Patricia S. Goldman-Rakic
1937–2003

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Amy F.T. Arnsten
and Pasko Rakic

NATIONAL ACADEMY OF SCIENCES

PATRICIA SHOER **GOLDMAN-RAKIC**

April 22, 1937–July 31, 2003

Elected to the NAS, 1990

By Amy F.T. Arnsten and Pasko Rakic

Patricia Shoer Goldman-Rakic made the groundbreaking discovery of how newly evolved, neuronal circuits in the primate prefrontal association cortex (PFC) are able to generate the mental representations that are the foundation of abstract thought, a process that culminates in the human brain. Her multidisciplinary research explained how neuronal circuits in the PFC generate and maintain goals for action based on personal memories. This can occur even in the face of considerable distractions—thus liberating our decision-making and behavior from dependence on sensory stimulation from the environment, as occurs in animals with simpler central nervous systems. This basic concept, which she initially named "representational knowledge," was later renamed as "working memory." Her discoveries created the biological foundation for the new field of cognitive neuroscience and for understanding the etiology of cognitive disorders such as schizophrenia, which had been previously considered to be beyond the realms of scientific inquiry. This neurobiological framework also inspired new treatment strategies for cognitive disorders now in widespread use. Her pioneering research revolutionized neuroscience and lit the path forward for women everywhere.

Personal Life

Patricia Shoer was born on April 22, 1937, in Salem, Massachusetts, to a Jewish family. Her mother, Jennie Pearl, was an immigrant from what is now Ostroh, Ukraine, and her father, Irving Shoer, was a wholesale dealer of poultry and eggs who was born in Michigan to Latvian immigrant parents. Pat and her sister Ruth were identical twins (Figure 1) and a third sister, Linda, followed five years later. Irving was affable, fun loving, and easy-going; Jennie, in contrast, was serious, sharp-witted, and a perfectionist. Although her parents had little to no formal education, they encouraged their daughters to excel. In an era when women were expected to become housewives, all three daughters eventually obtained doctorates in science from major universities.

Figure 1. Irving Shoer with his twin daughters Ruth and Pat circa 1939.

From an early age, Pat was multi-talented: she was an excellent artist and played both the piano and violin very well. As her sister Ruth said:

I believe her dexterity and steady hand carried over into her scientific work, enabling her to perform delicate and intricate brain surgery, even in utero. And her sense of aesthetics was evident in her choice of cover illustrations for the journals, in her slides, and in her diagrams of neuronal interactions which appear in many of her papers and which other scientists borrowed for use in their own publications.

Her first, brief marriage to Dr. Lawrence Goldman ended in divorce. At about that time, while at a scientific meeting, she met colleague scientist Dr. Pasko Rakic, who was on the faculty at Harvard Medical School working on the development and evolution of the primate brain. They dated at a distance, travelling on weekends between Washington and Boston and having long, daily telephone conversations for about four years (Figure 2), until Pasko was recruited by Nobel Laureate George Palade to the Yale School of Medicine to create the new Section of Neuroanatomy, which over time transformed into the Department of Neurobiology and now the Department of Neuroscience. Pat moved to New Haven to join him one year later, and they were married in 1979. For the next 24 years they worked together (Figure 3) to build a department at Yale Medical School that in 1995 was rated the best neurobiology department in the country, with a total of only ten faculty: 5 women and 5 men. They also created a highly successful journal, Cerebral Cortex, that as Dominick Purpura once articulated: "was Pat and Pasko's child."

Figure 2. Patricia's picture while on the phone with Pasko in the mid 1970's.

Figure 3. Patricia and Pasko Rakic in the mid1990's when Yale Neurobiology was ranked No.1 in the country.

Pat died tragically in 2003 at the peak of her career, struck by a car a few blocks from her home and suffering irreparable damage to her frontal lobes. As pointed out at her memorial service, which was attended by thousands of scientists from all over the world, Pat made great discoveries but also brought her feminine intuition to the personal dynamics of the workplace.[1, 2]

In the words of her husband, Pasko:

> *My Pat was strong and decisive as well as gentle and feminine. She was particularly struck by an observation about the challenges of studying the brain made by a fellow scientist, Rita Levi-Montalcini, who commented that if she had known how difficult understanding the brain was, she would never have attempted it. Pat knew how difficult it was and still pursued the most complex question in the universe—the biological basis of thought. She was both brilliant and brave.*[1]

It is generally acknowledged that Pat pioneered new roads for women in science.

Education and Career

After Pat graduated from Peabody High School with the coveted George Peabody Medal (reserved for the top students), she enrolled in the elite (but at the time exclusively female) Vassar College in 1955. Following graduation summa cum laude in 1963, she enrolled in a Ph.D. program in Developmental Psychology at the University of California at Los Angeles (UCLA). After graduation she held postdoctoral positions at UCLA and the American Museum of Natural History in New York. In 1965, Pat joined the National Institute of Mental Health (NIMH) in Bethesda, Maryland, as a Fellow in the Section of Neuropsychology. Thus, she had an excellent exposure to education at major institutions, but like most great scientists, she was self-made, not a follower but a trailblazer.

Figure 4. The Section of Developmental Biology at the National Institute of Mental Health in 1979, when Patricia was the Director.

In 1974, Pat spent a year in Dr. Walle Nauta's lab at the Massachusetts Institute of Technology in Cambridge, where she

Figure 5. Goldman-Rakic's laboratory at Yale in 1984; note the large number of women.

was exposed to a generation of scientists who created the new multidisciplinary field of neuroscience. In particular, she learned novel neuroanatomical tracing techniques that would transform her career. Following her return to NIMH, she was appointed to serve as Chief of the Section on Developmental Neurobiology (Figure 4). After moving to Yale University in 1979, she expanded the scope of her research to include the newest and most advanced methods, including cell and molecular biology. She also started the Ph.D. graduate program in Neurobiology at Yale. Pat's lab there was initially small but included many young women (Figure 5). It expanded quickly as she added new advanced techniques and tackled ever more challenging questions about frontal lobe structure, physiology, and function that required investigators of different expertise (Figure 6). At the time of her death, she was one of the best-funded scientists at Yale, with several research grants as well as large program projects. Patricia Goldman-Rakic published over 300 papers that were by any standard highly influential (over 90,000 citations in Google Scholar in 2020). She was elected to the National Academy of Sciences (USA), the American Academy of Arts and Sciences, and the National Academy of Medicine and served as president of the Society for Neuroscience. She received numerous prestigious awards and in 2001 CNN named her "America's Best Neuroscientist."

Figure 6. Goldman-Rakic's laboratory at Yale in 1995.

Groundbreaking Research on the Prefrontal Cortex

Pat started to work on the PFC at a time when it was not a popular subject. Although research on the visual cortex flourished, and scientists could apply for grants to their dedicated NIH Institute (the NEI), there was no institute dedicated to the PFC, the structure that is not only larger in primates, but also what makes us human. Pat was a lonely pioneer in this unexplored land (Figure 7). She selected the macaque monkey as the subject of her research because of its expansive PFC as compared to non-primate mammalian species. While at the NIMH, she began to explore the development of the macaque PFC and determined that it is the dorsolatral subregion of the PFC (dlPFC) along the principal sulcus that is necessary for visuospatial working memory. She established that the cortex surrounding the caudal two-thirds of the principal sulcus was essential for spatial working memory and that monkeys with principal sulcal lesions could perform visuospatial tasks that did not require memory or memory tasks that did use visuospatial information, but could not perform tasks that required memory of visuospatial information.[3, 4] This information defined the "bull's eye" for future studies of spatial working memory and gave the first hints of the parallel organization underlying cognitive operations. It was also at this time that she first discovered the importance of dopamine to dlPFC function, a breakthrough that was decades ahead of the field.

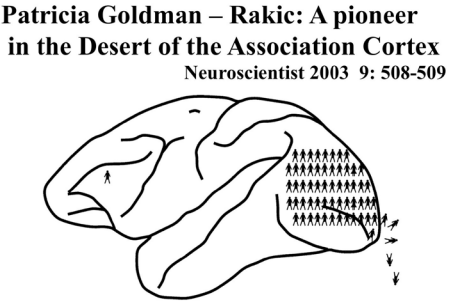

Figure 7. Pat as a lonely explorer of the PFC area while most researchers concentrated on the primary visual cortex, as illustrated by Pasko's cartoon.

After moving to Yale, she employed a range of anatomical, physiological, and behavioral techniques to determine the cellular basis of working memory, one of the first neuroscientists to employ a multi-spectrum approach to tackle an important question. This multi-dimensional approach reshaped the paradigm for neuroscientific inquiry, such that it is now expected that scientists will utilize a variety of techniques to address many sides of a question.

Pat mastered the most advanced anatomical tracing techniques to reveal the brain networks that subserve cognition. Prior to her research, it was thought that there was little topographic organization in the higher association cortices, such as the PFC.

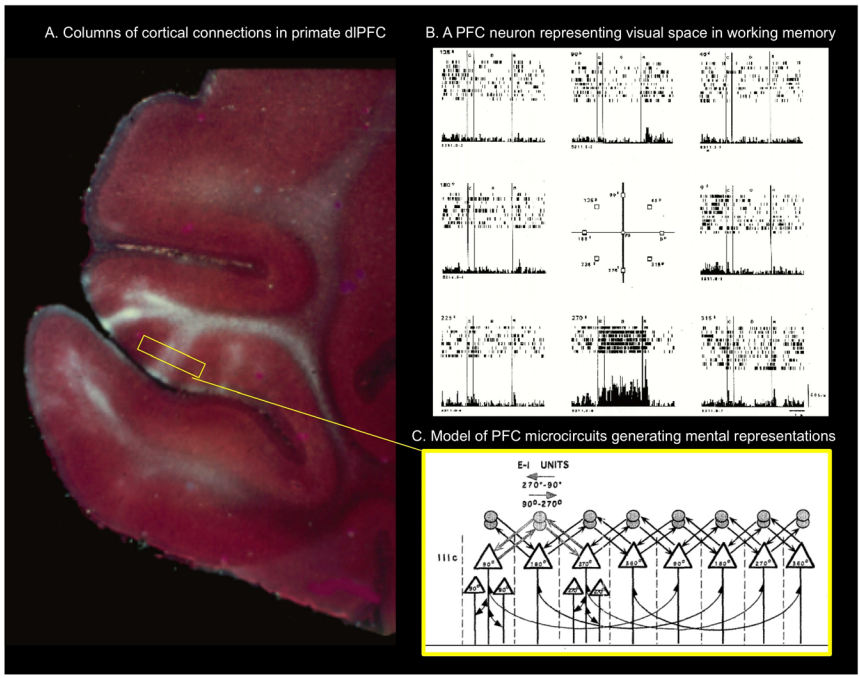

Figure 8. A. Patricia's discovery that radial columns are not present just in the sensory (visual) areas, but also in the most advanced association PFC signified that the PFC could be studied using the same tools as those used to understand visual neuroscience. B. A "Delay Cell" in monkey dlPFC that can represent a position in visual space without sensory stimulation through its persistent, spatially-tuned firing across the delay period in a working memory task. From[8]. C. Goldman-Rakic's model of the microcircuits in deep layer 3 of dlPFC that generate Delay cell firing. From her review in *Neuron* [9].

However, Pat discovered a columnar organization in PFC similar to the primary sensory cortices (Figure 8A), indicating that high-order cortex could be approached with the same strategies as sensory cortex. Her tract-tracing studies of the dlPFC revealed widespread parallel but interacting networks for the representation of visual space vs. features and for auditory space vs. features, creating a dorsal spatial zone and a more ventral feature domain in the rhesus monkey dlPFC (Figure 9). These networks included extensive subcortical connections, for example, among the striatum, thalamus, and

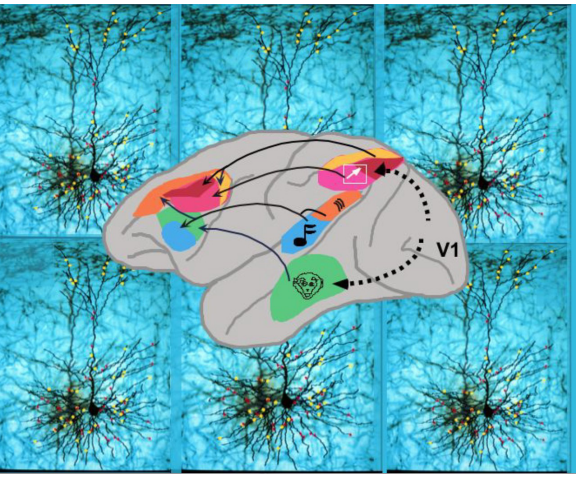

Figure 9. Pat's sketch of the parallel pathways for the analysis and representation of space vs. features in the visual and auditory domains proceeding into the frontal lobe. The background image illustrates a PFC pyramidal cell receiving dopamine inputs on dendritic spines.

brainstem.[5,6] These detailed connectome studies revealed coordinated, long-range circuits for higher cognition, for example, a spatial cognition network shared between the dlPFC and the parietal association cortex. Her discovery of neural networks for higher cognitive operations has been confirmed in human brain-imaging studies, such as where functional connectivity correlative analyses replicate many of her findings from the rhesus monkey brain. Her remarkable 1987 chapter summarizing this vast body of work has now been made available online for future generations to read.[7]

Pat also brought neurophysiological experts to her laboratory to record neurons in the dlPFC during working memory performance. Although previous researchers had shown that these cells had the ability to maintain firing across the delay period when an item was being remembered, her work extended these investigations to show that these neurons could represent a position in visual space without sensory stimulation (Figure 8B). Her work showed that these "delay cells" could elevate and maintain firing to remember one particular location in visual space but not other locations; that is, they had a preferred location/direction. Pat realized that the ability to generate and sustain an accurate representation of visual space relied on two key features: persistent firing across the delay period when the item was being remembered, and spatial tuning such that the firing only occurred for one location and not others. Together, these neural operations created the cellular basis for working memory.[8]

Pat next employed a mixture of physiological and anatomical studies to reveal the microcircuits within the dlPFC that generate persistent, spatially tuned neuronal firing. This work revealed that the persistent firing arises from clusters of pyramidal cells with similar spatial tuning exciting each other to maintain firing across the delay period, so-called "recurrent excitation." She showed that these circuits are focused in deep layer III, the

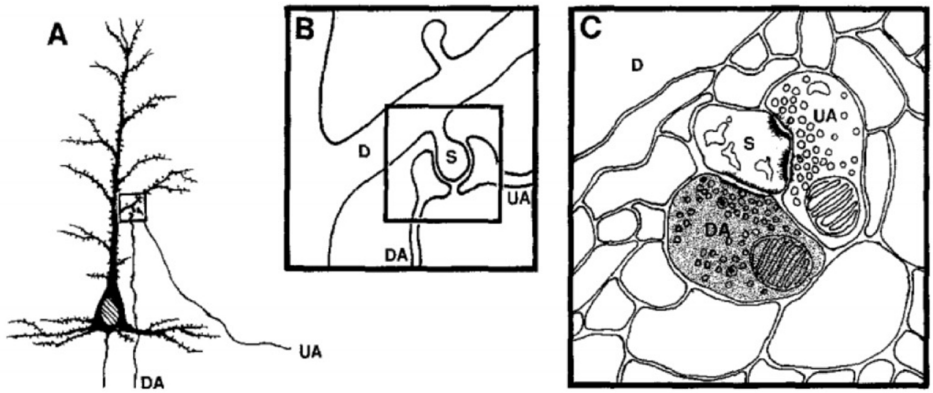

Figure 10. Famous triad: Pat's lab showed electron microscopic evidence that dopamine inputs can regulate glutamate afferents on the dendritic spines of PFC pyramidal cells, what she called a "synaptic triad". Her work had also shown that dopamine was essential for PFC physiology and working memory performance.

cortical layer that expands most in primate brain evolution. Conversely, the spatial tuning was refined by parvalbumin-containing GABAergic interneurons (basket and chandelier cells) activated by pyramidal cells to employ lateral inhibition. For example, delay cells preferring 90 degrees would activate interneurons to inhibit the firing of non-90º neurons, thus sharpening the representation of 90º in working memory. This work is summarized in her review in *Neuron*[9] in 1995 in the model shown in Figure 8C.

From the earliest stages of her career, Pat discovered the powerful influence of monoamines, and especially of dopamine, on dlPFC physiology and function. Her initial, landmark study showed that depletion of catecholamines from the dlPFC was as devastating to working memory as removing the cortex itself. She later demonstrated the key role of dopamine actions at D1 receptors in promoting working memory. She showed that D1 receptors were concentrated on dendritic spines in layer III of the dlPFC and that dopamine terminals sometimes formed a synaptic triad with a glutamatergic synapse onto the same spine (Figure 10).[10,11] She showed that the infusion of a D1R antagonist into the dlPFC greatly impaired working memory[12] and reduced delay cell firing.[13]

It was her hope that a D1R agonist could be developed to help those with dlPFC cognitive deficits, such as patients with schizophrenia, a goal still being pursued at the time of this writing.

Although Pat and Pasko worked in different subfields of neuroscience, they have a few publications together. For example, they provided evidence that surgical manipulation of the cortico-cortical connections during prenatal development in non-human primates can dramatically change the pattern of cerebral convolutions after birth.[14] This work provided experimental evidence for the competitive interactions among neuronal connections in utero that have consequences after birth. They also demonstrated that the number of neurons, their axons, dendritic spines, and synapses, as well as the amount of neurotransmitter receptors, are much greater just after birth and decline to adult levels during adolescence in primates, including humans.[15]

Pat was always trying to relate basic and translational neuroscience and looking for clinical significance. For example, she and her collaborators were the very first to show that the dlPFC is altered in schizophrenia, with loss of neuropil from the deep layer III microcircuits that generate thought.[16, 17] This work was confirmed and expanded by David Lewis's research, which showed loss of spines and dendrites specifically from this sublayer.[18] The loss of spines in deep layer III of the dlPFC would reduce the recurrent excitation needed for working memory, and indeed, the profound deficits in working memory seen in patients with schizophrenia correlate with hypofrontality during brain imaging and with symptoms of thought disorder. Thus, Pat's research provided the cellular basis for a complex cognitive disorder previously thought to be beyond the scope of science.

In collaboration with Amy Arnsten, Pat was also engaged in the complex process of creating medications for the treatment of prefrontal symptoms in a variety of disorders. Guanfacine (Intuniv), for example, was approved by the FDA for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and is also used for a range of disorders that benefit from strengthening PC connectivity, including child abuse/trauma, Tourette syndrome, autism spectrum disorders, and traumatic brain injury to the frontal lobe. These discoveries could not have occurred without research and testing on the non-human primate PFC.

In summary, Patricia Shoer Goldman-Rakic created a new landscape in neuroscience, providing the first cellular basis for the working memory functions that are foundational to abstract thought and that are the focus of injury in mental disorders.

For additional reading about the research of Goldman-Rakic, please see Arnsten.[19] Informative obituaries, including the quotes from many leading neuroscientists about her remarkable discoveries, can be found in several other tributes.[1, 20-23]

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