

# **Amazonian Ayahuasca and Mental Health Outcomes**

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*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 language. 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 heterogeneity 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-HT<sub>2A</sub> 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 <sup>18</sup>F-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 suppression 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 ayahuasca, 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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 centered 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-HT<sub>2A/C</sub> 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-aspartate (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 valenced 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-HT<sub>2A</sub> 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 ( $\geq 15$  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-HT<sub>2A</sub> 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 & Rumrill, 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/ $\beta$ -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 5HT<sub>1a</sub> 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 serotonergic 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-HT<sub>2A</sub>, 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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, undoubtedly 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 follow 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 $\beta$ -carboline constituents of ayahuasca	-Showed MAOI effect in vitro.  -Proposes that inhibition experiments using mixtures of $\beta$ -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 <i>P. viridis</i> .
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 $\beta$ -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.

		<p>-Subjects exposed five or more times to 3,4-methylenedioxymethamphetamine had less robust pupil diameter effects than those exposed two times of less.</p> <p>-Evidence that DMT is unique in the inability to develop tolerance to its psychological effects.</p>	
Smith et al. (1998)	Agonist properties of N, N-dimethyltryptamine at serotonin 5-HT <sub>2A</sub> and 5-HT <sub>2C</sub> receptors	<p>-DMT fully substituted for DOI. Intact choroid plexus was used to evaluate the agonist properties at endogenous 5-HT<sub>2C</sub> receptors.</p> <p>-DMT was a partial agonist at 5-HT<sub>2C</sub> receptors in this native preparation.</p> <p>-DMT behaves as an agonist at both 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors.</p> <p>-One difference was evident in that the 5-HT<sub>2C</sub>, but not the 5-HT<sub>2A</sub>, receptor showed a profound desensitization to DMT over time (suggestive of limited application for repeat prescription).</p>	-Evidence of DMT 5HT <sub>2a(c)</sub> agonism.
Callaway et al. (1999)	Pharmacokinetics of Hoasca alkaloids in healthy humans	<p>-THH shows PK profile independent to harmine.</p> <p>-Affinities and other PK values provided.</p>	<p>-Evidence that THH alone may be a weak SSRI.</p> <p>-Implies further synergistic effects on the serotonin system.</p>
Ott (1999)	Pharmahuasca: human pharmacology of oral DMT plus harmine	<p>-MAO inhibition from simultaneous ingestion of <math>\beta</math>-carbolines confirmed by eight self-experimenters.</p> <p>-Results of a total of some 70 bioassays are summarized and the literature on this subject is reviewed.</p>	<p>-Evidence that DMT and harmine in tablet form create similar effects to ayahuasca, further reinforcing the DMT MAOI interaction.</p> <p>-When orally ingested, DMT without harmine is non-active.</p>
Glennon et al. (2000)	Binding of $\beta$ -carbolines and related agents at 5-HT <sub>2</sub> , 5-HT <sub>1A</sub> , dopamine (D <sub>2</sub> ) and benzodiazepine receptors	-Affinity scores at 5-HT <sub>2</sub> for harmine/harmaline.	-Shows that other harmala alkaloids also bind to the 5HT <sub>2</sub> receptors, further suggesting synergistic potential in the serotonergic system.

Riba et al. (2003)	Human pharmacology of ayahuasca	<ul style="list-style-type: none"> <li>-Diastolic blood pressure significant increase.</li> <li>-Heart rate moderate increase.</li> <li>-Increased urinary normetanephrine excretion.</li> <li>-Deaminated monoamine metabolite levels did not decrease (contrary to typical MOAI effect profile).</li> <li>-The negligible harmine plasma levels found suggest a predominantly peripheral (gastrointestinal and liver) site of action for harmine.</li> </ul>	<ul style="list-style-type: none"> <li>-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca.</li> <li>-PK angle.</li> <li>-Small sample size (n=18).</li> </ul>
Riba et al. (2006)	Increased frontal and paralimbic activation following ayahuasca	<ul style="list-style-type: none"> <li>-Significant activation of frontal and paralimbic brain regions.</li> <li>-Increased blood perfusion observed bilaterally in anterior insula, gather intensity in right hemisphere, and anterior cingulate/frontal medial cortex of right hemisphere.</li> <li>-Increases observed in left amygdala/parahippocampal gyrus.</li> <li>-Concludes that ayahuasca interacts with neural systems that are central to interoception and emotional processing.</li> </ul>	<ul style="list-style-type: none"> <li>-Double-blind placebo controlled clinical trial using freeze-dried ayahuasca.</li> <li>-Neuroimaging angle.</li> <li>-Used SPECT.</li> </ul>
Fortunato et al. (2010)	Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus	<ul style="list-style-type: none"> <li>-Increased BDNF protein levels in rat hippocampus.</li> <li>-Concludes that findings within support the hypothesis that harmine could bring about behavioural and molecular effects.</li> </ul>	<ul style="list-style-type: none"> <li>-Further evidence that the synergistic mechanisms of DMT + harmine are more than just effects of MAOIs.</li> </ul>
dos Santos and	Autonomic, neuroendocrine, and immunological effects of	<ul style="list-style-type: none"> <li>-Significant increases in prolactin.</li> <li>-Percentage of CD3/4 were decreased, natural killer cells increased.</li> </ul>	<ul style="list-style-type: none"> <li>-Focuses on the synergistic effects of ayahuasca rather than individual action of compounds.</li> </ul>

Strassman (2011)	ayahuasca: a comparative study with D-amphetamine	<ul style="list-style-type: none"> <li>-Maximum changes occurred around 2 hours, returned to baseline after 24 hours.</li> <li>-Ayahuasca displayed moderate sympathomimetic effects, significant neuroendocrine stimulation, and time-dependent modulatory effect on cell-mediated immunity.</li> </ul>	<ul style="list-style-type: none"> <li>-Immunological, rather than neuropsychological, perspective.</li> </ul>
McIlhenny et al. (2011)	Methodology for determining the major constituents and metabolites of the Amazonian botanical medicine ayahuasca in human urine	<ul style="list-style-type: none"> <li>-Showed that the major metabolite of a DMT is the corresponding DMT-NO, the first time this metabolite has been described in <i>in vivo</i> studies in humans.</li> <li>-Very little DMT detected in urine, despite the MAOI.</li> <li>-Major alkaloid excreted was THH.</li> <li>-List of other products and metabolites quantified.</li> </ul>	<ul style="list-style-type: none"> <li>-Provides methodology for identifying and quantifying constituents of ayahuasca in human urine.</li> <li>-PK data of tested samples provided. Excretion and metabolism of THH should be further investigated.</li> </ul>
McIlhenny et al. (2012)	Methodology for determining major constituents of ayahuasca and its metabolites in blood	<ul style="list-style-type: none"> <li>-DMT concentrations lower than DMT-NO at all time points.</li> <li>-Harmine and harmaline present in most samples.</li> <li>-Plasma DMT-NO concentrations three to four times higher than DMT.</li> <li>-DMT-NO forms rapidly after drug administration.</li> </ul>	<ul style="list-style-type: none"> <li>-Single methodology combining HPLC and gas chromatography to identify ayahuasca constituents in blood following oral consumption.</li> <li>-First report of presence of DMT-NO in human blood following ayahuasca/DMT administration.</li> <li>-Method for the most complete profile of DMT, harmala alkaloids, and metabolite concentrations.</li> <li>-THH levels peaked at around 4.5 hours.</li> </ul>

Riba et al. (2012)	Metabolism and disposition of N,N-dimethyltryptamine and harmala alkaloids after oral administration of ayahuasca	<ul style="list-style-type: none"> <li>-Less than 1% of DMT excreted unchanged.</li> <li>-The recovery of each harmala alkaloid plus its 0-demethylated metabolite varied greatly (between 9 and 65%).</li> <li>-Fifty per cent was recovered as indole-3-acetic acid or DMT-NO.</li> <li>-Ten per cent was other MAO-independent compounds.</li> <li>-Recovery of DMT plus metabolites reached 68%.</li> <li>-Harmol, harmalol, and THH conjugates were abundant in urine.</li> </ul>	<ul style="list-style-type: none"> <li>-PK study with implications regarding alternative metabolic routes for DMT other than biotransformation by MAO.</li> <li>-Freeze-dried ayahuasca.</li> <li>-Urine samples obtained.</li> <li>-Small sample (n=10).</li> </ul>
Morales-García et al. (2017)	The alkaloids of <i>Banisteriopsis caapi</i> , the plant source of the Amazonian hallucinogen ayahuasca, stimulate adult neurogenesis <i>in vitro</i>	<ul style="list-style-type: none"> <li>-Significant neurogenesis in adult hippocampal cells <i>in vitro</i> with harmine.</li> </ul>	<ul style="list-style-type: none"> <li>-Suggests that ayahuasca brew may have more complex synergistic properties than we currently understand.</li> <li>-Shows that harmine alone could be partially responsible for the neurological changes seen in ayahuasca users.</li> </ul>
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	<ul style="list-style-type: none"> <li>-Magnetic resonance spectroscopy showed post-acute reductions in glutamate + glutamine, creatine, and N-acetylaspartate+N-acetylaspartylglutamate in the posterior cingulate cortex.</li> <li>-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.</li> </ul>	<ul style="list-style-type: none"> <li>-DMN activity decrease and increased neural connectivity to other areas of the brain.</li> <li>-Supported by other studies on 5HT2a agonists.</li> </ul>

-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.  
-Long-term neurological differences found after ayahuasca administration.  
-Post-acute neural changes predicted sustained elevations in nonjudging 2 months later.

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*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  $\beta$ -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  $\beta$ -carbolines and their role in treating mental health conditions (Dos Santos & Hallak, 2017). The

$\beta$ -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		Sample Size (n)	DMT (mg/ml)	THH (mg/ml)	Constituent		Total Dosing Sessions
	Tradition	Design				HRL (mg/ml)	HRM (mg/ml)	
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*

<b>Therapeutic and psychoactive effects</b>	<b>Reference</b>	<b>Harmine</b>	<b>Harmaline</b>	<b>Tetrahydroharmine</b>
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 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-HT<sub>2</sub> 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*

<b>Overview of Pharmacokinetics</b>	<b>DMT</b>	<b>Harmine</b>	<b>Harmaline</b>	<b>Tetrahydroharmine</b>
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  $\beta$ -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*  $\beta$ -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  $\beta$ -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

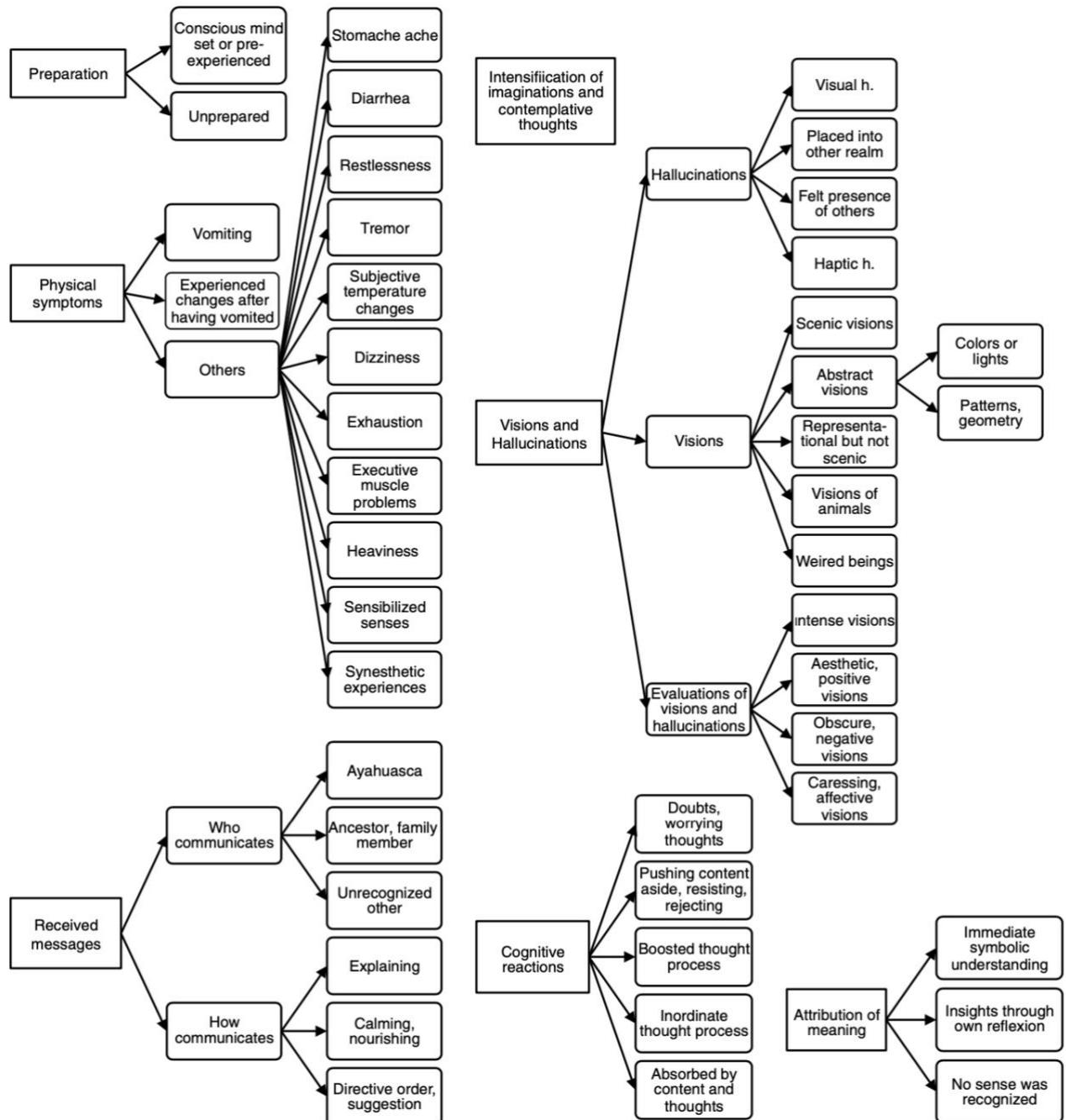
(coding units) were paraphrased to build up provisional main categories. Similar paraphrases with shared meaning were paraphrased again. In this way, abstract categories were formed. For the additional material, statements were used to build up subcategories, and further statements were either subsumed 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*.

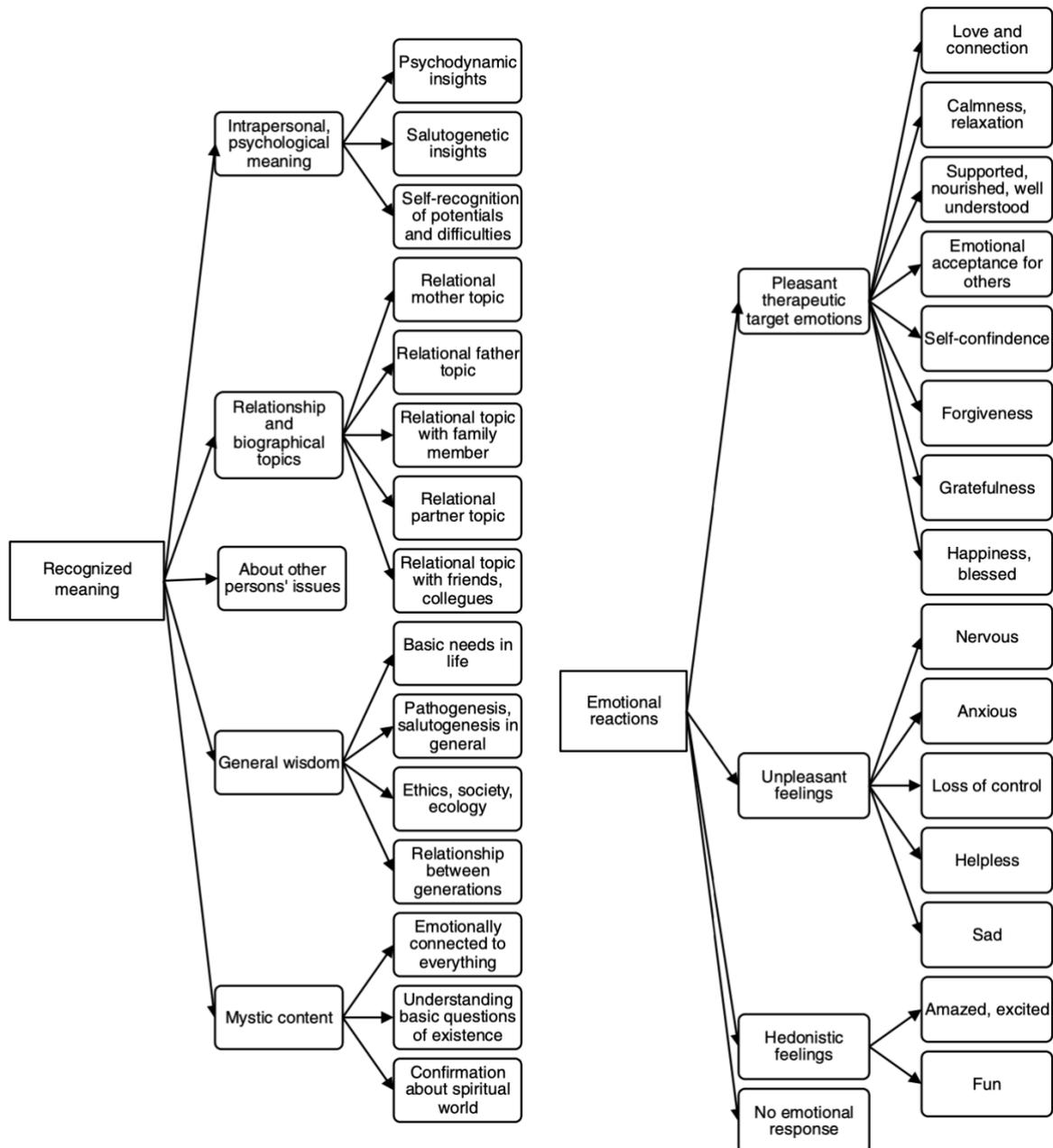
**Figure 1**

*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.*



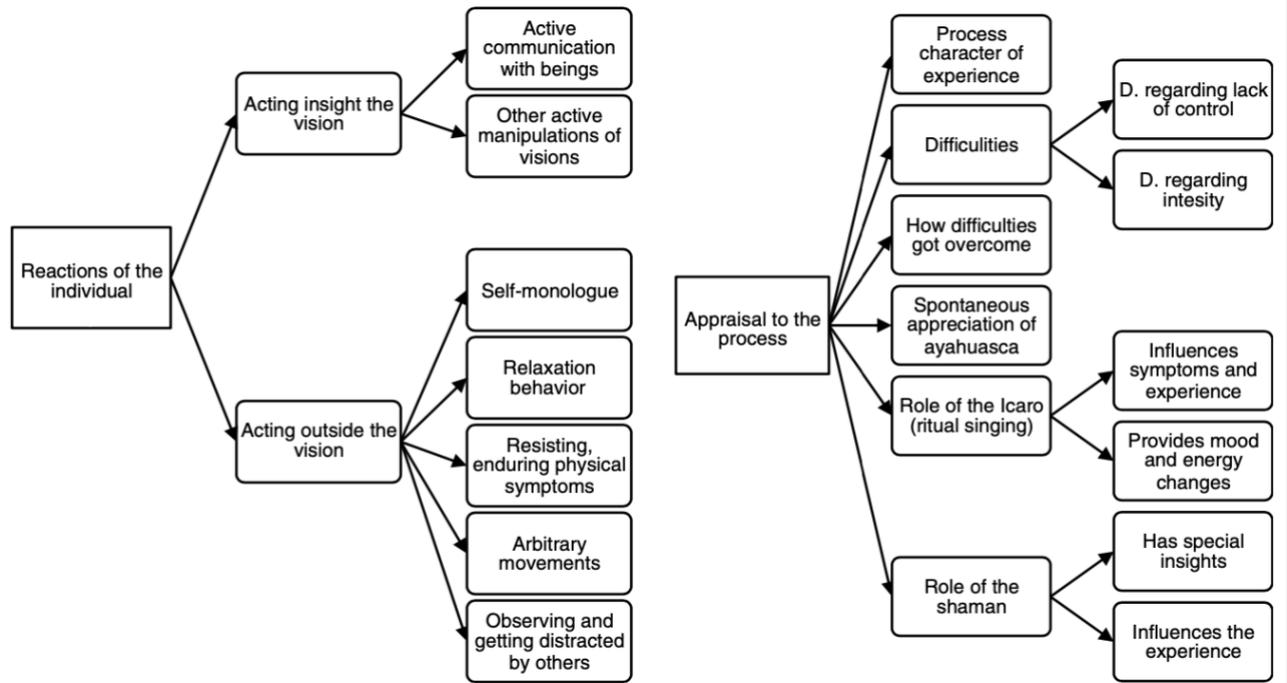
**Figure 2**

*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 decentering, 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 (Freckska 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 necessarily 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*

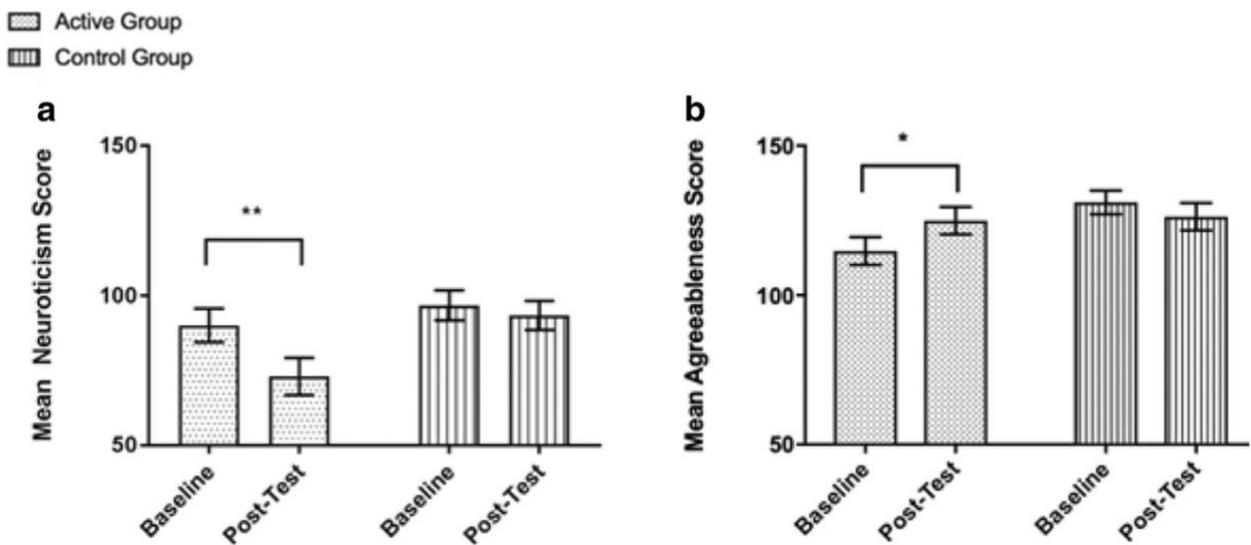
#### *Personality changes from baseline to post-treatment*

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*

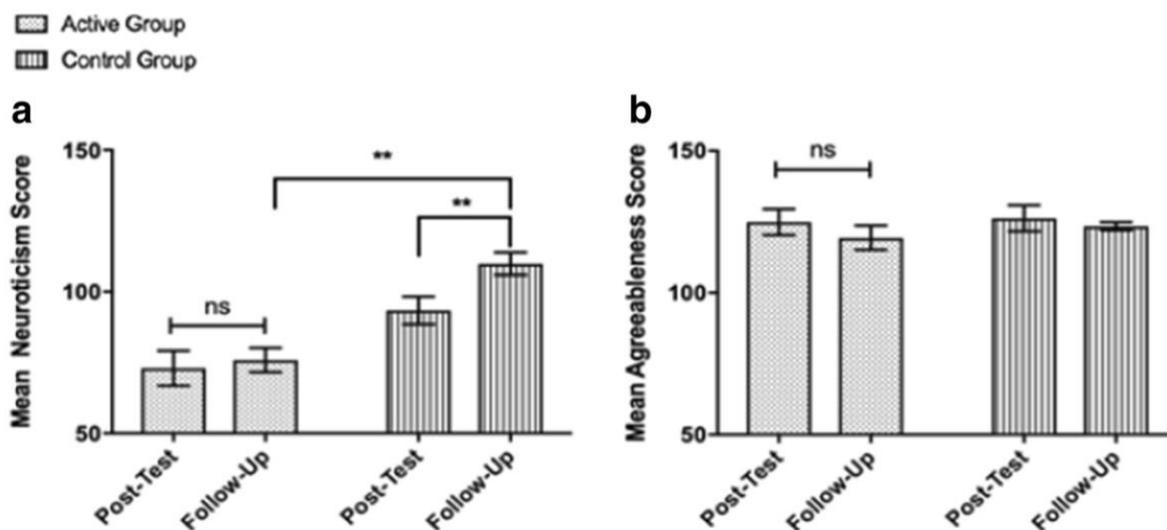
Spearman’s rank-order correlation revealed a medium significant negative correlation between Neuroticism change and MEQ scores from baseline to post-test in both the active and comparison groups ( $r_s(48) = - .56, p < .001$ ) (i.e. those who reported a greater degree of mysticism also experienced greater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

Measure (n)	Pre	Post	t (df)	p	Cohen's d
	M (SD)	M (SD)			
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*

	<b>BDI-II</b> <i>n</i> = 47	<b>STAI-S</b> <i>n</i> = 47	<b>STAI-T</b> <i>n</i> = 42
<b>NR-6</b> <i>n</i> = 24	-.623***	-.653**	-.485*

\* $p < .05$ , \*\*  $p < .01$ , \*\*\*  $p \leq .001$

*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*

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

<b>STAI-T</b> <i>n</i> = 42	-	-	-.600**	-.111
<b>NR-6</b> <i>n</i> = 24	-	-	.747**	-.084
<b>FFMQ</b> <i>n</i> = 38	-	-	-	.001

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\*  $p < .01$ , \*\*  $p \leq .001$

### *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/fpsy.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.

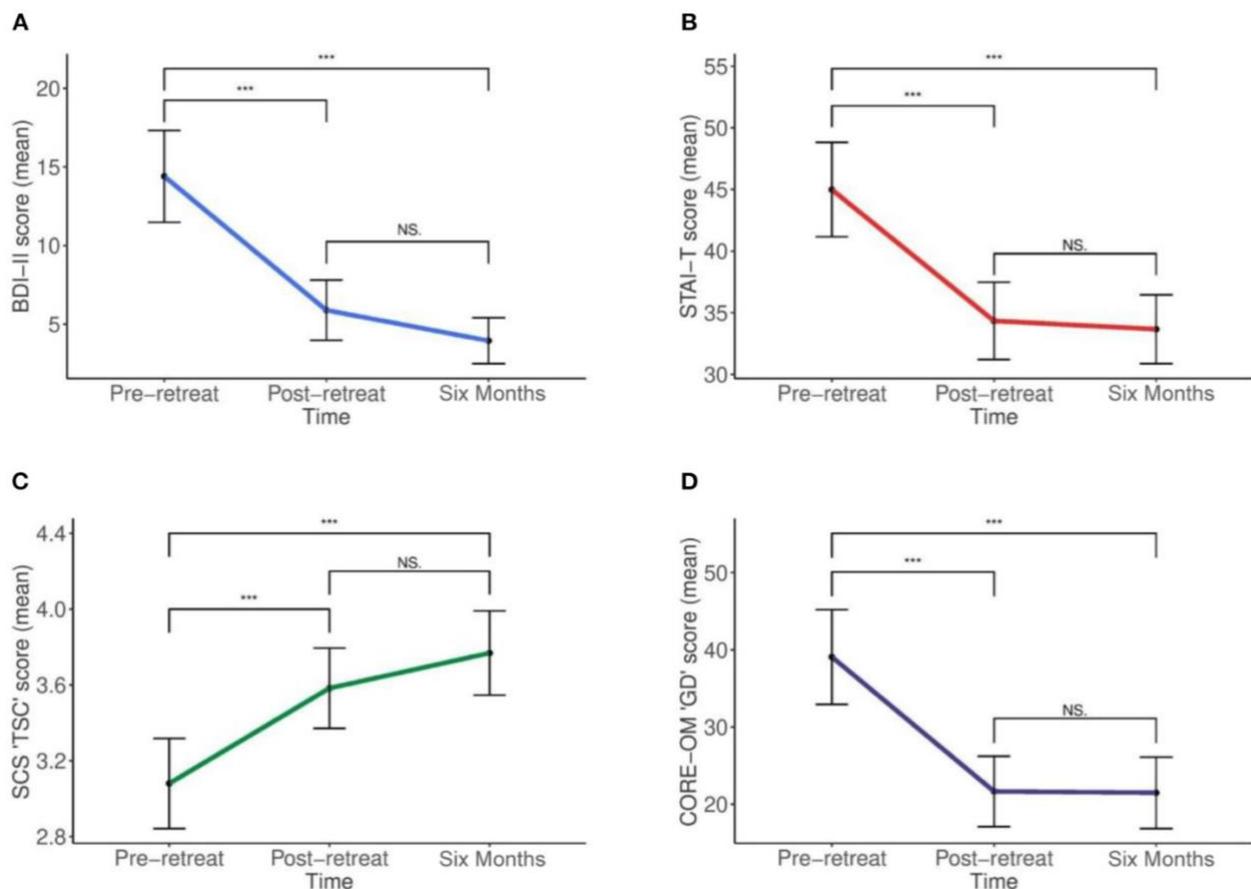
### *Summary of Results*

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 ( $P > 0.05$ ), \*\*\* $p \leq 0.001$ ].

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 correlate 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 mediating 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-HT<sub>1A</sub> 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 from 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 validity 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 detracted from the objective of the studies, which was to investigate traditional ayahuasca use in a retreat setting and would have significantly compromised the ecological validity 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 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 Illumina 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 & Rumrill, 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 & Rumrill, 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* performing 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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