Range of diseases may result when brain self-regulation goes awry, researchers say

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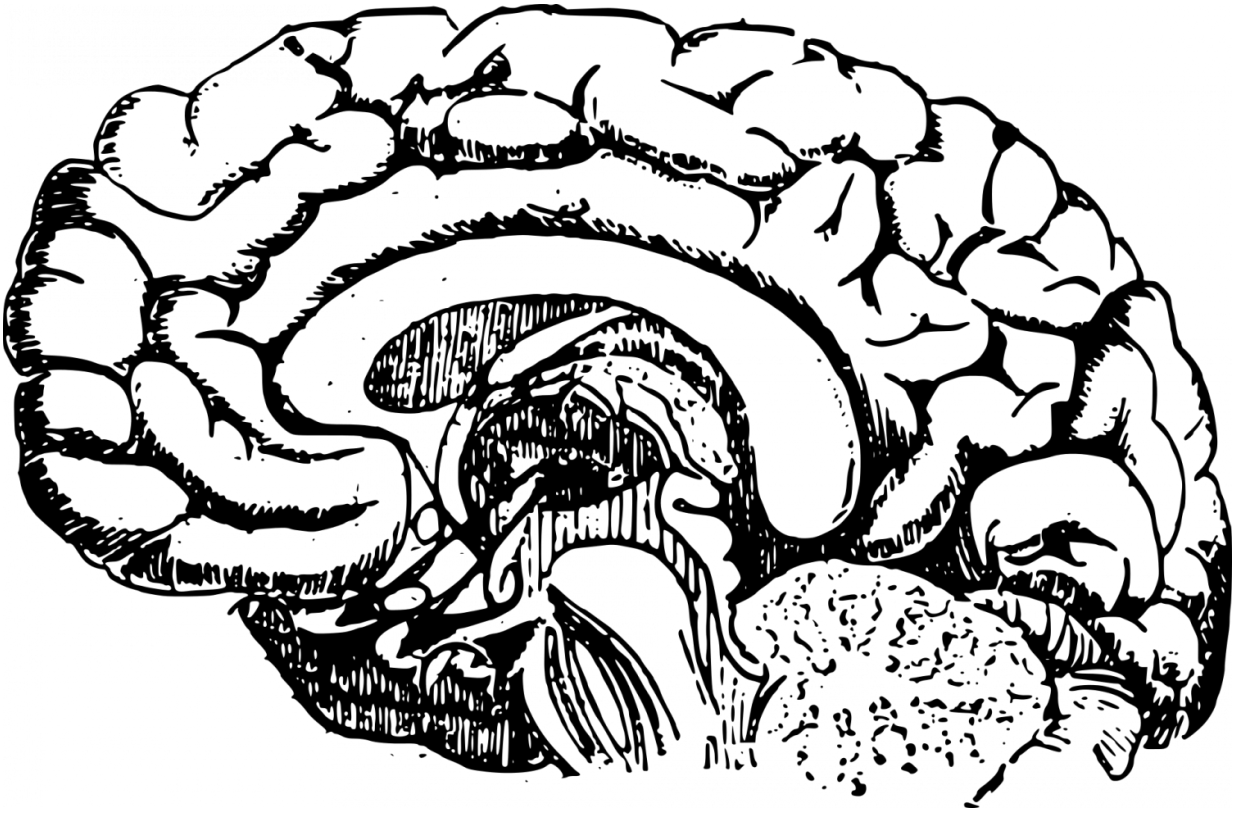

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After making many thousands of measurements in experiments spanning more than 10 years, scientists at UC San Francisco have discovered that two molecular partners interact at synapses to maintain stable neuronal function. The researchers said the study could help explain how the brain

is able to function efficiently and predictably over many decades, and may offer a new approach to a range of neurological and psychiatric disorders, including autism, schizophrenia, post-traumatic stress disorder, and addiction.

Every time we learn a new skill, pick up a new habit, or go through an emotional experience, our brain takes note and its circuits undergo change. But the brain's much-heralded "plasticity" is just part of the story: if everything changed all the time, how could we maintain the memories, skills, and knowledge that make us who we are? Plasticity only has value against a predictable, stable background, and factors that threaten this stability—from genetic mutations present at birth, to life experiences such as trauma, drug abuse, and aging—have the potential to trigger brain disorders, the researchers said.

As reported September 27, 2017 in *Nature*, in studies of fruit flies the researchers showed that when neural communication is experimentally disrupted, two proteins, called semaphorin and plexin (together dubbed "sema-plexin"), drive a compensatory reaction that rapidly restores normal function. Since fundamental aspects of neural communication in the fruit fly are shared by humans, the scientists said the newly discovered stabilization system could also act over the human lifespan to stand in opposition to any kind of mayhem in the nervous system.

"This system stabilizes neural function in response to perturbations," said Graeme "Grae" Davis, PhD, Morris Herzstein Distinguished Professor of Medicine at UCSF and senior author of the new study. "If you disrupt this stabilizer, you're going to be less resistant to a perturbation, whether an environmental toxin, a genetic mutation, infection or injury. So we're imagining a totally different way of approaching diseases—lessening their severity by making the nervous system more resilient to disease-causing disruptions."

The Homeostat is Like a Thermostat

The concept of homeostasis, which describes how cells adapt to survive in a constantly changing world, can be compared to the control of household temperature by a thermostat and furnace. You can set a thermostat to a comfortable temperature of 70 degrees. But if you open a window at night, and cold air rushes in, the thermostat senses the change in temperature, and signals to the furnace to produce heat. Then, as the house warms, the thermostat senses the return to the desired temperature and adjusts heat production to keep the house at 70 degrees.

In the late 1990s, Davis and colleagues discovered that neurons contain a "homeostat" that is capable of stabilizing how neurons function following perturbations that alter nerve cell activity or the chemical communication between neurons. Having a well-functioning homeostat means that the flow of information throughout the nervous system remains resilient to disturbances. The benefits are not just relevant to disease or injury. As noted, stable, predictable baseline function may allow important learning-related plasticity to stand out above all the noise created by our daily activity.

"The idea is that the homeostat improves the signal-to-noise ratio, and creates fidelity in the system," said Davis, a member of the UCSF Kavli Institute for Fundamental Neuroscience.

Over the past two decades, the Davis lab has meticulously observed the neural homeostat in action, but until the new study the precise molecular mechanism that makes its fine self-adjustments possible was unknown.

Semaphorin and Plexin Work Together

The sema-plexin duo was also first discovered about two decades ago in

the fruit fly Drosophila, but in a different role – as guidance molecules that help neurons find their correct targets as the nervous system wires itself up during development. But these molecules are still present in the mature, fully wired brain, and scientists weren't sure why. The new study shows that the sema-plexin signaling system, so crucial to proper brain development, is repurposed in the adult nervous system as a homeostat.

Davis and his team took advantage of a well-studied nexus of communication in Drosophila called the neuromuscular junction (NMJ), where an individual nerve cell send signals to a single muscle cell. Because nerve-muscle communication at the NMJ can be easily quantified, Davis's research group was able to measure it over and over, many thousands of times, searching for gene mutations that might disrupt homeostatic control. After more than a decade of such experiments, they hit upon semaphorin and plexin, a matched pair of molecules residing on opposite sides of the neuromuscular junction, as the crucial players in this process.

When the researchers perturbed the synapse at the NMJ by chemically reducing its strength with a neurotoxic compound, semaphorin sent signals from the muscle cell back to plexin on the nerve-cell ending. This signal stimulated enhanced release of chemical neurotransmitter, thus precisely restoring the correct magnitude of communication between nerve and muscle—and hence, maintaining stability.

"This is the first discovery of a coherent signaling system for neuronal homeostasis, connecting one cell with another," said Davis. "This is a big advance, but there remains a tremendous amount of work to do. We have yet to understand how you turn this signaling system on and how you control its magnitude—not to mention future work examining connections to diseases of the mammalian brain."

More information: Retrograde semaphorin–plexin signalling drives

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homeostatic synaptic plasticity. *Nature*. DOI: 10.1038/nature24017

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