A Meeting of Minds: Learning and Memory in 1999

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COMMENTARY

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Introduction

In late spring a diverse group of scientists converged on the Cold Spring Harbor Laboratory to meet and discuss the unwieldy, growing field of learning and memory research. The Learning and Memory meeting, held April 28–May 2, drew researchers in neurophysiology, behavior, computational neurobiology, cognitive psychology, and molecular biology, all eager to disseminate their particular points of view as well as to learn from colleagues they might otherwise rarely see.

When encompassing a topic as broadly defined as "learning and memory", one quickly realizes that no single approach or system predominates. The scientists at the meeting discussed operant conditioning in *Aplysia*, courtship conditioning in *Drosophila*, central pattern generators in invertebrates, motor learning in the cerebellum, and hippocampus-based memory in rats and primates, among other systems. Although it would be impossible to summarize all of this work in a brief report, the following overview offers highlights of the rich and varied interchange at this meeting.

The Role of the Hippocampus in Memory

Debate over the role of the hippocampus in mammalian memory continues to run high, as amply demonstrated during this meeting. To study this problem, researchers are updating the standard approaches, such as examining the effects of hippocampal inactivation or recording from multiple neurons in this region. Heading the lineup, Richard G. Morris (University of Edinburgh Medical School) reported on a method of reversibly inactivating hippocampal function in rats using the AMPA receptor antagonist LY293558 (R.G. Morris, unpubl.). Morris and colleagues blocked rats' hippocampal function at different stages during water-maze learning and observed whether the animals displayed concurrent or subsequent behavioral deficits as a result of the time-limited inactivation. As might be expected from previous work, they found that blocking hippocampal activity during the training period prevented subsequent recall; however, blocking during retrieval testing also prevented accurate recall, implicating the hippocampus in the retrieval of spatial memories. Interestingly, they found that blocking hippocampal function for a week or so between training and retrieval testing also impaired recall performance, bolstering the notion that the hippocampus is important for either storage or consolidation of spatial memories.

On the other hand, Larry Squire (University of California, San Diego) reported cognitive experiments in human subjects suggesting the hippocampus does not act as a storage site for long-term spatial memories, such as "mental maps" of one's old hometown. Squire and colleagues found that a patient with severe viral damage to his temporal lobes could nonetheless navigate a neighborhood he had lived in decades ago. In comparison with other individuals that had lived in the same area at the same time, the patient showed little deficit or difference in his ability to access these spatial memories. Some of the implicit contradictions between these results and those of Morris are resolvable if

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the rat hippocampus is necessary for the consolidation but not the actual storage of spatial memories. Moreover, it is not yet clear how to compare processes underlying very long-term memory in humans and behavioral memory in rats.

Another approach to understanding hippocampal function is to record from multiple neurons in the behaving animal. This method in fact helped popularize the idea that the hippocampus—in rats, at least—is concerned with spatial mapping, because of the discovery that hippocampal neurons show location-specific activity. Spirited discussion at the meeting marked a decline in the rigidity of this view, with several researchers reporting that hippocampal neurons often respond robustly to nonspatial cues and that spatial maps become rearranged depending on the context of nonspatial cues (Howard Eichenbaum, Boston University; Patricia Sharp, Yale University). Thus, researchers are moving towards a view of the hippocampus that relegates space to one of many variables influencing its function (Eichenbaum et al. 1999).

Memory in the Real World

In other arenas, researchers reported investigations on the physiological factors that modulate or interact with memory mechanisms. Among the factors considered were stress, age, and circadian rhythms (Jeansok Kim, Yale University; Carol Barnes, University of Arizona; Jerry Yin, Cold Spring Harbor Laboratory). Barnes reported a variety of changes in the rat hippocampus associated with aging, including a decrease in synapse density, differential activation of immediate-early genes and other, novel genes as a function of plasticity, and changes in the properties of synaptic transmission and long-term potentiation (LTP). In addition, Barnes reported that the stability of hippocampal spatial maps degrades in older animals. Kim presented research showing stress diminishes LTP in the rat hippocampus and enhances long-term depression (LTD), effects of real-life concern to the audience of overworked scientists. The effects of stress on plasticity correlate with impaired hippocampal-based memory and are blocked by NMDA receptor antagonists applied during the period of stress (Kim et al. 1996; see Fig. 1). Lesions to the amygdala also block these effects, suggesting that stress-induced blockade of hippocampal LTP is mediated by the amygdala.

Researchers also reported progress in understanding learning deficits associated with disease. Rui M. Costa (University of California, Los Angeles) from the lab of Alcino Silva described an animal model for neurofibromatosis type 1, an inherited neurological disorder characterized by tumor syndromes whose victims often have learning disabilities. The *Nf1* gene encodes a ras–GAP protein, and mice that are heterozygous mutants for *Nf1* display partial learning impairments on hippocampal-based memory tasks (Silva et al. 1997). Costa reported that homozygous mutants for an isoform of *Nf1* (*Nf123a*) display both hippocampal-based and motor learning deficits, offering a refined animal model for this disease. David Sweatt (Baylor College of Medicine) presented research on Angelman Syndrome, another inherited disorder resulting in learning defects; this syndrome arises from a mutation in UBE3A, a gene encoding a ubiquitin ligase. UBE3A exhibits an interesting imprinting pattern: The hippocampus and cerebellum express the maternal copy, whereas the other brain regions express the paternal copy. Sweatt reported that mice inheriting a mutation in *ube3a* from their

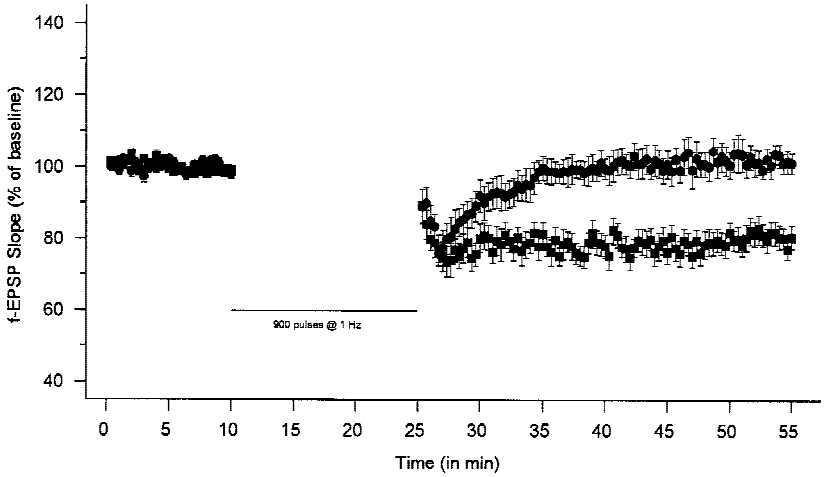

Figure 1: Stress enhances LTD in the rat hippocampus. Hippocampal slices were prepared from rats exposed to stress (restraint plus tail shocks). To induce LTD, low-frequency stimulation was applied to these slices (■) and to slices from control animals (●). LTD was greatly enhanced in slices from stressed animals. (Reprinted, with permission, from Kim et al. 1996.)

mothers displayed deficits in both hippocampal learning and the expression of LTP, again establishing a useful animal model for the disease (Jiang et al. 1998). These studies of disease-related learning impairments offer the potential not only of understanding disease states but also of elucidating molecular mechanisms involved in normal memory.

Plasticity Mechanisms

Perhaps the preponderance of presentations at this meeting focused on identifying molecular and structural changes underlying synaptic plasticity. Tobias Bonhoeffer (Max Planck Institut, Munich) ran a video showing growth of new dendritic spines after LTP induction in hippocampal slices. As images of fluorescent spines filled the screen, an appreciative audience applauded both the technical display and the insight into plasticity mechanisms. In these experiments, published soon after the meeting (Engert and Bonhoeffer 1999), Bonhoeffer and colleagues induced LTP in a spatially defined area of the slices and demonstrated that spines subsequently grew only in this area. A key question, of course, is whether the new spines support new synapses that underlie a long-term increase in synaptic strength, and future research on this question will generate great interest in the learning and memory community.

Bonhoeffer's presentation highlighted a general focus on postsynaptic modifications during plasticity. The labs of Cold Spring Harbor were well represented in this regard; in particular, Roberto Malinow (Cold Spring Harbor Laboratory) and colleagues gave several talks and posters focusing on the regulation of AMPA receptor expression in postsynaptic spines. They monitored AMPA receptor localization in postsynaptic neurons using various methods, most recently, visualization of expressed GFP-tagged receptors (GluR1–GFP) in hippocampal slices (Shi et al. 1999; see Fig. 2). With this technique, Malinow and colleagues found that synaptic activity induces the insertion of AMPA receptors into dendritic spines, providing a mechanism for increased synaptic transmission during plasticity. The group has also begun investigating the role of Ca^{2+}/calmodulin kinase II

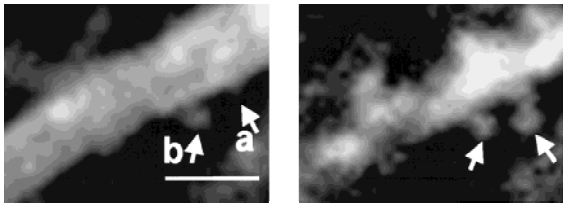

Figure 2: Localization of expressed GluR1–GFP before (*left*) and after (*right*) tetanic stimulation in hippocampal slices. Hippocampal neurons in the slices express GluR1–GFP throughout the intracellular compartment of the dendritic shaft. High-frequency stimulation induces delivery of GluR1–GFP to dendritic spines (arrows). (Reprinted, with permission, from Shi et al. 1999.)

(CaMKII) in this process by coexpressing the active enzyme with GluR1–GFP in hippocampal slices.

Finally, MAP kinase (MAPK) cascades clearly commanded the attention of molecular scientists studying mammalian memory (Yadin Dudai, Weizmann Institute of Science; Coleen Atkins, from David Sweatt's group at Baylor College of Medicine; Eric Norman and Edda Thiels, from Eric Klann's group at University of Pittsburgh; Pramod Dash, University of Texas Medical School). In keeping with the recent barrage of MAPK publications (Impey et al. 1999), these researchers reported changes in MAPK activity in a variety of plasticity and learning paradigms. For instance, Dudai reported that ERK1-2 are activated in the rat insular cortex when the animal samples a novel taste; long-term (but not short-term) memory of the novel taste is in turn suppressed by injection of MAPK cascade inhibitors (Berman et al. 1998). Atkins and Dash reported that MAPK activity is up-regulated in the rat hippocampus after training on two different hippocampal-dependent learning tasks (Atkins et al. 1999; Blum et al. 1999).

In general, researchers have paid less attention to the question of MAPK involvement in LTD, the synaptic weakening counterpart to LTP. At this meeting, Thiels showed data suggesting LTD in the rat hippocampus is accompanied by an increase in ERK-2 activity. On the other hand, Norman showed data suggesting that phosphatases known to be activated during LTD act to down-regulate ERK activity in the hippocampus. These results imply that MAPKs do play a role in LTD but do not yet present a clear picture of what this role might be. However, the sum of the data presented at the meeting shows that MAPK pathways interact with a number of other protein kinases and phosphatases previously implicated in synaptic plasticity and memory, such as PKA and PP2A. These findings prompted some to suggest that MAPK integrates signals from a variety of upstream molecules to determine the direction and magnitude of long-term plasticity.

How to Make a Memory: Neuronal Circuitry Underlying Memory Formation

Stepping from molecules to cellular systems, several speakers reported progress on mapping the neuronal circuits underlying a variety of learning processes. For example, Leslie Griffith (Brandeis University) presented efforts to determine the brain regions involved in *Drosophila* courtship conditioning, a learning paradigm in which male flies reduce courtship activity after exposure to previously mated females. Using the GAL4/UAS expression system, Griffith and colleagues created fly strains expressing

inhibited CaM kinase activity within specific brain areas, including the antennal lobes, mushroom bodies, protocerebrum, and central complex. By examining the behavioral and learning deficits displayed in flies with different inhibition patterns, they distinguished brain regions participating in memory formation during courtship conditioning from those underlying the basic behavior (Joiner and Griffith 1999).

Researchers also summarized recent progress in deciphering the brain circuitry of emotional memory. Joseph LeDoux (New York University) described pathways in the rat brain mediating fear conditioning, a type of learning in which animals learn to associate a neutral (conditioned) stimulus with a fearful (unconditioned) one. In the rat, this type of learning is mediated by the amygdala, and previous research pinpointed subregions responsible for integrating sensory stimuli (the lateral nucleus) and mediating the fearful response (the central nucleus). LeDoux additionally described efforts to show that the amygdala is the site of fear conditioning plasticity and that LTP is the mechanism by which amygdala synapses form fear conditioning associations (Rogan et al. 1997).

In turn, Raymond Dolan (Wellcome Department of Cognitive Neurology) reported efforts to elucidate the pathways of emotional memory in humans. Also focusing on associative learning paradigms, Dolan presented results from a series of experiments in which subjects learned to associate visual stimuli with a loud burst of noise. Subjects can learn these associations even when they are unconscious of the visual stimulus, as occurs during visual masking (when the stimulus is presented only milliseconds before another image). Using positron–emission tomography (PET), Dolan showed that the amygdala activates when subjects are presented with fear-conditioned stimuli and that the right amygdala activates in particular when the subject is unconscious of the conditioned stimulus (Morris et al. 1998). Furthermore, the perceptual attributes of the unconditioned stimulus (i.e., auditory, for a noise) appear to be stored with the fearful association.

Progress in learning and memory research has been accelerating. In the 2 years since the last Learning and Memory meeting at Cold Spring Harbor, researchers have made strides in uncovering the mechanisms of LTP and LTD, discovered additional molecular pathways conserved from invertebrate to mammalian memory systems, unearthed new links between developmental and adult learning mechanisms, and used advanced imaging techniques to address a broad range of molecular, cellular, and systems issues. Improvements in molecular approaches and imaging technologies (such as MRI and confocal microscopy) have done much to advance this field and will likely propel researchers to a deeper understanding of learning and memory in the 21st century.

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