Article

Entheogens, the Conscious Brain and Existential Reality: Part 3

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ABSTRACT

The purpose of this article is to provide a 'state of the art' research overview of what is currently known about how entheogens, including the classic psychedelics, affect the brain and transform conscious experience through their altered serotonin receptor dynamics, and to explore their implications for understanding the conscious brain and its relationship to existential reality, and their potential utility in our cultural maturation and understanding of the place of sentient life in the universe.

Part 3 contains the following sections: 8.Entactogens; 9.Doors of Delirium: Scopolamine and Muscarinic Acetyl-choline Antagonists; 10. Safety Considerations of Psychedelic Use; and 11. An Across-the-Spectrum Case Study.

Key Words: entheogens, conscious brain, existential reality, psychedelics, serotonin, conscious experience, sentient life, universe.

8. Ecstasy and the Entactogens

The entactogens have been included within the entheogen orbit because their emotional effects have made them the key to modern forms of ritual psychotropic agent use, associated with positive celebration of interconnectedness. Ecstasy, or MDMA, is the clear favourite among a series of mood enhancing molecules that work as serotonin releasing agents, promoting empathy and human bonding as well as acting as stimulants and sensory enhancers, leading to world-wide popularity. Its metabolite MDA has also been used as an entactogen psychedelic and some phenylethylamine psychedelics such as 2C-B are also regarded as entactogens. However attempts to make non-toxic variants such as MDAI (Nichols et al 1990) are less regarded for the quality of their effect and have been banned despite their lack of toxic effects. My own experience of MDMA is included in the case study.

The story of Ecstasy's action and the possible routes of any long-term damage are as complicated and challenging as the mechanisms of psychedelic entheogens. As already noted in fig 5, initial reports of serious neurotoxicity and blanket depletion of serotonin system function (McCann et al), disruption of serotonin axonal pathways (Hatzidimitriou et al), and dopamine damage, even on a single dose (Ricaurte et al), have proven to be bad science, with a key research paper retracted (Holden). Initial reports of Ecstasy causing Parkonsinism through dopamine damage also appear to be unfounded (Jerome et al) with later reports suggesting MDMA is protective against existing Parkinsons symptoms (Concar). Ecstasy has also been found to be of potential long-term benefit in therapy for trauma (Buchen). However more careful subsequent research still shows a degree of potential long-term change that is cause for concern.

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MDMA acts as a "releasing agent" of serotonin, norepinephrine, and dopamine (Partilla et al, Verrico et al). It enters neurons via the monoamine transporters. Once inside, MDMA inhibits the vesicular monoamine transporter, which supplies dopamine in vesicles as a function of pre-synaptic neuron excitation. This results in increased concentrations of serotonin, norepinephrine, and dopamine in the cytoplasm and enhances their release by reversing their respective transporters through phosphorylation. The releasing agent blocks the presynaptic cell's ability to use the vesicular transporter to package neurotransmitters into vesicles. The result is increased neurotransmitter release that is not dependent on the phasic activity of the presynaptic cell. MDMA has been identified as a potent agonist of TAAR1, trace amine-associated receptor 1, a G protein-coupled receptor located on the presynaptic membrane. Activation of TAAR1 inhibits transporter function via cAMP. These effects increase monoamine efflux and prolong the amount of time monoamines remain in the synapse.

MDMA also acts as a weak 5-HT1 and 5-HT2 receptor agonist, and its more efficacious metabolite MDA (7% of MDMA becomes MDA) likely augments this action. Its unusual entactogenic effects may be partly due to oxytocin secretion (Young), which facilitates bonding and the establishment of trust via agonizing the serotonin 5-HT1A receptor. A placebo-controlled study in 15 human volunteers found that 100 mg MDMA increased blood levels of oxytocin, and the amount of oxytocin increase was correlated with the subjective prosocial effects of MDMA (Dumont et al 2009). MDMA may also act by increasing ventromedial prefrontal activity and decreasing amygdala activity, which may improve emotional regulation and decrease avoidance, and by increasing norepinephrine release and circulating cortisol levels, which may facilitate emotional engagement (Johansen & Krebs).

Because it acts on transporters, MDMA causes a reduction in the concentration of serotonin transporters (SERTs) in the brain. Animal studies have demonstrated lasting serotonergic changes, but other studies suggest the process is reversible. Immediate depletion of serotonin in the days following Ecstasy use can be significantly alleviated by consumption of 5-hydroxy-tryptophan an immediate serotonin precursor. In an animal study an MDMA dose reducing serotonin levels below 35-50% were improved to 66-85% on 5-HTP supplementation (Wang et al).

Some human studies show MDMA may be neurotoxic (Reneman), however others suggest that any potential brain damage may be at least partially reversible following prolonged abstinence (Baggott, & Mendelson). The relevance to humans of animal studies on rodents documenting neurotoxic damage caused by MDMA is unclear, as different species metabolize drugs differently and at different rates (Baumann, de la Torre & Farre). The causes of neurotoxicity also remain unclear. Several studies have indicated a possible mechanism, through the reaction of α-methyldopamine, a principal metabolite, and glutathione, the major antioxidant in the human body. One possible product of this reaction, 2,5-bis-(glutathion-S-yl)-α-methyldopamine, has been demonstrated to produce the same toxic effects observed in MDMA (Miller et al), while MDMA, and alpha-methyldopamine have been shown to be non-neurotoxic (McCann & Ricaurte). Various metabolites of MDMA may interfere with the mitochondrial electron transport system, leading to increased leakage of reactive oxygen species (ROS) from the mitochondria. ROS and catalytic cycles of P450-mediated MDMA metabolism may oxidatively modify cellular macromolecules such as lipids, DNA, and proteins (Song et al).

Many of the reported deficits associated with MDMA may actually result from concurrent use of other party drugs, including stimulants such as amphetamines (Kish et al). Methamphetamine is a potent dopamine releasing agent with lesser effects on norepinephrine and serotonin, which is a known neurotoxin, shown to cause dopaminergic degeneration. When dopamine breaks down, it produces reactive oxygen species. It is likely that the approximate twelvefold increase in dopamine levels and subsequent oxidative stress that occurs after taking methamphetamine mediates its neurotoxicity. Dopamine oxidation, particularly close to synaptic vesicles, produce oxidative stress that in turn leads to exacerbation of autophagy that can destroy axons and dendrites (Larsen et al).

Toxicity and entactogenic effects of MDMA may depend to some extent on the two chiral versions of the molecule. (S)-MDE produced elevated mood, impairments in conceptually driven cognition and marked right frontal activation. In contrast, (R)-MDE produced increased depression, enhanced visual feature processing, and activation of visual cortical and left frontal areas. Plasma concentrations were higher for the (R)-enantiomer. The so-called entactogenic effects of MDE are likely to be caused by the (S)-enantiomer, whereas (R)-MDE appears to be responsible for neurotoxic effects (Spitzer et al). It is possible anti-oxidants might help alleviate this. The effects may also vary significantly between the sexes (Allott & Redman). Two studies have also found changes in hormone expression (Gerraa et al), and emotional facial recognition (Hoshi et al 2004), with ACTH and cortisol levels higher but more blunted under stress in Ecstasy users, and heightened ability to recognize fearful facial expressions on day 0 but reduced capacity on day 4, suggesting lowered serotonin.

Depression (Falck et al., Verheyden S. et al) and deficits in memory have been shown to occur more frequently in long-term MDMA users (Ainsworth, Lawton). The most pronounced effects are on associative and prospective memory. Focused attention, the ability to zoom in quickly on a new task is affected, though sustained attention is not. The difficulty with these studies is removing confounding factors. Ecstasy use varies from occasional single tablets to bingeing on up to ten at a time (Parrot 2005), and Ecstasy users are also frequently multiple drug pill users, often taking stimulants such as amphetamines as well, which are known to cause significant detriments. Furthermore it remains uncertain exactly what is actually in underground tablets, which often contain other ingredients, and not Ecstasy at all.

Consistent with these confounding variables, a study of neurocognitive function (Hoshi et al 2007) found recreational drug use in general, rather than Ecstasy use per se, can lead to subtle cognitive impairments and that recent drug use appears to impact most strongly on cognitive performance.

Some studies claim a consistent decrement in performance with increasing Ecstasy use. One review (Zakzanis et al) found small-to-medium effects across all cognitive domains with learning and memory being most impaired and that total lifetime ingestion of MDMA appeared to be negatively associated with performance on tasks ranging from attention and concentration to learning and memory. In another ‘meta-analysis’ (Varbaten et al) ecstasy users had lower verbal short and long term memory scores, reacted more slowly and made more errors. However the meta-regression coefficients were not significant, indicating no support for a linear relationship between the mean effect size values and total lifetime

Ecstasy exposure, raising questions over whether it was Ecstasy use or confounds causing the effect.

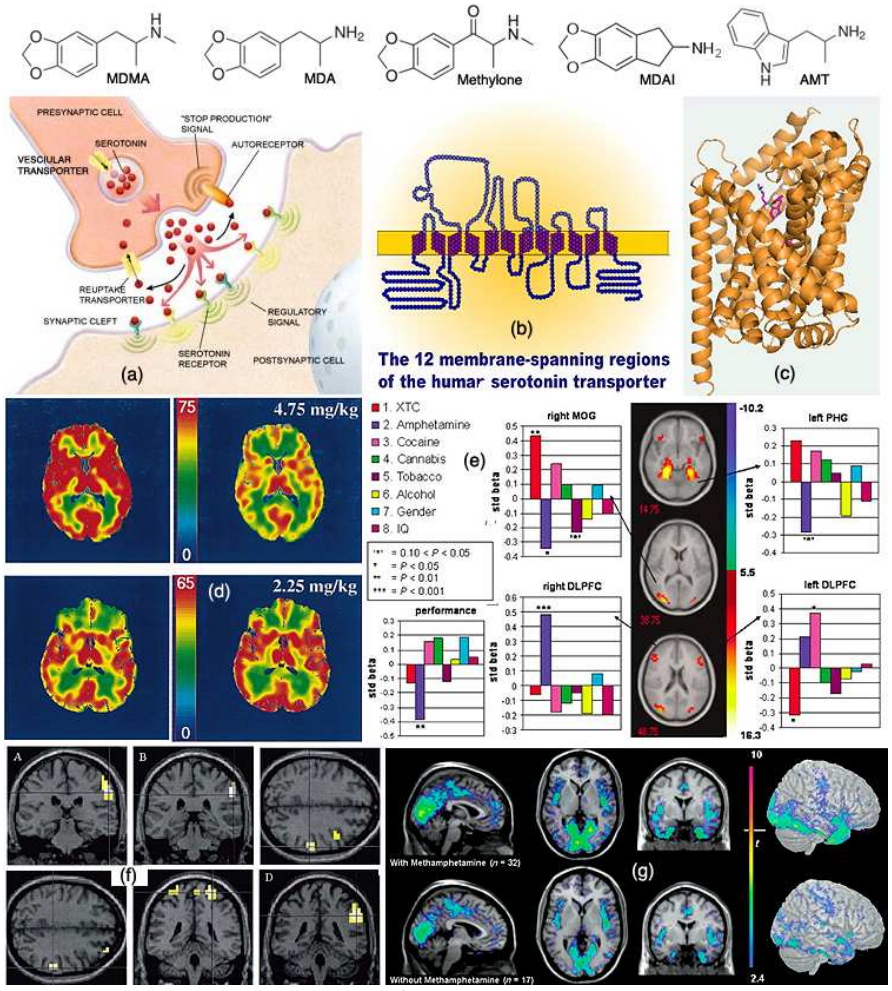


Fig 19: (Top) Entactogens (a) The role of the transporter in the synapse, (b,c) 2D and 3D structures of the serotonin transporter SERT (d) Levels of serotonin at Ecstasy dose and 3 weeks after for low and high doses (Chang et al) (e) Comparable enhancement of activation in various brain areas under several psychotropic agents suggests MDMA causes hyperexcitation (Jager et al) (f) A study comparing MDMA users against controls for differences in brain function (Daumann et al). (g) Decrements in serotonin transporter density with MDMA use above with and below without methamphetamine use (Kish et al).

In two other studies (Montgomery et al, Wareing et al) Ecstasy users performed worse than nonusers, in the former on all, and in the latter on some cognitive measures. However in another study (Fisk et al), Ecstasy users were unimpaired on all measures of random generation performance although Ecstasy users scored significantly lower on one test, the computation span measure.

A low dose study, (Schlilt 2007, 2008) found initial Esctasy use (mean 3.2 tablets) had a significant dose-related negative effect on verbal delayed recall after adjusting for the use of other drugs, suggesting that even a first low cumulative dose of Ecstasy can be associated with decline in verbal memory, although the performance of the group of Ecstasy users is still

within the normal range and the immediate clinical relevance of the observed deficits is limited.

In a study of prospective memory, remembering to do things on a delayed schedule (Rendell et al), Ecstasy users were significantly impaired irrespective of the task demands, after controlling for marijuana use, level of psychopathology, and sleep quality, but not apparently for other drugs such as methamphetamine. Parrott (2006) has suggested that cannabis might offset some of the acute and toxic effects of MDMA. A second study of prospective memory (Rodgers et al) gave conflicting results. An association was found between the lifetime use of ecstasy and self-reported difficulties in long-term prospective memory for some ecstasy users. However participants accessing the research via an ecstasy-related bulletin board showed no association between long-term prospective memory and use of ecstasy, and any association was markedly reduced when nicotine and cannabis were included as covariates. The researchers suggest nicotine may have been a confounding factor.

In a series of brain scan studies designed to complement direct tests of competency, two studies (Bauernfeind et al, Jager et al) found evidence of increased cortical excitability in Ecstasy users completing a cognitive task. The latter found use of Ecstasy had no effect on working memory and attention, but drug use was associated with reduced associative memory performance. Multiple regression analysis showed that associative memory performance was affected by amphetamine much more than by Ecstasy.

An fMRI investigation of motor function (Salomon et al) suggested prior MDMA use was associated with BOLD deficits in coherence and connectivity, among motor pathways, but one would imagine any significant effects being noticeable to the subjects and reported in the medical literature.

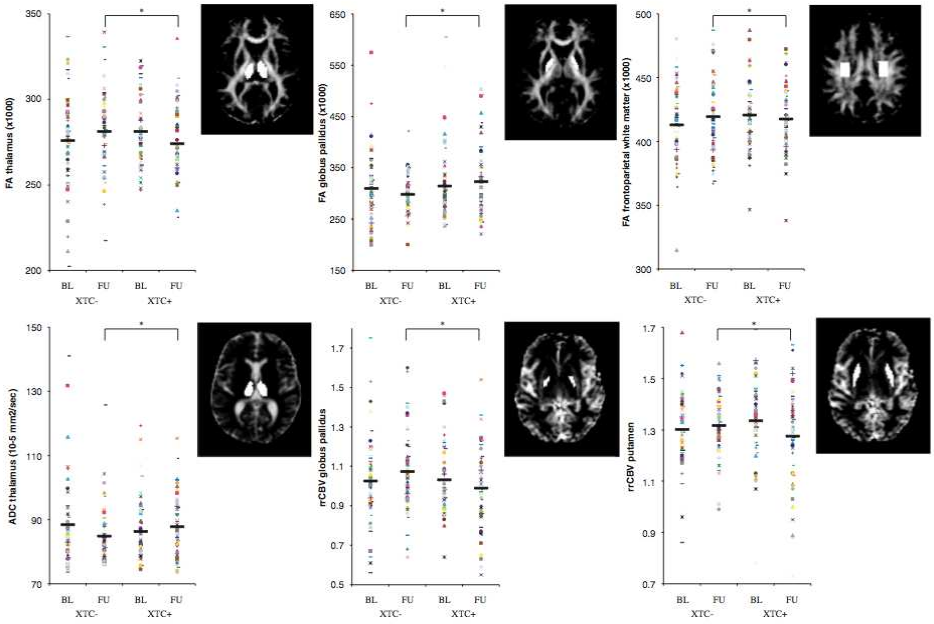


Fig 20: Changes in FA, rrCBV and ADC (de Win et al 2008) at baseline (BL) and follow up (FU). These changes are very moderate, but so is the consumption (de Win et al 2008).

A pair of studies (de Win et al 2007, 2008) explored specific changes in rrCBV - relative regional blood volume; FA - fractional anisotropy of the diffusional motion of water molecules in the brain, which gives an indication of axonal integrity; and ADC - apparent diffusion coefficient. In the first study comparing first Ecstasy users after 2 weeks with non-users, a variety of metabolic tests were normal and after correction for multiple comparisons, only the rrCBV decrease in the dorsolateral frontal cortex remained significant. In the second study, which also compared novel low-dose ecstasy users (mean 6.0, median 2.0 tablets) to non-users, showed decreased rrCBV in the mid brain globus pallidus and putamen; decreased FA in thalamus and fronto-parietal white matter; increased FA in the globus pallidus and increased ADC in the thalamus. No changes in serotonin transporter densities and brain metabolites were observed. These changes, although subtle, do suggest sustained effects of ecstasy on brain microvasculature, white matter maturation, and conceivably, axonal damage due to low dosages of ecstasy.

However other brain studies show only marginal differences and/or signs of long term recovery to norms. In a study examining blood distribution volume ratio (Buchert et al), this was significantly reduced in the mesencephalon and the thalamus in Ecstasy users. However in former Ecstasy users it was very close to drug-naive control subjects in all brain regions, suggesting recovery. In another study examining cerebal blood flow (Chang et al) abstinent MDMA users showed no significantly different global or regional CBF compared to the control subjects. However, within 3 weeks after MDMA administration, regional CBF remained decreased in several areas compared to baseline and was markedly more pronounced in subjects who received the higher dosage of MDMA. Likewise a study of Ecstasy users (50+ tablets) two weeks after abstinence showed reduced SERT binding in the occipital cortex (Schouw et al).

In a study in which subjects were given a working memory performance task and given fMRI sacns (Daumann et al), there were no significant group differences in working memory performance and no differences in cortical activation patterns for a conservative level of significance, however, for a more liberal criterion, both user groups showed stronger activations than controls in right parietal cortex, and, heavy users had a weaker blood oxygenation level-dependent (BOLD) response than moderate users and controls in frontal and temporal areas. The effects were thus relatively minor but suggestive.

In studies in which more rigorous attempts have been made to remove confounding factors, the deficits in cognitive function reported for MDMA tend to disappear.

One study (Bedi & Redman) assessed 45 currently abstinent Ecstasy polydrug users, 48 cannabis polydrug users and 40 legal drug users. Standardized neuropsychological tests were used to measure attention, verbal, visual and working memory and executive function. Prospective memory function was also assessed. It was not possible to discriminate between groups on the basis of the cognitive functions assessed. Although the results suggest that heavy use of Ecstasy is associated with some lowering of higher-level cognitive functions, they do not indicate a clinical picture of substantial cognitive dysfunction.

A second study (Halpern et al) designed to minimize limitations found in many prior investigations, in particular minimal exposure to other drugs, failed to demonstrate marked residual cognitive effects in Ecstasy users. The authors comment: “This finding contrasts

with many previous findings - including our own - and emphasizes the need for continued caution in interpreting field studies of cognitive function in illicit Ecstasy users."

Halpern is sharply critical of the quality of the research that has linked ecstasy to brain damage: "Too many studies have been carried out on small populations, while overarching conclusions have been drawn from them," he said. For a start, some previous research has studied users who were taken from a culture dominated by all-night dancing, which thus exposed these individuals to sleep and fluid deprivation - factors that are themselves known to produce long-lasting cognitive effects. Non-users were not selected from those from a similar background, which therefore skewed results. In addition, past studies have not taken sufficient account of the fact that ecstasy users take other drugs or alcohol that could affect cognition or that they may have suffered intellectual impairment before they started taking ecstasy. In Halpern's study only ecstasy users who took no other drugs and who had suffered no previous impairment were selected (McKie).

9. Doors of Delirium: Scopolamine and Muscarinic Acetyl-choline Antagonists

Muscarinic acetyl-choline antagonist deliriants have been used for centuries, both as hallucinogenic agents in medieval Europe, Asia and Native American cultures, and in rites of passage of manhood to forget childhood, as well as for criminal and military purposes. Although they have been sporadically used recreationally, their severe effects of anterograde and temporary global amnesia combined with delirious and often manic behaviour and panoramic hallucinations which the subject confuses with reality, talking to non-existent people and engaging with imaginary spectacles, often also accompanied with unconsciousness and coma, leave these agents off the spectrum of legitimate entheogens, except for the continuing evidence of their cultural use.

Scopolamine, despite its severe hallucinogenic and amnesiac properties, is used in minute quantities for motions sickness, for treatment of addiction and as an anti-depressant (Furey & Drevits). Hyoscyamine is the active chiral component of atropine an essential WHO core medicine. The belladonna genus Atropa is named after one of the three Greek fates, who chose how a person was to die. It has been used historically as an anaesthetic, to dilate the pupils to make women more attractive (bella donna) and to commit murder, as evidenced by the actions of the wives of Augustus and Claudius. Four second-hand accounts of its acutely disabling and dangerous affects are included in the case study.

Early in the 20th century physicians began to employ scopolamine, along with morphine and chloroform, to induce a state of "twilight sleep" during childbirth. Yet physicians noted that women in twilight sleep answered questions accurately and often volunteered exceedingly candid remarks. In 1922 Robert House, a Dallas obstetrician, arranged to interview under scopolamine two prisoners in the Dallas county jail whose guilt seemed clearly confirmed. Under the drug, both men denied the charges on which they were held; and both, upon trial, were found not guilty. Enthusiastic at this success, House concluded that a patient under the influence of scopolamine "cannot create a lie ... and there is no power to think or reason." His experiment and this conclusion attracted wide attention, and the idea of a "truth" drug was thus launched upon the public consciousness, although barbiturates later came to be more of a drug of choice in interrogation (Bimmerle). Nevertheless scopolamine like drugs, including

3-quinuclidinyl benzilate and n-ethyl-3-piperidyl benzilate continued to be developed as incapacitating chemical warfare agents.

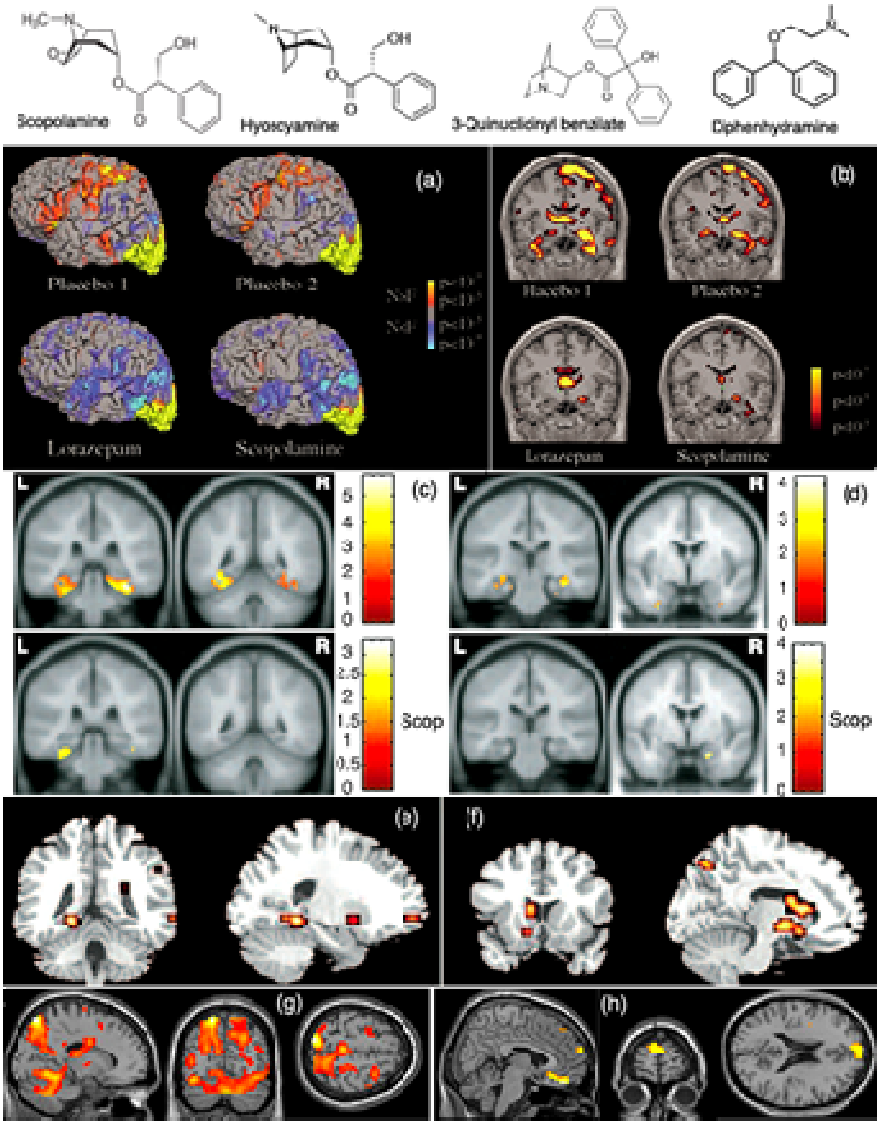


Fig 21: (Top row) four hallucinogenic deliriants. Scopolamine and hyoscyamine are present in Datura, and Brugmansia species and related solonaceous plants such as belladonna (deadly nightshade), henbame and mandrake. 3-Quinuclidinyl benzilate is a chemical warfare incapacitating agent also called BZ. Diphenhydramine (benadryl) is an anti-histamine which also has muscarinic acetyl-choline antagonist activity. (a,b) Reduction of cortical and hippocampal activation under scopolamine novel face-name pairs vs. fixation, for diazepam and scopolamine (Sperling et al). (c) Right and left hippocampal inactivation under scopolamine under active maintenance analysis (d) match and non-match memory tasks also showing hippocampal inactivation (Schon et al)). (e,f) Hippocampal inactivations and striatal activations under scopolamine in a spatial memory task (Antonova et al). (g,h) Inactivations and activations under scopolamine during a memory task matching 2 images back (Voss et al). All of these studies used a moderate 0.4 mg dose of scopolamine by injection.

Following World War II, the United States military investigated a wide range of possible nonlethal, psychobehavioral chemical incapacitating agents to include psychedelic indoles such as LSD-25, marijuana derivatives, certain tranquilizers like ketamine or fentanyl, as well as several glycolate anticholinergics. Copious amounts of phencyclidine are also documented as having been tested on active military personnel such as in the Edgewood Arsenal experiments. One of the anticholinergic compounds, 3-quinuclidinyl benzilate, was assigned the NATO code BZ and was weaponized at the beginning of the 1960s for possible battlefield use. BZ was invented by Hoffman-LaRoche in 1951. In 1959 the United States Army began to show interest in using the chemical as a chemical warfare agent. The agent commonly became known as "Buzz" because of this abbreviation and the effects it had on the mental state of its casualties. In February 1998, the British Ministry of Defence accused Iraq of having stockpiled large amounts of a glycolate anticholinergic incapacitating agent known as Agent 15, chemically either identical to BZ or closely related to it.

Scopolamine has also been used criminally as a poison or spray that can incapacitate a person, or cause them to become obedient to a criminal's intent. In Colombia the criminal administration of Datura or Brugmansia extracts, known as Burundanga, appeared during the 1950s. In the early 1980s, pure scopolamine began to be used. In a Colombian city of 500,000 people around 100 cases were reported in 1980-81. In one instance, a young professional woman was approached by a man, who possibly sprayed her face, resulting in her becoming docile, going to work inebriated and withdrawing her salary, her money from ATMs and her jewelry from her apartment and giving it to her assailant before lapsing into amnesiac somnolence. In hospital, scopolamine and fenotiazine were found in her urine (Ardila & Moreno).

Learning and memory (Deutsch) as well as attention and processing speed are critically modulated by the cholinergic neurotransmitter acetylcholine. Dale in 1914 showed that acetycholine acts at two pharmacologically different receptors, nicotinic, which form ligand-gated ion channels and muscarinic, which are G protein coupled. Muscarinic receptors represent the majority of cholinergic brain receptors. The neocortex has a mixed muscarinic population with 67% M1 receptors, with high affinity for pirenzepine and 33% M2 muscarinic receptors. Hyoscyamine (atropine) and probably scopolamine are M1 antagonists. Increase in the number of muscarinic receptors in the hippocampus of rats has been observed as a consequence of long-term scopolamine administration (Ardila & Moreno). The cholinergic system constitutes one of the most important transmission systems for mediating cognitive processes in humans, with cholinergic projections originating in the nucleus basalis of Meynert and the substantia innominata in the basal forebrain, which has wide projections across the neocortex. By projecting to the hippocampus and to frontal areas, they mediate fundamental cognitive processes (Voss et al).

Studies utilizing scopolamine to examine the effects on cognition have consistently shown that it impairs cognitive functions like learning, memory, verbal fluency and attention. Alzheimer’s and schizophrenia patients present cognitive deficits while at the same time exhibiting specific alterations of the cholinergic system as evidenced by post-mortem studies. Early studies in India on monkeys smoking cannabis and datura suggested that datura alkaloids cause brain shrinkage while cannabis does not. Virtually all the brain scan research

cited focuses on using scopolamine as an experimental drug in learning about memory impairment, emphasizing its major impact on memory.

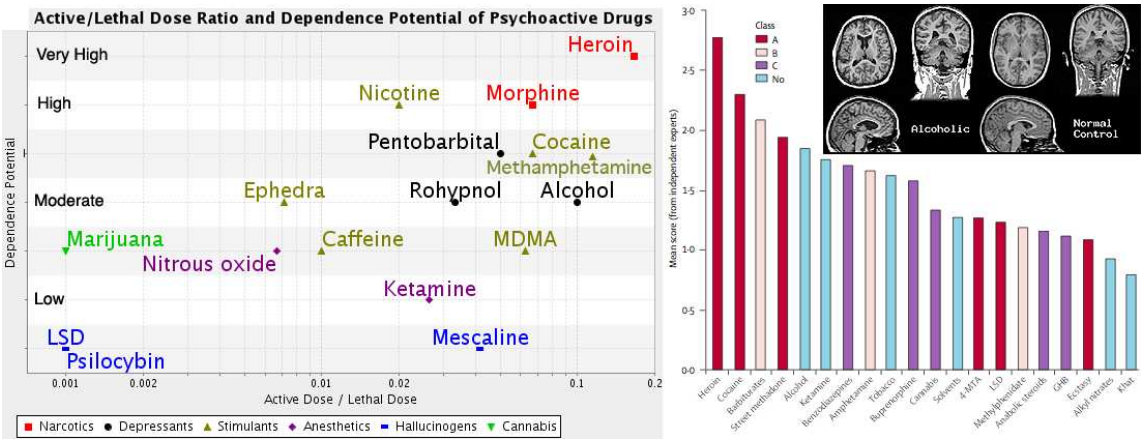


Fig 22: Relative safety of a spectrum of psychoactive drugs (left) in terms of dependence versus active/lethal dose (Wikipedia) and (right) in terms of several measures of relative harm (Nutt et al). In both perspectives psychedelics rate as very safe and having harm potential decisively below legal drugs alcohol and tobacco. (Top right) Putative effects of alcoholism on an MRI scan, showing enlarged ventricles and a shrunken brain.

10. Safety Considerations of Psychedelic Use

The potential long-term health effects and risks of NMDA antagonists, cannabinoids and entactogens have already been extensively discussed. We now turn back to the classic psychedelics. By all measures, as noted in fig 22, psychedelics, even the unpredictable genie in the bottle LSD, do not have evidence of long-term physical damage and rank far below legal alcohol and tobacco as socially or physically damaging agents. This cannot be said for street drugs, even some of those purchased over the internet, or for the more savage members such as the fly series, which have toxic or lethal effects not far above the active dose. A Danish man whose friend died on bromodragonfly had this to say of it: “It was like being dragged to hell and back again. Many times. It is the most evil [thing] I've ever tried. It lasted an eternity”.

I will here focus on the natural psychedelics and in particular psilocybin of sacred mushrooms, but many of the same considerations apply to mescaline bearing cacti and ayahuasca. Although sacred mushrooms were pejoratively claimed to cause premature senility in apocryphal earlier accounts, there is no evidence psilocybin, sacred mushrooms, mescalin cacti, or ayahuasca cause long-term physical harm. Both my peyote roadman Tellus Goodmoring and Maria Sabina the mushroom curandero lived well into their nineties and Senor Trinico the brujo I first took ayahuasca with remained in good heath when I visited him 20 years after my first experience, despite being in remission from leprosy.

The physical side effects resulting from psilocybin consumption are generally not considered significant. Nausea and vomiting can occur, particularly with wild mushrooms, which can contain bacteria, or be partly spoiled. High and or low blood pressure changes can sometimes result in fainting. Other adverse effects less frequently reported include panic attacks,

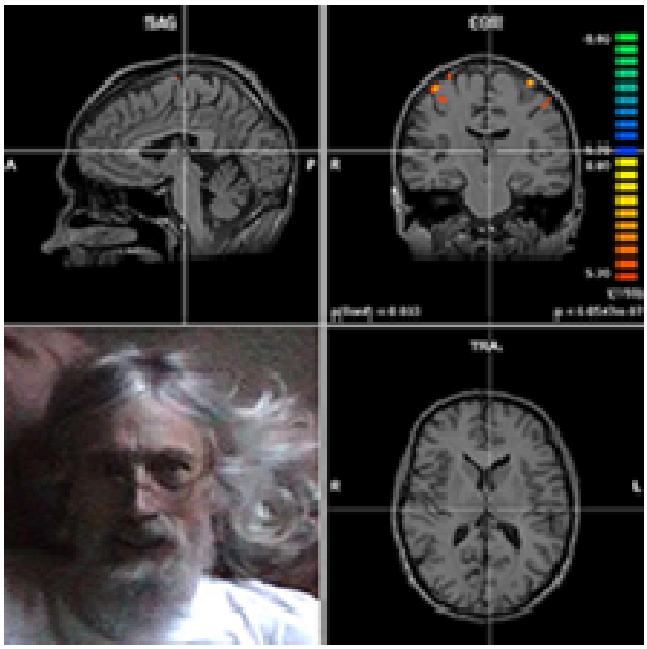
paranoia, confusion, derealization, disconnection from reality, and mania. Neither flashbacks, nor hallucinogen persisting perception disorder, are commonly associated with psilocybin usage (Carhart-Harris & Nutt) as they have been with LSD (Abraham & Duffy). Unsurprisingly, usage by those with schizophrenia can induce acute psychotic states. A 2010 study on the short- and long-term subjective effects of psilocybin administration in clinical settings concluded that despite a small risk of acute reactions such as dysphoria, anxiety, or panic, "the administration of moderate doses of psilocybin to healthy, high-functioning and well-prepared subjects in the context of a carefully monitored research environment is associated with an acceptable level of risk" (Studerus et al). All of these show that use of hallucinogens should be undertaken only in a protective environment where there are people able to look after individuals and protect them from immediate harm.

In addition to the beneficial effects of mystical-type experiences (Griffiths et al) already reported, a pilot study (Vollenweider & Geyer) found that the use of psilocybin was associated with substantial reductions in OCD symptoms, possibly caused by psilocybin's ability to reduce the levels of the serotonin-2a receptor. In a second study (Sewell et al), half of patients with cluster headache, often considered not only the most painful type of headache but "one of the worst pain syndromes known to mankind," reported that psilocybin aborted the attacks, and most reported extended remission periods. Preliminary results indicate that low doses of psilocybin can improve the mood and reduce the anxiety of patients with advanced cancer, and that the effects last from two weeks to six months (Vollenweider & Geyer).

There are thus no scientific grounds to continue to ban the use of entheogens, particularly those of a natural origin, nor to incarcerate people for long periods for consuming or possessing them. Safe and comfortable protected social contexts for use with sane guidance need to be developed. Sacred mushrooms, peyote and ayahuasca are intrinsically safer than either street drug phenylethylamines (which can have lethal consequences, when the drug is impure, or the dosages are confused), or LSD (which had some very unpredictable consequences among our friends in the 1970s, including a bout of amnesia lasting several days, a psychotic episode lasting a month, and an acute manic break requiring physical restraint followed by coma perceived later as a rebirth experience).

11. An Across-the-Spectrum Case Study

To round off this investigation, I am going to include a case study in the first person. No matter how much investigation goes into understanding the properties of entheogens, they remain *sine qua non* agents of transformation of subjective consciousness, which need to be understood in the subjective. Short of readers experiencing these agents for themselves, the closest we can come to an understanding is through first-hand subjective reports. First person accounts, although they are once-removed, can give a far deeper description of the changes induced by these substances than brain scans, or EEGs can. So in the interests of a more enlightened approach to entheogens, in parallel with writing this paper, and as the original inspiration to write it, I have made a spectral investigation, sampling the conscious states key members of these agents invoked in my own consciousness.



I will thus discuss the subjective effects of the classic psychedelic psilocybin (sacred mushrooms), the entactogen MDMA (Ecstasy), a selective 5HT2a agonist n-benzyl-phenylethylamine psychedelic (25C-NBOMe), the dissociative anaesthetic ketamine, and salvinorin-A in terms of their capacity to induce a full-blown entheogenic experiences. Each experience is written as an account to my sister who hasn't tried any of these agents to explain some features of the experience that struck me in the evening afterwards. There is one dreaming account during the time of these case studies to examine provocative anticipatory features of dreaming consciousness. To gain an idea of the severe effects of muscarinic acetyl-choline antagonists such as scopolamine, which I have never been prepared to try, I have included three medieval accounts and a current one.

Sacred Mushrooms and Psilocybin

A couple of days ago, for the first time in a year and a half, because, like most people, I am habitually fearful of my mind being torn apart by visionary transcendence, I persuaded myself to imbibe a powerful whack of the very best crisp dried sacred mushrooms, as a devotional meditation, lest the passage of the years carry me unrequited at the age of 67 ever closer to the edge of dissolution, before I have fulfilled my covenant with destiny. As the great wave of reverie broke over me, they gave me an overflowing and integrated vision of how cosmic consciousness comes about in the universe, in one of the cleanest, and yet strongest, spiritual experiences I have had, totally restoring my sense of psychic vitality and meaning, as they have done countless times in younger days, as the sheet-sail for my tortuous journey through life.

As noted, I have also taken mescalin in the form of San Pedro and peyote in a traditional peyote meeting at Taos Pueblo with the roadman Tellus 'Goodmorning' and on the peyote fields of el Catorce Real in Mexico, sacred mushrooms at Palenque, and DMT and harmine in the form of ayahuasca with Senor Trinico at Yarinacocha, Pucallpa in Amazonian Peru (see fig 3), as well as pure LSD in the days of orange sunshine, so have a reasonably comprehensive familiarity with psychedelic entheogens.

Real religious sacraments have to be able to be powerful enough agents to be able to transport us into the *mysterium tremendum*. They also require meditative vigil to enter deeply into the experience. I try to retreat into reflective solitude, without thought processes, or internal dialogue, lying watchfully, with eyes sometimes open and sometimes closed, and often half-open and half-closed, as the Buddha is depicted as doing, tuning consciousness with my breathing into a resonant state of attention, sensitive to the ensuing visionary miasma. I begin lying quietly and over about twenty minutes I can begin to feel the effects coming on. Often I feel anxious and restless before the peak, something I am coming to associate with the possible effect of the 2c receptor, and I note Griffith's statement that a key to gaining a positive experience for his study participants, depends on getting just the right dose. This time I have measured just 1.3 grams of very crisp dried psilocybe shoots, and this proved to be an ideal dose in the company of a mild measure of cannabinoids. The first real effects if I am lying quietly are a combined synesthesic rush of pattern and sound that often rises almost to a shrieking peak as the first wave strikes. If I let go of my surroundings I can fall into or flow into these resonant patterns, so they become visions and experiential spaces utterly different from the waking world, as if I am not only witnessing my brain generating consciousness but the nature of disembodied consciousness in the bardo.

I won't go into all the incidental details of the retinal circus, the complex dynamically interlacing 3-D fibers and fractals, their rushing vortices and echoing currents, of entering many interconnected layers of dreaming and waking reality, or even a vision of being transported to join God in heaven, with Saint Peter ushering me in on a comic stage vibrating like a New Orleans carnival. The key is the overwhelming power, truth, beauty and integrity of the experience, convincing me in its full intuitive detail, yet again, that the living sacraments contain the genuine royal blood, or *sang raal*, route to religious knowing, beneficial to all life. This is a state that seems to emerge out of the entheogenic experience as a fully integrated knowledge, or gnosis. It is not something you can put together philosophically or explain in terms of its details and it can't be taken back in its entirety to the everyday world, except as an enchanted memory and a source of life-enhancing wisdom.

By entering into the entheogenic state of reverie without thought in a meditative calm, one enters a state where there is a resonance with the patterns and sounds, which one can fall into, and once one does, it is as if one has entered another reality, as different from waking life as dreaming is, with its own existential implications, one of which is gnosis about the flow of life, the meaning of life, and the sense of one's ego dissolution, in becoming one with the conscious process that drives all sentient life in the universe. It is a state of being amid the patterns in the stillness of the conscious void that is evidentially true, palpable, felt at once in one's emotions and in the stillness of one's mind. By the same connection I inherit a personal responsibility to unfold this experience for others, for the sake of life and the planetary future. Of course one can take sacred mushrooms recreationally and have an adventurous experience, but for me it is like returning home to a place where I become my true self, and navigate my life with some grace and insight, as one takes an intercontinental sailing journey across the Styx between birth and our eventual demise.

Ecstasy or MDMA

Today I finally tried the fabled Ecstasy because I had to eventually discover what it was all about, 20 years after I first came upon it. The mushrooms last week were so beneficent and

yet powerful that I felt it was finally time to conquer and understand the E experience as part of figuring out the different actions of serotonin entheogens and entactogens.

And it was a lovely experience too and highly intriguing although its not a transcendental molecule, but rather a sensual and sensitive molecule, to be more precise an entactogen - that is it makes the ones you love seem even more tactile, cuddly and nice to be with, bonded and trusting, through the oxytocin it facilitates, at the same time as an exhilarated feeling of visual brightness and alertness. As the effects came fully on, the strength was almost too much. My eyeballs seemed to be shaking and I literally felt awash with serotonin as if I was standing in a shower. The garden seemed to be bulging out at me with an odd brightness that I could tell could be awesome in a dance hall setting. I found myself clenching my teeth tightly almost to the point of forcing them into my gums, but the sensation felt good and right - a form of keen concentration.

This was definitely a strong 'high' but clear of the mental confusion that can happen with full blown psychedelics, so one can carry on a conversation and engage a social process with heightened empathy and compassionate appreciation of others. Rather than stare at the ceiling and become lost in a psychedelic trance, I wanted to sit closer to my bemused partner, who seemed to have become feathery, as if both she and I had tingles running down our spines and over our skin. Its not that I had fallen madly in love but just had the insane sensual urge to crawl into bed and hug one another. And I felt very positively disposed, warm, relaxed and positive, in a mood with a lot of reserve and no paranoia, able to engage and enjoy social situations. And I felt exhilarated, energized and insanely clear, struck by the fact that this agent has a very good social affect, which can really bring people out of themselves so they bond as friends, or lovers in a vastly superior way to alcohol, which is why people at rave parties loved it until it got hunted down. I have to ask myself "Why was this banned?" "Why was no real assessment made of its capacity to induce far better social climates of tolerance and empathy than alcohol?"

I do have a concern about the risks of neurotoxicity, even if they are less than earlier studies reported, just because this drug is dumping heaps of serotonin and reversing the transporters as well, which is a fairly massive intervention. To avoid the Tuesday blues I take 5-hydroxy-tryptophan supplements over the ensuing 24 hours and have no ill after effects, except for being a little closer to tearfulness, but no worse than a night on psychedelics with too little sleep.

25C-NBOMe a Selective 5HT2a Psychedelic

Today I experimented with a super-potent psychedelic developed to significantly activate only the one kind of brain receptor 5HT2a believed to be involved in the entheogenic state and no others that can cause anxiety, or dreaminess, or shatter the thought process. The active dose to smoke is 150-300 micrograms, an amount as small as a grain of salt you can barely see, let alone measure, but the effects can be overwhelming. I took two very small inhalations of the smoke and could probably have 50% more, but needed to measure the effect carefully. And yes it was fully entheogenic - both very powerful and ever so delicate! It begins with a pronounced serotogenic 'high' almost immediately but the full effects take a few minutes to settle in. Initially it seems to effect higher visual areas without as pronounced geometrical features as psilocybin, but that impression is deceptive. I had also had some cannabinoids and by the time the two were activated, I found I was falling into a rich kaleidoscopic sea of

visions and entering the familiar eeriness of the entheogenic visionary trance. It has a very nice pure feeling, not only pure as a super-potent molecule, but also pure because its action is selective for the 2a receptor, confirming that this is the site of the entheogenic process, and evoking an experience free of the other potentially anxious effects of 2c and the loss of vigilance due to 1a.

Imagine looking at a still pool in the moonlight and something changes, so that, when a little breeze blows on the pool, causing ripples in the moonlight, instead of them dying away, as we look at them and pay curious attention, our hair stands a little on end as they respond as to a resonance and become brighter and clearer, and begin to come ever more alive, but this isn't just a pool 'out there' - it is one's entire conscious psyche 'in here' AND 'out there', one's vision, audition, tactile sensation, emotional feelings, the space between us and the space in and beyond the room, looking down deep down into the abyss, the tingles that run down one's spine, the musical spectra of the fat sizzling in the pan, the meaning behind the meaning behind - the whole experiential universe, be it dream, or reality, resonating uncannily as it becomes one with the conscious void filled with unfolding patterns and memories and dreams of memories and memories of dreams, all now resonating with the one that is all of our minds together experiencing the universe unfolding. Then, just as the void is alive and shining and at the same time empty in its peacefulness, as one's breathing comes to a standstill, the still point of the turning world, the dew drops into the shining sea and we slip back into the room around us, realizing yet again that we have made the unspeakable connection to the mystery that lies at the foundation of all conscious life, as we move in space-time towards our realization, and all of our destinations.

Ketamine

To take ketamine I insufflated powdered crystals from therapeutic sources. The effects are very peculiar to say the least. About three minutes later I have become aware that my consciousness is becoming vastly deranged. It's a feeling I can recognize because I have also experienced pure salvinorin-A, which has a similar dissociative effects. This can be very disconcerting, because your normal relation with your body and the world around you can take on very strange manifestations, where you literally become part of the surroundings, not just a fly on the wall, but you ARE the wall. You may feel you have turned inside out. It sounds ridiculous, but its evidentially true! And everything you look at, and everything if you close your eyes, is wildly disassociated into alien kinds of conscious structure, in wild motion, as if your internal model of reality has come loose and is resynthesizing on different principles

For the first few minutes, maybe five or six, I'm trying not to swallow, and spit out occasionally, because, if it gets down the back of your throat, it can make you quite nauseous. Then I realize my nose feels cool and I am entering a state of peace. The anesthetic effect is taking me deep into a psychedelic reverie through pranayamic breathing. I fall deeper into the dissociated state and I realize that coming backwards through it all is an ever so overwhelming complete entheogenic experience similar in kind and feel to the classic psychedelics of simply awesome depth. A depth so inscrutable, you are touched by it, swept into silent awestruck oblivion - but still conscious - still there - still aware - somewhere in the aether, as the void breathes its delicate structured emptiness.

At some point, my partner knocks and opens the door to make sure I am okay. All I can say

barely through the ice of immobility is that it is like the divining salvia 10,000 times over. I continue to witness drifting in and out of the entheogenic trance and note that this is a definite confirmation that, although the initial experience seemed more like salvinorin dissociation, the state is also able to manifest something intimately recognizable as a deep serotonin-like psychedlic reverie, confirming in my mind the deep association between the classic psychedelics and dissociatives, hinted at in the 5HT2a, MGluR2 and NMDA interactions discussed in the article. I begin to become curious what ketamine would be like taken along with a classic psychedelic. But then I realize that it would be impossible because my hands and feet are like clay tablets, or I have been set in quick drying cement.

I continue to recognize the depth and mystery of what I am witnessing. But then things take a more sinister turn. My mind is becoming memory-less. It's as if all my brain and memory circuits are reprogramming themselves and all the needles are beginning to point every which way. I know it's going to be alright, but it sure feels as if I am going to be stark staring mad forever. So I decide just to ride with the experience, because I will probably be able to remember it all when things settle down at the end of an hour or so. And I'm thinking about my hippocampus because I know what it does to your memory centers, and then suddenly its as if the dials have connected to the master index of all my life experiences, and here they are flashing before my eyes, just as they say about someone who is drowning, and near death experiences, but its not just my life experiences, but the very peak experiences, like the chain of the Himalayas.

I am suddenly looking right into the peak experience I had on the Vine of the Soul in Amazonian Peru in 1980, and all the other times I have been outside the inside out, as if every moment were written on a stack of cards and now they were flashing past in a flying shuffle. I realize I am looking back down on them in the same way Moses might look down on his life and the life of everyone from the mountain top, and that all the experiences of my life are coming into one cosmic focus of meaning and destiny. At this point I suddenly realize that everything I have ever done and everything I will ever do has been brought to this very moment and this very experience, and it is 'God', and my destiny coming to its true destination at this point, which is beyond time and space, coming from the very beginning, and for ever. I have this overpowering feeling of having been taken so far it is the full age of the universe and I have so far to get back to the land of the living. It is the same thing I have read about in near-death experiences where one’s life flashes before one’s eyes and one feels one is uniting with the universal self and could go with it or return to the incarnate world of individuals. But at the same time it is the universal mind coming to know and understand itself. At that point it seemed almost as if my life was now over. I had made the connection which gave my life its central meaning and though I might in future do nothing else and maybe I would never be able to come to this point again, my life had meaning in giving ultimate meaning to the totality witnessing and knowing itself.

If I look out at the room I still feel deranged, although feeling a little flatter though still depersonalized, or derealized is probably the better term. And then things come a little more into focus, and I realize I'm coming out and suddenly I am hit with the unbearable lightness of being, a ridiculous case of laughing gas splitting my sides, because of course nitrous oxide is a milder anesthetic of the same basic NMDA antagonist class, and I am simply hilarious that its all going to be okay again!

And I look at the clock and its only an hour later, and so I lie there trying to soak up the

experience, completely awe struck at the inscrutable point of no return, in becoming one with the eye of the universe coming to meet its destiny in knowing, as I am knowing and by the enormous journey I have taken. And so I try to express to my partner what it was like, but words still won't come and all I can do is utter complete existential overcharge in a fulminating cry "Aaaahhh!!!" And I stagger out into the living room with feet like snow boots, the outside world through the windows still looking like a dream, while I try to piece together the experience and whether it is all going to be lost in the oblivion of the sleep of forgetfulness.

How do you express these experiences? What do they all mean? Was this God? Was this a complete delusion? What is the final answer? Would you ever have a better chance on the edge of life and death? Or is the living brain the crucible of existence and the one chalice of the infinite through which the universe can pass?

And what of the effects and consequences? Ketamine is a strong anaesthetic and I worry about the cumulative effects on memory of repeated use of a drug which both has very strong effects on neuronal excitability and manifest effects on the memory process, which is something we have at best limited conscious control over, so it is definitely something I wouldn't consider taking often. The strange sensations I had about my memory during the experience is enough to convince me of this, although afterwards I have been able to recall as much of the experience as in any other entheogenic experience, and cannabinoids can also disrupt short-term memory.

Salvinorin-A

When taken directly from the leaves of *Salvia divinorum*, salvinorin has a mildly disturbing effect on both consciousness and memory which is different from the classic psychedelics in that it appears to involve crumpled surfaces rather than kaleidoscopic geometries and has an odd effect on memory as if one feels that one's memory has always been submerged in this condition when one knows this is not true. The two times I have taken pure salvinorin, around 0.7-1 mg vaporized, the effects have been totally dissociative and completely overpowering, with my body image completely unraveled. The first time I felt I was in an enormous aircraft hangar with a gigantic wheel rolling over my body flattened and rolled out like a sheet of paint. The second time I fell to the floor as my body turned inside out and broke into the flagellating surfaces breaking up the space of the room around me. By the time I have realized I can handle the experience it is already beginning to fade. Yes these experiences are profound but they are also transient and leave little time to come to terms with them contemplatively and they do have strong undertones of dysphoria, although fascinating and challenging. So I don't class them as entheogens but as hallucinogenic dissociatives.

Dreaming

I have had many strange dreams in my life, some apparently precognitive and some manifestly lucid. In one, I looked at my hands and found my consciousness split in three, one self was lucid, but lost in the dream universe, desperately wondering how I could ever find the way back to the Ixtlan of the real world, one shooting upwards ever faster as a blast of spray hit my body, and the third bumping on the ceiling of my bedroom, reassuringly

witnessing my body asleep in the bed below. But here I relate a time-spanning dream during this entheogenic discovery process.

I dreamed I was at a place like a school and someone had been shooting at some other people and there were little silver bullets on the ground. Then later I realized I had to leave and worried that I would become a target myself. As I was walking anxiously down a drive through the site I realized there was a right turn just before the end which went down an alley lined by an avenue of trees, so it was hard for the shooter to get a line on me. I managed to slip anxiously away and then managed to take off on my motor cycle around the block, where I ran into a very crowded situation trying to push the heavy bike up hill. I then found myself on a crowded truck but at the same time thought I was in a physics lab and wondered why I had spent so much time in the lab session and had had few or no lectures.

The episodes with the shiny bullets and the physics lab have strong echoes in two television programs we were watching the night before, Castle about a murder in which the bullets were crucial evidence, and The Big Bang Theory, which is about nerdy physics graduates. However there are two features of the dream, the right turn down the alley and pushing my bike up a hill, which appear as a lock and key to future events that happened after the dream.

The next day, I was fixing a lock on one of our French doors and suddenly remembered I had thought of looking for a locksmith's supplies I had visited a few years before in case the lock was cheaper there. It was long enough ago that I had to look up the name and address on the internet, but when I rode out around the block on my push bike the destination was down a cull de sac on the right just before the end of a short side street and when I arrived at the place, I found that I had to push my bike up a steep slope and couldn't ride it to get out again.

Thus two incidental components of the dream, neither of which related to my immediate past, were combined in a form which together point to an experience I was going to have after the dream, reflecting the double blind study in "An Experiment with Time" (Dunne). Since the role of subjective consciousness in evolution appears to be critically to anticipate threats to survival, in situations where computational processes become intractable and such choices may also depend on contingencies which have yet to arise in future, further exploration of the anticipatory capacity of waking, dreaming and entheogenic experience is an urgent priority for our understanding of life and consciousness.

Before the alkaloid in *Banisteriopsis caapi* was found to be harmine, (along with related tetrahydro-harmine and harmaline), it was initially named 'telepathine' because of reports about ayahuasca's telepathic powers, in association between harmine as MAO inhibitor and the DMT from *Psychotria viridis* in the brew. Maria Sabina's description of her mushroom experiences also contain references to thier 'prophetic' propensities. Without succumbing to the naïve claims made by some psychedelic writers, we need to keep an open mind about exploring the space-time properties of the entheogenic experience. Because it allows the brain to witness its own inner dynamics consciously in a way which is responsive to our attention it is effectively the mental equivalent of a cloud or bubble chamber, a unique facility for fundamental research we cannot afford to suppress, given the conscious mind being both the central arena through which all our life and action passes and the deepest enigma facing the scientific description of reality.

Scopolamine and Hyoscyamine

Porta, a colleague of Galileo reported a "man would sometimes seem to be changed into a fish, and flinging about his arms would swim on the ground, another would believe himself turned into a goose and eat grass, beat the ground with his teeth and flap his wings". "My teeth were clenched, and a dizzy rage took possession of me. I knew that I trembled with horror, but also that I was permeated with a sense of well-being. My feet were growing lighter, expanding loose and breaking from my body. Each part of my body seemed to be going off on its own. At the same time I experienced an intoxicating sense of flying. The frightening certainty that my end was near through the dissolution was balanced by an animal joy in flight ... the clouds the lowering sky, herds of beasts, falling leaves quite unlike ordinary leaves, billowing streamers of steam and rivers of molten metal."" (Rudgeley 95).

Johannes Nieder (1692) gives the following account: "having placed a large bowl on top of a stool, she stepped into it and sat herself down. Then rubbing ointment on herself to the accompaniment of magic incantations, she lay her head back and fell asleep. With the labour of the devil she dreamed of Mistress Venus and other superstitions so vividly that crying out with a shout and striking her hands about, she jarrd the bowl in which she was sitting and falling down from the stool seriously injured herself about the head. As she lay there awakened the priest cried out "Where are you? You are not with Diana ... you never left this bowl!" (Harner (ed) 131).

“The James-Town Weed (which resembles the Thorny Apple of Peru, and I take to be the plant so call'd) is supposed to be one of the greatest coolers in the world. This being an early plant, was gather'd very young for a boil'd salad, by some of the soldiers sent thither to quell the rebellion of Bacon (1676); and some of them ate plentifully of it, the effect of which was a very pleasant comedy, for they turned natural fools upon it for several days: one would blow up a feather in the air; another would dart straws at it with much fury; and another, stark naked, was sitting up in a corner like a monkey, grinning and making mows [grimaces] at them; a fourth would fondly kiss and paw his companions, and sneer in their faces with a countenance more antic than any in a Dutch droll. In this frantic condition they were confined, lest they should, in their folly, destroy themselves — though it was observed that all their actions were full of innocence and good nature. Indeed, they were not very cleanly; for they would have wallowed in their own excrements, if they had not been prevented. A thousand such simple tricks they played, and after eleven days returned themselves again, not remembering anything that had passed.” – The History and Present State of Virginia.

An overdose on butylscopolamine. “It felt so indescribably weird. It was as if nothing was real and I began to forget who I, and everybody around me, was. I remember looking at the ceiling and it started bubbling. I remember seeing some very real hallucinations and feeling intensely energized and happy. I blacked out - my brother’s friends found me in the woods, I was conscious upon their arrival but collapsed in mid-discussion, they brought me home. I remember a little about coming home, it was a familiar place, but a new type of magical presence was animating it. At this point I had forgotten I took the drug and I went to my room to sit on my couch (I don’t have a couch in my room). I remember lighting up cigarette after cigarette and having a great old time talking to random strangers at a very social and easy going party (I don’t smoke cigarettes, and the only people who came in my room that night were my parents and brother). They drove me down [to hospital] and apparently the whole way there I thought we were riding some type of laser train. When I got there I got

really violent with the nurses so they strapped me to the bed and the first 24 hours after being admitted to intensive care I can't remember at all, the next two days I remember vividly accompanied with memories of outrageous things like talking snakes calling me names (the serious delirium began to subside after about four days). I saw my baby sister sit up in her cradle and shoot lasers into the air, I got into a very heated argument with a cardboard smiley faced sun on the wall. At one point all my family was standing around me asking me who they were and all I knew was my father's name (but I couldn't remember that he was my father). I didn't remember anything at first but as time went on and my family told me stories some of it came back" (Erowid).

[References at end of Part 4]