Taking the Magic Out of Magic Mushrooms

Nick Fernandez was in hell — one filled with fire and skulls and the long-legged elephants from a Salvador Dalí painting. A spirit had guided him there after his funeral; other stops on their journey included Grand Central Terminal, the top of the Empire State Building and the sewers flowing beneath New York City. Their final destination was a cave where Mr. Fernandez encountered his own body, hung up on a clothes hanger. By examining his body in this way, he was able to come to peace with all that it had been through and accept it as his own.

Mr. Fernandez was tripping on a very large dose of psilocybin, the psychoactive ingredient in magic mushrooms. He took the drug as part of a clinical trial at New York University for people dealing with anxiety and depression following a cancer diagnosis.

That study and several others have found that psychedelic drugs like psilocybin are remarkably good at alleviating symptoms of depression and anxiety — even in many people who do not respond to currently prescribed medications. They need to be taken only a few times (most clinical trials consist of two or three psychedelic sessions) instead of daily for months or years. Some experts say the therapy could be thought of as a surgery that solves a problem with a single procedure instead of a continuing treatment to manage a chronic condition.

Whether hallucinations like the ones Mr. Fernandez experienced are key to psychedelics' effectiveness is now a question of great debate among researchers. The answer could determine whether millions of people receive much-needed treatment, and it could provide new insight into how mental health disorders are treated going forward.

Psilocybin is expected to receive approval for depression from the Food and Drug Administration by the end of the decade, possibly in the next few years. But in its current form, psychedelic therapy will only ever be available for a select few. For one thing, it is not an easy, convenient treatment to undergo. It involves several therapy sessions in addition to the full-day intensive trips, which can be physically and emotionally taxing, not to mention expensive. More concerning, recent reports have emerged of clinicians taking advantage of patients during sessions, when they are in an incredibly vulnerable state. People with a personal or family history of schizophrenia are also currently ineligible for the treatment because of concerns that tripping may exacerbate an underlying risk for psychosis.

In response to these obstacles, some scientists are working to develop molecules based on psychedelics that provide the therapeutic benefits of the drugs but without the hallucinations.

"When you consider the fact that one in five people will suffer from a neuropsychiatric disease at some point in their lifetime, we're talking a billion people worldwide," said David Olson, an associate professor of chemistry, biochemistry and molecular medicine at the

University of California, Davis. “We need scalable treatments, and for that, I think we really need medicines that are easily administered.”

Dr. Olson and others think that psychedelics’ effects on the brain are what give them their therapeutic properties, not the trip they take people on, and that the subjective experience of the drugs can be removed while their impact on depression remains. Research conducted in rodents and petri dishes over the past few years suggests this may be possible. Several studies published by Dr. Olson and others have identified new molecules that act like psychedelics in the brain and maintain their antidepressant properties without causing rodents to hallucinate.

Other researchers are skeptical that these new compounds will work in humans. To them, the powerful emotional and mystical experiences caused by psychedelics are what lead to people’s therapeutic breakthroughs.

“To get the kinds of persisting benefits that we’re seeing, which are weeks, months, even over a year later, that would seem to suggest that there’s some kind of cognitive shift or changes to one’s meaning-making that are going on,” said David Yaden, an assistant professor of psychiatry and behavioral sciences at the Johns Hopkins Center for Psychedelic and Consciousness Research.

People participating in psychedelic studies often say the experience was among the most meaningful of their lives, on a par with the birth of a child or death of a parent. Many report feeling a sense of connectedness with the universe. “This psilocybin journey was the single most transformative experience of my life,” Mr. Fernandez wrote in a Medium post in 2018. “It forced me to reconcile with the mortality of being human. It alleviated my anxiety and gave meaning to my life.”

It is this existential catharsis and the personal insights that accompany it that Dr. Yaden and others believe are so important to people’s healing. Backing up the theory, several studies have found that the feelings of connectedness and meaningfulness and the mystical-type experiences people have during their trip correlate with their therapeutic outcomes.

Regardless of which side is right, the pursuit of an answer to how psychedelics treat depression brings scientists one step closer to understanding not only how to relieve the symptoms of mental illness, but also potentially how to remove them. That’s because the truly revolutionary vision of both psychedelic therapy and its non-psychedelic chemical cousins is to take the medications not on a daily or weekly basis, but only once or twice and potentially be healed for good. “Wouldn’t it be wonderful if we had a drug that you can take at bedtime and you woke up the next day and you were no longer depressed?” said Dr. Bryan Roth, a professor of pharmacology at the University of North Carolina, Chapel Hill, who is also working to develop non-hallucinatory psychedelic compounds.

Beginning in the 1960s, scientists thought that depression resulted from having low levels of the neurotransmitter serotonin in the brain, and traditional antidepressant drugs, such

as selective serotonin reuptake inhibitors, worked by correcting that chemical imbalance. But there were holes in this hypothesis. Most notably, S.S.R.I.s raise serotonin levels immediately, but symptoms of depression typically don't alleviate until several weeks after starting the medication.

A new theory emerged in the 1990s and early 2000s that depression, as well as anxiety and PTSD, may stem from the loss of synapses in the brain — the connections between neurons. Scientists discovered that people with depression have less volume in regions of the brain important for mood, executive control and feelings of reward. Chronic stress and genetics are thought to contribute to the atrophying of neurons and their connections.

It turned out that antidepressant drugs were able to regrow those lost synapses — a process known as plasticity. It's possible that by forging new connections in the brain, people can start to change negative thought patterns and regain control over anxious or depressive impulses.

Plasticity also happens naturally, with connections growing every time you learn something new. The location and amount of plasticity will differ depending on the experience, though. Formative life events like becoming a parent and grieving a lost loved one can change the brain in significant ways. The brains of Buddhist monks and other expert meditators — people intimate with mystical experiences — undergo changes, too. There's even research suggesting that talk therapy works in part by altering patterns of brain activity. The brain doesn't change by a huge amount during adulthood, not as it does during childhood, when millions upon millions of neurons and synapses are grown and lost, but it's not static.

These organic changes tend to be subtle. You don't see long-legged elephants while you meditate, and no one thinks having a child will instantly cure your depression or get you to stop smoking — another potential therapeutic use of psychedelics. People with depression also appear to have less ability to activate plasticity naturally, so medication can be important to jump-start that process.

Like traditional antidepressants, psychedelics are thought to confer their therapeutic benefits by inducing plasticity in the brain. But they work much faster and more intensely. Ketamine, psilocybin and LSD stimulate prolific cell growth and provide psychological relief within a matter of hours. Psychedelics may be a way to amplify the neuronal changes that are possible with S.S.R.I.s or therapy or other profound human experiences, or they might act like a shortcut. Some people refer to psychedelic treatment as being like 10 years of therapy in a day.

It is this explosive property of psychedelics that scientists are trying to recreate in the new compounds. They think that by rapidly rewiring neural circuits, they can change an unhealthy brain into a healthy one.

“We’re not trying to produce the next Prozac,” Dr. Olson said. Instead, the goal is to alter the brain in such a way that it produces lasting, positive changes — changes that could look like a cure.

But some researchers caution that plasticity by itself isn’t necessarily a good thing. Putting the brain in a malleable state without proper guardrails could even cause someone’s symptoms to worsen. That concern is one reason taking psychedelics in a recreational setting is not the same as using them in combination with therapy, experts say.

“Plasticity, as defined in the dictionary, is the ability of a thing to be shaped or molded,” said Robin Carhart-Harris, a professor of neurology and psychiatry at the University of California, San Francisco. “That’s all you’re doing when you’re increasing plasticity, and you could shape someone in a bad direction. You don’t want to do that. That’s why we do psychedelic therapy.”

To Dr. Carhart-Harris, the idea that psychedelics could be beneficial not only without therapy but also without the trip is highly unlikely. “I just think it rests on flawed assumptions that you can get the plasticity effect” without an alteration in consciousness, he said. “They might create something akin to psychedelic tofu or microdosing or something that isn’t that trippy, that does a little bit of plasticity but it’s not really transformative.”

This line of thinking implies that the extreme, rapid plasticity induced by psychedelics is what causes the hallucinations, emotional changes and feelings of connectedness. If correct, it would suggest that you can’t change your brain that much that quickly without feeling it — and experiencing something extraordinary — and if you don’t feel anything, you may not have changed all that much.

Even if the new molecules are successful at decoupling the drugs’ therapeutic benefits from their existential or mystical qualities, Dr. Yaden said something will be lost by removing the psychedelic journey. And given how meaningful many people consider their trips, he said denying patients that experience could even be an ethical issue. “I struggle to find rationale for withholding such a meaningful experience,” he said, in cases where people do not have a medical or psychiatric risk.

Dr. Olson’s response is that traditional psychedelics, and all that come with them, should still be available to people who want the experience of psychedelic therapy. But he hopes that the new compounds could be a better alternative to currently available antidepressants for people who can’t or won’t undergo the full journey.

At stake in this debate is not only the intellectual question of how drugs that take you to hell and back can cure your depression, but also the future of how they are administered as medications and in what form they make it to market.

In the United States, an estimated 8.9 million adults take antidepressants to treat major depressive disorder, but for approximately 30 percent of them, the medications don’t

work. If psychedelics were effective for even a fraction of these individuals, it would be an enormous boon for behavioral health, and the psychedelic industry. Already, more than 50 publicly traded companies have popped up to try to capitalize on the enthusiasm around psychedelics, transforming the drugs from a fringe movement to a billion-dollar market. And that's without F.D.A. approval or legalization. If the effectiveness of psychedelics for depression were maintained but the hurdles and hallucinations were removed, that valuation could explode.

Several of the researchers involved on both sides have financial skin in the game, with biotech companies they've either founded or consult for racing to become the next psychedelic — hallucinatory or not — to gain approval from the F.D.A. (A variation of the drug ketamine was authorized for depression in 2019.)

Until then, the researchers will continue their pursuit through the incremental and uncertain work of formulation, preclinical testing and hopefully clinical trials. "I'm agnostic. I fall into the bin of 'I don't know.' But it's a hypothesis that's worth testing," said Dr. Roth. "There's no definitive data for either you need a psychedelic experience or you don't need a psychedelic experience. One can interpret the data either way, I think. What I say is, I would like to find out. And that's what we're trying to do."

https://www.nytimes.com/2022/07/15/opinion/hallucinations-psychedelics-depression.html