Health & Medicine

Minding the Brain

Neurobiologist Eric Kandel searches for memory, cell by cell.

By
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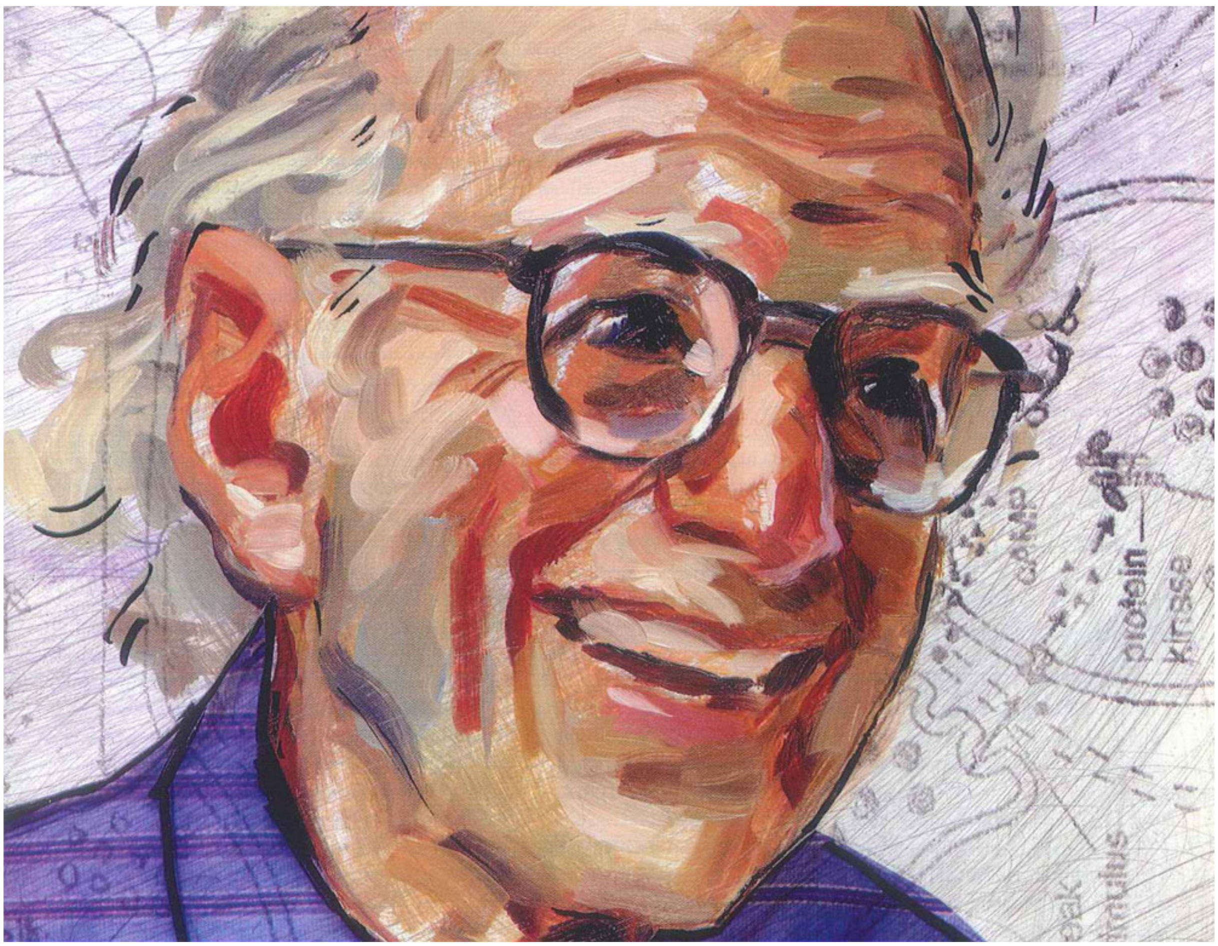

Joseph Adolphe

In 1955, Eric Kandel, a New York University medical student training as a psychiatrist, told Columbia University neurophysiologist Harry Grundfest, with whom he was taking a course, that he wanted to find where the id, ego, and superego live in the gelatinous folds of the brain. In Kandel's recent book, *In Search of Memory: The Emergence of a New Science of Mind* (W.W. Norton, 2006), he recounts Grundfest's patient response. "He explained that my hope of understanding the biological basis of Freud's structural theory was far beyond the grasp of contemporary brain science," Kandel writes. "Rather, he told me, to understand the mind we needed to look at the brain one cell at a time."

More than 50 years later, Kandel sits in his corner office at the New York State Psychiatric Institute on Columbia University Medical Center's (CUMC) Washington Heights campus. His eyes light up through his large eyeglasses as he speaks. He is slight and dapper, and wears a gray suit and a red bow tie. His hair drifts off his head like smoke.

"We're at the beginning of a great ascent on a huge mountain," he says, looking out the window at a sweeping view of the Hudson and the Palisades beyond it. In the houseplant-lined corridor outside his office, a series of framed cover stories on the walls from the journals *Cell and Neuron* read like a history of his accomplishments: "Long-Term Memory in Aplysia," "Spatial Memory and Hippocampal LTP," "Regulating Memory of Fear," but they only hint at the implications of his work.

Kandel is director of Columbia's Center for Neurobiology and Behavior; University Professor of Physiology and Cell Biophysics, Psychiatry, and Biochemistry and Molecular Biophysics; and a senior investigator at the Howard Hughes Medical Institute. He laughs with his mouth opened wide, and has the air of a benevolent mad scientist. Kandel can think big and small at the same time: As he speaks about the neural roots of good and evil, he is drawing connections with the neurons of the giant sea snail, *Aplysia californica*, a foot-long lump that lives on seaweed off the California coast.

Kandel's "new science of mind" is an integration of neuroscience, biology, and the study of behavior that will connect the workings of individual neurons in the brain with philosophy, sociology, economics, art, war, and manifestations of human culture. "Neuroscience is the Esperanto," Kandel says, "the humanistic language that binds it all together." His research into the molecular and cellular basis of short- and long-term memory forms the foundation for the understanding of this language. His work illuminating how signals move through neurons earned him the Nobel Prize in Physiology or Medicine in 2000, alongside Arvid Carlsson from the University of Göteborg in Sweden and Paul Greengard of Rockefeller University. Kandel is, as

Grundfest suggested 50 years ago, taking the next step in the study of the mind. “I think it’s likely that a variety of social phenomena are going to be explored at the biological level,” he says.

From History to Biology

Kandel was born in Vienna in 1929 to lower-middle-class Jewish parents who owned a toy store. He was eight when Hitler invaded Austria, and in his book he describes how most Austrians greeted the Nazis not with resistance or indifference, but with an abrupt, primal enthusiasm that shocked even the young Kandel. Kristallnacht came just two days after his ninth birthday. Seemingly overnight, Jews in Austria went from being accepted, largely integrated members of society to being ostracized, marginalized, and threatened. By 1939, Kandel’s family had escaped to Brooklyn with the help of the Jewish Community Council of Vienna. His last year in Vienna left a profound impression.

“To try to understand how a cultivated, cultured people can turn from being concerned with the beauties of the world to killing Jews is difficult,” Kandel says with a sigh. “The evolution of my thinking came from that, certainly. I began with history, trying to understand it from a historical perspective, then moved to psychoanalysis to get a deeper understanding, and then sort of veered off into medicine and biology.”

Freud on the Brain

After his conversation with Grundfest in 1955, Kandel began to move away from Freudian psychiatry and toward basic science. At the National Institutes of Health in the late 1950s, he settled on the cell-by-cell approach to studying memory. He chose the large and easily manipulated neurons of *Aplysia* for his future work, contrary to contemporary thinking and despite discouragement from other neuroscientists, who thought human behavior was too complex to be inferred from simple systems.

Following a psychiatry residency at a Harvard University teaching hospital, Kandel spent 14 months in 1962 and 1963 in Paris working with Ladislav Tauc, a biophysicist then at the Institut Morey, who pioneered the study of nerve cells in *Aplysia*. It was there that Kandel learned how to simulate memory in neurons from *Aplysia*, which he would later apply to show, for the first time, the cascade of signals and chemical messengers that create short- and long-term memories from sensations. “No one really knew how learning and memory occurred,” he says. Kandel was given his own research group at New York University in 1965. In 1974 he succeeded Grundfest at Columbia.

In the 1990s Kandel had expanded his work from *Aplysia* to *Mus musculus*, the common house mouse, to study attention, memory, and the regions of the brain that mice use to store knowledge of their surroundings, as well as the neural roots of feelings of fear and well-being. His great fascination now is how the brain perpetuates memory, and how to prevent long-term memories from fading. In the coming years, Kandel will lead Columbia’s new Jerome L. Greene Science Center, along with two other Howard Hughes investigators from the biochemistry and molecular biophysics department: Professor Thomas Jessell and fellow Nobel laureate University Professor Richard Axel.

The Mind of Man

In his office, Kandel discusses how the “new science of mind” can be applied to current issues and complex behavior in humans. He supposes that certain antisocial behaviors — hypocrisy, hatred, or aggression, for example — have unconscious roots and specific homes in the folds of the brain. Kandel speculates that when tribal, national, or cultural groups form, individuals may encounter the same experiences, share the same belief systems, and have similar memories. This shared memory could create a collective soul built from a repeating pattern of neural circuits, and may find a defensive advantage in hating or marginalizing another group of people.

“If you think of any of our recent conflicts,” Kandel says, “these are all based in collective memory.” The ongoing strife between Israel and the Arabs, he suggests, is built on cultural memory. In a way, our wars, as well as the hatred Kandel saw as a child, are neurally based, and therefore are part of human nature. “It’s evolutionary,” he says. “The capability for good and evil is probably built into the genome.”

This also means potential for new paths in art, creativity, and beauty. “It is inconceivable to me,” Kandel says, “that as we learn more about how the brain perceives the outside world, that would not influence artists to try new kinds of experiments in art.” Impressionists, for example, explored perception and the mind; a new generation of artists, informed by knowledge of the brain, may experiment in ways we never imagined.

As he shifts the conversation from war to art, Kandel walks to a series of cabinets on the wall that contain his many publications, with indexes on the doors like a card-catalog system. It takes him several minutes to find a reprint of an article he co-wrote in 2003 for the *Annals of the New York Academy of Sciences*, entitled “A Parallel Between Radical Reductionism in Science and in Art.”

“People are worried that if you really understand the mind, you’ll take the mystery out of it,” he says as he places the reprint on the table. “And I make the argument that it won’t.” The paper draws parallels between the use of Aplysia in neurobiology and Mark Rothko’s radical reductionism to say that neurobiology and art run along the same tracks and that simplification and understanding only change the style and scale of mystery, not its nature. For all the questions neurobiology can answer, it will inevitably create more. “We have reason to believe we can make great progress,” Kandel says. “But we have a long way to go.”

A Snail Remembers

Our minds are made of countless tiny connections between neurons, through which ions, proteins, chemical messengers, and electrical signals travel. At one time this language of the mind was mysterious and impenetrable, but now we see that the workings of the brain are complex, understandable, and based in natural laws. Eric Kandel’s work on the giant sea snail, *Aplysia californica*, has made great strides toward explaining these fundamental processes and forming the foundation of neuroscience in the 21st century.

Aplysia has a withdrawal reflex that protects the sensitive gills when the foot-long gastropod is under threat. Using this reflex and *Aplysia*’s large neurons, Kandel’s lab modeled simple forms of learning with a series of benign touches and electrical shocks. As the snails’ giant neurons were stimulated in the right patterns, they began to “learn,” that is, respond to stimuli in predictable ways. With this experimental set-up, Kandel showed how synapses, or the connections between specific neurons, strengthen or weaken under the right conditions — first as short-term memory, and later as long-term memory.

In short-term memory, he found that a stimulus such as a shock to the tail makes a sensory neuron release the chemical messenger serotonin to another neuron. The serotonin then binds to the outside of the neuron, which makes the cell produce another molecule called cyclic AMP. This small regulating molecule interacts with protein kinase A, which enhances the release of a chemical messenger called glutamate to a motor neuron that signals the snail's gill to retract. The persistence of these molecules leads to a heightened sensitivity to stimuli for a short period — a short-term memory.

For long-term memory, repeated stimuli cause the same kinases as in short-term memory to move to the cell's nucleus, where, through a prescribed series of molecular mechanisms, they goad a gene into making a new protein that causes the growth of new terminals or connections. Additional proteins are produced locally, within the cell and at the site of the new connection, to reinforce it as part of a specific long-term memory.

Among the important concepts that Kandel established was that short-term memory is created by changes in the function of cells, while long-term memory comes from changes in the structure of the cell, and requires gene expression. The resulting patterns of connections are products of the genetic hardwiring of our brains and environmental influences — decades of learning. Genes provide the fixed mechanisms and architecture, and superimposed on that is a malleable, plastic network of strong and weak connections, the overlay of a lifetime on a mind. "Our adult repertoire represents a combination and interaction of these two sets of behavioral inventories," says Kandel.

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