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Effects of the South American Psychoactive Beverage *Ayahuasca* on Regional Brain Electrical Activity in Humans: A Functional Neuroimaging Study Using Low-Resolution Electromagnetic Tomography

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Key Words

Ayahuasca · N,N-Dimethyltryptamine · Psychedelics · Electroencephalography · Low-resolution electromagnetic tomography · Humans

Abstract

Ayahuasca, a South American psychotropic plant tea obtained from *Banisteriopsis caapi* and *Psychotria viridis*, combines monoamine oxidase-inhibiting β-carboline alkaloids with N,N-dimethyltryptamine (DMT), a psychedelic agent showing 5-HT_{2A} agonist activity. In a clinical research setting, *ayahuasca* has demonstrated a combined stimulatory and psychedelic effect profile, as measured by subjective effect self-assessment instruments and dose-dependent changes in spontaneous brain electrical activity, which parallel the time course of subjective effects. In the present study, the spatial distribution of *ayahuasca*-induced changes in brain electrical activity was investigated by means of low-resolution electromagnetic tomography (LORETA). Electroencephalography recordings were obtained from 18 volunteers after the administration of a dose of encapsulated freeze-dried *ayahuasca* containing 0.85 mg DMT/kg body weight and placebo. The intracerebral power density distribution was computed with LORETA from spectrally analyzed data, and subjective effects were measured by means of the Hallucinogen Rating Scale (HRS). Statistically significant differences compared to placebo were observed for LORETA power 60 and 90 min after dosing, together with increases in all six scales of the HRS. *Ayahuasca* decreased power density in the alpha-2, delta, theta and beta-1 frequency bands. Power decreases in the delta, alpha-2 and beta-1 bands were found predominantly over the temporo-parieto-occipital junction, whereas theta power was reduced in the temporomedial cortex and in frontomedial regions. The present results suggest the involvement of unimodal and heteromodal association cortex and limbic structures in the psychological effects elicited by *ayahuasca*.

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Introduction

The psychoactive plant tea known as *ayahuasca*, a Quechua name meaning vine of the souls or vine of the dead, is a traditional shamanic inebriant used in the Upper Amazon since pre-Columbian times for religious and medicinal purposes [1]. In the second half of the last century, the use of *ayahuasca* reached the urban areas of Amazonian countries, where it is used by mestizo 'ayahuasqueros' for healing and divination. However, modern nonindigenous use of *ayahuasca* mainly takes place within the context of syncretic religious groups, particularly the Brazilian 'Santo Daime' and 'União do Vegetal', which have combined Old World religious beliefs with the sacramental use of the beverage [2]. In recent years, groups of followers of these Brazilian religions have become established in the United States and in several European countries [3].

Botanical research into the plant sources of *ayahuasca* has shown that the main ingredient of the tea is the woody vine *Banisteriopsis caapi* (Malpighiaceae). *Ayahuasca* is obtained by infusing the pounded stems of the vine either alone or more frequently in combination with the leaves of *Psychotria viridis* (Rubiaceae) or *Diplopterys cabrerana* (Malpighiaceae). *B. caapi* contains notable amounts of β-carboline alkaloids, mainly harmine and tetrahydroharmine, and to a lesser extent harmaline and traces of harmol and harmalol [4, 5]. *P. viridis* and *D. cabrerana* also contain indole alkaloids, mainly the potent short-acting psychedelic agent N,N-dimethyltryptamine (DMT) [4]. DMT is structurally related to the neurotransmitter serotonin, and like better-characterized psychedelics such as LSD and mescaline (a phenethylamine), binds to the 5-HT_{2A} receptor sites in the central nervous system (CNS), where it acts as an agonist [6].

The combination of DMT from *P. viridis* with the β-carboline alkaloids from *B. caapi* in a single oral preparation is most remarkable from the pharmacological point of view. It takes advantage of the pharmacodynamic properties of the β-carbolines, which allow access to the system of the otherwise orally inactive tryptamine component. Indeed, DMT is known for its lack of psychoactivity when orally ingested [7], probably due to metabolism by the enzyme monoamine oxidase [8]. On the other hand, the β-carbolines present in *ayahuasca*, particularly harmine and harmaline, are potent natural monoamine oxidase inhibitors [5], apparently preventing the extensive gut and liver first-pass effect on DMT, which is subsequently able to reach the systemic circulation and the CNS unaltered.

In a clinical research setting, *ayahuasca* has been found to induce transient modifications in perception, thought processes and mood that fit a combined stimulatory and psychedelic effect profile, as measured by subjective effect self-assessment instruments [9, 10]. Furthermore, the central effects of *ayahuasca* have also been evidenced by means of objective neurophysiological measures such as topographic pharmaco-electroencephalography (EEG). The effects of *ayahuasca* on the human EEG are characterized by an overall reduction in absolute power in the classical frequency bands (more pronounced in the slow delta and theta bands), and also by an acceleration of the center-of-gravity frequency. These actions on the spontaneous EEG follow a dose-response pattern and closely parallel the time course of subjective effects [11].

The aim of the present study was to assess the differential involvement of cortical brain regions in the acute central effects of *ayahuasca* by means of a recently developed neuroimaging technique: low-resolution electromagnetic tomography (LORETA). Based on the scalp electrical potential distribution obtained by means of classical EEG measures, LORETA provides three-dimensional information regarding the cortical neural generators of brain electrical activity [12]. Furthermore, LORETA computes a unique three-dimensional intracerebral power density distribution for the different EEG frequency bands, allowing their separate analysis. Unlike dipole modeling, LORETA makes no a priori assumptions about the number of sources involved. The only constraint implemented is that of maximal smoothness of the solution, based on the assumption that neighboring neuronal sources are likely to be similarly active (i.e. have similar orientations and strengths). The distribution obtained is thus the smoothest of all possible inverse solutions, as it is considered the most plausible. In a new implementation of LORETA, an additional neuroanatomical constraint restricts the solution space to cortical gray matter volume [13]. The technique has previously been used in the evaluation of acute effects of psychoactive drugs [14, 15].

To our knowledge, regional brain electrical activity has not been evaluated previously by means of LORETA following the administration of *ayahuasca* or other psychedelics with 5-HT_{2A} agonist activity. It is consequently difficult to establish an a priori hypothesis regarding the brain areas involved in the effects of *ayahuasca* on the EEG. However, PET and SPECT investigations of blood flow and glucose metabolism after acute psilocybin (an indoleamine structurally similar to DMT) and mescaline administration have evidenced increased activation in the prefrontal cortex [16–18]. Consequently, we postulated that changes in electrical activity would be identified at least in these regions.

Subjects and Methods

Volunteers

Eighteen healthy volunteers (15 males and 3 females) participated in the study. Eligibility criteria included prior experience with psychedelic drugs on at least five occasions without sequelae derived therefrom, no current or previous history of a neurological or psychiatric disorder, and no family history of an Axis-I psychiatric disorder in first-degree relatives. Volunteers were given a structured psychiatric interview (DSM-III-R) and completed the trait anxiety scale from the State-Trait Anxiety Inventory. Exclusion criteria included alcohol or other substance dependence, and high scores on the trait anxiety scale (over 1 standard deviation above the normative mean). Each participant underwent a complete physical examination that included a medical history, laboratory tests, ECG and urinalysis. Their mean age was 25.7 years (range 19–38 years), mean weight was 66.47 kg (range 50.7–79.5 kg) and mean height was 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 drug 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'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. Written informed consent was obtained from all participants.

Drug

The *ayahuasca* employed in the present study was not administered in its original liquid form, but as a lyophilizate. The freeze-dried homogenized material had been obtained from a 9.6-liter batch of *ayahuasca*. The DMT content in the lyophilizate had been determined by HPLC, as described by Callaway et al. [19], and the β-carboline constituents were determined following a modification of the method described in that study. The 9.6-liter batch yielded 611 g of freeze-dried powder, containing 8.33 mg of DMT, 14.13 mg of harmine, 0.96 mg of harmaline and 11.36 mg of tetrahydroharmine per gram. Based on tolerability and subjective effects assessed previously [9], an *ayahuasca* dose containing 0.85 mg DMT/kg body weight was administered to the volunteers. The calculated individual dose for each volunteer was administered by combining 00 gelatin capsules containing 0.5, 0.25 or 0.125 g of freeze-dried *ayahuasca*. Placebo capsules were 00 gelatin capsules containing 0.75 g of lactose. These were administered on the placebo day, and were also combined with active *ayahuasca* capsules when necessary, so that all volunteers took the same number of capsules on each experimental day.

Study Design and Experimental Procedure

EEG recordings were obtained in a double-blind placebo-controlled randomized crossover clinical trial. Two weeks prior to the beginning of the experimental procedure, volunteers were requested to abstain from any medication or illicit drug use until the completion of the study. Volunteers also abstained from alcohol, tobacco and caffeinated drinks 24 h prior to each experimental day. Urine was screened for illicit drug use on each experimental day. Experimental days were at least 1 week apart.

On each experimental day, volunteers remained in the clinical research unit for a period of approximately 10 h. Following arrival in the morning under fasting conditions, EEG electrodes were placed on the scalp, and drug/placebo capsules were administered at approximately 10.00 a.m. with 250 ml of tap water. EEG recordings were obtained at baseline and at regular intervals after treatment administration. For the first 4 h, volunteers remained seated in a reclining chair in a quiet and dimly lit room. The experimenter remained outside the room during the EEG recordings. The last recording was performed at 8 h, and volunteers were discharged approximately 9 h after drug administration.

EEG Acquisition and Processing and LORETA Analysis

Nineteen-lead EEG recordings were obtained by means of scalp electrodes placed according to the international 10/20 system: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2, referenced to averaged mastoids. Additionally, vertical and horizontal electrooculograms were recorded. The signal was acquired through a Neuroscan SYNAMPS amplifier. Three-minute vigilance-controlled EEG with eyes closed was recorded at baseline, prior to drug administration and at different time points after dosing. During the vigilance-controlled 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 band-pass filtered at 0.3–30 Hz, and digitized on-line with a sampling frequency of 100 Hz. EEG recordings were obtained prior to drug administration (–15 min and baseline), and 30, 60, 90, 120, 180, 360 and 480 min after dosing.

A two-step artifact processing procedure was used [20]. It included ocular artifact minimization based on regression analysis in the time domain, as described by Semlitsch et al. [21], and automatic artifact rejection based on a time and frequency domain approach as described by Anderer et al. [22]. Validity of the artifact processing procedure was visually assessed. After recomputation to average reference, spectral analysis was performed for artifact-free 5-second epochs. For each recording, the spectral power of six 5-second epochs of artifact-free, vigilance-controlled EEG was averaged. Data were digitally filtered into seven frequency bands according to Kubicki et al. [23]: delta (1.5–6 Hz), theta (6–8 Hz), alpha-1 (8–10 Hz), alpha-2 (10–12 Hz), beta-1 (12–18 Hz), beta-2 (18–21 Hz) and beta-3 (21–30 Hz).

Subsequently, LORETA was used to estimate the three-dimensional intracerebral current density distribution from the voltage values recorded at the scalp electrodes. The LORETA version employed implements a three-shell spherical head model [24] registered to the human brain atlas of Talairach and Tournoux [25] available as a digitized MRI from the Brain Imaging Centre, Montréal Neurological Institute. The EEG electrode coordinates reported by Towle et al. [26] were used for registration between spherical and realistic head geometry. The LORETA solution space was restricted to the cortical gray matter and hippocampus, based on the Digitized Probability Atlas corresponding to the Talairach atlas and also available from the Brain Imaging Centre, Montréal Neurological Institute. A voxel was included in the solution space if its probability of being gray matter was higher than 33%, and higher than its probability of being either white matter or cerebrospinal fluid. The final solution space consisted of 2,394 voxels with a spatial resolution of 0.343 cm^3 [13]. The EEG lead field was computed numerically with the boundary element method [27]. LORETA images represent the power (i.e. squared magnitude of computed intracerebral current density) in each of the 2,394 voxels. 'LORETA power', synonymous to 'EEG power', refers to the spectral power of current density as estimated by

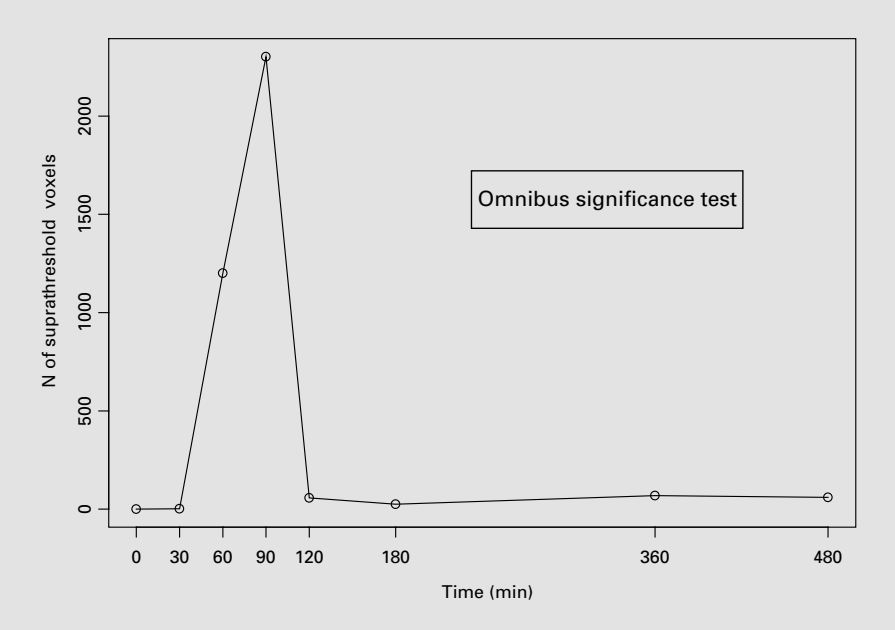


Fig. 1. Omnibus significance test. The total number of suprathreshold voxels at different time points after *ayahuasca* (0.85 mg DMT/kg body weight) administration are shown.

LORETA. Thus, in a first step, current density values were estimated based on the EEG cross-spectral matrix and then squared for each voxel and frequency band [15].

Subjective Effects

Volunteers were requested to answer the Hallucinogen Rating Scale (HRS), a self-report questionnaire measuring psychedelic-induced subjective effects [28]. 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 finally 'intensity', which reflects the strength of the overall experience. In the present study, a Spanish version of the questionnaire was used [29]. The HRS was administered 240 min after administration of *ayahuasca* and placebo.

Statistical Analysis

LORETA Data. In a first step, in order to explore the time course of *ayahuasca* effects, paired-sample t tests were computed for log-transformed LORETA power at each voxel and frequency band for the different time points. To correct for multiple comparisons, a nonparametric single-threshold test was applied on the basis of the theory for randomization and permutation tests developed by Holmes et al. [30]. The omnibus null hypothesis of no activation anywhere in the brain was rejected if at least one t value (i.e. voxel, t_{MAX}) was above the critical threshold (t_{CRIT}) for $p = 0.05$ determined by 5,000 randomizations. The total number of suprathreshold voxels was plotted versus time in order to select the time points with the largest effects. Subsequently, LORETA images were computed for log-transformed normalized data for each separate frequency band at the selected time points and following the same statistical approach. On the basis of the Structure-Probability Maps Atlas [31], the number of significant voxels in each lobe (frontal, parietal, occipital, temporal, limbic and sublobar), gyrus and Brodmann area (BA) of the left and the right hemisphere was computed separately for each suprathreshold region.

Subjective Effects. Scores on the HRS questionnaire after *ayahuasca* administration were compared with those after placebo by means of paired-sample Student's t tests.

Results

LORETA Data

Figure 1 shows the results for the omnibus significance test performed for all voxels and frequency bands at the different time points in order to explore the time course of effects.

A steep rise in the number of suprathreshold voxels was observed 60 min following drug administration, and the pharmacodynamic peak occurred 90 min after dosing. LORETA images were thus computed for the *ayahuasca*-versus placebo-induced changes at these two time points.

The voxel-by-voxel statistical comparison of *ayahuasca*-induced versus placebo-induced effects 60 min after drug administration (0.85 mg DMT/kg body weight dose), followed by Holmes correction, showed statistically significant decreases mainly in the alpha-2 frequency band (459 suprathreshold voxels). As listed in table 1, power density decreases were found in the parietal (135), occipital (79), temporal (170) and limbic (69) lobes in both hemispheres, and at the left frontal (3) and sublobar level

Table 1. *Ayahuasca*- versus placebo-induced decreases in alpha-2 power (10–12 Hz) 60 min after administration

Gyrus	Suprathreshold voxels					
	left hemisphere			right hemisphere		
	N_{sig}	N_{total}	%	N_{sig}	N_{total}	%
Frontal lobe						
Subcallosal gyrus	2	7	29	0	7	0
Precentral gyrus	1	38	3	0	37	0
Parietal lobe						
Postcentral gyrus	6	39	15	6	44	14
Supramarginal gyrus	2	10	20	11	11	100
Superior parietal lobule	16	24	67	4	17	24
Precuneus	48	73	66	18	65	28
Inferior parietal lobule	1	56	2	13	50	26
Angular gyrus	3	4	75	7	7	100
Occipital lobe						
Cuneus	9	35	26	2	30	7
Lingual gyrus	4	38	11	13	31	42
Superior occipital gyrus	3	4	75	5	5	100
Middle occipital gyrus	16	26	62	20	24	83
Inferior occipital gyrus	5	10	50	2	9	22
Temporal lobe						
Superior temporal gyrus	10	85	12	20	95	21
Middle temporal gyrus	30	89	34	30	88	34
Inferior temporal gyrus	10	51	20	4	52	8
Fusiform gyrus	43	58	74	18	53	34
Subgyral	4	12	33	1	9	11
Limbic lobe						
Cingulate	8	8	100	1	8	13
Posterior cingulum	1	15	7	1	20	5
Parahippocampal gyrus	32	33	97	12	31	39
Uncus	14	24	58	0	24	0
Sublobar						
Insula	3	38	8	0	32	0

The number of significant voxels (N_{sig}), the total number of voxels (N_{total}) and the percentage of significant voxels (%) for each gyrus and hemisphere are given (n = 18).

Table 2. *Ayahuasca*- versus placebo-induced decreases in delta power (1.5–6 Hz) 90 min after administration

Gyrus	Suprathreshold voxels					
	left hemisphere			right hemisphere		
	N_{sig}	N_{total}	%	N_{sig}	N_{total}	%
Parietal lobe						
Postcentral gyrus	1	39	3	9	44	20
Supramarginal gyrus	5	10	50	8	11	73
Superior parietal lobule	9	24	38	13	17	76
Precuneus	37	73	51	17	65	26
Inferior parietal lobule	4	56	7	21	50	42
Angular gyrus	4	4	100	7	7	100
Occipital lobe						
Cuneus	10	35	29	1	30	3
Superior occipital gyrus	4	4	100	5	5	100
Middle occipital gyrus	20	26	77	19	24	79
Inferior occipital gyrus	8	10	80	3	9	33
Temporal lobe						
Superior temporal gyrus	19	85	22	15	95	16
Middle temporal gyrus	62	89	70	42	88	48
Inferior temporal gyrus	20	51	39	24	52	46
Fusiform gyrus	41	58	71	40	53	75
Limbic lobe						
Parahippocampal gyrus	0	33	0	3	31	10

The number of significant voxels (N_{sig}), the total number of voxels (N_{total}) and the percentage of significant voxels (%) for each gyrus and hemisphere are given (n = 18).

(3). Suprathreshold voxels were thus found over extensive cortical areas around the temporo-parieto-occipital junction predominantly in the angular gyrus, supramarginal gyrus, precuneus, superior and middle temporal gyri and fusiform gyrus. In the limbic lobe, suprathreshold voxels covered mainly the cingulate and the parahippocampal gyrus. The BAs showing the highest percentage of suprathreshold voxels were BA 7 in the parietal lobe, BA 19 in the occipital lobe, BA 39 and BA 37 in the temporal lobe, and BA 36 and BA 35 in the limbic lobe.

Figure 2 shows LORETA axial brain slices as statistical nonparametric maps corresponding to the suprathreshold regions found for the alpha-2 frequency band, 60 min after drug administration.

In addition to the above results, power decreases were observed for the delta frequency band in a small area covering 15 suprathreshold voxels in the border between the left occipital and temporal lobes in BA 19, BA 37 and BA 21. Finally, decreases in the theta band fell short of statistical significance, with the lowest t value equal to –3.58 (p = 0.0522; cutoff t value = 3.61). This local minimum was located in BA 24 in the medial frontal cortex.

As shown in figure 1, the largest number of suprathreshold voxels, i.e. the pharmacodynamic peak, was observed 90 min after administration of *ayahuasca*. At this time point, statistically significant decreases were found for the delta, theta and beta-1 frequency bands. Alpha-2 power density was also reduced relative to placebo, but contrary to what was observed 60 min after

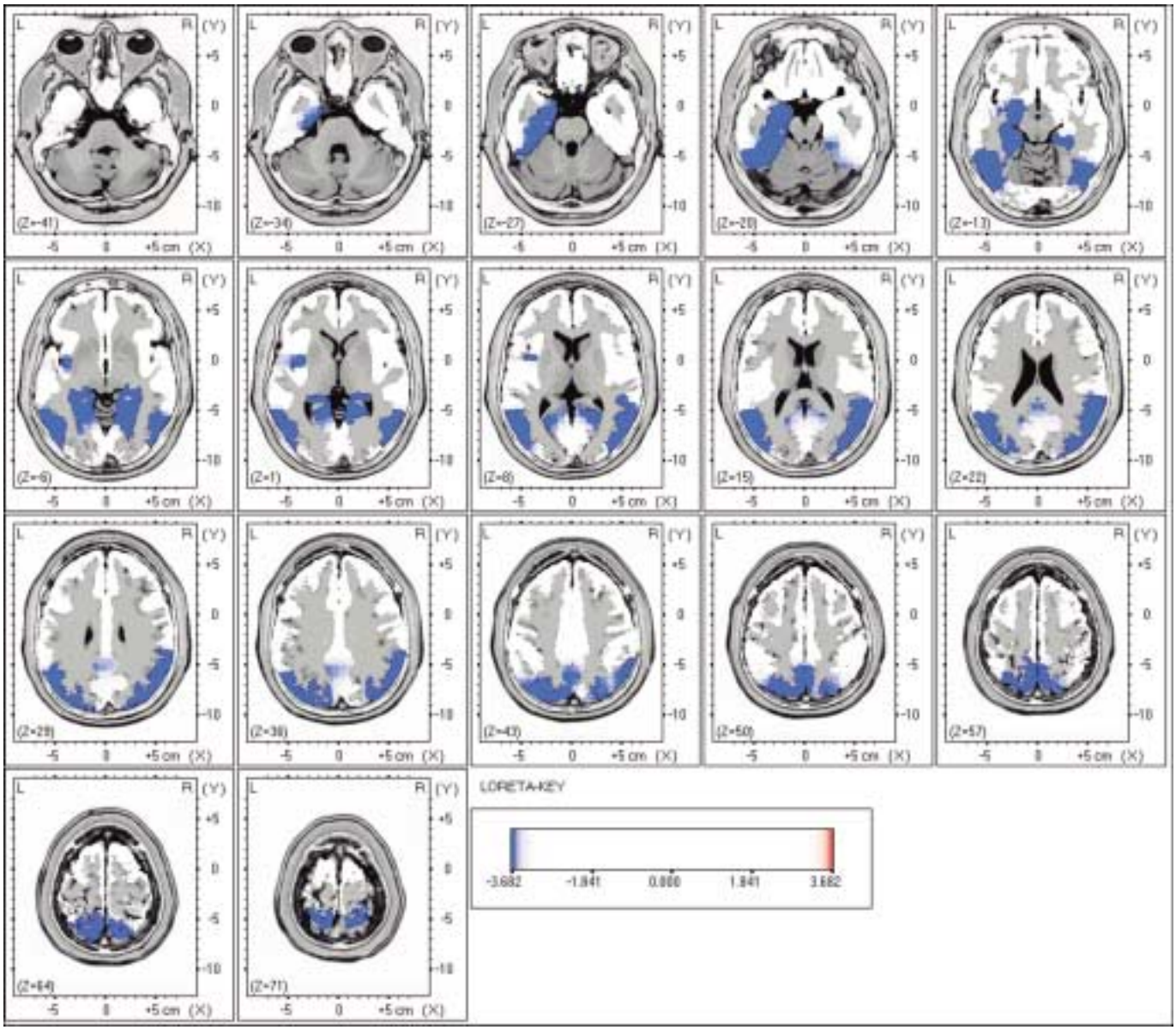


Fig. 2. Effects of *ayahuasca* (0.85 mg DMT/kg body weight) on regional cortical electrical activity 60 min after administration (n = 18). Shown are statistical nonparametric maps based on t values of differences between *ayahuasca*-induced and placebo-induced changes in the alpha-2 (10–12 Hz) frequency band. Blue indicates significant decreases after Holmes correction ($p < 0.05$) as compared to placebo. Axial slices (head seen from above, nose up; L = left; R = right) in steps of 7 mm from most inferior (Z = –41) to the most superior (Z = 71) are shown.

administration, these decreaseswere not statistically significant.

Table 2 lists the anatomical distribution of the power decreases observed for the delta frequency band. Thus, 471 suprathreshold voxels were located in the parietal (135), occipital (70), temporal (263) and limbic (3) lobes in both hemispheres. Suprathreshold voxels were found over extensive cortical areas around the temporo-parieto-occipital junction predominantly in the angular gyrus, superior occipital gyrus, middle temporal gyrus and fusiform gyrus. The BAs showing the highest percentage of suprathreshold voxels were BA 37, BA 19 and BA 39.

Figure 3 shows LORETA axial brain slices as statistical nonparametric maps corresponding to the suprathreshold

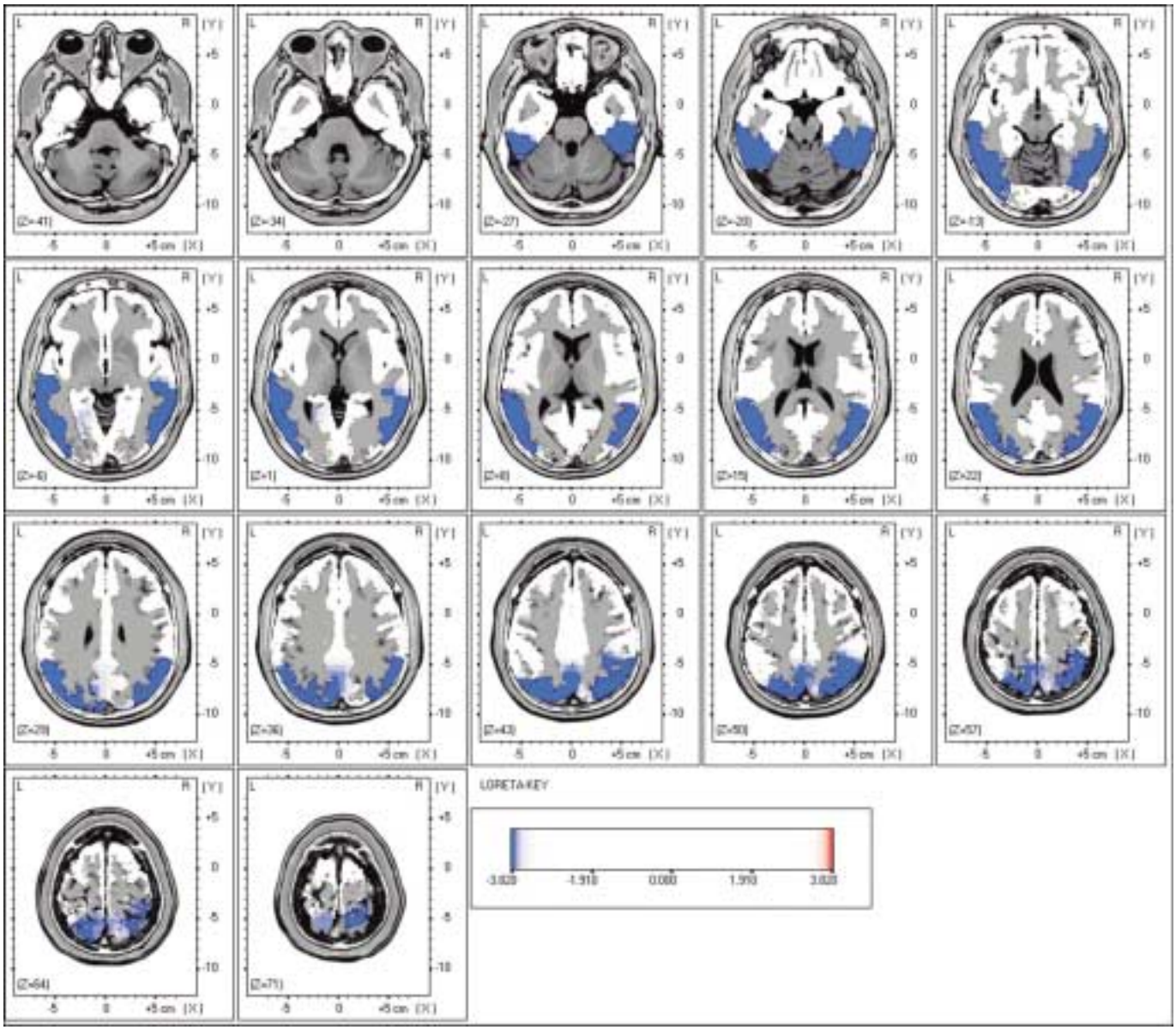


Fig. 3. Effects of *ayahuasca* (0.85 mg DMT/kg body weight) on regional cortical electrical activity 90 min after administration (n = 18). Shown are statistical nonparametric maps based on t values of differences between *ayahuasca*-induced and placebo-induced changes in the delta (1.5–6 Hz) frequency band. Blue indicates significant decreases after Holmes correction ($p < 0.05$) as compared to placebo. Axial slices (head seen from above, nose up; L = left; R = right) in steps of 7 mm from most inferior (Z = –41) to the most superior (Z = 71) are shown.

regions found for the delta frequency band. Note the marked overlap between these brain areas and those found at 60 min for the alpha-2 frequency band.

Areas of power density decrease in the theta frequency band are indicated in table 3. One hundred and twenty-eight voxels showed t values below the statistical threshold. These suprathreshold voxels were found in the frontal lobe (13), in the temporal lobe (58) and in the limbic lobe (57). Suprathreshold voxels were found distributed in three nonconfluent areas, i.e. in the medial and superior frontal gyri (BA 6, 8), in the anterior cingulate (BA 24, 32) and in the left temporomedial cortex comprising mainly the fusiform and parahippocampal gyri and the uncus (BA 36, 35, 28).

Table 3. *Ayahuasca*- versus placebo-induced decreases in theta power (6–8 Hz) 90 min after administration

Gyrus	Suprathreshold voxels					
	left hemisphere			right hemisphere		
	N_{sig}	N_{total}	%	N_{sig}	N_{total}	%
Frontal lobe						
Medial frontal gyrus	2	61	3	2	59	3
Superior frontal gyrus	4	100	4	5	98	5
Temporal lobe						
Middle temporal gyrus	1	89	1	0	88	0
Inferior temporal gyrus	13	51	25	0	52	0
Fusiform gyrus	43	58	74	0	53	0
Subgyral	1	12	8	0	9	0
Limbic lobe						
Anterior cingulum	2	25	8	2	25	8
Cingulate gyrus	8	42	19	7	41	17
Cingulate	6	8	75	0	8	0
Parahippocampal gyrus	18	33	55	0	31	0
Uncus	14	24	58	0	24	0

The number of significant voxels (N_{sig}), the total number of voxels (N_{total}) and the percentage of significant voxels (%) for each gyrus and hemisphere are given (n = 18).

Figure 4 shows LORETA orthogonal slices (axial, sagittal and coronal views) as statistical nonparametric maps corresponding to the three nonconfluent suprathreshold regions found for the theta frequency band, through the voxel of the extreme t value.

Areas of beta-1 power density decrease are shown in table 4. These comprised 139 suprathreshold voxels, located in the parietal lobe (122), occipital lobe (3), temporal lobe (5) and limbic lobe (9). Suprathreshold voxels were found on two nonconfluent areas. The first area comprised voxels in the parietal lobe, extending medially and bilaterally from the posterior cingulate gyrus (BA 30, 31) to the precuneus and superior parietal lobule (BA 7, 19). The second area comprised voxels in the right supramarginal and angular gyri (BA 39).

Figure 5 shows LORETA orthogonal slices (axial, sagittal and coronal views) as statistical nonparametric maps corresponding to the two nonconfluent suprathreshold regions found for the beta-1 frequency band, through the voxel of the extreme t value.

Subjective Effects

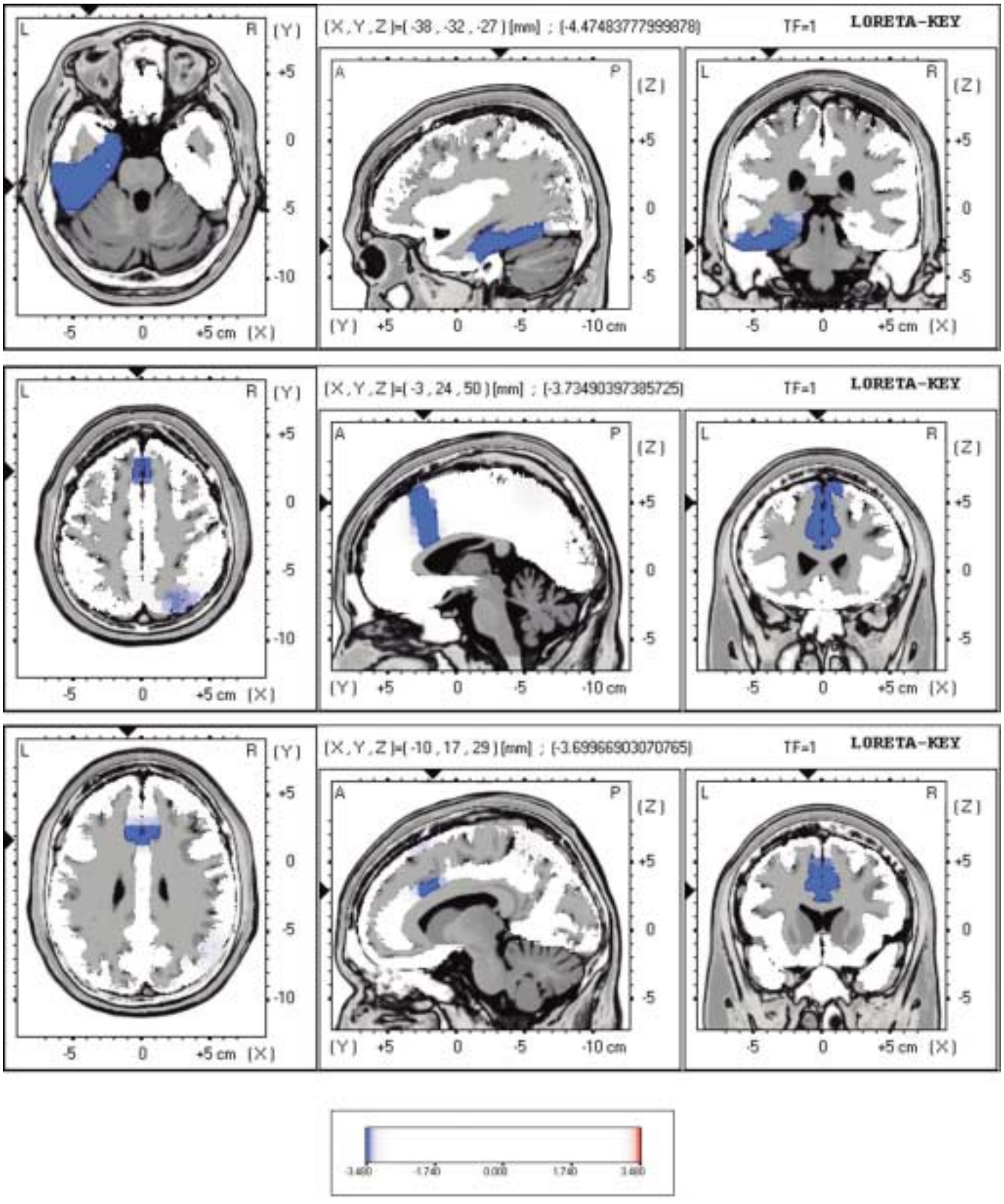
Ayahuasca induced a series of perceptual, mood and cognitive modifications with a characteristic psychedelic pattern, as measured by the HRS questionnaire. Table 5 shows the mean values obtained after placebo and *ayahuasca* for the HRS scores, and the results of the statistical analyses performed.

Drug-induced subjective effects were first noted as early as 15 min, became more marked between 30 and 45 min, showed a steep rise at 60 min, reached a maximum between 90 and 120 min, and decreased thereafter, disappearing entirely at 360 min. All volunteers experienced somatic modifications, which included altered bodily sensations, pins and needles, increased skin sensitivity and physical comfort. Visual and auditory phenomena were also frequently reported but varied greatly in quality and intensity between volunteers, ranging from distortions of objects and sounds to elaborate visions with eyes closed and perception of nonexistent noises. Five subjects reported experiencing auditory and visual synesthesia. In the cognitive sphere, the sense of time was altered, thought speed increased and the ability to focus attention was subjectively perceived to be reduced. Mood modifications were also present, the experience being globally regarded as satisfactory, with most volunteers reporting having experienced happiness, excitation and a 'high'. It is important to note that, at the doses administered, *ayahuasca* did not induce full-blown psychotic symptoms and none of the participants lost awareness of the drug-induced nature of the psychological effects experienced.

Discussion

The analysis of brain electrical activity by means of LORETA identified significant drug-induced changes in the intracerebral power density distribution 60 and 90 min following *ayahuasca* administration. At the peak of

Fig. 4. Effects of *ayahuasca* (0.85 mg DMT/kg body weight) on regional cortical electrical activity 90 min after administration (n = 18). Shown are statistical nonparametric maps based on t values of differences between *ayahuasca*-induced and placebo-induced changes in the theta (6–8 Hz) frequency band. Blue indicates significant decreases after Holmes correction ($p < 0.05$) as compared to placebo. Orthogonal (axial, sagittal, coronal) slices for each of the three nonconfluent suprathreshold regions, i.e. temporomedial (upper row), frontomedial (middle row) and cingulate (lower row), through the voxel of the extreme t value are shown. The Talairach coordinates (X, Y, Z) of the displayed extreme t value are indicated by black triangles on the coordinate axes. L = Left; R = right; A = anterior; P = posterior.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(X,Y,Z)=(-10,17,29) [mm] ; (-3.69966903070765)
TF=1
LORETA-KEY
-3.480
-1.740
0.000
1.740
3.480

4

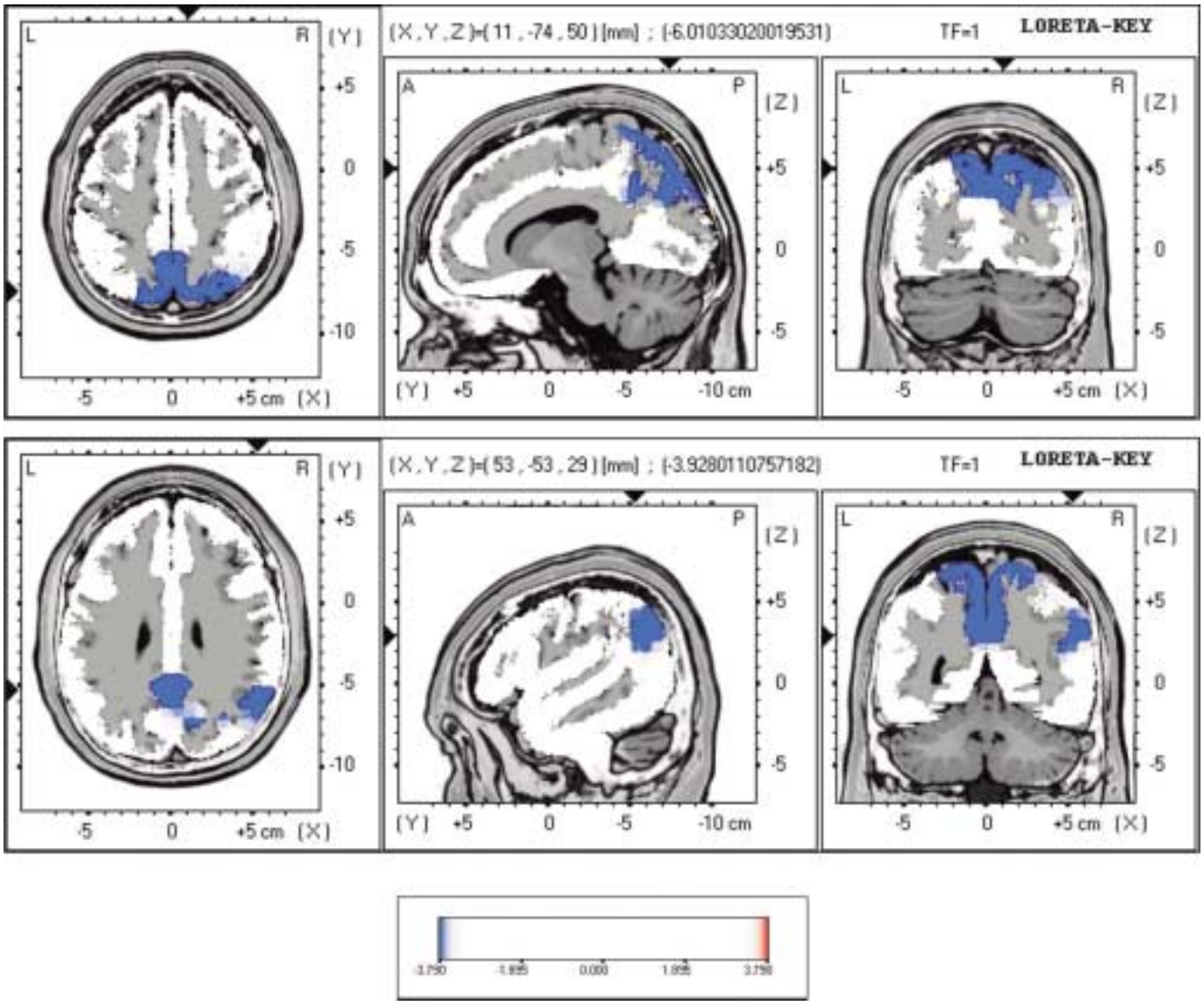

Fig. 5. Effects of *ayahuasca* (0.85 mg DMT/kg body weight) on regional cortical electrical activity 90 min after administration (n = 18). Shown are statistical nonparametric maps based on t values of differences between *ayahuasca*-induced and placebo-induced changes in the beta-1 (12–18 Hz) frequency band. Blue indicates significant decreases after Holmes correction ($p < 0.05$) as compared to placebo. Orthogonal (axial, sagittal, coronal) slices for each of the two nonconfluent suprathreshold regions, i.e. parietomedial (upper row) and parietolateral (lower row), through the voxel of the extreme t value are shown. The Talairach coordinates (X, Y, Z) of the displayed extreme t value are indicated by black triangles on the coordinate axes. L = Left; R = right; A = anterior; P = posterior.

the pharmacodynamic effects, the slow delta rhythm was decreased in posterior brain regions. Additionally, decreases in theta were observed in the medial frontal and medial temporal cortices. Similar effects, although less intense (delta) or bordering on statistical significance (theta), were also observed in analogous brain regions 60 min after dosing. At this time point, however, a widespread power reduction in the alpha-2 band was observed in posterior areas, showing considerable overlap with those demonstrating significant decreases in delta power 90 min after administration. These modifications of the EEG power spectrum were accompanied by a constellation of perceptual, cognitive and mood modifications typical of the psychedelics, as evidenced by significant increases in all subscales of the HRS. The pattern of subjectively reported effects corresponded qualitatively and

Table 4. *Ayahuasca*- versus placebo-induced decreases in beta-1 power (12–18 Hz) 90 min after administration

Gyrus	Suprathreshold voxels					
	left hemisphere			right hemisphere		
	N_{sig}	N_{total}	%	N_{sig}	N_{total}	%
Parietal lobe						
Postcentral gyrus	6	39	15	6	44	14
Supramarginal gyrus	0	10	0	3	11	27
Superior parietal lobule	9	24	38	9	17	53
Precuneus	38	73	52	45	65	69
Inferior parietal lobule	0	56	0	2	50	4
Angular gyrus	0	4	0	4	7	57
Occipital lobe						
Cuneus	0	35	0	3	30	10
Temporal lobe						
Superior temporal gyrus	0	85	0	3	95	3
Middle temporal gyrus	0	89	0	2	88	2
Limbic lobe						
Cingulate gyrus	4	42	10	3	41	7
Posterior cingulum	1	15	7	1	20	5

The number of significant voxels (N_{sig}), the total number of voxels (N_{total}) and the percentage of significant voxels (%) for each gyrus and hemisphere are given (n = 18).

Table 5. Means ± SD of the scores obtained for the HRS questionnaire subscales, and results of the statistical comparisons performed by means of paired-sample Student's t tests (n = 18)

	HRS scores	
	placebo	*ayahuasca*
Somaesthesia	0.07 ± 0.10	0.97 ± 0.40**
Perception	0.09 ± 0.19	1.10 ± 0.67**
Cognition	0.06 ± 0.16	0.96 ± 0.59**
Volition	0.81 ± 0.79	1.35 ± 0.61**
Affect	0.32 ± 0.21	1.02 ± 0.38**
Intensity	0.24 ± 0.45	1.85 ± 0.51**

** $p < 0.01$.

with respect to the time course with previous results obtained in a smaller sample of volunteers [9]. It is of particular interest that these effects involving perceptive and cognitive modifications were regarded by the majority of volunteers as positive and desirable, in contrast with the more psychosis-like profile, including paranoid thoughts and fear of control loss, reported in studies in which other psychedelics, such as psilocybin, have been administered to drug-naive subjects [17]. The fact that the volunteers who enrolled in the present study had prior experience with psychedelics may account for these differences.

The effects of *ayahuasca* on the EEG power spectrum are compatible with its proposed neurochemical mechanism of action. Decreases in slow activity, i.e. delta and theta power, are a general feature of psychostimulants, such as amphetamine and methylphenidate, serotonin releasers such as fenfluramine, and psychedelics displaying 5-HT_2 agonist activity [32–34]. Early pharmaco-EEG research on LSD, a 5-HT_{2A} agonist like DMT – the main psychotropic principle found in *ayahuasca* – had also shown decreases in slow activity after acute drug administration [32]. Delta activity has traditionally been thought to reflect inhibitory activity, and increases in theta have been observed in relaxed and meditative states. Thus, the present results would rather suggest an excitatory or arousing effect for *ayahuasca*. This assumption is further supported by the fact that major tranquilizers with D_2 or mixed D_2/5-HT_2 antagonist activity, such as chlorpromazine and risperidone, are characterized by their delta- and theta-promoting effects [34, 35]. An important difference between *ayahuasca* and psychostimulants is the alpha-2-decreasing properties of the former found in the present study. In addition to slow wave-dampening effects, amphetamine is known to enhance alpha power, a feature not shared by *ayahuasca*. As mentioned above, Itil and Fink [32] found that LSD had inhibitory effects on slow waves, but also reduced alpha. Interestingly, other drugs, such as scopolamine or ketamine, with various mechanisms of action and different overall EEG profiles but able to elicit hallucinatory states, also display an alpha-suppressing effect. Thus, *ayahuasca* would combine alpha-dampening effects, a feature shown by other perception-altering drugs, with slow wave reduction properties, in an overall profile which would bring it closer to drugs such as LSD rather than to pure psychostimulants.

Given the exploratory nature of the present study, it is the authors' view that some hypotheses should be postulated regarding the brain networks and processes targeted by *ayahuasca,* based on the spatial information provided by the LORETA analysis. The changes in intracerebral electrical source distribution showed considerable overlapping between frequency bands, mainly between alpha-2 and delta, although these effects were observed at different time points. Delta and alpha-2 power decreases were located bilaterally over somatosensory, auditory and visual association cortices and over the temporo-parietal heteromodal association cortex [36]. Power decreases in

the beta-1 frequency band were predominantly found in the somatosensory and visual association cortex, and also in the heteromodal association cortex. Areas showing a theta power decrease, however, did not predominate in the association cortex, but in paralimbic structures with relevant roles in emotion and memory processes [36]. Thus, it can be hypothesized that drug-induced bioelectrical changes in the unimodal sensory association cortex may have played a role in the modality-specific modifications in the visual, somatic and auditory perception reported. Additionally, it appears reasonable to assume that effects on transmodal brain areas could account for more complex cognitive modifications which also characterize the subjective experience elicited by *ayahuasca* [9, 10]. In this respect, the temporo-parietal and frontomedial heteromodal association cortex, the cingulate and the temporomedial cortices play relevant roles in the neurobiology of attention, emotion and memory [37–39].

The results obtained in the present study show interesting similarities to, but also differences from, previous SPECT and PET studies involving psychedelics. A recent PET investigation revealed that the most important metabolic increases after psilocybin administration to humans occur predominantly in the temporomedial, frontomedial, frontolateral and anterior cingulate cortices [17]. These areas largely coincide with those showing theta decreases after *ayahuasca* administration. Nevertheless, PET and SPECT studies following psilocybin and mescaline have revealed a hyperfrontality pattern, i.e. increased blood perfusion or glucose metabolism in frontal regions [16, 17]. Metabolic increases in frontomedial regions, and more specifically in the anterior cingulate cortex, appear to be a common feature of psychedelic drug effects, as these have been observed after psilocybin [17, 18] and after subanesthetic doses of ketamine [40]. In the present study, however, only small areas within the frontal lobes were found to show drug-induced changes in the power density distribution. Besides the obvious differences in the drugs being administered, a possible explanation for this divergence could be the different nature of the variables under study (regional brain electrical activity vs. glucose metabolism or blood perfusion). Also, the aforementioned differences in the reported pattern of subjective effects should be taken into consideration.

In conclusion, the effects of *ayahuasca* on the EEG power spectrum involved mainly reductions in the slow delta and theta activity together with decreases in beta-1 and in the alpha-2 frequency band. The assessment of the spatial distribution of intracerebral power density changes singled out the temporo-parieto-occipital junction, and temporomedial and frontomedial areas as target regions of *ayahuasca* in the CNS. These areas comprise the unimodal association cortex in the somatosensory, auditory and visual perception modalities, the heteromodal association cortex, and also key regions within the limbic neural network involved in the integration of multimodal sensory information, and in emotion and memory processes. Future studies specifically addressing drug effects on these aspects of human cognition are needed in order to further our understanding of the complex psychological modifications elicited by *ayahuasca*.

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