Obituary

Patricia Goldman-Rakic

The quintessential multidisciplinary scientist

Pat Levitt

Neuroscience, by its very nature, incorporates most other scientific disciplines in a quest to discover the roots of such complex functions as sensation, movement, emotion, and cognition. But it is a rare individual who has the courage to embrace multiple disciplines to fundamentally advance understanding of the relationship between brain and behavior. The career and life of Patricia Goldman-Rakic, cut short in late July this year by a tragic accident, embodied the passion of discovery and the daring of a scientific pioneer. Many tributes have been written about Pat’s accomplishments: from her election to the National Academy of Sciences and the Institute of Medicine and her tenure as president of the Society for Neuroscience to her strong publication record of over 250 articles. Here’s a view of Pat Goldman-Rakic, the research scientist.

Pat’s multidisciplinary approaches were focused on defining the mechanisms of working memory, the kind of memory we use to remember a telephone number as we reach for the receiver. Pat often used the metaphor “blackboard of the mind” to describe the essence of working memory. It is, fundamentally, the ability to hold information “online” during the processing of a task that requires retrieval and manipulation of information at successive steps to perform associations with new ideas and incoming data. The key issue for Pat, as it is for those who work in the field of cognitive neuroscience in general, was to determine how mental representations are held in the brain and how such information can be accessed. She believed that understanding the essence of working memory would lead naturally to a new perspective on neuropsychiatric disorders that disrupt the central processes of cognition, such as schizophrenia.

Pat was not alone in attributing an important role in working memory to the frontal lobes, an area of the neocortex largely expanded in primates. She was, however, rare in her unwavering belief that the key to understanding something as complex as working memory lies in understanding the interactions of multiple elements found in this cortical region. These cellular players include driving inputs from the thalamus and from other areas of the cortex, output neurons, local cells that suppress outputs, and also the neuromodulatory systems, the monoamines, that influence the processing of neurophysiological information by dampening or enhancing function. For Pat, there was no shortcut around this complex of biological elements to understanding cognition—one simply had to use whatever tools were necessary to study the component parts of the system. Moreover, she recognized the need to study an animal model in which such complex function could be evaluated as it developed and then probed as it reached maturity.

The journey for Pat started several decades ago, as a young psychologist whose travels brought her from graduate school at the University of California at Los Angeles eventually to the National Institute of Mental Health (NIMH) in the mid-1960s, where she was to be influenced greatly by the eminent cognitive neuroscientist Haldor Rosvold, who established the first laboratory at NIMH for the study of higher cortical function and complex behavior. Realizing that the fundamental biological substrates for working memory would only come from the ability to study and manipulate systems and cells, Pat adopted the non-human primate as a model system. In the context of elucidating the component psychological parts of working memory, Pat performed a series of experiments to document now well-known developmental lesion effects. Although the ability of the brain to reorganize and recover functions in early life is now a topic of much investigation, Pat’s own studies in the 1970s showed that working memory recovers remarkably well when injury to the frontal cortex occurs early in life, but that the effects are much more detrimental when injury occurs in post-adolescence. She soon followed these studies by demonstrating behavioral plasticity with modern neuroanatomical tools to illustrate a pronounced reorganization of frontal lobe circuitry accompanying restoration of working-memory functions.

It was from those early anatomical studies that Pat became interested in the columnar organization of the cortex. Prior work, including the Nobel Prize-winning studies of David Hubel and Torsten Wiesel, had established that in the cortices receiving basic sensory information, functionally similar neurons were grouped vertically in columns. These columns were proposed to be a basic unit of cortical processing. Pat discovered that these unique structural components were in fact alive and well in the frontal cortex, too. In the 1980s, Pat’s laboratory went on to produce...
the largest body of evidence that illustrated a conserved organization of the neocortex, extending well beyond visual and other primary sensory systems to the frontal lobe, with parallel streams of information flowing across cortical areas, as well as subcortically via the basal ganglia to effector systems. The transformation of Pat’s laboratory continued in the late 1980s and 1990s as the focus moved from defining the long-distance circuitry, much as had been done by others in the visual and somatosensory cortex, to begin the difficult task of discovering just what these circuits do. This meant incorporating complex neurophysiological approaches to monitor neuronal activity before, during, and after a working-memory exercise.

Using a task in which animals were trained to remember the location of a target in order to make a rapid eye movement to it—an oculomotor delayed-response task—Pat and her colleagues saw a remarkable profile of activity for different populations of neurons during different phases of repeated behavioral trials. Some neurons explicitly fired during the planning stage of the task, some during the period of delay, when information must be held online, and some at completion, and all in a highly reproducible pattern. The data led to their hypothesis that neurons in the dorsal and lateral prefrontal cortex carry out component processes of the working-memory task and that neurons performing different functions are in fact located in distinct positions along the essential organizing unit of the neocortex, the column. Just as in the visual cortex where columns of neurons could process different fields of the visual world, Pat proposed the existence of memory fields in the prefrontal cortex. In recent years, this brain-behavior link may not seem so surprising, but this was an attempt to deconstruct thought processes, heretofore abstract and unapproachable for the cellular and molecular neuroscientist.

To complete her picture of the frontal cortex, Pat’s most recent efforts interdigitated these landmark neurophysiological and anatomical studies with detailed analyses of the regional and subcellular organization of neurotransmitter systems, from inputs to receptors. She was particularly fond of the dopamine system, because of the natural link to neuropsychiatric disorders and their dopamine-associated drug therapies and because of the profound modulatory influence that dopamine seemed to provide for memory systems. Pat integrated these data from each domain (molecular, cellular, and neuroanatomical) to provide an in-depth understanding of the frontal circuitry that governs working memory. Her contributions extended well beyond normal function to novel hypotheses about the molecular and cellular development of cortical circuitry and about schizophrenia as a disease of synaptic development and maintenance in the prefrontal cortex.

Pat’s versatility did not extend to pulling pipette tips in the laboratory or purifying a new receptor antibody. But she knew what would be necessary to tackle the next great challenge in understanding human cognition. Pat’s hands and head were part of every experiment, from her surgical wizardry to her own intellectual fearlessness. Those who were fortunate to be mentored and challenged by Pat, in her laboratory and in the field of neuroscience, understand the rare gifts that she has bestowed on all of us.

Further Reading
Goldman-Rakic PS (1996) Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A 93: 15473–15480.

Book Review/Science in the Media
A Field Trip to the Mesozoic
Luis M. Chiappe

Traveling through time has become extremely popular. Since H.G. Wells’ famed novel, scientists have designed machines that can actually beam you into the future or into the deepness of time with the snap of a finger. Of course, destinations vary. Engineers and architects have a preference for Giza, 4,500 years ago, when the Great Pyramid was built. Resort enthusiasts might fancy the Dulce Vita of Herculanum and its neighboring Pompeii, making sure they set the time dial to precede ad 63! Naturalists and outdoor buffs like to travel further in time, into the era of the large dinosaurs, to ponder these wonders of evolution, and the writer Henry Gee and the artist Luis Rey have provided them with a valuable asset to take along on their perilous journey.

A Field Guide to Dinosaurs is indeed a boon for the dinosaur enthusiast, but its contents are still as imaginary as is this futuristic scenario. In this book, we learn about the color of dinosaurs, their techniques for hunting and defense, and their mating preferences and social structures, and in some instances the authors even venture into dinosaur genomics. Although much of what Gee and Rey tell us is speculation, they fully acknowledge their fantastical approach and they rightfully emphasize that the true world of the dinosaurs was probably far more bizarre than the portrait their book offers.

The introductory 20% of A Field Guide to Dinosaurs provides a wide range of background information about how the appearance of dinosaurs could be reconstructed, a concise history of dinosaur discoveries, and a brief overview of their dynamic world, classification, and partial extinction—partial because, as Gee and Rey correctly emphasize in their

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narrative and feathered illustrations, birds are the descendants of a group of small predatory dinosaurs, and, as such, dinosaurs are still ubiquitous in both natural and urban environments. The rest of the book is subdivided into four temporal sections, each giving the time traveler a sampling of what he or she is about to see. Here, however, is where the time traveler needs to be careful, for even if much has been learned about dinosaurs since their first fossil remains became known to science in the 1820s, our knowledge about the biology of these animals is still in its infancy.

The reasons for such ignorance are simple: the vast majority of the evidence comes in the shape of fossilized bones. Studies of the cellular structure of these bones, which are often preserved in exquisite detail, and of the ancient environments in which bones are buried have made it possible to infer certain aspects of the physiology and ecology of dinosaurs. Yet the understanding of their behavior has been a far more difficult task. In most cases, dinosaur behavior is best inferred from its preserved products because behaviors themselves do not fossilize. As products of locomotor behavior, dinosaur footprints have allowed paleontologists to make a host of inferences about the trackmakers, from speed to limb kinematics to herd structure, but well-preserved trackways are not very common. Likewise, the spatial and stratigraphic distribution of dinosaur egg-clutches, fossilized products of their reproductive behavior, has provided the basis for inferences on nesting conduct, including nest construction and gregariousness. Yet, although egg-clutches are relatively common, embryonic remains that allow clutches to be identified are extremely rare, thus making it difficult to associate the inferred behaviors to specific dinosaur groups. Furthermore, behavioral inferences derived from trace fossils such as trackways or nest structures require detailed analyses of the sedimentology of the fossil-bearing rocks, something missing from most behavioral studies.

Fortunately, some aspects of behavior can also be inferred from what we know about the genealogical relationships of dinosaurs to other vertebrates. Because all Mesozoic dinosaurs are bracketed by modern crocodiles and birds—the two living groups of archosaurs—the behaviors shared by these modern vertebrates can be extrapolated to their extinct Mesozoic relatives. For example, some degree of parental care can be inferred for all Mesozoic dinosaurs because such a behavior exists in both crocodiles and birds. Furthermore, although exceedingly rare, spectacular fossils can occasionally provide a precise glimpse into dinosaur behavior. These exceptional occurrences include adults brooding their own egg-clutches, foes buried in mortal combat, and stomach contents. For instance, a handful of brooding oviraptorid adults have documented the presence of this avian behavior among predatory dinosaurs, and the discovery of a Velociraptor eviscerating the herbivorous Protoceratops—a distant relative of horned dinosaurs such as Triceratops—has offered a snapshot of the food preferences of Jurassic Park’s vicious celebrity (Figure 1). Similarly, the juvenile remains of Coelophysis contained inside the abdominal cavity of an adult specimen of this carnivorous dinosaur has documented the cannibalistic behavior of this primitive dinosaur species.

Even though several lines of analysis have been used to infer dinosaur behavior, the message to remember is that interpreting the behavior of organisms that died millions of years ago is extremely difficult and that, in most cases, those enterprises involve a great deal of speculation. Gee and Rey are clearly aware of this, and their examples draw extensively from these and other cases in which the behavior of long-extinct dinosaurs can be inferred with confidence. Even so, A Field Guide to Dinosaurs ventures far beyond this limited collection of inferrable behaviors. Such license may ruffle the feathers of the well-informed audience, but in my opinion, those critical readers should not rush to discount the value of this book on the basis of such an overt incursion into conjecture. A Field Guide to Dinosaurs does not aim to be factual so much as to be an enjoyable and provocative exercise in dinosaur biology, something the authors have made as clear as water. Thus, if you are ready for a trip to the Mesozoic, get comfortable, fasten your seatbelt, and don’t worry if you forget your binoculars—you may not need them after all!

**Book Reviewed**

Gee H, Rey LV (2003) A field guide to dinosaurs: The essential handbook for travellers in the Mesozoic. New York: Barrons Educational. 144 pp. ISBN (hardcover) 0-764-15511-3. US$24.95.

**Figure 1. Inferred Dinosaur Behavior**

The discovery of skeletons of Velociraptor and Protoceratops locked in a mortal combat has provided the basis for inferring the predatory behavior of the former. (Illustration kindly provided by Raul Martin.)

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