Articles

The Neurobiology of Learning and Memory

RICHARD F. THOMPSON

Study of the neurobiology of learning and memory is in a most exciting phase. Behavioral studies in animals are characterizing the categories and properties of learning and memory; essential memory trace circuits in the brain are being defined and localized in mammalian models; work on human memory and the brain is identifying neuronal systems involved in memory; the neuronal, neurochemical, molecular, and biophysical substrates of memory are beginning to be understood in both invertebrate and vertebrate systems; and theoretical and mathematical analysis of basic associative learning and of neuronal networks is proceeding apace. Likely applications of this new understanding of the neural bases of learning and memory range from education to the treatment of learning disabilities to the design of new artificial intelligence systems.

AMONG THE MOST IMPORTANT AND BAFFLING QUESTIONS in science are how the brain codes, stores, and retrieves memories. The uniqueness of each human being is due largely to the memory store—the biological residue of memory from a lifetime of experience. The cellular basis of this ability to learn can be traced to simpler organisms. In the past generation, understanding of the biological basis of learning and memory has undergone a revolution. It now seems possible to identify the circuits and networks that participate in learning and memory, localize the sites of memory storage, and analyze the cellular and molecular mechanisms of memory.

The roots of this new understanding lie in several different disciplines. From psychology has come a characterization of the behavioral properties of learning and a developing conceptual and theoretical analysis of the nature of the associative and nonassociative processes that form the basis of learning and memory. From behavioral neuroscience has come the recognition that identifiable neural memory systems and circuits in the brain can be characterized and analyzed. From network analysis and cognitive science we are learning how memory and cognitive properties can emerge as collective properties of systems of neurons. From neurobiology we are learning about the cellular, biophysical, and molecular mechanisms that may underlie elementary forms of associative learning in neural circuits.

The success of this collective approach has been the source of great optimism and will probably lead to fundamental insights into the physical basis of memory over the next few years. These insights will be significant not only for basic science but for applied and clinical uses as well. The most common complaint in normal aging is memory impairment. In a range of organic disorders (for example, amnesia and Alzheimer's disease), the most prominent sign is a disorder of memory. At the other extreme is the memory retrieval and information processing of the expert (for example, chess master). The human brain is an extraordinary parallel information processing system quite unlike current digital computers. More generally, education, a multibillion dollar industry in the United States alone, strives to achieve the most effective and meaningful learning. The science most basic to all these conditions and endeavors is the neurobiology of learning and memory—how the brain codes, stores, and retrieves memories.

Definitions and Issues

Lasting changes in behavior resulting from prior experience can be characterized as the result of learning, memory, and retrieval processes. Most psychologists would agree on the existence of several forms or categories of learning, but would be less likely to agree on the properties that uniquely distinguish them. At this point, it is useful to keep the basic definition of learning broad. Thus, bacteria have a kind of memory—their behavior can change as a result of experience (for example, after exposure to certain molecules), and this change can persist after the experience. This example does not fit neatly into any of the common categories of learning but it may serve as a model (*1*).

It has been useful to distinguish two basic categories of learning—nonassociative and associative. Nonassociative learning results from experience with a single type of event. Habituation—a decrease in response to repeated stimulation—and sensitization—an increase in response after (usually strong) stimulation—are examples. Associative learning, resulting from the conjunction of two or more events, is commonly categorized into Pavlovian (or classical) and instrumental conditioning (*2*). At the most basic level, associative learning concerns the causal relations between events occurring in the organism's environment (*3*). From a neurobiological point of view, Pavlovian conditioning as an experimental tool has several advantages over instrumental learning—the most important being that the effects of experimental manipulations on learning (rather than on performance) can be more easily evaluated (*4*)—but both exhibit similar basic properties of associative learning.

Currently, the most productive research strategy for investigating the neural basis of learning is the model systems approach (*5, 6*): selection of an organism that exhibits a given form of learning and memory and that has a nervous system amenable to analysis. Certain invertebrate preparations are valuable as model systems because some of their behavioral functions are controlled by ganglia that contain relatively small numbers of large, identifiable cells—cells that can be consistently identified in different individuals of the species (*5, 7–9*). With vertebrate model systems, these goals are considerably more difficult to attain. Specialized forms of learning in birds—imprinting and song learning—have proved to be most

The author is a professor of psychology at Stanford University, Stanford, CA 94305.

useful models (*10*). But we are mammals—the ultimate goal is to understand how the human brain stores memories.

The problem of localizing the neuronal substrates of learning and memory, first explored in depth by Lashley (*11*) and later by Hebb (*12*), has been the greatest barrier to progress and remains fundamental to all work on the biological basis of learning and memory. To analyze the biophysical mechanisms that form memory traces it is necessary to localize the memory traces, and this in turn requires identification of the essential memory trace circuits. By "essential memory trace circuit" I mean the neuronal circuitry from receptors to effectors that is necessary and sufficient for learning and memory in a given training paradigm. By "essential memory trace" I mean the neuronal processes of plasticity that are necessary and sufficient to store the memory in question. The latter is far more difficult to establish than the former. In the mammalian brain, identification of essential memory trace circuits for associative learning is only now being achieved, and evidence for localization of memory traces for some types of learning is just now being developed.

Identification of Essential Memory Trace Circuits in the Mammalian Brain

Recent evidence strongly supports the view that memory trace circuits, and by inference memory traces, are localized rather than widely distributed in the mammalian brain. But "localized" may include multiple sites, and within a site the trace or traces can still be distributed among the neural elements or ensembles. Although controversies still exist, the weight of evidence argues against the possibility that essential memory traces are localized to sensory relay nuclei below the level of the thalamus, motor nuclei, or reflex pathways (*4, 13*). The structures currently thought to be most involved in memory trace formation are the cerebellum, hippocampus, amygdala, and cerebral cortex.

Essential circuitry for learning of discrete, adaptive behavioral responses. Recent evidence based primarily on eyelid conditioning as a model system (*6, 14*) overwhelmingly favors an essential role for the cerebellum in both learning and memory of discrete, adaptive behavioral responses to aversive events, thus supporting the general spirit of earlier theories of the role of the cerebellum in motor learning (*15, 16*). Through the use of lesions, electrophysiological recordings, electrical microstimulation, microinfusion of drugs, and anatomical methods, it has been shown that a region of the cerebellum ipsilateral to the trained eye (lateral interpositus nucleus) is essential for the learning and memory of the conditioned eye-blink response but not for the reflex response (*17, 18*). Kainic acid lesions of the interpositus nucleus abolish the conditioned response (CR), with no attendant degeneration in the inferior olive (*19*). These effects are ipsilateral: unilateral cerebellar lesions do not impair learning of responses on the contralateral side of the body. This effect also holds across conditioned stimulus (CS) modalities, skeletal response systems, species, and perhaps instrumental contingencies (*20*). Electrophysiological analysis reveals several localized regions of cerebellar cortex and the lateral interpositus nucleus where neurons, including identified Purkinje cells, develop patterned changes in discharge frequency that precede and predict the occurrence and form of the learned behavioral response within trials and predict the development of learning over training trials (*21, 22*). Electrical microstimulation of the interpositus nucleus in untrained animals elicits behavioral responses by way of the superior cerebellar peduncle—for example, eye-blink and leg flexion—the nature of the response being determined by the locus of the electrode. Collectively, these data suggest that the memory traces are afferent to the efferent fibers of the superior cerebellar peduncle, for example, in the interpositus, the cerebellar cortex, or in systems for which the cerebellum is a mandatory efferent.

The essential efferent CR pathway seems to consist of fibers that exit from the interpositus nucleus ipsilateral to the trained side of the body in the superior cerebellar peduncle, that cross to relay in the contralateral magnocellular division of the red nucleus, and that cross back to descend in the rubral pathway to act ultimately on motor neurons (*23*). Whether other efferent systems also control the CR is not known, but descending systems originating rostral to the midbrain are not necessary for learning or retention of the CR (*24*).

Recent lesion and microstimulation evidence suggests that the essential reinforcement pathway for the unconditioned stimulus (US), which is the necessary and sufficient pathway conveying information about the US to the cerebellar memory trace circuit, is constituted of climbing fibers from the dorsal accessory olive (DAO) projecting through the inferior cerebellar peduncle. Thus, lesions of the appropriate region of the DAO prevent acquisition and produce normal extinction of the behavioral CR with continued paired training in animals that have already been trained (*25*). Electrical microstimulation of this same region elicits behavioral responses and serves as an effective US for normal learning of behavioral CR's; the exact behavioral response elicited by DAO stimulation is learned as a normal CR to a CS (*26*). The inferior olive–climbing fiber system also plays an important role in adaptation of the vestibulo-ocular reflex and in recovery from motor abnormalities induced by labyrinthine lesions (*27*).

Lesion and microstimulation data suggest that the essential CS pathway includes mossy fiber projections to the cerebellum via the pontine nuclei. Thus, sufficiently large lesions of the middle cerebellar peduncle prevent acquisition and immediately abolish retention of the eyelid CR to all modalities of the CS (*28*), whereas lesions in the pontine nuclear region can selectively abolish the eyelid CR to an acoustic CS (*29*). Electrical microstimulation of the mossy fiber system is an effective CS, producing rapid learning (on average more rapid than with peripheral CS's) when paired with, for example, a corneal airpuff US (*30*). If animals are trained with left pontine nuclear stimulation as the CS and then tested for transfer to right pontine stimulation, transfer is immediate (that is, it occurs in one trial) if the two electrodes have similar locations in the two sides, suggesting that under these conditions the traces are not formed in the pontine nuclei but rather beyond the mossy fiber terminals in the cerebellum (*31*). Finally, appropriate forward pairing of mossy fiber stimulation as a CS and climbing fiber stimulation as a US yields normal behavioral learning of the response elicited by climbing fiber stimulation (*32*). Lesion of the interpositus abolishes both the CR and the UR in this paradigm. A hypothetical and much simplified schematic of the essential memory trace circuit is shown in Fig. 1. All these results taken together would seem to build an increasingly strong case for localization of the essential memory traces to the cerebellum, particularly in the "reduced" preparation with stimulation of mossy fibers as the CS and of climbing fibers as the US. In the normal animal trained with peripheral stimuli, the possibility of trace formation in brain stem structures has not yet been definitively ruled out.

We initially suggested that such memory traces might be formed in the cerebellar cortex (*33*) where, as Eccles and others have stressed, there is more neuronal machinery than in the interpositus nucleus. However, none of the cerebellar cortical lesions that we have made permanently abolish the CR. Yeo *et al.* (*34*), using different stimulus and training conditions, reported that complete removal of the cortex of Larsell's cerebellar lobule H VI permanently abolished the eye-blink CR. Complete removal of H VI did not abolish the CR in three separate studies in our laboratory (*35*).

Recently, we repeated the stimulus and training conditions of Yeo *et al.* and found that complete removal of H VI causes only transient loss of the CR; all animals eventually relearned (*36*). But these results do not rule out multiple parallel cortical (and interpositus) sites for the memory trace. Cortical lesions that have been tried may not have removed all such sites; the flocculus has not been lesioned, and electrical microstimulation of the flocculus can elicit eye blinks in the rabbit (*37*). In general, the larger the cerebellar cortical lesion, the more pronounced and prolonged the transient loss of the CR. Further, cerebellar cortical lesions made before training can prevent learning in some animals (*38*). The possibility of multiple cortical sites is consistent with the organization of somatosensory projections to the cerebellum (*39*).

Plasticity of the vestibulo-ocular reflex, discussed in recent reviews (*40–42*), is an intriguing example of a learning-like change in behavior as a result of altered visual input. Gain control can be altered by using lenses or by moving the visual field and the head. The vestibulo-ocular reflex (VOR) shows a persisting (hours to days) adaptation to the changed gain. It differs from associative learning and memory in at least one important way: there is no sign of long-term retention, that is, neither the rate of adaptation nor the rate of recovery increases with repeated exposures (*40, 41, 43*). Such savings with repeated training sessions is characteristic of associative learning and even of nonassociative learning processes such as habituation.

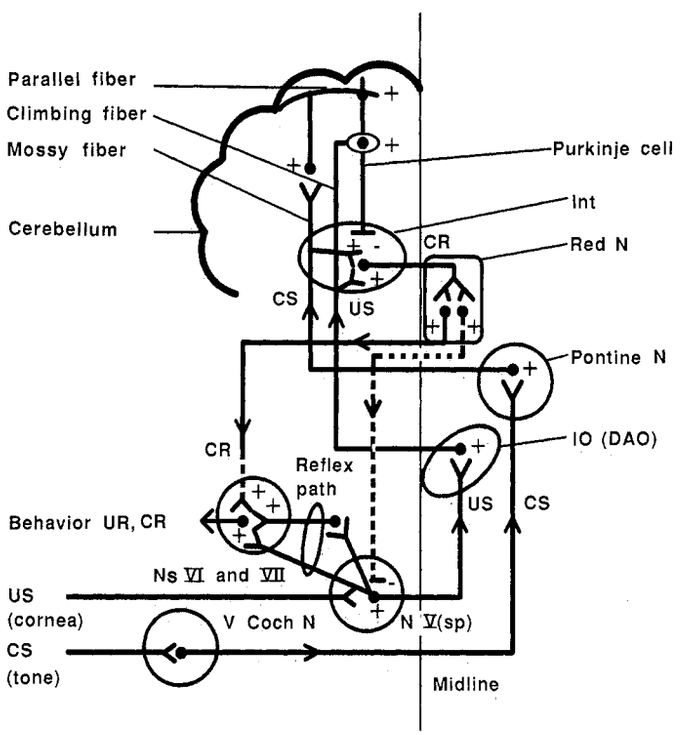

Fig. 1. Simplified schematic of hypothetical memory trace circuit for discrete behavioral responses learned as adaptations to aversive events. The US (corneal airpuff) pathway seems to consist of somatosensory projections to the dorsal accessory portion of the inferior olive (DAO) and its climbing fiber projections to the cerebellum. The tone CS pathway seems to consist of auditory projections to pontine nuclei (Pontine N) and their mossy fiber projections to the cerebellum. The efferent (eyelid closure) CR pathway projects from the interpositus nucleus (Int) of the cerebellum to the red nucleus (Red N) and via the descending rubral pathway to act ultimately on motor neurons. The red nucleus may also exert inhibitory control over the transmission of somatic sensory information about the US to the inferior olive (IO), so that when a CR occurs (eyelid closes), the red nucleus dampens US activation of climbing fibers. Evidence to date is most consistent with storage of the memory traces in localized regions of cerebellar cortex and possibly interpositus nucleus as well. Pluses indicate excitatory and minuses inhibitory synaptic action. Additional abbreviations: N V (sp), spinal fifth cranial nucleus; N VI, sixth cranial nucleus; N VII, seventh cranial nucleus; V Coch N, ventral cochlear nucleus.

Ablation of the flocculus or of the vestibular cerebellum including the flocculus abolishes VOR adaptation in rabbit, cat, and monkey (*40*). Utilizing recording of Purkinje cell activity, lesions, and electrical stimulation, Ito developed evidence that the plasticity occurs in the cerebellum (flocculus) in the rabbit (*41, 42*). Miles and Lisberger (*40*) proposed an alternative argument, based on Purkinje cell recording in the monkey flocculus, that both brain stem and cerebellum are involved but that plasticity is primarily in the brain stem. But Watanabe's (*43*) recent Purkinje cell recording in monkey flocculus seems consistent with Ito's hypothesis. Workers agree that the flocculus is necessary for VOR adaptation. Recent evidence supports Ito's view that plasticity can be established in the flocculus of the rabbit by use of conjoint electrical stimulation of mossy or parallel fibers and climbing fibers.

An extensive literature argues that the cerebellum plays a critically important role in the performance of skilled (learned) movements in higher mammals (*44*). In an earlier Soviet literature it was reported that complete removal of the cerebellum in dogs abolished or severely impaired the conditioned leg flexion and salivary responses (*45*). Lesion of the cerebellar vermis has been reported to abolish long-term habituation of the acoustic startle response and abolish the conditioned heart rate response in rats (*46*). The cerebellum may play a much wider role in learning and memory processes than was thought.

Classically conditioned cardiovascular responses ("fear" learning). A relatively consistent picture is emerging from studies on cardiovascular conditioning in three vertebrate species. The paradigm in classical conditioning in which an auditory or visual CS several seconds long terminates with an electric shock US to some portion of the head or body. In the baboon, small, discrete bilateral lesions of the perifornical region of the hypothalamus abolish the entire learned cardiovascular response complex—heart rate increase, blood pressure increase, and so forth—completely, permanently, and selectively (*47*). The lesion has no effect on reflex cardiovascular responses, on cardiovascular responses associated with exercise, and on a behavioral measure of conditioned "fear"—conditioned suppression of lever pressing. It is not known whether the effective lesion is to neuron somas or to fibers of passage. The use of lesions, electrical stimulation, neural unit recording, microinfusion of drugs, and anatomical methods has permitted the identification of much of the essential circuitry for cardiovascular conditioning in the pigeon and rabbit (*48*). The essential efferent pathway includes portions of the amygdala, hypothalamus, and descending pathways to the brain stem and spinal cord. In the rabbit, the lateral subthalamic region seems to be a critical portion of the efferent pathway from the amygdala. In the pigeon, with a visual CS, any one of three visual pathways can support conditioning, and training-induced modification of neural unit activity occurs at, but not afferent to, central thalamic optic relays. Although it is not yet known where the memory traces are located, the amygdala is a possibility; it seems more generally involved in conditioned emotional responses (fear) (*49*). A new and unexpected finding is that a lesion of the cerebellar vermis selectively abolishes conditioned bradycardia in the rat (*50*). Gold and Cohen earlier reported that cerebellectomy does not abolish conditioned tachycardia in the pigeon (*51*).

Davis *et al.* have used conditioned potentiation of the acoustic startle response in the rat as a model of conditioned emotional state. Having earlier defined the acoustic startle reflex pathway [ventral cochlear nucleus–nuclei of lateral lemniscus–nucleus reticularis pontis caudalis–spinal interneurons–motor neurons (*52*)], they deter-

mined that the potentiating effect of a light, previously paired with shock, on the startle response seems to act on the startle circuit at the ventral nucleus of the lateral lemniscus (*53*). Essential components of the potentiation circuit include the geniculo-cortical visual system and the amygdala (*54*), as in the cardiovascular learning circuit for a visual CS in the pigeon.

Cerebral cortex and hippocampus. Karl Lashley pioneered the study of the role of the cerebral cortex in visual discrimination learning and memory. In classic studies he showed that the striate (primary visual) cortex in rats is essential for learning and memory of visual pattern discriminations but not for brightness discrimination, which is relearned postoperatively in about the same number of trials as original learning required (*55*), thus providing a useful model for study of recovery of function (*56*). Mishkin (*57*) has worked out the afferent limb of the essential circuit for one aspect of pattern vision memory in the monkey—two-dimensional pictures of visual forms. In brief, the circuit is striate cortex to prestriate cortex, corpus callosum between prestriate cortices of the two hemispheres, and on to an area in the inferotemporal cortex (TE). Either hemisphere or a combination will do, as long as information can get from one striate cortex to one area TE. This part of the circuit is also essential for recent visual memory, but the actual locations of the memory traces for visual patterns remain elusive.

Studies of human amnesia implicated the hippocampus in learning and memory (*58*), but this syndrome proved difficult to replicate in animals [see Squire (*59*) for an extended discussion]. Mishkin showed that a deficit in recent memory function (delayed nonmatching to sample) can be produced in monkeys subjected to bilateral ablation of both the hippocampus and the amygdala (*60*). He identified the afferent limb of the recent visual memory circuit—primary visual cortex, visual association areas (prestriate cortex), information transfer via corpus callosum between prestriate areas of the two hemispheres, inferotemporal cortex, and hippocampus-amygdala. Recording studies in a delayed matching-to-sample task identified some neurons in area TE as responding in relation to relatively short-term aspects of this type of recognition memory but not to longer term aspects (*61*).

Lesions of the hippocampus (and septal nuclei) severely impair learning of spatial tasks in the rat (*62*), as do frontal cortical lesions (*63*). Consistent with the effects of hippocampal lesion are electrophysiological data demonstrating a striking correlation between increased firing of certain hippocampal neurons and the location of an animal in space (*64*). This evidence has been interpreted within the framework of "spatial memory," but an alternative interpretation can be made in terms of "working memory" (*62, 65*). It is not yet clear whether the spatial correlates of hippocampal neurons develop as a result of learning (*66*). Neuronal activity in the hippocampus becomes massively engaged in simple classical and instrumental learning tasks, often selectively under conditions of learning, even though the hippocampus is not essential for the learning or memory of these tasks (*67*). But the hippocampus can become important when more complex demands are placed on the animal, even in classical conditioning (*4*).

A long-established behavioral deficit in primates resulting from lesions of one portion of the frontal lobes (in sulcus principalis) is seen in the delayed-response problem (*68*) as an inability to remember, even briefly, which cup a reward is placed under if a screen is lowered during the delay. The delayed response deficit with a frontal lesion is one of the rare cases in which analogous "lesions" seem to produce analogous deficits in short-term memory in monkeys and humans (*69*). Recent studies have characterized a portion of the cortico-cortical circuitry for this portion of the frontal lobe. Thus, afferent projections from the contralateral principal sulcus and from the ipsilateral parietal association cortex form interdigitating zones in the principal sulcus (*70*). There are also projections from the temporal auditory and visual association areas. In monkeys performing delayed response and delayed alternation tasks, single units in the frontal cortex show several patterns of response including sustained discharge during the delay period that seems to be related to performance of the task (*71*). Such cellular activity is consistent with the notion that this region may participate in a form of short-term memory.

In sum, the results of animal studies demonstrate a marked involvement of the hippocampus in a wide range of learning and memory phenomena, and lesions in the primate have replicated aspects of human amnesia. But all available evidence indicates that long-term or "permanent" memory traces themselves are not stored in the hippocampus in humans or other animals. Although it is widely assumed that the cerebral cortex is a principal site of long-term storage, the evidence from studies in infrahuman animals is surprisingly sparse; current evidence does suggest involvement of the neocortex in shorter term memory processes. The clinical literature suggests that "language memory" is stored in the cerebral cortex (*72*), but lesion evidence, per se, cannot demonstrate storage locus, only necessary involvement. The cerebral cortex would seem to be critically important for "cognitive" processes in higher mammals and humans.

Neural Mechanisms of Learning

Numerous candidate mechanisms of neural plasticity could be responsible for learning and memory—these include all the biophysical changes that affect the functional properties of neurons, plus phenomena that have not been discovered (*73, 74*). I will focus on putative mechanisms for which some empirical evidence exists. All evidence to date indicates that the mechanisms of memory storage are local and do not involve the formation of new projection pathways. Furthermore, to the extent that they have been identified, essential memory trace circuits in the vertebrate brain (and, by inference, memory traces) are localized. Local changes could include the formation of new synapses, structural and chemical alterations in neurons and synapses, and alterations in membrane properties that influence functional properties of preexisting synapses.

A large proportion of work on putative brain substrates of instrumental learning and memory in mammals (usually the rat) has been done in the context of the consolidation hypothesis, which provided a general framework for mechanisms of storage. This hypothesis states that there are two phases in memory formation, an initial phase in which memories can be altered by subsequent treatments and a later phase in which they are relatively impervious to treatment (*75, 76*). The empirical evidence shows that a range of posttraining treatments alter subsequent retention performance: electroconvulsive shock and inhibitors of protein synthesis severely impair retention, and many drugs facilitate retention (*77, 78*).

The great majority of animal studies have used a single posttraining treatment, in which peripheral factors seem to be critical. Thus, peripheral doses of β-endorphin and [Met]- and [Leu]enkephalin too low to have any detectable central effects can attenuate amnesia in rats (*79*). The amnesia produced by central administration of puromycin can be prevented by removing the adrenal gland; removal of the adrenal medulla prevents facilitation by amphetamine, effects of opioids, and impairment by electrical stimulation of the amygdala (*80*). The key role of the adrenal gland in these animal studies may be related to the profound effect of emotional state on the ability of humans to remember experiences. Memory consolidation is discussed by Squire (*59*).

Structural alterations in neurons. Now classic studies demonstrated

that early visual deprivation can result in both functional and anatomical alterations in neocortical neurons and in visual function (*81*). Cortical and cerebellar neurons in animals given "enriched" environments show substantial anatomical alterations—greater dendritic branching, more spines, and higher spine densities (and by inference more synapses) (*82, 83*); such animals are superior in a variety of learning tasks to deprived controls (reared singly) (*84*). Anatomical changes have been described for neocortical and hippocampal neurons with several types of learning tasks (*85*). But in many of these studies, the tissues involved are not essential for learning and memory of the tasks. Nonetheless, results of such studies on the relation between morphological changes in specific brain areas and specific behavioral learning tasks are provocative.

Alterations in preexisting synapses. Among the simplest ways to modify the strength of a preexisting synapse is to change transmitter release from presynaptic terminals by changing the conductance of certain ion channels, a mechanism that appears to operate in several invertebrate and vertebrate models. Thus, short-term habituation appears to be presynaptic and seems to result from homosynaptic depression (*5, 9, 86*), which in turn may result from decreased transmitter release (*87*). The biophysical basis of this presynaptic form of homosynaptic depression in *Aplysia* is apparently a reduced availability of Ca^{2+} to participate in the release of the transmitter as a result of repeated activation.

Sensitization, on the other hand, is a superimposed, independent process of facilitation in most systems (*5, 88*). In the *Aplysia* gill withdrawal circuit, a facilitator interneuron becomes activated and acts on sensory neuron terminals to increase the level of intracellular adenosine 3′,5′-monophosphate, which, through a cascade of intracellular reactions not fully understood, causes a particular class of potassium channels in the sensory neuron to close, thereby reducing the overall efflux of K^+ at the time of depolarization by the action potential. Because the repolarization of the neuron is due to an efflux of K^+, a decreased outward movement of K^+ ions results in a longer period of depolarization produced by each action potential, which in turn results in an increased influx of extracellular Ca^{2+} and transmitter release (*89*).

Two invertebrate models of classical conditioning, in *Aplysia* and *Hermissenda*, deal with changes in ionic conductance. In *Aplysia*, a short-term pairing-specific presynaptic increase in transmitter release from sensory neuron terminals develops by a process analogous to that producing sensitization. The increased influx of Ca^{2+} from the action potential in the sensory neuron terminal is thought to modulate the adenylate cyclase system in a temporally specific manner in association with the action of the modulator from the facilitator interneuron (*90*). In the *Hermissenda* model, persistent postsynaptic changes occur in the type B photoreceptor cell as a result of pairing a visual CS and vestibular US (*91*). These changes appear to be due to reduction in two species of outward K^+ currents in the type B cell (*92*).

There is some evidence for learning-induced alterations in ion channel conductance in mammalian systems. Woody (*74*), using a form of eyelid-blink conditioning in the cat, found that neurons in the motor cortex show increased excitability that apparently resulted from alterations in conductance, which in turn might be the result of alterations in a second messenger system. Eyelid conditioning in mammals markedly increases the within-trial responses of pyramidal neurons in the hippocampus (*93*). Recent evidence suggests that such training may decrease after-hyperpolarization in pyramidal neurons by decreasing a Ca^{2+}-activated outward K^+ conductance (*94*). But other persistent changes occur as well in hippocampal tissue in eyelid conditioning, including a prolonged learning-specific increase in glutamate receptor binding (*95*). An important aspect of all these findings in mammalian systems, whether or not they reflect the formation of memory traces, is that persisting local changes do occur in cortical neurons as a result of training—the increased neuronal responsiveness is not due simply to increased activation from elsewhere.

Long-term potentiation. Long-term potentiation (LTP) has become popular as a putative mechanism of memory in the vertebrate brain (*96*). A brief tetanic electrical stimulus (for example, a few seconds at 100 Hz) to certain pathways induces an increased synaptic excitability that can persist for days or weeks (*97*). It was first found in the perforant path to granule cells in the dentate gyrus and for some time was thought to be unique to the hippocampus, but it has now been reported in other brain regions as well (*96*). LTP resembles posttetanic potentiation (PTP), a phenomenon early proposed as a mechanism of memory (*98*), except that LTP lasts much longer. The mechanisms underlying LTP are not yet known. The fact that LTP, per se, does not involve convergent inputs (from CS and US) seemed a problem until the phenomenon of "cooperativity" was demonstrated: tetanic stimulation must be above a certain strength to induce LTP; below this level only facilitation, augmentation, and PTP are seen (*99*). Further, associative-like LTP by appropriate stimulation of two inputs has been demonstrated (*100*), thus providing a possible model of the "Hebb synapse" (*101*). The most detailed hypothesis relating LTP to memory is that of Lynch and Baudry (*102*). In brief, increased intracellular calcium is hypothesized to rapidly and irreversibly increase the number of receptors for glutamate (a probable neurotransmitter) in forebrain synaptic membranes by activating a protease that degrades a specific protein, which in turn could produce long-lasting changes in synaptic chemistry and ultrastructure. Evidence suggests that "new" synapses may be formed in the hippocampus in as short a time as 10 minutes after induction of LTP (*82, 103*).

Long-term depression. Ito has described a process in the cerebellum complementary to LTP, termed long-term depression (LTD) (*41, 42, 104*). The initial demonstration was a stimulation analog of VOR adaptation: electrical stimulation of the vestibular nerve (activating mossy fibers to the flocculus) and of the inferior olive (climbing fibers) conjointly in the high decerebrate rabbit (*104*). This produced both a brief (10 minutes) and prolonged (1 hour) depression in the Purkinje cell response to vestibular nerve stimulation. The same result was obtained with direct stimulation of parallel fibers and climbing fibers, with conjoint glutamate application and climbing fiber stimulation, and with conjoint parallel fiber and white matter stimulation (Purkinje cell excitatory postsynaptic potentials) in guinea pig cerebellar slice in vitro (*105, 106*). The effect is maximal with close temporal contiguity, but can occur over a wide range—from the onset of parallel fiber stimulation 20 msec prior to that of climbing fibers, to the onset of climbing fiber stimulation at least 375 msec prior to that of parallel fibers (*107*). The timing requirements for behavioral learning (eye-blink CR) with conjoint stimulation of mossy fibers (CS) and climbing fibers (US) are different from those producing LTD, but in close accord with the requirements for classical conditioning of skeletal responses in general (*14*): learning is maximal if the onset of mossy fiber stimulation precedes that of climbing fiber stimulation by about 200 to 400 msec, even if the mossy fiber stimulus occurs only at the onset of the CS interval; no learning occurs if the mossy fiber precedence is 50 msec or less (that is, close contiguity does not yield behavioral conditioning) (*32*).

Insofar as the putative mechanism of LTD is concerned, Ekerot and Kano (*107*) suggested that the critical event is the climbing fiber–evoked depolarizing plateau-like potential, which, in distal Purkinje cell dendrites, may last several hundred milliseconds. It is presumed to represent an influx of Ca^{2+} ions into Purkinje cell dendrites (*108*). If Purkinje cells are inhibited (stimulation of "off-

beam" parallel fibers inducing inhibition via stellate and basket cells) simultaneously with climbing fiber activation, the plateau-like potential does not develop, nor does LTD (*107*). Thus, Ca^{2+} influx may be necessary for LTD and argues against the possibility that an extracellular factor released by climbing fiber terminals is critically involved (*41*). In addition, there is evidence that quisqualate-sensitive glutamate receptors may be specifically activated in LTD (*106*).

Mossy and climbing fibers have different timing requirements for stimulation to induce behavioral associative learning and LTD; although this difference may imply a different mechanism, the same mechanism could operate and the different timing requirements be the result of network properties. Depression of Purkinje cell activation from parallel fibers will of course increase the excitability of Purkinje target nuclear cells, the Albus model of how the cerebellum might function in motor learning (*109*). In the awake, untrained rabbit, those Purkinje cells that respond to a tone typically show evoked increases in discharge frequency. In trained animals (eye-blink CR), Purkinje cells in several regions (H VI, crus I, crus II, and paramedian lobules) show alterations that correlate closely with and precede the occurrence of the learned behavioral CR, the most common pattern being a within-trial decrease in frequency of discharge (simple spike), although increases have also been observed (*22, 110*).

Climbing fiber responses (complex spikes) of Purkinje cells evoked by the US onset (corneal airpuff) are prominent in untrained animals and in those beginning training, but much less frequent in well-trained animals (*110*). This result is similar to that of a recent report that activation of the red nucleus can depress somatosensory activation of the inferior olive (*111*). In a trained animal with a well-established eye-blink CR, there is a marked activation of interpositus neurons that would be expected to activate red nucleus neurons via the superior cerebellar peduncle; this activation is maximal at about the time of onset of the US. Thus, climbing fiber activation of Purkinje cells could function as an "error signal" when the CR fails to occur, somewhat analogously to the role hypothesized by Ito for climbing fibers in VOR adaptation (Fig. 1). Such a system could provide a mechanism to account for the behavioral learning phenomenon of blocking (*112*).

Neurochemical processes. This review would be incomplete without specific reference to neurochemical processes involved in learning and memory. Much of this work has been done in the context of memory consolidation. A wide range of chemicals can influence memory performance, and learning involves many alterations in neurotransmitter systems and other chemical processes (*77, 78, 113*). It would be astonishing if this were not the case since synaptic transmission is largely a chemical process and proteins are the structural substrates of cells. Memory traces almost certainly involve physicochemical changes in neurons and very likely involve DNA. But it will only be when memory traces have been localized and mechanisms understood to some degree that specific chemical processes involved in memory storage can be elucidated.

Overview

Analysis of mechanisms of neural plasticity involved in learning is but one step in understanding the neurobiology of learning and memory. Characterizing mechanisms of plasticity entails identifying the circuitry responsible for a form of learning, determining the sites of plasticity within the circuit, and then elucidating the cellular mechanisms involved. It is still necessary to bridge the gap from mechanisms to the behavioral phenomena of learning and memory. Groves and Thompson (*114*) and Hawkins and Kandel (*115*) provided qualitative examples of how findings from the cellular analysis of learning in simplified preparations might be generalized to account for a variety of learning phenomena observed in both vertebrates and invertebrates.

A relatively new aspect of the neurobiology of learning and memory concerns theoretical and computational modeling of learning and memory circuits and networks in the brain (*16, 116*). As memory circuits are defined empirically in both invertebrate and vertebrate nervous systems, it becomes essential to determine quantitatively what these circuits and their associated neurobiological processes can do. This can be achieved only by mathematical and computational modeling. Changes on a cellular level must be related to learning and memory storage on a network level. Such quantitative modeling and mathematical analysis will form strong bridges between artificial intelligence, cognitive science, and empirical studies of memory circuits and networks in the brain (*117*).

REFERENCES AND NOTES

1. H. C. Berg, *Nature (London)* **254**, 389 (1975); D. E. Koshland, *Bacterial Chemotaxis as a Model Behavioral System* (Raven, New York, 1980).
2. In classical conditioning, two stimuli are presented with the conditioned stimulus (CS) onset preceding the unconditioned stimulus (US) onset. Typically the CS does not elicit the response that is elicited by the US before training, but comes to elicit a (usually) similar response as a result of temporally paired or contingent, but not uncontingent, presentations of CS and US. In instrumental learning, presentation of the US is made contingent on the behavior of the organism, as in pressing a lever to obtain food or flexing a limb to avoid shock.
3. A. Dickinson, *Contemporary Animal Learning Theory* (Cambridge Univ. Press, Cambridge, 1980); R. A. Rescorla, *Psychol. Rev.* **74**, 71 (1967).
4. R. F. Thompson, T. W. Berger, J. Madden IV, *Annu. Rev. Neurosci.* **6**, 447 (1983).
5. E. R. Kandel, *Cellular Basis of Behavior: An Introduction to Behavioral Neurobiology* (Freeman, San Francisco, 1976).
6. R. F. Thompson *et al.*, *Am. Psychol.* **31**, 209 (1976).
7. J. J. Chang and A. Gelperin, *Proc. Natl. Acad. Sci. U.S.A.* 77, 6204 (1980); W. J. Davis and R. Gillette, *Science* **199**, 801 (1978); D. L. Alkon, *ibid.* **210**, 1375 (1980).
8. F. B. Krasne, *J. Exp. Biol.* **50**, 29 (1969).
9. J. J. Wine, F. B. Krasne, L. Chen, *ibid.* **63**, 433 (1975).
10. G. Horn, *Proc. R. Soc. London Ser. B* **213**, 101 (1981); F. Nottebohm, *Condor* **86**, 227 (1984); M. Konishi, *Annu. Rev. Neurosci.* **8**, 125 (1985).
11. K. S. Lashley, *Brain Mechanisms and Intelligence* (Univ. of Chicago Press, Chicago, 1929).
12. D. O. Hebb, *The Organization of Behavior* (Wiley, New York, 1949).
13. N. M. Weinberger, in *The Neural Basis of Behavior*, A. L. Beckman, Ed. (Spectrum, Jamaica, NY, 1982); ———, W. Hopkins, D. M. Diamond, *Behav. Neurosci.* **98**, 171 (1984).
14. I. Gormezano, in *Classical Conditioning II: Current Research and Theory*, A. H. Black and W. F. Prokasy, Eds. (Appleton, New York, 1972), pp. 151–181.
15. M. Ito, *Brain Res.* **40**, 81 (1972); J. S. Albus, *Math. Biosci.* **10**, 25 (1971); J. C. Eccles, *Brain Res.* **127**, 327 (1977).
16. D. Marr, *J. Physiol. (London)* **202**, 437 (1969).
17. D. A. McCormick *et al.*, *Bull. Psychon. Soc.* **18** (no. 3), 103 (1981); G. A. Clark, D. A. McCormick, D. G. Lavond, R. F. Thompson, *Brain Res.* **291**, 125 (1984); D. G. Lavond, J. S. Lincoln, D. A. McCormick, R. F. Thompson, *ibid.* **305**, 323 (1984); D. A. McCormick and R. F. Thompson, *Science* **223**, 296 (1984); R. F. Thompson, D. A. McCormick, D. G. Lavond, in *One Hundred Years of Psychological Research in America*, S. H. Hulse and B. F. Green, Jr., Eds. (Johns Hopkins Univ. Press, Baltimore, 1986), p. 125.
18. D. A. McCormick and R. F. Thompson, *J. Neurosci.* **4**, 2811 (1984).
19. D. G. Lavond, T. L. Hembree, R. F. Thompson, *Brain Res.* **326**, 179 (1985).
20. N. H. Donegan, R. W. Lowry, R. F. Thompson, *Soc. Neurosci. Abstr.* **9**, 331 (1983); B. E. Polenchar and M. M. Patterson, *ibid.* **10**, 123 (1984); C. H. Yeo, M. J. Hardiman, M. Glickstein, *Behav. Brain Res.* **13**, 261 (1984).
21. M. R. Foy, J. E. Steinmetz, R. F. Thompson, *Soc. Neurosci. Abstr.* **10**, 122 (1984); D. A. McCormick and R. F. Thompson, *J. Neurosci.* **4**, 2811 (1984).
22. N. H. Donegan, M. R. Foy, R. F. Thompson, *Soc. Neurosci. Abstr.* **11**, 835 (1985).
23. D. G. Lavond, D. A. McCormick, G. A. Clark, D. T. Holmes, R. F. Thompson, *Physiol. Psychol.* **9**, 335 (1981); D. A. McCormick, P. E. Guyer, R. F. Thompson, *Brain Res.* **244**, 347 (1982); D. A. Haley, D. G. Lavond, R. F. Thompson, *Soc. Neurosci. Abstr.* **9**, 643 (1983); J. Madden IV, D. A. Haley, J. D. Barchas, R. F. Thompson, *ibid.*, p. 830; P. F. Chapman, J. E. Steinmetz, R. F. Thompson, *ibid.* **11**, 835 (1985); M. E. Rosenfield, A. Dovydaitis, J. W. Moore, *Physiol. Behav.* **34**, 751 (1985).
24. R. J. Norman, J. S. Buchwald, J. R. Villablanca, *Science* **196**, 551 (1977); M. D. Mauk, thesis, Stanford University (1983).
25. D. A. McCormick, J. E. Steinmetz, R. F. Thompson, *Brain Res.* **359**, 120 (1985).
26. M. D. Mauk and R. F. Thompson, *Soc. Neurosci. Abstr.* **10**, 122 (1984).
27. R. Llinás, K. Walton, D. E. Hillman, C. Sotelo, *Science* **190**, 1230 (1975).
28. P. R. Solomon, J. L. Lewis, J. J. LoTusco, J. E. Steinmetz, R. F. Thompson, *Bull. Psychon. Soc.* **24**, 75 (1986).
29. J. E. Steinmetz, C. G. Logan, D. J. Rosen, D. G. Lavond, R. F. Thompson, *Soc. Neurosci. Abstr.*, in press.
30. J. E. Steinmetz, D. G. Lavond, R. F. Thompson, *Bull. Psychon. Soc.* **23**, 245

(1985); J. E. Steinmetz, D. J. Rosen, P. F. Chapman, D. G. Lavond, R. F. Thompson, *Behav. Neurosci.*, in press.
31. J. E. Steinmetz, D. J. Rosen, D. S. Woodruff-Pak, D. G. Lavond, R. F. Thompson, *Int. J. Neurosci. Res.*, in press.
32. J. D. Steinmetz, D. G. Lavond, R. F. Thompson, *Soc. Neurosci. Abstr.* **11**, 982 (1985).
33. D. A. McCormick *et al.*, *Bull. Psychon. Soc.* **18**, 335 (1981).
34. C. H. Yeo, M. J. Hardiman, M. Glickstein, *Exp. Brain Res.* **60**, 87 (1985).
35. D. S. Woodruff-Pak, D. G. Lavond, R. F. Thompson, *Brain Res.* **348**, 249 (1985); D. S. Woodruff-Pak, D. G. Lavond, C. G. Logan, J. E. Steinmetz, R. F. Thompson, *Soc. Neurosci. Abstr.* **11**, 1112 (1985).
36. D. G. Lavond, J. E. Steinmetz, M. Yokaitis, J. Lee, R. F. Thompson, *Soc. Neurosci. Abstr.*, in press.
37. S. Nagao, M. Ito, L. Karachot, *Neurosci. Res.* **1**, 149 (1984).
38. D. A. McCormick, thesis, Stanford University (1983).
39. G. M. Shambes, J. M. Gibson, W. Welker, *Brain Behav. Evol.* **15**, 94 (1978); J. Kassel, G. M. Shambes, W. Welker, *J. Comp. Neurol.* **225**, 458 (1984).
40. F. A. Miles and S. G. Lisberger, *Annu. Rev. Neurosci.* **4**, 273 (1981).
41. M. Ito, *The Cerebellum and Neural Control* (Raven, New York, 1984).
42. M. Ito, in *Recent Achievements in Restorative Neurology I: Upper Motor Neuron Functions and Dysfunctions*, D. Eccles, Ed. (Karger, Basel, 1985), p. 222.
43. E. Watanabe, *Neurosci. Res.* **3**, 20 (1985).
44. V. B. Brooks and W. T. Thach, in *Handbook of Physiology*, J. M. Brookhart, V. B. Brooks, S. R. Geiger, Eds. (American Physiological Society, Bethesda, MD, 1981), p. 877.
45. A. I. Karamian, V. V. Fanardijian, A. A. Kosareva, in *Neurobiology of Cerebellar Evolution and Development*, R. Llinas, Ed. (American Medical Association, Chicago, 1969); V. K. Krasusky, *Zh. Vyssh. Nervn. Deyat. im I. P. Pavlova* **7**, 733 (1957); N. N. Lifshitz, in *Tr. Fiziol. Inst. I. P. Pavlova Akad. Nauk SSR* **2**, 11 (1947); N. F. Popov, in *Higher Nervous Activity Com. Acad. Press Moscow* **1**, 140 (1929).
46. R. N. Leaton and W. F. Supple, *Science*, in press.
47. O. A. Smith, C. A. Astley, J. L. DeVit, J. M. Stein, K. E. Walsh, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **39**, 2487 (1980).
48. D. H. Cohen, in *Neural Mechanisms of Goal-Directed Behavior and Learning*, R. F. Thompson, L. H. Hicks, V. B. Shvyrkov, Eds. (Academic Press, New York, 1980), p. 283; in *Conditioning: Representation of Involved Neural Functions*, C. D. Woody, Ed. (Plenum, New York, 1982); B. S. Kapp, M. Gallagher, C. D. Applegate, R. C. Frysinger, *ibid.*, p. 581; N. Schneiderman *et al.*, in *Classical Conditioning III: Behavioral Neurophysiological, and Neurochemical Studies in the Rabbit*, I. Gormezano, W. F. Prokasy, R. F. Thompson, Eds. (Erlbaum, Hillsdale, NJ, in press).
49. R. P. Kesner and M. W. Wilbrun, *Behav. Biol.* **10**, 259 (1974).
50. W. F. Supple and R. N. Leaton, *Proc. Eastern Psychol. Assoc.*, in press.
51. M. R. Gold and D. H. Cohen, *Science* **214**, 345 (1981).
52. M. Davis, D. S. Gendelman, M. D. Tischler, P. M. Gendelman, *J. Neurosci.* **2**, 791 (1982).
53. M. D. Tischler and M. Davis, *Brain Res.* **276**, 55 (1983).
54. J. Hitchcock and M. Davis, *Behav. Neurosci.* **100**, 11 (1986).
55. K. S. Lashley, *Comp. Psychol. Monogr.* **11**, 43 (1935).
56. D. R. Meyer and P. M. Meyer, *Physiol. Psychol.* **5**, 133 (1977).
57. M. Mishkin, in *Frontiers in Physiological Psychology*, R. W. Russell, Ed. (Academic Press, New York, 1966), p. 93; in *The Brain and Human Behavior*, A. G. Karczmar and J. C. Eccles, Eds. (Springer, New York 1972).
58. B. Milner, in *The Brain and Human Behavior* (ARNMD vol. 36) (Williams & Wilkins, Baltimore, 1958), p. 244.
59. L. R. Squire, *Science* **232**, 1612 (1986).
60. M. Mishkin, *Nature (London)* **273**, 297 (1978); *Philos. Trans. R. Soc. London Ser. B* **298**, 85 (1982).
61. G. C. Baylis and E. T. Rolls, *Soc. Neurosci. Abstr.* **9**, 26 (1983).
62. J. O'Keefe and L. Nadel, *The Hippocampus as a Cognitive Map* (Oxford Univ. Press, New York, 1978).
63. B. Kolb, R. J. Sutherland, I. Q. Whishaw, *Behav. Neurosci.* **97**, 13 (1983).
64. J. O'Keefe, *Exp. Neurol.* **51**, 78 (1976); ——— and D. H. Conway, *Exp. Brain Res.* **31**, 573 (1978); D. S. Olton, M. Branch, P. J. Best, *J. Exp. Neurol.* **57**, 87 (1978); V. M. Miller and P. J. Best, *Brain Res.* **194**, 311 (1980).
65. D. S. Olton, J. T. Becker, G. E. Handelmann, *Behav. Brain Sci.* **2**, 313 (1979); *Physiol. Psychol.* **8**, 239 (1980).
66. A. J. Hill, *Exp. Neurol.* **62**, 282 (1978); J. L. Kubie and J. G. Ranck, Jr., in *Conditioning: Representation of Involved Neural Functions*, C. D. Woody, Ed. (Plenum, New York, 1982).
67. T. W. Berger and R. F. Thompson, *Brain Res.* **145**, 323 (1978); S. A. Deadwyler, M. O. West, J. H. Robinson, *Science* **211**, 1181 (1981); J. Olds, J. F. Disterhoft, M. Segal, C. L. Hornblith, R. Hirsch, *J. Neurophysiol.* **35**, 202 (1972).
68. C. F. Jacobsen, *Comp. Psychol. Monogr.* **23**, 101 (1936); K. H. Pribram, M. Mishkin, H. E. Rosvold, S. J. Kaplan, *J. Comp. Physiol. Psychol.* **45**, 567 (1952); G. M. French and H. F. Harlow, *J. Neurophysiol.* **25**, 585 (1962).
69. B. Milner and M. Petrides, *Trends Neurosci.* **7**, 403 (1984).
70. P. S. Goldman-Rakic and M. L. Schwartz, *Science* **216**, 755 (1982); P. S. Goldman-Rakic, *Trends Neurosci.* **7**, 425 (1984).
71. J. M. Fuster and G. E. Alexander, *Science* **173**, 652 (1971); J. M. Fuster, *Trends Neurosci.* **7**, 408 (1984); K. Kubota and H. Niki, *J. Neurophysiol.* **34**, 337 (1971).
72. A. R. Damasio and N. Geschwind, *Annu. Rev. Neurosci.* **7**, 127 (1984).
73. T. H. Bullock, in *Information Processing in the Nervous System*, H. M. Pinsker and W. D. Willis, Eds. (Raven, New York, 1980).
74. C. D. Woody, *Memory, Learning, and Higher Function—A Cellular View* (Springer, New York, 1982).
75. R. W. Gerard, *Am. J. Psychiatry* **106**, 161 (1949); C. P. Duncan, *J. Comp. Physiol. Psychol.* **42**, 32 (1949).
76. D. O. Hebb, *The Organization of Behavior* (Wiley, New York, 1949).
77. B. W. Agranoff, H. R. Burrell, L. A. Dokas, A. D. Springer, in *Psychopharmacology: A Generation of Progress*, M. A. Lipton, A. DiMascio, K. F. Killam, Eds. (Raven, New York, 1978), p. 623.
78. J. L. McGaugh and M. J. Herz, Compilers, *Memory Consolidation* (Albion, San Francisco, 1972); A. J. Dunn, *Annu. Rev. Psychol.* **31**, 343 (1980); L. R. Squire, *Trends Neurosci.* **3**, 52 (1980).
79. G. E. Koob and F. E. Bloom, *Annu. Rev. Physiol.* **44**, 571 (1982).
80. J. B. Flexner and L. B. Flexner, *Proc. Natl. Acad. Sci. U.S.A.* **66**, 46 (1970); J. L. McGaugh, *Annu. Rev. Psychol.* **34**, 297 (1983); P. E. Gold and S. F. Zornetzer, *J. Behav. Neural Biol.* **38**, 151 (1983).
81. L. Ganz and M. Fitch, *Exp. Neurol.* **22**, 638 (1968); D. H. Hubel and T. N. Wiesel, *Nature (London)* **225**, 41 (1970); K. L. Chow and D. L. Stewart, *Exp. Neurol.* **34**, 409 (1972); D. H. Hubel, T. N. Wiesel, S. LeVay, *Philos. Trans. R. Soc. London Ser. B* **278**, 377 (1977).
82. M. C. Diamond *et al.*, *J. Comp. Neurol.* **128**, 117 (1966); R. W. West and W. T. Greenough, *Behav. Biol.* **7**, 279 (1972); M. K. Floeter and W. T. Greenough, *Science* **206**, 227 (1979).
83. W. T. Greenough, *Trends Neurosci.* **7**, 229 (1984).
84. R. N. Walsh and W. T. Greenough, *Environments as Therapy for Brain Dysfunction* (Plenum, New York, 1976); M. R. Rosenzweig, in *Recovery of Function: Theoretical Considerations for Brain Injury Rehabilitation*, P. Bach-y-Rita, Ed. (University Park Press, Baltimore, 1980).
85. E. Fifkova and A. Van Harreveld, *Soc. Neurosci. Abstr.* **4**, 257 (1978); D. N. Spinelli, F. E. Jensen, G. V. DiPresco, *Exp. Neurol.* **68**, 1 (1980); F. L. F. Chang and W. T. Greenough, *Brain Res.* **232**, 283 (1982).
86. R. F. Thompson and W. A. Spencer, *Psychol. Rev.* **173**, 16 (1966); I. Kupfermann, V. Castellucci, H. Pinsker, E. Kandel, *Science* **167**, 1743 (1970); P. B. Farel, D. L. Glanzman, R. F. Thompson, *J. Neurophysiol.* **36**, 1117 (1973).
87. R. S. Zucker, *J. Neurophysiol.* **35**, 599 (1972); *ibid.*, p. 621; E. R. Kandel, M. Brunelli, J. Byrne, V. Castellucci, in *Cold Spring Harbor Symp. Quant. Biol.* **60**, 46 (1976); M. Klein, E. Shapiro, E. R. Kandel, *J. Exp. Biol.* **89**, 117 (1980).
88. R. F. Thompson and W. A. Spencer, *Psychol. Rev.* **173**, 16 (1966).
89. R. D. Hawkins, V. F. Castellucci, E. R. Kandel, *J. Neurophysiol.* **45**, 315 (1981); E. R. Kandel and J. H. Schwartz, *Science* **218**, 433 (1982).
90. T. W. Abrams, T. J. Carew, R. D. Hawkins, E. R. Kandel, *Soc. Neurosci. Abstr.* **9**, 168 (1983); R. D. Hawkins, T. W. Abrams, T. J. Carew, E. R. Kandel, *Science* **219**, 400 (1983); E. T. Walters and J. H. Byrne, *ibid.*, p. 405.
91. T. J. Crow and D. L. Alkon, *Science* **201**, 1239 (1978).
92. D. L. Alkon, *ibid.* **226**, 1037 (1984).
93. T. W. Berger, P. Rinaldi, D. J. Weisz, R. F. Thompson, *J. Neurophysiol.* **50**, 1197 (1983).
94. J. F. Disterhoft, D. A. Coulter, D. L. Alkon, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
95. L. A. Mamounas, R. F. Thompson, G. Lynch, M. Baudry, *ibid.* **81**, 2548 (1984).
96. L. W. Swanson, T. J. Teyler, R. F. Thompson, Eds., *Mechanisms and Functional Implications of Hippocampal LTP* (MIT Press, Boston, 1982).
97. P. Anderson, S. H. Sundberg, O. Sveen, J. N. Swann, H. Wigstrom, *J. Physiol. (London)* **302**, 463 (1980); T. V. P. Bliss and T. Lomo, *ibid.* **232**, 331 (1973); T. Lomo, *Acta Physiol. Scand.* **68**, 128 (1966).
98. J. C. Eccles, *The Physiology of Synapses* (Springer-Verlag, Berlin, 1964); W. A. Spencer and R. S. April, in *Short-Term Changes in Neural Activity and Behavior* (Cambridge Univ. Press, Cambridge, 1970), p. 433.
99. B. L. McNaughton, R. M. Douglas, G. V. Goddard, *Brain Res.* **157**, 277 (1978).
100. G. Barrionuevo and T. H. Brown, *Proc. Natl. Acad. Sci. U.S.A.* **80**, 7347 (1983); S. R. Kelso and T. H. Brown, *Science* **234**, 85 (1986). J. Larson and G. Lynch, *ibid.* **232**, 985 (1986). W. B. Levy and O. Steward, *Brain Res.* **179**, 233 (1979); W. B. Levy, S. E. Brassel, S. D. Moore, *Neuroscience* **8**, 799 (1983); B. R. Sastry, J. W. Goh, A. Auyeung, *Science* **232**, 988 (1986).
101. S. R. Kelso, A. H. Ganong, T. H. Brown, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
102. G. Lynch and M. Baudry, *Science* **224**, 1057 (1984).
103. F. L. F. Chang and W. T. Greenough, *Brain Res.* **309**, 35 (1984); K. S. Lee, M. Oliver, F. Schottler, G. Lynch, in *Electrophysiology of Isolated Mammalian CNS Preparations*, G. A. Kerkut and H. V. Wheal, Eds. (Academic Press, New York, 1981), p. 189.
104. M. Ito, M. Sakurai, P. Tongroach, *J. Physiol. London* **324**, 113 (1982).
105. M. Sakurai, *Neurosci. Lett. Suppl.* **22**, S26 (1985).
106. M. Kano and M. Kato, *ibid.*, p. S26.
107. C. F. Ekerot and M. Kano, *Brain Res.* **342**, 357 (1985).
108. R. Llinas and M. Suguimari, *J. Physiol. (London)* **305**, 197 (1980).
109. J. S. Albus, *Math. Biosci.* **10**, 25 (1971).
110. M. R. Foy and R. F. Thompson, *Soc. Neurosci. Abstr.*, in press.
111. C. Weiss, M. L. McCurdy, J. C. Houk, A. R. Gibson, *ibid.* **11**, 182 (1985).
112. In blocking, training is first established to a CS_1; subsequent training trials with simultaneous CS_1 and CS_2 yields much less learning to CS_2 than if no prior CS_1 training were given.
113. A. J. Dunn, *Annu. Rev. Psychol.* **31**, 343 (1980); V. E. Shashoua, *Adv. Cell. Neurobiol.* **3**, 97 (1982); L. R. Squire, *J. Neurosci.* **1**, 635 (1981).
114. P. M. Groves and R. F. Thompson, *Psychol. Rev.* **77**, 419 (1970).
115. R. D. Hawkins and E. R. Kandel, *ibid.* **91**, 375 (1984).
116. S. Grossberg, *Prog. Theor. Biol.* **3**, 51 (1974); R. S. Sutton and A. G. Barto, *Psychol. Rev.* **88**, 135 (1981); G. M. Edelman and G. N. Reeke, Jr., *Proc. Natl. Acad. Sci. U.S.A.* **79**, 2091 (1982); L. N. Cooper, in *J. C. Maxwell, the Sesquicentennial Symposium*, M. S. Berger, Ed. (Elsevier, Lausanne, 1984); F. Crick, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 4586 (1984); G. E. Hinton, T. J. Sejnowski, D. H. Ackley, *Carnegie-Mellon Tech. Rep.* **84**, 119 (1984); K. J. Gingrich and J. H. Byrne, *J. Neurophysiol.* **53**, 652 (1985); R. G. Coss and D. H. Perkel, *Behav. Neural Biol.* **44**, 151 (1985); M. A. Gluck and R. F. Thompson, *Psychol. Rev.*, in press.
117. R. F. Thompson, N. H. Donegan, D. G. Lavond, in *Steven's Handbook of Experimental Psychology*, R. C. Atkinson, R. J. Herrnstein, G. Lindzey, R. D. Luce, Eds. (Wiley, New York, ed. 2, in press).
118. Supported in part by Office of Naval Research grant ONR-N00014-83K-0238, National Science Foundation grant BNS81-06648, the McKnight Foundation, and the Sloan Foundation. I am particularly indebted to colleagues who have coauthored earlier reviews with me: N. Donegan, D. Lavond, and T. Berger and to my many other collaborators in the work reported here.