

Dose-dependent modulation of visual imagery by Ayahuasca and dampening of visual processing away from external input: a placebo-controlled pharmacoinaging study

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Abstract

Ayahuasca, an amazonian brew containing the serotonergic psychedelic substance N,N-dimethyltryptamine (DMT), induces distinctive visual perceptual phenomenology, yet the neural mechanisms underlying the interplay between external visual drive and internal imagery remain unknown. Using a placebo-controlled, within-subject fMRI design, the present study investigated the impact of multiple doses of Ayahuasca upon strong bottom-up visual drive using high contrast periodic dynamic stimuli processing in 11 participants. Subjective ratings indicated psychedelic effects regarding visual perception and imagery, with dose-dependent increases in simple and complex visual imagery and intensity ratings. At the neural level, high-dose Ayahuasca attenuated this strong stimulus-evoked activation in ventral visual regions and reduced stimulus-evoked deactivation in the precuneus, while early visual cortex responses remained unaffected at this high stimulus drive level. Functional connectivity analyses revealed that Ayahuasca decreased the de-coupling between early visual cortex and a midline associative region, spanning the cuneal cortex and precuneus. These findings support the view that Ayahuasca biases visual processing away from externally driven input toward internally oriented processing, consistent with predictive coding and the REBUS model of psychedelic action.

Introduction

The human visual system is responsible for processing both externally driven and internally generated visual experiences. In everyday perception, there is a delicate balance between these processes that enables us to generate internal visual representations (mental imagery) while maintaining the ability to differentiate them from external stimuli. This balance between external perception and internal imagery is profoundly altered under the influence of serotonergic psychedelics, which can induce vivid hallucinations, enhanced mental imagery, and perceptual distortions (Aday et al., 2021). Among these substances, Ayahuasca, a traditional Amazonian brew containing N,N-Dimethyltryptamine (DMT), is well known for its ability to induce intense visual experiences (Shanon, 2002).

Ayahuasca-induced visual phenomena are often described as bright, geometric, and immersive, and play a central role in its use during shamanic practices (Shanon 2002; De Araujo et al., 2012). These experiences frequently blur the distinction between eyes-open and eyes-closed states, suggesting that internally driven imagery can dominate over external sensory input (Shanon 2002; Kometer & Vollenweider, 2018). However, the neural mechanisms by which Ayahuasca alters the balance between externally and internally driven visual processing remain unclear. In particular, how these effects compare to externally driven visual processing and how psychedelics modulate responses to external stimuli remain open questions. Therefore, the present study employed functional MRI (fMRI) to investigate neural mechanisms underlying Ayahuasca-induced visual imagery and its relationship to externally driven visual perception.

Psychedelics induce a wide range of visual effects, which can be categorized along a continuum from enhanced imagery to pseudohallucinations and full hallucinations. Enhanced imagery involves

intensified and vivid mental imagery that remains under the subject's voluntary control, while pseudohallucinations are more vivid and less controlled, but still recognized as self-generated. At higher doses, psychedelics often induce full-blown hallucinations - internally generated perceptual phenomena indistinguishable from reality (Kometer & Vollenweider, 2018).

Psychedelic-induced visual imagery can be distinguished as simple/elementary or complex. Elementary hallucinations, including geometric patterns, spirals, and lattices, are closely tied to the functional architecture of the primary visual cortex (V1) and are consistently reported across individuals, cultures and substances (Bressloff et al., 2002; Klüver & Critchley, 1966; Kometer & Vollenweider, 2018; Siegel, 1977). In contrast, complex hallucinations involve the perception of people, animals, or landscapes, which recruit extrastriate visual cortex, and are often charged with deeply personal or symbolic meaning. They emerge at higher doses, are less frequently reported, are influenced by culture and context, and are thought to depend on associative brain regions in particular in the visual ventral stream (Shanon, 2002; Cott & Rock, 2008; Kometer & Vollenweider, 2018; Leptourgos et al., 2020).

The perceptual effects of psychedelics can be understood within the framework of predictive coding, which describes perception as an interaction between bottom-up sensory inputs and top-down predictions (K. Friston & Kiebel, 2009). According to this framework, the brain continuously generates expectations (or high-level priors) that shape sensory experience by filtering and interpreting incoming information. Normally, high-level priors stabilize perception and suppress irrelevant or ambiguous sensory input. One of the most widely accepted neuroscientific models of psychedelic action, the Relaxed Beliefs Under Psychedelics (REBUS) model proposes that psychedelics relax high-level priors within higher-order brain regions (e.g. the Default Mode Network), increasing the flow of bottom-up sensory signals from low-level areas (R. L. Carhart-Harris & Friston, 2019). Supporting this framework, neuroimaging studies also indicate that psychedelics diminish the normal anticorrelation between the DMN and task-positive attention networks, leading to less distinction between internally and externally directed processing (Stoliker et al., 2023). While this model can explain some aspects of psychedelic visual phenomenology (e.g. enhanced brightness, colors and contrast), it doesn't account for the highly structured and distinctive visual hallucinations experienced under psychedelics (Aqil & Roseman, 2023). Aqil and Roseman (2023) argue that rather than being a passive consequence of weakened priors, activity in low-level sensory areas (but not extrastriate visual regions) might be the primary driver of psychedelic hallucinations.

This view is more consistent with the subjective shift from externally to internally generated imagery and is also in line with the neurophysiological mechanisms of action of psychedelics. Psychedelics act as 5-HT_{2A} receptor agonists, which are also expressed in the visual cortex, including V1, leading to increased overall excitability of the visual cortex (Kometer & Vollenweider, 2018; Moreau et al., 2009). Computational models suggest that this increase in excitability can push early visual cortex into oscillatory dynamics, which is hypothesized to produce the recurring geometric patterns characteristic of elementary hallucinations (Bressloff et al., 2002; Kometer & Vollenweider, 2018).

Neuroimaging findings are also in line with the idea that psychedelics increase cortical excitation in visual areas and shift perception toward internally generated imagery. Increased resting-state activity in visual areas and increased functional connectivity between visual and higher-order areas have been consistently reported under psychedelics (Castelhano et al., 2021; dos Santos et al., 2016). In a study by de Araujo et al. (2012), Ayahuasca increased activity in V1 during voluntary mental imagery to a level comparable to actual visual perception, which suggests that psychedelics induce a state in which internally generated imagery is processed as if it were externally driven visual input. In line with this idea, Roseman et al., (2016b) found that LSD enhanced functional connectivity between early visual cortical regions with matching retinotopic representations, even with eyes closed - suggesting that the visual system behaves as if it were processing spatially localized visual input in the absence of external stimuli. Further supporting the role of early retinotopic visual cortex in specific psychedelic phenomenology, Pais et al. (2024) found that inhaled DMT significantly enlarged population receptive fields (pRFs) in peripheral V1, hypothesized to underlie tunnel vision and other perceptual distortions.

Another relevant finding is the reduction of alpha power in occipital regions in psychedelic states. Psilocybin and Ayahuasca have been found to suppress occipital alpha oscillations, which are thought to normally inhibit spontaneous visual activity (Kometer et al., 2013; Valle et al., 2016). Alpha-suppression is correlated with the intensity of visual hallucinations and both disappear when 5-HT_{2A} receptor activity was blocked with ketanserin (Kometer et al., 2013; Valle et al., 2016).

Together, these findings suggest a framework whereby psychedelic visual hallucinations arise from a complex interplay between heightened excitability in early sensory regions and high-level integrative processes, creating a state where internally generated imagery dominates perception.

The present study aims to further elucidate how psychedelics modulate the balance between externally and internally driven visual processing, by investigating the interaction between visual stimulation and psychedelic-induced changes in neural dynamics. Enhanced visual imagery and hallucinations under psychedelics have also been linked to profound psychological effects, including awe and a re-evaluation of self-referential beliefs (Aqil & Roseman, 2023), which might be relevant to psychedelic-assisted therapy, where visual experiences might play a key role in facilitating therapeutic outcomes (Aqil & Roseman, 2023; Császár-Nagy et al., 2019).

We aimed at understanding whether Ayahuasca alters visual stimulus-evoked brain activity in key regions compared to placebo and if there is a dose-dependent effect of Ayahuasca on activation in early visual cortex (V1–V3) during visual stimulation. Moreover, we aimed at

understanding its effects on functional connectivity between early visual cortex and other brain regions during visual stimulation, and whether its changes in neural activation/functional connectivity correlate with subjective experiences.

Methods

The present research used data collected from a study at the ICNAS/CIBIT - University of Coimbra, employing a placebo-controlled within-subjects design. Ethical approval has been obtained by the Ethics Committee of the Faculty of Medicine of the University of Coimbra and conducted in accordance with the principles of the Declaration of Helsinki.

Participants

Twelve healthy volunteers with normal or corrected-to-normal vision were enrolled in the study; one did not complete the last session, leaving 11 participants for analysis (8 males and 3 females, mean age = 40.36, SD = 6.87). Participants were required to have prior experience with psychedelics with no history of significant adverse reactions. Participants were excluded in case of personal or family history of psychiatric disorders, a past or current history of substance dependence, a history of neurological, cardiac, or liver dysfunction, current use of psychoactive, antihypertensive, or sympathomimetic medications, immunosuppression, being or suspected of being pregnant, or breastfeeding. All participants provided informed consent prior to participation.

Procedure

Before the start of the study, participants underwent a comprehensive clinical and neuropsychiatric evaluation conducted by a medical doctor and two trained psychologists. Once enrolled, they received detailed information about the experimental procedures along with preparatory and training materials (Fig. 1).

The study involved three experimental sessions, spaced at least one month apart, with a different treatment administered in each session: ayahuasca containing 0.5 mg/kg DMT, ayahuasca containing 0.8 mg/kg DMT, or a placebo (a mixture of water, brewer's yeast, zinc sulfate, and citric acid). We selected a high dose of 0.8 mg/kg DMT (in Ayahuasca brew) based on prior human studies showing robust psychedelic effects at comparable doses. For example, Riba et al. (2003) identified 0.85 mg/kg DMT as a high dose producing strong subjective and physiological responses in healthy volunteers. A lower dose of 0.5 mg/kg DMT was included to assess dose-dependent effects. The placebo and low dose (0.5 mg/kg DMT) were double-blind and randomized, while the highest dose (0.8 mg/kg DMT) was always administered on the last session for ethical and practical reasons (to ensure tolerance of lower doses first and to prevent unblinding early in the study).

To ensure safety and psychological wellbeing, participants attended two online preparation sessions before each treatment session (one week and one day prior). After each session, they completed two online integration sessions (one day and one week later) to process and integrate their experiences.

During each treatment session, participants received the substance or placebo and underwent fMRI scanning 40 minutes after substance administration to account for the pharmacokinetic profile. Before

receiving the administration and after the scanning session, they completed various questionnaires assessing their subjective experience.

Subjective Measures

The Hallucinogen Rating Scale (HRS)

The Hallucinogen Rating Scale (HRS; Strassman et al., 1994) is a comprehensive 100-item questionnaire designed to assess the subjective effects of hallucinogenic substances. Participants rate each item on a four-point intensity scale (*0 = not at all, 4 = extremely*). The items are grouped into six domains that capture distinct aspects of the psychedelic experience: 1) Somaesthesia, including interoceptive, visceral, and tactile sensations; 2) Affect, covering emotional and affective reactions; 3) Perception, encompassing visual, auditory, gustatory, and olfactory experiences; 4) Cognition, involving changes in thought processes or content; 5) Volition, reflecting alterations in the ability to willingly interact with oneself, the environment, or specific aspects of the experience; and 6) Intensity, reflecting the overall strength or magnitude of the experience. Participants completed the HRS after each scanning session.

The Vividness of Visual Imagery Questionnaire-Revised Version (VVIQ-RV)

The VVIQ-RV is a standardized 32-item questionnaire used to assess the quality of visual imagery, originally developed by Marks (1973) and adapted into Portuguese by Pinho et al. (2007). Participants are asked to visualize specific scenarios, such as a rising sun, and rate the vividness of these mental images using a four-point scale (*0 = no image at all, 4 = perfectly clear and as vivid as real seeing*). An overall imagery vividness score is calculated by adding the item responses, with higher values reflecting more vivid and lower values reflecting less vivid mental imagery (ranging from 16 to 80). Participants filled out the VVIQ-RV twice, once before drug administration, and once after the scanning session.

Visual Analog Scale (VAS)

Participants also completed a custom Visual Analog Scale (VAS) to retrospectively assess subjective experiences during the session, including visual and emotional experiences. The VAS was filled out twice: once with reference to the peak phase of the experience, and once with reference to a later timepoint when the effects had begun to diminish. Participants were instructed to reflect on these distinct moments and rate each item accordingly. Responses were recorded on a scale ranging from 0 to 10, with 0 indicating '*not more than usually*' and 10 indicating '*much more than usually*'.

Neurophenomenological Approach

To enable the integration of neural findings with real-time subjective experience, intensity ratings were collected throughout the experimental session. The intensity of subjective effects was orally assessed at every 30 minutes after substance intake. During fMRI acquisition, participants' state of consciousness and the intensity of their subjective experience (on a scale from 0 to 10) were evaluated verbally via the MRI speaker after each functional run. Debriefing and administration of retrospective questionnaires were conducted only after participants reported that the subjective effects had fully subsided (i.e., intensity rating of 0). On the following day, a microphenomenological interview was conducted by two trained research psychologists, following the guidelines established by Petitmengin (2006). The microphenomenological interview was not analyzed within the scope of this paper.

fMRI Acquisition and Task Design

fMRI Imaging was performed using a 3T MRI scanner (MAGNETOM Prisma, Siemens Medical Solutions) with a 64-channel head-coil. Functional data were collected using T2*-weighted echo-planar imaging (EPI) with a voxel size of 2x2x2 mm (TR = 2000 ms, TE = 30 ms, FA = 90°).

The fMRI protocol consisted of a series of scans designed to investigate both task-based and resting-state brain activity. Each session began with a 7-minute resting-state functional scan, followed by a visual stimulation paradigm consisting of two 10-minute runs. This was followed by a 10-minute T1-weight structural scan and a 10-minute retinotopy mapping block. The present study focuses on the visual stimulation paradigm, specifically designed to investigate the neural mechanisms underlying Ayahuasca-induced visual alterations.

The visual paradigm employed a block design, in which participants were exposed to periodic circular empty-field flicker (Ganzflicker) stimuli intended to induce elementary visual imagery similar to those reported in psychedelic states. Bartossek et al. (2021) demonstrated that flicker light stimulation can induce visual hallucinations comparable in intensity to psychedelic substances. By using this paradigm, we aimed to provide strong externally driven visual input known to engage the early visual cortex, allowing us to examine how Ayahuasca influences externally driven visual processing in early visual areas and the interaction with internally generated imagery. The paradigm consisted of two runs of 10 min 8 s, each divided into three experimental conditions presented in blocks (Fig. 1). Stimulus blocks were presented for 20, 22, or 24 seconds, interspersed with rest blocks of 12, 14, or 16 seconds. Each condition was repeated six times per run, resulting in 12 repetitions per condition across the two runs.

Data Analysis

Subjective Measures

To assess the subjective effects of the Ayahuasca intervention, the Hallucinogen Rating Scale (HRS), the Vividness of Visual Imagery Questionnaire (VVIQ), the Visual Analog Scale (VAS) and the intensity ratings of the neurophenomenological assessment were analyzed using SPSS version 30.0.

For the HRS, total scores and scores on the *Perception* subscale were computed, as well as a score reflecting a cluster of visual domain-specific items (HRS items 57–68). This cluster included items related to changes in object brightness, visual distinctiveness, visual field vibration, pattern overlay, and altered dimensionality. Each subscale score was computed as the mean of the respective items. Repeated-measures ANOVA was conducted separately for each subscale, with Dose (placebo, 0.5 mg/kg, 0.8 mg/kg) as the within-subjects factor.

For the VVIQ-RV, pre- and post-session total scores were calculated for each session as the mean of all items. A two-way repeated-measures ANOVA was conducted on the total scores with Time (Pre, Post) and Dose (placebo, 0.5 mg/kg, 0.8 mg/kg) as within-subjects factors.

For the VAS, only peak-phase ratings of the items related to visual perception were included in the analysis (6 items). For each VAS item as well as a total score calculated by averaging all six items, a repeated-measures ANOVA was conducted with Dose (placebo, 0.5 mg/kg, 0.8 mg/kg) as the within-subjects factor. The visual VAS items included:

I could see images from imagination or memory with extreme clarity”, “Image details seemed clearer and sharp (augmented)”, “I experienced simple visual patterns”, “I experienced complex/elaborate visual images”, “Colors were brighter” “Colors were intense

For the intensity ratings, the intensity scores collected immediately after the visual paradigm within the scanner were analyzed. Repeated-measures ANOVA was conducted on these intensity scores, with Dose (placebo, 0.5 mg/kg, 0.8 mg/kg) as the within-subjects factor.

fMRI Neural Activation

MRI Data Preprocessing. Anatomical and functional MRI data preprocessing were performed using BrainVoyager 23.2 (Brain Innovation, Maastricht, The Netherlands; Goebel et al., 2006). Runs with excessive motion (above 5 mm) were excluded from the analysis, resulting in the exclusion of 4 runs across 2 participants. Anatomical data were corrected for intensity inhomogeneities and normalized to MNI space. Functional preprocessing included mean intensity adjustment, slice timing correction, 3D rigid body motion correction, and high-pass temporal filtering using a Discrete Cosine Transform (DCT) basis set with 3 basis functions to remove low-frequency drifts. Intra-session alignment was performed using the first volume of the first functional run. EPI distortion correction was performed using BrainVoyager’s COPE plugin based on reverse phase-encoding images (Bremner et al., 2020). Functional scans were co-registered to the anatomical images and normalized to MNI space. Spatial smoothing with an 8 mm FWHM Gaussian kernel was applied to enhance the signal-to-noise ratio.

Whole-Brain General Linear Model (GLM). Whole-brain General Linear Model (GLM) analyses were conducted using BrainVoyager 23.2 to identify brain regions showing differential activation during visual stimulus processing under Ayahuasca compared to placebo. Preliminary analyses indicated insufficient statistical power to detect condition-specific effects among the three visual stimulus types. Furthermore, we did not predict in this experiment that differences would emerge as a function of stimulus type,

therefore, they were merged into a single "Stimulus" condition to assess the overall effect of visual stimulation.

For each run of each participant, a voxel-wise general linear model (GLM) was computed. A single stimulus predictor (combining all three visual conditions) was defined and convolved with BrainVoyager's default canonical hemodynamic response function (HRF). The baseline (rest) was modeled implicitly. To account for motion-related variance, six rigid-body motion parameters, their temporal derivatives (12 regressors in total), and spike regressors were included as nuisance covariates in the first-level design matrices. Voxel time courses were normalized to percent signal change.

Group-level GLM analyses were performed under the random-effects (RFX) assumption to allow the generalizability of the findings beyond the sample. To improve anatomical specificity and reduce the number of multiple comparisons, group-level analyses were restricted to cortical tissue using an MNI-based mask excluding background voxels, ventricles, and white matter.

To examine the general effect of the visual stimulus on neural activation, the Stimulus condition was contrasted against the implicit baseline (Stimulus > Rest) across all Ayahuasca doses. To identify brain regions in which Ayahuasca significantly modulated the neural response to the visual stimulus, the stimulus effect was compared between the different Ayahuasca dosages (Stimulus High Dose > Stimulus Placebo; Stimulus Low Dose > Stimulus Placebo; Stimulus High Dose > Stimulus Low Dose).

Group-level statistical maps were corrected for multiple comparisons using cluster-level thresholding as implemented in BrainVoyager's ClusterThresh plugin (Forman et al., 1995; Goebel et al., 2006). A cluster-defining threshold of $p < 0.001$ (uncorrected) was used, and the minimum cluster size (k) required for cluster-level significance ($p < 0.05$, FWE-corrected) was determined via 1000 Monte Carlo Simulations.

Region of Interest (ROI) Analysis of Early Visual Cortex. To test the effect of Ayahuasca specifically in early visual regions and enhance statistical power, a region of interest (ROI) analysis was conducted. Early retinotopic visual areas were defined using a probabilistic functional atlas of retinotopic areas (Benson & Winawer, 2018), including bilateral V1, V2, and V3. These regions were merged into a single early visual ROI (center of gravity: $x = 0.85$, $y = -86.66$, $z = 1.58$ MNI) and constrained using individual functional activation maps derived from the contrast of visual stimulation versus rest to ensure subject-specific relevance.

ROI analyses were carried out using BrainVoyager's multi-subject VOI analysis tool with an RFX GLM model. The following contrasts were tested to assess dose-dependent activation changes across drug conditions: (1) Stimulus High Dose > Stimulus Placebo; (2) Stimulus Low Dose > Stimulus Placebo; and (3) Stimulus High Dose > Stimulus Low Dose.

fMRI Functional Connectivity - Generalized Psychophysiological Interaction (gPPI)

To investigate network-level changes that may not be captured by activation-based methods, a generalized psychophysiological interaction (gPPI) analysis was conducted to investigate whether Ayahuasca alters task-dependent functional connectivity. gPPI assesses how functional connectivity (correlation) between a seed region and the rest of the brain changes depending on experimental conditions (K. J. Friston et al., 1997; McLaren et al., 2012). In this approach, a general linear model (GLM) is constructed that includes: (1) the psychological task regressors (e.g., stimulus blocks), (2) the physiological regressor (i.e., the seed region's BOLD time series), and (3) their interaction term, which capture task-specific connectivity changes. The interaction regressors are computed as the element-wise product of the seed time series and the task regressors. This allows the model to identify brain regions that show increased or decreased correlation with the seed region during task conditions, above and beyond the main effect of task or baseline connectivity (K. J. Friston et al., 1997; McLaren et al., 2012).

The gPPI analysis tested how Ayahuasca modulates the effect of the visual paradigm on functional connectivity between early visual regions and the rest of the brain, compared to placebo. As the prior GLM analysis did not reveal any significant effects of the low dose Ayahuasca condition, this condition was omitted from the gPPI analysis to focus only on differences between the high dose and placebo conditions. The gPPI analyses were performed using CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012; RRID:SCR_009550) release 22.v2407 (Nieto-Castanon & Whitfield-Gabrieli, 2022) and SPM (Penny et al., 2007; RRID:SCR_007037) release 25.25.01.02. The early visual ROIs (V1-V3) defined in the prior ROI GLM analysis were imported to CONN and used as subject-specific seed regions. Seed time series were extracted as the average BOLD signal across all voxels within each seed region.

MRI Data Preprocessing and Denoising. For the gPPI analysis, functional and anatomical data were preprocessed again in CONN using a modular preprocessing pipeline (Nieto-Castanon, 2020). Preprocessing steps included realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and MNI-space normalization, and spatial smoothing using a 8 mm FWHM Gaussian kernel. In addition, functional data were denoised using a standard denoising pipeline (Nieto-Castanon, 2020) including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors; Friston et al., 1996), outlier scans (below 55 factors; Power et al., 2014), and linear trends (2 factors) within each functional run, and simultaneous bandpass frequency filtering of the BOLD timeseries (Hallquist et al., 2013) between 0.008 Hz and 0.09 Hz. This band-pass filter preserves the block design frequency (≈ 0.03 Hz), and thus retains stimulus-related BOLD fluctuations.

gPPI Analysis. Separately for each pair of seed and target areas, a generalized psychophysiological interaction model (gPPI) was defined with the seed BOLD signal as the physiological factor, boxcar signals characterizing the stimulus condition convolved with an SPM canonical hemodynamic response function as psychological factors, and the product of the two as the psychophysiological interaction term. Functional connectivity modulation during stimulus blocks was characterized by the multivariate

regression coefficient of the psychophysiological interaction terms in each model, modeled separately for each drug condition.

Group-level analyses were performed using a General Linear Model (GLM). For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory (Nieto-Castanon, 2020; Worsley et al., 1996). Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected $p\text{-FDR} < 0.05$ cluster-size threshold (Chumbley et al., 2009). The following contrasts were tested:

1. Visual Stimulus > Rest across both drug conditions: This contrast identified brain regions showing task-related changes in functional connectivity with the seed region during stimulus blocks, averaged across both the placebo and ayahuasca conditions.
2. Visual Stimulus Ayahuasca > Visual Stimulus Placebo: This contrast identified brain regions showing greater task-related changes in functional connectivity with the seed region during stimulus blocks under the ayahuasca condition compared to the placebo condition.

Correlation of Neural Results and Subjective Experience

To examine the relationship between brain activation and subjective experience, Spearman's correlation analysis was performed between the neural results and behavioral scores.

For each participant, stimulus-related beta values were extracted from each significant cluster (ROI) identified in the group-level GLM. Additionally, gPPI beta values were extracted for each participant from the cluster identified as significant in the whole-brain seed-to-voxel gPPI analysis. For both types of beta values, subject-level difference scores between the high-dose Ayahuasca and placebo conditions ($\Delta\beta = \beta_{\text{high}} - \beta_{\text{placebo}}$) were computed. Likewise, subject-level differences in behavioral ratings were calculated for the Hallucinogen Rating Scale (HRS; Total, Perception, Visual), relevant VAS items (Simple and Complex Visual Patterns) and Intensity scores, resulting in Δ scores per participant. Spearman correlations were then computed between each $\Delta\beta$ and Δ behavioral scores, using a significance threshold of $p < 0.05$.

Results

Subjective Experience

Hallucinogen Rating Scale – HRS, Vividness of Visual Imagery Questionnaire – VVIQ, Visual Analog Scales – VAS and Intensity Ratings

Repeated-measures ANOVAs were conducted across measures of subjective experience (see Fig. 2). The most prominent effects were found for online monitoring of intensity ratings (as expected because they follow the time course of Ayahuasca effects, and visual perceptual effects measured by VAS, with dose and time dependent effects also observed for VVIQ (see below).

Regarding the HRS scores, the analysis revealed no significant differences across doses (total score, $F(2, 20) = 1.95, p = .168$, HRS perception scores, $F(2, 20) = 1.94, p = .169$, HRS visual subscale, $F(2, 20) = .40, p = .673$).

Regarding subjective intensity ratings differed across the three dosing conditions (placebo, low dose, high dose) the analysis revealed a significant main effect of dose on intensity ratings, $F(2, 20) = 5.65, p = .011$. Follow-up polynomial contrasts indicated a significant linear trend, $F(1, 10) = 9.46, p = .012$, suggesting a dose-dependent increase in subjective intensity.

Two-way repeated-measures ANOVA were performed to examine the effects of time (pre vs. post) and dose (dose 1, 2, 3) on VVIQ scores. Results show a significant main effect of time, $F(1, 9) = 15.48, p = .003$, indicating that vividness scores were significantly higher after the sessions ($M = 62.67, SE = 4.50$) compared to before ($M = 55.67, SE = 4.09$). There was also a significant main effect of dose, $F(2, 18) = 3.60, p = .048$. Pairwise comparisons using Bonferroni correction revealed that scores in dose 2 ($M = 62.75, SE = 4.39$) were significantly higher than in Session 3 ($M = 56.75, SE = 3.50$), $p = .014$, while differences between other Sessions were not significant. A significant interaction between time and dose was observed, $F(2, 18) = 3.59, p = .049$. Follow-up comparisons showed that VVIQ scores significantly increased from pre- to post-session in dose 1 (M difference = 7.00, $p = .023$) and dose 2 (M difference = 11.10, $p = .005$), but not in dose 3 (M difference = 2.90, $p = .146$).

Regarding visual analog scale (VAS), although the total VAS score did not differ significantly across sessions, $F(2, 18) = 2.80, p = .088$ (dose 1, $M = 0.95, SD = 1.04$, dose 2 $M = 2.46, SD = 2.89$, dose 3 $M = 2.46, SD = 2.46$), a significant main effect of session was observed for the individual VAS item “*I experienced simple visual patterns*”, $F(2, 18) = 5.50, p = .014$. Pairwise comparisons indicated a significant increase from dose 1 ($M = 0.30$) to dose 2 ($M = 2.77$) and dose 3 ($M = 3.12$). A significant linear trend was also observed, $F(1, 9) = 8.59, p = .017$, indicating increasing ratings with dose. The item “*I experienced complex/elaborate visual images*” showed a marginally significant effect, $F(2, 18) = 3.56, p = .050$. A significant linear contrast confirmed an increase across doses, $F(1, 9) = 5.32, p = .046$. All other VAS items did not show significant differences across doses.

Neural Activation

Effect of the Visual Stimulus

A random effects (RFX) GLM analysis was conducted to assess the neural response to the visual stimulation paradigm across all sessions. As expected, robust activation was observed in areas involved in visual processing, including bilateral lateral geniculate nucleus (LGN) and bilateral occipital regions

including the primary visual cortex (V1) and extrastriate visual areas in occipital and temporal cortices. In addition, widespread deactivation was observed in non-visual areas, particularly in frontal, parietal, and temporal cortices. These deactivations may reflect reduced engagement of networks not directly involved in the processing of external visual input, such as the default mode network (DMN). These results confirm the effectiveness of the stimulus in engaging visual processing pathways, including the lateral geniculate nucleus (Fig. 3, top). **Figure 3.** Top: Group-Level RFX Activation Map for the Visual Stimulus Contrast. Activation maps are overlaid on an average anatomical image computed from all participants, thresholded using cluster-level correction ($p < .001$ voxel-level threshold (uncorrected), $p < 0.05$ cluster-level threshold (FWE-corrected), $k \geq 84$ voxels). Warm colors indicate significantly greater activation during visual stimulation compared to baseline (positive t -values). Cool colors indicate significant deactivation (negative t -values). Bottom: Clusters Exhibiting Increased Stimulus - Related Activation under Ayahuasca (High Dose vs. Placebo). Activation maps are overlaid on an average anatomical image computed from all participants, thresholded using cluster-level correction ($p < .001$, uncorrected voxel-level threshold, cluster FWE $k \geq 39$ voxels). Warm colors indicate significantly greater activation under Ayahuasca compared to placebo (positive t -values).

Effect of Ayahuasca on Visual Stimulus Processing

To assess the effects of Ayahuasca on visual processing at the population level, an RFX GLM was performed contrasting stimulus effects under high dose versus placebo, low dose versus placebo, and low dose versus high dose. Cluster-level correction was applied using a cluster-defining threshold of $p < .001$ (uncorrected), a cluster level threshold of $p < 0.05$ (FWE-corrected) and a minimum cluster size was determined by 1000 Monte Carlo simulations. The contrasts involving the low dose (low dose > placebo and high dose > low dose) yielded no significant clusters. The high-dose versus placebo contrast revealed five significant clusters ($k \geq 39$ voxels), indicating altered stimulus-related activation under the influence of high-dose Ayahuasca (Fig. 3 bottom, and Fig. 4, see Supplementary Fig. 1 Clusters Exhibiting Decreased Stimulus - Related Activation under Ayahuasca (High Dose vs. Placebo)).

The largest cluster (1,245 voxels), centered at $[+7, -76, +38]$, showed increased activation, with a peak in the precuneus and additional overlap in the left cuneal cortex. A second positive cluster (379 voxels), centered at $[-7, -64, +57]$, also showed increased activation and was also located in the precuneus. The remaining three clusters showed decreased activation under Ayahuasca. The largest of these (420 voxels), centered at $[+38, -50, -6]$, peaked in the right temporal occipital fusiform cortex (R TOFusC) and extended into the right inferior temporal gyrus, temporo-occipital part (R toITG). The second negative cluster (413 voxels), centered at $[+46, +4, +30]$, peaked in the right precentral gyrus (R PrCG). The last cluster (314 voxels), centered at $[+33, -79, +5]$, showed a peak in the right lateral occipital cortex, inferior division (R iLOC). Looking at the magnitude and direction of activation changes, these results indicate a pattern in which Ayahuasca reduced the typical stimulus-driven activation of ventral stream visual regions (toITG and iLOC), while simultaneously reducing stimulus-related deactivation in

the precuneus (Fig. 11). Peak cluster statistics and anatomical locations are summarized in Table S1 of Supplementary Material.

Relationship Between Neural Activation and Subjective Experience

Three significant negative correlations were observed (Fig. 5). First, larger Δ HRS Total scores were associated with lower positive $\Delta\beta$ values in the anterior precuneus ($\rho = -0.62$, $p = 0.048$), indicating that participants reporting stronger psychedelic effects showed less reduction of stimulus-related deactivation in this region under high-dose Ayahuasca. Second, larger Δ HRS Visual scores were associated with more negative $\Delta\beta$ values in the right iLOC ($\rho = -0.66$, $p = 0.027$), reflecting greater reductions of stimulus-related activation under high-dose Ayahuasca. Finally, larger Δ Intensity scores were associated with lower positive $\Delta\beta$ values in the posterior precuneus ($\rho = -0.64$, $p = 0.034$), again reflecting less reduction of stimulus-related deactivation under high-dose Ayahuasca.

ROI Analysis of Early Visual Cortex

To examine dose-dependent effects of Ayahuasca on stimulus processing in early visual regions, a random-effects general linear model (RFX-GLM) analysis was conducted on mean beta values extracted from the early visual ROI (combined bilateral V1–V3). The analysis tested differences in stimulus-related activation between placebo, low-dose Ayahuasca, and high-dose Ayahuasca conditions.

The contrast between high-dose Ayahuasca and placebo did not reveal a significant difference in activation within the ROI, $t(10) = -0.309$, $p = .76$. Similarly, the comparison between high-dose and low-dose Ayahuasca was not significant, $t(10) = -1.309$, $p = .22$. The contrast comparing low-dose Ayahuasca to placebo also yielded no significant effect, $t(10) = 0.546$, $p = .60$. These findings suggest that visual stimulus-related activation in early visual cortex (V1 - V3) was not significantly modulated by Ayahuasca administration at either dose, compared to placebo (see Supplementary Table 2).

Functional Connectivity – gPPI

Effect of Visual Stimulus

The contrast testing the average effect of visual stimulus across both drug conditions revealed five significant clusters showing decreased functional connectivity with the early visual seed ROI during visual stimulation, and one cluster showing increased connectivity ($p < .001$ voxel-level, $p\text{-FDR} < .05$ cluster-level corrected). The largest negative cluster (510 voxels), centered at $[+30, -42, -10]$, showed the greatest overlap with the right temporal occipital fusiform cortex (TOFusC).

The second largest negative cluster (152 voxels), centered at $[+34, -84, +30]$, was located predominantly in the right lateral occipital cortex, superior division (sLOC; 123 voxels). The third negative cluster (89 voxels) was centered at $[-32, -82, +16]$ spanned the left sLOC (64 voxels). The fourth

negative cluster (76 voxels), centered at $[-32, -54, -16]$, was centered across the left temporal occipital fusiform cortex (TOFusC; 45 voxels, 59%) and the left lingual gyrus (LG; 27 voxels, 36%). The last negative cluster (61 voxels), centered at $[+42, -74, +14]$, was located primarily in the right sLOC (46 voxels, 75%) with additional overlap in the right iLOC (12 voxels, 20%). The positive cluster (79 voxels), centered at $[+24, -64, -36]$, was situated in the right cerebellum, with most voxels falling within Crus I (57 voxels, 72%) (see Supplementary Table 3).

Effect of Ayahuasca on Stimulus-Related Connectivity

The contrast testing the differential effect of Ayahuasca relative to placebo on stimulus-related functional connectivity revealed one significant positive cluster (94 voxels) where the stimulus induced greater connectivity with the seed ROI under Ayahuasca, reflecting reduced stimulus-related decoupling compared to placebo ($p < .001$ voxel-level, $p\text{-FDR} < .05$ cluster-level corrected, Fig. 6). This cluster, centered at $[+16, -72, +28]$, was located primarily in the right cuneal cortex (64 voxels, 68%) and extended into the precuneus cortex (22 voxels, 23%), see **Supplementary Table 4**.

Relationship Between Functional Connectivity and Subjective Experience

No significant correlations were found between changes in functional connectivity and scores on the HRS, VAS and intensity ratings.

Discussion

The present pharmacoinaging study investigated the neural correlates of visual processing under the influence of different doses of Ayahuasca using functional magnetic resonance imaging (fMRI) in combination with subjective measures. By integrating subjective ratings with task-based measures of neural activation and connectivity, this study aimed to explore how different doses of Ayahuasca affect neural responses to visual input that mimics the visual psychedelic experience and alters functional interactions between early visual cortex and higher-order brain regions.

Ayahuasca Induced Subjective Psychedelic Effects

Subjective measures indicated that psychedelic effects were present specifically when perceptual and imagery effects were considered, but not for other phenomenological aspects. This may explain the absence of effects for the Hallucinogen Rating Scale (HRS) in contrast with the reports of enhanced vividness of visual imagery as measured by the VVIQ. Vividness scores improved post-session compared to pre-session. Notably, we found evidence for strong expectation effects with some placebo sessions being perceived as real which may explain why some participants also reported Ayahuasca related neurophenomenology.

Regarding the 10-point Visual Analog Scales (VAS) for specific visual phenomena, the VAS items, related in particular to simple and complex imagery showed a significant increase from placebo to both

Ayahuasca doses and a linear dose trend, suggesting that these aspects of visual experience increased with dose, with a stronger effect size for simple geometric patterns. In sum, the results suggest that subjectively, Ayahuasca induced noticeable visual effects. This aligns with the reports debriefing. The subjective effects were weaker than expected from literature, e.g., Riba et al (2003) reported robust hallucinations at 0.85 mg/kg. Possible reasons could include the testing environment (the research context, MRI machine and tasks could distract from the experience), and the fact that all our participants were highly experienced.

Ayahuasca modulated visual processing in higher-order visual regions, but not in early visual regions

Under the influence of Ayahuasca, the neural processing of visual stimuli showed also significant alterations. Whole-brain GLM analysis revealed that Ayahuasca modulated stimulus-related activation in downstream, higher-order visual and frontal areas. In all regions, Ayahuasca attenuated the typical BOLD response to visual stimulation, particularly at the high dose. Our visual stimuli elicited deactivation in the precuneus and activation in lateral ventral visual regions and precentral gyrus in contrast with very strong activation of early visual pathways, including the lateral geniculate nucleus. Ayahuasca significantly dampened these effects, although the direction of the response remained the same in each region (deactivation in the precuneus but to a smaller extent, activation in ventral visual areas and precentral gyrus but to a smaller extent).

The general pattern of diminished visual extrastriate (but not early visual cortical) response to very strong bottom-up external stimulation under Ayahuasca is consistent with our expectations. As outlined in the introduction, Ayahuasca is thought to disrupt the normal balance between externally and internally driven visual processing, leading to a state in which internally generated imagery becomes more dominant. Within the predictive coding and REBUS frameworks, this can be understood as a relaxation of high-level priors and a corresponding reduction in the precision weighting of sensory inputs. The observed attenuation of stimulus-evoked activation in lateral ventral visual areas, along with reduced deactivation in the precuneus, under strong visual input, aligns with this account. The precuneus is a high-level associative region frequently implicated in internally oriented processes such as mental imagery, self-referential thought, and memory retrieval (Cavanna & Trimble, 2006; Dadario & Sughrue, 2023). In contrast, the fusiform gyrus and lateral occipital cortex are part of the ventral visual stream, involved in processing of object categories (the representation of stable visual features such as shape, color, and texture) supporting complex visual recognition (Kravitz et al., 2013). These findings suggest that Ayahuasca dampens the typical engagement of the ventral stream in response to external input, while reducing the suppression of a region associated with internally directed cognition and imagery. Together, this pattern indicates that Ayahuasca may alter the brain's allocation of attentional and perceptual resources, weaken the neural representation of external stimuli while enhancing internally focused processing.

The precuneus and ventral visual regions have been implicated in previous human neuroimaging studies of classic psychedelics, although findings across studies are somewhat mixed. The precuneus has mainly been investigated in psychedelic research due to its role as a central hub of the default mode network (DMN), a resting-state network involved in self-referential processing, autobiographical memory, and internally directed thought (Raichle et al., 2001). Altered DMN activity and connectivity are thought to be key neural correlates of the psychedelic state (Soares et al., 2023), typically marked by reduced resting-state activity and within-network connectivity, and increased connectivity with other brain networks (Gattuso et al., 2022). Unlike these resting-state studies, our study employed a task-based design that has not been previously used in psychedelic research, making direct comparisons challenging, while providing a complementary view. The most comparable study is that of de Araujo et al. (2012), who observed increased precuneus activation during a mental imagery task under Ayahuasca, consistent with our findings. Regarding ventral visual areas, a recent meta-analysis by Castelhamo et al. (2021) identified consistent BOLD alterations - primarily deactivations - in visual fusiform areas across psychedelic studies, regardless of the task employed. Nonetheless, some resting-state studies (e.g., Carhart-Harris et al., 2012; Rieser et al., 2023) have reported increased cerebral blood flow (CBF) in occipitotemporal regions. Such inconsistencies may reflect methodological variability across studies, including differences in experimental paradigms and analytic approaches.

Contrary to our expectations, no activation changes were observed in the early visual cortex in the whole-brain and ROI analyses. This null finding suggests that early visual cortex response to external stimuli, which was already quite large for these periodic stimuli, which showed strong activation of the LGN was not modulated by Ayahuasca. This is quite striking because participants reported elementary visual effects which are thought to emerge from early visual cortical activity. This does not preclude the changes in visual response properties as prior research has found early visual cortex effects in population receptive field properties and psychedelic visual experiences (Pais et al., 2024; Roseman et al., 2016a).

One possible explanation for our pattern of results is a “ceiling” effect due to strong external stimulation. As discussed by de Araujo et al. (2012), the BOLD response in primary visual cortex during visual stimulation can already reach high levels under placebo, leaving little range for further modulation by psychedelics. In such cases, stimulus-evoked responses may be saturated from a strong bottom-up drive.

However, the absence of a mean BOLD signal change in early visual regions does not preclude a role under spontaneous resting state conditions. For example, studies employing multivariate pattern analysis (MVPA) decoding methods have shown that V1 can represent the contents of mental imagery or visual working memory even when the mean BOLD response is at or near baseline (Albers et al., 2018; Harrison & Tong, 2009; Senden et al., 2019). Additionally, ultra-high field laminar fMRI has revealed that visual imagery and hallucination-like percepts can differentially engage specific cortical layers in V1 without producing robust changes in gross BOLD amplitude (Bergmann et al., 2024). These findings

highlight that early visual cortex may still contribute to altered perception under Ayahuasca under conditions where bottom-up drive is not substantial.

Ayahuasca induced changes in functional connectivity between early visual cortex and higher-order visual cortex

In terms of functional connectivity, the gPPI analysis revealed that Ayahuasca modulated stimulus-related interactions between early visual cortex and higher-order regions. Specifically, during visual stimulation, a right midline parieto-occipital cluster encompassing the cuneal cortex and precuneus exhibited significantly greater coupling with V1–V3 in the high-dose condition compared to placebo. These findings indicate that under Ayahuasca, these regions remain more synchronized when external visual stimulation is present.

This pattern of increased stimulus-related coupling aligns with prior evidence of altered context dependent functional connectivity in psychedelic states. For example, Carhart-Harris et al. (2016) reported enhanced resting-state connectivity between V1 and widespread cortical regions under LSD, which was strongly correlated with both elementary and complex visual hallucinations. The current findings also align with prior observations of altered precuneus connectivity under psychedelics; several studies have demonstrated increased global or cross-network connectivity of the precuneus under LSD (Müller et al., 2018; Preller et al., 2018; Tagliazucchi et al., 2016).

This effect is consistent with the idea that psychedelics alter hierarchical brain dynamics and promote increased communication between sensory and association areas. Carhart-Harris & Friston (2019) have described the psychedelic state as one where normally distinct hierarchies in the brain break down, allowing lower-level sensory areas and higher-level associative areas to interact more freely. Our findings extend this model to task-based connectivity, showing that Ayahuasca reduces the typical functional segregation between early visual cortex and midline associative areas involved in mental imagery, such as the precuneus, during sensory engagement.

Relationship between neural results and subjective effects

While Ayahuasca produced significant changes in neural activation and connectivity, the corresponding subjective effects were modest and did not consistently scale with dose. Notably, although the high dose produced stronger neural effects, subjective effects tended to show distinct effects depending on the scale. Notably, intensity ratings were collected in real time during the scanning session, showing clear dose-dependent differences, with significantly higher ratings under the medium and high dose compared to placebo. This pattern aligned more closely with both the experimental design and the neural findings, suggesting that real-time measures may more accurately capture the subjective effect of the substance.

One would expect that larger Ayahuasca-induced changes in subjective experience should be accompanied by larger neural differences between high dose and placebo conditions (i.e., higher Δ

subjective scores should correlate with higher-magnitude $\Delta\beta$ values). In line with this expectation, stronger visual experiences (higher Δ HRS Visual scores) were associated with greater reduction of activation in the right iLOC. In contrast, correlations in the precuneus showed the opposite pattern: larger increases in HRS Total and Intensity scores were linked to smaller positive $\Delta\beta$ values in the anterior and posterior precuneus, indicating less reduction of deactivation under Ayahuasca.

Taken together, these results suggest that the link between subjective reports and neural response is not linear, especially when considering the neural processes elicited by psychedelic substances and their interaction with a visual stimulus.

Limitations and Future Directions

Our study employed a placebo-controlled, within-subject crossover design integrating neuroimaging and subjective measures, providing a controlled and comprehensive approach to investigating the neural correlates of visual experiences under Ayahuasca. As a limitation, we must highlight important caveats in the use of retrospective self-report measures in psychedelic research. This highlights the importance of using precise and real-time assessment of psychedelic phenomenology, and the critical interpretation of self-report data, particularly in research involving altered states of consciousness.

The statistical power of this study was limited in spite of the within-subject design. Additionally, although placebo and low-dose conditions were randomized, the high dose was always administered in the final session, to avoid potential unblinding.

Conclusion

In conclusion, the present study shows that Ayahuasca alters visual processing by modulating activity and connectivity in higher-order visual regions, while leaving early visual cortex responses to strong drive imposed by external stimuli largely intact. Specifically, Ayahuasca reduced stimulus-evoked activation in ventral visual areas and decreased deactivation in the precuneus, alongside enhanced functional connectivity between early visual cortex and a midline associative region. These effects emerged in association with changes in visual subjective experience. The observed pattern - reduced engagement with external input and stronger integration with internally oriented regions - supports the idea that psychedelics relax hierarchical processing constraints, biasing perception toward internally generated imagery. These findings align with predictive coding accounts of psychedelic states and contribute to a growing understanding of how classic psychedelics reshape the functional architecture underlying visual consciousness.

Declarations

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Data Availability

The data supporting the current findings are available from the corresponding author upon reasonable request.

Author Contributions

AG: Investigation, Methodology, Formal analysis, Writing – Original Draft, Reviewing and Editing; MT: Investigation, Methodology, Formal analysis, Data Acquisition, Writing - Reviewing and Editing; MP: Investigation, Methodology, Formal analysis, Data Acquisition, Writing - Reviewing and Editing; GL: Investigation, Data Acquisition; CS: Investigation, Data Acquisition, CC: Investigation, Methodology, Reviewing and Editing PR Investigation, Methodology, Reviewing and Editing, RG: Supervision, Project Administration, Writing – Reviewing and Editing MCB: Conceptualization, Supervision, Funding Acquisition, Project Administration, Writing – Reviewing and Editing.

Competing Interests declaration

The authors declare that they have no competing interests.

Disclosure of Generative AI in the Writing Process

During preparation of this work we used ChatGPT to improve the structure, clarity and flow of my writing. Following the use of this tool/service, we reviewed and edited the content as necessary.

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Figures

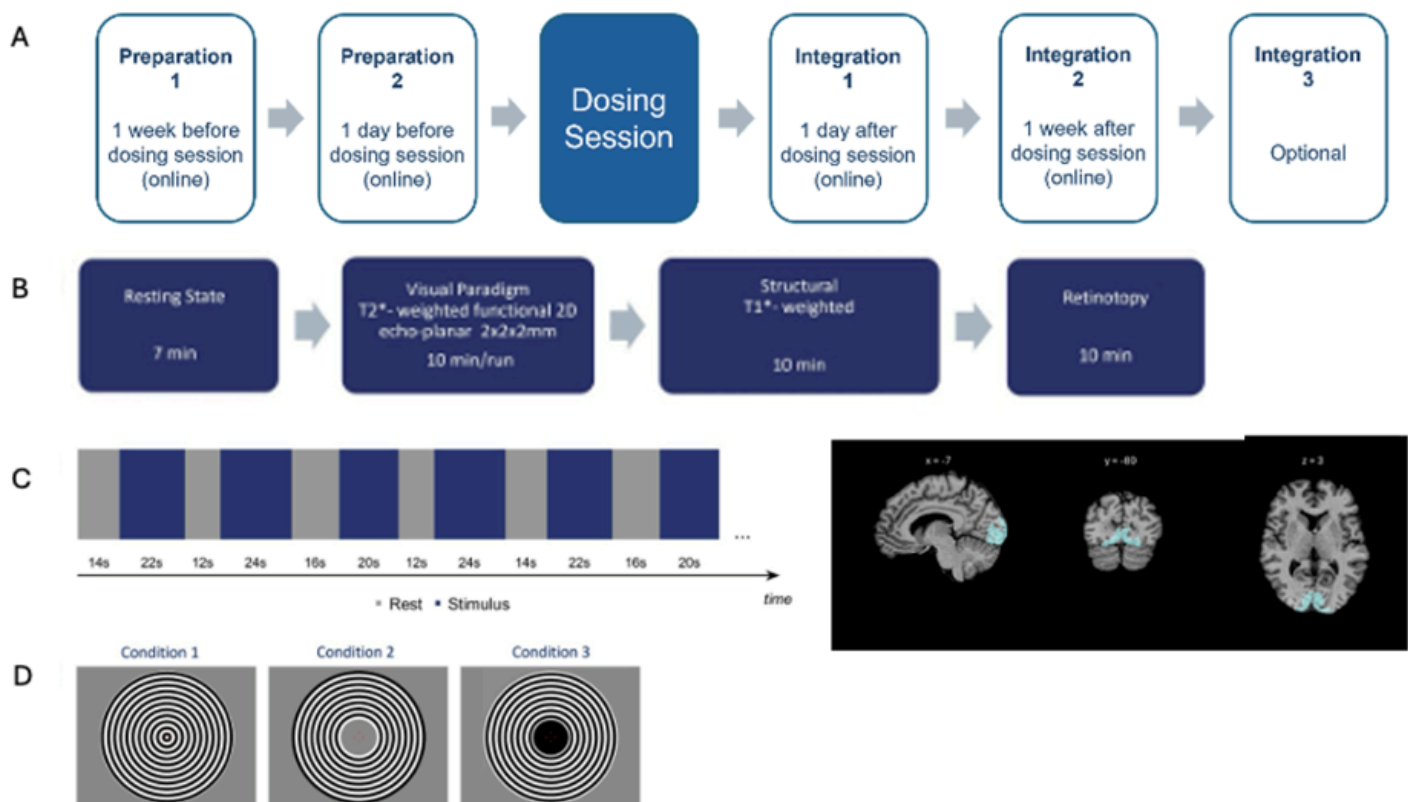


Figure 1

Overview of Study Sessions (A) and overview of the fMRI Scanning Session and Visual Task Protocol (B, C, D). Panel B illustrates the sequence of scans in the fMRI session, including resting state, visual task paradigm, structural scan, and retinotopy. Panel C shows the block design of the visual paradigm, alternating stimulus (dark blue) and rest (gray) periods with varying durations. Panel D presents examples of the dynamic circular grating stimuli shown during the stimulus blocks. Visual stimuli were presented in 3 conditions intended to induce different intensities of visual hallucination-like phenomena: expanding rings with no central mask (condition 1), expanding rings with a gray central mask (condition 2), and expanding rings with a flickering central mask (condition 3). Panel E shows the early visual ROI (V1-V3) displayed on the anatomical scan of one participant.

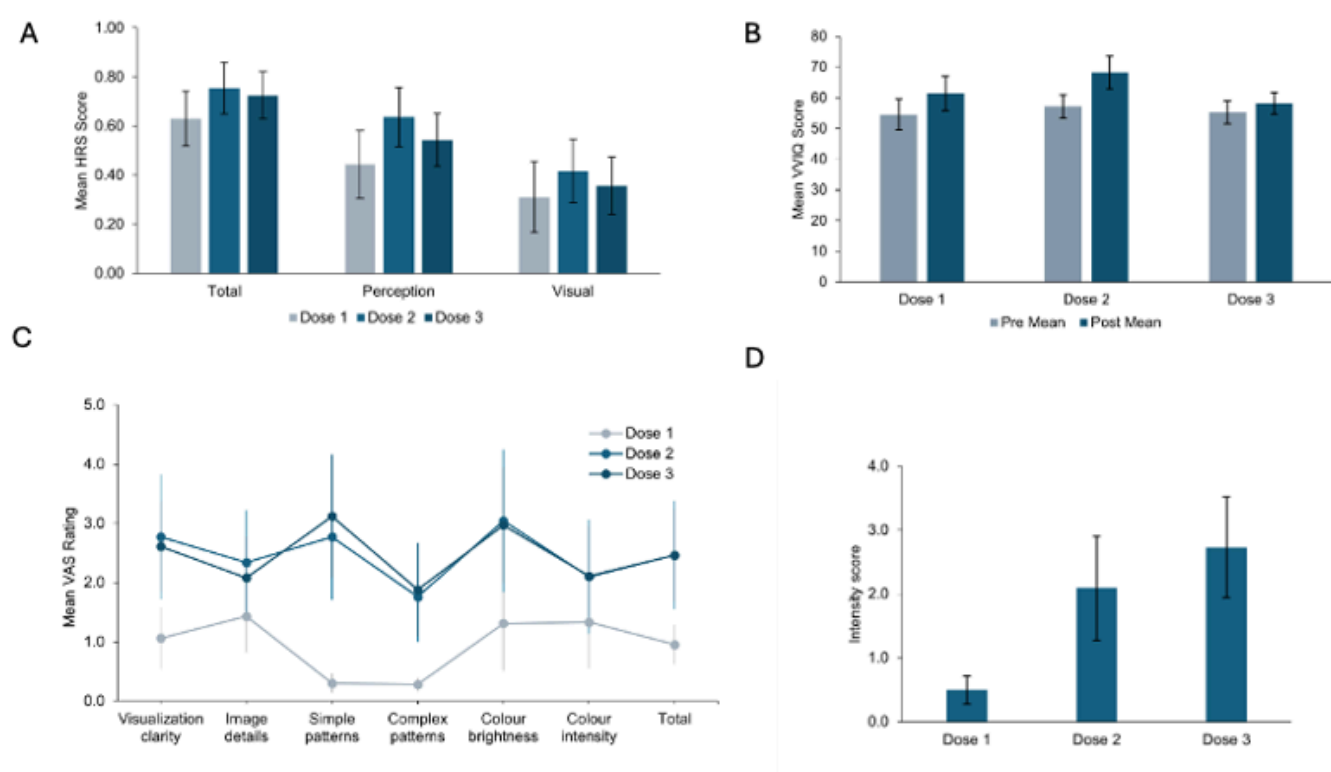


Figure 2

A Mean HRS total, perception, and visual subscale scores across three dose conditions **B** Mean VVIQ scores before and after each session. **C** Mean visual analog scale (VAS) ratings are shown for six individual items - visualization clarity, image details, simple patterns, complex patterns, colour brightness, and colour intensity - as well as the total score across three experimental sessions. Ratings were given on a scale from 0 to 10. Error bars represent standard errors of the mean. Dose 1 = placebo, Dose 2 = 0.5 mg/kg, Dose 3 = 0.8 mg/kg. **C** VAS peak ratings per item and total score across three sessions **D**. Mean subjective intensity ratings across the three dose conditions. Error bars represent standard errors of the mean. Average intensity scores were calculated for the time point immediately after the visual stimulation paradigm.

Ratings were given on a scale from 0 to 10. Error bars represent standard errors of the mean. Dose 1 = placebo, Dose 2 = 0.5 mg/kg, Dose 3 = 0.8 mg/kg.

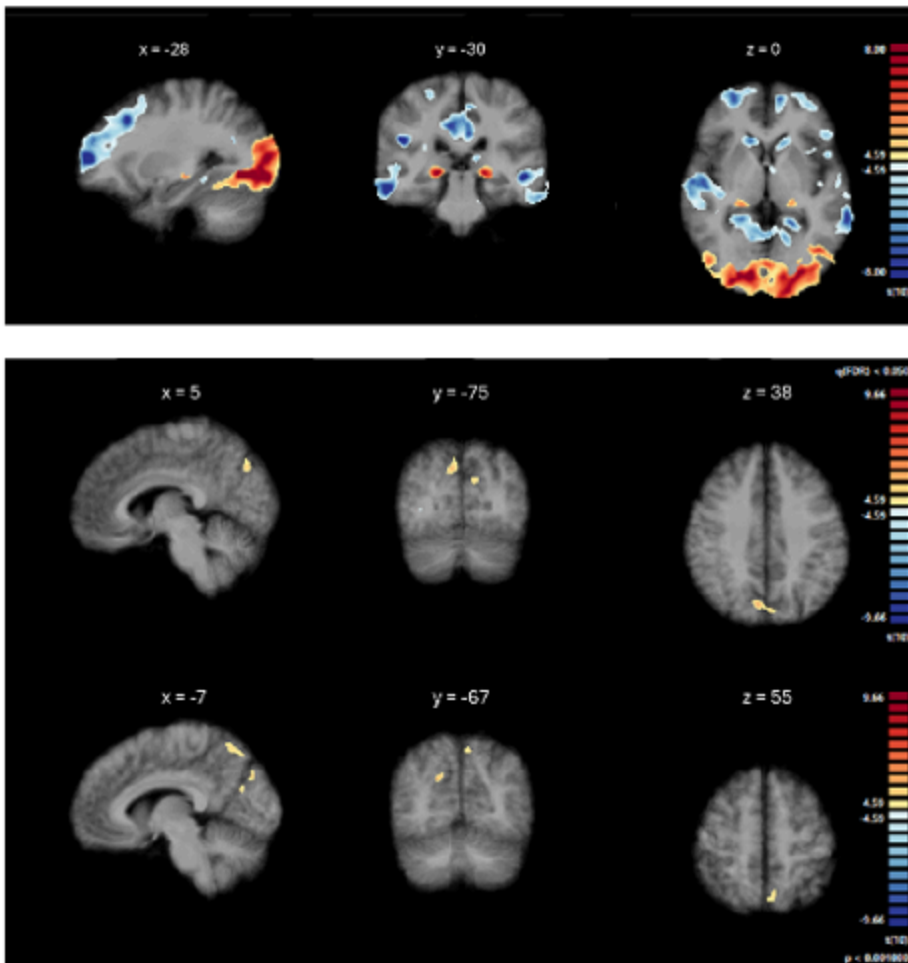


Figure 3

Top: Group-Level RFX Activation Map for the Visual Stimulus Contrast. Activation maps are overlaid on an average anatomical image computed from all participants, thresholded using cluster-level correction ($p < .001$ voxel-level threshold (uncorrected), $p < 0.05$ cluster-level threshold (FWE-corrected), $k \geq 84$ voxels). Warm colors indicate significantly greater activation during visual stimulation compared to baseline (positive t-values). Cool colors indicate significant deactivation (negative t-values). Bottom: Clusters Exhibiting Increased Stimulus - Related Activation under Ayahuasca (High Dose vs. Placebo). Activation maps are overlaid on an average anatomical image computed from all participants, thresholded using cluster-level correction ($p < .001$, uncorrected voxel-level threshold, cluster FWE $k \geq 39$ voxels). Warm colors indicate significantly greater activation under Ayahuasca compared to placebo (positive t-values).

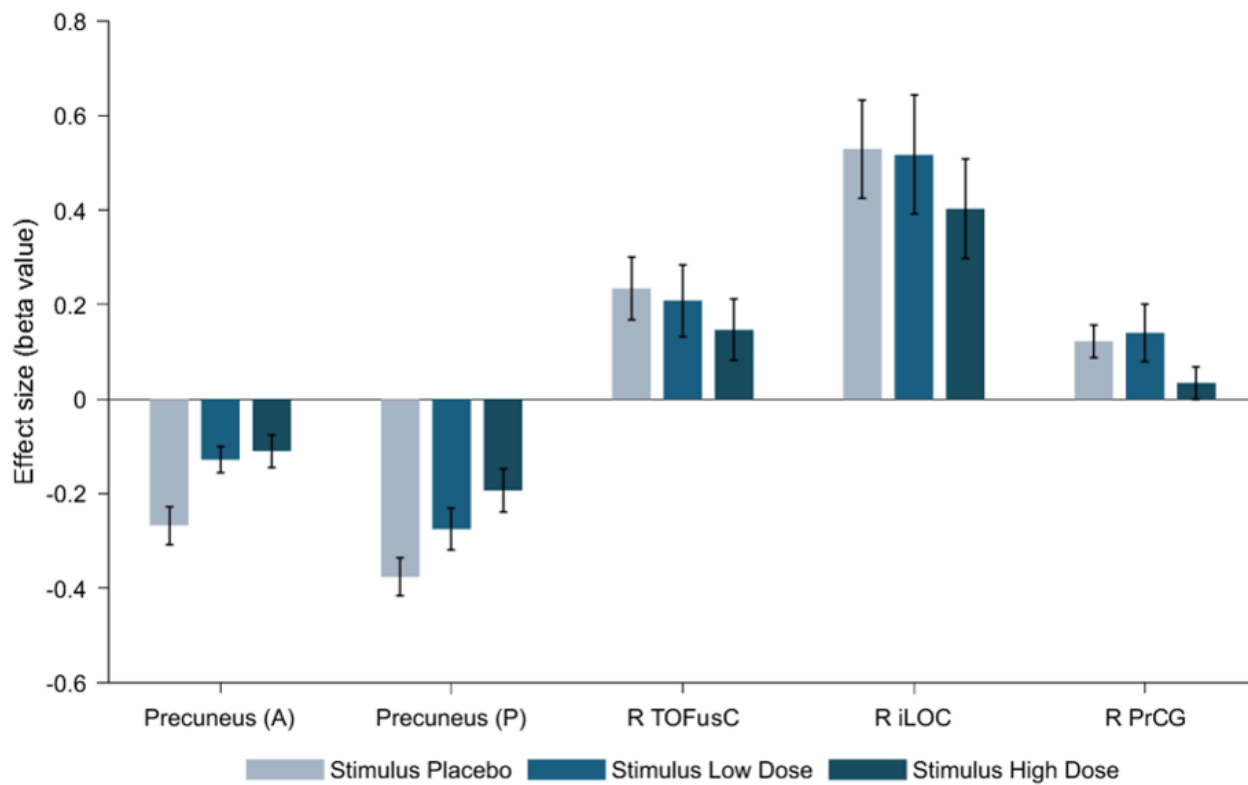


Figure 4

Mean stimulus-evoked beta values in significant clusters across Ayahuasca doses. Bars represent mean beta values (effect sizes) for each condition (Placebo, Low Dose, High Dose), averaged across participants. Bar plots illustrate reduced stimulus-driven activation in ventral stream regions and reduced deactivation in the precuneus under high-dose Ayahuasca compared to placebo. Error bars indicate the standard error of the mean (SEM).

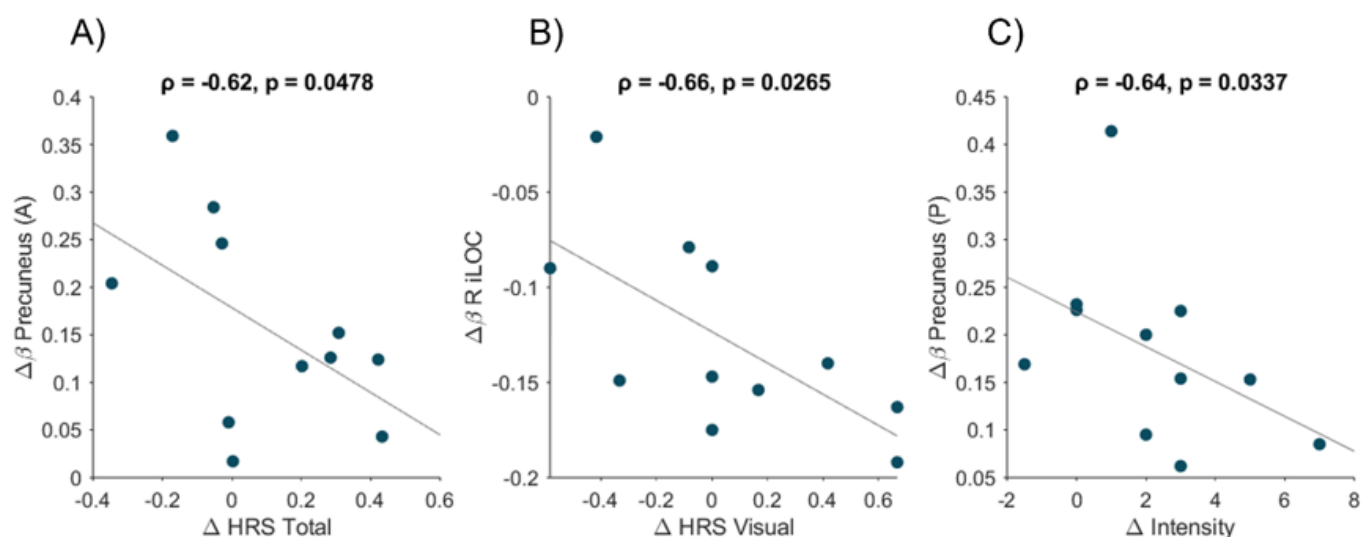


Figure 5

Correlation Between Neural Activation and Subjective Measures. $\Delta\beta$ values are defined as (high dose - placebo). Positive $\Delta\beta$ values indicate stronger activation/less deactivation, whereas negative values indicate weaker activation/stronger deactivation under high-dose Ayahuasca compared to placebo. (A) Larger Δ HRS Total scores were associated with lower positive $\Delta\beta$ values in the anterior precuneus. (B) Larger Δ HRS Visual scores were associated with more negative $\Delta\beta$ in the right iLOC. (C) Larger Δ Intensity scores were associated with lower positive $\Delta\beta$ in the posterior precuneus. Each dot represents one participant.

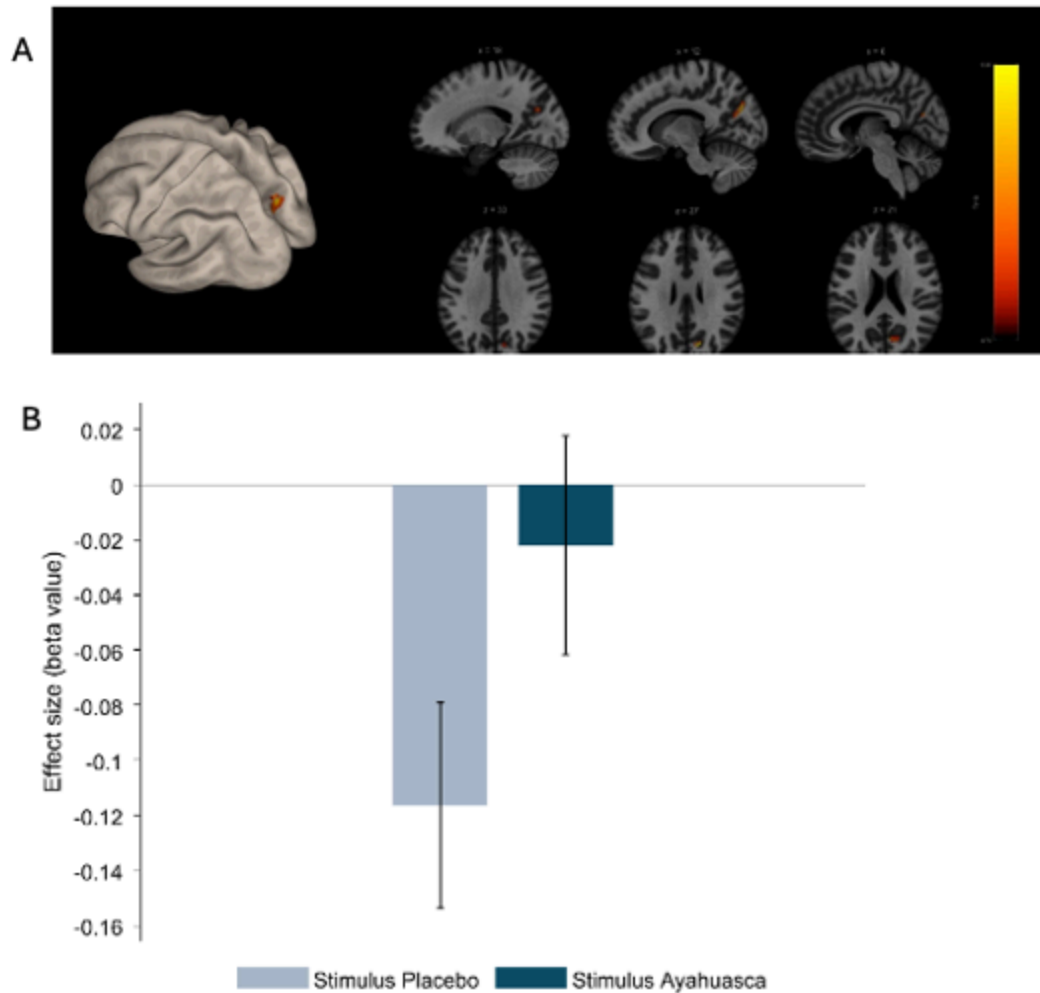


Figure 6

A Group-Level Results for the Effect of Ayahuasca on Stimulus-Related Connectivity

Note. Statistical maps are displayed on an inflated cortical surface (left) and sagittal and axial brain slices (right) in MNI space. The figure shows a single cluster where functional connectivity with the seed ROI during stimulus blocks was significantly greater under the ayahuasca condition compared to the placebo condition. Warm colors indicate increased connectivity (positive t-values). **B ROI-Based Effect Sizes for Task-Modulated Functional Connectivity.** Bars represent average beta values from the gPPI analysis. Error bars indicate 90% confidence intervals.

Supplementary Files

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