Treating depression with psilocybin or escitalopram found to result in different hierarchical brain reconfigurations

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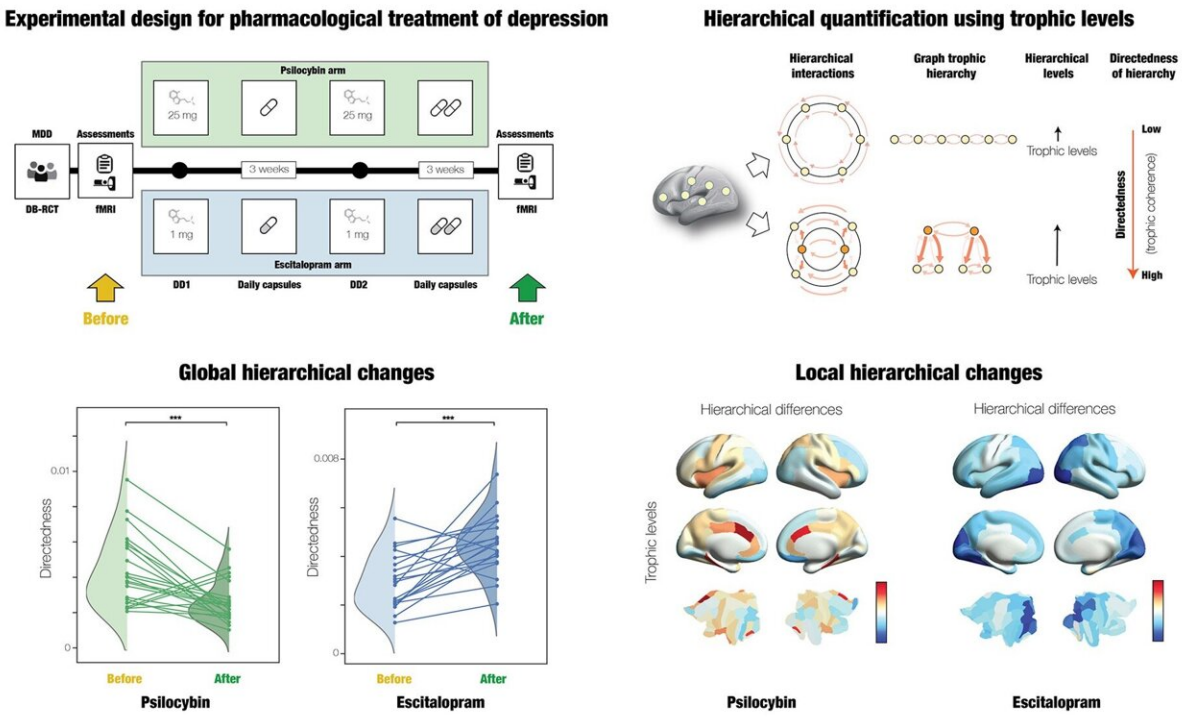

A cartoon of the pipeline and sketch of the results. Credit: Deco et al.

Depression is one of the most common mental disorders, affecting an estimated 300 million people worldwide. While there are currently numerous pharmacological treatments for depression, how different

treatments impact the brains of the patients they are administered to is not yet fully understood.

Selective serotonin re-uptake inhibitors (SSRIs) are among the most well-established antidepressant drugs worldwide. SSRIs can increase the activity of the neurotransmitter serotonin, which plays a key role in the regulation of sleep, mood, appetite and learning.

A more recently explored treatment option for depression is the naturally occurring psychedelic compound psilocybin, which is found in so-called "magic mushrooms." This compound has also been found to interact with serotonin receptors in the brain, which can improve the mood of individuals after consuming it.

Researchers at Universitat Pompeu Fabra, University of Oxford and other institutes across Europe recently carried out a study investigating the effects of these two different types of treatments on the brains of individuals diagnosed with depression, particularly on the brain's hierarchical organization following the intake of the drugs. Their paper, published in *Nature Mental Health*, suggests that these two treatment options result in very different hierarchical brain reconfigurations.

"We have long been interested in the orchestration of brain hierarchy in many different brain states and have been able to demonstrate in many papers that the human brain is hierarchically organized, orchestrating the global dynamics in order to perform effectively distributed computation," Gustavo Deco and Morten L. Kringelbach, co-authors of the paper, told Medical Xpress.

"We were interested in how hierarchy changes in treatment-resistant depression. Thanks to a recent randomized control trial, we were able to investigate two different pharmacological treatments."

As part of their recent paper, the researchers compared the effects of psilocybin to those of escitalopram, which is among the commonly prescribed SSRI drugs. All the study participants received two doses of psilocybin three weeks apart. For a period of six weeks, one group of participants also received a daily dose of escitalopram, while the other was administered a placebo (i.e., a neutral substance with no psychoactive effects).

"Our key idea was to study reconfiguration of the hierarchical organization of the brain in depression after different pharmacological treatment," said Deco and Kringelbach. "The experimental data was obtained from a two-armed double-blind phase II randomized controlled trial comparing psilocybin therapy (22 patients) with escitalopram (20 patients) from co-author Prof Carhart-Harris."

The researchers recorded the clinical outcomes of the two treatment plans followed by participants. They also collected scans of the patients' brains using functional magnetic resonance imaging (fMRI), both at the beginning of the study and after the patients had completed the 6-week treatment period.

"We used advanced whole-brain modeling, which fits a personalized computer model to the patient's empirical functional brain scans," explained Deco and Kringelbach. "We designed a framework to assess hierarchical reconfiguration by the global level of directedness of the generative effective connectivity (GEC) matrix underlying the whole-brain model. The GEC reflects the underlying anatomical structure and the dynamical functional activity in an asymmetric matrix which captures the hierarchical organization."

Using machine learning algorithms, Deco, Kringelbach and their colleagues were able to extract hierarchical features of the brain from the scans they collected. To frame their findings, they used a theoretical

construct known as the "trophic coherence" framework, which in ecology describes the hierarchical food chain (i.e., carnivores eating herbivores, who in turn eat plants).

"According to this framework, a flat hierarchy is characterized by equal trophic levels and low directedness, which reflects low asymmetry in a network," said Deco and Kringelbach. "In contrast, a strong hierarchy is associated with high directedness and strong asymmetric connections in a many-layered network."

The researchers found that the hierarchical organization of brain dynamics is a highly precise measure of change following treatments. As part of their study, they used the trophic coherence framework to determine how the two treatments they assessed had reorganized the brain dynamics of the patients who received them.

"This approach allowed us to gather insights into the underlying mechanisms of depression and may in time lead to even better interventions," said Deco and Kringelbach. "Our results also confirm the hypothesis that problems with the main regions of the global workspace orchestrating brain dynamics could be the main cause of neuropsychiatric disorders. Future larger studies should further investigate this hypothesis focusing on different neuropsychiatric diseases."

Essentially, the findings gathered by these researchers suggest that while both psilocybin and escitalopram can be effective treatments for depression, these two compounds resulted in significantly different brain hierarchy reconfigurations. Using machine learning-based computational models, the team was also able to predict patients' responses to treatment with an impressive accuracy of 85%.

Collectively, this study shows that SSRIs and psilocybin rebalance brain

dynamics in completely different ways. In the future, the insight it gathered could inform pharmacological and psychiatric studies, contributing to the improvement of therapeutic interventions for depression.

"We now plan to use this novel framework to understand the orchestration of brain hierarchy in any brain state, since this would allow us to find novel ways to rebalance the brain in disease," added Deco and Kringelbach.

"The present whole-brain modeling framework could be used for treatment studies using any kind of effective intervention, whether pharmacological, electrical or behavioral. We also plan to use this methodology to study hierarchical reconfiguration in cognitive/behavioral tasks, and different brain states in healthy participants."

More information: Gustavo Deco et al, Different hierarchical reconfigurations in the brain by psilocybin and escitalopram for depression, *Nature Mental Health* (2024). DOI: 10.1038/s44220-024-00298-y.