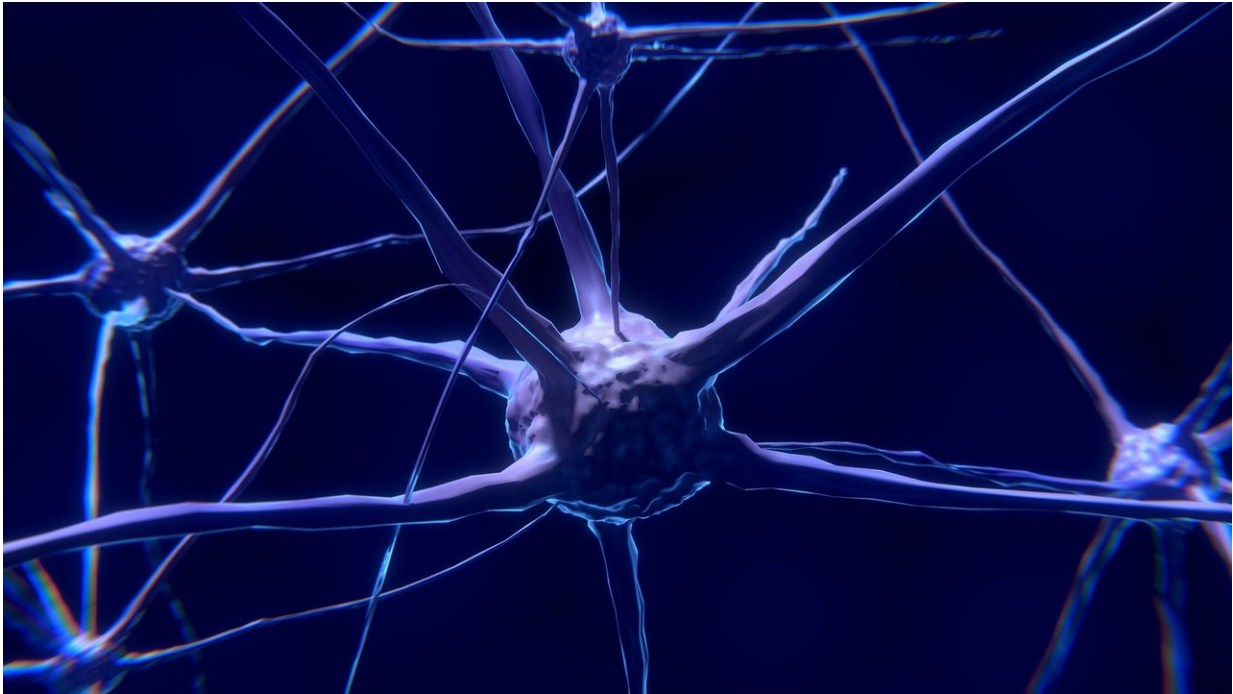


Creating custom brains from the ground up

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Scientists studying how genetics impact brain disease have long sought a better experimental model. Cultures of genetically-modified cell lines can reveal some clues to how certain genes influence the development of psychiatric disorders and brain cancers. But such models cannot offer the true-to-form look at brain function that can be provided by genetically-modified mice.

Even then, carefully breeding mice to study how [genes](#) impact the [brain](#) has several drawbacks. The breeding cycles are lengthy and costly, and the desired gene specificity can only be verified—but not guaranteed—when mouse pups are born.

In today's *Nature*, scientists from Boston Children's Hospital and UC San Francisco describe a new way to create customized mouse models for studying the brain. First, a natural toxin can be used in mouse embryos to kill off the young brain cells that normally grow into the forebrain. The animals' developing forebrains can then be reconstituted from genetically engineered stem cells containing the specific genetic modifications desired for study.

This "forebrain substitution" results in fully functioning mouse pups that have tightly controlled genetics, allowing scientists to study how specific genes influence disorders of the brain with a greater degree of control.

"We think of this strategy as a completely new platform for neurobiologists to study many aspects of the brain, from basic knowledge of which genes control brain development to potentially finding new gene therapies for brain cancers and [psychiatric disorders](#)," says Fred Alt, Ph.D., a co-senior author on the new paper and the director of the Boston Children's Program in Cellular and Molecular Medicine.

"Mice with embryonic-stem-cell-derived brain regions are indistinguishable from normal mice in memory and learning tasks," notes Bjoern Schwer, MD, Ph.D., a former trainee in Alt's lab who is now an assistant professor at UCSF and co-senior author on the paper.

Alt and his team, including Schwer, are also publishing a detailed set of instructions so that scientists around the world can rapidly implement the technique in their own neurobiology laboratories.

Studying gene breakage and rare brain diseases

A particular goal of the Alt lab in developing this technique is to use it as a platform to study a set of genes that they recently discovered are highly susceptible to breaking in mouse brain progenitor cells. They want determine the frequency and mechanisms by which these genes may break, and determine whether this breakage process contributes to neuropsychiatric diseases and brain cancers.

What's more, Alt and Schwer believe the technique could be implemented to aid personalized medicine. By creating custom mouse brain models, physician-scientists could mimic the unique genetic profile of undiagnosed patients with rare brain diseases and disorders.

More information: Neural blastocyst complementation enables mouse forebrain organogenesis, *Nature* (2018). [DOI: 10.1038/s41586-018-0586-0](https://doi.org/10.1038/s41586-018-0586-0) , www.nature.com/articles/s41586-018-0586-0

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