Psychedelic drugs' therapeutic potential for a range of psychiatric disorders

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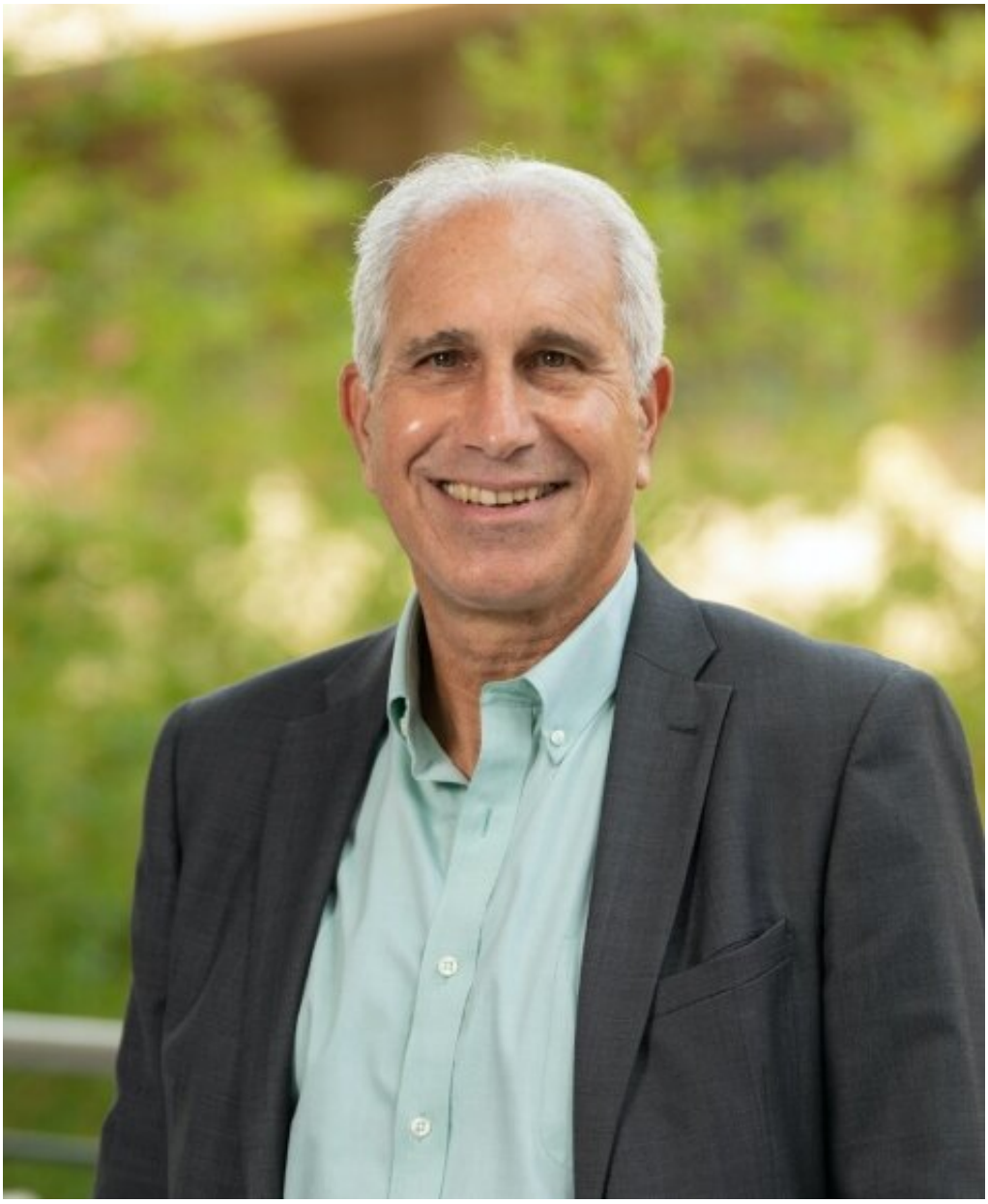

Robert Malenka studies psychedelics for their potential in treatment of psychiatric disorders. Credit: Fontejon Photography for the Wu Tsai Neurosciences Institute

There's been newfound attention to, and a new respect for, so-called psychedelic drugs—chemicals that alter our senses, emotions, thought processes and/or behavior. Robert Malenka, MD, Ph.D., the Nancy Friend Pritzker Professor in Psychiatry and the Behavioral Sciences, has conducted seminal work regarding how individual nerve cells, or neurons, react to different experiences; how those neurons interact in the brain's all-important reward circuitry; and how those interactions influence social motivation, depression and addiction.

In recent years, Malenka has been probing psychedelic drugs' therapeutic potential for a range of psychiatric disorders. Malenka—whom the Society for Neuroscience and the Federation of European Neuroscience Societies recently awarded the Peter Seeburg Integrated Neuroscience Prize—explained how one link in this chain led to another.

In the 1980s and 1990s you did groundbreaking research on a phenomenon called 'synaptic plasticity.' What's synaptic plasticity, and what role does it play in human learning, memory, behavior and habit formation?

Neurons are constantly firing off electrical impulses, which propagate along wires we call axons. At the end of every axon is a terminal that contacts another neuron; that's the synapse. When the electrical impulse reaches that terminal, a chemical is released—in most cases, one called glutamate. Glutamate diffuses across the tiny space separating one

neuron from the next and attaches to receptor proteins in the adjoining neuron. These receptors contain pores through which ions (charged atomic particles) now flow, producing an electrical current that, in turn, can change that neuron's propensity to fire electrical impulses.

All of the brain's amazing functions—our ability to see, hear, feel, think—depend entirely on these synapses. Remarkably, this neuron-to-neuron communication isn't fixed or hardwired. It's highly plastic. The term "synaptic plasticity" describes synapses' ability to change the strength of their connections in response to the experiences the brain is having.

The two major forms of synaptic plasticity are long-term potentiation and long-term depression. Long-term potentiation (LTP) means communication between two neurons becomes stronger, while long-term depression (LTD) means communication becomes weaker.

My past research helped show that the brain's response to any experience—for example, a stressful event or ingestion of a drug—causes LTP and LTD to occur in thousands if not millions of different synapses in different parts of the brain. Furthermore, synaptic plasticity is essential for the proper development of the brain's complex circuitry as we grow from infants to young adults. Without synaptic plasticity, we'd never learn anything new or change anything about how we think, behave and feel. We'd be stuck in some primitive state, like a sponge, and not survive.

In the 2000s and 2010s you started studying pathways in the brain collectively called the reward system. What's that, what's its evolutionary purpose and how does it lead us astray?

The brain's reward system comprises a group of neurons in the middle of the brain that produce and use the chemical messenger dopamine. In general, whenever we experience something that's rewarding, it's because these dopamine neurons are firing electrical impulses and releasing dopamine into another part of the brain: the nucleus accumbens. That's the brain's way of telling us something important is happening, or that it's about to. Usually, when we do something important for our survival—say, eating something when we're really hungry, or drinking water when we're really thirsty—it feels pretty good. That makes us want to learn and repeat the behaviors that led to that rewarding experience.

All addictive drugs, such as cocaine, heroin, nicotine and alcohol, are highly rewarding: They trigger the release of dopamine in the nucleus accumbens to a degree not achieved by natural rewards such as food or sex. But with repeated use, they lead to addiction. I thought that drugs of abuse might be causing LTP or LTD in dopamine neurons and neurons in the nucleus accumbens, fostering the behavioral changes that accompany addiction. In the early 2000s, my lab undertook a series of experiments that confirmed this prediction and supported the idea that addiction can be seen as a pathological form of learning and memory: Drugs of abuse usurp the same synaptic-plasticity mechanisms the brain uses for learning and remembering. Some experimental therapies being tested in addiction are aimed at reversing the pathological synaptic plasticity generated by the drugs.

3. Do other psychiatric disorders besides addiction involve glitches in the brain's reward system?

Yes. For example, a hallmark of depression is the inability to experience pleasure. We and others have found in mice that altered synaptic plasticity in the nucleus accumbens and in dopamine neurons contribute to behavioral changes accompanying depression.

For most of us, hanging out with friends is a highly rewarding experience. Synaptic plasticity plays an important role in generating the rewarding aspects of these social interactions. But we've found, to our surprise, that although dopamine is released in the nucleus accumbens during social interactions, another special chemical messenger called serotonin appears to be even more important. We've shown that serotonin release in the nucleus accumbens is critical to positive, non-aggressive social interactions. At least in mouse models of autism spectrum disorder, this serotonin release is abnormal.

We examined a drug that mimics some of serotonin's actions in the nucleus accumbens, and we showed that this drug can restore more normal social behavior in mice. A biotech company I co-founded [with Stanford professor of bioengineering and of psychiatry and behavioral sciences Karl Deisseroth, MD, Ph.D.] is pursuing these findings and will be testing a related drug in individuals with autism spectrum disorder in the next few months. Similar social deficits accompany schizophrenia and depression.

Most recently, you've been exploring the therapeutic potential of certain psychedelic drugs that are banned because of their addictive or other worrisome properties. What's their clinical potential?

The psychedelic drug I've studied the most, with my colleague Boris Heifets [MD, Ph.D., assistant professor of anesthesiology, perioperative and pain medicine] is MDMA, also known as ecstasy or molly. MDMA promotes positive, prosocial interactions and feelings in human beings. And it's known to cause the massive release of serotonin in the brain. Using mice, we have tied MDMA's prosocial effects to this release of serotonin in the nucleus accumbens. Because MDMA seems to have similar effects in mice and human beings, we reason that anything we

find in mice should have direct relevance to how it works in people.

MDMA is being tested as a treatment for several different psychiatric conditions, notably post-traumatic stress disorder. In clinical trials, its efficacy in enhancing the usefulness of psychotherapy is very promising, and it may get approved by the FDA in the next year or two. But MDMA is an amphetamine derivative, so it has abuse potential and addictive liability. This aspect of MDMA's action, we learned, is due to its causing dopamine release in the nucleus accumbens. A "better" MDMA-like compound with MDMA's prosocial effects, but with little or no abuse potential, could be useful in treating a broad range of illnesses that are accompanied by social withdrawal.

Do any other psychedelic drugs show promise?

Heifets and I are studying psilocybin. Small clinical trials suggest that it may have great therapeutic utility in, for example, severe forms of depression. Drugs such as MDMA and psilocybin are powerful probes of brain function. We can experiment with mice to figure out exactly which synapses and brain pathways these drugs are modifying to mediate their powerful behavioral effects. With appropriate ethical constraints, we can give these substances to human volunteers and use brain imaging to figure out whether the brain pathways in mice that are modified by these drugs are also changed in human brains.

A lot more research needs to be done before these drugs can be used safely as therapies. They're very powerful; they can do damage as well as good. We need to understand how they work so we can use them appropriately and make better versions of them.

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