Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 13435–13437, November 1996
Colloquium Paper

This paper serves as an introduction to the following papers, which were presented at a colloquium entitled "Memory: Recording Experience in Cells and Circuits," organized by Patricia S. Goldman-Rakic, held February 17–20, 1996, at the National Academy of Sciences in Irvine, CA.

Memory: Recording experience in cells and circuits: Diversity in memory research

PATRICIA S. GOLDMAN-RAKIC

Section of Neurobiology, Yale University School of Medicine, New Haven, CT 06510

The study of memory, once the exclusive province of psychology, has come to include cellular mechanisms and neural circuitry as well as behavior. This psychologically and biomedically significant process was the subject of a National Academy of Sciences-sponsored conference, "Memory: Recording Experience in Cells and Circuits," held in Irvine, CA, February, 17–20, 1996. The conference was organized by Alan Baddeley, Patricia Goldman-Rakic (Chair), Eric Kandel, Donald Price, and Larry Squire, with the goal of reviewing some of the major research accomplishments in this field. We are indebted to the National Institute of Neurological Diseases and Stroke and the National Institute of Aging for generous grants that supported the expenses of graduate students who attended the meeting and to Interneuron Pharmaceuticals for additional support of a social event.

One of the long-standing and challenging issues that memory research continues to confront is the dilemma of localizing a complex function in an exquisitely anatomically differentiated central nervous system. Is memory a mental function that can be identified with an isolated neural structure or specific groups of neurons? Traditionally, this question has been framed by psychological inquiry. The 19th century school of "faculty psychology" divided mental processes into separate and distinct human attributes such as "courage" and "ambition," encouraging the anatomist, Gall (1), to impose the multiple attributes of human psychological make-up onto a physical map of the brain. Although this naive view of psychological process was widely repudiated, it nevertheless spawned the powerful and ultimately validated idea that specific functions can be relegated to particular brain structures or regions. Clinical observations in patients with focal lesions in the last century clearly established a correspondence between specific symptoms and localized regions of injury, most notably left hemisphere frontal sites with expression of speech (2) and left hemisphere posterior temporal lobe sites with speech comprehension (3). These and subsequent cases strengthened the localizationist view of brain function which has rightly dominated the study of brain–behavior research to the present day. It was not unreasonable to expect that other mental processes, like memory functions, could similarly be localized to circumscribed areas of the cortex. This expectation was not and still is not easily fulfilled, however. Lashley's (4) quest for the proverbial "engram" was not successful, as the behavioral effects of lesions made in rats correlated with the size of the lesion and not their location. Lashley (4) was led to conclude that the engram, as a single entity, is not located in specific cortical sites but is distributed widely over the neocortex with each area making an equal and essential contribution.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Since the time of Lashley, it has become increasingly clear that memory is divisible into processes and subprocesses and takes heterogeneous forms based on the type of memory (e.g., classical conditioning versus procedural), the content of memory (e.g., episodic versus semantic), the temporal parameters of memory (short term versus long term), and the level of processing (encoding, retrieval). It is precisely because of this diversity that memory cannot be localized to a single anatomical structure. The cerebellum, for example, has long been regarded as an exquisitely designed "neuronal learning machine" for specific classically conditioned motor systems (5, 6) and the prefrontal cortex is now considered a critical structure for short-term memory processes, including retrieval (7) and "on-line" processing (8). Concurrent activation of these and other structures is a common finding in functional imaging studies of cognitive function in human subjects. The diversity of memory phenomena argues for a broadening of focus from a single place in the nervous system and a singular concept, "memory," to a variety of systems and specializations for neuronal plasticity throughout the nervous system. Once this more differentiated localization of memory systems is achieved, and great strides have been made in this endeavor, questions about the cellular and physiological mechanism that underlies each subtype and process of memory can be addressed. It is one or the other of these objectives that drives the work of the speakers at this conference.

The classification of memory systems in human subjects helps to set the parameters of investigation at the neurobiological level. Accordingly, Alan Baddeley (9) started off the meeting by describing the system of memory referred to as "working memory" and provided the background evidence for distinguishing this form of memory from long-term forms. Elizabeth Warrington (10) described new evidence showing that memory loss prior to medial temporal lobe injury can no longer be considered as an all-encompassing "global amnesia," but that retrograde memory, like anterograde memory, is compartmentalized. Daniel Schacter (11) presented evidence on illusory memory and the phenomenon of confabulations and showed how these distinctively human processes can be studied with ingenious behavioral tasks and additionally while the human brain is imaged. For example, Schacter reported evidence that the hippocampal formation is activated in human subjects when they experience false memories as true.

Richard Thompson (5) illustrated how multiple systems may be concurrently activated during performance of a memory task. In addition, he reviewed new experiments on genetically engineered mice which support the body of evidence that long-term depression plays a role in eyelid conditioning in the cerebellar cortex. Mice lacking the metabotropic glutamate receptor, mGluR1, show marked impairments in cerebellar cortical long-term depression and conditioning. Hampson and Deadwyler's work (12) complemented the study of storage mechanisms *in vitro* with the powerful approach of multielec-

trode recording in animals as they perform memory tasks. Recording from 10–16 neurons simultaneously, they showed that different patterns of activity within the ensemble were predictive of behavioral responses and errors made by the animals. Mark Bear's presentation (13) focused on the rules by which a given neuron in the sensory cortex comes to respond selectively to one of its many inputs. An important finding to come from this work is the demonstration that long-term potentiation and long-term depression occurs at the same synapses and in the cerebral cortex as well as in the CA1 pyramidal neurons of the hippocampus. Additionally, Bear used light- and dark-rearing to show that the immediate past "experience" of a neuron (of excitation or depression) alters the cross-over point or threshold for a neuron to respond by excitation or depression to a present stimulus.

From a variety of perspectives, no classification is more basic than the distinction between short-term and long-term processes. Eric Kandel (14) reviewed the considerable evidence indicating that short-term change in synaptic efficacy involves alterations in existing proteins and connections while long-term change requires protein and RNA synthesis, resulting in the nuclear activation of cAMP response element-binding protein-related (CREB-related) transcription factors that, in turn, activate cAMP-inducible genes. Similar learning-associated mechanisms appear to hold in *Aplysia* and in *Drosophila* and may possibly extend to mammalian systems. Tim Tully (15) provided the conference with an up-to-date and informative picture of the technical possibilities and conceptual complexities involved in the genetic dissection of complex traits. Particularly exciting was the promise of the reverse genetic approach by which the expression of a transgene can be limited to a specific time period—e.g., 3 hr before training—or a specific area of the nervous system to pinpoint the nature of the process affected and the locus of that process.

The hippocampus continues to hold fascination for neuroscientists and the mechanism of long-term potentiation is widely favored as the synaptic basis of information storage in this structure. More recently, however, the focus of study has moved from an exclusive preoccupation with the hippocampus proper to an important role of adjacent structures. Larry Squire (16) reviewed a series of studies in macaque monkeys showing that cortical areas adjacent to the hippocampal formation, including the entorhinal, perirhinal and parahippocampal cortices are an essential part of the medial temporal lobe memory system associated with the processing of facts and events. The dissections of the functional contributions of these different portions of the medial temporal lobe system was, in part, the subject of Howard Eichenbaum's presentation (17). He described a series of lesion and recording studies on the rodent olfactory system which, by virtue of its circuitry, make it a useful model system for the study of cortical–hippocampal interactions. The physiological evidence reported by Eichenbaum indicated that there is a division of labor between the parahippocampal cortex and the hippocampus proper, with the latter having a more significant role in the persistence of representations and the former operating as a comparator and/or organizer of representations. James McGaugh (18) extended the analysis of the medial temporal lobe to the amygdala which has been shown to be involved in emotional arousal and the modulation of memory storage in other sites of the brain. His recent studies provide evidence that the effects of stress-related hormones on memory are mediated through the amygdala. Imaging studies in humans now show that the amygdala is activated during the recall of emotionally charged material. Temporal lobe regions were also the topic of Robert Desimone's presentation (19), which showed that repeated experience with the same stimulus leads to suppression of neuronal responses in the temporal lobe. While this process is thought to be important for perceptual learning and priming and considered to be an intrinsic process of the medial temporal cortex, extrinsic signals from the prefrontal cortex were highlighted as the input to the temporal lobe which produces enhancement and temporal extension of neuronal responsivity in temporal lobe neurons to behaviorally relevant stimuli in working memory tasks.

Short-term memory processing was also the focus of a session on "working memory" which is known to engage prefrontal neurons that are capable of sustained responding over time intervals or delays interposed between sequential events. Goldman-Rakic (20) discussed the cellular and circuit basis of this mnemonic process in prefrontal neurons. She described studies which showed that the dopamine D1 receptor regulates excitatory transmission in the neurons which maintain a memory in an active and usable state. Eve Marder (21) discussed a variety of biophysical properties of neurons in simplified circuits and showed how knowledge of channel behavior could be integrated with information on the sustained activity of neurons engaged in working memory. As the information that is to be recalled must first be consolidated, next stored, and ultimately retrieved, it is not surprising that one or more of these subfunctions is altered in Alzheimer disease, Parkinson disease, and schizophrenia. Advances in understanding the psychological aspects of memory dysfunction were described by Marilyn Albert (22) and John Gabrieli (23) who collectively have examined memory capacity in normal aging and in Alzheimer disease, Parkinson disease, Huntington disease, or Korsakoff syndrome. The findings from Gabrieli's laboratory indicate that several of these conditions—normal aging, Alzheimer disease, and Parkinson disease—are each marked by a different form of memory impairment, and often with different time courses. Thus, like the nature of memory itself, memory disorders can be differentiated. Marilyn Albert provided evidence that Alzheimer disease patients, even in early stages of the disorder, exhibit profound impairment in the manipulation of multiple information sources. On the topic of normal aging, Albert reviewed data that showed that normal elderly "do not forget what they have learned more rapidly than the young," if they are given adequate opportunity to learn new material. Donald Price reviewed a number of molecular approaches, including that of genetic engineering, designed to produce animal models of Alzheimer disease, and Allan Levey (24) provided the conferees with a review of the mammalian cholinergic system and subtype-specific muscarinic receptors that have been implicated in the pathophysiology of AD.

Consideration of the presentations at the colloquium which appear also in this issue of the *Proceedings* indicate that there has been a major shift in the psychology of memory: memory has many facets and levels of analysis ranging from the study of molecules to human behavior. Further, a diversity of structures are involved in widespread areas of the brain during consolidation, storage, and retrieval, depending upon the nature of information that is stored. Indeed, in the present volume, memory mechanisms are studied in the perirhinal cortex of the temporal lobe (16, 19), the amygdala (18), the olfactory cortex (17), the hippocampus (12, 16), the prefrontal cortex (19, 20), the visual cortex (13), and cerebellum (5), as well as in a variety of structures in invertebrate models of elegant simplicity (14, 15, 21). Whether or not there is an all-purpose memory device, studies in a wide variety of structures and paradigms are becoming the empirical foundation for understanding the mechanisms of synaptic modifiability and neuronal plasticity which are most fully elaborated in the human brain.

1. Gall., F. J. (1825) *Sur les fonction du cerveau et sur celles de chacune des ses parties* (Bailliere, Paris), Vol. 6, pp. 1822–1825.
2. Broca, P. P. (1861) in *Some Papers on the Cerebral Cortex*, translated by von Bonin, G. (1960) (Thomas, Springfield, IL), pp. 49–72.

3. Wernicke, C. (1874) *Der aphasische Symptomemkomplex* (Cohn and Weigart, Breslau, Germany).
4. Lashley, K. S. (1950) *Symp. Soc. Exp. Biol.* **4,** 454–482.
5. Thompson, R. F. & Kim, J. J. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13438–13444.
6. Raymond, J. L., Lisberger, S. G. & Mauk, M. D. (1996) *Science* **272,** 1126–1131.
7. Tulving, E. (1972) in *Episodic and Semantic Memory*, eds. Tulving, E. & Donaldson, W. (Academic, New York), pp. 381–403.
8. Goldman-Rakic, P. S. (1995) *Neuron* **14,** 477–485.
9. Baddeley, A. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13468–13472.
10. Warrington, E. K. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13523–13526.
11. Schacter, D. L. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13527–13533.
12. Hampson, R. E. & Deadwyler, S. A. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13487–13493.
13. Bear, M. F. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13453–13459.
14. Bailey, C. H., Bartsch, D. & Kandel, E. R. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13445–13452.
15. Tully, T. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13460–13467.
16. Squire, L. R. & Zola, S. M. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13515–13522.
17. Eichenbaum, H., Schoenbaum, G., Young, B. & Bunsey, M. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13500–13507.
18. McGaugh, J. L., Cahill, L. & Roozendaal, B. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13508–13514.
19. Desimone, R. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13494–13499.
20. Goldman-Rakic, P. S. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13473–13480.
21. Marder, E., Abbott, L. F., Turrigiano, G. G., Liu, Z. & Golowasch, J. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13481–13486.
22. Albert, M. S. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13547–13551.
23. Gabrieli, J. D. E. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13534–13540.
24. Levey, A. I. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13541–13546.