Researchers identify subtype of depression using surveys, cognitive tests, and brain imaging

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Scientists at Stanford Medicine conducted a study describing a new category of depression—labeled the cognitive biotype—which accounts

for 27% of depressed patients and is not effectively treated by commonly prescribed antidepressants.

Cognitive tasks showed that these patients have difficulty with the ability to plan ahead, display self-control, sustain focus despite distractions and suppress inappropriate behavior; imaging showed decreased activity in two brain regions responsible for those tasks.

Because depression has traditionally been defined as a mood disorder, doctors commonly prescribe antidepressants that target serotonin (known as selective serotonin reuptake inhibitors or SSRIs), but these are less effective for patients with cognitive dysfunction. Researchers said that targeting these cognitive dysfunctions with less commonly used antidepressants or other treatments may alleviate symptoms and help restore social and occupational abilities.

The study, published June 15 in *JAMA Network Open*, is part of a broader effort by neuroscientists to find treatments that target depression biotypes, according to the study's senior author, Leanne Williams, Ph.D., the Vincent V.C. Woo Professor and professor of psychiatry and behavioral sciences.

"One of the big challenges is to find a new way to address what is currently a trial-and-error process so that more people can get better sooner," Williams said. "Bringing in these objective cognitive measures like imaging will make sure we're not using the same treatment on every patient."

Finding the biotype

In the study, 1,008 adults with previously unmedicated major depressive disorder were randomly given one of three widely prescribed typical antidepressants: escitalopram (brand name Lexapro) or sertraline

(Zoloft), which act on serotonin, or venlafaxine-XR (Effexor), which acts on both serotonin and norepinephrine. Seven hundred and twelve of the participants completed the eight-week regimen.

Before and after treatment with the antidepressants, the participants' depressive symptoms were measured using two surveys—one, clinician-administered, and the other, a self-assessment, which included questions related to changes in sleep and eating. Measures on social and occupational functioning, as well as quality of life, were tracked as well.

The participants also completed a series of cognitive tests, before and after treatment, measuring verbal memory, working memory, decision speed and sustained attention, among other tasks.

Before treatment, scientists scanned 96 of the participants using functional magnetic resonance imaging as they engaged in a task called the "GoNoGo" that requires participants to press a button as quickly as possible when they see "Go" in green and to not press when they see "NoGo" in red. The fMRI tracked neuronal activity by measuring changes in blood oxygen levels, which showed levels of activity in different brain regions corresponding to Go or NoGo responses. Researchers then compared the participants' images with those of individuals without depression.

The researchers found that 27% of the participants had more prominent symptoms of cognitive slowing and insomnia, impaired cognitive function on behavioral tests, as well as reduced activity in certain frontal brain regions—a profile they labeled the cognitive biotype.

"This study is crucial because psychiatrists have few measurement tools for depression to help make treatment decisions," said Laura Hack, MD, Ph.D., the lead author of the study and an assistant professor of psychiatry and behavioral sciences. "It's mostly making observations and

self-report measures. Imaging while performing cognitive tasks is rather novel in depression treatment studies."

Pre-treatment fMRI showed those with the cognitive biotype had significantly reduced activity in the dorsolateral prefrontal cortex and dorsal anterior cingulate regions during the GoNoGo task compared with the activity levels in participants who did not have the cognitive biotype. Together, the two regions form the cognitive control circuit, which is responsible for limiting unwanted or irrelevant thoughts and responses and improving goal selection, among other tasks.

After treatment, the researchers found that for the three antidepressants administered, the overall remission rates—the absence of overall depression symptoms—were 38.8% for participants with the newly discovered biotype and 47.7% for those without it. This difference was most prominent for sertraline, for which the remission rates were 35.9% and 50% for those with the biotype and those without, respectively.

"Depression presents in different ways in different people, but finding commonalities—like similar profiles of brain function—helps medical professionals effectively treat participants by individualizing care," Williams said.

Depression isn't one size fits all

Williams and Hack propose that behavior measurement and imaging could help diagnose depression biotypes and lead to better treatment. A patient could complete a survey on their own computer or in the doctor's office, and if they are found to display a certain biotype, they might be referred to imaging for confirmation before undergoing treatment.

Researchers at the Stanford Center for Precision Mental Health and Wellness, which Williams directs, in partnership with the Stanford

Translational Precision Mental Health Clinic, which Hack directs, are studying another medication—guanfacine—that specifically targets the dorsolateral prefrontal cortex region with support from Stanford University Innovative Medicines Accelerator. They believe this treatment could be more effective for patients with the cognitive subtype.

Williams and Hack hope to conduct studies with participants who have the cognitive biotype, comparing different types of medication with treatments such as transcranial magnetic stimulation and cognitive behavioral therapy. In transcranial magnetic stimulation, commonly referred to as TMS, magnetic fields stimulate nerve cells; in cognitive behavioral therapy, patients are taught to use problem-solving strategies to counter negative thoughts that contribute to both emotional dysregulation and loss of social and occupational abilities.

"I regularly witness the suffering, the loss of hope and the increase in suicidality that occurs when people are going through our trial-and-error process," Hack said. "And it's because we start with medications that have the same mechanism of action for everyone with depression, even though depression is quite heterogeneous. I think this study could help change that."

Researchers from the Sierra-Pacific Mental Illness Research, Education and Clinical Center; the Veterans Affairs Palo Alto Health Care System; Brain Dynamic Centre, Westmead Institute for Medical Research; and the University of Sydney, Westmead, contributed to the work.

More information: Laura M. Hack et al, A Cognitive Biotype of Depression and Symptoms, Behavior Measures, Neural Circuits, and Differential Treatment Outcomes, *JAMA Network Open* (2023). DOI: 10.1001/jamanetworkopen.2023.18411