ETHNOPHARMACOLOGIC SEARCH FOR PSYCHOACTIVE DRUGS

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YEARS *of*
RESEARCH
1967–2022

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55th Anniversary Symposium › May 23 – 26, 2022
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Foreword

On reading all of the papers in this book my greatest regret is that I did not attend the ESPD55 conference upon which it is based. This resulting book is a most important contribution to the study of psychedelic plants and fungi. It is full of good science and many interesting accounts of personal experiences of their use. The chapters here vary from descriptions of ritual and sacred ceremonies to DNA barcoding, the detailed molecular chemistry of sponges and neuroimaging. Many fascinating stories are told here, but this is not about the casual or tourist use of these compounds, rather it is a serious demonstration of the potential of these substances for medical uses based on good science. Something that immediately stood out to me is the great respect that the authors of each chapter have for the indigenous peoples with whom they associate or collaborate. This is a book in which the indigenous original discoverers of many of these chemical compounds are given due credit varying from the Matsigenka of southern Peru to the San people of Botswana. Richard Schultes who was one of the founding fathers of the ethnobotanical study of psychedelic plants is acknowledged in many chapters here. I am glad about this because, as Schultes was not present at the conference to write for himself, there is a chapter here about him and his huge contribution to research and teaching written by one of his former students Mark Plotkin. Two other people who are so frequently cited in the papers here for their contribution to the topic of this book are the McKenna brothers Terence and Dennis who really opened up this field of study. Dale Millard and Luis Eduardo Luna describe well the Wasiwaska Ethnobotanical Garden for medicinal plants that Terence helped them to set up in Florianopolis, Brazil. What a wonderful array of mind-altering plants are described here in some detail and that are cultivated in that garden. The existence of these species in this garden-preserve is increasingly important today as several of the psychedelic plant species are now seriously threatened by overharvesting.

In addition to accounts of contemporary research on psychedelics there is much interesting history of their uses given here which helps to put things into context and also helps us to understand the ancient uses of sacred plants. For example, we read about the uses of visionary plants by the ancient Tiwanaka and Wari people of Bolivia in 300-900 A.D. or the history of the sacred drink of the Zoroastrians of Iran. The use of the images depicted on ancient ceramics of the Pre-Columbian cultures Cupisnique, Paracas and Nazca clearly demonstrates the importance of the hallucinogenic *Anadenanthera* to them. Archeobotany has an important contribution to make about the ancient uses of psychedelic plants. Jonathan Lu in his chapter explains the long history of medicinal plants in China and shows that mind-altering substances from plants and fungi have played an important and often hidden role throughout the history of China. This chapter is an interesting comparison of the different attitudes to psychoactive substances between eastern and western cultures and it opens up a world that has been much neglected in the west. Another contribution from Asia is the chapter by Chris McCurdy on the alkaloid rich

leaves of Kratom (*Mitragyna speciosa*) a popular stimulant tea in southeast Asia, and a possible alternative to opioids in the west.

As a botanist it impresses me to see the wide range of the plant kingdom and even beyond which is used in some way to stimulate or calm the brain. This varies from *Ephedra*, a conifer in Eurasia, a lily bulb (*Boophone disticha*) in South Africa for leshoma, to many higher plants, such as the San Pedro cactus (*Echinopsis* species) and the forest liana that is the source of ayahuasca (*Banisteriopsis caapi*). But in addition, here we also read about the fungi that produce psilocybin and the marine sponges that contain tryptamines. I am also glad to see a chapter about the hunting medicines of the Matsigenka, as this is an aspect I have come across several times in my ethnobotanical research, particularly with the Guaraní.

There is much about the use of medicinal plants here. Elaine Elizabetzky seeks to use her ethnopharmacological research to improve the discovery of new drugs. Michelle St. Pierre and Zach Walsh demonstrate the potential use of psychedelics for the reduction of interpersonal violence and other psychotic disorders following up on some of the original ideas of Timothy Leary. Andrew Weil gives a very personal account of his use of coca in therapeutics. Coca also features in a good review of the history of its uses by Wade Davis. Both authors make an important plea for the legalisation of coca. It is distressing that this mild stimulant and calmant that so many of us have used is so vilified outside its use by indigenous peoples. This is one of the sacred plants of the peoples of South America that could easily be produced sustainably and used more widely if its use were to become legal. Can we convince the world of the difference between using a whole entire coca leaf from the isolation of the cocaine molecule? The pathways toward the legalisation of prohibited substances are well covered here in the chapter by Carey Turnbull which also discusses the rash of unwarranted patents on these substances. I am glad to see a chapter on intellectual property rights covered by David Rodríguez-Mora using ayahuasca and the Kofán people as a fine example of Community-Based Participatory Research.

There are three things that particulrly stand out to me. Firstly, is that most of the medicines and substances used are mixtures rather than a pure compound. So much of the effect produced is from the chemical interactions between a mixture of plant parts that occurs in the brew. Ayahuasca is not the same without chacruna (*Psychotria viridis*) and in coca it is the whole leaf that is used and not just pure isolated cocaine. Secondly the plant species involved do not always produce a consistent amount or quality of the compound involved. There are many genetic varieties of most plants that may have different levels of production. In addition, the production of a particular compound may be strongly influenced by the environment, the soil, or the climate conditions. Thirdly the authors here understand the magical and sacred nature of the plants that they are studying, and this is often through their own personal experience of their use in authentic ceremonies with the native peoples. Those of us who have been through various ceremonial plant practices with our indigenous friends are often concerned about the use of these plants outside their place of origin. Jeronimo Mazarrasa provides here a very astute and useful analysis of this indicating both the positive and negative aspects.

In these times of environmntal crisis I am glad to see concern expressed in several chapters about the threats of extinction by over harvesting of some of these sacred plants. This generally happens when the use extends beyond that of the indigenous peoples who know how use them

sustainably. There is a great need to promote sustainable production rather than the harvest of the last specimens from their natural habitats as is emphasised here both by Michael Coe and Barrett McBride for the case of ayahuasca. Laurel Sugden and Josip del Rio emphasise that the endangered San Pedro cactus (*Echinopsis*) of Peru is fast disappearing as a result of massive over-harvesting. These authors are even cautious not to mention exact location of the plants to protect them from harvest by tourist or commercial users rather than serious indigenous users. Andrea Langlois and Jeronimo Mazarrasa show how the commercialization of ayahuasca, iboga and magic mushrooms are all seriously overharvested due to their increasing popularity. They also address the important question of: What happens when the rituals become commercial products? In promoting the conservation of the species involved we also need to do as much as possible to preserve the cultural knowledge associated with them. Most of the writers here have experienced and understand the sacred nature of their use and this must not be lost amongst the creators of these rituals.

It is good to see that the study of psychedelic plants is continuing well as Sugden and some of the other authors, including Colin Domnauer, were doctoral candidates when they wrote their chapters for this book. The work of the pioneers such as Schultes, the McKenna brothers and Tim Plowman is continuing on in good hands for the benefit of future generations.

—Ghillean T Prance FRS, FLS, VMH

Beyond the Doors of Perception: What Else Can William Blake Tell Us about How Psychedelics Work?

David Nutt, PhD

Professor of Neuropsychopharmacology and Head of the Centre for Psychedelic Research, Division of Psychiatry, Imperial College London

"Our recent neuroimaging studies of depressed patients recovering after psilocybin treatment reveals that the increased connectivity seen during the trip persists for weeks afterwards and is associated with increased flexibility of brain function, an outcome not seen with traditional antidepressant treatments." —David Nutt

David Nutt shares with us how psychedelics work both in the brain and clinically. He also shares a fascinating perspective on how artist, poet and thought leader William Blake from England in the 1700's is connected to the psychedelics movement.

Many people are aware that Aldous Huxley used a famous phrase from William Blake as the title of his first book on the psychedelic experience – The Doors of Perception. The title of his is later book on psychedelics, "Heaven and Hell" was also taken from one of Blake's works "The Marriage of Heaven and Hell". Clearly Blake had a major impact on Huxley's understanding of the impact of psychedelics on his mind. As a child Huxley had had ambitions to become a scientist like many of his family (his half-brother Andrew Huxley later won the Nobel Prize for medicine and physiology), but eye problems precluded this possibility, so he turned to the study of literature whilst keeping close to science.

Like Huxley I encountered Blake before psychedelics, in my case via his "songs of innocence and experience" that were being studied at the time (1968) by my then girlfriend Jan. When I went up to Cambridge in 1969, she and I visited an exhibition of his paintings at the Fitzwilliam Museum where I discovered Blake was also an artist. But it wasn't until I started reading the works of Aldous Huxley that the importance of Blake's writings for him became apparent and I began to reflect further on Blake's insights and philosophy of the mind. More recently as my own research on psychedelics has developed, they have helped me make sense of the effects of psychedelic drugs on the workings of the human mind.

In this chapter I review how modern neuroscience studies on psychedelics have revealed Blake's insights to have been extraordinarily prescient. I then explore some of the other writings

and art of Blake that further help us understand the human mind and how psychedelics may work to change these, ending with the tension between science and feelings that underpinned Blake's disagreements with Newton.

The Neuroscience of Psychedelics

The last ten years have provided a revolution in the science of psychedelics. One of the prime movers of this has been a series of brain imaging studies, mostly fMRI but also EEG/MEG, that have revealed an unexpected disorganisation of brain rhythms during the psychedelic experience. This state has been called the entropic brain and helps explain many of the features of the psychedelic trip. The entropic state is produced by psychedelics activating the serotonin 5-HT2A receptors on a group of neurons that are located in the deeper layers of the cerebral cortex – the layer 5 pyramidal neurons. These neurons are critical for the ability of the brain to connect its vast range of different activities; they provide cross-cortical information transfer that allows the brain to construct the range of images, sounds, feelings, thoughts and ideas of which it is capable. When the function of these neurons is disrupted, the brain cannot perform its normal integrative processes and so a state of altered consciousness is produced.

To understand these effects, we have first to understand some basic aspects of how the brain works. A description of this for the visual system is provided in Figure 1. The brain is not a camera, it does not take millions of pictures of the world day after day. This would be extremely energy inefficient and would use up the memory capacity of the brain very quickly. The way the brain allows us to "see" is by creating a hypothesis of the outside world based on the electrical signals that reach it from the retina. This process is explained in Figure 1.

When we look at anything, photons of light from the outside image enter the retina and activate photoreceptors (rods and cones) in the eye. This photoreceptor activation then changes the firing of neurons in the retina which begin to organise and collate inputs from many receptors, and then send their own outputs as electrical impulses to the brain via the optic nerve. Different retinal outputs go to different regions of the visual cortex system which are located at the back of the brain. Different regions of the visual cortex are responsible for receiving and then decoding specific elements of the retinal outputs- e.g. colour – shape – movement. Then these different analyses are pulled together to create an estimate of what is outside – i.e. what has generated the retinal signals. In other words, the visual cortex creates a hypothesis of the outside world based on analysing the light entering the eye.

Often the brain then tests this hypothesis – e.g. when we see something that looks like an appetising piece of food we might move to eat it. If it isn't food but maybe a piece of coloured paper, we rapidly learn this. The hypothesis is then re-framed and we don't repeat the mistake the next time we see the coloured paper. Such learning processes occur very early in life as babies begin to explore the world, and continue till death. Similar inferential processes apply to all different forms of sensory inputs – all sensations are brain constructs that are then tested out and either validated or re-made. In the words of one of the founders of modern neuroscience Helmholtz "the brain is an inference-making machine". This explains why the brain is so much more energy efficient than any computer. Its software is analytical and iterative. The brain continually

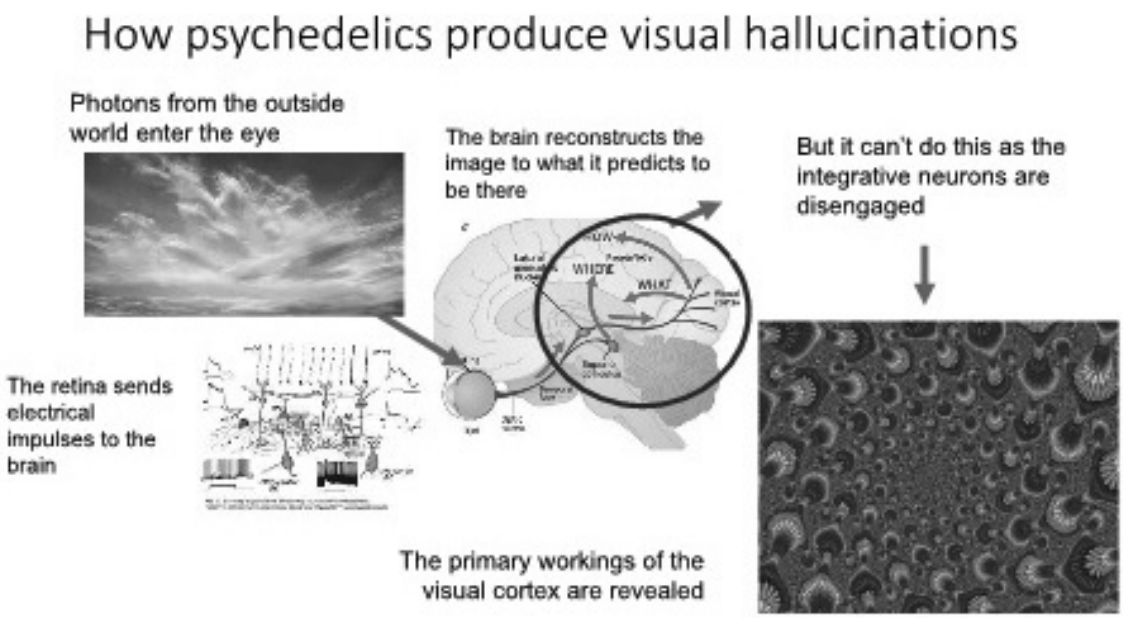

Fig.1 How psychedelics affect vision. Images sourced from (Orpwood 2013).

upgrades the estimates it makes. Modern AI computing programmes use a similar approach to learn and improve their decision-making as it repeats its assessments.

As mentioned earlier serotonin-receptor acting psychedelics such as psilocybin and LSD powerfully disrupt these predictive processes. This is because the neurons responsible for the integration of the activity of different parts of the brain (the layer 5 neurons of the cortex) have a very dense expression of the 5-HT2A receptors that psychedelics bind to. When psychedelics bind to these receptors this activates and dramatically increases the firing of these neurons. This disrupts their ability to integrate activity across different regions – so this critically important function of the brain breaks down.

So, for example in the visual cortex this means that a normal hypothesis (the "picture" that the brain produces) of the outside world cannot be generated because the different parts of the cortex that need to work together to produce this "picture" are not optimally integrated. Therefore, they cannot produce their usual best estimates of what is out there producing the retinal inputs. The sensory inputs from the retina are still present and can be experienced, but not computed into a full image. The pretty coloured simple (elemental) visual hallucinations (often described as like Christmas tree lights) so common with psychedelics I think can be explained as the person experiencing the early workings of the primary visual cortex.

We know from work in other animals such as frogs the first stage of a brain creating images from retinal inputs is to create simple shapes, that are then coalesced into more complex images. These simple geometric images are normally not seen because they are immediately fused into a whole completed image which the person perceives as the outside world. So, one remarkable aspect of the psychedelic state is that it allows people to experience this early-stage primary level

function of the visual system. This is a special experience that probably only previously happens in the very early weeks of a baby's life before the visual system's cortical networks become fully developed and functionally integrated.

Another much rarer example of this disrupting phenomenon of visual reconstruction was shared with me by a magic mushroom user who in a memorable (maybe unforgettable?) trip had a period when the world was upside-down. To understand how this could occur we have to remember that the lens of the eye inverts the light form the outside world, so the image of the outside world on the retina is upside down. Our brain learns from a very early age to adjust for this this, to flip the images to the same plane as we are, so we can function in our usual upright mode. I think the experience of the upside-down world was because under psilocybin this process was interrupted: for the upside-down period the person saw what the retina sees all the time, an upside-down image of the world.

Sometimes psychedelics especially *Amanita Muscaria* can produce alterations in the perceived size of objects – think of Alice in Wonderland and the growing and shrinking potions. The perception of the size of objects in the outside world is a special feature of the visual system that is particularly affected by the active ingredient in *Amanita Muscaria*– muscimol. This stimulates GABA receptors that are highly expressed in the visual cortex and so alters function in that part of the visual cortex that predicts the perceived size of objects.

Another profound experience produced by psychedelics is the sense of body disorganisation or dissolution. People often describe a sense of changing body form and position, sometimes moving into another place or different dimension. Other times they experience a sense of atomisation with their body dispersing into atoms. These experiences occur because the psychedelic disrupts a part of the brain called the posterior cingulate cortex, where our sense of self is generated. If this self-generation process is interrupted, we can feel our body as being very different and possibly somewhere else. Electrical stimulation of this part of the brain performed during brain surgery can produce similar "out of body" experiences.

The initial hypotheses (inferences) the brain generates and then tests are called "priors". These exist in relation to both the external world of the senses e.g., what we expect to see in a particular place, and to the internal world of all brain processes such as language, cognition, emotions etc. Of course, these are harder for the brain to evaluate than those predicting sensory inputs because they are harder to test. That requires introspection, self-awareness and perhaps communication with others of our species. In this way the brain orchestrates and defines the content of its productions and activity in relation to both the outside and inside worlds. This then becomes the content of the mind – the brain determines the content and hence the focus of the mind.

I now believe that conditions such as depression and addiction come to dominate a person's behaviour because their brain develops false assumptions and then fails to correct them. These incorrect ways of thinking (priors) are wrong or maladaptive but become more and more dominant because the evaluation system has broken down. Worse – in some cases rather than reappraising the priors they become reinforced; more on this later.

As well as altering perception psychedelics also open the mind. This is graphically illustrated in the image below in which different brain regions are positions around the edge of the circle

and the connectivity between as the size of the black lines. The left-hand image shows the connectivity of the brain after placebo and the right-hand image that after psilocybin. Each image has the same number of connections but in the normal (placebo) brain state these are mostly around the edge – local connectivity within specific brain circuits e.g., within the visual network or auditory networks. This is called the "small-world" brain. It is developed in all of us by years of generating and testing inferences about the inner and outer worlds that started as babies and is reinforced by schooling and other forms of education. These connections are very efficient in allowing normal daily life functions. Although this form of brain functionality is very efficient in terms of energy use and explains why the brain is ten times more efficient than any known computer, it comes at a cost – inflexibility and loss of creativity. And if the efficient connections are maladaptive then mental illness can result.

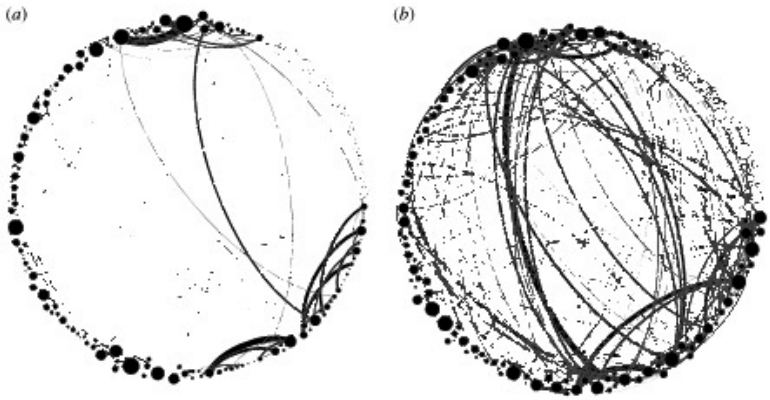

Fig.2 Graphic illustrations that show different brain regions connectivity after placebo (a) and after psilocybin (b) (Petri et al, 2014).

Under psilocybin there is a massive increase in connectivity because the control centres of the brain are disrupted. This allows areas that have been functionally disconnected since childhood to reconnect during the trip. We believe that this enhanced connectivity explains why psychedelic trips allow people to think differently about their past and remember events that have been supressed. It also allows new ways of thinking about how they might deal with these memories and also gives new insights into how they might deal with the future providing new solutions to old problems. Moreover, the enhanced neuroplasticity that psychedelics also produce can help these new ideas and plans embed in the brain and so endure well beyond the trip. This explains the long-lasting clinical outcomes of psychedelic therapy which we cover in the next section.

The psychedelic opening of the mind, allowing it to return to a more child-like state is a remarkable finding. We have already mentioned how Huxley utilised Blake's concept of "the doors of perception" to explain his psychedelic experience and will talk more about that later. But another of Blake's great creations were his poems for children, the songs of Innocence and Experience. Here is one that sums up that transition from the innocent open mind of a child where all things are possible and pleasurable to the adult experience of loss and depression.

The Garden of Love

I went to the Garden of Love,
And saw what I never had seen:
A Chapel was built in the midst,
Where I used to play on the green.
And the gates of this Chapel were shut,
And Thou shalt not. writ over the door;
So I turn'd to the Garden of Love,
That so many sweet flowers bore.
And I saw it was filled with graves,
And tomb-stones where flowers should be:
And Priests in black gowns, were walking their rounds,
And binding with briars, my joys & desires.

Clinical Research With Psychedelics

Psychedelic drugs such a psilocybin LSD and DMT/ayahuasca offer remarkable insights into how the brain works. They also change user's minds, an experience established by many who have taken them and perhaps best encapsulated in the recent book by Michael Pollan, "How to change your mind".

In a way psychedelics have also changed my mind. When I started out using neuroimaging to explore the effects of these drugs on the brain, I had no inkling that I would soon be writing grants to study psilocybin as a treatment for depression. My neuroimaging work was undertaken to explore the nature of the psychedelic experience and to gain insights into the role of the serotonin 5-HT2A receptors that these drugs stimulate. At the start of this research, I was clueless to the fact that it would explode into the revolution in neuroscience and psychiatry it is today: I saw them initially as tools to explore brain function.

The fact that they are now the most significant innovation in psychiatry treatments in the past 50 years tells us several things. One is that psychiatric medicine hasn't made much progress over the past 50 years. All the drugs we use today are derivatives of drugs discovered by serendipity in the 1950s. True their molecular structures have been refined so they are safer especially in overdose, but there has been no equivalent improvement in efficacy. Treatment innovation hasn't developed as predicted in parallel with the massive rise in neuroscience knowledge that has occurred in the past 30 years.

The second is that basic research into brain mechanisms can be relevant to treatment innovation. We had no idea that the brain images we obtained from our first psilocybin MRI studies would uncover a new more powerful route to treat depression, especially those which had failed to respond to conventional antidepressant and psychotherapy treatments. Our transition from imaging psychedelic effects on the brain to treating depression is a remarkable example of translational medicine. Our brain imaging revealed psilocybin to have an impact on the brain circuits that underpin depression in a manner similar to that seen with other treatments of depression

such as antidepressant drugs, electroconvulsive therapy (ECT) and even Cognitive Behavioural Therapy (CBT). Like all these other successful treatments psilocybin decreased activity in a part of the brain that is known to drive depressive thinking, the (sub-genual) pre-frontal cortex. This led us to argue a trial in depression was warranted, the UK Medical Research Council agreed, and the results were remarkable.

We treated 20 people whose depression had not responded to at least two antidepressant medicines (some had tried over ten) and all had not responded to CBT. These patients were very much treatment resistant. We found a single psychedelic (25mg) dose of psilocybin produced more powerful antidepressant effects than any previously reported antidepressant treatment in treatment-resistant patients before. It halved the depression scores within a week (usually the effect was seen the very next day) and in a few of these patients the depression has stayed at bay for over 8 years. Sadly, in the majority of the patients the depression began to creep back over the next 6 months and some eventually returning to as bad a state as they were in before (Carhart-Harris et al, 2016).

How can we make sense of these phenomena? How does depression get set in the brain to an extent it doesn't respond to traditional antidepressant medicines or to psychotherapy? A key feature of depression is rumination, repetitive thought loops with negative valence, often of low self-worth or guilt. Even when the person realises that these are plainly wrong or at least out of proportion to what they have done the thoughts can be very hard to stop. And eventually they can become so ingrained that the person doesn't even challenge them, they become "true". The biological basis of this ingraining – sometimes called thought canalisation – is discussed in depth in this recent review (Carhart-Harris et al, 2022).

This is not a new idea, and can be seen in the concept of Buddhist "formations", as described by Andy Olendzki, a Buddhist scholar (Germer and Siegel 2012):

> *'An image is offered in the Pali texts of early Buddhism to help us understand what formations are, and I think it is an image remarkably adaptable to our current understanding of the brain and its architecture. Picture a chariot driving across a dusty plain. The chariot may presumably be steered wherever its driver wishes to go, within the constraints of the terrain. It might have to dodge around some rocks or stay away from the swampy areas, but it is under the driver's volitional control. This image captures the first sense of formations: the intention or executive function in the mind that makes moment-to-moment decisions.*
>
> *Then, as the chariot actually traverses one path or another, it makes an imprint of the wheel upon the earth. This imprint represents the actual carrying out of an action or activity. In Buddhist thought every moment entails some sort of action, by body, speech, or mind, and all such activity is called karma, a word that basically just means "action." The second meaning of "formations" has to do with the fact that volitional activity leaves traces—the tracks of the chariot are embedded in the dust on the plain for all to see. One can gaze out over that plain and have a very good idea of where the chariot has been because it leaves a. clear record of its activity carved in the ground. Moreover, if it takes the same route many times over, a path (or even a rut) gets constructed, so the entire history of that chariot's activities is recorded in the patterns it has laid down on the plain".*

We can use the analogy of the ruts to explain how depressive thinking gets more and more ingrained in the brain. The more we go over the same thought the deeper the rut it produces, so escaping from it gets harder and harder, its less and less under volitional control.

The reasons for the return of the depression are at present unclear. It seems that the longer the depression has been present the more likely it will be to come back. We presume the more times the person has gone over a negative thought the more ingrained it and the depression becomes, so the harder it is to eliminate fully. Though psychedelics can disrupt ongoing depressive thinking the underlying brain processes might remain dormant and later resurface if not fully dealt with.

How best to prevent relapse is one of the biggest questions facing the field at present with a number of possible options. One is more intensive or enduring integration psychotherapy such as the new ACER approach developed by the lead therapist on our trials, Dr Rosalind Watts.[1] An alternative would be to use another "top-up" dose of psychedelic when the depression creeps back. A third option would be to reinstate one of the antidepressants that had previously proved ineffective, since it might now work in a prophylactic fashion in the new improved brain state: perhaps even a mood stabiliser against depression such as lamotrigine might work?

Subsequent trials by us and other groups at Johns Hopkins university and the new pharmaceutical company COMPASSPathways have confirmed the antidepressant effects of psilocybin (Goodwin et al, 2022). Moreover, our comparative study of psilocybin versus the gold standard selective serotonin reuptake inhibitor (SSRI) escitalopram (Carhart-Harris et al, 2021) confirmed our hypothesis that psilocybin worked in quite a different way to the SSRI's (Carhart-Harris and Nutt, 2017). Again, using fMRI neuroimaging we found that psilocybin increased connectivity and flexibility in the brain whereas escitalopram did not (see later). However as predicted escitalopram reduced activity in the emotional circuit of the brain – especially the amygdala – whereas psilocybin had no impact there.

These findings mirror the reported experiences of patients. Those who recovered on psilocybin report increased flexibility of thinking with greater connectedness to other people, to nature and to the world. They often use computer analogies to explain this feeling. Some say it's like when you reformat or de-frag the hard drive of a computer to clear away the bugs or background programmes that are interfering with its normal running. Others talk about cleaning out a virus that impedes fluent running. Most say that their minds are much freer- they have escaped from the internal loops of negative thinking that are the cardinal feature of depressive thought processes. These experiences probably explain why wellbeing is so markedly improved after psilocybin treatment (Watts et al, 2017).

In contrast escitalopram lifts mood by protecting the emotional circuits of the brain from stress. These regions become super-sensitive in depression and so perpetuate the low mood and other disturbances such as loss of appetite and insomnia. Escitalopram in common with all SSRI's and other traditional antidepressant medicine dampens stress-reactivity in this circuit, and so allows that part of the brain to heal. This process takes many weeks, which is why SSRI's do not reveal their full therapeutic effect for 6-10 weeks. But one drawback of the suppression of activity in this brain circuit is that the responses to all emotions are supressed, and many patients on SSRI's complain of an unwanted dampening of positive emotions that accompanies the (desired) dampening of their sensitivity to stress.

As a result of this and many other supporting studies from other research labs we can now be pretty certain that psychedelics offer a new and unique was of lifting depression, quite different from that of traditional antidepressants. This is exciting for researchers and pleasing for patients – they now know if one treatment fails, they have another totally different one to try – once psychedelics become approved medicines.

The Mind Of William Blake

As a child Blake was moted for seeing visions of religious figures, for example at a garden party he claimed to see the Prophet Elijah under a tree. This ability to "see" things that were not there, or at least that others could not see, is common in great artists, performers and visionaries. Blake knew he was different from most others. In a letter written in 1799 he said "*I know that This World Is a World of Imagination & Vision; I see Everything I paint In This World, but Everybody does not see alike. (...) Some See Nature all Ridicule & Deformity & by these I shall not regulate my proportions, & Some Scarce see Nature at all. But to the Eyes of the Man of Imagination Nature is Imagination itself. As a man is So he Sees."*

Seeing things that others can't is reminiscent of the impact of psychedelics on perception, particularly the tendency for believers to experience religious content or contact with meaningful others such as entities. It is thought that this power of Blake's to see things very differently to others underpinned the very novel and "unworldly" nature of much of his art. And of course, he was aware that others couldn't see in the same way as he could – being limited in their vision by social norms, education and ignorance. It was this insight that led to the quote *"If the doors of perception were cleansed everything would appear to man as it is, infinite. For man has closed himself up, till he sees all things thro' narrow chinks of his cavern"*. Many users of psychedelics would confirm that only in the trip can the human mind really appreciate the infinite.

This quote was used by Huxley for the Doors of Perception because Huxley realized that mescaline had opened the chinks in his mind's cavern, allowing him to see things very differently. He then made the logical inference that if mescaline had opened his mind something must have been closing it. The most likely explanation for Huxley was that that something was the brain and so he theorized that "*the brain is an instrument for focusing the mind"*. This hypothesis of Huxley's was conceived in 1953 and has been substantiated over the subsequent decades by sophisticated neuroscience research from many pre-clinical labs. The final proof that this is true for humans I believe came from the current neuroimaging studies of psychedelics. As described above psychedelics alter brain function in a way that disrupts the long-practiced predictive ongoing processing of external inputs and internal constructs. This disruption changes consciousness usually in a direction that is mind-opening. Hence Huxley was correct – psychedelics change brain function and so allow the mind to open.

But Blake's quote meant more than just open your eyes, he understood that all aspects of human consciousness were limited in the same way, in all aspects of life most of us fail to see the bigger picture. What is less well known is that more of Blake's insights and visions are also relevant to other aspects of psychedelics and psychedelic therapy.

The paintings of Blake such as his image of God, other biblical characters and the scientist

Newton are some of the most recognised works of English art. Though ignored and actively opposed in his own time for his liberal philosophies he is now universally recognised, which is why he is considered by Jonathan Jones the 21st-century art critic to be *"far and away the greatest artist Britain has ever produced"*. Blake was also very religious but from a personal spiritual perspective, and so conflicted with the Church of England and other organised religions. The poem already quoted – The Garden of Love – clearly expresses his view of the established religion of the time.

Blake was a supporter of the ideas of the French and American revolutions and the philosophy of Thomas Paine who in his treatise on the Rights of Man said *""Whatever is my right as a man is also the right of another; and it becomes my duty to guarantee as well as to possess."*
Blake's poem "The little black boy" shows his support for racial equality:

My mother bore me in the southern wild,
And I am black, but O! my soul is white;
White as an angel is the English child:
But I am black as if bereav'd of light.

And thus I say to little English boy.
When I from black and he from white cloud free,
And round the tent of God like lambs we joy:
I'll shade him from the heat till he can bear,
To lean in joy upon our fathers' knee.
And then I'll stand and stroke his silver hair,
And be like him and he will then love me.

Blake was also a committed rationalist building on the social aspirations of the Enlightenment. He was vocally anti-war and anti-slavery and in favour of female equality, three traits that made him a threat to the establishment of the time. This fear was rekindled in the 1960s by the rising use of LSD in freethinkers who too wanted to change society to one that was more just and equal and, especially in the 1960s, not engaged in warfare, particularly with Vietnam.

He was once tried in court for his views. This originated in a war of words with a soldier called Skofeld that led Blake to being accused of treason and taken to court. Though acquitted, this episode led him to write in his most famous work, *Jerusalem,* how soldiers were controlled and made to fight because society had made them tie themselves up with their "*mind forged manacles'*. After this episode Blake produces the print shown on the next page.

There is little doubt that after the *"doors of perception"* Blake's most well-known phrase is *"mind forged manacles"*. Though he first applied it to soldiers it had more general applicability e.g. to those workers choosing to leave the countryside and go to work in the "*dark satanic mills"* of the northern industrial towns. The theme of the Jerusalem book is this enslavement of the people, their complicity in this process because of their manacled thinking, and how insights such as the "*arrows of desire"* could be used to help them escape from these manacles.

Fig.3 The Emanation of the Giant Albion Plate 51. Here Skofeld' is wearing "mind forged manacles" in Jerusalem.

"Mind forged manacles" is a powerful analogy for how the brain controls behaviour. This is now a central aspect of my neuroscientific view of how the brain is involved in conditions such as depression and addiction and helps offer new ways to think about how psychedelic treatments work. Earlier we discussed how the brain creates inferences about the outside world – so called priors – and then tests them through trial and error. In the same way the brain also creates the internal constructs we call thoughts, plans, memories, imaginations etc.

For most of us these internal constructs are positive – happy memories, positive plans for the future etcetera. But for some people for example those with depression, OCD, anorexia or substance/behavioural dependences, these contracts are negative thoughts or damaging and ultimately self-destructive behaviours. Many such individuals know that that their thoughts and desires are not what they want but they can't stop them. It is as if they become habitual rather than volitional. What might start off in the case of addiction as a desire with pleasurable outcomes, over time ends up becoming a curse. Many people dependent on alcohol and other drugs continue to use them despite getting no pleasure from them, and they do not just use them to deal with withdrawal symptoms. Substance use, which started as a mind-made decision ends up becoming a sub-conscious reflex behaviour or habit that has escaped from conscious override- it has become manacled to action. The mind that started the behaviour is no longer able to

unshackle it because the behaviour it is now embedded in brain systems below conscious control. As described above thinking loops become deeply rutted or canalised.

In the case of OCD most people know that their compulsive thoughts or rituals are pointless, but they can't stop them. OCD was the first mental illness to have its brain circuits characterised: an overactivity of the orbitofrontal cortex to caudate nucleus pathway was discovered. Further neuroimaging research showed that over time both pharmacological and psychotherapy interventions dampened down this over-activity. Many depressed people feel the same about their negative thoughts but can't stop this rumination. In this case we know that this thinking process is driven by overactivity of parts of the frontal cortex.

Brain imaging studies mentioned above show a profound disruption of normal ongoing brain activity following psilocybin. So, could this disrupt the thinking processes underpinning depression? And what are these anyway? Here again Blake has a profound insight with his quote *"For man has closed himself up, till he sees all things thro' narrow chinks of his cavern"*. For most of us though our view through the chinks is limited the content of our vision is generally positive – blue skies white clouds etc. But people with mental illness see things differently. Depressed people see a bleak dark grey miserable landscape, people with OCD see threats, germ-containing objects etc. Addicts see their love objects, for example a vodka bottle, a hypodermic syringe, a white powder or a roulette wheel.

Figure 4 below helps to explain the neural processes of cognitive biases that underpin these mental illnesses again using the visual system as the exemplar. The mind begins the process but over time the brain takes over and determines the cognitive and thinking processes. The ill person becomes trapped by their brain in their thinking and behaviour processes. In one way Blake was wrong, these are not "mind forged manacles" but brain-forged ones.

Psychedelics by disrupting the brain processes of entrapment can free people from their illness. The rutted loops of thinking from which they have not been able to escape are flattened so they can think differently. For some this may be temporary, but at least during the trip they can understand (in colloquial terms "see") that there is the possibility of escape from them (recovery): whereas for some lucky ones the escape can be permanent.

Our most recent research helps throw a light on the brain mechanisms underpinning the more enduring effects of psychedelics (Daws et al, 2022). This is shown schematically in figure 4.

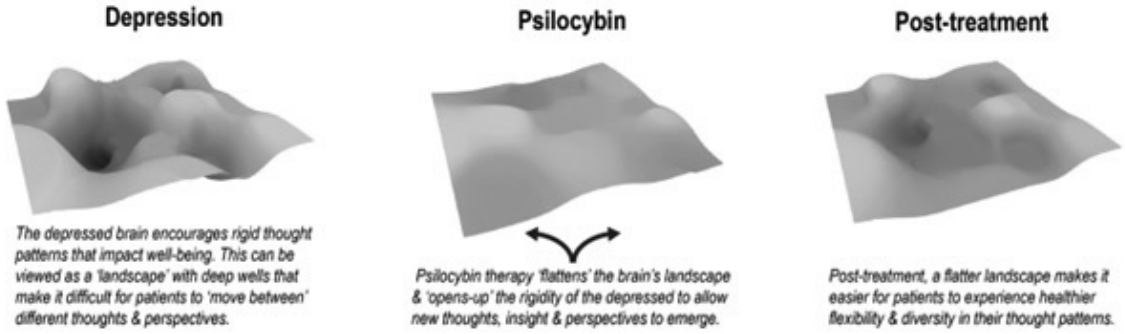

Fig 4. The energy landscape of the brain in different states

Colour Vision

Blakes pictures are some of the most unique and recognised pieces of printed art in the world, for both their design and colour. His use of white to express innocence and closeness to God – a colour experience commonly encountered during trips that take people to heaven, holy places and even God. This aspect of the psychedelic experience is like that reported in near death experiences and probably reflects similar physiological changes in visual processing areas. Black of course represented death and the dark reality and psychology of human life especially in the industrial cities – "*those dark satanic mills*". One advantage of Blakes special copper-plate printing process was that he could experiment with different colours in progressive prints, evolving and exploring the impact of altered shades and colours.

But colour was at times a challenge to Blake as he explained innovation an 1804 letter to William Hayley: "*Suddenly, on the day after visiting the Truchsessian Gallery of pictures, I was again enlightened with the light I enjoyed in my youth, and which has for exactly twenty years been closed from me as by a door and by window-shutters*". Why this transformation occurred is not known but the gallery comprised over 900 pictures, the greatest selection in one place ever assembled and the sheer scale and content seemed to jolt Blake back into an interest in both colour and form.

Psychedelics can also do this. Most are familiar with the wonder-filled descriptions of Hofmann and Huxley on how psychedelics made colours more vivid, more discrete, and more awesome. Similar experiences are commonly reported by many less well-known users; in fact this is one of the more generally reported phenomena of the psychedelic experience. Perhaps paradoxically improvements in colour perception are also reported by people with colour-blindness, enabling them to see colours better. One such person spontaneously emailed me some years ago saying "*all my life I suffered from red-dichromacy/ protanopia*[2]*. One day during a magic mushroom trip my brother showed me a screen image of Monet's San Giorgio Maggiore at Dusk. A painting which I had previously seen as a dull mass of brown and blue. All of the colours I was previously unable to see were there on the screen, and the emotion that I felt made me unable to speak for about half an hour*". This report started us asking our volunteers in previous psychedelic imaging studies if they had colour blindness and we discovered that several had, and many of these reported improved colour perception during and after the trip.

Because of this intriguing feedback we then put a special short questionnaire into the Global Drug Survey addressing this specific point. We asked colour blind respondents to comment on the impact that psychedelic use had on their colour vision. Of the 47 colour-blind people who responded nearly half (23) stated that their colour vision had improved during the use of a psychedelic with many reporting this effect lasted for weeks or months (Anthony et al, 2020).

How can we explain this? It seems unlikely that psychedelics can normalise a genetic change in the photoreceptor protein. There are 5-HT2A receptors on cells in the retina so it might be that stimulating these somehow enhances the gain from the photoreceptors into the neurons transmitting colour signals to the brain. More likely I think is that psychedelics release a degree of suppression of colour perception that is commonly present in the "small world" brain described earlier. For most of us (artists excepted) colour is a useful but not essential aspect of visual life. This whole chapter has gotten by without it! The function rather than the colour of objects tends

to dominate our interactions with them: knowing a door is in front of you is more important than knowing its colour. I suspect colour perception becomes diminished in importance in the brain as we mature through childhood, perhaps even actively supressed. Psychedelics release this minimisation of the value of colour by the brain and so allow it to resume its previous place as a vital aspect of vision. In the next section you will discover just how Blake had foreseen this.

Blake And Newton: Two Different Visions Of Vision?

Although the lives of these two great pillars of British intellectual thought did not overlap (Blake lived 1757-1827 and Newton 1642-1726) Newton clearly had a great influence on Blake as he did on most other thinkers that followed him. Blake's print of Newton scaling the world is one of his most famous and is thought to reflect Blake's opposition to a simple scientific view of the world. He was particularly opposed to Newton's view that reason and logic (scientific materialism) could explain everything. In Jerusalem Blake states *"I will not Reason & Compare: my business is to Create"*.

Fig 5. William Blake painting of Newton scaling the world 1795-c.1805 (Tate, 2018).

Where Blake most opposed Newton was in relation to colour perception. One of Newton's great discoveries was, from the use of the prism, that white light was composed of lights of different colours – as we see in a rainbow. But Blake thought the physics of optics were inadequate to explain humans' appreciation of colour. He argued there were two aspects to vision, the simple "vegetive eye" that does the seeing, and the spiritual appreciation of that vision. Eventually Blake developed a four level explanation of visual experience which directly challenged the "single vision" of Newton, whose "natural religion" he characterized as like being asleep.

"Now I a fourfold vision see
And a fourfold vision is given to me
'Tis fourfold in my supreme delight
And three fold in soft Beulah's night
And twofold Always. May God us keep
From Single vision & Newtons sleep"
—Excerpt from a letter from William Blake to Thomas Butts[3]

The fourfold vision is a state of ecstatic or mystical bliss. Threefold vision arises naturally from Beulah, which, in Blake's mythology, is the place of poetic inspiration and dreams, "*where Contrarieties are equally True*". Twofold vision is seeing not only with the eye, but through it, seeing contexts, associations, emotional meanings, connections. Single vision is the literal, rational, scientific or Newtonian view of the world: for the artist the least important. One can argue that psychedelics support Blake's theories by opening the doors to the higher stages of vision.

This early challenge to science that Blake's visionary experiences produce has been much more eloquently discussed by Aldous Huxley in his book "Heaven and Hell". Many users of psychedelics would undoubtedly side with Blake in the idea that there are different (possibly higher) levels of consciousness that psychedelics reveal to them. They pose a major, maybe the greatest challenge to modern neuroscience: can they be explained in the context of current theories of brain activity? Blake would likely say we don't need to. I would say that if we could, then this would be an advance equivalent to that made for physics by the Theory of Relativity. Whatever the outcome the question will stand, and Blake will remain as one of the leading thinkers in this field.

Endnotes

Beyond the Doors of Perception: What Else Can William Blake Tell Us About How Psychedelics Work?

1. For more information on this see https://acerintegration.com.
2. Protanopia is a hereditary type of colour blindness that comes from insensitivity to red light, which causes confusion of reds, greens and yellows.
3. You can read more about William Blake archives and letters (The William Blake Archive, 1977)

Bibliography

Anthony, Jec, Adam R. Winstock, Jason Ferris, and David J. Nutt. 2020. "Improved Colour Blindness Symptoms Associated with Recreational Psychedelic Use: Results from the Global Drug Survey 2017." *Drug Science, Policy and Law* 6 (November): 205032452094234. https://doi.org/10.1177/2050324520942345.

Daws, Richard E., Christopher Timmermann, Bruna Giribaldi, James Sexton, Matthew B. Wall, David Erritzoe, Leor Roseman, David J. Nutt, and Robin L. Carhart-Harris. 2022. "Increased Global Integration in the Brain after Psilocybin Therapy for Depression." *Nature Medicine* 28 (4): 844–51. https://doi.org/10.1038/s41591-022-01744-z.

Carhart-Harris, Robin L., Mark Bolstridge, James Rucker, Camilla M. Day, David Erritzoe, Mendel Kaelen, Michael a P Bloomfield, et al. 2016. "Psilocybin with Psychological Support for Treatment-Resistant Depression: An Open-Label Feasibility Study." *The Lancet Psychiatry* 3 (7): 619–27. https://doi.org/10.1016/s2215-0366(16)30065-7.

Carhart-Harris, Robin L., and David J. Nutt. 2017. "Serotonin and Brain Function: A Tale of Two Receptors." *Journal of Psychopharmacology* 31 (9): 1091–1120. https://doi.org/10.1177/0269881117725915.

Carhart-Harris, Robin L., Bruna Giribaldi, Rosalind Watts, Michelle Baker-Jones, Ashleigh Murphy-Beiner, Roberta Murphy, Jonny Martell, Allan Blemings, David Erritzoe, and David J. Nutt. 2021. "Trial of Psilocybin versus Escitalopram for Depression." *The New England Journal of Medicine* 384 (15): 1402–11. https://doi.org/10.1056/nejmoa2032994.

Carhart-Harris, Robin L., S Chandaria, David Erritzoe, Adam Gazzaley, Manesh Girn, Hannes Kettner, P a M Mediano, et al. 2022. "Canalization and Plasticity in Psychopathology." *Neuropharmacology* 226 (December): 109398. https://doi.org/10.1016/j.neuropharm.2022.109398.

Germer, Christopher K., and Ronald A. Siegel. 2012. "Wisdom and Compassion in Psychotherapy: Deepening Mindfulness in Clinical Practice." *American Psychological Association*, January. https://psycnet.apa.org/record/2012-13277-000.

Goodwin, Guy M., Scott T. Aaronson, Oscar Alvarez, Peter C Arden, Annie Lilian Baker, James C. Bennett, Catherine Bird, et al. 2022. "Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression." *The New England Journal of Medicine* 387 (18): 1637–48. https://doi.org/10.1056/nejmoa2206443.

Nutt, David J., David Erritzoe, and Robin L. Carhart-Harris. 2020. "Psychedelic Psychiatry's Brave New World." *Cell* 181 (1): 24–28. https://doi.org/10.1016/j.cell.2020.03.020.

Orpwood, Roger. 2013. "Qualia Could Arise from Information Processing in Local Cortical Networks." *Frontiers in Psychology* 4 (March). https://doi.org/10.3389/fpsyg.2013.00121.

Petri, Giovanni, Paul Expert, Federico Turkheimer, Robin L. Carhart-Harris, David J. Nutt, Peter J. Hellyer, and Francesco Vaccarino. 2014. "Homological Scaffolds of Brain Functional Networks." *Journal of the Royal Society Interface* 11 (101): 20140873. https://doi.org/10.1098/rsif.2014.0873.

Tate. 2018. "'Newton', William Blake, 1795–c.1805 | Tate." October 2018. https://www.tate.org.uk/art/artworks/blake-newton-n05058.

The William Blake Archive. 1977. "A Suggested Redating of a Blake Letter to Thomas Butts | E. B. Murray | Blake/An Illustrated Quarterly | Volume 13, Issue 3." Https://Www.Blakearchive.Org/. 1977. https://bq.blakearchive.org/13.3.murray.

Watts, Rosalind, Camilla M. Day, Jacob Krzanowski, David J. Nutt, and Robin L. Carhart-Harris. 2017. "Patients' Accounts of Increased 'Connectedness' and 'Acceptance' After Psilocybin for Treatment-Resistant Depression." *Journal of Humanistic Psychology* 57 (5): 520–64. https://doi.org/10.1177/0022167817709585.