PROFILE

Profile of Charles D. Gilbert

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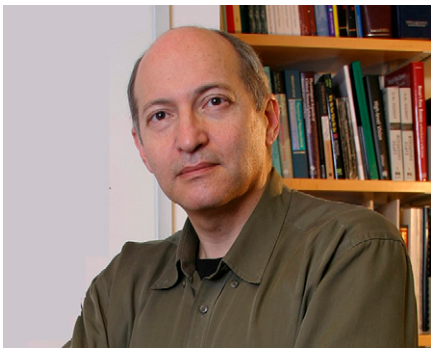
Neuroscientists once thought that the brain's wiring was fixed in early life, but the pioneering research of National Academy of Sciences member Charles Gilbert continues to show that the adult brain is remarkably dynamic. Evidence supporting that view is presented in Gilbert and colleagues' studies of the neural mechanisms underlying visual perception, learning, and memory. Gilbert, the Arthur and Janet Ross Professor of Neuroscience at The Rockefeller University, and his team have discovered long-range, lateral neuronal connections within the visual cortex and have determined that this region of cells at the back of the brain is capable of altering its functional properties and circuitry. Gilbert and colleagues' latest work strengthens evidence for a new general theory of brain function that helps explain the brain's plasticity and provides insight into how recovery may occur following certain lesions and neurodegenerative disease, such as macular degeneration.

Drawn to Biomedical Research

Gilbert's parents were both academics who imparted their interest in science to their three sons. His father, a Chairman of the Psychology Department of Long Island University, served as a prison psychologist during the Nuremberg, Germany, war crime tribunal of 1945–1946 and was interested in the factors that influence human behavior. Gilbert was inspired by his father's work, but from a young age he forged his own path in the sciences. "I was always drawn to biology, but not so much psychology, so it's therefore interesting that my own work has migrated in the direction of perception and brain function in general, though coming from a biological perspective," he says.

Gilbert attended Amherst College, where he earned a B.A. in biophysics in 1971. While at Amherst, Gilbert became an undergraduate research participant at the Cold Spring Harbor Laboratory in New York. The experience provided opportunities to interact with leading molecular biologists. Although he enjoyed his initiation into laboratory work in a bacteriophage laboratory, his interests gravitated to integrative, systems-level studies. In hindsight, Gilbert says, "Studying the brain was perhaps the craziest leap in complexity one could make from bacteriophage." He was able to capitalize on this interest when the late Canadian neurophysiologist David Hubel of Harvard University visited Amherst and encouraged him to apply to Harvard's Department of Neurobiology. In 1977, Gilbert earned both his PhD in neurobiology and MD in medicine at Harvard.



Charles Gilbert. Image courtesy of The Rockefeller University.

Pivotal Mentors and Collaborators

Gilbert remained at Harvard for 5 years after earning his degrees, serving as a Teaching Fellow in neurobiology, Principal Research Associate, and Assistant Professor. While at Harvard, he collaborated with neurophysiologist Torsten Wiesel. Hubel and Wiesel later shared the 1981 Nobel Prize for their discoveries concerning information processing in the visual system. Gilbert says, "The visual system at the time was providing the best avenue to understanding higher brain function at the level of individual neurons and neural circuits, so one could have parallel interests in general mechanisms of brain function as well as the specific mechanisms of visual perception."

Both Hubel and Wiesel inspired Gilbert, who admired not only their abilities as scientists but also their leadership and communication skills within and outside their laboratories. Psychophysicist Gerald Westheimer, then at the University of California at Berkeley, additionally influenced Gilbert. "While David and Torsten approached the brain from the perspective of the function of individual neurons, Gerald explored the visual system from the direction of human visual perception," Gilbert says. "Joining together the neuronal and perceptual perspectives has been invaluable in guiding my own research."

Discovery of Lateral Neuronal Connections in Visual Cortex

At the time, cortical connections were thought to be primarily interlaminar and restricted in their lateral extent. As such, each neuron was thought to respond only to a particular location in visual space, referred to as its "receptive field." Studying the cat and monkey visual cortex, Gilbert and Wiesel negated this hypothesis in a series of articles (1–3). They discovered that cortical pyramidal neurons instead form long-range horizontal

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connections that link distant locations in the cortical map. The neurons they imaged were receiving visual input from parts of the visual field that were outside their receptive fields.

The discovery required a rethinking of the definition of the receptive field. As Gilbert says, "In effect, the responses of neurons are as dependent on contextual influences surrounding the receptive field as they are on the stimuli within the receptive field." He explained that the observed horizontal connections mediate an association field, a system by which information is linked across cortical maps. The findings contribute to the Gestalt laws of perceptual grouping, whereby objects in a scene group preattentively as the brain filters and processes what is deemed important.

Adult Cortical Plasticity, Perceptual Learning

Gilbert, Wiesel, and other Harvard colleagues moved to The Rockefeller University in 1983. Their research on the visual cortex continued, often using intracellular recordings, and built upon studies of cortical circuitry that they had begun to develop at Harvard. The following year, Gilbert won the 1984 Presidential Young Investigator Award. In 1985, he was promoted to Associate Professor. Gilbert subsequently earned a full professorship at the university in 1991. As neuronal imaging advanced, his team began to use a viral labeling system, which fills neurons with fluorescent proteins and then images dendritic and axonal arbors in an intact, living brain with a high-resolution two-photon microscope.

Gilbert and colleagues' anatomical characterization of the horizontal neuronal connections within the visual cortex led to the further discovery that these connections play a central role in adult cortical plasticity (4–7). He says, "We have seen this plasticity in the recovery of function and remapping of cortical functional architecture following retinal lesions." He and his team determined that, while there is a baseline turnover of axonal boutons, namely nerve fiber enlargements at synapses (8), the horizontal neuronal connections underlying experience-dependent plasticity undergo exuberant sprouting and pruning (6), which the researchers have characterized at the functional, anatomical, and molecular levels.

Gilbert and his team have also observed changes in the functional properties of neurons within the visual cortex during the course of normal perceptual learning, wherein the ability of sensory systems to respond to stimuli is improved through experience and practice in performing specific tasks (9–11). An important finding from this work is that neurons exhibit the properties associated with learning only when animals perform the learned task. As a consequence, neurons are dynamically tuned, taking on different functions according to top-down influences of perceptual task, expectation, and attention.

New Theory of Circuit Mechanism of Brain Function

For his achievements, Gilbert was elected as a Fellow of the American Academy of Arts and Sciences in 2001 and won the W. Alden Spencer Award in 2002 and the 2015 Edward M. Skolnick Prize in Neuroscience. Gilbert's PNAS inaugural article (12), following his election to the academy in 2006, as well as other studies over the past 5 years (13–15), have contributed to a new general theory of brain function based on his findings that neurons are adaptive processors. He suggests that neurons select subsets of inputs to carry task-relevant information and that they do so by an interaction between feedback connections, which carry the top-down information about the task requirements, and intrinsic circuits within the target area. The latter circuits carry information about stimulus characteristics.

In effect, the feedback connections provide what Gilbert and colleagues refer to as a "pointer" that dynamically links bits of information that are mapped across each cortical area. He says, "The interdependence of effective connectivity between multiple cortical connections suggests a mechanism by which top-down influences enable neurons to carry task-relevant information." Gilbert and colleagues' latest article provides further evidence for his theory, using an analytical tool known as "conditional Granger causality," which permits analysis of data from large-scale recordings of visual cortex circuitry (16).

His team is currently extending the findings on top-down influences, adaptive processing, and connectivity dynamics in the primary visual cortex to other areas of the visual pathway. Using psychophysics and imaging in rodent models, they are also exploring the idea that behavioral disorders, such as autism, may have a perceptual component and could involve a disruption in the operation of top-down influences.

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