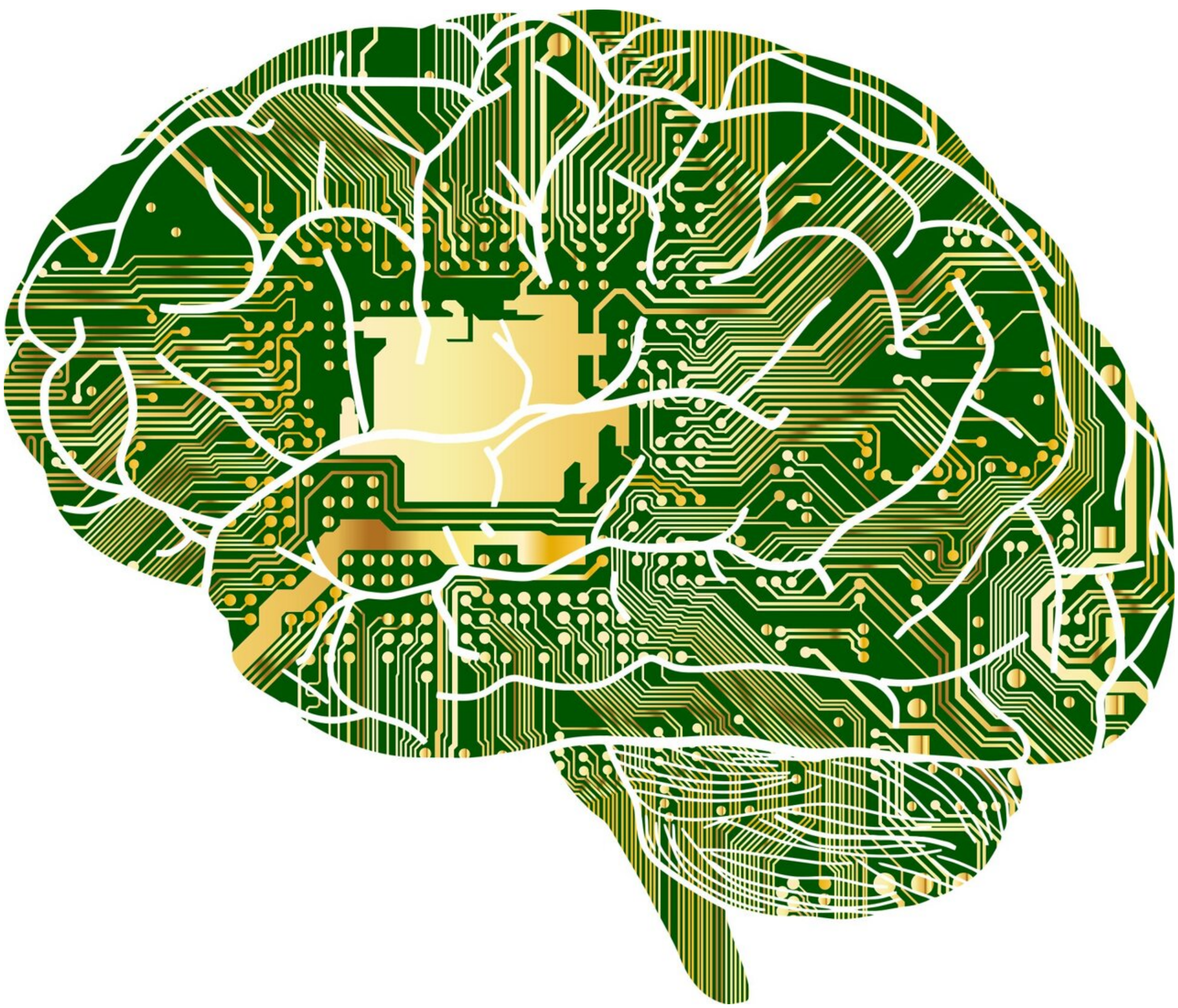
Researchers identify crucial biomarker that tracks recovery from treatment-resistant depression

September 20 2023



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A team of leading clinicians, engineers, and neuroscientists has made a groundbreaking discovery in the field of treatment-resistant depression. By analyzing the brain activity of patients undergoing deep brain stimulation (DBS), a promising therapy involving implanted electrodes that stimulate the brain, the researchers identified a unique pattern in brain activity that reflects the recovery process in patients with treatment-resistant depression.

This pattern, known as a biomarker, serves as a measurable indicator of disease recovery and represents a significant advance in treatment for the most severe and untreatable forms of depression.

The team's findings, published online in the journal *Nature* on September 20, offer the first window into the intricate workings and mechanistic effects of DBS on the brain during treatment for severe depression.

DBS involves implanting thin electrodes in a specific brain area to deliver small electrical pulses, similar to a pacemaker. Although DBS has been approved and used for movement disorders such as Parkinson's disease for many years, it remains experimental for depression. This study is a crucial step toward using objective data collected directly from the brain via the DBS device to inform clinicians about the patient's response to treatment. This information can help guide adjustments to DBS therapy, tailoring it to each patient's unique response and optimizing their treatment outcomes.

Now, the researchers have shown it's possible to monitor that antidepressant effect throughout the course of treatment, offering clinicians a tool somewhat analogous to a blood glucose test for diabetes or blood pressure monitoring for heart disease: a readout of the disease state at any given time. Importantly, it distinguishes between typical day-to-day mood fluctuations and the possibility of an impending relapse of the depressive episode.

The research team, which includes experts from the Georgia Institute of Technology, the Icahn School of Medicine at Mount Sinai, and Emory University School of Medicine, used artificial intelligence (AI) to detect shifts in brain activity that coincided with patients' recovery.

The study involved 10 patients with severe treatment-resistant depression, all of whom underwent the DBS procedure at Emory University. The study team used a new DBS device that allowed brain activity to be recorded. Analysis of these brain recordings over six months led to the identification of a common biomarker that changed as each patient recovered from their depression. After six months of DBS therapy, 90% of the subjects exhibited a significant improvement in their depression symptoms and 70% no longer met the criteria for depression.

The high response rates in this study cohort enabled the researchers to develop algorithms known as "explainable artificial intelligence" that allow humans to understand the decision-making process of AI systems. This technique helped the team identify and understand the unique brain patterns that differentiated a "depressed" brain from a "recovered" brain.

"The use of explainable AI allowed us to identify complex and usable patterns of brain activity that correspond to a depression recovery despite the complex differences in a patient's recovery," explained Sankar Alagapan Ph.D., a Georgia Tech research scientist and lead author of the study. "This approach enabled us to track the brain's recovery in a way that was interpretable by the clinical team, making a major advance in the potential for these methods to pioneer new therapies in psychiatry."

Helen S. Mayberg, MD, co-senior author of the study, led the first experimental trial of subcallosal cingulate cortex (SCC) DBS for treatment-resistant depression patients in 2003, demonstrating that it could have clinical benefit. In 2019, she and the Emory team reported the technique had a sustained and robust antidepressant effect with ongoing treatment over many years for previously treatment-resistant patients.

"This study adds an important new layer to our previous work, providing measurable changes underlying the predictable and sustained antidepressant response seen when patients with treatment-resistant depression are precisely implanted in the SCC region and receive chronic DBS therapy," said Dr. Mayberg, now Founding Director of the Nash Family Center for Advanced Circuit Therapeutics at Icahn Mount Sinai.

"Beyond giving us a neural signal that the treatment has been effective, it appears that this signal can also provide an early warning signal that the patient may require a DBS adjustment in advance of clinical symptoms. This is a game changer for how we might adjust DBS in the future."

"Understanding and treating disorders of the brain are some of our most pressing grand challenges, but the complexity of the problem means it's beyond the scope of any one discipline to solve," said Christopher Rozell, Ph.D., Julian T. Hightower Chair and Professor of Electrical and Computer Engineering at Georgia Tech and co-senior author of the paper.

"This research demonstrates the immense power of interdisciplinary collaboration. By bringing together expertise in engineering, neuroscience, and clinical care, we achieved a significant advance toward translating this much-needed therapy into practice, as well as an increased fundamental understanding that can help guide the development of future therapies."

The team's research also confirmed a longstanding subjective observation by psychiatrists: as patients' brains change and their depression eases, their facial expressions also change. The team's AI tools identified patterns in individual facial expressions that corresponded with the transition from a state of illness to stable recovery. These patterns proved more reliable than current clinical rating scales.

In addition, the team used two types of magnetic resonance imaging to identify both structural and functional abnormalities in the brain's white matter and interconnected regions that form the network targeted by the treatment.

They found these irregularities correlate with the time required for patients to recover, with more pronounced deficits in the targeted brain network correlated to a longer time for the treatment to show maximum effectiveness. These observed facial changes and structural deficits provide behavioral and anatomical evidence supporting the relevance of the electrical activity signature or biomarker.

"When we treat patients with depression, we rely on their reports, a clinical interview, and psychiatric rating scales to monitor symptoms. Direct biological signals from our patients' brains will provide a new level of precision and evidence to guide our treatment decisions," said Patricio Riva-Posse, MD, Associate Professor and Director of the Interventional Psychiatry Service in the Department of Psychiatry and Behavioral Sciences at Emory University School of Medicine, and lead psychiatrist for the study.

Given these initial promising results, the team is now confirming their findings in another completed cohort of patients at Mount Sinai. They are using the next generation of the dual stimulation/sensing DBS system with the aim of translating these findings into the use of a commercially available version of this technology.

More information: Christopher Rozell, Cingulate dynamics track depression recovery with deep brain stimulation, *Nature* (2023). DOI: 10.1038/s41586-023-06541-3.
www.nature.com/articles/s41586-023-06541-3

Provided by The Mount Sinai Hospital

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