



# Long-term ayahuasca use is associated with preserved global cognitive function and improved memory: a cross-sectional study with ritual users

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## Abstract

Although several studies have been conducted to elucidate the relationship between psychedelic consumption and cognition, few have focused on understanding the long-term use influence of these substances on these variables, especially in ritualistic contexts. To verify the influence of ritualistic ayahuasca consumption on the cognition of experienced ayahuasca religious users (> 20 years) and beginners (< 3 years), which participated in rituals of the Centro Luz Divina (CLD), a Santo Daime church in Brazil. Observational, descriptive, and cross-sectional study was carried out in which 48 people participated divided into three groups: (a) experienced ayahuasca users (n = 16), (b) beginner ayahuasca users (n = 16) and (c) control group (n = 16). All groups were matched by sex, age, and education and contained 8 women and 8 men. Cognition was assessed with the WASI (intelligence quotient), Digit Span (verbal working memory), Corsi Block-Tapping Task (visuospatial-related and working memory), Rey–Osterrieth Complex Figure test (visual perception, immediate memory), and Wisconsin Card Sorting and Five Digit Test (executive functions). Groups were homogenous in terms of sociodemographic characteristics, with participants presenting average intellectual performance. There was no evidence of cognitive decline amongst ayahuasca users. The experienced group showed higher scores compared to the less experienced group in the Digit Span and Corsi Block-Tapping tasks, which assess working verbal and visuospatial memories respectively. We confirmed the botanical identities of *Psychotria viridis* and *Banisteriopsis caapi* and the presence of the alkaloids both in the plants and in the brew. Short and long-term ayahuasca consumption does not seem to alter human cognition, while long-term use seems to be associated with improvements in aspects of working memory when compared with short-term use.

**Keywords** Ayahuasca · Cognition · Santo Daime · *Banisteriopsis caapi* · *Psychotria viridis*

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## Introduction

Ayahuasca is as a beverage originally used by indigenous and mestizo populations in South America as part of their traditional medicine. It is obtained from the decoction of the bark and stems of the liana *Banisteriopsis caapi* (Spruce ex Griseb.) Morton (Malpighiaceae) and the leaves of the shrub *Psychotria viridis* Ruiz & Pav. (Rubiaceae), and in some parts of Brazil is traditionally consumed within religious rituals. Although there are many religious contexts in which ayahuasca is ritualistically utilized, the most well-known are Barquinha, União do Vegetal (UDV), and Santo Daime, which may be found active in Brazil and many other countries [36].

Regarding ayahuasca's psychoactive composition, *P. viridis* is known to contain the hallucinogenic alkaloid N, N-Dimethyltryptamine (DMT), while *B. caapi* is a source for the  $\beta$ -carbolines harmine (HRM), harmaline (HRL), and tetrahydroharmine (THH) [58]. These substances are indole alkaloids, with DMT presenting a remarkably similar chemical structure to the neurotransmitter serotonin (5-HT), a fact that hints at its serotonergic mechanism of action [12]. More specifically, DMT's effects are believed to result from its agonism at 5-HT<sub>2A</sub> receptors, which are also the main molecular target of psilocybin (found in a variety of fungi, especially from the genus *Psilocybe*), LSD, and mescaline (found in the peyote cactus, *Lophophora williamsii*) [48]. When orally consumed, DMT is rapidly and extensively metabolized by the enzyme monoamine oxidase type A (MAO-A), which renders it inactive through this administration route. However,  $\beta$ -carbolines are selective and reversible inhibitors of this enzyme, which in turn make it possible for DMT to reach the Central Nervous System through this administration route. Moreover,  $\beta$ -carbolines are also known to contribute to the psychoactive effects of ayahuasca, having many mechanisms of action and molecular targets of their own [63]. Therefore, the psychoactive effects of ayahuasca are a result of the synergy between its different chemical components [60].

Preclinical evidence has reported neuroplastic and neuroprotective effects of the alkaloids found in ayahuasca [16, 39], and it is believed that these effects could not only be related with the possible therapeutic effects of the brew but could also be associated with cognitive improvements [22]. A range of neuropsychological variables has been evaluated comparing ayahuasca users with controls, including verbal intelligence (Word Accentuation Test), attention (Trail Making Test), verbal learning (Los Angeles Auditory Verbal Learning Test), short-term memory (Rey–Osterrieth Complex Figure Test), verbal working memory (Wechsler Adult Intelligence Scale) and executive

function (Wisconsin, Stroop, and Tower of London Tests) [3, 8, 9, 19, 29]. None of these works reported detrimental or negative effects on cognition in regular ayahuasca users, including adolescents [19]. On the contrary, compared to controls, Bouso et al. [8] reported better performance in long-term ayahuasca users for executive (Stroop) and working verbal memory (Wechsler Adult Intelligence Scale), while Barbosa et al. [3] reported a better score on a measure of memory (California Verbal Learning Test—CVLT). Moreover, in a study assessing the acute effects of ayahuasca intake in ritual users, 24 ayahuasca users (11 long-term experienced users and 13 occasional users) were assessed in their habitual setting using the Stroop, Sternberg, and Tower of London tasks prior to and following ayahuasca intake. Lower scores in the Sternberg test and a reduction in the response latency time during the Stroop test were observed for both groups, while only occasional users showed increased execution and resolution times and number of movements in the Tower of London test, which was inversely correlated with lifetime ayahuasca use [9]. From a structural perspective, long-term ( $\geq 15$  years) ayahuasca use has been linked with changes in the thickness of the anterior and posterior cingulate cortex and corpus callosum, although there is no direct evidence that these changes are related to cognitive performance alterations [10, 68].

From a therapeutic point of view, acute and long-term consumption of ayahuasca is linked to better mental and physical health and quality of life overall [21, 31]. More specifically, the brew has been evaluated with positive results as a possible treatment for substance use disorders [62, 73], as a rapid-acting antidepressant [21, 53], as an anxiolytic agent [20, 64] and other therapeutic potentials including promoting well-being, positive lifestyle changes, and enhancing coping strategies [34, 51]. Corroborating these results, positive effects on mental health and enhanced cognitive flexibility have all been recently reported with the administration of other psychedelics such as psilocybin and LSD, both in normal and microdosing regimes [23, 52, 56]. Available evidence from laboratory- and hospital-based studies show that these drugs seem to be safe and well tolerated, although there are adverse outcomes, such as headache, nausea, vomiting, confusion, anxiety, dissociation, and increased blood pressure. It is noteworthy to mention that such effects are transient and of mild-to-moderate severity [23, 52, 53, 56, 60]. In the specific case of ayahuasca, evidence from experimental [60] and clinical studies [53] corroborate these findings, showing that the most common adverse effects are transient nausea and vomiting. Evidence from observational studies also show that ayahuasca produces adverse effects. A recent online survey reported that the most common adverse effects were physical (primarily vomiting, 69.9% of the sample) and mental (55.9% of the sample [7]). Interestingly, 88% of the sample considered these mental effects as part of a positive

process of growth, and physical adverse effects were related to older age, having a physical health condition, higher lifetime and last year ayahuasca use, having a previous substance use disorder, and taking ayahuasca in a non-supervised context.

Although promising, current results for ayahuasca's positive effects are mostly preliminary and there is an evident need for further evaluations on its short and long-term safety and tolerability, including from a cognitive perspective. With this in view, the objective of the present study was to verify the influence of ayahuasca consumption on cognition in a ritualistic context among experienced users (more than 20 years of consumption) and beginners (less than 3 years of consumption) who were regularly participating in rituals from the Centro da Luz Divina (CLD) church, located in Piedade, São Paulo, Brazil. Moreover, we also compared the results from the ayahuasca groups with normative and/or standardization data from the tests [25, 32, 33]. For instance, the study by Figueiredo and Nascimento [25] was selected because it is the Brazilian study of standardization of the Wechsler Intelligence Scales for Adults (WAIS) and the Wechsler Intelligence Scale for Children (WISC) tests, that contain the Digits subtest (Digit Span) used in this study. Therefore, due to the lack of reliable Brazilian population studies, we chose this to compare our results. The reason we used Kessels' studies was: (a) standardization of the Corsi Block-Tapping task and normative data, (b) Corsi Block-Tapping task and its association with the WAIS-III Digit Span.

## Materials and methods

### Ethical aspects

This research was approved by the Ethics Research Committee (CEP) of the Federal University of São Paulo (UNIFESP) under registration #2.877.224. All participants signed the Informed Consent Form. We also registered this research within the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SISGEN), under registration #A4A9C67. Both the Chico Mendes Institute for Biodiversity Conservation (ICMBio) and the Biodiversity Authorization and Information System (SISBIO) (under registration #73,895) from the Ministry of the Environment (MMA) granted authorization for the collection and management of biological material of the plants used in ayahuasca.

### Plant material, traditional recipes and sample preparation

*P. viridis* and *B. caapi* samples were collected via dry method [45], in July 2018 in the vicinity of the CLD. They were used in the preparation of the two recipes (First Degree Bevegare—sample 1, and Second Degree

Beverage—sample 2) in the same month and year and analyzed in the present study (Fig. S1). The recipes were recorded through a semi-structured interview [6] with the church leader, where a series of questions about the ways of preparation were asked through open questions to obtain a detailed step-by-step of each recipe. The First Degree Bevegare (sample 1) is prepared with 40 kg of vines (*B. caapi*) and 18 kg of leaves (*P. viridis*), arranged in alternating layers in a pan of 100 L. This is then filled with water and boiled until half the water has evaporated. Separating the resulting liquid from the botanical material gives sample 1. To make the Second Degree Beverage (sample 2), the same procedure is used, but the water is substituted with sample 1. With this in view, sample 2 ends up with a higher alkaloid concentration than sample 1.

The taxonomic evaluation of the collected plants was made by MCHM and CPB. Both were deposited in the Herbarium of the Federal University of São Paulo (HUFSP), Diadema Campus, São Paulo, under voucher numbers HUFSP 424, 427, 428 and 433 for *B. caapi* and HUFSP 423, 425, 426, 429, 430 and 431 for *P. viridis*. After collection, samples from these plants were analyzed in the laboratory. As such, three extracts were prepared: (a) 200 g of *P. viridis* leaves, (b) 200 g of *B. caapi* vine and (c) 200 g of a combination of the two plants. The hot aqueous extraction was performed using a Soxhlet extractor, using 250 mL of distilled water for each extract. The temperature varied between 70 and 90 °C, and the time for each process lasted, on average, 10 h. After this period, the extracts were lyophilized to obtain a powdered dry mass of each extracted material. Chemical Analysis details can be found on the Supplemental Material.

### Study design and sample selection

This was an observational, descriptive, and cross-sectional study. Inclusion criteria consisted of being over 18 years old and being a member of the CLD church. Exclusion criteria included any mental disorder diagnosis. All Santo Daime followers from the CLD church, in the municipality of Piedade – SP, Brazil, were invited to participate. A total of 32 followers agreed to participate, equally distributed into two groups: experienced users with more than 20 years of regularly consuming ayahuasca; and beginner users with less than 3 years of regular ayahuasca consumption. Sampling was done by convenience [24]. Furthermore, we also recruited 16 volunteers from the general population who had never used ayahuasca before for a control group. Therefore, the three study groups comprised 16 volunteers (total  $n=48$ ), with 8 men and 8 women in each group. The control group was paired by sex, age, and education.

## Data collection

Data collection took place between July 2018 and January 2019. A neuropsychological evaluation (see tests below) was applied individually by one of the authors (AMF) in a reserved room on the premises of the church with guaranteed anonymity. The adherents of that church were not under the influence of ayahuasca during the evaluation, which was carried out on average eight days after the last consumption of the drink. The control group was interviewed and evaluated in the researcher's private office. Besides specific scales, semi-structured individual interviews were carried out [6] collecting the following sociodemographic data: frequency of ayahuasca use (lifetime use, last use, current use), age, sex, marital status, educational level, employment status, monthly income, and tobacco (current use) and alcohol use (lifetime use, last year use, last month use, current use) [47, 66].

## Neuropsychological evaluation

### Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI measures general cognitive ability and specific cognitive skills used across a wide age range (6–89 years) and in a variety of contexts. It provides scores on Vocabulary (VC), Similarities (SI), Block design (BD), Matrix Reasoning (MR), Full-Scale Intelligence Quotient (FSIQ), Verbal Intelligence Quotient (VIQ), and Performance Intelligence Quotient (PIQ) [70].

### Digit Span (DS)

Digits is a public domain task [1] that it is also found in test batteries such as the Digit Span (DS) subtest of the Wechsler Intelligence Scales for Adults (WAIS-III), which was adapted for the Brazilian population by Nascimento [46]. It is a range test in which attention span is measured by evaluating the storage capacity of the verbal working memory, corresponding to the maximum range of sequences that the examinee can correctly reproduce both forwards and backward. It also evaluates concentration/focus maintenance and stress tolerance [15, 38].

### Corsi Block-Tapping Task (CBT)

The Corsi Block-Tapping Task [32] is also a span task, considered to be a visuospatial analog to the Digit Span test. This task assesses non-verbal cognitive functions, specifically visuospatial-related and working memory [32, 38].

### Rey–Osterrieth Complex Figure test (ROCF)

The Rey–Osterrieth Complex Figure test was designed by André Rey and adapted and validated for the Brazilian population by Oliveira et al. [49]. This test is used in clinical practice and aims to investigate the neuropsychological functions of visual perception, immediate memory, and some functions of action planning and execution.

### Wisconsin Card Sorting Test-64 (WCST-64)

This test is considered the gold standard in the assessment of executive functions [59, 61]. In the present study, the computerized version (WCST-64) was used.

### Five Digit Test (FDT)

This test is an instrument designed by Sedó [67], which was adapted and validated for the Brazilian population by Sedó et al. [67]. The FDT is a multilingual test used to measure cognitive processing speed, the ability to focus and reorient attention, and executive functions (inhibitory control and cognitive flexibility) and is based on minimal linguistic knowledge such as reading the digits of 1–5.

## Statistical analyzes

The analysis of the sample distribution was performed using the Kolmogorov Smirnov and Shapiro–Wilk tests, using the SPSS 21.0 software. As the sample presented normal distribution, the statistical test multivariate analysis of variance (MANOVA) was used, which also offers some protection against type I error. All neuropsychological test results were treated as dependent variables. Groups (experienced, beginners, and control), sex, and interactions between these variables were considered independent variables. The assumptions of homogeneity of variances were evaluated using the Levene test, as well as the homogeneity of the covariance matrices using the Box test. In the post-hoc analyses, multiple comparisons were adjusted via Bonferroni's method and Tukey's b when the requirements were met. Percentages and other descriptive measures were also extracted for categorical data, and associations were evaluated using the chi-square test. Statistical significance was set at  $p \leq 0.05$ .

## Results

### Chemical analyzes

After taxonomic identification, the plants collected were identified as *Banisteriopsis caapi* (Spruce ex Griseb.) Morton (Malpighiaceae) and *Psychotria viridis* Ruiz & Pav.

(Rubiaceae) as expected. The results for the alkaloid quantification in all samples acquired are shown in Table 1 below.

### Sociodemographic characteristics

Table 2 shows that the sociodemographic data of the control and study groups (experienced and beginner) are homogeneous, as is the distribution by sex. Participants in the control group were matched by sex, age, and education level in relation to the study group, which provided uniformity. There was statistical significance ( $p=0.001$ ) only in the time of ayahuasca use: mean of 26 years and 7 months for the experienced group and mean of 1 year and 3 months for the beginner group. There was no statistical significance between any of the groups regarding the other measures.

*M* mean, *SD* standard deviation; *t*: teste t de student, *F* test ANOVA;  $X^2$  test chi square

\*Significant for  $p \leq 0.05$

<sup>a</sup> $\geq 6$  uses in the last month

<sup>b</sup> $\geq 4$  (women) or  $\geq 5$  (men) uses in the same occasion

### Neuropsychological evaluation

We found significant differences between the control and ayahuasca groups (experienced and beginners) in relation to the weighted scores of the WASI subtests VC [ $F_{(2,47)} = 7,86$ ;  $p < 0,01$ ], SI [ $F_{(2,47)} = 7,09$ ;  $p < 0,01$ ], BD [ $F_{(2,47)} = 5,05$ ;  $p = 0,01$ ], MR [ $F_{(2,47)} = 4,11$ ;  $p = 0,02$ ], VIQ [ $F_{(2,47)} = 8,55$ ;  $p < 0,01$ ], PIQ [ $F_{(2,47)} = 4,76$ ;  $p = 0,01$ ] and FSIQ [ $F_{(2,47)} = 8,31$ ;  $p < 0,01$ ]. Statistical analyzes also found significant differences between control and ayahuasca groups for the FDT [ $F_{(2,47)} = 3,97$ ;  $p = 0,02$ ], ROCF [ $F_{(2,47)} = 9,60$ ;  $p < 0,01$ ], DS [ $F_{(2,47)} = 6,15$ ;  $p < 0,01$ ] and CBT [ $F_{(2,47)} = 4,12$ ;  $p = 0,02$ ]. The WCST-64 test did not show significance with any group. Results are detailed in Table 3 below. In summary, the beginner group showed lower performance than controls for the WASI subtests, reading time of the FDT and Copy total score from the ROCF, while the experienced group showed equivalent performance than controls in most tests.

Table 4 below shows the performance of the Digit Span (DS) task in the control and ayahuasca groups (experienced and beginners) and a comparison to the study by Figueiredo and Nascimento [25], showing the means and standard deviations of the raw scores in the Forward Digit Span (FDS), Backward Digit Span (BDS), the sum and differences between FDS and BDS, and mean ages of participants in both studies. The experienced group (9.9) was better in retaining digits in the FDS, surpassing the beginner group (7.7) and participants from the study by Figueiredo and Nascimento [25] (6.8 and 6.9). The same occurred with digits in the BDS, where the experienced group (5.8) was superior to the beginner group (3.6) and adult participants (4.8) in the study by Figueiredo and Nascimento [25].

Table 5 below presents the performance in the CBT task for the control and ayahuasca groups (experienced and beginner), and a comparison with the studies by Kessels et al. [32] and Kessels et al. [33]. Results are displayed as means and standard deviations for the raw scores of the Corsi Forward (CF), Corsi Backward (CB), CF + CB, the total score, participants' mean age, and proportion between men and women of all studies. Results show that the experienced group had superior performance in the sum of CF and CB compared to the beginner group and Kessels et al. [32] and similar results to Kessels et al. [33]. The experienced group also showed a higher total score than the beginner group and the studies by Kessels et al. [32, 33].

*CF* Corsi Forward, *C*: Corsi Backward

<sup>a</sup>Healthy volunteers

<sup>b</sup>Healthy volunteers aged 50–59 years

### Discussion

In the present observational, cross-sectional study, ayahuasca users showed average intellectual performance compared to controls, with no differences in executive functions and immediate memory. The beginner group showed lower performance than controls for the WASI subtests, reading time of the FDT, and Copy total score

**Table 1** Alkaloid quantification results for all samples analyzed

Sample	DMT (mg/mL)	HRL (mg/mL)	HRN (mg/mL)	THH (mg/mL)
Sample 1	0.19	0.02	0.30	0.28
Sample 2	0.14	0.03	0.42	0.34
<i>B. caapi</i> *	–	0.07	1.06	1.44
<i>P. viridis</i> *	5.43	–	–	–
<i>B. caapi</i> + <i>P. viridis</i> (1:1)*	4.14	0.07	0.15	0.53

*DMT* N, N-Dimethyltryptamine, *HRL* Harmaline, *HRN* Harmine, *THH* Tetrahydroharmine

Sample 1 (First Degree Beverage); Sample 2 (Second Degree Beverage)

\*Aqueous extract

**Table 2** Sociodemographic characteristics of the groups and pattern of ayahuasca, alcohol and tobacco use

	Control (n = 16) M (SD)	Experienced (n = 16) M (SD)	Beginner (n = 16) M (SD)	Statistical Testing	p value
<b>Frequency of ayahuasca</b>					
Time of use (months)	–	321.00 (± 73.64)	15.94 (± 12.45)	t (30) = 16.33	0.001*
Time since first use (days)	–	8.56 (± 7.72)	10.36 (± 7.34)	t (30) = 0.68	0.502
Age	43.06 (± 15.06) n (%)	46.81 (± 13.81) n (%)	38.69 (± 14.11) n (%)	F <sub>(2,45)</sub> = 1.29	0.285
<b>Frequency of current use</b>					
Monthly	–	4 (25.00)	1 (6.20)	X <sup>2</sup> = 2.30	0.317
Fortnightly	–	11 (68.70)	13 (81.20)		
Weekly	–	1 (6.20)	2 (12.50)		
Daily	–	0.00	0.00		
<b>Sex</b>				X <sup>2</sup> = 0.00	1.000
Male	8 (50.00)	8 (50.00)	8 (50.00)		
Female	8 (50.00)	8 (50.00)	8 (50.00)		
<b>Marital status</b>					
Single	7 (43.80)	4 (25.00)	6 (37.50)	X <sup>2</sup> = 3.54	0.738
Married	7 (43.80)	9 (56.30)	9 (56.30)		
Separated/divorced	2 (12.50)	2 (12.50)	1 (6.30)		
Others	0 (0.00)	1 (6.30)	0 (0.00)		
<b>Education level</b>					
Postgraduate	3 (18.80)	2 (12.50)	1 (6.30)	X <sup>2</sup> = 13.85	0.086
Higher education	1 (6.30)	6 (37.50)	0 (0.00)		
High school	10 (62.50)	5 (31.30)	13 (81.30)		
Elementary School	1 (6.30)	1 (6.30)	1 (6.30)		
Incomplete elementary school	1 (6.30)	2 (12.50)	1 (6.30)		
<b>Employment status</b>					
Housewife	1 (6.30)	1 (6.30)	0 (0.00)	X <sup>2</sup> = 8.80	0.185
Retired	3 (18.80)	2 (12.50)	1 (6.30)		
Employed	9 (56.30)	7 (43.80)	4 (25.00)		
Self-employed	3 (18.80)	6 (37.50)	11 (68.80)		
<b>Monthly income</b>					
1–4 basic salary	13 (81.30)	12 (75.00)	16 (100.00)	X <sup>2</sup> = 4.43	0.114
5–9 basic salary	3 (18.80)	4 (25.00)	0 (0.00)		
<b>Tobacco and alcohol use</b>					
Current smokers	2 (12.50)	5 (31.3)	3 (18.8)	X <sup>2</sup> = 1.77	0.412
Current alcohol drinkers	5 (31.30)	1 (6.3)	1 (6.3)	X <sup>2</sup> = 5.35	0.068
<b>Pattern of alcohol use</b>					
12 months	7 (43.80)	5 (31.30)	9 (56.30)	X <sup>2</sup> = 2.96	0.813
30 days	7 (43.80)	3 (18.80)	8 (50.00)		
Frequent <sup>a</sup>	8 (50.00)	1 (18.80)	8 (50.00)		
Binge <sup>b</sup>	5 (31.30)	1 (6.30)	4 (25.00)		

from the ROCF, while the experienced ayahuasca group performed better the novice ayahuasca group in tasks involving verbal and visuospatial memory. In general, ayahuasca do not seem to present cognitive or neuropsychological impairments. Below we discuss these results in detail.

### Sociodemographic characteristics

The sociodemographic data of the control and study groups (experienced and beginner) were homogeneous, with time of ayahuasca use as the only significant difference. Although there was no statistical significance, it is important

**Table 3** Results of the multivariate analysis of variance (MANOVA) between control and ayahuasca groups (experienced and beginner) for the neuropsychological tests

Tests	Control (n = 16) M (SD)	Experienced (n = 16) M (SD)	Beginner (n = 16) M (SD)	F	Sig	n <sup>2</sup>
<b>Wechsler Abbreviated Scale of Intelligence (WASI)</b>						
Vocabulary (VC) <sup>b</sup>	50.93 (± 12.77)	40.62 (± 15.43)	34.31 (± 7.96)	7.86	< 0.01*	0.273
Similarities (SI) <sup>b</sup>	53.37 (± 12.10)	46.25 (± 12.75)	37.68 (± 11.49)	7.09	< 0.01*	0.252
Cubes (BD) <sup>a,b</sup>	52.37 (± 6.02)	54.00 (± 7.49)	45.62 (± 9.12)	5.05	0.01*	0.194
Matrix Reasoning (MR) <sup>a,b</sup>	56.75 (± 8.40)	56.68 (± 9.06)	48.93 (± 8.46)	4.11	0.02*	0.164
Verbal Intelligence Quotient (VIQ) <sup>b</sup>	104.18 (± 19.30)	91.06 (± 19.36)	79.12 (± 13.47)	8.55	< 0.01*	0.289
Performance Intelligence Quotient (PIQ) <sup>a,b</sup>	107.31 (± 10.22)	107.31 (± 13.76)	95.43 (± 12.42)	4.76	0.01*	0.185
Full-Scale Intelligence Quotient (FSIQ) <sup>a,b</sup>	106.25 (± 15.48)	99.18 (± 15.44)	85.68 (± 12.24)	8.31	< 0.01*	0.284
<b>Five Digits Test (FDT)<sup>†</sup></b>						
Reading time <sup>b</sup>	19.81 (± 3.74)	22.00 (± 4.14)	23.81 (± 4.02)	3.97	0.02*	0.159
Counting time	24.37 (± 4.44)	25.43 (± 2.92)	27.06 (± 4.34)	1.92	0.15	0.084
Choice time	36.81 (± 6.40)	36.25 (± 6.01)	42.31 (± 9.74)	2.99	0.06	0.125
Alternation time	47.56 (± 8.60)	51.56 (± 9.75)	55.56 (± 13.20)	2.2	0.12	0.095
Percentile inhibition	34.06 (± 25.37)	47.18 (± 28.51)	30.00 (± 25.16)	1.77	0.18	0.078
Percentile flexibility	35.31 (± 20.61)	35.00 (± 31.57)	24.06 (± 21.84)	1.3	0.36	0.047
<b>Wisconsin Card Sorting Test-64 (WCST-64)</b>						
Number of tests	64.06 (± 0.25)	64.00 (± 0.00)	64.12 (± 0.50)	0.6	0.55	0.028
Time (seconds)	465.18 (± 166.60)	444.31 (± 143.18)	381.00 (± 62.36)	1.92	0.15	0.084
Total corrects	39.75 (± 11.61)	39.00 (± 10.10)	34.37 (± 9.81)	1.17	0.31	0.053
Total incorrects	24.31 (± 11.55)	25.00 (± 10.10)	29.75 (± 9.88)	1.21	0.3	0.055
Conceptual response level	30.37 (± 13.44)	30.06 (± 12.65)	23.93 (± 12.70)	1.2	0.31	0.054
Completed categories	2.43 (± 1.50)	2.06 (± 1.28)	1.75 (± 1.23)	1	0.37	0.046
First category essays	17.25 (± 12.20)	19.12 (± 14.31)	13.93 (± 7.57)	0.8	0.45	0.037
Failures to maintain context	0.43 (± 0.81)	0.68 (± 0.70)	0.31 (± 0.47)	1.43	0.25	0.064
<b>Rey–Osterrieth Complex Figure test (ROCF)</b>						
Copy total score <sup>a,b</sup>	31.40 (± 4.48)	30.59 (± 3.41)	25.40 (± 5.51)	9.6	< 0.01*	0.314
Copy time (minutes)	3.68 (± 1.07)	4.31 (± 1.40)	3.75 (± 1.43)	1.12	0.33	0.051
Total memory score	18.87 (± 7.91)	16.10 (± 7.44)	13.06 (± 5.70)	2.58	0.08	0.11
Memory time (minutes)	2.62 (± 0.71)	2.31 (± 1.01)	2.37 (± 0.71)	0.6	0.55	0.028
Digit Span (DS) <sup>a</sup>	11.25 (± 3.10)	13.00 (± 2.58)	9.62 (± 2.18)	6.15	< 0.01*	0.227
Corsi Block-Tapping Task (CBT) <sup>a</sup>	9.06 (± 3.23)	9.68 (± 2.72)	6.93 (± 2.54)	4.12	0.02*	0.164

F MANOVA test, n<sup>2</sup> partial eta squared

<sup>a</sup>Experienced ≠ beginner

<sup>b</sup>Control ≠ beginner

\*Significant for p ≤ 0.05

<sup>†</sup>Execution time in seconds

to highlight the use of tobacco and alcohol among Santo Daime followers. The experienced group (n = 5, 31.3%) had the highest number of smokers. The use of tobacco by followers of the Barquinha and UDV religious lines is disapproved, whereas in Santo Daime there is no standardization of its use by its members [28]. Regarding alcohol use, the highest number of current alcohol drinkers was in the control group (n = 5, 31.3%). In relation to the pattern of alcohol use, the beginner group had the largest number of people using it in the last 12 months (n = 9, 56.3%) and in the last

30 days (n = 8, 50.0%). For frequent alcohol use, both the control group and the beginner group had the same number of people (n = 8, 50.0%). For binge use, the largest number of people was in the control group (n = 5, 31.3%). Overall, the experienced group had lower pattern of alcohol use.

A growing number of studies suggest that ayahuasca may have beneficial effects in the treatment of substance use disorders [62]. Specifically, several studies indicate that ritual and recreational ayahuasca users have lower alcohol consumption and fewer alcohol-related problems than control

**Table 4** Results of the Digit Span (DS) and a comparison with previous findings

Raw Scores	Our results			Figueiredo e Nascimento (2007)	
	Control (n = 16) M (SD)	Experienced (n = 16) M (SD)	Beginner (n = 16) M (SD)	WISC-III (n = 801) M (SD)	WAIS-III (n = 788) M (SD)
FDS	8.50 (± 2.30)	9.93 (± 1.52)	7.75 (± 2.11)	6.88 (± 2.11)	6.93 (± 2.22)
BDS	5.12 (± 2.30)	5.87 (± 2.18)	3.62 (± 1.58)	3.66 (± 2.11)	4.81 (± 2.35)
FDS + BDS	6.81 (± 2.17)	7.90 (± 1.67)	5.68 (± 1.50)	–	–
FDS—BDS	3.37 (± 1.54)	4.06 (± 1.73)	4.12 (± 2.21)	3.22 (± 1.84)	2.12 (± 1.92)
Age	43.06 (± 15.06)	46.81 (± 13.81)	38.69 (± 14.11)	All ages	All ages
Men:Women	8:8	8:8	8:8	392:409	–

FDS: Forward Digit Span; BDS: Backward Digit Span; WISC: Wechsler Intelligence Scale for Children-Third Edition (WISC-III); WAIS: Wechsler Intelligence Scale for Adults-Third Edition (WAIS-III)

**Table 5** Results for the Corsi Block-Tapping (CBT) task and a comparison with previous findings

Raw Scores	Our results			[32]	[33]
	Control (n = 16) M (SD)	Experienced (n = 16) M (SD)	Beginner (n = 16) M (SD)	Sample <sup>a</sup> (n = 70) M (SD)	Sample <sup>b</sup> (n = 37) M (SD)
CF	8.00 (± 1.70)	8.00 (± 1.54)	6.62 (± 1.54)	–	7.6 (± 1.30)
CB	6.50 (± 2.82)	6.81 (± 1.93)	5.62 (± 2.36)	–	7.8 (± 1.70)
CF + CB	7.25 (± 1.99)	7.40 (± 2.73)	6.12 (± 3.33)	6.2 (± 1.30)	7.7 (± 1.50)
Total score	82.62 (± 35.29)	83.06 (± 25.94)	60.25 (± 25.87)	55.7 (± 20.30)	40.8 (± 11.60)
Age	43.06 (± 15.06)	46.81 (± 13.81)	38.69 (± 14.11)	31.2 (± 14.10)	56.2 (± 2.50)
Men:Women	8:8	8:8	8:8	43:27	11:26

groups [4, 13, 29, 37]. As an example, Barbosa et al. [4] conducted a study involving the use of alcohol and tobacco in 1,947 UVD members over 18 years of age in which they were evaluated in terms of years of membership and attendance at ceremonies during the last 12 months. Levels of alcohol and tobacco use disorder among UDV members were compared to data from the II Household Survey on the Use of Psychotropic Drugs in Brazil: 2005 [14]. This household survey assessed a sample of 7,939 individuals across Brazil to estimate the Brazilian prevalence of substance use disorders using a Brazilian version of the Substance Abuse and Mental Health Services questionnaire [65]. Regression analyzes revealed a significant impact of participation in ritual ayahuasca ceremonies during the past 12 months and years of UDV membership on reducing alcohol and tobacco use disorder. Alcohol use disorders were significantly lower in ayahuasca users than in controls across all age groups (18–24 years: 4.9% vs. 19.2%, 25–34: 2.3% vs. 14.7%; ≥ 35: 1.0% vs. 10.4%).

It is important to highlight that among followers of the ayahuasca religions, ayahuasca is not considered a drug or a hallucinogen. Specifically in Santo Daime, it is considered a sacrament, such as "the blood of Christ" or a "divine being" that has great powers. Thus, according to Santo Daime

members, every time a person drinks ayahuasca they can "come into direct contact with the divine" (referring to the entheogenic effect; [41]). According to Pelaez [55], Santo Daime members consider the body as a sacred space where the human spirit resides. For them, the body must be at the service of the spirit, and not the other way around. Thus, they learn to control the impulses of pleasure or gratification to keep the *aparelho* ("device") clean, avoiding intoxicating it with heavy foods, drugs, or a disordered life. For Santo Daime members not only a physical cleansing occurs, but also a "moral" cleansing. Within the churches there is a great emphasis on placing "drugs" in the sphere of "evil" and "error", while ayahuasca represents "light", "order", "cleanliness" and "rightfulness" [42]. In this sense, it is possible to argue that the lower patterns of alcohol use in the experienced group could be due to the long period of ayahuasca use (mean of 26 years) and subsequent changes in behavior and philosophy of life.

### Intellectual performance

Regarding the results for the WASI, in general, the beginner group presented significantly lower scores than the other two groups, with large effects sizes ( $n^2 = 0.164\text{--}0.289$ ). As



to specific subtests, the experienced group and the control group had similar intellectual performance (FSQI), both significantly higher than the beginner group. Likewise, concerning the PIQ, the experienced group and the control group achieved equal scores, both significantly higher than the beginner group. Although the beginner group showed lower scores, all groups are classified as “average” in relation to executive intelligence. From these results, despite the large effects sizes, the performance intelligence (related to the degree and quality of the individual's non-verbal contact with the environment, the ability to integrate perceptual stimuli, and to evaluate visuospatial information) was maintained in the participants of the present study [15]. In the BD subtest, again the beginner group scored lower. Apparently, for the other two groups, the task of organizing models, which aims at skills related to visuospatial conceptualization, visuomotor coordination, perceptual speed, abstract conceptualization, and problem-solving strategy, seems to be preserved, which is a measure of organization perceptual and general intelligence [15, 38]. In the MR subtest, the experienced group and the control group performed identically with beginners scoring lower. Apparently, the measure of non-verbal fluid reasoning seems preserved in all participants of the present study, as well as the abilities to mentally manipulate abstract symbols and perceive the relationship between them [15, 38]. Lastly, the beginner group also scored lower than the controls for VIQ, VC, and SI. VIQ refers to the cognitive ability to express ideas using verbal symbols. Good verbal ability is positively correlated with the acquisition of knowledge, so the greater the verbal ability of a person, the greater the knowledge regarding the world. This ability is acquired and depends on the relationship/interaction of the individual with the environment, and the level of education (years of study) [15].

Although there was no significant difference regarding educational level, it is important to highlight some characteristics of the experienced and beginner groups. For instance, the number of people with higher education training was eight (50.0%) in the experienced group, while in the beginner group there is no person with higher education (the vast majority have completed secondary education, 13 people or 81.25%). Papalia and Feldman [54] state that there is an influence of education (years of study) on the assessment of IQ, as years of study seem to increase the intelligence tested through psychometric tests. Lezak et al. [38] state that IQ scores have a high correlation with academic performance and the individual's cultural context. Da Silva [17] assures that intelligence influences an individual's decision to remain at school, thus, remaining in the school environment can increase their IQ or prevent it from declining. According to the same author, each additional month that a student remains at school

can contribute to increasing their IQ above what would be expected if they had escaped from the classroom. Another factor that could be influencing verbal ability is that Santo Daime adherents may already have this cognitive difficulty before joining the ritual, or perhaps the use of ayahuasca may initially disorganize this cognitive function, which is then restored with continued use of ayahuasca.

#### Executive functions.

Within the FDT we found significant differences (with a large effect size ( $n^2=0.159$ ) only for the beginner group when compared with controls in reading time, with beginners taking longer to read and thus showing worse performance [67]. Regarding the WCST-64, we did not find any significant differences between groups. A previous investigation reported better performance for experienced ayahuasca users in relation to controls for the Stroop test, but not for the WCST [8]. Trends for total correct answers ( $p=0.055$ ) and total errors ( $p=0.081$ ) when comparing experienced ayahuasca users with controls have also been previously reported [10]. Given these conflicting results, to date, the published data seems to be inconclusive regarding the effects of ayahuasca consumption on executive functions.

#### Visual perception and immediate memory.

In the copy total score for the ROCF test the beginner group showed significantly lower scores than the control and experienced groups (with a large effect size ( $n^2=0.314$ )). Regarding the percentiles, 8 people in the control group (50%) obtained a classification equal to or greater than the 50th percentile (average classification); in the experienced group, 5 people (31.2%) obtained the same classification with both groups showing adequate visual perception capacity within the estimated classification for the Brazilian population. In the beginner group, 14 people (87.5%) were rated between the 10–20 percentile (less than average rating), which suggests the presence of some considerable impairment in visual perception capacity [50]. This interferes with the perception of visual information contained in the figure to be copied (the location of parts, proportions, and categorization of elements), formation and search for mental visual images (associative and visual memory), and the practice of graphic production that encompasses planning and programming through motor actions [30]. The question remains whether these Santo Daime adherents already had this difficulty before joining the ritual or whether the use of ayahuasca initially disorganizes this cognitive function which is later restored with continued ayahuasca use. The results reported here corroborate previous findings concerning the absence of significant differences between ayahuasca users and controls in relation to the immediate memory subtest of the ROCF [19].

## Verbal and visuospatial working memory

In the DS task, the average weighted score of the experienced group was higher (13.00) compared to the beginner group (9.62), with a large effect size ( $n^2=0.227$ ). According to Cunha [15], adults with average intelligence can retain at least 5 digits in FDS and 3 in BDS. Baron [5] ensures that children aged 7 to 9 years are expected to reach 5 digits in the FDS and 3 digits in BDS. After 9 years of age, the average range for BDS increases to 4 digits. The experienced group retained 9.9 digits on average in the FDS, twice the amount indicated in the literature [15], higher than the beginner group and the participants from the study by Figueiredo and Nascimento [25]. The retention of digits in the BDS of the experienced group was on average 5.87 digits, while the literature indicates 4 [5]. In this regard, the experienced group obtained one point more than the adult participants (4.81) described by Figueiredo and Nascimento [25], and more than two points in relation to the beginner group (3.62). Regarding the difference between FDS and BDS, the experienced group scored twice as much (4.0) in relation to Figueiredo and Nascimento's [25] sample of adult participants (2.12). Moreover, the literature states that a difference of 3 points between FDS and BDS is significant [5]. Therefore, the experienced group is above average on this score compared to the studies presented. In the experienced group, 14 individuals (87.5%) had a difference greater than 3 between FDS and BDS in the DS task. These results corroborate previous findings where regular ayahuasca users presented a better performance in the Sequence of Numbers and Letters (WAIS-III, this task also assesses attention and working memory) when compared with controls [8]. On the other hand, Doering-Silveira et al. [19] did not report significant differences between ayahuasca users and controls on the DS task. In summary, the experienced group stood out in the DS task both in the forward and backward orders of the digits. This data shows superior performance in this type of task, suggesting an unprecedented finding among experienced users of ayahuasca in a ritualistic context. The difference (greater than 3 digits) was also higher than the control group and the cited studies, which, according to Glasser and Zimmerman [27], evidence excessive rigidity of thought or lapses in attention due to an increase in anxiety.

In the CBT task, the weighted average score of the experienced group was higher (9.68) compared to the beginner group (6.93). Table 4 shows that the experienced group achieved superior performance in the sum of Corsi Forward (CF) and Corsi Backward (CB) (on average), in relation to the beginner group and Kessels et al. [32], with similar scores to those reported by Kessels et al. [33]. The experienced group also showed a better result in the total score (on average) when compared with the beginner group and the studies by Kessels et al. [32, 33]. The degree of difficulty

presented in carrying out this task, both in the forward and backward orders is the same [33, 71]. Although there are no quantitative differences in performance between the two orders, this does not mean that they have the same underlying cognitive mechanisms [33]. Vandierendonck et al. [71] carried out a study in which they analyzed the CBT task in relation to the working memory theory conceived by Baddeley [2]. A relationship was observed between the task and the subcomponents of working memory (central executive, phonological loop, and visuospatial sketch), through an interference paradigm. Therefore, they found results that indicate that both CF and CB require support from visuospatial processing. However, in items with long sequences, resources from central executive functions were also requested, indicating an increase in cognitive demand. It can be observed in Table 3 that the experienced group obtained superior performance, in the sum of CF and CB (on average), in relation to beginners and participants from Kessels et al. [32], with similar results to those reported by Kessels et al. (2008). In the average of the total score, the experienced group obtained a higher score than the beginner group and Kessels et al. [32], and double when compared with Kessels et al. [33]. This data shows superior performance in this type of task, suggesting a novel finding among experienced users of ayahuasca in a ritualistic context.

It is now known that new neurons are produced in some adult brain regions in several species of mammals, including humans. This perhaps plays a role in repairing brain damage, learning, and maintenance of healthy neural functioning and well-being [26, 38]. Studies with serotonergic psychedelics have shown these substances can increase neurogenesis and/or spinogenesis in vitro and living beings. The main alkaloids present in Ayahuasca (DMT, HRM, HRL, and THH) are reported to increase cell proliferation of the dentate gyrus of the hippocampal formation in non-human mammals [11, 39, 40, 43, 44] and in human cells [11, 16]. Preclinical studies suggest that HRM may have neuroprotective and cognitive-enhancing effects, thus prolonged use of HRM-rich ayahuasca may be associated with better neuropsychological functioning [22].

Zhang and Stackman Jr. [72] found that the role of the 5-HT<sub>2A</sub> serotonergic receptor is closely related to functions involving working memory and spatial cognition, indicating that the prolonged use of ayahuasca may favor these cognitive functions. These authors claim that visual hallucinations induced by 5-HT<sub>2A</sub> may have a potential influence on guided spatial cognition. Serotonergic psychedelics stimulate c-fos expression in the medial prefrontal and anterior cingulate cortices and increase the expression of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex [10]. Furthermore, these substances modulate neuronal plasticity and are associated with cognitive aspects related to memory and attention [57].

Another aspect is that hymns are the main doctrinal instrument of the Santo Daime, acting as an authentic structured “semantic” body of this religious practice [35]. Thus, the adherents are encouraged to pay attention and memorize verbal information (hymns) under the psychedelic effect of the drink. It is likely that adepts, especially experienced ones, deal with the experience in a very individual way, effectively carrying out the internally generated *trabalho* (“work”) as if it was a cognitive task. Moreover, regular ritualized practice most likely influences memory skills that occur during the highly active mental state induced by the brew [18, 22, 72]. Moreover, the specific set + motivation + beliefs + doses used and the religious setting in which ayahuasca is used may act as a protection against adverse events from ayahuasca use.

Finally, important limitations of the study include the small sample size, lack of detailed information of use of illegal drugs, potential sampling biases affecting results, and the lack of experimental design (preventing inference of causality). Future studies could improve such limitations by increasing sample size, including detailed information regarding illegal drug use, perform such studies in non-religious or ritual users (to avoid sampling biases), and performing controlled, experimental studies in laboratory settings. Moreover, future studies could use these same or similar tasks and tests used in the present study to properly compare results, and the present results could inform future experimental and clinical trials on which cognition aspects could be assessed. As a strength, this study included control, experienced, and beginner groups, and experienced users had a mean of more than 26 years of ayahuasca use.

In relation to causation, it is important to highlight the fact that these results need to be interpreted considering that these individuals are ritual ayahuasca users in a controlled setting. Previous studies with these drugs showed that they seem to be safe and well tolerated in controlled settings, with most adverse effects being transient and of mild-to-moderate severity (headache, nausea, vomiting, confusion, anxiety, dissociation, increased blood pressure) [23, 52, 53, 60]. In the specific case of ayahuasca, evidence from both experimental [53, 60] and observational [7] studies show that the most common adverse effects are transient nausea and vomiting. Often, adverse effects of psychedelics are associated with improper set (presence of a history of personal or familial psychosis or underlying mood disorders, in particular bipolar type I) and setting (unsecure, noncontrolled) [69].

## Conclusion

The plants identified are in accordance with the commonly used species to prepare ayahuasca in religious/ritualistic contexts in Brazil. Participants from the present study showed

average intellectual performance. In executive functions, no differences were found between the control and ayahuasca groups, and research is inconclusive concerning ayahuasca users and neuropsychological performance in these tests. Concerning immediate memory, no differences were found between the control and ayahuasca groups, a fact which was corroborated by previous results. The experienced group performed better than the novice group in the DS, in the forward and backward order, and the difference between both (greater than 3 digits) was also higher than the control group's previous results. The experienced group also showed better results than the beginner group in the CBT task. These tasks involve verbal and visuospatial memory, respectively. These data offer evidence of a novel finding among experienced users of ayahuasca in a ritualistic context. Finally, the participants of the present study do not seem to present cognitive or neuropsychological impairments, and in general, the test results denoted global preservation of the evaluated cognitive functions. However, more research is needed to better understand the effects of short and prolonged use of the ayahuasca drink and its therapeutic potential. This study helps to better understand the prolonged effects of ayahuasca in ritual users and could improve our knowledge regarding the effects of prolonged stimulation of the 5-HT<sub>2A</sub> serotonergic receptor.

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**Data availability** Available upon request for the authors.

## Declarations

**Conflict of interest** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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