. Furthermore, they demonstrate that there is an association between nature relatedness and mental health outcomes such as anxiety and depression. Nature relatedness has also been shown to be a key predictor of concern for the environment and pro-environmental behaviours have been shown to be linked to ayahuasca usage, among both Western and indigenous populations (Mackay & Schmitt, 2019; Schultz et al., 2004; Zylstra et al., 2014). It has been argued that even when participants of an ayahuasca ceremony are prioritising individual healing, personal development, or psychonautical curiosity, feelings of wider environmentalism may emerge (Harms, 2021). Such shifts are likely underpinned by increases in nature relatedness, this being a key predictor of pro-environmental behaviours (Forstmann & Sagioglou, 2017; Whitburn et al., 2020). Members of a Brazilian ayahuasca church were found to have a more respectful relationship with nature following their ayahuasca usage

(Grob, 1996). More generally, as Saez (2016) states, it "*is difficult to dissociate current ayahuasca groups and environmental concerns'* (p. 74) and as reported by Metzner (1999) "*many people who have experienced ayahuasca … become deeply involved in ecological preservation and sustainability projects"* (p. 291). Interventions that aim to enhance nature relatedness, both for therapeutic purposes and to foster pro-environmental behaviour, are lacking and further research is required to better understand the role of ayahuasca retreats in each of these areas.

Ceremonial Ayahuasca in Amazonian Retreats—Mental Health and Epigenetic Outcomes From a Six-Month Naturalistic Study

Ruffell, S. G., Netzband, N., Tsang, W., Davies, M., Butler, M., Rucker, J. J., Tófoli, L. F., Dempster, E. L., Young, A. H, & Morgan, C. J. (2021). Ceremonial ayahuasca in amazonian retreats—mental health and epigenetic outcomes from a six-month naturalistic study. *Frontiers in Psychiatry, 12,* 898. DOI 10.3389/fpsyt.2021.687615 (Appendix E).

SR contributed to the conceptualisation, design, data collection, and write-up of this manuscript.

Study Rationale

To date, no studies have assessed epigenetic change and mental health outcomes associated with trauma following psychedelic use. I therefore conducted a study to evaluate, through naturalistic means, whether ayahuasca improved mental health conditions related to trauma,

and whether this was associated with epigenetic change. I assessed the severity of childhood trauma in participants to provide insight into whether ayahuasca could be used as a potential treatment for developmental trauma, as suggested by anecdotal evidence (Jessica L Nielson & Julie D Megler, 2014).

Methodology

A prospective naturalistic study design was used to evaluate 63 participants who attended ayahuasca rituals at the Ayahuasca Foundation, located in the Amazon rainforest in Peru. Standardised questionnaires were administered to participants prior to their first ceremony (pre), the day after their last ceremony (post), and six-months after their final ceremony. 4 ml of saliva was also collected under the guidance of researchers at this time point for epigenetic analysis. Post retreat measures were completed on laptops in a quiet space at the retreat site on the morning before travelling back into Iquitos, 4ml of saliva was again collected. The six-month follow up questionnaires were collected electronically via email. Participants completed the *Beck Depression Inventory II* (BDI-II) (Beck et al., 1996), *State Trait Anxiety Inventory* (STAI) (Spielberger et al., 1983), *Self-Compassion Scale* (SCS) (Neff, 2016), *Clinical Outcomes in Routine Evaluation-Outcome Measure* (CORE-OM) (Evans et al., 2002), and the *Sentence Completion for Events From the Past Test* (SCEPT) (Raes et al., 2007) at all three time-points. The *Childhood Trauma Questionnaire* (CTQ) (Bernstein et al., 1998) was completed at time point one and the MEQ at time point two only.

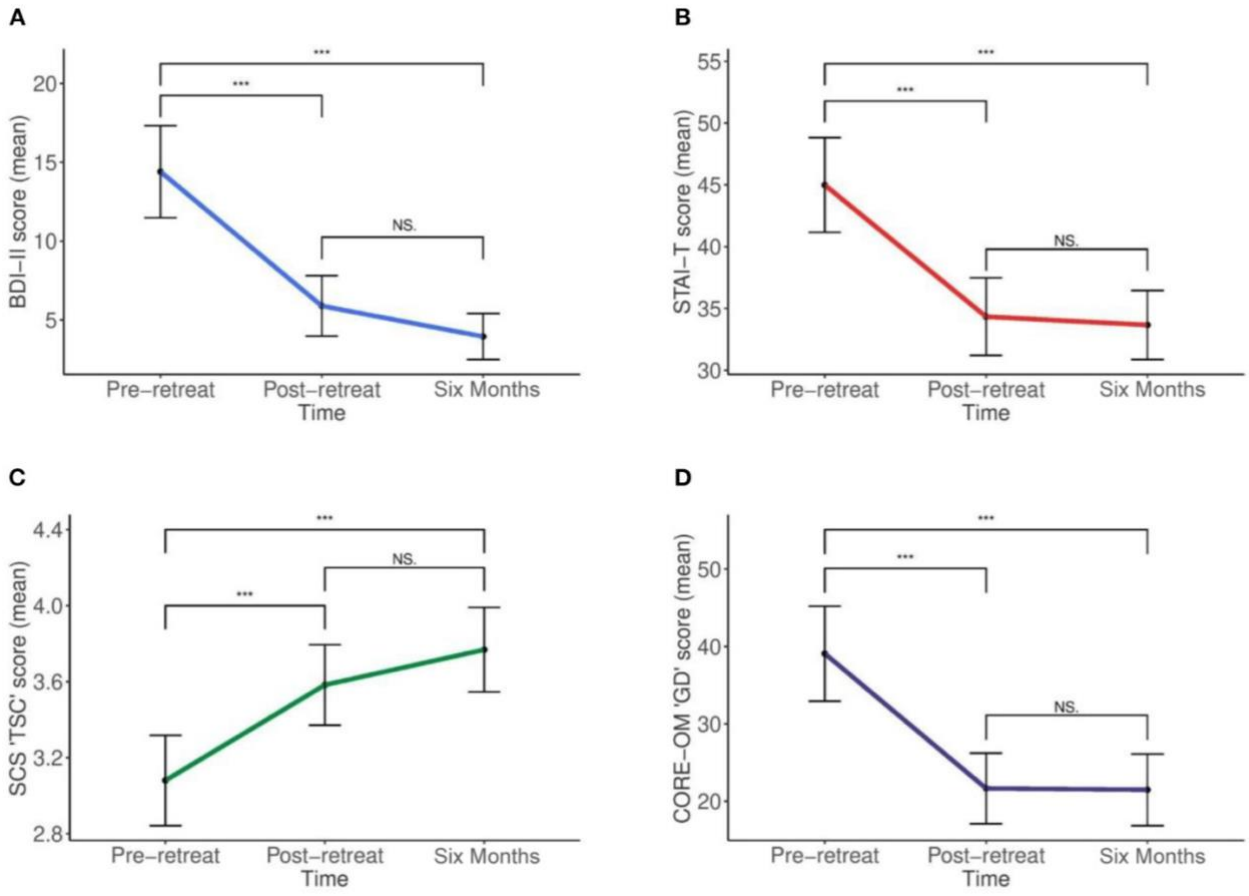
Summary of Results

Mean outcome scores all differed statistically significantly between time points (see Figure 6, plates A-D) for the BDI-II: $d = 1.15$, $p < 0.001$; STAI-T: $d = 0.87$, $p < 0.001$; SCS: $d = 0.78$, $p < 0.001$; and the CORE-OM: $d = 0.83$, $p < 0.001$. *Post hoc* tests using the Bonferroni corrected

pairwise comparisons revealed a reduction in all severity scores from pre- to post- retreat for the BDI-II; STAI-T; and CORE-OM, which were all statistically significant at the $p < 0.001$ level. Six-month follow-up scores further reduced for the BDI-II; STAI-T; and CORE-OM, which was all statistically significant compared with pre-retreat scores at the $p < 0.001$ level, but not post-retreat scores (BDI- II, $p = 0.153$; STAI-T, $p = 1.0$; CORE-OM, $p = 1.0$), suggesting sustained improvement. For the SCS, there was an increase from pre to post retreat, which was statistically significant ($p < 0.001$); follow-up SCS score further increased and was significant compared with pre-retreat ($p < 0.001$), but not post-retreat ($p = 0.138$), again suggesting sustained improvement. Only total scores from measures were used in the analysis.

Figure 6

Changes in outcome scores over time



*(A) BDI-II. (B) STAI—Trait Anxiety Score. (C) SCS—Changes in Total self-compassion (TSC) score. (D) CORE-OM: changes in mean CORE-OM Global Distress (GD) score [NS, non-significant (P > 0.05), ***p ≤ 0.001].*

No significant changes in memory specificity were found on the SCEPT. However, new variables of total positive and negative memory scores for each time point were computed to assess changes in memory valance. Significant reductions in negative valanced memories from pre-retreat to follow-up ($p = 0.004$), suggesting improvement over time.

Correlation Analysis With Number of Ceremonies, Length of Retreat, and Frequency of Ayahuasca Use Prior to Retreat

Pearson's correlations were computed between number of ceremonies, length of retreat, and frequency of ayahuasca use prior retreat and improvement scores on the BDI-II, STAI-T, CORE-OM, and SCS. There were no significant correlations.

Predictors of Change in Psychopathology

To minimise the risk of type I errors, Pearson's correlations were computed with CTQ and MEQ total scores and subscales and BDI-II change scores (the latter chosen as a proxy for all outcomes given similar patterns of findings across all outcome measures). Greater change in BDI-II post-retreat was correlated with higher overall CTQ scores ($r = 0.318$, $p = 0.011$ for overall population) scores. These figures were however not significantly correlated with BDI-II change at six-month.

DNA Methylation Analysis

BDNF analyses failed due to an error, therefore only SIGMAR1 and FKBP5 were analysed. The SIGMAR1 assay showed a statistically significant increase in DNA methylation across the 5 analysed CpG sites (paired *t*-test: $t = 2.58$, $df = 38$, $p = 0.01$). FKBP5 DNA methylation did not show any statistically significant change ($p = 0.13$).

SIGMAR1 Methylation Correlation Analyses

Methylation change scores were calculated for SIGMAR1 and Pearson's correlation performed with CTQ total scores. There was a significant correlation ($r = 0.387$, $p = 0.015$), indicating those with higher childhood trauma had increased methylation changes in SIGMAR1 post retreat. In order to reduce the risk of type I errors, SIGMAR1 methylation changes were correlated with BDI-II as a proxy for all outcome measures; there was no significant correlation in this analysis.

Integration with extant literature

Ayahuasca dosing led to a statistically significant reduction in depression, global distress, and state and trait anxiety with scores post-retreat maintained at six-month follow-up. In addition, self-compassion scores also significantly increased and were sustained at follow-up. I hypothesised that change in mental health outcomes would be associated with change in *overgeneral autobiographical memory* (OGM). This inability to access specific autobiographical memories has been demonstrated to corelate with both major depressive disorder (MDD) and PTSD (Williams et al., 2007). More specifically, childhood trauma, particularly sexual trauma, has been found to be associated with the development of OGM in later life (de Decker et al., 2003; Kuyken & Brewin, 1995). In order to avoid retrospective accounts, Valentino et al. (2009) evaluated OGM in families with active social services input.

Recruited through the Department of Human Services, children who had suffered abuse or neglect were found to exhibit more OGM. The idea that trauma could be a meditating pathway resulting in OGM was the basis of including the Childhood Trauma Questionnaire (CTQ) within the study inventory.

Memory Recall and Mental Health Outcomes

Although no change in memory specificity was identified on the Mean Sentence Completion for Events from the Past Test (SCEPT), general negative memory recall decreased between time point one and long-term follow-up. In a recent study, Weiss et al. (2021) found the reappraisal of challenging experiences was a strong mediator of change in psychometric outcomes. This construct resembles various psychotherapeutic techniques, including acquiring new meaning from traumatic events (Resick et al., 2016), assessing the accuracy of various belief systems (Hollon & Beck, 2013), encouraging psychological flexibility in order to derive meaning (Elliott et al., 2013; Hayes et al., 2011), and striving to achieve courage (Hollon & Beck, 2013). Continued investigation into the extent to which psychedelic-induced processes overlap with psychotherapy is warranted.

Ayahuasca and Trauma

It has been proposed that ayahuasca may be beneficial in treating PTSD and other disorders related to trauma (Jessica L Nielson & Julie D Megler, 2014). It has been suggested that the acute psychedelic effects of the brew and recall of repressed memories may aid users in assigning a new context to traumas (Jessica L Nielson & Julie D Megler, 2014). Ayahuasca use has been shown to elicit neural activation in limbic and higher cognitive regions involved in the formation of memories and emotional processing (de Araujo et al., 2012; Riba et al., 2006). Mechanistic theory, supported by preliminary data, has suggested that this process

occurs via the modulation of SIGMAR1, with the alkaloids present in ayahuasca enhancing synaptic plasticity and neurogenesis as well as promoting memory reconsolidation and fear extinction through dopamine release (Inserra, 2018). In those with trauma-related disorders, there may be the potential for re-traumatisation if the user is in an inappropriate setting or mindset preceding use (Jessica L Nielson & Julie D Megler, 2014). However, most of the evidence surrounding ayahuasca use in the management of trauma is anecdotal or speculative, with few studies examining memory recall.

Epigenetic Change

The epigenetic analysis included within this thesis is the first to assess the impact of any psychedelic on epigenetics. The analysis indicated that drinking ayahuasca in an Amazonian retreat setting could impact the epigenetic expression of the SIGMAR1 gene. Epigenetic regulation of neuronal gene transcription, via methylation of deoxyribonucleic acid (DNA), have been implicated in susceptibility to psychiatric disorders (Zannas & West, 2014). It is currently unclear if the mean increase in DNA methylation of 2.09% reflects actual changes in gene expression or suggests any significant impact biologically. Although increases in the DNA methylation of SIGMAR1 might result in receptor upregulation, hypermethylation, according to standard DNA methylation principles, usually leads to transcriptional silencing (Zannas & West, 2014). As with the above findings, further research with larger samples assessing both clinical and non-clinical populations is required to ascertain the impact of ayahuasca epigenetically.

Study Relevance

This study is amongst the first to prospectively collect quantitative data concerning the impact of Shipibo-style Amazonian ayahuasca retreats on common mental health conditions such as

depression and anxiety. Given the recent surge in interest in Amazonian ayahuasca retreats, with large proportions of people seeking out the brew for its anecdotal effects on a number of common mental health difficulties, this study provides data in support of these claims. Although previous studies have evaluated the potential psychological mechanisms of change, this is the first to look at epigenetics as a biological mechanism of change, not only in ayahuasca but in any psychedelic. Recent studies have suggested that trauma can be passed on intergenerationally via epigenetic change (Yehuda & Lehrner, 2018) and my study indicates that further research is needed to fully establish whether ayahuasca could be a potential treatment for individuals with trauma symptoms. As retreat centres continue to operate as a thriving business and the medicalisation of ayahuasca seems increasingly likely (Psychae Institute 2021; Sacred Medicines 2021), information is required to better understand this intriguing brew, from potential biological impact to the psychological processes underlying its therapeutic effect.

Discussion

This body of work prospectively explored Amazonian ayahuasca use in a Shipibo-style retreat setting as a potential agent to influence personality, mental health outcomes, and nature relatedness. Phenomenological analyses and pharmacological reviews were undertaken to further understand the potential mechanisms of action underlying the effects of the brew. Although our current understanding of the pharmacology of ayahuasca is limited, the available data suggest less understood synergistic mechanisms may be at play. Despite this, the data presented within this thesis suggest that participation in indigenous-led Amazonian ayahuasca retreats does influence various psychometric outcomes and could have a positive impact on mental health.

Summary of Main Results

Pharmacology

The pharmacology of ayahuasca is still relatively poorly understood, with potential synergistic mechanisms between the compounds of the brew ill-defined. The complexity of a typical brew containing *Banisteriopsis caapi* and *Psychotria viridis* is evident from the current literature, with at least four active compounds at variable concentrations, depending on the organic matter and subsequent preparation (Callaway, 2005; Kaasik et al., 2020). Adding to the complexity, there are often numerous admixtures included in the brew (McKenna et al., 1984). It is extremely difficult to determine the extent of the pharmacological interactions occurring in various brews. Studies suggest that there are more complex processes taking place than we are

currently aware of, whilst many aspects of the brew point towards clinical and therapeutic applications. Further scientific investigation is required to accumulate data to fully establish legitimate applications within the modern medical paradigm. The first systematic review of its kind, Ruffell et al. (2020; Appendix A) provides a foundational understanding of the pharmacological mechanisms of action in ayahuasca, elucidating potential mechanisms of therapeutic change.

Subjective experiences

The phenomenological analysis of participants experiences in ayahuasca ceremonies (Wolff et al., 2019; Appendix B) identified one overarching category: *experiences during the ceremony,* along with two side categories: *appraisal of the process* and *preparedness*. Various subthemes were identified from the main category, including *physical symptoms, received messages, visions and hallucinations, cognitive reactions, attribution of meaning, recognised meaning, emotional reactions, and reactions of the individual.* In eight of nine participants, psychotherapeutic target emotions were present alongside unpleasant emotions in ayahuasca ceremonies, suggesting psychodynamic processes may be occurring.

Personality

In Ruffell et al. (2020; Appendix C), levels of neuroticism were found to significantly decrease, both immediately after retreat and at six-month follow-up, and were negatively correlated with the degree to which participants reported having undergone a mystical experience. Interestingly, in contrast to previous research (MacLean et al., 2011), levels of Openness did not significantly increase, potentially due to the high baseline level of Openness in the sample group resulting in a ceiling effect. Furthermore, increases in Agreeableness were found, both

immediately after retreats and at long-term follow-up. These results support existing literature suggesting the potential of serotonergic psychedelics therapeutically.

Common Mental Health Outcomes

In Appendix E (Ruffell et al., 2021), significant decreases in global distress, anxiety, and depression were found immediately after retreats, as were further reductions at six-month follow-up, with 24 of the 31 participants who qualified as depressed according to the Beck Depression Inventory (BDI) no longer meeting diagnostic threshold, both post retreat and at six-month follow-up. Self-compassion was found to increase post-retreat and similarly was sustained at six-month follow-up. Although no specific changes were found in memory specificity, significant reduction in memories with a negative hedonic tone were apparent between pre-retreat and six-month follow-up. Moreover, the degree of trauma participants experienced in childhood was found to significantly correlate with change in depression scores (BDI was used as a representation for all measures due to comparable results) post-retreat, but not at follow-up. Scores on the Childhood Trauma Questionnaire (CTQ) were also found to correlate with increases in sigma non-opioid intracellular receptor 1 (SIGMAR1) DNA methylation post-retreat. MEQ mystical experience subscale scores were only found to correlate with change on the BDI in the depressed subsample post retreat, in contrast to my study investigating personality (Ruffell et al., 2020; Appendix C). Results from this study suggest that the ceremonial use of ayahuasca in Amazonian retreat settings may positively impact mental health and well-being outcomes.

Nature Relatedness

As predicted in Ruffell et al. (2022; Appendix D), levels of self-reported nature relatedness increased after drinking ayahuasca. These changes correlated negatively with participants

ratings of depression and anxiety as well as positively correlating with mindfulness scores. Interestingly, no significant correlation was found between the Mystical Experience Questionnaire (MEQ) and other research measures, suggesting nature relatedness may be associated with change in mental health and well-being outcomes over mystical experience. The number of ceremonies attended was not found to be associated with outcomes in any of the studies included within this thesis.

Implications and Integration with Existing Literature

Personality

Neuroticism

Reductions in Neuroticism in response to ayahuasca ingestion are in line with results from previous research, with both prospective (Barbosa et al., 2009; Fernández et al., 2014; Sanches et al., 2016) and cross-sectional studies (Barbosa et al., 2016; Bouso et al., 2012; Bouso et al., 2015; Grob, 1996) assessing ayahuasca and personality characteristics such as self-directedness, harm avoidance, and worry. Erritzoe et al. (2018) also found reduced levels of Neuroticism in patients who suffer from TRD after consuming psilocybin. Palhano-Fontes et al. (2019) demonstrated that ayahuasca consumption in hospital settings improved symptoms in those with MDD, a condition associated with neurotic traits (Barnhofer & Chittka, 2010).

Roberts et al. (2017) conducted a meta-analysis evaluating decreases in Neuroticism post intervention in over 20 000 participants. The authors found on average a decrease in effect size of d = .57 immediately following intervention, compared to d = .59 in Ruffell et al. (2020; Appendix C) and d = .79 by Weiss et al. (2021). The statistical analysis used in Ruffell et al.

(2020; Appendix C) did not directly compare changes in personality domains between time point one and time point three, rather between time points two and three, establishing no significant change had taken place. Direct comparison between time points one and three would allow the effects size to be determined, rather than assessing the lack of change which arguably provides less valuable information. The subsequent research in this thesis has assessed change between time points one and three to correct for this shortcoming. Regarding the magnitude of the effect, Roberts et al. (2017) concluded that interventions with a duration of less four weeks were associated with small effect sizes. Participants in Ruffell et al. (2020; Appendix C) drank ayahuasca six times over a period of two weeks and displayed significant decreases in Neuroticism with effects sizes similar to those displayed with over four weeks of intervention. In addition, Weiss et al. (2021) and Erritzoe et al. (2018) found moderate effect size reductions in Neuroticism at three month follow-up (d = -.53 and d = -.57 respectively). Taken together, it is reasonable to conclude that ceremonial ayahuasca use does have a significant impact on personality, particularly in relation to Neuroticism.

Physiological mechanisms underlie the psychological effects associated with the mystical experience (Carhart-Harris et al., 2018; Carhart-Harris & Goodwin, 2017). This is also the case when considering reductions in Neuroticism after ceremonial ayahuasca use. Callaway et al. (1994) demonstrated that individuals who drink ayahuasca show increases in serotonin transporter sites when compared to a control group. Combined with the findings in a study by Hirvonen et al. (2015), which showed Neuroticism to be correlated with low 5-HT1A receptor binding, ayahuasca might be occasioning decreases in Neuroticism via neurobiological changes to the serotonin system.

Agreeableness

Significant increases in levels of Agreeableness were observed in my research both in the short- and long-term (Ruffell et al., 2020; Appendix C). Interestingly, Erritzoe et al. (2018) did not find such changes when assessing psilocybin in a hospital setting. However, increases in Agreeableness were replicated by Weiss et al. (2021) when looking at ayahuasca in a ceremonial retreat setting. Whereas I found changes in Agreeableness were not associated with mystical experiences, Weiss et al. did identify an association. This may be because Weiss et al. had greater statistical power in comparison to my relatively underpowered study, and the authors were consequently able to detect such changes. Higher levels of Agreeableness were also noted to predict greater adaptive change, encompassing further increases in Agreeableness as well as Openness, Conscientiousness, Extraversion and decreases in Neuroticism (Weiss et al., 2021). In addition, both Ruffell et al. (2020; Appendix C) and Weiss et al. took place in retreat centres with a focus on community, with pro-social behaviour being associated with agreeableness (Caspi et al., 2003).

Openness

In contrast to MacLean et al. (2011) and Erritzoe et al. (2018), Ruffell et al. (2020; Appendix C) did not find significant increases in Openness following psychedelic consumption. Trend-level increases were, however, found which continued to rise from post-retreat to six-month follow-up, partially supporting previous research (Barbosa et al., 2016; MacLean et al., 2011). As the sample used in Ruffell et al. displayed higher baseline levels of Openness when compared to the general population, our results suggest participants may have been primed to be more open than usual, or alternatively show their propensity to be novelty seeking.

Common Mental Health Outcomes

Depression and Anxiety

The empirical research within this thesis adds to the growing body of evidence that ayahuasca may have clinical potential in psychopathology, supporting findings from other studies. A small open-label study found that ayahuasca has antidepressant and anxiolytic effects which are rapid in onset (Osório et al., 2015). Furthermore, a double-blind, parallel-arm, randomized placebo-controlled trial assessing 29 subjects suffering from treatment-resistant depression showed significant antidepressant effects of ayahuasca compared to placebo (Palhano-Fontes et al., 2019); notably, placebo effect was also high in this study. In Ruffell et al. (2021; Appendix E) and Ruffell et al. (2022; Appendix D), significant decreases in depression and anxiety were found after attending ayahuasca retreats, consistent with the existing literature.

While I found that attending ayahuasca retreats reduced anxiety in both the short-term and at six-month follow-up (Ruffell et al., 2021; Appendix E), this is in contrast to some, but not all existing research. Santos et al. (2007) identified that, during the acute intoxication phase, although ayahuasca reduced scores on hopelessness and panic scales in comparison to controls, it had no effect on state- or trait-anxiety on the STAI scale. In a recent study, however, Uthaug et al. (2021) found that levels of anxiety and depression significantly decreased after European neo-shamanic ayahuasca retreats in the short-term, in keeping with Ruffell et al. (2021; Appendix E) and Ruffell et al. (2022; Appendix D), although it should be noted that Uthaug et al., also found the same improvements in their placebo arm, with no difference in outcome between the two groups.

At this stage it cannot be determined if the effects occasioned are a result of pharmacology, the shamanic framework, or of a combination of the two. Recent evidence, including the work presented within this thesis (Ruffell et al., 2020, Appendix C; Ruffell et al., 2021, Appendix E; Ruffell et al., 2022, Appendix D; Wolff et al., 2019, Appendix B), suggests the latter is the most likely. However, three studies undertaken in Brazil have demonstrated that one dose of ayahuasca in a clinical setting can have a rapid antidepressant effect (Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016), suggesting outcomes may also be apparent in non-ceremonial settings.

Trauma

Adverse Childhood Experiences (ACEs), encompassing *highly stressful, and potentially traumatic, events or situations*, have been shown to impact negatively in later life in a cumulative fashion (Felitti et al., 1998). The ACE study showed those who underwent four or more ACEs were four to 12 times as likely to experience depression, addiction, or to attempt suicide, with the findings having been replicated in recent years (Bellis et al., 2017; Giovanelli et al., 2016). Furthermore, ACEs have been shown to be relatively common (Felitti et al., 1998). Ruffell et al. (2021; Appendix E) showed those with higher scores on the CTQ had greater decreases in depression (BDI was used as a proxy for other measures due to similar patterns in finding and to reduce the chance of type 1 errors). It is possible that CTQ scores would be higher if a clinical population were to be used; with questions focusing on areas such as emotional, physical, and sexual abuse. While the impact of MDMA on trauma symptoms is well documented in the literature (Mithoefer et al., 2019; Mithoefer et al., 2018; Mithoefer et al., 2013), no other studies to date have explored the impact of ayahuasca on childhood trauma, making Ruffell et al. (2021; Appendix E) the first of its kind. Two theoretical papers have investigated the use of ayahuasca in treating PTSD (Jessica L Nielson & Julie D Megler, 2014)

and childhood trauma (Perkins & Sarris, 2021), identifying the brew as a potential candidate therapy in this area.

One potential explanation for my findings is that subjects with higher CTQ scores were more prone to both absorption and dissociation (Allen et al., 2002), enhancing therapeutic outcomes associated with ayahuasca use. Childhood trauma is associated with increased levels of both dissociation and absorption (Eisen & Carlson, 1998). Absorption is positively associated with vivid imagery, deep involvement in nature and aesthetics, synaesthesia, as well as Openness to imagistic, perceptual, and cognitive experiences (Roche & McConkey, 1990). It predicts the response of participants to psychedelics in areas such as visual effects, mystical experiences, and overall alteration of consciousness as well as other methods of inducing altered states, such as meditation and hypnosis (Haijen et al., 2018; Pekala et al., 1985; Studerus et al., 2012; Vaitl et al., 2005). Dissociation encompasses a range of experiences, from mild emotional detachment from one's surroundings to extreme disconnect from emotional and physical reality. In its extreme form, dissociative disorder can be a disabling psychiatric condition and is often associated with traumatic experiences (Ellason & Ross, 1997). Dissociation and absorption are not without their similarities. In fact, dissociative-absorption is defined as the propensity to absorption in external stimuli or imagination (Soffer-Dudek, 2019). Although it should be noted that trauma does not guarantee dissociation, further research in clinical populations may help shed light on the mediating role dissociative absorption could have on psychological outcomes.

Predictors of Change in Psychopathology

Lukoff et al. (1992) define the mystical experience as a transitory feeling of being in harmony with all of existence. Two of the studies included within this thesis demonstrate a correlation

between perceived mystical experiences and change in psychometric outcomes (Ruffell et al., 2020, Appendix C; Ruffell et al., 2021, Appendix E). These results support previous data suggesting the role of mystical states in psychedelic-assisted therapy (Erritzoe et al., 2018; Griffiths et al., 2018; MacLean et al., 2011; Roseman, Nutt, et al., 2018). The fact that the DMN has been suppressed and a temporarily altered state has been induced perhaps provides the individual with insight beyond their ordinary state, promoting objectivity and re-evaluation of stressors and life issues (Carhart-Harris et al., 2014; Fresco et al., 2007; Millière et al., 2018; Murphy-Beiner & Soar, 2020).

Mystical experiences can encompass a sense of connectedness, oneness, and a diminished sense of self or *ego-dissolution* (Barrett et al., 2015). These states have been found to predict improved mental health outcomes as well as increased wellbeing in the long-term following psychedelic therapy (Carhart-Harris & Goodwin, 2017; Griffiths et al., 2006). Furthermore, research has demonstrated emotional breakthrough, psychological insight, and personal meaning may also be associated with therapeutic outcomes (Davis et al., 2020; Roseman et al., 2019). Carhart-Harris et al. (2018) suggest the perception of connectedness is key in achieving positive mental health outcomes, with evidence suggesting it mediates improvements in psychological wellbeing (Cervinka et al., 2012). Moreover, the feeling of disconnectedness is often also found in depression (Karp, 2017).

Previous research has suggested that the experience of a single form of consciousness through altered states may also lead to changes in psychometrics (Erritzoe et al., 2018; Palhano-Fontes et al., 2019; Roseman, Nutt, et al., 2018; Schmid & Liechti, 2018). Nature connectedness is one specific way in which this feeling of being united with a larger reality may present, and according to the results presented within this thesis may also potentiate change in mental health

outcomes, perhaps to a greater degree than mystical experience (Ruffell et al., 2022; Appendix D). Interestingly, this sense of connection is present in a wide number of psychological and spiritual doctrines, including the *bond with the universe* and the *oceanic feeling* described by Freud (1930), peak-experiences as described by Maslow (1964), and the *revelatory theory* described by Jung (1982).

It should however be noted that not all studies identify each aspect of the mystical experience, as measured with the MEQ, as predictive of psychological change. Palhano-Fontes et al. (2019) found three of the four factors included within the MEQ did not correlate with changes in depression scores in those with treatment resistant depression. Only *transcendence of time and space* was found to correlate, with *mystical, ineffability* and *positive mood* showing no significant association. Similarly, in Ruffell et al., (2021; Appendix E), only the *mystical* subscale was found to correlate with research outcomes in the depressed subsample. Furthermore, in Ruffell et al. (2022; Appendix D), the NR-6 moreover the MEQ, was correlated with lower levels of depression and anxiety in the modest sample of participants. Although the MEQ30 does include an element of connection to a greater whole, my results suggest nature connectedness may be worth investigating as a stand-alone factor and a potential pathway to improved therapeutic outcomes.

Ceremony Attendance and Mental Health Outcomes

Neither Ruffell et al. (2021; Appendix E), nor Ruffell et al. (2022; Appendix D), found an association between the number of ayahuasca ceremonies attended and outcomes on research measures. While this might seem counterintuitive, this is in keeping with previous literature that found no relationship between the number of ayahuasca ceremonies attended and alterations in personality as measured by the NEO-PI3 (Weiss et al., 2021). One possible

explanation for this is that once mystical experiences were occasioned, no further consumption of the brew was necessary. This supports the notion that mystical experiences are fundamental to the therapeutic outcomes associated with ayahuasca and other psychedelics, which is well documented in the literature (Erritzoe et al., 2018; Griffiths et al., 2018; MacLean et al., 2011; Roseman, Nutt, et al., 2018).

Nature Relatedness

Interestingly, when assessing nature relatedness, the MEQ was not found to correlate with decreases in anxiety and depression when the NR-6 was, and the number of days spent at the Amazonian retreat centre showed a trend towards significance (Ruffell et al., 2022; Appendix D). Nature relatedness has previously been connected with participants' self-perception of personal growth (Pritchard et al., 2020). Desire for personal growth is a common motivation for people using ayahuasca, while also a commonly reported outcome of usage (Bresnick & Levin, 2006; Franquesa et al., 2018; Kavenská & Simonová, 2015; Kjellgren et al., 2009; Loizaga-Velder, 2013; Winkelman, 2005). Ayahuasca users have also been found to have higher ratings of life purpose, life meaning, life satisfaction, and wellbeing (Bouso et al., 2012; Jiménez-Garrido et al., 2020; Thomas et al., 2013; Uthaug et al., 2018), and such cognitive and affective shifts are associated with higher ratings of nature relatedness (Gandy et al., 2020). Further research is required to see if the results from this modestly powered study replicate, and to investigate whether nature relatedness could moderate change in depression, anxiety, and mindfulness.

Subjective Experience of Ayahuasca Ceremonies

Various research is in existence describing the subjective aspect of ayahuasca ceremonies. Luna and Amaringo (1999) describe changes in perception as a result of drinking the brew, and

Shanon (2002) goes as far as to outline a typology of visions, as well as describing participants' interactions with complex beings seemingly from another dimension. Similar to my data (Wolff et al., 2019; Appendix B), both the above authors also describe participants receiving teachings from supportive beings (Luna, 1986; Shanon, 2014). Researchers such as Kjellgren et al. (2009) have expanded on these descriptions, associating *changes in worldview* as a result of ayahuasca consumption with potential therapeutic benefit. Although introspection and mystical experience have been found to correlate with the psychotherapeutic benefits of the brew, the underlying processes are still poorly understood (Franquesa et al., 2018).

Two qualitative studies have been conducted with the aim of determining the psychotherapeutic processes of participants in ayahuasca ceremonies. Loizaga-Velder and Pazzi (2014) identified body-oriented, insight oriented, cognitive, emotional/social, and transpersonal processes as potentially therapeutic in 14 participants treated with 15 therapists for addiction. The bodily effects described largely related to purging and were frequently mentioned by participants as was the case in my study (Wolff et al., 2019; Appendix B). Meaning in life and a sense of purpose was also frequently described. Renelli et al. (2020) similarly explored the therapeutic processes associated with consumption of the brew in a study of 16 participants suffering from eating disorders. Acceptance, self-love, processing painful memories and emotions as well as healing through spirituality were identified as potentially psychotherapeutic processes. Again, the categories identified by the authors are similar to those identified in Wolff et al. (2019; Appendix B), including interpersonal and psychological meaning making and pleasant therapeutic target emotions such as love and connection. Furthermore, Villaescusa (2002) found members of the Santo Daime described insights into psychological, physical, and spiritual wellbeing which subsequently resulted in beneficial life changes such as reduced drug and alcohol intake as well as improved diet, mirroring some

categories identified in Wolff et al., including wisdom derived from mystic content and interpersonal and psychological insights.

Broader Implications

Potential Therapeutic Avenues for Psychoactive Plants and Extracts

Medical marijuana illustrates how previously classified drugs can open therapeutic avenues following change in legislation. It was previously assumed that the cannabis plant contained approximately 70 cannabinoids, all of which were deemed *of no therapeutic value* under UK and US drugs legislation (Bostwick, 2012). Since decriminalisation in the US, the figure is now 113 cannabinoids (and continues to rise), many of which are being investigated as potential treatments for specific conditions (Aizpurua-Olaizola et al., 2016). Cannabidiol (CBD) has received the most attention of the cannabinoids, largely due to it being one of the more abundant compounds within the plant. There is growing appreciation that plants have evolved to have balanced constituents that act synergistically (Casey et al., 2017; King et al., 2017). This is reflected in the GW pharmaceuticals product, *Sativex,* a standardised full-plant aerosol extract which has been approved in the UK and is prescribed to treat spasticity, neuropathic pain, symptoms of multiple sclerosis, and overactive bladder (MHRA, 2016; Tallon, 2020).

It is likely that similar routes will be explored for other plant extracts, ayahuasca included. MDMA was originally extracted from the Sassafras tree (Gimeno et al., 2005) and is now being synthesised and used in clinical trials to treat PTSD (Jerome et al., 2020; Mitchell et al., 2021; Mithoefer et al., 2018). These trials are now in Phase III, with similar research into the therapeutic applications of psilocybin, the active compound in psilocybe mushrooms, also

taking place (Carhart-Harris et al., 2021; Mitchell et al., 2021; Rucker et al., 2019). With compounds structurally similar to those found in ayahuasca showing therapeutic potential, it is reasonable to consider that the constituents of the brew could also provide some medicinal benefits.

Ayahuasca Therapy and Randomised Controlled Trials

The majority of RCTs investigating the use of psychedelics have assessed psilocybin and MDMA (Carhart-Harris et al., 2021; Mitchell et al., 2021; Mithoefer et al., 2018; Ross et al., 2016; Rucker et al., 2019). To date there has been one RCT investigating ayahuasca and treatment-resistant depression, with groups in Australia and North America announcing their intention to start clinical trials with ayahuasca in 2022 (Palhano-Fontes et al., 2019; Psychae, 2021; Sacred-Medicines, 2021). Ayahuasca-assisted therapy generally follows the same format as other psychedelics used in a clinical trial setting. Three phases are defined: preparation, dosing, and integration (Carhart-Harris et al., 2021; Mitchell et al., 2021; Mithoefer et al., 2018; Palhano-Fontes et al., 2019; Ross et al., 2016; Rucker et al., 2019). Optimisation of participants' mental state, both before and throughout the acute phase of psychedelic sessions, has a significant role in impacting clinical outcomes (Carhart-Harris, Leech, et al., 2012; Johnson et al., 2008; Nunes et al., 2016). Not only does professional psychological input influence the quality and even the intensity of the experience but is required to help the processing of both emotion and trauma (Johnson et al., 2008). The psychological support provided in preparatory sessions develops rapport, helps the participant understand how to approach challenging experiences, provides psychoeducation surrounding psychedelics and their effects, and is an opportunity to gather information relating to the participants' history and to agree on boundaries, both inside and out of the session (DeKorne, 2011; Watts & Luoma, 2020). During experimental sessions an affirming, non-directive approach is utilised, and

participants are advised to engage with the process as much as possible, reserving conversation and discussion surrounding the experience and its contents for the integrative sessions. Encouragement and emotional support are provided when challenging experiences occur (Guss et al., 2020; Mithoefer et al., 2008; Palhano-Fontes et al., 2019). When done effectively, this can provide the participant with new meaning, understanding of self, and changes in perspective capable of treating addiction and affective disorders (Carhart-Harris, Leech, et al., 2012; Johnson et al., 2008; Nunes et al., 2016).

Although experimental sessions using ayahuasca and other psychedelics generally take place in a hospital setting, effort is taken to remove or conceal medical items and prepare the room in such a way to induce a relaxed state. Pleasing artwork, plants and dim lighting are often used to create a calming atmosphere (Guss et al., 2020; Mithoefer et al., 2008). Unlike other psychedelics, participants often describe particularly intense somatic effects after consuming ayahuasca (Mabit, 2007; Wolff et al., 2019). As such, meditation to promote increased somatic awareness can be recommended after the ayahuasca preparation has been administered (Ruffell et al., in progress). As with most RCTs investigating the use of psychedelics, an appropriate music playlist is used throughout the dosing session (Guss et al., 2020; Mithoefer et al., 2008).

Commencing the day following dosing, integration sessions aim to evaluate and potentially consolidate any insights and changes in mindset that might have occurred (Gorman et al., 2021). Psychological support is provided to help initiate any lifestyle changes that might assist in the recovery from mental illness and promote wellbeing (Guss et al., 2020; Mithoefer et al., 2008). Alongside reviewing the participant's experience, psychological techniques, such as Acceptance and Commitment Therapy (ACT) (Zettle, 1982), can be used to help support beneficial patterns of cognition and behaviour (Guss et al., 2020; Mithoefer et al., 2008).

Integration is especially beneficial in the two months following acute ayahuasca sessions, known as the *afterglow* period, thought to be occasioned by the secondary effects of 5HT2a agonism (Sampedro et al., 2017).

Ayahuasca Psychotherapy: When Therapies Converge

The Western biomedical approach to healthcare, in contrast to the Amazonian perspective, distinguishes psychological causes of illness from physical or social causes, unless specifically stated i.e. *psychosomatic* or *psychosocial* illness (Marcus & Fotiou, 2019). Furthermore, diagnostic categories, such as those implemented by the Diagnostic and Statistical Manual of mental disorders (DSM-V, 2013), serve to further the distance between the mind and the body, as well as society and the individual (Marcus & Fotiou, 2019). For many, concerns have been raised by the clash of paradigms that arises when Western ayahuasca participants expect *corrective* treatment for their brain-based illnesses and are instead met with a situation in which they are presented with ancestors, community relations and entity encounters (Loizaga-Velder & Pazzi, 2014).

As the number of clients attending ayahuasca retreat centres continues to rise, so does the need to establish effective psychotherapeutic integration processes. This is especially important for those attending with the intention of treating psychological ailments (Kavenská & Simonová, 2015). The dramatic increase in the number of centres offering ayahuasca retreats run by Westerners throughout South America and beyond has resulted in *therapeutic pluralism*, where biomedicine meets traditional Amazonian therapies, often alongside psychotherapy, Chinese medicine, yoga, meditation, Ayurveda and even Reiki (Marcus & Fotiou, 2019). This has resulted in an international therapeutic community, comprised of shamans, neo-shamans, and Western mental health professionals. It is now commonplace to see *psychedelic integration*

therapy presented at conferences, offered in workshops, and recommended on psychedelic retreat centre websites (Watts et al., 2017). As well as integrating psychedelic sessions with various Western psychotherapeutic modalities, such as ACT (Sloshower et al., 2020), *Internal Family Systems* (Perkins et al., 2022), or elements of psychodynamic psychotherapy (Mithoefer et al., 2008), a phenomenon is now occurring which has been described as *reverse-colonisation* (Labate & Cavnar, 2014). Interestingly, as foreigners become increasingly immersed in the cosmology of the Amazonian traditions, their focus appears to diverge form the individualistic way of thinking, working instead for the good of their community, and even their ancestors (Foucault, 1988; Marcus & Fotiou, 2019). This blending of paradigms is, however, not without its issues, and can lead to difficulties such as *ontological shock*, which is discussed further in the following section.

Potential Therapeutic Challenges

Although ayahuasca consumption can yield a range of beneficial therapeutic effects, various challenges have also been identified. Unpleasant experiences can arise as a result of the challenging emotional content that emerges when the brew is consumed, for example repressed trauma from childhood (Shanon, 2002). Ayahuasca has been known to disable defence mechanisms, leaving participants to face challenging experiences and intense emotions directly (Jessica L Nielson & Julie D Megler, 2014; Perkins & Sarris, 2021). Large cross-sectional surveys of those drinking ayahuasca in non-clinical settings found a significant proportion of participants encountered psychological and emotional challenges after consuming the brew. Furthermore, the severity of these difficulties was found to correlate with worse mental health outcomes in the long-term (Perkins, Schubert, et al., 2021). Particularly intense experiences have been found to correlate with challenges in integration, and in some cases can result in psychological harm (dos Santos, Osório, et al., 2017; Perkins, Schubert, et al., 2021).

The metaphysical framework used by indigenous communities to explain experiences with ayahuasca can be difficult to interpret through a Western lens. The Shipibo understanding of the world is largely based on *Animism*, the concept that all things have spirit and consciousness, even the inanimate (Shanon, 2010). Furthermore, ayahuasca experiences are often accompanied by descriptions of timeless realms associated with the essence of truth, a concept referred to as *Platonism* (Shanon, 2010). Most traditional practitioners who work with ayahuasca consider it to have a spirit, and it is the spirit that largely results in healing within ceremony. Ayahuasca is used by Shipibo practitioners to *magnify* disease energetically and consequently reveal blockages that need to be addressed (Weiss et al., 2021). Four types of blockages are identified; *shinan* (psychological), *nete* (pertaining to the individual), *yora* (related to the physical body), and *winti* (encompassing desires) (Weiss et al., 2021). A holistic view of health is generally taken in the Shipibo tradition, and is seen to be influenced by connection, encompassing connection to self, community, and the planet. Metaphysical concepts such as those listed above are rarely encountered in Western cultures, and consequently may lead to confusion when first met. There is also the potential of *ontological shock*, the psychological state in which one is forced to question their world view (Lemmens, 2019).

There are various cases in the literature describing problematic insights from ayahuasca ceremonies, resulting in grandiosity, egotistical thinking, and what has been come to be known as *spiritual narcissism* (Fericgla, 2018; Fernández & Fábregas, 2014a; Gastelumendi, 2010; Loizaga-Velder & Pazzi, 2014). Consequently, this can result in bizarre behaviour, whereby such individuals try to express their perceived insights and questionable beliefs (Fernández & Fábregas, 2014a; Shanon, 2002). In addition, it is also important to question the assumption

that ayahuasca, and psychedelics in general, inherently work to improve well-being through increased feelings of connectedness to others, self, and the wider environment (Watts et al., 2017). Pace and Devenot (2021) illustrate this by giving examples of various neo-Nazi organisations that use psychedelics, namely LSD, as a means of radicalising new recruits. The authors go on to describe psychedelics as *non-specific amplifiers* primarily influenced by set and setting (Pace & Devenot, 2021).

Strengths and Limitations

Strengths

Originality

The research included in this thesis is amongst the first to prospectively collect quantitative data evaluating participants undertaking ayahuasca ceremonies in a Shipibo-style retreat setting in the Peruvian Amazon. Furthermore, it includes the first investigation into the effects of any psychedelic on epigenetic change. In turn, I believe the present work is a relevant and timely contribution to the scientific literature pertaining to ayahuasca.

The Use of Comparison Groups

One of the strengths of the study investigating the effect of ceremonial ayahuasca on personality is the inclusion of a comparison group not drinking ayahuasca but backpacking in Peru (Ruffell et al., 2020; Appendix C). Collecting data from people traveling in a foreign country, likely undertaking new experiences, helped reduce potential biases such as regression to the mean (Bland & Altman, 1994). Quite surprisingly the comparison group also displayed changes on the NEO-PI3, including significant increases in Neuroticism six months after

completing their initial inventory. It is possible that this was due to returning home and reencountering everyday stressors. This suggests personality may be significantly affected by experiences such as travel, opening new potential avenues of research.

Observational Investigation of Indigenous Practices

Data were collected at an ayahuasca retreat centre in the Peruvian Amazon. Although RCTs are generally the gold standard for research, there are several advantages of conducting observational research in a ceremonial setting. Firstly, the ceremonial practices associated with ayahuasca have developed over hundreds (Gow, 1994), if not thousands of years (Narby & Cronin, 1998). It is therefore fair to assume that studying these well-established rituals might provide some insight into psychedelic-assisted therapy in the West. Furthermore, there has been a recent emphasis on *decolonising psychology* and science in general (Dobles et al., 2015). Approaching indigenous paradigms with openness and curiosity may help combat epistemological bias and work towards the decolonisation of science (Reiter, 2020).

Limitations

Limitations of Observational Research

There are, however, limitations associated with conducting observational research in a naturalistic setting (Gallagher, 2004; Verster et al., 2019). As with most psychedelic research, especially when conducted in naturalistic settings, I was unable to use a placebo-control group or blind participants. Although one of the quantitative studies did use a comparison group (Ruffell et al., 2020; Appendix C), the remainder were prone to biases such as *demand effects*, whereby participants alter their behaviour subconsciously to fit their interpretation of the study's purpose (Rosenthal & Rosnow, 2009), and expectancy effects (Aday et al., 2021; Bland

& Altman, 1994), as well as the *Hawthorne effect*, a form of bias in which participants change their behaviour as a result of their interactions with, or care from, the study investigators (Sedgwick & Greenwood, 2015). The lack of placebo-control significantly limits the conclusions that can be drawn surrounding the impact of ayahuasca as a substance in comparison to the role of the retreat setting on psychometric outcome measures. Furthermore, the samples were heterogenous, and I had no role in the recruitment of participants onto the retreat, as the screening of participants was undertaken by the Ayahuasca Foundation. This also limits the reliability with which conclusions can be drawn from specific sub-populations.

The retreats provided various potentially psychotherapeutic elements, such as relief from work and home commitments, temporarily living in a biodiverse nature reserve, additional plant medicines, disconnect from everyday society, travel to a foreign country, clean diet, smoke and vapour baths, group sharing circles, abstinence from alcohol and drugs and a sense of community. It is likely that these elements influenced scores on psychometric measures to some degree and acted as confounding variables. As a result, causation cannot be inferred from correlations between ayahuasca use and change in psychological and biological outcomes. Furthermore, some participants engaged in private psychological integration sessions following the retreats, potentially complicating conclusions regarding maintenance effects (all participants who partook in further ayahuasca sessions during follow-up were removed from analyses in Ruffell et al., 2021; Appendix E). Laboratory-based research would attempt to control for such variables, with the aim of demonstrating that changes in participants' outcomes were due to the intervention in question. My research however was not solely assessing the impact of ayahuasca on participants, rather I sought to investigate retreat centres providing ayahuasca ceremonies in the Amazon rainforest as a multidimensional intervention, which include a variety of treatments in addition to ayahuasca. Although this limits the conclusions

that can be drawn in relation to the effects of ayahuasca, my research question was much broader than solely the impact of the brew. Indeed, according to traditional frameworks such as that of the Shipibo, ayahuasca is only one, albeit important, aspect of the traditional treatment regime (Ayahuasca Foundation, 2022). It could be argued that reducing the traditional ayahuasca experience down to the chemicals ingested not only lacks ecological validly but also uses a potential medicine in an inappropriate context, fundamentally biasing results. Future research should strive to utilise culture-controlled methodologies to further evaluate what are potentially vital aspects of traditional treatment regimes, not yet fully recognised by Western clinical healthcare.

The strength of the ayahuasca administered may have differed between ceremonies as well as differing between retreats. Furthermore, set doses of ayahuasca were not used. In fact, each participant was given an entirely subjective dose, dependent on the shaman's recommendation and the individual's willingness. The dose and ratio of the pharmacological components were uncontrolled. Attempting to standardise these features would have retracted from the objective of the studies, which was to investigate traditional ayahuasca use in a retreat setting and would have significantly compromised the ecological validly of the research. Ayahuasca samples were taken to undergo mass spectrometry and consequently determine DMT to harmaloid ratios, however, this was never completed due to the outbreak of COVID-19, which was declared a pandemic in March 2020 (World Health Organisation, 2022). Although this would not control for the quantity of ayahuasca provided, constituent analyses would give information regarding ratios and components in the brew, as well as variability in the tea between retreats.

When participants gave consent to be included in the study, they were informed that that they were free to withdraw consent at any time, that their data would be kept confidential, and that

some of the inventories and semi-structured interviews included as part of the study could trigger emotional reactions. The data collected were largely dependent on participant self-disclosure. As such, I was unable to confirm participants' medical or psychiatric histories. This consequently led to potential issues concerning safeguarding. Fortunately, there were no adverse events during retreats, and I was present as a medical doctor for much of the data collection. It is possible, however, that ayahuasca could result in negative consequences if participants chose not to disclose various conditions. This raises ethical concerns regarding ayahuasca retreats in general. Confirming diagnoses with official medical records in future studies may help to improve the external validity of results, as well as protect from potential safeguarding concerns. As a medical doctor, conducting naturalistic studies at the Ayahuasca Foundation, there was potential for my role at the centre to be misinterpreted. I therefore set up a not-for-profit research organisation under the name of Onaya Science, clearly explaining my affiliation was to this organisation, rather than to the Ayahuasca Foundation. When engaging with participants regarding therapeutic matters outside of official data collection, I maintained a low threshold for re-directing participants to facilitators. This was important to avoid a *duty of care*, where participants were receiving treatments within a paradigm that I am not trained in. In such a situation that an emergency arose, either psychiatric or medical, it was previously decided that I would be available to support participants.

Participants are required to cease their current medication regimes before engaging in ayahuasca retreats (Ayahuasca Foundation, 2022). This has the potential to result in both psychological and physical complications. Furthermore, participants often attend ayahuasca retreats to treat addiction (Fernández & Fábregas, 2014b), and are required to stop using all substances before attending retreats (Ayahuasca Foundation, 2022). Due to the nature of addiction it is possible for participants to relapse, with potential risks associated with the

combination of ayahuasca with substances such as cannabis (dos Santos, 2011). Urine and blood drug tests are not available to ensure cessation of such substances, increasing the risk of negative interactions with ayahuasca and other plant medicines provided.

The use of psychedelic substances such as ayahuasca also has the potential to result in false memory recall and confusion surrounding the material that arises during sessions (Healy, 2021). This was the case in the psilocybin for treatment-resistant depression trials conducted at Imperial College London in 2012, where a participant *reexperienced* being smothered with a pillow by his father when he was a child (Wates, 2018). Since his father was deceased, the participant described confusion following the experience and was unsure as to whether the event occurred or was metaphorical. As the participant described a good relationship with his father, this understandably resulted in psychological distress (Wates, 2018). Furthermore, participants may experience therapeutic challenges such as inappropriate meaning making and ego inflation, discussed further in the *Potential Therapeutic Challenges* section of this thesis.

Unlike clinical trials investigating the use of psychedelic substances, preparation and integration sessions are not routinely offered at ayahuasca retreat centres (Ayahuasca Foundation, 2022; Mithoefer et al., 2011; Mithoefer et al., 2013; Temple of the Way of Light, 2022). Participants were therefore required to arrange their own integration sessions, with the vast majority not receiving formal psychological support, potentially increasing the risk of psychological harm (Timmermann et al., 2022). Due to the observational nature of the research, we were unable to offer such sessions. Concerns have also been raised surrounding the risk of re-traumatisation. Participants on ayahuasca retreats often describe reexperiencing memories (Wolff et al., 2019), and those with a history of trauma may reexperience traumatic memories when drinking ayahuasca (Jessica L. Nielson & Julie D. Megler, 2014). Although reframing

these experiences may be an essential part of treatment, without the necessary support there is a risk of worsening the mental state of the participant (Jessica L. Nielson & Julie D. Megler, 2014).

As previously mentioned, sexual misconduct in ayahuasca circles is unfortunately no longer a rare occurrence (Kavenská & Simonová, 2015; Prayag et al., 2016). It was therefore extremely important to ensure the shamans who led the retreats within which data collection took place maintained a high level of integrity. Fortunately, neither Don Rono Lopez, nor Don Miquel Lopez, the shamans who led the retreats, had engaged in any known incidences of sexual, or any other forms of misconduct. Unlike Western medicine, there is no written protocol for retreats at the Ayahuasca Foundation. Rather, in keeping with the shamanic paradigm, the treatment regime is based largely on the intuition of the shaman, available plants, and the willingness of participants to engage in the treatment. Deviations from protocol are therefore difficult to document, with the potential for additional plants to be added to the ayahuasca brew, such as tobacco, increasing the risk of adverse drug reactions (Kaasik et al., 2021). In addition, there is no official training program for shamans or Western facilitators. As such there is no guarantee that practitioners at ayahuasca centres have received adequate training, nor is there an official background check (such as the Disclosure and Barring Service) to ensure they have not previously committed misconduct. In addition, there is a risk participants may experience a degree of *culture shock*, whereby emersion in a foreign culture can lead to stress and identity confusion (Ward et al., 2020), when receiving treatment in an indigenous paradigm.

A clear limitation of these studies is the self-selected nature of participants, thereby introducing selection bias. There are various barriers to attending ayahuasca retreats in the Amazon rainforest, including taking time off work and the cost of retreats (which are usually thousands

of US dollars). Those who attend ayahuasca retreats also tend to have high levels of Openness, leading to problems with generalisation (Weiss et al., 2021). In my studies, demographic data revealed participants were largely White, had an annual income of $50 – 150K, and many had previous experience with psychedelic substances. Future studies should attempt to assess participants with different characteristics, both demographic and psychological, to allow for reliable generalisations to be made. The retreat setting also lends itself to expectancy effects, largely due to the financial and personal costs associated with traveling to the Amazon rainforest. Metzner (1998) emphasised that individuals attend such ceremonies with specific intentions, for example to acquire healing or spiritual guidance. Further research assessing the use of ayahuasca in different environments with less of an emphasis on ceremony would allow the effects of set and setting to be investigated further. Ayahuasca was administered within a traditional shamanic ceremonial setting, which had been customised for Western participant groups. The placebo effect of the studies within this thesis, in which subjects experienced more than just ayahuasca, should not be underestimated.

Weiss et al. (2021) found baseline personality scores were a strong moderator of adaptive change for those drinking ayahuasca in retreat settings, with low levels of Openness, Extraversion, Conscientiousness and Agreeableness and high Neuroticism seemingly resulting in greater adaptive change i.e., greater reductions in Neuroticism and increases in Openness, Extraversion, Conscientiousness and Agreeableness. It is also worth considering the impact that baseline personality as a potential moderating factor is likely to have on the results in this thesis. If outcomes are largely dependent on the mean scores of personality prior to dosing, variation in samples would likely account for changes seen, providing a potential explanation as to why there are conflicting results regarding the effect of psilocybin on Neuroticism in hospital-based studies (Erritzoe et al., 2018; MacLean et al., 2011). Utilising samples with a

variety of baseline factors could help reduce expectancy effects, and the removal of extreme scores might control regression to the mean. In addition, characteristics such as self-transcendence, absorption, and mindfulness could be measured prior to dosing sessions to evaluate any prediction or moderation effects. Qualitative interviews may also enhance our understanding of the phenomenological mechanism of symptom reduction.

A particular weakness in the personality study (Ruffell et al., 2020; Appendix C) is the failure to compare those who disclosed psychiatric diagnoses on the self-reported measures to those who did not; the relatively small sample size was deemed too small to make such analyses worthwhile. My subsequent work (Ruffell et al., 2021; Appendix E) has examined if there are differences between those with diagnosed conditions and healthy individuals. This helps to establish whether such practices may be useful, not only for individuals with diagnosed psychiatric conditions, but also for people who are considered healthy. Giving ayahuasca to those in good health more closely resembles the format in which traditional communities of the Amazon basin use plant medicine, with treatments employed for a range of reasons, rather than solely for treating mental illness (Lewis, 2008). This is vastly different when compared to the majority of psychedelic-therapy trials, aside from a minority which assesses cognition and emotional functioning in healthy subjects (Rucker et al., 2019) and couples therapy in which participants are permitted to undergo PAP with their partner to improve general wellbeing and relational issues alongside conditions such as PTSD (Monson et al., 2020).

This thesis is comprised of field experiments, thereby limiting the amount of equipment that could be utilised. With an equipped laboratory, neurophysiological, neurobiological, and pharmacokinetic correlates could be added to findings. This could easily be achieved via plasma and other appropriate samples. Ayahuasca sample analysis combined with

microdialysis or cerebrospinal fluid assessments would provide greater clarity into the neuropharmacological outcomes of the specific ayahuasca brews consumed.

Ceiling effects may have limited resolution in my data, especially with shorter item measures, where it can be difficult to assess positive change in those with high baseline scores (Barrable & Booth, 2020; Kossack & Bogner, 2012). This was found to be the case in both the personality paper (Ruffell et al., 2020; Appendix C), with high baseline levels of Openness, and the nature relatedness paper (Ruffell et al., 2022; Appendix D), with high baseline levels of nature relatedness. The use of psychometrically superior instruments could be considered in future studies with accompanying qualitative interviews to avoid common methodological biases and consolidate the validity of findings (Otto et al., 2018).

Attrition

Unfortunately, six-month follow-up failed in the ayahuasca and nature connectedness study (Ruffell et al., 2022; Appendix D). I was personally present at the retreat centre collecting data for the other studies included within this thesis (Ruffell et al., 2020, Appendix C; Ruffell et al., 2021, Appendix E; Wolff et al., 2019, Appendix B). In addition, I gave a short talk at the beginning of retreats to provide information on the study and answer any questions. When contacting participants online for six-month follow-up, the fact that I knew them personally and they had a reasonable understanding of the study most likely contributed to an extremely high retention rate (around 90% for each study). In contrast, participants involved in the nature relatedness study were provided with an information sheet outlining the purpose of the study and asked to complete 30 minutes' worth of questionnaires on a laptop computer. The lack of personal communication and therefore investment in the study likely led to the extreme attrition

rate (less than 10% response rate at six-month follow-up). A decision was therefore made not to include the six-month follow-up data.

The ayahuasca and nature relatedness study (Ruffell et al., 2022; Appendix D) was intended to function as a pilot, and several changes have been made based on the outcomes of the research. A full-time assistant has now been employed at the centre to assist with data collection as well as to introduce studies and answer questions. It should, however, be noted that although this will likely increase sample sizes and reduce attrition rates in subsequent studies, other issues are likely to arise. Unlike with smaller samples when participants attend the same retreat, data will be collected continuously from many different retreats. This will introduce inconsistencies dependent on the availability and variability of plant medicines, different shamans leading ceremonies, different facilitators, variability in food and even the ayahuasca brew itself. I have consequently made amendments to the study design to collect as much of this data as possible, in an attempt to control for these potential variables.

I have professionally filmed an introductory video that is to be sent to participants before they reach the centre. It is hoped that these measures will help to engage participants in the research projects, both when they are on retreat and at long-term follow up. As my presence on the retreats possibly resulted in bias – participants potentially not wanting to disappoint with their results – it is hoped that the video along with an assistant separate from the research will help to reduce attrition whilst also reducing bias. In future studies I shall provide updates via email regarding the progress of the research, both to maintain contact with participants throughout long-term follow-up and to encourage participants to engage in the study. Despite 58 participants enrolling on to the nature relatedness study, I was only able to use data from 24 of the participants to assess change in nature relatedness. Unfortunately, the position of the NR-6

questionnaire on the computer screen appeared to generate confusion. As it was located under another questionnaire, it appears many of the participants did not see it or thought this was optional and consequently did not complete the inventory. By using software that does not allow participants to proceed with incomplete responses, missing data should be avoided moving forward.

Contextual factors, such as the biodiverse setting of the retreat centre, may also mediate change in psychometric outcomes. Interestingly, while the number of ceremonies attended was not found to correlate with scores of nature relatedness in my ayahuasca and nature relatedness study, there was a trend towards significance with number of days spent on retreat (Ruffell et al., 2022; Appendix D). This may be a result of the lack of connection to work and home stressors due to limited internet and phone signal, or the impact of a biodiverse environment on nature relatedness. Although the relevance of these findings is currently uncertain, and the modest sample size must be taken into consideration, this result suggests further research is required to fully understand the role contextual factors such as a jungle retreat setting.

Epigenetics

Epigenetic analysis showed a significant but small increase in the methylation of SIGMAR1 (Ruffell et al., 2021; Appendix E). This result should, however, be interpreted with caution. Ayahuasca doses were not standardised, making it increasingly difficult to infer causality from results. As the analysis followed a candidate gene approach, the results are potentially open to bias. Future studies could utilise hypothesis free methodology to assess DNA methylation across the genome, for example the llumina Human Methylation EPIC BeadChip (EPIC) or 450k arrays. Although the increase in methylation of SIGMAR1 was relatively small, this may be indicative of more substantial processes occurring at the neuronal level, where both DMT

and MAOIs are particularly active (Ruffell et al., 2020; Appendix A). It should be noted, however, that the saliva samples contained peripheral cells which may not be representative of changes that occur in the central nervous system. Saliva comprises a mix of different cells, including lymphocyte and endothelial cells, and consequently genes can differ in their patterns of expression at baseline (Theda et al., 2018). Individuals also show variability due to factors such as oral hygiene. Ideally, neuronal samples would be required to avoid the confounding variables associated with the use of saliva samples, but it is unclear how this would be achieved in human populations (Solomon et al., 2018).

Overcoming Broader Methodological Issues in Psychedelic Research

As research into psychedelic substances continues to emerge as a new field, various methodological issues have been encountered (Aday et al., 2021). One such issue is that of participant masking. Participants are often able to determine whether they received an active psychedelic dose, largely as a result of the subjective experience these substances evoke. To combat the issue of blinding, researchers have used *active placebos*. These compounds mimic the side effects of the experimental substance, but do not provide any of the associated therapeutic benefit (Doering et al., 2014). Crossover designs have been recommended largely to address confounding variables unrelated to the experimental substance as participants control themselves (Aday et al., 2021). However, many of the psychedelic trials to date have shown durability in treatment outcomes, making carry-over effects particularly problematic (Barbosa et al., 2009; Bouso et al., 2012; Griffiths et al., 2019). Grob et al. (2011) conducted a trial investigating psilocybin utilising a crossover design with niacin as an active placebo. Participants were largely able to recognise their treatment condition. Unfortunately, it appears that crossover designs may introduce more confounding variables than the standard parallel arm RCT. As such, psychedelic research is particularly prone to the *placebo effect*, where

positive expectations regarding treatment result in improvements in symptoms, rather than the treatment in question (Aday et al., 2021). Interestingly, some researchers have questioned whether it would be of greater benefit to work to enhance such expectancy effects to the betterment of clinical outcomes (Colloca & Barsky, 2020), with positive expectations having been demonstrated to have a helpful impact on various treatments (Bingel et al., 2011; Kaptchuk et al., 2020).

Psychedelic trials are also particularly prone to various sources of bias. Researchers have specifically raised concerns surrounding the Hawthorne Effect. This phenomenon can lead to an overestimation of therapeutic effect as a result of treatment non-specific factors (Aday et al., 2021). Psychedelic research may also be prone to demand effects, as well as factors unrelated to treatment, such as regression to the mean (Aday et al., 2021). Many participants choose to enrol in experimental treatments such as psychedelics when their symptoms are especially troubling, with extreme scores naturally returning to the average over time. Barnett et al. (2005) recommend multiple observations at baseline, with participants only eligible for selection when they have two or more stable baseline assessments to reduce the effects of regression to the mean.

To date, the majority of RCTs investigating the use of psychedelic compounds have utilised a relatively consistent psychotherapeutic component, often focusing on therapeutic modalities such as ACT (Guss et al., 2020; Mithoefer et al., 2008; Tai et al., 2021). It is likely, however, as the field progresses and researchers begin to evaluate which psychotherapeutic frameworks are most appropriate in combination with psychedelics that new confounding variables will emerge (Horton et al., 2021).

Ethical Considerations Surrounding the Globalisation of Ayahuasca

Ayahuasca Tourism

Drug tourism describes the use of drugs that are illegal in the tourist's home country or destination (Uriely & Belhassen, 2005). Drug related tourism has been increasing since the turn of the millennium, largely by those seeking help for psychological problems, looking to alleviate past traumas or to find spiritual insights (De Rios & Rumrrill, 2008). Lower travel costs, easily available information over the internet, and the growing number of people failing to respond to Western psychiatric treatments has likely led to an increase in ayahuasca tourism over recent years (Kavenská & Simonová, 2015). This, however, is not without its issues. It is largely dependent on the individual to assess whether the people they drink with are safe, or even qualified, with no official vetting for practitioners in Peru. In Amazonian cities there are growing numbers of individuals becoming instant traditional healers without undergoing an apprenticeship period with appropriate teachers. Such people are known as *new shamans, charlatans,* or *neo-shamans* (Fotiou, 2010). Neo-shamans frequently use second-hand information to run ceremonies and deliver treatments that can have negative consequences for participants, both physically and mentally (Homan, 2011).

Issues Surrounding Safety

Financial, emotional, and sexual exploitation has also been reported by individuals imitating *healers* (Prayag et al., 2016). The continued rising interest in ayahuasca has subsequently resulted in an equivalent rise in ill-equipped ayahuasca practitioners (Homan, 2011). Kavenská and Simonová (2015) investigated the most common concerns of those planning on drinking

ayahuasca and found fear of being raped or damaged psychologically by charlatans were prominent. Furthermore, some participants reported that in their ceremonies the shaman appeared drunk, tired, or was even asleep. One participant disclosed she had sexual intercourse with a shaman during her retreat, with another explaining the shaman attempted to engage in sexual activity with female participants in ceremony (Kavenská & Simonová, 2015). Furthermore, in 2014, news outlets reported that a 19-year man from the UK had died in Putumayo, Columbia after ingesting a leaf containing the powerful toxin *scopolamine* and then later ingesting *yage* (ayahuasca; Morris, 2018). Long-term mental disorders, adverse reactions, and even deaths have been documented as a result of the distribution of toxic plants or bad reactions to ayahuasca when participants have not been adequately screened (Tófoli, 2011).

Cultural Appropriation

As the use of ayahuasca continues to grow worldwide, issues surrounding cultural appropriation have arisen. Ayahuasca is considered by many to be a sacrament, and perceived inappropriate use of the brew by those of other communities has raised concerns (DeRios, 1994). For some, ayahuasca retreat centres have become a lucrative business (De Rios & Rumrrill, 2008). Moreover, medicalisation opens the door to an even larger potential market. Many perceive Western individuals making profit from indigenous plant medicine as problematic, especially if sufficient reciprocal arrangements are not in place (Schenberg & Gerber, 2021).

Future Directions

Despite methodological limitations, the present work provides novel, encouraging data for ayahuasca as a medicinal agent, adding to the growing body of literature suggesting it could have therapeutic benefit in a number of psychological conditions. Recent research evaluating the use of ayahuasca in retreat centres has suggested that baseline personality, metacognitive reappraisal, various shamanic elements, as well as mystical-type experiences may reliably predict change in outcome measures (Weiss et al., 2021). Although previous studies evaluating ayahuasca have attempted to create convincing placebo ayahuasca concoctions, none have used a placebo retreat. Uthaug et al. (2021) and Santos et al. (2007) provided placebo ayahuasca in a single ceremony, however these studies did not account for the additional elements that comprise Shipibo-style ayahuasca retreats in the Amazon rainforest. Only after attending a full retreat and receiving a convincing placebo would expectancy and Hawthorne biases be truly controlled for. Although such a study is difficult to implement for logistical and financial reasons, thanks to additional funding I hope I will be able to achieve this in the next two years.

As the effect of most antidepressant agents generally reduces over time (Uher & Pavlova, 2016), it would be prudent to investigate the therapeutic effects of ayahuasca beyond six-month follow-up. Although I did initially attempt 12-month follow-up in the personality study included in this thesis, the attrition rate was extremely high, and the longer-term follow-up was abandoned. It may well be that monetary incentives are required to acquire this data, although this would arguably introduce a new source of bias.

Although there have been some imaging studies assessing the impact of ayahuasca on brain function, this is a relatively understudied area (de Araujo et al., 2012; Palhano-Fontes et al., 2015). This is possibly because compounds such as psilocybin are more easily studied than ayahuasca, both due to the complexity of the brew and the settings in which it is consumed,

and consequently cause and effect is more easily determined. Researchers have not yet embarked on a study comparing different psychedelic compounds. This would be a particularly interesting area of study, with the potential to determine if different entheogens were better suited to specific clinical conditions. Comparative functional imaging could also be of benefit. As psychedelic research and psychedelic-assisted therapy continues to progress, studies comparing MDMA with psilocybin and DMT-harmaloid concoctions could provide valuable insights and work towards treatment optimisation. Assessing clinical outcomes in a variety of different settings could also be informative, especially when considering ayahuasca. Experientially the psychedelic state is known to be largely impacted by set and setting, yet there is currently limited data on this topic. Studies that have attempted to compare jungle to urban and neo-shamanic to shamanic ayahuasca use have been open label, limiting the generalisations that can be made (Fábregas et al., 2010; Kavenská & Simonová, 2015).

Various technologies could be utilised to further our understanding of the physiological effects of ayahuasca. Firstly, every study conducted should aim for high-performance liquid chromatography (HPLC) analyses. This will allow for chemical profiles to be correlated against other findings, providing foundational pharmacological data. The compounds present in ayahuasca could then be investigated in various combinations and in conjunction with secondary constituents. This would help to provide an improved understanding of the interactions between constituents in the brew. Researchers should then aim to utilise as many sophisticated techniques as possible from isolate to interaction studies. Further, fMRI, both pre-post and during ayahuasca sessions, would enhance understanding of the neuronal activity associated with consumption of the brew.

Although epigenetic analysis showed a mean change in SIGMAR1 methylation of 2%, this could be indicative of more prominent processes occurring in neural tissue, the primary site of action of ayahuasca. Research should continue to explore the effect of ayahuasca on SIGMAR1, both in larger human samples and animal models. Studies should also aim to determine if ayahuasca administration affects genes other than SIGMAR1. Although BDNF was also a target gene in my final study (Ruffell et al., 2021; Appendix E), unfortunately there was an error with the analysis, and it was not possible to repeat the process due to the COVID-19 pandemic. BDNF is involved in the differentiation, growth, and maintenance of neurones (Binder & Scharfman, 2004). Furthermore, Kim et al. (2017) suggest BDNF could be a potential biomarker for PTSD and its expression has been found to correlate with PTSD in rodents. In addition to epigenetics, other methods of gene regulation such as alternative splicing due to ayahuasca could be considered.

Despite numerous potential avenues of research, governments have historically appeared reluctant to direct finances towards the investigation of psychoactive compounds for an array of reasons, from political to religious (Sessa, 2012). Most countries have had very tight restrictions over such compounds, making it practically impossible for scientists to access them (Sessa, 2012). Fortunately, this appears to be changing with recent moves towards medical marijuana and the funding of RCTs investigating psilocybin, MDMA and DMT-harmaloid combinations (Australian Government Department of Health, 2022; Sessa, 2012). Despite this, significant logistical barriers remain that prevent research of these substances and sample sizes in human trials remain small. Continued controlled investigation is warranted, given the promising data with few adverse events and large effects sizes. Further work is needed to standardise ayahuasca formulations for such trials, according to pharmaceutical GMP, and to develop appropriate therapeutic treatment models in which to use it.

Conclusions

The data presented within this thesis provide encouraging preliminary results. Despite this, further research is required to ascertain whether ayahuasca in a traditional Shipibo-style Amazonian retreat setting could be used therapeutically. Controlled trials are required to further explore the independent and potentially interacting roles of the ceremonial setting, differing ratios of components within the brew, and the traditional framework. The key features of the traditional format include the group setting, the *purge*, the *maloka* or ceremonial space, the singing of *icaros* and the role of the shaman (*curandero*). Despite these unique elements, there are various similarities with current psychedelic assisted therapy protocols, such as the use of music, relative sensory deprivation (through either the use of eye shades and headphones or drinking ayahuasca at night), the supportive role of the *shaman*/therapist, and the emphasis on introspection with minimal communication during the sessions (Guss et al., 2020; Mithoefer et al., 2008).

There are, however, elements that make ceremonial ayahuasca use quite unique. Music is performed live by the *shaman* and retreats take place in a communal setting in which multiple people reside and drink ayahuasca together for anywhere between days and months. The communal aspect may have various therapeutic benefits, such as providing opportunities to engage in a new way of relating to others, normalising difficulties with mental health, and encouraging trust, bonding, empathy, and vulnerability (Trope et al., 2019). Furthermore, such settings may induce states of *communitas*, defined as a transient dissolution of power dynamics

and social structure, demonstrated to mediate increases in social connectedness and well-being (Kettner et al., 2021; Turner, 2012). Ayahuasca retreats often include *sharing circles*, providing a space for participants to discuss their experiences, interpretations of sessions, and current mental state in a supportive group setting (Fotiou, 2020; Ayahuasca Foundation, 2022). This is reminiscent of group therapy, which can be effective in treating various conditions, such as trauma-related difficulties (Ford et al., 2009) and substance misuse (Weiss et al., 2004), in some instances proving more effective than individual psychotherapy (Scheidlinger, 2000; Toseland & Siporin, 1986). Furthermore, the physical presence of the *shaman* preforming in ceremony may act to further induce mystical experiences, a factor which has been associated with greater change in psychometric measures throughout psychedelic research (Carhart-Harris et al., 2018; Carhart-Harris & Goodwin, 2017; Erritzoe et al., 2018; Griffiths et al., 2018; MacLean et al., 2011; Mitchell et al., 2021; Mithoefer et al., 2018; Perkins, Opaleye, et al., 2021; Perkins, Schubert, et al., 2021; Russ et al., 2019). Although difficult to comprehend through a Western lens, one should not disregard the notion that shamanic psychospiritual healing could help occasion the beneficial changes observed in this body of research. It is yet to be determined whether Western psychedelic-assisted therapy can provide more benefit than traditional shamanic practices, however, a less polarised view, considering both with an open mind, is advisable. A fusion between the two, taking beneficial elements from each, is likely, as has been the case with the integration of techniques such as mindfulness and yoga into Western culture (Purser, 2019). However, individual preference and suitability is of prime importance.

The traditional practices of indigenous communities like the Shipibo are only just starting to be investigated using scientific methods, yet knowledge and appeal of their techniques appear to be spreading quickly through the Western media space (Yaden et al., 2021). Emphasis must

be placed on preventing history from repeating itself, whereby psychedelics are not naively glamorised as they were in the 1960s, which resulted in the complete restriction of scientific testing on potentially useful compounds and the birth of the *War on Drugs* (Rucker, 2015). Rather, they should be investigated using solid scientific methods in a range of frameworks. Only then will we be able to fully establish their legitimate potential, and thus enable novel treatments which could minimise suffering for a range of conditions.

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Brazilian Journal of Psychiatry
BJP
Revista Brasileira de Psiquiatria

www.neip.info
Braz J Psychiatry. 2020 xxx-xxx;00(00):000-000
doi:10.1590/1516-4446-2020-0884
Brazilian Psychiatric Association
BY-NC

SPECIAL ARTICLE

The pharmacological interaction of compounds in ayahuasca: a systematic review

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Ayahuasca is a South American psychoactive plant brew used as traditional medicine in spiritual and in cultural rituals. This is a review of the current understanding about the pharmacological mechanisms that may be interacting in ayahuasca. Searches were performed using PubMed, PsycINFO, and Web of Science databases and 16 papers were selected. As hypothesized, the primary narrative in existing research revolved around prevention of deamination of N,N-dimethyltryptamine (N,N-DMT, also referred to as DMT) by monoamine oxidase inhibitors (MAOIs) in ayahuasca. Two of the constituents, DMT and harmine, have been studied more than the secondary harmala alkaloids. At present, it is unclear whether the pharmacological interactions in ayahuasca act synergistically or additively to produce psychoactive drug effects. The included studies suggest that our current understanding of the preparation's synergistic mechanisms is limited and that more complex processes may be involved; there is not yet enough data to determine any potential synergistic interaction between the known compounds in ayahuasca. Our pharmacological understanding of its compounds must be increased to avoid the potential risks of ayahuasca use.

Keywords: Dimethyltryptamine; B-carboline; ayahuasca; tetrahydroharmine; monoamine oxidase inhibitor

Introduction

Ayahuasca is a South American psychoactive plant brew used as traditional medicine in spiritual and in cultural rituals. Within indigenous communities in Brazil, Peru, and Colombia, ayahuasca is believed to have healing properties that are employed to treat spiritual, physical, and psychological ailments. The brew is use often related to mystical experiences and spiritual encounters.[1] The name ayahuasca loosely translates to "vine of the soul" or "vine of the dead."[2] Traditional practices usually involve a shaman, or curandero, who facilitates the experience for individuals in their respective communities.[1] Since the 20th century, the globalization of ayahuasca has spread beyond native indigenous groups and has been incorporated in syncretistic churches, indigenous-like, and non-indigenous ("neo-shamanic") practices.[1]

An ayahuasca brew usually consists of two plant constituents: *Psychotria viridis*, commonly known as "chacruna," and *Banisteriopsis caapi*, also independently referred to as the "ayahuasca vine" or simply "ayahuasca." *Psychotria viridis* contains the psychoactive compound N,N-dimethyltryptamine (N,N-DMT, also referred to as DMT), and *Banisteriopsis caapi* contains β-carbolines, mainly harmine, harmaline, and tetrahydroharmine (THH) ("harmala alkaloids"). Although DMT is psychoactive when smoked or infused intravenously, when ingested orally it is broken down by the stomach enzyme monoamine oxidase, rendering its psychoactive properties void. β-carbolines are reversible inhibitors of monoamine oxidase-A (MAO-A) and act to prevent the deamination of DMT when present in the ayahuasca brew.[3,4] Thus, the psychotropic effects of the brew are a result of combining the compounds in the two plant species. A range of other ingredients is often used in ayahuasca preparations, yet it is understood that the basic mechanism of action is psychoactivity resulting from the increased bioavailability of DMT when ingested with monoamine oxidase inhibitors (MAOIs). Mechanistic data on the psychopharmacological interactions in ayahuasca have been relatively under-researched, focusing on the interaction between DMT and MAOIs. Not much more is known about these pharmacological interactions and how they specifically contribute to the effects or side effects experienced by users.

Strassman et al.[5] administered intravenous DMT (negating the need for a MAOI) to 60 volunteers, finding that DMT's psychoactive effects are much shorter than when ingested in ayahuasca, usually lasting between 10 and 30 minutes, similar to smoked DMT.[5] DMT is a structural analogue of serotonin and melatonin and a functional

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Submitted Jan 31 2020, accepted May 06 2020.

How to cite this article: Ruffell S, Netzband N, Bird C, Young AH, Juruena MF. The pharmacological interaction of compounds in ayahuasca: a systematic review. Braz J Psychiatry. 2020;00:000-000. http://dx.doi.org/10.1590/1516-4446-2020-0884

analogue of other tryptamines, such as 4-AcO-DMT, 5-MeO-DMT, 5-HO-DMT, psilocybin (4-PO-DMT), and psilocin (4-HO-DMT).[6] When orally ingested and combined with MAOI alkaloids, the psychotropic effects last longer, between 4 and 6 hours.[7] Riba et al.[8] obtained 24-hour urine samples from six participants who had consumed 25 mg of DMT, assessing the concentration of compounds present before and after either smoking or oral ingestion of DMT. Those who smoked DMT were found to experience the full psychoactive effects of the drug, with metabolized DMT and DMT-NO comprising 10 and 28% of the metabolites found in urine, respectively. When taken orally, 97% of the compounds recovered were MAO-dependent indole-3-acetic acid, with 3% DMT-NO. An inverse correlation was apparent between the indole-3-acetic acid/DMT-NO ratio and the participants' intensity rating. The authors suggested this is indicative of a change in metabolism from MAO to CYP-dependent.[8] This correlates with the psychoactive effects experienced in the above study, as well as those from the combination of DMT and MAOIs found in ayahuasca. MAOIs have also been found to increase levels of other tryptamines, such as 5-MeO-DMT. Halberstadt[9] found that MAOIs directly affect the pharmacodynamics of 5-MeO-DMT, leading to higher levels in the nervous system.

Acute users of DMT-containing ayahuasca have reported feelings of transcending time and space, euphoria, meaningful encounters with seemingly sentient entities, and a sense of oneness.[7] Narrative accounts of the DMT experience present considerable overlap with phenomena associated with a near-death experience, including out-of-body experience, the presence of an irreversible threshold, travelling towards light via a tunnel or a void, and life review.[10] DMT has been colloquially called "the spirit molecule."[4] DMT is a serotonergic psychedelic drug, a class including psilocybin and lysergic acid diethylamide. Evidence from animal and human studies demonstrates that the psychedelic effects of these substances, including distorted sensation and perception, are mediated by binding action at the 5-HT2A receptor.[11,12] These drugs also bind to a number of 5-HT receptor subtypes, as well as other monoamine receptors.[12] DMT, specifically, binds to 5-HT1A, 5-HT1B, 5HT-1D, 5HT2A, 5-HT2B, 5-HT2c, 5-HT5A, 5-HT6, and 5-HT7A.[11] It has been found that lesser-known tryptamines, such as 5-MeO-DMT, also have an affinity for 5HT receptors. Halberstadt[9] used rat models to show that 5-MeO-DMT can disrupt pre-pulse inhibition by activating 5-HT2A receptors and can act on 5-HT1A.

After a research hiatus following the UK's Misuse of Drugs Act 1971, psychedelic drugs are again being investigated. New techniques, such as positron emission topography and functional magnetic resonance imaging are studying the neurobiological activity of these compounds. The DMT-containing brew is more complicated than many of its psychedelic counterparts since it contains multiple psychoactive compounds. This makes it difficult to produce standardized, medical grade ayahuasca for clinical research. This is further exacerbated by variation in the DMT/MAOI proportions used in ayahuasca preparations (and often, the addition of other plant compounds) across studies.[13-15] To achieve dose uniformity, encapsulated lyophilized (freeze-dried) ayahuasca has been used in a number of studies[8,13] involving oral administration of ayahuasca. The DMT and alkaloid concentrations in ayahuasca preparations have been quantified via various methodologies.[14,15]

This review aims to investigate the current literature on the pharmacological interaction of compounds present in ayahuasca. Although it is generally accepted that interaction between DMT and MAOIs makes the DMT bioavailable, it is unclear how DMT and MAOIs interact pharmacologically in ayahuasca, whether synergistically or additively, to produce the substance's unique psychoactive, psychedelic, and adverse effects.

Methods

The PubMed, PsycINFO, and Web of Science databases were searched through September 2019 for the following terms: (ayahuasca OR DMT OR dimethyltryptamine) AND (B-carboline OR constituents OR chemistry OR harmine OR harmaline OR harmala alkaloids OR tetrahydroharmine OR harmalol OR MAOI OR monoamine oxidase inhibitor OR pharmacology OR pharmacokinetics OR pharmacodynamics OR psychopharmacology OR synergy).

The reference lists of relevant studies were checked for additional papers, and secondary searches were performed using related keywords. This database was also manually searched to find abstracts or titles including the aforementioned search terms. A total of 2,141 papers were identified, of which 1,957 were extracted, following the removal of duplicates. A review of the titles and abstracts eliminated all but 202 papers, which were screened in greater detail for eligibility. The abstracts, methods, and findings of these papers were assessed, reducing the number to 57 for full text analysis. A total of 16 studies examined the pharmacology of ayahuasca as a brew or its known active compounds, either isolated or synergistically, and were included in the review. Only papers that had undergone full peer review and were published in English were included. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16]

Data from the included studies were identified and collected in a standardized form by two researchers. The data collected included the authors, date, study design, sample characteristics (sample size, age, sex), measures, and key findings – including established pharmacological mechanisms of action and limitations. The review employed a two-phase content synthesis: the literature was first analyzed according to study design, and findings across studies were then included to provide a depiction of the pharmacological action of the compounds present in ayahuasca. Risk of bias was assessed, including randomization, handling of missing data, and selective reporting. When discrepancies in article inclusion arose, consensus was reached via discussion.

A summary of the findings is shown in Table 1.

Table 1 List of research studies included in the systematic review

Authors	Year	Title	Findings	Further comments
Mckenna[4]	1984	Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and ß-carboline constituents of ayahuasca	Showed MAOI effect in vitro. Proposes that inhibition experiments using mixtures of ß-carbolines indicate that their effects in combination are additive, rather than synergistic or antagonistic.	Original proposal regarding DMT deamination prevention via MAOI in harmala alkaloids from *P. viridis.*
Callaway[17]	1994	Platelet serotonin uptake sites increased in drinkers of ayahuasca	Increased number of serotonin mRNA transporter sites in regular ayahuasca drinkers against control group.	-Shows an increased number of binding sites in platelets. -No evidence of this for DMT alone, which is suggestive of a synergistic effect.
Strassman[5]	1994	Dose-response study of N, N-dimethyltryptamine in humans	-Peak DMT blood levels and subjective effects were seen within 2 minutes after drug administration and were negligible at 30 minutes. -DMT dose-dependently elevated blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to elevating blood concentrations of ß-endorphin, corticotropin, cortisol, and prolactin. Growth hormone blood levels rose equally in response to all doses of DMT, and melatonin levels were unaffected. -Threshold doses for significant effects relative to placebo were also hallucinogenic ($>$ 0.2 mg/kg) -Subjects exposed five or more times to 3,4-methylenedioxymethamphetamine had less robust pupil diameter effects than those exposed two times of less. -Evidence that DMT is unique in the inability to develop tolerance to its psychological effects.	Dose-response data for IV DMT fumarate, neuroendocrine, cardiovascular, autonomic, and subjective effects in a group of experienced hallucinogen users.
Smith[18]	1998	Agonist properties of N, N-dimethyltryptamine at serotonin 5-HT2A and 5-HT2C receptors	-DMT fully substituted for DOI. Intact choroid plexus was used to evaluate the agonist properties at endogenous 5-HT2C receptors. -DMT was a partial agonist at 5-HT2C receptors in this native preparation. -DMT behaves as an agonist at both 5-HT2A and 5-HT2C receptors. -One difference was evident in that the 5-HT2C, but not the 5-HT2A, receptor showed a profound desensitization to DMT over time (suggestive of limited application for repeat prescription).	Evidence of DMT 5HT2a(c) agonism.
Callaway[19]	1999	Pharmacokinetics of Hoasca alkaloids in healthy humans	-THH shows PK profile independent to harmine. -Affinities and other PK values provided.	-Evidence that THH alone may be a weak SSRI. -Implies further synergistic effects on the serotonin system.
Ott[20]	1999	Pharmahuasca: human pharmacology of oral DMT plus harmine	-MAO inhibition from simultaneous ingestion of ß-carbolines confirmed by eight self-experimenters. -Results of a total of some 70 bioassays are summarized and the literature on this subject is reviewed.	-Evidence that DMT and harmine in tablet form create similar effects to ayahuasca, further reinforcing the DMT MAOI interaction. -When orally ingested, DMT without harmine is non-active.

Continued on next page

Table 1 (*continued*)

Authors	Year	Title	Findings	Further comments
Glennon[21]	2000	Binding of ß-carbolines and related agents at serotonin (5-HT2 and 5-HT1A), dopamine (D2) and benzodiazepine receptors	Affinity scores at 5-HT2 for harmine/harmaline.	Shows that other harmala alkaloids also bind to the 5HT2 receptors, further suggesting synergistic potential in the serotonergic system.
Riba[22]	2003	Human pharmacology of ayahuasca	-Diastolic blood pressure significant increase. -Heart rate moderate increase. -Increased urinary normetanephrine excretion. -Deaminated monoamine metabolite levels did-not decrease (contrary to typical MOAI effect profile). -The negligible harmine plasma levels found suggest a predominantly peripheral (gastrointestinal and liver) site of action for harmine.	-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca. -PK angle. -Small sample size (n=18).
Riba[23]	2006	Increased frontal and paralimbic activation following ayahuasca	-Significant activation of frontal and paralimbic brain regions. -Increased blood perfusion observed bilaterally in anterior insula, gather intensity in right hemisphere, and anterior cingulate/frontal medial cortex of right hemisphere. -Increases observed in left amygdala/parahippocampal gyrus. -Concludes that ayahuasca interacts with neural systems that are central to interoception and emotional processing.	-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca. -Neuroimaging angle. -Used SPECT.
Fortunato[24]	2010	Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus	-Increased BDNF protein levels in rat hippocampus. -Concludes that findings within support the hypothesis that harmine could bring about behavioral and molecular effects.	Further evidence that the synergistic mechanisms of DMT + harmine are more than just effects of MAOIs.
dos Santos[25]	2011	Autonomic, neuroendocrine, and immunological effects of ayahuasca: a comparative study with D-amphetamine	-Significant increases in prolactin. -Percentage of CD3/4 were decreased, natural killer cells increased. -Maximum changes occurred around 2 hours, returned to baseline after 24 hours. -Ayahuasca displayed moderate sympathomimetic effects, significant neuroendocrine stimulation, and time-dependent modulatory effect on cell-mediated immunity.	Focuses on the synergistic effects of ayahuasca rather than individual action of compounds. Immunological, rather than neuropsychological, perspective.
McIlhenny[26]	2011	Methodology for determining the major constituents and metabolites of the Amazonian botanical medicine ayahuasca in human urine	-Showed that the major metabolite of a DMT is the corresponding DMT-NO, the first time this metabolite has been described in *in vivo* studies in humans. -Very little DMT detected in urine, despite the MAOI. -Major alkaloid excreted was THH. -List of other products and metabolites quantified.	-Provides methodology for identifying and quantifying constituents of ayahuasca in human urine. -PK data of tested samples provided.Excretion and metabolism of THH should be further investigated.

Continued on next page

Table 1 (*continued*)

Authors	Year	Title	Findings	Further comments
McIlhenny[27]	2012	Methodology for determining major constituents ofayahuasca and its metabolites in blood	-DMT concentrations lower than DMT-NO at all time points. -Plasma DMT-NO concentrations three to four times higher than DMT. -DMT-NO forms rapidly after drug administration. -THH levels peaked at around 4.5 hours. -Harmine and harmaline present in most samples.	-Single methodology combining HPLC and gas chromatography to identify ayahuasca constituents in blood following oral consumption. -First report of presence of DMT-NO in human blood following ayahuasca/DMT administration. -Method for the most complete profile of DMT, harmala alkaloids, and metabolite concentrations.
Riba[13]	2012	Metabolism and disposition of N, N-dimethyltryptamine and harmala alkaloids after oral administration of ayahuasca	-Less than 1% of DMT excreted unchanged. -Fifty per cent was recovered as indole-3-acetic acid or DMT-NO. -Ten per cent was other MAO-independent compounds. -Recovery of DMT plus metabolites reached 68%. -Harmol, harmalol, and THH conjugates were abundant in urine. -The recovery of each harmala alkaloid plus its 0-demethylated metabolite varied greatly (between 9 and 65%).	-PK study with implications regarding alternative metabolic routes for DMT other than biotransformation by MAO. -Freeze-dried ayahuasca. -Urine samples obtained. -Small sample (n=10).
Morales-Garcia[28]	2017	The alkaloids of *Banisteriopsis caapi*, the plant source of the Amazonian hallucinogen ayahuasca, stimulate adult neurogenesis *in vitro*	Significant neurogenesis in adult hippocampal cells *in vitro* with harmine.	Suggests that ayahuasca brew may have more complex synergistic properties than we currently understand. Shows that harmine alone could be partially responsible for the neurological changes seen in ayahuasca users.
Sampedro[29]	2017	Assessing the psychedelic ‘‘after-glow’’ in ayahuasca users: post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities	-Magnetic resonance spectroscopy showed post-acute reductions in glutamate + glutamine, creatine, and N-acetylaspartate + N- acetylaspartylglutamate in the posterior cingulate cortex. -Connectivity was increased between the posterior cingulate cortex and the anterior cingulate cortex, and between the anterior cingulate cortex and limbic structures in the right medial temporal lobe. -Glutamate + glutamine reductions correlated with increases in the ‘‘nonjudging’’ subscale of the Five Facets Mindfulness Questionnaire-Increased anterior cingulate cortex-medial temporal lobe connectivity correlated with increased scores on the self-compassion questionnaire. -Post-acute neural changes predicted sustained elevations in nonjudging 2 months later.	-DMN activity decrease and increased neural connectivity to other areas of the brain. -Supported by other studies on 5HT2a agonists. -Long-term neurological differences found after ayahuasca administration.

BDNF = brain-derived neurotropic factor; DMN = default mode network; DMT = N,N-dimethyltryptamine; DMT-NO = DMT-N-oxide; DOI = 2,5-dimethoxy-4-iodoamphetamine; HPLC = high-performance liquid chromatography; IV = intravenously; MAO = monoamine oxidase; MAOI = MAO inhibitor; PK = pharmacokinetic; SPECT = single photon emission tomography; SSRI = serotonin reuptake inhibitor; THH = tetrahydroharmine.

Description of studies

Mechanistic data of DMT as an isolated compound

Strassman et al.[5] provided dose-response data regarding the neuroendocrine, cardiovascular, autonomic, and subjective effects of intravenously administered dimethyltryptamine fumarate in a group of experienced hallucinogen users. Peak DMT blood levels and subjective effects were seen within 2 minutes of drug administration and were negligible at 30 minutes. Intravenous DMT elevated blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to dose-dependent elevation of blood concentrations of β-endorphin, corticotropin, cortisol, and prolactin. Blood levels of growth hormone rose equally in response to all doses of DMT, although melatonin levels were unaffected. Threshold doses for significant effects relative to placebo were also psychedelic (0.2 mg/kg and higher). Subjects exposed five or more times to 3,4-methylenedioxymethamphetamine demonstrated less robust pupil diameter effects than those exposed two times or less.

Smith et al.[18] produced supporting data using intact choroid plexuses, evaluating agonist properties at endogenous 5-HT2A/C receptors. These receptors are highly expressed on layer V pyramidal neurons in the cortex and are also found in the hippocampus, striatum, and amygdala.[30] It was concluded that although DMT behaves as an agonist at both 5-HT2A and 5-HT2C receptors, it was only a partial agonist at 5-HT2C receptors. In addition, the 5-HT2C, but not the 5-HT2A, receptor showed a profound desensitization to DMT over time. Finally, this study showed that DMT's 5HT affinity was equal to that of 2,5-dimethoxy-4-iodoamphetamine. DMT has an affinity with numerous other serotonergic receptors, including 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2B, 5-HT5A, 5-HT6, and 5-HT7.[11]

It has been suggested that DMT may be an endogenous ligand of the sigma-1 receptor, which implies that it could play a role in neuromodulation of 5-HT, as well as being a 5-HT agonist.[12] This hypothesis has not yet received any support, since it has not been validated with scientific methods.[31] It should also be noted that DMT's affinity for sigma-1 is 100 times lower than its affinity for 5-HT2A. Furthermore, since there is a relatively low level of endogenous DMT circulating in the body, it appears unlikely that sigma-1 plays a major role in relation to endogenous DMT.[32]

The pharmacological interaction between DMT and MAOs

McKenna et al.[4] demonstrated that the β-carbolines in ayahuasca have an inhibitory effect on MAO *in vitro*. Ott,[20] achieved the same effect *in vivo* using tablet-form DMT combined with the β-carboline alkaloid harmine, providing evidence that without MAOIs, DMT would be non-psychoactive when orally ingested. McKenna[4] reported that inhibition experiments using mixtures of β-carbolines and DMT indicated that their combined effects are additive, rather than synergistic or antagonistic.

Harmala alkaloids have been shown to primarily inhibit MAO-A, rather than MAO-B. The effective concentrations necessary to inhibit MAO-A have been reported as 8×10^{8} M for harmine, 6×10^{-8} M for harmaline, and 1.4×10^{-5} M for THH. At higher concentrations, both harmine and harmaline begin to inhibit MAO-B.[33] In addition, a case study of β-carboline alkaloid intoxication following ingestion of *Peganum harmala* seed extract also found that they had affinity for 5-HT receptors independently of DMT.[34] Ataxia, hallucinations, vomiting, and confusion have been attributed to CNS stimulation by MAOIs, as has the ability of THH to inhibit the reuptake of serotonin in the presynaptic membrane.[35]

Glennon et al.[21] investigated the affinity values of β-carbolines and related agents at 5-HT2 and 5-HT1A, as well as at dopamine and benzodiazepine receptor sites, concluding that harmala alkaloids also bind to 5-HT2 receptors with a potency comparable to that of DMT. Callaway et al.[17] found that regular ayahuasca drinkers had more 5-HT mRNA transporter sites in platelets than non-ayahuasca drinking controls. This finding suggests that, when prepared as a brew, ayahuasca causes an upregulation of 5-HT receptors. It appears that this is not the case with DMT as an isolated compound or with chronic administration of β-carbolines alone. Taken together, this suggests that the complexity of ayahuasca's synergistic mechanisms may be greater than is currently understood.[36]

Isolated harmine had an antidepressant effect in a rat model after chronic administration in hippocampal tissue, leading to increased brain-derived neurotrophic factor protein levels.[24] Nevertheless, as with all animal studies, caution is necessary when applying the results to humans.

Another study by Callaway et al.[37] showed that the pharmacokinetic profile of THH is independent of any of the other β-carbolines present in *B. caapi*, particularly in contrast to harmine. This study established that THH acts as a weak serotonin reuptake inhibitor (SSRI), providing evidence that it is the only harmala alkaloid that causes neurochemical shifts in presynaptic tissue. This again implies that synergistic mechanisms are at play when ayahuasca is consumed as a brew, since it increases the amount of 5-HT in synaptic clefts and has a direct serotonin agonist effect on postsynaptic receptors. Morales-García et al.[28] studied the impact of harmala alkaloids (vs. a saline control sample) on human hippocampal tissue *in vitro*, finding that harmine triggers neurogenesis in stem cells.

The neurobiological effects of ayahuasca

Using single-photon emission computed tomography (SPECT), Riba et al.[23] carried out a double-blind placebo-controlled clinical trial using freeze-dried ayahuasca. Significant activation of the frontal and paralimbic brain regions was observed. Increased blood perfusion was observed bilaterally in the anterior insula, with greater intensity in the right hemisphere. This was also the case in the anterior cingulate and frontal medial cortex of the right hemisphere. Increased activation of the left amygdala and

parahippocampal gyrus were also recorded. The authors concluded that ayahuasca interacts with neural systems that are central to introspection and emotional processing, increasing serotonergic neurotransmission in these processes. The study had a small sample (n=15) consisting only of men of a limited age range (28-48).[23]

Using magnetic resonance spectroscopy technology, Sampedro et al.[29] found post-acute reductions in glutamate and glutamine, creatine, and N-acetylaspartate + N-acetylaspartylglutamate in the posterior cingulate cortex. Increased activity was observed between the posterior cingulate cortex and the anterior cingulate cortex, as well as between the anterior cingulate cortex and limbic structures in the right medial temporal lobe. Glutamate and glutamine reductions correlated with increases in "non-judging" subscale scores in the Five Facets Mindfulness Questionnaire. Additionally, increased anterior cingulate cortex-medial temporal lobe connectivity correlated with increased scores in the Self-Compassion Questionnaire. Post-acute neural changes predicted sustained elevation in non-judging after two months, which was deemed a long-term result. This study could provide a mechanistic explanation for the often described experiential effect of post-ayahuasca "after-glow."[29]

McIlhenny et al.[26] provided methodological guidelines for identifying the constituents of ayahuasca samples, using sample dilution and high-performance liquid chromatography in human urine. They also provided pharmacokinetic profiles of the constituent compounds of ayahuasca. They found that that the major metabolite of N, N-DMT is the corresponding N-oxide. This was the first time that this metabolite has been described in human *in vivo* studies. Minute amounts of DMT were detected in urine samples from three individuals, despite the fact that MAOIs were present in the administered ayahuasca. The major alkaloid excreted was THH. The presence of other β-carbolines was deemed to be below significant thresholds. The authors conducted a follow-up study to determine the metabolites of ayahuasca constituents in blood following oral consumption of the brew, using a combination method of high-performance liquid chromatography and gas chromatography.[27] The plasma concentration of DMT-N-oxide (DMT-NO) was three to four times that of DMT. This is the first study to find DMT-NO in human blood following ayahuasca/DMT consumption. DMT-NO levels peaked 1.5 hour after ayahuasca administration ($\sim$ 45 μg/mL). THH was observed to peak at around 4.5 hours ($\sim$ 55 μg/mL), being the major harmala excretion product in human urine.[26] Harmaline, harmine, harmalol, harmol, 7-hydroxy-THH (THHOH), and 2-methyl-1,2,3, 4-tetrahydro-P-carboline (2-MTHBC) were found in most samples. Significant increases of plasma levels of indoleacetic acid were observed.[27]

Riba et al.[13] added greater scope to the above findings. Using pharmacokinetic assessment of urine, they found that less than 1% of the excreted DMT remained unchanged. A total of 50% was recovered as indole-3-acetic acid and DMT-NO, with 10% other MAO-independent compounds. However, 68% of DMT plus metabolites was recovered, and harmol, harmalol, and tetrahydroharmine conjugates were abundant. The recovery of each harmala alkaloid plus its O-demethylated metabolite varied between 9 and 65%. These results imply that there may be another metabolic route for DMT besides biotransformation by MAO. It should be noted that the sample was small (n=10) and consisted solely of men, limiting generalization of the results.

In a previous double-blind placebo-controlled trial with freeze-dried ayahuasca, Riba et al.[22] found significantly increased diastolic blood pressure, moderate increases in heart rate, as well as increased urinary excretion of normetanephrine. However, deaminated monoamine metabolite levels did not decrease, unlike a typical MOAI effect profile. Furthermore, negligible harmine plasma levels were found, suggestive of predominantly peripheral (gastrointestinal and liver) sites of action.

Dos Santos et al.[25] investigated the autonomic, neuroendocrine, and immunological effects of short term ayahuasca use, principally from a synergistic perspective. Focusing on immunological implications of the brew, neuropsychological outcomes were of secondary importance. They observed significant increases in prolactin, along with a decrease in the percentage of CD3/4 T cell co-receptors. Significant increases in natural killer cells were also recorded. Such changes peaked around 2 hours and returned to baseline after 24 hours. The sample was of limited size and all male. They concluded that ayahuasca had moderate sympathomimetic effects, significant neuroendocrine stimulation, and time-dependent modulatory effect on cell-mediated immunity.

Discussion

This review clearly demonstrates that the published research is insufficient to determine potential synergistic interactions between the known compounds of ayahuasca. Although it has been previously suggested that the mechanisms may be additive, rather than synergistic or antagonistic,[4] the data presented here suggest that such conclusions cannot be drawn from our current understanding.

The majority of studies that have reached conclusions have focused on DMT and harmine, both as isolated compounds or in combination with each other, finding that DMT deamination in the gut is prevented when the compounds are combined.[4,20] The exception to this is Riba et al.,[38] who suggest that there may be more complex metabolic routes for DMT. It is evident at this stage that even the most basic principles of interaction are not thoroughly understood. In addition to this, much of the data may not be directly applicable *in vivo* to humans, with the majority of findings being from either animal or *in vitro* studies. Human samples are limited by small size and/or gender and age range issues.

Cortical oscillatory activity is a key part of brain function due to its connection in input selection, temporal activity management, and synaptic plasticity. Changes in oscillatory activity have been related to schizophrenia, and the study of brain oscillations between frequencies has been considered a useful instrument in schizophrenia research. Variations in cortical oscillatory activity also occur in other models of psychosis.[39] The neurobiological basis of

hallucinogenic action suggests that changes in primary sensory areas (V1) and the prefrontal association cortex are associated.[23] Schenberg et al.[40] used electroencephalogram recordings to demonstrate that ayahuasca has a biphasic effect on the brain. Fifty minutes after ayahuasca was ingested, power was reduced in the alpha band, largely apparent in the left parieto-occipital cortex. After 75-125 minutes, both fast and slow wave gamma power increased. The increase in fast wave gamma power was located in the right frontal, left frontal temporal, right parietal-occipital, and left central-parietal-occipital cortices, whereas the slow wave increase occurred in the left frontal temporal, left central-parietal-occipital, and right frontal cortices. Circulating levels of DMT, β-carbolines, and some of their metabolites, were found to correlate with these changes.[40] Similarly, through electroencephalogram monitoring, Valle et al.[41] found decreases in alpha, theta, and delta bands in people who had consumed ayahuasca. The intensity of visual imagery was inversely correlated with the density of alpha oscillations found in the occipital and parietal cortex.

Heise & Brooks[42] reviewed a total of 538 ayahuasca exposure reports made to the American Association of Poison Control Centers' National Poison Data System. The most frequent clinical manifestations reported were hallucinations (35%), tachycardia (34%), agitation (34%), hypertension (16%), mydriasis (13%), and vomiting (6%). Endotracheal intubation was required in 28 cases, cardiac arrest was reported in four cases, respiratory arrest in seven, seizure in 12, and death in three. Further research that includes broad drug testing will be needed to better identify the risks and effects of ayahuasca.

It has been determined that DMT binds to multiple 5-HT receptors,[18] which is also the case for β-carbolines harmine and harmaline.[21] Thus, all of these compounds have a direct agonist effect on serotonin pathways by affecting postsynaptic tissue. Valle et al.[41] administered the 5-HT2A antagonist ketanserin alongside ayahuasca in a double-blind placebo control experiment. Ketanserin inhibited the subjective and neurophysiological effects of ayahuasca, illustrating the role of 5-HT2A receptors in the ayahuasca experience. Callaway et al.[19] found that THH is a weak SSRI, making it the only known β-carboline that affects presynaptic membranes. With all of these compounds present in a typical ayahuasca preparation, it is reasonable to assume that this is a display of synergistic pharmacology in humans, and could account for some of the effects. Callaway et al.[19] also found that regular ayahuasca users had more serotonin mRNA transporter sites, which implies that synergistic mechanisms are at work. Kummrow et al.[43] tested ayahuasca samples and concluded that they are mutagenic, which partially explained one of the β-carbolines present in the beverage. Other mutagenic compounds seem to be present and should be further investigated. This is further supported by the fact no such effects have been observed to result from DMT alone or any isolated β-carbolines. This suggests that further research is needed regarding mutagenic compounds in ayahuasca samples.

In addition to inhibiting MAOI-A in the gut and liver, reducing the first-pass effect of DMT and increasing its circulation by minimizing deamination, it has been suggested that harmine, harmaline, and THH exert psychoactive effects independently of DMT.[7,44,45] The independent administration of harmine has been found to result in locomotor ataxia, agitation, both visual and auditory hallucinations, nausea, vomiting, and confusion.[34] β-carboline alkaloids have also been found to interact with benzodiazepine receptors, as well as to intercalate into DNA and inhibit both topisomerase and cyclin-dependent kinases.[45] Grella et al.[46] demonstrated that β-carbolines have a non-specific binding profile and can bind to most receptor types, with the exception of a modest affinity for α-adrenergic receptors. Specifically, harmaline displays little/no affinity for serotonergic, dopaminergic, and norepinephrine neurotransmitter transporters and can bind with low affinity at most receptors.[46]

Ayahuasca is becoming increasingly available in Latin America, Central America and, more recently, much of the Western world, often administered by neo/pseudo-shamans with limited experience in its use.[47] The Western media has also reported a large number of anecdotal stories about ayahuasca's healing potential.[48] Globally, ayahuasca use is increasing[49] and it does not appear that it will slow down any time soon. The complexity of a typical preparation containing *B. caapi* and *P. viridis* has been outlined above. There are at least four active compounds present, all at varying levels per brew.[14] It is also well reported that many other admixtures go under the name of ayahuasca.[49] In addition to the globalization of ayahuasca, combinations of synthetic compounds analogous to ayahuasca have become increasingly popular worldwide. The use of MAO-A inhibitors and tryptamines capable of producing psychedelic effects has been referred to as "pharmahuasca."[44,50] The extent of the pharmacological interactions that may be taking place in ayahuasca are unknown. More research is required to identify the potential risks of use.

Research methods that could further our understanding of how ayahuasca works in the body and lead to better standardization of ayahuasca constituents for practical research purposes are outlined below. Clinical testing should aim to isolate each compound and test them individually at set doses, in line with standardized early-phase testing of multi-target combination drugs. Once achieved, the isolated ayahuasca compounds can be tested in combination with each other, adding in secondary constituents in order of their overall prevalence. Such a methodology would provide a better understanding of the interactions with each compound, as well as the safety and efficacy of combining them. The polypharmacology paradigm is a useful framework within which to consider the multitarget actions of ayahuasca components.

Blending MAOIs (e.g., some β-carbolines) with monoaminergic and serotoninergic substances (e.g., SSRIs, tryptophan, or antidepressants) might result in serotonin syndrome. The irreversible, nonselective MAOIs phenelzine and tranylcypromine are associated with serotonin syndrome, and cases have also been described with opiates, analgesics, tricyclic antidepressants, SSRIs, and antimigraine drugs.[51,52]

There are known interactions between irreversible MAOIs and certain drugs and food. The right combination, including tyramine and MAOIs, can potentially lead to hypertensive crisis and other typical adverse effects.[52,53] Studies with healthy volunteers have shown that non-selective irreversible MAOIs interact more with tyramine than selective reversible MAO-A inhibitors. There is less risk of interaction between tyramine and reversible MAO-A inhibitors than between tyramine and irreversible MAOs.[53,54] However, a study with moclobemide, a reversible MAO-A inhibitor, in healthy volunteers indicated that moclobemide levels during long-term drug administration (300 mg daily) were low and, thus, large fluctuations of drug levels occurred between doses. This suggests that larger doses or more frequent smaller doses, or both, may induce adverse events.[54] As previously described, harmala alkaloids primarily inhibit MAO-A, rather than MAO-B. The effective concentrations for inhibiting MAO-A have been reported as 8 $\times$ 108 M for harmine, 6 $\times$ 10-8 M for harmaline, and 1.4 $\times$ 10-5 M for THH. At higher concentrations, both harmine and harmaline also begin to inhibit MAO-B.[29] Therefore, β-carbolines have a higher selectivity for MAO-A than MAO-B, as well as a lower affinity for liver MAO. High concentrations could inhibit both MAO-A and MAO-B.[55]

Callaway & Grob.[55] reported a case of serotonin syndrome in a patient who used the SSRI fluoxetine in conjunction with ayahuasca. St. John's wort, Ginseng, amphetamine, or the empathogen-entactogen 3,4-methylendioxymethamphetamine ("ecstasy"), dextromethorphan might also have a risky interaction with ayahuasca.[51,52,55-58] Studies have found that harmine is a selective inhibitor of the human cytochrome P450 isozyme 2D6 (CYP2D6), which also metabolizes harmaline.[22,59-61] Adding drugs that inhibit cytochrome isoform CYP2D6 to the therapeutic use of selective SSRIs has been associated with serotonin syndrome.[51,52] Given that drugs such as psilocybin, mescaline and cannabis can also produce significant interactions with ayahuasca,[43,50,52,61] the combined use of DMT-containing ayahuasca and other drugs, such as cannabis and 3,4-methylendioxymethamphetamine, can cause meaningful interactions.[50] Although there is a paucity of literature on the interactions between ayahuasca and cannabis, case reports suggest that possible risks include anxiety and panic reactions, psychotic reactions, and potential cardiac problems.[62] Consumption of either cannabis or ayahuasca alone can, in some cases, produce states of extreme anxiety, panic, or psychosis.[52,63,64] Umut et al.[64] describes a case in which the subject developed psychotic symptoms immediately after consuming a mixture of DMT and cannabis, concluding that DMT worsened the symptoms of previous chronic cannabis use-induced mania. In one reported case, a combination of ayahuasca and cannabis resulted in a psychotic episode[65] in a subject with no history of psychosis. The subject had used cannabis regularly for 6 years prior to the onset of these symptoms. It is possible that the psychoactive properties (e.g., hallucinogenic effects) of both cannabis and ayahuasca are potentiated with combined use. Clinical studies demonstrated a lack of cross tolerance between Δ9-tetrahydrocannabinol (one of the main psychoactive constituents of cannabis) and lysergic acid diethylamide, whose mechanisms of action are similar to and overlap those of DMT.[61,66]

This systematic review has shown that the basic principles of ayahuasca pharmacology have not yet been established. SPECT, positron emission topography, electroencephalogram and functional magnetic resonance imaging could be used where appropriate. Animal studies should aim to use microdialysis following adequate mapping of activation sites. Cerebrospinal analysis could also aid in determining the metabolites of ayahuasca and subsequent changes in neurotransmitter production and neurobiology. At this stage, it is clear that only basic pharmacokinetic and pharmacodynamic principles have been determined. Although absorption, distribution, metabolism and excretion values have been preliminarily outlined by a number of studies listed in this paper, all of these are limited and lack detailed constituent analysis.

Sklerov et al.[67] described the fatal intoxication of a 25-year-old white male following ingestion of 5-MeO-DMT in an ayahuasca preparation. No anatomical cause of death was found at autopsy. Toxicological analysis of heart blood identified N, N-dimethyltryptamine (0.02 mg/L), 5-methoxy-N, N-dimethyltryptamine (1.88 mg/L), THH (0.38 mg/L), harmaline (0.07 mg/L), and harmine (0.17 mg/L). The medical examiner ruled that the cause of death was hallucinogenic amine intoxication and that the manner of death was undetermined. Several cases of intoxication or even death associated with the abuse of 5-MeO-DMT and harmaline have also been reported in humans. In addition, depending on the combined dose, CYP2D6 genotype/phenotype influences harmaline-5-MeO-DMT DDI, despite the fact that the CYP2D6 enzyme inactivates harmaline and activates 5-MeO-DMT.[68] The lack of literature describing the pharmacological and toxicological properties of tryptamine hallucinogens limits assessment of potential harm to public health following 5-MeO-DMT-containing ayahuasca use.

As outlined above, ayahuasca contains at least four primary active compounds, and others may be discovered. Current models simply do not adequately cater for such intricacy. This review shows that two of the constituents, DMT and harmine, have been studied to a greater extent than secondary harmala alkaloids (MAOIs). Based on data from individual constituents, which often show overlapping biochemical pharmacokinetic and pharmacodynamic action, it seems that there are more synergistic mechanisms involved than is currently understood. It is unclear at present whether these actions are of a true synergistic nature.

This systematic review concludes that current pharmacological understanding of the compounds in ayahuasca is limited, and their possible synergistic properties are even less well understood. The results of the included studies suggest that we are not fully aware of the complexity of the processes involved. It is clear that greater effort is required to investigate the pharmacology of the chemical constituents in ayahuasca. Only then can the pharmacokinetic and pharmacodynamic effects of

ayahuasca and its components be better understood and help prevent the potential risks of use.

Disclosure

The authors report no conflicts of interest.

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ORIGINAL ARTICLE

Journal of Psychedelic Studies 3(3), pp. 295–307 (2019)
DOI: 10.1556/2054.2019.007
First published online March 29, 2019

A phenomenology of subjectively relevant experiences induced by ayahuasca in Upper Amazon *vegetalismo* tourism

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(Received: August 24, 2018; accepted: February 20, 2019)

Aims: This heuristic study reports observations on the phenomenology of ayahuasca experiences of nine foreign tourist participants of an ayahuasca retreat in Peru. *Methods:* Narrative interviews, reflecting individual experiences after ayahuasca "night ceremony," have been analyzed by qualitative content analysis using a data-driven strategy in order to extract themes and categories inherent in the interviews. Previously, a demographic questionnaire was given. The dose–response connection was uncontrolled, which is typical for this naturalistic setting. *Results:* The typical structure of spontaneously reported experiences includes: personal preparation, physical symptoms, visual phenomena, cognitive and emotional phenomena, reactions of the individual within the psychedelic "world" as well as within ordinary reality, and appraisal to the process. Emotional reactions were subsumed under pleasant (psychotherapeutic "target emotions" and hedonistic emotions) and unpleasant emotions. For a majority, the presence of psychotherapeutic target emotions seemed to involve the presence of unpleasant emotions in the same session – possibly as transitional emotional states. *Conclusions:* This suggests that psychodynamic processes, for example, possible activation of emotional conflicts – can take place spontaneously, during ayahuasca intake in this particular setting. Some participants attributed symbolic meaning to the visionary content, which was more likely to take place in psychotherapeutically motivated clients. The specific setting influence as well as corresponding expectations of the participants in native wisdom could have considerable influence on experiences and interpretations, such as communication with entities as well as receiving personal teachings.

Keywords: ayahuasca, DMT, phenomenology, qualitative research, hallucinations, subjective experiences

INTRODUCTION

Over the past 20 years in Peru, ayahuasca tourism has developed into a thriving business (Grunwell, 1998). Several studies have assessed the reasons of use and found that this is in part due to the increasing demand from western tourists for experiences that can offer spiritual insights and epiphany, emotional catharsis, psychosomatic healing, and an "adventurous experience" (De Rios, 1994; Fiedler, Jungaberle, & Verres, 2011; Fotiou, 2010; Hudson, 2011; Kristensen, 1998; Losonczy & Mesturini, 2010; Schmid, 2010; Winkelmann, 2005; Wolff, 2018).

"Ayahuasca" is a Quechua word for South American beverages containing several species of the vine *Banisteriopsis* (*B. caapi* and *B. muricata*). It often also includes *Psychotria viridis* or *Diplopterys cabrerana* leaves, which cause psychoactive experiences sought out in psychedelic ethno-tourism. That psychoactive effect is also part of traditional healing practices in the Upper Amazonian *vegetalismo* (Beyer, 2009; Incayawar, 2007; Luna, 2005). *N,N*-Dimethyltryptamine is a naturally occurring psychoactive compound that mainly affects the serotonergic system in the CNS. The reversible MAO-A-inhibiting indol-alkaloids – harmine, tetrahydroharmine, and harmaline – prevent it from being deaminated in the digestive tract (McKenna, Towers, & Abbott, 1984; Riba, 2003). During the peak plasma level of DMT, ayahuasca drinkers are known to experience vivid and colorful imagery, changes to their thought processes, and a state of heightened awareness. Perceptual and "inner experiences" – mainly cognitive and emotional – undergo changes while the sensorium remains intact (Callaway et al., 1999; Grob et al., 1996;

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Riba et al., 2001). Nausea, vomiting, and diarrhea are the common effects of drinking ayahuasca, sometimes categorized as side-effects or "adverse symptoms" in pharmacological literature (Riba, 2003, p. 57); however, for many ayahuasca practitioners, these effects, along with their corresponding visual, synesthetic, emotional, and interpretative experiences, are considered to be intended main effects since the beverage is often called "la purga" (Spanish: the purge; Beyer, 2009, pp. 209, 213–214; Labate & Pacheco, 2011; Shanon, 2014, pp. 62–63).

Members of the Brazilian ayahuasca churches "Santo Daime" and "União do Vegetal" have reportedly experienced "*extraordinary visuals, kaleidoscopic lights, geometrical forms, tunnels, animals, humans and supernatural beings coinciding with sensations of peace, harmony and inner calm*" (Barbosa, Giglio, & Dalgalarrondo, 2005). Synesthetic phenomena such as simultaneous visions, sounds, and smells have also been reported (Luna & Amaringo, 1999). Shanon (2002, p. 431) found that animals, phantasmagoric creatures, royalty and religious figures, magic and art objects, and divine beings are often reported. Autobiographical content appears to occur less frequently for experienced drinkers (Shanon, 2002, p. 432) but can reveal patterns of personality to the drinker (Shanon, 2002, p. 114). Benny Shanon provides a typology of visions that includes two-dimensional pop art or comic book style imagery, complex geometry and architecture with fluorescent-colored lines, expansive panoramic views of landscapes and worlds, visuals in the style of the painter Henri Rousseau, as well as baroque style or "fairy tale" visual experiences (Shanon, 2002, pp. 96–97). He also describes interactions with phantasmagoric beings (Shanon, 2002, p. 97). Some individuals, however, reported few or no visions (Shanon, 2002, pp. 96–98).

The appearance of supportive entities (Beyer, 2009, pp. 239–244; de Rios, 1972; Luna, 1986) and receiving teachings from the personified ayahuasca have been reported following traditional ayahuasca ingestion. The reports of these "teachings from entities" play a significant role in traditional Upper-Amazon vegetalism (Beyer, 2009, pp. 110–111; Luna, 1986; Shanon, 2014, pp. 65–67). It also has been reported to occur in an ibogaine-induced state of consciousness (Schenberg, 2013) as well as occasionally from western substance-supported psychotherapy, for example, guiding spirits from family members during psilocybin ingestion (Belser et al., 2017, pp. 365–366). Psilocybin and (to a lesser extent) ketamine are also known to produce similar complex imagery (Studerus, Gamma, & Vollenweider, 2010). This may indicate the significance of individual circumstance and the setting in which psychoactive substances are ingested, in terms of influencing similar perceptional content.

To clarify, for the purpose of this paper, we will be distinguishing *visions* from *hallucinations*. Hallucinations, in contrast to the visions induced by ayahuasca, give the subjective impression that what is being seen is a part of reality, to the extent that the person can hardly distinguish between a shared reality and the hallucinatory experience.

In a study using semi-structured questionnaires, Kjellgren, Eriksson, and Norlander (2009) found that when reflecting on the process of experiencing an ayahuasca trip, participant's reports included the following stages: (a) motivation to take ayahuasca (prior to ingesting), (b) contractile frightening state, (c) a sudden change or transformation of the experience, (d) a limitless expansive state with transpersonal experiences, (e) reflection on the experience, and (f) changed worldview and new orientation to life. The final stage of the process feeds back into the first stage, as at this point they are able to recognize the potential psychotherapeutic benefits.

Based on analyses of a great number of LSD and mescaline trips, Masters and Houston (1966) described a general psychedelic model of depth stages: (a) sensory stage with perceptual changes and altered awareness of the body; (b) recollective-analytic stage with in-depth thinking about personal problems, relationship problems, life goals, past experiences, and emotional abreactions; (c) symbolic stage with visualized landscapes and architecture, historical, mythic, ritualistic, and archetypal scenes and communication with beings; and (d) integral stage with transcendent and mystical experiences.

As Franquesa et al. (2018) point out, documented improvements in different pathologies have been attributed to the introspective qualities of ayahuasca, although the possible underlying psychotherapeutic processes are not yet well understood. Anecdotal benefits often include dissolution of the ego, a reprioritization of what is important, understanding oneself better, improved ability to understand others, acceptance of oneself and past life events, and personal growth (Bresnick & Levin, 2006 quoted in Franquesa et al., 2018).

Mystical experiences such as oneness, ego-dissolution, and connectedness may predict a long-term increase in well-being, as well as clinical improvements after psychedelic therapies (Carhart-Harris & Goodwin, 2017; Griffiths, Richards, McCann, & Jesse, 2006). Carhart-Harris, Erritzoe, Haijen, Kaelen, and Watts (2018) believe that a feeling of connectedness is a key factor for good mental health. There is evidence that a feeling of connectedness facilitates psychological well-being (Cervinka, Roderer, & Hefler, 2012), and that a sense of disconnectedness is a factor in depression (Karp, 2017). Experiences of connectedness have commonly been reported by people who have used ayahuasca (Shanon, 2002, p. 205).

Franquesa et al. (2018) found evidence of therapeutic processes in ayahuasca inebriations, which are also known in other psychotherapies: decentered introspection, attribution of meaning (which was also proposed by Shanon, 2003) as well as alterations in meaningful, guiding values in life (also discussed by Kavenská & Simonová, 2015; Liester & Pricket, 2012 and others). Some psychedelic therapies aim to create "meaningful visual phenomena," as well as changes to the personal narratives of patients (Belser et al., 2017, p. 372). Concepts of generating and altering meaning are common in psychotherapy and have been described under various terms (see Batthyany & Russo-Netzer, 2014; Cade, 1992; Frankl, 1986; Lichtenberg, Lachmann, & Fosshage, 2016; Mattila, 2001; Mittelmark et al., 2017; Roediger, 2011; Ruf & Schauer, 2012; Yalom, 1980). They have also been generalized as a psychotherapeutic effect factor; "new self-narration" in a broader sense is defined as the development of a coherent rewording of the patient's life history, as well as a new assessment of their identity and relationship to the environment (Jørgensen, 2004).

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Emotional release is not only a typical effect of ayahuasca (Shanon, 2014, p. 64), but also of other psychedelics such as LSD and psilocybin in psychotherapeutic settings (Belser et al., 2017; Gasser, Kirchner, & Passie, 2014). It indicates typical process-elements that have been previously described from therapies with entactogens, and are typically accompanied by emotional activation; "acceleration of psychological processes," "regression," "rescripting of past behaviors," "problem actualization and corrective new experience," as well as "transpersonal experiences" (Passie, 2012). Emotional release is seen as closely related to meaningful experiences, especially those described as "*alternative simulations of formative situations from the past, encapsulated in an inner realm*" (Passie, 2012).

Gaining diagnostic insight into other peoples' social and psychosomatic issues may be of particular interest in medical anthropology, as ethnographic literature documents that local *vegetalistas* of the Amazon claim to gain insight into the causes of the diseases through ayahuasca (Luna, 1986), diseases often being thought of as physical symptoms of social ills (Beyer, 2009, pp. 178–180).

Due to the study's heuristic aim and qualitative paradigm, no particular explicit hypothesis was tested. The heuristic study aims to contribute to the investigation of the phenomenology of ayahuasca in western clients, as well as possible implications for psychedelic-assisted psychotherapy. For this, the study aims to explore more comprehensively, the common structure of acute subjective experiences and emotions elicited by ayahuasca in the context of ceremonial western ayahuasca tourism in the Amazon.

METHODS

Ethics and confidentiality

An informed consent form about participation in the study was signed by all participants prior to starting the retreat. Only individuals who had already booked the retreat independently of the study were invited to participate. Participants were not invited to ingest ayahuasca specifically for this study.

Confidentiality and the voluntary nature of participation was assured and reiterated throughout the research and publishing procedure. The procedure was aligned with the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (WMA, 2013). BPS guidelines have been followed throughout the study design.

Sampling and recruitment

This investigation took place at the *Ayahuasca Foundation* facility located in the Amazon rain forest near the Peruvian town Iquitos (https://www.ayahuascafoundation.org). It is a typical "healing center," run by an US-American apprentice of a local *vegetalista*, offering shorter and longer ayahuasca retreats for western clients, as many other centers in the region do. Initial contact was established via an Internet search. All nine participants were asked at the beginning of the 13-day period whether they would be happy to be interviewed during the retreat, which they agreed to.

Procedure

Upon signing the informed consent form, a demographic questionnaire was completed. Six ayahuasca ceremonies were conducted in group settings at night. Interviews took place in the morning, immediately after the second ayahuasca night ceremony had finished.

Qualitative interviews

A narrative interview strategy was chosen (Helfferich, 2011, p. 114; Küsters, 2009) to minimize any potential bias or leading questions relating to the study (Patton, 2002, p. 39). This meant that we were able to identify the elements that were subjectively most relevant to participants, as they were self-reported by the interviewee without prompting. Participants were asked to report what they had experienced during the ceremony, for example, "please tell me about your experiences during the ceremony as openly as possible." An open question about emotional experience was subsequently added to the narrative interview since, in contrast to traditional local ayahuasca use in the upper Amazon region (de Rios, 1972; Luna, 2004), the focus of the providers of ayahuasca for western clients is on psychotherapeutic processes of "emotional purging" and "emotional healing" (Beyer, 2009, p. 348). Interviews were sound-recorded.

Method of analysis

Participants reported their experience of ayahuasca with minimal prompting from interviewers during narrative interviews. We surmise that more frequently mentioned elements of the experience may have more subjective value to the participants than those seldom or not mentioned at all. The coding frame aims to identify the commonly shared inner structure of the analyzed narratives, and the coding frequencies represent the subjective importance or relevance for the narrators.

After transcription, interviews were analyzed through qualitative content analysis (QCA) using a mixed data-driven strategy. A progressively paraphrasing strategy was combined with a subsuming strategy (Schreier, 2012, pp. 115–120). For the first interview, the material was cut into single statements; all statements (coding units) were paraphrased, in order to build up provisional main categories. Similar paraphrases with shared meaning were paraphrased again. In this way, abstract categories were formed. For the additional material, statements were used to build up subcategories, and further statements were either subsumed under these already existing subcategories or new subcategories were formed. The coding-frame was built up successively until a point of saturation was reached. After the ninth interview, no further categories had to be introduced in order to classify new material. In qualitative research, it is not yet fully possible to calculate reliability indices. Content analysis conceptualizes reliability through consistency. Consistency is operationalized either through the level of intersubjective rater agreement or stability over time. The concept is related to the plausibility of the interpretation (Schreier, 2012, pp. 167–175). In order to ensure reliability, the material was completely recoded by the same coder after

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a period of 3 weeks, and the percentages of agreement and Cohen's κs were calculated for each category. Both are common criteria in qualitative research. All of the compared categories were found to be reasonably consistent ($94.91 \leq \text{Percentage}_A \geq 100$; $0.43 \leq \kappa \geq 1$). Categories were also analyzed in terms of how often they were discussed by the different participants (how many participants talked about a certain theme), as well as coding units (number of statements about a particular topic compared with the overall number of statements).

Characteristics of participants

The ages ranged between 27 and 71 years ($N = 9$, median = 33, interquartile range = 10).

- Gender: six males and three female participants.
- Previous experiences with hallucinogens: eight participants.
  - Psilocybin: ("magic mushrooms") ranging from one trial to monthly use, and from 1-year use up to 10 years;
  - LSD: ranging from one trial to monthly use, and from 1-year use up to 10 years;
  - MDMA (Ecstasy): ranging from one trial to monthly use, and from 1-year use up to 10 years.
- History of psychotherapeutic consultations: five participants.
- Previous medical conditions such as hypertension, knee replacement, hypothyroidism, pneumonia, appendectomy, choroid ocular melanoma: six participants.
- Previous psychiatric conditions such as depression or anxiety disorder: three participants.
- Eight out of nine participants graduated from college or university. Reported professions: nurse, dietician, marine engineer, medical doctor, pharmacist, and psychologist.

RESULTS

The narrative structure of reports of ayahuasca experiences consisted of the overarching main topic, "experiences during the ceremony" (Figures 1–3), and two side categories: "preparedness" (Figure 1) and "appraisal of the process" (Figure 3). Often the narratives started with a short discussion about preparation for the experience, followed by a long discussion addressing the focus of the study, the actual experience of taking ayahuasca, and ending with an appraisal of the process. Reflecting the initial interview question, the most frequent statements made were about the actual experience. The internal structure – depicted in the coding frame – is complex and contains several themes, subthemes, and categories. It is presented category by category and also as a graphic overview (Figures 1–3, respectively).

Preparedness

Typical statements about personal preparedness were about *motivation* and the *level of pre-knowledge*. Overall, the topic was only touched on briefly.

Appraisal of the process

This side theme refers to the appraisal and general characterization of the experience as a dynamic process, which changes in intensity and quality over time. Sometimes, difficulties during the process were mentioned such as lack of control, unpredictability, and difficulties regarding the intensity or the speed of the perceived flow of psychedelic content.

Although not frequently, the role and influence of the shamanic singing on the experience was spontaneously mentioned by more than half of the participants. The ritual singing was reported to affect physical sensations within participants' bodies and influence visions, as well as help to direct attention and stimulate mood or energy changes. The shaman himself was adept at regulating the experience. As a setting variable, the singing was a modulating factor, affecting the intensity and quality of the psychedelic as well as physical experience. For this reason, we grouped it into this category.

Experiences during ceremony

The following themes and subthemes were subsumed under "experiences during the ceremony" (Figures 1–3). Note that most of the themes contain several subcategories that are presented later:

- physical symptoms;
- visions, hallucinations, properties of visions, and evaluation;
- intensified imagination and contemplative thoughts;
- received messages;
- attribution of meaning (immediate symbolic understanding and insights through own reflection);
- different types of meaning attributed to psychedelic content (interpersonal, relational, about other people's issues, general wisdom, mystical, spiritual, or religious content); and
- emotional and other psychological reactions of the individual, such as acting within and outside the visions, cognitive reactions.

Physical symptoms

The experience of physical symptoms as a result of taking ayahuasca is a common and frequent topic that was mentioned by all participants (12.43% of all statements; ranging from 3.13% to 37.14% per interview). Vomiting and nausea are the most common and frequently reported phenomena (seven and five participants) and as such, the subjectively most relevant physical symptoms. Changes in the quality of the experience with regard to visions, thoughts, and the level of inner agitation after vomiting were spontaneously reported by a minority (three of nine participants). Other physical symptoms reported include stomach pain, diarrhea, restlessness, tremor, raised temperature, fuzziness, exhaustion, heaviness, executive muscle problems, sensitized senses, and synesthetic-like experiences such as visualizing sounds.

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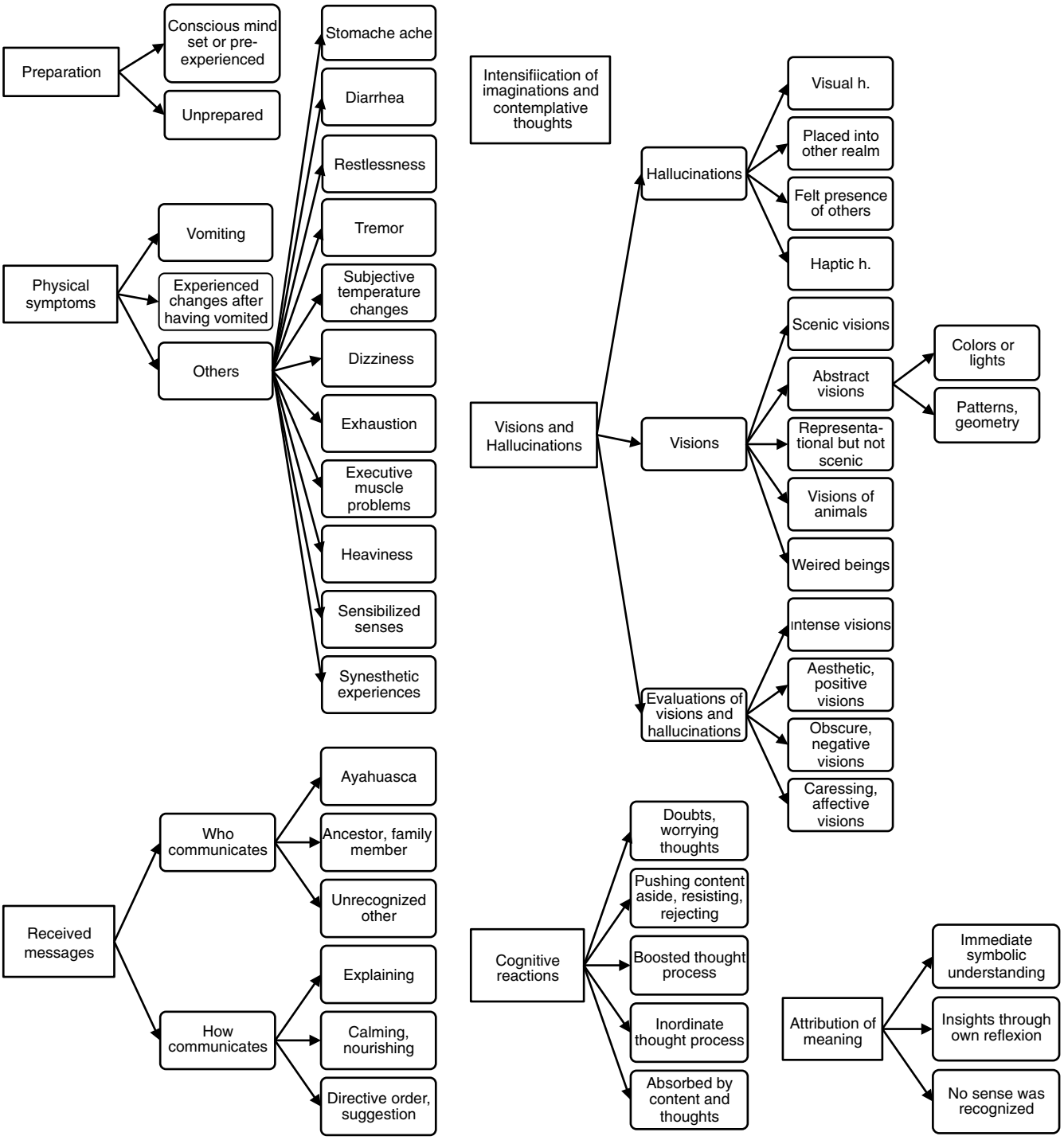

Figure 1. Preparation, physical symptoms, phantasies, visions, received messages, cognitive reactions, and attribution of meaning reported after a shamanic ayahuasca ceremony in the Amazon region in narrative interviews of nine foreign participants using qualitative content analyses

Visions and hallucinations

Visions were a common and frequent topic (eight of nine participants, overall statement frequency = 11.86%). We use the term *visions* because it is commonly used among ayahuasca users. Visions are vivid geometrical patterns, scenes, persons, creatures, and objects, most often perceived with closed eyes or in complete darkness. Visions can appear for a participant when their eyes are open, but are seldom. The ability to distinguish between visions and the perception of the surrounding reality remains intact in most cases. True visual hallucinations (seeing things that are not there) as well as hallucinatory misjudgments of real objects or persons (pseudo-hallucinations) do occur, but are less common and less frequent than visions (five participants, 4.52% of all statements). "Haptic hallucinations" refer to the sense of being touched or caressed in the absence of external stimuli. Other phenomena subcategorized into "visions and hallucinations" are the "felt presence of another person/being," and the sensation of "being placed entirely into

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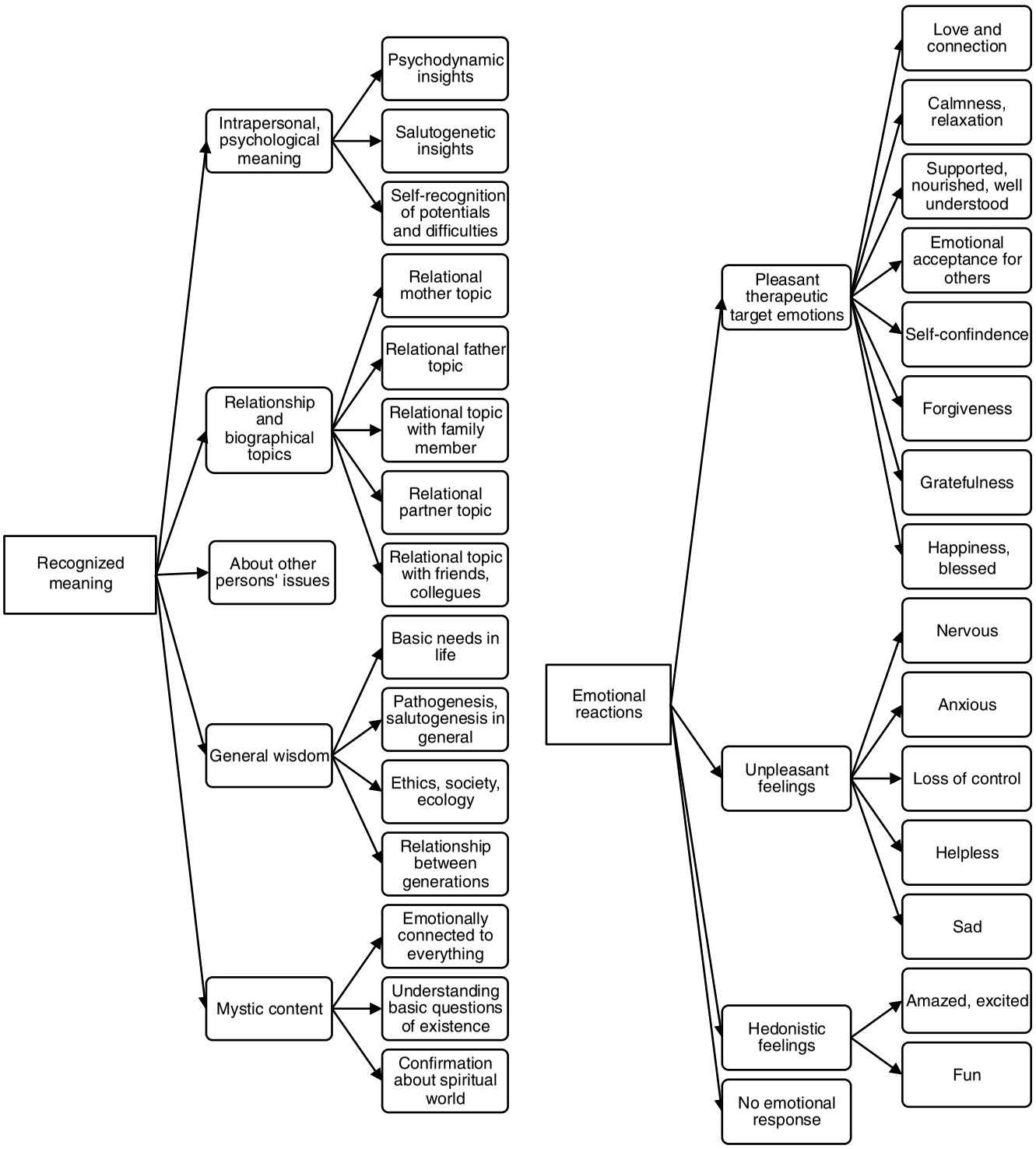

Figure 2. Recognized meaning of psychedelic content and emotional reactions reported after a shamanic ayahuasca ceremony in the Amazon region in narrative interviews of nine foreign participants using qualitative content analyses

another realm" for parts of the session. The visions and hallucinations were spontaneously evaluated as being intense, aesthetically positive, and affectively kind or obscure.

Abstract visions composed of colors, complex geometric patterns or symmetrical shapes were the most common type (eight participants, statement frequency = 5.65%).

Other less common and less frequent types of visions reported included "representational objects" (one participant), "scenes and people" (three participants, frequency = 4.25%), "animals" (one participant, frequency = 1.41%), and "fantastic or weird creatures" (four participants, frequency = 1.13%).

> *No, just abstract, totally. No there was no connection between anybody at all. Not somebody I had seen in my life before or a love. Just to describe them is almost impossible. I wondered how the hell I could ever do that. And very vivid colors. But rather they were almost symmetrical in certain aspects, a lot of them. And it just looked so beautiful.* (2)

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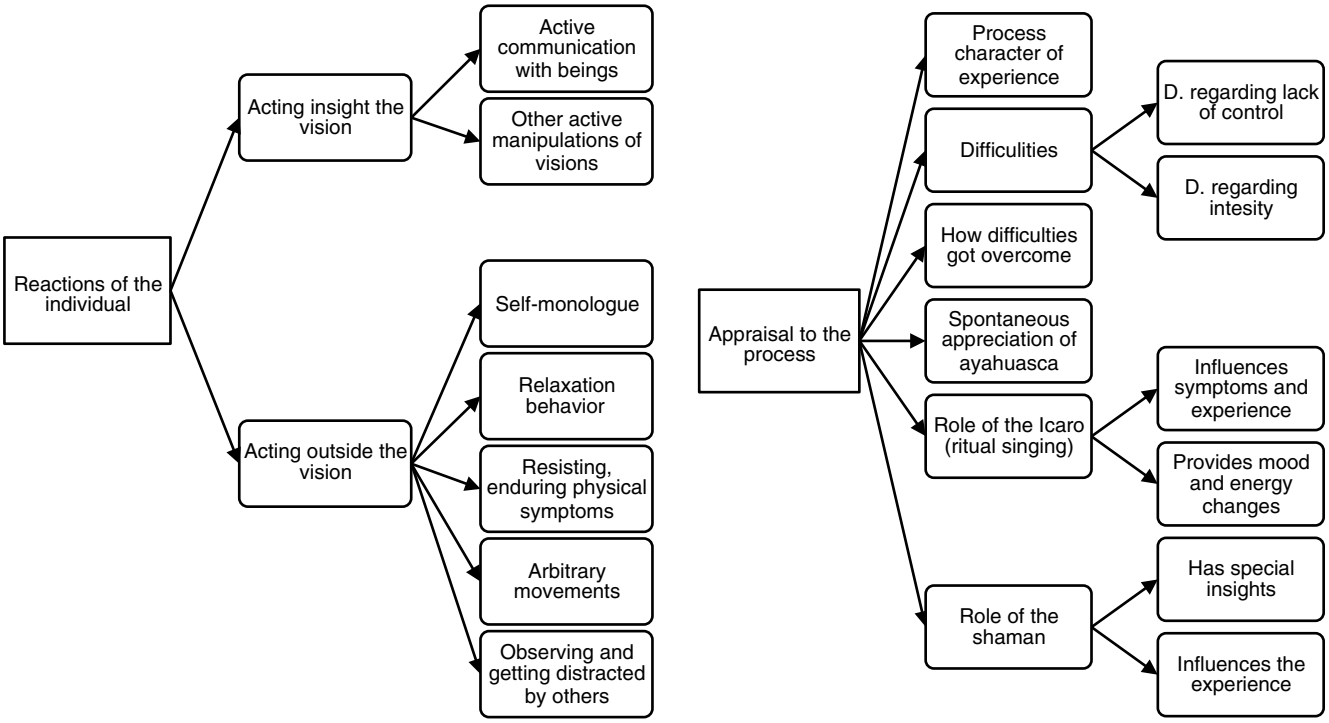

Figure 3. Appraisal of the process, role of ritual singing and of the shaman, individual reactions reported after a shamanic ayahuasca ceremony in the Amazon region in narrative interviews of nine foreign participants using qualitative content analyses

Intensified imagination and contemplative thoughts

Participants reported that thoughts and imagined experiences were intensified. They were able to make a distinction between visions and imagination or fantasies in general.

Attribution of meaning

In general, having meaningful experiences either through immediate symbolic understanding or through personal reflections during an ayahuasca ceremony was a common and spontaneously occurring phenomenon among our interviewees. Eight out of nine participants used altogether 7.91% of all coding units for this category. Eight out of nine interviewees found parts of the perceived material "insightful." A minority of three participants explicitly reported that they could not understand the meaning of specific content. The spontaneous recognition of content as symbolic was an uncommon phenomenon in the material. It occurred for one participant who stated:

> *And then suddenly it occurs to me this is just a symbol for my inner child.* (1)

Insights as a result of intensified reflective processes during the ceremony were reported more often than recognizing content as symbolic:

> *And, me to kind of resolve, that just to move on with my life and just never have to think about that again and start, you know, a better relationship with somebody else.* (3)

Received messages

Direct messages from "entities" were infrequent for most of the sample. They were concentrated with an overall statement frequency = 4.24% in three out of nine participants. One participant claimed to have received voice-like messages directly from "Mother Ayahuasca." Another participant received messages from a family member, and another from an unspecified entity. The subjectively perceived communication was received in an "explaining" or "teaching" style, as a therapeutic order or suggestion, or in a supportive and calming manner:

> *When I go into the medicine I have something I can hold onto, like jewelry or a stone or something. I also have this jewelry that is from my mum. I tried . . . it was somewhere on my mattress . . . I tried to find it because I thought I was to connect again to this sacred holy space [of her mother]. And I couldn't find it, I couldn't, oh my God, I want to find it because I want to connect, and suddenly I heard the voice of my mum and she says: You don't have to find anything, I am always here. I am always here. You just have to turn to me, towards me. And I am here anyhow, because I am your mum. My love is always here. You are the one who turned away. You are the one who decided to go away. The moment you turn around I am always here.* (1)

Recognized meaning of content

Seven out of nine participants reported spontaneously gaining "insightful personal meaning" during the ceremony, with an overall statement frequency = 17.51%. Five subthemes of meaning containing further subcategories were found in the material (Figure 2), including:

– interpersonal psychological insights: three participants, overall statement frequency = 4.52%;

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- insights into relational, social biographic themes: six participants, overall statement frequency = 7.34%;
- insight into motives or issues of other people: two participants, overall statement frequency = .8%;
- general social, ethical, healing of mankind, or environmental wisdom: four participants, statement frequency = 3.38%;
- mystical, spiritual, and religious insights and experiences: five participants, overall statement frequency = 4.8%.

Interpersonal insights point to the origin of personal problems and symptoms. This includes psychodynamic insights and personal learning history, salutogenesis, resolving psychosomatic problems, self-awareness and self-recognition regarding personal potential, traits, and problems. In the following example, a participant received sudden and subjectively convincing revelations about a psychodynamic pathogenesis model of her eating disorder, after she had the highly affective vision of being caressed by her mother. She identified a hunger for emotional nourishment rooted in early childhood as a conflict that leads to compensatory eating and bonding behavior:

> *And then mother ayahuasca was telling me: This is the nourishment you are looking for. This is the reason why you eat too much. Even though you eat too much you never feel really fulfilled . . . This is the nourishment you are looking for . . . and of course the medicine was just pointing out: 'this is the place.' You have to connect here, don't connect with a cat. That is just a substitute. It's not really what it is about. Don't connect with your husband. Your inner Child has to connect with your mum and from this space you get the nourishment that you need and then you can handle that your cat is dying or whatever. This is a special kind of nourishment. It can only come from there.* (1)

Another participant reflected about a conflicting aspect of her personality without having any psychodynamic insights. She realized her ability to easily perceive the emotional states of others and explored its pros and cons. Finally, she could reframe this as a special ability rather than an exclusively problematic aspect:

> *The emotion? Empathy, I guess. I was very worried about the people around me, which is something I do way too much as a nurse. And I feel I have always done so – like when somebody is going through something or having hard times. Even with my patients, I struggle with that at work, because it is just like I feel if anyone gets sad or crying like oh I'm going to, I can just feel that. So that I just could feel that emotions around, going on around me, the emotions. I felt pretty happy. I was like: yeah, that is awesome.* (4)

Two participants reported to have been preoccupied with their relationship with their mother. One person mentioned being preoccupied with a relational issue with their father and one person about relational issues with other family members. Partner issues were mentioned by three participants (overall statement frequency = 1.69%) and relationships issues with friends, colleagues, or others were mentioned by four participants (overall statement frequency = 1.69%).

"Mystical, spiritual, and religious content" is a collective category that refers to statements regarding experiences of oneness, global connectedness, overwhelming general empathy, sudden knowledge and understanding of existential questions and paradoxes, the impression of clarity and the confirmation and renewal of faith, and religious belief in the existence of a spiritual world beyond the mundaneness of existence:

> *But then I just drift off into something really obscure. I started getting quite profound insights into what I consider consciousness. Thinking about how we all are just fragments of something a lot bigger.* (8)

> *And I started asking ayahuasca questions. Questions I think most people think about, like: why is there life on earth, what happens after you die? Questions you can never normally have an answer to. And I felt those questions were just answered immediately. The answers were kind of implanted into my brain. I remember just lying on my mat, thinking: how can this possibly be?* (9)

> *It is true. I do not believe it is just hallucination. I believe that there is something real there. That there is some sort of real connection to the spiritual world. It confirms that there is probably something happening outside of this. Sometimes I do worry that, you know, we die, that there is just darkness and that the experience is just over. Ayahuasca is so profound, that one has to believe that we are, you know, that something is happening after this world, and that we all are connected. It brings a feeling of love and those things.* (3)

Acting inside the visions

Two participants not only perceived but also directly responded to visual experiences. They acted within the visions in an attempt to communicate with entities (two participants) and interact with the perceived visionary content (one participant):

> *Because my mind was like: I do not want to be in one space with my mum. I want to eject my mum. And then the medicine told me, already showed me, there are different energy strings. And one is unconditioned mother love, then next to that, there is expectation and then next to this is one's own needs. The medicine told me that I have to find the string that is only mother-love. And I thought I could agree on that. So I found this string, which had a yellow and orange color. And it became a little seed, it looked just like a [grain of] rice (laughs). And it was like, 'you can take it or you cannot take it' and I think: ok I'm gonna put it in my heart. And from this moment somehow she said: 'feel it, feel it, feel it'. I felt like, ok this is the nourishment I am looking for, ok this is really good for me.* (1)

> *I saw a little kind of joker being. And I asked him, as I was told to do, if it was medicine - to stay and if it was not*

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medicine - to go away. And then I was transported into that really brightly colored

room . . . (9)

Acting outside the visions

Acting outside of the visions was more commonly (eight of nine participants) and frequently reported (8.76%). Typical actions included repeating words to self in a monologue, behavior that indicated relaxing such as changing into a comfortable position, resisting physical distress, for example, holding back vomit, arbitrary or general mannerism movements, and being attentive to other participants (Figure 3).

Other cognitive reactions

Cognitive reactions were common (eight out of nine participants) and frequent (overall statement frequency =11.86%; Figure 1). "Doubts and worrying thoughts" were moderately common (six participants) followed by "controlling and rejecting content" (five participants) and "getting absorbed" by the experience (four participants). "Intensified thoughts" or a flurry of ideas were less common (three participants). Only one participant mentioned an "inordinate thought process" during the ceremony.

Emotional reactions

Emotional reactions were mentioned by all participants (overall statement frequency = 18.64%). It can be distinguished between therapeutically desirable emotional states, unpleasant emotional states, and hedonistic emotional states.

Pleasant and therapeutically desirable emotions have been found in the narratives of eight participants, overall statement frequency = 10.73% (Figure 2):

- "love and connection" (five participants);
- "calmness and relaxation" and "happiness and feeling blessed" (four participants);
- "gratitude" (three participants);
- "supported, nourished, well understood, and self-confident" (two participants);
- "acceptance and openness to others" and "forgiveness" (one participant).

And somehow I could allow this sense of love – just rejected all the bullshit that my mum was carrying, and all the expectation. I just [left it] by the side and just concentrated 100% on this mother honey, the sense of it – holy. It even felt like being with her in a holy space that nobody can disturb and nobody can enter. And that is very unique in this world. (1)

Unpleasant emotions (nine participants, overall statement frequency = 5.37%) were:

- "anxiety" (eight participants);
- "nervousness" (three participants);
- "loss of control or orientation," "helpless," and "sadness" (one participant each).

Typical hedonistic emotions, mentioned by four of nine participants (overall statement frequency = 2.54%), were "amazement" (two participants) and "enjoyment" (one participant). Sexual content was not mentioned.

In eight of nine cases, unpleasant emotions appeared alongside therapeutically desirable emotions in the same ceremony. Four participants did not explicitly mention any emotional reactions (overall statement frequency = 1.7%).

Participants 1, 5, and 9 described a pleasant and therapeutically productive experience, describing the resolution of inner conflicts, whereas Participant 4 described an emotional process with more unpleasant (sad, nervous, and worrying self-blame) as well as hedonistic emotions (fun and enjoyment, three statements), instead of desirable therapeutic emotion (empathy, mentioned once). She also twice mentioned the absence of emotion when she would have expected to feel something. Participant 2 reported no therapeutic target emotion whatsoever, alongside unpleasant and hedonistic episodes with the absence of emotion (Table 1).

DISCUSSION

The presented analysis helps to document in greater detail the phenomenology of altered states of consciousness in western ayahuasca tourists. Regarding visual phenomena, the categories of abstract, representational and scenic material, and animals and weird beings are in agreement with previous reports (Barbosa et al., 2005; Shanon, 2002). As already noted by Shanon (2014, pp. 67–69), ayahuasca drinkers usually find themselves in the role of spectator of visual phenomena; however, intense ayahuasca experiences can involve acting within the visions and even interactions with entities, such as relatives, ayahuasca itself, and phantasmagoric creatures. Personal teachings in an explaining or directive manner were reported to take place for some of the interviewees. Schenberg (2013) see psychotherapeutic potential in such directive messages from entities. The personal long-term impact of these teachings, their uncontrollable nature, as well as the possible role of individual expectations and the influences of the setting could be a topic of future research.

Our findings are consistent with previous literature in which dealing with physical stresses such as nausea and vomiting is dominant in ayahuascsa trip reports (Shanon, 2014, pp. 62–63). The same applies to ibogaine, but not to LSD, mescaline, and psilocybin (Schenberg, 2013). Hallucinatory auditory phenomena seem to be less common than in ibogaine ingestions (Schenberg, 2013).

Changes in the quality and intensity of the psychedelic process after vomiting have been reported. This points toward a possible bottleneck-like effect during ayahuasca ceremonies, which were previously described by Kjellgren et al. (2009) as "*sudden transformation of the experience*."

The interviews contain elements of all general depth stages of psychedelic experiences, from perceptual changes through mystical experiences (Masters & Houston, 1966). Unfortunately, the narratives revealed little details about the temporal sequences of the reported phenomena, so that we can contribute only little to the phase-typical sequence of psychedelic depth stages with our unstructured method.

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Table 1. Distribution of statements of different emotional categories in narrative interviews of nine foreign participants of a shamanic ayahuasca ceremony in the Peruvian Amazon region

Participant no.	Therapeutically desirable emotions	Unpleasant feelings	Hedonistic feelings	No emotional response
1	9	3	0	0
2	0	1	1	2
3	1	2	0	0
4	1	3	3	2
5	9	1	1	1
6	1	1	0	0
7	2	3	0	1
8	3	1	0	0
9	12	4	4	0

Intensification of imagination and contemplative thoughts was reported, previously also known in conjunction with deep "self-search" and psychological analysis, creativity, metaphysical ideas, and new personal perspectives (Shanon, 2014, pp. 69–70).

Some people were not able to infer meaning from these psychedelic experiences. For others, symbolic meaning was immediately evident without intellectual interpretation. Some interviewees reported to have gained personal insights through intensified thinking, which Shanon (2014, pp. 69–70) calls "mentation." We did not find this distinction in the previous literature; however, we consider it to be significant because of the unique ways individuals experience ayahuasca inebriations, and not least because of the high level of subjective persuasiveness that immediate symbolic understanding can have.

The narratives show that a moderate number of participants were able to increase their self-awareness about personal ability, traits, and difficulties. However, only one psychotherapeutically preexperienced participant explicitly reported psychodynamic insights into origins of personal issues, and one other reported salutogenic insight into solving personal issues. It does not appear self-evident in our interviews that ethno-psychedelic ayahuasca experiences lead to psychotherapeutic insights, which would automatically become integrated into an altered personal narrative about meaning and values. For some, it was simply a fascinating or bizarre adventure with no evidence of any impact on self-actualization, reframed perception of self, or new self-narration. Although the reason that it should occur in some cases over others is not clear, it may be a combination of reasons based on the heterogeneity of tourist participants; intention, cognitive style, personality, life-situation, and psychotherapeutic preparedness.

Ayahuasca tourism does not usually include post-session or post-retreat care. Subjectively relevant insights occur but immediate symbolic understanding does not seem to happen spontaneously in untrained individuals of our interviewed group. Individuals who do not have the immediate emotional and cognitive meaning-making of their inner images and visions may benefit particularly from further discussion after they have processed the experience in order to develop meaning-making and personal relevance during the integration phase. Particularly, since the generation and immediate understanding of symbolic material as meaningful (Belser et al., 2017, p. 372), as well as the later meaning-making (Belser et al., 2017, p. 355), is central to modern psychedelic supported therapy. Therefore, the categorization of recognized meaning of psychedelic content in western ayahuasca drinkers seems to be of particular interest to us, that is, interpersonal psychological meaning, relationship, and biographical topics, about other persons' issues, general wisdom, and mystic content. These categories, except "about other people's issues," seem to relate to the health-related personal values and introspective processes previously mentioned in the literature (Franquesa et al., 2018).

The spontaneous appearance of relationship issues in a small majority of participants is consistent with previous ayahuasca reports from Shanon (2003). It was also observed in psychedelic experiences with other substances (Belser et al., 2017).

Participants reported a spontaneous emotional release as well as corrective emotional experiences. The high frequency of spontaneous mention of emotional responses in reports when using ayahuasca suggests a high subjective priority of emotions during and shortly after ingestion. A majority reported the appearance of pleasant as well as unpleasant emotions. Both seem to be a common part of the ayahuasca experience. Having "no emotional response" could be interpreted as a defense mechanism in psychoanalytic terminology. On the contrary, it could also be a sign of having overcome a conflict, emotional exhaustion, or of overload inhibition. Subjectively successful experiences of ayahuasca appear to be characterized by the presence of unpleasant emotions as an expression of the activation of relevant conflictive material and the inner struggle with it, as well as pleasant and desirable or "target" emotions with possible "salutatory impact" (Shanon, 2014, p. 64) as an expression of resolution.

Hedonistic feelings as well as emotional blockages, or the absence of emotional response to emotionally relevant material, seem less dominant. It is worth exploring the relationship between pleasant and unpleasant emotions within the same session in more depth, as a possible indication of therapeutically successful ayahuasca trips, possibly described as the aforementioned "*sudden transformation of the experience*" by Kjellgren et al. (2009).

Insights into or solutions for other people's issues were rare among the nine participants. Either the phenomenon is exaggerated in local healing traditions, or it is a culturally dependent phenomenon that might only be relevant to native or local practitioners. It is also possible that certain

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personalities may be more inclined toward this phenomenon, or that it may require extensive experience with ayahuasca that tourists do not generally have, as the local perspective of vegetalism would suggest.

Experiences of connectedness, spiritual confirmation, and answering existential questions suggest that ayahuasca rituals may have some of the described health-related potentials of mystical experiences previously described in the literature; however, the conditions of the individual affinity and the interindividual predictability under ayahuasca remain unclear. This should be better investigated in relation to outcome measures.

The phenomenology of experiences of different subgroups and cultures could be systematically investigated by purposeful case selection as well as other methods, using greater samples. In general, analyzing the possible relation between some of the subjective phenomena of ayahuasca and their outcomes could be helpful in developing ayahuasca supported psychotherapy.

Limitations

Although theoretical saturation of the coding frame was reached, the small number of participants from only one retreat center may be a limitation since other participants may provide new themes not yet covered in the coding frame. On the other hand, it could be argued that the natural selection of tourists in this study already provides a large heterogeneity of relevant demographic and mental health related variables such as age, educational level, physical and mental preloading, and previous experience with psychotherapeutic thinking. Most participants came from dose, amount, and ratio of the pharmacological components remained uncontrolled. An interpretative uncertainty when defining categories and subsuming units of meaning (single statements) to it lays in the method of QCA. We met this with a determination of reliability.

Another limitation can be seen in the chosen narrative interview method. Although on one hand, an interviewer bias is largely avoided by means of a narrative interview strategy; on the other hand, the method has the disadvantage that areas of interest cannot be explored by hypothesis-driven questioning and therefore may not be reported.

Acknowledgements: TJW contributed in research plan, project management, analyses, and writing up of the manuscript. SR and NN contributed in field work and manuscript revision. TP contributed in critical manuscript revision and provided relevant literature. There is no funding source provided for this article.

Conflict of interest: The authors declare no conflict of interest.

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Psychopharmacology (2020) 237:3161–3171
https://doi.org/10.1007/s00213-020-05601-0

ORIGINAL INVESTIGATION

Modulatory effects of ayahuasca on personality structure in a traditional framework

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Received: 3 February 2020 / Accepted: 26 June 2020 / Published online: 23 July 2020
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Abstract

Ayahuasca is a psychoactive plant brew containing dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOIs). It originates from the Amazon basin, where it is used primarily for ceremonial purposes. Ayahuasca tourists are now entering certain communities seeking alternative physical or psychological healing, as well as spiritual growth.

Rationale Recent evidence has shown that the similar acting psychedelic compound, psilocybin, facilitated long-term increases in trait openness following a single administration.

Objectives This paper assesses the impact of ayahuasca on personality in a traditional framework catering for ayahuasca tourists.

Method Within a mixed design, we examined the effect of ayahuasca on participants' personality (measured by the NEO Personality Inventory 3 questionnaire) across time (pre- to post-ayahuasca administration, and 6-month follow-up), relative to a comparison group (who did not ingest ayahuasca).

Results The results demonstrated significant increases in agreeableness pre- and post-ayahuasca administration and significant reductions in neuroticism in 24 participants, relative to the comparison group. Both of these changes were sustained at 6-month follow-up, and trait level increases were also observed in openness at this stage. Additionally, greater perceived mystical experience (measured using the Mystical Experience Questionnaire 30) was associated with increased reductions in neuroticism.

Conclusions These findings, which indicate a positive mediating effect of ayahuasca on personality, support the growing literature suggesting potential therapeutic avenues for serotonergic psychedelics.

Keywords Ayahuasca · Dimethyltryptamine · Personality · Mystical/peak experience · Psychedelic · Entheogen · Psychopharmacology

Introduction

Anthropological data suggests that psychoactive compounds have been used throughout history and are still used to this day by various traditional communities. Some examples include the Huichol peoples of northern Mexico, using peyote cactus (mescaline) (Schaefer 2006); the Mazatec use of psilocybin mushrooms (Metzner 2005); the Bantu tribes of Gabon who use iboga; and a number of communities within the Amazonas which use ayahuasca. These traditions appear to share similarities, despite the vastness of their geographical separation (Luna 2011), the most obvious being the type of compound used, often existing in different species of plant or fungi; similarities in ritual; shape of ceremonial buildings; the use of music and perfumes; and often resemblances in spiritual themes (Winkelman 2013). These features appear to have evolved independently, with examples on entirely different continents (Clottes and Lewis-Williams 1998). From this, it can be deduced that these practices possess some form of therapeutic efficacy, given that the same conclusions appear to have been reached. Scientists have begun looking at these practices in order to investigate their potential applicability in medicine (Sessa 2012).

Ayahuasca is an Amazonian plant brew mix in the entheogenic (i.e. spirituality inducing) bracket of psychedelics

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(Tupper 2009). The term ayahuasca originates from the Quechua words 'Aya'—meaning soul or spirit—and 'Waska'—meaning rope or vine (Santos et al. 2007). These names relate to one of the primary ingredients, the *Banisteriopsis caapi* vine, also independently referred to as ayahuasca. Currently, the most widely used brew contains *Banisteriopsis caapi* alongside one other dimethyltryptamine (DMT)–containing plant, usually *Psychotria viridis* (Rivier and Lindgren 1972).

Ayahuasca's psychoactive effects are largely a result of DMT, which remains orally active due to monoamine oxidase inhibitors (MAOIs) present in *Banisteriopsis caapi* (McKenna 2004). Monoamine oxidase (MAO) is an endogenous enzyme which ordinarily breaks down DMT when orally ingested (McKenna et al. 1984), inhibiting its psychoactive properties. Combining the two plants allows DMT to be slowly absorbed in the digestive tract, triggering an experience lasting between 4 and 6 h (Riba et al. 2003), frequently encompassing powerful shifts in perception (Shanon 2002). In addition, users can experience purgative effects (Gershon 2004) such as vomiting (Tafur 2017).

The primary activation site for DMT is the 5-hydroxytryptamine (5-HT2A) receptor (Aghajanian and Marek 1999), similar to that of other serotonergic psychedelics with DMT-like chemical structures, such as lysergic acid diethylamide (LSD) and psilocybin (Nichols 2016). The 5-HT2A receptor has been linked to conditions such as depression (Celada et al. 2004), suggesting that psychedelics may hold therapeutic value in psychiatric disorders due to their prominent affinity here. Evidence suggests that these 5-HT2A agonists can decrease functional connectivity in the default mode network (DMN) (Carhart-Harris et al. 2016). This disruption in neural connectivity has been proposed to underlie subjective reports encompassing a loss of sense of self, ego-dissolution, often described as a transcendental state of awareness or mystical experience (Barrett and Griffiths 2017a).

A systematic review (dos Santos et al. 2016) assessing 28 publications on ayahuasca drew the following conclusions: acute ayahuasca administration was well tolerated (Fortunato et al. 2009); it was found to alter visual perceptions in participants (de Araujo et al. 2012), activate frontal and paralimbic regions (Riba et al. 2006), decrease DMN activity (Palhano-Fontes et al. 2015), and impair working memory but decrease stimulus-response interference (Bouso et al. 2013). Post-acute effects included improved planning and inhibitory control (Bouso et al. 2012), anti-depressive (Osório et al. 2015), and anti-addictive properties (Berlowitz et al. 2019; Fábregas et al. 2010; Thomas et al. 2013). Long-term ayahuasca use was associated with the increased cortical thickness of the anterior cingulate cortex and cortical thinning of the posterior cingulate cortex (Bouso et al. 2015).

Subacute and long-term ayahuasca use was not associated with increased psychopathology or cognitive deficits (Bouso et al. 2012) but was associated with enhanced mood and cognition (Bouso et al. 2012) and reduced impulsivity (Bouso and Riba 2014). Furthermore, several Brazilian studies have shown that a single dose of ayahuasca can have a rapid antidepressant effect on patients suffering from recurrent depression (Osório et al. 2015; Palhano-Fontes et al. 2019; Sanches et al. 2016).

Animal studies indicate that the median lethal dose of DMT in humans would amount to 20 times more than that used in ceremonial ayahuasca practice (Gable 2007), and neither acute ayahuasca administration nor long-term consumption seems to be toxic to humans (dos Santos 2013). Use of the brew in religious ceremonies has a safety margin comparable to codeine, mescaline, or methadone (Gable 2007), with minimal risk of sustained psychological disturbance. Cardiovascular risk has been found to be low (Riba et al. 2003), as has the addiction potential of the brew (Fábregas et al. 2010). In fact, no serious conditions have been established when consumed by healthy individuals (dos Santos 2013).

Despite evidence pointing to an acceptable safety profile for ayahuasca, there have nonetheless been cases observed where acute ingestion has been a contributing factor to psychotic manifestations (dos Santos et al. 2017; Tófoli 2011). For example, a number of such cases have been documented by churches utilizing ayahuasca, such as the União do Vegetal (UDV). However, it has been impossible to directly infer causality due to factors such as temporality (Tófoli 2011) and additional use of substances such as cannabis (dos Santos and Strassman 2008). It should also be noted that incidences of psychotic illnesses recorded within the UDV were estimated to be similar to those of the general population—around 1% (Gable 2007; Stilo and Murray 2010).

In a legal battle regarding ayahuasca use, the Supreme Court of the United States (Gonzales 2006) concluded that 'many or most of these psychological problems were transient and resolved', and in 'a review of the case histories… either no truly psychotic incident was identified or no causal link to *hoasca* (ayahuasca) was found'. Overall, psychotic reactions to ayahuasca seem rare. When this phenomenon does occur, it is often associated with factors such as substance abuse, inappropriate, unsupervised settings, and predisposing psychological characteristics (dos Santos et al. 2017). Such cases further highlight the need for appropriate screening, setting, and support (Zinberg 1986).

Several studies have suggested that ayahuasca use can result in positive changes across different psychological and personality domains. In studying Santo Daime church members 1 to 2 weeks following their first-time ritualistic ayahuasca use, Barbosa et al. (2005) found significant reductions in minor psychiatric symptoms, as well as mood and behavioural changes related to greater assertiveness, serenity, and joy. In a sample of ayahuasca tourists which included one-time drinkers using the Personality Styles and Disorder Inventory

(Kuhl and Kazén 2009), Kavenská and Simonová (2015) found significant increases in traits such as optimism, intuition, ambition, helpfulness, and charm. Authors noted that compared with controls, those using ayahuasca demonstrated more trustful, pleasant, empathic, and optimistic personality styles.

In exploring the effects of longer-term use, Barbosa assessed members of the UDV and Santo Daime churches for personality changes after drinking ayahuasca regularly for 6-months (Barbosa et al. 2009). Using the Temperament and Character Inventory (Cloninger et al. 1993), experimental groups showed significant reductions in reward dependence at 6-month follow-up which positively correlated with intensity of use. These findings supported the findings of an earlier, similar study (Grob et al. 1996). Barbosa and colleagues further found that Santo Daime members exhibited greater confidence and optimism at 6-month follow-up, which correlated positively with improvements in mental health and reduced minor psychiatric symptoms (Barbosa et al. 2009). This was supported by Bouso and his colleagues (Bouso et al. 2012) under both jungle and urban settings. Using the Big Five Inventory (BFI) (Goldberg 1990), significantly higher ratings of agreeableness and openness were observed in regular ayahuasca users (Barbosa et al. 2016).

When assessing psilocybin, another 5-HT2a agonist structurally-likened to DMT, positive changes have been identified. In a randomised controlled trial using the Neuroticism-Extraversion-Openness Personality Inventory (NEO-PI; Costa and McCrae 1992), MacLean and colleagues (MacLean et al. 2011) found significant increases in openness which persisted after 12 months. This finding positively correlated with levels of perceived mystical experience (measured using the Mystical Experience Questionnaire, MEQ). More recently, Erritzoe et al. (2018) conducted a similar study on individuals suffering from unipolar depression, observing significant increases in extraversion and openness, as well as significant reductions in Neuroticism, which also correlated positively with levels of perceived mystical experience. Such personality changes have been associated with reduced anxiety, depression, and alcohol and substance misuse (Kotov et al. 2010; Malouff et al. 2007; Ruiz et al. 2008).

Together, these studies provide foundational evidence suggesting that ayahuasca and similar compounds, like psilocybin, have the potential to bring about positive and sustainable changes to personality structures. Additionally, under the five-factor personality model (or Big Five), the literature suggests that around 30 is the age at which personality is seen to stabilise, with openness to experience considered to be the most substantially heritable trait (e.g. Costa and McCrae 1992; Jang et al. 1996; Terracciano et al. 2010). Since the aforementioned studies conducted under the Big Five model (i.e. those utilising the BFI and NEO-PI) involved participants mostly beyond age 30, it is further suggested that these compounds may influence sustainable change to personality traits previously thought to be largely inherited and stable.

In the current study, understood to be the first of its kind, we aimed to evaluate ayahuasca administration in a non-church-based traditional Amazonian setting investigating effect on personality, in both the short-term and six-month follow-up. Given its potential positive effects on personality and treatment implications of psychiatric disorders, coupled with the continued rise in ayahuasca tourism, this area of research holds great importance. Our study was conducted within an indigenous Shipibo community of the Peruvian Amazon. The Ayahuasca Foundation, affiliated with the Multidisciplinary Association for Psychedelic Studies (MAPS), allows for 'ayahuasca tourists' to participate in Shipibo-style ceremonies which closely resemble the traditional use of the plants within this area of the Amazon basin.

Methodology

This field study was conducted using an observational repeated measures design.

Location and retreat information

Data was collected at the Ayahuasca Foundation, an ayahuasca retreat and research centre within the Allpahuayo-Mishana National Reserve, approximately 20 miles from Iquitos. Each retreat lasted 12 days and included six ayahuasca ceremonies every other day. A range of other plants were used during the retreats, none of which is known to be directly psychoactive.

The administration of ayahuasca was conducted in the format of a non-religious ceremony, with its traditions rooted in Shipibo culture. These were led by a local curandero (shaman), alongside four to five facilitators trained by the foundation. Ayahuasca ceremonies generally began after sunset at around 20:00, lasting approximately 6 h. The circular wooden building where these occurred (i.e. the 'maloka') was set up with single mattresses evenly spaced out around the inside perimeter for each participant, with individual buckets for purging provided. Ceremonies were conducted in groups of around 10 to 12 participants. Throughout, participants remain silently on their mattresses in complete darkness, without making contact with one another. Toilet breaks were allowed, with assistance from facilitators if necessary. After the curandero presents each with the ayahuasca brew at the start, he and the facilitators would sing traditional medicine songs ('icaros') for the duration of the ceremony.

To ensure participants' peace of mind on retreats, the foundation provided security measures such as locked rooms and over-night guards against potential threats from the jungle. A medical doctor accredited with primary qualifications was around in case medical assistance was needed, and aftercare remote professional counselling sessions were also offered following retreats to promote integration.

Sample group

Twenty-four English-speaking individuals (15 males, 9 females, mean age = 37.6) participated. Twenty-one were either of white American, Canadian, British, or European ethnicity, with the remainder being Asian or Latin. All were vetted by the Ayahuasca Foundation staff for eligibility regarding physical and mental health. Half of the participants had either historical or ongoing diagnosed psychiatric conditions (including depression, anxiety, and post-traumatic stress disorder), who met the Ayahuasca Foundation's inclusion criteria. Five had chronic on-going physical ailments. Nine had suffered previous physical ailments which had resolved. Four had no diagnostic history of either physical or psychiatric conditions. All participants received full-time education until the age of 16. Nine of these further received qualifications at A-level or college level. Ten continued further on to the university and postgraduate level. Half reported previously having experienced drinking ayahuasca prior to the retreat.

Exclusion criteria The Ayahuasca Foundation excluded individuals with current or historic psychosis-related conditions, such as bipolar depression or schizophrenia. All individuals are encouraged to abstain from licit and illicit substances (including prescription medication) for a period of 2 weeks prior to retreats. Medical records were not checked, and therefore, participants were accepted based on their subjective account of their medical history.

Comparison group

Comparison group participants were English-speaking individuals on holiday in Peru who were initially approached on the premise that they had no previous experiences with ayahuasca reported. In total, 65 data sets were obtained, with 24 subjects (11 males, 13 females, mean age = 32.6 years) being selected for a matched comparison group. An independent samples t test revealed no significant difference between the comparison and sample groups on age, t (46) = 1.43, $p = .160$. Chi-squared tests also revealed no significance difference between the two groups on gender, X^2 (1) = 0.75, $p = .386$; education, X^2 (2) = 3.11, $p = .211$; whether they had historic or current psychiatric diagnoses, X^2 (1) = 0.09, $p = .768$; and physical health issues, X^2 (1) = 0.33, $p = .564$.

Measures

The *NEO-PI3* (NEO henceforth) (Costa Jr and McCrae 2008) was selected as a robust personality measurement with high overall validity and reliability. The questionnaire identifies five primary personality domains, each of which has six subfacets: openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism.

The Mystical Experience Questionnaire (MEQ30; Barrett and Griffiths 2017b) was used to assess levels of perceived mystical experience.

Procedure

Written consent and demographic information were obtained the day before the first ayahuasca ceremony, followed by a time one baseline personality measurement using the NEO. Time two NEO scores were recorded at the end of the retreat following six ceremonies. In the post-phase, the MEQ was also administered.

The 6-month follow-up NEO scores were obtained electronically via email. This also included a follow-up questionnaire assessing the potential long-term impact of the retreat in terms of behavioural, physical, and psychological changes.

Over the 12-day retreat, semi-structured interviews were conducted. These qualitative findings are presented in a separate publication (Wolff et al. 2019).

Ethics

This study has been approved by the institutional ethics committee and was independently assessed by the British Psychological Society (BPS).

Data analysis

We first assessed whether the ayahuasca sessions led to changes in personality from baseline to post-test, using a mixed ANOVA, with time (baseline, post-test) and personality (neuroticism, extraversion, conscientiousness, agreeableness, openness to experience) as the within-participants variables, and group (active vs. comparison) as the between-subjects variable (see Table 1 for descriptive statistics). To correct for multiple comparisons, the Benjamini-Hochberg procedure (Benjamini and Hochberg 1995) was applied for all follow-up pairwise comparisons with a false discovery rate (FDR) of 0.1. The Greenhouse-Geisser correction was used in instances where the assumption of sphericity was violated (Mauchly's $W < .05$). After confirming that neuroticism reduced significantly, we used a bivariate Spearman's

Table 1 NEO Personality scores for the active and comparison group

	Baseline		Post-test		6-month follow-up	
	(M, SD)	Range	(M, SD)	Range	(M, SD)	Range
Active group						
Neuroticism	90.08 (27.68)	48–155	73.00 (30.56)	29–136	75.90 (23.69)	31–116
Conscientiousness	113.79 (21.82)	75–154	118.21 (23.46)	62–156	118.00 (17.49)	80–155
Extraversion	113.21 (17.35)	83–150	117.79 (22.72)	74–159	120.57 (19.40)	89–156
Agreeableness	114.75 (22.99)	74–152	124.88 (22.47)	82–161	119.33 (19.57)	82–158
Openness to experience	128.58 (18.06)	84–159	135.50 (23.06)	67–166	135.48 (17.99)	101–167
Comparison group						
Neuroticism	96.79 (24.54)	58–143	93.42 (24.07)	61–137	109.83 (15.01)	70–135
Conscientiousness	108.50 (15.58)	84–141	106.83 (15.59)	77–136	118.83 (7.56)	102–131
Extraversion	121.13 (21.70)	84–167	119.88 (19.10)	89–150	117.46 (10.45)	92–134
Agreeableness	131.00 (19.49)	90–169	126.21 (22.53)	65–169	123.38 (6.97)	110–139
Openness to experience	132.67 (16.83)	103–165	131.08 (20.42)	75–161	117.08 (8.25)	95–130

rank-order correlation to assess the relationship between neuroticism and the mystical experience reported by participants.

Results

Personality changes from baseline to post-treatment

Analysis observed a significant reduction in neuroticism scores in the active group at post-test, as indicated by a significant interaction between time, personality, and group (Pillai's trace = 0.24, $F(2.03, 93.44) = 5.50$, $\eta_p^2 = .11$, $p = .005$). Pairwise comparisons revealed a significant reduction in Neuroticism scores from baseline measures to post-test in the active group (Mdiff = 17.08, 95% CI (10.12, 24.05), $p < .001$), $d = 0.59$, not the control group (Mdiff = 3.38, 95% CI (−3.59, 10.34), $p = .335$, $d = 0.14$). Given that there were non-significant differences in baseline neuroticism scores between the active and comparison groups, Mdiff = 6.71, 95% CI (−8.49, 21.91), $p = .379$, $d = 0.26$, our results suggest a significant reduction in neuroticism in the active group following the ayahuasca sessions. Pairwise comparisons also revealed a significant increase in agreeableness scores from baseline measures to post-test in the active group (Mdiff = 10.13, 95% CI (2.34, 17.91), $p = .012$), $d = 0.45$, not the comparison group (Mdiff = 4.79, 95% CI (−3.00, 12.58), $p = .222$) (Fig. 1). Consistent with our original hypothesis, there was a trend towards a significant increase in openness scores from baseline to post-test in the active group (Mdiff = 6.92, 95% CI (0.32, 13.51), $p = .040$); however, this test did not survive the correction for multiple comparisons.

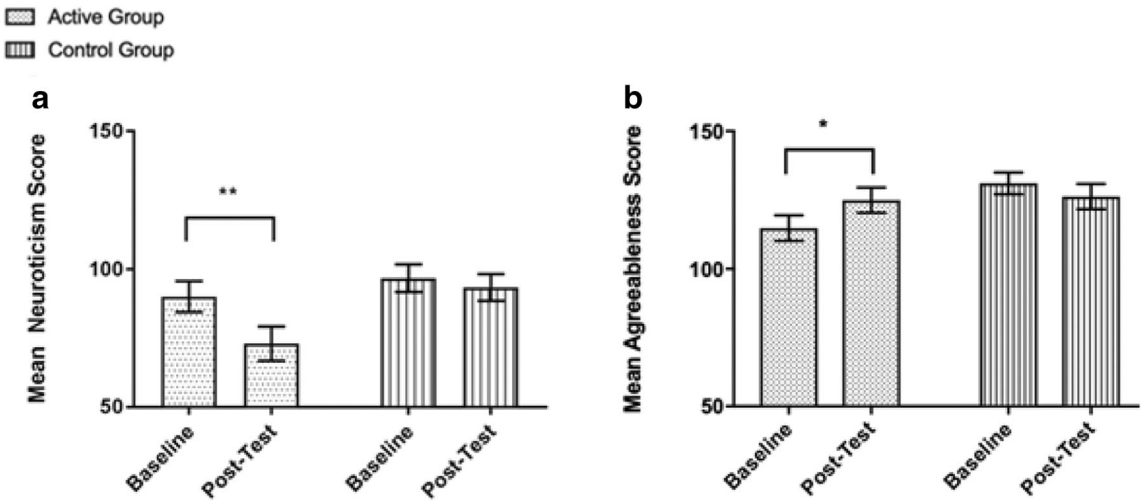

Fig. 1 Significant reduction in neuroticism (**a**) and increase in agreeableness (**b**) observed in the active group from baseline to post-test, compared with the comparison group. Asterisk indicates $p < .05$, double asterisk indicates $p < .001$. Bars represent the standard error of the mean (SEM)

Relationship between neuroticism, agreeableness, and mystical experience

To assess whether the reduction in neuroticism and increase in agreeableness observed in the active group were associated with the degree of mystical experience reported by participants, we conducted a Spearman's rank-order correlation between neuroticism and agreeableness change scores from baseline to post-test in both the active and comparison groups and their MEQ scores. This analysis revealed a medium significant negative correlation between neuroticism change and MEQ scores, $r_s(48) = -.56, p < .001$ (i.e. those who reported a greater degree of mysticism also experienced greater reductions in neuroticism) (Fig. 2). We can also report a non-significant correlation between baseline neuroticism and MEQ scores, $r_s(48) = .02$, $p = .883$, which suggests that it is the change in neuroticism from baseline to post-test that is driving the significant association with MEQ scores. In contrast, there was a non-significant correlation between agreeableness change and MEQ scores, $r(48) = 0.18$, $p = .211$.

Personality changes from post-treatment to follow-up

Out of the 24 participants in the active group, three did not provide NEO scores at the 6-month follow-up. Therefore, the 6-month follow-up analyses were conducted with 21 participants in the active group (12 males, mean age = 34.2 years) and 24 participants in the comparison group.

Our data suggests the significant reduction in neuroticism scores observed in the active group remains stable at 6-month follow-up, relative to participants in the comparison group, as indicated by a significant interaction between time, personality, and group, Pillai's trace = 0.22, $F(3.17, 136.24) = 4.32$, $p = .005$, $\eta_p^2 = .09$ (Fig. 3). Pairwise comparisons revealed that the reduction in neuroticism scores observed in the active group at post-test remained was stable at the 6-month follow-up assessment ($M = 75.91$, SEM = 4.26), Mdiff = 2.29, 95% CI (− 5.16, 9.73), $p = .539$, $d = 0.08$, and remained significantly lower than those observed in the comparison group ($M = 109.83$, SEM = 3.99), Mdiff = 33.93, 95% CI (22.16, 45.70), $p < .001$, $d = 1.71$. In addition, the short-term increase in agreeableness that was observed in the active group was maintained at 6-month follow-up ($M = 119.33$, SEM = 3.12), Mdiff = 6.14, 95% CI (− 2.33, 14.62), $p = .151$, $d = 0.26$ (Fig. 4). Lastly, at 6-month follow-up, we also observed significantly greater openness to experience scores in the active group ($M = 135.48$, SEM = 2.98) compared with the control group ($M = 117.08$, SEM = 2.79), Mdiff = 18.39, 95% CI (10.15, 26.63), $p < .001$, $d = 2.20$.

Discussion

The current study shows that a 12-day ayahuasca retreat in a traditional framework adapted for ayahuasca tourists led to significant reductions in neuroticism, which remained stable at 6-month follow-up. Additionally, MEQ scores were found to correlate with reductions observed in neuroticism. These findings are in line with previous research (Erritzoe et al. 2018). Increases in agreeableness were observed from baseline to post-test in both the short and long term, supporting findings by Barbosa et al. (2016). Trait level increases in openness were also observed, which further increased between the post-test and 6-month follow-up, a finding which again is partially supportive of previous findings (Barbosa et al. 2016; Maclean et al. 2011).

Results show that reductions in neuroticism were more pronounced than we anticipated. In addition, levels of neuroticism in the comparison group were found to unexpectedly increase at 6-month follow-up. We speculate that as the majority of participants had returned home from travel by this point, those

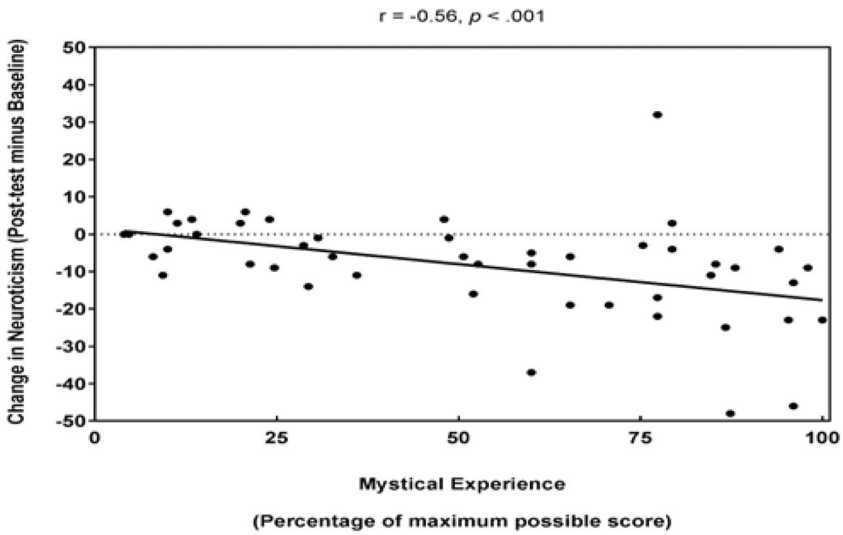

Fig. 2 Graph to show the change in neuroticism scores in both the active and comparison group as a function of mystical experience, including a line of best fit

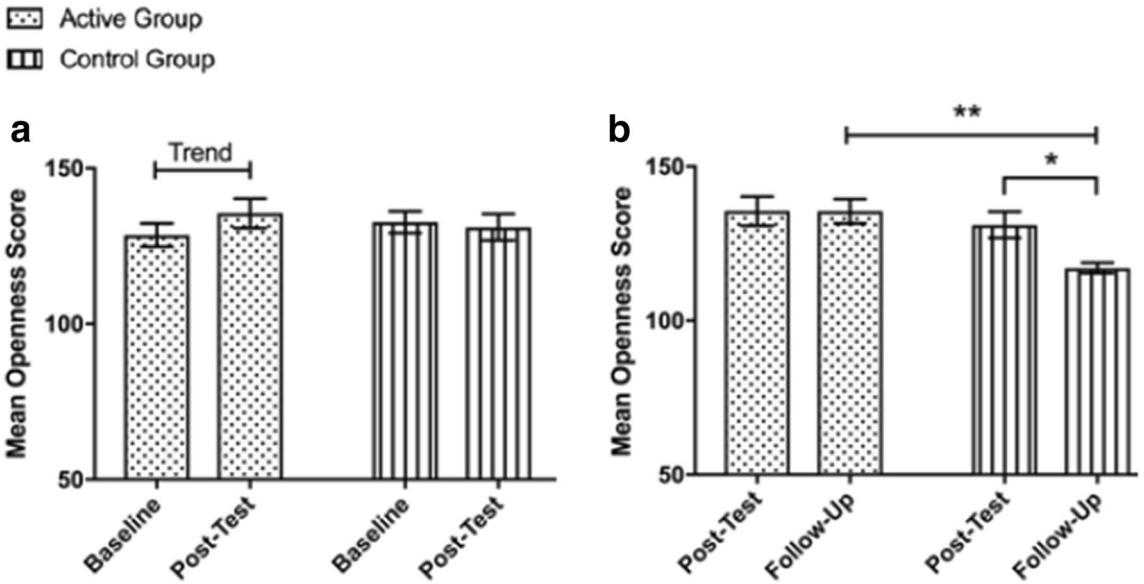

Fig. 3 Trend level increases in openness which were observed in the active group from baseline to post-test (A), and the significant decrease in openness which was observed in the comparison group from post-test to six-month follow-up. At 6-month follow-up participants in the active group had significantly greater openness scores than the comparison group. Asterisk indicates $p < .005$, double asterisk indicates $p < .001$. Bars represent SEM

increases in neuroticism may represent changes in a frame for the personality requirements of the individual, i.e. they became more neurotic upon return to their non-travelling lives. These findings are particularly interesting as personality is often seen to be stable by age 30, unless a significant life event occurs (Costa and McCrae 1992). It is suggested that personality may in fact not be as rigid as advocated by Costa and McRae.

Neuroimaging data has shown that serotonergic psychedelics may amplify the mechanism of neuroplasticity (Carhart-Harris et al. 2012), the brain's ability to be flexible and form new pathways (Costandi 2016). Ayahuasca may be unique in its ability to induce such processes. A study conducted by Morales-Garcia et al. (2017) demonstrated evidence that the alkaloids present in *B. caapi* stimulate neurogenesis in human hippocampal tissue in vitro. These results, when combined with the implications of functional suppression of the DMN (Palhano-Fontes et al. 2015) and increases in neuroplasticity induced by DMT (dos Santos and Hallak 2019), suggest that ayahuasca as a concoction may possess serious power for bringing about neurological alterations in

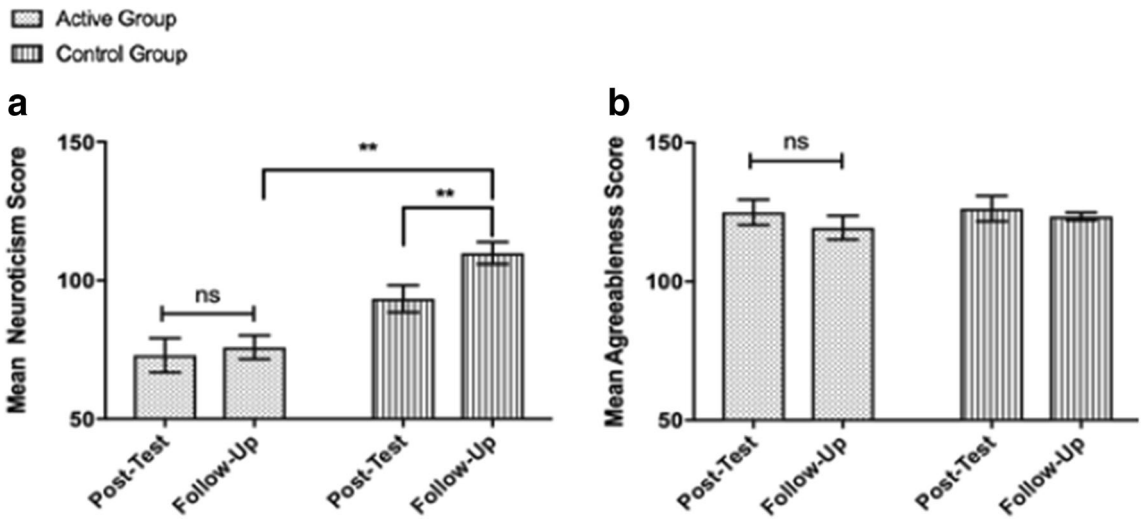

Fig. 4 Significant reduction in neuroticism (**a**) and increase in agreeableness scores (**b**) observed in the active group at post-test remained stable at 6-month follow-up and were significantly reduced in comparison with the comparison group at follow-up. In contrast, we observed a significant increase in neuroticism scores in the comparison group from post-test to 6-month follow-up. Double asterisk indicates $p < .001$. Bars represent SEM

the brain. It must be noted however that the findings by Morales-Garcia have not yet been replicated in vivo. Direct transferability into humans at this point is therefore solely speculative. Regardless, these findings have opened up fascinating research avenues for conditions such as neurodegenerative disorders, or even age-related cognitive deficits.

A recent study (Erritzoe et al. 2018) showed significant reductions in neuroticism in patients suffering from treatment-resistant depression. However, the inclusion criteria for the above study are much more restrictive than those in the current paper (diagnosed patients vs. self-selection); the validity of comparing these findings is therefore questionable. Future studies should aim to examine the differences in outcomes between healthy individuals and those with diagnosed conditions with a basis in neurosis (e.g. affective disorders), when receiving psychedelic therapy.

In contrast to the findings observed by Maclean et al. (2011), we observed no significant effect on levels of openness, only observing trait level increases. However, the sample group in the current study reported higher levels of openness relative to the general population, where openness was already at or close to ceiling level. High levels of openness may reflect their natural inclination to seek out new experiences, or potentially that they may have already been primed to be more open than they would be in their day to day lives.

Therapeutic implications

The results in this study are consistent with the growing body of data suggesting psychedelics have therapeutic implications. High levels of neuroticism are associated with a range of psychiatric conditions, such as anxiety, depression, and obsessive-compulsive disorder. The therapeutic applications of increased levels of agreeableness are however less obvious. Agreeableness can be defined as an individual's pro-social behaviour relating to characteristics such as altruism, empathy, and cooperativeness (Caspi et al. 2005). It has previously been suggested that agreeableness may be a reliable predictor of substance misuse (Turiano et al. 2012); however, this is not the case for all substances. It has been found to be protective against the problematic use of cannabis (Terracciano et al. 2008), alcohol (Turiano et al. 2012), and polydrug use (Lackner et al. 2013). Agreeableness, along with neuroticism, is associated with traits of anger proneness (Caspi et al. 2005). Neuroticism refers to the way in which aggression is experienced through angry emotions, whereas agreeableness is associated with poor control expressed through aggression (Martin et al. 2000).

Much emphasis has been placed on the psychotherapeutic frameworks surrounding psychedelic sessions in determining therapeutic outcomes, a case of optimising set and setting (Erritzoe et al. 2018; Hartogsohn 2016; Mithoefer et al. 2018). Most of the psychedelics showing promise in publications appear to be 5-HT2A/C agonists. This suggests a potential link between this receptor site and neurotic behaviour. Many researchers (including MacLean et al. 2012) suggest this receptor is responsible for inducing peak, or mystical, states. It is currently unclear whether direct agonism of the receptor, without experiential effects, may bring about reductions in neuroticism and increases in agreeableness, or indeed if this is possible. It is also unclear whether or not changes in psychological state are the primary mediator, or the degree to which this is affected by set and setting. Repeating this study in a variety of settings, such as neo-shamanic or clinical, would aid in providing greater insight.

Ayahuasca has been found to elicit changes in personality structure in a number of studies in different settings (Barbosa et al. 2009; Grob et al. 1996; Kavenská and Simonová 2015). Many of the changes recorded suggest therapeutic implications for affective disorders, often associated with high levels of neuroticism (Duggan et al. 1995). In addition, increasing agreeableness and decreasing neuroticism on the NEO may benefit those suffering from cluster C personality disorders, such as obsessive-compulsive personality disorder. This study demonstrated a positive relationship between the extent of a perceived mystical experience and changes in personality structure. This finding is consistent with recent work that suggests the therapeutic relevance of mystical states in psychedelic therapy (e.g. MacLean et al. 2011). It is important to continue studying traditional communities and the efficacy of their practices while also being mindful of the limitations to adapting them to Western frameworks.

Ethical issues surrounding 'ayahuasca tourism'

It should be noted that the recent increase in 'ayahuasca tourism' is not without risks. Individuals claiming to be 'neo-shamans' who have not undergone the extensive training typically required to bear such a title is a prime example of this (De Rios 2009). These happenings raise a vast array of concerns, such as the safe preparation of brews, potential contra-indications, financial and other types of exploitation, and potential cases of sexual abuse by predatory folk masquerading as healers (Prayag et al. 2016). In Peru, there is practically no regulation or vetting for practitioners. It is therefore up to the individual to ensure the expertise and intentions of people they choose to drink with. There are also issues surrounding cultural appropriation as the use of ayahuasca grows. This is principally due to its status as a sacrament within certain communities (Tupper 2009). Although it is beyond the scope of this paper to discuss, readers should be aware that so-called 'retreat centres' based in locations such as the Amazon have come under scrutiny, with opposition to the potential financial gain some non-indigenous individuals stand to make from ayahuasca tourism and other schemes surrounding plant medicines.

Limitations

Some limitations should be considered when interpreting our findings. Firstly, this was a field experiment, which naturally gave rise to a number of confounding variables researchers were unable to control for. Readers should therefore exercise caution when inferring causality and generalising findings outside the setting outlined in this study. For instance, researchers were limited in access to equipment which could have established neurobiological and pharmacokinetic correlates to findings, via plasma and other appropriate biological data, as well as potential epigenetic markers. As several other non-psychoactive plants and treatments were used in conjunction with ayahuasca, it is impossible at this stage to quantify the potential impact of these variables on our outcome measures. This was principally a resource issue as a result of being independently funded.

Although participants were asked to abstain from psychoactive substances between the retreat and 6-month follow-up, it was impossible to ascertain the extent to which this was adhered to. Namely, the current study format did not allow for us to stringently control, test, or exclude anyone engaging in psychoactive substance use. According to the self-reported data at follow-up, drug use appears to have decreased overall following ayahuasca sessions within our participants. Future consideration should be put into longitudinal designs which allow the controlling of restricted, or at least minimised, psychoactive substance use.

Similarly, other potentially impactful lifestyle variables were not monitored. This largely relates to integration or psychological support individuals may have engaged in which may have affected the validity of long-term findings.

Due to the nature of the retreat, no set doses of ayahuasca were specified. Instead, each dose was based upon both the curandero's recommendation and the individual's will on the day of the ceremony. While this may mean scientific standardisation is unmet, insistence on consistent dosing would have deviated from the traditional framework on which this culture-specific observational study was based. Furthermore, due to the study being an independent self-funded project, funds/resources were insufficient for constituent analysis of ayahuasca samples (e.g. use of high-performance liquid chromatography).

It is likely that the results obtained are subject to self-selection bias, as individuals who opted into the study have made time/financial sacrifices to attend the retreat. Such would naturally elicit some degree of expectations which may well affect outcomes.

Finally, the observational nature of the study also gave rise to potential safeguarding concerns. While there was a medical doctor on-site and evidence suggests an acceptable safety profile for ayahuasca use, participants' medical records were not obtained to confirm self-reported medical and psychiatric histories. It was therefore difficult to adequately safeguard against unreported conditions having potentially unknown negative interactions with ayahuasca use. Fortunately, no medical assistance was required for the current sample, but this nonetheless raises ethical considerations for ayahuasca retreats more broadly. Greater control of inclusion/exclusion criteria in future studies may potentially cater for both safeguarding considerations and external validity of findings.

Summary

Increasingly, traditional practices are being incorporated into modern therapeutic frameworks. It is feasible that other treatments, such as variations on the South American shamanic practices, may one day be conducted in clinical settings, as cultures continue to converge.

As interest in psychedelics grows both in the scientific community and the public, the efficacy and safety of these compounds require further investigation using rigorous research design, under state-sanctioned regulation, in a range of frameworks. In doing this, we can fully investigate therapeutic avenues for these 'novel treatments', particularly as these compounds appear to possess what appears to be powerful potential for aiding the human condition on an every-day level.

The current study goes some way in validating the effectiveness of adapted traditional ayahuasca retreats on ayahuasca tourists, by providing personality data which may imply therapeutic avenues.

Acknowledgments The research team would like to express gratitude to The Ayahuasca Foundation staff, Carlos Tanner, Kieron 'Keyo' Orbell, Márcia Medeiros Lim, the Lopez brothers, Dr. Paul Richardson, and Noya Rao for their support and contributions to this project. This article was made open access with the support of King's College London.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This observational study complies with the ethical standards set out by the Declaration of Helsinki.

Informed consent Informed consent was obtained from all participants.

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Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Participation in an indigenous Amazonian led ayahuasca retreat associated with increases in nature relatedness – a pilot study

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Abstract

Indigenous Amazonian shamanic ayahuasca practice is deeply rooted in nature and it is employed as an ecological mediating agent and in collective environmental decision-making processes by some of the groups that use it. Phenomenologically, the ayahuasca experience is often rich in nature-based themes and content, and its usage has been associated with eliciting shifts in perspectives and attitudes towards nature. In this proof of concept study, participation in an ayahuasca retreat in a traditional indigenous Amazonian context (with a mean of 5.85

ceremonies attended) was associated with significant increases in nature relatedness (n = 24; Cohen's d = .51) and mindfulness (n = 38; Cohen's d = .75), and improvements in depression (n = 47; Cohen's d = 1.18), state anxiety (n = 47; Cohen's d = 1.02), and trait anxiety (n = 42; Cohen's d = .88). Furthermore, significant negative correlations were found between changes in nature relatedness and depression (r = -.623, p = .001), state anxiety (r = -.542, p = .008), and trait anxiety (r = -.485, p = .022), with a significant positive correlation between change in nature relatedness and mindfulness (r = .747, p = .001). It is currently unclear if the changes seen were due to consumption of the brew, participation in ceremony, or the retreat setting itself. Although this pilot study suggests a potential therapeutic role for Amazonian ayahuasca retreats as a multidimensional intervention, further work is required to assess the role of possible mediators underlying such shifts, while evaluating to what extent these are sustained long-term.

Introduction

A growing human psychological disconnection from the natural world has been linked to environmental destruction and negative impacts on mental health. In spite of the utmost urgency warranted in reversing this, there is a lack of interventions which can effectively reconnect individuals to the natural world. Ayahuasca is a psychedelic plant-derived decoction containing beta-carboline MAOI alkaloids and the psychedelic compound DMT with a long-history of shamanic usage in Amazonia. Ayahuasca experiences often feature a strong phenomenological component of nature, with nature-based content and themes commonly described (Metzner, 2006; Shanon, 2002; Winkelman, 2005), including experiences of interconnection with nature (Argento et al., 2019; Kavenská & Simonová, 2015; Prayag et al., 2016; Thomas et al., 2013; Trichter et al., 2009). Traditional Amazonian shamanic ayahuasca

practice is deeply rooted in nature, with shamanic rituals and teachings often emphasising the shared interconnection of humans with nature (Fernández & Fábregas, 2014; Fotiou, 2010; Weiss et al., 2021), with this also applying to European (Harms, 2021) and Australian (Gearin, 2016) neoshamanic contexts. Ayahuasca plays a prominent role as an ecological mediating agent among some Amazonian indigenous groups that use it, as a bridge between humans and non-human life and the wider forest landscapes (Descola, 1998; Kohn, 2013), and it can play a role in collective environmental decision-making processes (Keifenheim, 1999; Lagrou, 2018).

Nature relatedness (sometimes referred to as nature connectedness in the literature) is a measure of one's self identification with nature, encompassing "one's appreciation for and understanding of our interconnectedness with all other living things on the earth" (Nisbet et al., 2009), and it is tied to a sense of kinship with the wider natural world as part of a larger community of nature (Mayer et al., 2009). It has been linked to better overall mental and physical health (Dean et al., 2018) and strongly associated with eudaimonic well-being (for a review, see Pritchard et al., 2020), far exceeding the association between the latter and socio-economic status in one study (Martin et al., 2020). It is also associated with greater contact with nature, while being an important mediator for some of the benefits to mood and cognition yielded by the latter (for a review, see Gandy et al., 2020) and it is a key predictor of pro-nature attitudes and behaviours (Martin et al., 2020; Whitburn et al., 2020; Zylstra et al., 2014).

Nature relatedness appears to be a deeply held and stable trait (Dornhoff et al., 2019; Nisbet et al., 2009, 2011; Schultz et al. 2004), and resistant to change like other environmental attitudes (Nisbet et al., 2009; Nisbet & Zelenski, 2014; Wright & Matthews, 2015). Human connection to nature is being increasingly eroded, partly through increasing urbanisation (Cox et al., 2017; Cumming et al., 2014) and a loss of green space (Lin et al., 2015), meaning

increasing numbers of people are inhabiting nature-depleted environments (Fretwell & Greig, 2019; Soga & Gaston, 2016, 2020). This can result in a diminished potential for everyday interactions with nature or an 'extinction of experience', and this reduced capacity for nature contact and connection has detrimental implications for health, wellbeing, and propensity towards experiencing positive emotions (Soga & Gaston, 2016). While there are a range of nature relatedness enhancing interventions, including nature immersion retreats (Barton et al., 2016), nature-based educational programmes (Barrable & Booth, 2020; Chawla, 2020), and nature-based engagement programmes (Richardson et al., 2016; Richardson & McEwan, 2018), these may be time and resource heavy and variable in their effectiveness, with a need for reliable and robust interventions (Richardson & Sheffield, 2017).

Psychedelic mystical experiences have been associated with states of interconnectedness (Barrett & Griffiths, 2018; MacLean et al., 2011) and frequently correlated with positive changes in people's relationship with nature (Kangaslampi et al., 2020). In addition, mystical experiences have been identified as a factor contributing to reductions in depression and anxiety associated with ayahuasca usage (van Oorsouw et al., 2022; Sarris et al., 2021). This formed the rationale for assessing the degree to which mystical experiences were correlated with shifts in nature relatedness and associated with changes in depression and anxiety.

Ayahuasca has also been associated with enhancing mindfulness (Murphy-Beiner & Soar, 2020; Sampedro et al., 2017; Soler et al., 2018; Thomas et al., 2013), which shares a positive reciprocal relationship with nature relatedness (Howell et al., 2011; Wolsko & Lindberg, 2013; Schutte & Malouff, 2018). Nature relatedness has been associated with lower levels of state and trait anxiety (Martyn & Brymer, 2016), of mental distress and antidepressant medication prescription usage (White et al., 2021), and positively associated with

psychological resilience (Ingulli & Lindbloom, 2013). However, aspects of nature relatedness tied to self-identification with nature and a concern for conserving nature have been linked to increased depression, anxiety, and stress, possibly due to an increased awareness of human driven ecological destruction (Dean et al., 2018).

This paper assesses whether participation in Amazonian ayahuasca retreats, as a multidimensional intervention, results in change in nature relatedness. Furthermore, this study evaluates whether changes in mystical experience, mindfulness, depression, trait, and state anxiety are associated with shifts in nature relatedness. While previous studies have highlighted an association between experience with classical psychedelics and nature relatedness (Forstmann & Sagioglou, 2017; Kettner et al., 2019; Lyons & Carhart-Harris 2018; Nour et al., 2017), this is the first study to prospectively assess the effect of participation in an indigenous Amazonian shaman led ayahuasca retreat in the Peruvian Amazon on nature relatedness. Inferring from previous research, it is expected that participation in an ayahuasca retreat will likely enhance levels of nature relatedness.

Methodology

Setting

Data was collected at the Ayahuasca Foundation (AF). This ayahuasca retreat centre is situated three hours from the nearest city, Iquitos, in the Peruvian Amazon. The self-selected sample were required to travel by car and then by boat to reach the centre. The retreat and research centre is located in the Allpahuayo-Mishana National Reserve. The Mishana community is 20 miles from Iquitos, has no mains electricity and is almost completely free from phone signal and internet access.

Participants

58 participants were enrolled in total after meeting the retreat centre's eligibility criteria. The information provided was self-reported and diagnoses were not confirmed with medical records by the researchers (see Table 1 for participant demographics). Participants were asked to report their lifetime use of substances, defined as use of a substance on at least one occasion during their lifetime. 11 (18.96%) reported previous use of ayahuasca, ranging between 1–42 times (see Table 2 for lifetime use of substances amongst participants). Data was collected from participants across eight jungle retreats. Number of participants per retreat length were 34 (58.62%) in the 8-day, 6 (10.34%) in the 14-day, 6 (10.34%) in the 18-day, and 12 (20.69%) in the 28-day retreat. All data from varying retreat lengths were included in the analyses, with subsequent analyses conducted to determine the effect of differing retreat duration as well as the number of ceremonies attended on outcomes.

Table 1

Participant demographics

Participant Demographics	**N=58**	**%**
Age (years)		
Mean (SD)	41.72 (±11.52)	
Gender		
Male	28	48
Female	30	52
Ethnicity		

White	35	60
Hispanic	8	14
Black	5	9
Asian	2	3
Other	4	7
Unanswered	4	7
Employment		
Full-time	28	48
Freelance	7	12
Unemployed	6	10
Students	4	7
Retired	3	5
Part-time	1	2
Other	5	9
Unanswered	4	7
Income		
< $10k	7	12
$10-50k	12	21
$50-100k	15	26
> $150k	10	17
Unanswered	14	24
Physical health characteristics		
No diagnosed physical health problems	27	47
Hypertension	4	7

	Chronic pain	4	7
	Cancer	3	5
	Seizures	1	2
	Irritable bowel syndrome	1	2
	Other conditions e.g. ankylosing spondylitis, coeliac disease, scoliosis	14	24
	Unanswered	4	7
Mental health characteristics			
	No diagnosed psychiatric disorders	27	47
	Depression	18	31
	PTSD	4	7
	Anxiety	4	7
	Other	1	2
	Unanswered	4	7

SD = standard deviation

Table 2

Lifetime use of substances (at least once in their lifetime) amongst participants

Substance	**N=58**	**%**
Ayahuasca	11	19
Psychedelics	12	21
MDMA	8	14
Cannabis	23	40

Amphetamine	7	12
Methamphetamine	4	7
Benzodiazepines	5	9
Cocaine	6	10
Crack cocaine	0	0
Ketamine	7	12
LSD	5	9
Psilocybin mushrooms	7	12
DMT	4	7
2CI, 2CE, 2CB	0	0
Heroin	0	0
Other	6	10

Previous research has documented moderate-to-high effect sizes (e.g., Cohen's *d*) for responses to psychedelic interventions (*ds* = .91-1.38 González et al., 2020; González et al., 2021), as well as moderate-to-high correlations between pre-post change scores (*r*s = .53-.55; González et al., 2020; González et al., 2021). Although we did not perform a formal *a priori* power analysis, the sample size of 58 participants provides 80% power to detect weak effects ($d > .37$, $r > .35$), assuming two-tailed alpha = .05 (G* Power 3.1; Faul et al., 2013), which suggests that the present sample was sufficient to detect effects similar to, and much smaller than, those reported in previous studies. Unfortunately, there was significant missing data on several measures, however, even when accounting for the reduced sample size, a sample of 24 participants provides 80% power to detect moderate effects ($d > .59$, $r > .51$), assuming two-

tailed alpha = .05, which indicates that even the analyses performed on the data with the smallest sample size were sufficiently powered to detect effects similar to those reported in previous studies.

Design

This study followed an observational, naturalistic design. Participants attending the retreats were informed of the research by the AF two weeks before arriving at the centre. Retreat facilitators provided potential research participants with information sheets outlining the research upon arrival in Iquitos. Participation was voluntary and participants were able to withdraw consent at any time.

The AF collected information from participants before they were accepted onto retreats. Online forms were utilised, with questions surrounding medications and physical and mental health conditions. Participants were forbidden from attending retreats if they disclosed personality disorders or conditions that were psychotic in nature (schizophrenia, bipolar disorder etc). The decision to include participants on the retreats was made solely by the AF and independently of the research team.

Ethical approval was acquired (#CLESPsy000893 v2.0) and the study is in concordance with the declaration of Helsinki.

Retreat preparation

Participants were required to adhere to a "washout period" before attending retreat. For the two weeks prior to retreat commencement, abstinence from drugs (both prescription and

recreational), fatty food, salt, red meat and sugar was required. Dietary restrictions were largely to lower levels of tyramine, which, when combined with MAOIs has the potential to result in nausea, cardiovascular overactivity, and headaches (Dos Santos, 2013).

Measures

Short form Nature Relatedness Scale

For the sake of parsimony, a validated six-item measure, the Short form Nature Relatedness Scale (NR-6) scale (Nisbet & Zelenski, 2013) was used to assess people's subjective sense of self-identification with nature, or their connectedness to it, this being a short form version of the larger Nature Relatedness (NR) scale (Nisbet et al., 2009). Participants rated the degree to which they agreed with six statements on a 5-point Likert scale (1 = 'disagree strongly' to 5 = 'agree strongly'). The six items were: 'My ideal vacation spot would be a remote, wilderness area'; 'I always think about how my actions affect the environment'; 'My connection to nature and the environment is a part of my spirituality'; 'I take notice of wildlife wherever I am'; 'My relationship to nature is an important part of who I am' and 'I feel connected to all living things and the earth'. The mean of the answers across the six items was used as a measure of nature relatedness, with higher scores corresponding to higher ratings of nature relatedness. The NR-6 has been shown to demonstrate temporal stability, with high one-month test-retest reliability (r = .93), as well as predicting happiness and environmental outcomes similarly to the full scale (Nisbet & Zelenski, 2013). A reliability analysis carried out on the NR-6 for internal consistency indicated that it reached acceptable reliability in our sample (Cronbach's alpha = .80).

Unfortunately, there was a significant amount of missing data associated with this scale. Missing NR-6 responses were likely due to unclear formatting when completing the electronic battery, in which participants were required to scroll further after previous questions. Of the total sample of 58 participants, 24 successfully completed the NR-6 scale with 34 leaving the questionnaire incomplete. This has now been addressed for follow up studies.

Beck Depression Inventory—Second Edition

The Beck Depression Inventory—Second Edition (BDI-II) is one of the most frequently used self-report measures of depression severity. This 21-item scale assesses the psychological symptoms of depression such as irritability and hopelessness, cognitions including guilt or feelings of being punished as well as physical symptomatology including shifts in sexual desire, weight loss and fatigue. Each question is scored on a four-point Likert scale ranging from zero to three. Higher scores suggest more severe depression, with scores between 0–13 indicative of minimal depression, 14–19 mild depression, 20–28 moderate depression and 29–63 severe depression (Beck & Steer, 1984). The BDI-II has been demonstrated to be valid, with high one-week test-retest reliability (r = .93), demonstrating a lack of sensitivity to daily mood fluctuations (Beck et al., 1996). A reliability analysis carried out on the BDI-II for internal consistency indicated that it displayed strong reliability in our sample (Cronbach's alpha = .95).

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) is comprised of 40 items assessing two distinct forms of anxiety in two subscales, the State-Trait Anxiety Inventory – State (STAI-S) and State-Trait Anxiety Inventory – Trait (STAI-T). Trait anxiety refers to a stable feature of personality, whereas state anxiety describes an emotional state, transient in nature. The scale utilises 20 items to assess trait and 20 items to assess state anxiety. Brief statements are presented for

example ‘I am worried’, and participants are required to rate each on a four-point Likert scale ranging from 1= ‘almost never’ to 4= ‘almost always’. Possible scores range from 20 to 80, with higher levels of anxiety correlating with higher scores on the inventory (Spielberger et al., 1999). The STAI has been found to demonstrate both construct and concurrent validity (Spielberger et al., 1989). Spielberger (1983) found test-retest reliability coefficients ranging between .65 and .75 over a two-month period. A reliability analysis indicated that the STAI state anxiety items exhibited strong reliability in our sample (Cronbach’s alpha = .95), as did the trait anxiety items (Cronbach’s alpha = .95).

Mystical Experience Questionnaire

The Mystical Experience Questionnaire **(**MEQ) comprises 30 items and measures peak experiences. This validated tool assesses four factors; Transcendence of Time and Space (a sense of being outside of the past and the future), Positive Mood (feelings of tranquillity and peace), Ineffability (incapability to describe the experience in words) and Mystical Experience (items pertaining to both internal and external unity as well as possessing a noetic quality; MacLean et al., 2012). Participants are required to rate the intensity with which they experienced each of the items on a six-point scale ranging from 0= ‘not at all; none’ to 5= ‘more than ever before in my life and stronger than 4; extreme’ (Griffiths et al., 2006). Participants were considered to have undergone a ‘complete mystical experience’ when ≥ 60% of the maximum possible score on each subscale was endorsed (Barrett et al., 2015). The MEQ has been shown to demonstrate sensitivity when assessing the effects of ayahuasca in previous research (Schenberg et al., 2017). A reliability analysis carried out on the MEQ indicated that it reached acceptable reliability in our sample (Cronbach’s alpha = .97). Data was only collected using this tool at time point two to evaluate the effect of the retreat. As such, ratings reflected the entire retreat, rather than single ceremonies.

Five Facets Mindfulness Questionnaire

The Five Facets Mindfulness Questionnaire **(**FFMQ) is a self-report measure comprised of 39 items assessing the five facets; Acting with awareness, Observing, Describing, Nonreactivity and Nonjudging (Baer et al., 2006). Acting with awareness describes one's ability to attend to the present moment. Observing refers to the ability to notice experiences, both internal and external, for example emotions and bodily sensations. Describing involves putting experiences into words. Nonreactivity is the ability to refrain from one's involvement in thoughts and emotions, allowing them to pass freely. Finally, Nonjudging involves refraining from the evaluation of thoughts and emotions. Each of the items are measured on a 5-point Likert-type Scale (1 = 'very rarely true', 5 = 'very often true'), for example 'I pay attention to physical experiences such as the wind in my hair or the sun on my face'. Scores for each facet range between 8-40, other than Nonreactivity, which ranges between 7-35. Scores can be used for the five subscales individually or combined to form an overall mindfulness score, with higher scores representing a greater degree of mindfulness (Baer et al., 2006). The FFMQ has been demonstrated to show both discriminant and convergent validity as well as adequate internal reliability in both clinical and non-clinical samples (Baer et al., 2006; Baer et at., 2008). Veehof and colleagues (2011) found test–retest reliability coefficients of the FFMQ facets ranging between .61 (acting with awareness) to .84 (nonjudging). A reliability analysis carried out on the FFMQ indicated that it reached acceptable reliability in our sample (Cronbach's alpha = .95).

Procedure

The AF administers ayahuasca in an adapted traditional Shipibo format. Retreat length varies, from eight days to one month. Participants were offered either four, six, nine, or eleven ayahuasca ceremonies, although participation was voluntary. The exact number of ceremonies attended was recorded.

Ayahuasca ceremonies lasted for around six hours and took place at night. Two to three Western facilitators assisted a shaman (curandero) throughout the rituals. Ceremonies took place in the 'maloka', a circular wooden structure, with participants sitting around the edge. Each participant was provided with a bucket for 'the purge' – vomiting that is typically associated with the brew. Participants were evenly spaced on individual mattresses and instructed to avoid contact with one another throughout the ceremony. Ayahuasca was consumed at around 20:00 after intentions for the ceremony had been set. Following this the curandero sang 'icaros' (traditional medicine songs), with facilitators helping participants if required. The dose of ayahuasca was left to the curandero and the participants discretion (usually 150-200ml).

Participants completed inventories before their first ceremony and the morning after their final ceremony. Pre-retreat data collection took place at a hotel in Iquitos, and post-retreat data collection at the AF in the Mishana community. Laptop computers were provided in each instance.

Data Analysis

Data is analysed using SPSS 27.0. Paired-samples two-tailed t-tests were used to compare mean differences across time and only total scores were used in the present analysis. The multistage effect sizes were calculated using Cohen's *d* and were considered large when .80 ($d > .80$)

(Cohen 1988). The Holm-Bonferroni procedure was applied to analyses to correct for multiple comparisons (Holm, 1979). It should be noted that there were a large number of missing datasets in this study. 47 of the 58 enrolled participants completed the BDI-II pre and post retreat, 47 completed the STAI-S, 42 the STAI-T, 38 the FFMQ, 24 the NR-6 and 50 the MEQ at time point two. Pearson's bivariate correlation analyses were used to compute *r* values. Correlation coefficients ranging between .30 and .70 were deemed moderate. Explorative correlation analyses were conducted with an alpha level set at .01 to control for multiple comparisons. All data were normally distributed (Shapiro-Wilk test), and outliers were assessed for using boxplots and scatterplots. Four outliers were removed from the correlation analyses, one from the primary analysis and three from the exploratory analyses, after being identified on scatterplots and have been reported in the results.

Results

Pre and Post Ayahuasca Retreat Outcomes

Our first set of analyses examined whether participation in Amazonian ayahuasca retreats was associated with changes in the different research measures utilised (see Table 3 for descriptive and inferential statistics). Paired samples *t*-tests showed that participation in Amazonian ayahuasca retreats was associated with significant improvements on all measures, with medium to large effect sizes. This suggests that participation in such retreats as a multidimensional intervention could evoke significant changes in a variety of domains.

Table 3

Descriptive and inferential statistics for research measures as a function of time point (pre- vs. post-Amazonian ayahuasca retreat attendance)

	Pre	**Post**			
Measure (*n*)	***M (SD)***	***M (SD)***	***t* (df)**	***p***	**Cohen's *d***
BDI -II (47)	18.49 (13.44)	4.26 (4.08)	8.12 (46)	<.001**	1.18
STAI-T (42)	50.28 (13.21)	37.71(14.54)	5.73 (41)	<.001**	.88
STAI-S (47)	39.38 (13.05)	25.94 (8.93)	7.01 (46)	<.001**	1.02
FFMQ (38)	122.76 (25.75)	140.13 (26.89)	4.63 (37)	<.001**	.75
NR-6 (24)	4.10 (.64)	4.36 (.62)	2.52 (23)	.019*	.51

*M = mean, df = degrees of freedom, *p < .05, **p ≤ .001, BDI-II = Beck Depression Inventory—Second Edition, STAI-T = State-Trait Anxiety Inventory – Trait, STAI-S = State-Trait Anxiety Inventory – State, FFMQ = Five Facets Mindfulness Questionnaire, NR-6 = Short form Nature Relatedness Scale*

Primary correlation analysis of change scores

A priori analyses involved correlating the NR-6 with the BDI-II, STAI-S, and STAI-T. One outlier was removed from the NR-6 and STAI-S correlation and the remaining assumptions for correlations were met. A statistically significant negative correlation with moderate effect size was found between NR-6 change scores and BDI-II, STAI-S, and STAI-T change scores (see Table 4 for primary correlation analyses). This suggests that changes in nature relatedness is associated with decreased scores on clinical outcome measures after attending Amazonian ayahuasca retreats in our sample.

Table 4

Primary correlation analyses of change scores

	BDI-II *n* = 47	**STAI-S** *n* = 47	**STAI-T** *n* = 42
NR-6 *n* = 24	-.623***	-.653**	-.485*

**p<.05, ** p<.01, *** p≤.001, BDI-II = Beck Depression Inventory—Second Edition, STAI-S = State-Trait Anxiety Inventory – State, STAI-T = State-Trait Anxiety Inventory – Trait, NR-6 = Short form Nature Relatedness Scale*

Exploratory Correlation Analyses

Subsequent exploratory analyses were conducted, correlating the remaining research measures, and also investigating demographic and retreat variables. The alpha level was set at .01 to control for multiple comparisons. One outlier was removed from the BDI-II and STAI-T correlation, one from the FFMQ and STAI-T correlation, and one from the FFMQ and NR-6 correlation, and all remaining assumptions were met. A statistically significant positive correlation with a large effect size was found between the NR-6 and FFMQ change scores (see Table 5 for correlation matrix of pre-post change scores). The MEQ was not found to significantly correlate with any of the change scores in research measures, despite 34 of the 42 participants (81.0%) who answered the MEQ qualifying for a "complete mystical experience", defined as a score of 60% or more on each of the four subscales (Barrett et al., 2015).

Table 5

Correlation matrix of pre-post change scores in research measures

	STAI-S *n* = 47	**STAI-T** *n* = 42	**FFMQ** *n* = 38	**MEQ** *n* = 50
BDI-II *n* = 47	.616**	.513**	-.192	.170
STAI-S *n* = 47	-	.490**	-.289	-.263
STAI-T *n* = 42	-	-	-.600**	-.111
NR-6 *n* = 24	-	-	.747**	-.084
FFMQ *n* = 38	-	-	-	.001

** p<.01, ** p≤001, BDI-II = Beck Depression Inventory—Second Edition, STAI-S = State-Trait Anxiety Inventory – State, STAI-T = State-Trait Anxiety Inventory – Trait, FFMQ = Five Facets Mindfulness Questionnaire, NR-6 = Short form Nature Relatedness Scale, MEQ = Mystical Experience Questionnaire*

In a final set of exploratory analyses (with a correction for multiple analyses; alpha=.01), Pearson's correlations revealed a trend towards a positive association (after correcting for multiple comparisons) between the number of days spent on the retreat and pre-post changes in the NR-6 $r(22)=.48$, $p=.016$, whereas no significant correlation was observed between NR-6 and the number of ayahuasca ceremonies attended during the retreat $r(22)=.321$, $p=.126$. Similarly, no significant correlation was found between the number of ayahuasca ceremonies attended and pre-post changes in the BDI-II $r(44)=-.152$, $p=.314$, STAI-S $r(44)=-.088$, $p=.563$ or STAI-T $r(40)=-.013$, $p=.936$, nor the number of days spent on retreat and pre-post changes in the BDI-II $r(44)=-.182$, $p=.266$, STAI-S $r(44)=-.144$, $p=.541$, or STAI-T $r(40)=-.007$, $p=.964$. Independent-samples *t*-tests and Pearson's correlations showed no significant relationship between pre-post changes in the NR-6 and age $r(21)=-.013$, $p=.936$, gender $t(23)$

=-.996, p = .330), history of ayahuasca use $t(18)$ =.666, p = .679, or other psychedelic use $t(17)$ =.250, p = .449). These results suggest that there was no association between the number of ceremonies attended by participants and change in their anxiety, depression, or nature relatedness scores. Similarly, we did not find a relationship between the number of days participants spent on retreat and changes in anxiety or depression scores, however, there was a trend towards an association with change in nature relatedness. Changes in nature relatedness were not associated with either demographic factors (age and gender) or historical use of psychedelics (including ayahuasca).

Discussion

Participation in Amazonian ayahuasca retreats in a traditional indigenous context (with a mean attendance of 5.85 ceremonies) was associated with reductions in depression, state, and trait anxiety, and increases in mindfulness and nature relatedness. Increases in nature relatedness were found to be negatively correlated with depression, state, and trait anxiety, and positively correlated with mindfulness scores. Thus, this multidimensional intervention identified positive changes. However, the mechanisms of change, including the contributions of each component to effect change, need to be explored further. No relationship was found between age, gender, and history of past ayahuasca or psychedelic usage.

Ayahuasca and nature relatedness

The finding that participation in Amazonian ayahuasca retreats was associated with a significant increase in nature relatedness builds on previous research reporting links between

ayahuasca usage and shifts in individuals' relationships with nature (see Table 3). The mean baseline nature relatedness of participants in this study was high (4.10/5), with a mean nature relatedness of 4.36 post ayahuasca retreat participation, with a number of pooled studies reporting that mean baseline scores ranged from 3.00-3.44 in Canadian student and community populations sampled (Nisbet & Zelenski, 2013). Mean levels of nature relatedness following ayahuasca retreat participation exceed median nature relatedness levels reported in one study (4.2) with a sample of individuals reporting a broad range of lifetime psychedelic usage (Nour et al., 2017) and were similar to mean levels of nature relatedness (4.45) in one study sample comprising individuals reporting over 100 psychedelic experiences (Kettner et al., 2019).

It is important to acknowledge the possible influence of contextual factors in this study. Traditional, indigenous shaman led ayahuasca ceremonies have an inclination towards nature-based content and themes (Fernández & Fábregas, 2014; Weiss et al., 2021) and likely act as a mediating influence that affects people's relationship with nature, aside from the direct pharmacodynamic effects of ayahuasca itself (Harms, 2021). It is noteworthy that while no correlation was found between the number of ayahuasca ceremonies individuals participated in and shifts in nature relatedness, there was a trend towards significance when comparing number of days spent at the retreat centre and changes in nature relatedness, suggesting the rainforest setting may have influenced individuals' nature relatedness above and beyond ayahuasca ceremonies alone. Contact with biodiverse or nature-rich environments may promote greater nature relatedness (Dornhoff et al., 2019; Hamlin & Richardson, 2021; Wyles et al., 2019), and nature-based experiences or interventions of greater time duration are more likely to elicit increases in nature relatedness (Barrable & Booth, 2020; Braun & Dierkes, 2017; Schultz & Tabanico, 2007). Furthermore, given limited electricity and a lack of phone signal or internet access at the retreat centre, retreat participants would have been forced to disconnect from technology for the duration of their time there. This may have facilitated greater

connection to nature while attending the retreat, with usage of electronic entertainment technology and smartphones negatively associated with nature relatedness (Larson et al., 2018; Pergams & Zaradic, 2006; Richardson et al., 2018).

Ayahuasca commonly changes the way users perceive their relationship with nature during and after the experience (Prayag et al., 2016) and healing relationships with nature is a commonly reported beneficial outcome of ayahuasca usage (Trichter et al., 2009). People report a greater interconnection with nature, greater sensitivity towards it, and a proclivity to spend more time in nature with feelings of safety and confidence following ayahuasca usage (Kavenská & Simonová, 2015). Ayahuasca usage has also been associated with generating more respectful relationships with nature (Grob et al., 1996), inspiring nature-orientated interests (Kjellgren et al., 2009) and in generating pro-environmental awareness and attitudes (Harms, 2021). Such shifts are likely mediated in part through an increase in nature relatedness.

While this study did not assess long-term changes in nature relatedness, inferring from previous research, such shifts are likely to be enduring. Positive changes to people's relationship with nature and their connection to it following a psychedelic experience has been found to be sustained for at least 1-2 years according to past research and increased nature relatedness and a deepened appreciation of nature can occur after 1-2 psychedelic sessions (Kettner et al., 2019; Lyons & Carhart-Harris, 2018; Studerus et al., 2011). Further research could assess to what degree increases in nature relatedness elicited by Amazonian ayahuasca retreat participation are sustained long-term.

Nature relatedness increase correlating with reductions in depression and anxiety

The occurrence of mystical experiences assessed via the MEQ was not correlated with changes in nature relatedness, mindfulness or depression and anxiety scores, while nature relatedness was found to be significantly negatively correlated with depression, trait, and state anxiety, and positively correlated with mindfulness scores. Other research has found nature relatedness to be more consistently associated with measures assessing happiness, positive affect, and personal growth than depression and negative affect, particularly after controlling for general connectedness (Zelenski & Nisbet, 2014). The only other published prospective study that has examined a potential link between changes in nature relatedness elicited by psychedelic administration and depression found no correlation, but this study was limited by a small sample size (n=7) (Lyons & Carhart-Harris, 2018).

The lack of evidence demonstrating a link between the occurrence of mystical experiences and changes in clinical outcomes is noteworthy, being in contrast to other studies where the occurrence and intensity of mystical experiences was found to be a significant factor predicting improvements in depression and anxiety (Davis et al., 2019, 2020; Roseman et al., 2018; Sarris et al., 2021; van Oorsouw et al., 2022). However, one randomised placebo-controlled trial evaluating the antidepressant potential of ayahuasca found that only one factor of the MEQ (transcendence of time and space) showed a significant association with a reduction in depression scores, whereas the other three factors (ineffability, mystical and positive mood) did not (Palhano-Fontes et al., 2019). In our sample, 81.0% of participants qualified for a “complete mystical experience”, scoring 60% or more in each of the four core dimensions of the MEQ. This is a large proportion of subjects when compared to other psychedelic research, exceeding that reported in early work conducted by Pahnke (1967), which reported complete mystical experiences in 30-40% of participants, and in a range of naturalistic survey studies (see Gandy, 2022) and in a more recent study where 61.1% of participants qualified for a complete mystical experience following psilocybin administration

(Griffiths et al., 2008). Higher ratings of complete mystical experiences have been reported with psilocybin administered in a mindfulness meditation retreat context among Zen Buddhist meditation practitioners, with 95% reporting such experiences (Smigielski et al., 2019), and in association with usage of 5-MeO-DMT in a supportive context, with such experiences reported among 75% (Barsuglia et al., 2018) and 83% (Sepeda et al., 2020) of participants in the latter studies. The high scores on the MEQ in our sample may result from the non-standard use of the scale to measure the entire retreat, rather than for a single psychedelic session as it was designed (MacLean et al., 2012). This methodological limitation may account for the lack of relationship between MEQ scores and anxiety and depression, which is well established in the literature (for a review, see Gandy, 2022). While no association was found between the number of ceremonies attended and nature relatedness, there was a trend association between retreat duration and nature relatedness. This could indicate that the retreat environment itself may have a greater impact on nature relatedness than attending ayahuasca ceremonies and the mystical experiences associated with ceremonial ayahuasca consumption. Further research with larger sample sizes is however required to explore this before any conclusions can be drawn.

While other studies have identified factors such as psychological insight, personal meaning and emotional breakthrough experiences as being important determinants of clinical response associated with psychedelics (Davis et al., 2020; Roseman et al., 2019; Sarris et al., 2021), this is the first study to suggest that nature relatedness increase associated with the psychedelic experience may also have clinical relevance. While the potential implications of enhancing nature relatedness through psychedelic administration has largely been overlooked until recent times, it has been argued that maximising enhancement of nature relatedness when administering psychedelics may constitute an important supplemental pathway to improved mental health outcomes (Gandy et al., 2020).

Participation in Amazonian ayahuasca retreats in the present study was associated with increased mindfulness and change in nature relatedness scores were found to positively correlate with mindfulness as assessed via the FFMQ (see Tables 3 and 5). Previous studies have found ayahuasca usage to be associated with higher levels of an aspect of mindfulness referred to as decentering (Domínguez-Clavé et al., 2016; Franquesa et al., 2018; González et al., 2020, 2021; Kiraga et al., 2021; Murphy-Beiner & Soar, 2020; Soler et al., 2016). Decentering involves a non-judgmental and accepting perspective of inner psychological content, having been defined as "the realization that thoughts, feelings, and reactions are transitory patterns of mental activity, that they are not necessarily true representations of the self and events" (Lebois et al., 2015). Nature relatedness was found to have a borderline significant negative association with rumination (a propensity to dwell on negative thoughts or the symptoms of one's distress) in one study (Richardson & Sheffield, 2015), and there is a strong association between rumination and depression and anxiety disorders (for reviews, see Nolen-Hoeksema, 2000; Olatunji et al., 2013). Rumination and decentering can be considered as opposing and inversely correlated psychological processes (Fresco et al., 2007; Kaiser et al., 2015; Mori & Tanno, 2015), and decentering has been associated with mediating reductions in anxiety and depression (Fresco et al., 2007; Bennett et al., 2021), while also mediating the relationship between trait or dispositional mindfulness and nature relatedness (Hanley et al., 2017). Increases in nature relatedness and associated decreases in depression and anxiety following Amazonian ayahuasca retreat participation may partly occur through a decentering-mediated disidentification with internal psychological content which may in turn liberate mental resources to allow contextual awareness to expand (Fresco et al., 2007; Garland et al., 2015), so increasing receptivity to the external, natural world.

Study Limitations and Future Research

This was a proof-of-concept study with no control group. There was a significant attrition rate, which prevented long-term follow up, and a future study protocol has been amended in order to mitigate this to help ensure collection of long-term data. It should be noted that this study was underpowered due to a large number of missing data points and results regarding nature relatedness should be interpreted with caution. Further, constituent analysis of the brew was not possible for logistical reasons, preventing us from comparing outcomes to the levels of DMT and harmala alkaloids ingested. Generalisability of findings are limited due to the self-selected nature of the sample and participants being mainly Western and of higher income status. Further research should seek to assess a broader demographic of individuals. Positive sample bias may be a factor in this population, in that people attending a retreat with the intention of ingesting a psychedelic such as ayahuasca may have a greater than average openness towards new experiences (Kettner et al., 2019). Personality trait openness is one of the primary personality correlates of nature relatedness (Nisbet et al., 2009; Lee et al., 2015; Richardson & Sheffield, 2015). There may be a ceiling effect issue when assessing change in connection to nature using short item scales when baseline measures are already high (Barrable & Booth, 2020), as they were in this sample. While shorter item measures are convenient for research purposes, one potential way of mitigating this issue would be to use longer but psychometrically superior measures such as the Disposition to Connect with Nature scale (Brügger et al., 2011).

It is important to acknowledge the potential influence of the biodiverse setting of the Allpahuayo-Mishana National Reserve in the Peruvian Amazon rainforest on retreat participants' nature relatedness. The potential additive benefits of this nature-rich setting and other contextual factors such as the disconnection from technology and the nature-orientated

shamanic context in influencing nature relatedness in comparison to a Western clinical context warrants further attention. Future research could investigate the contribution of these various factors and a mediation analysis could be conducted to ascertain the level of contribution of the various potential mediators of nature relatedness change when compared to the pharmacodynamic effects of ayahuasca alone. Qualitative interviews of ayahuasca session participants may provide in-depth resolution into the phenomenological aspects underlying shifts in individuals' connection to nature.

A further methodological limitation is the lack of a consistent environment in which participants completed the inventories. Pre-retreat data collection took place at a hotel in Iquitos, whereas post-retreat data collection was completed at the AF in the Mishana community. The differences in location of nature relatedness sampling may have influenced participant's responses, leading to difficulties in determining the effect of the retreat opposed to the setting in which the questionnaire was completed. The setting in which inventories are completed will be standardised in future studies.

Whilst our data suggest nature relatedness could be related to changes in mental health outcomes such as depression and anxiety, our modest, uncontrolled sample does not allow for the generalisation of results. Future studies with larger samples and long term follow up will shed more light on the initial findings presented in this pilot study. Control groups for studies investigating psychedelics in retreat settings have proved problematic, with various authors attempting to address this issue (Netzband et al. 2020; Uthaug et al., 2021). As we continue to evaluate the effects of ayahuasca in Amazonian retreat settings we plan to run a "placebo" retreat. This will follow the same structure as a regular ayahuasca retreat, however during ceremonies no ayahuasca will be served. It is hoped this will go some way towards controlling some of the numerous confounding variables, such as the shamanic-ceremonial context,

immersion in nature, use of other plant treatments, smoke and vapour baths, and disconnection from electronic technology and the Western world in general.

Enhancing Nature Relatedness

The practice of journaling has been found to effectively supplement psychedelic sessions, enhancing the long-term psychological benefits obtained (Griffiths et al., 2018). Journaling about nature (recording three things one enjoys about nature each day for five days) has been found to increase nature relatedness in a robust and sustained way (Richardson & Sheffield, 2017). Application of such a practice before and after an ayahuasca experience may supplement the enhancement of nature relatedness. Building on this study, another reported that mindful walking in natural settings for 30 minutes a day (noting things that were enjoyed) was associated with increased nature relatedness, well-being, and positive affect (Keenan et al., 2021). This suggests that this simple and cost-effective practice could be a beneficial way for individuals to supplement increases in nature relatedness and these benefits to mental health following participation in ayahuasca ceremonies.

Mindfulness practices have been found to synergise with psilocybin administration, enhancing the long-term psychological benefits reported (Griffiths et al., 2018; Smigielski et al., 2019) while also enhancing nature relatedness (Aspy & Proeve, 2017; Nisbet et al., 2019; Schutte & Malouff, 2018; Unsworth et al., 2016), so application of mindfulness practices may augment the psychological benefits of ayahuasca while synergising with increases in nature relatedness. Contact with nature-based settings can promote mindfulness, and mindfulness in turn can enhance the benefits of contact with such settings (Van Gordon et al., 2018). The practice of Shinrin-Yoku (forest bathing), an active form of nature-based mindfulness practice (Hansen et al., 2017) may be a beneficial exercise both prior to and post ayahuasca experiences,

to help facilitate mindful and soothing contact with nature. Such practices may be particularly beneficial for people following ayahuasca experiences when integrating back into city life (Fernández & Fábregas, 2014). For additional suggestions on how to incorporate more nature-based content, practices, and settings into psychedelic sessions, see Gandy et al., 2020.

Ayahuasca usage in a traditional shamanic context (in the same setting as the present study) has also been found to significantly reduce neuroticism, with changes sustained at 6-month follow up (Netzband et al., 2020). Lower neuroticism scores are associated with greater psychological benefits obtained through contact with nature (Ambrey & Cartlidge, 2017). Ayahuasca usage could result in people adopting more beneficial nature-centric lifestyles, with nature contact heavily underutilised and undervalued as a health promoting intervention (Bratman et al., 2019; Maller et al., 2006; Summers & Vivian, 2018).

Conclusion

This pilot study tentatively suggests that participation in ceremonial ayahuasca retreats in the Amazon rainforest may increase individuals' psychological connection to nature and associated benefits for mental health and well-being, mindful of methodological limitations. Further research should seek to elucidate to what degree this shift in individuals' connection to nature is sustained, further explore the specific factors that mediate this shift, and how it might be enhanced. Given that a growing disconnection from nature is implicated with both environmentally damaging behaviour and poor psychological health (Bragg, 1996; Kellert, 1997; Conn, 1998), reversing this trend could help promote synergistic improvements in human and planetary health (Ives et al., 2018; Martin et al., 2020; Zylstra et al., 2014).

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frontiers in Psychiatry

ORIGINAL RESEARCH
published: 09 June 2021
doi: 10.3389/fpsyt.2021.687615

Ceremonial Ayahuasca in Amazonian Retreats—Mental Health and Epigenetic Outcomes From a Six-Month Naturalistic Study

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

Received: *30 March 2021*
Accepted: *14 May 2021*
Published: *09 June 2021*

Citation:
Ruffell SGD, Netzband N, Tsang W, Davies M, Butler M, Rucker JJH, Tófoli LF, Dempster EL, Young AH and Morgan CJA (2021) Ceremonial Ayahuasca in Amazonian Retreats—Mental Health and Epigenetic Outcomes From a Six-Month Naturalistic Study. Front. Psychiatry 12:687615. doi: 10.3389/fpsyt.2021.687615

Ayahuasca is a natural psychoactive brew, used in traditional ceremonies in the Amazon basin. Recent research has indicated that ayahuasca is pharmacologically safe and its use may be positively associated with improvements in psychiatric symptoms. The mechanistic effects of ayahuasca are yet to be fully established. In this prospective naturalistic study, 63 self-selected participants took part in ayahuasca ceremonies at a retreat centre in the Peruvian Amazon. Participants undertook the Beck Depression Inventory (BDI-II), State-Trait Anxiety Inventory (STAI), Self-compassion Scale (SCS), Clinical Outcomes in Routine Evaluation-Outcome Measure (CORE-OM), as well as secondary measures, pre- and post-retreat and at 6-months. Participants also provided saliva samples for pre/post epigenetic analysis. Overall, a statistically significant decrease in BDI-II (13.9 vs. 6.1, $p < 0.001$), STAI (44.4 vs. 34.3 $p < 0.001$) scores, and CORE-OM scores were observed (37.3 vs. 22.3 $p < 0.001$) at post-retreat, as well as a concurrent increase in SCS (3.1 vs. 3.6, $p < 0.001$). Psychometric improvements were sustained, and on some measures values further decreased at 6-month follow-up, suggesting a potential for lasting therapeutic effects. Changes in memory valence were linked to the observed psychometric improvements. Epigenetic findings were equivocal, but indicated that further research in candidate genes, such as sigma non-opioid intracellular receptor 1 (SIGMAR1), is warranted. This data adds to the literature supporting ayahuasca's possible positive impact on mental health when conducted in a ceremonial context. Further investigation into clinical samples, as well as greater analyses into the mechanistic action of ayahuasca is advised.

Keywords: ayahuasca, epigenetic, psychedelic, mental health, trauma, ceremony, retreat, DMT

INTRODUCTION

Ayahuasca, meaning "vine of the soul" in the Quechua language (1), is a natural psychoactive plant brew traditionally used for medicinal and spiritual purposes by indigenous populations throughout the Western Amazon basin (2). Scientists first became aware of the Amazonian use of ayahuasca

around 150 years ago (3), although its use likely far predates this (4), with some evidence suggesting it may have been used for over 1,000 years (5). In the 1930s, it became introduced to religious settings in small Brazilian urban centres; by the 1980s, prevalence of use had spread to larger cities internationally, with syncretic churches integrating ayahuasca as part of their communions. The most famous of these being the Santo Daime and the União do Vegetal (6). Today, Westerners travel to South America in increasing numbers to participate in ayahuasca rituals, primarily seeking improved insight, personal growth, and emotional or physical healing (7).

The ayahuasca brew is usually prepared by boiling the broken stems of the *Banisteriopsis caapi* vine, alongside leaves from the *Psychotria viridis* shrub or leaves of the *Diplopterys cabrerana* (8). *B. caapi* is rich in the β-carboline alkaloids harmine, harmaline, tetrahydroharmine, amongst others, which act as potent reversible monoamine oxidase inhibitors (MAOIs) (9). Pharmaceutical form MAOIs are widely used as antidepressants (10). *P. viridis* and *D. cabrerana* also contain the psychedelic tryptamine N,N-dimethyltryptamine (DMT), an agonist of the serotonin 2A receptor ($5HT_{2A}R$) and sigma non-opioid intracellular receptor 1 (SIGMAR1). Agonism of these receptors have been associated with antidepressive and anxiolytic effects (11, 12).

When consumed together, the MAOIs in *B. caapi* renders the DMT from *P. viridis* orally active by preventing its deamination (which usually occurs *via* monoamine oxidase in the gastrointestinal tract). This allows for its uptake into the central nervous system, inducing powerful psychedelic effects which often last for ∼4–6 h (13). While MAOIs and DMT are both somewhat psychoactive independently, unique phenomenology and pharmacodynamics arise from their interaction in ayahuasca brews (9, 14, 15). A recent review of the literature suggests that such effects are likely synergistic as opposed to simply additive (16).

The ayahuasca experience has been characterised by profound alterations to one's sense of self and reality, emotional and cognitive processing, and spatiotemporal orientation (17). Visual phenomena are also often reported, ranging from colourful geometric patterns to vivid dream-like experiences, alongside transient dissociation, enhanced introspection and initial anxiety followed by euthymia (9, 15, 18–20). Furthermore, ayahuasca's effects have been linked to transcendental and mystical experiences, such as being connected to spirit realms in traditional Amerindian perspectives, and divinity in religious contexts (21). Researchers attempt to measure these experiences using the Mystical Experience Questionnaire (22).

Ayahuasca is safe when used with due caution (23) and has a low dose tolerance and addictive potential (24). Rapid and sustained antidepressant and anxiolytic effects have been shown in both animals (25, 26), and humans (27–30). More broadly, ayahuasca has been associated with improved psychosocial well-being, quality of life, and positive traits such as assertiveness, confidence, optimism, and emotional maturity as well as decreases in neuroticism (25, 31–33). Subacute "after-effects" of ayahuasca include increased mindfulness, ability to decentre and reduced self-judgment and inner reactivity (34). Qualitative reports of greater self-love and compassion have also been suggested, however quantitative measurements have yet to be adequately established (35).

Ayahuasca experiences have been likened to that of intense psychotherapy (36), with a number of authors suggesting it as a treatment candidate for trauma and related disorders (37–39), potentially *via* reprocessing of autobiographic and emotional memories which can be elicited with the ayahuasca-induced dream-like state (17). Anecdotally, abuse victims and recovered addicts report that through ayahuasca-induced visions, they were able to retrieve long-forgotten traumatic memories to work through, which served as a basis for personal life restructuring (40). Neurological evidence also suggests that ayahuasca increases activity in the left hemisphere amygdala and parahippocampal gyrus, areas associated with memory and emotional arousal (41). Despite growing speculation for ayahuasca's efficacy as an intervention for trauma-related conditions, supporting evidence in these conditions is primarily anecdotal, and we suggest further studies.

It is possible that ayahuasca has direct pharmacological effects on trauma-related neurobiology. It has been proposed that the alkaloids present in ayahuasca act *via* the sigma non-opioid intracellular receptor 1 (SIGMAR1) to promote neurogenesis, synaptic plasticity, memory reconsolidation, and fear extinction (42). SIGMAR1 is a stress-responsive neuro-receptor found primarily on the surface of the endoplasmic reticulum. Rodent models of stress-induced downstream SIGMAR1 receptor activation have indicated its potential as a target in post-traumatic stress disorder [PTSD (43)]. Other candidate receptors include FKBP5, which is strongly associated with stress response pathways, and primarily as a co-chaperone of the glucocorticoid receptor activity; it has been implicated in the pathogenesis of stress-related disorders (44). Changes in the DNA methylation pattern within *FKBP5* has also been suggested as a potential proxy marker for response to meditation treatment in PTSD (45).

Thus far, most empirical human studies on ayahuasca have been carried out amongst Brazilian syncretic church members (46), with a small number of studies investigating the use of the brew in retreat centres following a traditional framework (33, 47, 48) and neoshamanic settings (49, 50). While it is important for researchers to investigate ayahuasca use in its varied contexts and traditions, this has been limited by the brew's illicit status in most countries.

In this study, we attempted to ascertain whether ceremonial ayahuasca use may be associated with positive effects on mental health when used in an indigenous framework with foundations in the Shipibo traditions of the Peruvian Amazon. We set out to investigate levels of depression, anxiety, self-compassion and global distress in healthy volunteers before and after an Ayahuasca retreat.

We included secondary measures of autobiographical memory and childhood trauma to investigate potential mediating effects. Measures of subjective mystical experiences were also recorded (33, 51). Lastly, we looked to explore mechanistic hypotheses for potential benefits of ayahuasca. Epigenetic changes *via* DNA methylation of three candidate genes with stress-induced psychopathology were explored; namely FKBP5, BDNF, and SIGMAR1 (44, 52, 53).

We hypothesise that psychological outcomes will improve immediately following the ayahuasca retreat and be maintained at 6-month follow up. Furthermore, these changes will correlate with higher scores on the Mystical Experience Questionnaire post-retreat, and Childhood Trauma Questionnaire scores taken pre-retreat. Finally, changes in DNA methylation of candidate genes may be observed post-retreat vs. pre-retreat.

METHODS

Participants and Design

The study was conducted at the Ayahuasca Foundation (AF), an ayahuasca retreat and research centre, located in the Amazon rainforest near Iquitos, Peru. The sample group were self-selected.

This was an observational, naturalistic study. Individuals who signed up to the retreat were electronically informed about the research by experimenters the fortnight prior to their retreats commenced, and again upon arrival in Iquitos before transferring to the retreat site. Prospective participants were provided an information sheet and the option to ask questions before giving informed consent to participate in the study before each retreat (the research team were not involved in the recruitment to the retreats, nor dosing of participants). Participation was voluntary with rights to withdraw at any time.

Prior to acceptance onto the retreats, each participant was required to complete an online screening questionnaire on the centre's website. The questionnaire requires information on mental, physical health conditions, and any medications taken. Exclusion criteria includes those with a known diagnosis of psychosis, schizophrenia, bipolar affective, and personality disorders from attendance. All inclusion criteria were determined by the collaborative organisation, the AF.

This study has been approved by the institutional research ethics committee (#CLESPsy000893 v2.0) and complies with the declaration of Helsinki. The research team included a doctor with recognised primary medical qualifications who was present for the duration of the retreats to provide medical assistance if necessary.

Preparation for Retreat—"Washout Period"

For 2 weeks' prior to attending the retreat, each participant was given instructions by AF to engage in a "washout period," abstaining from any substances (prescribed and non-prescribed) with possible or known interactions with the constituents of ayahuasca. Furthermore, in order to reduce serum tyramine levels and minimise potential side effects, dietary restrictions on red meats, salt, sugar, and fats were also advised by AF. Lower tyramine levels lessen the likelihood of headaches, nausea, and increased cardiovascular activity which can result from the brew's MAOIs (54).

Procedure

Ayahuasca was administered to participants in a traditional Shipibo setting adapted for tourists. Retreats varied in length between 8 days to 1 month, including 8-day (four ayahuasca ceremonies), 2-week (six ayahuasca ceremonies), 3-week (nine ayahuasca ceremonies), and 1-month (11 ayahuasca ceremonies) retreats. It was not compulsory for individuals to participate in all ceremonies offered, therefore the researchers recorded the number of ceremonies that each individual participated in.

Ayahuasca ceremonies generally commenced around 20:00, lasted ∼5 h, and were led by the local curandero (shaman) with assistance from four to five specially trained facilitators employed by AF. The ceremony space (i.e., the "maloka") is a round wooden building where single mattresses for each participant are laid out in a circle along the perimeter. A bucket each for "purging" was also provided, due to the brew's typical emetic effect. Participants were instructed to prepare their mindset and set "intentions" regarding what they hoped to achieve leading up to retreats and before ceremonies. Participants were advised to not have physical or verbal contact with one another for the duration of the ceremonies. Ceremonies were undertaken in darkness, with the curandero and facilitators singing traditional medicine songs (i.e., "icaros") throughout, and providing appropriate care when necessary (e.g., supporting participants to the bathroom). On average, participants consumed ∼150 ml of the prepared ayahuasca brew, presented by the curandero at the beginning of the ceremony.

Standardised questionnaires were administered to participants prior to their first ceremony (pre-), the day after their last ceremony (post-), and 6 months after their final ceremony. The pre-retreat data was completed by participants on laptops in a quiet space in the hotel the night before travelling into the jungle for their first ceremony; 4 ml of saliva was also collected under the guidance of researchers at this time point for epigenetic analysis. Post retreat measures were completed on laptops in a quiet space at the retreat site on the morning before travelling back into Iquitos, 4 ml of saliva was again collected. The 6-month follow up questionnaires were collected electronically *via* email. Qualitative data was also collected throughout the retreat and is included a separate article.

Measures

Beck Depression Inventory—Second Edition

The 21 item BDI-II is one of the most widely used psychometric tests for measuring depression severity. It is composed of items relating to depression symptomatology such as hopelessness, irritability, cognitions such as guilt or feelings of being punished, as well as fatigue, weight loss, and lack of sexual interest (55). For the purposes of this study, we used the following cut-off points as recommended by the authors of the BDI-II: "not depressed" (0–13), "mild depression" (14–19), "moderate depression" (20–28), "severe depression" (29–63) (56).

State-Trait Anxiety Inventory

The STAI is a 40-item psychological inventory measuring two types of anxiety—State Anxiety, or anxiety about an event, and Trait Anxiety, or anxiety as a personality characteristic. Higher scores indicate higher levels of anxiety (57). In this study for analysis of long-term change, the STAI Trait (STAI-T) score was used rather than the State (i.e., lasting changes moreover how participants felt at the time).

Self-Compassion Scale

The 26 item SCS is a validated measure of self-compassion. Alongside a total score, it is comprised of six subscales, including three positive constructs of Self-Kindness, Common Humanity, Mindfulness, and their negative opposite constructs of Self-Judgement, Isolation, and Over-Identification (58).

Clinical Outcomes in Routine Evaluation-Outcome Measure

The CORE-OM consists of 34 items measuring Global Distress, which subdivide into four subscales outlining four dimensions comprising Global Distress. These include subjective Well-being, Problems/Symptoms, Functioning, and Risk. The CORE-OM is a widely used initial screening and monitoring clinical tool with high internal and test-retest reliability (59).

Childhood Trauma Questionnaire

The CTQ is a 28-item measure inquiring about five types of maltreatment in childhood. These include Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, and Physical Neglect, with a three-question screening for false-negative reports of trauma. The CTQ can be used for both clinical and non-clinical samples with strong psychometric properties (60). The CTQ was completed at pre-retreat only.

Mystical Experience Questionnaire

The 30 item MEQ is a validated measure of psychedelic-occasioned spiritual/peak experiences. The total score is comprised of four dimensions; Mystical Experience, Positive Mood, Transcendence of Time/Space, and Ineffability (22). The MEQ was administered at post-retreat only to capture participants' perceptions of their ayahuasca experiences. The inventory was scored in relation to the entire retreat, rather than individual sessions.

Sentence Completion for Events From the Past Test

The SCEPT is a sentence completion task devised as a sensitive measure of over-generality in autobiographical memory. Participants were required to complete 11 sentence stems in reference to past events (e.g., "When I think back to/of…"). Raters coded for memory specificity and into positive and negative memories.

SCEPT Inter-rater Reliability

A coding cheque was conducted on 25% of the data from the SCEPT by two researchers to ensure inter-rater reliability. Intraclass correlation coefficients revealed high levels of agreement between raters across the measure (see **Table 1**).

TABLE 1 | Inter-rater reliability statistics for the SCEPT by intraclass correlation coefficients.

	Inter-rater reliability
Total specific memories	0.83
Positive specific memories	0.76
Negative specific memories	0.90
Total general memories	0.85
Positive general memories	0.76
Negative general memories	0.85

Data Analysis

Data is analysed using SPSS 26.0 (61) and Rstudio Desktop 1.4. In any case where a value was missing from the dataset, the participant was excluded from that particular analysis.

Unless otherwise stated, continuous data is presented as mean (standard deviation; SD). Repeated measures ANOVA with a Greenhouse-Geisser correction were used to compare mean differences across time. *Post-hoc* tests using the Bonferroni corrected pairwise comparisons were then performed to assess significance between time points. Pearson bivariate correlation analysis was used to produce r values.

The paired *t*-test statistic was used to determine if there was a change in DNA methylation at the two candidate genes investigated after ayahuasca administration.

Epigenetic Analysis

Saliva samples were collected pre- and post- retreat (2× 4 ml). In total, 55 paired samples (pre- and post- retreat) were obtained. DNA extraction was carried out using Isohelix GeneFiX Saliva-Prep DNA Kit (1 ml protocol) as per manufacturers specifications.

Bisulfite Conversion

DNA samples were all diluted to 25 ng/ml using ultra high-quality H_2O. Bisulfite conversion was carried out using the EZ Methylation—Gold Kit D5005 & 5006 according to manufacturer's instructions. In total, 48 of the 55 paired samples were used for this report's data due to time constraints and plate sizes.

Bisulfite Pyrosequencing

The SIGMAR1 assay was designed to span 5 CpGs located in the promoter of the gene, while the FKBP5 assay was a re-designed assay based on one from (62) (see **Table 2**). Optimisation of these assays was then carried out using fully methylated DNA (positive control) and a negative control. PCR was run for 40 cycles to ensure adequate PCR product for all primers (Stage 1: 95°C for 15 min, Stage 2: 95°C for 15 s, 56°C for 30 s, 72°C for 30 s, Stage 3: 72°C for 10 min). PCR optimisation and bisulfite pyrosequencing included 100% fully methylated positive control.

Pyrosequencing used to obtain individual gene DNA methylation data per DNA sample, using the Qiagen Pyromark Q48 Autoprep Pyrosequencer. The process was carried out as per manufacturer's instructions. In total, 48 sample discs were loaded with between 10 and 17 μl PCR product and 3 μl magnetic beads. The variation in PCR product was dependent on gene-specific optimisation assays run on the pyrosequencer; if the nucleotide signal peaks obtained from sequencing output had low detection from 10 μl PCR product, more PCR product for the specific assay was added to increase sensitivity for the data collection experiments (FKBP5b = 14 μl, SIGMAR1 = 10 μl). Sequencing primer was 4x diluted in annealing buffer before addition to machine cartridge.

TABLE 2 | Bisulfite pyrosequencing assays.

Assay	Forward primer	Reverse primer	Sequencing primer	Target region coordinates (hg19)
FKBP5	GTTGGGATAATAATTTGGAGTTATAGTG	/5Biosg/CTACCAAATAACTCCTTAAA AAAATAAAAT	GGAGTTATAGTGTAGGTTTT	chr6:35,558,488-35,558,515
SIGMAR1	GTGTGGGGATAGTGAGATTTAGAAT	/5Biosg/CCACCCTAAAACTCCCAACTT	GGGATAGTGAGATTTAGAATG	Chr9:34638039-34638081

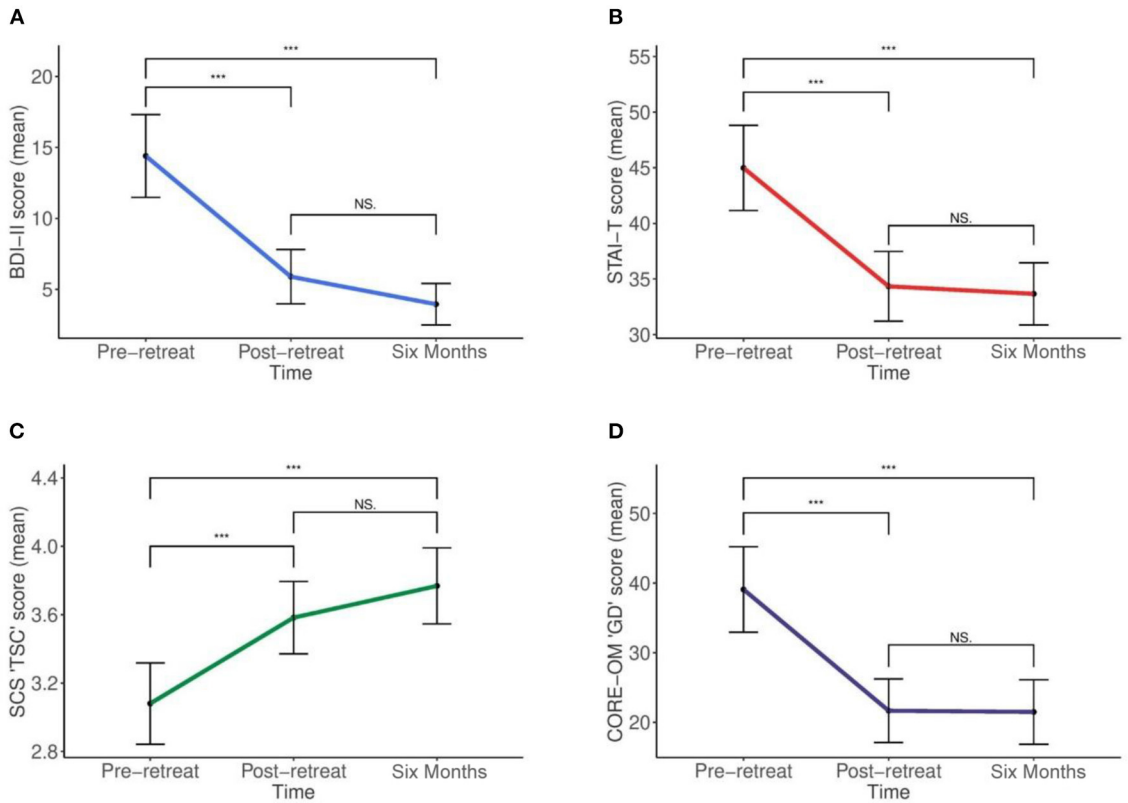

FIGURE 1 | Changes in outcome scores over time. **(A)** Beck Depression Inventory II (BDI-II). **(B)** State and Trait Anxiety Inventory (STAI)—Trait Anxiety Score. **(C)** Self Compassion Scale (SCS)—Changes in Total self-compassion (TSC) score. **(D)** Clinical Outcome Routine in Routine Evaluation (CORE-OM): changes in mean CORE-OM Global Distress (GD) score [NS, non-significant ($P > 0.05$), ***$p \leq 0.001$].

RESULTS

Sample Demographics

The sample consisted of 63 participants in total, 35 males (55.6%) and 25 females (44.4%), aged between 19 and 63 (Mean = 37.0, SD = 9.7). Most participants were White (79.4%). In total, 26 were in full-time employment (41.3%), 17 freelance (27.0%), eight unemployed (12.7%), six part-time (9.5%), and six (9.5%) were students. Annually, 25 earned between $10 and 50K (39.7%), 22 between $50 and 100K (34.9%), and the remainder earning either more (14.3%) or less (9.5%).

Forty-eight participants (76.2%) reported no diagnosed physical health problems; three reported hypertension (3.2%), one reported irritable bowel syndrome, one reported seizures (1.6%), and 11 reported "other" conditions (e.g., ankylosing spondylitis, coeliac disease, scoliosis; 17.5%). In total, 42 participants reported no diagnosed psychiatric disorders (66.7%), 15 reported depression, 15 anxiety (19.0%), five ADHD (two comorbid. 4.8%), and five PTSD (4.8%). In total, 27 participants (42.9%) disclosed having experienced problem substance use, including alcohol, tobacco, or caffeine.

In total, 37 (58.7%) stated no previous ayahuasca use, with the rest reporting previous use ranging 1–80 times (Mean = 5.9, SD = 13.2). Number of participants per retreat length in this study were 18 (28.6%) in the 8-day, 12 (19.0%) in the 14-day, 12 (22.2%) in the 21-day, and 19 (30.2%) in the 28-day retreat.

The mean CTQ score in our sample was 48.3 (SD 17.6) Physical abuse = 8.1 (3.7) [ranked "low"], Sexual abuse = 7.8 (5.7) [ranked low], Emotional neglect = 12.5 (5.3) [ranked low], Physical neglect = 8.5 (3.8) [ranked low], Minimisation = 0.1 (0.4) [ranked "minimal"].

TABLE 3 | Summary of means and standard deviations for all scales and subscales.

	Pre-retreat *Mean (SD)*	Post-retreat *Mean (SD)*	T1–T2 D (*p*)	Six month Follow up *Mean (SD)*	T1–T3 D (p)
BDI-II	14.4 (11.6)	5.9 (7.6)	0.87 (<0.001)	4 (5.5)	1.15 (<0.001)
STAI					
- Trait anxiety	45 (15.1)	34.3 (12.3)	0.77 (<0.001)	33.7 (10.6)	0.87 (<0.001)
- State anxiety	40.1 (13.4)	28 (9.2)	1.05 (<0.001)	30.3 (8.8)	0.86 (<0.001)
SCS					
- Total	3.1 (1.1)	3.6 (0.8)	0.57 (<0.001)	3.8 (0.9)	0.78 (<0.001)
- Self kindness	3.1 (1.0)	3.7 (0.8)	0.67 (<0.001)	4 (0.8)	0.95 (<0.001)
- Self judgement	3.2 (1.1)	2.6 (1.1)	0.56 (0.001)	2.4 (1)	0.79 (<0.001)
- Common humanity	3.3 (1)	3.8 (0.9)	0.46 (0.008)	3.8 (1)	0.45 (0.005)
- Isolation	3 (1.2)	2.4 (1.1)	0.46 (0.001)	2.3 (1.1)	0.63 (0.001)
- Mindfulness	3.5 (0.9)	3.9 (0.8)	0.46 (<0.001)	4.1 (0.8)	0.72 (<0.001)
- Over-identification	3.1 (1.1)	2.6 (1.1)	0.42 (0.015)	2.5 (1.2)	0.54 (<0.001)
CORE-OM					
- Global distress	39.1 (24.4)	21.7 (18.1)	0.81 (<0.001)	21.5 (17.4)	0.83 (<0.001)
- Global distress minus risk	37.5 (22.9)	21.3 (17.8)	0.79 (<0.001)	21.1 (16.7)	0.82 (<0.001)
- Subjective well-being	5.6 (4.4)	2.9 (3.2)	0.69 (0.001)	3.1 (3.2)	0.65 (<0.001)
- Problem/symptoms	18 (10.8)	10.8 (9.5)	0.71 (<0.001)	9.8 (8.7)	0.84 (<0.001)
- Life functioning	14 (9)	7.4 (6.6)	0.83 (<0.001)	8.2 (6.1)	0.75 (<0.001)
- Risk/harm	1.6 (2.8)	0.4 (0.9)	0.59 (0.013)	0.5 (1.2)	0.52 (0.011)
SCEPT					
All Memories					
- Specific	2.5 (1.9)	2.9 (1.8)		2.3 (1.5)	
- General	8.0 (2.1)	7.8 (1.7)		8.3 (2.0)	
- Omissions	0.5 (1.1)	0.3 (1)		0.5 (1.6)	
Positive Memories					
- Total	6.5 (2.2)	7 (2.1)		7.2 (2)	
- Specific	1.7 (1.6)	2.1 (1.6)		1.8 (1.3)	
- General	4.8 (1.9)	4.9 (1.9)		5.5 (2.1)	
Negative Memories					
- Total	4.2 (1.9)	3.8 (1.9)		3.3 (1.6)	
- Specific	0.8 (0.9)	0.9 (1.0)		0.5 (0.7)	
- General	3.4 (1.6)	2.9 (1.7)		2.8 (1.4)	
CTQ					
- Total	48.3 (17.6)	–		–	
- Physical abuse	8.1 (3.7)	–		–	
- Sexual abuse	7.8 (5.7)	–		–	
- Emotional neglect	12.5 (5.3)	–		–	

(Continued)

TABLE 3 | Continued

	Pre-retreat *Mean (SD)*	Post-retreat *Mean (SD)*	T1–T2 D (*p*)	Six month Follow up *Mean (SD)*	T1–T3 D (p)
- Physical neglect	8.5 (3.8)	–		–	
- Minimisation	0.1 (0.4)	–		–	
MEQ					
- Total	–	115.1 (30.1)		–	
- Mystical experience	–	57.6 (17.3)		–	
- Positive mood	–	24.0 (6.2)		–	
- Transcendence	–	22.1 (6.3)		–	
- Ineffability	–	11.8 (3.6)		–	

Effect sizes (D) for four main outcome measures are reported as Cohen's d. P-values obtained from repeated ANOVAs are corrected for multiple comparisons through Bonferroni post-hoc analysis.

Outcome Measures

Mean outcome scores all differed statistically between time points (see **Figure 1**, plates A-D) for the BDI-II: $F_{(2, 55)} = 30.3$, $p < 0.001$; STAI-T: $F_{(2, 53)} = 30.6$, $p < 0.001$; SCS: $F_{(2, 53)} = 21.5$, $p < 0.001$; and the CORE-OM: $F_{(2, 55)} = 21.3$, $p < 0.001$. *Post-hoc* tests using the Bonferroni corrected pairwise comparisons revealed a reduction in all severity scores from pre- to post-retreat for the BDI-II; STAI-T; and CORE-OM, which were all statistically significant at the $p < 0.001$ level. Six-month follow-up scores further reduced for the BDI-II; STAI-T; and CORE-OM, which was all statistically significant compared with pre-retreat scores at the $p < 0.001$ level, but not post-retreat scores (BDI-II, $p = 0.153$; STAI-T, $p = 1.0$; CORE-OM, $p = 1.0$), suggesting sustained improvement. For the SCS, there was an increase from pre to post retreat, which was statistically significant ($p < 0.001$); follow-up SCS score further increased and was significant compared with pre-retreat ($p < 0.001$), but not post-retreat ($p = 0.138$), again suggesting sustained improvement. Only total scores from measures were used in the present analysis, for further detail of subscale means and standard deviations, please see **Table 3**.

No significant changes in memory specificity were found on the SCEPT. However, new variables of total positive and negative memory scores for each time point were computed to assess changes in memory valance. Mean SCEPT negative valanced memory scores differed statistically significantly between time points, $F_{(2, 110)} = 5.68$, $p < 0.005$. While not reaching significance, there were trend levels of reduction in negatively valanced memories from pre to post-retreat, and post retreat to follow-up. There were, however, significant reductions in negative valanced memories from pre-retreat to follow-up ($p = 0.004$), suggesting improvement over time (**Figure 2**).

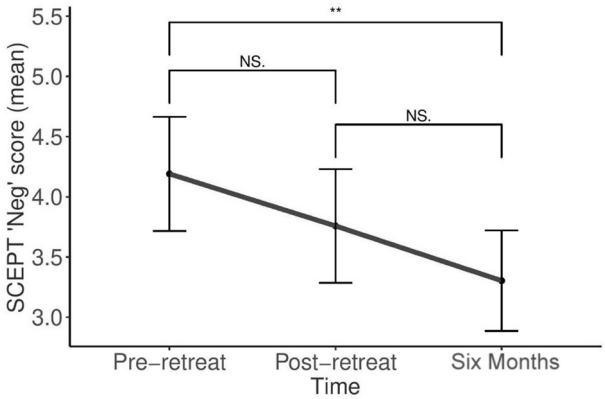

FIGURE 2 | Sentence Completion for Events from the Past Test (SCEPT): Changes in SCEPT negative valanced memory scores over time [NS, non-significant ($P > 0.05$), $^{**}p \leq 0.01$].

Subsample Meeting Screening Cut-Off for Depression

At pre-retreat, 31 of the participants met cut-offs for depression based on BDI-II scores as detailed under *Methods* (11 mild depression, 11 moderate depression, and nine severe depression). This subsample had a mean score of 24.2 (median 23.0). At post-retreat, 24 (77.4%) were no longer depressed, four had mild depression, one moderate, and two severe (mean 8.7, median 5.0). At 6-month, 24 were remained not depressed, two mild, and one severe (four missing values) (mean 5.2, median 4.0). Changes in BDI-II score in the depressed subsample was significant between time points, $F_{(2, 25)} = 55.5$, $p < 0.001$.

Repeated measures ANOVA found no significant changes in the SCEPT "total specific" and total "overall general" subscales, suggesting no change in memory specificity as a function of time in the depressed subsample. There was also no difference between total CTQ scores in the depressed ($n = 31$, mean 50.5, SD 19.0) and the non-depressed ($n = 32$, mean 46.2, SD 16.2) subsample on *t*-test, $t(61) = 0.97$, $p = 0.915$.

Correlation Analysis With Number of Ceremonies, Length of Retreat, and Frequency of Ayahuasca Use Prior Retreat

Note: As not all participants took part in every ayahuasca ceremony offered on retreat, "number of ceremonies" was recorded as it varied between participants.

Pearson's correlation was performed between number of ceremonies, length of retreat, and frequency of

ayahuasca use prior retreat and improvement scores on the BDI-II, STAI-T, CORE-OM, and SCS. Due to multiple comparisons, alpha was set at 0.01. There were no significant correlations.

Predictors of Change in Psychopathology

To minimise the risk of type 1 errors, Pearson's correlations were conducted with CTQ and MEQ total scores and subscales and BDI-II change scores (the latter chosen as a proxy for all outcomes given similar patterns of findings across all outcome measures). Greater change in BDI-II post-retreat was correlated with higher overall CTQ scores ($r = 0.318$, $p = 0.011$ for overall population and $r = 0.393$, $p = 0.029$ for clinically depressed population) scores. These figures were however not significantly correlated with BDI-II change at 6-month. In the depressed subsample alone, only the mystical experience subscale of the MEQ was negatively correlated (i.e., those with greater scores had greater improvements in BDI scores) with change in BDI-II post-retreat ($r = -0.357$, $p = 0.049$). This correlation was not sustained at 6-month and there was no correlation at either time point in the overall sample. For a full breakdown these correlation analyses, please see **Table 4**.

DNA Methylation Analysis

BDNF analyses failed due to an error, therefore only SIGMA and FKBP5 were analysed.

SIGMAR1

The SIGMAR1 assay showed a statistically significant increase in DNA methylation across the 5 analysed CpG sites (paired *t*-test: $t = 2.58$, $df = 38$, $p = 0.01$) (see **Figure 3**).

FKBP5

FKBP5 DNA methylation did not show any statistically significant change ($p = 0.13$).

SIGMAR1 Methylation Correlation Analyses

Methylation change scores were calculated for SIGMAR1 and Pearson's correlation performed with CTQ total scores. There was a significant correlation ($r = 0.387$, $p = 0.015$), indicating those with higher childhood trauma had increased methylation changes in SIGMAR1 post retreat (**Figure 4**). In order to reduce the risk of type I errors, SIGMAR1 methylation changes were correlated with BDI-II as a proxy for all outcome measures; there was no significant correlation in this analysis.

DISCUSSION

In this naturalistic study we examined the associations between ayahuasca use and a number of mental health outcomes. We found that ayahuasca was associated with reductions in depression, anxiety, and global distress from baseline to post-retreat which were sustained at 6-month follow-up. Many patients meeting clinical scores for depression pre-retreat did not do so after the ayahuasca retreat. We also observed reductions in negative memory valance on a sentence completion task from baseline to after the retreat, with no changes in recall specificity. There was evidence of a change in DNA methylation at loci on the SIGMAR1 receptor gene between pre- and post- retreat.

Depression

The results of the current study suggest that ayahuasca use in ceremonial settings may be associated with improvements in well-being, particularly depression and its related conditions.

TABLE 4 | Correlation coefficients vs. BDI-II change scores at post-retreat and 6 month follow-up.

	Pearson correlation coefficient vs. BDI-II post-retreat change score (p)		Pearson correlation coefficient (r) vs. BDI-II follow-up change score (p)	
	Overall population ($n = 63$)	**Depressed population only ($n = 31$)**	**Overall population ($n = 57$)**	**Depressed population only ($n = 27$)**
Childhood trauma questionnaire				
Total score	**−0.318 (0.011)**	**−0.393 (0.029)**	0.189 (0.148)	−0.250 (0.208)
Physical abuse	−0.119 (0.354)	−0.306 (0.095)	0.045 (0.742)	−0.061 (0.764)
Sexual abuse	**−0.263 (0.038)**	−0.345 (0.057)	−0.077 (0.570)	0.071 (0.726)
Emotional neglect	**−0.260 (0.039)**	−0.180 (0.333)	**−0.305 (0.021)**	−0.376 (0.053)
Physical neglect	−0.246 (0.052)	−0.340 (0.061)	−0.195 (0.146)	−0.291 (0.140)
Minimisation/denial	0.105 (0.415)	0.035 (0.854)	0.129 (0.340)	0.151 (0.452)
Emotional abuse	**−0.292 (0.20)**	−0.352 (0.052)	−0.150 (0.266)	−0.286 (0.149)
Mystical experience questionnaire				
Total score	−0.061 (0.637)	−0.274 (0.136)	0.067 (0.622)	−0.112 (0.579)
Mystical experience	−0.102 (0.428)	**−0.357 (0.049)**	0.097 (0.475)	0.016 (0.938)
Positive mood	−0.043 (0.737)	−0.351 (0.053)	0.104 (0.441)	−0.194 (0.332)
Transcendence	−0.164 (0.200)	−0.213 (0.250)	−0.116 (0.388)	−0.094 (0.642)
Ineffability	−0.143 (0.265)	−0.338 (0.063)	0.064 (0.636)	−0.101 (0.616)

Depressed population is those with BDI-II score ≥14 at baselines (four lost to follow-up). Results significant at alpha = 0.05 level are highlighted in bold. Negative correlation equates to greater changes in BDI-II related to higher scores on CTQ and MEQ.

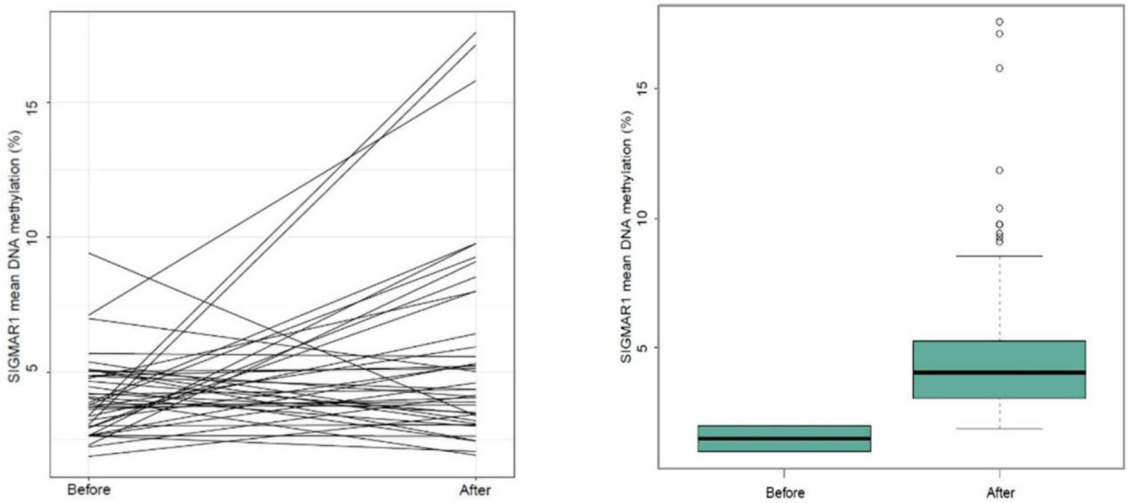

FIGURE 3 | Mean changes in DNA methylation across 5 CPG positions within the SIGMAR1 gene (paired *t*-test $p = 0.01$; $n = 38$).

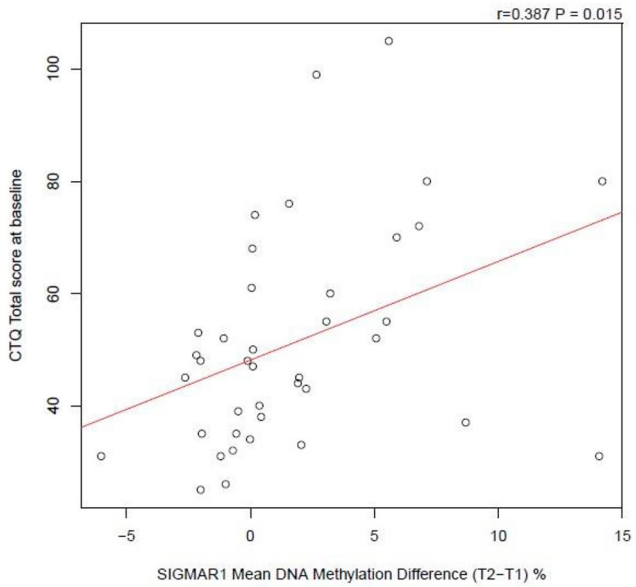

FIGURE 4 | Correlation analysis of CTQ total score at baseline against SIGMAR1 Mean DNA Methylation Difference (from T2 to T1).

It should be noted that although significant improvements in depression symptoms were shown, mean BDI-II ratings in the overall sample pre-retreat were nonetheless below threshold for likely depression diagnoses. To this end, we subsequently conducted further analysis on those within our sample meeting threshold for depression according to the BDI-II at pre-retreat; the majority of those meeting the cut off for depression pre-retreat no longer did so at post-retreat or follow-up. As most within this subsample reported mild depression, it was perhaps unsurprising to find no correlation between change in BDI-II score and memory specificity according to the SCEPT on this subsample.

Similarly, we also found no relationship between memory specificity with the BDI-II for our overall sample. This tallies with past research, which has suggested that changes in overgeneral autobiographical memory tends to emerge only when comparing healthy participants to clinical populations with depression (63). Although no changes in recall specificity were found, a reduction in negatively valanced memories from pre-retreat to 6-month follow-up was observed in our total sample. Overgeneralised negative memory is a characteristic in depression (64), and is proposed as an aetiological factor. The observed reduction in the tendency to recall negative information could be a cognitive correlate antecedent of the improvements suggested.

In line with our original hypotheses and data from previous studies (33, 65, 66), we found associations between perceived mystical effects and improved psychometric scores at follow up. Participants in the depressed subpopulation who reported a greater degree of mystical experience improved to a greater degree post-retreat. Within semi-structured interviews conducted with these participants, many reported that the ritualistic element of the ceremonies amplified their perceived mystical states. Analysis of this data was beyond the scope of the current study; and will be presented separately within a qualitative analysis.

Our findings suggesting improvements in depressive outcomes are consistent with previous studies including a small open-label ayahuasca study (27) and a parallel-arm, double-blind randomised placebo-controlled trial with 29 treatment-resistant depression patients assessing ayahuasca vs. placebo (28). Improvements in depressive symptoms are consistent with previous fMRI data, which has revealed attenuated default mode network (DMN) activity following ayahuasca use (67). The DMN is a neural network known to be hyperactive in major

depressive disorder patients and those suffering from severe anxiety, underlying ruminations and self-referential processes (68, 69).

Anxiety and Well-Being

In our study, ayahuasca use was associated with reductions in trait anxiety and improvements in general well-being. These findings are consistent with recent research in traditional frameworks in the Amazon basin (33, 48), neoshamanic settings (49, 50), and church settings previously (70, 71). In one study, ceremonial ayahuasca was found to be associated with reductions in levels of neuroticism, a personality trait underlying anxiety disorders (33). Improvements in CORE-OM scores in our current sample also supports previous evidence suggesting improvements in general well-being and quality of life (33, 48).

Contextual Factors

Our study did not show direct correlation between the number of ayahuasca ceremonies and outcome measures, ostensibly indicating no potential benefit of engaging in greater numbers of ceremonies. Although individual sessions may be beneficial, the effects resulting from individual psychedelic therapies are often difficult to predict. Qualitative studies suggest transformative experiences may occur spontaneously in individual ceremonies (20). Psychological "breakthroughs" are sometimes even described as independent of the dose and number of sessions (72). That is, improvement in psychological well-being as a result of ayahuasca use may be non-linear. Future research should seek to investigate this further with qualitative measures and by characterising the nature, and not just frequency, of sessions.

The current study took place at a retreat centre that describes itself as "*rooted in the Shipibo ayahuasca tradition*." Ayahuasca is given at night in a ceremonial setting that takes place in the darkness with minimal contact between participants. Ayahuasca churches usually provide the brew in well-lit rooms to entire congregations who subsequently sing or engage in conversation surrounding topical issues (6). Despite these differences, the results of our study are in line with those based in both syncretic church settings and controlled studies in laboratories. This may suggest that commonalities could be induced by the drug and not just expectancy effects. Similarities that do exist however, may be defining factors in forming outcomes regardless of context. Even laboratory studies in this area of research typically display features seen in ritualistic settings, such as the role of music (28, 73).

The ritualistic context surrounding ayahuasca also appears to play a crucial role in safeguarding and minimising risks associated with its use (74). Without a supportive "*set and setting*" (75), ayahuasca experiences may not produce benefit, and could even be traumatic (74, 76). Clinical data into ayahuasca suggests that a supportive context can also be achieved in laboratory settings (28, 77). It is possible that the likelihood of therapeutic outcomes is dependent on the individual's affect and perceptions within the given context. Outcomes appear to be, at least partly, determined by a perceived sense of safety and/or support whilst entering psychedelic states (78, 79). For some, greatest benefit may be achieved in the Amazon rainforest with a curandero, whilst for others a clinical setting may be more appropriate. Catering for subjective factors which allows the participant to feel optimally safe is therefore imperative.

Epigenetics

Our results suggest that ayahuasca exposure affects the epigenetic regulation of SIGMAR1. However, the mean increase (2.1% increase) in DNA methylation is small, and it remains unclear if this change in DNA methylation has biological impacts and alterations to gene expression. It is possible that an increase in SIGMAR1 DNA methylation enables increased expression of the receptor, however, this model is less likely, a common DNA methylation rules mean hypermethylation results in transcriptional silencing. At this stage, the implications of these findings are uncertain. However, these findings are the first of their kind and consolidate indications that SIGMAR1 expression is regulated *via* an epigenetic process.

It is possible that the modest changes in methylation in our sample was due in part to the minimal trauma history of many of our participants. Our overall CTQ scores are in line with previous research utilising the CTQ in non-clinical samples (80, 81), and is lower than expected from clinical samples (82)—this is despite our depressed subsample not having a significantly different CTQ score to our non-depressed subsample.

Coupled with previous evidence for the marker's role in trauma (42, 43), the correlation (albeit weak) between childhood trauma and changes in SIGMAR1 methylation, alongside the improvements in mental health outcomes observed in our present sample, we propose that future research should investigate SIGMAR1 as a potential mechanism of action underlying ayahuasca.

STRENGTHS AND LIMITATIONS

To our knowledge, this study is the first to investigate the effects of a psychedelic on epigenetics. A fundamental limitation of this study is the absence of a control group and the likelihood of self-selection bias. Given the time and financial sacrifices necessary to take part in ayahuasca ceremonies, it is likely that participants had strong positive a priori expectations.

Participants were subject to more than simply ayahuasca dosing (i.e., contextual factors such as being in a retreat setting, with a group, without internet in the Amazon rainforest), and therefore the placebo effect is likely to be significant. It was also difficult to control for the impact of maturation and life events between post-retreat and 6-month follow up, which further complicates the inference of causality (e.g., nine participants used ayahuasca again during this time and were excluded from the analysis). Additionally, not all participants were naive to ayahuasca prior to their first ceremony at AF, although no correlations were found between frequency of previous use and psychological outcomes in our present sample.

As the researchers had no access to participants' medical records, it was not possible to adequately confirm medical histories of the current sample. It should also be noted that the quantity of ayahuasca given to participants was not standardised.

The curandero provided each participant with what they deemed to be an appropriate dose. Although this could be seen as a limitation, given the observational nature of the study it was deemed appropriate to follow the traditional framework rather than intervene in the ceremonies.

Limitations of Epigenetic Analyses

As biological samples were taken from peripheral cells (i.e., saliva samples), results may not represent epigenetic changes in the central nervous system. The approach taken here is arguably open to bias, as it was a candidate-gene style analysis. Other researchers have suggested the need for neuronal samples to provide valid epigenetic results (83); however, it is unclear how this would be achieved due to ethical and logistical considerations. Our epigenetic analyses were limited to three candidate genes, future studies should continue to assess the potential epigenetic regulation of other genes, including epigenetic changes in genes related to other mental disorders. Other epigenetic mechanisms like microRNAs were not studied in this project, and we suggest future research considers additional methods of analysis. Gene regulation outside of epigenetics, such as alternative splicing as a result of ayahuasca consumption is also a potential area for future research.

AYAHUASCA TOURISM

The researchers wish to highlight some issues surrounding "ayahuasca tourism" (84). As interest in ayahuasca continues to grow, so do issues around safety and cultural appropriation. As well as this, lack of regulation throughout Peru, and beyond, has led to individuals labelling themselves as "shamans" without appropriate training and experience (85), potentially resulting in dangerous practises. Furthermore, although ayahuasca is considered a sacrament by various communities, many of the retreat centres in the Amazon are owned by Westerners and the use of ayahuasca and other plants for financial gain has been called into question (6). It is vital that scientists and the public alike proceed cautiously given risks regarding safety and the cultural sensitivity of the practises in question.

CONCLUSIONS

The findings of this study suggest ayahuasca use in a traditional Amazonian setting is associated with significant improvements in a number of mental health outcomes. These changes were sustained at 6-month follow-up without further dosing, suggesting lasting therapeutic potential. Our study is the first study to directly examine epigenetic effects correlated with psychedelic use. These findings support hypotheses that SIGMAR-1 may be involved mechanistically in the positive outcomes of ayahuasca use. Future research should aim to investigate the effects of ayahuasca by increasing the scope of biological markers and exploiting neuroimaging technology in randomised controlled trials of clinical populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Exeter. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SR and CM: conceptualisation. SR, NN, WT, and CM: methodology. SR and NN: data collection. WT and MB: data analysis. SR, NN, and WT: writing—original draft preparation. SR, NN, WT, MB, LT, AY, and CM: writing—review and editing. MD and ED: epigenetic analysis. JR, LT, ED, AY, and CM: supervision. All authors contributed to the article and approved the submitted version.

FUNDING

Funding received from the Medical Research Council, UK, with additional funding from King's College London, UK and GCRF: Trauma and Adverse Childhood Experiences Springboard (TrACES) (Grant number: MC_PC_MR/R019991/1). Professor Young's independent research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

ACKNOWLEDGMENTS

The authors would like to thank Noya Rao and Carlos Tanner for their guidance and support with this project; Don Enrique, Don Miguel, and Don Rono for their knowledge and expertise; the Ayahuasca Foundation staff as well as the Allpahuayo-Mishana community for their warmth and hospitality.

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