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Researchers treat depression by reversing brain signals traveling the wrong way

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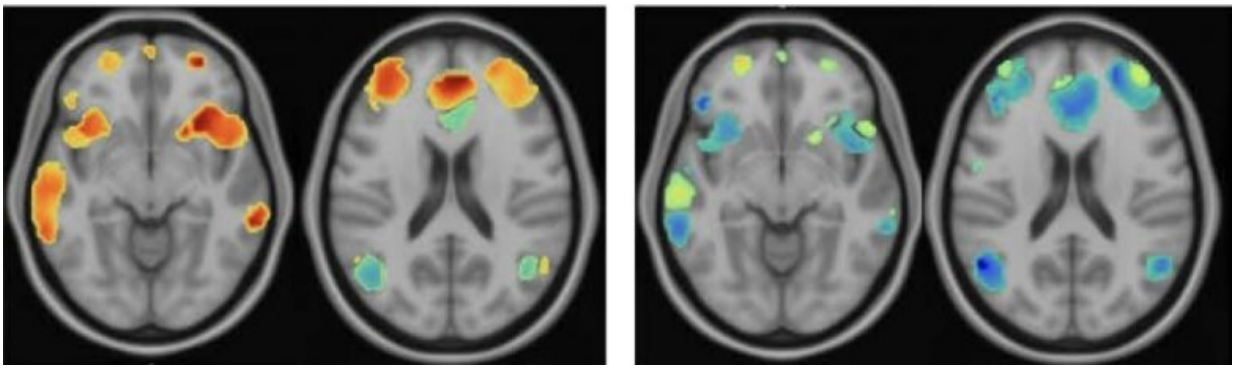

Brain images from a patient with major depression before (left) and after treatment with Stanford neuromodulation therapy, which restores the normal timing of activity in the anterior cingulate cortex. Credit: Stanford University Medical Center

Powerful magnetic pulses applied to the scalp to stimulate the brain can bring fast relief to many severely depressed patients for whom standard treatments have failed. Yet it's been a mystery exactly how transcranial magnetic stimulation, as the treatment is known, changes the brain to dissipate depression. Now, research led by Stanford Medicine scientists has found that the treatment works by reversing the direction of abnormal brain signals.

The findings also suggest that backward streams of neural activity

between key areas of the brain could be used as a biomarker to help diagnose depression.

"The leading hypothesis has been that TMS could change the flow of neural activity in the brain," said Anish Mitra, MD, Ph.D., a postdoctoral fellow in psychiatry and behavioral sciences. "But to be honest, I was pretty skeptical. I wanted to test it."

Mitra had just the tool to do it. As a graduate student at Washington University in Saint Louis, in the lab of Mark Raichle, MD, he developed a mathematical tool to analyze functional magnetic resonance imaging, or fMRI—commonly used to locate active areas in the brain. The new analysis used minute differences in timing between the activation of different areas to also reveal the direction of that activity.

In the new study, published May 15 in the *Proceedings of the National Academy of Sciences*, Mitra and Raichle teamed up with Nolan Williams, MD, associate professor of psychiatry and behavioral sciences, whose team has advanced the use of magnetic stimulation, personalized to each patient's brain anatomy, to treat profound depression. The FDA-cleared treatment, known as Stanford neuromodulation therapy, incorporates advanced imaging technologies to guide stimulation with high-dose patterns of magnetic pulses that can modify brain activity related to major depression. Compared with traditional TMS, which requires daily sessions over several weeks or months, SNT works on an accelerated timeline of 10 sessions each day for just five days.

"This was the perfect test to see if TMS has the ability to change the way that signals flow through the brain," said Mitra, who is lead author of the study. "If this doesn't do it, nothing will."

Timing is everything

The researchers recruited 33 patients who had been diagnosed with treatment-resistant major depressive disorder. Twenty-three received SNT treatment, and 10 received a sham treatment that mimicked SNT but without magnetic stimulation. They compared data from these patients with that of 85 healthy controls without depression.

When they analyzed fMRI data across the whole brain, one connection stood out. In the normal brain, the anterior insula, a region that integrates bodily sensations, sends signals to a region that governs emotions, the anterior cingulate cortex.

"You could think of it as the anterior cingulate cortex receiving this information about the body—like heart rate or temperature—and then deciding how to feel on the basis of all these signals," Mitra said.

In three-quarters of the participants with depression, however, the typical flow of activity was reversed: The anterior cingulate cortex sent signals to the anterior insula. The more severe the depression, the higher the proportion of signals that traveled the wrong way.

"What we saw is that who's the sender and who's the receiver in the relationship seems to really matter in terms of whether someone is depressed," Mitra said.

"It's almost as if you'd already decided how you were going to feel, and then everything you were sensing was filtered through that," he said. "The mood has become primary."

"That's consistent with how a lot of psychiatrists see depression," he added. "Even things that are quite joyful to a patient normally are suddenly not bringing them any pleasure."

When depressed patients were treated with SNT, the flow of neural

activity shifted to the normal direction within a week, coinciding with a lifting of their depression.

Those with the most severe depression—and the most misdirected brain signals—were the most likely to benefit from the treatment.

"We're able to undo the spatio-temporal abnormality so that people's brains look like those of normal, healthy controls," Williams said.

A biomarker for depression

A challenge of treating depression has been the lack of insight into its biological mechanisms. If a patient has a fever, there are various tests—for a bacterial or viral infection, for example—that could determine the appropriate treatment. But for a patient with depression, there are no analogous tests.

"This is the first time in psychiatry where this particular change in a biology—the flow of signals between these two brain regions—predicts the change in clinical symptoms," Williams said.

Not everyone with depression has this abnormal flow of neural activity, and it may be rare in less severe cases of depression, Williams said, but it could serve as an important biomarker for triaging treatment for the disorder. "The fMRI data that allows precision treatment with SNT can be used both as a biomarker for depression and a method of personalized targeting to treat its underlying cause," he said.

"When we get a person with severe depression, we can look for this biomarker to decide how likely they are to respond well to SNT treatment," Mitra said.

"Behavioral conditions like depression have been difficult to capture

with imaging because, unlike an obvious brain lesion, they deal with the subtlety of relationships between various parts of the brain," said Raichle, who has studied brain imaging for more than four decades. "It's incredibly promising that the technology now is approaching the complexity of the problems we're trying to understand."

The researchers plan to replicate the study in a larger group of patients. They also hope others will adopt their analytic technique to uncover more clues about the direction of brain activity hidden in fMRI data. "As long as you have good clean fMRI data, you can study this property of the signals," Mitra said.

More information: Anish Mitra et al, Targeted neurostimulation reverses a spatiotemporal biomarker of treatment-resistant depression, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2218958120

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