New World Tryptamine Hallucinogens and the Neuroscience of Ayahuasca

Dennis McKenna and Jordi Riba

Abstract New World indigenous peoples are noted for their sophisticated use of psychedelic plants in shamanic and ethnomedical practices. The use of psychedelic plant preparations among New World tribes is far more prevalent than in the Old World. Yet, although these preparations are botanically diverse, almost all are chemically similar in that their active principles are tryptamine derivatives, either DMT or related constituents. Part 1 of this paper provides an ethnopharmacological overview of the major tryptamine-containing New World hallucinogens.

Keywords Tryptamine derivatives · Tryptamine · Hallucinogen · Hallucinogenic · New World · Shamanism · Botany · Chemistry · Ethnopharmacology

Contents

D. McKenna (✉)
Director of Ethnopharmacology, Heffter Research Institute, Santa Fe, NM, USA
e-mail: mcken031@gmail.com

J. Riba
Human Neuropsychopharmacology Group, Sant Pau Institute of Biomedical Research (IIB-Sant Pau), C/Sant Antoni María Claret, 167, 08025 Barcelona, Spain
e-mail: jriba@santpau.cat

J. Riba
Department of Pharmacology and Therapeutics, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

1 Part 1: Botany, Chemistry, and Ethnopharmacology of New World Tryptamine Hallucinogens—Introduction

The indigenous cultures of the New World are infinitely more sophisticated than their Old World counterparts in their knowledge and utilization of vision-producing, or hallucinogenic, plants. Fewer than 100 genera have been identified as "major hallucinogens," meaning that they form an important component of ethnomedical and ritual practices in one or more indigenous societies; fully sixty genera are used by New World aboriginal peoples, while only a dozen or so are utilized in Old World indigenous cultures (Schultes 1970a, b). This curious asymmetry in the ethnographic utilization of visionary plants has never been satisfactorily explained. Various more or less plausible theories have been proposed; the most likely explanation is that the New World became colonized in the Late Paleolithic by nomadic migrants from Siberia, who expanded into the new continent via the land-bridge that is thought to have existed between the Alaskan Peninsula and what is now the Bering Strait. These nomadic populations brought with them a strong shamanic tradition based on the use of the Fly Agaric mushroom, *Amanita muscaria*, as a ritual intoxicant to achieve states of trance or stupor for purposes of divination, diagnosis, and sorcery. The *Amanita*-based shamanism was already ancient, and its roots lost in the mists of prehistoric time, by the time the first nomadic tribes appeared in the New World (Wasson 1967).

Those early immigrants into the North American continent may have brought with them both a tradition and a technology of psychoactive plant utilization; as these populations gradually expanded southward into the fecund rainforest ecosystems of Central and South America, they would have encountered an increasingly unfamiliar and biodiverse flora. In those tropical regions, rich in biodynamic plant species, the innate human drive to access shamanic dimensions via divine intoxication reached its full symbiotic expression. The legacy of that Paleolithic application of human ingenuity and curiosity to empirical psychopharmacological experimentation in an ecology of incredible biochemical diversity persists to the present day, in the many traditions involving the use of psychoactive plants that can still be found among New World aboriginal peoples.

While the ingenuity displayed by the New World Indians in discovering and utilizing psychoactive plants drawn from numerous families and genera is remarkable, perhaps equally remarkable is the fact that in most instances, the active principles responsible for their psychoactive properties can be traced to chemical compounds known as tryptamines. With only three exceptions—the peyote cactus of North America and Mexico, the morning glories (*ololiuqui*) of Central America, and the columnar San Pedro cacti of the Andes—almost all of the "major" New World hallucinogens are derived from plants containing tryptamine derivatives. This section of this chapter presents an ethnopharmacologic overview of tryptamine-containing New World hallucinogens, including their botanical sources, chemistry and pharmacology, and their geographical and ethnographic distribution.

2 Chemistry, Botany, and Pharmacology

Tryptamine derivatives are simple indole alkaloids, derived biosynthetically from tryptophan, an essential amino acid that is universally distributed in all plants and animals (although many animals, including man, cannot synthesize tryptophan de novo and must obtain it from dietary sources; that is why it is considered an "essential" amino acid). Decarboxylation of tryptophan by aromatic amino acid decarboxylase, an enzyme fundamental to basic metabolic processes in plants and animals, yields tryptamine, the structurally simplest of the tryptamine derivatives. Hydroxylation of tryptamine at position 5 on the indole ring yields 5-hydroxytryptamine (5-HT), also known as serotonin. Serotonin is widely distributed in plants where it functions as a defensive, irritant compound, e.g., in the leaves of nettles (*Urtica* spp.). Serotonin is also a major central nervous system neurotransmitter, and most hallucinogenic drugs are thought to be agonists at 5HT2a receptors, one of about fourteen subtypes of serotonin receptors. Tryptamine itself is not psychoactive, nor is serotonin, apart from a mild sedative effect; similar sedating and tranquilizing effects have been ascribed to tryptophan itself, undoubtedly because it is a precursor to serotonin in the central nervous system. A trivial chemical modification of tryptamine, viz. the addition of two methyl groups (CH_3) groups to the side-chain nitrogen, yields the simplest of the hallucinogenic tryptamines, *N,N*-dimethyltryptamine or DMT. A closely related compound, bufotenine or 5-hydroxy-*N,N*-dimethyltryptamine (5-OH-DMT), can be derived from serotonin by a similar methylation reaction; bufotenine is so named because it is found in the skins of certain toads belonging to the genus *Bufo*. There is some controversy as to whether bufotenine is hallucinogenic or otherwise psychoactive, as it putatively does not cross the blood/brain barrier and purportedly displays only peripheral autonomic effects. However, careful self-bioassay experiments by Ott (2001) have established definitively that bufotenine is indeed psychoactive, although its activity is critically affected by dose and route of administration, as well as the chemical form of the alkaloid (salt or free base). Two further minor modifications of bufotenine can result in potent hallucinogens.
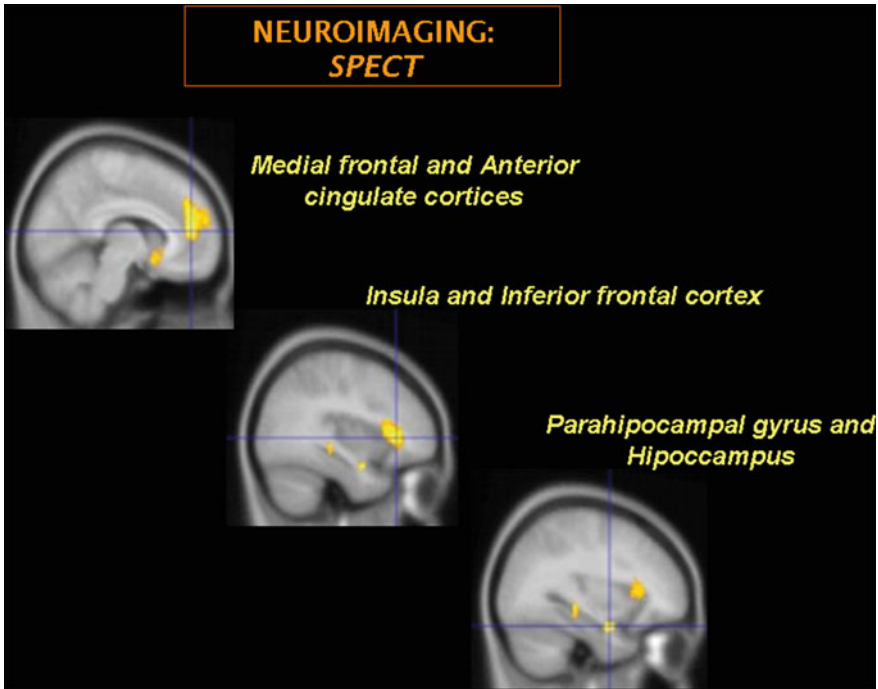
Fig. 1 Results of the neuroimaging SPECT study. The analysis showed significant areas of increased regional cerebral blood flow during the peak effects of ayahuasca. Significant clusters were located in: **a** the right anterior cingulate/right medial frontal gyrus; **b** the right insula/right inferior frontal gyrus; **c** the left insula/left inferior frontal gyrus; **d** the ventral anterior cingulate/subcallosal gyrus; and **e** the amygdala/parahippocampal gyrus. Results are shown at a *p* value of $p < 0.002$ uncorrected for an $n = 15$ subjects

The *O*-methylation of the hydroxy group of bufotenine yields 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), a compound similar to DMT in that it is a short-acting hallucinogen, but approximately 10 times more potent, on a per weight basis. The 4-hydroxy analog of bufotenine is psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine), which is the active principle in the hallucinogenic "magic" mushrooms, first described from Mexico. This compound is derived from psilocybin, which is simply the 4-phosphoryl ester of psilocin; psilocybin is converted to psilocin in the body and it is psilocin that is thought to be the active form of psilocybin. This completes the list of naturally occurring psychoactive tryptamine derivatives; two other classes of psychoactive indole compounds, however, are closely related to tryptamine derivatives and deserve to be mentioned here. One of these is the ß-carbolines, which, like tryptamines, are structurally simple and widely distributed in the plant kingdom. ß-carbolines have a tricyclic structure, with the tryptamine side-chain incorporated into a third heterocyclic ring, while tryptamine derivatives have only two fused rings that comprise the indole nucleus. ß-carbolines

are derived biosynthetically from tryptamine or other simple tryptamines, and often are present in the same plants that contain hallucinogenic tryptamines. ß-carbolines can be important for the pharmacology of tryptamines, as will be discussed below. Lysergic acid derivatives are another class of naturally occurring psychoactive indoles that can be regarded, in some sense, as complex tryptamine derivatives. The extraordinarily potent hallucinogen LSD-25 is a semisynthetic member of this class, but does not itself occur in nature. Other, less potent but definitely psychoactive lysergic acid derivatives are found in plants, notably the sacred morning glories of Mexico and Central America (members of the genera *Ipomoea*, *Rivea*, and *Turbina*) as well as in the well-known ergot fungus (*Claviceps purpurea* and other *Claviceps* spp.). Other than ergot fungi and the morning glory family (Convolvulaceae), however, lysergic acid derivatives are rare in nature and will not be discussed further here, since they do not strictly conform to the definition of simple tryptamine derivatives, that is, they are not indolealkylamines (Schultes and Hofmann 1981).

The simple hallucinogenic tryptamine derivatives, by which is meant here DMT and its derivatives, 5-MeO-DMT, psilocin, psilocybin, and bufotenine are widely distributed in nature, occurring in animals as well as plants and fungi (Smith 1977). Tryptamine derivatives have been reported from over 26 higher plant families; those including hallucinogenic derivatives such as DMT, 5-MeO-DMT, and bufotenine are the Aizoaceae, Apocynaceae, Poaceae, Fabaceae, Malpighiaceae, Myristicaceae, Pandanaceae, Rubiaceae, Rutaceae, and Urticaceae. Not all of the genera in which these compounds occur are used in shamanic traditions; in fact, it may be argued that the majority of them are not, since their hallucinogenic components were comparatively recent discoveries of modern science, and they were either overlooked or rejected by aboriginal psychopharmacologists. In fact, based on the known numbers of species in each genus reported to contain psychoactive tryptamines, these compounds are potentially present in over 4,860 higher plant species! Since DMT is only two biosynthetic steps from tryptophan, these numbers are probably a serious underestimate. Psilocybin and psilocin are apparently restricted to higher fungi and are found primarily in mushrooms of the genera *Psilocybe*, *Stropharia*, and *Panaeolus*, although they have also been reported from other genera of basidiomycetes as well. These compounds have not been reported from any higher plant, although from a biosynthetic standpoint, there is no a priori reason why they could not occur in a higher plant. Bufotenine and other tryptamine derivatives are principle constituents of the parotid gland secretions of New World toads belonging to the genus *Bufo*, for which the compound was named when first isolated. Curiously, DMT or 5-MeO-DMT has not been reported from any *Bufo* species, with a single exception: *Bufo alvarius*, which contains 5-MeO-DMT instead of bufotenine; rather staggering concentrations of up to 10 % dry weight of the parotid gland have been reported by some investigators (Daly and Witkop 1971; Weil and Davis 1994).

The hallucinogenic tryptamines also display a unique pharmacology that bears importantly on their methods of utilization in the context of New World shamanic traditions. DMT and 5-MeO-DMT are both potent, extremely short-acting hallucinogens whose total duration of action is less than 30 min from "baseline" to

"baseline." Neither of these derivatives is orally active, due to degradation by the enzyme monoamine oxidase (MAO), which is present in the liver and gut, as well as the brain, of humans and other mammals. Thus, in order to experience the hallucinogenic effects of these compounds, they must be taken parenterally as a snuff or enema (although synthetic DMT is injected, or more commonly, smoked as a free base). If orally ingested, they must be protected from peripheral degradation by a monoamine oxidase inhibitor (MAOI). Traditional shamanic practitioners have ingeniously employed all three of these strategies. In contrast, psilocin, the active tryptamine in the "magic" mushrooms, is orally active and elicits an intense psychedelic experience lasting 4–8 h. Psilocin is orally active by itself and does not require an MAOI for activation; as a result, no special preparation is required to experience the effects of the magic mushrooms. They are quite active when plucked and eaten fresh, although they are often dried or kept in honey; these practices are a means of preservation, rather than a specific attempt to alter or activate the pharmacology. Psilocybin is readily converted to psilocin in the body and should properly be considered a "pro-drug"—the physiologically active form of which is psilocin.

3 Survey of New World Tryptamine Hallucinogens

3.1 Psilocybe Mushrooms

Just as DMT can be regarded, in some respects, as the prototype hallucinogen, the so-called "magic mushrooms" of Mexico qualify as the prototype of the New World hallucinogens. The Spanish conquistadores encountered a flourishing mycolatrous religion among the Aztecs at the time of the arrival of Cortés in the court of Moctezuma in 1519. Wasson (1980) has adduced evidence that the use of the magic mushrooms was spread throughout Mesoamerica at this time, and in some parts of the region, the practice may have dated well before the Christian era. Based on linguistic analyses of lexicons compiled by the Spanish missionaries, Wasson has presented convincing evidence that the inebriating mushrooms were known, not only to the Aztecs and Maya, but also to the Nahua, Otomi, Matlatzinca, Mazahua, Tarascan, Huastecan, Totomac, Mixe, Zoque, Mazatec, Zapotec, Chatino, Mixtec, and Chinantla linguistic groups. The discovery of "mushroom stones," carved effigies in the shape of mushrooms from the highlands of Guatamala, lend additional credence to his arguments. Some of these have been dated to the sixth century BC, indicating the considerable antiquity of the Mesoamerican mycolatry (Borhegyi 1961).

The Spanish missionaries, following close upon the coattails of Cortés, regarded the Aztec's ritual and religious use of *teonanácatl,* a name erroneously translated as "god's flesh" by one of their number, one Motolinía, as a particularly odious and blasphemous parody of the Christian Eucharist. They lost no time in pursuing the

vigorous suppression of *teonanácatl* in all of its diabolical manifestations and, backed by the considerable intimidatory powers of the Spanish Inquisition, succeeded in driving the practice underground for the next 400 years (Wasson 1980). Despite the most energetic efforts to stamp out the use of the inebriating mushrooms in Mesoamerica, their employment in a religious and ritual context persisted into the twentieth century, when it was rediscovered and made known to the world by the famous team of R. Gordon and Valentina Wasson, in an article published in <u>Life</u> magazine in May, 1957 (Wasson and Wasson 1957). The repercussions of that event are still being felt, as this was really the first representation in popular media that such peculiar agents as "psychedelic drugs" even existed (LSD and peyote had been known for some decades but were familiar only to a few psychiatrists and literati). The Swiss chemist Albert Hofmann, the discoverer of LSD, shortly succeeded in isolating and characterizing the active principles of the magic mushrooms, psilocybin and psilocin, from material Wasson had brought to him from Mexico, thus marking yet another milestone in the history of psychedelic psychopharmacology (Heim and Hofmann 1958). The availability of these compounds for research from Sandoz in the early 1960s piqued the curiosity of one young Harvard psychologist, Dr. Timothy Leary, and the revelations he gained after a number of self-experiments with these novel substances led him to found the psychedelic movement that would shortly sweep North America and the world. Thus it happened that a persecuted and reviled substance that had been at the heart of Mesoamerican religion since prehistoric times began a second career in the twentieth century. The possible clinical uses of psychedelics are only now being re-discovered after a hiatus of some 40 years following their blanket prohibition in 1970. Of the many compounds that show promise for therapeutic use, psilocybin is one of the most promising; its lack of toxicity, short duration of action, and profound yet manageable psychedelic effects make it ideal for use in clinical settings.

The magic mushrooms encountered and collected by Wasson and his colleague, French mycologist Roger Heim, comprised about a dozen members of the genera *Psilocybe*, *Paneolus*, and *Stropharia* and were for the most part strict endemics, native only to the highlands of Central America. Subsequent work by ethnomycologists has shown that other species of psilocybin-containing mushrooms have a cosmopolitan and global distribution; in the tropics, this is exemplified by *Psilocybe cubensis* (formerly classified as *Stropharia cubensis*, one of the species collected by Wasson and Heim), while in temperate regions, the diminutive "Liberty Cap" mushroom, *Psilocybe semilanceata*, can be found in grassy meadows throughout North America and Europe. Guzmán et al. (2000) published a comprehensive list of the 186 known psilocybin-containing species in an Italian journal; the list can be found on the Erowid.org database (Erowid.org 2001a). The majority of the known species belong to the genus *Psilocybe*, but other genera reported to contain psilocybin include *Agrocybe*, *Conocybe*, *Copelandia*, *Paneolina*, *Paneolus*, *Galerina*, *Gymnopilus*, *Inocybe*, *Pluteus*, *Hypholoma*, *Gerronema*, and *Mycena*. Besides Mexico and Central America, another part of the New World that is particularly rich in psilocybian species is the Pacific Northwest of North America, where over 30 species are endemic. Curiously, although the "recreational" use of some of these

species has become a popular pastime in recent years, there is no record or indication that these mushrooms or their properties were known to any of the aboriginal groups who inhabited the Northwest Coast. These groups, including the Haida, Tlinglit, Tsiamsham, Salish, and others, have never admitted knowledge of these species to ethnographers, although they possess a strong shamanic tradition and much of their traditional art could be characterized as "visionary" in nature. There is similarly no definitive evidence that psilocybian mushrooms had a place in shamanic practices in South America, although Schultes and Hofmann (2001) speculate that seventeenth century reports by Jesuit missionaries referring to the use of a "tree fungus" for preparation of an intoxicating beverage by the Yurimaguas of the Peruvian Amazon may have referred to *Psilocybe yugensis*, a wood-growing species. In the same volume, they also mention the so-called telephone bell gods, anthropomorphic gold pectorals with dome-shaped ornaments on the head. These artifacts are reported from the Simu region of northern Colombia and from the Calima region on the Pacific coast. The hemispherical ornaments, complete with a stem or stipe, are strongly suggestive of a mushroom effigy. Similar artifacts have been reported from Panama, Costa Rica, and Yucatan, suggesting that the prehistoric Mesoamerican mushroom cults may have extended as far south as modern-day Colombia Guzmán et al (2004). In any case, there is no evidence for contemporary use of psilocybian mushrooms in indigenous shamanic practices in South America.

3.2 Anadenanthera Snuffs

Now let us shift our focus southward, to the tryptamine-based hallucinogens that are endemic to the South American continent, for it is here that such plants and the sophisticated technologies used in employing them reached their fullest expression.

Among the many medicinal plants that Columbus encountered in his earliest visits to the New World, the intoxicating snuff prepared from the seeds of the Fabaceoustree, *Anadenanthera peregrina* (formerly *Piptadenia peregrina*), may be considered the paradigm of hallucinogenic New World snuffs. While presumably Columbus observed the use of the snuff powder on his initial voyage, it was not until his second landing in the New World that he commissioned Friar Ramon Pane to undertake an ethnographic documentation of the use of *cohoba* (or *cogioba*), as it was known to the Taino people, the indigenous inhabitants of what is now Haiti:

> The cogioba is a certain powder which they take sometimes to purge themselves, and for other effects which you will hear of later. They take it with a cane about a foot long and put one end in the nose and the other in the powder, and in this manner they draw it into themselves through the nose and this purges them thoroughly... [the *bohuti*, physician] takes a certain powder called *cohoba* snuffing it up his nose which intoxicates them so that they do not know what they do and in this condition they speak many things incoherently in which they say they are talking with the *cemis* and that by them they are informed how the sickness came upon them... (Wassén 1964)

Some scholars have asserted that the Taino word *cohoba* stood for tobacco, but Wassén cites evidence that the words *cohoba*, *cohobha*, *cahoba*, *cojoba-cogioba*, *cojioba*, *cohiba*, and *coiba* are equivalent and refer to a plant that was used by the medicine men to induce a state of trance and that this was recognized as distinct from tobacco by the early chroniclers. To confuse matters further, the powdered *Anadenanthera* seeds may have been mixed with tobacco, at least on some occasions; the Jirara and Caquetio tribes of Venezuela, considered closely related to the West Indian Taino, commonly employ a mixture of tobacco and *Anadenanthera* snuff. The practice is also widespread among other snuff using South American tribes (Wassén 1967).

Possibly as a result of this confusion of the two plants by the explorers in Columbus' party, as well as the rather more spectacular method of smoking tobacco that he observed among the peoples of the Antilles on his first voyage in 1492, Columbus took tobacco seeds back to Europe, but neglected to take seeds of *Anadenanthera*. Tobacco smoking quickly became a popular custom and diffused into Spanish society, and "within a few decades, there were more Spaniards converted to smoking than Indians converted to Christianity" (Emboden 1979). One is tempted to speculate how different our contemporary civilization might be had Columbus returned with the seeds of *cohoba*, rather than tobacco!

More modern ethnographic investigations have shown that the historical use of *cohoba* in the West Indies marks the easternmost boundary of the custom. The *Anadenanthera peregrina* used in that region were probably introduced cultivars from the South American mainland; the center of concentration of the species is the Orinoco valley of Colombia, Venezuela, and adjacent parts of Brazil, where it is known as *yopo*, or *niopo*. Archeological evidence in the form of carved snuff trays and snuffing tubes has placed the practice as far north as Costa Rica (Wassén 1967).

Further to the south, in the Atacama desert, another snuff, known as *vilca* or *huilca* in Peru and Bolivia and *cébil* in Northern Argentina, was similarly prepared from a different *Anadenanthera* species native to this region, *A. colubrina*. Many well-preserved grave sites containing snuffing implements, including carved snuff trays, snuffing tubes, and woven bags containing snuff powders, have been excavated in this area and dated to as early as 570 AD. A chemical and contextual analysis of the powders and implements recovered from these sites established the presence of tryptamine alkaloids in the snuff powders, thus confirming their identity as derived from *Anadenanthera* species (Torres et al. 1992). This evidence, combined with the archeological documentation of the antiquity of this practice in this region, has raised questions as to the true geographic origins of the practice, since it predates by approximately 1,000 years any similar documented use of *Anadenanthera* snuffs in the Orinoco valley or the West Indies. It has been generally assumed among archeologists and ethnographers that the practice originated in the Orinoco valley and from there diffused north to Central America, east to the Antilles, and south to coastal Peru and Chile. This more recent evidence, however, suggests the possibility that the practice may have originated in the Atacama region and diffused north and eastward into the Orinoco basin, where the closely related native species, *A. peregrina*, was substituted for the more endemic southerly species, *A. colubrina*.

The excavation of paraphernalia, specifically snuff trays and snuffing tubes, enables estimation of the antiquity of the use of *Anadenanthera* snuffs. The oldest known snuffing implements have been dated to 1200 BC. from an excavation by Junius Bird from the site of HuacaPreita in the Chicama Valley on the central Peruvian coast (Torres 1995).

The primary indole alkaloid constituents of *Anadenanthera* species have been exhaustively reviewed by Torres and Repke (2006). The most abundant alkaloids reported from *A. peregrina* and *A. colubrina* are bufotenine, DMT, and 5-methoxy-DMT. However, trace concentrations of a number of structurally related alkaloids, including *N*-methyl-tryptamine (NMT), 5-methoxy-*N*-methyl-tryptamine (5MeO-NMT) DMT-*N*-oxide, serotonin, *N*-methyl-serotonin, bufotenine-*N*-oxide, and three ß-carbolines, viz. 2-methyl-tetrahydro-ß-carboline, 2-methyl-6-methoxy-tetrahydro-ß-carboline, and 1,2-dimethyl-6-methoxy-tetrahydro-ß-carboline have been detected.

3.3 Virola Snuffs and Pastes

Ethnographers had long assumed, apart from tobacco snuff and the occasional use of coca as a snuff, that *Anadenanthera* species comprised the sole botanical source of psychotomimetic snuffs in use among indigenous peoples in the Amazon Basin (Cooper 1949). However, subsequent investigations by ethnobotanist R.E. Schultes and toxicologist Bo Holmstedt in the 1950s and 1960s established that the use of *Anadenanthera* snuffs was less prevalent than formerly thought and that tribes belonging to the Waika groups in the upper Orinoco valley prepare an intoxicating snuff from the resin (sap) of several species of the genus *Virola*, in the Myristicaceae, or nutmeg family (Schultes and Holmstedt 1968). In addition to the Orinoco valley, the use of *Virola* snuffs is concentrated in the Colombian Vaupés and north of the Rio Negro in Brazil. Some overlap in the native nomenclature has undoubtedly contributed to the confusion regarding the distinction between *Virola* and *Anadenanthera* snuffs. Terms vary in different tribes, but *Virola* snuff is known as *yá-kee*, *yá-to*, and *paricá* in Colombia and Venezuela, and *epéna*, *ebene*, *paricá*, and *nyakwána* in Brazil. However, *paricá* may also refer to *Anadenanthera* snuff, and *epéna*, or *ebene* can be used as a general term for snuff (Schultes 1970a, b).

The principle species implicated in the preparation of hallucinogenic snuffs in the Colombian Amazon are *V. calophylla* and *V. calophylloidea*, while *V. theiodora* and *V. elongata* are the species utilized among the Waika, Paumari, and Taiwanos. There is considerable taxonomic confusion in the genus, however, and *V. theiodora* and *V. elongata* are regarded as equivalent by some taxonomists. *Virola cuspidata* and *V. rufula* have also been reported as snuffs. Occasionally, ashes or powdered leaves of other plants are used as admixtures to the snuffs. Among the Waika, one commonly employed admixture is the aromatic herb, *Justica pectoralis* var. *stenophylla*, which also is occasionally used as the sole ingredient of a snuff. Earlier reports of tryptamines in *Justicia* are apparently erroneous, although the plant does

contain umbelliferone and other coumarins (Macrae and Towers 1984a). Interestingly, the resin of *Virola* species among the Waika is also occasionally used in the preparation of an arrow poison that is applied to darts used in hunting small animals. Macrae and Towers (1984b) investigated the possible mechanisms contributing to this activity in animal experiments. They found that, in their assays, extracts containing the tryptamine alkaloids were not highly toxic and did not interfere markedly with locomotion or motor activity. They isolated an alkaloid-free fraction containing lignans, however, and found that this fraction produced a marked inhibition of motor activity and apparent sedation of the test animals. They concluded that the lignans, rather than the tryptamines, were likely the agents responsible for the effectiveness of *Virola* arrow poison.

The reddish, resinous exudate of the inner cambial layer of the *Virola* species used as snuffs contains high concentrations of tryptamine alkaloids, including *N*-methyltryptamine(NMT), 5-MeO-*N*-methyltryptamine, DMT, and 5-MeO-DMT, of which the latter usually predominates, and often may be the sole constituent. Traces of ß-carbolines, including 2-methyl-1,2,3,4-tetrahydro-ß-carboline, 6-methoxy-2-methyl-1,2,3,4-tetrahydro-ß-carboline, and 6-methoxy-1,2-dimethyl-1,2,3,4-tetrahydro-ß-carboline have also been reported in some species (Holmstedt and Lindgren 1967). Both the source plants and the snuffs prepared from them exhibit considerable chemical variation.

In the Colombian Putumayo, marked on the north by the Rio Igaraparaná, and on the south by the Rio Yaguasyacu and Ampiyacu, the Bora, Witoto, and Muinane prepare an orally active hallucinogen from the resin of *Virola theiodora*, *V. elongata*, and *V. pavonis* (Schultes 1969). In this practice, the drug, which is known as *oo-koo-he* among the Witoto and *kú-ru-ku* among the Bora, is prepared by stripping the bark, collecting the resin, and concentrating it to a thick, syrupy consistency. This is then mixed with the ashes of other plants (usually *Gustavia peoppigiana* or *Theobroma* spp.) and rolled into pellets or boluses. Oral ingestion of two or three of these pellets is said to induce a rapid and violent intoxication, an effect that the author was able to confirm in self-experiments during fieldwork on the Rio Ampiyacu (McKenna et al. 1984a). Since the psychotomimetic tryptamines, DMT and 5-MeO-DMT, the major alkaloids in the preparation, are not orally active unless activated by a peripheral MAOI, the documented oral activity of these *Virola* pellets raises some interesting pharmacological questions. Phytochemical analyses have shown that ß-carbolines, while potent MAO inhibitors, are only present in trace concentrations in the *Virola* pellets and hence are unlikely to have any pharmacological significance. In vitro assay of extracts prepared from the pellets showed a somewhat weak MAOI activity, which moreover was shown to be due to the tryptamines alone; extracts from which the tryptamines were removed did not display any MAOI activity. At present, the pharmacological basis for the oral activity of the *Virola* pellets remains incompletely elucidated (McKenna et al. 1984a).

3.4 Ayahuasca

The orally active *Virola* pellets always had a restricted ethnographic distribution, and the practice is now verging on extinction as a result of encroaching acculturation among the tribes that formerly used it. In contrast, the hallucinogenic beverage known variously as *ayahuasca*, *yagé*, *caapi*, *natema*, or *hoasca* is the premier hallucinogen of the Amazon, and its use, far from dying out, is rapidly diffusing from aboriginal and mestizo society into mainstream South American (and global) culture. Like the *Virola* pellets, *ayahuasca* is also an orally active tryptamine-based hallucinogen, but its mechanism of action is relatively well understood.

Ayahuasca is prepared by boiling the bark or crushed stems of a Malpighiaceous jungle liana, *Banisteriopsis caapi*, together with various admixture plants, especially the leaves of *Psychotria viridis*, a member of the Rubiaceae. In the Colombian Putamayo and parts of Ecuador, the leaves of *Diplopterys cabrerana*, (formerly classified as *Banisteriopsis rusbyana*) (Gates 1979) a liana in the same family as *Banisteriopsis*, are often substituted for those of *Psychotria viridis*. It is the admixture plants, *Psychotria* or *Diplopterys*, that contain the hallucinogenic alkaloid necessary for the activity; the leaves of both species contain substantial concentrations of DMT (Der Marderosian et al. 1968; Pinkley 1969). The *Banisteriopsis* liana, on the other hand, contains high concentrations of ß-carboline alkaloids, primarily harmine and tetrahydroharmine, with lesser amounts of harmaline (Rivier and Lindgren 1972; Schultes and Hofmann 1981). These compounds are potent peripheral MAO inhibitors, and it is the combination of DMT in the admixtures and the MAO-inhibiting ß-carbolines that provide the mechanism for the oral activity of this drink. The ß-carbolines are able to protect the DMT from degradation in the liver and gut, thus enabling it to cross the blood–brain barrier intact and exert its effect in the central nervous system (McKenna et al. 1984b).

Unlike the hallucinogenic snuffs or the *Virola* pellets, the custom of using *ayahuasca* has a widespread distribution among aboriginal groups in the Amazon, including the Guahibo, Jivaro, Colorado, Ingano, Siona, Kofan, Witoto, Tukano, Desana, Yakuna, and more than 20 others. In view of this widespread use, it is not surprising that the practice has diffused into mestizo society; in Peru and parts of Colombia and Ecuador, *ayahuasca* (or *yagé*, as it is known in the Colombian Putamayo) occupies a central position in the ethnomedical armamentarium of mestizo shamans. These practitioners consume the beverage themselves as a diagnostic and divinatory tool and also administer it to their patients as a panacea reliably able to cleanse both the body (it is often referred to as "la purga") and spirit. Regular consumption of *ayahuasca*, along with a special diet, sexual abstinence, and ingestion of other medicinal plants also constitutes an essential part of shamanic training for a mestizo healer. Thus, *ayahuasca* is the primary "teacher" enabling the apprentice medicine man to learn about the curative properties of other plants (often by consuming them in the form of admixtures to *ayahuasca*), which are also conceived of as "plant teachers." (Luna 1984; McKenna et al. 1995). It is

also through the medium of *ayahuasca* that the shaman acquires his "icaros," magical songs that are used in curing, and establishes alliances with his helping spirits, which may be conceived as animals, plants, or spirits (Luna 1984).

The origin of the use of *ayahuasca* by indigenous Amazonian peoples is lost in antiquity, and there is evidence that the practice was already centuries old by the time of the Columbian contact. Unlike snuffs, which leave unambiguous archeological evidence in the form of snuff trays and tubes, *ayahuasca* is consumed as a decoction, and there is no definitive link to ceramic or other vessels that may have been used to consume the beverage. Based on ambiguous evidence, Naranjo (1995) speculates that the earliest use of *ayahuasca* can be placed sometime between 500 BCE and 500 AD.

Whatever its historic context has been, in recent decades, the ceremonial use of *ayahuasca* in a religious context has begun to diffuse from mestizo society into a wider cultural milieu. In Brazil, where it is known as *hoasca* or *Daime*, the beverage has become the central sacrament of several syncretic religious movements. The largest and most visible of these is the *Santo Daime* cult, which incorporates many elements of Christian liturgy in their practices and belief systems (Dale 1991) and the *União do Vegetal*, in which a collective spiritualism emphasizing ecology and harmony with nature plays a more prominent role. These cults have burgeoned from a few hundred members to thousands of members within the last two decades. The Brazilian government, recognizing that these are legitimate religious movements and perceiving little or no physical or moral detriment from their use of *ayahuasca*, has officially sanctioned *ayahuasca* by lifting legal restrictions against its sacramental use within a religious context (Erowid 2001b). In the United States, judicial rulings by the Supreme Court and the U.S. District Court in Oregon have sanctioned the religious use of *ayahuasca* for practicing members of the UDV and Santo Daime churches (Erowid.org 2006, 2012).

3.5 Bufo spp. and Jurema (Mimosa spp.)

All of the New World tryptamine hallucinogens that we have discussed to this point—the psilocybin mushrooms, the *Anadenanthera* snuffs, the *Virola* preparations, and *ayahuasca*—have an extensive history and an association with New World shamanism that is Paleolithic in their origins. Their impact and influence on the cultures that utilized them is abundant and well documented, both in the ethnographic literature and in the art and iconography of the peoples who use the plants.

In the case of two other tryptamine hallucinogens, however, the information on their use in the New World is sparser, and as a result, they are all the more fascinating; these are uncharted ethnopharmacological waters.

3.5.1 *Bufo* Species

It was mentioned above in the section on the distribution of the tryptamines in nature that bufotenine (5-hydroxy-DMT), as its name implies, was first isolated from the venom of toads of the genus *Bufo*, and that in at least one instance, *Bufo alvarius*, the potent hallucinogen 5-MeO-DMT, was a major ingredient of the venom. While it is true that the toad occupies a prominent position in Mayan, Aztec, and Olmec iconography (Kennedy 1982) and is often depicted together with mushrooms and stylizations of other "sacred" plants, there is no unambiguous proof that toad venom was used as a hallucinogen in Mesoamerica. A major source of controversy has been that the candidate species favored by most ethnographers has involved *Bufo marinus*, which is a highly toxic species that would require a rather sophisticated preparation if it were to be consumed safely. Davis and Weil have extensively reviewed the evidence for the hallucinogenic use of *B. marinus*, and they argue that *Bufo alvarius* is the more likely candidate to have been used, on both pharmacological and ethnographic evidence (Davis and Weil 1992a, b).

3.5.2 Mimosa Species

Schultes reports that several tribes of eastern Brazil prepared the root of *Mimosa hostilis*, a scrubby, leguminous shrub native to the dry area, into a "miraculous drink" known as *ajuca* or *vinho de jurema*. Early reports of the *jurema* ceremony date back as far as 1788, and the practice is apparently ancient, having been practiced by a number of extinct tribes: Guegue, Acroa, Pimenteira, and Atanayé. A major application of the *jurema* ceremony at one time was apparently to prime the priests and warriors for going off to war (Schultes and Hofmann 1981).

In 1946, Brazilian chemist Oswaldo Gonçalves de Lima isolated a single alkaloid from the roots of a related species, *Mimosa tenuiflora* (*jurema preta*) which he named nigerine. Although this initial isolation was only partially pure, it was subsequently shown to be identical to *N,N*-dimethyltryptamine (DMT) when Gonçalves de Lima provided a group of American researchers with a sample of *M. tenuiflora* root bark. These workers were able to unequivocally isolate DMT from the sample in 0.57 % yield (Pachter et al. 1959). The history of this significant discovery—the first identification of DMT as a naturally occurring alkaloid—has been exhaustively reviewed by Ott (1998). Although as Ott points out, priority for the first **unequivocal** identification of DMT as a natural compound must be given to Fish et al. (1955) who reported DMT in the seeds of *Anadenanthera peregrina* (under its former name, *Piptadenia peregrina*). DMT is known to be orally inactive unless ingested with an MAO inhibitor, and in the traditional psychedelic brew *ayahuasca*, the DMT is protected from peripheral degradation by the ß-carboline alkaloids present in the bark of one of the plant components, the liana *Banisteriopsis caapi*. *Vinho de Jurema*, however, is prepared as a beverage without the use of ß-carboline containing admixture plants, and it has long been speculated that there must have been some long forgotten admixture added to enable its oral activity.

Ott (1998), however, conducted careful self-experiments using oral decoctions of *M. tenuiflora* (*Jurema preta*) and reported that it was potently psychoactive without the inclusion of any other admixture plants. So the mechanism of its oral activity remains a mystery, but the mystery may have been partially solved by the recent identification of another alkaloid, yuremamine, by J.C. Callaway and co-workers (Vepsäläinen et al. 2005). This compound, present in the stem bark of *Mimosa tenuiflora* at concentrations comparable to DMT, contains an unusual structure that incorporates the structure of DMT fused with phenolic moieties. The authors suggest that this novel compound may be active as an MAO inhibitor, and if confirmed, this would account for the oral activity of this unusual preparation. Alternatively, cleavage of the D ring of the yuremamine molecule could free the DMT "caged" in the yuremamine structure. It is possible that the yuremamine is absorbed intact through the gut and the DMT subsequently becomes bioavailable through this mechanism. A third possibility is that yuremamine itself is halluci-nogenic, and thus accounts for the oral activity of traditional single-plant *jurema* preparations. Resolution of this question must await the isolation of sufficient quantities of pure yuremamine to permit human bioassay. This interesting and little-
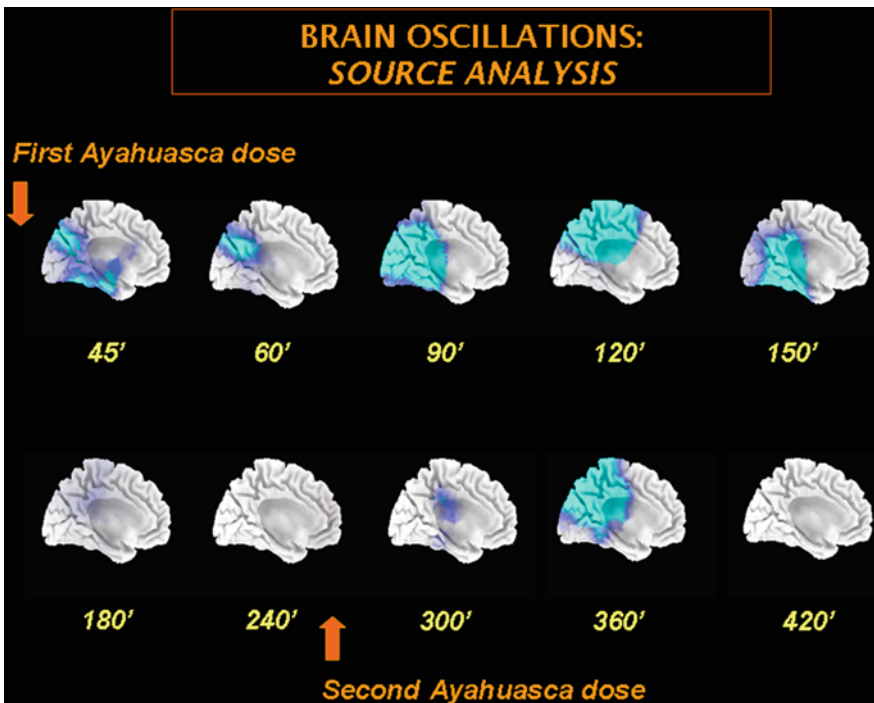

Fig. 2 Result of the current source density analysis. The figure shows areas of significant current density decreases in the alpha band of the electroencephalogram following two consecutive doses of 0.75 mg DMT/kg ayahuasca. *Blue* indicates significant decreases at $p < 0.05$ corrected as compared to placebo. Note the prominent decreases in posterior brain regions

known New World hallucinogenic is yet another incompletely explored niche of ethnopsychopharmacology, awaiting the time and interest of some devoted investigator.

4 Part 2: The Neuroscience of Ayahuasca

The complex mixture of alkaloids in ayahuasca induces a series of neurochemical, bioelectrical, and metabolic modifications in the central nervous system that constitute the biological basis of the ayahuasca experience. These modifications interact with each individual's psyche, leading to an experience that is unique for each person.

To try to understand the biological mechanisms underlying the perceptual modifications, associations, and insights that compose the complex cognitive effects of ayahuasca, we have conducted a series of studies involving the administration of ayahuasca to experienced participants. In what follows, we present the findings of these studies and propose a model of brain function under psychedelics that binds together the results obtained in our studies using various assessment modalities.

5 The Nuclear Medicine Approach

Using single photon emission tomography or SPECT, we conducted a neuroimaging study to assess the acute effects of a high ayahuasca dose in 15 healthy volunteers. We administered a dose of freeze-dried ayahuasca equivalent to 1.0 mg DMT per kg body weight in one experimental session and a placebo in another session. A radiotracer was injected at the peak of the experience, 1 h and 40 min after ayahuasca intake. Subsequently, we obtained brain images showing regional cerebral blood flow at the time of injection (Riba et al. 2006).

As shown in Fig. 1, the statistical comparison between the images obtained after ayahuasca and the images obtained after a placebo revealed changes in a number of brain regions. These changes after ayahuasca were always increases in blood flow, and to our surprise, they were not found in low-level primary visual or auditory areas where we had expected changes based on the well-known effects of the ayahuasca on perception. Instead of effects on these hierarchically low sensory-selective regions, the increases occurred in regions placed higher in the information processing hierarchy, predominantly in anterior brain regions. We located significant clusters of activation in the medial aspects of the frontal lobe in an area encompassing parts of the anterior cingulate and medial frontal gyri. Increases were also observed in the medial temporal lobe (MTL) around the amygdala, hippocampus, and parahippocampal gyrus.

The medial frontal lobe plays a prominent role in cognitive control and in the binding of affective and cognitive processes, while the MTL plays a role in emotional arousal and episodic memory. The pattern of activation we observed was in line with findings by other researchers who had also administered serotonergic psychedelics and used the same nuclear medicine technique or the more advanced positron emission tomography (PET). In 1992, Hermle and his team described a hyperfrontality pattern following the administration of mescaline (Hermle et al. 1992). The groups led by Vollenweider and by Gouzoulis-Mayfrank both observed increased fluorodeoxyglucose uptake in the medial prefrontal cortex after the administration of acute psilocybin (Vollenweider et al. 1997; Gouzoulis-Mayfrank et al. 1999). This converging evidence highlights the frontal cortex with its prominent role in executive function as a key target of psychedelic drugs.

6 Spectral Analysis of Brain Electrical Activity

In a previous study involving 18 participants and an ayahuasca dose equivalent to 0.85 mg DMT/kg body weight, we recorded the brain's spontaneous electrical activity (EEG) with sensors placed on the scalp (Riba et al. 2004). The spectral analysis of the ayahuasca-induced changes in the EEG showed reductions in absolute power in all the classical frequency bands of the EEG. We subjected these power changes to intracerebral current density analysis in order to find their brain sources. The results showed only a partial overlap with the findings from the SPECT study. While there were reductions in the MTL and in the medial frontal lobe that matched the SPECT findings, we also found current density reductions in an extensive area in the posterior part of the brain, in the temporo-parieto-occipital junction that includes areas of the parietal, temporal, and occipital lobes. We found them specifically over the angular gyrus, the superior parietal lobule, the supra-marginal gyrus, the precuneus, and the posterior cingulate cortex. We have replicated these findings more recently in another study involving the administration of two consecutive doses of ayahuasca, as shown in Fig. 2, and they have been independently corroborated by other researchers using magnetoencephalography (Muthukumaraswamy et al. 2013).

It is noteworthy that the brain areas identified using current density analysis correspond predominantly to association areas rather than primary sensory cortex. The temporo-parieto-occipital junction is involved in the secondary processing of visual and auditory information and has been found to play a role in the voluntary generation of visual imagery (Roland and Gulyás 1994). Additional support for a role of these structures in ayahuasca-induced effects is provided by other authors who have postulated that, rather than requiring activation of the striate cortex, visual imagery is based on a more complex phenomenon involving the retrieval from memory of visual information stored in the temporal association cortex (Sakai and Miyashita 1994). An effect of ayahuasca at this level could explain phenomena such as synesthesia between the auditory and visual sensory modalities, given the lack of

direct projections interconnecting primary sensory cortices or modality-specific areas (Mesulam 2000).

The targeted areas are characterized by their capacity to act as directories binding distributed components of sensory representations and associations (Mesulam 2000). They are believed to operate as gateways for integrating and accessing diffusely stored information. Increased excitability in these areas which intervene in higher order processing and integration of information could underlie the complex cognitive modifications reported by users such as novel associations, insights, and revelations. It seems reasonable to assume that direct excitatory actions at these key structures can effectively modify the flow of information between regions and consequently modify the ongoing mental activity.

7 Structural Brain Modifications in Long-Term Users

A recent study we conducted in long-term ayahuasca users provides additional support for the involvement of the high-order association cortex in the effects of ayahuasca (Bouso et al. in press). We obtained high-definition structural images of the brain from 22 users of ayahuasca and 22 controls matched for age, sex, years of education, and two intelligence measures, verbal and fluid IQ. We then compared the cortical brain layer in the two groups, and we also tested the participants for neuropsychological performance. The rationale behind this study was data from pharmacological studies that showed that psychedelic $5\text{-}HT_{2A}$ agonists, such as DMT, stimulate neurotrophic factors (Gewirtz et al. 2002), and transcription factors (Frankel and Cunningham 2002; González-Maeso et al. 2007), associated with synaptic plasticity. By comparing the structural images, we expected we would detect areas of the brain where structural changes such as increased dendritic arborization, enhanced vascularization, and glial cell proliferation might have occurred.

Interestingly, the analysis found differences in cortical thickness (CT) in anterior and posterior brain midline structures, specifically in the anterior and posterior cingulate cortices. Whereas CT had increased in the ACC, thinning was observed in the PCC (see Fig. 3). In the latter, the degree of thinning showed a correlation with lifetime ayahuasca intake. Given that the study was cross-sectional rather than longitudinal, we cannot establish a causal relationship between ayahuasca and the observed modifications, although the data indicate they are closely related. It is of note that the mentioned structural changes were observed in the absence of any impairment in neuropsychological tasks. In fact, ayahuasca users performed better than controls in the two-back test (a measure of working memory), in the Wisconsin Card Sorting Test (a measure of executive function), and in the task-switching task (a measure of set shifting) (Bouso et al. in press). Increased CT in the ACC, an area involved in attention and cognitive control, could explain the better performance in these tasks, a finding previously observed in experienced ayahuasca users (Bouso et al. 2012, 2013).
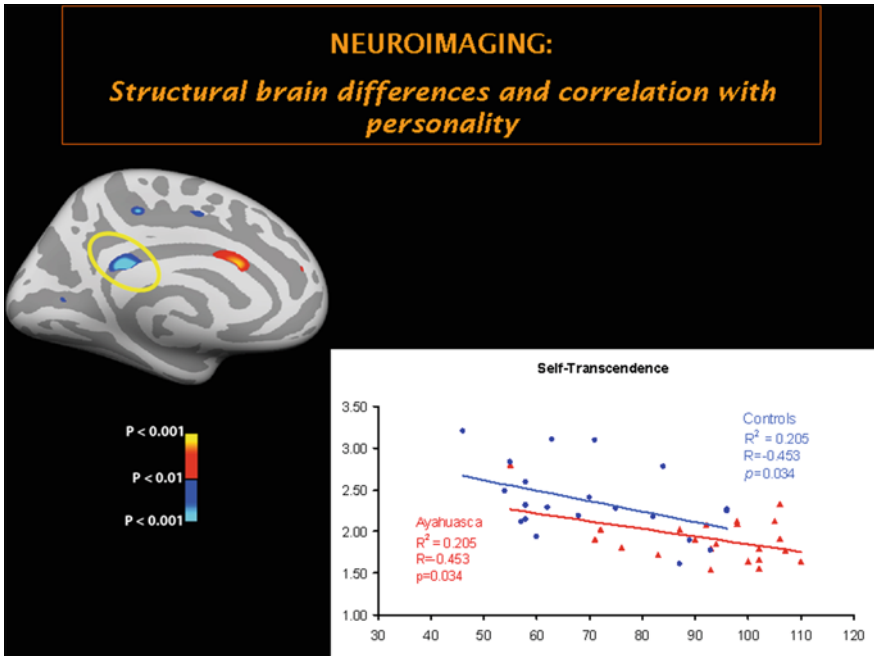
Fig. 3 Results of the structural analysis of T1 magnetic resonance images. The maps show areas of significant cortical thickness (CT) differences between ayahuasca users and controls displayed onto an inflated cortex. Regions with significantly lower CT in the ayahuasca group are shown in cool colors (*blue–cyan*), and regions with significantly higher CT appear as warm colors (*red–yellow*). Note that CT in the posterior cingulate cortex shows an inverse correlation with the personality dimension of self-transcendence

Another interesting aspect of the CT study was that changes in the PCC were associated with differences in personality between the two samples. The ayahuasca users scored higher in self-transcendence (ST) than controls, and scores showed a negative correlation with CT in the PCC. ST is a character dimension of the TCI personality questionnaire developed by Cloninger et al. (1993). It measures the individual's degree of religiousness and spirituality. A possible role for the PCC mediating this facet of personality is of particular interest. The PCC is a key region within the default mode network or DMN, a series of functionally connected structures that has been associated with intimate the sense of self (Cavanna and Trimble 2006). Research in the 1960s showed that psychedelic experiences could be profound and lead to a more spiritual and less materialistic attitude. Our study suggested that these personality changes could have a neural basis and highlighted the involvement of the medial aspects of the frontal and parietal lobes in the (long-term) effects of ayahuasca and potentially in the effect of other psychedelics (Fig. 4).
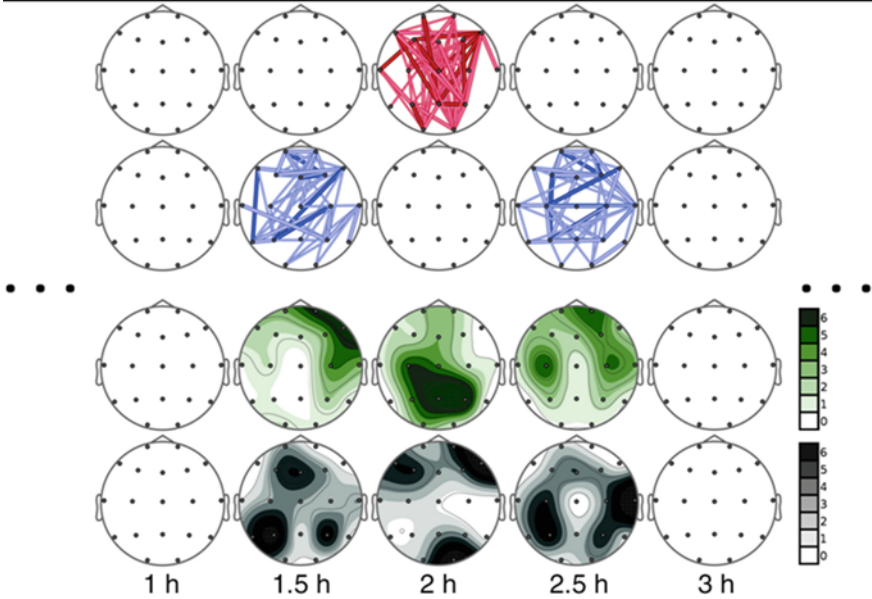
Fig. 4 Results of the transfer entropy (TE) analysis. The *first two rows* show maps of significant changes in connections between the corresponding electrodes. Warm colors indicate significant increases (*first row*), and cold colors (*second row*) indicate significant decreases. Thick dark-colored connections indicate statistically significant changes with *p*-values lower than 0.01, whereas thick and thin light-colored connections indicate *p*-values lower than 0.05 and 0.1, respectively. The *third* and *fourth rows* show the directionality maps depicting the number of outgoing (in *green*) or incoming (in *gray*) connections for each electrode. Note the decrease in anterior-to-posterior information transfer at 1.5 and 2.5 h and the increase in posterior-to-anterior information transfer at 2 h

8 Functional Connectivity of Brain Oscillations

The structural study mentioned above provided evidence of the involvement of both anterior and posterior brain regions in the effects of ayahuasca. In our most recent study, we corroborated this finding, reconciling the seemingly contradictory results of the initial SPECT and electrical source location studies. We assessed how ayahuasca modifies the normal flow of information within the brain during its acute effects. To do so, we studied the coupling of electrical signals using transfer entropy. Transfer entropy is a mathematical measure of functional connectivity based on information theory that is model-free and takes into account both the linear and nonlinear components of signals. This measure can be applied to

electrical brain oscillations; it identifies causal relationships and allows inferences regarding the directionality of information flow. Transfer entropy from y to x measures the amount of uncertainty reduced in the future values of x by taking into account the past values of y, as compared to when only the past values of x are used. Mathematically this can be expressed as:

$$\text{TE}_{y \to x} = \sum_{x_{n+1}} p(x_{n+1}, x_n, y_n) \log \left(\frac{p(x_{n+1}, x_n, y_n) p(x_n)}{p(x_n, y_n) p(x_{n+1}, x_n)} \right)$$

When the time series associated with spontaneous brain electrical activity was analyzed using TE, results showed significant ayahuasca-induced changes in the coupling of signals between anterior and posterior recording sites. Frontal sources decreased their influence over central, parietal, and occipital sites. At the same time, sources in posterior locations increased their influence over signals measured at anterior locations (see Fig. 3). These modifications were maximal at the time point when DMT plasma levels were highest and subjective effects most intense.

These findings indicate that ayahuasca modifies the functional coupling of oscillatory signals along the anterior-to-posterior axis. Given the asymmetric nature of transfer entropy, the results indicate a decrease in the predictability of activity in posterior areas based on information available at anterior sites. They also indicate an increase in the predictability of activity in anterior areas when information at posterior sites is taken into account. Thus, the dynamics of the interaction between the higher order frontal regions and the more sensory-selective posterior areas is modified. These results are in line with findings in a functional MRI study in which functional connectivity between the frontal and parietal cortices was also found to be reversed under ayahuasca (de Araujo et al. 2012). Thus, under the effects of ayahuasca, the normal hierarchical structure regulating the flow of information is altered. Top-down or feedback control is reduced and bottom-up or feed-forward information is increased. This temporary disruption of normal information processing leads to a change in the "internal dialogue" and the experience of the world, as explained below.

9 A Model of Psychedelic Drug Effects on the Human Brain

Using the comprehensive data we have gathered using several techniques, we propose a model of how ayahuasca and, by extension, other serotonergic psychedelics work on the human brain. As shown above, these compounds target association cortex, that is responsible for the secondary processing of sensory information and, more importantly, higher level areas binding information from different sensory modalities and data stored in memory. As we have seen from the TE analysis, ayahuasca transiently disrupts the hierarchies governing the flow of information during normal consciousness.

Classical models of brain function have focused mainly on the bottom-up or feed-forward flow of information from primary sensory areas to the modality-specific association areas and from there to the multimodal association cortex that combines all incoming elements into a meaningful whole. However, more recent views also take into account top-down or feedback projections from hierarchically high nodes to low nodes in the network (see Fig. 5a). These models propose that top-down control also plays a significant role in the interpretation of sensory information. Thus, the experience of reality would involve feed-forward and feedback loops, rendering the interpretation of incoming signals (both external and internal) dependent on previous knowledge and expectations (Friston 2005; Mesulam 2008). In this framework, each level in the hierarchy sends backward projections that modulate incoming information based on pre-established constraints. The whole network would be under the executive control of the frontal cortex.

We propose that the interaction of a psychedelic with this network will reduce top-down constraints and increase excitability in various levels of the hierarchy. In the modified state of awareness induced by ayahuasca, weak endogenous activity, be it sensory or mnestic, will be able to reach higher levels in the hierarchy and become consciously perceptible. This would explain the endogenous visual and auditory phenomena reported for psychedelics and the distortion of external stimuli. Even in the absence of strong external sensory input (eyes closed), visions will emerge due to increased activity in brain areas processing visual information. The higher excitability in multimodal brain areas such as the posterior association cortex, the cingulate, and the MTL (Riba et al. 2004, 2006) would explain the rapidly evolving modifications in thought content and the novel associations that stand as characteristic features of they psychedelic experience. Mismatch signals or "discrepancies" with predictions will be sent upstream, and a constant updating of these predictions will be necessary in the brain's attempt to "make sense" of the experience. The novelty and spontaneity of the thought associations occurring, the facilitation of insight, and the new perspective gained into a given matter are dramatic effects of psychedelics. These sensations of novelty and deep meaning are sometimes so compelling that they are experienced as revelations. See for example the compilations by Metzner 1999, McKenna 2000.

Individual differences such as personality, mood, and prior experience with psychedelics will be part of each person's pre-established constraints and will consequently modulate the experience. The degree to which each person lets go of the cognitive grip exerted by frontal executive control will also influence the experience and could explain the common lack of effects reported by users when ayahuasca is taken for the first time. Directing attention to external cues such as the ritual and other participants or the desire to remain "in control" frequently leads to experiencing very weak effects or none at all. Typically, in subsequent sessions, the participant lets go and prominent effects are finally experienced.
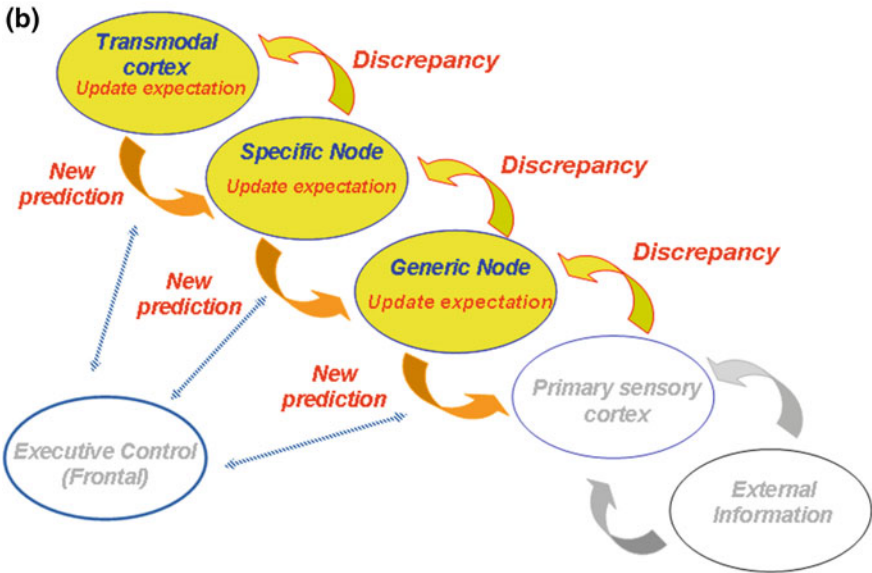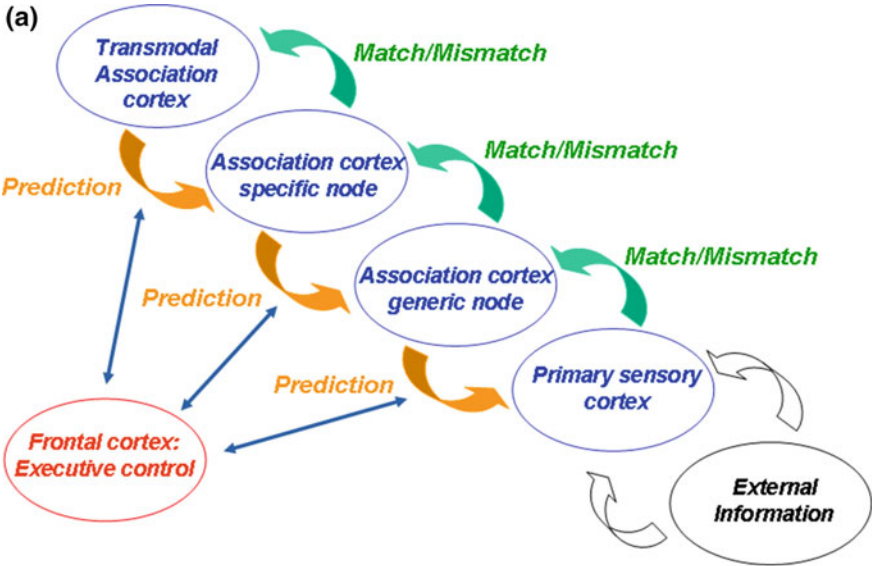
◀**Fig. 5** Model of ayahuasca and other psychedelics on the human brain. **a** Bottom-up progress of external sensory information from sensory-specific primary cortex to secondary association and multimodal cortex under physiological conditions. Top-down constraints send inferences to lower order nodes regarding the nature of the incoming information. Depending on the match or mismatch with the inference, an upward error message is sent and an updated prediction generated. The whole inference–prediction error is governed by executive control mechanisms at the frontal cortex. Adapted from (Mesulam 2008). **b** Under ayahuasca and other psychedelics, secondary association and multimodal cortex shows enhanced excitability. The nature of information traveling up the hierarchy does not fit top-down predictions, and an error message (discrepancy) is sent upwards. New updated predictions need to be generated. Iterations can be maintained even in the absence of incoming external information. A decrease in overall executive control exerted by the frontal cortex leads to a breakdown of "constancies" and a modification of internal dialogue. Elements of information can be associated in unusual ways and new "meaning" ascribed to sensory inputs and internal thoughts. The subjective state generated by the psychedelic is characterized by its novelty and sometimes by its overwhelming nature

10 Concluding Remarks

The use of nuclear medicine and neurophysiological techniques has allowed us to identify brain structures targeted by ayahuasca areas and the dynamics underlying the cognitive effects induced by the tea. By acting on key nodes of brain association cortex, ayahuasca modifies the flow of information through the brain. The temporary modification of neural hierarchies induces dramatic changes in cognition. The capacity to provide a new outlook on internal and external reality constitutes the uniqueness of ayahuasca and other psychedelics and distinguishes them from all other psychotropic drugs.

Literature Cited

Borhegyi SF (1961) Miniature mushroom stones from Guatemala. Am Antiq 26:498–504

Cooper JM (1949) Stimulants and narcotics. In: Handbook of South American Indians, vol 5. Bureau of American Ethnology Bulletin # 143. Smithsonian Institution, Washington

Dale GD (1991) The Santo Daime doctrine: an interview with Alex Polari de Alverga. Shaman's Drum 22:30–41

Daly JW, Witkop B (1971) Chemistry and pharmacology of frog venoms. In: Bücherl W, Buckley EE (eds) Venomous animals and their venoms, vol. II. Academic Press, London

Davis W, Weil AT (1992a) *Bufo alvarius*: a potent hallucinogen of animal origin. J Ethnopharmacol 41:1–8

Davis W, Weil AT (1992b) Identity of a new world psychoactive toad. Ancient Mesoamerica 3:51–59

Der Marderosian AH, Pinkley HV, Dobbins MF (1968) Native use and occurrence of N,N-dimethyltryptamine in the leaves of Banisterioposisrusbyana. Am J Pharm 140:137–147

Emboden W (1979) Narcotic plants. Collier Books, New York

Erowid.org (2001a) A list of the (186) known psilocybian mushrooms. https://www.erowid.org/plants/mushrooms/mushrooms_info12.shtml. Accessed 27 Dec 2014

Erowid.org (2001b) Legal status of ayahuasca in Brazil. http://www.erowid.org/chemicals/ayahuasca/ayahuasca_law6.shtml. Accessed 29 Dec 2014

Erowid.org (2006) UDV wins Supreme Court decision on preliminary injunction http://www.erowid.org/chemicals/ayahuasca/ayahuasca_law22.shtml. Accessed 29 Dec 2014

Erowid.org (2012) Santo Daime wins court decision http://www.erowid.org/chemicals/ayahuasca/ayahuasca_law24.shtml. Accessed 29 Dec 2014

Fish MS, Johnson NM, Horning EC (1955) *Piptadenia* alkaloids—indole bases of *Piptadenia-peregrina* (L.) Benth and related species. J Am Chem Soc 77:5892–5895

Gates B (1979) New names in *Banisteriopsis* and *Diplopterys* (Malpighiaceae) of the Guayana highland. Brittonia 31:108–109

Guzmán G, Allen JW, Garrtz J (2000) A worldwide geographical distribution of the neurotropic fungi, an analysis and discussion. AnnalideiMuseocivico - Rovereto, Italia. 14:189–280 (in English)

Guzmán G, Ramírez-Guillén F, Torres G (2004) The hallucinogenic species of Psilocybe (Fr.) P. Kumm (Agaricomycetideae) in Colombia, their Indian use, new records, and new species. Int J Med Mushrooms 6:83–93

Heim R, Hofmann A (1958) Isolement de la Psilocybine à partir du Strophariacubensis Earle etd'autresespèces de champignons hallucinogènesmexicainsappartenant au genre Psilocybe. In: Extrait des Comptesrendus des séances de l'Académie des Sciences, t. 247:557–561

Holmstedt B, Lindgren JE (1967) Chemical constituents and pharmacology of South American snuffs. In: Efron DH, Holmstedt B, Kline NS (eds) Ethnopharmacologic search for psychoactive drugs, U.S. Public Health Service Publication # 1645. U.S. Government Printing Office

Kennedy AB (1982) Ecce Bufo: the toad in nature and in Olmec Iconography. Curr Anthropol 23:273–290

Luna LE (1984) The concept of plants as teachers among four mestizo shamans of Iquitos, northeastern Peru. J Ethnopharmacol 11:135–156

Macrae WD, Towers GH (1984a) *Justiciapectoralis*: a study of the basis for its use as a hallucinogenic snuff ingredient. J Ethnopharmacol 12:93–111

Macrae WD, Towers GH (1984b) An ethnopharmacological examination of *Virolaelongata* bark: a South American arrow poison. J Ethnopharmacol 12:75–92

McKenna DJ, Luna LE, Towers GH (1995) Biodynamic constituents in *Ayahuasca* admixture plants: an uninvestigated folk pharmacopoeia. In: von Reis S, Schultes RE (eds) Ethnobotany: evolution of a discipline. Dioscorides Press, Portland

McKenna DJ, Towers GH (1984) Biochemistry and pharmacology of tryptamine and ß-carboline derivatives: a minireview. J Psychoactive Drugs 16:347–358

McKenna DJ, Towers GH, Abbott FS (1984a) Monoamine oxidase inhibitors in South American hallucinogenic plants Pt. II: constituents of orally active Myristicaceous hallucinogens. J Ethnopharmacol 12:179–211

McKenna DJ, Towers GH, Abbott FS (1984b) Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and ß-carboline constituents of Ayahuasca. J Ethnopharmacol 10:195–223

Naranjo P (1995) Archeology and psychoactive plants. In: von Reis S, Schultes RE (eds) Ethnobotany: evolution of a discipline. Dioscorides Press, Portland

Ott J (1998) Pharmahuasca, anahuasca, *vinho de Jurema*: human pharmacology of oral DMT + harmine. In: Müller-Ebeling C (ed) Special: psychoactivity. Yearbook for Ethnomedicine and the study of consciousness 6/7 (1997–1998). VWB, Berlin

Ott J (2001) Pharmañopo-psychonautics: human intranasal, sublingual, intrarectal, pulmonary and oral pharmacology of bufotenine. J Psychoactive Drugs 33:273–281

Pachter IJ, Zacharius DE, Ribeiro O (1959) Indole alkaloids of *Acer saccharinum* (the silver maple), *Dictylomaincanescens*, *Piptadeniacolubrina*, and *Mimosa hostilis*. J Org Chem 24:1285–1287

PInkley HV (1969) Plant admixtures to *ayahuasca*, the South American hallucinogenic drink. Lloydia 32:305–314

Rivier L, Lindgren J (1972) *Ayahuasca*, the South American hallucinogenic drink: ethnobotanical and chemical investigations. Econ Bot 29:101–129

Schultes RE (1969) *Virola* as an orally administered hallucinogen. Harvard Bot Mus Leaflets 22:229–240

Schultes RE (1970a) The New World Indians and their hallucinogenic plants. Morris Arboretum Bull 21:3–14

Schultes RE (1970b) The plant kingdom and hallucinogens (Part III). Bull Narc XXII:25–53

Schultes RE, Holmstedt B (1968) The vegetal ingredients of the Myristicaceous snuffs of the Northwest Amazon. Rhodora 70:113–160

Schultes RE, Hofmann A (1981) The botany and chemistry of hallucinogens, 2nd edn. Charles C. Thomas Publishers, Springfield, Ill

Schultes RE, Hofmann A (2001) Plants of the gods: their sacred, healing, and hallucinogenic powers. Healing Arts Press, Randolph

Smith TA (1977) Tryptamine and related compounds in plants. Phytochemistry 16:171–175

Torres CM (1995) Archeological evidence for the antiquity of psychoactive plant use in the central Andes. Ann Mus Civ Revoreto 11:291–326

Torres CM, Repke DB (2006) *Anadenanthera*: visionary plant of ancient South America. Haworth Herbal Press, Routledge

Torres CM, Repke DB, Chan K, McKenna D, Llagostera A, Schultes RE (1992) Botanical, chemical, and contextual analysis of archaeological snuff powders from San Pedro de Atacama, Northern Chile. Curr Anthropol 32:640–649

Vepsäläinen JJ, Auriola S, Tukiainen M, Ropponen N, Callaway JC (2005) Isolation and characterization of yuremamine, a new phytoindole. Planta Med 71:1053–1057

Wassén SH (1967) Anthropological survey of the use of South American snuffs. In: Efron DH, Holmstedt B, Kline NS (eds) Ethnopharmacologic search for psychoactive drugs, U.S. Public Health Service Publication # 1645. U.S. Government Printing Office

Wassén SH (1964) Some general viewpoints in the study of native drugs especially from the West indies and South America. Ethnos 1–2:97–120

Wasson RG (1967) Fly agaric and man. In: Efron DH, Holmstedt B, Kline NS (eds) Ethnopharmacologic search for psychoactive drugs, U. S. Public Health Service Publication # 1645. U.S. Government Printing Office

Wasson RG (1980) The wondrous mushroom: mycolatry in Mesoamerica. McGraw-Hill Book Company, New York

Wasson RG, Wasson V (1957) Seeking the magic mushroom. Life Magazine May 13, 1957

Weil AT, Davis W (1994) Bufo alvarius: a potent hallucinogen of animal origin. J Ethnopharmacol 41(1–2):1–8

References

Bouso JC, Fábregas JM, Antonijoan RM, Rodríguez-Fornells A, Riba J (2013) Acute effects of ayahuasca on neuropsychological performance: differences in executive function between experienced and occasional users. Psychopharmacology (Berl) 230:415–424

Bouso JC, González D, Fondevila S, Cutchet M, Fernández X, Ribeiro Barbosa PC, Alcázar-Córcoles MÁ, Araújo WS, Barbanoj MJ, Fábregas JM, Riba J (2012) Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of ayahuasca: a longitudinal study. PloS One 7:e42421

Bouso JC, Palhano-Fontes F, Rodríguez-Fornells A, Ribeiro S, Sanches R, Crippa JA, Hallak JEC, de Araujo DB, Riba J (in press) Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. Eur Neuropsychopharmacol

Cavanna AE, Trimble MR (2006) The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129:564–583

Cloninger CR, Svrakic DM, Przybeck TR (1993) A psychobiological model of temperament and character. Arch Gen Psychiatry 50:975–990

De Araujo DB, Ribeiro S, Cecchi GA, Carvalho FM, Sanchez TA, Pinto JP, de Martinis BS, Crippa JA, Hallak JEC, Santos AC (2012) Seeing with the eyes shut: neural basis of enhanced imagery following Ayahuasca ingestion. Hum Brain Mapp 33:2550–2560

Frankel PS, Cunningham KA (2002) The hallucinogen d-lysergic acid diethylamide (d-LSD) induces the immediate-early gene c-Fos in rat forebrain. Brain Res 958:251–260

Friston K (2005) A theory of cortical responses. Philos Trans R Soc Lond B Biol Sci 360:815–836

Gewirtz JC, Chen AC, Terwilliger R, Duman RC, Marek GJ (2002) Modulation of DOI-induced increases in cortical BDNF expression by group II mGlu receptors. Pharmacol Biochem Behav 73:317–326

González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, Lira A, Bradley-Moore M, Ge Y, Zhou Q, Sealfon SC, Gingrich JA (2007) Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. Neuron 53:439–452

Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, Arning C, Thelen B, Spitzer M, Kovar KA, Hermle L, Büll U, Sass H (1999) Neurometabolic effects of psilocybin, 3,4-methylenedioxy-ethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 20:565–581

Hermle L, Fünfgeld M, Oepen G, Botsch H, Borchardt D, Gouzoulis E, Fehrenbach RA, Spitzer M (1992) Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: experimental psychosis as a tool for psychiatric research. Biol Psychiatry 32:976–991

McKenna DJ (2000) An unusual experience with "hoasca": a lesson from the teacher. In: Ayahuasca reader, encounters with the Amazon's sacred vine, pp 154–157. Synergetic Press, Santa Fe

Mesulam M (2008) Representation, inference, and transcendent encoding in neurocognitive networks of the human brain. Ann Neurol 64:367–378

Mesulam MM (2000) Behavioral neuroanatomy: large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In: Mesulam MM (ed) Principles of behavioral and cognitive neurology. Oxford University Press, New York, pp 1–120

Metzner R (1999) Ayahuasca: hallucinogens, consciousness and the spirit of nature. Thunder's Mouth Press, New York

Muthukumaraswamy SD, Carhart-Harris RL, Moran RJ, Brookes MJ, Williams TM, Errtizoe D, Sessa B, Papadopoulos A, Bolstridge M, Singh KD, Feilding A, Friston KJ, Nutt DJ (2013) Broadband cortical desynchronization underlies the human psychedelic state. J Neurosci 33:15171–15183

Riba J, Anderer P, Jané F, Saletu B, Barbanoj MJ (2004) Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low-resolution electromagnetic tomography. Neuropsychobiology 50:89–101

Riba J, Romero S, Grasa E, Mena E, Carrió I, Barbanoj MJ (2006) Increased frontal and paralimbic activation following ayahuasca, the pan-Amazonian inebriant. Psychopharmacology (Berl) 186:93–98

Roland PE, Gulyás B (1994) Visual imagery and visual representation. Trends Neurosci 17:281–287; discussion 294–297

Sakai K, Miyashita Y (1994) Visual imagery: an interaction between memory retrieval and focal attention. Trends Neurosci 17:287–289

Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J (1997) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16:357–372