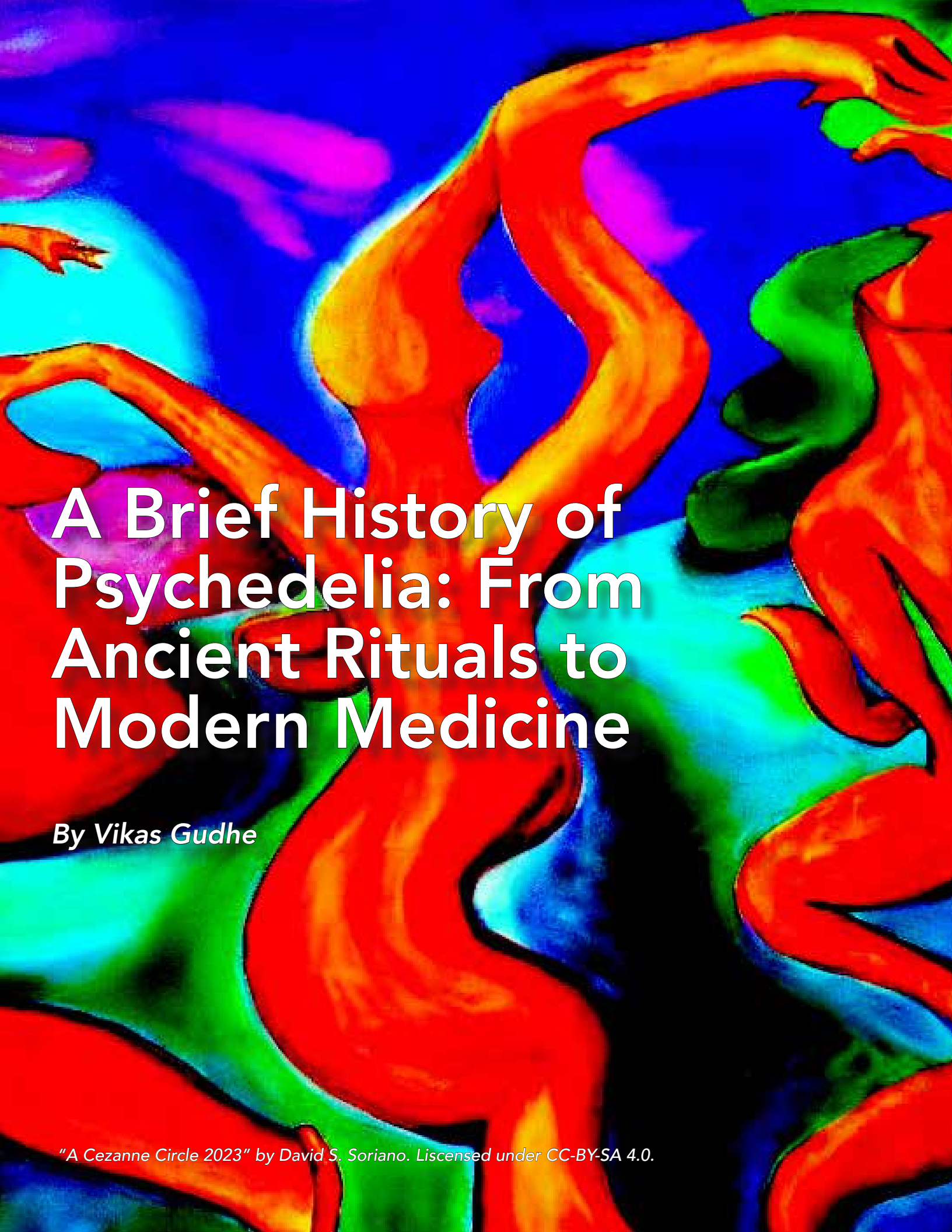

A Brief History of Psychedelia: From Ancient Rituals to Modern Medicine

By Vikas Gudhe

Clara never smiled. She tried everything she possibly could—therapeutic protocols and drugs by the dozen—but nothing would make her depression go away. They labeled her "treatment-resistant" [1]. But little did she know, in a lab at Imperial College in West London was a young neuroscientist by the name of Robin Carhart-Harris who, working in Professor David Nutt's laboratory, had just secured a grant from the government of the United Kingdom (UK) to conduct a small pilot study using a peculiar psychedelic substance called psilocybin. The targets of this study were patients who had not responded to the usual treatments and protocols, as they suffered from "treatment-resistant depression" [2].

A Clincal Success

In 2005, about a decade before the aforementioned study, Carhart-Harris came to meet Nutt all prepped and ready to propose studying psychedelics with a carefully thought-out funding plan and a recommendation from Amanda Fielding–a fellow researcher and acquaintance of Nutt's. He was given a staunch rejection– especially because at this point Carhart-Harris had no prior neuroscience experience. But, enamored by his determination, Nutt offered Carhart-Harris the chance to complete a PhD with him but advised to start with something less ambitious [1]. Fast forward to 2009 and one day, working in Nutt's lab, he received approval from UK's National Health Service to study psilocybin's effects in the brain using functional magnetic resonance imaging (fMRI), which isa technique that measures brain activity based on blood flow [3]; a study that was the first of its kind. That first study has now led to Nutt prescribing psilocybin to Clara, who over the course of several meetings he had "never once seen smile". As he watched the drug take effect, the edges of her lips began to curl upward only to be followed by her saying "It's nice to smile" [2].

Bel-Air Drive-In theater advertisement for the psychedelic counterculture film, The Trip. Image from American International Pictures, November 22 1967.

What followed however, was not surprise; nor was there the thrill of discovery for Nut and Carhart-Harris after this immensely successful result. They already knew that psilocybin could do this. In fact, this experiment was not even the first time psilocybin was used to treat depression—let alone the first time in a non-clinical setting. Despite this, around the same time, David Nutt was actually fired from his position as chair of the government's Advisory Council on the Misuse of Drugs for empirically assessing the risks of numerous psychoactive (meaning affecting the mind) drugs. He had concluded that alcohol was more dangerous than cannabis, LSD, and ecstasy; the government's drug policy needed serious reformation [1][2]. Nutt suggested the sentence that likely got him sacked was "of course I am!" in response to reporters on live T.V. asking "You're not seriously telling us that LSD is less harmful than alcohol, are you?" [3]. What's crazy is, Nutt had not made any scientific errors, merely a political one. Psilocybin, LSD, and several other psychedelic compounds are characterized as "Schedule I" under the "Controlled Substances Act". This means, despite a wealth of scientific evidence stating otherwise, the government believes that the drugs: have a high potential for abuse, have no currently accepted medical use in treatment, and that there is a lack of accepted safety

for use even under medical supervision.

The History

It was not always like this, however. Going back to the late 1930s, Swiss pharmaceutical company Sandoz had asked a young chemist named Albert Hoffman to painstakingly synthesize every molecule in the alkaloids produced by ergot. Ergot, a fungus known to infect grain and occasionally send those who consume the infected bread into "bouts of insanity" was also theorized to be connected to the Dancing Plague of 1518, a case in Strasbourg, Alsace, in the Roman Empire, where somewhere between 50 to 400 people took to uncontrollably dancing for weeks; some of who, danced to their death [10]. But the historical use by midwives to induce labor and treat postpartum bleeding is what piqued the interest of Sandoz. As Hoffman kept working, he synthesized the twenty-fifth compound which he named lysergic acid diethylamide 25 or LSD-25 for short. This is what is now commonly referred to as simply LSD. At the time, tests on animals did not prove to be promising, as they only seemed to grow restless, and so the formula was shelved [4].

But five years later, Hoffman said that he distinctly remembers "a peculiar presentiment" that drove him to give the compound another chance. Peculiar indeed, as when a formula is discarded, "it is usually permanent." Despite his usual pinpoint precision and straight-as-a-ruler adherence to safety procedures, Hoffman "was interrupted in [his] work by unusual sensations", which he would quickly figure out was due to a small amount of LSD absorbing through his skin – resulting in the world's first LSD trip. Hoffman went to lie down as he grew restless and was suddenly thrown into a "dreamlike state", where he says to have seen "an uninterrupted stream of fantastic pictures, extraordinarily shaped with intense, kaleidoscopic play of colors" [4].

Intrigued, Hoffman then conducted an experiment on himself (supposedly quite common back in the day) by ingesting 0.25 milligrams of LSD. While usually considered an extremely small dose for any other drug, Hoffman was soon about to discover that this was quite the opposite. Unlike the first time however, this story led to the world's first bad acid trip. Hoffman decided to pedal home after beginning to feel

Figure 1. *Photo of Psilocybe mushroom. Image taken from unsplash.com*

restless and by some miracle, got home and said that he felt "a demon had invaded [him], had taken possession of [his] body, mind, and soul. [He] jumped up and scream[ed], trying to free [him]self from him [the demon], but then sank down again and lay helpless on the sofa." He was convinced he was dying. Scary, right? Interestingly, however, when a doctor arrived to examine him, all of Hoffman's vitals were normal with the only thing that gave away his lack of sobriety being his dilated pupils. Furthermore, once the drug's effects wore off, he said that he felt an "afterglow" and that "everything glistened and sparkled in a fresh light." The world was as if

Figure 2. *Illustration of LSD, Serotonin, and Psilocybin. Image created with ChemDraw by Vikas Gudhe*

Eyes-wide-shut by the New Illuminati. From flickr https://www.flickr.com/photos/67194724@N03/8358110584/

newly created." This day, April 19, would henceforth become known as "Bicycle Day" and deservedly so, as this trip convinced Hoffman that LSD could be of immense value to psychiatry, possibly as a model of schizophrenia [4][9]. Despite its ups and downs, in the late 1950s LSD finally began to gain some recognition among researchers and mental health professionals with still-limited appearances in the public eye. As research progressed and positive evidence for treating various addictions, anxiety, and depression kept piling on, LSD along with psilocybin (which has an interesting and much older history of its own that we will get into later) were regarded as "miracle drugs". The public perception was positive. Too positive. LSD and psilocybin (now christened "shrooms") quickly became drugs of abuse and the emergence was linked to the anti-hierarchy counterculture movement that defined the early 1960s. The movement gained momentum with the public alongside prominent (albeit controversial) academics like Timothy Leary conducting a series of studies at Harvard – of which a particularly famous one became known as the "Good Friday Experiment." By the end of the next decade however, sentiment had begun to shift in the opposite direction, with increasing coverage of bad trips, psychotic breaks, suicides and more. Until one day, Richard Nixon declared Timothy Leary "the most dangerous man in America" and began the war on drugs – putting an end to government funded psychedelic research for the foreseeable future… publicly at least. In 1975, it was disclosed that the CIA was running LSD experiments in Maryland under the code name MKUltra, with the goal of trying to achieve complete mind-control. These experiments, of course, failed, but an interesting fact to note is that Ted Kaczynski, better known as the Unabomber, was one of the subjects of these experiments, in which participants were dosed without consent. But after news broke, civilians were rightfully angered and the last of any psychedelic research had been shut down for good [5].

Interestingly, psychedelics seem to have a history of scaring puritanical cultures into believing they had no choice but to forcefully suppress knowledge of their existence. Psilocybin, produced in a small brown mushroom, has been used for hundreds of years across indigenous people in Mexico and Central America. The Aztecs even referred to the mushrooms as "flesh of the gods", but the letter at the end of god indicating plurality certainly did not sit well with the strictly Roman Catholic Spanish conquistadors at the time. As such, the mushrooms and subsequently psilocybin were driven away from the public eye for hundreds of years [4][6].

R. Gordon Wasson, an amateur mycologist and banker, "rediscovered" magic mushrooms with the help of a local in the Mexican state of Oaxaca, which led to him to publish his experience in Life magazine in 1957. Wasson is often credited for introducing psychedelics to the West, as knowledge of LSD was almost entirely limited to laboratories at the time. Wasson was so enamored by these mushrooms, he sent some samples to none other than Albert Hoffman himself. Albert, in turn, successfully

isolated the psychoactive compounds psilocybin and psilocin. Psilocin is the prodrug (the compound that is metabolized after a drug's taken to result in the effects of the drug - in this case psilocin, which is what psilocybin turns into once ingested, is ultimately the compound that's interacting with your brain)[4].

Psilocybin and LSD share a remarkable resemblance in that they are both compounds that fall under the chemical family of tryptamines. The most famous of tryptamines that even non-scientists may have heard of, 5-hydroxytryptamine (5-HT) or Serotonin, is a chemical neurotransmitter in the brain that has been linked to regulation of mood, sleep, appetite, and digestion. In fact, Hoffman's discovery of LSD and the fact that it was active at a thousandths of milligram inspired scientists to find the endogenous (meaning internal origin or cause) chemical that is Serotonin, purely to explain how these molecules could affect the brain in such a substantial way [4]. What took years of painstaking research to explain back then can be seen in plain sight when we compare the chemical structures of Psilocybin, LSD, and Serotonin. Imagine a lock (the receptor that accepts neurotransmitters in the brain, in this case the 5-HT or serotonin receptors) that's key is serotonin. Due to Psilocybin and LSD's structural similarities, they function just like keys that can utilize the "locks" that are the serotonin receptors. Serotonin and psychedelic science were so integral to both fields, that observing LSD's effects at such small doses led to the development of SSRIs–the most common antidepressants (drugs primarily used to treat Major Depressive Disorder) in use today. But that is where we left off before the books of academic research on psychedelics closed for nearly 40 years

A Mystical Experience

It wasn't until 1998, that a clinical psychologist by the name of Roland Griffiths, decided to take a political gamble and submit a grant proposal to study psilocybin's effects on a small group of volunteers. The gamble eventually resulted in the prestigious Eddy Award from Johns Hopkins University, with nominators stating that his psychedelic work played a crucial role in his contributions to the scientific field. In fact, Griffith's most popular peer-reviewed paper had a strange title: "Psilocybin Can Occasion Mystical-Type Experienced Having Substantial and Sustained Personal Meaning and Spiritual Significance." Keep in mind that his paper was published in the well-respected journal of Psychopharmacology.

The study had thirty participants who had no history of prior psychedelic use and were given either a pill of synthetic psilocybin or methylphenidate (Ritalin) as control. The study utilized a scientifically rigorous double-blind placebo controlled methodology. This meant that neither the participants nor the researchers knew who would be receiving psilocybin and who would be receiving a placebo (a dummy treatment); this was done to limit bias and ensure the results are not influenced by the expectations of either the volunteers or researchers. The participants were told to put on eye shades and headphones and lay down on a couch with two therapists attending to them throughout the whole experience. Those that received a high dose of psilocybin reliably described having a "mystical experience", which was typically defined as the dissolution of one's ego and a "feeling of oneness with the universe"[6]. This may not come as a surprise given Hoffman's experience with LSD and to the academics who studied psychedelics before their total ban, but for modern scientists this was remarkable. Even more incredible was that two-thirds of

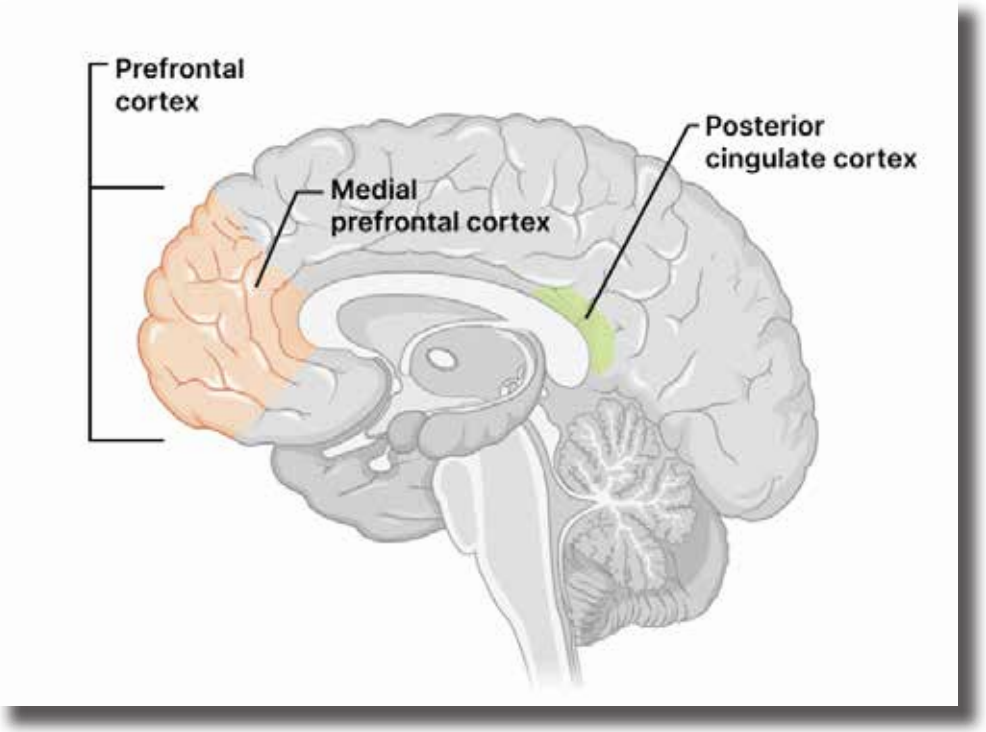

Figure 3. *Illustration of brain highlighting mPFC and PCC. Image created with BioRender by Vikas Gudhe*

the participants in the study stated that the psilocybin experience was one of the "most meaningful in their lives", with one third even going on to say it was the most significant. These ratings only dropped minimally after fourteen months. Foreshadowing some of Griffith's future work, the volunteers reported significant improvements among other things in their "life satisfaction and personal well-being"[6]. Griffiths went on to complete studies that provide evidence for the "mystical experience" occasioned by psilocybin being effective in treating end-of-life anxiety for cancer patients, smoking cessation with an 80% success rate–previously unprecedented, and even showing large reductions in depression symptoms of patients labeled as treatment-resistant [6,] [7], [8].

As Griffiths' work gained traction, momentum finally started to shift back in a positive direction for psychedelics and neuroscientists began to take note. While the subjective effects of psychedelics have been studied in-depth, very little is known about the mechanisms behind the "mystical experience" and why it's so effective in treating a variety of psychological disorders. In fact, serotonin, despite its popularity, is still largely a mystery as well– it binds to many receptors and to complicate things further, it can make them fire or inhibit them depending upon context! In 1998, Franz Vollenweider, demonstrated that blocking the serotonin receptor 5-HT2A stops both psilocybin and LSD from producing any effects and found the first piece of a puzzle that has yet to be solved [9]. 5-HT2A is found throughout an area of the brain called the default mode network (DMN), which is called "default" because it's the area of our brain that is most active when we "ruminate, daydream, reflect, and worry"; or when we have no specific mental tasks to perform. Interestingly, LSD has a stronger affinity (or attraction) for 5-HT2A than serotonin itself. Scientists are still speculating whether there is another endogenous chemical that exists solely to bind to 5-HT2A.

During the first round of psychedelic research, subjective experiences became well documented, but today scientists can correlate brain activity recorded using various imaging methods that were previously unavailable. This is exactly what Robin Carhart-Harris (hope you did not forget him!) set out to do in 2009. Using fMRI and magnetoencephalography (MEG), Carhart-Harris and his team injected volunteers with LSD and psilocybin across multiple studies to identify "neural correlates", physical changes that are happening inside the brain during the psychedelic experience. Carhart-Harris hypothesized that the brain on psilocybin "would look like the dreaming brain", with increases in activity throughout. Surprisingly, blood flow (an indicator of brain activity) decreased in many areas with one particular network having a serious reduction–the default mode network (DMN) [11].

The DMN is generally interacting with attentional networks to crop out extraneous data to make sure we aren't overloaded with information from all of our senses and is most active when we engage in higher level processes such as mental constructions (including self/ego), theory of mind (ability to attribute mental states to others) and moral reasoning. This explains why high doses of psychedelics often result in participants stating they feel their ego disappear. It results in a feeling of oneness with the universe since their DMN is offline and unable to construct their ego. Interestingly, these processes are thought to be exclusive to humans and even within humans—the DMN isn't fully operational until late adolescence. What's more, humans have the longest adolescence period of any species, which developmental psychologists suggest is due to the increased burden of learning for human children as opposed to other animals [12]. As we age, our brain removes or "prunes" neural connections that we don't use often, and as the number of connections reduces, some remaining ones can become "stronger" and areas of the brain that are strongly connected are characterized as "coupled".

"Visionary Art 2022 A Glimpse of Madness" by David S. Soriano. Liscensed under CC-BY-SA 4.0.

In Carhart-Harris's study "Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin", fMRI data showed that the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), which are crucial parts of the DMN, can become "decoupled" in response to psilocybin. Prior studies have shown that "over coupling" of the mPFC and PCC was quite common in disorders such as anxiety and depression, with the DMN described as being in an "over stable" state [13]. Evidence indicates that psilocybin may work via stimulating the 5-HT2A receptor and decreasing activity in the mPFC and PCC, since 5-HT2A is

present in high concentrations in both of these areas. This reduction in activity is thought to disrupt the DMN and open up the possibility for the brain to start making new connections [11]. In essence, Carhart-Harris suggests that psilocybin may "shake the snow globe" and disrupt both the connections in the brain and negative behavior patterns to allow the opportunity to build new connections and habits respectively.

From seeing gods, brutal repression, to political nightmare, and finally back to scientific miracle, psychedelics have had one of the most complex and politically charged histories of any compound. While the sheer complexity of the brain affords us no charity, psychedelic compounds have been a part of human history for hundreds of years and continue to aid us in discovering more about the brain and various psychiatric disorders. As the scientific evidence of treatment efficacy is building up, the US government has taken notice and funding for psychedelic research has skyrocketed in the past decade. With the help of modern technology and a renewed interest in psychedelic science, we are on the cusp of a new age of Neuroscience, in which a future where "treatment-resistant" may not have to be a label physicians utilize for much longer.

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