Entheogens, the Conscious Brain and Existential Reality

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Complementary video: Entheogens, Culture and the Conscious Brain http://youtu.be/pY2MDqdv-No

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 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.*

Contents

1: Cultural and Historical Introduction

Human societies have been actively using psychoactive substances since the earliest cultures emerged. In "The Alchemy of Culture" Richard Rudgley notes that European cave depictions, from the paleolithic on, abound with both herbivorous animals of the hunt and geometrical entopic patterns similar to the phosphenes seen under sensory withdrawal and under the effects of psychotropic herbs. By the time we find highly-decorated pottery 'vase supports' in Middle Neolithic France, we have evidence consistent with their ritual use as opium braziers. At 4200 BC at the Cueva de los Murciélagos site in Spain we find burials with bags containing *Papaver somniferum* capsules. During the 18th Egyptian dynasty 1550-1295 BC there was an active trade with Cyprus of juglets, whose form is neatly in the shape of an inverted poppy pod, indicating they contained opium. This trend is confirmed in detail in the terracotta Goddess figurines discovered from a small shrine at Gazi west of Knossos in Crete, dated to 1350 BC, whose headdress consists of a row of three poppy heads explicitly slit in the exact way opium resin is extracted from the poppy to this day. A goddess with the same emblems - three poppies - in her hand is depicted also in a gold signet ring from Mycenae from 1500 BC.

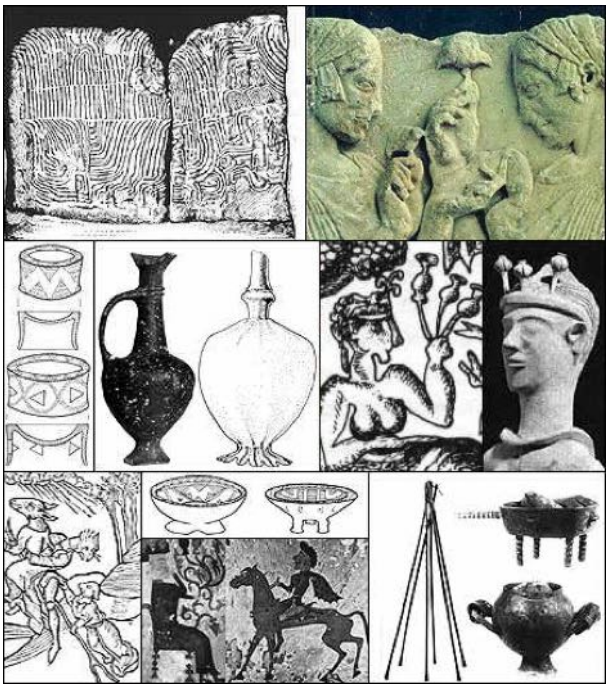


Fig 1: Phosphene-like finger markings Neolithic tomb of Gaverinus, Brittany. Persephone passing what looks like a liberty bell psilocybe to Demeter, Er Lannic pottery possibly used for opium, opium juglets from Cyprus (Rudgley), poppies being offered and the poppy goddess with slit poppy heads on her crown, the oldest illustration of witches, polyploidy bowls which may have been used for vaporizing cannabis, the Scythian goddess showing a horseman the tree of life, braziers and pots in the Scythian ritual use of cannabis (Schultes & Hofmann).

The origin of cannabis converges on the northeastern Tibetan Plateau, in the general vicinity of Qinghai Lake 19.6 Ma. This co-localizes with the first steppe community that evolved in Asia. From there, Cannabis first dispersed west (Europe by 6 Ma) then east (eastern China by 1.2 Ma). Cannabis pollen in India appeared by 32.6 thousand years (ka) ago. The earliest

archaeological evidence was found in Japan, 10,000 bce, followed by China (McPartland et al. 2019). Cannabis use thus dates back over 11,500 years (Long et al. 2017). The earliest cultural evidence of Cannabis comes from the oldest known Neolithic culture in China, the Yang-shao, which appeared along the Yellow River valley about 6,500 years ago. The clothes the people wore, the nets they fished and hunted with, and the ropes they used in their earliest machines was said to be made from hemp. Evidence for *Cannabis sativa* use in Europe also dates back to the neolithic, where there is evidence that it was used for rope and for its psychotropic and potentially hallucinogenic effects. Polyploid bowls with rope imprints again look to be braziers for consuming plant vapours. Pipe cups dating from a third millennium BC burial site in Romania explicitly contain charred hemp seeds, consistent with their being the remains of a smoked cannabis pipe. According to The Living Torah kaneh-bosm (Hebrew: קְנֵה-בֹשֶׂם) identified with cannabis may have been one of the ingredients of the holy anointing oil mentioned in various sacred Hebrew texts. The Scythians of southern Central Asia used Cannabis to attain trance during funeral rites, using a metal tripod censer. Censers have been found still containing hemp seed (Rudenko). Herodotus, more than 2000 years ago, described the way Scythians burned portions of the plant in metal tripod censers, beneath small tent structures that enclosed the vapors inhaled for ritualistic and euphoric purposes (Merlin, Schultes & Hofmann). "The Scythians then take this seed of hemp and, creeping under the mats, they throw it on the red-hot stones; and, being so thrown, it smolders and sends forth so much steam that no Greek vapour bath could surpass it. The Scythians howl in their joy at the vapour bath." The Yanghai Tombs of Xinjiang have revealed the 2700-year-old grave of a shaman. Near the head and foot was a large leather basket and wooden bowl filled with 789g of cannabis, superbly preserved by climatic and burial conditions. This material still contained the active ingredient THC. Cannabis use in the Indian subcontinent may also go back to the earliest cultures. Cannabis is first referred to in Hindu Vedas between 2000 and 1400 BC, in the Atharvaveda. Shiva, who is the patron deity of Cannabis, can be seen in Mohenjo-Daro in a meditating pose with trident, as Pashupatinath Lord of the Animals surrounded by his beasts. Cannabis or Ganga carries the name of the sacred river itself, and the endocannabinoid anandamide was named after bliss.

Fig 1b: Left: Cannabis plants from a tomb in the Jiayi cemetery of Turpan, NW China 2800-2400 years old (Jiang et al. 2016). Centre Left: Gold artefacts from a Scythian grave mound (Curry 2016) Criminologists in nearby Stavropol to analyzed a black residue inside the vessels. The results came back positive for opium and cannabis, confirming a practice first reported by Herodotus. The Greek historian claimed that the Scythians used a plant to produce smoke "that no Grecian vapour-bath can surpass … transported by the vapor, [they] shout aloud." A database of historical cannabis finds (Long et al. 2017) indicates the herb entered the archaeological record of Japan and Eastern Europe at almost exactly the same time, between about 11,500 and 10,200 years ago and spread across Europe and Asia 5000 years ago probably due to the Yamanya migrations as evidenced by a clay vessel remains of carbonized hemp seed at Gurbanesti Romania c 4800 bp (Anthony 2007 363).Centre Right: Brazziers from the Jirzankal Cemetery (ca. 500 BCE) in the eastern Pamirs region. CBN, which is the oxidative metabolite of THC, cannabidiol (CBD), and cannabicyclol (CBL) are all preserved in ancient cannabis on all of the burnt residues, except for one, from the inside of the wooden braziers and on two of the stones. This phytochemical analysis indicates that cannabis plants were burned in wooden braziers during mortuary ceremonies, smoked as part of ritual and/or religious activities in western China by at least 2500 years ago and that the cannabis plants produced high levels of psychoactive compounds (Ren et al. 2019). Right: Francincense and Cannabis residue found at Judaic temple in Arad Israel guarding Judah's southern border in a layout similar to the first Temple of Jerusalem. The cannabis remains contained active THC and were mixed with cow dung ostensibly to burn at a lower temperature (Arie, Rosen & Namdar 2020).

Likewise by the fourth millennium BC, we also find evidence of alcohol use, probably initially from date palms and then the grape vine *Vitis vinifera*. Barley beer is referred to in early Sumerian and Akkadian texts. The soma or haoma of the Indo-Aryans extolled in the Rig Veda and the Avesta remains a botanical enigma, but nevertheless shows another psychotropic concoction which was extolled to semi-divine status, which has been attributed to Syrian rue *Peganum harmala* which contains psychoactive monoamine oxidase inhibitor harmaline and to the muscimol-containing *Amanita muscaria* which has also been ritually used by Siberian shamans, because references to it suggest it was recycled in excreted urine. There is also an enigma surrounding the Eleusian epoptea which was said to be a sacramental repast of visionary transformative power, which has been associated with various psychotropic agents, including the liberty cap Psilocybe

species which Persephone appears to be passing to Demeter on a stele as noted by Graves (O'Prey), and ergot fungus containing rye (Wasson et al).

In medieval times, in the midst of Christian persecution against all manner of heretics, witches and mystics, stemming from the Crusade against the Albigenses, there are also frequent references to the use of 'devilish' witching herbs which were an underlying part of pre-Christian European history and folklore, including Mandrake, Henbane, and Belladonna which are highly toxic deliriants which were rubbed on the body as herbal ointments causing sensations of flying, joining the sabbat, or lovemaking with an imagined suitor, due to the libido enhancing effects of hyoscyamine, and related muscarinic acetyl-choline receptor antagonists, followed by unconsciousness. These were pursued by the Inquisitors, as evidence of witchcraft and their practitioners condemned to death by drowning or burning at the stake. To compound matters, there were also episodes of mass poisoning due to lysergic acid derivatives in ergot fungus on the rye, resulting in outbreaks of collective madness, sometimes accompanied by the loss of appendages from gangrene caused by the vasoconstrictive effects of the alkaloids.

The term entheogen is derived from ancient Greek, ἔνθεος (entheos) "full of the god, inspired, possessed," the root of the English word 'enthusiasm', and γενέσθαι (genesthai) "to come into being." Thus, an entheogen is a substance that causes one to become inspired or to experience feelings of inspiration, often in a religious or "spiritual" manner. In a strict sense, only those vision-producing drugs that can be shown to have figured in shamanic or religious rites would be designated entheogens, but in a looser sense, the term can also be applied to other drugs, both natural and artificial, that induce alterations of consciousness similar to those documented for ritual ingestion of traditional entheogens. Evidence for the first use of entheogens may come from Tassili, Algeria, with a cave painting of a mushroom-man, dating to 8000 BP and mushroom idols from the Konya plain and the Vinca site in Europe (McKenna).

Part of the difficulty facing the acceptance of entheogens in European culture is that the most potent psychedelic entheogens have natural habitats in the Americas, where European cultures have come upon them as alien diabolical practices by often violent warrior pre-Colombian cultures such as the Aztecs, who themselves had horrific sacrificial practices worshipping gods of war regarded as heathen and devilish by the conquistadores. Christianity and conservative European culture, still reeling from its own paranoid religious conflicts, as flagellating Penitente Catholics set out for a new world, regarded all such practices with horror, and although Christianity was also a sacramental religion with an equally bloodthirsty Eucharist of the *soma* and *sangre* of Christ, violently repressed all such use of visionary sacraments.

Nevertheless potent psychedelic entheogens were ritually used and held sacred by diverse pre-Colombian cultures for centuries and even millennia before the arrival of Columbus. Long before the Aztecs the Mayans record the use of sacred mushrooms belonging to the *Psilocybe* genus in both frescos and mushroom stones dating back as far as 1000 BC which show obvious evidence of use as a visionary agent. The sacred use of the mushroom *teonanactl* or 'flesh of the gods' continued as an unbroken tradition for 1,500 years to Columbus and then secretly for another 500 years to the present day.

The Aztecs a particularly vicious sacrifical warrior culture nevertheless freely embraced sacred mushrooms in their own frenzied way, seen through the distorting prisms of Conquistador diabolization. Friar Sahagun, one of the first conquistadors to chronicle *teonanacatl*, flesh of the gods, remarked:

"when they become excited by them start dancing, singing, weeping. Some do not want to sing but sit down and see themselves dying in a vision; others see themselves being eaten by a wild beast; others imagine they are capturing prisoners of war, that they are rich, that they possess many slaves, that they have committed adultery and were to have their heads crushed for the offence . . . and when the drunken state had passed, they talk over amongst themselves the visions they have seen" (Schultes and Hofmann 1979 146).

"During the coronation feast of Moctezuma in 1502, teonanacatl (the divine mushroom) was used to celebrate the event. War captives were slaughtered in great numbers to honour Moctezuma's accession to the throne. Their flesh was eaten, and a banquet was prepared after the victims' hearts were offered to the gods. After the sacrifice was over, everyone was bathed in human blood. Raw mushrooms were given to the guests, which one writer described as causing them to go out of their minds-in a worse state than if they had drunk a great quantity of wine. In his description, these men were so inebriated that many took their own lives. They had visions and revelations about the future, and Duran thought the devil was speaking to them in their madness. When the mushroom ceremony ended, the invited guests left. Moctezuma invited rival rulers to feasts, which were held three times a year. One of these important feasts was called the Feast of Revelations, when the invited dignitaries and Moctezuma, or his representative, ate the wild mushrooms. " ... "During the Aztec king Tizoc's enthronement feast, all those present ate wild mushrooms - the kind that made men lose their senses.

After four days of feasting, the newly crowned Tizoc gave his guests rich gifts and sacrificed the Metztitlan victims" (Dobkin de Rois 142).

By contrast the Mazatecs continued to use sacred mushrooms for divination and curing maladies in absolute secret, a secret so assiduously kept that all trace of magic mushroom worship became lost to the world at large until Maria Sabina accepted Gordon Wasson into the mysteries of the little flowers.

At the same time, Mexico was rich with other entheogenic sacraments. Various peoples consumed the mescalin-containing cactus *peyotl* or 'hairy one', the Huichols undertaking an annual pilgrimage across Mexico to collect it from the high deserts around their sacred mountain of Wirikuta, describing the effects of the cactus as opening the *nierika* or portal to the spirit world where everything becomes one:

"There is a doorway within our minds that usually remains hidden and secret until the time of death. The Huichol word for it is nieríka. Nieríka is a cosmic portway or interface between so-called ordinary and non-ordinary realities. It s a passageway and at the same time a barrier between the worlds. … When the mara'akáme passes through the nieríka [visionary tunnel] he moves just as the smoke moves; hidden currents carry him up and in all directons at once ... as if upon waves, flowing into and through other waves ... the urucate. As the mara'akáme descends and passes through the nieríka on the return, his memory of the urucate and their world fades; only a glimmer remains of the fantastic journey that he has made" (Halifax 239).

Evidence of peyote use goes back to the Toltecs in 500 BC where a snuffing pipe with a deer holding a peyote in its mouth has been found at Monte Alban. Others used the lysergic acid amide containing black seeds or *bardo negroh* of the morning glory, and the Herb of the Shepherdess, *Salvia divinorum* to induce visions when sacred mushrooms were not available.

In the southern continent, an equally diverse spectrum of entheogenic sacraments had been discovered, from the mescalin-containing San Pedro cactus *Trichocereus pachanoi* (holding the keys to the golden gate), through snuffs such as and *epena* from *Virola* species and the famous pan-Amazonian brew *ayahuasca* of "Vine of the Soul" containing DMT from plants such as *Psychotria viridis*, beta-carboline MAO inhibitors such as harmine from the vine *Banisteriopsis caapi* and occasionally solonaceous alkaloids from *Brugmansia* a tree-datura having deliriant effects similar to the witching herbs of Old Europe.

Archaeological records of sacred use likewise go back to ancient times, with evidence of San Pedro use, in the cactus found alongside a leopard in Chavin culture (1200-600 BC), evidence of sacred mushroom use in Paracas culture (800-100 BC), and San Pedro and snuff use among Nazca (100-800 CE). As well, as an energetic mainstay and spiritual guide, the coca leaf was chewed, along with stimulants such as caffeine.

Likewise in the African subcontinent, two of the oldest human cultures the Bushmen and Pygmies have traditional sacred use of psychotropics. Biaka pygmies use the hallucinogen *Tabernanthe iboga* and there is also a pattern of Cannabis use among the Bushmen, to complement their trance dancing visitations. Although this is an imported tradition, it is done in a unique ancient manner, filling a hole in the ground with plant material, from which the herb is smoked cool.

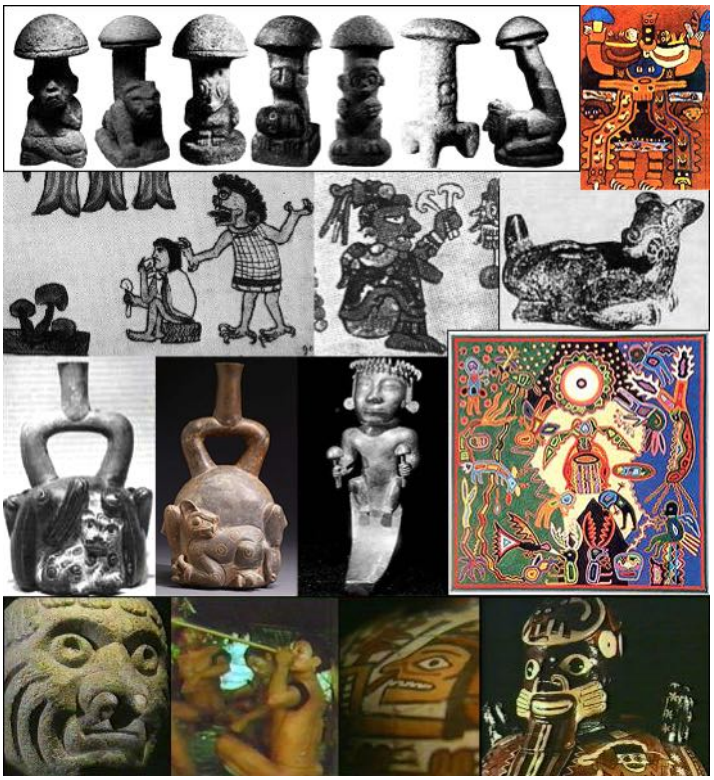


Fig 2: Diverse sacramental use over millennia in the Americas. Mayan sacred mushroom stones (1000 BC), a blue topped mushroom carried by a shaman Paracas culture, Aztec murals showing sacred mushroom deities (Magliabecciano Codex), the deer snuffing pipe holding a peyote from Monte Alban (500 BC), two Chavin urns with jaguar beside San Pedro cacti, a sacred mushroom deity from South America the Huichol nierika or visionary portal opened by peyote, a Chavin statue and Nazca gourd showing nasal discharge from hallucinogenic snuffing, and a Nazca pottery showing San Pedro use.

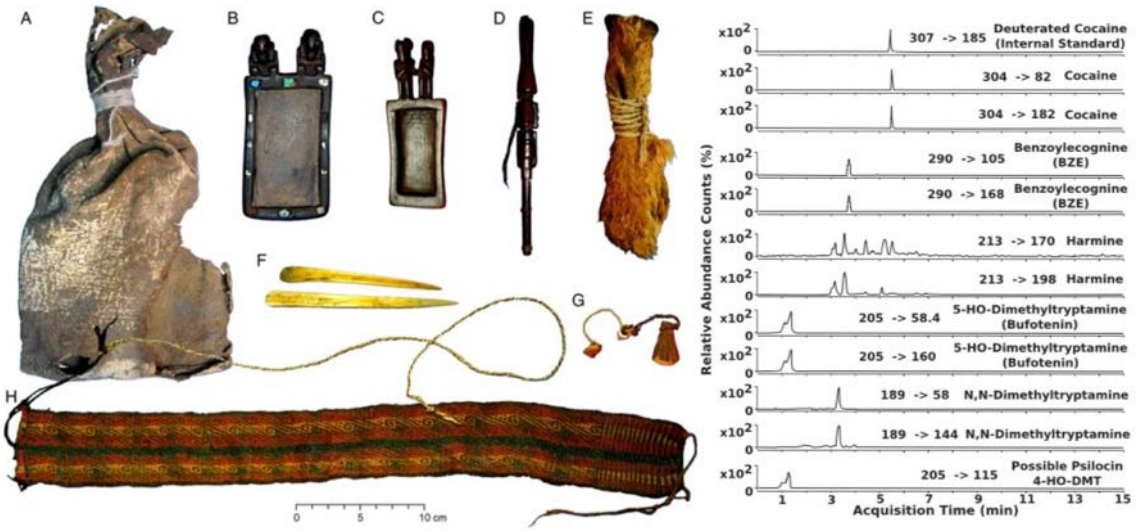
We need to examine at this point why diverse pre-Columbian cultures have consistently managed to incorporate enthogens successfully into their highest cultural expressions, remaining as a spiritual record for archaeologists to discover, while so-called emancipated Western society has made them an absolute taboo, ring-fenced by dire penalties of long-term imprisonment or even death, amid threats of insanity and permanent brain, or genetic damage.

We can again see currents of the schizophrenic attitude of Western society to psychotropic agents in its romantic and demonic attitudes to opium and cocaine. While Samuel Taylor Coleridge composed “Kubla Khan” in 1797, according to his preface, one night after he experienced an opium influenced dream, and Sigmund Freud extolled the virtues of cocaine in his 1884 paper "On Coca", Great Britain had become deeply involved in the trafficking of opium from factories in India to China, against Chinese legislation, in the Opium Wars (1839-1860) with the explicit purpose of addicting the Chinese population, to redress an unfavourable trade balance between the countries. At the same time the Victorian press was hot with scandalous stories of debauchery and dissolution in the opium dens of London. By 1886 Arthur Conan Doyle was writing of the hideous dependence of Sherlock Holmes on cocaine injection and the stage was again set for regarding psychotropic drugs as agents of evil.

At the turn of the twentieth century, long after its spread to the plains Indians in the 15th century, there had been a resurgence of religious peyote use in the US in the form of the Native American Church (Anderson), which has fought a long and tortuous battle for the legal use of the sacrament.

Speak to the peyote with your heart, with your thoughts. And the peyote sees your heart ...
And if you have luck, you will hear thingsand receive things that are invisible to others,
but that god has given you to pursue your path(Schultes and Hofmann).

"God told the Delawares to do good even before
He sent Christ to the whites who killed him ...
God made Peyote It is His power. It is the power of Jesus.
Jesus came afterwards on this earth, after peyote." (Anderson).



Left: Cueva del Chileno ritual bundle from the Lípez highlands of southwestern Bolivia radio-carbon dated to approximately 1,000 C.E. consisting of: outer leather bag (A), expertly carved and decorated wooden snuffing tablets with anthropomorphic figurines (B and C), intricate anthropomorphic snuffing tube with two human hair braids attached to it (D), animal-skin pouch constructed of three fox snouts (L. culpaeus) stitched together (E), two camelid (L. glama) bone spatulas (F), two small pieces of dried plant material attached to wool and fibre strings (G), and a polychrome woven textile headband (H). Artifacts (E and G) were tested using LC-MS/MS analysis. Right: LC-MS/MS results from the fox-snout pouch indicating the presence of cocaine, BZE, harmine, bufotenine, DMT, and peak potentially corresponding to psilocin (Millera et al. 2019).

In 1897 Arthur Heffter isolated the alkaloid mescalin from peyote and the modern era of psychedelic, or “mind manifesting” research began. William James author of “Varieties of Religious Experience” who had tried many psychoactive agents unfortunately had a bad intestinal reaction in 1896 and missed out on its “chromatic” effects, but noted "all kind of odd experiences, mescal, ecstasies etc. give them indeterminate possibilities". It is said that round 1911 the young Adolf Hitler took peyote during his formative period, provided him by apothecary Wilhelm Pretzsche (Andrews 417-425). In 1938 Albert Hofmann synthesized

LSD, but had to wait five years before accidentally absorbing enough on his fingers in 1943 to discover its psychedelic effects. Interviewed shortly before his hundredth birthday, he called LSD "medicine for the soul" and was frustrated by the subsequent worldwide prohibition of it. Nevertheless for several decades these substances remained research materials and were not regarded as dangerous drugs of abuse.

While both opium and cocaine had essentially been legal in the 1800s, cultural migration had begun to cause social problems both through patterns of addiction and through racial prejudice and cultural profiling. Chinese populations in the US were perceived to be addicted to opium and Negro populations were accused of abusing cocaine resulting in rape of white women and improved marksmanship among criminals. A series of tax and drug laws were passed leading to successively tighter restrictions. By 1930 the newly formed Federal Bureau of Narcotics, headed by Harry J. Anslinger, as part of the government's broader push, to outlaw all recreational drugs, advertising marijuana as a “killer drug” inviting “Murder! Insanity!” and “Death!” By 1935 the Geneva Trafficking Conventions outlawed international trafficking in opium, cocaine and cannabis, but the US, headed by Anslinger, refused to sign the final draft because it didn’t include cultivation, production, manufacture and distribution and considered it too weak in relation to extradition, extraterritoriality and the confiscation of trafficking profits. Given these Calvinistic attitudes, it is not hard to understand how the vastly more confounding entheogens might come to be treated.

All records of sacred mushroom use had been lost to history by the turn of the 20th century and it had become assumed that the sacred mushroom was a case of mistaken identity for peyote. However in 1938 Blas Reko and Richard Evans Schultes traveled to Huautla de Jiménez, where Robert Weitlaner had a year earlier located a specimen and managed to find four species of *Paneolus* and *Psilocybe*, including *caerulescens* and *cubensis* (Ott). A year later Weitlaner’s daughter Irmgard witnessed a mushroom velada without partaking, but war intervened. Then in 1953 Gordon Wasson would finally meet Maria Sabina the Mazatec curandero, in Huautla, after strong encouragement from Robert Graves.

It was in his own words, an entheogen - "the divine mushroom of immortality", calling it "Ecstasy!" after Greek *ekstasis* - flight of the soul from the body. “In truth he is the five senses disembodied, all of them keyed to the height of sensitivity, and awareness, all of them blending into one another most strangely until, utterly passive he becomes a pure receptor infinitely delicate of sensation. … Your very soul is seized and shaken until it tingles, until you feel that you will never recover your equilibrium”. He also noted that Greeks call mushrooms *broma theon* "the food of the gods" and specifically likened the experience to the epoptea of Eleusis "For me there is no doubt that the secret of Eleusis lies in hallucinogens". Wasson was to describe the experience as Pentecost and the long-held secret of sacred mushroom again greeted the world. "By comparison with the mushroom, the Element in the Christian agape seems pallid. The mushroom holds the key to a mystical union with God, whereas only rare souls can attain similar ecstasy and divine communion by intensive contemplation of the miracle of the Mass" (Riedlinger, Furst).

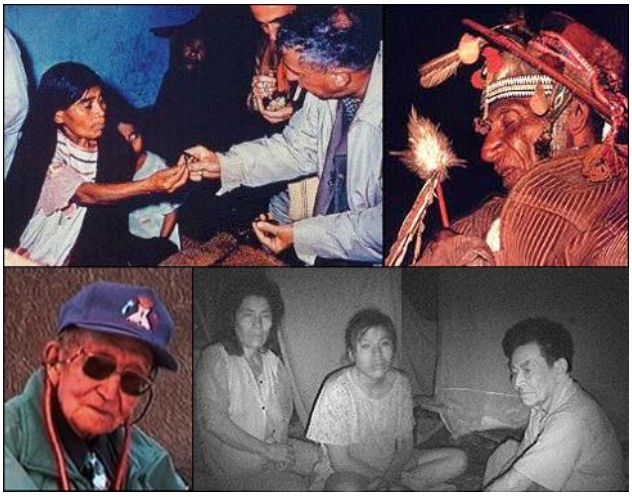


Fig 3: Maria Sabina passing the sacred mushroom to Gordon Wasson (Riedlinger). The renowned Huichol elder Don Jose Matsuwa (Schultes & Hofmann), Tellus ‘Goodmorning’, the roadman at my first peyote meeting in 1976, attending his son’s meeting in 1992 at the age of 93. Senor Trinico by infra-red video in the dark during our ayahuasca ceremony in 1999.

"On both nights RGW stood up for a long time in Cayetano's room at the foot of the stairway, holding on to the rail transfixed in ecstasy by the visions that he was seeing in the darkness with his open eyes. For the first time that word 'ecstasy' took on a subjective meaning for him. ... There came one moment when it seemed as though the visions themselves were about to be transcended, and dark gates reaching upward beyond sight were about to part, and we were to find ourselves in the presence of the Ultimate. We seemed to be flying at the dark gates as a swallow at a dazzling lighthouse, and the gates were to part and admit us. But they did not open, and with a thud we fell back gasping. We felt disappointed, but also frightened and half relieved, that we had not entered into the presence of the ineffable, whence, it seemed to us at the time, we might not have returned, for we had sensed that a willing extinction in the divine radiance had been awaiting us. … The spirit of the agape of which we have already spoken was a prelude to a wave of generous tender feelings that the mushroom aroused in everyone ... Twice in the course of the night the

Senora reached out her right hand to me and sought contact with my fingers in friendly greeting, across the chasm of the language barrier - Gordon Wasson & Valentina Wasson - Mushrooms Russia & History (Riedlinger).

To Maria Sabina, although also using it for curing maladies, it was also an entheogen, reciting it's illumination in her chants:

"Woman who thunders am I, woman who sounds am I.
Spiderwoman am I, says hummingbird woman am I says
Eagle woman am I, says important eagle woman am I.
Whirling woman of the whirlwind am I, says
woman of a sacred, enchanted place am I, says
Woman of the shooting stars am I. ...
I'm a birth woman, says I'm a victorious woman, says
I'm a law woman, says I'm a thought woman, says I'm a life woman,
I am a spirit woman, says I am a crying woman, says
I am Jesus Christ, says ... I'm the heart of the virgin Mary."
(Mushroom Ceremony - Smithsonian Institute)

Her vision of the inner world of the sacred mushroom is both entheogenic and prophetic:

"There is a world beyond ours, a world that is far away, nearby and invisible. And there is where God lives, where the dead live, the spirits and the saints, a world where everything has already happened and everything is known. That world talks. It has a language of its own. I report what it says. The sacred mushroom takes me by the hand and brings me to the world where everything is known. It is they, the sacred mushrooms that speak in a way I can understand. I ask them and they answer me. When I return from the trip that I have taken with them I tell what they have told me and what they have shown me. The more you go inside the world of teonanacatl , the more things are seen. And you also see our past and our future, which are there together as a single thing already achieved, already happened . . . I saw stolen horses and buried cities, the existence of which was unknown, and they are going to be brought to light. Millions of things I saw and knew. I knew and saw God: an immense clock that ticks, the spheres that go slowly around, and inside the stars, the earth, the entire universe, the day and the night, the cry and the smile, the happiness and the pain. He who knows to the end the secret of teonanacatl - can even see that infinite clockwork" (Schultes & Hofmann).

The reaction of the US government was swift. Within a few days, a Mexican botanist had phoned the CIA to confirm Wassons find, and a CIA agent James Moore was dispatched as a mole on Wasson's return trip, so that the government could use it as a mind-altering drug in chemical warfare and interrogation, in Project MKULTRA, demonstrating the Western establishment's proactively malign attitude and complete failure to understand the nature and potential social benefits of entheogenic sacraments (Riedlinger), also implicated in the mass hallucinogenic poisoning at Pont-Saint-Esprit Frace in 1951 (Thomson).

In 1948, Rappoport had discovered a hormone, named serotonin for its effect on vascular tone in cow blood serum, which was identified in 1952 to be 5-hydroxytryptamine, or 5HT, and was discovered in high concentrations in brain tissue in 1953. By 1954 Gaddum and Hameed, and Woolley and Shaw, both suggested the effects of LSD might arise from 5HT receptor agonism, or antagonism, because of the obvious similarity with psilocin (Braden). However as late as 1973 electron donation was still being advanced for the 'LSD receptor' for the obvious reason that serotonin itself, although a 5HT receptor agonist, did not cause hallucinations (Nature 242, 367).

By 1954 Aldous Huxley had captured the imagination of young readers in his description in "The Doors of Perception" of his experiences with mescalin:

"Confronted by a chair which looked like the Last Judgment - or, to be more accurate, by a Last Judgment which, after a long time and with considerable difficulty, I recognized as a chair - I found myself all at once on the brink of panic. This, I suddenly felt, was going too far. Too far, even though the going was into intenser beauty, deeper significance. The fear, as I analyze it in retrospect, was of being overwhelmed, of disintegrating under a pressure of reality greater than a mind, accustomed to living most of the time in a cosy world of symbols, could possibly bear. The literature of religious experience abounds in references to the pains and terrors overwhelming those who have come, too suddenly, face to face with some manifestation of the Mysterium tremendum. In theological language, this fear is due to the incompatibility between man's egotism and the divine purity, between man's self-aggravated separateness and the infinity of God. Following Boehme and William Law, we may say that, by unregenerate souls, the divine Light at its full blaze can be apprehended only as a burning, purgatorial fire. An almost identical doctrine is to be found in The Tibetan Book of the Dead, where the departed soul is described as shrinking in agony from the Pure Light of the Void, and even from the lesser, tempered Lights, in order to rush headlong into the comforting darkness of selfhood as a reborn human being, or even as a beast, an unhappy ghost, a denizen of hell. Anything rather than the burning brightness of unmitigated Reality - anything!"

The eloquently expressed popularity of these agents began to illuminate the public imagination, particularly among young people breaking out of a conservative post-war colonial Christian straight-jacket. From 1960 to 1962, Timothy Leary, Richard Alpert, Ralph Metzner and others ran a series of projects involving mescaline and psilocybin now referred to as the Harvard Psilocybin Project. In the Marsh Chapel Experiment, run by a Harvard Divinity School graduate student under Leary's supervision, Boston area graduate divinity students were administered psilocybin as a part of a study designed to determine if the drug could facilitate the experience of profound religious states, and nine out of the ten divinity students reported such experiences.

Leary's espousal of LSD, originated from an entheogenic religious experience with sacred mushrooms:

"Three years ago on a sunny afternoon in the garden of a Cuernavaca villa, I ate seven of the so-called 'sacred mushrooms', which had been given me by a scientist from the University of Mexico. During the next five hours, I was whirled through an experience which could be described in many extravagant metaphors, but was above all and without question the deepest religious experience of my life. … A profound transcendent experience should leave in its wake a changed man and a changed life. Since my illumination in August 1960, I have devoted most of my energies to try to understand the revelatory potentialities of the human nervous system and to make these insights open to others. I have repeated this biochemical and (to me) sacramental ritual over fifty times personally and, almost every time, I have been awed by religious revelations as shattering as the first experience" (Weil).

At about the same time a rubber tapper José Gabriel da Costa in Porto Vehlo, Brazil inspired by his visions under the potion, began a church the UDV or União do Vegetal based on the Amazonian entheogenic brew ayahuasca, partaken by diverse tribal cultures claiming roots back to the tenth century BC. Also contemporaneous was the discovery by Calvin Stevens of ketamine, named a "dissociative anaesthetic" by the wife of Edward Domino, the first person to test it on humans after describing his amazement at seeing a person who was fully awake but "not there." It was found to be a potent hallucinogenic drug, and the effects were described as trance-like (Jansen).

However reaction to the experimental use psychedelics including LSD led by 1962 to end of the official experiments, an investigation by the Massachusetts Department of Public Health that was eventually dropped, and the firing of Leary and Alpert, ruining promising academic careers, and sending them on a mission to popularize their affects with student culture in a collision course with conventional society, encouraging the next generation to 'turn on, tune in and drop out' - in retrospect a naïve and fanciful attempt to convert a mono-phasic society (Walsh & Grob) lacking the multi-layered spiritual traditions which had enabled the ritual use of such substances for millennia in pre-Columbian cultures. At the time only mescaline and the peyote cactus were illegal, with some uncertain exceptions for the Native American church. By 1966 psilocybin had become a schedule I prohibited drug, swept along by social anxiety about LSD use, and scientific research outside animal studies came to a halt for decades.

History now embarks on the florid journey that led immediately to Ken Kesey and the Merry Pranksters, the Electric Kool-aid Acid tests, the Grateful dead singing "Dark Star" and the Beatles "Lucy in the Sky with Diamonds", and the hippie revolution of free love, all the time denounced by the authorities and treated as social mayhem by the traditional media. At Stanford in 1959, Ken Kesey had volunteered to take part in MKULTRA at the Menlo Park Veterans Hospital, where he worked as a night aide studying the effects of LSD, psilocybin, mescaline, cocaine, AMT, and DMT on people. Kesey wrote many detailed accounts of his experiences with these drugs, both during the Project MKULTRA study and in the years of private experimentation that followed.

On the basis of a few iconic cases such as Charles Manson, who was a manifest psychopathic long before his hippie debut, who had pleaded to be allowed to stay in jail at the age of 32, having spent more than half his life in institutions, the whole flower power movement was consigned to suppression echoing the suppression of the Gnostics in the witch hunts and Inquisition. Timothy Leary became a cultural whipping post for the establishment's paranoiac vendetta. Having been caught with a couple of marijuana roaches in 1965 and 1968, he appealed the 1965 offence successfully to the Supreme Court and stood for Governor of California, inspiring the Beatles song 'come together' as a campaign number. However in 1970, Leary was sentenced to 20 years in prison for the 1968 possession charge but later used his psychological guile to escape. He and his wife were smuggled out of the US by the Weathermen leading to a long international manhunt, refusal by Switzerland to extradite, and eventual capture on board a US airliner in Afghanistan. On his re-incarceration he played double agent and secured early release without incurring the ire of the underground.

Fig 4: Timothy Leary, Alex and Anne Shulgin with one of his phenylethyamine molecules (Alex Grey), Albert Hofmann (Robert Venosa), Ken Kesey and the Merry Pranksters beside the freak bus, the Grateful Dead playing at Haight Ashbury.

Stanley Owsley was a sound producer for the Grateful Dead, who in September 1965 became the primary LSD supplier to Ken Kesey and the Merry Pranksters. By this time, Sandoz LSD was hard to come by. While touring the country with the Dead, Tim Scully met Stanley and claimed that they perfected a pure process. Between 1965 and 1967, Stanley produced more than 1.25 million doses of LSD moving their laboratory out of California when LSD became illegal there. They briefly made DOM or STP but ceased production when it quickly gained a bad reputation. Nick Sand was a humanities student, when he took Mescaline in 1961. He also often visited Millbrook, the communal home of Timothy Leary's League for Spiritual Discovery. During a vision quest on DMT, Sand came to believe that he should devote his life entirely to manufacturing entheogens. He became a criminal as a matter of principle and as an act of civil disobedience, because he believed he was working for a higher good.

In 1969, Nick Sand worked with Tim Scully, producing millions of doses of the Orange Sunshine LSD. Sand was a member of "a secretive group of hippie acid dealers and hashish smugglers known as the Brotherhood of Eternal Love. The purpose of the group was "the aim of transforming the world into a peaceful utopia by promoting consciousness-expanding drug experimentation through LSD. Eventually both were arrested. At his trial, Tim Scully said that his intention was to "turn on the world" and as far as LSD chemists go, "we were doing a public service." Sand relocated to Canada. For roughly twenty years, he formed the core of international LSD manufacturing, producing about 250 million doses. In 1996, he was arrested in Vancouver, Canada, where his laboratory was found with 42 grams of LSD, or roughly 200,000 moderate doses, tested above 100% pure by the government's chemists. By late 2000, he was given an early release from prison, serving just under four years.

This stark cultural division has resulted in a continuing schizoid fracture in Western society pitting forcibly protecting a supposed emancipated society from its own freedom of choice against the right to have personal transformative experiences induced by other psychotropic substances than alcohol or tobacco. Given the prodigious production of Nick Sand alone and the lack of concrete evidence of physical or manifest social harm ensuing from such widespread consumption, and the safety of psychedelics rating far below alcohol and tobacco in terms of risks, as demonstrated in fig 21, the situation is clearly irrational and socially counterproductive.

The varying names associated with these substances illustrate society’s schizoid attitude towards them. The traditional name “hallucinogen” implies ‘mind-wandering’, seeing things that aren’t there. “Psychedelic” or ‘mind manifesting’ puts a more positive spin. “Psychotomimetic” incorrectly implies mimicking psychosis - the way such substances are cited in models of schizophrenia, in contradiction to their capacity to induce integrative healing and restorative life experiences. Finally we have “entheogen” highlighting the commonly reported experience that the altered state manifests a spiritual dimension of union with divinity.
The war on drugs has led relentlessly to the rise of major marijuana, cocaine, heroin and methamphetamine trafficking on an international basis and a cultural civil war in Western society fuelled by the unquenchable appetite of the very culture seeking to repress it, and the insatiable curiosity of the taboos generated by this suppression, fuelling an endemic subterranean underground, leading on to the euphoric dance culture of ecstasy, and with each successive banning to the diversification of a multitude of designer drugs with varied and unpredictable consequences. This is a war of attrition, filling US prisons with social casualties, with distinct racial undertones. This can end well only in the legitimization of psychotropic agents and dealing with undesirable social consequences of hard drugs as a medical problem. The alternative is the complete suppression of any agent that can mimic, or be construed to transform, or liberate consciousness from its cultural straight-jacket - clearly not a conscionable outcome.

Meanwhile many of the people formative of the most creative processes in society today admit they owe a central place in the meaning in their life's quest to entheogens. To take six examples on LSD: Francis Crick, Nobel prizewinning co-discoverer of the structure of DNA later told a fellow scientist that it was LSD, that helped him to unravel the discovery that won him the Nobel Prize (Alun Rees, Mail on Sunday 8/8/04). Kary Mullis controversial Nobel prize-winning discoverer of the polymerase chain reaction for amplifying DNA " I found it to be a mind-opening experience. It was certainly much more important than any courses I ever took. What if I had not taken LSD ever; would I have still invented PCR? I don't know. I doubt it. I seriously doubt it" (BBC Psychedelic Science). Steve Jobs said taking LSD was one of the two or three most important things he had done in his life. He said there were things about him that people who had not tried psychedelics - even people who knew him well, including his wife - could never understand" (The New York Times, 10/5/11). Alex Gray: "Twenty-five years ago I took my first dose of LSD. The experience was so rich and profound, coupled as it was with the meeting of my future wife, Allyson, that there seemed nothing more important than this revelation of infinite love and unity. Being an artist, I felt that this was the only subject worthy of my time and attention. Spiritual and visionary consciousness assumed primary importance as the focal point of my life and art. My creative process was transformed by my experience with entheogens." Stanislav Groff: "In one of my early books I suggested that the potential significance of LSD and other psychedelics for psychiatry and psychology was comparable to the value the microscope has for biology or the telescope has for astronomy. My later experience with psychedelics only confirmed this initial impression." Albert Hofmann: "When you study natural science and the miracles of creation, if you don't turn into a mystic you are not a natural scientist. I think that in human evolution it has never been as necessary to have this substance LSD. It is just a tool to turn us into what we are supposed to be."

We like to look back on previous cultures with irony at the severe taboos they instituted, such as stoning women for adultery, burning people at the stake for heresy, or throwing the early Christians to the lions for their somewhat obsessive beliefs. In retrospect, these penalties look like desperate attempts to repress natural reproductive and intellectual choices, in societies who perceive these individual freedoms as existentially threatening because the society itself is founded on false premises that leave it vulnerable unless dire measures are taken to repress such feared individual freedoms. It thus serves us well to ponder why our so-called emancipated Western society has chosen to taboo the very agents that might bring us a new understanding of the fabric of existence and our place in the universe.

"All the cultures in human history except the Western industrial civilization have held holotropic states of consciousness in great esteem. They induced them whenever they wanted to connect to their deities, other dimensions of reality, and with the forces of nature. … They spent much time and energy to develop safe and effective ways of inducing them" (Grof).

Essentially, as already noted, the problem comes down to Western society lacking any social process for deep mental exploration in a safe sheltered setting, guided by respected elders, or people who have personal experience of transformative agents, who are able to provide protective guidance to ensure a safe passage and a healing outcome. In the sophistication of modern society, this is a contradiction because this has been a common feature of human traditional peoples throughout human history. An entertaining account of the transition from the birth of psychedelics to the current era of psychedelic science can be found in "How to Change Your Mind" (Pollan 2018).

Although Christianity is a nominally sacramental religion, centered on the Eucharist, the Christian roots of Western culture are maladapted to inner mysteries conveyed through forbidden fruit, quickly condemned as diabolical or at least false agents of insanity and decadence. The mystical path has been under siege in Christianity from the fourth century, when Athanasius repressed the Gnostic gospels in favour of the social conformity of the Catholic canon, despite reemergence of mystical traditions in the Cathars and Albigenses, the Free Spirit Movement and mystics, from Meister Eckart to Margurete Porete, who was burned at the stake for writing "Mirror to the Simple Mind". Compounding this, particularly in the US, is the role of a government whose electoral majority depends on appeasing the conservative vote, and the consequent oppressive use of the law, strongly aligned with the capitalist ideal of a mindless consumer society, like Huxley's "Brave New World", where drugs are only accepted as pacifiers of the ongoing consumer culture, tranquillizers and anti-depressants are compulsively over-prescribed, and agents which seem to manifestly unhinge these cultural norms are perceived as existential threats.

The rapidity with which psilocybin was outlawed, without evidence of physical, or social harm, in contradiction, both to the historical evidence of long-held spiritual devotion, and ongoing experiments confirming fulfilling spiritual and religious experiences in Western subjects, shows the process to have been

driven by cultural paranoia rather than the public good. The consequence has been that, in an era of very rapid scientific progress, unearthing sweeping discoveries, scientific research into entheogens in humans was consigned to oblivion. It has thus taken the work of a few researchers, including the those at the Heffter Institute in Europe, MAPS conferences, Erowid, and of course the work of Shulgin, Nichols, Stamets, Griffiths and others in the US to bring us to the point, nearly fifty years later, where the socially beneficial properties of these agents are again becoming recognized and in particular their capacity to elicit mystical experiences of long lasting value and significance years later, as reported by both the subjects and their partners and acquaintances (Griffiths et al. 2006, 2008, 2001, Szalavitz 2011a, Brown, Pollan).
Although MDMA, or ecstasy, is an entactogen, and not strictly an entheogen, it has clearly become a drug of emotionally transformative ritual use, so this history would not be complete without including the story of E. The term entactogen, for any chemical agent that induces feelings of empathy and connectedness in the user, was coined by David Nichols as an alternative to empathogen, owing to the potential for improper association of the latter with negative concepts related to the Greek root "pathos" (suffering).

The tale of Ecstasy (Jennings) forms another chapter in the futility and confusion of the war on drugs. MDMA was first accidentally synthesized in Merck's laboratories in 1912, but lay forgotten until Sasha Shulgin resynthesized it in 1976. Shulgin saw it as a valuable therapeutic psychological drug and it remained largely in therapy circles until Michael Clegg, an ex-priest, who had married, and found MDMA opened the boundaries of positive emotions and empathy between people, named it “ecstasy” and came to the conviction that his “mission was to get ecstasy to the wide world”. He began to produce hundreds of thousands of ecstasy tablets and distribute them legally in Dallas Texas where an exponentially rising demand led by 1985 to him producing 500,000 tablets a month, making him the first ecstasy millionaire.

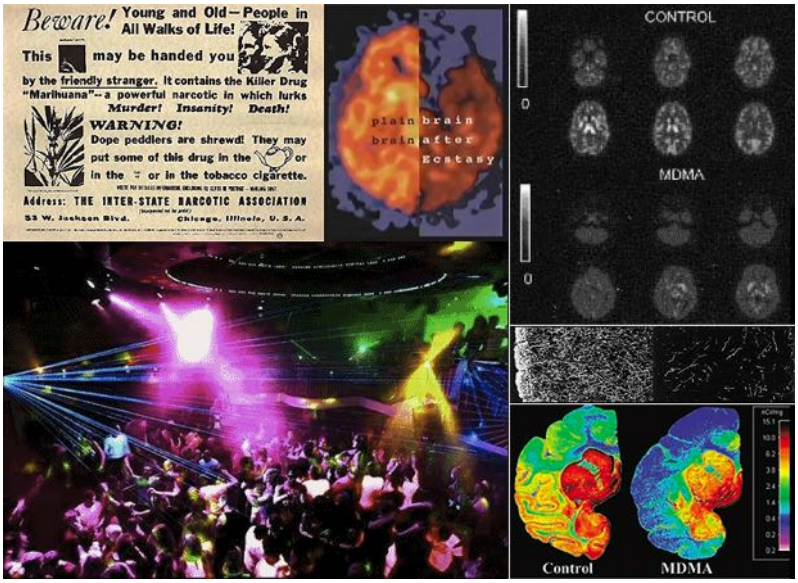


Fig 5: (Clockwise) Nothing new under the sun. Late 1930s scare marijuana poster “Murder! Insanity! Death! Late 1990s brain full of holes on ecstasy poster. Lancet study used as a basis (McCann et al). Claimed damage to serotonin Raphe pathways seven years after monkeys were dosed with MDMA (Hatzidimitriou et al). Claimed evidence of MDMA dopaminergic damage in baboons later retracted (Ricaurte et al). The trance rave has become the ritual celebration of empathy of an entire generation.

However the DEA, threatened by ecstasy's manifest lack of harm and socially positive profile, being used by relatively ordinary people rather than a bunch of weird hippies, felt it imperative to suppress the phenomenon, lest it undermine the entire attempt to treat recreational drugs as dangerous enemies of society. Ecstasy was thus, without any evidence of social harm, in 1985 classified as schedule 1, along with cocaine and heroin, ending its legitimate therapeutic use and driving its manufacture underground. A major part of ecstasy production then transferred to Europe with increasingly massive black market imports arriving back in the US.

Ecstasy became the drug of choice in the rave party scene, driven as much by ecstasy's pro-social bonhomie as by trance music and light shows. The NIDA then embarked on a public campaign to strike fear into prospective ecstasy users, by claiming that a single dose could permanently damage the brain, using a factually flawed scientific study by George Ricaurte of the Johns Hopkins School of Medicine claiming to show vast areas of the brain of ecstasy users were full of full of holes due to loss of serotonin function. When in 2002 Ricaurte published a follow up study in Science purportedly of MDMA’s effects on rodent brains, he was forced to retract it, claiming the chemical supply company had incorrectly labeled methamphetamine as MDMA, which the company overseen by the DEA denied, suggesting intentional scientific fraud on the part of the US government. When these two strategies failed, attempts were made to exaggerate the number of cases of ecstasy deaths, however James Gill, Deputy Chief Medical Examiner New York City states that of 19,000 deaths undergoing autopsy over a 3 year period, only 22 people had ecstasy in their system at the time of death and of these only 2 could be construed to have died as a result of ecstasy alone. Around 2100 people die from drug overdoses in NY in a 3 year period, around 20% of which are due to paracetamol,

dwarfing the ecstasy deaths. Given the fact that, according to the DEA up to 110 million doses of ecstasy were consumed in the NY area during this time, these claims also have to be seen as part of a campaign of disinformation. Nevertheless MDMA has been found to be neurotoxic in rodents and there is some evidence of long-term effects in humans, which we will examine in due course.

2: The Enigma of Subjective Consciousness

Part of the reason psychedelic entheogens pose such a paradox for Western society is that, although we have decoded the human genome, come close to discovering the theory of everything describing the fundamental forces of nature and the cosmological process, and become a global society driven by digital computer technology, with the powers of nuclear self-destruction and global impact on the biosphere, the nature and origin of subjective consciousness remains an unresolved abyss in the scientific description.

This leads to the so-called ‘hard problem in consciousness research’ (Chalmers) - the fact that conscious qualia and other attributes of subjective experience are so fundamentally and qualitatively different from the objects and processes of the objective description that no brain processes such as electrical activity associated with cognitive processes in the gamma band (Crich & Koch), or conceptual models such as multiple drafts (Dennett), can form an adequate explanation. The best we can do is link coherent excitations in the global workspace with conscious processes as opposed to the incoherent unconscious processing of different brain regions (multiple references under Consciousness and Global Workspace).

Although the scientific description tells us the world around us is made out of molecular matter and that we as biological organisms are dependent on our fragile brains to survive and remain conscious, we gain this understanding only as a consensus agreement about our subjective conscious experiences, which are our only veridical access to the physical universe, from birth to death. Although brain science sees subjective experience as merely an internal model of reality constructed by the brain, it is actually through our subjective consciousness that we build up our consensual description of the physical world, both in early childhood and through learning scientific ideas of the natural world, so in this sense, subjective experience is primary and the physical world is inferred. Moreover the existential status of internal experiences, from dreaming REM sleep to meditative and visionary experiences, remains undetermined. From the subjective point of view, dreams can be as real and rich as waking experiences, and their explanation purely in terms of memory consolidation processes remains ambiguous.

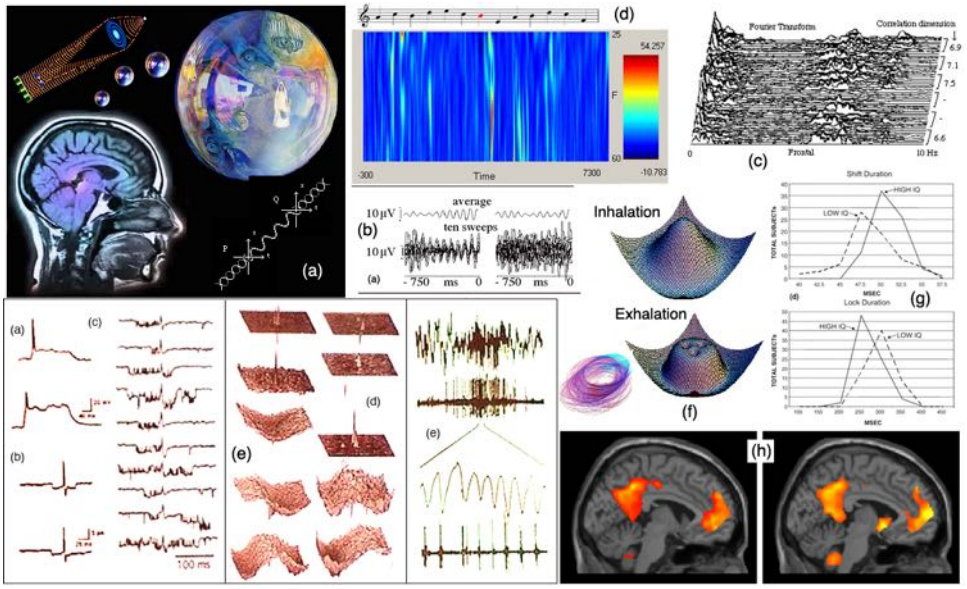


Fig 6: (a) The existential nature of subjective experience and its relationship with autonomous will remains unresolved. It’s anticipatory properties could be a manifestation of quantum properties, here illustrated by the Wheeler delayed choice experiment and the transactional interpretation of quantum mechanics. (b) responses gain wave coherence (left) when their temporal occurrence becomes anticipated (Basar et al). (c) The eeg consists of broad-spectrum oscillations characteristic on non-linear chaos, also manifest (d) in active brain states such as recognizing an odd note in the wavelet transform frequency profile (King ROC). (e) Discrete change at an ion-channel can excite a hippocampal cell which in turn can result in cortical excitations through stochastic resonance (Liljenström & Uno). (f) Freeman’s model of learning through chaotic excitations forming new strange attractors (Skarda & Freeman, Freeman). (g) High IQ is associated positively with phase shift durations and negatively with phase lock duration consistent with phase coherence and transitions involving disordered intermediates (Jung-Beeman). (h) Brain states involving envisaging future situations are almost indistinguishable from those dealing with past memories suggesting the brain is organized to deal with past and future using a single space-time process (Addis et al, see also Marshall, Hassabis et al, Szpunar et al).

This suggests that the subjective and objective aspects of existential reality might be complementary. The tantric origin says precisely this - that the existential origin lies in intimate coital fusion of subject and object, which in their retreat from union become the subjective conscious mind (Shiva) dancing the dance of Maya or illusion, in which the cosmic consciousness of the observer becomes lost in the manifold phenomena of the objective world (Shakti), perceived by individual sentient beings. Likewise the Tao is a complementarity between creative and receptive Yang and Yin principles in nature. The quantum description of the physical universe is similarly founded on complementary wave-particles, leading to a series of other complementarities, such as between matter-forming fermions and force-bearing bosons.

Current cultural perspectives on existential reality remain in a schizophrenic state between a purely materialistic perspective and religious cosmologies inconsistent with physical reality. The materialistic view is that we are simply chemical machines, that subjective consciousness is just an internal model of reality constructed by the biological computer of the brain, that mind is an illusion which can have no effect on matter and that all human action is no more and no less than a complex mechanism. If we took this description at face value, there would be no point in life, no meaning in existence, and the simplest act of voluntarily deciding to go for a walk in the park would be a catatonic delusion, for in the harsh light of reality, our conscious minds would have no control over our physical bodies.
At the other extreme religious people believe that the universe was created in seven days by God producing the plants before the Sun and Moon, that flawed nature is going to be discard in the Rapture, where we are all going to be assigned to a heavenly life in the skies, or condemned to eternal hell-fire and damnation amid visions of feathery-winged angels and the intimate presence of God in the form of an ancient man with white hair. This is clearly a mentally driven-description, consistent only with a naïve flat-Earth view of the heavens as great domes in which the stars are set, while we know the upper atmosphere is a vacuum, and there is no place for the heavenly host in intergalactic space. Looked at with any integrity we can see that all religious visions, from Genesis to Revelation, are imaginative mental fantasies of the subjective mind, coming from dreams, prophecies and visionary states.

In reality neither of these descriptions are remotely adequate and Western society stands at a cross-roads, where the central enigma of existence is still a complete conundrum pivotal to our understanding of who we are, what we are doing on the planet and how to care for an ever more fragile biosphere and protect the diversity of life and the future generations of humanity from extinction due to our own lack of foresight.
We can gain hints of a possible solution to this existential dilemma by looking more closely at the evolutionary process and at the relation between quantum mechanics and the neurodynamic brain. Firstly the quantum universe is not a deterministic mechanism. Quantum uncertainty means many fundamental processes, such as Schrodinger's cat experiment are unpredictable. Many physicists interested in the mind-brain problem have pointed out the quantum uncertainty could in-principle provide a causal loophole making it possible for conscious mental states to influence a critically poised brain state without physical contradiction. Many processes in neurodynamics, including self-organized criticality, chaotic sensitivity and stochastic resonance show that critically-poised brain states can have tipping points triggered by a single cell, synapse of ion channel, demonstrating quantum events could indeed influence whole brain states. Chandelier cells have been shown to have such recruiting properties (Molnar et al, Woodruff & Yuste).

Notably, although pyramidal neurons have pulse-coded action potential intensities, pattern discrimination in the cerebral cortex depends not on discrete digital signals, but broad spectrum wave fronts, whose phase coherence distinguishes an attended stimulus or attended process from the ground swell of extraneous stimuli. Global phase coherence of excitations across cortical regions is also the basis of the most plausible current idea of how conscious brain states differ from unconscious peripheral processing. Phase coherence of the wave function is precisely the process underlying quantum dynamics as well, since the uncertainty relation between energy and frequency is derived from counting wave fronts.

To understand subjective consciousness it is fruitful to consider how it evolved in biological organisms. Neurosystems are not just electro-dynamic systems but heavily dependent on chemical neurotransmitters. Many of these molecules go back to the first single-celled organisms. Serotonin, our pivotal example for entheogens, has a very early origin with photosynthesis, where the indole group of tryptophan is the receptor of excited electrons. Serotonin and melatonin thus emerge as signalling molecules as soon as bacterial photosynthetic processes provided oxidation potential (Azmitia in Müller & Jacobs) and may have become ubiquitous through horizontal gene transfer (Iyer et al). At another extreme, immune reactions to soil bacteria appear to be able to induce an antidepressant effect in the prefrontal cortex through serotonin emission at the Raphe nuclei (Lowry et al). The hepta-helical protein family, common to G-protein linked serotonin receptors and many other neurotransmitters, as well as the rhodopsin of the eye, although one of the most

sophisticated and diverse receptor types, occupying two percent of the human coding genome, is also one of the earliest to appear in evolution (Azmitia in Müller & Jacobs).

This evolutionary picture means that most of the critical features of both electrochemical excitation, and biochemical modulation, were already in place in excitable single eucaryote cells, in providing them with complex and diverse responses to their environment. One can see this in the neural nets of coelenterates, such as hydra, which has twelve distinct modes of locomotion, where it is not the structured organization of the nervous system which provides for complex behaviour, as there is only a disordered primitive net, which can reassemble along with the entire organism if it is turned inside out, but the dynamic sophistication of the individual neural cells (King 2008).

This picture addresses one fallacy, coming from the artificial intelligence school of thought, that the brain is just a very complex sophisticated computer, which, given the right kind of firmware and software design, could be replicated in principle by a digital computer thus showing consciousness is only a question of computer design. There are several reasons why this is in fundamental conflict with the way the brain evolved. Most, if not all, environmental decision-making problems are computationally intractable and prone to exponential runaway, like the travelling salesman problem, because the complexity of the computation grows super-exponentially with the factorial of the number of incident factors involved. The gazelle can't afford to wait at the cross roads until its computer solves each survival issue or it will surely get jumped by the tiger without ever having made the decision, so the brain has to find a way to make real time decisions regardless of classical complexity.

The brain appears to have solved this problem by utilizing massively parallel processing rather than a set of serial processors with only nominal parallel capacity. However parallel processing is not naturally suited to digital signalling because the traffic management problem of parallel threads becomes unmanageable. To avoid this, the brain appears to use a combination of wave front coherence processing and chaotic sensitivity. Wavefront coherence is ideally suited to parallel processing in precisely the way a hologram is, the wave fronts can be continuously superimposed and only the phase-coherent ones will reinforce. Dynamically this spatial superposition is complemented by non-linear temporal dynamics, which provides for transitions in and out of sensitively-dependent chaos, enabling the dynamics to remain tuned to its own self-organized criticality.

This brings us to an even deeper problem complementing subjective consciousness, that of intentional or 'free' will. All our ideas of personal accountability, and the rule of law and religious guilt, let alone our sense of sanity and personal autonomy, hinge around the notion that we can make conscious decisions about the physical world. Yet science tends to argue that this is an illusion and that we are really helpless victims of our brain state. Hence genetic predispositions have become commonplace defence arguments against criminal culpability.

However many of the environmental decisions our gazelle must make do not depend on determining factors, but on unrevealed contingencies, events yet to happen, and on situations where several choices might all lead to viable outcomes, something akin to collapsing the wave function of Schrodinger's cat in the quantum description. There may be a lion on the mountain path and a tiger on the jungle path, or neither today. What matters is anticipation, and it is here that subjective consciousness is tuned to do two things, firstly to give an immediate hunch which path to take, and secondly to be acutely sensitive in an anticipatory way to existential threats that may be about to strike as the gazelle goes to the water hole.

This gives us a much clearer idea of why the blind watchmaker of evolution arrived at the sappy biochemical conscious brain, rather than a blue gene super-digital computer. And why, despite having 10^{11} neurons and 10^{15} synaptic junctions, the human brain is a lousy computer, no better than a cheap pocket calculator. The brain is not a computer at all, but a real-time space-time anticipator using chaotic sensitivity, wave super-positions and quantum entanglement to anticipate reality, by setting up dynamically unstable global brain states limiting in effective cat paradox experiments, possibly utilizing unusual aspects of quantum reality in the process. Quantum theories including quantum electrodynamics are time-reversible and examples, from the Wheeler delayed-choice experiment, to many manifestations of quantum entanglement and the handshaking processes in the transactional interpretation, illustrate 'spooky' potentialities spanning space and time.

Intriguingly recent brain scan studies have shown the cortical regions excited by looking into the future to be virtually identical to those involved in memorizing the past (Addis et al, Marshall, Szpunar et al) and damage

to episodic memory structures also prevents subjects being able to envisage future events (Hassabis et al), suggesting the way the brain is going about this is in a sense 'time symmetric'. This raises all manner of to be elucidated questions about the anticipatory capacity of subjective consciousness, including reports and studies of precognitive dreaming (Dunne).

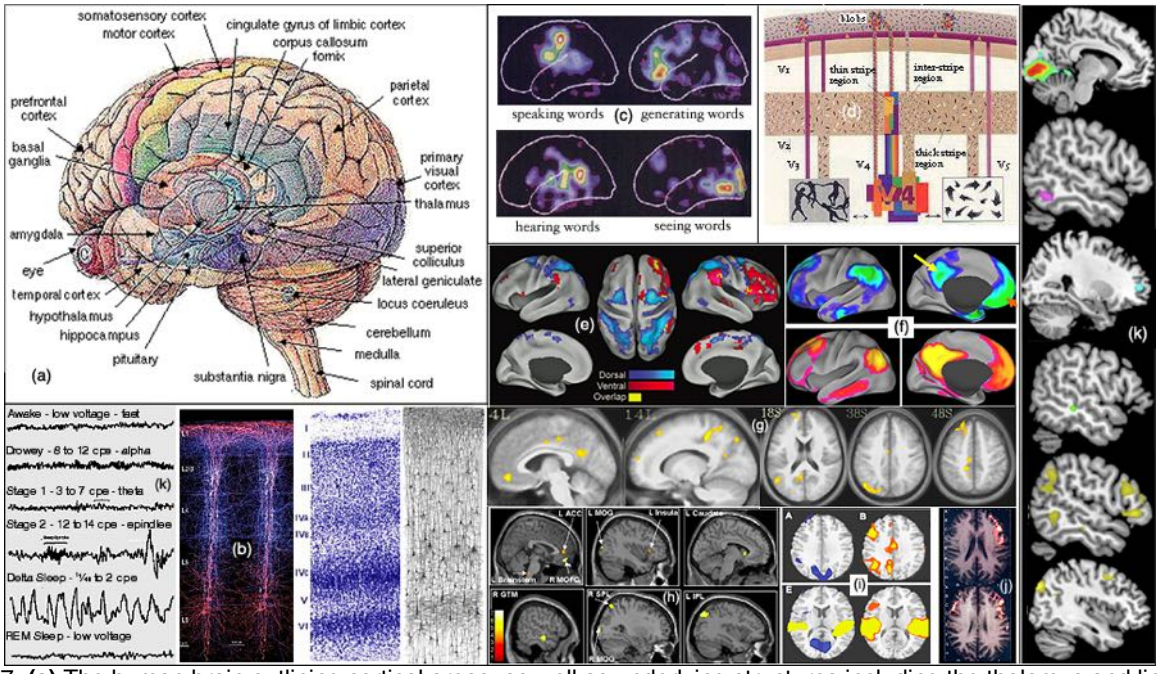


Fig 7: **(a)** The human brain outlining cortical areas, as well as underlying structures including the thalamus and limbic system, including the hippocampus processing long term episodic memory and the amygdala dealing with multi-sensory reactions to flight and fight survival and basal brain structures, including the Raphe nuclei and Locus coeruleus involved in sleep wakefulness cycles. **(b)** The cortex consists of up to six layers of neurons in which pyramidal cells provide the excitatory output from one region to another while inhibitory and excitatory inter-neurons provide lateral inhibition and feedback. The 10^{11} cells in the cortex are believed to be organized into around 10^{8} mini-columns each processing a single feature. The cortex is dynamically organized into functional regions processing features of experience in massively parallel 'computation' here illustrated in verbal tasks **(c)** involving Broca's vocal expression and Wernicke's semantic interpretation areas and parallel processing of visual features **(d)** e.g. of colour and motion. **(e)** There are believed to be two attention systems in the human brain (Fox et al.) a bilateral dorsal attention system (blue) involved in top-down orienting of attention and a right-lateralized ventral attention system (red) involved in reorienting attention in response to salient sensory stimuli which occupies location in the right hemisphere somewhat complementary to the left hemisphere language areas, although the language areas tend to be more bilateral in females, who also show differences in the balance of focal and salient attention responses to crisis. **(f)** A third network has also been associated with mental activity not tied to the immediate stimuli loosely entitled the default circuit, or default network (Raichle et al, Raichle & Snyder, Mason et al, Fox D, Horovitz et al, Buckner et al), because it was found to have decreased activity when attending a sensory task (above) while the same areas become active when resting, following a stream of thought, or daydreaming. This is believed to be involved in rehearsing future scenarios (Marshall) to aid survival. Different forms of meditation display structured forms of control of the attention process and brain activation. **(g)** Zen meditation studies (Pagnoni et al, Ritskes et al) in which subjects are asked to switch from a verbal task to contemplation show transient activity consistent with the default circuit which is more quickly suppressed by experienced meditators more effectively inhibiting verbal thought. **(h)** Carmelite nuns entering oneness with God show fMRI activations in areas in very specific frontal, parietal, temporal and basal areas consistent with directed control (Beauregard & Paquette). **(i)** Likewise Tibetan Buddhists performing compassion meditation for other people's suffering show specific activation in limbic regions including cingulate cortex and insula, consistent with an empathic response to another's pain (Lutz et al 2008). (j) Sex differences in language areas (Shaywitz et al). (k) Three areas involved in Theory of Mind and religious notions top to bottom (Kapogiannisa et al. 2009): (1) Experiential knowledge vs (2) Doctrinal knowledge. (3) God's love vs anger (4), God's lack of involvement (5,6).

3: Fathoming the Mind-Brain Relationship and Experiential Modalities

Both electrodynamic magnetodyamic EEG and MEG investigations and metabolic PET and fMRI scans utilizing radioactive metabolites and nuclear magnetic resonance have provided windows on the active brain in live subjects which give us a much clearer idea of how brain processes correspond to conscious experience. The former have good temporal but low spatial resolution while the latter are slow in time evolution but spatially more precise.

The mammalian brain is dominated by the cerebral cortices, a wrinkled pair of envelopes of neural tissue forming a sheet about a quarter of a metre in area populated by some 10^{11} neurons in five to six distinct layers, consisting of excitatory pyramidal cells mediating the output, innervated by a variety of inhibitory and excitatory inter-neurons, the 'grey' matter, with different regions connected by bundles of axon fibres, the 'white' matter connecting different cortical regions, including traversing the two hemispheres, in a massive conduit called the corpus callosum. Each pyramidal cell has dendrites permeating all the layers, with up to 10^4 incoming excitatory and inhibitory synaptic junctions involving a spectrum of distinct neurotransmitters. It is believed the cortex is organized into around 10^8 mini-columns each consisting of 50-100 neurons responding to one common feature. It is believed that the basis of the EEG's brain waves consists of resonant excitatory and inhibitory circuits in the cortex, and that fast oscillatory activity in the gamma band 30-80 Hz may correspond to active cognitive processes.

With the exception of olfaction, which has direct input through the olfactory bulbs, sensory input to the cortex and output from it, pass through a series of ganglia in the thalamus. Excitation of the cortex is maintained both by active loops between the thalamus and cortex, and by a series of basal brain centres including the Reticular Activating System, and centres mediating specific neurotransmitters, including the Raphe nuclei, and Locus coeruleus, mediating ascending serotonin and nor-adrenaline (nor-epinephrine) pathways which fan out widely across the cortex, entering specific layers to modulate excitatory tone and mediate conscious arousal and the cycles of REM and non-REM sleep. A similar dopamine pathway fans out into the frontal cortex to do with reward. An intriguing slant on the complex role of serotonin in mood is that knockout mice lacking tryptophan hydroxylase 2 which cannot synthesize serotonin, lack all sexual selection in mating, which is reversed by supplementing with 5-hydroxytryptophan (Liu et al). In addition there are loops of activity running from the cortex to the striatum and basal ganglia, to the thalamus and back to the cortex - the CSTC loop, involved in learned motor activities such as piano playing, which also play a role in learned cognitive behavior and can be disrupted by Parkinson's and Huntingdon's diseases. Another loop runs through the cerebellum, to do with bodily balance and finely-timed movement, which also plays a role in finely-timed cognition.

The regions of the cortex broadly form a mathematical transform akin to a hologram (Pribram), consisting of a set of sensory and abstract features defining each subjective experience. Thus each experience consists of multiple features and each feature can be associated with multiple experiences. There is thus no specific cortical centre associated with consciousness and the best correspondence that can be made between conscious thought, as opposed to subconscious processing, is that conscious processing corresponds to globally coherent excitations channelled through the major attention networks, as opposed to regional processing which is 'out of phase with major global processes but might come to contribute to them with the changing brain state.

A good idea of the way features are mapped across the cortex can be gleaned from examining the major cortical areas. The rear occipital cortex contains primary visual areas responding to lines of a given orientation, and with increasing abstraction, more abstract features such as human faces, facial expressions, and as we move forward across the parietal lobe, spatial relationships, such as finding one's way through the city. Colour and motion are processed in parallel in complementary regions and over twenty different visual areas have been identified dealing with different visual aspects.

Where the parietal deals with spatial relationships, where things are, the temporal deals with what they are. Hearing is processed to either side of each cortex in the temporal lobes, which also have major functions in representing temporal processes like melodies, semantic memory, and associating a given situation, with a variety of others sharing abstract features with the current one. Many features of hearing, such as melody, pitch and rhythm are processed in parallel in different areas, although the primary auditory cortex is believed to have a tonotopic map similar to the line detectors of the visual system.
Separating frontal areas of the cortex from the parietal is the deep fold of the Sylvian fissure. To the rear of this is the somato-sensory cortex with a map of the bodily areas, complementing our visual experience of the outside world with our tactile sensations of ourselves. To the frontal side of the fissure we have a corresponding motor map of musculature and bodily actions. As we move further forward into the prefrontal cortex we have increasingly abstract features of action, consisting of how we apply focussing attention to control our thought processes, and our idea of our active goals and what we want to achieve in life. Many specific prefrontal areas governing forms of executive control have been elucidated from studies of the effects of damage to these areas. Some prefrontal areas affect cognitive control of attention while others such as the orbito-frontal leave intellect and IQ unaffected but disrupt the person's capacity to make realistic emotional life decisions. The region around the principal sulcus of the frontal lobes contains both an active

representation of the visual field, enabling working memory to anticipate actions in time, and a representation of what these things are, forming a complementary relationship with parietal and temporal regions in working memory (Kandel et al). We can thus envisage conscious thought processes in terms of a 'global workspace' consisting of major feedback resonances between the frontal cortex and the temporal and parietal mediating the spatial and temporal aspects of the ongoing decision-making process.

On the inner side of the cortical sheet facing the centre plane is the cingulate cortex, dealing with emotional representations. This is also connected with the extreme of the temporal lobe and two other centres on the periphery of the cortical sheet, the amygdala and hippocampus in a global feedback loop loosely entitled the 'limbic system', associated with emotional dynamics. The amygdala has a role in integrating sensory experiences in relation to flight and fight survival and the hippocampus has a pivotal role in laying down experiences into sequential memory. Temporal lobe epilepsy can give rise to complex orchestrated experiences, some of which can be given a quasi-mystical status by the subject. This caused the neuroscientist Ramachandran to suggest that Temporal lobe excitation carrying across to the amygdala could be the basis of religious experiences of emotional exaltation combined with overwhelming significance - the so-called "God spot". At the least this gives an interesting interpretation of religious fervour as an idiopathic brain state (Ramachandran & Blakeslee, Persinger, Bielo). Kapogiannisa et al. (2009) propose an integrative cognitive neuroscience framework for understanding the cognitive and neural foundations of religious belief. Their analysis reveals 3 psychological dimensions of religious belief (God's perceived level of involvement, God's perceived emotion, and doctrinal/experiential religious knowledge), which functional MRI localizes within networks processing Theory of Mind regarding intent and emotion, abstract semantics, and imagery, well-known brain networks, thus supporting theories that ground religious belief within evolutionary adaptive cognitive functions.

Several key processes, including language, are believed to be lateralized, enabling the two cortices to have complementary functions. For example, language meaning is processed in the left temporal Wernicke's area and fluent execution in the left frontal Broca's area, although women often appear to have a more bilateral processing of language, in which right hemisphere activity might be associated with creative use of language. Due partly to some intriguing experiments in which the corpus callosum of intractable epileptics has been severed, the concept of lateralization has led to some fanciful concepts with only partial validity, stylizing the left hemisphere connected to the right hand with structured organized processing and the elusive right hemisphere with intuitive and creative processing.

Consistent with this view, two opposing global attention systems have been identified, one the dorsal attention network deals with focal attention in the global workspace and is bilateral connecting areas such as the frontal eye fields to parietal and other areas. Complementing this is the ventral attention network whose role is to bring in salient stimuli, important to the subject, from the periphery. Intriguingly this has lateralized activity in the right cortex, complementing the left hemisphere regions traditionally associated with language, lending support to the above model of lateralization. A third system sometimes called the salience network (Seeley et al. 2007), closely overlapping with the ventral network (Farrant & Uddin 2015), connects the frontal anterior insula and the anterior cingulate, involving fast-transmitting von Economo neurons, and may mediate integrated bodily interoception, emotional and cognitive awareness and timed framing of the immediate present, forming a central process of self-consciousness (Allman et al, Cauda et al, Craig, Williams C). It may also be associated with intentional will (Parvizi et al. 2013).

A fourth system, the 'default network', which acts in complementary mode to the salience network is associated with mental activity not grounded to any immediate activity. It was first discovered because there were areas with enigmatic deactivation in a variety of brain studies. When subjects were then tested just resting or daydreaming the same areas were activated. The default circuit is activated by processes as diverse as autobiographical memory, envisioning the future, theory of mind, moral decision-making (Buckner et al, Mason et al, Raichle M. & Snyder), as well as mind-wandering activities such as daydreaming and worrying. The default circuit is believed to be a state in which we aid our survival strategies by using down time to rehearse impending situations of significance to enhance our ability to cope with them successfully. It has also been associated with improved creative thinking over focussed working memory, for example in solving counter-intuitive puzzles (Christoff et al).

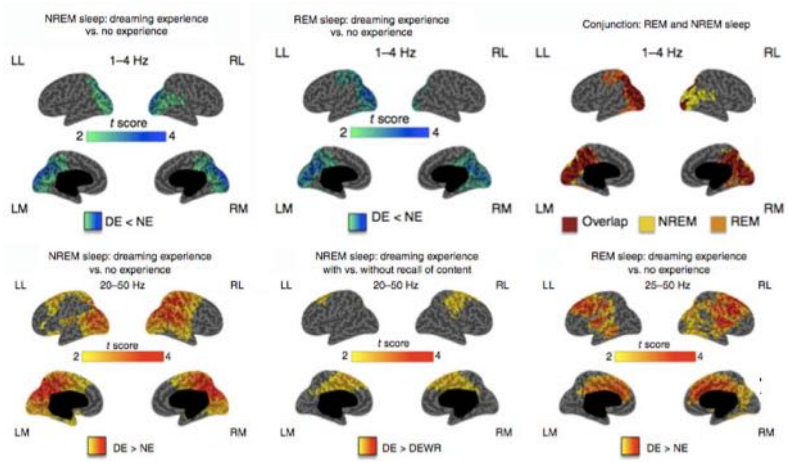


Fig 7b: Dreaming is conventionally associated with periods of REM or rapid eye movement sleep in which the EEG closely resembles waking brain waves, rather than the slow, high amplitude waves of deep sleep, but the above EEG portraits show that dreaming is more closely associated with high frequency activation of key hotspots involving visual and other areas in a manner that can occur in both REM and NREM sleep (Siclari et al. 2017).

Dreaming, or REM sleep remains an enigmatic and life-shaping aspect of subjective experience whose physiological and experiential status remains unresolved. Sleep begins with shorts EEG bursts called sleep spindles interrupting waking EEG and enters a series of cycles, in which waves of deep slow wave SWS sleep alternate with rapid eye movement REM or dreaming sleep. During phasic REM bursts, separated by tonic REM where there is residual alertness the cortex has an EEG similar to the waking state, with pronounced thalamo-cortical activity (Wehrle et al), and the body, except for the eyes, is effectively paralysed by a filter in the basal brain. The cycles of deep sleep are driven by synchronous burst firing in the thalamus interrupting the low voltage asynchronous passage of information to the cortex, associated with the activity of waking and REM sleep. Sleep cycles, although they appear to occur widely across the animal kingdom from arthropods (Shaw et al, Hendricks et al) to vertebrates (Hobson), vary a great deal among mammals with different circadian habits (Siegel 2001, 2005, 2008). The sleep cycle, like the default network, has been associated with aiding the brain in forming better responses to strategically stressful situations plaguing waking life. Although the REM state is similar to waking EEG, fMRI and PET scans show reduction of prefrontal activity and heightened activity in visual areas, as shown in fig 11.

Both REM and non-REM sleep have been associated with memory re-encoding and consolidation. Non-declarative aspects of memory, from solving the towers of Hanoi to physically manipulating an unstable object, show significant improvements from the learned plateau with specific sleep phases, from REM, through light stage 2, to deep SWS sleep. Episodic memories are thought to consist of multiple hippocampally linked memory traces located within neocortical regions and dependent on the hippocampus for their integrated recall, Cycles of SWS and REM sleep appear to be associated with re-encoding of emotionally significant memories, with information passing between the hippocampus holding space-time indices of significant recent experiences into long term optimized form in the prefrontal cortex. Hippocampal activity is enhanced over other activity in REM as against both waking and non-REM sleep, while the dorsolateral prefrontal cortex, involved in decision-making and memory, becomes further inactivated. Low cortisol and reduced reticular acetyl-choline activation early in sleep favours cycles of deep SWS, with cortisol rising slowly over the night, as periods of REM sleep become more accentuated. Studies have detected replays of spatial tasks in the hippocampus, time-compressed in SWS, and then in REM. REM is also believed to enhance synaptic plasticity resulting from adapting to novel environments, enhancing the adaptive response (Payne & Nadel, Stickgold, Stickgold et al, Maquet et al, Nielsen).

These cycles are mediated by reciprocal changes in activation between the reticular activating acetyl-choline system and serotonin, nor-adrenaline and dopamine pathways fanning out across the cortex from the hypothalamus and basal brain nuclei (Saper et al). In REM, the Raphe nucleus serotonin and Locus coeruleus nor-adrenaline pathways mediating cortical responsiveness and arousal in the waking state are silent, while there is reticular activation of acetyl-choline pathways, in excess of the waking state and an EEG similar to waking, rather than the light sleep spindles, or slow waves of deep sleep.

Memory processing may be consistent with many of the experiential features of dreaming, such as bizarre content, which may appear to mix features of many experiences, and dreams being perceived as direct experiences in the present, often having emotionally charged character. Although dreams can be hard to remember, and episodic memory is idiosyncratic, dreams and particularly intense nightmares, can have substantial episodal content. Furthermore a person can often retrogressively remember quite long sequences of dream episodes on lying still on waking from a dream provided the weird disconnections plaguing dreaming experience can be negotiated. Brain scans of REM sleep show strong activations of

perceptual, e.g. visual areas, while the prefrontal cortex has reduced activity consistent with the relative difficulty we have controlling the direction of our dreams and also with the memory consolidation model.

Dreams can have a very rich existential status, often as convincing to the experiencer as waking life, making it hard to give oneself criteria to distinguish dream from reality, for example to endeavour to enter a lucid dreaming state. The existential status of dreaming experience remains undetermined, along with any perceived implications for subconscious discovery or prophetic precognitive hunches. Although dreaming reality may be just a manifestation of memory processing, just as waking life may be just an internal model of reality constructed by the brain, the existential nature of dreaming experience remains a challenging and very different realm from waking experience, whose potentialities remain to be fully explored.

By contrast with the rich and bizarre nature of dreaming, mental states associated with prayer and meditation tend to involve focused control and suppression of the wandering mind through limiting the verbal thought process, or focussing on a spot. While these mental states are highly varied, they share common features of intentional control of the mental process. Zen meditators in fMRI studies show more rapid and complete suppression of the mind-wandering of the default network (Pagnoni et al), with increased activity in the prefrontal cortex and basal ganglia and decreased activity in the occipital (visual) cortex and anterior cingulate processing emotion (Ritskes et al). In EEG studies they showed a significant increase in frontal alpha and occipital beta power, whereas an average increase of theta power was observed in controls indicating loss of concentration (Huang et al). Consistent with one-pointed concentration, Zen meditators recalled more subliminal messages than controls (Strick et al).

Tibetan Buddhist meditators in PET and fMRI studies have increased blood flow in the cingulate, inferior and orbital frontal cortex, dorsolateral prefrontal cortex and thalamus (Newberg et al 2001, Hanky). EEG studies show greater activation in attentional regions, including fronto-parietal, cerebellar, temporal, para-hippocampal, and posterior occipital, possibly due to the attended dot (Brefczynski-Lewis et al). They have also been found to enter high-amplitude gamma-band oscillations with high phase-synchrony during meditation, consistent with a one-pointed concentration with heightened attention (Lutz et al 2004). By contrast, compassion meditators under PET show similar activations to a person feeling empathy for a person in pain (Lutz et al 2008). In a more recent fMRI study contrasting “focused-based” and “breath-based” practice. In the first, blood flow increased in the medial prefrontal cortex and left caudate, but decreased in parietal and occipital regions. The second induced activation in several limbic structures and the left superior temporal cortex (Wang et al). A study investigating neural correlates of personally meaningful spiritual experiences (Miller et al. 2018) found reduced activity in the left inferior parietal lobule compared with neutral-relaxing experiences, suggesting it may contribute to perceptual processing and self-other representations during spiritual experiences. Compared with stress cues, spiritual cues invoked reduced activity in the medial thalamus and caudate, regions associated with sensory and emotional processing.

Investigation of Transcendental meditators by PET (Newberg et al 2006b) also found bilateral prefrontal activation associated with relaxed attention on the mantra, other increases in frontal, occipital and parietal areas and a decrease in the thalamus and hippocampus. An fMRI study, centered on the capacity of the relaxed state to be helpful in dealing with an induced painful stimulus saw reductions in the prefrontal cortex, anterior cingulate cortex, and thalamus (Orme-Johnson et al), and has been suggested to be linked to hormonally induced increases in GABA (Elias et al). Catholics observing a Marian image saw increases in the ventrolateral prefrontal cortex and brain stem leading up to the thalamus (Wiech et al).

Brain studies of Carmelite (Beauregard & Paquette) and Franciscan nuns (Bielo) in professed ‘union with god’, which they admitted was difficult to achieve in a noisy MRI tunnel, show different structured activations, with increased activity in the caudate nucleus associated with learning, memory and falling in love, the insula processing body sensations and social emotions, the inferior parietal processing spatial awareness, in contradiction to the Zen studies, the medial orbito-frontal and prefrontal cortices dealing with emotional and executive decision-making, and the middle of the temporal lobe. Most prevalent brain waves were long, slow alpha waves such as those produced by sleep, consistent with a relaxed state. By contrast with the prefrontal control evidenced in Buddhist meditation, during speaking in tongues, by Christian women who had practiced glossolalia for more than 5 years, there was a decreased blood flow in the frontal lobes bilaterally and in the left caudate, indicating relaxation of executive controls (Newberg et al. 2006a).

In comparing these highly varied and contradictory results, one can conclude that claimed states of higher spirituality are varied products of different forms of concentration, which share the feature of overall focused control, but otherwise look like distinct humanly-generated states of mind, rather than convergence on the

‘divine’. One needs to consider the possibility that the profound transformations of the cortical dynamic induced both by dreaming and by entheogens may give rise to deeper potential for exploratory existential processes, which might nevertheless be enhanced by contemplative repose.

4: Doors of Perception: Classic Psychedelics and Serotonin Receptor Agonists

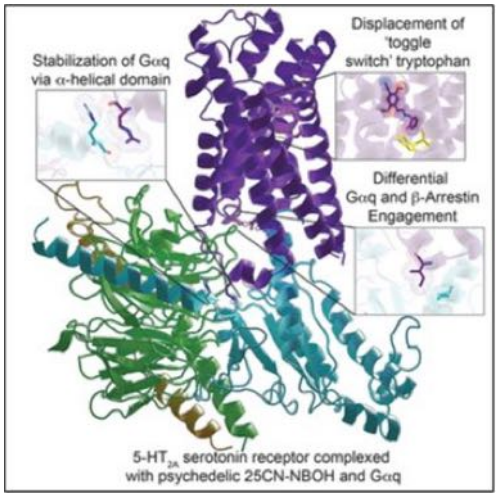


Fig 7c: Detailed model of psychedelics acting on the 5HT2a receptor (Kim et al. 2020)

In fig 8 are shown a selection of the classic psychedelic entheogens, along with MDMA and methamphetamine for comparision and salvinorin and Ketamine which have different action but entheogenic reputations. Although many of are phenylethylamines, rather than indoles like serotonin, and might be more expected to act on the nor-adrenalin receptor, they have been shown to exert their psychedelic action through a common pathway, via serotonin receptors (Lyon et al), and in particular 5HT2a (Ray), because competitive 2a antagonists, such as ketanserin, block psychedelic activity and mice genetically engineered to lack 5HT2a receptors lose the psychedelic head-twitching response (González-Maeso et al 2007). Molecular QSAR studies have also been made (Clare, Schulze-Alexandru, Thakur).

The tryptamine psychedelics are agonists for 2a, 2c and 1a. Broadly speaking 2a seems to produce the kaleidoscopic visionary effects, 2c a degree of anxiety and disordered thought, and 1a shuts down the Raphe serotonin secreting nuclei, causing a dream-like effect. The 2c receptor is X-linked, so polymorphisms can affect the sexes differently. Splicing appears to be regulated by the small nucleolar RNA SNORD115. Phenylethylamines act on 2a and 2c (Moya et al), although all agents act on multiple receptors (fig 8 right). LSD remains an enigma to this day because it is only a weak partial agonist of 2a and has diverse effects on a variety of receptors (see figs 8 and 14), including the above, which provides no explanation why it is so potent. 13-OH-LSD, a potent major metabolite, may induce dopamine related paranoia late in an LSD trip (Nichols). A study of the confirmation of the crystallographic binding of LSD to the 5HT2b receptor (Wacker et al. 2017) indicates long-term capture, consistent with long-lasting effects and high potency. Molecular dynamics simulations suggest that LSD's slow binding kinetics may be due to a 'lid' formed at the entrance to the binding pocket. Whereas most endogenous agonists, such as serotonin, activate both G-protein and β-arrestin pathways which dampen activation, some compounds can stabilize distinct receptor conformations, thereby preferentially activating select signal transduction pathways. This phenomenon has been termed 'functional selectivity' or 'biased agonism'. Confirmation of the specificity of 5HT2a receptor to the subjective effects also comes from the negation of these effects under joint administration of the selective 5HT2a antagonist ketanserin (Preller et al. 2016). A recent study also links the non-addictive nature of psychedelic 5HT2c receptors to changes in potassium Kv1.x channels opposite to those of addictive drugs (Canal & Murnane 2016).

Beginning with the mescaline molecule, Sasha Shulgin and others, by educated hunches, synthesized a variety of phenylethylamine variants making minor modifications to the groups around the benzene ring to bring the H-bonding and hydrophobic parts of the molecule closer in line with the side chains on the active surface of the 5HT receptor. This resulted in a series of molecules with much greater potency than mescalin. DOM, also known as STP, carrying an amphetamine methyl group, had an active dose of 3-10 mg, rather than the 400 mg of mescaline, and a duration of 14-20 hours. DOB had 1-3 mg and 18-30 hours. The 2C series without the amphetamine methyl had shorter milder activity, with a dose of 2C-B being 12-24 mg and a duration of 4-8 hrs. Cyclizing the side methoxy groups and retaining the amphetamine methyl resulted in super-potent molecules such as bromodragonfly (Nickson, Chambers et al, Schultz et al), with dangerous physical effects including seizures, gangrene, organ failure and death, particularly when confused with 2C series molecules. The active dose is around 0.2-0.8 mg and the effects last up to 72 hours, indicating very strong binding, with doses of a few mg being dangerously toxic. In 1999 the n-benzyl-phenethylamine super-potent selective 5HT2a receptor agonist class was discovered, including 25I-NBOMe (Braden et al). The dose by smoking is 0.15-0.3 mg and the duration 3-8 hours. My subjective experiences of both psilocybin and 25C-NBOMe are included in the case study.

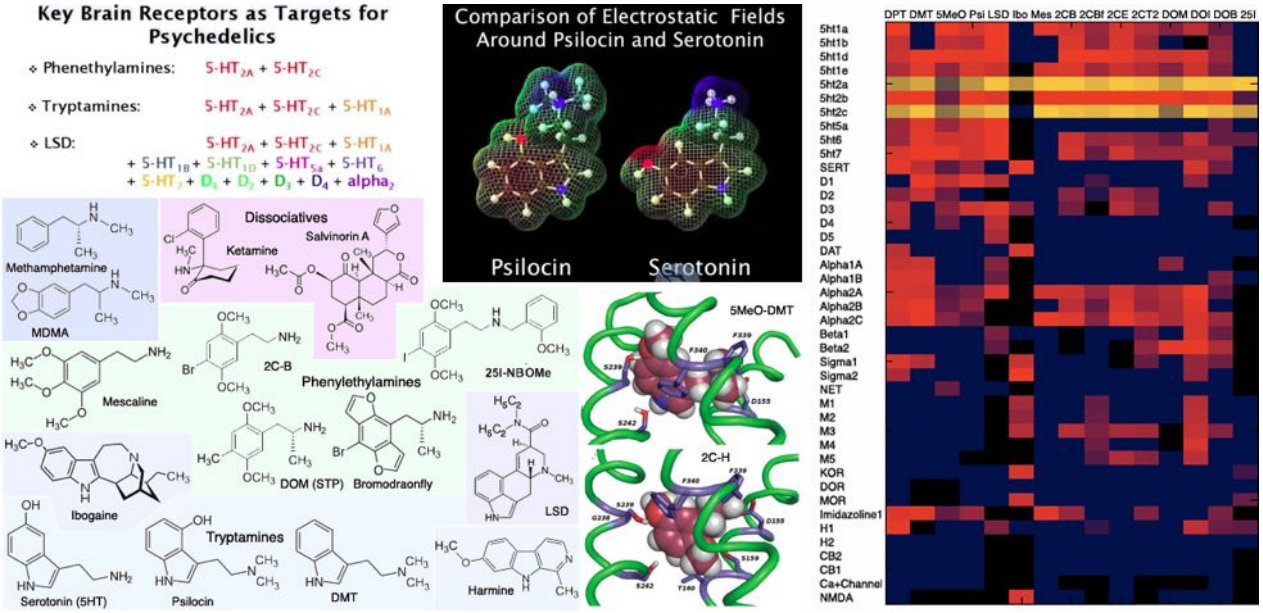


Fig 8: **(Lower left)** Classic psychedlic hallucinogens (Nichols 2004, Schultes & Hofmann) are either tryptamines (psilocin, DMT, with LSD and ibogaine as modified members, with harmine included as a monoamine-oxidase inhibitor potentiator of DMT in the Amazonian brew ayahuasca) or phenylethylamines (e,g, mescalin, DOM, 2C-B, bromodragonfly and 25I-NBOMe), which are full or partial agonists of serotonin receptors. Psychedelics are also referred to pejoratively as psychotomimetics, or hallucinogens and affirmatively as entheogens, providing long-term spiritual and psychological coherence (Griffiths et al 2006, 2008, 2011, Khamsi, Frood, Barbosa et al). Two other molecules which are referred to as entheogenic dissociative hallucinogens are ketamine and salvinorin A, which have distinct effects and act at completely different receptors, the NMDA (N-methyl d-aspartate) glutamate receptor and κ-opioid receptors respectively. The phenylethylamine derivates have been modified with a view to optimize receptor binding through appropriately located H-bonding and hydrophobic interactions. The amphetamine moiety in DOB and in addition the ring structures in Bromodragonfly result in a strongly binding super-potent molecule with slow onset and very long-lasting effects, which can be a life-threatening combination which can cause catastrophic organ and peripheral tissue damage. There may be some commonality between ketamine and the classic psychedelics through linkage between 5HT2a and glutamate mGluR2 receptors and in turn with the NMDA target of dissociatives. Ecstasy (MDMA) although it is a serotonin releasing agent, like many related serotonin uptake inhibitor antidepressants, is not a psychedelic entheogen, but rather an entactogen. Methamphetamine, which is a stimulant, rather than psychedelic, is a dopamine releasing agent, but also forms a moiety in many phenylethylamine psychedelics and MDMA. **(Lower right)** Although the phenylethylamine psychedelics, (e.g. 2C-H) more closely resemble dopamine and nor-epinephrine than the indole-based serotonin, the way they fold at the serotonin receptor (Braden, Braden & Nichols) leads to similar 5HT2a activation to the tryptamines (e.g. 5-methoxy-DMT). **(Upper left)** Key brain receptors as targets for psychedelics (Nichols 2011). While phenylethylamines affect 5HT 2a and 2b, tryptamines also affect 1a and LSD has multiple affects on several serotonin, dopamine and other receptor types leading to a complex effect. The n-benzyl phenethylamines such as 25I-NBOMe are strongly selective for the 2a receptor (Braden et al), so are experimental tools for investigating the 2a receptor. The central psychedelic effect is believed to be driven principally by 2a (Nichols & Nichols), because competitively-binding 2a antagonists such as ketanserin, and genetic modification, in animal studies (González-Maeso et al 2007), show repeatable psychedelic side-effects, such as 'head twitching', are obliterated by loss of 2a agonism. The other serotonin receptors are believed to have secondary action, with 2c contributing up to half the head twitching effect in animal studies (Canal et al). The fact that 2c antagonists are anxiolytic suggest 2c agonism may promote anxiety and ensuing disordered thought processes. Some of the initial anxiety caused by selective serotonin reuptake inhibitors, or (SSRIs is believed to be due to excessive 2c signalling. 2c is X-linked and so can have differing effects both between males and females and between individuals leading to different degrees of anxiety. Agonism of 1a in the tryptamines paradoxically silences the Raphe nucleus responsible for serotonin innervation of the cortex (Braden, Nichols 2011), as occurs in REM, or dreaming, sleep. The effects of psilocybin on 1a when 2a (& 2c) were selectively blocked with ketanserin still showed reduced attentional tracking ability, but there was no significant effect on spatial working memory under psilocybin (Carter et al). **(Upper center)** Psilocin (the active metabolite of psilocybin) and serotonin electric fields compared, showing the 4-OH and dimethyl moieties come together in psilocin to alter the charge polarities and spatial distribution (Nichols 2011). **(Right)** Heat map of normalized receptor interactions shows a wider distribution than the simplified list upper left (Ray). Activity dark blue=0 to red=4 (orange for 2a and 2c, black no data). Profiles of DPT, DMT, 5MeO-DMT, psilocin, LSD, ibogaine, mescalin, 2C-B, 2C-B-fly, 2C-E, 2C-T-2, DOM, DOI, DOB, 25INBMeO (Nicholls et al). The mescalin profile is corrected for 5HT2a,c binding using PubChem Assay (http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?cid=4076). Notice the huge spread of receptor activity in DOI compared with DOB, and the manifest difference in activity between DMT and 5MeO-DMT consistent with their different subjective effects.

Work has also gone into modifications of the tryptamine psychedelics, mostly by elongating the N-dimethyl groups or adding to or shifting the 4-OH. Dimethyltryptamine, or DMT, is a short-acting highly potent psychedelic, which can be smoked, or consumed by mouth with monoamine oxidase inhibitors, such as harmaline. It occurs widely in nature and in trace amounts in the human body. 5-methoxy-DMT is more potent but has a reputation for being a near death experience lacking joy or colour. 5-hydroxy-DMT or bufotenine, which stands intermediate between serotonin (5-hydroxy-T) and psilocin (4-hydroxy-DMT), has a controversial reputation for physical affects, including cyanosis on intravenous use, but according to Ott has effects similar to DMT and psilocybin lasting about 90 minutes when taken intra-nasally, without deleterious side effects (Ott 2001). LSD remains the most potent and spectacular molecule in its class. Comparison of the electric fields around psilocin and serotonin shows how the combined effect of the OH moved to the 4 position and the N-dimethyl alter the charge distribution in the top of the receptor site in such a way as to

alter the protein cascade. A variety of molecules, from LSD to 25I-NBOMe, all fit the 2a receptor in such a way as to bond to critical amino-acid side chains and elicit a psychedelic response.

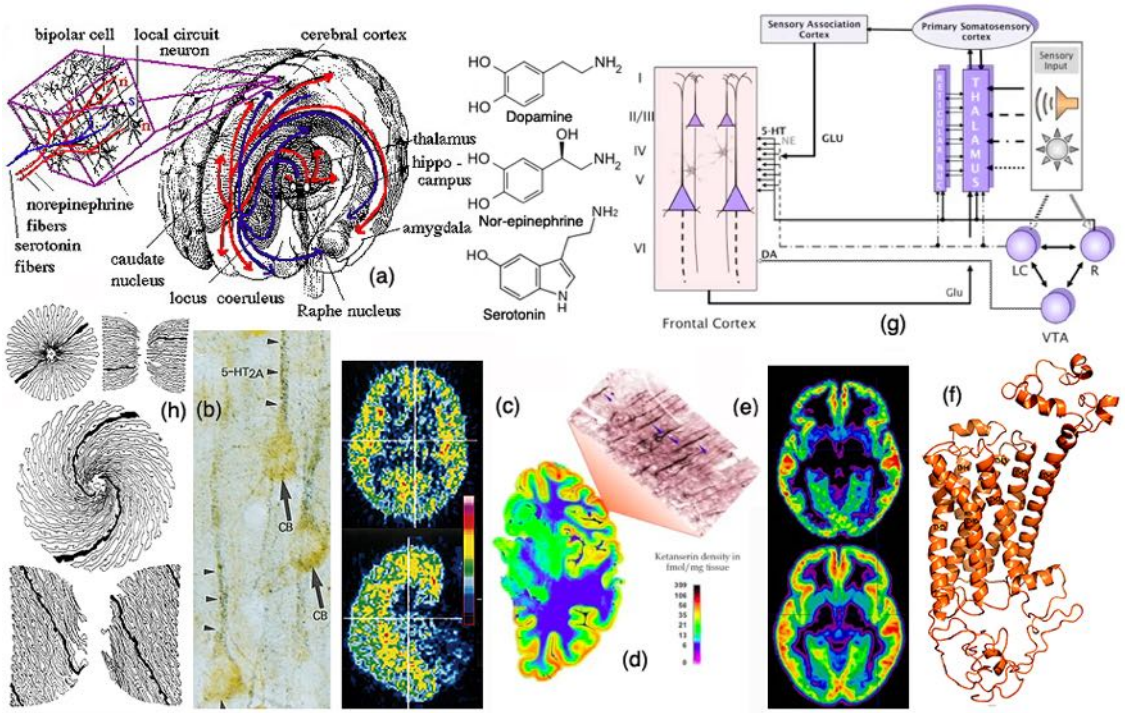


Fig 9: **(a)** Ascending pathways from the Raphe nucleus (R) and Locus coeruleus (LC) innervate wide areas of the cortex via serotonin and nor-epinephrine synapses. Dopamine pathways from the ventral tegmental area (VTA) likewise mediate dopamine synapses to areas of the cortex. Dopamine is involved in the reward system, nor-epinephrine in arousal, and serotonin in a variety of modulating effects. **(b)** 5HT 2a receptors are located on apical dendrites close to the pyramidal cell body (Jakab & Goldman-Rakic). The action of 1a and 2a receptors on pyramidal cells appears to be opposed. **(c,d)** Excitatory 5HT2a receptors are widely distributed across the cortex with significant concentrations in the frontal and visual areas. Inset shows an arrow pointing to their location on the pyramidal cell (Stein et al, Nichols 2011). **(e)** A healthy individual (below) shows greater 2a activation than a mentally 'at-risk' patient (Hurlemann R et al). **(f)** Model of the 5HT2a receptor, a hepta-helical rhodopisn-like G-protein coupled receptor (Kanagarajadurai). Rhodopsin is effectively a neuroreceptor agonised by the conversion of retinal from the 11-cis to the all-trans state by an incident photon. **(g)** Model of the possible action of psychedelics involves several possible alterations of serotonin pathways, including altering the signalling pathways of cortical pyramidal 5HT2a receptors, possibly affecting glutamate excitatory responsiveness (Muschampa et al), reducing lateral inhibition of cortical inter-neurons, leading to the ramification of patterns from cortical column to cortical column across the cortex, the shutting down of Raphe nucleus serotonin activity through 5HT1a activation, paralleling its silencing in REM dreaming and alteration of cortico-striatal-thalamo-cortical CSTC feedbacks mediated by serotonin receptors. This would also be consistent with a another model - reduction of filtering functions in the thalamus causing a sensory flood in the cortex (Nichols 2011, Scrugs et al, Vollenweider) Both glutamate excitation and thalamic models have been challenged (Béïque et al), but only using the phospholipase-C pathway (fig 10), they suggest that 5HT2a receptors 'facilitate intrinsic networks within the PFC'. **(h)** Tunnel and spiral patterns may originate from enhanced wave fronts running across the occipital cortices (Contreras, Benussi et al) due to the complex logarithmic map between the cortex and perceived visual field (Bresslof et al). This suggests that one mechanism of psychedelic activity is reduction of lateral inhibition between cortical mini-columns setting up an additional dynamical excitation to the deep white matter connections of pyramidal cells.

In seeking an explanation for how classic psychedelics cause their profound changes of subjective consciousness, we need to understand how the critical 5HT receptors are distributed and how they modulate major brain circuits. 2a receptors are widely distributed throughout the cerebral cortex with particular concentrations in frontal and occipital areas. They have a major role in mood and sleep wakefulness cycles. Serotonin reuptake inhibitors such as Prozac have become popular anti-depressants but neither they nor serotonin, or a variety of other 5HT2a agonists are psychedelics. We thus also need to discover why some 5HT agonists are psychedelics while others such as serotonin itself are not. The serotonin receptors are G-protein linked receptors so they do not open an ion channel, but set off one or more chain reactions between proteins and other signalling molecules inside the target neuron. Current think is that psychedelic molecules are not only 5HT2a agonists but bind to the receptor in such a way as to fundamentally alter the ensuing protein cascade.

One of the major sites of 5HT2a receptors is on the apical dendrites of pyramidal cells, which are the main output neurons from a given area of the cortex, and penetrate all the cortical layers, forming up to 10,000 synapses with a variety of inter-neurons having many different types of neurotransmitter, both inhibitory and excitatory. Serononergic agonism has been found to increase excitatory post-synaptic currents in layer V pyramidal cells of prefrontal cortex, but intriguingly by an asynchronous mode of glutamate release suggesting the involvement of pre-synaptic receptors (Aghajanian & Marek). There are also receptors on the connections between the thalamus and cortex which provide the main sensory and motor pathways and a series of reciprocal connections between the two believed to be integral to maintaining a state of active consciousness and memory functions. The reticular nucleus surrounding the thalamus, which has rich serotonin receptors (Rodríguez et al). There are also serotonin receptors on cortical interneurons, whose feedback properties can also be affected by psychedelics. The serotonin receptors in the cortex are fed by an ascending neural pathway of serotonin-secreting axons from the Raphe nucleus in the basal brain that innervates wide areas of the cortex forming synapses with pyramidal neurons on their apical dendrites. However the serotonin emitting Raphe neurons also have 5HT1a receptors, which in the case of psilocin turn off the serotonin pathway.

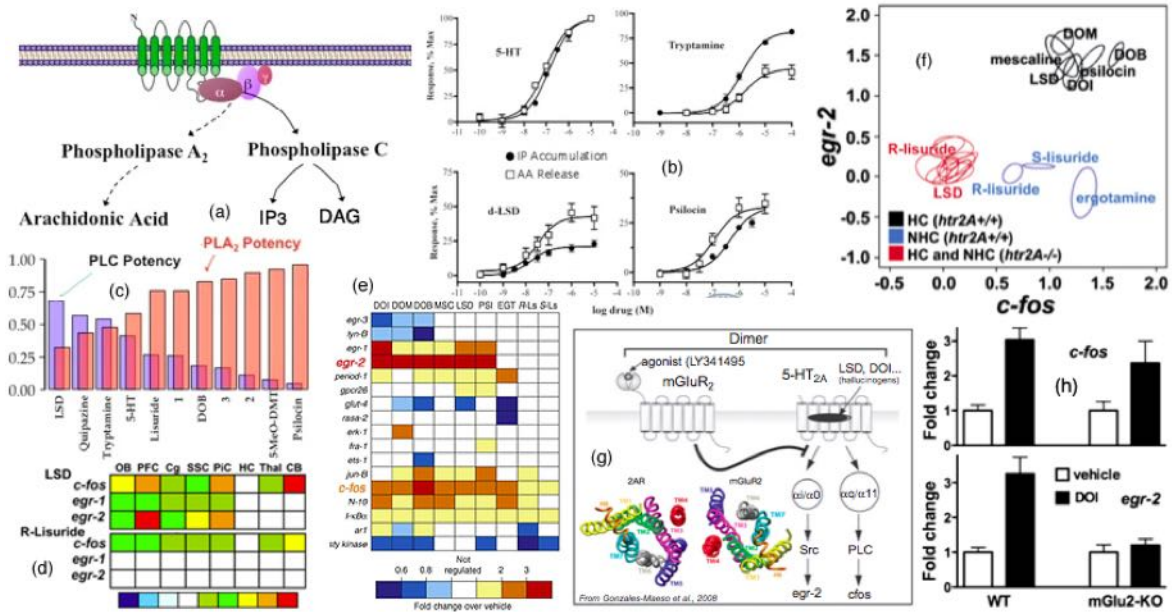


Fig 10: In seeking for an explanation of how psychedelics, such as psilocin, cause profound changes of consciousness, apparently through 5HT2a receptors, but other 2a agonists such as serotonin itself do not, interest has focused on the idea that the 2a receptor can be activated in different ways by molecules with slightly differing binding, so that the resulting G-linked protein cascades have significantly different outcomes. One area of interest **(a)** is in the differing activations of the central phospholipase-C pathway and the phospholipase-A2 pathway (Felder et al, Nichols 2011), which seems to be differentially more activated **(b)** by psychedelics, such as psilocin and LSD, but these show contradictory responses **(c)** in terms of actual potency (Nichols 2011). Note the paradoxically weak agonist effect of LSD in (b). Cox-2 (Mackowiak et al) and MAP kinase activation (Nichols & Sanders-Bush 2004, Kurrasch-Orbaugh et al) and PSD-95 (Abbas et al) have been found to be elicited by DOI and LSD. **(d,e)** In vitro and in vivo investigation of gene activations caused by receptor activation has shown a consistent differential activation of *egr*-2 (early growth response 2) a three-finger transcription factor, as opposed to *c-fos* (Nichols & Sanders-Bush 2002), with all 2a agonists promoting *c-fos*, which is rapidly upregulated by many stimulatory pathways and by action potentials, but only psychedelics (DOI, DOM, DOB Mescalin, LSD and psilocybin) promoting *egr*-2. In turn LSD vs psychedelically inactive R-Lisuride is seen to activate *egr*-2 in OB, olfactory bulb; PFC, prefrontal cortex; Cg, cingulate cortex; SSC, somatosensory cortex; PiC, piriform (olfactory) cortex; but not in HC, hippocampus; Thal, thalamus; CB, cerebellum. (Gonzalez-Maeso & Sealfon, Gonzalez-Maeso et al. 2003, 2007). This suggests a primarily cortical level of psychedelic activation. **(f)** Similar responses in 2a+/+ mice obliterated in 2a-/- knockout mice (ibid). **(g)** Serotonin agonism also appears to be linked to a pairing of 5HT2a with an adjacent glutamate mGluR2 metabotropic (G-protein-linked) receptor (ibid, Bockaert et al in Müller & Jacobs, Fribourg et al, Kondo & Sawa, Uslaner et al, Gewirtz & Marek) in which psychedelic effects such as 'head twitching' in animal studies are also abolished by the mGluR2 agonist LY379268 (Molinaro et al), or **(h)** by removal of the mGluR2 receptor altogether in knockout mice (Moreno et al 2011a), suggesting this may be a key link between serotonin and glutamate modulation of pyramidal neurons. The link is mutual and opposing. mGluR2 agonists increase the affinity of 2a for hallucinogen binding, while 2a agonists decrease the affinity of mGluR2 agonists for glutamate receptor binding (Kreuts & Carlo). Activation of G proteins by 2a was altered by co-expression of mGluR2. Induction of the gene, *egr*-2 that is selectively stimulated by hallucinogenic 2a agonists was blocked by an mGluR2 agonist, whereas induction of *c-fos*, which responds both to hallucinogenic and non-hallucinogenic 2a agonists, was unaffected by the same treatment. The heteroduplex mechanism has been contested (Delille et al) and it may just be one instance of a more general phenomenon of receptor cross-talk essential for multimodal modulation of neurotransmitter action.

All of these processes are possible targets for the effects of psychedelics and all of these have been invoked as possible contributors to the psychedelic state. One idea that gives some explanation of the kaleidoscopic patterning is that psychedelics modulate interneuron feedback in such a way as to allow patterns of excitation to leak from one mini-column to another thus setting off waves of excitation across the cortex, in addition to deep pyramidal connections, which could be perceived as patterns, and sounds. Perception of tunnels and spirals is consistent with such simple waves of excitation travelling across the visual cortex through the complex log transform between occipital cortex and perceived visual field. However synesthesias also suggest modulation of deeper connections between cortical areas. Another possible mechanism is the serotonin modulation of reciprocal connections between the cortex and the thalamus via the striatum, the CSTC loop (Marek et al 2000). More directly one can examine the 5HT2a receptors on pyramidal cells for mechanisms that would directly alter pyramidal excitation, possibly through connection to glutamate excitatory expression. Finally one can invoke changes to the ascending serotonin pathways. The Raphe nucleus monitors vigilance, so its silencing could result in drowsiness. Psychedelics also increase the burst firing of the locus coeruleus nor adrenaline pathways, resulting in experience of novelty and surprise. The full effects could involve any or all of these in varying combinations, as noted in fig 9(g).

Fig 10 outlines some of the prevailing ideas about how the protein cascade resulting from psychedelic receptor agonism might be altered. The 2a receptor has been found to have two immediate pathways, the central one involving phospholipase-C and the other via phospholipase-A2. Psychedelics appear to have greater differential activity on the A2 pathway, but the effect is not consistent across different psychedelics when we consider the actual potency of an agent to elicit either pathway at a given concentration. Gene studies then sought to elucidate *in vitro* gene expression differences and found a consistent activation of *egr*-2 only in psychedelics, while all 2a agonists activated *c-fos*. *Egr*-2 is further discussed in fig 12. 5HT2a receptors are also found peripherally, e.g. on blood vessels, where their activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency (Yu et al).

An intriguing connection then emerged between the 5HT2a receptor and the G-linked glutamate receptor mGluR2. A reciprocal functional inhibition of 5HT2a agonism and mGlu2/3 agonism has been described in the prefrontal cortex of rat. In these studies, 5HT2a receptor activation induced excitatory postsynaptic currents (EPSCs) in the medial prefrontal cortex (Aghajanian & Marek), and a mGlu2/3 antagonist further enhanced the frequency and amplitude of EPSCs (Marek et al., 2000). By contrast mGlu2/3 agonists or 5-HT2A receptor antagonists suppressed EPSCs and attenuated behavioral effects of both serotonergic hallucinogens (e.g. LSD) (Gewirtz & Marek), and dissociative anesthetics (e.g. PCP) (Moghaddam & Adams). Extensive subsequent research is discussed and illustrated in figs 10 and 12.

These two receptors may lie adjacent in the pyramidal cell membrane. Competitive agonists for the glutamate receptor abolish psychedelic effects in animal studies and they are also absent in knockout mice lacking the glutamate receptor. The link between these two receptor types is mutual, with mGluR2 agonists increasing the affinity of hallucinogens for 2a binding, whereas 2a agonists decrease the affinity of mGluR2 agonists for glutamate receptor binding. Moreover, activation of G proteins by 2a was altered by co-expression of mGluR2. Induction of *egr*-2 was blocked by an mGluR2 agonist, whereas induction of *c-fos*, which responds both to hallucinogenic and non-hallucinogenic 2a agonists, was unaffected. This model, and the parallel connection with dissociatives in the next section suggests both these agents may have a deeper common mode of action.

Non-psychedelic serotonin modulators also have central roles as psychotropic drugs. MDMA, or 'ecstasy' has become famous as an entactogenic club drug. MDMA inhibits the vesicular monoamine transporter, which results in increased concentrations of serotonin, norepinephrine, and dopamine in the cytoplasm, and induces their release by reversing their respective transporters, resulting in a strong serotonin 'high' accompanied by oxytocin (Young) and dopamine release causing feelings of empathy and exhilaration. Most antidepressants enhance serotonin. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), both of which enhance serotonin levels are popular anti-depressants. Their effects may result partly from promoting neurogenesis in the hippocampus through secondary action on the glucocorticoid receptor (Anacker et al). Monoamine-oxidase inhibitor antidepressants also increase serotonin. MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine and also acts on dopamine. Conversely, several atypical antipsychotics, are serotonin antagonists. Risperidone for example is believed to exert its effect through being a 5HT2a antagonist, but is also a broader-spectrum antagonist of serotonin, dopamine and nor-adrenaline.

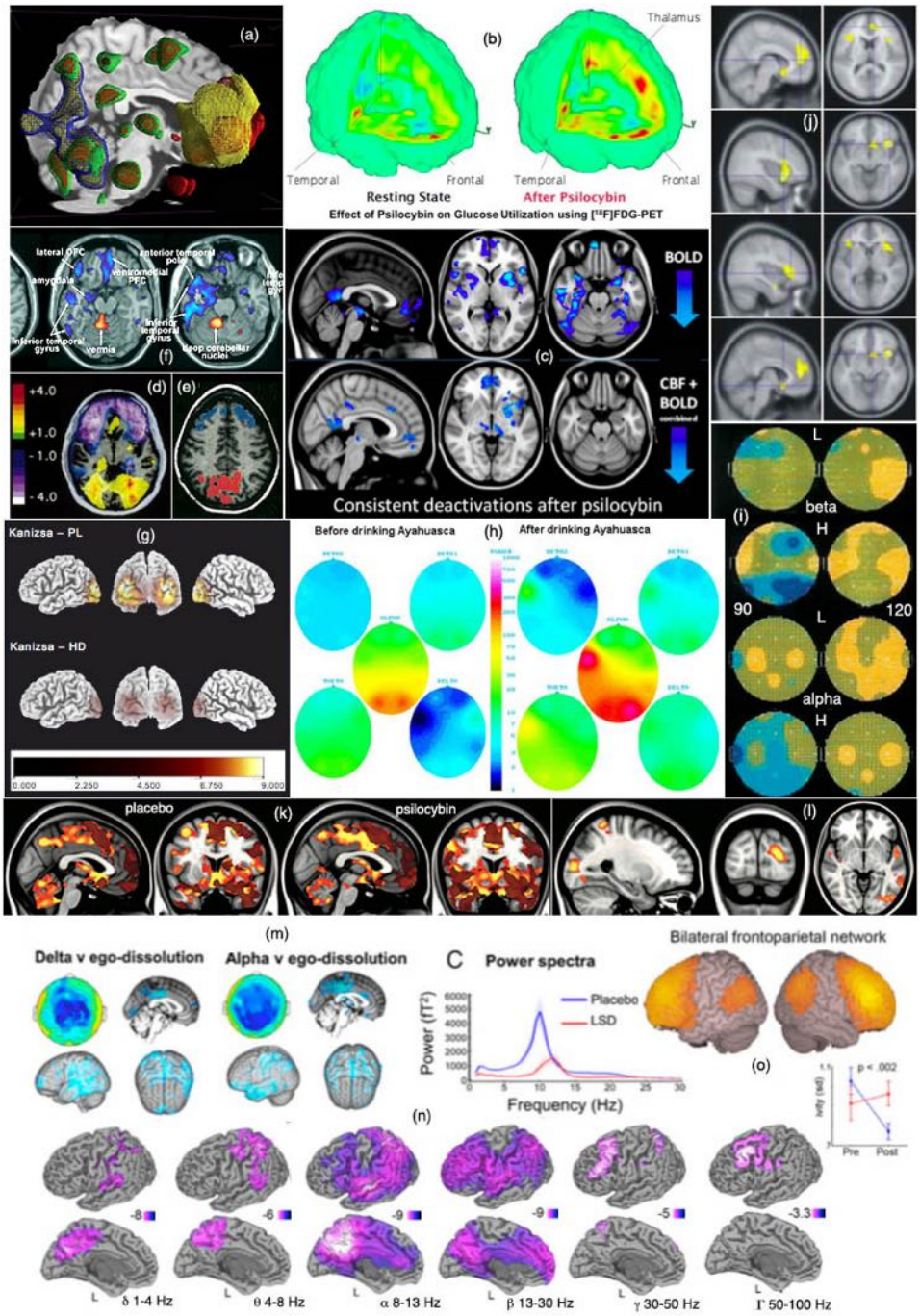


Fig 11: **(a)** PET study of 5HT2a sites where psilocybin acts with red and yellow having highest density (Hasler and Quednow). **(b)** PET study of 15-20 mg psilocybin taken orally over a 48 minute period 90 minutes after consumption, which shows frontal activation by comparison with a resting state (Vollenweider et al). This result contrasts markedly with a later fMRI study **(c)** of a recording during the 12 minutes after intravenous administration of 2mg (~15 mg orally), which shows reduced activity in medial frontal cortex (mPFC), posterior cingulate cortex (PCC) and other areas (Carhart-Harris et al 2012a, Lee & Roth). Franz Vollenweider, lead author of the first study commented: "We have completed a number of similar studies and we always saw an activation of these same areas. We gave the drug orally and waited an hour, but they administered it intravenously just before the scans, so one explanation is that the effects were not that strong." Neuropsychologist Keith Laws suggested confound anxiety at the stat of the experience: "Deactivation of the mPFC and PCC are linked to anxiety and anticipation of pleasant and unpleasant experiences. This is a stressful situation, even for experienced drug users, and I suspect that they measured something to do with anxiety" (Costandi, Laws, Zhao et al, Simpson et al). These results are compared with a PET **(d)** and fMRI BOLD study **(e)** of REM dreaming sleep compared with wakefulness, showing similar reductions in frontal activity and increases in occipital activity (Braun). Given the fact that subjects are still able to actively engage in trains of thought and conversation depending on the circumstances, both increases and decreases might be expected to be more extreme than the placebo state, depending on the degree to which the subjects are engaged in active ideation, as opposed to lying quietly in the apparatus as the effects just begin to come on. **(f)** PET scan of healthy women achieving clitoral orgasm shows similar frontal and other reductions with increases only in the deep cerebellar nuclei and vermis (Georgiadis et al, LePage). **(g)** Low resolution electromagnetic tomography sLORETA of subjects viewing a Kazaniga triangle showing disruption of their object-completion activation by psilocybin hallucinations (HD=high dose) (Kometer et al). **(h)** Activation of alpha, theta and delta EEG activity with reduced beta during an ayahuasca session (Hoffmann et al). **(i)** Reduced alpha and beta (and theta) in a second ayahuasca session, L, H doses at 90, 120 min (Riba et al 2002). **(j)** Increases in fMRI in frontal and paralimbic brain regions in an ayahuasca session (Riba et al 2006). **(k)** Increases in activity associated with autobiographical memories on psilocybin. **(l)** Greater late phase activations during autobiographical recollection under psilocybin than placebo (Carhart-Harris et al. 2012b). (m) Reductions in alpha (8-15 Hz) and delta (1-4 Hz) MEG power with ego-dissolution on LSD attributed to cortical desynchronisation (Carhart-Harris et al 2016a). (n) Corresponding decreases in MEG for psilocybin (Muthukumaraswamy et al. 2013). (o) Source localisation of one of several networks with reduced power, again associated with desynchronisation (Ibid).

Fig 11 gives an overview of a few studies looking at PET, fMRI and EEG in subjects under the influence of psychedelics. In the PET study subjects were given 15-20 mg of psilocybin by mouth and measured over a 48 minute period 90 minutes later. This shows an increase of frontal activity on psilocybin. Both ketamine and psilocybin led to a marked metabolic activation of the frontal cortex and a number of overlapping metabolic changes in other brain regions. Ego dissolution and derealization phenomena correlated with the increase of metabolic activity in the frontal cortex including the anterior cingulate, and also with changes in the temporal cortex and basal ganglia (Vollenweider et al 1997a). Vollenweider considers this to support the CSTC model. In a comparable study on ayahuasca increased blood perfusion was observed bilaterally in the anterior insula, with greater intensity in the right, and in the anterior cingulate/frontomedial cortex of the right hemisphere, implicated in somatic awareness, subjective feeling states, and emotional arousal. Additional increases were observed in the left amygdala/parahippocampal gyrus, a structure also involved in emotional arousal (Riba et al 2006).

By contrast, the second fMRI study (Carhart-Harris et al. 2012a) taken for just 12 minutes after a much smaller 2 mg intravenous injection of psilocybin scaled to approximate the intensity of a larger oral dose. Here the subjects had barely had time to adjust to their experience and were measured only for a few minutes, so as noted above, the scan may have measured anxious anticipation as the effects became pronounced rather than the activity of a person accustomed to the effects of their experience. It has been associated with a reduction in activity of the default network. A drop in prefrontal activation would be consistent with an experience of watching the process without attempting to exert control over it, as noted previously in the meditation and glossolalia studies and in dreaming REM sleep, as illustrated above, consistent also with the experience of ego-loss, and an eerie similarity to the effects of female orgasm, satirically described as a ‘complete turn off’. However later experiments Muthukumaraswamy et al. (2013), performing MEG on a similar doasge showed similar reduction consistent with silencing of the default mode network and ego dissolution as also discussed at length in Carhart-Harris et al. (2014) where entropy is used as an indicator of reductions associated with a reduction in oscilotory coherence resulting from upwelling of peripheral activity that would normally be suppressed. The results are also consistent with both fMRI and MEG results from the more recent LSD study (Carhart-Harris et al. 2016), where the same reductions were noted in default mode associated regions but increases in activity related to visua areas where visionary excitation would be expected to be present.

In a subsequent experiment (Carhart-Harris et al. 2012b) to test whether psilocybin facilitates access to personal memories and emotions comparing responses to autobiographical memories under psilocybin and placebo, robust activations to the memories were seen in limbic and striatal regions in the early phase and the medial prefrontal cortex in the late phase in both conditions. There were additional visual and other sensory cortical activations in the late phase under psilocybin that were absent under placebo. Ratings of memory vividness and visual imagery were significantly higher after psilocybin and there was a significant positive correlation between vividness and subjective well-being at follow-up. In a third experiment (Tagliazucchi et al. 2014) the team found a decrease in frontal cortical activity combined with an increase in the anterior cingualte and hippocampus including increased coherence, which the researchers suggest gives an explanation for psilocybins capacity to induce mind-expanding and dream-like effects.

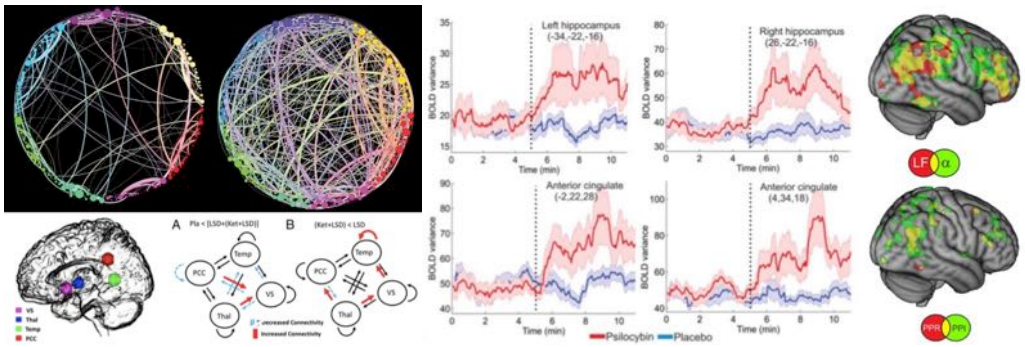


Fig 11b: Above Left: Persistence homological scaffolds for placebo (left) and psilocybin (right) (Petri et al). Lower left: Changes in connectivity under LSD modulated by the inhibitor ketanserin between the thalamus, the ventral striatum (VS), the posterior cingulate cortex (PCC), and the superior temporal gyrus (Preller et al). Right: BOLD Variance time courses (obtained over a 1 min. sliding win- dow) into the four regions of peak statistical significance defined in Table I for the psilocybin and the placebo infusion. Maps of statistical significance for decreased low frequency power (LFP) and power spectrum scaling exponent a after psilocybin infusion. Maps of statistical significance of increased power point rate (PPR) and decreased point process interval (PPI) after psilocybin infusion (Tagliazucchi et al. 2014).

In a late 2014 study a team including Nutt and Cahart-Harris (Petri et al) explored homological scaffolds, representing the features of the correlation network. The results show a dramatic change post-psilocybin, characterized by the appearance of many transient structures of low stability and of a small number of persistent ones that are not observed in the case of placebo, giving an intriguing portrait of the experiential richness of the psychedelic state. The team is conducting a study of the effects of LSD on brain function using both fMRI and MEG (*People's brains scanned while on LSD* BBC 5 Mar 2015). Another Carhart-Harris team, Atasoy et al. (2017), have also found that LSD alters the energy and the power of individual harmonic brain states in a frequency-selective manner, leading to an expansion of the repertoire of active brain states, suggestive of a general re-organization of brain dynamics that follows power-laws indicating a re-organization of the dynamics at the edge of criticality. Letheby and Gerrans (2015) sugest ego loss associated with psychedelics is assocated with relative changes in the default and salience networks. Preller et al. (2018) have since investigated changes in neural connectivity under LSD. The REBUS model (Carhart-Harris & Friston 2019, Singleton et al. 2021) also assoicates psychedelic states with lowered free energy barriers between individual brain states enabling the reversal of top-down filtering of sensory input, throwing open the ”doors of perception”.

The field still remains sparse due to the effective suppression of virtually all human scientific research over half a century, stemming from their schedule 1 classification. There are other substantial problems due to the variable nature of the setting route of administration, whether they are meditating, or thoughtlessly watching the patterns or the novel appearances, or their mind is racing while suffering a bout of anxiety, and whether the subjects are engaged in an active task, which they may or may not relate to under the influence, or actively enjoying the experience and its effects. Given the fact that psychedelics are agents that can have profound affects on what we are engaging with, but which enable people to engage in a variety of activities, enhancement or reduction of brain activity in given regions will be highly variable.

Four EEG studies likewise show up the difficulties of setting a meaningful experimental paradigm. The first looks at low-resolution electromagnetic tomography of a person looking at a Kazaniga triangle showing the activation associated with object completion is diminished. The experimenters correctly conclude that the subjects ‘hallucinations’ may be masking the basic task processing. The second two show that subjects on ayahuasca have some general reductions in the EEG power of their alpha, beta and theta waves, which again is to be expected just from mood changes and the fact that they are dealing with a mind-altering experience. A fourth study (Stuckey et al) of two experienced ayahuasca users clarifies these results, showing increases in global EEG coherence in the gamma band believed to accompany perceptual and cognitive processes (36-44 Hz and 50-64 Hz) along with increased modal EEG alpha frequency and global power decreases across the cortex in most frequency bands, suggesting increased gamma processing reducing power in other modes, consistent with the Zen EEG results.

Clinical trials have found that two doses of psilocybin is sufficient to lift resistant depression in all 12 volunteers for three weeks, and to keep it away in five of them for three months (Carhart-Harris et al. 2016b, 2017). As noted in Scientific American, this is a better remission rate than achieved with SSRIs, which commonly require long-term continuous dosage. A study by Davis et al. (2020) has shown that psilocybin is about 4 times more effective than antidepressants for major depressive disorder. These have also been replicated in studies involving depression as a result of a terminal illness (Griffiths et al. 2016, Ross et al. 2016), supported also by wider-ranging scientific reviews (Mahapatra & Gupta 2016, dos Santos et al. 2016). In a behavioral study (Kometer et al 2012), psilocybin enhanced positive mood and attenuated recognition of negative facial expression, increased goal-directed behavior toward positive compared with negative cues, facilitated positive but inhibited negative sequential emotional effects, and attenuated the P300 event related potential. In a second study (Erritzoe et al. 2018) Neuroticism scores significantly decreased while Extraversion increased following psilocybin therapy, predicted by the degree of insightfulness experienced during the session. Openness scores also significantly increased, while Conscientiousness showed trend-level increases. Psilocyin has subsequently been given “breakthough therapy” status by the FDA (Hess 2018). While Kuypers et al. (2016) found recreational doses of Ayahuasca improved divergent thinking performance but reduced convergent thinking performance, Prochazkova et al. (2018) found that microdosing with ~1/3g of dried magic mushroom "truffles" increased both measures of creativity, although the results of Polito & Stevenson R (2019) are more equivocal.

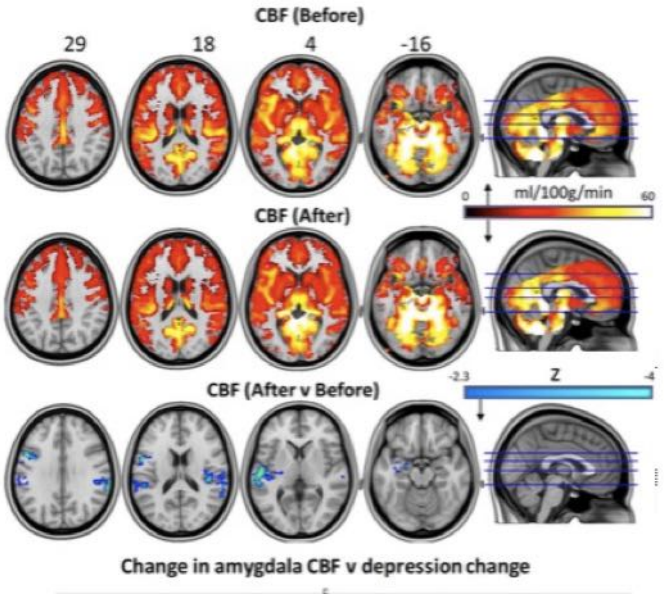


Fig 11b2: Reduction in amygdala activity in patients with treatment-resistant depression under psilocybin. Stabilization of the default circuit also occurred. Half of patients ceased to be depressed and experienced changes in their brain activity that lasted about five weeks (Carhart-Harris R et al. 2017).

In a survey by Griffiths' group of extreme, challenging experiences (Barrett et al. 2016, Carbonaro et al. 2016), 1993 individuals (mean age 30 yrs; 78% male) completed an online survey about their single most psychologically difficult or challenging experience (worst "bad trip") after consuming psilocybin mushrooms. 39% rated it among the top five most challenging experiences of his/her lifetime. 11% put self or others at risk of physical harm; factors increasing the likelihood of risk included estimated dose, duration and difficulty of the experience, and absence of physical comfort and social support. 2.6% behaved in a physically aggressive or violent manner and 2.7% received medical help. Of those whose experience occurred >1 year before, 7.6% sought treatment for enduring psychological symptoms. Three cases appeared associated with onset of enduring psychotic symptoms and three cases with attempted suicide. Intriguingly, the degree of difficulty was positively associated with enduring increases in well-being. Despite difficulties, 84% endorsed benefiting from the experience and the researchers noted that the incidence of risky behavior or enduring psychological distress is extremely low when psilocybin is given in laboratory studies to screened, prepared, and supported participants.

In a long term study on traditional peyote use the peyote group showed no significant deficits compared those with minimal substance use, on the Rand Mental Health Inventory or any neuropsychological measures, whereas a former alcoholic group showed significant deficits on every scale of the RMHI and on two neuropsychological measures. Within the peyote group, total lifetime peyote use was not significantly associated with neuropsychological performance (Halpern et al. 2005). In a proof-of-concept study psilocybin also proved effective at reducing alcohol dependence (Bogenschutz et al. 2015).

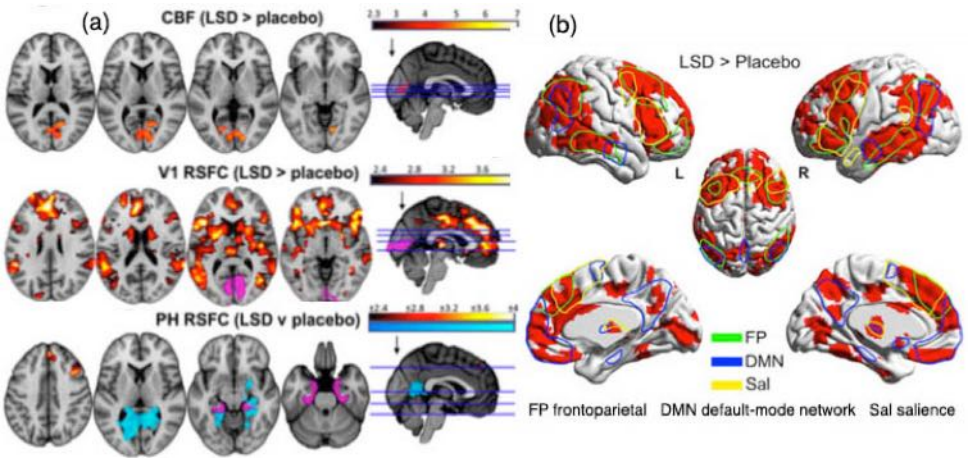


Fig 11c: (a) Differential effects of LSD on the resting brain (Carhart-Harris et al. 2016). (b) LSD increases global functional connectivity of higher-level integrative cortical and sub-cortical regions (Tagliazucchi et al. 2016).

In a ground-breaking study in 2016 three complementary neuroimaging techniques: arterial spin labeling (ASL), blood oxygen level-dependent (BOLD) measures, and magnetoencephalography (MEG), implemented during resting state conditions, revealed marked changes in brain activity after LSD that correlated strongly with its characteristic psychological effects. Increased visual cortex cerebral blood flow (CBF), decreased visual cortex alpha power, and a greatly expanded primary visual cortex (V1) functional connectivity profile correlated strongly with ratings of visual hallucinations, implying that intrinsic brain activity exerts greater influence on visual processing in the psychedelic state, thereby defining its hallucinatory quality. LSD's marked effects on the visual cortex did not significantly correlate with the drug's other characteristic effects on consciousness, however. Rather, decreased connectivity between the parahippocampus and retrosplenial cortex (RSC) correlated strongly with ratings of 'ego-dissolution' and 'altered meaning,' implying

the importance of this particular circuit for the maintenance of 'self' or 'ego' and its processing of 'meaning.' Strong relationships were also found between the different imaging metrics, enabling firmer inferences to be made about their functional significance. This uniquely comprehensive examination of the LSD state represents an important advance in scientific research with psychedelic drugs at a time of growing interest in their scientific and therapeutic value (Carhart-Harris & Goodwin). Robin Carhart-Harris notes: We saw many more areas of the brain than normal were contributing to visual processing under LSD, even though volunteers' eyes were closed," he said. The more prominent the effect, the more intense people rated their dreamlike visions. Under the influence, brain networks that deal with vision, attention, movement and hearing became far more connected, leading to what looked like a 'more unified brain' (Carhart-Harris et al. 2016).

Nevertheless two things are clear. Firstly although psychedelics do cause profound changes to the subjects sensory processing so they see patterns, hear sounds, experience synaesthesias and may experience complex visions, all of these require the same sorts of complex brain processing we know take place in waking life and in dreaming REM sleep. Secondly, unlike the scopolamine of datura and related species, where people can no longer distinguish between the things they are seeing and the world around them, people on psychedelics know they are perceiving additional sensory experience, but they generally have no trouble distinguishing this from external reality, except perhaps for short periods after entering a deep repose, or when their thoughts are transiently disrupted. Thus, although there may be some elements of distortion of time and space processing (Wittmann et al), underlying brain functions remain intact. We thus cannot expect gross disabling changes in cortical processing, and should find variability depending on the set and activity or otherwise taking place.

Update from [Symbiotic Existential Cosmology]

While one might expect that something causing visions, or even hallucinations, might result in enhanced brain excitation, some aspects of the psychedelic state, such as ego loss might also arise from a reduction in activity. Early scans of subjects on psilocybin, fig 34(f) indeed showed increases, as has a later study on LSD when the visual areas are examined, fig 34(o), but the scientific community was surprised when a team led by Robin Carhart-Harris and David Nutt, fig 34(j), found that there was a significant and unexpected reduction in activity. At the time, Franz Vollenweider commented: "*We have completed a number of similar studies and we always saw an activation of these same areas. We gave the drug orally and waited an hour, but they administered it intravenously just before the scans, so one explanation is that the effects were not that strong*." Carhart-Harris et al. injected psilocybin and waited only a short period before the scans began. Psilocybin is a pro-drug, which is converted to psilocin, the active ingredient. The former is converted to the latter both by stomach acids and in the liver by alkaline phosphatase (Dinis-Oliveira 2017).

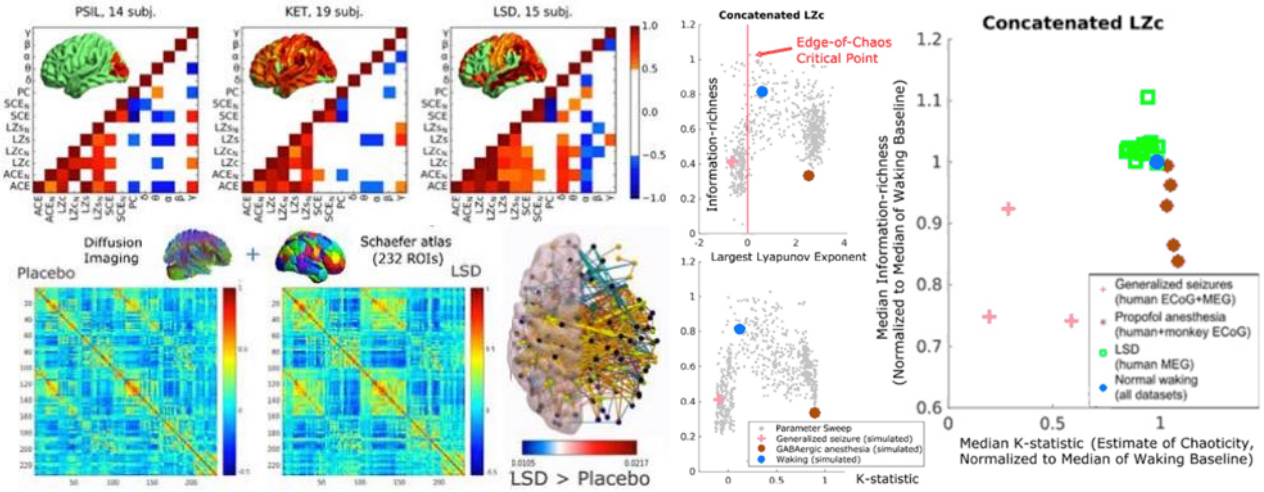


Fig 35: LEFT (Above) MEG complexity measures are greater for waking consciousness than sedative-induced anaesthesia, but greater still for psychedelics. Increased complexity and correlations of measures. For all three there is reliably higher spontaneous signal diversity, than placebo even when controlling for spectral changes (Schartner et al. 2017). Below left: Structural-functional similarity calculated as the Spearman correlation between vectorised structural and functional connectivity matrices. Below right: Brain networks of significant functional connectivity differences (r values) between placebo and LSD. LSD makes globally segregated brain sub-states more complex and more decoupled from structural constraints, as well as reducing functional connectivity of the anterior medial PFC, which is thought to subserve processes of reality monitoring (Luppi et al. 2021). RIGHT: Upper Left: Simulation of Lempel-Ziv complexity against Lyapunov exponent measured for a deterministic system. Lower left: The same measure in terms

of the experimental K-statistic . Right: LSD, propofol anaesthesia and seizures normalised to the conscious state show that LSD enhances complexity, and brings the conscious brain state closer to edge-of-chaos criticality (Toker et al. 2022).

However Robin Carhart-Harris subsequently associated these results with a reduction in the activity of the default mode network (DFM). This was discovered a few years earlier from a pattern of apparent reductions in activity in certain areas during specific tasks that showed up as increased activity when resting (Raichle et al. 2001, Raichle & Snyder 2007). The DFM is thought to have a critical survival role in formulating responses to actual or incipient crises, making active use of the brain during down times from activity to be better prepared. In fact there are many resting state networks and the fundamental idea is that the brain has two complementary modes of activity which can occur together, a passive role responding to incoming environmental or sensory priorities and an active role generating activity beneficial to the organism's survival, with both of these processes superimposing during activities, so one or the other appears more prominent. Areas noted in these studies as having reductions were the medial frontal cortex (mPFC), posterior cingulate cortex (PCC), parahippocampal (PH) and the retrosplenial cortex (RSC). The PCC in particular is characterised in measuring how much you are "caught up" in your feelings and responses, as opposed to just having them. Carhart-Harris et al. (2013) also investigated (v) the connection between the DMN and other networks such as the saliency (SAL) and dorsal attention (DAN) networks and found psilocybin increased functional connectivity between several areas which normally have orthogonal non-interactive relationships confirming the increased functional connectivity of diverse regions under psychedelics.

Carhart-Harris cites the results as evidence of a reduction in default mode network activity consistent with silencing the internal dialogue and ego loss (Pollen 2018). A second researcher Justin Brewer has also found a similar reduction in people meditating (Brewer et al. 2011). This has led to the idea that stopping the internal dialogue of the default mode can result in ego dissolution, because the distinctions between self and other become blurred and the role of the ego as the strategic basis of the default mode network means that silencing it could induce a state of union, in which self and universe become one. Functional imaging has linked the precuneus, an integral component of the default mode network to the processes involved in self-consciousness, such as reflective self-awareness, that involve rating one's own personality traits compared to those judged of other people (Cavanna & Trimble 2006). This thesis supports the notion that both psychedelics and meditation can induce states of ego loss, but the effects of psychedelics are very profound and striking and experientially different from a meditative state of controlled repose, so quietening the resting state networks is a necessary gateway to both, but is not sufficient to explain the vast experiential territory of the psychedelic conscious state.

Millière R et al. (2018) express it this way: "*even forms of putative "total" self-loss involving the radical disruption of both narrative and multisensory aspects of self-consciousness are best thought of as a family of states which can differ from a phenomenological perspective with respect to variables that are not directly related to self-consciousness. Indeed, strong forms of drug-induced ego dissolution may involve a very vivid and rich sensory phenomenology, perhaps as a result of decreased sensory gating, while available evidence on some "selfless" states induced by meditation suggests that their phenomenal content is very sparse (e.g., in states of so-called "pure consciousness" achieved in Samadhi practice).*"

Carhart-Harris also compared the degree of reduction with subjects' personal reports of the experience during the session and found that the reduction was greater in subjects who reported evidence of ego or subject-world dissolution such as "*I existed only as an idea, or concept*", or "*I didn't know where I ended and my surroundings began*", suggesting the effect is genuine. The result is also consistent with heightened activity in other brain areas, particularly those involved in the subjective effects of visions and synesthesia [1], which would tend to affect sensory areas rather than associative or frontal areas.

Subsequent studies, both on psilocybin and LSD using MEG fig 34(p, q), give further insights into this situation. The psilocybin study was again by injection but the listed subjective responses showed marked effect differences between subject and placebo, indicative of the psychedelic state. In both studies there was found to be a reduction in oscillatory power, which in the LSD study was strongly associated with ego loss.

[1] *Synesthesia*: a perceptual phenomenon in which stimulation in one sensory or cognitive mode leads to experiences in a second mode.

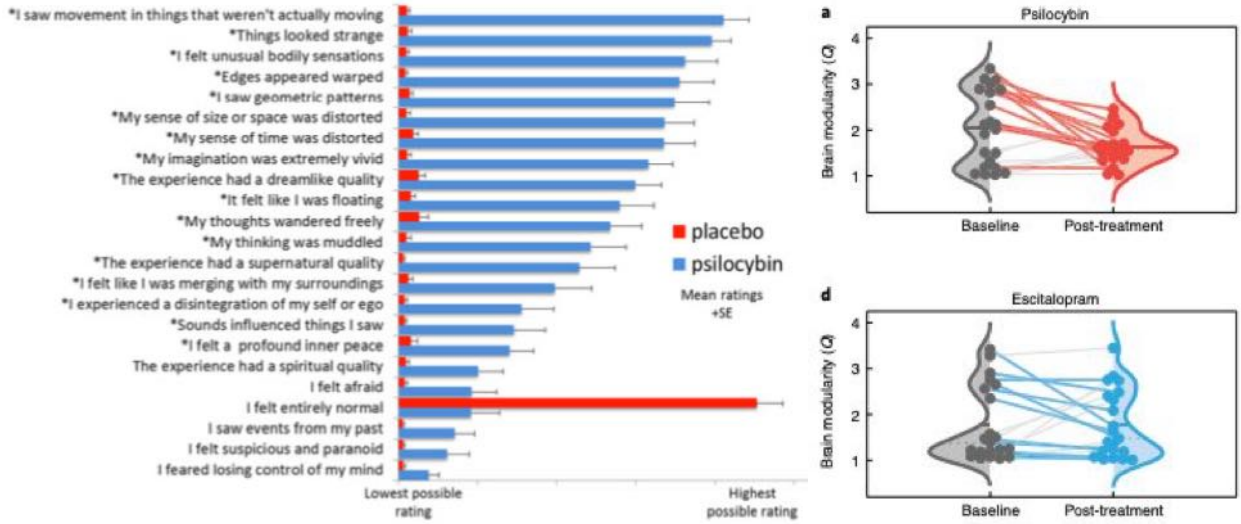


Fig 36: Left: Subjective responses within 15 mins of exiting the scanner (Muthukumaraswamy et al. 2013).
Right: Increased global integration in the brain after psilocybin therapy for depression, but not for escitalopram (Daws 2022).

This reduction in overall power is consistent with increased desynchronisation in the signals, as in wave superposition of decoherent signals, which rise and fall at different instants are more likely to cancel one another, resulting in lower net oscillatory power. This is consistent with diverse interacting signals arising from the stimulatory effects of the psychedelic on usually less associated areas, resulting in more information arising to the conscious level which would normally be filtered out, disrupting the usual flow of attention identifying and streamlining the ordered thought process. The psilocybin study also attempted to identify the source localisation of the resting state networks using independent component analysis (ICA) which determined up to seven, rather than just one, as illustrated in fig 34(r).

Evidence corroborating this interpretation came from a further ingenious experiment from another team led by Carhart-Harris, to analyse "homological scaffolds" of brain activity under psychedelics. Fig 34(e) shows the result, in which there is a far richer network of homological scaffolds in play under psilocybin (right) with the "doors of perception" thrown open than in the normal mental state (left). This technique takes filtered correlations between the time series of the fMRI voxels, forms linkage graphs between each correlated series and then applies algebraic topology using the cliques of three or more to determine and weight the connections. Their evolution over time is also used to show that, while most of the population of psychedelic scaffolds have shorter duration than the fewer number in the placebo state, some psychedelic ones last significantly longer. This is also supported fig 34(s, t), by increased fMRI variance in the hippocampus and anterior cingulate and changes in power spectrum and other measures (Tagliazucchi et al. 2014). A further study (Lord et al. 2019) has explored recurrent BOLD phase-locking patterns (PL states). A similar result 5(i) shows LSD increases global functional connectivity of higher-level integrative cortical and sub-cortical regions (Tagliazucchi et al. 2016).

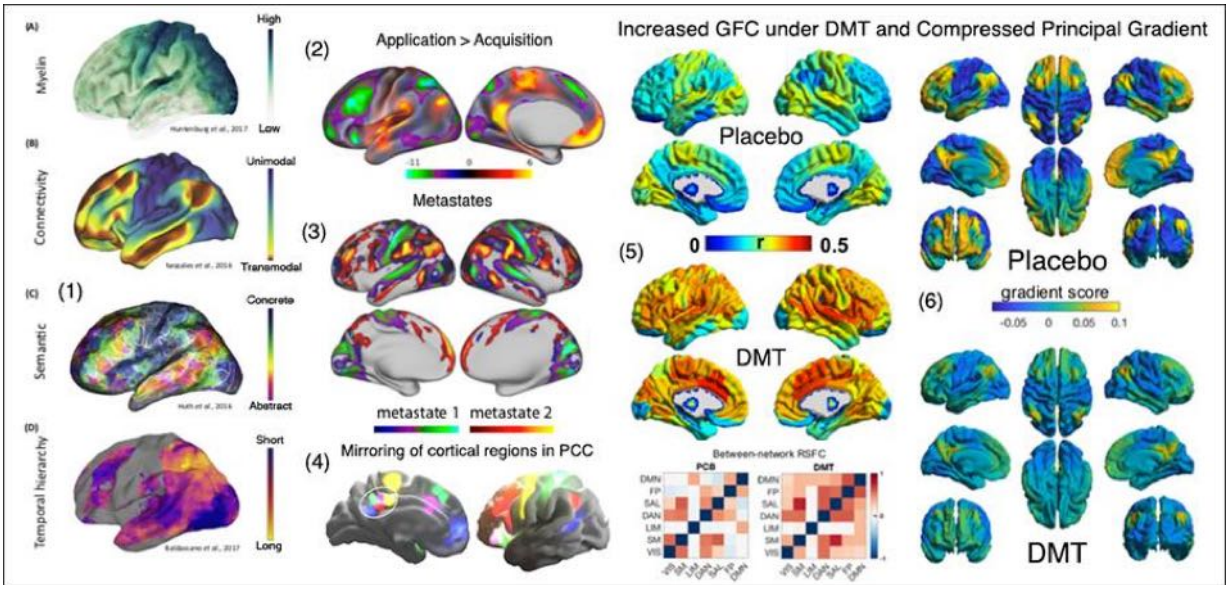


Fig 36b: (1) The principal cortical gradient of the transmodal association cortex pole (or "TOP") of the human brain, expressed in a variety of measures, forming a hierarchical gradient down to primary sensory areas (Huntenburg et al. 2018). (2) Vatansever et al. (2017) used task-based fMRI to illustrate how the default mode network (DMN) and the fronto-parietal network (FPN), work collectively in cognition to guide complex behaviour. These demonstrate that the FPN is active after a rule change — the "acquisition phase"—suggesting its involvement in encoding the contingencies upon which the decision is based. Later, the "application phase" — when the individual understands the rule, activity within the FPN is reduced, and activity within the DMN increases (Margulies & Smallwood 2017). (3) Vidaurre et al. (2017) show that ongoing states are hierarchically organised, forming temporal groupings referred to as "metastates." These reflect a dissociation between states anchored by regions of the cortex concerned with constrained neural processing (such as the sensorimotor systems), from those anchored by transmodal regions of the cortex. Spending time in states anchored in transmodal cortex, including those dominated by the DMN, predict better executive control and higher intelligence. (4) Subregions of the posterior cingulate cortex (PCC) within the white ellipse) and how each is functionally connected with ("echoes") different whole brain intrinsic connectivity networks (shown by colour) (Braga & Leech 2015). The motor cortex has similar subdivisions sampling sensory and cognitive data (Gordon et al. 2023). (5) Timmermann et al. (2023) show increased global functional connectivity (GFC) under DMT, with corresponding decreased resting state between-network segregation in FPN, DMN, salience (SAL) and limbic (LIM). (6) Timmermann et al. (2023), (as well as Girn et al. 2022), show a compressed principal gradient under DMT (as well as LSD and psilocin), consistent with dysregulation of the separation between abstract associative areas and sensory processing.

In a 2023 study to explore the changes induced by the psychedelic DMT on fundamental neurodynamic networks, including the default mode (DMN) and fronto-parietal (FPN), a them led by Robin Carhart-Harris has performed the first experiment combining combining concurrent fMRI and EEG investigations.

At dosages consistent with the study, they note:

DMT, induces a deeply immersive and radically altered state of consciousness. DMT is thus a useful research tool for probing the neural correlates of conscious experience. Here, fMRI results revealed robust increases in global functional connectivity (GFC), network disintegration and desegregation, and a compression of the principal cortical gradient under DMT. The present findings advance on previous work by confirming a predominant action of DMT – and likely other 5-HT2AR agonist psychedelics – on the brain's transmodal association pole, i.e., the neurodevelopmentally and evolutionarily recent cortex that is associated with species-specific psychological advancements, and high expression of 5-HT2A receptors.

The transmodal association cortex pole (or "TOP") of the human brain sits at the upper end of a hierarchical gradient of cortical organisation, while unimodal sensory areas sit at the lower end. The TOP is linked to abstract semantic representations, longer temporal windows of information processing, and is relatively more detached from sensory input, while also appearing later in primate cortical expansion and development. These findings suggest that the subjective effects of psychedelics depend on the dysregulation of the association cortices. Evidence from neuroimaging studies also suggests that this cortical dysregulation may result in the disinhibition of "lower", evolutionarily and developmentally "earlier" systems such as the limbic system. This also throws light on aspects of the role of the DMN, not just in the resting state, or phenomena of ego loss, but in active situations, in which the FPN plays a role in cogitative planning of solutions, while the DMN takes over once these strategies are established and have become familiar. It is also consistent with the phenomena of a sensory flood, as lower level sensory and perceptual networks become more globally interactive with higher abstract networks involving our entire conception of reality.

Deco et al. (2018) have in a similar vein, combined multimodal imaging (dMRI, fMRI, and PET) in a causal whole- brain model to explain the functional effects of 5-HT2a receptors with LSD in healthy humans. The model identifies the mechanisms for non-linear interactions between the neuronal and neurotransmitter systems. The model identified the causative mechanisms for the non-linear interactions between the neuronal and neurotransmitter system, which are uniquely linked to (1) the underlying anatomical connectivity, (2) the modulation by the specific brain-wide distribution of neurotransmitter receptor density, and (3) the non-linear interactions between the two.

Barrett et al. (2020) found that psilocybin significantly decreased both the amplitude of low frequency fluctuations as well as the variance of BOLD signal in the left and right claustrum. Psilocybin also significantly decreased functional connectivity of the right claustrum with auditory and default mode networks (DMN), increased right claustrum connectivity with the fronto-parietal task control network (FPTC), and decreased left claustrum connectivity with the FPTC. DMN integrity was associated with right-claustrum connectivity with the DMN, while FPTC integrity and modularity were associated with right claustrum and left claustrum connectivity with the FPTC, respectively. This suggests a major role for altered claustrum signalling in psilocybin's effects.

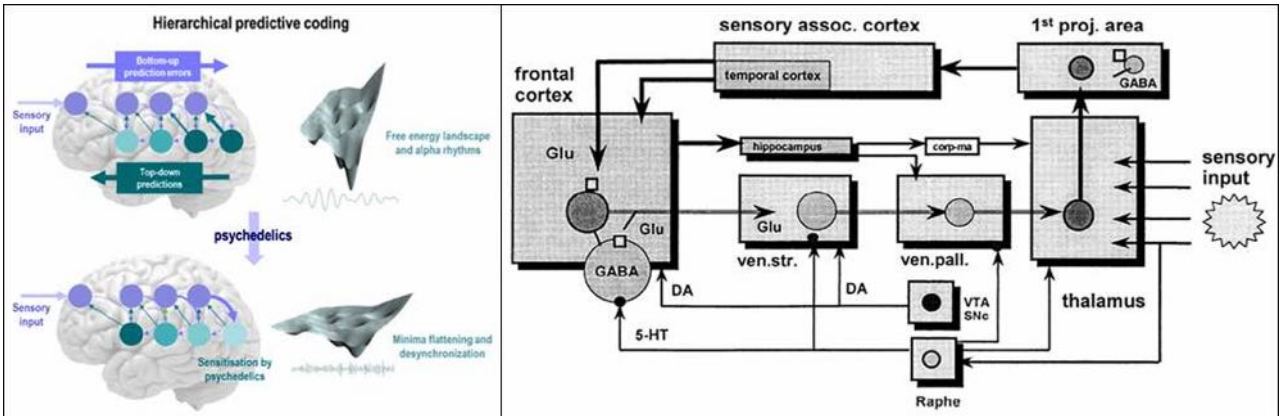


Fig 37: Left: REBUS model of lowered potential energy landscapes causing increased upwelling on psychedelics. Right: CTSC model of thalamic filtering. The filter function of the thalamus, under the control of the CSTC feedback loops, is postulated to protect the cortex from exteroceptive sensory information overload, as well as from internal over-arousal. The model predicts that sensory overload of the cortex may result from thalamic gating deficits, which may be caused by ketamine e.g. by blockade of NMDA-mediated glutamatergic (Glu) cortico-striatal neurotransmission, or excessive stimulation of 5-HT2 receptors—e.g., by psilocybin. James et al. (2022) have also applied Keppler's (2018) zero point field model of consciousness to ayahuasca and DMT.

A theoretical idea advanced to explain salient features of the brain dynamics in psychedelic experiences is the notion of increased entropy. Carhart-Harris et al. (2014) note that "*There is an emerging view in cognitive neuroscience that the brain self-organizes under normal conditions into transiently stable spatiotemporal configurations that this instability is maximal at a point where the global system is critically poised in a transition zone between order and chaos*". The paper then goes on to identify "metastability" of a brain network in terms of the variance in the network's intrinsic synchrony over time and to claim the psychedelic state has higher entropy than the normal waking mental state. While the dynamical details of this have been criticised (Papo 2016), they do serve to have conceptual explanatory power. Papo's critique incorrectly pivots on metastability and the argument is squarely refuted by Toker et al. (2022). Edge-of-chaos dynamics and transitions from chaos to order in critically poised sensitive states are essential to a dynamical model of the brain to avoid the dynamics becoming locked into sub-optimal ordered states, by using the butterfly effect and its "ergodic" ability to fully permeate the space of possibilities.

A distinction is then made between two modes of cognition, **primary consciousness** "*a mode of thinking the mind regresses to under certain conditions, e.g., in response to severe stress, psychedelic drugs and in REM sleep*", including magical thinking, "*a style of cognition in which supernatural interpretations of phenomena are made*" and **secondary consciousness** "*the consciousness of mature adult humans*". The article then takes the view that "*the mind has evolved (via secondary consciousness upheld by the ego) to process the environment as precisely as possible by finessing its representations of the world, so that surprise and uncertainty (i.e., entropy) are minimized*." It then argues "*that secondary consciousness actually depends on the human brain having developed/evolved a degree of sub-criticality in its functionality, i.e., an extended ability to suppress entropy and thus organize and constrain cognition. It is argued that this entropy-suppressing function of the human brain serves to promote realism, foresight, careful reflection and an ability to recognize and overcome wishful and paranoid fantasies. Equally however, it could be seen as exerting a limiting or narrowing influence on consciousness*". This leads to the conclusion that "*that the underlying neurodynamics of primary states are more "entropic" than secondary states i.e., primary states exhibit more pronounced characteristics of criticality and perhaps supercriticality than normal waking consciousness — implying that the latter is slightly sub-critical, if not perfectly critical*."

This leads to a discussion of the role the default mode network is claimed to have maintaining the ego through the internal dialogue, leading to forms of mental illness involving the oppression of over-weaning order, such as depression, where repetitious rounds of internal dialogue occur, reinforcing a pessimistic existential outlook. It is also an ongoing feature of the fear of inevitable death that plagues human society.

As noted, there are some major issues with simply using entropy as a measure of criticality (Papo 2016). Highly entropic systems can be products either of chaotic criticality, or noisy randomness and entropy is itself not a measure of either complexity or criticality. That said, the general theme of balancing novelty with uncertainty is characteristic of brain dynamics, much of which has characteristics of pink, or 1/*f* noise displayed by edge-of-chaos dynamics, and human creations such as musical compositions, which ideally balance history and novelty.

A second notion is the cortico–striato–thalamo–cortical (CSTC) model which involves circuits between the cortex and the thalamus that mediate control of sensory information flow to the cortex and awareness and attention (Vollenweider and Geyer, 2001). This model highlights 5-HT2a receptor activation on circuits between the thalamus and cortex to explain the subjective effects of psychedelics (Geyer and Vollenweider, 2008). In this view, psychedelics

impede sensory gating functions of the thalamus, allowing increased sensory and interoceptive information flow from thalamus to cortical regions. This reduction in sensory gating is proposed to lead to sensory overload of the cortex that results in both the observed perceptual effects and cognitive changes.

A third related notion, extending the entropy idea is that psychedelics may act to "flatten the potential energy landscape" between attracting brain states (Carhart-Harris & Friston 2019), which has received some tentative support in an LSD study (Singleton et al. 2021). The 2019 paper notes "*We call this formulation 'relaxed beliefs under psychedelics' (REBUS) and the anarchic brain, founded on the principle that — via their entropic effect on spontaneous cortical activity— psychedelics work to relax the precision of high-level priors or beliefs, thereby liberating bottom-up information flow, particularly via intrinsic sources such as the limbic system.*"

A key characteristic of some neural nets using an energy landscape to reach and optimum is to run the simulation at a higher temperature of random fluctuations at first to avoid the system getting stuck in an "alpine lake", gradually lowering the temperature to reach a quasi-optimal minimum, in a process called annealing. This is a similar process to using a transition from chaos to order to enter a quasi-optimal strange attractor. The idea is that the higher energy landscape is a way the brain filters the doors of perception, by impeding upwelling stimuli using top-down control and that when the landscape is flattened using psychedelics, new information can flood into conscious awareness.

A core basis of this argument is valid – that the brain has evolved to streamline conscious existence for survival, by filtering out uncertainty to enable rapid and decisive decision-making, ensuring organismic survival, consonant with Aldous Huxley's (1954) notion in "The Doors of Perception "that everyday reality imposes a filter and that psychedelics, by reducing the filter can enable individual consciousness to perceive the "mind at large".

Summarising the research to date Drew (2022) has the following overview:

Studies of functional connectivity have shown that the brain contains various discrete networks. Most scientists think there are about seven or eight discrete networks, including an attention or salience network, with others related to vision, hearing, sensorimotor processing and executive control. When a person is at ease, activity is seen across a collection of areas called the default mode network (DMN).

In many studies, the researchers have tried to identify specific connectional changes that correlated well with the self-reported intensity of the trip, or with some particular aspect of it, such as a sense of ego dissolution. These indicate that psychedelics lead to "more connections between networks, and less connectivity within networks,". Brain areas that usually have strong functional connections — and operate in a network that has a fairly circumscribed function — become less connected, suggesting that the drugs disrupt those networks' normal outputs. And brain areas whose activity is normally only weakly correlated become more connected. Most findings are consistent with the brain's sensory areas having more influence on overall brain activity after psychedelics were taken.

Another idea that Carhart-Harris et al.'s [2014] paper on the entropic brain considered was that psychedelics dissolve a person's sense of self by weakening connections within the DMN — an idea that gained traction far beyond the research community. Both hypotheses have been influential, but they have their critics.

"We don't know how large the contribution of the default mode network is, because there are ten other brain networks that are also altered," Katrin Preller says. Similarly, several researchers consider entropy to be too nonspecific.

In 2019, Carhart-Harris proposed the REBUS model and the anarchic brain (where REBUS stands for 'relaxed beliefs under psychedelics'), building on Karl Friston;s diea of the brain as a prediction machine that constantly forms models of what it expects to perceive in the world, then tests whether incoming sensory data confirm these models. REBUS proposes that psychedelics weaken the constraints that a person's preexisting beliefs place on their perception of the world and of themselves. Under the influence of psychedelics, sensory inputs and recalled memories are freer to influence the brain and conscious experience.

Girn et al. (2022) found that LSD and psilocybin compress the usual hierarchy of connectivity between sensory and association networks. "These sensory areas — and their bare, concrete processing of the external world — become less separate from the processes conceivably related to our abstract thinking and beliefs," Girn says. "It doesn't fully validate the REBUS model, but it's consistent."

From research began in the 1990s in humans and animal models, Vollenweider proposed the CSTC or thalamic gating model. The thalamus is a brain area that processes and filters sensory information en route to the cortex, regulated by the cortex through axons that express the 5HT2A receptor. Psychedelics seem to interfere with the thalamus's filtering operation, resulting in more sensory signals reaching the cortex. This is proposed to be central to the psychological effects of psychedelics.

In addition to these theories, Doss et al. (2022) claim that fMRI findings suggest a central role for the claustrum, a small subcortical region rich in 5HT2A receptors. Like the thalamus, the claustrum exists in a loop with the cortex.

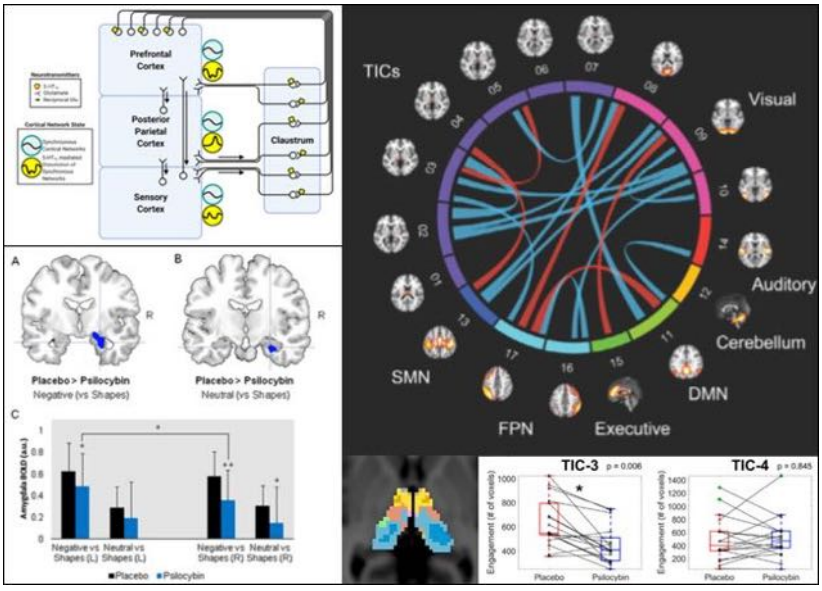
At its core, the entropic brain hypothesis proposes that the quality of any conscious state depends on the system's entropy measured via key parameters of brain function.

Cieri et al. (2021) note: *According to the free energy principle (FEP; Friston et al., 2006) the brain is an open, adaptive, complex system far from equilibrium and as with any adaptive self-organizing biological system in nonequilibrium steady-state with the environment, it must reduce its free energy to resist a natural tendency to disorder (Ashby, 1947; Friston, 2010).* They further explain that the neural complexity and brain entropy (BEN) of spontaneous neural activity decreases during states of reduced consciousness. This evidence has been showed in primary consciousness states, such as psychedelic states, under the name of "the entropic brain hypothesis", by contrast with physiological and pathological ageing, where BEN is reduced.

However the free energy principle is inadequate because consciousness existence is not just homeostatic, in terms of autopoiesis. Conscious volition is creative and isn't just homeostatic. But the theory is consistent with Huxley's view of the doors of perception being opened to the "mind at large" through psychedelics, so it does have explanatory value.

What feels like enlightenment from the inside looks like disorder from without. The idea here is that the brain processes impose a filter on the cosmic mind so that it can only behave in a way that serves the immediate survival interests of the organism, which makes it virtually impossible for a human to reach moksha. Then psychedelics paradoxically opening the filters causes ultimate reality at large to flood in. But this doesn't mean that the psychedelic experience is just a load of entropic junk – a kind of false vision. It's not this because the combination of sensory overload and self-annihilation allows the brain dynamic to run free of organismic constraints and respond to the underlying dynamic, closer to a disengaged cosmic phenomenon. From the outside, when we don't know the significance, yes this does look like forms of entropy relative to the organismic constraints.

The emerging picture is that, despite using wide varieties of techniques which are often not directly comparable, there is some support for all of these models, which illustrates how pervasive the psychedelic state is on the generation of conscious experience and serves to underline what a comprehensive transformation of our world view the psychedelic state actually entails, based on the wide distribution of 5HT2a receptors.



Fg 37b: (Top-left) claustrum model of psychedelic effects (Doss et al. 2022). (Lower left) reduction in amygdala activity under enhanced positive mood on psilocybin (Kraehenmann et al. 2015). (Right) increases in cortical and thalamic activation over placebo induced by psilocybin (red) and decreases (blue) (Gaddis et al. 2022).

As novel studies continue, further findings continue to emerge. Kraehenmann et al. (2015) demonstrate reduction of amygdala activity during enhanced positive mood on psilocybin emphasising the positive aspects of the experience. Gaddis et al. (2022) showing significant psilocybin-induced alterations in spatial organisation of intra-thalamic components. Increased auditory-sensorimotor–thalamic connectivity is also shared between LSD, MDMA and stimulants (Avram et al. 2022). Barnett et al. (2020) have noted decreased directed functional connectivity in the psychedelic state, while Jobst et al. (2021) noted increased sensitivity to strong perturbations in a whole-brain model of LSD and Olsen et al. (2022 noted) time-varying functional connectivity, associated with plasma psilocin and subjective effects. Moliner et al. (2023) show that LSD and psilocin directly bind to TrkB the BDNF receptor promoting neural plasticity, with affinities 1,000-fold higher than those for other antidepressants. Nardou et al. (2023) have also found that in young mice, psychedelics reopen the social reward learning critical period leading to long-term pro-social behaviour noting that reorganization of the extracellular matrix is a common downstream mechanism underlying psychedelic drug-mediated critical period reopening. There are also hints that psychedelics, such as DMT, which it is also believed occurs naturally to some extent in the brain has neurogenerative effects. Ly et al. (2018) report that, like ketamine, serotonergic psychedelics are capable of robustly

increasing neuritogenesis and/or spinogenesis both in vitro and in vivo. Calder & Hasler (2023) reinforce this with details of dendritogenesis and neural plasticity.

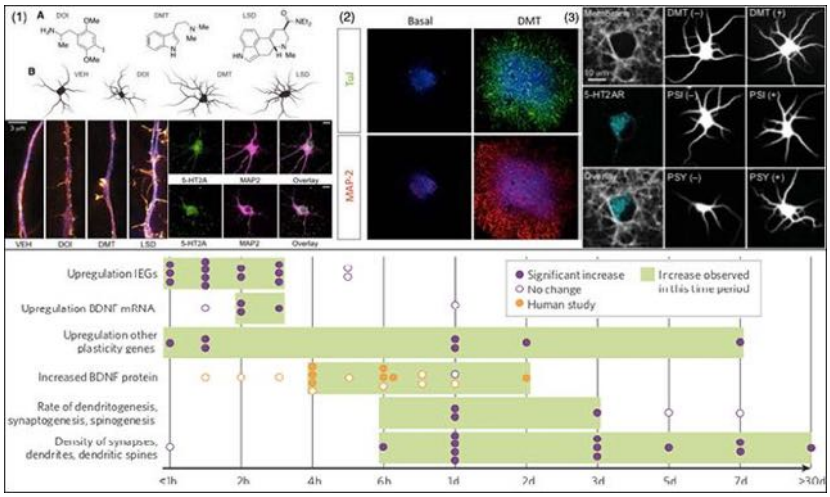


Fig 38: Upper: (1) Changes in neuronal structure, spinogenesis and the involvement of the 5-HT2a receptor in neural plasticity. (2) The involvement of DMT in neurogenesis. Neurospheres were cultured for 7 days in the presence of DMT. (3) Live-cell images of rat embryonic cortical neurons (DIV6) expressing Myc–5-HT2AR–CFP, b2AR-ECFP, or ECFP. Signals from the fluorescent protein and fluorescent plasma membrane marker in cyan and white (Vargas et al. 2023). Widefield images of rat embryonic cortical neurons (DIV6) that were administered compounds DMT, psilocin and psilocybin with (+) and without (−) electroporation, which creates temporary openings in the plasma membrane, which enables highly charged molecules to pass through and access the intracellular space. The membrane-permeable 5HT2a agonists DMT and psilocin were able to promote dendritogenesis regardless. (Lower) Timeline showing the earliest and latest observations of various changes in neuroplasticity following treatment with a single dose of the serotonergic psychedelics LSD, psilocybin/psilocin, DMT, or DOI. One dot represents one study and time point. Human studies are shown in yellow; animal and in vitro studies are shown in purple. BDNF = brain-derived neurotrophic factor, IEGs = immediate early genes. Based on data for synaptic density, it is assumed that rates of dendritogenesis and synaptogenesis also increase at 6 h post-treatment (Calder & Hasler 2023).

These changes are accompanied by increased synapse number and function. DMT treatment has also been found to activate the subgranular neurogenic niche regulating the proliferation of neural stem cells, the migration of neuroblasts, and promoting the generation of new neurons in the hippocampus, therefore enhancing adult neurogenesis and improving spatial learning and memory tasks (Morales-Garcia et al. 2020). Increased hippocampal neurogenesis also occurred in mice treated with 0.1 mg/Kg, who also extinguished cued fear conditioning significantly more rapidly (Catlow et al. 2013). Similar plasticity changes have been attributed to all classic psychedelics (Ly e al. 2018, 2021, Sotille et al. 2022. Vargas et al. (2023) further show fig 38(3) that this is common to classic psychedelics and involves intra-neuronal 5HT2a receptors also consistent with the metabotropic findings of fig 34 (b, c, d and u).

6 Therapy and Quantum Change: The Results from Scientific Studies

The theme of ego-dissolution and the DMN is also discussed with Robin Carhart-Harris at length in Michael Pollen's (2018) work. It provides a general perspective in which to understand the basis of some of the outstanding claims about the mental states psychedelics induce. As noted, psychedelics have been found to share characteristics both with meditative states and religious contemplation, in which experimenters have found a reduction in the activity of the DFM. Silencing of the internal dialogue in ego dissolution also involves extensive sensory-existential changes in which the boundary between self and other/world becomes blurred. It is important to understand that dissolving of the DMN in the acute psilocybin phase is naturally followed by a reintegration to an active and more functional DMN than in depressive illness. Carhart-Harris extends this blurring to explaining the magical thinking that frequently leads people experiencing deep insights under psychedelics to describe them as veridically true – revealed truths rather than just a personal opinion. He suggests that one explanation of this is that relative judgment that something is just a personal opinion requires separation of subjectivity to carry weight, but in the state of union no such distinction exists.

This raises a fundamental question. Are the insights real or illusory? This is the same question that plagues the status volitional will. Reductionistic materialists attempt to finesse this position by claiming we are simply the product of our circumstances and the causality of brain processes and that the notion of 'free-will" is just an illusion resulting from evolution requiring us to invest in the notion as a rationale to proceed on the basis of an organismic personal autonomy that doesn't actually exist. Subjective consciousness then becomes an epiphenomenon, having no causal effect on the material world.

However, most people and the law act on the conviction that we are intentional beings who have consequences on the world around us and that we are accountable for our actions. Premeditation is in criminal law the defining foundation of conscious intent that determines the severity of a crime. We thus need to assess deep psychedelic

experiences by the same token. Reports from very astute and trustworthy individuals consistently declare that a genuine veridical experience has taken place, having the nature of truth of the same status as both swearing legal evidence and a replicable observation of the physical world.

Aldous Huxley [2] wrote in The Doors of Perception: "*Each person is at each moment capable of remembering all that has ever happened to him and of perceiving everything that is happening everywhere in the universe. The function of the brain and nervous system is to protect us from being overwhelmed and confused by this mass of largely useless and irrelevant knowledge, by shutting out most of what we should otherwise perceive or remember at any moment, and leaving only that very small and special selection which is likely to be practically useful. According to such a theory, each one of us is potentially Mind at Large*" … "*In the final stage of egolessness there is an 'obscure knowledge' that All is in all — that All is actually each. This is as near, I take it, as a finite mind can ever come to 'perceiving everything that is happening everywhere in the universe.*"

Fig 38b: Huxley's reducing valve (Swanson 2018). The word psychedelic means "psyche revealing", where psyche means the human mind, soul, or spirit and dēlos means 'clear, manifest'. Thus, Osmond's (1957) proposed name-change— psychedelic—was intended to capture the spirit of filtration theory, by inhibiting certain brain processes which normally maintain their own inhibitory constraints on our perceptions, emotions, thoughts, and sense of self.

Huxley is highly critical of the limiting nature of the doors of perception's usual filter: "*To make biological survival possible, Mind at Large has to be funnelled through the reducing valve of the brain and nervous system. What comes out at the other end is a measly trickle of the kind of consciousness which will help us to stay alive on the surface of this particular planet. To formulate and express the contents of this reduced awareness, man has invented and endlessly elaborated those symbol-systems and implicit philosophies which we call languages. Every individual is at once the beneficiary and the victim of the linguistic tradition into which he or she has been born — the beneficiary inasmuch as language gives access to he accumulated records of other people's experience, the victim in so far as it confirms him in the belief that reduced awareness is the only awareness and as it be-devils his sense of reality, so that he is all too apt to take his concepts for data, his words for actual things*."

This criticism has become even more urgent and critical in a time of planetary climate and ecocrisis, when this reduced tribal awareness driven by ego-consciousness is causing dire risk of a mass extinction of the diversity of life and potentially the extinction of the human species. To a reader not familiar with these states, it is hard to give credibility to the notion that a person under the influence of an agent originally labelled as an "hallucinogen" that is known to have both transcendent and potentially diabolically dysphoric dimensions as Huxley emphasised in "Heaven and Hell" (1956) can also have experiences with the long-lasting therapeutic relief or mystical insight, let alone be literally and veridically true.

However this is precisely what a number of studies, where precisely these insights under psychedelics have been repeatedly shown to have long lasting insights and benefits, both in severe depression and in people suffering a terminal condition and in normal people experiencing mystical states (Carhart-Harris t al. 2016b, Griffiths et al. 2006, 2008, 2011, 2016, **2021**).

The titles of these research papers indelibly attest to the genuine long-term effects that these experiences induced:

"*Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance*", "*Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later*", and "*Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer*".

The most striking finding from this 14-month follow-up evaluation of the effects of psilocybin ... administered to hallucinogen-naïve volunteers is that a large proportion of volunteers rate their "psilocybin experience" as among the most personally meaningful and spiritually significant of their lives. Fifty-eight percent and 67% of volunteers, respectively, rated the experience as being among the five most personally meaningful experiences of their lives, and the five most spiritually significant experiences of their lives; 11% and 17%, respectively, indicated that it was the single most meaningful experience, and the single most spiritually significant experience. Furthermore, 64% of the volunteers also indicated that the psilocybin experience increased their sense of well-being or life satisfaction moderately or very much, and no volunteer rated the experience as having decreased well-being or life satisfaction.

Ketamine has similarly shown promise in treatment-resistant depression, though effects do not last as long as those observed with psilocybin. A possible mechanism has been found in the disassembly of perineuronal nets restraining new synapse formation in established learned memories (Venturino et al. 2021). Other evidence suggests a potentially shared mechanism wherein both ketamine and SPs may engender rapid neuroplastic effects in a glutamatergic activity-dependent manner (Kadriu et al. 2021). The notion due to Craddock, that ketamine and

[2] This follows in line with the filter theories of Henri Bergson Matière et Mémoire (1896) and William James Human Immortality. (1898)

psychedelics share an interaction with microtubules affecting consciousness does not at this point have evidential support.

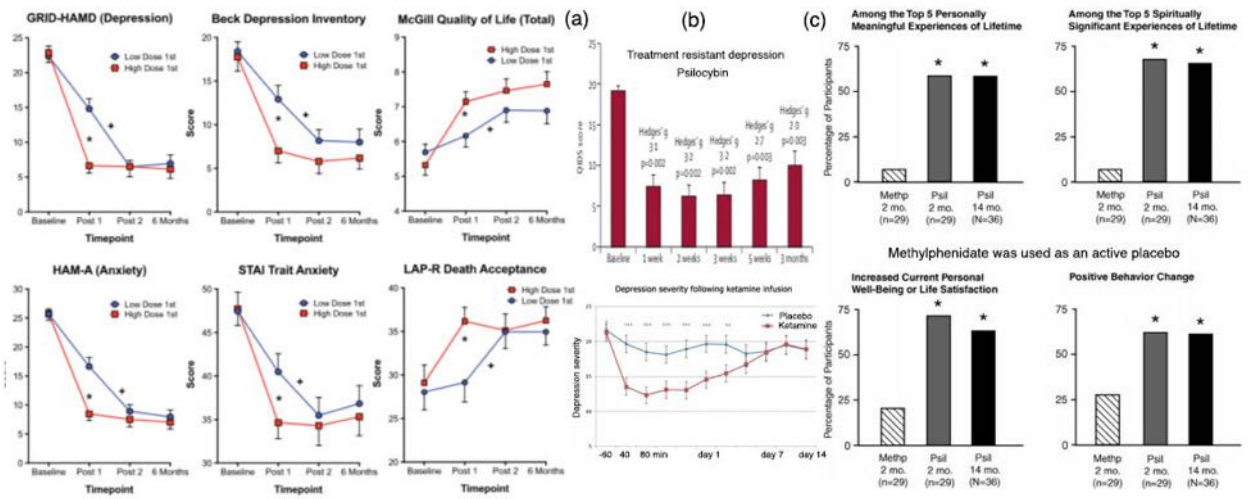


Fig 39: (a) Assessments of improvement in depression, anxiety and quality of life up to 6 months after psilocybin study in subjects facing life-threatening cancer (Griffiths et al. 2016) (b) Improvements in subjects with treatment-resistant depression after psilocybin study (Carhart-Harris et al. 2016b), compared with Ketamine (Zarate et al. 2012). (c) Assessments 2 & 14 months after the psilocybin study Griffiths et al. (2006, 2008). The largest study of its kind (Goodwin et al. 2022) has confirmed these findings for a one-dose treatment for a treatment-resistant episode of major depression.

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A later study (Griffiths et al. 2018) combined the use of psilocybin with meditation and other spiritual practices, echoing the way in which movements such as the Native American Church and the Union Vegetale provide a spiritually conducive context to engender positive outcomes, designed to tap into **quantum change experiences** – sudden, distinctive, benevolent, and often profoundly meaningful experiences that are said to result in personal transformations that affect a broad range of personal emotions, cognitions and behaviours (Miller, 2004; Miller and C'de Baca, 2001).

The discussion notes: "*The study showed robust interactive positive effects of psilocybin dose and added support for spiritual practices on a wide range of longitudinal measures at 6 months including interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and rating of participants by community observers. Analyses suggest that the determinants of these effects were the intensity of the psilocybin occasioned mystical experience and the rates of engagement with meditation and other spiritual practices. Most broadly, as a model system for studying so-called quantum change experiences, which have been described for centuries but which have eluded rigorous prospective experimental analysis, further investigation of psilocybin-occasioned experiences may have broad implications for the development of drug and non-drug interventions in both therapeutic and nontherapeutic applications in order to engender enduring positive trait-level changes in attitudes and behavior and in healthy psychological functioning".*

Miller (2004) notes: "*The person typically experiences mystical quantum change passively, not a product of personal will or control, and has a difficult time expressing the experience in words. They usually are intensely positive, joyful experiences, and often the person senses the presence of an awe-inspiring transcendent Other. Often there is a noetic element of revelation, a sudden knowing of a new truth. An experience of unity is common; for example, an ineffable oneness with all of humankind, with nature, or the universe. In these respects, the mystical type of quantum change is similar to common reports of near-death experiences (Lorimer 1990). At the most mystical level, quantum changers seemed to become more alike, as if they had in some way glimpsed the same truth. They often voiced the experience of being interconnected with and part of all of humanity and creation. Those who had experienced themselves in the presence of a transcendent Other gave strikingly similar descriptions. They felt awe but rarely fear, for in its presence they had experienced unspeakable love and acceptance. The insightful type of quantum change lacks most of the mystical components save one: the noetic element of sudden realization or knowing with great and sudden force, and in the moment of seeing, the person recognizes them for authentic truth (or Truth). Their effect tends to be a reorganization of one's perceptions of self and reality and a cathartic, ecstatic, sense of relief and release. They knew instantly they had passed through a one-way door through which there was no return. They were changed, freed right then, and knew it immediately. Often, characteristics that had been valued least became most important [spirituality and generosity] , and those that had ranked as highest priorities [such as status and possessions] fell to the bottom".*

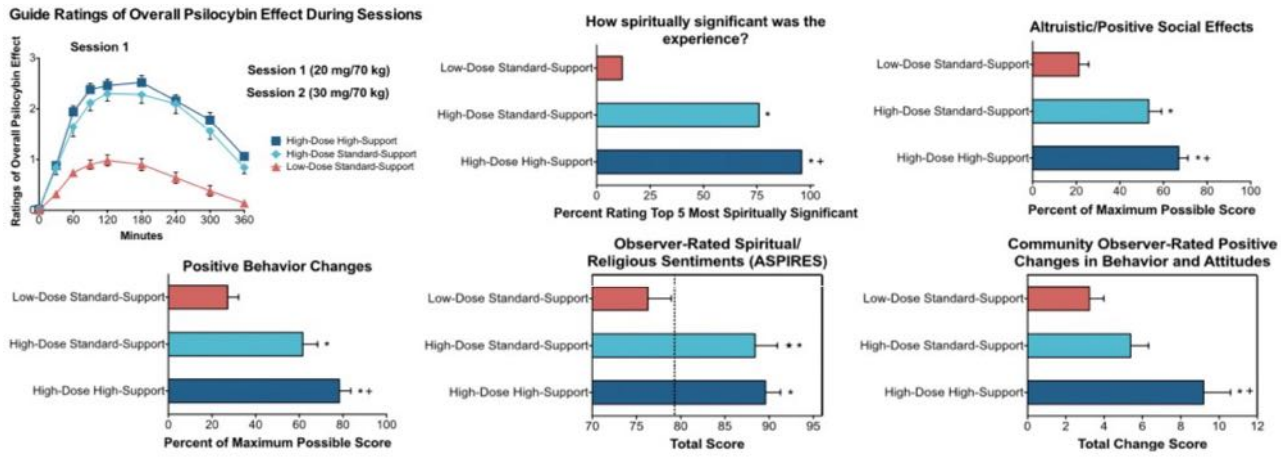


Fig 40: Selected results from Griffiths et al. (2018). All at 6-months after, except for the top-left rating of psilocybin effect.

A further study (Griffiths et al. 2019) compared "God-encounter experiences" under classic psychedelics and naturally. While *"the Non-Drug Group was most likely to choose "God" as the best descriptor of that which was encountered while the psychedelic groups were most likely to choose "Ultimate Reality." Most participants reported vivid memories of the encounter experience, which frequently involved communication with something having the attributes of being conscious, benevolent, intelligent, sacred, eternal, and all-knowing. … These experiences were rated as among the most personally meaningful and spiritually significant lifetime experiences, with moderate to strong persisting positive changes in life satisfaction, purpose, and meaning attributed to these experiences"*. A long-term increase in mindfulness is also noted (Madsen et al. 2020).

Having these mystical experiences, the patient is able to overcome their depression or reframe that depression and return to a more baseline mental being. It really seems to restore … the wellness and balance in the life of the patient. It's quite magical. We don't know yet, but I strongly suspect that you cannot separate the two [effects therapeutic and psychedelic]. Hallucinating is an essential part of the way these drugs work. Chris Koch chief scientist of the *Allen Institute's MindScope Program*.

Bill Richards [3] notes that mystical experience isn't something vague, but a specific form of human consciousness. '*When it's expressed through questionnaires you can find evidence of six categories, which [are]: unity; transcendence of time and space; intuitive knowledge (what William James called the noetic quality); a sense of sacredness or awesomeness; deeply felt positive mood, such as joy, peace, love, purity; and claims of ineffability and what we call paradoxicality — that it's very hard to put these experiences into words and when people try to express it they keep contradicting themselves, that's the paradoxicality: 'I died but I've never been so alive, the ultimate reality was one but it was many, it was beyond time but it included time' — ultimately the Buddhist claim of the nothingness that contains all reality. And it seems contradictory, but mystics would say the problem isn't in the experience; it's in our ability to express the experience within language, at this point in the development of language. And that the answer, the truth is always "both and" rather than "either or".*'

As a warning to unsupported experiences in a bad setting, a survey by Griffiths' group of extreme, challenging experiences (Barrett et al. 2016, Carbonaro et al. 2016), 1993 individuals (mean age 30 yrs; 78% male) completed an online survey about their single most psychologically difficult, or challenging experience (worst "bad trip") after consuming psilocybin mushrooms. 39% rated it among the top five most challenging experiences of his/her lifetime. 11% put self or others at risk of physical harm; factors increasing the likelihood of risk included estimated dose, duration and difficulty of the experience, and absence of physical comfort and social support. 2.6% behaved in a physically aggressive or violent manner and 2.7% received medical help. Of those whose experience occurred >1 year before, 7.6% sought treatment for enduring psychological symptoms. Three cases appeared associated with onset of enduring psychotic symptoms and three cases with attempted suicide. Intriguingly, the degree of difficulty was positively associated with enduring increases in well-being. Despite difficulties, 84% endorsed benefiting from the experience and the researchers noted that the incidence of risky behaviour or enduring psychological distress is extremely low when psilocybin is given in laboratory studies to screened, prepared, and supported participants.

It is extremely significant that facing the fear of immanent death, possibly in pain and debilitation, which is the most real and terrifying crisis any conscious mortal being can face, can be redeemed on an ongoing, not just a transient basis, by a psychedelic experience. This attests to these experiences not being illusory but evidential to the conscious mind as the antidote to the mortal dilemma. This is precisely what "moksha", the primary goal of all Eastern spirituality, seeks to attain through a lifetime of renunciation and devoted meditation. It also stands as highly evidential that in their signature work "The Psychedelic Experience", Leary, Alpert and Metzner (1964) presented a guide for readers to navigate the psychedelic state, framed as a modern representation of the Bardo Thodol or

[3] Bob Jesse and Bill Richards are co-authors of Roland Griffith's 2006, 2008 mystical experiences studies.

Tibetan Book of the Dead – "*The Great Liberation upon Hearing in the Intermediate State"* – (Lāma Kazi Dawa-Samdup Eng trans 1927), the Tibetan Buddhist manual for successfully negotiating death and rebirth.

Michael Pollen notes a conversation with Roland Griffiths, in which, despite being a world renowned academic researcher leading the field, he has to pick his words very carefully: "*The first time I raised [Bob] Jesse's idea of the betterment of well people with Roland Griffiths, he seemed to squirm a bit in his chair and then chose his words with care 'Culturally right now that is a dangerous idea to promote*' ". However Roland later commented "*We're all dealing with death – this is far too valuable to limit to sick people*", afterwards carefully amending it to "*This will be far too valuable to limit to sick people*".

A Psychedelics Pioneer Takes the Ultimate Trip Marchese (2023) NYT

As the founding director of the Johns Hopkins Center for Psychedelic and Consciousness Research, Dr. Roland Griffiths has been a pioneer in investigating the ways in which psychedelics can help treat depression, addiction and, in patients with a life-threatening cancer diagnosis, psychological distress. He has also looked at how the use of psychedelics can produce transformative and long-lasting feelings of human interconnectedness and unity. Griffiths, who is 76, has been diagnosed with Stage 4 metastatic colon cancer, in all likelihood terminal, that has brought forth transcendently positive feelings about existence that he calls the great mystery of consciousness. "We all know that we're terminal," says Griffiths, "So I believe that in principle we shouldn't need this cancer diagnosis to awaken. I'm excited to communicate, to shake the bars and tell people, 'Come on, let's wake up!' "

In spite of the diagnosis, life has been more beautiful, more wonderful than ever. When I first got that diagnosis, because I work out regularly, I watch my diet, I sleep well, this came out of left field. There was this period in which it felt like I was going to wake up and say, "Boy, that was a bummer, a bad dream." But soon I started to contemplate the different psychological states that would be naturally forthcoming: depression, anxiety, denial, anger, or adopting some belief system of religious outcomes, which as a scientist I was not cut out to do. I went through those, exploring what life would be like if I inhabited those reactions, and I quickly concluded that that was not a wise way to live. I have a long-term Vipassana meditation practice and the focus there is on the nature of mind, of consciousness, and one comes to see that thoughts, emotions, are transient. That practice — and some experience with psychedelics — was incredibly useful because what I recognized is that the best way to be with this diagnosis was to practice gratitude for the preciousness of our lives. Grasping for the cure wasn't useful.

After getting the diagnosis, I had no immediate interest in psychedelics. I felt in many respects that I was having a very psychedelic-like experience. There was this awakening, this aliveness, and I hesitated to take a psychedelic because I wondered whether it was going to disrupt that. Then a question arose: Is there something I'm avoiding by not taking a psychedelic? Am I defending against some dark, fearful thing I'm in denial about? Am I papering it over with this story of how great I'm doing and actually I'm scared to death? I thought, Well, this would be an interesting stress test. So I did a session with LSD. First, asking myself, "Is there something I am not dealing with?" The answer came back: "No, the joy you're experiencing is great. This is how it should be." Then I asked a question directly of the cancer: "What are you doing here? I got nothing back. Then I wanted to humanize it, and I said: "I really respect you. I talk about you as a blessing. I have had this astonishing sense of well-being and gratitude, despite everything that's happening, and so I want to thank you. This process, is it going to kill me?" The answer was, "Yes, you will die, but everything is absolutely perfect; there's meaning and purpose to this that goes beyond your understanding, but how you're managing that is exactly how you should manage it." So then I said: "OK, there's purpose and meaning. I'm not ungrateful for the opportunity, but how about giving me more time?" [Laughs.] I got no response to that. But that's OK.

Our first study was in cancer patients. Ironically enough, these were cancer patients who were depressed and anxious because of a life-threatening diagnosis. The findings of that study were profound: A single treatment of psilocybin produced large and enduring decreases in depression and anxiety. I've had some limited experience with psychedelics since then. We've now treated hundreds of participants with psychedelics and before sessions, one of the key things that we teach them is that upon taking a psychedelic, there's going to be an explosion of interior experiences. What we ask them to do is be with those experiences — be interested and curious. You don't have to figure anything out. You're going to have guides, and we're going to create this safety container around you. But here's the trick: These are not necessarily feel-good experiences. People can have experiences in which they feel like they come to this beautiful understanding of who they are and what the world is, but people can also have frightening experiences. The preparation we give for these experiences is to stay with them, be curious and recognize the ephemeral nature of them. If you do that, you're going to find that they change. The metaphor we use is, imagine that you're confronted with the most frightening demon you can imagine. It's made by you, for you, to scare you. I'll say: "There's nothing in consciousness that can hurt you. So what you want to do is be deeply curious and, if anything, approach it." If your natural tendency is to run, it can chase you for the

entire session. But if you can see it as an appearance of mind, then you go, "Oh, that's scary, but yeah, I'm going to investigate that."

Fig 40c: Griffiths in one of the psilocybin treatment rooms.

The approach that you're describing is pretty far from the typical mind-set of many doctors, who are working within a framework of curing, fixing, prevention. So if the ultimate goal is to help more otherwise healthy people get safe access to the potential benefits of using psychedelics, which of course would need to be used in a safe setting and supervised by trained experts, wouldn't that require a radical rethinking by medical practitioners about what helping people even means?

Yes, it will. One of the inspirations for the endowment is that it's not aimed at patient populations. Right now, there's money pouring into this area, but that's all going to be patient-related — there's a pathway to medical approval. I do have concerns that we don't replicate the mistakes that occurred in the 1960s, which over-promoted psychedelics' use culturewide. They're so powerful that if misaligned with cultural institutions, they can result in cultural kickback. In the 1960s they became aligned with the antiwar movement and radicalized-youth movement that was terrifying to existing political structures and institutions, and as a consequence, legislation was put up against them, funding dried up. We need to proceed cautiously. It's going to be critically important not to threaten existing cultural institutions. So I've been a proponent of medicalization, because with medicalization, we already have regulatory structures in place. It goes through F.D.A. approval; they're going to set standards to maximize safety by specifying who should be eligible to receive, who is authorized to prescribe, and under what conditions treatment should occur. So I'm cautious, but that's why I'll have the endowment in perpetuity. If we look at the long range, this could be critical to the survival of our species.

It is Griffiths's belief that humanity has developed — and is developing — technologies that could threaten its ongoing survival. He also believes that psychedelic experiences can provide the basis for moral and ethical principles that would lessen the likelihood that humanity will drive itself off a cliff. Because there's something about the nature of these experiences under these certain conditions that produce remarkable experiences of interconnectedness of all things. At the deepest level, if we recognize we're all in this together, then we have the kernel of what I suspect is most religious traditions and impulses and that is realizing that the Golden Rule makes a lot of sense. After we spoke, Griffiths mailed me a medallion embossed with an image of mushrooms and inscribed with the phrase "May you remain aware of awareness."

I've noticed that often when you discuss human consciousness and our awareness of the preciousness of life, you talk about those things as an awe-inspiring "mystery." What do you get out of putting it in those terms? Because consciousness may be a mystery now, but I've read theories that are convincing, to a layperson like me, that thoughts come from emotions and our emotions are one of the body's mechanisms of maintaining homeostasis. Or as far as the awareness that life is precious, I could easily imagine that biophilia has evolutionary advantages. So I don't see why these states of being have to be understood as mysteries. Does it diminish them to see them as explainable?

I can easily inhabit an evolutionary account that explains how we have come to be who we are — with the exception of the question of interiority! Why would evolution waste its precious energy on our having interior experiences at all? I don't get that. To me, it's a very precious mystery, and that mystery, if you want to put it in religious terms, is God. It's the unknowable. It's unfathomable. I don't believe in God as conceptualized within different religious traditions, but the mystery thing is something that strikes me as undeniable. I want everyone to appreciate the joy and wonder of every single moment of their lives. We should be astonished that we are here when we look around at the exquisite wonder and beauty of everything. I think everyone has a sense of that already. It's leaning into that more fully. There is a reason every day to celebrate that we're alive, that we have another day to explore whatever this gift is of being conscious, of being aware, of being aware that we are aware. That's the deep mystery that I keep talking about. That's to be celebrated!

On the question of authenticity, of the psychedelic experience, opinions vary. David Nichols (**2011**), the Perdue pharmacologist who founded the Hefter Institute to support psychedelic research and synthesised the psilocybin for Griffith's experiments said "*If it gives them peace, if it helps people to die peacefully with their friends and their family at their side, I don't care if it's real or illusion*". But Roland Griffiths acknowledges "*authenticity is a scientific question not yet answered – all we have to go by is the phenomenology*" – i.e. the quality of personal reports. In response to Michael's "*staunchly materialist*" world view Roland replied "*Okay then, but what about the miracle that we are conscious? Just think about that for a second, that we are aware and that we are aware that we are aware! How unlikely is that?*"

Primary consciousness associated with reduction of the internal dialogue and ego-dissolution is not just a question of flawed magical thinking that the mind regresses to, but is shared by psychedelics, meditation and deep religious contemplation, all of which in varying ways seek to calm the internal dialogue, attributed to inhibition of the DMN. Michael Pollen cites a number of themes relating to this, including the undifferentiated inclusive mentality of the child mind advanced by Alison Gopnik who co-hosted a talk with Robin Carhart-Harris (**2016**), echoing sayings of Yeshua and Don Jose Matsuwa. Gopnik refers to a wider nuanced "lantern awareness" which becomes a starker "spotlight awareness" of the Cartesian theatre in adulthood, which as we age, becomes more and more locked into habitual routines that have been found successful in the past. It also applies to releasing the inability of the ordered mind to think outside the box and to be creative, as opposed to conservative and analytic consciousness, which is strongly history-based, rather than novelty-based.

But there are also outstanding differences between psychedelic experiences and meditative and contemplative ones, which are essential to understand and are pivotal to the central enigma of existential cosmology. Mediation seeks to achieve enlightenment by careful top down control, mediated by equanimity, rejection of grasping desires, one-pointed concentration and compassionate emotion. Religious contemplation seeks repose in prayer and devotion. Thus the person involved finds a degree subjective fulfilment, amid acceptance of a spiritual or religious doctrine they are already committed to. Although these experiences of ego dissolution may induce positive outcomes for the individual, they also tend to confirm established beliefs, rather than open the floodgates to new ideas challenging one's preconceived assumptions. By contrast, psychedelics are liable to induce insights of a novel and existentially challenging nature, such as the somewhat baffling notion of "the mind at large" as a spontaneous discovery.

Psychedelics provide a complex cyclonic perturbation of existential and sentient consciousness, not a simple "enlightenment pill". Bill Richards notes: '*The relation of the drug to the experience is not like taking an aspirin to get rid of your headache. What the psychedelic substance … they all seem to be skeleton keys that open up the mind, that give you an opportunity to explore, but where you go and what happens depends on who you are, kind of who you are, your maturity, your life history, your capacity to be able to choose to trust unconditionally, your feeling of safety, your courage. So much more is involved than just taking the drug*.'

What we are dealing with in psychedelics is a whole constellation of mental states, depending on the circumstances and mind set of the person involved. They can take on visionary aspects of traditional notions such as soul theft and sorcery and invoke complex detailed visions from which the word 'trip' arises, including specific socio-cultural motifs such as snakes and animistic visionary deities. Some of these can be hilarious, others frightening. Some can be profound, others frivolous or meaningless. Some can lead to messianic delusions and others to creative art, musical composition and scientific discoveries. Albert Hoffman has stated that Karry Mullis, who invented the polymerase chain reaction that is now identified to be the core of molecular biology techniques and essential for Covid-19 testing, told him he credited its discovery to his use of LSD in his student days where he synthesised LSD. It was reported that he was actually coming down from a trip when the idea struck him. We are dealing with an agent invoking as many diverse features as existence can provide. The critical issue underlying this retinal carnival of experiences is how it can reveal underlying experiential knowledge difficult or impossible to gain through any other route.

Their political liberalism and nature-relatedness dimensions have been confirmed (Nour et al. 2017, Lyons & Carhart-Harris 2018). Nearly nine hundred participants provided information about their naturalistic psychedelic, cocaine, and alcohol use, and answered questions relating to personality traits of openness and conscientiousness, nature relatedness, – "*I am not separate from nature but part of nature*" – and political attitudes. Participants also rated the degree of ego dissolution experienced during their "most intense" recalled psychedelic experience. Analysis revealed that lifetime psychedelic use (but not lifetime cocaine use or weekly alcohol consumption) positively predicted liberal political views, openness and nature relatedness, and negatively predicted authoritarian political views, after accounting for potential confounding variables. Ego dissolution correlated significantly with these effects.

Psychedelics clearly have political and revolutionary implications that can lay siege to traditional cultural values. It is admitted that the initial wave of repression of psychedelics was political in nature in response to a social movement rejecting the core tenets of a consumer society polarised between materialistic exploitation and religious and sexual conservatism. Fifty three years later, we find ourselves only moderately emerging from a period of repression lasting half a century, still tightly regulated, so as to be applicable only to scientific studies, largely on pathological conditions of depression and terminal illness, or direct scientific inquiry but not for the betterment of sane and healthy people. There is a deep parallel between the Catholic repression of gnostic elements in the Inquisition that arose ultimately from cross fertilisation of ideas during the Crusades, and of the witch hunts against older spiritual beliefs centred

around the ancient European Goddess whose practices Christianity replaced and the reaction to the social values emerging from psychedelics in the 1960s.

The same repressive end result as the middle ages Christian repressions of dissent occurred when LSD become popularised and suddenly, because it had not yet become illegal, huge quantities of very pure acid flooded into rock culture, by devoted underground chemists not seeking financial rewards but for the "common good", celebrated by the Beatles' "Tomorrow Never Knows" citing Leary's Bardo Thodol, and "Lucy in the Sky with Diamonds", while on the East Coast of the US, Timothy Leary was pronouncing "turn on, tune in and drop out" and on the West Coast, the Grateful Dead, playing "Dark Star" on acid, the Electric Kool-aid Acid tests and the Merry Pranksters, were blowing young peoples minds, while the infectious ethic of free love was shredding conventional sexual morality. This blew the cover on just how seriously the political and revolutionary implications of psychedelics were laying siege to traditional cultural and particularly commercialistic political and religious values.

Despite the fact that many of these events passed safely without incident, that LSD didn't split peoples chromosomes, that groups of people hadn't stared at the sun until they went blind, by the mid-1960s the backlash against the use of LSD and its perceived corrosive effects on the values of the Western middle class resulted in governmental action to restrict the availability of psychedelics by making any use of them illegal. Both LSD and psilocybin were declared "Schedule One" substances. The governors of Nevada and California signed bills into law on May 30, 1966 and the rest of the world followed shortly after, fulfilling the dark ending of Huxley's (1962) allegory in "Island", in which the people of Pala consume yellow mushrooms which they call "moksha" to induce visionary states, but are in the end subjected to a military takeover by a neighbouring conservative religious culture. The picture hardened with the case of Charles Manson. The prosecution contended that, while Manson never directly ordered the murders, his ideology constituted an overt act of conspiracy.

However schedule 1 didn't stop consumption of psychedelics, which have remained an underground transformative staple at music festivals, forming the entheogenic [4] counterpoint to MDMA's entactogenic love-in rave party experience. Entheogen (see Ott 1993) is a term that, by its own meaning infers that deity emerges from the sacrament rather than vice versa, confirming the overwhelming impression from this class of agents that they have transcendent dimensions. Stanislav Groff coined the term "holotropic" [5], to cover wholeness seeking in all its forms from experiencing the totality as in the mind at large to peri-natal experiences of a physical rebirth struggle.

But repressive legislation of the war on drugs has still had a mind-numbingly counter-productive effect. People are incarcerated for long periods for simple possession of psychedelics. For four decades they were effectively eliminated from scientific knowledge, or assessment. Society as a whole has had almost no opportunity to figure out what role these profoundly transformative agents have in world culture, despite the fact that the natural entheogens have been used for millennia for spiritual and therapeutic purposes in every culture that has consumed them. This means that the role of entheogens has until subtly in the 21st century, been suppressed entirely by the very world societies that have claimed to be the pillar of scientific enlightenment. At the same time, while psychedelics continue to be used devotedly by an underground network of devoted psychonauts, they tend to be trivialised as mere entertainment. Their potential impact on society's, and the planet's future, remains occluded as an illegal recreational playground of no confirmed value, or significance.

Currently natural psychedelics are used scientifically in research, and particularly into therapy for pathological conditions of depression and terminal illness. They also continue to be used in some settings for religious and spiritual purposes such as Santo Daime, the Union Vegetale and the Native American Church, much as they have for centuries. Finally they are used recreationally as an illegal but sometimes tolerated fringe activity, partly because they are easy to cultivate and almost impossible to eradicate. All of these uses create a gloss on the phenomenon which clouds its full potential. Recreational use tends to trivialise it and reduce it to the pursuit of pleasure. Spiritual and religious use tends to reinforce existing attitudes, from Christian doctrine to tribal sorcery and witchcraft.

Demonstrating just how complex the discourse on sacred mushrooms are, Andy Letcher in "*Mad Thoughts on Mushrooms"* (2007) cites three dominant discourses in a Foucauldian sense: (1) **Psychotic** where hallucinogens are perceived to induce psychosis, (2) **Therapeutic**, where they are seen to have therapeutic value when confined to the clinic, and (3) **Prohibitionary** when they escape the clinic and should be suppressed by the full force of the law. In this

[4] *entheogen* – "*god (theos) within*", is a psychoactive substance that induces alterations in perception, mood, consciousness, cognition, or behaviour for the purposes of engendering spiritual development or otherwise in sacred contexts. (Wikipedia)

[5] *holotropic* "wholeness seeking" – states which aim towards wholeness and the totality of existence – e.g. Brahman–atman.

view the pendulum swung firstly from (1) –> (2) –> (3) and is now swinging back towards (2) while still remaining a discourse of containment and marginalisation on the part of academics, out of realistic fear of a regulatory backlash.

Running counter to these three dominant discourses are four resistive discourses: (4) **Recreational** ,in which breaking the bounds is advocated both for the pleasure these experiences brain and for the pleasure of transgression against the imposed restrictive order; (5) **Psychedelic,** for their ability to reveal or make manifest the hidden dimensions of the self; (6) **Entheogenic,** stemming ultimately from Gordon Wasson's religious experiences on mushrooms in a group conference in which Carl Ruck coined the term, meaning "generating God within," or "becoming God within", and finally; (7) **Panpsychic** / **Animistic,** that is, they evoke, not theophany but animaphany. Here, mushrooms are not regarded as altering, consciousness but as adjusting what it is possible to perceive, and therefore the spirits and beings occasioned by mushrooms are neither hallucinations nor some aspect of the self, but beneficent discarnate entities with whom the practitioner attempts to forge relationships. They thus tend to evoke states of consciousness in which the consciousness of animals and plants, to other, e.g. spirit entities, or the mind at large, are experienced.

David Luke (2020) also lists a diverse collection of anomalous experiences spanning the transpersonal and psychedelic including (a) synesthesia, (b) extra-dimensional percepts, (c) out-of-body experiences, (d) near death experiences, (e) entity encounters including (mythological beings, chimeras, extraterrestrials, angels and celestial beings, semi-divine beings such as Jesus or Buddha, demons, monsters and beings of death), (f) interspecies communication, (g) possession, and (h) telepathy, precognition, clairvoyance and psychokinesis. DMT is particularly prone to spirit images, as illustrated in "Ayahuasca Visions" (Luna & Amaringo 1991). Shaun Smith (2015) notes the contrasting neurotheological view of theistic phenomena being explained through neurobiology with the theoneurological view of Robert Strassman (2001,2014) in which God or deity is able to alter neurobiology through "the spirit molecule" DMT. Not all of the examples cited by Luke are psychedelic induced and several of the psychedelic examples echo in greater intensity and embellishment those in dreaming and hypnagogic imagery, in which the subject finds themselves immersed in perceived situations and encounters with entities that evaporate with arousal. These can be considered as visions at the periphery of the nierika portal.

At an extreme, we have Terrence McKenna's far-fetched statement identifying mushroom spores, rather than the cosmological consciousness and visions they evoke, as galactic entities of enlightenment spread across the universe:

"I am old, older than thought in your species, which is itself fifty times older than your history. Though I have been on earth for ages, I am from the stars. My home is no one planet, for many worlds scattered through the shining disc of the galaxy have conditions which allow my spores an opportunity for life." (McKenna 1993 210).

There is a fine line between this kind of statement, which most people will find unbelievable fantasy, and a much more widely held, meaningful and validating discourse that the mushroom experience can evoke a universal consciousness that may inform in meaningful, or even urgent ways, the ensuing direction a person's life needs to take.

Yaden et al. (2021) call for epistemic humility [6] regarding psychedelics and the hard problem: "*We conclude by calling for epistemic humility regarding the potential for psychedelic research to aid in explaining the hard problem of consciousness while pointing to ways in which psychedelics may advance the study of many specific aspects of consciousness.*" Epistemic humility is applying a rule that we can't assess reality in itself – the very core of the psychedelic experience of "ultimate reality" unless we do so with the filters of the doors of perception slammed shut! How they can say this, while holding the purse strings of the dominant therapeutic discourse, is extremely troubling.

Their reasoning is not really about psychedelics but about the confounding nature of the hard problem: "*The hard problem of consciousness is currently not scientifically answered, and it is not clear that a scientific answer is even possible, which is why it is called "a hard problem*." They then note that the hard problem is often described in terms of the "explanatory gap" (Levine, 1983), noting: "*This phrase may be an understatement – there is far more than a gap, but rather a yawning chasm between our current scientific understanding and the prospect of explaining the hard problem of consciousness*." This is the chasm of the psychedelic experience in which materialistic science fails the test because it can't explain conscious volitional will either. To use the term scientific in this way is a contradiction to the meaning of science as a word which embraces knowledge more generally than physical investigation.

Although psychedelics may not of themselves automatically solve the hard problem, the psychedelic experience cited in this article has led to the cosmological description in this article, which does provide a concise solution to the hard

[6] ***epistemic humility*** – a posture of scientific observation rooted in the recognition that (a) knowledge of the world is always interpreted, structured, and filtered by the observer, and (b) scientific pronouncements must be built on the recognition of observation's inability to grasp the world in itself.

problem. The problem is not with psychedelics, but the assumptions of materialism and physicalism of the current dominant fashion in scientific exploration of brain states. This is confirmed by their statement that: "*it is not clear that a scientific answer is even possible*". This highlights what the author sees as a dangerous development in psychedelic research, where the agent most startlingly evoking subjective changes to experience is being filtered through a materialistic filter by the very academics acting as the mediators of therapeutic use and research into these agents. This looks to be an example of the dominant discourse in therapeutic use being applied by the mediators of the research to undermine both the psychedelic and the unrestrained entheogenic resistive discourses and the validity of psychedelics outside the laboratory as agents of cosmological investigation.

At the opposite extreme, Bernardo Kastrup (2013), proposes analytical idealism as an alternative, the notion that reality is essentially mental and inseparable from mind:

The scientific method allows us to study and model the observable patterns and regularities of nature … But our ability to model the patterns and regularities of reality tells us little about the underlying nature of things.

Mind is the medium of everything that you have ever known, seen, or felt; everything that has ever meant anything to you. Whatever has never fallen within the embrace of your mind, might as well have never existed as far as you are concerned. Your entire life and universe – your parents and the people you love, your first day at school, your first kiss, every time you were sick, the obnoxious boss at work, your dreams and aspirations, your successes, your disappointments, your worldview, etc. – are and have always been phenomena of your mind, existing within its boundaries.

Kastrup (2016, Kastrup & Kelley 2018), has taken the position that psychedelics are precisely what the term indicates – mind manifesting, and sought to contend that psychedelics manifest the idealist principle and that the commentary on the emerging psychedelic research, even by the papers' authors is biased to justify a materialist interpretation of the results. Kastrup cites the research of Carhart-Harris and others showing reductions in activity to be evidence for the basis of "mind-expansion" not being physical in origin, particularly when accompanied by mystical peak experiences and that accompanying research such as the homological scaffolds indicating are of marginal value added to ensure a physicalist interpretation of psychedelic brain states, when the reality of reduced activity indicates they are mind states per se. David Nutt (2023) argues that we don't need to adopt an untestable metaphysical worldview to explain the subjective richness of psychedelic experiences.

The position of Symbiotic Existential Cosmology agrees that conscious experience is primary, but acknowledges that psychedelics are chemical neurotransmitter analogues means that the brain is critically involved in the psychedelic state and that the universe is necessary for the psychedelic state to occur and for our biological survival as well, and that a reduction in default mode activity is consistent with peak experiences, and increasing decoherence of activity correlates both with a reduction in coherent power and with increasing inter-connectivity between brain regions.

Symbiotic Existential Cosmology thus does not conform to the philosophical classification in Yaden et al. (2021) into 3 broad categories: materialist, dualistic, and monistic. Symbiotic Existential Cosmology is a form of interactive complementary aspect monism with is implicitly panpsychic so it is not materialist, but neither is it simple dualism or monism. It is a description based on complementarity, extending the wave-particle complementarity of quantum physics to a cosmological subject-object complementarity in which the two complements cannot be separated in a dualism, just as wave and particle aspects are alternate manifestations of a single quantum identity which cannot be separated, yet it is not monistic because it is a complementarity, not simply a monistic theory of a cosmic mind alone.

Yaden et al. (2021) attempt to justify their conclusion by citing four authors, (Blackmore, 2013; Letheby, 2015; Bayne and Carter, 2018; Johnson, 2020). A viewing of Susan Blackmore's 2020 Tucson talk however makes clear that she considers the debate whether psychedelics reveal new discoveries or merely cause distortions of the psyche will only be revealed by the new wave of psychedelic research which I support. Bayne and Carter do not treat the hard problem as such, but critique the idea of layers of consciousness and the simplistic notion that psychedelics per se invoke a "higher" form of consciousness, or even that what psychedelics do reveal can be classified in terms of one-dimensional layers, with which this article again agrees. In fact the notion of the nierika advanced in this article is more like a cyclonic vortex having a multitude of divergent experiential features, some illusory and some informative, with the centre of the cyclone providing a portal to deeper forms of experience which may have abstract or cosmological value. This is not a linear indexed description and the subjective process of entering such states requires going "deeper into the abyss" of unconstrained consciousness rather than any simplistic view of "higher" conscious states.

Link Swanson (2018) provides a comprehensive review of theories of the psychedelic state, from the first discovery of mescalin, through the psychotomimetic era of researchers experiencing its effects, but using their experiences to treat

the experience as a form of reduced control shared by psychopathic states, to filter theories of Huxley and others and then on to more recent theories as outlined above, as well as ones we shall explore in the brain consciousness section such as integrated information theory and Friston's free energy principle:
He notes that Friston's theory can also be interpreted in terms of psychedelics:

In one model of global brain function based on the free-energy principle (Friston, 2010), activity in deep-layer projection neurons encodes top-down inferences about the world. Speculatively, if deep-layer pyramidal cells were to become hyperexcitable during the psychedelic state, information processing would be biased in the direction of inference—such that implicit models of the world become spontaneously manifest—intruding into consciousness without prior invitation from sensory data. This could explain many of the subjective effects of psychedelics (Muthukumaraswamy et al., 2013).

Summing up he sees common threads in these perspectives, in a view that's sees psychedelic research as an "acid test" of grand unified theories of brain function:
The four key features identified in filtration and psychoanalytic accounts from the late 19th and early 20th century continue to operate in 21st-century cognitive neuroscience: (1) psychedelic drugs produce their characteristic diversity of effects because they perturb adaptive mechanisms which normally constrain perception, emotion, cognition, and self-reference, (2) these adaptive mechanisms can develop pathologies rooted in either too much or too little constraint (3) psychedelic effects appear to share elements with psychotic symptoms because both involve weakened constraints (4) psychedelic drugs are therapeutically useful precisely because they offer a way to temporarily inhibit these adaptive constraints. … Psychedelic drugs offer a unique way to iteratively develop and test such big-picture explanatory frameworks: these molecules can be used to probe the links between neurochemistry and neural computation across multiple layers of neuroanatomy and phenomenology. Meeting the challenge of predicting and explaining psychedelic drug effects is the ultimate acid test for any unified theory of brain function.

Letheby invokes three descriptions of psychedelic experience: (1) **Yes** – by inducing mystical states of consciousness, psychedelics afford direct knowledge of supernatural, transcendent dimensions of reality (the entheogenic resistive discourse). (2) **No** – since materialism or physicalism is true, there are no transcendent realities, and psychedelics just cause compelling hallucinations or delusions (the dominant hallucinogenic and psychotomimetic discourse). (3) **Neither** – a third view that psychedelics can afford genuine epistemic benefits, even if materialism is true and there is no transcendent reality. Rather than helping us learn new factual information, psychedelics then allow us to understand or appreciate already-known (or otherwise knowable) facts in deep, vivid, affectively and motivationally significant ways. This is again taking a position with implicit dependence on a materialistic viewpoint, while conceding psychedelics may reveal epistemic benefits, so it is confining its own conclusion by its founding assumption of materialism. The symbiotic cosmology is again neither simply an old view, nor is it materialistic. It has resemblances to Upanishadic thought dating back to 700 BC, but it is not a monist theory and is based extensively on detailed investigation of quantum reality, chaotic systems, evolutionary origins of membrane excitability and neuroscience in a novel cosmological description induced by a mushroom experience.

Matt Johnson (2020) , who is both a cited reference and also a co-author of Yaden et al., takes issue with the very concept of consciousness itself as "sloppy", noting that "*one might question whether the different concepts associated with consciousness should even be identified under a singular construct*." This has some validity, for example the subjectivity of consciousness is distinct from its features of coherent attentiveness and from the distinct nature of specific qualia and with notions of self-consciousness and the cognitive mind of thoughts and verbal processes. But consciousness is all these things in a coherent concept, integral to our existential condition, so "sloppy" is derogatory and unscientific. Consciousness is our most enduring and all-encompassing arena of experience. It is not sloppy! It is fundamental and essential!

In dealing with the hard problem, he says "*Explaining the existence of experience itself, which is the "hard problem" of consciousness, is at present something that appears outside of the realm of empirical science. Some philosophers and scientists have disputed the existence of this hard problem, but I do not think the problem should be dismissed*".
But empiric [7] means "experience", as does experiment, and there is abundant evidence coming also out of the Johns Hopkins team attesting to experiments confirming experiential observations of quantum change involving "ultimate reality" (Griffiths et al. 2018, 2019). These represent statistical evidence, just as the moksha epiphany does. The claims about consciousness and the experiments on mystical states are thus presenting mutually-contradictory academic reasoning. A critique is made of psychedelic states as having no evidential value based on a preamble assessment that the hard problem is empirically unscientific. This contradicts the definition of empirical, whose root lies in subjective accounts, by invalidating veridical reporting. The legal system depends centrally on veridical evidence. It is integral to interrogating the subjective condition sine qua non. So the materialist assumption is empirically counterproductive.

[7] ***empirical*** based on, concerned with, or verifiable by observation or experience rather than theory or pure logic.
Etym. ***empiric*** via Latin from Greek empeirikos, from empeiria 'experience', from empeiros 'skilled' (based on peira 'trial, experiment').
experimental late 15th century 'having personal experience', also 'experienced, observed': from Latin experimentum practical experience

In summing up Johnson states: "*I suggest that psychedelic science has, to date, not provided substantial advancement in our understanding of any of these concepts [easy or hard] purported to relate to consciousness*". This is a very pessimistic and confounding view for research in psychedelic science that is showing real promise of cultural benefit. Given a priori assumption of the hard problem's quasi-unscientific status, it is hard to see how substantial advancement could ever occur on either the role of psychedelics as an informant of the nature of reality, or the status of the hard problem itself. This again underlines the fallacy of academic reasoning that is subservient to the materialistic hypothesis to the extent that no other type of cosmology can be entertained and no empirical result can be gained except by objective means. But biogenic/panpsychic cosmology is biologically precise and seamlessly consistent with multiple steps of the evolutionary pathway so it is a meticulous natural description, consistent with quantum and dynamical physics and with neuroscience. Therefore such reasoning is integral to the scientific discourse.

This critique of empiricism applies critically to symbiotic cosmology because the principal evidence for it has to come veridically from first person reports. We can't directly see the consciousness of others, so it is impossible to see the consciousness in simpler life forms or physical processes directly. One can rightly conclude that this is the only class of cosmology in which conscious volitional intent is real, so by the veridical test of validity Occam's razor cuts for panpsychism as a necessity. This is because volitional will implies the conscious mind affect the physical brain and hence the physics of the universe. Therefore mind is a complementary aspect of the physical universe. To a materialist this appears to be adding something that is unnecessary but from the veridical perspective it is essential, because materialist cosmology does not admit conscious volitional will. The inescapable solution is quantum panpsychism.

The problem for mechanists is that intervening states of consciousness are largely inaccessible. But organismic consciousness is evident in humans and mammals generally and is accessible also in other forms in deeply unbounded mental states of meditation or psychedelic transcendence, in which organismic consciousness is asymptotically convergent to an unbounded abstract state identifiable to the subject with the mind at large. Thus the two accessible avenues for scientific discovery are the organismic state and the mind at large. This is why the role of psychedelics becomes sine qua non optimal. If you take them out of the equation, you really have only sparse states of meditative vigil and the dreaming state. Thus to discount the importance of psychedelics is futile and counterproductive.

Yaden et al. nevertheless do concede the potentiality of psychedelics to address the hard problem: "*The scientific study of psychedelics and consciousness, in all of its meanings, is still nascent. While we cannot, at present, see any clear scientific traction resulting from the intersection of psychedelics and the hard problem of consciousness, we are open to the possibility of being proven wrong.*" This article now of full book length monograph articulates a strategic response.

Moreover several researchers state that the subjective experience of psychedelics, not just their physiological or neurochemical attributes are potentially pivotal in their beneficial effects. Yaden and Griffiths (2020) conclude that:

Based on the results from experimental studies of moderate to high dose psychedelics we believe that the case for subjective effects playing a major role in enduring beneficial effects is compelling. Across a number of studies, when the intensity of the subjective psychedelic effect is controlled, certain subjective effects predict desirable outcomes. Underlying neurobiological mechanisms are likely necessary but not sufficient to confer full and enduring beneficial effects.

Johnson (2022) in reviewing Chris Letheby's "Philosophy of Psychedelics" (2021) concurs with both this viewpoint and the central role of a "natrualism" that leads to a more supernatural worldview that is not just a comforting delusion:

Letheby argues based on the evidence that subjective experience does play a causal role in long-term benefit. This is supported by studies showing that the mystical-type nature of the experience can predict how therapeutic or otherwise positive the sessions will be in the long term, providing information in some cases that is above and beyond the predictive value of the dose itself or the participants' ratings of drug intensity. Letheby posits that the subjective experience causes lasting therapeutic benefit independent of whether the session involved or left patients with supernatural ideation. He argues, successfully in my opinion, that the core mechanism of psychedelic therapy benefit is not the provision of a comforting delusion, for example, one in which people shift to a more supernatural worldview. He argues instead that "naturalism" is the lens through which the key mechanisms of psychedelic therapy can be understood by combining empirical evidence across multiple disciplines through scientific reasoning. … Letheby believes that changes in self-representation are the missing link connecting mystical experiences to therapeutic outcomes.

Safron & Johnson (2022) examining both present trends and future possibilities, note the relationship between psychedelics and natural dreaming states:

While we agree that some psychedelic experiences may be understood as a transient form of psychosis, we would add that the same thing can be said about dreaming. … Intriguingly, while the mechanisms of action for both classic and non-classic psychedelics vary, there appear to be multiple pathways for inducing states in involving greater tendencies for imagining novel scenarios under

states of more vivid and intense conscious experience, potentially contributing to the phenomenology of a "waking dream." While a detailed exploration is beyond the scope of the present discussion, partially overlapping effects from classic psychedelics, anticholinergic drugs (e.g. tropanes), kappa- receptor agonists (e.g. Salvia divinorum), and NMDA-receptor antagonists (e.g. dextromethorphan, or ketamine) suggest that anything that disrupts global integration processes while maintaining (potentially elevated) consciousness has the potential to induce profoundly altered states, and potentially altered traits.

They conclude the following about the future of psychedelics as a discovery process in the context of formative quantum change experiences:

While we must continue to seek the most powerful and encompassing models we can find, we must also avoid the temptation of assuming that a single account will be adequate for explaining the diverse range of effects associated with different psychedelics under different sets and settings. Some may suggest that the mystic nature of psychedelic experiences reveal the truth of a perennial religion, and perhaps even the veracity of metaphysical principles that some would consider to be supernatural (Timmermann et al., 2021). Others might conclude that egoless experiences reveal that selves were illusions all along (Millière et al., 2018; Milliere and Metzinger, 2020), so pointing to the veracity of some schools of Buddhist thought.

In particular Timmermann et al. (2021) cite a move away from physical materialism:

Results revealed signifcant shifts away from 'physicalist' or 'materialist' views, and towards panpsychism and fatalism, post use. With the exception of fatalism, these changes endured for at least 6 months, and were positively correlated with the extent of past psychedelic-use and improved mental-health outcomes. Path modelling suggested that the belief-shifts were moderated by impressionability at baseline and mediated by perceived emotional synchrony with others during the psychedelic experience.

On the other hand, Millière et al. (2018) cite a diversity of selfless states in both psychedelic and meditative experiences:

We suggest that there are important phenomenological differences even between conscious states described as experiences of self-loss. As a result, we propose that self-consciousness may be best construed as a multidimensional construct, and that "self-loss," far from being an unequivocal phenomenon, can take several forms. Indeed, various aspects of self-consciousness, including narrative aspects linked to autobiographical memory, self-related thoughts and mental time travel, and embodied aspects rooted in multisensory processes, may be differently affected by psychedelics and meditation practices.

Milliere and Metzinger, (2020) go further and address the foundational question of the link between subjective consciousness and self-awareness in states of ego-dissolution:

Let us call the general claim that some basic form of self-consciousness or sense of self is ubiquitous to all conscious experiences, ***the Ubiquity Thesis****. For example, the subjective effects of certain psychoactive drugs, and particularly those of classic psychedelic drugs such as LSD, psilocybin, or 5-MeO-DMT, present a special interest for the assessment of the Ubiquity Claim. Indeed, these drugs are known to have dramatic effects on self-consciousness, and some reports even suggest that they might temporarily suppress any form of self-consciousness – a phenomenon known as 'drug-induced ego dissolution' in the scientific literature (Nour & Carhart-Harris, 2017).*

In his article "Being for no-one: psychedelic experience and minimal subjectivity", Chris Letheby (2020) asks whether reports of drug-induced ego dissolution provide us with solid evidence against so-called "subjectivity theories of consciousness", according to which phenomenal consciousness constitutively involves a minimal form of self-awareness or "subjectivity". Letheby argues that the alternative notion that putatively selfless states of consciousness associated with depersonalization might not in fact be phenomenally conscious at all, does not work well for reports of selfless states of consciousness induced by classic psychedelic drugs, particularly potent and fast-acting psychedelics such as DMT and 5-MeO-DMT, because there is little doubt that the relevant states are phenomenally conscious.

Miguel Sebastián (2020) argues that given a proper understanding of a minimal form of self-awareness that he labels "Perspectival First-Person Awareness" (or PFP-awareness), it becomes apparent that even putatively selfless states of consciousness do not entirely lack self-awareness. PFP-awareness is anchored in a non-conceptual, identification-free self-attribution that defines the ultimate origin of the first-person perspective of conscious experience. … He concentrates on the phenomenology of states induced by psychedelic drugs, meditation and dreams, as they have been claimed to present the biggest threat to the Ubiquity Thesis. First, he argues that although there are good reasons to think that some forms of self-awareness that typically accompany our ordinary experience can be compromised in altered states of consciousness, this does not mean PFP-awareness is absent in these states.

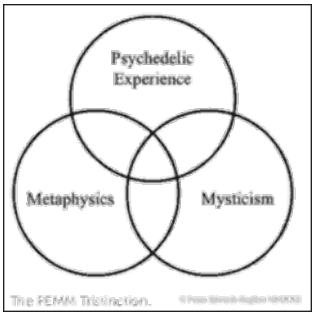


Fig 40b: The PEMM Tristinction (Sjöstedt-Hughes 2023).

Sjöstedt-Hughes (2023) sees psychedelic states as trisecting with both metaphysics and mystical states, noting that psychedelic-induced metaphysical experiences should be integrated and evaluated with

recourse to metaphysics in which one sees the potential bridge between reason-based philosophy and practical therapy — with psychedelic-assisted psychotherapy there is the potential and mutually beneficial fusion of philosophy with practical science. Thus we see overall that paradoxically, the psychedelic experience, although being regarded as a highly exotic mental state, also has foundational insights about the universality of both subjective consciousness and self-consciousness.

The thesis in this monograph takes a form of a scientific investigation that sets up a verifiable framework to present a cosmology, consisting of interlocking biogenic, panpsychic and symbiotic aspects, scientifically accounting for the flowering of conscious life in the universe, that has components of discourse (2) that they are therapeutic, (5) that they reveal the self, (6) that they induce moksha and (7) in that this is not a theistic description of reality, but one in which consciousness as we know it is widespread in all eucaryote organisms, and in the mind at large through them, so that the animistic actually has a valid cosmological basis.

The Indigenous Psychedelic Dimension

Kerowen Cornelius (2023) reviewing the ethical implications of the scientific explosion of interest in psychedelics as therapeutic tools, for indigenous communities, who have a long history of sacred and medicinal use, cites Yulia Celidwen's (2023) efforts to form a consortium to address these concerns:

Over thousands of years, Indigenous communities have cultivated relationships with and accumulated knowledge on psychedelics such as psilocybin mushrooms, the Amazonian botanical brew ayahuasca, and the West African shrub iboga. More recently, psychedelics have exploded onto the stage of Western science. Clinical trials of these substances in the past 15 years have produced remarkable results in the treatment of depression, addiction, post-traumatic stress disorder, and end-of-life anxiety. Media buzz has generated a rush to legalize their therapeutic use, catapulting the global psychedelic drugs market from $3.8 billion in 2020 to an estimated $11.82 billion by 2029. But both Native and non-Native critics say the industry is ignoring the emotional, cultural, and ecological harms it is causing the Indigenous peoples who originated psychedelic medicine.

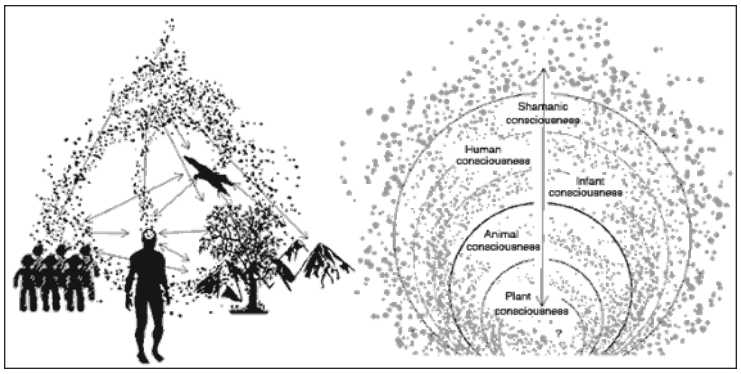


Fig 40c: Indigenous models of consciousness exemplified by animistic individual consciousness as the embodiment of global consciousness and its nested types (Lorencova & Trnka 2023).

Many Indigenous Nations are concerned they are being excluded from psychedelic spaces that extract their knowledge, threaten what they see as their intellectual property, and detach their medicines from their spiritual contexts, the paper finds. In addition, international demand is driving people to unsustainably harvest iboga, the plants used to make ayahuasca, and the hallucinogenic cactus peyote. Meanwhile, burgeoning retreat centers that offer psychedelic therapy often charge thousands of dollars for experiences that culturally appropriate Indigenous traditions yet share few benefits with these often impoverished communities. …The resurgence of Western psychedelic research and practice has led to increasing concerns from many Indigenous Nations regarding cultural appropriation, lack of recognition of the sacred cultural positioning of these medicines, exclusionary practices in research and praxis, and patenting of traditional medicines. Indigenous voices and leadership have been notably absent from the Western psychedelic field currently widely represented by Westerners. An Indigenous-led globally represented group of practitioners, activists, scholars, lawyers, and human rights defenders came together with the purpose of formulating a set of ethical guidelines concerning traditional Indigenous medicines current use in Western psychedelic research and practice. A global Indigenous consensus process of knowledge-gathering was engaged which identified eight interconnected ethical principles, including: ***Reverence, Respect, Responsibility, Relevance, Regulation, Reparation, Restoration, and Reconciliation****. A summary of the work is presented here with suggested ethical actions for moving forward within Western psychedelic research and practice spaces.*

The first and foremost of these is reverence for nature and the diversity of life.

Reverence for Mother Nature *Traditional Indigenous medicine is an ethical, ecosystem-protective, and holistic system of medicine that interconnects humans and the environment. A sense of reverence for the planet guides all relationships, as well as a commitment to preserve all life. Traditional Indigenous medicine from a systems and relational perspective prompts insight for compassionate living and awareness of collective care to sustain the well-being of the medicines themselves as well as all future generations.*

Concrete problem *Western psychedelic research and practice has its roots within traditional Indigenous medicines systems yet have turned 'kincentric' approaches (treating all relationships, including medicines, as kin) to anthropocentric approaches (human-centric). This anthropocentric approach fails to adequately reference or acknowledge Indigenous paradigms in Western procedures, thus expropriating Indigenous knowledges while separating the medicines from the context of their original environments.*

Reverence-governed actions *The explicit acknowledgement of Indigenous Peoples and their traditional medicines and practice as the root of Western psychedelic research and practice; Western psychedelic research and practice references Indigenous concepts of reverence as guided by local Indigenous scholars and communities; the Western psychedelic research and practice community takes action to support*

Indigenous Nations protection of the at-risk land and natural environments where these traditional Indigenous medicines originate; support Indigenous Peoples in their fulfilment of the right to life and of the right to live in peace on ancestral lands.

Four later sections in this work – Psychedelic Agents in Indigenous American Cultures, Shipibo: Split Creations and World Trees, Meso-American Animism and the Huichol and Redemption of Soma and Sangre in the Sap and the Dew, deal in detail with indigenous use as a pivotal heritage of psychedelic knowledge.

Very significantly there is no evidence for psychedelics causing an increase in incidence of psychosis, or psychological distress and classical psychedlic use is associated with reduction in suicide rates (Hendricks et al 2015, Johansen & Krebs 2015). Some people do occasionally experience hallucinogen persisting perception disorder (HPPD), involving incessant distortions in the visual field, shimmering lights and coloured dots. The second time I took a large dose of LSD in 1966 this happened to me for weeks, combined with an unjustified fear that I had split my chromosomes from the false evidence at the time. Every time I looked at a trippy of Bob Dylan's curly hair it would set me off into a mini-flashback. However afer a break of several years, I took acid many times more with no such symptoms.

There are three neurotransmitter models of psychosis. The first involves the dopamine D2 receptor, exemplified by the paranoid psychosis accompanying methamphetamine overdose, and antagonized by the typical antipsychotics The second, that of atypical anti-psychotics involves 5HT2a antagonists. Thirdly we have those involving glutamate mGluR2 agonists. Thus we are discovering that several of the pieces of the psychedelic puzzle appear to be coming together into a common explanation of psychosis as well (Snyder, González, Maeso et al. 2008, Moreno et al 2011b). However, the notion that psychedelics are psychotomimetic, or form a model for schizophrenia, is a dangerous and confused generalization, contradicted by the capacity of psychedelics to induce long-term positive life-changing experiences in controlled studies (Griffiths et al, Barbosa et al). Franz Vollenweider and co-workers have also found a decrease in amygdala activity associated with correlated with enhanced positive mood in healthy volunteers (Kraehenmann et al. 2015) and similar enhancements of mood with LSD (Schmid et al. 2015).

Furthermore, we need to understand that changes in serotonin receptors have slowly varying long-term effects not consistent with the vast dynamic changes psychedelics impose on consciousness. In fact the binding of an agonist such as psilocybin has a half-life of receptor activation of some hours, so we need to look deeper into the more rapidly changing aspects of brain dynamics, such as the changes in pyramidal glutamate-based excitation, to gain an insight into how these changes in consciousness occur.

We thus turn to another intriguing possible connection between serotonin receptor psychedelics and the equally bizarre subjective affects of NMDA antagonist dissociatives such as ketamine and PCP, which may have a deep commonality of action through their related actions on glutamate activation through similar reciprocally opposite interactions of NMDA blocking agents with mGluR2. This suggests these two very different classes of agent may give rise to common deep similarities of visionary effect, as noted in the subjective case study at the end of this paper. Support for this link has also been found in investigations of changes in glutamate metabolism induced by psilocybin (Mason et. al 2020). Negative ego dissolution experiences correlated with glutamate changes in the medial prefrontal cortex and positive ego dissolution experiences seemed to be linked to changes in hippocampal glutamate.

Fig 12 illustrates the putative mechanism by which the action of the psychedelics and dissociatives might each have linked dynamics through a common opposing action with mGluR2. Features of this mechanism remain to be replicated although the work by Gonzalez-Maeso's group has been well documented. The actual sites of differential activations of all three receptors 5HT2a, mGluR2 and NMDA, whether in the prefrontal or other cortices, thalamic or other sub-cortical centres, whether they are pre- or post-synaptic, and whether they are merely cross-talk or arise from hetero-duplexes all remain uncertain, although the expression of *egr*-2, fig 10, suggests the 5HT2a psychedelic action is cortical. Nevertheless this receptor relationship does open an intriguing basis for a common action of both visionary and anti-psychotic changes to the central nervous system. Moreover, on the basis that mGluR2 agonism reduces overall glutamate excitability through inhibiting the c-AMP chain, this provides a possible central mechanism for entheogens catalysing rapidly changing phenomena in conscious experience through the smoothing effects of mGLUR2 glutamate inhibition being reduced via serotonin agonism linked to suppression of mGluR2. Findings also suggest that the glutamatergic surge mediated by 5HT2a receptors in cortical neurons leads to increased expression of AMPA receptors causing the release of brain derived neurotrophic factor (BDNF), suggesting

that psychedelics contribute to enhanced neural plasticity (http://neurowiki2012.wikispaces.com/Entheogens+and+the+Brain).

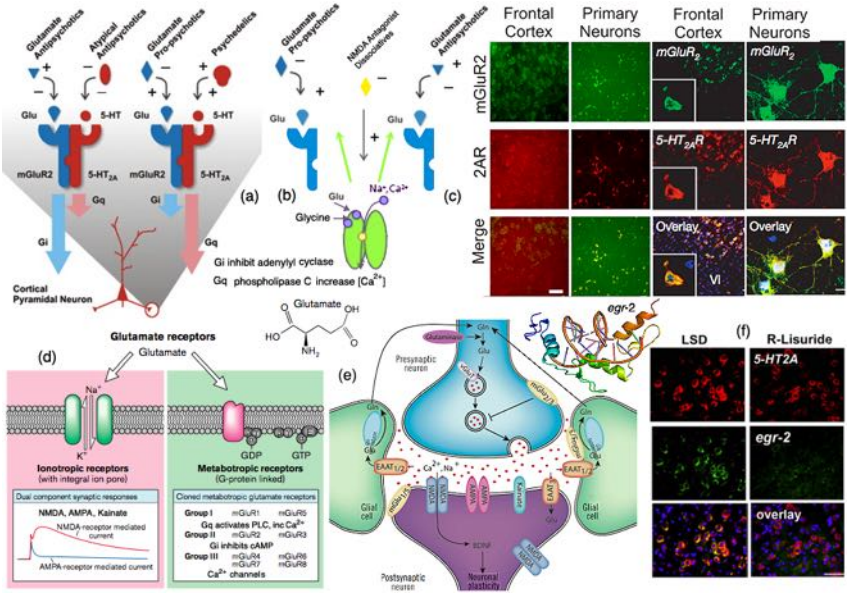


Fig 12: (a) Hypothetical push-pull heteroduplex formation between mGluR2 and 5HT2a and its opposing effects on psychedelics and anti-psychotics (Fribourg et al). This heteroduplex action has not been fully replicated in a related study although cross-talk has been established (Delille et al). Upper row + agonist, - antagonist, lower row + psychedelic/pro-psychotic. - anti-psychotic. (b) Parallel opposing mechanism between NMDA dissociative antagonists and mGluR2 (Dong et al, Moghaddam & Adams), which may arise from subcortical NMDA inhibition of prefrontal pyramidal glutamate release (Lorain et al, González-Maeso & Sealfon, Gonzalez-Maeso et al 2007, 2008) but since group II mGluR agonists have also been found to enhance NMDA currents (Tyszkiewicz et al) the two may act on the same synaptic junctions. This process appears to work through PKC phosphorylating NMDA directly through a phospholipase C and inosine-triphosphate pathway. Conversely studies using in vivo microdialysis have confirmed that administration of NMDA channel blockers causes increased glutamate release in frontal cortex (Delille et al). AMPA glutamate antagonists are also able to antagonize hyperactivity induced by PCP NMDA blockade in rats. NMDA antagonists have also been found to interact with 5HT2a sites extending the relationship (Martin et al, Millan et al). (c) Staining correspondence between 5HT2a and mGluR2 shows corresponding cellular locations apparently to the dendritic and synaptic level (Fribourg et al, Gonzalez-Maeso et al 2008). (d) Glutamate receptor types (ex Forsythe & Barnes-Davies). (e) Involvement of glutamate receptors at the synaptic junction involves a variety of mGlu G-protein linked types, pre- and post-synaptically and on glial astrocytes (Loane et al), as well as NMDA and AMPA and Kainate ionotropic channels (Kelmendi et al). Although mGluR2 occurs presynaptically to modulate glutamate release it also does occur post-synaptically (Petralia et al, Renger et al, Tyszkiewicz et al). (f) Corresponding images for LSD and R-lisuride showing differing egr-2 expression (Gonzalez-Maeso et al 2007). Egr-2, also called Krox-20, is associated with early development of the CNS, and is widely expressed in the CNS, in neuronal conduction and repair (Mengozzi et al), neuronal plasticity and long-term potentiation in memory. Paradoxically although psychedelics result in egr-2 expression, NMDA blockers, inhibit egr-2 expression in the hippocapus (Williams et al), however psychedelics do not appear to express egr-2 in the hippocampus either (fig 10). Changes in its expression are also associated with autism (Swanberg et al).

5: Doors of Dissociation: Ketamine and the NMDA Receptor Antagonists

Dissociative hallucinogens, such as ketamine (Jansen), are antagonist blocking agents of the NMDA or n-methyl-d-aspartate ionotropic receptor, which promotes activation, learning and memory processes. Dissociatives are a class of hallucinogen anesthetics, which reduce or prevent signals from various parts of the brain reaching the conscious mind. The NMDA receptor's connection with the memory formation process and the fact that they act in the hippocampal formation and prefrontal cortex, explain ketamine's profound effects on memory and thought. As noted in fig 12, cortical effects of dissociatives may result from subcortical NMDA blockage. These effects inhibit the filtering function of the brain and may mirror the sensory overload associated with schizophrenia and may include experiences of flying and union with god. Ketamine is also a weak μ-opioid agonist (Sarton et al). The history of ketamine is noted in Stewart's (2018) review.

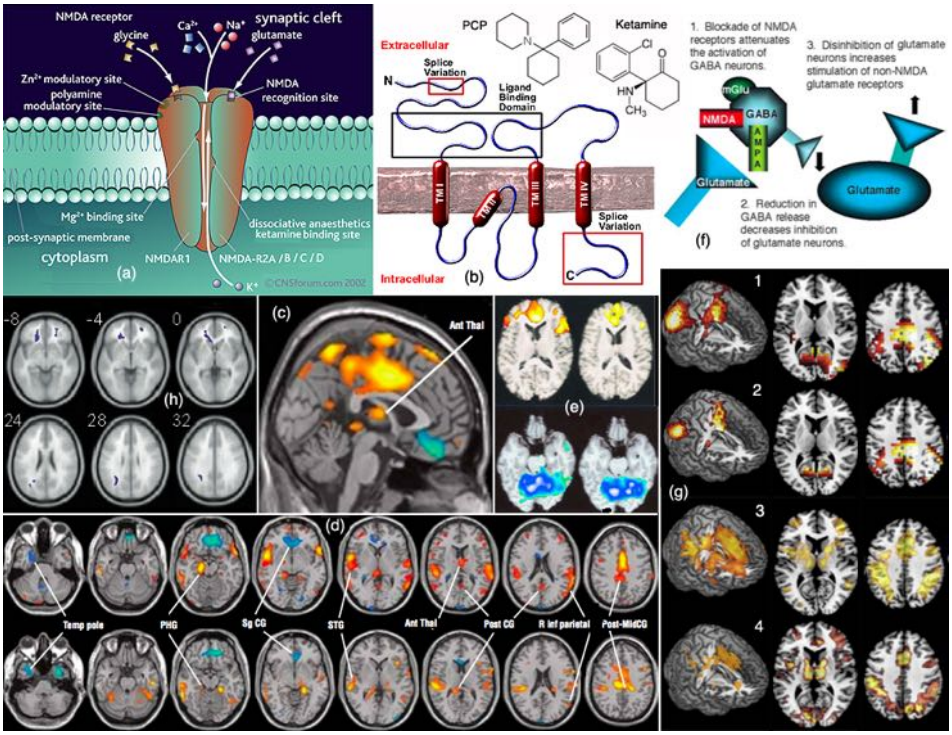


Fig 13: (a) Structure of the NMDA ionopore receptor, (b) protein structure with splice variations. The receptor is activated by glycine together with glutamate, with the ketamine-blocking site mid channel (CNSforum.com). (c) Effects of ketamine using fMRI BOLD. Warm colours increases in activity, cool decreases (Deakin et al). Ketamine induced a decrease in ventromedial frontal cortex, including orbitofrontal cortex and subgenual cingulate, consistent with its dissociative effects, and increased activity in mid-posterior cingulate, thalamus, and temporal cortical regions. (d) Inhibition of ketamine activity by lamotrigine, a sodium channel blocker that decreases glutamate release (Deakin et al). (e) PET increases (frontal and anterior cingulate) and decreases (cerebellum) on administration of ketamine (Holcomb et al). (f) Proposed mechanism to explain pyramidal cell excitation through NMDA inhibition of GABA neurons (Krystal et al 2003). (g) sLORETA (EEG) attenuation of P300 response to oddball visual task 1 placebo 2 ketamine, fMRI BOLD reduction 3 placebo, 4 ketamine (Musso et al). (h) White matter decrements in long-term ketamine users (Liao et al). Timothy Leary observed that ketamine and Salvinorin A were the most profound psychedelic drugs in terms of the perceived depths of the experience (Leary & Sirius).

At sub-anesthetic doses, they alter many of the same cognitive and perceptual processes affected by other hallucinogenic drugs such as mescaline, LSD, and psilocybin; hence they are also considered hallucinogenic, and psychedelic with additional dissociative effects, including: depersonalization, the feeling of being unreal, disconnected from one's self, or unable to control one's actions; and derealization, the feeling that the outside world is unreal or that one is dreaming. At sufficiently high doses, users may experience what is coined the "K-hole", a state of deep dissociation whose effects are thought to mimic the phenomenology of schizophrenia (Giannini, Deakin et al) and near death experiences (Jansen).

Although the direct action of the dissociatives is through a completely different pathway from psychedelics, it may have a common basis of action, through interactions with the mGluR2 G-linked glutamate receptor, which from the previous section, is linked in turn with the 5HT2a serotonin receptor of psychedelics, as already detailed in fig 12. Potentiation of the glutamate receptor mGluR2 by biphenyl indanone-A (BINA) inhibits the effects of NMDA dissociatives in animal studies - phencyclidine (PCP)-induced hyperlocomotion and prepulse inhibition deficits in mice (Hackler et al). The mGluR2 agonist LY379268 likewise ameliorates the effects of NMDA antagonist MK-801, (ibid, Dong et al), suggesting dissociatives such as PCP and ketamine, may have an indirectly common pathway of psychedelic action. Research has also shown that mGluR2 agonists reversibly increase NMDA receptor currents and antagonists reduce them, providing a similar link between NMDA and mGluR2 (Tyszkiewicz et al, Kammermeier).

In a ground-breaking study (Vesuna et al. 2020), researchers have found that the dissociative state is sourced in a 1-3 Hx rhythm established in the retrosplenial cortex with rhythmic coupling of the retrosplenial cortex with anatomically connected components of thalamus circuitry, but uncoupling from most other brain regions. The electroencephalographic and PET and fMRI scan results for ketamine are otherwise somewhat contradictory just as they were for psilocybin (Vollenweider et al 1997d, Deakin et al, Holcomb et al). Some PET studies show prefrontal activation on ketamine while others show consistent deactivation. One EEG study has seen an increase in gamma activity, suggesting increased processing (Maksimow et al). Mismatch negativity, a preattentive auditory event-related potential generated by a stimulus that deviates e.g. in pitch, intensity, or duration, from a repeated series is an NMDA related function, which predicts the strength of ketamine but not psilocybin effects in a given individual (Umbricht et al).

The effects of ketamine and NMDA blocking antagonists on glutamate driven excitation may be dosage dependent, with smaller sub-anaesthetic doses causing excitation while larger doses cause a reduction. A suggested mechanism for the excitation at lower doses is NMDA antagonism suppressing GABA inhibition of pyramidal excitation. This phenomemon in rodent studies led to concern at the description of Olney's 'holes in the brain' lesions in rodents (Olney et al 1989). Olney and Farber (1995) suggested that NMDA antagonists block excitation of gamma-aminobutyric acid (GABA) interneurons, resulting in removal of GABA restraint of cholinergic, serotonergic, and glutamatergic afferents to posterior cingulate cortex. This, they suggested, caused a triple excitotoxic effect on posterior cingulate pyramidal cells, accounting for the focal neurodegeneration they had observed after phencyclidine administration. However Olney's lesions in rodents have not been replicated in primates, possibly because of species differences in neuroexcitation.

In addition to its anesthetic and hallucinogenic effects, Ketamine has been found to be a potent anti-depressant (Straton, Berman et al, Correll & Futter, Maeng & Zarate, Zarate et al). It has also been shown to provide antidepressant affect for a week after a single dose, acting in part by increasing synthesis of BDNF, a nerve growth factor that supports the health of brain cells, helps them grow and can promote the development of new neurons. (Autry, Szalavitz 2011b). Blockade of NMDAR-dependent bursting activity in the 'anti-reward center', the lateral habenula mediates the rapid antidepressant actions of ketamine in rodent models (Yang et al. 2018). It has been suggested that the glutamate activity resulting from ketamine may induce synaptogenic changes helping the depressed brain repair itself (Murphy). This action is potentiated by a single dose of GSK-3 inhibitors such as lithium chloride (Liu et al). The metabolite (2S,6S;2R,6R)-hydroxynorketamine has been found to be essential for its antidepressant effects, exerting behavioural, electroencephalographic, electrophysiological and cellular antidepressant-related actions in mice, independently of NMDA inhibition involving early and sustained activation of AMPA receptors, explaining why other NMDA receptor inhibitors do not share ketamine's anti-depressant effect (Zanos et al. 2016). As of 2019 the FDA has recommended approval of ketamine nasal spray for depression (Carey 2019, Reardon 2019). It has also been found to cultivate new nerve cell connections in mice (Moda-Sava et al. 2019).

That said, many recreational users of ketamine report signs of negative effects from long-term recreational use, including memory deficits (Morgan et al, Curran & Morgan, Morgan & Curran), sleep paralysis, semi-permanent visual changes, long term tolerance which may be associated with changes in the numbers of their NMDA receptors or the elicited protein profiles, and white matter decrements. Notable proponent John Lilly was for years in and out of hospital due to ketamine bouts and Marcia Moore died apparently having injected herself with ketamine, entering a hypothermic coma in a wintery forest (Jansen). My own experience of ketamine is included in the case study.

6: Salvinorin-A and κ-Opioid Dissociatives

The diterpenoid κ-opioid agonist Salvinorin A is the main active psychotropic molecule in Salvia divinorum, a Mexican plant which has a long history of use as an entheogen by indigenous Mazatec shamans. Salvinorin A is considered to be a dissociative, exhibiting atypical psychedelic effects, including sensations of motion, or being pulled or twisted by forces, visions of membranes, films and various two-dimensional surfaces, merging with or becoming objects, overlapping realities, such as the perception of being in several locations at once, uncontrollable laughter, past memories, such as revisiting places from childhood memory and strange memories that things have always been this way (Turner).

There are three classes of opioid receptor, μ, δ, and κ. While the former two cause dependence and manifest co-dependence, which may result from their enhancement of the mesolimbic dopamine system, κ-opioid receptor KOPr agonists produce an aversive effect. The κ-opioid receptor and its endogenous ligand dynorphin are enriched in the ventral tegmental area, involved in dopamine release and the nucleus accumbens and prefrontal cortex regulating mood and motivation. κ-opioid receptor activation in these regions decreases dopamine transmission, explaining the dysphoric reaction (Shippenberg). There is also evidence κ-opioid receptor agonists can alleviate the symptoms of opiate withdrawal. Opiates are agonists for the μ-opioid receptor and because κ has an opposing action to μ it appears to be able to redress the opioid receptor balance sufficiently to facilitate withdrawal (Pfeiffer et al).

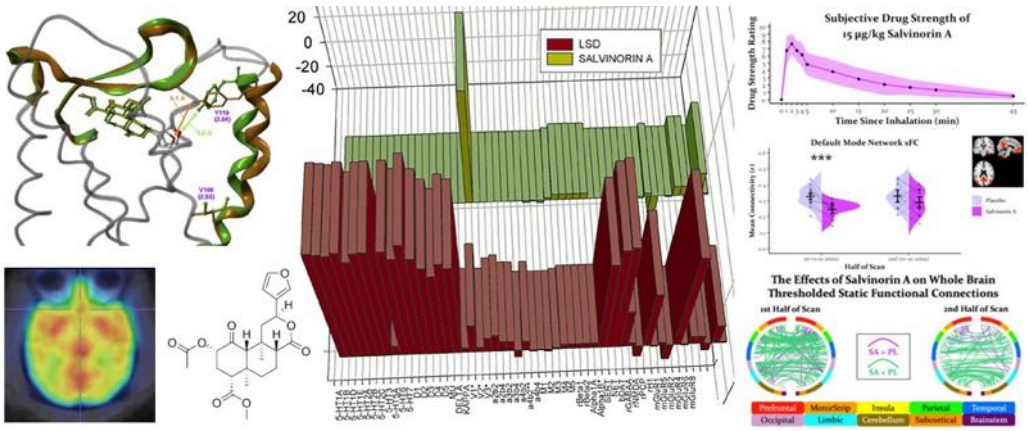


Fig 14: (Left) κ-opioid receptor with salvinorin-A attached (Vortherms et al) with below a baboon PET scan showing [^{11}C]-salvinorin A binding 3-7 mins (Hooker et al) and the salvinorin-A diterpinoid molecule. Onset of binding was extremely rapid and faded after 7 mins. (Right) Salvinorin-A and LSD receptor binding profiles compared showing kappa selectivity for salvinorin and broad spectrum affinity for LSD across 5HT and dopamine receptors with a notable negative interaction with mGluR2 and rNMDA (Roth et al). Right: Results of an fMRI study (Doss et al 2020).

This is the basis of the use of ibogaine in addiction treatment (Ross). Because of the ibogaine molecule's tryptamine core, it acts as an agonist for the 5-HT2a receptor set like other psychedelic tryptamines (such as DMT and psilocybin) and other serotonergic psychedelics like LSD and mescaline. However what makes ibogaine's pharmacodynamic properties and subjective experience unique from that of other psychedelic tryptamines and serotonergic psychedelics is that it also acts as a dissociative through antagonism of the NMDA receptor set (like ketamine) as well as acting as an agonist for the κ-opioid receptor (like salvinorin A). Ibogaine's agonism of the κ-opioid receptors is thought to be what is responsible for its anti-addictive properties, as salvinorin A exhibits a similar alleviation of withdrawal symptoms in individuals addicted to opiates and methamphetamine. However ibogaine also has an $\alpha 3\beta 4$ nicotinic antagonist effect, a mechanism of action shared with anti-smoking drugs like bupropion and mecamylamine, as well as methadone, which may also be responsible for its effects on addiction.

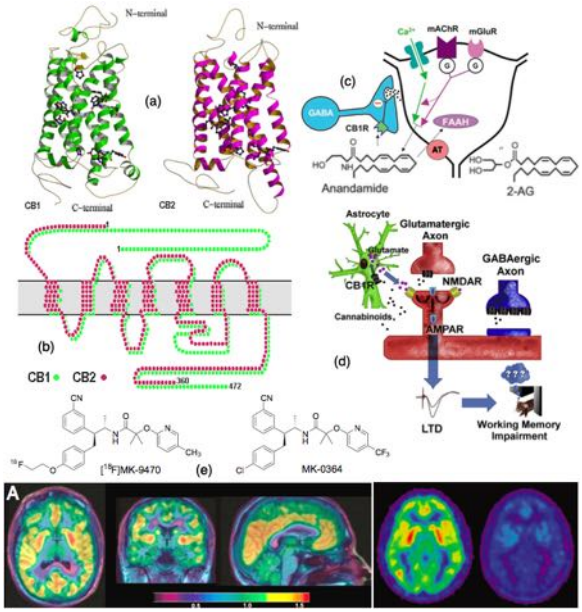
Both κ-opioid agonists and NMDA antagonists are classed as dissociatives and have subjective effects with remarkably significant parallels, suggesting there is also a commonality of action between these two as well. The research here is sparse, but there are some indications of a functional connection (Sershen et al, Trujillo) and the action of ibogaine on opiate addiction has been attributed to a combined effect of its NMDA antagonist and κ-opioid agonist properties (Glick et al).

Doss et al. (2020) used fMRI to measure how inhaled salvinorin-A (SA) alters brain functional connectivity (sFC) in humans. Similar to classic psychedelics and dissociative anaesthetics, SA tended to decrease sFC within resting-state networks, especially within the DMN, and increase sFC between these networks. Whereas the brain-wide decreases in dFC under SA were less consistent with the increased variance and entropy produced by other hallucinogens, one study found LSD to decrease fMRI signal variance across the brain, and another study found ketamine to reduce dFC across the brain. Furthermore, SA was found to increase eFC across the brain, though such changes were not found to be statistically significant. Finally, connectome-based classification highlighted the importance of DMN interactions to the effects of SA. Overall, these findings are strikingly similar to those of classic psychedelics and dissociative anaesthetics.

7: Cannabinoids

Although they are not psychedelics, cannabinoids have to be classed as entheogens, because cannabis has been used for centuries, as a spiritually transformative agent, from the Shiva sadhus of India through the San Bushmen of the Kalahari to the Rastafarians.

Fig 15: (a) Structures of the central nervous cannabinoid CB1 and immune system CB2 receptors (Montero et al) (b) 2-D representation in the membrane (Wikipedia) (c) Action of natural cannabinoids on GABA neurons coupled to pyramidal neurons (Alger) (d) Interference with working memory is believed to result from secondary action of glial astrocytes on hippocampal pyramidal, cells resulting in long term depression (Han et al) although the direct action of cannabinoids on these cells is excitatory (Kawamura et al). Opiates also show glial-linked effects (Bland et al.) (e) PET mapping of CB1 receptors in the brain using the cannabinoid agonist [^{18}F]MK-9470, with confirmatory displacement by the competitive antagonist MK-0364 at right (Burns et al). Brain derived neurotrophic factor (BDNF) belongs to the neurotrophin gene family and has well-established roles in neuronal survival, development and maturation as well as synaptic transmission and plasticity. It has been found that in the hippocampus, BDNF induces the mobilization of the endogenous cannabinoid 2-AG that acts retrogradely to suppress GABA release (Selvam et al. 2018).



Cannabinoid receptors have a variety of functions. CB1 occurs widely in the brain and CB2 is expressed on cells of the immune system where it has an immunomodulatory effect, reducing inflammatory response where it plays a role in processes including implantation of the fertilized embryo. Debate about the significance of the effects of cannabis and its principal active cannabinoid (-)-trans-Δ9-tetrahydrolcannabinol, or THC, on the capacity of the immune system to target infectious disease and cancer continue with conflicts between laboratory studies (Klein et al, Hegde et al, Gabrilovich & Nagaraj, Pacifici et al, Roth et al, Zurier) and social heath statistics on HIV patients using medicinal cannabis, which see no deleterious effect (Kaslow et al).

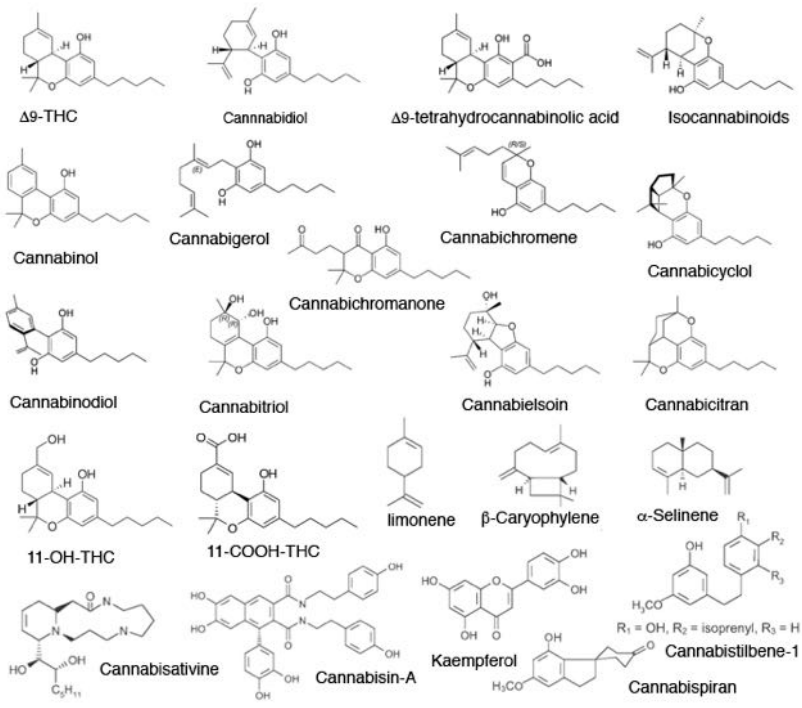


Fig 16: Natural cannabis molecules show a great deal of diversity. While THC is the principle psychoactive, cannabidiol has anti-psychotic properties. Action in the immune system CB2 receptors modulates immunity and reduces inflammation. There are also significant angiogenesis inhibiting and anti-oxidant components.

The active endogenous ligands for CB1 and CB2 are anandamide (Devane et al) and 2-AG, or 2-arachidonylglycerol, (Pertwee) both of which are close derivatives of arachidonic acid, a principal fatty acid which is a second signalling molecule involved in the cleavages of phospholipases C and A2 in the 5HT2 receptor, and a component of key phospholipids such as phsophatidyl-choline and is one of the most abundant fatty acids in the brain. A psychoactive andamide transporter FLAT has been discovered (Fu et al, Marsicano & Chaouloff).

CB1 receptors are thought to be one of the most widely expressed G protein-coupled receptors in the brain. This is due to endocannabinoid-mediated depolarization-induced suppression of inhibition, a very common form of short-term plasticity in which the depolarization of a single neuron induces a reduction in GABA-mediated neurotransmission. CB1 knockout mice do respond to THC, which shows that either CB2 or unknown cannabinoid receptors also have pharmacologic significance (Zimmer et al). However mice lacking

glial receptors have no memory deficit although those lacking neuronal receptors do, showing glial activation is responsible for the memory effects of cannabinoids (Williams R).

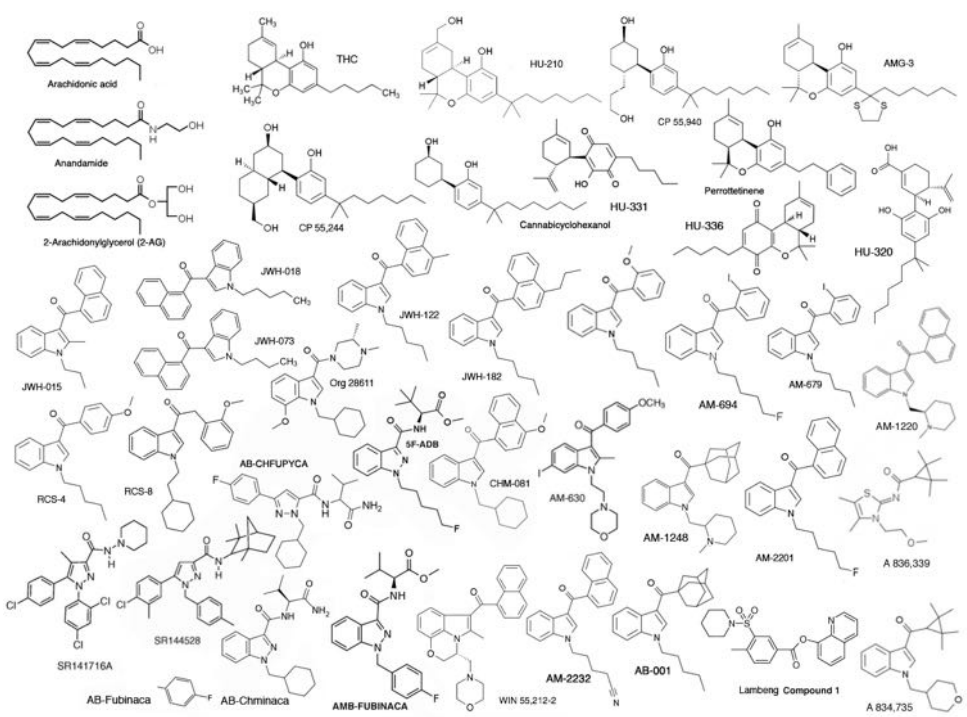


Fig 17: Natural and synthetic cannabinoids grouped by type. Top-left natural active cannabinoids anandamide and 2-AG are minor modifications of the major brain fatty acid arachidonic acid. Successive modifications to the right produce super-potent variants of THC. Other variants such as the JWH series are based on the naphthoyl-indole (Huffman et al) and arylsulfonamide structures (Lambeng). Three synthetics related to cannabidiol are HU-320, which has strong antiinflammatory and immunosuppressive effects, but no psychotrophic effect, HU-331 with efficacy against oncogenic human cells, by strongly inhibiting DNA topoisomerase II with negligible effect on topoisomerase I, and HU-336 a strong angiogenesis inhibitor. Perrottetinene is a natural putative cannabinoid found in *Radula marginata*. AB-C or AB-Chiminaca is a relative of AB-Fubinaca first synthesized by Pfizer as an analgesic in 2009 and discovered on the Japanese market. Small Chinese labs offer such substances to the world at claimed 99% purity (Davidson 2015). AMB-Fubinaca, also first synthesized by Pfizer, but tested only in animals, has been widely distributed, leading to zombie-like states in the US and 5F-ADB has been implicated in 10 unexplained deaths in Japan. AB-CHFUPYCA has structural similarity to the CB1 inverse agonist rimonabant (SR141716) an anti-obesity drug, banned after resulting in suicide, depression and other serious side effects.

Brain regions in which cannabinoid receptors are very abundant are the basal ganglia, associated with movement control; the cerebellum, associated with body movement coordination; the hippocampus, associated with learning, memory, and stress control; the cerebral cortex, associated with higher cognitive functions; and the nucleus accumbens, regarded as the reward center of the brain.

They are also associated with fear extinction in situations of risk of injury. The endocannabinoids anandamide and 2-arachidonoylglycerol are degraded by fatty acid amide hydrolase (FAAH). The FAAH inhibitor, AM3506 (5-(4-hydroxyphenyl)pentanesulfonyl fluoride) decreased fear during a retrieval test in a mouse model of impaired extinction. Mice carrying a low-expressing FAAH variant exhibited quicker habituation of amygdala reactivity to threat, and had lower scores on the personality trait of stress-reactivity (Gunduz-Cinar O et al). A recent tragic drug trial of BIA 10-2474, an FAAH inhibitor may have resulted from collateral activity on other proteins unrelated to FAAH, as seven trials of such agents had previously been authorised in Germany and were completed with no serious incidents. However an investigation is now under way in to this class of agents.

∆9-THC is only one of a very diverse series of bioactive molecules present in the cannabis plant, a sample of which are illustrated in fig 16. Several others have differing action, either as antioxidants, or possible angiogenesis inhibitors. Cannabidiol has been found to have anti-psychotic properties (Leweke et al, Zuardi et al 2006, 2012), which may offset the negative side effects of paranoia that can accompany some cultivated high-THC forms of cannabis extract (Campos et al). Millennia of cultural use suggest its use as a medicinal, spiritual and recreational substance is not profoundly harmful. It is also an inverse agonist of CB2 receptors, which would offset the effects of THC on immune responses. Studies have shown CBD may reduce schizophrenic symptoms due to its apparent ability to stabilize disrupted or disabled NMDA receptor pathways in the brain, which are shared and sometimes contested by norepinephrine and GABA (ibid, Long et al). Traditional hashish has equal concentrations of THC and cannabidiol and the latter may actually stabilize and maintain the effects of the former. There has never been a documented human fatality from

overdosing on tetrahydrocannabinol or cannabis in its natural form. Cannabidiol has been found to halve the incidence of seizures in Dravet's syndrome, a devastating and potentially lethal epileptic condition (Devinsky et al. 2017) and in June 2018 the FDA approved Epidiolex containing CBD for this condition and Lennox-Gastaut Syndrome (LGS), another rare childhood-onset form of epilepsy very resistant to treatment.

A 2015 study (Koch et al) has discovered that pro-opiomelanocortin (POMC) neurons play a key role in the cannabis "munchies". POMC neurons in the brain release both a hunger-suppressing hormone, and also one that promotes appetite. Which hormone is secreted is regulated by a protein in the mitochondria. When the CB1 receptor is activated, this protein induces POMC to switch from secreting the substance that suppresses apetite to one that encourages it.

Certain tumors, especially gliomas, express CB2 receptors. Δ9-THC and WIN-55,212-2, two non-selective cannabinoid agonists, induce the regression or eradication of malignant brain tumors in rats and mice (Galve-Roperh et al). THC and cannabidiol have been found to act synergistically with radiation therapy to stop high-grade glioma a very aggressive form of brain cancer in mice (Scott et al.) and cases of remission of glioma on taking cannabis oil have been widely reported (McGee). CB2 selective agonists are effective in the treatment of pain, various inflammatory diseases in different animal models, osteoporosis, atherosclerosis and Alzheimer's (Ofek et al, Steffens et al. Whiteside et al, Eubanks et al.) THC has been found to block Alzheimer's-associated beta amyloid inflammation (Currais et al.). Brain scans show the affect on pain is by reducing its emotional impact (Lee).

In a study of traumatic brain injury (Nguyen at al. 2014), researchers reviewed data on 446 adults. Overall, approximately one in five patients tested positive for THC and one in 10 patients died after their injury. About 2.4 percent of people who tested positive for THC died, compared to about 11.5 percent of those with negative THC tests. People who tested positive for THC were about 80 percent less likely to die, compared to people with negative THC tests, after adjusting the statistics to account for age, gender, injury severity and type. Previous studies have also suggested that alcohol may protect the brain in traumatic brain injuries but in the study cannabis was found to be more protective than alcohol.

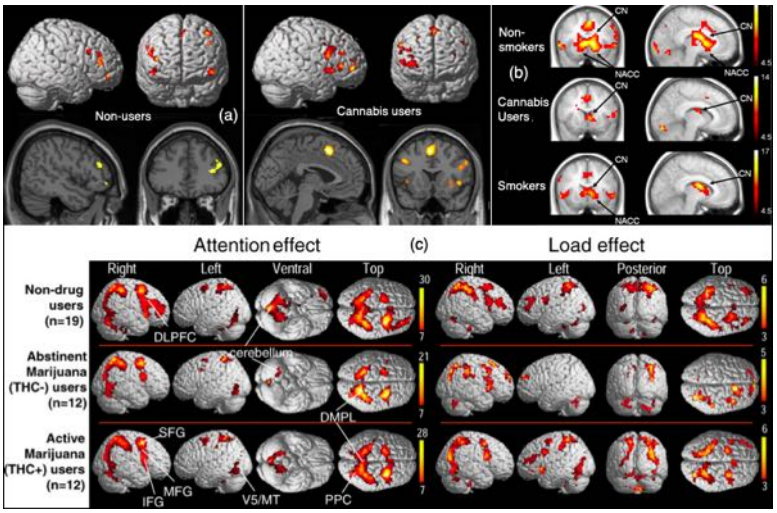


Fig 18: (a) Recent cannabis users displayed greater and more widespread brain activation than normal subjects when attempting to perform a spatial working memory task. This observation suggests that recent cannabis users may experience subtle neurophysiological deficits, and that they compensate for these deficits by "working harder" - calling upon additional brain regions to meet the demands of the task. Short-delay response task minus a perception task control (Kanayama et al). (b) Reward anticipation activity in the caudate nucleus is lowered in cannabis users (van Hell et al), (c) Evidence of reorganized visual-attention network and cerebellar hypoactivation. Subjects are instructed to track 2, 3 or 4 of 10 moving balls on a screen once the target balls are identified (4 are highlighted in the figure), and push a response button if the same target balls are re-highlighted. Surface maps demonstrate the effect of attention (independent of load, left) and the effect of attentional load (increasing difficulty from tracking 2 to 3 to 4 balls, right) cannabis users had different brain organization although there were no significant differences in performance on this task, nor in all but 2 of 31 other neuropsychological tests (Chang et al 2006).

The fact that active cannabinoids are modified fatty acids means that a wide spectrum of molecules with significant hydrophobic character and appropriate hydrogen bonding in their folded state can act with varying affinities as CB1 and CB2 agonists. Fig 17 shows a variety of these, including modifications of THC with increased potency. For example HU-210, HU for Hebrew University, (Mechoulam et al) has 100-800 times the potency of THC which itself is active in quantities of around 1-5 mg. It also encourages hippocampal neurogenesis and thus has anti-anxiety and antidepressant effects (Jiang et al). It is also implicated in preventing inflammation caused by amyloid beta proteins in Alzheimer's disease, in addition to preventing cognitive impairment and loss of neuronal markers, induced through the activation of cannabinoid receptors, which prevents microglial activation that elicits the inflammation (Ramírez et al).

The JWH family named after John W. Huffman, of Clemson University, consists of naphthoylindoles (Huffman et al). JWH-018 is a full agonist of both the CB1 and CB2 cannabinoid receptors and has been associated with unpleasant effects, including seizures, possibly associated with GABA inhibition and dissociative and anxiety episodes. There have been few studies of the metabolites of synthetic cannabinoids (Zhang et al, Kraemer et al) suggesting some reactive epoxide metabolites.

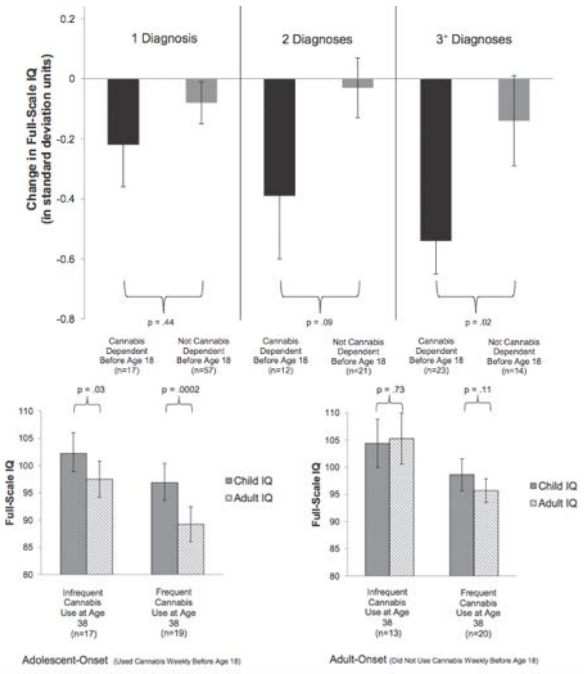


Fig 19: Significant decline in adult IQ associated with cannabis use in adolescence before the brain has fully developed (Meier et al). However a later study (Meier et al 2016) found no long-term effects of chronic cannabis use apart from gum disease, suggesting it is in some way protective against the carcinogenic effects of cannabis smoking.

This paucity of real information comes amid conflicting unsubstantiated accounts of cancer in mice (Morris), and anonymous reports linked to suppliers showing no deleterious effects (Synchronium). JWH-073 acts as a partial agonist at both the CB1 and CB2 cannabinoid receptors. It is five times more selective for the CB2 subtype. JWH-081 by contrast is ten times more selective for CB1. Other cannabinoid types include the diverse AM-series named after Alexandros Makriyannis of Northeastern University and the arylsulfonamide type (Lambeng et al). Two fluorinated compounds XLR-11 and AM-2201 have recently been associated with acute kidney damage (Murphy et al).

The sheer diversity of these cannabinoids, combined with the obvious capacity to design further and further analogues shows that the war on drugs, as applied to cannabinoids, is both damaging and futile, not least because some synthetic cannabinoids are dangerous and can result in seizures, sudden death, or organ failure, giving them, by contrast with the low incidence of emergency treatment of cannabis itself, a social risk profile exceeded only by methamphetamine (see fig 25). Given potent synthetic cannabinoids with either CB1 or CB2 selectivity, one can separate agents acting primarily on the brain from those acting on the immune and other peripheral systems (Gardin et al). Sequential banning of every molecule which appears as a legal alternative to cannabis, or alrady banned cannabinoids, simply knocks out the best molecules discovered, resulting in an ad-hoc mix of any molecule someone can come up with a novel design for, which doesn't mimic known banned configurations, but still acts on the cannabinoid CB1 receptor, whose side effects are not yet known. Either one has to declare any change to brain receptors illegal, which is impossible, since our endogenous neurotransmitters and many therapeutic drugs do precisely this, or legitimize cannabinoids that have good selectivity and minimal side effects.

While cannabis has been used for millennia as an intoxicant, there is evidence for a variety of potential long-terms effects including the brain, immune system, and hormonal systems (Nat. Acad. Sci., Eng. & Med. 2017). The effects on the immune system are immunomodulatory, and may reduce inflammatory (Zurier R et al) and auto-immune conditions, but do appear to result in a reduction of killer cells (Klein et al, Pacifici et al) and massive mobilization of myeloid-derived suppressor cells with potent immunosuppressive properties (Hegde et al). Animal models show that cannabinoids alter multiple hormonal systems, including suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and the activation of hypothalamic, pituitary and adrenal systems, by binding to the cannabinoid receptors in the hypothalamus. Despite this, the effects in humans have been inconsistent. The long-term consequences of marijuana use in humans on endocrine systems remain unclear (Brown & Dobs). In a 2012 genetic study (Lachance et al) it was found the the Hadza gatherer-hunters of Tanzania have evolved a novel CB2 receptor gene suggesting adaption to immune responses to disease resulting from their traditional cannabis use.

Long-term effects on the brain remain ambiguous. A 2012 study (Meier et al) has shown that use of cannabis in adolescence (before 18) has a marked detriment of up to 8 points in subsequent adult IQ scores, demonstrating that cannabis should not be taken by adolescents, but the effects when use begins in adulthood, even resulting in dependence are marginal. A followup study, which takes into account social status factors as confounds has contradicted these findings (Garrett-Walker 2013). In a study of long-term

marijuana users (Jager et al) fig 20(e) no firm evidence was found for long-term deficits in working memory and attention. However there were subtle dynamic differences in processing. In the superior parietal cortex, cannabis users failed to reduce activity in response to practice, compared with controls. In (para)hippocampal regions and the right dorsolateral prefrontal cortex there was reduced activity, however, lower brain activation was not correlated with changes in tissue composition and was unrelated to associative memory performance. Similar results have been found in the three studies discussed in detail in fig 18. For a current review of acute and long-term studies see Bhattacharyya & Sendt (2012). A study reporting a significant reduction in recognition memory associated with the synthetic cannabinoid WIN 55,212-2 when given to mice in 1 mg/kg doses over 30 days (Mouro e al. 2018). However this molecule is a full CB1 agonist with a much higher affinity than THC and is also an agonist of the PPARα and PPARγ nuclear receptors.

Cannabis has been ambiguously associated with schizophrenia, but the evidence is inconclusive and it is possible the association is because schizophrenics find it alleviates their symptoms (Szalavitz 2010). A study comparing genetic load of schizophrenia related genes showed increased cannabis consumption, consistent with this idea (Power 2014). Two studies have suggested a possible causal link (Arseneault et al, Andréasson et al) however there is no evidence for increasing rates of schizophrenia in countries with massive increases in cannabis consumption nor lower rates in countries with low consumption (Degenhardt L, et al, Frisher et al). One possible source of concern is young people carrying two copies of the short version of the COMT (catechol-o-methyl transferase) gene, which breaks down dopamine. A research study in NZ shows this group to be 10 times more likely to develop psychosis, smoking cannabis as a teenager (Lawton 2005).

Silins et al. (2014) investigated the association between the maximum frequency of cannabis use before age 17 years and seven developmental outcomes assessed up to age 30 years. They recorded consistent dose-response relations between the frequency of adolescent cannabis use and adverse outcomes in terms of high-school completion, attainment of university degree, cannabis dependence, use of other illicit drugs, suicide attempt, depression, and welfare dependence. The study however establishes only correlation, not causation (Slezak 2014). Slezak's commentary notes there are many such alternative possibilities that are consistent with the data. Students with more ambition or more interest in intellectual activities may be less likely to become heavy cannabis users and are also more likely to do well in school. Adolescents who use marijuana more than occasionally may have other aspects of their lives that make them more susceptible to poor outcomes during adulthood. Prof. David Nutt notes: "It is likely that significant proportion of the users have pre-existing problems and seek cannabis as a way out", although the study tried to rule out a spectrum of more obvious confounding disorders.

More recently, (Gobbi G et al. 2019) a meta-study has reported increased rates of depression, anxiety, and suicidality in cannabis users who start in adolescence. Two economic studies (Krieg Economic Inquiry, Zölitz & Marie Review Of Economic Studies) have also reported declining grades and a further one less study time in university students in Washington State in favour of recreation.

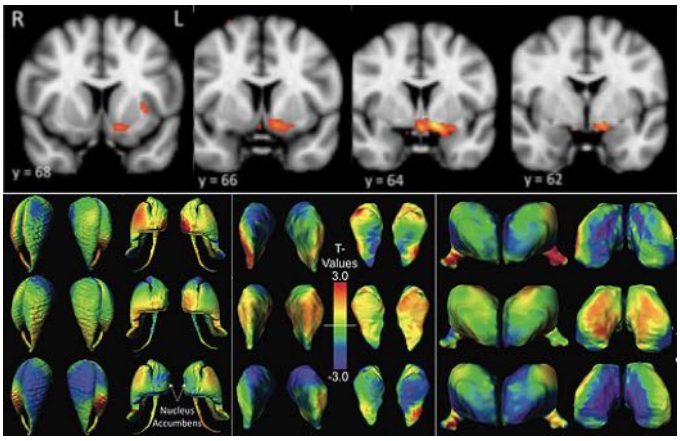


Fig 19a Above: ‘Abnormal’ gray matter increases in casual cannabis users (Gilman et al. 2014) Below: Changes in shape (red outward - blue inward) of striatum (left), globus pallidus (centre), and thalamus (right) in subjects with cannabis use disorder (top) schizophrenia (middle) and both (bottom) (Smith et al. 2014).

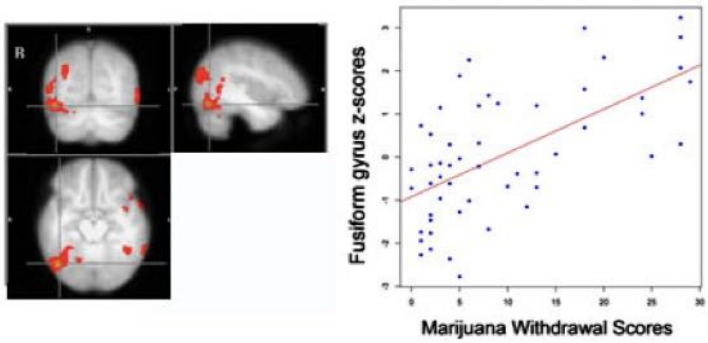
A study by Gilman et al. (2014) found increased gray matter density in the nucleus acumbens and amygdala in recreational cannabis users, claiming these ‘abnormalities’ indicated drug-dependency mechanisms of reinforcement consistent with unrevealed addictive changes. However it remains unclear whether these changes, which could also be associated with learning and adaption are necessarily an indication of abnormal activity. Sounding a note of moderation Prof Nutt notes: "Whatever cannabis does to the brain its not in the same league as alcohol which is a proven neurotoxin."

In another study, comparing users with the newly defined cannabis use syndrome (CUD), and clean and cannabis using schizophrenics with healthy controls, changes in the size and shape of three central brain

areas, leading to an overall reduction, were noted in a way which highlights parallels between CUD and schizophrenic changes which are exacerbated when both occur together (Smith et al. 2014). However unlike the previous study this is comparing people with a diagnosed overuse syndrome indicating mental problems with those with a diagnosed mental condition. Again correlation does not mean causation.

A study of the effects of THC on people with existing paranoid ideation, has also found THC enhances paranoid reactions in vulnerable individuals through the generation of negative affect and anomalous experiences (Freeman et al. 2014). Two studies have associated these effects with changes in dopamine function (Bloomfield et al. 2014, Madras 2014). Skunk cannabis used on a daily basis has been found to be associated with a 3-4 fold increase in psychosis (Di Forti et al. 2014, 2019), which is not shared by hashish, which retains a balance of THC and cannabidiol, which has compensating antipsychotic effects. A popular book by Alex Berensen (2019) has been widely debunked[8] as both cherry picking and incorrectly claiming causation by correlation. A study of stress reactions (Cuttler et al. 2017) shows long-term cannabis use bluntens stress responses, consistent with its use by some people to alleviate stress.

Fig 19b: Marginal correlations between brain changes and cannabis dependence.



In an attempt to demonstrate addictive changes in cannabis users, researchers demonstrated for the first time that long-term marijuana users had more brain activity in the mesocorticolimbic-reward system when presented with cannabis cues than with natural reward cues. When presented with marijuana cues compared to fruit, marijuana users showed enhanced response in the brain regions associated with reward, such as the orbitofrontal cortex, striatum, anterior cingulate gyrus, precuneus and the ventral tegmental area (Filbey et al. 2016). One of the authors Francesca Filbey claims "This study shows that marijuana disrupts the natural reward circuitry of the brain, making marijuana highly salient to those who use it heavily. In essence, these brain alterations could be a marker of transition from recreational marijuana use to problematic use," however the correlations are marginal and the study really only shows heavy long-term cannabis users identify cannabis cues as more pleasurable than fruit. Cannabis has also been associated with susceptibility to false memories (Kloft et al. 2020). Changing interactions between astroglial mitochondria and neurons involving lactate and increased oxidative stress appear to modulate anti-social behaviour in mice (Jimenez-Blasco et al. 2020).

Finally, a very encouraging article from Andreas Zimmer and colleagues (Bilkei-Gorzo et al. 2017). They administered a small quantity of THC to mice aged 2, 12 and 18 months over four weeks. Mice given a placebo displayed natural age-dependent learning and memory losses. In contrast, the cognitive functions of the animals treated with cannabis were just as good as the two-month-old control animals. First of all, the scientists discovered that the brain ages much faster when mice do not possess any functional CB1 receptors for THC. With increasing age, the quantity of the cannabinoids, such as anandamide, naturally formed in the brain reduces. The researchers also examined the brain tissue and gene activity of the treated mice. The number of links between the nerve cells in the brain also increased again. "The treatment completely reversed the loss of performance in the old animals. When the activity of the cannabinoid system declines, we find rapid ageing in the brain. It looked as though the THC treatment turned back the molecular clock," says Zimmer.

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

[8] https://en.wikipedia.org/wiki/Tell_Your_Children:_The_Truth_About_Marijuana,_Mental_Illness_and_Violence

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 long-term benefit in therapy for trauma and post-traumatic stress syndrome (Buchen, Frood 2008, 2012, Mithoefer et al 2011, 2012, Oehen, Mitchell et al. 2021).

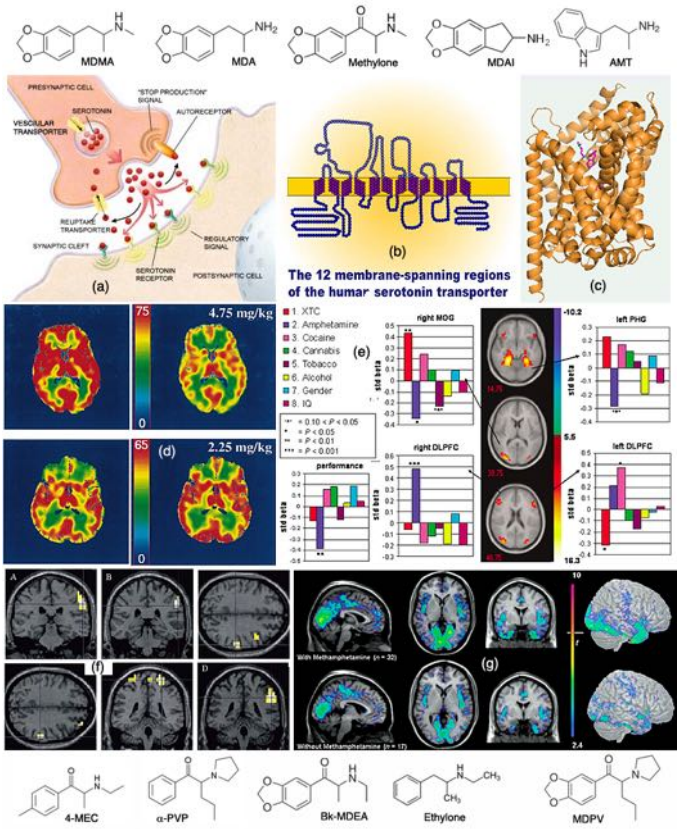


Fig 20: (Top) Entactogens **(a)** The role of the transporter in the synapse, **(b,c**) 2D and 3D structures of the serotonin transporter SERT **(d)** Levels of serotonin at Ecstasy dose and 3 weeks after for low and high doses (Chang et al 2000) **(e)** Comparable enhancement of activation in various 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 concurrent methamphetamine use (Kish et al). (Bottom) Undesirable consequences of banning MDMA. Four molecules, 4-MEC, Bk-MDEA, ethylone, and α-PVP found together in pills marketed as MDMA, intrinsically more dangerous than MDMA itself (Savage). MDPV, also called 'bath salts', presents another party drug substitute for MDMA, notorious for violent incidents, which is a nor-epinephrine and dopamine reuptake inhibitor, resulting in hypervigilance attacks. One person was reported as disembowelling himself and throwing his intestines at police trying to subdue him (Campbell).

The prosocial effect of MDMA has been confirmed in experiments where subjects played prisoners' dilemma games in an MRI scanner. When they were given MDMA, they became euphoric and talkative. "Some of them wanted to hug me," says Gabay the lead researcher. In this state, they cooperated twice as often as when they had played the game after being given a placebo - if their opponent was usually trustworthy. But if their opponent usually betrayed them, they acted the same way, playing less cooperatively, regardless of whether they had taken MDMA or a placebo, "They were nice but not stupid". Brain scans showed that MDMA boosted activity in several brain areas linked to social behaviour, including the right superior temporal sulcus. Recent work has shown the serotonin transporter activated by MDMA is found at the highest concentrations in the superior temporal sulci on both sides of the brain, as well as the other areas that became more active in the study. Decreased right insula/salience network functional connectivity has also been found under MDMA (Walpola et al. 2017), correlated with baseline trait anxiety and acute experiences of altered bodily sensations under MDMA.

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). Two studies also suggest possible heart valve defects (see section 10).

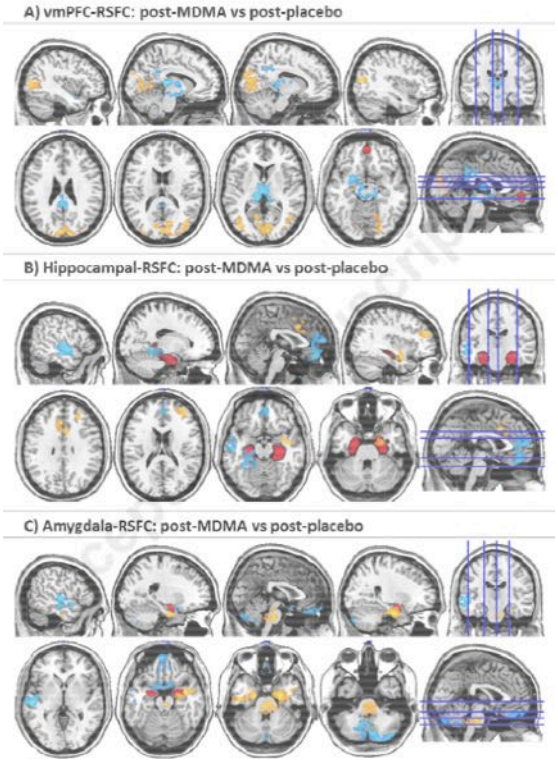


Fig 20b: MDMA was orally administered to 25 physically and mentally healthy individuals in a double-blind, placebo- controlled, balanced-order study. Arterial spin labelling (ASL) and seed-based resting state functional connectivity (RSFC) were used to produce spatial maps displaying changes in cerebral blood flow (CBF) and RSFC after MDMA. MDMA produced marked increases in positive mood. Only decreased CBF was observed after MDMA and this was localised to the right medial temporal lobe (MTL), thalamus, inferior visual cortex and the somatosensory cortex. Decreased CBF in the right amygdala and hippocampus correlated with ratings of the intensity of MDMA's global subjective effects. The RSFC results complemented the CBF results, with decreases in RSFC between midline cortical regions, the medial prefrontal cortex and MTL regions, and increases between the amygdala and hippocampus. There were trend-level correlations between these effects and ratings of intense and positive subjective effects.

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).

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)-alpha-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).

In a first for legitimate drug research into the actual effects of entactogens, a team led by Nutt and Carhart-Harris has used *f*-MRI to investigate the effects of MDMA on volunteers (Carhart-Harris et al 2013, Lawton 2012, White). They note that MDMA decreases cerebral blood flow (CBF) in the right hippocampus and amygdala, the visual cortex, pre-supplementary motor area, superior frontal gyrus and primary somatosensory cortex. They note that decreased hippocampal-ventromedial prefrontal cortex coupling predicts intense and euphoric effects after MDMA and that decreased right amygdalal and hippocampal CBF predicts intense subjective effects after MDMA.

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 2009). 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 MDMA.

Serotonin functions to smooth connections between the prefrontal cortex (ventral anterior cingulate cortex and ventrolateral PFC) and amygdala involved in processing anger, and serotonin depletion has also been shown to affect respnses to perceived anger and promote impulsive aggression (Passamonti et al).

De Win et al (2007) note the degree of controversy and scientific inconsistency in the ongoing research: “There is increasing evidence that Ecstasy is toxic to the human brain, especially to the serotonergic system, although the validity of these findings is still highly debated (Turner and Parrott, Grob, Kish). Many human studies are littered with methodological problems, including inadequate sampling of subjects and controls, lack of drug use analysis, and lack of baseline data.”

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.

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.

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.

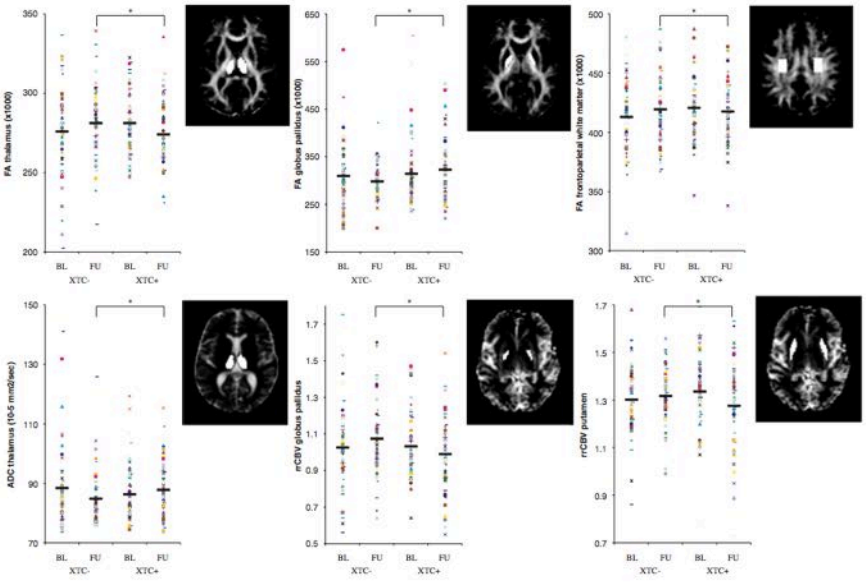


Fig 21: Changes in FA, rrCBV and ADC (de Win et al 2008) at baseline (BL) and follow up (FU). These changes are very moderate, but so is the consumption (de Win et al 2008).

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 2000) 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.

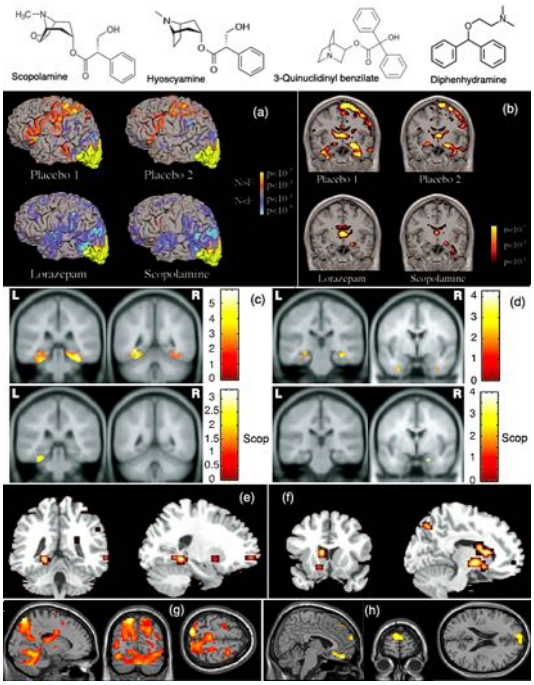


Fig 22: (Top row) four hallucinogenic deliriants. Scopolamine and hyoscyamine are present in Datura, and Brugmansia species and related solonaceous plants such as belladonna (deadly nightshade), henbane and mandrake. 3-Quinuclidinyl benzilate is a chemical warfare incapacitating agent also called BZ. 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.

Although they have been sporadically used recreationally, their severe effects of anterograde and temporary global amnesia combined with delirious behaviour and 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. It can cause box lock amnesia by affecting the basal nucleus of Meynert, which is an important structure for amnesic functions, especially the retention of memory. Moreover, it can block free will, in which victims become docile and agree to withdraw their money from ATMs without protest. For this reason it is used in drug-facilitated robberies and drug-facilitated sexual assaults. It is also known as “burundanga” within the circles of people who abuse it. It is tasteless and odorless, easily absorbed in the digestive tract, and can be delivered orally, dermally, or via inhalation e.g. blowing it someones face (Reichert et al. 2017).

Scopolamine, despite its severe hallucinogenic and amnesiac properties, is used in minute quantities (0.5-1 mg) for motion sickness, the prescription drug buscopan containing 10-20 mg, is used for intestinal cramps, and it is used for treatment of addiction and as an anti-depressant (Furey & Drevits). A recreational dose is hard to determine but might be between 85 and 120 mg (Sáiz et al. 2013, Strano-Rossi et al. 2021). 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.

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.

Scopolamine has also been used criminally as a poison, powder or spray that can incapacitate a person, or cause them to become obedient to a criminal's intent (Reichert et al. 2017). 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 all it may have been used 500,000 times in South America and has also spread to Europe. 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.

10: Safety Considerations of Psychedelic Use and Global Drug Policy

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 23, 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. Case reports of long-term psychiatric problems attributed to LSD, include psychosis, panic attacks, other anxiety disorders, and depression. There are very few case reports of prolonged psychiatric symptoms following psilocybin or mescaline. However any long term case reports now look to be due to the coincidental incidences of mental illness unrelated to psychedelic use. In a study of 130,152 respondents, randomly selected to be representative of the adult population in the US, 21,967 of which (13.4% weighted) reported lifetime psychedelic use, there were no significant associations between lifetime use of any psychedelics, lifetime use of specific psychedelics (LSD, psilocybin, mescaline, peyote), or past year use of LSD and increased rate of any of the mental health outcomes. Rather, in several cases psychedelic use was associated with lower rate of mental health problems (Krebs & Johansen).

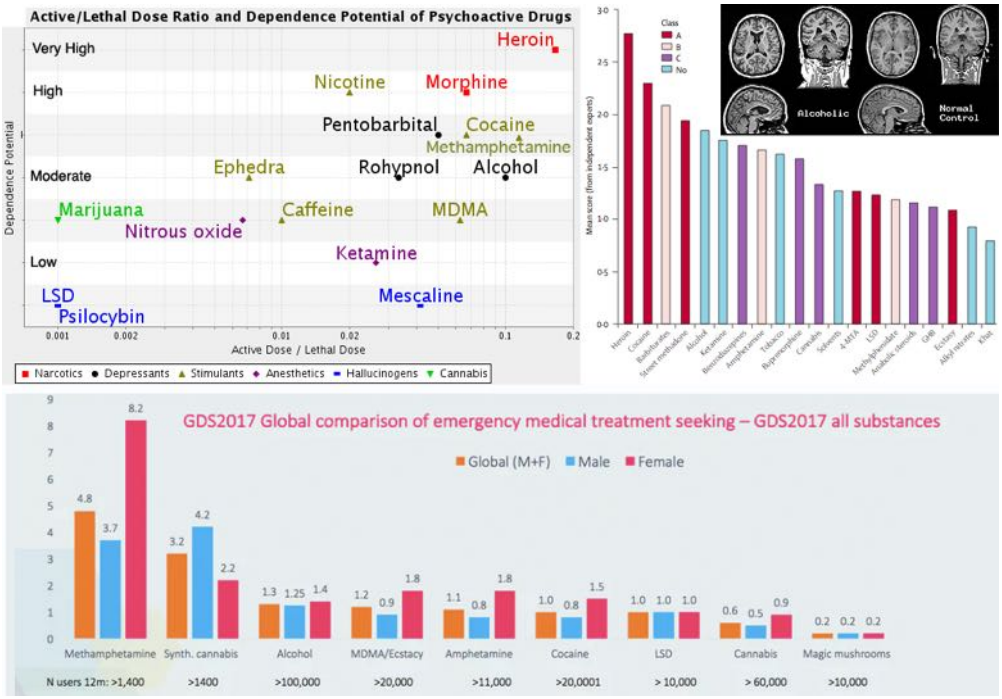


Fig 23: Relative safety of a spectrum of psychoactive drugs (upper left) in terms of dependence versus active/lethal dose (Wikipedia), also (upper right) in terms of several measures of relative harm (Nutt et al) and below the GDS2017 report (www.globaldrugsurvey.com) showing magic mushrooms to be the safest recreational drug of all. In all three 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.

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”. Most serotonin agonists also have peripheral, including vasoconstrictor, effects. Virtually all psychedelics and entactogens have strong 5HT2b binding. Prolonged use in the case of some 5HT2b agonist and serotonin releasing pharmaceutical drugs, such as fenfluramine, have resulted in heart valve anomalies (Rothman et al, Roth 2007, Schade et al, Zanettini et al), and entactogens MDMA and MDA have also been shown to have similar effects (Setola et al, Droogmans et al). Some psychedelics also cause such effects, but only permit intermittent use. Binding of ergotamine and to a lesser extent LSD to 5HT2b receptors invokes the β-arrestin pathway over G-protein signalling (Wang et al, Wacker et al).

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, mania, and isolated cases of temporary paralysis and cardiac malfunction after eating less common forest species (Yokoyama, Borowiak et al). 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.

(Left): Real time clock of costs of the War on Drugs for the year, of $30.6 billion (http://www.drugsense.org/cms/). (Right: Three organizations promoting research and policy reform Global Commission on Drug Policy (http://www.globalcommissionondrugs.org/), Multidisciplinary Association for Psychedelic Studies (MAPS) (http://www.maps.org/), and the Hefter Research Institute (http://www.heffter.org/). The War on drugs costs around $30 billion annually. While the world invests billions in scientific discovery, it wastes much greater sums preventing discovery of alternative conscious states. Compare this with an overall budget of $7 billion for the Large Hadron Collider and $3 billion for the Human Genome Project. If half the money spent in the War on Drugs were dedicated instead to public education and health it would be more than enough and leave $15 billion a year in surplus for research and discovery - two LHCs per annum! A tiny fraction of this would be enough to fund psychotropic research into the foundations of consciousness. For a 2014 world position from the Global Commission on Drug Policy, a group including former Presidents of major countries and Kofi Annan, see: “Take Control: Pathways to Drug Policies That Work” http://www.gcdpsummary2014.com/. In Oct 2015 Richard Branson released an embargoed report from the UNODC overseeing policy on drug control recommending decriminalization http://www.virgin.com/richard-branson/finally-a-change-in-course-on-drug-policy. See also the Beckley Foundation http://www.beckleyfoundation.org/.

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).

More generally, the war on drugs, based on prohibition, incarceration, and capital punishment, even when applied to manifestly more dangerous drugs, such as morphine, heroin, cocaine and methamphetamine simply feeds militant gang violence and fosters uncontrollable global criminal enterprise. It is extremely costly in terms of broken familes, soaring murder rates and dangerous impure street drugs. The International Centre for Science in Drug Policy in its 2013 report (Werb et al) concludes the war on drugs has failed. Illegal drugs are now cheaper and purer globally than at any time over the last 20 years. The report said street prices of drugs had fallen in real terms between 1990 and 2010, while their purity and potency had increased. In Europe, for example, the average price of opiates and cocaine, adjusted for inflation and purity, decreased by 74% and 51% respectively between 1990 and 2010 accompanied by a substantial increase in most parts of the world in the amount of cocaine, heroin and cannabis seized by law enforcement agencies. It concluded: "These findings suggest that expanding efforts at controlling the global illegal drug market through law enforcement are failing."

This failed strategy is a corrupt pawn of political expedience and urgently needs to cease in favour of an attitude of public health for those suffering from abuse and respect for the rights of individuals to make autonomous decisions about their altered states in a safe setting (Carlsen, Jahangir et al, Nutt et al, Torrens & Ruiz-Goirena, Travis, White). The paradox of the situation is emphasized by the virtual impregnability of the drug market Silk Road behind the Tor anonymizer which is in turn partly funded by the US government free internet initiative (Ball http://www.guardian.co.uk/world/2013/mar/22/silk-road-online-drug-marketplace). For an excellent documentary focused on the Global Commission on Drug Policy, see: Breaking the Taboo http://www.breakingthetaboo.info/. Join Stop the Harm http://stoptheharm.org/. See also: Q&A: Mexico's drug-related violence http://www.bbc.co.uk/news/world-latin-america-10681249, US marijuana legalisation fuels Mexico drugs war debate http://www.bbc.co.uk/news/world-latin-america-20397335, The trouble with using police informants in the US http://www.bbc.co.uk/news/magazine-21939453.

A Plea for Legitimising Recreational Cannabis Use

Anandamide, the principal natural cannabinoid, fig 17, is a slightly modified form of arachidonic acid, a principal fatty acid comprising 10-20% of the fatty acid component of the brain, by adding a small polar tail. The nature of heptahelical G-protein liked receptors, figs 25 and 25b, in the context of anandamide have left them open to an extremely wide array of molecular types bearing no resemblance to anandamide except for having a non-polar core with scattered polar moieties forming a similar 3D interactive structure to anandamide. Fig 17 shows just how diverse these molecules are. Essentially with all the recreational drugs, we are dealing with agonists or transport modulators of the sappy neurotransmitters that evolved for complex social responses in single celled eucaryotes (see evolution section) before the brains of multi-celled organisms evolved. Attempting any form of cultural legislation by coercive force is futile, both because many natural species generate potent psychoactive variants and because the very evolution of all animal brains pivots on neurotransmitters as central modes of motivation, survival and adaption.

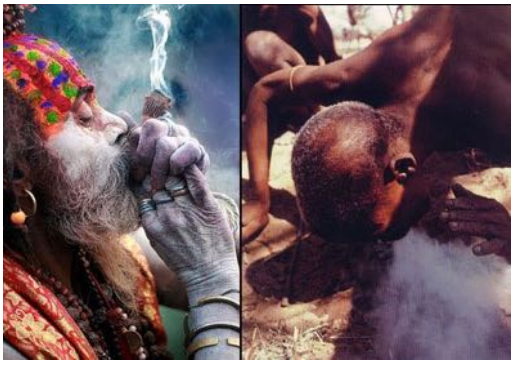
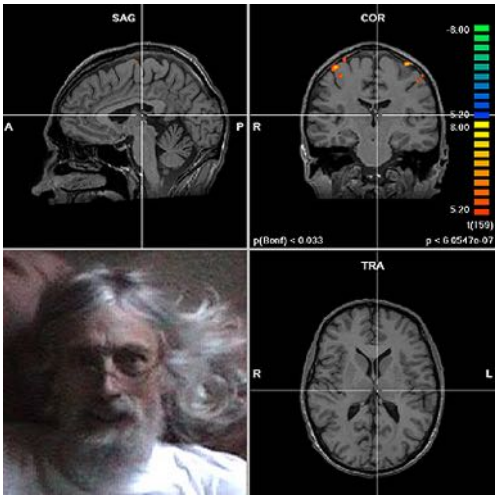


Fig 23b: Shiva sadhu smoking chillum and Kalahari Bushman, our oldest surviving culture[9] smoking cannabis from a water hole in the ground.

In the case of cannabinoids we have one key species, with cultural use going back to the neolithic and probably before, with no manifest basis for prohibition, from the Sadhus of India to the smoking holes in the ground of the Kalahari Bushmen (right). THC is a partial rather than a complete agonist, so has a softer effect profile, associated CBD is antipsychotic and other cannabis constituents are anti-cancer to the extent that the National Institutes report (Nat. Acad. Sci., Eng. & Med. 2017) indicates moderate evidence of no correlation between smoking cannabis and lung cancer, which is highly significant in itself. However the synthetic cannabinoids are (a) so diverse it is almost impossible to regulate them (b) untested long-term (c) several have manifest serious side effects including epileptiform seizures, zombie like states, cumulative dependency and a spate of multiple deaths from one shipment in New Zealand alone (d) several have worse selectivity for CB1 versus immune CB2 receptors (e) some are dirt cheap to produce and potent in close to microgram doses.

A few years ago, it was possible to literally design mail order molecules and have them posted from China in sufficient quantities for a lifetime supply. I have tried a spectrum of these while they were legal. They are definitely anandamide receptor agonists but they have inferior and often more disquieting effects than natural cannabis. There has also been a very disturbing trend from dilettante designer molecules and the spice packets that were legally sold in dairies here which were not too increasingly harmful, to black market street drugs pedalled for low production cost despite the distributors knowing they are distributing a much more dangerous product. For example, fubinaca (fig 17) and chiminaca, known for multiple deaths in Japan, and New Zealand. Basically these substances are the fentanyls of the anandamide world. We can deal with opium from the plant, but the transition to heroin, fentanyl and carfentanyl becomes increaingly perilous. The same way, coca is consumed safely in the Andes but pasta becomes a scourge, although not as badly as crystal meth, which is manifestly cortico-toxic.

The best way to avoid an entrenched market in potentially diabolical cannabinoids which are as extremely easy to black market, as fentanyl is, is to legitimise the use of cannabis, as it has been used for millennia. This doesn't mean it is absolutely safe, but that its social and individual harms are no greater than any of the other legal activities humans engage from drinking alcohol to eating junk food or hiking in the wilderness. To suggest that society should continue to ban cannabis use by retaining criminal classification and censure with potential incarceration is counterproductive and contrary to the very nature of autonomous democracy and the long-standing traditions of human culture. The earliest evidence for potent cannabis use noted in fig 1b was in a sacred context because it provides a portal to the unseen conscious world, just as psychedelics have been used. This is also a reason people get high recreationally and it is valid and central to us all finding out how to care for and preserve the living planet. Shutting down the safety valves of the doors of perception could lead to our own collective extinction as a species and a mass extinction of biodiversity, not just some social harms or jail terms.



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

[9] https://www.dhushara.com/paradoxhtm/culture.htm

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. At the age of 67, in tender retirement, I also feel I owe it to younger generations to test out what they are doing to themselves and pass some sort of judgment on the diverse mind-altering agents in common currency.

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.

A Personal History

My involvement with psychedelics began in 1966 in the era before Sergent Pepper when I arrived in England as a grad student. Pink Ffloyd was still a local band coming to play in a VW combi at the university student rec centre and Lucy in the Sky with Diamonds hadn't been written. Some of my friends had LSD in the early form of sugar cubes. I tried one and found it so hauntingly intriguing that I thad to take the train back down to London the same week and got two more cubes and proceeded to drop them on my return. What had been a captivating floral banquet on one cube became a depersonalizing maelstrom on two. I became convinced I had died and for days afterwards had lingering iridescent phosphenes in my peripheral vision. Worse still news came out that LSD split one's chromosomes and I kept having visual flash backs every time I looked at a metallic reflecting poster of Bob Dylan with his curls made into psychedelic auras. Of course the story about genetic damage proved to be a spurious tale put out by the authorities, but it was several years later until I became brave enough to try LSD again. When I did I set off on a journey of relentless psychonautic exploration, buying 100 trips at a time of the purest kind. The original Orange Sunshine, tiny gelatin window panes and blotters made by a mad American scientist who lived in the same town and always wore white plastic clothing. After years of this experimentation which came ever closer to Samadhi, I ended up going to a peyote ceremony in Taos and later, while baby sitting for one of the members of the church, ended up trying a packet of magic mushrooms, having a beautiful gentle trip. I realized this was a pure natural experience with thousands of years of tradition behind it, which could be propagated in perpetuity. Moreover, although psilocin was less overwhelming than strong acid, I felt a deeper attunement with the forces of nature, chaos and the subliminal levels of consciousness somehow interacting with the flow of life and karma around me. I became a de facto shaman, both preserving, and practicing the traditions of entheogenic mysticism. As noted in fig 3, I have also taken mescalin in the form of San Pedro, 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, DMT and harmine in the form of ayahuasca with Senor Trinico at Yarinacocha, Pucallpa in Amazonian Peru, and experimented with psilocybin containing sacred mushrooms, potentiated by the natural monoamine oxidase inhibitor harmaline, with DMT and cannabis in combination, so have a reasonably comprehensive familiarity with psychedelic entheogens. For 40 years I have confined myself to natural sacred species to avoid the impurities of street drugs and follow traditions of cultural use established and respected over millennia, so this is also an exploration into a diversifiying field of designer drugs.

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 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.

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.


Dilated pupil on an earlier session of psilocybin with harmaline.

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 ('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, with Synthetic Cannabinoids

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 is 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.

The synthetic cannabinoids are also a new experience. Very sharp and electric and easily reaching a level where one’s thought processes are running away to the point of mild anxiety, yet identifiably a cannabis type ‘stone’. The smoking involved with milligram quantities of relatively pure substance appears vastly less harmful than a tarry marijuana joint, although they are largely untested entities.

Entactogen (‘MDA’) plus Entheogen (25C-NBOMe) and Cannabis

On a second occasion I combined an entactogen, believed to be MDA, with a stronger dose of 25C-NBOMe. The entactogen taken in the early afternoon gave a clear, pleasant, sociable high, promoting a strong desire to converse intimately with my companions. Cannabinoids around 4pm gave the experience a wilder tinge on a walk over the nearby mountain. Toward evening, I inhaled an unspecified quantity of 25C-NBOMe and became launched into a paradoxical visionary state, in which the entactogen and entheogen combined to give a very positive emotional spin on the whole experience - wholesome as well as awesome! This is well known combination appreciated by LSD trippers in the 1960s. 25C-NBOMe is a deceptively strong, very pure psychedelic, which can move from appearing to be merely a glow on the surroundings one minute, to falling into a deep kaliedoscopic entheogenic trance the next. It has a very deep clear entheogenic effect when one falls into it. I class it as a very valuable research entheogen.

A problem emerged later in the evening, when my left eye began to have severely disrupted retinal vision with eerie haloes and vision loss unless I lay flat on my back, compounded by the psychedelic effect. I have had a similar effect transiently in the other eye on Viagra, probably due to vasodilation against the optic nerve, but the mix of serotonin releasers and agonists seemed to be exacerbating a vasoconstricting effect into a retinal migraine. I partially controlled this with a power walk back up the mountain, which was a scintillating experience of psychedelic lights. However the blurring didn't dissipate until next evening, in a throbbing red eyeball.

Now this turned out to be an indirect godsend. With this condition, anything that dilates your pupils can bring on an acute attack. A couple of months later when the conditon recurred on quiet evenings I had an eye check and found I had acute closed-angle glaucoma. I was promply sent to the accident emergency and given a laser operation on the spot to puncture a passage through each iris, which promptly relieved the condition. Had I not taken the psychedelics, I might have not had the condition fixed before I seriously lost my vision.

However one has to watch out carefully for peripheral vasoconstrictor effects in serotonin agents. Although 25C-NBOMe is strongly 5HT2A selective, 5HT2A receptors occur on both neurons and blood vessels. Closely related 25I-NBOMe has been associated with one acute hospitalization emergency in a susceptible individual, ostensibly at a carefully titrated dose - subject unresponsive, blue lips and systemic loss of ion balance (Elover).

Despite sleep and additional 5-hydroxytryptophan, next day I am somewhat brittle and hypoglycaemic. Day two I'm in fine form, but I have three observations about entactogens. Firstly, although they give a wealth of good feeling on the occasion and are very attractive as socially-bonding party drugs, they have higher costs than entheogens in the come down from excessive dumping of serotonin into the synaptic junctions and longer term reductions in transporter function. Secondly the drug wars are completely demented. It would be far better to legitimize MDMA and have people consuming certified pure entactogens than street drugs with a mix of more dangerous analogues and mimics, with possibly harmful impurities (see fig 20). Finally, serial dosing with entactogens and stimulants, combined with lack of sleep is a recipe for long-term functional depletion. The experience tends to make me gravitate back to natural entheogens, which have been safely consumed for millennia with minimal risk of harm, so here we go.

Maria Sabina consuming her sacred mushrooms.

Psilocybin again

A week later I checked out this performance against a second round of psilocybe mushrooms, which I have had a safe 36-year relationship with, after discovering a wonderful heritage movie of Maria Sabina doing a mushroom velada at Huautla de Jiminez (María Sabina: Mujer Espíritu http://www.youtube.com/watch?v=WEGeVUkrPRo). Of course again I fell into an entheogenic trance void amid the shrill sonic vibrations mushrooms are prone to, but the one advantage of the selective 5HT2A agonists is that they are a very clear mind state, free of the anxious thought rushes that can beset mushroom experiences. The reports of Aztec partakers fearing their heads were going to be crushed between two stones for being caught in adultery are not empty fantasies! On the other hand these disturbances can also be liberating when they bring to the surface and help resolve repressed conflicts and bring new realizations.

One needs to point out here that the entheogenic experience is deep, vast and complicated. We have up to four plausible processes, each potentially affecting the conscious state, 'kaleidoscopic' fractal waves of excitation travelling across the cortex, 'synesthesic' enhanced resonances between distinct cortical areas such as seeing and hearing, 'dream-like' changes to the Raphe nucleus and Locus coeruleus affecting arousal and reverie, and possible changes to thalmo-cortical feedbacks. It is one thing to see visual kaleidoscopes or experience visual-auditory synesthesia, but what is a fractal excitation of temporal episodic or semantic memory or parietal areas dealing with spatial relatioships and those dealing with complex scenes? What is synesthesia between our internal and external areas in the somatosensory and cingulate cortices going to do to our ideas of oneness with one-another and the universe? These complexities underlie the more subtle, far reaching, aspects of ego dissolution and the visionary condition.

Now let me get to the nub of this whole question of entheogens and the entheogenic experience. Human consciousness is caught between a rock and a hard place - the devil and the deep blue sea. This is the sentient aspect of the free-will dilemma - if we have no autonomous conscious will and are just the products of our brain dynamics, are the feelings we have of making personal conscious decisions delusory? No sane person wants to invest in this assumption. The sentient version is just as appalling. If subjective consciousness is just an internal model of reality constructed by the brain for our animal survival, all our personal experiences of the world are nothing more than a mirage, and we are caught in this infernal bottle, born alone to die alone, with no hope of a life hereafter, despite the subjective delusions of love and togetherness, in what is essentially a schizophrenic, existentialist nightmare, despite all our attempts to make meaning of the world. Yes I know we can make a claim that this is the evolutionary condition and that our neurotransmitters are giving us the feeling of togetherness, reinforced by our mirror neurons, still this is the stuff of a psychotic nightmare and why some people go to pieces faced with the enormity of psychedelic reality. The other option is that there is more to it. The second, saner option also has profound implications - that subjective consciousness, despite being a product of our fragile brains, is somehow a real phenomenon which possibly has influence on our physical circumstances, not just an internal 'epiphenomenal shadow', and our subjective experiences of reality, from birth to death, are somehow complementary to our physical presence in the natural world. It is this second option that is also the motivating raison d'etre for all our 'spiritual' and religious traditions. What the entheogens provide is a disembodied abstract form of existential consciousness, which is transiently freed from the boundaries imposed by the organismic framework of survival, so that it can come to terms of understanding of its own condition.

This is not something which can necessarily be seen objectively or retrieved and classified, as an external structure can be, but is a participatory form of abstract consciousness, which can take a variety of forms, just as the dreaming state, as a palpable sensory reality on a similar existential footing to waking reality, can adopt almost any kind of situation imaginable, but in the psychedelic condition, unlike the projected realities of dreaming, consciousness can adopt altogether different, more abstract forms, from spaitial kaleidoscopic structures, through visions of scenes, to a deep intimate sense of 'spiritual' integration and meeting with the essential conscious forces shaping the experiential condition. When I enter the entheogenic void I experience a return to this source condition, not as just an emotional feeling but as a veridical self-validating sensory experience, just as dreaming is not just imagination, but an inner sensory reality. It conveys to me a return of my consciousness to its unconstrained natural state, reflreshing my life journey by a return to its source condition. A condition from which the meaning and direction of my life takes form.

Complementary to this is the whole question we have investigated in detail in this article, about how each of the psychotropic substances affect brain dynamics through their receptor and transporter activities, and both by discovering how they act experimentally, and through their subjective experiences bringing us to a closer and more decisive understanding of how the conscious brain performs its elegant and complex tasks of cognitive and sensory processing, along with memory formation and anticipation of future situations. Thus discovering experimentally how the glutamate connection may facilitate both psychedelic and dissociative brain changes in rapidly fluctuating activation dynamics provides a compelementary insight to the deep subjective commonalities of peak experience, despite the profound differences of action of these two types of agent.

The psychedelic experience is often described as a ‘trip’ because these experiences of falling into the cosmic condition can happen in the midst of the other things we are doing, as we lie beck for a moment or two in reverie and find we have entered this enchanted realm. Sometimes it may feel a little demented and we might again ask, “Is this redemption or a lonely dysphoric nightmare?” but as the experience progresses, one realizes one has made some kind of intimate contact with the utimate ground of sentient being, and when one comes back down from this tangled journey and pieces together the experiences, one often genuinely feels one has had an encounter with the ineffable source of existence. It is this entangled journey that lies at the heart of the rejuvenating and fulfilling experiences reported in the ‘genuine spiritual type’ experiences reported by Griffiths et al and ironically originally by Leary et al, in the Marsh Chapel experiments that triggered the psychedelic fall from grace. And it is here that the importance of accepting the central role of entheogens in our discovering our own inner identities, for entheogens present the best route we have to understanding the abstract fundamentals of consciousness, just as the LHC, as chaotic fundamental particle billiards, does for the foundations of physical cosmology.

Let me explain why. Psychedelics, and the dissociatives, induce profound changes in how the conscious envelope of subjective experience is generated, in a manner which induces phenomena extra-ordinary to waking and even dreaming reality, from deep fractal kaleidoscopic image spaces, through complex visionary sequences, to primal experiences of cosmic union. Many of these features share parallels with the sensitive dependence on boundary conditions possessed by chaotic systems and with edge of chaos complexity. The fact that they occur in an abstract form and present archetypal features, suggests the subject’s brain is being thrown into a state of internal chaotic resonance with its own internal dynamics, which may reflect deeper underlying principles of how subjective consciousness is generated, giving them a fundamental complementarity to dreaming experience and waking life. In so doing, they may bring us closer to understanding the essential nature of subjective consciousness than any other avenue, although this may be a dynamic participatory experience whose features cannot be fully described externally, requiring first-hand experience to fully fathom, consistent with the essentially first-person nature of subjective experience and in contrast to the second and third person accounts of religious doctrines and beliefs.

In this they may even hold a key to the way the brain uses the physics of quantum entanglement to anticipate events in real time and thus lead to a new deeper understanding of cause and effect central to our idea of free will and the existential dilemma. Animals possess subjective consciousnes not to compute probabilities alone but to anticipate immanent threats to survival and avoid them. Probabilities are insufficient to solve this because the lion can be on any path about to strike. The conscious brain uses wave function processing with many features in common with the wave-particle complementarity of quantum physics. Psychedelics may thus take us into an undiscovered realm of spooky space-time interactions which science is only beginning to uncover. Thus some aspects of shamanic thinking may be an intuitive investigation into founding cosmological principles.

Because psychedelics appear to operate through a second 5HT2a pathway, rather than disrupting all serotonin signaling pathways, they can achieve their powerful effects without grossly disrupting cognitive and memory processes in the way that delirants and to a lesser extent dissociatives do, so they have the greatest potential for investigation and discovery of the generative nature of consciousness. Science has hardly begun to have a model for extending subjective consciousness to the cosmological condition, and current descriptions, such as the Buddhist Bardo, or Vishnu dreaming cosmic reality tend to stem entirely from religious traditions. Our investment in intentional autonomy and the belief that our subjective conscious intentions can alter world futures extends to a description in which the universe at large also possesses subjective intentionality, which has profound implications for world futures in a situation where current attitudes are in a vacuum of schizophrenic views between apocalyptic religion and materialistic tragedy of the commons. Entheogens may hold a key to a description of universal consciousness consistent with the long-term future of our planetary survival, in replenishing the Earth, in the closing circle of the biosphere, rather than the scorched-Earth divisiveness of competing moral-apocalyptic theologies.

To ban psychedelics for half a century under penalties of long incarceration has been the most damning indictment of the shallowness of our culture and exposes the innate fear of the powers that be, controlling capitalist society, that the discovery of these internal realities might seriously unravel both our contrived religious traditions and our materialist consumer society in one fell swoop. But in turn, if they do provide a key to the nature of subjective experience, they could hold an oracle to the foundations of life, the universe and everything. This is the key existential question we all face in the mortal condition. Again this is not just a ‘spiritual’ question, although it has religious dimensions, but is a fundamental ‘cosmological’ question about how the conscious universe manifests itself and ourselves in space-time.

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 ayahuasca, 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 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.

Return to Forever: Sacred Mushrooms

Today a little over six months after the psychedelic episodes just before my emergency laser eye surgery as a proof of principle for the cure, I set out to have a heroic dose of sacred mushrooms to test the water after months of parched ground, leaving me drifting in mid life crisis. The little sprout fruiting buds I consumed were severely hyper-potentiated. What could have become a mushroom with a cap 10 cms across only gets to be the size of a pea, but with all the active ingredient of the never-to-become giant cap caught in its base, so 1.5 gms of this crispy dried stuff can be a dose of epic proportions. Coming out the helter-skelter tunnel of an overwhelming mushroom experience - what do I make of the role of entheogens? Are they beneficent world-healing allies? Are they here to heal the biosphere and show us the secret of the existential quest?

As previously noted, the experience comes on with a symphony of shrilling vibrations that, as they overtake me, spiral me into the visions. I love this herald of the onslaught of sacred mushrooms dearly. It is for me a synesthesia, which is sensitive to my mental awareness, a tunable whiplash that takes it far beyond a drug effect into the continuum of shamanistic non-ordinary reality. Visions come and go of impossible experiences I know I have had and witnessed first-hand yet know I could never have happened.

"And you also see our past and our future, which are there together as a single thing already achieved, already happened . . . I saw stolen horses and buried cities, the existence of which was unknown, and they are going to be brought to light." Maria Sabina

At the peak I felt as if I was suspended in a state of light-induced electrocution. It was searingly high and at the same time utterly pure. If I were on any form of synthetic I would be on the verge calling for an ambulance. It's only because it is a natural agent of the highest, purest quality that one can do something so extreme. And this makes it a living path, a living sacrament. I could barely get up from the bed and walk down the hall. As I sat breathless in the living room, non-ordnary reality was bursting out of my sub-conscious and across my peripheral vision so I was simultaneously in about five places at once. I was overwhelmed but at the same time didn't feel poisoned, just physically illuminated - animated to the point of annihilation. Idyllically my eyes didn't throw any of the previous acute primary angle closure crises from my previous case studies before my laser operation, even though I could barely read because my pupils were so dilated.

My whole creative life has been defined and fertilized by sacred mushrooms. All my scientific research, all my shamanic and messianic journeys, many of my love affairs and all of my spiritual quest. I consider myself a direct protege of Maria Sabina and hold true to the path of the teonanactl shaman - which my whole life journey is an expression of. If this wasn't a first schedule toxin I would have spent my entire life teaching all and sundry the path of the living sacrament of the Tree of Life true to my name and destiny. So you are right! ... how can I pretend that the sacred mushroom of immortality doesn't have a pivotal role in unfolding the healing of humanity?

That said, we need to be very cautious. My anxieties about the misuse of ultimately potent visionary agents is very real. Maria Sabina herself has done some mortifying things leading to a young person dying of fear and the ayahuasceros and yopo snuffers have plotted curses against their enemies for witchcraft and resorted to poisoning their victims. All the societies that have used entheogens have in various extreme ways abused them too, setting up fearful shamanic visions of conflict, violence and mortality. So these allies and agents do have the power to heal the planet, but only in the hands of enlightened people who are selfless and devoid of delusions and pretenses. We need to be guides if we can muster the strength of character and non-violence to show people the way of unfolding. How can a person who claims to be a/the messiah of the Tree of Life not have delusions of grandeur? Because the mushroom speaks, I have no need of pretenses or any form of grandeur. Mushrooms made me realize my calling as Christo Rey twenty years before the millennium on a wild moonlit night in the wilderness. They took me to the Holy Land, where instead of being shut away in the Jerusalem syndrome psych ward, I was welcomed by liberal Jewish people as a kindred spirit and given the spiritual keys to the city.

I have taken and immensely enjoyed the intensity of ayahuasca, despite its nauseating dimensions, but for me sacred mushrooms provide the kindest, most organically acceptable face of the entheogenic abyss. They aren't quite as colourful as ayahuasca but the depths of the non-ordinary reality is as inscrutably potent and sufficient to bring one to terms with the ultimate incarnations of the bundle of life, death, the hereafter and the primordial beginning, alpha to omega. As the recent psychedelics conference in Oakland laments, the greatest tragic injustice of the entire Western tradition is the tabooing of entheogens by mainstream society under pain of inquisitional repression. This applies acutely to the repression of the sacred mushroom.

Mushrooms have given me extraordinary and horrific visions whose significance I still ponder to this day. Far from the Chilean ayahuasca messiah who burned his own baby alive because he thought it was the antichrist, I have nurtured all my children faithfully in the sacred way. I had a horrific vision that my firstborn daughter would be doomed to an obstruction to her own fertility as some sort of hideous sacrifice to my own destiny. Then her first offspring had Downs syndrome. What am I supposed to make of this? Is it sheer coincidence? Is it destiny? Is what happened somehow a consequence of having that deluded vision? Was it a prophecy, or was it a curse? What is the relationship between prescience and history? These are the difficult questions shamans have to learn to ponder, often with no answer but continuing participation in this 'magical' world, so long as we both shall live.

So, as the effects begin to stabilize, I look up at Maria Sabina's image, which always sits as a shrine on our mantle altar, and ponder the karmic connection I have with sacred mushrooms, with world destiny and with the healing of the planetary future and reflowering of sexual reunion of the generations of humanity, and of all life. Without sacred mushrooms I would be a nobody reading about mysticism and wondering what the mystery was. With sacred mushrooms, my life unfolds before me as a great journey, tacking my way up an endless fjord, with veladas marking the major tipping points where the journey of meaning turns about and we all duck for cover as the mainsail boom swings over our heads, amid strange affirmations from the world around us that this is not just an dream-like fantasy but the unfolding living universe to which we have become inordinate sensitives.

Because I partook mid afternoon, by mid to late evening the effects had returned to a mild high and I could sleep a reasonable night. Next morning I am fresh and clear in the sparkling sunshine. A new man in a world reborn with the youthful freshness of a new day, my creativity and sense of emergence rekindled.

"But I, I am lord of two ways. I am master of up and down. I am as a man who is a new man, with new limbs and life, and the light of the Morning Star in his eyes."
D H Laurence The Plumed Serpent

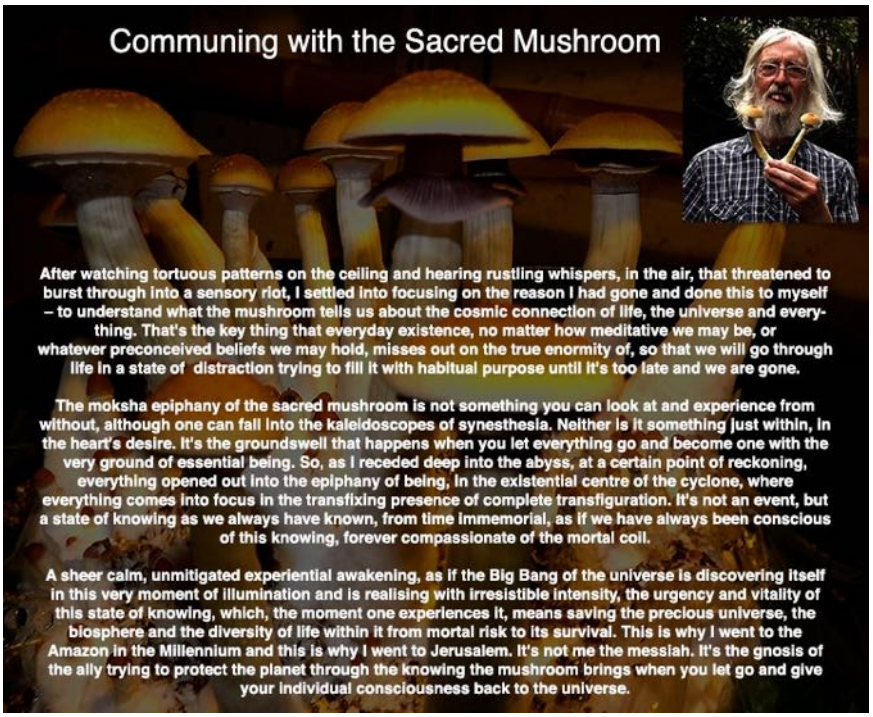
Is it my karma to tell the world that sacred mushrooms are the living sacrament of the Tree of Life, consummating the destiny of the living planet? That Christianity is merely a shadow - a sacrificial husk of a sacramental tradition lacking its sang-raal, instead living the sacrificial filicide of a God killing his only begotten Son to provide the empty sacrament of soma and sangre - bread and wine so that, instead of discovering the gates of immortality ourselves, we must believe in Him in the delusion that such violence of consuming the flesh and blood of the dead god will provide eternal life. At best one can say traditional religions in their delusion were pointing prophetically to this realization, so that Christianity as our precursor in the sacramental tradition is a forerunner of the unveiling of the holy grail.

The tragedy here as I see it is that sacred mushrooms are the most beneficent of the natural visionary sacraments but their tradition has been stifled by the DEA ad the war on drugs. Ayahuasca was never able to be conquered in the same way, because the Amazon is a law unto itself and the traditions of ayahuasca use have stayed strong in tribal traditions, amid resurgences of endemic worship like Santo Daime and the UDV. What is key to the unfolding is showing the world that sacred mushrooms are the holy communion which doesn't make one puke and actually feels pure and clean, so it could really become incorporated into the very fabric of an advanced enlightened society and become its raison d'etre without being a hard road to hoe.

So do I have a karmic connection here or what? Of course I am just one of a host of people who have taken sacred mushrooms and one of many enlightened people who try in their art, in their music, in their scientific research, or social projects, from remission of terminal angst, to inducing genuine spiritual experience among middle aged straight subjects, try to pave the way for an new world order of visionary emancipation. But the karmic connection remains. Who else stands alongside me as the Cristo Rey of the sacred mushroom in this way? Who else can show the way to bring the whole tortured tide of history, belief and delusion to its natural consummation? We know life is a free naked lunch, but how do we give back the flood tide of abundance while we still walk on this magical Earth?

Post-Covid Redoubt June 2021 Age 76. Today I finally took the bit in my teeth after several years of psychedelic abstinence. I had spent six months finally having my eye lenses replaced to eliminate the closed angle glaucoma that had threatened to bling me when psychedelics dilated my pupils, so I now again have 20-20 vsion and summoned up the courage to shatter my equanimity with another visionary experience.

After a bit of sex in the sack with my beloved partner, on a sunny winter morning, and a bike ride up to Mount Eden to flex my muscles, I took some home made cannabis butter at 3.40 to allow it advanced absorption and at 4 began to set a lemon tak tea. I used just 1.5 gm of dried mushrooms, ground in a mortar and pestle, added fresh lemon juice to cover and waited 20 minutes to convert the psilocybin to psilocin. I then tipped it into a tea strainer and poured boiling water from the kettle through it to fill the glass and soaked it for a minute lifting the tea strainer in and out to dissolve the active ingredient in the glass of lemon juice, added honey and down the hatch it went. The key is that this provides a relatively pure psilocin trip, because the lemon juice converts the psilocybin to active psilocin and the tea contains only the water soluble ingredients avoiding digestive discomfort. The result was a stunning mushroom high – pure and clean – absolutely no discomfort or anxiety – all food is wonderful – everything is fine except that I am rapidly peaking, leading to the moksha epiphany that ensued (right).



This is the most aesthetic mushroom trip I have experienced. Very intense, clean and relatively short. If you just have the one draft, at 4.30pm, by 10.30pm one is well back into relaxed normality with a light stone. Not debilitated. Very healthy. Completely affirming.

But then what to do about it? Well the psychedelic climate is getting more supportive as the planetary climate enters crisis. What I always would have been going to do is foster a mushroom-based nature movement based reflowering the living planet. Maybe it's gradually becoming possible.

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, I walked up to a woman, and stared down deep into her eyes desperately asking how I could ever find the way back to the Ixtlan of the real world, but she just shook her head smiling as a blast of spray hit my body on the promenade, one self was shooting upwards ever faster, and the third was bumping on the ceiling of my bedroom, reassuringly witnessing my body asleep in the bed below. In another formative expereince, I had two consecutive nightmares that I was being stung. My wife awoke before me to feed our infant daughter and I went back to sleep after telling her of the nightmare. An hour later I was stung wide-awake by a wasp which had crawled under the covers after my wife opened the bedroom window. This opened my eyes to the implications of precognitive dreaming. But here I relate a time-spanning dream during this entheogenic discovery process.

Last night I had another clear example. After not having had psychedelics for a year, I dreamed I was in a room with a group of people who were investigating a strange psychedelic which seemed to be affecting the nature of reality in a disquieting way, which I commented was unlike the psychedelics I knew, which didn't have such untoward effects. When I awoke it was a stormy late-Autumn morning and I noticed the forecast was for thunder. This made me think of my song "Thunder on the Plain" http://dhushara.com/nino/thunder.mp3 about magic mushrooms, and I suddenly recalled the dream I had had and described it in detail to my partner. A little while later while reading the science news I came upon an article and suddenly found myself uncannily facing the same reality: https://www.sciencenews.org/article/designer-drugs-hit-dangerous-lows-bring-new-highs. In the article is a report about people on a new psychedelic with an unexpected physical effect - stabbing themselves in panic - after taking what appeared to have been 25I-NBOMe. They specifically comment that neither LSD nor magic mushrooms are known to cause these harmful effects. So I dreamed an expereince, reported the dream physically in the real world and then had the experience it was about, in that order - a dream prescient of an about-to-happen reality. This raises ultimate existential questions about the nature of conscious experience. This anticipatory property of consciousness may be essential to avoid imminent threats in the wild (King 2014). A month before 9-11 I produced a song whose lyrics were uncannily anticipative of the event (ibid section 8).

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 and one study (Millay) claims success above random levels with remote viewing on psilocybin. 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

Oliver Sacks (2012) recounts the following experience with Artane – a muscarinic antagonist like scopolamine illustrating why I am reluctant to take this class of drug:

One Sunday morning I counted out twenty pills, swallowed them with a mouthful of water, and sat down to await the effect. Would the world be transformed, newborn, as Huxley described in "The Doors of Perception," and as I myself had experienced with mescaline and LSD? … I had a dry mouth and large pupils, and found it difficult to read, but that was all. There were no psychic effects whatever - most disappointing. I did not know exactly what I expected, but I expected something. I was in the kitchen, putting on a kettle for tea, when I heard a knocking at my front door. It was my friends Jim and Kathy; they often dropped round on a Sunday morning. "Come in, door's open," I called out, and as they settled themselves in the living room I asked, "How do you like your eggs?" Jim liked them sunny side up, he said. Kathy preferred them over easy. We chatted away while I sizzled their ham and eggs - there were low swinging doors between the kitchen and the living room, so we could hear each other easily. Then, five minutes later, I shouted, "Everything's ready," put their ham and eggs on a tray, walked into the living room - and found it empty. No Jim, no Kathy, no sign that they had ever been there. I was so staggered I almost dropped the tray. … I was not only shocked but rather frightened, too. With LSD and other drugs, I knew what was happening. The world would look different, feel different, there would be every characteristic of a special, extreme mode of experience. But my "conversation" with Jim and Kathy had no special quality; it was entirely commonplace, with nothing to mark it as a hallucination.

"Careful, Oliver," I said to myself. "Take yourself in hand. Don't let this happen again." Sunk in thought, I slowly ate my ham and eggs (Jim and Kathy's, too) and then decided to go down to the beach, where I would see the real Jim and Kathy and all my friends, and enjoy a swim and an idle afternoon. I was pondering all this when I became conscious of a whirring noise above me. It puzzled me for a moment, and then I realized that it was a helicopter preparing to descend, and that it contained my parents, who, wanting to make a surprise visit, had flown in from London and, arriving in Los Angeles, had chartered a helicopter to bring them to Topanga Canyon. I rushed into the bathroom, had a quick shower, and put on a clean shirt and pants - the most I could do in the three or four minutes before they arrived. The throb of the engine was almost deafeningly loud, so I knew that the helicopter must have landed on the flat rock beside my house. I raced out, excitedly, to greet my parents - but the rock was empty, there was no helicopter in sight, and the huge pulsing noise of its engine was abruptly cut off. The silence and emptiness, the disappointment, reduced me to tears. I had been so joyful, and now there was nothing at all. I went back into the house and put on the kettle for another cup of tea, when my attention was caught by a spider on the kitchen wall. As I drew nearer to look at it, the spider called out, "Hello!" It did not seem at all strange to me that a spider should say hello (any more than it seemed strange to Alice when the White Rabbit spoke). I said, "Hello, yourself," and with this we started a conversation, mostly on rather technical matters of analytic philosophy. Perhaps this direction was suggested by the spider's opening comment: did I think that Bertrand Russell had exploded Frege's paradox? Or perhaps it was its voice - pointed, incisive, and just like Russell's voice, which I had heard on the radio.

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).

12: Why the Neurotransmitters: Cosmology and Evolution

This brings us back to a fundamental question. Why does the brain use these neurotransmitters in such characteristic ways to do with emotion, wakefulness and sleep, vigilance and reward? This takes us back all the way to the emergence of life and to the cosmological relationships defining the biomolecules, from ATP to RNA, and the various biological amino acids. The elementary neurotransmitter types, many of which are fundamental amino acids (glutamate, glycine, GABA) or amines derived from amino acids (serotonin, dopamine, histamine, choline) have primordial relationships with the membrane, as soluble molecules with complementary charge relationships with the hydrophilic ends of the phospholipids.
Tryptophan, the amino acid from which serotonin is generated, plays a key role in the transfer of electric charge in the earliest forms of photosynthesis. In *Rhodobacter sphaeroides*, there are 39 tryptophan residues surrounding the porphyrin center. Initiation of the electron transfer reaction by excitation results in a transient change in the absorbance at UVB, near the peak of the tryptophan absorbance band.

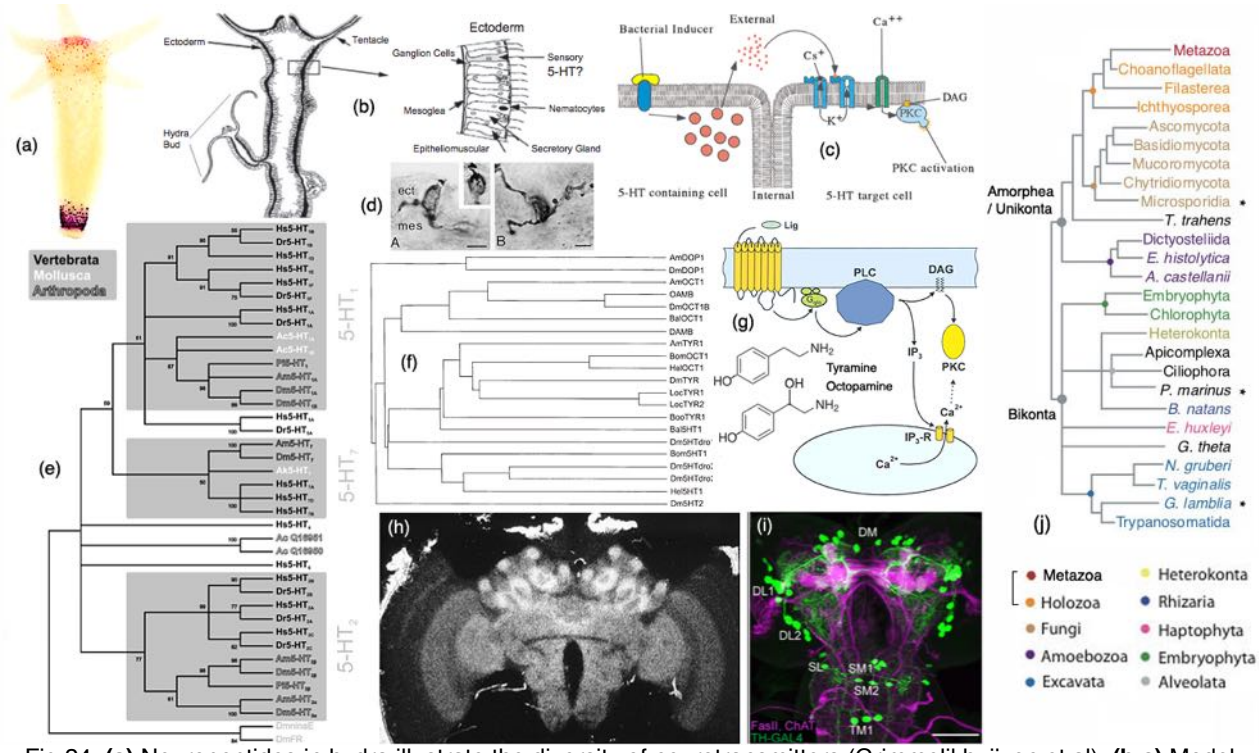


Fig 24: **(a)** Neuropeptides in hydra illustrate the diversity of neurotransmitters (Grimmelikhuijzen et al). **(b,c)** Model mechanism of serotonin signalling in coelenterates causing metamorphosis (McCauley et al) includes the diacylglycerol PKC pathway and **(d)** involves ectodermal neurons (Umbriaco et al). **(e)** Evolutionary diversification of 5HT1 and 5HT2 receptor families occurred before the diversification of molluscs, arthropods and vertebrates (Blenau & Thamm). **(f)** Evolutionary diversification of insect receptors showing serotonin, dopamine, taurine and octpamine (Blenau & Baumann). **(g)** Arthropod signalling uses the same pathways as in vertebrates (Blenau & Baumann). **(h)** Serotonin staining neurones in the honey bee, especially in mushroom bodies facilitating associative learning and olfaction (Blenau & Thamm). **(i)** Dopamine neurones (green) in the furit fly (Selcho et al). **(j)** Tree of G-protein coupled receptor components extends back to the last eucaryote common ancestor LECA (Mendoza et al. 2014) making this signalling pathway, central to the nervous systems of higher animals, a founding unit of eucaryote evolution. All except those marked with * had one or more GPCR components and all clades included species possessing canonical GPCR, across both unikonta and bikonta, implying a common origin with LECA.

To make serotonin from tryptophan, oxygen is needed, and in the earliest geological times the Earth's atmosphere had little oxygen. Thus, serotonin is made specifically in unicellular systems capable of photosynthesis and the cellular production of oxygen. Consequently serotonin is up to 100 times more plentiful in plants and animals have ceased to synthesize tryptophan depending on plants for their supply. This relationship with light continues to this day in human use of melatonin to define the circadian cycle and serotonin in wakefulness and sleep, with light deprivation causing depression through serotonin.

The fundamental components of the G-protein coupled receptor system, including the canonical GPCR appear to go right back to LECA the last eucaryote common ancestor as they are shared across all major eucaryote branches (Mendoza et al. 2014). From the gene diversity for serotonin receptors, the 5-HT1a receptor is estimated to have evolved 750 million to 1 billion years ago, before the muscarinic, dopaminergic and adrenergic receptor systems (Peroutka & Howell, Peroutka) and long before the Cambrian radiation defining multicellular animals. This places the emergence of receptor proteins and their neurotransmitters as occurring before the multicellular nervous systems as cell-to-cell signaling molecules essential for survival and positive and negative responses to nutrition and danger. The need for multimodal molecular messengers thus arises from the need for cells to have a variety of signaling molecules modulating key motivational and aversive aspects of survival strategy.

It also explains that neurotransmitters originated from direct signalling pathways between the cell membrane and gene expression in the nucleus of single cells, highlighting why changes in gene expression such as that of *egr*-2 in psychedelics may be central to psychedelic neurotransmitter action, rather than just flow-on excitation. It has also been suggested that key enzymes in neurotransmitter pathways may have become ubiquitous through horizontal gene transfer from bacteria (Iyer et al).

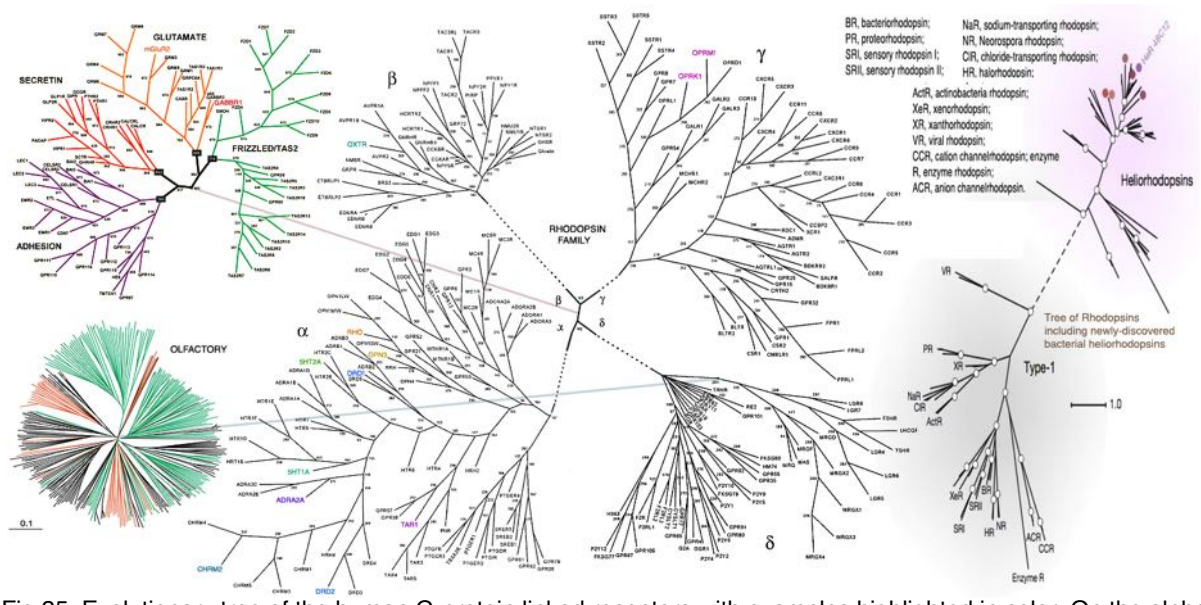


Fig 25: Evolutionary tree of the human G-protein linked receptors with examples highlighted in color. On the alpha branch are serotonin 5HT1A and 5HT2A, dopamine D1, and D2 (DRD1, DRD2), adrenergic α2a (ADRA2A), muscarinic acetylcholine (CHRM2), trace amine TAR1, as well as rhodopsin (RHO) and encephalopsin (OPM3). On the glutamate branch are metabotropic glutamate mGluR2 and GABA GABBR1. On the beta branch is oxytocin (OXTR) surrounded by vasopressin receptors and Ghrelin. On the gamma branch are opioid κ and μ (OPRK1, OPRM1). Olfactory and the non-rhodopsin receptors are linked to their respective points on the rhodopsin tree. (Fredriksson et al, Zozulya S. et al). Vertebrate olfaction also involves trace amine TARs, and rhodopsin-like and glutatmate-like vomeronasal receptors (Spehr & Munger). Insect olfaction uses both G-linked receptors and ionotropic receptors related to the NMDA receptor class (Abuin et al, Croset et al, Silbering et al). The 5HT receptors form evolutionary families in terms of the G-coupling types (Nichols & Nichols, Bockaert et al in Müller & Jacobs, Roth et al 2000). Gq/11-coupled 5HT receptor 2a, 2b, 2c activation leads to the hydrolysis of membrane phospho-inositides, resulting in the formation of diacyl-glycerol (DAG) and inositol phosphates, which then act as signaling molecules to activate, for example, protein kinase C (PKC) and elevate intracellular calcium, respectively. Gs-coupled 5HT receptor 4, 6, 7 activation leads to stimulation of adenylyl cyclases, resulting in the conversion of ATP to cyclic AMP (cAMP). Cyclic AMP is a ubiquitous intracellular messenger that interacts with numerous targets, including cyclic nucleotide-gated ion channels and the phosphorylating enzyme protein kinase A (PKA). Gi/o-coupled 5HT receptor 1a-f and 5a,b activation leads to inhibition of adenylyl cyclase and decreased production of cAMP as the primary functional end point. These receptors also form heterodimers both with one another e.g. 1a and 4 and with other receptors e.g. 2a and mGluR2. Dimerization can alter signaling pathway activation. Psychedelics are also believed to alter the G-protein expresso of the 2a receptor (fig 10). 5HT3 is an evolutionarily distinct ionotropic receptor. Right: Newly-discovered branch of bacterial heliorhodopsins (Pushkarev et al. 2018). Microbial and animal visual rhodopsins (classified into type 1 and 2 rhodopsins correspondingly). Microbial rhodopsins are currently considered to be universal and the most abundant light harvesting proteins on Earth. Rhodopsins are present in all the three domains of life (bacteria, archaea and eukaryotes) as well as in giant viruses (Kovalev et al. 2019). Despite diversity of their functions and differences in the structures, all these rhodopsins are oriented in the membranes in the same way. Their N termini always face the outside of the cells. In 2018 a new large family of rhodopsins, named heliorhodopsins were discovered, facing the cytoplasmic space of the cell with their N termini. It was found that they are also present in Archaea, Bacteria, Eukarya and viruses.

This ancient origin is confirmed by the fact that receptor proteins, second signaling pathways and key neurotransmitters are known to occur widely in single-celled protists. Both *Crithidia* and *Tetrahymena* were demonstrated to contain norepinephrine, epinephrine, and serotonin (Blum 1969). The aggregation of slime molds such as *Dictyostelium* is mediated by cyclic-AMP, in association with serotonin and MAOA and uses glutamate and GABA (Halloy et al, Goldbeter, Taniura et al, Anjard & Loomis, Baskar, Mani & Hyde). The ciliated protozoan *Tetrahymena pyriformis* (Brizzi & Blum, Essman) and flagellated *Crithidia fasciculata* (Janakidevi et al) utilize serotonin, and the former also metabolizes dopamine and epinephrine (Takeda & Sugiyama, Nomura et al). *Tetrahymena pyriformis* also has circadian light-related melatonin expression (Köhidai et al). Tetrahymena utilizes histamine, serotonin, epinephrine, melatonin, and triiodothyronine (T3), can be found in it, as well as peptide hormones, such as insulin, adrenocorticotropic hormone (ACTH), epidermal growth factor (EGF), endocannabinoids, endorphins and c-AMP and GMP. The receptors are selective and very sensitive; sometimes a concentration of 10–21 M is enough to provoke a cell's reaction. Hormones such as insulin which influences sugar metabolism, and thyrotropic hormone (TSH) which influences a cell's T3 content, in a similar manner to the effect of these hormones in mammals. Furthermore, interaction between the receptor and an adequate concentration of a signalling molecule causes a prolonged change in the cell's response to future encounters termed 'hormonal imprinting. This type of reactivity

remained after 500 to 1000, generations, indicating that an epigenetic change transmitted to the progeny. Thus signalling molecules in single celled eucaryotes appear to further long-term adaption through cross-generational epigenetic changes (Csaba 2012, 2014).

Trypanosoma cruzi could be induced to differentiate by increased cAMP levels that resulted from addition of epinephrine (Gonzalez-Perdomo et al). Species of Entamoeba secrete serotonin and the neuropeptides neurotensis and substance P (McGowan et al) and release and respond to catecholamine compounds during differentiation from the trophozoite stage into the dormant or transmissible cyst stage (Eichinger et al) and Plasmodium falciparum malaria replication can be blocked by 5HT1a agonists (Locher et. al).

Consequently the major neuroreceptor classes have a very ancient origin, with the 5HT1 and 5HT2 families diverging before the molluscs, arthropods and vertebrates diverged, close to the level of the founding metazoa. Sponges, with only two cell types, express serotonin (Wayrer et al) and have been shown to have the critical gene networks to generate synapses, in a pre-coordinated form (Conaco et al). Coelenterates already have all the key components of serotonin pathways, involved in signaling by sensory cells and neurons, despite having only a primitive nerve network (McCauley et al, Umbriaco et al).

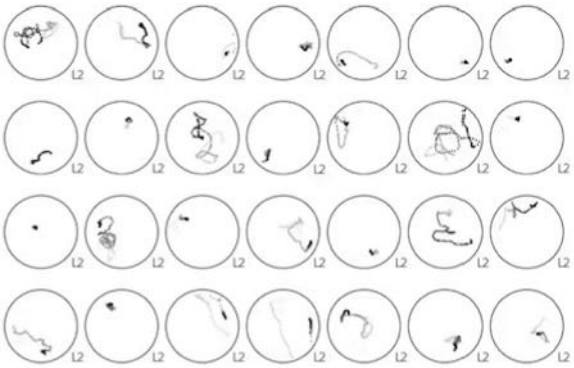


Fig 25a: Variations in foraging behaviour.

In the nematode worm Caenorhabditis elegans, dopamine, serotonin, and some neuropeptides have stage-specific effects on behavior, implying a modular temporal program controlled by neuromodulators. In addition, a fraction of individuals within isogenic populations raised in controlled environments have consistent, non-genetic behavioral biases that persist across development. Several neuromodulatory systems increase or decrease the degree of non-genetic individuality to shape sustained patterns of behavior across the population. The researchers explored several mutated clones which lacked serotonin or dopamine function or that of other neuropeptides. A mutation that disrupted dopamine affected the worms' roaming speed during late development. Other mutations affected behavioral patterns within each developmental stage, suggesting that different neuromodulators influence behavior over different timescales. Removing the chemical messenger serotonin from a population of worms drastically reduced the number of worms that displayed unique roaming patterns, or individuality. Indeed, without serotonin, all of the worms exhibited the same foraging behavior at the same time — a finding that suggests how important individuality is to survival (Stern, Kirst, and Bargmann 2018). Complementing this is a study of octopi, in which MDMA was seen to induce social behaviour reminiscent of human responses, confirming a similar significance of serotonin in social behaviour in molluscs (Edsinger & Dolen 2018). This finding is paralleled by the evolutionary conservation of the binding site of MDMA in the serotonin transporter (SERT, encoded by the Slc6A4 gene) in the *O. bimaculoides* genome, thus activating the transporter in the same way as in human beings.

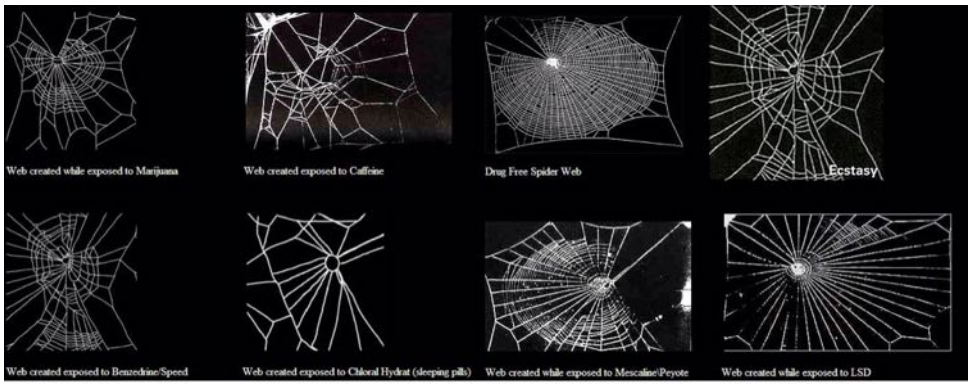


Fig 25a2: Variations in web spinning by spiders under the invluence of various of the psychoactive molecules mentioned.

A second indication of the commonality of neurotransmitters across wide branches of the animal kingdom are the varying webs spun by spiders under the influence of various psychoactive drugs as shown if fig 25a2.

Given this ancient origin, serotonin is also found to play a key role in development and embryogenesis. In Molluscs, serotonin is involved in the determination of the animal pole during early blastula stages (Buznikov et al). [H^3]–5-HT binding is seen in the blastula and gastrula of sea urchins (Brown and Shaver). In mammals, the expression of serotonin receptors occurs at the earliest stages of ontogeny and is activated by

circulating plasma serotonin from the mother. In the early stages of brain development, serotonergic neurons formed in the midbrain immediately sent out extensive fibers to the forebrain (Azmitia in Müller & Jacobs). In humans, 5-HT1a receptors are at their highest levels before birth (Bar-Peled et al). Thus we can see how the survival modalities of complex organisms have continued to be mediated by classes of neurotransmitters modulating key motivational, aversive and social dynamics with ascending central nervous system complexity. There are thus strong parallels in how the key classes of neurotransmitters modulate affect in organisms as diverse as arthropods and vertebrates.

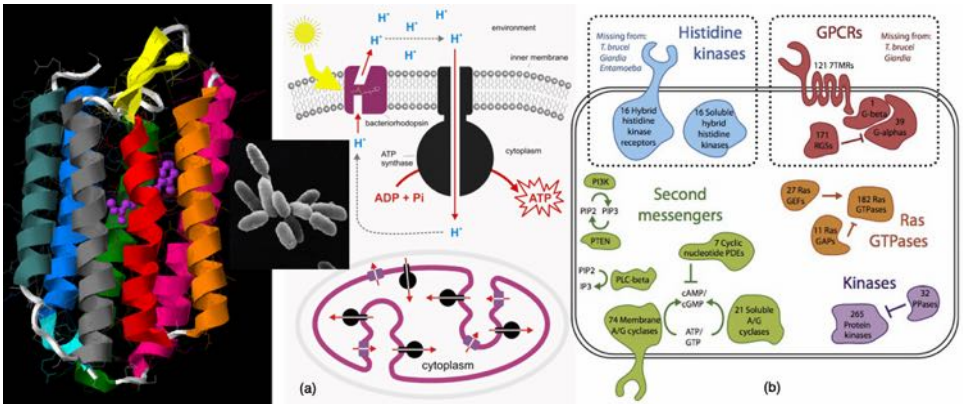


Fig 25b: (a) The extremely ancient origin of the rhodopsin family of heptahelical receptors can be seen from the ultra-primitive archaeal photosynthesis in the archaeal Halobacterium (inset), which lacks any form of electron transport, relying on direct coupling between photo-stimulated chemiosmotic H^+ pumping and H^+ generated ATP formation, based on bacteriorhodopsin, which is heptahelical, uses retinal and may share distant sequence homology with vertebrate rhodopsin (Pardo et al, Taylor & Agarwal, Soppa, Ihara et al, Shen et al. (2013). (b) Complement of signalling systems found in *Naegleria gruberi* (Fritz-Laylin et al. 2010), a free living single celled bikont amoebo-flagellate, belonging to the excavata, which include some of the most primitive eucaryotes such as Giardia and Trichomonads, showing that these organisms have lost ancestral functionality. *Naegleria* is capable of both oxidative respiration and anaerobic metabolism and can switch between amoeboid and flagellated modes of behavior. The Naegleria genome sequence has indicated that it contains actin and microtubule cytoskeletons, mitotic and meiotic machinery, several transcription factors and a rich repertiore of signalling molecules, including G-protein coupled receptors, histidine kinases and second messengers including cAMP. One strain analyzed is a composite of two distinct haplotypes indicating hybridization.

Functional studies in the honey bee and fruit fly have shown that serotonergic signaling participates in various behaviors including aggression, sleep, circadian rhythms, responses to visual stimuli, and associative learning (Blenau & Thamm). Serotonin in lobsters regulates socially relevant behaviors such as dominance-type posture, offensive tail flicks, and escape responses (Kravitz, 2000, Sosa et al. 2004). 5-HT-regulated social and mental behaviors increased in number and complexity as these functions became more advanced and complicated. The reward system in insects uses octopamine, which is the presumed arthropod homolog of norepinephrine, rather than dopamine. In insects, dopamine acts instead as a punishment signal and is necessary to form aversive memories (Barron et al, Schwaerzel et al, Selcho et al).

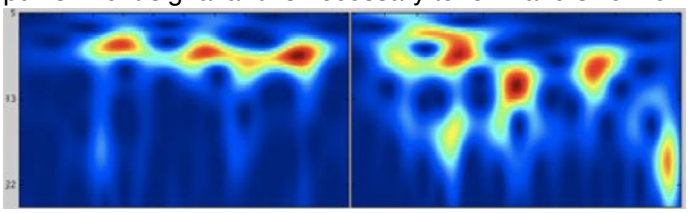


Fig 25c: Continuous wavelet transforms of human EEG left and fly H1 visual motion cell recording (Higgins) right show comparable time-dependent broad frequency excitation, suggesting similar modes of wave processing despite major anatomical differences.

Experimental evidence suggests that in flies dopamine modulates locomotor activity, sexual function and the response to cocaine, nicotine, and alcohol (Hearn M et al). Octopamine regulates desensitization of sensory inputs, arousal, initiation, and maintenance of various rhythmic behaviors and complex behaviors such as learning and memory, endocrine gland activity and induces mobilization of lipids and carbohydrates (Farooqui). Web building in spiders is likewise affected by stimulants and psychedelics (Dunn).

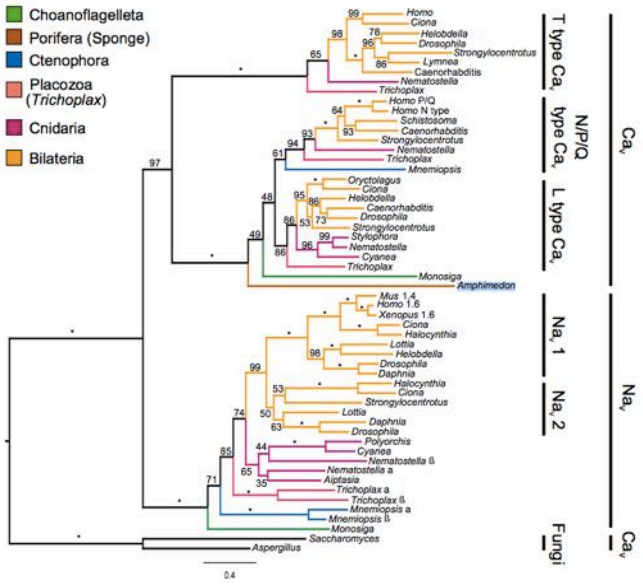


Fig 26: Evolutionary diversification of Na^{+} channels from Ca^{++} channels, essential for the action potential, appears to have occurred before the existence of nervous systems in founding single-celled eucaryotes leading to the metazoa before the choanoflagelates such as monosiga (Liebeskind et al).

The many reports of increased social dominance in primates (Edwards and Kravitz, 1997) and improved mood and confidence in social interactions in humans after using drugs which increase serotonin levels are well documented (Kramer, 1993; Young and Leyton, 2002). In these higher animals, 5-HT continues in its role of a homeostatic regulator in adjusting the dynamic interactions of these many functions within the organism, and how the organism interacts with the outside world. Similarly, dopamine and nor-epinephrine pathways modulate reward and vigilance, forming a spectrum of fundamental strategic responses in humans now phenomenally elaborated into an extremely complex CNS, but nevertheless modulated in its major organismic feedbacks through the same signaling pathways already evident in the amoebae and other protozoa. While in mammals only neurons and mast cells secrete serotonin, all cell types possess serotonin receptors, emphasizing the fact that it plays a key role, not just in brain-generated emotion, but the entire bodily tone. The serotonin systems are still in a state of rapid evolution. In the sea slug aplysia's nervous system there are only a few neurons that contain serotonin, and these neurons are large, with extensive connections. In the rodent brain, the 5-HT neurons are arranged in large groupings along the midline of the mescencephalon. The axons from these neurons ascend towards the forebrain in large bundles using mainly the ancient medial fore-brain bundle. In primates, the distribution of serotonergic neurons in the mescencepahlon is into smaller clusters of neurons. In addition, many of the axons from these neurons are now myelinated. This new arrangement facilitated more precise and rapid delivery of serotonin to forebrain targets (Azmitia, 1987).

Turning now to both metabotropic and ionotropic glutamate and GABA receptors, we find evidence of even more ancient origin in prokaryotes. Firstly the metabotropic glutamate and GABA receptors go back to the social amoeba Dictyostelium discoideum, where there is a family of no less than 17 GABA and a glutamate receptor involved in differentiation, showing these receptors too go back to single-celled eucaryotes.

The ionotropic receptors fall into three superfamilies: (1) the nictoninic and GABA receptors, as well as 5HT3, the cys-loop family, forming pentameric channels, (2) the ATP-binding channels, which also go back to amoebae, and (3) the tetrameric glutamate ionotropic receptors, including NMDA, AMPA and Kainate, which in the case of NDMA, have two types of monomer, binding glycine and glutamate respectively. The glutamate-binding “fly trap” section of both ionotropic and metabotropic glutamate receptors show homologies with the bacterial periplasmic amino-acid binding protein essential for maintaining bacterial molecular membrane sensitivity.

The membrane-spanning section of the iGluRs also show homology with the bacterial voltage-gated K^{+} channel, which appears to have been inverted in membrane orientation and inserted between the two extra-cellular glutamate-binding sections of the “fly trap”. These changes are already in place in the cyanobacterial GluR0 ionotropic glutamate receptor. Hence the two critical domains of this unit have arisen through genetic transfer of functional domains. The fact that an iGluR has also been found in *Arabidopsis* shows this class entered the eucaryotes before the plants, animals and fungi diverged. Elements of the protein signallinging pathways, such as protein kinase C, essential to neuronal synaptic contact likewise originated close to the eucaryote origin (Emes et al, Ryan & Grant). Likewise the *Dlg* family of postsynaptic scaffold proteins, which bind neurotransmitter receptors and enzymes into signaling complexes originated before the divergence of the vertebrates and arthropods but underwent two gene duplications in vertebrates leading to vertebrate cognitive complexity (Nithianantharajah et al).

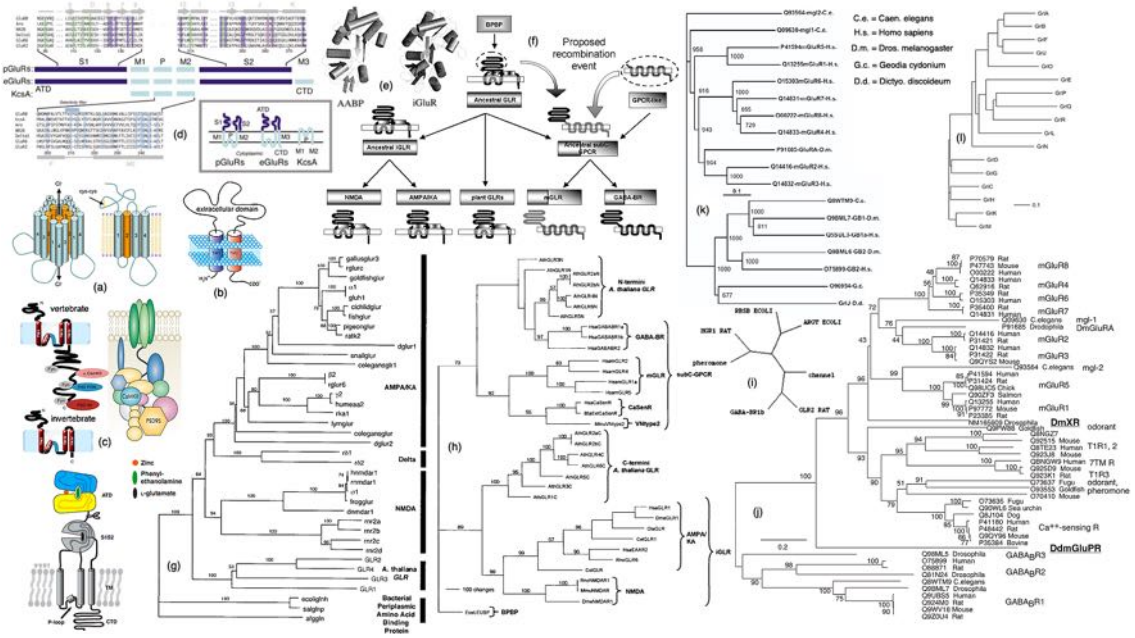


Fig: 27 The ligand gated ion channels consist of three evolutionary superclusters **(a)** The cysteine-loop receptors including 5HT3, GABAa and nicotinic acetyl-choline receptor, which are pentameric. The nicotinic acetyl-choline receptor occurs in vertebrates, insects nematodes and molluscs again suggesting an early common origin (Tsunoyama & Gojobori, van Nierop et al) **(b)** The ATP gated channels, which are active in trimers. P2X receptors are present in a diverse array of organisms including vertebrates, *Dictyostelium*, the platyhelminth *Schistosoma*, and the green alga *Ostreococcus* and possibly in *Drosophila* (North, Fountain et al, Burnstock & Verkhratsky, Dolezelova et al). **(c)** The ionotropic iGluR glutamate receptors NMDA, AMPA and kainate type, forming tetramers, in the case of NMDA consisting of two units each responding to glycine and glutamate (Ryan et al, Ryan & Grant, Karakas et al). NMDA recptors are shared by vertebrates, *Drosophila* and *Caenorhabditis* (Teng et al). **(d)** The membrane-spanning portions of iGluRs, including the GluR0 from cyanobacterium *Synechocystis*, and those of eucaryotes, consist of sections with sequence homology to the bacterial voltage-gated K^+ channel inverted so the extra-cellular orentiation is reversed (Chen et al). The “fly-trap” (Felder et al) binding domain to glutamate on the NMDA receptor has homology with the bacterial periplasmic amino-acid binding protein (Oh et al, Lampinen et al). **(e)** Homologous domains (Tikhonov D. & Magazanik). **(f)** This leads to a model of functional domain transfer to form the glutamate-binding region of both ionotropic and metabotropic glutamate receptors, including the plant ionotropic glutamate receptor form in *Arabidopsis*, confirming it entered eucaryotes before the divergence of plants, animals and fungi (Turano et al). **(g,h)** This evolutionary relationship linking prokaryotes and eucaryotes is confirmed in evolutionary trees with homolgies spanning both ionotropic and metabotropic glutamate receptors (Chiu et al, Turano et al). **(i)** Tree of bacterial periplasmic amino-acid binding proteins and related receptors in eucaryotes (Felder et al). **(j)** Evolutionary tree of metabotropic glutamate receptors showing that from the slime mold amoeba *Dictyostelium discoideum* as well as *Drosophila* and Vertebrate mGluRs (Taniura et al). **(k,l)** 17 member metabotropic GABAb family in *Dictyostelium discoideum* (Anjard & Loomis, Prabhu et al, Eichinger et al).

13: Conclusion

In an era when humanity has decoded the human genome and come close to unravelling the cosmological theory of everything shaping the universe, the nature of subjective consciousness remains an enigma confounding the scientific description of reality, which remains the central abyss confronting our understanding of nature. We need to open the doors of perception to understand the conscious condition.

In an era in which humanity has developed weapons of mass destruction, and is impacting on the planetary biosphere, potentially causing irreversible climatic change and a mass extinction of biological and genetic diversity, we need above all to come to better terms of understanding of our place in the universe, the role of sentient life in it and how to protect our unborn future generations.

For both these reasons, we cannot afford to taboo research and discovery into the nature of entheogens, which may form a central part of the solution to both these pressing problems. The capacity to experience the entheogenic state should be accepted as a fundamental right of every sentient being. Society needs to find safe, supportive and conducive ways of bringing the enthoegens back to the revered place they have held in virtually all societies throughout history.

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