Simple mathematical computations underlie brain circuits

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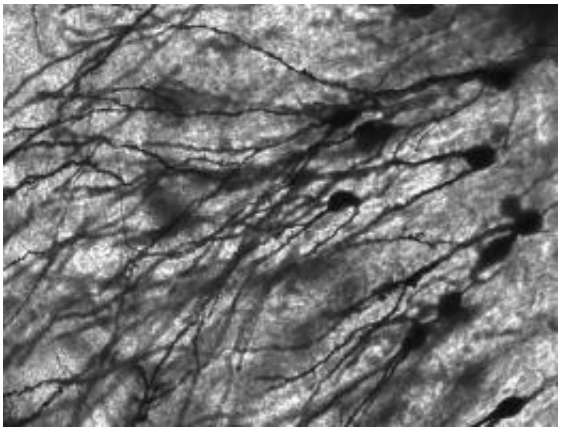

An image of Golgi stained neurons in the dentate gyrus of an epilepsy patient. Image: wikipedia/MethoxyRoxy

(Medical Xpress) -- The brain has billions of neurons, arranged in complex circuits that allow us to perceive the world, control our movements and make decisions. Deciphering those circuits is critical to understanding how the brain works and what goes wrong in neurological disorders.

MIT neuroscientists have now taken a major step toward that goal. In a new paper appearing in the Aug. 9 issue of *Nature*, they report that two major classes of brain cells repress neural activity in specific mathematical ways: One type subtracts from overall activation, while the other divides it.

"These are very simple but profound computations," says Mriganka Sur, the Paul E. Newton Professor of Neuroscience and senior author of the Nature paper. "The major challenge for neuroscience is to conceptualize massive amounts of data into a framework that can be put into the language of computation. It had been a mystery how these different cell types achieve that."

The findings could help scientists learn more about diseases thought to be caused by imbalances in brain inhibition and excitation, including autism, schizophrenia and bipolar disorder.

Lead authors of the paper are grad student Caroline Runyan and postdoc Nathan Wilson. Forea Wang '11, who contributed to the work as an MIT undergraduate, is also an author of the paper.

A fine balance

There are hundreds of different types of neuron in the brain; most are excitatory, while a smaller fraction are inhibitory. All sensory processing and cognitive function arises from the delicate balance between these two influences. Imbalances in excitation and inhibition have been associated with schizophrenia and autism.

"There is growing evidence that alterations in excitation and inhibition are at the core of many subsets of neuropsychiatric disorders," says Sur, who is also the director of the Simons Center for the Social Brain at MIT. "It makes sense, because these are not disorders in the fundamental way in which the brain is built. They're subtle disorders in brain circuitry and they affect very specific brain systems, such as the social brain."

In the new Nature study, the researchers investigated the two major classes of inhibitory neurons. One, known as parvalbumin-expressing (PV) interneurons, targets neurons' cell bodies. The other, known as

somatostatin-expressing (SOM) interneurons, targets dendrites — small, branching projections of other neurons. Both PV and SOM cells inhibit a type of neuron known as pyramidal cells.

To study how these neurons exert their influence, the researchers had to develop a way to specifically activate PV or SOM neurons, then observe the reactions of the target pyramidal cells, all in the living brain.

First, the researchers genetically programmed either PV or SOM cells in mice to produce a light-sensitive protein called channelrhodopsin. When embedded in neurons' cell membranes, channelrhodopsin controls the flow of ions in and out of the neurons, altering their electrical activity. This allows the researchers to stimulate the neurons by shining light on them.

The team combined this with calcium imaging inside the target pyramidal cells. Calcium levels reflect a cell's electrical activity, allowing the researchers to determine how much activity was repressed by the inhibitory cells.

"Up until maybe three years ago, you could only just blindly record from whatever cell you ran into in the brain, but now we can actually target our recording and our manipulation to well-defined cell classes," Runyan says.

Taking a circuit apart

In this study, the researchers wanted to see how activation of these inhibitory neurons would influence how the brain processes visual input — in this case, horizontal, vertical or tilted bars. When such a stimulus is presented, individual cells in the eye respond to points of light, then convey that information to the thalamus, which relays it to the visual cortex. The information stays spatially encoded as it travels through the

brain, so a horizontal bar will activate corresponding rows of cells in the brain.

Those cells also receive inhibitory signals, which help to fine-tune their response and prevent overstimulation. The MIT team found that these inhibitory signals have two distinct effects: Inhibition by SOM neurons subtracts from the total amount of activity in the target cells, while inhibition by PV neurons divides the total amount of activity in the target cells.

"Now that we finally have the technology to take the circuit apart, we can see what each of the components do, and we found that there may be a profound logic to how these networks are naturally designed," Wilson says.

These two types of inhibition also have different effects on the range of cell responses. Every sensory neuron responds only to a particular subset of stimuli, such as a range of brightness or a location. When activity is divided by PV inhibition, the target cell still responds to the same range of inputs. However, with subtraction by SOM inhibition, the range of inputs to which cells will respond becomes narrower, making the cell more selective.

Increased inhibition by PV neurons also changes a trait known as the response gain — a measurement of how much cells respond to changes in contrast. Inhibition by SOM neurons does not alter the response gain.

The researchers believe this type of circuit is likely repeated throughout the brain and is involved in other types of sensory perception, as well as higher cognitive functions.

Sur's lab now plans to study the role of PV and SOM inhibitory neurons in a mouse model of autism. These mice lack a gene called MeCP2,

giving rise to Rett Syndrome, a rare disease that produces autism-like symptoms as well as other neurological and physical impairments. Using their new technology, the researchers plan to test the hypothesis that a lack of neuronal inhibition underlies the disease.

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