The Sum of Its Parts

Many of the brain's sophisticated functions may ultimately arise from the straightforward process of addition.

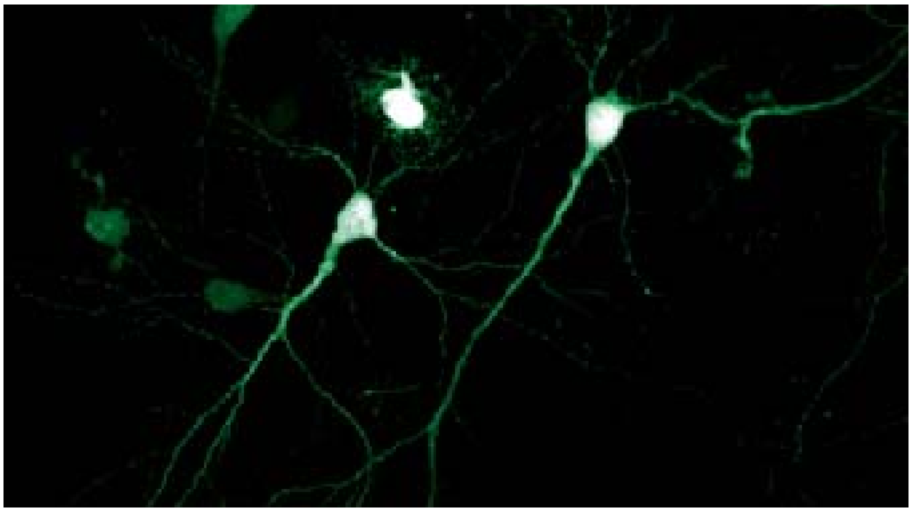
WHEN NEUROSCIENTIST RAFAEL Yuste likens the human brain to a computer, he is zeroing in on its breathtaking simplicity, a circuitry whose logic, he postulates, is the stuff of first-grade math. ¶ Yuste, an HHMI investigator at Columbia University, studies the cortex, the seat of perception, memory, and language. He and his colleagues treat the cortex in the same way engineering students are taught to treat a device of unknown function: "We take apart the box, look at the wires and transistors, and try to identify the logic of its circuitry."

The potential of this reverse-engineering approach is evident in Yuste's recent investigation of an item in the cortical "parts list" called the dendritic spine.

In most cortical neurons, these tiny knob-like features are liberally scattered over the surface of dendrites—the projections emanating from neuronal cell bodies. When one neuron sends a signal to another, the impulse moves from its cell body, through its axon, to its axon terminals, across a gap, or synapse, to the head of a spine on the receiving dendrite and then to the cell body of the neuron.

The fact that most cortical neurons are covered with as many as 20,000 dendritic spines suggests the spines' importance in processing impulses. Yuste's postdoctoral work revealed that spines are containers for calcium, which controls the strength of the neuron-to-neuron connection. But in a series of papers published over the last two years in *Proceedings of the National Academy of Sciences*, Yuste provides evidence, using slices of mouse brains, that spines also serve an electrical function, perhaps even more important in the neuron's processing of incoming nerve signals.

Working with Roberto Araya, a postdoctoral associate in Yuste's lab, and Kenneth Eisenthal from Columbia's chemistry department, Yuste started with evidence that nerve signals can be transmitted between neurons that *lack* spines. While such neurons are comparatively rare in the cortex, their ability to function without the help of spines—still able to marshal the calcium associated with nerve transmission—



These live dendrites in the brain are covered with slender-necked spines that help to accurately sum all incoming nerve signals.

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RAFAEL YUSTE

Science Image courtesy of Yuste lab Photo: Clark Jones / AP, ©HHMI

suggested that "nature doesn't need spines to accomplish this."

Unable to believe that ubiquitous spines were superfluous, the researchers pursued a hunch that spines had an undiscovered electrical role. Using lasers, they "turned on" individual spines to mimic the arrival of an incoming nerve input. Then they measured the voltage generated in the cell body of the same nerve cell, finding that the amount of current delivered through the spine to the soma was inversely proportional to the length of the slender neck supporting the head of the spine.

Now it was time to do some reverse engineering to find out why spines were "filtering," or impeding, incoming nerve signals. Why, after all, would evolution select an architecture that diminished incoming signals at the very point where they were received? It occurred to them that "maybe the logic of the design is to enable the nerve cell to add arithmetically, just as you would teach a child to do," Yuste explains. "The spine neck could serve to electrically isolate inputs, thus enabling the soma to add every input without interference."

They then found that, when two spines on the same dendrite were simultaneously stimulated, the voltage they conveyed to the soma was precisely the sum of their signals. At the same time, when two regions devoid of spines were stimulated, they interfered with each other, and the resulting voltage was much smaller than the sum of the two inputs. Thus, not only do spines compartmentalize calcium to regulate synaptic strength, but they also help the neuron accurately add inputs.

The implication, Yuste hypothesizes, is that dendritic spines enable cortical neurons to work in a linear fashion and serve as adding machines. In a brain marked by a "distributed" circuitry, in which neurons sample incoming information over the widest possible area, a mechanism that accurately sums many signals would gather all possible information.

Yuste's speculation goes further. Perhaps, based on simple addition, nature found algorithms that could be used to build a diverse set of mental functions. Yuste aims to demonstrate this notion in human tissue. If he succeeds, linear summation would be shown to be the elegant operation that renders the cortex a kind of universal computer, able to mobilize elementary math to accomplish such complex (and, paradoxically, nonlinear) ends as thinking, remembering, and imagining. ■

–PETER TARR

NEURONS ON PATROL

HHMI INVESTIGATOR RAFAEL YUSTE is driven by more than a theoretical interest in the structure and function of the cerebral cortex. As a physician-scientist, he also wants to see what happens when cortical circuits *mal*function and what clinicians can do about it. >> **WHEN HE STARTED HIS LAB AT COLUMBIA,** Yuste, took an interest in epilepsy, a major disease involving the cortex. The first to use calcium imaging to visualize a circuit, Yuste and graduate student Tudor Badea "were able to image the spread of an epileptic seizure, neuron by neuron, for the very first time," Yuste says. More recently, Yuste and postdoc Andrew Trevelyan (also a physician-scientist) carried out experiments aimed at discovering how epileptic seizures—or at least their analogs in mice—spread through cortical territory. Their findings, reported over the past year in the *Journal of Neuroscience*, showed that seizures advance in a series of small steps controlled by a specialized type of inhibitory neuron. >> **"WHEN THEY ARE WORKING PROPERLY** and firing, these inhibitory neurons prevent epilepsy from spreading," says Yuste. "You can think of them as policemen, each responsible for a 'neighborhood' of cortical neurons." Three or four officers might patrol a beat encompassing some 1,000 neurons. When they detect an approaching epileptiform wave, the inhibitory neurons fire, discharging γ-aminobutyric acid (GABA), a neurotransmitter, directly into the cell bodies of neighborhood neurons. >> **SO LONG AS THEY HAVE A RESERVE** of GABA, the neuronal police can stop the wave. A person with epilepsy might experience this as a seizure whose effects are localized. But if the GABA-releasing neurons exhaust their supply, the wave passes through, recruits nearby neurons, and prepares to invade the next territory—leading to a full-blown seizure. >> **WHILE CAUTIONING THAT THE WORK** to date involves mouse cells, Yuste believes it could eventually lead to new targets for better treatments in people. "Unfortunately, in 2007 the only 'cure' for severe epilepsy is still neurosurgery," he says. "But instead of cutting out a whole section of the cortex, we might find a way of stimulating this specific class of inhibitory cells so that they can stop progression of a seizure." —*P.T.*