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Subjective experiences of ayahuasca naïve users

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Dissertation presented to the Programa de Pós-Graduação em Psicologia of PUC-RIO in partial fulfillment of the requirements for the degree of Master em Psicologia.

Advisor: Daniel Corrêa Mograbi

Rio de Janeiro,
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ABSTRACT

Cruz, Lucas Villar Magalhães da; Mograbi, Daniel Correa (Advisor). **Subjective experiences of ayahuasca naïve users**. Rio de Janeiro, 2025. 73p. Dissertação de Mestrado – Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

Ayahuasca is a psychoactive infusion that has been used as an entheogen for centuries, with recent research indicating its potential as a promising treatment for certain clinical disorders. Despite the growing scientific literature on its effects, there remains a scarcity of studies examining the subjective experiences of naïve ayahuasca users. The first study in this dissertation aimed to assess the subjective experiences of naïve individuals, including those with depression and healthy controls, following ayahuasca consumption. The second study evaluated the relationship between prior ayahuasca experience and health outcomes, beliefs, and cognitive factors, comparing naïve, low/moderate, and high-experience users who consumed ayahuasca in naturalistic settings.

Keywords

Ayahuasca; naïve; depression; beliefs; self-reports

Resumo

Cruz, Lucas Villar Magalhães da; Mograbi, Daniel Correa. **Experiências subjetivas de usuários naive de ayahuasca.** Rio de Janeiro, 2025, 73p. Dissertação de Mestrado - Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

A ayahuasca é uma infusão psicoativa utilizada como enteógeno há séculos, com pesquisas recentes indicando seu potencial como um tratamento promissor para certos transtornos clínicos. Apesar do crescente corpo de literatura científica sobre seus efeitos, ainda há uma escassez de estudos que investiguem as experiências subjetivas de usuários ingênuos de ayahuasca. O primeiro estudo desta dissertação teve como objetivo avaliar as experiências subjetivas de indivíduos ingênuos, incluindo aqueles com depressão e controles saudáveis, após o consumo de ayahuasca. O segundo estudo avaliou os efeitos da experiência prévia com ayahuasca em desfechos de saúde, crenças e fatores cognitivos, comparando usuários ingênuos, de experiência baixa/moderada e alta, que consumiram ayahuasca em settings naturalísticos.

Palavras-chave

Ayahuasca; naïve; depressão; crenças; auto-relatos

Summary

1. Introduction

1.1 Ayahuasca – Brief history and therapeutic potential

Ayahuasca, a Quechua word meaning "vine of the soul," is a decoction prepared by combining the plant *Psychotriaviridis*, also known as chacruna, and the vine *Banisteriopsiscaapi*, or jagube. Chacruna contains N,N-Dimethyltryptamine (DMT) in its composition, while jagube contains chemical compounds such as harmine, harmaline, and tetrahydroharmine, which act as monoamine oxidase inhibitors (MAOIs) (Palhano-Fontes et al., 2022). When orally consumed, these inhibitors prevent the degradation of DMT by monoamine oxidase-A enzymes in the intestine and liver, allowing it to enter the bloodstream and reach the brain, where it exerts its psychoactive effects (Simão et al., 2020).

Although ayahuasca has traditionally been consumed by indigenous people from the Amazon basin (Frecska, Bokor & Winkelman, 2016), its use expanded in Brazil beyond these communities during the 20th century, becoming more prominent in urban environments. This expansion was partly driven by the integration of ayahuasca into syncretic religions, such as Santo Daime, União do Vegetal, and Barquinha, which spread to large cities (Dos Santos & Hallak, 2021). Considering its unique position in Brazilian society, ayahuasca has been authorized for ritual and religious use since 1987 (Relatório Final, 1987), with Brazil recognizing its legitimacy through various state acts. Its current regulation is governed by CONAD Resolution No. 1/2010, which establishes guidelines such as self-identification of religious groups and the prohibition of its commercialization. These measures aim to balance the protection of religious freedom with the prevention of misuse. This resolution also encouraged the development of scientific research on the therapeutic potential of ayahuasca use (Labate & Feeney, 2012).

Scientific research on ayahuasca has increasingly highlighted potential clinical applications. Preliminary evidence, for instance, suggests some efficacy in treating conditions such as grief (González et al., 2019), hopelessness, panic-related symptoms (Santos, 2007), and substance use disorders (Berlowitz et al., 2019; Thomas et al., 2013). While research on various conditions is promising, the most robust evidence, to date, comes from studies focused on the treatment of depression (Palhano-Fontes et al., 2019; Sanches et al., 2016).

Depressive disorders have a high prevalence among mental disorders (Gutiérrez-Rojas et al., 2020), with rising figures over time (Proudman, Greenberg & Nellesen, 2021). Furthermore, these disorders pose a significant economic burden on governments and societies, both in terms

of medication costs and the provision of therapeutic care. The global economic impact of mental health conditions is projected to rise substantially, increasing from $2.5 trillion in 2010 to $6 trillion by 2030 (The Lancet Global Health, 2020). Among these conditions, major depressive disorder (MDD) is one of the primary contributors, affecting a substantial portion of the global population. In addition to causing severe adverse impacts on individuals, MDD generates high costs for insurers, employers, patients, and caregivers (Proudman, Greenberg & Nellesen, 2021).

Traditional antidepressants, particularly selective serotonin reuptake inhibitors, have been widely prescribed, but their efficacy remains a subject of debate. For instance, a recent reanalysis of a network meta-analysis questions whether antidepressants produce effects significantly stronger than placebo in the treatment of adult depression (Munkholm, Paludan-Müller & Boesen, 2019). In a meta-analysis conducted by Levkovitz, Tedeschini & Papakostas (2011), which included 44,240 patients across 177 studies, 54% of patients responded to antidepressant treatment, while 38% responded to placebo. Other significant challenges in antidepressant therapy include the possibility of spontaneous patient improvement and the frequent lack of response to different antidepressant treatments, particularly in cases of chronic depression (Murphy & Byrne, 2012).

Given this challenging scenario, novel therapeutic approaches have been explored, including the use of psychedelic substances like ayahuasca in clinical settings. Palhano-Fontes et al. (2019) evaluated a sample of individuals with treatment-resistant depression and a history of unsuccessful antidepressant treatments. The study observed a significant reduction in depression severity among participants who received a single dose of ayahuasca, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) and the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967). This reduction was evident on days one, two, and seven following administration, compared to the placebo group.

The open-label study by Sanches et al. (2016) also aimed to evaluate the antidepressant effects of ayahuasca in a sample of 17 patients with recurrent depression. Participants received an oral dose of ayahuasca and were assessed using various psychiatric scales (such as the HAM-D and the MADRAS) during the acute effects and up to 21 days post-administration. The results showed a significant reduction in depression symptoms, with effects lasting up to day 21. Additionally, increased blood perfusion was observed in brain regions involved in

mood regulation, such as the left nucleus accumbens and the right insula. The study suggests that ayahuasca may have fast-acting and sustained antidepressant properties.

1.2 Set, setting and user experience

Treatment with ayahuasca, and psychedelics in general, exhibits certain characteristics to a larger extent than traditional pharmacological interventions. Among these, it is well established that such substances are more strongly influenced by "set" (intrinsic subjective factors, such as expectations, preparation, personality, and intention) and "setting" (extrinsic factors, such as the surrounding environment and social context of the experience; Hartogsohn, 2017). Another concept frequently integrated into psychedelic research is "matrix," which encompasses the environment the individual comes from, the circumstances in which the psychedelic therapy takes place, and the post-treatment setting (Eisner, 1997). Specifically, in the case of ayahuasca consumption, "set" and "setting" characteristics may positively influence users' acute experiences, leading to better mental health outcomes and enhanced well-being (Perkins et al., 2021).

Moreover, in psychedelic studies, clinical research involving inexperienced users is of particular relevance, as it enables direct exploration of these substances' effects on individuals without prior usage history or tolerance. In this context, Garrido et al. (2020) evaluated both "naïve" users (individuals with no history of substance use) and long-term ayahuasca users, identifying significant mental health improvements. Among the 40 naïve participants, 45% met diagnostic criteria for a psychiatric disorder before using the substance. However, after consumption, over 80% demonstrated significant clinical improvements, with substantial reductions in depression and psychopathology symptoms lasting up to six months. Furthermore, in a sub-study examining 23 long-term users, it was observed that they exhibited lower levels of depression and higher scores of self-transcendence and quality of life compared to inexperienced users.

Other studies involving naïve subjects corroborate these findings. For example, Osório et al. (2015) assessed six individuals with depression and observed reductions in depression scores of up to 82% on days one, seven, and twenty-one following ayahuasca administration. The study, conducted in an open-label format, used validated instruments such as the HAM-D, MADRS, and the Anxiety and Depression subscale of the Brief Psychiatric Rating Scale (BPRS).

Beyond clinical applications, exploring the experiences of first-time users is increasingly important, given the recent growth in ayahuasca use worldwide. It is estimated that over four million people across America, Europe, Australia, and New Zealand have consumed ayahuasca at least once in their lifetime. (International Center for Ethnobotanical Education, Research and Service, 2023). The number of spiritual retreats in various South American countries has risen, attracting tourists with diverse motivations for consuming the beverage, such as curiosity, the desire to address mental health issues, the quest for self-knowledge, an interest in psychedelic medicine, spiritual development, and the search for life direction (Kavenská & Simonová, 2015). Altogether, findings from clinical studies, as well as the growing numbers of ayahuasca users, highlight the need for further research into the experiences of first-time users.

1.3 Set and setting in ayahuasca research

An aspect that warrants further exploration in clinical experiences with ayahuasca is the subjective reports, which comparatively have received less attention than questionnaires assessing psychological characteristics. However, these subjective aspects are fundamental for a deeper understanding of the experiences and effects of the substance, which extend beyond the objective data frequently reported.

Several studies have assessed the subjective experiences of ayahuasca users, highlighting its impact on perception and mood. For example, Riba et al. (2001) conducted a single-blind, placebo-controlled clinical trial with six healthy male participants who had prior experience with ayahuasca. The study administered three increasing doses of freeze-dried ayahuasca (0.5, 0.75, and 1.0 mg DMT/kg body weight) and found dose-dependent increases in perceptual, affective, cognitive, and somatic changes. Effects were noted 30-60 minutes post-consumption, peaked at 60-120 minutes, and resolved by 240 minutes. Similarly, Riba et al. (2003) employed a double-blind, placebo-controlled design with 18 participants, administering two doses (0.6 and 0.85 mg DMT/kg body weight). The study reported significant subjective effects, including perceptual modifications and positive mood increases, peaking at 1.5-2 hours. The pharmacokinetic profile revealed that the Tmax for DMT coincided with the peak of subjective effects, supporting the link between these pharmacodynamic and experiential changes. Additionally, Osório et al. (2015) conducted an open-label trial to evaluate ayahuasca's effects on six individuals with depression. The study revealed significant reductions in depressive symptoms—up to 82%—observed across multiple scales (HAM-D, MADRS, BPRS) within

one to seven days post-administration, without inducing mania or significant thought disorders. These studies underscore the importance of considering subjective experiences and methodological rigor when evaluating ayahuasca's effects. A self-report approach provides valuable insights into the phenomenological dimensions of these substances, which may help elucidate their therapeutic potential (Yaden & Griffiths, 2020).

In relation to setting of studies, a recurrent limitation in psychedelic studies is that many are conducted in controlled clinical settings. While this provides experimental control and ideal conditions to explore causal relationships, these settings differ significantly from the traditional environments where these substances are most often used. In this regard, naturalistic studies play a crucial role in bridging this gap. Naturalistic studies are conducted in real-world settings, without controlled experimental interventions, aiming to understand phenomena in their authentic conditions while respecting associated contextual and cultural characteristics. These studies provide a unique opportunity to comprehend how ayahuasca affects individuals in everyday environments, respecting the ritualistic and cultural context in which it is typically consumed. Factors such as music, ritual guidance, and natural settings are crucial elements in shaping the effects of the substance, making naturalistic studies even more relevant (Perkins et al., 2021). This approach is essential for evaluating ayahuasca's effectiveness in real-world conditions, as its therapeutic effects appear to be more heavily influenced by factors beyond pharmacological mechanisms (Uthaug et al., 2021).

2. Objectives

Considering the above, the general objective of the present dissertation is to investigate the effects of ayahuasca in naïve users. For this purpose, two studies were conducted, with the following specific objectives:

– To explore the subjective structure of self-reports from naïve ayahuasca users with and without depression;

– To evaluate the impact of the ayahuasca experience on health outcomes, beliefs and cognitive factors, comparing 'naïve' with more experienced users.

The first study examined the self-reported experiences of ayahuasca-naïve users using tools for quantitative textual analysis. Reports from participants with or without depression, that took part on a previous clinical trial (Palhano-Fontes et al., 2019), were explored with a textual analysis software. The second study of this dissertation explored the impact of ayahuasca on various health outcomes, beliefs and cognitive factors among users in ritualistic settings. Data from a survey conducted by our group was used, with a focus was on understanding how previous ayahuasca experience affected characteristics of those taking willing to part in rituals.

3. ARTICLES SECTION

Article 1

Cruz, L., Bienemann, B., Palhano-Fontes, F., Tófoli, L. F., Araújo, D. B., & Mograbi, D. C. (2023). A quantitative textual analysis of the subjective effects of ayahuasca in naïve users with and without depression. Scientific reports, 13(1), 19635. https://doi.org/10.1038/s41598-023-44193-5

3.1 A QUANTITATIVE TEXTUAL ANALYSIS OF THE SUBJECTIVE EFFECTS OF AYAHUASCA IN NAÏVE USERS WITH AND WITHOUT DEPRESSION

A quantitative textual analysis of the subjective effects of ayahuasca in naïve users with and without depression

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Abstract

Ayahuasca is a brew with psychoactive properties that has been used as an entheogen for centuries, with more recent studies suggesting it is a promising treatment for some clinical disorders. Although there is an emerging scientific literature on its effects, to the best of our knowledge no study has explored the self-reported experiences of first-time ayahuasca users with quantitative textual analysis tools. Accordingly, the current study aimed to analyze the subjective experience of naive individuals with depression and healthy controls after consuming ayahuasca. For this purpose, responses from a subsample of participants from a previous clinical trial to open-ended questions regarding their experience with ayahuasca underwent textual analysis. Data from nine patients with treatment-resistant depression and 20 healthy individuals were included, and quantitative textual analysis was performed using IRaMuTeQ 0.7 alpha 2 and R 3.1.2. The analysis identified five clusters: alterations in the state of consciousness, cognitive changes, somatic alterations, auditory experiences, and visual perceptual content. Additionally, findings suggest specific features of the experience of people with depression with ayahuasca, such as increased aversive bodily reactions. The results are consistent with previous findings indicating central axes of the psychedelic experience, and may inform therapeutic approaches using ayahuasca.

Introduction

Ayahuasca is a brew with psychoactive properties made from the decoction of Jagube vine (*Banisteriopsiscaapi*) and Chacrona leaf (*Psychotriaviridis*). Indigenous groups have consumed it for centuries as entheogens (Rodrigues et al., 2019), and in the past century syncretic religious organizations, such as *União do Vegetal*, *Barquinha*, and *Santo Daime*, have also used it ritualistically (Dos Santos & Hallak, 2021). Clinical research on ayahuasca has indicated potential therapeutic effects for different mental health conditions and symptoms, such as panic-like and hopelessness symptoms (Santos et al., 2007) and substance abuse disorder (Hamill et al., 2019; Politi et al., 2021; O'Shaughnessy et al., 2021). In addition, improvements in neuropsychological functioning have also been observed (Bouso et al., 2012).

Ayahuasca has shown promise for the treatment of some clinical disorders. In particular, depression is one of the conditions that may benefit the most from ayahuasca. Epidemiological data show that depression affects more than 300 million people worldwide (Trivedi, 2020). Between 2010 and 2018, the incremental economic burden of adults with major depressive disorder (MDD) increased from $US236.6 billion to 326.2 billion. In this context, antidepressants, particularly selective serotonin reuptake inhibitors, have been largely prescribed, but their efficacy is discussed. For instance, a recent reanalysis of a network meta-analysis questions the efficacy of antidepressants for depression in adults, discussing whether they have stronger effects than placebo or not (Munkholm, Paludan-Müller & Boesen, 2019). This highlights the urgent need for innovation in the management of depression, with more research needed into potential treatment alternatives.

In this context, recent studies with ayahuasca in depressive patients have shown potential therapeutic effects (Palhano-Fontes et al., 2022; Sanches et al., 2016). Palhano-Fontes (2019) assessed a sample of people with treatment-resistant depression who had previously attempted antidepressant therapy unsuccessfully previously. The study observed that depression severity was significantly reduced in participants who were dosed with ayahuasca, as assessed through scores on the Montgomery-Asberg Depression Rating Scale – MADRS (Montgomery &Asberg, 1979) and Hamilton Depression Rating Scale – HAM-D (Hamilton, 1967). This reduction was observed one, two, and seven days after dosing when compared to placebo.

Unlike traditional pharmacological interventions, substances such as ayahuasca may be highly linked to characteristics of set (intrinsic subjective factors, such as expectation, preparation, personality, and intention) and setting (extrinsic factors, such as the surrounding environmental

and social context of the experience; Hartogsohn, 2017). Specifically for ayahuasca consumption, set and setting features may contribute positively to users' acute experiences, with better mental health outcomes and increased well-being (Perkins et al., 2021). One way of exploring directly the effects of set is to have studies recruiting participants with and without clinical disorders, allowing the comparison of their subjective experiences.

Studies with ayahuasca, especially clinical investigations, have generally focused on quantitative measures of psychological characteristics. The integration with subjective aspects of the experience may be particularly relevant considering it has been argued these are necessary for the therapeutic effects of psychedelics (Yaden & Griffiths, 2020; but see Olson, 2020). Considering the studies that investigated subjective reports, Wolff et al. (2019) used qualitative content analysis to explore experiences after an ayahuasca ceremony, indicating that visual content may play an important role for therapeutic processes, with the possibility of users attributing symbolic meaning to them. This is in line with the work by Shanon (2010) exploring the epistemics of ayahuasca visions, suggesting they were intrinsically related to personal ideations, leading to various types of knowledge and teaching patterns. Beyond individual expectations, context has been shown to exert an important effect in subjective experiences. This has been explored in Israeli and Palestinians individuals, suggesting that sociopolitical group affiliation may affect the psychedelic experience in a relational sense (Roseman, 2021).

Findings from a thematic categorical analysis approach by Fernández et al. (2014) suggest that clinical and non-clinical groups may experience the subjective effects of ayahuasca in different ways. Clinical population reports had content such as biographical review, insights and experiences of emotions or death that may have high therapeutic value, while the content of healthy subjects was more related to thoughts about human culture, religion, and philosophy. Loizaga-Velder & Verres (2014) exploratory study suggests that ayahuasca may assist pee with substance-abuse disorder to overcome psychological issues, for instance with higher integration of bodily and mental experience. Thus, exploring further how clinical and non-clinical groups respond to ayahuasca may bring important information for therapeutic approaches.

The analysis of qualitative data may also help revealing central axes of the psychedelic experience. Apud et al. (2022) investigated participants of a therapeutic center, mainly treated for substance use disorder (SUD), but also with other therapeutic demands. Their results suggest five components of the experience, which included emotional, corporal, spiritual/transcendental, personal elements and visions. Trichter and colleagues (2009)

explored changes in spirituality in first time ayahuasca users, with their qualitative interviews indicating ten main themes in participants' reports: presence of light/geometric patterns, sense of honor, respect, gratitude and/or awe, sense of connection, self-reflection and/or insights of personal life, spiritual experience, supernatural experiences, sense of peace and/or calm, healing, death/near-death experiences and desolation. Despite these studies, to the best of our knowledge, no previous research has used quantitative methods to analyze self-reported data of first-time ayahuasca users, including clinical and non-clinical participants.

In the last three decades, research on psychedelics has been conducted mostly in developed regions and high-income countries (Inserra, 2019). For substances such as dimethyltryptamine (DMT), mescaline, and psilocybin, this is paradoxical considering that their traditional use emerged in developing regions, particularly in Latin America. In the case of ayahuasca, in particular, its religious use is legally protected in Brazil, and the considerable number of users reinforces the need for more research into its effects. Further research conducted in developing regions is important not only to address these social needs, but also to investigate the extent to which the effects of psychedelics are universal.

Considering this, the current study explores the subjective experience of people with depressive and healthy controls who consumed ayahuasca. Specifically, a subsample of participants from the Palhano-Fontes et al. (2019) study answered open-ended questions about their experience with ayahuasca, with these data undergoing textual analysis. Although subjective experiences of users have been reported before, as indicated no one has investigated quantitatively the self-reported experiences of first-time ayahuasca users. Additionally, by exploring the perceptions of people with and without depression, the current work can shed light into the effects of set in the experience of ayahuasca, with particular implications for future clinical use of this substance.

Methods

Sample

To investigate the antidepressant effect of ayahuasca against a placebo, a randomized double-blinded placebo-controlled trial was conducted, with the results being reported previously elsewhere (Palhano-Fontes et al., 2019). The primary investigation was a double-blind randomized placebo-controlled clinical trial aiming to test the antidepressant effects of ayahuasca on adults aged 18-60 with treatment-resistant depression. Participants were randomly assigned (1:1) to receive ayahuasca or placebo. All patients were naïve to ayahuasca, with no previous experience with any other psychedelic substance.

In the current study, data from nine patients with treatment-resistant depression and 20 healthy individuals were included. Only participants who took ayahuasca were included in the current analysis. All subjects in the study had no prior experience with ayahuasca. The exclusion criteria adopted were: diagnosis of current clinical disease (example: heart disease; diabetes) based on anamnesis, physical and laboratory examination; pregnancy; history of neurological diseases; history of bipolar affective disorder or schizophrenia; history of mania or hypomania; substance abuse. Patients were referred from psychiatric units of the Onofre Lopes University Hospital (HUOL), in Natal/RN, Brazil, and healthy volunteers were recruited through media and internet advertisements. All procedures took place at the HUOL. Socio-demographic characteristics of participants can be seen in Table 1.

PLEASE INSERT TABLE 1 HERE

Procedures

Participants received a single dose of 1 mL/kg of ayahuasca. A single ayahuasca batch was used throughout the study, containing on average (mean ± SD): 0.36 ± 0.01 mg/mL of N,N-DMT, 1.86 ± 0.11 mg/mL of harmine, 0.24 ± 0.03 mg/mL of harmaline, and 1.20 ± 0.05 mg/mL of tetrahydroharmine, quantified by mass spectroscopy analysis. The batch was prepared and provided free of charge by a branch of the Barquinha church, Ji-Paraná, Brazil. The placebo

was formulated as a liquid designed to mimic the color and flavor of ayahuasca.

Throughout the sessions, participants were given specific instructions to maintain silence, keep their eyes closed, and concentrate on their physical sensations, thoughts, and emotions. They were also provided with a predefined musical playlist to enhance their experience. In addition, two researchers were in an adjacent room to provide support whenever requested by the participants. The primary outcome measure was changes in the severity of depression, measured by the HAM-D scale, seven days after dosing (D7). The secondary outcome was changes in MADRS scores from baseline to 1 day (D1), 2 days (D2), and 7 days (D7) after dosing.

At the end of the dosing session, approximately 4 h after ayahuasca ingestion, when the acute effects had already ceased, we asked the participants to freely report their experience. Reports were recorded using an MP3-type recorder. These reports were later transcribed (Audiotext company, Curitiba/Brazil).

Interviews, extraction of data and construction of textual corpus

Two researchers conducted the interviews, which were carried out right after the end of the acute effects of ayahuasca. Interviews had an average duration of 13.7 min and started with an open-ended question ("Can you please freely describe your experience?"). When participants gave brief answers, or when further clarification was needed, they were probed with follow-up questions (e.g. "I saw a person" "Was that person known to you? Can you please provide more details?").

The transcribed reports were carefully reviewed and refined to ensure that no language or typing errors were present. To facilitate analysis by the software, dashes, quotation marks, and indentations were removed from the text. Reports had an average of 1002.6 words (for a model, see S1) and were categorized according to sociodemographic (sex, age, marital status, ethnicity, religion, educational achievement, and household income), and clinical variables (depressed/healthy individuals, past use of cannabis, alcohol or tobacco) of respondents. Sociodemographic and clinical variables were dichotomized to power the analyses. Missing values were classified as *null*.

Data analysis

Exploratory and qualitative data analyses were conducted to generate familiarity with the content. Exploratory and qualitative data analyses were conducted to generate familiarity with the content. Interviews were read, one by one, by two co-authors (LC and BB). This was done to familiarize researchers with the context in which terms appeared, helping with the interpretation of the results provided by the automated analysis. IRaMuTeQ 0.7 alpha 2 (Ratinaud, 2012) and R 3.1.2. (R Core Team, 2017) were used to run the quantitative analysis. The analysis was implemented using text-segments (TS). Through TS, texts are divided by the context in which words appear and sized in accordance with the corpus extension. For this study, the default Iramuteq option was used (40 words per text segment, see S1). Reports were analyzed in their original language (Brazilian Portuguese), to avoid any loss of content and context, with the software output being translated into English for the presentation of results in the current article.

Descending Hierarchical Analysis (DHA, Reinert Method), Specificities and Correspondence Factor Analysis (CFA) were used. DHA organizes textual content in clusters with specific meanings, separated by the frequency of their vocabularies, similarity, and association. Specificities and CFA is a method that plays the role of associating texts with variables and indicate tendencies, proximities, and oppositions of the text segments (TS) in graphical visualization, locating those elements in a Cartesian graphic with factors based on their classifications and allowing graphic visualization of the co-occurrence between the words and the possible clusters they are part of (Loubère, 2014). The index of co-occurrence between the words (i.e., the relationship of the words between them and the communities formed by clusters composed of words that are most associated) are indicated by the specificities of the analysis. Specificities analysis highlights the co-occurrence between words and the communities formed by associated words. Words and categories were included in their respective classes by DHA based on the criteria of having a frequency greater than the mean of occurrences in the corpus and chi-square value with the cluster greater than 3.84.(the critical value for $p < .05$ with df = 1; Reid, 2013). The words of interest (active forms) selected for analysis were adjectives, nouns, pronouns, verbs, adverbs, and forms not recognized by the IRaMuTeQ dictionary. In addition, when words had other associated forms (e.g. look, looking), the most frequent form was included in the graphic representation. Chi-square test was used to indicate the association

between words and their clusters (Loubère, 2014). Cramer's V was reported as a measure of effect size for the association (Kim, 2017). α was set at .001 to avoid inflation of type I error.

Ethical issues

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Research Ethics Committee of the Onofre Lopes University Hospital (# 579.479), and all subjects provided written informed consent prior to participation. This study was registered on 26/09/2016 at http://clinicaltrials.gov (NCT02914769).

Results

Descending hierarchical analysis

The analysis by DHA retained 75.03% of the total corpus, a percentage indicated as acceptable for the corpus to be considered for this type of analysis. The corpus was divided into 869 TS, relating 2968 words that occurred 29029 times (mean of occurrence for TS = 33.41). Of these, the active forms formed 1829 words, with 691 words with a frequency equal to or greater than 3.

As seen in dendrogram form (Figure 1), DHA resulted in five clusters of words. Initially, the clusters were grouped into distinct branches: with the first one consisting only of Cluster 5 ('Visual perceptual content' – 206 TS and 22.13% of total forms classified); the second was divided into two other branches with Cluster 3 ('Somatic alterations' – 118 TS and 18.10%) isolated, and all the other clusters together. Of these remaining clusters, Cluster 4 ('Auditory experiences' – 192 TS and 29.45%) splits first, with the last split separating Clusters 2 ('Cognitive changes' – 95 TS and 14.57%) and 1 ('Alterations in the state of consciousness' – 99 TS and 15.18%). For the association between words and clusters (degrees of freedom = 4), considering the five words with the highest association in each cluster, Cramer's V indicated small, medium, and, particularly in Cluster 2, large effect sizes.

Figure 1 also shows the association of participants' characteristics with each cluster. Cluster 1

was associated with middle-aged participants [χ^2 (1) = 15.41; p < .001; V = .09], while Cluster 2 was associated with high-income [χ^2 (1) = 21.61; p < .001; V = .11], male gender [χ^2 (1) = 13.53; p < .001; V = .08] and cannabis users [χ^2 (1) = 12.82; p < .001; V = .08]. Cluster 3 was associated with depression diagnosis [χ^2 (1) = 19.86; p < .001; V = .10]. Cluster 4 was associated with female participants [χ^2 (1) = 19.42; p < .001; V = .10] and those without religion [χ^2 (1) =32.62; p < .001; V = .13]. Cluster 5 was associated with low income [χ^2 (1) = 30.95; p < .001; V = .13], single or widowed marital status [χ^2 (1) = 19.30; p < .001; V = .10], non-tobacco users [χ^2 (1) = 16.24; p < .001; V = .09] and healthy (non-depressed) individuals [χ^2 (1) = 11.02; p < .001; V = .08].

[PLEASE INSERT FIGURE 1 HERE]

Correspondence factor analysis

Results of correspondence factor analysis (CFA) can be seen in Figure 2 (see also S2). The CFA indicated that the clusters are divided mainly into three areas, with Clusters 1, 2, and 4 being strongly related to each other, while Clusters 3 and 5 are isolated.

[PLEASE INSERT FIGURE 2 HERE]

Specificities analysis

The specificities analysis, indicating the index of co-occurrence between the words, can be seen in Figures 3 (Cluster1), 4 (Cluster2), 5 (Cluster 3), 6 (Cluster 4), and 7 (Cluster 5).

[PLEASE INSERT FIGURE 3 HERE]

[PLEASE INSERT FIGURE 4 HERE]

[PLEASE INSERT FIGURE 5 HERE]

[PLEASE INSERT FIGURE 6 HERE]

[PLEASE INSERT FIGURE 7 HERE]

Discussion

In this study, we sought to analyze subjective aspects of the experience of people with depression and healthy controls after the consumption of a single dose of ayahuasca. The textual analysis, which congregate words repeated with high frequency during the participants' reports describing the experience, identified five clusters. Broadly speaking these clusters refer to experiencing an altered state of consciousness, encompassing cognitive changes, somatic alterations, auditory experiences, and visual perceptual content. Each of these clusters showed specific associations with sociodemographic (e.g. age, gender, income, marital status) or clinical variables (depression diagnosis, substance use), but effect sizes were generally small.

Cluster 1 (14.5% of the TS) seems to indicate the onset and experience of an altered state of consciousness. The importance of the visual component at the beginning of the experience is notable (Császár-Nagy, Kapócs & Bókkon, 2019), which seems to be the central mediator of consciousness during this adaptive process. A central feature of the ayahuasca experience is that, according to user reports, visual hallucinations can be "switched on" or "off" by closing or opening the eyes. This highlights the crucial role of visual processing in the altered states of consciousness induced by ayahuasca consumption, which is also reflected in the strong association between the word "eye" and "open" and "close" in Cluster 1. It has been suggested that ayahuasca visions are often coupled with insights and topics with high personal relevance, including philosophical, metaphysical and spiritual epiphanies (Shanon et al., 2010), potentially contributing to the therapeutic effects of the substance (Wolff, 2019). These alterations in consciousness states can also be perceived initially as a decrease in the level of consciousness, which may explain the presence of words like “sleep”, “slow” and “nap”, in addition to content suggesting dream-like experiences (“dream”) and changes in time perception (“hour”). Middle-aged participants showed a significant association with this cluster, with a small effect size, which may suggest more marked consciousness alterations in naïve older participants, but without further data that remains speculative.

Cluster 2 (15.1% of the TS) includes a number of cognitive processes, through verbs such as “remember”, “ question”, “look” and “understand”. It may indicate a sensory-perceptive integration of experience, with the association between “look” and “reality” or “look” and “understand”. The use of psychedelic substances may lead to an intense modification in one's perception of reality (Alonso et al., 2015), which is reflected in this cluster through words such as “blurred” or “strange”. Furthermore, a central word in this cluster word co-occurrence graph

was “same”, which can mark an attempt to compare the perceived reality withan ordinary state of consciousness. This cluster is closely linked to Cluster 1, with shared characteristics of altered states of consciousness and their perception. Small effect sizes were observed for associations between this cluster with male, high income, and cannabis-user participants, which may reflect possible cognitive biases in these groups (e.g. more rumination in cannabis users, Horvath et al., 2022), but further research in this area is required to establish more robust conclusions.

Auditory characteristics of the experience and setting are highlighted in Cluster 4 (which gathered 29.4% of the TS), with words such as “music”, “speak”, “listen”, “sound”, “silence”, and “voice”. Most words in this cluster are associated with music, emphasizing the essential role of the music setting in shaping the experience (O'Callaghan et al., 2020). In the word co-occurrence graph, it is possible to see how participants reacted positively or negatively to music (through words like “relax” or “bother”, for example). Speech was also an essential component of the experience. Some word associations can help us to understand speech as a process of understanding and dealing with the experience during it, such as links between “speak” – “good” – “better” or “speak” – “think” – “calm”. These auditory elements were particularly present in the reports of female participants and those without religion, which suggests these setting features were more salient for these groups. These findings also underscore the potential significance of spoken guidance provided during psychedelic experiences.

Cluster 3 (18.1% of the TS) includes words such as “vomit”, “pain”, “bathroom”, “hungry”, “stomach”, “breathe”, and “dizziness”, describing somatic aspects of the experience, particularly aversive feelings. That is in line with the purgative characteristic of ayahuasca, with users often going through difficult phases of the experience at its initial stages. Notably, the only category associated with this cluster was a diagnosis of depression. This may indicate a higher occurrence of negative somatic feelings in people with depression, consistent with the idea that depression is not only characterized by ideational, but also somatic symptoms (be, 2006). By contrast, this may represent cognitive biases in people with depression (Beevers et al., 2019), leading to more negative evaluation, recall, and reporting of experiences.

Cluster 5 (22.7% of the TS) seems to describe specific visual content. The word “see” is quite central in the co-occurrence graph, being linked to “color”, which then connects to specific colors. Human-like figures (“puppet”, “woman”) and their potential actions (“dance”, “jump”) are also represented. It is interesting to highlight the presence of neutral and positive biases (for example, the word co-occurrence graph reveals a link between “see” and “beautiful”) in this

cluster, given that it is associated with people without depression. This may indicate, in contrast with Cluster 3, more benign experiences in healthy participants. This cluster is also associated with low income, living alone, and not using tobacco. Further studies may explore whether this represents a sampling artefact or if these associations are consistent.

The current findings are in agreement with those reported by Apud and colleagues (2022), who also recruited a clinical group (SUD). The five clusters indicated in their work show some overlap with the results reported here, for instance the 'visual perception content' and 'somatic alterations' clusters are linked to their 'visions' theme and 'corporal experiences' themes. Similar findings have also been reported by first-time ayahuasca users without clinical conditions (Tritcher et al., 2009). It is possible that these core features of psychedelic experience can be measured by specific questionnaires. For instance, psychometric analysis indicates that the 5D-ASC questionnaire (Dittrich, 1998) has a factor linked to Vigilance Reduction (VIR), which may capture phenomena described in Cluster 1, containing words such as "sleep", "slow", "nap", and "dream". Similarly, Cluster 4 has words such as "music", "speak", "listen", "sound", "silence", and "voice" that are potentially related to a factor measuring Auditive Alteration (AVE). Future studies should explore the relationship between psychometric scales and verbal reports of experiences, trying to identify to which extent common dimensions of the psychedelic experience are assessed by existing instruments, leading to their refinement and development of new measurements.

In contrast to previous research (Apud et al., 2022), current findings include a distinct cluster centered on auditory experiences, which encompasses both music and speech-related information, but lack a significant number of reports describing emotional and spiritual/transcendental aspects of the ayahuasca experience. This may be linked to characteristics of setting, with the current study being conducted in a university hospital, as opposed to previous investigations that took place in ritualistic (Wolff et al., 2019) or psychotherapy settings (Apud et al., 2022).

In addition to potential setting effects, findings from the current study also support the idea that the set, specifically previous emotional state of participants, is linked to a more or less challenging experience. For example, Cluster 3 ('somatic alterations'), describing mainly negative physical experiences, has a stronger association with individuals of depression, while Cluster 5 ('visual perceptual content'), with more neutral and positive content, is more prevalent in reports of individuals without depression. This is in line with previous studies indicating that belonging to a clinical group modulates the experience with ayahuasca, for

example with the study by Fernandez and Fábregas (2014) suggesting that reports by people with depression focused on topics with higher therapeutic value in comparison to healthy individuals.

As indicated, the need of subjective effects of psychedelics for therapeutic efficacy has been debated. Recent research on non-hallucinogenic psychedelic analogs with therapeutic potential has suggested that neural plasticity and neurotrophic factors may be fostered independently of subjective experience (Cameron et al., 2021; Cao et al., 2022). While our study explored subjective states through quantitative analysis self-reports, it did not seek a direct comparison between subjective experience and therapeutic potential. Current results do indicate that the subjective state (depression, in this case) appears to influence how individuals assess and remember their experience. Whether attributed meaning has causal potential or is an epiphenomenon, it is undeniable that human beings live in the context of their symbolic representations, so it is unlikely that future therapeutic perspectives will reach its full potential by ignoring this fundamental dimension of human experience.

The current study has some important limitations. The sample investigated was limited in size, which may have reduced statistical power and ability to generalize results. Nevertheless, the number of participants recruited is consistent with that reported in other experimental studies in which psychedelic substances are administered to participants (e.g. Davis et al., 2021 [n = 27]; Ross et al., 2016 [n = 29]; Sanches et al., 2016 [n = 17]). Additionally, in the scope of the current work, it was not possible to explore the relationship between specific symptoms and profiles of depression with the subjective experience of consuming ayahuasca. Future studies should investigate this further, given the potential clinical benefits of ayahuasca for people with depression (Sarris, 2021; Palhano-Fontes, 2019).

In summary, this study is the first to employ quantitative methods to analyze the subjective experiences of people with depression and healthy controls after the consumption of ayahuasca in a clinical setting. Findings highlight certain features of the psychedelic experience, such as visual content, effects on cognition, and somatic alterations, as well as specific aspects of how people with depression react to ayahuasca, such as increased aversive bodily reactions. Future studies should try to combine subjective reports with physiological data, aiming to elucidate specific mechanisms of the cognitive changes, including therapeutic effects, caused by ayahuasca. Given the context sensitivity of psychedelic experiences, studies in different settings may also help clarifying the extent to which contextual factors affect the perception of users of their experience.

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Competing interests

The author(s) declare no competing interests.

Data availability statement

The dataset used for the current study is available from the corresponding author on reasonable request.

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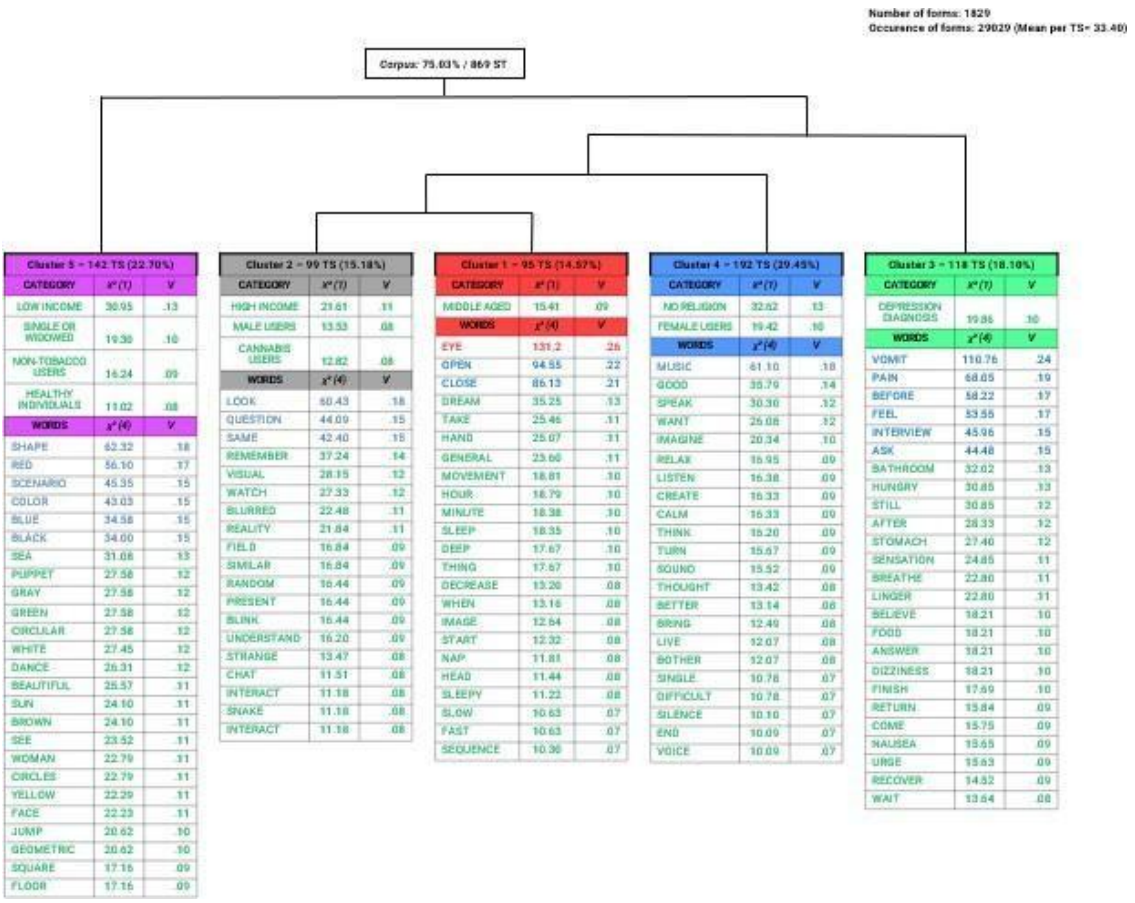
Tables and figures

Table 1 – Socio-demographic data for participants (n = 29)

Variable	**n**
Gender (male/female)	11/18
Age*	32.2 (8.7)
Marital Status (living alone/with others)	21/8
Ethnicity (White/Asian/Black or Mixed)	16/2/11
Religion (Catholic/no religion/others)	11/10/7
Academic level (with/without higher education)	18/11
Income (high/low)	19/10
Cannabis user (yes/no)	5/24
Alcohol user (yes/no)	18/11
Tobacco user (yes/no)	4/25
Depression (yes/no)	9/20

* Mean (standard deviation)

Figure 1 – Dendrogram with words significantly associated (p < .001) with each cluster (max. words = 25) in interviews (n = 29) with individuals who consumed ayahuasca, including both volunteers (n = 20) and those with depression (n = 9), with an average of 1002.6 words per report.



Large (red), medium (blue) and small (green) effect sizes, according to Kim (2017)

Figure 2 – Relationship between clusters.

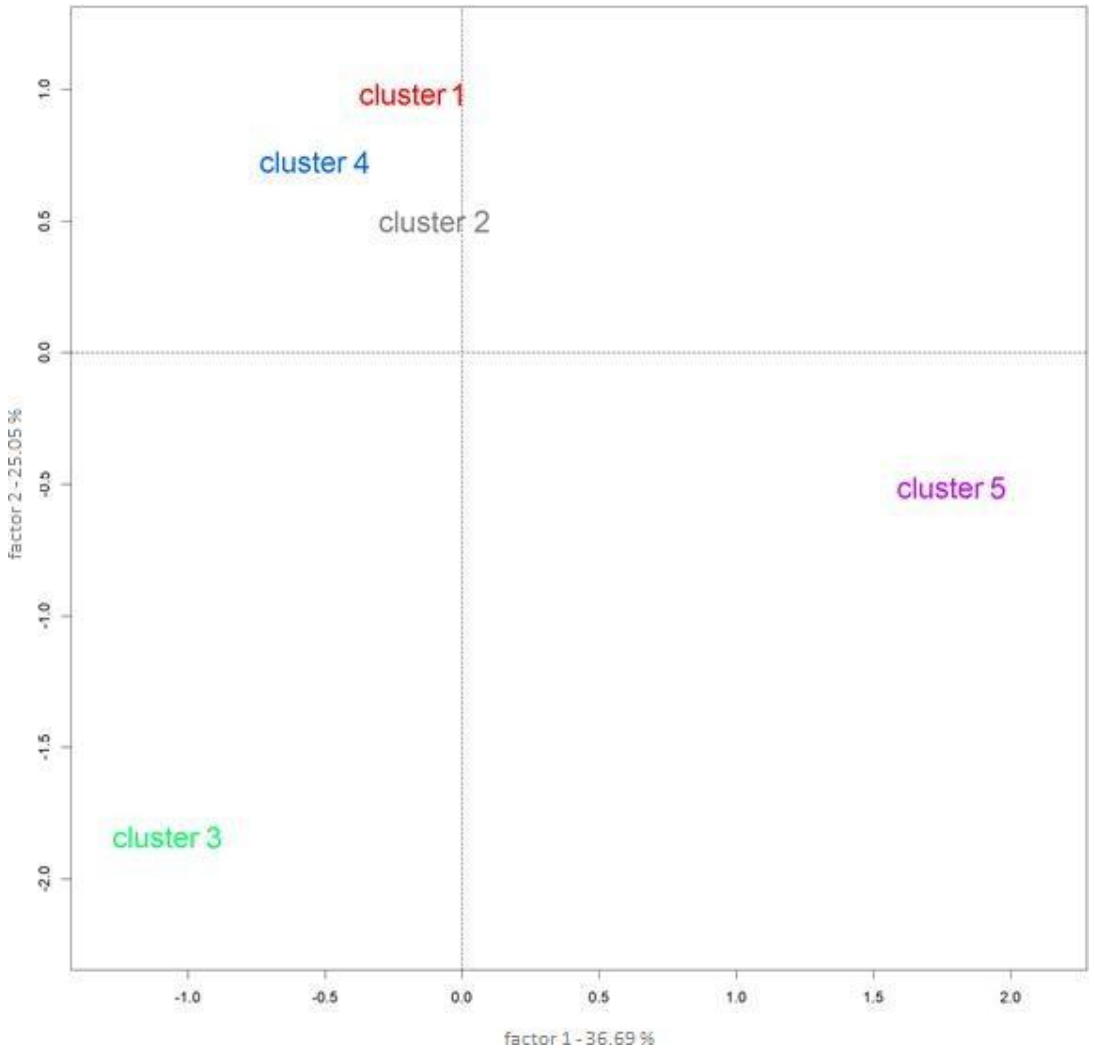


Figure 3 – Co-occurrence and communities for words in Cluster 1

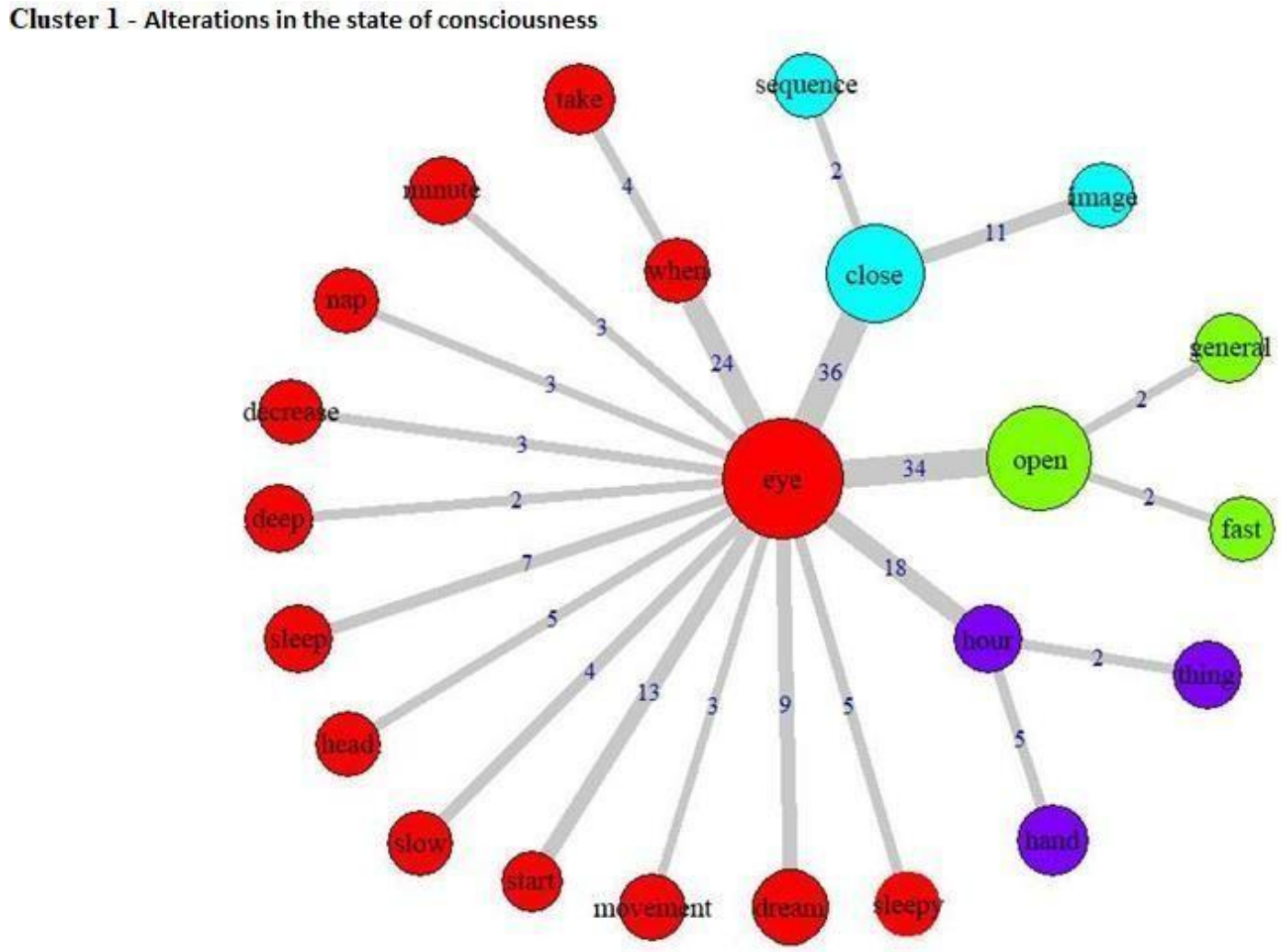


Figure 4 – Co-occurrence and communities for words in Cluster 2

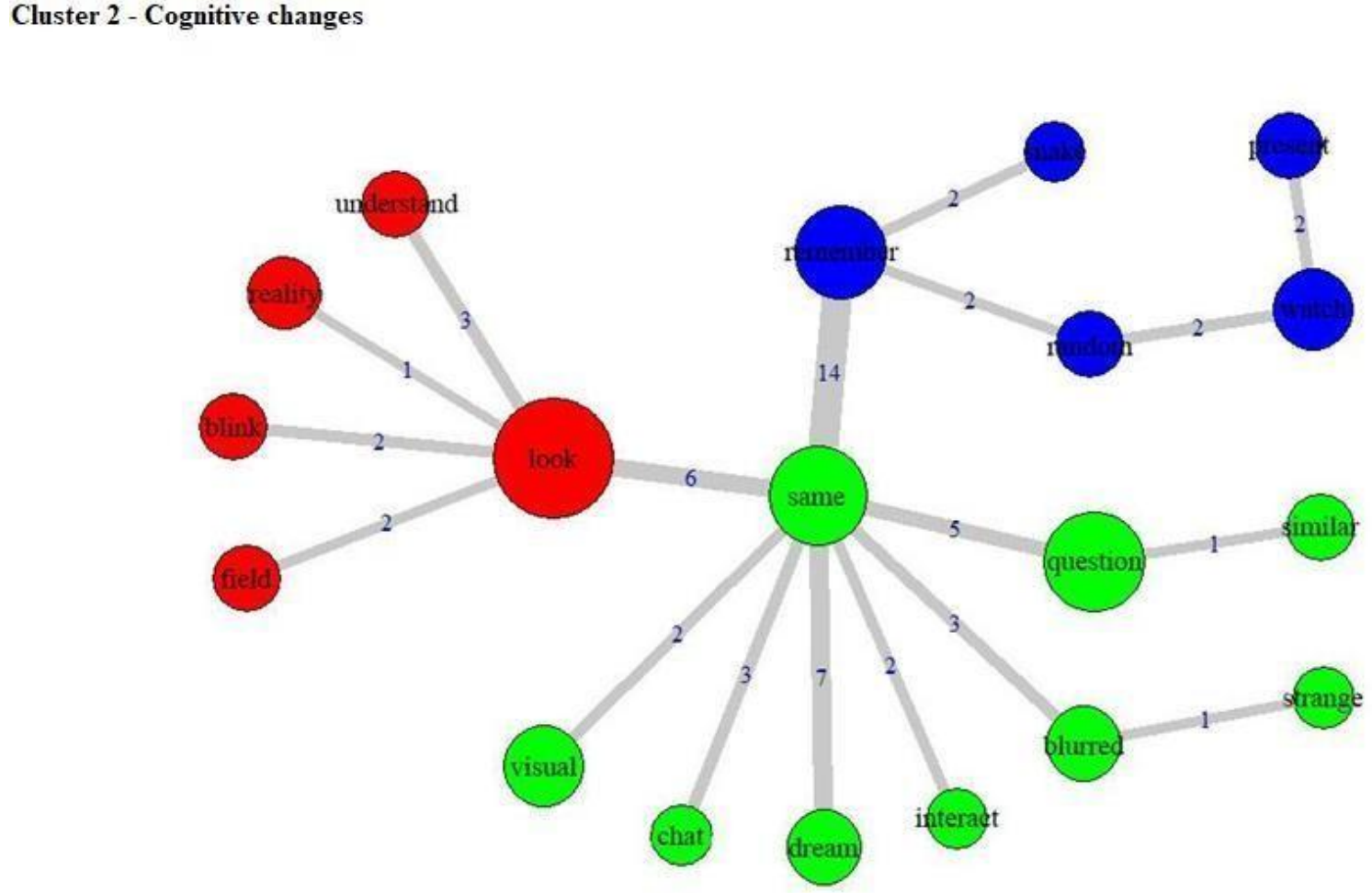


Figure 5 – Co-occurrence and communities for words in Cluster 3

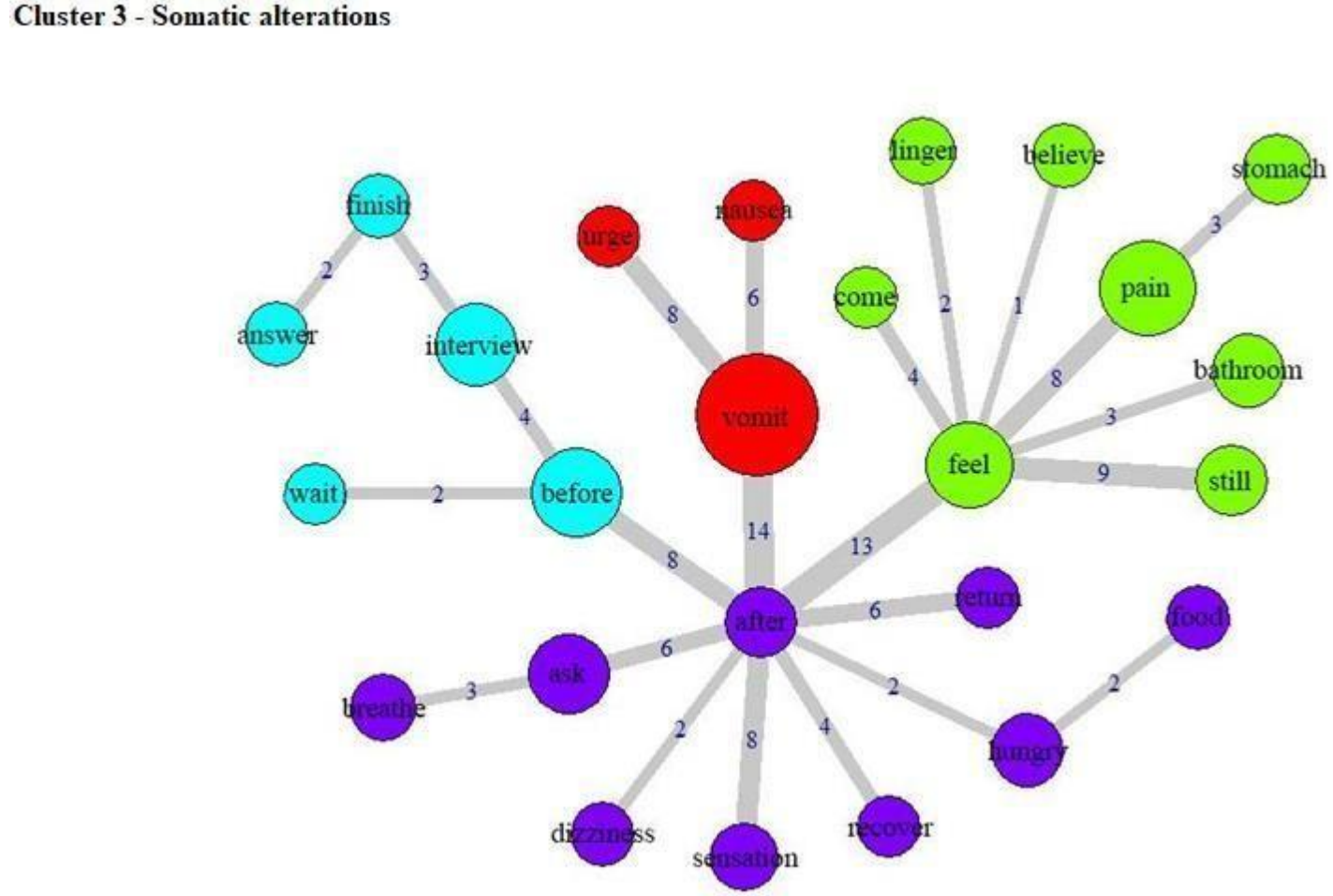


Figure 6 – Co-occurrence and communities for words in Cluster 4

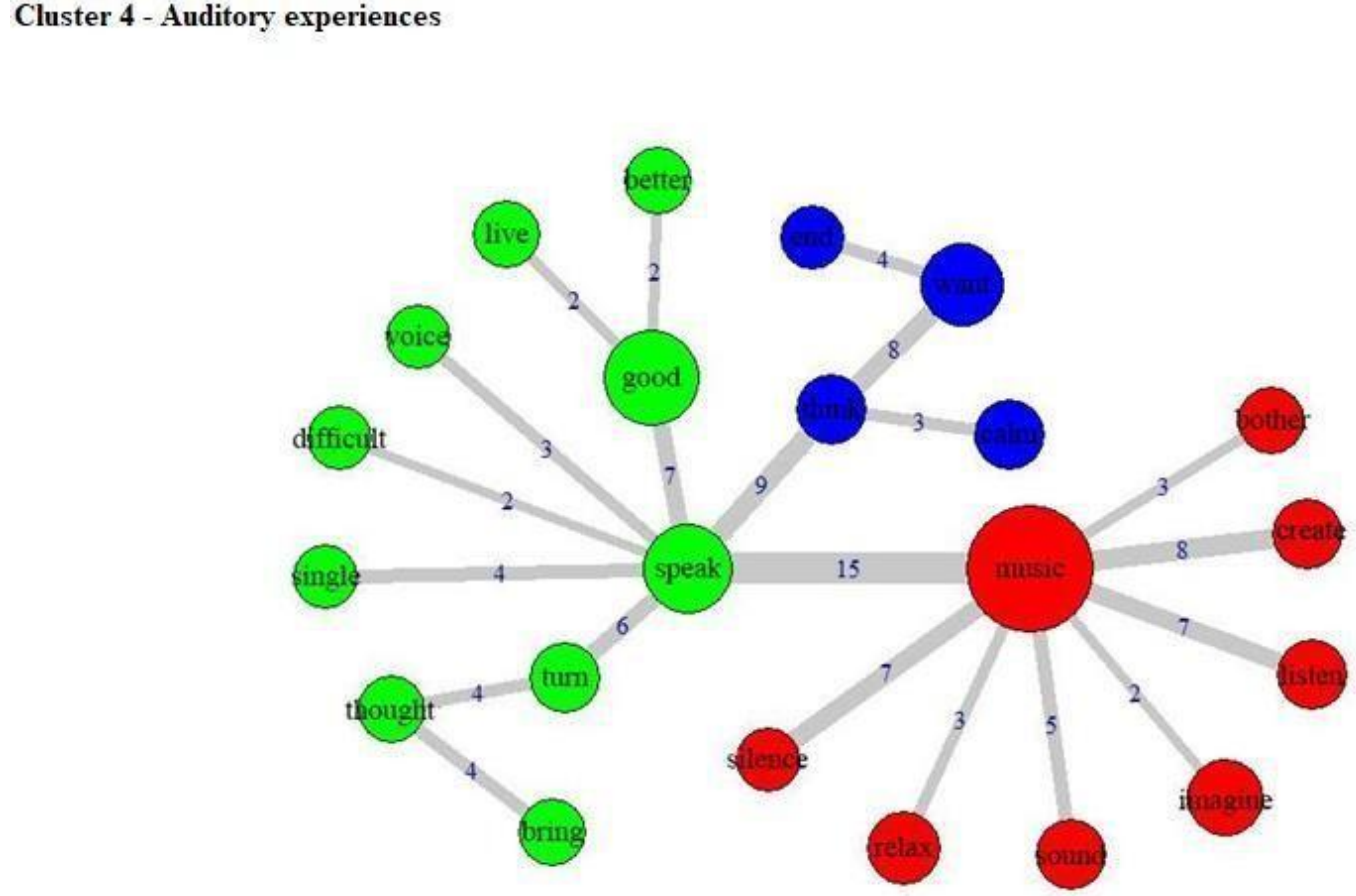
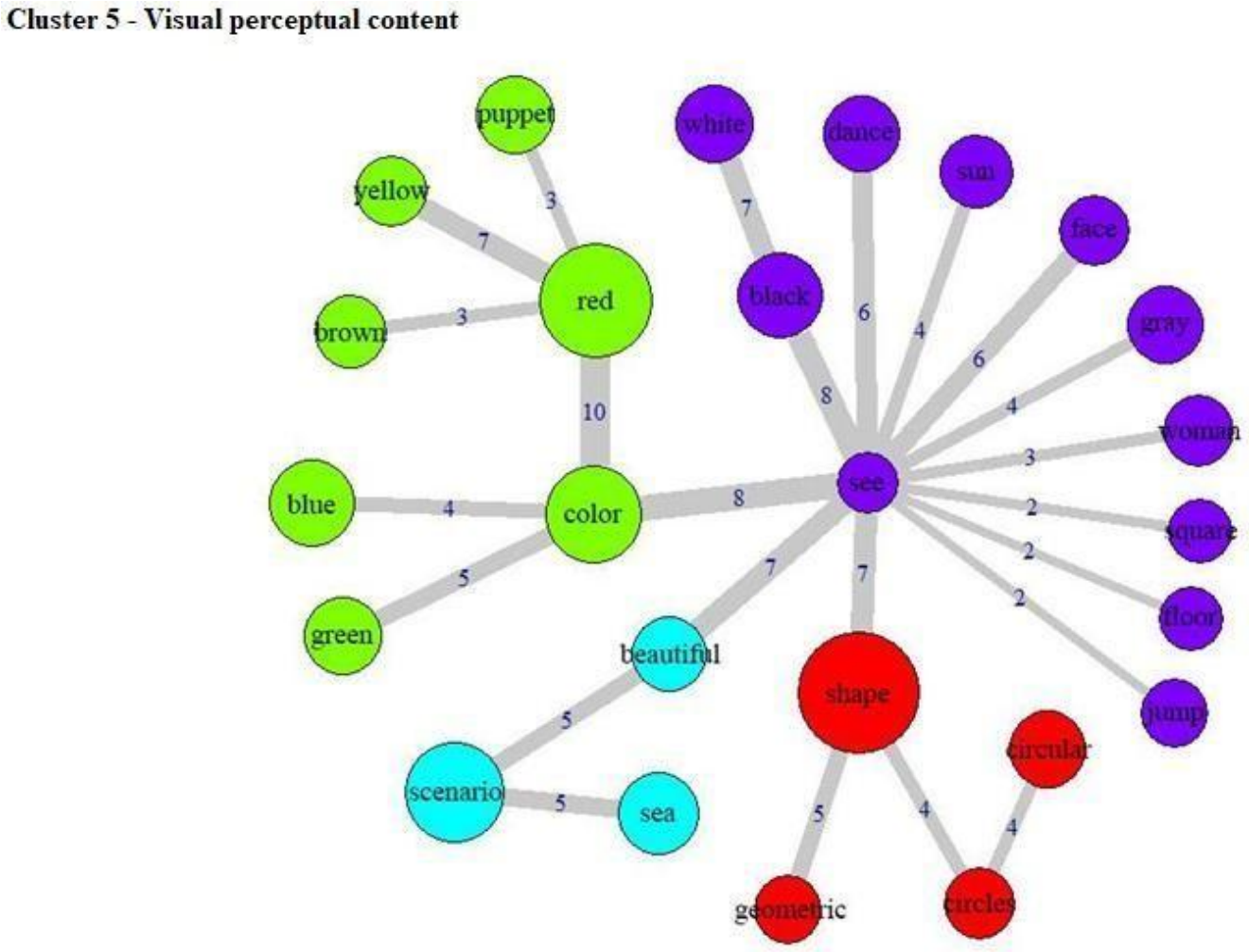


Figure 7 – Co-occurrence and communities for words in Cluster 5



Article 2

Cruz, L.; Longo, M.; Arruda-Sanchez, T.; Mograbi, D. (2025). The impact of ayahuasca experience on health outcomes, beliefs and cognitive factors (manuscript in preparation).

3.2 **THE RELATIONSHIP OF AYAHUASCA EXPERIENCE AND HEALTH OUTCOMES, BELIEFS AND COGNITIVE FACTORS**

Abstract

This study aimed to examine the relationship of prior ayahuasca experience and health outcomes, beliefs and cognitive factors. Participants were categorized into three groups based on their prior use: naïve users, low/moderate users, and high-experience users. Data were collected through a survey before upcoming ayahuasca use, including scales on substance use, depression, anxiety, stress, mental well-being, spiritual well-being, aberrant salience, metaphysical beliefs and nature-relatedness. High-experience users reported lower levels of alcohol use, depression, anxiety, and stress, and higher levels of mental well-being, spirituality, and nature-relatedness. These findings suggest that ayahuasca use, particularly with greater experience, may enhance psychological and spiritual well-being, with possible effects on substance use and cognitive measures being less pronounced. The results highlight the potential positive effects of ayahuasca on diverse health outcomes, as well as changes in cognitive processing, suggesting the need for further investigation into its therapeutic uses.

Keywords: Ayahuasca; mental health; beliefs; cognition; naïve.

Introduction

The leaves of *Psychotriaviridis* and the vine of *Banisteriopsiscaapi* are the two primary components of ayahuasca, an Amazonian brew prepared by decocting these plants. The leaves contain N,N-dimethyltryptamine (DMT), a psychoactive alkaloid with serotonergic effects, which acts as an agonist at the 5-HT2A receptors, similar to other classic psychedelics. In contrast, the vine contains monoamine-oxidase inhibitors (MAOIs) that inhibit the metabolism of DMT by the liver and gut, allowing it to reach the central nervous system (Domínguez-Clavé et al., 2016; Ruffell et al., 2023). These distinct pharmacological components work synergistically, enabling the psychoactive effects of ayahuasca.

Although ayahuasca shows potential for addressing various mental health conditions, the most consistent findings so far relate to its effectiveness in treating depression (e.g. Palhano-Fontes et al., 2019; Sanches et al., 2016). Additional research has explored its use for conditions such as anxiety, substance use disorders, grief, eating disorders, and post-traumatic stress disorder, though the evidence for these is less extensive (Maia et al., 2023).

In the context of depression, research has particularly focused on understanding the acute, subacute, and long-term effects of the substance, along with its safety and efficacy (Palhano-Fontes, 2019; Sanches, 2016; Osório, 2015). There are also studies exploring outcomes related to anxiety and associated constructs, but the results remain inconsistent (Giovannetti et al., 2020; Santos et al., 2007; Dos Santos et al., 2021). Observational studies have also reported lower rates of substance use, particularly alcohol, tobacco, and cocaine, as well as reduced cravings in patients with SUD following ayahuasca use (Berlowitz et al., 2019; Thomas et al., 2013). Furthermore, survey data also suggest a similar trend, showing reductions in alcohol and tobacco consumption (Perkins et al., 2022; Daldegan-Bueno et al., 2022).

In addition to its health effects, ayahuasca has also been linked to changes in personal beliefs and spiritual experiences. Trichter (2009) found that individuals who reported higher peak experiences during an ayahuasca ceremony also showed greater scores on mysticism scales, suggesting a potential connection between intense psychedelic experiences and shifts in spirituality. Furthermore, ayahuasca has been associated with changes in self-awareness (Mograbi et al., 2024), autobiographical memory (Bouso et al,

2013), and emotional regulation (Arruda-Sanchez et al., 2024). These shifts in worldview and sense of self may be particularly significant when ayahuasca is consumed in ritualistic contexts, where the experience is often deeply intertwined with cultural and spiritual frameworks (Pontual et al., 2022; Apud et al., 2023). However, further exploration is needed to better understand how ayahuasca influences belief systems, especially in naturalistic settings.

Beyond health and beliefs outcomes, psychedelics have been suggested to influence various cognitive processes (Bălăeț, 2022), such as potential effects of ayahuasca on cognitive flexibility (Murphy-Beiner & Soar, 2020) and enhanced working verbal and visuospatial memories (Fonseca et al., 2024). Additionally, ayahuasca intake has been linked to neural activation in areas associated with interoception, memory, emotions, and self-awareness (Riba et al., 2006; Mograbi et al., 2024). Nevertheless, while promising, these findings are still preliminary, and further research is needed to explore these cognitive effects more comprehensively.

One important limitation of existing studies, however, is that most involved individuals with prior experience with the substance. According to Dos Santos (2016), there is a need for research involving naïve users, as the majority of studies in real-life settings focus on those with previous exposure. First-time users can provide valuable insights into the effects of the substance on unadapted brains, with lower tolerance, leading to a more comprehensive assessment of the experience. Additionally, comparing naïve users with intention to use versus users with low and high experience mitigates, in part, sampling biases, allowing the exploration of the effects of frequent use on participants with a similar psychological profile.

Additionally, a growing number of clinical studies with ayahuasca rely on randomized controlled trials and open-label designs (Gonçalves et al., 2023; Maia et al., 2023). While these methodologies are known for their high level of experimental control, they have inherent limitations. In particular, samples in these studies tend to be stringently selected, for example, avoiding people with family or personal history of psychiatric disorders. This may limit knowledge on how the substance acts in real-world settings.

One promising approach to achieving this is through naturalistic (non-laboratory) studies. These studies assess participants in their usual environments without manipulating experimental variables, allowing users to consume the substance in familiar contexts and

preserving all elements present during their regular use. This method enables a more authentic and contextualized evaluation of the reported experiences.

Despite the growing body of research, few studies have explored the experiences of naïve ayahuasca users, particularly in naturalistic settings (e.g., Perkins et al., 2021; Perkins et al., 2024). Therefore, the current article analyses data obtained from a survey of people about to use ayahuasca. and aims to examine the effect of previous ayahuasca experience on health outcomes, beliefs, and cognitive factors. By exploring how these dimensions are influenced by ayahuasca experience, the research aims to provide insights into its long term and continued effects.

Methods

Procedures

This study is part of an observational project investigating the effects of ayahuasca use in naturalistic contexts (mostly in rituals). For the current study, the sample consisted of individuals who indicated they were about to use ayahuasca in the near future. Data were collected online via SurveyMonkey and Gorilla platforms.

Participants

The sample included Brazilian individuals aged between 18 and 65 years, who planned to use ayahuasca soon. Participants provided responses to online questionnaires a week before ayahuasca consumption. Inclusion criteria were the intention to use ayahuasca and the capacity to answer the questionnaires (e.g., literacy and online access). The study was advertised through social media, online ads, and contact with ayahuasca user groups.

A total of 751 individuals completed sociodemographic data, but not all participants provided full measures. For questionnaire data, sample sizes varied due to missing or invalid responses. Only complete datasets were analyzed, with the final sample consisting of 634 individuals.

Considering the main purpose of the article, namely, to explore the relationship of ayahuasca experience and different outcomes, the sample was divided into three groups: naïve participants, participants with low to moderate experience with ayahuasca (1 to 20

previous uses), and participants with high experience (21 or more uses). The naïve group contained 64 participants. The low-to-medium-experience group had 291 participants, and the high-experience group had 279 participants. These categories were adopted considering not only the previous experience of users, but also the need to power the analyses with sufficient numbers in each subgroup.

Instruments

In addition to sociodemographic data (age, gender, educational level, sexual orientation, income, and marital Status), the following instruments were used:

- Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST; Henrique et al., 2004): The ASSIST evaluates the use of substances such as alcohol, tobacco, and other drugs. It consists of questions about usage, frequency, intense cravings, related problems (health, social, legal, financial), impact on behavior, third-party concerns, and attempts to control. The ASSIST has 7 main questions, with sub-items for each substance class, totaling 10 substance classes. In the current study, a shortened version of the scale, focusing on alcohol and tobacco, was used.

- Depression, Anxiety, and Stress Scale-21 (DASS-21; Patias et al., 2016): This 21-item scale assesses levels of depression, anxiety, and stress, based on experiences from the past few weeks. Each statement is evaluated on a scale from 0 (symptom did not occur) to 3 (symptom occurred most of the time). The questions address symptoms such as difficulty relaxing, feeling nervous, worried, irritated, or unable to have positive thoughts.

- Warwick-Edinburgh Mental Well-Being Scale (WEMWBS; Tennant et al., 2007; Santos et al., 2015): The 14-item WEMWBS evaluates mental well-being, focusing on feelings and thoughts from the past 14 days. Participants indicate the frequency with which they felt a certain way, using a 5-point response scale ranging from "never" to "always." The scale addresses aspects such as optimism, feelings of usefulness, relaxation, interest in others, and emotional connection with the self.

- Aberrant Salience Inventory (ASI; Cicero, Kerns, & McCarthy, 2010): This instrument with 29 item investigates attitudes and life experiences related to the perception of special meanings in trivial events or unusual psychological states. Participants are asked to provide binary (yes/no) responses to questions such as the meaning of seemingly

insignificant details or the feeling of being close to a great revelation or power. The scale is designed to identify periods of heightened perception and mystical experiences.

- Metaphysical Beliefs Questionnaire (MBQ; Timmermann et al., 2021): This 9 item questionnaire investigates metaphysical beliefs related to the nature of consciousness and reality. The statements are answered on a scale from 1 to 7, ranging from "Strongly disagree" to "Strongly agree." The focus is on beliefs about the unification of the universe, the material or scientific explanation of reality, and the interaction between human consciousness and the material world.

- Open-minded Cognition Scale (OMCS; Price et al., 2015): This 6 item scale assesses the willingness to consider multiple points of view and ideas. It measures openness to hearing different opinions and patience for dealing with opposing arguments. Participants evaluate on a scale from 1 (totally agree) to 7 (totally disagree) how much they agree with statements such as "I am open to considering other viewpoints" and "I generally ignore messages I disagree with."

- WHO Quality of Life Spirituality, Religiousness, and Personal Beliefs (WHOQOL-SRPB BREF; Zimpel et al., 2019): The abbreviated version of this scale has 9 item and investigates how spiritual, religious, and personal beliefs affect quality of life. The questions are applicable to a wide range of beliefs and address themes such as the sense of purpose in life, the help received from spiritual forces in difficult times, and inner peace. Responses are given on a scale from 1 to 5, reflecting the degree of importance and influence these beliefs have on the participant's life.

- Short Version of the Nature Relatedness Scale (NR6; Nisbet & Zelenski, 2013; Longo et al., submitted): This 6-item scale assesses emotional and behavioral connection to nature and the environment. The statements are answered on a scale from 1 to 5, ranging from "Strongly disagree" to "Strongly agree." It measures how much the individual values nature, reflects on the environmental impact of their actions, and considers nature as part of their spirituality.

Data Analysis

Data analysis was conducted using Stata software (version 18.0) and IBM SPSS Statistics 29. As indicated, the sample was divided into three groups based on prior ayahuasca use: naïve, low/moderate, and high experience. These groups were first compared in terms of sociodemographic characteristics, including gender, age, educational level, income, and marital status. Sociodemographic variables were dichotomized as follows: gender (male/female), educational level (with higher education/without higher education), income (Classes D and E: up to USD 660 / Classes A, B, and C: above USD 660, according to the Brazilian classification system), and marital status (married or in a stable union / widowed, single or divorced). Age was analyzed as a continuous variable. Nominal variables were analyzed using the chi-square test, with the exception of age.

For the main analysis, Multivariate Analysis of Variance (MANOVA) was used to assess differences in dependent variables across the three groups. The following dependent variables were included: ASSIST (tobacco and alcohol); DASS-21 (depression, anxiety and stress); WEMWBS; ASI, MBQ, OMCS, WHOQOL SPRB BREF and NR6. For all scales and subscales total scores were used.

Box's M test was performed to evaluate the equality of covariance matrices between the group. For significant dependent variables in the MANOVA, follow-up ANOVAs were performed, with Benjamini-Hochberg correction to control for Type I error (adjusting p-values for the 11 variables included in the model). Effect sizes were reported as partial eta squared (η_p^2). For significant ANOVAs, post hoc pairwise comparisons, again with Benjamini-Hochberg corrections, were calculated.

Ethical issues

All participants provided informed consent. The study was approved by the research ethics committee of the Institute of Psychiatry of the Federal University of Rio de Janeiro (IPUB-UFRJ; CAAE: 58002422.5.0000.5263).

Results

Sample characteristics

The sociodemographic data of the participants are presented in Table 1. There were no significant differences for age ($F(2, 631) = 1.76$, $p = .174$), gender ($\chi^2(2) = 1.08$, $p = .582$), education ($\chi^2(2) = 0.47$, $p = .789$), sexual orientation ($\chi^2(2) = 5.99$, $p = .050$), income ($\chi^2(2) = 1.60$, $p = .449$), and marital status ($\chi^2(2) = 0.91$, $p = .633$).

MANOVA

Box's M test of equality of covariance matrices was significant (Box's M = 291.952, $F(132, 101249.382) = 2.12$, $p < .001$), suggesting heterogeneity of covariances across groups. The analysis was still conducted because MANOVA is robust to violations of this assumption with larger sample sizes (Olson, 1976). Additionally, Pillai's Trace, the most conservative method in cases of heterogeneity of variances (Ateş et al., 2019), was used.

The effect of the independent variable (ayahuasca experience) on the dependent variables was significant (Pillai's Trace = 0.15, $F(22, 1244) = 4.52$, $p < .001$,$\eta_p^2 = .07$).

ANOVAs

No significant effects were observed for the ASSIST tobacco subscale ($F(2, 631) = 1.40$, $p = .247$, $\eta_p^2 < .01$) or the OMCS ($F(2, 631) = 0.12$, $p = .884$, $\eta_p^2 < .01$). Significant effects were found for the ASSIST alcohol subscale ($F(2, 631) = 8.11$, $p < .001$, $\eta_p^2 = .02$), with pairwise comparisons indicating lower scores for the experienced group in relation to naïve ($p = .009$) and low experience groups ($p = .008$), but no difference between naïve and low experienced participants ($p = .568$).

Regarding the DASS21 Depression subscale, the analysis also indicated a significant effect ($F(2, 631) = 16.59$, $p < .001$, $\eta_p^2 = .05$), with pairwise comparisons showing lower scores for the experienced group compared to the naïve group ($p < .001$) and the low experience group ($p = .002$). Additionally, scores were lower for the low experience group compared to the naïve group ($p = .007$).

For the DASS21 Anxiety subscale, a significant effect was also observed ($F(2, 631) = 5.51$, $p = .004$, $\eta_p^2 = .02$). Pairwise comparisons indicated lower scores for the experienced

group compared to the naïve group (p = .015), but no differences were found between the experienced and low experience groups (p = .296) or between the low experience and naïve groups (p = .149).

The DASS21 Stress subscale demonstrated a significant effect (F (2, 631) = 12.64, p = .001, η_p^2 = .04). Scores were lower for the experienced group compared to the naïve group (p < .001) and the low experience group (p < .001), with no significant difference between the low experience and naïve groups (p = .133).

For the WEMWBS scale, a significant effect was found (F (2, 631) = 18.82, p <.001, η_p^2 = .06). Pairwise comparisons showed higher scores for the experienced group compared to the naïve group (p < .001) and the low experience group (p < .001). No differences were observed between the low experience and naïve groups (p = .095).

Regarding the WHOQOL SRPB BREF scale, the analysis revealed a significant effect (F (2, 631) = 36.89, p = .001, η_p^2 = .10). Pairwise comparisons indicated higher scores for the experienced group compared to the naïve group (p < .001) and the low experience group (p < .001). Additionally, higher scores were observed for the low experience group compared to the naïve group (p < .001).

The ASI scale also demonstrated a significant effect (F (2, 631) = 4.46, p = .012, ηp^2 = .01). Pairwise comparisons indicated no significant differences between the high experience and low experience groups (p = 1), nor between the high experience and naïve groups (p = .074). However, there was a significant difference between the low experience and naïve groups (p = .027).

For the NR6 scale, a significant effect was observed (F (2, 631) = 8.22, p < .001, η_p^2= .02). Scores were significantly higher for the experienced group compared to the naïve group (p < .001), but the comparison between the experienced and low experience groups did not reach statistical significance (p = .068). No significant difference was found between the low experience and naïve groups (p = .073)

Finally, the MBQ scale presented a significant effect (F (2, 631) = 4.70, p = .009, η_p^2 = .01). Pairwise comparisons showed higher scores for the experienced group compared to the naïve group (p = .021), but no differences were observed between the experienced and low experience groups (p = .092) or the low experience and naïve groups (p = .859).

The graphs presented below show the means and standard errors for the different groups, along with the p-values and effect sizes (ηp^2) for each scale. Statistical differences

between groups are also indicated.

[PLEASE INSERT FIGURE 1 HERE]

Discussion

This study investigated the impact of ayahuasca on health, cognitive and beliefs variables, by comparing users with different levels of prior experience. Significant effects were observed for substance use (ASSIST Alcohol subscale), psychological distress (DASS-21 Depression, Anxiety, and Stress subscales), mental well-being (WEMWBS), spiritual quality of life (WHOQOL SRPB BREF), aberrant salience (ASI), metaphysical beliefs (MBQ), and nature-relatedness (NR6). High-experience users consistently showed lower levels of alcohol use, depression, anxiety, stress, alongside higher levels of mental well-being, spirituality, religiosity, personal beliefs, quality of life, metaphysical beliefs, and nature-relatedness compared to naïve users. Differences between the low/moderate experience group and other groups were observed but were generally less pronounced. For example, low-experience users scored lower on depression compared to naïve users but did not differ significantly on other measures, such as beliefs and religiosity. No significant differences were found for the ASSIST Tobacco subscale or the OMCS.

The largest effect size, with highly significant differences between all groups, was observed for the WHOQOL SRPB BREF scale, which assesses how spiritual, religious, and personal beliefs affect quality of life. This finding underscores the strong association between ayahuasca use and spiritual quality of life. These results align with prior research using this questionnaire in populations engaged in practices such as ayahuasca ceremonies (e.g., Rush et al., 2024; Giovannetti et al., 2020). Additionally, the WEMWBS, which measures mental well-being, also showed a moderate effect size, with experienced users reporting significantly higher scores compared to both naïve and low/moderate users. Ayahuasca seems to have a broad impact on mental well-being, as evidenced by studies exploring various related constructs. For instance, Perkins et al. (2022) identified significant increases in variables such as positive mood, self-efficacy, authentic living, extraversion, agreeableness, open-mindedness, spirituality, and satisfaction with relationships. However, it is also possible that individuals with higher levels of well-being are more likely to consume ayahuasca, which could influence these outcomes. Although ayahuasca may influence open-mindedness, this effect was not observed in our data. Similarly, Houle (2021) reported that ayahuasca consumption may influence mindfulness and is linked to benefits for self-acceptance and overall well-being.

The significant effects observed for depression, approaching a medium effect size, are consistent with the literature. There were significant differences for all groups, which aligns with research suggesting the potential antidepressant effects of ayahuasca (e.g., Sanches et al., 2016; Palhano-Fontes et al., 2019). Findings from Jiménez-Garrido et al. (2020) further support this, showing that long-term ayahuasca users report lower levels of depression and higher quality of life scores compared to naïve users. While the anxiety and stress results were also significant, effect sizes were smaller, suggesting that while ayahuasca may offer benefits for mood regulation, its anxiolytic and anti-stress effects are less robust or consistent. These findings are consistent with studies showing mixed results regarding the effectiveness of ayahuasca in reducing anxiety (e.g., Osório et al., 2015; Santos et al., 2007; Dos Santos et al., 2016), and highlight the need for further research to better understand the potential of ayahuasca in managing stress.

In our analysis, no statistically significant differences were found between groups on the ASSIST Tobacco subscale. Studies such as Daldegan-Bueno et al. (2022) suggest that ayahuasca may serve as a potential tool for smoking cessation, with its effects possibly mediated by mystical experiences. Conversely, significant differences were found on the ASSIST Alcohol subscale, although the effect sizes were small. Results indicated that experienced users reported significantly lower scores compared to both naïve and low-experience participants, suggesting lower levels of problematic alcohol use among experienced ayahuasca users. No significant differences were observed between naïve and low-experience participants. This supports the idea of a potential protective effect of ayahuasca use on alcohol consumption, particularly among experienced users. Thomas et al. (2013) reported self-reported declines in alcohol, tobacco, and cocaine use following ayahuasca-assisted therapy, though statistically significant reductions were observed only for problematic cocaine use. Altogether, these findings underscore the potential of ayahuasca in supporting behavioral changes related to substance use, although the effects on tobacco consumption may be variable and influenced by individual or contextual factors. Further research is needed to better understand the specific mechanisms and conditions under which ayahuasca may aid in smoking cessation and reduce problematic alcohol consumption.

Differences in cognitive variables had small effect sizes or were non-significant. High-experienced ayahuasca users showed no significant differences in ASI scores compared to low-experienced users, suggesting similar tendencies in attributing aberrant salience to irrelevant stimuli. However, low-experienced users demonstrated significantly lower

scores compared to naïve users, indicating a potential difference in how they perceive the relevance of stimuli. No significant differences were observed between high-experienced and naïve users. Pasquini et al. (2020) found that ayahuasca increased connectivity within the salience network and between the salience and default mode networks 24 hours after use, with these changes correlating with altered somesthesia and affect. Our findings may suggest that these changes are particularly pronounced in users with low experience when compared to naïve users, which may represent a potential shift in the perception of salience early in ayahuasca use. However, no evidence of further adaptation was observed in users with higher experience, as no significant differences were found between the high-experience and low-experience groups. The link between psychedelics and aberrant salience has been explored previously, with findings in the context of LSD indicating a correlation between salience and mystical experiences. It has been suggested that the link between the psychotic and therapeutic models of psychedelics lies in mystical experiences (Wießner et al., 2023).

No significant differences were observed on the OMCS. While ayahuasca has been associated with possible cognitive changes and enhanced cognitive flexibility in some studies (Murphy-Beiner & Soar, 2020), the lack of significant findings in this context may reflect the complexity of cognitive outcomes, which can depend on factors such as the type of cognitive measure used, individual differences, or the specific ceremonial and experiential context. Further research is warranted to explore how ayahuasca influences cognitive functions across different user profiles and settings. Regarding beliefs, the results for the NR6 and MBQ scales revealed significantly higher scores for high-experience users compared to naïve users, with small effect sizes. While statistically significant, these findings suggest modest practical differences.

This study has several limitations. First, the cross-sectional design limits the ability to establish causal relationships between ayahuasca use and the observed outcomes. Longitudinal or experimental designs are necessary to clarify the temporal dynamics of these effects. Additionally, while the sample size was large and allowed detecting of group differences even in the cases of very small effect sizes, the imbalance in group sizes, with a considerably larger number of low-experienced and high-experienced users compared to naïve participants, is a limitation. While the study provides insights into a Brazilian sample, incorporating international samples in future research could enhance the generalizability of the findings. The reliance on self-reported measures also presents a limitation, as these are subject to response biases. Integrating objective methods, such

as behavioral tasks or physiological measures would strengthen future studies.

Despite these limitations, this study sheds light on the impact of ayahuasca use on mental health, beliefs, and cognitive factors. The findings align with previous research, suggesting higher scores in spiritual well-being scales among experienced users, alongside the potential antidepressant effects of ayahuasca. These results underscore the importance of further investigating ayahuasca's potential therapeutic benefits and its role in shaping psychological and cognitive outcomes. Furthermore, the significant scores in spiritual well-being scales observed in this study highlight the need to consider this dimension as a potential therapeutic outcome in future clinical research.

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Competing interests

The author(s) declare no competing interests.

Data availability statement

The dataset used for the current study is available from the corresponding author on reasonable request.

Figure

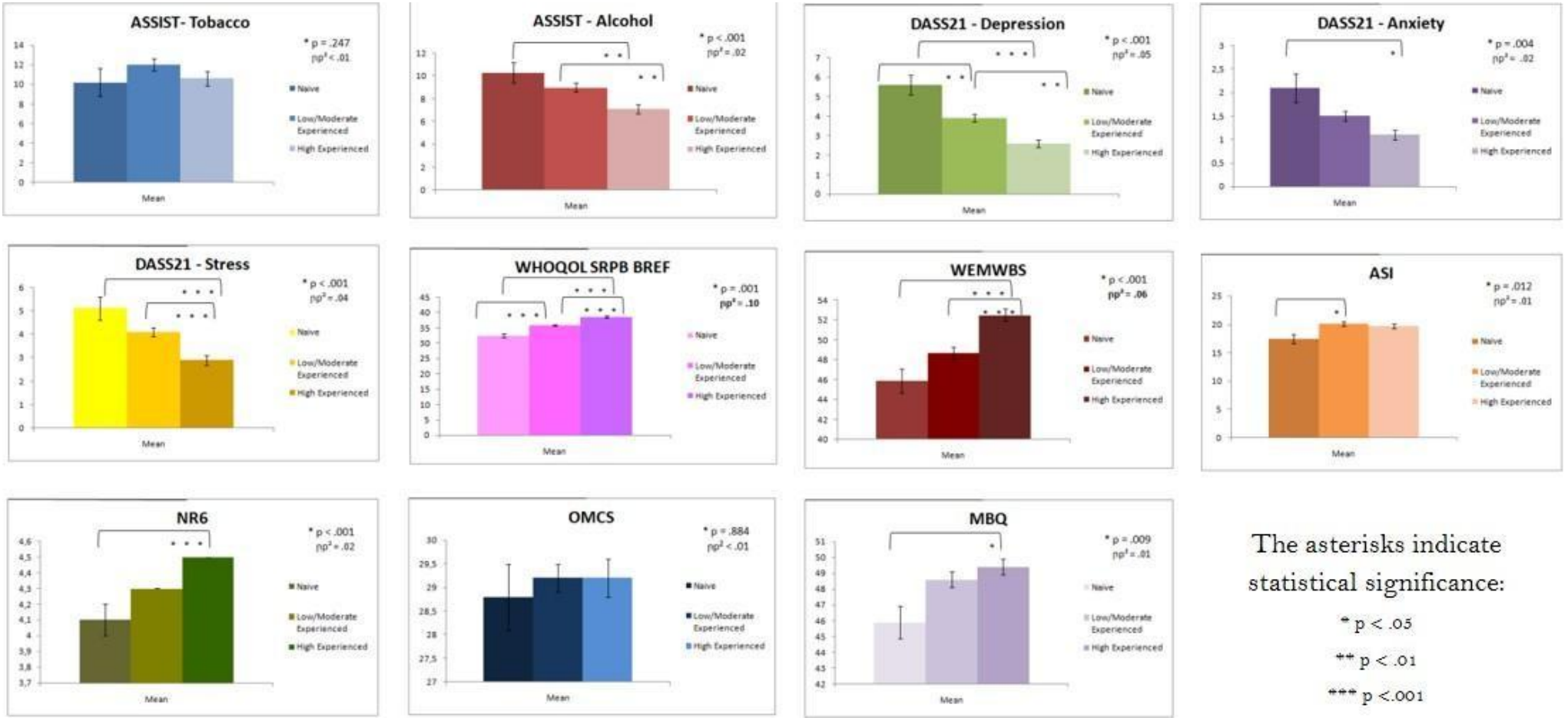
ASSIST- Tobacco
* p = .247
ηp² < .01
Naive
Low/Moderate Experienced
High Experienced
Mean
ASSIST - Alcohol
* p < .001
ηp² = .02
DASS21 - Depression
* p < .001
ηp² = .05
DASS21 - Anxiety
* p = .004
ηp² = .02
DASS21 - Stress
* p < .001
ηp² = .04
WHOQOL SRPB BREF
* p = .001
ηp² = .10
WEMWBS
* p < .001
ηp² = .06
ASI
* p = .012
ηp² = .01
NR6
* p < .001
ηp² = .02
OMCS
* p = .884
ηp² < .01
MBQ
* p = .009
ηp² = .01
The asterisks indicate statistical significance:
* p < .05
** p < .01
*** p <.001

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Table

Table – Background variables divided by group

Variable	Naïve (n = 64)	1 to 20 uses (n = 291)	21+ uses (n = 279)
Age*	40.9 (11.01)	39.7 (9.3)	41.3 (10.05)
Gender (women/men); mv = 5	43/21	200/88	181/96
Higher education (with/without);	50/14	234/57	228/51
Sexual Orientation (heteross./LGBT+)	53/11	206/85	217/62
Income (low/medium or high)	18/46	65/226	73/206
Marital Status (single widow. or div /married/)	36/28	168/123	150/129

Analysis of differences in the gender variable using chi-square test; other analyses using t-tests

* Mean and Standard Deviatio

4. Discussion

This dissertation examined the effects of ayahuasca on naïve users and the impact of previous experience of ayahuasca, focusing on subjective experiences, health outcomes, beliefs, and cognitive factors. With two complementary studies, this research explored self-reported experiences of individuals with and without depression, as well as the broader impact of ayahuasca in naturalistic contexts, addressing gaps in the literature. By centering on individuals with no prior experience with ayahuasca, this work offered valuable insights into how first-time users respond to the substance, also indicating the impact of previous experience on a number of different outcomes. The findings contribute to a deeper understanding of ayahuasca's impact on mental health, and by situating the responses of naïve users within this framework, the dissertation adds to the understanding of ayahuasca's potential as a therapeutic tool, while reinforcing the value of integrating subjective dimensions and naturalistic approaches in future research.

The first study of this dissertation represents a sub-analysis of the data from Palhano-Fontes et al. (2019), exploring the effects of ayahuasca in a sample of nine patients with treatment-resistant depression and 20 healthy individuals. The study identified distinct clusters representing different facets of the ayahuasca experience, namely alterations in the state of consciousness, cognitive changes, somatic alterations, auditory experiences, and visual perceptual content, which were influenced by both sociodemographic and clinical factors. The results highlight central axes of the psychedelic experience, but also suggest that clinical factors, particularly the presence of depression, modulates the way ayahuasca’s effects are perceived. In our study, participants with depression reported more aversive somatic experiences, such as nausea and dizziness, which may reflect negative cognitive biases affecting their perception of physical discomfort during the experience. These findings support the idea that cognitive and emotional biases, driven by specific depressive symptoms, can shape the subjective evaluation of psychedelic experiences.

The second article of the dissertation is an analysis of survey data of people about to consume ayahuasca, with findings consistent with the literature on the effects of ayahuasca on mental health and spiritual well-being. The results indicate that individuals with more experience using the substance report lower levels of alcohol use, depression, anxiety, and stress, as well as higher levels of mental well-being and spiritual quality of life. These findings are particularly relevant when considering the stronger effect sizes
observed for the WHOQOL-SRPB BREF, which assesses how spiritual, religious, and personal beliefs affect quality of life. The relationship between ayahuasca experience and

spiritual well-being underscores the idea that, over time, ayahuasca use may foster significant psychological and spiritual benefits. (Rush et al., 2024; Giovannetti et al., 2020) However, the effects observed on cognitive variables were more modest, with smaller differences between groups and some variables showing no statistically significant differences.

Both studies reveal the crucial role of individual differences, particularly in terms of prior experience with the substance, in shaping the outcomes of ayahuasca use. In the first study, the presence of depression was found to influence the perception of somatic discomforts such as nausea and dizziness, aligning with the idea that depression encompasses not only ideational but also somatic symptoms (Kapfhammer, 2006). These findings suggest that individual psychological predispositions, such as depressive symptoms, may shape the subjective experience of ayahuasca, particularly its emotional and somatic dimensions. While the emotional and spiritual effects of ayahuasca appear more consistent in the literature (Arruda-Sanchez et al., 2024; Jiménez-Garrido et al., 2020), differences in cognitive variables observed in the current study were modest, with smaller effect sizes and some non-significant results.

Despite the modest cognitive differences observed, previous research has highlighted the potential of psychedelics, including ayahuasca, to influence cognitive processes. For instance, studies have reported increased cognitive flexibility (Murphy-Beiner & Soar, 2020) and enhanced working verbal and visuospatial memories (Fonseca et al., 2024), both with large effect sizes. Additionally, ayahuasca has been associated with neural activation in regions related to interoception, memory, emotions, and self-awareness (Riba et al., 2006; De Araujo et al., 2012; Schenberg et al., 2015). These findings suggest that cognitive changes may require prolonged use or emerge under specific conditions, such as ritualistic settings or individual psychological contexts. Further research is needed to identify the conditions under which ayahuasca might elicit cognitive benefits and to explore its broader impact on cognition, complementing its emotional and spiritual effects. However, it is important to note that the cognitive constructs employed in these studies differ from those used in the current research. Further investigation is needed to refine these constructs and draw more definitive conclusions about the cognitive effects of ayahuasca.

Findings from the second study, which examined the broader impact of ayahuasca use in naturalistic settings, support the hypothesis that regular ayahuasca use can foster psychological and spiritual growth. Given that most participants had prior ayahuasca experience in ritualistic settings, these results align with theoretical frameworks such as Pontual et al. (2022), which emphasize the critical role of the environment in shaping experiences under ayahuasca. Their study highlights how an appropriate setting can reduce challenging experiences while enhancing transformative and mystical outcomes, underscoring the therapeutic potential of ayahuasca when used in supportive contexts.

The connection between cognitive and emotional responses to ayahuasca, as explored in the first study, also complements the findings of the second study, particularly regarding the role of depressive symptoms. While the first study indicated that individuals with depression reported more aversive somatic experiences, the second study highlighted that ayahuasca use may lead to improvements in emotional well-being over time. This apparent contrast may stem from the purgative phase often associated with ayahuasca experiences. According to Fotiou and Gearin (2019), the therapeutic role of purging should not be dismissed as a mere side effect or rooted in irrational beliefs. Instead, it warrants reconsideration for its potential therapeutic benefits, as it may serve as a meaningful process that integrates physical and psychological healing. For individuals with depression, this purgative stage may be more pronounced, potentially amplifying initial discomfort to the extent that immediate improvements in well-being are not yet perceptible. Over time, however, the process of purging—combined with the supportive, ritualistic context – may mediate these initial challenges, fostering emotional regulation and psychological growth.

Despite the insights provided by this dissertation, several limitations must be acknowledged. Firstly, the cross-sectional design of the studies does not allow for causal inference, limiting the ability to understand long-term changes or the enduring effects of ayahuasca. Additionally, the sample size of the first study was relatively small, which may affect the generalizability of the results. The reliance on self-reports also means the data may be subject to memory biases or perceptual distortions, especially regarding subjective experiences.

This dissertation provides valuable insights into the potential therapeutic applications of ayahuasca, highlighting its impact on psychological well-being and spiritual growth in both naïve and experienced users, as well as its effects on subjective experiences

specifically in naïve users. The findings emphasize the critical role of naturalistic settings in facilitating emotional and spiritual benefits, underscoring the need for further studies exploring these contexts and for direct comparisons between naturalistic and clinical settings. While cognitive effects were modest in this research, they reveal important avenues for future exploration, particularly regarding the interplay between emotional, spiritual, and cognitive processes in shaping therapeutic outcomes. Clinically, these results suggest that the differential responses observed in naïve and experienced users underscore the importance of personalized approaches, considering individual psychological profiles as key factors in treatment planning. Additionally, the findings from naturalistic settings provide critical insights into how supportive and culturally grounded environments may enhance the emotional and spiritual benefits of ayahuasca, offering a framework for designing therapeutic approaches that respect and incorporate these contextual factors. These findings contribute to a deeper understanding of the contextual and individual factors that influence ayahuasca's effects, offering a foundation for future research aimed at optimizing its application in diverse therapeutic and cultural contexts.

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