UC San Diego Health

The Brain's Balancing Act

Researchers discover how neurons equalize between excitation and inhibition

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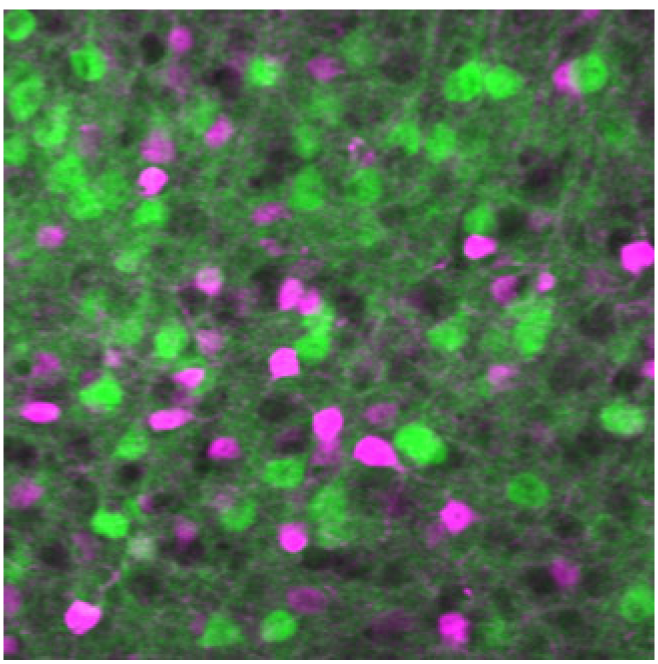
Researchers at the University of California, San Diego School of Medicine have discovered a fundamental mechanism by which the brain maintains its internal balance. The mechanism, described in the June 22 advanced online publication of the journal *Nature*, involves the brain's most basic inner wiring and the processes that control whether a neuron relays information to other neurons or suppresses the transmission of information.

Specifically, the scientists have shown that there is a constant ratio between the total amount of pro-firing stimulation that a neuron receives from the hundreds or thousands of excitatory neurons that feed into it, and the total amount of red-light stop signaling that it receives from the equally numerous inhibitory neurons.



A fluorescent image shows excitatory neurons in green and inhibitory neurons in magenta.

This constant ratio, called the E/I ratio, was known to exist for individual neurons at a given time. This study goes a step further and shows that the E/I ratio is constant across multiple neurons in the cortex of mice and likely also humans, since the fundamental architecture of mammalian brains is highly conserved across species.

“Neurons in our brain drive by pushing the brake and the accelerator at the same time,” said Massimo Scanziani, PhD, professor of neurosciences, Howard Hughes Medical Institute investigator and co-author. “This means that there is no stimulus that you can apply that will activate purely excitatory neurons or purely inhibitory ones.”

“There is always a tug-of-war. It's weird but very clever. It allows the brain to exert very subtle control on our response to stimuli.” For example, Scanziani said it prevents both runaway neuronal firing (excitation) and permanent quiescence (inhibition) because excitation and inhibition are always coupled.

In experiments, the scientists also showed how the brain maintains a constant E/I ratio across neurons: The adjustment is carried out by the inhibitory neurons through the appropriate strengthening or weakening of inhibitory synapses. A synapse is the gap or juncture between two neurons and synaptic strength refers to the degree to which a passed signal is amplified in the juncture.

“Our study shows that the inhibitory neurons are the master regulators that contact hundreds or thousands of cells and make sure that the inhibitory synapses at each of these contacts is matched to the different amounts of excitation that these cells are receiving,” Scanziani explained. If, for example, the level of excitatory stimulation that a nerve cell is receiving is doubled, the inhibitory synapses over a period of a few days will also double their strength.

In terms of clinical applications, the scientists said that neurological diseases such as autism, epilepsy and schizophrenia are believed to be a problem, at least in part, of the brain’s ability to maintain an optimal E/I ratio.

“If this E/I balance is broken, it completely alters your perception of the world,” Scanziani said. “You will be less able to adjust and adapt appropriately to the range of stimulation in a normal day without being overwhelmed or completely oblivious, and E/I imbalances may be most easily noticed in social interactions because these interactions require such nuance and subtle adjusting.”

Scientists have also proposed that some neurodegenerative diseases, such as Parkinson’s and Huntington’s disease, may be associated with a shift in the E/I balance.

Minghan Xue, a postdoctoral researcher in neurobiology and the study's lead author, said “now that we know how this E/I balance is regulated in a normal brain, we can begin to understand what goes wrong in the diseased state. It paves the way for interventions that might restore the balance in the brain.”

Co-authors include Bassam Atallah, PhD, Champalimaud Neuroscience Programme, Chamaplimaud Centre for the Unknown, Portugal.

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