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Cult-Hoasca: A Model for Schizophrenia.

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Abstract

The experimental psychosis observed after drinking *Hoasca* reproduces the pathologic transmethylation theory of schizophrenia. The occurrence of *N*,*N*-dimethyltryptamine (DMT) in the *Hoasca* drink and in the urine samples of subjects supports now that the biological and neuropsychological effects are produced by this methylated indolealkylamine assisted by the β-carboline derivatives. These results further confirm that the urinary hallucinogenic compounds detected in healthy subjects (post-*Hoasca*, but not before) are the same as those found in the urine samples of acute psychotic unmedicated patients. The ability of *Hoasca* to modulate serotonergic receptors was evaluated, and thereby to which extent cortisol, prolactin and serotonin levels as well as perceptual and cognitive processes were affected. The degree of *Hoasca* monoamine oxidase (MAO) inhibition was directly correlated with the concentration of MAO- inhibiting β–carbolines. The additive combination of harmine and tetrahydroharmine (THH) accounts for the MAO inhibition exhibited by *Hoasca***.**

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Schizophrenia and affective disorders such as mania and depression are involved in a generic term 'psychosis', which is then used to describe usually 'functional', *e.g.* of unknown origin, and sometimes 'organic' disorders, being thus associated with morphological, metabolic or endocrinological disturbances. Nevertheless, the aethiology of schizophrenia self is not fully understood[1]. In order to find a rational explanation for schizophrenia a variety of hypotheses have been attempted over the years. One of them is the dopamine theory[2] based on the observation that all the drugs used to treat psychosis are dopamine antagonists. This dopamine theory states that the symptoms of schizophrenia are due to overactivity of dopamine systems in the brain. Consequently, any tendency to increase dopaminergic activity will exarcerbate the symptoms. Controversial viewpoints have been reported [3]. Another well-known theory is the so-called transmethylation theory of schizophrenia[4,5], which seems to fit the observed facts related to indolealkylamines[6].

According to the transmethylation hypothesis of schizophrenia[6-8] , as a result of enzymatic disturbances, schizophrenic patients produce high amounts of *N*,*N*-dimethyl indolealkylamines, such as bufotenin (5-hydroxy-*N*,*N*-dimethyltryptamine), 5-methoxy-*N*,*N*-dimethyltryptamine and *N*,*N*-dimethyltryptamine (DMT), which are strong hallucinogenic compounds for healthy subjects. These psychomimetic substances are preferential substrates for monoamine oxidase (MAO) [9], in a way that when a high single dose is given, thirty minutes later only 1% can be recovered from blood and/or urine. In spite of this high turn-over, *N,N*-dimethyl indolealkylamines have been detected in urine of psychiatric patients, not only schizophrenics[10-12].

We have previously related in agreement with other authors, the occurrence of these compounds with perceptual disturbances, remarking the fact that true hallucinations together with subtle perceptual disturbances are present in several entities. Consequently, *N,N*-dimethyl indolealkylamines are playing the role of State Markers from clinical and subclinical psychoses more than being a trait of any diagnostic category.

Accumulation of *N,N*-dimethyl indolealkylamines may be due to an acceleration of their production rate or, and most probably, to a decrease in the kinetics of the enzyme MAO [9] responsible for the breakdown of the *N,N*-dimethyl indolealkylamines. A variety of reports on a decreased MAO activity in schizophrenia are known, thus in agreement with this theory. A decreased MAO activity allows the accumulation of *N*,*N*-dimethyl indolealkylamines, which are not necessarily produced within CNS, thus crossing blood brain barrier (BBB) and acting on central nervous system (CNS).

We found an experimental psychosis model that resembles the transmethylation hypothesis of schizophrenia, and unequivocally associates DMT to a psychotic state. This experimental model provides transient induced psychotic states in man, during which neuroendocrine and psychometric, sensory as well as behavioural conditions may be assessed, and the effects in subjects adequately analysed.

The psychosis caused upon drinking the hallucinogenic *Hoasca* drink is mainly due to the inhibition of the MAO enzyme. The *Hoasca* drink is prepared by boiling two plants, one, *Banisteriopsis caapi,* containing β–carbolines, which are strong natural MAO inhibitors, and the other, *Psychotria viridis* with high amounts of DMT. This particular combination reproduces in vivo what is supposed to occur under pathologic conditions of different psychoses.

This drug practice dates to the precolumbian times, and later was integrated into the ethnomedical traditions of the *mestizo* culture. Shamans have used it for healing, divination and as a magical tool. Religious ceremonies of Amazon natives are centered around the use of this psychoactive drink[13,14]. More recently its use has been spread to non-aboriginal syncretic religious movements, such as *Uniao do Vegetal* (UDV)[15] in Brazil, where the infusion is known as *Hoasca*, also *Hoasca* drink and *Ayahoasca*. Ethnobotanical and ethnochemical have been extensively discussed[16,17].

We were interested in studying this *Hoasca* drink and the plant materials used to prepare it. As this cult is not known in our country Argentina, the samples and plant material were kindly provided by the brazilian cult-members, to whom we are especially indebted.

Two different samples of *Hoasca*, types 1 and 2, were identified in our laboratories, different from those previously described[16,18]. But both contained nearly the same amount of alkaloids, 65 to 70 mg/100ml, the same β–carbolines to DMT relation, 6.5:1 and 7:1, nearly the same concentration of DMT (8.5 to 9.5 mg/100ml; *ca.* 0.5 mM), and both were devoid of 1-methyl-7-methoxy-3,4-dihydro-β–carboline (harmaline) or it was present only in traces. The main difference was the relative composition of the β–carbolines, 1-methyl-7-methoxy-1,2,3,4-tetrahydro-β–carboline (THH): 2-methyl-THH (*N*-Me-THH): 1-methyl-7-methoxy-β–carboline (harmine) being *ca.* 1:1:12 in type 1 and 3:3:1 in type 2.

Hoasca drink type 1 (Fig. 1) contained, in average, 0.065% w/v total alkaloids, t_R 15.72 min DMT (14.1%; 9.1 mg/100 ml), 19.70 min THH (6.5%; 4.2 mg/100ml), 19.83 min *N*-Me-THH (6.3%, 4.1 mg/100ml), 20.23 min harmaline (traces, < 0.1%) and 20.47 min harmine (73.1%; 47.5 mg/100 ml) (t_R refers to GC-MS). The other typical *Hoasca* drink type 2, in average contained, 0.070% w/v total alkaloids, t_R 15.73 min DMT (12.5%; 8.8 mg/100 ml), 19.65 min THH (37.8%; 26.5 mg/100ml), 19.80 min *N*-Me-THH (36.4%, 25.5 mg/100ml), and 20.58 min harmine (13.2.1%; 9.2 mg/100 ml).

Since the concentrations of β-carbolines and DMT in both *Hoasca* types were different from those previously reported as beverages of the Amazon[18], with nearly intermediate values, upon comparison of the constituents we concluded that **what is relevant is the relative concentration of β–carbolines and DMT**, and furthermore, the corresponding β–carboline levels required for producing MAO inhibition. The amounts of β–carbolines in the typical dose of these two types of *Hoasca* drinks are well below the threshold at which they are hallucinogens themselves (*ca.* 300-500 mg for harmaline and THH; *ca.* 1000 mg for harmine, and 400 mg for physical symptoms), but within the range for being highly selective inhibitors of MAO-A, the form for which serotonin (5-HT), and other tryptamines such as DMT, are the preferred substrates[9,19]. *In vitro* β–carbolines are MAO inhibitors at *ca*. 10mM, which is 2 to 3 orders of magnitude lower than the hallucinogenic dose. Moreover, the non-synergistic β-carboline mechanism makes necessary larger amounts of these compounds for

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hallucinogenic effect. Although both *Hoasca* types contained apparently low DMT levels, they are within the active range, which is lower under MAO inhibition than those reported for *i.m.* and *i.v.* administration[20, 21].

The selectivity of β–carbolines for MAO-A over MAO-B as well as their relatively lower affinity for liver MAO than for brain MAO explains why there are no risk of hypertensive crises *post*-ingestion of *Hoasca*, in particular in the case of consumers of tyramine-containing foods.

Urine samples were analysed searching for DMT in controls, new and usual consumers, and drug-free acute schizophrenic patients (Fig. 1). Results showed that urine samples of controls and new consumers *prior* to *Hoasca* intake were devoid of DMT, while new and common users showed urinary DMT occurrence after drinking *Hoasca*, which was positively correlated with the perceptual alterations. *Prior* to *Hoasca* intake, DMT was detected only in the urine samples of usual consumers of *Hoasca*. Finally, drug-free acute schizophrenic patients showed an appreciate amount of urinary DMT (t_R 15.53 min; Fig. 1).

Serotonin, prolactin and cortisol were analysed in blood samples *prior* to and after *Hoasca* intake in order to obtain information about the serotonergic response to *Hoasca*.

In this study we used the highly specific double antibody radioimmunoassay to prevent the interferences observed with less specific antisera used in other RIA procedures[22].

Sequential measures of prolactin and cortisol showed significant responses[20,21,23,24] in blood levels nearly 1 h after *Hoasca* intake in agreement with the beginning of the hallucinogenic effect, and subjects could be grouped accordingly. New consumers of *Hoasca* showed increasing neuroendocrine response, correlating with a pronounced perceptual response, and in agreement with previous dose-dependently studies with synthetic DMT and other hallucinogens, such as lysergic acid diethylamide (LSD), which are acting mainly *via* serotonin 5-HT2 receptors. Neuroendocrine blood levels and heart rate responses significantly decreased, similar to synthetic DMT administration. The lack of psychological tolerance supported a role for DMT in naturally-occurring psychoses[25].

Usual consumers showed instead a continued raise of both cortisol and prolactin, together with a decrease in serotonin. In all cases the response was short in time, but could be maintained with a second intake 1 h after the first drink. New and usual consumers as well as controls evidenced expected different perceptual effects with values in agreement with the individual biochemical responses, indicating that psychedelic effects may be required to perturb biological effects. All these effects may be mediated by 5-HT-2A, 5-HT-2C, or 5-HT-1A subtype activation, as in the case of synthetic DMT[20].

The determination of the receptor subtype accounting for the effects of psychedelic compounds is hampered by the fact that 5-HT-2 receptors are pharmacologically and structurally closely related[24], *e.g.* 5-HT2, 5-HT1C and the recently cloned 5-HT2F, which were proposed to be recalled 5-HT2A, 5-HT2C and 5-HT2B, respectively. The human anatomical studies on the distribution of serotonin receptors suggest that the possible targets for the action of hallucinogenic drugs is widespread, and could be associated with neocortical, limbic and also with mechanisms mediated through the basal ganglia in the human brain[26].

Results from Hoffer & Osmond Test (HOD test) and neuropsychological evaluation[6-8] are shown in Fig. 2 and 3.

No effects were reported up to 35 minutes after *Hoasca* intake, at this moment one group of subjects reported marked perceptual alterations in the sense of distortion of true perceptions, mainly visual. No auditive hallucinations were reported at any time by the subjects. Some subjects experienced strong perceptual alterations (Fig. 2), while others only reported slight time-space disorientation. All evidenced mood changes with unmotivated laughing. Comparison of the results showed that *Hoasca* had slight effects on attention and memory processes and stronger effects on visuospatial construction. Wais-R Digit Symbol Test (DSY) decreased significatively after *Hoasca*, meaning interference with sustained attention. Buschke Selective Reminding Task showed a decrease in Consistent Long Term Retrieval (CLTR) but not significative changes in Long Term Storage (LTS), Long Term Retrieval (LTR) and Total Recall (TR). Visuoperceptual processes were significatively affected, as shown by the results of the Complex-Figure (Ray-Osterrieth) [8] (Fig. 3).

The perceptual distortions were visual, light flashes, colours, abstract forms and figures, illusions, geometrical patterns, moving very fast, having sometimes very deep emotional content and connotation. Subjects were unable to keep attention focused on any utside event. There was an enhanced dependence on the environment for structure and for symbolic meanings, and increased association. It is outstanding the rapid onset and the short-lasting effect.

Hoasca results in a well-controlled hallucinogenic state compared with parenteral synthetic DMT administration.

β-Carbolines of *Hoasca* are strong MAO inhibitors, thus preventing DMT to be destroyed by liver MAO. Therefore, DMT reaches and crosses blood brain barrier, exerting 5-HT2 agonist effects on the CNS. This 5-HT2 agonism accounts for the biological and behavioral disturbances induced by the drink.

Our previous papers [6-8] were related to the occurrence of DMT in urine from psychiatric patients and the level of perceptual alterations. Also shown here due to the strong effects on perception because of drinking *Hoasca*.

Our neuropsychological findings support that *Hoasca* affects more visuospatial functions due to subtle perceptual interference, than cognitive processes. This was confirmed here by HOD Test results, which clearly recorded perceptual alterations in all groups of subjects, except controls.

Biological parameters supported a serotonergic agonism, mainly over 5-HT2 receptors, which have been involved in a regulatory effect on synthesis and release of DA, and allows to explain the raise in prolactin levels. Serotonin has also a regulatory effect on hypothalamic cortisol regulation, in a way that 5-HT2 receptors agonism can raise cortisol levels. Both, at least, in first-time consumers.

Recently and especially in the last years interest was focused on serotonergic mechanisms in psychoses pathogenesis in relation to the mechanism of action of the so called 'Atypical Antipsychotics' [27], *e.g.* clozapine, risperidone, ritanserine. However, the Transmethylation Hypothesis of Schizophrenia proposed this participation more than 40 years ago [4], receiving then little attention. Part of the antipsychotic effect is related to blocking the DMT activity on the 5-HT2 receptor.

Nevertheless, a strong relationship between 5-HT and DA neurons activity has been reported[28]. *Hoasca* represents an

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experimental psychosis with common features with the transmethylation hypothesis of schizophrenia.

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Figure 1

Examples of GC/MS of Hoasca tea, leaves of *P. viridis*, Stems of *B. caapi*, probandi and patients

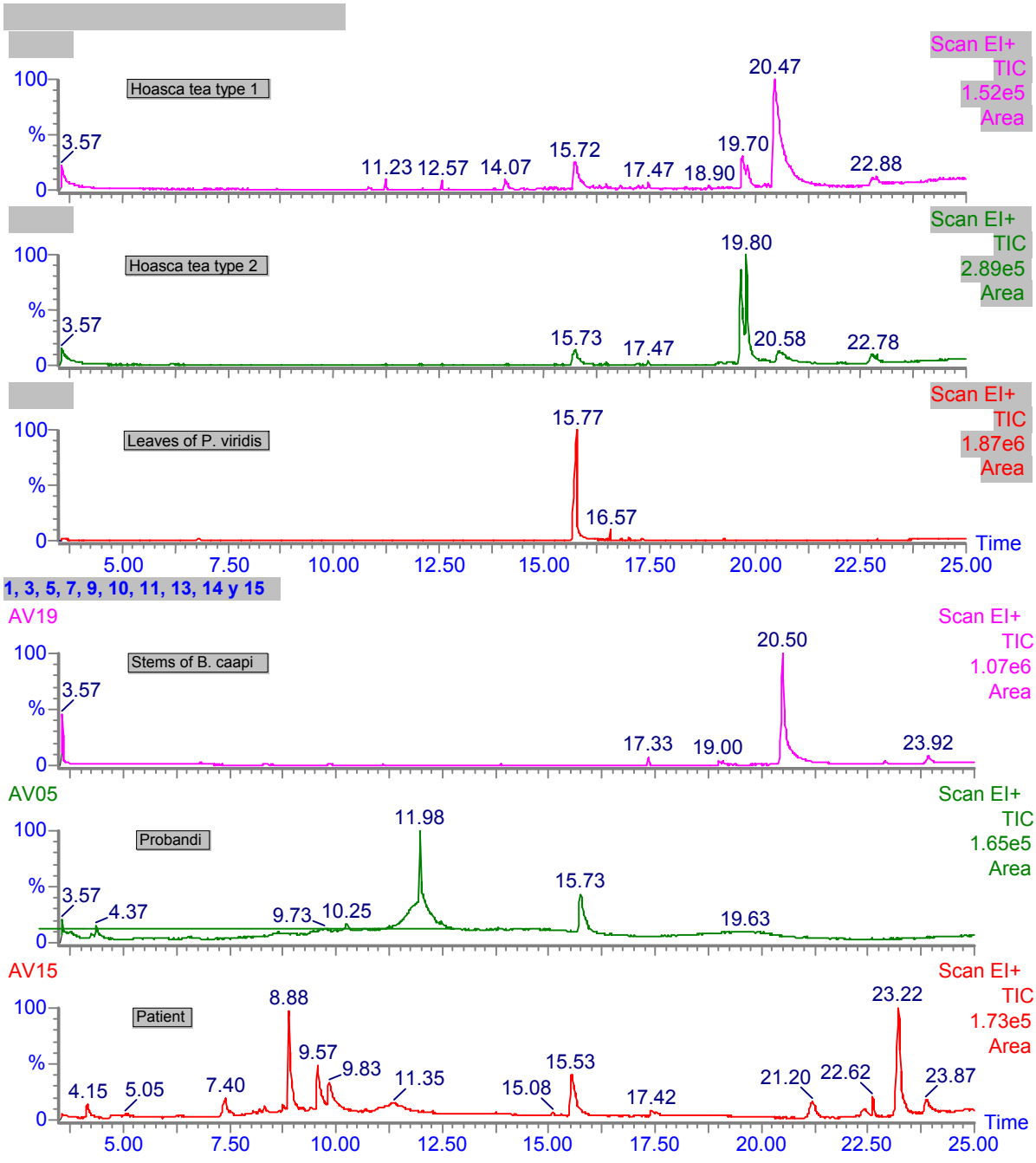

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Figure 2

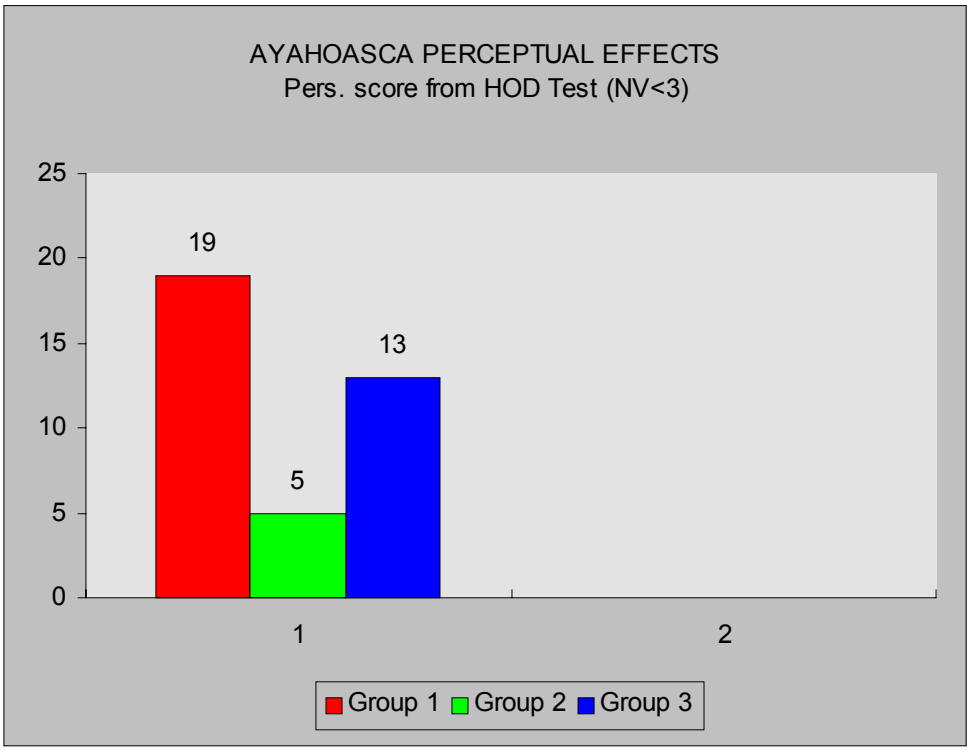
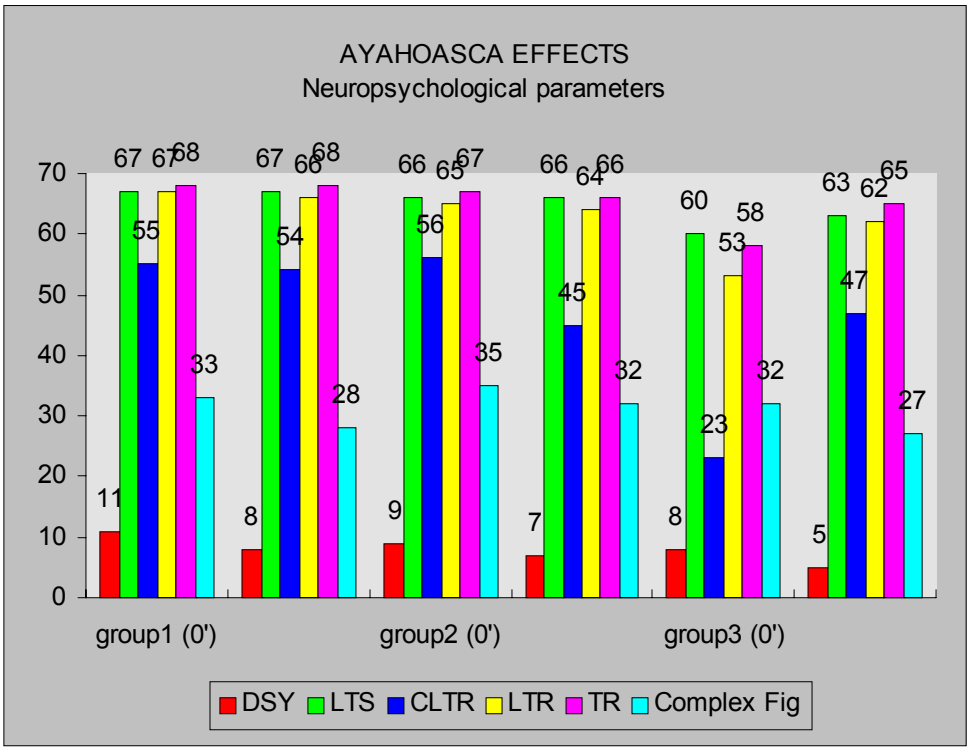


Figure 3



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Methods

The plant material was composed of stems of *Banisteriopsis caapi* (Spruce ex Griseb.) Morton (Malpighiaceae) and leaves of *Psychotria viridis* Ruiz et Pavon (Rubiaceae), from which voucher specimens were deposited. A standard *per-os* dose accounted for *ca.* 100 ml of *Hoasca* prepared by the UDV brazilian members. DMT as well as commercial samples of harmine and harmaline were used as standards. TLC and HPTLC were performed on silica gel GF_{254} glass-backed precoated plates and CH_2Cl_2-EtOH-28% NH_4OH (85:14:1, in volume) as solvent and the spots were visualized by spraying with Dragendorff's reagent.

Acute psychological and physiological effects of *Hoasca* drink were assessed in subjects. Experienced test volunteers refer to cult-members, who consume the drink anyway as members of these religious groups. Other volunteers refer to *Hoasca* non-users, who drank the beverage for the first time or were as controls without knowing their role. All of them were aware of the meaning of the experience, drug-free and no concomitant disease was present. *Prior* to *Hoasca* intake all were subjected to HOD test to assess the presence of perceptual alterations, and they were neuropsychologically evaluated, to check memory processes and visuospatial coordination. These tests were also taken one hour after drinking *Hoasca*. Tests used were: Wais-R Digit Symbol Test (DSY), Complex-Figure (Ray-Osterrieth) and Buschke Selective Reminding Task.

Cortisol, prolactin and serotonin levels in blood were assessed before, 1h after and 2 h after drinking *Hoasca*. Urine samples [29] were obtained at the same times in order to detect DMT. Serotonin was quantified by HPLC [29] in serum (fluorometric detector: 18 nm slit width, 1.5 s time constant; RP-C_{18} column: 10µm, 250 mm length x 4.6 mm id.). Prolactin and cortisol were measured in serum by Immunoradiometric Assay-Magnetic Solid Phase (Prolactin MAIA clone kit; Serono Diagnostics) and a 125-I Radioimmunoassay Double Antibody [22], respectively.

Urinary constituents of control and test subjects (*Hoasca* probandi) as well as those of psychotic patients were also analysed. Comparative analyses of the composition of *B. caapi, P. viridis*, and *Hoasca* drinks were also performed by GC-MS: VG TRIO-2 Mass Lab with helium carrier gas. Split: 100:1. Column pressure: 10 psi. Data were processed by the Lab Base GC- MS Data system. Mass scanning was performed in the range 30-800 for each peak sample. A SPB−1, 30 m length x 0.20 mm i.d., fused-silica capillary column was used with the following temperature programm: 60°C for 1 min, 60-290°C (10°C/min) and 5 min at 290°C.

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