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ORIGINAL INVESTIGATION

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Effects of *ayahuasca* on sensory and sensorimotor gating in humans as measured by P50 suppression and prepulse inhibition of the startle reflex, respectively

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Abstract *Rationale: Ayahuasca*, a South American psychotropic plant tea, combines the psychedelic agent and 5-$HT_{2A/2C}$ agonist *N*,*N*-dimethyltryptamine (DMT) with β-carboline alkaloids showing monoamine oxidase-inhibiting properties. Current human research with psychedelics and entactogens has explored the possibility that drugs displaying agonist activity at the 5-$HT_{2A/2C}$ sites temporally disrupt inhibitory neural mechanisms thought to intervene in the normal filtering of information. Suppression of the P50 auditory evoked potential (AEP) and prepulse inhibition of startle (PPI) are considered operational measures of sensory (P50 suppression) and sensorimotor (PPI) gating. Contrary to findings in lower animals, unexpected increases in sensorimotor gating have been found in humans following the administration of the serotonergic psychedelic psilocybin and the serotonin releaser 3,4-methylenedioxymethamphetamine (MDMA). In addition, to our knowledge P50 suppression has not been assessed previously in humans following the administration of a 5-$HT_{2A/2C}$ agonist. *Objectives:* To assess the effects of the acute administration of *ayahuasca* on P50 suppression and PPI in humans, in order to evaluate the drug's modulatory actions on these measures of sensory and sensorimotor gating. *Methods:* Eighteen healthy volunteers with prior experience of psychedelic drug use participated in a clinical trial in which placebo or *ayahuasca* doses (0.6 mg and 0.85 mg DMT/kg body weight) were administered according to a double-blind, cross-over balanced design. P50 and startle reflex (pulse-alone and 60 ms, 120 ms, 240 ms and 2000 ms prepulse-to-pulse intervals) recordings were undertaken at 1.5 h and 2 h after drug intake, respectively. *Results: Ayahuasca* produced diverging effects on each of the two gating measures evaluated. Whereas significant dose-dependent reductions of P50 suppression were observed after *ayahuasca*, no significant effects were found on the startle response, its habituation rate, or on PPI at any of the prepulse-to-pulse intervals studied. *Conclusion:* The present findings indicate, at the doses tested, a decremental effect of *ayahuasca* on sensory gating, as measured by P50 suppression, and no distinct effects on sensorimotor gating, as measured by PPI.

Keywords *Ayahuasca* · DMT · Psychedelics · Prepulse inhibition of startle · P50 suppression · Sensory gating · Sensorimotor gating · Human

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Introduction

Ayahuasca is a powerful psychotropic plant concoction, which contains the serotonergic psychedelic agent *N*,*N*-dimethyltryptamine (DMT) (Rivier and Lindgren 1972; Schultes and Hofmann 1980). This beverage, which is the shamanic inebriant par excellance in the Upper Amazon River Basin (Schultes and Hofmann 1982; Dobkin de Rios 1984), is obtained by infusing the stems of the woody vine *Banisteriopsis caapi* (malpighiaceae) together with the leaves of *Psychotria viridis* (rubiaceae) or *Diplopterys cabrerana* (malpighiaceae). *Banisteriopsis caapi*'s chief contribution to the infusion is a series of β-carboline alkaloids, namely harmine, tetrahydroharmine and, to a lesser degree, harmaline, while *Psychotria viridis* and *Diplopterys cabrerana* contribute varying amounts of DMT (Rivier and Lindgren 1972; Schultes and Hofmann 1980).

When administered parenterally, DMT is a potent ultra-short-acting psychedelic agent (Strassman et al. 1994), which binds to the 5-$HT_{2A/2C}$ receptor sites in the central nervous system (CNS), where it acts as an agonist

(Pierce and Peroutka 1989; Smith et al. 1998). Interestingly, this compound is entirely inactive after oral ingestion (Ott 1999), probably due to metabolic breakdown by gut and liver monoamine oxidase (MAO) (Suzuki et al. 1981). However, the β-carboline alkaloids present in *ayahuasca* display MAO inhibitory properties (McKenna et al. 1984). By combining both plants in a single oral preparation, the extensive first-pass effect on DMT can be diminished thanks to the reversible inhibition of MAO elicited by the β-carbolines, thus enabling DMT to reach the systemic circulation and the CNS.

Ayahuasca has attracted the interest of biomedical researchers as its use has spread in recent years, reaching the urban areas of South America, Europe, and North America, where it is used in the context of divination, traditional medicine, and syncretic religions (Dobkin de Rios 1996a, 1996b; Anonymous 2000). In previous studies we found that in a clinical setting *ayahuasca* was able to induce dose-dependent perceptual cognitive and affective modifications characteristic of the psychedelics, as measured by self-report, subjective-effect measures (Riba et al. 2001a) and a pattern of changes in spontaneous brain electrical activity analogous to that caused by other drugs displaying agonist activity at the 5-HT_2 and D_2 receptor sites (Riba et al. 2002).

Recently, the disruptive activity of psychedelics on the "gating" of sensory information has been postulated (Vollenweider 1994). This hypothesis is based on the assumption of the existence of brain mechanisms directed at filtering out, under normal conditions, the flow of sensory information reaching consciousness. Decreases in gating had been initially proposed as an underlying deficit common to a number of neuropsychiatric disorders, where a sensory overflow is postulated (Braff et al. 2001). According to this model, serotonergic psychedelics, dopaminergic agonists, and *N*-methyl-D-aspartate (NMDA) antagonists would interact with brain structures involved in the gating mechanisms, temporarily decreasing their functionality and giving rise to the characteristic perceptual and cognitive effects elicited by these agents (Vollenweider 1994).

Two neurophysiological measures have been developed to evaluate the functionality of neural gating mechanisms: suppression of the P50 auditory evoked potential (AEP) and prepulse inhibition of the startle reflex (PPI). The P50 AEP is a midlatency potential appearing about 50 ms after the presentation of an auditory stimulus (Picton et al. 1974). The consecutive administration of two identical stimuli, conditioning (C) and testing (T) stimuli, at a certain inter-stimulus interval, typically 500 ms, leads to a decrease in the amplitude of the second P50 wave (Adler et al. 1982). The amplitude decrement seen for the T stimulus is thought to obey active inhibitory mechanisms triggered by the C stimulus (Freedman et al. 1983). P50 suppression is regarded as a measure of sensory gating, and its neural substrates have been located in the hippocampus, in the mesial temporal lobe (Adler et al. 1998).

The second operational measure, PPI, is based on the inhibitory effect of a weak sensory stimulus (the prepulse) on the motor response caused by a stronger startle reflex-eliciting stimulus. The startle reflex is a brainstem reflex occurring after the presentation of intense and sudden sensory stimuli. PPI is obtained when the startling stimulus is preceded 15–400 ms by the prepulse, and it manifests as a decrease in the intensity of the reflex (Blumenthal 1999). In contrast to P50, PPI is considered a measure of sensorimotor gating, given that the response measured is the motor output to the presented stimulus. While the neural circuit mediating the startle reflex is located in the brainstem, PPI is regulated by descending projections from areas in the forebrain. These areas are interconnected in a complex circuitry combining excitatory and inhibitory synapses (Swerdlow et al. 2001).

Pharmacological challenge studies in humans have shown dopaminergic agents to disrupt PPI and P50 suppression (Adler et al. 1994a; Hutchinson and Swift 1999; Light et al. 1999), while unexpected increases in PPI have been observed after the administration of serotonergic psychedelics/entactogens, such as psilocybin and 3,4-methylenedioxymethamphetamine (MDMA) (Gouzoulis-Mayfrank et al. 1998; Vollenweider et al. 1999). To our knowledge no study has been carried out to date on the influence of serotonergic psychedelics/entactogens on the human P50 suppression paradigm.

The aim of the present study was to evaluate both P50 suppression and PPI in a single group of healthy volunteers after the acute administration of *ayahuasca* and to assess a possible differential drug modulation of these two measures.

Materials and methods

Volunteers

Eighteen healthy volunteers (15 males and 3 females) with no current or previous history of neurological or psychiatric disorder and no family history of axis-I psychiatric disorder in first degree relatives were included in the study. Eligibility criteria included prior experience with psychedelic drugs on at least five occasions without sequelae derived thereof. The volunteers were given a structured psychiatric interview [Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R] and completed the trait-anxiety scale from the State-Trait Anxiety Inventory (Spielberger et al. 1970). Exclusion criteria included a present or past history of axis-I disorders and alcohol or other substance dependence, and high scores on trait anxiety. Volunteers were given a complete physical examination that included a medical history, laboratory tests, electrocardiogram (ECG), and urinalysis. Mean age was 25.7 years (range 19–38 years), mean weight 66.47 kg (range 50.7–79.5 years) and mean height 175.11 cm (range 158–188 cm). In addition to their prior intake of psychedelics, all volunteers had previous experience with cannabis and cocaine. Although prior exposure specifically to *ayahuasca* was not required for participation, two of the volunteers had ingested the beverage before inclusion in this study. The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans and was approved by the hospital ethics committee and the Spanish Ministry of Health. The volunteers received detailed information on the nature of *ayahuasca* and the general psycho-

logical effects of psychedelics and their possible adverse effects, as reported in the psychiatric literature. All volunteers gave their written informed consent to participate.

Drug

Two *ayahuasca* doses containing 0.6 mg and 0.85 mg DMT/kg body weight were chosen as the low and high doses, respectively, based on tolerability and subjective effects assessed in a previous study (Riba et al. 2001a). The *ayahuasca* was not administered in its original liquid form, but as a liophilizate. The freeze-dried homogenized material was obtained from a 9.6-l batch of *Daime* obtained from Cefluris, a Brazilian-based religious organization related to the *Santo Daime* church. The DMT contents had been determined by means of high-performance liquid chromatography (HPLC), as described by Callaway and coworkers (1996), and the β-carbolines according to a modified version of the method described therein. As reported in a previous paper, the 9.6-l batch yielded 611 g freeze-dried powder, containing 8.33 mg DMT, 14.13 mg harmine, 0.96 mg harmaline, and 11.36 mg THH per gram. These alkaloid contents corresponded to the following concentrations in the original tea: DMT 0.53 mg/ml, harmine 0.90 mg/ml, harmaline 0.06 mg/ml, and THH 0.72 mg/ml (Riba et al. 2001a). The calculated individual dose for each volunteer was administered by combining 00 gelatin capsules containing 0.5, 0.25, or 0.125 g freeze-dried *ayahuasca* and placebo capsules containing 0.75 g lactose. Placebo capsules were added when necessary, so that all volunteers took the same number of capsules on each experimental day.

Study design and experimental procedure

The volunteers participated in four experimental sessions. Volunteers were informed that they would randomly receive on each experimental day a single oral dose of encapsulated freeze-dried *ayahuasca* (one low and one high dose) or placebo and a random repetition of one of the three mentioned treatments. In actual fact, they all received a placebo on the first experimental day in a single-blind fashion, followed by one of the three treatments from day 2 to day 4 in a double-blind balanced fashion, according to a randomization table. The first non-randomized placebo was administered in order to familiarize the volunteers with the experimental setting and to minimize the stress associated with the experimental interventions. The data obtained during the first session was not included in the statistical analysis performed and is not reported. Two weeks prior to the beginning of the experimental sessions, volunteers abstained from any medication or illicit drug and remained drug free throughout the four study weeks. Urinalysis for illicit drug use was made for each experimental session. Additionally, volunteers abstained from alcohol, tobacco, and caffeinated drinks 24 h prior to each experimental day. There was a 7-day washout period between experimental days.

On each experimental day, participants arrived at the laboratory in the morning under fasting conditions, and capsules were administered by approximately 10,00 hours with 250 ml tap water. The P50 and PPI sessions were begun at 1.5 h and 2 h after drug administration, respectively, coinciding with the peak of subjective effects (Riba et al. 2001a). The recordings were undertaken in a quiet room with the volunteers seated in a reclining chair. The experimenter remained in the neighboring room for the entire time of the recordings and monitored volunteers for alertness. Four hours after administration of the capsules, the volunteers answered subjective-effect questionnaires and had a meal. They remained in the research unit throughout the afternoon and were discharged approximately 9 h after administration.

Measurements

P50 elicitation and recording

One hundred and twenty pairs of auditory stimuli were delivered by means of air earphones. Auditory stimuli were 75-dB [A], 1000-Hz pure-tone pips of 4-ms duration, with a 500-ms inter-stimulus separation and a constant interval between pairs of 8 s. No background noise was presented during the session. Electroencephalogram (EEG) recordings were obtained by means of nineteen electrodes placed on the scalp according to the international 10/20 system, plus leads for horizontal and vertical eye-movement monitoring. All scalp electrodes were referenced to the averaged mastoids. Impedance was kept below 5 kΩ. Throughout the entire recording session, volunteers remained with eyes open with sight on a fixation point. High- and low-pass filters were set at 0.1 Hz and 100 Hz, respectively. The digitation rate was 250 Hz. The continuous recordings were epoched at an interval between 100 ms pre-stimulus and 1000 ms post-stimulus and baseline corrected (–100, 0). This was followed by rejection of any trial showing an activity exceeding $\pm$75 μV. All artifact-free epochs were averaged to obtain the average AEP including the first or C stimulus and the second or T stimulus. The obtained averages were re-filtered between 10 Hz and 50 Hz to facilitate P50 identification (Jerger et al. 1992). P50 identification and scoring was carried out on average individual waveforms at Cz as described by Adler et al. (1994b). The C peak was identified as the greatest positivity between 40 ms and 80 ms after stimulus presentation. If more than one peak of equal amplitude was detected, the later one was selected. Peak amplitude was assessed as the difference between this peak and the preceding negative N40 trough. In cases where no N40 could be identified, the P50 amplitude was measured to pre-stimulus baseline (Cardenas et al. 1997). The T peak was identified in the same way, with the further constraint that it had to appear at a latency between $\pm$10 ms of the latency value found to the P50 wave to the C stimulus (Adler et al. 1994b).

Startle reflex elicitation and recording

Startle stimuli were 1-KHz pure tones of 116 dB [A], with a 50-ms duration and an instantaneous rise/fall time. Acoustic stimuli were presented binaurally through air headphones. Prepulses were non-startling 1-KHz pure tones of 80 dB [A] and a 20-ms duration. No background noise was presented during the session. The electromyogram (EMG) signal was recorded bipolarly from the orbicularis oculi muscle by means of two 0.5-cm diameter silver surface disc electrodes, placed 1 cm below and 1 cm medial from the external canthus of the right eye (Fridlund and Carcioppo 1986). Two electrodes placed above and below the left eye were used to control spontaneous and voluntary blinking. The ground electrode was placed on the forehead. Impedance level was maintained below 5 KΩ. Amplifier filters were set at 10 Hz (high pass) and 500 Hz (low pass). The EMG signal was digitized at a 1000-Hz rate.

Each startle sequence was initiated with an acclimation phase comprising five pulse-alone startle stimuli, which were not used later in the calculation of PPI. These were followed by three blocks of trials comprising pulse-alone trials and prepulsed trials at the following prepulse-to-pulse intervals: 60, 120, 240, and 2000 ms. Each block included three pulse-alone trials and three prepulsed trials at each of the four intervals used. Thus, 45+5 startle stimuli were delivered in the course of a startle reflex recording session. The mean inter-trial interval was 20 s (range 10–29 s). Four different sequences of stimuli were used throughout the study, each subject receiving a different sequence on each experimental day. The order of the sequences was varied according to a randomization table and was counterbalanced across subjects. The order of presentation of each trial type was pseudo-random and varied across blocks and across sequences.

The recorded EMG signal was full-wave rectified off-line and smoothed using a five-point moving average filter. Peak eye-blink amplitude was defined as the highest point in the EMG response

within a time window of 120 ms after stimulus administration. Baseline EMG was computed as the mean EMG in the 30-ms preceding stimulus onset. Reactivity was defined as blink magnitude in the pulse-alone trials. Trials in which the apparent response had an onset latency of less than 20 ms after stimulus administration and/or a rise time greater than 95 ms were rejected. In those trials in which no response was detected, amplitude was scored as 0 μV. Epochs were screened and rejected if artifacts were present.

Subjective ratings

Volunteers were requested to answer two questionnaires measuring psychedelic-induced subjective effects. The first questionnaire was the Hallucinogen Rating Scale (HRS) (Strassman et al. 1994). The HRS includes six subscales: *somaesthesia*, reflecting somatic effects; *affect*, sensitive to emotional and affective responses; *volition*, indicating the volunteer's capacity to willfully interact with his/her "self" and/or the environment; *cognition*, describing modifications in thought processes or content; *perception*, measuring visual, auditory, gustatory and olfactory experiences; and *intensity*, which reflects the strength of the overall experience. In the present study, a Spanish version of the questionnaire was used (Riba et al. 2001b).

The second questionnaire administered was a Spanish version of the Altered States of Consciousness Questionnaire ("Ausser-gewöhnliche Psychische Zustände", APZ) developed by Dittrich (1998). It includes 72 items distributed in three subscales: *oceanic boundlessness* ("Ozeanische Selbstentgrenzung", OSE), measuring changes in the sense of time, derealization and depersonalization phenomena subjectively experienced as positive; *dread of ego-dissolution* ("Angstvolle IchAuflösung", AIA), measuring thought disorder and decreased body and thought control associated with arousal and anxiety; and *visionary restructuralization* ("Visionäre Umstrukturierung", VUS), referring to visual phenomena, such as illusions, hallucinations and synesthesia and to changes in the significance of objects. This instrument has been extensively used in studies involving the administration of psychedelics to humans. Volunteers were requested to answer the HRS and the APZ 4 h after drug intake.

Statistical analysis

P50 auditory evoked potential

Three measures related to response amplitude were derived from average waveforms at Cz for each subject and drug condition: P50 AEP amplitude values after the C and T stimuli, difference amplitude calculated as C–T, and finally percentage suppression calculated as [1–(T/C)]×100. Latency to peak after the C stimulus was also assessed. Amplitude values for the C stimulus were analyzed by means of a repeated-measures one-way analysis of variance (ANOVA) with drug as factor, in order to test for drug actions on the amplitude of the C trial. A repeated-measures, two-way ANOVA was subsequently performed, with drug and stimulus type (C vs T) as factors on amplitude values. Finally, repeated-measures, one-way ANOVAs with drug as factor were performed on difference amplitude, percentage suppression, and latency to peak values.

Startle reflex measures

Blink magnitude values were obtained from the recordings and averaged for each trial type (i.e., nine trials for each of the five trial types: pulse-alone, 60 ms prepulse-to-pulse indicated as PP60, 120 ms prepulse-to-pulse indicated as PP120, 240 ms prepulse-to-pulse indicated as PP240 and 2000 ms prepulse-to-pulse indicated as PP2000). The following variables were calculated: reactivity (magnitude of the startle response in the pulse-alone trials), magnitude of the startle response in the prepulsed trials (PP60, PP120, PP240, and PP2000), percentage PPI (PP60, PP120, PP240, PP2000), and percentage habituation. Percentage PPI for each prepulse condition was calculated as follows: [1–(prepulsed trial magnitude/pulse-alone magnitude)]×100. Percentage habituation was calculated as the difference of the averaged magnitude of pulse-alone trials in the first block minus the averaged magnitude of pulse-alone trials in the third block divided by magnitude in the first block and multiplied by 100 (i.e., %Hab = [(first block–third block)/first block]×100).

Reactivity was analyzed by means of a repeated-measures, two-way ANOVA with drug and block as factors. Percentage habituation was analyzed by means of a repeated-measures, one-way ANOVA with drug as factor. Magnitude of the startle response in the prepulsed conditions was analyzed by means of a repeated-measures, two-way ANOVA with drug and prepulse condition as factors. Finally, PPI data were subjected also to a repeated-measures, two-way ANOVA with drug and prepulse condition as factors.

Subjective reports

Scores on HRS and APZ subscales were analyzed by means of a one-way, ANOVA with repeated measures, with drug as factor. In all ANOVAs performed, Greenhouse-Geisser epsilon was used to correct possible violations of the sphericity assumption and to reduce type-I errors. *P* values after correction are shown. When ANOVA showed statistically significant differences between drug conditions, pair-wise comparisons were carried out by means of *t*-tests. Results were considered statistically significant for $P<0.05$.

Correlations

The Pearson's *r* was used to evaluate correlations between drug-induced changes in neurophysiological measures and in subjective-effect scores, and also between drug-induced changes in PPI and in P50 measures.

Results

Usable recordings of both PPI and P50 in all three experimental sessions for a given volunteer were obtained for 15 of the total 18 volunteers enrolled in the study. The results presented below were obtained from analysis of data corresponding to this subgroup of 15 volunteers (13 males and 2 females).

P50 auditory evoked potential

Figure 1 shows grand average AEP waveforms at the Cz site after the C and T stimuli for the three drug conditions. Figure 2 presents mean P50 amplitude values for C and T, difference amplitude values (C–T), and percentage suppression [1–(T/C)]×100, under the three drug conditions. Amplitude values of the P50 response after the C stimulus showed a decrease with dose, which did not reach statistical significance in the ANOVA ($F_{2,28}=2.57$, $P=0.10$, $\varepsilon=0.906$). Mean P50 amplitude (μV)±SEM for the C stimulus under the three drug conditions was 2.93±0.42 for placebo, 2.56±0.28 for the low dose, and 2.05±0.22 for the high dose. The two-way ANOVA with drug and stimulus type (C vs T) as factors showed the following results: whereas no significant main effect of

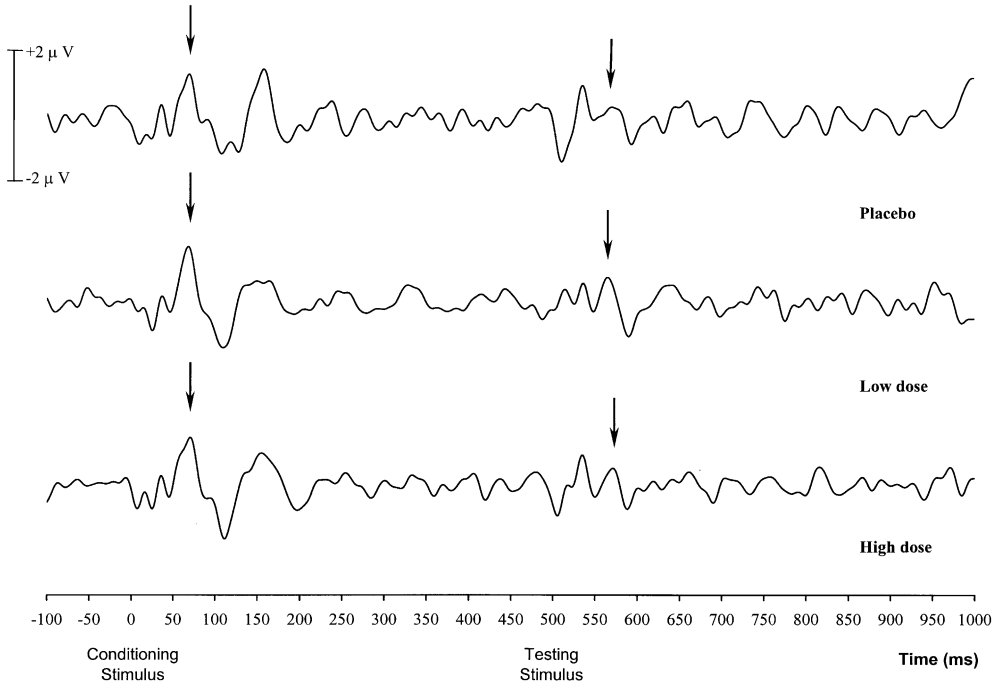

Fig. 1 Grand average band-pass filtered (10–50 Hz) auditory evoked potential (AEP) waveforms at the Cz site under the three drug conditions (n=15). The P50 component after the conditioning and testing stimuli are indicated with *arrowheads*

drug was seen on the overall amplitude of the P50 response ($F_{2,28}$=0.80), significant effects of stimulus type ($F_{1,14}$=38.49, P<0.001; linear contrast $F_{1,14}$=38.49, P<0.001; mean amplitude ±SEM: 2.53±0.21 μV for the C stimulus, 1.36±0.13 μV for the T stimulus), and the interaction drug × stimulus type ($F_{2,28}$=4.96, P<0.05, ε=0.856; linear contrast $F_{1,14}$=6.70, P<0.05) were obtained. An analogous significant effect was obtained for the difference amplitude variable (C–T), pointing out that *ayahuasca* reduced the P50 amplitude response difference to the C and T stimuli ($F_{2,28}$=4.96, P<0.05, ε=0.856; linear contrast $F_{1,14}$=6.70, P<0.05; mean difference amplitude ±SEM under the three drug conditions: 2.12±0.42 μV for placebo, 0.93±0.34 μV for the low dose, and 0.52±0.31 μV for the high dose). Pair-wise comparisons showed statistically significant differences from placebo both at the low (t_{14}=2.29, P<0.05) and the high (t_{14}=2.59, P<0.05) *ayahuasca* doses for difference amplitudes. A significant drug effect on percentage suppression was observed after *ayahuasca* ($F_{2,28}$=4.78, P<0.05, ε=0.844; linear contrast $F_{1,14}$=7.93, P<0.05; mean percentage suppression ±SEM under the three drug conditions: 71.86±8.41 for placebo, 24.57±17.17 for the low dose, and 6.00±18.10 for the high dose). Pair-wise comparisons showed statistically significant differences from placebo both at the low (t_{14}=2.83, P<0.05) and the high (t_{14}=2.82, P<0.05) *ayahuasca* doses for percentage suppression.

Finally, latency to peak of the P50 wave after the C stimulus decreased non-significantly after *ayahuasca* ($F_{2,28}$=2.76, P<0.1, ε=0.844; mean latency to peak ±SEM under the three drug conditions was 70.13± 1.91 ms for placebo, 68.53±1.17 ms for the low dose, and 65.20±2.14 ms for the high dose).

Startle reflex measures

Startle reactivity under the three drug conditions was analyzed by means of a two-way ANOVA with drug (placebo, *ayahuasca* low dose, *ayahuasca* high dose) and block of trials (first, middle and last block of the recording session) as factors. Figure 3, upper panel, shows pulse-alone startle magnitude values for each block of trials under the three drug conditions. A robust decrease of startle magnitude was observed as the recording session progressed, as evidenced by a significant effect of block ($F_{2,28}$=12.91, P<0.01, ε=0.687; linear contrast $F_{1,14}$=15.98, P<0.01; mean magnitude ±SEM for the first block was 104.96±19.63 μV, second block 66.97±13.39 μV, and third block 50.16±11.33 μV) in the ANOVA. Although mean magnitude values increased after the *ayahuasca* high dose, no significant effect of drug was seen in the ANOVA ($F_{2,28}$=1.97; mean magnitude ±SEM was 68.13±17.58 μV for placebo, 59.62±11.27 μV for the low dose, and 94.35±21.61 μV for the high dose). Finally, no significant drug × block interaction was observed ($F_{4,56}$=0.86). Similarly, a one-way ANOVA with drug as factor revealed no significant effect in percentage habituation ($F_{2,28}$=0.49; percentage habituation ±SEM was 41.74±13.25 for placebo, 37.64±11.51 for the low dose, and 36.65±46.06 for the high dose).

The effects of *ayahuasca* on global startle magnitude in the pulse-alone trials and in the prepulsed trials at the different prepulse-to-pulse intervals are shown in Fig. 3, lower panel. A two-way ANOVA with drug and prepulse condition as factors revealed a main effect of prepulse condition ($F_{3,42}$=15.02, P<0.001, ε=0.509; linear contrast $F_{1,14}$=18.95, P<0.01; mean magnitude ±SEM at the

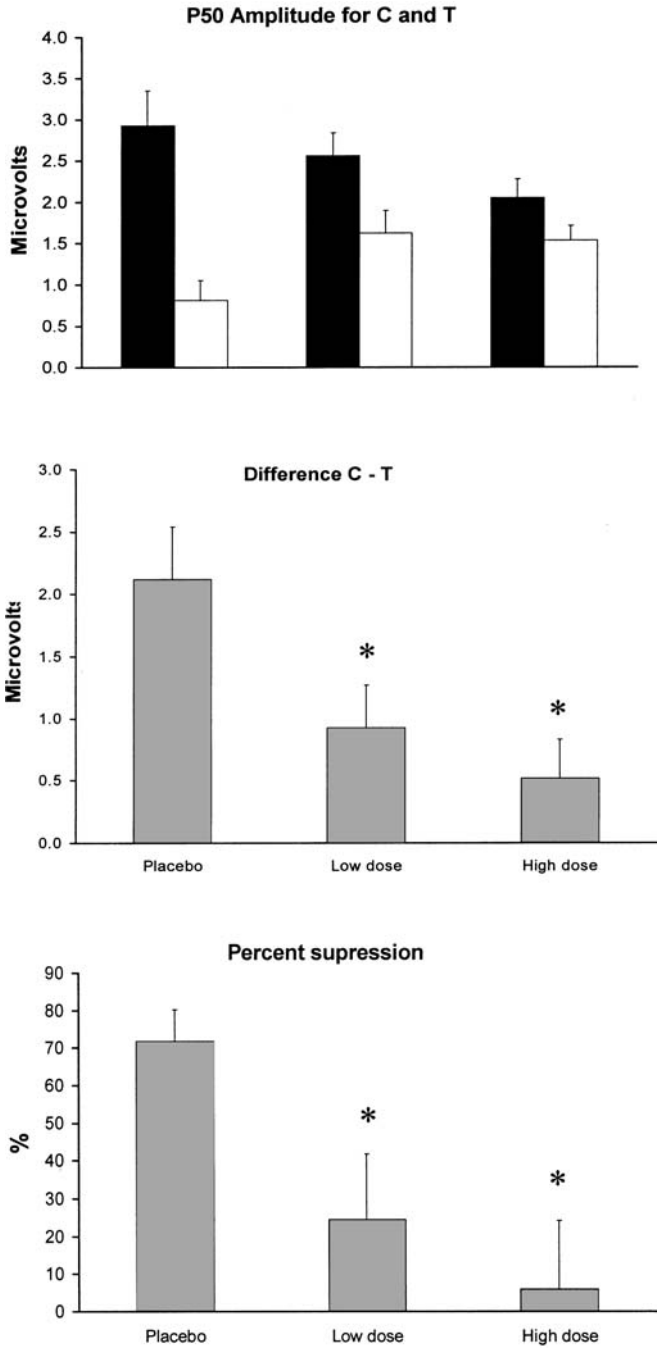

Fig. 2 *Upper panel* P50 amplitude to the conditioning (*closed square*) and testing (*open square*) stimuli under the three drug conditions. *Middle panel* Difference (conditioning–testing) of P50 amplitude values under the three drug conditions. *Lower panel* Percentage suppression values under the three drug conditions. In all three panels, *error bars* denote 1 SEM, and an *asterisk* indicates $P<0.05$ relative to placebo ($n=15$)

different prepulse-to-pulse intervals was: 74.03±13.79 μV pulse-alone, 21.14±3.80 μV PP60, 26.64±5.92 μV PP120, 48.65±11.45 μV PP240, and 80.79±16.96 μV PP2000). No significant effects of drug ($F_{2,28}=1.19$) or drug × prepulse condition ($F_{6,84}=0.65$) were observed.

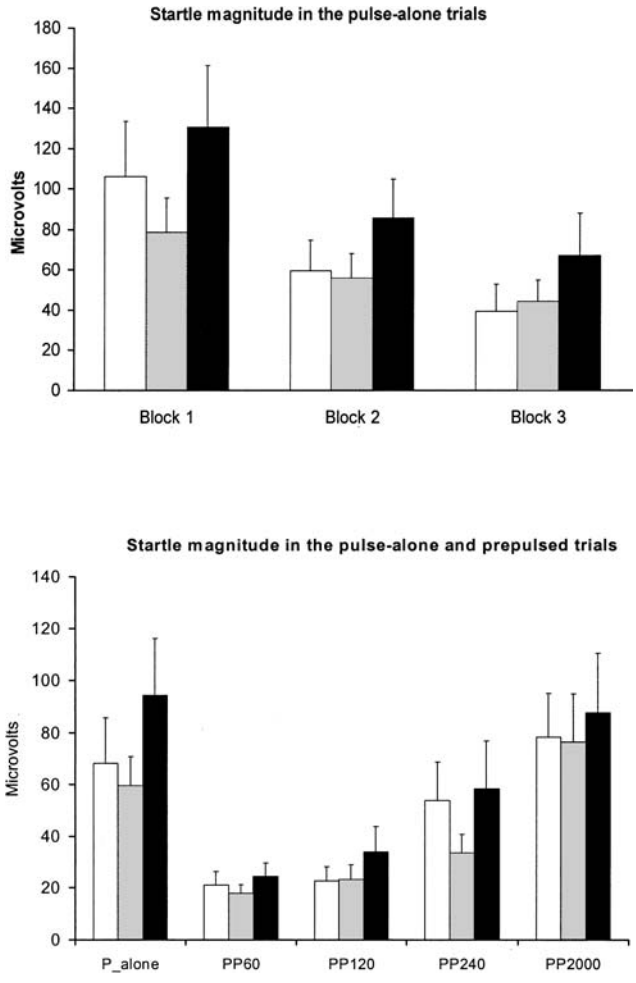

Fig. 3 *Upper panel* Mean startle magnitude values in the pulse-alone trials in each of the three blocks of trials comprising a recording session, after each of the three drug conditions. A main effect of block was found in the ANOVA ($F_{2,28}=12.91$, $P<0.01$), while no effects of drug or drug × block were observed. *Lower panel* Mean startle magnitude values after the pulse-alone and at each of the four prepulse-to-pulse intervals after each of the three drug conditions. In both panels (*open square*) placebo, (*shaded*) low dose, (*closed square*) high dose. *Error bars* denote 1 SEM ($n=15$). A main effect of prepulse condition was found in the ANOVA ($F_{3,42}=11.85$, $P<0.001$), while no effects of drug or drug × prepulse condition were observed

Figure 4 shows percentage inhibition (expressed as percentage facilitation for PP2000) values at the different prepulse-to-pulse intervals under the three drug conditions. A two-way ANOVA with drug and prepulse condition as factors revealed a main effect of prepulse condition ($F_{3,42}=11.85$, $P<0.001$, $\varepsilon=0.565$; linear contrast $F_{1,14}=36.35$, $P<0.001$; percentage inhibition in the four prepulse-to-pulse intervals ±SEM was: 59.16±5.93 PP60, 56.46±7.27 PP120, 21.13±20.87 PP240, and –19.89± 12.65 PP2000). No significant effect was seen for factor drug ($F_{2,28}=2.88$, $P<0.1$, $\varepsilon=0.938$; linear contrast $F_{1,14}=4.89$, $P<0.05$; percentage inhibition ±SEM across the four prepulse-to-pulse intervals for each drug condition was: 16.07±14.15 for placebo, 32.71±8.57 for the low dose,

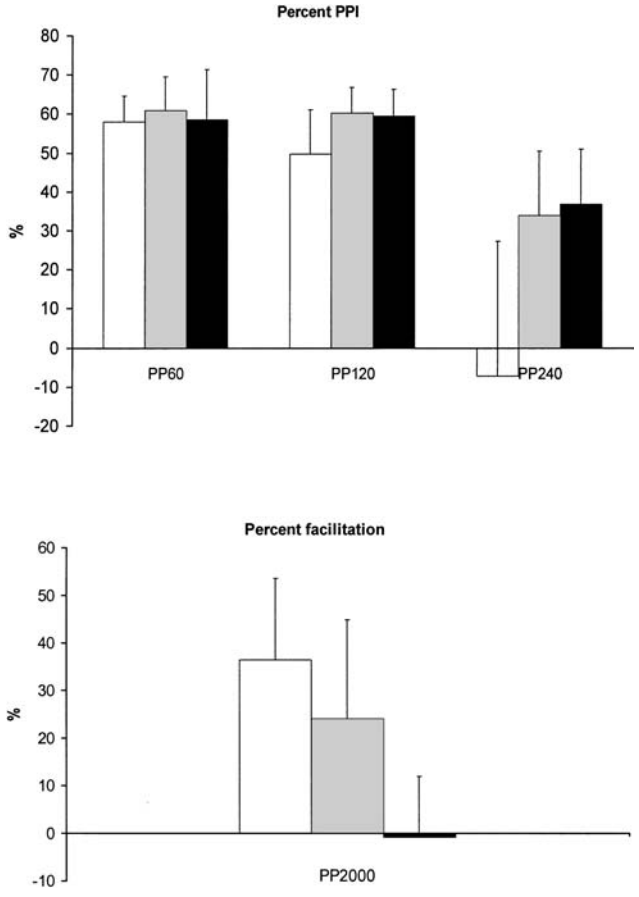

Fig. 4 *Upper panel* Mean values of percentage inhibition of the startle response at the 60, 120 and 240-ms prepulse-to-pulse intervals. *Lower panel* Mean values of percentage facilitation of the startle response at the 2000-ms prepulse-to-pulse interval. In both panels, (*open square*) placebo, (*shaded*) low dose, (*closed square*) high dose. *Error bars* denote 1 SEM (n=15). No effects of drug or drug × prepulse condition were observed

and 38.86±8.66 for the high dose). Finally, the interaction drug × prepulse condition was not found to be significant ($F_{6,84}$=1.42).

Subjective effects

The administration of the selected *ayahuasca* doses to a group of healthy volunteers with experience in the use of psychedelics induced a pattern of subjective effects that was reflected as increases in the scores of the HRS and APZ subscales, as shown in Table 1.

All HRS and APZ subscales showed statistically significant increases relative to placebo after *ayahuasca* administration, except for *volition*. The characteristic psychedelic pattern of effects reported by the volunteers had an overall duration of 4–6 h, reaching its maximum intensity between 90 min and 120 min. The most frequently reported perceptual effects were in the somatosensory and visual modalities. Somatosensory effects comprised altered bodily sensations, such as pins and needles, and increased skin sensitivity. Visual perception was characteristically modified, volunteers experiencing distortions of the visual field with eyes open, and more or less elaborate visions with eyes closed. Auditive phenomena were also present and consisted typically of alterations in external sounds, with true auditory hallucinations being less frequently reported. This modified state of awareness was also accompanied by changes in the cognitive sphere, with increased thought speed and associations, a reduction in the capacity to focus attention, and changes in mood, usually consisting of feelings of happiness and excitation. At the doses administered, *ayahuasca* did not induce full-blown psychotic symptoms and none of the participants lost insight into the

Table 1 Means (±SD) of the scores obtained for the Hallucinogen Rating Scale (HRS) and Spanish version of the Altered States of Consciousness (APZ) questionnaire subscales (n=15), and results of the statistical analysis performed. Student's t-tests were followed by Bonferroni correction. *ns* not significant

Variable	ANOVA		Student's t- test		
	P value	Placebo	vs Placebo		vs Low dose High dose
			Low dose	High dose	
HRS					
Somaesthesia	***	0.08±0.10	0.42±0.40*	0.93±0.36**	**
Perception	***	0.11±0.20	0.57±0.52**	1.11±0.68**	**
Cognition	***	0.07±0.18	0.44±0.48*	1.01±0.63**	**
Volition	(*)	0.93±0.81	1.23±0.68 ns	1.38±0.57 ns	ns
Affect	***	0.35±0.21	0.60±0.36*	1.02±0.38**	*
Intensity	***	0.22±0.44	1.27±0.79**	1.80±0.53**	**
APZ					
AIA	**	0.20±0.56	1.33±2.23 ns	3.40±2.77**	ns
OSE	***	0.20±0.41	2.53±2.90*	4.40±2.95**	ns
VUS	***	0.00±0.00	2.07±2.71*	4.07±3.33**	*

(*)P<0.1
*P<0.05
**P<0.01
***P<0.001

drug-induced nature of the psychological effects experienced.

Correlations

No significant correlations were found between drug-induced changes in P50 and PPI measures. Thus, the following results were obtained between drug-induced changes in (a) P50 difference values and drug-induced changes in PPI at the 60-ms (r=–0.253, P=0.362), 120-ms (r=0.212, P=0.449), 240-ms (r=0.151, P=0.590), and 2000-ms (r=0.412, P=0.127) intervals; and (b) P50 percentage suppression values and drug-induced changes in PPI at the 60-ms (r=–0.066, P=0.815), 120-ms (r=0.381, P=0.162), 240-ms (r=0.212, P=0.448), and 2000-ms (r=0.366, P=0.179) intervals.

Given that significant drug effects were found on P50 measures, these were correlated with subjective-effect scores. Again, no correlations were found between changes in (a) P50 difference values and drug-induced changes in HRS-somaesthesia (r=–0.244, P=0.382), HRS-perception (r=–0.313, P=0.255), HRS-cognition (r=–0.281, P=0.310), HRS-volition (r=–0.474, P=0.075), HRS-affect (r=–0.387, P=0.155), HRS-intensity (r=–0.225, P=0.421), APZ-AIA (r=–0.490, P=0.063), APZ-OSE (r=–0.319, P=0.246), and APZ-VUS (r=–0.393, P=0.147) scores; and (b) P50 percentage suppression values and drug-induced changes in HRS-somaesthesia (r=–0.207, P=0.458), HRS-perception (r=–0.321, P=0.243), HRS-cognition (r=–0.101, P=0.722), HRS-volition (r=–0.439, P=0.102), HRS-affect (r=–0.278, P=0.316), HRS-intensity (r=–0.235, P=0.400), APZ-AIA (r=–0.393, P=0.147), APZ-OSE (r=–0.247, P=0.374), and APZ-VUS (r=–0.186, P=0.507) scores.

Discussion

The results obtained in the present study indicate diverging effects for *ayahuasca* on P50 suppression and PPI. Whereas a statistically significant dose-dependent reduction of P50 suppression was observed following drug administration, no significant effects were seen on PPI values. Additionally, the rate of habituation of the startle reflex, another form of startle plasticity thought to reflect gating mechanisms, was not modified by *ayahuasca*. In addition, at the doses administered, *ayahuasca* induced a pattern of subjective effects, similar in nature to those reported in a previous study involving a smaller sample of volunteers (Riba et al. 2001a), as was evidenced by the self-report questionnaires administered.

The present results would argue for a disruptive effect of psychedelics on P50 suppression. Nevertheless, this conclusion should be regarded as preliminary and interpreted with caution, considering the presence of other pharmacologically active alkaloids in *ayahuasca*. The only studies that have evaluated the effects of pharmacological challenge on this measure in humans have concentrated mainly on cathecolaminergic drugs and NMDA antagonists. Thus, both D-amphetamine and the α_2-adrenoceptor antagonist yohimbine, a drug that increases noradrenaline release, have been shown to impair P50 suppression in healthy volunteers (Adler et al. 1994b; Light et al. 1999). Furthermore, while the dopamine agonist bromocriptine has also been found to disrupt P50 suppression (Adler et al. 1994a) in humans, a low dose of the NMDA antagonist ketamine failed to decrease P50 suppression (van Berckel et al. 1998).

Regarding data from animals, suppression of the N40 potential in rodents in a paired stimuli paradigm, homologous to that of the human P50, appears to be highly dependent on the integrity and functionality of cholinergic pathways (Adler et al. 1998). However, inhibition can be disrupted by amphetamine (Adler et al. 1986; Stevens et al. 1991) – analogously to data from humans – and by phencyclidine (Adler et al. 1986). This loss of N40 suppression has been found to depend on the noradrenergic and dopaminergic properties of these drugs, also in the case of phencyclidine (Stevens et al. 1991; Miller et al. 1992). The psychostimulant cocaine has also been found to cause a loss of N40 suppression (Boutros et al. 1994). Thus, increased catecholamine neurotransmission seems to exert the same disruptive effects on sensory gating in humans and lower animals. However, in the only study reported to date on the effects of 5-HT_2 modulation of N40 suppression, an unexpected disruptive effect was found for the 5-$HT_{2A/2C}$ antagonist ketanserin. Conversely, the 5-$HT_{2A/2C}$ agonist DOI increased filtering and was also capable of reverting the reductions in filtering caused by ketanserin and amphetamine (Johnson et al. 1998).

The effects of *ayahuasca* on PPI did not reach statistical significance at any of the prepulse-to-pulse intervals tested. In the only other human study performed to date involving serotonergic psychedelics, the administration of psilocybin provoked a mild though significant increase of PPI at a prepulse-to-pulse interval of 100 ms, with no significant effects on habituation (Gouzoulis-Mayfrank et al. 1998). Both in the present study and in that by Gouzoulis-Mayfrank and coworkers, the drug doses administered were moderate and, although causing modifications in thought processes and the sensorium, they did not induce a clear-cut psychotic syndrome. Vollenweider and coworkers (1999) administered the serotonin releaser MDMA to a group of healthy volunteers and found a significant increase in PPI at the prepulse-to-pulse interval of 120 ms, but no significant effects on habituation. Results in the present study replicate the absence of effects found for psychedelics and MDMA on the rate of habituation.

Recently, a mechanistic study has shown that pretreatment with the 5-$HT_{2A/2C}$ antagonist ketanserin has no effect on the PPI-enhancing activity of MDMA, even though the antagonist was able to attenuate some of the effects of the drug, fundamentally the MDMA-induced perceptual modifications (Liechti et al. 2001). Conversely, these authors reported a decrease in PPI after pretreatment with the serotonin re-uptake inhibitor citalo-

pram and concluded that the effects of MDMA on human PPI seem to be more dependent on serotonin release than on an interaction at the 5-$HT_{2A/2C}$ level. These results would question the role of the human 5-$HT_{2A/2C}$ site in the modulation of PPI, despite the fact that recent human data provide additional support to the role of these receptors in the genesis of the psychological effects of psychedelics (Vollenweider et al. 1998). Unfortunately, no studies to date have evaluated the effects of the blockade of this receptor on psychedelic-induced increases of PPI in humans. Interestingly, the pattern of effects shown by serotonergic drugs on the human PPI in the limited number of studies conducted to date is opposed to that by dopaminergic/noradrenergic agonists. Thus, D-amphetamine and bromocriptine have been shown to impair PPI in healthy volunteers (Abduljawad et al. 1998, 1999; Hutchinson and Swift 1999).

In contrast to the above data, a coincidental pattern of effects on startle habituation and PPI has been observed for dopaminergic and 5-$HT_{2A/2C}$ agonists in lower animals. Braff and Geyer (1980) demonstrated an impairment in habituation of tactile startle in rats after administration of the mixed serotonergic agonist LSD. PPI has also been found to be impaired in rats after the 5-$HT_{2A/2C}$ agonist DOI, an effect which can be prevented by mixed 5-$HT_{2A/2C}$ (Sipes and Geyer 1994) and selective 5-HT_{2A} antagonists (Sipes and Geyer 1995; Padich et al. 1996). In a recent article, LSD was found to disrupt PPI in rats, and this effect was prevented only by selective 5-HT_{2A} antagonists. Other antagonists with affinity for the 5-HT_{2C}, 5-$HT_{2B/2C}$, 5-HT_{1A}, and 5-HT_6 did not counteract LSD-induced disruptions (Ouagazzal et al. 2001). Similarly, in rats PPI is disrupted by systemic administration of dopamine agonists, such as apomorphine, amphetamine, or the D_2 agonist quinpirole, and reversed by antipsychotic agents showing anti-D_2 activity (Geyer et al. 2001). One aspect that may have been overlooked and that could be involved in the differences in PPI modulation found for indole psychedelics between species is the fact that these drugs interact with both the 5-$HT_{2A/2C}$ and 5-HT_{1A} sites. Activation of these receptors has been shown to mediate opposite behavioral effects (Krebs-Thomson and Geyer 1998) in animals, and 5-HT_{1A} activation has recently been found to increase PPI in mice (Dulawa et al. 2000). The degree to which either receptor is activated after indole psychedelics could vary between species, and, consequently, the overall drug-induced effects on PPI could also vary.

The diverging results obtained on PPI and P50 suppression after *ayahuasca* administration to humans seemingly indicate a differential drug action. In addition to differences in receptor-level interactions, P50 suppression and PPI may reflect different stages of information processing and involve different brain structures. While P50 suppression is essentially viewed as a hippocampal process (Freedman et al. 1996; Adler et al. 1998), based on data from animal studies, PPI is thought to be modulated by a complex circuit involving the limbic cortex, striatum, pallidum, and pontine tegumentum, (Swerdlow and Geyer 1999; Swerdlow et al. 2001), offering many targets for pharmacological modulation. Swerdlow et al. (2000) have postulated that P50 and PPI are interrelated to the extent that hippocampal circuitry participates in both processes. Thus, the sites of pharmacological action and the subsequent modulation of each gating measure by different neurotransmitter systems may consequently show considerable variation.

In conclusion, at the doses administered, *ayahuasca* induced a different pattern of effects on PPI and P50. The results obtained seemingly indicate no effect, or at best, a mild enhancing effect of the drug on PPI, a measure of sensorimotor gating. On the contrary, the observed significant dose-dependent decreases in P50 suppression after *ayahuasca* suggest a suppressing effect of the drug on normal sensory gating in humans. This differential modulation of sensorimotor and sensory gating by *ayahuasca* in humans could be due to differential drug effects on brain structures participating in each process. However, the fact that the subjective-effect profile induced by *ayahuasca*, which was typical of the psychedelics, did not resemble that of acute psychosis should also be taken into consideration. In addition, the pharmacological characteristics of the beverage, which combines MAO-inhibitors and DMT, precludes the generalization of the present findings to all 5-$HT_{2A/2C}$ agonists. Future studies with *ayahuasca* should examine wider dose ranges to better characterize the effects of this drug on gating mechanisms in the CNS.

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