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Obituary

Patricia Goldman-Rakic: A Remembrance

Patricia Goldman-Rakic

In the 1960s, scientists were conquering improbable frontiers: the moon was about to be walked upon; the brain cracked open. Neuroscientists were discovering that the secrets of the visual cortex could be broken with single-cell recordings and new anatomical tracing techniques, revealing an extraordinary organization: columns of cells responsive to only one eye; single cells tuned to a specific orientation. But the cortex under study was anesthetized. The Mind was not considered an appropriate topic for neuroscientific inquiry. Schizophrenia was thought to result from bad mothering; state mental hospitals were overflowing with chronically ill patients, little different from Bedlam hundreds of years before. Some were veterans of the pre-Thorazine age and wore the scars of frontal lobotomies—a last resort to control their violent behavior.

Patricia Shoer Goldman arrived as a Fellow in the Section of Neuropsychology at the NIMH in 1965. There was an opening in the lab of Haldor Enger Rosvold, who, with a handful of others around the world, was studying the effects of prefrontal cortical lesions on behavior in monkeys. About that time, Walle Nauta wrote that the frontal lobe

> has remained the most mystifying of the major subdivisions of the cerebral cortex. Unlike any of the great cerebral promontories, the frontal lobe appears not to contain a single sub-field that could be identified with any particular sensory modality, and its entire expanse must accordingly be considered association cortex. It should, perhaps, not be surprising in view of this circumstance alone that loss of frontal cortex, in primate forms in particular, leads to a complex functional deficit, the fundamental nature of which continues to elude laboratory investigators and clinicians alike.

Rosvold, together with Mort Mishkin, would lesion the dorsolateral versus orbital surfaces of prefrontal cortex to try to characterize the complexity of the ensuing deficits. They had trained at Yale in Fulton's Department of Physiology, where Jacobsen had performed the very first studies of prefrontal cortex in monkeys in the 1930s. Jacobsen created the spatial delayed response task, a test of spatial memory that required constant updating of memory for spatial position. Large lesions of the prefrontal cortex produced a striking loss of short-term spatial memory. Thirty years later at Yale, Karl Pribram improved the neurosurgical method, and Pat adopted his procedure when she arrived in the Rosvold lab. She was an exquisite surgeon; her superb technical abilities allowed her to develop a research program on the consequences of neonatal frontal lesions to cognitive function, even performing frontal lesions in utero for the very first time. She was undaunted by technical challenge.

Goldman's studies at NIMH continued on adult primates, trying to decipher the "fundamental nature" of prefrontal cortical function. She made increasingly smaller lesions and defined the caudal two-thirds of the principal sulcal cortex as that most critical for the spatial memory deficit. She determined that the task must have both visuospatial and mnemonic components, or the animal would not be impaired. These were her first hints of underlying specificity in the dorsolateral prefrontal cortex.

While lesion studies had been the paradigm for the study of frontal lobe, new anatomical tracing methods were being discovered that would permit unprecedented visualization of brain circuits. In 1974, Pat spent a year in Walle Nauta's lab at MIT to learn these techniques. (She also had an ulterior motive to come to Boston, as Pasko Rakic was at that time at Harvard!) Pat injected tritiated amino acids into the sulcus principalis and found stunning results: patches of input in striatum (the very first description of the patch/matrix organization of this structure) and columns of input in the contralateral PFC. The discovery of columns in the PFC had great symbolic importance to Pat. If there was a columnar organization in the PFC as there was in sensory cortex, the association cortices could be penetrated, could be studied using the same methods that had been so successful in V1. The photo of columns in the principal sulcal cortex shown in Figure 2 hung on her office wall or perched against her desk from then on, serving as a talisman. Vernon Mountcastle understood the significance of these findings:

> I first met her shortly after her return to NIH from Nauta's laboratory, where her two papers on the columnar distribution of cortico-cortical connections provided the first substantial anatomical confirmation of the hypothesis of columnar organization. This was a major contribution, for it was made in the face of continued disbelief on the part of anatomists, and some contumely directed at me, even by my anatomical colleagues here at Hopkins. PGR's later papers on the columnar convergence of parietal and frontal

Figure 2. The Photograph of Columnar Inputs to the Principal Sulcal Prefrontal Cortex

Pat Goldman and Walle Nauta injected tritiated amino acids into the contralateral principal sulcus and traced the anterograde connections to cortical and subcortical structures. This photo hung in her office from then on.

> lobe efferents, to 15 different cortical areas, were of equal importance, and still escape physiological explanation.
>
> Shortly after her return to NIH I invited her for a seminar at Hopkins, and we were friends ever after.
>
> All the world of Neuroscience knows of her career of continuing important contributions, across an unbelievably wide spectrum—I'll not belabor that. What I do wish to say that in spite of all that she retained the charm and gentleness that made her (not only a great scientist) but a great lady.

Despite her many talents and her increasing scientific progress, she told friends that she felt uncertain that she could make it in a "Man's World." Yet on her return to NIMH she soon became Chief of the Section on Developmental Neurobiology. She expanded her research to understand the role of monoamines in primate cortex. The NIMH was home to Axelrod's discoveries of the catecholamines, and she wanted to apply this information to cortex. She brought in Roger Brown, who had just learned HPLC assays in Carlson's lab, to map the catecholamine inputs to the primate cortex. She brought in Tom Brozoski to delineate their function in prefrontal cortex, discovering the devastating consequences of catecholamine depletion in principal sulcal cortex to spatial working memory (their 1979 paper now a citation classic). Pat's modus operandi was already evident: bring in scientists with diverse skills and state-of-the-art methods to address an important question. She was a perfectionist; the study had to be done as impeccably as possible: she had a lot to prove. Without knowing it, they created the foundation for an entire new field of research that was to have huge effects on neuropsychiatry.

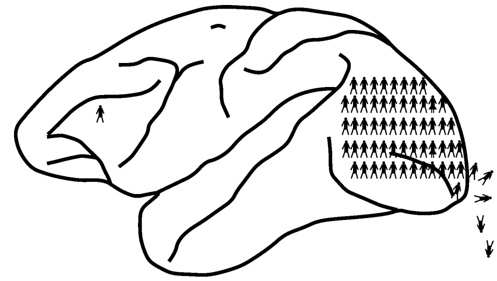

Figure 3. A Version of the Humorous Slide Pat Would Show in the Early 1980s, Schematically Depicting the Paucity of Scientists Researching Prefrontal Cortex

> Pat initiated the modern era of neurobiological research into the prefrontal cortex—a brain region implicated in just about every neuropsychiatric disorder, and as a result she had huge impact on diverse fields such as psychiatry and computational neuroscience, as well as the thinking of researchers into basic aspects of neuroscience.
>
> —Trevor Robbins

In 1979, Pat married Pasko Rakic and the two came to Yale, to the same building where Jacobsen and Fulton had performed their pioneering studies more than 40 years before. At first, she had only a small lab of her own and had to share some of Pasko's lab space. But she quickly created a large and multifaceted lab, continuing to do anatomical, developmental, and pharmacological studies of prefrontal cortex. During that time period she often showed a humorous slide during her talks, representing the very few scientists researching prefrontal cortex and the multitudes studying visual cortex (shown in Figure 3). Studies of visual cortex defined a paradigm for understanding cortical processing, and few had ventured farther afield.

Working with Mike Schwartz, Lynn Selemon, Carmen Cavada, and others, Pat began methodically mapping the inputs and outputs of the principal sulcal cortex. She was never so happy as when looking through a microscope. The 1980s brought a new organizational structure to the visual system: parallel circuits for the analysis of visual space versus visual features. Pat saw that this same segregation continued into the frontal lobes, where there were discrete areas for the reception of visual spatial versus visual feature information (Figure 4). The principal sulcal cortex that she had defined as the critical region for spatial delayed response performance received a discrete input from area 7a of parietal cortex, the cortical region which analyzes visuospatial position. The two cortical areas shared reciprocal, columnar connections, forming a higher-order network. Adapting 2-deoxyglucose methods to the primate with Harriet Friedman, they showed that the two cortical areas activated together, particularly in layer III, the lamina specialized for cortical-cortical interactions. She saw an overarching organization of networks throughout the forebrain and

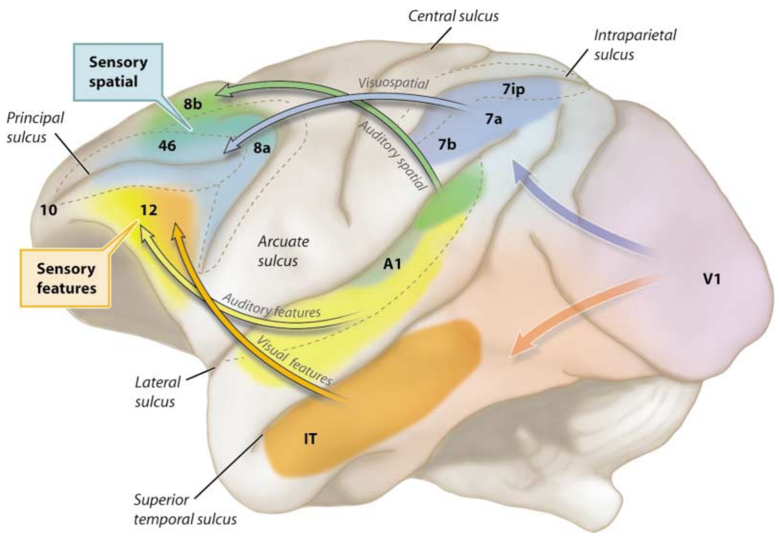

Figure 4. An Artistic Depiction of the Sensory Inputs to Prefrontal Cortex, as Interpretted by Pat's Former Graduate Student, S. Mark Williams, Duke University

wrote about it in her now famous 1987 paper, "Circuitry of the primate prefrontal cortex and the regulation of behavior by representational memory," now listed as one of the 100 most influential papers in cognitive science. Later, with Liz Romanski, Pat saw a similar dissection of spatial versus feature auditory information into disparate areas of prefrontal cortex. Lesions that obeyed the boundaries of these anatomical inputs produced modality-specific deficits.

> ...the cerebral cortex is a unified structure with the mnemonic processes of its frontal lobe grafted in part upon the architecture of its sensory systems.
>
> —Goldman-Rakic, 1995

Pat wanted to integrate her evolving cortical maps with physiology, to see if circuits defined function at the cellular level. The first physiological recordings from PFC neurons in monkeys performing the delayed response task had been published in the early 1970s by Fuster in the United States and by Kubota and Niki in Japan. They discovered that there were cells in the PFC that continued to fire in the absence of a stimulus, maintaining its trace over time. Pat wanted to elaborate on these initial findings. She brought Charlie Bruce to Yale; Charlie had helped to define the frontal eye fields with his electrophysiological recordings just caudal to principal sulcus and knew how to track a monkey's eye movements with great accuracy. She then brought Shintaro Funahashi into her own lab, and Charlie and Shintaro worked together to characterize the firing patterns of neurons in the principal sulcal cortex as the monkey engaged in an oculomotor delayed response task. This version of Jacobsen's task provided unprecedented precision in assessment of spatial position and allowed them to see for the first time memory fields of visual space. Cells were tuned for a particular spatial position: they would increase their firing during the delay period based on where a visual stimulus had been and could decrease their firing to stimuli that had been in an opposing spatial position (Figure 5A). The mnemonic and spatial processes were beautifully integrated. Pat originally spoke of the prefrontal cortex guiding behavior based on representational knowledge, e.g., the guidance of an eye movement based on the representation of a visuospatial position. She then realized that the process she was depicting had much in common with Baddeley's description of working memory in humans, the mental sketch pad, and from then on used that term. Pat's identification of delay-related activity as the cellular basis for working memory linked neurobiological studies of frontal lobe to cognitive science. The term "working memory" has come to mean different things to different kinds of scientists, especially those studying cognitive processes in humans, where one can most readily dissect cognitive operations. For Pat, delay-related activity was the essence of mind:

> ...the brain's working memory function, i.e., the ability to bring to mind events in the absence of direct stimulation, may be its inherently most flexible mechanism and its evolutionarily most significant achievement. At the most elementary level, our basic conceptual ability to appreciate that an object exists when out of view depends on the capacity to keep events in mind beyond the direct experience of those events.
>
> —Goldman-Rakic, 1995

Pat thought that this elemental process could elaborate to sustain information for longer periods, to inhibit inappropriate actions, to suppress distraction, to confer mental flexability, and to plan for the future, but she considered working memory to be the fundamental basis for all these operations. It is an idea that many of us have rediscovered for ourselves and affirmed with new appellations, but we are usually describing the same phenomenon.

Pat thought that a neuron's response was strictly defined by its anatomical inputs. Fraser Wilson joined her lab and recorded from cells ventral to the principal sulcus in the region that received visuo-feature information from inferior temporal cortex. They found that cells ventral to principal sulcus responded best to faces, while those in principal sulcus responded best to spatial information, corresponding to their inputs. These regions have many other connections which likely provide addi-

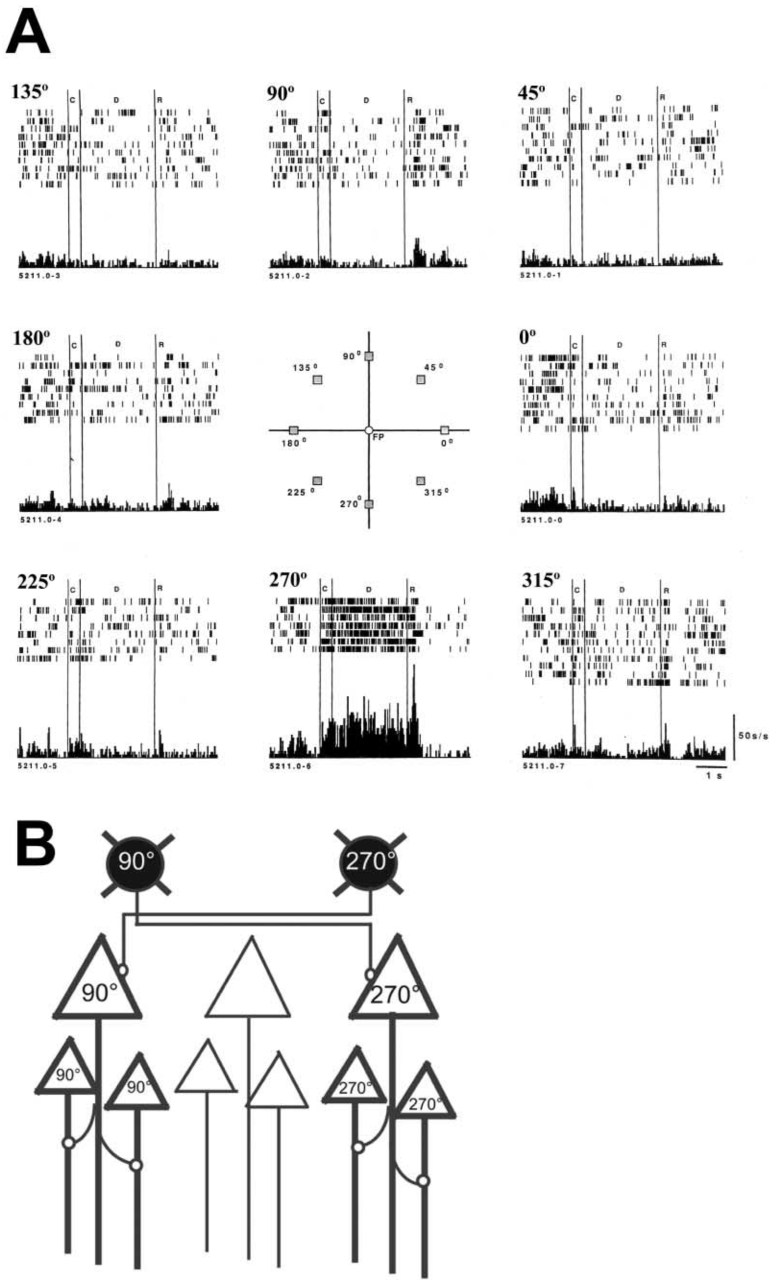

Figure 5. A Representative Memory Field of a Neuron in the Prefrontal Cortex of a Monkey Performing the Oculomotor Delayed Response Task, and the Circuitry which Pat Thought Created This Response Profile

(A) The memory field of a prefrontal cortical neuron that responds best to stimuli that had been flashed at the 270° position and is inhibited when stimuli had been in the 90° position. The task is schematically represented in the center of the figure; the monkey would view a cue at one of the eight spatial positions and then remember this information over a delay period of several seconds. FP signifies fixation point.

(B) The neural circuitry that may underlie delay-related activity. Excitatory pyramidal cells are represented by triangles; inhibitory interneurons by circles. Adapted from Goldman-Rakic, 1995.

tional layers of organization. For example, the outputs to varied motor areas described by Pat and Julie Bates and others likely confer an organization based on response—an arm that reaches versus an eye that shifts. And the complex connections between regions within prefrontal cortex likely give rise to the elaboration of cognitive operations and integration of sensory modalities that represent yet a higher level of organization. But ultimately, Pat thought that a neuron was limited by its inputs. She would tell us “A neuron can change its tune but not its tuning.”

> The prefrontal cortex was terra incognita. Its damage produces a gamut of problems and a correspondingly wide range of functions have been assigned to it. Pat was one of the pioneers that offered a unifying principle: working memory. In elegant experiments on the properties of cells with spatial “memory fields”, Pat and her colleagues linked neural activity in the prefrontal cortex to this fundamental cognitive operation.
>
> —Earl Miller

Pat also uncovered the microcircuitry that creates delay-related activity and spatial tuning. With Kritzer and Leavitt, she made tiny injections of anatomical tracers into the principal sulcal tissue to determine the vertical connections within columns and more broadly ranging horizontal connections, reminiscent of the circuits underlying orientation columns in V1. More recently, she was beginning to study the excitatory connections between pyramidal cells to determine whether they could create reverberating circuits to sustain delay-related activity. She examined the role of GABAergic interneurons in sculpting spatial tuning. She found pyramidal cells and interneurons near to each other with opposite tuning and speculated that the interneuron inhibited the pyramidal cell's response to positions opposite from its preferred direction (Figure 5B). This hypothesis was supported when, with Williams and Rao, she found that iontophoresis of GABAergic antagonists onto prefrontal cells destroyed their spatial tuning. This work has formed an important bridge between computational neuroscience and cognitive neuroscience, identifying cellular players in cognitive circuitry.

Throughout her career, Pat studied the impact of dopamine on prefrontal function at ever deepening levels. She followed forth on her pioneering research with Brown and Brozoski to show that D1 receptors were essential to working memory. With reseachers such as Lidow, Smiley, and Mrzljak, she identified the location of dopamine receptors in prefrontal layers and on prefrontal cells; her diagrams of pyramidal cells looked like Christmas trees covered with ornamental receptors. And she attacked dopamine at the functional level as well. Sawaguchi and Goldman-Rakic found that blocking D1 receptors in prefrontal cortex markedly eroded the ability to guide behavior—the eye wandered off its mental target. My own work with her identified that excessive dopaminergic activity in prefrontal cortex, e.g., during stress, was as harmful as insufficient dopamine, a finding later echoed at the cellular level by Williams and Goldman-Rakic. Her current work brought dopamine to the level of the slice, examining how dopamine alters excitability and excitatory inputs within and between prefrontal cells in slices from monkey prefrontal cortex. And her work had begun to dive inside the cell, with Clare Bergson and Bob Levinson, mining proteins linked to D1 receptors that transmit dopamine's actions to intracellular cascades. Their recent discovery of calcyon, a protein that links D1 receptors to phosphotidyl inositol as well as adenylyl cyclase signaling, has been especially exciting, as this protein has now been found to be overexpressed in the prefrontal cortex of schizophrenic patients.

Pat understood that her basic work on prefrontal circuits had direct relevance to our understanding of schizophrenia and the "hypofrontality" so evident in imaging studies of schizophrenic patients. She thought that deficits in working memory abilities contributed substantially to the cardinal symptom of thought disorder. As she described it,

> Working memory provides…the temporal and spatial continuity between our past experience and present actions. Working memory has been invoked in all forms of cognitive and lingistic processing and is fundamental to both the comprehension and construction of sentences. It is essential to the operations of mental arithmetic, to playing chess,…to fantasizing and planning ahead.

Thus, with profound disruption of working memory abilities, a person would not be able to sustain a line of thought sufficiently to complete a sentence. Distracted from one phrase to the next, language would deteriorate into word salad. Lynn Selemon, Grazna Rajkowska, and Pat carefully examined schizophrenic cortex and found changes in neuronal packing density consistent with loss of neuropil. These findings resonated with others in the field, who subsequently found loss of spines and loss of GABAergic inhibitory inputs from Chandelier cells in schizophrenic prefrontal cortex. Taken together with the physiological findings from Pat's lab, a framework has begun to emerge of altered neural architecture resulting in weakened cellular tuning in schizophrenic prefrontal cortex.

> Patricia Goldman-Rakic came to research in mental illness relatively late in her career, but she revolutionized the field and profoundly impacted our understanding of schizophrenia. She was reluctant at first to deviate from her pioneering work in the nonhuman primate to tackle the human brain in mental illness, especially because this frontier had discouraged many neuroscientists before her. But, once committed, she transformed the landscape. Her discoveries about the prefrontal cortex reverberated throughout the world of schizophrenia research. She singlehandedly elevated it from phenomenology and speculation, to an understanding of basic mechanisms of disease. Her seminal discoveries about how dopamine and GABA tune the response fields of prefrontal pyramidal neurons explained the role of these neurotransmitters in abnormalities of prefrontal information processing in schizophrenia. Because of her findings, working memory is a centerpiece of all aspects of schizophrenia research, from neuroimaging, to genetics, to therapeutic trials. Her work and her voice was the point of reference for a generation of scientists trying to make biologic sense out of the most complex of human brain disorders.
>
> —Daniel Weinberger

Some changes are so large you cannot see that they have happened. Pat effected such change. She made it possible to study the neural basis of mind. She made it possible to study schizophrenia as a neurobiological disorder. She served as a role model for countless numbers of young women who hoped that they too could make a difference in science.

> Pat's dedication to science was unfaltering. The characteristic that I admired the most, however, was how she carried her determination, steadfastness and intellect in an undeniably feminine form. It was critical for me, as a means of envisioning my own future, to have had a mentor as successful as Pat who openly accepted the challenges facing female scientists in lieu of compromising her identity as a woman. She has helped pave the way for many young female scientists.
>
> —Lila Davachi

Pat's marriage to Pasko was a source of great happiness and strength to her, and she knew how important it was for women to be able to have both marriage and a career:

> Whatever success I've had in science, I attribute entirely to Pat. When it seemed to me that starting a family and moving away from Yale meant giving up my career, she insisted that I continue and found a way for me to work from home. I could not have weathered those tough years of juggling family and career without her encouragement and support, and I am not alone in benefiting from her mentorship. In the 21 years that I worked with Pat, I saw a steady

stream of young women (and men) pass through her laboratory. In her own inconspicuous way, she nurtured the careers of many women in neuroscience.

—Lynn Selemon

Patricia Goldman-Rakic's guidance and mentoring has helped shape my scientific career from its earliest days. But the personal caring she expressed and the generous giving of her time, efforts and energy are for me what made our relationship exceptional and something I have cherished. Although it has been several years since we've worked together, Pat has remained a ready and greatly appreciated source of insightful and important personal and professional support. I have many, many reasons to thank her.

—Mary Kritzer

And she was an inspiration from afar:

For me, Pat was a fellow traveler—a partner in crime—along the complicated and challenging road of science and life that we all follow. We shared many experiences in parallel in our jobs, in our love of neuroscience, and Pat forged paths that I followed thereafter.

The world of being a successful and powerful scientist is complicated enough, but then add to that being a woman, and you have a handful! Pat was a unique friend and colleague with whom I could really share experiences! After all, how many of us senior women Neuroscientists are there? While we may not have talked a lot over the years, the example that she set in what she DID was inspiring and more than enough for me.

—Carla Shatz

In recent years, many scientists have come from other fields to research the frontal lobes. A quick search on Medline will document the magnitude of Pat's influence on neuroscience: in the 16 years before the publication of her seminal 1987 paper on prefrontal cortical circuitry and function, only 628 papers were published on prefrontal cortex. In the 16 years since 1987, there have been over 6800, an astounding escalation. Pat was bemused by this explosion in prefrontal research, and remembering her humorous slide, would kid that researchers were now falling off the frontal pole. "Soon everyone will be doing research on prefrontal cortex!" she would jokingly complain.

Pat demystified the prefrontal cortex; she made it anatomically comprehensible and functionally logical by relating it to working memory. Her research caught my attention as early as 1982 when as part of a committee at Columbia we read her papers, realized their seminal importance and awarded her the Spencer Award for distinguished accomplishments by a young neural scientist. Her influence on me persisted and I now find myself working on prefrontal cortex stimulated by her pioneering studies.

In a larger sense, Pat was a pioneer in cognitive neuroscience bringing together functional neurobiology of the association cortex with the study of higher mental processes. She was also a leader of our scientific community and one of the early people in our field to show that there is no glass ceiling for women in neural science. Her loss is tragic. Fortunately one knows that the pain of losing her will fade with time. But we also know that the impact of her person and her contributions will remain for our lifetimes.

—Eric Kandel

She was also an inspiration to those closest to her:

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.

—Pasko Rakic

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