

broadest similarity between learning and neural development: the recruitment of cellular programs of growth by signaling molecules.

These cellular programs can include alterations in the display of cell surface adhesion molecules. For example, long-term sensitization training in *Aplysia* causes a transcription-dependent down-regulation of NCAM-related cell adhesion molecules on the surface of sensory neurons (18). If this were generally the case, then in a sense, Sperry's circle is squared. Activity initiated by experience could lead to the release of signaling molecules that engage transcriptional control mechanisms, which modulate cell surface receptors so as to regulate cell-cell interactions.

The development of stem cell techniques for homologous recombination in mice (19) has provided a useful tool for testing genetically whether a particular mechanism is important for LTP in the hippocampus of the adult organism and whether LTP in the hippocampus is causally required for learning (20). These gene ablation methods can now be extended to determine whether synaptic modulation during development resembles memory storage only phenotypically or whether they actually share common molecular mechanisms (20). We should therefore soon be in a position to see whether solutions to the problems of learning and memory will yield, as an extra bonus, insights into synapse development and vice versa. If the study of learning and synapse development prove to be mutually reinforcing on the molecular level, then the Decade of the Brain, which we hope will relate molecules to mind, will be off to a particularly good start.

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The Physiology of Memory: Recordings of Things Past

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Our conception of the process of memory—how we remember and recognize—is now undergoing a revolution similar to the dramatic changes seen over the past two decades in our understanding of how sensory information is processed. Sensory systems are now known to comprise a large number of separate cortical areas with complex interconnections; this complexity replaces the old notion of a primary sensory area with one or two cortical subsidiary areas. Likewise, memory is being fractionated as a result of recent studies—psychological, physiological, and anatomical (1).

This fractionation of memory systems was inevitable, as it now appears that most or all of the adult brain undergoes learning-dependent changes. Each biological change contributes to one or more of the numerous memory systems, which are defined behaviorally or psychologically. One class of memory system underlies declarative, or explicit, memories, which are the memories of specific facts and events. Within this class, it is useful to distinguish short-term (working memory) processes from long-term ones, and recognition processes from recall, as well as numerous material-specific systems, such as memory for faces, words, objects, and so on. The other class underlies nondeclarative, or implicit, memories, which include stimulus-response "habits," perceptual learning, conditioning, cognitive and motor skill learning, various types of priming, and habituation.

The mnemonic contributions of a given brain structure are usually closely related to its non-mnemonic functions. For example, the responses of neurons in premotor cortical areas change during visuomotor conditional learning (2); neurons in prestriate visual

areas concerned with stimulus orientation respond in relation to working memory for the orientation of visual stimuli (3); the responses of neurons in the inferior temporal cortex, which is important for visual discrimination, change as visual objects become more familiar (4); and prefrontal and posterior parietal areas concerned with spatial relations contain neurons that respond in relation to working memory for spatial location (5). Likewise in humans and animals, lesions of the cerebellum, a motor control structure, impair the acquisition of classically conditioned motor responses (6); lesions or disease of portions of the striatum, which normally functions in sensorimotor integration, impair stimulus-response learning of habits (7, 8); lesions of inferior temporal cortex, an area important for visual discrimination, impair visual recognition and associative memory (8, 9); and lesions of superior temporal cortex, an area important for auditory discrimination, impair auditory recognition memory (10).

The medial temporal lobe is a major site of multimodal convergence, and it contains neurons that are sensitive to the configuration of many environmental stimuli as well as to the behavioral context in which events occur (11); thus, it is not surprising that this region is critical for forming long-term explicit memories (8, 12), which depend on just this sort of configurational information. Although the ultimate storage sites for explicit memories appear to be in the cortex, the medial temporal lobe plays a critical enabling, or buffering, role necessary for storage to take place. The hippocampus, ventromedial temporal cortex, and amygdala may each make selective contributions to explicit memory in the medial temporal lobe (13).

With such an abundance of memory mechanisms, are there any common physiological underpinnings? Neuronal record-

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ings in animals suggest at least four ways in which neuronal activity is altered during formation or expression of memory traces (see figure): tuning, adaptive filtering, sustained activation, and association.

Tuning mechanisms come into play as a result of sensory experience. Frequency-selective neurons in auditory cortex of animals classically conditioned to specific tones, for example, tend to shift their preferred frequency to that of the conditioned stimulus (14). Likewise, animals taught tactile discriminations develop enlarged representations of the relevant portion of their body in somatosensory cortex, and, in some cases, the receptive fields of neurons in that region sharpen (15). The most extreme changes in cortical maps occur when part of the peripheral sensory system is removed (such as in limb deafferentation), causing expansion of the representation of remaining parts (16). Tuning mechanisms are

















needed for working memory. For example, in posterior parietal and prefrontal cortex, neurons that respond to a visual stimulus presented at a particular spatial location remain activated when the stimulus is no longer present, as long as the monkey holds that location "in mind" (5). Comparable results have been reported for some inferior temporal neurons when monkeys hold the visual memories of objects in mind (18) and in several sensorimotor structures when animals delay a particular behavioral response. Such processes probably contribute to associative recall (see below) as well as to working memory.

Finally, associative mechanisms are engaged as a result of pairings of different sensory stimuli. If two arbitrary visual stimuli occur repeatedly within a short time of each other, neurons in temporal cortex will tend to respond to both of them more commonly than would be expected by

chance pairings of responses (19). Another example is in the representation of the hand in somesthetic cortex, in which neurons normally respond to stimulation of just one finger. However, if two fingers are surgically attached, so that they are frequently stimulated at the same time, neurons will begin to respond to stimulation of both (15). Associative mechanisms may also interact with sustained activation ones. When

lobe, suggesting the sustained activation of neurons in this region. By contrast, subjects who viewed word fragments from a list of words that they had seen before showed less activation of the temporal cortex than when they viewed new fragments, suggesting that neuronal responses to the familiar words were suppressed due to the operation of the adaptive filtering mechanism in temporal cortex. Another study measured brain activation while subjects learned a visuo-motor pursuit task and found that some of the same cortical areas normally involved in the performance of the task (motor and supplementary motor cortex) showed increased activation during learning (22).

The linkage of activation and lesion studies with physiological analyses, and the subsequent linkage of the physiological studies with cellular and molecular approaches, hold great promise for elucidating the myriad of memory mechanisms in the human brain.

	A neuron that initially responds to	After experience with	Now responds to
Tuning	 or 		
Adaptive filtering	 or 		
Sustained activation			
Association		 + 	 or 

Mechanisms of memory. Four ways in which neuronal activity is modified during the formation or expression of memory traces.

likely involved in perceptual learning, such as learning to hear the individual words in continuous speech or to feel the letters in Braille text after practice and experience.

In adaptive filtering, incoming sensory information is filtered by neurons according to how similar it is to information already held in either short- or long-term memory. In monkeys, for example, some of the neurons in inferior temporal cortex that respond selectively to particular object features, such as color or shape, give their best response to objects that contain those features but which are new, unexpected, or not recently seen (4, 17). As new stimuli become familiar, synaptic weights in the cortex adjust so that the neuronal response is dampened, a case of "familiarity breeding contempt" for neuronal responses. Adaptive filtering may be critical for several behaviorally defined memory mechanisms, including long-term memory, working memory, and repetition priming.

In sustained activation, neurons are activated when previously stored information

monkeys are taught that stimulus A predicts stimulus B, for example, presentation of A causes a sustained activation of some of the neurons that would normally respond only to B (20).

One way of looking at tuning, adaptive filtering, and associative processes is that they provide a means of incorporating "knowledge" into the structure of the brain. Tuning mechanisms can be used to incorporate knowledge of the physical structure of the environment, adaptive filtering can be used for temporal structure, and associative mechanisms for both. Sustained activation provides a means for working with this incorporated knowledge, when the original information is no longer present.

An exciting development of the past year is the potential for distinguishing different memory mechanisms by using positron emission tomography to map brain activity in humans. In one recent study (21), subjects asked to recall words showed activation of the right medial temporal

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