Brain Structure, Learning, and Memory

Edited by Joel L. Davis, Robert W. Newburgh, and Edward J. Wegman

AAAS Selected Symposium **105**

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ARTHUR HERSCHMAN
Head, Meetings
and Publications
American Association for
the Advancement of Science

Preface

In science, a few areas particularly capture the imagination because of a combination of excitement, substantial technical progress, and implicit significance in affecting the nature and quality of life. Perhaps no area of science exhibits these characteristics more abundantly than that dealing with the brain. Once shrouded in the mystical, studies in modern brain science are dramatically enhancing our understanding of brain function and its impact on learning and memory. It is perhaps the union of pragmatic and mystical aspects that makes this such an exciting arena of science.

The Office of Naval Research (ONR) began an intensive effort in 1983 on the topic of the neural basis for learning and memory. This effort was aimed at providing the scientific understanding of how learning takes place. It is the expectation that a neurological understanding of learning processes will lead to the formulation of learning strategies that will significantly enhance performance. This is important in a civilian and military population faced with serious manpower problems requiring a few individuals to be more expert with technologically intensive systems. With these motivations in mind, two of us (EJW and RN) formulated a full-day symposium at the AAAS annual meeting held in New York, May 1984.

As an outgrowth of that very successful session, AAAS invited us to prepare this volume, which is a comprehensive and current version of research funded under ONR's research thrust in the neural basis for learning and memory. Conceptually, that program, as well as this book, is organized along two major thrusts: the cellular and the computational.

The past few decades have witnessed an explosion of information gathering in the neurosciences. Some of the most interesting research strategies have been driven by a search for how neuronal tissue is able to store informa-

tion. Until now, biological approaches to understanding memory mechanisms have typically centered either on processes within the individual cell or on more complex cellular systems. The four contributors to the first section of the volume have eschewed the cell/system dichotomy to incorporate a more global approach to the issue. They are also united in their use of model systems; coupling techniques of classical neurophysiology, neurochemistry, and behavior; and employing strategies that reveal a strong system or circuit analysis influence.

These chapters demonstrate that the analysis of the physical-chemical substrates of some of the simpler learning and memory phenomena will soon result in a characterization of brain circuits as information processing networks. Richard Thompson's work is based upon the identification, localization, and analysis of one essential memory circuit—classical conditioning of learned eyelid closure response. Thompson and others have chosen eyelid conditioning because it represents a paradigm in which the stimuli are easy to control, the response is discrete and relatively easy to measure, and because animals from fish and birds to humans learn the conditioned eyelid response in the same way and exhibit the same basic laws and properties of Pavlovian conditioning. The search for the circuit that controls this behavior has led to the cerebellum, and Thompson's current results suggest that the hippocampus and cerebral cortex must exert their influence through what is essentially a cerebellar circuit.

Gary Lynch has adopted a research strategy that begins not with behavioral data, but instead with a well-defined anatomical network in the rat brain that can be demonstrated to store information. Again, the emphasis is not on the immensely complicated neocortex with its unknown cortical circuitries, but rather on the olfactory cortex and hippocampus which, like the cerebellum, are both considerably simpler in their cytoarchitecture and have precisely defined afferents and efferents. In addition, recent neurobehavioral data indicate that the type of olfactory memory studied by Lynch can be observed at many phylogenetic levels, including man. Lynch's neural systems analysis, coupled with his model of post-synaptic change for the membrane event that codes permanent storage, provides a strong multi-level approach to understanding biological intelligence from the molecular to the organismal level.

Hawkins and Clark's neural model for learning is taken from the marine snail *Aplysia californica.* The utility of such invertebrate preparations is now well accepted. The properties of their cellular systems allow for observations and cross-comparisons on the same cell from individual to individual. In addition, fundamental behavioral paradigms such as sensitization, habituation, and classical conditioning exhibit most of the same properties that are observed in mammalian preparations. More specifically, all of these paradigms reflect a temporal specificity that must be coded by the neural system. The authors' results suggest that the mechanism for temporal specificity can be found at the level of the cell membrane. Calcium influx into sensory cells

in the abdominal ganglion serves to prime adenylate cyclase, which in turn, produces an increase in cAMP. Details of the timing of these transmembrane events may explain some of the constraints in the temporal sequence of stimulus presentation that are required to produce phenomena of neural plasticity.

The last chapter in this section describes an experimental and modeling study that attempts a detailed description of plastic changes in another well-defined neuroanatomical structure. Though perhaps less highly regular than hippocampus, cerebellum, or *Aplysia* abdominal ganglion, the primary mammalian somatosensory cortical system contains well-defined functional neuronal models whose afferent and efferent connections are well known. Although somatosensory cortex (and other sensory neocortex) has traditionally been assumed to be less plastic than other areas hypothesized to control "higher functions," recent advances in this field suggest somatic sensory cortex to be extremely plastic under appropriate conditions. Whitsel and Kelly's approach differs from the other investigators represented in this section because they include a strong mathematical component in their research strategy. Their information processing model uses the connectional information provided by neuroanatomical tracing techniques to provide constraints. Therefore, the model is much more biologically plausible than many previous attempts to describe behaviors generated from neural circuitry.

In parallel to the cellular work of the first section, a tradition of mathematical model-based computational work has also been evolving. Indeed, if as experimental evidence suggests, the physiological basis of learning and memory resides in the modification of synapses between neurons, then the global understanding of learning phenomena resides in a mathematical understanding of the massive neural network that is the brain. The phenomena of distributed memory and the communications provided by discrete-event stochastic processes over this complex neural network offer incredibly rich problems to the computationally oriented mathematical modeler. This is the subject of the second section.

Leon Cooper provides a summary of recent theoretical and experimental results related to plasticity in the visual cortex, and by inference, results related to changes that take place in the nervous system when learning occurs and when memory is stored. Modeling memory is perhaps the most difficult task insofar as memory must function holographically. That is, in spite of loss of individual neurons, memory persists. Hence, it must not reside at any individual site, but in a distributed fashion. Individual memory sites hold superimposed information concerning many events. Cooper provides a model of learning and memory in neural networks which seeks to synthesize properties of long- and short-term memory and to account for local and global controller functions.

In contrast to the macroscopic work of Cooper, Habib and Sen focus on the detailed understanding of processes in the synaptic junction. Their work

comes from a tradition of stochastic communication theory, and seeks to model aspects of electrical activity in the nervous system at the cellular and multicellular levels. In particular, they develop highly accurate micro-models of the subthreshold behavior of the membrane potential of individual neurons, and relate the parameters of the models to physiologically meaningful quantities. Through the measurement of physiologically significant quantities, they are able to estimate parameters and calibrate their models. Closely related to the mathematical understanding of the individual synaptic mechanism is the understanding of the spike-train process driving that mechanism. Habib and Sen also offer nonstationary point process models for these trains of action potentials, completing a microscale model for synaptic behavior.

Another macroscale aspect of learning and memory is the explanation of the brain's function as a self-organizing system, that is, the spontaneous emergence of recognition categories as a function of an individual's experience. Carpenter and Grossberg focus on principles and mechanisms that are capable of self-organizing stable recognition systems in response to arbitrary temporal sequences of input patterns. These principles and mechanisms lead to the design of neural networks whose parameters can be specialized for applications to particular sensory domains such as speech and vision. Carpenter and Grossberg review recent work related to speech and language and to visual form and color in the context of these models, and offer neural network models that accommodate a wide variety of the known phenomena.

Granger, Schlimmer, and Young focus on yet another aspect of learning and memory, in particular, contingency and latency. Learning stimuli occur in an extremely stimuli-intensive (noisy) environment. The extraction of salient features from a noisy environment is thus a critical phenomenon which must be explained by any complete model of brain function. Called contingency, this together with latency, the learned timing of responses to stimuli, are modeled by Granger *et al.* The authors provide a computational analysis of a set of empirical data on contingency and latency in classical and instrumental conditioning. Their model is presented in the framework of an information processing architecture that describes a set of modules which operate in parallel and asynchronously to store, retrieve, and modify experimental information.

Taken together, these four chapters present mathematically based, computationally oriented models of both micro- and macro-scale phenomena associated with learning and memory. While none of these models stands as a complete description of all phenomena, together they demonstrate the complexity of the nervous system and illuminate the current state-of-the-art.

Joel L. Davis
Robert W. Newburgh
Edward J. Wegman

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Chapter 1 — *Clark & Hawkins*

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Chapter 3 — *Thompson*

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Gregory A. Clark and Robert D. Hawkins

1. Learning and the Single Cell: Cellular Strategies for Information Storage in the Nervous System

For the better part of the last century, the study of learning has held a special intellectual appeal for psychologists and biologists alike. This attraction has arisen not only from the realization that the processes underlying learning are eminently approachable experimentally, but from an appreciation for the rich conceptual importance that learning holds for the understanding of both brain and behavior. One of the most intriguing features of learning is its remarkable specificity. Animals must not simply change their behavior, they must change it in specific ways to meet particular environmental demands. Under one set of conditions, it may be important to increase a behavior, while another set of circumstances might require that the behavior be suppressed. Similarly, animals must learn to pay attention to some stimuli, but ignore others. Associative forms of learning, such as classical conditioning and operant conditioning, further require that the animal associate one stimulus with another, or a stimulus with a response.

The challenge for the neurobiologist interested in the biological bases of learning is to determine how this specificity is achieved. Since neural circuitry appears relatively predetermined, learning must involve precise modification of particular neural elements. But what mechanisms determine *which* neurons are modified, and how are these neurons modified in appropriate ways? Moreover, different types of learning would seem to require different mechanisms. How are these mechanisms related? Do different forms of learning require different storage sites, or can a single neuron store more than one type of information? And can a single neuron store more than one memory at a time, or do new memories erase the old?

To address such questions, it is desirable to compare the mechanisms for several forms of learning in a single behavior. The analysis of the gill and

siphon-withdrawal reflex in the marine snail *Aplysia californica*, pioneered largely by Drs. Eric Kandel, James Schwartz, and colleagues, has provided this opportunity (for a review, see Kandel and Schwartz 1982). As we shall discuss, this simple defensive reflex exhibits several forms of learning, including habituation, sensitization, and classical conditioning. As might be expected, these different forms of learning utilize different cellular mechanisms. In this chapter, we shall try to indicate how these three different forms of learning can be accounted for by three different types of synaptic plasticity in a single cell type, and how the properties of these cellular mechanisms confer the types of behavioral specificity characterizing each form of learning.

Habituation and Sensitization of the Gill and Siphon-Withdrawal Reflex

Behavioral Studies

While several behaviors in *Aplysia* exhibit learning (Kandel and Schwartz 1982; Walters *et al.* 1979, 1981; Susswein and Schwarz 1983; Cook and Carew 1984; Hawkins *et al.* 1985), we have focused primarily on the gill and siphon-withdrawal response. As shown in Figure 1.1, the gill—the respiratory organ for *Aplysia*—is covered by the mantle shelf, a flap of skin which terminates in a small fleshy spout known as the siphon. A tactile stimulus to the siphon causes the siphon to withdraw and the gill to contract. Like several defensive reflexes in mammals, the amplitude and duration of this reflex can be modified by various forms of learning, involving both decreases (habituation) and increases (sensitization and classical conditioning) in responding. Because the characteristics of these forms of learning in *Aplysia* are quite similar to those found in mammals, we are encouraged to believe that at least some of the mechanisms of learning may be conserved on a cellular level across different species.

Habituation is a simple form of learning that involves a decrease in responding to a repeated stimulus. Thus, if a tactile stimulus to the siphon is given repeatedly, it elicits a smaller and smaller response (Fig. 1.1) (Pinsker *et al.* 1970; Carew *et al.* 1972). If only a few stimuli are presented, the response will largely recover, following a rest interval in which the siphon is no longer stimulated. However, if the siphon is stimulated repeatedly over several training sessions, habituation will be relatively permanent. Despite its simplicity, habituation is an important form of learning, for it allows the animal to ignore irrelevant environmental events.

Because environmental conditions may change, it may become important for an animal to increase its response to a stimulus that could previously be safely ignored. The gill and siphon-withdrawal response can be enhanced by

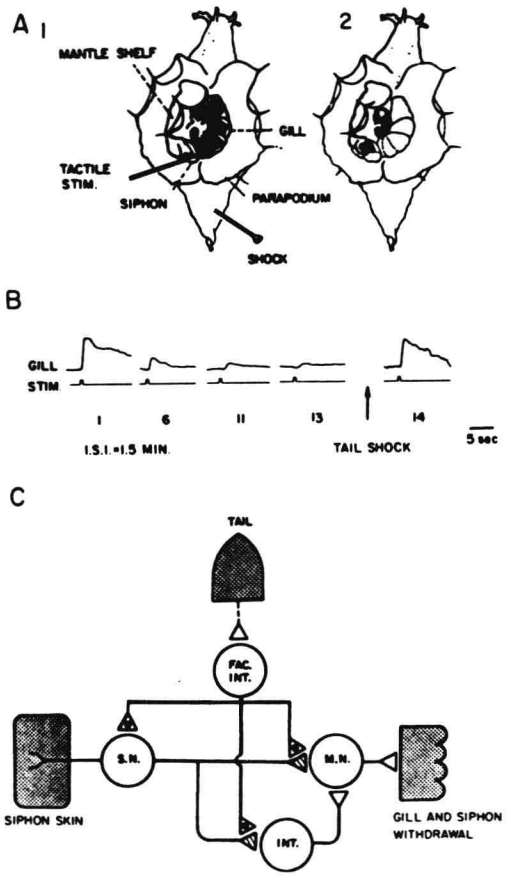

Figure 1.1. Habituation and sensitization of the gill and siphon-withdrawal response in *Aplysia*. *A:* Experimental arrangement for behavioral studies in the intact animal showing gill and siphon in a relaxed (A_1) and contracted (A_2) position. The parapodia and mantle shelf are shown retracted to reveal the gill and siphon. *B:* Photocell recordings showing habituation and sensitization of the gill-withdrawal response. A tactile stimulus to the siphon (*bottom trace*) elicited a gill withdrawal response (*top trace*) which habituated with repeated stimulus deliveries (interstimulus interval, 1.5 min). Application of a noxious tail shock (at *arrow*) caused marked sensitization of the gill-withdrawal response. *C.* Neural circuit mediating gill and siphon-withdrawal responses. The siphon skin is innervated by a group of approximately 24 mechanoreceptor sensory cells (*SN*) whose soma are located in the LE cluster in the abdominal ganglion. The siphon sensory cells project both monosynaptically and through interneurons (*INT*) to gill and siphon motorneurons (*MN*), many of which are also located in the abdominal ganglion. Effects of sensitizing stimuli in the abdominal ganglion are mediated by a group of facilitator interneurons (*FAC INT*) which terminate on sensory cells in synaptic and somatic regions. Habituation of the reflex has been shown to involve a decrease in transmitter release from sensory neuron terminals (*shaded*), while sensitization and classical conditioning of the reflex have been shown to involve an increase in transmitter release. (Adapted from Kandel and Schwartz 1982.)

both sensitization and classical conditioning. Sensitization is an increase in responding to a given stimulus as a result of the presentation of a second, usually strong stimulus. Thus, a strong shock given to the head or tail of *Aplysia* will enhance the gill and siphon-withdrawal response to a tactile siphon stimulus, even if the response had previously been habituated (Fig. 1.1) (Pinsker *et al.* 1970, 1973). Like sensitization, classical conditioning involves the effect of one stimulus upon the response to another. However, classical conditioning has the additional requirement that the two stimuli must be temporally paired. We will return to consider this point in more detail.

Cellular Analyses of Habituation and Sensitization

The marine snail *Aplysia californica* offers several advantages for a cellular analysis of learning. For one, the nervous system of *Aplysia* is relatively simple, containing only about 20,000 neurons. Moreover, many of the cells are large and readily identifiable (Kandel 1976). Thus, one can return to the same cells from preparation to preparation, and so determine their behavioral function and how they change during learning.

The first task in attempting to delineate the biological changes underlying learning is to determine the neural elements involved in the behavior. The fact that the *Aplysia* nervous system contains such a small number of neurons (relative to the mammalian brain) has simplified this task enormously. As shown in Figure 1.1, the gill and siphon-withdrawal reflex is mediated by a group of approximately 24 mechanosensory neurons (Castellucci *et al.* 1970; Byrne *et al.* 1974) that project both monosynaptically and polysynaptically to the gill and siphon motor neurons (Kupfermann and Kandel 1969; Kupfermann *et al.* 1974; Perlman 1979). The critical elements mediating this behavior are thus contained in a relatively simple circuit.

Subsequent analyses have focused on determining which of these cells undergo changes as a function of learning. Such studies have found that both habituation and sensitization (and, as we shall see later, classical conditioning as well) share a common locus of plasticity: the synapses of siphon sensory cells onto gill and siphon motor neurons and interneurons. In habituation, synaptic transmission is depressed, while in sensitization (and classical conditioning), synaptic transmission is enhanced. While it seems possible that changes may also occur in other types of neurons (Frost and Kandel 1984; Frost, Clark, and Kandel 1985), these changes in sensory neuron properties appear to contribute substantially to the changes observed in behavior (Kandel 1976). By focusing on this plasticity in sensory neurons, Kandel and colleagues have been able to progress relatively directly to the analysis of the underlying cellular and molecular mechanisms. Because the cells involved in learning will change from task to task and species to species, this approach seemed the one most likely to elucidate general principles underlying learning.