Brain-wave pattern can identify people likely to respond to antidepressant, study finds

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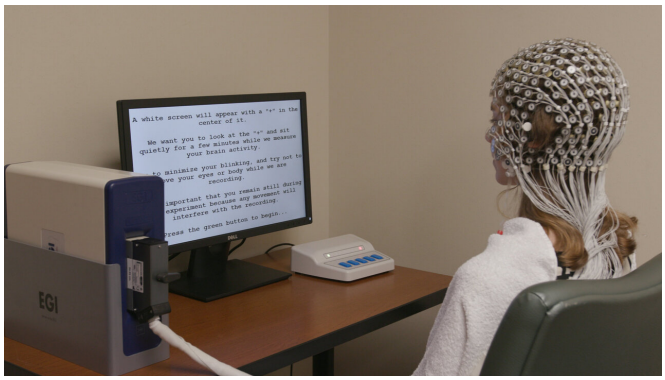

Research shows artificial intelligence can accurately predict whether an antidepressant will work based on a patient's brain activity. Credit: UTSW

A new method of interpreting brain activity could be used in clinics to help determine the best treatment options for depression, according to a Stanford-led trial.

Stanford researchers and their collaborators used electroencephalography, a tool for monitoring electrical activity in the brain, and an algorithm to identify a brain-wave signature in individuals with depression who will most likely respond to sertraline, an antidepressant marketed as Zoloft.

A paper describing the work will be published Feb. 10 in *Nature Biotechnology*.

The study emerged from a decades-long effort funded by the National Institute of Mental Health to create biologically based approaches, such as blood tests and brain imaging, to help personalize the treatment of depression and other mental disorders. Currently, there are no such tests to objectively diagnose depression or guide its treatment.

"This study takes previous research showing that we can predict who benefits from an antidepressant and actually brings it to the point of practical utility," said Amit Etkin, MD, Ph.D., professor of psychiatry and behavioral sciences at Stanford. "I will be surprised if this isn't used by clinicians within the next five years."

Instead of functional magnetic resonance imaging, an expensive technology often used in studies to image brain activity, the scientists turned to electroencephalography, or EEG, a much less costly technology.

Etkin shares senior authorship of the paper with Madhukar Trivedi, MD, professor of psychiatry at the University of Texas-Southwestern. Wei Wu, Ph.D., an instructor of psychiatry at Stanford, is the lead author.

The paper is one of several based on data from a federally funded depression study launched in 2011—the largest randomized, placebo-controlled clinical trial on antidepressants ever conducted with brain imaging—which tested the use of sertraline in 309 medication-free patients. The multicenter trial was called Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care, or EMBARC. Led by Trivedi, it was designed to advance the goal of improving the trial-and-error method of treating depression that is still in use today.

"It often takes many steps for a patient with depression to get better," Trivedi said. "We went into this thinking, 'Wouldn't it be better to identify at the beginning of treatment which treatments would be best for which patients?'"

Most common mental disorder

Major depression is the most common mental disorder in the United States, affecting about 7% of adults in 2017, according to the National Institute of Mental Health. Among those, about half never get

diagnosed. For those who do, finding the right treatment can take years, Trivedi said. He pointed to one of his past studies that showed only about 30% of depressed patients saw any remission of symptoms after their first treatment with an antidepressant.

Current methods for diagnosing depression are simply too subjective and imprecise to guide clinicians in quickly identifying the right treatment, Etkin said. In addition to a variety of antidepressants, there are several other types of treatments for depression, including psychotherapy and brain stimulation, but figuring out which treatment will work for which patients is based on educated guessing.

To diagnose depression, clinicians rely on a patient reporting at least 5 of 9 common symptoms of the disease. The list includes symptoms such as feelings of sadness or hopelessness, self-doubt, sleep disturbances—ranging from insomnia to sleeping too much—low energy, unexplained body aches, fatigue, and changes in appetite, ranging from overeating to undereating. Patients often vary in both the severity and types of symptoms they experience, Etkin said.

"As a psychiatrist, I know these patients differ a lot," Etkin said. "But we put them all under the same umbrella, and we treat them all the same way." Treating people with depression often begins with prescribing them an antidepressant. If one doesn't work, a second antidepressant is prescribed. Each of these "trials" often takes at least eight weeks to assess whether the drug worked and symptoms are alleviated. If an antidepressant doesn't work, other treatments, such as psychotherapy or occasionally transcranial magnetic stimulation, may also be tried. Often, multiple treatments are combined, Etkin said, but figuring out which combination works can take a while.

"People often feel a lot of dejection each time a treatment doesn't work, creating more self-doubt for those whose primary symptom is most often self-doubt," Trivedi said.

Looking for a biomarker

The EMBARC trial enrolled 309 people with depression who were randomized to receive either sertraline or a placebo.

For their study, Etkin and his colleagues set out to find a brain-wave pattern to help predict which depressed participants would respond to sertraline. First, the researchers collected EEG data on the participants before they received any drug treatment. The goal was to obtain a baseline measure of brain-wave patterns.

Next, using insights from neuroscience and bioengineering, the investigators analyzed the EEG using a novel artificial intelligence technique they developed and identified signatures in the data that predicted which participants would respond to treatment based on their individual EEG scans. The researchers found that this technique reliably predicted which of the patients did, in fact, respond to sertraline and which responded to placebo. The results were replicated at four different clinical sites.

Further research suggested that participants who were predicted to show little improvement with sertraline were more likely to respond to treatment involving transcranial magnetic stimulation, or TMS, in combination with psychotherapy.

"Using this method, we can characterize something about an individual person's brain," Etkin said. "It's a method that can work across different types of EEG equipment, and thus more apt to reach the clinic."

Etkin is on leave from Stanford, working as the founder and CEO of the startup Alto Neuroscience, a company based in Los Altos, California, that aims to build on these findings and develop a new generation of biologically based diagnostic tests to personalize mental health treatments with a high degree of clinical utility. "Part of getting these study results used in clinical care is, I think, that society has to demand it," Trivedi said. "That is the way things get put into practice. I don't see a downside to putting this into clinical use soon."

Broad effort

When EMBARC was launched, it was part of a

broader effort by the NIMH to push for improvements in mental health care by using advances in fields such as genetics, neuroscience and biotechnology, said Thomas Insel, MD, who served as director of that institute from 2002 to 2015.

"We went into EMBARC saying anything is possible," Insel said. "Let's see if we can come up with clinically actionable techniques." He didn't think it would take this long, but he remains optimistic.

"I think this study is a particularly interesting application of EMBARC," he said. "It leverages the power of modern data science to predict at the individual level who is likely to respond to an antidepressant."

In addition to improving care, the researchers said they see a possible side benefit to the use of biologically based approaches: It could reduce the stigma associated with depression and other mental health disorders that prevents many people from seeking appropriate medical care.

"I'd love to think scientific evidence will help to counteract this stigma, but it hasn't so far," said Insel. "It's been over 160 years since Abraham Lincoln said that melancholy 'is a misfortune, not a fault.' We still have a long way to go before most people will understand that depression is not someone's fault." (President Lincoln suffered bouts of depression.)

More information: An electroencephalographic signature predicts antidepressant response in major depression, *Nature Biotechnology* (2020). DOI: 10.1038/s41587-019-0397-3 , nature.com/articles/s41587-019-0397-3

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