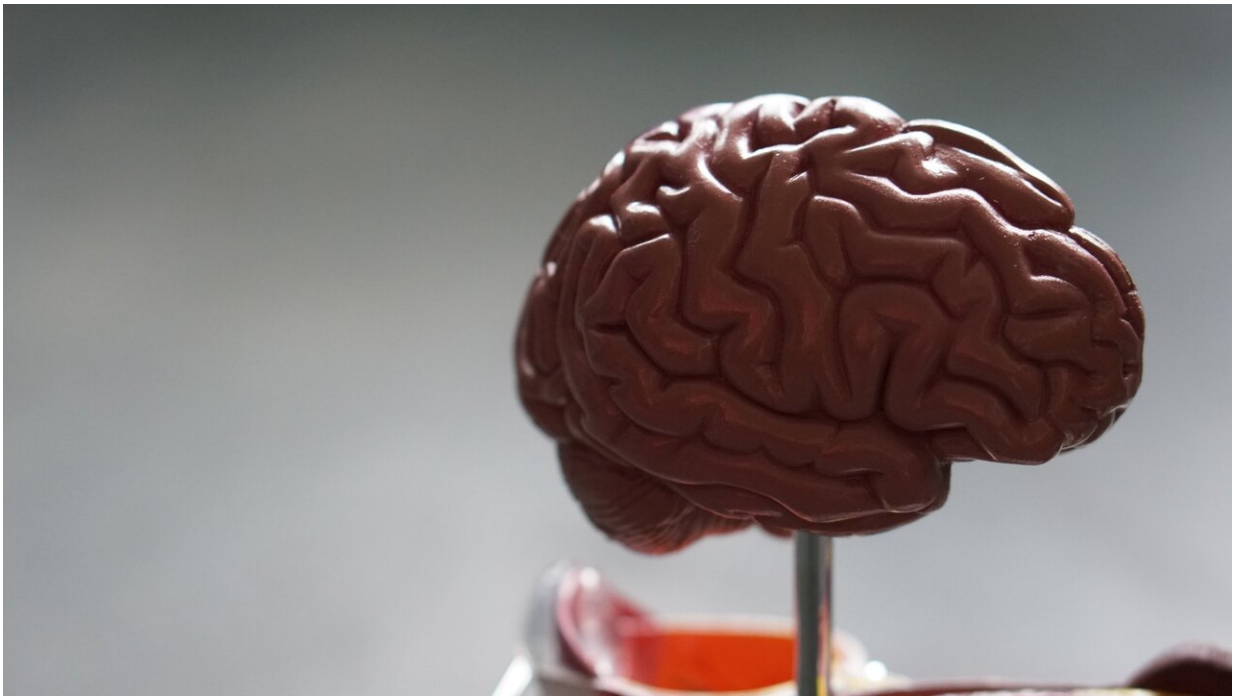
MedicalXpress

# Study maps key proteins linked to epilepsy, revealing new drug targets

March 25 2021



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An analysis of adult human brain tissue reveals over 900 proteins tied to epilepsy. The brain disorder, estimated to afflict more than 3 million Americans, is mostly known for symptoms of hallucinations, dreamlike states, and uncontrolled, often disabling bodily seizures.

Led by researchers at NYU Grossman School of Medicine, the study

examined molecular differences among the brains of 14 epilepsy patients and another group of 14 adults of similar age and gender who did not have the disease.

Study results showed that altered levels of brain proteins predominated in the hippocampus, a structure located deep inside the skull and responsible for memory and learning. However, some 134 proteins were significantly changed in both the hippocampus and frontal cortex, the front third of the brain, which is also responsible for controlling thought and body movements. Most of the changed proteins were tied to genes in charge of protein production and linked to epilepsy in much smaller, earlier studies, but four of the 20 most-altered proteins had never previously been associated with the disorder.

One particular protein, researchers say, stood out as the most significantly depleted across all brain regions. Called G Protein Subunit 1, or GNB1, the protein is known to play an important role in dozens of biological reactions, or pathways, involved in nerve growth and communication throughout the brain, but they say its precise role in epilepsy remains unclear.

Despite decades of research, researchers say, the causes of epilepsy remains unknown. Dozens of drugs are used to control seizures by targeting known protein weaknesses, excesses, or deficiencies, and the 'electrical storms' they trigger in the brain, but fail in one-third of patients to do so.

Publishing in the journal *Brain Communications* online March 9, the new investigation focused on regions of the frontal cortex and hippocampus that previous imaging and neurological studies had identified as most impacted by seizures.

"Our analysis identifies hundreds of potential new treatment targets for

epilepsy, focusing on areas of the brain mostly damaged by the disease," says study co-senior investigator Orrin Devinsky, MD, a professor in the departments of Neurology, Neuroscience and Physiology, Neurosurgery, and Psychiatry at NYU Langone Health.

"While our results point to the hippocampus as the brain region most vulnerable in epilepsy, further research is needed to confirm if this region is the primary source of the illness from which damage spreads out across other brain regions, as well as how epilepsy is mutually tied to other disorders, such as dementia and depression," says Devinsky, who also serves as director of the Comprehensive Epilepsy Center at NYU Langone.

"Of particular interest, these findings suggest that the G Protein Subunit 1 brain pathways are a strong target for new epilepsy therapies," says study co-senior author Thomas Wisniewski, MD.

Wisniewski, the Gerald J. and Dorothy R. Friedman Professor in the Department of Neurology and director of the Center for Cognitive Neurology at NYU Langone, says GNB1 pathways are already the target of more than a dozen drugs, such as nabilone and prazosine, used to treat conditions other than epilepsy, including nausea and high blood pressure.

Wisniewski says the NYU Langone team has plans to create a database that depicts "the brain landscape" of epilepsy protein and gene targets. They also plan initial clinical studies to determine how existing GNB1-altering medications may prevent or treat the disorder.

**More information:** Geoffrey Pires et al, Proteomic differences in the hippocampus and cortex of epilepsy brain tissue, *Brain Communications* (2021). DOI: 10.1093/braincomms/fcab021

Provided by NYU Langone Health