Psychedelics: reconnecting the brain to heal the mind

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Natural psychedelics such as magic mushrooms have a long history of human use of at least 7000 years. Their use underwent a resurgence in the 1950/1960s following the synthesis of LSD as a psychedelic and its use as a medicine with powerful therapeutic benefits. But because non-medical use led to massive cultural changes especially in young people, all psychedelics were banned globally in the early 1970s. Over the past 20 years, there has been a resurrection of psychedelic research. This has revealed their common modes of action as agonists (stimulators) of the serotonin 5-HT2A receptor in the brain and that this activity leads to profound alterations in neuro-circuitry, producing a more integrated and flexible pattern of activity. These brain changes found in healthy volunteers predicted utility in mental illnesses such as depression and addiction and subsequent trials revealed this to be true. A single psychedelic trip can lead to very long-lasting improvements in a range of mental illnesses. From these remarkable and consistent positive outcomes, it seems likely that psychedelic therapy will soon become widely approved in western medicine, as it has already been in Australia for treatment-resistant depression.

Introduction

When most people hear the term psychedelics, it conjures up images of 1960s' psychedelia, the revolution in art, literature and music that exploded from the use of LSD when it was legal and was intellectually underpinned by the writings of Aldous Huxley. This revolution is encapsulated by the Beatles Sgt Pepper's Lonely Hearts Club Band double LP with its psychedelic cover and several tracks paying homage to psychedelics, most obviously *Lucy in the Sky with Diamonds* (a.k.a. LSD). This change in the creative arts was associated with a profound cultural change, particularly in young people who opposed the Vietnam War and campaigned for 'Love not War' – a plea that sadly was ignored then and since.

However, psychedelics didn't start in the 1950s, with the invention of LSD by Albert Hofmann in 1943. Psychedelic drugs have been used by humans since the beginning of recorded history, starting with the depiction of magic mushrooms in North African cave art from 5000 BCE. The Ancient Greeks celebrated their Eleusinian Mysteries from about 1500 BCE with a drink called Kykeon, which was a mixture of wine and psychedelic chemicals related to LSD found in the ergot fungus and psilocybin from magic mushrooms. In South America, the drink ayahuasca, a drinkable form of DMT, was discovered and used for spiritual and healing purposes. Other tribes across the Americas used mescaline from cacti such as the peyote and San Pedro for similar purposes, and in Mexico and elsewhere, psilocybin from magic mushrooms was used. It is thought the drink Soma that is claimed to underpin Hindu religious beliefs contained psilocybin from magic mushrooms as well as cannabis and ephedra. In West Africa, ibogaine from a plant root was used. There are even animals that make psychedelic molecules, the most well known being the Sonora Desert toad that secretes 5-MEO-DMT from its skin.

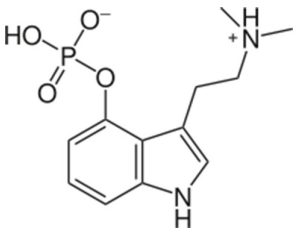
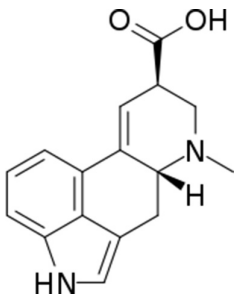
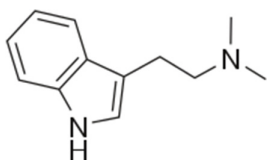
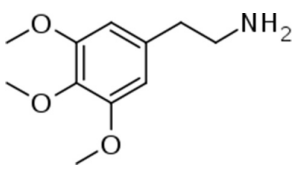
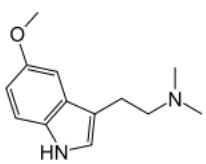
In the past 50 years, synthetic psychedelics have been made, starting with LSD made by modifying lysergic acid found in the ergot fungi and then the more potent synthetic variants of mescaline – the nBOME series – Table 1.

What all these uses show is that psychedelic use is inextricably linked to human culture. They have been used for different purposes such as gaining and expanding understanding of the mind, enhancing creativity, communing with gods and nature, as well as psychological healing. These historic uses of psychedelics are now being resurrected today and this article explains why and how they work.

Recent history of psychedelics

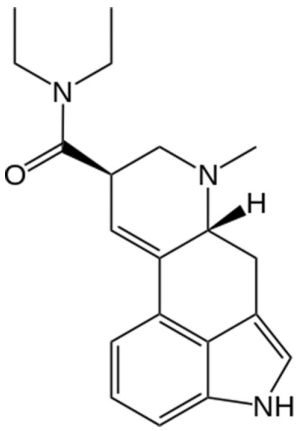
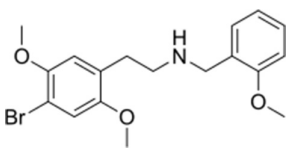
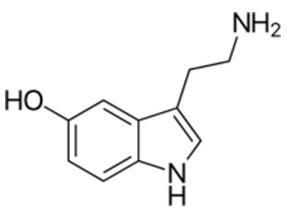
After the discovery of LSD in the 1940s by Albert Hofmann, his employer, the pharmaceutical company Sandoz, made it available for research in the 1950s and then made psilocybin a medicine too. With significant funding, particularly from the US National Institutes of Health, there was an explosion of research with around 40,000 patients with mental illnesses treated. This resulted in around 1000 clinical papers being published reporting that they were safe and effective treatments.

Table 1. The compounds responsible for the psychedelic effects of different sources

Source	Active ingredient	Structure	Psychedelic dose of pure compound	Notes
Magic mushrooms	Psilocybin		25 mg	Is a prodrug that is metabolized to psilocin
Ergot	Lysergamides		100s of mgs	Also used historically to treat migraine and uterine bleeding after childbirth
Ayahuasca	DMT plus harmine (MAO inhibitor)		20 mg	DMT alone only works if i.v./smoked
Peyote and San Pedro cacti	Mescaline		500 mg	Long lasting
Sonora toad	5-MEO-DMT		20 mg	Only works if i.v./ smoked

Continued

Table 1. Continued

Source	Active ingredient	Structure	Psychedelic dose of pure compound	Notes
Semi-synthetics	LSD		100 µg	Very long lasting
Synthetics	nBOMEs, e.g., Cimbi-36		<100 µg	
Serotonin/5-HT	Made from the amino-acid L-tryptophan		Need grams of L-tryptophan to increase brain 5-HT	5-HT not orally active

LSD, Lysergic Acid Diethylamide; DMT, NN-dimethyltryptamine; 5-MEO-DMT, 5-methoxy-dimethyltryptamine.

But, in 1971, psychedelics were banned under the UN Conventions on narcotic drugs. The reasons for this decision were largely political, especially the fear that non-medical LSD use was changing society through its association with rock music, hippies, psychedelic art and the anti-Vietnam war movement. The 1968 Nixon War on Drugs targeted psychedelics along with cannabis and opioids, so by 1971 almost all countries in the world

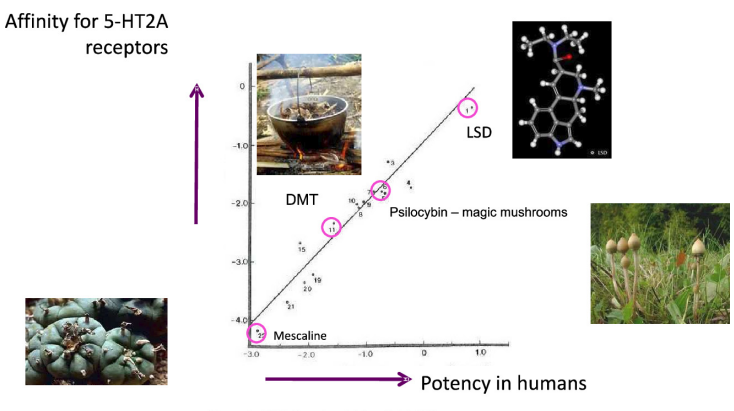


Figure 1. Serotonergic psychedelics are agonists at 5-HT2A receptors.

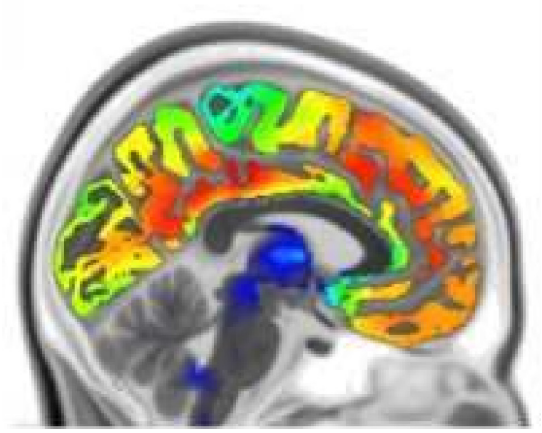


Figure 2. Location of 5-HT2A receptors in human brain

had signed up to the UN Conventions that banned most serotonin psychedelics. This ban effectively stopped all clinical research and treatment and is still enforced today. It is possible to get exceptions for research but this is costly and time consuming, so only a few centres are studying psychedelics. But, as you will read below, their results are spectacular, leading me to conclude that the international ban on psychedelics is the worst censorship of clinical treatment in the history of the world. It has denied potentially life-saving treatments to millions of people with mental illnesses for more than 50 years.

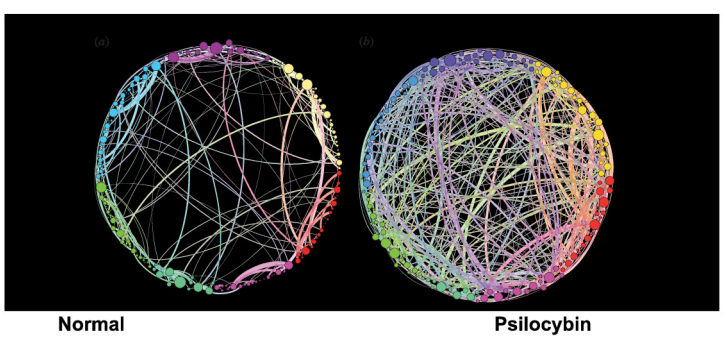
How psychedelics work

What all these psychedelics have in common is a molecular similarity to the neurotransmitter serotonin (aka 5-HT) so they are often called the serotonin psychedelics. There are 15 subtypes of serotonin receptors, but the psychedelic effects are mediated through a specific subtype, the 5-HT2A. We know this because of the very strong relationship between the affinity of these molecules for the 5-HT2A receptor and clinical dose – see Figure 1 – and the fact that antagonists of the 5-HT2A receptor such as ketanserin block their psychedelic effects.

The image in Figure 2 shows the distribution of 5-HT2A receptors in human brain. It is made using a psychedelic molecule Cimbi-36 that is radioactively labelled so we can see its binding to the receptors. The hotter the colour coding, the more receptors there are. You can see that most of the receptors are in the top part of the brain – the cortex. But within the cortex, the density varies a lot, being maximal in the red areas. These are those parts of the cortex that have massively expanded in the evolution of the human brain from our early hominid ancestors. They are the cortical regions that make us human because that is where we do our highest-level cognitive processes such as thinking, imagining, creating and problem solving.

Brain mechanisms of a trip

Human functional magnetic resonance (fMRI), magnetoencephalographic (MEG) and electroencephalographic (EEG) imaging studies in healthy volunteers have since revealed that psychedelics produce profound disruptions of cortical synchrony and circuits. This breakdown of normal structured activity leads to a great increase in connectivity in the brain as shown Figure 3. It would not be ethical to scan patients during their treatment trip as it might reduce the therapeutic efficacy, but we were able to scan them days or weeks afterwards and we found that even then, when the psychedelic is long gone from their brain, there is still increased connectivity. Remarkably, the size of these connectivity changes correlated with depression recovery, suggesting a causal relationship. The increase in physiological connectivity was mirrored by the subjective reports of the patients who often commented that after the psychedelic, their thoughts were more flexible and adaptable and the negative thought loops so characteristic of depression were gone or were less dominant. On top of that, the new connections made



Petri et al J. R. Soc. Interface 11: 20140873. http://dx.doi.org/10.1098/rsif.2014.0873

Figure 3. By switching of the 'control centres', psilocybin increases brain connectivity

Table 2. Evidence levels. ++++- multiple randomised clinical trial data. +++ - randomised clinical trial data. ++ - open trials. + - case reports. 1960s – older trials before the ban

Drug	Psilocybin	LSD	DMT/ayahuasca	Mescaline
Depression	++++		+++	+
End-of-life anxiety and depression	++++			
Alcohol addiction	+++	++++ (1960s)		+
Tobacco addiction	++			
Heroin addiction		+++ (1960s)		+
OCD	++			
Anorexia nervosa	++			
Pain syndromes	+	+		
Anxiety disorders		++		+

OCD, Obsessive Compulsive Disorder.

during the trip help them think differently about their past and future – often they find new solutions to old problems.

Our neuroimaging work has shown that psychedelic treatments work in a very different way to conventional treatments for mental illness – they are not just faster acting versions of current medicines. Psychedelics disrupt the high-level cortical-thinking abnormalities in these disorders and so work almost immediately, whereas current treatments, e.g., antidepressant drugs for depression, work to reduce stress-induced dysfunction in the emotional centres of the brain and so allow the brain to heal but this takes weeks or months.

Neuroplasticity

Perhaps, the most remarkable aspect of psychedelics is how enduring the effect of just a single trip can be. Many recreational users report they have changed their perspective on life for decades if not for ever, and many patients find their depression or addiction lifted for years. One explanation for such durable effects is profound psychological insights gained during a trip but recent pre-clinical research has reported that serotonin psychedelics can rapidly induce the growth of new neuronal processes – a phenomenon called neuroplasticity. This will facilitate encoding of new thoughts and insights gained from the trip. Human physiological evidence for neuroplasticity is now beginning to emerge.

Modern clinical studies of serotonin psychedelics

To date, most of the trials have used psilocybin, with a lot of trials in depression, two in end-of-life anxiety and depression and three in addictions (two in alcohol). These are listed in Table 2. Given that psychedelic studies are generally conducted in treatment-resistant patients, the results so far have been hugely impressive. This evidence underpinned the Australian medicines agency in July 2023 allowing psychiatrists to prescribe psilocybin for patients with treatment-resistant depression who had failed at least two other interventions. This was a ground-breaking decision as the drug will be provided by a charity – Mind Medicine Australia – not a pharmaceutical company. This is a highly novel approach to providing an innovative medical treatment in an area of large unmet need; in Australia, one first responder with mental illness commits suicide every day despite their having one of the best medical systems in the world. There seems no reason why such a compassionate use programme supported by charities or even governments could not be replicated in other countries, so bringing great benefits to similarly treatment-resistant patients. ■

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Further reading

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