Do our brains predict how we think? Psychedelics may help answer that question

Anil Ananthaswamy | August 12, 2021

Credit: Dreamstime

"Everything became imbued with a sense of vitality and life and vividness. If I picked up a pebble from the beach, it would move. It would glisten and gleam and sparkle and be absolutely captivating," says neuroscientist Anil Seth. "Somebody looking at me would see me staring at a stone for hours."

Or what seemed like hours to Seth. A researcher at the UK's University of Sussex, he studies how the brain helps us perceive the world within and without, and is intrigued by what psychedelics such as LSD can tell us about how the brain creates these perceptions. So a few years ago, he decided to try some, in controlled doses and with trusted people by his side. He had a notebook to keep track of his experiences. "I didn't write very much in the notebook," he says, laughing.

Instead, while on LSD, he reveled in a sense of well-being and marveled at the "fluidity of time and space." He found himself staring at clouds and seeing them change into faces of people he was thinking of. If his attention drifted, the clouds morphed into animals.

Seth went on to try ayahuasca, a hallucinogenic brew made from a shrub and a vine native to South America and often used in shamanistic rituals there. This time, he had a more emotional trip that dredged up powerful memories. Both experiences strengthened Seth's conviction that psychedelics have great potential for teaching us about the inner workings of the brain that give rise to our perceptions.

He's not alone. Armed with fMRI scans, EEG recordings, computational models of the brain and reports from volunteers tripping on psychedelics, a small but growing number of neuroscientists are trying to take advantage of these drugs and the hallucinations they induce to better understand how the brain produces perceptions. The connections are still blurry, but the studies are beginning to provide new support for a provocative, more-than-a–century-old hypothesis: that one of the fundamental functions of the brain — and the root of everything we perceive — is to make best guesses about the causes of information impinging on our senses at any given moment. Proponents of this idea have argued that these powers of prediction enable the brain to find meaning amid noisy and ambiguous sensory information, a crucial function that helps us make sense of and navigate the world around us.

When these predictions go haywire, as they seem to under psychedelics, the perceptual aberrations provide neuroscientists with a way to probe the workings of the brain — and potentially understand what goes wrong in neuropsychological conditions, such as psychosis, that cause altered perceptions of reality.

The predictive brain

The idea that the brain is, in essence, a prediction machine traces its modern roots to the 19th century German physicist and physician Hermann von Helmholtz. He noted that our brains have to make inferences about the possible causes of the signals we receive via our senses. He pointed in particular to our ability to perceive different things given the same sensory information (a good example of this would be the famous optical illusion that can appear either as the silhouette of two people facing each other or as the contours of a vase). Given that the sensory input isn't changing, Helmholtz argued that what we perceive must be based on the brain's prediction of what's there, based on prior knowledge.

Over the past century, these ideas have continued to intrigue philosophers, neuroscientists, computer scientists and others. The modern version of the theory is called predictive processing. In this view of perception, the brain is not a passive organ that simply collates information from the senses. Rather, it's an active coconspirator. It's constantly predicting the causes of incoming information, whether from the world outside or from within the body. In this view of perception, "the brain is actively … creating hypotheses that are the best explanation for the sensory samples that it's receiving," says computational neuroscientist Karl Friston of University College London. These predictions lead to perceptions, which can remain unconscious or enter conscious awareness.

The brain is constantly trying to predict the causes of sensory inputs, and these predictions lead to perceptions. When the sensory inputs are ambiguous, the predictions can keep changing. In this case, your brain may predict that you're seeing a vase — or two people facing each other. Credit: John Smithson

In a landmark 1999 paper that established predictive processing as a leading hypothesis of brain function, two computer scientists, Rajesh Rao and Dana Ballard (now at the University of Washington in Seattle and the University of Texas at Austin, respectively) developed a detailed model of predictive processing — specifically, addressing regions of the brain involved in recognizing objects and faces. Those regions comprise levels of a pathway that begins in the retina, moves on to the lateral geniculate nucleus of the thalamus and then to higher and higher levels of the cerebral cortex, named V1, V2, V4, IT and onward.

In Rao and Ballard's model, each brain area that constitutes a level in such a hierarchy makes predictions about the activity of the level below: V2, for example, predicts the neural activity it expects of V1, and sends a signal down to V1 indicating this prediction. Any discrepancy between the prediction and the actual activity in V1 generates an error signal that moves up from V1 to V2, so that V2 can update its expectations of V1. So predictions flow down, from higher to lower layers, and errors move up, from lower to higher layers. In this way of thinking, the lowest layer — the one closest to the retina — makes predictions about the incoming sensory information, and the highest layers — IT and above — hypothesize about more complex features like objects and faces. Such predictions, continually updated as we move around, are what we perceive.

In the years since Rao and Ballard's paper, neuroscientists have begun to find experimental evidence that supports such computational models. For example, the theory predicts that sensory stimuli that are expected or unsurprising should generate less neural activity in lower levels of the hierarchy (because they generate fewer error signals). And fMRI scans of neural activity in the lower layers of the visual cortex in people looking at computer-generated images bear this out.

But predictive processing can go wrong, posit behavioral and clinical neuroscientist Paul Fletcher and his student Juliet Griffin of the University of Cambridge in the UK — and when that happens, we may perceive things that aren't real, be they aberrations of sight, sound or other senses. It's an idea that piques the interest of those who study conditions such as schizophrenia, which is often accompanied by psychosis. "If predictive processing helps us to understand how the mind connects to external reality, I think it follows that it is a useful way of understanding situations in which the mind seems disconnected from reality," says Fletcher. Indeed, Fletcher notes, such disconnection is essentially the definition of psychosis. (Griffin and Fletcher explored the potential connection between predictive processing and psychosis in the 2017 *Annual Review of Clinical Psychology*.)

Prior expectations

An important aspect of predictive processing is that each hypothesis generated by a level in the hierarchy is associated with a notion of confidence in the hypothesis, which in turn is based on prior expectations. The higher the confidence, the more a given level ignores error signals from the level below. The lower the confidence, the more a given level listens to upward-moving error signals. Could psychedelics be altering our perception of reality by messing with this process? Friston and Robin Carhart-Harris, a psychologist and neuroscientist at Imperial College London, think so. In 2019, they put forward a model called REBUS, for "relaxed beliefs under psychedelics." According to their model, psychedelics reduce the brain's reliance on prior beliefs about the world. "We feel them with less confidence," says Carhart-Harris. "They are less reliable under psychedelics."

If that's what psychedelics do, one result could be an increase in cognitive flexibility. Conversely, blocking the receptors in the brain that are activated by psychedelics might do the opposite — make beliefs more rigid.

Neuroscientists often think of the brain as organized into hierarchical levels. The concept of predictive processing holds that each level makes predictions about the activity of the level below. These predictions flow down the hierarchy, and lower levels generate an error signal that indicates the difference between the predicted and actual sensory inputs. These error signals flow upward, and higher levels use them to refine their predictions. Predictions at the highest level help to create perceptions.

Some evidence for this comes from experiments with rats in which researchers gave the animals a drug that blocks the main type of receptor on the surface of neurons that responds to LSD and other classic psychedelic drugs. These receptors, called 5-HT2A serotonin receptors, are densely distributed in the regions of the cortex responsible for learning and cognition. Blocking 5-HT2A receptors, it turns out, makes rats cognitively inflexible: They are no longer able to spontaneously change from one behavior to another in order to get a reward. In the context of predictive processing, the finding suggests that the 5-HT2A-blocker made the rats' brains more tightly constrained by prior beliefs about the world.

Conversely, when psychedelics bind to 5-HT2A receptors, they seem to make the brain less reliant on prior expectations and more reliant on actual sensory information. This could account for the vivid perceptual experiences they cause. According to the predictive processing model, a brain on psychedelics gives more weight to information entering the lower layers, which deal with concrete visual features — say, the shape and color of a flower. Constraints imposed by abstract beliefs and expectations about the flower are relaxed. "All of these higher-level constructs have been dissolved," says Friston. "It can be a very pleasurable experience."

If psychedelics mess with prior beliefs, that might also explain why they cause one to hallucinate a reality that's untethered from real-world expectations. Take, for example, Seth's experience of seeing clouds morphing into familiar faces. According to Friston, the brain's visual system has strong prior beliefs — for instance, that clouds are up in the sky. Another prior belief would be that there are no faces up there. Normally, this would make it nearly impossible to perceive, say, Lucy in the sky (with or without diamonds). But as psychedelics take hold, higher levels of the predictive processing hierarchy begin to make otherwise untenable predictions about the world outside. These predictions become perceptions. We start hallucinating.

Of course, psychedelic hallucinations are not only visual. They can involve all types of altered perceptions. In 2017, for example, neuropsychologist Katrin Preller of the University Hospital for Psychiatry Zurich in Switzerland and colleagues found that people listening to music that they normally considered meaningless or neutral felt heightened emotions and attributed an increased sense of meaningfulness to the music while on LSD.

Friston argues that these altered perceptions extend even to our sense of self, which in the predictive processing framework is based on the brain's internal models of all aspects of our own being. Psychedelics would, again, loosen the hold of these internal models. "You now lose a precise sense of self," says Friston. Indeed, a survey by Carhart-Harris and colleagues suggests that a breakdown of the boundaries of the self could be one explanation for why some people on psychedelics report mystical feelings of a sense of unity with their surroundings.

Disrupted connections

If psychedelics do act on the brain to change predictive processing, it's not clear how they do it. But in recent studies, researchers have found ways to approach these questions. One way to gauge changes occurring in brains on psychedelics is to measure something called Lempel-Ziv complexity, a tally of the number of distinct patterns that are present in, say, recordings of brain activity over the course of milliseconds using a method called magnetoencephalography (MEG). "The higher the Lempel-Ziv complexity, the more disordered over time your signal is," says Seth.

The most famous psychedelic compound, LSD (short for lysergic acid diethylamide), was synthesized in 1938 by Swiss chemist Albert Hofmann. In 1943, after apparently absorbing some LSD through his fingertips by accident, Hofmann experienced hallucinations and had to rush home from work. Hofmann later continued his experiments and went on to document in detail the psychedelic effects of LSD. Credit: Novartis International

To determine the degree of disorder of human brains on psychedelics, Seth's team, in collaboration with Carhart-Harris, looked at MEG data collected by researchers at the Cardiff University Brain Research Imaging Centre in Wales. The volunteers were given either LSD or psilocybin, the hallucinogenic ingredient in "magic mushrooms." On psychedelics, their brain activity was more disordered than it was during normal waking consciousness, according to an analysis of the MEG signals that was published in 2017. Seth says that while the increase in disordered brain signals does not definitively explain people's psychedelic experiences, it's suggestive. "There's a lot of mind-wandering and vagueness going on," says Seth. "The experience is getting more disordered and the brain dynamics are getting more disordered." But he says there's more work to do to establish a clear connection between the two.

More recently, Seth, Carhart-Harris and colleagues took another look at the brain on psychedelics, using a statistical metric called Granger causality. This is an indication of information flow between different regions of the brain, or what neuroscientists call functional connectivity. For example, if activity in brain region A predicts activity in brain region B better than the past activity of B itself does, the Granger causality metric suggests that region A has a strong functional connection to region B and drives its activity. Again, using MEG recordings from volunteers on psychedelics, the team found that psychedelics decreased the brain's overall functional connectivity.

One possible interpretation of these Granger and Lempel-Ziv findings is that the loss of functional organization and increase in disorder is disrupting predictive processing, says Seth. Verifying that would involve building computational models that show exactly how measures of Granger causality or Lempel-Ziv complexity change when predictive processing breaks down, and then testing to see if that's what happens in the brains of people on psychedelics.

In the meantime, evidence that psychedelics mess with functional connectivity is mounting. In a randomized, double-blind study published in 2018, Preller and colleagues gave 24 healthy people either a placebo, LSD or LSD along with a 5-HT2A blocker that impeded the drug's effects. The subjects were then scanned inside an MRI machine, allowing researchers to measure activity in different brain regions and assess their connectedness.

Those people on LSD alone showed widespread changes: Their brains showed an increased connectivity between lower-order brain regions responsible for processing sensory input, but decreased connectivity between brain regions that are involved in the conceptual interpretation of sensory inputs. Preller thinks this might explain the heightened sensory experiences caused by LSD. Indeed, the team also found corroborating evidence, using data from the Allen Human Brain Atlas, a detailed map of gene activity: Areas of the brain that produce the 5-HT2A receptor overlapped with the regions of altered connectivity, suggesting that LSD affects these brain regions the most.

A woody vine that grows in the Amazon and Orinoco river basins in South America, Banisteriopsis caapi is used alone or with other plants to make ayahuasca tea — a drink with psychotropic effects long a part of rituals and shamanic healing practices. Studies have shown B. caapi to have antidepressant effects. Credit: E. W. Smith/Hallucinogenic Plants (A Golden Guide)

Then Preller and colleagues did a more targeted study, using fMRI data to look for changes in functional connectivity between the thalamus and the cortex. The thalamus sits in the center of the brain and processes information from the senses before sending relevant signals up to the cortex. But information also flows in the other direction. In the predictive processing model, signals going down from the cortex to the thalamus would represent predictions, and signals flowing up to the cortex would represent errors. Researchers have long hypothesized that psychedelics may cause the thalamus to function less effectively, says Preller. This may be happening on LSD: Her study, published in 2019, showed that the flow of information from the thalamus up to certain cortical areas increased in people on LSD and the flow going in the opposite direction decreased.

These fMRI brain scans show how LSD alters communication among regions of the human brain (shown here from different angles in the four panels). Red and orange regions show stronger functional connectivity under LSD, and blue regions show reduced connectivity.

Altered brain waves

Additional hints of how psychedelics could interfere with predictive processing have come from an entirely different way of looking at brain function. In 2019, Carhart-Harris got intrigued by a paper he read about potential brain signatures of predictive coding (which is how researchers refer to the way predictive processing may be realized in the brain). He saw a way to test the hypothesis that psychedelics are messing with the brain's prior beliefs.

The paper by computational neuroscientist Andrea Alamia of Centre de Recherche Cerveau et Cognition, CNRS, in Toulouse, France, and a colleague, involved a simplified model of predictive coding. Each level represents a population of neurons — in, say, the LGN and V1 layers of the visual system. The input to the model is a random sequence of numbers, where each number represents the intensity of a light signal. The model has two key parameters. One is the time it takes for a prediction or error to travel from level to level. The other is the time it takes for a population of neurons to return to their baseline activity after the input has waned. The team found that as the model tries to predict the intensity of the input and each level tries to update itself based on the error signal it gets when its predictions are wrong, the model produces waves of signals with a frequency of about 10 hertz, which researchers call alpha waves. These waves ripple up and down through the levels of the model.

In the presence of inputs, the alpha waves travel up from the lower to the higher levels in the hierarchy. In the absence of inputs, the waves travel down. “These are all computational results,” says Alamia. So, to check their model against actual data, the team looked at EEG recordings of electrical brain activity previously collected in volunteers who had been asked to either gauge the intensity of light signals (presence of input) or close their eyes (absence of input). The team found traveling alpha waves that move up in the presence of inputs and down when the eyes were closed — exactly as in their model of predictive coding.

Carhart-Harris found the results exciting. “I wrote the French team, and I said, ‘Look, we've got psychedelic data, and I have a very clear hypothesis for you,’” he says. The hypothesis was simple. Start with EEG recordings of people with their eyes closed, without psychedelics. The alpha waves should be traveling down. Then, inject them with a psychedelic. They'll start having visual hallucinations and the alpha waves should switch direction. That's because the psychedelic, according to the REBUS model, should cause information to flow from lower to higher levels, even with eyes closed and in the absence of real sensory input. “There's just a drug on board that makes you see all these crazy visions,” says Carhart-Harris.

As it happens, his team had EEG recordings from an earlier study of volunteers who had been injected with DMT, the main active component of ayahuasca. They sent these recordings to the French team, who analyzed them, and found the data to be remarkably consistent with the hypothesis. “The drug goes in … and the waves just shift,” says Carhart-Harris.

“I think all this stuff is brilliant,” says Seth. But he says that such research, including his, will have to get nuanced to say something more definitive. Psychedelics have a powerful and widespread effect on the brain, he notes: “It's very hard to find something that doesn't change under psychedelics," he says. "One of the concerns I have at the moment is that basically everyone — and this is the pot calling the kettle black, I'm guilty of this too — takes their favorite analysis and throws it at psychedelics and says, 'Look, it changed.' OK — but everything changes."

Seth thinks a way forward is to experiment with microdosing: giving minuscule quantities of psychedelics to subjects so that they remain cognitively capable of doing specifically designed tasks rather than simply hallucinating inside scanners. "They're not seeing unicorns promenading around the sky, but you're still activating the same system," says Seth. People given microdoses of LSD could be tested on how quickly they detect visual stimuli, for example, as researchers induce shifts in attention, and their reaction times could be compared against computational models of predictive processing.

Such ideas, which are only just emerging, might one day allow researchers to determine if predictive processing is indeed the right model for how the brain creates perceptions.

It's a trippy thought.

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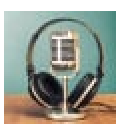

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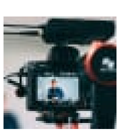

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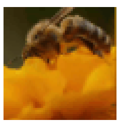

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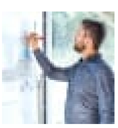

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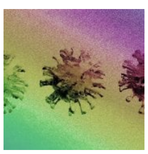

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