Reopen your mind

Psychedelic drugs are transforming the way we think about mental illness, says **Sam Wong**

HE WASN'T the first person to say it, and he probably won't be the last, but Tom Insel's accusation carried extra weight thanks to his job title: director of the US National Institute of Mental Health. Towards the end of his 13-year tenure, Insel began publicly criticising his own organisation, and psychiatry in general, for its failure to help people with mental illness. "There are great examples in other areas of medicine where we've seen innovation really make a difference," says Insel. "Not so much for patients with schizophrenia, post-traumatic stress disorder or depression."

It's hard to argue. Mental illness has reached crisis proportions, yet we still have no clear links between psychiatric diagnoses and what's going on in the brain – and no effective new classes of drugs. There is one group of compounds that shows promise. They seem to be capable of alleviating symptoms for long periods, in some cases with just a single dose. The catch is that these substances, known as psychedelics, have been outlawed for decades.

A psychedelic renaissance has been feted many times, without ever delivering on the high hopes. But this time feels different. Now there is a growing band of respected scientists whose rigorous work is finally bearing fruit – not only in terms of benefits for patients, but also unprecedented insights into how psychedelics reset the brain. If the latest results stand up to closer scrutiny, they will transform the way we understand and treat mental illnesses.

The idea that psychedelic drugs might be used to treat mental illness emerged in the 1950s, a decade or so after Swiss chemist Albert Hofmann first described his experiences of taking LSD. By the mid-1960s, roughly 40,000 people had been given LSD as part of treatments for all manner of mental illnesses, from obsessive compulsive disorder to addiction, depression and schizophrenia.

It looked like we were onto something. Then psychedelics escaped the lab and took off among the counterculture. The backlash meant that by 1970, they had been banned in the US, Canada and Europe. Research ground to a halt.

In the meantime, treatment for depression, the most common mental illness, came to be dominated by drugs called selective serotonin reuptake inhibitors (SSRIs), which boost levels of the neurotransmitter serotonin in synapses by blocking its reabsorption by neurons. Their success in early trials fuelled the idea that depression is caused by a deficiency in serotonin. But recently, this idea has been called into question, as more and more studies suggest SSRIs aren't as effective as we thought.

"The psychedelic revival is finally bearing fruit with a series of startling results"

That comes as no surprise to many psychiatrists. Despite their ubiquity – 8.5 per cent of people in the US take them – SSRIs work for just 1 in 5 people. Even when they do work, there are problems, not least that coming off the drugs brings severe side effects. The picture is no less grim for other mental illnesses: there is a chronic shortage of new treatments and precious few ideas about where fresh options might come from.

That's part of the reason why a psychedelic revival has always been so tantalising. The first push came in the late 1990s, driven primarily by a US non-profit called the Multidisciplinary Association for Psychedelic Studies (MAPS). After a few individuals were determined enough to go through the arduous process of getting approval to work with psychedelics, the US Food and Drug Administration (FDA) decided to treat psychedelics like other drugs, meaning researchers were not banned from working with them.

Two decades later, those efforts are finally paying off. The psychedelic renaissance is entering a new stage, with a series of startling insights gracing the pages of leading journals and clinical trials making progress.

MDMA, better known as the party drug ecstasy, is the furthest along. Although not a classic psychedelic in that it doesn't induce hallucinations, MDMA works by flooding the brain with serotonin, which makes users feel euphoric. These mood-altering effects are the reason researchers became interested in using it as a tool to assist psychotherapy for people with post-traumatic stress disorder (PTSD).

PTSD will affect roughly 7 per cent of people in the US at some point in their lives. The most effective treatment involves memory reconsolidation. People are asked to recall traumatic events so that their memories of them can be stripped of fearful associations by processing them in a new way. The problem is that recall can sometimes be so terrifying that they have to stop receiving this form of therapy. MDMA appears to help, not only because it extinguishes anxiety and stress, but also because it triggers the release of oxytocin, ›

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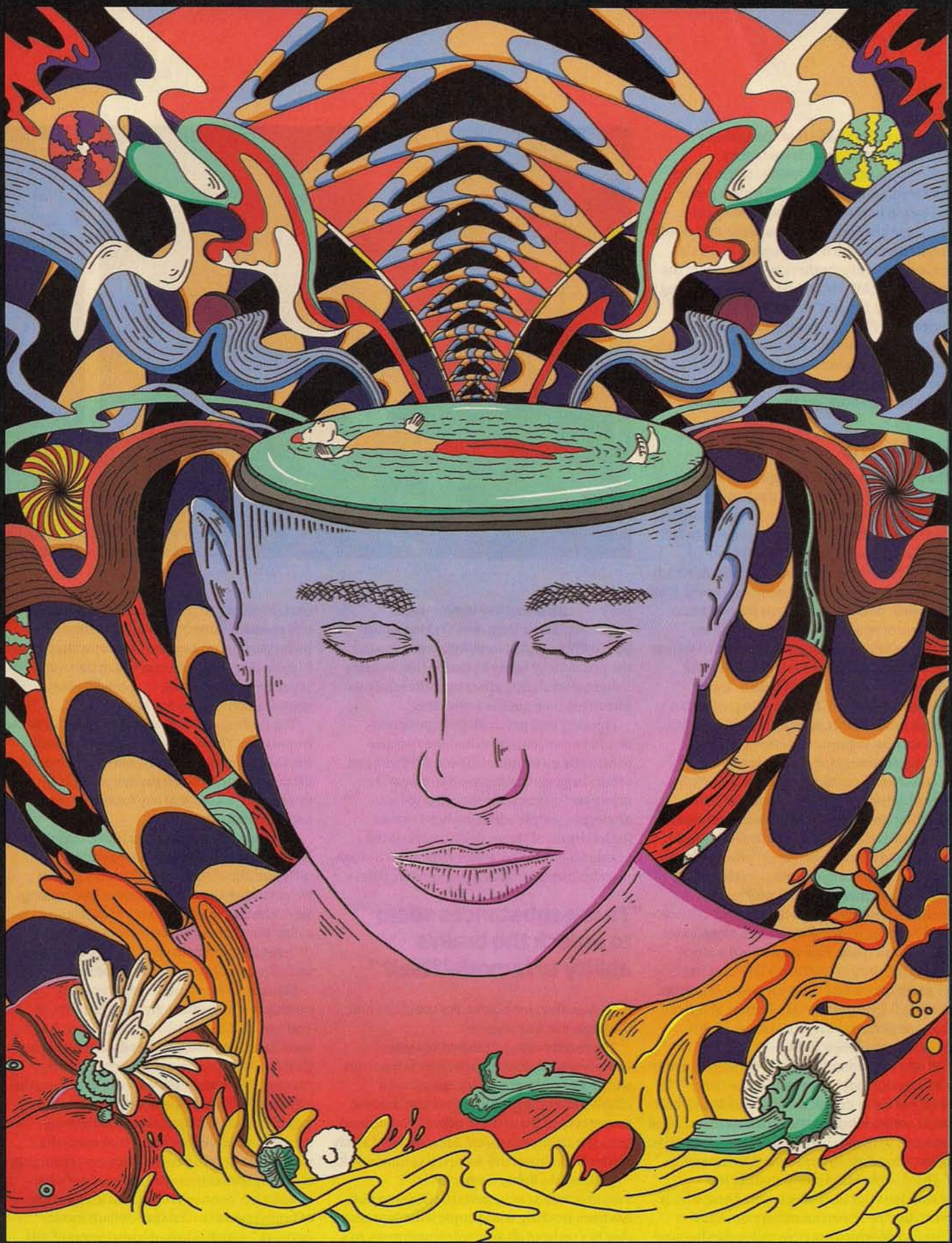


a pro-social hormone that strengthens feelings of trust towards therapists.

Last year, at the Psychedelic Science 2017 conference in Oakland, California, a group led by Michael Mithoefer at the Medical University of South Carolina presented results from trials in which 107 people with PTSD underwent a psychotherapy while under the influence of MDMA. A year or so after having the therapy, roughly 67 per cent of them no longer had PTSD, according to a measure based on symptoms such as anxiety levels and frequency of nightmares. About 23 per cent of the control group, which had psychotherapy and a placebo drug, got the same benefit.

Healing trip

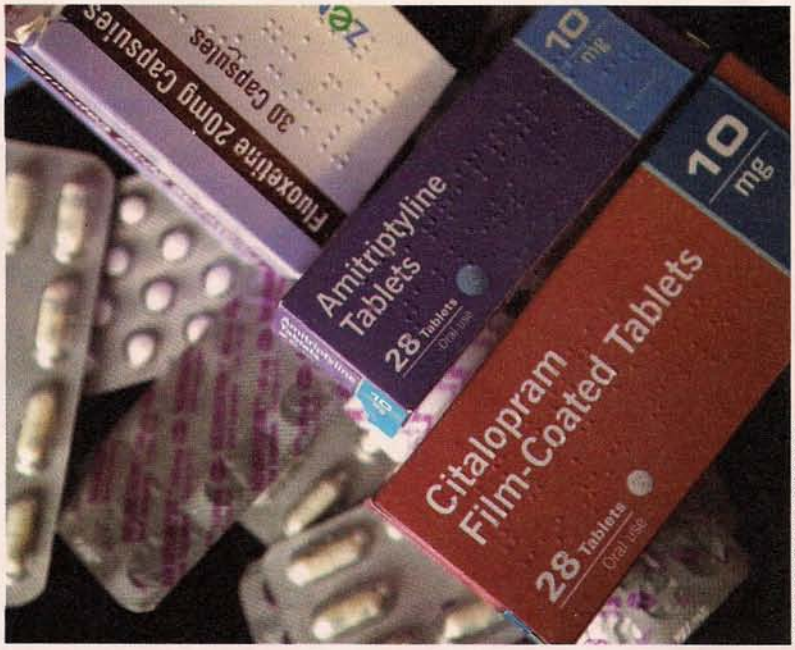
That convinced the FDA to give the nod for Mithoefer's group to carry out further trials involving more participants, the last hurdle to clear before the drug can be approved. In fact, the FDA was so impressed that it granted MDMA "breakthrough therapy" status, which will accelerate the path towards approval. If all goes well, it could be in use as soon as 2021.

If recent results are anything to go by, however, true psychedelics – those that induce hallucinations – might end up having the biggest impact on mental health. That's because psilocybin, the active ingredient in magic mushrooms, is beginning to look like the real deal: a genuinely effective, long-lasting treatment for depression.

It started in 2006, when Roland Griffiths, a psychiatrist and neuroscientist at Johns Hopkins University in Baltimore, replicated the results of a notorious study from 1962. He showed that a large dose of psilocybin can induce mystical experiences in volunteers without any mental health problems, including feelings of ego dissolution, a sense of revelation, ineffability and transcendence of time and space. Fourteen months after taking the drug at Griffiths's lab, 22 of the 36 participants said the experience improved their well-being or life satisfaction, and rated it as one of the top five most meaningful experiences of their lives.

It was a landmark study. As Solomon Snyder, also at Johns Hopkins, wrote at the time: "The ability of these researchers to conduct a double-blind, well-controlled study tells us that clinical research with psychedelic drugs need not be so risky as to be off-limits to most investigators."

In a double-blind study, neither the researchers nor the participants know who is receiving the experimental treatment. It is tricky to do with drugs like psilocybin because the hallucinations they induce mean volunteers know they aren't taking a placebo. But Griffiths and his colleagues got around the problem by using a placebo that induces a slight stimulating effect to trick recipients into think they got the active drug.



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Figuring that psychedelic experiences would be particularly valuable to people confronting a terminal illness, Griffiths and others began trials designed to assess the safety and efficacy of psilocybin to treat anxiety in people with advanced cancer. In the largest of those, Griffiths recruited 51 volunteers. Half of them were given a small placebo-like dose during one session, then a high dose five weeks later. For the other half, the sequence was reversed.

"These substances seem to unlock the brain's ability to remodel itself"

The results were published last year. There was a marked reduction in depression and anxiety symptoms compared with placebo after the high-dose session, and for 80 per cent of them those benefits continued to be felt six months later. An associated study at New York University reported similar results.

Meanwhile, Robin Carhart-Harris, a neuroscientist at Imperial College London, has been working with people with depression that has resisted all available treatments. In a trial involving 20 people, participants had two sessions – one on a single low dose of psilocybin (10 milligrams), one on a single high dose (25 mg) – during which they each separately lay listening to specially chosen music, accompanied by therapists.

The findings, also reported last year, were impressive. Those two doses, combined with the psychological support, were sufficient to lift depression in all 20 participants for three weeks, and to keep it at bay for five of them for three months.

That is in stark contrast to the best available antidepressants. "What's weird and so different about these [psychedelics] is that we're talking about a single dose having long-term effects," says Insel, now at a start-up called Mindstrong. "That's a remarkably different approach to what we've been doing, with drugs that people take chronically."

Hints as to why psychedelics work so quickly and so enduringly have come from brain scans. Since 2010, Carhart-Harris has used functional magnetic resonance imaging (fMRI) to scan the brains of people without mental illness while they are experiencing the effects of different psychedelic drugs. He has found that LSD and psilocybin both cause activity in parts of the brain that normally work separately to become more synchronous, meaning the neurons fire at the same time. In addition, connectivity across a collection of brain regions called the "default mode network", which is linked to our sense of self,

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Antidepressants (left) don't work for 1 in 5 people. Psychedelic therapy (right) might be more effective

or ego, is drastically reduced. The more this network disintegrates, the more volunteers report a dissolving of the boundaries between themselves and the world around them.

Carhart-Harris thinks psilocybin therapy interrupts the spirals of rumination and negative thoughts that depressed people get caught up in. In that sense, it seemed telling that people in his psilocybin-for-depression trial who experienced aspects of a spiritual or mystical experience saw a bigger decrease in their depression scores than those who didn't.

To see what effect the drug had, however, Carhart-Harris and his colleagues scanned the brains of their participants before and after they received psilocybin-assisted therapy. Contrary to expectations, the integrity of the default mode network, meaning the extent to which neurons across its separate brain regions fire together, had increased one day after therapy. What's more, the magnitude of this effect correlated with the extent to which the volunteers' depression had lifted.

Since the volunteers weren't scanned during the acute drug experience, interpreting this result requires a bit of speculation, but Carhart-Harris sees this as a "reset process". "You take something that's ordered, but pathologically ordered perhaps; you shock it and scramble it and then it returns, but it returns to a healthier mode," he says.

For Carhart-Harris, this trick of unlocking the brain's ability to remodel itself, known as plasticity, is what makes psychedelics so unique and valuable. The effect isn't intrinsically therapeutic, he says, but when combined with psychotherapy it appears to have an unparalleled capacity to alleviate mental illness or behavioural problems.

Back to the future?

And the insights gleaned by peering into the brains of the people who volunteered for his psilocybin trial don't end there. Participants were shown pictures of happy and frightened faces as they lay in the fMRI machine. The amygdala, a part of the brain that deals with emotions, including fear, typically lights up in response to such stimuli. SSRIs dampen those responses. But after the combined psilocybin-psychotherapy session, the amygdala lit up. And again, this effect correlated with how well people did: the greater the response in the amygdala, the more their symptoms improved.

This suggests a profound change in the processing of emotions, which fits with what participants reported in interviews. While SSRIs blunt both positive and negative feelings, it seems psilocybin does the opposite, helping people reconnect with their emotions. Those may not always be positive, but the idea is that connection with emotions is better than numbness.

The usual caveats apply, of course: all of these studies are relatively small and Carhart-Harris's recent trial lacked a control group to directly contrast with those taking psilocybin. "One needs to be cautious," says Paul Summergrad at Tufts University in Boston, who is a former president of the American Psychiatric Association. "The history of psychiatry and medicine is full of things people get excited about that don't play out."

If larger studies produce similarly compelling outcomes, however, the implications would be profound. "The conversation now with psilocybin and MDMA is very different than what we've had with the development of other antidepressants and anti-anxiety drugs," says Insel. "We're now talking about psilocybin-assisted therapy,

"Some doctors have gone rogue, offering illegal psychedelic treatments"

meaning that it's not just about the chemical but the role the chemical can have in a psychotherapeutic experience," he says.

For Insel, the fact that they are psychedelics is irrelevant. "I'm excited to think that there might be compounds that could be used in a new way to give us something that will make a difference for people who haven't received much assistance from the drugs we have."

So what now? The short answer is more trials. UK firm Compass Pathways plans to conduct a placebo-controlled psilocybin trial in 400 people with depression across eight European countries in the next year. Griffiths is also preparing for a placebo-controlled trial, and Carhart-Harris is planning one to compare psilocybin with a leading SSRI.

One problem is that drug development is an eye-wateringly expensive business. In preparation for MDMA being licensed for PTSD, however, MAPS has set up a public benefit corporation that will market the drug and use the profits to push through other promising psychedelics.

The biggest danger now might be that history repeats itself. The first wave of psychedelics research was to a great extent doomed by excessive enthusiasm. Today, as the revival has gathered steam, some doctors have likewise grown impatient and gone rogue, offering their patients underground psychedelic treatments. Hence the current crop of researchers are at pains to preach patience and rigour.

Insel put it more bluntly at last year's Psychedelic Science conference: "Don't screw this up." ■

Sam Wong is a reporter at *New Scientist*