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Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage *ayahuasca* in healthy volunteers

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Aims *Ayahuasca* is a traditional South American psychoactive beverage used in Amazonian shamanism, and in the religious ceremonies of Brazilian-based syncretic religious groups with followers in the US and several European countries. This tea contains measurable amounts of the psychotropic indole *N*,*N*-dimethyltryptamine (DMT), and β-carboline alkaloids with MAO-inhibiting properties. In a previous report we described a profile of stimulant and psychedelic effects for *ayahuasca* as measured by subjective report self-assessment instruments. In the present study the cerebral bioavailability and time-course of effects of *ayahuasca* were assessed in humans by means of topographic quantitative-electroencephalography (q-EEG), a noninvasive method measuring drug-induced variations in brain electrical activity.

Methods Two doses (one low and one high) of encapsulated freeze-dried *ayahuasca*, equivalent to 0.6 and 0.85 mg DMT kg^{-1} body weight, were administered to 18 healthy volunteers with previous experience in psychedelic drug use in a double-blind crossover placebo-controlled clinical trial. Nineteen-lead recordings were undertaken from baseline to 8 h after administration. Subjective effects were measured by means of the Hallucinogen Rating Scale (HRS).

Results *Ayahuasca* induced a pattern of psychoactive effects which resulted in significant dose-dependent increases in all subscales of the HRS, and in significant and dose-dependent modifications of brain electrical activity. Absolute power decreased in all frequency bands, most prominently in the theta band. Mean absolute power decreases (95% CI) at a representative lead (P3) 90 min after the high dose were -20.20 ± 15.23 μV^2 and -2.70 ± 2.21 μV^2 for total power and theta power, respectively. Relative power decreased in the delta (-1.20 ± 1.31% after 120 min at P3) and theta (-3.30 ± 2.59% after 120 min at P3) bands, and increased in the beta band, most prominently in the faster beta-3 (1.00 ± 0.88% after 90 min at P3) and beta-4 (0.30 ± 0.24% after 90 min at P3) subbands. Finally, an increase was also seen for the centroid of the total activity and its deviation. EEG modifications began as early as 15–30 min, reached a peak between 45 and 120 min and decreased thereafter to return to baseline levels at 4–6 h after administration.

Conclusions The central effects of *ayahuasca* could be objectively measured by means of q-EEG, showing a time pattern which closely paralleled that of previously reported subjective effects. The modifications seen for the individual q-EEG variables were in line with those previously described for other serotonergic psychedelics and share some features with the profile of effects shown by pro-serotonergic and pro-dopaminergic drugs. The q-EEG profile supports the role of 5-HT_2 and dopamine D_2-receptor agonism in mediating the effects of *ayahuasca* on the central nervous system.

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Introduction

Ayahuasca is the Quechuan name for both the Amazon woody vine *Banisteriopsis caapi* (Malpighiaceae) and the sacred psychoactive beverage obtained from it. The beverage, also known by the names *Yajé*, *Natema*, *Santo Daime* and *Vegetal*, has been used throughout the Amazon Basin by shamans and healers since pre-Columbian times for medicinal purposes and as a means to contact the supernatural [1, 2]. More recently, syncretic religions combining the use of *ayahuasca* with Christian beliefs, particularly the *Santo Daime* and the *União do Vegetal*, have been established in Brazil, where they enjoy legal protection. Outside Brazil, smaller groups of followers have begun to consume the tea in the United States and in several European countries, including Germany, Great Britain, Holland, France and Spain [3]. Even though the number of users is still relatively small, adverse reactions associated with the simultaneous use of *ayahuasca* and other centrally active drugs have raised concern for public health [4], and extensive clinical data on its somatic, psychological and neurophysiological effects are warranted.

Banisteriopsis caapi, the basic ingredient of the beverage, is seldom found alone in *ayahuasca*. The tea is generally obtained by infusing the stems of the vine together with the leaves of other plants, namely *Psychotria viridis* (Rubiaceae) or *Diplopterys cabrerana* (Malpighiaceae) [5]. Chemical analyses have shown that *B. caapi* contains notable amounts of β-carboline alkaloids, mainly harmine and tetrahydroharmine (THH), followed by harmaline and trace amounts of harmol [5, 6]. *P. viridis* and *D. cabrerana* also contain indole alkaloids, mainly the potent short-acting psychedelic agent *N*,*N*-dimethyltryptamine (DMT) [5, 7].

This combination of *B. caapi* and *P. viridis* in a single oral preparation is a remarkable achievement of empirical ethnopharmacological knowledge, as psychoactivity arises from combining the pharmacodynamic actions of the β-carbolines and of DMT. Similarly to other indole and phenethylamine psychedelics such as LSD and mescaline [8], DMT shows affinity for the 5-$HT_{2A/2C}$ receptor sites in the central nervous system (CNS), where it displays agonist activity [9]. However, unlike most psychedelics, DMT is *a priori* only active when parenterally administered, because the oral ingestion of the drug alone leads to its metabolic breakdown by the enzyme monoamine oxidase (MAO) [10]. Interestingly, harmine and harmaline, and to a lesser extent THH, are potent MAO inhibitors [6]. Thus, it is widely accepted that the MAO-inhibiting action of the β-carbolines present in the tea allows the viable access of DMT to the systemic circulation and the CNS. In addition to facilitating a direct agonist action of DMT at the 5-$HT_{2A/2C}$ sites, the MAO-inhibiting properties of the β-carbolines may contribute to the overall effects of *ayahuasca*, firstly, by prolonging the effects of DMT due to its decreased metabolism, and secondly, by simultaneously enhancing the levels of endogenous catecholamines and serotonin [11].

In a previous study conducted to characterize the tolerability and psychological effect profile of *ayahuasca* [12], this tea was found to induce a pattern of psychostimulant and psychedelic effects, which qualitatively resembled those of other classical serotonergic agents, such as psilocybin, and parenteral DMT [13, 14]. *Ayahuasca* was able to induce dose-dependent perceptual, cognitive and affective modifications, with a milder intensity and longer duration than those previously described for intravenous DMT [14], but with an overall duration shorter than that of better characterized psychedelics such as LSD or mescaline [15].

The aim of the present study was to assess the central actions of *ayahuasca* by means of quantitative-electroencephalography (q-EEG), an objective noninvasive method used to evaluate drug effects on the CNS with high temporal resolution [16]. We intended thus to demonstrate its cerebral bioavailability and subsequent psychoactivity by means other than subjective self-report instruments, and implementing a double-blind randomised placebo-controlled design. Recordings of brain electrical activity were carried out before and at different time points after the administration of two different doses of encapsulated freeze-dried *ayahuasca* to a group of healthy volunteers with previous experience in the use of psychedelics.

Methods

Volunteers

Eighteen healthy volunteers (15 males and three 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 at least on five occasions without sequelae derived therefrom. The volunteers were given a structured psychiatric interview (DSM-III-R) and completed the trait-anxiety scale from the State-Trait Anxiety Inventory [17]. 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 medical history, laboratory tests, ECG and urinalysis. All volunteers gave their written informed consent to participate. Mean age was 25.7 years (range: 19–38), mean weight 66.47 kg (range: 50.7–79.5) and

mean height 175.11 cm (range: 158–188). In addition to their prior intake of psychedelics, all volunteers had previous experience with cannabis and cocaine. Although prior exposure to *ayahuasca* was not required for participation, two of the volunteers had ingested this tea before inclusion. The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans, and was approved by the hospital's ethics committee and the Spanish Ministry of Health. The volunteers received detailed information on the nature of *ayahuasca*, the general psychological effects of psychedelics and their possible adverse effects, as reported in the psychiatric literature.

Drug

The *ayahuasca* doses administered to the volunteers in the present study as the low and the high dose were the equivalent to 0.6 and 0.85 mg DMT kg^{-1} body weight. These doses were chosen based on tolerability and subjective effect data gathered in a previous study [12]. The *ayahuasca* was not administered in its original liquid form, but as a liophilizate. The DMT contents in the liophilizate had been determined by h.p.l.c., as described by Callaway and coworkers [18], and the β-carboline constituents following a modification of the method described therein. The concentrations found were: 8.33 mg DMT, 14.13 mg harmine, 0.96 mg harmaline and 11.36 mg THH per gram of freeze-dried material. These alkaloid contents corresponded to the following concentrations in the original tea: DMT 0.53 mg ml^{-1}, harmine 0.90 mg ml^{-1}, harmaline 0.06 mg ml^{-1} and THH 0.72 mg ml^{-1}. The calculated individual dose for each volunteer was administered by combining 00 gelatin capsules containing 0.5 g, 0.25 g or 0.125 g of 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), a 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 days 2 to 4 in a double-blind balanced fashion, according to a randomization table. The first nonrandomized placebo was administered in order to familiarize the volunteers with the experimental setting and to minimize the stress associated with the experimental interventions. Two weeks prior to the beginning of the experimental sessions, volunteers were requested to abstain from any medication or illicit drug until the completion of the study. Volunteers also abstained from alcohol, tobacco and caffeinated drinks 24 h prior to each experimental day. Urinalysis for illicit drug use was performed for each experimental session and was found negative for amphetamines, cocaine, opioids, benzodiazepines and alcohol. A 7 day washout period was established between experimental days.

On each experimental day participants arrived in the laboratory in the morning under fasting conditions. EEG electrodes were placed on the scalp and treatment capsules were administered at approximately 10.00 h with 250 ml tap water. EEG recordings were obtained at baseline and at regular intervals after treatment administration. The experimental sessions were undertaken in a quiet and dimly lit room with the volunteers seated in a reclining chair. The experimenter remained outside the room during the EEG recordings. At 4 h after administration of the capsules, when the most prominent subjective effects associated with the drug had disappeared, the volunteers answered subjective effect questionnaires, and had a meal. The last recording was performed at 8 h and volunteers were discharged approximately 9 h after drug administration.

Measurements

EEG acquisition and analysis

EEG recordings were obtained through 19 electrodes placed on the scalp according to the international 10/20 system on the following locations: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2, referenced to averaged mastoids by means of a Neuroscan SYNAMPS amplifier. Additionally, vertical and horizontal electrooculograms (EOG) were recorded. Vigilance controlled EEG (V-EEG) for 3 min with eyes closed was recorded at −15 (PRE-1), baseline (PRE-2), +15, +30, +45, +60, +90, +120, +150, +180, +210, +240, +360 and +480 min from drug administration. During the V-EEG recordings, the experimenter tried to keep the volunteers alert; as soon as drowsiness patterns appeared in the EEG they were aroused by acoustic stimulation. The EEG signal was recorded using high-pass and low-pass filters of 0.3 Hz and 30 Hz, respectively, and digitized online with a sampling frequency of 100 Hz.

A two-step artefact processing procedure was used. It included ocular artifact minimization based on regression analysis in the time domain, as described by Semlitsch *et al.* [19], and automatic artifact rejection based on a time and frequency domain approach as described by Anderer *et al.* [20]. Subsequently, validity of the artifact processing procedure was visually inspected [21].

After recomputation to average reference, spectral analysis was performed for artefact-free 5 s epochs, resulting in a frequency resolution of 0.2 Hz. The spectral density curves for all artifact-free EEG epochs were averaged for a particular experimental situation. These mean spectral curves, containing data from 1.3 to 30 Hz, were quantified into 34 target variables: total power, absolute and relative power in 11 different frequency bands (delta [1.3–3.5 Hz], theta [3.5–7.5 Hz], alpha-1 [7.5–10.5 Hz], alpha-2 [10.5–13 Hz], beta-1 [13–16 Hz], beta-2 [16–20 Hz], beta-3 [20–25 Hz], beta-4 [25–30 Hz], combined delta-theta, alpha and beta), the dominant frequency in Hz, absolute and relative power of the dominant frequency, the centre-of-gravity frequency (centroids) and the frequency variability (centroid deviations) of the combined delta-theta, alpha and beta bands as well as of the total activity. Additionally, the vigilance alpha/delta-theta index was also calculated.

Topographic maps were computed by cubic interpolation of the values of the four nearest electrodes.

Subjective ratings

Volunteers were requested to answer the Hallucinogen Rating Scale (HRS), a self-report questionnaire specifically developed to quantify different aspects of psychedelic-induced subjective effects. The questionnaire 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 finally *Intensity*, which reflects the strength of the overall experience [14]. In the present study a Spanish adaptation of the questionnaire was used [22].

Statistical analysis

EEG recordings

Statistical analysis of EEG recordings was performed following the IPEG (International Pharmaco-EEG Group) guideline on statistical design and analysis of pharmacodynamic trials [23]. Accordingly, the inferential strategy of descriptive data analysis (DDA) [24], as proposed for application to the mapping situation [25], was applied. In short, descriptive tests, preferably of simple null hypotheses such as equality of two treatment effects, are performed at all observation times, locations and measurements (variables). A nominal α-level for each test is chosen at 5%, and all P values lower than 0.05 are clearly distinguished in the graphical demonstration of the results. Therefore, the formal P value is calculated for each test, leading to certain pattern of P values in the whole data structure, of which the 'small' P values are indicative of areas of potentially true drug-effect-differences. Rather than considering these P values (should they be smaller than α) as a decision criterion for rejecting local null hypotheses (a procedure which would not be indicated in the absence of an α-correction measure), in DDA these patterns of small P values are analysed in a descriptive way in order to interpret results. This interpretation should be done not just by looking at the P values alone but by simultaneously taking into account the biomedical expectations based on the structure of the study. Therefore, the calculated P values and their pharmacologically sound patterns are used as 'judgement criteria'. Statistics included multivariate methods such as Hotelling T^2 to test overall differences between drugs, and paired t-tests to evaluate changes and interdrug differences in detail at different hours post-administration. According to the experimental design used, pharmacologically sound patterns of P values <0.05 would be those showing: (a) spatial clustering (b) time courses, and (c) dose dependencies. These results were displayed as significance probability maps. Additionally, dose/treatment-effect and time-effect relationships were explored by means of a multivariate, nonparametric approach [20]. Friedman tests and multiple Wilcoxon tests based on sign-adjusted changes in 28 V-EEG variables were applied. In all tests performed (parametric and nonparametric) PRE-2-values were considered as the predrug baseline, and comparisons were conducted with the randomized placebo.

Subjective ratings

HRS scores were analysed by means of a one-way analysis of variance (ANOVA) with repeated measures, with treatment (randomized placebo, *ayahuasca* low dose, *ayahuasca* high dose) as factor. Greenhouse-Geisser epsilon was used to correct possible violations of the sphericity assumption and to reduce Type I errors. Differences were considered statistically significant for $P<0.05$. When ANOVA showed significant differences between treatments, pairwise comparisons were carried out by means of t-tests, followed by Bonferroni correction.

Results

EEG recordings

(1) Pharmaco-EEG maps: multivariate analysis

In order to test the hypothesis that *ayahuasca* exerts significant central effects which induce modifications in brain electrical activity as compared with placebo, a multiple analysis of variance (MANOVA) with repeated measures was performed for V-EEG for each of the 19 electrodes. Treatment (randomized placebo, *ayahuasca*),

time (PRE-2, post) and the following set of variables: log-transformed absolute power values in the delta, theta, alpha-1, alpha-2, beta-1, beta-2, beta-3 and beta-4 frequency bands were considered in the MANOVA. Hotelling T^2 values were used in the significance probability maps to indicate differences between *ayahuasca*-induced and placebo-induced changes in brain electrical activity from baseline through 8 h after drug administration.

As shown in Figure 1, *ayahuasca* administration induced dose-dependent central effects as measured by the derived EEG variables, which were greater and longer lasting after the high dose. Thus, after the low 0.6 mg DMT kg^{-1} body weight dose, statistically significant differences with placebo were obtained only at isolated electrode locations between 45 min and 2.5 h postadministration. After the high 0.85 mg DMT kg^{-1} body weight dose, however, EEG changes were found over extensive scalp areas. These effects first attained statistical significance at 1 h, showed a peak between 1.5 and 2 h and gradually decreased thereafter, to disappear at 6–8 h. At the peak of the pharmacodynamic effects, variations in brain electrical activity were measured all over the scalp, with the greatest intensity in the central and right temporo-occipital electrodes.

(2) Pharmaco-EEG maps: univariate analysis

Topographic brain maps based on *t*-tests are described to show detailed drug-induced changes in the individual EEG variables.

Total power As shown in Figure 2, *ayahuasca* produced a significant and dose-dependent reduction in total power in electrodes located all over the scalp, with a temporal peak at 90 min after administration of the high dose. Both the centroid of the total activity and its deviation showed significant and dose-dependent increases peaking at 120 and 90 min, respectively.

Slow activity The effects of *ayahuasca* on slow activity are shown in Figure 3. Absolute power of the combined delta-theta activity was decreased in a dose-dependent manner after dosing with *ayahuasca*, with the peak

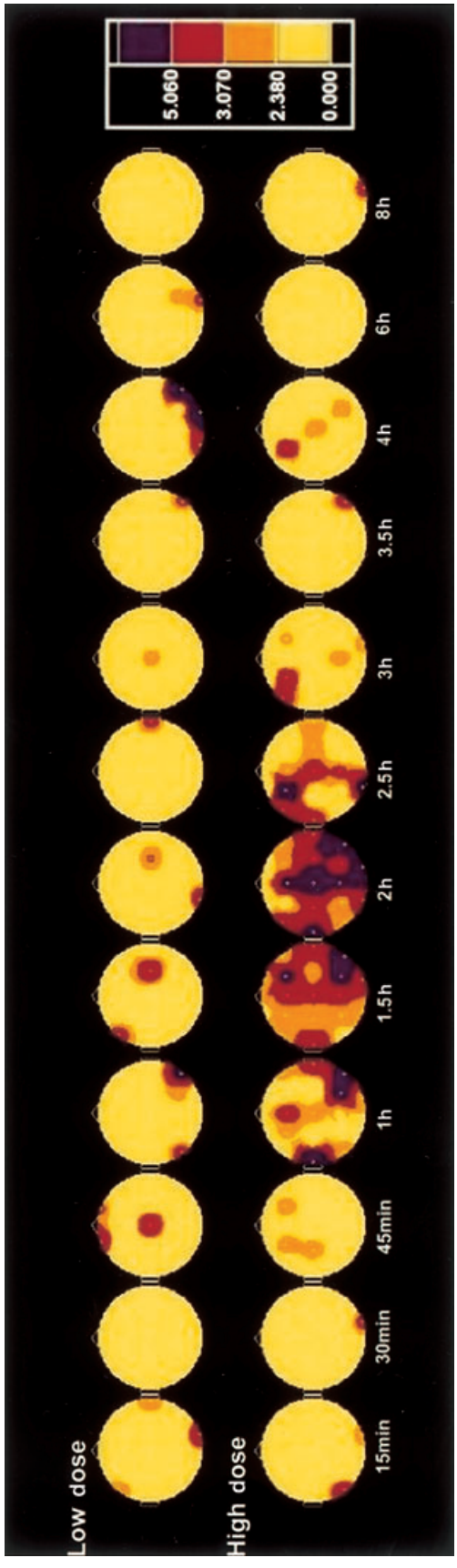
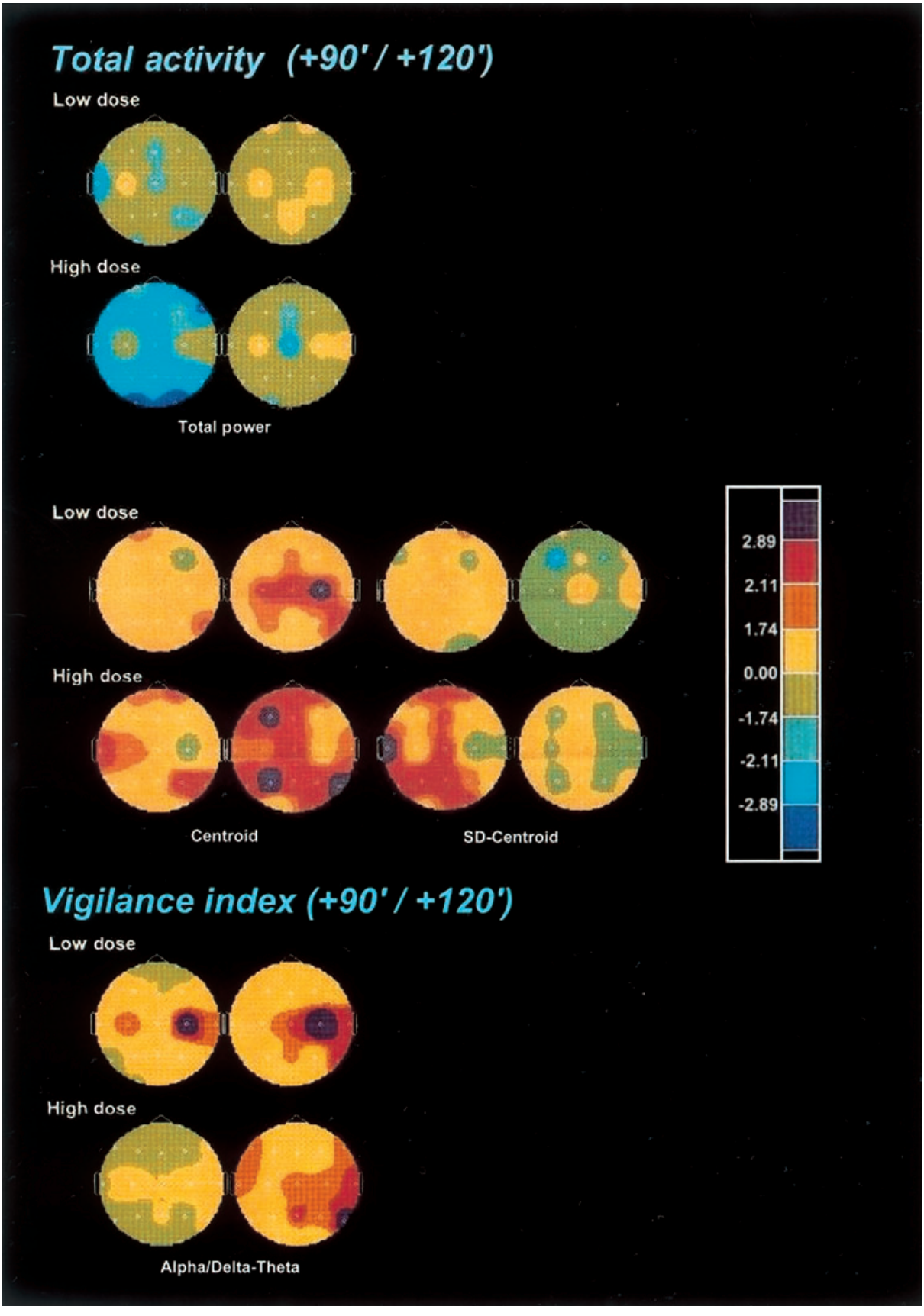


Figure 1 Significance probability maps showing differences between *ayahuasca*-induced and placebo-induced central effects at 12 time points *vs* baseline values (PRE-2) after low (upper row) and high (lower row) doses of *ayahuasca* ($n=18$). The vertex view shows the nose at the top, the left ear to the left, the right ear to the right. Electrode positions are indicated by white dots. Maps are based on Hotelling T^2 obtained from multivariate tests in repeated measures ANOVAs on eight logarithmically transformed absolute power values in delta, theta, alpha-1, alpha-2, beta-1, beta-2, beta-3 and beta-4 frequency bands. The colour key shows T^2 values with hot/red colours indicating significant differences: $T^2>2.38=P<0.10$, $>3.07=P<0.05$ and $>5.06=P<0.01$.



decreases at 90 min for the low dose and between 90 and 120 min for the high dose. When examined separately, both the delta and theta frequency bands showed decreases in absolute power. However, the most dramatic decreases were found in the theta band, an effect which showed a dose-dependent pattern and peaked between 90 and 120 min.

Relative power of the combined delta-theta bands was also dose-dependently decreased, with the peak reductions at 120 min. Decreases in relative power were marginal for the delta band, while they were prominent and dose-dependent for the theta band. These reductions in relative power were maximal at 120 min, showing a widespread distribution all over the scalp.

The centroid of the combined delta-theta activity showed a significant though modest deceleration, with a significant increase of its deviation. Nevertheless, although dose-dependent, the deceleration of the centroid was not uniformly distributed over the scalp, showing the greatest decreases at C3, T4 and O1 at the high *ayahuasca* dose at 90 min after administration. At the high dose, the significant increase seen for the deviation of the centroid was obtained at 120 min and was restricted to the Pz and P3 leads.

Alpha activity The effects of *ayahuasca* on alpha activity are shown in Figure 4. Absolute alpha activity was significantly and dose-dependently decreased after *ayahuasca*. The decreases were more prominent at the high dose in the left-temporal and centro-parieto-occipital electrodes. The maximal decrease was observed at 90 min after administration. When separately examined, the alpha-2 band showed more significant and more widely distributed decreases than the alpha-1 band. Differently from the maximal total alpha and alpha-1 power decreases, the reductions in absolute power for the alpha-2 band peaked at 60 min after administration (not shown).

Relative alpha activity was significantly increased at 120 min after administration, showing an inverse dose-reponse pattern, with maximal increase after the low dose. While this increase was consistently observed in the alpha-1 sub-band, in the alpha-2 sub-band a decrease which reached the highest significance at 60 min after the intake was seen (not shown).

No consistent pattern of changes was observed after *ayahuasca* in the dominant frequency within the alpha band (not shown). A tendency towards statistical significance was seen in the absolute power of the dominant frequency (predominantly decreases) which reached significance marginally in some electrode sites between 45 and 120 min after administration of the high dose. Conversely, relative power of the dominant frequency did show statistically significant increases after the low and the high *ayahuasca* doses at 120 min after administration. Finally, no consistent drug-induced effects were found either for the centroid of the alpha activity or its deviation.

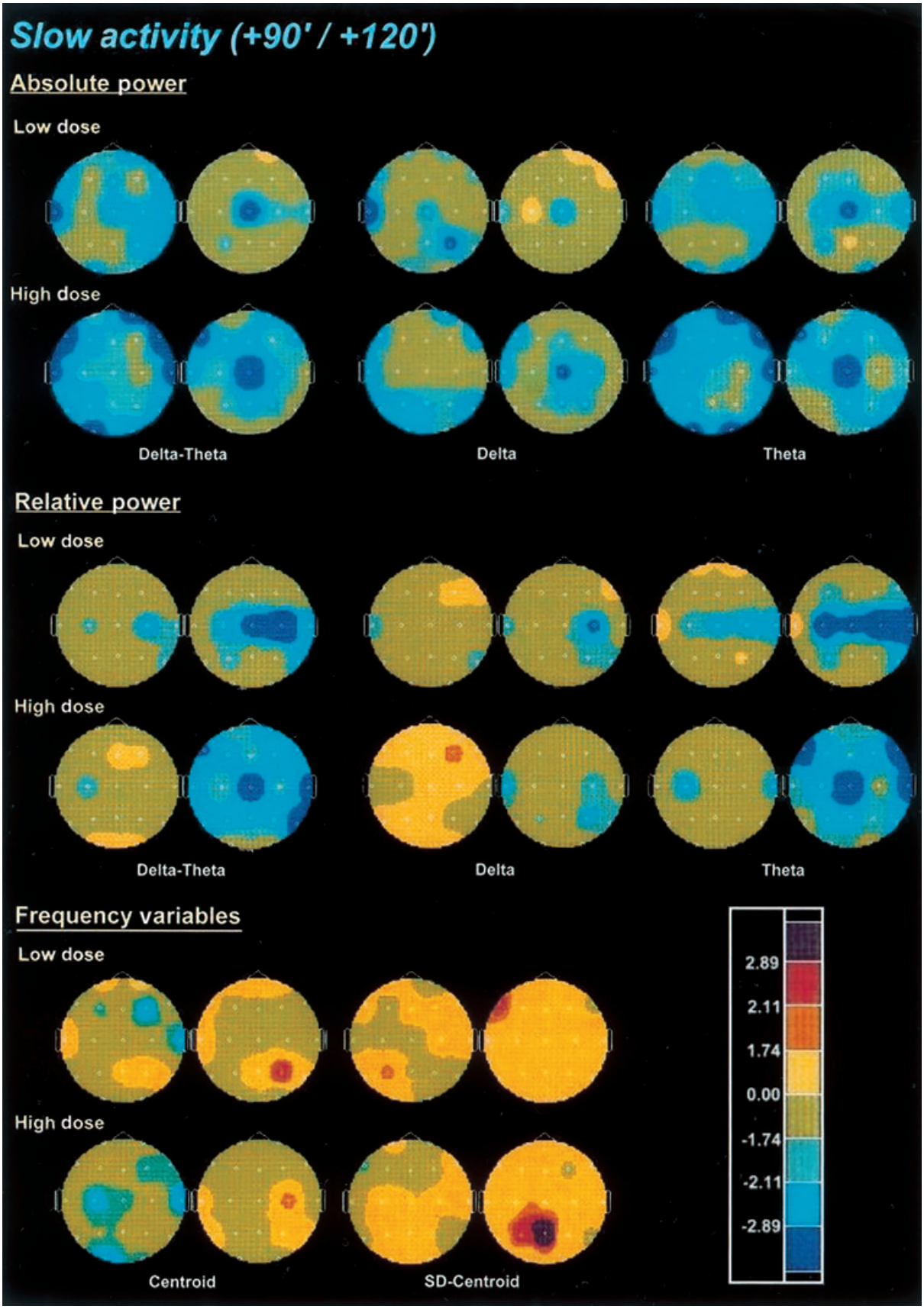
Fast activity The effects of *ayahuasca* on fast activity are shown in Figure 5. The absolute power of global beta activity was dose-dependently decreased by *ayahuasca*, with a maximal decrement at 90 min after administration. When split between the four frequency subbands, absolute power decreases were found to be more intense in the beta-1 range, with power decreases becoming less prominent as one moved to beta-2, beta-3 and beta-4. Peak decreases were observed at 90 min after administration, except for beta-3 which were more prominent at 45 min (not shown).

As far as relative power in the beta frequency range is concerned, statistically significant increases were found, these being more intense and longer-lasting at the high relative to the low *ayahuasca* dose. The maximal increments were obtained between 45 and 90 min after administration. Compared with absolute power values, the examination of relative power in the individual beta subbands rendered an inverse pattern of variation. Thus, relative power increases were marginally significant for the beta-1 band, became more widespread over the scalp for beta-2, more significant for beta-3 and were maximal for beta-4. Increases in the relative power of the beta-4 frequencies showed a predominant central and parieto-temporal distribution. Statistical significance for relative power increases for beta-2, beta-3 and beta-4 was obtained between 45 and 120 min after administration, with the maximal increase at 90 min.

The centroid of the beta frequency range showed a statistically significant and dose-dependent shift toward the higher values after *ayahuasca*, which also peaked at 90 min after administration. The deviation of the centroid was not significantly modified by the drug.

Table 1 lists 95% confidence intervals for changes in absolute (μV^2) and relative (%) power in all frequency bands at 90 and 120 min following the administration of

Figure 2 Significance probability maps showing differences between *ayahuasca*-induced and placebo-induced changes in total power and frequency variables of the EEG total activity (1.3–30 Hz), and in the alpha/delta-theta vigilance index, after low (upper rows) and high (lower rows) doses of *ayahuasca* ($n=18$) at 90 min (left) and 120 min (right) after administration *vs* baseline values (PRE-2). The vertex view shows the nose at the top, the left ear to the left, the right ear to the right. Electrode positions are indicated by white dots. Eight-colour scale represents drug-induced changes as compared with placebo based on *t*-values: lilac, increase at $P<0.01$; red, increase at $P<0.05$; ochre, increase at $P<0.10$; pale yellow, trend towards increase; pale green, trend towards decrease; bright green, decrease at $P<0.10$; light blue, decrease at $P<0.05$; dark blue, decrease at $P<0.01$.



the low and high *ayahuasca* doses in a single representative electrode (P3).

Vigilance index: alpha/delta-theta The alpha/delta-theta ratio (Figure 2) was also calculated for each of the recorded time points. This index showed a significant increase, relative to placebo, both after the low and the high *ayahuasca* doses between 90 and 150 min, with the maximal increase at 120 min.

(3) Non-parametric multilead EEG analysis

Dose/treatment-effect relationships were calculated using Friedman and multiple Wilcoxon tests of sign-adjusted changes from PRE-2-values in 28 V-EEG variables obtained in the 19 leads. As shown in Table 2, based on the rank-sums, administered at the low dose *ayahuasca* could only be differentiated from randomised placebo at 45 min and 60 min after dosing. At the high dose, however, statistically significant differences were found from 45 min through 120 min after administration. Pairwise comparisons considering the total rank-sum showed statistically significant differences between randomised placebo and each of the *ayahuasca* doses, and between the low and high *ayahuasca* doses.

Time-effect relationships were calculated using Friedman and multiple Wilcoxon tests for randomised placebo-corrected sign-adjusted changes from PRE-2-values in 28 V-EEG variables obtained in the 19 leads, as shown in Figure 6. After *ayahuasca* administration, changes on EEG variables were seen as early as 15–30 min, followed by a steep increase at 45 min in rank-sum values. At the high dose, *ayahuasca* showed the pharmacodynamic peak between 45 and 90 min, with rank-sum values gradually decreasing thereafter and approaching baseline at 4–6 h after administration. At the low dose, an analogous curve was found, with the pharmacodynamic peak between 45 and 90 min having an analogous subsequent decrease to that of the high dose. Compared to baseline values, at the low dose increases in rank-sum values did not reach statistical significance at any of the time points evaluated. At the high dose, statistically significant differences were found at 45, 60 and 90 min after administration.

Subjective ratings

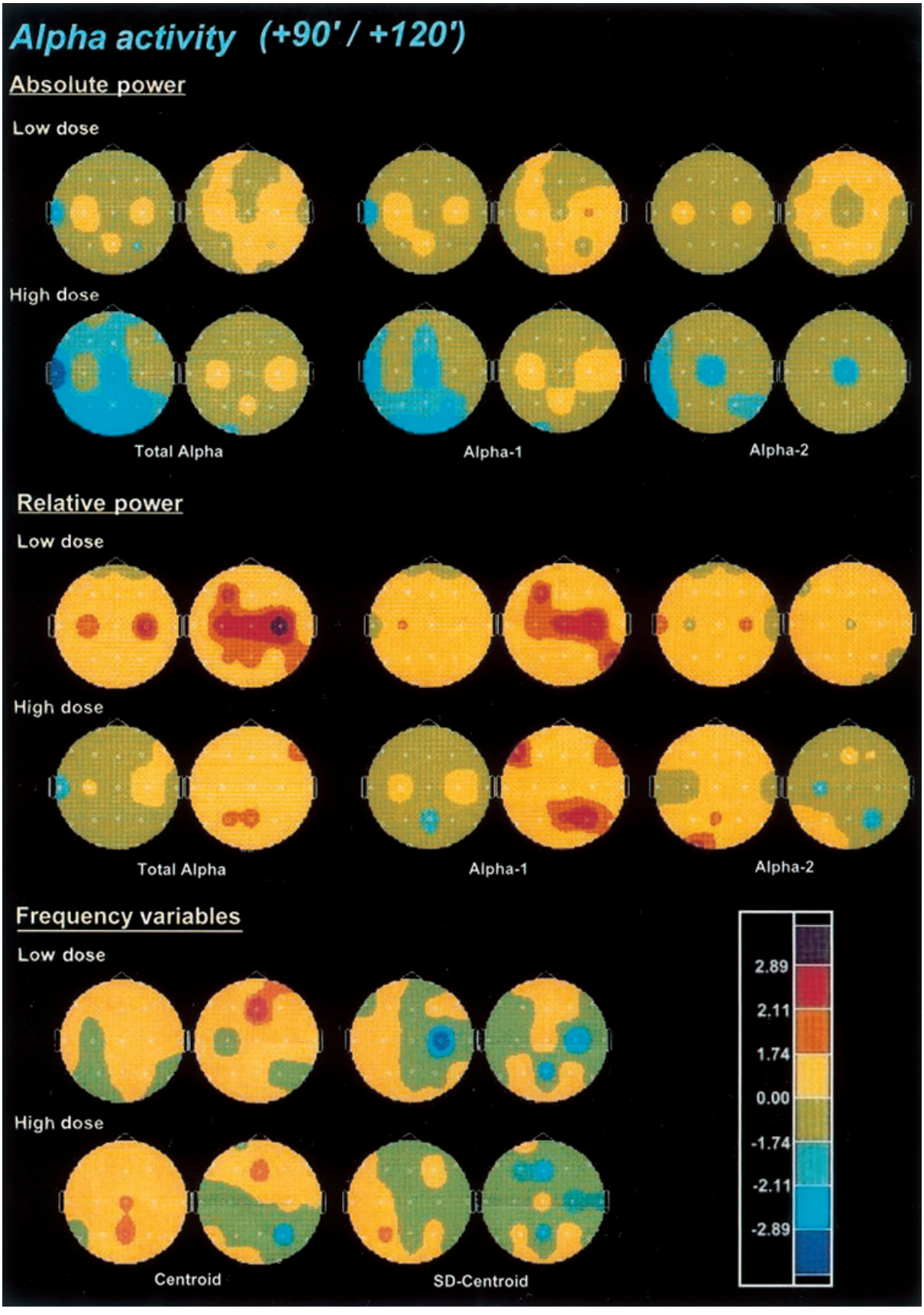
As shown in Table 3, *ayahuasca* induced significant dose-dependent increases in all subscales of the HRS, an instrument specifically designed to quantify the effects of psychedelic drugs. *Ayahuasca* was thus capable of inducing a modified state of awareness in which a psychedelic profile was prominent. At the low dose, all HRS subscales showed statistically significant increases relative to placebo, except for Volition, a measure of impairment in the capacity of the volunteer to interact with his/herself and his/her surroundings. This subscale however, reached statistical significance at the high dose, indicating that of the six aspects measured by the HRS, this was the least modified by *ayahuasca*. Qualitatively, the profile of effects induced by *ayahuasca* included paresthesias and perceptual modifications of predominantly visual, and to a lower extent, auditive nature. This coexisted with more elaborated modifications in thought, associations and emotion, in a global experience described as similar to dreaming activity.

Discussion

The administration of *ayahuasca* to a group of healthy volunteers induced a dose-dependent pattern of subjective effects typical of the psychedelics, replicating the profile obtained in a previous study [12]. In addition to results obtained by means of self-assessment instruments, the implementation of q-EEG demonstrated a significant effect of *ayahuasca*, as compared with placebo, on the human CNS. These effects consisted of an overall decrease in absolute power for all the frequency bands evaluated, and an acceleration of the centre-of-gravity frequency. Absolute power decreases were most prominent in theta, delta and slow beta bands, while the alpha and fast beta rhythms were less intensely affected. Relative power was found to be significantly decreased in the theta, and to a lower extent, delta band. In the alpha band, relative power showed an increase, predominantly in the alpha-1 subband, and significant increases were also obtained in relative power in the beta frequency band. These increases in relative fast activity were most prominent in the beta-3 and beta-4 subbands. Additionally, the alpha/delta-theta ratio, an index of activation, was found to be increased after *ayahuasca*.

The evaluation of the plots of the rank-sums of changes measured at the 19 leads over time showed the first increases between 15 and 30 min, which were followed by a steep rise at 45 min, reaching the maximum effects between 45 and 90 min EEG measures gradually declined thereafter to reach baseline values around 4–6 h after administration. Most remarkably, these objectively measured effects of the drug on the spontaneous brain electrical

Figure 3 Significance probability maps showing differences between *ayahuasca*-induced and placebo-induced changes in absolute power, relative power and frequency variables of the combined slow activity (1.3–7.5 Hz), delta (1.3–3.5 Hz) and theta (3.5–7.5 Hz) frequency bands after low (upper rows) and high (lower rows) doses of *ayahuasca* ($n = 18$), at 90 min (left) and 120 min (right) after administration *vs* baseline values (PRE-2). For technical description of the maps and explanation of the colour key see Figure 2.



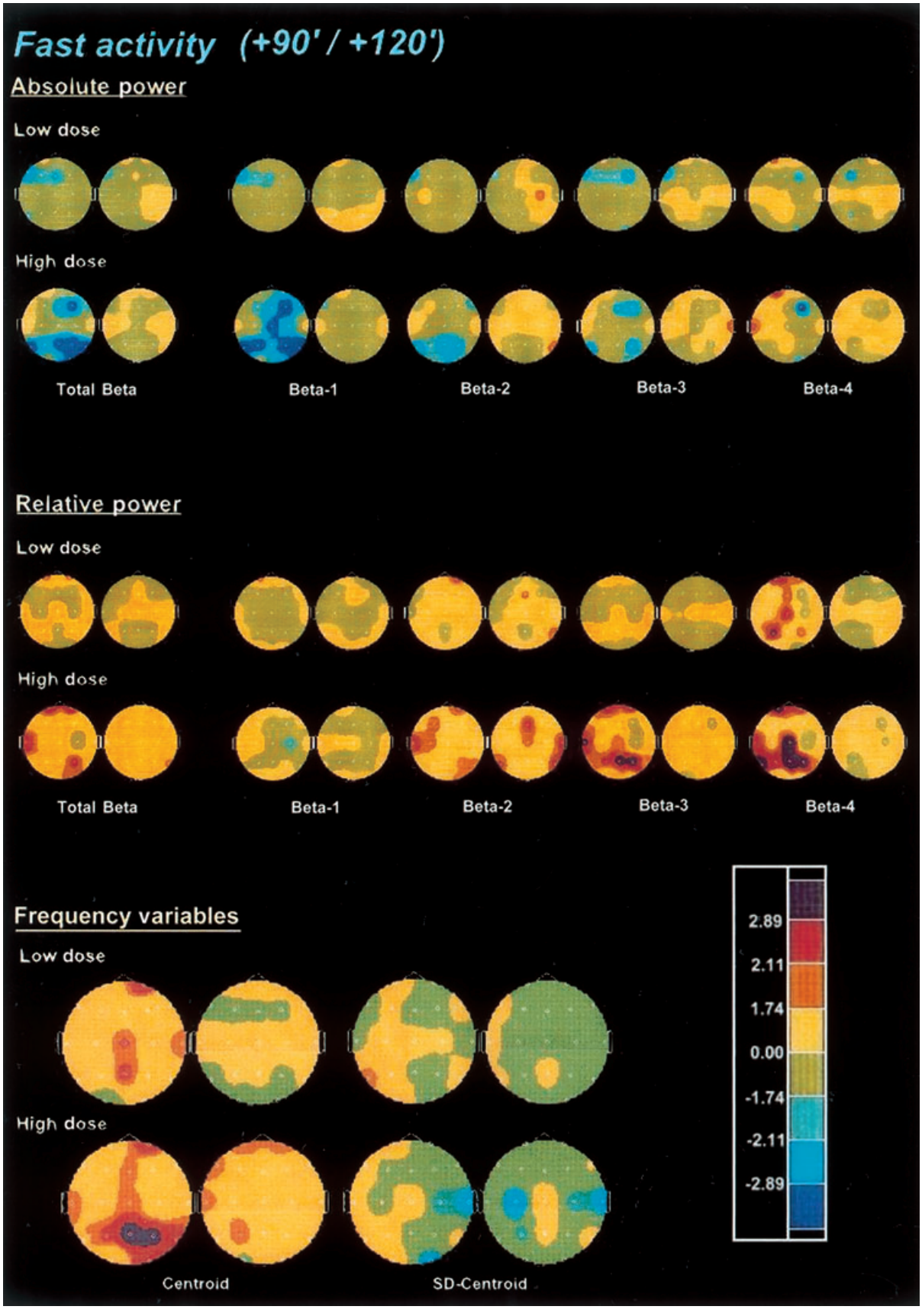
activity closely paralleled the time course of subjectively experienced effects, measured by means of self-report visual analogue scales, as previously reported [12].

To our knowledge, only one previous study has addressed the evaluation of EEG activity in humans after the ingestion of *ayahuasca*. A recent article reported the evaluation of the EEG effects of *ayahuasca* in a group of nine subjects in field conditions [26]. In the cited study, EEG recordings were obtained in the course of a ritual *Daime* session in Brazil. The study was conducted in the absence of a placebo control, and only with an approximate knowledge of the ingested *ayahuasca* dose, this being on average 0.67 mg DMT kg^{-1} body weight. These investigators reported significant changes after *ayahuasca* in relation to baseline values only in the 36–44 Hz band. Given that this frequency range was not evaluated in the present study, it is impossible to establish a comparison with the results obtained in the aforementioned study. Nevertheless, Don *et al.* also reported a pattern of changes in the classical frequency bands which did not reach statistical significance but which bore similarities to that observed in the present study. These nonsignificant variations included a 'slight increase in beta', and a 'slight decrease in theta and alpha'.

The changes in brain electrical activity observed in the present study are difficult to relate entirely to any pharmaco-EEG profile characteristic of the main psychotropic drug groups. Even a direct comparison with other psychedelics is far from easy. Virtually no studies have been conducted in the last 30 years regarding the effects of these drugs on the human EEG. The quantitative approach to the effects of psychedelics on the human EEG was absent at the time they attracted the greatest interest from psychiatry and psychopharmacology researchers in the 1950s and 1960s. Most of the information available from the early research conducted with these compounds is essentially qualitative. In these studies only marginal changes were described after the administration of psilocybin, mescaline or LSD on the visually inspected EEG trace, reporting at most an increase in fast rhythms and an overall decrease in signal amplitude [27]. Itil and coworkers, however, conducted a number of studies combining visual inspection and power spectrum analysis of the recordings obtained after administering anticholinergic compounds with true hallucinogenic properties, such as atropine, and serotonergic psychedelics like LSD. These researchers found almost opposite EEG patterns for these two groups of compounds. While atropine caused the alpha rhythm to disappear and the predominance of low-voltage slow waves, they concluded that the most characteristic effects of LSD were a reduction of theta activity and slow waves in general, as well as an increase in fast activity [27, 28]. In line with these observations, in the present study both absolute and relative power of slow activity decreased after *ayahuasca*, specially in the theta band. With regard to fast activity, while absolute power was decreased following *ayahuasca* administration, a marked enhancing effect was obtained for relative power. The milder increases were found for the slower beta-1 and beta-2 sub-bands and the most intense in the faster beta-3 and beta-4 sub-bands.

Ayahuasca shares the decremental effects seen on delta and theta power with both psychostimulants, such as amphetamine and methylphenidate, and serotonin releasers such as fenfluramine [29, 30]. Interestingly, psychostimulants act predominantly enhancing dopaminergic neurotransmission, in contrast with the serotonergic properties of psychedelics. However, a recent neuroimaging study in humans has shown that dopamine release takes place in the basal ganglia and the ventral striatum after the administration of psilocybin to humans [31], pointing to a role of dopaminergic neurotransmission in the effects of the classical psychedelics. Additional similarities are also to be found between the relative beta-3 and beta-4 band enhancing properties found for *ayahuasca*, and the analogous effect obtained after tricyclic antidepressants, which characterizes the group [29]. Drugs belonging to this pharmacological class inhibit the re-uptake of monoamines, which leads to increased levels of these endogenous compounds in the synapse [32]. (+)-Fenfluramine and the selective serotonin reuptake inhibitor fluoxetine also lead to increases in relative beta power [30, 33], an effect which is also shared by antidepressants showing MAOI properties [34]. It is consequently reasonable to assume that the blocking effects of the β-carbolines on MAO may have led to increased levels of monoamines, due to the blockade of their metabolism, which in turn may have contributed to the relative beta-promoting effect of *ayahuasca*. Regarding slow activity, the theta-dampening activity of psychostimulants and psychedelics is diametrically opposed to the theta-enhancing action of the classical neuroleptics such as haloperidol and chlorpromazine [30, 35]. This theta-enhancing action has also been observed in drugs with a mixed anti-D_2 and anti-5-HT_2 profile, such as risperidone [36], or the more selective 5-HT_2 blocker ketanserin [37], suggesting a

Figure 4 Significance probability maps showing differences between *ayahuasca*-induced and placebo-induced changes in absolute power, relative power and frequency variables of total alpha activity (7.5–13 Hz), alpha-1 (7.5–10.5 Hz), and alpha-2 (10.5–13 Hz) frequency bands after low (upper rows) and high (lower rows) doses of *ayahuasca* ($n = 18$), at 90 min (left) and 120 min (right) after administration *vs* baseline values (PRE-2). For technical description of the maps and explanation of the colour key see Figure 2.



pro-dopaminergic and pro-serotonergic activity for *ayahuasca*.

DMT, the main psychotropic agent in *ayahuasca*, not only binds to the 5-$HT_{2A/2C}$ receptors, located mainly at a postsynaptic level, but also shows affinity for the 5-HT_{1A} sites, which in certain brain regions correspond predominantly to somatodendritic autoreceptors [38]. Thus, DMT probably displays agonist activity also at the 5-HT_{1A} sites, a pattern shared by other indole psychedelics, in contrast with the phenethylamines like mescaline, which interact only with the 5-$HT_{2A/2C}$ receptors [39]. The pharmaco-EEG profile of drugs displaying selective agonist or partial agonist activity at the 5-HT_{1A} site has been described, allowing a more detailed discussion on the probable biochemical mechanisms involved in the EEG effects of *ayahuasca*. Indeed buspirone, a partial 5-HT_{1A} agonist, has been shown to produce marked increases in theta power, in the absence of other relevant EEG modifications [40]. As an opposed pattern was seen for the theta band after *ayahuasca*, one could postulate that 5-HT_{1A} agonism does not seem to be the predominant contribution at a molecular level to the EEG effects of *ayahuasca*. This is consistent with data from a previous study, in which increases in the intensity of the psychological effects elicited by intravenous DMT following blockade of the 5-HT_{1A} sites by pindolol were reported [41]. The observed increases suggest both that agonism at the 5-HT_{1A} site is not essential to obtain a psychedelic effect profile, and that a decreased binding of DMT at the 5-HT_{1A} sites leads to an increase in the amount of DMT available to interact with the 5-HT_2 receptors, and consequently to the enhanced subjective effects experienced by the volunteers. Thus, the present q-EEG findings would rather support a preponderant involvement of the 5-HT_2 receptor in the genesis of the central effects of the beverage.

To sum up, the cerebral bioavailability and psychoactivity of *ayahuasca* could be objectively measured by means of q-EEG, which evidenced a clear dose-dependent effect at the doses administered. Remarkably, the time

Table 1 95% confidence intervals for changes in absolute (μV^2) and relative (%) power in all frequency bands at 90 and 120 min, following the administration of the low 0.6 mg DMT kg^{-1} body weight, and high 0.85 mg DMT kg^{-1} body weight *ayahuasca* doses, in a single representative electrode (P3). All changes *vs* baseline (PRE-2) and randomized placebo. Data from 18 volunteers, showing mean change ±1.96 s.e.mean.

	Low dose		*High dose*	
	90 min	*120 min*	*90 min*	*120 min*
Absolute power (μV^2)				
Total power (1.3–30 Hz)	−5.70±18.62	−5.60±13.72	−20.20±15.23★	−8.30±18.07
Delta (1.3–3.5 Hz)	−1.20±1.57	−1.30±1.82	−1.40±1.10★	−1.70±1.84
Theta (3.5–7.5 Hz)	−1.10±2.70	−1.70±1.45★	−2.70±2.21★	−2.00±2.45
Alpha-1 (7.5–10.5 Hz)	−0.40±7.84	−3.00±8.41	−11.30±11.07★	−1.70±11.11
Alpha-2 (10.5–13 Hz)	−2.00±3.58	0.70±2.74	−2.60±3.65	−2.00±4.90
Beta-1 (13–16 Hz)	−0.30±0.53	0.01±1.96	−0.80±0.49★	−0.40±0.71
Beta-2 (16–20 Hz)	−0.50±0.82	−0.20±0.57	−1.00±0.98★	−0.30±0.84
Beta-3 (20–25 Hz)	−0.20±0.35	0.10±0.65	−0.40±0.53	−0.10±0.49
Beta-4 (25–30 Hz)	0.01±1.96	−0.10±0.12	−0.01±0.10	−0.01±0.06
Relative power (%)				
Delta (1.3–3.5 Hz)	−1.20±3.35	−1.80±2.70	0.50±1.63	−1.20±1.31
Theta (3.5–7.5 Hz)	−1.30±3.65	−3.20±2.98★	−1.40±2.12	−3.30±2.59★
Alpha-1 (7.5–10.5 Hz)	1.70±6.66	3.10±5.06	−2.70±5.88	4.40±5.39
Alpha-2 (10.5–13 Hz)	0.20±3.92	1.90±2.86	2.00±3.57	0.10±1.96
Beta-1 (13–16 Hz)	−0.20±0.65	0.01±1.96	−0.20±0.78	−0.40±0.61
Beta-2 (16–20 Hz)	0.30±0.59	0.10±0.39	0.40±0.57	0.30±0.53
Beta-3 (20–25 Hz)	0.20±0.49	−0.10±0.65	1.00±0.88★	0.20±0.65
Beta-4 (25–30 Hz)	0.20±0.14★	−0.10±0.16	0.30±0.24★	−0.10±0.27

Statistically significant differences *vs* placebo (★$P<0.05$) obtained after Student's *t*-test are indicated.

Figure 5 Significance probability maps showing differences between *ayahuasca*-induced and placebo-induced changes in absolute power, relative power and frequency variables of the combined fast activity (13–30 Hz), beta-1 (13–16 Hz), beta-2 (16–20 Hz), beta-3 (20–25) and beta-4 (25–30) frequency bands after low (upper rows) and high (lower rows) doses of *ayahuasca* ($n=18$), at 90 min (left) and 120 min (right) after administration *vs* baseline values (PRE-2). For technical description of the maps and explanation of the colour key see Figure 2.

Table 2 Dose/treatment-effect relationships after single oral doses of randomized placebo (A), low dose 0.6 mg DMT kg^{-1} body weight *ayahuasca* (B), high dose 0.85 mg DMT kg^{-1} body weight *ayahuasca* (C), and non-randomized placebo administered on the first (adaptation) experimental session (D). Data from 18 volunteers, based on sign-adjusted changes in 28 V-EEG variables (rank-sums, means of 19 electrodes, differences from PRE-2 baseline values).

Time (min)	*Randomized placebo (A)*	*Low dose (B)*	*High dose (C)*	*Adaptation placebo (D)*	χ^2	*Multiple Wilcoxon*
15	71.8	69.3	69.9	69.0	0.1	
30	63.5	76.8	79.9	59.8	6.3	
45	51.4	76.7	92.6	59.4	22.3**	A : B*, A : C**, D : C**
60	53.1	85.6	85.9	55.4	21.5**	A : B**, A : C** D : B**, D : C**
90	55.7	77.8	94.8	51.7	26.3**	A : C** D : B*, D : C**
120	62.0	72.5	90.3	55.2	15.2**	A : C* D : C*
150	62.1	74.8	86.3	56.8	11.3**	A : C(*) D : C*
180	65.9	74.7	74.4	64.9	1.5	
210	75.1	60.8	73.4	70.7	2.7	
240	76.3	62.1	71.4	70.3	2.6	
360	80.6	62.0	75.1	62.4	5.9	
480	70.2	62.7	83.7	63.3	5.9	
Total	787.7	855.8	977.7	738.9	57.7**	A : B*, C** D : B**, C** B : C**

(*) $= P<0.1$; *$P<0.05$; **$P<0.01$.

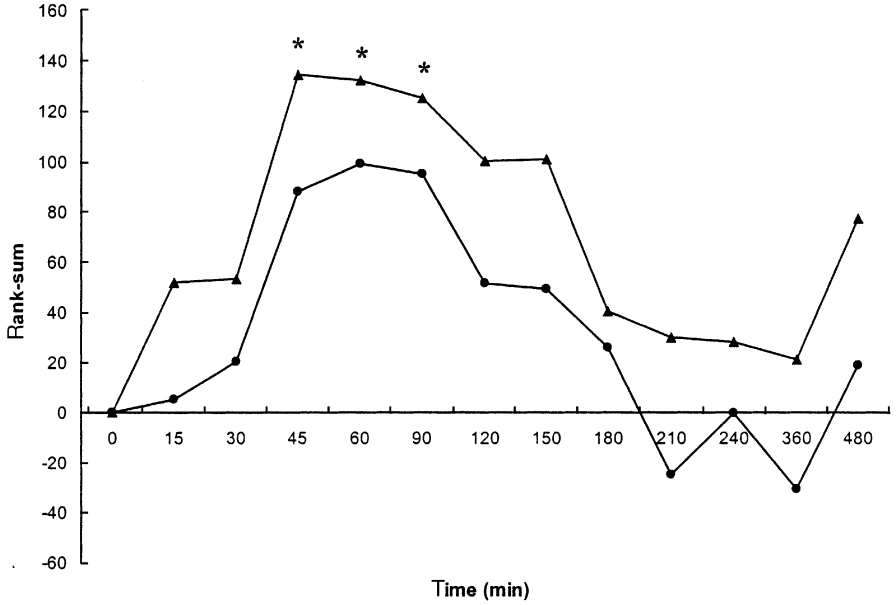


Figure 6 Time-effect relationships after single oral doses of 0.6 mg DMT kg^{-1} body weight *ayahuasca* (low dose) [●], and 0.85 mg DMT kg^{-1} body weight *ayahuasca* (high dose) [▲]. Plots show differences from baseline values (PRE-2) of sign-adjusted changes in 28 V-EEG variables (rank-sums, means of 19 electrodes, randomized placebo-corrected) from 18 volunteers. An asterisk indicates significant differences form baseline values obtained by means of multiple Wilcoxon.

pattern obtained for EEG effects closely paralleled that of previously reported subjective effects. The global reduction in total power and the shift toward higher frequencies after *ayahuasca* are in line with older reports on the classical serotonergic psychedelics, which described an amplitude reduction and a suppresion of slow activity in the human EEG. Finally, the detailed assessment of *ayahuasca* effects on the different EEG variables indicated common features

Table 3 Means (s.d.) of the scores obtained for the HRS questionnaire subscales ($n=18$) after single oral doses of randomized placebo, low dose 0.6 mg DMT kg^{-1} body weight *ayahuasca* and high dose 0.85 mg DMT kg^{-1} body weight *ayahuasca*, and results of the statistical analyses performed. Student's *t*-tests were followed by Bonferroni correction.

	ANOVA		*Student's* t-*test* vs *Placebo*		vs *Low dose*
Variable	P *value*	*Placebo*	*Low dose*	*High dose*	*High dose*
HRS					
Somaesthesia	***	0.07 (0.10)	0.50 (0.41)**	0.97 (0.40)**	**
Perception	***	0.09 (0.19)	0.55 (0.49)**	1.10 (0.67)**	**
Cognition	***	0.06 (0.16)	0.4 (0.45)**	0.96 (0.59)**	**
Volition	*	0.81 (0.79)	1.11(0.69)	1.35 (0.61)*	NS
Affect	***	0.32 (0.21)	0.65 (0.36)**	1.02 (0.38)**	**
Intensity	***	0.24 (0.45)	1.32 (0.73)**	1.85 (0.51)**	**

*$P<0.05$; **$P<0.01$; ***$P<0.001$; NS = not significant.

with the profile shown by pro-dopaminergic and pro-serotonergic drugs, and supports the involvement of serotonergic 5-HT_2 and dopaminergic D_2-receptor agonism in the central effects of *ayahuasca*.

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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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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 ±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 ±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

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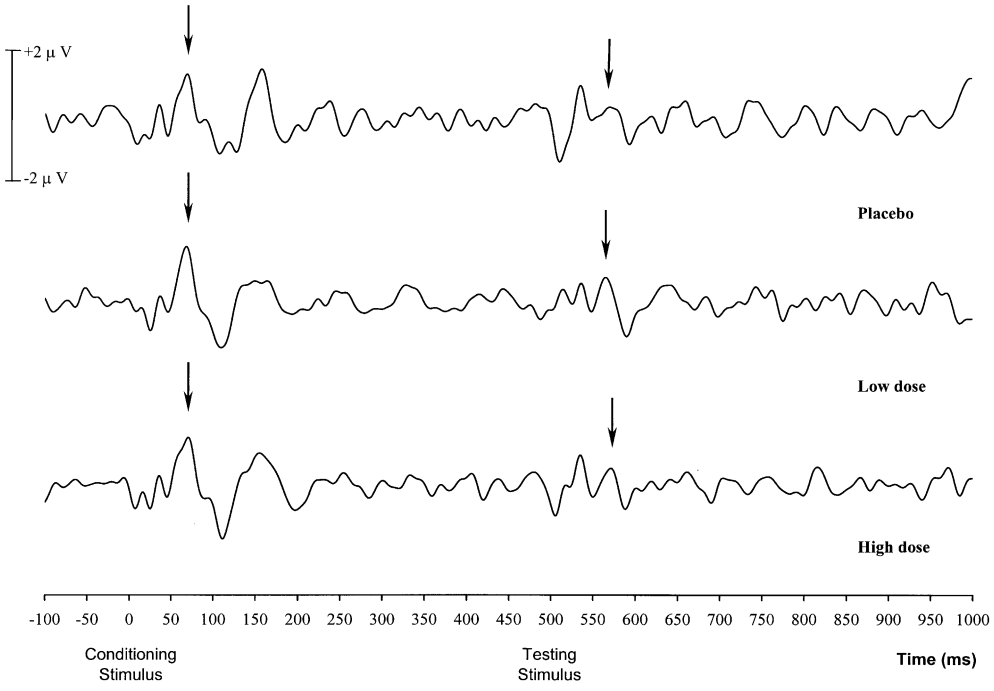

Fig. 1 Grand average band-pass filtered (10–50 Hz) auditory evoked potential (AEP) waveforms at the Cz site under the three drug conditions (n=15). The P50 component after the conditioning and testing stimuli are indicated with *arrowheads*

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

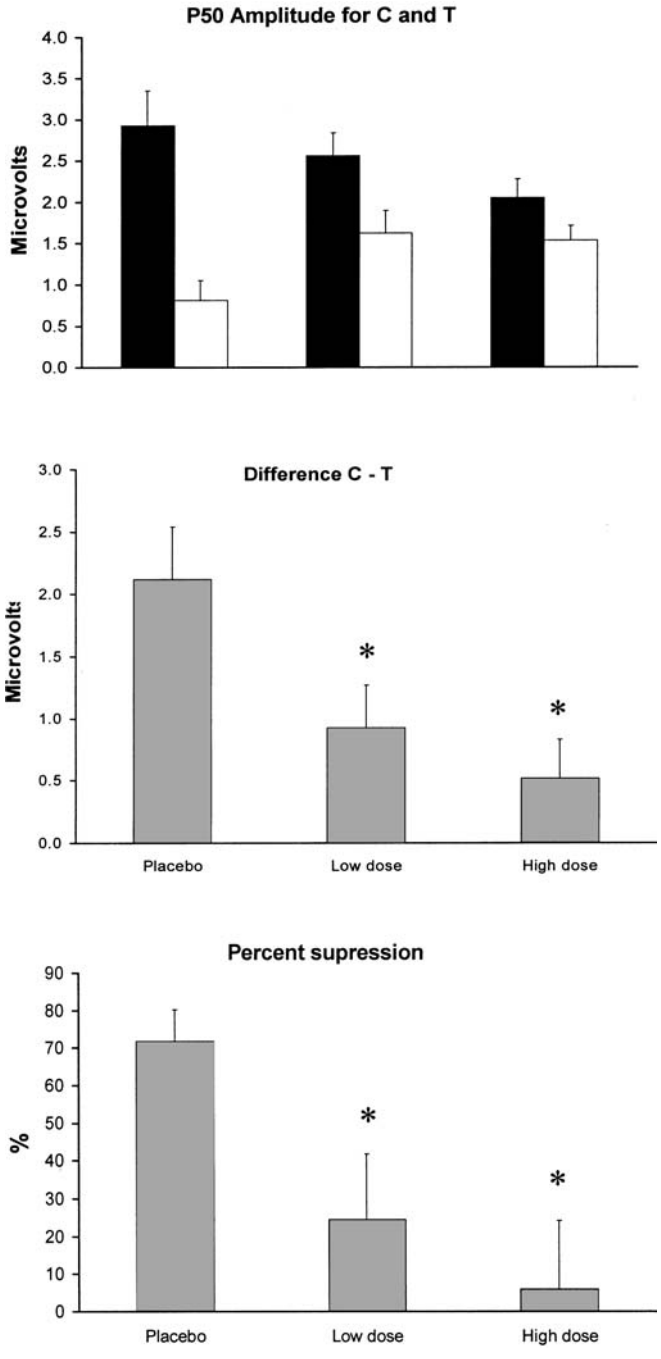

Fig. 2 *Upper panel* P50 amplitude to the conditioning (*closed square*) and testing (*open square*) stimuli under the three drug conditions. *Middle panel* Difference (conditioning–testing) of P50 amplitude values under the three drug conditions. *Lower panel* Percentage suppression values under the 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.

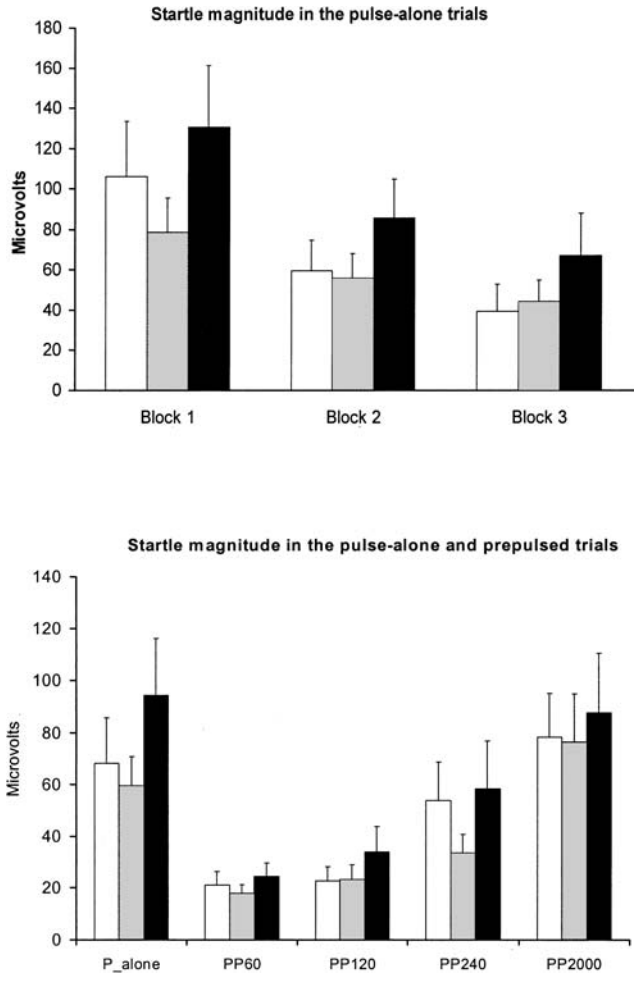

Fig. 3 *Upper panel* Mean startle magnitude values in the pulse-alone trials in each of the three blocks of trials comprising a recording session, after each of the three drug conditions. A main effect of block was found in the ANOVA ($F_{2,28}=12.91$, $P<0.01$), while no effects of drug or drug × block 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,

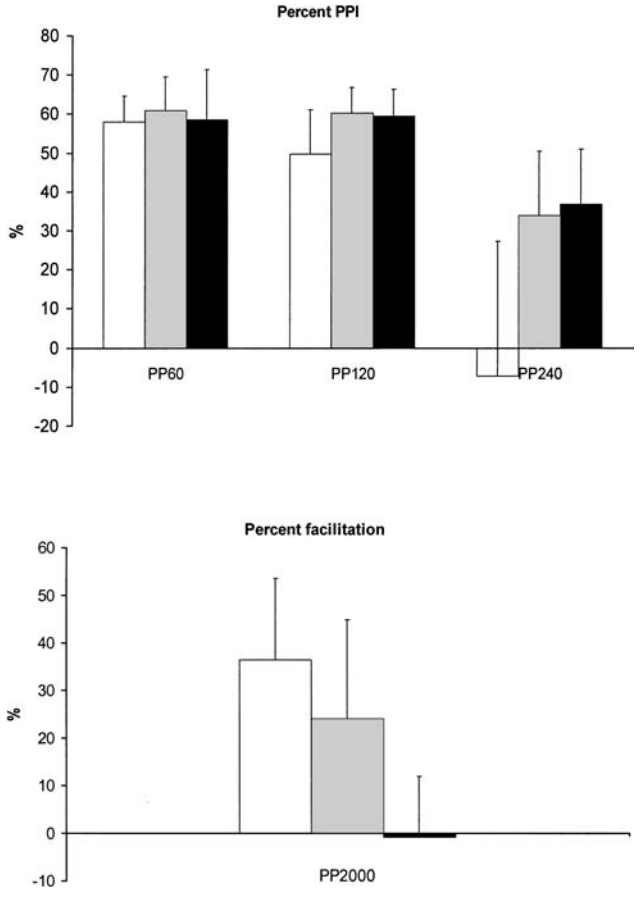

Fig. 4 *Upper panel* Mean values of percentage inhibition of the startle response at the 60, 120 and 240-ms prepulse-to-pulse intervals. *Lower panel* Mean values of percentage facilitation of the startle response at the 2000-ms prepulse-to-pulse interval. In both panels, (*open square*) placebo, (*shaded*) 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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