Neuropsychological effects of rapid-acting antidepressants may explain their clinical benefits, new research finds

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Rapid-acting antidepressants, including ketamine, scopolamine and psilocybin, have been found to have immediate and lasting positive

effects on mood in patients with major depressive disorder but how these effects arise is unknown. New research led by the University of Bristol explored their neuropsychological effects and found that all three of these drugs can modulate affective biases associated with learning and memory.

The paper, published in *Science Translational Medicine* was carried out in collaboration with researchers at Compass Pathways, Boehringer Ingelheim, and the University of Cambridge.

Negative affective biases are a core feature of major depressive disorder . Affective biases occur when emotions alter how the brain processes information and negative affective biases are thought to contribute to the development and continuation of depressed mood.

The research team used an affective bias test, based on an associative learning task, to investigate the effects of rapid-acting antidepressants (RAADs) in rats. They found that all the treatments were able to reduce negative affective biases associated with past experiences but there were additional characteristics of the dissociative anesthetic, ketamine, and the serotonergic psychedelic, investigational COMP360 psilocybin (Compass Pathways' proprietary formulation of synthetic psilocybin), which could explain why the effects of a single treatment can be long-lasting.

The findings suggest that these sustained effects are due to adaptive changes in the brain circuits which control affective biases, and these can influence how past experiences are remembered. The effects at low doses were very specific to affective bias modulation and were localized to the prefrontal cortex of the brain, a region known to play an important role in mood.

Emma Robinson, Professor of Psychopharmacology in the School of

Physiology, Pharmacology & Neuroscience at Bristol, and lead author, said, "Using a behavioral task we showed that drugs that are believed to have rapid and sustained benefits in depressed patients, specifically modulate affective biases associated with past experiences, something which we think is really important for understanding why they can improve a patient's mood so quickly.

"We also found differences in how ketamine, scopolamine and COMP360 psilocybin interact with these neuropsychological mechanisms which may explain why the effects of a single treatment in human patients can be long-lasting, days (ketamine) to months (psilocybin).

"By using an animal model, we have been able to investigate these important interactions with learning and memory processes and neural plasticity and propose a two-stage model that may explain the effects we observe."

In the task, each animal learned to associate a specific digging material with a food reward under either treatment or control conditions. The treatment condition is designed to generate a change in the animal's affective state and a choice test is used to quantify the affective bias this generates.

Acute treatment with the RAADs ketamine, scopolamine, or psilocybin prevented the retrieval of the negative affective bias induced in this model. However, the most exciting finding was at 24 hours after treatment when low, but not high, doses of ketamine and psilocybin led to a re-learning effect where the negatively biased memory was retrieved with a more positive affective valence. Only psilocybin, but not ketamine or scopolamine treatment also positively biased new experiences.

Exploring in more detail the re-learning effects of ketamine in our studies, the researchers found they were protein synthesis-dependent, localized to the medial prefrontal cortex and could be modulated by cue-reactivation, consistent with their predictions of experience-dependent neural plasticity.

The study's findings propose a neuropsychological mechanism that may explain both the immediate and sustained effects of RAADs, potentially linking their effects on neural plasticity with mood.

More information: Justyna Hinchcliffe et al, Rapid-acting antidepressant drugs modulate affective bias in rats, *Science Translational Medicine* (2024). DOI: 10.1126/scitranslmed.adi2403. www.science.org/doi/10.1126/scitranslmed.adi2403

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