FAST RELIEF OR FRAGILE FIX?

Psychedelics can disrupt brain patterns & may offer relief for depression based on various factors

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DEPRESSION does not always arrive with reason, nor does it leave on command. It settles gradually, folds into habit and lingers long after the moments that shaped it have passed. Neuroscience has never framed this as a weakness. Instead, it sees something more mechanical, more stubborn: patterns of neural activity that repeat until they become the mind's default setting.

The question then becomes clear: can these patterns be changed in minutes or hours, instead of months or years?

Across laboratories worldwide, that question is unfolding in unexpected ways. Certain compounds, broadly grouped as psychedelics, are drawing attention for their ability to rapidly shift perception, emotion and behaviour, sometimes within a single session. For a field used to slow, incremental treatments, this speed is both promising and unsettling. "These drugs have very powerful effects, but they have many effects. So it is important to understand them well before you can think about clinical translation," says Vidita Vaidya, senior professor in the Department of Biological Sciences at Tata Institute of Fundamental Research.

Inside her laboratory, the work is precise, almost surgical in its intent. In a 2024 study published in *Neuron*, her team identified what she describes as a "switch", a specific neural mechanism linked to the acute anti-anxiety effects of a synthetic psychedelic compound known as DOI. The finding pointed to the activation of parvalbumin-positive interneurons in the ventral hippocampus, which reduced anxiety-like behaviour in animal models without necessarily triggering the hallucinatory effects commonly associated with psychedelics.

The discovery shifts the conversation. If therapeutic effects can be separated from the psychedelic experience, it opens the door to more targeted treatments, ones that retain the biology without the unpredictability.

Yet observing change is not the same as understanding it. Brain imaging revealed striking activity networks lighting up, signals moving in unfamiliar ways but interpretations diverged, seen either as a breakdown of structure or a form of reorganisation.

Only recently has the picture sharpened. An April 2026 *Nature Medicine* mega-analysis of 500+ brain scan across psychedelics — LSD, psilocybin, mesca line, DMT and ayahuasca — found a consisten pattern: brain systems that usually functio separately began to communicate more freely softening the boundaries between perception memory and self-reflection.

The implication is subtle but significant. Depression may be less a deficit to fix than a pattern to disrupt. This idea is now shaping clinical research, with trials testing whether these shifts lead to measurable relief. Early findings, including studies pairing psilocybin with psychotherapy, show meaningful reductions in treatment-resistant depression, though results remain mixed.

Biologically, these compounds act on serotonin systems, particularly the 5-HT2A receptor, altering how information is processed rather than simply increasing or decreasing neural activity. What emerges is not a straightforward treatment model. Psychedelics do not appear to "correct" the brain in the way conventional medications aim to. Instead, they seem to make it temporarily more flexible, increasing its capacity to change. Preclinical research points to elevated levels of brain-derived neurotrophic factor (BDNF), alongside shifts in synaptic structure.

For a brief window, the brain becomes more adaptable, but it is not inherently guided towards recovery. Rather than adding something new, these compounds loosen the brain's existing structure, opening it to change without determining the direction that change will take. Psychedelics, in this sense, remain far from a cure-all or a shortcut.

That loosened structure introduces a more complicated question: if the brain becomes more flexible, what determines the direction it takes? The answer, researchers suggest, lies beyond the compound itself. According to Dr Sudheer of Apollo Hospitals, outcomes are shaped by what clinicians term "set and setting", the individual's mindset, expectations and emotional state, alongside the environment in which the experience unfolds. Dose, preparation and follow-up support all play a role in determining whether it leads to insight, distress, or something in between.

In controlled clinical settings, participants are carefully screened and guided before and after administration. Beyond these safeguards, the risks change. Unsupervised use can trigger adverse psychological reactions, prolonged distress, or unpredictable outcomes. Even within structured trials, limitations persist—from challenges in maintaining blinding to uncertainty over how durable the benefits truly are.

Here, the line sharpens, not between drug and no drug, but between controlled intervention and uncontrolled exposure. Globally, research is advancing unevenly. Some compounds are in advanced trials, with limited therapeutic use emerging in a few countries, yet the field remains unsettled.

In India, that uncertainty is reflected in law. Under the Narcotic Drugs and Psychotropic Substances Act, 1985, these substances remain illegal outside tightly regulated research, with no approved therapeutic use or clinical framework.

The promise is real, but so is the uncertainty. If depression can be disrupted, what ensures it does not return in another form?

HOW PSYCHEDELICS ACT ON THE BRAIN

THESE COMPOUNDS PRIMARILY ACT ON THE SEROTONIN SYSTEM, ESPECIALLY THE 5-HT2A RECEPTOR, WHICH PLAYS A KEY ROLE IN PERCEPTION AND COGNITION

1. Instead of simply increasing or decreasing brain activity, they alter how information is processed across neural networks
2. They are linked to increased brain plasticity, including higher BDNF levels and changes in synaptic connections
3. This results in a temporary loosening of rigid neural patterns that are often associated with depression

WHAT BRAIN SCANS REVEAL

- Brain imaging shows increased communication between regions that usually function independently
- Sensory processing areas begin interacting more with networks linked to memory and self-reflection
- The boundaries between perception and interpretation become less defined during the experience
- Rather than chaos, the brain appears to shift into a more flexible and interconnected state

WHY THIS MATTERS FOR DEPRESSION

- Depression is increasingly understood as a pattern of repetitive and rigid neural activity
- Psychedelics may temporarily disrupt these entrenched patterns, creating space for change
- This does not "fix" the condition directly, but opens a window where new patterns can form
- The outcome depends on how that window is used, not just the drug itself

SET AND SETTING

- Outcomes are strongly influenced by the individual's mindset, expectations and emotional state
- The environment, whether clinical or uncontrolled, plays a crucial role in shaping the experience
- Factors such as dosage, preparation and psychological support significantly affect results
- The same substance can lead to insight, distress, or mixed experiences, depending on these conditions

2024 STUDY

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EXPRESS ILLUSTRATION

Common psychedelics

Psilocybin (magic mushrooms) may reduce depression and anxiety in therapeutic settings but remains unpredictable without supervision. LSD can improve cognitive flexibility and reduce anxiety, though its 8–12 hour duration can prolong distress and trigger panic. DMT or ayahuasca may offer psychological insights but can also cause intense mental and physical effects