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ORIGINAL INVESTIGATION

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Increased frontal and paralimbic activation following *ayahuasca*, the pan-amazonian inebriant

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Abstract *Rationale:* Ayahuasca is a South American psychoactive plant tea which contains the serotonergic psychedelic *N*,*N*-dimethyltryptamine (DMT) and monoamine-oxidase inhibitors that render DMT orally active. Previous investigations with ayahuasca have highlighted a psychotropic effect profile characterized by enhanced introspective attention, with individuals reporting altered somatic perceptions and intense emotional modifications, frequently accompanied by visual imagery. Despite recent advances in the study of ayahuasca pharmacology, the neural correlates of acute ayahuasca intoxication remain largely unknown. *Objectives:* To investigate the effects of ayahuasca administration on regional cerebral blood flow. *Methods:* Fifteen male volunteers with prior experience in the use of psychedelics received a single oral dose of encapsulated freeze-dried *ayahuasca* equivalent to 1.0 mg DMT/kg body weight and a placebo in a randomized double-blind clinical trial. Regional cerebral blood flow was measured 100–110 min after drug administration by means of single photon emission tomography (SPECT). *Results:* Ayahuasca administration led to significant activation of frontal and paralimbic brain regions. Increased blood perfusion was observed bilaterally in the anterior insula, with greater intensity in the right hemisphere, and in the anterior cingulate/frontomedial cortex of the right hemisphere, areas previously implicated in somatic awareness, subjective feeling states, and emotional arousal. Additional increases were observed in the left amygdala/parahippocampal gyrus, a structure also involved in emotional arousal. *Conclusions:* The present results suggest that ayahuasca interacts with neural systems that are central to interoception and emotional processing and point to a modulatory role of serotonergic neurotransmission in these processes.

Keywords Ayahuasca · Dimethyltryptamine · Psychedelics · SPECT · Regional cerebral blood flow · Human

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Introduction

The psychotropic ayahuasca tea, a central element of Amazonian shamanism (Schultes and Hofmann 1987), is commonly obtained by infusing together the stems of the *Banisteriopsis caapi* liana and the leaves of the *Psychotria viridis* bush, two plants endemic to the region (Schultes and Hofmann 1980, 1987). In the past, ayahuasca use among the indigenous inhabitants of the Amazon was traditionally restricted to medicine men and was only open to lay members of the group during certain communal celebrations and rites of passage into adulthood (Reichel-Dolmatoff 1990). However, in recent years, it has given way to more

widespread use. "Ayahuasca tourism" is on the rise in the region (Halpern 2004; McKenna 2004; Salak 2004), and several Brazilian-based religious groups who use ayahuasca in their rituals are seeking legal authorization to practice their religion in the United States and Europe (Greenhouse 2005; Halpern 2004; McKenna 2004).

From the early 19th century accounts written by explorers (Spruce 1908; Villavicencio 1858) to present day clinical trials (Riba et al. 2001b), reports on the subjective effects elicited by ayahuasca have described a remarkable modified state of awareness in which introspective attention is typically enhanced. Subjects report experiencing a highly emotional state in which bodily sensations are modified or intensified and in which visual imagery frequently emerges, often laden with a marked personal content (Riba et al. 2001b). Within the context of traditional use, this modified state of awareness is reportedly used by shamans to diagnose and treat the psychological and physical afflictions of their patients (Dobkin de Rios 1984), whereas among the Brazilian ayahuasca churches, the tea is considered a sacrament that allows contact with the divine (Labate and Araújo 2002). From a medical perspective, the spread of ayahuasca use to Europe and North America in the last decade has raised concern among public health authorities (Anonymous 2000). However, in a wave of renewed psychiatric interest in psychedelics as therapeutic agents (Check 2004; Kotler 2005; Melton 2004), there have been claims of its potential use as a treatment for substance-related and other psychiatric disorders (McKenna 2004).

Chemical analyses and pharmacological studies conducted with ayahuasca have shown that the tea combines in a single preparation the orally labile serotonergic psychedelic *N*,*N*-dimethyltryptamine (DMT) from *P. viridis* with monoamine oxidase (MAO)-inhibiting β-carboline alkaloids (Buckholtz and Boggan 1977) from *B. caapi* (McKenna et al. 1984). Remarkably, these β-carbolines block the metabolic breakdown of DMT by the visceral MAO, allowing its access to systemic circulation (Riba et al. 2003). In the central nervous system, DMT binds to the serotonin-2A receptor, where it acts as a partial agonist (Rabin et al. 2002). Neuroendocrine measures after acute ayahuasca administration (Callaway et al. 1999) and peripheral serotonin transporter levels in long-term users (Callaway et al. 1994) further support an interaction between ayahuasca and serotonergic neurotransmission.

Although various aspects of the pharmacology of ayahuasca in humans have been described in recent years (Callaway et al. 1999; Riba et al. 2001b, 2003), the biological substrates underlying the psychological modifications it elicits remain largely unknown. To examine the neural correlates of acute ayahuasca effects, we conducted a blood perfusion single photon emission tomography (SPECT) study in a group of fifteen male volunteers who had prior experience in the use of psychedelics. SPECT scans conducted after administration of a single dose of a freeze-dried and encapsulated formulation of ayahuasca were compared with scans obtained after a placebo.

Materials and methods

Volunteers

Fifteen male volunteers experienced in the use of psychedelics, i.e., minimum use on at least ten occasions, were recruited. Volunteers were in good physical health, confirmed by medical history, laboratory tests, ECG and urinalysis, and psychological health (structured psychiatric interview for the DSM-IV). Exclusion criteria were as in previous studies (Riba et al. 2001b, 2003) and included current or previous history of psychiatric disorders and alcohol or other substance dependence. Participants had a mean age of 28 years (range 20–38), mean weight 66.8 kg (range 60.1–85), and mean height 176.2 cm (range 163–196). Participants had used psychedelics from ten to hundreds of times. The most commonly used psychedelics were psilocybian mushrooms (15/15) followed by LSD (14/15) and ketamine (9/15). Some volunteers had experienced using peyote (5/15) and mescaline (2/15) and only one had taken ayahuasca before his participation in the study. Besides psychedelics, volunteers had consumed cannabis (15/15), cocaine (15/15), MDMA (13/15), and amphetamines (13/15). 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. All volunteers gave their written informed consent to participate.

Drug

An encapsulated freeze-dried formulation of ayahuasca was obtained as described in previous studies (Riba et al. 2001b, 2003). The ayahuasca batch employed contained 8.33 mg DMT, 14.13 mg harmine, 0.96 mg harmaline, and 11.36 mg THH per gram of freeze-dried material. The dose administered in the present investigation was of 1 mg DMT/kg body weight, and was chosen based on an earlier work in which it had been proven to elicit full-blown psychotropic effects (Riba et al. 2001b). Placebo capsules contained 0.75 g lactose.

Study design

In a double-blind randomized fashion, each volunteer received either a single oral dose of encapsulated freeze-dried ayahuasca or a placebo in two experimental sessions at least 1 week apart. Volunteers were requested to abstain from any medication or illicit drug use 2 weeks before the beginning of the experimental sessions and until the completion of the study. Volunteers also abstained from alcohol, tobacco, and caffeinated drinks 24 h before each experimental day. Urinalysis for illicit drug use was performed for each experimental session. After arrival at 9:00 a.m. under fasting conditions, volunteers had a light breakfast and a cannula was inserted in an arm vein for

radiotracer administration. Capsules with either the drug or placebo were administered at 12:00 noon with 250 ml tap water. Throughout the experimental session, the volunteers remained seated on a comfortable reclining chair in a quiet, dimly lit room until SPECT image acquisition. All volunteers remained overnight in the laboratory and were discharged at 12:00 noon of the following day.

Study methods

SPECT imaging

At 100–110 min after drug administration, an injection of 30 mCi technetium-99m-labeled ethylcysteinate dimer was administered through the previously placed intravenous cannula. The volunteers, sitting on a comfortable reclining chair in the same room since drug administration, were instructed 5 min before bolus injection to close their eyes and remain as relaxed as possible during the injection procedure and to remain with eyes closed for an additional 10 min after completion of the bolus. After this time, they were allowed to open their eyes again and they remained in the room until image acquisition, which was conducted 1 h later, at 3 h after drug administration.

SPECT imaging of the brain was performed with the volunteer's head supported by a headrest using a two-headed HELIX gamma camera (General Electric Medical Systems) equipped with fan-beam collimators. Data were acquired using a 128×128 image matrix in three degree steps. The total acquisition procedure lasted for around 50 min. Images were reconstructed by filtered back-projection using a Metz filter and the Chang method for attenuation correction using a factor of 0.075.

Statistical analyses were conducted on a voxel-by-voxel basis using the SPM2 software (The Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm/spm2.html) on a Matlab platform (Mathworks). Images were converted to the analyze format and were spatially normalized to the Montreal Neurological Institute (MNI) standard anatomical space. Standardized images were then smoothed using a 16-mm gaussian kernel. The statistical analysis used a "multiple subjects, conditions, and covariates" model, with the gray matter threshold set at 0.8 and normalization of global cerebral blood flow to 50 with proportional scaling. Contrasts were used to search for voxels of relative change between ayahuasca and placebo. Results are presented at p-value <0.002, uncorrected for multiple comparisons, corresponding to a t-value of 3.44. Only activations involving clusters with more than 50 voxels are reported. Maximum t-values within an activation cluster are reported in MNI coordinates.

Subjective effect measures

Self-rated subjective effects were measured by administering Spanish versions of the Hallucinogen Rating Scale or HRS (Riba et al. 2001a) and the Addiction Research Center Inventory or ARCI (Lamas et al. 1994). The HRS (Strassman et al. 1994) measures psychedelic-induced subjective effects and includes six scales: *Somesthesia*, 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. The range of scores for all HRS scales is 0 to 4. The ARCI (Martin et al. 1971) consists of five scales or groups: MBG, morphine–benzedrine group, measuring euphoria and positive mood; PCAG, pentobarbital–chlorpromazine–alcohol group, measuring sedation; LSD, lysergic acid diethylamide scale, measuring somatic–dysphoric effects; BG, the benzedrine group, measuring intellectual energy and efficiency, and the A scale, an empirically derived scale measuring amphetamine-like effects. The range of scores is 0 to 16 for MBG, −4 to 11 for PCAG, −4 to 10 for LSD, −4 to 9 for BG, and 0 to 11 for A. Volunteers answered the ARCI immediately before drug administration, and 4 h after drug intake, whereas the HRS was only answered at 4 h postadministration.

Before statistical analysis, ARCI scores were transformed to differences from preadministration values. The transformed ARCI scores and raw HRS scores were analyzed by means of t tests with drug (placebo, *ayahuasca*) as factor. In all tests performed, differences were considered statistically significant for p-values lower than 0.05.

Results

SPECT

The results of the statistical parametric mapping analysis between ayahuasca and placebo scans are shown in Fig. 1. Ayahuasca administration led to bilateral activation of the anterior insula/inferior frontal gyrus, with greater intensity in the right hemisphere. Additional areas of increased blood perfusion were observed in the frontomedian wall of the right hemisphere. At this level, the largest cluster of suprathreshold voxels was located in the anterior cingulate/medial frontal gyrus. A smaller cluster was found in the ventral anterior cingulate/subcallosal gyrus. In the left hemisphere, activation was also observed in an area corresponding to the amygdala/ parahippocampal gyrus. No significant decreases in regional cerebral blood flow were observed anywhere in the brain.

Subjective effects

Subjective effect results are shown in Table 1.

Ayahuasca administration induced significant increases in all six HRS scales. The ARCI questionnaire showed statistically significant increases in the A scale measuring

stimulatory effects, the MBG scale measuring positive mood and euphoria, and the LSD scale measuring somatic symptoms. Scores on the BG scale measuring intellectual efficiency and the PCAG scale measuring sedation were not significantly different from placebo.

Discussion

At the dose administered in the present study, ayahuasca induced manifest psychotropic effects as evidenced by the significant increases in various subscales of the measurement instruments administered. Effects included characteristic changes in somatic sensations (HRS–Somesthesia, ARCI–LSD), modifications in thought content and increased arousal (HRS–Cognition, ARCI–A), modifications in visual perception and visions with eyes open and closed (HRS–Perception), and mood modifications (HRS–Affect, ARCI–MBG). The general pattern of these effects was analogous to that found and described in previous studies and placed ayahuasca among the psychedelics (Riba et al. 2001b, 2003).

Table 1 Means (SD) of the scores obtained for the HRS and ARCI questionnaires subscales (n=15), and results of the statistical analysis performed. Statistically significant differences with placebo are indicated by asterisks

	Placebo	Ayahuasca
HRS		
Somaesthesia	0.62 (0.18)	1.32 (0.80)***
Affect	0.31 (0.12)	1.41 (0.72)***
Perception	0.02 (0.08)	1.65 (1.04)***
Cognition	0.02 (0.07)	1.54 (1.13)***
Volition	0.85 (0.68)	1.77 (0.67)***
Intensity	0.03 (0.13)	2.20 (1.07)***
ARCI		
A	0.20 (0.77)	3.20 (2.21)***
BG	0.27 (0.96)	−0.8 (2.81)
MBG	−0.33 (1.11)	2.87 (4.31)**
PCAG	−0.60 (4.15)	0.53 (4.72)
LSD	0.33 (1.63)	4.40 (2.64)***

**P<0.01, ***P<0.001

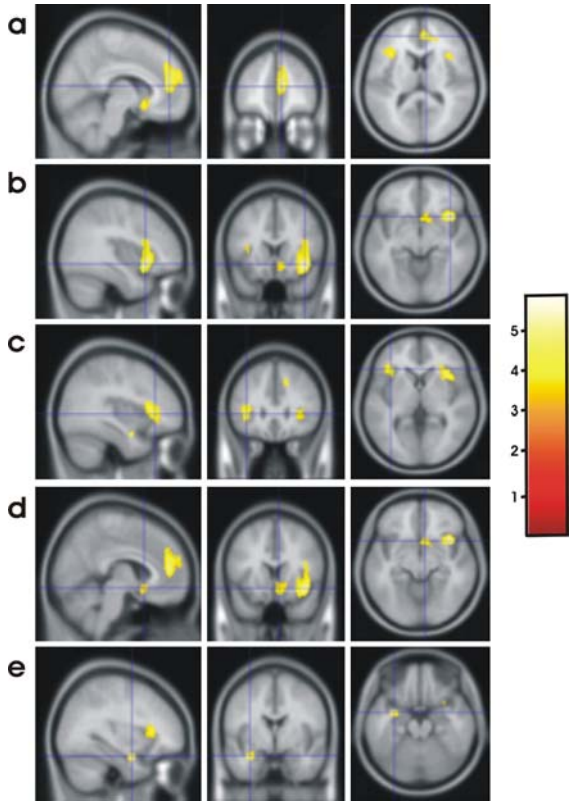

Fig. 1 Statistical parametric maps of increases in regional cerebral blood flow in each of the five clusters showing suprathreshold voxels. Each cluster is shown in the three orthogonal views (*left*, sagittal; *middle*, coronal; *right*, transverse) through the voxel with the maximum t-value. MNI coordinates (x, y, and z) and the number of voxels in each cluster are provided. **a** Right anterior cingulate/right medial frontal gyrus (8, 46, 12; n=594, t=5.39); **b** right insula/right inferior frontal gyrus (38, 16, −8; n=674, t=5.79); **c** left insula/left inferior frontal gyrus (−36, 28, 2; n=347, t=4.78); **d** ventral anterior cingulate/subcallosal gyrus (6, 14, −10; n=119, t=3.97); **e** amygdala/parahippocampal gyrus (−32, −2, −20; n=74, t=5.71). Results are shown at a p value <0.002 uncorrected, superimposed on an SPM T1 NMR template corresponding to the average of 152 subjects

Regarding the intensity of the reported subjective effects, HRS scores in the present study were higher than in a previous study by our group in which 0.6 and 0.85 mg DMT/kg doses were administered (Riba et al. 2003). They were also higher than those reported by Grob et al. (1996) after the administration of an ayahuasca dose containing approximately 0.5 mg DMT/kg body weight. Compared with intravenous DMT as described by Strassman et al. (1994), HRS scores after the present ayahuasca dose fell between those reported after 0.2 and 0.4 mg/kg IV DMT.

The above subjective effects were accompanied by increased regional cerebral blood flow in paralimbic and neocortical areas of the forebrain, with the highest significance values in the statistical comparison attained in the right anterior insula, the left amygdala/parahippocampal gyrus, and the right anterior cingulate/medial frontal gyrus. Consistent with the deeply introspective experience induced by ayahuasca, these structures, especially the right anterior insula, have recently been proposed to be key structures of a neural system supporting interoception (Craig 2002, 2003). In this respect, thalamocortical projections relay to the anterior insula cutaneous and visceral homeostatic information thought to represent the physiological condition of the entire body (Craig 2002, 2003). Recent research has shown bilateral insular and cingulate activation in tasks requiring interoceptive attention, with the right anterior insula specifically subserving explicit awareness of bodily processes (Critchley et al. 2004). This neural system supporting interoceptive awareness has been proposed to provide the basis for subjective feeling states and self-awareness (Craig 2002). A recent magnetic resonance imaging study with experienced meditators found increased cortical thickness in the right anterior insula. The long-term meditators enrolled in the study had practiced a form of meditation whose main goal

was to focus attention on internal states. The authors interpreted the observed cortical thickness increases as an increased awareness of interoceptive stimuli such as breathing sensations (Lazar et al. 2005).

Damasio (2003) and Craig (2002, 2003) have postulated that access to representations of bodily states supported by the right anterior insula plays a key role in the generation of subjective feelings. In fact, activation of the right anterior insula has been observed in many studies of recall-generated emotions (Damasio et al. 2000; Phan et al. 2002; Reiman et al. 1997). Similar to our present results, these experiments have frequently revealed a concomitant activation of the anterior insula and the medial prefrontal/anterior cingulate gyrus—a brain area associated with the motivational aspects of emotion (Devinsky et al. 1995; Paus 2001), and also of the amygdala, which has been associated with negative emotional valence and more recently with general emotional arousal (Hamann 2003; Phan et al. 2002).

It is worth mentioning that similar patterns of brain activation have been observed in previous SPECT and PET studies using other classical psychedelics. These studies have typically found increased activation of frontal regions. Hermle et al. (1992) conducted a SPECT study after mescaline (a psychedelic phenylethylamine) administration and found a "hyperfrontality pattern". A PET investigation of psilocybin (a psychedelic tryptamine) found increased fluorodeoxyglucose uptake in the frontomedial and frontolateral cortices, the ACC, and the temporomedial cortex (Vollenweider et al. 1997). In another PET study of psilocybin, the highest increases in fluorodeoxyglucose uptake were found in the anterior cingulate cortex, followed by the right frontal operculum (Gouzoulis-Mayfrank et al. 1999).

DMT and the other classical psychedelics mentioned in the previous paragraph have a well-known serotonergic mechanism, binding with high affinity to the 5-HT_{1A} (the indolethylamines) and the 5-HT_{2A} receptor (the phenylethylamines and indolethylamines) where they act as partial agonists (McKenna et al. 1990; Pierce and Peroutka 1989; Titeler et al. 1988). Evidence supporting this serotonergic mechanism has been obtained in a human study that found 5-HT_{2A} antagonists to block the psychotropic effects elicited by these drugs (Vollenweider et al. 1998). Furthermore, their neuroendocrine profile is also compatible with serotonergic activation (Strassman and Qualls 1994), and long-term users of ayahuasca have been found to show an increase in the density of platelet serotonin transporters (Callaway et al. 1994). Considering all this evidence, it can be postulated that the activation of paralimbic and prefrontal structures observed in the present study was mediated by drug-induced changes in serotonergic neurotransmission. This opens the interesting possibility that serotonergic neurotransmission via the 2A receptor may play a modulatory role in neural processes subserved by these brain areas.

In conclusion, the present findings indicate that acute ayahuasca administration is associated with the activation of brain regions recently postulated to play prominent roles in the neurobiology of interoception and emotional processing. An interaction at this level could underlie the characteristic subjective effects elicited by the drug. Furthermore, results point to a potential modulatory role of serotonergic neurotransmission in these processes—a possibility that merits further investigation.

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