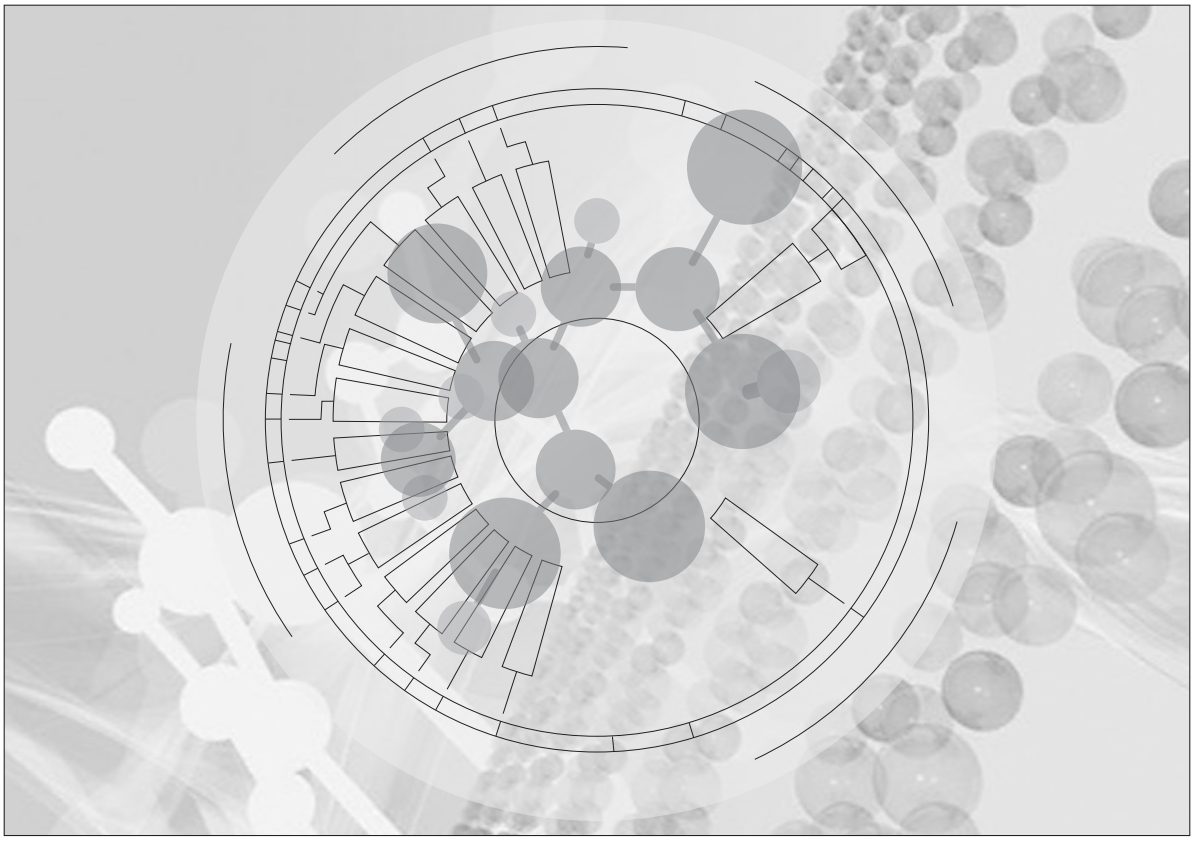

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Elusive Neuronal Targets of Deep Brain Stimulation Identified

Shooting steady pulses of electricity through slender electrodes into a brain area that controls complex behaviors has proven to be effective against several therapeutically stubborn neurological and neuropsychiatric disorders. Now, a new study has found that this technique, called Deep Brain Stimulation (DBS), targets the same class of neuronal cells that are known to respond to physical exercise and drugs such as Prozac.

The study, led by Associate Professor Grigori Enikolopov, Ph.D., of Cold Spring Harbor Laboratory (CSHL), is the cover story in the January 1st issue of The Journal of Comparative Neurology.

The targeted neuronal cells, which increase in number in response to DBS, are a type of precursor cell that ultimately matures into adult neurons in the brain's hippocampus, the control center for spatial and long-term memory, emotion, behavior and other functions that go awry in diseases such as Alzheimer's, Parkinson's, epilepsy and depression. DBS has been successful in treating some cases of Parkinson's. And recently, it has also proven to work against other brain disorders such as epilepsy and severe depression.

"But the clinical application of DBS to treat neuropsychiatric disorders is still problematic because there isn't a clear rationale or a guide for which brain regions need to be stimulated to achieve maximum therapeutic benefit," says Enikolopov. "Our study now points to the brain region whose stimulation results in new cell growth in the hippocampus, an area that is implicated in many behavioral and cognitive disorders."

Enikolopov has long been interested in understanding how neuronal and neuroendocrine circuits are involved in mood regulation. "To that end, the question we've been asking is whether different types of stimuli, such as exercise or drugs or DBS, target different types of brain cells and circuits or converge on the same targets," he explains.

"There is a well-established correlation between the use of antidepressants and new neuronal growth in the hippocampus," says Enikolopov. "But what we didn't know was which steps in the cascade of events that eventually leads to the birth of new neurons are actually affected." Brain stem cells eventually differentiate into mature neurons following a cascade of steps, each of which produces a different intermediary cell type or precursor.

To identify the specific cell type affected by DBS, the CSHL team developed mouse models in which different classes of neural cells such as stem and progenitor cells produce different fluorescent colors. This enabled the scientists to visually track these cell populations and quantitatively assess how they change in response to neuronal triggers such as DBS.

To examine the effect of DBS on the hippocampus, Enikolopov teamed up with Andres Lozano, M.D., a Leading Canadian Neurosurgeon who pioneered its use against depression. The scientists found that stimulating the anterior thalamic nucleus -- an area in the mouse brain that is equivalent to a human brain area where DBS is often therapeutically applied -- resulted in an increase in cell division among the neural stem and progenitor cells, which in turn manifested as an increase in the number of new adult neurons in the hippocampus.

"By tracking new cell growth in the hippocampus and using it as a sensitive readout, we could potentially pinpoint other brain sites at which therapeutic DBS or other stimuli such as drugs might work best for various neurological and psychiatric conditions," explains Enikolopov.

Juan M. Encinas, Clement Hamani, Andres M. Lozano, Grigori Enikolopov. Neurogenic hippocampal targets of deep brain stimulation. The Journal of Comparative Neurology, 2011; 519 (1): 6 DOI: 10.1002/cne.22503