Press Release

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Progress in unlocking the brain's "code" for depression

Philadelphia, March 16, 2023 – Clinical depression is a common psychiatric condition with often devastating consequences. A new study in *Biological Psychiatry*, published by Elsevier, advances our fundamental understanding of the neural circuitry of depression in the human brain.

Treatment of depression is complicated by the disease's high heterogeneity and notable complexity. Medication to treat depression is available, but one third of patients do not respond to these first-line drug treatments. Other treatments such as deep brain stimulation (DBS) can provide patients with substantial relief, but previous results have been inconsistent. The development of more personalized treatments and improved outcomes requires a better understanding of the neurophysiological mechanisms of depression.

Led by Sameer Sheth, MD, PhD, at Baylor College of Medicine, together with Wayne Goodman, MD, and Nader Pouratian, MD, PhD, the researchers collected electrophysiological recordings from prefrontal cortical regions in three human subjects, all of whom experienced severe treatment-resistant depression.

The prefrontal cortex plays a significant role in psychiatric and cognitive disorders, influencing one's ability to set goals and form habits. These highly evolved brain regions are particularly difficult to study in non-human models, so data collected from human brain activity are particularly valuable.

The researchers made electrophysiological recordings of neural activity from the surface of the brain using implanted intracranial electrodes, and they measured each participant's depression severity for nine days. The patients were undergoing brain surgery as part of a feasibility study for treatment with DBS.

The researchers found that lower depression severity correlated with decreased low-frequency neural activity and increased high-frequency activity. They also found that changes in the anterior cingulate cortex (ACC) served as the best predictive area of depression severity. Beyond the ACC, and in alignment with the diverse nature of the pathways and symptoms of depression, they also identified individual-specific sets of features that successfully predicted severity.

"In order to use neuromodulation techniques to treat complex psychiatric or neurological disorders, we ideally need to understand their underlying neurophysiology," Dr. Sheth said. "We are thrilled to have made initial progress in understanding how mood is encoded in human prefrontal circuits. As more such data become available, we will hopefully be able to identify which patterns are common across individuals and which are specific. This information will be critical in designing and personalizing next-generation therapies for depression such as DBS."

John Krystal, MD, Editor of *Biological Psychiatry*, said of the work, "We now have a growing collection of approaches that can be applied to mapping the circuits and characterizing the neural codes underlying depression. This knowledge will guide next-generation brain stimulation treatments and inform the way we understand and treat depression, broadly."

Notes for editors

The article is “Decoding Depression Severity from Intracranial Neural Activity," by Jiayang Xiao, Nicole R. Provenza, Joseph Asfouri, John Myers, Raissa K. Mathura, Brian Metzger, Joshua A. Adkinson, Anusha B. Allawala, Victoria Pirtle, Denise Oswalt, Ben Shofty, Meghan E. Robinson, Sanjay J. Mathew, Wayne K. Goodman, Nader Pouratian, Paul R. Schrater, Ankit B. Patel, Andreas S. Tolias, Kelly R. Bijanki, Xaq Pitkow, and Sameer A. Sheth (https://doi.org/10.1016/j.biopsych.2023.01.020). It appears as an Article in Press in *Biological Psychiatry*, published by Elsevier.

The article is openly available at https://www.biologicalpsychiatryjournal.com/article/S0006-3223(23)00048-3/fulltext.

Copies of this paper are also available to credentialed journalists upon request; please contact Rhiannon Bugno at +1 254 522 9700 or Biol.Psych@sobp.org. Journalists wishing to interview the authors may contact Sameer Sheth, MD, PhD, at sameer.sheth@bcm.edu.

The authors’ affiliations and disclosures of financial and conflicts of interests are available in the article.

John H. Krystal, MD, is Chairman of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale-New Haven Hospital, and a research psychiatrist at the VA Connecticut Healthcare System. His disclosures of financial and conflicts of interests are available here.

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Biological Psychiatry is the official journal of the Society of Biological Psychiatry, whose purpose is to promote excellence in scientific research and education in fields that investigate the nature, causes, mechanisms and treatments of disorders of thought, emotion, or behavior. In accord with this mission, this peer-reviewed, rapid-publication, international journal publishes both basic and clinical contributions from all disciplines and research areas relevant to the pathophysiology and treatment of major psychiatric disorders.

The journal publishes novel results of original research which represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also encouraged.

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