Researchers uncover new understanding of certain psychiatric diseases

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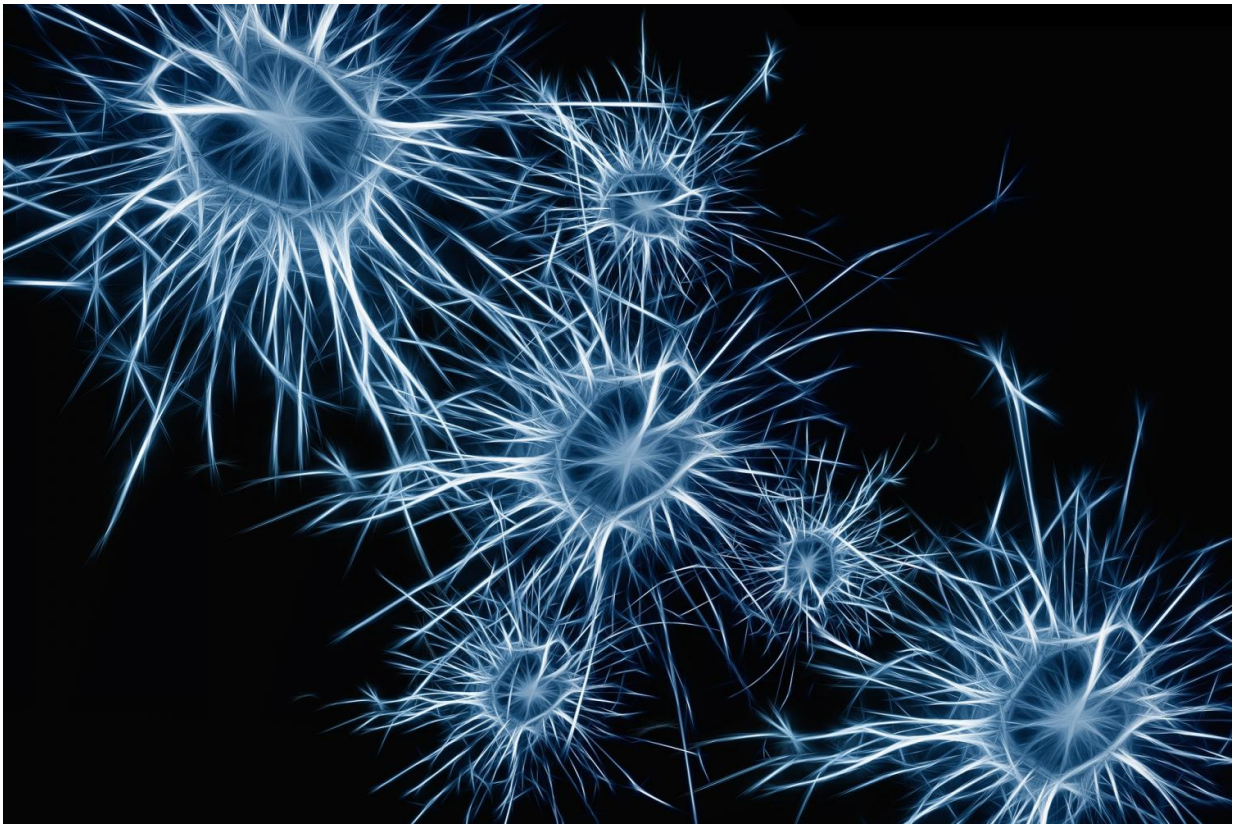

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Research scientists from The Feinstein Institute for Medical Research and the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in Hempstead, NY, in conjunction with their

colleagues at Rockefeller University in New York City, have developed a new understanding of how certain psychiatric diseases—those that involve uncontrollable reactions to stimuli such as the high and low experiences attributed to bi-polar disorder, the impulsivity of an individual suffering from attention deficit hyperactivity disorder (ADHD), and even suicidality—manifest and potentially can be treated. These findings were published today in *Proceedings of the National Academy of Sciences* (*PNAS*).

The paper, entitled "Molecular Profiling of Reticular Gigantocellularis Neurons Indicates that eNOS Modulates Environmentally Dependent Levels of Arousal," focuses on the neurons that are specialized cell transmitting nerve impulses of the medullary reticular nucleus gigantocelluraris (NGC), an area deep in the brainstem just above the spinal cord that activates response to stimuli. Researchers used a recently-developed technique called "retro-TRAP" that allows for the identification of messenger ribonucleic acid (mRNA) molecules or pathways within neurons. The study identified the presence within the mRNA of an enzyme known as endothelial nitric oxide synthase (eNOS), which previously was found primarily in blood vessels—not in neurons.

"Discovering that eNOS was in neurons was quite unexpected and led to further studying when and how the eNOS within neurons is activated, and how such activation manifests in the body," said Joel N.H. Stern, Ph.D., co-senior author of the paper and associate professor, departments of neurology, surgery, science education, and molecular medicine at the Zucker School of Medicine and the Feinstein Institute for Medical Research, and co-director of the Autoimmune Brain Disorder Center at Lenox Hill Hospital.

Hypothesizing that mutated eNOS in NGC brain cells might be responsible for incongruous reactionary behavior that continues well

after the stimulating event passes, the researchers conducted two key experiments on mice: First, they tested under which conditions eNOS was active. Because it is a molecule that produces nitric oxide (NO), researchers were able to monitor its level of activity by monitoring the levels of oxidation in the cells. While the mice were in a familiar environment in their home cage, eNOS was not very active. When these mice were then exposed to various new environments and experiences, the activity of the eNOS increased significantly during the period of exposure and immediately after.

Next, the researchers sought to understand what behavior would manifest if eNOS in NGC brain cells were blocked or inhibited. A chemical that inhibited the production of nitric oxide (NO), effectively preventing eNOS from functioning, was precisely microinfused specifically into the NGC of the mice. Then mice with and without active eNOS were exposed to different environments and experiences where they were able to freely explore. When the mice with inactivated eNOS were returned to their cages after exposure to the stimuli, they behaved in a hyperactive way long after the stimuli were removed.

"A human analogy might be when a person gets excited by something good that happens and cannot come down from that high, or alternatively, gets stuck in a depressive state after a negative experience," Dr. Stern said.

Since multiple prior studies have found genetic mutations in the eNOS gene (NOS-III) in humans with various aspects of bipolar and major depressive disorder, including suicidality, the implications of this study may be far reaching. It suggests that NOS-III mutations may contribute to the development of these psychiatric problems, and relief may perhaps come in the form of optimizing the production of nitric oxide.

"The discovery of the presence of eNOS in NGC brain cells, and the

effect of eNOS on the length of reactions to stimuli, may signal a new understanding and the discovery of a new mechanism for how certain psychiatric diseases that involve a mutation of the NOS-III gene can potentially be treated or controlled," said Dr. Stern.

More information: Inna Tabansky el al., "Molecular profiling of reticular gigantocellularis neurons indicates that eNOS modulates environmentally dependent levels of arousal," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1806123115

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