# Altered State of Consciousness and Mental Imagery as a Function of N, N-dimethyltryptamine Concentration in Ritualistic Ayahuasca Users

# Altered State of Consciousness and Mental Imagery as a Function of *N*, *N*-dimethyltryptamine Concentration in Ritualistic Ayahuasca Users

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## Abstract

■ Consumption of the psychedelic brew ayahuasca is a central ritualistic aspect of the Santo Daime religion. The current observational, baseline controlled study was designed to assess whether members ($n$ = 24) of the Santo Daime church would show enhanced capacity for mental imagery during an ayahuasca experience. In addition, this study assessed whether the effects of ayahuasca on consciousness and mental imagery were related to peak serum concentration of *N*, *N*-dimethyltryptamine (DMT), the main psychoactive component. Measures of altered states of consciousness (5-Dimensional Altered States of Consciousness Questionnaire) and ego dissolution (Ego Dissolution Inventory [EDI]) as well as measures of mental imagery (visual perspective shifting, vividness of visual imagery, cognitive flexibility, associative thinking) were taken on two subsequent days on which members of Santo Daime were sober or drank a self-selected volume of ayahuasca. Measures of altered states of consciousness revealed that feelings of oceanic boundlessness, visual restructuralization, and EDI increased most prominently after drinking and shared a positive correlation with peak DMT concentration. Measures of mental imagery did not noticeably differ between the baseline and ayahuasca condition, although subjective ratings of cognitive flexibility were lower under ayahuasca. Two measures related to mental imagery, that is, perspective shifts and cognitive flexibility, were significantly correlated to peak DMT concentrations. Peak concentrations of DMT and other alkaloids did not correlate with ayahuasca dose. These findings confirm previous notions that the primary phenomenological characteristics of ayahuasca are driven by DMT. Compensatory or neuroadaptive effects associated with long-term ayahuasca intake may have mitigated the acute impact of ayahuasca in Santo Daime members on mental imagery. ■

## INTRODUCTION

Ritualistic and religious use of ayahuasca has been reported to occur in several South American Indigenous cultures (Dos Santos & Hallak, 2021; Miller, Albarracin-Jordan, Moore, & Capriles, 2019; Labate & Feeney, 2012). Ayahuasca is a plant brew that is traditionally made from the *Psychotria viridis* leaves and the vine of *Banisteriopsis caapi*, which respectively contain the serotonergic 2A receptor agonist *N*, *N*-dimethyltryptamine (DMT), and β-carboline alkaloids such as harmine, harmaline, and tetrahydroharmine (Labate & Feeney, 2012). The latter are monoamine oxidase inhibitors allowing DMT to reach the central nervous system for a prolonged period (Riba et al., 2003). DMT is a psychedelic 5HT2A agonist that can produce intense alterations in perception and sensory integration, and can give rise to a spiritual, entheogenic state of consciousness (McKenna & Riba, 2015; Palhano-Fontes et al., 2015; Winkelman, 2005; Riba et al., 2001, 2003).

From the 1930s on, ayahuasca consumption expanded to syncretic religious groups such as Santo Daime (De Rios & Grob, 2005; McKenna, Towers, & Abbott, 1984). Originally, these were mainly established in Brazilian urban centers but its rituals and beliefs also spread throughout Europe and North America (Hartogsohn, 2021; Metzner, 2014) during the 1980s. Core to the Santo Daime religion is the ritual consumption of the ayahuasca brew (referred to as Daime) during congregations that involve musical performance of ritual hymns that are referred to as "works," a designation that signifies the laborious nature of Santo Daime rituals (Hartogsohn, 2021). During such works the Santo Daime religion utilizes the ritual space while under the influence of ayahuasca to facilitate transcendental experiences (Hartogsohn, 2021).

The ability of classic psychedelics such as DMT to induce visual hallucinations and enhance aesthetic appreciation are well documented (Aqil & Roseman, 2023; Leptourgos et al., 2020; Nichols, 2016; Kometer, Schmidt, Jancke, & Vollenweider, 2013; de Araujo et al., 2012). Ayahuasca was even reported to trigger the "mind's eye" and to increase the ability to visualize memories in a man with aphantasia (Dos Santos, Enyart, Bouso, Pares, & Hallak,

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2018), a condition in which people report having no visual experience when they attempt to imagine something. Neuroimaging research has shown that mental imagery involves a range of brain areas including the frontal cortex and sensory areas that are overlapping with the default mode network that is known to be active during resting state, and that can operate like a weak form of perception (Pearson, 2019). These brain areas are densely populated with 5HT2A receptors (Norgaard et al., 2021; Mengod, Palacios, & Cortes, 2015) that mediate visual experiences upon stimulation by psychedelics (Schartner & Timmermann, 2020; Kometer et al., 2013; Carter et al., 2005). Stimulation of the 5HT2A receptors with psychedelics has also been shown to affect neural networks involved in mental imagery. That is, psychedelics acutely reduce the activity and functional connectivity of the default mode network when people are at rest, induce a state of hyperconnectivity between sensory brain regions (Kwan, Olson, Preller, & Roth, 2022; McCulloch et al., 2022), and reduce top–down cognitive control while increasing the bottom–up influence of sensory processing (Doss et al., 2022; Vollenweider & Preller, 2020; Carhart-Harris & Friston, 2019). Cognitive processes that largely rely on mental imagery for normal function include episodic and visual working memory (Pearson, 2019). Moreover, there is supportive evidence that mental imagery contributes to a wider range of cognitive processes such as moral judgment (Amit & Greene, 2012), mind wandering (Christian, Miles, Parkinson, & Macrae, 2013), creativity (Palmiero, Nori, & Piccardi, 2016), ambiguous perception switching (Scocchia, Valsecchi, & Triesch, 2014; Pearson, Clifford, & Tong, 2008), cognitive flexibility and creativity (Pearson, 2019), and the occurrence of false memories (Robin, 2011; Pezdek, Blandon-Gitlin, & Gabbay, 2006; Gonsalves et al., 2004).

The current observational, baseline-controlled, crossover study was designed to assess the acute effects of ayahuasca on consciousness and mental imagery of Santo Daime members and how these would be related to acute DMT concentrations in blood. Measures of altered states of consciousness and mental imagery and measures of cognitive processes that are sensitive to altered mental imagery (e.g., flexible cognition, ambiguous perception switching) were taken on two separate days on which members of Santo Daime did or did not drink ayahuasca. We hypothesized that ayahuasca would increase mental imagery, most noticeably in individuals with the highest DMT concentrations.

## METHODS

### Participants

Twenty-four volunteers (14 men, 10 women) were enrolled in a within-subject, fixed-order observational study. The cohort consisted of experienced members of the Dutch chapter of the church of Santo Daime who met exclusion criteria comprising absence of ferromagnetic devices/implants (MRI contraindications), pregnancy, and use of (medicinal) substances in the past 24 hr. All participants were experienced ayahuasca users with a mean (*SD*) membership duration of 14.2 (8.3) years and a mean (*SD*) attendance of Santo Daime ceremonies of 563 (650) times. Mean (*SD*) age and weight were 55.2 (10.2) years and 75.5 (12.6) kg, respectively. All participants were fully informed of all procedures, possible adverse reactions, legal rights and responsibilities, expected benefits, and their right to voluntary termination without consequences. The study was conducted according to the Declaration of Helsinki (1964) and amended in Fortaleza (Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and was approved by the Academic Hospital and University's medical ethics committee (NL70901.068.19/METC19.050).

### Study Design and Procedures

Participants underwent two consecutive test days during a weekend. On the first test day (Saturday), they were sober (baseline) and did not drink ayahuasca. On the second testing day (Sunday), participants drank ayahuasca. Participants self-administered a single volume of ayahuasca equivalent to their usual dose (mean: 24 mL, *SD*: 8.16), prepared from a single batch by the Church of Santo Daime. To facilitate the communal use of ayahuasca, participants drank ayahuasca brew while initiating the works in company of fellow members. The collective works (i.e., six participants) consisted of praying, singing, and meditation for about 1 hr at the onset of the second test day. Participants would continue their work individually during successive drinking sessions that were spaced 90 min apart. Participant dosing schedules were stratified across each laboratory visit with testing performed within four pairs of visits (six participants per cycle) with each participant being tested at the same time schedule at every test day as to minimize diurnal variation. The alkaloid concentrations in a sample of the ayahuasca brew were determined after dissolution in 25 mL of water using high-performance liquid chromatography coupled to mass spectrometry (LC–MS) which was calibrated with pure reference substances of DMT (Cerilliant), harmine, harmaline (Aldrich Chemistry), and tetrahydroharmine (LGC Standards; Kiraga et al., 2021; Uthaug et al., 2021). The ayahuasca brew used contained 0.14 mg/mL of DMT, 4.50 mg/mL of harmine, 0.51 mg/mL of harmaline, and 2.10 mg/mL of tetrahydroharmine. Each ceremony was organized and supervised by the Santo Daime church. The research team was not involved in the organization of the ceremonies nor the production, dosing, or administration of ayahuasca.

On each day upon arrival to the laboratory, absence of drug and alcohol use was assessed via a urine drug screen and a breath alcohol test. An additional pregnancy test was

given if participants were female. Each visit consisted of a 30-min wait period, followed by a 1-hr MRI scanning session occurring 1 hr after intake. On Day 2, venous blood samples were collected approximately 60 and 160 min after ayahuasca intake to assess serum concentrations of alkaloids according to laboratory protocols using LC–MS. Imaging data (Mallaroni et al., 2022) and metabolomics analysis of blood (Madrid-Gambin et al., 2022) have been reported elsewhere. Cognitive tests and questionnaires related to altered state of consciousness and mental imagery will be reported here. These were completed after the MRI sessions, between 150 and 210 min after drinking ayahuasca. Tasks and questionnaires were available in Dutch and English versions. Two participants completed the English version because they were not native Dutch speakers. All other participants completed the Dutch versions.

### Psychedelic State Questionnaires

The 5-Dimensional Altered States of Consciousness Questionnaire (5D-ASC; Studerus, Gamma, & Vollenweider, 2010) is a 94-item self-report scale that assesses the participant's alterations from normal waking consciousness. The participant is asked to make a vertical mark on the line below each statement to rate to what extent the statements applied to their experience in retrospect (e.g., from "No, not more than usually" to "Yes, more than usually"). The 5D-ASC measures five key dimensions: oceanic boundlessness, anxious ego dissolution, visionary restructuralization, auditory alterations, and reduction in vigilance. Their internal consistency as measured by Cronbach's alpha was .96, .71, .93, .52, and .74, respectively, in the current study.

The Ego Dissolution Inventory (EDI; Nour, Evans, Nutt, & Carhart-Harris, 2016) is an eight-item self-report scale that assesses the participant's experience of ego dissolution. Sample items for the scale include the following: "I experienced a dissolution of my "self" or ego" and "I felt at one with the universe." The purpose of this scale is to acquire a better understanding of the experiences the participants had about ego dissolution during the psychedelic experience. The participant answers the scale with endpoints of either 0 = "No, not more than usually" or 100 = "Yes, I experience this completely/entirely." The EDI is scored by calculating the mean of all the eight items (range = 0–100). The higher the total score, the stronger the experience of ego dissolution. Internal consistency of the EDI score was high in the current study as indicated by Cronbach's alpha = .91.

### Mental Imagery: Tasks and Questionnaires

The Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1989) is a self-report questionnaire for which participants have to form a visual mental image of a person, item, or situation, and rate the vividness with which it is imagined. The VVIQ consists of 16 items in four groups of four (e.g., group: Think of a country scene that involves trees, mountains, and a lake; item: The contours of the landscape). The participants use a 5-point scale ranging from 1 (No image at all, you only "know" that you are thinking of the object) to 5 (Perfectly clear and vivid as real seeing). The questionnaire was completed twice, once with eyes open and once with eyes closed. The summed scores on the VVIQ in the current study ranged between 36 and 89 with a mean of 35 in the nondrinking condition, suggesting a normal imaginative capability among the participants (Zeman, Dewar, & Della Sala, 2015). The average score across all 16 items and the eyes open/eyes closed condition was taken as the primary outcome variable.

The ambiguous image Perspective Switching Task (Hodgins & Adair, 2010) uses three different ambiguous images to measure perspective switching. The task was explained with the widely known old woman/young woman image. The three experimental images were drawings that could be viewed as (1) a duck versus a rabbit, (2) a cowboy versus an old man, and (3) a saxophone-playing figure versus a woman's profile. Participants press a key as quickly as possible after identifying an image. They view an image, write a description, view it a second time to identify an alternative perspective, and write a second description. Dependent variable is the number of times that a participant observed one out of two possible perspectives (based on the descriptions).

The Cognitive Flexibility Scale (CFS; Martin & Rubin, 1995) contains 12 items that are rated on a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree). These items assess cognitive flexibility based on the components (a) awareness that in any given situation there are options and alternatives available, (b) willingness to be flexible and adapt to the situation, and (c) self-efficacy in being flexible. The higher the score, the higher the cognitive flexibility.

In the Chain Free Association Task (CFAT; Marron et al., 2018) participants are required to verbalize a "chain" of single-word associations that come to mind, each association relating to the previous one (e.g., wax, candle, fire, hot, summer, love). The participants were instructed to produce associations freely—whatever comes to their mind—with as little inhibition as possible. Dependent measure is the instantaneous forward flow of any particular thought as calculated by its average semantic distance from all preceding thoughts (Christensen & Kenett, 2021; Gray et al., 2019). Mean fluency, the number of words in the word chain, is a secondary measure. Forward flow was calculated using a continuous bag of words, built on a concatenation of the British National Corpus (around 2 billion words), ukwac corpus, and the 2009 Wikipedia dump (~800 million tokens) using a context window size of 11 words, 400 dimensions, and the most frequent 300,000 words, which has previously been shown to strongly

predict human creativity and novelty ratings across a range of tasks (Beaty & Johnson, 2021).

Parallel versions of the CFAT were used on test days. All other tasks employed the same version on test days.

### Statistics

Statistical analyses on mental imagery measures were carried out in SPSS, using a linear mixed model with restricted maximum likelihood method and a first-order autoregressive residual covariance structure. The model included condition (two levels) as fixed effects, and a random intercept. Pearson *r* correlations were employed to determine associations between ayahuasca dose and peak DMT/β-carboline alkaloids concentrations (Cmax) in serum, and between peak DMT in serum and measures of the psychedelic state and mental imagery. A priori, the study was designed to include up to 24 participants depending on the availability and willingness of members of the Santo Daime church to participate in this observational study. Previous within-subject studies (baseline or placebo controlled) revealed that a sample size around 6–18 participants is sufficient to detect ayahuasca-induced changes in consciousness, mood, and cognition (Uthaug et al., 2021; Sampedro et al., 2017; Bouso, Fabregas, Antonijoan, Rodriguez-Fornells, & Riba, 2013; Dos Santos et al., 2012; Riba et al., 2001, 2003).

## RESULTS

Self-selected, individual doses of the ayahuasca brew ranged between 11 and 40 mL among participants. On average, participants consumed 24 mL of the ayahuasca brew during the ayahuasca condition. Individual serum peak concentration of the main ayahuasca components (i.e., DMT, harmaline, harmine, and tetrahydroharmine) also varied considerably between participants. Individual doses of the ayahuasca brew and peak DMT and β-carboline alkaloid concentrations, however, were not significantly correlated. Mean (*SD*) and individual ayahuasca doses, peak drug concentrations, and their correlations are shown in Figure 1.

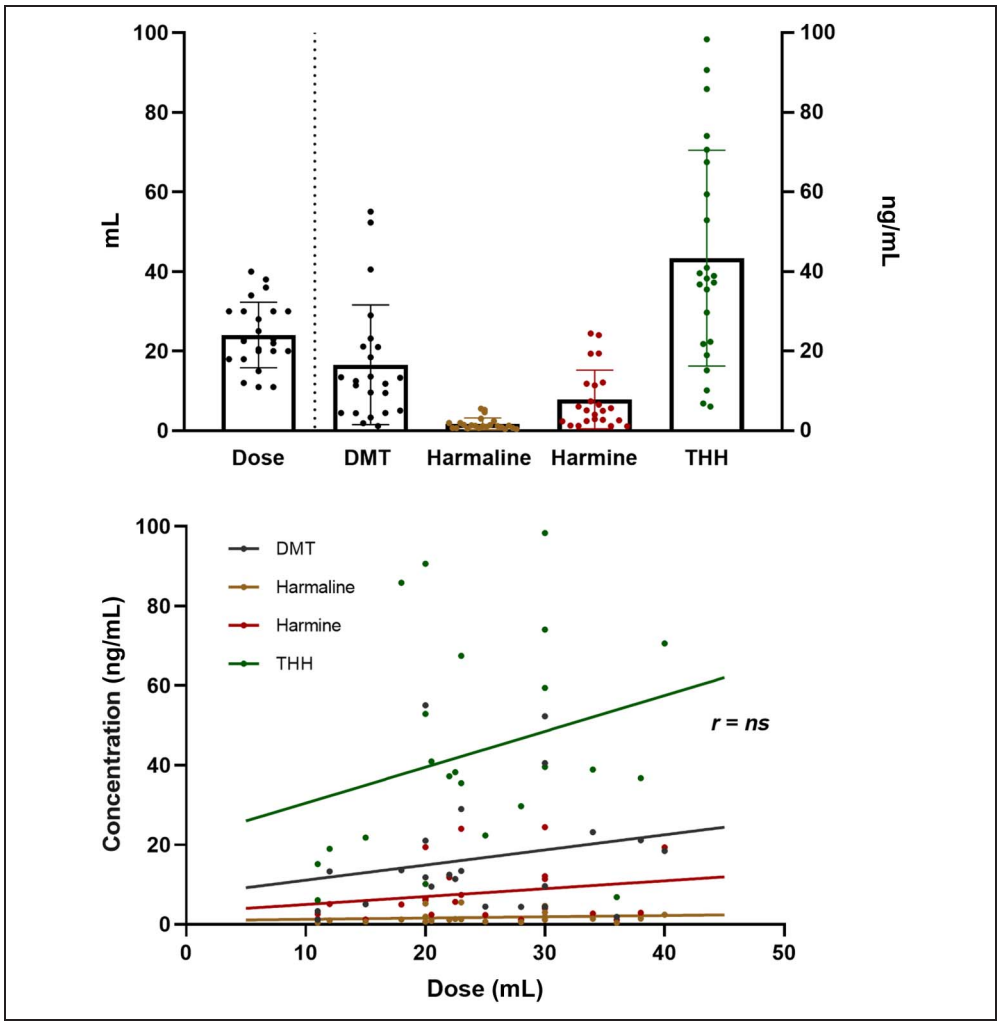


**Figure 1.** The upper panel shows mean (*SD*) and individual ayahuasca doses and mean (*SD*) and individual peak concentrations of DMT, harmaline, harmine, and tretrahydroharmine (THH). The lower panel shows the (lack of) association between ayahuasca dose and peak DMT, harmaline, harmine, and THH concentrations in blood.

Mean and individual ratings of altered states of consciousness of participants in the ayahuasca condition are shown in Figure 2. Ratings on all key dimensions of the 5D-ASC ($t$ = 3.79–8.23; $df$ = 23; $p < .001$) and on the EDI significant ($t$ = 7.89; $df$ = 23; $p < .001$) increased. EDI and total 5D-ASC ratings were highly correlated ($r$ = .75; $p < .001$). Mean ratings of oceanic boundlessness, visual restructuralization, and ego dissolution were most affected and ranged between 30% and 40% of the maximal score. Maximal individual ratings on these dimensions ranged between 70% and 100%. Individual ratings of oceanic boundlessness ($r$ = .47; $p$ = .023), visual restructuralization ($r$ = .58; $p$ = .004), and ego dissolution ($r$ = .52; $p$ = .012) were positively correlated to individual peak DMT concentrations. In general, peak β-carboline alkaloids concentrations were not significantly correlated to subjective measures of state of consciousness, although the association between harmaline concentration and EDI achieved significance ($r$ = .41; $p$ = .048). Individual ayahuasca dose was not correlated with individual ratings of the altered state of consciousness.

Mean and individual performances on primary measures of mental imagery or measures affected by mental imagery are shown in Figure 3. The number of perspective shifts, vividness of imagery, and measures of word association did not differ between the baseline and the ayahuasca condition, although the difference in mean word fluency during baseline and under ayahuasca in the CFAT just failed significance, $F(1, 22.3) = 4.02$; $p = .057$. However, cognitive flexibility ratings were lower in the ayahuasca condition as compared with baseline, $F(1, 22.5) = 4.91$; $p = .037$; $\eta_p^2 = .17$. Individual measures of perspective shifts were positively correlated with peak DMT concentration ($r$ = .56; $p$ = .007), whereas individual ratings of cognitive flexibility were negatively correlated with peak DMT concentration ($r$ = −.42; $p$ = .042) and peak harmine concentration ($r$ = −.45; $p$ = .032). None of the other measures were significantly correlated to peak concentrations of DMT and β-carboline alkaloids.

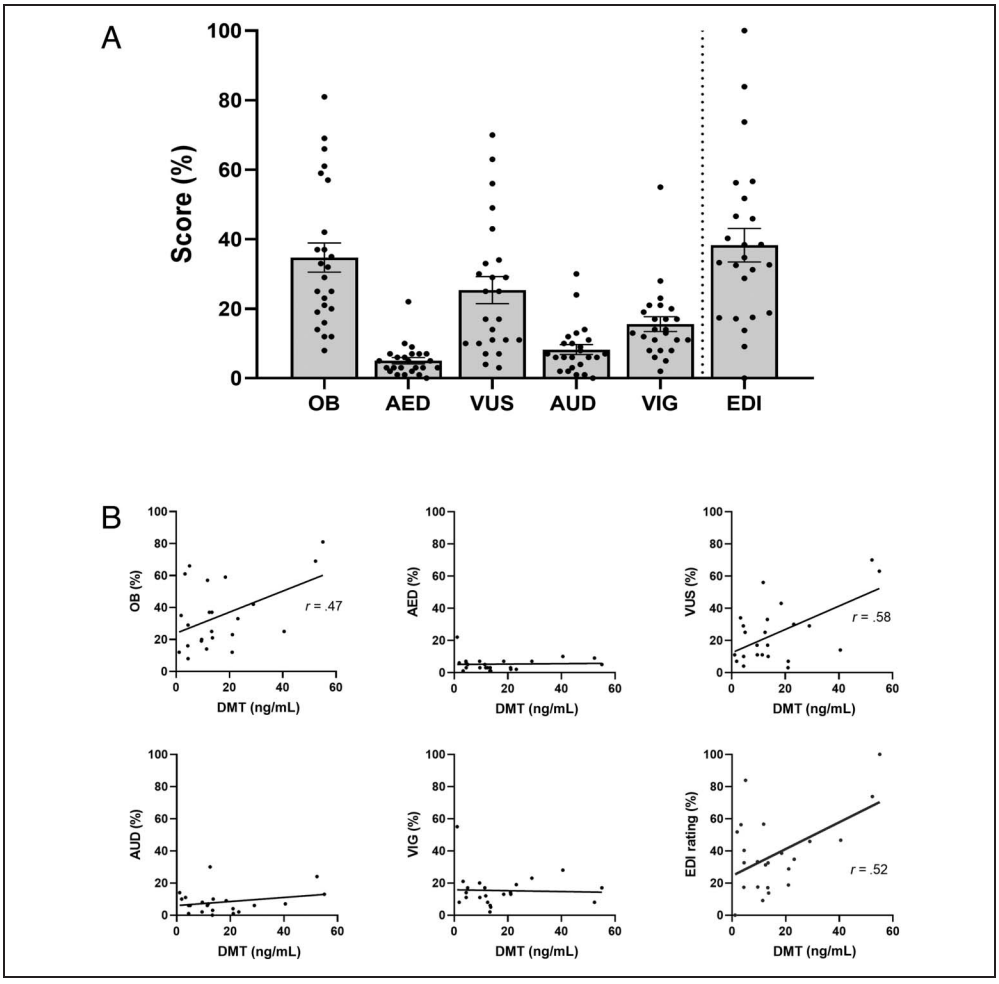


**Figure 2.** (A) Mean (*SE*) and individual ratings of the five key dimensions of the altered states of consciousness (5D-ASC) scale and the EDI after drinking ayahuasca. (B) Associations between peak DMT concentration and the subjective experience during the ayahuasca condition. OB = oceanic boundlessness; AED = anxious ego dissolution; VIS = visionary restructuralization; AUD = auditory alterations; VIG = reduction in vigilance.

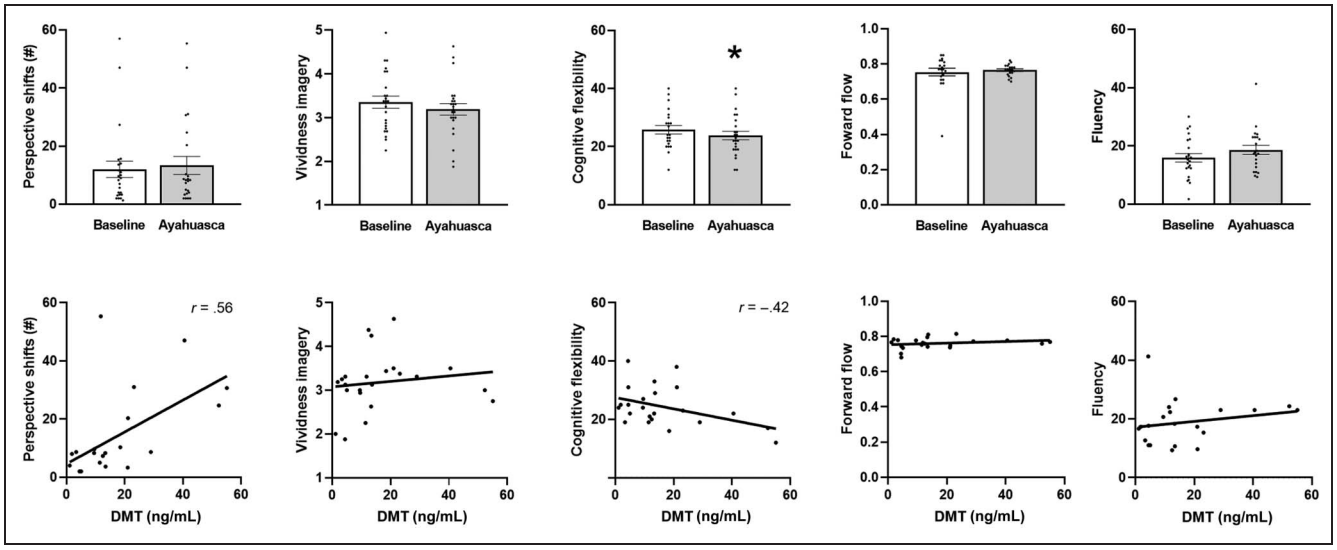


**Figure 3.** The upper row shows mean (*SE*) and individual number of perspective shifts, vividness of imagery, cognitive flexibility as assessed with the Perspective Switching Task, VVIQ, and CFS, respectively, and mean (*SE*) and individual scores of forward flow and fluency as assessed with the CFAT. The lower row shows the association between peak DMT concentration and number of perspective shifts, vividness of imagery, cognitive flexibility, forward flow, and fluency (*$p < .05$).

## DISCUSSION

The current study was designed to assess the acute effects of ayahuasca on consciousness and mental imagery of Santo Daime members and how these are related to peak DMT concentrations in blood. Subjective measures of altered states of consciousness revealed that feelings of oceanic boundlessness, visual restructuralization, and ego dissolution were most prominent after drinking ayahuasca. Ratings of cognitive flexibility were lower under ayahuasca as compared with baseline. Subjective ratings of the psychedelic state and two measures related to mental imagery, that is, perspective shifts and cognitive flexibility, were significantly correlated to peak DMT concentrations. Peak concentrations of DMT and β-carbolines did not correlate with ayahuasca dose.

Analyses of the ayahuasca sample revealed that the DMT, harmaline, harmine, and tetrahydroharmine were the major alkaloids present in the brew, which is in line with previous analyses of ayahuasca brews (Rodriguez et al., 2022; Kaasik, Souza, Zandonadi, Tofoli, & Sussulini, 2021). The strength of ayahuasca brews used in religious ceremonies can differ considerably depending on the grade of the brew (Kaasik et al., 2021). The most traditional brew is a first grade Daime that is made from two successive boilings of fresh plants and water, whereas higher grades contain higher concentrations of alkaloids by additional boiling (Kaasik et al., 2021). In the present study a higher grade of Daime brew was consumed that was exposed to three subsequent brews of the already used plants ("três por um" = 3 × 1). In the present ayahuasca sample, alkaloid concentrations were comparable to those reported previously in 3 × 1 ayahuasca samples, although the DMT concentration appeared more comparable to those reported in first grade brews (Kaasik et al., 2021). Peak serum concentrations of the alkaloids varied between participants, whereas mean alkaloid concentrations were similar or higher as compared with those previously reported in religious ayahuasca users (Lanaro et al., 2021) or in healthy volunteers after controlled administrations (Schenberg et al., 2015; Riba et al., 2003; Callaway et al., 1996). Self-selected doses of the ayahuasca brew also varied considerably between participants but were not significantly correlated to serum alkaloid concentrations. This suggests that individual differences in peak serum concentrations of DMT and β-carbolines that were observed in the present study were not related to individual variations in the ayahuasca dose, and rather may have been caused by individual differences in absorption and metabolism of ayahuasca (Riba, McIlhenny, Bouso, & Barker, 2015; Riba, McIlhenny, Valle, Bouso, & Barker, 2012). It should be noted however that additional pharmacokinetic studies that include multiple assessment of drug concentration over time across a number of standardized doses are needed to establish a dose–concentration relationship for ayahuasca that is generalizable beyond the current study sample.

Mean ratings of the psychedelic experience as assessed with the 5D-ASC dimensions and the EDI varied between 5% and 40% of the maximal score, indicating that overall participants experienced moderate levels of altered states of consciousness under ayahuasca. Similar mean intensities after drinking ayahuasca have been reported using in regular participants of ayahuasca ceremonies as assessed with the 5D-ASC and EDI (Kiraga et al., 2021; Uthaug et al., 2018, 2021), in healthy volunteers in controlled studies as measured with the Hallucinogen Rating Scale (HRS; Dos Santos et al., 2012) and in clinically depressed patients in observational studies as measured with the 5D-ASC and EDI (van Oorsouw,

Toennes, & Ramaekers, 2022). However, somewhat higher ratings on the HRS and the mystical experience questionnaire after a single dose of ayahuasca have been reported as well in a clinical trial with depressed patients (Fernanda Palhano-Fontes et al., 2019). Individual ratings of the psychedelic experience with the 5D-ASC and the EDI however varied considerably, with maximal intensity ratings ranging between 70% and 100%. Oceanic boundlessness, visual restructuralization and ego dissolution were the most affected during the ayahuasca experience. This finding is in line with previous reports indicating that visual phenomena, numinousness, peacefulness, and insights are among the most salient phenomenological characteristics of the ayahuasca experience (Barbosa, Giglio, & Dalgalarrondo, 2005; Riba et al., 2001, 2003). Typically, ratings of oceanic boundlessness, visual restructuralization, and ego dissolution correlated positively with peak DMT concentrations confirming that DMT is the major component in the ayahuasca brew that is driving the psychedelic experience under ayahuasca (Riba et al., 2003). This finding is in contrast with a healthy volunteer study in which the magnitude of the psychedelic experience, as measured with the HRS, did not correlate with DMT and harmaline concentrations following a single dose of ayahausca (Schenberg et al., 2015). However in that same study, peak DMT and harmaline did correlate with alterations in oscillatory EEG power during the ayahuasca experience and correlations were most prominent for DMT (Schenberg et al., 2015). The present finding is also in line with previous research on related tryptamines such as psilocybin showing that the intensity of the psychedelic experience increases with drug concentration in blood and is moderated through increased 5HT2A receptor occupancy in the brain (Stenbaek et al., 2021; Madsen et al., 2019). It can therefore be expected that 5HT2A receptor occupancy under ayahuasca varied considerably between participants in the current study, and that high levels of 5HT2A receptor occupancy were primarily achieved in participants with high DMT concentrations in blood. Importantly, the psychedelic experience under ayahuasca did not correlate to dose, which stresses the notion that a fixed dose of ayahuasca, or other tryptamines such as 5-MeO-DMT (Reckweg et al., 2021) and psilocybin (Madsen & Knudsen, 2021), will not necessarily bring about a similar intensity of the psychedelic experience across users. These findings suggest that evaluation of a psychedelic blood concentration, rather than dose, is important when predicting and maximizing 5HT2A receptor occupancy that underlies the psychedelic experience at the individual level.

Measures of mental imagery or of cognitive processes that are sensitive to mental imagery generally did not differ between the baseline and ayahuasca condition, with the exception of subjective ratings of cognitive flexibility. These were significantly decreased under ayahuasca as compared with baseline. Furthermore, individual decrements in cognitive flexibility were negatively correlated to individual peak DMT and harmine concentrations. Reductions in cognitive function such as working memory (Dos Santos, Balthazar, Bouso, & Hallak, 2016; Bouso et al., 2013) and convergent thinking during acute intoxication with ayahuasca (Kiraga et al., 2021; Kuypers et al., 2016) and related tryptamines (Mason et al., 2021) have been previously reported. However, improvements in cognitive flexibility (Bouso et al., 2013) and divergent thinking (Kuypers et al., 2016) under ayahuasca as assessed with objective measures such as a Stroop task and a Picture Concept Task have been reported as well. The present study revealed some, but not strong, support for an increase in mental imagery and associative thinking under ayahuasca. Perspective shifting was positively correlated with peak DMT concentration, suggesting increased mental imagery in participants with high peak DMT concentrations. In addition, mean word fluency during the CFAT was higher under ayahuasca as compared with baseline, suggesting under ayahuasca participants were able to come up with slightly more associations, but this difference just failed statistical significance ($p = .057$). Possibly, the general absence of any strong and widespread effects of ayahuasca on mental imagery or cognitive functions associated with mental imagery might be related to the fact that Santo Daime participants in the present study were highly experienced ayahuasca users. A previous comparison of the impact of neuropsychological performance during acute ayahuasca intoxication in occasional and experienced ayahuasca users demonstrated that memory impairments as well increased cognitive flexibility were mostly present in occasional users, but not in experienced users (Bouso et al., 2013). It has been suggested that compensatory or neuroadaptive effects associated with long-term ayahuasca intake could mitigate the impact of acute ayahuasca intoxication on neurocognitive function in experienced users, who may develop coping skills to navigate the altered state more easily as the ayahausca experience becomes increasingly familiar with repeated use (Bouso et al., 2013).

The lack of a widespread impact of ayahuasca on mental imagery and cognitive functions associated with mental imagery in highly experienced ayahuasca users (mean = 563 times) could have been caused by various mechanisms. From a psychological perspective, familiarity with the psychedelic state under ayahuasca causing experienced users to become less distracted (Bouso et al., 2013) or less stimulated by the acute effects of ayahuasca while performing mental imagery tasks or tasks related to mental imagery. Alternatively, chronic long-term use of ayahuasca may have caused tolerance to some of the acute effects of ayahuasca on mental imagery. Preclinical studies have demonstrated reduced 5HT2A receptor density and signaling after repeated administration of psychedelic compounds (Buchborn, Schroder, Dieterich, Grecksch, & Hollt, 2015; Buckholtz, Zhou, Freedman, & Potter, 1990) that may mitigate the acute impact of ayahuasca

on cognition. For compounds such as cannabis, it has been shown that tolerance can develop selectively for the acute impact of the drug on neurocognitive performance, even in the presence of a significant level of subjective high (Ramaekers, Mason, & Theunissen, 2020). Similarly, chronic 5HT2A receptor downregulation may explain why in the present study cognitive functions of Santo Daime participants were not or only mildly affected after drinking ayahuasca even in the presence of a psychedelic experience. Alternatively, stimulatory effects of ayahuasca on mental imagery have appeared subacutely, rather than acutely during the psychedelic experience. Impairment of cognitive flexibility as observed under ayahuasca in the present study was also reported during acute exposure to psilocybin (Mason et al., 2021). Yet, divergent thinking of participants in the latter study actually improved 7 days after administration of psilocybin and both the acute decrement as well as the subacute increment in divergent thinking were predicted by decreased functional connectivity in the default mode network during the acute psychedelic state (Mason et al., 2021). Indeed, previous work has found that although psychedelics decrease functional connectivity within the default mode network acutely, they increase functional connectivity subacutely (Barrett, Doss, Sepeda, Pekar, & Griffiths, 2020; Smigielski, Scheidegger, Kometer, & Vollenweider, 2019; Carhart-Harris et al., 2017), potentially via a neuroplastic effect on brain network function (Vollenweider & Preller, 2020; Ly et al., 2018). Likewise, recent neuroimaging study comparing brain function of experienced ayahuasca users before and after drinking ayahuasca revealed postacute reductions in glutamate in the posterior cingulate cortex and increased functional connectivity between the posterior cingulate cortex, the anterior cingulate cortex, and limbic structures (Sampedro et al., 2017). At present, it is unknown how long such neuroadaptations in the brain persist and how these may affect neuropsychological function during or after an acute ayahuasca experience, but observational studies have reported increments in decentering and mindfulness that lasted for up to 4 weeks (Kiraga et al., 2021; Soler et al., 2016, 2018; Uthaug et al., 2018) or 1 year after drinking ayahuasca (van Oorsouw et al., 2022). It also not known how and if such neuroadaptations pertained in Santo Daime participants in the current study who potentially drank ayahuasca every fortnight over a period of 15 years and whether such neuroadaptions may have boosted their mental imagery performance at baseline.

This study also comes with limitations. The order in which participants were tested was not balanced. Participants always drank ayahuasca on the day after they completed a baseline session. Potentially, this may have introduced learning effects that could have positively affected performance of participants during their second test day when they drank ayahuasca. Yet, it is unlikely that this happened during tasks for which parallel versions were administered on test days such as the CFAT. In addition, if learning effects did occur, these did not prevent the detection of impairment in cognitive flexibility under ayahuasca nor the detection of association between cognitive performance and peak DMT concentrations as assessed with the perspective shifting task and the CFS. It should also be noted that we employed closed questionnaires and structured tasks to assess mental imagery, but did not solicit additional descriptors of mental imagery with open questions. Finally, we did not collect data regarding the subacute effects of ayahuasca on mental or spiritual well-being of Santo Daime members and therefore cannot exclude the possibility that also subacute effects of ayahuasca might be related to DMT and harmaline concentrations achieved acutely.

In summary, the present study demonstrated that the altered state of consciousness during an acute ayahuasca experience in experienced members of the Santo Daime community was positively correlated to peak DMT concentrations in serum, confirming previous notions that the primary phenomenological characteristics of ayahuasca are driven by DMT. Overall, measures of mental imagery did not noticeably differ between the baseline and ayahuasca condition and only two measures related to mental imagery significantly correlated to peak DMT concentrations. This suggests that compensatory or neuroadaptive effects associated with long-term ayahuasca intake may have mitigated the acute impact of ayahuasca in Santo Daime members that participated in the current study.

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## Data Availability Statement

Data can be shared upon reasonable request to the first author.

## Author Contributions

Johannes G. Ramaekers: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing—Original draft. Pablo Mallaroni: Data curation; Formal analysis; Investigation; Methodology; Writing—Review & editing. Lilian Kloft: Conceptualization; Data curation; Investigation; Writing—Review & editing. Johannes T. Reckweg: Data curation; Formal analysis; Investigation; Writing—Review & editing. Stefan W. Toennes: Data curation; Formal analysis; Methodology; Writing—Review & editing. Kim van Oorsouw: Conceptualization; Data curation; Formal analysis; Investigation; Writing—Review & editing. Natasha L. Mason: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—Review & editing.

## Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

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