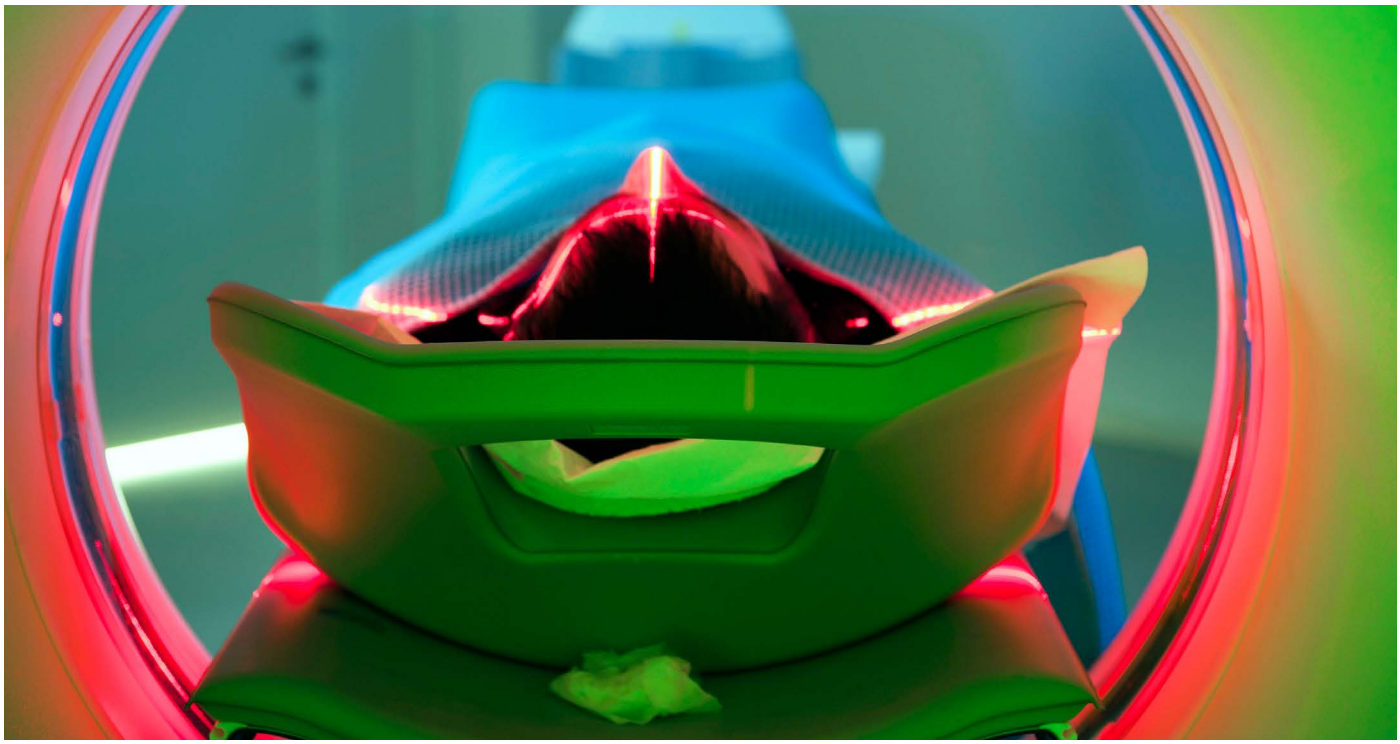

BARANOZ DEMIR/GETTY

Brain imaging is an important tool as researchers try to understand the effects of psychedelic drugs.

Your brain on psychedelics

Mind-altering drugs are shaking up medicine — but how they actually work remains a mystery. A flurry of imaging studies could clarify the picture. **By Liam Drew**

In a 1964 book, *The Psychedelic Experience*, psychologists Timothy Leary, Ralph Metzner and Richard Alpert wrote[1] that a psychedelic drug is like "a chemical key" that "opens the mind, frees the nervous system of its ordinary patterns and structures".

In the 1950s and 1960s, many scientists and psychiatrists were fascinated by psychedelics — both natural ones, such as psilocybin (from 'magic mushrooms') and mescaline (from certain cacti), and artificial ones, such as LSD, which was first synthesized in 1938. They asked how psychedelics reshape consciousness, perception and cognition; how these drugs shake people's sense of self; and whether psychedelics could be used to treat psychiatric disorders.

The speculative answers that this generation of investigators offered were constrained by the tools they possessed. Evidence that psychedelics interfered with the function of the neurotransmitter serotonin was rudimentary, and the techniques used for probing brain function were coarse. When that first enthusiastic wave of investigation started to fade amid a political backlash against psychedelics in the 1970s, many psychological ideas remained unlinked to neurobiological mechanisms.

Researchers working in today's 'psychedelics renaissance' are wrestling with same core questions but have at their disposal much sharper tools. In particular, they have access to neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). And, thanks to volunteers willing to experience the effects of psychedelics in the confines of brain scanners, the way these drugs reconfigure human brain activity has been observed in real time.

These studies have revealed that psychedelics cause brain regions whose activity is normally robustly coupled to become less coordinated. And many regions that are usually only loosely connected start to communicate with each other more.

Most researchers agree with this broad summary, but reaching a consensus on the details is proving difficult. Robin Carhart-Harris, who studies psychedelics at the University of California, San Francisco, thinks the actions of these drugs are now "pretty well" understood. But Felix Müller, a psychiatrist at the University of Basel in Switzerland, is less convinced: "Everything is quite unclear," he says.

So far, neuroimaging studies have been small and their results inconsistent. Researchers hope that a new data-sharing initiative will help establish which findings are robust, but different types of experiments will be needed to resolve unanswered questions.

Different views

Classic psychedelic drugs, such as LSD and psilocybin, disrupt neural activity by diffusing through the brain and activating a serotonin

receptor known as the 5-HT_{2A} receptor. Once stimulated, these receptors make neurons more excitable, and their blanket activation by psychedelics causes widespread changes to neural networks.

There are 5-HT_{2A} receptors throughout the brain, but they are most abundant in the cerebral cortex, particularly in areas responsible for cognition and self-awareness. Furthermore, 5-HT_{2A} receptors are highly expressed in the visual cortex, and on the ends of axons that cortical neurons send elsewhere in the brain, such as the thalamus, where sensory information is processed. This is consistent with psychedelics causing perceptual distortions.

In 2019, neuroscientist Patrick Fisher at Copenhagen University Hospital used PET imaging to show that, after a person took a relatively high dose of psilocybin, its psychoactive metabolite psilocin occupied 72% of the brain's 5-HT_{2A} receptors[2]. He also found that a trip's subjective intensity correlated strongly with how many of these receptors were occupied.

Researchers now want to use imaging to help establish how psychedelics change the way the brain processes information. In the 1990s, PET imaging showed that psilocybin increased brain metabolism in the frontal cortex, but also in the visual cortex. Scientists are now mainly addressing this question using a form of imaging known as resting-state fMRI. "If you want to have a general overview of what happens in the brain," says Katrin Preller, a neuroscientist at the University of Zurich in Switzerland, "resting-state fMRI is the best way to do that."

Most fMRI involves researchers observing which brain areas are active when people are actively doing something, such as viewing emotionally loaded images or performing a memory task. With resting-state fMRI, the brain's fluctuating blood flow is recorded when a person lies quietly absorbed in their thoughts for tens of minutes at a time.

Researchers then divide the brain scan into regions and use statistical methods to look for correlations in blood flow between two or more regions. When correlations are found, the assumption is that these brain regions are communicating and are engaged in the same cognitive processes — they are said to be functionally connected.

Studies of functional connectivity have shown that the brain contains various discrete networks. Most scientists think there are about seven or eight discrete networks, including an attention or salience network, with others related to vision, hearing, sensorimotor processing and executive control. When a person is at ease, activity is seen across a collection of areas called the default mode network (DMN).

These networks and their connections might be called, in Leary and colleagues' words[1], the brain's "ordinary patterns and structures". The question is whether psychedelics free a person from them.

Integration and disintegration

So far, according to a review[3] published this year, roughly 300 volunteers have taken a dose of various psychedelics — most commonly psilocybin or LSD — across 17 investigations using resting-state fMRI. Every study found that the drug changed the brain's connectivity patterns. In many, the researchers tried to identify specific connectional changes that correlated well with the self-reported intensity of the trip, or with some particular aspect of it, such as a sense of ego dissolution.

"Signal complexity is reliably increased with psychedelics, and it tracks the intensity of the subjective experience."

Together, these studies indicate that psychedelics lead to "more connections between networks, and less connectivity within networks," says Manesh Girn, a PhD student who studies psychedelics at McGill University in Montreal, Canada. In other words, brain areas that usually have strong functional connections — and that operate in a network that has a fairly circumscribed function — become less connected, suggesting that the drugs disrupt those networks' normal outputs. And brain areas whose activity is normally only weakly correlated become more connected. Most findings are consistent with the brain's sensory areas having more influence on overall brain activity after psychedelics were taken.

Researchers are now using these neuroimaging data to develop descriptive theories of how psychedelics alter the way brains process information. In 2014, Carhart-Harris introduced the idea that psychedelics make the brain more entropic[4]. Adapting from physics this fundamental metric — which quantifies how unpredictable or complex a system is — he proposed that psychedelics make the brain less ordered.

Carhart-Harris has since published multiple papers looking at brain signals, acquired through fMRI, electroencephalography (EEG) and other methods, and used mathematical analyses to study their complexity. "Signal complexity is reliably increased with psychedelics," he says, "and it tracks the intensity of the subjective experience very closely."

Another idea that Carhart-Harris's paper[4] on the entropic brain considered was that psychedelics dissolve a person's sense of self by weakening connections within the DMN — an idea that gained traction far beyond the research community.

Both hypotheses have been influential, but they have their critics. Preller, for example, is sceptical about the role of the DMN. "We don't know how large the contribution of the default mode network is, because there are ten other brain networks that are also altered," she says.

Similarly, several researchers consider entropy to be too nonspecific. Fisher is troubled by how many different methods have been used to assess it. "You've got eight different papers talking about entropy," he says, "and nobody has any idea whether they're communicating the same message."

Preller's concerns lie with how entropy measurements can be related to specific neural mechanisms. "We really do not understand what they tell us about the biology."

In 2019, Carhart-Harris folded the idea of the entropic brain into a grander theory of psychedelics' actions, termed the REBUS model and the anarchic brain[5] (where REBUS stands for 'relaxed beliefs under psychedelics'). The model builds on a previous theory of total brain function that conceptualizes the brain as a prediction machine that constantly forms models of what it expects to perceive in the world, then tests whether incoming sensory data confirm these models. The REBUS model proposes that psychedelics weaken the constraints that a person's pre-existing beliefs place on their perception of the world and of themselves. This means that, under the influence of psychedelics, sensory inputs and recalled memories are freer to influence the brain and conscious experience.

This year, Girn published an analysis of existing fMRI data that supports the model. He found that LSD and psilocybin compress the usual hierarchy of connectivity between sensory and association networks[6]. "These sensory areas — and their bare, concrete processing of the external world — become less separate from the processes conceivably related to our abstract thinking and beliefs," Girn says. "It doesn't fully validate the REBUS model, but it's consistent."

For Preller, such inconclusive results are a problem. "It's difficult to really test the REBUS model because the predictions are somewhat unspecific," she says. Her work instead centres on a model developed by Franz Vollenweider, a neuroscientist at the University of Zurich who introduced her to psychedelics research. "It is more a model rooted in brain anatomy and brain function," Preller says. From research Vollenweider began in the 1990s in humans

and animal models, he proposed the thalamic gating model.

The thalamus is a brain area that processes and filters sensory information en route to the cortex. This filtering, or gating, is regulated by the cortex through axons that express the 5-HT_{2A} receptor. Psychedelics seem to interfere with the thalamus's filtering operation, resulting in more sensory signals reaching the cortex. This is proposed to be central to the psychological effects of psychedelics. "Using fMRI, we looked at functional and effective connectivity to test what happens in the brain," Preller says, and the thalamic gating model "aligned very well with what we saw."

Preller acknowledges that the gating model and REBUS both focus on sensory data gaining greater influence over global brain function — and accepts they are not mutually exclusive.

In addition to these theories, Manoj Doss, a cognitive neuroscientist at Johns Hopkins Medical School in Baltimore, Maryland, says that fMRI findings suggest a central role for the claustrum[7], a small subcortical region rich in 5-HT_{2A} receptors. Like the thalamus, the claustrum exists in a loop with the cortex.

What next?

Resting-state fMRI studies have often come to contradictory conclusions, making it difficult to know which theory best explains the effects of psychedelics. This uncertainty led Fisher to coordinate a systematic review[3] that was concerned about the small sample sizes of these studies. It also highlighted many methodological differences, including the drug dose used, how scanning data were processed, and what methods of data analysis were used. "For many of those decision points," Fisher says, "there's not a clear-cut right or wrong answer." But he thinks a more standardized approach would increase the reliability of the data.

His review offered several recommendations, such as always having research participants close their eyes to minimize variability in sensory inputs. But getting researchers to do this could be difficult. "If you're keeping people's eyes closed, they're going to fall asleep in the placebo condition," says Doss. "Then you're comparing that to a condition in which people are wide awake, because you can't fall asleep on psychedelics."

Fisher's review is indicative of growing efforts to unite the field. Notably, Girn is joint leader of a new data-sharing project that will allow investigators to analyse each other's results. "Everyone is out there with their small data sets," Girn says. "What if you pool it all together?"

One goal, Girn says, is to examine models of psychedelics' actions and have researchers collectively decide what specific functional connectivity changes would lend support to each. The next step is to see whether such changes are detected across multiple data sets.

THOMAS ANGUS, IMPERIAL COLLEGE LONDON

Robin Carhart-Harris discusses how psilocybin can be used to treat depression.

But many researchers doubt that reanalysing existing data will provide all the insights needed to understand psychedelics. Müller and Doss say the effects of psychedelics should be compared with those of other psychoactive substances. Even caffeine increases measures of brain entropy, says Doss, casting doubt on the idea that increased entropy is a straightforward indicator of psychedelic states.

This year, Müller published a study of LSD alongside two powerful psychoactive drugs that are not classic psychedelics: MDMA (often known as ecstasy) and amphetamine. LSD increased functional connectivity between the thalamus and sensory cortices, which is consistent with the thalamic gating model. But so did MDMA and amphetamine, showing that this action is not specific to the psychedelic[8]. What made LSD stand out was something else: it increased the connectivity between the attention–salience network and the rest of the brain.

Doss also wonders whether resting-state fMRI has become too dominant. Instead of letting people's minds run free in the scanner, he wants researchers to run specific tests of cognition, memory and perception to observe the changes in brain activity that accompany alterations to these processes. He points to a study led by Vollenweider that used fMRI to assess the reaction of the amygdala — a region of the brain that processes emotions — when people were shown faces with fearful expressions[9]. LSD dampened that response. "We should be constraining cognition," Doss says, "and trying to get at these smaller mechanisms."

Researchers also need to confront the diversity of psychedelic experiences. These vary, both between and within trips, from sublime to terrifying, from profound to frivolous, and from introspection to wonder at the universe's infinitude. "Within a trip, you can go to heaven and hell," says Carhart-Harris.

He will soon use neuroimaging to examine psychedelic substates to look at the connectivity changes that relate to struggle and bliss states. "The assumption is that they'll have quite different dynamic signatures," he says.

Also unfolding is a drive to use neuroimaging to understand not just the acute effects of psychedelics, but also longer-term effects that might underlie psychedelics' proposed medicinal effects. Such studies have already begun, hinting at functional connectivity changes potentially associated with antidepressant actions, for instance (see page S87).

For now, though, these small studies and their inconclusive, often controversial, results are again stoking much debate. Preller welcomes calls for larger, more rigorous studies and for more researchers to get involved. "This is a sign of a maturing field," she says. "Eventually, we'll get there."

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1. Leary, T., Metzner, R. & Alpert, R. *The Psychedelic Experience* (University Books, 1964).
2. Madsen, M. K. *et al. Neuropsychopharmacology* **44**, 1328–1334 (2019).
3. McCulloch, D. E.-W. *et al. Neurosci. Biobehav. Rev.* **138**, 104689 (2022).
4. Carhart-Harris, R. L. *et al. Front. Hum. Neurosci.* **8**, 20 (2014).
5. Carhart-Harris, R. L. & Friston, K. J. *Pharmacol. Rev.* **71**, 316–344 (2019).
6. Girn, M. *et al. NeuroImage* **256**, 119220 (2022).
7. Doss, M. K. *et al. Brain* **145**, 441–456 (2022).
8. Avram, M. *et al. Biol. Psychiat. Cogn. Neurosci. Neuroimag.* https://doi.org/10.1016/j.bpsc.2022.04.003 (2022).
9. Kraehenmann, R. *et al. Biol. Psychiat.* **78**, 572–581 (2015).