Obituary

Patricia S. Goldman-Rakic (1937–2003)

Neuroscientist who revolutionized the study of higher brain function

It was a snowy winter day in 1998 and I had just heard Patricia Goldman-Rakic talk about her recent studies of the cerebral cortex and its abnormal functioning in schizophrenia. Driving home together from Massachusetts, the slow traffic gave us ample time to delve into the implications of her findings. Goldman-Rakic's work addressed one of the last frontiers of human knowledge: the neural mechanisms in the brain that control thought and planning, reasoning and attention. She used a uniquely wide array of experimental tools, in non-human primates and in humans, to explore these mechanisms under normal and pathological conditions. Yet this only begins to explain the enormous loss to the field caused by her untimely death in a car accident on 31 July 2003.

Goldman-Rakic's work focused on the brain's frontal lobes, in particular the prefrontal cortex. From an evolutionary point of view, this is the most recently developed part of the brain, and is greatly advanced in primates compared with other mammals. Still, not much was known about it in 1965, when Goldman-Rakic started working on the region as a junior research fellow at the National Institute of Mental Health (NIMH) in Bethesda. She had recently completed her PhD at the University of California, Los Angeles, where she studied rodent models of stress.

Over the next ten years, Goldman-Rakic and her colleagues, along with other groups, created small lesions in the brains of adult rhesus monkeys and other non-human primates, documenting for the first time that the prefrontal cortex is essential for a form of cognition termed working memory or executive function. This refers to the ability of an individual to keep something 'in mind' while attending to other tasks. Working memory was measured with 'delayed-response' tasks; these come in many forms, but the basic principle is that a monkey is required to maintain a mental representation of something, such as where a food reward is located, which guides its subsequent responses to obtain this reward.

In the 1970s, by which time Goldman-Rakic was chief of the Section on Developmental Neurobiology at NIMH, she and her colleagues had extended this work to show that damage to the monkey prefrontal cortex early in life causes cognitive abnormalities that become noticeable during adolescence. At about the same time, she demonstrated a crucial role for the neurotransmitter dopamine in regulating prefrontal cortical function. Both findings related to schizophrenia, a common and debilitating syndrome that was at the time defined by 'positive symptoms' (hallucinations and delusions) and 'negative symptoms' (blunted emotions). As with Goldman-Rakic's monkeys, schizophrenia develops in adolescence and early adulthood. Moreover, dopamine was known to influence the symptoms of schizophrenia, because all anti-schizophrenic medications were (and still are) molecules that block dopamine receptors on neurons.

In 1979 Goldman-Rakic moved her laboratory to Yale University, where she joined the newly created Section of Neuroanatomy. The years that ensued brought remarkable productivity, as her research evolved in several new directions. She characterized the three-dimensional structure of individual prefrontal cortical nerve cells and the several thousand connections (synapses) that each nerve cell forms with its inputs. She identified parallel streams of sensory information that feed into the prefrontal cortex. She and her co-workers also defined exactly where on these nerve cells different types of receptor for dopamine and other neurotransmitters are located.

The Goldman-Rakic laboratory also began to record the electrical activity of individual prefrontal cortical neurons while monkeys were performing delayed-response tasks. They discovered nerve cells that respond to visual and spatial cues involved in working memory, but not to other types of sensory stimulus. This work supported the view that the prefrontal cortex is organized according to sensory modality, and defined several subregions of the prefrontal cortex into which these modalities are segregated. In addition, Goldman-Rakic discovered how dopamine affects the function of individual neurons and correlated the different effects of dopamine with particular behavioural actions, which ranged from improved attention to impaired performance in working-memory tasks.

Goldman-Rakic applied this growing understanding of the prefrontal cortex in monkeys to studies of schizophrenia. Her laboratory carefully defined cellular abnormalities in autopsy specimens taken from the prefrontal cortex of people with schizophrenia. By the use of brain imaging, her group began to define areas of the prefrontal cortex that function abnormally in schizophrenia. Although the exact nature of these abnormalities in the prefrontal cortex is still incompletely understood, Goldman-Rakic's work helped to spark new ideas about where in the brain to search, and what types of cellular abnormalities to look for, in schizophrenia. Indeed, the growing evidence for a role of the prefrontal cortex in schizophrenia drove the field — relatively recently — to recognize cognitive abnormalities, particularly in working-memory processes, as a third major clinical feature of this syndrome.

Translational — bench-to-clinic — research in neuroscience is as difficult as it is necessary, yet Goldman-Rakic succeeded brilliantly. She tackled the complex nature of working memory at the neural, cellular and molecular levels. Moreover, her findings have led to a fundamental revisiting of the effects of dopamine on cortical function, and hence to efforts to develop new drugs for treating schizophrenia.

The depth and breadth of Goldman-Rakic's contributions to the study of the prefrontal cortex and schizophrenia led to many honours. In a field still dominated by men, she was one of all too few senior women scientists. Her death deprives the field of still more discoveries and insights. But her work defines the elegant process of scientific inquiry that will be needed to solve the riddle of thinking, and its derangement in schizophrenia. **Eric J. Nestler**

Eric J. Nestler is in the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9070, USA.
e-mail: eric.nestler@utsouthwestern.edu