

In the Groove

Scientists are learning more about how signal strength at the junctions between brain cells affects learning and memory.

WHEN PEOPLE FEEL AS IF A FAVORITE SONG HAS WORN GROOVES into their brain, they're not far off. Repeated stimulation of the synapse, the site of communication between two neurons, induces chemical and structural changes that strengthen connections between those cells. ¶ As a result, nerve signals flow more easily across the synapses, connecting neurons involved in learning and memory, so that hearing the first notes of "A Hard Day's Night" instantly recalls the entire Beatles song.

Alteration of synaptic signal strength underlies "neural plasticity," the brain's ability to be changed by a person's experience—in other words, learning and memory—without manufacturing new brain cells.

Recent discoveries led by HHMI investigators Michael Ehlers at Duke University Medical Center and Pietro De Camilli at Yale School of Medicine have clarified some of the mechanisms that dial signal strength up and down. Their findings may also expand understanding of Alzheimer's disease and suggest new avenues for prevention or treatment.

The discoveries, reported separately in the fall of 2008, involve the "postsynaptic" side of the junction, where signals that have jumped the gap stimulate antenna-like receptors in the dendrites—the branching projections of the receiving nerve terminal. Much more is known about the transmitting, or "presynaptic," mechanisms: "We're at very early days in the postsynapse," says Ehlers. Both teams' experiments were designed to explore trafficking of neurotransmitters and

receptors to and from neuronal membranes on either side of the synapse.

Most neurons involved in learning and memory secrete glutamate neurotransmitters into the synaptic gap, where they stimulate specific receptors (termed AMPA and NMDA receptors) anchored in the postsynaptic membrane. The number of these receptors determines the neuron's sensitivity—and as a result, the power of the signal. The receptors are located in nub-like "spines" that protrude from dendrites—neuronal branches that carry the signal from the synapse to the main nerve cell body.

Tiny sac-like vesicles deliver neurotransmitters and their receptors to the synaptic space by fusing with the surface membranes of the pre- and postsynaptic cells, respectively, through a process called exocytosis. After offloading their cargo, the empty vesicles merge with the cell surface membrane and new carrier vesicles form by recycling and pinching off part of this surface membrane, a process called endocytosis.

De Camilli has spent nearly three decades investigating vesicle recycling. In 1996, he discovered an enzyme, synaptojanin1, or SJ1, that degrades a lipid compound called PIP2 in cell membranes, including vesicle membranes. In the absence of SJ1, PIP2 prevents vesicles from shedding their cage-like coating, which they need to do to recycle the membrane for another shipment. The result: a logjam of accumulated vesicles and a shortage of membrane to create new ones.

Until recently, "we thought that SJ1 affected endocytosis just on the presynaptic side," De Camilli says. "But then we began to realize that there is a little synaptojanin everywhere in the neuron, and that it could be involved in postsynaptic vesicle recycling as well."

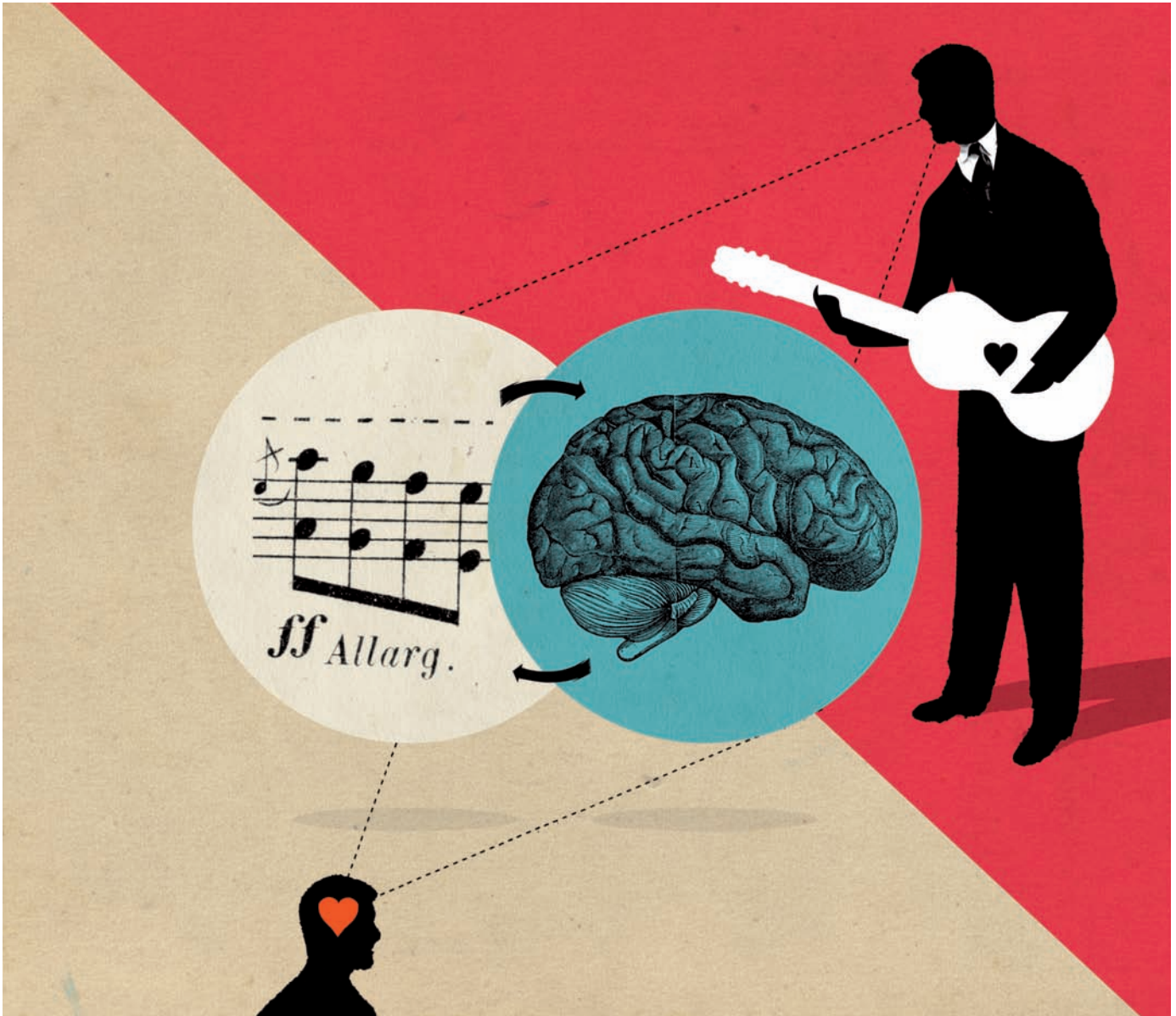
To measure the effect of knocking out SJ1 on synaptic signaling, De Camilli focused on the hippocampal region of the brain, a major memory center that is rich in glutamate synapses. In the November 11, 2008, *Proceedings of the National Academy of Sciences*, he reported that cultured postsynaptic hippocampal nerve cells lacking SJ1 responded more strongly to stimulation than unmodified neurons. The absence of SJ1 on the postsynaptic side hampered the endocytosis and recycling of receptor-carrying vesicles, so receptors accumulated in the membrane, increasing its sensitivity to nerve signaling. In other words, SJ1's normal task in postsynaptic structures is to dampen signal strength.

"A major point is that while pre- and postsynaptic compartments play different and complementary functions, they adapt for those functions some of the same funda-

"We're at very early days in the postsynapse. ¶"

MICHAEL EHLERS





mental molecular mechanisms,” says De Camilli. “SJ1, a protein thought to be only presynaptic is also postsynaptic.”

De Camilli is also investigating a possible link between SJ1 and Alzheimer’s disease. The same PIP2 lipid degraded by SJ1 has recently been found by his former postdoctoral fellow, Gilbert DiPaolo, now an independent scientist at Columbia University, to protect brain cells from the toxicity of amyloid-beta, a peptide implicated in Alzheimer’s disease. Thus, lowering SJ1 levels could increase the amount of

PIP2 in brain neurons, potentially slowing amyloid-beta poisoning.

Ehlers’ discovery also involved the exocytosis and endocytosis of receptors in the postsynaptic neuron—specifically, within dendritic spines.

To move receptors from the interior of the dendritic spine to the synaptic membrane, the cell deploys endosomes, containers akin to vesicles but larger. Exactly how endosomes move was a puzzle until Ehlers identified a “molecular motor” that tows them toward the membrane when

the synapse is active. The motor is a specific form of myosin—a contractile protein found in muscle—called myosin Vb. He reported the finding October 31, 2008, in *Cell*.

Because this transport mechanism can be triggered in a single dendritic spine of a brain neuron, Ehlers says, it helps explain the fine-tuning that enables a nerve signal to stimulate a single synapse without exciting nearby synapses—a prerequisite for neuronal plasticity.

As much as scientists are discovering about synaptic transmission and plasticity, Ehlers says, the “fundamental mystery” remains to be solved—how the changes that occur in the synaptic membrane within “tens of seconds” are maintained in the much longer term, and why we can call up those Beatles classics years after the songs became hits. ■ -RICHARD SALTUS



“Pre- and postsynaptic compartments adapt some of the same molecular mechanisms.”

PIETRO DE CAMILLI